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ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

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Cover art, titled *From Data to Dawn*, by Ann Meredith Garcia Trinidad, MD. Used with permission.

About the cover art: Ann Meredith Garcia Trinidad is Head of the Section of Medical Oncology at Dagupan Doctors Villaflor Memorial Hospital in the Philippines. She received an ASCO International Development and Education Award in 2020, and has served as an Advisory Panelist for Cancer.Net. Inspired by her work in oncology and patient education, she uses paper quilling to transform the science of cancer into a visual narrative of healing. Her featured piece, *From Data to Dawn*, intersperses Kaplan-Meier curves, DNA helices, antibodies, and the tumor microenvironment to symbolize precision oncology. The cancer ribbon and the path towards the sunrise represent the patient journey—anchored in hope, guided by evidence, and sustained by care.

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EPIDEMIOLOGY AND PREVENTION

1

Christin B. DeStefano, MD, and John L. Vaughn, MD, MS

RECENT UPDATES

- Blood-based cancer screening uses fragments of DNA shed by tumors into the bloodstream to detect cancer early and noninvasively. Validated tests for colorectal cancer show high sensitivity (83.1%) and specificity (89.6%) in average-risk adults.[1] Emerging multicancer early detection (MCED) platforms analyze DNA fragment patterns, chromatin, and methylation patterns to identify dozens of cancers and predict where they started, offering a single-test approach to broad cancer screening for high-risk populations.
- The National Cancer Institute Vanguard Study (NCT06995898) is a feasibility trial enrolling up to 24,000 participants across multiple sites to assess the operational viability of using MCED blood tests for population-based screening of cancers including pancreatic, ovarian, liver, lung, bladder, breast, colorectal, esophageal, stomach, and prostate. Primary endpoints focus on feasibility of recruitment, adherence, and representative enrollment, while secondary endpoints assess timeliness of result return, diagnostic resolution of abnormal tests, and impact of blinding on adherence and screening behavior.[2]

OVERVIEW

Cancer providers who are charged with the diagnosis, treatment, and management of cancer and related treatments operate at the far end of the cancer life cycle. However, the origins of cancer lie far before these clinical encounters, rooted in an individual's genetic background, environmental exposures, behaviors, and the complex interplay between these factors. Although the care of patients with cancer is crucial for improving outcomes of current and potentially future patients, individual oncology services are insufficient to alter the cancer's impact at the population level. Epidemiology provides the tools to understand cancer at the population level and the opportunity for interventions to reduce the impact of cancer and ultimately improve the outcomes of cancer. Understanding epidemiology empowers clinicians to extend care beyond the patient to the population through targeted interventions in patients' communities. For example, collection of risk factor information, such as tobacco and alcohol use, body mass index, and family history of cancer, can be used to provide advice and guidance to patients (eg, tobacco use cessation) and to guide recommended strategies for primary prevention, secondary prevention (eg, early detection), and tertiary prevention (improving outcomes).

DISTRIBUTION OF CANCER IN POPULATIONS

Epidemiology is the study of the distribution of disease (descriptive epidemiology) and disease determinants (analytic epidemiology) in populations. Characterizing the distribution of cancer in populations is a critical first step to understanding the scope of the problem posed by cancer. Central to this process are ongoing surveillance activities to rigorously track the occurrence of cancer in defined populations according to characteristics of patients with cancer, including where they live and the disease onset. Population-based cancer registries are ongoing surveillance systems designed to ascertain newly diagnosed cases of cancer and deaths resulting from cancer or other etiologies such as secondary cancers or complications of cancer therapy. In the United States, the National Cancer Institute (NCI) sponsors the Surveillance, Epidemiology, and End Results (SEER) Program, which provides data (45.9% of the US population) on cancer incidence, survival, treatment patterns, and county-level data, facilitating epidemiology research.[3] The NCI's Virtual Pooled Registry (VPR) enables secure linkage between external research cohorts and state cancer registries, further supporting epidemiological cancer research and longitudinal cancer surveillance.

MEASURING THE DISTRIBUTION OF CANCER

Cancer statistics use population rates, typically expressed as cases per 100,000 people per year, to describe both the number of new diagnoses and the overall burden of the disease. These rates are age adjusted to allow for meaningful comparisons because

cancer incidence frequently rises with age. Variations in the prevalence of risk factors contribute to differences in how often cancer occurs and its resulting outcomes. The population-attributable risk represents the proportion of new cancer cases that can be linked to specific risk factors within a population. Cancer incidence and survival data are reported in cancer registries throughout the world. These data may be limited by lag times in reporting and missing data.

Key measures include the following:

- Incidence: New cancer cases (reflects effectiveness of primary and secondary prevention, the former will decrease incidence, while the latter will increase incidence).
- Mortality: The cancer mortality includes deaths from cancer (influenced by stage at diagnosis, tumor biology, treatments received, and access to care), and non-cancer mortality includes deaths from competing etiologies (such as cardiovascular disease, motor vehicle accident, etc.).
- Survival: The percentage of patients alive after a specific time (reflects treatment effectiveness). Overall survival takes into consideration deaths from any cause. Overall survival is a common endpoint in clinical trials. Relative survival is a measure of cancer survival that is commonly used in population-based cancer studies. The SEER Program reports relative survival.
- Prevalence: The total number of people living with active cancer (reflects new cases and survival time).

Further information on cancer statistics can be found at the SEER Program.

DESCRIBING THE DISTRIBUTION OF CANCER

An initial step to describe the distribution of cancer in a population involves describing it according to the characteristics of patients (person), including where they live (place), and when they are diagnosed (time).

Real-World Example

A compelling real-world example highlights the importance of detailed analysis: although the overall incidence of colorectal cancer had been decreasing,[4] further analysis based on age groups revealed a concerning trend: an increasing incidence among people younger than 50 years.[5] This observation was corroborated by data from other regions globally[6] and ultimately served as a key factor in the decision to lower the recommended starting age for colon cancer screening in the United States from 50 to 45 years.[7]

Person. Understanding the characteristics of people diagnosed with cancer, such as age, sex, race, ethnicity, and occupation, is crucial for identifying disparities and tailoring interventions. Characteristics of persons measured in US cancer registries principally include age at diagnosis, sex, race, and Hispanic ethnicity. For most cancer types, survival rates are observed to be lower for Black people compared with White people. Exceptions include pancreatic and kidney cancers, where survival rates are similar between these two groups. However, after adjusting for sex, age, and stage at diagnosis, the risk of death from cancer is 33% higher in Black people and 51% higher in American Indian/Alaska Native people compared with their White counterparts.[8] Identification of populations experiencing disparities in incidence and/or mortality has led to research to determine the root causes of these disparities so that they can be reduced. Disparities research entails multilevel assessments to identify and address factors such as social determinants of health, individual socioeconomic characteristics, structural racism, access to and use of health care, lifestyle and behavioral factors, and biological factors that affect outcomes. In the equal-access US military health system, where active-duty service members maintain regular physical fitness, undergo routine drug testing, and receive free unlimited comprehensive care, cancer mortality is significantly lower than in matched civilian populations, and disparities by race or socioeconomic status are markedly smaller than in the standard US health care system.[9,10]

Place. Comparing cancer rates between populations in different locations can distinguish high- and low-risk areas. Age-adjusted breast cancer mortality among non-Hispanic Black women ranges from 33.6 per 100,000 in the District of Columbia to 19 per 100,000 in Massachusetts, reflecting differences in prevalence of risk factors as well as access to and use of prevention and treatment services.[11] Geographic variations in cancer incidence and mortality could reflect access to care, risk factors such as obesity and smoking, environmental exposures, policy differences, and infrastructure for regional screening and clinical trials.

Time. Documentation of the cancer occurrence in populations across time may lead to new hypotheses about the etiology and outcomes of cancer. Increases in incidence may result from population-level increases in risk factors, decreases in protective factors, or both. Compliance with secondary preventive strategies, such as screening for lung, breast and prostate cancer, will also lead to increased cancer incidence. Decreases in incidence may result from large-scale primary prevention interventions or other determinants of population-level decreases in risk factors. Decreases in mortality rates may result from decreased incidence, improved screening that detects cancer at earlier stages, novel treatments, and/or adoption of lifestyle changes such as weight loss and structured exercise that promote longer survival or more effective cures.

- The rapid rise in prostate cancer incidence after 1985 and subsequent fall are largely attributed to the introduction and widespread use of the prostate-specific antigen (PSA) test for screening.[12]
- The COVID-19 pandemic led to a decline in the diagnosis of six major cancers, including localized breast, colorectal, lung, prostate, thyroid, and pancreatic cancers, between March and May 2020. The decline has been attributed to missed or delayed cancer screenings and preventive care visits that occurred in 2020 because of the suspension of nonessential medical care to help control the spread of the disease.[13]

Analyzing cancer trends across time is therefore essential for understanding disease etiology, evaluating interventions, and anticipating future challenges.

DETERMINANTS OF CANCER

Cancer research seeks to identify causes for prevention. A "cause" in epidemiology increases disease frequency when present and decreases it when absent. Cancer typically has multiple causes, and truly necessary causes (eg, human papillomavirus [HPV] for cervical cancer) are uncommon. Modifiable factors play a role in attribution of about 40% of cancers,[14,15] and in almost half of cancer-related deaths worldwide. Establishing a causal link requires a strong association between the factor and the disease, the factor preceding the disease (temporality) with latency considered, and consistent findings across different studies. Epidemiologists use observational studies (cohort, case-control, and cross-sectional studies) to investigate these associations. These studies analyze exposures (eg, diet, environment, occupation) and measure the link to disease using relative risk, odds ratios, hazard ratios, or standardized incidence ratios. Each study type has advantages and disadvantages related to time, resources, and potential biases (Table 1-1). Cohort studies are best for establishing temporality. Replicating findings across various studies, populations, and time periods is crucial for confirming robust causal relationships. Additional details summarizing study designs can be found at the Centre for Evidence-Based Medicine website by the University of Oxford.[14]

Table 1-1 Hierarchy of Evidence by Study Design

Study Type	Evidence
Pooled analysis/ meta-analysis	One of the highest levels of evidence and more generalizable given that it uses multiple data sources, provided inclusion of high-quality studies. Meta-analysis uses published results, whereas pooled analysis reanalyzes individual-level data
Randomized clinical trial	Highest-quality evidence, but use is limited to testing health-enhancing interventions (new treatments, preventive or screening interventions)
Cohort (prospective or retrospective)	Highest-quality observational evidence because of measurement of exposure and follow-up for occurrence of the outcome
Case-control	Useful for studying rare diseases, such as specific cancer types, but susceptible to information and selection biases because of measurement of exposure after the occurrence of disease and challenges of selecting and recruiting a control group representative of the population from which the cases arose
Cross-sectional	Limited by studying only prevalent cancer and measurement of exposure and outcome at a point in time
Ecologic	Unit of observation is group-level data (typically geographically defined), not individuals; results can be useful for evaluating policies aimed at reducing cancer risk factor prevalence that vary geographically
Case series	Commonly used clinical design, but lack of a comparison group severely limits inferences

Study designs higher up in the table tend to provide stronger evidence because of higher internal validity (or lower likelihood of bias).
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KEY POINTS

- Epidemiology is the study of the distribution and determinants of disease in populations.
- The distribution of cancer incidence, prevalence, mortality, and survival can be compared across demographic characteristics of populations to identify high-risk populations and cancer disparities.
- Criteria for a casual inference in cancer epidemiology include consistency, strength of association, temporal precedence, and latency.

EXTRINSIC AND INTRINSIC FACTORS ASSOCIATED WITH CANCER RISK

Cancer risk is a result of both extrinsic influences (environmental exposures, lifestyle, infectious agents) and intrinsic factors (genetic predisposition, internal biological factors). Although the relative importance of each is still debated, both contribute significantly. The fact that only some smokers develop lung cancer, despite the strong extrinsic factor of smoking, suggests the involvement of intrinsic genetic susceptibility. Therefore, an individual's risk of cancer reflects both their levels and duration of exposure to carcinogens and their own susceptibility, including their genetic predispositions to metabolize exposures or to repair damage induced by a carcinogenic exposure. This interaction between genes and the environment is a central focus of study in molecular epidemiology.[16]

EXTRINSIC FACTORS

Epidemiological studies have identified associations between many extrinsic factors and cancer risk (Table 1-2). For some extrinsic factors, clear-cut causal associations have been established. These are discussed in more detail in the "Interventions for Preventing Cancer" section of this chapter.

Table 1-2 Associations Between Extrinsic Factors and Cancer Risk

Exposure	Cancer Type(s)	Notes
Cigarette smoking	Lung, oral cavity, larynx, esophagus, bladder, kidney, pancreas, stomach, cervix, colon, rectum, liver, acute myeloid leukemia	Causal association; estimated 48% of deaths from cancer in the United States attributable to smoking[17]
Ionizing radiation	Leukemia, non-Hodgkin lymphoma, thyroid, breast (female), lung, colon, bladder	Established cause[18,19] In the Life Span Study on Japanese atomic bomb survivors, after high-dose radiation there was an elevated leukemia risk early on, and an elevated solid tumor risk long-term. A heightened risk of hematological malignancies has been established after lower doses of radiation exposure from medical imaging in children and adolescents[20-22]
UV radiation	Melanoma, nonmelanoma skin cancers	Major cause (sunlight, tanning devices)[18]
HPV (oncogenic strains)	Cervix, penis, vagina, anus, oropharynx	Strong association[23]
Hepatitis B and C viruses	Liver, splenic marginal zone lymphoma	Strong association[23]
Epstein-Barr virus	Burkitt lymphoma, nasopharyngeal carcinoma	Strong association[23]
Helicobacter pylori	Gastric cancer	Strong association[23]
High BMI/obesity	Endometrial, esophageal, meningioma, breast, multiple myeloma, gallbladder, gastric, colorectal, kidney, liver, ovarian, pancreatic, and thyroid cancer[25]	Strong association; 4%-9% of new cancer cases in adults attributable to high BMI[24] Glucagon-like peptide 1 receptor agonists may decrease the risk of obesity associated cancers[26]
Alcohol	Breast cancer, liver, colorectal, oral cavity, esophageal (squamous cell)	Causal association[27,28]
Occupational exposures	Various (eg, melanoma and prostate cancer in pilots/aviators,[29] scrotal carcinomas in chimney sweeps)	2%-8% of cancers attributable to occupational causes[30,31]
Particulate matter (air pollution)	Lung	Classified as human lung carcinogen[32]
HIV infection	Non-Hodgkin lymphoma, cervical cancer, Kaposi sarcoma, anal cancer, Hodgkin lymphoma, lung cancer, skin cancer, oropharyngeal cancers, liver cancer[33]	Risk of non-AIDS-defining cancers (eg, Hodgkin lymphoma, liver, anal, lung) remains elevated even with immune reconstitution on ART. Therefore effective ART reduces, but does not eliminate, excess cancer risk. Coinfections (HPV, HBV, HCV) and lifestyle factors (eg, smoking, alcohol use) further modify risk

Exposure	Cancer Type(s)	Notes
Medications	Immunosuppression or immunomodulators such as lenalidomide can heighten the risk of lymphoid and other malignancies,[34] tamoxifen and uterine cancer risk[35]	Lenalidomide plus high-dose melphalan with autologous stem cell rescue increases the risk of therapy- related myeloid neoplasms[36]
Sedentary lifestyle	Increases the risk of multiple cancers as well as cancer-related mortality[37,38]	The CHALLENGE trial reported a significant reduction in disease-free survival as well as long-term overall survival in colon cancer survivors who underwent a 3-year structured exercise program. Reduced cancer mortality in patients physically fit is exemplified by the healthy soldier effect[39,40]
Circadian rhythm disruptions	Breast, prostate, colorectal, liver, lung cancers	The International Agency for Research on Cancer (IARC) has identified night shift work as a probable carcinogen (group 2A); it is hypothesized that DNA repair, apoptosis, and cell cycle regulation are regulated by circadian genes[41]
Diet	Colorectal cancer	Processed red meat has been linked with an increased colorectal cancer risk[42]

Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus.
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INTRINSIC FACTORS

In addition to external influences, a range of intrinsic factors inherent to a person significantly contributes to their cancer risk (Table 1-3): age, sex, ethnicity, family cancer history, and molecular characteristics encompassing inflammation, immune function, hormones, oxidative stress, and genetic/epigenetic variations.

Table 1-3 Associations Between Intrinsic (Host) Factors Related to Cancer Risk

Intrinsic Factor Category/ Specific Factor	Description/Examples	Cancer Type(s) Associated	Notes
Nonmolecular			
Age	Cancer risk generally increases with age for most cancer types	Most cancers increase in incidence with increasing age	Strong association because of accumulated exposures and cellular changes over time
Sex	Differences in cancer incidence and mortality exist between sexes because of hormonal, genetic, and other factors	Various (eg, breast cancer in women, prostate cancer in men)	Strong; sex-specific cancers, hormonal influences, and other biological differences
Ethnicity/race	Cancer rates can vary across different ethnic and racial groups because of genetic, environmental, and socioeconomic factors	Various	Complex interplay of genetics, environment, and social determinants of health
Family history	Positive family history of cancer can increase risk, particularly for cancers with strong genetic components	Various (eg, breast, ovarian, colon)	Suggests shared genetic susceptibility and/or environmental exposures within families
Personal history	A personal history of cancer increases the risk of a subsequent malignant neoplasm[43,44]	Various	Increased risk likely multifactorial from an elevated baseline inherent risk, immunosuppression from therapy, and DNA damage from certain chemotherapeutic agents or radiotherapy

Intrinsic Factor Category/ Specific Factor	Description/Examples	Cancer Type(s) Associated	Notes
Molecular			
Inflammation and immune dysregulation	Inflammation and autoimmunity can contribute to cancer development; immune system dysfunction can increase cancer risk	Various (marginal zone lymphoma, gastric cancer with autoimmune gastritis, large granular lymphocytic leukemia)	Strong; inflammation can damage DNA and promote cell growth; immune system surveillance plays a role in cancer prevention
Endogenously produced hormones	Hormones play a role in the development of some cancers	Breast, endometrial, prostate, and so on	Strong for hormone-sensitive cancers
Oxidative stress	Imbalance between free radicals and antioxidants can damage DNA and contribute to cancer	Various	Implicated in cancer development, but precise role is still being researched
Host genetic variation			
Rare, moderate or high-penetrance mutations	Mutations with low frequency but high impact on cancer risk (eg, *BRCA1, BRCA2, TP53, ATM, PALB2, CHEK2, CDH1*)	Breast, ovarian, prostate (*BRCA1/2*), Li-Fraumeni syndrome (*TP53*), and so on	Significantly increased inherited susceptibility
Common, low-penetrance polymorphisms (SNPs)	Common DNA sequence variations with small individual effects (often identified through GWAS)	Various	Small individual risk contribution; large potential public health impact; used in polygenic risk scores
Epigenetic variations	Changes in gene expression that do not involve alterations to the DNA sequence itself	Various	Can influence cancer risk, but mechanisms and specific roles are still being studied

Abbreviations: GWAS, genome-wide association study; SNP, single nucleotide polymorphism.
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About 5% to 10% of cancers are hereditary. Genetically, cancer susceptibility can be categorized by the frequency and impact of gene variations. Rare, high-penetrance mutations, such as germline pathogenic *BRCA1/2* mutations significantly elevate inherited risk. In contrast, more common low-or moderate penetrance germline pathogenic mutations, such as in *CHEK2* or *PALB2*, have a smaller effect on an individual's risk, but their widespread prevalence means they could still have a substantial impact on public health. Although common variations may interact with environmental factors—for example, CYP450 enzymes and smoke carcinogens—strong evidence for many such interactions is still needed. Data from genome-wide studies have identified numerous genetic variations linked to cancer, although their precise biological roles often remain unclear. This information can be used to develop polygenic risk scores for potential risk prediction.[45,46]

To illustrate the interplay of these intrinsic and extrinsic factors in real-world scenarios, the following case studies will explore how these influences can contribute to cancer development and outcomes.

PRESENTING CASE STUDIES

Patient 1

A 65-year-old postmenopausal woman presents to the oncology clinic to discuss next steps after undergoing lumpectomy for pT2pN0cM0, estrogen receptor (ER)–positive, progesterone receptor (PR)–positive, HER2–negative invasive ductal carcinoma of the left breast, with a low-risk gene expression score. She has a history of obesity (body mass index [BMI], 32 kg/m^2), hypertension, which she manages with amlodipine, and prediabetes. Menarche occurred at age 12, menopause at age 52, and first pregnancy at age 24. She has been on estrogen replacement therapy (ERT) with estradiol since age 54. She has three sisters and two daughters but reports no family history of breast or ovarian cancer. She consumes approximately 6 ounces of wine four evenings per week and leads a sedentary lifestyle. Physical

examination reveals well-healed surgical sites from the lumpectomy and axillary dissection, and vital signs are within the reference range. She is looking for guidance on adjuvant therapy and risk reduction.

Patient 2

A 35-year-old premenopausal woman seeks to understand her recent diagnosis of pT2pN0cM0, ER-positive, PR-positive, HER2-negative invasive ductal carcinoma of the left breast after she sought care for a palpable breast mass. Despite maintaining a healthy lifestyle with a Mediterranean diet and regular cardiovascular exercise, she is concerned about potential contributing factors, particularly given her family history of breast cancer in her mother at age 45 and ovarian cancer in her sister at age 37. Her only medication is an oral contraceptive pill, and she reports moderate alcohol consumption. A gene expression assay reveals a low-risk score. Physical examination reveals well-healed surgical sites, and vital signs are within the reference range. She would like to discuss adjuvant therapy and risk assessment.

Compare and contrast the potential extrinsic and intrinsic risk factors that may have contributed to the development of breast cancer in these two patients, considering their differences in age, lifestyle, family history, and medical history.

These patient cases emphasize the multifactorial nature of cancer risk, highlighting the interplay between extrinsic and intrinsic factors. Extrinsic factors include environmental exposures, lifestyle choices, or external agents that influence cancer development. Intrinsic factors, in contrast, are inherent to a person's physiology, such as genetic predispositions or inherited traits. Both types of factors contribute to a patient's overall cancer risk.

Comparative analysis of cases

Patient 1 presents several notable extrinsic risk factors:

- Obesity: Her BMI of 32 kg/m^2 indicates obesity, which is linked to increased estrogen levels and chronic inflammation, both implicated in breast cancer development. Adipose tissue acts as an endocrine organ, producing estrogen and inflammatory cytokines that can promote tumor growth. Research suggests a clear association between obesity and postmenopausal breast cancer risk, with a relative risk increase ranging from 1.5 to 2.5.
- ERT: Long-term ERT use, particularly for more than 10 years, is associated with an increased risk of breast cancer. The estrogen component of ERT stimulates breast tissue proliferation, potentially increasing the risk of developing malignant cells. Studies have shown a relative risk increase of 1.33 for breast cancer in women using combined estrogen-progestin ERT for 5 years or longer.
- Sedentary lifestyle: Physical inactivity can contribute to hormonal imbalances, reduced immune function, and increased inflammation, potentially influencing breast cancer risk. Regular exercise has been shown to have protective effects against various cancers, including breast cancer.
- Alcohol consumption: Although her alcohol intake is moderate, it is worth noting that even moderate alcohol consumption can affect estrogen metabolism, potentially increasing breast cancer risk.[47]

Intrinsic factors may also play a role, but they are less prominent in this case. Although the patient has no family history of breast or ovarian cancer, it is important to remember that a significant proportion of breast cancers occur in women without a known genetic predisposition. Age is also an intrinsic factor, because breast cancer risk increases with age.

In contrast to Patient 1, Patient 2's risk profile leans more heavily toward intrinsic factors:

- Family history: Her family history of breast cancer (mother diagnosed at age 45) and ovarian cancer (sister diagnosed at age 37) raises significant concern for a potential genetic predisposition. Pathogenic germline mutations in high-penetrance genes like *BRCA1* and *BRCA2*, associated with hereditary breast and ovarian cancer syndrome, could be contributing factors. Although a low-risk gene expression assay was performed, it did not rule out all possible genetic risks. Other genes and mutations may be involved, and further genetic counseling and testing are warranted to explore this possibility.

- Age: Although she is relatively young for personal history of cancer, her strong family history substantially elevates her breast cancer risk at an earlier age than typically expected.

Extrinsic factors are less prominent in this case because of her healthy lifestyle, including a balanced diet and regular exercise. However, it is important to consider the potential impact of the following:

- Oral contraceptives: Although oral contraceptives have been associated with a slightly increased risk of breast cancer, the absolute risk remains low, particularly in younger women. It is crucial to discuss the risks and benefits with patients who have a family history of cancer.
- Alcohol consumption: Even moderate alcohol consumption can increase breast cancer risk.

Contrasting analysis of cases

These cases illustrate the diverse nature of breast cancer risk. Patient 1's case highlights the impact of modifiable lifestyle factors, whereas Patient 2's case emphasizes the significance of genetic predisposition. It is crucial to recognize that both extrinsic and intrinsic factors can interact and contribute to an individual's overall risk.

Personalized cancer risk assessment

Understanding the interplay between extrinsic and intrinsic risk factors is essential for personalized risk assessment and management. By identifying and addressing modifiable risk factors, such as obesity, ERT use, and sedentary lifestyle, the risk of breast cancer can be reduced. For people with a strong family history or other indications of genetic predisposition, genetic counseling and testing are crucial for informed decision-making regarding risk-reduction strategies, such as increased surveillance or chemoprevention. Both patients should be encouraged to engage in shared decision-making with their health care providers to develop personalized plans that address their unique risk profiles and preferences.

INTERVENTIONS FOR PREVENTING CANCER

Cancer primary prevention aims to reduce the incidence of cancer, secondary prevention aims to detect cancer early, which will inadvertently result in an increased cancer incidence, and tertiary prevention aims to reduce cancer mortality. Therefore, the cancer prevention paradigm operates on a continuum. Epidemiology and basic sciences contribute to the discovery of cancer risk factors, the mechanisms by which they cause cancer, and factors that contribute to cancer-related morbidity and mortality. This knowledge helps to identify opportunities to (1) predict future risk based on combinations of risk factors, (2) detect cancer before the development of symptoms (cancer screening), (3) diagnose cancer early in symptomatic persons (early detection), and (4) address gaps in health care access or social determinants of health. This section reviews the risk factors and the different strategies currently available for the prevention of specific cancers.

TOBACCO

- Cigarette smoking is the leading cause of preventable morbidity and premature mortality in the United States and is causally associated with 13 different malignancies: cancers of the lung, oral cavity, larynx, esophagus, bladder, kidney, pancreas, stomach, cervix, colon, rectum, and liver, as well as acute myeloid leukemia.[17] An estimated 48% of all cancer deaths in the United States are attributable to cigarette smoking. Secondhand smoke is a known cause of lung cancer in nonsmokers, indicating that there is no safe level of exposure to cigarette smoke.[17]
- The risks of malignancy and death caused by cigarette smoking are dose dependent; the risk of most smoking-associated cancers increases with both the duration of smoking (years) and the intensity (cigarettes per day). Quitting smoking is associated with an immediate decrease in cancer risk compared with continued smoking. However, former smokers remain at a higher risk for most smoking-associated cancers compared with never-smokers, even after decades of cessation.
- Pipes and cigars are strongly linked to lung cancer risk although the associations are generally weaker than those for cigarette smoking. This is primarily because these products are typically used less frequently, and the smoke is often inhaled less deeply than with cigarettes.[17] The tobacco marketplace has changed significantly in the last 15 years, most notably with a surge in e-cigarette use (ie, vaping), particularly among youth and young adults.[48] The long-term health effects of e-cigarettes are still under investigation, but the vapor contains known carcinogens, raising concerns that e-cigarette use may increase cancer risk.[48]

Smoking Cessation

Smoking cessation at any point, before, during, or after cancer treatment, improves survival, reduces treatment complications, and lowers the risk of second primary malignancies. Most US adult smokers initiate smoking before the age of 18. Therefore, smoking prevention interventions targeting pediatric and adolescent populations are a major public health priority. Research indicates that a physician's simple advice to avoid or quit smoking can substantially increase the likelihood of a quit attempt and successful cessation.[49,50] Despite this evidence, a survey reported that although more than 80% of oncologists assess their patients' smoking behavior, fewer than 20% feel confident in intervening effectively in this critical area.[51] Given the well-documented negative impact of cigarette smoking on the prognosis of patients with cancer, providing smoking cessation services is essential in the oncology setting.[50] Smoking is an addiction, and evidence shows that smokers are most likely to succeed with a multifaceted cessation program that includes counseling, behavioral strategies, and drug therapy. Recommended first-line drug therapies include nicotine replacement therapy, bupropion, and varenicline, with clonidine and nortriptyline as potential second-line options. Even a small amount of encouragement from a health care provider can significantly enhance smoking cessation efforts. The process of quitting involves identifiable stages for the smoker, including contemplation, action, and maintenance. Numerous effective strategies beyond counseling exist for advising and assisting motivated patients in achieving their goal.[49,50,52]

In addition to individual-level tobacco control, policy-level interventions have demonstrated a reduction in smoking prevalence. Important examples of tobacco control policies include tax increases on cigarettes, smoke-free workplace legislation, and raising the minimum legal age for tobacco product access. Comprehensive tobacco control policies have led to substantial progress in reducing smoking prevalence. Currently, approximately 12.5% of the US population are smokers, which should contribute to continued downward trends in the burden of smoking-caused cancer.[53] Regardless, cigarette smoking remains a major cancer risk factor, and lung cancer is the leading cause of cancer mortality worldwide.

E-CIGARETTE USE (VAPING)

The potential role of e-cigarettes and heated tobacco products in tobacco control is controversial. In the United States, the prevalence of e-cigarette use among youth has increased markedly. Evidence strongly indicates that, beyond the direct harmful effects of e-cigarettes (both known, such as nicotine addiction, cough, and wheezing, and those still under investigation), e-cigarette use is a significant risk factor for the initiation of combustible tobacco cigarette smoking among never-smokers.[48] However, among adult addicted smokers, e-cigarettes have the potential to be a tool to enhance smoking cessation.[54] Nevertheless, the known and potential adverse effects of e-cigarettes preclude their use as a first-line smoking cessation strategy; the full extent of these adverse health effects is still being characterized. In addition to nicotine, e-cigarettes contain numerous compounds with adverse health effects although these are substantially fewer than those found in combustible tobacco cigarettes.[54]

The Centers for Disease Control and Prevention (CDC) recommends "not using e-cigarette, or vaping, products that contain THC [tetrahydrocannabinol] or any e-cigarette, or vaping, products obtained from informal sources. E-cigarette, or vaping, products should never be used by youths, young adults, or pregnant women."[55,56] The CDC provides additional guidelines on the risks of using e-cigarettes.[57] Heated tobacco products, also known as noncombusted cigarettes, differ from e-cigarettes in that they heat, but do not burn, processed tobacco leaf sufficiently to release a vapor containing nicotine. A recent review of randomized clinical trials among cigarette smokers concluded that these products reduce exposure to tobacco carcinogens. However, there was insufficient evidence to conclude that heated tobacco products are effective for smoking cessation.[58]

No data currently exist on the short- or long-term health effects of heated tobacco products. The CDC recommends that people not use heated tobacco products as alternatives to cigarette smoking or e-cigarettes.[59,60]

MARIJUANA

Given evolving legalization and increasing use, continued surveillance and mechanistic research are needed to clarify marijuana's long-term effects on cancer risk. Forty states and the District of Columbia have passed laws legalizing marijuana use in some form. Although most studies on marijuana use and cancer risk have focused on the upper aerodigestive tract and lung, current evidence does not establish a clear positive association between marijuana use and these cancers.[61] Additionally, an association between marijuana use and testicular germ cell tumors has been observed in three case-control studies although a biological explanation for this association has not been established.[61]

ALCOHOL

Moderate alcohol consumption is associated with an elevated risk of breast cancer compared to never consuming alcohol, and heavy consumption is a well-established cause of liver cancer. Although alcohol consumption has previously been associated with cancers of oral cavity, pharynx, larynx, esophagus, and colorectum, the National Academies of Science, Engineering and Medicine recently found insufficient evidence to confirm these associations.[28] The associations between alcohol consumption and cancer are often dose dependent[27] and do not vary substantially based on whether beer, wine, or liquor is ingested.[62] It has been estimated that alcohol consumption is responsible for approximately 6% of all cancer cases and 6% of deaths resulting from cancer globally.[27]

Based on this evidence, ASCO guidelines for alcohol use recommend no more than two drinks per day for men and one drink per day for women, and those who do not drink alcohol are advised to continue to abstain.[27] Furthermore, synergistic interactions between cigarette smoking and alcohol consumption have been established. The ASCO statement on alcohol and cancer emphasizes the importance of alcohol screening and intervention within the oncology setting.[27]

UV RADIATION EXPOSURE

Exposure to UV radiation, either from sunlight or from indoor tanning devices, is the predominant cause of both melanoma and nonmelanoma skin cancers.[18] The major determinant of the occurrence of skin cancer in populations is cumulative UV radiation exposure in combination with sun-sensitive phenotypes (eg, propensity to sunburn on UV radiation exposure, fair skin, freckles). UV radiation exposure in childhood and adolescence is associated with an increased risk of skin cancer in adulthood. The use of tanning beds is causally associated with the risk of melanoma,[63] and the associations between tanning bed use and nonmelanoma skin cancer are also consistent with a causal association. Reduction in sun exposure throughout life by using protective clothing and sunscreen and avoidance of the most intense and direct sunlight (between 10:00 AM and 4:00 PM in the continental United States) are recommended as ways to lower the risk of skin cancer.[64] Interventions to prevent the use of UV radiation–emitting tanning devices include educational interventions and policy-level interventions, such as issuing health warnings and increasing the minimum legal age of access.

OBESITY

Obesity is classically defined as a body mass index (BMI) of at least 30 kg/m^2.[65] Although BMI remains the most common definition of obesity, abdominal obesity is defined as waist circumference of 102 cm or larger for men and 88 cm or larger for women, independent of BMI, and increases health risks and all-cause mortality.[66] Obesity and overweight are epidemic in the United States. Currently, less than one-third of the US adult population is within the normal BMI range. The International Agency for Research of Cancer (IARC) concluded that there is sufficient evidence demonstrating risk associations for obesity and 13 cancers, including esophageal adenocarcinoma, meningioma, multiple myeloma,[24] gastric cardia, colorectal, liver, gall bladder, pancreatic, postmenopausal breast, uterine, ovarian, renal cell, and thyroid cancers. Additionally, IARC concluded that limited evidence supports risk associations for obesity and three additional cancers, including male breast and prostate cancers and diffuse large B-cell lymphoma. Importantly, excess adiposity in people with normal BMI is associated with an increased risk of postmenopausal breast,[67,68] endometrial,[69] and colorectal cancers, suggesting that the public health burden of obesity-related cancers is even higher than that estimated by BMI. Excess adiposity also increases cancer recurrence risk and cancer-specific mortality and reduces treatment efficacy in multiple cancers.[70,71] Excess adiposity drives insulin resistance, cytokine synthesis, and related adipokines, potentially from the adipocyte or macrophages within the adipose tissue, to establish a proinflammatory state.[72,73] Humoral products stimulate both cancer and epithelial stem cell self-renewal.

Weight loss and bariatric surgery are associated with reduced risks of multiple cancers.[74] For example, a study of approximately 37,000 postmenopausal women in the Women's Health Initiative showed that intentional weight loss was associated with a reduced risk of endometrial cancer. During an 11-year follow-up, women who had a greater than 5% intentional weight loss over a 3-year period had a 29% lower risk of endometrial cancer compared with women with a stable weight (hazard ratio [HR], 0.71; 95% CI, 0.54-0.95). Those who gained weight had an increased risk of endometrial cancer.[75] The metabolic effects of bariatric surgery rapidly precede clinical weight loss. These effects include shifting of adipokines and the hormonal environment toward a lower level of chronic inflammation, thus reducing the inflammatory state resulting from obesity-associated metabolic syndrome.[74,75] Observational data indicate that medical weight loss therapy with incretin mimetics, specifically GLP1 receptor agonists, is associated with relative risk reductions for several obesity-associated conditions.[26]

DIET

The observation that rates of breast, colon, endometrium, and prostate cancers are notably higher in North America and Western Europe compared with Asia suggests a potential role for environmental factors. This is further supported by the finding that Asian immigrants and their offspring tend to acquire a greater risk of these cancers after residing in the United States for some time. These epidemiologic patterns, in conjunction with data from studies on model organisms, underpin the hypothesis that dietary modifications could significantly reduce cancer risk in the US population.[76]

Diet represents a complex and multifaceted exposure involving a vast array of nutrients and chemical compounds. Within this complexity, certain dietary components have been identified as potentially protective against cancer. These include polyphenolics, found in foods like those containing curcuminoids, resveratrol, and ginger, as well as sulfur-containing compounds present in green vegetables, such as sulforaphane and flavones.[77] Furthermore, dietary patterns characterized by low-fat content, typically involving reduced consumption of processed red meat and increased intake of fruits and vegetables, may also offer some protection. This benefit is likely attributable to the high levels of antioxidants found in vegetables, fruits, legumes, nuts, and grains.

However, despite these promising epidemiologic associations and supporting biomarker data, establishing a definitive causal link between overall dietary fat intake and cancer has proven challenging.[78] Case-control and cohort studies investigating this relationship have yielded inconsistent results. Moreover, no prospective clinical trial to date has conclusively demonstrated that reducing dietary fat can prevent cancer. For instance, the large-scale Women's Health Initiative randomized trial found no significant effect of a low-fat diet on the incidence of breast or colon cancer.[79,80]

Interestingly, although the broad link between low-fat diets and overall cancer prevention remains unclear, a more specific benefit has emerged in certain contexts. Among women diagnosed with early-stage breast cancer, a low-fat dietary approach seems to offer a survival advantage. The Women's Health Initiative randomized trial involving more than 2400 women with early-stage breast cancer indicated that those assigned to a low-fat diet, in addition to receiving standard adjuvant therapy, experienced a meaningful improvement in survival compared with women maintaining a regular diet (HR, 0.76; 95% CI, 0.60-0.98).[81]

Beyond the focus on overall fat intake, specific dietary patterns and food groups have also been implicated in cancer risk. For example, a high intake of smoked and cured meats, coupled with limited consumption of fresh fruits and vegetables, is associated with an increased risk of gastrointestinal malignancies.[8]

Another significant area of concern involves the consumption of sugar-sweetened beverages and energy-dense foods, such as traditional fast food or heavily processed items. The increased intake of these products elevates the risk of excess adiposity, which is itself a well-established risk factor for at least 13 different malignancies. Importantly, beyond their contribution to obesity and metabolic syndrome, the independent metabolic effects of glucose and fructose, the primary sugars in these products, also seem to contribute to cancer risk.

The potential impact of sugar-sweetened beverages on cancer risk is further underscored by the findings of a comprehensive meta-analysis. This analysis, which included 27 cohort and case-control studies, revealed a positive association between higher intake of sugar-sweetened beverages and an increased risk of both breast cancer (relative risk, 1.14; 95% CI, 1.01-1.30) and prostate cancer (relative risk, 1.18; 95% CI, 1.10-1.27). The meta-analysis also found a positive link between higher fruit juice intake and an elevated risk of prostate cancer (relative risk, 1.03; 95% CI, 1.01-1.05) when comparing the highest and lowest intake categories defined in the individual studies.[82] Furthermore, positive associations were observed between sugar-sweetened beverage consumption and the risk of colorectal and pancreatic cancers.

In light of this growing body of evidence, global health organizations, including the American Cancer Society and the World Cancer Research Fund/American Institute for Cancer Research, have issued recommendations to limit the consumption of sugar-sweetened beverages as a key strategy for the prevention of several obesity-related cancers.[83]

VITAMINS AND SUPPLEMENTS

Most randomized trials of vitamin supplements have not shown cancer prevention benefit; indeed, in some instances, they have shown harm.[84] Table 1-4 lists examples of data demonstrating that supplementation of micronutrients beyond basic dietary requirements has not been associated with reduced incidence of common cancers. Therefore, dietary supplements are not recommended for cancer primary prevention. Additionally, because concomitant use of herbal supplements or certain vitamins during cancer treatment may lead to adverse interactions, discontinuing dietary supplements after a cancer diagnosis is advised.[85]

Table 1-4 Contrast Between Observational and Randomized Studies for Supplements

Supplement/Outcome	Observational Study Findings	Randomized Study Findings	Notes
Selenium and vitamin E/prostate cancer	High intake of selenium and vitamin E were associated with lower risk of prostate cancer	SELECT trial (large, placebo controlled): no reduction in incidence. Small skin cancer trial and secondary analysis of ATBC trial: supported observational findings	Conflicting results; large, well-designed trial showed no benefit[86-88]
Calcium/colon cancer	High-calcium diets were associated with lower risk of colon cancer	Women's Health Initiative and VITAL trial: no lower incidence of colorectal cancer. Two trials: supplemental calcium reduces adenomatous polyps risk (~25%). One trial: calcium supplementation decreased polyp recurrence, but a more recent trial failed to confirm	Mixed results; some benefit seen for polyp reduction but not for overall colorectal cancer incidence[89-95]

Supplement/Outcome	Observational Study Findings	Randomized Study Findings	Notes
Carotenoids and beta-carotene/lung cancer	High intake of carotenoid-rich fruits and vegetables and beta-carotene were associated with lower risk of lung cancer	ATBC and CARET trials (high-risk patients): increased lung cancer incidence and mortality in beta-carotene groups	Clear example where observational studies suggested benefit, but randomized trials showed harm[96,97]
Retinoids/squamous cell cancer (head and neck)	Limited efficacy as preventive agents	One trial: 13-*cis*-retinoic acid reduced second primary head and neck cancer. Two follow-up trials (lower doses): no clinical effectiveness	Initial positive result not replicated with lower, less toxic doses[98-101]
Vitamin D and cancer	Low levels of vitamin D were associated with increased risk of cancer[102]	VITAL trial: Vitamin D supplementation did not result in a lower incidence of cancer[91,103]	Observational studies were likely confounded by multiple variables including outdoor physical activity
Nicotinamide and skin cancer	Nicotinamide use was associated with a 14% reduction in risk of skin cancer[104]	One trial found that nicotinamide was effective at reducing the rates of new nonmelanoma skin cancers and actinic keratoses in high-risk patients.[105] Another trial of solid organ transplant patients did not observe a benefit[106]	The trial in transplant patients was stopped early due to poor accrual

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PHYSICAL ACTIVITY

Approximately 25% of the US population is considered sedentary, and this aspect of lifestyle is considered responsible for up to 5% of cancers.[107] Most of these associations were independent of body size or smoking history.[108] In addition to the role of physical activity in reducing cancer risk, increases in physical activity may be helpful for cancer survivors. Evidence suggests a potential dose-response relationship, where greater amounts of physical activity are associated with a reduced risk of various cancers. For instance, a study by Matthews et al[109] indicated that engaging in 150 to 300 minutes of physical activity per week is linked to a lower risk of many cancer types.

Furthermore, among cancer survivors, physical activity has been associated with decreased cancer recurrence and progression, as well as improved overall survival. The most pronounced benefits of physical activity in this population have been reported for survivors of colorectal, breast, and prostate cancers.[107,110,111]

In the CHALLENGE trial, structured exercise after adjuvant chemotherapy for high-risk colon cancer, defined as stage III or stage II with poor prognostic features, improved 5-year disease-free survival (HR 0.72) and reduced overall mortality (HR 0.63) supporting exercise as a critical survivorship intervention.[39]

INFECTIONS

HPV vaccination using the nine-valent vaccine effectively reduces the incidence of cervical carcinoma. HPV vaccination proportions in the United States for adolescents, especially those in the target age range of 9 to 13 years, remain low (coverage of at least one dose: girls, 22%; boys, 24%).[112] Adolescents 13 to 19 years have higher coverage proportions (girls, 69%; boys, 44%).[113] Because these same viruses are involved in other cancers, the incidence of anal, vaginal, penile, and oropharyngeal cancers may also decrease if a sufficient percentage of the population can be protected from HPV through vaccination.

An estimated 1 million deaths in the world annually are attributed to chronic hepatitis B infection. Since the hepatitis B vaccine was introduced in Taiwan in 1984, the risk of hepatocellular carcinoma (the leading cancer in that country) has dropped more than 70% among those vaccinated.[114] The hepatitis C virus (HCV) infects 1.3% of the population in the United States. Antiviral therapy for HCV with direct-acting viral protease inhibitors eradicates the virus. Treatment with viral protease inhibitors is associated with a 54% reduction in all-cause mortality, including reduced mortality as a result of hepatocellular carcinoma.[115] Similarly, it is possible that regular screening and treatment of HCV will result in a lower incidence of HCV-related lymphomas.

Prior to World War II, gastric adenocarcinoma was a prevalent malignancy in the United States. Infection with *Helicobacter pylori* is recognized as a risk factor for gastric cardia carcinoma. However, the effectiveness of eradicating *H. pylori* to lower the

risk of this specific type of stomach cancer differs across populations. Studies have shown that eliminating *H. pylori* is linked to a decreased risk of gastric cancer in Asian populations. In contrast, this protective association has not been consistently demonstrated in studies conducted in US populations.[116-119]

H. pylori is also strongly associated with the development of gastric extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).[120] *H. pylori* infection causes gastritis that leads to T-lymphocyte activation and B-cell expansion. In some cases, this may result in the development of MALT lymphoma.[121] Eradication of *H. pylori* infection has emerged as the standard first-line treatment option for patients with concomitant *H. pylori* infection and gastric MALT lymphoma,[122] supporting a causative relationship between *H. pylori* and gastric MALT lymphoma.

DRUGS/MEDICATIONS

Compounds of interest in clinical cancer prevention include anti-inflammatory agents, antioxidants, differentiating agents, hormone modulators, obesity medications, and vaccines. A long-term randomized placebo-controlled clinical trial is generally necessary to establish the efficacy of a clinical preventive agent.

Nonsteroidal Anti-inflammatory Drugs and Colorectal Cancer Prevention

Nonsteroidal anti-inflammatory drugs (NSAIDs) encompass both aspirin and nonaspirin compounds. Meta-analyses of randomized controlled trials have demonstrated the effectiveness of aspirin in preventing colorectal cancer.[89,123] Although trials evaluating COX-2 inhibitors and other nonaspirin NSAIDs have shown promise in preventing the development of colorectal adenomas, their use for colorectal cancer prevention is currently not recommended because of an associated increased risk of cardiovascular disease.

Notably, the ASCOLT trial, a large randomized study, did not find that daily 200 mg of acetylsalicylic acid (ASA) improved disease-free survival in patients with stage III or high-risk stage II colon cancer. However, in the ALASCCA trial, low-dose aspirin reduced recurrence in patients with PI3K pathway altered stage I–III colorectal cancer (HR 0.49, 95% CI: 0.24-0.98; $P = .04$) for those with somatic *PIK3CA* hotspot mutations.[124]

Despite the lack of broad recommendations for aspirin in colorectal cancer prevention, data suggesting that NSAIDs can reduce neoplastic progression in patients with familial nonpolyposis colon cancer (Lynch syndrome) indicate that interventions targeting inflammatory pathways may be beneficial in high-penetrance genetic syndromes. Furthermore, the use of NSAIDs for patients with familial adenomatous polyposis after colectomy may be a reasonable consideration in conjunction with ongoing endoscopic screening. Looking ahead, the results of a randomized study evaluating eflornithine and sulindac in patients with treated colorectal cancer are anticipated in the coming years (ClinicalTrials.gov identifier NCT01349881).

Hormone and Testosterone Replacement Therapy

The Women's Health Initiative reported an increased risk of breast cancer (odds ratio, 1.24; 95% CI, 1.01-1.54) among postmenopausal women taking active hormone replacement estrogens with progestins.[125] A parallel trial of estrogen alone compared with placebo for women with prior hysterectomy did not show an increased risk of breast cancer among women taking estrogen.[126] There is no benefit of postmenopausal estrogens for women beyond a short-term reduction in perimenopausal symptoms.[127]

Testosterone therapy is increasingly common in the United States, with millions of men receiving some form of replacement. No cohort study large enough has been conducted to date to adequately address the question of whether this low-dose of androgen supplementation increases the risk of prostate cancer incidence or mortality. The American Urologic Association recommends that clinicians obtain baseline PSA level in men > age 40 and hemoglobin/hematocrit before starting testosterone replacement therapy (TRT), and engage in shared decision-making particularly for men with a history of prostate cancer given that evidence is insufficient to quantify the risk/benefit in this group.

Selective Estrogen Receptor Modulators and Aromatase Inhibitors

Expert guidance from the USPSTF and ASCO recommends either tamoxifen (20 mg/d for 5 years) or raloxifene (60 mg/d for 5 years) to reduce the incidence of estrogen receptor–positive invasive breast adenocarcinoma in high-risk populations including those with breast cancer precursor conditions.[128-130] Notably, neither drug reduces estrogen receptor–negative invasive breast adenocarcinoma incidence nor breast cancer–specific or all-cause mortality. Low-dose tamoxifen (5 mg/d) seems to have similar preventative efficacy to high-dose tamoxifen (20 mg/d), with reduced toxicity.[131] Although aromatase inhibitors have not been approved by the US Food and Drug Administration for chemoprevention, they are included in the ASCO guidelines for preventive therapy and are a reasonable option for postmenopausal women.

ASCO patient selection guidelines for offering preventive therapy:

- All women with atypical hyperplasia (ductal or lobular) or lobular carcinoma in situ who are age 35 or older, have completed childbearing, and have no medical contraindications should be offered preventive therapy.

- Women who are 35 to 59 years with a calculated 5-year risk of at least 3% or with a 10-year absolute risk of at least 5% (based on the National Cancer Institute Breast Cancer Risk Assessment Tool or equivalent measures) should be offered preventive therapy.
- For women who are 60 to 69 years with a 5-year absolute risk of 3% (based on the National Cancer Institute Breast Cancer Risk Assessment Tool or equivalent measures), the risks versus benefits are less clear, and the risk of serious adverse effects is higher than that in younger women.

Antiandrogens: Targeting Androgen Signaling in Prostate Cancer

Given the crucial role of androgens in stimulating prostate cell proliferation and driving prostate carcinogenesis, strategies to reduce androgen signaling are vital. Finasteride and dutasteride achieve this by inhibiting 5-alpha reductase, the enzyme responsible for converting testosterone into its more active form, dihydrotestosterone, within the prostate. Randomized, placebo-controlled clinical prevention trials have demonstrated that these 5-alpha reductase inhibitors can reduce the incidence of prostate cancer by approximately 20%.[132]

An initial finding from early studies suggested a potential concern: men treated with finasteride who developed invasive prostate cancer seemed to have lesions with a higher Gleason score (7-10) compared with those in the placebo group.[133] However, this observation was not supported by longer-term follow-up data.[134] In fact, after 18 years of follow-up, treatment with the 5-alpha reductase inhibitor finasteride showed no significant impact on overall survival.[135] Furthermore, the use of finasteride and dutasteride was associated with a higher incidence of sexual function adverse effects, including erectile dysfunction, loss of libido, and gynecomastia.

Medications to Treat Hematologic Precursor Conditions

The future of treating plasma cell precursor conditions is shifting toward proactive cancer prevention, especially in patients with plasma cell precursor conditions such as smoldering myeloma or high-risk clonal hematopoiesis or clonal cytopenia. While clinical trials are assessing therapeutic drug interventions for patients with monoclonal gammopathies, emerging evidence suggests that dietary or microbiome-directed interventions could modulate antigenic drive and reduce the risk of progression.

PROCEDURAL AND SURGICAL PREVENTION

Esophageal adenocarcinoma is a growing health problem because of its rapidly rising incidence, substantial morbidity, and high mortality. Barrett esophagus, a serious complication of gastroesophageal reflux disease caused by persistent esophageal columnar cell exposure to gastric and duodenal contents, is the only known precursor of esophageal adenocarcinoma. Esophageal adenocarcinoma develops in patients with Barrett esophagus at an annual rate of 0.12%.[136] Endoscopic eradication therapies consisting of mucosal resection, radiofrequency ablation, and cryotherapy are now recommended in patients with dysplastic Barrett esophagus.[137] Such therapies fail in 10% of patients with high-grade dysplasia, and 40% of patients develop recurrence of dysplasia or metaplasia.[96] Cervical cancer is another example in which procedures directed to precursor lesions, cervical dysplasia, or intraepithelial neoplasia can reduce progression to invasive malignancy. Options include conization, loop electrosurgical excision procedure, cryosurgery, electrocauterization, and laser ablation.

Prospective studies in which women self-select for mastectomy or close surveillance have found that the short-term risk of breast cancer is lower for women with certain *BRCA1* and *BRCA2* mutations who choose prophylactic mastectomy. However, prophylactic bilateral mastectomy to prevent breast cancer has not been assessed in a rigorously randomized trial. Because this surgery leaves some breast tissue behind, a patient's risk is reduced by approximately 95%.[138] A Cochrane review concluded that bilateral prophylactic mastectomy for those at very high risk of breast cancer (eg, those with deleterious *BRCA* mutations) was effective in reducing the incidence and subsequent mortality resulting from breast cancer.[139] Colectomy is used as a preventive measure for patients at extremely high risk of colorectal cancer as a result of a history of ulcerative colitis or a genetic predisposition to the disease, such as familial adenomatous polyposis.[128] For women at a very high risk of ovarian cancer because of a *BRCA* genetic mutation, bilateral salpingo-oophorectomy after completion of childbearing remains the treatment of choice.[140] Women with Lynch syndrome associated with large and small bowel polyps and cancers are at an elevated risk of endometrial and ovarian cancers. For these women, prophylactic hysterectomy and bilateral salpingo-oophorectomy may also be recommended. Additionally, in MEN2A and MEN2B syndromes, prophylactic thyroidectomy is recommended before age 5 or even before age 1, respectively, based on germline *RET* mutation risk level, to prevent medullary thyroid carcinoma.[141]

KEY POINTS

- Physical activity and avoidance of obesity are associated with a lower risk of at least 13 cancers.
- Most randomized trials of vitamins or nutritional supplements as clinical preventive agents have had negative results.
- Tamoxifen, raloxifene, and aromatase inhibitors are established breast cancer preventative agents.

- Aspirin and other nonsteroidal anti-inflammatory drugs are not recommended for a majority of patients with colorectal cancer although recent data suggest a benefit for colorectal cancers harboring a somatic *PI3K* mutation.
- Vaccination or antiviral therapy for cancer-causing infectious agents, such as hepatitis B and C and HPV, has led to reduced incidence of and/or mortality as a result of associated cancers (hepatocellular carcinoma, cervical, and other anogenital cancers).
- Risk-reducing surgeries are an appropriate and effective intervention for select high-risk patients, such as those with deleterious *BRCA* mutations or Lynch syndrome.

SECONDARY PREVENTION: CANCER SCREENING AND EARLY DETECTION

RATIONALE AND CONCEPTS

Screening is an attempt to detect preneoplastic lesions and noninvasive or invasive neoplasms in asymptomatic patients with the goal of intervening and decreasing morbidity and mortality. A screening test is not typically diagnostic for cancer; rather, it determines whether a neoplastic lesion has a high probability of being present and whether additional definitive testing, such as imaging or biopsy, is necessary. To be of benefit, screening must lead to earlier treatment that offers a better outcome, usually reduced mortality, compared with treatment that starts at the onset of symptoms. The ideal evaluation of a screening approach is through the assessment of disease-specific and overall mortality in a randomized clinical trial. The ability of a screening test to detect a localized invasive neoplasm does not automatically imply benefit, because (1) not all locally invasive neoplasms can be treated effectively, and (2) some locally invasive neoplasms never progress to cause symptoms (ie, overdiagnosis; Fig. 1-1; Table 1-5).

POTENTIAL BIASES

The evaluation of the benefits of a screening test is subject to several potential biases, including lead time, length time, and healthy volunteer effect biases. Lead and length time biases both can make it seem that there is a benefit to a screening test, when there is actually none; there may even be a net harm. Lead time bias results when screening detects a cancer earlier in its natural history (ie, at an earlier stage) than had it not been detected through screening. Patients with screen-detected cancer therefore will always seem to have longer survival than those whose cancer was not detected early, even if the treatment of the cancer is ineffective. Length bias occurs because, at any point in time, screening is more likely to identify cancers that are relatively slow growing. These cancers are also less likely to contribute to a patient's death. The early detection of mostly slow-growing cancers will seem to improve survival statistics without reducing mortality. The healthy volunteer effect, a type of selection bias, occurs because volunteers for cancer prevention trials are more health conscious and are likely to have better prognoses or lower mortality rates, regardless of whether they are screened. The influences of these biases are substantially reduced in a properly designed and executed randomized trial.[142] Finally, screening, regardless of benefit, will usually increase the number of specific cancers diagnosed, resulting in an increased cancer incidence. Overdiagnosis occurs when a slow-growing invasive neoplasm fulfills the histological criteria for cancer but has a clinically indolent course and is not life threatening.[143] Older people may be more likely to die from competing comorbidities, such as heart disease, than of an indolent cancer.

ACCURACY

The results of screening tests can be classified into four categories. The accuracy of any medical test is usually described by sensitivity and specificity. Positive predictive value and negative predictive value measure test performance as applied to a specific population. Sensitivity and specificity are relatively independent of the underlying prevalence or risk in the population being screened, but the positive predictive value is highly dependent on cancer prevalence. In other words, cancer screening programs are most effective—in terms of benefit, efficiency, and cost—when they target either a cancer that occurs frequently in the overall population or specific groups within the population who are already known a priori to have a higher risk of developing that particular cancer. Sensitivity need not be extremely high. The key criterion for the public health recommendation of a screening test is that it can reduce cancer mortality (Table 1-5).

If a screening test is not effective in reducing mortality in people at average risk of a particular cancer, it will also not be effective in reducing mortality if used in a population with a higher risk of that same cancer. On the other hand, if a screening test does demonstrate effectiveness in reducing mortality, it is undoubtedly more beneficial to prioritize its use in populations at higher risk (for example, those with a family history of the disease).

POTENTIAL HARMFUL EFFECTS

People can be harmed because of screening. Harm can result from the test itself, the workup of positive results of screening tests (both true-positive and false-positive results), and adverse events from the treatment of true-positive results. Screening can detect some cancers that would never have caused medical problems; unnecessary treatment of these cancers can be harmful.

Figure 1-1 Deriving Specificity: Organized Data From a Hypothetical Mammogram Study

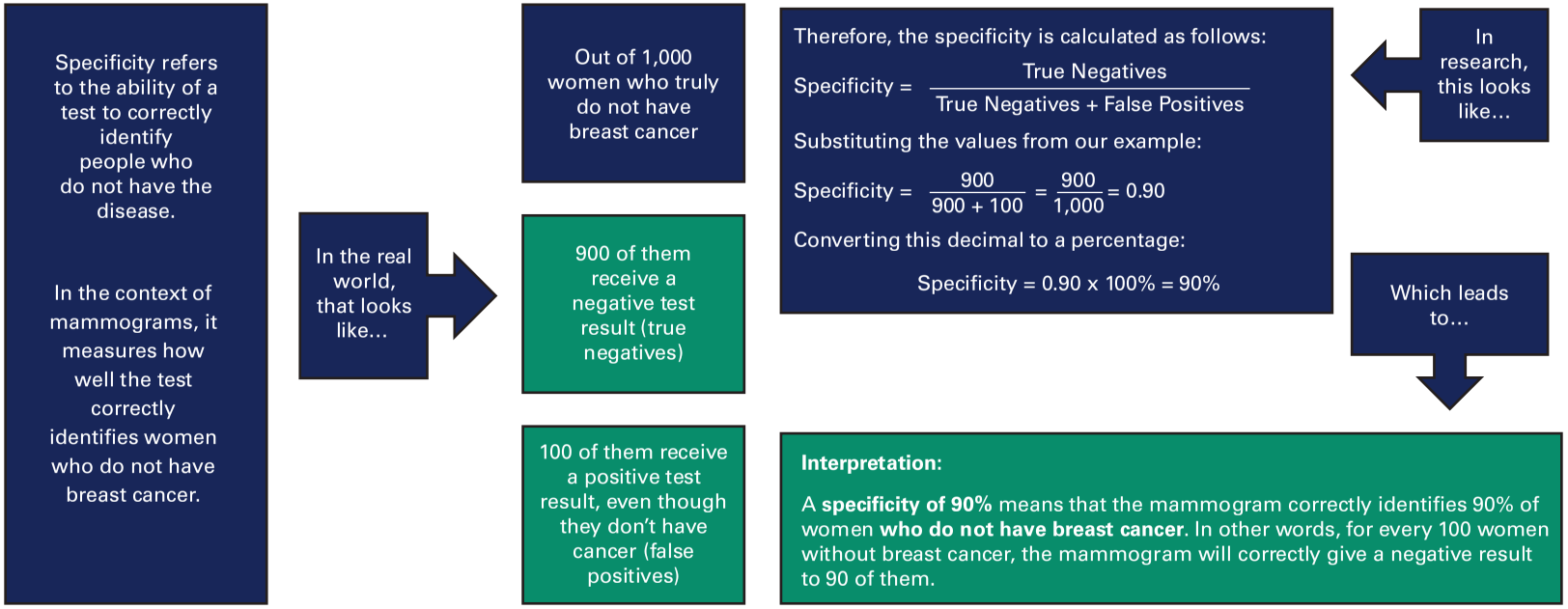

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Table 1-5 **Indices for Describing Accuracy of Screening Tests**

Term	Definition	Ability of Test	Equation
Sensitivity	Proportion of people with the disease who have a positive result on a screening test	To detect disease when it is present	A/(A + C)
Specificity	Proportion of people who do not have the disease who have a negative result on a screening test	To correctly identify the absence of disease	D/(B + D)
Positive predictive value	Proportion of people with a positive result on a screening test who have the disease; increases as disease prevalence in a population increases	To accurately predict the presence of disease	A/(A + B)
Negative predictive value	Proportion of people who have a negative result on a screening test who truly do not have the disease; increases as disease prevalence in a population decreases	To accurately predict the absence of disease	D/(C + D)

A, true-positive result; B, false-positive result; C, false-negative result; D, true-negative result.
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In addition to the adverse health effects of screening, financial and emotional costs are associated with screening and with all the additional diagnostic tests and treatments. A good example is low-dose computed tomography (CT) for the early detection of lung cancer. In 1.7% of patients screened, false-positive results lead to invasive procedures (eg, needle biopsy, bronchoscopy, thoracotomy).[144]

KEY POINTS

- Evaluation of the benefits/efficacy of a cancer screening test is far more complicated than simply performing the test and detecting localized cancers.
- Biases that complicate the assessment of screening benefits are lead time, length, and healthy volunteer effect.
- These biases can make a screening test seem beneficial when there is no benefit, or the test may even cause harm.
- Overdiagnosis occurs when a screening test identifies indolent cancers that do not pose a mortal threat. The costs of overdiagnosis are high: unnecessary screening of large populations, unnecessary medical procedures, and emotional and financial harm.
- To offset these biases, a randomized trial is the best way to assess a screening test, with the endpoint of reduction in cancer-related mortality.
- Sensitivity, specificity, and positive predictive value can be important measures of the accuracy of a screening test and the rate of false-positive and false-negative results. However, these metrics are not used to decide whether a screening test should be used on a large-scale; the main criterion for this purpose is reduction in mortality.

CURRENT SCREENING AND EARLY DETECTION GUIDELINES BY ORGAN SITE

There is convincing evidence that screening for cervical, colorectal, lung, and breast cancers is beneficial at certain ages for people at average risk. Although increased surveillance of people at high risk of specific cancers due to family history or genetic risk may be prudent, few studies have been performed to assess the benefits of this approach. The USPSTF[145-148] and American Cancer Society[149] are among the more prominent organizations publishing screening recommendations after rigorous independent review processes consisting of a structured evaluation of the literature by experts (Table 1-6).

Table 1-6 **Screening Recommendations for Asymptomatic Patients With Average Risk by Guideline Setting Organization**

Test or Procedure	Organization		
	US Preventative Services Task Force[150]	**Canadian Task Force on Preventive Health Care**[151]	**American Cancer Society**[152]
Colorectal	2021	2016	2018
HSgFOBT or FIT	Annual HSgFOBT or FIT, starting at age 45 years	FOBT or FIT every 2 years, starting at age 50 years	Annual FOBT or RT, starting at age 45 years (qualified recommendation); age 50 years (strong recommendation: FIT preferred)
Flexible sigmoidoscopy	Every 5 years starting at age 45 years	Flexible sigmoidoscopy every 10 years, starting at age 50 years	Every 5 years, starting at age 45 years (qualified recommendation); age 50 years (strong recommendation)
Flexible sigmoidoscopy plus FIT	Every 10 years plus annual FIT, starting at age 45years	Not recommended	Not recommended
Colonoscopy	Every 10 years, starting at age 45 years	Not recommended	Every 10 years, starting at age 45 years (qualified recommendation); age 50 years (strong recommendation)
CT colonography	Every 5 years starting at age 45 years	Not recommended	Every 5 years, starting at age 45 years (qualified recommendation); age 50 years (strong recommendation)
Prostate	2018[a]	2014	2023
DRE	No change	No change	May be performed in men who want to be screened with PSA
PSA	No change	No change	Shared decision-making starting at age 50 years in men at average risk of prostate cancer who have a life expectancy of 10 years or more; men who choose to be tested and have a PSA level <2.5 ng/mL may only need to be retested every 2 years; men whose PSA level is ≥2.5 ng/mL should be screened annually
Cervical	2018	2013	2020
Pap cytology	Women aged <21 years should not be screened; for women age 21-29 years, Pap test every 3 years; for women aged 30 to 65 years, screening every 3 years with Pap cytology alone; women aged 65+ years who have had adequate prior screening and are not otherwise at high risk of cervical cancer should not be screened; women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (ie, CIN grade 2 or 3) or cervical cancer should not be screened	Women aged <25 years should not be screened; starting at age 25years, screen every 3 years to age 69 years; for women aged 70+ years who have been adequately screened (eg, three successive negative Pap tests in the last 10 years), routine screening may cease; for women aged ≥70 years who have not been adequately screened, continue screening until three negative test results have been obtained	Women aged 25-65 years: a Pap test alone every 3 years; women aged 65+ years who have had three normal Pap tests and no abnormal tests in the last 10 years and no history of CIN II or more serious diagnosis within the last 25 years should stop screening; women who have had total hysterectomy (unless hysterectomy was done as treatment for cervical cancer or precancer) should not be screened

Test or Procedure	Organization		
	US Preventative Services Task Force[150]	Canadian Task Force on Preventive Health Care[151]	American Cancer Society[152]
HPV DNA	For women aged 30-65 years, every 5 years with hrHPV testing alone or every 5 years with hrHPV testing in combination with Pap cytology (ie, cotesting)	No recommendation	Women aged 25-65 years: primary hrHPV test every 5 years; if a primary hrHPV test is not available, acceptable options include a cotest (hrHPV test done at the same time as a Pap test) every 5 years
Breast	2024	2018	2015
BSE	No change	No change	No change
CBE	No change	No change	
Mammography	Women aged 40-74 years: screen every 2 years; for women aged ≥75 years, there is insufficient evidence to form a recommendation	No change	No change
Lung	2021	2016	2023
LDCT	Adults aged 50-80 years: annual screening if the patient also has at least a 20-pack-year smoking history and currently smokes or quit smoking <15 years ago	Adults aged 55-74 years: three consecutive annual screenings if the patient also has at least a 30-pack-year smoking history and smokes or quit smoking <15 years ago	Adults aged 50-80 years: annual screenings if the patient also has at least a 20-pack-year smoking history and smokes or previously smoked

Abbreviations: BSE, breast self-examination; CBE, clinical breast examination: CIN, cervical intraepithelial neoplasia; DRE, digital rectal examination; FIT, fecal immunochemical test; FOBT, fecal occult blood testing; HPV, human papillomavirus: hrHPV, high-risk human papillomavirus; HSgFOBT, high-sensitivity guaiac fecal occult blood testing; LDCT, low-dose CT; Pap, Papanicolaou; PSA, prostate-specific antigen; RT, radiation therapy.
[a]Update coming.
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COLORECTAL CANCER

Fecal Occult Blood Test Screening

Fecal occult blood tests (FOBTs) screen for colorectal neoplasms by detecting traces of blood in the stool. Positive FOBT results require follow-up screening using colonoscopy. There are two main types of FOBTs: guaiac-based FOBT (gFOBT) and immunohistochemistry-based FOBT (iFOBT) or fecal immunochemical test (FIT).

gFOBT

Annual or biennial screening with gFOBTs has been shown to reduce colorectal cancer mortality by 15% to 33%.[153-155] Furthermore, this reduction in colorectal cancer mortality resulting from gFOBT screening is durable over at least three decades.[156] However, it is important to note that gFOBTs are not specific for human blood. Consequently, they tend to generate a relatively high proportion of false-positive results.

iFOBT (FIT)

FITs offer an advantage over gFOBTs by specifically detecting human hemoglobin. This specificity eliminates false-positive results generated from gFOBTs because of nonhuman hemoglobin present in the diet.[157]

Although FITs demonstrate higher sensitivity for detecting colorectal cancers (ranging from 61% to 91%), their sensitivity for detecting adenomas (precancerous polyps) is lower, ranging from 16% to 31%.[158,159]

A comprehensive meta-analysis, pooling data from 19 randomized trials or observational cohorts that used 8 different commercially available FITs, reported an overall sensitivity of 79% for the detection of colorectal adenocarcinoma and a specificity of 94%.[160]

It is also worth noting a multitarget stool DNA test, which combines the FIT with multiplexed methylated DNA markers. This test exhibits high sensitivity for detecting colorectal cancer. However, currently, there are no published data demonstrating that Cologuard reduces the incidence or mortality of colorectal cancer. Furthermore, the test's performance in detecting adenomas decreases significantly.[161]

Endoscopy and Imaging

Several techniques allow for the visual inspection of the inner lining of the colon and rectum to detect and remove polyps, thereby reducing an individual's risk of developing colorectal cancer. These primary methods include flexible sigmoidoscopy, colonoscopy, and CT colonography.

Flexible Sigmoidoscopy

Screening with flexible sigmoidoscopy, which examines the lower (distal) portion of the colon and the rectum, has been shown to reduce the incidence and mortality of distal colon cancer by 22% to 26%.[162,163] However, this method does not provide a benefit for cancers located in the upper (proximal) colon.

Colonoscopy

Population-based cohort studies evaluating colonoscopy screening, which allows for the visualization of the entire colon, have also demonstrated a reduction in colorectal cancer mortality. Interestingly, this benefit has been observed primarily in the distal colon, with less clear evidence of mortality reduction in the proximal colon.[164-166] This discrepancy has been attributed to factors such as variations in endoscopic quality, the technical challenges of detecting lesions in the right-sided colon, and the more frequent occurrence of flat and depressed precancerous lesions in that region.[164,167-169]

CT Colonography

CT colonography, a noninvasive imaging technique, has demonstrated a reported sensitivity ranging from 67% to 94% for detecting adenomas (precancerous polyps) measuring at least 10 mm. The specificity of CT colonography for these larger adenomas ranges from 86% to 98%.[167] However, there are currently no published studies that directly compare the mortality benefit of CT colonography with that of standard colonoscopy. Although CT colonography appear to be capable of adequately detecting precursor lesions 6 mm or larger (similar to colonoscopy), potential harms associated with this technique include cumulative radiation exposure from repeated examinations and the detection of incidental, often noncancerous, findings.[170]

Guidelines

Among the various screening tests available for colorectal cancer, the USPSTF has concluded that no single test demonstrates superiority to others.[145] Consequently, its guidelines recommend screening for colorectal cancer in average-risk people, defined as those without a history of polyps or precancerous lesions on prior endoscopic examinations, from age 45 to 75 years. This screening should be conducted using a shared decision-making approach, where patients are offered the following options:

- **Annual stool-based screening.** This includes either a high-sensitivity standard gFOBT performed annually or an FIT or a combined FIT-DNA test performed every 1 to 3 years.
- **Endoscopic procedures.** These options include flexible sigmoidoscopy screening conducted once every 5 years in conjunction with an annual FIT or a colonoscopy performed every 10 years.
- **CT colonography.** For people at high risk of colorectal cancer, such as those with a genetic predisposition, a personal history of colorectal cancer or large adenomatous polyps, or inflammatory bowel disease, colonoscopy is the recommended screening method.

Over the last two decades, the incidence and mortality rates of colorectal cancer in the United States have generally decreased. However, more recent data from the SEER Program have revealed a concerning trend: a significant increase in colorectal cancer incidence among younger people. Currently, 20% of all colorectal cancers and 30% of all rectal cancers are diagnosed in patients younger than the age typically associated with this disease.[171]

Recognizing the disproportionately higher mortality and risk of early-onset colorectal cancer among Black people, the US Multisociety Task Force (representing three gastroenterological societies) issued a recommendation in 2017 to begin colorectal cancer screening for Black patients at age 45. Subsequently, in 2018, the American Cancer Society also updated its guidelines to recommend that average-risk people, including Black people, begin colorectal cancer screening at age 45.[172]

PROSTATE CANCER: BALANCING EARLY DETECTION WITH RISK OF OVERDIAGNOSIS

Digital rectal examination (DRE) and measurement of serum PSA levels are commonly used in the United States for the early detection of prostate cancer. However, most professional organizations advocate for a cautious approach to the use of these screening tools. Although PSA testing and DRE can identify many asymptomatic prostate cancers, their ability to reliably distinguish between indolent tumors that pose minimal threat and aggressive, potentially lethal yet curable cancers is limited. Indeed, the USPSTF estimates that a substantial proportion, ranging from 22% to 42%, of screen-detected localized prostate cancers represent overdiagnosis.[146]

The treatment of screen-detected prostate cancers is not without potential harm, often leading to excess morbidity, such as impotence and urinary incontinence, and carrying a small but definite mortality risk. Current screening guidelines have been

significantly influenced by the findings of two large, randomized prostate cancer screening trials: the PLCO (Prostate, Lung, Colorectal and Ovarian) screening trial and the ERSPC (European Randomized Study of Screening for Prostate Cancer). Notably, the PLCO trial found no reduction in prostate cancer mortality,[171] whereas the ERSPC reported a 21% reduction in cancer-specific mortality associated with screening.[172]

The discrepancy in outcomes between the PLCO and ERSPC trials has been attributed to at least two key differences in their designs. First, a significant proportion (estimated at 80%) of the control arm in the PLCO trial underwent PSA screening outside of the study protocol, effectively reducing the observed difference between the screened and unscreened groups. In contrast, such off-protocol screening was comparatively uncommon in the ERSPC control arm. Second, the PLCO trial focused on absolute mortality reduction, which represents the actual likelihood of a patient avoiding death from prostate cancer. Conversely, the ERSPC reported relative mortality reduction, which reflects the proportional decrease in the risk of dying from prostate cancer compared with the risk in the absence of screening.

Based on its assessment of the balance between risks and benefits, the USPSTF concluded that population-based, PSA-based screening did not offer sufficient net benefit to warrant a universal recommendation. Their current (2018) recommendations state: "For men aged 55 to 69 years, the decision to undergo periodic PSA-based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men."[146,173]

To address the challenge of overdiagnosis associated with PSA screening, alternative approaches are being explored. One such strategy involves the use of a prostate cancer risk calculator, developed from long-term longitudinal data from the Prostate Cancer Prevention Trial. This tool enables the prediction of both low-grade (Gleason score <7) and high-risk cancers, thereby aiding in informed biopsy and treatment decisions.[174] Another approach uses risk stratification algorithms that integrate age-specific PSA levels along with other epidemiologic risk factors to identify men who would benefit most from frequent screening and additional diagnostic procedures.[175]

In men presenting with clinical symptoms suggestive of prostate cancer, magnetic resonance imaging (MRI) of the prostate prior to biopsy consideration has demonstrated the potential to reduce biopsy rates[176] and the incidence of overdiagnosis.[177] Extending this to the screening setting, among men with elevated PSA levels (>3 ng/mL), MRI of the prostate with MRI-targeted biopsy, compared with traditional biopsy based on risk-prediction models, resulted in a lower detection rate of clinically insignificant cancers. This suggests that prebiopsy MRI may offer an avenue to mitigate the harms associated with PSA screening.[178]

CERVICAL CANCER: CYTOLOGY AND HPV DNA TESTING

For the past 60 years in high-income countries, early detection of cervical neoplasia, both noninvasive and invasive, has primarily relied on cervical cytology, also known as the Papanicolaou (Pap) test. This method has a reported sensitivity of 78% (range, 30%-87%) and a specificity of 62% (range, 61%-94%).[179]

However, cytological screening is susceptible to limitations, including tissue sampling errors, issues with cellular preservation, and the inherent subjectivity of cytotechnologist interpretation. Furthermore, because colposcopy referral is typically triggered only by positive cytology results, the rate of false-negative findings is challenging to accurately measure but has been reported to be as high as 50%.[179]

In contrast, the HPV DNA test has emerged as another important screening modality. A meta-analysis of 8 studies involving more than 3,700 women demonstrated that a single HPV DNA test yielded a pooled sensitivity of 90% (95% CI, 88%-93%) for cervical intraepithelial neoplasia grade 2 (CIN 2) and 95% (95% CI, 93%-97%) for cervical intraepithelial neoplasia grade 3 (CIN 3), both of which are considered precancerous lesions. Although highly sensitive, HPV testing demonstrated consistently lower specificity when directly compared with parallel cervical cytology: 88.5% (95% CI, 87%-90%) for CIN 2 and 89% (95% CI, 87.2%-88.5%) for CIN 3.[180]

USPSTF Guidelines

The USPSTF provides the following recommendations for cervical cancer screening[148]:

- **Women who are 21 to 29 years:** cervical cytology screening every 3 years
- **Women who are 30 to 64 years:** one of the following:
  - Cervical cytology alone every 3 years; or
  - High-risk HPV DNA molecular testing alone every 5 years; or
  - Combined cervical cytology and high-risk HPV DNA molecular testing every 5 years.

Rationale for Guidelines

In women younger than 30 years, the high prevalence of transient HPV infections, which carry minimal long-term risk of disease progression, reduces the specificity of HPV testing. More frequent screening in this age group can lead to unnecessary additional procedures and treatment of these transient lesions without providing incremental clinical benefit.

The decreasing cost and increasing accessibility of HPV DNA molecular testing have contributed to higher rates of women being screened. Importantly, screening remains recommended even for women who have received the prophylactic HPV vaccine. This is because the original quadrivalent vaccine does not offer protection against all high-risk HPV types. It is anticipated that this recommendation may be revised as the nine-valent vaccine, which provides broader protection, becomes more widely used globally. Notably, ASCO cervical screening guidelines are consistent with those of the USPSTF.[181]

BREAST CANCER SCREENING: MAMMOGRAPHY AND BREAST SELF-EXAMINATION

Breast Self-Examination

The results of the largest randomized controlled study of breast self-examination conducted to date, in a population without access to mammography, demonstrated an increased rate of biopsy and enhanced detection of benign lesions. However, the study showed little to no stage shift in cancer diagnosis and no reduction in breast cancer mortality.[182]

Mammography

Multiple randomized clinical trials have consistently shown that screening women at average risk using mammography alone or mammography combined with clinical breast examination every 1 to 2 years leads to a reduction in breast cancer mortality ranging from 20% to 30%. Although individual trials have faced specific methodologic criticisms, the consistency of these observations across numerous studies outweighs these concerns. The introduction of mammographic screening in the United Kingdom starting in 1991 for women aged 49 to 64 years has been associated with an estimated overall reduction in breast cancer mortality of 21%.[179] Consensus publications from the USPSTF[183] and the Canadian Task Force on Preventive Health Care[148] recommend mammographic screening every 2 to 3 years for average-risk women between the ages of 50 and 69 years (Canadian recommendation) or 50 and 74 years (US recommendation).

The role of mammographic screening for women aged 40 to 49 years at average risk remains a subject of debate. Although studies have shown an approximately 18% reduction in breast cancer mortality in this age group, the accompanying high number of false-positive screening results was a significant factor in the Canadian Task Force on Preventive Health Care and the 2016 USPSTF recommendations against routine population-based screening in this age range. However, in 2024 the USPSTF issued new recommendations that lowered the starting age for biennial screening mammography to 40 years.[184] This change in the USPSTF recommendation was not primarily due to a change in the moderate net benefit of screening mammography in this age group. Instead, it reflected a consideration of the increasing incidence of breast cancer among women in their 40s and the higher mortality rate of breast cancer observed among Black women. In contrast, the American Cancer Society currently recommends that screening for women at average risk begin at age 45.[180]

MRI for Breast Cancer Screening in High-Risk Populations

MRI has demonstrated better sensitivity compared with mammography or ultrasound in detecting breast cancer among women carrying *BRCA1* or *BRCA2* mutations. Although its high cost and the lack of proven mortality benefit make it unsuitable for average-risk women, MRI can be a cost-effective tool for increasing cancer detection yield in younger *BRCA* mutation carriers and other women at very high risk of breast cancer.[185]

The American Cancer Society has established guidelines for MRI use in women who have a calculated lifetime risk of breast cancer of at least 20%, as determined by one of several validated mathematic models. Another group of women considered to be at an elevated risk includes those with dense breasts. Recommendations for screening these women are varied and sometimes include supplemental imaging with ultrasound, MRI, or other tests in addition to mammography. However, the 2024 recommendation from the USPSTF acknowledges the enhanced detection capabilities of these additional imaging procedures but does not recommend their routine use for screening women with dense breasts. This stance is based on concerns regarding increased false-positive results and imprecisely estimated clinical endpoints because of limited available data.[184]

LUNG CANCER: THE ROLE OF LOW-DOSE CT

Lung cancer is a compelling target for screening initiatives because of the existence of a well-defined high-risk group, composed primarily of heavy cigarette smokers, and its characteristically long preclinical phase. This extended preclinical period offers a significant window of opportunity during which treatment interventions could be particularly effective in reducing mortality. Consequently, the primary screening strategy that has been extensively investigated involves imaging of the lungs.

Initial investigations into lung cancer screening using chest radiography combined with sputum cytology failed to demonstrate any reduction in lung cancer mortality.[186] However, subsequent research has yielded more promising results. Notably, screening with low-dose spiral CT scanning has been shown to reduce lung cancer mortality by approximately 20%.[187]

Although low-dose spiral CT scans increase the number of pulmonary lesions diagnosed, which inevitably leads to a greater number of diagnostic and therapeutic procedures being performed, cost-benefit analyses for this screening modality have generally concluded that the benefits for specific subgroups of heavy smokers outweigh the potential harms associated with overdiagnosis and false-positive results.[188]

Based on this evidence, most expert organizations now recommend CT screening for people who are current or former heavy smokers with a smoking history of at least 20 pack-years. The USPSTF recommends initiating screening at age 50 for persons with a smoking history of 20 or more pack-years.[189] The American Cancer Society provides a similar recommendation in their updated 2023 guidelines.[172]

HEPATOCELLULAR CARCINOMA: TARGETING HIGH-RISK POPULATIONS

The USPSTF recommends screening for hepatitis B virus (HBV) infection in populations identified as being at high risk. This high-risk designation includes people who have immigrated to the United States or whose parents originated from countries with a prevalence of hepatitis B surface antigen (HBsAg) of at least 2%.[187] Screening is also recommended for other high-risk groups defined by clinical and behavioral characteristics associated with an HBsAg prevalence of 2% or greater.[187] Although the optimal frequency of screening is not definitively established, intervals based on clinical judgment are recommended. In addition to educational interventions, a significant proportion, ranging from 20% to 40%, of positive screening results will require treatment. International screening recommendations for hepatocellular carcinoma are further detailed in the "Screening for Other Cancers Globally" section of this chapter.

OVARIAN CANCER: LACK OF EFFECTIVE STRATEGIES FOR MORTALITY REDUCTION

Several modalities, including adnexal palpation, transvaginal ultrasound, and measurement of serum cancer antigen 125 (CA-125), have been investigated for their potential in screening for ovarian cancer. However, randomized trials evaluating these approaches, whether used individually or in combination, have consistently failed to demonstrate a reduction in ovarian cancer mortality.[190]

A significant challenge in developing effective ovarian cancer screening is the relatively low incidence of the disease within the general population. Consequently, any screening modality used would likely result in an unacceptably high rate of false-positive findings. These false positives could then lead to expensive and potentially risky invasive diagnostic procedures, such as laparotomy, in women who do not have cancer.

SKIN CANCER SCREENING: LACK OF EVIDENCE FOR MORTALITY REDUCTION WITH VISUAL EXAMINATION

Although nonmelanoma skin cancers (basal and squamous cell carcinomas) represent the most common cancer types in the United States, they are rarely fatal. In contrast, cutaneous melanomas are associated with significant mortality. To date, no randomized controlled study has definitively assessed whether a clinical skin examination screening program reduces melanoma-specific mortality. A nationwide routine screening program implemented in Germany reported a higher proportion of melanoma-related deaths in the unscreened group compared with the screened group; however, this difference was diminished after multivariable adjustment.[191]

Furthermore, potential harms associated with routine skin cancer screening may be considerable, including the need for repeated biopsies and the risk of overdiagnosis and subsequent overtreatment. Considering these factors, the USPSTF 2023 recommendations conclude that the current evidence remains insufficient to determine the balance of benefits and harms of visual skin examination by a clinician for screening for skin cancers in adults.[192]

LOWER-ESOPHAGEAL ADENOCARCINOMA SCREENING: ADDRESSING THE RISING INCIDENCE

The substantial increase in the incidence of esophageal adenocarcinoma over the last two decades has raised significant concerns regarding prevention strategies. Barrett esophagus is recognized as the primary precursor lesion to esophageal adenocarcinoma. Consequently, preventing the development of Barrett esophagus or using ablation techniques for dysplastic mucosa arising within Barrett metaplastic epithelium could potentially reduce an individual's risk of this cancer. A major risk factor for Barrett esophagus is gastroesophageal reflux disease (GERD), a condition that has also seen a dramatic rise in prevalence,[193] possibly linked to the increasing rates of obesity.

Guidelines from the American College of Gastroenterology (ACG) recommend upper endoscopic screening in people identified as being at high risk of Barrett esophagus. Its criteria for high risk include men with chronic GERD (defined as >5 years' duration) and the presence of three or more additional risk factors: age older than 50 years, White race, central obesity (waist circumference >102 cm or waist-to-hip ratio >0.9), current or past history of smoking, and a confirmed first-degree family history of Barrett esophagus or esophageal adenocarcinoma.[194] It is important to note that current evidence from both randomized controlled trials and observational studies does not support a mortality benefit associated with upper endoscopic screening, even in these high-risk people.

Cancer Screening Based on Genetic Risk

NCCN guidelines on Genetic/Familial High-Risk Assessment are rapidly evolving and expanding and include cancer screening based on genetic risk. As we learn more about the effects on cancer risk in various patient populations with specific pathogenic or

likely pathogenic germline mutations in high- or moderate-penetrance genes, guidelines are evolving to include cancer screening recommendations. For example, tailored cancer screening recommendations are included for patients with known variants in genes such as *BRCA1/2, TP53, ATM, BARD1, BRIP1, CDKN2A, CHEK2, NF1, PALB2, PTEN, STK11, CDH1, MSH2, MLH1, PMS2, EPCAM*, and *RAD51C/D*. For some germline variants, screening for cancers not typically screened for are now recommended, including pancreatic cancer screening at experienced centers with magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound. The age at which to begin screening depends on the specific mutation and family history.

SCREENING FOR OTHER CANCERS GLOBALLY

This chapter primarily focuses on cancer screening practices in the United States. However, it is important to recognize that global variations in cancer incidence and prevalence lead to corresponding geographic differences in screening recommendations. The following examples illustrate cancer screening guidelines implemented outside of the United States.

India

Oral cavity cancer is the most prevalent malignancy among men in India, largely attributable to the widespread use of tobacco products and betel quid (with or without tobacco). A randomized controlled trial demonstrated that visual screening of the oral cavity resulted in an approximate one-third reduction in mortality among people who used alcohol, tobacco, or both.[195]

East Asia and Africa

The Shanghai trial, involving more than 18,000 carriers of HBV, randomly assigned participants to either a serum α-fetoprotein (AFP) test plus ultrasonography every 6 months or no screening for hepatocellular carcinoma. This study found a 37% reduction in mortality in the screened group.[196] Furthermore, the combined use of ultrasonography and MRI has been shown to detect most hepatocellular carcinomas at an early stage when surgical resection is more likely to be feasible.[197]

Japan

Gastric cancer screening guidelines in Japan recommend either radiographic upper gastrointestinal imaging or endoscopy. These recommendations are primarily based on observational studies because no randomized controlled trials have yet confirmed the efficacy of these tests in reducing gastric cancer mortality.[198]

China

An observational cohort study reported that endoscopic screening for squamous cell carcinoma of the esophagus in endemic regions of China was associated with a 50% reduction in mortality.[194] Additionally, screening for exposure to Epstein-Barr virus (EBV) using a plasma EBV DNA test can identify persistently positive patients who may benefit from further nasopharyngeal cancer screening. In an observational cohort of 20,174 plasma screens conducted in Shanghai, 5.5% yielded positive results, with approximately one-quarter of these being persistently positive. These persistently positive patients underwent further endoscopic evaluation, and 34 cases of nasopharyngeal carcinoma were detected, predominantly at an early stage. Notably, only one carcinoma developed among patients who were EBV negative.[197] A randomized clinical trial is warranted to definitively determine whether plasma screening for EBV DNA reduces mortality from nasopharyngeal carcinoma.

THE FUTURE OF CANCER SCREENING: MULTICANCER EARLY DETECTION TESTS

Current recommendations for cancer screening are largely specific to individual organs and diseases. However, advancements in genomics and computational power have opened the possibility of blood-based screening using cell-free DNA for multiple cancers, regardless of their origin. Multicancer early detection (MCED) tests are among those currently under development. Using a single blood sample, these tests aim to detect signals from over 50 different cancers and predict the organ of origin if a cancer signal is identified. In a large US-based study of the Galleri test, cancer was detected in 1.4% of the 6621 participants who had a positive cancer signal, with 38% of these being true positives. Importantly, many of the cancers detected in this study would not have been identified under current standard screening paradigms. This test, along with other similar ongoing research efforts, suggests the potential for successful development and implementation of multicancer detection tests in the near future.[2] The NCI Vanguard Study (NCT06995898) is a feasibility trial enrolling up to 24,000 participants across over 20 US sites to assess the operational viability and potential harms of using MCED blood tests for population-based screening of cancers including pancreatic, ovarian, liver, lung, bladder, breast, colorectal, esophageal, stomach, and prostate. Primary endpoints focus on feasibility of recruitment, adherence, and representative enrollment, while secondary endpoints assess timeliness of result return, diagnostic resolution of abnormal tests, impact of blinding on screening behavior, and potential harms such as unnecessary procedures or anxiety triggered by false positives.

It is possible that in the future, MCED could be used to complement traditional cancer screening in high-risk populations, such as based on age, a history of toxic exposures, high-risk occupations (such as aviators or space travelers), and germline predisposition.

KEY POINTS

- Evidence-based screening information for cancers of the lung, colorectum, prostate, and ovary includes the following:
- Chest radiography is ineffective as a lung cancer screening tool.
- Sigmoidoscopy and colonoscopy are effective in reducing mortality resulting from colorectal cancer.
- CA-125 and transvaginal ultrasonographic screening for ovarian cancer are not effective in reducing mortality.
- The effectiveness of PSA screening for prostate cancer in reducing mortality remains uncertain.
- Mammographic screening for breast cancer among women aged 50 years or older reduces mortality; however, whether mammographic screening meaningfully reduces mortality in women younger than 50 years remains unclear.
- Decisions regarding PSA-based prostate cancer screening should be individualized and involve a thorough discussion of potential risks and benefits between the patient and clinician.
- Low-dose spiral CT screening is an established approach for reducing lung cancer mortality among heavy smokers.
- The use of HPV DNA molecular testing in conjunction with the Papanicolaou test for women aged 30 years or older allows for an extension of the interval between cervical cancer screenings to 5 years.
- Multiple options, specifically FOBT, sigmoidoscopy, and colonoscopy, are recommended as screening modalities for colorectal cancer.

HIGH-YIELD TAKEAWAYS

- Cancer Disparities and High-Risk Populations: Recognize demographic variations in cancer incidence and mortality to guide equitable screening and prevention, especially in hereditary syndromes and underserved groups.
- Evidence-Based Prevention Strategies: Apply established chemopreventive agents (eg, tamoxifen, aspirin), risk-reducing surgeries (eg, *BRCA*), and cancer-preventive vaccines (HPV, HBV) in counseling and clinical decision-making.
- Screening Principles and Biases: Evaluate screening tests using concepts such as lead-time bias, length bias, and healthy volunteer bias; prioritize mortality reduction over surrogate endpoints such as sensitivity or PPV.
- Guideline-Driven Screening: Implement current screening recommendations for lung (LDCT), breast (mammography ± MRI), colorectal (colonoscopy, FOBT), cervical (HPV/Pap), prostate (individualized PSA), and HCC (AFP + ultrasound in HBV carriers).
- Avoid Harmful or Ineffective Screening: Recognize when screening lacks mortality benefit (eg, ovarian cancer in average-risk women, melanoma via routine clinical exams, and esophageal adenocarcinoma outside high-risk GERD populations) to prevent overdiagnosis and unnecessary procedures.

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We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

EPIDEMIOLOGY AND PREVENTION

1

CHAPTER SUMMARY GUIDE

KEY POINTS

- Epidemiology is the study of the distribution and determinants of disease in populations.
- The distribution of cancer incidence, prevalence, mortality, and survival can be compared across demographic characteristics of populations to identify high-risk populations and cancer disparities.
- Criteria for a casual inference in cancer epidemiology include consistency, strength of association, temporal precedence, and latency.
- Physical activity and avoidance of obesity are associated with a lower risk of at least 13 cancers.
- Most randomized trials of vitamins or nutritional supplements as clinical preventive agents have had negative results.
- Tamoxifen, raloxifene, and aromatase inhibitors are established breast cancer preventative agents.
- Aspirin and other nonsteroidal anti-inflammatory drugs are not recommended for a majority of patients with colorectal cancer although recent data suggest a benefit for colorectal cancers harboring a somatic *PI3K* mutation.
- Vaccination or antiviral therapy for cancer-causing infectious agents, such as hepatitis B and C and HPV, has led to reduced incidence of and/or mortality as a result of associated cancers (hepatocellular carcinoma, cervical, and other anogenital cancers).
- Risk-reducing surgeries are an appropriate and effective intervention for select high-risk patients, such as those with deleterious *BRCA* mutations or Lynch syndrome.
- Evaluation of the benefits/efficacy of a cancer screening test is far more complicated than simply performing the test and detecting localized cancers.
- Biases that complicate the assessment of screening benefits are lead time, length, and healthy volunteer effect.
- These biases can make a screening test seem beneficial when there is no benefit, or the test may even cause harm.
- Overdiagnosis occurs when a screening test identifies indolent cancers that do not pose a mortal threat. The costs of overdiagnosis are high: unnecessary screening of large populations, unnecessary medical procedures, and emotional and financial harm.
- To offset these biases, a randomized trial is the best way to assess a screening test, with the endpoint of reduction in cancer-related mortality.
- Sensitivity, specificity, and positive predictive value can be important measures of the accuracy of a screening test and the rate of false-positive and false-negative results. However, these metrics are not used to decide whether a screening test should be used on a large-scale; the main criterion for this purpose is reduction in mortality.
- Evidence-based screening information for cancers of the lung, colorectum, prostate, and ovary includes the following:
- Chest radiography is ineffective as a lung cancer screening tool.
- Sigmoidoscopy and colonoscopy are effective in reducing mortality resulting from colorectal cancer.
- CA-125 and transvaginal ultrasonographic screening for ovarian cancer are not effective in reducing mortality.
- The effectiveness of PSA screening for prostate cancer in reducing mortality remains uncertain.
- Mammographic screening for breast cancer among women aged 50 years or older reduces mortality; however, whether mammographic screening meaningfully reduces mortality in women younger than 50 years remains unclear.
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- Multiple options, specifically FOBT, sigmoidoscopy, and colonoscopy, are recommended as screening modalities for colorectal cancer.

CHAPTER TABLES AND IMAGES

Table 1-1 Hierarchy of Evidence by Study Design

Study Type	Evidence
Pooled analysis/ meta-analysis	One of the highest levels of evidence and more generalizable given that it uses multiple data sources, provided inclusion of high-quality studies. Meta-analysis uses published results, whereas pooled analysis reanalyzes individual-level data
Randomized clinical trial	Highest-quality evidence, but use is limited to testing health-enhancing interventions (new treatments, preventive or screening interventions)
Cohort (prospective or retrospective)	Highest-quality observational evidence because of measurement of exposure and follow-up for occurrence of the outcome
Case-control	Useful for studying rare diseases, such as specific cancer types, but susceptible to information and selection biases because of measurement of exposure after the occurrence of disease and challenges of selecting and recruiting a control group representative of the population from which the cases arose
Cross-sectional	Limited by studying only prevalent cancer and measurement of exposure and outcome at a point in time
Ecologic	Unit of observation is group-level data (typically geographically defined), not individuals; results can be useful for evaluating policies aimed at reducing cancer risk factor prevalence that vary geographically
Case series	Commonly used clinical design, but lack of a comparison group severely limits inferences

Study designs higher up in the table tend to provide stronger evidence because of higher internal validity (or lower likelihood of bias).
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Table 1-2 **Associations Between Extrinsic Factors and Cancer Risk**

Exposure	Cancer Type(s)	Notes
Cigarette smoking	Lung, oral cavity, larynx, esophagus, bladder, kidney, pancreas, stomach, cervix, colon, rectum, liver, acute myeloid leukemia	Causal association; estimated 48% of deaths from cancer in the United States attributable to smoking[17]
Ionizing radiation	Leukemia, non-Hodgkin lymphoma, thyroid, breast (female), lung, colon, bladder	Established cause[18,19] In the Life Span Study on Japanese atomic bomb survivors, after high-dose radiation there was an elevated leukemia risk early on, and an elevated solid tumor risk long-term. A heightened risk of hematological malignancies has been established after lower doses of radiation exposure from medical imaging in children and adolescents[20-22]
UV radiation	Melanoma, nonmelanoma skin cancers	Major cause (sunlight, tanning devices)[18]
HPV (oncogenic strains)	Cervix, penis, vagina, anus, oropharynx	Strong association[23]
Hepatitis B and C viruses	Liver, splenic marginal zone lymphoma	Strong association[23]
Epstein-Barr virus	Burkitt lymphoma, nasopharyngeal carcinoma	Strong association[23]
Helicobacter pylori	Gastric cancer	Strong association[23]
High BMI/obesity	Endometrial, esophageal, meningioma, breast, multiple myeloma, gallbladder, gastric, colorectal, kidney, liver, ovarian, pancreatic, and thyroid cancer[25]	Strong association; 4%-9% of new cancer cases in adults attributable to high BMI[24] Glucagon-like peptide 1 receptor agonists may decrease the risk of obesity associated cancers[26]
Alcohol	Breast cancer, liver, colorectal, oral cavity, esophageal (squamous cell)	Causal association[27,28]
Occupational exposures	Various (eg, melanoma and prostate cancer in pilots/aviators,[29] scrotal carcinomas in chimney sweeps)	2%-8% of cancers attributable to occupational causes[30,31]
Particulate matter (air pollution)	Lung	Classified as human lung carcinogen[32]
HIV infection	Non-Hodgkin lymphoma, cervical cancer, Kaposi sarcoma, anal cancer, Hodgkin lymphoma, lung cancer, skin cancer, oropharyngeal cancers, liver cancer[33]	Risk of non-AIDS-defining cancers (eg, Hodgkin lymphoma, liver, anal, lung) remains elevated even with immune reconstitution on ART. Therefore effective ART reduces, but does not eliminate, excess cancer risk. Coinfections (HPV, HBV, HCV) and lifestyle factors (eg, smoking, alcohol use) further modify risk
Medications	Immunosuppression or immunomodulators such as lenalidomide can heighten the risk of lymphoid and other malignancies,[34] tamoxifen and uterine cancer risk[35]	Lenalidomide plus high-dose melphalan with autologous stem cell rescue increases the risk of therapy- related myeloid neoplasms[36]
Sedentary lifestyle	Increases the risk of multiple cancers as well as cancer-related mortality[37,38]	The CHALLENGE trial reported a significant reduction in disease-free survival as well as long-term overall survival in colon cancer survivors who underwent a 3-year structured exercise program. Reduced cancer mortality in patients physically fit is exemplified by the healthy soldier effect[39,40]

Exposure	Cancer Type(s)	Notes
Circadian rhythm disruptions	Breast, prostate, colorectal, liver, lung cancers	The International Agency for Research on Cancer (IARC) has identified night shift work as a probable carcinogen (group 2A); it is hypothesized that DNA repair, apoptosis, and cell cycle regulation are regulated by circadian genes[41]
Diet	Colorectal cancer	Processed red meat has been linked with an increased colorectal cancer risk[42]

Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus.
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Table 1-3 **Associations Between Intrinsic (Host) Factors Related to Cancer Risk**

Intrinsic Factor Category/ Specific Factor	Description/Examples	Cancer Type(s) Associated	Notes
Nonmolecular			
Age	Cancer risk generally increases with age for most cancer types	Most cancers increase in incidence with increasing age	Strong association because of accumulated exposures and cellular changes over time
Sex	Differences in cancer incidence and mortality exist between sexes because of hormonal, genetic, and other factors	Various (eg, breast cancer in women, prostate cancer in men)	Strong; sex-specific cancers, hormonal influences, and other biological differences
Ethnicity/race	Cancer rates can vary across different ethnic and racial groups because of genetic, environmental, and socioeconomic factors	Various	Complex interplay of genetics, environment, and social determinants of health
Family history	Positive family history of cancer can increase risk, particularly for cancers with strong genetic components	Various (eg, breast, ovarian, colon)	Suggests shared genetic susceptibility and/or environmental exposures within families
Personal history	A personal history of cancer increases the risk of a subsequent malignant neoplasm[43,44]	Various	Increased risk likely multifactorial from an elevated baseline inherent risk, immunosuppression from therapy, and DNA damage from certain chemotherapeutic agents or radiotherapy
Molecular			
Inflammation and immune dysregulation	Inflammation and autoimmunity can contribute to cancer development; immune system dysfunction can increase cancer risk	Various (marginal zone lymphoma, gastric cancer with autoimmune gastritis, large granular lymphocytic leukemia)	Strong; inflammation can damage DNA and promote cell growth; immune system surveillance plays a role in cancer prevention
Endogenously produced hormones	Hormones play a role in the development of some cancers	Breast, endometrial, prostate, and so on	Strong for hormone-sensitive cancers
Oxidative stress	Imbalance between free radicals and antioxidants can damage DNA and contribute to cancer	Various	Implicated in cancer development, but precise role is still being researched
Host genetic variation			
Rare, moderate or high-penetrance mutations	Mutations with low frequency but high impact on cancer risk (eg, *BRCA1, BRCA2, TP53, ATM, PALB2, CHEK2, CDH1*)	Breast, ovarian, prostate (*BRCA1/2*), Li-Fraumeni syndrome (*TP53*), and so on	Significantly increased inherited susceptibility
Common, low-penetrance polymorphisms (SNPs)	Common DNA sequence variations with small individual effects (often identified through GWAS)	Various	Small individual risk contribution; large potential public health impact; used in polygenic risk scores
Epigenetic variations	Changes in gene expression that do not involve alterations to the DNA sequence itself	Various	Can influence cancer risk, but mechanisms and specific roles are still being studied

Abbreviations: GWAS, genome-wide association study; SNP, single nucleotide polymorphism.
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Table 1-4 **Contrast Between Observational and Randomized Studies for Supplements**

Supplement/Outcome	Observational Study Findings	Randomized Study Findings	Notes
Selenium and vitamin E/prostate cancer	High intake of selenium and vitamin E were associated with lower risk of prostate cancer	SELECT trial (large, placebo controlled): no reduction in incidence. Small skin cancer trial and secondary analysis of ATBC trial: supported observational findings	Conflicting results; large, well-designed trial showed no benefit[86-88]
Calcium/colon cancer	High-calcium diets were associated with lower risk of colon cancer	Women's Health Initiative and VITAL trial: no lower incidence of colorectal cancer. Two trials: supplemental calcium reduces adenomatous polyps risk (~25%). One trial: calcium supplementation decreased polyp recurrence, but a more recent trial failed to confirm	Mixed results; some benefit seen for polyp reduction but not for overall colorectal cancer incidence[89-95]
Carotenoids and beta-carotene/lung cancer	High intake of carotenoid-rich fruits and vegetables and beta-carotene were associated with lower risk of lung cancer	ATBC and CARET trials (high-risk patients): increased lung cancer incidence and mortality in beta-carotene groups	Clear example where observational studies suggested benefit, but randomized trials showed harm[96,97]
Retinoids/squamous cell cancer (head and neck)	Limited efficacy as preventive agents	One trial: 13-*cis*-retinoic acid reduced second primary head and neck cancer. Two follow-up trials (lower doses): no clinical effectiveness	Initial positive result not replicated with lower, less toxic doses[98-101]
Vitamin D and cancer	Low levels of vitamin D were associated with increased risk of cancer[102]	VITAL trial: Vitamin D supplementation did not result in a lower incidence of cancer[91,103]	Observational studies were likely confounded by multiple variables including outdoor physical activity
Nicotinamide and skin cancer	Nicotinamide use was associated with a 14% reduction in risk of skin cancer[104]	One trial found that nicotinamide was effective at reducing the rates of new nonmelanoma skin cancers and actinic keratoses in high-risk patients.[105] Another trial of solid organ transplant patients did not observe a benefit[106]	The trial in transplant patients was stopped early due to poor accrual

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Table 1-5 **Indices for Describing Accuracy of Screening Tests**

Term	Definition	Ability of Test	Equation
Sensitivity	Proportion of people with the disease who have a positive result on a screening test	To detect disease when it is present	A/(A + C)
Specificity	Proportion of people who do not have the disease who have a negative result on a screening test	To correctly identify the absence of disease	D/(B + D)
Positive predictive value	Proportion of people with a positive result on a screening test who have the disease; increases as disease prevalence in a population increases	To accurately predict the presence of disease	A/(A + B)
Negative predictive value	Proportion of people who have a negative result on a screening test who truly do not have the disease; increases as disease prevalence in a population decreases	To accurately predict the absence of disease	D/(C + D)

A, true-positive result; B, false-positive result; C, false-negative result; D, true-negative result.

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Table 1-6 **Screening Recommendations for Asymptomatic Patients With Average Risk by Guideline Setting Organization**

Test or Procedure	Organization		
	US Preventative Services Task Force[150]	**Canadian Task Force on Preventive Health Care**[151]	**American Cancer Society**[152]
Colorectal	2021	2016	2018
HSgFOBT or FIT	Annual HSgFOBT or FIT, starting at age 45 years	FOBT or FIT every 2 years, starting at age 50 years	Annual FOBT or RT, starting at age 45 years (qualified recommendation); age 50 years (strong recommendation: FIT preferred)
Flexible sigmoidoscopy	Every 5 years starting at age 45 years	Flexible sigmoidoscopy every 10 years, starting at age 50 years	Every 5 years, starting at age 45 years (qualified recommendation); age 50 years (strong recommendation)
Flexible sigmoidoscopy plus FIT	Every 10 years plus annual FIT, starting at age 45years	Not recommended	Not recommended
Colonoscopy	Every 10 years, starting at age 45 years	Not recommended	Every 10 years, starting at age 45 years (qualified recommendation); age 50 years (strong recommendation)
CT colonography	Every 5 years starting at age 45 years	Not recommended	Every 5 years, starting at age 45 years (qualified recommendation); age 50 years (strong recommendation)
Prostate	2018[a]	2014	2023
DRE	No change	No change	May be performed in men who want to be screened with PSA
PSA	No change	No change	Shared decision-making starting at age 50 years in men at average risk of prostate cancer who have a life expectancy of 10 years or more; men who choose to be tested and have a PSA level <2.5 ng/mL may only need to be retested every 2 years; men whose PSA level is ≥2.5 ng/mL should be screened annually
Cervical	2018	2013	2020
Pap cytology	Women aged <21 years should not be screened; for women age 21-29 years, Pap test every 3 years; for women aged 30 to 65 years, screening every 3 years with Pap cytology alone; women aged 65+ years who have had adequate prior screening and are not otherwise at high risk of cervical cancer should not be screened; women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (ie, CIN grade 2 or 3) or cervical cancer should not be screened	Women aged <25 years should not be screened; starting at age 25years, screen every 3 years to age 69 years; for women aged 70+ years who have been adequately screened (eg, three successive negative Pap tests in the last 10 years), routine screening may cease; for women aged ≥70 years who have not been adequately screened, continue screening until three negative test results have been obtained	Women aged 25-65 years: a Pap test alone every 3 years; women aged 65+ years who have had three normal Pap tests and no abnormal tests in the last 10 years and no history of CIN II or more serious diagnosis within the last 25 years should stop screening; women who have had total hysterectomy (unless hysterectomy was done as treatment for cervical cancer or precancer) should not be screened

Test or Procedure	Organization		
	US Preventative Services Task Force[150]	**Canadian Task Force on Preventive Health Care**[151]	**American Cancer Society**[152]
HPV DNA	For women aged 30-65 years, every 5 years with hrHPV testing alone or every 5 years with hrHPV testing in combination with Pap cytology (ie, cotesting)	No recommendation	Women aged 25-65 years: primary hrHPV test every 5 years; if a primary hrHPV test is not available, acceptable options include a cotest (hrHPV test done at the same time as a Pap test) every 5 years
Breast	2024	2018	2015
BSE	No change	No change	No change
CBE	No change	No change	
Mammography	Women aged 40-74 years: screen every 2 years; for women aged ≥75 years, there is insufficient evidence to form a recommendation	No change	No change
Lung	2021	2016	2023
LDCT	Adults aged 50-80years: annual screening if the patient also has at least a 20-pack-year smoking history and currently smokes or quit smoking <15 years ago	Adults aged 55-74years: three consecutive annual screenings if the patient also has at least a 30-pack-year smoking history and smokes or quit smoking <15 years ago	Adults aged 50-80 years: annual screenings if the patient also has at least a 20-pack-year smoking history and smokes or previously smoked

Abbreviations: BSE, breast self-examination; CBE, clinical breast examination: CIN, cervical intraepithelial neoplasia; DRE, digital rectal examination; FIT, fecal immunochemical test; FOBT, fecal occult blood testing; HPV, human papillomavirus: hrHPV, high-risk human papillomavirus; HSgFOBT, high-sensitivity guaiac fecal occult blood testing; LDCT, low-dose CT; Pap, Papanicolaou; PSA, prostate-specific antigen; RT, radiation therapy.
[a]Update coming.
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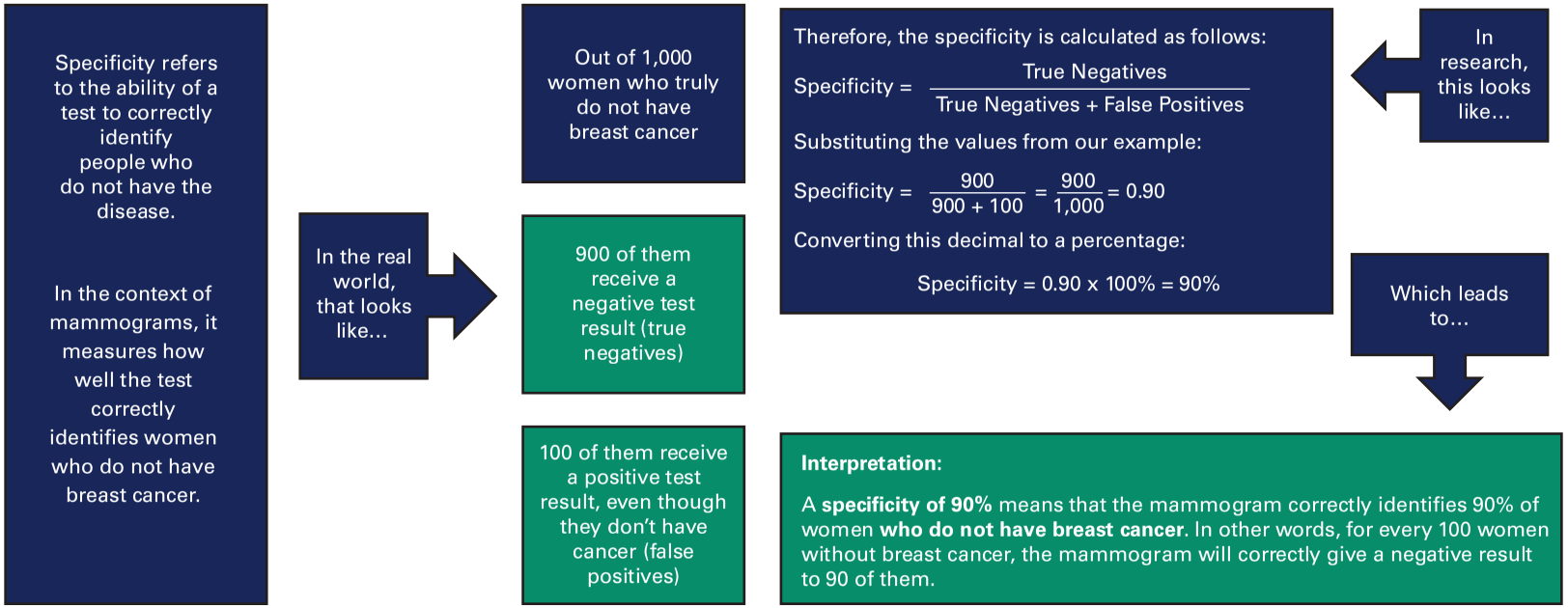
Figure 1-1 Deriving Specificity: Organized Data From a Hypothetical Mammogram Study



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MOLECULAR BIOLOGY 2

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RECENT UPDATES

- US FDA oncology drug approvals in 2025 include molecularly targeted agents, such as an alkylating agent, a hormone receptor-antagonist, small-molecule inhibitors against different kinases, as well as monoclonal antibodies, antibody-drug conjugates, a bispecific T-cell engager, a proteasome activator, and berahyaluronidase alfa-pmph, an endoglycosidase.
- Pathways targeted by these drugs include hormone signaling (estrogen receptor), cell survival (hepatocyte growth factor receptor [HGFR/cMET], receptor tyrosine-protein kinase erbB-2 [ERBB2/HER-2], epidermal growth factor receptor [EGFR], exon 20 insertions [mutated *EGFR*], histone mutation [H3 K27M], mitogen-activated protein kinase 1/2 [MEK1/2], rapidly accelerated fibrosarcoma kinase [RAF], focal adhesion kinase [FAK], proline-rich tyrosine kinase-2 [Pyk2]), improper cell function attenuation (programmed cell death 1, programmed death-ligand 1), and immune cell engagement (B-cell maturation antigen).
- Technological advances continue to revolutionize molecular biology, offering deeper insights into the intricacies of cellular processes. Techniques such as single-cell sequencing, clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) gene editing, and advanced imaging technologies now enable researchers to better understand the molecular mechanisms underlying diseases. This increased precision allows for the development of targeted therapies tailored to individual genetic profiles, and breakthroughs in computational biology and artificial intelligence are facilitating the analysis of vast data sets, accelerating the identification of potential drug targets and biomarkers.[1]

OVERVIEW

The clinical applications of insights into molecular oncology and the technologies linked to them are rapidly evolving, and our understanding of the genes and processes that drive tumorigenesis continues to expand. Recent studies have taken advantage of these technological advances, particularly high-throughput sequencing of DNA and RNA, which provides unprecedented depth and breadth of analysis of individual cancer samples. Identification of rare yet important cancer genes has revealed surprising new cancer pathways, and this knowledge has fueled the development of therapeutics that target specific oncogenic processes.

It is now both feasible and rational to perform detailed molecular analyses of each patient's cancer sample in a matter of days to weeks. This improvement in turnaround time has enabled clinicians to rationally select targeted therapies to treat individual cancers when locally confined approaches like surgery or radiotherapy have been exhausted or are no longer applicable because of the generalized nature of the cancer. In addition, DNA sequencing can provide phenotypic information, such as microsatellite instability (MSI) and tumor mutation burden, both of which may predict the benefit of therapy with immune checkpoint inhibitors, independently of tumor type or location. As our therapeutic armamentarium continuously expands to include new molecularly targeted agents to complement older traditional cytotoxic compounds, it is essential that cancer care providers have at least a basic understanding of the molecular basis of cancer, as well as the established and emerging technologies used to aid in cancer diagnosis, prognosis, and therapy.

The information selected for this chapter aims to provide the reader with an understanding of cancer's proclivity to constantly evolve and provide a scientific rationale at the molecular level for how diagnostic testing and drugs can be deployed most effectively. It has become essential as well as practical for oncologists at any level and in any practice setting to acquire a basic understanding of the biology to comprehend the torrent of targeted and other drugs coming down the pipeline and increasingly being approved for daily use in patient care.

MULTISTEP TUMORIGENESIS

The development of fully malignant cancers requires many independent genetic and epigenetic events that dysregulate normal cellular processes sufficiently to transform the cells into a malignant state. Although the mutations that cause

human cancers vary greatly among cancer types and individuals, the broad consequences of these mutations are abnormal phenotypes that are shared by most cancers. Hanahan and Weinberg[2] originally proposed six hallmarks of cancer that they defined as "distinctive and complementary capabilities that enable tumor growth and metastatic dissemination."[3] These include the following:

1. Sustained proliferative signaling
2. Evading growth suppressors
3. Resisting cell death
4. Enabling replicative immortality
5. Inducing angiogenesis
6. Activating invasion and metastasis

These capabilities can be acquired in a different order, and in some cases, a single genetic mutation might provide more than one capability. This conceptualization provides a framework within which to consider multistep tumorigenesis. The first three of these acquired capabilities involve mutations within the mitogenic signaling, cell cycle, and cell death pathways. The activation of mitogenic signaling pathways promotes uncontrolled cell proliferation, whereas dysregulation of cell-cycle pathways leads to unchecked cell division, contributing to tumor growth. Simultaneously, impairment of cell death pathways allows cancer cells to evade apoptosis, facilitating their survival and progression. The fourth category involves the acquisition of cellular immortality in tumors. Normal cells are limited in the number of times they can divide, even when they are provided with all the normal mitogenic stimuli required for cell division. By contrast, many cancer cells can divide with apparently limitless potential. One fundamental mechanism that limits human cell division involves repetitive nucleotide sequences, called telomeres, at the ends of chromosomes. Telomeres protect the ends of chromosomes from deterioration. They shorten with each cell division (the length of the telomeres of a cell reflects the number of divisions it has undergone) and eventually are shortened to the point where they can no longer protect the chromosome ends. This leads to a condition termed telomere crisis and, ultimately, to cell death. Unlike normal cells, cancer cells maintain their telomere length during cell division. Maintenance of telomere length usually results from expression of the enzyme telomerase that adds nucleotides back to the telomere. Telomerase activity can be detected in 85% to 90% of cancers, and the remaining tumors maintain their telomeres through a mechanism involving recombination (Fig. 2-1).

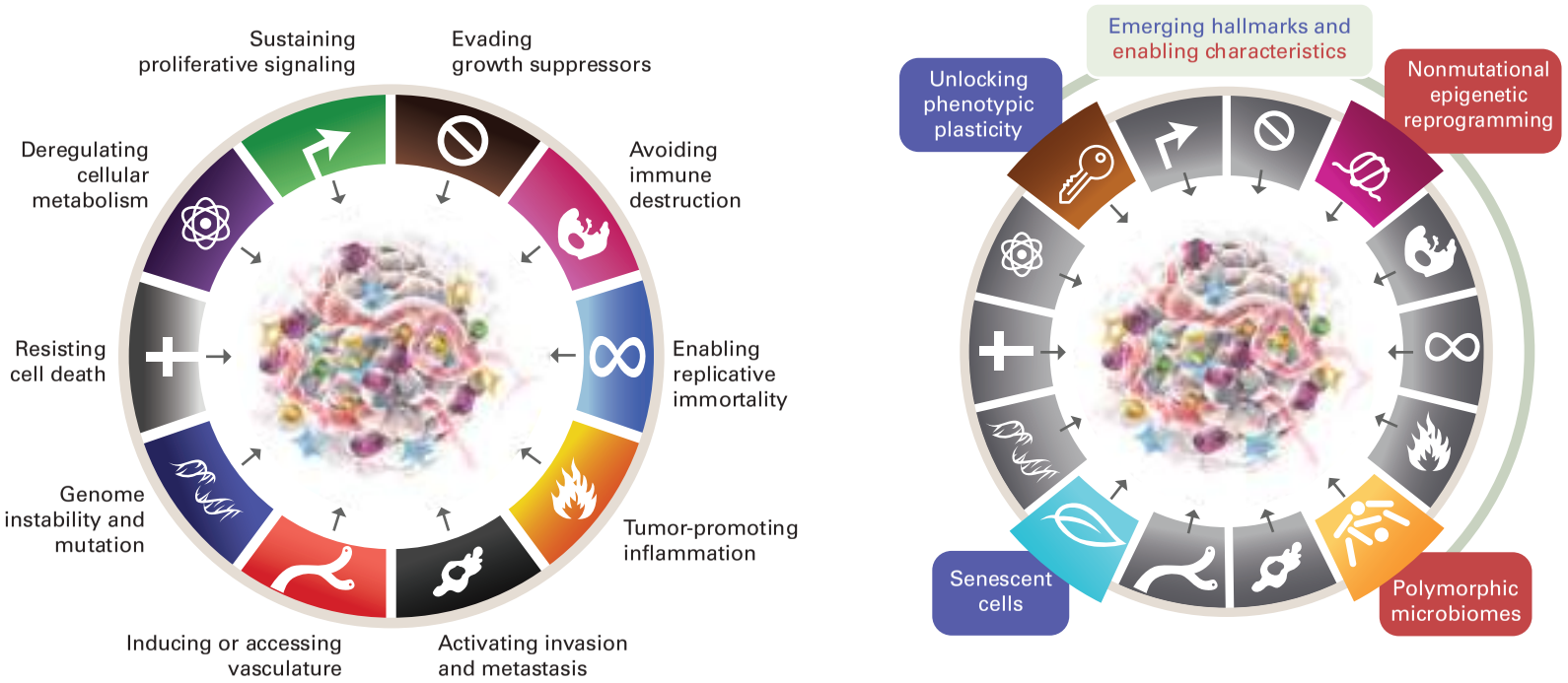
The fifth capability of induced angiogenesis reflects the need of tumors to actively recruit vasculature to grow once they have outgrown their existing oxygen/blood supply. In normal tissues, the development of new blood vessels is highly regulated by both positive and negative signals. Tumor cells promote angiogenesis by upregulating the pathways that promote blood vessel formation (eg, increased expression of angiogenic factors, such as vascular endothelial growth factor [VEGF] and fibroblast growth factor [FGF]) and reducing the activity of inhibitory pathways. Some of these pathways involve transcriptional networks under the control of other genes, such as *VHL* mutations in renal cell carcinoma. The 2021 Food and Drug Administration (FDA) approval of belzutifan underlines the practical implications of the hallmarks.[4] So far, targeting the different hallmarks is challenging because of the involvement of the targets in physiologic functions, and it remains the essence of basic oncology research. The importance of these pathways in tumor cell growth is well established, and a multitude of drugs have been developed that target angiogenesis, including both antibody and small-molecule inhibitors of the VEGF pathway.

The sixth hallmark comprises tissue invasion and metastasis, accounting for most cancer fatalities. Specific gene products are associated with the ability of tumor cells to metastasize to different organ sites. The composition of the tumor stroma, which is a complex mixture of extracellular matrix components and various cell populations, including fibroblasts, endothelial cells, and immune cells, has a major influence on metastasis as well. Elegant animal models as well as transcriptional profiling of human cancers show that metastasis includes alterations in genes involved in cell adhesion, cell fate, integrin signaling, growth factor and chemokine signaling, and extracellular proteolysis.

Ten years after their initial report on cancer hallmarks,[2] Hanahan and Weinberg[3] expanded on their original work, defining two emerging hallmarks and two enabling characteristics that make it possible for tumor cells to acquire the six core hallmarks. The two emerging hallmarks are deregulating cellular energetics and avoiding immune destruction. These two are now regarded as sufficiently validated to be part of the core set of cancer hallmarks.[5]

- Deregulating cellular energetics is based on growing knowledge that tumors deregulate metabolism to facilitate growth. Whereas normal cells tend to use mitochondrial oxidative phosphorylation for energy production, cancer cells use glycolysis, even when oxygen is available, a process termed aerobic glycolysis, also known as the Warburg effect. Other metabolic pathways are similarly altered in cancers.[6]
- Evading immune destruction is now validated as an effective strategy to overcome this evasion. Immunotherapies are key components of current therapy for cancer in many organ sites and are discussed in other chapters in this book.

Figure 2-1 Hallmarks of Cancer



The latest version of the hallmarks of cancer includes two emerging hallmarks and two enabling characteristics (right). These include unlocking phenotypic plasticity and senescent cells (emerging hallmarks) and non-mutational epigenetic reprogramming and polymorphic microbiomes (emerging enabling characteristics).
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The two enabling characteristics are properties of cancer cells that facilitate the acquisition of the core hallmarks:

- Genomic instability drives the acquisition of multiple mutations required for multistep tumorigenesis.
- Tumor-promoting inflammation reflects the rapidly advancing concept that inflammatory responses can facilitate tumor initiation and progression.

In the 2022 revision, two emerging enabling characteristics and two emerging hallmarks were identified[5]:

- Non-mutational epigenetic reprogramming is an emerging enabling characteristic of cancer that allows gene expression to be shaped through its interaction with the tumor microenvironment. Examples include hypoxia-modulating ten-eleven translocation (TET) demethylases or reversible induction of tumor invasiveness during epithelial-to-mesenchymal transition.
- Polymorphic microbiomes are an emerging enabling characteristic, based on the impacts of the microbiome from the gut and other barrier tissues on cancer biology. The most direct evidence supporting this emerging hallmark has been observed with the gut microbiota affecting colorectal cancer.
- Senescence is an emerging hallmark of cancer. Senescence is a type of cellular aging characterized by irreversible proliferative arrest. This process has historically been considered protective against cancer because these cells cannot proliferate or act aggressively. However, this view has been called into question by studies that have found that the presence of senescent cells may stimulate or activate cancer programs in adjacent tumor cells, leading to their provisional addition as an emerging cancer hallmark. Efforts to develop therapeutics that either induce the death of senescent cells (senolytics) or specifically attenuate the functionality of senescent cells (senomorphics) are currently underway.
- Unlocking phenotypic plasticity is another emerging hallmark of cancer. It is increasingly recognized that various cancer deregulations can release cancers from a limited potential differentiated state to a less-differentiated state in which they more freely proliferate and invade. Examples include dedifferentiation in colorectal cancer, blocked differentiation in acute promyelocytic leukemia, and transdifferentiation of prostate adenocarcinoma into neuroendocrine tumors through loss of retinoblastoma (RB) protein. In addition, the use of *KRAS* G12C inhibitors in non–small cell lung cancer (NSCLC) has been associated with histologic transformation, where adenocarcinoma exhibits plasticity by transitioning into a squamous histology, affecting the phenotypic landscape.[7]

One important aspect of the enabling characteristics concept is that it also provides a framework for the development of mechanism-based targeted therapies, which target both hallmarks and enabling characteristics. Examples of such combinatorial therapies include angiogenesis inhibitors and immune checkpoint inhibitors, as discussed here as well as in other chapters of this book.

KEY POINTS

- Tumorigenesis is a multistep process that requires the gain of multiple mutations or characteristics that subvert safeguards preventing normal cells from transforming into cancer cells.
- All tumors share a number of hallmarks that contribute to their malignant phenotypes, but the specific molecular events that produce these phenotypes vary greatly among tumor types and individuals.
- Understanding of the hallmarks of cancer informs the development of targeted therapies.

PRECISION ONCOLOGY

Large studies using next-generation sequencing (NGS) to study cancer genetics have radically altered our understanding of the genomic landscape of cancers and demonstrated the immediate effect of targeted gene panels and genome-scale analyses on clinical oncology.

A comprehensive review of the explosion of cancer genomic studies enabled by NGS and other technologies is beyond the scope of this chapter, but some examples follow to highlight the power and importance of these approaches. Also, two databases have been introduced that permit individual exploration of publicly funded research (the Catalogue of Somatic Mutations in Cancer [COSMIC][8] and cBioPortal, which focuses particularly on the publicly funded and available American Association for Cancer Research GENIE data set). Two early studies described an integrative approach that included the sequencing of protein-coding genes (exome sequencing), analyses of DNA copy number, and RNA sequencing to assess gene expression, which led to an in-depth understanding of the genes and pathways mutated in pancreatic cancers and glioblastomas.[9,10] The use of these combined modalities has helped distinguish mutations that likely play a causal role in tumorigenesis (driver mutations) from mutations that may be irrelevant (passenger mutations). Importantly, one of these studies[10] found that an isocitrate dehydrogenase

(*IDH*) gene, previously unrecognized as an oncogene, was mutated in 12% of glioblastomas. *IDH1* and *IDH2* mutations have subsequently been found in other cancers, including acute myeloid leukemia (AML), chondrosarcoma, and cholangiocarcinoma. Importantly, *IDH1*/*IDH2* mutations cause epigenetic dysregulation and DNA hypermethylation,[11] and pharmacologic IDH inhibitors are proving successful in the clinic; ivosidenib and enasidenib were approved for use in patients with *IDH*-mutated AML.

Dozens of large-scale cancer genomic studies, many of which have been coordinated by The Cancer Genome Atlas (TCGA; a consortium sponsored by the National Institutes of Health), have identified the molecular features of the most common and many uncommon cancer types.[12] The molecular features that have been catalogued include whole-exome sequencing, RNA sequencing/RNA expression, copy-number variation, DNA methylation, microRNA (miRNA) expression, and protein analysis. These studies have provided unprecedented insights into cancer biology and revealed many new targets for therapeutic interventions. TCGA initially studied tumor types individually, revealing drivers of specific diseases. For example, TCGA analysis of adult AMLs revealed that AMLs contain fewer mutations than other adult cancers, with an average of 13 mutations per sample, only five of which involve recurrently mutated genes.[13] As these studies of individual tumors were completed, TCGA went on to perform combined cross-cancer analyses across all tumor types, generating the PanCanAtlas. One common theme that has emerged from this work is that although specific organ sites exhibit unique mutational spectra, other pathways are mutated in many types of cancer.[14,15]

These global approaches set the stage for the use of NGS, in real time, to assist with clinical decision-making. Indeed, basing treatments on specific mutations present in a given patient's tumor is a key feature of personalized cancer medicine. Assays can include focused molecular diagnostic assays with clearly defined therapeutic implications, namely, identifying known driver mutations, such as *EGFR*, anaplastic lymphoma kinase (*ALK*), and other genes in lung cancers; identifying human epidermal growth factor receptor 2 (HER2) overexpression in breast and gastroesophageal cancers; or evaluating rat sarcoma virus protein (*RAS*) status in colorectal cancers. In contrast to these focused approaches, individual patient tumor samples can be studied with NGS panels, which analyze up to several hundred known and often targetable cancer genes for genetic alterations. These panels identify rare driver mutations that suggest treatment with specific targeted agents may be clinically beneficial, even if these agents have not been previously evaluated in the tumor type. This trend toward tumor-agnostic therapies, which are based on molecular mutations rather than tissue of origin, is another advancement of precision medicine. Larger-scale sequencing, such as whole-exome sequencing or even whole-genome sequencing, is emerging to further inform and potentially guide therapies for individual patients. The high cost and extended turnaround time required for these approaches were previously prohibitive, but this is no longer the case. Although the complexity of data analysis remains a barrier, it is anticipated that an increasing number of patients with cancer will have their tumors analyzed with more comprehensive approaches in the future.

All these techniques are based on basic principles of molecular biology, which will be introduced/reviewed in subsequent subchapters. It is important to understand the underlying principles and caveats to be able to discuss molecular diagnoses in an informed manner to provide patients and their families with the best available evidence for shared decision-making.

BASIC PRINCIPLES OF MOLECULAR BIOLOGY

The human genome contains approximately 3 billion nucleotides partitioned among 23 chromosomes. Approximately 1% of the genome is composed of coding DNA, which contains the gene sequences that encode proteins. The other 99% is considered noncoding DNA, which contains instructions for the formation of specialized RNA molecules (eg, transfer RNA and ribosomal RNA), as well as structural (eg, centromeres, telomeres, and G-quadruplexes), regulatory (eg, promoters, enhancers, and silencers), and other elements (eg, transposons, retrotransposons, and interspersed nuclear elements). Most human cells contain a complete genomic copy of DNA, but there are exceptions. As examples, erythrocytes contain no genomic DNA, mature lymphocytes delete fragments of DNA within either immunoglobulin or T-cell receptor genes to generate antigen-recognition proteins, and megakaryocytes contain extra copies of the genome that result from the process of endoreduplication (ie, successive duplications of the genome without intermediary mitosis).

DNA is a macromolecule comprising nucleotides containing one of four bases (adenine [A], guanine [G], cytosine [C], or thymine [T]) plus a deoxyribose sugar and a phosphate group. Each nucleotide base is connected to a deoxyribose sugar, forming a nucleoside, and phosphodiester bonds between the sugar moieties form the DNA strand. The nucleosides of one DNA strand form hydrogen bonds with nucleosides on the complementary strand (C pairs with G, and A pairs with T) to create a DNA double-strand helix. When DNA is replicated, the strands separate, and each provides a template for an exact complement to be synthesized, thereby generating two identical helices, a process that occurs in normal and tumor cells alike.

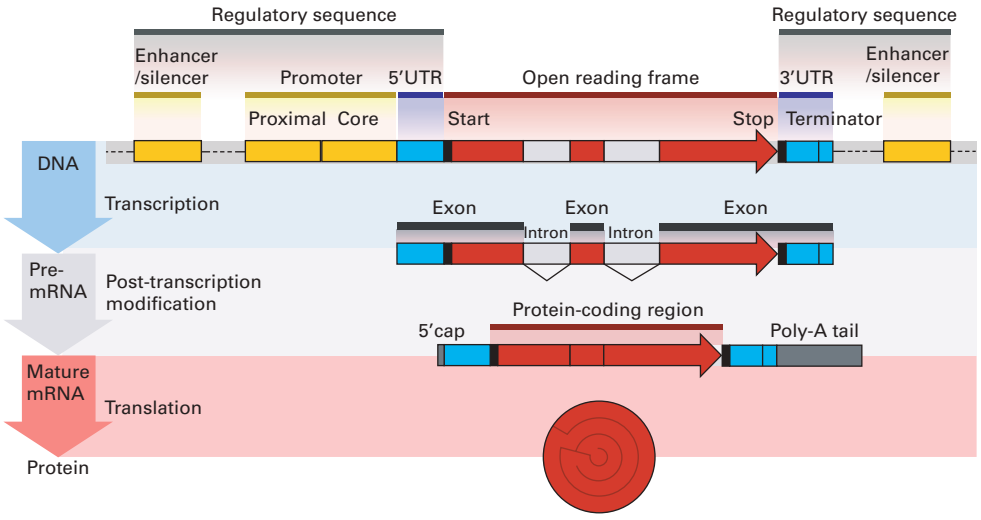
GENES AND GENE EXPRESSION

A gene is a DNA sequence that encodes a protein or functional RNA.[16] Gene expression refers to the process by which specific genetic sequences direct the synthesis of these gene products. This process is highly regulated, and individual cell types express only a subset of the full complement of genes. Specific gene expression programs fundamentally drive many biological processes, including growth and development, cellular differentiation, and neoplastic transformation.

Although protein-coding genes account for only a small portion of chromosomal DNA, they are regarded as the central determinants of cellular and organismal phenotypes. Most clinically relevant DNA mutations occur within such genes, and many targeted cancer therapies are directed against specific genetically encoded protein pathways (Fig. 2-2).

- The first step in protein synthesis is transcription of the DNA template into a linear RNA copy, known as messenger RNA (mRNA).
- Most protein-coding genes are arranged in segments, with coding elements called exons and noncoding elements called introns.
  - Additional noncoding DNA elements that dictate gene expression include regulatory elements, such as promoters (which direct the site of transcription initiation) and enhancers (which increase transcription).[17]
  - Regulatory elements are recognized by proteins, called transcription factors, which establish the timing and tissue-specific characteristics of gene expression. Many transcription factors bind directly to these regulatory elements and recruit additional regulatory proteins into the transcription complex.
  - Proteins that mediate the assembly of active transcription complexes by recruiting factors or facilitating chromatin changes that promote transcription are termed coactivators, and those that inhibit transcription are corepressors.[18]

Figure 2-2 Schematic Diagram of an Idealized Gene



Schematic diagram of an idealized gene, including promoter elements, an enhancer, and the transcribed region of the gene. Regulatory sequences control when and where the protein-coding region is expressed. Promoter and enhancer regions regulate the transcription of the gene into a pre-mRNA, which is modified to add a 5′ cap and poly-A tail and remove introns. The mRNA 5′ and 3′ UTRs regulate translation of the final protein product.
Abbreviations: mRNA, messenger RNA; UTR, untranslated region.
Reproduced under Creative Commons license. Source: Shafee T, Lowe R. Eukaryotic and prokaryotic gene structure. *WikiJournal Med*. 2017;4, figure 1. doi:10.15347/WJM/2017.002

Gene transcription first results in pre-mRNA, which contains both exons and introns. The introns are spliced out to generate a mature mRNA that contains a continuous coding sequence. Importantly, alternative splicing of pre-mRNAs can generate distinct mRNA molecules that include or exclude distinct sets of exons, effectively allowing a single gene to encode multiple related mRNAs that, in turn, translate to multiple protein products, termed isoforms. Another feature of mature mRNAs is that they comprise the 5′- and 3′-untranslated regions, which extend beyond the coding regions and regulate mRNA stability and translational efficiency.

After a mature mRNA is produced, the process of protein translation uses the mRNA sequence to guide the production of a protein. This process requires ribosomes, which are protein- and RNA-containing structures that bind mRNAs and read nucleotide triplets, termed codons, that specify which amino acids will be incorporated into a nascent polypeptide chain. Once a complete protein is produced, the amino acid sequence can be further modified by posttranslational processes, such as phosphorylation, acetylation, ubiquitination, or methylation. These dynamic and often reversible changes can control protein activity, stability, cellular localization, and multiprotein complexes.

Even with the completion of the Human Genome Project in 2003, the exact number of human protein-coding genes remains unclear. Currently, it is estimated that there are approximately 20,400 protein-coding genes; however, the total number of distinct human proteins is considerably greater. Genes can be alternatively spliced into distinct mRNAs to produce multiple protein

isoforms, and proteins can undergo posttranslational modification to produce multiple forms of proteins, called proteoforms. It is estimated that the full set of human proteins, known as the proteome, contains 250,000 to 1 million distinct proteoforms.

Protein-coding genes are often emphasized; however, there is another major class of genes termed noncoding RNAs. As their name suggests, these transcriptional units generate RNA sequences that do not code for proteins but have important cellular functions. These classically include ribosomal RNA and transfer RNA, which comprise key components of the translational machinery, as well as part of the spliceosome. Additional functional noncoding RNA units include miRNAs and long noncoding RNAs, both of which regulate gene expression and other cellular processes, in part by interacting with mRNA.

- miRNAs are short (21-23 nucleotides) RNA molecules encoded within longer primary RNA transcripts.
- More than 2,000 miRNA genes have been identified in humans, where they regulate diverse cellular processes, including differentiation, migration, proliferation, and apoptosis.[19]
- miRNAs decrease the expression of specific protein-coding genes through direct interaction with mRNA molecules with complementary sequences, which leads to degradation and/or modified translation of target mRNAs.[20,21]
- miRNA analyses have been developed as molecular tools in cancer diagnosis and prognosis.[22,23] It has long been hypothesized that miRNA signatures would serve as ideal biomarkers because of the stability of miRNA over time.[22,23]

Long noncoding RNAs are a second group of noncoding RNAs that affect many diverse cellular processes.[24]

- These RNAs are generally longer than 200 nucleotides, but they can vary in length.
- Long noncoding RNAs have the ability to repress gene expression through increased degradation of mRNAs; however, they have much more varied functions, including silencing transcription, modulating chromatin in time and space, altering mRNA splicing, regulating mRNA translation, and influencing posttranslational modifications of proteins.
- Several long noncoding RNAs are implicated in carcinogenesis in experimental models, including the following:
  - NKILA, which modulates breast cancer phenotype through altered protein phosphorylation;
  - MALAT1, which regulates mRNA splicing and may play a role in multiple cancers;
  - TERC, which influences telomere length to increase cell lifespan and is amplified in multiple cancer types[25]; and
  - One of the largest known long noncoding RNAs, the 17,000-nucleotide RNA expressed from the X-inactive specific transcript (*XIST*) gene, which serves to inactivate one X chromosome in female cells to ensure proper levels of expression from the single active X.[26]

EPIGENETIC GENE REGULATION

Epigenetic gene regulation, or epigenetics, refers to heritable processes that profoundly influence gene expression without changing the DNA nucleotide sequence. Epigenetic gene regulation occurs primarily through two processes: DNA methylation and histone modification.[27] DNA methylation occurs when DNA methyltransferases catalyze the addition of methyl groups onto CG dinucleotides in genomic DNA.[28] When CGs lie in gene promoters or other regulatory regions, methylation represses gene transcription. Distinct DNA methylation patterns can be seen in cells at different stages of development or between different cell types, suggesting that DNA methylation controls global gene transcription to define cell identity. Similarly, DNA methylation patterns are altered in various disease states, including cancer, where many tumor suppressor genes are silenced by promoter methylation. Prominent examples include the *MLH1* gene promoter, which is methylated in a variety of cancers, suppressing the expression of this DNA mismatch repair (MMR) enzyme, and the *CDKN2A* gene promoter, which is methylated in many tumor types, leading to decreased expression of the p16 tumor suppressor protein. Although some genes can be inactivated by either mutation or gene silencing, it is now understood that certain cancer-associated genes are inactivated only through genetic mutation, whereas others can also be inactivated through epigenetic gene silencing resulting from aberrant methylation. Thus, the study of methylation patterns in human cancer genomes has identified previously unknown tumor suppressor genes.

The second major type of epigenetic regulation results from modifications of highly abundant DNA-associated proteins known as histones.[29] Human DNA is packaged and condensed through association with histones and other nuclear proteins to form chromatin. Within a chromatin fiber, DNA is wrapped around octamers of eight histone proteins to form a nucleosome.[30] This not only compacts DNA sufficiently to allow it to fit within the cell nucleus but also adds another level of control over which regions of the genome are transcriptionally active or silent at any given time. Histones are modified covalently (eg, by acetylation, methylation, phosphorylation, and ubiquitylation), by changes in subunit composition (eg, replacement of core histones by specialized histones), and by repositioning. Each of these modifications renders DNA either more or less accessible to transcription by RNA polymerase. Histone methylation and acetylation are particularly important. Histone methylase and demethylase enzymes regulate methyl-, dimethyl-, or trimethylation of lysine residues; methylation on some sites facilitates transcription, whereas on others, it represses transcription. Histone acetylation is also regulated by opposing enzymes; acetylation is found in actively transcribed genes, whereas histone deacetylation correlates with repression.

Because of their influence on gene expression, the enzymes that catalyze epigenetic modifications are themselves important targets for cancer therapeutics. The hypomethylating agents 5-azacytidine and 5-aza-2′-deoxycytidine (decitabine) inhibit DNA methyltransferase enzymes, which leads to lower methylation of gene promoters. These drugs are used to treat myelodysplastic syndromes and other hematologic malignancies and are thought to function in part by reestablishing the expression of tumor suppressor genes repressed by methylation.[31] Histone deacetylase inhibitors, including vorinostat, panobinostat, and belinostat, constitute another example of epigenetic therapy.[32,33] These drugs have global effects on histone modification and can broadly alter gene expression to inhibit the growth of some cancers, including T-cell lymphoma and multiple myeloma. In addition to these global inhibitors, there has been progress in more selective inhibitors of specific methyltransferases. Tazemetostat is a specific inhibitor of EZH2 methyltransferase, which is approved for follicular lymphoma.[33] Tulmimetostat, a next-generation EZH2/1 inhibitor, received FDA fast-track designation for the treatment of patients with advanced, recurrent, or metastatic endometrial cancer[34] harboring *ARID1A* mutations. Other clinical trials are testing inhibitors of specific histone methyltransferases, such as DOT1L and KDM1A, which are upregulated in distinct cancer types.[31] These agents have so far been less active in solid tumors.

KEY POINTS

- Genes are functional units of DNA that control the production of RNAs and proteins.
- Cells express only a subset of the genes contained within their genomes. Protein-coding genes are transcribed into mRNA in a process that is controlled by regulatory DNA elements (eg, enhancers and promoters).
- Noncoding RNAs, including miRNAs and long noncoding RNAs, are important regulators of gene expression and are often deregulated in human cancers.
- Gene expression is also regulated by epigenetic modifications of DNA and histones. Such chromatin modifications, which include methylation and acetylation, play a major role in determining the timing and extent of gene expression.
- Enzymes that catalyze epigenetic modifications are potential targets for cancer therapeutics.

NUCLEIC ACID ANALYSIS AND DETECTION OF CANCER-ASSOCIATED MUTATIONS

DNA

DNA Polymorphisms Facilitate Genetic Analysis of Complex Diseases

Before the development of modern DNA amplification and sequencing techniques, the analysis of cancer genetics on a broad scale was largely limited to familial cancer syndromes. This research was painstaking and imprecise, but resulted in the identification of cancer genes in cancer-prone families. This work was facilitated by the study of genetic polymorphisms, which are DNA sequences that exhibit substantial variability in a population. Genome-wide maps of polymorphic markers were important tools in the analysis of genetic traits. Through linkage analysis of pedigrees in which family members did or did not develop early-onset cancer, the genetic polymorphisms that segregated with the cancer-development phenotype identified many hereditary cancer genes, including those involved in breast cancer (eg, *BRCA1* and *BRCA2*).

- DNA sequencing technologies are the predominant method for cataloguing single-base changes throughout the genome, termed single-nucleotide variations (SNVs; formerly single-nucleotide polymorphisms).
- SNVs are the most common polymorphisms and represent approximately 1% of the human genome.[35,36]
- Geneticists can now apply complex statistical methods of analysis to large populations of people to determine the associations of specific SNVs with specific phenotypes, including cancer.
- Experimental validation has confirmed hypotheses generated through genome-wide association studies (eg, common polymorphisms can affect cellular proliferation, gene transcription and silencing, and sensitivity to specific cancer therapeutics in vitro).
- Importantly, these polymorphisms are rarely found in the coding regions of the affected genes, but rather, they are more likely to be located in close proximity to the functional gene or mutation. Therefore, we mostly consider them to be indicators but not the causes of cancer risk.
- SNVs may also affect cancer therapy (eg, several inactive or less active variants of dihydopyrimidine dehydrogenase [DPD], the enzyme responsible for the turnover of fluoropyrimidines, a class of widely used chemotherapeutic drugs).[37] The presence of these variants may result in life-threatening toxicities in such patients. The FDA has issued the requirement to test for DPD heterozygosity and homozygosity in October 2025, and an amendment in the capecitabine and 5-fluorouracil prescribing information.
- Another relatively common type of polymorphism occurs in the microsatellite regions of DNA, which are tandem repeats of two to six nucleotides that occur in thousands of locations in the genome.[38] One common type of microsatellite is composed of cytosine and adenine (CA) dinucleotide repeats, mainly located near the end of the chromosome. These regions of the genome are susceptible to imperfect DNA replication, thus leading to a higher mutation rate, creating genetic variation

among individuals and allowing for facile DNA genotyping. These microsatellite polymorphisms allow for the fingerprinting of DNA, and the shorter ones have long been used in forensic examinations, because they can distinguish DNA from individuals with simple analyses. Under ordinary circumstances, these satellite repeats differ among individuals but are uniform in all somatic cells. Somatic variations in microsatellite regions can occur in tumors. The primary cause of microsatellite variation is an error in DNA MMR.

- This loss of functional MMR enzymes is a result of either mutation or epigenetic silencing of MLH1, MSH2, MSH6, and PMS2.
- These MMR enzymes that normally suppress DNA replication errors are mutated in some familial cancers, such as hereditary non-polyposis colon cancer/Lynch syndrome.
- Loss of a second functional MMR gene, occurring most commonly in gastrointestinal and endometrial cancers, increases variation in altered microsatellite sequences occurring in tumors.
  - This trait, termed MSI, serves as a harbinger of widespread tumor-specific point mutations throughout other regions of the genome.
  - MSI is highly suggestive of Lynch syndrome, which should prompt genetic counseling; however, it can occasionally occur spontaneously in tumors without a heritable germline mutation.[39]
  - In addition to its value in identifying familial cancer syndromes, MMR deficiency (dMMR)/MSI also predicts the likelihood of response to immune checkpoint inhibitors in diverse cancer types.
  - MMR/MSI is thought to make tumors more immunogenic, because the altered protein products encoded by the highly mutated cancer genome generate novel antigens (neoantigens) that are presented to the immune system on major histocompatibility complex class I.[39]

Polymerase Chain Reaction

Accurate and high-throughput DNA analysis is generally dependent on error-free amplification of partial or whole genomes. The development of the polymerase chain reaction (PCR) was a watershed technological advance because it made the synthesis of large quantities of specific DNA sequence fragments from minuscule quantities of template a routine procedure.[40] PCR was essential for producing the draft sequence of the human genome; amplified copies of countless small fragments of the human genome were cloned, sequenced, and aligned to one another. A wide variety of PCR-based techniques have revolutionized virtually all methods used to manipulate, detect, and analyze nucleic acids.

Next-Generation DNA and RNA Sequencing

NGS technologies have increased the speed and dramatically reduced the cost of DNA and RNA sequencing. NGS methods apply massively parallel sequencing to obtain millions of DNA sequence reads simultaneously.[41] Although technology platforms vary, most read relatively short DNA sequences, typically measuring 100 to 200 bp. The sequence reads are highly specific, allowing millions to be uniquely mapped to specific genes or regions of the human genome, even when they contain mutations or small sequencing errors. NGS detects mutations, alterations, and structural changes in the genome. DNA translocations can also be detected, although they generally require a 100- to 200-bp read to cross the boundary of the translocation, which is difficult because the boundary can differ greatly among cancers. As a complementary approach, assays have been developed that evaluate mRNA sequences, which can more efficiently detect these fusion boundaries.

- One challenge with NGS is that tumors are heterogeneous and composed of both cancer and non-cancer cells, whereas most of the genetic alterations are somatic (ie, they are found only in the cancer cells).
- This issue can be overcome by sequencing at a greater depth, which is the measure of the average number of reads that map to any one region of the genome.
- Sufficient depth of coverage allows for mutation detection in at least some of the reads. The fraction of reads that have the mutation is often reported as the variant allele frequency or simply allele frequency.

The cost and speed of NGS are rapidly improving. For example, in 2008, two human genome sequences could be completed in a few months at a cost of approximately $1 million per genome. By 2019, rapid human genome sequencing was available, with costs in the range of $1,000 and timeframes of less than 1 week. Rapid and low-cost NGS has enormous implications for understanding cancer biology, prognosis, diagnosis, and treatment, enabling individualized treatments based on genome-scale sequence data (ie, precision oncology).[42] In recent years, NGS has given way to comprehensive genomic profiling approaches for testing of clinical tumor specimens for treatment decision-making. Therefore, targeted resequencing approaches that cover actionable somatic mutations are used widely, as is whole-exome sequencing (ie, the totality of expressed genes).

NGS also allows epigenetic studies on a genome-wide scale. For example, chromatin immunoprecipitation (ChIP) followed by sequencing is a method that uses antibodies that recognize specific modifications (eg, histone methylation) to isolate fragments of DNA associated with the modified histone, and NGS is then applied to identify all DNA regions that contain the modification.[43] This strategy has produced highly detailed maps of the epigenetic markers that regulate gene expression. ChIP is used mainly

in basic research for the identification of sites that are hyper- or hypomethylated. Patients with diseases with these features are amenable to epigenetic drugs like azacytidine.[43]

Similar approaches have shown that CG methylation is a highly dynamic process that changes greatly during cellular differentiation and that distinct CG methylation patterns can distinguish between normal and cancerous tissues.[44] The Encyclopedia of DNA Elements (ENCODE) project has used NGS approaches to catalog transcription factor–binding sites as well as chromatin and histone modifications across the human genome.[45] These technologies are expanding our understanding of how gene expression is regulated in health and disease.

RNA

Reverse Transcription and Real-Time PCR

PCR-based methods used for RNA analysis first use reverse transcription, a viral enzyme that converts mRNA to a complementary strand of DNA, called complementary DNA (cDNA). When followed by PCR, the DNA is amplified into many identical double-stranded copies, using primers, which are short synthetic fragments of DNA specific to the sequence of interest. This general strategy is termed reverse transcription PCR to reflect both the reverse transcription and PCR steps.

- Reverse transcription PCR can be used to amplify, detect, or sequence RNA transcripts of interest.
- Quantitative reverse transcription PCR methods are used to precisely measure RNA abundance in cells and tissues.
- Real-time PCR assays use fluorescent dyes to measure the amount of PCR product synthesized in each amplification cycle in real time, as PCR progresses.[46]
- One approved diagnostic test uses real-time PCR to assess the mRNA levels (ie, expression) of 21 genes to predict the benefit of adjuvant chemotherapy in women with early-stage ER-positive breast cancer.[47]

Digital Droplet PCR

Although PCR detects small quantities of specific DNA sequences through amplification, it typically cannot detect specific low-abundance mutations within those sequences, such as one in 10,000 sequence reads. To overcome this limitation, digital droplet PCR uses water-in-oil droplets, which partition the DNA into thousands of droplets, each of which is PCR amplified separately. After amplification, specific mutations are detected by the TaqMan fluorescent assay. In this manner, rare mutations can be detected and quantified in samples, determined by their presence in a limited fraction of droplets. Examples of this would be the use of circulating DNA to detect mutations of *ALK, PIK3CA*, or *ESR1*. Although modern NGS methods can now directly sequence mutations at a high depth, there are tradeoffs in efficiency that still favor digital droplet PCR in specific circumstances, such as ultrasensitive detection (eg, in minimal residual disease), routinely applied for hematologic malignancies, and quantification of specific point mutations (eg, for therapeutic monitoring of resistance development toward a particular drug).

Microarrays, NGS, and Global Analyses of Transcription

Some RNA analyses measure the expression of thousands of genes simultaneously, and these typically use microarray chips or, more commonly today, NGS (Fig. 2-3).

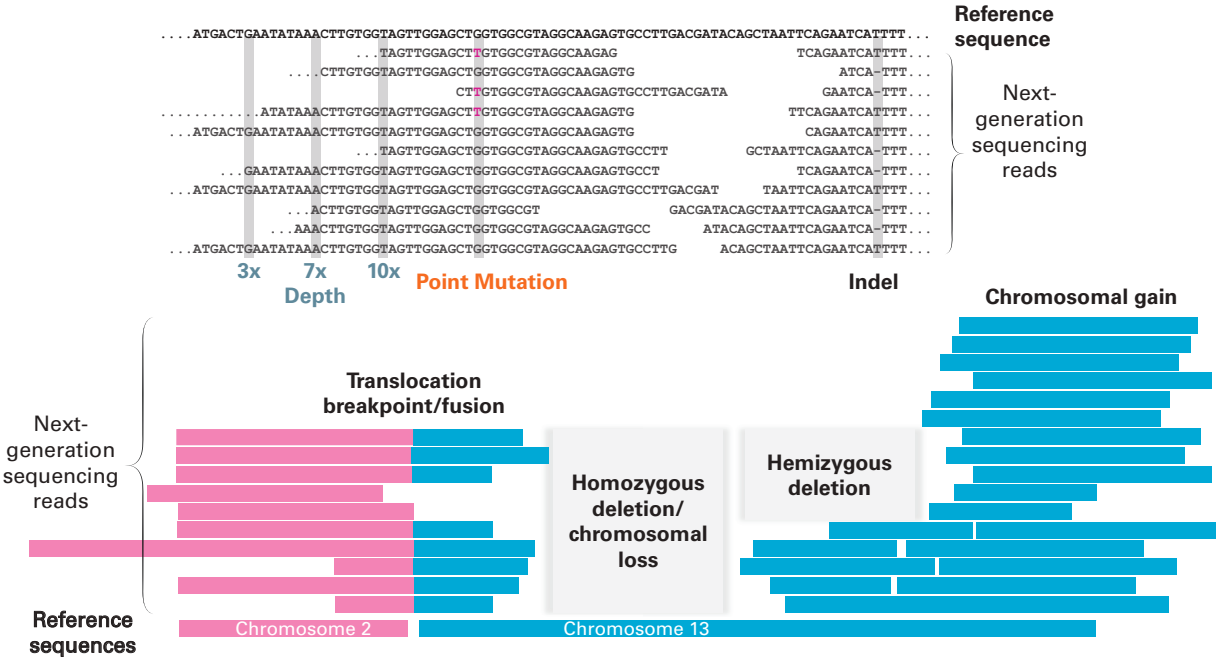
- Microarray chips are small slides on which either oligonucleotides or cDNA probes are spotted in a defined array. By hybridizing cDNA from different conditions onto the oligonucleotides on the chip, each labeled with a different fluorescent dye, it is possible to uncover relative differences in gene expression.
- NGS has largely supplanted array technologies for gene expression analyses, because reads can be mapped to specific gene mRNAs, providing quantitative measures of gene expression.
- Whole-transcriptome sequencing overcomes many of the technical limitations of microarrays by taking an untargeted approach to sequencing that quantifies all transcripts within a given tumor sample.
- RNA sequencing can now be used routinely in some assays for cancer diagnosis and treatment, including separating large-cell lymphomas into high- and low-risk groups and predicting outcomes and therapeutic benefits for women with breast cancer.

Single-cell genomics is now providing crucial insights into tumor heterogeneity and the interactions between tumor cells and stroma. Several technological advances have enabled the application of sequencing to single cells.

- Improved NGS technologies: sequencers such as NovaSeq can provide 20 billion nucleic acid reads of up to 120 bp per run.
- Improved reagents for library preparation: these effectively amplify DNA from single cells, whether genomic DNA or cDNA reverse transcribed from RNA extracted from single cells.
- Cells are barcoded with unique synthesized DNA sequences ligated to each DNA or cDNA before amplification.
- DNAs from all cells are pooled to go on a large sequencing run, and their relationship with each cell is determined by sequencing.

- Unique molecular identifiers are an extension of this concept that overcomes unpredictable biases occurring in nucleic acid amplifications.
- A distinct molecular identifier unique to each DNA molecule is included in the ligated DNA sequence. If a given molecule of DNA or cDNA is amplified in a biased fashion, the repeated unique molecular identifier will allow it to be counted only once.
- Improved microfluidic platforms, such as Drop-seq and the 10× microfluidics platform, allow single cells to be efficiently isolated for nucleic acid extraction, ligation, cDNA preparation, and amplification.
- Emerging techniques include spatial barcoding to preserve spatial relationships through additional barcodes.[48,49]

Figure 2-3 Types of Mutations Discovered by Next-Generation Genomic Sequencing



The upper diagram illustrates the alignment of different sequence reads created during NGS. Sequences are aligned to cover the reference genome. Sequencing depth describes the number of sequences produced, identified, and aligned around a specific region. The point mutation example shows the *KRAS* complementary DNA sequence as a reference and a c.34G > T mutation that results in the G12C variant of *KRAS*. Note that the mutation is not present in all reads of this analysis. Less common variants require a higher number of reads (ie, greater depth of sequencing). The small deletion (indel) has been inserted for illustration purposes only. The lower diagram presents a broader perspective of NGS results. It illustrates the translocation t(2;13) of *PAX3* on chromosome 2 with *FKHR* on chromosome 13, a translocation frequently found in alveolar rhabdomyosarcoma. Also shown are examples of a homozygous or hemizygous loss of chromosome 13, which occurs frequently in retinoblastoma, breast cancer, and prostate cancer, among others. In addition, chromosomal gain may occur in other settings, such as metastatic colorectal cancer.
Abbreviation: NGS, next-generation sequencing.
Created for ASCO. Copyright © 2026 by American Society of Clinical Oncology.

Single-cell methods are being used to generate comprehensive tumor atlases characterizing the genomic, epigenetic, transcriptomic, and spatial relationships between individual cells within tumors.[50,51] These analyses generate a truly staggering amount of data, with a goal, for example, of providing unprecedented insights into how tumors recruit or evade the immune system, a problem particularly suited for single-cell analyses. Single-cell NGS analyses have been proposed to improve the prediction of which patients may benefit from immunotherapy.[52] These efforts transcend oncology and include atlases such as the Human Biomolecular Atlas Program (HuBMAP) and the Cellular Senescence Program (SenNet) at the National Institutes of Health, which seek to provide an open and global map of human cells.

Research Tools for Modulating Gene Expression and Engineering Genomes: Small Interfering RNAs and CRISPR/Cas9

Knowledge of miRNA function has enabled the development of simple yet powerful laboratory techniques for the inhibition of the expression of virtually any gene in the cell. These techniques, termed RNA interference, use synthetic double-stranded

miRNAs known as small interfering RNAs to efficiently catalyze the degradation of their cognate mRNAs in vitro. Although genes can be inhibited individually, RNA interference is readily scalable such that genome-wide small interfering RNA screens can be used to dissect complex biological pathways to ascertain gene function globally and identify drug targets in cancer cells.[53,54] RNA interference is also making its way to the clinic, because small interfering RNAs can serve as drugs to inhibit gene function. The first RNA interference–based therapy was FDA-approved agent in 2018 for complications associated with a rare hereditary disease, transthyretin amyloidosis. Many RNA interference–based cancer therapies are currently being tested in clinical trials,[55] although applications in oncology are limited.

The recent development of simple and robust genome-editing technologies using the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) system has revolutionized science. Cas9 was discovered as a component of the adaptive immune system in bacteria. There are two components to this system. Cas9 is a protein that picks up structured guide RNA molecules to identify and bind specific cognate DNA sequences and then destroys them by cleavage catalyzed by a nuclease domain. CRISPR is an adaptive part of the bacterial genome that constitutes a memory of all bacterial viruses (phages) previously encountered. CRISPR produces guide RNAs that target Cas9 to any of the previously encountered phages. This system can be readily applied to elicit double-strand breaks at a specific location in any genome simply by designing a guide RNA targeting the desired region; this advance led to the 2020 Nobel Prize in Chemistry being awarded to Emmanuelle Charpentier and Jennifer Doudna.

- CRISPR/Cas9 is routinely used in the laboratory for genome engineering to delete or knock out a gene of interest by creating specifically directed double-stranded DNA breaks.
- Alternatively, specific DNA edits can be generated to create or repair mutations by introducing separate DNA fragments that serve as repair templates.
- CRISPR/Cas9 has supplanted RNA interference for whole-genome screens, because synthetic RNA libraries are now available targeting all protein-encoding genes.[56] Key uses of this technology include the following:
  - Discovery of *PTPN2* as a gene involved in immune evasion.
  - Functional characterization of all *BRCA1* variants through saturation genome editing, creating virtually all possible mutations, largely eliminating the historical need to classify variants of unknown significance on this gene.[57]
  - CRISPR/Cas9 can also be used for lineage tracing; one study used this system in mice to continuously generate genetic marks over time, from which the ancestral relationships of every cell in a tumor and metastases could be determined.[58]
  - Ongoing clinical trials are using this technology to genetically reprogram T cells to fight cancer; revert disease-causing mutations in specific diseases, such as sickle cell anemia and muscular dystrophy; and knock out dominant oncogenes, such as human papillomavirus (HPV) *E6*/*E7* in cervical cancer.

However, CRISPR/Cas9 technology has some limitations. Unanticipated off-target effects can occur, particularly when an undesired region of the genome has a sequence similar to that of the target site.[59] In addition, Cas9 screens are more readily useful for loss-of-function screens, where they induce gene deletions rather than gene activations. This has been partly overcome by modifying Cas9 to remove the nuclease domain and replace it with other functions that can increase gene expression or even edit DNA sequences through deamination.[60] In this manner, the CRISPR/Cas9 system can be adapted for virtually any desired enzymatic activity at any particular site in the genome.

KEY POINTS

- NGS methods use computational analysis of short nucleic acid sequence reads aligned with reference genome sequence information.
- NGS can define full mutational landscapes of individual tumor samples, including alterations in DNA sequence, as well as structural changes and epigenetic changes.
- Single-cell NGS provides insights into tumor heterogeneity and the complex cellular interactions within the tumor immune microenvironment.
- Analyses of mRNA by techniques such as reverse transcription PCR or RNA sequencing measure the expression of specific genes in tumor samples. This provides insights into cancer biology, as well as important diagnostic and prognostic information.
- Whole-genome genetic screens using small interfering RNA or CRISPR/Cas9 technologies can identify genes that promote or suppress cancer or mediate resistance to chemotherapy.

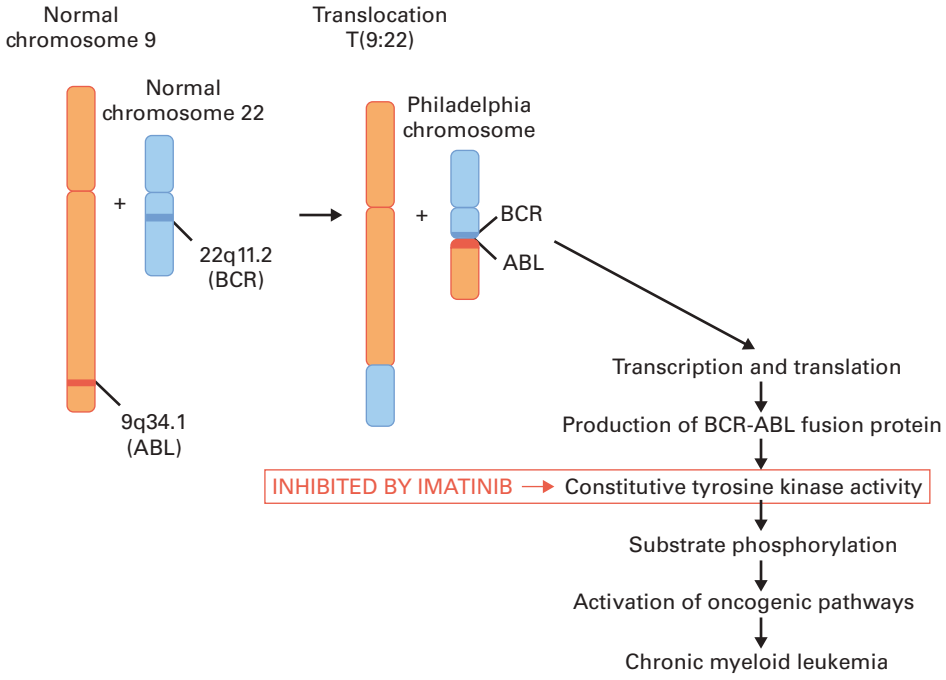
CHROMOSOMAL ANALYSIS

Cytogenetics is the study of chromosomal changes in cells and tissues. Cancer cells often exhibit chromosomal abnormalities that are pathognomonic for specific diseases. Karyotype analyses examine the entire chromosomal complement of a cell or person. Classically, chromosomes are identified from metaphase spreads based on banding patterns and morphology. This process

requires culturing live cells in the laboratory under conditions in which a sufficient number enter mitosis, where they can be captured in metaphase; therefore, this is more suitable for bone marrow specimens and proliferative hematologic malignancies.

Classic karyotyping is often augmented with newer techniques that are more sensitive and can reliably identify specific chromosomes or genetic loci (places on a chromosome that encode a gene). One example is fluorescence in situ hybridization (FISH), which uses fluorescently labeled synthetic nucleic acid probes of prespecified sequences that are incubated with fixed cells and can detect DNA, whether the cell is in interphase (with intact nuclei) or metaphase (with condensed chromosomes). The probes hybridize to their cDNA sequences in the cell, which allows visual inspection of the structure of specific genes using a fluorescence microscope. Chromosome- and gene-specific probes are used to determine the copy number of specific oncogenes. For example, amplification of the *HER2* gene is detected by a high ratio of FISH probe for the HER2 locus (eg, red color) relative to a control region on chromosome 17 (eg, green color); such amplification predicts sensitivity to anti-HER2 therapies. Another common FISH technique uses probes that detect gene fusions (fusion probes) and chromosomal translocations (break-apart probes). For example, the *BCR::ABL* fusion is diagnostic of chronic myeloid leukemia (CML) and is sometimes found in acute leukemias (Fig. 2-4). Similarly, the *EML4::ALK* translocation defines a subgroup of NSCLCs. The identification of these translocations is clinically relevant because it confers sensitivity to tyrosine kinase inhibitors (TKIs). The ability of FISH methods to identify rare cells with abnormal karyotypes makes it useful for detecting residual disease when malignant cells harbor a cytogenetic marker and in diagnostics and treatment stratification (eg, sarcomas with translocations *EWSR1::CREB* [*ATF1, CREB1*], *EWSR1/FUS::NFATC1/2, EWSR1::WT1, ETV6::NTRK3, YAP1::MAML2*, or *EWSR1/FUS::CREB3L1/CREB3L2* or the prominent *MDM2* amplification).[61]

Figure 2-4 Translocation Leading to the Ph Chromosome and Role of BCR::ABL in the Pathogenesis of CML



The Ph chromosome is a foreshortened chromosome 22 resulting from an exchange between the long arms of chromosomes 9 and 22. This leads to the production of a BCR::ABL fusion protein that has constitutive kinase activity and promotes the development of CML. The tyrosine kinase inhibitor imatinib inhibits this constitutive kinase activity and can lead to long-term control of CML.
Abbreviations: CML, chronic myeloid leukemia; Ph, Philadelphia.
Reproduced under Creative Commons license. Source: Schematic of the Philadelphia chromosome. Wikimedia. Published December 8, 2014. Updated January 22, 2019. Accessed April 09, 2025. https://commons.wikimedia.org/wiki/File:Schematic_of_the_Philadelphia_Chromosome.svg

KEY POINTS

- Karyotyping reveals gross chromosomal structural anomalies in tumor cells, such as translocations and chromosomal deletions.
- FISH techniques detect structural alterations, such as translocations, deletions, fusions, and copy-number variations, directly inside cancer cells.
- Genome alterations identified by FISH are clinically relevant because they can predict sensitivity to molecularly targeted therapies and can be used to detect residual disease in hematologic cancers.

PROTEIN ANALYSIS

As noted, the human genome has approximately 20,400 protein-coding genes yet can generate more than 250,000 distinct proteoforms (protein forms), including exon splicing variants and additional posttranslational modifications, such as phosphorylation, methylation, acetylation, ubiquitination, and sumoylation, among others. Understanding protein production, regulation, and function is integral to understanding cancer. Low-to-intermediate-throughput antibody-based assays for protein detection have been commonly used for decades. Newer methods to study large sets of proteins simultaneously, collectively termed proteomics, are powerful tools to enhance the understanding of cancer and offer the potential for diagnostics that might advance cancer care beyond that achieved with NGS.

ANTIBODY-BASED METHODS

Western Blot and ELISA

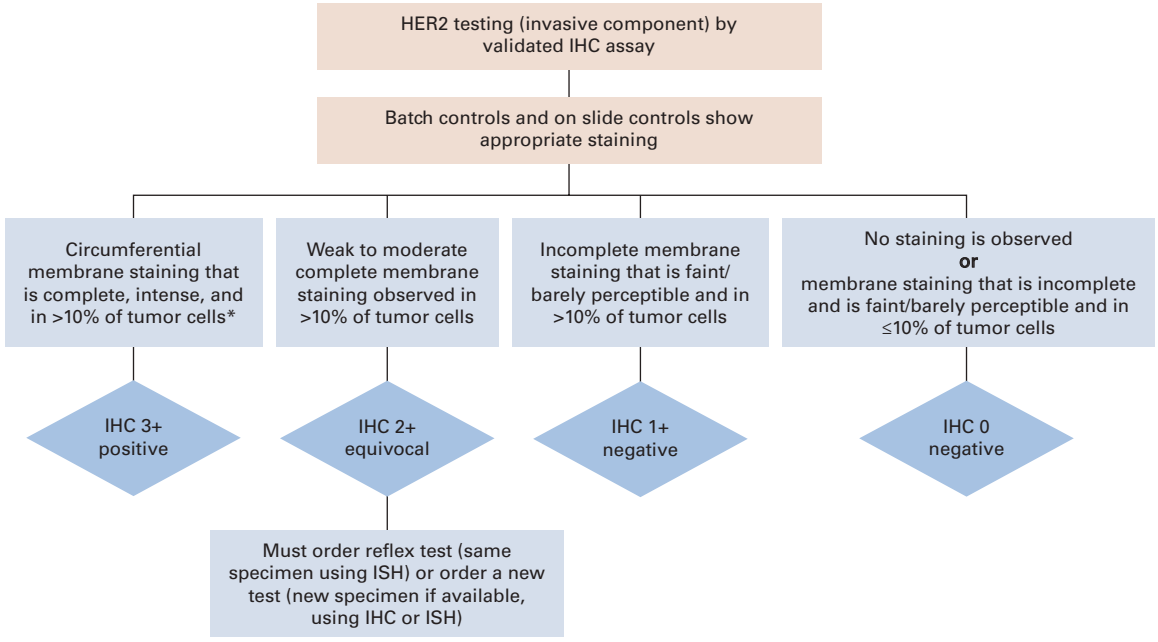
- A common laboratory technique for protein analysis is called Western blotting (or immunoblotting), where proteins are solubilized, denatured, and separated by size using gel electrophoresis.
  - After transferring to membranes, the membranes are exposed to detection probes, most commonly antibodies specific to the proteins of interest in the sample.
- Enzyme-linked immunosorbent assay (ELISA) is an analogous technique that allows more precise protein quantification.
  - In ELISA, fixed whole cells or solutions of solubilized proteins from tissue or blood specimens are bound to 96-well plates; specific proteins are then detected using antibodies that have been optimized for sensitivity and specificity.
  - A standard curve can be generated by plating purified protein at various concentrations, thereby allowing quantification of protein levels in test samples.
  - Novel multiplex ELISA technologies measure multiple proteins at one time, allowing for the development of multivariate protein signatures.
- Together, these techniques can detect protein abundance, posttranslational modifications (eg, phosphorylation), and changes in protein size (eg, isoforms of different length).[62]
  - The main limitation of Western blots is the amount of input material, because the target protein cannot be amplified like a nucleic acid. Another limitation is the availability of a specific antibody for the detection of small changes within the protein.

Immunohistochemistry

There are many uses of immunohistochemistry (IHC), especially in tumor subtyping (eg, breast cancer, sarcoma, cancer of unknown primary), prognostic biomarkers (prostate cancer), predictive biomarkers (breast cancer, gastric cancer), diagnosis (lymphoma), detection of molecular alterations, and hormone receptors (prostate cancer, breast cancer; Fig. 2-5).

- Pathology laboratories routinely use antibody-based IHC methods to detect the expression of specific proteins in tumor cells.
  - IHC can be used as a diagnostic tool to define the origins of poorly differentiated cancers or determine squamous cell carcinoma or adenocarcinoma differentiation in lung cancers.
  - IHC is frequently used to subclassify human tumors to refine prognosis and determine treatment.
  - p16 overexpression is a marker for HPV-associated oropharyngeal cancers, which have a more favorable prognosis compared with non-HPV-associated cancers.[63,64]
- HER2 overexpression can be detected by IHC, and this overexpression has both prognostic and therapeutic significance in a subset of breast, gastroesophageal, and other cancers, because these cancers frequently respond to anti-HER2 therapies.[65]
- So far, prognostication and identification for HER2-targeted therapy with anti-HER2 antibodies are limited to cases of strong circumferential membrane staining with IHC alone or a circumferential staining in more than 10% of the cells by IHC, together with a shown amplification as demonstrated by FISH.[66] Amplification of the HER2 locus alone, without detectable overexpression of HER2 at the protein level, does not qualify a patient for anti-HER2 therapy. Despite the positive outcome of the DESTINY-Breast04 trial, further distinction of IHC staining positivity has not been recommended by ASCO in collaboration with the College of American Pathologists (CAP).
- IHC for the detection of MMR proteins has long been used to identify cancers associated with Lynch syndrome, but has now gained much broader use, because clinical data show that dMMR predicts sensitivity to immunotherapy across diverse tumor types.[67]
- IHC largely depends on the preservation method, along with a validated primary antibody. Positive and negative controls are essential, as outlined by CAP.

Figure 2-5 Algorithm for Evaluation of HER2 Protein Expression by IHC Assay of the Invasive Component of a Breast Cancer Specimen



Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
*Readily appreciated using a low-power objective and observed within a homogeneous and contiguous invasive cell population.
Reprinted from Wolff AC, Somerfield MR, Dowsett M, et al. Human epidermal growth factor receptor 2 testing in breast cancer: ASCO–College of American Pathologists guideline update. *J Clin Oncol*. 2023;41(22):3867-3872. doi:10.1200/jco.22.02864
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Flow Cytometry

- Flow cytometry is another important diagnostic technique that can detect multiple proteins on the cell surface.
- Flow cytometry has high sensitivity and throughput and can quantify proteins in individual cells, allowing for the detection of small numbers of tumor cells, such as residual leukemia in normal bone marrow.
- Living or fixed cells are stained with fluorescently labeled antibodies that attach to specific cell-surface proteins. As the cells are applied to the flow cytometer, the fluorescent dyes are excited by a laser with intensity proportional to protein abundance.
- This process, known as immunophenotyping, can classify leukemias and lymphomas based on their cell-surface proteins.
- Flow cytometry can determine eligibility for the rapidly expanding array of monoclonal antibody-based therapies and chimeric antigen receptor T cells, including those targeting CD19 and CD20 (for lymphoma and leukemia), CD30 (for Hodgkin and other lymphomas), CD33 (for acute leukemias), and CD38 (for multiple myeloma).

One limitation of flow cytometry is that the existing fluorescent dyes and lasers are generally limited in the number of proteins that can be simultaneously detected. To extend this, new flow cytometric approaches have been developed to use other methods of detection distinct from fluorescence. One newer technique, known as CyTOF, quantitatively measures up to 100 proteins across thousands of cells, using antibodies each labeled with a distinct mixture of heavy metals that is detected by mass spectrometry (MS).[68] CyTOF is now providing unprecedented high-dimensional information about the many proteoforms detected both in the circulation and in the tumor.

MS-BASED PROTEOMICS

Analogous to the large-scale genomic analyses of DNA sequence or RNA expression, MS is a high-throughput technology that can analyze thousands of proteins simultaneously. MS forms the core of modern proteomics and is used in combination with bioinformatics to quantify and identify the large numbers of proteins present in complex biological samples.[69] These methods are informed by the genome-wide sequencing that allowed the construction of the comprehensive databases used to identify the peptides analyzed by MS. In addition, MS can interrogate protein modifications, such as protein phosphorylation and ubiquitylation, on a large scale.

- MS analysis of tumor samples or serum from patients with cancer can be used to generate proteomic signatures that may influence the selection of therapy.[70]
- Proteomic research involves early cancer detection based on defining protein signatures indicative of early-stage cancers in tissues or peripheral blood.[71]
- Metabolomics, in which MS is used to measure hundreds of cellular metabolites, provides clues as to how metabolic changes affect cancer development and survival, potentially allowing for the development of anticancer therapies.[72]
- MS is most reliable in detecting high-abundance proteins, posttranslational modifications, and cellular metabolites.
- One limitation of MS is that there are no methods to amplify signals comparable to PCR amplification of DNA, affecting the ability to detect small quantities of protein in the sample.

Traditional MS detection of protein involves fragmentation using enzymes such as trypsin to obtain small fragments suitable for MS. The various protein isoforms, truncations, and modifications (eg, methylation, phosphorylation, and acetylation) can then be detected, and the protein forms can be inferred, in what is now termed a bottom-up approach. However, this classic bottom-up approach disallows relating these modifications across a single protein molecule. For example, it is possible that two modifications are present on opposite ends of the protein but are mutually exclusive in a single protein molecule, which could not be detected. To overcome this, top-down proteomics is now becoming available to characterize proteins without trypsin fragmentation. Top-down proteomics can reveal which permutations of modifications exist on each protein molecule; this approach can thereby reveal the many unique proteoforms associated with a given gene.[68]

AFFINITY-BASED HIGH-THROUGHPUT PROTEOMIC APPROACHES

Novel high-throughput proteomic platforms that can measure thousands of proteins have been developed and can better bridge the gap between the proteome and disease. In the past, the gold standard for the detection of growth factors and cytokines in blood was the use of standard ELISAs; however, high-throughput proteomic approaches offer an attractive alternative approach for protein analyses. Platforms such as Olink and SomaLogic allow for the measurement of multiple analytes simultaneously from a single sample. Olink technology is similar to ELISA-based assays in that it uses distinct antibody pairs. However, the system integrates the use of DNA reporter sequences on the antibody pairs, allowing for amplification of the signal via real-time PCR. These additional DNA reporter sequences limit the cross-reactivity of the antibodies and maintain a high degree of sensitivity and specificity. SomaLogic is a different technology that provides high-content protein information. This platform uses aptamers, short synthetic peptide sequences, instead of antibodies for binding to the selected target protein. By modulating the aptamer, key components such as reproducibility, specificity, and sensitivity can be optimized, providing the ability to assess thousands of proteins in a single assay.

KEY POINTS

- Protein analyses reveal protein abundance, as well as functional modifications, such as phosphorylation and acetylation.
- Antibody-based protein detection techniques, such as Western blotting, ELISA, IHC, and flow cytometry, are used in a wide variety of clinical settings, including immunophenotyping for cancer diagnosis and classification, detection of minimal residual disease, and selection of therapy.
- Novel high-throughput protein analyses allow for large numbers of proteins to be analyzed in highly multiplexed fashions.
- MS-based proteomics allows for large-scale analyses of protein expression and modifications in tumor tissues.

ONCOGENES AND TUMOR SUPPRESSORS: ACCELERATORS AND BRAKES ON THE ROAD TO CANCER

Transformation of a normal cell into a malignant cell requires mutations or deletions of genes, termed oncogenes and tumor suppressor genes.[73] To date, several hundred human genes have been implicated as proto-oncogenes, which are genes that have the potential to be converted into oncogenes. Once converted, oncogenes carry dominant gain-of-function mutations (cells with a mutated protein encoded by the oncogene gain a new function, such as evasion of apoptosis), whereas tumor suppressor genes carry recessive mutations that sustain loss of function (tumor suppressor genes cause cancer when they are inactivated by a mutation). Studying oncogene and tumor suppressor gene functions and the processes they control is integral to understanding cancer biology and, increasingly, cancer therapy.

IDENTIFICATION OF ACTIVATED DOMINANT ONCOGENES

Numerous mechanisms, including gene translocations, amplifications, and point mutations, can activate oncogenes. These different types of alterations lead to distinct functional outcomes and often provide important diagnostic and prognostic information.

Chromosomal Translocations and Gene Fusions

Cancers often contain recurrent chromosomal translocations; this is particularly true of many hematologic malignancies, which are characterized by chromosomal translocations that involve immunoglobulin and T-cell receptor genes.[74] Specific translocations have important diagnostic and prognostic implications, serve as molecular markers for the detection of residual disease, and are increasingly recognized as targets for therapeutic intervention. The regions of DNA commonly involved in translocations are termed breakpoints, and they often contain proto-oncogenes that are activated by DNA rearrangement. Although some translocations are evident using conventional cytogenetics or FISH, most clinically relevant translocations in solid tumors have been discovered using NGS technologies, particularly those that cause gene fusion.[75]

Chromosomal translocations can activate proto-oncogenes in two general ways: gene fusion or dysregulated expression without fusion.[76] The more common gene fusion occurs when the translocation joins genes normally separated on the same or different chromosomes into a single translational reading frame, resulting in the production of a novel protein partly encoded by each of the two fused genes. Fusion proteins often involve transcription factors or tyrosine kinases and have biologic activities that differ from those of the parental proto-oncogene. Indeed, several translocations are highly relevant to cancer biology and therapy.

- In hematologic cancers, the *BCR::ABL* fusion that results from the reciprocal exchange of DNA between chromosomes 9 and 22 is known as the Philadelphia chromosome. The resultant gene produces a hybrid mRNA that codes for the BCR::ABL oncoprotein, which constitutively activates the tyrosine kinase activity normally associated with the c-ABL protein.
- In Ewing sarcoma, translocations fuse the *EWS* gene on chromosome 22 to the *FLI1* gene on chromosome 11, and this creates a transcription factor containing a DNA-binding domain derived from FLI1 and a transcriptional activation domain from EWS.[77]
- Alveolar rhabdomyosarcomas also contain pathognomonic translocations, which fuse the *PAX3* or *PAX7* and *FOXO1* transcription factor genes. The presence of these fusions may predict unfavorable clinical outcomes.[78]
- In prostate cancer, translocations that join the androgen-responsive *TMPRSS2* gene with two *ETS* transcription factor genes, *ETV1* and *ERG*, occur frequently and result in abnormal ETS expression driven by the androgen-responsive regulatory elements in the *TMPRSS2* gene.[79]
- In cholangiocarcinoma, *FGFR2* fusions to various upstream partners are commonly found (10%-20%). Tumors with these fusions respond to pemigatinib (overall response rate [ORR] with pemigatinib was 36% in the study that led to FDA approval).[80]
- *NTRK1-3* fusions refer to a highly related group of gene fusions that occur infrequently but can be found across many tumor types. Tumors harboring these fusions are highly responsive (up to 63% ORR) to the TRK inhibitors larotrectinib and entrectinib.[81]
- *RET* fusions to various upstream partners are found in a small fraction of NSCLCs. Tumors harboring these fusions are highly responsive (up to 84% ORR) to selpercatinib.[82]
- Neuregulin 1 (NRG1) fusions with HER3 have been identified to occur in different solid neoplasms, with a frequency of <1%, but are enriched in invasive mucinous adenocarcinoma of the lung and *KRAS* wild-type pancreatic cancer. As of 2024, Zenocotuzumab, a humanized, full-length IgG1 bispecific antibody directed against HER2 and HER3, was approved for these indications.[83-85]

The second type of oncogenic translocation activates proto-oncogenes by deregulating their expression without affecting the structure of the protein they encode.

- An example of this type of translocation is found in Burkitt lymphoma, characterized by translocations that cause the *CMYC* oncogene, located on chromosome 8, to be juxtaposed with immunoglobulin genes that are located on chromosomes 14, 2, and 22. In each case, the translocation deregulates *CMYC* expression by placing it under the control of transcriptional elements contained within the immunoglobulin locus.
- Other examples of proto-oncogenes that are activated by translocations involving immunoglobulin genes include *CCND1*, which encodes the cell-cycle driver cyclin D (found in mantle cell lymphoma and multiple myeloma), and *BCL2*, which encodes the antiapoptotic protein B-cell lymphoma 2 (BCL-2; found in various non-Hodgkin lymphomas).
- Other genomic rearrangements, such as chromosomal segment inversions, create fusion proteins with important therapeutic implications, including the *EML4::ALK* fusion discussed in the previous section.

DNA Amplification

DNA amplification, which results from the duplication and multiplication of the gene locus within the tumor DNA, is another mechanism by which cancer cells increase the expression of a gene product.[74] Amplification is known as high copy number, which describes the excess reads that arise that map to a given oncogene. Normal cells typically harbor two copies of any given gene, but amplification can elevate this to tens or hundreds of copies. Gene amplification can be directly detected, using cytogenetic and

NGS approaches, or indirectly detected, using protein assays, such as IHC, to examine downstream protein expression resulting from the amplification.

- Detection of amplified genes provides important prognostic and treatment-related information, as in cases of HER2 amplification in breast, gastroesophageal, and other cancers, and NMYC amplification in neuroblastoma.
- DNA amplification can also be a mechanism of resistance to targeted therapy. For example, the androgen receptor gene AR is amplified in some castration-resistant prostate cancers.

Point Mutations

Point mutations (changes in only one or a few nucleotides in a gene sequence) can inactivate or impair protein function, and many recurrent point mutations activate dominant oncogenes. Examples of this mechanism of oncogene activation include mutations that alter *KRAS* function in colorectal and other cancers and activating mutations of *EGFR* in lung cancer. Because some common oncogenes, such as *KRAS*, are activated by only a few specific point mutations, these mutations were some of the first that were routinely screened for in cancer specimens.

- NGS can now identify most potentially oncogenic point mutations in primary tumor samples and can do so in timeframes that allow genomic-based treatment decisions.[86]
- One common strategy uses targeted sequencing to interrogate panels of commonly mutated and actionable proto-oncogenes. This approach can provide genomic data in a timeframe and at a cost more concordant with clinical interventions than broader approaches that sequence all protein-coding regions or even whole genomes.

IDENTIFICATION OF TUMOR SUPPRESSOR GENES

Many tumor suppressor genes were first identified through their association with hereditary cancer syndromes. Importantly, the genes responsible for familial cancers are often the same tumor suppressor genes that are inactivated in sporadic cancers. In most familial cancer syndromes, an individual inherits a mutated copy of a tumor suppressor gene and later in life acquires a mutation or deletion of the other normal allele, leaving him or her without a functional copy of the gene, which can lead to cancer development. Recessive oncogenes, in which disruption of both alleles is associated with cancer formation, are known as two-step (Knudson) tumor suppressors, named after classic studies of the *RB* tumor suppressor in RB.[87]

Important exceptions to the Knudson model expand our understanding of how tumor suppressor genes are mutated in cancers. One situation in which a tumor suppressor will not conform to the Knudson model is when the tumor suppressor is inactivated by an epigenetic mechanism, such as when the *CDKN2A* cell-cycle inhibitor gene is silenced by DNA methylation in cancers. In other cases, loss of a single allele of a tumor suppressor is sufficient to confer cancer susceptibility or contribute to neoplastic progression, even when a normal allele persists. This is termed a haploinsufficient tumor suppressor gene.[88] So-called dominant-negative mutations also result in non-canonical tumor suppressor inactivation, because they inhibit the function of the wild-type protein produced by the normal allele, thereby removing the selective pressure to mutate both alleles. As in the haploinsufficient case, only one allele of the tumor suppressor gene will contain a mutation, such as is seen with the *FBXW7* and *SPOP* ubiquitin ligase genes or the *TP53* gene.

Loss of tumor suppressor gene alleles occurs commonly in cancers.[89] In classic studies, delineating a locus involved by allelic loss in a tumor type was often the first step toward identifying a tumor suppressor gene, such as the breast cancer susceptibility gene *BRCA1*.[90] Sites of allelic loss were thus determined by analyzing polymorphic markers, and disease genes were localized to within the smallest common region of allelic loss (Presenting Case Study 1). Today, NGS-based technologies are becoming the method of choice for detecting allelic losses in tumors. NGS approaches also detect numerous other mechanisms that disrupt tumor suppressor gene function, including inactivating point mutations, deletions that lead to premature termination and/or nonfunctional proteins, and promoter methylation.

PRESENTING CASE STUDY 1

A 44-year-old woman presents to her primary care clinician after noticing a left breast lump. Mammography confirms a suspicious lesion in the left breast. Biopsy demonstrates invasive ductal carcinoma that is negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2; ie, triple-negative breast cancer). Her family history is notable for cancer in multiple first-degree relatives, including breast cancer in her maternal aunt and sister and ovarian cancer in her mother. Genetic testing reveals a germline mutation in *BRCA1*.[91] Staging studies demonstrate no evidence of regional or distant disease, and she is treated with surgery and appropriate adjuvant therapy. Three years later, she presents with weight loss, cough, and headache and is found to have extensive metastatic

disease in her lungs, liver, and brain. After brain irradiation, she receives the PARP inhibitor olaparib, which controls her disease for 24 months.[92]

How do the described patient characteristics inform your decision about genetic testing, that is, whole-genome/-exome sequencing?

Tumor sequencing studies have cataloged many different mutations in *BRCA1* or *BRCA2* that can affect the risk of breast and other cancers, including ovarian, prostate, and pancreatic cancers. Importantly, although *BRCA1* was first identified as a cause of familial cancers, rare sporadic tumors also harbor mutations in this gene. The BRCA1 protein is now known to be a key component of the normal cellular response to DNA damage, one of the hallmarks of cancer. The loss of the DNA-damage response results in selective sensitivity to certain drugs, including PARP inhibitors and platinum compounds, and some patients with *BRCA*-mutated cancer show prolonged responses to these agents. Patients with *BRCA* mutations more frequently exhibit triple-negative breast cancer, which is often known to metastasize and does not respond to drugs that work in several other subtypes of breast cancers, like anti-hormones, aromatase inhibitors, or anti-HER2-directed antibodies, as well as chemotherapies. The underlying biology of these tumors calls for a different approach, and PARP inhibitors have shown some benefit.[92]

Because cells can function well with a single copy of a tumor suppressor, these genes are commonly associated with heritable cancer predisposition syndromes, such as RB, Li-Fraumeni syndrome (*TP53*), Cowden syndrome (*PTEN*), and hereditary breast and ovarian cancer syndrome (*BRCA1* and *BRCA2*). Individuals with these syndromes can develop cancer through loss of heterozygosity of the residual gene copy in an at-risk tissue.[93]

Due to the hereditary nature of *BRCA* mutations, patients in this category develop tumors much earlier than people without these mutations, oftentimes before reproduction. Certainty about the nature of a potential tumor predisposition may inform decisions on reproductive health, as well as preemptive surgeries like prophylactic mastectomy or salpingo-oophorectomy.

Information about the heritable nature of this disease might be relevant to any relatives of the patient since it will inform their decisions on genetic testing and its possible consequences.

KEY POINTS

- Proto-oncogenes are normal cellular genes that can be converted into oncogenes by mutations or epigenetic mechanisms, which alter their normal function or expression.
- Oncogenes encode proteins that are activated in tumors by mechanisms such as amplification, point mutation, and translocation. Oncogenes operate dominantly, and alteration of a single gene is sufficient to promote transformation.
- Tumor suppressor genes are inactivated in tumors by mechanisms such as deletion, point mutation, and gene silencing. Because they act in recessive fashion, the other copy of the gene must be deleted, typically by loss of heterozygosity.

CELLULAR FUNCTIONS OF ONCOGENES AND TUMOR SUPPRESSORS

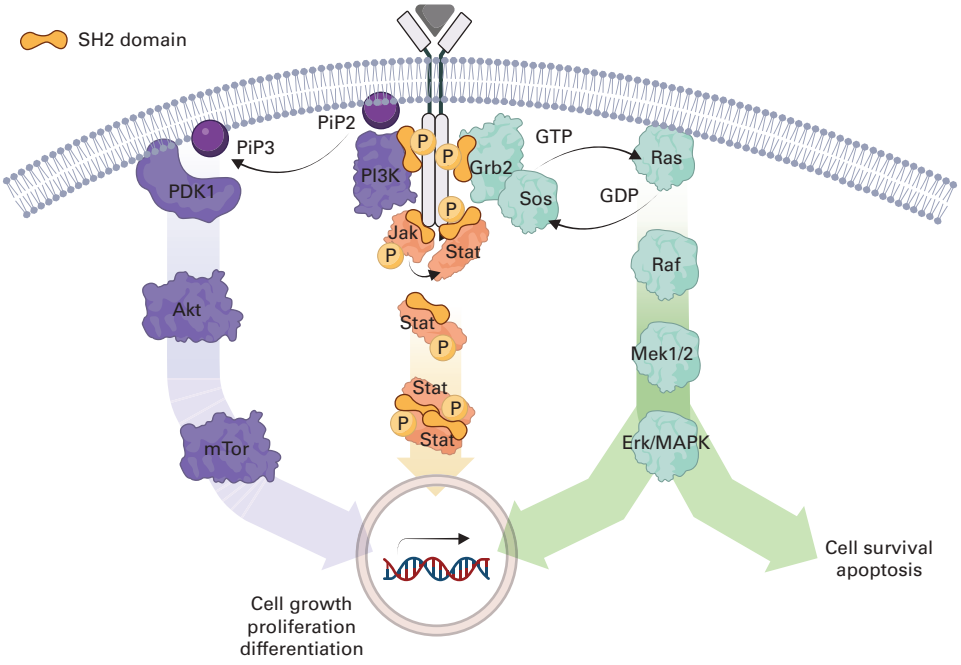
- Many oncogenes are found within the pathways that govern cell division and differentiation in response to specific signals.
- Oncogene mutations also affect other global cellular pathways and processes, including metabolism, programmed cell death (apoptosis), and protein degradation.
- Oncogene alterations are gain of function, which means that only one copy, or allele, of the gene needs to be mutated to impart biologic effects.
- Tumor suppressors serve to counter the effects of oncogenes and have a particularly important role in maintaining the integrity of the genome by suppressing errors during DNA replication and coordinating the response and repair mechanisms triggered by DNA damage.
- Tumor suppressors restrain oncogenic transformation, and typically, their function must be completely lost to confer cancerous transformation. Typically, one copy of a tumor suppressor is mutated, and the other is deleted.
- Deletion is termed loss of heterozygosity because the tumor seems to have only one copy of the gene, which is mutated.

MITOGENIC SIGNAL TRANSDUCTION PATHWAYS

Cell division is triggered by signal transduction pathways that are stimulated when growth factors bind to specific cell-surface receptors. Most growth factor receptors are anchored in the cell membrane such that an extracellular domain is available for

growth factor (ligand) binding and an intracellular domain interacts with downstream signaling molecules (Fig. 2-6). The intracellular portion of a class of growth factor receptors, called receptor tyrosine kinases (RTKs), catalyzes the addition of phosphate to tyrosine residues. Ligand binding causes RTKs to dimerize and autophosphorylate, which recruits signaling proteins that transmit the mitogenic signal down several parallel pathways. Cytoplasmic tyrosine kinases also transduce these mitogenic signals. Kinases are often activated in cancer through dominant mutations, amplifications, and translocations. These genetic alterations lead to overactive signaling, often by nullifying or bypassing negative regulatory processes that would usually attenuate these pathways. Essentially, the checks and balances that are present in normal cells are disrupted in cancer cells, leading to uncontrolled growth.

Figure 2-6 Mitogenic Signaling



This figure shows schematically the binding of an extracellular signal (dark gray triangle) to a transmembrane receptor (light gray structure transversing the cell membrane) that is being phosphorylated in the process, usually on tyrosine residues, yielding phosphotyrosines (Ps in yellow circles). Adapter molecules containing SH2 domains bind to the phosphotyrosines and recruit effector proteins in doing so. The examples in this figure (purple) are phosphoinositide 3-kinase (PI3K) and its downstream target phosphoinositide 3-kinase-dependent kinase (PDK1), which, in turn, activates protein kinase B (Akt). Akt activates the mammalian target of rapamycin (mTor), that is exerting promitogenic transcription, differentiation, or cell growth in the cell nucleus. Also, SH2 domain-containing molecules may recruit (orange pathway) Janus kinases (Jaks) and signal transducers and activators (Stats). Jaks phosphorylates Stats on tyrosine residues, amplifying the original signal from the transmembrane receptors. Stats themselves can shuttle into the nucleus and initiate or promote the described processes. The green route illustrates the amplification of the original phosphotyrosine signal via the growth factor-bound protein 2 (Grb2) and rat sarcoma protein (Ras) and its subsequent effectors. Activation of this route may lead to cell growth, proliferation, and differentiation, or cell survival and diminished apoptosis.

Reproduced under Creative Commons license. Source: Diop A, Santorelli D, Malagrino F, et al. SH2 domains: folding, binding and therapeutical approaches. *Int J Mol Sci*. 2013;23(24), figure 4. doi:10.3390/ijms232415944

RAS proteins are membrane-tethered intracellular enzymes that transduce signals for cell division. RAS activity is regulated by binding to guanosine triphosphate (GTP) or guanosine diphosphate (GDP).[94] Thus, RAS activity reflects a balance of G nucleotide exchange factors that activate RAS by replacing bound GDP with a new molecule of GTP and GTP-activating proteins, which hydrolyze RAS-bound GTP to GDP. There are three closely related RAS family members (*KRAS, NRAS*, and *HRAS*), and all are mutated in human cancers. Oncogenic *RAS* mutations affect amino acids that interface with GTP-activating proteins at residues 12 and 13, which results in overactivity of proliferative signaling pathways. Furthermore, GTP-activating proteins themselves can function as recessive oncogenes (eg, the *NF1* gene is a GTP-activating protein that acquires a loss-of-function mutation in neurofibromatosis).[94]

Of the *RAS* genes, *KRAS* is most commonly activated through mutation in a variety of cancers, including pancreatic cancer, NSCLC, and colorectal cancer. Most activating *KRAS* mutations mutate the glycine at position 12. Mutations that alter this side chain, most commonly G12D, G12V, or G12C, constitutively activate the GTPase activity of *KRAS*. Tumor cells that harbor this activity are thus not well suited to targeting upstream signaling events (Presenting Case Study 2).

RAS drives mitogenic signaling via three parallel signal transduction pathways: the mitogen-activated protein kinase (MAPK) pathway (which activates transcription factors), the RAL/CDC42 pathway (which regulates membrane and cytoskeletal changes), and the PI3K pathway (which affects many cellular functions, including protein synthesis and apoptosis). In addition to activation by RAS, the MAPK and PI3K pathways can be activated independently of RAS by mutations in other pathways that also use these signaling components.

- The MAPK pathway is stimulated by the RAF serine/threonine kinase and signals to additional downstream cytoplasmic serine/threonine kinases, which ultimately activate MAPKs and other effectors. MAPK signaling activates nuclear proto-oncogenes, which are transcription factors, such as FOS, JUN, and MYC.
- Mutations of the BRAF gene, specifically V600E mutations, are found in approximately 50% of malignant melanomas.
- The PI3K-AKT pathway phosphorylates various target proteins to stimulate transcriptional and translational responses that affect diverse cellular processes, including cell growth and division, apoptosis, protein synthesis, and cellular metabolism.
- AKT is a protein kinase that is downstream of PI3K and is often amplified and/or overexpressed in cancers.[95]
- Cancers exhibit elevated AKT activity caused by mutations in regulatory genes, such as the PTEN tumor suppressor, which is commonly deleted in cancers, opposing PI3K and preventing AKT activation.[95]
- Each of these processes may be abnormal in cancers with PI3K mutations, which are among the most common mutations found in cancer cells.[8,95,96]

PRESENTING CASE STUDY 2

During a routine visit in 2009, a 37-year-old woman who quit smoking 5 years prior was diagnosed with colorectal cancer (CRC) that seemingly infiltrated neighboring structures. The doctor determined that it should be removed surgically and referred the patient accordingly. She received neoadjuvant 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) therapy to shrink the tumor, thereby making it amenable to surgery. The left-sided tumor was removed and staged as ypT4aN0.[97]

Postoperatively, she presented for regular follow-up, and after 8 years, a singular 3-cm liver metastasis was discovered and surgically removed. The liver metastasis was analyzed at the molecular level to provide hints for further definitive treatment options. Because molecular testing indicated wild-type *RAS*, wild-type epidermal growth factor receptor (*EGFR*) status, and a mutated p53 gene (*TP53*), she continued with six rounds of FOLFOX with cetuximab within a clinical trial.[98] She remained tumor and metastasis-free for the next 3 years, until an 8-cm lesion was discovered on the liver, with smaller lesions in her lungs. She received external-beam radiation therapy to the lung and six rounds of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) with cetuximab. The liver metastasis shrank to 5 cm in diameter, but major vessels were still in the way of surgery. She then received brachytherapy to the liver. Re-biopsy showed a newly acquired *RAS* mutation. With limited therapeutic options available, she opted to participate in a clinical trial evaluating the combination of pembrolizumab and lenvatinib, an immunotherapy agent combined with a novel tyrosine kinase inhibitor.[99]

One year into the clinical trial, she experienced excruciating stomach pain and decided with her oncologist to continue pembrolizumab and discontinue lenvatinib, owing to its severe side effects and the threat of a perforated stomach. Her stomach pain resolved with antacid and nonsteroidal anti-inflammatory drug usage, and she slowly restarted lenvatinib. Shortly after, she developed severe jaundice. Initial attempts at resolving the biliary obstruction failed, and she was weaned off pembrolizumab and given glucocorticoids to resolve the noninfectious hepatitis. She remained jaundiced and was in and out of the hospital over the next 7 months. Ascites fluids were removed twice before she was hospitalized again with severe hepatitis. Her physicians explained her late palliative situation.

How would recent advancements in tumor biology impact the treatment decisions in this case?

In recent years, there has been a shift in CRC occurrence toward a younger age (<50 years). Often, this shift coincides with the reproductive age of those affected. Surgery is still the mainstay of treatment for locally confined and advanced CRC, perhaps followed and/or preceded by chemotherapy, usually 3 to 6 months of FOLFOX or capecitabine and oxaliplatin (CAPOX), depending on the risk of recurrence. Even today, this approach of surgery and (neo)adjuvant chemotherapy remains the standard of care. However, more comprehensive molecular testing of the tumor would have been performed, now that better tests and more therapeutic agents are available.

When this patient's tumor was initially evaluated, limited testing was available, and precision oncology had limited integration into clinical practices. The tumor showed no microsatellite instability, deeming her eligible for chemotherapy. Wild-type *KRAS* status meant that the tumor would most likely be susceptible to EGFR inhibition. The fact that *KRAS*-mutated clones dominated the subsequent biopsy indicates both the clonal evolution of this tumor and the necessity for a treatment change. Vascular endothelial growth factor (VEGF)-targeted agents had not been part of this patient's previous regimens and seemed a valid option at the time. Her participation in a clinical trial involving pembrolizumab and lenvatinib highlights the ongoing search for effective treatment for CRC in the metastatic setting, yielding negative results more frequently than anticipated.

How does the p53 mutation play a role in the treatment decision?

A p53 mutation conveys an inferior prognosis compared to wild-type p53.[100] Individuals who smoke often exhibit p53 inactivation, either in an epigenetically silenced form or as a somatic mutation.[101]

What about mutated *KRAS*?

Initially, the tumor presented as a KRAS wild-type tumor, but later converted to a KRAS-mutant tumor upon subsequent biopsies. Mutated *KRAS* meant a tumor was no longer amenable to EGFR-directed therapy. However, in the current landscape, this limitation has been overcome using agents that specifically target mutated KRAS. Sotorasib in combination with panitumumab and adagrasib in combination with cetuximab are now approved as *KRAS G12C* inhibitors for patients with metastatic CRC who have undergone FOLFOX/IRI treatment and experienced recurrence. Therapeutic development in this area continues to expand.

Should all possible options be tried?

While pembrolizumab is active in a subset of CRCs, patients with microsatellite instability-high and microsatellite-stable disease have not been shown to benefit from immunotherapy, and in today's therapeutic landscape, a patient with a microsatellite-stable tumor would not receive checkpoint inhibitors. Lenvatinib is a tyrosine kinase inhibitor that primarily acts on the VEGF receptor. Stomach ulceration is a frequent adverse event resulting from lenvatinib, as is noninfectious inflammation with immune checkpoint inhibitors, both of which tend to be difficult to control under real-world conditions. The patient's hope for prolongation of life while enrolling in the trial played a pivotal role in clinical decision-making and all subsequent treatments.[99] Today, knowing the negative results of the trial, we would discourage the patient from participating and opt for the highest quality of life possible, ideally with comfort measures.

TARGETING MITOGENIC KINASES IN CANCER CHEMOTHERAPY

The concept of specifically inhibiting mutated oncoproteins in cancer falls under the umbrella term targeted therapy and has been heavily applied to mitogenic kinases in cancer. In cases where the roles of individual kinases in specific cancers have been recognized for a long time, such as HER2 in breast cancer and BCR::ABL in CML, targeted therapies are already well established. However, the NGS-driven revolution in molecular oncology now allows targeted approaches to be directed against a much larger number of cancers that contain sensitizing gene mutations. Although targeted therapies will be discussed in detail in subsequent chapters in the context of specific organ sites and therapies, a general overview of these concepts is provided here. Several therapeutic strategies that target aberrant RTKs are in clinical use.

- One approach uses antibodies that bind to and inhibit RTK activation. Examples include trastuzumab, which antagonizes HER2 activity and is used in the treatment of breast cancers with *HER2* amplification,[102-104] and cetuximab, an inhibitory antibody that binds to EGFR and is approved for use in metastatic colon cancer and head and neck cancers.[103,104]
- Another important strategy to target RTKs and mitogenic kinases in cancers uses small-molecule inhibitors, such as imatinib, erlotinib, crizotinib, vemurafenib, and larotrectinib, which bind to specific kinases and inhibit their catalytic activity. The most recently approved TKIs are mentioned at the beginning of this chapter.
- Many available inhibitors have improved efficacy in tumors that contain mutations within the target kinase. The concept of directing small-molecule inhibitors against tumors with specific activating gene mutations lies at the crux of precision oncology.
- Kinase inhibitors can also be used to treat tumors that depend on the activity of a kinase pathway but do not have mutations in the kinase itself. Examples of this approach include the treatment of chronic lymphocytic leukemia with idelalisib (which inhibits PI3K-δ) and the treatment of mantle cell lymphoma and chronic lymphocytic leukemia with ibrutinib (which inhibits BTK).[105]

RESISTANCE TO KINASE INHIBITORS

Despite the remarkable activity of small-molecule kinase inhibitors, the development of resistance limits the durability of clinical responses. An exception to this is the use of imatinib and related drugs to inhibit BCR::ABL in CML, where responses are extremely durable, lasting more than 10 years on average.[106] In other cancers, impressive initial responses eventually give way to resistant and progressive disease much more quickly, often in 1 year or earlier (eg, use of BRAF inhibitors in melanoma).[107] However, this is not the case for all situations, because durable responses exceeding 2 years have been reported in *NTRK* fusion cancers treated with larotrectinib and *RET*-altered cancers treated with selpercatinib.[108,109] Tumors acquire resistance to kinase inhibitors in several ways.[14]

- First, new mutations develop in the target kinases, which render the targeted therapy ineffective. In some cases, the mutated kinases can still be effectively inhibited by related small molecules. An example of this mechanism occurs in CML, where the acquisition of *BCR::ABL* mutations leads to the production of proteins that can no longer be inhibited by imatinib, but related agents, such as nilotinib, can reinstate inhibition.
- Second, bypass pathways develop, where tumor cells rewire their mitogenic signaling to use alternative pathways. In this case, although the target kinase is still sensitive to the pharmacologic inhibitors, the tumors have escaped kinase inhibition through the activation of alternative signaling pathways. An example of this mechanism is the activation of alternative RTKs in lung cancers being treated with EGFR inhibitors. One approach to overcome this type of resistance is the use of additional kinase inhibitors to block the bypass pathway, such as targeting both the BRAF and MAPK pathways in melanoma.

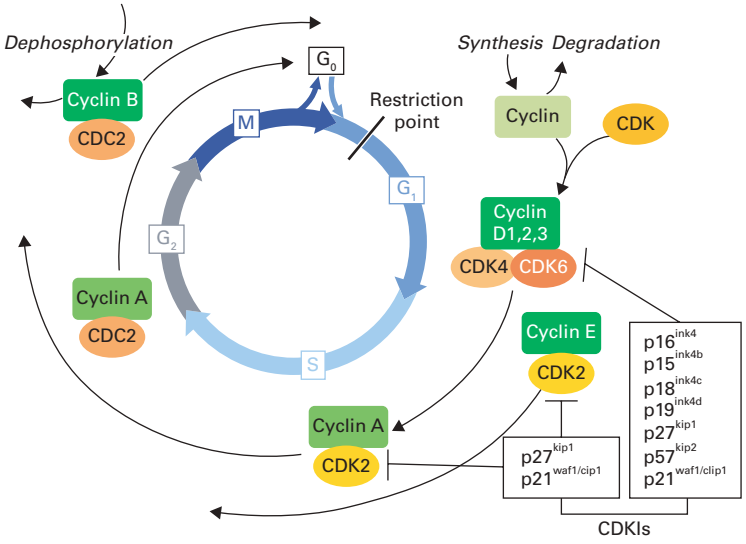
CELL-CYCLE CONTROL

Cell cycles are divided into four phases that coordinate cell growth, DNA replication, and cell division (Fig. 2-7). Under ordinary conditions, cells execute the cell division cycle faithfully, but in cancer, several steps can go awry.

- The G1 phase is a period of growth between mitosis and the onset of DNA synthesis during which cells integrate mitogenic signals and, under certain conditions of mitogenic drive, commit to the onset of DNA replication.
- The S phase is the period of DNA synthesis during which a cell replicates its genomic material.
- The G2 phase follows the S phase and is the second period of cell growth.
- In mitosis, or M phase, chromosomes are segregated to daughter cells, and cell division occurs.

Cyclin-dependent kinases (CDKs) are the master regulators of the cell cycle. CDKs drive cell-cycle transitions by phosphorylating proteins, driving altered functional roles specific to the new phase of cell division. CDKs are composed of two subunits: a catalytic

Figure 2-7 The Cell Cycle



The cell cycle is divided into four phases (G1, S, G2, and M). Progression through the cell cycle is promoted by CDKs, which are regulated positively by cyclins and negatively by CDK inhibitors. The restriction point is the point at which cells progress through the cell cycle independently of external stimuli.
Abbreviation: CDK, cyclin-dependent kinase.
Reproduced with permission from Schwartz GK, Shah MA. Targeting the cell cycle: a new approach to cancer therapy. *J Clin Oncol*. 2005;23:9408-9421. doi:10.1200/JCO.2005.01.5594

subunit (the CDK) and a regulatory subunit (the cyclin) that activates the CDK. Specific CDK-cyclin pairs are involved in distinct cell-cycle transitions. Innate protein CDK inhibitors counteract CDK activity to prevent premature cycling. A balance between these two opposing activities is central to the regulated control of cell growth and division.

- Cyclins and CDKs can act as dominant oncogenes.
- The cyclin D gene (*CCND1*) is rearranged by chromosome inversion in parathyroid adenomas, translocated to the immunoglobulin G heavy-chain locus in mantle cell lymphomas, and amplified in 10% to 15% of solid tumors.
- The cyclin E gene (*CCNE1*) is the second most commonly amplified gene in ovarian cancer,[110] and cyclin E is upregulated in cancers by increased transcription or prolonged protein stability.[111]
- CDKs can also be mutated; for example, the *CDK4* mutation found in familial melanomas prevents its inhibition by INK4 proteins.[112] Pharmacologic inhibitors of CDK4 and CDK6 cancers, including palbociclib, ribociclib, and abemaciclib, are used with antiestrogens to treat hormone receptor–positive breast cancer.[113]
- Genes encoding CDK-inhibiting proteins are often tumor suppressors.

APOPTOSIS

Cell death can occur via multiple mechanisms, including necrosis, which is an unregulated process triggered by various cellular insults, and apoptosis, an active and highly regulated physiologic process whereby complex biochemical pathways control whether a cell lives or dies. Tumor growth is a consequence of both unrestrained cell division and decreased apoptosis, and the pathways that mediate apoptosis contain proto-oncogenes and tumor suppressor genes that are altered in cancers (Fig. 2-8). There are two distinct apoptotic pathways[114]:

- The intrinsic or mitochondrial pathway results from a number of stimuli, such as radiotherapy and chemotherapy, and involves changes in the mitochondrial membrane that affect the release of cytochrome C into the cytoplasm. The intrinsic pathway also activates a caspase cascade that ultimately leads to DNA fragmentation and cell death.
- The extrinsic pathway is signaled when ligands, such as tumor necrosis factor α (TNF-α) and Fas ligand, bind to cell-surface death receptors, such as TNF receptor 1 and FAS. Ligand binding to death receptors initiates a sequence of events leading to activation of proteases, termed caspases, which execute the apoptotic response.

The BCL-2 family comprises proteins that regulate apoptosis, which are either proapoptotic (promote cell death) or antiapoptotic (promote cell survival).[115] *BCL2* was first identified as the gene activated by the t(14;18) translocation that is found in follicular lymphomas. The realization that BCL-2 functions to prevent apoptosis was pivotal to understanding the relationship between aberrant apoptosis and cancer biology. The precise mechanisms by which BCL-2 prevents cell death are not fully elucidated, but they involve interactions with proapoptotic family members, as well as alterations in mitochondrial functions. One important consequence of BCL-2 overexpression in tumorigenesis is that it prevents the apoptosis normally triggered by dominant oncogenes, such as *CMYC*, and this likely underlies the aggressive behavior of double-hit lymphomas, which contain activating translocations of both the *CMYC* and *BCL2* genes.[116] Because of their potential to induce apoptosis in tumor cells, drugs that target the BCL-2 protein family are being widely studied in clinical trials, and venetoclax is now approved for treatment of chronic lymphocytic leukemia and AML (Presenting Case Study 3).[35,117-119]

PRESENTING CASE STUDY 3

A 76-year-old man presents to the clinic with decreasing energy and pallor over the last few weeks. Complete blood count shows pancytopenia. Bone marrow evaluation demonstrates myelodysplasia as well as AML with complex cytogenetics. Chronic medical comorbidities include chronic obstructive pulmonary disease, congestive heart failure, and stroke. The patient is treated with the demethylating agent 5-azacytidine in combination with venetoclax, a B-cell lymphoma 2 (BCL-2) inhibitor.[117] He requires blood and platelet transfusions but otherwise tolerates therapy reasonably well, with no need for hospitalization, minimal decline in performance status, and no dose reductions. The treatment combination leads to a sustained partial response before he eventually develops marked cytopenias. Repeat bone marrow evaluation shows AML progression, and his therapy is discontinued. He dies under hospice care shortly thereafter.

Given the patient's age and comorbidities, which course of action would you have taken?

Usually, the treatment of patients with AML comprises induction therapy to generate remission. Subsequently, patients may undergo further chemotherapy, radiation therapy, or, ideally, a stem cell transplant. This patient's age

and comorbidities disqualify him from induction chemotherapy, for example, with idarubicine and cytarabine.[120] Cytosine methylation inhibitors have long been known to have clinical activity in hematologic cancers, including myelodysplastic syndromes and AML. Furthermore, large-scale analysis of human myelodysplastic syndromes and AML samples with methylation arrays showed that abnormal methylation is an important driver of cancer progression, because early, intermediate, and transformed myelodysplastic syndromes have increasing levels of methylation. This underscores the relevance of an emerging hallmark of cancer, non-mutational epigenetic reprogramming (see Fig. 2-1).

Although abnormal apoptosis, another hallmark of cancer, was not inferred to be a major driver of AML, preclinical laboratory studies showed that inhibitors of the antiapoptotic protein BCL-2 had clear clinical activity. Given the relatively low toxicity associated with methylation inhibitors and BCL-2 inhibitors, trials combining these two approaches were initiated in patients unfit for standard intensive chemotherapy. The dramatic effectiveness of this approach led to trials evaluating this combination in fit patients as well.[35,117]

Many cancer genes interact with the core apoptotic pathways. The most common mutations that impair apoptosis in tumors involve the *TP53* tumor suppressor gene. Apoptosis is one outcome of TP53 activation by cellular stress, and impaired cell death is an important consequence of TP53 loss in cancer. Another signaling pathway that prevents apoptosis is the PI3K-AKT pathway. The interactions of AKT with apoptotic signaling are complex and include direct effects on the mitochondrial membrane, as well as functional interactions with BCL-2 family members, FOXO transcription factors, nuclear factor κB, and p53.

Classically, apoptosis is one of four major types of cell death, the others being autophagy, necrosis, and entosis, the cellular process in which one cell invades and is engulfed by another living cell, leading to the formation of a single hybrid cell.[121] The first two types of cell death were classified as programmed death; however, recent discoveries have upset the ontology of programmed cell death. For example, ferroptosis, discovered in 2012, is an iron-dependent mechanism of programmed cell death.[56] The relevance of ferroptosis and other mechanisms of programmed cell death in cancer therapy is not clear.

KEY POINTS

- Mitogenic signaling pathways contain broadly acting proto-oncogenes, and their products are tyrosine kinases. Small-molecule kinase inhibitors and antibody-based therapeutics target many of these proteins.
- Genes that promote or inhibit the normal cell cycle are commonly mutated in cancer cells and are becoming important targets for cancer treatment.
- Many oncogenic mutations disrupt normal apoptotic responses. Inhibitors of proapoptotic proteins constitute another important new class of anticancer drugs.

UBIQUITIN-MEDIATED PROTEIN DEGRADATION

The precise control of protein abundance within a cell is critical to many cellular processes. The rapid degradation of specific proteins is accomplished through the ubiquitin-proteasome system. This process first requires site-specific modification, typically phosphorylation, of the protein to be degraded, which serves as a flag that the protein is no longer required in the cell. Next, a multienzyme process catalyzes the transfer of chains of the small protein ubiquitin to the phosphorylated target. Families of enzymes, known as E1s, E2s, and E3s, play specific roles in this ubiquitination step. Finally, this polyubiquitination causes the protein to be recognized and then degraded by a proteolytic organelle called the proteasome.[122] Additional control of this process is provided by a family of deubiquitinating enzymes, which can remove polyubiquitin chains before degradation takes place. Furthermore, shorter forms of ubiquitin chains can be added to proteins to signal events in addition to degradation, such as protein-protein interactions and intracellular signaling events.

Given their critical role in the control of protein abundance, enzymes involved in the ubiquitin-proteasome pathway are often altered in cancers. E3 ubiquitin ligases, the enzymes that catalyze the final transfer of ubiquitin to substrates targeted for degradation, are particularly important oncogenes and tumor suppressors.

- The E3 ubiquitin ligase *FBXW7* is one of the most commonly mutated tumor suppressor genes across cancer types.[123] The Fbxw7 protein targets numerous key oncoproteins for degradation, including cyclin E, c-MYC, Notch, and c-JUN, whereas inactivating *FBXW7* mutations prevent degradation of these oncoproteins.
- The *SPOP* ubiquitin ligase gene was recently identified as a tumor suppressor gene and is also involved in the DNA repair process. *SPOP* mutations may predict sensitivity to DNA-damaging agents.[124]

- von Hippel-Lindau (VHL) syndrome is diagnosed by the presence of germline-inactivating *VHL* mutations. One critical VHL target is hypoxia-inducible factor 1α, a transcription factor that regulates genes in response to hypoxia, including an angiogenic transcriptional program that contributes to the highly vascular tumors associated with VHL loss.
- Inactivating mutations of the VHL E3 ubiquitin ligase are the cause of VHL syndrome, which is associated with susceptibility to renal cell carcinoma, central nervous system hemangioblastomas, pheochromocytoma, pancreatic tumors, and other neoplasms.
- In other cases, E3s are overexpressed and act as dominant oncogenes. One example of this involves MDM2, a ubiquitin ligase that targets the p53 protein for degradation, and the abundance of which is increased in cancers by mechanisms such as gene amplification.[125]

Proteasome inhibitors, which block protein proteolysis by the proteasome, have emerged as important antineoplastic agents, particularly for the treatment of hematologic cancers.[126,127] Bortezomib, carfilzomib, and ixazomib are useful in the treatment of multiple myeloma and other hematologic malignancies. Other inhibitors of the proteasome or more specific proteasomal pathways are currently being studied in clinical trials. Given that general proteasome inhibitors affect a large number of proteins normally degraded by the proteasome, the mechanisms that account for the therapeutic index associated with these inhibitors remain unclear. In addition to general proteasome inhibitors, activators or inhibitors of specific components of the ubiquitin ligase pathway are of great clinical interest. For example, inhibitors of the SPOP ubiquitin ligase have been developed and show activity in kidney cancer models.[128]

The ubiquitin-proteasome system also plays a role in the actions of other chemotherapeutics. For example, thalidomide and related drugs cause the cereblon E3 ubiquitin ligase to abnormally degrade specific protein substrates, which may explain their efficacy in myelodysplastic syndromes with chromosome 5q deletions and in multiple myeloma.[129]

New therapeutics, known as proteolysis-targeting chimeras or selective degraders, are being designed to hijack the ubiquitin-proteasome system to selectively degrade a protein of interest. These small molecules operate with two active domains: one that binds a target protein with high affinity, and a second that engages an E3 ubiquitin ligase. In this manner, an oncogene or another desired therapeutic protein target can be selected for cancer therapy.

CONTROL OF CELLULAR DIFFERENTIATION AND CELL FATE

Most somatic cells exist in a terminally differentiated postmitotic state, which is established by complex transcriptional pathways. Master regulators of cellular differentiation and related processes are often involved in cancer.

Wnt/β-Catenin Pathway

An important example of this concept is the Wnt/β-catenin pathway, which has vital roles in development and cellular self-renewal. Indeed, abnormal Wnt signaling is implicated in many cancers.[130]

- Soluble Wnt proteins bind to membrane-bound receptors, and this prevents the ubiquitin-dependent degradation of β-catenin by the proteasome. β-Catenin then translocates to the nucleus, where it stimulates a transcriptional program in concert with the T-cell factor/lymphoid enhancer factor transcription factor.
- Regulation of this pathway is quite complex, and many proteins augment or restrain Wnt pathway activation.
- The best-characterized role of Wnt pathway activation in human cancer is in familial adenomatous polyposis, a hereditary colon cancer syndrome caused by deletion of the adenomatous polyposis coli (APC) tumor suppressor[131] (also described in Chapter 13).
- APC loss upregulates Wnt signaling by increasing β-catenin stability, leading to inappropriate transcription. Although first described in familial adenomatous polyposis, *APC* mutations are found in most sporadic colon cancers and are an early step in colorectal cancer progression.[132]
- Many other cancers also have aberrant Wnt signaling, including uterine cancers, brain cancers, and some leukemias.[14]

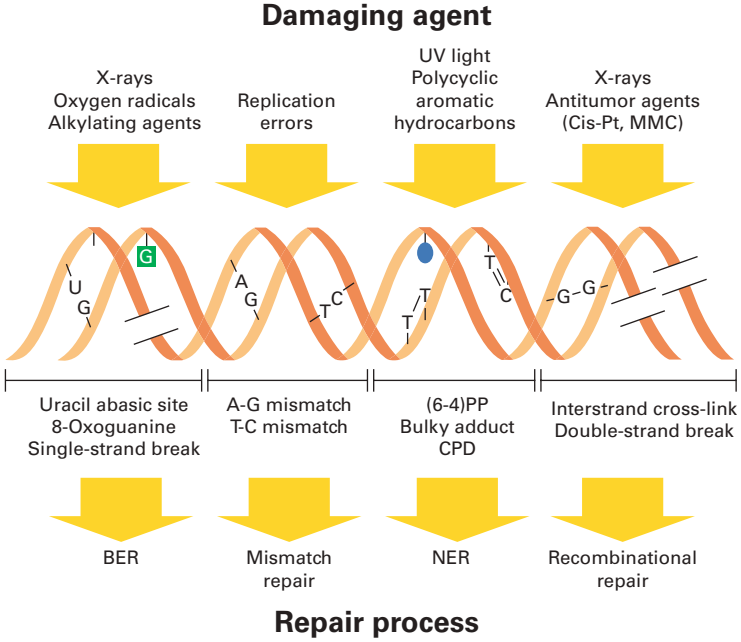
Other Pathways Regulating Cellular Differentiation

Many other proto-oncogenes affect the pathways that regulate differentiation.[133]

- Retinoic acid receptor α (RARα) is rearranged in several translocations found in acute promyelocytic leukemia, most commonly t(15;17), which produces a PML::RARα fusion protein. This fusion protein acts as a dominant-negative mutation that inhibits expression of RARα target genes and blocks differentiation.
  - The PML::RARα fusion is targeted by all-*trans* retinoic acid, which is used in conjunction with combination chemotherapy to induce remission in patients with acute promyelocytic leukemia. All-*trans* retinoic acid binds to the fusion protein and prevents it from bringing corepressors to RARα target genes, reversing the differentiation block and allowing promyelocytes to proceed down their normal differentiation pathway.[134]

- Core-binding factor is another transcription factor regulating hematopoietic differentiation that is involved in translocations found in acute leukemia. These translocations [inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*] produce dominant-negative proteins that inhibit core-binding factor target gene expression, which is thought to impair hematopoietic cell differentiation.[135]
- *NOTCH* genes encode transmembrane receptors that influence transcriptional programs involved in cell fate and differentiation and are frequently altered in human cancers.[136]
- NOTCH signaling is activated by ligand binding, which causes NOTCH proteins to be cleaved, forming intracellular domains that translocate to the nucleus and activate transcription.
  - NOTCH proteins play important roles in lymphoid differentiation and are likely drivers of hematologic cancers. *NOTCH1* was first described in a subset of patients with T-cell acute lymphocytic leukemia, and activating *NOTCH1* mutations occur in as many as 50% of patients with this disease.[137]
  - *NOTCH* may act as a tumor suppressor in some cancers, because 20% of squamous cell carcinomas show inactivating mutations in these genes. How *NOTCH* acts as an oncogene in some clinical situations and as a tumor suppressor in others remains poorly understood.[138]
  - Nirogacestat, a γ-secretase inhibitor that blocks the activation of NOTCH, is approved for the management of desmoid tumors.[139]
- The hedgehog signaling pathway is another example of a molecular process intricately involved in development and cell fate decisions that is hijacked by cancer cells to promote abnormal growth.
  - Hedgehog itself is an extracellular ligand that binds to and activates the Ptch1 cell-surface receptor, which, in turn, allows activation of the Smo cell-surface receptor. Smo sends intracellular signals that ultimately lead to the Gli transcription factor activating gene expression programs that drive cellular phenotypes.
  - Mutations or other alterations in hedgehog signaling components can be found in both hereditary and sporadic tumors and are especially important in basal cell skin cancers and medulloblastomas.
  - Specific inhibitors of components of this pathway, including the Smo inhibitors erismodegib, glasdegib, and vismodegib, are approved for the treatment of basal cell cancers and leukemias and are being tested in other disease states. Arsenic trioxide, which is approved for the treatment of acute promyelocytic leukemia, is thought to function in part because of the inhibition of Gli transcription factors.[140]

Figure 2-8 DNA Lesions and Repair Mechanisms



Common DNA-damaging agents (top), examples of lesions that can be introduced by these agents into the DNA double helix (middle), and the most frequently used repair mechanisms for such lesions (bottom). Distinct damaging sources can induce similar types of DNA lesions, and any one agent often induces more than one type of damage. The lesion spectra of different repair pathways may overlap.
Abbreviations: BER, base excision repair; CPD, cyclobutane pyrimidine dimer; MMC, mitomycin C; NER, nucleotide excision repair.
Reprinted from de Boer J, Hoeijmakers JH. Nucleotide excision repair and human syndromes. *Carcinogenesis.* 2000;21:452-460, by permission of Oxford University Press.

DNA REPAIR PATHWAYS

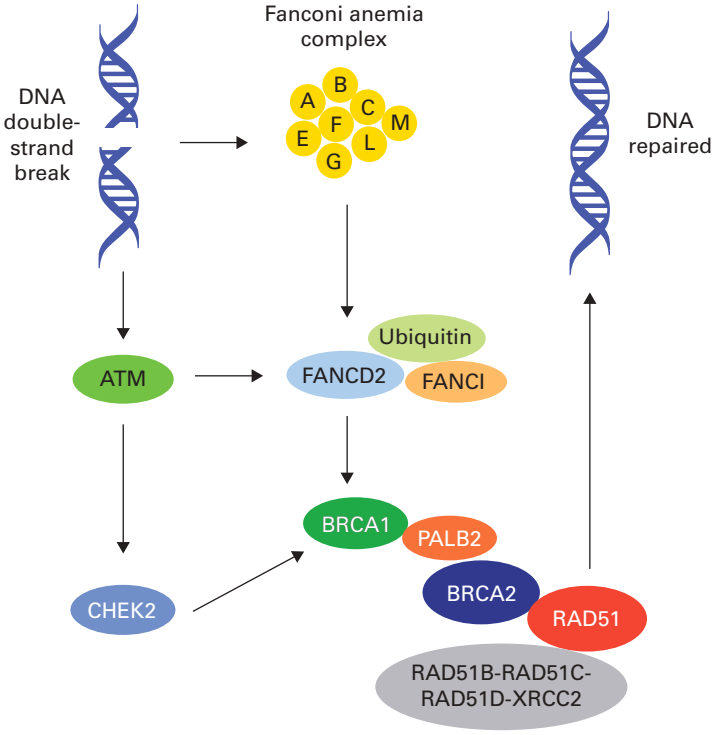
Mammalian cells use three major DNA repair pathways to maintain genomic integrity. The nucleotide excision-repair (NER) pathway recognizes and repairs UV light–induced nucleotide dimers and other DNA adducts. DNA recombination repair corrects double-strand DNA breaks induced by ionizing radiation and other agents. Finally, the DNA MMR pathways correct errors during DNA replication by removing the mismatched strand and enabling subsequent repair of the DNA. Mutations that disrupt these pathways cause genetic instability and are associated with inherited diseases characterized by sensitivity to DNA-damaging agents and by cancer predisposition (Fig. 2-8).

NER Pathways

NER pathways correct nucleotide lesions induced by UV light and adducts induced by chemical carcinogens, such as platinum substances.[141] There are two NER pathways: a global repair pathway and a transcription-coupled repair pathway that repairs DNA damage occurring during transcription. Germline mutations affecting these pathways give rise to sun-sensitive and developmental disorders, including xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. Xeroderma pigmentosum is an autosomal-recessive disorder leading to neurodegeneration, sensitivity to UV light, abnormalities in skin pigmentation, and cancer predisposition. People with this disorder have a risk of skin cancer that is estimated to be 2,000 times higher than that of the general population. Eight genes have been associated with xeroderma pigmentosum; seven code for excision-repair proteins, and one is a DNA polymerase required for accurate replication of damaged DNA. Patients with NER deficiency are platinum resistant. By contrast, Cockayne syndrome is associated with two genes, *CSA* and *CSB*, which are involved in transcription-coupled DNA repair. Trichothiodystrophy is caused by a mutation of either *ERCC2/XPD* or *ERCC3/XPB*; both encode helicase subunits of the TFIIH transcription complex. Neither Cockayne syndrome nor trichothiodystrophy is associated with an increased cancer risk.

Base excision repair is a related process that can repair damaged DNA via a process that begins with excising the damaged base from the deoxyribose backbone and is suited to repairing a string of 1 to 10 nucleotides. *MUTYH* is an example of a DNA glycosylase that initiates this process, and germline mutations in this gene can predispose individuals to colorectal cancer.

Figure 2-9 Recombinational Repair of DNA Double-Strand Damage



DNA double-strand breaks recruit protein kinase ATM and also activate the Fanconi anemia core complex (FANCA/B/C/E/F/G/L/M) that monoubiquitinates the downstream targets FANCD2 and FANCI. ATM activates (phosphorylates) CHEK2 and FANCD2, and, in turn, CHEK2 phosphorylates BRCA1. Ubiquitinated FANCD2 complexes with BRCA1 and RAD51. The PALB2 protein then acts as a hub, bringing together BRCA1, BRCA2, and RAD51 at the site of a DNA double-strand break and also binds to RAD51C, a member of the RAD51 paralog complex RAD51B-RAD51C RAD51D-XRCC2 (BCDX2). The BCDX2 complex recruits RAD51 or stabilizes the damage sites. RAD51 plays a major role in homologous recombinational repair of DNA during double-strand break repair. In this process, an ATP-dependent DNA strand exchange takes place in which a single strand invades base-paired strands of homologous DNA molecules. RAD51 is involved in the search for homology and the strand-pairing stages of the process.
Reproduced under Creative Commons license. Source: Fanconi Anemia. Wikipedia. Accessed December 1, 2022. https://en.wikipedia.org/wiki/Fanconi_anemia#/

Homologous Recombination Pathway

Damage to DNA by radiation, chemicals (eg, chemotherapy), and other insults produces double-strand breaks, which are recognized and repaired by a coordinated response that involves proteins encoded by a wide range of tumor suppressor genes (Fig. 2-9). Germline mutations of some of these genes cause inherited syndromes with highly variable clinical manifestations. Ataxia telangiectasia is characterized by progressive cerebellar ataxia, telangiectasia, immunodeficiency, and increased tumorigenesis (most commonly hematopoietic neoplasms). The ataxia telangiectasia gene (*ATM*) encodes a large protein kinase with homology to PI3K. ATM is activated by serine phosphorylation in response to DNA breaks and phosphorylates a number of downstream substrates with critical roles in DNA repair and checkpoint pathways, including CHK2, TP53, BRCA1, and NBS1.[142] Cells derived from patients with ataxia telangiectasia exhibit increased DNA damage from radiation, as well as defects in normal cell-cycle responses to DNA damage, called checkpoints.

Fanconi anemia is an autosomal-recessive disease characterized by developmental abnormalities, bone marrow failure, and susceptibility to cancers, particularly AML, squamous cell cancer of the head and neck, gynecologic cancers, and esophageal cancer. Similar to ataxia telangiectasia, cells derived from patients with Fanconi anemia display aberrant responses to DNA-damaging agents. However, Fanconi anemia cells are not hypersensitive to ionizing radiation; rather, they are hypersensitive to DNA cross-linking by agents, such as diepoxybutane and mitomycin C. Classic studies defined many Fanconi anemia complementation groups, and 13 Fanconi anemia genes have now been cloned. Remarkably, many of these genes encode proteins that form a complex that catalyzes the monoubiquitination of two Fanconi anemia proteins, FANCD2 and FANCI.[139] Monoubiquitinated FANCD2 and FANCI become localized to nuclear repair foci after DNA damage, and these foci also contain FANCD1 (identical to the *BRCA2* breast cancer gene) and other proteins, including BRCA1 and NBS1. The intersection of the BRCA1 and FA pathways underscores the central importance of this DNA-damage sensing and repair mechanism in carcinogenesis.

The NBS1 protein is another component of nuclear repair foci implicated in a chromosome breakage syndrome. Nijmegen breakage syndrome is an autosomal-recessive disease characterized by microcephaly, immunodeficiency, and increased frequency of hematopoietic cancers that is caused by mutations in the *NBS1* gene. NBS1 forms a complex with MRE11 and RAD50, which binds to BRCA1 in nuclear repair foci. Deficiency of the NBS1 protein blocks the formation of the MRE11-NBS1-RAD50 complex, and this impairs the S-phase surveillance responses triggered by ATM. Accordingly, many of the symptoms of this disease are identical to the symptoms of ataxia telangiectasia.

Mutations in many components of the DNA-damage response (DDR) pathway can be found in both hereditary and sporadic cancers. Identification of these mutations is clinically relevant because they may predict sensitivity to PARP inhibitors and DNA-damaging agents, such as cisplatin. Ongoing studies are testing the efficacy of these agents in various tumor types with mutations in DDR components. Interestingly, tumors associated with germline DDR mutations may respond much more dramatically than those with somatic DDR mutations, suggesting that the timing of the mutation during tumor development is important.

DNA MISMATCH REPAIR

DNA MMR corrects errors that occur during DNA replication, which are primarily single-base mismatches or short insertions or deletions.[143] A complex of proteins binds to a DNA mismatch, identifies the DNA strand with a mismatch, and then excises and repairs the mismatch. Several of the MMR proteins are tumor suppressors involved in hereditary nonpolyposis colon cancer. People with hereditary nonpolyposis colon cancer/Lynch syndrome are at significantly increased risk of colon and uterine cancers, with increased risk of cancers in other organ sites as well.[144] The two most commonly mutated MMR genes in Lynch syndrome are *MSH2* and *MLH1. MSH2* is involved in the initial recognition of the mismatch, whereas *MLH1* helps determine which DNA strand contains the correct sequence. Mutations in other MMR genes are less commonly associated with hereditary nonpolyposis colon cancer and include *MSH6, PMS1*, and *PMS2*. Patients with hereditary nonpolyposis colon cancer inherit a nonfunctional MMR gene allele, and a subsequent loss of the remaining allele in a somatic cell ultimately gives rise to a tumor. Importantly, impaired MMR causes a hypermutable phenotype, as evidenced by MSI, which is readily detected in tumors by PCR-based assays that evaluate specific tumor DNA microsatellite fragments. Although MSI is the hallmark of hereditary nonpolyposis colon cancer, it is also found in a subset of sporadic colon cancers, but in these cases, *MLH1* is typically silenced by promoter hypermethylation rather than by gene mutation. Although dMMR proteins have been classically analyzed using IHC methods, NGS DNA analysis approaches can now be used to detect the presence of MSI in tumors, as described earlier.

The detection of dMMR/MSI in tumors is of high clinical relevance because it predicts a high probability of deep and prolonged responses to immune-modulating programmed cell death 1 (PD-1) inhibitors, including nivolumab and pembrolizumab.[39] High MSI (dMMR) was the first FDA-approved biomarker that was tissue agnostic and not based on the site of anatomic origin of the tumor. More recently, tumor mutation burden, which quantifies the number of mutations present in a specific cancer specimen and is likely a surrogate marker of defective MMR, also predicts the efficacy of immune-modulating agents.[145] Outside of dMMR, high tumor mutation burden can be driven by highly mutagenic oncogenic stimuli, such as chemical carcinogens, or by mutations in the proofreading domains of DNA polymerases α and ε, encoded by POLD1 and POLE, respectively.[49] Pembrolizumab is now FDA approved for solid tumors with high tumor mutation burden, as defined by at least 10 mutations per megabase.[145] It should be noted that although the FDA approval was tumor agnostic, the efficacy at this cut point was more prominent for some cancer types (eg, uterine and colorectal cancers) than others.

KEY POINTS

- Enzymes that promote protein degradation by the proteasome can function as tumor suppressors.
- Pharmacologic proteasome inhibitors are approved for the treatment of multiple myeloma and other hematologic cancers.
- Genes that regulate cellular differentiation are often mutated in hematologic cancers. Drugs that restore normal differentiation are important treatments for these diseases.
- DNA repair pathways contain many tumor suppressor genes that are mutated in both familial and sporadic cancers. Mutations that disable different elements of DNA repair pathways are associated with specific cancer syndromes.
- Inactivation of DNA-damage repair genes may predict response to PARP inhibitors and DNA-damaging agents.
- Inactivation of DNA MMR enzymes leading to MSI and high tumor mutation burden predicts response to PD-1 inhibitors.

CHECKPOINTS: CROSSROADS OF DNA REPAIR, CELL-CYCLE REGULATION, AND GENETIC INSTABILITY

The fidelity of the enzymes that replicate DNA and segregate chromosomes is largely responsible for the accurate propagation of genetic information. However, these enzymes have an intrinsic error rate, and the frequency of errors is increased by genotoxic insults. Normal cells continually monitor DNA replication and mitosis and stop the cell cycle if these do not occur correctly, allowing the damage to be repaired before proliferation resumes or apoptotic and/or senescent responses are initiated to block cell growth. The pathways that link cell-cycle progression to the accurate execution of prior cell-cycle events are called cell-cycle checkpoints.[146] (Note that this section refers to checkpoints as molecular processes that safeguard the genome from damage; such checkpoints are wholly distinct from the checkpoints present in the immune system that are targeted by immunotherapy.)

Mammalian cells have checkpoints that operate in each phase of the cell cycle and are intricately interwoven with the cell cycle and DNA repair machinery. The G1 and G2 checkpoints recognize DNA damage that occurs during these cell-cycle phases and initiate responses leading to either cell-cycle arrest or cell death. The S-phase checkpoint is also activated by DNA damage, as well as by inhibition of the proper function of the replication machinery (eg, by chemotherapeutics, such as hydroxyurea and cytarabine).

Checkpoint pathways are composed of sensors/mediators, signal transducers, and effectors. Sensors and mediators detect DNA damage and form protein complexes that accumulate in DNA repair foci. The DNA-damage signal is then transmitted by kinases, first ATM and ATR, and subsequently CHK1 and CHK2, which ultimately activate effectors, such as p53 and Cdc25. These regulate key processes, including cell-cycle progression, apoptosis, and DNA repair. Small-molecule inhibitors of many of these checkpoint kinases have been evaluated as anticancer therapeutics, although the activity to date has been modest at best. Importantly, checkpoint pathways, particularly p53 signaling, are disrupted in a large fraction of human cancers, where they are central drivers of genetic instability and tumor progression.

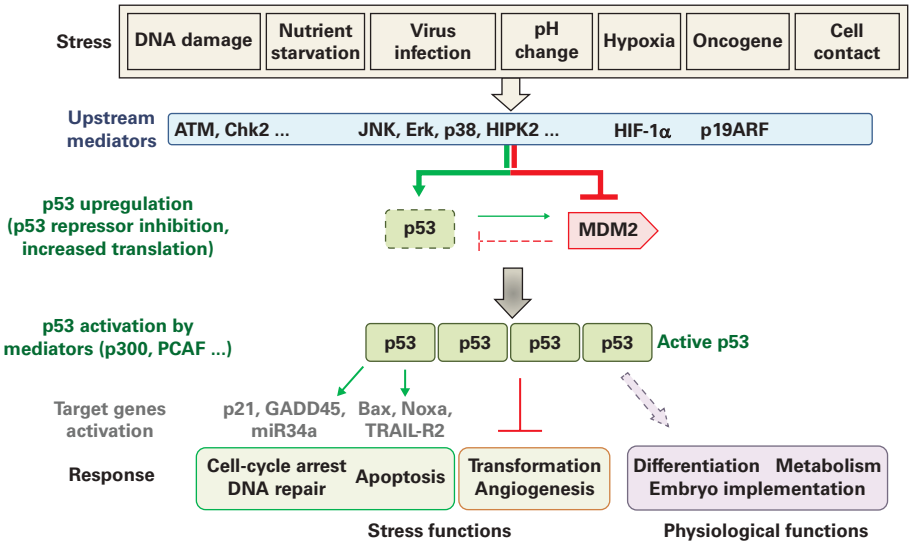
P53 PATHWAY

The p53 protein plays a central role in checkpoint pathways, and its cognate *TP53* gene is the most frequently mutated human tumor suppressor (Fig. 2-10).[147,148] Although *TP53* is mutated in up to half of all spontaneous cancers, its role as a tumor suppressor first came to light in studies of Li-Fraumeni syndrome, a rare autosomal disorder associated with the development of a wide variety of early-onset cancers, including soft tissue and bone sarcomas, as well as breast, brain, and colon cancers.

- The p53 protein is a transcription factor that is activated by many triggers, including DNA damage and replication stress.
- Activation of p53 can lead to cell-cycle arrest, apoptosis, or cellular senescence.
- Tumors most commonly inactivate *TP53* by a combination of loss of one gene copy coupled with mutation of the other copy, resulting in the expression of a protein with inactivating amino acid changes within critical functional domains.
- Another mechanism of suppression of p53 in tumors involves the MDM2 ubiquitin ligase.[125] *MDM2* gene expression is induced by p53, and the MDM2 protein functions in a negative feedback loop to downregulate p53 through ubiquitination.
- MDM2 is overexpressed in a wide spectrum of neoplasms, where it leads to decreased p53 abundance and function.
- Another gene that affects p53 degradation is the *ARF* tumor suppressor, which is frequently deleted in cancers.[149]
- ARF normally binds to MDM2, and this prevents MDM2 from ubiquitinating p53; however, when the *ARF* gene is deleted, MDM2 activity is unrestrained, causing p53 to be degraded.
- ARF expression is induced by oncogenes such as *MYC* and plays an important role in TP53 activation by oncogenic signaling. Thus, loss of ARF disables an important protective mechanism against oncogenic transformation.

There is enormous interest in developing cancer treatment strategies that target the p53 pathway, because studies in model systems have shown that restoration of p53 function has potent antitumor activity. Strategies that target the p53 pathway range from peptides that restore p53 protein function in cells with mutated p53 proteins to recombinant adenoviruses that selectively

Figure 2-10 The p53-MDM2-ARF Network



The activation of p53 classically occurs in response to many other cellular stresses that produce DNA damage, including oncogene-induced stress. Depending on the nature of the inducing signal, these DNA-damage responses activate a myriad of upstream mediators that lead to upregulation and activation of p53. This, in turn, results in activation of p53 target genes that serve to counteract the initiating cellular stress and protect the cell from further damage. When p53 is mutated or deleted, as it is in most cancers, these critical safeguards no longer function, and cellular stress continues unabated.
Uncovering the role of p53 splice variants in human malignancy: a clinical perspective by Surgent et al, taken from OncoTargets and Therapy © 2014 Surget et al. This work is published by Dove Medical Press Limited, and licensed under Creative Commons Attribution—Noncommercial (unported, v3.0) License. This is an Open Access article distributed under the terms of the Creative Commons Attribution-Noncommercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited, reprinted by permission of Informa UK Limited, trading Taylor & Francis Ltd, https://www.tandfonline.com

kill cells with *TP53* gene mutations. However, targeting remains a challenge because no clear targetable synthetic lethal vulnerability specific to TP53 has emerged since Wee1 inhibitors failed in clinical trials. It is now known that specific *TP53* mutations may have distinct functional activities. Specific mutations of *TP53* can elicit gain-of-function mutations.[150] This suggests that different therapeutic approaches might be required for each type of *TP53* mutation.

MITOTIC SPINDLE CHECKPOINT

The mitotic spindle assembly checkpoint ensures that chromosomes are equally segregated to daughter cells during mitosis.[151] It is the key safeguard against the gain or loss of whole chromosomes and other changes in chromosome structure, known collectively as chromosomal instability (CIN).

- During mitosis, chromosomes attach to the mitotic spindle through complex submicroscopic protein structures called kinetochores.
- In normal cells, the presence of unattached kinetochores signals that mitosis should not proceed to divide chromosomes toward the incipient daughter cells. This signal involves a conformational change of MAD2 into a closed form that binds Cdc20 and inactivates anaphase-promoting complex/cyclosome (APC/C; not to be confused with the adenomatous polyposis coli gene, known as *APC*).
- Kinetochores that are unattached to the mitotic spindle recruit MAD2 in the open conformation to bind MAD1. This interaction switches MAD2 to the closed form, which is released from the kinetochore as a soluble factor, instructing the cell to wait.
- A single unattached kinetochore is sufficient to maintain this wait signal, ensuring that the APC/C ubiquitin ligase remains in the off state until the cell is ready for accurate chromosome separation. Once all kinetochores are attached, the soluble signal from closed MAD2-Cdc20 is lost, and the APC/C activates to initiate the ubiquitination and turnover of cyclin B and securin, allowing cells to commit to chromosome segregation to new daughter cells.
- CIN is a common feature of cancer, more common than MSI.[152] Unlike in DNA-damage checkpoint genes, mutations in the genes controlling the mitotic checkpoint are rarely found in human cancers.

Perhaps the best-known case is in mosaic variegated aneuploidy, an extremely rare heritable condition characterized by CIN (variegated aneuploidy) and high cancer risk and caused by mutation of the kinetochore protein, BubR1.[153] The cause of CIN in

most tumors remains a mystery, given the dearth of mutations in kinetochore or mitotic regulatory proteins. These findings suggest that most CIN is caused indirectly by loss of other cell-cycle checkpoints or nongenetic changes, such as extra centrosomes that create error-prone cell divisions.[154] Furthermore, CIN is not simply present or absent in a tumor but can occur to various degrees in cancer, leading to distinct cancer behaviors. However, no standard or direct measures of CIN are available for routine use, and this feature, cell-by-cell variability of karyotypes in a tumor, is not measured by routine DNA sequencing, which averages the DNA levels across thousands of cells in a tumor.

KEY POINTS

- Checkpoints ensure the fidelity of cell division and protect against genomic instability.
- Checkpoint pathways are often dependent on normal tumor suppressor gene and DNA repair protein functions.
- Loss of checkpoint functions causes genomic instability and fosters the accumulation of multiple mutations in cancer cells.
- *TP53* is the most commonly mutated cancer gene, and it participates in diverse checkpoint responses. The p53 protein senses and responds to cellular stress by activating pathways that regulate processes such as cell-cycle progression and apoptosis.
- The mitotic checkpoint protects against chromosome loss, but this process is error-prone in many cancers, leading to CIN.

INFECTIOUS AGENTS AS DRIVERS OF CANCER

Infectious agents contribute to the pathogenesis of approximately 15% of all cancers worldwide, affecting more than 2 million people.[155] Examples of cancers that are associated with chronic viral infection are as follows:

- HPV: squamous cell carcinomas of the head and neck, cervix, penis, vulva, vagina, and anus
- Epstein-Barr virus: Burkitt and other types of lymphoma, nasopharyngeal carcinomas, and some stomach cancers
- Hepatitis B and C viruses: hepatocellular carcinoma
- HIV and Kaposi sarcoma–associated herpesvirus: Kaposi sarcoma
- HTLV-1: adult T-cell lymphoma
- Merkel cell polyomavirus: Merkel cell carcinoma

Extensive research has elucidated some of the molecular mechanisms infectious agents use to drive carcinogenesis. As noted, retroviruses can cause cancer through insertional mutagenesis. Other cancer-causing viruses express proteins that interfere with critical cancer pathways.

- HPV E6 protein promotes degradation of the tumor suppressor p53, affecting the DDR and DNA repair response, and HPV E7 promotes degradation of the cell-cycle inhibitor RB, driving cell growth, division, and proliferation.
- Whereas Epstein-Barr virus-associated lymphomas are characterized by a translocation involving the CMYC oncogene, Epstein-Barr virus also promotes B-cell survival and transformation via molecular mimicry, because Epstein-Barr virus gene products mimic activated cell-surface receptors and antiapoptotic proteins.
- Hepatitis B and C proteins promote the expression of genes associated with angiogenesis, enhanced cell motility, invasion, and metastasis.

In fact, many oncogenic viruses produce protein products that affect most of the hallmarks of cancer.[156] Given that virus-associated cancers frequently subvert normal cellular processes, the study of these cancers often yields insights into the biology of sporadic cancers. These insights include the identification of new oncogenes or tumor suppressor genes, as well as more complex aspects of tumor biology (eg, immune surveillance).

Although viruses are most commonly associated with cancer, other pathogens also contribute to carcinogenesis. Chronic infection with the intestinal bacteria *Helicobacter pylori* is associated with stomach cancers and low-grade lymphomas.[157] Similarly, hepatobiliary cancers, which are much more common in Southeast Asian populations, are in some cases associated with endemic infection with liver flukes.[158] Although less is known about the molecular mechanisms driving these cancers, chronic inflammation likely plays a major role.

Given the large number of human cancers associated with infections, there is much interest in preventing and/or treating the pathogens that increase cancer risk. Examples include the use of HPV vaccines to prevent squamous cell carcinoma and universal vaccination against the hepatitis B virus to decrease the incidence of hepatocellular cancers.[159] Elimination of *H. pylori* may prevent gastric cancer and often induces remission of gastric mucosa–associated lymphoid tissue lymphoma.[160,161] As more is learned about the molecular mechanisms driving infection-related cancers, targeted agents that specifically block the functions

of viral gene products will likely be developed. Finally, viral proteins expressed on the surface of pathogen-associated cancer cells represent attractive targets for various immunotherapeutics.

KEY POINTS

- Infection-associated cancers are common, affecting more than 2 million people per year worldwide, and most of these cancers result from chronic viral infections.
- Infectious agents frequently subvert molecular pathways related to the hallmarks of cancer, including cell-cycle checkpoints, proliferation, and apoptosis.
- The study of infection-associated cancers provides insights into the molecular basis of sporadic cancers.

EMERGING CONCEPTS IN TUMOR HETEROGENEITY AND EVOLUTION

Whereas initial studies from TCGA and other consortia were aimed at cataloging gene mutations and other changes in primary tumors from a wide range of organ/tissue types, later efforts included analyses of multiple biopsies from the same tumor, concurrent biopsies of primary and matched metastatic lesions (synchronous), and multiple biopsies over time (metachronous). Newer studies include single-cell NGS approaches. These data allow comprehensive studies of genetic heterogeneity within a single tumor, as well as the dynamic process of tumor evolution at various stages of the disease and its treatment.[15,162] It is now apparent that tumors may exhibit heterogeneous cell populations with distinct genetic changes at their earliest stages and that the idea of a linear progression of tumor evolution is overly simplistic.[15] In one seminal example, analysis of separate regions within a single primary renal cell carcinoma revealed marked genetic heterogeneity.[163] Heterogeneity has important implications for the selection of therapies based on the presence of targetable mutations in a single biopsy specimen, and it also informs our understanding of tumor evolution. For example, inactivation of the tumor suppressor *VHL* was the only genetic lesion present in all samples from a single renal cell carcinoma in the study by Gerlinger et al.[163] By contrast, other frequently mutated genes exhibited multiple and distinct mutations within different areas of the tumor. This suggests a model where the heterogeneous landscape of primary tumors serves as the substrate for subsequent tumor evolution, during which specific clones are enriched or lost as tumors grow, invade, and metastasize.

Molecular comparisons of metastatic lesions with their antecedent primary tumors reveal a similarly complex picture of tumor evolution, including the maintenance and/or enrichment of founder mutations, as well as new mutations unique to the metastatic lesions.[164,165] Indeed, discrete metastases can have markedly different genetic profiles. Together, these types of studies reveal complex models of tumor evolution, such as parallel evolution, where subclones within a single tumor may evolve independently of one another, and convergent evolution, where unique clonal populations develop molecularly distinct, but functionally equivalent, alterations in common cancer pathways. It should be noted that many studies of tumor evolution are based on exome or genome sequencing only; therefore, other molecular events such as copy-number variation, epigenetic effects, and proteomic changes are less understood. Finally, large-scale genetic changes, such as CIN or chromothripsis (extensive DNA rearrangements that cluster in specific genomic regions), can be seen in both primary and metastatic tumors. Whether these changes are causes or consequences of tumor evolution remains controversial, but there is much interest in targeting these processes in the clinic.[166,167]

Although understanding the heterogeneity and evolution of a patient's tumor could greatly affect therapeutic decisions, serial tumor sampling via invasive biopsy techniques is not readily feasible or favored by patients. However, leveraging improved technology for liquid biopsy, where a variety of circulating biomarkers can be isolated from routine blood draws, allows for easier sampling across the cancer continuum, from diagnosis to treatment to surveillance.[168] At diagnosis, liquid biopsies may simplify the identification of targetable mutations, especially when primary biopsy specimens are limited or uninformative. Commercially available genetic panels can be used to look for driver mutations in lung and other cancers using whole blood. Because liquid biopsies can monitor tumor evolution in real time, they can also serve as adjuncts to standard assessments of tumor response/progression after therapy has begun. For example, serial sampling of circulating tumor DNA from patients with *KRAS* wild-type colorectal cancer was used to investigate mechanisms of resistance to cetuximab.[169] This analysis showed evidence of *KRAS*-mutated subclones that were enriched after prolonged cetuximab therapy. Notably, cetuximab withdrawal led to resensitization of the tumor to this agent. Similarly, in lung cancer, blood can be used to look for secondary resistance mutations in driver genes, such as *EGFR* T790M, that arise after treatment with certain kinase inhibitors. The specific driver mutation can provide clues that influence drug choice in subsequent lines of therapy.

Finally, as the tools for monitoring become more sensitive, liquid biopsy may prove useful in other disease settings. Current studies are underway to explore the use of circulating biomarkers for early detection (tumor screening in asymptomatic individuals) and minimal residual disease (surveillance for recurrence after therapy). However, for now, these approaches remain investigational.

MODELS OF HUMAN CANCER

Genetic techniques developed over the last two decades now make it possible to create mouse models that recapitulate sporadic human cancers with increasing fidelity. The first generation of genetically engineered mouse models involved expressing oncogenes from transgenes (genes injected into oocytes) or developing knockout strains in which genes were inactivated by homologous recombination in mouse embryonic stem cells.[170] Hundreds of genes have been studied with these techniques, which have led to important advances in the understanding of gene functions in development and tumorigenesis. In fact, these methods are still in wide use today. However, these strategies affect gene expression early in development and, in the case of knockouts, affect every cell in an organism. These characteristics limit the ability to model human cancers, which sequentially acquire rare mutations in somatic cells.

Many cancer genes are lethal when disrupted in the mouse germline or lead to rapidly developing neoplasms in one tissue, precluding studies of slower-growing cancers. Various mouse genetic engineering strategies have been developed to circumvent these problems, for example, by restricting mutations to specific cell types or tissues or by temporally controlling gene mutation through the use of molecular switches. These approaches have led to mouse models that much more closely recapitulate human cancers.[171] Furthermore, the use of CRISPR/Cas9 gene editing systems to produce mouse strains with engineered oncogenic mutations is also revolutionizing the development of mouse cancer models, particularly by allowing the rapid development of mice with multiple mutations across different genes in a single step.[172]

Sophisticated xenografting methods, in which human cells are grown in murine hosts, are increasingly used for cancer biology research and may be useful tools to help guide treatment decisions in the future. Patient-derived xenografts (PDXs) are human tumor explants that are directly grown in immunocompetent mice, which is a more physiologic approach than establishing tumor cell lines in petri dishes. PDXs can be readily subjected to sequencing and screening approaches that seek to identify therapeutic vulnerabilities. Moreover, there is the potential to use PDX-bearing avatar mice to determine which chemotherapy drugs may be effective for the patient from whom the PDX was derived.[173] At present, widespread use of PDX models is hampered by high expense, high failure rates, and the prolonged time required to establish and propagate models. In addition, the investigation of novel immunotherapeutic approaches is hampered by the cross-species model of a human tumor in the background of the mouse immune system. To overcome this limitation, the development of mice with a humanized immune system is being used to further test immuno-oncology hypotheses in this model system.

Patient-derived organoids have recently been developed to characterize the biology and behavior of normal tissues and tumors.[174] Patient-derived organoids can be rapidly cultured directly from fresh tumor biopsies or surgical specimens in three-dimensional culture. This addresses some of the challenges of PDXs to allow broader use of real-time chemotherapy-sensitivity testing in the future. However, patient-derived organoids do not necessarily recapitulate immunologic responses because of their rapid growth and synthetic environment.

Although recent studies suggest that drug testing on patient-derived organoids can predict clinical treatment response, existing methods for making patient-derived organoids remain slow and costly. New approaches using novel emulsion microfluidics-based technology can create patient-derived micro-organospheres, a novel high-fidelity model of a patient's tumor generated in days, at low cost and with a high success rate. The technology generates thousands of microfluidics-based droplet organoids by mixing suspended cells from a small fraction of a biopsied tumor. Thousands of micro-organospheres can be generated quickly, tracked over weeks, and passaged indefinitely. A recent study highlighting this approach in patients with metastatic colorectal cancer used micro-organosphere technology and demonstrated that it could reliably assess tumor drug response in a timeframe that could be used for treatment decision-making.[175]

KEY POINTS

- NGS offers revealing, transformative, and comprehensive insights into cancer genomics.
- These technologies may enable personalized, targeted cancer therapy strategies based on specific mutations detected in a patient's tumor cells.
- Serial tumor biopsy reveals marked tumor heterogeneity and provides insights into tumor evolution that affect the selection of cancer therapies.
- Gene targeting and transgenic methods are used to create mouse models that mimic the genetic mutations found in human cancers. These models are invaluable for understanding the mechanisms underlying tumorigenesis and are used to determine the role of specific mutations in multistep tumorigenesis.
- Xenografting of patient tumor samples into mice is an additional aspect of personalized cancer medicine; it provides a potential platform to study tumor biology and treatment response in a timeframe that could allow therapeutic decisions to be based on results obtained with animal models.

HIGH-YIELD TAKEAWAYS

- Cancer develops through defined hallmarks, with oncogene activation, tumor suppressor loss, and inflammation driving tumor initiation, progression, and therapeutic targeting.
- NGS enables precision oncology by identifying actionable mutations and detecting inherited cancer risks, such as BRCA-related breast and ovarian cancers and Lynch syndrome–associated colorectal and endometrial cancers.
- Targeted therapies and immunotherapies (eg, HER2 inhibitors, immune checkpoint blockade) improve outcomes by exploiting oncogenic and immune vulnerabilities, though resistance mechanisms remain a major challenge.

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

MOLECULAR BIOLOGY 2

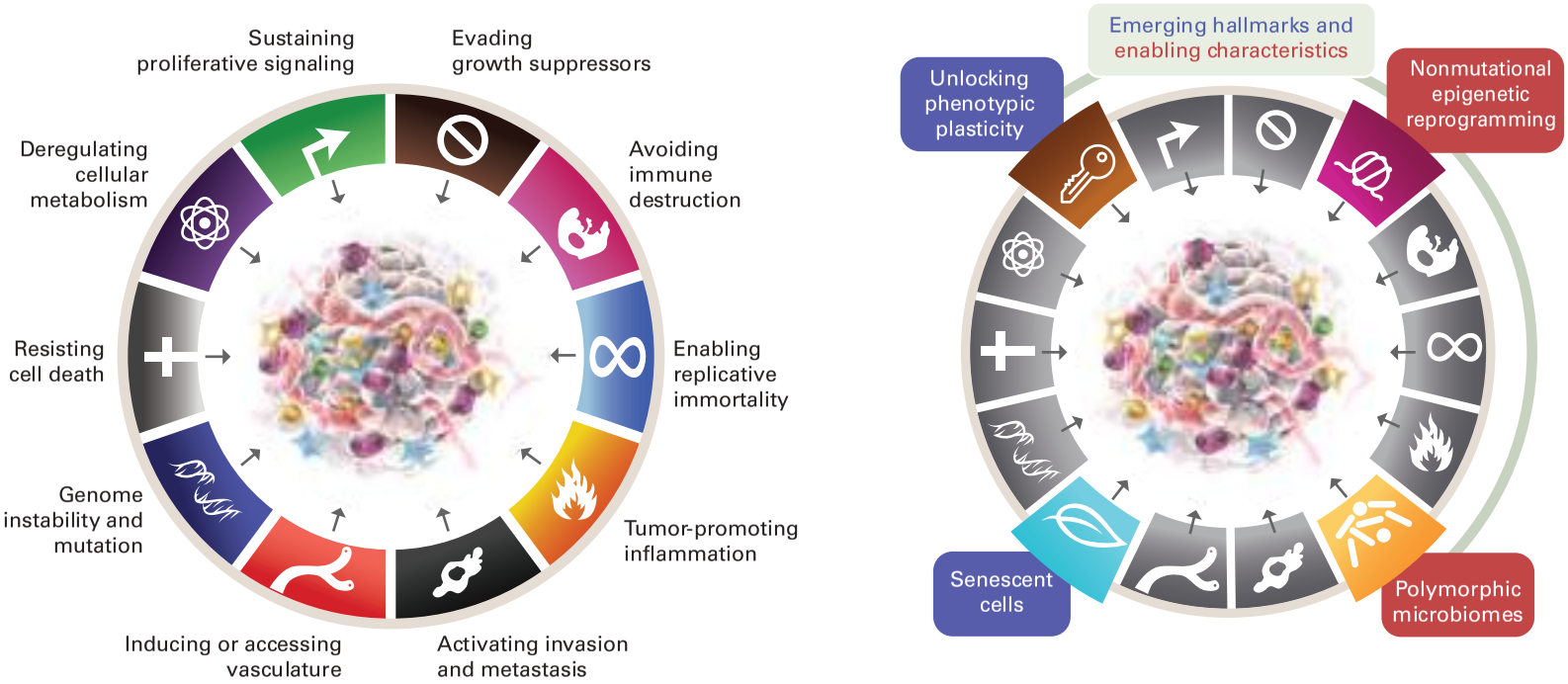
CHAPTER SUMMARY GUIDE

KEY POINTS

- Tumorigenesis is a multistep process that requires the gain of multiple mutations or characteristics that subvert safeguards preventing normal cells from transforming into cancer cells.
- All tumors share a number of hallmarks that contribute to their malignant phenotypes, but the specific molecular events that produce these phenotypes vary greatly among tumor types and individuals.
- Understanding of the hallmarks of cancer informs the development of targeted therapies.
- Genes are functional units of DNA that control the production of RNAs and proteins.
- Cells express only a subset of the genes contained within their genomes. Protein-coding genes are transcribed into mRNA in a process that is controlled by regulatory DNA elements (eg, enhancers and promoters).
- Noncoding RNAs, including miRNAs and long noncoding RNAs, are important regulators of gene expression and are often deregulated in human cancers.
- Gene expression is also regulated by epigenetic modifications of DNA and histones. Such chromatin modifications, which include methylation and acetylation, play a major role in determining the timing and extent of gene expression.
- Enzymes that catalyze epigenetic modifications are potential targets for cancer therapeutics.
- NGS methods use computational analysis of short nucleic acid sequence reads aligned with reference genome sequence information.
- NGS can define full mutational landscapes of individual tumor samples, including alterations in DNA sequence, as well as structural changes and epigenetic changes.
- Single-cell NGS provides insights into tumor heterogeneity and the complex cellular interactions within the tumor immune microenvironment.
- Analyses of mRNA by techniques such as reverse transcription PCR or RNA sequencing measure the expression of specific genes in tumor samples. This provides insights into cancer biology, as well as important diagnostic and prognostic information.
- Whole-genome genetic screens using small interfering RNA or CRISPR/Cas9 technologies can identify genes that promote or suppress cancer or mediate resistance to chemotherapy.
- Karyotyping reveals gross chromosomal structural anomalies in tumor cells, such as translocations and chromosomal deletions.
- FISH techniques detect structural alterations, such as translocations, deletions, fusions, and copy-number variations, directly inside cancer cells.
- Genome alterations identified by FISH are clinically relevant because they can predict sensitivity to molecularly targeted therapies and can be used to detect residual disease in hematologic cancers.
- Protein analyses reveal protein abundance, as well as functional modifications, such as phosphorylation and acetylation.
- Antibody-based protein detection techniques, such as Western blotting, ELISA, IHC, and flow cytometry, are used in a wide variety of clinical settings, including immunophenotyping for cancer diagnosis and classification, detection of minimal residual disease, and selection of therapy.
- Novel high-throughput protein analyses allow for large numbers of proteins to be analyzed in highly multiplexed fashions.
- MS-based proteomics allows for large-scale analyses of protein expression and modifications in tumor tissues.
- Proto-oncogenes are normal cellular genes that can be converted into oncogenes by mutations or epigenetic mechanisms, which alter their normal function or expression.
- Oncogenes encode proteins that are activated in tumors by mechanisms such as amplification, point mutation, and translocation. Oncogenes operate dominantly, and alteration of a single gene is sufficient to promote transformation.
- Tumor suppressor genes are inactivated in tumors by mechanisms such as deletion, point mutation, and gene silencing. Because they act in recessive fashion, the other copy of the gene must be deleted, typically by loss of heterozygosity.
- Mitogenic signaling pathways contain broadly acting proto-oncogenes, and their products are tyrosine kinases. Small-molecule kinase inhibitors and antibody-based therapeutics target many of these proteins.
- Genes that promote or inhibit the normal cell cycle are commonly mutated in cancer cells and are becoming important targets for cancer treatment.

- Many oncogenic mutations disrupt normal apoptotic responses. Inhibitors of proapoptotic proteins constitute another important new class of anticancer drugs.
- Enzymes that promote protein degradation by the proteasome can function as tumor suppressors.
- Pharmacologic proteasome inhibitors are approved for the treatment of multiple myeloma and other hematologic cancers.
- Genes that regulate cellular differentiation are often mutated in hematologic cancers. Drugs that restore normal differentiation are important treatments for these diseases.
- DNA repair pathways contain many tumor suppressor genes that are mutated in both familial and sporadic cancers. Mutations that disable different elements of DNA repair pathways are associated with specific cancer syndromes.
- Inactivation of DNA-damage repair genes may predict response to PARP inhibitors and DNA-damaging agents.
- Inactivation of DNA MMR enzymes leading to MSI and high tumor mutation burden predicts response to PD-1 inhibitors.
- Checkpoints ensure the fidelity of cell division and protect against genomic instability.
- Checkpoint pathways are often dependent on normal tumor suppressor gene and DNA repair protein functions.
- Loss of checkpoint functions causes genomic instability and fosters the accumulation of multiple mutations in cancer cells.
- *TP53* is the most commonly mutated cancer gene, and it participates in diverse checkpoint responses. The p53 protein senses and responds to cellular stress by activating pathways that regulate processes such as cell-cycle progression and apoptosis.
- The mitotic checkpoint protects against chromosome loss, but this process is error-prone in many cancers, leading to CIN.
- Infection-associated cancers are common, affecting more than 2 million people per year worldwide, and most of these cancers result from chronic viral infections.
- Infectious agents frequently subvert molecular pathways related to the hallmarks of cancer, including cell-cycle checkpoints, proliferation, and apoptosis.
- The study of infection-associated cancers provides insights into the molecular basis of sporadic cancers.
- NGS offers revealing, transformative, and comprehensive insights into cancer genomics.
- These technologies may enable personalized, targeted cancer therapy strategies based on specific mutations detected in a patient's tumor cells.
- Serial tumor biopsy reveals marked tumor heterogeneity and provides insights into tumor evolution that affect the selection of cancer therapies.
- Gene targeting and transgenic methods are used to create mouse models that mimic the genetic mutations found in human cancers. These models are invaluable for understanding the mechanisms underlying tumorigenesis and are used to determine the role of specific mutations in multistep tumorigenesis.
- Xenografting of patient tumor samples into mice is an additional aspect of personalized cancer medicine; it provides a potential platform to study tumor biology and treatment response in a timeframe that could allow therapeutic decisions to be based on results obtained with animal models.

Figure 2-1 Hallmarks of Cancer



The latest version of the hallmarks of cancer includes two emerging hallmarks and two enabling characteristics (right). These include unlocking phenotypic plasticity and senescent cells (emerging hallmarks) and non-mutational epigenetic reprogramming and polymorphic microbiomes (emerging enabling characteristics).
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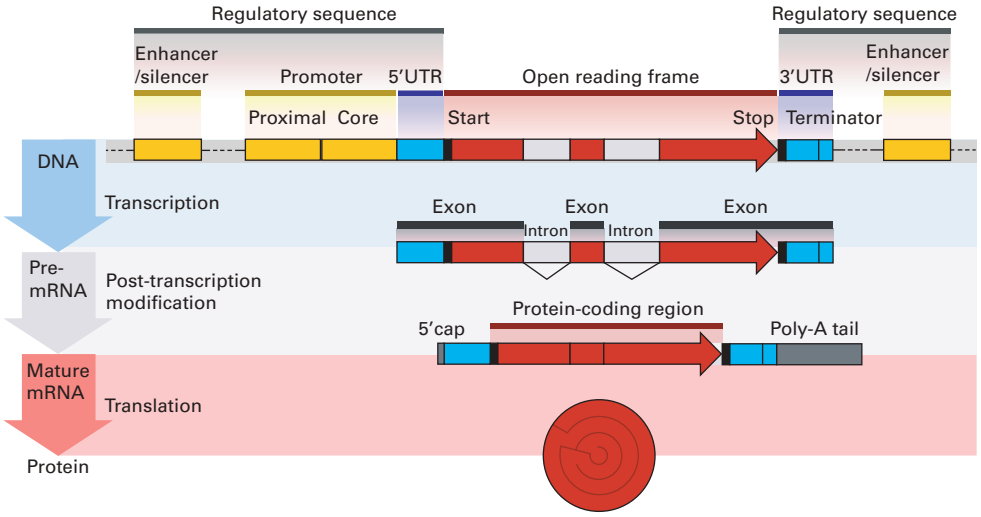
Figure 2-2 Schematic Diagram of an Idealized Gene



Schematic diagram of an idealized gene, including promoter elements, an enhancer, and the transcribed region of the gene. Regulatory sequences control when and where the protein-coding region is expressed. Promoter and enhancer regions regulate the transcription of the gene into a pre-mRNA, which is modified to add a 5′ cap and poly-A tail and remove introns. The mRNA 5′ and 3′ UTRs regulate translation of the final protein product.
Abbreviations: mRNA, messenger RNA; UTR, untranslated region.
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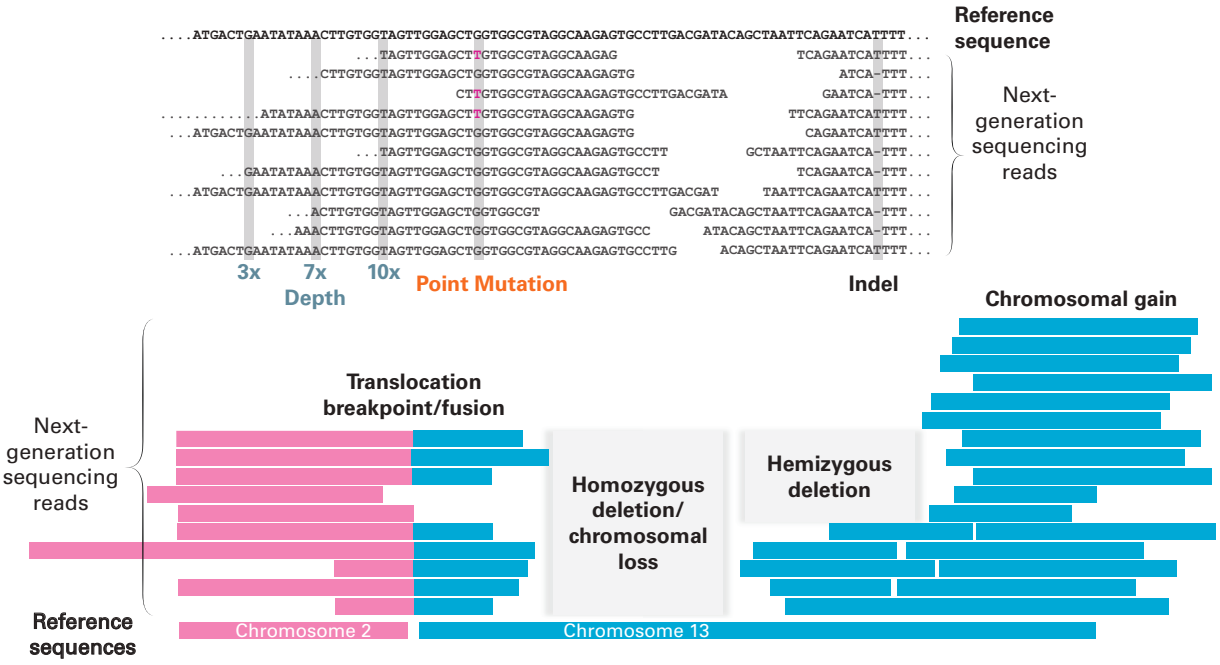
Figure 2-3 Types of Mutations Discovered by Next-Generation Genomic Sequencing



The upper diagram illustrates the alignment of different sequence reads created during NGS. Sequences are aligned to cover the reference genome. Sequencing depth describes the number of sequences produced, identified, and aligned around a specific region. The point mutation example shows the *KRAS* complementary DNA sequence as a reference and a c.34G > T mutation that results in the G12C variant of *KRAS*. Note that the mutation is not present in all reads of this analysis. Less common variants require a higher number of reads (ie, greater depth of sequencing). The small deletion (indel) has been inserted for illustration purposes only. The lower diagram presents a broader perspective of NGS results. It illustrates the translocation t(2;13) of *PAX3* on chromosome 2 with *FKHR* on chromosome 13, a translocation frequently found in alveolar rhabdomyosarcoma. Also shown are examples of a homozygous or hemizygous loss of chromosome 13, which occurs frequently in retinoblastoma, breast cancer, and prostate cancer, among others. In addition, chromosomal gain may occur in other settings, such as metastatic colorectal cancer.
Abbreviation: NGS, next-generation sequencing.
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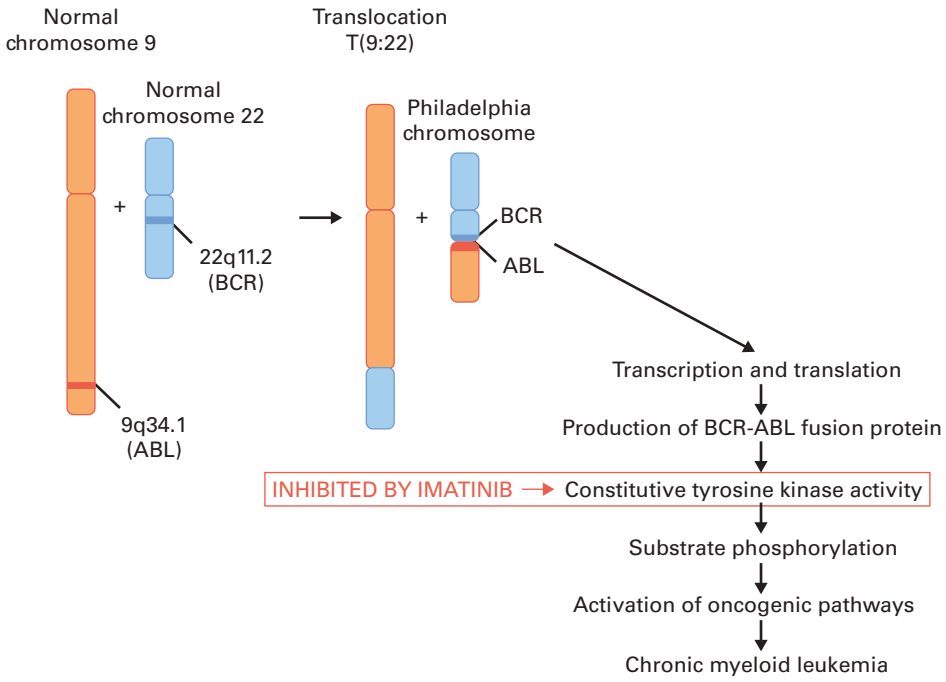
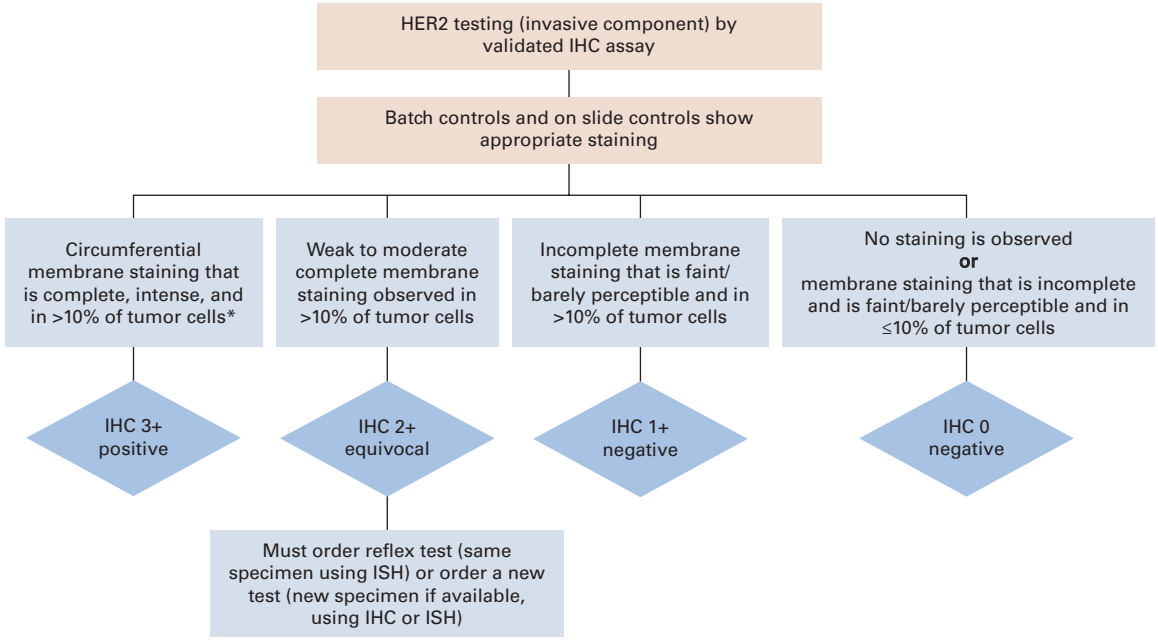
Figure 2-4 Translocation Leading to the Ph Chromosome and Role of BCR::ABL in the Pathogenesis of CML



The Ph chromosome is a foreshortened chromosome 22 resulting from an exchange between the long arms of chromosomes 9 and 22. This leads to the production of a BCR::ABL fusion protein that has constitutive kinase activity and promotes the development of CML. The tyrosine kinase inhibitor imatinib inhibits this constitutive kinase activity and can lead to long-term control of CML.
Abbreviations: CML, chronic myeloid leukemia; Ph, Philadelphia.
Reproduced under Creative Commons license. Source: Schematic of the Philadelphia chromosome. Wikimedia. Published December 8, 2014. Updated January 22, 2019. Accessed April 09, 2025. https://commons.wikimedia.org/wiki/File:Schematic_of_the_Philadelphia_Chromosome.svg

Figure 2-5 Algorithm for Evaluation of HER2 Protein Expression by IHC Assay of the Invasive Component of a Breast Cancer Specimen



Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
*Readily appreciated using a low-power objective and observed within a homogeneous and contiguous invasive cell population.
Reprinted from Wolff AC, Somerfield MR, Dowsett M, et al. Human epidermal growth factor receptor 2 testing in breast cancer: ASCO–College of American Pathologists guideline update. Published online June 7, 2023. doi:10.1200/jco.22.02864
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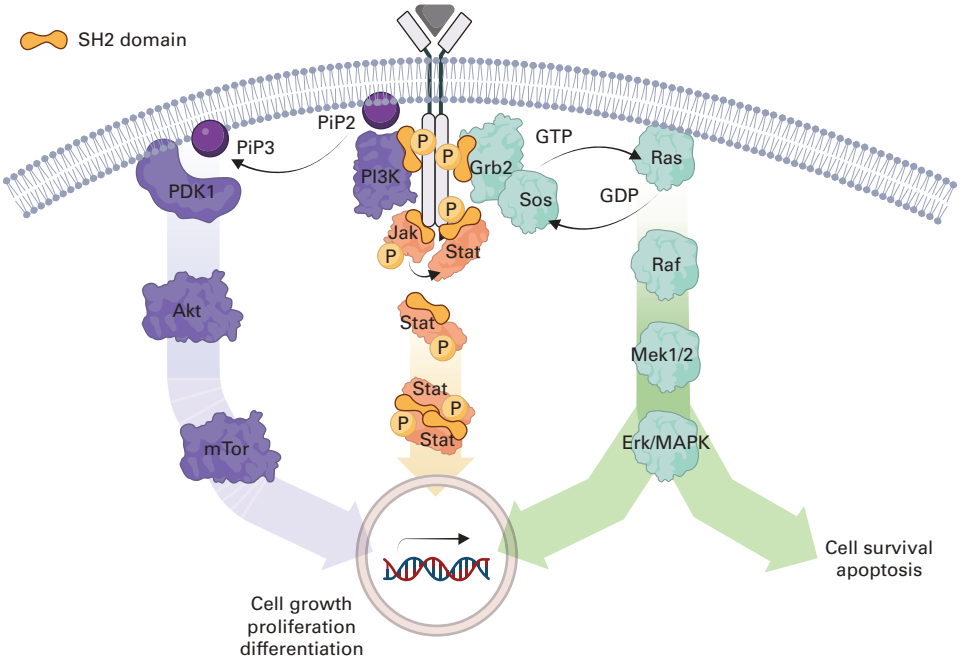
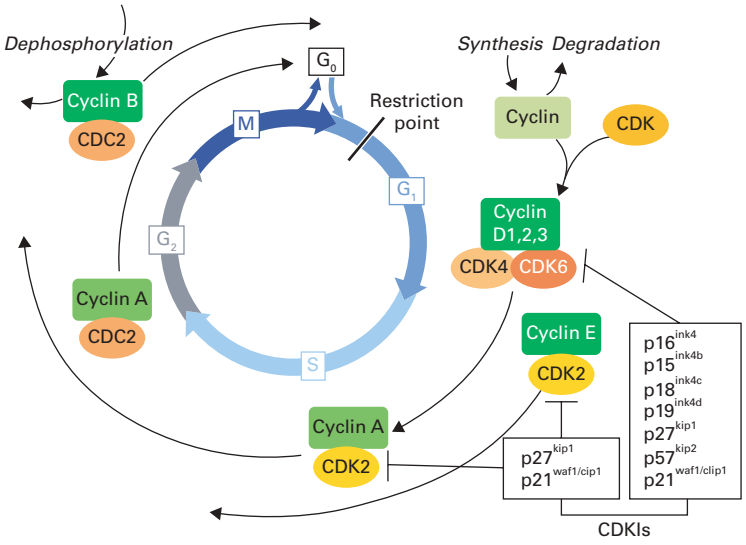
Figure 2-6 Mitogenic Signaling



This figure shows schematically the binding of an extracellular signal (dark gray triangle) to a transmembrane receptor (light gray structure transversing the cell membrane) that is being phosphorylated in the process, usually on tyrosine residues, yielding phosphotyrosines (Ps in yellow circles). Adapter molecules containing SH2 domains bind to the phosphotyrosines and recruit effector proteins in doing so. The examples in this figure (purple) are phosphoinositide 3-kinase (PI3K) and its downstream target phosphoinositide 3-kinase-dependent kinase (PDK1), which, in turn, activates protein kinase B (Akt). Akt activates the mammalian target of rapamycin (mTor), that is exerting promitogenic transcription, differentiation, or cell growth in the cell nucleus. Also, SH2 domain-containing molecules may recruit (orange pathway) Janus kinases (Jaks) and signal transducers and activators (Stats). Jaks phosphorylates Stats on tyrosine residues, amplifying the original signal from the transmembrane receptors. Stats themselves can shuttle into the nucleus and initiate or promote the described processes. The green route illustrates the amplification of the original phosphotyrosine signal via the growth factor-bound protein 2 (Grb2) and rat sarcoma protein (Ras) and its subsequent effectors. Activation of this route may lead to cell growth, proliferation, and differentiation, or cell survival and diminished apoptosis.

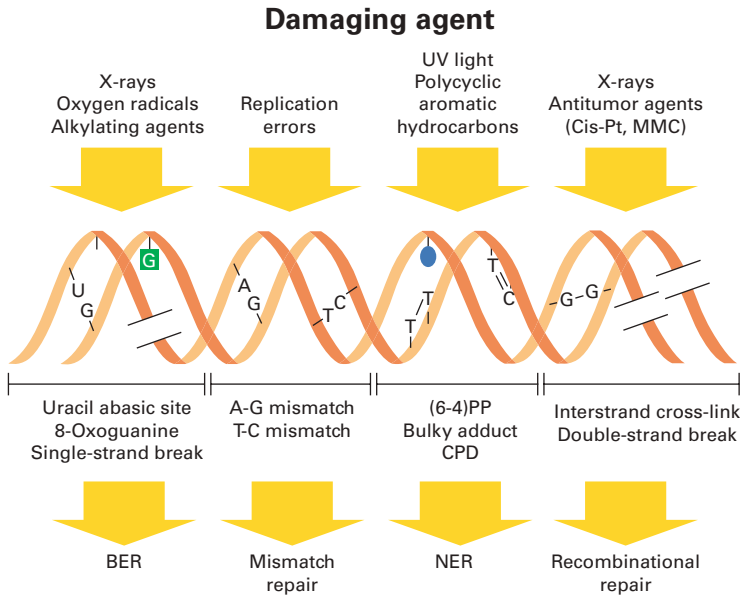
Reproduced under Creative Commons license. Source: Diop A, Santorelli D, Malagrino F, et al. SH2 domains: folding, binding and therapeutical approaches. *Int J Mol Sci*. 2013;23(24), figure 4. doi:10.3390/ijms232415944

Figure 2-7 The Cell Cycle



The cell cycle is divided into four phases (G1, S, G2, and M). Progression through the cell cycle is promoted by CDKs, which are regulated positively by cyclins and negatively by CDK inhibitors. The restriction point is the point at which cells progress through the cell cycle independently of external stimuli.
Abbreviation: CDK, cyclin-dependent kinase.
Reproduced with permission from Schwartz GK, Shah MA. Targeting the cell cycle: a new approach to cancer therapy. *J Clin Oncol*. 2005;23:9408-9421. doi:10.1200/JCO.2005.01.5594

Figure 2-8 DNA Lesions and Repair Mechanisms



Common DNA-damaging agents (top), examples of lesions that can be introduced by these agents into the DNA double helix (middle), and the most frequently used repair mechanisms for such lesions (bottom). Distinct damaging sources can induce similar types of DNA lesions, and any one agent often induces more than one type of damage. The lesion spectra of different repair pathways may overlap.
Abbreviations: BER, base excision repair; CPD, cyclobutane pyrimidine dimer; MMC, mitomycin C; NER, nucleotide excision repair.
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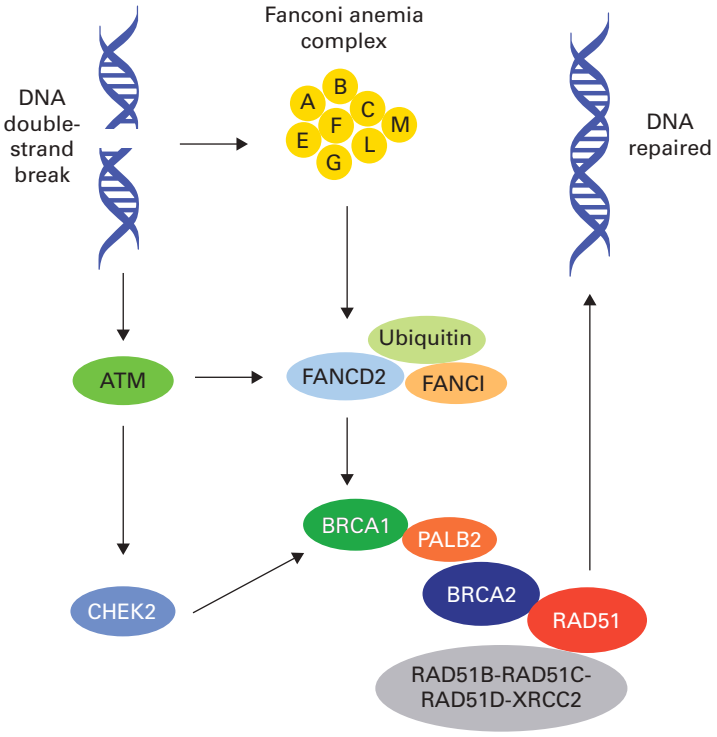
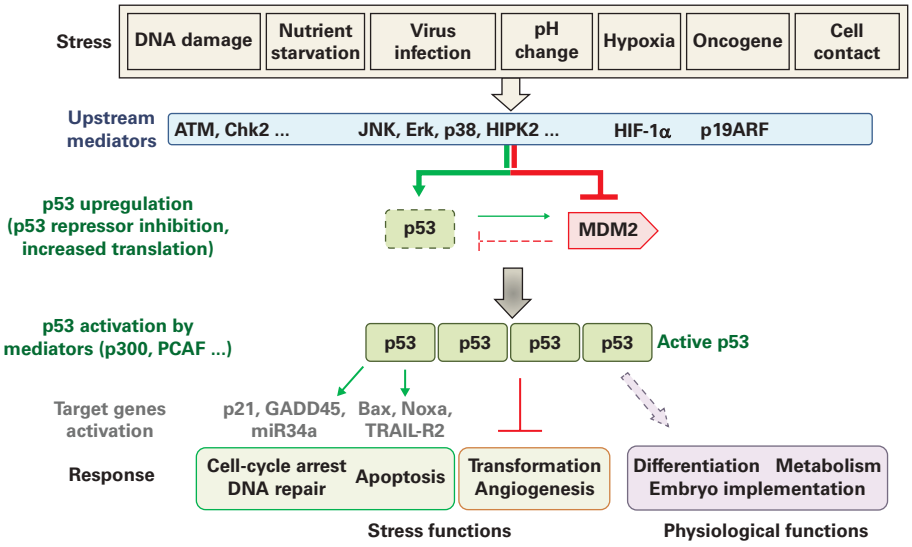
Figure 2-9 Recombinational Repair of DNA Double-Strand Damage



DNA double-strand breaks recruit protein kinase ATM and also activate the Fanconi anemia core complex (FANCA/B/C/E/F/G/L/M) that monoubiquitinates the downstream targets FANCD2 and FANCI. ATM activates (phosphorylates) CHEK2 and FANCD2, and, in turn, CHEK2 phosphorylates BRCA1. Ubiquitinated FANCD2 complexes with BRCA1 and RAD51. The PALB2 protein then acts as a hub, bringing together BRCA1, BRCA2, and RAD51 at the site of a DNA double-strand break and also binds to RAD51C, a member of the RAD51 paralog complex RAD51B-RAD51C RAD51D-XRCC2 (BCDX2). The BCDX2 complex recruits RAD51 or stabilizes the damage sites. RAD51 plays a major role in homologous recombinational repair of DNA during double-strand break repair. In this process, an ATP-dependent DNA strand exchange takes place in which a single strand invades base-paired strands of homologous DNA molecules. RAD51 is involved in the search for homology and the strand-pairing stages of the process.
Reproduced under Creative Commons license. Source: Fanconi Anemia. Wikipedia. Accessed December 1, 2022. https://en.wikipedia.org/wiki/Fanconi_anemia#/

Figure 2-10 The p53-MDM2-ARF Network



The activation of p53 classically occurs in response to many other cellular stresses that produce DNA damage, including oncogene-induced stress. Depending on the nature of the inducing signal, these DNA-damage responses activate a myriad of upstream mediators that lead to upregulation and activation of p53. This, in turn, results in activation of p53 target genes that serve to counteract the initiating cellular stress and protect the cell from further damage. When p53 is mutated or deleted, as it is in most cancers, these critical safeguards no longer function, and cellular stress continues unabated.

Uncovering the role of p53 splice variants in human malignancy: a clinical perspective by Surgent et al, taken from OncoTargets and Therapy © 2014 Surget et al. This work is published by Dove Medical Press Limited, and licensed under Creative Commons Attribution—Noncommercial (unported, v3.0) License. This is an Open Access article distributed under the terms of the Creative Commons Attribution-Noncommercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited, reprinted by permission of Informa UK Limited, trading Taylor & Francis Ltd, https://www.tandfonline.com

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CLINICAL PHARMACOLOGY 3

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RECENT UPDATES

The US Food and Drug Administration (FDA) approved 49 oncologic drugs in 2024, including 18 novel drugs and 31 new indication expansion.[1] Notable approvals include 11 new drugs and an expanded indication for the first half of 2025. Key updates on recent approval include the following:

Small Molecules

- Avutometinib in combination with defactinib for the treatment of *KRAS*-mutated recurrent low-grade serous ovarian cancer, a first-in-class, RAF/MEK clamp that inhibits MEK kinase activity.
- Sotorasib in combination with panitumumab for the treatment of *KRAS* G12C-mutated metastatic colorectal cancer.[2]
- The second-generation, brain-penetrant, oral estrogen receptor antagonist, imlunestrant, was approved by the FDA for the treatment of estrogen receptor–positive, HER2 negative.
- Dordaviprone,[3] a protease activator, represents the first systemic therapy approved for recurrent H3 *K27M*-mutant diffuse midline glioma, a rare and aggressive brain tumor.

Biologics

- Datopotamab deruxtecan-dlnk, a TROP-2 direct antibody and topoisomerase inhibitor conjugate, for the treatment of locally advanced or metastatic epidermal growth factor receptor (EGFR)-mutated non–small cell lung cancer (NSCLC) patients who have received EGFR-directed therapy and platinum-based chemotherapy and for the treatment of unresectable or metastatic, hormone receptor–positive, HER2-negative breast cancer patients who have received prior endocrine-based therapy and chemotherapy.
- A next-generation ROS1 inhibitor, taletrectinib, for ROS1-positive NSCLC.
- Telisotuzumab vedotin, an antibody-drug conjugate with a monomethyl auristatin E cytotoxic payload for the treatment of NSCLC with high c-met protein expression defined as a strong (3+) membrane and/or cytoplasmic staining on at least ≥50% of tumor cells.
- Tafasitamab-cxix[4] for relapsed or refractory follicular lymphoma, a humanized monoclonal antibody that targets and binds to the CD19 protein on the surface of B-cells, including those found in B-cell lymphomas.[5]
- Penpulimab-kcqx,[4] an anti–PD-1 monoclonal antibody for recurrent or metastatic non–keratinizing nasopharyngeal carcinoma,[6] in combination with platinum-based chemotherapy or as monotherapy.[7]
- Zenocutuzumab-zbco, a monoclonal antibody that targets HER3 and blocks interaction with HER2, for the treatment of metastatic NSCL and metastatic pancreatic cancer harboring an *NRG1* gene fusion.[8]
- *ESR1*[2]-mutated advanced breast cancer progressed after at least one line of endocrine therapy.[9]
- Cell therapy obecabtagene autoleucel (a CD19-directed genetically modified autologous T cell immunotherapy) for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).[10,11]

Drug Label Updates

- A recent FDA safety announcement highlighted the important awareness to the product labeling of capecitabine and fluorouracil (5-FU). The change in product labeling elevates the clinical significance and consequences of dosing fluoropyrimidines to patients with DPD enzyme deficiency from warnings and precautions to a black box warning. Serious or fatal adverse reactions may occur in patients with certain homozygous or compound heterozygous DYPD variants that result in complete DPD deficiency. Test for genetic variants of DYPD prior to initiating treatment is advised unless immediate treatment is necessary.[12]

OVERVIEW

Cancer therapy has changed dramatically, with biomarker-driven targeted therapies, immunotherapy, antibody-drug conjugates, radioligand therapies, and bispecific targeted therapies representing major recent advances. While patients still benefit from traditional hormone therapy and cytotoxic chemotherapy in selected cancer types, they are often given in combination or sequentially with novel therapies. Several anticancer drugs exhibit a narrow therapeutic window, with a tight difference between a toxic dose and a therapeutic dose requiring a careful balance between the anticancer treatment benefit and the adverse effects on normal tissue. This chapter provides an overview of the relevant issues and considerations related to anticancer drug therapy.

PRINCIPLES OF HORMONAL THERAPY, CHEMOTHERAPY, TARGETED THERAPIES, ANTIBODY-DRUG CONJUGATES, AND IMMUNOTHERAPIES

HORMONAL THERAPY FOR CANCER

Hormonal therapies are mostly used to treat breast cancer and prostate cancer. They work by altering the production of hormones, blocking the hormone receptors (HRs) on cancer cells, or substituting chemically similar agents for the active hormones. Hormonal therapies are categorized based on their function and/or the type of hormone that is affected. Cyclin-dependent kinase (CDK) inhibitors are used in combination with hormonal therapies for the treatment of HR-positive, HER2-negative metastatic breast cancer.

Selective Estrogen Receptor Modulator (Tamoxifen)

- Mechanism of action: Selective estrogen receptor modulators (SERMs) such as tamoxifen bind to the estrogen receptor and thereby alter the action of estrogen. Their mechanism of action depends on the activation of different hormone-binding domains, which determine antagonist, agonist, or mixed-response therapeutic action. Tamoxifen has estrogen receptor antagonist activity in the breast and agonist activity in bone. It also manifests the agonist activity in the endometrium (uterus), which increases the risk of endometrial cancer.[13]
- Adverse effects/toxicities: SERM induces menopausal symptoms such as hot flashes, nausea, and vomiting. Additional toxicities include vaginal bleeding, bone pain, menstrual irregularities, headache, and depression. Rare toxicities include retinal toxicity and thromboembolic disorders, including pulmonary emboli. Concomitant warfarin therapy with tamoxifen may increase the risk of bleeding because of an interaction via the CYP2C9 enzyme.

Aromatase Inhibitors

- Mechanism of action: Aromatase inhibitors are a class of drugs that inhibit the enzyme aromatase, which converts circulating androgens to estrogens. Aromatase inhibitors are not effective in premenopausal patients with breast cancer in whom the ovaries are the main source of estrogen production. To overcome this liability, ovarian suppression or ablation has been used in combination with aromatase inhibitors in premenopausal women with breast cancer.
- There are two types of aromatase inhibitors: steroidal and nonsteroidal. Exemestane is a steroidal irreversible aromatase inhibitor, and anastrozole and letrozole are nonsteroidal reversible aromatase inhibitors.
- Adverse effects/toxicities: Aromatase inhibitors can cause hot flashes, vaginal dryness, musculoskeletal pain, and headache.
- Aromatase inhibitors have not been associated with an increased risk of endometrial cancer as seen with tamoxifen. However, they are known to increase the incidence of bone fractures and osteoporosis because of profound suppression of estrogen levels.[14] Bone mineral density assessment is recommended before starting an aromatase inhibitor and every 2 years thereafter.

Selective Estrogen Receptor Degrader (Fulvestrant, Elacestrant, and Imlunestrant)

- Mechanism of action: In contrast to SERMs, selective estrogen receptor degraders (SERDs) are antiestrogens designed to bind to the estrogen receptor and induce its destabilization and degradation, thereby inhibiting dimerization and abolishing the estrogen receptor signaling pathway. A common mechanism of endocrine therapy resistance is the acquisition of estrogen receptor 1 (*ESR1*) mutations.[15] The first-generation SERD fulvestrant is a pure estrogen receptor antagonist with no known agonistic activity, but it has modest activity against *ESR1*-mutant tumors. Efforts to develop second- and third-generation SERDs with superior bioavailability, pharmacokinetic properties, and potent antiestrogenic activity have led to the discovery of orally available SERDs such as elacestrant and imlunestrant. These new oral selective estrogen receptor degraders effectively target ESR1 mutations, which commonly confer resistance to endocrine therapy.
- Adverse effects/toxicities: As a class, the adverse effect profile of SERDs is generally comparable with that of aromatase inhibitors, given their systemic pure antiestrogenic activity.

Fulvestrant

- Mechanism of action: Fulvestrant is a steroidal analog of 17β-estradiol that competitively binds to the estrogen receptor in cancer cells, producing a nuclear complex that leads to a dose-related downregulation of estrogen receptors and inhibits cancer growth.
- It is effective in tamoxifen-resistant, estrogen receptor–positive breast cancer.

- Adverse effects/toxicities: Fulvestrant can cause hot flashes, increased liver enzymes (over 15% incidence), abdominal pain, constipation, diarrhea, and arthralgia.

Elacestrant and Imlunestrant

- Elacestrant and imlunestrant are the oral SERDs approved by the FDA for adults with estrogen receptor–positive, HER2-negative, *ESR1* mutation–positive advanced, or metastatic breast cancer with disease progression after at least one line of endocrine therapy.
- Mechanism of action: Elacestrant and imlunestrant inhibit 17β-estradiol–mediated cell proliferation at concentrations that result in estrogen receptor alpha degradation. In vitro and in vivo data suggested these agents exhibited antitumor activity in cancer models that are resistant to fulvestrant and CDK 4/6 inhibitors, as well as in models carrying *ESR1* mutations.
- Adverse effects/toxicities: Elacestrant and imlunestrant can cause hypercholesterolemia and hypertriglyceridemia, musculoskeletal pain, hot flashes, nausea, vomiting, and fatigue.

Antiandrogens

Prostate cancer depends on testosterone for its growth. Consequently, androgen receptor inhibition results in decreased proliferation of tumor cells and a reduction in tumor volume.

First-Generation Antiandrogens (Flutamide, Bicalutamide, and Nilutamide)

- Mechanism of action: First-generation non–steroidal antiandrogens competitively inhibit the binding of androgens (testosterone and dihydrotestosterone) to the androgen receptors and thereby inhibit tumor growth.
- Half-life: Bicalutamide and nilutamide have longer half-lives of 7 and 2 days, respectively, which allows for once-daily dosing compared with a 6- to 8-hour half-life for flutamide.
- Adverse effects/toxicities: Adverse effects observed with non–steroidal antiandrogens are considered a class effect associated with the blockade of the androgen receptor. These include gynecomastia, breast pain, hot flashes, decreased libido, hepatotoxicity, and gastrointestinal (GI) symptoms.
- To avoid tumor flare from the initial testosterone surge with a gonadotropin-releasing hormone analog, first-generation antiandrogens are usually started at least 1 week before giving the gonadotropin-releasing hormone agonist. This blocks the androgen receptor from binding to testosterone.

Second-Generation Antiandrogens (Enzalutamide, Apalutamide, and Darolutamide)

- Mechanism of action: These offer advantages to overcome disease resistance. They provide stronger binding affinity to the androgen receptors and prevent androgen receptor translocation, DNA binding, and receptor-mediated transcription.
- Adverse effects/toxicities: As a class effect, second-generation antiandrogens increase the risk of seizures because of off-target g-aminobutyric acid A inhibition. Enzalutamide has the highest risk of seizures compared with apalutamide and darolutamide, given the degree of central nervous system (CNS) penetration.

Luteinizing Hormone (Gonadotropin)–Releasing Hormone Analogs (Goserelin and Leuprolide) and Antagonist (Degarelix and Relugolix)

- Mechanism of action: Luteinizing hormone (gonadotropin)–releasing hormone (LHRH/GnRH) analogs bind to the LHRH/GnRH receptor on the hypothalamus, causing an initial surge in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). With prolonged administration, LHRH/GnRH agonists desensitize the pituitary gland, downregulate the GnRH receptor, thereby decreasing the production of LH and FSH. Reduced LH and FSH results in suppression of the production of sex hormones.
- Degarelix and relugolix are unique antagonists that target and block gonadotropin-releasing HRs, leading to a rapid decrease in testosterone without a surge in secretion of LH and FSH. An advantage of using degarelix and relugolix is the avoidance of tumor flare (manifested as bone pain).
- Adverse effects/toxicities: These can cause hot flashes, weight gain, impotence, reduced libido, GI disturbances (constipation, nausea, and vomiting), gynecomastia, and peripheral edema. Long-term androgen deprivation therapy prolongs the QT interval and can increase the risk of cardiovascular disease, including myocardial infarction, hypertension, and stroke.

Abiraterone Acetate

- Mechanism of action: Abiraterone is a pregnenolone derivative that irreversibly inhibits 17α-hydroxylase/17,20-lyase, an enzyme that converts pregnenolone and progesterone into androgens, dehydroepiandrosterone, and androstenedione. These androgens are then converted into testosterone and dihydrotestosterone in peripheral tissues. Enzymes such as 17α-hydroxylase/17,20-lyase involved in steroid synthesis are often upregulated in hormone-refractory prostate cancer. Abiraterone lowers serum testosterone concentration to castrate levels without significantly affecting serum hydrocortisone levels.

- In addition, because of 17α-hydroxylase/17,20-lyase inhibition, abiraterone can cause increased mineralocorticoids as a result of compensatory upregulation of the hypothalamic-pituitary-adrenal axis. Consequently, this may result in hypertension, hypokalemia, and fluid retention. Concomitant administration with corticosteroids is vital and reduces the incidence and severity of these adverse events.
- Adverse effects/toxicities: These include cardiovascular issues (congestive heart failure and arrhythmias), adrenal insufficiency, adrenocortical insufficiency, and hepatotoxicity.

CYTOTOXIC CHEMOTHERAPY

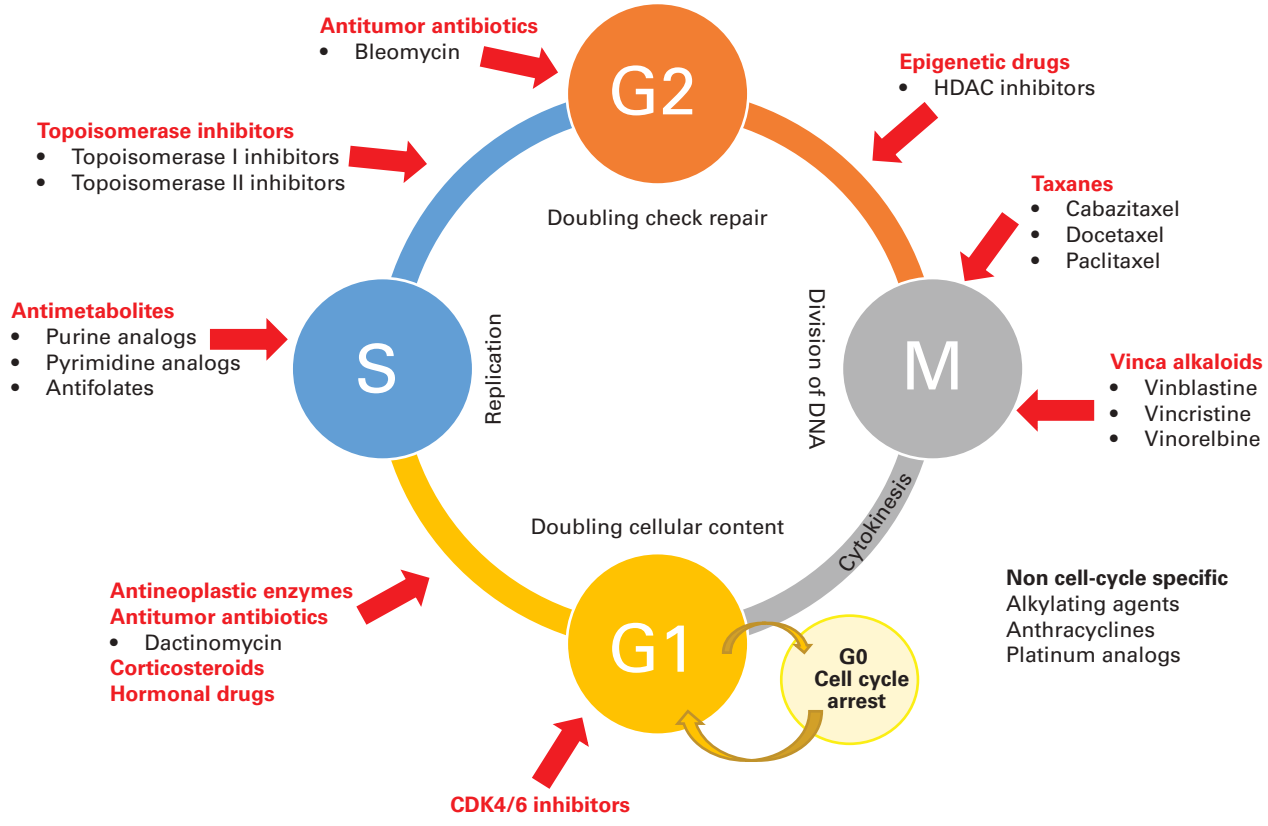
Cytotoxic chemotherapy is commonly used for the treatment of a wide variety of cancers. While this is a heritage therapy introduced to the clinic decades ago, it remains the most frequently prescribed class of drugs. The goal is to inhibit cell proliferation and growth, thus avoiding cancer cell invasion and metastasis. The cytotoxic effect of chemotherapy is most significant during the S phase, as it interferes with DNA synthesis, entry into M phase, and mitosis. Three basic principles underlie the use of cytotoxic chemotherapy:

1. The fractional cell kill hypothesis, which states that a constant proportion of cells are killed per cycle;
2. A linear relationship between drugs administered and cell kill; and
3. The Goldie-Coldman hypothesis, which suggests that tumors acquire a spontaneous mutation that confers drug resistance.

These principles apply best to rapidly growing cancers, such as leukemias and lymphomas, and they at least partially explain why cytotoxic chemotherapy is most effective in rapidly growing cells. Based on these principles, cytotoxic chemotherapy is typically administered for multiple cycles at the highest tolerable dose, in combination with other agents with different mechanisms of action and non–overlapping adverse effects. They have a narrow therapeutic index, and adverse effects can be severe and sometimes fatal. These agents are potentially curative in some malignancies, such as testicular cancer.[16] However, clinical use of cytotoxic chemotherapy depends on the ability to balance the killing of cancer cells with minimizing toxicity to the normal cells.

Chemotherapy agents can be classified based on their effects on the cell cycle. Cell cycle–specific agents preferentially kill proliferating cells while non–cell cycle–specific agents kill both normal and cancer cells. Each of the transitions in the cell cycle requires activation of CDKs. Chemotherapy can be divided into several categories based on its mechanism of action (Fig. 3-1).

Figure 3-1 Cell Cycle and Site of Cytotoxic Agents



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Alkylating Agents

- Mechanism of action: There are six classes of alkylating agents: (1) alkyl sulfonates (bendamustine and busulfan), (2) DNA methylating (procarbazine), (3) ethyleneimines (thiotepa), (4) nitrogen mustards (cyclophosphamide, ifosfamide, and melphalan), (5) nitrosoureas (carmustine), and (6) triazenes (dacarbazine and temozolomide). Their mechanism of action involves interfering with the DNA replication process, causing DNA cross-linking and preventing the strands of DNA from separating. They also inhibit cell division and replication by inhibiting the transcription of DNA to RNA, thereby stopping protein synthesis.
- Cyclophosphamide and ifosfamide are prodrugs that require cytochrome P450 metabolism to release active alkylating metabolites: phosphoramide mustard and acrolein. Mesna is usually administered with these agents to prevent acrolein-induced hemorrhagic cystitis.
- Adverse effects/toxicities: The primary dose-limiting toxicity is bone marrow suppression, with secondary limiting effects on the proliferating cells of the intestinal mucosa. The extent and onset of leukocyte, platelets, and red cell suppression vary among agents, with a nadir at 6 to 10 days and recovery in 14 to 21 days (post-dosing). Nausea and vomiting are frequent side effects of alkylating agents. The frequency and severity are dependent on the dose of the alkylating agent. Important delayed toxicities include cardiotoxicity, non–infectious pneumonitis, peripheral neuropathy, infertility, veno-occlusive disease, and secondary malignancies.
- The highly lipid-soluble alkylating agents can cross the blood-brain barrier and cause CNS toxicity, including seizures, altered mental status, cerebellar dysfunction, and cranial nerve palsies.
- The functionality of one alkylating agent, temozolomide, is limited in the presence of the DNA repair enzyme *O*-6-methylguanine-DNA methyltransferase (MGMT).

Platinum Analogs (Carboplatin, Cisplatin, and Oxaliplatin)

- Mechanism of action: Platinum analogs bind to the N7 position of guanine and adenine residues, leading to the formation of intrastrand or interstrand cross-links, thereby preventing the DNA strands from unwinding properly during replication. These cross-links trigger cellular signaling pathways that recognize DNA damage, leading to cell cycle arrest.
- Adverse effects/toxicities: Most common and significant side effects are bone marrow suppression, nausea and vomiting, diarrhea, nephrotoxicity, ototoxicity, hypersensitivity reactions, and electrolyte imbalances. To mitigate these toxicities, vigorous hydration and electrolyte supplementation are often administered before treatment with platinum analogs. With repeated administrations, hypersensitivity reactions become a significant problem with platinum analogs. Several strategies have been proposed, including switching to other platinum agents, skin testing,[17] desensitization,[18] step-up dosing, and prolonged duration of infusion.
- Because of structural differences from other platinum analogs, oxaliplatin can affect sensory neurons and cause peripheral neuropathy, which may be exacerbated by cold temperatures. The risk of developing neuropathy increases with cumulative doses of oxaliplatin.

Antimetabolites

- Mechanism of action: Antimetabolites interfere with DNA and RNA synthesis by competing for the binding sites on key enzymes for nucleotide synthesis and mimicking natural metabolites. Examples of antimetabolites are (1) purine analogs (cladribine, clofarabine, fludarabine, mercaptopurine, nelarabine, pentostatin, and thioguanine), (2) pyrimidine analogs (capecitabine and fluorouracil), (3) folate antagonists (methotrexate, pemetrexed, and pralatrexate), and (4) cytidine analogs (cytarabine and gemcitabine). Notably, fluorouracil is commonly coadministered with leucovorin; the L isomer enhances the effect of 5-fluorouracil (5-FU) by inhibition of thymidylate synthetase. The cytotoxic effects of antifolates are mediated by their respective polyglutamate metabolites, which are potent and directly inhibit enzyme dihydrofolate reductase, thymidylate synthase, and other key enzymes involved in purine biosynthesis.
- Adverse effects/toxicities: The main side effects are myelosuppression, mucositis, skin rash, hepatotoxicity, neurotoxicity, nephrotoxicity, and GI toxicity. Methotrexate-induced nephrotoxicity results from the intratubular precipitation of its metabolites in acidic urine. In addition, renal excretion is inhibited in the presence of other drugs such as probenecid, penicillin, cephalosporins, aspirin, and non–steroidal anti-inflammatory drugs. High-dose methotrexate can be fatal unless reversed by leucovorin initiated within 42 hours.

Topoisomerase Inhibitors

- Mechanism of action: There are two main types of topoisomerases: (1) topoisomerase I (TOP1) and (2) topoisomerase II (TOP2). TOP1 acts by untwisting the DNA duplex, thereby allowing DNA supercoiling relaxation. TOP1 inhibitors include the camptothecins (irinotecan and topotecan). TOP2 acts by allowing the passage of an intact DNA duplex through the DNA double-strand break generated by the enzymes, after which TOP2 relegates the broken duplex. In addition, intercalations between base pairs in the DNA are formed, causing additional DNA breaks. Examples of TOP2 inhibitors are anthracyclines (doxorubicin, daunorubicin, idarubicin, and mitoxantrone) and epipodophyllotoxins (etoposide and teniposide).

- Topoisomerase inhibitors have become an important payload class for antibody-drug conjugates (ADCs) in recent years. They can be effective against tumors resistant to traditional microtubule-targeting ADC payloads (eg, MMAE and DM1).
- Adverse effects/toxicities: The most common side effects are myelosuppression, GI toxicity, mucositis, alopecia, and cardiac toxicity. Rare but serious side effects include secondary malignancies such as myelodisplastic syndromes (MDS) and acute myeloid leukemia, particularly from alkylating agents and topoisomerase II inhibitors. All anthracyclines can cause cardiotoxicity, where the risk is increased with cumulative doses. Myocardial damage can occur with doxorubicin, with incidences from 1% to 20% for cumulative doses from 300 to 500 mg/m^2 when administered every 3 weeks.

PRESENTING CASE STUDY 1

A 65-year-old man with a 6-month history of early satiety and weight loss of 10% body weight (20 pounds) presents with gastric adenocarcinoma and extensive liver metastasis. The tumor is HER2 negative, microsatellite stable proficient, and has a combined positive score of 0. The patient tolerates first-line 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) and achieves tumor shrinkage for 6 months. At the time of progression (10 months after first dose of FOLFOX), his Eastern Cooperative Oncology Group (ECOG) performance status is 1, and he requests continued treatment. Laboratory findings support full-dose therapy, notable for an absolute neutrophil count of 3,500 cells/μL, aspartate aminotransferase two times the upper reference limit, alkaline phosphate level 1.5 times the upper reference limit, and bilirubin level 1.1 times the upper reference limit. He tolerates 3 months of single-agent irinotecan with stable disease and returns to the clinic for the next course of treatment. Complete blood count shows no change in values, and he is moved directly to the chemotherapy administration area, which is busy, with subdued lighting. Full-dose irinotecan is administered. Later that afternoon, his bilirubin level is 3.5 times the upper reference limit. The patient is instructed by his oncologist to return to the clinic the next day for management of expected irinotecan toxicity. By the clinic room window, icteric sclera is noted.

If you had known that the patient's bilirubin level was high, how would you have approached dosage?

Metastatic gastric cancer in a patient with an ECOG performance status of 0 or 1 and acceptable organ function is an indication for standard first-line therapy. Given the patient's biomarker status, the oncologist selected FOLFOX as an appropriate first-line therapy. Median progression-free survival in this setting is about 6 months. The oncologist in this scenario selected irinotecan as a second-line therapy. Clinics routinely have rapid complete blood count testing available, which is used to evaluate patients' myelosuppressive therapy, while the chemistry panel (eg, serum bilirubin) typically requires more time to process. An icteric sclera can be identified when a bilirubin level is greater than 3.0 mg/L or approximately 2.5 times the upper reference limit.

How would you improve clinical workflow to ensure timely detection of irinotecan toxicity, considering the limitations of rapid laboratory tests and the importance of clinical observation?

Complete blood count with differential and chemistry panels should be routinely monitored before each irinotecan administration. Electrolyte levels should be corrected if outside of the reference range, particularly in the setting of severe or chronic diarrhea. In patients with a history of severe neutropenia, *UGT1A1* genotyping should be considered for the **28* and **6* alleles to determine *UGT1A1* metabolizer status before starting therapy with irinotecan or liposomal irinotecan. Dose reduction should be considered for patients known to be homozygous for the *UGT1A1*28* or **6* alleles.

The most common adverse event of irinotecan toxicity is diarrhea (early or late onset).[19] Early-onset diarrhea usually occurs within several hours of infusion and may be accompanied by cholinergic symptoms (eg, abdominal cramping, rhinitis, lacrimation, and salivation). The mean symptom duration is about 30 minutes and is usually well controlled by anticholinergic agents such as atropine. Late-onset diarrhea associated with irinotecan is usually unpredictable and noncumulative and can occur at any dose level. The pathophysiology of late diarrhea is multifactorial, involving dysmotility, secretory factors, and a direct toxicity of the intestinal mucosa. Late-onset diarrhea can be life-threatening and should be treated promptly with antidiarrhea agents (eg, loperamide). Patients with diarrhea should be monitored and given fluids and electrolytes as needed.[19] Antibiotic therapy can be instituted if patients develop ileus, fever, or severe neutropenia. There is no known antidote for irinotecan overdose.[19]

Clinical Pharmacology Pearl: While checking complete blood count with differential testing is routinely performed before giving myelosuppressive agents, tests that assess the drug's metabolic pathway can be overlooked at times. Dose adjustment is recommended in patients with elevated bilirubin from baseline values. Use is not recommended in patients with a bilirubin level higher than 2.0 mg/dL. See Tables 3-9 and 3-10 in the Hepatic Impairment section of this chapter for further guidance.[20]

UGT1A1 tests do not typically cover the **6* alteration in the first exon but measure **28*. The **6* alteration is most common in Asian populations. The allele frequency typically ranges from 10% to 30% and is rare in White and Black populations.[21]

Microtubule-Targeting Agents

- Mechanism of action: Agents targeting microtubules can be broadly classified as microtubule-stabilizing agents, such as taxanes (docetaxel, paclitaxel, cabazitaxel, and nab-paclitaxel) and epothilones (ixabepilone) or microtubule-destabilizing agents, such as vinca alkaloids (vincristine and vinblastine) according to the effects on tubulin polymerization. Stabilization or destabilization of microtubules disrupts cell mitosis, leading to cell cycle arrest. Other tubulin agents, such as eribulin, a synthetic analog of the marine macrolide halichondrin B, work by inhibiting tubulin polymerization.
- Adverse effects/toxicities: The common side effects are myelosuppression, alopecia, peripheral neuropathy, fatigue, nausea and vomiting, diarrhea, skin rash, and mucositis. Hypersensitivity reactions are commonly seen with taxanes because of the solvent used in formulation. All vinca alkaloids can be fatal if given intrathecally. These agents undergo biliary excretion and require dose adjustment for hepatic impairment. Neurotoxicity and syndrome of inappropriate antidiuretic hormone secretion (SIADH) are unique side effects of vinca alkaloids.

Epigenetic Modifying Agents

- Mechanism of action: Epigenetic modifying agents alter the epigenetic status of genes and influence gene expression without changing the underlying DNA sequence. They can be broadly classified into two main forms: (1) DNA methylation and (2) histone modifications. DNA methyltransferase inhibitors such as azacitidine and decitabine inhibit the enzymes responsible for adding methyl groups to DNA, leading to hypomethylation. Histone deacetylase inhibitors such as vorinostat, romidepsin, and panobinostat prevent the removal of acetyl groups from histones, thereby inducing cell apoptosis. Tazemetostat inhibits the zeste homolog 2 enzyme (EZH2) that adds the methyl groups to histone protein, a process called histone methylation.
- Adverse effects/toxicities: The common toxicities associated with these agents are bone marrow suppression, nausea and vomiting, diarrhea, and fatigue.

SMALL-MOLECULE TARGETED ANTICANCER DRUGS

- Mechanism of action: They exert their effect on specific "targeted receptors" that are involved in cancer growth, metastasis, and immortality. Most of them inhibit important cancer targets, such as serine, threonine, and tyrosine kinase inhibitors (TKIs); proteasome; and other proteins involved in DNA damage repair, cell cycle progression, and signal transduction pathways. For example, therapy that inhibits TKIs prevents TKIs from phosphorylating tyrosine residues on their substrates. They block activation of downstream signaling pathways that control cell growth in both cancer and normal cells.
- Inhibition of one gene of a pathway, either because of the presence of a mutation or by pharmacological intervention, may not result in cell death. However, simultaneous inhibition of two genes or pathways can result in cell death, a concept referred to as "synthetic lethality." Tumors with compromised ability to repair double-strand DNA breaks by homologous recombination, including those with defects in the *BRCA1* and *BRCA2* genes, are highly sensitive to inhibition of the base excision repair pathway by poly ADP ribose polymerase (PARP) inhibitors (see Table 3-1).
- Unlike larger monoclonal antibodies that frequently target extracellular receptors, small-molecule cancer drugs are much smaller in size, allowing them to translocate through plasma membranes and bind to intracellular receptors. They are typically oral and administered continuously because of their short lifespan compared with monoclonal antibodies.
- Metabolism typically occurs via the cytochrome P450 system. This creates an environment where drug-drug interactions occur.
- Food and other medications that alter gastric pH or gastric enzymes can increase or decrease absorption of oral anticancer agents, induce or inhibit metabolism, leading to changes in plasma concentrations, and compromise efficacy or increase adverse effects. In addition, certain small-molecule inhibitors can target multiple cell surface receptors and other intracellular proteins, leading to off-target toxicities.[22]

Table 3-1 **Targeted Therapies With Biomarker Selection: EGFR and MET Inhibitors**

	Sensitive Mutation/ Required Biomarkers	Food Effect	pH Dependent (Yes/No)	Drug Interactions	Use	Notes
EGFR inhibitors						
Erlotinib	Exon 19 deletions, exon 21 L858R	Empty stomach	Yes	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors and grapefruit	Advanced NSCLC; first line or subsequent lines; *EGFR* mutant	Approved before the discovery of EGFR biomarker; has a maintenance indication in unselected patients
Gefitinib	Exon 19 deletions, exon 21 L858R	With or without food	Yes	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors and grapefruit	Advanced NSCLC; first line or subsequent lines; *EGFR* mutant	Initially approved on phase 2 data in unselected populations; failed in phase 3 trial and was taken off the market
Afatinib	Exon 19 deletions, exon 21 L858R, S7681, L861Q, and G719X	Empty stomach	No	Not metabolized by CYP	Advanced NSCLC; first line or subsequent lines; *EGFR* mutant	Retains activity in erlotinib- or gefitinib-resistant patients; has a maintenance indication in unselected patients
Dacomitinib	Exon 19 deletions, exon 21 L858R	With or without food	Yes	Strong CYP2D6 inhibitor; inhibits the metabolism of drugs that are metabolized by CYP2D6	Advanced NSCLC; first line or subsequent lines; *EGFR* mutant	More effective than gefitinib, but also has more adverse effects
Osimertinib	Exon 19 deletions, exon 21 L858R, T790M	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors and has the potential for QT prolongation	Adjuvant treatment of early-stage, locally advanced, and metastatic *EGFR*-mutated NSCLC	Improved PFS in first-line setting compared with gefitinib or erlotinib; preferred if CNS penetration is needed
Lazertinib	Exon 19 deletions, exon 21 L858R substitution	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors.	First-line treatment of locally advanced or metastatic NSCLC with exon 19 deletion or exon 21 L858R substitution	Use in combination with amivantamab. Prophylactic anticoagulation should be given for the first 4 months of treatment
Sunvozertinib	Exon 20 insertion	With food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Locally advanced or metastatic NSCLC with EGFR exon 20 insertion	Take with food to reduce GI toxicities
MET inhibitors						
Capmatinib	MET exon 14 skipping	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Metastatic NSCLC with MET exon 14–skipping mutation	
Tepotinib	MET exon 14 skipping	With food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Metastatic NSCLC with MET exon 14–skipping mutation	A clinical trial used a liquid biopsy for assignment

Abbreviations: CNS, central nervous system; CYP, cytochrome P450; EGFR, epidermal growth factor receptor; GI, gastrointestinal; NSCLC, non–small cell lung cancer; PFS, progression-free survival.

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- Adverse effects/toxicities: Most "on-target" adverse effects are driven by excessive interruption of receptor signaling pathways. Kinase inhibitors that have higher affinities to certain receptors and are considered more specific to a target intracellular receptor may be more tolerable and have fewer side effects. Irreversible kinase inhibitors covalently bind to their target receptors or enzymes and, therefore, cannot be readily reversed. Compared to reversible kinase inhibitors, irreversible kinase inhibitors may exert more on- and off-target effects. However, most TKIs have off-target side effects related to the molecule's lack of specificity. Some later generations of targeted therapy can increase activity and reduce off-target toxicity, such as the first- and second-generation Bruton TKIs.[22]

Targeted therapies have been a mainstay treatment of a variety of cancers, particularly those with actionable mutations; unfortunately, the development of resistance and disease progression frequently occurs. A now common drug development strategy is to develop second- and third-generation agents that target the same pathway but have improved pharmacologic properties compared with the first-generation agents or are able to target known resistance mechanisms. An example is osimertinib, an epidermal growth factor receptor (EGFR) inhibitor that has additional activity in the presence of the known *EGFR* T790M resistance mutation.

Tables 3-1, 3-2, 3-3, 3-4, and 3-5 list small-molecule targeted therapies that require a biomarker for use, the associated biomarkers, and drug and food effects. Combinations of small-molecule targeted therapies, cytotoxic chemotherapy, and/or immunotherapy are currently being evaluated in clinical trials.

PRESENTING CASE STUDY 2

Four years ago, a 65-year-old woman with a history of hypertension and mild irritable bowel disease was diagnosed with chronic myelogenous leukemia (CML). After starting imatinib, she achieved a complete cytogenetic and molecular response, which continued until 3 months ago when imatinib resistance was noted. The hematologist selected nilotinib as her next therapy. Before initiating nilotinib, a 12-lead electrocardiogram (ECG) demonstrated a Fridericia-corrected QT interval (QTcF) of 420 milliseconds. After 1 week, she returned to the clinic for a scheduled follow-up. Repeat 12-lead ECG showed a QTcF of 460 milliseconds. Her blood pressure was within the upper reference limit on current antihypertensive medication. She reported grade 1 diarrhea and nausea, which she attributed to anxiety that the nilotinib may not achieve the complete response she experienced while on imatinib.

Over the ensuing week, the patient's diarrhea continued, and her nausea progressed with some vomiting. She sought help from a local urgent care center which prescribed ondansetron and metronidazole with advice to increase fluid intake and eat a banana, rice, applesauce, toast (BRAT) diet. Over the next 2 days, her symptoms improved, and ondansetron was continued to prevent nausea and vomiting.

Yesterday, she collapsed while working at an outpatient center. The rapid response team was called to perform resuscitation. The team was aware of the new CML therapy she was taking but not the addition of symptomatic care for nausea and vomiting. The team noted torsade de pointes. She was given a magnesium infusion to correct this serious cardiac arrhythmia. She was stabilized and moved to the cardiac care unit until the rate, rhythm, and intervals were within the reference range. Upon discharge, her electrolytes returned to within reference range, and ECG revealed sinus rhythm with a QTcF of 420 milliseconds. Her discharge summary revealed torsade de pointes secondary to hypokalemia and hypomagnesemia due to persistent diarrhea and vomiting.

How would this recently reported laboratory abnormality influence your decision to review the patient's current medications?

Nilotinib is a more potent, second-generation BCR-ABL tyrosine kinase inhibitor that demonstrates superior efficacy over imatinib in achieving deeper and more sustained molecular responses in CML. A higher incidence of cardiovascular events has been reported with nilotinib. The precautions for its use are well described in the black box warning, including QT prolongation and sudden death. Use should be avoided in patients with hypokalemia and hypomagnesemia while periodically monitoring the QTc interval. This patient showed an acceptable QTc interval after 1 week of nilotinib treatment and continued to take the medication. Over time, her gastrointestinal adverse events persisted, leading to an electrolyte imbalance. In addition, the two concomitant medications added for symptomatic control of nausea, vomiting, and diarrhea are known to elevate the risk of torsade de pontes. In this patient, those multiple risk factors led to a life-threatening cardiac event. Fortunately, the clinic staff reacted quickly and appropriately.[26,27]

When administering a therapy with a high potential for drug-drug interactions, careful assessment of risk for clinical sequelae and patient education is crucial. The oncologist had reviewed the risks with the patient and her family before starting therapy. Continuation of care, including informing the healthcare team when a new concurrent medication is used while on treatment, should be maintained via traditional communication methods (eg, phone call) or an automated alert system integrated with an electronic health record. While all signs and symptoms that comprise adverse events are important to report to a healthcare professional on the team, identifying the signs and symptoms that can lead to a serious adverse event needs to rise in priority through patient education and reminders. Using the black box warning of nilotinib (as well as the warning and precaution) can assist the health care practitioner in establishing priority.[26,27]

MONOCLONAL ANTIBODIES

- Mechanism of action: Monoclonal antibodies are therapeutic agents bioengineered to target specific antigens that are either unique to or overexpressed by tumor cells. The main direct mechanism of many monoclonal antibodies is to block growth factor receptor signaling; other mechanisms involve immune-mediated cell killing and payload delivery or have specific effects on the tumor vasculature and stroma.
- While the first monoclonals were murine based, over time, hybrid and humanized monoclonals have been developed. To understand the source, the stem will be different; ximab is chimeric, and zumab will be humanized, and umab is human. Therapies with less human structure may have more therapy-related side effects. For example, cetuximab and rituximab are chimeric human-mouse monoclonal antibodies, which can cause more infusion reactions compared with fully humanized antibodies such as bevacizumab, panitumumab, pertuzumab, and trastuzumab.

Examples of a few tumor antigens that have been successfully targeted using monoclonal antibodies are EGFR, vascular endothelial growth factor (VEGF), and erythroblastic oncogene B (ERBB2) receptor TKI or HER2, HGFR, insulin-like growth factor-1 receptor (IGF-1R), platelet-derived growth factor receptor (PDGFR), and cluster of differentiation CD20.

- For example, bevacizumab is an antibody directed toward soluble VEGF, the ligand for the VEGF receptor that drives angiogenesis.[28,29] Therefore, inhibition of VEGF by the monoclonal antibody bevacizumab decreases angiogenesis. Inhibiting VEGF is also the target for ziv-aflibercept (a recombinant fusion protein) by a different mechanism.
- The FGFR family consists of FGFR1, FGFR2, FGFR3, and FGFR4. Signaling through FGFR activates downstream signaling through the MAPK and PI3K/AKT pathways to regulate cell differentiation, proliferation, survival, and migration. Erdafitinib and pemigatinib are FDA-approved FGFR inhibitors for the treatment of urothelial carcinoma with *FGFR2* or *FGFR3* alteration and for the treatment of cholangiocarcinoma with *FGFR2* fusions or rearrangement, respectively.
- Daratumumab is among the therapies utilized for first-line treatment of multiple myeloma. It is an IgG1κ human monoclonal antibody that binds to CD38 and inhibits the growth of CD38-expressing tumor cells.
- Monoclonal antibodies often are large proteins that are resistant to degradation, which allows them to remain in circulation for longer periods compared with small-molecule targeted inhibitors. A longer half-life, however, also means a slower reversal of toxicity after treatment interruption or withdrawal.
- In addition, monoclonal antibodies often do not require dosage adjustments for liver or kidney dysfunction.

Targeted monoclonal antibodies tend to have fewer adverse effects compared with cytotoxic chemotherapy, but they have unique adverse effects, such as infusion reactions and dermatologic toxicities related to the antigens they target. For example, cetuximab, an antibody that acts on EGFR, which is found on normal skin cells and cancer cells, can consequently cause a serious skin rash in some patients. Antibodies to HER2, such as trastuzumab, have a black box warning for cardiotoxicity requiring cardiac monitoring.[30]

ANTIBODY-DRUG CONJUGATES

ADCs are a type of monoclonal antibody designed to increase therapeutic efficacy while minimizing the toxicity of anticancer agents. An ADC consists of three parts: an antibody drug that is highly specific with high binding affinity, long circulating half-life, and low immunogenicity[31]; a cytotoxic chemotherapy drug with stability, solubility, and amenability to conjugation; and a linker that connects the antibody to the cytotoxic chemotherapy.

Table 3-2 **Targeted Therapies With Biomarker Selection: ALK, ROS, and BRAF Inhibitors**

	Sensitive Mutation/ Required Biomarkers	Food Effect	pH Dependent (Yes/No)	Drug Interactions	Use	Notes
ALK and/or ROS1 inhibitors						
Crizotinib	*ALK* translocation	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors and has the potential for QT prolongation	Advanced NSCLC; first line or subsequent lines; *ALK* or *ROS1* positive; unresectable, recurrent, or refractory inflammatory anaplastic lymphoma, *ALK* positive	More effective than chemotherapy, but less effective than alectinib; only ALK inhibitor with ROS1 indication
Ceritinib	*ALK* translocation	With food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors and grapefruit	Advanced NSCLC; first line or subsequent lines; *ALK* positive	More effective than chemotherapy
Alectinib	*ALK* translocation	With food	No	Not metabolized by CYP	Advanced NSCLC; first line or subsequent lines; *ALK* positive	Improved PFS over crizotinib; preferred if CNS penetration is needed
Brigatinib	*ALK* translocation	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Advanced NSCLC; after failure of crizotinib; *ALK* positive	Improved PFS over crizotinib; blood pressure should be controlled before initiation
Lorlatinib	*ALK* translocation	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Advanced NSCLC; after crizotinib and one other drug; *ALK* positive	See reference[23]
Ensartinib[24]	*ALK* translocation	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors; Avoid P-gp inhibitor	Advanced NSCLC; ALK inhibitor naive; *ALK positive*	Monitor uric acid while on treatment
Repotrectinib	ROS1 rearrangement	With or without food	No	CYP3A4 inducer; interacts with CYP3A4 inducers and inhibitors	Advanced NSCLC; first line or subsequent lines; *ROS1* fusion positive	Inhibits both wild-type and G2032R-mutant *ROS1* fusions; may be better for patients with brain metastases[25]
Taletrectinib[4]	ROS1 rearrangement	Empty stomach	Yes	CYP3A4 inducer; interacts with CYP3A4 inducers and inhibitors	Advanced NSCLC; first line or subsequent lines; *ROS1* positive	Monitor uric acid and skeletal fractures while on treatment

	Sensitive Mutation/ Required Biomarkers	Food Effect	pH Dependent (Yes/No)	Drug Interactions	Use	Notes
BRAF inhibitors						
Dabrafenib	V600E, V600K	Empty stomach	No	CYP3A4 and CYP2CB substrate; interacts with CYP3A4 and CYP2C8 inducers and inhibitors	First line; adjuvant melanoma, metastatic melanoma, metastatic NSCLC, metastatic anaplastic thyroid, *BRAF* mutant; unresectable or metastatic solid tumors with *BRAF* V600E mutation	Improved PFS and OS over dacarbazine as a single agent; used in combination with the MEK inhibitor to prevent resistance
Vemurafenib	V600E, V600K	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	First-line, metastatic melanoma, Erdheim-Chester disease, *BRAF* mutant; refractory NSCLC with *BRAF* V600 mutation	Improved PFS over dacarbazine as the single agent; used in combination with the MEK inhibitor to prevent resistance
Encorafenib	V600E, V600K	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	First-line, metastatic melanoma, *BRAF* mutant; first-line, metastatic colon cancer, *BRAF* mutant	Only BRAF inhibitor indicated for colon cancer in combination with cetuximab; correct hypokalemia or hypomagnesemia before treatment initiation
Tovorafenib	*BRAF* fusion or rearrangement, V600E mutation	Empty stomach	Yes	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Relapsed or refractory low-grade glioma	Monitor uric acid, CPK level, and skeletal fractures while on treatment

Abbreviations: CYP, cytochrome P450; H2, H2 histamine antagonists (eg, famotidine); NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; PPI, proton pump inhibitors (eg, omeprazole).

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Table 3-3 **Targeted Therapies With Biomarker Selection: NTRK and PARP Inhibitors**

	Sensitive Mutation/ Required Biomarkers	Drug Interactions	Use	Notes
NTRK inhibitors				
Entrectinib	*NTRK, ROS1* fusions	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Metastatic NSCLC; *ROS1* rearrangement; solid tumor with known *NTRK* fusion	
Larotrectinib	*NTRK* fusion	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Solid tumor with known *NTRK* fusion	First small-molecule disease–agnostic approval
Repotrectinib	NTRK fusion	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Locally advanced or metastatic NSCLC with ROS1 positive; Solid tumors with *NTRK* gene fusion positive	
PARP inhibitors				
Olaparib	BRCA1/BRCA2	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Metastatic breast cancer, HER2 negative, germline *BRCA* mutated; ovarian cancer maintenance, *BRCA* mutant; metastatic prostate cancer with homologous recombination repair gene-mutated; pancreatic cancer with germline *BRCA* mutated; first-line maintenance	Because of the difference in dosing and bioavailability, do not substitute capsules for tablets
Rucaparib	BRCA1/BRCA2	Moderate CYP1A2 inhibitor; inhibits the metabolism of drugs that are metabolized by CYP1A2	*BRCA*-mutant recurrent ovarian cancer maintenance; metastatic prostate cancer castration resistant, *BRCA* mutated; locally advanced or metastatic pancreatic cancer, germline *BRCA2*-mutated maintenance therapy	Associated with a moderate or high emetic potential, antiemetics are recommended to prevent nausea and vomiting
Niraparib	Testing not required	Not metabolized by CYP	Recurrent ovarian cancer, maintenance therapy	Associated with a moderate or high emetic potential, antiemetics are recommended to prevent nausea and vomiting
Talazoparib	BRCA1/BRCA2	Not metabolized by CYP	Locally advanced or metastatic breast cancer, *BRCA* mutant	

Abbreviations: CYP, cytochrome P450; NSCLC, non–small cell lung cancer; PARP, poly ADP ribose polymerase.
All are not pH dependent. All can be provided with or without food.
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Table 3-4 **Targeted Therapies With Biomarker Selection: FLT3 and IDH Inhibitors**				
	Sensitive Mutation/ Required Biomarkers	**Drug Interactions**	**Use**	**Notes**
FLT3 inhibitors				
Midostaurin	ITD, point mutations	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Newly diagnosed AML, *FLT3* mutation positive; in combination with chemotherapy during induction and consolidation therapy	First-in-class FLT3 inhibitor
Gilteritinib	ITD, point mutations	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Relapsed or refractory AML, *FLT3* mutant	
Quizartinib	ITD, point mutations	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Newly diagnosed AML, *FLT3* mutation positive; in combination with chemotherapy during induction and consolidation therapy	Second-generation FLT3 inhibitor
IDH1/IDH2 inhibitors				
Enasidenib	IDH2	No known drug interactions	Relapsed or refractory AML, *IDH2* mutant	First-in-class IDH2 inhibitor
Ivosidenib	IDH1	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Relapsed or refractory AML, *IDH1* mutant; newly diagnosed acute myeloid leukemia with *IDH1* mutation in combination with azacytidine; locally advanced or metastatic *IDH1*-mutated cholangiocarcinoma	First-in-class IDH1 inhibitor
Vorasidenib	IDH1 or IDH2	Interact with CYP2C8 inhibitors and inducers; sensitive CYP3A4 substrates	Astrocytoma or oligodendroglioma with a susceptible *IDH1* or *IDH2* mutation	May promote tumor growth in patients with NF1 tumors

Abbreviations: AML, acute myeloid leukemia; AUC, area under the curve; ITD, internal tandem duplication.
All are not pH dependent. Except for midostaurin, all can be provided with or without food; with ivosidenib, avoid high-fat meals (increases AUC by 25%).
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Table 3-5 **Targeted Therapies With Biomarker Selection: Various Inhibitors**					
	Sensitive Mutation/ Required Biomarkers	**Food Effect**	**Drug Interactions**	**Use**	**Notes**
FGFR inhibitors					
Erdafitinib	*FGFR2, FGFR3* mutations and fusions	With or without food	CYP3A4 and CYP2C9 substrates; interacts with inducers and inhibitors of both enzymes	Locally advanced or metastatic urothelial carcinoma with *FGFR3* or *FGFR2* alterations	First-in-class FGFR inhibitor; better activity in *FGFR3* point mutations over *FGFR3* and *FGFR2* fusions
Futibatinib	*FGFR2* fusion or rearrangement	With or without food	CYP3A4, CYP2D6, and CYP2C9 substrates; interacts with inducers and inhibitors of both enzymes	Locally advanced or metastatic cholangiocarcinoma with *FGFR2* fusion or rearrangement	

	Sensitive Mutation/ Required Biomarkers	Food Effect	Drug Interactions	Use	Notes
Pemigatinib	*FGFR2* fusion	With or without food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Previously treated, locally advanced, or metastatic cholangiocarcinoma with *FGFR2* fusion; relapsed or refractory myeloid/ lymphoid neoplasms with *FGFR1* rearrangement	
RET inhibitors					
Selpercatinib	*RET* fusions or mutations	With or without food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	*RET* mutant and *RET* fusion–positive medullary thyroid cancer; locally advanced or metastatic *RET*-positive NSCLC; locally advanced or metastatic *RET* fusion–positive solid tumors	First-in-class RET inhibitor; optimize blood pressure before treatment initiation
Pralsetinib	*RET* fusions	Empty stomach	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	*RET* mutant and *RET* fusion–positive medullary thyroid cancer; metastatic NSCLC with *RET* fusion	Do not administer for at least 2 weeks after major surgery and until after adequate wound healing has occurred
PI3K inhibitors					
Alpelisib	*PIK3CA* mutations	With food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors; CYP2C9 inducer; avoid sensitive substrates such as warfarin	Postmenopausal women and men with HR-positive, HER2-negative, *PIK3CA* mutated with advanced or metastatic breast cancer	Approved in combination with fulvestrant; first-in-class PIK3CA inhibitor; optimize blood glucose before treatment initiation
Inavolisib	*PIK3CA* mutations	With or without food	BCRP/ABCG2 and P-gp/ABCB1 substrate	Endocrine-resistant, *PIK3CA*-mutated, HR-positive, HER2-negative locally advanced or metastatic breast cancer	Reduce the dose for moderate renal impairment
AKT inhibitors					
Capivasertib	*PIK3CA, AKT1*, and *PTEN* alterations	With or without food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	HR-positive, HER2-negative, locally advanced, or metastatic breast cancer with genetic alterations in one or more of these genes: *PIK3CA, AKT1*, and *PTEN*	Improved PFS with benefits observed in the overall population and among patients with AKT pathway-altered tumors

	Sensitive Mutation/ Required Biomarkers	Food Effect	Drug Interactions	Use	Notes
PDGFRA inhibitors					
Avapritinib	*PDGFRA* exon 18 mutation	Empty stomach	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Unresectable or metastatic GIST with *PDGFRA* exon 18 mutation	First-in-class PDGFRA inhibitor; associated with a moderate or high emetic potential risk; antiemetics may be recommended to prevent nausea and vomiting
EZH2 inhibitors					
Tazemetostat	*EZH2* gain-of-function mutations, *SMARCA* loss-of-function mutations	With or without food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Adults and children age 16 or older with metastatic or locally advanced epithelioid sarcoma, relapsed or refractory follicular lymphoma salvage therapy, or those with *EZH2* mutation	First-in-class EZH2 inhibitor
MEK inhibitors					
Trametinib	*BRAF* V600E, V600K	Empty stomach	None	First-line, adjuvant melanoma, metastatic melanoma, metastatic NSCLC, metastatic anaplastic thyroid cancer, *BRAF* mutant; low-grade recurrent serous ovarian cancer; solid tumors, unresectable or metastatic with *BRAF* V600E mutation	Only approved in combination with dabrafenib
Cobimetinib	*BRAF* V600E, V600K	With or without food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	First-line, metastatic melanoma, *BRAF* mutant; treatment of histiocytic neoplasms	Only approved in combination with vemurafenib; causes severe photosensitivity
Binimetinib	*BRAF* V600E, V600K	With or without food	None	First-line, metastatic melanoma, *BRAF* mutant	Only approved in combination with encorafenib; LVEF >50% required
Selumetinib	MEK1, MEK2	Empty stomach	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Children aged 2 years or older with NF1 and plexiform neurofibromas	
Mirdametinib	MEK1, MEK2	With or without food	None	Children aged 2 years or older with NF1 and plexiform neuroblastomas	

	Sensitive Mutation/ Required Biomarkers	Food Effect	Drug Interactions	Use	Notes
RAS inhibitors					
Sotorasib	*KRAS* G12C		Caution with CYP3A4 inducers and inhibitors, PgP substrates and acid-reducing agents	*KRAS* G12C mutated locally advanced or metastatic NSCLC	>20% diarrhea, hepatotoxicity, cough, and musculoskeletal pain
Adagrasib	*KRAS* G12C	With or without food	Caution with CYO3a4 inducers, inhibitors, substrates, CYP2c9, cyp 2d6, P-gp substrates, drugs that prolong QTc	*KRAS* G12C mutated locally advanced NSCLC and CRC	Diarrhea, QTc prolongation, hepatotoxicity, and ILD/pneumonitis

Abbreviations: CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; HR, hormone receptor; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; NF1, neurofibromatosis type 1; NSCLC, non–small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; P-gp, P-glycoprotein.
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- Mechanism of action: An ADC works by binding to the receptor differentially found on cancer cells. The cancer cells will engulf the ADC, and cytotoxic chemotherapy is released to cause cancer cell destruction with relative sparing of normal cells. How cytotoxic chemotherapy is released inside the cancer cells depends on the design of the linker: cleavable or noncleavable.
- Noncleavable linkers enhance stability in plasma to prevent premature cytotoxic chemotherapy cleavage and decrease the potential for off-target toxicity. They depend on mature lysosomes for linker degradation and cytotoxic agent release,[32] such as ado-trastuzumab emtansine.
- Cleavable linkers, conversely, rely on physiologic conditions such as pH, glutathione concentrations, and proteases to cleave the cytotoxic agent from the linker.[33] ADCs with cleavable linkers may be advantageous in some settings in which there is heterogeneity in target expression because not all tumor cells uniformly express the ADC antigen target, and surrounding cell killing occurs with local release of chemotherapy, known as the "bystander effect."
- Adverse effects/toxicities: Possible adverse effects seen with ADCs are often caused by the release of cytotoxic payload into the bloodstream before reaching the cancer cell. These can include peripheral neuropathy, hepatotoxicity, visual changes, mucositis, and hematologic effects.
- Infusion reactions can also occur with ADCs, with typical onset occurring during the infusion and 24 to 48 hours after infusion. Reactions may range from pyrexia, dyspnea, rigors, and hypotension to anaphylaxis. Selecting appropriate premedications is essential for specific ADCs and often includes antihistamine and acetaminophen with or without corticosteroids.

IMMUNOTHERAPY

Immunotherapy is defined as a therapeutic approach that targets or manipulates the immune system and ultimately seeks to harness the host's adaptive and innate immune responses to eliminate cancer cells.[34]

- Mechanism of action: Immunotherapy induces the patient's immune response and results in the development of specific immune effectors (ie, antibodies and T cells).
- Cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) was the first T-cell checkpoint to be identified. CTLA-4 is a downregulator of T-cell activation pathways. Ipilimumab is a recombinant human immunoglobulin G1 monoclonal antibody that binds to CTLA-4 and consequently blocks its effect, leading to enhanced T-cell activation and proliferation.
- The CTLA-4 inhibitor, along with programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors, is an example of active immunotherapy. They do not target cancer cells but work by reactivating or promoting antitumor immunity.[35] CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation.
- PD-L1 expressed on some cancer cells binds to PD-1 on T cells, resulting in T-cell deactivation. The PD-1 and PD-L1 inhibitors block this receptor-ligand signaling pathway, overcome immune escape mechanisms, and enhance T-cell response,

leading to T-cell activation and proliferation.[36] Therefore, PD-1 and PD-L1 inhibitors rely on the host immune system for anticancer effects. Overall, this class of therapy is effective, particularly in tumors that display a positive tumor proportion score (TPS), a high combined positive score (CPS), or a high tumor mutational burden (TMB). TPS is defined as the number of PD-L1–positive tumor cells as a % of the total number of viable tumor cells; CPS is defined as the number of positive tumor cells, lymphocytes, and macrophages as a % of the total number of viable tumor cells. A high CPS generally refers to a score of 1% or higher. TMB is the number of mutations found in the DNA of cancer cells. A TMB of 10 mutations per megabase or greater is considered TMB high.

- Lymphocyte activation gene 3 (*LAG3*), which is expressed by B cells, T cells, NK cells, and tumor-infiltrating lymphocytes (TILs), is used to regulate immune checkpoint pathways. *LAG3*-blocking antibodies restore the effector function of exhausted T cells and increase their ability to attack tumor cells.
- Adverse effects/toxicities: Immune-mediated toxicities may involve any organ but commonly involve the GI (colitis), hepatic, endocrine, and pulmonary systems. Toxicologic events may occur with different onsets, with some developing within days, whereas others may have delayed onsets in months or years during treatment and after discontinuation.

PD-L1 expression is a commonly used clinical biomarker of checkpoint inhibitor response, and some FDA-approved indications are based on the level of biomarker positivity, although many indications do not require biomarker positivity, and patients without these biomarkers can respond to checkpoint inhibitor therapy.

PD-1–targeting immune checkpoint inhibitors have demonstrated durable clinical responses in patients with microsatellite instability-high (MSI high)/mismatch repair–deficient tumors, leading to the FDA approval of the checkpoint inhibitor, pembrolizumab, for this indication.

TMB is another commonly used biomarker. In June 2020, the FDA approved the anti–PD-1 therapy pembrolizumab for treating patients with advanced and refractory cancers with a high TMB. Several other biomarkers (ie, TILs, immune signatures) are actively being investigated.[37,38] PD-1 pathway inhibitors may be combined with CTLA-4 inhibitors for the treatment of melanoma and renal cell carcinoma and with cytotoxic chemotherapy for some solid tumors; however, they are also commonly used as single agents. More recently, they have been used in combination with a LAG3 inhibitor for the treatment of unresectable or metastatic melanoma.

Adoptive cell therapy, such as TILs, gene-modified T cells expressing novel T-cell receptors, chimeric antigen receptors, or bispecific T-cell engager antibodies, is another strategy to modify the host immune system to recognize tumor cells, thereby enhancing cytotoxic T-cell activity. Immune-mediated toxicities include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and infusion-related reactions (see "Cellular Therapies" chapter for more information).

BISPECIFIC T-CELL ENGAGERS

- Mechanism of action: Bispecific T-cell engager binds to two different antigens simultaneously, with one arm binding to a tumor-associated antigen and the other arm binding to an immune cell receptor, commonly CD3 on T cells. This dual binding brings a T cell into close contact with a tumor cell, forming an immunological synapse. Examples of FDA-approved bispecific T-cell engagers are elranatamab, linvoseltamab, and teclistamab, which bind to the B-cell maturing antigen on myeloma cells and the CD3 receptor on the patient's T cell.
- Adverse effects/toxicities: Among the therapy-related adverse events are the black box warning of CRS and ICANS. Infusion reactions usually occur early during the initial step-up dosing and particularly during the first infusion. The incidence and severity of these reactions often decrease with subsequent infusions. Target organ effects may also occur given target dual blockers by bispecific T-cell engagers.
- Delta-like ligand 3 (DLL3), a notch ligand that is highly expressed on fast-growing tumor cells such as small cell lung cancer (SCLC) and neuroendocrine tumors, has become an emerging target for bispecific T-cell engagers. Examples of DLL3/CD3 bispecific T-cell engagers that are approved by the FDA are tarlatamab and tislelizumab-isgr for the treatment of extensive stage SCLC.

KEY POINTS

- Hormonal therapies are most commonly used to treat breast cancer and prostate cancer. They work by altering the production of hormones, blocking the activity of particular HRs in the body, or substituting chemically similar agents for the active hormones.
- Cytotoxic chemotherapy remains an important component of many cancer therapy regimens in the neoadjuvant, adjuvant, and metastatic settings for solid tumors and for hematologic malignancies.
- Small-molecule targeted receptor inhibitors offer distinct advantages as therapeutics. Most can be administered orally.
- Monoclonal antibodies are therapeutic agents bioengineered to target specific extracellular receptors or cell surface antigens that are either unique to or overexpressed by tumor cells.
- ADCs are anticancer agents that consist of an antibody, a cytotoxic payload, and a linker that work to enhance the therapeutic effect while minimizing toxicity to normal cells.

- Immune checkpoint inhibitor immunotherapy results in durable clinical benefit in some patients and is associated with a unique spectrum of adverse effects known as immune-related adverse effects, which include dermatologic, GI, hepatic, endocrine, and other less common inflammatory effects.
- CRS and ICANS are common with cellular therapy and can be managed by interleukin-6 (IL-6) inhibitors and corticosteroids. Patients are usually hospitalized for proper monitoring and management of these adverse effects.

BIOMARKERS FOR DRUG SELECTION OF TARGETED THERAPIES

Cancer is associated with an accumulation of mutations. Most mutations are neutral (passenger mutations), but a few driver mutations give cancer cells a selective advantage. Targeting these mutations with small molecules is an effective treatment strategy, and the mutation itself is a predictive biomarker.

Novel therapies emerge with new targets such as talquetamab, a bispecific GPRC5-CD3T cell engager, or capivasertib, the first-in-class AKT inhibitor. New drugs are typically more potent and can overcome mutational resistance or limitations seen with first-generation agents, such as better CNS penetration or different adverse effects or drug interaction profiles. Variability in pharmacologic properties is used to guide drug selection. In addition, resistance often develops in targeted small molecules after therapy. For example, EGFR inhibitors bind in the TKI domain of EGFR, and when a mutation occurs in the binding pocket, the drug can no longer bind, and resistance develops. Mutations such as the T790M mutation in EGFR exon 20 prevent binding of first- and second-generation TKIs to the ATP-binding site of EGFR.[39] The next-generation EGFR inhibitor osimertinib is FDA approved for the treatment of metastatic EGFR T790M-positive non–small cell lung cancer (NSCLC).[40] Earlier generations of ROS1 (ROS proto-oncogene 1) TKIs that are approved for treatment of *ROS1* fusion–positive NSCLC may lead to the development of resistance and have limited intracranial activity. Repotrectinib is a next-generation ROS1 TKI with activity against *ROS1* fusion–positive cancers, including resistance mutations such as ROS1 G2032R. First- and second-generation BTK inhibitors have been available for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma. They all share common resistance mechanisms, predominantly through mutations in BTK at C481, affecting the binding ability of the drugs, or by mutations in the downstream target PLCG2. Pirtobrutinib is the first non–covalent reversible BTK inhibitor approved by the FDA this year for the treatment of adult patients with relapsed or refractory mantle cell lymphoma after two previous lines of systemic therapies, and it inhibits both wild-type and C481-mutant BTK.

Biomarker testing is continually evolving to be incorporated into clinical decisions. Recently, ASCO convened an expert panel to update the biomarkers to guide systemic therapy for metastatic breast cancer guidelines.[41] The panel recommended that tests for *PIK3CA* mutations should be performed to determine eligibility for alpelisib or inavolisib, and testing for the *BRAF* V600 mutation should be performed before initiating treatment with vemurafenib, encorafenib, or dabrafenib.

PHARMACOKINETICS

Pharmacokinetics, used to describe dose-concentration relationships, is the mathematical relationship describing the time course of absorption, distribution, metabolism, and excretion (ADME) of drugs and metabolites in the body,[33,42,43] and is often described as "what the body does to the drug" (see Table 3-6 and Fig. 3-2).

Table 3-6 Basic Pharmacokinetics Definitions

Parameter Abbreviation	Definition	Equation	Use/Association
C_{max}	Maximal drug concentration	Visual extrapolation	Can be associated with acute adverse effects
T_{max}	Time at which the maximum drug concentration is achieved	Visual extrapolation	Time that acute adverse effects occur
$t_{1/2}$	Time required for the plasma concentration to decrease by half, or half-life	$T_{1/2}$ 0.698 × Vd/clearance	Determines how long a drug is measurable in the plasma in the body
AUC	Area under the curve	Dose/clearance	Measure of systemic drug exposure
Vd	Volume of distribution	Dose/concentration at time 0 (extrapolated)	Where the drug goes in the body
Cl	Clearance	Dose/AUC	How fast the drug is eliminated

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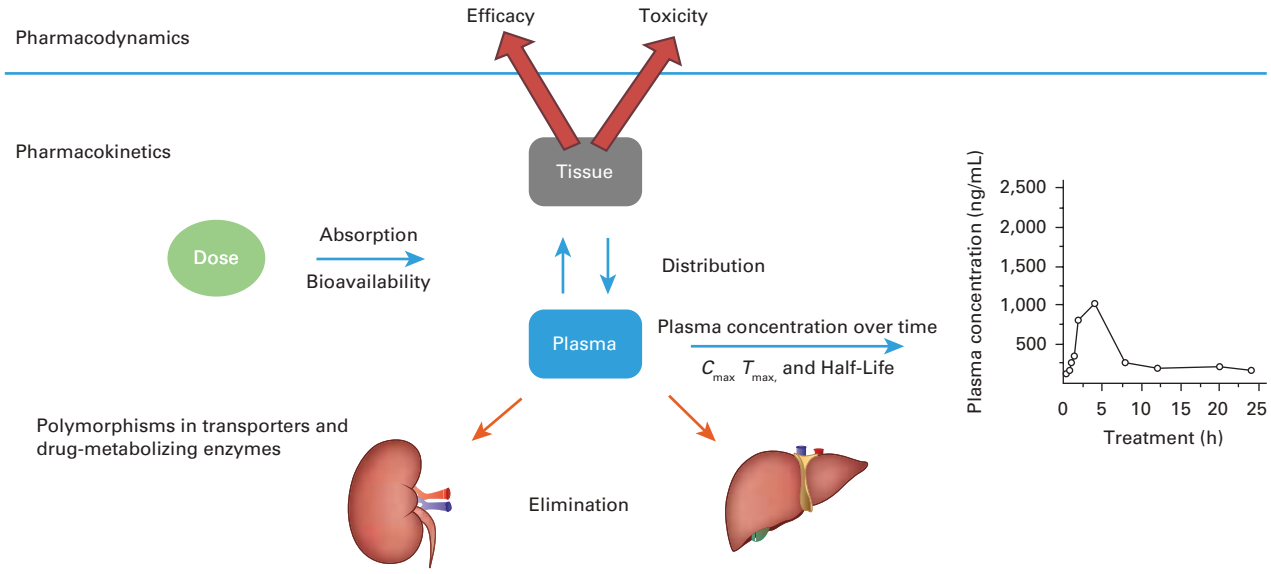
Figure 3-2 Overview of Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics



Abbreviations: C_{max}, maximum concentration; T_{max}, time at which maximum concentration is achieved.
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The biologic, physiologic, and physicochemical factors that influence the transfer processes of drugs in the body also influence the rate and extent of ADME of those drugs in the body. Typically, pharmacokinetic parameters are determined by measuring drug concentrations in plasma or other relevant distribution sites. The ADME properties of a drug determine the amount of drug exposure in the body, including the target site.

The starting point for introducing any drug into the body is its administration. Common routes of administration include oral, intravenous, intramuscular, subcutaneous, and intrathecal. The proportion of the drug that reaches the systemic circulation after administration is the pharmacokinetic parameter bioavailability (abbreviated as "F" in applicable equations and some texts).

Historically, almost all anticancer agents were administered intravenously, and the bioavailability of intravenously administered agents is defined as 100%, simplifying pharmacokinetic modeling for these agents. However, small-molecule targeted agents are typically administered orally, making bioavailability an important consideration. Adequate exposure can be achieved with oral administration of small-molecule agents.

Factors that influence oral bioavailability include route of administration, absorption factors, and metabolism factors.

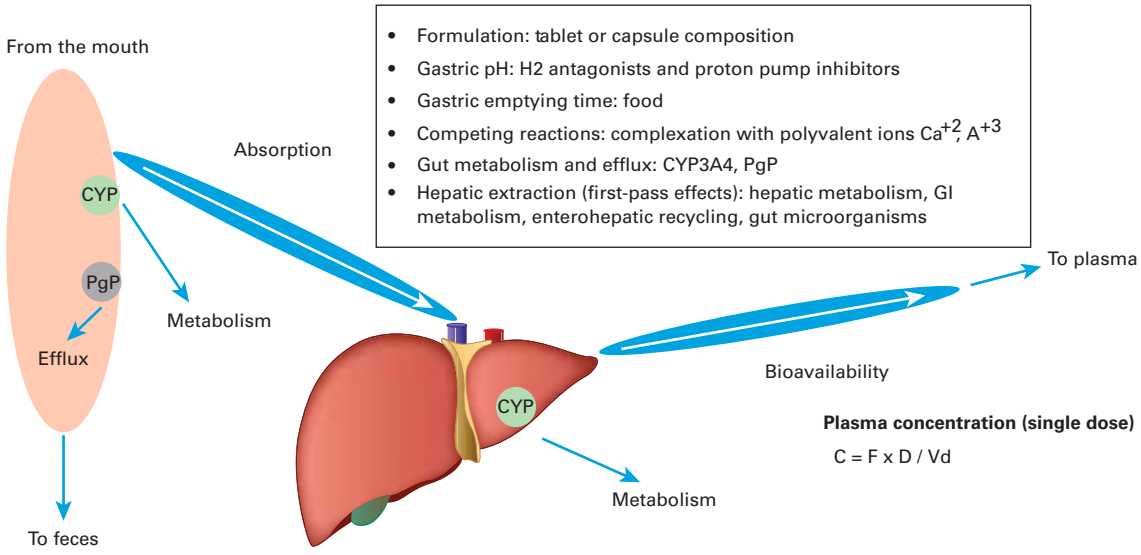
- Absorption is often pH dependent and is discussed in the Drug Interactions section of this chapter. In addition, the fraction of drug lost during the process of absorption, or the first-pass effect, also reduces drug bioavailability (Fig. 3-3).[44]

The purpose of pharmacokinetics in clinical drug development is to assess relationships between plasma concentrations and clinical outcomes of interest, typically efficacy and adverse effects. Many important pharmacokinetic parameters can be estimated by visual inspection of the plasma versus time concentration curve.

- The maximum concentration (C_{max}) is the highest observed concentration. The time when C_{max} occurs is the T_{max}.
- C_{max} is useful clinically for predicting acute toxicity, including infusion reactions and electrocardiogram (ECG) changes. T_{max} is useful in predicting when these toxicities are likely to occur.
- Measured concentration and time data are used to determine pharmacokinetic parameters, which may be primary or secondary.

Primary pharmacokinetic parameters depend on the physiology of the body and the physiochemical properties of the drug, and they include clearance, volume of distribution, and bioavailability.

Figure 3-3 Factors Influencing Oral Absorption



Abbreviations: A, aluminum; C, concentration; Ca, calcium; CYP, cytochrome P450; D, dose; F, bioavailability; H2, histamine 2; k, elimination rate constant; PgP, P-glycoprotein; Vd, volume of distribution.
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- Clearance is the amount of drug eliminated per unit of time.
  - It informs the dose and schedule of drug administration.
  - It is assumed to be constant and is the process by which a drug is removed from the body either as an unchanged drug through renal elimination or by metabolism and subsequent elimination through the urine or feces.
  - It is a proportionality factor that relates the concentration of a drug measured in the body to the rate of elimination and is a function of renal or hepatic activity.
- Volume of distribution is a proportionality constant that relates the amount of drug in the body to the concentration of the drug that was measured.
  - The larger the volume of distribution, the more likely the drug will be found in the tissues of the body, typically at the sites of action.
  - Drugs with a volume of distribution of no more than 3 L are considered confined to the plasma. If the volume of distribution is greater than 50 L, the drug is considered to be distributed to all tissues in the body, especially the fatty tissue. Conceptually, the volume of distribution describes the location of the drug in the body.
- Bioavailability is the proportion of a drug that enters the systemic circulation. Half-life and area under the curve (AUC) are secondary pharmacokinetic parameters because they can be calculated from primary parameters (if those are known). They can also be determined from the concentration versus time curve.
- The AUC represents the total drug exposure over time and can be used to predict response and chronic adverse effects. The AUC depends on the drug amount that enters the systemic circulation (ie, dose and bioavailability) and on the system's ability to eliminate the drug (ie, clearance).
- The half-life is the time required for the concentration to decrease by half and is primarily determined by clearance.
- Drugs and biologics are considered to be eliminated after five half-lives have elapsed. Notably, small molecules generally have shorter half-lives (5-FU is 8-20 minutes and paclitaxel 13-52 hours), while biologics generally have much longer half-lives (trastuzumab 2-13 days).
- The half-life is used clinically to determine dosing frequency and washout periods in clinical trials or when starting new medications.
- For example, erlotinib has a half-life of approximately 36 hours, so in a patient whose disease is progressing on erlotinib therapy and who is switching to osimertinib therapy, typically 1 week of not taking erlotinib should be allowed (180 hours or approximately 7 days) to prevent the development of additive adverse effects.
- Any significant dysfunction of the primary organ responsible for drug excretion, prolonged drug clearance, and third fluid spacing may necessitate dose reduction or schedule alteration.

KEY POINTS

- C_{max}, which occurs at T_{max}, can predict acute toxicity, such as ECG changes, infusion reactions, and acute blood pressure elevations.
- The AUC best reflects systemic exposure and can predict response for some antineoplastics.
- Pharmacokinetic assessments are important in determining drug-drug interactions and making recommendations on the dose and schedule of anticancer agents.
- Half-life guides the frequency of administration and determines washout periods in clinical trials. Dosing in clinical trials often considers the half-life of targeted therapies. For example, patients are often not eligible for initiating dosing of a study agent in a clinical trial until five half-lives of the targeted therapy have elapsed.

PHARMACODYNAMICS

Pharmacodynamics is often summarized as the study of "what a drug does to the body."[45,46] Most anticancer drugs are developed to interact with a biological structure (eg, receptor, enzyme, and transporter) and that interaction leads to a pharmacodynamic effect or an anticancer effect, although off-target effects also occur that can result in adverse effects. Predicting pharmacodynamic effects is critical to drug development. In some cases, such as the carboplatin AUC that predicts thrombocytopenia, plasma pharmacokinetics predict pharmacodynamic effects. However, assessing anticancer activity in solid tumors is challenging. The difficulty arises from an incomplete understanding of a drug's mechanism of action and from difficulties in measuring drug activity at its target or in the cancer cell. For example, to measure the activity of a TKI, a relevant pharmacodynamic study would be to measure TKI activity by assessing the phosphorylation of key substrates in the cancer cells before and after treatment with the drug. Technical and clinical issues make this type of study difficult because repeated tumor biopsies and real-time enzyme assays would be required. Enhancing the ability to assess pharmacodynamic markers in peripheral blood or surrogate tissue is an active area of clinical investigation.

In the absence of a measurable pharmacodynamic biomarker, the coupling of pharmacodynamic mathematical models with plasma pharmacokinetic data is an effective strategy for the study of exposure to response and clinical trial simulations. New strategies include the development of physiologic models that recognize that blood flow to the cancer varies from plasma blood flow. In addition to pharmacokinetic and pharmacodynamic data, these models incorporate physiologic properties (eg, blood flow and organ volume) and drug properties (eg, partition across organs). Incorporation of a predictive preclinical pharmacokinetic/pharmacodynamic model in preclinical studies and early-stage clinical trials can inform the drug development process and reduce the failure rate in later-stage clinical trials.

PHARMACOGENETICS

Pharmacogenetics is the study of variability in drug response due to heredity. In this context, there are germline polymorphisms (occurring in all host cells) in drug-metabolizing pathways or drug targets that are inherited and can affect individual responses to drugs in terms of therapeutic and adverse effects. Notably, with the exception of uridine diphosphate glucuronosyltransferase 1A (UGT1A), which is associated with Gilbert's syndrome, polymorphisms do not typically cause medical conditions. Much of this genetic variation is in the form of single-nucleotide polymorphisms (SNPs). SNPs are defined as variants with population frequencies of at least 1% that can alter the amino acid sequence of the encoded protein or alter RNA splicing, leading to altered kinetics and catalysis of the protein. The concordance between genotype and phenotype is not complete. Many individuals who experience adverse effects will not have an SNP in a known drug-metabolizing pathway for a given anticancer agent. Likewise, not all SNPs are functional. To aid in the use and interpretation of pharmacogenetic results, all drugs with biomarker information (ie, protein targets, germlines, and tumor mutations) in their product labeling are listed on the FDA website,[47] and evidence-based clinical practice guidelines for using pharmacogenetic information are available from the Clinical Pharmacogenetics Implementation Consortium (https://cpicpgx.org/).[48] The consortium's practice guidelines also include polymorphism frequency by ethnicity.

Examples below highlight some notable drugs with pharmacogenetic associations that may indicate an impact on a drug's safety or a patient's response (see Table 3-7).

5-FLUOROURACIL AND CAPECITABINE

- Metabolism: Dihydropyrimidine dehydrogenase (DPD; encoded by *DPYD*) catalyzes the first and rate-limiting step in the conversion of 5-FU to dihydrofluorouracil.

Some polymorphisms result in reduced activity of DPD, which subsequently results in reduced clearance and increased half-life of 5-FU, and they are associated with adverse effects, including severe myelosuppression, neurotoxicity, and GI toxicity.

Capecitabine, a prodrug of 5-FU, is converted to 5-FU and metabolized by DPD. Therefore, toxic effects are similar in patients with decreased or non–functioning *DPYD* variants.

Table 3-7 **Drugs Commonly Used in Oncology That Have Pharmacogenetic Implications**

Drug	Gene	Variant Genotype	Consequence of Variant Genotype	Recommendation	Strength of Recommendation*
Capecitabine/ fluorouracil	DPYD	IM	Increased toxicity	IM: Reduce starting dose	Strong
		PM		PM: Avoid if possible, or reduce dose by 75%	
Irinotecan, liposomal irinotecan	UGT1A1	PM	Increased toxicity	Select alternative therapy if possible	Moderate
Mercaptopurine	TPMT, NUDT15	IM	Increased toxicity	IM: Reduce dose by 50%	Strong
		PM		PM: Reduce dose 10-fold	
Tamoxifen	CYP2D6	PM	Decreased efficacy	Select an alternative agent not metabolized by CYP2D6 (eg, aromatase inhibitor if postmenopausal)	Weak

Abbreviations: IM, intermediate metabolizer; PM, poor metabolizer.
*Clinical Pharmacogenetics Implementation Consortium evidence level, except for irinotecan, for which the recommendations are the authors' opinion.
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Multiple meta-analyses have demonstrated the relationship between these genetic polymorphisms and adverse effects; guidelines recommend dose reductions for patients who do not metabolize these drugs well, and alternative dosing strategies have been proposed.[49] DPYD variants should be routinely assessed before initiation of 5-FU or capecitabine based therapy.

ASCO guidelines on DPYD testing align with the FDA labeling updates to test patients for genetic variants of DPYD prior to initiating treatment unless immediate treatment is necessary. Other oncology guidelines for DYPD testing may differ among various organizations considering insurance coverage determination and testing turnaround times. Molecular analysis of patients with DPD deficiency has identified over 128 mutations and polymorphisms in the DPYD gene that may result in partial or total loss of DPD activity. A complete DPD deficiency generally refers to variants on DYPD*2A, DPYD*13 and DPYD HapB3, patients with certain homozygous or compound heterozygous of these variants should avoid treatment with 5-FU or capecitabine based therapy. For patients with partial DPD deficiency or DYPD intermediate metabolizer, doses should be individualized or reduced with closer monitoring for severe diarrhea, mucositis and pancytopenia. While testing for a patient's level of DPD activity is widely available, the turn-around time for availability of the test result can be several days. Reducing the turn-around time has been identified as an important component in delivering safer therapy in a clinically relevant time period.[50]

IRINOTECAN AND LIPOSOMAL IRINOTECAN

- Metabolism: Irinotecan, a prodrug, is metabolized in vivo to 7-ethyl-10-hydroxycamptothecin (SN-38), which is a potent inhibitor of topoisomerase 1. 7-Ethyl-10-hydroxycamptothecin is inactivated by glucuronidation to form the glucuronide conjugate 7-ethyl-10-hydroxycamptothecin G (SN-38G) in a reaction catalyzed by the polymorphic hepatic enzyme UGT1A1.[51]
- A dinucleotide repeat polymorphism in the TATA box in the promoter for *UGT1A1* results in reduced hepatic *UGT1A1* expression and is considered the most common cause of Gilbert syndrome (mild unconjugated hyperbilirubinemia).[52]
- Patients homozygous for the *UGT1A1*28* polymorphism have substantially lower 7-ethyl-10-hydroxycamptothecin glucuronidation rates and substantially higher rates of grade 4 or 5 neutropenia and severe diarrhea when treated with irinotecan than those who do not carry this genetic variant.[53]
- Despite an FDA label change recommending dose reduction for patients who metabolize this drug poorly, the irinotecan dose is infrequently adjusted clinically for this polymorphism.

THIOPURINES (MERCAPTOPURINE AND 6-THIOGUANINE)

Mercaptopurine and 6-thioguanine are purine antimetabolites used clinically to treat pediatric and adult leukemias.

- Metabolism: Thiopurines are metabolized, in part, by *S*-methylation and catalyzed by the enzyme thiopurine *S*-methyltransferase (TPMT).
- Individuals with reduced activity experience substantially increased adverse effects when receiving mercaptopurine.

- TPMT activity, measured either by a phenotypic enzyme test or by sequencing for polymorphisms with subsequent dose reductions in patients with intermediate and poor metabolism of the drugs, is routinely performed in clinical practice.[54-58]
- Polymorphisms in nucleoside diphosphatase (*NUDT15*), which catalyzes the conversion of cytotoxic thioguanine triphosphate metabolites to the less toxic thioguanine monophosphate, are associated with thiopurine adverse effects and have been reported more recently, and assessment is moving into clinical practice.[59]
- Patients with TPMT or NUDT15 deficiency are at increased risk for severe toxicity at conventional mercaptopurine doses and generally require dose reductions.

TAMOXIFEN

- Metabolism: Tamoxifen is a prodrug activated by CYP2D6 to its active metabolite endoxifen.
- Patients with little or no CYP2D6 activity may have a poor response to tamoxifen because of inadequate conversion to the active drug.
- This relationship is controversial, with conflicting literature reported. The majority of the literature discusses the adjuvant treatment of estrogen receptor–positive breast cancer, wherein patients with little or no CYP2D6 activity have an increased risk of recurrence; however, there are insufficient data at this time to suggest that this affects survival.[60]
- Current guidelines recommend selecting an alternative therapy in patients who have little or no CYP2D6 activity, which is a reasonable strategy because aromatase inhibitors are preferred for use by postmenopausal women, and therapeutic alternatives are available for premenopausal women (eg, ovarian suppression and aromatase inhibitors with or without additional targeted therapies). CYP2D6 activity levels can be determined using a test to identify a patient's CYP2D6 genotype from genomic DNA extracted from a whole-blood sample. Similar to the data on patients with little or no CYP2D6 activity, the literature is also conflicting regarding concurrent use of CYP2D6 inhibitors and tamoxifen, which is the pharmacologic equivalent of the poor metabolism genotype.

Initially, a prospective study reported that plasma endoxifen concentrations were substantially lower in patients receiving concurrent tamoxifen and strong inhibitors of CYP2D6, whereas weak inhibitors had little effect.[61] However, a recently reported population cohort study that included more than 14,000 women concurrently receiving tamoxifen and selective serotonin reuptake inhibitors (SSRIs) showed no increased risk of death among women receiving SSRIs that were weak inhibitors of CYP2D6 compared with those taking strong inhibitors of CYP2D6, although follow-up was short, at less than 2 years.[62] Given the availability of SSRIs such as venlafaxine that are weak CYP2D6 inhibitors, avoiding the use of strong CYP2D6 inhibitors such as fluoxetine and paroxetine concurrently with tamoxifen seems prudent.

The two most common therapeutic strategies for patients with variant genotypes are dose reduction or use of an alternative agent. However, with the exception of the thioguanines, pharmacogenetic testing is rarely performed in clinical practice for a variety of reasons, including lack of clinical trial evidence supporting appropriate dose reduction, lack of insurance coverage for testing, lack of alternative therapeutic options, physician preference for dose adjustments after toxicity, and the inability to get test results returned in time to affect chemotherapy dosing or drug selection. A recent trend in increased direct-to-consumer pharmacogenetic testing may actually encourage the use of pharmacogenetic information in clinical practice.[63-65]

DRUG INTERACTIONS

Drug interactions are typically pharmacokinetic and result from one drug or effect, when used concomitantly, causing a change in the plasma concentrations of another drug by affecting the drug's absorption (eg, food and pH), metabolism, or elimination. The risk of an adverse event due to drug interactions is higher when multiple medications, particularly those that are metabolized by cytochrome P450 enzymes, are prescribed concomitantly. Examples of common CYP enzymes involved in drug metabolism include CYP3A4, CYP2D6, CYP2C8, CYP2C9, CYP1A2, and CYP2D19.[66,67]

ABSORPTION

The proportion of the drug that reaches the systemic circulation after administration is the pharmacokinetic parameter bioavailability, which is calculated as drug exposure attained relative to that attained with intravenous administration of the same drug. Changes in absorption often affect bioavailability.

Factors that affect drug absorption and bioavailability are as follows:

- Food and pH effects can interfere with drug absorption and are major considerations when developing oral drugs. The FDA typically requires a food effect study for all new agents.
- Food (in particular, food with a high-fat content) may increase, decrease, or not affect drug bioavailability, depending on the drug, which is measured by differences in the pharmacokinetic parameters (ie, C_{max} and AUC ratios) between the fed and fasted states.

- An example of this food effect is the concomitant use of abiraterone acetate with food, in which increased drug exposure after abiraterone administration occurred in a fed state compared with the fasted state. This food effect is more pronounced with a high-fat meal than a low-fat meal. Consequently, prescribing information recommended that the standard dose (1,000 mg once per day) of abiraterone is to be taken on an empty stomach, with no food consumed for at least 2 hours before and for at least 1 hour after dosing, to minimize variability in drug exposure.

pH effects such as acid suppression therapy, including antacids, histamine H2 antagonists, and proton pump inhibitors, lower gastric pH and can influence absorption of concurrently administered medications, especially those with pH-dependent solubility.[68]

Antacids work by binding to and neutralizing stomach acid, resulting in a rapid onset and short duration of effect (approximately 2 hours).

- Histamine H2 receptor antagonists reversibly compete with histamine at the H2 receptors to reduce gastric acid secretion, with effects lasting approximately 12 hours after the dose.
- Proton pump inhibitors irreversibly bind to the proton pump that secretes gastric acid, resulting in at least 24 hours of gastric acid suppression. All therapies can increase gastric pH to greater than 6. In addition, polyvalent cations found in antacids can bind to some drugs, forming insoluble chelates that limit drug absorption.[69]

If a drug has reduced solubility above a pH of 6, drug interaction studies are typically required by the FDA and are of designs similar to those described for food effects. The results of drug interaction studies also inform the product label: If the AUC or C_{max} ratio falls outside the 90% CI, a significant drug interaction between acid-lowering therapies is determined. Of note, pH-dependent absorption is not always a class effect. For example, bosutinib, dasatinib, and nilotinib have pH-dependent absorption, with reduced absorption at a lower pH; however, imatinib has pH-independent absorption.[70]

METABOLISM

The majority of metabolism occurs in the liver and, to a lesser extent, in the GI tract for orally absorbed drugs. Drugs may be inducers, inhibitors, or substrates of a drug-metabolizing enzyme. A complete list of substrates, inhibitors, and inducers of the CYP enzymes can be found on the FDA website,[71] although CYP3A4 is most commonly involved in drug interactions involving oral targeted therapies. Observed changes arising from metabolic drug-drug interactions can be substantial (an order of magnitude or more decrease or increase in the plasma concentrations of a drug or metabolite) and can include formation of toxic and/or active metabolites or increased exposure to a toxic parent compound. These large changes in exposure can alter the safety and efficacy profile of a drug and/or its active metabolites in important ways. For many newer medications, dose adjustments are included in the product labeling. For example, erlotinib is metabolized primarily by CYP3A4, and the prescribing information recommends that dose decreases of erlotinib should be considered if it is concurrently administered with strong CYP3A inhibitors.

The magnitude of CYP-mediated drug interactions can be assessed by changes in pharmacokinetics following administration of perpetrators using the FDA classifications of strong, moderate, or weak as below:

- Strong inducer: a drug that decreases the AUC of substrates by ≥80%
- Moderate inducer: a drug that decreases the AUC of substrates by 50% to <80%
- Weak inducer: a drug that decreases the AUC of substrates by <50%
- Strong inhibitor: a drug that increases the AUC of substrates by >5-fold or >80% decrease in clearance
- Moderate inhibitor: a drug that increases the AUC of substrates by 2 to <5-fold or 50% to 80% decrease in clearance
- Weak inhibitor: a drug that increases the AUC of substrates by 1.25 to <2-fold or 20% to 50% decrease in clearance

TRANSPORT-MEDIATED INTERACTIONS

Some chemotherapy drugs are substrate for influx transporters, like organic anion transporting polypeptides (OATPs), BCRP, and P-glycoprotein (P-gp). The transporters can modulate intratumoral levels of chemotherapy and, in some settings, cause ineffective concentrations of active chemotherapy.

- P-gp: P-gp is a transmembrane ATP-binding cassette (ABC) transporter that is involved in chemotherapy resistance by actively pumping a wide range of chemotherapeutic agents out of cancer cells. By reducing tumor concentrations, chemotherapy activity can become ineffective. P-gp substrates include doxorubicin, daunorubicin, vincristine, vinblastine, etoposide, paclitaxel, and docetaxel.
- Breast cancer resistance protein (BCRP, also known as ABCG2): BCRP is also among the ABC proteins. Substrates of this efflux protein transporter include topotecan, mitoxantrone, and methotrexate.
- OATPs *OAT1B1* and OATP1B3: These influx transport proteins facilitate a wide variety of drugs into liver cells. Substrates include irinotecan/SN38, paclitaxel, methotrexate, doxorubicin, and some TKIs.

KEY POINTS

- Drug interactions with oral cancer therapies, particularly TKIs, are common and may be clinically important.
- Drug interactions affecting gastric absorption are usually related to food or pH effects. These can be managed by avoiding concurrent administration of pH-lowering agents.
- Food effects can be managed by counseling patients on when to take their medication (ie, with or without food). Some drugs may require administration with a low-fat meal.
- Drug interactions related to metabolism or elimination can be managed by avoiding concurrent administration, if possible, or by adjusting doses.
- Grapefruit, grapefruit juice, Seville oranges, and star fruit are CYP3A4 inhibitors. Patients should be instructed to avoid consuming these products while taking cancer therapies that are metabolized via CYP3A4.
- Patients with TPMT or NUDT15 deficiency are at increased risk for severe toxicity at conventional mercaptopurine doses and generally require dose reductions.
- DPD is an enzyme encoded by the DPYD gene and promotes the first step of the fluorouracil degradation pathway. This pathway helps convert majority of drug to its inactive metabolites. Patients with partially or complete DPD deficiency cannot adequately degrade fluoropyrimidines, are at increased risk of severe, potentially fatal toxicity. Test for DPD deficiency before starting 5-FU or capecitabine therapy should be performed. Avoid use in patients with complete DPD deficiency and reduce dose in those with partial DPD deficiency.[50]

ANTIDOTES FOR CHEMOTHERAPY OVERDOSES

GLUCARPIDASE FOR INTRAVENOUS AND INTRATHECAL METHOTREXATE OVERDOSE

Glucarpidase is a rescue agent approved by the FDA for use in patients with delayed methotrexate excretion. The medication is a recombinant bacterial enzyme that cleaves methotrexate into inactive metabolites. It has a rapid onset of action, with greater than 97% reduction in methotrexate concentration within 15 minutes of intravenous administration, and is able to maintain a reduced methotrexate concentration for up to 8 days. Because glucarpidase can falsely elevate methotrexate immunoassay measurements for approximately 48 hours after administration, a chromatographic method should be used during this time.

Consensus guidelines suggest that optimal glucarpidase administration is within 48 to 60 hours from the start of high-dose methotrexate, usually defined as intravenous doses of at least 500 mg/m^2 given over 2 to 36 hours.[72] A repeat glucarpidase dose within 48 hours of the first dose is not recommended because it would have less efficacy. Leucovorin calcium is a substrate for glucarpidase and may compete with methotrexate for binding sites. It should be administered at least 2 hours before or 2 hours after a glucarpidase dose and should be continued for the first 48 hours after glucarpidase administration.

Overdoses of intrathecal methotrexate can occur when methotrexate doses meant for systemic administration are given intrathecally. Data from a limited number of patients studied suggest that glucarpidase may also be beneficial for overdoses of intrathecal methotrexate.[73] Adverse reactions related to glucarpidase include nausea and vomiting, hypotension, paresthesia, hot flashes, and headache.

URIDINE TRIACETATE FOR 5-FLUOROURACIL OR CAPECITABINE OVERDOSE OR EARLY-ONSET TOXICITY

Uridine triacetate is indicated for emergency treatment of 5-FU or capecitabine overdose (regardless of the presence of symptoms) or early onset of severe toxicities, including acute cardiomyopathy, altered mental status, mucositis, severe nausea and diarrhea, and neutropenia. Potential errors leading to overdose or severe toxicities can be related to 5-FU chemotherapy pump malfunctions or misprogramming and accidental ingestion of capecitabine tablets. In addition, genetic enzyme variants, such as those with homozygous or heterozygous DPD mutations, can lead to an increased risk for acute early-onset toxicity.[74] FDA recently approved changes in safety labeling for FU in patients with DPD deficiency and has recommended *DPYD* testing as part of a boxed warning. Dose reduction is recommended in patients carrying deleterious germline variants.

Uridine works by competing with fluorouridine triphosphate, a 5-FU metabolite, which can be incorporated into the RNA of hematopoietic cells and GI cells to reduce 5-FU toxicity in normal cells.[75] Adult dosing consists of uridine triacetate 10 g orally every 6 hours for 20 doses beginning as soon as possible and within 96 hours after the end of 5-FU or capecitabine administration; pediatric patients received 6.2 g/m^2 (maximum of 10 g) orally every 6 hours.

SODIUM THIOSULFATE TO REDUCE THE RISK OF OTOTOXICITY ASSOCIATED WITH CISPLATIN

Sodium thiosulfate is indicated to reduce the risk of cisplatin-induced ototoxicity in pediatric patients 1 month or older with localized solid tumors. It is reserved for patients receiving cisplatin infusion of less than or equal to a 6-hour duration. For a duration greater than 6 hours, irreversible ototoxicity may have already occurred, and therefore, sodium thiosulfate may not be efficacious.

The most common adverse reactions associated with sodium thiosulfate are vomiting, nausea, hypernatremia, hypokalemia, and decreased hemoglobin. Before each dose of sodium thiosulfate, antiemetic therapy should be given, and the sodium level should be measured to ensure that it is within normal limits.

The recommended sodium thiosulfate dose is based on surface area according to actual body weight. It is administered as an intravenous infusion over 15 minutes after cisplatin infusions of 1 to 6 hours duration.

METHYLENE BLUE FOR IFOSFAMIDE-INDUCED ENCEPHALOPATHY

Methylene blue currently does not have FDA approval for use in ifosfamide-induced encephalopathy; adverse reactions include confusion, ataxia, weakness, seizures, somnolence, and hallucinations. Onset may be 2 to 48 hours after commencing treatment. When reversible, symptoms usually resolve within 1 to 3 days. However, available data from case reports indicate that methylene blue is an option to reverse ifosfamide neurotoxicity. It inhibits monoamine oxidase, thereby preventing the generation of the neurotoxic chloroacetaldehyde metabolite. Methylene blue can be given orally or intravenously, with an initial dose of 50 mg in adults or every 4 to 8 hours until symptoms resolve. It should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency because it may result in hemolysis and anemia.

KEY POINTS

- One avenue to combat toxicities and prevent permanent sequelae is to administer antidotes if a chemotherapy overdose occurs.
- Uridine triacetate is indicated for emergency treatment of 5-FU or capecitabine overdose.
- Glucarpidase is a rescue agent approved by the FDA for use in patients with delayed methotrexate excretion.
- Methylene blue is an option for use in patients with ifosfamide-induced encephalopathy. It should be used with caution in patients with glucose-6-phosphate deficiency.

SPECIAL POPULATIONS

RENAL IMPAIRMENT

Most drugs are cleared by elimination of an unchanged drug by the kidney and/or by metabolism in the liver. For a drug eliminated primarily through renal excretory mechanisms, impaired renal function may alter its pharmacokinetics and pharmacodynamics.[76] An accurate assessment of renal function is critical to dosing chemotherapy, and both the NCCN and the International Society of Geriatric Oncology recommend assessment of renal function before initiating chemotherapy, although there is currently no consensus on the best method. Creatinine clearance (CrCl) can be measured directly with a 24-hour urine collection, although this is often impractical in terms of time, cost, and convenience. There are also several equations to calculate CrCl. The Cockcroft-Gault equation[77] is commonly used; however, guidance from the FDA for assessing clinical trial eligibility based on renal function now suggests that any "contemporary, widely accepted, and clinically applicable equation" is usually sufficient.[78] "Renal clearance of a drug is proportional to the individual's GFR (expressed as mL/minute). Hence, when providing a recommended dosage in adult patients with renal impairment, use the eGFR as mL/minute." Refer to local prescribing information for current recommendations on dose adjustments for renal impairment. See Table 3-8 for dose adjustment for patients with renal dysfunction. Although the most common type of change arising from renal impairment is a decrease in renal excretion or possibly renal metabolism of a drug or its metabolites, renal impairment has also been associated with other changes, such as those in absorption, hepatic metabolism, plasma protein binding, and drug distribution.[76] These changes may be more important in patients with severely impaired renal function and have been observed even when the renal route is not the primary route of elimination of a drug.

Table 3-8 **Dosing Guidelines of Selected Anticancer Agents for Patients With Renal Dysfunction**

Agent	Dose Adjustment in Renal Dysfunction
Bleomycin	CrCl 40-50 mL/min, 70% of the full dose
	CrCl 30-40 mL/min, 60% of the full dose
	CrCl 20-30 mL/min, 55% of the full dose
	CrCl 10-20 mL/min, 45% of the full dose
	CrCl 5-10 mL/min, 40% of the full dose
Capecitabine	CrCl 30-50 mL/min, 75% of the full dose
	CrCl <30 mL/min, omit

Agent	Dose Adjustment in Renal Dysfunction
Carboplatin	Dose based on GFR, using the Calvert formula: Dose (mg) = target AUC × (GFR + 25). AUC = 5–7 Hemodialysis: Carboplatin dose (mg) = Target AUC × 25, administer on a non–dialysis day; hemodialysis should occur between 12 and 24 hours after carboplatin dose
Carmustine	CrCl 45-60 mL/min, 80% of the full dose
	CrCl 30-45 mL/min, 75% of the full dose
	CrCl <30 mL/min, 70% of the full dose
Cisplatin	CrCl 46-60 mL/min, 50% of the full dose
	CrCl 31-45 mL/min, 25% of the full dose
	CrCl <30 mL/min, omit
Cladribine	CrCl 10-50 mL/min, 75% of the full dose
	CrCl <10 mL/min, 50% of the full dose
Cyclophosphamide	CrCl 10-20 mL/min, 75% of the full dose
	CrCl <10 mL/min, 50% of the full dose
Cytarabine	High and intermediate dose (1 g/m^2 or more per dose)
	CrCl 30-59 mL/min: 50% of the full dose
	CrCl <30 mL/min: use is not recommended, consider an alternative agent
Dacarbazine	CrCl 30-60 mL/min, 75% of the full dose
	CrCl 10-30 mL/min, 50% of the full dose
	CrCl <10 mL/min, omit
Daunorubicin	Scr >3 mg/dL, 50% of the full dose
	CrCl 30-50 mL/min, 75% of the full dose
	CrCl <30 mL/min, 50% of the full dose
Etoposide	CrCl 15 to 50 mL/min, 75% of the full dose
	CrCl <15 mL/min, 50% of the full dose
Fludarabine	CrCl 30-70 mL/min, 50% of the full dose
	CrCl <30 mL/min, omit
Hydroxyurea	CrCl 45-60 mL/min, 80% of the full dose
	CrCl 30-45 mL/min, 75% of the full dose
	CrCl 10-30 mL/min, 50% of the full dose
	CrCl <10 mL/min, 20% of the full dose
Ifosfamide	CrCl 46-60 mL/min, 80% of the full dose
	CrCl 31-45 mL/min, 75% of the full dose
	CrCl 10-30 mL/min, 70% of the full dose
	CrCl <10 mL/min, omit
Lenalidomide (use for MDS/myelofibrosis osteosclerosis)	CrCl 30-60 mL/min, 5 mg once every 24 hours
	CrCl <30 mL/min (not requiring dialysis), 5 mg once every 48 hours
	CrCl <30 mL/min (requiring dialysis), 5 mg 3 × per week after each dialysis
Lenalidomide (use for multiple myeloma)	CrCl 30-60 mL/min, 10 mg once every 24 hours
	CrCl <30 mL/min (not requiring dialysis), 15 mg once every 48 hours
	CrCl <30 mL/min (requiring dialysis), 5 mg once per day; dose after dialysis on dialysis days
Lomustine	CrCl 45-60 mL/min, 75% of the full dose
	CrCl 30-45 mL/min, 70% of the full dose
	CrCl <30 mL/min, omit
Melphalan	CrCl 45-60 mL/min, 85% of the full dose
	CrCl 30-45 mL/min, 75% of the full dose
	CrCl 10-30 mL/min, 70% of the full dose

Agent	Dose Adjustment in Renal Dysfunction
	CrCl <10 mL/min, 50% of the full dose; for high dose (>1 g/m^2), consider TDM
	CrCl <10 mL/min, omit
Methotrexate	CrCl <30 mL/min, avoid use
	CrCl <10 mL/min, omit
Oxaliplatin	CrCl <30 mL/min, omit
Pemetrexed	CrCl <45 mL/min, omit
Pentostatin	CrCl 45-60 mL/min, 70% of the full dose
	CrCl 30-45 mL/min, 60% of the full dose
	CrCl <30 mL/min, consider using alternative drugs, if possible
Topotecan	CrCl 30-60 mL/min, 75% of the full dose
	CrCl 10-30 mL/min, 50% of the full dose
	CrCl <10 mL/min, omit

Abbreviations: AUC, area under the curve; CrCl, creatinine clearance; GFR, glomerular filtration rate; MDS, myelodisplastic syndromes; TDM, therapeutic dose monitoring.

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HEPATIC IMPAIRMENT

The liver is involved in the clearance of many drugs through a variety of oxidative and conjugative metabolic pathways and/or through biliary excretion of unchanged drug or metabolites.[79] Alterations of these excretory and metabolic activities by hepatic impairment can lead to drug accumulation or, less often, failure to form an active metabolite.[80] The level of hepatic impairment (drug-induced liver injury [DILI]) is typically defined more by the level of total bilirubin rather than transaminase levels. Greater levels of liver damage are associated with serious adverse events and death. Values of liver dysfunction as an alarm to consider the discontinuation were initially defined by gastroenterologist Hyman Zimmerman, who proposed what is now known as Hy's law.

Briefly, Hy's law cases have the following three components: (1) The drug causes hepatocellular injury, generally shown by a higher incidence of threefold or greater elevations above the upper limit normal (ULN) of alanine transaminase (ALT) or aspartate transaminase (AST) than the (nonhepatotoxic) control drug or placebo. (2) Among trial subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3 × ULN, one or more also show elevation of serum TBL to more than 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase [ALP]). (3) No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.[80]

Hepatic disease can alter the absorption and the disposition of drugs (pharmacokinetics) as well as their efficacy and safety (pharmacodynamics). Refer to local prescribing information for current recommendations on dose adjustments for hepatic impairment (see Tables 3-9 and 3-10).

Table 3-9 Dosing Guidelines of Selected Anticancer Agents for Patients With Hepatic Dysfunction

Agent	Dose Adjustment in Hepatic Dysfunction
Cabazitaxel	Mild impairment (total bilirubin >1-1.5× ULN or AST $ 1.5× ULN, dose at 20 mg/m^2)
	Moderate impairment (total bilirubin >1.5-3× ULN and any AST), dose at 15 mg/m^2
	Total bilirubin >3× ULN, omit
Docetaxel	Transaminase >1.5× ULN and ALP >2.5× ULN, the recommended dose is 75 mg/m^2
	Total bilirubin >ULN and/or transaminase >3.5× ULN, associated with ALP >6× ULN, should not be used unless strictly indicated
Doxorubicin (liposomal)	Total bilirubin 1.2-3.0 mg/dL or AST 60-180 units/L, 50% of the full dose
	Total bilirubin >3.0 mg/dL or AST >180 units/L, 25% of the full dose
	Total bilirubin >5.0 mg/dL, omit
Fluorouracil	Total bilirubin >5.0 mg/dL, omit
Gemcitabine	Increased AST: no need for dose adjustment; increased total bilirubin: reduce dose by 20% (ie, from 1,000 to 800 mg/m^2) and increase if tolerated

Agent	Dose Adjustment in Hepatic Dysfunction
Irinotecan	Increased transaminase <3× ULN if no liver metastasis OR <5× ULN if liver metastasis are present. Total bilirubin >2 dosing should not be administered
Ixabepilone (monotherapy)	Total bilirubin <1.5× ULN and AST <10× ULN and AST:ALT ratio <10× ULN, reduce the dose to 32 mg/m^2
	Total bilirubin 1.5-3× ULN and transaminase <10× ULN, dose at 20 mg/m^2; may escalate dose up to 30 mg/m^2 maximum in subsequent cycles if tolerated
Ixabepilone (in combination with capecitabine)	Total bilirubin >ULN or transaminase >2.5× ULN, omit
Mitoxantrone	Total bilirubin 1.5-3.0 mg/dL, 50% of the full dose
	Total bilirubin >3.0 mg/dL, 25% of the full dose
Paclitaxel (3-hour infusion and first course of therapy)	Transaminase <10× ULN and total bilirubin 1.26-2× ULN, recommended dose = 135 mg/m^2
	Transaminase <10× ULN and total bilirubin 2.01-5× ULN, recommended dose = 90 mg/m^2
	Transaminase 10× ULN or total bilirubin >5× ULN dosing is not recommended
Paclitaxel (24-hour infusion and first course of therapy)	Transaminase 2-10× ULN and total bilirubin <1.5 mg/dL, dose 5× at 100 mg/m^2
	Transaminase <10× ULN and total bilirubin 1.6-7.5 mg/dL, dose 5× at 50 mg/m^2
	Transaminase 10× ULN or total bilirubin >7.5 mg/dL, omit
Sorafenib	Total bilirubin 1.5× ULN: 400 mg twice per day
	Total bilirubin 1.5-3× ULN: 200 mg twice per day
	Total bilirubin >3× ULN: omit
Vinblastine	Total bilirubin 1.5-3.0 mg/dL or AST 60-180 units/L, 50% of the full dose
	Total bilirubin >3.1 mg/dL or AST >180 IU/L, omit
Vincristine	Total bilirubin 1.5-3.0 mg/dL or AST 60-180 units/L, 50% of the full dose
	Total bilirubin >3.1 mg/dL or AST >180 units/L, omit
Vinorelbine	Total bilirubin 2.1-3× ULN: 50% of dose
	Total bilirubin >3× ULN: 25% of dose

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.
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Table 3-10 Dosing Guidelines for Selected Anticancer Agents for Patients With Renal and Hepatic Dysfunction

	Dose Adjustment	
Agent	**In Renal Function**	**In Hepatic Dysfunction**
Bendamustine	Renal impairment: CrCl <40 mL/min, omit	Moderate (transaminase 2.5-10× ULN and total bilirubin 1.5-3× ULN) or severe (total bilirubin >3× ULN), omit
Cyclophosphamide	CrCl <10 mL/min, 50% of the full dose	Total bilirubin >3.1-5.0 mg/dL or AST >180 IU/L, 75% of the full dose
		Total bilirubin >5.0 mg/dL, omit
Daunorubicin	Serum creatinine >3 mg/dL, 50% of the full dose	Total bilirubin 1.5-3.0 mg/dL or AST 60-180 IU/L, 75% of the full dose
		Total bilirubin >3.1-5.0 mg/dL or AST >180 IU/L, 50% of the full dose
		Total bilirubin >5.0 mg/dL, omit
Doxorubicin	CrCl <10 mL/min, 75% of the full dose	Total bilirubin 1.5-3.0 mg/dL or AST 60-180 IU/L, 50% of the full dose
		Total bilirubin >3.1-5.0 mg/dL or AST >180 IU/L, 25% of the full dose
		Total bilirubin >5.0 mg/dL, omit

Agent	Dose Adjustment	
	In Renal Function	**In Hepatic Dysfunction**
Epirubicin	Serum creatinine >5 mg/dL, lower doses should be considered	Total bilirubin 1.2-3.0 mg/dL or AST 2-4× ULN, 50% of the full dose
		Total bilirubin >3.0 mg/dL or AST >4× ULN, 25% of the full dose
		Total bilirubin >5.0 mg/dL, omit
Erlotinib	CrCl <10 mL/min, omit	Total bilirubin 1-7 mg/dL or AST 2-3× ULN, 50% of the full dose
		Total bilirubin >7.0 mg/dL, omit
Etoposide	CrCl >15-50 mL/min, 75% of the full dose	Total bilirubin 1.5-3 mg/dL or AST 60-180 units, 50% of the full dose
	CrCl <15 mL/min, omit	Total bilirubin 2-3 mg/dL or AST >180 units, omit
Hydroxyurea/ hydroxycarbamide	CrCl 10-60 mL/min, 75% of the full dose	Total bilirubin 1.5-5.0 mg/dL or AST 60-180 units/L, 50% of the full dose
	CrCl <10 mL/min, 50% of the full dose	Total bilirubin >5.0 mg/dL or AST >180 units/L, omit
Idarubicin	Serum creatinine 2–2.5 mg/dL, dose reduction recommended	Total bilirubin 2.5-5.0 mg/dL, 50% of the full dose
		Total bilirubin >5.0 mg/dL, omit
Imatinib	CrCl 40-59 mL/min, doses >600 mg are not recommended	Initial dose: severe hepatic impairment
	CrCl 20-39 mL/min, 50% of the full dose; dose can be increased up to a maximum of 400 mg	Initial dose: 75% of the full dose
	CrCl <20 mL/min, use with caution (in two patients with severe renal impairment, doses of 100 mg/d were tolerated)	Hepatic toxicity during treatment: transaminases >5× ULN or total bilirubin >3× ULN; omit
		Restart at reduced doses (reduce from 400 to 300 mg, from 600 to 400 mg, or from 800 to 600 mg) when transaminases <2.5× ULN and total bilirubin <1.5× ULN
Methotrexate	For low dose (<1 g/m^2), CrCl 30-60 mL/min, 50% of the full dose	Total bilirubin 3.1-5.0 mg/dL or AST >180 units, 75% of the full dose
	CrCl <30 mL/min, omit	Total bilirubin >5.0 mg/dL, omit
	For high dose (>1 g/m^2), consider TDM	Total bilirubin >5.0 mg/dL, omit
Mitomycin C	CrCl 30-60 mL/min, 75% of the full dose	Total bilirubin 1.5-3.0 mg/dL, 50% of the full dose
	CrCl 10-30 mL/min, 50% of the full dose	Total bilirubin >3.0 mg/dL or transaminase >3× ULN, 25% of the full dose
	CrCl <10 mL/min, omit	

Abbreviations: AST, aspartate transaminase; CrCl, creatinine clearance; TDM, therapeutic dose monitoring; ULN, upper limit of normal.
Reproduced under Creative Commons license. Source: Hendrayana T, Wilmer A, Kurth V, et al. Anticancer dose adjustment for patients with renal and hepatic dysfunction: from scientific evidence to clinical application. *Sci Pharm*. 2017;85:8. doi:10.3390/scipharm85010008

OLDER ADULT PATIENTS

Usually, there are no significant differences in pharmacokinetics for cytotoxic agents on the basis of age alone.[81,82] Although a number of age-related changes in drug ADME can contribute to differences in treatment tolerance between older and younger patients, these changes are influenced by many other factors, and age alone is a poor predictor of drug tolerability. With the exception of conditioning regimens used for stem cell transplantations, no empirical dose reductions are recommended that are based solely on age. For patients with cancer who are older than 65 years, the 2018 ASCO Guideline recommends that a geriatric assessment be performed. Using a geriatric assessment tool to evaluate patients besides their chronological age may provide a complementary evaluation of an adult's fitness for cancer therapy.[83]

An important potential issue in older adult patients is renal clearance. Over a life span, renal mass decreases by approximately 25% to 30%, and renal blood flow decreases by 1% per year after the age of 50 years.[84] The decline in glomerular filtration rate with age is estimated at 0.75 mL/min per year after age 40 years; however, approximately one-third of patients have no change in CrCl, with age. Because of the physiologic decline in renal function with age, chemotherapy agents primarily excreted renally must be dosed with caution in older patients, although routine dose reductions are not recommended.

Recently, tools that predict chemotherapy toxicity have been developed to determine severe chemotherapy toxicity in older adults. Extermann et al.[85] developed the Chemotherapy Risk Assessment Scale for High-Age Patients to predict grade 3 or greater nonhematologic toxicity and grade 4 or greater hematologic toxicity. Therefore, incorporating geriatric assessment domains would allow clinicians to better identify at-risk older adult patients who are vulnerable to morbidity and/or mortality from cancer therapies.

OBESITY

The ratio of adipose tissue to lean body mass is altered in obesity and can affect the volume of distribution of lipid-soluble medications. Lipid-soluble medications can accumulate in adipose tissue, which serves essentially as a depot, thus prolonging the duration of drug effect and increasing the total amount of drug in the body.

The weight used for dosing is another important concern. Typically, chemotherapy dosing is based on body surface area (BSA), which is commonly calculated with the Mosteller or Dubois method and is based on actual height and weight. Because of toxicity concerns, clinicians sometimes use either ideal body weight or adjusted ideal body weight, or cap the BSA at 2.0 m^2 rather than use the actual body weight to calculate BSA. Observational studies have shown that no more than 40% of obese patients are dosed lower than their actual body weight.[86-88] Treating patients with less than full weight-based dosing of chemotherapy is thought to contribute to the higher mortality rate observed in obese patients. ASCO convened an expert panel to evaluate the literature about obesity and dosing. The panel concluded that there was no evidence that actual weight dosing in obese patients resulted in more adverse effects, and the panel recommended that full weight-based chemotherapy doses be used, although high-dose conditioning regimens are exceptions.[89]

KEY POINTS

- Empirical dose reductions are recommended for some drugs in patients with underlying hepatic and/or renal dysfunction.
- With the exception of conditioning regimens used for stem cell transplants, no empirical dose reductions are recommended that are based solely on age.
- Selecting the appropriate initial dose for a patient can be based upon patients' comorbidity, age, and fragility, concurrent medications known to inhibit or induce drug metabolism, and/or known genetic polymorphism. Recommended starting dose can be varied depending on the countries where the drug or treatment is authorized and their regulatory policies.
- Dose modification during treatment is common and determined based on the patient's tolerability.
- Actual body weight and actual BSA should be used for dosing obese patients with drugs that use weight-based dosing.[90-93]

DOSE SELECTION

INITIAL DOSE SELECTION FOR A GIVEN PATIENT

Selecting the initial dose for a patient is part of the art and science of being an oncologist. While the frequency of incorrect dose modifications as part of standard of care is low, the percentage of oncologists who modify dose in a manner different from guidelines is substantial (ref). Publications have described that the decision process, particularly for patients with metastatic disease, involves the considerations of the patient's age, ability to tolerate the therapy-related side effects, trade-offs between safety and efficacy, and discussion with the patient. In addition to these clinician-based assessments, it is important to have the knowledge of the approved dose supported by the dosing instructions from the original study (peer-reviewed publication) that determined safety and efficacy in that patient population, as well as publication based on the larger clinical database from the pivotal study that has been reviewed by the FDA, EMEA, and other agencies in granting approval for clinical use when making the decision on the initial dose and dose modification. For example, the published clinical evidence that demonstrated superior efficacy of a PDL-1 inhibitor to etoposide and platinum and gained approval for clinical use included a Kaplan-Meier curve for survival and a safety table, all totaled with 16 rows of safety results. The publication does not include advice on dose modification. To gain agency approval, the entire clinical database is submitted for agency review, and agency investigators inspect the records at sites that contributed to the safety and efficacy results for primary source verification. From this evaluation, the advice on starting dose and specific toxicity-based dose modifications is generated and published. That publication included several pages of important safety information as well as toxicity-based dose modification schemas. When selecting an initial dose for an individual patient, this information should also be reviewed and considered.

TOXICITY-BASED DOSE MODIFICATION

For subsequent cycles, the patient's tolerability of the previous cycle is reviewed, and the decision is made to select the dose for the next cycle. Clinical experience in the evaluation of the patient's history of the previous cycle's signs and symptoms, review of laboratory results, and physical exam is integrated into this decision. Awareness and review of the agencies' dose modification schema (or the schema used in the pivotal trial's protocol) are important considerations in selecting the initial dose and subsequent modifications. The schema can include a defined toxicity (on its own) that requires no dose modification, a toxicity that advises dose modification, a toxicity that advises dose discontinuation, as well as treatment for the defined toxicity.

Tables 3-11 and 3-12 are hypothetical examples of a dose modification schema that would advise dose modification based on tolerability reported in the previous cycle. Such tables are specific to the agent used and the patient setting in which the therapy is administered. The tables direct the investigator to make modifications when such a graded event occurs. For oncology agents used in clinical practice as standard of care, the guidance issued by the respective countries' regulatory agencies are excellent sources of this information.

Table 3-11 Example of Dose Modification Schema for Hematologic Toxicity

Event ANC	Postponement of Cycle	Dose Reduction
ANC >1.5 × 10^9/L	No cycle postponement.	No dose reduction
ANC 1.0-1.5 × 10^9/L	Postpone treatment until ANC is >ANC 1.5 × 10^9/L. Resume cycle with GCSF.	No dose reduction
ANC 0.5-1 × 10^9/L	Postpone treatment until ANC is >ANC 1.5 × 10^9/L. Resume cycle with GCSF.	Reduce dose by 15%
ANC <0.5 × 10^9/L	Postpone treatment until ANC is ANC 1.0-1.5 × 10^9/L. Resume cycle with GCSF. If no recovery to ANC >1.5 × 10^9/L by day 29, stop treatment.	Reduce dose by 25%

Abbreviations: ANC, absolute neutrophil count; GCSF, granulocyte-colony stimulating factor.
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Table 3-12 Example of Dose Modification Schema for Hepatic Toxicity

Event	Dose Modification Algorithm
ALT <3.0× URL	Continue study treatment at the current dose
ALT 3-5× URL without bilirubin elevation	Interrupt study treatment, monitor subject closely, perform liver panel at least weekly until ALT returns to grade 1. If there is no recovery in 6 weeks, permanently discontinue therapy. If ALT recovers to <3× ULN within 6 weeks, readminister at reduced dose and monitor ALT weekly
ALT >5× URL without bilirubin elevation	If no recovery to grade 1 in 2 weeks, permanently discontinue. If recovery in 2 weeks, readminister at a reduced dose and monitor ALT weekly. If ALT elevations recur >3× ULN, permanently discontinue therapy
ALT >3× URL and bilirubin elevation	Permanently discontinue therapy. Initiate a potential Hy's law evaluation for drug-induced liver injury immediately. Consider a hepatology consultation

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal; URL, upper reference limit.
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PROJECT OPTIMUS AND THE ONCOLOGY DOSING TOOLKIT

Historically, drug development for cytotoxic agents focused almost exclusively on identifying the maximum tolerated dose (MTD), often with less emphasis on determining the optimal dose for a given population. While this approach established clinical benefits, it frequently failed to identify regimens that provided the highest clinical activity with the lowest toxicity.

To address this, the FDA launched Project Optimus, a multidisciplinary effort to reform dose-finding paradigms in oncology. As a central part of this initiative, the FDA developed the Oncology Dosing Toolkit to provide developers with a practical framework for implementing these new optimization standards.[94]

TOOLKIT'S ROLE IN DOSE SELECTION

The Oncology Dosing Toolkit is designed to support decision-making throughout the development lifecycle. It provides the methodology to address three critical overarching questions central to the Project Optimus mission:

1. **Dose Escalation:** Which dosages will be evaluated during the initial dose-escalation phase?
2. **Dose Investigation:** Which dosages will be chosen for further investigation (eg, in a randomized dosage evaluation)?
3. **Registration:** What dosages will be selected for the final registration trial(s)?

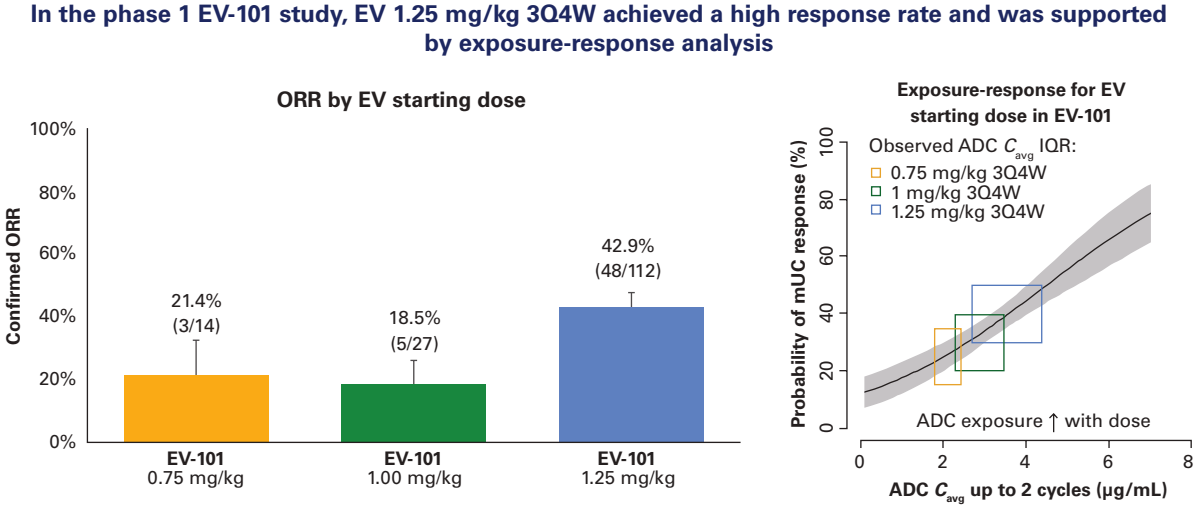
By utilizing the toolkit early, investigators gain access to FDA guidance on key design issues, including translational evidence, pharmacokinetic characteristics, safety/efficacy data, and modeling and simulation approaches.

CASE STUDY: ENFORTUMAB VEDOTIN (EV-101)

A practical application of these optimization principles was presented at the 2024 ASCO Annual Meeting regarding enfortumab vedotin (EV). The evidence supporting the current clinical dose was determined across multiple cohorts, ensuring a sufficient patient population to confirm a favorable benefit-risk profile, a hallmark of the Project Optimus approach.

Figure 3-4 illustrates the dose-response relationship, showing a rise in overall response rate correlated with increasing dose. The insert curve shows a predictable increase in systemic exposure, providing assurance that dose modifications will result in expected changes in adverse events. Figure 3-5 further confirms this via the dose-toxicity relationship.

Figure 3-4 EV-101 Clinical Dose Selection by Dose Response and Exposure Response



Abbreviations: 2L+, second and later lines; 3Q4W, days 1, 8, and 15 of a 28-day cycle; ADC, antibody-drug conjugate; C_{avg}, time-averaged exposure up to two cycles; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; ORR, objective response rate.
Error bar = one standard deviation. Analysis populations for both dose-response and exposure-response were based on actual treatment arms.
Adapted from Petrylak DP, Chia YL, Yu EY, et al. Impact of exposure on outcomes with enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer. Presented at: Annual Meeting of the American Society of Clinical Oncology; May 29, 2024; Chicago, IL.
https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.4503
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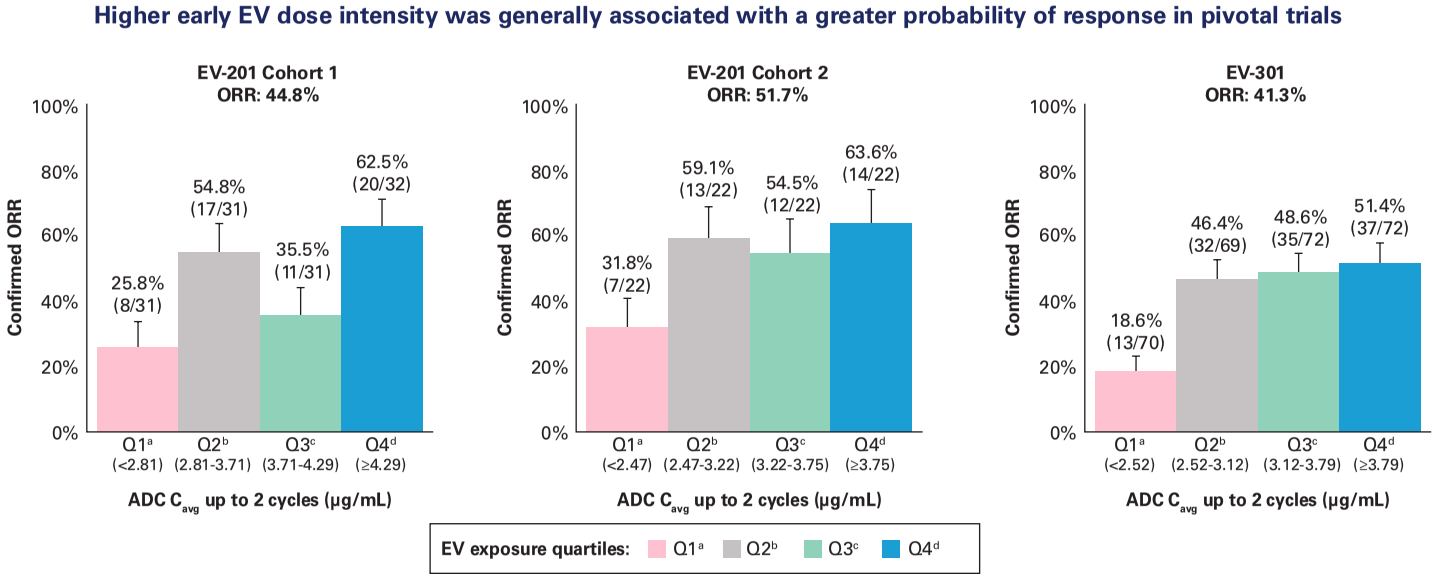
According to FDA reviewers, the proposed regimen of 1.25 mg/kg (up to 125 mg) was selected based on a superior benefit/risk ratio observed in study EV-101. While the 1.25 mg/kg dose was associated with greater tumor response, it also required more frequent dose reductions (32%) compared to lower dose levels (0% at 0.75 mg/kg; 10% at 1 mg/kg). Weight-based dosing for EV was ultimately supported by population pharmacokinetic modeling and simulation analyses, consistent with the toolkit's emphasis on exposure-response data.

EVOLUTIONARY SHIFT IN METHODOLOGY

The landscape of dose optimization has evolved significantly since the launch of Project Optimus in 2021. Industry practice has shifted from the traditional "3+3" design toward Bayesian methods. Data from one high-volume phase I center of excellence indicate that the use of Bayesian methods increased from 48% in 2021 to 75% in 2024. This evolution toward improved precision in MTD determination and dose-level toxicity is expected to deliver clinical regimens with enhanced therapeutic benefit and manageable toxicity profiles.

Figure 3-5 EV-101 Clinical Dose Selection Confirmation and Exposure Response



Abbreviations: ADC, antibody-drug conjugate; C_{avg}, time-averaged exposure up to two cycles; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; ORR, objective response rate; Q, quartile.

All data presented are from a post hoc, explanatory analysis. Error bar = one standard deviation.

Average ADC exposures were divided into four quartiles: [a]Q1 represents the EV exposures between 0% and 25%; [b]Q2: 25% to 50%; [c]Q3: 50% to 75%; [d]Q4: 75% to 100% (the highest EV exposure quartile).

Adapted from Petrylak DP, Chia YL, Yu EY, et al. Impact of exposure on outcomes with enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer. Presented at: Annual Meeting of the American Society of Clinical Oncology; May 29, 2024; Chicago, IL. doi:10.1200/jco.2024.42.16_suppl.4503

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DRUG DEVELOPMENT: NOVEL CLINICAL TRIAL DESIGN AND SPECIAL POPULATIONS

Clinical trials are critical to the development of new anticancer therapies, and an understanding of novel clinical trial designs for targeted therapies is critical.

NOVEL TRIAL DESIGNS

With molecular characterization of cancers becoming routine in clinical practice, treating tumors according to molecular characteristics rather than histologic classification is becoming more widespread, requiring new study designs. Common designs include umbrella and basket trials. In umbrella trials, multiple mutations in a single tumor type are targeted by different drugs. An example is a current National Cancer Institute (NCI) Clinical Trials Network study in second-line squamous cell cancer of the lung in which mutations in *MET, PI3K, CDK4/6*, and others are targeted by different agents.[47,94] Basket trials use targeting of a specific molecular aberration, regardless of the tissue of origin. An example of a basket trial is the National Cancer Institute Molecular Analysis for Therapy Choice trial (NCI-MATCH), which has now led to the newer trial, ComboMATCH. Novel trial designs and criteria for assessment of tumor response are being used to evaluate immunotherapies and agents targeting the tumor microenvironment. A form of basket trial is the use of expansion cohorts, each recruiting a defined tumor type, after the completion of the rising-dose phase I stage of a first-time-in-human study.

KEY POINTS

- With the emergence of molecularly targeted agents, novel study designs such as umbrella and basket trials have been introduced.
- Dose optimization strategies during drug development are essential to ensure maximum efficacy while minimizing toxicity.[95]

HIGH-YIELD TAKEAWAYS

- Coadministered supportive care drugs, like antifungal azoles and some HIV and antiseizure medicines, can inhibit or induce CYP3A4, thereby altering the clearance and effect of existing anticancer therapy.
- Patients with DPD deficiency receiving 5-FU can experience enhanced myelosuppression, which can be fatal. Patients with the *UGT1A1*28* homozygous genotype receiving irinotecan can experience enhanced myelosuppression and diarrhea.
- EFGR-directed therapy, particularly TKIs, can cause interstitial lung disease (shortness of breath and dry cough) and usually requires permanent discontinuation of therapy.

Acknowledgments

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CLINICAL PHARMACOLOGY 3

CHAPTER SUMMARY GUIDE

KEY POINTS

- Hormonal therapies are most commonly used to treat breast cancer and prostate cancer. They work by altering the production of hormones, blocking the activity of particular HRs in the body, or substituting chemically similar agents for the active hormones.
- Cytotoxic chemotherapy remains an important component of many cancer therapy regimens in the neoadjuvant, adjuvant, and metastatic settings for solid tumors and for hematologic malignancies.
- Small-molecule targeted receptor inhibitors offer distinct advantages as therapeutics. Most can be administered orally.
- Monoclonal antibodies are therapeutic agents bioengineered to target specific extracellular receptors or cell surface antigens that are either unique to or overexpressed by tumor cells.
- ADCs are anticancer agents that consist of an antibody, a cytotoxic payload, and a linker that work to enhance the therapeutic effect while minimizing toxicity to normal cells.
- Immune checkpoint inhibitor immunotherapy results in durable clinical benefit in some patients and is associated with a unique spectrum of adverse effects known as immune-related adverse effects, which include dermatologic, GI, hepatic, endocrine, and other less common inflammatory effects.
- CRS and ICANS are common with cellular therapy and can be managed by interleukin-6 (IL-6) inhibitors and corticosteroids. Patients are usually hospitalized for proper monitoring and management of these adverse effects.
- C_{max}, which occurs at T_{max}, can predict acute toxicity, such as ECG changes, infusion reactions, and acute blood pressure elevations.
- The AUC best reflects systemic exposure and can predict response for some antineoplastics.
- Pharmacokinetic assessments are important in determining drug-drug interactions and making recommendations on the dose and schedule of anticancer agents.
- Half-life guides the frequency of administration and determines washout periods in clinical trials. Dosing in clinical trials often considers the half-life of targeted therapies. For example, patients are often not eligible for initiating dosing of a study agent in a clinical trial until five half-lives of the targeted therapy have elapsed.
- Drug interactions with oral cancer therapies, particularly TKIs, are common and may be clinically important.
- Drug interactions affecting gastric absorption are usually related to food or pH effects. These can be managed by avoiding concurrent administration of pH-lowering agents.
- Food effects can be managed by counseling patients on when to take their medication (ie, with or without food). Some drugs may require administration with a low-fat meal.
- Drug interactions related to metabolism or elimination can be managed by avoiding concurrent administration, if possible, or by adjusting doses.
- Grapefruit, grapefruit juice, Seville oranges, and star fruit are CYP3A4 inhibitors. Patients should be instructed to avoid consuming these products while taking cancer therapies that are metabolized via CYP3A4.
- Patients with TPMT or NUDT15 deficiency are at increased risk for severe toxicity at conventional mercaptopurine doses and generally require dose reductions.
- DPD is an enzyme encoded by the DPYD gene and promotes the first step of the fluorouracil degradation pathway. This pathway helps convert majority of drug to its inactive metabolites. Patients with partially or complete DPD deficiency cannot adequately degrade fluoropyrimidines, are at increased risk of severe, potentially fatal toxicity. Test for DPD deficiency before starting 5-FU or capecitabine therapy should be performed. Avoid use in patients with complete DPD deficiency and reduce dose in those with partial DPD deficiency.[50]
- One avenue to combat toxicities and prevent permanent sequelae is to administer antidotes if a chemotherapy overdose occurs.
- Uridine triacetate is indicated for emergency treatment of 5-FU or capecitabine overdose.
- Glucarpidase is a rescue agent approved by the FDA for use in patients with delayed methotrexate excretion.
- Methylene blue is an option for use in patients with ifosfamide-induced encephalopathy. It should be used with caution in patients with glucose-6-phosphate deficiency.
- Empirical dose reductions are recommended for some drugs in patients with underlying hepatic and/or renal dysfunction.

- With the exception of conditioning regimens used for stem cell transplants, no empirical dose reductions are recommended that are based solely on age.
- Selecting the appropriate initial dose for a patient can be based upon patients' comorbidity, age, and fragility, concurrent medications known to inhibit or induce drug metabolism, and/or known genetic polymorphism. Recommended starting dose can be varied depending on the countries where the drug or treatment is authorized and their regulatory policies.
- Dose modification during treatment is common and determined based on the patient's tolerability.
- Actual body weight and actual BSA should be used for dosing obese patients with drugs that use weight-based dosing.[90-93]
- With the emergence of molecularly targeted agents, novel study designs such as umbrella and basket trials have been introduced.
- Dose optimization strategies during drug development are essential to ensure maximum efficacy while minimizing toxicity.[95]

Table 3-1 **Targeted Therapies With Biomarker Selection: EGFR and MET Inhibitors**

	Sensitive Mutation/ Required Biomarkers	Food Effect	pH Dependent (Yes/No)	Drug Interactions	Use	Notes
EGFR inhibitors						
Erlotinib	Exon 19 deletions, exon 21 L858R	Empty stomach	Yes	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors and grapefruit	Advanced NSCLC; first line or subsequent lines; *EGFR* mutant	Approved before the discovery of EGFR biomarker; has a maintenance indication in unselected patients
Gefitinib	Exon 19 deletions, exon 21 L858R	With or without food	Yes	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors and grapefruit	Advanced NSCLC; first line or subsequent lines; *EGFR* mutant	Initially approved on phase 2 data in unselected populations; failed in phase 3 trial and was taken off the market
Afatinib	Exon 19 deletions, exon 21 L858R, S7681, L861Q, and G719X	Empty stomach	No	Not metabolized by CYP	Advanced NSCLC; first line or subsequent lines; *EGFR* mutant	Retains activity in erlotinib- or gefitinib-resistant patients; has a maintenance indication in unselected patients
Dacomitinib	Exon 19 deletions, exon 21 L858R	With or without food	Yes	Strong CYP2D6 inhibitor; inhibits the metabolism of drugs that are metabolized by CYP2D6	Advanced NSCLC; first line or subsequent lines; *EGFR* mutant	More effective than gefitinib, but also has more adverse effects
Osimertinib	Exon 19 deletions, exon 21 L858R, T790M	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors and has the potential for QT prolongation	Adjuvant treatment of early-stage, locally advanced, and metastatic *EGFR*-mutated NSCLC	Improved PFS in first-line setting compared with gefitinib or erlotinib; preferred if CNS penetration is needed
Lazertinib	Exon 19 deletions, exon 21 L858R substitution	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors.	First-line treatment of locally advanced or metastatic NSCLC with exon 19 deletion or exon 21 L858R substitution	Use in combination with amivantamab. Prophylactic anticoagulation should be given for the first 4 months of treatment
Sunvozertinib	Exon 20 insertion	With food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Locally advanced or metastatic NSCLC with EGFR exon 20 insertion	Take with food to reduce GI toxicities
MET inhibitors						
Capmatinib	MET exon 14 skipping	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Metastatic NSCLC with MET exon 14–skipping mutation	
Tepotinib	MET exon 14 skipping	With food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Metastatic NSCLC with MET exon 14–skipping mutation	A clinical trial used a liquid biopsy for assignment

Abbreviations: CNS, central nervous system; CYP, cytochrome P450; EGFR, epidermal growth factor receptor; GI, gastrointestinal; NSCLC, non–small cell lung cancer; PFS, progression-free survival.

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Table 3-2 **Targeted Therapies With Biomarker Selection: ALK, ROS, and BRAF Inhibitors**

	Sensitive Mutation/ Required Biomarkers	Food Effect	pH Dependent (Yes/No)	Drug Interactions	Use	Notes
ALK and/or ROS1 inhibitors						
Crizotinib	*ALK* translocation	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors and has the potential for QT prolongation	Advanced NSCLC; first line or subsequent lines; *ALK* or *ROS1* positive; unresectable, recurrent, or refractory inflammatory anaplastic lymphoma, *ALK* positive	More effective than chemotherapy, but less effective than alectinib; only ALK inhibitor with ROS1 indication
Ceritinib	*ALK* translocation	With food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors and grapefruit	Advanced NSCLC; first line or subsequent lines; *ALK* positive	More effective than chemotherapy
Alectinib	*ALK* translocation	With food	No	Not metabolized by CYP	Advanced NSCLC; first line or subsequent lines; *ALK* positive	Improved PFS over crizotinib; preferred if CNS penetration is needed
Brigatinib	*ALK* translocation	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Advanced NSCLC; after failure of crizotinib; *ALK* positive	Improved PFS over crizotinib; blood pressure should be controlled before initiation
Lorlatinib	*ALK* translocation	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Advanced NSCLC; after crizotinib and one other drug; *ALK* positive	See reference[23]
Ensartinib[24]	*ALK* translocation	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors; Avoid P-gp inhibitor	Advanced NSCLC; ALK inhibitor naive; *ALK positive*	Monitor uric acid while on treatment
Repotrectinib	ROS1 rearrangement	With or without food	No	CYP3A4 inducer; interacts with CYP3A4 inducers and inhibitors	Advanced NSCLC; first line or subsequent lines; *ROS1* fusion positive	Inhibits both wild-type and G2032R-mutant *ROS1* fusions; may be better for patients with brain metastases[25]
Taletrectinib[4]	ROS1 rearrangement	Empty stomach	Yes	CYP3A4 inducer; interacts with CYP3A4 inducers and inhibitors	Advanced NSCLC; first line or subsequent lines; *ROS1* positive	Monitor uric acid and skeletal fractures while on treatment

	Sensitive Mutation/ Required Biomarkers	Food Effect	pH Dependent (Yes/No)	Drug Interactions	Use	Notes
BRAF inhibitors						
Dabrafenib	V600E, V600K	Empty stomach	No	CYP3A4 and CYP2CB substrate; interacts with CYP3A4 and CYP2C8 inducers and inhibitors	First line; adjuvant melanoma, metastatic melanoma, metastatic NSCLC, metastatic anaplastic thyroid, *BRAF* mutant; unresectable or metastatic solid tumors with *BRAF* V600E mutation	Improved PFS and OS over dacarbazine as a single agent; used in combination with the MEK inhibitor to prevent resistance
Vemurafenib	V600E, V600K	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	First-line, metastatic melanoma, Erdheim-Chester disease, *BRAF* mutant; refractory NSCLC with *BRAF* V600 mutation	Improved PFS over dacarbazine as the single agent; used in combination with the MEK inhibitor to prevent resistance
Encorafenib	V600E, V600K	With or without food	No	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	First-line, metastatic melanoma, *BRAF* mutant; first-line, metastatic colon cancer, *BRAF* mutant	Only BRAF inhibitor indicated for colon cancer in combination with cetuximab; correct hypokalemia or hypomagnesemia before treatment initiation
Tovorafenib	*BRAF* fusion or rearrangement, V600E mutation	Empty stomach	Yes	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Relapsed or refractory low-grade glioma	Monitor uric acid, CPK level, and skeletal fractures while on treatment

Abbreviations: CYP, cytochrome P450; H2, H2 histamine antagonists (eg, famotidine); NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; PPI, proton pump inhibitors (eg, omeprazole).

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Table 3-3 **Targeted Therapies With Biomarker Selection: NTRK and PARP Inhibitors**

	Sensitive Mutation/ Required Biomarkers	Drug Interactions	Use	Notes
NTRK inhibitors				
Entrectinib	*NTRK, ROS1* fusions	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Metastatic NSCLC; *ROS1* rearrangement; solid tumor with known *NTRK* fusion	
Larotrectinib	*NTRK* fusion	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Solid tumor with known *NTRK* fusion	First small-molecule disease–agnostic approval
Repotrectinib	NTRK fusion	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Locally advanced or metastatic NSCLC with ROS1 positive; Solid tumors with *NTRK* gene fusion positive	
PARP inhibitors				
Olaparib	BRCA1/BRCA2	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Metastatic breast cancer, HER2 negative, germline *BRCA* mutated; ovarian cancer maintenance, *BRCA* mutant; metastatic prostate cancer with homologous recombination repair gene-mutated; pancreatic cancer with germline *BRCA* mutated; first-line maintenance	Because of the difference in dosing and bioavailability, do not substitute capsules for tablets
Rucaparib	BRCA1/BRCA2	Moderate CYP1A2 inhibitor; inhibits the metabolism of drugs that are metabolized by CYP1A2	*BRCA*-mutant recurrent ovarian cancer maintenance; metastatic prostate cancer castration resistant, *BRCA* mutated; locally advanced or metastatic pancreatic cancer, germline *BRCA2*-mutated maintenance therapy	Associated with a moderate or high emetic potential, antiemetics are recommended to prevent nausea and vomiting
Niraparib	Testing not required	Not metabolized by CYP	Recurrent ovarian cancer, maintenance therapy	Associated with a moderate or high emetic potential, antiemetics are recommended to prevent nausea and vomiting
Talazoparib	BRCA1/BRCA2	Not metabolized by CYP	Locally advanced or metastatic breast cancer, *BRCA* mutant	

Abbreviations: CYP, cytochrome P450; NSCLC, non–small cell lung cancer; PARP, poly ADP ribose polymerase.
All are not pH dependent. All can be provided with or without food.
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Table 3-4 **Targeted Therapies With Biomarker Selection: FLT3 and IDH Inhibitors**

	Sensitive Mutation/ Required Biomarkers	Drug Interactions	Use	Notes
FLT3 inhibitors				
Midostaurin	ITD, point mutations	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Newly diagnosed AML, *FLT3* mutation positive; in combination with chemotherapy during induction and consolidation therapy	First-in-class FLT3 inhibitor
Gilteritinib	ITD, point mutations	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Relapsed or refractory AML, *FLT3* mutant	
Quizartinib	ITD, point mutations	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Newly diagnosed AML, *FLT3* mutation positive; in combination with chemotherapy during induction and consolidation therapy	Second-generation FLT3 inhibitor
IDH1/IDH2 inhibitors				
Enasidenib	IDH2	No known drug interactions	Relapsed or refractory AML, *IDH2* mutant	First-in-class IDH2 inhibitor
Ivosidenib	IDH1	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Relapsed or refractory AML, *IDH1* mutant; newly diagnosed acute myeloid leukemia with *IDH1* mutation in combination with azacytidine; locally advanced or metastatic *IDH1*-mutated cholangiocarcinoma	First-in-class IDH1 inhibitor
Vorasidenib	IDH1 or IDH2	Interact with CYP2C8 inhibitors and inducers; sensitive CYP3A4 substrates	Astrocytoma or oligodendroglioma with a susceptible *IDH1* or *IDH2* mutation	May promote tumor growth in patients with NF1 tumors

Abbreviations: AML, acute myeloid leukemia; AUC, area under the curve; ITD, internal tandem duplication.
All are not pH dependent. Except for midostaurin, all can be provided with or without food; with ivosidenib, avoid high-fat meals (increases AUC by 25%).
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Table 3-5 **Targeted Therapies With Biomarker Selection: Various Inhibitors**

	Sensitive Mutation/ Required Biomarkers	Food Effect	Drug Interactions	Use	Notes
FGFR inhibitors					
Erdafitinib	*FGFR2, FGFR3* mutations and fusions	With or without food	CYP3A4 and CYP2C9 substrates; interacts with inducers and inhibitors of both enzymes	Locally advanced or metastatic urothelial carcinoma with *FGFR3* or *FGFR2* alterations	First-in-class FGFR inhibitor; better activity in *FGFR3* point mutations over *FGFR3* and *FGFR2* fusions
Futibatinib	*FGFR2* fusion or rearrangement	With or without food	CYP3A4, CYP2D6, and CYP2C9 substrates; interacts with inducers and inhibitors of both enzymes	Locally advanced or metastatic cholangiocarcinoma with *FGFR2* fusion or rearrangement	
Pemigatinib	*FGFR2* fusion	With or without food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Previously treated, locally advanced, or metastatic cholangiocarcinoma with *FGFR2* fusion; relapsed or refractory myeloid/ lymphoid neoplasms with *FGFR1* rearrangement	
RET inhibitors					
Selpercatinib	*RET* fusions or mutations	With or without food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	*RET* mutant and *RET* fusion–positive medullary thyroid cancer; locally advanced or metastatic *RET*-positive NSCLC; locally advanced or metastatic *RET* fusion–positive solid tumors	First-in-class RET inhibitor; optimize blood pressure before treatment initiation
Pralsetinib	*RET* fusions	Empty stomach	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	*RET* mutant and *RET* fusion–positive medullary thyroid cancer; metastatic NSCLC with *RET* fusion	Do not administer for at least 2 weeks after major surgery and until after adequate wound healing has occurred
PI3K inhibitors					
Alpelisib	*PIK3CA* mutations	With food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors; CYP2C9 inducer; avoid sensitive substrates such as warfarin	Postmenopausal women and men with HR-positive, HER2-negative, *PIK3CA* mutated with advanced or metastatic breast cancer	Approved in combination with fulvestrant; first-in-class PIK3CA inhibitor; optimize blood glucose before treatment initiation

	Sensitive Mutation/ Required Biomarkers	Food Effect	Drug Interactions	Use	Notes
Inavolisib	*PIK3CA* mutations	With or without food	BCRP/ABCG2 and P-gp/ABCB1 substrate	Endocrine-resistant, *PIK3CA*-mutated, HR-positive, HER2-negative locally advanced or metastatic breast cancer	Reduce the dose for moderate renal impairment
AKT inhibitors					
Capivasertib	*PIK3CA, AKT1*, and *PTEN* alterations	With or without food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	HR-positive, HER2-negative, locally advanced, or metastatic breast cancer with genetic alterations in one or more of these genes: *PIK3CA, AKT1*, and *PTEN*	Improved PFS with benefits observed in the overall population and among patients with AKT pathway-altered tumors
PDGFRA inhibitors					
Avapritinib	*PDGFRA* exon 18 mutation	Empty stomach	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Unresectable or metastatic GIST with *PDGFRA* exon 18 mutation	First-in-class PDGFRA inhibitor; associated with a moderate or high emetic potential risk; antiemetics may be recommended to prevent nausea and vomiting
EZH2 inhibitors					
Tazemetostat	*EZH2* gain-of-function mutations, *SMARCA* loss-of-function mutations	With or without food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Adults and children age 16 or older with metastatic or locally advanced epithelioid sarcoma, relapsed or refractory follicular lymphoma salvage therapy, or those with *EZH2* mutation	First-in-class EZH2 inhibitor
MEK inhibitors					
Trametinib	*BRAF* V600E, V600K	Empty stomach	None	First-line, adjuvant melanoma, metastatic melanoma, metastatic NSCLC, metastatic anaplastic thyroid cancer, *BRAF* mutant; low-grade recurrent serous ovarian cancer; solid tumors, unresectable or metastatic with *BRAF* V600E mutation	Only approved in combination with dabrafenib

	Sensitive Mutation/ Required Biomarkers	Food Effect	Drug Interactions	Use	Notes
Cobimetinib	*BRAF* V600E, V600K	With or without food	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	First-line, metastatic melanoma, *BRAF* mutant; treatment of histiocytic neoplasms	Only approved in combination with vemurafenib; causes severe photosensitivity
Binimetinib	*BRAF* V600E, V600K	With or without food	None	First-line, metastatic melanoma, *BRAF* mutant	Only approved in combination with encorafenib; LVEF >50% required
Selumetinib	MEK1, MEK2	Empty stomach	CYP3A4 substrate; interacts with CYP3A4 inducers and inhibitors	Children aged 2 years or older with NF1 and plexiform neurofibromas	
Mirdametinib	MEK1, MEK2	With or without food	None	Children aged 2 years or older with NF1 and plexiform neuroblastomas	
RAS inhibitors					
Sotorasib	*KRAS* G12C		Caution with CYP3A4 inducers and inhibitors, PgP substrates and acid-reducing agents	*KRAS* G12C mutated locally advanced or metastatic NSCLC	>20% diarrhea, hepatotoxicity, cough, and musculoskeletal pain
Adagrasib	*KRAS* G12C	With or without food	Caution with CYO3a4 inducers, inhibitors, substrates, CYP2c9, cyp 2d6, P-gp substrates, drugs that prolong QTc	*KRAS* G12C mutated locally advanced NSCLC and CRC	Diarrhea, QTc prolongation, hepatotoxicity, and ILD/pneumonitis

Abbreviations: CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; HR, hormone receptor; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; NF1, neurofibromatosis type 1; NSCLC, non–small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; P-gp, P-glycoprotein.
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Table 3-6 **Basic Pharmacokinetics Definitions**

Parameter Abbreviation	Definition	Equation	Use/Association
C_{max}	Maximal drug concentration	Visual extrapolation	Can be associated with acute adverse effects
T_{max}	Time at which the maximum drug concentration is achieved	Visual extrapolation	Time that acute adverse effects occur
$t_{1/2}$	Time required for the plasma concentration to decrease by half, or half-life	$T_{1/2}$ 0.698 × Vd/clearance	Determines how long a drug is measurable in the plasma in the body
AUC	Area under the curve	Dose/clearance	Measure of systemic drug exposure
Vd	Volume of distribution	Dose/concentration at time 0 (extrapolated)	Where the drug goes in the body
Cl	Clearance	Dose/AUC	How fast the drug is eliminated

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Table 3-7 **Drugs Commonly Used in Oncology That Have Pharmacogenetic Implications**

Drug	Gene	Variant Genotype	Consequence of Variant Genotype	Recommendation	Strength of Recommendation*
Capecitabine/ fluorouracil	DPYD	IM	Increased toxicity	IM: Reduce starting dose	Strong
		PM		PM: Avoid if possible, or reduce dose by 75%	
Irinotecan, liposomal irinotecan	UGT1A1	PM	Increased toxicity	Select alternative therapy if possible	Moderate
Mercaptopurine	TPMT, NUDT15	IM	Increased toxicity	IM: Reduce dose by 50%	Strong
		PM		PM: Reduce dose 10-fold	
Tamoxifen	CYP2D6	PM	Decreased efficacy	Select an alternative agent not metabolized by CYP2D6 (eg, aromatase inhibitor if postmenopausal)	Weak

Abbreviations: IM, intermediate metabolizer; PM, poor metabolizer.
*Clinical Pharmacogenetics Implementation Consortium evidence level, except for irinotecan, for which the recommendations are the authors' opinion.
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Table 3-8 **Dosing Guidelines of Selected Anticancer Agents for Patients With Renal Dysfunction**	
Agent	**Dose Adjustment in Renal Dysfunction**
Bleomycin	CrCl 40-50 mL/min, 70% of the full dose
	CrCl 30-40 mL/min, 60% of the full dose
	CrCl 20-30 mL/min, 55% of the full dose
	CrCl 10-20 mL/min, 45% of the full dose
	CrCl 5-10 mL/min, 40% of the full dose
Capecitabine	CrCl 30-50 mL/min, 75% of the full dose
	CrCl <30 mL/min, omit
Carboplatin	Dose based on GFR, using the Calvert formula: Dose (mg) = target AUC × (GFR + 25). AUC = 5–7 Hemodialysis: Carboplatin dose (mg) = Target AUC × 25, administer on a non–dialysis day; hemodialysis should occur between 12 and 24 hours after carboplatin dose
Carmustine	CrCl 45-60 mL/min, 80% of the full dose
	CrCl 30-45 mL/min, 75% of the full dose
	CrCl <30 mL/min, 70% of the full dose
Cisplatin	CrCl 46-60 mL/min, 50% of the full dose
	CrCl 31-45 mL/min, 25% of the full dose
	CrCl <30 mL/min, omit
Cladribine	CrCl 10-50 mL/min, 75% of the full dose
	CrCl <10 mL/min, 50% of the full dose
Cyclophosphamide	CrCl 10-20 mL/min, 75% of the full dose
	CrCl <10 mL/min, 50% of the full dose
Cytarabine	High and intermediate dose (1 g/m^2 or more per dose)
	CrCl 30-59 mL/min: 50% of the full dose
	CrCl <30 mL/min: use is not recommended, consider an alternative agent
Dacarbazine	CrCl 30-60 mL/min, 75% of the full dose
	CrCl 10-30 mL/min, 50% of the full dose
	CrCl <10 mL/min, omit
Daunorubicin	Scr >3 mg/dL, 50% of the full dose
	CrCl 30-50 mL/min, 75% of the full dose
	CrCl <30 mL/min, 50% of the full dose
Etoposide	CrCl 15 to 50 mL/min, 75% of the full dose
	CrCl <15 mL/min, 50% of the full dose
Fludarabine	CrCl 30-70 mL/min, 50% of the full dose
	CrCl <30 mL/min, omit
Hydroxyurea	CrCl 45-60 mL/min, 80% of the full dose
	CrCl 30-45 mL/min, 75% of the full dose
	CrCl 10-30 mL/min, 50% of the full dose
	CrCl <10 mL/min, 20% of the full dose
Ifosfamide	CrCl 46-60 mL/min, 80% of the full dose
	CrCl 31-45 mL/min, 75% of the full dose
	CrCl 10-30 mL/min, 70% of the full dose
	CrCl <10 mL/min, omit
Lenalidomide (use for MDS/myelofibrosis osteosclerosis)	CrCl 30-60 mL/min, 5 mg once every 24 hours
	CrCl <30 mL/min (not requiring dialysis), 5 mg once every 48 hours
	CrCl <30 mL/min (requiring dialysis), 5 mg 3 × per week after each dialysis

Agent	Dose Adjustment in Renal Dysfunction
Lenalidomide (use for multiple myeloma)	CrCl 30-60 mL/min, 10 mg once every 24 hours
	CrCl <30 mL/min (not requiring dialysis), 15 mg once every 48 hours
	CrCl <30 mL/min (requiring dialysis), 5 mg once per day; dose after dialysis on dialysis days
Lomustine	CrCl 45-60 mL/min, 75% of the full dose
	CrCl 30-45 mL/min, 70% of the full dose
	CrCl <30 mL/min, omit
Melphalan	CrCl 45-60 mL/min, 85% of the full dose
	CrCl 30-45 mL/min, 75% of the full dose
	CrCl 10-30 mL/min, 70% of the full dose
	CrCl <10 mL/min, 50% of the full dose; for high dose (>1 g/m^2), consider TDM
	CrCl <10 mL/min, omit
Methotrexate	CrCl <30 mL/min, avoid use
	CrCl <10 mL/min, omit
Oxaliplatin	CrCl <30 mL/min, omit
Pemetrexed	CrCl <45 mL/min, omit
Pentostatin	CrCl 45-60 mL/min, 70% of the full dose
	CrCl 30-45 mL/min, 60% of the full dose
	CrCl <30 mL/min, consider using alternative drugs, if possible
Topotecan	CrCl 30-60 mL/min, 75% of the full dose
	CrCl 10-30 mL/min, 50% of the full dose
	CrCl <10 mL/min, omit

Abbreviations: AUC, area under the curve; CrCl, creatinine clearance; GFR, glomerular filtration rate; MDS, myelodisplastic syndromes; TDM, therapeutic dose monitoring.

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Table 3-9 **Dosing Guidelines of Selected Anticancer Agents for Patients With Hepatic Dysfunction**	
Agent	**Dose Adjustment in Hepatic Dysfunction**
Cabazitaxel	Mild impairment (total bilirubin >1-1.5× ULN or AST $ 1.5× ULN, dose at 20 mg/m^2)
	Moderate impairment (total bilirubin >1.5-3× ULN and any AST), dose at 15 mg/m^2
	Total bilirubin >3× ULN, omit
Docetaxel	Transaminase >1.5× ULN and ALP >2.5× ULN, the recommended dose is 75 mg/m^2
	Total bilirubin >ULN and/or transaminase >3.5× ULN, associated with ALP >6× ULN, should not be used unless strictly indicated
Doxorubicin (liposomal)	Total bilirubin 1.2-3.0 mg/dL or AST 60-180 units/L, 50% of the full dose
	Total bilirubin >3.0 mg/dL or AST >180 units/L, 25% of the full dose
	Total bilirubin >5.0 mg/dL, omit
Fluorouracil	Total bilirubin >5.0 mg/dL, omit
Gemcitabine	Increased AST: no need for dose adjustment; increased total bilirubin: reduce dose by 20% (ie, from 1,000 to 800 mg/m^2) and increase if tolerated
Irinotecan	Increased transaminase <3× ULN if no liver metastasis OR <5× ULN if liver metastasis are present. Total bilirubin >2 dosing should not be administered
Ixabepilone (monotherapy)	Total bilirubin <1.5× ULN and AST <10× ULN and AST:ALT ratio <10× ULN, reduce the dose to 32 mg/m^2
	Total bilirubin 1.5-3× ULN and transaminase <10× ULN, dose at 20 mg/m^2; may escalate dose up to 30 mg/m^2 maximum in subsequent cycles if tolerated
Ixabepilone (in combination with capecitabine)	Total bilirubin >ULN or transaminase >2.5× ULN, omit
Mitoxantrone	Total bilirubin 1.5-3.0 mg/dL, 50% of the full dose
	Total bilirubin >3.0 mg/dL, 25% of the full dose
Paclitaxel (3-hour infusion and first course of therapy)	Transaminase <10× ULN and total bilirubin 1.26-2× ULN, recommended dose = 135 mg/m^2
	Transaminase <10× ULN and total bilirubin 2.01-5× ULN, recommended dose = 90 mg/m^2
	Transaminase 10× ULN or total bilirubin >5× ULN dosing is not recommended
Paclitaxel (24-hour infusion and first course of therapy)	Transaminase 2-10× ULN and total bilirubin <1.5 mg/dL, dose 5× at 100 mg/m^2
	Transaminase <10× ULN and total bilirubin 1.6-7.5 mg/dL, dose 5× at 50 mg/m^2
	Transaminase 10× ULN or total bilirubin >7.5 mg/dL, omit
Sorafenib	Total bilirubin 1.5× ULN: 400 mg twice per day
	Total bilirubin 1.5-3× ULN: 200 mg twice per day
	Total bilirubin >3× ULN: omit
Vinblastine	Total bilirubin 1.5-3.0 mg/dL or AST 60-180 units/L, 50% of the full dose
	Total bilirubin >3.1 mg/dL or AST >180 IU/L, omit
Vincristine	Total bilirubin 1.5-3.0 mg/dL or AST 60-180 units/L, 50% of the full dose
	Total bilirubin >3.1 mg/dL or AST >180 units/L, omit
Vinorelbine	Total bilirubin 2.1-3× ULN: 50% of dose
	Total bilirubin >3× ULN: 25% of dose

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.
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Table 3-10 **Dosing Guidelines for Selected Anticancer Agents for Patients With Renal and Hepatic Dysfunction**

Agent	Dose Adjustment	
	In Renal Function	**In Hepatic Dysfunction**
Bendamustine	Renal impairment: CrCl <40 mL/min, omit	Moderate (transaminase 2.5-10× ULN and total bilirubin 1.5-3× ULN) or severe (total bilirubin >3× ULN), omit
Cyclophosphamide	CrCl <10 mL/min, 50% of the full dose	Total bilirubin >3.1-5.0 mg/dL or AST >180 IU/L, 75% of the full dose
		Total bilirubin >5.0 mg/dL, omit
Daunorubicin	Serum creatinine >3 mg/dL, 50% of the full dose	Total bilirubin 1.5-3.0 mg/dL or AST 60-180 IU/L, 75% of the full dose
		Total bilirubin >3.1-5.0 mg/dL or AST >180 IU/L, 50% of the full dose
		Total bilirubin >5.0 mg/dL, omit
Doxorubicin	CrCl <10 mL/min, 75% of the full dose	Total bilirubin 1.5-3.0 mg/dL or AST 60-180 IU/L, 50% of the full dose
		Total bilirubin >3.1-5.0 mg/dL or AST >180 IU/L, 25% of the full dose
		Total bilirubin >5.0 mg/dL, omit
Epirubicin	Serum creatinine >5 mg/dL, lower doses should be considered	Total bilirubin 1.2-3.0 mg/dL or AST 2-4× ULN, 50% of the full dose
		Total bilirubin >3.0 mg/dL or AST >4× ULN, 25% of the full dose
		Total bilirubin >5.0 mg/dL, omit
Erlotinib	CrCl <10 mL/min, omit	Total bilirubin 1-7 mg/dL or AST 2-3× ULN, 50% of the full dose
		Total bilirubin >7.0 mg/dL, omit
Etoposide	CrCl >15-50 mL/min, 75% of the full dose	Total bilirubin 1.5-3 mg/dL or AST 60-180 units, 50% of the full dose
	CrCl <15 mL/min, omit	Total bilirubin 2-3 mg/dL or AST >180 units, omit
Hydroxyurea/ hydroxycarbamide	CrCl 10-60 mL/min, 75% of the full dose	Total bilirubin 1.5-5.0 mg/dL or AST 60-180 units/L, 50% of the full dose
	CrCl <10 mL/min, 50% of the full dose	Total bilirubin >5.0 mg/dL or AST >180 units/L, omit
Idarubicin	Serum creatinine 2–2.5 mg/dL, dose reduction recommended	Total bilirubin 2.5-5.0 mg/dL, 50% of the full dose
		Total bilirubin >5.0 mg/dL, omit
Imatinib	CrCl 40-59 mL/min, doses >600 mg are not recommended	Initial dose: severe hepatic impairment
	CrCl 20-39 mL/min, 50% of the full dose; dose can be increased up to a maximum of 400 mg	Initial dose: 75% of the full dose
	CrCl <20 mL/min, use with caution (in two patients with severe renal impairment, doses of 100 mg/d were tolerated)	Hepatic toxicity during treatment: transaminases >5× ULN or total bilirubin >3× ULN; omit
		Restart at reduced doses (reduce from 400 to 300 mg, from 600 to 400 mg, or from 800 to 600 mg) when transaminases <2.5× ULN and total bilirubin <1.5× ULN

Agent	Dose Adjustment	
	In Renal Function	**In Hepatic Dysfunction**
Methotrexate	For low dose (<1 g/m^2), CrCl 30-60 mL/min, 50% of the full dose	Total bilirubin 3.1-5.0 mg/dL or AST >180 units, 75% of the full dose
	CrCl <30 mL/min, omit	Total bilirubin >5.0 mg/dL, omit
	For high dose (>1 g/m^2), consider TDM	Total bilirubin >5.0 mg/dL, omit
Mitomycin C	CrCl 30-60 mL/min, 75% of the full dose	Total bilirubin 1.5-3.0 mg/dL, 50% of the full dose
	CrCl 10-30 mL/min, 50% of the full dose	Total bilirubin >3.0 mg/dL or transaminase >3× ULN, 25% of the full dose
	CrCl <10 mL/min, omit	

Abbreviations: AST, aspartate transaminase; CrCl, creatinine clearance; TDM, therapeutic dose monitoring; ULN, upper limit of normal.
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Table 3-11 **Example of Dose Modification Schema for Hematologic Toxicity**		
Event ANC	**Postponement of Cycle**	**Dose Reduction**
ANC >1.5 × 10^9/L	No cycle postponement.	No dose reduction
ANC 1.0-1.5 × 10^9/L	Postpone treatment until ANC is >ANC 1.5 × 10^9/L. Resume cycle with GCSF.	No dose reduction
ANC 0.5-1 × 10^9/L	Postpone treatment until ANC is >ANC 1.5 × 10^9/L. Resume cycle with GCSF.	Reduce dose by 15%
ANC <0.5 × 10^9/L	Postpone treatment until ANC is ANC 1.0-1.5 × 10^9/L. Resume cycle with GCSF. If no recovery to ANC >1.5 × 10^9/L by day 29, stop treatment.	Reduce dose by 25%

Abbreviations: ANC, absolute neutrophil count; GCSF, granulocyte-colony stimulating factor.
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Table 3-12 **Example of Dose Modification Schema for Hepatic Toxicity**	
Event	**Dose Modification Algorithm**
ALT <3.0× URL	Continue study treatment at the current dose
ALT 3-5× URL without bilirubin elevation	Interrupt study treatment, monitor subject closely, perform liver panel at least weekly until ALT returns to grade 1. If there is no recovery in 6 weeks, permanently discontinue therapy. If ALT recovers to <3× ULN within 6 weeks, readminister at reduced dose and monitor ALT weekly
ALT >5× URL without bilirubin elevation	If no recovery to grade 1 in 2 weeks, permanently discontinue. If recovery in 2 weeks, readminister at a reduced dose and monitor ALT weekly. If ALT elevations recur >3× ULN, permanently discontinue therapy
ALT >3× URL and bilirubin elevation	Permanently discontinue therapy. Initiate a potential Hy's law evaluation for drug-induced liver injury immediately. Consider a hepatology consultation

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal; URL, upper reference limit.
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Figure 3-1 Cell Cycle and Site of Cytotoxic Agents

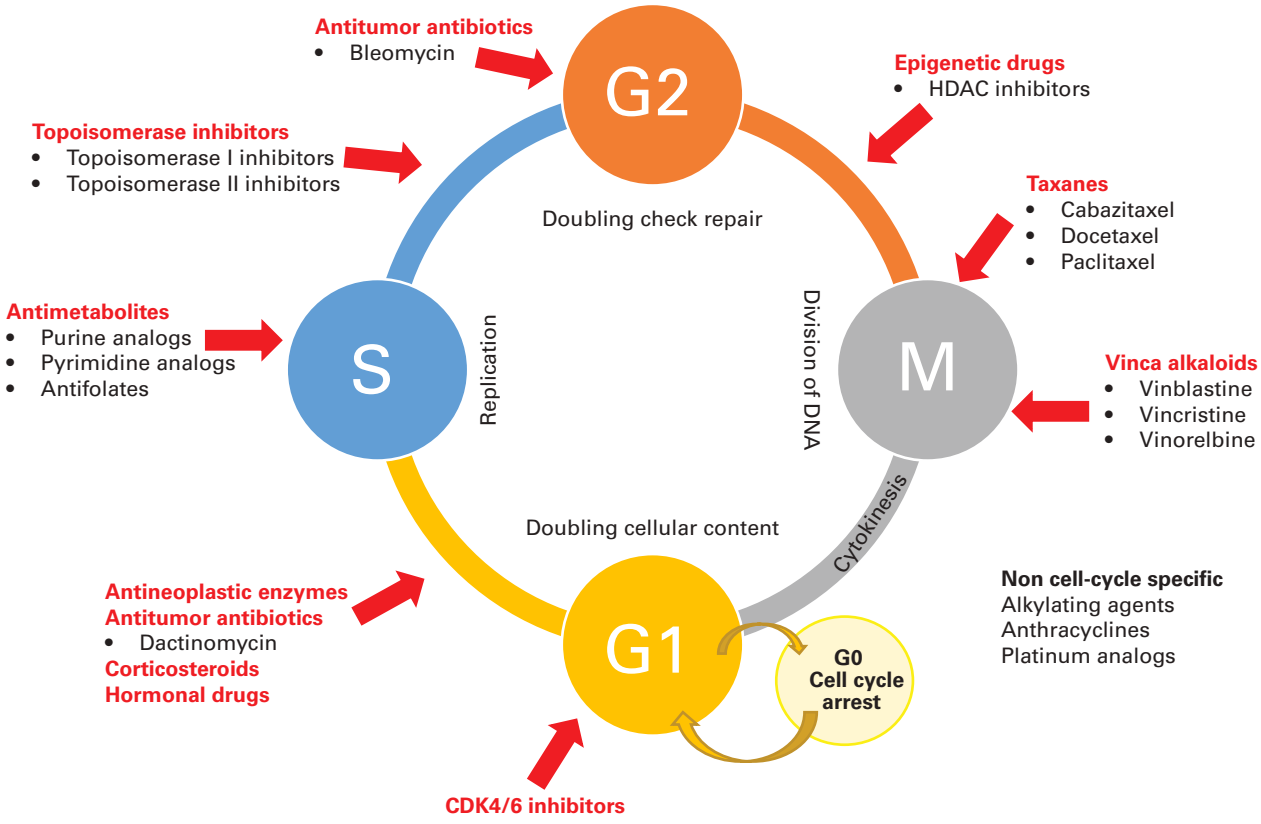

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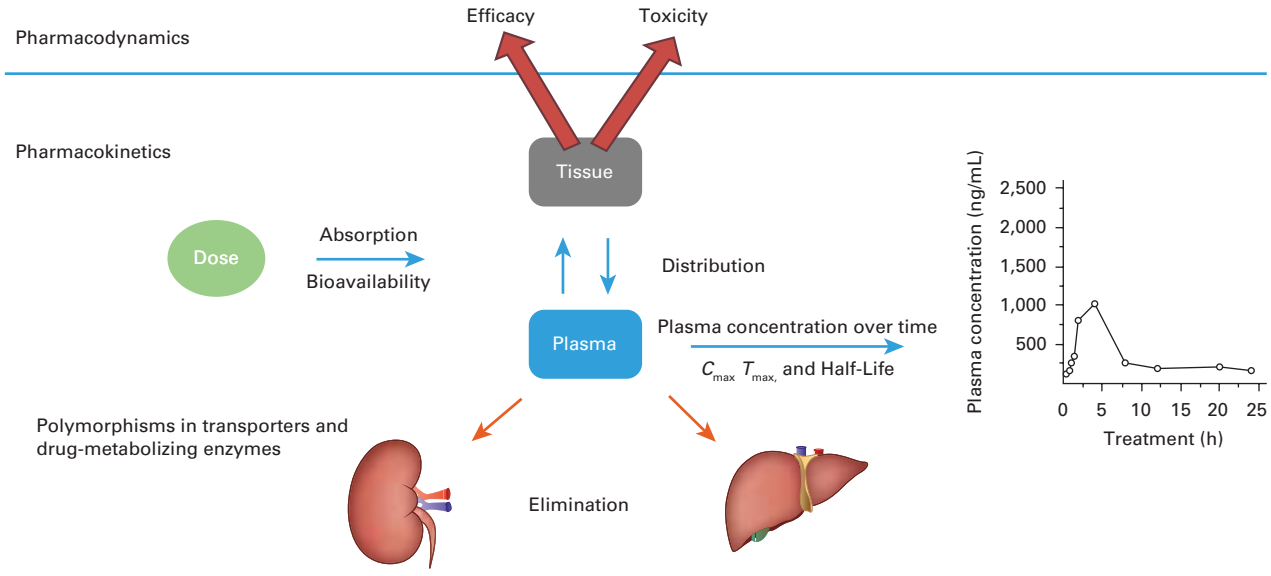
Figure 3-2 Overview of Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics



Abbreviations: C_{max}, maximum concentration; T_{max}, time at which maximum concentration is achieved.
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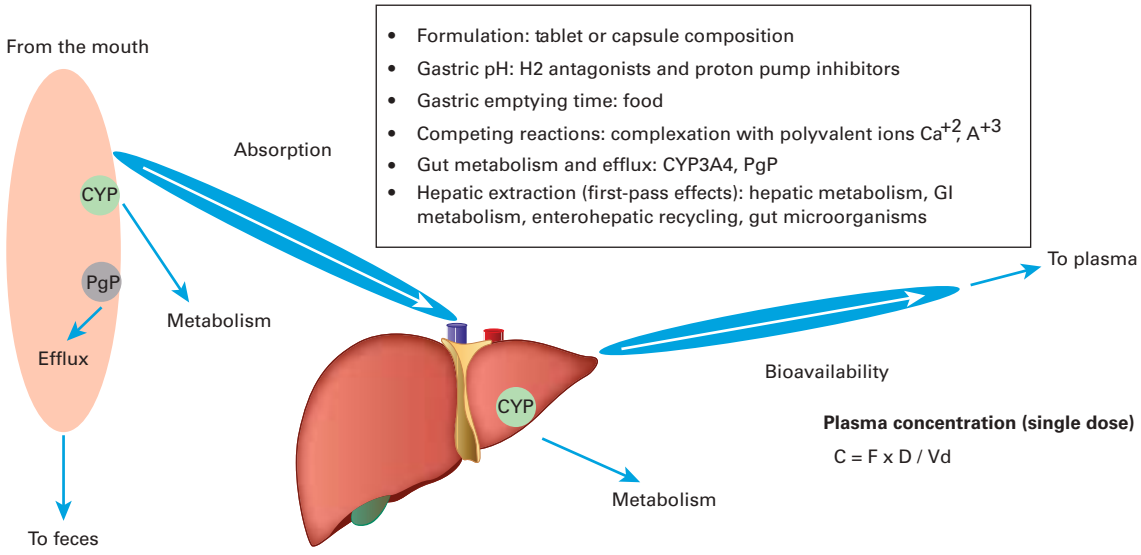
Figure 3-3 Factors Influencing Oral Absorption



Abbreviations: A, aluminum; C, concentration; Ca, calcium; CYP, cytochrome P450; D, dose; F, bioavailability; H2, histamine 2; k, elimination rate constant; PgP, P-glycoprotein; Vd, volume of distribution.

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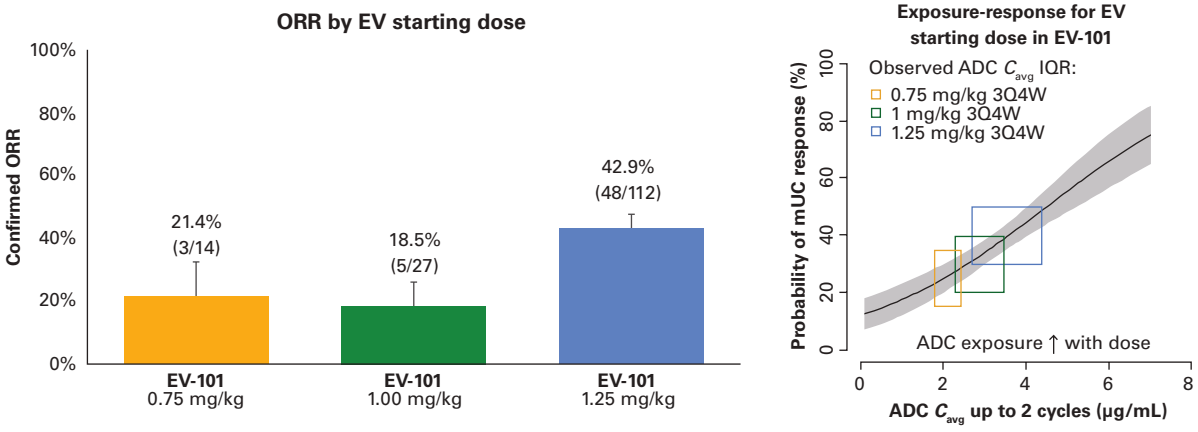
Figure 3-4 EV-101 Clinical Dose Selection by Dose Response and Exposure Response



Abbreviations: 2L+, second and later lines; 3Q4W, days 1, 8, and 15 of a 28-day cycle; ADC, antibody-drug conjugate; C_{avg}, time-averaged exposure up to two cycles; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; ORR, objective response rate.
Error bar = one standard deviation. Analysis populations for both dose-response and exposure-response were based on actual treatment arms.
Adapted from Petrylak DP, Chia YL, Yu EY, et al. Impact of exposure on outcomes with enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer. Presented at: Annual Meeting of the American Society of Clinical Oncology; May 29, 2024; Chicago, IL.
https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.4503
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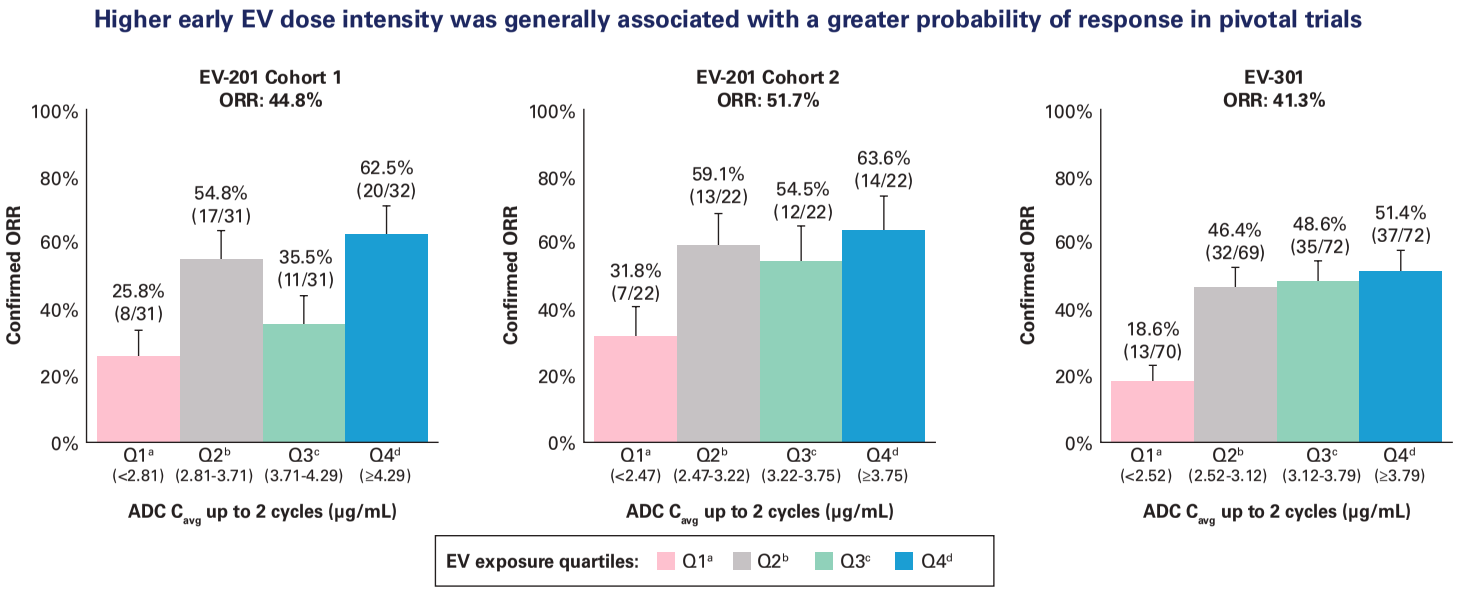
Figure 3-5 EV-101 Clinical Dose Selection Confirmation and Exposure Response



Abbreviations: ADC, antibody-drug conjugate; C_{avg}, time-averaged exposure up to two cycles; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; ORR, objective response rate; Q, quartile.

All data presented are from a post hoc, explanatory analysis. Error bar = one standard deviation.

Average ADC exposures were divided into four quartiles: [a]Q1 represents the EV exposures between 0% and 25%; [b]Q2: 25% to 50%; [c]Q3: 50% to 75%; [d]Q4: 75% to 100% (the highest EV exposure quartile).

Adapted from Petrylak DP, Chia YL, Yu EY, et al. Impact of exposure on outcomes with enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer. Presented at: Annual Meeting of the American Society of Clinical Oncology; May 29, 2024; Chicago, IL. doi:10.1200/jco.2024.42.16_suppl.4503

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PRINCIPLES OF IMMUNO-ONCOLOGY AND BIOLOGIC THERAPY

4

Christos Fountzilas, MD, and Ulka Vaishampayan, MD

OVERVIEW

Knowledge of immuno-oncology and biologic therapies has become essential for the practicing oncologist, given the wide clinical application. Since the introduction of interferon (IFN) more than 25 years ago, progress in biologic therapy for cancer has been rapid. The introduction of immune checkpoint inhibitors has had a major effect on the management of many malignancies and paved the way for the development of single-agent and combinatorial approaches addressing immune mechanisms. Cellular therapy has produced remarkable results in patients with refractory hematologic malignancies and is now under evaluation for solid tumors. This chapter focuses on the basic principles of immune and biologic therapy, including immunology, pharmacology, and toxicology in cancer therapeutics. A more detailed review of the clinical application of specific agents is provided in tumor-specific chapters.

IMMUNE SURVEILLANCE AND IMMUNOEDITING

The immune system protects against microbial pathogens while maintaining tolerance to self.[1,2] In addition, the immune system continually recognizes and removes malignant cells that arise throughout an individual's lifetime (immune surveillance) through antigen-specific (adaptive immunity) and antigen-nonspecific (innate immunity) mechanisms. Patients with suppressed immune systems (such as organ transplant recipients) are unable to adequately perform this immune surveillance and are at increased risk for developing malignancy. Further evidence of the role of immune surveillance in cancer control is provided by the reports of spontaneous regression of cancer, as well as cancer responses to withdrawal of immunosuppression. An activated immune system is a positive prognostic factor in multiple cancers.

Brisk infiltration in tumor specimens by subpopulations of lymphocytes, especially $CD8^+$ T cells, is an independent positive prognostic factor in melanoma, ovarian, and lung cancer.[3-5] Likewise, the natural occurrence of a humoral immune response to a tumor-associated antigen is associated with a favorable clinical outcome in cancers such as breast cancer.[6] Most importantly, pharmacologic modulation of the immune response with cytokines and various types of antibodies has produced objective tumor responses in patients.

Animal models have demonstrated the existence of immunoediting, in which activation of immune mechanisms initially destroys tumor cells (elimination phase). Over time, tumor cells may escape the immune pressure and enter a dormancy state where the immune system can still control the net growth of the cancer (equilibrium phase). Finally, secondary to tumor- and/or host-specific changes, cancer cells escape immune surveillance. The tumor then grows progressively, leading to the establishment of clinically apparent disease (escape phase).[7-9]

MEDIATORS OF IMMUNE SURVEILLANCE AND THE TUMOR MICROENVIRONMENT

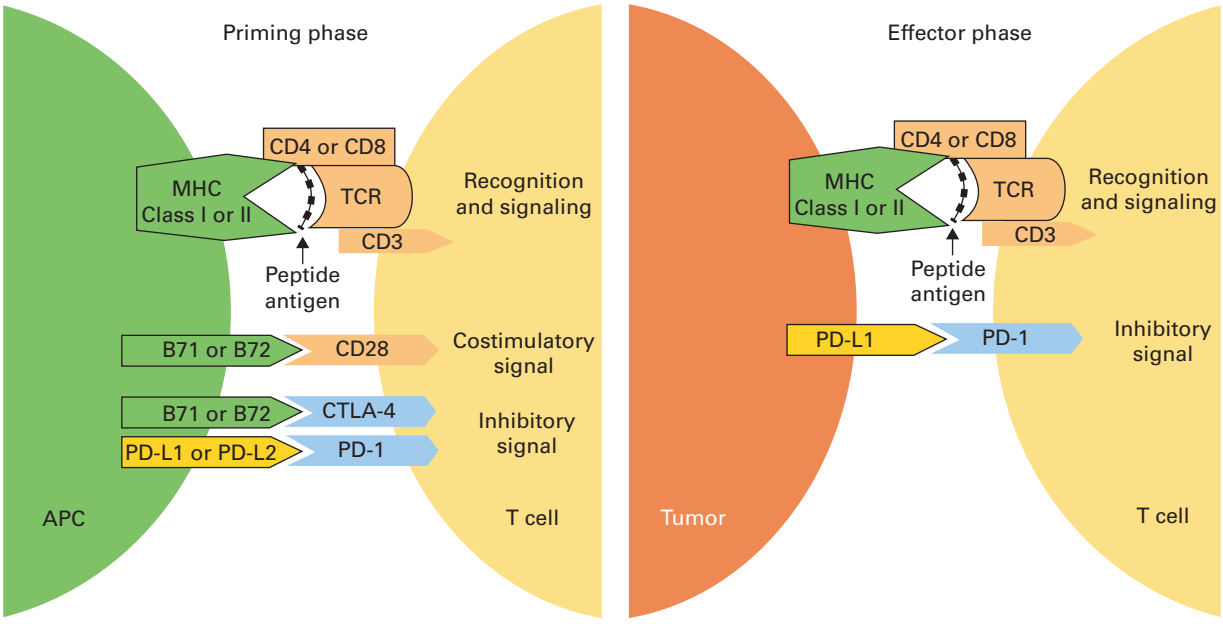
A diverse set of immune cell populations and secreted factors (cytokines, chemokines, growth factors) mediates immune surveillance. Their effect, depending on the context and other host- and tumor-related factors, may be either antitumor or tumor-promoting factors. For example, mutations involving pathways that are part of the immune activation cascade, such as disruptive mutations or, conversely, amplifications of JAK1 or JAK2 (implicated in IFN-dependent signaling), and activation of the WNT/β-catenin pathway can influence antitumor immune responses.[10] Tumors can vary in how they interact with the immune system. They may be spontaneously immune-infiltrated, ignored, not yet detected by the immune system, actively suppressed, or can form a defensive barrier from the immune system by activating tumor-intrinsic gene expression profiles. Tumors not only can escape immune response but also can exploit the immune response to promote their growth, invasion, and metastasis. Local tumor growth within the stroma is promoted by angiogenesis, mediated by interleukin (IL)-1, IL-8, and

the vascular endothelial growth factor (VEGF), which can be secreted by a variety of different immune cells. In addition to angiogenic factors, macrophages produce matrix metalloproteinases (MMPs) that degrade the extracellular matrix, facilitating cell invasion and metastasis. Many tumor cells express chemokine receptors and respond to chemokines in vitro. These chemokines can serve as tissue-specific attractants, promoting tumor cell migration or metastasis. Transforming growth factor-β (TGF-β), tumor necrosis factor (TNF)-α, and IL-6 can directly promote the growth of some tumors while suppressing the growth of others.

T CELLS AND IMMUNE CHECKPOINTS

T cells play a central role in adaptive immune responses as both effectors and regulators. The signaling complex of T cells includes the T-cell receptor (TCR), the accessory molecules (CD4 or CD8), and the CD3 signal transduction module.[11] The TCR only binds to peptide fragments of antigens that are noncovalently complexed with major histocompatibility complex (MHC) molecules, which are integral membrane glycoproteins (Fig. 4-1). There are two types of MHC molecules. Class I MHC molecules (eg, human leukocyte antigen-A [HLA-A], HLA-B, HLA-C) are expressed on most cell types and serve as the antigen-presenting molecules recognized by $CD8^+$ T cells (mainly cytotoxic T-cell lymphocytes [CTLs]). Class II MHC molecules (eg, HLA-DR, HLA-DP, HLA-DQ) are recognized by $CD4^+$ T cells (mainly helper T cells [Th]) and are present primarily on antigen-presenting cells (APCs) but can also be present on other cells, including tumor cells. Polymorphisms within MHC molecules determine whether a peptide fragment will complex with the MHC molecule and, therefore, whether a T cell from an individual will respond to a specific epitope of an antigen (MHC restriction). Effective surveillance requires that the tumor antigens are recognized by the immune system with high affinity against specific HLAs. Examples of tumor antigens/therapeutic targets of interest are described in Table 4-1. A high tumor mutation burden (TMB) increases the likelihood that some of these mutations will give rise to neoantigens—abnormal peptides displayed on the tumor cell surface by MHC molecules that the immune system can recognize as "non-self."[12,13] When a tumor expresses many neoantigens, it becomes more visible to the immune system, particularly to cytotoxic $CD8^+$ T cells capable of recognizing and attacking these antigen-bearing cells. This heightened immunogenicity helps explain why tumors with a high TMB, such as mismatch repair–deficient (dMMR) tumors,[14] are more likely to respond to immune checkpoint inhibitors (ICIs).

Figure 4-1 Regulation of T-Cell Priming and Effector Function



During the priming phase of T-cell activation, antigens are presented to T cells through the TCR as peptide fragments within MHC molecules on APCs. The primary costimulatory signal is delivered through the CD28 receptor on the T cell after engagement of its ligands B7-1 or B7-2 on the APC. Fully effective engagement also depends on interactions among several other molecules, such as adhesion molecules (not shown). Failure of the costimulatory B7/CD28 complex to be engaged results in either a nonactivated T cell or anergy. Engagement of CTLA-4 on the T cell by the same B7-1or B7-2 ligands results in inhibition of the response. Similarly, engagement of the PD-1 receptor with one of its two ligands, PD-L1 or PD-L2, on APCs also results in inhibition of the response. PD-L1 is also expressed by tumors. During the effector phase, engagement of PD-1 on the activated T cell by PD-L1 on the tumor results in inhibition of T-cell function.

Abbreviations: APC, antigen-presenting cell; CTLA-4, CTL antigen 4; MHC, major histocompatibility complex; TCR, T-cell receptor.

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Table 4-1 **Clinical Applications of Immunotherapy and Biologic Therapy**

Biologic Agent	Examples of Agents and Common Indications	Mechanism of Action	Significant Adverse Effects
Cytokines	Interleukin-2 (melanoma, renal cell carcinoma)[15-20]	T- and NK-cell activation/ stimulation	Fever, chills, hypotension, capillary leak syndrome
	Interferon-α (hairy cell leukemia)[21]	Upregulation of MHC type I, NK-cell stimulation, antiproliferative, and antiangiogenesis	Fever, chills, myalgia, fatigue, depression, liver dysfunction, and myelotoxicity
	Filgrastim/pegfilgrastim (prevention of neutropenic fever)	Induction of the production and release of neutrophils from the bone marrow enhances their functional capacity in the periphery	Bone pain, local skin reactions
Unconjugated monoclonal antibodies[22]	Bevacizumab* (colorectal cancer) Ramucirumab** (colorectal and gastric/gastroesophageal cancer) [23,24]	Anti-VEGF/VEGFR	Hypertension, proteinuria, wound healing complications, thromboembolic events, bleeding, and reversible posterior leukoencephalopathy[25]
	Cetuximab (RASwt and $KRAS^{G12C}$ colorectal cancer in combination with adagrasib; head and neck cancer)[26-29] Panitumumab (RASwt and $KRAS^{G12C}$ colorectal cancer in combination with sotorasib)[27,30-32]	Anti-EGFR, CMC, ADCC	Acneiform rash, infusion-related reaction, hypomagnesemia
	Zolbetuximab (gastric and gastroesophageal cancer)[33,34]	Anti-Claudin 18.2, ADCC, CMC	Nausea, vomiting, anorexia
	Rituximab (B-cell NHL)[35] Ofatumumab*** (CLL)[36] Obinutuzumab**** (CLL, follicular lymphoma)[37-39]	Anti-CD20, CMC, ADCC	Infusion-related reaction, hypogammaglobulinemia, progressive multifocal leukoencephalopathy,[40] and HBV reactivation[41,42]
	Tafasitamab***** (follicular lymphoma, diffuse large B-cell lymphoma)	Anti-CD19, ADCC, ADCP	Neutropenia, fever, infection, and diarrhea
	Daratumumab# (myeloma)[43-45]	Anti-CD38, CMC, ADCC	Infusion-related reaction, fatigue, nausea, fever, and respiratory symptoms
	Elotuzumab# (myeloma)[46]	Anti-SLAMF7, ADCC	Infusion-related reaction, infections, hepatotoxicity, and secondary primary malignancies
	Trastuzumab^ (breast, colorectal, gastric cancer, endometrial cancer)[47-50] Pertuzumab^^ (breast cancer)[51,52]	Anti-HER2, CMC, ADCC	Cardiotoxicity and hypersensitivity reactions

Biologic Agent	Examples of Agents and Common Indications	Mechanism of Action	Significant Adverse Effects
Immune checkpoint inhibitors	Pembrolizumab (melanoma, renal, lung cancer, MSI-H cancers, esophageal cancer, and biliary cancer)[47,53-60] Nivolumab (melanoma, renal, lung cancer, hepatocellular carcinoma, MSI-H colorectal cancer, and esophageal cancer)[55,61-68] Penpulimab (nasopharyngeal carcinoma)[69] Retifanlimab (anal cancer)[70] Toripalimab (nasopharyngeal)[71]	Anti-PD-1	Fatigue, pruritus, rash, diarrhea, and arthralgia; immune-related toxicities can be seen at any organ system Most common: (1) thyroid dysfunction, (2) adrenal insufficiency, (3) pneumonitis, (4) colitis, (5) dermatitis, and (6) arthritis Less common: (1) nephritis, (2) hepatitis, (3) hypophysitis, (4) encephalitis, (5) neuritis, (6) myositis, (7) uveitis, and (8) mucositis
	Durvalumab (hepatocellular carcinoma, lung, biliary cancer, and bladder)[72-76] Atezolizumab (hepatocellular carcinoma)[77] Avelumab (bladder cancer)[78] Cosibelimab (cutaneous squamous cell carcinoma)	Anti-PD-L1	
	Ipilimumab (lung cancer, melanoma, renal cell carcinoma, hepatocellular carcinoma, and MSI-H colorectal cancer)[61-66] Tremelimumab (hepatocellular carcinoma)[72]	Anti-CTLA-4, ADCC[79]	
	Relatlimab (melanoma)[80]	Anti-LAG-3	

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cell-mediated phagocytosis; CLL, chronic lymphocytic leukemia; CMC, cell-mediated cytotoxicity; CTLA-4, CTL antigen 4; EGFR, epidermal growth factor receptor; Fc, fraction-crystallizable; HBV, hepatitis B virus; HER2, human epidermal receptor 2; LAG-3, lymphocyte activation gene 3; MHC, major histocompatibility complex; MSI-H, microsatellite instability-high; NHL, non-Hodgkin lymphoma; NK, natural killer; VEGF, vascular endothelial growth factor.
*Bevacizumab targets VEGF-A.
**Ramucirumab targets VEGFR-2.
***Ofatumumab binds to both the small and the large loops of the CD20 molecule on B cells. Its location is closer to the membrane, which, in theory, allows for more effective complement deposition and subsequent B-cell killing. Preclinical data have suggested improved CMC and ADCC compared with rituximab.
****Obinutuzumab is a humanized anti-CD20 monoclonal antibody that has been glycoengineered to reduce core fucosylation, conferring enhanced affinity for the human FcγRIIIa receptor on effector cells and, hence, enhanced ADCC. As a type 2 monoclonal antibody, obinutuzumab has a lower capacity to relocalize CD20 into lipid rafts upon binding, compared with the type 1 antibodies rituximab and ofatumumab, and is less potent in inducing CMC. It is, however, more potent in mediating cell adhesion and direct cell death. Obinutuzumab and rituximab bind adjacent and partially overlapping epitopes on CD20 but acquire different orientations upon binding, which most likely contributes to the different biologic characteristics of type 1 and 2 antibodies.
*****Tafasitamab is a humanized engineered anti-CD19 monoclonal antibody, which incorporates S239D and I332E mutations into the Fc region of humanized anti-CD19 immunoglobulin G, enhancing its affinity for FcγRIIIa and subsequently ADCC and increased ADCP.
#Use of monoclonal antibodies in myeloma can interfere with the usual assays used to monitor M-protein.
^Trastuzumab targets the HER2 extracellular domain epitope IV.[81]
^^Pertuzumab targets the HER2 extracellular domain near the junction of domains I, II, and III.[82]
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T-cell activation requires not only the presentation of an antigen within the context of an MHC molecule and stimulation through the CD3 module but also costimulatory signals (Fig. 4-1). Activation, in turn, is regulated by coinhibitory signals, which are essential in limiting the magnitude of the immune response (and potential autoimmunity) (Fig. 4-1). The CD28 family of receptors includes the stimulatory receptor CD28 and the inhibitory receptors CTL antigen 4 (CTLA-4; also called CD152) and

PD-1. Receptors of the CD28 family interact with the B7 family of ligands, which include B7-1 (also called CD80), B7-2 (also called CD86), and PD-L1 (also called B7-1H) and PD-L2 (also called B7-DC). Several other receptor-ligand engagements can act as modulators of the immune response, collectively known as immune checkpoints, including those mediated by the following costimulatory and coinhibitory molecules (Table 4-2). PD-1–expressing T cells can secrete IFN-β upon initial T-cell activation, and this, in turn, upregulates PD-L1 on tumor cells, conferring on the tumor and T-cell interaction a dependence on this ligand-receptor association that can be therapeutically targeted by antibodies.

Table 4-2 Positive and Negative Immune Checkpoints

Costimulatory Receptors	Coinhibitory Receptors
CD28	CTLA-4 (CD152)
4-1BB (CD137)	PD-1 (CD279)
CD27	BTLA (CD272)
CD40L (CD154)	LAG-3 (CD223)
OX40 (CD134)	TIM-3 (CD366)
ICOS, (CD278)	PD-1H (VISTA)
GITR (TNFRSF18)	CD160
	CD244 (NK-cell receptor 2B4)
	TIGIT (CD)

Abbreviations: BTLA, B- and T-cell attenuator; GITR, glucocorticoid-induced tumor necrosis factor (TNF) receptor-related protein; ICOS, inducible T-cell costimulatory; LAG-3, lymphocyte activation gene 3; NK, natural killer; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domains; TIM-3, T-cell immunoglobulin and mucin-domain containing 3; VISTA, V-domain immunoglobulin suppressor of T-cell activation.
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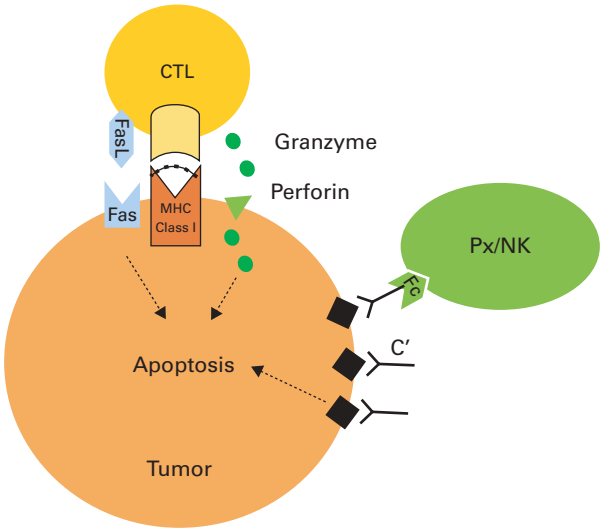
Once a T cell has been activated and differentiates into a cytotoxic T cell, the predominant mechanism of CTL cytotoxicity is granule exocytosis and the release of perforin and granzymes. The second mechanism is mediated by the death activator Fas ligand, which is expressed on the cell surface of CTLs (Fig. 4-2). Both mechanisms cause cells to undergo apoptosis. When CTL cells are appropriately activated, they produce cytokines, such as IFN-γ and IL-2, among others, that also can directly mediate or enhance antitumor effects.[83] CTLs can move to another cell and, by reorienting their granules to another region of contact, destroy it. In this manner, CTLs can kill many tumor cells, resulting in a robust and specific serial killing response that is considered to play a central role in immune-mediated tumor rejection (Fig. 4-2).

Helper $CD4^+$ T-cell lymphocytes (Th) secrete cytokines that regulate all immune cells. They are essential in generating CTLs, regulating B-cell antibody production, and activating phagocytes. Depending on the context of the antigen encounter and its uptake and the activation status of the APCs, several types of responses can be promoted, including a cellular immune response mediated by CTLs and macrophages, referred to as a Th-cell type 1 (Th1) response, or a humoral response mediated by an antibody, referred to as a Th2 response. Predominant cytokines produced in a Th1-associated response are IFN-γ and IL-2. Predominant cytokines produced in a Th2-associated response are IL-4, IL-5, and IL-13. Th cells are required in an antitumor response largely to help naive $CD8^+$ T cells, leading to their differentiation and activation into tumor-specific CTLs and the development of antigen-specific memory. Cytokines produced by Th cells may also mediate antitumor effects by activating macrophages and NK cells. Other types of responses include inflammatory Th17 responses (named for the IL-17 family of cytokines produced) and regulatory responses. Few T-cell responses are purely Th1 or Th2; often, a complex mix of cytokines is produced, but the Th1/Th2 axis provides a useful framework, with Th1 responses generally considered as antitumor and Th2/Th17 as tumor promoting.[84]

Regulatory T (Treg) cells are subsets of T cells capable of antigen-specific and antigen-nonspecific cell recognition.[85] In healthy individuals, Treg cells maintain tolerance by suppressing the expansion of effector cells directed against self-antigens. Treg cells that express CD4, CD25, low levels of CD127 (IL-7 receptor), and forkhead box P3 (FOXP3; a forkhead family transcriptional regulator) play a central role in maintaining immune self-tolerance. The mechanism of suppression of self-reactive lymphocytes is not yet clear, but it does involve direct cell-to-cell contact or the production of IL-10 or TGF-β. Given that tumors express antigens that are normal self-constituents, $CD4^+CD25^+FOXP3^+$ Treg cells engaged in the maintenance of self-tolerance may impede tumor-reactive T cells. In cancer, the prognostic significance of both circulating and intratumoral Treg cells may be context- and time-dependent and affected by the tumor type, the other cells in the tumor microenvironment, and soluble molecules that vary with treatment. In most cancers, data show that an abundance of intratumoral Treg cells confers a poorer prognosis; however, for some cancers, such as colorectal and esophageal cancers, they seem to be associated with a better prognosis.[86]

Figure 4-2 Mechanisms of Cell Killing by CTLs and Antibodies



After attaching to the MHC-peptide complex, CTLs discharge cytoplasmic granules containing perforin and granzymes by exocytosis. Perforin molecules insert themselves into the plasma membrane of target cells, which enables granzymes to enter the cell. Granzymes are serine proteases that, once inside the cell, activate caspases that cause the cells to undergo apoptosis. When CTLs bind to their target, they also upregulate Fas ligand on their surface, which binds with the Fas receptor on the surface of the target cell, leading to its death (also by apoptosis). Antibodies recognize an antigen in its native conformation. After binding, when a complement-reactive site on the antibody is present, a cascade of reactions can be set into motion, including the activation of many molecules of the complement system, which, in turn, activate increasing amounts of a series of enzymes that ultimately result in complement-dependent cytotoxicity. A product of the complement cascade also strongly activates phagocytosis by macrophages and neutrophils. These phagocytes, as well as natural killer (NK) cells, bind their Fc receptor (CD16) to the antibody and destroy the ADCC. Antibody-recognizing cell surface molecules that regulate cell signaling or growth can directly elicit apoptosis. Antibody binding can also block receptor-ligand binding and natural downstream signaling.
Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; C′, complement; CTL, cytotoxic T-cell lymphocyte; Fc, fraction-crystallizable.
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NK CELLS

NK cells comprise less than 10% of circulating lymphocytes. They are part of the innate non-antigen-specific response to pathogens and transformed cells. Although their cytotoxic mechanisms are similar to those of CTLs, NK cells do not require recognition of MHC molecules (non-MHC-restricted lysis). In fact, class I MHC molecules send a negative regulatory signal through receptors on the NK cells (killer inhibitory receptors) that inhibit NK-cell lytic function. Conversely, loss of class I MHC molecules on tumor cells may result in NK-cell killing of cells that could otherwise escape T-cell recognition. Under normal homeostatic conditions, multiple families of NK-cell receptors that inhibit their activation exert the predominant effects, whereas inflammation and infection, as well as malignancy, may lead to activation through a number of other activating receptors that recognize soluble and cell membrane ligands on tumors and infected cells. In addition, in contrast to CTLs, NK cells express fraction-crystallizable (Fc) receptors (CD16) and, therefore, can mediate antibody-dependent cellular cytotoxicity (ADCC). When activated, NK cells also produce IFN-γ. Although NK cells do not require activation for lytic activity, the stimulation of NK cells with IFNs and IL-2 markedly enhances their antitumor activity. In contrast to CTLs, which can kill multiple cells, evidence shows that NK cells must rearm themselves by exposure to IL-2 before they are effective against new targets.[87]

DENDRITIC CELLS

Dendritic cells (DCs) are a widely distributed heterogeneous population of APCs. DCs function at the intersection of innate and adaptive immune responses. Upon stimulation and activation provided by microbes (through toll-like receptors), cytokines, and/or T-cell signals (eg, CD40 ligand), DCs undergo additional maturation and migrate to secondary lymphoid tissues, where they present antigens to T cells. The nature of the immune response elicited depends on a variety of factors, including the mode and duration of activation and the cytokine milieu. Two distinct DC lineages have been described in humans. Myeloid DCs express the receptor for granulocyte-macrophage colony-stimulating factor (GM-CSF) and other myeloid markers. Plasmacytoid DCs lack myeloid cell markers and express the receptor for IL-3 (CD123). Myeloid DCs reside in tissues and are the most efficient APCs, particularly with regard to the primary activation of naive T cells, and they stimulate tumor-reactive CTLs, which include IL-12-dependent mechanisms. Plasmacytoid DCs reside in peripheral blood, and, after encountering a virus, they secrete large amounts of IFN-γ. The role of plasmacytoid DCs in antitumor immunity is under investigation.

MACROPHAGES

Macrophages mediate a variety of functions and play a central role in both innate and adaptive immunity. Macrophages are specialized phagocytes that function through the enzymatic generation of reactive oxygen and nitrogen species and by proteolytic digestion. Phagocytosis is mediated through surface receptors for complement and other opsonins. Macrophages can act as APCs, express Fc receptors (CD16) for antibodies mediating ADCC, and secrete VEGF. Distinct activation states of macrophages have been described; M1 macrophages (antitumor) produce high levels of inducible nitric oxide synthase, IL-12, and TNF, whereas M2 macrophages (tumor promoting) produce arginase, IL-10, TGF-β, and prostaglandin E_2. Whereas M2 macrophages are associated with a decrease in survival for patients with cancer, M1 macrophages have been associated with improved survival.[3] Like the Th1/Th2 paradigm, M1/M2 is a useful framework but does not account for the enormous heterogeneity in myeloid cells. In tumor tissues, tumor-associated macrophages (TAMs) are a subtype of macrophages that are often associated with poor outcomes.[88] The tumor immune adaptation, difficulty in selectively targeting M2, and inherent plasticity of these cells make targeting them challenging.

MYELOID-DERIVED SUPPRESSOR CELLS

Myeloid-derived suppressor cells (MDSCs), present in tumors and lymphoid organs, can inhibit T-cell functions and play a role in tumor-associated immune suppression. They have been described in patients with many types of solid tumors.[86,89,90] Human MDSCs are more poorly defined than those in murine models but include $CD14^+$ myeloid cells, $CD15^+$ polymorphonuclear leukocyte cells, and reduced HLA-DR. MDSCs express the common myeloid markers CD33 and CD11b. The precise nature of this regulatory cell population depends on the tumor and tumor-derived factors of the host. In patients with cancer, an increased number of MDSCs seems to correlate with poor outcomes in multiple settings.[91,92] This highly plastic population suppresses T-cell functions through different molecular pathways, mostly involving arginase metabolism products, inducible nitric oxide synthase, reactive oxygen species, and/or production of soluble inhibitory factors such as TGF-β, IL-10, prostaglandin E_2, and nitric oxide.

KEY POINTS

- Cells of the antigen-nonspecific innate and antigen-specific adaptive immune systems contribute to antitumor immunity.
- Immune responses are highly regulated to maintain tolerance to self and limit immune-mediated damage to normal tissues.
- This continuous interaction between tumor cells and immune cells is characterized as immune surveillance and immunoediting. Immune surveillance has three phases: elimination, equilibrium, and escape.
- Immune cells can have both antitumor and tumor-promoting effects.
- The interaction between tumor and immune cells is bidirectional.
- Tumors can subvert the immune response by stimulating the production of immune cell factors that promote angiogenesis, invasion, and metastasis.
- Immune cell cytokines may also function as tumor growth factors.
- T cells recognize antigens presented to their TCRs as peptide fragments within MHC molecules (MHC restriction). T-cell activation requires stimulation not only through the TCR but also through immune costimulatory receptors.
- Interactions with coinhibitory receptors on T cells, referred to as immune checkpoints, suppress unwanted and harmful self-directed immune activities as well as antitumor immune responses.
- Recognition of tumor cells by the immune system can be influenced by a variety of factors, including the tumor's intrinsic antigenic potential (eg, mutational burden and neoantigen signature, strength of immunogenicity of tumor antigens), pre-existing host immune condition, and products of genomic aberrations that affect pathways driving the immune response.
- Th cells promote Th1-associated immune responses (antitumor) through the production of cytokines, such as IFN-γ and IL-2, and promote Th2-associated immune responses (tumor promoting) through the production of cytokines, such as IL-4 and IL-5.
- CTLs and NK cells kill tumors by apoptosis through granule exocytosis and Fas-mediated mechanisms.
- DCs are the most efficient APCs.
- Several lymphoid and myeloid cell populations suppress immune responses, including TAMs, Tregs, and MDSCs.

MECHANISMS OF IMMUNE ESCAPE

There are several mechanisms tumors can use to escape immune surveillance. Tumors can be highly heterogeneous; the repertoire of tumor antigens on the cells of one tumor may be variable, often within the same patient, and can evolve over time. Tumors can also escape the immune system by modifying factors on both the T-cell and tumor side of the equation. On the T-cell side, downregulation of class I MHC molecules and other components of the antigen-presentation process can occur frequently.

Downregulation of the CD3 ζ-chain of the TCR complex and impairment of function have been shown in T cells isolated from patients with cancer.[93] On the tumor side, tumor expression of PD-L1 and PD-L2 is considered a significant mediator of immune evasion. The expression of Fas ligand by some tumor cells may help to maintain a state of immune privilege by inducing apoptosis of Fas-sensitive T and NK effector cells (ie, the Fas counterattack). There is also evidence that a tumor's expression of antiapoptotic molecules, which prevent perforin- or death receptor–dependent cytotoxicity, can result in escape, despite expression of the target antigen. In addition, tumor-associated factors, such as underglycosylated tumor-associated mucins, have been shown to reduce the binding of antibodies to tumor cell surfaces.

A high degree of immunologic tolerance naturally exists, limiting the generation of potent immune effectors. This can be exploited by tumors where Treg cells engaged in the maintenance of self-tolerance may impede tumor-reactive T cells. The Th-cell response may also be skewed toward a Th2 phenotype that leads to impaired Th1 responses.[94] The balance between CTL- and NK-attracting (ie, CCL5, CXCL9, CXCL10) versus MSDC- and Treg cell–attracting (ie, CCL2, CCL22, CXCL8, CXCL12) chemokines can drive the capacity for mounting an adequate antitumor immune response. Tumor cells and the surrounding stroma may release a number of suppressive cytokines and other soluble factors, such as prostaglandin E_2, inhibiting antitumor immunity.[95] Cancer-associated factors inhibit the production and stimulatory capacity of DCs.[96] TGF-β is produced by host as well as tumor cells. TGF-β can inhibit the differentiation of T cells into CTLs and Th cells and promote the generation of Treg cells. By producing cytokines (eg, GM-CSF), cancers can promote the infiltration of M2-polarized macrophages and MDSCs that can inhibit T-cell function.

KEY POINTS

- Although immune checkpoints are necessary to prevent unchecked autoimmunity, tumors can co-opt these mechanisms to escape immune-mediated elimination.
- Cancer evasion of the immune system results not only from immunosuppressive factors secreted by or expressed on the tumor but also from the ability of the tumor to modulate antigen expression and be endowed with or later develop mechanisms of resistance to immune effectors.
- The recognition of evasion mechanisms involved in tumor immune escape can be exploited therapeutically.

BIOLOGIC AGENTS

Biologic agents can exert their antineoplastic effect through either immune or nonimmune pathways. The immune response can be activated through (1) the increase in the activity and or numbers of immune effector cells and (2) the modification of tumor cells so that they are more susceptible to immune effector cells. Some agents, such as the anti-epidermal growth factor receptor (anti-EGFR) and human epidermal receptor 2 (HER2) antibodies, can have both immune- and nonimmune-mediated antitumor effects. Some biologics are administered not to promote direct antitumor responses but, rather, to ameliorate the adverse events of therapy, including immune-related adverse events (irAEs), or mitigate the risk of complications as supportive approaches. These include growth factors used in the setting of chemotherapy-related myelotoxicity, suppressive immune modulators used in the context of irAEs (eg, infliximab, tocilizumab, vedolizumab), and monoclonal antibodies used to palliate tumor-related complications (eg, denosumab).

The pharmacokinetics of biologic agents are quite variable. Elimination half-lives for most cytokines are measured in minutes to hours and, for most antibodies, in days to weeks. Infused cells can persist for months.

Clinically available biologic agents can be broadly categorized into the following:

- Cytokines
- Monoclonal antibodies
- Antibody-drug conjugates (ADCs)
- Bispecific antibodies
- Cellular therapies
- Vaccines
- Viral oncolytic therapies

A detailed description of each agent in clinical use today is beyond the scope of this chapter. Table 4-1 summarizes some of the most commonly used agents, their mechanism of action, and adverse events.

CYTOKINES

Cytokines are a diverse group of small proteins released by immune and nonimmune cells distributed throughout the body. Cytokines play integral roles in innate and adaptive immunity as effector and regulatory molecules and play a role in a variety of other biological

processes. Cytokines, which are active physiologically at low concentrations, generally act locally (autocrine or paracrine), but also at a distance (endocrine). They are characterized by pleiotropy (one cytokine, multiple effects), redundancy (multiple cytokines, one effect), and synergy (the sum of the responses together is greater than the sum of the individual responses). There is also a contextual aspect to cytokines where their effects can depend on the overall milieu in which they are found.

THERAPEUTIC MONOCLONAL ANTIBODIES AND ADCS

Most of the approved antibodies in oncology are either IgG1 or IgG2 monoclonal antibodies, engaging Fc receptors on NK cells and macrophages and mediating successful complement cell-mediated cytotoxicity (CMC) and ADCC, or blocking IgG4 monoclonal antibodies, designed to block downstream signaling but not able to mediate CMC or ADCC.

Therapeutic monoclonal antibodies come in the following three forms:

- Chimeric (ie, murine variable chain fused to a human constant chain, termed ximab, and 65%-90% human)
- Humanized (ie, murine hypervariable or complementarity-determining regions grafted to human Ig, termed zumab, and 95% human)
- Fully human (termed umab).

Triggering of tumor antigen-specific cellular immunity by monoclonal antibody, in conjunction with immune escape mechanisms used by tumor cells, may contribute to differential clinical responses to monoclonal antibody–based immunotherapy.[79] The antigenic heterogeneity of most tumors presents challenges, as does the small fraction of administered antibodies that bind to tumors because of the occasional inability of antibodies to penetrate large tumor masses. Furthermore, binding of antibodies to antigens in circulation can also limit delivery to the tumor. In addition, therapeutic antibodies can elicit immune responses with the formation of antidrug antibodies, a phenomenon that has potential implications for antitumor activity for some agents.[97,98] Although now rare, because of the use of prophylaxis with premedications and broader incorporation of fully human antibodies, immune responses to artificial humanized antibodies can still be problematic, causing hypersensitivity reactions or neutralization of the antibody. Whether they target tumor cell membrane determinants, factors involved in tumor progression such as angiogenesis, or immune checkpoints, monoclonal antibodies are mainstays of cancer therapy.

Monoclonal antibodies have been used to deliver toxins, cytotoxic drugs, or radiation to malignant cells (as opposed to activating host antitumor mechanisms).[99] These agents—ADCs,[100-109] antibody-toxin conjugates,[110] or radiopharmaceutical conjugates[111-113]—can promote antitumor immunity by aiding tumor cell killing with the toxic cargo in a specific way through the specificity of the antibody-targeting aspect. The tumor antigen release can lead to antigen uptake by endogenous APCs when present in the tumor microenvironment. In addition, ADCs can have a bystander effect—tumor cell death in the vicinity of the target tumor cells after intracellular or extracellular release of the payload—that can potentiate the antitumor effect.[114] Pulmonary toxicity is an uncommon yet very serious adverse event of commonly used ADCs.[115,116]

ADCs combine a monoclonal antibody with a payload of a cytotoxic drug. The antigen is usually a receptor or protein on the cell surface that is solely or dominantly expressed on cancer cells—such as HER2 or TROP-2. The antibody and payload are connected by a chemical bond called a linker, which dissolves when the antibody binds the antigen and releases the payload into the cell. This enables targeted drug delivery. While ADCs primarily exert their cytotoxic effect on the cancer cells, they can also affect other cells that express the targeted antigen, and the release of the cytotoxic payload can induce similar toxicities as seen with that class of agents when administered directly, such as peripheral neuropathy for antimicrotubule agents or nausea, diarrhea, and myelosuppression for topoisomerase-1 inhibitors.[117,118]

KEY POINTS

- Cytokines are cell-to-cell signal mediators designed to act locally, but are detectable systemically, and can enhance the activity of antitumor immune effector cells.
- Monoclonal antibodies can mediate antitumor activity through immune mechanisms and nonimmune mechanisms (eg, direct induction of apoptosis, interference with target signaling).
- Because of infusion reactions, premedication is required for treatment with many monoclonal antibodies.
- Unique and often severe organ toxicity related to the molecule being targeted can be seen.
- Pulmonary toxicity is an uncommon but very serious adverse event from some ADCs.

IMMUNE CHECKPOINT INHIBITORS

ICIs (mainly anti-PD-1/PD-L1 and anti-CTLA-4 monoclonal antibodies) as monotherapy and in combinations have successfully been used in multiple solid tumors, including but not limited to melanoma,[61] renal cell carcinoma,[62] non–small cell lung cancer (NSCLC),[63] hepatocellular carcinoma,[64,72] and microsatellite instability-high (MSI-H) or dMMR colorectal cancer.[65] Furthermore,

combinations of anti-PD-1 and anti-LAG-3 (lymphocyte activation gene 3) monoclonal antibodies are effective as initial treatment of advanced melanoma.[80] Importantly, ICI use has been expanded in earlier-stage disease as adjuvant[53,54,66] or neoadjuvant[119] therapy. In addition, combinatorial approaches, including ICIs and distinct classes of antineoplastic drugs, have been investigated in randomized trials and incorporated into clinical practice. Anti-PD-1/PD-L1 monoclonal antibodies in combination with chemotherapy[55,56,67,68,73-75] and small-molecule inhibitors[57,58,120] or other monoclonal antibodies[77] and ADCs[121] are some examples that have become available for clinical use in specific scenarios.[59,60,71,75]

ICIs can cause irAEs that are similar to autoimmune diseases, including the following:

- Dermatologic: rash and inflammatory dermatitis
- Gastrointestinal: colitis and hepatitis
- Renal: nephritis
- Nervous system: peripheral neuropathy and encephalitis
- Endocrine: hypophysitis leading to adrenal insufficiency and hyper/hypothyroidism
- Musculoskeletal: inflammatory arthritis
- Hematologic: hemolytic anemia
- Lung: pneumonitis

Rarely, irAEs can include autoimmune conditions such as rheumatoid arthritis, type 1 diabetes, aplastic anemia, autoimmune hemolytic anemia, autoimmune neutropenia, hemophagocytic lymphohistiocytosis, and immune thrombocytopenic purpura.

The type of ICI and the patient's cancer type can affect the frequency and type of irAEs. For example, patients with melanoma are more likely to experience skin and gastrointestinal irAEs, while patients with NSCLC are more likely to experience pulmonary irAEs.[122] In most cases, irAEs can be treated with temporary immunosuppression using glucocorticoids, tumor necrosis factor-alpha antagonists, or mycophenolate mofetil. Infliximab is not advisable in patients with liver dysfunction. In severe cases, such as myocarditis, severe pneumonitis, colitis, or encephalitis, it is necessary to permanently discontinue the use of ICIs. IrAEs can impact multiple organs and require a multidisciplinary team of experts for treatment. They are unpredictable in timing, can affect one or multiple systems, and if clinically significant, will require immunosuppression, usually with steroids. Some of the irAEs can lead to permanent irreversible conditions.[122-126]

In general, ICI combinations (especially anti-PD-1/PD-L1 combined with anti-CTLA-4) are associated with a significant increase in the incidence of irAEs compared with either agent alone, requiring experience and close communication among the treating clinician, the patient, and other members of the healthcare team. Identification of predictors that will allow patients to be selected for single or combined therapy is awaited. Lower or priming doses of anti-CTLA-4 and alternative dosing schedules may also be appropriate toxicity-mitigation strategies.[72] Guidelines that encompass a thorough review of irAEs and detailed management recommendations have been published and are useful tools for the mitigation of risks associated with these agents.[123-126]

NUANCES OF RESPONSE ASSESSMENT WITH IMMUNOTHERAPY

The unique mechanisms of action of ICIs targeting CTLA-4, PD-1, and PD-L1 make the assessment of response by conventional criteria difficult, and atypical patterns of response have been documented. Although immune-related response criteria have been proposed, the applicability and, more importantly, interpretation in clinical practice remain challenging.[127] Patients may infrequently have atypical patterns of response. Pseudoprogression describes a phenomenon where infiltration of the tumor microenvironment by immune cells presents radiographically as initial apparent worsening of the disease (ie, initial enlargement of existing lesions and/or appearance of new lesions) that is followed by subsequent response. With the limitation of inconsistency in the definition of this phenomenon, the incidence is <10% and does not appear to differ depending on tumor type.[128] In addition, delayed responses after initial radiographic progression, although rare, can occur. As such, treatment beyond the first documented radiographic progression may be acceptable in select situations, particularly in the setting of clinical stability or symptomatic improvement. Occasionally, radiographic responses can take longer to become apparent compared with those with cytotoxic or targeted therapy. Continued disease regression and disease control can be seen after immunotherapy is completed. Furthermore, some patients who do not meet criteria for objective response can have prolonged periods of stable disease that are clinically relevant.

Patients with organ transplants and autoimmune conditions are at increased risk of toxicity from immunotherapy. The incidence of graft rejection is 36% and varies depending on the transplant type (decreased risk of rejection in non-kidney transplant), ICI–based strategy (decreased risk with anti-CTLA4 monotherapy and concomitant use of chemotherapy), type of immunosuppression (decreased risk with steroids and mTOR inhibitors), and use of ICI before the transplant with long washout time (>60 days).[129-131] The cancer-related outcomes are worse in patients with melanoma and other solid tumors compared to squamous skin cancer.[130] In HIV patients, treatment with ICIs was noted to be safe in a retrospective analysis from the Cancer Therapy Using Checkpoint Inhibitors in People Living With HIV-International (CATCH-IT) Consortium.[132] In this study, 30% of the patients had

CD4 counts <200 cells/μL, and 94% had viral load <400 copies/mL. The adverse event rate was no different than that seen in non-HIV patients. The efficacy and long-term outcomes of ICIs in this patient population were also similar to those of non-HIV patients. In a smaller prospective observational study, the incidence of grade 3 or higher irAEs was increased in patients diagnosed with HIV for more than 17 years, with CD4 counts <200 cells/μL, positive cytomegalovirus serology, or history of cancer surgery (39179255). In a prospective phase 1 trial, 32 patients with HIV-associated Kaposi sarcoma were treated with pembrolizumab, the overall response rate was 62% in all patients and 87% in patients without prior systemic treatment.[133] There was no difference in response based on CD4 cell count. On the contrary, in a phase 1 study of nivolumab in HIV patients with Kaposi sarcoma and other solid tumors, objective responses were only observed in patients with CD4 counts ≥200 cells/μL.[134] If possible, patients with HIV should be treated with antiviral therapy before starting therapy. Autoimmune diseases are relative contraindications. The decision to treat with ICI therapy can be made based on the severity of the condition and the extent of immunosuppression needed within the process of shared decision-making.[135] The risk of flare of the underlying autoimmune disease and new irAE is 41% and 33%, respectively, with at least moderate severity in 7% and 12%, respectively.[136] The overall management of these patients should be personalized, and the treating oncologist must be in close communication with the patient's rheumatologist for the appropriate preventive measures and treatment strategy should a flare occur.

KEY POINTS

- Immune checkpoint blockade with antibodies against CTLA-4, PD-1, PD-L1, and LAG-3 is an effective method for reversing cancer immunosuppression and promoting immune responses against several cancer types.
- Checkpoint inhibition is associated with a unique spectrum of adverse events called irAEs, which can occur unpredictably and have the potential to affect any organ system.
- The combination of ICIs (anti-PD-1 in combination with anti-CTLA-4 agents or LAG-3) may result in improved response rates and disease control at a cost of greater toxicity. However, increased incidence of long-term remission is reported in some malignancies such as metastatic melanoma.
- ICIs can be safely combined with other therapeutics, including chemotherapy, ADCs, and small-molecule inhibitors, and lead to increased response in several cancer types.
- ICIs can be safely administered in patients with HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) with careful monitoring. Antiviral therapy should be initiated before treatment if possible.
- Treatment with ICIs in patients with underlying autoimmune disease can lead to disease flare. Treatment with ICIs can be considered in these patients after shared decision-making and after the autoimmune disease is optimized while minimizing immunosuppressive medication exposure.

BISPECIFIC ANTIBODY THERAPY

A bispecific antibody is a synthetic protein composed of fragments of two different monoclonal antibodies and consequently binds to two different types of antigens. Bispecific monoclonal antibodies have been developed to simultaneously bind to two or more targets on the same cell surface or to an immune effector cell and a tumor cell to destroy the tumor cell.[137]

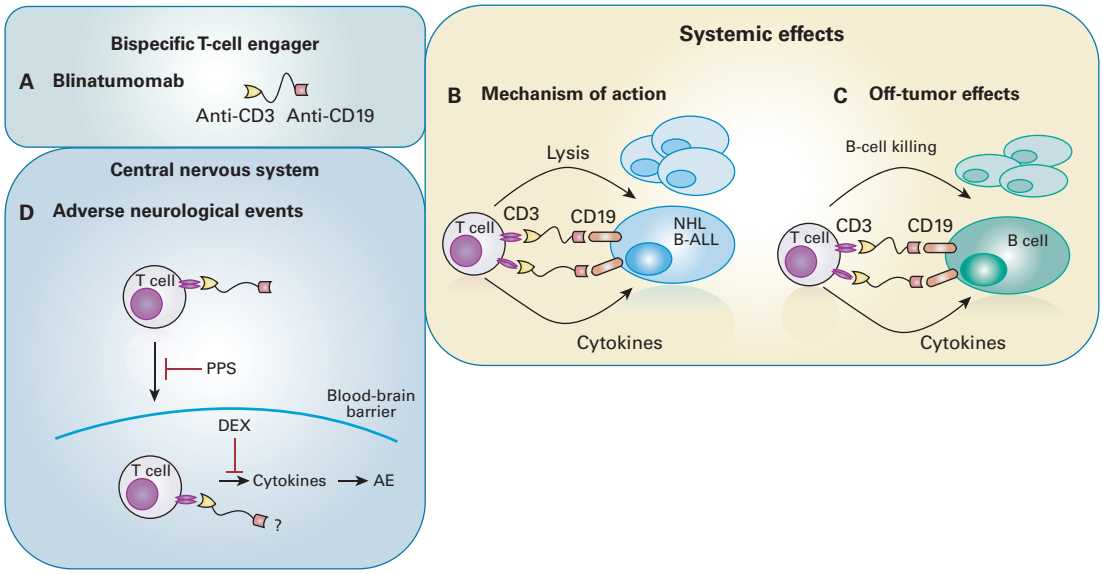
Blinatumomab was the first FDA-approved bispecific antibody that simultaneously targets CD3 (T-cell specific) and CD19 (B-cell specific). Blinatumomab belongs to a class of constructed antibodies known as bispecific T-cell engagers (Fig. 4-3). Blinatumomab brings a $CD3^+$ cytotoxic T cell into proximity with the CD-19-expressing malignant B cells. Once they are bound, the T cells rapidly activate and induce perforin-mediated death to the targeted tumor cells. Blinatumomab is approved by the FDA for the treatment of Philadelphia chromosome–negative relapsed or refractory B-lineage acute lymphocytic leukemia (ALL) in adult patients on the basis of the results from the phase 3 TOWER study.[138] It is also approved in adult and pediatric patients in first or second complete remission with detectable minimal residual disease.[139]

Glofitamab is a novel CD3/CD20 targeting bispecific T-cell engager approved with adults with refractory diffuse large B-cell lymphoma.[140] Bispecific T-cell engagers targeting the B-cell maturation antigen (BCMA) or GPRC5D are also approved for patients with refractory multiple myeloma.[141,142] Linvoseltamab-gcp is a bispecific BCMA-directed CD3 T-cell engager for adults with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody.

Tebentafusp-tebn is a bispecific T-cell engager approved for metastatic uveal melanoma that targets the glycoprotein 100 (gp100) peptide presented by HLA-A02:01 on uveal melanoma cells and CD3 on T cells, thereby redirecting T cells to lyse tumor cells.[143] Tarlatamab is a bispecific T-cell engager targeting DLL3 and CD3, and it is approved for use in previously treated small-cell lung cancer.[144]

The toxicities of bispecific T-cell engagers are related to activation of the immune system as well as other on-target effects. Notable examples of the former are the cytokine release syndrome (CRS) and the immune effector cell–associated neurotoxicity syndrome (ICANS).[145] The CRS is marked by symptoms that mimic a systemic inflammatory response syndrome, ranging from mild constitutional symptoms to life-threatening hypotension, hypoxia, fever, and multiorgan dysfunction. The CRS is largely attributed to the secretion of cytokines and chemokines by T cells, monocytes or macrophages, and DCs, including IL-1, IL-2, and

Figure 4-3 Bispecific T-Cell Engagers as Treatment of B-Cell Lymphoma



Activity of the bispecific T-cell engager blinatumomab (A). This bispecific T-cell engager protein can connect a T cell and (B) a CD191 tumor cell or (C) a CD191 B cell by simultaneously binding CD3 and CD19. When both single-chain variable fragments bind to their target antigens, T-cell activation is triggered, which leads to the release of cytotoxic granules and cytokines (eg, IFN). Lysis of the tumor cell or B cell involves membrane perforation followed by programmed cell death induced by granzymes. Bispecific T-cell engagers trigger serial killing by activated T cells. (D) Approaches to limit adverse neurologic events caused by blinatumomab treatment include the blocking of activated T-cell migration into the CNS through PPS treatment or the reduction of cytokine activity through the use of corticosteroids, such as DEX. Which cells blinatumomab may recognize in the CNS (eg, tumor cells) is unknown, but the adverse effects resolve when treatment is discontinued.
Abbreviations: AE, adverse event; B-ALL, B-cell acute lymphoblastic leukemia; CNS, central nervous system; DEX, dexamethasone; NHL, non-Hodgkin lymphoma; PPS, pentosan polysulfate.
Data reproduced from Smits NC, Sentman CL. Bispecific T-cell engagers (BiTEs) as treatment of B-cell lymphoma. *J Clin Oncol*. 2016;34:1131-1133.
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IL-6. Patients with bulky disease and comorbidities are at increased risk of CRS development. Based on underlying mechanisms, anti-IL-6 receptor agents (eg, tocilizumab, siltuximab) represent the cornerstones in the management of severe CRS. ICANS has a less understood pathogenesis and may be characterized by confusion, ataxia, aphasia, seizures, and cerebral edema or increased intracranial pressure.[146] Anti-IL-6 agents and corticosteroids are also effective tools in reversing ICANS. Tebentafusp-tebn can cause skin toxicity (dry skin, rash) as a result of targeting of gp100-positive melanocytes. These adverse events decrease in frequency and severity after the initial doses of tebentafusp-tebn.

Amivantamab, an EGFR and mesenchymal-epithelial transition factor (MET) bispecific antibody, is approved for patients with exon 20 insertion–positive NSCLC as monotherapy after progression during or in combination with platinum-based chemotherapy.[147,148] It is also approved in combination with lazertinib as first-line treatment for patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.[149] Amivantamab leads to tumor regression by simultaneous inhibition of the EGFR and MET pathways as well as ADCC.[150] The most common adverse reactions to amivantamab monotherapy are rash, infusion-related reactions, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting.[147] The addition of amivantamab to chemotherapy increases skin toxicities (paronychia, rash), diarrhea, infusion-related reactions, and neutropenia.[148] Note that the dosing recommendations of amivantamab are different when used as monotherapy versus in combination with platinum-based chemotherapy.

KEY POINTS

- Bispecific T-cell engagers have been developed to simultaneously bind a tumor cell to an immune effector cell, leading to tumor cell lysis.
- Amivantamab is a bispecific antibody that simultaneously targets and downregulates both the EGFR and MET pathways, leading to cell death.

CELLULAR THERAPY

Adoptive cell therapy refers to the infusion of immune cells that have been expanded or engineered ex vivo. A variety of immune effector cells have been explored for adoptive cellular therapy and tested in clinical trials. Early efforts examined the infusion of

lymphokine-activated killer cells, which had little activity and required coadministration of high-dose IL-2 to maintain it. Initial studies of patients with advanced melanoma and renal cell carcinoma demonstrated antitumor activity. Comparable results, however, were subsequently seen with high-dose IL-2 alone. Methods of generating antitumor CTLs by culturing peripheral blood, lymph nodes, or tumor-infiltrating lymphocytes (TILs) with cytokines and tumor antigens ex vivo have also been evaluated clinically over the last 2 to 3 decades. Response rates of 50% or higher among selected patients with metastatic melanoma accompanied by long progression-free survival were observed with the infusion of TILs in nonrandomized studies, which served as important proof of principle for the antitumor potency and durable responses possible with this approach.[151] Treatment with TILs is superior to ipilimumab in regard to progression-free survival in patients with advanced melanoma with prior anti-PD-1 therapy in a randomized phase 3 clinical trial.[152]

CHIMERIC ANTIGEN RECEPTOR AND TCR-MODIFIED T CELLS

Chimeric antigen receptors (CARs) are composed of an extracellular immunoglobulin-derived antigen recognition domain, a transmembrane domain, and an intracellular T-cell signal domain that includes a CD3 complex–derived chain and costimulation signaling domains (eg, CD28, 4-1BB). CARs redirect T-cell specificity toward antibody-recognized surface antigens and are not MHC restricted. CAR T cells targeting CD19 have demonstrated significant activity in refractory B-cell malignancies.[153,154] Similarly, CAR T cells targeting BCMA are approved for the treatment of relapsed or refractory myeloma.[155,156] The results from first-generation CAR T cells in solid tumors are not as encouraging, with the exception of the GD2-targeting CAR T cell for neuroblastoma.[157] TCR-modified T cells have demonstrated activity in the treatment of solid tumors (including melanoma and sarcomas) as well as hematologic malignancies (eg, acute myeloid leukemia),[158] but are structurally dependent on HLA type and antigen expression on the MHC molecules of the target cell.[159,160]

Adoptive transfer of expanded and activated effector cells is not limited to engineered T cells. NK cells are also being tested, particularly allogeneic NK cells that are engineered for high effector function.[161,162] Adoptive cellular therapy with ex vivo expanded autologous TILs is approved for patients with refractory melanoma.[163,164] Sipuleucel-T is an autologous cellular immunotherapy derived from peripheral blood mononuclear cells that are cultured ex vivo with PA2024, a fusion protein consisting of prostatic acid phosphatase and GM-CSF. It is approved for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.[164,165] The approach is designed for the GM-CSF portion of the fusion molecule to activate blood monocytes and APCs to present prostatic acid phosphatase as a tumor antigen.[164,165] Because the clinical benefit is very modest, current investigations are testing sipuleucel-T as neoadjuvant therapy[166] or in combinations.[167]

The toxicities of adoptive T-cell therapies can be severe and include B-cell aplasia (for B-cell-targeting T-cell therapies), CRS, and ICANS. The cytokine secretion in CRS can be due to tumor target recognition and response or off-target/off-tumor responses, which can be due to nontumor expression of the target antigen or to unexpected mimicry of the target by a highly related gene.[168] Anti-IL-6 agents and corticosteroids represent the cornerstones in the management of CRS occurring after CAR T-cell therapy. ICANS has a less understood pathogenesis and may be characterized by confusion, ataxia, aphasia, seizures, and cerebral edema or increased intracranial pressure.[146]

DONOR LYMPHOCYTE INFUSION

Cells infused in allogeneic hematopoietic stem cell transplantation represent an effective adoptive cellular therapy in clinical use. An allogeneic graft-versus-leukemia effect, which is a restricted form of graft-versus-host disease, has been suggested by the increased relapse rate for recipients of T-cell–depleted allografts, higher relapse rates after either syngeneic or autologous transplantation, and lower frequency of relapse for patients who develop graft-versus-host disease. Given these clinical observations, donor leukocyte infusion was tested among patients whose hematologic malignancies relapsed after allogeneic transplantation. Numerous reports have documented the success of donor leukocyte infusion for patients with chronic myeloid leukemia; the majority of these patients achieved durable complete molecular remission.[169] Acute myeloid leukemia has only modest response rates, and ALL rarely responds. Donor leukocyte infusion can also eradicate Epstein-Barr virus–associated post-transplantation lymphoproliferative disease after allogeneic transplantation. More recent studies have identified potential target antigens among patients responding to donor leukocyte infusion. The major drawback of donor leukocyte infusion is graft-versus-host disease, which is a major cause of transplantation-related mortality, and methods of promoting the graft-versus-leukemia effect over graft-versus-host disease are under active investigation. New investigational approaches aimed at improving the efficacy of donor leukocyte infusion include priming of donor lymphocytes to recipient tumor antigens ex vivo and infusions of alloreactive NK cells.

KEY POINTS

- Many cells of the immune system generated and/or modified ex vivo can be administered to an individual to induce an antitumor immune response.
- The use of reprogrammed CAR- and TCR-modified T cells has produced robust results in hematologic malignancies; nevertheless, the applicability of these approaches remains restricted to specialized centers, and toxicities can be limiting.

- Toxicities resulting from CAR T-cell therapies include CRS and ICANS and may require directed approaches that include the use of anti-IL-6 and anti-IL-6 receptor agents.
- Autologous cell immunotherapies and donor leukocyte infusion after allogeneic hematopoietic stem cell transplantation are examples of cellular therapies in clinical use and under active investigation.

ONCOLYTIC VIRUSES

Oncolytic viruses are emerging as important agents in cancer treatment.[170] They offer the attractive therapeutic combination of tumor-specific virus infection and replication (leading to tumor cell lysis) together with immune stimulation from the viral pathogen signals, thereby acting as potential in situ tumor vaccines. Talimogene laherparepvec (T-VEC) is a genetically engineered attenuated herpes simplex virus. It is approved for cutaneous melanoma with dermal/cutaneous mets amenable to intratumoral injection. T-VEC invades cancerous and healthy cells but can only replicate in cancer cells, where it secretes GM-CSF in the process. T-VEC kills tumor cells by direct oncolysis. In addition, the virus-produced GM-CSF recruits and activates dendritic cells, which process and present these antigens to T cells, thereby promoting a tumor-specific adaptive immune response. T-VEC is approved for the treatment of melanoma.[171] Most adverse events included constitutional symptoms and injection site reactions.[172]

KEY POINTS

- Oncolytic viruses are wild-type or genetically modified viruses that can selectively kill tumor cells via cell lysis (direct antitumor effect) or via the activation of antitumor immune responses.
- The efficacy of oncolytic viruses as single agents is limited.

PRESENTING CASE STUDY

A 70-year-old man presents to the clinic with hematuria. Cystoscopy reveals a bladder mass, and biopsy confirms high-grade urothelial cancer. CT scan shows multiple enlarged abdominal and pelvic lymph nodes and liver metastases. Liver biopsy indicates metastatic cancer consistent with urothelial primary. The patient's Eastern Cooperative Oncology Group performance status is 1; he is experiencing mild fatigue and weakness but is otherwise healthy and active. His creatinine clearance is 80 mL/min, and his hypertension is well controlled on current medication. He has no history of diabetes or coronary arterial disease.

The patient begins treatment with a combination of enfortumab vedotin, a nectin-4-targeted antibody-drug conjugate, and pembrolizumab, a PD-1 immune checkpoint inhibitor. He tolerates the first two cycles well, and CT demonstrates evidence of tumor response. After the third cycle, the patient is hospitalized for severe weakness and dizziness. His blood pressure is 80/50 mm Hg with tachycardia, and a rash with scattered ill-defined scaly erythematous papules on his chest, arms, and thighs is identified on physical examination. Laboratory values are as follows: sodium, 128 mEq/L; potassium, 5.6 mEq/L; creatinine, 5.8 mg/dL; and glucose, 722 mg/dL. Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin levels are within the upper reference limit. He has a leukocyte count of 5,800/μL, hemoglobin level of 10.2 g/dL, and platelet count of 165,000/μL. The patient's differentials are within the upper reference limit.

After initiating enfortumab vedotin and pembrolizumab for this patient, what key clinical factors and potential risks, specifically regarding overlapping toxicities, would you consider? How would you plan for early detection and management?

This case exemplifies the overlapping toxicities of enfortumab vedotin (hyperglycemia and rash) and pembrolizumab (immune skin toxicity, immune nephritis, and type 1 diabetes mellitus induced by immunotherapy). Renal dysfunction can be related to dehydration and hyperglycemia or could be an immune-related adverse event of nephritis.

The patient's hyperglycemia should be treated with insulin and hydration; however, if the renal dysfunction and/or rash presentation is related to pembrolizumab, then intervention with steroids is required. It is not possible in the initial presentation stages to clearly separate the cause of the toxicities. As a result, it is important to consider steroid therapy such as prednisone at a minimum dose of 1 to 2 mg/kg despite the patient's hyperglycemia and taper gradually as the condition reverses.

The patient responds well to the steroids and supportive care, and his rash improves. His glucose level returns to normal, and he is monitored on insulin therapy.

Rechallenge Decision

If a patient is in remission, ongoing observation and surveillance for cancer progression may be considered. If repeat therapy is initiated, it is advisable to start with a reduced enfortumab vedotin dose for one cycle and evaluate the patient's tolerability. If the patient tolerates treatment well, therapy can be continued, and pembrolizumab resumption can be reconsidered at a later date with precautions for close monitoring of renal function and for skin rash.

HIGH-YIELD TAKEAWAYS

- The main types of biologic anticancer therapies are as follows: cytokines, antibodies, viral oncolytic, immune checkpoint therapies, ADCs, bispecific T-cell engagers/T-cell engagers, and cellular therapies.
- Immunotherapy is rapidly becoming the backbone of cancer therapy and has the potential to induce long-term remissions.
- Immune checkpoint therapies have been proven to be safe to use in HIV, HBV, and HCV patients with careful monitoring. Antiretroviral therapy should be continued in HIV patients.
- Immune checkpoint therapies have adverse effects that can occur anytime during therapy and can impact any system within the body. These side effects can be severe and life-threatening, so immunosuppressive therapy should be used to reverse the toxicities.
- CAR T-cell therapies have demonstrated efficacy and are indicated in hematologic malignancies.
- MSI-H or dMMR status is a predictive biomarker for benefit from ICIs in all cancer types.

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We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

PRINCIPLES OF IMMUNO-ONCOLOGY AND BIOLOGIC THERAPY

4

CHAPTER SUMMARY GUIDE

KEY POINTS

- Cells of the antigen-nonspecific innate and antigen-specific adaptive immune systems contribute to antitumor immunity.
- Immune responses are highly regulated to maintain tolerance to self and limit immune-mediated damage to normal tissues.
- This continuous interaction between tumor cells and immune cells is characterized as immune surveillance and immunoediting. Immune surveillance has three phases: elimination, equilibrium, and escape.
- Immune cells can have both antitumor and tumor-promoting effects.
- The interaction between tumor and immune cells is bidirectional.
- Tumors can subvert the immune response by stimulating the production of immune cell factors that promote angiogenesis, invasion, and metastasis.
- Immune cell cytokines may also function as tumor growth factors.
- T cells recognize antigens presented to their TCRs as peptide fragments within MHC molecules (MHC restriction). T-cell activation requires stimulation not only through the TCR but also through immune costimulatory receptors.
- Interactions with coinhibitory receptors on T cells, referred to as immune checkpoints, suppress unwanted and harmful self-directed immune activities as well as antitumor immune responses.
- Recognition of tumor cells by the immune system can be influenced by a variety of factors, including the tumor's intrinsic antigenic potential (eg, mutational burden and neoantigen signature, strength of immunogenicity of tumor antigens), pre-existing host immune condition, and products of genomic aberrations that affect pathways driving the immune response.
- Th cells promote Th1-associated immune responses (antitumor) through the production of cytokines, such as IFN-γ and IL-2, and promote Th2-associated immune responses (tumor promoting) through the production of cytokines, such as IL-4 and IL-5.
- CTLs and NK cells kill tumors by apoptosis through granule exocytosis and Fas-mediated mechanisms.
- DCs are the most efficient APCs.
- Several lymphoid and myeloid cell populations suppress immune responses, including TAMs, Tregs, and MDSCs.
- Although immune checkpoints are necessary to prevent unchecked autoimmunity, tumors can co-opt these mechanisms to escape immune-mediated elimination.
- Cancer evasion of the immune system results not only from immunosuppressive factors secreted by or expressed on the tumor but also from the ability of the tumor to modulate antigen expression and be endowed with or later develop mechanisms of resistance to immune effectors.
- The recognition of evasion mechanisms involved in tumor immune escape can be exploited therapeutically.
- Cytokines are cell-to-cell signal mediators designed to act locally, but are detectable systemically, and can enhance the activity of antitumor immune effector cells.
- Monoclonal antibodies can mediate antitumor activity through immune mechanisms and nonimmune mechanisms (eg, direct induction of apoptosis, interference with target signaling).
- Because of infusion reactions, premedication is required for treatment with many monoclonal antibodies.
- Unique and often severe organ toxicity related to the molecule being targeted can be seen.
- Pulmonary toxicity is an uncommon but very serious adverse event from some ADCs.
- Immune checkpoint blockade with antibodies against CTLA-4, PD-1, PD-L1, and LAG-3 is an effective method for reversing cancer immunosuppression and promoting immune responses against several cancer types.

- Checkpoint inhibition is associated with a unique spectrum of adverse events called irAEs, which can occur unpredictably and have the potential to affect any organ system.
- The combination of ICIs (anti-PD-1 in combination with anti-CTLA-4 agents or LAG-3) may result in improved response rates and disease control at a cost of greater toxicity. However, increased incidence of long-term remission is reported in some malignancies such as metastatic melanoma.
- ICIs can be safely combined with other therapeutics, including chemotherapy, ADCs, and small-molecule inhibitors, and lead to increased response in several cancer types.
- ICIs can be safely administered in patients with HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) with careful monitoring. Antiviral therapy should be initiated before treatment if possible.
- Treatment with ICIs in patients with underlying autoimmune disease can lead to disease flare. Treatment with ICIs can be considered in these patients after shared decision-making and after the autoimmune disease is optimized while minimizing immunosuppressive medication exposure.
- Bispecific T-cell engagers have been developed to simultaneously bind a tumor cell to an immune effector cell, leading to tumor cell lysis.
- Amivantamab is a bispecific antibody that simultaneously targets and downregulates both the EGFR and MET pathways, leading to cell death.
- Many cells of the immune system generated and/or modified ex vivo can be administered to an individual to induce an antitumor immune response.
- The use of reprogrammed CAR- and TCR-modified T cells has produced robust results in hematologic malignancies; nevertheless, the applicability of these approaches remains restricted to specialized centers, and toxicities can be limiting.
- Toxicities resulting from CAR T-cell therapies include CRS and ICANS and may require directed approaches that include the use of anti-IL-6 and anti-IL-6 receptor agents.
- Autologous cell immunotherapies and donor leukocyte infusion after allogeneic hematopoietic stem cell transplantation are examples of cellular therapies in clinical use and under active investigation.
- Oncolytic viruses are wild-type or genetically modified viruses that can selectively kill tumor cells via cell lysis (direct antitumor effect) or via the activation of antitumor immune responses.
- The efficacy of oncolytic viruses as single agents is limited.

Table 4-1 **Clinical Applications of Immunotherapy and Biologic Therapy**

Biologic Agent	Examples of Agents and Common Indications	Mechanism of Action	Significant Adverse Effects
Cytokines	Interleukin-2 (melanoma, renal cell carcinoma)[15-20]	T- and NK-cell activation/ stimulation	Fever, chills, hypotension, capillary leak syndrome
	Interferon-α (hairy cell leukemia)[21]	Upregulation of MHC type I, NK-cell stimulation, antiproliferative, and antiangiogenesis	Fever, chills, myalgia, fatigue, depression, liver dysfunction, and myelotoxicity
	Filgrastim/pegfilgrastim (prevention of neutropenic fever)	Induction of the production and release of neutrophils from the bone marrow enhances their functional capacity in the periphery	Bone pain, local skin reactions
Unconjugated monoclonal antibodies[22]	Bevacizumab* (colorectal cancer) Ramucirumab** (colorectal and gastric/ gastroesophageal cancer) [23,24]	Anti-VEGF/VEGFR	Hypertension, proteinuria, wound healing complications, thromboembolic events, bleeding, and reversible posterior leukoencephalopathy[25]
	Cetuximab (RASwt and $KRAS^{G12C}$ colorectal cancer in combination with adagrasib; head and neck cancer)[26-29] Panitumumab (RASwt and $KRAS^{G12C}$ colorectal cancer in combination with sotorasib)[27,30-32]	Anti-EGFR, CMC, ADCC	Acneiform rash, infusion-related reaction, hypomagnesemia
	Zolbetuximab (gastric and gastroesophageal cancer)[33,34]	Anti-Claudin 18.2, ADCC, CMC	Nausea, vomiting, anorexia
	Rituximab (B-cell NHL)[35] Ofatumumab*** (CLL)[36] Obinutuzumab**** (CLL, follicular lymphoma)[37-39]	Anti-CD20, CMC, ADCC	Infusion-related reaction, hypogammaglobulinemia, progressive multifocal leukoencephalopathy,[40] and HBV reactivation[41,42]
	Tafasitamab***** (follicular lymphoma, diffuse large B-cell lymphoma)	Anti-CD19, ADCC, ADCP	Neutropenia, fever, infection, and diarrhea
	Daratumumab# (myeloma)[43-45]	Anti-CD38, CMC, ADCC	Infusion-related reaction, fatigue, nausea, fever, and respiratory symptoms
	Elotuzumab# (myeloma)[46]	Anti-SLAMF7, ADCC	Infusion-related reaction, infections, hepatotoxicity, and secondary primary malignancies
	Trastuzumab^ (breast, colorectal, gastric cancer, endometrial cancer)[47-50] Pertuzumab^^ (breast cancer)[51,52]	Anti-HER2, CMC, ADCC	Cardiotoxicity and hypersensitivity reactions

Biologic Agent	Examples of Agents and Common Indications	Mechanism of Action	Significant Adverse Effects
Immune checkpoint inhibitors	Pembrolizumab (melanoma, renal, lung cancer, MSI-H cancers, esophageal cancer, and biliary cancer)[47,53-60] Nivolumab (melanoma, renal, lung cancer, hepatocellular carcinoma, MSI-H colorectal cancer, and esophageal cancer)[55,61-68] Penpulimab (nasopharyngeal carcinoma)[69] Retifanlimab (anal cancer)[70] Toripalimab (nasopharyngeal)[71]	Anti-PD-1	Fatigue, pruritus, rash, diarrhea, and arthralgia; immune-related toxicities can be seen at any organ system Most common: (1) thyroid dysfunction, (2) adrenal insufficiency, (3) pneumonitis, (4) colitis, (5) dermatitis, and (6) arthritis Less common: (1) nephritis, (2) hepatitis, (3) hypophysitis, (4) encephalitis, (5) neuritis, (6) myositis, (7) uveitis, and (8) mucositis
	Durvalumab (hepatocellular carcinoma, lung, biliary cancer, and bladder)[72-76] Atezolizumab (hepatocellular carcinoma)[77] Avelumab (bladder cancer)[78] Cosibelimab (cutaneous squamous cell carcinoma)	Anti-PD-L1	
	Ipilimumab (lung cancer, melanoma, renal cell carcinoma, hepatocellular carcinoma, and MSI-H colorectal cancer)[61-66] Tremelimumab (hepatocellular carcinoma)[72]	Anti-CTLA-4, ADCC[79]	
	Relatlimab (melanoma)[80]	Anti-LAG-3	

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cell-mediated phagocytosis; CLL, chronic lymphocytic leukemia; CMC, cell-mediated cytotoxicity; CTLA-4, CTL antigen 4; EGFR, epidermal growth factor receptor; Fc, fraction-crystallizable; HBV, hepatitis B virus; HER2, human epidermal receptor 2; LAG-3, lymphocyte activation gene 3; MHC, major histocompatibility complex; MSI-H, microsatellite instability-high; NHL, non-Hodgkin lymphoma; NK, natural killer; VEGF, vascular endothelial growth factor.

*Bevacizumab targets VEGF-A.

**Bamucirumab targets VEGFR-2.

***Ofatumumab binds to both the small and the large loops of the CD20 molecule on B cells. Its location is closer to the membrane, which, in theory, allows for more effective complement deposition and subsequent B-cell killing. Preclinical data have suggested improved CMC and ADCC compared with rituximab.

****Obinutuzumab is a humanized anti-CD20 monoclonal antibody that has been glycoengineered to reduce core fucosylation, conferring enhanced affinity for the human FcγRIIIa receptor on effector cells and, hence, enhanced ADCC. As a type 2 monoclonal antibody, obinutuzumab has a lower capacity to relocalize CD20 into lipid rafts upon binding, compared with the type 1 antibodies rituximab and ofatumumab, and is less potent in inducing CMC. It is, however, more potent in mediating cell adhesion and direct cell death. Obinutuzumab and rituximab bind adjacent and partially overlapping epitopes on CD20 but acquire different orientations upon binding, which most likely contributes to the different biologic characteristics of type 1 and 2 antibodies.

*****Tafasitamab is a humanized engineered anti-CD19 monoclonal antibody, which incorporates S239D and I332E mutations into the Fc region of humanized anti-CD19 immunoglobulin G, enhancing its affinity for FcγRIIIa and subsequently ADCC and increased ADCP.

#Use of monoclonal antibodies in myeloma can interfere with the usual assays used to monitor M-protein.

^Trastuzumab targets the HER2 extracellular domain epitope IV.[81]

^^Pertuzumab targets the HER2 extracellular domain near the junction of domains I, II, and III.[82]

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Table 4-2 **Positive and Negative Immune Checkpoints**	
Costimulatory Receptors	**Coinhibitory Receptors**
CD28	CTLA-4 (CD152)
4-1BB (CD137)	PD-1 (CD279)
CD27	BTLA (CD272)
CD40L (CD154)	LAG-3 (CD223)
OX40 (CD134)	TIM-3 (CD366)
ICOS, (CD278)	PD-1H (VISTA)
GITR (TNFRSF18)	CD160
	CD244 (NK-cell receptor 2B4)
	TIGIT (CD)

Abbreviations: BTLA, B- and T-cell attenuator; GITR, glucocorticoid-induced tumor necrosis factor (TNF) receptor-related protein; ICOS, inducible T-cell costimulatory; LAG-3, lymphocyte activation gene 3; NK, natural killer; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domains; TIM-3, T-cell immunoglobulin and mucin-domain containing 3; VISTA, V-domain immunoglobulin suppressor of T-cell activation.
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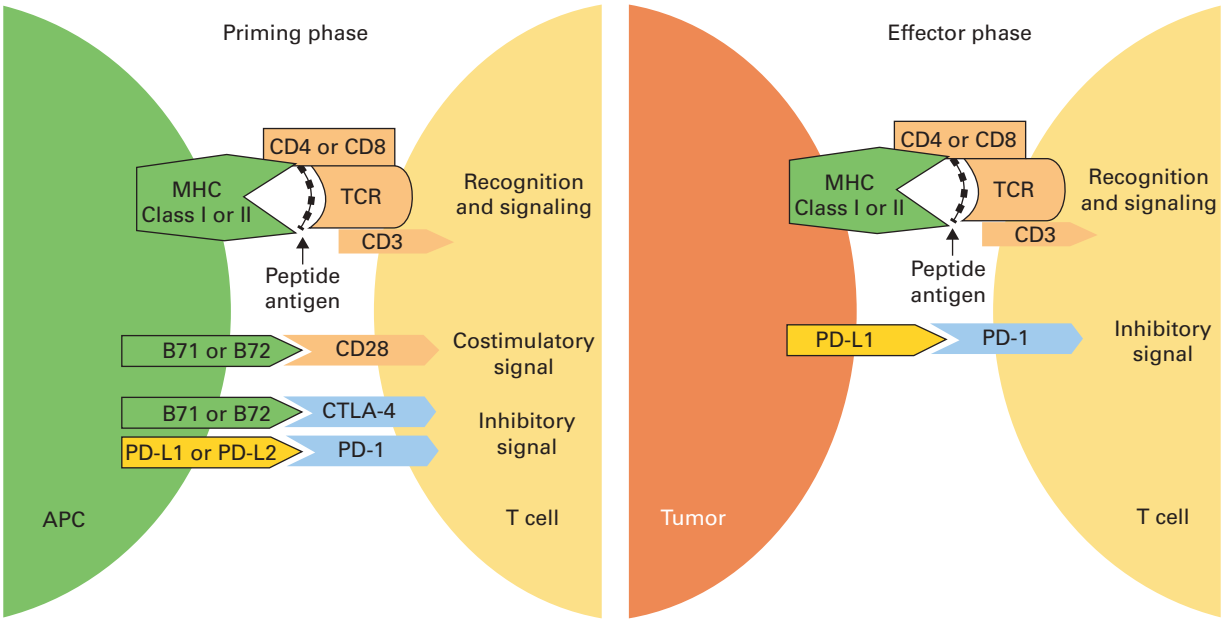
Figure 4-1 Regulation of T-Cell Priming and Effector Function



During the priming phase of T-cell activation, antigens are presented to T cells through the TCR as peptide fragments within MHC molecules on APCs. The primary costimulatory signal is delivered through the CD28 receptor on the T cell after engagement of its ligands B7-1 or B7-2 on the APC. Fully effective engagement also depends on interactions among several other molecules, such as adhesion molecules (not shown). Failure of the costimulatory B7/CD28 complex to be engaged results in either a nonactivated T cell or anergy. Engagement of CTLA-4 on the T cell by the same B7-1or B7-2 ligands results in inhibition of the response. Similarly, engagement of the PD-1 receptor with one of its two ligands, PD-L1 or PD-L2, on APCs also results in inhibition of the response. PD-L1 is also expressed by tumors. During the effector phase, engagement of PD-1 on the activated T cell by PD-L1 on the tumor results in inhibition of T-cell function.

Abbreviations: APC, antigen-presenting cell; CTLA-4, CTL antigen 4; MHC, major histocompatibility complex; TCR, T-cell receptor.

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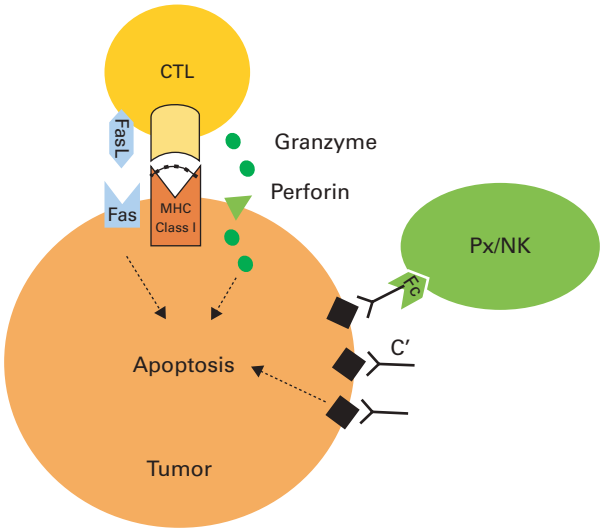
Figure 4-2 Mechanisms of Cell Killing by CTLs and Antibodies



After attaching to the MHC-peptide complex, CTLs discharge cytoplasmic granules containing perforin and granzymes by exocytosis. Perforin molecules insert themselves into the plasma membrane of target cells, which enables granzymes to enter the cell. Granzymes are serine proteases that, once inside the cell, activate caspases that cause the cells to undergo apoptosis. When CTLs bind to their target, they also upregulate Fas ligand on their surface, which binds with the Fas receptor on the surface of the target cell, leading to its death (also by apoptosis). Antibodies recognize an antigen in its native conformation. After binding, when a complement-reactive site on the antibody is present, a cascade of reactions can be set into motion, including the activation of many molecules of the complement system, which, in turn, activate increasing amounts of a series of enzymes that ultimately result in complement-dependent cytotoxicity. A product of the complement cascade also strongly activates phagocytosis by macrophages and neutrophils. These phagocytes, as well as natural killer (NK) cells, bind their Fc receptor (CD16) to the antibody and destroy the ADCC. Antibody-recognizing cell surface molecules that regulate cell signaling or growth can directly elicit apoptosis. Antibody binding can also block receptor-ligand binding and natural downstream signaling.
Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; C′, complement; CTL, cytotoxic T-cell lymphocyte; Fc, fraction-crystallizable.
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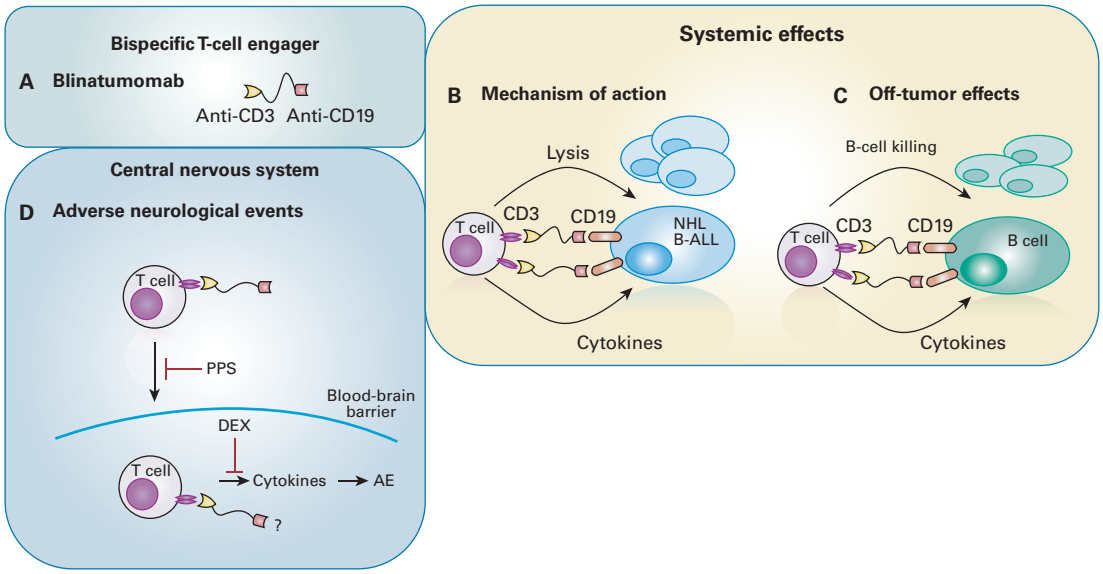
Figure 4-3 Bispecific T-Cell Engagers as Treatment of B-Cell Lymphoma



Activity of the bispecific T-cell engager blinatumomab (A). This bispecific T-cell engager protein can connect a T cell and (B) a CD191 tumor cell or (C) a CD191 B cell by simultaneously binding CD3 and CD19. When both single-chain variable fragments bind to their target antigens, T-cell activation is triggered, which leads to the release of cytotoxic granules and cytokines (eg, IFN). Lysis of the tumor cell or B cell involves membrane perforation followed by programmed cell death induced by granzymes. Bispecific T-cell engagers trigger serial killing by activated T cells. (D) Approaches to limit adverse neurologic events caused by blinatumomab treatment include the blocking of activated T-cell migration into the CNS through PPS treatment or the reduction of cytokine activity through the use of corticosteroids, such as DEX. Which cells blinatumomab may recognize in the CNS (eg, tumor cells) is unknown, but the adverse effects resolve when treatment is discontinued.

Abbreviations: AE, adverse event; B-ALL, B-cell acute lymphoblastic leukemia; CNS, central nervous system; DEX, dexamethasone; NHL, non-Hodgkin lymphoma; PPS, pentosan polysulfate.

Data reproduced from Smits NC, Sentman CL. Bispecific T-cell engagers (BiTEs) as treatment of B-cell lymphoma. *J Clin Oncol*. 2016;34:1131-1133.

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CLINICAL TRIALS AND BIOSTATISTICS

5

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OVERVIEW

Clinical trials are the foundation for the development of novel drugs, interventions, and devices for the treatment, diagnosis, and prevention of diseases in humans. The primary objective of a study is the principal clinical research question framed as a scientific hypothesis to be investigated and tested using prospective clinical data. The study outcome is defined by the measured variables (eg, change in tumor burden per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) collected during the study. The endpoint is computed from the measured outcome. The primary endpoint should be clinically relevant, objectively measurable, and interpretable; sensitive to the effects of an intervention; and central to the sample size calculation required to detect a clinically meaningful effect size. For example, a study might be undertaken to assess the efficacy of a particular drug in a specific cancer type (objective), using tumor measurements (outcome) to estimate tumor response (endpoint).

The objectives, outcome measures, and endpoints of a particular clinical trial will be dictated by the type of clinical trial under consideration. To ensure confidence at the conclusion of a study, the effect of the study intervention must be measured with minimal bias and reasonable variation. Essential in achieving this goal are many fundamental clinical trial design features and biostatistical approaches described and discussed in this chapter.

Development of the clinical trial design is an iterative collaboration between the clinical investigators and the trial statistician. This process includes determinations regarding the selection of appropriate endpoints, control comparators, use of randomization, power analysis and sample size calculation, and feasibility and evaluation of various possible trial design options. Both clinical and statistical input are critical during trial design to ensure that research questions are well formulated and can be answered by the clinical trial.

STUDY OBJECTIVES

The primary objective of a clinical study is the principal clinical research question. A well-defined study question allows for specific hypothesis testing that can be quantified. Secondary research questions, often included in many studies, do not generally dictate statistical design considerations. When multiple outcomes are considered of primary importance, for example, progression-free survival (PFS) and overall survival (OS) in cancer, coprimary endpoints can also be used.

HYPOTHESIS TESTING

Hypothesis testing is used to determine whether there is evidence from the sample data to conclude that the underlying populations differ. For example, a researcher might be interested in knowing whether the survival distribution of patients treated with two distinct treatments differs. If there is evidence from the sample data that the difference in survival distribution between the groups is not 0 (on a log scale), it might be concluded that one treatment is better than the other. Hypothesis testing evaluates the amount of evidence in a sample and determines whether there is a statistically significant difference between groups, considering measures such as median survival or OS distribution, often summarized by the hazard ratio (HR). Many aspects of clinical trial design are framed in terms of hypothesis testing (Table 5-1).

Table 5-1 **Hypothesis Test Decisions and Error Types**

		Truth Based on Population (Universe)	
		Null Hypothesis Is True	**Null Hypothesis Is False**
Decision based on sample (data)	Reject the null hypothesis	Type I error	Correct decision (power)
	Do not reject the null hypothesis	Correct decision	Type II error

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A statistical hypothesis test involves three components:

1. Formulation of the null and alternative hypotheses
2. Collection and analysis of data from a sample
3. Decision to either reject or not reject the null hypothesis (the phrase "do not reject" instead of the term "accept" is deliberate)

The null hypothesis (H0) is not the same as a scientific hypothesis and is often framed as the hypothesis of no difference in the parameter of interest.

The alternative hypothesis often reflects the scientific question and can be either a two-tailed (all possible values of the parameter of interest are considered except the null) or a one-sided alternative (the parameter of interest will vary from the null in only one direction). For example, in a trial of a new therapy, the scientific belief or hypothesis is likely that the new therapy will be more efficacious than the currently used standard therapy. However, the null hypothesis would be that the new therapy has the same efficacy as the standard therapy. In the clinical trial setting, the desired scientific outcome is usually to reject the null hypothesis. The amount of evidence against the null hypothesis is determined from the observed sample data. It is done this way because the null hypothesis is specific, so we can quantify the level of evidence with the *P* value, as described later. In contrast, the scientific hypothesis is not specific, meaning that it merely states that the new therapy is more efficacious than the standard therapy; it does not state how efficacious the new therapy is. Given the vagueness, it is not possible to quantify the evidence that supports this hypothesis. Therefore, we determine the evidence against the null hypothesis rather than the evidence for the alternative (ie, the scientific) hypothesis.

Two types of errors are possible when testing a hypothesis (Table 5-1). Type I error occurs when the null hypothesis (no difference between groups) is true but is rejected. The type I error rate, α, is the probability of making this type of error and arriving at a false-positive conclusion that the treatment groups are different when in reality they are not. On the other hand, a type II error occurs when the null hypothesis is not rejected when in fact it is not true (treatment groups are different). The type II error rate, β, is the probability of arriving at a false-negative conclusion that the treatment groups are not different when they actually do.

- Type I error rate (α): probability of rejecting the null hypothesis when the null hypothesis is true
- Type II error rate (β): probability of not rejecting the null hypothesis when this hypothesis is not true

What is more commonly of interest is the probability of correctly rejecting the null hypothesis when the alternative hypothesis is true, which is called power ($1 - \beta$).

Hypothesis tests require the calculation of a test statistic using sample data corresponding to one or more different groups (eg, different treatments). The computation of a test statistic and the associated *P* value differs by the type of trial endpoint, and the analysis is often performed using statistical software. Parametric tests are derived using a specific assumption about the distribution of the data within the population (eg, normal, binomial, exponential), whereas nonparametric tests make fewer assumptions. Although the latter feature is desirable, a nonparametric test will generally have less statistical power than a parametric test that is correctly matched to a specific distribution. These considerations usually become less important with the increasing sample size (eg, n ≥ 30 per group is widely used as the threshold). For large samples, the choice between a parametric or nonparametric test is less critical; for smaller ones, it is recommended that the investigator consult with a biostatistician about the most appropriate test (Tables 5-2 and 5-3).

Table 5-2 Choosing a Statistical Analysis Approach

Endpoint Type	One Predictor	Multiple Predictors or a Single Continuous Predictor
Binary (yes vs no)	χ^2 test or Fisher exact test	Logistic regression
Time to event	Log-rank test	Cox proportional hazards regression
Continuous	*t* test or Wilcoxon test	Linear regression
Paired/correlated data	Continuous: paired *t* test or signed rank test; binary: McNemar test	Mixed models or generalized mixed models
Categorical or ordinal	χ^2 test or Fisher exact test	Multinomial regression or proportional odds regression
Count data	Poisson or negative binomial regression	Poisson or negative binomial regression

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Table 5-3 **Description of Common Statistical Tests**

Outcome	Setting	Test	Definition and Description
Continuous	Comparing means	Two-sample *t* test	Used to compare means between two groups for a quantitative variable; normal distribution and equal variance in each group are assumed; an unequal variance *t* test can be used if unequal variances are expected in the two groups; generally robust to small sample size and nonnormal distributions, but sensitive to outlying values, which inflate estimates of variability
		Paired *t* test	Used to compare paired quantitative data; for example, a paired *t* test can be used to determine whether there is a nonzero change in a quantitative characteristic measured before and after treatment in each patient; same sensitivity to outlying values as the two-sample *t* test
Continuous	Comparing medians or distributions	Wilcoxon rank sum (Mann-Whitney)	Nonparametric alternative to the two-sample *t* test; less sensitive to outlying values than the two-sample *t* test, although can be somewhat more conservative compared with *t* test (eg, if the data are normally distributed)
		Wilcoxon signed rank	Nonparametric alternative to the paired *t* test; less sensitive to outlying values than the paired *t* test, although somewhat more conservative
Binary	Comparing proportions	χ^2	Used to compare proportions between two or more groups; fairly robust to small sample sizes, unless there is an imbalance between groups
		Fisher exact	Used to compare proportions with small sample sizes; a commonly used rule of thumb is to use the Fisher exact test if <5 observations are expected in any of the cells of a contingency table; this test may be somewhat more conservative compared with the χ^2 test
		McNemar	Used to compare paired proportions; for example, a binary characteristic assessed before and after treatment in each patient; it is based only on the discordant pairs (where outcome is different) and is not used to assess concordance
Time to event	Comparing survival distribution	Log rank	Used to compare survival distributions between two or more groups; also, the Kaplan-Meier approach is used to estimate the survival distribution (curve)

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OUTCOME MEASURES

The primary outcome is the measure that the clinical trial design team considers the most efficient or important for answering the scientific hypothesis. The primary outcome is determined at the planning stage of the trial and forms the basis for computing the sample size. The primary outcome needs to be defined a priori on the basis of assumptions or empirical evidence. A single primary outcome is typically designated to protect against the risk of an inflated false-positive error arising from the application of statistical tests to a large number of trial outcomes (endpoints) and/or the selection of the most favorable findings.

As an example, an investigator plans to evaluate a new therapy in patients with a particular malignancy. The investigator decides the new therapy will be administered to patients, and tumor measurements, toxicity, biomarkers, and patient-reported outcomes will be collected. All of these are outcome measures or dependent variables. The investigator decides that the tumor measurements are the primary outcome measure, keeping the other variables as secondary or exploratory outcomes. Using changes in tumor burden measurements, the investigator could consider estimating the objective response rate (ORR) as a result of the intervention or estimating PFS. On the basis of the selection of the ORR or PFS, the sample size will likely differ, and one of

these results will be the primary determinant of whether the study is considered a success or failure. The remaining assessments are hierarchically less important and are designated secondary or exploratory outcomes.

In cancer studies, OS is generally the primary outcome of interest, but in cancers with better prognosis or earlier lines of treatment it may take a long time to observe and can be influenced by subsequent therapies. As a result, intermediate endpoints such as best overall tumor response or PFS are often used because they can be assessed earlier and are believed to correlate with clinical benefit and OS although in many disease settings these associations may be weak or absent.

Formally, a surrogate endpoint is defined as a substitute for a direct measure of the primary endpoint of interest (ie, OS) and is expected to predict clinical benefit but does not measure it directly. To formally establish endpoint surrogacy, rigorous statistical validation is required, which often involves demonstrating a high correlation between the surrogate endpoint and OS at the individual level, as well as a high concordance between the treatment effect of the surrogate endpoint and that of OS across multiple randomized clinical trials.

STUDY ENDPOINTS

In clinical trials, the study endpoint can be measured objectively to determine whether the intervention being studied is beneficial. Endpoints can be continuous, binary, ordinal, categorical, or time to event. As in the example discussed in the preceding section, tumor measurements before and after therapy are the outcome measures, and on the basis of changes in those measures, the study endpoint could be the ORR or PFS. Other common examples of endpoints are OS and improvements in quality of life and relief of symptoms.

A majority of medical interventions have safety risks. Therefore, a study endpoint should be clinically meaningful, such as improved survival, or a benefit that is detectable to the patient, such as an improvement in symptoms, functional capacity, or disease prevention.

Before study initiation, the selected study endpoint should accurately assess the hypothesis being tested, be clinically meaningful, and not be subject to bias. Although OS is the gold standard for efficacy in oncology trials, it has limitations; for example, in good-prognosis settings, follow-up time may be too long to observe enough events (deaths), and it may also be confounded by subsequent therapies. A key component of the study design process is the commitment to collect high-quality data in accordance with objective standards to aid with analysis and future applications. One such tool to harmonize data quality across clinical research is the National Cancer Institute Common Data Elements effort. Adoption of these constraints aims to improve quality and reproducibility across disparate sources of clinical research through standard semantic and syntactic representations of any and all produced research data.

SAMPLE SIZE AND POWER CALCULATIONS

Sample size estimation and power analysis for a clinical trial generally require formulation and preliminary data for the following:

1. Set up statistical hypotheses for the primary outcome
2. Choose power and type I error rate
3. Select effect size
4. Determine variability of the outcome measure

- During clinical trial design, clinical research questions are formulated in terms of statistical hypotheses based on the selected primary endpoint. For example, in a randomized trial comparing an experimental treatment versus control with the primary outcome of tumor response (a binary endpoint), the null hypothesis would be that response rates are equal for the two treatments, and the alternative hypothesis would be that the two treatments are different (two-sided hypothesis test) or that the experimental treatment is better than the control (one-sided hypothesis test). The specified magnitude of the difference in response rates between treatments is called the effect size.
- Power is the probability of correctly rejecting the null hypothesis when it is not true. Stated differently, it is the probability of finding a statistically significant difference between groups when it exists. This probability should be sufficiently high, and in clinical trials, it is usually set at 80% or 90%. At the same time, the trial must maintain a sufficiently low probability of type I error rate α (making a false-positive conclusion), which is often set at $\alpha = 0.05$ in phase 3 trials. Higher power or a lower α level requires a larger sample size. If the alternative hypothesis is one sided, then the sample size is smaller compared with that necessary for a two-sided test when other parameters remain the same. Whether to use a one- or two-sided hypothesis test depends on the particular study setting and must be prespecified during study design. The approach of setting the type I error rate for one-sided tests at half the conventional type I error for two-sided tests is preferable in regulatory settings.[1] For instance, using a one-sided α of 0.025 instead of a two-sided α of 0.05 in a superiority trial can reduce the required sample size while preserving regulatory control of type I errors. Some journals may require planned two-sided tests when reporting efficacy results, especially secondary endpoints, for consistency across literature.

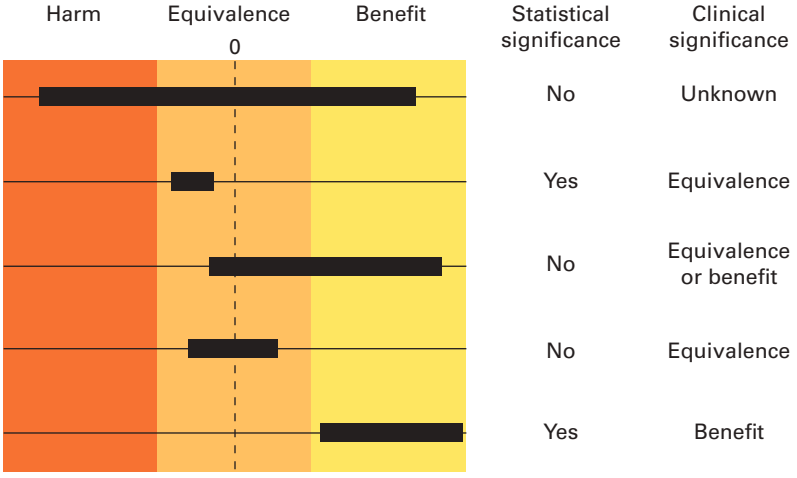
- Generally, the effect size is the smallest effect that would be considered clinically or biologically of interest; it is the minimum difference that is considered to be of clinical significance.[2] Depending on the type of primary endpoint in the study, the effect size may be expressed as a difference in proportions, a difference in means, or an HR. For continuous outcomes, standardized effect size $\delta = (\mu_1 - \mu_2)/\sigma$, which expresses the difference in means μ relative to the standard deviation σ, can be used as a convenient summary to be compared across outcomes measured on different scales. However, the use of the standardized effect size alone for power calculations is insufficient, and a clinically meaningful difference on the actual scale used to measure the outcome must be considered. The effect size magnitude has a large impact on the sample size; the smaller the effect size, the larger the sample size must be to detect it.
- Variability of the outcome measure resulting from sampling and measurement error is of primary importance. Higher variability indicates that the outcome cannot be measured precisely, and a larger sample size is necessary to make robust conclusions about group differences, whereas required sample size decreases with decreasing variability. During trial design, assumptions about variability of an outcome are often based on preliminary data from published studies or investigators' estimates from their own research.

The reader is referred to the freeware for sample size computation for simple one- and two-arm designs.[3] Commercial statistical software is also available for sample size calculations for a broader range of study designs.

Details of the clinical trial design and power calculations, including rationale for the selection of the effect size and justification of the underlying assumptions about variability, are included in the clinical trial protocol with sufficient details so that they can be reproduced by another statistician.

Care should be taken in making a distinction between clinical significance and statistical significance (Fig. 5-1). It is possible to have a statistically significant result that is not clinically significant. For example, a large clinical trial of early-stage disease could show a median improvement of 1 month in OS between two treatment arms that is statistically significant ($P = .001$). In this case, the result is statistically significant at the .05 level but has little clinical importance, with a median difference in OS of only 1 month. In contrast, it is also possible to have a clinically meaningful difference, for example, a survival difference of 6 months, that is not statistically significant ($P = .15$). This latter case may occur when studies are underpowered because of a sample size that is too small, and a larger study is required to quantify this difference with higher confidence.

Figure 5-1 Relationship Between Estimates and Confidence Intervals (CIs) and Their Statistical and Clinical Significance



Dashed line at 0 represents no difference between groups.
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Sample size is sensitive to the effect size. In most cases, halving the effect size results in an approximately four-fold increase in the sample size requirement, with all other factors unchanged. Conversely, doubling the effect size leads to an approximately 75% reduction in the required sample size. Therefore, it is critically important to carefully consider the effect size that is clinically meaningful for a study.

One method to calculate the approximate clinical significance of a trial result is to generate a net benefit value. Net benefit assists with determining whether a treatment or test would do more harm than good. Net benefit puts benefits and harms on the same scale. In the diagnostic setting, the trade-off is between diagnosing patients with disease versus ordering unnecessary additional testing for those who are healthy. In the therapeutic setting, the variables may be treatment response minus toxicity

or OS minus quality of life. During the trial design process, an exchange rate, a clinical judgment of the relative value of benefits and harms associated with the study intervention, can be formulated. Typical considerations in the model might be the number of patients who need to be treated for a patient to derive benefit. A range of acceptable net benefit values can be obtained from a decision curve. For additional resources related to this topic and worksheets to calculate the net benefit, refer to the ASCO Value Framework[4] and European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (https://www.esmo.org/guidelines/esmo-mcbs).

STATISTICAL ANALYSIS PLAN

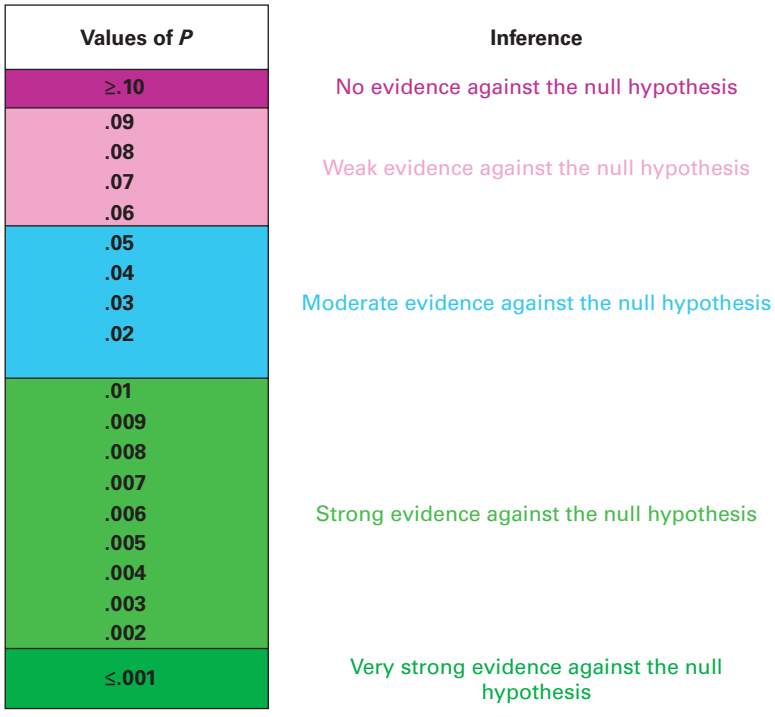
A statistical analysis plan (SAP) must be included in the clinical trial protocol and is an a priori description of the principal features of the eventual statistical analysis methods[1] that will be used to analyze trial data. An additional SAP document containing additional technical and statistical details may also be written after the protocol has been finalized but before the trial commences and is often used as a key regulatory document. The SAP is expected to provide sufficient details such that another statistician will be able to implement all planned analyses. It has been recommended that while developing the formal SAP, a minimum of 55 items be included, and these are divided into 6 major sections[5]:

1. Title and trial registration (11 items and subitems)
2. Introduction (2 items)
3. Study methods (9 items and subitems)
4. Statistical principles (8 items and subitems)
5. Trial population (8 items and subitems)
6. Analysis (17 items and subitems)

P VALUES

One of the most commonly used values in the statistical analysis of medical data, and possibly the most often misunderstood, is the *P* value (Fig. 5-2). The *P* value is calculated from the sample data, and it measures the strength of the evidence against the null hypothesis. Essentially, the *P* value is the probability that a result different from (or more different than) the one observed could be produced by chance alone, assuming that the null hypothesis is true. That is, it calculates the probability of obtaining the observed data, or data more in favor of the alternative hypothesis, if the null hypothesis is true. If the *P* value is small (close to 0), the sample data are not likely to be observed if the null hypothesis is true. This is evidence

Figure 5-2 Relationship Between *P*-Value Ranges and the Strength of Statistical Evidence Against the Null Hypothesis



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against the null hypothesis and suggests the data are due to a systematic effect. More concretely, it was recently reported that in a trial for men with high-risk localized prostate cancer, the 4-year OS rate was 89% for androgen suppression plus radiation treatment (two-treatment arm) compared with 93% for androgen suppression plus radiation treatment plus docetaxel (three-treatment arm), with an HR of 0.69 and a one-sided *P* value of .034.[6] Here, the null hypothesis is not explicitly stated, as is often the case. However, for a one-sided test, it is implied that the null hypothesis is that the three-treatment arm is equal to or worse than the two-treatment arm with respect to OS. In this case, the alternative hypothesis is that the three-treatment arm would see better results than the two-treatment arm because it has one additional treatment. This is a one-sided alternative hypothesis that will have a one-sided *P* value. Statisticians determine whether there is evidence against the null hypothesis as defined for the one-sided comparison. If there is evidence against the null hypothesis, they then reject the null hypothesis in favor of the alternative hypothesis. Typically, as in this example, a level of significance of .05 is used to determine if there is sufficient evidence to reject the null hypothesis. The *P* value is then calculated by assuming that there is no difference between the treatment arms (which would be an HR of 1) and determining how likely it would have been to observe an HR of 0.69 (the value computed from the trial data) or even lower. In this case, an HR of less than 1 favors the three-treatment arm. Because the *P* value is .034, meaning that if the HR were 1, the chance of observing an HR of ≤0.69 would be .034. Because this is lower than the level of significance (eg, $P = .034$ is lower than the level of significance of .05), the conclusion is that the three-treatment arm has better OS than the two-treatment arm.

What constitutes a small *P* value? This is set by stating a level of significance at the time the study is designed, which is called the level of significance or the significance level. In clinical research, $P < .05$ is commonly used to indicate statistical significance, meaning it is sufficient evidence against the null hypothesis. This number is arbitrary but often used in phase 3 trials. However, other significance levels are used in clinical research. For example, phase 2 trials often use a .10 significance level, because if the result is found to be statistically significant, it will be followed by a more stringent phase 3 trial to confirm its efficacy. Studies designed to determine associations of genomic/genetic measures with outcome often use a significance level that is substantially lower than .05 to minimize the overall false-positive rate. In the formal hypothesis-testing paradigm, it is equivalent to rejecting the null hypothesis when the type I error rate is set at 5%. There are a couple of common misinterpretations of the *P* value:

- Misinterpretation: The *P* value is the probability that the null hypothesis is true. Explanation: Because the *P* value is calculated by assuming that the null hypothesis is true, it cannot be a statement of the probability that the null hypothesis is true.
- Misinterpretation: When the *P* value is large or not statistically significant, this means that there is no difference. Explanation: When a result is not statistically significant, it means only that chance is one possible explanation for the observed data, if the null hypothesis is true. It does not mean that it has been established or proven that the null hypothesis is true. That is, absence of evidence against the null hypothesis is not evidence proving the null hypothesis.

What does a large *P* value mean? In the absence of any other information and assuming that the data arise from a properly designed study, the safest and most accurate interpretation is that there is insufficient evidence that the null hypothesis is false (Fig. 5-2). The reality is that the *P* value, whether small or large, actually carries little information. It conveys no information about the direction or magnitude of an effect, no information about the uncertainty in the estimated effect, and no information about the clinical significance of the effect. Even a small *P* value is no guarantee that an effect has clinical significance. In studies with a large sample size, even a modest departure from the null hypothesis can be associated with a high degree of statistical significance, but the departure from the null hypothesis may have little practical meaning. For example, it is possible to obtain $P < .0001$ with an observed difference in median survival between two treatments of only 1 month (which is statistically significant but not clinically meaningful) if the sample sizes are sufficiently large.

Recent articles in the statistical literature have recommended that investigators concentrate on reporting and interpreting uncertainty measures, such as the confidence interval (CI), rather than focusing on *P* values.[7] The CI represents a range that is likely to contain the true population value (Fig. 5-1). An interval with a 95% CI will be expected to contain the true value of the effect 95% of the time and miss it 5% of the time. Note that for any particular CI, it is unknown whether it contains the true value. The *P* value is only a statement about whether an observed result, or one more extreme, is due to chance, assuming that the null hypothesis is true. A CI for an HR crossing 1 implies that there is no difference between the treatments.

There is a relationship between significance levels and CIs. For example, if the null hypothesis is testing that there are no differences in survival time between two treatments, it can be written as an HR of 1. If the *P* value for the tests of the hypothesis is greater than the level of significance (eg, two-sided .05), then the 95% CI will contain 1 (value under the null hypothesis). Similarly, if a 95% CI for an HR does not contain 1, the implication is that the result is statistically significant at the .05-level of significance (ie, there is evidence of a difference in survival). The fallacy of thinking the null hypothesis value is the true value when the *P* value is greater than .05 is readily apparent, because the null value is only one among a range of possible values that could reasonably have produced the observed data.

CHOOSING A STATISTICAL ANALYSIS APPROACH

Choosing the type of statistical analysis to use involves the following key questions (Tables 5-2 and 5-3):

- What type of outcome measure is being used (eg, continuous, binary, time to event)?
- How many independent (explanatory) variables are being considered?
- Are any observations correlated (eg, pre- and posttreatment measurements, replicate or longitudinal assessments)?

Once these have been established, an appropriate statistical analysis method, or methods, can be determined using Table 5-2. For example, if at the start of a study, body mass index (a continuous measure) is being compared between patients with and without a certain genetic mutation (one explanatory variable that has two groups), we would use a two-sample *t* test or the Wilcoxon rank sum test because the two groups (with and without mutation) include different patients and there are no correlated observations. Similarly, if we want to compare response rates (binary outcome) between patients with or without the mutation, we would use a χ^2 or Fisher exact test, and when comparing OS (time-to-event outcome), we would use the log-rank test. If, however, we wanted to compare response rate or OS between patients with and without mutation, adjusting for their age, sex, and smoking history (multiple explanatory variables), we would use the logistic and Cox regression models, respectively. The statistical tests and regression models described here are the most commonly used methods. A variety of other more comprehensive statistical methods have been developed for more complex situations; for example, quantile regression models may be more appropriate for outcomes with skewed distributions where the median, rather than the mean, of the outcome may be of interest. Additional considerations when selecting the statistical analysis approach can be found in the article by Kim et al.[8]

KEY POINTS

- The primary objective of a clinical study is the principal clinical research question or the hypothesis to be tested.
- The primary outcome measure is the variable that will be measured during the clinical trial and on which the study endpoint will be based.
- Study endpoints are clinically meaningful results obtained after the study intervention.
- A false positive (type I error) is when the null hypothesis is true and incorrectly rejected; it is designated as α.
- A false negative (type II error) is when the null hypothesis is false and incorrectly not rejected; it is designated as β.
- Statistical contributions to the clinical trial design are essential, and trial design development is a collaboration between clinical investigators and the statistician.
- The American Statistical Association's six principles of statistical significance and *P* values are as follows[9]:

  1. *P* values can indicate how incompatible the data are with a specified statistical model.
  2. *P* values do not measure the probability that the studied hypothesis is true or the probability that the data were produced by random chance alone.
  3. Scientific conclusions and business or policy decisions should not be based only on whether a *P* value passes a specific threshold.
  4. Proper inference requires full reporting and transparency.
  5. A *P* value, or statistical significance, does not measure the size of an effect or the importance of a result.
  6. By itself, a *P* value does not provide a good measure of evidence regarding a model or hypothesis.

CLINICAL TRIAL DESIGN

Clinical trials play a fundamental role in progress on cancer research and in the development of novel interventions, prevention, and detection devices.[10] The traditional paradigm has classified clinical trials according to the general phases of drug development based on cytotoxic drugs. Although this classification does not account for all clinical trials relevant to oncology, it is a useful starting point for describing the key elements of trial design, which necessarily vary according to the objectives of the trial.

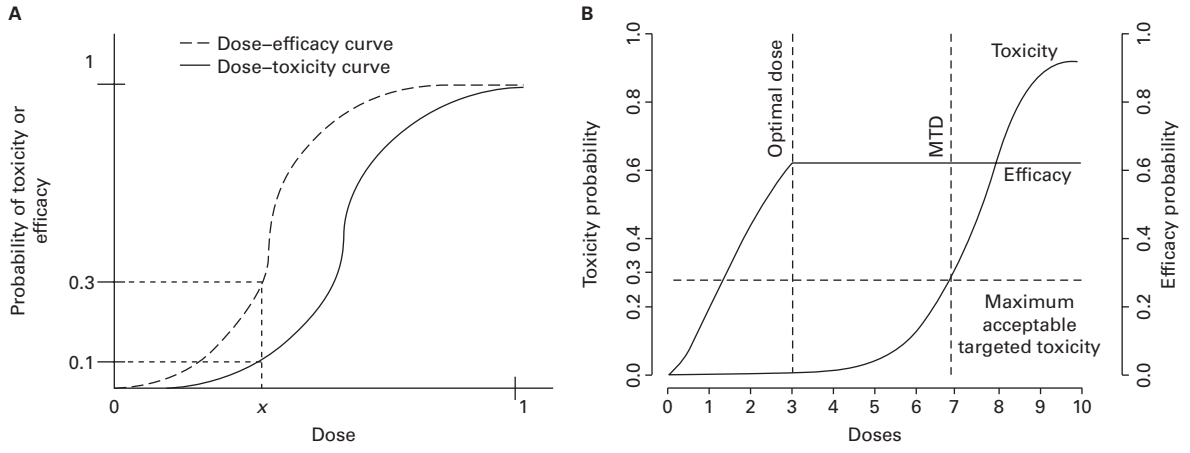
Phase 1 trials are often the first use of a drug or a drug combination in humans and focus on toxicity, with the goal of determining a dose that would have acceptable toxicity if the drug were effective. Phase 2 trials are designed to provide a preliminary indication of whether a therapy has anticancer effects. The result is considered preliminary because the study may be uncontrolled, use a surrogate endpoint (eg, tumor response instead of survival), or be too small to rule out false-positive findings. A phase 3 trial is typically a randomized controlled trial (RCT) that is sufficiently large to distinguish chance effects from true treatment effects. The definitive distinction between trial phases has become less precise in the era of precision medicine, and other trial classifications have been commonly used, including phase 1/2, 1b, 2/3, or 4. There is no recognized governing body for trial nomenclature, and trial sponsors are free to attach whatever labels they wish to a particular study. Sometimes, the label selected is motivated by regulatory or insurance considerations. For example, the US Food and Drug Administration (FDA) mandates definitions of trial phases for studies that it regulates, and insurers may decline coverage for patients participating in certain phase trials.

The considerations for power and type I error vary across phases. In phase 1 trials, which primarily focus on safety and dose finding, there is typically no formal consideration of statistical power or type I error because the sample size is small and not hypothesis driven. Phase 2 trials aim to assess preliminary efficacy and often prioritize high statistical power to detect potential signals of efficacy although they may tolerate a higher type I error rate to avoid prematurely discarding promising treatments. In contrast, phase 3 trials, designed to confirm efficacy and safety in a larger sample, require reasonably high statistical power (eg, 80% to 90%) to ensure reliable and generalizable results and strict control of type I error (commonly set at two-sided $\alpha = 0.05$) to maintain credibility and minimize false-positive findings.

PHASE 1 TRIALS

The goal of the initial phase of testing a new anticancer strategy in humans is finding a dose or schedule that yields an acceptable level of toxicity. What is deemed acceptable depends on the disease in question. In diseases such as cancer that have significant morbidity and mortality rates, the acceptable level of toxicity may be relatively high. It is often the case with cytotoxic drugs that drug toxicity is a measure of its potential efficacy, meaning that greater efficacy is expected with higher doses (Fig. 5-3A). However, higher doses mean more toxicity, and the goal is to find the highest dose with an acceptable level of toxicity. With newer targeted therapy or immunotherapy, the presumed relationship of toxicity and efficacy may differ, where higher doses of a targeted therapy or immunotherapy may yield undesirable off-target effects, and the design of appropriate phase 1 trials for these agents can be challenging (Fig. 5-3B). The major objective of a phase 1 trial is to find an acceptable drug dose to be used in subsequent phase 2 and higher trials, which is often referred to as the recommended phase 2 dose (RP2D). Phase 1 dose-finding trials are not designed to test drug efficacy although drug efficacy outcomes can often be assessed using, for example, disease-specific expansion cohorts in phase 1b trials, and the findings can be used to inform subsequent drug development and prioritization.

Figure 5-3 Dose-Response and Dose-Toxicity Relationships for Cytotoxic Versus Molecular Targeted Treatments



(A) Typical dose-toxicity and dose-efficacy curves for cytotoxic agents. This example illustrates that at dose *x*, the probability of efficacy is 30% and the probability of toxicity is 10%; hence, the therapeutic index of the drug at dose *x* is 10% divided by 30% = 1/3. (B) Illustration of dose-toxicity and dose-efficacy relationship for molecularly targeted agents.
Abbreviation: MTD, maximum tolerated dose.
Data adapted from (A) Le Tourneau et al. *J Natl Cancer Inst.* 2009;101:708-720, by permission of Oxford University Press. (B) Riviere et al. *Stat Methods Med Res.* 2018;27:466-479.
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STUDY OBJECTIVES AND PATIENT POPULATION

Traditionally, the objective of a phase 1 trial is to determine the maximum dose of an agent, either alone or in combination with other therapies (including radiation therapy), that yields an acceptable level of adverse events when administered on a specific schedule and by a specific route. This dose is referred to as the maximum tolerated dose (MTD) and is often selected as the RP2D for cytotoxic therapies. Phase 1 trials are necessarily small for ethical reasons because it is not expected that many patients enrolled in these trials will obtain benefit, particularly at lower doses. Typically, patients enrolled in phase 1 trials have received multiple lines of therapy, and there are no additional standard treatment options available. The patient population is generally heterogeneous with respect to the type of cancer but at times may be restricted to patients with specific cancers or tumor molecular profiles, depending on the agent being tested and its mechanism of action.

STUDY OUTCOME MEASURES

The outcome measures evaluated in phase 1 studies are toxicities related to the study intervention. The most common standard for rating the severity of adverse events is the National Cancer Institute Common Terminology Criteria for Adverse Events list, which provides specific objective criteria for grading a wide range of adverse events on a numeric scale: 0 (none), 1 (mild), 2 (moderate), 3 (severe), 4 (life threatening), and 5 (fatal). Beyond the severity of an adverse event, it is important to document the onset, resolution, and relatedness of the adverse event (eg, whether the adverse event is related to the study therapy, a concomitant medication, or underlying disease condition). Phase 1 study participants are generally evaluated at discrete regular intervals of a short cadence to capture the time course of adverse events.

STUDY ENDPOINTS

At the conclusion of a phase 1 clinical trial, the primary goal is to estimate a dose that can be taken forward into later phase studies. Most dose-escalation designs aim to identify the MTD, which is the highest dose associated with an acceptable risk of dose-limiting toxicity (DLT). The RP2D is usually determined after the MTD is identified and often reflects additional information beyond acute toxicity. These considerations may include data from dose expansion cohorts, cumulative or delayed toxicities, pharmacokinetic and pharmacodynamic findings, and preliminary evidence of activity.

Although the MTD is the most common primary endpoint in traditional cytotoxic trials, the RP2D may differ from the MTD when longer term tolerability or biological activity suggests a lower or occasionally higher dose is more appropriate. Some contemporary dose-finding designs, particularly those used with molecularly targeted agents or immunotherapies, may aim to identify an optimal biological dose (OBD). An OBD focuses on achieving adequate target engagement or biological activity with acceptable toxicity, especially in settings where the MTD is not reached or is not clinically informative.

The adverse event criteria are used to determine the MTD on the basis of the severity of the experienced adverse events. Adverse events of severity or duration such that further exploration of higher doses is unacceptable because of toxicity are said to be DLTs. A dose below the level where DLTs are experienced generally defines the MTD. Phase 1b trials may also include one or more dose-expansion cohorts, usually at the MTD, for additional safety evaluation before a phase 2 trial is initiated, as well as for preliminary activity evaluation, for example, in different types of cancer. Other factors may be considered that may result in the RP2D being lower than the MTD. For example, for molecularly targeted agents, efficacy may increase initially but then plateau, whereas toxicity may be low in this dose range and the MTD may not be reached (Fig. 5-3B). For such agents, the goal is to find the optimal , which is the lowest safe dose at which the highest efficacy is achieved.

One of the most important criteria in a phase 1 trial is the definition of a DLT. Although most phase 1 trials have a similar definition for what constitutes a DLT, the definition can be tailored to reflect adverse events expected on the basis of the mechanism of action of the agent. Most definitions of DLTs exclude grade 1 or 2 adverse events and possibly some grade 3 toxicities, if these are expected and manageable (eg, neutropenia, nausea/vomiting). A typical definition of a DLT might be a grade 3 or worse nonhematological adverse event or a grade 4 or worse hematological adverse event that is attributable to the agent being tested. This is the starting definition of a DLT for most trials, and the study team may make modifications on the basis of expected manageable adverse events, yielding, for example, any grade 3 or worse nonhematological adverse event other than diarrhea or a grade 4 or worse hematological adverse event that is attributable to the tested agent. Assigning attribution to the adverse event is also important, and DLT definition usually includes only the adverse events attributed to treatment rather than the underlying disease.

It is also important to specify the DLT assessment window, during which adverse events will be evaluated for dose-escalation decisions. Duration of the DLT evaluation window is often driven by the pharmacokinetics and the mechanism of action of the agent. For cytotoxic therapies, this is typically a relatively short time, often just the first treatment cycle (eg, 28 days), and reflects only acute adverse events. For novel anticancer therapies, including immunotherapy, as well as for radiation therapy, delayed-onset toxicities are common, and the DLT assessment window must be long enough to capture a majority of treatment-related toxicities. Adverse events that occur after the DLT assessment period are typically not used for dose-escalation decisions as part of trial design but may affect the selection of the RP2D or how the agent is used in subsequent phase 2 trials.

Trials should also define who is considered evaluable for toxicity.[11] For example, patients who discontinue treatment before completion of the DLT assessment period without having a DLT may be considered non-evaluable for toxicity. Modern phase 1 dose-escalation statistical designs, including the Bayesian optimal interval (BOIN), which is described later in this chapter, can accommodate situations when some patients at a particular dose level are non-evaluable by providing decision rules for each possible sample size at that dose level. Non-evaluable patients may also be replaced during dose escalation, which would also need to be prespecified in the protocol.

DOSE RANGE SELECTION

Phase 1 trials prespecify the starting dose of the treatment being evaluated for the first cohort of patients as well as a sequence of doses to be tested in subsequent cohorts. If the agent in question has not yet been assessed in humans, the initial dose is typically derived from animal experiments. If the agent has been used in humans but with a different route of administration, on a

different schedule, or in combination with different treatments (including as a monotherapy) than currently being tested, the starting dose is selected on the basis of all available human experience with the treatment. For trials that are testing the agent for the first time in humans, a common starting dose ranges from one-tenth to one-third of the mouse lethal dose for 10% of mice. Subsequent dose levels are determined by increasing the preceding dose by decreasing fractions, for example, 100%, 67%, 50%, 40%, and 33%. This sequence and those with slight variations are called modified Fibonacci dose levels. Starting dose levels for agents that are likely to be well tolerated, such as biological agents, may be determined by log (ie, 10-fold) or half-log increases of the preceding dose.

DESIGN OPTIONS

Many considerations go into determining an appropriate phase 1 dose-escalation design, and as with other clinical studies, it is important for clinical investigators to work closely with statisticians to refine the trial objectives and ensure that an appropriate design is chosen. The dose-escalation rules in phase 1 must address how patients should be allocated to doses, and at the end of the trial, the design should provide the RP2D. Additional key design questions[11] include whether the MTD or biologically optimal dose should be selected for further study; how many agents are escalated in combination treatments; acceptable toxicity (DLT) rate, DLT definition, and assessment window; dose-escalation cohort size and the expected sample size; which doses should be evaluated; and trial operating characteristics. These components of phase 1 design are often overlooked but must be addressed in collaboration with the statistician.

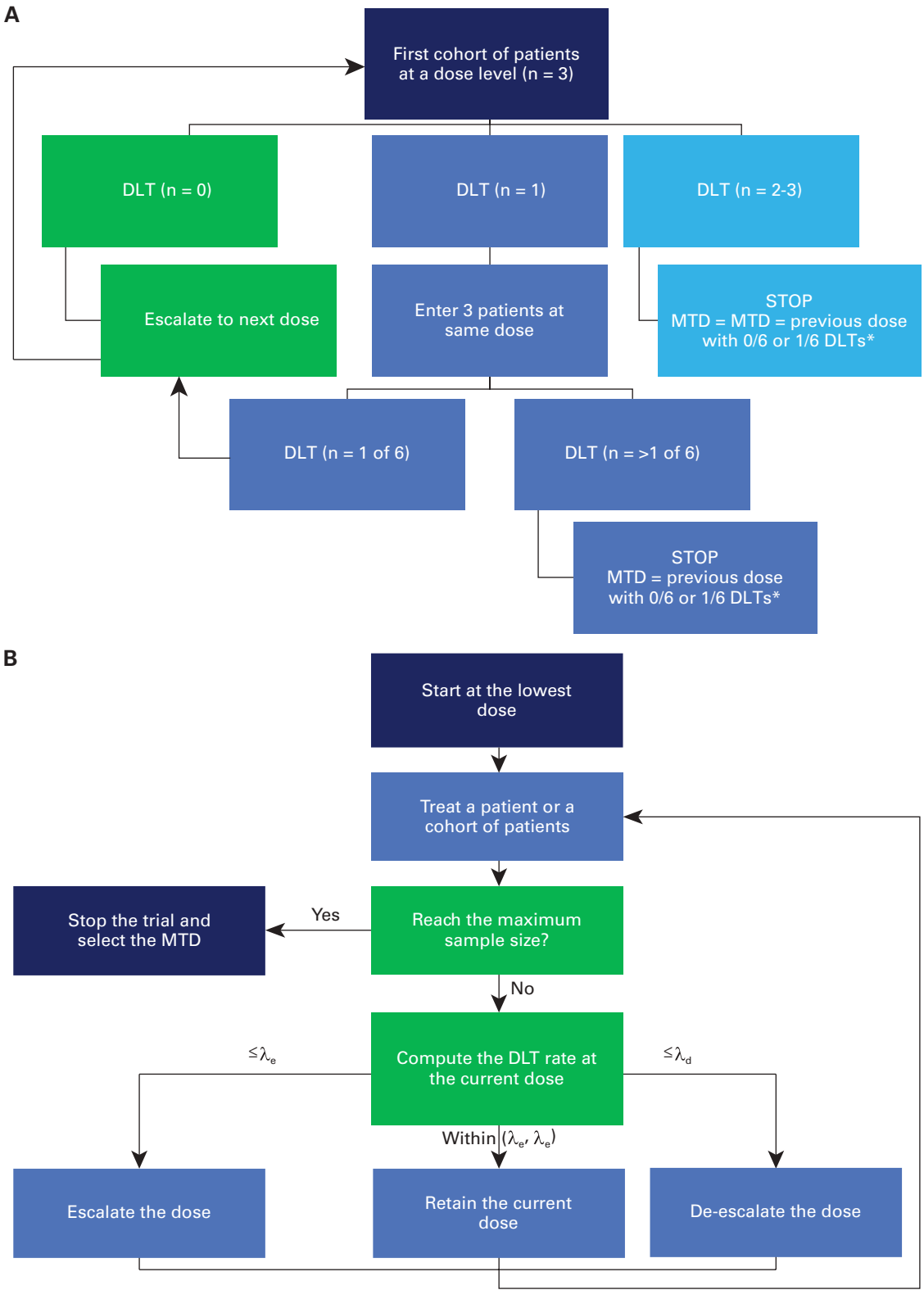
Dose-finding phase 1 trial designs can be classified as algorithm based, model based, or model assisted.[12] Algorithm-based designs use simple prespecified rules for dose escalation and de-escalation, and this class includes the 3 + 3 design (Fig. 5-4A) and its extensions, such as the accelerated titration and the rolling 6 designs. Although commonly used because of their simplicity, they have poor operating characteristics. Model-based designs use a statistical model (eg, logistic model) to estimate the underlying dose-toxicity curve, which is used to allocate patients to doses. These designs include the continuous reassessment method (CRM) and its extensions, as well as the Bayesian logistic regression model (BLRM), and provide excellent operating characteristics but can be difficult to implement in practice. Model-assisted designs combine the simplicity of use of algorithm-based designs with the superior performance of model-based designs and include modified toxicity probability interval (mTPI-2)[13] and BOIN (Fig. 5-4B)[14,15] designs and their extensions (Presenting Case Study 1). These designs use an underlying statistical model to provide a lookup table for dose-escalation and de-escalation decisions based only on the observed number of patients enrolled and experiencing a DLT at a given dose level. The performance and operating characteristics of different designs, such as the probability of correctly identifying the MTD, allocation of a high proportion of patients to the MTD, good overdose control, expected sample size, and study duration (for trials with delayed-onset adverse events) can be evaluated using simulation studies. In all of these dose-finding designs, patients who discontinue early or do not meet predefined criteria for DLT evaluation may be replaced to ensure an adequate number of evaluable patients for dose-escalation decisions. Evaluable patients are those who have received a sufficient amount of investigational treatment to allow a reliable assessment of DLT.

There are two important considerations in phase 1 trial designs: (1) minimization of the total number of patients, because there is little likelihood that enrolled patients will benefit from participating in the trial, and (2) minimization of the number of patients who experience serious adverse events.

Until recently, the most commonly used phase 1 dose-escalation design was the 3 + 3 design, which was developed in the 1950s. It is an algorithm-based design, in which cohorts of three patients are entered in the trial at dose levels beginning with the prespecified initial dose level. If there is no observed DLT in all three patients treated at the specified dose, the next cohort of three patients is entered at the next higher dose level. If two of three patients experience a DLT at a specified dose, then the adverse event rate associated with that dose is considered unacceptable, and the dose level below it (if any was tested) is considered the MTD. If one of the three patients experiences a DLT, an additional cohort of three patients is entered at the same dose level. If no DLT is seen among the additional three patients, the next cohort of patients will be treated at the next higher dose level; otherwise, the toxicity is considered unacceptable, and the dose level below it is considered the MTD. If the starting dose is too low and/or the spacing of doses is too short relative to the steepness of the dose-response curve, it is possible a large number of patients will be enrolled at doses that likely have no therapeutic benefit. In response to this concern, an accelerated titration design was proposed, in which the cohort size for the initial dose level is a single patient, and subsequent patients are treated at the next higher dose level until a grade 2 or worse drug-related adverse event is observed. Once this happens, a standard 3 + 3 design is implemented starting at the next lower dose level from that where the grade 2 or worse adverse event was observed. These designs are generally used for treatments in which there is some human experience with the agent, and the toxicity profile is manageable.

Another design option is the continual reassessment method, which uses a Bayesian approach (refer to the discussion on Bayesian statistics later in this chapter) and is a model-based design. Although there are many variations of continual reassessment methods, the basic idea is to specify an acceptable probability of a DLT (eg, 20% or 33%), specify a mathematic model for the dose-response curve,

Figure 5-4 Typical Dose-Finding Phase 1 Design Algorithms



(A) 3 + 3 phase 1 trial design. Note that patients who are non-evaluable for DLTs may be replaced. (B) BOIN design.
Abbreviations: BOIN, Bayesian optimal interval; DLT, dose-limiting toxicity; MTD, maximum tolerated dose.
*Six patients must be treated at a dose level before it can be declared an MTD.
Data adapted from https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware/Index/99
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and update the mathematic estimate of the dose-response curve after each patient experiences a DLT. The dose level for the next patient (or cohort) who will be treated is the one at which the estimated probability of a DLT is closest to the specified target. The advantage of this method is that it produces more-accurate estimates of the MTD and minimizes the number of patients who are treated at nontherapeutic levels or levels that are too toxic. In addition, these methods are good approaches for testing combination drugs. The continual reassessment method and partial-order approaches require submission of DLT data to statisticians in real time to determine the dose assignment for the next patient, which makes the application of these designs logistically challenging.

The BOIN design is simple to implement and has better performance than the 3 + 3 design.[14] This design computes probability intervals defined as underdosing, proper dosing, and overdosing. Dose-escalation decisions are easily made on the basis of these dosing intervals; they can be described using simple lookup tables for ease of application. Observed DLT rate at the current dose level can then be compered to these intervals, or alternatively DLT counts can be compared to the pre-specified lookup table. The BOIN design tends to treat fewer patients at doses greater than the MTD and is more likely than the 3 + 3 design to identify the true MTD. It is also easy to implement because the tables are generated before the trial starts, so there is no need to perform real-time computation to determine the dose level to treat the next patient (or cohort). The website www.trialdesign.org provides an easy-to-use app for BOIN and its extensions.[16]

For some biologic or targeted treatments, toxicity across the anticipated therapeutic dose range may be limited. In these settings, dose finding focuses less on identifying an MTD and more on determining a dose or dose range that produces adequate biological activity with acceptable tolerability. The goal is to identify an OBD, which is the lowest dose that achieves the desired biological effect without unnecessary toxicity. This approach is particularly relevant for targeted therapies and immunotherapies, where therapeutic effects depend on modulation of specific biologic pathways rather than on dose-dependent cytotoxicity.

Backfilling is an strategy used to support dose optimization in this context. Backfilling refers to the enrollment of additional participants at previously tested dose levels to gather more detailed information on safety, tolerability, pharmacokinetics, and pharmacodynamic activity. Traditionally, backfilling occurs after an MTD is identified, but newer designs such as BOIN Backfill allow backfilling to occur while dose escalation is still ongoing. Allowing backfill enrollment in parallel with escalation improves efficiency because escalation does not need to pause while additional data are collected at lower or intermediate doses. This approach strengthens the evidence base used to select the RP2D or OBD.

Recent regulatory initiatives, including Project OPTIMUS, highlight the importance of rigorous dose optimization for targeted and immune therapies. These initiatives encourage the use of strategies such as backfilling and biomarker informed expansion cohorts so that the RP2D reflects both biological activity and longer term tolerability rather than relying primarily on acute toxicity. Successful implementation depends on factors such as biomarker availability, reliable assays for biological response, and transparent criteria for selecting doses to expand. When applied carefully, these approaches can improve confidence that the dose carried forward into phase 2 studies is both active and well tolerated.

PRESENTING CASE STUDY 1

An investigator is designing a phase 1 trial of a novel cytotoxic chemotherapy agent for patients with advanced solid tumors. Preclinical studies suggest dose-dependent antitumor activity, but human toxicity is uncertain. The protocol defines a dose-limiting toxicity (DLT) as any grade 3 or higher nonhematological toxicity attributable to treatment, or grade 4 hematological toxicity lasting more than 7 days, assessed during cycle 1 (28 days). The target DLT rate is 25%. Five dose levels (DL1 through DL5) are prespecified using modified Fibonacci increments.

To illustrate how design choice affects patient allocation, consider the following hypothetical pattern of observed DLTs.

A. What happens under a 3 + 3 design

The trial starts at DL1. Suppose 0 of 3 patients experience a DLT, so the trial escalates to DL2. Again, 0 of 3 report a DLT, so it escalates to DL3. At DL3, suppose 1 of 3 patients experiences a DLT. Under 3 + 3, the cohort expands to 6 at DL3. If no additional DLTs occur, DL3 has 1 of 6 DLTs and escalation proceeds to DL4. At DL4, suppose 2 of 3 patients experience a DLT. DL4 is then considered too toxic, and DL3 is declared the maximum tolerated dose (MTD). In this example, the 3 + 3 design reaches DL4 quickly, but it can treat multiple patients at doses that may later prove too toxic or at early doses that may be subtherapeutic.

B. What happens under Bayesian Optimal Interval (BOIN) with a 25% target

Escalation and de-escalation decisions are based on a prespecified decision table calibrated to the target toxicity. Starting at DL1 and DL2 with 0 of 3 DLTs would typically lead to escalation, similar to 3 + 3. The difference emerges at DL3. With

a 25% target, observing 1 DLT among 3 patients is treated as a signal of potential overdosing, and the design recommends de-escalation to DL2 rather than automatically expanding DL3. The next cohort is treated at DL2 to gather additional information. If DL2 continues to show an acceptably low DLT rate, escalation back to DL3 can occur, but only when the accumulated evidence supports that DL3 is near the target toxicity. In practical terms, BOIN may be more conservative in the face of early toxicity signals, which can reduce exposure to overly toxic doses and concentrate enrollment near doses that appear acceptable.

C. What happens under continual reassessment method (CRM)

CRM also targets a prespecified DLT rate but uses a statistical model to update the estimated dose-toxicity relationship as data accrue. After observing 1 of 3 DLTs at DL3, CRM would typically revise the dose-toxicity curve upward and may recommend treating the next cohort at DL2 or DL3 depending on the posterior estimate. The potential advantage is more efficient learning about the dose-toxicity relationship, but it requires real-time statistical updating and timely dose assignment.

D. Selecting the Recommended Phase 2 Dose (RP2D)

Even if a design identifies an MTD, the RP2D may be informed by additional data, including expansion cohorts, cumulative toxicities, and pharmacokinetic or pharmacodynamic findings. This is one reason modern phase 1 programs often separate the technical selection of an MTD from the clinical decision about the RP2D.

Formal simulation studies are often used to compare the operating characteristics of dose-escalation designs across a range of toxicity scenarios, including their ability to identify the true MTD and control overdosing. Such evaluations are beyond the scope of this chapter, but the example illustrates how different design frameworks can lead to distinct escalation paths and patient allocation even when starting from the same observed data.

KEY POINTS

- Phase 1 trial objectives are as follows:
  1. Identify the safe dose or MTD of a novel therapy or therapy combination.
  2. Ascertain a dose or dose range for subsequent phase 2 studies.
  3. Determine clinical drug behavior through pharmacokinetic and/or biomarker studies.
  4. Assess preliminary antitumor efficacy.

PHASE 2 TRIALS

Phase 2 trials encompass a wide array of trial designs. These range from small single-arm trials with a dozen patients to RCTs with several hundred patients. Nevertheless, there are common features that characterize a phase 2 trial. The primary endpoint is related to efficacy or drug activity, the sample size is moderately small relative to the corresponding definitive phase 3 trial, the efficacy endpoint is short term and/or not definitive for patient benefit, and the study relies on historical experience as context for judging whether the result is promising enough to carry forward to a phase 3 trial. This is the type of trial that will be considered phase 2 for the purposes of this discussion.

Phase 2 trial objectives are as follows:

- Assess the antitumor efficacy/activity of a therapeutic intervention.
- Gain additional experience with the regimen or collect further toxicity data.
- Make a go or no-go decision regarding the further development of a therapeutic regimen.
- Provide data for an effect-size estimate for a subsequent phase 3 study.
- Assess biomarkers in a larger and more homogeneous patient population.

STUDY OBJECTIVES AND PATIENT POPULATION

The general objective of a phase 2 trial is to evaluate the potential efficacy of a drug or regimen in a specific patient population. The patient population is usually somewhat narrowly defined (eg, patients with recurrent glioblastoma). Typically, patients enrolled in phase 2 trials have experienced treatment failure with at least one or two standard therapies. However, there are

scenarios in which a phase 2 trial is conducted with patients with newly diagnosed disease who have not yet been treated (eg, in diseases with no effective therapy or when a new agent is to be added to the standard of care). Finally, a phase 2 study may be used to evaluate an established treatment in a different patient population (eg, a different type of cancer, a subtype of cancer defined by a genetic or another biological marker).

STUDY OUTCOME MEASURES

The overarching goal of a phase 2 study is to determine whether there is potential anticancer efficacy for the treatment approach under study. Therefore, the outcome measure incorporated into the study design tends to be a marker of therapeutic response, such as tumor measurements on radiology or validated blood-based tumor markers. In addition, a phase 2 study provides an opportunity to collect adverse event data on a larger group of participants than typically included in a phase 1 study, and the adverse events associated with longer-term drug administration can also be assessed. Therefore, toxicity data, survival data, and biomarkers and surrogate markers of efficacy are often included in the design of these studies.

STUDY ENDPOINTS

As noted, the primary endpoint of a phase 2 trial is a measure of potential efficacy or anticancer activity. The specific endpoint balances the ability to assess it in a relatively short time (ie, weeks, months) and its validity as a measure of long-term benefit. Many trials for solid tumors use tumor response (complete or partial), as assessed by imaging, as the primary endpoint, which usually can be ascertained within 3 to 6 months from the time a patient starts treatment. For neoadjuvant trials, a common endpoint is pathological complete response, which is determined by pathological examination of tissue obtained at the time of surgery. There are also trials that use other endpoints; some examples are 3-month PFS rate or 6-month disease-free survival (DFS) rate.

The most common methodology for determining tumor response in solid tumors is RECIST 1.1 (Table 5-4). Most response definitions for solid tumors are based on the change in size of measurable lesions over the course of a trial. Tumor responses are classified as complete response, partial response, stable disease, progressive disease, or unevaluable. Determining disease response status on the basis of RECIST depends on targeted and nontargeted lesions. A targeted lesion must be measurable. If there is more than one measurable lesion, a maximum of five lesions are selected.[17] A measure of disease is the sum of the largest diameter of the targeted lesions. All other lesions (either nonmeasurable lesions or measurable lesions not designated as targeted) are called nontargeted. The RECIST criteria depend on the changes in the size of the targeted lesions as well as on the changes in nontargeted lesions.[17] In cancer immunotherapy trials, a modified consensus guideline (ie, iRECIST, where responses assigned have a prefix of "i" for immune) has been developed by the RECIST Working Group.[18] Different response criteria are necessary for specific tumor types, such as the Response Assessment in Neuro-Oncology (RANO) criteria for brain tumors and the Prostate Cancer Working Group 3 (PCWG3) criteria for metastatic castration-resistant prostate cancer (mCRPC). Hematological malignancies also require tailored response criteria depending on the disease type. Regardless of the criteria used, the trial design must specify how and when a response will be assessed. The assessment of the primary endpoint must be performed the same way for all patients within the trial and should be reasonably comparable to what was used in other trials or how it was assessed in historical controls. In addition, especially in multicenter phase 3 open-label trials, blinded independent central review (BICR) of tumor responses is often adopted to overcome potential biases associated with locally performed tumor response evaluations.[19]

Table 5-4 RECIST 1.1 Definitions of Response and Disease

Response	Target Lesions	Nontarget Lesions
CR	Disappearance of all target lesions	Disappearance of all nontarget lesions and normalization of tumor marker level
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters	Persistence of ≥1 nontarget lesion and/or maintenance of tumor marker level above the normal limits
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study; in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm	Unequivocal progression of existing nontarget lesions; appearance of ≥1 new lesion is also considered progression
SD	Neither sufficient shrinkage to quality for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters during the study	NA

Abbreviations: CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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Sometimes, a phase 2 trial uses a tumor biomarker as the primary endpoint. For example, prostate cancer trials often use the increase, progression, or recurrence of prostate-specific antigen (PSA) levels at a specific time, such as 3 or 6 months, as a phase 2 endpoint. PSA progression is typically defined as a confirmed increase of 25% or greater in the PSA level from the nadir (lowest PSA level observed after starting treatment), with an absolute increase of 2 ng/mL or more. A biomarker is a single trait or composition of traits, often called a signature, used to determine disease status. These traits may include an assessment of tumor genomics or genetic aberrations or a molecular assessment of circulating tumor DNA. There is heightened interest in biomarkers for targeted therapies, which may have specific mechanisms of action that are measured by a variety of assays, possibly from blood or tumor samples that can be obtained quickly and easily. The rationale is that if the mechanism of action is truly understood for a targeted treatment, it should be possible to measure the effect of the treatment on the intended target. Biomarkers have many different uses in cancer research. In phase 2 studies, biomarkers are most commonly used as the primary endpoint as surrogates for treatment efficacy. However, the appropriate use of biomarkers as surrogate endpoints requires specific criteria that may be difficult to validate. A full discussion of these issues is beyond the scope of this chapter, but in general, one should be cautious when evaluating claims of effectiveness based on biomarkers or other surrogate endpoints.[20] For guidance on the appropriate use of surrogate endpoints in cancer drug and biological approvals, the FDA provides detailed recommendations in Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: Guidance for Industry.[20]

TRADITIONAL SINGLE-ARM PHASE 2 DESIGN

A commonly used phase 2 design is a single-arm trial using historical outcomes as points of reference for the design and interpretation of the trial. The primary analysis is to compare the observed outcome in the single-arm trial with the historical control value to determine if there is a statistically significant difference. For example, suppose the primary endpoint is tumor response, and the historical tumor response rate for the standard-of-care regimen is p_0. Furthermore, suppose p_1 is the minimum tumor response rate that would represent meaningful improvement compared with the standard of care. In other words, if there is evidence that the new treatment response rate is higher than p_0, it would be of interest for further study. In addition, investigators want reasonable power to reject the null hypothesis if the true treatment response rate is p_1.

The hypothesis-testing paradigm assumes that at the end of the trial, one will conclude that either (1) the true response rate for the regimen is greater than p_0 or (2) there is no evidence that the response rate for the regimen differs from p_0. The design parameters must also include a specification of α and the desired power (see "Hypothesis Testing" section earlier in the chapter). The false-positive error rate is the probability of falsely concluding that the true response rate for the regimen is greater than p_0, when in fact, it is equal to p_0. Power is the probability of correctly concluding that the true response rate for the regimen is greater than p_0, when in fact, it is greater than p_0. For phase 2 trials, α is typically set at 10%. The power is evaluated at p_1, the target response rate of interest. Phase 2 trials typically are designed with high power, often 90%. The possibility of relatively high error rates is accepted, because smaller sample sizes are yielded and because the results of a phase 2 trial will be confirmed in

Table 5-5 **Examples of Single-Stage Phase 2 Designs**

Design Criteria				Resulting Design	
p_0	p_1	α	Power[a]	n	r
0.1	0.25	0.05	0.9	55	10
0.1	0.25	0.05	0.8	40	8
0.1	0.25	0.1	0.9	40	7
0.1	0.25	0.1	0.8	31	6
0.1	0.25	0.05	0.9	33	7
0.1	0.25	0.05	0.8	25	6
0.1	0.25	0.1	0.9	25	5
0.1	0.25	0.1	0.8	18	4
0.5	0.7	0.05	0.9	53	33
0.5	0.7	0.05	0.8	37	24
0.5	0.7	0.1	0.9	39	24
0.5	0.7	0.1	0.8	28	18

Abbreviations: α, type I (false-positive, one-sided) error rate if $p = p_0$; n, smallest sample size that satisfies design criteria; p_0, response rate under null hypothesis; p, response rate under alternative hypothesis; r, minimum number of responses required to reject null hypothesis and conclude that $p > p_0$ using the exact test for one proportion.

[a]Power refers to the probability of rejecting the null hypothesis if $p = p_1$.

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a phase 3 trial. However, differences between p_0 and p_1 have considerably greater impacts on the sample size than the values of α and power (Tables 5-5 and 5-6). The larger the difference between p_0 and p_1, the smaller the required sample size. A balance needs to be considered between the desire for smaller sample sizes and the ability to detect differences between p_0 and p_1 that would be of clinical interest.

Table 5-6 CIs for True Response Rates

Observed Rate = 10%			Observed Rate = 50%		
n	*r*	95% CI (%)	n	*r*	95% CI (%)
10	1	0.3-44.5	10	5	18.7-81.3
20	2	1.2-31.7	20	10	27.2-72.8
30	3	2.1-31.7	30	15	31.3-68.7
40	4	2.8-23.7	40	20	33.8-66.2
50	5	3.3-21.8	50	25	35.5-64.5
60	6	4.9-17.6	60	30	39.8-60.2

Abbreviations: CI, confidence interval; n, sample size; *r*, observed number of responses.
Computations can be performed using the online calculator at https://stattools.crab.org/Calculators/binomialConfidence.htm
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The primary endpoint of a phase 2 trial may not be a binary outcome, such as tumor response; rather, it may be based on a time-to-event endpoint, such as PFS. Unfortunately, there are some cancers for which the median time to death or progression is measured in weeks or months. If historical data suggest that the median PFS with standard of care is 3 months, this can be recast in a way that parallels testing a tumor response rate. Specifically, a median survival of 3 months is equivalent to specifying that the percentage of patients alive and progression free at 3 months, p_0, is 50%. It is relatively straightforward to convert a hypothetical improvement in the median PFS with the new treatment into a value of p_1 at 3 months, the percentage of patients who are progression free at 3 months.

As mentioned previously, it would not be good practice in reporting the results of a clinical trial to merely provide the *P* value for comparing p_1 with p_0 or merely state that the null hypothesis has been rejected and there is evidence that the new treatment has a higher tumor response rate than the standard-of-care treatment. It is important to also report an estimate of the response rate for the tested treatment as well as its corresponding CI. Knowing the estimate of the tumor response rate of the new treatment allows investigators to place this in context with a host of other factors before deciding whether additional trials are warranted. The estimated response rate is relatively imprecise for phase 2 trials because of the small sample sizes and provides only a rough indication of the response rate. The CI can be computed using standard binomial distribution.

The term optimal relates to a mathematic criterion, which sometimes leads to a design with an imbalance in the sizes of stages that seems impractical, for example, by assigning 70% of the enrollment to the first stage. In such cases, there are almost always alternatives that are mathematically not quite optimal but are more appealing in terms of the split between stages while still

Table 5-7 Examples of Two-Stage Phase 2 Designs (Optimal Simon Design)

Design Criteria				Resulting Design			
				First Stage		Overall	
p_0	p_1	α	Power[a]	n_1	r_1	n	*r*
0.10	0.25	0.05	0.9	21	2	66	10
0.10	0.25	0.10	0.9	21	2	50	7
0.25	0.45	0.10	0.9	22	6	57	19
0.40	0.6	0.10	0.9	25	11	66	32
0.50	0.7	0.10	0.9	24	13	61	36

Abbreviations: α, one-sided type I (false-positive) error rate if $p = p_0$; n, total sample size after both stages; n_1, sample size for first stage; p_0, response rate under null hypothesis (usually based on external control group rate); p_1, response rate under alternative hypothesis; *r*, minimum number of responses required to reject null hypothesis and conclude that $p > p_0$; r_1, if r_1 or fewer responses are observed during stage I, the trial is stopped early for futility (if r_1 or fewer responses are observed by the end of stage II, then no further investigation of the drug is warranted).
[a]Power refers to the probability of rejecting the null hypothesis if $p = p_1$.
Data adapted from https://cancer.unc.edu/biostatistics/program/ivanova/SimonsTwoStageDesign.aspx
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satisfying the other design parameters. For example, another commonly used approach is to minimize the maximum possible sample size; this is called a minimax design. The reader is referred to the work of Ivanova[21] for sample size computation based on different designs, including the optimal Simon design (Table 5-7).

ADDITIONAL PHASE 2 DESIGNS

A Bayesian Optimal Phase 2 (BOP2) design considers a flexible Bayesian approach for a phase 2 clinical trial. The BOP2 design accommodates various types of endpoints, including binary, ordinal, and survival endpoints, within a unified framework.[22,23] It allows for incorporating prior information and adjusting the trial based on accumulating data while controlling the type I error rate. The BOP2 design demonstrates higher power and lower risk of incorrect trial termination compared with existing Bayesian designs and allows for pretrial enumeration of stopping boundaries. In contrast, the Simon two-stage design, a frequentist approach, is simpler and more rigid and used for trials with binary outcomes only. It does not accommodate real-time data adjustments or a range of endpoint types as BOP2 does.

In addition to single-arm designs, whether BOP2 or Simon two stage, phase 2 trials are increasingly using randomization to allocate patients to two or more different arms. The reasons motivating randomized phase 2 designs with multiple therapeutic arms are numerous. Perhaps the most compelling reason for a randomized phase 2 trial is the uncertainty in or even absence of (eg, in a newly defined population based on molecular characteristics) outcome estimates from the historical data. For a more rigorous pilot evaluation of efficacy, the so-called randomized screening phase 2 design has been advocated and is increasingly being used.[24] To maintain a relatively small sample size, this design features larger type I (eg, up to 20%) and type II (20%) errors than typically used in single-arm trials, while protecting against an overly large type I error that would essentially nullify the screening effect or overly large type II error that runs a higher risk of dismissing a potentially useful regimen. However, a positive result in a randomized phase 2 trial, even with a robust endpoint such as OS, should not be seen as conclusive. Such positive findings should be interpreted similarly to interim analyses in phase 3 trials, requiring stricter criteria for positivity. Further validation through a phase 3 trial is generally necessary and expected.

Additionally, some studies do not plan to compare the arms even when randomization is used. In this case, each arm is regarded as an independent trial of a regimen. These trials aim to identify the most promising treatment among experimental options, not to compare them directly. Each treatment arm targets the same patient population, and random assignment is simply a mechanism to ensure that the arms enroll patients with similar characteristics. These are essentially parallel single-arm phase 2 trials. Such designs are often referred to as a randomized phase 2 selection design or pick-the-winner design[25] (Table 5-8). The noncomparative nature allows one to ensure the selected treatment is likely superior without confounding as a result of randomization. This design suits situations where no experimental regimen is initially preferred. Additionally, any chosen regimen must meet a minimum efficacy threshold compared with historical controls before further testing.

Table 5-8 Minimum Sample Size (per Arm) for Simon's Pick-the-Winner Randomized Phase 2 Designs[a]

	Two Arms (p_1, p_2)		Three Arms (p_1, p_2, p_3)	
Difference ($p_2 - p_1$)	Power[b] = 0.80	Power = 0.90	Power = 0.80	Power = 0.90
0.10	36	82	68	123
0.15	16	37	31	55
0.20	9	21	17	31

Abbreviations: p_1, lower (lowest) response rate, 0.4; p_2, higher (highest) response rate.
[a]A conventional type I error rate is not defined for pick-the-winner randomized phase 2 designs because no formal null hypothesis is tested. These designs are intended for treatment selection rather than hypothesis testing, and their operating characteristics are summarized by the probability of correct selection rather than false-positive control.
[b]Power refers to the probability that the arm with highest true response rate has the highest observed response rate.
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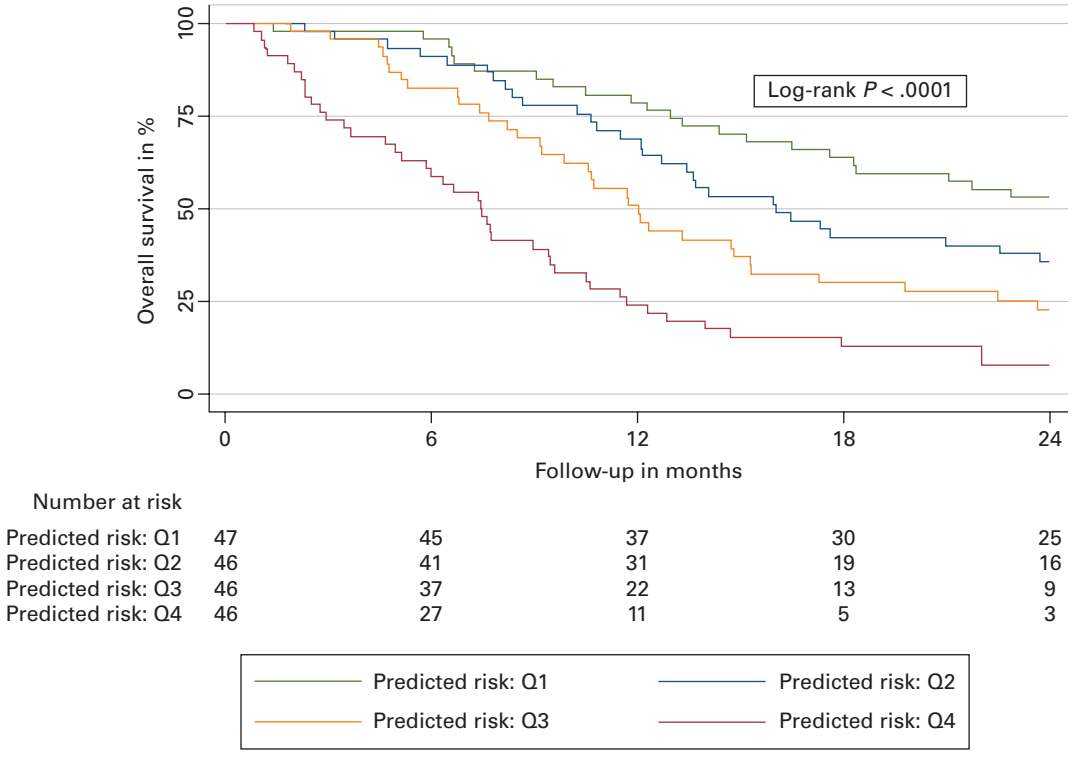
BIOMARKER-BASED PHASE 2 DESIGNS AND MASTER PROTOCOLS

Recently, there have been several innovative designs in oncology trials that incorporate biomarkers.[26,27] Biomarkers may be prognostic or predictive. A prognostic biomarker affects the risk of the outcome regardless of treatment choice, whereas a predictive biomarker changes the outcome in response to a particular targeted treatment. Prognostic biomarkers are related to the natural history of the disease and can be used to identify high-risk patients, so enriching the patient population for those with the biomarker can make it easier to detect a signal because of the higher event rate. For a biomarker to be prognostic, it must have a statistically significant association with the outcome, regardless of treatment (Fig. 5-5). In contrast, predictive biomarkers are associated with treatment and help to identify a subset of patients who are more likely to respond to a specific treatment. That is, if the biomarker is predictive for a particular therapy, then a biomarker subgroup (positive or negative) is expected to have a stronger efficacy signal, with no or little efficacy in the biomarker-negative group. Predictive biomarkers are often determined

from large randomized trials by testing for the interaction term of the treatment biomarker in logistic regression (for a binary outcome) or in a proportional hazards model (for a time-to-event outcome). To evaluate whether a biomarker is predictive, it is necessary to have four groups of patients: (1) those with the biomarker who receive the treatment of interest, (2) those with the biomarker who do not receive the treatment of interest, (3) those without the biomarker who receive the treatment of interest, and (4) those without the biomarker who do not receive the treatment of interest (Fig. 5-5).

Figure 5-5 Kaplan-Meier Survival Curves According to Biomarker-Based Prognostic Score



Note that patient outcomes are stratified in quartiles according to individual predicted risk of mortality.
Reproduced under Creative Commons license. Source: Moik F, Zöchbauer-Müller S, Posch F, et al. Systemic inflammation and activation of haemostasis predict poor prognosis and response to chemotherapy in patients with advanced lung cancer. *Cancers*. 2020;12(6):1619. doi:10.3390/cancers12061619

Phase 2 trials might use enrichment designs, enrolling patients with specific biomarkers indicative of a response to targeted treatments. These designs require quick, precise biomarker assessment and confidence in their relevance to treatment benefits (Table 5-9). However, issues arise if the biomarker screening is not accurate, potentially affecting response rates or excluding benefiting patients. Another approach, marker-stratified design, involves biomarker screening and randomized treatments within biomarker-defined strata, allowing for assessments of treatment benefits relative to biomarker status. This approach demands larger sample sizes but aids in identifying patients who benefit and determining the correct biomarker threshold. Strategy designs incorporate biomarkers differently, using them post-determination for treatment selection. These designs and their variations are detailed in various reviews and articles and are increasingly being applied in both phase 2 and 3 trials.

Master protocols have been used because of their operational efficiency. Generally speaking, master protocols include multiple parallel drug sub-trials designed and conducted under one protocol. Common master protocols include basket and umbrella designs and multistage multiphase designs. Another important class is the platform trial, which evaluates multiple therapies within a single trial infrastructure, often using a shared control group, and allows treatment arms to be added or dropped over time using prespecified decision rules. Platform trials can improve efficiency and speed identification of promising treatments, but they introduce additional statistical and operational complexities that must be carefully prespecified, and shared controls may be susceptible to temporal bias if trial conduct or patient mix changes over time. A high-profile example is the I-SPY 2 trial in breast cancer. Basket trials are designed to enroll patients with similar tumor molecular characteristics across multiple tumor locations, and the patients are treated with the same biomarker-targeted treatment (Fig. 5-6). In such trials, it is likely that there is an arm for each cancer type, and the trial is essentially conducting parallel single-arm studies. Umbrella trials enroll patients with a single tumor origin or histology and test many different treatments. Patients are matched to a treatment on the basis of the biomarker their tumor contains. The advantage of an umbrella trial is that it can test many different biomarker-treatment

Table 5-9 **Factors Affecting Success of Biomarker-Driven Trials**	
Factors	**Key Points and Impact on Trial Success**
Analytically validated biomarker assay	Positive if validated, negative if not. Analytical validation is a prerequisite for credible classification and reproducible results.
Known actionable target	Positive if known, negative if unknown. Actionability supports a clear biological rationale for enrichment or matching.
Large magnitude of difference in clinical outcome	Positive if large, negative if small. Bigger effects are easier to detect and less sensitive to misclassification or heterogeneity.
Moderate to high prevalence	Positive if moderate to high, negative if lower than expected. Low prevalence drives screen failures, slow enrollment, and early closure risk.
High accrual rate	Positive if high, negative if low. Accrual refers to fast enrollment of eligible patients, not screening volume per se, although low prevalence can force high screening to achieve adequate accrual.
Baseline and longitudinal biomarker collection	Positive if baseline plus longitudinal, negative if baseline only. Longitudinal sampling better captures evolving disease biology and resistance.
Prognostic or genomic model as stratification factor: homogeneity within strata	Positive. Improves interpretability and precision by reducing within stratum heterogeneity.
Prognostic or genomic model as stratification factor: heterogeneity across strata	Positive. Creates clinically distinct strata, supports effect modification evaluation, and improves design efficiency.
Validated cutoff point of biomarker	Positive if well validated, negative if not. Unstable cutoffs increase misclassification and reduce reproducibility.
Near real-time readout from assay	Positive if near real time, negative if delayed. Turnaround time affects feasibility, timely assignment, and accrual.
Strong stakeholder buy-in	Positive if strong, negative if weak. Buy-in is critical in biomarker trials, especially master protocols requiring multi-party coordination.

Data adapted from Halabi S, Niedzwiecki D. Advancing precision oncology through biomarker-driven trials: theory vs. practice. *Chance.* 2019;32:23-31. doi:10.1080/09332480.2019.1695438

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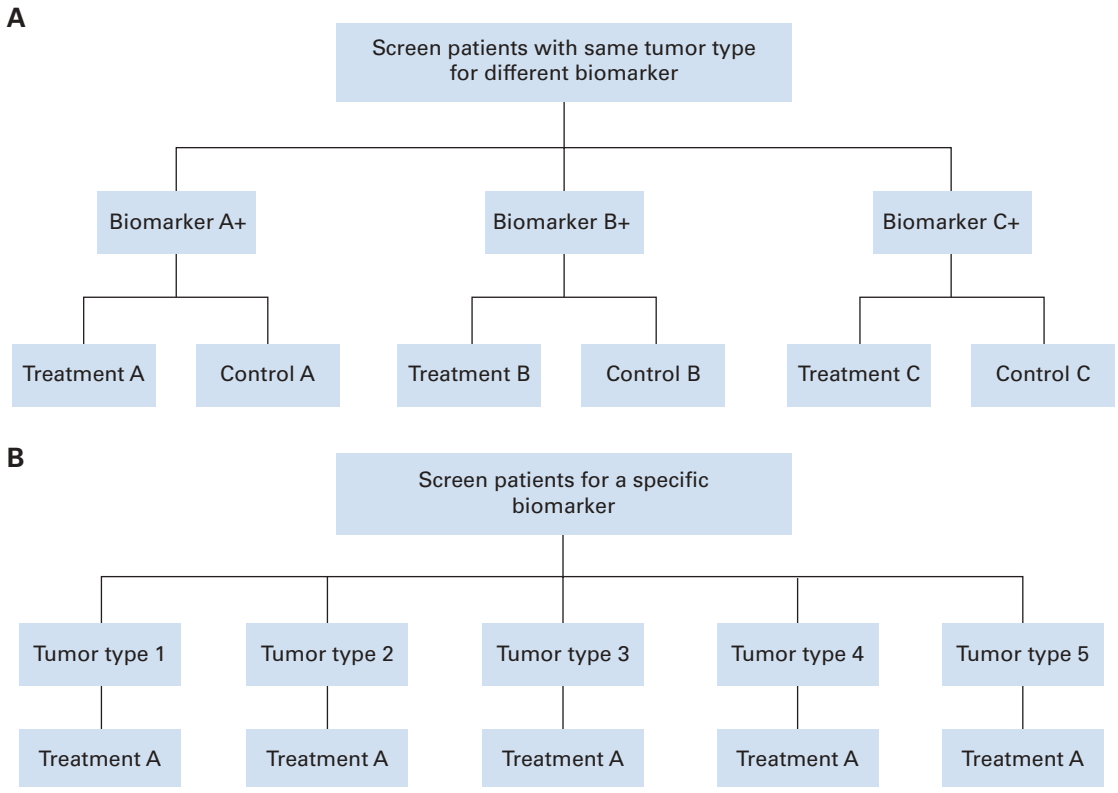
combinations within a single protocol rather than having to have a separate protocol for each different marker-treatment combination. An example of an umbrella trial is Lung-MAP.[28] In contrast, a basket trial tests a single treatment and single biomarker across different tumor origins or histologies. Similarly, an advantage of a basket trial is that it more efficiently tests the biomarker-treatment combination across different tumor types compared with having a separate protocol for each. Examples of basket trials include NCI-MATCH,[29] which evaluates targeted therapies across multiple tumor types based on specific genetic alterations, such as *BRAF* V600–mutated tumors,[30] and the ASCO TAPUR trial.[31]

BIAS IN PHASE 2 TRIALS

Among all the phases of therapeutic development, single-arm phase 2 trials are fraught with the potential for bias. The major source of bias is the absence of contemporaneous randomized comparison groups. Historical outcomes vary widely for many reasons, and past experience may reflect many factors besides the agents being tested. These can include the eligibility criteria defining the patient population; the definition, timing, and methods used to assess outcome; standards of supportive care that vary by institution and over time; the use of surrogate endpoints; and, of course, simple random variation. This is more pronounced for endpoints other than tumor response rates because tumor response rates are less affected by difference in prognostic factors than endpoints such as PFS and OS. Even in the absence of any systematic bias (an ideal unlikely to be achieved), the random outcomes observed in relatively few patients could lead to many false conclusions. One should be cautious in using single-arm designs to evaluate cancer combination therapies,[32] because it can be particularly difficult to attribute positive outcomes solely to the combination therapies under investigation, when an existing single agent is at least somewhat active. The aforementioned factors, including small sample sizes and patient selection biases, could further skew results in these settings and thus frequently yield inconclusive or misleading results in evaluating combination therapies.

Figure 5-6 Umbrella and Basket Trial Designs



(A) Illustration of an umbrella trial design in which patients with the same tumor type are tested for different biomarkers and then are assigned to a treatment group that targets the biomarker. In this example, patients are randomly assigned to a treatment versus control arm. An alternative design could be a single-arm design with the patients with a particular biomarker receiving treatment meant to target that biomarker. (B) Illustration of a basket trial design in which all patients are tested for a particular biomarker and then are entered into a cohort for their tumor type. All patients receive the same targeted treatment that is believed to potentially benefit patients with tumors with the biomarker. This shows each cohort is a single-arm trial, but the cohort could be randomly assigned to treatment and control arms.
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The most observable of these are false-positive results, that is, agents that look promising in phase 2 trials but then fail to be effective in phase 3 trials. Less observable, but just as unfortunate, are agents that, in truth, are effective but fail to show positive results in phase 2 trials. Randomized control arms are sometimes used in phase 2 trial settings to remove potential sources of bias resulting from historical control comparisons[26]; however, they introduce additional variability in the treatment effect estimate. As a result, they typically require larger sample sizes and may use a higher type I error rate to maintain sufficient power to identify promising agents in the phase 2 setting. They may also appeal less to potential participants because patients are less likely to receive an experimental therapy with a randomized design.[33,34]

Randomized phase 2 trials are increasingly recommended to reduce bias by incorporating a control group, particularly for combination therapies, heterogeneous populations, and time-to-event endpoints (Presenting Case Study 2). However, single-arm designs remain acceptable in specific contexts, such as rare cancers, novel agents, or when robust historical data are available. As reported by Grayling et al,[33] despite the push for randomization, only 28% of randomized comparative phase 2 trials have reported positive outcomes, compared with 72.7% of single-arm trials, underscoring the potential for overestimation of efficacy in single-arm studies.

Nevertheless, even randomized phase 2 oncology trials often overestimate treatment effects relative to subsequent phase 3 trials. Liang et al[34] found that treatment effects for PFS and OS in randomized phase 2 trials were, on average, 26% to 27% larger than those observed in phase 3 trials. This overestimation is influenced by factors such as optimism bias, publication bias, and differences in trial designs and patient populations. Moreover, the staged development paradigm, where promising phase 2 results drive progression to phase 3 trials, inherently selects treatments with inflated early effect sizes. Addressing these challenges requires cautious interpretation of phase 2 results, the application of statistical adjustments, and rigorously designed phase 3 trials to ensure robust validation of findings.

PRESENTING CASE STUDY 2

A clinical investigator is designing a phase 2 trial to evaluate the activity of a novel immunotherapy agent as monotherapy for patients with advanced stage cancer. Phase 1 trials have established the RP2D, and preliminary safety data are reassuring.

Historical data indicate that the current standard-of-care treatment has a response rate of 20%, providing a benchmark for comparison. The investigator is considering a single-arm trial to efficiently determine whether the new therapy demonstrates a meaningful improvement over this threshold while minimizing the number of patients exposed to an unproven treatment. A practical choice for the primary endpoint is objective response rate (ORR) assessed at a prespecified time point using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or, for immunotherapy, iRECIST, because response can often be evaluated within months. Alternatively, if response is uncommon or not the most clinically relevant signal, the endpoint could be a short-term time-to-event measure such as 3-month progression-free survival (PFS) rate, which can be framed similarly to a binary endpoint for design purposes.

To enhance trial efficiency, the investigator plans to incorporate a futility stopping rule, allowing early termination if interim results suggest the immunotherapy agent is unlikely to be superior to the standard of care. However, concerns remain about whether a single-arm design will provide sufficiently robust evidence to justify further development or if a randomized controlled trial (RCT) would be more appropriate.

What factors would inform your selection of optimal trial design for evaluating a new therapy?

Selecting between a single-arm trial and an RCT involves balancing feasibility (smaller sample size in single-arm trials) with the strength of evidence generated (stronger evidence in randomized trials). Given the goal of assessing whether the new immunotherapy agent outperforms the 20% historical response rate, a single-arm design may initially seem appealing. However, this choice comes with limitations that must be carefully evaluated.

Hypothetical example: single-arm phase 2 design

Suppose the primary endpoint is ORR. Let $p_0 = 0.20$ represent the historical benchmark, and let $p_1 = 0.35$ represent the minimum ORR that would be considered promising. A common approach is a two-stage design with early stopping for futility, which specifies a one-sided type I error (often around 0.10) and high power (often around 0.90) to detect p_1. For example, the trial could enroll an initial stage of patients and stop early if too few responses are observed and otherwise continue to the full sample size. This provides a concrete go or no-go rule while limiting exposure if the regimen is inactive.

Advantages of a single-arm trial

- Efficiency and feasibility: A single-arm trial requires fewer patients, making it faster and more resource efficient, particularly for rare diseases or early-phase trials.
- Early signal of activity: If response rates significantly exceed 20%, this can justify further development in a larger study.
- Use of a futility rule: An early stopping rule allows the trial to terminate if activity seems insufficient, reducing unnecessary patient exposure.

Limitations of a single-arm trial

- Lack of a concurrent control group: Relying on historical data assumes that the 20% benchmark is comparable to the current patient population. Differences in patient selection, treatment patterns, time trends, or response assessment can introduce bias and reduce comparability.
- Potential for overestimation: Response rates in single-arm trials may seem inflated because of selection bias or unmeasured confounders.
- Regulatory and clinical credibility: Regulatory agencies often prefer RCTs for definitive evidence because single-arm studies may not provide sufficient comparative effectiveness data.

Advantages of an RCT

- Stronger evidence of efficacy: Randomization minimizes bias by ensuring balanced patient characteristics between treatment arms.
- Comparability with standard of care: Directly comparing the new therapy with existing treatment provides more reliable evidence for decision-making.
- More generalizable results: An RCT reduces confounding factors and allows for robust assessment of clinical benefit.

Limitations of an RCT

- Larger sample size and higher cost: More patients and resources are required to adequately power the study.
- Potential ethical concerns: If the new therapy is expected to be superior, randomly assigning patients to the standard of care may raise ethical questions.

Hypothetical example: randomized phase 2 design

If historical response estimates are uncertain or the population is evolving, a randomized phase 2 screening design can compare the novel immunotherapy against a concurrent control while keeping the sample size modest by using a higher type I error and type II error than in phase 3. For example, the trial might randomize patients 1:1 to immunotherapy versus standard of care, using ORR or a short-term PFS milestone as the primary endpoint, and prespecify a one-sided type I error as high as 0.20 with power around 0.90 to identify a promising regimen for phase 3 confirmation. A positive finding would be considered a screening signal rather than definitive proof, similar in spirit to an interim look that requires confirmation in a later-phase trial.

Considering these advantages and limitations, how should you proceed?

For this trial, a single-arm design may be appropriate for generating an early efficacy signal, but it must be carefully justified given the reliance on historical controls. Historical control estimates based on studies from similar institutions, a recent timeframe, a larger sample size, and multiple studies reporting similar estimates would enhance the credibility of a single-arm trial. Incorporating a futility rule can improve efficiency by stopping the trial early if the agent fails to show promise. However, if the goal is to provide definitive evidence of superiority, an RCT would be preferable, ensuring a robust comparison against the standard of care. The choice ultimately depends on feasibility, regulatory expectations, and the strength of evidence required to support further development.

In this scenario, a single-arm phase 2 trial with a prespecified futility rule is an appropriate initial approach to efficiently screen for activity, assuming the historical response benchmark is well defined and relevant. If the observed signal is encouraging but uncertainty about historical comparability remains, a randomized phase 2 design should follow to generate more robust comparative evidence for further development.

KEY POINTS

- The typical sample sizes used in phase 2 trials provide imprecise estimates of outcome.
- Basket and umbrella trials efficiently evaluate several treatment-marker or treatment-histology combinations.
- Results among phase 2 trials, especially single-arm trials, are difficult to compare because so many factors can vary from trial to trial.

PHASE 3 TRIALS

Phase 3 clinical trials are typically randomized clinical trials, which are the gold standard of clinical research. In general, these studies are designed to change the practice of medicine and, as such, are designed to demonstrate and confirm the safety and efficacy of a treatment strategy for approval by regulatory authorities. The classic goal of a phase 3 trial is to compare an experimental treatment with a standard treatment.

STUDY OBJECTIVES AND PATIENT POPULATION

The primary objective of a phase 3 trial is to establish the efficacy of a treatment regimen in a specific patient population compared with an accepted standard-of-care treatment. The patient population is usually narrowly defined as patients with a particular stage of cancer and in a particular clinical scenario (eg, patients with metastatic colon cancer who have received no prior therapy). The alternative hypothesis for a typical phase 3 trial is that the new therapy will be more efficacious than the currently used standard therapy, known also as a superiority trial. Following this, the null hypothesis would be that the new therapy has the same efficacy as the standard therapy. The phase 3 clinical trial is then designed to reject the null hypothesis.

STUDY OUTCOME MEASURES

In phase 3 trials, the interest is to demonstrate prolongation in survival or reduced pain and improved quality of life for patients. Therefore, the outcome considered for a phase 3 trial must be as definitive as possible, with no or minimal variability or room for interpretation. In phase 3 trials, OS is defined as the time interval between random assignment and death or last follow-up. Note that OS events include deaths resulting from any cause and not just those resulting from the cancer of interest. Pivotal phase 3 trials can be designed around other outcomes if these have been validated as meaningful outcomes or as surrogates for meaningful outcomes. The design of clinical trials to validate correlative studies, biomarkers, or surrogate markers can be complex and is discussed later in this chapter. A list of surrogate endpoints that were the basis of drug approval or licensure is maintained by the FDA and can be used when considering potential surrogate endpoints in different settings.[35]

STUDY ENDPOINTS

Phase 3 clinical trials intend to establish whether the treatment being investigated provides a direct clinical benefit to patients above the standard of care. The patient population for a phase 3 trial is composed of people for whom the treatment is intended to be used. Typically, phase 3 trials have fewer restrictions on patient eligibility than phase 1 and 2 trials. The current trend is to reduce unnecessary eligibility requirements so that the trial results will be more generalizable to the target clinical population.[36] In the oncology setting, an improvement in survival is often the gold standard for demonstrating such a benefit. However, other endpoints are also used to demonstrate clinical benefit while yielding efficiencies in trial design. Other endpoints commonly used in phase 3 trials include, but are not limited to, the following:

- PFS: the time from random assignment to date of disease progression or death resulting from any cause, whichever occurs first. PFS is generally used in advanced-disease settings.
- DFS: the time from random assignment to date of disease relapse/recurrence or death resulting from any cause, whichever occurs first. DFS is generally used in adjuvant settings.
- Event-free survival: the time from random assignment to date of the event of interest, which may include other outcomes in addition to death and disease progression, whichever occurs first.

The advantage of using an outcome other than OS is that it can be observed before death and so can speed up trial completion. However, the interpretation of clinical benefit using other outcomes is more difficult. Superiority in terms of time to progression, PFS, or DFS can occur despite a therapy causing more deaths resulting from toxicity, and superiority of PFS or DFS can occur as a result of a more favorable safety profile, without any therapeutic effect on the cancer. Often, PFS or DFS may not be an established surrogate endpoint for OS, meaning that it is not known whether an improvement in these endpoints actually correlates with an improvement in OS. This makes it unclear whether an improvement in PFS or DFS really represents a direct clinical benefit to patients, especially in the presence of treatment toxicities. Endpoints may be subject to assessment bias, so additional trial design considerations are important, including patient and physician blinding, independent endpoint review committees, and regular disease evaluations.

Patient-reported outcomes use questionnaires to measure how a patient feels and functions; therefore, patient-reported outcomes can also be important for assessing the direct clinical benefit of a treatment being evaluated in a clinical trial. These instruments must undergo rigorous development and testing to ensure that they are measuring what is expected and that they are reliable. Several distinct aspects of patient-reported outcomes are important for understanding the benefits and toxicities of treatment, including the burden of disease symptoms, physical functioning and the ability to perform activities of daily life, and symptomatic adverse events. Blinding in the trial design is important for these outcomes to avoid assessment bias, and completeness of data collection is crucial to minimize the effect of missing patient-reported outcome data and the biases that this may introduce.

STUDY DESIGN PRINCIPLES

The primary goal of a phase 3 trial is to provide a comparison of treatments that is free of many biases that occur when trying to compare phase 2 trials conducted at different times, at different institutions, among different patient populations, and so on. Randomization is the gold standard for the best design in clinical trials because it minimizes bias. It balances

baseline known and unknown prognostic factors in patients between the treatment groups although some imbalances may occur by chance alone.

The most common randomization strategy is equal allocation among treatment arms, or one-to-one randomization. From the standpoint of statistical power, this is the most efficient allocation that results in the smallest sample size, as well as the most compatible one with the notion of clinical equipoise. A common variation of simple randomization is stratified randomization, which seeks to ensure even greater balance between arms by randomly assigning patients within strata defined by factors that strongly predict outcome. In addition, the randomization may be in blocks, which generally refers to a form of stratification designed to keep the number of patients allocated to each arm balanced over time. Stratification and blocking are most useful in small trials, in which random imbalances large enough to skew the composition of the treatment arms are possible. When the trials become larger (several hundred patients), these devices are largely superfluous because it becomes highly unlikely that the arms will become meaningfully imbalanced by chance. Another alternative randomization procedure is dynamic allocation. This type of randomization is considered adaptive because assignment of a patient to a treatment arm is influenced by the current balance of allocated treatments.

Departures from equal allocation sometimes occur, for example, a two-to-one allocation between the experimental and control arms. Most commonly, this is justified with the argument that it makes the trial more attractive to potential patients and their physicians, particularly when there is no way to get access to an experimental agent except through participation in the trial. It also allows one to generate more experience with the new agent. However, this argument seems to presume that the experimental therapy is likely to be more effective than the standard therapy, which contradicts the principle of equipoise. Furthermore, as mentioned, a two-to-one allocation will require a larger sample size than one-to-one randomization, with all other trial parameters being the same.

Other common, but by no means necessary, components of a phase 3 design include the use of a placebo and the implementation of blinded (to the patient) or double-blinded (to both the patient and physician) treatment assignments. Although random assignment can help ensure that treatment arms are balanced with respect to patient characteristics at the start of the trial, it cannot remove bias that occurs after the start of the trial, when differences arise between arms with respect to the conduct of the trial or the evaluation of trial data. This bias can be entirely unintentional and unconscious, but it reflects behavior by either patients or physicians that compromises the benefits of randomization. The susceptibility of trials to bias can vary considerably depending on the endpoint in question. For example, placebo effects and ascertainment bias are probably unlikely to affect a trial in which mortality is the primary endpoint. In contrast, assessment of tumor response without blinding to treatment assignment could be subject to subtle bias, and studies with self-reported quality-of-life endpoints are obviously prone to placebo effects.

The use of a placebo as the control arm in therapeutic oncology trials is extremely rare because usually some form of therapy is available, even if it has limited efficacy. A placebo control is much more likely to be used in adjuvant trials or in trials of combination therapy in which a new agent is being added to an existing combination. Although one may question the extent to which placebo effects play a role in such settings, if a placebo is feasible, it adds credibility to a trial, even if the likelihood of placebo effects is small. Placebos are more commonly used for double-blind evaluation of oral therapies, where placebos can be made identical in appearance to the medication. In some cases, of course, the nature of the treatments differs largely that neither a placebo nor blinding is feasible. Blinding may also be a deterrent to patients' willingness to participate, and all of these factors must be carefully evaluated when designing the clinical trial.

INTENTION TO TREAT

The most acceptable primary analysis of a phase 3 trial is using the intention-to-treat principle. This approach includes all patients enrolled in an arm of a randomized trial, no matter what happens thereafter; for example, if patients are unable to receive the full course of treatment, they cross over to another treatment, and so on. Because any of these contingencies can be related to the treatment itself and to the effectiveness of the treatment, an unbiased analysis must incorporate that information. For example, if a new drug is potentially effective, but many patients will not take it because of its adverse effects, then as a practical matter it may not be as effective as a drug with fewer adverse effects.

Nevertheless, alternative secondary analyses may be undertaken that deviate from the intention-to-treat principle. To emphasize, these are secondary analyses performed after the completion of the primary intention-to-treat analysis. Secondary analyses may involve an evaluation of a subset of patients (eg, those who received a minimum amount of therapy) or definition of the treatment groups according to the treatment actually received instead of the treatment to which patients were randomly assigned. These secondary analyses can be informative but must be interpreted cautiously and are problematic when the results differ markedly from those of the primary intention-to-treat analysis.

Other subset analyses may be undertaken to evaluate whether treatment differences, if any, vary according to other factors, such as disease stage, age, or presence of a biomarker. Even if specified in advance, the results of such subset analyses must be interpreted cautiously. Phase 3 studies are almost never large enough to have reliable power in subsets of patients; conversely, examining many subsets of patients in a trial with an overall negative result can lead to spurious findings that are caused merely

by random fluctuation. Instead, forest plots can be an effective approach to show the consistency (or any inconsistency) of the treatment effects (eg, HR) over diverse factors rather than showing statistical significance in a specific subgroup.

INTERIM ANALYSIS

Randomized phase 3 trials can be large, expensive, and take several years to complete. For this reason, most phase 3 trials have a provision for interim analysis at one or more points, with the possibility of terminating the trial early. The indications for early termination can be varied and are generally specified in advance. These may include strong evidence that the experimental therapy is better than the control therapy, strong evidence that it is worse, or a determination that the trial will not be conclusive (futility). Interim analyses are also ethically important because early information may be sufficient to alter trial conduct or even clinical practice.

A number of statistical approaches to interim analysis, known as group sequential design, codify the timing and nature of the analyses and the threshold required to terminate the trial early. If the trial is to be stopped early because of evidence that the experimental therapy is superior, the overall false-positive rate (type I error rate) for the trial needs to be quantified and controlled because multiple sequential analyses of the data without adjustment can lead to an increase in type I error rates. Because small sample sizes are subject to much random variation, the threshold for stopping a trial early generally involves a high degree of statistical significance, meaning type I error rates that are much lower than a standard .05 level of significance (eg, as low as .001 or .0001). In addition, if a proportion of the type I error rate is "spent" during interim analyses, then the significance level for the final analysis will be lower than the stated trial value of α. For example, a decision may be that the overall trial should have a type I error rate of 5% with one planned interim analysis in which the threshold for stopping the trial will be $P < .01$. Because .01 was spent on the interim analysis, the level of evidence required at the end of the study is $P < .04$. This ensures that the overall trial will have the desired level of significance of .05 (.01 for the interim analysis and .04 for the final analysis). The threshold significance levels at the interim analyses and final analysis constitute the stopping boundaries. Among the various α spending approaches used in group sequential designs, the Lan-DeMets α spending function with O'Brien-Fleming boundaries is the most commonly applied in randomized phase 3 trials.[37,38] This method allows for flexible interim analysis timing while maintaining statistical rigor, setting more conservative early stopping boundaries and preserving most of the type I error rate for the final analysis.

Interim analyses may also indicate that the observed difference between treatment arms is smaller than initially hypothesized or that there is little evidence of a meaningful difference. On the basis of accumulated data and assumptions about the true treatment effect, it is possible to estimate the probability of ultimately demonstrating superiority. If this probability is too low, the trial may be terminated early to avoid unnecessary time and expense, a decision referred to as stopping for futility. However, it is important to distinguish an inability to demonstrate a difference from proving equivalence. A trial stopped early for futility may yield inconclusive results. In some cases, completing the trial, even when a treatment benefit seems unlikely, may be justified if doing so strengthens the evidence supporting the absence of benefit.

The interim analysis plan for a phase 3 trial should be prespecified and is considered an integral part of the trial design. However, the decision to stop a trial early involves complex and important issues that cannot be summarized in a simple statistical test. Typically, the results of an interim analysis will be reviewed by a data and safety monitoring board. The role of this board is to independently review the results of an interim analysis, consider the results in context with a host of other factors (eg, scientific, ethical, legal, financial), and make a recommendation about whether to continue the trial. Additional factors leading to trial termination include poor accrual or the clinical question becoming irrelevant during the course of the trial because of new scientific findings.

Please refer to the "Presenting Case Studies" sections for examples of interim analyses from completed randomized phase 3 trials that were stopped early for efficacy (PACIFIC) or futility (KEYNOTE-598).

MULTIPLICITY

Multiplicity in clinical trials refers to the challenge of managing multiple statistical analyses within a single study. This situation often arises when researchers test several hypotheses or conduct multiple comparisons between treatment groups. The primary concern with multiplicity is the increased risk of type I errors (false positives) where a treatment seems to be effective, but this has merely occurred by chance. This risk increases with each additional hypothesis tested, potentially leading to erroneous conclusions about a drug's efficacy or safety. In clinical research, especially in phase 3 trials, such errors can have significant implications. A false positive might suggest that a treatment is beneficial when it is not, potentially leading to the adoption of ineffective or even harmful medical interventions. Conversely, excessive caution in avoiding false positives can result in false negatives, overlooking genuinely effective treatments. To address these challenges, various statistical methods have been developed and used in different contexts. Each of these methods requires careful consideration and planning to ensure the integrity and validity of a trial's conclusions, while maintaining statistical rigor.

In trials with multiple primary endpoints, α splitting is a common method. It involves dividing the overall type I error probability (α) among the various endpoints to maintain the overall error rate within acceptable limits. For instance, in a trial with

two coprimary endpoints, the α level of 0.05 might be split into two 0.025 segments for each endpoint. This ensures that the probability of making at least one type I error across all endpoints remains controlled. This approach, however, can lead to a loss of power, so it is essential to balance the need for error control with the potential reduction in statistical power.

Group sequential designs are particularly relevant here. These designs incorporate several planned interim analyses at certain points in the trial. At each interim analysis, data are evaluated to determine whether the trial should be stopped early for reasons of efficacy or futility or sometimes safety. The use of group sequential methods allows for early stopping while controlling the overall type I error rate through statistical methods such as the O'Brien-Fleming or Pocock boundaries. These methods adjust the criteria for significance at each interim analysis, typically making it more stringent to stop early for efficacy.

Subgroup analyses in phase 3 trials are crucial for understanding treatment effects in different patient segments. However, they raise concerns about multiple testing and the potential for spurious findings. To address this, statistical adjustments are often made. One common approach is the hierarchical or stepwise testing method,[39,40] where primary endpoints are tested first, followed by key secondary endpoints and then subgroup analyses. This method controls the type I error rate across the hierarchy of tests. Additionally, using prespecified hypotheses and limiting the number of subgroups analyzed can help to reduce the risk of false positives.

Additional discussions of multiplicity in the context of translational research can be found in the "Translational Medicine Studies" section. Please refer to the Case Studies section for an example of multiplicity control from the PACIFIC trial, a randomized phase 3 trial in locally advanced non–small cell lung cancer (NSCLC).

DESIGN OPTIONS

Equivalence and noninferiority designs do not attempt to establish that a new treatment is superior to a standard treatment but instead aim to establish that the new treatment has equivalent efficacy or is noninferior compared with a standard treatment or that its efficacy is only slightly worse than that of a standard treatment. Although most phase 3 trials are undertaken with an underlying goal of demonstrating a difference between treatment arms, there are circumstances in which the goal is merely to demonstrate that one therapy is equivalent, or at least not inferior, to another. The main motivation to designing noninferiority trials is that the new treatment or device might be less toxic, less inconvenient, less expensive, or less invasive, but less effective, than the standard treatment.

It is impossible to design a trial to demonstrate that two therapies are equivalent, and, in reality, it is highly unlikely. Instead, one specifies the smallest difference that would be of practical clinical significance, for example, a 5% difference in 10-year survival, and then designs a trial that has high power to reject the null hypothesis (low type II error rate) if such a difference truly exists. A successful trial from the standpoint of equivalence would then reject the null hypothesis if a true difference exists. Note that the concept of a false-positive or false-negative conclusion is, in a way, reversed from the usual design perspective, and the typical rates of type I and type II errors used in such designs might need to be reconsidered. Equivalence studies are notoriously large because the difference in outcome said to define equivalence is typically smaller than the difference hypothesized for a superiority trial, which dramatically affects the sample size. A trial with an equivalency threshold set at a 5% difference requires a sample size four times as large as that for a superiority trial powered to detect a 10% difference.

An alternative to an equivalency design that requires a somewhat smaller sample size is the noninferiority design (Table 5-10).[41] In this case, one specifies a noninferiority margin, which provides the maximum acceptable loss in efficacy for the new treatment compared to the control. The trial is designed by formulating a null hypothesis that the new therapy has that level of inferiority, or worse, and then is powered to reject the null hypothesis for a specified alternative assumption (which might be equivalence, a lesser degree of inferiority, or even superiority). This usually results in a smaller sample size than that needed for an equivalence design, partly because it involves a one-sided hypothesis test but often by claiming a wider limit of acceptability for noninferiority than for equivalence.[41] For example, if the study is designed with an noninferiority margin of .20 and assuming p_0 (proportion of response in the standard arm) = .50 (also for p_1 proportion in experimental arm = same as the standard arm), equal allocation between the two arms, one-sided $\alpha = 0.05$, and power of .90, then a total of 214 participants (107 per arm) is required.

Table 5-10 Required Sample Size (per Arm) for Noninferiority Trials With Binomial Endpoint

Allowable Difference or Noninferiority Margin ($p_0 - p_1$)	Sample Size per Arm
0.20	107
0.15	191
0.10	428
0.05	1713

Note: $p_0 = 0.50$, $\alpha = 0.05$, and power = 0.90. Computation was completed using binomial noninferiority tool (https://stattools.crab.org/R/Binomial_Non_Inferiority.html).

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After having demonstrated noninferiority or equivalence, one might then proceed to show that one treatment is less toxic or preferred by patients because of improved quality of life to justify selecting one treatment over another.[42-45]

Please refer to the "Practical Interpretations for Clinical Trials" section for an example of a noninferiority design from the completed randomized phase 3 trial (RTOG-0415).

PRACTICAL INTERPRETATIONS FOR CLINICAL TRIALS

Here we describe three recent randomized phase 3 clinical trials to illustrate the use and implications of interim analyses, with the PACIFIC trial (ClinicalTrials.gov identifier NCT02125461) as an example of early stopping for superiority and KEYNOTE-598 (ClinicalTrials.gov identifier NCT03302234) as an example of early stopping for futility. Because both trials had coprimary endpoints of PFS and OS, as well as planned interim analyses, they also illustrate the use of multiple comparison adjustment approaches, such as α splitting and α recycling, to control the overall type I error rate. The RTOG-0415 trial (ClinicalTrials.gov identifier NCT00331773) comparing hypofractionated radiotherapy (H-RT) with conventional radiotherapy (C-RT) in men with low-risk prostate cancer is an example of a trial with a noninferiority design.

PACIFIC Trial: Early Stopping for Superiority

The PACIFIC trial was a landmark study that redefined the standard of care for patients with stage III unresectable NSCLC. This phase 3 randomized, double-blind trial evaluated whether durvalumab, administered as consolidation therapy after platinum-based chemoradiotherapy, could improve clinical outcomes. Patients were randomly assigned in a 2:1 ratio to receive durvalumab or placebo for up to 12 months. The trial's coprimary objectives were to determine whether durvalumab could delay disease progression, as measured by PFS, and extend OS. With coprimary endpoints of PFS and OS, the statistical framework split the overall $\alpha = 5\%$ type I error equally between these endpoints to ensure strict control of the false-positive findings rate. Additional statistical techniques, such as a hierarchical hypothesis testing framework and α exhaustive recycling strategy, were also used and enabled reallocation of α from a rejected hypothesis to subsequent endpoints lower in the hierarchy of endpoints and prespecified hypothesis tests.

To evaluate the coprimary endpoints at different stages of data maturity, the study was designed with interim analyses at four data cutoff points. The first interim PFS analysis occurred after approximately 30 months, when 367 PFS events had been observed, and only PFS was analyzed to maintain the integrity of subsequent OS analyses. The first interim analysis for OS was performed at the same time as the primary (final) PFS analysis at approximately 36 months, with subsequent interim and final OS analyses scheduled as OS events accumulated. This staged approach ensured that clinically meaningful results could be shared in a timely manner without jeopardizing the statistical validity of long-term findings and other endpoints.

The interim analysis,[46] based on the first data cutoff point (February 13, 2017) when the accrual target was met (N = 713) and 371 PFS events were observed, demonstrated that durvalumab significantly improved PFS compared with placebo (median, 16.8 vs 5.6 months; HR, 0.52; $P < .001$), with a manageable safety profile. This early result was critical in establishing durvalumab as the new standard of care, allowing it to reach patients sooner. Without this planned interim analysis, the trial's findings might have been delayed, potentially postponing access to a life-extending therapy for patients with limited treatment options.

Long-term results, published in *Journal of Clinical Oncology* in 2022, reinforced the interim findings, demonstrating consistent and durable benefits. Durvalumab significantly improved OS (HR, 0.72; 95% CI, 0.59-0.89), and the 5-year survival rates were substantially higher for durvalumab compared with placebo. The alignment between PFS and OS findings highlighted the utility of PFS as a surrogate endpoint for OS, particularly in a setting where durable disease control translated into meaningful survival gains. These results underscored the robustness of the trial design and the reliability of the interim findings as predictors of long-term outcomes.

The PACIFIC trial exemplifies the power of a well-designed clinical trial to drive meaningful advancements in patient care. By combining innovative statistical methodologies with a rigorous testing framework, the trial not only delivered reliable and impactful results but also accelerated the adoption of an effective therapy. The consistency between the interim and long-term results further validates the trial's approach and highlights the importance of integrating early- and late-phase analyses in oncology research.

We note that although the PFS coprimary endpoint was met at the first interim analysis, the study had already completed full enrollment at that time. The positive interim analysis results were announced without having to wait for the final analysis time point, which is often referred to as early stopping of a trial. Early stopping does not necessarily preclude longer term follow-up for additional endpoints, such as the coprimary OS endpoint, or other important secondary endpoints. In trials where interim analyses occur before completion of enrollment, early stopping at an interim analysis has the additional advantage of reducing the trial sample size.

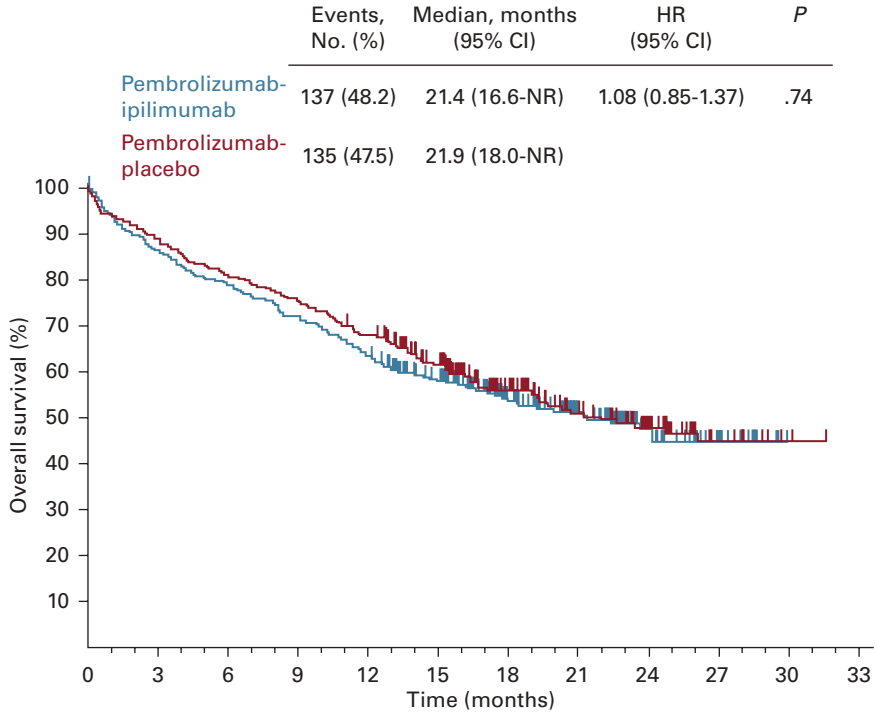
KEYNOTE-598 Trial: Early Stopping for Futility

KEYNOTE-598 is an example of a trial that was stopped early for futility. It was a randomized, double-blind, phase 3 trial in which patients with previously untreated metastatic NSCLC with a programmed cell death ligand 1 (PD-L1) tumor proportion

score of 50% or greater and no sensitizing *EGFR* or *ALK* aberrations were randomly allocated 1:1 to receive pembrolizumab plus ipilimumab or pembrolizumab plus placebo every 6 weeks for up to 18 doses. The coprimary endpoints were PFS and OS. With a planned sample size of 568 participants, the trial was designed to achieve 87% power to detect an HR of 0.69 for PFS in favor of pembrolizumab plus ipilimumab treatment with one-sided α of 0.006 with one planned interim analysis for superiority and to achieve 90% power to detect an HR of 0.7 with a one-sided type I error α of 0.019 with two planned interim analyses. The family-wise type I error rate was one-sided $\alpha = 0.025 = 0.019 + 0.006$, which is an example of α splitting, where portions of the overall α level are allocated to different endpoints or interim analyses.[42] Additional information and discussion of statistical methods for designing clinical trials with multiple endpoints can be found in the FDA guidance document.[43]

At the time of the first interim analysis, 568 participants were randomly assigned (284 per arm), and 272 deaths were observed in both arms. Both PFS and OS appeared to be similar at the first interim analysis; the median PFS was 8.2 and 8.4 months in the two arms, and the median OS was 21.4 and 21.9 months, respectively. Although the protocol did not specify a futility analysis, futility criteria and a formal analysis were requested by the external data and safety monitoring committee. Results of the futility analysis showed that the addition of ipilimumab to pembrolizumab in this setting was unlikely to demonstrate efficacy, and the trial was stopped early for futility. Lack of difference between arms can be seen in the Kaplan-Meier estimates of OS in the two arms (Fig. 5-7 from the report by Boyer et al[47]).

Figure 5-7 KEYNOTE-598: Kaplan-Meier Plot of Overall Survival (OS)



Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.
Reprinted from Boyer M, Şendur MAN, Rodríguez-Abreu D, et al. Pembrolizumab plus ipilimumab or placebo for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥50%: randomized, double-blind phase III KEYNOTE-598 study. *J Clin Oncol*. 2021;39(21):2327-2338. doi:10.1200/JCO.20.03579

RTOG-0415: Noninferiority Trial

RTOG-0415 trial was a phase 3 randomized noninferiority study comparing H-RT with C-RT in men with low-risk prostate cancer. The trial aimed to determine whether H-RT, a shorter and more convenient treatment schedule (70 Gy in 28 fractions), was noninferior to the standard C-RT regimen (73.8 Gy in 41 fractions) in terms of 5-year DFS.[44,45]

The rationale for conducting a noninferiority trial in this context stems from several key factors. C-RT schedules require 40 to 45 treatments over 8 to 9 weeks, posing significant time and cost burdens to patients. Advances in imaging and radiation delivery

have enhanced precision, reducing risk to normal tissues and making hypofractionation, which involves fewer treatments with higher doses per fraction, a viable alternative. Additionally, the radiobiology of prostate cancer, with its low α/β ratio, suggests it is particularly well suited to H-RT. A noninferiority design allowed the trial to formally evaluate whether H-RT could achieve comparable DFS outcomes to C-RT while offering the added benefits of greater convenience, reduced cost, and broader accessibility, positioning H-RT as a potential new standard of care.

The trial was powered to detect noninferiority with 90% power and a one-sided type I error of 5%. The noninferiority margin was set at a 7.65% absolute difference in 5-year DFS rates, corresponding to an HR of 1.52. This margin was chosen based on approximately half the absolute 5-year DFS improvement observed in contemporary dose-escalation superiority trials (15% difference) in similar patients. The sample size of 1067 patients accounted for up to 10% ineligibility or missing data, with definitive analysis planned after observing 238 DFS events.

The trial included three planned interim analyses after 60, 120, and 179 DFS events. These analyses allowed early stopping for noninferiority (if H-RT was deemed comparable to C-RT) or futility (if noninferiority could not be achieved). At the third interim analysis, with 185 DFS events observed (78% of the planned total), the data monitoring committee recommended early disclosure of results. At this stage, the criterion for rejecting the null hypothesis of inferiority ($P \leq .011$) was met, supporting the conclusion that H-RT was noninferior to C-RT.

After a median follow-up of 12.8 years, the trial demonstrated that H-RT was noninferior to C-RT for 5-year DFS. The 12-year DFS rates were 56.1% for C-RT and 61.8% for H-RT (HR, 0.85; 95% CI, 0.71-1.03; $P < .001$ for noninferiority). H-RT also significantly reduced biochemical failure rates compared with C-RT (9.9% vs 17.0%; HR, 0.55; 95% CI, 0.39-0.78; $P < .001$). OS rates were similar between arms, with 12-year OS rates of 69.9% for H-RT and 68.7% for C-RT (HR, 1.01; 95% CI, 0.82-1.24).

The findings of RTOG-0415 established H-RT as a safe and effective alternative to C-RT for low-risk prostate cancer. With comparable outcomes in DFS, OS, and adverse events and the added benefit of a shorter treatment schedule, H-RT offered a more convenient option for patients while maintaining oncological efficacy. These results have important implications for standardizing radiotherapy regimens in this patient population.

KEY POINTS

- Phase 3 clinical trials are typically randomized and are designed to be pivotal; that is, they aim to demonstrate and confirm the safety and efficacy of a treatment strategy to obtain approval by regulatory authorities.
- Phase 3 study outcomes/endpoints should be previously validated as meaningful and selected to minimize variability in interpretation.
- Phase 3 trials require careful consideration of study design parameters, including randomization, blinding, and choice of endpoint, to minimize bias in the assessment of the treatment benefit.

ADAPTIVE DESIGNS

Recently, there has been an increased use of adaptive designs in oncology trials, particularly in phase 1 and 2 trials (Table 5-11). Adaptive trials are those that include a provision for change in key trial design parameters during their conduct by using current accumulated data. The modification in design is intentionally planned and is prespecified at the planning stage of the trial to achieve scientific validity. In adaptive designs, frequent looks at the data will be undertaken during trial execution, and modifications of the design of the trial generally fall into the following areas[48]: randomization ratio (adaptive randomization), adding or dropping of treatment arms, sample size re-estimation, population enrichment, and interim analysis (stopping rules for safety, efficacy, or futility). These rules should be applied to only one of the design elements. Both frequentist and Bayesian approaches (also refer to the "Bayesian Statistics" section) can be used, although adequate statistical resources must be dedicated if adaptive designs are used because extensive simulation will be used to fine tune key trial characteristics during trial conduct.

Table 5-11 **Examples of Adaptive Designs**

Design	Idea
Continual reassessment method	Model-based dose escalation to estimate the MTD
BOIN designs	Model-assisted dose-finding design to estimate MTD
Group sequential	Include options to stop the trial early for safety, futility, or efficacy
Sample size re-estimation	Adjust sample size to ensure the desired power
Multiarm multistage	Explore multiple treatments, doses, durations, or combinations with options to "drop losers" or "select winners" early

Design	Idea
Population enrichment	Narrow down recruitment to patients more likely to benefit (most) from the treatment
Biomarker adaptive	Incorporate information from or adapt based on biomarkers
Adaptive randomization	Shift allocation ratio toward more promising or informative treatment(s)
Adaptive dose ranging	Shift allocation ratio toward more promising or informative dose(s)
Seamless phase 1/2	Combine safety and activity assessment into one trial
Seamless phase 2/3	Combine selection and confirmatory stages into one trial

Abbreviations: BOIN, Bayesian optimal interval; MTD, maximum tolerated dose.
Adapted under Creative Commons license. Source: Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med*. 2018;16:29. doi:10.1186/s12916-018-1017-7

In adaptive trials that use outcome-adaptive randomization, the allocation of patients to treatment assignment depends on provisional or definitive outcomes observed thus far. Trials that use adaptive randomization start by randomly assigning patients in equal proportions to each arm. As outcome data on these patients accumulate, the randomization scheme is altered so that it favors the arms in which the strength of the evidence that the response rate is greater than p_0 or greater than the control arm is greatest. Conversely, it reduces the likelihood that a patient would be randomly assigned to the arm in which the strength of evidence is weakest and, ultimately, may drop arms altogether if the strength of evidence falls too low. Adaptive randomization has been used in biomarker-based designs, such as in the I-SPY2 trial[49] in breast cancer, so that patients with certain biomarker profiles who respond more favorably to certain treatments would be randomly assigned more frequently to those agents. Although adaptive randomization seems like a rational way to select among competing experimental regimens, in practice, it is often difficult to conduct such a trial because of practical challenges, and special statistical methods must be used to provide proper inference with such a design. The different agents likely have different sponsors and advocates, all of whom naturally have a principal interest in their own agents and may be reluctant to cede control of their evaluation to an external process. Others have some ethical discomfort with the notion of unequal allocation based on evidence of efficacy, believing that this violates the principle of clinical equipoise (ie, that one truly is unable to say which treatment is better for the patient population to be enrolled). In addition, it has some disadvantages. The first is that although, theoretically, it minimizes the number of patients randomly assigned to ineffective treatment, the overall sample size for a trial with adaptive randomization is larger than that for a trial with fixed randomization, as is true for upfront unequal randomization allocations (eg, 1:2). Because it is possible that imbalance will be in the wrong direction, with more patients assigned to the inferior treatment arm, a run-in period with 1:1 randomization may be required before a stable estimate in favor of one of the arms is obtained. There are many other issues, and there is a split among statisticians regarding whether the benefits of adaptive randomization outweigh the drawbacks.[50-52]

Adaptations in phase 3 trials may differ depending on whether the changes are made blinded or unblinded to the available data on treatment differences; for example, increasing the sample size because of a lower-than-expected overall event rate has a minimal effect on the final analysis because it does not actually use the treatment differences. In contrast, unblinded adaptation is subject to greater scrutiny and requires careful attention to statistical methodology and operational procedures to ensure that the results are free from bias. Several types of adaptations in late-stage clinical trials have been considered. Seamless phase 2/3 clinical trials combine the phase 2 trial (which may involve dose selection from among multiple doses) and the phase 3 trial (which uses the final selected dose for inference). This can be operationally efficient because it eliminates time between phases 2 and 3, and it can be statistically efficient because the data from the two stages are combined for inference. Sample size re-estimation designs allow for an increase in the sample size based on interim assessments of the treatment effect, particularly when the interim treatment effect is in a promising zone in which the study may be underpowered. An adaptive population enrichment design allows for restricting enrollment to a biomarker-based subgroup at an interim analysis, if it seems that the patients positive for the biomarker may benefit from treatment and the patients negative for the biomarker do not.

BAYESIAN STATISTICS

Most of the familiar statistical concepts and applications encountered in medical research are based on a frequentist view of statistics and probability. From the frequentist perspective, probability is a quantity that reflects the underlying long-term frequency with which an event will occur under repeated observation. This frequency is governed by unknown, but fixed, parameters that define a probability distribution. For example, in a frequentist view, the probability that the flip of a coin will result in heads up is equal to the number of times heads is observed when the coin is flipped a large number of times. If the coin is fair, this probability will be one-half, which will equal the proportion of heads we observe in a large number of flips. The statistical procedures derived from this perspective are all based on relating observed data to the fixed parameters of the probability model that generates the data.

Bayesian statistics also seek to relate observed data to the probability model that generates the data. The term Bayesian derives from a basic theorem known as the Bayes rule, which was formulated by the Reverend Thomas Bayes in the mid-18th century. The Bayesian formulation allows the incorporation of a more subjective notion of probability. The notion of probability is a measure of the strength of one's belief in a single outcome, for example, the probability that it will rain tomorrow. It also allows the application of this view of probability to unknown parameters governing a probability distribution, for example, the probability that the rate of response to a treatment exceeds a specified value. This is not a meaningful concept in a frequentist framework, where the response rate is viewed as a fixed number.

The Bayesian approach to statistical inference involves three basic steps[53]:

1. Specification of a probability distribution for the unknown parameter (called a prior distribution) based on existing knowledge
2. Collection of data
3. Use of the data to update the prior distribution, resulting in a posterior distribution (or updated probability distribution for the unknown parameter)

A simple example involves an imperfect diagnostic test. For a randomly selected individual, it would be reasonable to assume that the probability that this person has a disease is equal to the prevalence of the disease (the prior distribution). After the test is performed, the result will be either positive or negative (the data). This information can be used to recalculate the probability that the person has the disease, which is no longer equal to the disease prevalence (the posterior distribution).

Most clinical trials are designed and analyzed on the basis of a frequentist approach. Basically, there is a null hypothesis and an alternative hypothesis. The null hypothesis would be that there is no difference in outcome between the two treatment arms. A two-sided alternative hypothesis would be that there is a difference in outcome between the two treatment arms. The data are collected, and a *P* value is computed on the basis of the observed data, which are compared with the level of significance to determine whether the null hypothesis will be rejected. Again, the *P* value is the probability of observing the data obtained or data more extreme (more in favor of the alternative hypothesis), assuming that there is no difference in outcome between the treatment arms. If this value is sufficiently small (lower than the level of significance), we conclude that there is evidence against the null hypothesis. This means that we would reject the hypothesis that the two treatment arms have similar outcomes.

The Bayesian approach would be used to determine a probability distribution for the difference in outcome between the two treatment arms; this is called the prior distribution. Often, a noninformative prior is used, which essentially assumes that all possible differences in outcomes between the two arms are equally likely. Once data are obtained, a new distribution, the posterior distribution, is generated that combines the information in the prior distribution and the data. This posterior distribution describes the likelihood of each possible difference in outcome between the two treatment arms. The posterior distribution is then used to decide which treatment arm has better outcomes. For example, using the posterior distribution, the probability that arm A is better than arm B can be computed. If this probability is large, for example, there is a 90% chance that arm A has better outcomes than arm B, the decision is then that arm A is the better treatment.

Frequentist designs evaluate the evidence against the null hypothesis by determining how likely it would have been to obtain the results observed, or more extreme results, assuming that the null hypothesis were true. Small *P* values mean that the result is unlikely if the null hypothesis is true, and so, it is taken as evidence against the assumption that the treatments yield the same outcomes. Bayesian designs allow a calculation of the probability that one treatment is better than the other. However, these designs require investigators to state a prior distribution for the possible differences in outcomes between the two treatment arms.

The potential controversy in applying Bayesian methods to medical research lies in the specification of the prior distribution, which is allowed to incorporate subjective judgments about the quantity under investigation. Many statisticians argue that prior beliefs about an unknown quantity represent a form of bias that should be avoided in scientific research; others argue that ignoring prior knowledge is in itself a bias. It is possible to use a Bayesian framework in a way that minimizes the use of information contained in prior beliefs, thereby letting the data speak for themselves. This is done by choosing a prior distribution that is said to be uninformative with respect to the quantity under study (also sometimes called a flat prior). Interestingly, statistical procedures conducted using uninformative priors are often similar, or even identical, to those conducted within a frequentist framework, and they produce similar results. They simply use different mathematical machinery and terminology. When Bayesian methods have been used in the design or analysis of a research study, one should always be able to ascertain the nature of the prior distribution. If a subjective or informative prior distribution has been used, its rationale and appropriateness should be carefully considered, and it should be recognized that the choice of a prior distribution could influence the interpretation and conclusions of the study.

Bayesian methods have become more popular, particularly for phase 1 and 2 studies that use adaptive designs. They are somewhat less common for phase 3 studies although the FDA does provide guidance documents for Bayesian analyses of phase 3 trials, which require more pre-specification.

TRANSLATIONAL MEDICINE STUDIES

A formal definition of translational medicine is an "interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and community."[54] In oncology, translational studies are often focused on evaluating whether measurable attributes of a patient or a patient's disease at a particular time are associated with subsequent outcomes and eventually the clinical benefit of treatments. These attributes may be measured before the start of treatment, possibly with a view toward predicting the therapy most likely to be effective, or after treatment has been initiated, with the intent of predicting whether the treatment is working. Often the attributes being investigated are not clinically apparent and must be assessed using various testing approaches, including imaging, immunohistochemistry, gene expression, or any of a wide range of other clinical or laboratory investigations.

Translational studies can be conducted throughout the entire span of therapeutic development and can be conducted independently of therapeutic trials (eg, using biomarkers from tissue samples available through a tumor bank) but are also often explicitly incorporated as secondary or exploratory objectives in therapeutic trials. The potential range of research questions that can be posed in such correlative studies is broad, and the statistical methods and designs vary greatly depending on the study research questions, disease setting, and the data being collected and may not involve an actual analysis of correlation as the name may suggest. Below we give several examples of a basic measure of correlation and illustrate some common pitfalls in the evaluation of correlation, including the relationship between correlation and causation and the issue of multiple comparisons.

Correlation

Correlation is often used as a generic term to describe almost any type of association, but in statistics, it has a more precise definition and most commonly refers to the linear association between two continuous measures. Correlation between two variables (x and y) can be visualized using an x-y scatterplot, which is a visual representation of how one variable varies as a function of the other variable.[55] The Pearson correlation coefficient r is a measure of the linear correlation between two variables; a value of +1 means perfect correlation, a value of 0 means no correlation, and a value of −1 means perfect inverse correlation. The associated value r^2 ranges from 0 to 1 and is interpreted as the proportion of the variation in one variable that is explained by variation in another. For r^2, variation is measured by the sum of squared deviations from the mean, but there are many other measures of variation. The degree of correlation is a function of three factors: (1) the magnitude of the association (ie, whether the change in one variable is associated with a large or small change in the other), (2) the consistency of the relationship (ie, whether the changes are consistent or highly variable), and (3) the linearity of the relationship. The first two factors pertain generally to any measure of correlation. The third, linearity, is an important consideration for the Pearson correlation coefficient; one can, for example, envision two variables with a perfect quadratic association (eg, $y = x^2$). In this case, the variables are definitely associated, but the correlation coefficient r will be 0 (Fig. 5-8).

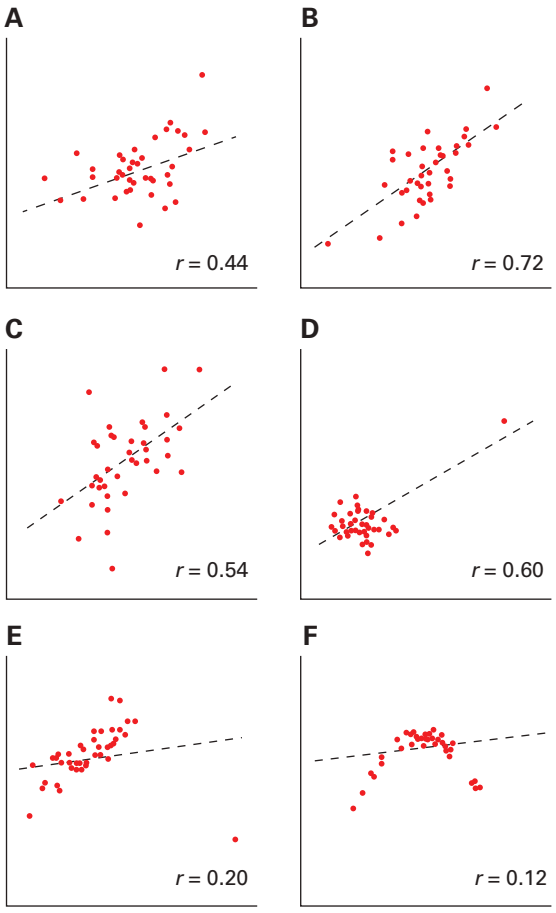
In studies of agreement (eg, when two measurement techniques are applied to the same subject with the goal of determining agreement of measurements), correlation is often an inappropriate measure of agreement; for example, when measuring weight in different units (eg, pounds and kilograms) with extremely accurate scales, measurements would be highly correlated but would not agree, because the measurement units are different. In such situations, the Bland-Altman plot, which examines the difference between two measurements versus the average, can be used.[56]

Correlation and Causation

Correlative studies are common in the development of targeted therapies. These therapies are designed around specific attributes of tumors, which can be quantified by measuring some biological parameter referred to as the biomarker. It may be possible to establish a clear correlation between this biomarker and prognosis. It may also be possible to establish that a targeted therapy has an effect on the biomarker in a direction that would imply a more favorable prognosis. Taking these two correlations together, it might appear that this is a clear indication that the therapy would be effective for that cancer, but this is not necessarily the case. The common saying "correlation is not causation" means that just because two things are correlated does not necessarily mean that one causes the other. Establishing causal relations is complex, and methods from causal inference, which is a branch of statistics that considers assumptions, mechanisms, study designs, and estimation strategies to allow researchers to draw causal conclusions, are often used.[57]

A familiar analogy would be the association of elevated blood pressure and cholesterol levels with various forms of cardiovascular disease. Although there are many drugs that lower blood pressure and cholesterol levels (biomarkers in this scenario), there is no guarantee that these drugs will be effective in lowering the risk of cardiovascular disease (clinically meaningful outcome). For this to be true, the elevation of blood pressure or cholesterol levels must be part of the causal pathway to the cardiovascular event (Fig. 5-9),[58] not just a marker or symptom of the severity of the disease process. The same must hold true for the effect of a targeted therapy on a cancer biomarker to be considered an indicator of efficacy; that is, the biomarker must reflect at least part of the direct causal pathway by which growth or spread of the tumor has an effect on the survival of the patient.

Figure 5-8 Scatterplot Examples of Linear Correlation



The six graphs illustrate possible correlations between two variables, *x* and *y*. The dashed line indicates the least squares line fit to the data, and *r* is the Pearson correlation coefficient. (A) Data have a positive correlation of moderate strength. (B) Compared with the data in panel (A), there is an increased slope in the data and a stronger correlation. (C) Data have the same slope as the data in panel (B), but the correlation is weaker (ie, the points have more variability about the best fitting line). (D) Computed correlation is stronger than that in the bulk of the data because of the influence of one outlier point. If this point were removed, the correlation would be smaller. (E) Correlation with the outlier is weaker than the correlation for the remainder of the data. If the outlier were removed, the correlation would increase. (F) There is a strong nonlinear relationship in the data, but the correlation is weak, because the correlation measures the strength of linear relationship.

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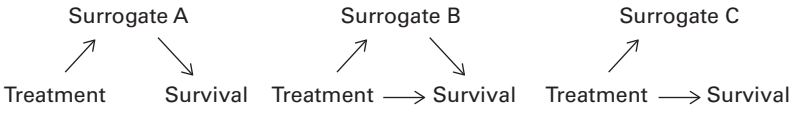
Figure 5-9 Causal Links Between Surrogate and Final Endpoint



(A) Casual surrogate. (B) Potential surrogate. (C) Independence. Causal diagrams illustrating pathways that involve treatment, a candidate surrogate, and the final endpoint, in this case survival (see text for explanations). Arrows indicate direct treatment effects: treatment effect on the surrogate, treatment effect on survival, and effect of surrogate on survival.

Adapted under Creative Commons license. Source: Buyse M, Saad ED, Burzykowski T, et al. Surrogacy beyond prognosis: the importance of "Trial-Level" surrogacy. *Oncologist.* 2022;27(4):266-271. doi:10.1093/oncolo/oyac006

Correlative Biomarker Studies

Many correlative studies are designed to evaluate potential biomarkers. Two important types of biomarkers are used in correlative studies: prognostic and predictive biomarkers. A prognostic biomarker is associated with the outcome, regardless of the type of treatment administered. An example of a prognostic marker would be metastatic status for a survival outcome; in general, patients with metastatic disease have shorter survival than patients who have localized disease, regardless of the type of treatment they receive. A predictive biomarker is used to select a specific treatment for a patient. If the patient has the biomarker, a particular

treatment will provide benefit, and if the patient does not have the marker, no or little benefit will result from the treatment. An example of a predictive biomarker is *HER2* status for women with breast cancer. If a woman has *HER2*-positive breast cancer, she obtains benefit (ie, longer survival) if treated with trastuzumab. In contrast, a woman who has *HER2*-negative breast cancer does not experience benefit from trastuzumab treatment. The goal of a biomarker study is to identify either prognostic or, preferably, predictive markers.

There are two common methods to include a biomarker in a clinical trial. Integrated biomarkers are used to evaluate a specific hypothesis in a study (eg, association of the biomarker with patient outcomes), with the goal of either discovering an association of the biomarker with the outcome or validating that a previously observed association exists between the biomarker and the outcome. Integrated biomarkers are integrated into the study design with planned objectives. Integral biomarkers, in contrast, are part of the study design, assessed in real time and used for patient stratification or to make treatment decisions in a clinical trial. One way this might happen is to use the biomarker to screen patients for trial entry. Specifically, if it is thought that only patients with the marker will potentially benefit from the treatment, then patients with the marker will be enrolled and those without the marker will not be enrolled. For example, *HER2* status (positive vs negative) was used in trastuzumab trials to screen patients who were eligible to enroll. Another example of an integral biomarker was the use of Oncotype DX recurrence score to determine treatment cohorts in the TAILORx trial and other biomarkers in the ASCO TAPUR trial. Additionally, planned use of a biomarker in the primary analysis, even if not used for eligibility or randomization, is an example of integral biomarker use. Division of the patient population by the biomarker may show that one group benefits from the treatment, whereas the other group does not. Use of integrated and integral biomarkers in prospective trials can provide information on causality, unlike exploratory translational analyses.

More detailed discussion regarding biomarker-driven phase 2 designs can be found in the "Phase 2 Trials" section.

Multiple Comparisons in Omic Studies

Advances in molecular technology have made it possible to assess hundreds, thousands, or even millions of potential biomarkers within reasonable limits of expense and time. This is particularly true in the field of genomics, in which single chips have the ability to simultaneously quantify the expression of 20,000 genes or to genotype more than 1 million single-nucleotide polymorphisms. Although some sophisticated statistical methodology may underlie the quantification of gene expression or assignment of a genotype, the basic methodology for evaluating a correlation with outcome could be based on a simple t or χ^2 test that is repeated thousands or hundreds of thousands of times.

From the hypothesis-testing point of view, if each of these tests of association has a positive (type I) error rate set at a conventional level, such as 5%, then the number of false-positive correlations found will be enormous. For example, consider a gene expression study of 20,000 genes that are to be correlated with tumor response with the aim of determining one or more markers that signal a high likelihood of treatment failure. Even if the 20,000 genes have been selected to represent a range of plausible causal pathways, only a small fraction is likely to be truly correlated with outcome. As an order-of-magnitude calculation, the number of false-positive correlations that will result from 20,000 hypothesis tests conducted with a 5% type I error rate is 1000, which is far too many to represent practical progress.

Although it is obvious in this setting that some measure must be taken to decrease the number of false-positive correlations, it is not always clear the specific target to be set. For example, if one insists that the rate of any false-positive correlation must be 5%, then a simple, although conservative, method is to apply the Bonferroni correction, which divides the nominal single-test error rate by the number of tests. In the example at hand, this would mean conducting each test with a type I error rate of 0.0000025. Although there are methods to make this conservative adjustment more accurate, it is not clear that this is even a reasonable goal. For example, it seems unduly conservative to demand that the rate of even a single false-positive result across 20,000 tests be only 5%. Unless the size of the study is increased, a reduction in the false-positive error rate by four orders of magnitude will increase the false-negative error rate, perhaps to the point at which correlations of a plausible magnitude cannot be detected.

Another method of controlling false-positive correlations considers the error rate among the tests that have been declared positive (ie, not among all hypotheses tested). This is called the false discovery rate. With this approach, if there were 100 positive tests, a false discovery rate of 5% would mean that, on average, five would be falsely positive. Most researchers would consider such a result highly successful. In fact, 10 positive tests with a false discovery rate of 20% to 30% could be considered an excellent result and would greatly reduce the scale of the subsequent studies required to replicate and validate the findings. The false discovery rate method is generally less conservative than a strict Bonferroni adjustment, although as previously noted, there are ways to calibrate the Bonferroni approach (eg, through permutation) to make it more comparable to the false discovery rate approach.

Although examples have been described previously in which the need to account for multiple tests is obvious, the problem of false-positive correlations remains even when dealing with 5 to 10 biomarkers. Explicit accounting of the multiple tests is often omitted in such situations, but this does not obviate the need for independent replication and validation of any apparent correlation.

KEY POINTS

- Common measures of correlation assess the linear correlation between variables. Lack of linear correlation does not necessarily mean that the variables are not related.
- Measures of correlation may be sensitive to a few outlying observations.
- Correlation, by itself, does not imply causation. Even though a biomarker may be correlated with both treatment and outcome, this is not sufficient to establish that the biomarker is a useful surrogate endpoint.
- Multiple comparisons increase the type I error above the desired significance level if the *P* values (or significance level) are not adjusted.

STATISTICAL ANALYSIS METHODS

In this section, we discuss some of the more important and advanced statistical methods that are common in oncology studies. Of course, all of these are themselves the subjects of entire books; therefore, only the most basic features of these methods can be covered here. The greater part of this section is devoted to the analysis of survival or time-to-event data, which are ubiquitous in the evaluation of clinical research. Some other advanced methods that may be encountered are also covered.

A common feature of the analytic methods discussed here is that they can be extended to incorporate the simultaneous effects of multiple variables on outcome, referred to as regression analysis. Regression analysis involving multiple variables is frequently referred to as multivariable analysis, in contrast with univariable analysis, which considers only one variable at a time. Many investigators erroneously use the term multivariate analysis rather than multivariable analysis. A multivariate analysis refers to the simultaneous analysis of multiple outcome variables, which is rarely done in medical research. Adjustment for multiple variables is particularly important in comparative studies using retrospective or other nonrandomized data or in the development of predictive models to evaluate multiple possibly correlated factors.

BINARY DATA ANALYSIS

In contrast to time-to-event analysis, there are occasions when the outcome of a clinical trial or other exercise may be summarized by the presence or absence of an event, outcome, or characteristic. This dichotomization of outcome is said to constitute binary data. Such data do not necessarily exclude aspects of time. For example, if outcome can be ascertained for all patients, then the occurrence of an event during a defined period can be a binary outcome. This is referred to as risk, but binary outcomes can refer to things other than risk. For instance, two groups of patients with breast cancer might be compared with respect to the percentage of patients with estrogen receptor–positive disease. The same or similar statistical methods may be applied to both scenarios.

χ^2 ANALYSIS

For basic statistical analysis of binary endpoints, such as comparing one or more groups in terms of the risk of an event or the percentage with a certain characteristic, the most common methodology is based on the χ^2 test. For small sample sizes, the accuracy of *P* values from the χ^2 analysis may be in doubt, and the Fisher exact test is the most common alternative although it is generally quite conservative.

Like the log-rank test for survival analysis, the basic methods associated with binary data provide a test of equality but not necessarily a measure of effect. The most straightforward measure of effect is the simple difference in proportions. Other common measures of effect associated with binary outcomes[59] must be used with some caution in typical applications involving clinical data. For example, if p is the risk of an event, then the odds of the event are $p/(1 - p)$. Conversely, if c is the odds of an event, then the risk of the event is $c/(1 + c)$. In certain epidemiological settings, where p is small, the ratio of the odds of an event between groups (odds ratio) will be approximately equal to the ratio of the risks (relative risk) and is a standard measure of association or effect. In clinical settings, however, the values of p associated with risk are not necessarily small. Although the same underlying statistical methods may be applicable, the odds ratio in such settings may be nonintuitive or even misleading. For example, consider a patient group with a risk of recurrence of 90% compared with another group with a risk of recurrence of 80%. The odds ratio for risk of recurrence is 2.25, but clearly, the risk of recurrence is not nearly doubled. Similar considerations apply when interpreting an HR in survival analysis. If the risk of an event is not too large, then an HR will approximate a risk ratio; however, the divergence between a risk ratio and an HR is not as dramatic as that between a risk ratio and an odds ratio. For example, a risk ratio of 2.0 (0.4/0.2) corresponds to an odds ratio of 2.67 and to an HR of 2.25 (under an exponential assumption).

KEY POINT

- Binary data analysis is used for outcomes with yes/no or binary responses. The χ^2 or Fisher exact test is used to compare proportions between groups. Logistic regression is used to model the odds of a response, where the effect of a covariate is summarized through an odds ratio.

SURVIVAL ANALYSIS

Because of the potentially long temporal course of the disease, a large part of the evaluation of cancer and its treatment involves extended periods of follow-up, often spanning many years. Measures of therapeutic efficacy or prognostic value are frequently defined by the percentage of patients alive at a particular time or alive and free of recurrence at a particular time. Conversely, one might be interested in the median time to death, recurrence, or some other defining event. Often, it is not possible to observe all patients until the defining event occurs or even until they have reached a specified length of follow-up.

The analysis of data related to the duration of time until an event is generically referred to as a time-to-event analysis or survival analysis. The methods used in such an analysis must take into account that some patients will not be observed until the time of the event but will provide partial information about the length of that time, that is, the length of time from the start of follow-up until the time of analysis. The discontinuation of follow-up before a defining event is called censoring. The proportion of event times that are censored may range from near zero in settings where almost all patients die or have recurrent disease to more than 90% in settings with excellent survival.

The most common graphical way to represent survival data is the survival curve. This is an estimate of the underlying survival function $S(t)$ that defines the probability of surviving past time t or, more generally, that the time to a defining event exceeds t. Although this is the way that data are visualized, the statistical analysis of such data is more often based on a related quantity called the hazard function $\lambda(t)$, which is the underlying rate at which events occur among the population of patients at risk. This is feasible because there is a well-defined and fundamental mathematic relationship between the survival function and hazard function; intuitively, if the rate of events increases, then the probability of surviving without that event decreases.

The most common methods associated with displaying and analyzing time-to-event data are described below. There are two key assumptions underlying all these methods. One is that the censoring of event times, if they occur, is not related to the subsequent occurrence of the event, that is, that the reason for censoring is noninformative with respect to what happens afterward. One particular example of a violation of this principle is censoring a survival time because of a change in therapy just before a patient experiences the expected event (eg, disease progression or death). Another fundamental principle of survival analysis, because survival is a predictive quantity, is that only past information can be used in modeling and analyzing future events. An example in which the latter principle is not met would be dividing patients into two groups, depending on whether they had a tumor response, and evaluating time to death from the time of initiation of therapy. Because tumor response is not known at the initiation of therapy, this will lead to a biased comparison, sometimes known as immortal time bias. The solution is to start survival after a fixed time period so that tumor response is known at the start time, called a landmarked analysis, although other more complex methods have been developed as well.

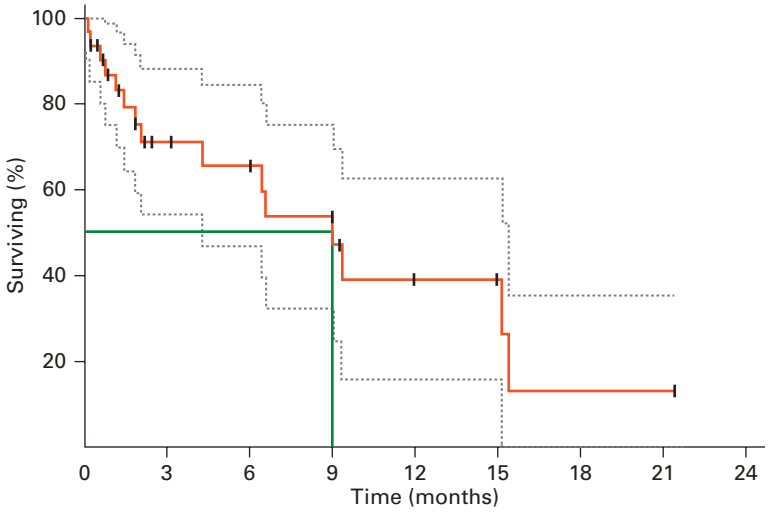
KAPLAN-MEIER CURVES

The universal standard for providing estimates of survival curves is the Kaplan-Meier estimator (also called the product-limit estimator). This is typically plotted as a step function, with a step occurring at every unique death time (Fig. 5-10). The calculation involved in the Kaplan-Meier estimator is actually quite simple; the height of each step is the height of the curve at the previous step multiplied by the proportion of patients at risk at the particular death time who survive beyond that time. The number of patients at risk at a particular point is the number of patients who have not died or have been censored before that time. For example, suppose the time until death or censoring is measured to the nearest week. If the estimated survival probability just before 14 weeks is 0.6, there are 10 patients who have not died or been censored before 14 weeks, and one patient dies at 14 weeks, then the height of the curve drops at that time from 0.6 to 0.54 ($0.6 \times [9/10]$). In plots of Kaplan-Meier curves, it is common to indicate points of censoring with tick marks or provide a table indicating the numbers of patients at risk at convenient benchmarks.

Because the Kaplan-Meier estimate is the product of fractions with progressively smaller denominators, the precision of the estimate decreases over time. This is readily apparent if CIs are provided because the CIs will grow increasingly wider over time. In almost all cases, the CIs provided with a Kaplan-Meier curve are based on pointwise estimates of the variability of the survival estimate; it is generally not correct to infer that the bands contain the entirety of the true survival curve with the stated level of confidence. The step after the last observed time of death is often extended as far as the last censoring time, although technically, the estimate is undefined after the last death. As previously noted, the steps in the right-hand tail of the estimated curve become steeper as the number of patients at risk decreases. If the last patient under observation dies, then the estimated survival probability drops to zero at that point.

Although the previous discussion referred only to deaths, the Kaplan-Meier method readily encompasses the concepts of PFS, DFS, and event-free survival. For example, the estimate of DFS counts both deaths and relapses as events, and the curve steps down whenever either event occurs, using the same calculation. The term OS is usually meant to refer to a survival curve that counts only deaths as events. The Kaplan-Meier method should not be used when the intent is to estimate the probability of being free of a particular kind of event (eg, a particular cause of death). This is a competing risks problem and requires the use of methods described later in the chapter.

Figure 5-10 Survival Curve Plot and Related Quantities



Orange line is an example of a Kaplan-Meier curve for a group of 33 patients. At any time point, the curve estimates the probability of surviving at least as long as that time. Gray lines indicate the 95% CIs for the survival probability calculated at each point. Tick marks indicate times at which surviving patients were last known to be alive and are censored. Green line indicates how median survival would be calculated. In this curve, the survival probability drops to less than 50% at 9 months.
Abbreviation: CI, confidence interval.
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Comparing Kaplan-Meier Curves

The comparison of survival curves can be approached in several ways: (1) by comparing the estimated survival probability at a fixed point in time; (2) by comparing the time at which the estimated survival probability is a fixed value, usually the median; or (3) by comparing the survival curves across the entire period of follow-up. Although the first two methods provide convenient descriptive metrics, in general, they should be avoided for statistical testing unless there is a strong justification for focusing on a particular survival time or percentile; focusing on a single metric ignores the rest of the survival distribution, which leads to reduced power and sometimes bias. The third method is suitable and preferable for statistical inference because it uses all the available data.

The most common way to compare whether survival curves differ between groups is the nonparametric log-rank statistic, which compares DFS in a hypothetical clinical trial of an experimental compared with a control treatment. Perhaps somewhat surprisingly, this statistic is not based directly on the calculated survival estimates; rather, it is based on a comparison of the number of events observed in one group with the number of events that would have been expected in that group if the deaths occurred solely in proportion to the numbers of patients at risk. A difference that is too extreme (as reflected in a *P* value) provides evidence that the underlying event rates in the groups are different. The standard log-rank test is most sensitive to situations in which the event rates in the groups differ by the same ratio across time. There are weighted versions of this test that are appropriate if the differences are expected to occur primarily during the early or later periods of follow-up; however, the intent to use a weighted log-rank test should be specified before observing where the differences in event rates occur.

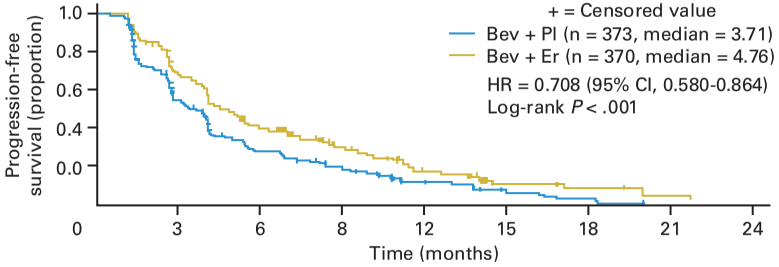
The comparison of survival curves is a special case of hazard rate analysis, performed through Cox proportional hazards regression, which is discussed later. In fact, the log-rank test is also a test of the equality of hazard rates in the two groups. Cox proportional hazards model rely on the assumption that the ratio of hazards in the two groups is constant over time. Deviations from this assumption, called nonproportional hazards, can often be seen using Kaplan-Meier plots and manifest through crossing curves (Fig. 5-11A and B).

COMPETING RISKS AND CUMULATIVE INCIDENCE

As noted previously, when there are multiple types of events that define event-free survival, or multiple causes of death, then probabilities associated with a specific type of event or a specific cause of death should not be estimated with the Kaplan-Meier approach. For example, suppose one is interested in comparing breast cancer mortality as opposed to all-cause mortality (the complement of OS) between two treatment groups. The relevance of this comparison might be debated because cause-of-death classification can be fairly subjective. A common but incorrect approach to this problem is to censor patients at the time of death resulting from a cause other than breast cancer and to plot the complement of the resulting Kaplan-Meier curve as a

Figure 5-11 Plots to Compare Survival Curves

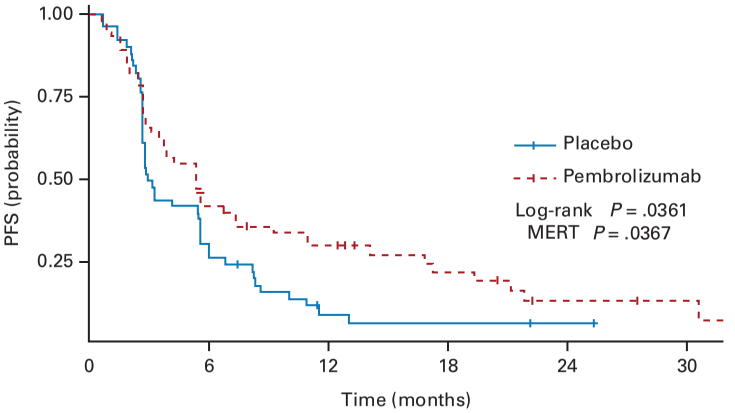
A PH



No. at risk									
Bev + Er	370	180	80	43	20	5	3	1	0
Bev + Pl	373	143	57	28	15	6	3	0	0

Time Since Random Allocation	Bevacizumab + Placebo (n = 373) Patients With Event	Bevacizumab + Placebo (n = 373) Kaplan-Meier Percent Event Free (Pointwise 95% CI)	Bevacizumab + Erlotinib (n = 370) Patients With Event	Bevacizumab + Erlotinib (n = 370) Kaplan-Meier Percent Event Free (Pointwise 95% CI)
3 months	138 (37.0%)	54.1 (48.2-59.6)	92 (24.9%)	68.4 (62.7-73.4)
6 months	200 (53.6%)	28.2 (22.7-33.9)	160 (43.2%)	40.2 (34.1-46.2)
9 months	216 (57.9%)	19.3 (14.3-24.9)	177 (47.8%)	30.2 (24.2-36.5)
12 months	226 (60.6%)	12.1 (7.8-17.5)	193 (52.2%)	17.8 (12.3-24.1)

B Non-PH



No. at risk						
Placebo	52	15	3	2	1	0
Pembrolizumab	55	21	14	8	3	2

(A) PH assumption is satisfied. (B) PH assumption is violated.
Abbreviation: CI, confidence interval; HR, hazard ration; MERT, mixed effects regression tree; PH, proportional hazards.
Data adapted from (A) Johnson BE, Kabbinavar F, Fehrenbacher L, et al. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol*. 2013;31(31):3926-3934, figure 3. Reprinted from (B) Galsky MD, Mortazavi A, Milowsky MI, et al. Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer. *J Clin Oncol*. 2020;38:16, figure 2A.

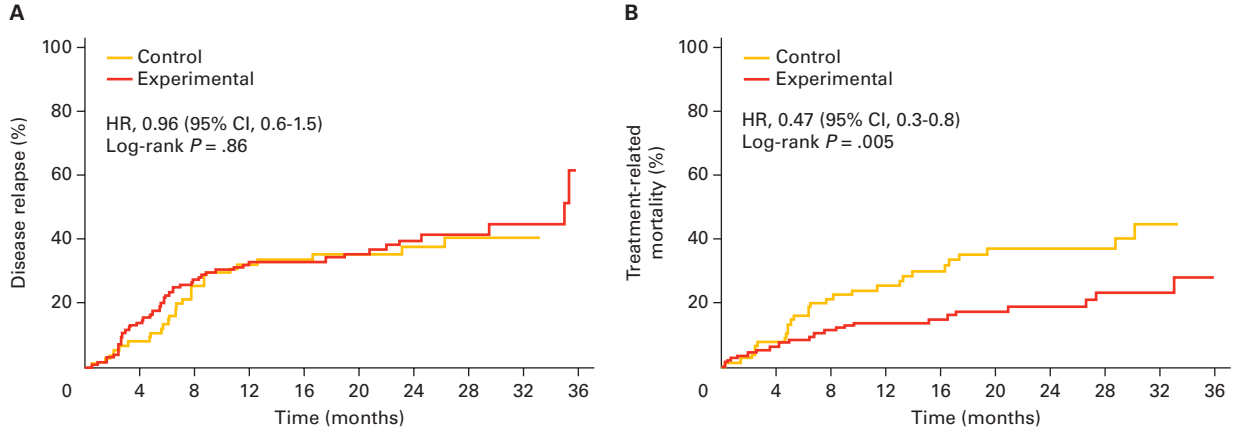
representation of cumulative breast cancer mortality over time. The problem with this approach is that patients who die as a result of other causes are not even hypothetically at risk of future death as a result of breast cancer. The implicit assumption that they are, which is appropriate for the standard types of censoring, results in an overestimation of the probability of death resulting from breast cancer.

The correct calculation of cumulative incidence in the competing risks setting must take into account the probability of remaining at risk (or being event free). When this is done, the sum of the cumulative incidence probability for each type of event is exactly the complement of the event-free survival probability. For example, at any point in time, (1) the OS probability, (2) the probability of death resulting from breast cancer, and (3) the probability of death resulting from a cause other than breast cancer will sum to 100%.

Although Kaplan-Meier methods are generally inappropriate for generating estimates of cumulative incidence in the presence of competing risks, the comparison of cumulative incidence curves is properly handled using the same previously discussed log-rank statistic, with events other than the type of interest being censored at the time of their occurrence. This seeming contradiction relates to the fact that in neither case is the log-rank statistic based directly on the estimates of the event probabilities themselves. Rather, it is based on the relative numbers of events that occur in each patient group, given the numbers of patients remaining at risk in each group over time. Therefore, it is appropriate, for this purpose, to censor patients who experience competing events at the time of the event, because they are no longer at risk of the event of interest.

At the risk of making the issue seem overly complicated, it should be noted that in the competing risks setting, the results of statistical analysis may not always seem concordant with the visual interpretation of cumulative incidence curves (Fig. 5-11). This is because incidence is a composite result of (1) the rate at which events occur among those at risk (the hazard rate) and (2) the size of the population at risk. For example, consider a setting in which toxic regimens with potentially fatal complications are used in a setting with high rates of relapse. The events of death as a result of relapse and death resulting from a cause other than relapse constitute competing risks (Fig. 5-12). Suppose one regimen is much more effective than the other in preventing relapse but has the same underlying toxicity based on a hazard rate analysis showing equivalent hazard rates for death resulting from a cause other than relapse in the two groups. In this case, the cumulative incidence of death resulting from a cause other than relapse will seem higher in the group receiving the more effective therapy. This is because the effectiveness of the therapy in preventing relapse places more patients at risk of death resulting from a cause other than relapse.

Figure 5-12 Plot of Cumulative Incidence Curves for Competing Risks



Data are decomposed into the two competing risks of (A) relapse and (B) treatment-related mortality. Most of the improvement in DFS in the experimental arm is attributable to a decrease in treatment-related mortality; there is no observed difference in the rate of relapse between arms among those at risk of relapse.
Abbreviations: CI, confidence interval; HR, hazard ratio.
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The intent of the previous example is not to imply that the hazard rate analysis is correct or that the cumulative incidence analysis is misleading. The important point is that competing risks should not be evaluated in isolation. Factors that influence one type of event may or may not influence another type, and an informed interpretation of data from a competing risks setting should consider each type of event. Furthermore, a complete analysis should evaluate not only the underlying rates of the event types, which may be biologically more meaningful, but also the net outcome reflected in their cumulative incidence, which may affect clinical interpretation.

KEY POINTS

- Survival analysis techniques are used to analyze outcomes describing the time until an event occurs, which may be subject to censoring or competing risks.
- Although Kaplan-Meier curves are the universal standard for graphically representing time-to-event endpoints, the statistical analysis of such curves is usually not based on a direct comparison of the curves themselves. Rather, the comparison is based on the underlying hazard rate (the rate of events among patients remaining at risk) using the log-rank test.
- Comparisons of cumulative incidence curves are performed similarly to comparisons of survival curves.

MULTIVARIABLE REGRESSION MODELS

Although many clinical trials can be analyzed using only the abovementioned methods, there are many settings in which one wishes to incorporate more information about patient characteristics than just the treatment arm to which the patients were assigned. This is particularly true in adjusting for imbalances at randomization or identifying prognostic factors of clinical outcomes. Although accounting for these imbalances is in no way a substitute for randomization, it is helpful, nevertheless, to evaluate the extent to which patient characteristics influence the difference, or lack of difference, among treatment groups. In other cases, the interest is not in comparing the arms of a clinical trial but in determining factors that are predictive of better or worse survival. This information is useful in designing trials, counseling patients about their likely prognosis, or gaining increased biological understanding.

Two commonly used models are the proportional hazards and logistic regression models. Like other regression models, the Cox regression model relates patient characteristics, called covariates, to outcome, which is a time-to-event outcome, such as survival or PFS. These models can accommodate any number of variables. A Cox model summarizes the association between a variable and the outcome with an HR. The Cox model might include either fixed or time-dependent covariates. Fixed covariates are measured at baseline, whereas time-dependent covariates measure the variable through the trial. When these measurements are updated over time, this covariate might provide a more accurate prognosis of a patient's hazard of dying than having only baseline measurements.[60] In clinical trials, only baseline covariates are adjusted. An exception might be the measurement of serial biomarkers during the trial and relating recent biomarker values to subsequent outcomes. The method for incorporating covariate effects on a binary outcome is logistic regression. A logistic model summarizes the association between a variable and the outcome with an odds ratio.

There are two strategies in modeling the relationship between a covariate and time-to-event endpoints in competing risks. They model the dependence of either the cause-specific hazard function or the subdistribution hazard function. Both approaches are valid although they will have different interpretations and might have different associations. In the first approach, k regression models can be fitted to the kth cause of interest. In each of the Cox models, the event times for the other competing risks are censored. In the second approach, the kth event type can be modeled using the Fine-Gray subdistribution hazard. This approach allows for modeling the effect of covariates on the cumulative function.[61] An important feature of this approach is that patients who experience a competing event remain in the risk set (instead of being censored), although they are in fact no longer at risk of the event of interest.

KEY POINTS

- Cox regression is used to model the hazard rate in time-to-event outcomes, where the effect of a covariate can be summarized through an HR.
- Logistic regression is used to model the odds of a response, where the effect of a covariate is summarized through an odds ratio.

EVALUATION OF BIOMARKERS

In the evaluation of a biomarker, the goal is to determine whether it can discriminate among patients. For a prognostic biomarker, an evaluation is performed to determine whether the biomarker can distinguish between patients who have good prognosis and those who have poor prognosis. If the outcome of interest is binary (eg, good vs poor prognosis), the discrimination ability is determined using the area under the curve of a receiver operator characteristic (ROC) curve. ROC curves apply to biomarkers that have continuous values. The ROC curve plots the true-positive rate against the false-positive rate for various threshold values (eg, values that would determine whether a patient has a good vs poor prognosis). The true-positive rate is also called sensitivity, which is the ability of the marker to predict the outcome of interest when that outcome actually occurs (eg, the marker would classify a patient as having a good prognosis and that patient actually did have a good prognosis). The false-positive rate is determined as 1-specificity. Specificity is the ability of the marker to classify the patient as not having the outcome of interest when the patient does not have the outcome of interest. A biomarker that has perfect discriminatory ability has an area under the curve of 1. This means that it always correctly classifies patients according to the event of interest. If the event is prognosis, the biomarker can perfectly predict the patients with a good prognosis and patients with a poor prognosis. A biomarker that has

no discriminatory ability is one with an area under the curve of 0.5. This means that its ability to predict whether a patient has the outcome of interest is the same as flipping a fair coin. Area under the curve analysis is used to determine the performance of prognostic biomarkers. In general, for a prognostic biomarker to potentially be useful in clinical practice, it requires a high area under the curve level (perhaps >0.80), although this cutoff depends on the setting.

To determine the potential utility of a biomarker in a clinical trial, it is good to evaluate the strength of the association of the biomarker with the outcome of interest. When the outcome is a time-to-event outcome, the strength of the association will be determined with an HR from a Cox model and by computing a measure of predictive accuracy using the Harrell C-index or integrated time-dependent area under the curve.[62] To determine whether the marker is prognostic, there must be a statistically significant association with the outcome, regardless of treatment. Thus, there would be an association regardless of the treatment the patient received.

KEY POINTS

- The discriminatory ability of a prognostic biomarker is measured by computing the area under the curve for an ROC curve. The closer the area under the curve is to 1, the better the discriminatory ability.
- To determine whether a biomarker is prognostic, an association between the biomarker and the outcome of interest must be established.
- To determine whether a biomarker is predictive, a statistically significant interaction must be established between biomarker status (present vs absent) and the treatment of interest (received vs did not receive) with respect to the outcome of interest.

LONGITUDINAL DATA ANALYSIS

In many studies, patients may be assessed repeatedly over extended periods. Data that arise from repeated measurements of the same patient over time are called longitudinal data or, sometimes, clustered data. Common examples of such data would be quality-of-life assessments or the evaluation of biomarker levels over time. Pharmacokinetic data are a specialized case of longitudinal data; there are specific methods for analysis of these data that are beyond the scope of this chapter.

It is possible to perform a useful analysis of longitudinal data using basic statistical methods, for example, by comparing groups at a fixed point or by comparing estimates at two time points using paired tests. However, such methods may not allow one to evaluate the trajectory of the quantity being studied as a whole and do not fully accommodate common features of longitudinal data, such as missing data, variable times of assessment, and risk factors that also change over time. To analyze all the data simultaneously, one must account for the fact that repeated observations from the same patient are likely correlated. For example, one patient may report a relatively high quality of life during the entire period of study and another may report a low quality of life, although both patients may experience a similar change over time.

Appropriately accounting for this within-patient correlation is not necessarily straightforward, and the methods involved may be quite complex and are beyond what can be presented in detail here. There are two fairly common approaches to handling longitudinal data analysis. Although the nomenclature may vary, one is generally referred to as a linear mixed-model approach and the other as a generalized estimating equation approach. The term mixed in the former refers to the simultaneous estimation of parameters that model the mean effects (the effects of clinical interest) and parameters that model the within-patient correlation structure of the data. One must make explicit assumptions about the latter, and the results may be sensitive to that assumption. The generalized estimating equation approach makes less explicit assumptions about the correlation structure. This is an advantage, particularly if one has no particular interest in the correlation structure itself, which is often the case when the interest is in comparing outcomes between groups or evaluating the effects of other factors on outcome.

KEY POINT

- Longitudinal data analysis is used to model outcomes that are assessed repeatedly over time. These methods must account for missing data commonly occurring in this setting, as well as for the correlation between measurements in the same individual.

SUMMARY

Statistical considerations comprise a key component in the design and analysis of clinical research studies. Proper study design allows one to control the systematic and random factors that affect patient outcomes in clinical studies, and proper analysis allows one to make the best possible judgment about which factors are more important. Few oncologists engaged in clinical research have sufficient statistical training or knowledge to do this on their own, which is why statisticians are in high demand in medical research and are considered vital to the research endeavor. Statisticians are also frequently engaged in evaluating research proposals for funding purposes and in reviewing research papers for publication in medical journals.

Although most clinical studies published in major medical journals likely involved a statistician in the design and conduct of the study and the review of the article, it is still essential for the practicing oncologist to have some rudimentary familiarity with common statistical concepts and terminology, which is the goal of this chapter. Such knowledge will enhance the oncologist's ability to evaluate the medical literature, explain treatment options to patients, and make informed decisions about joining research studies available to the community.

HIGH-YIELD TAKEAWAYS

- Most phase 1 designs identify an MTD based on DLTs, while the RP2D is often finalized later using expansion cohort safety and pharmacokinetic and pharmacodynamic data, and for some targeted therapies the goal is an OBD rather than an MTD.
- The 3 + 3 design is simple but can be inefficient, model assisted designs such as BOIN use prespecified decision tables and can improve patient allocation and overdose control.
- High-quality trials require a prespecified objective, clinically meaningful endpoint, appropriate design, justified sample size, and a prespecified statistical analysis plan.
- A *P* value quantifies evidence against a null hypothesis, it does not measure effect size or clinical importance, and statistical significance does not guarantee clinical benefit.
- Survival endpoints require methods that account for censoring, commonly Kaplan-Meier estimation, log-rank testing, and Cox regression, with method choice guided by the estimand and study design.

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

CLINICAL TRIALS AND BIOSTATISTICS

5

CHAPTER SUMMARY GUIDE

KEY POINTS

- The primary objective of a clinical study is the principal clinical research question or the hypothesis to be tested.
- The primary outcome measure is the variable that will be measured during the clinical trial and on which the study endpoint will be based.
- Study endpoints are clinically meaningful results obtained after the study intervention.
- A false positive (type I error) is when the null hypothesis is true and incorrectly rejected; it is designated as α.
- A false negative (type II error) is when the null hypothesis is false and incorrectly not rejected; it is designated as β.
- Statistical contributions to the clinical trial design are essential, and trial design development is a collaboration between clinical investigators and the statistician.
- The American Statistical Association's six principles of statistical significance and *P* values are as follows[9]:

    1. *P* values can indicate how incompatible the data are with a specified statistical model.
    2. *P* values do not measure the probability that the studied hypothesis is true or the probability that the data were produced by random chance alone.
    3. Scientific conclusions and business or policy decisions should not be based only on whether a *P* value passes a specific threshold.
    4. Proper inference requires full reporting and transparency.
    5. A *P* value, or statistical significance, does not measure the size of an effect or the importance of a result.
    6. By itself, a *P* value does not provide a good measure of evidence regarding a model or hypothesis.

- Phase 1 trial objectives are as follows:

    1. Identify the safe dose or MTD of a novel therapy or therapy combination.
    2. Ascertain a dose or dose range for subsequent phase 2 studies.
    3. Determine clinical drug behavior through pharmacokinetic and/or biomarker studies.
    4. Assess preliminary antitumor efficacy.

- The typical sample sizes used in phase 2 trials provide imprecise estimates of outcome.
- Basket and umbrella trials efficiently evaluate several treatment-marker or treatment-histology combinations.
- Results among phase 2 trials, especially single-arm trials, are difficult to compare because so many factors can vary from trial to trial.
- Phase 3 clinical trials are typically randomized and are designed to be pivotal; that is, they aim to demonstrate and confirm the safety and efficacy of a treatment strategy to obtain approval by regulatory authorities.
- Phase 3 study outcomes/endpoints should be previously validated as meaningful and selected to minimize variability in interpretation.
- Phase 3 trials require careful consideration of study design parameters, including randomization, blinding, and choice of endpoint, to minimize bias in the assessment of the treatment benefit.
- Common measures of correlation assess the linear correlation between variables. Lack of linear correlation does not necessarily mean that the variables are not related.
- Measures of correlation may be sensitive to a few outlying observations.
- Correlation, by itself, does not imply causation. Even though a biomarker may be correlated with both treatment and outcome, this is not sufficient to establish that the biomarker is a useful surrogate endpoint.
- Multiple comparisons increase the type I error above the desired significance level if the *P* values (or significance level) are not adjusted.
- Binary data analysis is used for outcomes with yes/no or binary responses. The χ^2 or Fisher exact test is used to compare proportions between groups. Logistic regression is used to model the odds of a response, where the effect of a covariate is summarized through an odds ratio.

- Survival analysis techniques are used to analyze outcomes describing the time until an event occurs, which may be subject to censoring or competing risks.
- Although Kaplan-Meier curves are the universal standard for graphically representing time-to-event endpoints, the statistical analysis of such curves is usually not based on a direct comparison of the curves themselves. Rather, the comparison is based on the underlying hazard rate (the rate of events among patients remaining at risk) using the log-rank test.
- Comparisons of cumulative incidence curves are performed similarly to comparisons of survival curves.
- Cox regression is used to model the hazard rate in time-to-event outcomes, where the effect of a covariate can be summarized through an HR.
- Logistic regression is used to model the odds of a response, where the effect of a covariate is summarized through an odds ratio.
- The discriminatory ability of a prognostic biomarker is measured by computing the area under the curve for an ROC curve. The closer the area under the curve is to 1, the better the discriminatory ability.
- To determine whether a biomarker is prognostic, an association between the biomarker and the outcome of interest must be established.
- To determine whether a biomarker is predictive, a statistically significant interaction must be established between biomarker status (present vs absent) and the treatment of interest (received vs did not receive) with respect to the outcome of interest.
- Longitudinal data analysis is used to model outcomes that are assessed repeatedly over time. These methods must account for missing data commonly occurring in this setting, as well as for the correlation between measurements in the same individual.

CHAPTER TABLES AND IMAGES

Table 5-1 Hypothesis Test Decisions and Error Types

		Truth Based on Population (Universe)	
		Null Hypothesis Is True	**Null Hypothesis Is False**
Decision based on sample (data)	Reject the null hypothesis	Type I error	Correct decision (power)
	Do not reject the null hypothesis	Correct decision	Type II error

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Table 5-2 **Choosing a Statistical Analysis Approach**

Endpoint Type	One Predictor	Multiple Predictors or a Single Continuous Predictor
Binary (yes vs no)	χ^2 test or Fisher exact test	Logistic regression
Time to event	Log-rank test	Cox proportional hazards regression
Continuous	*t* test or Wilcoxon test	Linear regression
Paired/correlated data	Continuous: paired *t* test or signed rank test; binary: McNemar test	Mixed models or generalized mixed models
Categorical or ordinal	χ^2 test or Fisher exact test	Multinomial regression or proportional odds regression
Count data	Poisson or negative binomial regression	Poisson or negative binomial regression

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Table 5-3 **Description of Common Statistical Tests**

Outcome	Setting	Test	Definition and Description
Continuous	Comparing means	Two-sample *t* test	Used to compare means between two groups for a quantitative variable; normal distribution and equal variance in each group are assumed; an unequal variance *t* test can be used if unequal variances are expected in the two groups; generally robust to small sample size and nonnormal distributions, but sensitive to outlying values, which inflate estimates of variability
		Paired *t* test	Used to compare paired quantitative data; for example, a paired *t* test can be used to determine whether there is a nonzero change in a quantitative characteristic measured before and after treatment in each patient; same sensitivity to outlying values as the two-sample *t* test
Continuous	Comparing medians or distributions	Wilcoxon rank sum (Mann-Whitney)	Nonparametric alternative to the two-sample *t* test; less sensitive to outlying values than the two-sample *t* test, although can be somewhat more conservative compared with *t* test (eg, if the data are normally distributed)
		Wilcoxon signed rank	Nonparametric alternative to the paired *t* test; less sensitive to outlying values than the paired *t* test, although somewhat more conservative
Binary	Comparing proportions	χ^2	Used to compare proportions between two or more groups; fairly robust to small sample sizes, unless there is an imbalance between groups
		Fisher exact	Used to compare proportions with small sample sizes; a commonly used rule of thumb is to use the Fisher exact test if <5 observations are expected in any of the cells of a contingency table; this test may be somewhat more conservative compared with the χ^2 test
		McNemar	Used to compare paired proportions; for example, a binary characteristic assessed before and after treatment in each patient; it is based only on the discordant pairs (where outcome is different) and is not used to assess concordance
Time to event	Comparing survival distribution	Log rank	Used to compare survival distributions between two or more groups; also, the Kaplan-Meier approach is used to estimate the survival distribution (curve)

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Table 5-4 **RECIST 1.1 Definitions of Response and Disease**

Response	Target Lesions	Nontarget Lesions
CR	Disappearance of all target lesions	Disappearance of all nontarget lesions and normalization of tumor marker level
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters	Persistence of ≥1 nontarget lesion and/or maintenance of tumor marker level above the normal limits
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study; in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm	Unequivocal progression of existing nontarget lesions; appearance of ≥1 new lesion is also considered progression
SD	Neither sufficient shrinkage to quality for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters during the study	NA

Abbreviations: CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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Table 5-5 **Examples of Single-Stage Phase 2 Designs**

Design Criteria				Resulting Design	
p_0	p_1	α	Power[a]	n	*r*
0.1	0.25	0.05	0.9	55	10
0.1	0.25	0.05	0.8	40	8
0.1	0.25	0.1	0.9	40	7
0.1	0.25	0.1	0.8	31	6
0.1	0.25	0.05	0.9	33	7
0.1	0.25	0.05	0.8	25	6
0.1	0.25	0.1	0.9	25	5
0.1	0.25	0.1	0.8	18	4
0.5	0.7	0.05	0.9	53	33
0.5	0.7	0.05	0.8	37	24
0.5	0.7	0.1	0.9	39	24
0.5	0.7	0.1	0.8	28	18

Abbreviations: α, type I (false-positive, one-sided) error rate if $p = p_0$; n, smallest sample size that satisfies design criteria; p_0, response rate under null hypothesis; p, response rate under alternative hypothesis; r, minimum number of responses required to reject null hypothesis and conclude that $p > p_0$ using the exact test for one proportion.

[a]Power refers to the probability of rejecting the null hypothesis if $p = p_1$.

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Table 5-6 **CIs for True Response Rates**

Observed Rate = 10%			Observed Rate = 50%		
n	***r***	**95% CI (%)**	**n**	***r***	**95% CI (%)**
10	1	0.3-44.5	10	5	18.7-81.3
20	2	1.2-31.7	20	10	27.2-72.8
30	3	2.1-31.7	30	15	31.3-68.7
40	4	2.8-23.7	40	20	33.8-66.2
50	5	3.3-21.8	50	25	35.5-64.5
60	6	4.9-17.6	60	30	39.8-60.2

Abbreviations: CI, confidence interval; n, sample size; *r*, observed number of responses.
Computations can be performed using the online calculator at https://stattools.crab.org/Calculators/binomialConfidence.htm
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Table 5-7 **Examples of Two-Stage Phase 2 Designs (Optimal Simon Design)**

Design Criteria				Resulting Design			
				First Stage		Overall	
p_0	p_1	α	Power[a]	n_1	r_1	n	r
0.10	0.25	0.05	0.9	21	2	66	10
0.10	0.25	0.10	0.9	21	2	50	7
0.25	0.45	0.10	0.9	22	6	57	19
0.40	0.6	0.10	0.9	25	11	66	32
0.50	0.7	0.10	0.9	24	13	61	36

Abbreviations: α, one-sided type I (false-positive) error rate if $p = p_0$; n, total sample size after both stages; n_1, sample size for first stage; p_0, response rate under null hypothesis (usually based on external control group rate); p_1, response rate under alternative hypothesis; r, minimum number of responses required to reject null hypothesis and conclude that $p > p_0$; r_1, if r_1 or fewer responses are observed during stage I, the trial is stopped early for futility (if r_1 or fewer responses are observed by the end of stage II, then no further investigation of the drug is warranted).

[a]Power refers to the probability of rejecting the null hypothesis if $p = p_1$.

Data adapted from https://cancer.unc.edu/biostatistics/program/ivanova/SimonsTwoStageDesign.aspx

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Table 5-8 **Minimum Sample Size (per Arm) for Simon's Pick-the-Winner Randomized Phase 2 Designs**[a]

	Two Arms (p_1, p_2)		Three Arms (p_1, p_2, p_3)	
Difference ($p_2 - p_1$)	**Power[b] = 0.80**	**Power = 0.90**	**Power = 0.80**	**Power = 0.90**
0.10	36	82	68	123
0.15	16	37	31	55
0.20	9	21	17	31

Abbreviations: p_1, lower (lowest) response rate, 0.4; p_2, higher (highest) response rate.
[a]A conventional type I error rate is not defined for pick-the-winner randomized phase 2 designs because no formal null hypothesis is tested. These designs are intended for treatment selection rather than hypothesis testing, and their operating characteristics are summarized by the probability of correct selection rather than false-positive control.
[b]Power refers to the probability that the arm with highest true response rate has the highest observed response rate.
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Table 5-9 **Factors Affecting Success of Biomarker-Driven Trials**	
Factors	**Key Points and Impact on Trial Success**
Analytically validated biomarker assay	Positive if validated, negative if not. Analytical validation is a prerequisite for credible classification and reproducible results.
Known actionable target	Positive if known, negative if unknown. Actionability supports a clear biological rationale for enrichment or matching.
Large magnitude of difference in clinical outcome	Positive if large, negative if small. Bigger effects are easier to detect and less sensitive to misclassification or heterogeneity.
Moderate to high prevalence	Positive if moderate to high, negative if lower than expected. Low prevalence drives screen failures, slow enrollment, and early closure risk.
High accrual rate	Positive if high, negative if low. Accrual refers to fast enrollment of eligible patients, not screening volume per se, although low prevalence can force high screening to achieve adequate accrual.
Baseline and longitudinal biomarker collection	Positive if baseline plus longitudinal, negative if baseline only. Longitudinal sampling better captures evolving disease biology and resistance.
Prognostic or genomic model as stratification factor: homogeneity within strata	Positive. Improves interpretability and precision by reducing within stratum heterogeneity.
Prognostic or genomic model as stratification factor: heterogeneity across strata	Positive. Creates clinically distinct strata, supports effect modification evaluation, and improves design efficiency.
Validated cutoff point of biomarker	Positive if well validated, negative if not. Unstable cutoffs increase misclassification and reduce reproducibility.
Near real-time readout from assay	Positive if near real time, negative if delayed. Turnaround time affects feasibility, timely assignment, and accrual.
Strong stakeholder buy-in	Positive if strong, negative if weak. Buy-in is critical in biomarker trials, especially master protocols requiring multi-party coordination.

Data adapted from Halabi S, Niedzwiecki D. Advancing precision oncology through biomarker-driven trials: theory vs. practice. *Chance*. 2019;32:23-31. doi:10.1080/09332480.2019.1695438

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Table 5-10 **Required Sample Size (per Arm) for Noninferiority Trials With Binomial Endpoint**

Allowable Difference or Noninferiority Margin ($p_0 - p_1$)	Sample Size per Arm
0.20	107
0.15	191
0.10	428
0.05	1713

Note: $p_0 = 0.50$, $\alpha = 0.05$, and power = 0.90. Computation was completed using binomial noninferiority tool (https://stattools.crab.org/R/Binomial_Non_Inferiority.html).
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Table 5-11 **Examples of Adaptive Designs**	
Design	**Idea**
Continual reassessment method	Model-based dose escalation to estimate the MTD
BOIN designs	Model-assisted dose-finding design to estimate MTD
Group sequential	Include options to stop the trial early for safety, futility, or efficacy
Sample size re-estimation	Adjust sample size to ensure the desired power
Multiarm multistage	Explore multiple treatments, doses, durations, or combinations with options to "drop losers" or "select winners" early
Population enrichment	Narrow down recruitment to patients more likely to benefit (most) from the treatment
Biomarker adaptive	Incorporate information from or adapt based on biomarkers
Adaptive randomization	Shift allocation ratio toward more promising or informative treatment(s)
Adaptive dose ranging	Shift allocation ratio toward more promising or informative dose(s)
Seamless phase 1/2	Combine safety and activity assessment into one trial
Seamless phase 2/3	Combine selection and confirmatory stages into one trial

Abbreviations: BOIN, Bayesian optimal interval; MTD, maximum tolerated dose.
Adapted under Creative Commons license. Source: Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med*. 2018;16:29. doi:10.1186/s12916-018-1017-7

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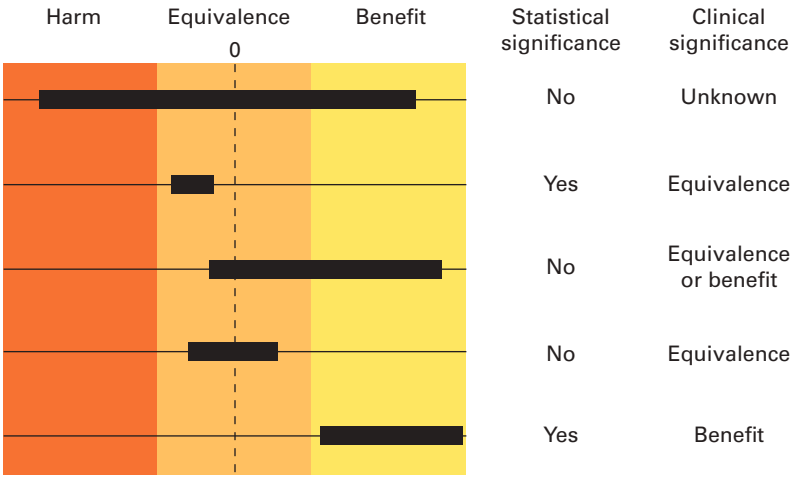
Figure 5-1 Relationship Between Estimates and Confidence Intervals (CIs) and Their Statistical and Clinical Significance



Dashed line at 0 represents no difference between groups.
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Figure 5-2 Relationship Between *P*-Value Ranges and the Strength of Statistical Evidence Against the Null Hypothesis

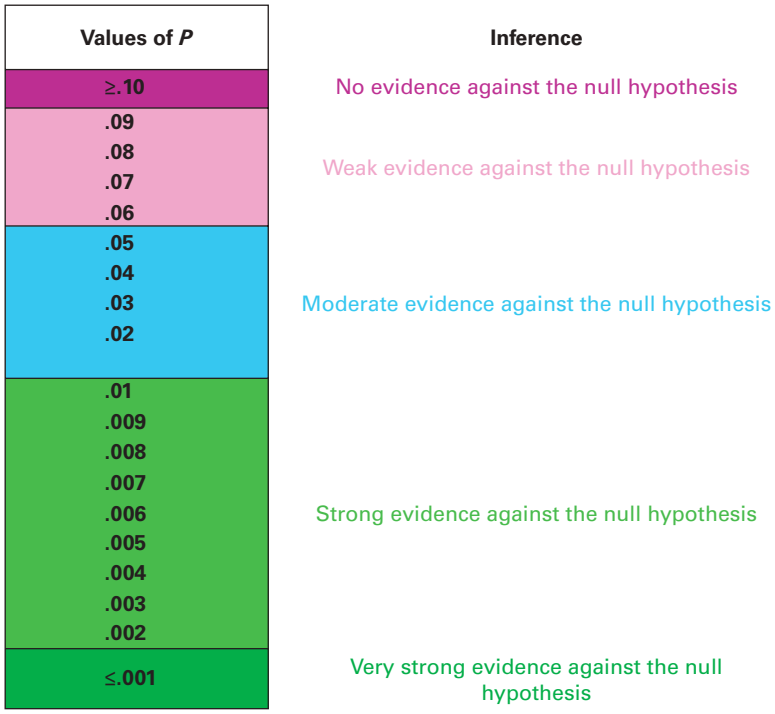

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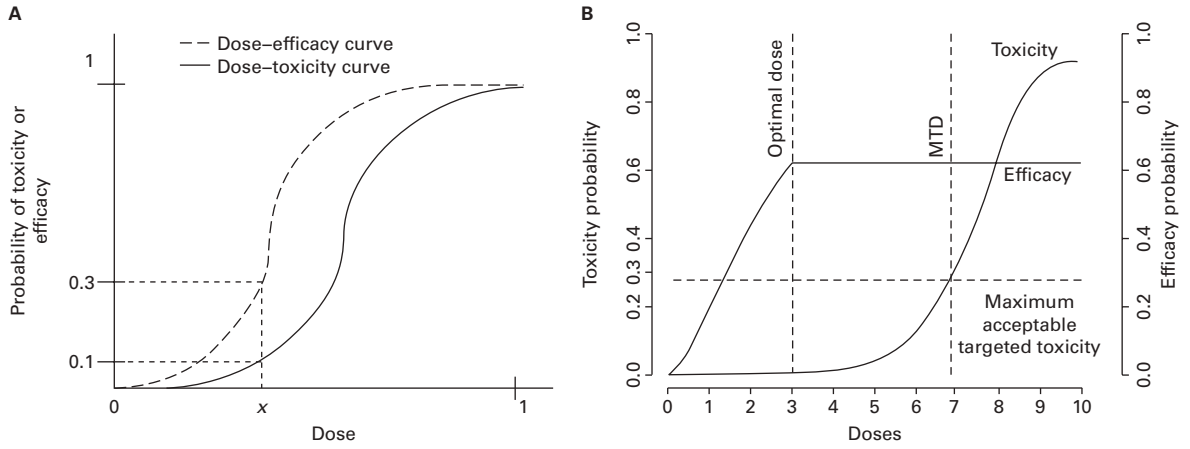
Figure 5-3 Dose-Response and Dose-Toxicity Relationships for Cytotoxic Versus Molecular Targeted Treatments



(A) Typical dose-toxicity and dose-efficacy curves for cytotoxic agents. This example illustrates that at dose *x*, the probability of efficacy is 30% and the probability of toxicity is 10%; hence, the therapeutic index of the drug at dose *x* is 10% divided by 30% = 1/3. (B) Illustration of dose-toxicity and dose-efficacy relationship for molecularly targeted agents.
Abbreviation: MTD, maximum tolerated dose.
Data adapted from (A) Le Tourneau et al. *J Natl Cancer Inst.* 2009;101:708-720, by permission of Oxford University Press. (B) Riviere et al. *Stat Methods Med Res.* 2018;27:466-479.
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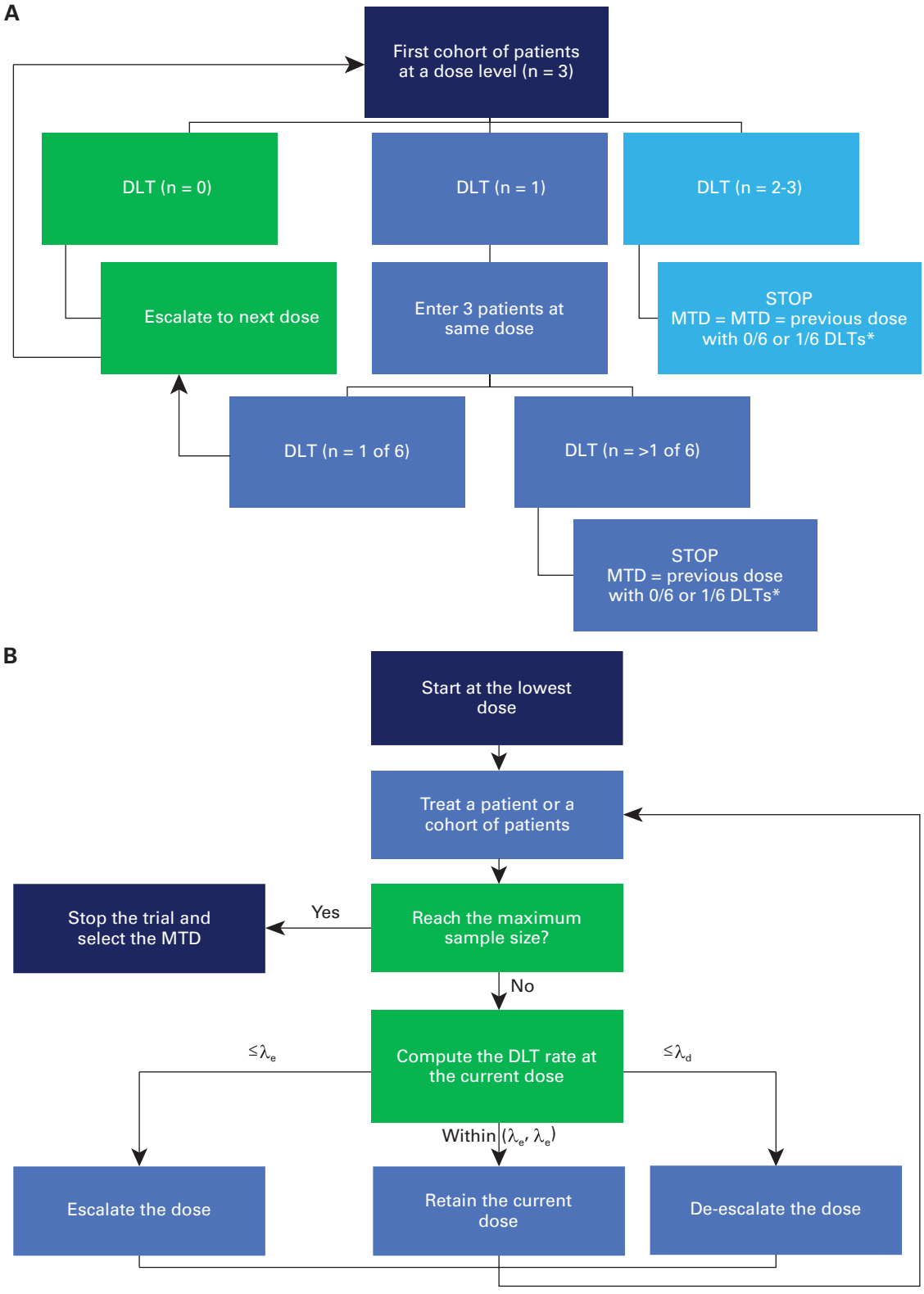
Figure 5-4 Typical Dose-Finding Phase 1 Design Algorithms



(A) 3 + 3 phase 1 trial design. Note that patients who are non-evaluable for DLTs may be replaced. (B) BOIN design.
Abbreviations: BOIN, Bayesian optimal interval; DLT, dose-limiting toxicity; MTD, maximum tolerated dose.
*Six patients must be treated at a dose level before it can be declared an MTD.
Data adapted from https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware/Index/99
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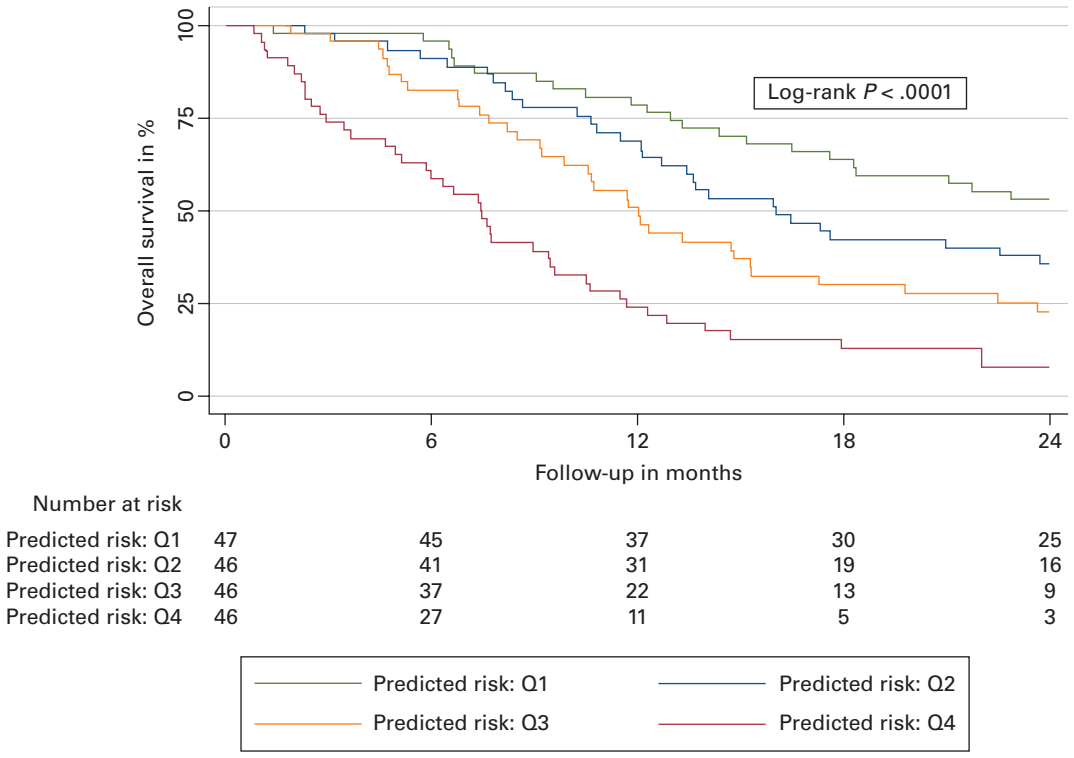
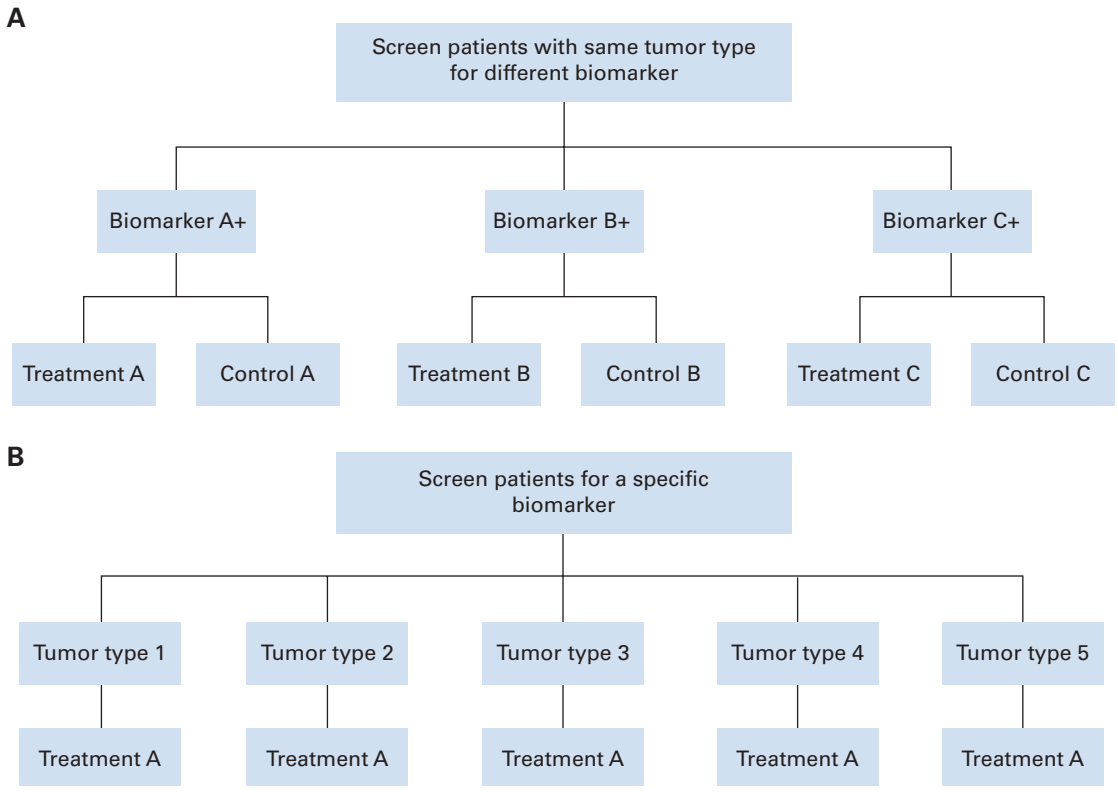
Figure 5-5 Kaplan-Meier Survival Curves According to Biomarker-Based Prognostic Score



Note that patient outcomes are stratified in quartiles according to individual predicted risk of mortality.
Reproduced under Creative Commons license. Source: Moik F, Zöchbauer-Müller S, Posch F, et al. Systemic inflammation and activation of haemostasis predict poor prognosis and response to chemotherapy in patients with advanced lung cancer. *Cancers*. 2020;12(6):1619. doi:10.3390/cancers12061619

Figure 5-6 Umbrella and Basket Trial Designs



(A) Illustration of an umbrella trial design in which patients with the same tumor type are tested for different biomarkers and then are assigned to a treatment group that targets the biomarker. In this example, patients are randomly assigned to a treatment versus control arm. An alternative design could be a single-arm design with the patients with a particular biomarker receiving treatment meant to target that biomarker. (B) Illustration of a basket trial design in which all patients are tested for a particular biomarker and then are entered into a cohort for their tumor type. All patients receive the same targeted treatment that is believed to potentially benefit patients with tumors with the biomarker. This shows each cohort is a single-arm trial, but the cohort could be randomly assigned to treatment and control arms.
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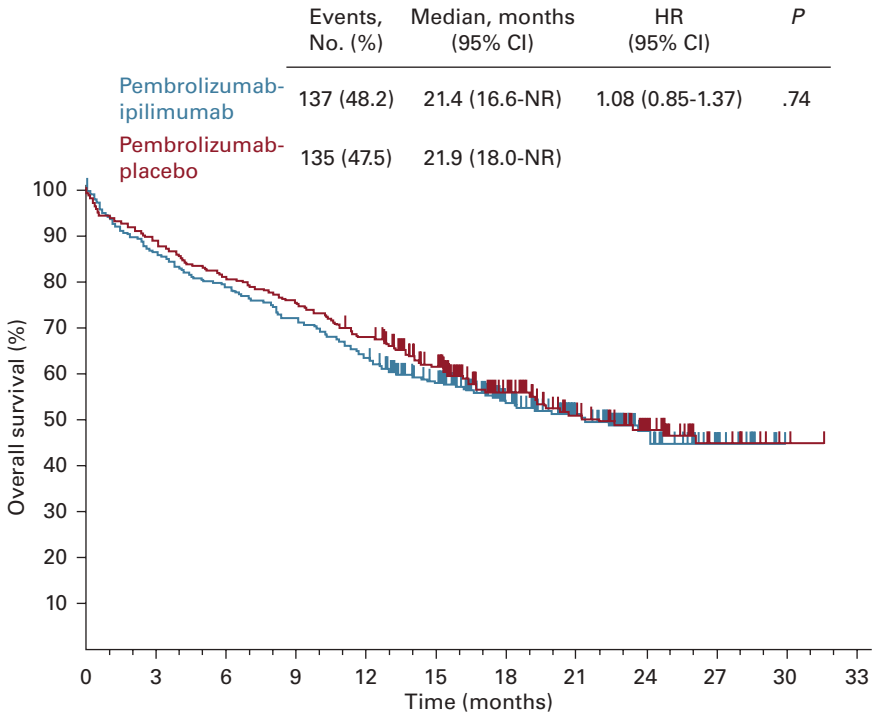
Figure 5-7 KEYNOTE-598: Kaplan-Meier Plot of Overall Survival (OS)

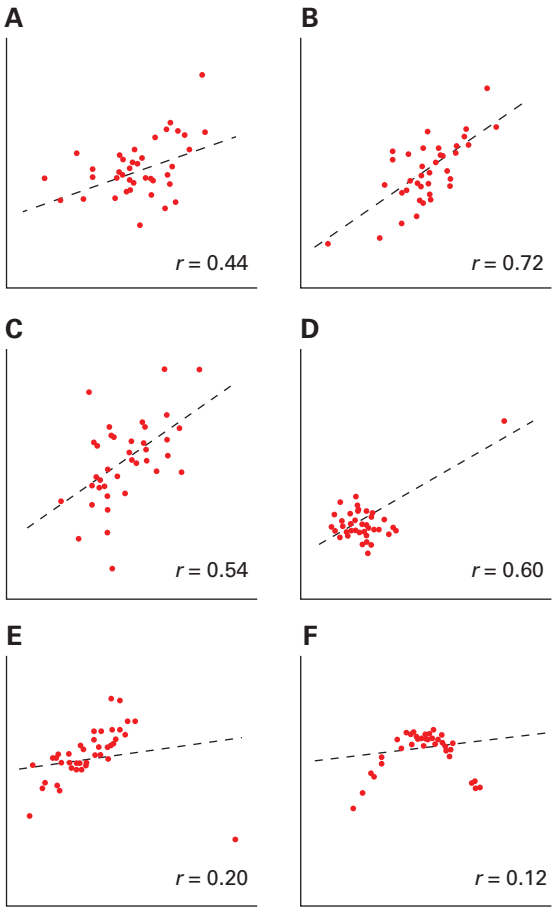


No. at risk

Pembrolizumab-ipilimumab	284	245	223	204	180	146	100	62	37	10	0	0
Pembrolizumab-placebo	284	252	230	215	192	154	111	77	41	15	2	0

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.
Reprinted from Boyer M, Şendur MAN, Rodríguez-Abreu D, et al. Pembrolizumab plus ipilimumab or placebo for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥50%: randomized, double-blind phase III KEYNOTE-598 study. *J Clin Oncol*. 2021;39(21):2327-2338. doi:10.1200/JCO.20.03579

Figure 5-8 Scatterplot Examples of Linear Correlation



The six graphs illustrate possible correlations between two variables, *x* and *y*. The dashed line indicates the least squares line fit to the data, and *r* is the Pearson correlation coefficient. (A) Data have a positive correlation of moderate strength. (B) Compared with the data in panel (A), there is an increased slope in the data and a stronger correlation. (C) Data have the same slope as the data in panel (B), but the correlation is weaker (ie, the points have more variability about the best fitting line). (D) Computed correlation is stronger than that in the bulk of the data because of the influence of one outlier point. If this point were removed, the correlation would be smaller. (E) Correlation with the outlier is weaker than the correlation for the remainder of the data. If the outlier were removed, the correlation would increase. (F) There is a strong nonlinear relationship in the data, but the correlation is weak, because the correlation measures the strength of linear relationship.
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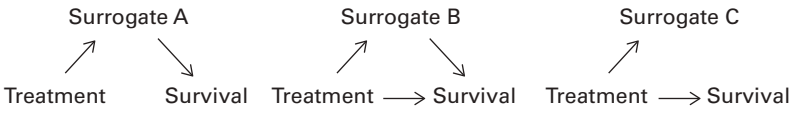
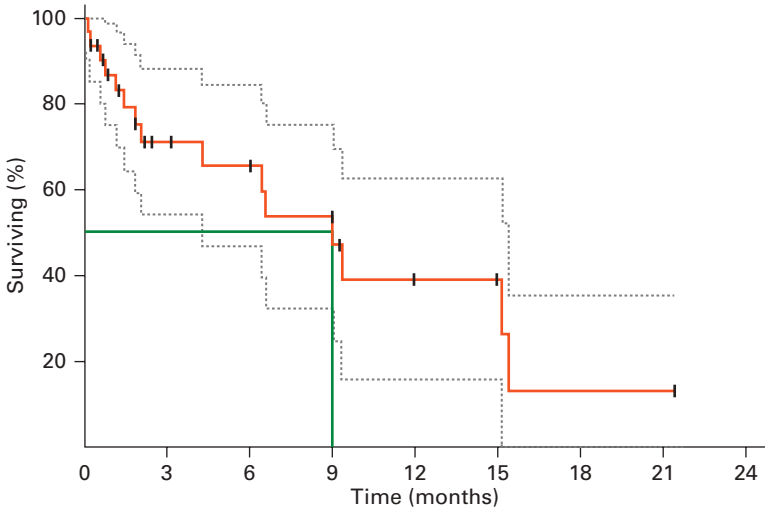
Figure 5-9 Causal Links Between Surrogate and Final Endpoint



(A) Casual surrogate. (B) Potential surrogate. (C) Independence. Causal diagrams illustrating pathways that involve treatment, a candidate surrogate, and the final endpoint, in this case survival (see text for explanations). Arrows indicate direct treatment effects: treatment effect on the surrogate, treatment effect on survival, and effect of surrogate on survival.
Adapted under Creative Commons license. Source: Buyse M, Saad ED, Burzykowski T, et al. Surrogacy beyond prognosis: the importance of "Trial-Level" surrogacy. *Oncologist.* 2022;27(4):266-271. doi:10.1093/oncolo/oyac006

Figure 5-10 Survival Curve Plot and Related Quantities



Orange line is an example of a Kaplan-Meier curve for a group of 33 patients. At any time point, the curve estimates the probability of surviving at least as long as that time. Gray lines indicate the 95% CIs for the survival probability calculated at each point. Tick marks indicate times at which surviving patients were last known to be alive and are censored. Green line indicates how median survival would be calculated. In this curve, the survival probability drops to less than 50% at 9 months.
Abbreviation: CI, confidence interval.
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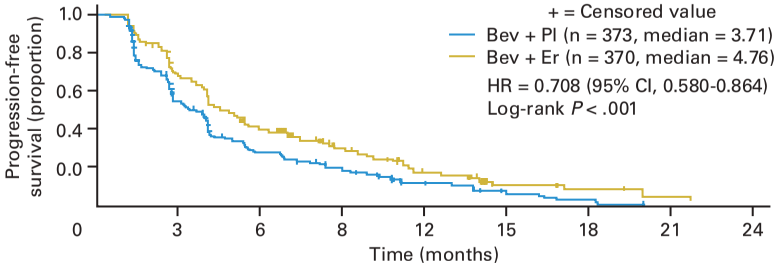
Figure 5-11 Plots to Compare Survival Curves

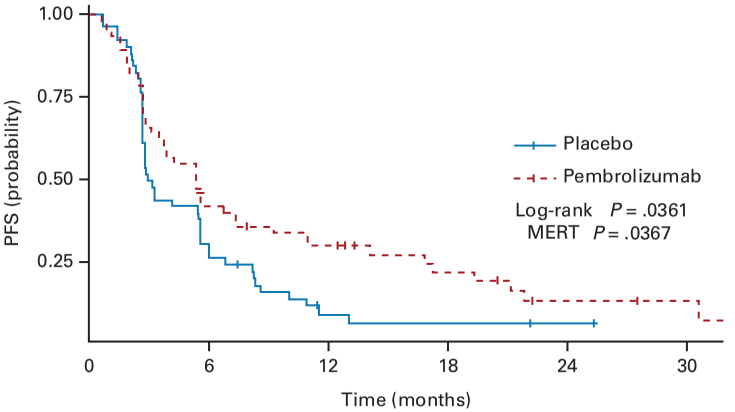
A PH



No. at risk									
Bev + Er	370	180	80	43	20	5	3	1	0
Bev + Pl	373	143	57	28	15	6	3	0	0

	Bevacizumab + Placebo (n = 373)		Bevacizumab + Erlotinib (n = 370)	
Time Since Random Allocation	Patients With Event	Kaplan-Meier Percent Event Free (Pointwise 95% CI)	Patients With Event	Kaplan-Meier Percent Event Free (Pointwise 95% CI)
3 months	138 (37.0%)	54.1 (48.2-59.6)	92 (24.9%)	68.4 (62.7-73.4)
6 months	200 (53.6%)	28.2 (22.7-33.9)	160 (43.2%)	40.2 (34.1-46.2)
9 months	216 (57.9%)	19.3 (14.3-24.9)	177 (47.8%)	30.2 (24.2-36.5)
12 months	226 (60.6%)	12.1 (7.8-17.5)	193 (52.2%)	17.8 (12.3-24.1)

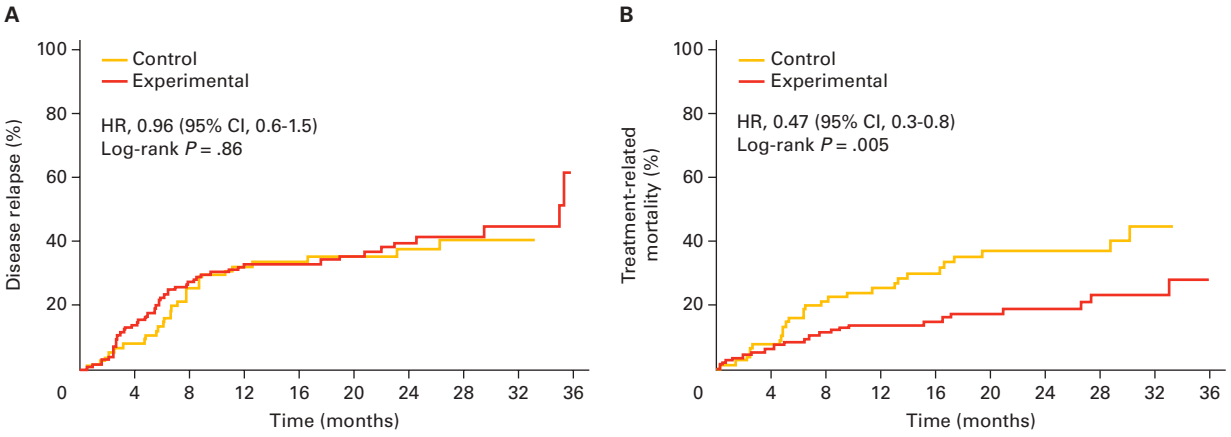
B Non-PH



No. at risk						
Placebo	52	15	3	2	1	0
Pembrolizumab	55	21	14	8	3	2

(A) PH assumption is satisfied. (B) PH assumption is violated.
Abbreviation: CI, confidence interval; HR, hazard ration; MERT, mixed effects regression tree; PH, proportional hazards.
Data adapted from (A) Johnson BE, Kabbinavar F, Fehrenbacher L, et al. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol*. 2013;31(31):3926-3934, figure 3. Reprinted from (B) Galsky MD, Mortazavi A, Milowsky MI, et al. Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer. *J Clin Oncol*. 2020;38:16, figure 2A.

Figure 5-12 Plot of Cumulative Incidence Curves for Competing Risks



Data are decomposed into the two competing risks of (A) relapse and (B) treatment-related mortality. Most of the improvement in DFS in the experimental arm is attributable to a decrease in treatment-related mortality; there is no observed difference in the rate of relapse between arms among those at risk of relapse.

Abbreviations: CI, confidence interval; HR, hazard ratio.

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GENETIC TESTING FOR HEREDITARY CANCER SYNDROMES

6

Lisle Nabell, MD, and Bita Nehoray, MS, CGC

RECENT UPDATES

- Cancer-specific mortality in a population-based sample[1] of 77,955 patients with breast (n = 70,272), colorectal (n = 5,822), and pancreatic (n = 1,861) cancers with *ATM, CHEK2*, and *PALB2* pathogenic germline variants (PGVs; please note that this abbreviation will be used throughout the chapter to indicate pathogenic and likely pathogenic germline variants unless otherwise indicated), was assessed and cancer mortality rates were similar for PGV carriers versus genetically tested patients with each cancer type. The study utilized SEER data from California and Georgia for individuals with stage 0-IV breast, colorectal, or pancreatic cancer between 2013 and 2019 with a mean follow-up of 3.9 years. Separate models (random effects model and fixed effects models) were used to calculate hazard ratios for three different breast cancers (estrogen receptor negative/progesterone receptor positive/HER-2 negative; HER2-positive; and triple negative), colorectal, and pancreatic cancers. By the fixed effects models triple-negative breast cancer cases with *ATM* PGVs had a higher mortality (hazard ratio 3.7), but not by random effects models (hazard ratio 1.2). Authors advised caution in inferring generalizability given the data was limited to two states, selection effects for those who received genetic testing, and shorter follow-up for more recently diagnosed cases due to censoring for survival after 2021.
- In a prospective cohort study[2] of 188 adolescents and young adults (AYA; age 39 years and younger) with *CDH1* PGVs, cancer-specific outcomes were not different in individuals with signet ring cell lesions managed with endoscopic surveillance versus those who underwent prophylactic total gastrectomy (PTG). Among the 104 in the surveillance group, occult signet ring cells were detected by endoscopic biopsy in 37 (36%), and none of the individuals who were undergoing surveillance developed an advanced gastric cancer. Of the 67 who underwent PTG, 62 (93%) had occult signet ring cell lesions, compared to 31/65 (48%) with signet ring cell lesions detected on preoperative endoscopy. In the PTG group, one patient had carcinoma in situ and four (6%) had no cancer detected on the gastrectomy specimen. Those who elected to have PTG were more likely to have signet ring cell lesions detected on preoperative endoscopy (P = .025). Given the low prevalence of advanced gastric cancers in this cohort, the authors postulate that AYA with signet ring cell lesions are at risk of overtreatment with PTG and that more research is needed to identify factors influencing the progression of signet ring cell precursors to advanced diffuse-type gastric cancer.
- Data derived from 217,824 participants in the All of Us Research Initiative were reviewed to assess the prevalence and clinical manifestations of Lynch syndrome (LS).[3] A total of 615 carriers (0.3%) of mismatch repair PGVs were identified, that is, 1 in 354 individuals. Analyses to evaluate phenotypic expression were limited to individuals with available medical records (n = 162,970), for which there were 457 individuals with PGVs, with the majority accounted for by *MSH6* and *PMS2*: 10.9% (50/457) in *MLH1*, 8.7% (40/457) in *MSH2*, 35.4% (162/457) in *MSH6*, and 44.8% (205/457) in *PMS2*. Probability of cancer development was time-to-first cancer by genotype, noting carriers of LS PGVs have higher probabilities of developing any cancer as compared noncarriers, but most pronounced for LS-associated cancers. Consistent with the literature, higher probabilities were observed with *MLH1* and *MSH2* as compared to *MSH6* and *PMS2*. Majority of the carriers in this study (up to 63.2%) had no medical records indicating LS, underscoring the need for optimizing the detection and management of individuals with LS discovered on genetic-testing panels. There is a need for optimizing the detection of individuals with LS.

▶ A prospective cohort study[4] to assess the utility of annual non-contrast whole-body MRI for screening in individuals with Li-Fraumeni syndrome (LFS) demonstrated that this modality aids in the detection of asymptomatic localized cancers: 162 individuals with LFS (127 adults, 35 pediatrics) from three academic medical centers in the United States underwent 477 non-contrast whole-body MRIs between 2012 and 2022, with 73% undergoing three or more during the study period. Follow-up studies were carried out for 55.6% of individuals, with rates of follow-up interventions decreasing with consecutive whole-body MRIs. Of the 37 types of cancers diagnosed in 33 individuals, 40.5% were detected by whole-body MRI; and 86% (13/15) were asymptomatic and were treated with curative intent. Authors endorse the use of this screening tool as part of a multimodal approach as recommended by recognized LFS guidelines. Similarly, a large single-center retrospective study[5] evaluating the use of whole-body MRI for adults with LFS reinforced its use[4] as a screening modality as it demonstrated high negative predictive value; 325 whole-body MRIs were performed in 75 adults from January 2012 to January 2024. Of the 325, 112 demonstrated abnormalities, with the majority (89/112) being benign incidental findings (that prompted 53 additional imaging tests) and the remaining 23 were noted to be lesions of concern. Nine of the concerning lesions were ultimately identified to be cancer (eight primary cancers, two metastatic cancers). In addition, eight interval cancers were diagnosed in seven individuals following a normal whole-body MRI scan. As a stand-alone tool, the authors reported whole-body MRI to have 95.5% specificity, 97.4% negative predictive value, and 42.9% sensitivity. While this study supports the continued use of whole-body MRI in this patient population, the authors call for the development of a novel early detection tool (such as cell-free DNA technology) to complement whole-body MRI and/or inform the diagnostic pathway in this population.

OVERVIEW

During the past two decades, the availability of clinical genetic counseling and testing for hereditary cancer predisposition syndromes has had a major impact on the practice of medical and preventive oncology. Recent large studies have shown that up to 13.3% of patients with solid tumors and 17% of patients with recurrent or metastatic cancer have pathogenic germline variants (PGVs).[6,7] In addition, a study from the UK BioBank identified that about 0.7% of the unselected general population have PGVs in *BRCA1, BRCA2*, or a mismatch repair gene associated with Lynch syndrome (LS).[8,9] More recent data from the UK BioBank expanding to a larger number of genes identified PGVs in 3.57% of non-cases across 16 genes, with carrier frequencies of 6.28% for those with at least one cancer and 8.36% for those with multiple primary cancers. The identification of patients with an inherited predisposition to cancer informs targeted treatment decisions and future management for patients and their families and is now one of the core elements of oncologic care. ASCO and other organizations have provided statements and guidelines on genetic testing and management.[10-15]

The goals of this chapter include the following:

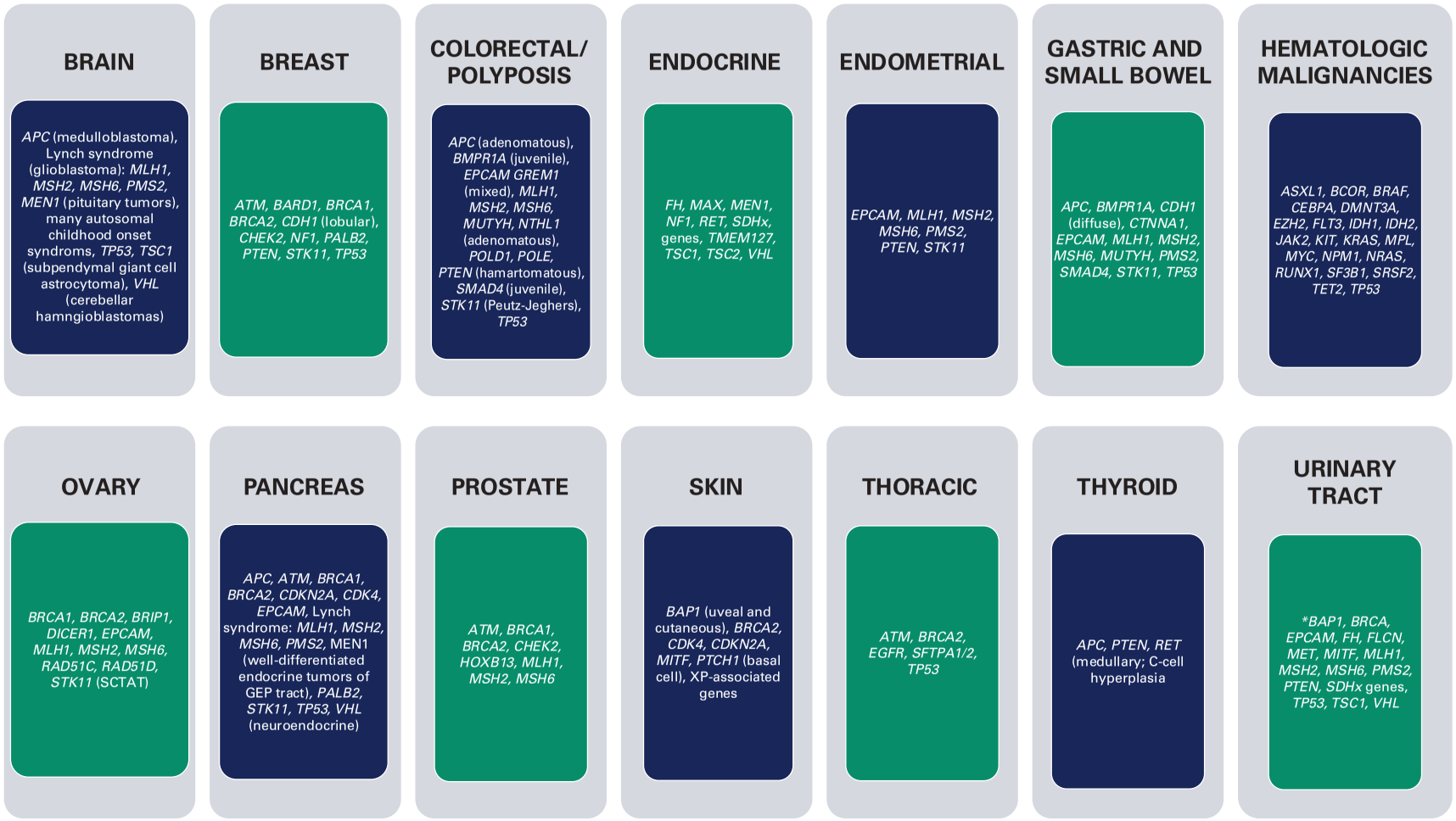
- Review the major principles that guide genetic counseling and testing.
- Highlight the differences between testing and counseling for high- versus moderate-penetrance cancer susceptibility genes.
- Discuss ways of integrating genetic test results into the care of oncology patients.
- Understand the impact of next-generation sequencing (NGS) technologies and tumor biomarker testing on germline analysis.
- Appreciate the ramifications of multigene panel testing for inherited cancer susceptibility and the increased identification of incidental or uncertain genetic findings.
- Recognize the importance of pre- and posttest genetic counseling and relationships with genetic counselors and other genetic specialists.[15,16]

In addition, many of the more common cancer predisposition syndromes are discussed elsewhere, when appropriate. Please refer to the specific chapters for additional information on breast cancer, gastrointestinal cancers, genitourinary cancers, gynecologic cancers, and leukemias (Chapters 10, 13, 14, 15, and 19, respectively).

THE HEREDITARY NATURE OF CANCER

The heritability of cancer has long been recognized, and, through the study of cancer-prone families who demonstrate Mendelian modes of inheritance, more than 100 cancer predisposition genes have been identified.[17] However, only a fraction of the familial risks of cancer is explained by the known high-penetrance cancer predisposition syndromes. For example, in the case of familial breast cancer, 10% of diagnoses are related to high-penetrance PGVs (eg, those of *BRCA1* and *BRCA2*), whereas the remainder are because of moderate-penetrance genes, or multiple factors (eg, additional shared, but currently undetectable or poorly understood, heritable factors, and/or shared environmental factors). Figure 6-1 shows germline PGVs associated with several major tumor types. In addition, Tables 6-1A to D summarize the characteristics of common hereditary cancer syndromes found on multigene panel tests.

Figure 6-1 Cancer Types and Select Associated Genes



Abbreviations: FH, fumarate hydratase, including type 2 papillary, tubular papillary, and collecting-duct carcinoma; FLCN, folliculin, oncocytoma, chromophobe, and oncocytic hybrid tumor; GEP, gastroenteropancreatic; MET, type 1 papillary; SCTAT, sex cord tumors with annular tubules; TSC1, TSC2, renal cell carcinoma, angiomyolipomas, and oncocytoma; XP, xeroderma pigmentosum.
*Urinary tract gene-associated pathologies. Gene-specific pathologies are listed in Tables 6-1A to D.
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Table 6-1A **Selected High- and Moderate-Risk Genes, Syndromes, and Management Considerations: A Through C**

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
APC	FAP, AFAP; variant: Turcot syndrome, GAPPS	Colorectal lesions (adenomatous polyposis and cancer), gastric and duodenal/small-bowel lesions (adenomatous polyps and cancer), desmoid tumors, thyroid (particularly cribriform-morula variant of papillary thyroid carcinoma), hepatoblastoma (usually in patients less than 5 years old), pancreatic cancer, medulloblastoma (Turcot syndrome), GAPPS	Colonoscopy (beginning as early as age 10 years) and total colectomy based on polyp burden; upper endoscopy, consideration of small-bowel visualization, thyroid examination, and consideration of ultrasonography; consideration of childhood liver palpation, abdominal ultrasonography, AFP measurement	Genotype-phenotype correlations between classic FAP and AFAP: mutations on the 5′ and 3′ ends of the gene correlate with AFAP; high de novo mutation rate (about 20%-25%); extracolonic features: CHRPE, osteomas, supernumerary teeth, desmoid tumors, epidermoid cysts, gastric fundic gland polyps; chemoprevention not a replacement for colonoscopy and colectomy	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18,19]
*APC**I1307K (c.3920T->A)		Colorectal cancer: moderate penetrance	Colonoscopy every 5 years beginning at age 40 years or earlier depending on family history; lifetime risk 5%-10%	Ashkenazi Jewish founder PGV; not associated with polyposis	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]; Katona et al[20]
ATM	Ataxia telangiectasia	Monoallelic carriers: breast (especially ER-positive), pancreas, possibly ovary, prostate; biallelic carriers: leukemia, lymphoma	Monoallelic carriers: breast screening with annual mammogram at age 40 and breast MRI starting at age 30-35 years or per family history*; pancreas screening beginning at age 50 years (or 10 years prior to earliest exocrine pancreatic cancer in the family); biallelic carriers: AT specialist for multidisciplinary management; consider annual prostate cancer screening at age 40 years	Monoallelic carriers: limited evidence for gastrointestinal cancers; risk of autosomal recessive AT condition in biallelic offspring of heterozygous carriers; AT: childhood cerebellar ataxia, telangiectasias of the conjunctivae, immunodeficiency, sensitivity to radiation	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15,21,22]
AXIN2	AXIN2-associated oligodontia and polyposis	Colorectal lesions (adenomatous polyposis ranging from 10s to 100s and cancer)	Colonoscopy every 2-3 years beginning at age 25-30 years; if polyps are found, every 1 to 2 years with consideration of surgery depending on polyp burden	Patients often also have oligodontia (absence of six or more permanent teeth excluding wisdom teeth) and ectodermal dysplasia	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial and Gastric[18]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
BARD1		ER-negative breast cancer, triple-negative breast cancer	Annual mammogram and consideration of breast MRI starting at age 40 years		NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]
BAP1	*BAP1* tumor predisposition syndrome	Atypical Spitz tumors, uveal melanoma, malignant mesothelioma, cutaneous melanoma, clear cell renal cell carcinoma, basal cell carcinoma	Eye examinations, dermatologic examinations, consideration of abdominal ultrasonography and/or MRI of the kidneys	Limited evidence for possible other associated tumors: non-small cell lung adenocarcinoma, breast cancer, cholangiocarcinoma, meningioma, neuroendocrine carcinoma	NCCN Kidney Cancer,[23] Pilarski et al,[24] Lalloo et al[25]
BMPR1A and *SMAD4*	Juvenile polyposis syndrome	GI lesions (juvenile/hamartomatous polyps and cancer [colorectal, stomach, small bowel])	Colonoscopy and upper endoscopy every 1-3 years beginning at age 12-15 years; surgical management based on polyp burden; HHT screening for *SMAD4* carriers	"Juvenile" refers to polyp histology, not age at onset; *SMAD4* mutations associated with HHT; *SMAD4* PGVs associated with massive gastric polyposis	Haidle et al,[26] NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial and Gastric[18]
BRCA1 and *BRCA2*	Hereditary breast cancer and ovarian cancer syndrome	Breast (*BRCA1*: often triple-negative tumor), male breast, ovarian (epithelial; high-grade serous), fallopian tube, primary peritoneal, prostate (high Gleason score), pancreatic adenocarcinoma	Breast screening with annual mammogram and breast MRI starting at age 25-30 years; male self-examination and clinical breast examination at 35 years; consideration of mammography in males; optional risk-reducing mastectomy in females; risk-reducing BSO between age 35 and 45 years*; PSA measurement and digital rectal examination starting at age 40 years; consideration of chemoprevention (eg, tamoxifen, OCPs); FDA approval of PARP inhibitors for select BRCA-associated breast, ovary, pancreas, prostate cancers; pancreas screening starting at age 50 years or per family history	Founder PGVs in certain populations (eg, Ashkenazi Jewish, Icelandic); risk of autosomal recessive Fanconi anemia with biallelic PGVs	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]
BRIP1		Ovarian (heterozygous carriers)	Consider risk-reducing BSO at age 45-50 years or per family history	Risk of autosomal recessive Fanconi anemia in biallelic offspring of heterozygous carriers	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]

Abbreviations: AFAP, attenuated familial adenomatous polyposis; AFP, alpha-fetoprotein; AT, ataxia telangiectasia; BSO, bilateral salpingo-oophorectomy; CHRPE, congenital hypertrophy of the retinal pigment epithelium; ER, estrogen receptor; FAP, familial adenomatous polyposis; GAPPS, gastric polyposis with APC promoter 1b mutations; HHT, hereditary hemorrhagic telangiectasia; OCP, oral contraceptive pills; PARP, poly ADP ribose polymerase; PGV, pathogenic germline variants; PSA, prostate-specific antigen.

Leukemia/lymphoma predisposition syndromes are not listed; refer to Chapters 19 and 20. Most childhood-onset conditions are not listed; refer to Lindor et al.[27]

*Earlier initiation of breast cancer surveillance should be determined based on personal/family history of breast cancer.[15]

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Table 6-1B **Selected High- and Moderate-Risk Genes, Syndromes, and Management Considerations: C Through G**

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
CDH1	Hereditary diffuse gastric cancer syndrome	Diffuse gastric cancer, lobular breast cancer (ER-positive)	A strategy of surveillance upper endoscopy with biopsies of the stomach, consideration of risk-reducing total gastrectomy, breast screening with annual mammography and breast MRI at 30, optional risk-reducing mastectomy	Can manifest as cleft palate	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15,19]
CDKN2A, CDK4	FAMMM syndrome	Melanoma and dysplastic nevi, pancreatic adenocarcinoma	Dermatologic examination, pancreas screening recommended beginning at age 40 years*	Risk of melanoma may be independent of genetic test result; *CDKN2A* (p16) founder PGV in the Netherlands; PGVs affecting p14ARF are associated with a different spectrum of tumors, including melanoma, sarcomas, nervous system tumors, and possibly breast cancer; consider full-body MRI and brain MRI for those with p14ARF PGVs	Goldstein et al,[28] Vasen et al,[29] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostates[15]
CHEK2		Breast cancer	For truncating pathogenic variants, breast screening with annual mammography at age 40 years and breast MRI starting at age 30-35 years, or per family history. Consider prostate cancer screening starting at age 40	Genotype-phenotype: different risks for truncating mutations versus missense mutations; Limited evidence for association with prostate, thyroid, and renal cancers, possibly leukemia and plasma cell neoplasms	Zeng et al,[30] Hanson et al,[31] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostates,[15] AlDubayan et al[32]
CHEK2 (low penetrance, including I157T/470T>C; S428F/ c.1283C>T; and T476M/ c.1427C>T)		Breast cancer; possibly leukemia and plasma cell neoplasms	Low-penetrance missense CHEK2 variants may not be actionable. Studies demonstrate the lifetime breast cancer risk is less than 20%. Management recommendations should be based on clinical assessment and family history	Genotype-phenotype: different risks for truncating mutations vs missense mutations; limited evidence for association with prostate, thyroid, and renal cancers	Zeng et al,[30] Hanson et al,[31] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreas,[15] AlDubayan et al[32]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
FH	HLRCC	Cutaneous leiomyomata, uterine leiomyomata, renal tumors (type 2 papillary, tubule-papillary, collecting-duct carcinomas; unilateral, solitary lesions); rare paraganglioma/ pheochromocytoma	Dermatologic and gynecologic examinations; evaluate for changes suggestive of leiomyosarcoma; medication or resection of leiomyomata, imaging for and surgical management of renal tumors; abdominal MRI (preferred) or CT, both exams with and without IV contrast, annually starting at age 8-10 years and performed every 3 years	FH enzyme assay might be helpful in some situations. Risk for uterine leiomyosarcoma is unclear. Biallelic FH PGVs cause a recessive disorder known as FH deficiency metabolic disorder, profound developmental delay, seizures, and fumaric aciduria	Kamihara et al,[33] Barrisford et al,[34] NCCN Kidney Cancer
FLCN	BHD syndrome	Benign cutaneous findings (fibrofolliculomas, trichodiscomas/ angiofibromas, perifollicular fibromas, acrochordons), pulmonary cysts, renal tumors (oncocytoma, chromophobe, oncocytic hybrid tumors)	No consensus at this time. Dermatologic care, imaging for and surgical management (nephron sparing) of renal tumors	Fibrofolliculomas are specific to BHD. Predisposition to multiple lung cysts may present as spontaneous pneumothorax. Renal tumors are multifocal, bilateral, and slow growing. Other features include parotid lesions, oral papules, and thyroid lesions. Data are unclear regarding colon cancer. There are possible genotype/phenotype correlations	van de Beek et al,[35] Sattler and Steinlein,[36] NCCN Kidney Cancer
GREM1	Hereditary mixed polyposis syndrome	Multiple polyps of multiple and mixed morphologies, including serrated lesions, Peutz-Jeghers polyps, juvenile polyps, conventional adenomas and colorectal adenocarcinoma	Colonoscopy every 2-3 years beginning at age 25-30 years unless polyps are found; consider total colectomy based on polyp burden	Founder PGV in Ashkenazi Jewish individuals; duplication spanning the 3′ end of the SCG5 gene and a region upstream of the *GREM1* locus	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]

Abbreviations: BHD, Birt-Hogg-Dube; ER, estrogen receptor; FAMMM, familial atypical mole melanoma syndrome; FH, fumarate hydratase; HLRCC, hereditary leiomyomatosis and renal cell cancer; IV, intravenous; OCP, oral contraceptive pills; PGV, pathogenic germline variants.

Leukemia/lymphoma predisposition syndromes are not listed; refer to Chapters 19 and 20. Most childhood-onset conditions are not listed; refer to Lindor et al.[27]

*Earlier initiation of breast cancer surveillance should be determined based on personal/family history of breast cancer.[15]

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Table 6-1C **Selected High- and Moderate-Risk Genes, Syndromes, and Management Considerations: M Through P**

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
MBD4	*MBD4*-associated neoplasia syndrome or *MBD4* biallelic PGVs	Colorectal polyposis, AML, uveal melanoma	Colonoscopy every 2-3 years starting at age 18-20 years, consider CBC at diagnosis, ophthalmology exam at diagnosis and annually	Unknown risks for heterozygous carriers	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]
MEN1	MEN-1	GEP tract, well-differentiated endocrine tumors, pituitary tumors (prolactinoma), parathyroid tumors, carcinoid tumors, adrenocortical tumors	Biochemical testing with emphasis on pancreatic and pituitary hormones and calcium, imaging of chest and abdomen every 1-3 years starting at age 8-15 years, brain MRI every 3-5 years starting at age 5 years, medical management of endocrinopathies, parathyroidectomy in setting of hyperparathyroidism	Primary hyperparathyroidism, hypercalcemia, oligomenorrhea/amenorrhea, galactorrhea, Zollinger-Ellison syndrome (gastrinoma), insulinoma, glucagonoma, VIP-secreting tumor (VIPomas); other features: skin (angiofibromas, collagenomas), lipomas, CNS lesions (meningioma, ependymoma), leiomyomas	Giusti et al[37] and NCCN Neuroendocrine and Adrenal Tumors[38]
MET (*c-MET*)	HPRC	Papillary renal cancer (multifocal, bilateral, type 1 papillary)	Imaging, surgical management		Coleman and Russo,[39] NCCN Kidney Cancer[40]
MLH1/MSH2/MSH6/PMS2/EPCAM	Lynch syndrome (formerly, HNPCC); variant: Muir-Torre syndrome; variant: Turcot syndrome; variant: CMMR-D syndrome (biallelic PGVs; recessive inheritance)	Colorectal, endometrial ovarian (epithelial), stomach, small bowel, urothelial, pancreas, hepatobiliary tract, sebaceous neoplasms of the skin (Muir-Torre syndrome), glioblastoma (Turcot syndrome), prostate	Colonoscopy every 1-2 years starting at age 20-25 years* (*MLH1* and *MSH2*) or every 1-3 years starting at age 30-35 years* (*MSH6* and *PMS2*); hysterectomy, and risk-reducing BSO (*MLH1, MSH2*) insufficient evidence and decision for risk-reducing hysterectomy and BSO for *MSH6* should be individualized); endometrial biopsy every 1-2 years starting at age 30-35 years can be considered upper endoscopy every 2-4 years starting at age 30-40 years; consideration of urinalysis or urine cytology, consider skin exam every 1-2 years (age to start surveillance can be individualized), and aspirin for chemoprevention (optimal dose to be determined); except for *PMS2*, pancreas screening starting at age 50 years or earlier if there is a family history of pancreatic cancer in a first- or second-degree relative; consider annual prostate cancer screening at age 40 years	Tumor analyses with IHC staining, MSI analysis, somatic tumor genetic analysis, *BRAF* V600E somatic analysis, MLH1 promoter hypermethylation analysis; Amsterdam criteria I and II, revised Bethesda guidelines; recommendations for universal screening of colorectal and endometrial cancers; risk of autosomal recessive CMMR-D syndrome (cafe-au-lait macules, solid tumors, hematologic cancers) in offspring	NCCN Genetic/Familial High-Risk Assessment: Colorectal[18]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
MLH3/MSH3	*MLH3*-and *MSH3*-associated polyposis	Biallelic PGV carriers: colorectal lesions (adenomatous polyposis and cancer); recently discovered so unclear	Colonoscopy every 2-3 years beginning at age 25-30 years unless polyps; consider total colectomy based on polyp burden	*MSH3* tumors exhibit EMAST (MSI of di- and tetranucleotide repeats); *MLH3* tumors did not	Olkinuora et al,[41] NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]
MUTYH	MAP	Biallelic PGV carriers: colorectal lesions (adenomatous polyposis and cancer; serrated and hyperplastic polyps also described), stomach, duodenal lesions (adenomatous polyps, cancer)	Colonoscopy every 1-2 years, starting at age 25-30 years; consider total colectomy based on polyp burden; upper endoscopy beginning at age 30-35 years	Phenotypically similar to AFAP; two northern European founder PGVs; no increased colorectal cancer risk in heterozygous carriers	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]
NF1	Neurofibromatosis type 1	Cutaneous neurofibromas, plexiform neurofibromas, optic nerve and other CNS gliomas, malignant peripheral nerve sheath tumors, breast (moderate risk), others: GIST, leukemia, paraganglioma/ pheochromocytoma	Neurofibromatosis type 1 specialist for management, physical and ophthalmologic examinations; imaging; surgical management; breast screening with annual mammography starting at age 30 years and breast MRI from ages 30-50 years, per family history*	Cafe-au-lait macules, axillary and inguinal freckling, iris Lisch nodules, learning disabilities, scoliosis, tibial dysplasia, vasculopathy	Friedman,[42] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostates[15]
NTHL1	*NTHL1*-associated polyposis	Biallelic PGV carriers: colorectal lesions (less than 50 adenomatous polyps and cancer)	Colonoscopy every 2-3 years beginning at age 25-30 years unless polyps; consider total colectomy based on polyp burden; EGD at age 30-35 years every 1-4 years based on findings; education regarding importance of prompt reporting of any abnormal uterine bleeding or postmenopausal bleeding; no other screening recommendations have been made to date for breast or the other extracolonic cancers	c.268c>T (p.GIn90*) variant is the most common truncating PGV and has higher prevalence in European cohorts. Tumors have mutation signature (COSMIC Signature 30). There are possible increased risks for breast, endometrial, basal cell, hematologic and cervical cancers, meningioma and bladder tumors	Grolleman et al,[43] NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]
PALB2		Breast cancer (particularly ER-positive), ovarian cancer, pancreatic cancer	Breast screening with annual mammogram and breast MRI with and without contrast starting at age 30; optional risk-reducing mastectomy in females; consideration of risk-reducing BSO between age 45 and 50 years. Pancreatic surveillance may be considered with or without family history of pancreatic cancer. Consider prostate cancer screening starting at age 40	Risk of autosomal recessive Fanconi anemia in biallelic offspring of heterozygous parents	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
POLE/POLD1	Polymerase proofreading-associated polyposis	Colorectal lesions (attenuated adenomatous polyposis and cancer), duodenal (adenomas and cancer), endometrial cancer	Colonoscopy every 2-3 years beginning at age 25-30 years unless polyps; consider total colectomy based on polyp burden; baseline upper endoscopy beginning at age 25-30 years; education regarding importance of prompt reporting of any abnormal uterine bleeding or postmenopausal bleeding	Two recurrent PGVs have been identified: *POLE* p.L424V and *POLD1* p.S478N. Nearly all the described PGVs are activating mutations in the exonuclease domain. It is probably associated with brain tumors and possibly endometrial and breast cancers	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]
PTCH1 *SUFU*	Gorlin syndrome/ nevoid basal cell carcinoma syndrome	Jaw (odontogenic) keratocysts, basal cell carcinomas, medulloblastoma PNET desmoplastic	Referral to a specialist for management; physical examination, avoidance of sun exposure and at least annual dermatologic examination, surgical management	Other features: congenital skeletal anomalies, cleft lip/palate, cerebral/falx calcifications, macrocephaly with frontal bossing, polydactyly, intellectual disability, lymphomesenteric or pleural cysts, palmar/ plantar pits, cardiac fibromas, ovarian fibromas, ocular abnormalities	Evans and Farndon[44] and Foulkes et al[45]
PTEN	Cowden syndrome/PTEN hamartoma tumor syndrome	Breast cancer, thyroid cancer (most often follicular), endometrial cancer, colorectal lesions (hamartomas, ganglioneuromas, cancer), renal cell carcinoma	Annual thyroid examination and ultrasonography starting at age 12 years, endometrial screening with random biopsy and ultrasonography starting at age 35 years, optional hysterectomy, colonoscopy every 5 years beginning at age 35 years unless polyps, renal ultrasonogram every 1-2 years starting at age 40 years	Major and minor criteria (tumors, physical and dermatologic/ mucocutaneous findings, developmental disability); macrocephaly, Bannayan-Riley-Ruvalcaba syndrome, PTEN-related *Proteus* syndrome, autism spectrum disorder, Lhermitte-Duclos disease	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]

Abbreviations: AFAP, attenuated familial adenomatous polyposis; AML, acute myeloid leukemia; BSO, bilateral salpingo-oophorectomy; CBC, complete blood count; CMMR-D, constitutional mismatch repair deficiency; CNS, central nervous system; EGD, esophagogastroduodenoscopy; EMAST, elevated microsatellite alterations at selected tetranucleotides; GEP, gastroenteropancreatic; GIST, gastrointestinal stromal tumor; HNPCC, hereditary nonpolyposis colorectal cancer; HPRC, hereditary papillary renal carcinoma; IHC, immunohistochemistry; MAP, MUTYH-associated polyposis; *MEN-1*, multiple endocrine neoplasia type 1; MEN1, menin 1; MSI, microsatellite instability; NF1, neurofibromin 1; PGV, pathogenic germline variants; PNET, primitive neuroectodermal tumors; VIP, vasoactive intestinal peptide.

Leukemia/lymphoma predisposition syndromes are not listed; refer to Chapters 19 and 20. Most childhood-onset conditions are not listed; refer to Lindor et al.[27]

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Table 6-1D **Selected High- and Moderate-Risk Genes, Syndromes, and Management Considerations: R Through V**

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
RAD51C		ER-negative breast cancer, triple-negative breast cancer, ovarian cancer	Annual mammogram and consideration of breast MRI starting at age 40 years; risk-reducing salpingo-oophorectomy at age 45-50 years	Risk of autosomal recessive Fanconi anemia	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]
RAD51D		Breast cancer, ovarian cancer	Annual mammogram and consideration of breast MRI starting at age 40 years; risk-reducing salpingo-oophorectomy at age 45-50 years		NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]
RB1	Retinoblastoma	Retinoblastoma (trilateral disease: cooccurrence of pinealoblastoma), bone or soft-tissue sarcomas, melanoma, others	Ophthalmologic examination and imaging; care by a multidisciplinary team; avoidance of radiation	Usually bilateral or multifocal disease; mosaic forms; therefore, analysis of tumor tissue and blood is important; RNA studies may also be recommended; low-penetrance mutations identified; parent-of origin effect in some families	Lohmann and Gallie,[46] Knudsen,[47] Abramson et al,[48] and Abramson and Frank[49]
RET	MEN-2; three subtypes: MEN-2A (aka, Sipple syndrome), familial medullary thyroid carcinoma, MEN-2B	Medullary thyroid carcinoma (multifocal, bilateral) and primary C-cell hyperplasia, pheochromocytoma (bilateral) (MEN-2A and 2B), parathyroid adenoma/hyperplasia (hyperparathyroidism, hypercalcemia, renal stones; MEN-2A)	Prophylactic thyroidectomy (varies from infancy to age 5 years, depending on specific *RET* PGV; genotype-phenotype correlations); surgical management of identified disease, serum calcitonin concentration, consideration of eligibility for treatment with kinase inhibitors, biochemical screening and imaging for pheochromocytoma and parathyroid abnormalities	Genotype-phenotype correlations MEN-2A: MTC in early adulthood; FMTC: MTC in middle age; MEN-2B: MTC in early childhood, mucosal neuromas (lips, tongue), dysmorphic features (large lips, "marfanoid" body habitus), GI ganglioneuromatosis; *RET* gene loss of function PGVs also associated with Hirschsprung disease	Eng and Plitt[50] and Wells et al[51]
SDHB/ SHDC/ SDHD/ SDHA/ SDHAF2, MAX, TMEM127	Hereditary paraganglioma/ pheochromo-cytoma syndrome	PGL-sympathetic and parasympathetic PCC, GISTs, renal clear cell carcinoma, and other less well-defined cancer risks such as papillary thyroid carcinoma	*SDHA* appears to have lower penetrance than other SDHx PGVs; screening in this population such as plasma-free fractionated metanephrines or 24-hour urine fractionated metanephrines (optional dopamine or 3-methoxytyramine) to screen for secreting PGL/PCC and whole-body MRI for PGL, PCC, renal cell carcinoma, and GIST is controversial because of conflicting guidelines	Secretory and nonsecretory PGL, high blood pressure, headache, anxiety, profuse sweating, palpitations, pallor; *SDHB*: high risk of malignant transformation; *SDHD*: parent-of-origin effect, disease-causing when paternally inherited; *SDHAF2*: possible parent-of-origin effect (paternal inheritance)	Hanson et al[52] and Amar et al[53]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
STK11 (LKB1)	PJS	GI lesions (PJS-type hamartomatous polyps; colorectal, stomach, small-bowel cancer), breast, pancreas, gynecologic (ovarian SCTAT sex cord tumor with annual tubules), cervix (minimum deviation adenocarcinoma), uterus, testes (Sertoli cell), lung	Colonoscopy and upper endoscopy with small-bowel visualization every 2-3 years beginning at about age 18 years, breast screening with annual mammography and breast MRI beginning at age 30, pancreas screening beginning at about age 30-35 years, gynecologic examination and annual pelvic ultrasonogram beginning at about age 18-20 years, annual testicular examination, including in the pediatric setting	Mucocutaneous hyperpigmentation of mouth, lips, nose, eyes, genitalia, fingers; may fade after puberty	McGarrity et al,[54] NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric,[18] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate
TP53	LFS	Soft tissue and bone sarcomas, breast cancer, brain cancer, adrenocortical carcinoma, leukemia, other cancers (GI, genitourinary, lung, lymphomas, thyroid, neuroblastoma, skin)	Screening beginning in childhood with comprehensive physical exam including neurological exam and CBC with differential every 3-4 months until age 18 years; annual full-body and brain MRI; ultrasound abdomen and pelvis every 3-4 months; blood biochemistry if unsatisfactory ultrasound quality; in adults (18 years or older), comprehensive physical exam every 6 months, ultrasound of the abdomen and dermatologic exam annually; blood biochemistry if unsatisfactory ultrasound quality; breast screening with annual breast MRI and mammography beginning at age 20 and 30 years, respectively; consideration of risk-reducing mastectomy; CBC with differential every 3-6 months in patients with prior cytotoxic chemotherapy or radiation exposures; physical examination, including dermatologic and neurologic examinations; pancreatic surveillance if an affected close relative; colonoscopy and upper endoscopy every 2-5 years starting at age 25 years; annual whole-body MRI with brain MRI, consideration of radiation avoidance, if clinically appropriate	Classic LFS criteria; Chompret criteria; consider genetic testing in *BRCA*-negative, isolated, early-onset breast cancer (age less than 31 years); breast cancers more likely to be ER, progesterone receptor, and HER2/neu receptor positive; consider additional *TP53* variant workup for individuals with variant allele fraction below heterozygous range (typically <30%) and/or in when LFS clinical criteria are not met	Schneider et al,[55] Li and Fraumeni,[56] Chompret et al,[57] Villani et al,[58] Kratz et al,[59] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and Prostate[15] and Achatz et al[60]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
TSC1 and *TSC2*	TSC	Kidney: renal cell carcinomas, angiomyolipomas (benign and malignant), epithelial cysts, oncocytoma (benign adenomatous hamartoma)	TSC specialist for management: imaging; dermatologic, dental, ophthalmologic examinations; echocardiography; electrocardiography; consideration of eligibility for treatment with mTOR inhibitors, surgical management	Skin (hypomelanotic macules, facial angiofibromas, shagreen patches, cephalic plaques, ungual fibromas); brain (cortical dysplasias, subependymal nodules and subependymal giant cell astrocytomas, seizures, intellectual disability/developmental delay, autism spectrum disorder, psychiatric illness); heart (rhabdomyomas, arrhythmias); lungs (lymphangioleiomyomatosis); genotype-phenotype correlations: higher risk of renal cell carcinoma in TSC2; possible association with neuroendocrine tumors	Northrup et al[61] and NCCN Kidney Cancer[23]
VHL	VHL syndrome	Clear cell renal cell carcinoma, pheochromocytoma, paragangliomas, pancreatic neuroendocrine tumors	Biochemical screening, imaging of the abdomen and CNS, renal sparing management of kidney cancers; consideration of belzutifan for prevention	Hemangioblastomas of the brain, spinal cord, and retina; renal cysts; pancreatic cysts; endolymphatic sac tumors; epididymal and broad ligament cysts; genotype-phenotype correlations: VHL type 1, type 2A, type 2B, type 2C with different risks of pheochromocytoma or renal cell carcinoma	Van Leeuwaarde et al[62] and NCCN Kidney Cancer[23]

Abbreviations: CNS, central nervous system; ER, estrogen receptor; FMTC, familial medullary thyroid carcinoma; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; LFS, Li-Fraumeni syndrome; MEN-2, multiple endocrine neoplasia type 2; mTOR, mechanistic target of rapamycin; NF1, neurofibromin 1; PCC, pheochromocytoma; PGL, paraganglioma; PGV, pathogenic germline variants; PJS, Peutz-Jeghers syndrome; SCTAT, sex cord tumors with annular tubules; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau.
Leukemia/lymphoma predisposition syndromes are not listed; refer to Chapters 19 and 20. Most childhood-onset conditions are not listed; refer to Lindor et al.[27]
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Outside the high-penetrance syndromes, shared heritable factors present in some families may include PGVs in moderate-penetrance genes and single nucleotide polymorphisms (SNPs).[15,63,64] Dozens of moderate-penetrance genes whose PGVs generally confer a modest degree of cancer risk with a relative risk of 2–5 have been identified. Although genetic testing for PGVs in such moderate-penetrance genes was not routinely undertaken in the past, with NGS and commercial multigene panel analyses, clinical evaluation of these genes has now become common. However, the value of testing for PGVs in some moderate-penetrance genes remains unproven because neither the clinical validity (ie, the accuracy with which a genetic test predicts the development of cancer) nor the clinical utility (ie, the degree to which the use of the genetic test informs clinical decision-making and leads to improved health outcomes) has been clearly proven.[15]

Reliable data about cancer risks (ie, disease penetrance) may help inform medical management; however, current risk estimates for *BRCA1* and *BRCA2* may not apply to PGV carriers in the general population because of selection bias in historical research designs, which commonly included only the highest-risk families.[65] Expanded multigene platforms and broader testing criteria have enabled increased identification of patients with inherited risk factors and allow for emerging genotype-phenotype associations and cancer risk/penetrance estimates.

Expert groups like the NCCN and American College of Medical Genetics and Genomics have guidelines for practitioners to institute intensive screening and other prevention measures in patients with PGVs in moderate-penetrance genes, including genotype-specific considerations with regards to *CHEK2* and *ATM*.[15,21,31] Cancer risk estimates and management recommendations for high- and moderate-penetrance genes are updated continuously.

Through genome-wide association studies, hundreds of additional low-penetrance genetic loci, usually in the form of SNPs, have been identified for nearly all the common malignancies. These low-penetrance loci are often associated with only a slight increase in risk of cancer (relative risk, approximately 1.1-1.5) and are largely derived from individuals of European ancestry.[66] Given the limited clinical validity and utility of SNPs with such small effect sizes, clinical testing for individual risk loci is not routinely performed, although research efforts are underway to incorporate low-penetrance risk alleles into models for risk stratification for public health programs and cancer screening, which may eventually make this feasible.[67] Some commercial laboratories now include polygenic risk scores using cancer risk SNPs in their test results for select patient populations, creating some controversy because their clinical validity and utility have not been demonstrated in prospective trials, and they may be primarily derived from testing in those of European ancestry at present. Additional work is ongoing to validate scores for other populations.[25]

KEY POINTS

- High-penetrance cancer predisposition genes account for up to 10%-20% of all cancer diagnoses.
- Familial risks outside the high-penetrance syndromes may be related to moderate-risk alleles and additional shared hereditable and/or environmental factors. Empiric risk assessment to account for familial risk may be indicated.
- Consider clinical validity and utility of genes when selecting a multigene panel.
- Inclusion of moderate-penetrance genes associated with a two- to fivefold increased risk of specific cancers is commonplace for panel testing.
- Cancer risk estimates and management recommendations for high- and moderate-penetrance genes are updated continuously.

GENETIC COUNSELING

The National Society of Genetic Counselors (NSGC) has defined genetic counseling as the "process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease."[68] The traditional model of genetic counseling for hereditary cancer syndromes includes pre- and posttest consultations with a genetic counselor, sometimes in conjunction with a gastroenterologist, surgeon, medical oncologist, advanced practice provider, and/or a geneticist. However, because of increases in the volume of patients who meet criteria for germline genetic testing, expanded pathways for testing and service delivery are emerging:

- Telemedicine, video, and telephone-based methods
- Genetic-testing stations in clinic, manned by personnel such as genetic counseling assistants[69,70]
- Group counseling and testing
- Genetic counseling provided by other practitioners, such as nurse counselors and oncologists, in the context of coordinated patient care[13]
- Genomic testing of oncology patients through NGS analyses of tumor, and sometimes nontumor, specimens for the purpose of clinical trial eligibility and guiding treatment decisions

GENETICS IN MEDICAL ONCOLOGY PRACTICE

Historically, the role of the medical oncologist in germline testing has been primarily to obtain family histories and identify patients appropriate for referral for genetic evaluation. However, increasing indications for germline testing, the relative shortage

of genetics providers, and the findings of potential germline results on somatic tumor testing are combining to bring germline testing into the medical oncologist's practice. Multiple studies have been conducted for "mainstreaming" of germline testing, which often consists of testing being ordered in the setting of the oncology visit (sometimes referred to as "point-of-care" testing) and genetics professionals reviewing results and consulting as needed for positive or complex results.[71-73] Marked reductions in time to testing and time to results have been reported with this approach.[74,75] Although this model seems to be acceptable in most cases, shortcomings such as the need for additional physician education[76,77] and lack of cascade testing for relatives of those with an identified PGV have also been identified.[78] Non-genetics professionals may not obtain sufficient informed consent from patients in this setting,[79] and testing of family members and prevention screening practices specific to a given germline variant may not be within the scope of many oncology practices and may require referral for longitudinal follow-up in a high-risk genetics clinic. In addition, oncology clinics may not have processes in place to notify patients or families about reclassifications of variants of uncertain significance (VUSs). Considering these issues, alternative models for large-scale germline testing continue to be under investigation to provide these essential components of care for oncology patients and their families.

Resources to find genetic specialists include the NSGC (www.findageneticcounselor.com) and the American Board of Genetic Counseling (https://abgc.learningbuilder.com/Search/Public/MemberRole/Verification). Resources to learn more about cancer genetics and risk assessment include the ASCO Education Cancer Genetics Program, the NSGC, and the National Human Genome Research Institute.

Regardless of which clinician provides genetic risk assessment, the principles of genetic counseling should be at the foundation of the patient interaction.

PRETEST GENETIC COUNSELING

Pretest genetic counseling traditionally includes the following:

- A complete medical history (personal and family history and pertinent physical exam findings) with personalized discussions of prior genetic testing
- Data analysis and risk assessment
- Education regarding differential diagnoses and genes
- Discussion of testing options and the likelihood of different testing outcomes, followed by selection of appropriate analyses and laboratories and informing patients about accuracy/limitations, costs, expected turnaround time for results, and alternatives to testing
- Discussion of the potential test implications in the context of that family history, including the risks, benefits, and limitations of genetic testing
- Exploration of the medical, psychosocial, familial, and possible financial consequences of testing

Pretest informed consent is always a vital step in helping patients and families determine whether genetic testing (and what extent of testing) is right for them.[80] Some states require informed consent before genetic testing (eg, New York),[13,81] and pretest genetic counseling is one of the ways to fulfill this requirement. To meet clinical guidelines, which recommend universal testing for an expanding number of cancers, pretest education using a short (<10 minutes) video, ideally in close collaboration with genetics professionals to provide results disclosure and posttest counseling/risk assessment, may be another acceptable way to communicate the essential elements for pretest informed consent. In a randomized study of prostate patients with cancer receiving genetic testing using a custom 67-gene panel with results disclosure by a genetics professional, no statistically significant differences were observed between the pretest video education arm and the standard pretest genetic counseling arm in terms of genetic testing uptake, genetics knowledge, and family communication, despite a possible trend in favor of standard pretest genetic counseling with regard to satisfaction and psychological impact.[82] Similarly, the MAGENTA study demonstrated that there were no significant differences in posttest distress (anxiety, depression, or decisional regret) for those who had pretest genetic counseling and those who did not have pretest genetic counseling (although it is important to note that the absence of counseling is distinct from informed consent). The MAGENTA study also showed that there was no difference in distress for those without PGV in whom posttest counseling was omitted.[83]

The collection of family history is an important part of genetic cancer risk assessments and may be performed as part of an initial patient consultation for many oncology patients. The recommended key elements for a minimum adequate cancer family history are highlighted in an ASCO expert statement and should help oncologists to identify patients who would benefit from referral to clinical cancer genetics specialists.[84] These key elements include information on the following:

- First-degree relatives: siblings, parents, children
- Second-degree relatives: grandparents, aunts, uncles, grandchildren, nieces, nephews, half-siblings
- Both maternal and paternal sides of the family
- Ethnicity
- Current ages or ages at death

- Consanguineous relationships
- For each cancer case in the family, establish the following:
  - Age at cancer diagnosis
  - Type of primary cancer (organ, histology and relevant histology features if known, bilaterality)
  - Results of any cancer predisposition testing in any relative

Particularly, it is standard to evaluate at least three generations of a patient's maternal and paternal lineages. Family history should be taken at diagnosis and updated periodically.

In addition, individuals of certain ancestries may have higher risks for specific hereditary syndromes because of the presence of founder PGV, such as the common *BRCA1* (c.68_69delT and c.5266dupC) and *BRCA2* (c.5946delT) founder PGV in the Ashkenazi Jewish population (carrier rate 1:40)[85]; therefore, the knowledge of Ashkenazi Jewish ancestral background may have an impact on testing eligibility and risk assessment. Finally, family structures may be truncated for a variety of reasons (see below), so threshold of when to offer germline genetic testing may be lower among individuals with limited female family structure.

Reasons for truncated family history could include the following:

- Number of births and miscarriages or terminations
- Sex (a paucity of female family members may explain a lack of gynecologic cancers)
- Adoption, divorce, early death from noncancer causes, or estrangement
- Sperm or egg donation

Selecting an ideal DNA source and test methodology are important considerations before genetic testing is ordered. A modestly improved PGV detection rate has been recognized through use of multigene panels that combine DNA and RNA analyses, which requires use of a blood specimen.[86,87] Furthermore, blood- or saliva-based testing is not typically ideal for patients with certain hematologic malignancies; a tissue sample may be required to avoid false-negative or false-positive results in those with leukemia or lymphoma, or those with mosaic results on blood- or saliva-based testing.

POSTTEST GENETIC COUNSELING

Elements of posttest genetic counseling include the following:

- Disclosure and interpretation of test results
- Education about medical risks and management options (screening, risk reduction, therapeutic implications), including appropriate referrals and resources
- Investigation of the psychological reaction and familial repercussions related to the test results, and an opportunity for the clinician to provide emotional support to the patient and family
- Planning for communication of the genetic test results and implications to at-risk family members[88]

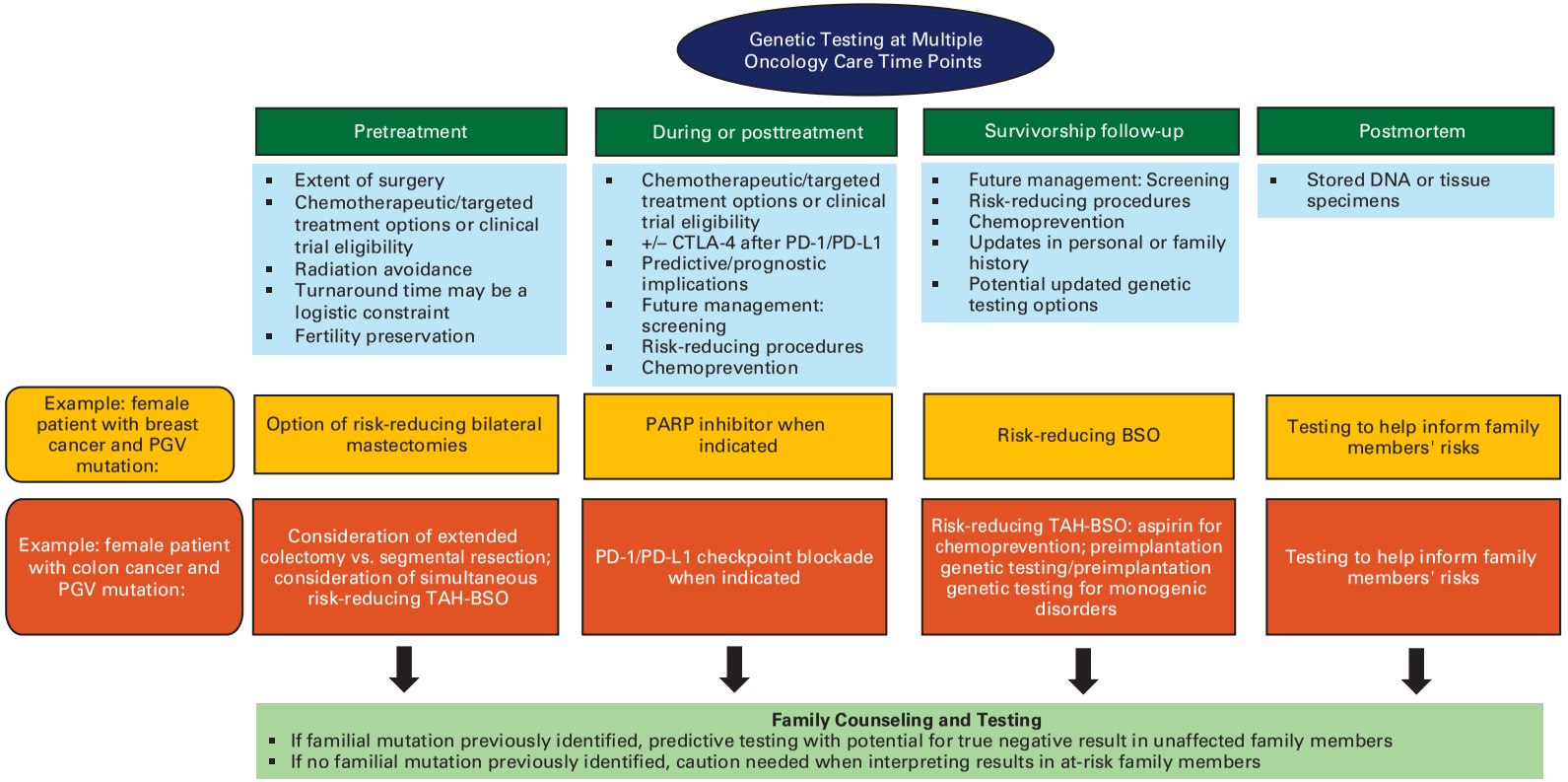
Even for patients who have negative or inconclusive results on genetic testing, posttest genetic counseling may still be critically important, because patients and families may still be considered at increased risk for disease and negative psychological reactions. Importantly, most family histories of cancer are not explained by PGVs in the known high-penetrance cancer predisposition genes. As such, many cases of familial breast cancer or familial colorectal cancer (CRC) remain unexplained, but individuals in these families may still qualify for enhanced management based on the empirical risk estimates or established screening guidelines that are based on family history of an increased risk for cancer and need for increased cancer surveillance. Because of the possibility that an individual with cancer may test negative for a PGV in a cancer susceptibility gene even though there is one running in their family (this is known as a phenocopy), consideration of additional genetic testing among other affected family members may be warranted. Failure for patients to understand the uninformative nature of a negative or inconclusive genetic test result may lead to nonadherence to medical recommendations.[16]

Although the model presented above is the classic posttest counseling process, use of tumor-normal tissue testing and regulations allowing patients direct access to results without interpretation may compromise this process. Providers need to be prepared to address and correct potential misinterpretations of results by patients in these settings.

INCORPORATING GENETIC COUNSELING AND TESTING INTO THE CARE OF THE ONCOLOGY PATIENT

Germline test results are increasingly desired, not only to guide personalized screening decisions for patients and their families but also to guide targeted therapeutics. Genetic counseling can occur at multiple points in the oncology setting, so it is important for an oncologist to determine, in conjunction with the patient, when genetic counseling and testing are most appropriate. However, because the peridiagnostic period may be emotional and overwhelming for patients, genetic counseling and testing may need to be completed at a later time (Fig. 6-2).

Figure 6-2 Incorporating Genetic Counseling and Testing Into the Care of Patients With Cancer



Abbreviations: BSO, bilateral salpingo-oophorectomy; PARP, poly-ADP ribose polymerase; PD-1/PD-L1, programmed cell death protein 1/programmed death ligand 1; PGV, pathogenic germline variant; TAH, total abdominal hysterectomy.

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PERIDIAGNOSIS OR PRETREATMENT COUNSELING AND TESTING

Identification of an inherited cancer predisposition syndrome may affect treatment decisions, including the following:

- Extent of surgery (eg, mastectomy for breast cancer paired with a contralateral risk-reducing mastectomy)
- Need for surgery (eg, emerging data suggesting microsatellite instability-high [MSI-H] rectal cancer may be treated with immunotherapy alone)
- Preoperative chemotherapy and/or targeted therapy choices

TREATMENT PERIOD

Genetic testing may allow patients and physicians to make informed decisions about chemotherapy and targeted therapeutic options and sequencing. Examples include the following:

- Poly ADP ribose polymerase (PARP) inhibitors and PGVs in the *BRCA* pathway
- Immunotherapy and microsatellite unstable cancers such as those related to LS
- Belzutifan and von Hippel-Lindau syndrome–related cancers[89]

These therapeutic options are discussed in greater detail in the appropriate disease site chapters.

POSTTREATMENT AND SURVIVORSHIP FOLLOW-UP PERIOD

Once a patient has completed treatment and is receiving follow-up care, genetic evaluation may assist in making decisions about the following:

- Future cancer surveillance and screening
- Prevention options such as chemoprevention
- Risk-reducing surgeries to manage the risk for new primary cancers

Although genetic evaluation for some individuals might not be indicated at the time of their cancer diagnosis, changes in their dynamic personal or family histories may lead to a referral for genetic testing in the future. Finally, it is important to note that updates in genetic testing (eg, new risk genes, new methodologies) may become available throughout a patient's oncology follow-up period.

It may be reasonable to consider re-referral for updated genetic evaluation and possibly repeat genetic testing in relation to the following:

- Roughly every 5 years for those with concerning personal or family history who have negative or inconclusive results on previous germline testing (or those who have PGVs that do not explain the personal and/or family history)
- New cancer diagnosis in the patient or family member
- New identification of PGV in family member
- For anyone tested before 2015 who likely did not have multigene panel testing using NGS

IDENTIFYING APPROPRIATE PATIENTS FOR REFERRAL TO GENETIC COUNSELING AND TESTING

Although most cancers are not caused by high-penetrance cancer predisposition syndromes, it is crucial for oncologists to be familiar with common "red flag" indications for referral for genetic counseling. These include the following:

- Early or unusual age at cancer diagnosis
- Multiple primary cancers (bilateral, synchronous, and/or metachronous diagnoses)
- Multiple individuals with related cancers in multiple generations
- Finding on somatic testing that is concerning for germline origin
- Unique features, including the following:
  - Certain numbers and types of gastrointestinal polyps
  - Certain dermatologic features
  - Certain neoplastic pathologies
- Certain ancestries (ie, those known to have founder PGVs)

For many common types of hereditary cancers, NCCN has published criteria for when referrals for genetic counseling and testing should be considered. In addition, some third-party payers have established their own criteria for when genetic testing is deemed medically indicated, which may not necessarily be congruent with NCCN guidelines. Although taking a thorough medical

and family history is important and will aid in identifying possible red flags, it is important for clinicians to realize that not all individuals or families who have a PGV actually fit into the classic syndrome phenotype descriptions.

With NGS being performed on patient tumors and sometimes germline specimens, a substantial number of patients are found to carry PGVs in genes that would have not been suspected based on their personal or family histories. For example, targeted NGS of matched tumor and germline specimens for 76 known cancer predisposition genes identified that 17.5% of patients with advanced cancer (182 of 1,040 patients) had an actionable PGV; 55.5% of these would not have been detected using clinical genetic testing guidelines alone.[90] The Mayo Clinic report of multigene panel testing in 2,984 patients with a solid tumor cancer identified PGVs in 397 of them (13.3%).[6,90] However, these studies included variants of low-penetrance genes and carriers of variants that only had recessive risks of cancer, so the actionability was indirect or lesser for some reported carriers.

Table 6-2 describes the prevalence of cancer susceptibility PGVs for unselected patients with specific types of cancer. Several studies on specific cancer types have recommended germline genetic testing of all patients with certain cancer subtypes, including the following:

- Epithelial ovarian, fallopian tube, and primary peritoneal cancer
- Metastatic prostate cancer
- Triple-negative breast cancer
- Pancreatic adenocarcinoma
- Colorectal, endometrial, gastric, or brain cancer diagnosed before age 50 years
- Myelodysplastic syndrome or acute myelogenous leukemia before age 50 years
- Nonclear cell renal cell carcinoma
- Paraganglioma/pheochromocytoma
- Medullary thyroid cancer
- Adrenocortical cancer
- Choroid plexus carcinoma

Specific pathologies associated with germline changes are listed in Table 6-3.

Table 6-2 Prevalence of Cancer Susceptibility Pathogenic Germline Variants for Unselected Patients

Cancer Type	Patients With Germline Variants, N/Total Patients	PGV Prevalence, %
Breast	83/959[91]	8.65-10.8
	494/4,581[92]	
Triple-negative breast	267/1,824[93]	14.60
Lung (advanced cancer only)	222/5,118[94]	4.3-5.8
	448/7,668[92]	
Colon	305/5,303[95]	5.8-9.9
	105/1,058[96]	
Prostate	247/2,887[95]	8.6-17.3
	620/3,607[97]	
Osteosarcoma	281/1,044[98]	28.00
Renal	85/1,336[92]	6.40
Pancreatic (adenocarcinoma)	273/3,535[99]	7.7-14.1
	25/177[92]	
Bladder/urothelial (advanced cancer only)	79/1,188[100]	6.6-14
	80/586[101]	
Ovarian	60/515 (*BRCA1/BRCA2* only)[92]	11.7-13.8
	380/2,756[92]	
Endometrial	76/1,542[102]	4.9-9.2
	35/381[92]	
Head/neck	51/1,218[92]	4.20
Cholangiocarcinoma	36/8,401[92]	4.30
Esophageal	36/747[92]	4.80
Gastric	48/243[103,104]	19.80

Abbreviation: PGV, pathogenic germline variant.

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Table 6-3 **Genetic Cancer Predisposition Syndromes and Selected Associated Pathologies**

Neoplastic or Preneoplastic Pathologies	Associated Genetic Syndromes and Genes
High-grade or poorly differentiated ductal breast cancer with estrogen receptor, progesterone receptor, and HER2/neu negativity	Hereditary breast and ovarian cancer syndrome (*BRCA1*); *BARD1, PALB2, RAD51C, RAD51D*
Lobular breast cancer	Hereditary diffuse gastric cancer syndrome (*CDH1*)
High-grade serous (papillary serous) ovarian	Hereditary breast and ovarian cancer syndrome (*BRCA1, BRCA2*)
Clear cell or endometrioid ovarian cancers	Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
Ovarian sex cord tumors with annular tubules	Peutz-Jeghers syndrome (*STK11*)
Clear cell or endometrioid endometrial cancers	Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
Uterine leiomyomas	Hereditary leiomyoma renal cell carcinoma syndrome (*FH*)
Minimal deviation adenocarcinoma (adenoma malignum of the cervix)	Peutz-Jeghers syndrome (*STK11*)
Colorectal cancer with tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring cells, medullary growth pattern	Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
Lauren diffuse type/signet ring cell/linitus plastica gastric cancer	Hereditary diffuse gastric cancer syndrome (*CDH1*); *CTNNA1*
Hamartomatous gastrointestinal polyps	Peutz-Jeghers syndrome (*STK11*); juvenile polyposis syndrome (*BMPR1A, SMAD4*); Cowden syndrome (*PTEN*)
Pancreatic neuroendocrine tumors	Multiple endocrine neoplasia type 1 (*MEN1*); von Hippel-Lindau (*VHL*)
Renal papillary type I carcinoma	Hereditary papillary renal cancer syndrome (*MET*)
Renal papillary type II, collecting duct, tubulopapillary carcinomas	Hereditary leiomyomatosis and renal cell carcinoma syndrome (*FH*)
Renal clear cell carcinoma	von Hippel-Lindau (*VHL*)
Renal oncocytoma	Birt-Hogg-Dube syndrome (*FLCN*); tuberous sclerosis complex (*TSC1, TSC2*)
Renal angiomyolipoma	Tuberous sclerosis complex (*TSC1, TSC2*)
Renal chromophobe	Birt-Hogg-Dube syndrome (*FLCN*)
Sertoli cell tumors of the testes	Peutz-Jeghers syndrome (*STK11*)
Medullary thyroid cancer	Multiple endocrine neoplasia type 2 (*RET*)
Cribriform-morular variant of papillary thyroid carcinoma	Familial adenomatous polyposis (*APC*)
Follicular thyroid cancer	Cowden syndrome (*PTEN*)
Medulloblastoma	Turcot syndrome variant of familial adenomatous polyposis (*APC*); Nevoid basal carcinoma syndrome (Gorlin) (*PTCH1*)
Glioblastoma	Turcot syndrome variant of Lynch syndrome (*MLH1, MSH2*, MSH6, *PMS2, EPCAM*); Li-Fraumeni syndrome (*TP53*)
Basal cell carcinoma	Xeroderma pigmentosum (multiple xeroderma pigmentosum-associated genes); Nevoid basal carcinoma syndrome (Gorlin) (*PTCH1*)
Sebaceous adenoma, sebaceous carcinoma, keratoacanthoma	Muir-Torre syndrome variant of Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
Fibrofolliculomas	Birt-Hogg-Dube syndrome (*FLCN*)
Facial trichilemmomas	Cowden syndrome (*PTEN*)

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Not all guidelines give the same recommendations. The American Society of Breast Surgeons has recommended that all women with breast cancer be offered germline genetic testing, and the US Preventive Services Task Force has recommended that, for women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1* or *BRCA2* genetic PGVs, primary care clinicians should use a brief familial risk assessment to evaluate the need for genetic counseling referral. More recently, ASCO and the Society for Surgical Oncology have recommended that *BRCA1/BRCA2* testing be performed in all breast patients with cancer aged 65 years or younger, and that it be considered in those over 65 years of age who may require treatment with PARP inhibitors.[105] Similarly, NCCN recommends considering germline testing for all patients with CRCs. Given these recommendations, it is important that genetic counseling models evolve and that clinicians who provide cancer-focused genetic counseling be skilled in discussing the implications of identified PGVs with patients and families, even in the absence of a significant history of cancer.

As genetic testing costs have dropped, there have been calls for general population screening for hereditary cancer risk, but there are pros and cons to this recommendation.

Pros:

- Testing may save lives and may be cost-effective.[106]
- A total of 80%-90% of patients who tested positive for hereditary cancer risk had not received prior testing.[107,108]
- Of those who test positive, 50%-70% would not have met published guidelines for clinical testing.[107,108]

Cons:

- The clinical utility of identifying lower-penetrance variants is undetermined.
- How to translate risk identification to uptake of clinical prevention in the general population is unclear.
- There is an insufficient number of cancer genetics providers to support general population testing.
- Underserved populations will be more likely to have uncertain results, lower access to genetic counseling, and lower access to screening for identified hereditary risks.

ETHICAL PRINCIPLES AND CHALLENGES IN GENETIC COUNSELING

Although there are multiple principles of ethics that come into play in the field of cancer-focused genetic counseling, the four key concepts are autonomy, nonmaleficence, equity, and duty to warn.

KEY POINTS

- Genetic counseling is a communication process that helps patients make informed genetic testing decisions and adapt to having a genetic condition.
- Genetic counseling is guided by principles of autonomy, nonmaleficence, equity, and duty to warn and has traditionally included pre- and posttest discussions.
- Thorough medical and family histories to assess for red flags are vital for accurate genetic risk assessments.

PHENOTYPIC AND TUMOR-DRIVEN ANALYSES

A patient's tumor pathology may provide the initial signal of the possibility of an inherited cancer predisposition syndrome. For example, triple-negative (ie, estrogen receptor–negative, progesterone receptor–negative, and human epidermal growth factor receptor 2/neu–negative) breast cancers are associated with an increased incidence of *BRCA1, BARD1, RAD51C*, and *RAD51D* PGVs, and genetic testing is considered medically indicated for all women who have this type of cancer. Similarly, all patients with medullary thyroid cancer should be referred for genetic testing of the *RET* gene. Individuals with 10-20 or more cumulative adenomatous colorectal polyps qualify for panel-based genetic testing, which includes *APC, MUTYH*, and multiple genes more rarely associated with adenomatous polyposis such as *MSH3, NTHL1, POLE, POLD1*, and others.

TUMOR ANALYSIS INFORMS GERMLINE SUSCEPTIBILITY: THE CASE OF LS

The hallmark feature of tumors associated with LS (previously known as hereditary nonpolyposis CRC) is the presence of MSI resulting from the accumulation of DNA insertions and deletions in the genome, especially at regions of repetitive DNA known as microsatellites, driven by deficient mismatch repair (dMMR). However, providers should appreciate that one in 10 CRCs in patients with LS is microsatellite stable, and so LS may be missed if only MSI is used for identification of this population.[109] Identification of dMMR may be pursued either through a polymerase chain reaction–based technique that assesses MSI at a designated set of markers by studying large numbers of microsatellites included in NGS tumor tests, or through immunohistochemistry (IHC) staining of the four DNA MMR proteins (MLH1, MSH2, MSH6, and PMS2) to assess loss of expression of one or more of them. MSI and MMR IHC analyses are highly concordant; however, a benefit of MMR IHC is that the pattern of protein loss

can sometimes help inform which of the LS genes may be malfunctioning as a result of germline or somatic events. On the other hand, both MSI and MMR IHC performed in a patient's tumor can be particularly helpful in the interpretation/classification of rare MMR variants identified on germline testing.

Screening of all CRCs by MSI polymerase chain reaction, MSI NGS, or MMR IHC analysis, along with MMR IHC for endometrial cancer and MMR IHC or MSI for gastroesophageal and small-bowel cancers, is recommended by the College of American Pathologists and ASCO to screen for eligibility for immune checkpoint inhibitor therapy.[18,110] For patients with a screening test result showing dMMR, various algorithms have been developed to guide subsequent evaluations, including the following:

- When IHC testing shows loss of MLH1/PMS2 expression, BRAF V600E somatic testing (for appropriate tumor types), followed by MLH1 promotor hypermethylation testing if BRAF is wild type
- MLH1 promoter hypermethylation alone when IHC testing shows loss of MLH1/PMS2 expression
- Immediate germline genetic testing for all patients
- If other testing (including germline testing) does not identify an explanation for the dMMR tumor, subsequent somatic analysis of the MMR genes to identify individuals with dMMR due to somatic loss of function of both alleles of one of the MMR genes[18]

Although tumor testing will continue to have a role identifying somatic pathogenic/likely pathogenic variants targetable by pharmaceutical agents, expert opinion is increasingly moving toward universal germline testing for all patients with CRC to screen for LS and rarer CRC syndromes using a multigene panel testing approach. A study of 3,310 patients with colorectal adenocarcinoma in Ohio demonstrated that universal tumor screening alone will miss 38.6% of colorectal patients with cancer with hereditary cancer syndromes, including 6.3% with LS.[111] Ranganathan et al[109] showed that 10% (10 of 99) of CRCs among individuals with LS were mismatch repair proficient (MMR-P), with 100% concordance between microsatellite-stable status and retained MMR protein staining. The majority of MMR-P tumors were observed in association with PGVs in *MSH6* and *PMS2.* A total of 33% (three of nine) of MMR-P CRCs did not meet testing criteria for LS.[109] However, in the absence of a universal germline testing approach, germline genetic testing for LS and other CRC predisposition genes should routinely be considered in the presence of early-onset disease (younger than 50 years) or a significant family history, even in patients with intact MMR in their tumors.[111]

TUMOR NGS: IMPLICATIONS FOR GERMLINE SUSCEPTIBILITY

NGS of tumors (ie, somatic pathogenic/likely pathogenic variant profiling or tumor genomic profiling) to help define therapeutic targets is increasingly commonplace across many tumor types in medical oncology. Somatic pathogenic/likely pathogenic variant profiling is available commercially and through academic institutions and generally consists of a multigene panel incorporating numerous genes previously implicated in carcinogenesis. Many of these genes will also be associated with germline cancer predisposition syndromes. Tumor sequencing may be performed with or without a matched normal specimen and could also be performed in the setting of whole-genome/whole-exome platforms.

Guidelines are available to help identify patients who need to be referred to cancer geneticists for germline genetic testing based on somatic pathogenic/likely pathogenic variant findings in their tumors.[112] Determination of referral considers the following:

- Frequency with which somatic findings are also present in the germline
- Variant allele fractions
- Variants considered likely pathogenic or pathogenic in ClinVar (particularly founder PGVs) or truncating variants, if new
- Whether the variant is present in a tumor associated with the gene's phenotype
- Patient's age at diagnosis

Some tumor testing laboratories are applying these guidelines and indicating that variants might be present in the germline on their reports, while others do not. Tumor testing results can be reviewed systematically to identify cases that need to be referred for germline genetic testing. However, because of variations of somatic testing platforms, gene coverage, and variant interpretation, the absence of somatic tumor pathogenic/likely pathogenic variants in inherited cancer susceptibility genes does not exclude the possibility of all PGVs, which may be detectable with currently available germline testing platforms. In a retrospective cohort study of 2023 patients with cancer who underwent germline testing and previously had tumor DNA sequencing, 8.1% of PGVs were missed by tumor sequencing.[113]

Somatic pathogenic/likely pathogenic variant profiling may also reveal variant patterns that predict the presence of a cancer susceptibility syndrome. For example, high burden on somatic profiling may identify hypermutated tumors, which may result from dMMR/MSI-H, a marker of LS, a somatic cause of MSI, or another rare cause of high tumor variant burden like somatic and/or *POLE* and *POLD1* PGVs.[114] As such, somatic pathogenic/likely pathogenic variant profiling that

reveals the presence of a hypermutated tumor should prompt MMR IHC or MSI testing and, if appropriate, genetic referral. Bioinformatic tools that predict MSI from somatic pathogenic/likely pathogenic variant profiling are incorporated into many somatic pathogenic/likely pathogenic variant profiling tests to help clinicians identify tumors with dMMR/MSI-H. Sixteen percent of patients with MSI-H tumors were found to have LS, in a large study of 15,045 patients with cancer representing more than 50 tumor types who underwent MSI testing by NGS on the tumor tissue and germline genetic testing on normal tissue and blood.[115]

PATHOGENIC GERMLINE VARIANTS IDENTIFIED ON TUMOR—NORMAL OR LIQUID BIOPSY

Increasingly, the use of molecular diagnostic tests to identify tumor targets for standard-of-care or other available precision therapies or to determine clinical trial eligibility for novel targeted therapeutics involves tumor DNA and germline DNA sequencing in parallel. In liquid tumor testing, this is more specifically circulating tumor DNA tested in parallel to germline DNA. These tests are often sent directly by the medical oncology team, with this practice referred to as mainstreaming. While, in these settings, germline DNA sequencing is not required to identify clinically actionable variants in the tumor, it can be useful to filter out unimportant variation in the germline DNA from the tumor DNA. As such, providers should be aware of whether the test they are ordering performs germline DNA sequencing and should discuss with their patients the potential to identify germline mutations associated with hereditary cancer risks. They should also be aware that some paired testing is done only for germline subtraction and does not report PGVs. After completion of testing, providers should be careful to review results with an eye for PGVs in common cancer predisposition genes. While some of these identified on tumor testing will be somatic only, many will also be found in the germline and should be followed up with referral to genetic counseling if the patient wants. Increasingly, many laboratories performing either matched tumor DNA (or circulating tumor DNA) and germline DNA sequencing will report PGVs, while others, especially those sequencing tumor only, may provide some indication on reports that an identified pathogenic variant could be germline and should be evaluated. Some studies have found that patients tested through mainstreaming programs may be less likely to complete posttest genetic counseling.[74] Data from Liu et al[116] have demonstrated that Black and Hispanic patients are less likely to seek genetic counseling than White patients and trend toward fewer family members benefiting from cascade testing.

KEY POINTS

- Evaluation for LS may start with tumor screening for MSI or dMMR, although universal multigene panel testing for all CRCs is gaining acceptance.
- Somatic tumor testing can potentially reveal PGVs that may be of significance for a patient and/or family members.
- The absence of somatic tumor pathogenic/likely pathogenic variants does not exclude the possibility of all identifiable PGVs. Genetic counseling and germline testing may still be warranted.

GERMLINE ANALYSES

SPECIMENS AND LABORATORY STANDARDS

Germline genetic testing platforms vary greatly from laboratory to laboratory, with notable differences in analytic coverage, specific genes analyzed, and even reporting standards for pathogenicity. For germline genetic testing, the most used biospecimen is blood because of its high DNA yield and, for some laboratories, the ability to incorporate RNA analysis to further evaluate cryptic regions and VUSs. Commercial laboratories are increasingly offering germline genetic analyses on saliva specimens; however, not all analyses may be validated for all sample types. Tissue, rather than blood or saliva, is necessary for germline analysis in patients who have undergone allogeneic bone marrow or stem cell transplantation or those with a hematologic malignancy, as all blood DNA and approximately two-thirds of saliva DNA are from lymphocytes. In addition, follow-up testing to germline testing performed on blood and/or saliva may be warranted in cases of PGVs identified at low variant allele frequencies to determine origin of the variant (eg, post-zygotic mosaicism, clonal hematopoiesis, or circulating tumor DNA). Alternative sources of germline DNA include the following:

- A skin punch biopsy specimen obtained for fibroblast culture
- Banked DNA or DNA extracted from formalin-fixed paraffin-embedded normal tissue
- Hair follicles or fingernails (in some laboratories)

Complete testing often is not possible in these cases, because variability in storage and extraction can interfere with analysis of copy number and large rearrangement.

RNA analysis is now available at some of the large commercial germline genetic testing companies as part of the original multigene panel test for a subset of genes or in follow-up to multigene panel testing to clarify uncertain or negative results. Although incorporation of RNA analysis is not currently a necessary laboratory standard per American College of Medical Genetics and

Genomics (ACMG) or other professional societies, this can sometimes help clarify the pathogenicity of splice site or missense variants or identify deep intronic variants that would have been missed by DNA testing alone.[87]

GERMLINE GENETIC TEST RESULTS

Pathogenic or Deleterious Variant

- Altered gene function and protein product are associated with disease risk, although genotype-phenotype associations should be carefully considered.
- Patients should be informed of disease risks, medical management implications, and familial ramifications.

Likely Pathogenic or Suspected Deleterious Variant

- There is high suspicion but not complete certainty about the pathogenicity.
- Patients should be informed of disease risks, medical management implications, and familial ramifications.
- Some caution must be taken when counseling a patient and family members, as reclassification to VUS or benign downgrading is possible. However, established medical management interventions, if available, should be implemented in the same manner as they are offered to patients with pathogenic variants.

Variant of Uncertain Significance

- The laboratory does not have enough data to allow for clinical classification or interpretation of the variant's effect.
- Patients and family members should be counseled about the ambiguity of the result and the continued need to interpret risk based on the personal and family history.
- The patients should not be managed as if they had tested positive for a PGV in the gene but, instead, should be managed based on their personal and family history of cancer. Predictive testing should not be offered to at-risk relatives for VUS results, although relatives may be tested to generate segregation analysis evidence for VUS reclassification.
- Clinical germline testing may still be indicated for other family members in the presence of additional red flags.
- With time and access to additional data, many laboratories reclassify these variants, and most VUSs are eventually reclassified as being benign.[117] A general recommendation is that patients and families found to have germline VUSs should check every 1 to 5 years depending on various factors (eg, changes to personal and/or family history, contact from the laboratory) with the healthcare provider who ordered the genetic test to inquire about updates in variant classification.[117]
- RNA analysis, if not previously performed, may be able to assist in the reclassification of certain VUSs, particularly those VUSs that may impact splicing on cryptic intronic regions that are not routinely analyzed by currently established reporting standards.
- Some laboratories do not report VUS results.
- Some laboratories do not perform active variant curation, so the provider or the patient needs to prompt the laboratory for assessment for reclassification.

Likely Benign Variant

- If an alteration is detected, but the laboratory has a low suspicion of it being associated with disease, it is a likely benign variant. Of note, laboratories usually do not report likely benign variants.

Reduced-Penetrance PGVs

Investigation into genotype-phenotype correlations is yielding insights into PGVs in high-risk genes with lower-than-expected cancer risks, termed reduced-penetrance pathogenic variants (RPPVs), that may modify associated cancer risk. For example, specific *BRCA1/2* PGVs have only two to four times increased breast cancer risk as compared with the higher risks associated with truncating variants.[118] These RPPVs have a new framework to standardize their interpretation and reporting, which, in turn, may lead to additional personalization of management recommendations and guidelines that prevent both under- and overtreatment. Knowledge of the specific variant within the cancer risk gene will therefore be of increasing importance, as guidelines may vary for different variants within the same gene.

Increased Risk Allele

Another result that may be found on genetic test results, although not part of the ACMG variant classification system, is an increased risk allele. This is defined as a variant that is not expected to directly cause a genetic condition on its own, but scientific evidence indicates that it can lead to a predisposition to develop the genetic condition in combination with other genetic variants or factors. Some of these increased risk alleles may have conditional recommendations for screening. For example, individuals with *SPINK1* variants may be candidates for pancreatic surveillance if they have a personal history of pancreatitis.

Negative/Normal Result

- No alterations of clinical or uncertain significance are reported.
- Negative results may be uninformative, and the patient and their family members may still harbor a PGV that the current technology cannot detect or for which they were not tested. There could be a predisposing gene variant in a different affected family member, or the patient may also have other significant polygenic or nongenetic familial risk factors.
- When an individual is being tested for a previously identified, familial PGV, a negative result is considered a true-negative result, and, for the specific syndrome-associated cancers, the individual is generally presumed to be back at the risk level of the general population. However, it is increasingly important to ensure proper selection of a germline testing platform that is capable of detecting a previously identified PGV. Notable examples include *MSH2* inversions and deep intronic variants that may be missed by standard DNA sequencing and del/dup platforms.
- It is important to understand that true-negative results were historically described in the setting of families with variants in high-penetrance genes, such as *BRCA1*. In families with moderate-penetrance genetic variants (eg, *CHEK2* variants), individuals who do not carry the familial variant may still be recommended to pursue cancer surveillance on the basis of family history, because the entire familial risk may not be attributed to the identified germline variant.[119]

PRESENTING CASE STUDY

Patient 1

A 40-year-old woman with a family history of breast cancer, in her maternal grandmother at age 68, presents to the outpatient oncology clinic following a recent diagnosis of stage II, hormone receptor–positive, HER2-negative invasive ductal carcinoma of the left breast. She undergoes germline genetic testing to guide surgical decisions and assess risk for future cancers. Testing reveals a heterozygous VUS in the *ATM* gene. She is anxious regarding treatment options and is requesting guidance on how this will impact management of her cancer in terms of breast-conserving therapy versus mastectomy and her future risk of cancer.

Patient 2

A 46-year-old woman with a history of hypertension and family history of a paternal uncle with prostate cancer and an elderly aunt with ovarian cancer presents with newly diagnosed, early stage I right breast cancer that is strongly hormone receptor positive and HER2-negative. She is concerned about management options and undergoes germline genetic testing, which demonstrates a heterozygous pathogenic variant in *BRCA2*.

Compare and contrast the risks associated with a VUS to a known pathogenic variant in terms of management of the current cancers and indication for future management of new cancers in these two patients.

The above patient cases illustrate how genetic testing can be used to refine cancer development risk and influence the patients' approach to decision-making and future surveillance.

Comparative analysis of cases

Patient 1 has a VUS in the *ATM* gene that may or may not be related to an increased risk of cancer development. The impact of this VUS may change over time with additional information, and assessment of the variants should be carried out by using the ClinVar database to evaluate any updated information. Review of this variant demonstrates that 10 independent laboratories have classified the variant as a VUS, with no labs reporting it as pathogenic or likely pathogenic. Thus, the VUS should not be a factor in raising the risk of other cancers in the future, and the patient's decision-making regarding breast conservation versus mastectomy should consider both her personal preference and the expertise of her breast cancer team. There is no indication of conducting tests in other family members, performing additional imaging for surveillance, or repeating tests in the future.

Patient 2 has a pathogenic variant that is associated with an increased risk of breast cancer in addition to other *BRCA2*-related cancers.

Women who are carriers for a pathogenic variant in *BRCA2* have an increased risk of breast, ovarian, and pancreatic cancers, as well as melanoma. The *BRCA2* variant may not influence the patient's consideration of optimal surgery for

her present breast cancer, as outcomes for breast conservation as compared to mastectomies have similar results, but she will face a slightly higher risk of contralateral breast cancer and should undergo annual breast MRI in addition to mammograms in the future if she elects for breast-conserving therapy. This information may aid her in her decision of how best to manage her cancer. She should also undergo risk-reducing bilateral salpingo-oophorectomy and consider pancreatic cancer screening beginning at age 50.

Contrasting analysis of cases

These cases illustrate recommended management processes in contrasting scenarios involving a pathogenic variant and a VUS not known to be associated with an increased risk of cancer. It is important to know how to interrogate a VUS for the most updated information to convey to patients for optimal management. In addition, detection of a pathogenic variant should inform development of a comprehensive management plan for early detection and/or risk-reducing purposes.

Conclusion

Genetic information is increasingly being utilized to assess future risks of cancer development and, with appropriate genetic counseling and help from healthcare providers, it can help patients make optimal decisions for their cancer care management. New pathogenic variants may require initiation of specific imaging or management strategies.

APPROACHES TO GERMLINE GENETIC TESTING

Genetic Testing Using Multigene Panels

In contrast to phenotype-driven testing, NGS technologies have enabled the use of multigene panels for germline analysis wherein multiple cancer susceptibility genes are assessed simultaneously. Disease-specific multigene panels for nearly all the common cancers (ie, breast, ovarian, uterine, colon, kidney, prostate) as well as pan-cancer panels are now widely available through commercial laboratories. The ease of use, cost, and time efficiency associated with multigene panel testing for cancer susceptibility have resulted in a dramatic increase in the application of this testing approach. It is an especially useful approach when significant genetic heterogeneity exists, or multiple genes or syndromes may be implicated based on phenotype or family history. On the other hand, multigene panels also have some limitations.

Additional information is available at Bedrosian et al[105] and Tung et al,[10] and NCCN HBOPP[15] and HCEG[18] guidelines referenced earlier in the chapter.

Pretest Genetic Counseling and Informed Consent

The in-depth discussion provided for single-gene testing in the traditional model of genetic counseling is not possible for a panel that may include 80 genes or more.

Unexpected Results

For panels that include high-penetrance genes such as *TP53* (associated with multiple tumors and childhood cancers) and *CDH1* (associated with recommended management by risk-reducing total gastrectomy), an unexpected positive result without pretest discussion and preparation may result in distress and anxiety. This is particularly the case when a patient's personal or family history is not in line with the hereditary syndrome identified using the multigene panel. For example, if a *CDH1* PGV is unexpectedly identified in a patient who has no personal or family history of diffuse gastric cancer or lobular breast cancer, the patient and healthcare provider are left with a clinical conundrum about accurate cancer risk estimates; current estimates are lower; and endoscopic surveillance can be considered as an alternative to risk-reducing total gastrectomy.

Another unexpected result is the presence of a variant at a low allele fraction. This can be due to constitutional mosaicism (in which the change may be present in germ cells and therefore could be passed on to offspring with associated cancer risks), circulating tumor DNA in patients with active disease, or clonal hematopoiesis of indeterminate potential, which can be associated with its own risks of leukemia and cardiac disease. Genetic consultation is appropriate in these instances to help clarify the source of the variant.

LIMITED UNDERSTANDING OF MODERATE-PENETRANCE GENES

Multigene panels generally include moderate-penetrance genes for which the associated cancer spectrum, lifetime risks, age-associated penetrance, and appropriate management recommendations have not been fully defined. Importantly, the presence or absence of a variant in a moderate-penetrance gene may not provide clarity with respect to a patient's personal and family history of cancer and their future cancer risk.

Genetic VUS

Multigene testing results in a higher incidence of VUS results, leading to additional difficulties with the interpretation of results.

Genetic Variants Associated With Reproductive Risks

Some genes included on multigene panels may be associated with severe autosomal recessive conditions when biallelic variants are inherited but associated with no or possibly limited disease risks when in monoallelic form (Table 6-4). In addition, established cancer risk genes can have different risks in heterozygotes and homozygotes, such as hereditary breast-ovarian cancer (heterozygous change in *BRCA2*) and Fanconi anemia (homozygous changes in *BRCA2*). It is important that clinicians make the patient and family members aware of the reproductive risks so that family planning options can be investigated, if desired.

Table 6-4 Genes With Autosomal Recessive Disease Risk

Gene	Syndrome
ATM	Ataxia telangiectasia
BLM	Bloom syndrome
BRCA1, BRCA2, BRIP1, PALB2, RAD51C	Fanconi anemia
FH	Fumarate hydratase deficiency
MLH1, MSH2, EPCAM, MSH6, PMS2	Constitutional mismatch repair deficiency syndrome
MUTYH, NTHL1, MSH3, MLH3, MBD4	MUTYH-associated polyposis, etc
NBN	Nijmegen breakage syndrome
WRN	Werner syndrome
DDB2, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, POLH, XPA, XPC	Werner syndrome

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PHENOTYPE-DIRECTED GENETIC TESTING

Increasingly, all testing is performed using multigene panel testing, with the main question being the size of the panel, which can be either a tumor specific or a more extensive pan-cancer panel. Decisions regarding the size of the panel and whether to include genes for which there are no management guidelines can be made on the basis of personal and family history of cancer and the patient's comfort level with uncertainty (more genes lead to a higher rate of VUS results, and the inclusion of genes without known management guidelines can lead to results for which there are no surveillance recommendations). Multigene testing options can therefore include the following:

- A large multidisease panel may be used, which may be considered in patients with complex personal and family history, where multiple genetic risks are being considered and where patient tolerance of uncertainty is favorable.
- A small disease-specific panel may be used, which follows a more phenotype-based approach for genetic testing wherein the selection of genes to be analyzed is based on the patient's personal or family cancer history.
- Another approach is an ancestry-specific founder variant panel. Founder variants are genetic alterations observed with high frequency in a distinct group that is or was geographically or culturally isolated. While this is rarely used now for patients with cancer, because multigene panel testing is more thorough and can identify PGVs that would be missed by ancestry-based testing, it has utility for population testing in high-risk populations.
- Cascade testing pertains to families with a previously identified PGV; in these cases, cascade testing (testing only for a known familial PGV) can be undertaken, but it may not be sufficient when the personal and/or family history of cancer is not fully explained by the familial PGV.

OTHER CONSIDERATIONS RELATED TO GERMLINE GENETIC ANALYSES

Multiple Actionable Findings in the Same Individual

With the increasing use of large multigene panels for testing, p patients who have PGVs in more than one cancer risk gene are now being identified. One term for this condition is multilocus inherited neoplasia allele syndrome (MINAS). A systemic review of the literature in this area included 385 individuals with multiple PGVs. Most (287) of the subjects had at least one PGV in *BRCA1* or *BRCA2*, but other involved genes varied. Clinical phenotypes were usually consistent with those of the individual genes involved, but some individuals did have multiple tumors or unusual tumor presentations, suggestive of complex interactions between the involved genes.[120]

Secondary Findings on Genome and Exome Analyses

Through clinical exome and whole-genome sequencing, PGVs may be uncovered in genes unrelated to the primary medical reason for testing; these findings have been termed secondary or incidental findings. Considerable debate has been prompted regarding the extent to which primary data should be analyzed for secondary findings and which, if any, PGVs discovered should be disclosed to patients. In an effort to standardize the reporting of actionable information from clinical genomic sequencing, in 2021, the ACMG designated over 70 medically actionable genes[121] in which PGVs are recommended to be reported because of the high likelihood of severe disease that may be preventable if identified before symptoms appear.[122] The ACMG recommendations provide patients the opportunity to opt out of the analyses of genes unrelated to the indication for testing, with the decision to be made during the process of informed consent before testing. Of note, 24 of the current ACMG and Genomics reportable genes are associated with cancer predisposition syndromes, highlighting the relevance of these recommendations to the field of medical oncology.

Germline Variant Classification Resources

The standardization of variant classification is a substantial challenge in the field of germline genetics because, at this time, a particular variant could be classified as pathogenic/likely pathogenic by one laboratory but as a VUS by another laboratory. Given the current inconsistencies among clinical molecular laboratories and clinical genomic sequencing analyses that have been highlighted, integration of multiple lines of support using standardized methods is necessary to classify genetic alterations into one of five categories: pathogenic, likely pathogenic, uncertain significance (VUS), likely benign, and benign (see earlier discussion about these classifications). To meet this challenge, the National Institutes of Health has supported the formation of a resource called ClinGen, an authoritative central resource aimed at defining the clinical relevance of genomic variants for use in precision medicine and research.[123]

The cornerstone of ClinGen is ClinVar, a free Web-based archive that is maintained by the National Center for Biotechnology Information that reports on interpretations of clinical significance of variants and allows deposition and retrieval of variant data and annotations.[124]

Other resources that may be useful to clinicians in variant interpretation include the following:

- The InSiGHT database (focused on the MMR genes of LS)
- UMD TP53 variant database
- ENIGMA variant database

DIRECT-TO-CONSUMER GERMLINE GENETIC ANALYSES

Direct-to-consumer genetic testing has challenged the traditional practical and ethical frameworks established in the field of clinical genetics. Traditionally, direct-to-consumer genetic tests are advertised and sold directly to individuals, without supervision by a healthcare professional. Saliva collection kits allow consumers to send their specimens directly to commercial laboratories; results generally are returned by mail, email, or phone. Initially, direct-to-consumer companies were told by the FDA that they could not report medically important variants, including cancer susceptibility genes, so direct-to-consumer genetic testing companies grew to offer panels of common SNPs for recreational genetics and ancestry purposes. Now, companies have been FDA approved to offer direct-to-consumer testing for targeted high-risk variants, including common *BRCA1* and *BRCA2* PGVs. Unfortunately, reporting partial *BRCA1* and *BRCA2* results for a few common PGVs or simply the presence of common founder PGVs in *MUTYH* may lead individuals to conclude that they have no risk, despite having been tested for only a few of the thousands of known PGVs. These targeted tests cannot rule out a hereditary cancer syndrome in an individual.

There is an emerging area of "consumer-initiated, physician-mediated" testing where a commercial laboratory advertises testing directly to consumers and contracts with a physician service to approve the tests ordered through the laboratory website. Some of these companies provide posttest genetic counseling to individuals with PGVs or others with concerns about their results as part of the cost of the test. However, companies offering consumer-initiated, physician-mediated testing typically avoid the overhead of reporting results in electronic health records, offering physician support for results, going through insurance reimbursement, and integrating with the healthcare system in other ways. It is increasingly common for patients to come to their physicians' seeking explanations of results from genetic testing that they have sought out independently.

TESTING OF MINORS

The appropriate age for germline testing can vary depending on the gene in question. For some conditions that have manifestations in childhood, such as familial adenomatous polyposis and Li-Fraumeni syndrome, testing for children or even infants is appropriate. For most hereditary cancer syndromes that have increased risk in adulthood, testing at or after age 18 years is appropriate.

PREIMPLANTATION GENETIC TESTING

Some individuals may consider using genetic test results to inform reproductive decisions. In vitro fertilization with preimplantation genetic testing of embryos has been used by many families in the setting of inherited cancer predisposition syndromes.

This process ensures that only embryos without the known familial PGV are transferred, thus substantially reducing the chance of passing on the cancer syndrome to the child. The use of donor gametes (ie, eggs, sperm), adoption, or prenatal diagnosis through chorionic villus sampling or amniocentesis are other family planning options that some individuals might consider.

INSURANCE COVERAGE AND PROTECTIONS

Most third-party payers include some level of coverage for genetic counseling and testing services. Some payers have established personal and family history criteria that must be met for medical necessity to be established; others may follow suggested testing guidelines that have been published by groups such as NCCN. Some payers require the involvement of a genetic counselor or geneticist in the pretest counseling and testing process.

Federal legislation through the Genetic Information Nondiscrimination Act (2008) and, in some cases, additional state legislation provide protection against genetic discrimination by one's employer and health insurance provider.[125] Unfortunately, protection against discrimination by life, disability, and long-term care insurance providers is not universal in the US at this time. This lack of protection may be a particular concern for some unaffected individuals who may be pursuing presymptomatic genetic testing.

RACIAL AND ETHNIC DISPARITIES

Notable disparities by race/ethnicity have been identified in terms of cancer mortality, referrals for genetic counseling, uptake of genetic counseling and genetic testing, and subsequent cancer screening and risk-reducing surgeries.[116,126-128] In a study of young breast cancer survivors, the most frequent reason for not using genetic services was lack of physician recommendation, with a higher proportion of Black women reporting no physician recommendation (n = 172, 50.6%) compared with White/other (n = 203, 39.1%; $\chi^2 = 10.97$, $P < .001$).[116,126] Disparities were observed in genetic services utilization in a random sample of young breast cancer survivors.[129,130] Uptake of recommended genetic counseling was lower among non-White patients with cancer compared with non-Hispanic White patients with cancer after disclosure of new PGVs from 2,239 patients undergoing matched tumor-normal testing in a large prospective cohort study, with the lowest uptake among Black patients (odds ratio [OR], 0.60; 95% CI, 0.37-0.97; $P = .036$). Uptake of genetic testing among a cohort of individuals at risk for hereditary cancer was significantly higher at sites offering a point-of-care testing model compared with sites with a genetic counseling referral model (34% POC vs 11% referral, $P < 0.001$). Non-Hispanic Black patients had lower odds of testing compared with non-Hispanic White patients (adjusted OR = 0.84; 95% CI, 0.71-1.00; $P = 0.049$) at genetic counseling referral sites; however, this disparity was not observed at POC sites.[70] Strategies to reduce barriers, including different workflows such as point-of-care testing and pretest educational video models, may increase uptake of genetic testing and mitigate existing health disparities.[70,116]

SOURCES OF DISPARITIES IN HEREDITARY GENETICS AND GENOMICS

- Differences in tumor characteristics
- Higher rates of VUS in minority populations leading to uninformative testing
- Awareness of genetics and perceived importance of genetic testing
- Education, cost, and socioeconomic barriers
- Medical mistrust
- Physician and healthcare provider recommendation
- Access to genetic counseling
- Language barriers
- Lack of awareness of family history

NEW STRATEGIES AND APPROACHES TO MITIGATE DISPARITIES

- Increased referrals for genetic counseling to improve access
- Testing materials and counseling available in the patient's primary language
- Culturally targeted interventions to support testing uptake and results dissemination
- Public health programs to mitigate financial barriers
- Initiatives to empower minority communities by improving knowledge of cancer risk factors[131]
- Alternative modes of genetic testing delivery, such as point-of-care testing, which can improve access for working patients, rural patients, and those with limited access to genetic counseling[70]

KEY POINTS

- Germline variants typically fall into one of five categories: pathogenic, likely pathogenic, uncertain significance (VUS), likely benign, and benign.
- Recommendations for management and predictive testing differ substantially based on the classification of the variant and should be assessed carefully.

- Multigene panel testing is challenging the traditional pretest counseling method and phenotype-directed approach to genetic testing, and it may be a cost- and time-efficient method.
- Multigene testing can result in unexpected PGVs, PGVs in genes that do not account for the personal/family history, and a higher VUS incidence.
- Inconsistencies in genetic variant classification are an important challenge that clinicians must understand.
- The Genetic Information Nondiscrimination Act of 2008 provides protection against genetic discrimination by an individual's employer and health insurance provider.
- Racial and ethnic disparities exist for oncology patients eligible for genetic counseling and testing, which should be minimized for optimal cancer prevention and treatment.

HIGH-YIELD TAKEAWAYS

- Regardless of site of origin, MSI-H or dMMR tumors (by IHC or molecular testing) have a higher likelihood of response to PD-1 inhibitors and may be due to LS or be sporadic from epigenetic silencing.
- PARP inhibitors work in *BRCA*-mutated tumors by preventing single-strand break repair, converting them to double-stranded breaks during replication that for BRCA-deficient cells results in cell death, known as synthetic lethality.
- Dedicated germline testing is the gold standard for detecting PGVs and is superior to liquid biopsies or tumor-normal sequencing.
- Testing for PGVs in *BRCA1* and *BRCA2* is indicated for all patients with ovarian and pancreatic cancers, as well as for patients with breast and prostate cancers who are diagnosed at a young age, have triple-negative disease (breast), have male breast cancer, have a suggestive family history, and/or are candidates for therapy with PARP inhibitors.
- Widely accepted options for risk management include high-risk screening of the breasts with MRI, risk-reducing mastectomy, risk-reducing bilateral salpingo-oophorectomy, and risk-reducing medications such as tamoxifen or aromatase inhibitors.
- LS is characterized by increased risk of colorectal, endometrial, ovarian, gastric, small bowel, pancreatic, hepatobiliary, and urothelial cancers, as well as glioblastoma and sebaceous cutaneous neoplasms. Consider germline genetic testing for all colorectal and endometrial cancers.
- Key components of risk management include colonoscopies every 1 to 3 years, consideration of aspirin chemoprevention, risk-reducing hysterectomy/bilateral salpingo-oophorectomy, and upper endoscopy.

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GENETIC TESTING FOR HEREDITARY CANCER SYNDROMES

6

CHAPTER SUMMARY GUIDE

KEY POINTS

- High-penetrance cancer predisposition genes account for up to 10%-20% of all cancer diagnoses.
- Familial risks outside the high-penetrance syndromes may be related to moderate-risk alleles and additional shared hereditable and/or environmental factors. Empiric risk assessment to account for familial risk may be indicated.
- Consider clinical validity and utility of genes when selecting a multigene panel.
- Inclusion of moderate-penetrance genes associated with a two- to fivefold increased risk of specific cancers is commonplace for panel testing.
- Cancer risk estimates and management recommendations for high- and moderate-penetrance genes are updated continuously.
- Genetic counseling is a communication process that helps patients make informed genetic testing decisions and adapt to having a genetic condition.
- Genetic counseling is guided by principles of autonomy, nonmaleficence, equity, and duty to warn and has traditionally included pre- and posttest discussions.
- Thorough medical and family histories to assess for red flags are vital for accurate genetic risk assessments.
- Evaluation for LS may start with tumor screening for MSI or dMMR, although universal multigene panel testing for all CRCs is gaining acceptance.
- Somatic tumor testing can potentially reveal PGVs that may be of significance for a patient and/or family members.
- The absence of somatic tumor pathogenic/likely pathogenic variants does not exclude the possibility of all identifiable PGVs. Genetic counseling and germline testing may still be warranted.
- Germline variants typically fall into one of five categories: pathogenic, likely pathogenic, uncertain significance (VUS), likely benign, and benign.
- Recommendations for management and predictive testing differ substantially based on the classification of the variant and should be assessed carefully.
- Multigene panel testing is challenging the traditional pretest counseling method and phenotype-directed approach to genetic testing, and it may be a cost- and time-efficient method.
- Multigene testing can result in unexpected PGVs, PGVs in genes that do not account for the personal/family history, and a higher VUS incidence.
- Inconsistencies in genetic variant classification are an important challenge that clinicians must understand.
- The Genetic Information Nondiscrimination Act of 2008 provides protection against genetic discrimination by an individual's employer and health insurance provider.
- Racial and ethnic disparities exist for oncology patients eligible for genetic counseling and testing, which should be minimized for optimal cancer prevention and treatment.

CHAPTER TABLES AND IMAGES

Table 6-1A Selected High- and Moderate-Risk Genes, Syndromes, and Management Considerations: A Through C

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
APC	FAP, AFAP; variant: Turcot syndrome, GAPPS	Colorectal lesions (adenomatous polyposis and cancer), gastric and duodenal/small-bowel lesions (adenomatous polyps and cancer), desmoid tumors, thyroid (particularly cribriform-morula variant of papillary thyroid carcinoma), hepatoblastoma (usually in patients less than 5 years old), pancreatic cancer, medulloblastoma (Turcot syndrome), GAPPS	Colonoscopy (beginning as early as age 10 years) and total colectomy based on polyp burden; upper endoscopy, consideration of small-bowel visualization, thyroid examination, and consideration of ultrasonography; consideration of childhood liver palpation, abdominal ultrasonography, AFP measurement	Genotype-phenotype correlations between classic FAP and AFAP: mutations on the 5′ and 3′ ends of the gene correlate with AFAP; high de novo mutation rate (about 20%-25%); extracolonic features: CHRPE, osteomas, supernumerary teeth, desmoid tumors, epidermoid cysts, gastric fundic gland polyps; chemoprevention not a replacement for colonoscopy and colectomy	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18,19]
*APC**I1307K (c.3920T->A)		Colorectal cancer: moderate penetrance	Colonoscopy every 5 years beginning at age 40 years or earlier depending on family history; lifetime risk 5%-10%	Ashkenazi Jewish founder PGV; not associated with polyposis	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]; Katona et al[20]
ATM	Ataxia telangiectasia	Monoallelic carriers: breast (especially ER-positive), pancreas, possibly ovary, prostate; biallelic carriers: leukemia, lymphoma	Monoallelic carriers: breast screening with annual mammogram at age 40 and breast MRI starting at age 30-35 years or per family history*; pancreas screening beginning at age 50 years (or 10 years prior to earliest exocrine pancreatic cancer in the family); biallelic carriers: AT specialist for multidisciplinary management; consider annual prostate cancer screening at age 40 years	Monoallelic carriers: limited evidence for gastrointestinal cancers; risk of autosomal recessive AT condition in biallelic offspring of heterozygous carriers; AT: childhood cerebellar ataxia, telangiectasias of the conjunctivae, immunodeficiency, sensitivity to radiation	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15,21,22]
AXIN2	AXIN2-associated oligodontia and polyposis	Colorectal lesions (adenomatous polyposis ranging from 10s to 100s and cancer)	Colonoscopy every 2-3 years beginning at age 25-30 years; if polyps are found, every 1 to 2 years with consideration of surgery depending on polyp burden	Patients often also have oligodontia (absence of six or more permanent teeth excluding wisdom teeth) and ectodermal dysplasia	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial and Gastric[18]
BARD1		ER-negative breast cancer, triple-negative breast cancer	Annual mammogram and consideration of breast MRI starting at age 40 years		NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
BAP1	*BAP1* tumor predisposition syndrome	Atypical Spitz tumors, uveal melanoma, malignant mesothelioma, cutaneous melanoma, clear cell renal cell carcinoma, basal cell carcinoma	Eye examinations, dermatologic examinations, consideration of abdominal ultrasonography and/or MRI of the kidneys	Limited evidence for possible other associated tumors: non-small cell lung adenocarcinoma, breast cancer, cholangiocarcinoma, meningioma, neuroendocrine carcinoma	NCCN Kidney Cancer,[23] Pilarski et al,[24] Lalloo et al[25]
BMPR1A and *SMAD4*	Juvenile polyposis syndrome	GI lesions (juvenile/hamartomatous polyps and cancer [colorectal, stomach, small bowel])	Colonoscopy and upper endoscopy every 1-3 years beginning at age 12-15 years; surgical management based on polyp burden; HHT screening for *SMAD4* carriers	"Juvenile" refers to polyp histology, not age at onset; *SMAD4* mutations associated with HHT; *SMAD4* PGVs associated with massive gastric polyposis	Haidle et al,[26] NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial and Gastric[18]
BRCA1 and *BRCA2*	Hereditary breast cancer and ovarian cancer syndrome	Breast (*BRCA1*: often triple-negative tumor), male breast, ovarian (epithelial; high-grade serous), fallopian tube, primary peritoneal, prostate (high Gleason score), pancreatic adenocarcinoma	Breast screening with annual mammogram and breast MRI starting at age 25-30 years; male self-examination and clinical breast examination at 35 years; consideration of mammography in males; optional risk-reducing mastectomy in females; risk-reducing BSO between age 35 and 45 years*; PSA measurement and digital rectal examination starting at age 40 years; consideration of chemoprevention (eg, tamoxifen, OCPs); FDA approval of PARP inhibitors for select BRCA-associated breast, ovary, pancreas, prostate cancers; pancreas screening starting at age 50 years or per family history	Founder PGVs in certain populations (eg, Ashkenazi Jewish, Icelandic); risk of autosomal recessive Fanconi anemia with biallelic PGVs	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]
BRIP1		Ovarian (heterozygous carriers)	Consider risk-reducing BSO at age 45-50 years or per family history	Risk of autosomal recessive Fanconi anemia in biallelic offspring of heterozygous carriers	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]

Abbreviations: AFAP, attenuated familial adenomatous polyposis; AFP, alpha-fetoprotein; AT, ataxia telangiectasia; BSO, bilateral salpingo-oophorectomy; CHRPE, congenital hypertrophy of the retinal pigment epithelium; ER, estrogen receptor; FAP, familial adenomatous polyposis; GAPPS, gastric polyposis with APC promoter 1b mutations; HHT, hereditary hemorrhagic telangiectasia; OCP, oral contraceptive pills; PARP, poly ADP ribose polymerase; PGV, pathogenic germline variants; PSA, prostate-specific antigen.
Leukemia/lymphoma predisposition syndromes are not listed; refer to Chapters 19 and 20. Most childhood-onset conditions are not listed; refer to Lindor et al.[27]
*Earlier initiation of breast cancer surveillance should be determined based on personal/family history of breast cancer.[15]
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Table 6-1B **Selected High- and Moderate-Risk Genes, Syndromes, and Management Considerations: C Through G**

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
CDH1	Hereditary diffuse gastric cancer syndrome	Diffuse gastric cancer, lobular breast cancer (ER-positive)	A strategy of surveillance upper endoscopy with biopsies of the stomach, consideration of risk-reducing total gastrectomy, breast screening with annual mammography and breast MRI at 30, optional risk-reducing mastectomy	Can manifest as cleft palate	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15,19]
CDKN2A, CDK4	FAMMM syndrome	Melanoma and dysplastic nevi, pancreatic adenocarcinoma	Dermatologic examination, pancreas screening recommended beginning at age 40 years*	Risk of melanoma may be independent of genetic test result; *CDKN2A* (p16) founder PGV in the Netherlands; PGVs affecting p14ARF are associated with a different spectrum of tumors, including melanoma, sarcomas, nervous system tumors, and possibly breast cancer; consider full-body MRI and brain MRI for those with p14ARF PGVs	Goldstein et al,[28] Vasen et al,[29] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostates[15]
CHEK2		Breast cancer	For truncating pathogenic variants, breast screening with annual mammography at age 40 years and breast MRI starting at age 30-35 years, or per family history. Consider prostate cancer screening starting at age 40	Genotype-phenotype: different risks for truncating mutations versus missense mutations; Limited evidence for association with prostate, thyroid, and renal cancers, possibly leukemia and plasma cell neoplasms	Zeng et al,[30] Hanson et al,[31] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostates,[15] AlDubayan et al[32]
CHEK2 (low penetrance, including I157T/470T>C; S428F/ c.1283C>T; and T476M/ c.1427C>T)		Breast cancer; possibly leukemia and plasma cell neoplasms	Low-penetrance missense CHEK2 variants may not be actionable. Studies demonstrate the lifetime breast cancer risk is less than 20%. Management recommendations should be based on clinical assessment and family history	Genotype-phenotype: different risks for truncating mutations vs missense mutations; limited evidence for association with prostate, thyroid, and renal cancers	Zeng et al,[30] Hanson et al,[31] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreas,[15] AlDubayan et al[32]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
FH	HLRCC	Cutaneous leiomyomata, uterine leiomyomata, renal tumors (type 2 papillary, tubule-papillary, collecting-duct carcinomas; unilateral, solitary lesions); rare paraganglioma/ pheochromocytoma	Dermatologic and gynecologic examinations; evaluate for changes suggestive of leiomyosarcoma; medication or resection of leiomyomata, imaging for and surgical management of renal tumors; abdominal MRI (preferred) or CT, both exams with and without IV contrast, annually starting at age 8-10 years and performed every 3 years	FH enzyme assay might be helpful in some situations. Risk for uterine leiomyosarcoma is unclear. Biallelic FH PGVs cause a recessive disorder known as FH deficiency metabolic disorder, profound developmental delay, seizures, and fumaric aciduria	Kamihara et al,[33] Barrisford et al,[34] NCCN Kidney Cancer
FLCN	BHD syndrome	Benign cutaneous findings (fibrofolliculomas, trichodiscomas/ angiofibromas, perifollicular fibromas, acrochordons), pulmonary cysts, renal tumors (oncocytoma, chromophobe, oncocytic hybrid tumors)	No consensus at this time. Dermatologic care, imaging for and surgical management (nephron sparing) of renal tumors	Fibrofolliculomas are specific to BHD. Predisposition to multiple lung cysts may present as spontaneous pneumothorax. Renal tumors are multifocal, bilateral, and slow growing. Other features include parotid lesions, oral papules, and thyroid lesions. Data are unclear regarding colon cancer. There are possible genotype/phenotype correlations	van de Beek et al,[35] Sattler and Steinlein,[36] NCCN Kidney Cancer
GREM1	Hereditary mixed polyposis syndrome	Multiple polyps of multiple and mixed morphologies, including serrated lesions, Peutz-Jeghers polyps, juvenile polyps, conventional adenomas and colorectal adenocarcinoma	Colonoscopy every 2-3 years beginning at age 25-30 years unless polyps are found; consider total colectomy based on polyp burden	Founder PGV in Ashkenazi Jewish individuals; duplication spanning the 3′ end of the SCG5 gene and a region upstream of the *GREM1* locus	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]

Abbreviations: BHD, Birt-Hogg-Dube; ER, estrogen receptor; FAMMM, familial atypical mole melanoma syndrome; FH, fumarate hydratase; HLRCC, hereditary leiomyomatosis and renal cell cancer; IV, intravenous; OCP, oral contraceptive pills; PGV, pathogenic germline variants.

Leukemia/lymphoma predisposition syndromes are not listed; refer to Chapters 19 and 20. Most childhood-onset conditions are not listed; refer to Lindor et al.[27]

*Earlier initiation of breast cancer surveillance should be determined based on personal/family history of breast cancer.[15]

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Table 6-1C **Selected High- and Moderate-Risk Genes, Syndromes, and Management Considerations: M Through P**

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
MBD4	*MBD4*-associated neoplasia syndrome or *MBD4* biallelic PGVs	Colorectal polyposis, AML, uveal melanoma	Colonoscopy every 2-3 years starting at age 18-20 years, consider CBC at diagnosis, ophthalmology exam at diagnosis and annually	Unknown risks for heterozygous carriers	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]
MEN1	MEN-1	GEP tract, well-differentiated endocrine tumors, pituitary tumors (prolactinoma), parathyroid tumors, carcinoid tumors, adrenocortical tumors	Biochemical testing with emphasis on pancreatic and pituitary hormones and calcium, imaging of chest and abdomen every 1-3 years starting at age 8-15 years, brain MRI every 3-5 years starting at age 5 years, medical management of endocrinopathies, parathyroidectomy in setting of hyperparathyroidism	Primary hyperparathyroidism, hypercalcemia, oligomenorrhea/amenorrhea, galactorrhea, Zollinger-Ellison syndrome (gastrinoma), insulinoma, glucagonoma, VIP-secreting tumor (VIPomas); other features: skin (angiofibromas, collagenomas), lipomas, CNS lesions (meningioma, ependymoma), leiomyomas	Giusti et al[37] and NCCN Neuroendocrine and Adrenal Tumors[38]
MET (*c-MET*)	HPRC	Papillary renal cancer (multifocal, bilateral, type 1 papillary)	Imaging, surgical management		Coleman and Russo,[39] NCCN Kidney Cancer[40]
MLH1/MSH2/MSH6/PMS2/EPCAM	Lynch syndrome (formerly, HNPCC); variant: Muir-Torre syndrome; variant: Turcot syndrome; variant: CMMR-D syndrome (biallelic PGVs; recessive inheritance)	Colorectal, endometrial ovarian (epithelial), stomach, small bowel, urothelial, pancreas, hepatobiliary tract, sebaceous neoplasms of the skin (Muir-Torre syndrome), glioblastoma (Turcot syndrome), prostate	Colonoscopy every 1-2 years starting at age 20-25 years* (*MLH1* and *MSH2*) or every 1-3 years starting at age 30-35 years* (*MSH6* and *PMS2*); hysterectomy, and risk-reducing BSO (*MLH1, MSH2*) insufficient evidence and decision for risk-reducing hysterectomy and BSO for *MSH6* should be individualized); endometrial biopsy every 1-2 years starting at age 30-35 years can be considered upper endoscopy every 2-4 years starting at age 30-40 years; consideration of urinalysis or urine cytology, consider skin exam every 1-2 years (age to start surveillance can be individualized), and aspirin for chemoprevention (optimal dose to be determined); except for *PMS2*, pancreas screening starting at age 50 years or earlier if there is a family history of pancreatic cancer in a first- or second-degree relative; consider annual prostate cancer screening at age 40 years	Tumor analyses with IHC staining, MSI analysis, somatic tumor genetic analysis, *BRAF* V600E somatic analysis, MLH1 promoter hypermethylation analysis; Amsterdam criteria I and II, revised Bethesda guidelines; recommendations for universal screening of colorectal and endometrial cancers; risk of autosomal recessive CMMR-D syndrome (cafe-au-lait macules, solid tumors, hematologic cancers) in offspring	NCCN Genetic/Familial High-Risk Assessment: Colorectal[18]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
MLH3/MSH3	*MLH3*-and *MSH3*-associated polyposis	Biallelic PGV carriers: colorectal lesions (adenomatous polyposis and cancer); recently discovered so unclear	Colonoscopy every 2-3 years beginning at age 25-30 years unless polyps; consider total colectomy based on polyp burden	*MSH3* tumors exhibit EMAST (MSI of di- and tetranucleotide repeats); *MLH3* tumors did not	Olkinuora et al,[41] NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]
MUTYH	MAP	Biallelic PGV carriers: colorectal lesions (adenomatous polyposis and cancer; serrated and hyperplastic polyps also described), stomach, duodenal lesions (adenomatous polyps, cancer)	Colonoscopy every 1-2 years, starting at age 25-30 years; consider total colectomy based on polyp burden; upper endoscopy beginning at age 30-35 years	Phenotypically similar to AFAP; two northern European founder PGVs; no increased colorectal cancer risk in heterozygous carriers	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]
NF1	Neurofibromatosis type 1	Cutaneous neurofibromas, plexiform neurofibromas, optic nerve and other CNS gliomas, malignant peripheral nerve sheath tumors, breast (moderate risk), others: GIST, leukemia, paraganglioma/ pheochromocytoma	Neurofibromatosis type 1 specialist for management, physical and ophthalmologic examinations; imaging; surgical management; breast screening with annual mammography starting at age 30 years and breast MRI from ages 30-50 years, per family history*	Cafe-au-lait macules, axillary and inguinal freckling, iris Lisch nodules, learning disabilities, scoliosis, tibial dysplasia, vasculopathy	Friedman,[42] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostates[15]
NTHL1	*NTHL1*-associated polyposis	Biallelic PGV carriers: colorectal lesions (less than 50 adenomatous polyps and cancer)	Colonoscopy every 2-3 years beginning at age 25-30 years unless polyps; consider total colectomy based on polyp burden; EGD at age 30-35 years every 1-4 years based on findings; education regarding importance of prompt reporting of any abnormal uterine bleeding or postmenopausal bleeding; no other screening recommendations have been made to date for breast or the other extracolonic cancers	c.268c>T (p.GIn90*) variant is the most common truncating PGV and has higher prevalence in European cohorts. Tumors have mutation signature (COSMIC Signature 30). There are possible increased risks for breast, endometrial, basal cell, hematologic and cervical cancers, meningioma and bladder tumors	Grolleman et al,[43] NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]
PALB2		Breast cancer (particularly ER-positive), ovarian cancer, pancreatic cancer	Breast screening with annual mammogram and breast MRI with and without contrast starting at age 30; optional risk-reducing mastectomy in females; consideration of risk-reducing BSO between age 45 and 50 years. Pancreatic surveillance may be considered with or without family history of pancreatic cancer. Consider prostate cancer screening starting at age 40	Risk of autosomal recessive Fanconi anemia in biallelic offspring of heterozygous parents	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
POLE/POLD1	Polymerase proofreading-associated polyposis	Colorectal lesions (attenuated adenomatous polyposis and cancer), duodenal (adenomas and cancer), endometrial cancer	Colonoscopy every 2-3 years beginning at age 25-30 years unless polyps; consider total colectomy based on polyp burden; baseline upper endoscopy beginning at age 25-30 years; education regarding importance of prompt reporting of any abnormal uterine bleeding or postmenopausal bleeding	Two recurrent PGVs have been identified: *POLE* p.L424V and *POLD1* p.S478N. Nearly all the described PGVs are activating mutations in the exonuclease domain. It is probably associated with brain tumors and possibly endometrial and breast cancers	NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric[18]
PTCH1 *SUFU*	Gorlin syndrome/ nevoid basal cell carcinoma syndrome	Jaw (odontogenic) keratocysts, basal cell carcinomas, medulloblastoma PNET desmoplastic	Referral to a specialist for management; physical examination, avoidance of sun exposure and at least annual dermatologic examination, surgical management	Other features: congenital skeletal anomalies, cleft lip/palate, cerebral/falx calcifications, macrocephaly with frontal bossing, polydactyly, intellectual disability, lymphomesenteric or pleural cysts, palmar/ plantar pits, cardiac fibromas, ovarian fibromas, ocular abnormalities	Evans and Farndon[44] and Foulkes et al[45]
PTEN	Cowden syndrome/PTEN hamartoma tumor syndrome	Breast cancer, thyroid cancer (most often follicular), endometrial cancer, colorectal lesions (hamartomas, ganglioneuromas, cancer), renal cell carcinoma	Annual thyroid examination and ultrasonography starting at age 12 years, endometrial screening with random biopsy and ultrasonography starting at age 35 years, optional hysterectomy, colonoscopy every 5 years beginning at age 35 years unless polyps, renal ultrasonogram every 1-2 years starting at age 40 years	Major and minor criteria (tumors, physical and dermatologic/ mucocutaneous findings, developmental disability); macrocephaly, Bannayan-Riley-Ruvalcaba syndrome, PTEN-related *Proteus* syndrome, autism spectrum disorder, Lhermitte-Duclos disease	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]

Abbreviations: AFAP, attenuated familial adenomatous polyposis; AML, acute myeloid leukemia; BSO, bilateral salpingo-oophorectomy; CBC, complete blood count; CMMR-D, constitutional mismatch repair deficiency; CNS, central nervous system; EGD, esophagogastroduodenoscopy; EMAST, elevated microsatellite alterations at selected tetranucleotides; GEP, gastroenteropancreatic; GIST, gastrointestinal stromal tumor; HNPCC, hereditary nonpolyposis colorectal cancer; HPRC, hereditary papillary renal carcinoma; IHC, immunohistochemistry; MAP, MUTYH-associated polyposis; *MEN-1*, multiple endocrine neoplasia type 1; MEN1, menin 1; MSI, microsatellite instability; NF1, neurofibromin 1; PGV, pathogenic germline variants; PNET, primitive neuroectodermal tumors; VIP, vasoactive intestinal peptide.

Leukemia/lymphoma predisposition syndromes are not listed; refer to Chapters 19 and 20. Most childhood-onset conditions are not listed; refer to Lindor et al.[27]

*Earlier initiation of breast cancer surveillance should be determined based on personal/family history of breast cancer.[15]

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Table 6-1D **Selected High- and Moderate-Risk Genes, Syndromes, and Management Considerations: R Through V**

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
RAD51C		ER-negative breast cancer, triple-negative breast cancer, ovarian cancer	Annual mammogram and consideration of breast MRI starting at age 40 years; risk-reducing salpingo-oophorectomy at age 45-50 years	Risk of autosomal recessive Fanconi anemia	NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]
RAD51D		Breast cancer, ovarian cancer	Annual mammogram and consideration of breast MRI starting at age 40 years; risk-reducing salpingo-oophorectomy at age 45-50 years		NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate[15]
RB1	Retinoblastoma	Retinoblastoma (trilateral disease: cooccurrence of pinealoblastoma), bone or soft-tissue sarcomas, melanoma, others	Ophthalmologic examination and imaging; care by a multidisciplinary team; avoidance of radiation	Usually bilateral or multifocal disease; mosaic forms; therefore, analysis of tumor tissue and blood is important; RNA studies may also be recommended; low-penetrance mutations identified; parent-of origin effect in some families	Lohmann and Gallie,[46] Knudsen,[47] Abramson et al,[48] and Abramson and Frank[49]
RET	MEN-2; three subtypes: MEN-2A (aka, Sipple syndrome), familial medullary thyroid carcinoma, MEN-2B	Medullary thyroid carcinoma (multifocal, bilateral) and primary C-cell hyperplasia, pheochromocytoma (bilateral) (MEN-2A and 2B), parathyroid adenoma/hyperplasia (hyperparathyroidism, hypercalcemia, renal stones; MEN-2A)	Prophylactic thyroidectomy (varies from infancy to age 5 years, depending on specific *RET* PGV; genotype-phenotype correlations); surgical management of identified disease, serum calcitonin concentration, consideration of eligibility for treatment with kinase inhibitors, biochemical screening and imaging for pheochromocytoma and parathyroid abnormalities	Genotype-phenotype correlations MEN-2A: MTC in early adulthood; FMTC: MTC in middle age; MEN-2B: MTC in early childhood, mucosal neuromas (lips, tongue), dysmorphic features (large lips, "marfanoid" body habitus), GI ganglioneuromatosis; *RET* gene loss of function PGVs also associated with Hirschsprung disease	Eng and Plitt[50] and Wells et al[51]
SDHB/ SHDC/ SDHD/ SDHA/ SDHAF2, MAX, TMEM127	Hereditary paraganglioma/ pheochromo-cytoma syndrome	PGL-sympathetic and parasympathetic PCC, GISTs, renal clear cell carcinoma, and other less well-defined cancer risks such as papillary thyroid carcinoma	*SDHA* appears to have lower penetrance than other SDHx PGVs; screening in this population such as plasma-free fractionated metanephrines or 24-hour urine fractionated metanephrines (optional dopamine or 3-methoxytyramine) to screen for secreting PGL/PCC and whole-body MRI for PGL, PCC, renal cell carcinoma, and GIST is controversial because of conflicting guidelines	Secretory and nonsecretory PGL, high blood pressure, headache, anxiety, profuse sweating, palpitations, pallor; *SDHB*: high risk of malignant transformation; *SDHD*: parent-of-origin effect, disease-causing when paternally inherited; *SDHAF2*: possible parent-of-origin effect (paternal inheritance)	Hanson et al[52] and Amar et al[53]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
STK11 (*LKB1*)	PJS	GI lesions (PJS-type hamartomatous polyps; colorectal, stomach, small-bowel cancer), breast, pancreas, gynecologic (ovarian SCTAT sex cord tumor with annual tubules), cervix (minimum deviation adenocarcinoma), uterus, testes (Sertoli cell), lung	Colonoscopy and upper endoscopy with small-bowel visualization every 2-3 years beginning at about age 18 years, breast screening with annual mammography and breast MRI beginning at age 30, pancreas screening beginning at about age 30-35 years, gynecologic examination and annual pelvic ultrasonogram beginning at about age 18-20 years, annual testicular examination, including in the pediatric setting	Mucocutaneous hyperpigmentation of mouth, lips, nose, eyes, genitalia, fingers; may fade after puberty	McGarrity et al,[54] NCCN Genetic/ Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric,[18] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate
TP53	LFS	Soft tissue and bone sarcomas, breast cancer, brain cancer, adrenocortical carcinoma, leukemia, other cancers (GI, genitourinary, lung, lymphomas, thyroid, neuroblastoma, skin)	Screening beginning in childhood with comprehensive physical exam including neurological exam and CBC with differential every 3-4 months until age 18 years; annual full-body and brain MRI; ultrasound abdomen and pelvis every 3-4 months; blood biochemistry if unsatisfactory ultrasound quality; in adults (18 years or older), comprehensive physical exam every 6 months, ultrasound of the abdomen and dermatologic exam annually; blood biochemistry if unsatisfactory ultrasound quality; breast screening with annual breast MRI and mammography beginning at age 20 and 30 years, respectively; consideration of risk-reducing mastectomy; CBC with differential every 3-6 months in patients with prior cytotoxic chemotherapy or radiation exposures; physical examination, including dermatologic and neurologic examinations; pancreatic surveillance if an affected close relative; colonoscopy and upper endoscopy every 2-5 years starting at age 25 years; annual whole-body MRI with brain MRI, consideration of radiation avoidance, if clinically appropriate	Classic LFS criteria; Chompret criteria; consider genetic testing in *BRCA*-negative, isolated, early-onset breast cancer (age less than 31 years); breast cancers more likely to be ER, progesterone receptor, and HER2/neu receptor positive; consider additional *TP53* variant workup for individuals with variant allele fraction below heterozygous range (typically <30%) and/or in when LFS clinical criteria are not met	Schneider et al,[55] Li and Fraumeni,[56] Chompret et al,[57] Villani et al,[58] Kratz et al,[59] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and Prostate[15] and Achatz et al[60]

Genes	Syndromes	Associated Neoplasms	Management Considerations	Other Notes	References
TSC1 and *TSC2*	TSC	Kidney: renal cell carcinomas, angiomyolipomas (benign and malignant), epithelial cysts, oncocytoma (benign adenomatous hamartoma)	TSC specialist for management: imaging; dermatologic, dental, ophthalmologic examinations; echocardiography; electrocardiography; consideration of eligibility for treatment with mTOR inhibitors, surgical management	Skin (hypomelanotic macules, facial angiofibromas, shagreen patches, cephalic plaques, ungual fibromas); brain (cortical dysplasias, subependymal nodules and subependymal giant cell astrocytomas, seizures, intellectual disability/developmental delay, autism spectrum disorder, psychiatric illness); heart (rhabdomyomas, arrhythmias); lungs (lymphangioleiomyomatosis); genotype-phenotype correlations: higher risk of renal cell carcinoma in TSC2; possible association with neuroendocrine tumors	Northrup et al[61] and NCCN Kidney Cancer[23]
VHL	VHL syndrome	Clear cell renal cell carcinoma, pheochromocytoma, paragangliomas, pancreatic neuroendocrine tumors	Biochemical screening, imaging of the abdomen and CNS, renal sparing management of kidney cancers; consideration of belzutifan for prevention	Hemangioblastomas of the brain, spinal cord, and retina; renal cysts; pancreatic cysts; endolymphatic sac tumors; epididymal and broad ligament cysts; genotype-phenotype correlations: VHL type 1, type 2A, type 2B, type 2C with different risks of pheochromocytoma or renal cell carcinoma	Van Leeuwaarde et al[62] and NCCN Kidney Cancer[23]

Abbreviations: CNS, central nervous system; ER, estrogen receptor; FMTC, familial medullary thyroid carcinoma; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; LFS, Li-Fraumeni syndrome; MEN-2, multiple endocrine neoplasia type 2; mTOR, mechanistic target of rapamycin; NF1, neurofibromin 1; PCC, pheochromocytoma; PGL, paraganglioma; PGV, pathogenic germline variants; PJS, Peutz-Jeghers syndrome; SCTAT, sex cord tumors with annular tubules; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau.
Leukemia/lymphoma predisposition syndromes are not listed; refer to Chapters 19 and 20. Most childhood-onset conditions are not listed; refer to Lindor et al.[27]
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Table 6-2 **Prevalence of Cancer Susceptibility Pathogenic Germline Variants for Unselected Patients**

Cancer Type	Patients With Germline Variants, N/Total Patients	PGV Prevalence, %
Breast	83/959[91]	8.65-10.8
	494/4,581[92]	
Triple-negative breast	267/1,824[93]	14.60
Lung (advanced cancer only)	222/5,118[94]	4.3-5.8
	448/7,668[92]	
Colon	305/5,303[95]	5.8-9.9
	105/1,058[96]	
Prostate	247/2,887[95]	8.6-17.3
	620/3,607[97]	
Osteosarcoma	281/1,044[98]	28.00
Renal	85/1,336[92]	6.40
Pancreatic (adenocarcinoma)	273/3,535[99]	7.7-14.1
	25/177[92]	
Bladder/urothelial (advanced cancer only)	79/1,188[100]	6.6-14
	80/586[101]	
Ovarian	60/515 (*BRCA1/BRCA2* only)[92]	11.7-13.8
	380/2,756[92]	
Endometrial	76/1,542[102]	4.9-9.2
	35/381[92]	
Head/neck	51/1,218[92]	4.20
Cholangiocarcinoma	36/8,401[92]	4.30
Esophageal	36/747[92]	4.80
Gastric	48/243[103,104]	19.80

Abbreviation: PGV, pathogenic germline variant.
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Table 6-3 **Genetic Cancer Predisposition Syndromes and Selected Associated Pathologies**	
Neoplastic or Preneoplastic Pathologies	**Associated Genetic Syndromes and Genes**
High-grade or poorly differentiated ductal breast cancer with estrogen receptor, progesterone receptor, and HER2/neu negativity	Hereditary breast and ovarian cancer syndrome (*BRCA1*); *BARD1, PALB2, RAD51C, RAD51D*
Lobular breast cancer	Hereditary diffuse gastric cancer syndrome (*CDH1*)
High-grade serous (papillary serous) ovarian	Hereditary breast and ovarian cancer syndrome (*BRCA1, BRCA2*)
Clear cell or endometrioid ovarian cancers	Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
Ovarian sex cord tumors with annular tubules	Peutz-Jeghers syndrome (*STK11*)
Clear cell or endometrioid endometrial cancers	Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
Uterine leiomyomas	Hereditary leiomyoma renal cell carcinoma syndrome (*FH*)
Minimal deviation adenocarcinoma (adenoma malignum of the cervix)	Peutz-Jeghers syndrome (*STK11*)
Colorectal cancer with tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring cells, medullary growth pattern	Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
Lauren diffuse type/signet ring cell/linitus plastica gastric cancer	Hereditary diffuse gastric cancer syndrome (*CDH1*); *CTNNA1*
Hamartomatous gastrointestinal polyps	Peutz-Jeghers syndrome (*STK11*); juvenile polyposis syndrome (*BMPR1A, SMAD4*); Cowden syndrome (*PTEN*)
Pancreatic neuroendocrine tumors	Multiple endocrine neoplasia type 1 (*MEN1*); von Hippel-Lindau (*VHL*)
Renal papillary type I carcinoma	Hereditary papillary renal cancer syndrome (*MET*)
Renal papillary type II, collecting duct, tubulopapillary carcinomas	Hereditary leiomyomatosis and renal cell carcinoma syndrome (*FH*)
Renal clear cell carcinoma	von Hippel-Lindau (*VHL*)
Renal oncocytoma	Birt-Hogg-Dube syndrome (*FLCN*); tuberous sclerosis complex (*TSC1, TSC2*)
Renal angiomyolipoma	Tuberous sclerosis complex (*TSC1, TSC2*)
Renal chromophobe	Birt-Hogg-Dube syndrome (*FLCN*)
Sertoli cell tumors of the testes	Peutz-Jeghers syndrome (*STK11*)
Medullary thyroid cancer	Multiple endocrine neoplasia type 2 (*RET*)
Cribriform-morular variant of papillary thyroid carcinoma	Familial adenomatous polyposis (*APC*)
Follicular thyroid cancer	Cowden syndrome (*PTEN*)
Medulloblastoma	Turcot syndrome variant of familial adenomatous polyposis (*APC*); Nevoid basal carcinoma syndrome (Gorlin) (*PTCH1*)
Glioblastoma	Turcot syndrome variant of Lynch syndrome (*MLH1, MSH2*, MSH6, *PMS2, EPCAM*); Li-Fraumeni syndrome (*TP53*)
Basal cell carcinoma	Xeroderma pigmentosum (multiple xeroderma pigmentosum-associated genes); Nevoid basal carcinoma syndrome (Gorlin) (*PTCH1*)
Sebaceous adenoma, sebaceous carcinoma, keratoacanthoma	Muir-Torre syndrome variant of Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
Fibrofolliculomas	Birt-Hogg-Dube syndrome (*FLCN*)
Facial trichilemmomas	Cowden syndrome (*PTEN*)

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Table 6-4 **Genes With Autosomal Recessive Disease Risk**

Gene	Syndrome
ATM	Ataxia telangiectasia
BLM	Bloom syndrome
BRCA1, BRCA2, BRIP1, PALB2, RAD51C	Fanconi anemia
FH	Fumarate hydratase deficiency
MLH1, MSH2, EPCAM, MSH6, PMS2	Constitutional mismatch repair deficiency syndrome
MUTYH, NTHL1, MSH3, MLH3, MBD4	MUTYH-associated polyposis, etc
NBN	Nijmegen breakage syndrome
WRN	Werner syndrome
DDB2, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, POLH, XPA, XPC	Werner syndrome

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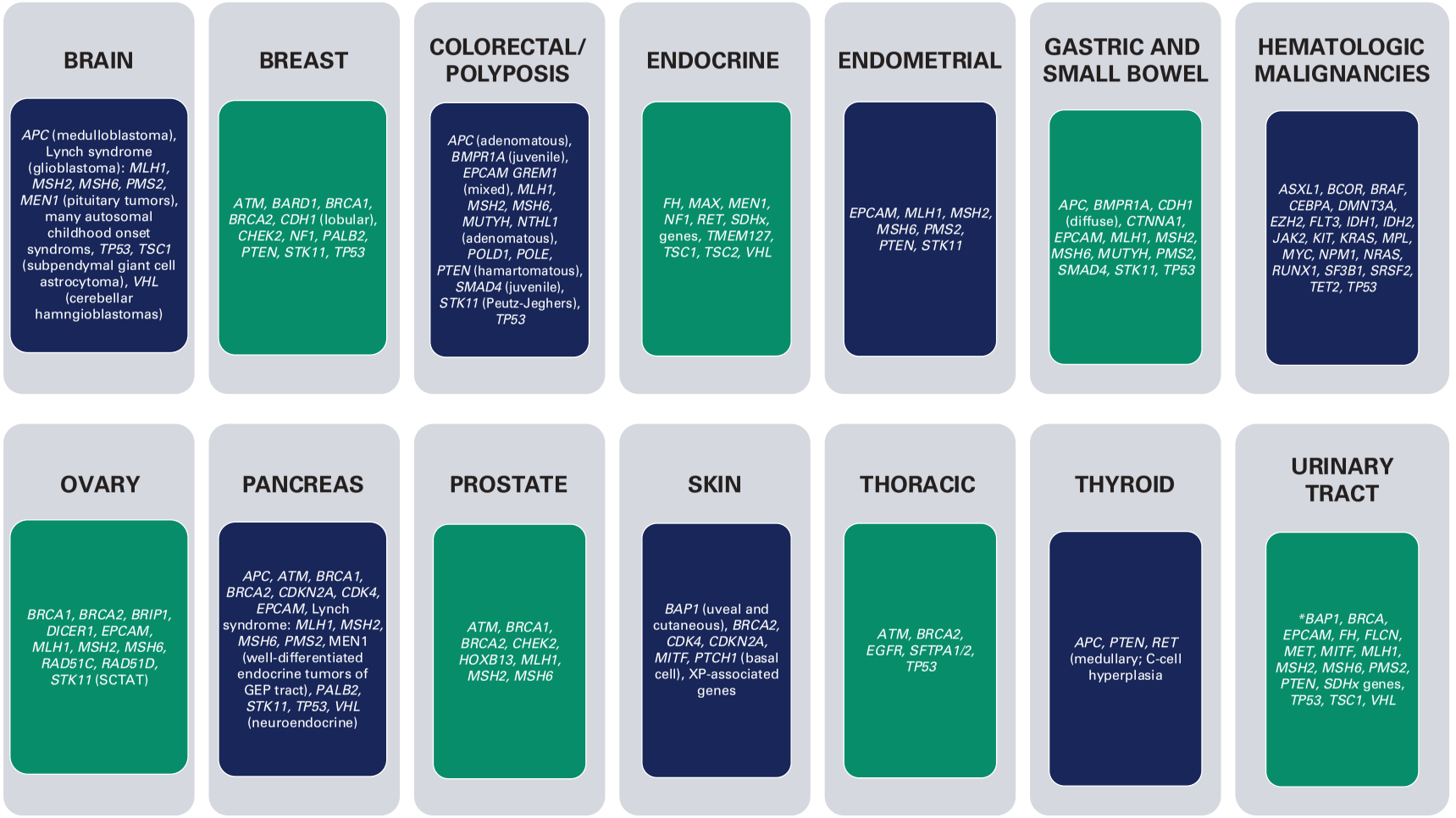
Figure 6-1 Cancer Types and Select Associated Genes



Abbreviations: FH, fumarate hydratase, including type 2 papillary, tubular papillary, and collecting-duct carcinoma; FLCN, folliculin, oncocytoma, chromophobe, and oncocytic hybrid tumor; GEP, gastroenteropancreatic; MET, type 1 papillary; SCTAT, sex cord tumors with annular tubules; TSC1, TSC2, renal cell carcinoma, angiomyolipomas, and oncocytoma; XP, xeroderma pigmentosum.
*Urinary tract gene-associated pathologies. Gene-specific pathologies are listed in Tables 6-1A to D.
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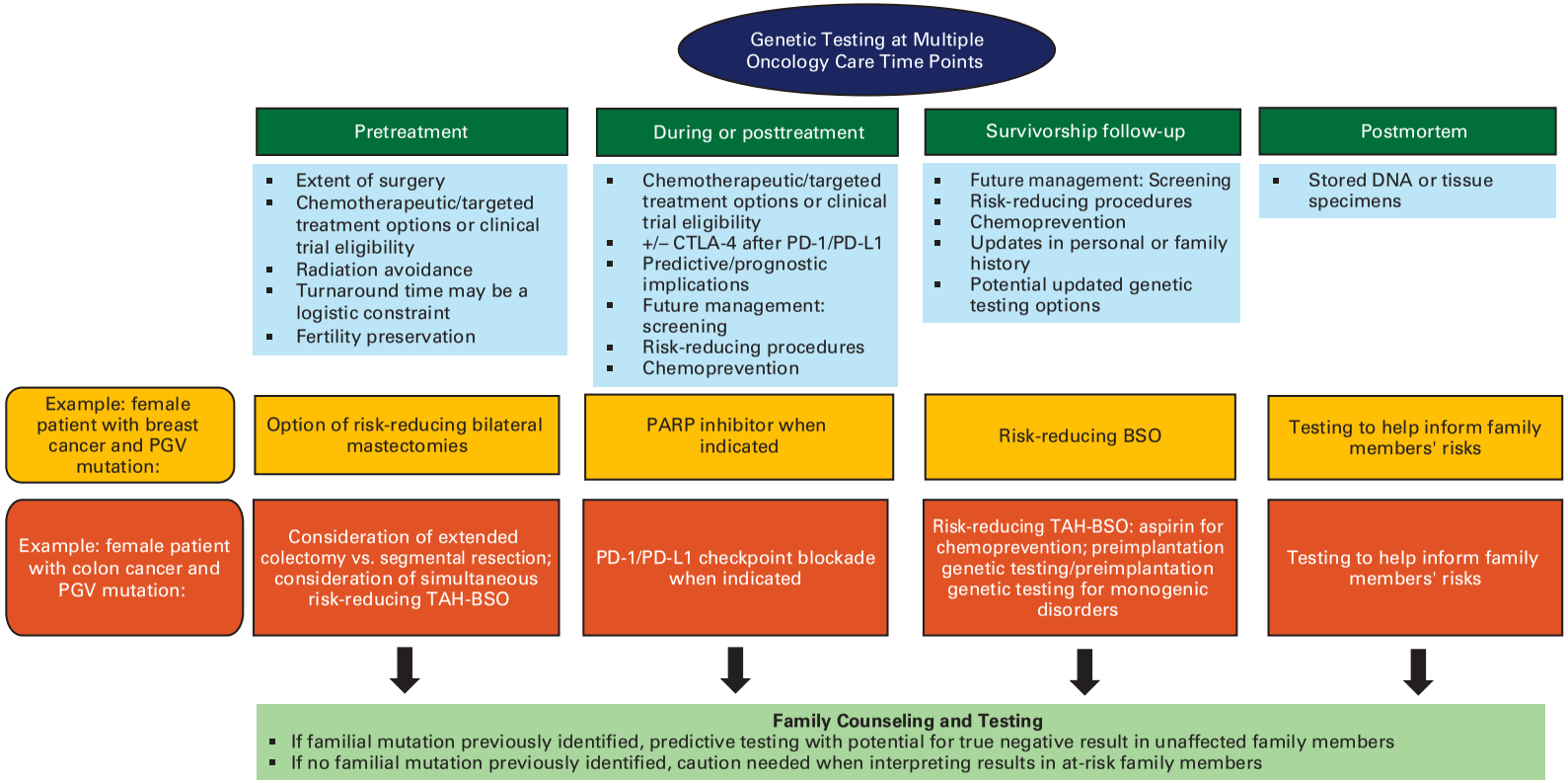
Figure 6-2 Incorporating Genetic Counseling and Testing Into the Care of Patients With Cancer



Abbreviations: BSO, bilateral salpingo-oophorectomy; PARP, poly-ADP ribose polymerase; PD-1/PD-L1, programmed cell death protein 1/programmed death ligand 1; PGV, pathogenic germline variant; TAH, total abdominal hysterectomy.

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CANCER IN THE OLDER ADULT 7

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RECENT UPDATES

- The updated ASCO geriatric oncology guidelines recommend that patients with cancer aged 65 years or older undergo a geriatric assessment; identified impairments should have geriatric assessment–guided management included in their care plan. The Practical Geriatric Assessment is one potential tool to implement geriatric assessments and guide management in clinical practice.
- A geriatric assessment can reduce treatment-related toxicity and patient-reported symptoms as well as can improve clinical outcomes. Eighty-six percent of patients reported at least one symptom of moderate or greater severity before initiating treatment. Patients who received geriatric assessment recommendations had decreased symptomatic toxicities compared with those who did not (usual care plus geriatric assessment without summary or treatment recommendations).[1]
- Older women with high-risk early breast cancer benefit from adjuvant chemotherapy, but treatment is complicated by adverse effects, resulting in dose reductions and delays. The recommended relative dose intensity (RDI) is 85% or higher for curative-intent chemotherapy. Older patients who received low RDI had inferior survival outcomes. Therefore, it is important to preserve dose intensity and identify and intervene on behalf of patients at risk for receiving low RDI.[2]
- The GIANT (EA2186) Trial[3,4] was recently presented, and it incorporated a baseline geriatric and quality of life assessment on treatment outcomes in patients with treatment-naive metastatic pancreatic cancer. In this study, patients who were considered vulnerable underwent a de-intensified treatment regimen.[4,5] There was no difference in the two chemotherapy treatment arms. Baseline geriatric vulnerabilities and quality-of-life scores correlated with overall survival (OS) and were not captured by physician-rated Eastern Cooperative Oncology Group performance status. The strongest correlation was seen with baseline nutritional status, function, depression scores, and all quality-of-life measures.
- A study evaluating more than 17,000 patients in the ACCENT/IDEA database was reported, focusing on comparing the benefits of oxaliplatin-fluoropyrimidine chemotherapy as adjuvant therapy in stage III colon cancer in patients who were 70 years old or older to the younger patients. In the 4,340 patients who were at least 70 years old and were enrolled on these clinical trials, the time to disease recurrence was similar to that in the younger patients, suggesting a similar anticancer benefit. However, the older patients had more frequent severe diarrhea, neutropenia, and mucositis, discontinued treatment earlier, and had a shorter OS, disease-free survival, and survival after recurrence. Taken together, these results suggest that fit, older patients can benefit from adjuvant oxaliplatin-based chemotherapy, but decisions should be based on individual discussions of risk and benefit.[3]
- In women aged 70 years and older with a higher risk for breast cancer recurrence based on a Genomic Grade Index, the ASTER70s randomized phase III study demonstrated that endocrine adjuvant therapy was non-inferior to 12 weeks of chemotherapy, followed by endocrine therapy, in terms of survival, with a median follow-up of 7.8 years. As anticipated, there were more severe toxicities in patients receiving chemotherapy.[6]
- SWOG 1826 demonstrated nivolumab-AVD was superior to brentuximab vedotin-AVD in patients older than 60 with advanced stage classical Hodgkin lymphoma. Two-year OS was 96% in N-AVD versus 85% in BV-AVD. In addition, the regimen was better tolerated.[7]

OVERVIEW

Geriatric oncology strives to improve care delivery and outcomes for older adults with cancer. Consensus is lacking on the specific chronological age that defines the older adult patient population with cancer. In developed countries, age 65 years or older

is generally accepted; in the United States, Medicare insurance eligibility is used as the common benchmark. The International Society of Geriatric Oncology (SIOG) defines a geriatric oncology patient as an adult aged 70 years or older with cancer. This cutoff can vary from 55 to 80 years and is highly dependent on social determinants of health and environmental exposures. Some refer to this as the biological age.[8] Accelerated aging can occur early, especially in patients with cancer, depending on the treatment modality used (eg, bone marrow transplantation can cause premature aging). Overall, cancer is a major health concern for older adults and is the second leading cause of death in the United States after heart disease.[9]

QUICK FACTS

- Age is the single most important risk factor for developing cancer.
- Twenty percent of the US population will be older than 65 years (70 million people) by 2030.
- Age 65 years or older: 60% of all newly diagnosed cancers and 70% of all cancer-related deaths.[10]
- Median age at cancer diagnosis: 68 to 74 years.
- Median range of age at death: 70 to 79 years.[9,10]
- Competing comorbidities can result in risk of polypharmacy and drug interaction.
- Decreased physiological reserve compromises the ability to tolerate cancer treatments.
- Health care providers' reluctance to provide cancer treatment to older adults results in age bias.
- Barriers to accessing care include transportation, fixed income, insufficient supplemental insurance coverage, and lack of access to technology.[9,11]

Communication between health care providers and older patients may be hampered by hearing, vision, cognition deficits and access to modern technology.[12] In addition, age-related concerns of patients and caregivers (eg, falls, cognitive impairment, and polypharmacy) are not generally accessed and addressed by oncology teams despite influencing unfavorable outcomes for older adults with cancer.[9-11] The older adult with cancer often has an older caregiver, and cancer diagnosis often affects the health-related quality of life of both individuals.[13-15]

These challenges have contributed to the definition of geriatric oncology as a true subspecialty, leading to the development of National Comprehensive Cancer Network (NCCN), SIOG, and ASCO guidelines that address special considerations for older adults with cancer.[16,17] Given the increasing number of older adults with cancer and the limited workforce of geriatricians available for co-management, it is imperative that oncology teams know how to integrate geriatric principles into oncology care for older adults with cancer and their caregivers.[18]

PRESENTING CASE STUDY

A 73-year-old woman with a medical history notable for hypertension, hyperlipidemia, hypothyroidism, and Barrett esophagus is diagnosed with locally advanced pancreatic adenocarcinoma encasing the celiac artery and extending along the hepatic artery. Staging scans do not identify evidence of distant metastases. Celiac plexus neurolysis is performed, resulting in good control of abdominal and back pain in combination with fentanyl patch and oxycodone. Next-generation sequencing does not show targetable mutations that would impact therapeutic recommendations.

Given this patient's age and locally advanced pancreatic cancer, what key factors would you consider when deciding on the initial treatment approach?

Comprehensive geriatric assessments (CGAs) are recommended for patients with cancer who are 65 years or older as part of systemic therapy evaluation. The geriatric assessment–driven intervention study demonstrated significantly decreased grade 3 and higher toxicity and greater chemotherapy completion rates in patients who underwent CGA before chemotherapy initiation compared with patients managed in the standard manner. Other randomized studies and meta-analyses have confirmed these findings.[19,20]

CGA confirms that the patient is frail, with a fatigue, resistance, ambulation, illness, and the loss of weight scale score of 5. Her Charlson comorbidity index is 5.

The Cancer and Aging Research Group (CARG) chemotoxicity calculator indicates a high risk of grade 3 to 5 toxicity:

- Standard-dose polychemotherapy, 92%; single-agent chemotherapy, 86%
- Reduced-dose polychemotherapy, 86%, single-agent chemotherapy, 78%

What treatment approach would you recommend, and how would you balance efficacy with minimizing harm?

The patient begins full-dose, single-agent gemcitabine, which she tolerates well, with essentially no toxicity aside from mild fatigue. The disease stabilized for 6 months, but the patient experiences mounting cytopenias. She is then treated with radiation and concurrent capecitabine, which controls the disease for 15 months without therapy before evidence of local progression.

This patient has unresectable disease; therefore, the goals of therapy are non-curative in nature. Without treatment, locally advanced pancreatic cancer induces suffering. However, the CGA and CARG chemotoxicity calculator suggest that polychemotherapy is likely to cause significant toxicity. Therapy in this case was personalized to balance these concerns. The GIANT trial (ECOG-ACRIN EA2186) revealed a high degree of frailty in this patient population. Eastern Cooperative Oncology Group performance status was not as strongly correlated with survival as baseline quality-of-life scores. The strongest correlations with survival were related to baseline nutritional status, depression, and functional status.

RELATIONSHIP BETWEEN AGING AND CANCER

The molecular, cellular, and physiological changes that are part of the aging process also predispose individuals to cancer. The landmark report by Hanahan and Weinberg[21] (refer to Chapter 2: Molecular Biology) delineates the hallmarks of cancer; however, a majority of these hallmarks represent common denominators of aging as well.[22] Carcinogenesis is a multistep process that includes initiation, followed by promotion and progression to disease. The various theories that link aging and cancer include the following[23-27]:

- Longer duration of carcinogenic exposure: Aging allows the time necessary for the accumulation of cellular events to result in neoplasms.
- Altered susceptibility of aging cells to carcinogens: Aging increases the susceptibility of normal cells and tissue to transformation into cancerous cells.
- Decreased ability to repair DNA: Aging cells are more likely to have an impaired ability to repair DNA.
- Oncogene activation or amplification or decrease in tumor-suppressor gene activity: These processes may be altered in an older individual, resulting in increased action, promotion, or differential clonal evolution.
- Telomere shortening and genetic instability: The functions of telomeres and telomerase are intimately involved in senescence and neoplastic processes. Telomeres shorten progressively as cells age, beginning at age 30 years, with a loss of approximately 1% per year. Because the major function of telomeres is to protect the stability of the more internal coding sequences (ie, allowing cells to divide without losing genes), this loss may lead to genetic instability, which may promote mutations in oncogenic or tumor-suppressor gene sequences. Telomere length is a predictor of death in people aged 60 years or older.[26]
- Immune system changes with age; this has major implications for the efficacy of cancer treatments (Table 7-1).
- Immunosenescence: This is a combination of changes within the immune system that occur with age that is characterized by changes in the bone marrow, the relative abundance of specific immune cell subsets, and circulating cytokines, resulting in a remodeling of the adaptive immune system.[27]
- Cellular senescence: There is an accumulation of changes in individual cells that leads to an irreversible cell-cycle arrest. Senescent cells can compromise tissue renewal capacity and secrete multiple factors (eg, interleukin-1 [IL-1] and matrix metalloproteinase 3) that alter tissue homeostasis and create a tissue environment that synergizes with mutation accumulation to facilitate malignant transformation.

Table 7-1 Age-Related Immune Phenotypes With Potential to Influence Immunotherapeutic Efficacy

Immunosenescence	Associated Phenotypes	Potential Consequences
Thymus	↑ Adiposity and epithelial cell attrition	↓ Naive T-cell pools with potential to recognize novel tumor antigens
	↓ Reduced IL-7 and mature T-cell production	
Bone marrow	↑ Myeloid: lymphoid progenitors	↓ Potential for adaptive immune responses to recognize novel tumor antigens
	↓ B-cell maturation	

Immunosenescence	Associated Phenotypes	Potential Consequences
T cells	↑ Memory: naive cells	↓ Diminished recognition and responses to novel tumor antigens
	↑ Immunosuppressive Tregs	↑ Antigen recall because of a larger memory pool
	↓ T-cell repertoire (two to fivefold)	
B cells	↑ Memory: Precursor cells	↓ Antibody production and diversity may limit response to novel tumor antigens
	↑ Proinflammatory B cells ($TNF\alpha^+$)	↑ Inflammation and autoantibody production may increase the probability of irAEs
	↓ Antibody production, diversity, and avidity	
Innate immunity	↓ Chemotaxis, phagocytosis of debris	↓ Activation and reduced diversity of tumor-specific $CD8^+$ cytotoxic T cells
	↓ Antigen presentation	
Inflammaging	↑ Chronic low-level inflammation	↑ Tumor mutagenesis by inflammatory mediators
	↑ Serum IL-6, IL-8, IL-18, TNFα, CRP	↓ Cytokine production in response to tumor antigens
Cellular senescence	↓ Telomere length and proliferation	↓ Expansion of responding B and T cells
	↑ Expression of cell-cycle inhibitors ($p16^{INK4a}$ and $p21^{CIP/KIP}$)	↓ Expansion of responding B and T cells
	↑ Proinflammatory cytokine and matrix remodeling factors	↑ Tumor metastasis, expansion, or recruitment of repressive immune cells (Tregs and MDSCs)

Abbreviations: CRP, C-reactive protein; IL, interleukin; irAE, immune-related adverse event; MDSC, myeloid-derived suppressor cell; TNF, tumor necrosis factor; Treg, regulatory T cell; ↓, decreased; ↑, increased.

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AGE-RELATED PHYSIOLOGICAL CHANGES

A decline in physiological functioning begins at the age of 30 years and continues at a rate of approximately 1% per year. The aging process occurs at a different rate in each person, as does the loss of individual organ reserve.[28,29] Changes of aging include but are not limited to changes in bone marrow, liver, and kidney function; thinning skin; increased bruising; decreased cardiac reserve; reduction in cardiac myocytes; increased vascular stiffness; and decreased gastrointestinal motility and absorption.[30,31]

KEY POINTS

- Physiological changes of aging can begin at age 30 years and vary by organ system and individual.
- Organ system changes must be considered when deciding on both the cancer treatment modality (surgery, radiation therapy, systemic treatment) and the type and dose of medications selected for both the cancer treatment and comorbidities.
- Multiple organ systems experience changes. With aging, many people experience changes in their kidney and liver function, which can result in decreased drug clearance and lead to increased cancer treatment–related adverse events.
- Bone marrow reserve is compromised in older adults, leading to a greater decline in blood cell counts compared with those of younger patients, which can complicate surgery, radiation therapy, and/or systemic cancer treatments.

TREATMENT APPROACHES

SURGERY

Surgery is a frequently used treatment modality and can offer the potential for a curative approach for older adults with cancer. Concomitant comorbidities, impaired wound healing, and decreased physiological reserve can contribute to prolonged hospital stays and rehabilitation after surgical and other procedures. Postoperative delirium is of particular concern and can occur in up to 50% of surgical patients with cancer, a majority of whom are older adults. Functional status is an important consideration when assessing surgical risk. Patients with frailty have poor postoperative outcomes and decreased long-term survival, especially those with early-stage cancers.[32] With regard to wound healing, inflammatory and proliferative responses are decreased, remodeling occurs to a lesser degree, and collagen formation is qualitatively different from that in younger individuals.[33,34] The normal repair process initiated by inflammation requires intact sensory nerves that stimulate increased blood flow and

growth-factor production. Loss of sensory neurons and comorbidities such as diabetes and vascular disease can contribute to delayed wound healing.

A review of patients undergoing surgery for rectal cancer, which included 36,315 patients, found that age above 65 years was associated with a statistically significant increase in both anastomotic leak and postoperative death. The American Geriatrics Society Task Force[35] and the American College of Surgeons provide general guidelines for older adults undergoing surgery, which are also applicable to older patients with cancer who are undergoing surgery.[36,37]

A growing body of evidence also supports the use of geriatric and frailty[38] assessment measures collected preoperatively to predict surgery complications and plan for possible supportive care interventions in advance.[39-42] Refer to the "Geriatric Assessment and Screening Tools" section for more details.

RADIATION THERAPY

Radiation therapy may be used both as a primary modality with either curative or palliative intent and as an effective adjunct to surgery and/or chemotherapy. Radiation therapy and/or locoregional treatment modalities such as ablation/chemoembolization represent particularly attractive treatment options for older adults because they provide noninvasive local therapy with potentially limited systemic adverse effects. The risk of adverse effects with radiation therapy is highly dependent on the location of the tumor being treated and the radiation exposure of proximal structures.

Specialized approaches may be used in the older adult population to mitigate the adverse effects of treatment,[43] to improve adherence, and to minimize daily transportation requirements. For example, a stereotactic radiosurgery (SRS) approach, such as stereotactic body radiation therapy (SBRT), has been found to have excellent local control for patients with early-stage non-small-cell lung cancer and localized prostate cancer.[44,45] For patients with brain metastases, SRS is associated with fewer fractions and lesser toxicity compared with whole brain radiotherapy (WBRT).[46] Therefore, for older adults, especially those who are frail or prefrail, SBRT and SRS are options that may limit the associated morbidity and mortality risk of anesthesia and surgery or WBRT, respectively. Hypofractionation is also a relevant treatment option for older adults who may lack the physical reserve needed to attend daily treatment sessions for several weeks. By shortening the required number of radiation therapy treatment visits, the use of hypofractionation can substantially improve older adults' compliance with and tolerance of treatment.[47]

Radiation therapy is an important treatment modality in older adults with cancer. Radiation-related toxicity and adverse effects depend on the type and dose of radiation used and the location of cancer. Radiation therapy can pose significant procedural, travel, and financial toxicity. In one trial, frail patients were more likely to receive treatment other than standard of care, and 28% of the time a comprehensive geriatric assessment led to modifications in the treatment plan.[48] A prospective study of 314 patients older than 65 years who received definitive prostate radiotherapy were found to have higher grade radiation toxicity if the comprehensive geriatric examination identified comorbidities.[49] Therefore, radiation oncologists have an opportunity to advance geriatric oncology by incorporating geriatric and frailty assessments to limit toxicities and improve quality of life.

SYSTEMIC THERAPY

Older adults are consistently underrepresented in clinical trials; therefore, many of the treatment data for this population are extrapolated from studies in predominantly younger, healthier patients.[50,51] The SIOG and European Organization for Research and Treatment of Cancer task force have put forth suggestions for clinical trial design and endpoints in geriatric oncology research, suggesting that oncology trials be conducted without an upper age limit, include quality of life measures, and report decreases in cancer-related symptoms.[52]

Age-related physiological changes, including decreases in renal and hepatic function and increased sensitivity to neurotoxicity, lead to unique considerations in treating older patients with cancer. In addition, polypharmacy related to underlying medical conditions may contribute to chemotherapy-related toxicity.[53] For example, an older adult treated for hypertension with three antihypertensive medications becomes hypotensive and dizzy while receiving chemotherapy because of decreased oral intake, resulting in orthostatic hypotension. The patient then falls and experiences a hip fracture. This example of a complex geriatric oncology case with a poor outcome and increased morbidity risk will become increasingly common if we are unable to recognize high-risk situations for older adults undergoing cancer treatment.

Chemotherapy

The ASCO guideline entitled "Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology" provides practical assessment and treatment best practices for older adults with cancer who are receiving chemotherapy.[16] The SIOG task force has also published guidelines for dose modification of chemotherapy agents for older patients with cancer.

Important considerations to consider when prescribing chemotherapy in older adults:

- Oral agent bioavailability may be compromised as a result of alterations in motility and absorption and conversion into active drug components.

- Interactions with other commonly prescribed medications among older adults, such as H2 blockers, antacids, and proton pump inhibitors, should be considered to ensure safe and effective use of oral chemotherapy agents.
- Higher likelihood of interaction with chemotherapy agents in patients with polypharmacy.[53]
- Increased likelihood of chemotherapy toxicity in patients with decreased glomerular filtration rate.
- Older patients with decreased albumin levels may be further predisposed to ifosfamide neurotoxicity in the setting of impaired renal function. Concomitant administration of drugs such as nonsteroidal anti-inflammatory drugs may further compromise renal function. Because lean body mass decreases in older adults, it is important to adjust the dose according to the creatinine clearance rate rather than the creatinine level.
- Acute toxicities, such as nausea and vomiting, occur less frequently in older adults; however, the lack of functional reserve can readily lead to dehydration, orthostatic hypotension, and renal insufficiency.
- Neurotoxicity related to taxanes, platinum agents, vinca alkaloids, high-dose cytarabine; and bortezomib; cardiotoxicity resulting from anthracyclines; and mucositis resulting from fluorouracil are all more common and severe in older patients.[54,55]
- Whether the risk of myelotoxicity increases with age remains a controversial issue, but studies indicate a longer duration of neutropenia in older patients.[53]

Older adults receiving chemotherapy are at risk for increased toxicity, resulting in dose reductions and treatment delays, which increase the likelihood of disease recurrence and death. The recent HOPE study was a prospective multicenter study of 322 patients, age 65 years or older, with early-stage breast cancer who were treated with current standard neoadjuvant/adjuvant chemotherapy regimens.[2] The investigators found that one in five women received low relative dose intensity (RDI) of the chemotherapy agents. Older women with low RDI had higher mortality than women who received at least 85% RDI. This study highlights the importance of identifying patients who are at risk for increased toxicity from chemotherapy. A pretreatment geriatric assessment or geriatric oncology screening tool is useful to predict the risk of toxicity in older patients (please see the "Geriatric Assessment and Screening Tools" section). In a randomized trial of vulnerable (Geriatric-8 [G8] score of 14) older adults receiving chemotherapy for colorectal cancer, geriatric assessment–guided interventions were associated with higher chemotherapy completion rates and improved quality of life and mobility.[56,57]

A recent meta-analysis suggested that a "start slow, go slow" approach to patients who are at risk of excess toxicity may reduce toxicity of treatments without affecting survival in patients with solid tumors.[58]

Targeted Agents

The advances in understanding tumor biology and mutational drivers through next-generation sequencing has allowed the development of more targeted therapy options, including tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin inhibitors, human epidermal growth factor receptor 2–targeted drugs, *BRAF* mutation–targeted drugs, epidermal growth factor receptor inhibitors, and vascular endothelial growth factor inhibitors. These therapy options have been increasingly used in patients with cancer in the last decade, particularly in the treatment of advanced solid tumors, such as lung cancer, breast cancer, and melanoma.[59] As in chemotherapy trials, data for older patients have been extrapolated from trials of predominantly younger patients. In addition, many targeted agents are metabolized by the cytochrome P450 system, increasing the risk of significant drug interactions. Many targeted therapies are oral medications requiring high adherence to dosing to ensure bioavailability and clinical efficacy. Consistent oral dosing requires appropriate functional ability, cognitive status, or direct support to perform. In terms of response to targeted therapies, many studies have shown that older adults benefit from the use of these drugs as much as their younger counterparts.[60] For example, a pooled analysis of trials testing the addition of a CDK4/6 inhibitor to antiestrogen therapy in advanced breast cancer showed similar efficacy among older (age older than 75 years) versus younger participants although with higher rates of toxicity. Older adults required more frequent dose reduction, but without evidence of compromise in benefit.[61] Cardiopulmonary toxicity is also a concern for older adults receiving TKIs such as osimertinib. Older adults can also be dramatically affected by extremity edema associated with new TKIs, such as capmatinib or tepotinib, for advanced non-small-cell lung cancer.

Immuno-Oncological Agents

Immune checkpoint inhibitors (ICIs), which affect immune function, are a new class of immuno-oncological agents used in the treatment of a variety of malignancies.[62] Expression of immune checkpoints on T cells increases with age, making immune checkpoint blockade a promising option for older patients with cancer. However, the effect of both inflammaging and cellular senescence on these agents is not clear. The term age-related immune dysfunction may be used to describe immune-related changes of aging and their potential interaction with immuno-oncological agents. Use in older patients is enhanced by a relatively low-toxicity profile compared with conventional chemotherapy. However, management of immunotherapy toxicity may be more complicated in older patients because of medical comorbidities.[62] In a meta-analysis of nine randomized clinical trials using ICIs comparing the efficacy in younger versus older patients, the authors showed a significant benefit in terms of overall survival (OS)

and progression-free survival in both groups. A recent observational study evaluating patients with advanced-stage lung cancer or melanoma starting single-agent checkpoint inhibitor therapy also showed no difference in the incidence of immune-related adverse events (irAEs) by age (age older than 70 vs. younger than 70 years). The G8 screening tool identified older adults at a higher risk of hospitalization and mortality.[63] The consequences of irAEs may differ by age, as suggested by a retrospective analysis, which showed a survival benefit for younger patients who experienced irAEs that was not observed among older adults with irAEs.[64] ASCO, in collaboration with the NCCN, has issued a clinical practice guideline on the management of irAEs in patients treated with ICIs that can be applied in the older adult population.[65] However, the impact and management of irAEs in the older adult population remain to be fully elucidated.

The challenge with irAEs is that steroids, either intravenous or oral, are often the first line of treatment. This can exacerbate many chronic conditions that older adults experience, such as diabetes, hypertension, and/or lower-extremity edema. It can also worsen the quality of sleep. Older adults may also experience delirium, increased falls, and/or dehydration with high-dose steroids. Steroid-sparing options, particularly for older adults, are urgently needed to treat irAEs, because ICIs are now used in multiple cancer types.

KEY POINTS

- In older patients, comorbidities, impaired wound healing, and decreased physiological reserve contribute to prolonged hospital stays and rehabilitation after surgery.
- Delivery, duration, and dosage of radiation therapy must be carefully planned on the basis of organ function, comorbidities, and geriatric evaluation because adverse effects may be more pronounced in older patients.
- Many chemotherapy toxicities are more common and more severe in older patients. Pretreatment geriatric assessment is useful for predicting the risk of chemotherapy toxicity.
- In older patients, comorbidities and polypharmacy may affect response to cancer therapy, and geriatric assessment is critical in the selection of treatment and dosing.
- Immuno-oncological drugs appear to be safe and less toxic compared with chemotherapy for use in older adults. However, irAEs and the treatment of irAEs can cause significant morbidity and mortality for older adults.

FRAILTY

Frailty characterizes "the group of patients that presents the most complex and challenging problems to the physician and all health care professionals"[66] because of the higher susceptibility to adverse outcomes, such as mortality and institutionalization. Currently, two main models of frailty exist: the phenotype model and the cumulative deficit model.[66]

FRAILTY PHENOTYPE MODEL

The phenotype model is based on a landmark study of 5,210 patients aged 65 years or older within the large prospective Cardiovascular Health Study.[67] A frailty phenotype was established with the following five variables: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. Patients with three or more of the five factors were considered to be frail, those with one or two factors to be prefrail, and those with no factors to be robust (or not frail). At 3- and 5-year follow-up, those categorized as frail were reported to have worse disability and worse mortality than the other two groups. The mortality rate at 7 years was 12%, 23%, and 43% for the not frail, prefrail, and frail groups, respectively. Phenotypic frailty has been associated with chemotherapy toxicity among older adults with cancer.[68]

CUMULATIVE DEFICIT MODEL

This clinical frailty scale was developed as part of the Canadian Study on Health and Aging, which was a large 5-year prospective cohort study of 10,263 patients designed to investigate the epidemiology and burdens of dementia among older adults in Canada (mean age, 82 years). Frailty was defined using 92 baseline variables of symptoms, signs, abnormal laboratory values, disease states, and disabilities (collectively referred to as deficits). The frailty index was a calculation of the presence or absence of each variable as a proportion of the total (eg, 20 of 92 deficits present gives a frailty index of 20/92 = 0.22). Frailty was defined as the cumulative effect of individual deficits, or "the more likely they are to be frail." Several studies using the deficit accumulation method have demonstrated that a comprehensive geriatric assessment–based deficit accumulation frailty index applied in patients with cancer is predictive of outcomes such as chemotherapy toxicity, hospitalization, mortality, and health-related quality of life.[69-71]

More recently, with the COVID-19 pandemic, Theou et al[72] aimed to reduce personal bias in the frailty classification. They developed a classification tree to improve the reliability of the clinical frailty scale in a variety of health care settings, both inpatient and outpatient. Although not specifically validated in patients with cancer, it is a useful tool for frailty assessment and prognostication.

GERIATRIC ASSESSMENT AND SCREENING TOOLS

Aging is a heterogeneous process that is affected by more than chronologic age.[73] Traditionally, in oncology, Eastern Cooperative Oncology Group (ECOG) performance status and Karnofsky performance status have been used to quantify patient well-being and determine whether patients can tolerate chemotherapy. However, these measures do not capture age-related domains such as risk for falls and cognitive impairment known to affect morbidity and mortality in older patients with cancer. Geriatric assessment is designed to screen and capture the functional age of older adults to identify those with organ reserve limitations, leading to a diminished life expectancy and/or increased risk of hospitalization and functional decline.[16] Geriatric assessment is multidimensional in that it uses validated, patient-reported, and administered measures to capture aging-related domains. Geriatric assessment includes high-priority aging-related domains known to be associated with morbidity and mortality[19,73] in older adults with cancer: functional status; comorbidities; polypharmacy; psychological, cognitive, and nutritional status; socioeconomic issues; and geriatric syndromes. Studies have demonstrated that geriatric assessment can identify older adults with cancer at increased risk for adverse outcomes and increased mortality across varied disease and treatment settings. Cohort studies evaluating older adults starting new chemotherapy regimens inclusive of varied cancer types have shown an association between prechemotherapy geriatric assessment measures and OS as well as early death (within 6 months of treatment). Two large randomized controlled trials demonstrated that prechemotherapy geriatric assessment with guided management recommendations lowers toxicity in older patients receiving chemotherapy for solid tumors.[20,74] This has led to the updated guideline recommendation that all patients with cancer older than 65 years with geriatric assessment–identified impairments should have a geriatric assessment–guided management plan (GAM). A GAM includes using geriatric assessment results to (1) inform cancer treatment decision-making and (2) address impairments through appropriate interventions, counseling, and referrals.[73] The updated ASCO guideline provides a practical approach to the assessment and management of vulnerabilities in older patients with cancer; the expert guideline panel recommends the Practical Geriatric Assessment (PGA) as one potential tool to facilitate the implementation of geriatric assessment and geriatric assessment–guided management in clinical practice (Fig. 7-1).[16,75]

The PGA is a composite tool that was developed to be efficient and therefore effective in various settings. The PGA evaluates seven key domains, including Physical Performance; Functional Status with Independent Activities of Daily Living; Cognitive Function; Comorbidities; Nutritional Status/weight loss; Social Support; Psychosocial Status. These domains may be assessed with information entered by the patient and/or caregiver before the clinician evaluates the patient. Another potentially important aspect of the PGA is the use of a chemotherapy toxicity tool, such as the Cancer and Aging Research Group (CARG) toxicity tool, which may impact decisions regarding chemotherapy regimen, such as single agent versus multiagent therapy, or dose administered.[16,75]

The use of geriatric assessment in all patients older than 65 years with cancer has been inconsistent. Numerous studies have examined the barriers to geriatric assessment, and they have found that the most cited barriers were the time required, the lack of adequate resources, and the lack of relevant knowledge or training.[76]

To increase the use of geriatric assessments, abbreviated screening instruments have been designed to determine who might benefit from full geriatric assessment. The Geriatric-8 (G8) and the Vulnerable Elders Survey-13 (VES-13) are both quick and validated assessments with high sensitivity that can be incorporated into oncological practice. The ELDERS study that demonstrated that a positive G8 screen (score 14 or less) was associated with higher risk of hospital admission (P = .03) and death (P = .01).[63] Patients with a positive screen were found to have a twofold increased risk of functional decline or death during a 2-year follow-up period.[77] Studies have also found that a positive VES-13 screen is also associated with increased treatment toxicity in older adults with cancer.[78] Once identified as being at higher risk through the initial screen, patients may then be triaged appropriately to receive a comprehensive geriatric assessment, be referred to a geriatrician, or establish care in a multidisciplinary geriatric oncology clinic.

Geriatric screening instruments can help identify patients who are at high risk of adverse outcomes and can be used to identify patients who would most benefit from a full geriatric assessment (ie, one that assesses all aging-related domains to guide decision-making and interventions).

KEY POINTS

- ECOG performance status is not a reliable tool for predicting treatment toxicity or functional decline in older adults with cancer.
- It is important to perform a geriatric screening assessment for new older adult patients with cancer to identify those at high risk of treatment-related adverse effects or functional decline and to provide intervention.
- The G8 and VES-13 are two examples of validated abbreviated geriatric screening assessment with high sensitivity that can be incorporated into everyday oncological practice.

USES OF GERIATRIC PRINCIPLES IN CANCER CARE

Various instruments for geriatric assessment have been used for more than a decade to examine multiple endpoints, including serious toxicity from chemotherapy, early mortality, hospitalization, and functional decline.

Figure 7-1 The Practical Geriatric Assessment

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living.
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PREDICTING CHEMOTHERAPY TOXICITY

There are currently several chemotherapy toxicity tools available to help clinicians obtain specific estimates on the risks of chemotherapy toxicity in older adults. The ASCO guideline recommends the use of one of these chemotherapy toxicity tools for all older adults 65 years or older.[73] Both options are available as online calculators (Table 7-2). The caveat with new accelerated drug releases is the lack of available data for older adult patients.

- CARG chemotherapy toxicity calculator: In a study by the CARG led by Hurria et al,[79,80] geriatric assessment variables, sociodemographic variables, tumor and treatment variables, and laboratory results were incorporated into a model that was predictive for chemotherapy toxicity in 500 older adults. A scoring system was used to risk stratify patients, with the risk score being the percent incidence of grade 3 to 5 toxicity. This identified older adults at low (0-5 points; 30%), intermediate (6-9 points; 52%), or high risk (10-19 points; 83%) of chemotherapy toxicity ($P < .001$).[80]
- CARG breast chemotherapy toxicity calculator: A breast cancer–specific chemotherapy toxicity tool was developed using the same CARG geriatric assessment measures in an observational study of 473 older adults initiating neoadjuvant or adjuvant chemotherapy for stage I to III breast cancer. A scoring system was developed from eight independent predictors of toxicity that identified those at low (0-5 points; 19%), intermediate (6-11 points; 54%), or high risk (≥12 points; 87%) of grade 3 to 5 chemotherapy toxicity.[81]

- Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) chemotherapy toxicity calculator: In another study of 518 older patients with cancer, led by Extermann et al,[82] 24 parameters, including geriatric assessment, were incorporated to create the CRASH score to predict grade 4 hematologic or grade 3 to 4 nonhematologic toxicities. In the CRASH risk categories, patients with low-risk scores had a 7% chance of hematologic and 33% chance of nonhematologic toxicities compared with patients with high-risk scores, with corresponding toxicity risks of 100% and 93%, respectively.

Table 7-2 **Tools Providing Estimates for Chemotherapy Toxicity**

Tool	Items	Study Population	Administration Characteristics	Considerations and Other Evaluation Options
CARG breast cancer toxicity tool: provides estimates for overall risk of grade 3-5 toxicity for older adults receiving adjuvant or neoadjuvant chemotherapy	Eight weighted items (points): • Anthracycline use (1) • Stage II or III (3) • Planned treatment duration >3 months (4) • Abnormal liver function tests (3) • Low hemoglobin <12 g/dL female (3) • Falls in the past 6 months (4) • Limited walking 1 mile (3) • Lack of social support (someone available to give advice in crisis) (3)	Patients aged 65 years or older with stage I-III breast cancer starting neoadjuvant or adjuvant chemotherapy	PRO/administered/ medical record review (<5 minutes); online calculator planned	Only three of eight items required; patient report to be included in history or obtained from GA if conducted
CARG toxicity tool: provides estimates for overall risk of grade 3-5 chemotherapy toxicity	Eleven items: • Previous falls (≥1 vs. none) • Hearing problems (deaf to excellent) • Limitations in walking one block (limited a lot, limited a little, not limited) • Difficulties with taking medications • Interference in social activities by physical health and/or emotional problems (all of the time to none of the time) • Age • Height • Weight • Sex • Cancer type (GI vs. genitourinary vs. other) • Dosage (standard vs. dose reduced), number of chemotherapy agents (monotherapy vs. polytherapy) • Hemoglobin level • Creatinine clearance	Patients aged 65 years or older with solid tumor malignancy or lymphoma starting new chemotherapy regimen (any line)	PRO/administered: 5 minutes; available online: https://www.mycarg.org/?page_id=2405	Can ask GA variables as part of history or include as part of PRO assessment

Tool	Items	Study Population	Administration Characteristics	Considerations and Other Evaluation Options
CRASH tool: provides estimates separately for risk of grade 3 hematologic and grade 3 to 4 nonhematologic toxicity	Assessment of risk of hematologic toxicity includes: • Diastolic blood pressure (>72 mm Hg), IADL score (<26) • LDH concentration (>459 U/L) • Assessment of risk of nonhematologic toxicity includes ECOG PS, MMSE (<30), and MNA (<28); chemotherapy intensity is assessed with MAX2 index	Patients aged 70 years or older with histologically proven cancer starting chemotherapy	PRO/administered: estimated time to completion is on par with full GA (20-30 minutes); available at: https://www.moffitt.org/for-healthcare-professionals/clinical-programs-and-services/senior-adult-oncology-program/senior-adult-oncology-program-tools/	

Abbreviations: CARG, Cancer and Aging Research Group; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; EGOG PS, Eastern Cooperative Oncology Group performance status; GA, geriatric assessment; GI, gastrointestinal; IADL, instrumental activities of daily living; LDH, lactate dehydrogenase; MAX2, an index that allows adjusting the toxicity of different chemotherapy regimens for comparison; MMSE, Mini-Mental State Examination; MNA, Mini Nutritional Assessment; PRO, patient-reported outcome.
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PREDICTING MORTALITY

Life expectancy is of substantial relevance when considering the benefit of cancer treatment in older adults. There exists great variability in life expectancy within older age groups. For many cancer treatments, there is a time lag to benefit in which patients receive a treatment earlier, to reduce their chance of a poor outcome later. For many adults, the time to benefit from some cancer treatments may be beyond their life expectancy.

Providers routinely overestimate prognosis but may also underestimate life expectancy for those older than age 75 years. For example, in the United States, the middle quartile of life expectancy for a woman aged 75 or 80 years is approximately 13 and 10 years, respectively.[83,84] Incorporating informative tools can enable tailored conversations and allow patients to weigh the value of specific cancer-directed therapy. The ASCO guideline on geriatric oncology recommends that clinicians use one of the validated tools (Schonberg or Lee Index) available at ePrognosis[85] to estimate life expectancy without including cancer as a diagnosis to determine whether patients have adequate life expectancy to expect benefits from specific cancer interventions, including chemotherapy. The most common domains included in indices developed to predict mortality in community-dwelling older adults are age, sex, chronic health conditions (eg, diabetes and chronic obstructive pulmonary disease), functional status, health behaviors and lifestyle factors (eg, smoking status and body mass index), and self-reported health.[74,86] The indices have presence of cancer as a relevant variable; indicating no to the question of cancer presence will allow for non-cancer life expectancy to consider competing risks of mortality.[16] An estimate of life expectancy outside of a cancer-specific estimate allows the oncologist to thoughtfully assemble a patient's prognosis and potential to benefit from treatment. Although the unique trajectory of a patient's illness is unknowable, prognostic estimation can support prognostication and informed decision-making.

PREDICTING FUNCTIONAL DECLINE

Many older adults have considered their wishes for when they may be faced with a serious illness or the end of life. Patients' individual goals, independence, and physical, emotional, and spiritual health are priorities. In a landmark study of patients aged 60 years or older who were terminally ill, researchers found that if the outcome was survival but with severe functional impairment or cognitive impairment, 74.4% and 88.8% of participants, respectively, would not choose treatment.[87] Therefore, it is important to weigh the risks and benefits of different types of cancer treatment and how they can contribute to functional decline.

Geriatric assessment items and brief geriatric assessment–based screening tools (G8 and VES-13) are predictive of functional decline among older adults receiving chemotherapy.[88] Hoppe et al[89] showed that depression and basic and instrumental activities of daily living are associated with early functional decline during chemotherapy. Owusu et al[90] demonstrated that the VES-13 can identify older women with breast cancer at risk for functional decline. Patients who experienced functional decline were more likely to have had lower baseline activities of daily living scores than those who did not experience functional decline, have lower instrumental activities of daily living scores, be Black (49% vs. 29%; $P = .02$), and have no more than a high school education.

DECISION-MAKING AND TREATMENT MANAGEMENT

Geriatric assessment can aid in decision-making for cancer treatment because it has been shown that results from geriatric assessment influence cancer treatment decisions 20% to 47% of the time toward less-intensive therapy.[17]

- In a systematic review by Hamaker et al,[19] the initial cancer treatment plan was modified in 39% of patients based on geriatric assessment evaluation. Two-thirds of these modifications resulted in less intensive treatment, likely an attempt to adjust treatment in patients who had geriatric assessment impairments.[91]
- In the ELCAPA01 study, one of the largest studies evaluating how geriatric assessment influences decision-making, geriatricians conducted a geriatric assessment in 375 older patients with cancer to identify factors associated with dose intensification, decrease, or delay of more than 2 weeks.[86] In multivariate analysis, functional status as assessed by activities of daily living score and presence of malnutrition were independently associated with changes in cancer treatment.[16]

The results of a geriatric assessment can also be used to decrease chemotherapy toxicity.

- A large multicenter study in community oncology clinics in the United States evaluated the effect of an algorithm-guided geriatric assessment–guided management intervention on toxicity from chemotherapy.[74] The GAP study[74] (N = 718) showed that, compared with usual care, providing a geriatric assessment summary and intervention recommendations to oncologists reduced the proportion of patients who experienced grade 3 to 5 toxicity (51% vs. 71%). The relative risk of grade 3 to 5 toxicity for intervention versus usual care was 0.74 (95% CI, 0.64-0.86; *P* = .0001), mostly because of nonhematologic toxicities (relative risk, 0.72; 95% CI, 0.52-0.99; *P* = .045), without compromising OS (72% vs. 75% at 6 months; *P* = .38).[74] A possible mechanism for survival preservation was that geriatric assessment influenced treatment dosing at cycle 1, with more patients in the intervention arm having reduced-intensity regimens but later having fewer dose modifications. This hypothesis is supported by an analysis demonstrating superior survival with early palliative care in non–small cell lung cancer (NSCLC), likely also driven by more use of first line therapy and less use of chemotherapy at the end of life (Temel, NEJM 2010).
- A second study, geriatric assessment-driven intervention (GAIN),[20] which enrolled 613 participants demonstrated that a geriatric assessment–guided management intervention also reduced toxicity from chemotherapy.[20] In this study, the investigators reported a 10.1% reduction in the incidence of grade 3 to 5 toxicity (95% CI, −1.5% to 18.2%; *P* = .02) in the interventional arm compared with patients receiving standard care (50.5% vs. 60.6%). In addition, researchers reported more patients completed advance directives, a secondary endpoint, in the interventional arm compared with those receiving standard care (28.4% vs. 13.3%; *P* < .001; Table 7-3).

Table 7-3 Clinical Trials of Geriatric Assessment

Reference	No. of Pts.	Malignancy	Improved Survival Outcomes?	Comment
Lund et al[56] GERICO	142	Colorectal	NR	Higher rates of chemotherapy completion without delay or reduction
Soo et al[92] INTEGERATE	154	Various	NR	Reduced hospital admission, decreased early discontinuation of chemotherapy due to toxicity
Dumontier et al[93]	160	Hematologic malignancies	No	More likely to have documented goals of care discussions
Corre et al[94] ESOGIA	494	Non-small-cell lung cancer	No	Decreased toxicities (all grades), and fewer toxicity related failures
Bergerot et al[95] GAIN-S	56	Various	No	Improved health-related quality of life

Abbreviation: NR, not reported.

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- A geriatric assessment can improve patient- and caregiver-centered outcomes.
- In a large phase 3 study, community oncology practices were randomly assigned to a geriatric assessment model of care versus usual care. As the practices enrolled in the intervention, oncologists received geriatric assessment information and targeted recommendations for aging-related impairments for patients enrolled in the study. The participating patients were aged 70 years or older, had at least one geriatric assessment domain impairment, and were receiving cancer treatment. In the intervention arm, substantially more aging-related concerns were discussed, leading to greater caregiver satisfaction and increased conversations about aging-related concerns.[12]

KEY POINTS

- Neither ECOG performance status nor Karnofsky performance status alone provides an accurate measure of the functional status of an older patient with cancer.
- Older adults highly value preserving functional independence and cognition in addition to survival. A geriatric assessment can be used to predict survival and risk of chemotherapy toxicity in older adults with cancer.
- A geriatric assessment can be used to guide treatment decision-making and interventions for older patients with cancer.
- Several randomized trials have demonstrated the benefit of geriatric assessment in decreasing chemotherapy toxicity for older adults with cancer.
- A geriatric assessment can assist in defining physiological reserve. The 2018 ASCO geriatric oncology guideline suggests that oncologists assess functional status, physical performance and falls, comorbid medical conditions, depression, social activity and support, nutritional status, and cognition as key domains of geriatric assessment.
- Frailty is associated with a severe loss of functional reserve and a lack of tolerance of or resiliency to medical interventions and treatments.

PALLIATIVE CARE AND END-OF-LIFE ISSUES

Palliative care is an essential component of care throughout the disease process and consists of more than end-of-life care. An interdisciplinary palliative care team focuses on improving quality of life for patients facing complex illnesses. Palliative care aims to prevent and relieve suffering through the early identification, assessment, and treatment of pain and other problems, whether physical, psychosocial, or spiritual. Palliative care can be provided regardless of disease stage or cancer-directed therapy plan. Palliative care should be offered to patients facing a complex illness regardless of age. The goals of palliative care for older adults are the same as those for younger adults, and accurate identification of all symptoms is particularly useful. Simplified instruments, such as the Edmonton Symptom Assessment Scale, which assesses nine symptoms common among patients with cancer (ie, pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath), are useful in providing a profile of symptom severity over time.

These issues are discussed in further detail in Chapter 9: Palliative Care and Care at the End of Life.

KEY POINT

- Palliative care is an essential component of care throughout the disease process for older patients, and accurately identifying symptoms is critical to alleviating them.

HIGH-YIELD TAKEAWAYS

- Given the patient's stage of life, children and other family members are often integral to goals-of-care conversations.
- Geriatric assessments are key in understanding unrecognized cognitive decline and fall history, as well as in minimizing toxicity associated with standard-of-care therapy.

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

CANCER IN THE OLDER ADULT 7

CHAPTER SUMMARY GUIDE

KEY POINTS

- Physiological changes of aging can begin at age 30 years and vary by organ system and individual.
- Organ system changes must be considered when deciding on both the cancer treatment modality (surgery, radiation therapy, systemic treatment) and the type and dose of medications selected for both the cancer treatment and comorbidities.
- Multiple organ systems experience changes. With aging, many people experience changes in their kidney and liver function, which can result in decreased drug clearance and lead to increased cancer treatment–related adverse events.
- Bone marrow reserve is compromised in older adults, leading to a greater decline in blood cell counts compared with those of younger patients, which can complicate surgery, radiation therapy, and/or systemic cancer treatments.
- In older patients, comorbidities, impaired wound healing, and decreased physiological reserve contribute to prolonged hospital stays and rehabilitation after surgery.
- Delivery, duration, and dosage of radiation therapy must be carefully planned on the basis of organ function, comorbidities, and geriatric evaluation because adverse effects may be more pronounced in older patients.
- Many chemotherapy toxicities are more common and more severe in older patients. Pretreatment geriatric assessment is useful for predicting the risk of chemotherapy toxicity.
- In older patients, comorbidities and polypharmacy may affect response to cancer therapy, and geriatric assessment is critical in the selection of treatment and dosing.
- Immuno-oncological drugs appear to be safe and less toxic compared with chemotherapy for use in older adults. However, irAEs and the treatment of irAEs can cause significant morbidity and mortality for older adults.
- ECOG performance status is not a reliable tool for predicting treatment toxicity or functional decline in older adults with cancer.
- It is important to perform a geriatric screening assessment for new older adult patients with cancer to identify those at high risk of treatment-related adverse effects or functional decline and to provide intervention.
- The G8 and VES-13 are two examples of validated abbreviated geriatric screening assessment with high sensitivity that can be incorporated into everyday oncological practice.
- Neither ECOG performance status nor Karnofsky performance status alone provides an accurate measure of the functional status of an older patient with cancer.
- Older adults highly value preserving functional independence and cognition in addition to survival. A geriatric assessment can be used to predict survival and risk of chemotherapy toxicity in older adults with cancer.
- A geriatric assessment can be used to guide treatment decision-making and interventions for older patients with cancer.
- Several randomized trials have demonstrated the benefit of geriatric assessment in decreasing chemotherapy toxicity for older adults with cancer.
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- Frailty is associated with a severe loss of functional reserve and a lack of tolerance of or resiliency to medical interventions and treatments.
- Palliative care is an essential component of care throughout the disease process for older patients, and accurately identifying symptoms is critical to alleviating them.

CHAPTER TABLES AND IMAGES

Table 7-1 Age-Related Immune Phenotypes With Potential to Influence Immunotherapeutic Efficacy

Immunosenescence	Associated Phenotypes	Potential Consequences
Thymus	↑ Adiposity and epithelial cell attrition	↓ Naive T-cell pools with potential to recognize novel tumor antigens
	↓ Reduced IL-7 and mature T-cell production	
Bone marrow	↑ Myeloid: lymphoid progenitors	↓ Potential for adaptive immune responses to recognize novel tumor antigens
	↓ B-cell maturation	
T cells	↑ Memory: naive cells	↓ Diminished recognition and responses to novel tumor antigens
	↑ Immunosuppressive Tregs	↑ Antigen recall because of a larger memory pool
	↓ T-cell repertoire (two to fivefold)	
B cells	↑ Memory: Precursor cells	↓ Antibody production and diversity may limit response to novel tumor antigens
	↑ Proinflammatory B cells ($TNF\alpha^{+}$)	↑ Inflammation and autoantibody production may increase the probability of irAEs
	↓ Antibody production, diversity, and avidity	
Innate immunity	↓ Chemotaxis, phagocytosis of debris	↓ Activation and reduced diversity of tumor-specific $CD8^{+}$ cytotoxic T cells
	↓ Antigen presentation	
Inflammaging	↑ Chronic low-level inflammation	↑ Tumor mutagenesis by inflammatory mediators
	↑ Serum IL-6, IL-8, IL-18, TNFα, CRP	↓ Cytokine production in response to tumor antigens
Cellular senescence	↓ Telomere length and proliferation	↓ Expansion of responding B and T cells
	↑ Expression of cell-cycle inhibitors ($p16^{INK4a}$ and $p21^{CIP/KIP}$)	↓ Expansion of responding B and T cells
	↑ Proinflammatory cytokine and matrix remodeling factors	↑ Tumor metastasis, expansion, or recruitment of repressive immune cells (Tregs and MDSCs)

Abbreviations: CRP, C-reactive protein; IL, interleukin; irAE, immune-related adverse event; MDSC, myeloid-derived suppressor cell; TNF, tumor necrosis factor; Treg, regulatory T cell; ↓, decreased; ↑, increased.

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Table 7-2 **Tools Providing Estimates for Chemotherapy Toxicity**

Tool	Items	Study Population	Administration Characteristics	Considerations and Other Evaluation Options
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CARG toxicity tool: provides estimates for overall risk of grade 3-5 chemotherapy toxicity	Eleven items: • Previous falls (≥1 vs. none) • Hearing problems (deaf to excellent) • Limitations in walking one block (limited a lot, limited a little, not limited) • Difficulties with taking medications • Interference in social activities by physical health and/or emotional problems (all of the time to none of the time) • Age • Height • Weight • Sex • Cancer type (GI vs. genitourinary vs. other) • Dosage (standard vs. dose reduced), number of chemotherapy agents (monotherapy vs. polytherapy) • Hemoglobin level • Creatinine clearance	Patients aged 65 years or older with solid tumor malignancy or lymphoma starting new chemotherapy regimen (any line)	PRO/administered: 5 minutes; available online: https://www.mycarg.org/?page_id=2405	Can ask GA variables as part of history or include as part of PRO assessment

Tool	Items	Study Population	Administration Characteristics	Considerations and Other Evaluation Options
CRASH tool: provides estimates separately for risk of grade 3 hematologic and grade 3 to 4 nonhematologic toxicity	Assessment of risk of hematologic toxicity includes: • Diastolic blood pressure (>72 mm Hg), IADL score (<26) • LDH concentration (>459 U/L) • Assessment of risk of nonhematologic toxicity includes ECOG PS, MMSE (<30), and MNA (<28); chemotherapy intensity is assessed with MAX2 index	Patients aged 70 years or older with histologically proven cancer starting chemotherapy	PRO/administered: estimated time to completion is on par with full GA (20-30 minutes); available at: https://www.moffitt.org/for-healthcare-professionals/clinical-programs-and-services/senior-adult-oncology-program/senior-adult-oncology-program-tools/	

Abbreviations: CARG, Cancer and Aging Research Group; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; EGOG PS, Eastern Cooperative Oncology Group performance status; GA, geriatric assessment; GI, gastrointestinal; IADL, instrumental activities of daily living; LDH, lactate dehydrogenase; MAX2, an index that allows adjusting the toxicity of different chemotherapy regimens for comparison; MMSE, Mini-Mental State Examination; MNA, Mini Nutritional Assessment; PRO, patient-reported outcome.
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Table 7-3 **Clinical Trials of Geriatric Assessment**

Reference	No. of Pts.	Malignancy	Improved Survival Outcomes?	Comment
Lund et al[56] GERICO	142	Colorectal	NR	Higher rates of chemotherapy completion without delay or reduction
Soo et al[92] INTEGERATE	154	Various	NR	Reduced hospital admission, decreased early discontinuation of chemotherapy due to toxicity
Dumontier et al[93]	160	Hematologic malignancies	No	More likely to have documented goals of care discussions
Corre et al[94] ESOGIA	494	Non-small-cell lung cancer	No	Decreased toxicities (all grades), and fewer toxicity related failures
Bergerot et al[95] GAIN-S	56	Various	No	Improved health-related quality of life

Abbreviation: NR, not reported.
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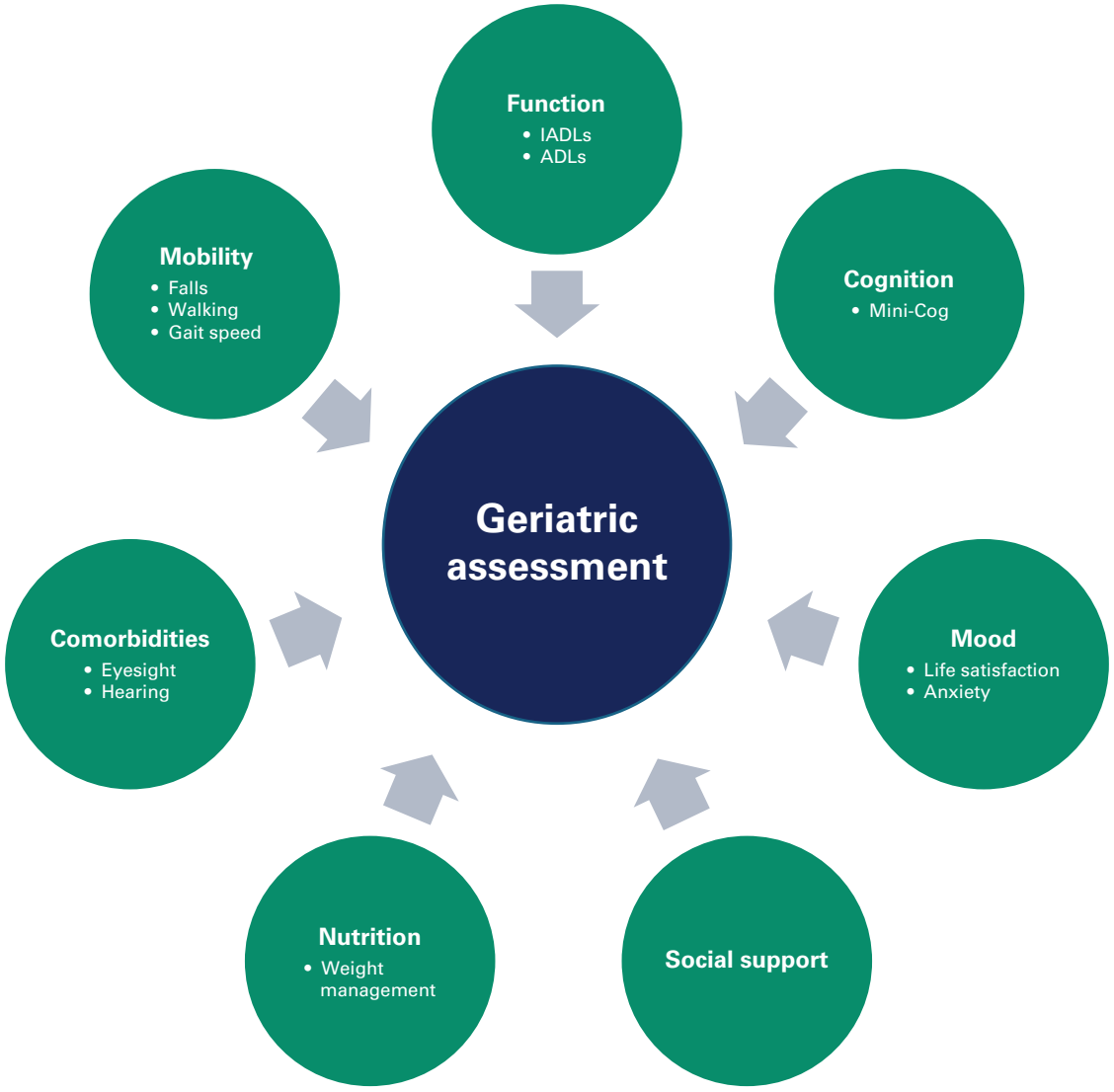
Figure 7-1 The Practical Geriatric Assessment



Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living.
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PAIN AND SYMPTOM MANAGEMENT

8

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RECENT UPDATES

- ASCO published guidelines regarding palliative care for patients with cancer, emphasizing early and systematic integration of palliative care, comprehensive assessment, and multidisciplinary management of symptoms.[1]
- NCCN Guidelines on Adult Cancer Pain now advise caution regarding the use of acetaminophen in combination with immunotherapy, as there is evidence that its use may negatively affect the efficacy of cancer treatment.
- ASCO published guidelines regarding the use of cannabis and cannabinoids in combination with guideline-recommended antiemetics for refractory chemotherapy-induced nausea and vomiting.[2]
- ASCO published a rapid guideline update for cancer cachexia recommending low-dose olanzapine to improve weight gain and appetite.[3,4]
- ASCO and the Society for Integrative Oncology (SIO) published a guideline for the management of fatigue in adult survivors of cancer.[5]

OVERVIEW

The management of symptoms in the context of cancer and cancer treatment remains a central priority within any framework for patient-centered cancer care. Suboptimal control of symptoms is associated with early discontinuation and treatment delays, whereas optimal supportive care improves cancer-related outcomes and quality of life (QoL). This chapter reviews the relevant pathophysiology and management of the following symptoms:

- Cancer-related pain, including chemotherapy-induced peripheral neuropathy (CIPN)
- Nausea and vomiting
- Cancer-related fatigue
- Cachexia
- Diarrhea associated with cancer and cancer therapy
- Oral mucositis
- Dyspnea
- Dermatological adverse effects
- Management of hormone-deprivation symptoms

Chapter 4 covers the management of immune-related adverse effects and Chapter 9 offers further review of palliative and end-of-life care.

SYMPTOM MONITORING

PATIENT-REPORTED SYMPTOMS

The clinical team often underestimates patient symptom burden and severity and may fail to recognize a patient's whole symptom complex, especially if the symptom is less readily perceptible.[6,7] Studies in which patients self-report their symptoms using validated questions or scales, such as patient-reported outcome (PRO) measures (eg, Clinical Align Pain Assessment, Brief Pain Inventory; Table 8-1), offer a mechanism by which all members of a clinical team can gain a more holistic picture of a person's cancer experience. PROs and other patient-reported measures are the gold standard for pain assessment, the downstream effect of pain on functional outcomes, and QoL.[8] A randomized trial of adults receiving outpatient chemotherapy[9,10] found that the

systematic collection of PROs, together with electronic alerts to the clinic team and printed reports to the physician, resulted in improved QoL, fewer emergency department visits, fewer hospitalizations, longer duration of palliative chemotherapy, and superior quality-adjusted survival. Furthermore, studies have demonstrated the feasibility of implementing PROs in the inpatient and community settings.[11] Hence, PROs should be integrated into every patient encounter to assess progress and adjust management accordingly.

Table 8-1 Examples of Validated Pain Instruments in Cancer Patients[12]

Instrument Name	Constructs Measured	Estimated Completion Time
Brief Pain Inventory Short Form	Pain severity, pain interference with physical and affective functioning, pain location	5 minutes
Edmonton Symptom Assessment System–Revised	Current pain severity, pain location	1 minute
Short-Form McGill Pain Questionnaire	Pain quality, pain location, pain severity	5-10 minutes
Verbal analog scales	Pain level	1 minute
Verbal rating scales	Pain level	1 minute
Wong-Baker FACES Pain Rating Scale[a]	Pain level	1 minute

[a]Validated in pediatric care; age 3 years or older.
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KEY POINTS

- Clinicians may inadvertently miss or underestimate the severity of patient symptoms.
- Symptom monitoring using PROs improves QoL and overall survival for patients who have advanced cancer.
- Daily patient-reported global symptom monitoring is feasible in hospitalized patients and outpatient settings who have advanced cancer.

CANCER-RELATED PAIN

Pain (ie, an unpleasant sensory and emotional experience and a complex biopsychosocial phenomenon) is the most common symptom associated with cancer.

Up to 90% of patients who have advanced cancer will experience moderate to severe pain,[13] making optimal pain management a key priority in cancer care. A multimodal approach to cancer patients with pain using pharmacological and non-pharmacological interventions is strongly recommended. Depending on the complexity and severity of the pain, expert consultation may be required (eg, pain management, palliative care, and other services like interventional radiologists).

PAIN ASSESSMENT

The first step is to assess and identify pain etiology and treat reversible causes when possible. A pain assessment should include a description of the location, radiation, duration, quality of the pain, and any factors that alleviate or aggravate the pain. In addition, information about the impact of pain on the patient's daily living, such as function and sleep, is critical to understand the pain patterns and trajectory. Clinicians should be familiar with the terms used to describe pain and know how to effectively assess the temporality and type of cancer-related pain (Table 8-2; Fig. 8-1).[14]

Table 8-2 Pain Terminology[15]

Term	Definition
Acute pain	Pain occurring over hours up to weeks, characterized by a well-defined temporal pattern of onset with subjective and objective physical signs and hyperactivity of the autonomic nervous system
Subacute pain	Pain present for between 6 weeks and 3 months
Chronic pain	Pain present more than 3 months, cause often not easily identified, usually multifactorial, may be nociceptive and/or neuropathic; characterized by vegetative signs (eg, anorexia, anhedonia, sleep disturbance) as well as physical and mental withdrawal

Term	Definition
Nociceptive pain	Somatic or visceral pain associated with actual or potential tissue damage caused by ongoing activation of intact nociceptors
Neuropathic pain	Pain resulting from injury to the peripheral or central nervous system, causing pain described as burning, shooting, tingling, stabbing, scalding, crawling, or painful numbness
Somatic pain	Localized pain causing activation of the μ-receptors and described as aching, stabbing, or throbbing
Visceral pain	Poorly localized pain resulting from activation of nociceptors in the viscera by obstruction, infiltration, ischemia, stretching, compression, and/or inflammation
Baseline pain	Average pain intensity experienced for 12 hours during a 24-hour period
Breakthrough pain	Transient increase in pain to greater than moderate intensity, occurring in addition to baseline pain
Incident pain	Specific experience of pain associated with an event or movement (eg, wound care)
Episodic pain	Transient exacerbation or recurrence of pain
Allodynia	Pain from light touch or mild pressure
Hyperalgesia	Increased pain response to a noxious stimulus
Dysesthesia	Unpleasant, abnormal sense of touch
Paresthesia	Abnormal dermal sensation (eg, tingling, pricking, chilling, burning, or numb sensation on the skin) with no apparent physical cause
Opiates	Natural substances that come from opium, including morphine and codeine
Opioid	Semisynthetic or synthetic products that bind to the same receptors as opiates but do not occur naturally; used broadly to include both natural or synthetic (or semisynthetic) substances acting on one of the three main opioid receptor systems (μ, κ, δ)
Adjuvant	Non-opioid medications used to enhance analgesia and minimize adverse effects, including anticonvulsants and antidepressants
End-of-dose failure	Predictable return of pain before the next scheduled dose of medication
Incomplete cross tolerance	Different levels of tolerance to an opioid of a different class

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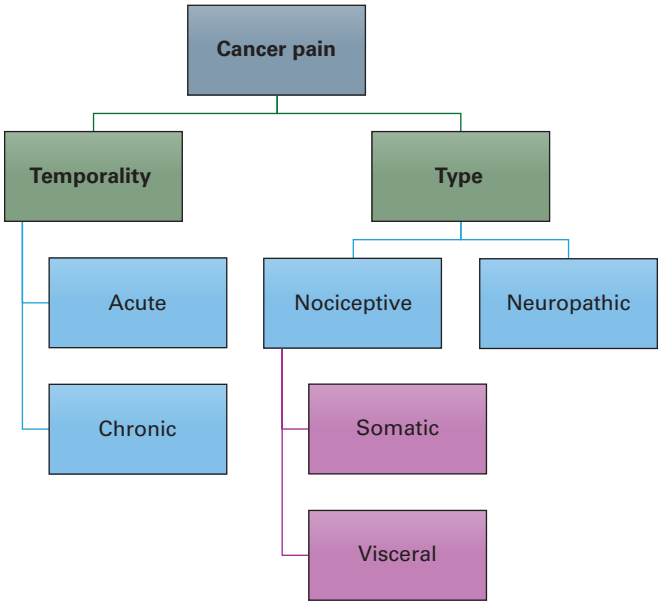
Figure 8-1 Characterization of Pain by Temporality and Type



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Temporality

Typically, we categorize pain temporality as acute or chronic. Acute pain occurs for hours up to weeks, with a well-defined pattern of onset, subjective and objective physical signs, and hyperactivity of the autonomic nervous system. This hyperactivity manifests as tachycardia, sweating, and hypertension. Usually self-limited, acute pain responds to treatment of its precipitating cause in combination with analgesics.

By contrast, chronic pain persists for longer than 3 months, with a less well-defined temporal onset and without the signs common to acute pain (eg, tachycardia, facial grimace). Chronic pain, rather, causes objective impairment in function (physical, psychological, social, or spiritual). Treatment of chronic pain in patients who have cancer requires a careful assessment of pain intensity and its multidimensional aspects, including psychosocial factors. Examples of psychosocial factors may include anxiety, maladaptive coping, history of substance use disorder, limited social support, cultural barriers to reporting pain, limited English proficiency, limited understanding of illness, or restricted access to medications.[16]

The temporal assessment should also include key features such as onset, duration, and course. Patients describe temporality in terms of their daily experience with pain. Constant pain is described as pain experienced for at least 12 hours per day; breakthrough pain is characterized as a transient increase in pain to greater than moderate intensity; incident pain is described as a specific experience of pain associated with an event or movement (eg, changing position, walking).

Pain Type

To understand the etiology of, and potential therapies for, pain in cancer patients, we characterize cancer-related pain as nociceptive, neuropathic, visceral, or mixed type. Nociceptive pain may be somatic or visceral and is often associated with actual or potential tissue damage caused by ongoing activation of intact nociceptors. Injury to the skin, soft tissue, bones, or joints causes somatic pain. Patients who have somatic pain can typically localize the pain and describe it as aching, stabbing, or throbbing. Visceral pain results from activation of nociceptors in the viscera by obstruction, infiltration, ischemia, stretching, compression, or inflammation. Patients may have difficulty localizing the pain and frequently experience referred pain, such as the left arm pain reported by patients who have myocardial ischemia. Patients describe visceral pain as cramping, pressure, gnawing, or squeezing. Injury to the peripheral or central nervous system (CNS) causes neuropathic pain. Neuropathic pain may share similar descriptors with nociceptive pain. Patients describe neuropathic pain as burning, shooting, tingling, stabbing, scalding, crawling, or painful numbness. It is also common to observe allodynia (pain from light touch or mild pressure) and hyperalgesia (abnormal sensitivity to sensory stimuli) with neuropathic pain. Examples of neuropathic syndromes include post-herpetic neuralgia, phantom pain syndrome, tumor infiltration into a nerve plexus, and CIPN.

Pain Trajectory

Developing an effective treatment plan requires a clear understanding of the pain diagnosis and its expected trajectory. For instance, medication selection, the balance between short- and long-acting opioids, and the frequency of pain reassessment will differ significantly between a patient experiencing severe post-radiation pain after curative therapy for head and neck cancer and another with progressive pain from advanced pancreatic cancer.

TREATMENT OF PATIENTS WITH CANCER EXPERIENCING PAIN

The goals of pain management are to optimize patient outcomes across these five dimensions:

- Analgesia: optimal pain relief
- Activities: improved function, including psychosocial and spiritual function
- Adverse effects: minimal adverse effects
- Aberrant drug use: prevention and recognition of substance use disorder
- Affect: the relationship between pain and mood

In addition to pharmacological approaches explored here, clinicians should consider non-pharmacological strategies when appropriate. These strategies are outlined in Table 8-3 and explored further across several recent ASCO guidelines, including (1) use of opioids for adults with pain from cancer or treatment, (2) the joint guideline with the Society for Integrative Oncology (SIO) on integrative medicine guidelines, and new ASCO guidelines for (3) anxiety and depression in patients with advanced cancer and (4) cannabis and cannabinoids in cancer care.[2]

PHARMACOLOGICAL APPROACHES TO CANCER PAIN: OPIOIDS AND ADJUVANTS

The World Health Organization ladder of pain management describes three levels of patient-reported pain corresponding to the selection of analgesic type: non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen for mild pain (step 1), a fixed combination of low-dose opioids and acetaminophen or NSAIDs for moderate pain or pain refractory to step 1 agents (step 2),

Table 8-3 **Non-Pharmacological Approaches to Treating Cancer Pain**[8]	
Category	**Treatment Type**
Alternative, complementary, or integrative strategies	Acupuncture, art therapy, massage, music therapy, physical/movement, aromatherapy
Interventional	Injection therapies, implant therapy, neural blockade, surgical neuroablation, orthopedic procedures
Rehabilitative	Hydrotherapy, occupational therapy, physical modalities such as ultrasound, therapeutic exercise, and therapy for specific disorders such as lymphedema
Psychological	Hypnotherapy, cognitive behavioral therapy, guided imagery, other forms of psychotherapy, psychoeducational interventions, relaxation therapy, stress management
Neurostimulation	Dorsal column stimulation, intrathecal drug delivery

The IMPACT trial recently showed that both acupuncture and massage improved pain, fatigue, insomnia, and quality of life over 26 weeks in advanced cancer patients, highlighting the importance of integrating non-pharmacological approaches to pain and symptom management when possible.[17]
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and higher doses of opioids for severe pain or pain refractory to step 2 agents (step 3). It is intended to be used bidirectionally in patients with cancer.

While the ladder suggests the use of NSAIDs and acetaminophen for mild pain, there are some studies that suggest that some NSAIDs, as well as the antidepressant imipramine, may be as good or better than opioids at controlling moderate to severe background cancer pain.[18] Conversely, evidence is inconclusive regarding the benefit of acetaminophen alone or in combination with

Table 8-4 **Non-Opioid Pharmacological Agents Targeting Neuropathic Pain**			
Pharmacological Agent Targeting Neuropathic Pain	**Mode of Action**	**Starting Dose/Max Dose**	**Adverse Effect**
Anticonvulsants	Decreased release of glutamate, norepinephrine, and substance P affects calcium channels		Sedation and dizziness should not be abruptly stopped
Gabapentin		100-300 mg 1-3× per day/1,200 mg 3× per day[a]	
Pregabalin		50 mg 3× per day/200 mg 3× per day	
Antidepressants			
TCAs: nortriptyline, desipramine	Inhibition of serotonin/norepinephrine reuptake, sodium channel blocking, and anticholinergic	25 mg/150 mg daily	Sedation, anticholinergic effect, cardiac arrhythmias, and nausea
SNRISs: duloxetine, venlafaxine	Inhibition of serotonin/norepinephrine reuptake	Duloxetine: 30 mg daily/60 mg 2× daily; venlafaxine: 37.5 mg daily or twice daily/225 mg daily	Nausea, insomnia, appetite loss, weight gain
Topical agents			
5% Lidocaine patch	Sodium channel blocking	1-3 patches/3 patches daily	Rash, local erythema
Capsaicin: cream, 8% patch	Highly selective agonist for TRPV1 receptors expressed in afferent neuronal C fibers and some Aδ fibers	Cream: 0.025%, 0.075%, and 0.1% creams; apply 3-4 times per day; 8% patch: 1 patch/4 patches applied for 60 minutes every 3 months[b]	Erythema and uncomfortable burning, stinging, or itching

Abbreviations: SNRIS, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.
[a]Need to adjust in those with renal insufficiency, especially those on renal replacement therapy.
[b]8% patch is applied by a medical provider only. Consideration of cost.
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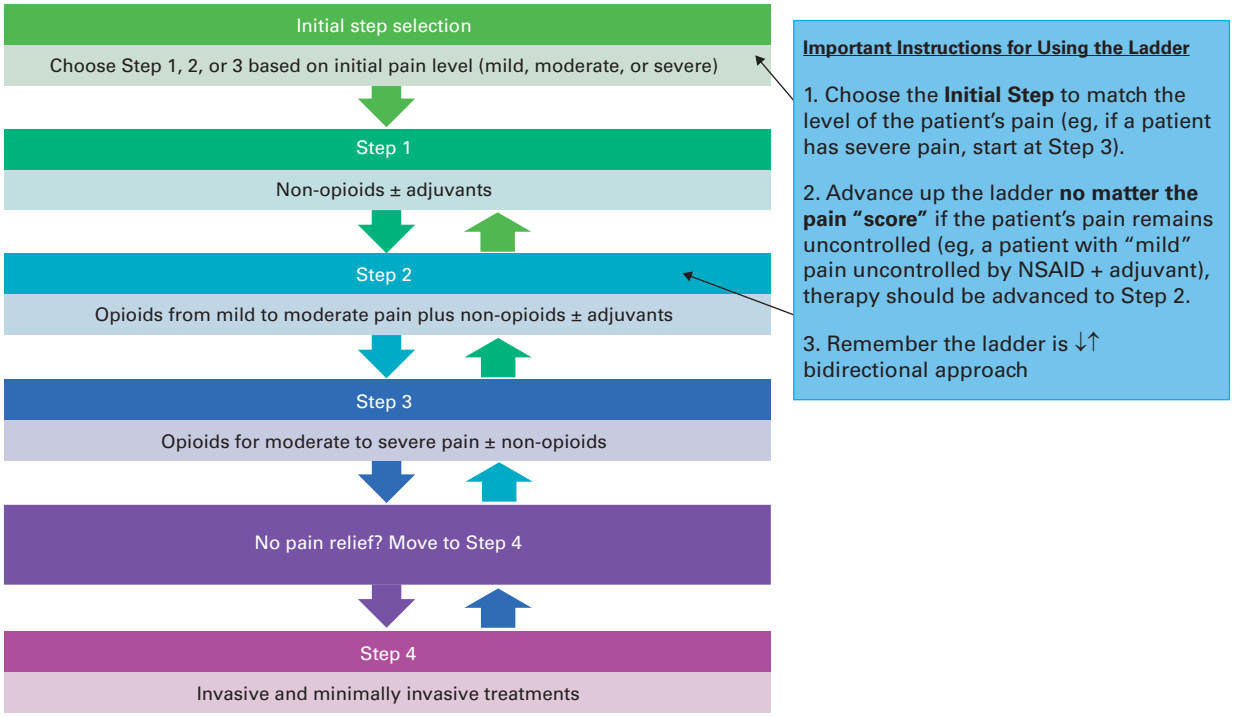
opioids for cancer patients with moderate to severe pain. In addition, there is growing evidence that the use of acetaminophen in combination with immunotherapy for cancer treatment may negatively impact the effect of the immunotherapy, and caution is advised.[19-21]

This ladder also includes adjuvant therapies.[22] Adjuvant medications that are non-opioid medications with evidence for pain improvement include anticonvulsants and antidepressants; adjuvants can be used at each step, particularly for patients with neuropathic pain (Table 8-4). Because of extensive feedback, the World Health Organization is in the process of revising the guideline and ladder. Many experts have suggested the addition of invasive and minimally invasive interventions, as well as an approach that includes the physical, psychological, and emotional causes of pain, to the guideline (Fig. 8-2).[23]

Figure 8-2 The Revised World Health Organization Analgesic Ladder



Adapted under Creative Commons license. Source: Anekar AA, Hendrix JM, Cascella M. WHO Analgesic Ladder. In: *StatPearls*. StatPearls Publishing; 2023.

The choice of opioid agent depends on pharmacokinetics, route of delivery, availability, cost, clinician experience, and patient factors such as age, renal function, comorbidities, and concomitant drugs (Table 8-5).[24] Generally, patients experiencing constant pain should receive a scheduled opioid. Sustained-release preparation of a short-acting agent or a transdermal fentanyl (TDF) or buprenorphine patch is indicated for constant pain that is likely to continue to be present, but this should be reserved for patients who have developed some tolerance to the common adverse effects of opioids. In patients who are opioid-naive and who are experiencing constant pain, a standing dose of a short-acting opioid (eg, morphine every 4 hours) should be initiated. Interval of opioid doses should be based on their specific half-life, to allow achieving steady-state levels of the drug after four to five half-lives. Once the effective 24-hour dose of opioid is determined, patients with constant pain should have a sustained-release or transdermal patch added to the regimen to provide longer-lasting pain relief. The short-acting opioid should be continued to relieve breakthrough or incident pain episodes. For example, a patient with constant pain from pancreatic cancer who experiences relief from 15 mg of oral morphine every 4 hours "around the clock" could be started on 30 mg of oral sustained-release morphine q8h. Alternatively, since the patient took 90 mg of oral morphine in 24 hours, a fentanyl patch of 37 mcg/h or, if the pain is still severe, 50 mcg/h could be initiated.

Some patients with complex mixed-pain syndromes, especially neuropathic pain, can benefit from methadone, which is an intermediate- to long-acting opioid. It is highly recommended to seek expert palliative/supportive care or anesthesia pain management consultation when initiating methadone because titration can be complex, and close monitoring is required.

Patients who have cancer often also experience breakthrough or incident pain; they can concomitantly use short-acting opioids for these episodes. Breakthrough doses can be safely administered at a frequency based on the time to maximum concentration (eg, 1 hour for oral morphine). Generally, the breakthrough dose is 10% to 20% of the total daily sustained-release dose

Table 8-5 **Opioids, Active Metabolites, and Pharmacokinetics**[25-27]

Opioid	Active Metabolites	Half-Life (Hours)	Equianalgesic	
			Parental	Oral
Morphine	Yes	2-4	10	30
Oxycodone	Yes	3-4	Not available in the United States	20
Hydrocodone	No	3-4	NA	30
Hydromorphone	Yes	2-3	1.5	7.5
Fentanyl	No	Transmucosal: 1-2 Transdermal: 48-72	Variable conversion methods available; may consider using ratio of 2.5-1 (oral morphine per day: TDF per hour); should not initiate in opioid-naive patients or patients receiving less than 60 mg MEDD	
Methadone	No	2-3 (distribution phase); 15-60 (elimination phase)	[a]	

Abbreviations: MEDD, morphine equivalent daily dose; NA, not applicable; TDF, transdermal fentanyl.
There is no clear consensus on opioid conversions; these serve as guidelines only.
[a]Methadone conversions should be supervised by a pain expert (palliative care specialist or acute/chronic pain management specialist).
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(except for methadone and short-acting fentanyl products). For example, a patient taking 15 mg of sustained-release morphine three times a day (ie, 45 mg in 24 hours) would take 5 to 10 mg of short-acting oral morphine for breakthrough or incident pain. For patients using a fentanyl patch, calculate the oral morphine equivalent and use 10% to 20% of that for the breakthrough dose. For example, for a patient using a 50 mcg/h patch, the oral morphine equivalent is approximately 100 mg, and the breakthrough dose would be 10 to 20 mg of liquid morphine or a 15-mg tablet.

NEUROPATHIC PAIN

Although opioids are effective for the management of acute and severe cancer pain of all types (nociceptive and neuropathic), when neuropathic pain is identified, additional agents are needed. Pharmacotherapies that target neuropathic pain will yield the highest effect. Common classes of drugs targeting neuropathic pain include antidepressants, anticonvulsants, and topical agents. To avoid sedation, these often require gradual titration over several weeks to achieve maximal effect. It is important to counsel patients about options and common adverse effects and set realistic expectations for symptom management. Monitoring patients closely for adverse effects is important because many of these pharmacotherapies can have multiple adverse effects and may interact with many other commonly used medications.

RENAL AND HEPATIC CONSIDERATIONS

With careful monitoring and appropriate dosing, opioids are safe and effective in patients with renal or hepatic dysfunction. For opioids other than fentanyl, buprenorphine, and methadone, the active drug half-life and drug metabolites increase in renal dysfunction. For example, the liver metabolizes morphine into its active metabolites of morphine-3-glucuronide and morphine-6-glucuronide. Renal dysfunction leads to the accumulation of morphine-6-glucuronide, manifesting as myoclonus or, rarely, seizures. Therefore, in the setting of severe renal dysfunction, morphine and codeine should be avoided, and hydromorphone or oxycodone should be used instead, with caution and close monitoring; methadone, fentanyl, and buprenorphine are the preferred long-acting options.

Cautious use of opioids is also necessary in severe liver dysfunction, because opioids can contribute to sedation, constipation, and encephalopathy if inappropriately dosed or not monitored carefully. Because patients who have hepatic insufficiency experience decreased opioid clearance, initial dose reductions and increased dosing intervals should be considered.[28] Oxycodone, tramadol, and hydromorphone should be avoided, but morphine and buprenorphine can be used with caution in the setting of severe hepatic dysfunction. Fentanyl and methadone can be used, but these are generally given at longer intervals than typical patients who have normal hepatic function. However, if patients who have cancer have mild or transient liver function changes, most opioids are safe and equally effective.

OPIOID TITRATION AND ROTATION

Unfortunately, we cannot predict the most effective and tolerable opioid for each patient. In clinical practice, opioid selection usually depends on availability, cost, and prior patient experience. If a patient experiences an intolerable adverse effect from one opioid, rotation to another opioid may be required. Of note, clinicians must differentiate anticipated adverse effects from an opioid (eg, transient nausea, pruritus) versus true allergic reactions (eg, hives, shortness of breath). Avoid labeling of anticipated adverse effects as true allergies, which occurs most commonly with morphine and codeine.[29]

Despite misconceptions about the drug morphine, it continues to be the most studied, evidence-based, cost-efficient opioid for treating cancer patients with pain. Equianalgesic tables and dosing charts are available to convert to a different route of administration or to rotate to a different opioid, but it should be noted that these guidelines originated from single-dose studies in healthy volunteers. Consequently, these conversions should be used with caution, because they serve as rough approximations and do not replace clinical judgment.

The indications to rotate opioids may include insufficient analgesic efficacy, intolerable adverse effects, ineffective administration route, drug interactions, development of tolerance, and financial constraints. To initiate an opioid rotation, the clinician should convert the daily opioid consumption to an oral morphine equivalent (or morphine equivalent daily dose) using an equianalgesic table, which a colleague should independently check. Although opioid conversion calculators can be found online, they should be used cautiously and should never replace clinical judgment.

Unless the patient is in severe pain, incomplete cross tolerance requires a dose reduction of 25% to 50% of the calculated equianalgesic dose of the new opioid. The difference between tolerance and incomplete cross-tolerance is that tolerance refers to the reduced analgesia that may occur with repeated opioid use, whereas incomplete cross-tolerance refers to a differential ability to tolerate an adverse effect, such as respiratory depression, between one opioid and another. It is, therefore, important to account for incomplete cross-tolerance when rotating a patient from one opioid to another. During opioid rotations, patients require careful monitoring and ready access to breakthrough doses of short-acting opioids. Converting other opioids to methadone requires additional care because of its unique pharmacokinetic profile and is best done in consultation with clinicians experienced with its use, such as palliative/supportive care clinicians.

Most Common Reasons for Opioid Rotation

- Severe, intractable, or refractory adverse effects
- Decrease in liver or renal function (expected to decrease opioid metabolism or elimination, causing accumulation of an opioid and its active metabolites)
- Possible or actual drug interactions, including prolongation of the heart rate-corrected QT interval (QTc; including with a clinical trial's investigational study drug [commonly seen with methadone])
- Access barriers including insurance limitations, stock availability at pharmacies, high out-of-pocket costs, and low health literacy
- Patient preference, high pill count, or barriers to administration (eg, loss of oral or enteral access)

Reasons Not to Rotate

- Patient tolerates the current pain regimen with minimal adverse effects and good analgesia.
- Patient declines recommended opioid. (Take this as an opportunity to explore their reasons further before changing the approach. For example, the patient may have heard about bad experiences with that opioid in the past. If the patient reports a personal experience of a serious adverse effect, consider using a different opioid.)

PARAMETERS FOR AVOIDING OR CHOOSING CERTAIN OPIOIDS

- Urinary retention: rotate to another opioid.
- Pruritus: consider opioids from a different class (eg, fentanyl ormethadone for patients on morphine, oxycodone, or hydromorphone).
- Renal failure: consider rotating to fentanyl, buprenorphine, or methadone for long-acting opioids. For short-acting or breakthrough opioids, consider oxycodone or hydromorphone over morphine.
- Liver failure: use opioids with an expectation to see increased half-life of both immediate (short-acting) and extended-release (long-acting) formulations; may need to use short-acting opioids for a few days until a new, effective, and tolerated dose is established at the new steady state.
- Respiratory insufficiency: use buprenorphine or scheduled doses of short-acting opioids until the patient develops tolerance.
- Sedation with good analgesia: may add methylphenidate. If sedation continues, decrease opioid dose by 25% to 50% and monitor; if sedation persists and analgesia is still adequate, further decrease dose or rotate opioid; if pain increases, obtain a palliative/supportive care consult.
- Altered mental status: decrease dose by 25% to 50%; if no improvement, rotate opioid.

- Constipation: increase laxative regimen and continue opioids. Ensure patients receive senna with or without polyethylene glycol (PEG); may need additional laxatives if constipation does not resolve. See the section below for management of constipation.
- Myoclonus: avoid morphine and hydromorphone. Consider the decrease in the gabapentin dose first.
- Prolonged QTc: correct contributing metabolic abnormalities (eg, hypokalemia, hypomagnesemia, hypocalcemia); avoid methadone for QTc greater than 500 milliseconds.

REASONS TO AVOID MORPHINE

- History of altered mental status or intolerable adverse effects (eg, visual hallucinations, myoclonus, severe nausea)
- Renal failure

METHADONE

Previously considered a late-line pain management option, clinicians experienced in its use can use methadone as first- or second-line treatment for patients with cancer-related pain. Methadone is a synthetic opioid with a chemical structure unrelated to opium derivatives. It is a unique opioid given its actions as a mu agonist and an *N*-methyl-D-aspartate receptor antagonist, making it particularly useful for treating patients with neuropathic cancer pain. It may be the only agent effective for patients with pain syndromes caused by invasion of a nerve plexus (eg, from invasion of the brachial, lumbosacral, or perineal plexus). Unlike other opioids, methadone has the advantage of lacking active metabolites, making it potentially safer in patients with renal and hepatic insufficiency. Unlike daily dosing for methadone maintenance therapy in patients recovering from opioid addiction, pain management and palliative/supportive care experts dose methadone every 8 to 12 hours for patients with cancer-related pain.

However, methadone is a complicated drug requiring expert oversight in its prescribing and monitoring. The complexities of methadone include oral bioavailability ranging from 40% to 99% and biphasic elimination-excretion coinciding with tissue distribution. A rapid and extensive distribution phase occurs at 2 to 3 hours, and a slow elimination phase occurs at 15 to 60 hours. Consequently, in the setting of a methadone overdose, patients must receive continuous naloxone rather than single or intermittent doses. The prescribing information states that although respiratory depression can happen at any point during the use of methadone, the risk is greatest at initiation of therapy and after an increase in the dose; therefore, patients need to be monitored very closely. In addition, the liver extensively metabolizes methadone with major CYP3A4, CYP2B6, CYP2D6, and CYP2C19 interactions, causing multiple drug-drug interactions. These drug interactions are a particular concern in patients who take concurrent medications prone to interactions, such as antiretroviral drugs metabolized through the CYP450 system, thereby evaluating all concomitant medications essential. Additional common interactions include hypoglycemia with high doses or rapid dose increase of methadone and QTc prolongation from methadone, requiring close monitoring, especially with concomitant medications also associated with QTc interval prolongation or electrolyte disturbances, such as hypokalemia, hypomagnesemia, or hypocalcemia, all of which also prolong the QTc.[30,31] In patients with end-stage cancer, the intensity of QTc monitoring should align with patient goals and preferences.[32]

For more information on common interactions, please see online resources, such as STATPearls.[33] Finally, converting routes of administration and equianalgesic dosing varies dramatically depending on the extent of previous exposure to opioids.[31] Clinicians should consider collaborating with a palliative/supportive care or anesthesia pain expert when converting a patient from another opioid to methadone.[30,33]

TRANSDERMAL OPIOIDS

Transdermal opioid patches (fentanyl and buprenorphine) offer an alternative long-acting formulation for cancer-related pain control, particularly if there are barriers to oral administration of drugs. By maintaining constant plasma drug levels, the transdermal route provides sustained pain relief and may reduce adverse effects. A TDF patch is applied to the skin over an area of adequate subcutaneous fat (and not over a tattoo or edema); a subcutaneous drug reservoir develops over approximately 12 to 18 hours. They are changed every 48 to 72 hours. A retrospective 2019 study suggested that there is no basis for avoiding TDF or modifying its dose in patients with cancer with low body mass index (BMI) and cachexia.[34] It is important to note that TDF is approved for opioid-tolerant patients; therefore, it is not recommended as a first-line opioid. Opioid-tolerant patients are those taking, for 1 week or longer, at least 60 mg of oral morphine equivalent daily. In addition, buprenorphine is an alternative option for those with advanced cancer, especially those with a concern for respiratory insufficiency or concurrent opioid use disorder (OUD).[34,35] Buprenorphine is a μ-opioid partial agonist, with higher affinity to μ-opioid receptors compared with other opioids. Buprenorphine patches do not need to be placed over a fatty area. They are changed every 7 days. It is important to note that the prescribing information advises that buprenorphine can potentially precipitate withdrawal in patients who are already on opioids. Furthermore, the prescribing information recommends avoiding buprenorphine in opioid-tolerant patients receiving more than 80 mg per day of morphine or its equivalent, because the highest formulation available in the United States (20 mcg/h) will not provide adequate analgesia for patients receiving these higher doses of opioids. See STATPearls for additional guidelines for

prescribing buprenorphine.[25,36] Oncology clinicians should collaborate with palliative care, anesthesia, pain, or addiction medicine specialists when caring for patients who may benefit from buprenorphine.

MANAGING OPIOID ADVERSE EFFECTS

When prescribing opioids for patients with cancer, prescribers must be informed about expected adverse effects and attempt to prevent them. All adverse effects associated with opioid use are transient except for opioid-induced constipation (OIC). Consequently, clinicians should consider appropriate education and prophylaxis in opioid-naive patients to prevent the attribution of expected adverse effects, such as constipation, to allergies.[29] Patient or family misunderstandings can prevent future use. If the medical chart notes an opioid as an allergy, the clinician should explore what specific reactions have occurred with its use and update the medical record accordingly.

Common adverse effects include nausea, pruritus, sedation, and constipation (see following section). Effective treatment of opioid-induced nausea includes antiemetics targeting dopaminergic receptors (eg, prochlorperazine, metoclopramide) rather than 5-hydroxytryptamine type 3 ($5HT_3$) receptor antagonists to avoid constipation associated with $5HT_3$ receptor antagonists. Non-sedating antihistamines (eg, cetirizine) can be used to prevent or treat pruritus. Diphenhydramine should be avoided, given the additive sedation it produces when administered with opioids, especially in patients with acute illness or who are elderly. Instead, change the opioid to a synthetic opioid or consider using a second-generation non-sedating antihistamine, such as cetirizine.[37]

Opioid-Induced Constipation

OIC is a particularly troublesome adverse effect that can lead patients to experience nausea, vomiting, and anorexia, and even discontinue their opioid medication. Opioids cause constipation by binding to μ receptors on enteric neurons, disrupting the neural coordination necessary for peristalsis and slowing bowel motility. They also increase the tolerance of the anal sphincter, already increased in elderly patients. The approach to OIC includes stimulant laxatives, such as senna (one to eight tablets daily) or bisacodyl (5-10 mg twice daily). Evidence has demonstrated no added benefit of a softener used along with sennosides for OIC.[38] A recent double-blind randomized controlled trial (RCT) of PEG versus sennosides in patients with cancer and OIC did not show a convincingly favorable efficacy for either agent.[39]

OIC prophylaxis with sennosides (senna) or PEG begins at the initiation of an opioid regimen and is done in a stepwise, additive fashion. Insoluble fiber (eg, psyllium) or other bulk-forming laxatives can worsen OIC in patients who cannot maintain adequate hydration. Patients should discontinue fiber or replace the insoluble fiber with a soluble fiber product.[40]

Lubiprostone is a drug that activates chloride channels to increase fluid in the intestines and is approved by the Food and Drug Administration (FDA) for use in opoid-induced constipation in non-cancer patients. Current NCCN guidelines recommend the use of lubiprostone in patients with cancer only in clinical trials. A retrospective cohort study of the use of the agent in cancer versus non-cancer patients showed that while it was equally effective in treating constipation, there was significantly more nausea and diarrhea experienced by cancer patients using lubiprostone, and more frequent discontinuation due to the adverse effects.

Peripheral-acting μ receptor antagonists (PAMORAs) are the latest class of constipation medications that block the peripheral effects of opioids on the gut. PAMORAs do not cross the blood-brain barrier and consequently do not reduce an opioid's central analgesic effects.[41] PAMORAs (eg, methylnaltrexone) are the best second-line therapy option for OIC, effective in up to three-fourths of patients who take opioids for cancer pain.[42,43]

Methylnaltrexone was the first US FDA-approved subcutaneous or intravenous injection to treat OIC. In the 2008 RCT, 48% of patients in the methylnaltrexone arm had a bowel movement within 4 hours of the first dose compared with 15% in the placebo arm; the treatment arm patients also had significantly lower rates of rescue laxative use; only 8% of the placebo arm had a bowel movement without rescue laxatives compared with 52% in the methylnaltrexone arm.[44] Methylnaltrexone, like other PAMORAs, should only be used after other measures have been ineffective, and the lower bowel has been emptied of stool. If a lower bowel impaction is present, methylnaltrexone can cause perforation of the upstream bowel. Methylnaltrexone causes abdominal cramping and diarrhea and is expensive. Additional oral PAMORAs (also expensive) include alvimopan, naloxegol, and naldemedine; naldemedine was recently shown to be effective for patients with cancer with OIC[45]; however, regulatory agencies have not approved these agents in the cancer setting.[46-48]

Opioid-Induced Hyperalgesia

Opioid-induced hyperalgesia is a state of nociceptive sensitization from exposure to high-dose opioids, causing pain exacerbation. The type of pain experienced might be different or the same as the underlying pain. Opioid-induced hyperalgesia is a distinct, definable, and characteristic phenomenon that may explain the loss of opioid efficacy in some patients. The most likely cause of opioid-induced hyperalgesia involves the central glutaminergic system, but the precise molecular mechanism is not yet understood.[49]

Clinicians should suspect opioid-induced hyperalgesia when escalating opioid doses to increase pain paradoxically without evidence of disease progression. Tremulousness, myoclonus, confusion, or allodynia, causing reports of pain wherever the patient is touched, may also accompany this increase in pain. Myoclonus may be masked, however, by concomitant use of benzodiazepines for anxiety or nausea. Concerns about opioid-induced hyperalgesia should not justify withholding or limiting opioid therapy, but when hyperalgesia is suspected, it is important to consider dose reduction, opioid rotation, or dose reduction combined with non-opioid interventions to prevent seizures, the most serious consequence of the toxicity. Nonetheless, concerns about opioid-induced hyperalgesia should not justify withholding or limiting opioid therapy. It is essential to differentiate between opioid-induced hyperalgesia and uncontrolled pain.

MANAGING OPIOID RISK

Over the last two decades, clinicians have witnessed a growing trend in the aberrant use of opioids. Clinicians should always advocate for ready access to opioids for medically indicated purposes, including cancer-related pain.[24] However, clinicians must also advocate for and attempt to ensure safe opioid use, storage, and disposal through close monitoring and patient and caregiver education.

OUD and Addiction

Clinicians must be clear about the phenomena and the terminology used to describe aberrant opioid use, because these terms continue to evolve and carry strong social meaning (Table 8-6). Most recently, to describe what was previously referred to as opioid addiction, the *Diagnostic and Statistical Manual for Psychological Disorders, Fifth Edition*,[50] introduced the term OUD. OUD is a problematic pattern of opioid use that leads to clinically significant impairment or distress, as manifested by at least 2 of 11 symptoms or behaviors. In short, OUD is an inability to take opioids as prescribed because of impaired control over drug use, compulsive use, continued use despite harm, and craving.

Table 8-6 Opioid Aberrancy Terminology[33,50-53]

Term	Definition
Aberrant	Actions departing from accepted, medically appropriate drug-taking behaviors
Abuse	A maladaptive pattern of prescription opioid use leading to clinically significant impairment and distress
Addiction	A primary, chronic, and neurobiological disease with manifestations influenced by genetic, psychosocial, and environmental factors, characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving
Chemical coping	Behaviors focused on obtaining opioids to relieve psychosocial distress rather than pain
Dependence	A state of adaptation indicated by a medication class-specific withdrawal syndrome produced by abrupt cessation, rapid dosage reduction, decreasing blood level of the drug, or administration of an antagonist
Misuse	The inappropriate use of a prescription opioid agent, whether intentional or unintentional, and regardless of motivation
Pseudo-addiction	An iatrogenic syndrome with behaviors that mimic addiction, driven by unrelieved pain
Substance abuse	Use of a substance in a manner outside of sociocultural conventions
Tolerance	Diminution of one or more drug effects caused by exposure to the drug that may require higher doses for effect
Withdrawal	An uncomfortable but non–life-threatening reaction that occurs after the abrupt cessation of opioids or use of naloxone, characterized by the presence of one or more of a variable group of symptoms and signs, including tremulousness, anxiety, insomnia, tachycardia, tachypnea, hypertension, nausea and vomiting, diarrhea, piloerection, and sweating

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The most accepted risk factors for OUD include a personal history of alcohol use disorder, drug abuse, tobacco dependency, major psychiatric disorder, or family history of alcoholism or drug abuse.[54] Other factors include youth, length of exposure to opioids, and history of preadolescent sexual abuse. Pseudo-addiction is a term for an iatrogenic condition that manifests as apparent drug-seeking behavior but is caused by incorrect frequency of opioid dosing for a patient requiring opioids for pain relief (eg, dosing oxycodone every 6 hours when the pain relief lasts at most 4 hours). Pseudo-addiction should be ruled out and assessments documented when treating a patient with apparent drug-seeking behaviors.[55,56]

Although patients who have cancer pain are appropriately excluded from most guidelines aiming to decrease prescriptions of opioids for patients who have other causes of pain, it is not uncommon to need to prescribe opioids for patients who have both severe cancer pain and a history of OUD. Management of cancer pain in these patients is complicated by the need to manage both the patient's pain and OUD at the same time.

It is essential to continue addressing and treating the OUD when treating pain in a patient with cancer. Having OUD may impair relationships with the clinical team and personal support systems and put patients at risk for undertreatment of pain and cancer.[57] Because most cancer hospitals do not offer treatment of patients with OUD, clinicians treating pain in patients with cancer should collaborate and coordinate care with local methadone or buprenorphine prescribers, especially if already involved in the patient's care.[58] If a patient with OUD comes to a cancer center on buprenorphine, the prescriber should be asked to continue prescribing buprenorphine for the OUD and to continue mental health counseling and support for the patient. If a local buprenorphine prescriber is not available, collaboration with the institution's pain, palliative/supportive care, or mental health clinicians certified to prescribe buprenorphine for OUD is indicated. If an addiction specialist is not available, an outside referral is strongly recommended for medication-assisted treatment of OUD. Stopping medication for treatment of OUD is not an acceptable option, because it has been found to lead to 50% of patients experiencing OUD relapse.[59]

Clinical Practice Safeguards When Managing Cancer Pain

Clinicians recognize the serious nature of OUD and their role in mitigating its negative effects. Prescribing clinicians should take a balanced approach, which includes taking universal precautions. To do this, clinicians prescribing opioids assess all patients for a history or risk of opioid misuse independent of demographic, social, or disease-related variables. Most of the data to support universal precautions in opioid prescribing originate from the non-cancer pain and cancer survivorship literature; nevertheless, this approach has clear applications for patients being actively treated for cancer or those patients with advanced disease not currently receiving treatment.[56] Instituting universal precautions in clinical practice requires outlining opioid-prescribing procedures and obtaining support from institutional leadership and colleagues. Once a clinical practice adopts an opioid-prescribing process, all clinicians must routinely use this process before prescribing opioids to any patient. Consultation and collaboration with a pain and addiction medicine specialist or a palliative/supportive care specialist should be considered when managing cancer pain in a patient with OUD.

The following approaches should be considered as part of universal precautions: prescription drug monitoring program reports, electronic prescribing, education, pain contracts/agreements, opioid aberrancy risk assessment, urine drug screens, safe storage, and disposal.

Prescription Drug Monitoring Plans

Nearly all states now provide prescription drug monitoring plans, which digitally store controlled substance dispensing information and make these data accessible to prescribers and pharmacies. Some states now require that clinicians review and document that they have reviewed an online prescription drug monitoring plan report before prescribing an opioid. The prescription drug monitoring plan is a vital tool to review current opioids, doses, names of prescribing clinicians, and names of pharmacies that dispensed the opioids. Furthermore, electronic prescribing of opioids is now available in most states and has many benefits. Overall, this provides a convenient, safe, and patient-centered approach to prescribing opioids and has become the new standard in opioid prescribing.[60]

Pain Agreements

Clinicians should also consider the routine use of pain agreements (or contracts) with patients receiving opioids. The primary aim of opioid agreements is to communicate clearly and document expectations of prescribing clinicians and patients.[61] Clinician expectations should outline the clinical team members involved, hours of operation, and policies around lost or stolen medications, and state that clinicians cannot prescribe opioids if not used for their intended medical purpose. Patient expectations may include clarity regarding participation at scheduled appointments and referrals, consent to tests such as pill counts and urine drug screens, abstinence from alcohol and other illicit drugs, and limiting the patient's opioid consumption. Published guidelines recommend written opioid agreements for all patients initiating therapy or patients at higher risk of aberrant drug-related behaviors.[62,63]

Assessment of Opioid Aberrancy Risk

In addition to personal and family risk factors, screening tools can be used to assess risks of OUD and monitor safety. Unfortunately, tools often used for risk stratification have not been validated in patients who have cancer pain. Some of the common screening and monitoring tools include the following:

- Opioid Risk Tool[64,65]
- Screener and Opioid Assessment Measure for Patients with Pain–Revised[66] or Screener and Opioid Assessment Measure for Patients with Pain Short Form[66]
- Cut Down, Annoyed, Guilty, and Eye-Opener Adapted to include Drugs Questionnaire
- Current Opioid Misuse Measure[51,67]

Based on the assessed risk for OUD, clinicians can inform patients about their potential risk for OUD, modify clinical assessment and opioid refill intervals, and use urine drug screens.[56] At initiation and periodically throughout opioid therapy, clinicians can use urine drug screens to enhance objective data regarding patient behaviors. Understanding of the methodological practices of testing (eg, immunoassays, gas chromatography–mass spectrometry) at each institution, including limitations, such as false-positive and false-negative rates, is required to interpret the screen results correctly. Before ordering a drug screen, the clinician should consider how this information will change the clinical management of the patient's pain.

Nasal Naloxone

There is an increasing number of states in which naloxone prescribing is recommended or required when prescribing opioids in excess of certain doses or in combination with other sedating medications.[68] Naloxone is also increasingly available at pharmacies without a prescription. Clinicians must educate caregivers on how and when to administer naloxone and should advise caregivers to call 911 if they use it. Not calling for help could result in the patient's death, especially when the overdose was caused by taking a long-acting opioid, such as methadone.

Opioid Storage and Disposal

Improperly stored opioids can lead to diversion or accidental poisoning. Patients and caregivers should remove expired or unused medicines from their homes when they are no longer needed by attending opioid take-back events, using mail-back envelope programs, or permanent collection sites.[69,70] Patients should be encouraged to consult with their local government about best practices for opioid disposal.

INTERVENTIONAL CANCER PAIN TREATMENTS

A vast majority of oncology patients will be able to achieve adequate pain control with aggressive management using systemic analgesics, adjuvants, and cognitive behavioral techniques. However, 5% to 10% of patients require interventional strategies to manage their pain. Interventional options should be integrated into an interdisciplinary approach toward effective oncological pain management along with medical management, supportive care, rehabilitative measures, and psychological management. Improved access to and knowledge of interventional options will allow for early diagnosis and access to effective analgesic treatments before advanced stages of disease. If pain is refractory or there is clinical suspicion that the patient may benefit from interventional pain approaches, consider consulting pain experts for further evaluation.

BONE PAIN

Painful bone lesions and spine fractures may be amenable to treatment with NSAIDs, bisphosphonates, receptor activator of nuclear factor κ-B ligand inhibitors, kyphoplasty, radiofrequency ablation, or single-fraction radiotherapy.[26] Patients who have diffuse bony metastases, such as those occurring in metastatic prostate cancer, who are refractory to androgen-deprivation treatments and do not have additional cytotoxic therapies planned may benefit from infusion of a radiopharmaceutical, such as the β emitter ^{153}Sm-SM lexidronam, the α emitter radium-223, or ^{177}Lu, targets prostate-specific antigen.[71,72] The limitation of these agents is the localization to metastases in major marrow areas, resulting in cytopenias.

A systematic review from 2019 of the effectiveness and safety of vertebral augmentation for malignant vertebral compression fracture showed clinically relevant improvements in pain, Oswestry Disability Index, and Karnofsky Performance Status in patients with malignancy treated with percutaneous vertebroplasty and kyphoplasty.[73]

PRESENTING CASE STUDY

A 65-year-old woman presents with worsening back pain due to progression of breast cancer metastases in the vertebrae. Previously, her bone pain was well-controlled with extended-release oral morphine sulfate (30 mg every 12 hours) and immediate-release oral morphine (7.5 mg every 4 hours as needed) for breakthrough pain; at baseline, she required two to three doses of immediate-release morphine per day. In the past week, her pain has been increasingly worse, and today she rates her pain severity as 10 out of 10. She describes her pain as aching and stabbing at times, and it is well localized to her mid- and lower back. She appears acutely distressed, tearful, and diaphoretic on physical examination. There are no changes in her strength or sensation. Vital signs include a temperature of 99.1°F (37.3°C), heart rate of 115 beats per minute, respiratory rate of 20 breaths per minute, and blood pressure of 150/95 mm Hg. Cervical, thoracic, and lumbar spinal MRI identifies multiple new lesions in her spine, but no impending fracture or spinal cord compression. She is admitted for pain control with intravenous (IV) morphine. Laboratory studies show renal function, hepatic function, vitamin D, and calcium levels were within reference limits.

Given the patient's acute and severe exacerbation of bone pain, requiring immediate inpatient management, why is the transition from oral to IV morphine the most appropriate initial step?

The primary goal in this scenario is to achieve rapid and effective pain relief. The patient's severe pain (10/10) and acute distress necessitate prompt intervention. IV opioid administration is the most appropriate initial step, as IV opioids provide a rapid onset of action, with peak effects occurring within approximately 10 minutes. This approach allows for immediate titration and precise dosing to achieve adequate analgesia. Since her renal and hepatic function are normal, IV morphine is a safe and reasonable option.

To provide adequate pain relief, convert her oral rescue dose to IV and consider doubling that dose because she is in severe pain (oral dose doubled = 15 mg; converted to IV = 5 mg IV). Consider ordering 3- to 5-mg IV morphine every 3 hours as needed in addition to continuing her oral extended-release morphine.

Alternatively, to provide continuous pain control and relieve her breakthrough pain, consider converting all oral opioids to an IV infusion either with a patient-controlled analgesia (PCA) or nursing boluses (60 mg oral morphine/24 hours = 20 mg IV morphine/24 hours). Because she has taken multiple breakthrough doses, it would be reasonable to start the morphine infusion at 1 mg/h. Nursing doses when required should be 10% to 20% of the 24-hour dose or 3- to 5-mg IV morphine every 3 hours. PCA bolus doses could be 0.5 mg IV every 15 minutes.

What are the potential drawbacks of alternative options?

Alternative management options that may be considered could include increasing oral opioids, changing oral opioids, or introducing a fentanyl patch, but none of these are preferred. Increasing either short-acting or long-acting oral opioids would be insufficient for rapid pain relief. Oral opioids have a longer time to peak effect (approximately 1 hour). Switching to oral hydromorphone, while a more potent opioid, would still result in a delayed onset of action like with other oral medications; as such, this option is not ideal for acute pain. This delay in effective pain control could lead to prolonged suffering and increased distress. Finally, fentanyl patches are designed for chronic pain management and have a very slow onset of action. They are not suitable for acute pain exacerbations requiring rapid titration.

- **Additional considerations.** In addition to IV opioids, adjunctive therapies should be considered. Nonsteroidal anti-inflammatory drugs can be effective for bone pain, provided there are no contraindications. Acetaminophen can be considered a co-analgesic, though studies showing additional benefit have had conflicting results. Administration of a bisphosphonate (eg, zoledronic acid) or a RANK-L inhibitor should be considered as a component of pain control; RANK-L inhibitors have modest benefit over bisphosphonates.

Once her acute pain is controlled, a comprehensive plan for pain management should include a transition strategy for oral or transdermal medications, if feasible, along with a plan for managing breakthrough pain. Further evaluation of the treatment of the new spinal lesions by radiation oncology, interventional radiologist (Kyphoplasty, nerve block) should be considered. Finally, it is important to address the patient's emotional and spiritual/existential distress and provide supportive care to help her cope with the progression of her disease.

By prioritizing rapid pain control with IV opioids and considering adjunctive therapies, clinicians can effectively manage acute exacerbations of cancer-related bone pain and improve patient comfort.

NEUROPATHIC PAIN

Sympathetic Blockade

The sympathetic chain is a known target for anesthetic interventions, and the sympathetic neural blockade is commonly used for visceral pain treatment. Pain in the midback related to upper abdominal malignancies can be debilitating and is often responsive to a celiac plexus block. A meta-analysis showed that 90% of patients achieve pain relief within 2 weeks, and 70% to 90% of patients achieve partial to complete relief until death or after 3 months or more. Common adverse effects include orthostatic hypotension and diarrhea. Less common complications include pneumothorax, back pain, and, rarely, paraplegia.[74]

Superior and inferior hypogastric blocks can be used effectively to treat advanced pelvic pain, with a retrospective study of 180 patients showing sustained visual analog scale reduction of 49.55% at 3 months.[75] The ganglion of impar has been successfully targeted for treatment of rectal and anal cancer pain, and a retrospective review has shown a reduction in morphine consumption at 3 months.[76]

SPINAL DRUG DELIVERY/NEUROLYSIS

Patients who have diffuse neuropathic pain syndromes, who have pain refractory to aggressive analgesic titration, or who are experiencing intolerable adverse effects should be referred for consideration of epidural or intrathecal drug delivery or destructive neurolytic procedures.[77] After successful treatment, a patient may require a significant reduction of systemic pain medications. Intrathecal drug delivery allows for lower doses of medications to be continuously delivered to the CNS to improve analgesia and reduce adverse effects.[78] Opioids, local anesthetics, clonidine, and ziconotide have all been used to effectively treat cancer-related pain. A 2002 RCT comparing an implantable drug delivery system and comprehensive medical management of pain in patients with advanced cancer showed that the implantable drug delivery system led to clinical success in pain control, reduced pain, and significant relief from common drug toxicities compared with medical management.

Spinal cord stimulation is a common pain treatment most often used for neuropathic pain and the treatment of complex regional pain syndrome in patients without cancer. However, current evidence is generally insufficient to support routine use for cancer-related pain.[79]

ANALGESIC AGENTS THAT ARE NOT RECOMMENDED

Mixed agonist-antagonists (ie, butorphanol, pentazocine) should not be used in combination with opioid agonist drugs for cancer pain management. Converting from an agonist to an agonist-antagonist could precipitate abstinence syndrome (withdrawal crisis).

Meperidine and placebos should not be used for patients with cancer pain. Meperidine is contraindicated for chronic pain, especially in patients with impaired renal function or dehydration, because accumulation of metabolites that are renally cleared may result in neurotoxicity (seizures) or cardiac arrhythmias. The use of a placebo in the treatment of pain is unethical.

Combination formulations of short-acting opioids with non-opioid medications, such as acetaminophen, are often used to treat cancer pain (eg, Percocet, Vicodin), although evidence of their efficacy is limited in moderate and severe cancer pain. These combined opioid/acetaminophen formulations are recommended to be prescribed for very short courses (<3 days) for moderate pain that is predicted to resolve because of the risk of liver toxicity from acetaminophen (amounts greater than 4 g in 24 hours) and potential for masking fevers in patients with cancer.

KEY POINTS

- A multimodal approach to managing the pain of cancer patients that includes pharmacological and non-pharmacological interventions is strongly recommended.
- Non-steroidal anti-inflammatory agents are first-line therapies for mild pain and can minimize the need for opioids in patients with somatic pain, including pain from bone metastases.
- Morphine is the most studied, evidence-based, cost-efficient opioid for the treatment of patients with cancer who have pain.
- Methadone is a mu agonist and *N*-methyl-D-aspartate receptor antagonist effective in treating neuropathic pain. Methadone is a complex drug that requires expert oversight in its prescribing and monitoring.
- TDF and buprenorphine patches are approved for opioid-tolerant patients.
- Methadone, buprenorphine, and fentanyl are the safest opioids in the setting of renal failure; however, they are not intended to be first-line options in those for whom other opioids can be considered or used.
- Avoid defining anticipated and transient opioid-associated adverse effects (eg, nausea, pruritus) as true allergies (eg, hives, shortness of breath).
- When prescribing opioids to patients who have cancer, it is important to anticipate expected adverse effects and develop strategies to prevent them.
- Stimulant laxatives (eg, senna, bisacodyl), not stool softeners, are the most effective approach to prevent and treat OIC. Polyethylene glycol is also effective.
- Consideration of interventional approaches for cancer pain should be discussed.
- Oncologists must use accurate terminology to describe OUD.
- Universal precautions describe an opioid-prescribing practice in which clinicians assess all patients for history or risk of opioid misuse regardless of demographic, social, or disease-related variables.
- Effective use of adjuvant agents for bone and neuropathic pain can provide more effective pain control with fewer adverse effects than opioids alone.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

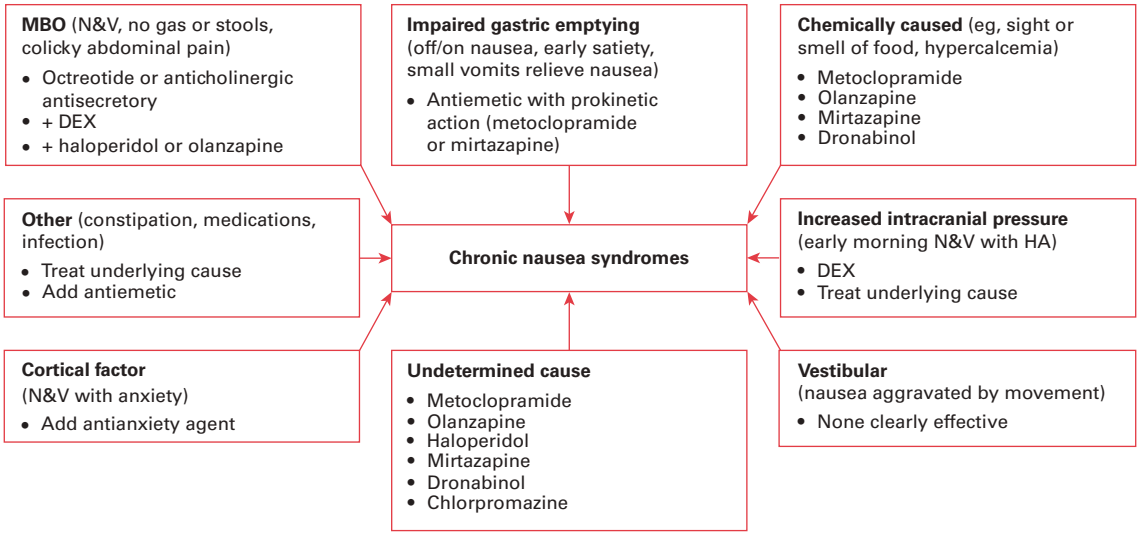
Nausea and vomiting in patients undergoing cancer treatment may significantly reduce their QoL and affect therapy adherence.[80] A summary of the causes of nausea and vomiting unrelated to cancer therapy and how to manage them is included in Figure 8-3.

The principal strategy for developing effective antiemetic agents for chemotherapy-induced nausea and vomiting (CINV) requires identifying and blocking key neurotransmitter receptors in the Chemoreceptor Trigger Zone: dopamine, serotonin, and substance P (Table 8-7). Blocking receptors for endocannabinoids, histamine, and acetylcholine may provide additional protection, as does dexamethasone, in some situations.

Choice of antiemetic regimen for CINV involves assessing the emetic risk of the chemotherapy itself and the neurotransmitters involved, along with individual patient risk factors. Chemotherapy falls into four emetic risk categories[81-83]:

- High (>90%)
- Moderately emetogenic chemotherapy (30%-90% risk)
- Low emetogenic chemotherapy (10%-30% risk)
- Minimal (<10%)

Figure 8-3 Nausea Management Options



Abbreviations: DEX, dexamethasone; HA, headache; MBO, malignant bowel obstruction; N&V, nausea and vomiting.
Adapted under Creative Commons license. Source: Wickham R. Nausea and vomiting not related to cancer therapy: intractable problem or clinical challenge? *J Adv Pract Oncol*. 2020;11(5):476-488. doi:10.6004/jadpro.2020.11.5.4

Individual patient risk factors also increase the risk of developing nausea and vomiting, including previous CINV, female sex, age younger than 50 years, low alcohol intake, motion sickness history, an expectation of experiencing nausea and vomiting, and a history of hyperemesis gravidarum.[61,85] Notably, patients who experience CINV during their first cycle of chemotherapy are up to five times more likely to experience nausea in subsequent cycles.[85] When patients have at least one of these risk factors, aggressive antiemetic use should be considered, especially before the first cycle of chemotherapy, to improve future treatment dose tolerance.

TYPES OF CINV

There are four types of CINV: acute, delayed, breakthrough, and anticipatory (Table 8-8). Acute CINV occurs no more than 24 hours after administration of chemotherapy. By contrast, delayed CINV occurs 2 to 5 days after the administration of chemotherapy and is most commonly associated with platinum chemotherapy. This delayed emesis is often of lesser intensity, but it can last longer. The antiemetic agents that effectively manage acute CINV differ from those used for delayed CINV; this difference suggests unique neurotransmitter mechanisms, if not different physical sites, involved in these two forms of CINV. Breakthrough CINV occurs despite receiving guideline-based antiemetic prophylaxis. Clinicians can use as-needed medications to treat breakthrough nausea, which have different mechanisms of action than the antiemetics used for prophylaxis. Finally, anticipatory nausea is a conditioned reflex that occurs after inadequate antiemetic protection during an earlier chemotherapy course.[86] Numerous stimuli trigger chemotherapy-associated anticipatory nausea (eg, proximity to the infusion center and smells), and symptoms can occur at any time. Clinicians can use non-pharmacological measures (eg, hypnosis) and benzodiazepines to treat the subsequent anxiety and decrease anticipatory nausea.

Table 8-7 **Selection of Antiemetics Based on Neurotransmitters Involved**[84]		
Anatomic Location	**Neurotransmitter Involved**	**Drug Class**
Cortex	Unknown	Dexamethasone
		Lorazepam
		Cannabinoids
	Dopamine	Haloperidol
Chemoreceptor trigger zone	Serotonin	Metoclopramide
		Prochlorperazine
		Ondansetron
		Oral granisetron
		Transdermal granisetron
	Dopamine	Metoclopramide
		Prochlorperazine
	Endocannabinoid	Cannabinoids
	Substance P inhibitors	Aprepitant
		Fosaprepitant
		Netupitant
		Rolapitant
Vomiting center/vestibular apparatus	Histamine	Cetirizine (preferred)
		Diphenhydramine
		Meclizine
		Hydroxyzine
	Acetylcholine	Scopolamine

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Table 8-8 **CINV Types**	
Types of CINV	**Time Frame**
Acute	Within 24 hours of chemotherapy administration
Delayed	2-5 days after chemotherapy administration
Breakthrough	Anytime, despite adequate prophylaxis
Anticipatory	Before the next treatment

Abbreviation: CINV, chemotherapy-induced nausea and vomiting.
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CINV PROPHYLAXIS

Adherence to evidence-based CINV prophylaxis guidelines significantly improves patient-centered outcomes.[61,87-89] One effective method to ensure adherence to antiemetic guidelines is to incorporate guideline-based antiemetic ordering as part of all chemotherapy regimen plans.[90] In 2020, ASCO convened a multidisciplinary panel to update antiemesis guidelines.[91] Highly emetogenic chemotherapy prophylaxis includes a neurokinin-1 receptor antagonist, a $5HT_3$ receptor antagonist, dexamethasone, and olanzapine; moderately emetogenic chemotherapy requires a $5HT_3$ receptor antagonist and dexamethasone; low emetogenic chemotherapy requires a single dose of a $5HT_3$ receptor antagonist or dexamethasone; and minimally emetogenic chemotherapy does not require routine antiemetic prophylaxis.[91] In patients receiving combination chemotherapy, the chemotherapeutic agent with the highest emetic risk determines the CINV prophylactic strategy. Patients receiving radiation based on risk category should receive evidence-based CINV prophylaxis (Table 8-9).

Olanzapine is an atypical antipsychotic drug initially developed for the treatment of schizophrenia and bipolar disorder. It affects multiple dopamine and serotonin receptors associated with nausea and vomiting (ie, dopamine 2 receptor, $5HT_{2A}$, $5HT_{2C}$, and $5HT_3$).[92-94]

At 5- and 10-mg doses, olanzapine is an effective agent that prevents and treats acute, delayed, breakthrough, and overall CINV and other chronic nausea and vomiting from highly emetogenic agents.[85,90,92,95] There is recent phase 3 RCT evidence for using olanzapine along with triple therapy for prevention of CINV in patients receiving moderately emetogenic chemotherapy.[96,97]

Table 8-9 **CINV Prophylaxis Based on Emetic Risk**	
Risk	**Recommended Prophylaxis**
High	NK-1 + $5HT_3$ + dexamethasone + olanzapine
Moderate	$5HT_3$ + dexamethasone
Low	$5HT_3$ or dexamethasone
Minimal	None

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In patients with cancer receiving highly emetogenic chemotherapy, 10 mg of olanzapine for 4 days and standard guideline-based prophylaxis antiemetics significantly improved acute CINV (74% vs. 45%; $P = .002$), delayed CINV (37% vs. 22%; $P = .002$), and overall CINV (37% vs. 22%; $P = .002$).[15] Taking olanzapine can cause sedation, but overall, it is well tolerated.[93] A phase 3 study in Japanese breast cancer patients compared olanzapine 5 mg versus placebo; patients who received olanzapine, given within 5 hours after chemotherapy completion, had excellent responses with less sedation.[98] Similarly, another phase 3 study from India comparing olanzapine 2.5 mg versus 10 mg showed non-inferiority in overall control of N/V while significantly reducing daytime somnolence (any grade; 65% vs. 90%, $P < .0001$).[99] Olanzapine has improved efficacy over metoclopramide in treating breakthrough CINV.[100] In patients who received highly emetogenic chemotherapy and evidence-based CINV prophylaxis, those who received olanzapine compared with metoclopramide experienced less vomiting (70% vs. 31%; $P < .01$) and nausea (68% vs. 23%; $P < .01$) over 72 hours.

MULTIPLE-DAY AND HIGH-DOSE CHEMOTHERAPY

In patients receiving chemotherapy over multiple days, including those with hematological malignancies, ASCO guidelines recommend CINV prophylaxis based on the chemotherapeutic agent with the greatest emetic risk; prophylaxis should be given each day of chemotherapy and continue for 2 days after completion. Specifically, for cisplatin-containing multiple-day regimens, ASCO guidelines support the use of a neurokinin-1 receptor antagonist, a $5HT_3$ receptor antagonist, and dexamethasone. An RCT in patients with germ cell tumors similarly supported using a combination of a neurokinin-1 receptor antagonist, a $5HT_3$ receptor antagonist, and dexamethasone to prevent both acute and delayed emesis.[101,102]

In patients receiving high-dose chemotherapy preparation for hematopoietic cell transplantation, data support a combination of a neurokinin-1 receptor antagonist, a $5HT_3$ receptor antagonist, and dexamethasone with or without olanzapine.[91,95,103-105]

RADIATION-INDUCED NAUSEA AND VOMITING

As with chemotherapy, radiotherapy can cause nausea and vomiting because 80% of the body's serotonin is located in the gastrointestinal tract, and gut serotonin is released by gut injury, such as that induced by radiation. Determinants of risk include the treatment field, dose of radiation, and fractionation pattern (Table 8-10).

Table 8-10 **Emetic Risk in Adults by Site of Radiation Therapy**		
Risk Level	**Site**	**Therapy Options**
High (>90%)	Total body irradiation	5-HT_3 antagonist with dexamethasone
Moderate (30%-90%)	Upper abdomen, craniospinal irradiation	5-HT_3 antagonist with or without dexamethasone
Low (10%-30%)	Brain, head and neck, thorax, pelvis	Brain: dexamethasone; head and neck, thorax, pelvis: $5HT_3$ antagonist or dexamethasone or dopamine receptor antagonist (use as rescue)
Minimal (<10%)	Extremities, breast	$5HT_3$ antagonist, dexamethasone, or dopamine receptor antagonist (use as rescue)

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Approximately 50% to 80% of patients undergoing radiotherapy will experience nausea and vomiting if they do not receive appropriate prophylaxis.[106] Guidelines state that total-body irradiation is associated with the highest risk (>90%), and radiation to the upper abdomen is associated with a moderate risk (30%-90%) of nausea and vomiting.[80,91] A meta-analysis suggests that $5HT_3$ receptor (ie, serotonin) antagonists are the preferred prophylaxis for radiotherapy-induced nausea and vomiting.[107] For those treated with highly emetogenic radiotherapy, recommendations include a $5HT_3$ receptor antagonist and dexamethasone.

Guidelines recommend a $5HT_3$ receptor antagonist and an optional 5-day dexamethasone course for patients receiving moderately emetogenic radiotherapy.[80]

In patients receiving combination chemotherapy and radiotherapy, clinicians should provide antiemetics based on the highest emetic risk of either the chemotherapy or the radiotherapy.[61,89-91]

DEXAMETHASONE-SPARING CINV PROPHYLAXIS STRATEGIES

Dexamethasone has been a central component of CINV prophylaxis for a long time. However, the multiple adverse effects of dexamethasone may limit its use (eg, hyperglycemia, insomnia, anxiety, gastric ulcers, poor wound healing). Four placebo-controlled RCTs and two meta-analyses have evaluated dexamethasone-sparing strategies comparing CINV outcomes for patients receiving highly emetogenic chemotherapy or moderately emetogenic chemotherapy.[108-112] These data support limiting the administration of dexamethasone to the first day of chemotherapy administration in patients intolerant of dexamethasone or those with few individual risk factors for CINV. Replacing dexamethasone with olanzapine should be considered for patients unable to tolerate dexamethasone.[61,91]

REFRACTORY CINV

Refractory CINV refers to nausea and/or vomiting that occurs during subsequent treatment cycles when adequate antiemetic prophylaxis and/or rescue has not been effective in earlier cycles. Different strategies can be used to control refractory CINV.

- Consideration for a change in the prophylactic antiemetic regimen. This may include escalation to the next higher category for CINV prophylaxis or using drugs with alternative mechanisms.
- For patients with anticipatory nausea or anxiety, the addition of a benzodiazepine could be considered.
- Cannabinoids: Dronabinol has been approved by the FDA for refractory CINV. Recommended starting doses are dronabinol oral solution at 4.2 mg/m^2 or dronabinol capsules at 5 mg/m^2 given three to four times a day.
- Dopamine receptor antagonists, such as metoclopramide or prochlorperazine, although not preferred secondary to the risk of extrapyramidal adverse effects, can be used rarely.
- In a retrospective study involving patients with refractory CINV, the addition of olanzapine at 5 to 10 mg to the nausea regimen in subsequent cycles demonstrated an overall success rate of 70%.[113]

KEY POINTS

- There are four types of CINV: acute, delayed, breakthrough, and anticipatory.
- Chemotherapy is classified into four emetic risk categories: highly emetogenic (>90% risk), moderately emetogenic (30%-90% risk), low emetogenic (10%-30% risk), and minimally emetogenic (<10% risk).
- Prevention of CINV is key because patients who experience CINV during the first cycle of chemotherapy are up to five times more likely to experience CINV in subsequent cycles.
- Olanzapine significantly reduces nausea and emesis in highly emetogenic chemotherapy regimens when combined with neurokinin-1 receptor antagonists, $5HT_3$ receptor antagonists, and dexamethasone.

CANCER-RELATED FATIGUE

Cancer-related fatigue is a multifactorial symptom defined as a distressing, persistent, subjective sense of physical, emotional, and cognitive exhaustion related to cancer or its treatment.[114] Cancer-related fatigue results in a decreased capacity for physical or mental activity and occurs in up to 80% of patients receiving chemotherapy and/or radiotherapy. Fatigue affects QoL by interfering with patients' abilities to fulfill their roles and participate in meaningful activities. The causes of cancer-related fatigue are multifactorial, and an in-depth assessment should first focus on identifying possible reversible underlying causes: medications causing fatigue, such as β-blockers, hypothyroidism, anemia, adrenal insufficiency, hypoglycemia, dehydration, hypercalcemia, hypogonadism, poorly controlled pain, depression, sleep disturbances, and deconditioning. A recent comprehensive study divided the experience of the patient coping with fatigue into five interrelated themes:

1. Discovering physical and emotional boundaries
2. Communicating support needs
3. Reorganizing and planning activities and rest
4. Letting go of one's habitual identity
5. Recognizing and accepting chronic cancer-related fatigue

Unpacking the physical, psychological, social, emotional, and spiritual/existential aspects of fatigue into these distinct categories can facilitate communication among patients, their families, and clinicians and help to make a shared decision about the

preferred treatments. Health professionals should make patients aware of the different options and refer them to their preferred treatment(s).[115] Identification and treatment of fatigue might include referral to appropriate specialties, such as endocrinology, physical therapy, psychology, and palliative care. In addition to treating the underlying contributing factors, there are non-pharmacological and pharmacological interventions for addressing cancer-related fatigue.

NON-PHARMACOLOGICAL APPROACHES

Cancer-related fatigue is unlikely to respond to increased rest; paradoxically, increased activity may benefit select patients.[114] Non-pharmacological therapies for cancer-related fatigue include physical exercise and psychological interventions. ASCO-SIO guidelines provide multiple options to help reduce fatigue during treatment, including the following[5]:

1. Exercise (aerobic and/or resistance; tailored to patient tolerance and ability), either in a supervised or non-supervised setting
2. Cognitive behavior therapy, with or without hypnosis
3. Mindfulness-based programs, including stress management
4. Low- to moderate-intensity tai chi or qigong
5. Psychoeducation

A meta-analysis of 113 studies and more than 11,000 patients found that exercise, psychological interventions, and the combination of both reduced cancer-related fatigue during and after primary treatment.[116]

Patients should be encouraged to engage in moderate-level physical activity (eg, brisk walking, stationary biking) as tolerated, encouraging 150 minutes per week of aerobic exercise, 2 days per week of strength training, and flexibility exercises on the remaining days of the week.[117] Patients should use any necessary walking aids to ensure safety and decrease the risk of falls.

In addition, there is insufficient evidence to make recommendations for or against acupressure, brain wave vibration meditation, music or music therapy, progressive muscle relaxation, reflexology, solution-focused therapy, biofeedback, social support, or yoga to reduce the severity of cancer-related fatigue in adults undergoing cancer treatment. However, such strategies can be explored based on the patient's preferences, provider experience, and resource availability.

PHARMACOLOGICAL INTERVENTIONS

The most widely used pharmacological management includes psychostimulants (eg, methylphenidate, modafinil), ginseng, or corticosteroids.[5] However, current ASCO-SIO guidelines recommend against the use of modafinil or armodafinil, methyphenidate, L-carnitine, or paroxitene. Investigators have also evaluated ginseng to treat cancer-related fatigue. In a phase 3 study, 8 weeks of American ginseng (*Panax quinquefolius*) improved fatigue compared with placebo, especially for patients actively receiving cancer-directed therapies.[118] A double-blind, randomized, placebo-controlled trial of Korean red ginseng (*Panaxginseng*) also demonstrated reduced fatigue in patients with colorectal cancer receiving combination chemotherapy (ie, modified fluorouracil, leucovorin, and oxaliplatin) over 4 months.[119] Current guidelines only conditionally recommend the use of American ginseng based on low-quality evidence. Finally, corticosteroids may show immediate benefit in mood and energy, but the duration of benefit is usually limited to days to 2 weeks, and patients experience associated adverse effects.

KEY POINTS

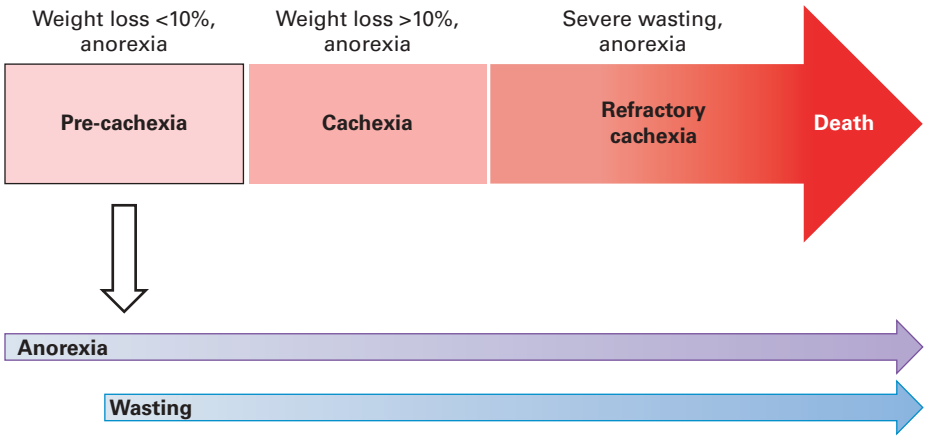
- Cancer fatigue is widespread and often multifactorial.
- In patients experiencing cancer-related fatigue, clinicians should evaluate and treat coexisting conditions, such as depression, anemia, thyroid dysfunction, and electrolyte disorders, and discontinue fatigue-inducing medications when possible.
- In patients who have cancer fatigue, moderate-intensity exercise, psychological interventions, and Tai Chi–based interventions can improve symptoms.
- National guidelines do not support the use of psychostimulants, antidepressants, or wakefulness agents to treat cancer-related fatigue.
- Two phase 3 studies demonstrated improved cancer-related fatigue with ginseng compared with placebo for patients undergoing cancer treatment.

ANOREXIA AND CACHEXIA

Cachexia is a hypermetabolic syndrome characterized by loss of appetite, weight, and skeletal muscle, leading to fatigue, functional impairment, increased treatment-related toxicity, poor QoL, and reduced survival.[120-123] According to international guidelines, cachexia can be categorized into three phases: precachexia, cachexia, and refractory cachexia (Fig. 8-4).[124] Multiple factors

contribute to cachexia, including metabolic dysregulation, increased fat and protein breakdown, decreased nutrient intake, and neurohormonal dysregulation of compensatory feeding stimuli. Consequently, these factors result in an energy imbalance and skeletal muscle loss.[124,125] Cancer cachexia is associated with increased toxicity of cancer treatment and predicts poor survival.[126] In a large population-based data set, the degree of weight loss and change in BMI predicted decreased survival. For example, a patient with a BMI of 28 kg/m^2 losing 2.5%, 2.5% to 6%, 6% to 11%, >11% expected median survival is 20.9, 14.6, 10.8, and 7.6 months.[126]

Figure 8-4 Stages of Cachexia: Precachexia, Cachexia, and Refractory Cachexia



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Anorexia (ie, loss of appetite) is a prominent feature of cancer cachexia. Potential causes of anorexia include constipation, emesis, mucositis, depression, decreased gastric emptying, dysphagia, food aversions, and fat malabsorption.

The intensity of symptoms of anorexia varies among patients. The lack of eating is often a bigger challenge for caregivers than for patients because a lack of appetite often does not cause patient distress. When patients abstain from eating, caregivers may believe that they have lost an important way to nurture their loved ones, or that their loved one is "giving up." Teaching caregivers that anorexia is a normal part of the advancing cancer and that they can substitute other nurturing activities (eg, help with bathing or massage) for preparing food may help assuage their concerns. Clinicians should provide support for the distress of caregivers as they witness their loved ones with anorexia develop weight loss, weakness, and decreased QoL.

The 2020 ASCO cachexia guideline and the 2023 ASCO rapid guideline cachexia update summarize available evidence in managing this distressing syndrome in patients who have advanced cancer. An informal consensus recommended that clinicians refer patients who have advanced cancer and loss of appetite and body weight to registered dieticians for assessment and counseling regarding nutritional interventions. Registered dieticians provide patients and caregivers with practical and safe advice for feeding (eg, high-protein, high-calorie, nutrient-dense food), cautioning about fad diets and other dietary habits that may be advocated in popular culture without the associated evidence.[120] A study of more than 400 patients who had esophagogastric cancer demonstrated a marginally lower incidence of weight loss at 3 months in the group of patients referred to a dietician at diagnosis (0% vs. 2%; P = .047).[127] In addition, a 2021 open-label phase 3 RCT of patients who had metastatic esophagogastric cancer compared interdisciplinary supportive care integrated early into standard oncological care versus standard care.[128] The early interdisciplinary supportive care included a team of gastrointestinal medical oncologists, oncology nurse specialists, dietitians, and psychologists. Patients who received early interdisciplinary supportive care within 8 weeks of diagnosis experienced improved survival (14.8 months vs. 11.9 months; hazard ratio, 0.68; 95% CI, 0.51-0.9; P = .021) along with less weight loss and improved emotional and cognitive functioning.[128]

NUTRITIONAL INTERVENTIONS

Clinicians should not routinely offer enteral tube feeding or parenteral nutrition to manage cachexia in patients who have advanced cancer. A time-limited trial of enteral or parenteral nutrition may be considered in highly selected, fit patients, including those with reversible bowel obstruction, short-gut syndrome, or malabsorption.[120] The most serious complication associated with enteral nutrition is aspiration, the incidence of which increases in patients who have delayed gastric emptying and advanced age. Other adverse effects of enteral nutrition include diarrhea, nausea, vomiting, abdominal cramping, bloating, and distention. Parenteral nutrition is hyperosmolar, calorie-dense nutrition administered via a central catheter. In general, when clinicians

must use parenteral nutrition, it should be limited to the preoperative setting of potentially resectable obstructing tumors over a period of less than 10 days. Risks of parenteral nutrition are primarily infectious (ie, catheter-associated sepsis and bacteremia) and metabolic (ie, hyperglycemia, electrolyte abnormalities, abnormalities in liver enzymes, essential fatty acid deficiency, and hypertriglyceridemia). Overall, studies demonstrate net harm when parenteral nutrition is routinely provided to patients who have cancer.[120] Evidence also suggests a decreased tumor response to chemotherapy, increased infections, and inferior survival when patients with cancer receive parenteral nutrition.

If nutritional support is required, enteral nutrition offers several advantages over parenteral nutrition, including fewer risks and complications, delivery of nutrients in a physiological manner, convenience for home use, and decreased cost.

POTENTIAL PHARMACOLOGICAL AGENTS FOR THE MANAGEMENT OF CANCER CACHEXIA

Multiple clinical trials have investigated drugs for the treatment of cancer cachexia, but the FDA has not approved any agent to date.[125] However, several recent high-quality trials have shown a notable effect on cachexia-related outcomes and now give oncology clinicians additional evidence-based pharmacological options.

Olanzapine

The 2023 ASCO rapid guideline update for cancer cachexia highlights the 2023 double-blind, placebo-controlled RCT of olanzapine for chemotherapy-related anorexia in patients who have locally advanced or metastatic gastric, hepatopancreaticobiliary, or lung cancer.[3,129] After starting chemotherapy, patients were randomly assigned to receive 2.5 mg of olanzapine once daily or a placebo for a total of 12 weeks. The study found that 60% of patients receiving olanzapine experienced a weight gain of more than 5% compared with 9% in those receiving the placebo ($P < .001$). Furthermore, patients in the olanzapine arm also reported improved appetite and a lower incidence of high-grade (grade 3 or higher) therapy-related toxicity (12% in the olanzapine arm compared with 37% in the placebo arm; $P = .002$). Olanzapine-related adverse events were not significantly different from those in the placebo arm. This study, taken together with past studies of olanzapine and weight gain and appetite, among other symptoms, led to the ASCO Guidelines Panel recommendation that clinicians consider a low dose (2.5 mg) of olanzapine once daily to improve weight gain and appetite in adults who have advanced cancer.[3,129]

Mirtazapine

Clinicians use mirtazapine (7.5-45 mg daily), a tetracyclic antidepressant, to treat cancer-related cachexia and anorexia. Until recently, one open-label pilot study and a single open-label phase 2 trial comprised all available data. However, a 2024 single-center, phase 3, double-blind, placebo-controlled trial randomly assigned 86 patients who had advanced non–small cell lung cancer to receive 15 mg of mirtazapine orally daily or placebo for 2 weeks, then increasing to 30 mg or placebo for 6 more weeks.[130] The outcomes of interest were appetite, as scored on the Anorexia Cachexia Scale, along with patient-reported caloric intake. The study found no significant difference in appetite scores between the two arms after both 4 and 8 weeks. However, after 4 weeks, patients in the mirtazapine arm had significantly greater intake of overall calories as well as proteins, carbohydrates, and fats; in fact, at 8 weeks, the fat intake in the mirtazapine cohort was 14.5 g compared with 0.7 g in the placebo group ($P = .02$). In addition, at 8 weeks, the mirtazapine arm had a significantly lower proportion of patients who had sarcopenia (57.1% compared with 82.8% in the placebo arm; $P = .03$). Although intriguing, these findings need further evaluation in a larger study before mirtazapine can be recommended for management of certain cancer-related wasting syndromes.

Steroid-Based Regimen

Clinicians may consider a short-term trial of a corticosteroid in patients experiencing loss of appetite and body weight but must balance risks and benefits.[120] The corticosteroid dexamethasone may transiently improve anorexia but does not enhance skeletal muscle mass. Dexamethasone is associated with multiple adverse effects (eg, Cushing syndrome, hyperglycemia, adrenal insufficiency, myopathy, infection risk, osteoporosis) related to duration and cumulative dose of dexamethasone.

Megestrol acetate, a synthetic derivative of the naturally occurring corticosteroid hormone progesterone, provides benefits for appetite, caloric intake, and weight gain that seem to plateau at 800 mg. However, the weight gained using megestrol is predominantly adipose tissue and not skeletal muscle. Serious adverse effects associated with megestrol use include increased risks of death (relative risk, 1.42; 95% CI, 1.04-1.94), thromboembolic events (relative risk, 1.84; 95% CI, 1.07-3.18), and edema (relative risk, 1.36; 95% CI, 1.07-1.72).[131] Studies have also demonstrated that megestrol can cause diarrhea, rash, impotence, and, if stopped abruptly, adrenal insufficiency. Most recently, Currow et al[132] completed a multisite RCT comparing megestrol acetate at 480 mg daily, dexamethasone at 4 mg daily, and placebo to evaluate their effect on appetite in patients with advanced cancer and anorexia (2 weeks or longer; 0-4 patient-reported anorexia score). In nearly 200 patients, there was no difference in anorexia (25% or greater improvement over baseline) observed among the three arms at 1 week. The 2023 ASCO rapid guideline update for cancer cachexia does suggest that clinicians may offer a short-term trial of a progesterone analog or a corticosteroid for weight loss and/or decreased appetite for patients who have advanced cancer who are unable to tolerate a low dose (2.5 mg) of olanzapine.[3]

Limited data support the combination of olanzapine plus megestrol acetate to treat cancer-related anorexia. Patients who have advanced gastrointestinal or lung cancer with anorexia and at least 5% weight loss from previous weight who took 5 mg

of olanzapine per day plus 800 mg of megestrol acetate per day (compared with those taking megestrol acetate alone) reported improved appetite and at least 5% weight gain at 8 weeks.[133] However, since olanzapine alone can produce these effects, the role of the additional megestrol acetate in producing these outcomes is unclear.

Newer Agents

Ponsegromab, a monoclonal antibody targeting growth differentiation factor 15 (GDF-15), increased weight gain among patients with cancer cachexia. A recent phase 2 double-blind study compared the GDF-15 inhibitor ponsegromab with placebo at three different doses. The study enrolled 187 adults with elevated serum GDF-15 with various cancer types and cancer cachexia to receive three doses of 100, 200, or 400 mg of ponsegromab subcutaneously or placebo every 4 weeks.[134] Patients had weight gain at all ponsegromab doses, and the drug showed increased overall activity at the highest dose.

Agents Without Evidence of Efficacy

Multiple pharmacological agents, including cannabinoids, androgens, and cyproheptadine, have been studied for the treatment of cancer cachexia but all show limited efficacy.[134,135] A phase 3 RCT of 243 patients with advanced cancer and weight loss (5% or greater over 6 months) evaluated the effect of cannabis extract (2.5 mg of *d*-9-tetrahydrocannabinol and 1 mg of cannabidiol), 2.5 mg of *d*-9-tetrahydrocannabinol, or placebo on appetite and QoL. Researchers found no difference in patient appetite or QoL among treatment arms over 6 weeks. Another commonly used cannabinoid is dronabinol, a synthetic *d*-9-tetrahydrocannabinol. Dronabinol is also less effective than megestrol acetate in producing weight gain, appetite, or improved QoL. Like megestrol acetate, dronabinol primarily increases adipose tissue and body fluid, and not lean muscle mass. Cannabinoids should be used with caution, especially in elderly and seriously ill patients because of their multiple adverse effects, including drowsiness, dizziness, dysphoria, euphoria, impaired cognition, and fall risk.[135]

Three RCTs evaluated androgens or selective androgen receptor modulators. One study comparing megestrol acetate, dexamethasone, and fluoxymesterone to treat patients with cancer cachexia and anorexia found no difference in weight gain across the three arms and showed that megestrol acetate improved appetite better than fluoxymesterone. Nandrolone decanoate (200 mg intramuscularly) administered weekly over 4 weeks to patients with incurable lung cancer receiving chemotherapy showed no difference over usual care.[136] In a double-blind, placebo-controlled, phase 2 trial evaluation of weekly injections of testosterone enanthate in 21 patients with advanced cancer receiving chemotherapy. Testosterone improved lean body mass and increased QoL and physical activity compared with placebo.[137,138] No phase 3 trials have been reported. Investigators compared placebo with two different doses of enobosarm (1 or 3 mg), an investigational selective androgen receptor modulator, in a phase 2 RCT.[34] Patients receiving enobosarm experienced greater increases in lean body mass than patients in the placebo arm, but no follow-up phase 3 trials have been reported.[139] Anamorelin, a ghrelin receptor agonist, showed significantly increased lean body mass but not handgrip strength in two randomized, placebo-controlled trials in 900 patients who had advanced non–small cell lung cancer and cachexia.[140] Anamorelin has not received FDA approval to date.

Cyproheptadine, a serotonin antagonist, produced only a mild increase in appetite and food intake and did not affect progressive weight loss in a large randomized controlled study using oral cyproheptadine at 8 mg three times daily. Cyproheptadine should be avoided, given its adverse effects, most notably sedation, and limited efficacy for patients who have cancer-related cachexia.

FAT MALABSORPTION

Fat malabsorption may occur in multiple cancer settings: pancreatic cancer and exocrine insufficiency, gastric resection, hematopoietic cell transplantation, short-gut syndrome, and chronic radiation enteritis. Vague abdominal pain, increased gas, steatorrhea, and increased stool odor characterize fat malabsorption. Exogenous oral pancreatic enzymes can minimize fat malabsorption. Enteric-coated pancreatic enzymes resist destruction or inactivation in gastric acid and release the enzymes in vivo in the duodenum at a pH greater than 5.5. In the duodenum and proximal small intestine, these exogenous enzymes replace physiological digestive enzymes secreted by the pancreas, catalyzing the hydrolysis of fats into monoglycerol and fatty acids, protein into peptides and amino acids, and starch into dextrans and short-chain sugars.

Pancreatic enzymes should be taken with food, initiated at the lowest recommended dose, and gradually increased based on clinical symptoms, degree of steatorrhea, and fat content in the diet. Prescribers base enzyme doses on lipase units. Initially, adults start at 500 lipase units/kg per meal, with titration to a maximum of 2,500 lipase units/kg per meal. Half of the prescribed dose should be given with snacks between meals. The degree of abdominal pain and steatorrhea reflects adherence and adequacy of enzyme doses and should be monitored.

KEY POINTS

- Categories of cachexia include precachexia, cachexia, and refractory cachexia.
- Cachexia is associated with increased treatment-related toxicity, decreased QoL, and poor survival.
- Overall, studies demonstrate a net harm when providing parenteral nutrition to patients who have cancer.

- There are no FDA-approved pharmacological treatments for weight loss associated with cancer cachexia.
- The weight gain associated with the use of megestrol acetate, dronabinol, and dexamethasone is primarily adipose tissue and fluid, not skeletal muscle.
- Deep vein thrombosis and adrenal suppression are two notable adverse effects of megestrol acetate.
- Clinicians must support caregivers given the paucity of effective treatment options and the distress cachexia causes when caregivers witness anorexia, weight loss, weakness, and decreased QoL in their loved ones.
- Pancreatic exocrine insufficiency is common in patients who have pancreatic cancer. Clinicians should treat patients with exogenous enzyme replacement and titrate to control abdominal symptoms and steatorrhea.

DIARRHEA

Diarrhea is characterized by frequent loose or liquid bowel movements. In patients who have cancer, diarrhea can result from cancer itself or its treatment. Examples include osmotic diarrhea associated with pancreatic cancer exocrine insufficiency (as described in the "Fat Malabsorption" section of this chapter) or secretory diarrhea associated with medullary thyroid cancer, carcinoid syndrome, and pancreatic islet cell cancer. Cancer treatments, such as chemotherapy, radiation to the abdomen, targeted therapy, immunotherapy, and graft-versus-host disease, can also cause diarrhea. The incidence of chemotherapy-induced diarrhea is approximately 50% to 80%.[140]

A careful history and physical examination are necessary to determine etiology. The history should include onset, frequency, approximate volume, presence or absence of blood, and other stool characteristics. Clinicians can classify diarrhea as acute (less than 2 weeks), persistent (2-4 weeks), or chronic (longer than 4 weeks). Complete abdominal examination, digital rectal examination, temperature, and assessment of hydration status are helpful. History and examination will guide potential diagnostic evaluations, which might include stool studies. Blood work may help in evaluating hydration status, and evidence of leukocytosis may suggest an infectious etiology. Acute diarrhea unrelated temporally to treatment (see "Chemotherapy-Induced Diarrhea" section) is often infectious (ie, viral, bacterial). Within a population of patients who have advanced chronic illness, *Clostridium difficile* infection should be considered if the patient has a history of *C. difficile* infection, recent hospitalization, or recent antibiotic use.

CHEMOTHERAPY-INDUCED DIARRHEA

In general, diarrhea is most common in patients receiving chemotherapy regimens that include antimetabolites. The most studied of these agents is 5-fluorouracil (FU). The risk of diarrhea from FU increases when leucovorin is administered as a modulating agent or with protracted infusions. As with infusions, daily oral capecitabine provides long-term exposure to FU and has toxicities similar to infusional FU. Patients who have severe or uncontrolled diarrhea with 5FU or capecitabine therapy should undergo dihydropyrimidine dehydrogenase (DPD) testing.[140] There has been an increasing uptake among US institutions regarding pre-treatment testing for DPD.

Other antimetabolites associated with diarrhea include the topoisomerase I inhibitors irinotecan and topotecan. The cholinergic adverse effects of irinotecan cause an acute onset of diarrhea accompanied by abdominal cramping, rhinitis, lacrimation, and salivation. The routine use of atropine effectively prevents this cholinergic reaction. After 24 hours, a more severe form of diarrhea occurs, correlating with peak plasma levels of the irinotecan metabolite SN38. The variant of UGT1A1 in approximately 10% of White individuals leads to poor metabolism of SN38 and predicts irinotecan toxicity. Patients receiving irinotecan should, therefore, be educated about the potentially life-threatening adverse effect of severe colitis and the need to report symptoms promptly.

For uncomplicated, non-infectious, mild-to-moderate diarrhea, management includes dietary counseling (discontinuing lactose- and caffeine-containing products, alcohol, high osmolar supplements [eg, Ensure]), hydration, and antidiarrheal medications). The antidiarrheal agents loperamide and combination diphenoxylate/atropine are used most often to treat acute diarrhea. Oral loperamide should be administered at 4 mg for the first dose and 2 mg every 4 hours (maximum, 16 mg/d) or after an unformed stool. Loperamide decreases intestinal motility and has minimal systemic effects because there is little to no absorption. Diphenoxylate/atropine combination is administered as two 5-mg tablets every 6 hours for the first day (maximum, 40 mg/d) and then one 5-mg tablet daily.

If diarrhea persists for more than 48 hours during loperamide therapy, diphenoxylate and atropine or other second-line agents, including deodorized tincture of opium, bulk-forming agents, or octreotide, should be considered. Deodorized tincture of opium is concentrated morphine (10 mg/mL) administered at 10 to 15 drops in water every 4 hours. A bulk-forming agent, such as psyllium, or a bile acid sequestrant, such as cholestyramine, should be considered for patients who have adequate hydration. However, in the setting of low performance status or inadequate hydration, these agents may cause more harm than benefit and are not recommended. Octreotide is a somatostatin analog that decreases the secretion of several gastrointestinal hormones and prolongs intestinal transit time. The recommended octreotide dose for diarrhea management is 100 to 150 mcg subcutaneously three times a day.[141] Studies have demonstrated improved control of diarrhea with the use of octreotide versus loperamide. However, given its short half-life, octreotide must be administered subcutaneously, or via continuous infusion.

TARGETED THERAPY–ASSOCIATED DIARRHEA

Studies of small-molecule inhibitors of epidermal growth factor receptor (EGFR; eg, erlotinib, gefitinib, afatinib) reported a diarrhea incidence of up to 90%, but only 15% of cases were severe. The human EGFR2-directed drugs lapatinib, neratinib, and pertuzumab cause diarrhea in up to 80% of patients.[142,143] The dose-limiting toxicity of neratinib, an inhibitor of human Her-2, Her-4, and EGFR, is severe diarrhea in 40% of patients, even with loperamide prophylaxis.[142,144] The monoclonal antibodies directed against EGFR (eg, cetuximab, panitumumab) cause diarrhea rates in the 20% range, but severe diarrhea incidence is minimal.[145]

Drugs that inhibit the vascular endothelial growth factor pathway (eg, sorafenib, sunitinib, axitinib, pazopanib, cabozantinib, lenvatinib, bevacizumab, and regorafenib) cause diarrhea in 30% to 80% of patients, with few experiencing grade 3 or 4 symptoms.[146,147]

Guideline-based recommendations should be followed to treat targeted therapy–induced diarrhea.[141] Treatment is generally supportive, including dietary counseling (discontinuing lactose- and caffeine-containing products, alcohol, high-osmolar supplements [eg, Ensure]), hydration, antimotility agents (as described in the "Chemotherapy-Induced Diarrhea" section of this chapter), and withdrawal of the offending drug until symptoms resolve.

IMMUNOTHERAPY-INDUCED DIARRHEA

Diarrhea associated with ipilimumab occurs in approximately 30% of patients, whereas PD-1 blockade produces diarrhea less frequently.[148,149] Patients receiving immunotherapy should be educated about the potentially life-threatening adverse effects of severe colitis and the need to report symptoms promptly.

Checkpoint inhibitor–induced diarrhea is managed differently than most other types of diarrhea, often requiring corticosteroids.[150] Antidiarrheal agents such as loperamide should be used with caution, because they can mask the underlying autoimmune pathology. In severe cases, high-dose intravenous corticosteroids (prednisone or methylprednisolone at 1-2 mg/kg per day) and infliximab at 5 mg/kg every 2 weeks should be administered.[140,151-154] For patients refractory to steroids, infliximab, vedolizumab, or ustekinumab can be considered.[155,156]

RADIATION-INDUCED DIARRHEA

Diarrhea is the most common adverse effect of abdominal and pelvic irradiation. Radiation damages the mucosa of the small and large intestines and, thus, can produce secretory diarrhea. The incidence and severity of diarrhea increase with the addition of FU. Several placebo-controlled clinical trials have evaluated drugs to prevent diarrhea induced by pelvic irradiation. RCTs have been performed supporting various formulations of probiotics and octreotide (100-150 mg subcutaneously three times a day).[157-159] Sucralfate provided mixed results, glutamine showed no improvement, and sulfasalazine exacerbated symptoms.[157-164]

HEMATOPOIETIC CELL TRANSPLANTATION/GRAFT-VERSUS-HOST DISEASE

Diarrhea in patients who undergo hematopoietic cell transplantation may result from graft-versus-host disease and infections related to immunosuppressive therapy. The epithelial damage caused by high-dose chemotherapy can activate alloreactive cytotoxic T cells, which release a cascade of inflammatory cytokines that contribute to necrosis of gut epithelial crypt cells.

At the first sign of acute gastrointestinal symptoms consistent with graft-versus-host disease, stools should be analyzed for bacterial, fungal, and viral pathogens. Supportive management should be simultaneously initiated, and a gastroenterologist consultation should be considered. If the stool evaluation findings are positive for pathogenic bacteria, appropriate antibiotics should be used for treatment. For patients with biopsy-proven graft-versus-host disease, systemic corticosteroids should be initiated, and prophylactic immunosuppression optimized. A time-limited trial of octreotide for 7 days (500 mg intravenously every 8 hours) may be considered, but if the patient has no response within 4 days, octreotide should be discontinued to avoid ileus. If there is no response to octreotide, second-line therapy with antithymocyte globulin or infliximab should be considered.[165]

KEY POINTS

- FU and topoisomerase I inhibitors (irinotecan, topotecan) commonly cause diarrhea.
- Irinotecan causes acute diarrhea because of a cholinergic mechanism, as well as subsequent, more severe diarrhea because of its active metabolite SN38.
- In addition to supportive measures, loperamide can be used effectively to treat chemotherapy-induced diarrhea. Second-line approaches include diphenoxylate and atropine, deodorized tincture of opium, and octreotide.
- In addition to supportive measures, radiotherapy-induced diarrhea should be treated with octreotide.
- Diarrhea is common with targeted therapy and is best treated with antimotility agents and withdrawal of the offending drug.
- Checkpoint inhibitors can cause life-threatening colitis that is best treated with corticosteroids and, rarely, infliximab.
- Graft-versus-host disease–associated diarrhea should be treated with corticosteroids, optimal immunosuppression, and octreotide.

MUCOSITIS

Oral mucositis and esophagitis are common complications of chemotherapy and radiotherapy. The overall incidence of oral mucositis is approximately 40% for patients who receive standard-dose chemotherapy. Incidence varies with chemotherapy agents used and increases substantially for patients who receive dose-intensified regimens. Mucositis and esophagitis are common in patients receiving radiation to susceptible areas, and concurrent chemotherapy may exacerbate symptoms. Mucositis may occur from direct injury by cytotoxic chemotherapy or radiotherapy, secondary infections from treatment-induced myelosuppression, or graft-versus-host disease. The severity of mucositis is dose and treatment-specific.

Mucositis typically starts 5 to 7 days after the initiation of chemotherapy. It often presents first as erythema on the soft palate, buccal mucosa, ventral surface of the tongue, and floor of the mouth. These symptoms may progress to generalized desquamation. Approximately 90% of ulcerations localize to the non-keratinized mucosa. Mucositis resulting from chemotherapy can resolve within a few days or last up to 3 weeks. Chemotherapy agents frequently associated with mucositis include the antimetabolites FU and methotrexate, and high-dose or prolonged infusions of chemotherapy. Newer targeted agents can also cause mucositis, including many tyrosine kinase inhibitors, such as everolimus, and immune checkpoint inhibitors.

Oral mucositis caused by radiotherapy typically lasts an average of 6 weeks.[166]

PREVENTION OF TARGETED CHEMOTHERAPY– OR RADIOTHERAPY-INDUCED MUCOSITIS

Clinical practice guidelines should be followed to prevent and treat cancer therapy–induced oral and gastrointestinal mucositis secondary to cancer therapy.[166] A dental evaluation is recommended before beginning radiotherapy involving the oral cavity to decrease risks of local and systemic infections. If worn during radiotherapy, fluoride carriers (delivering oral fluoride) maintain tooth integrity and help to prevent radiation scatter from metal dental work.

Preventive and treatment strategies depend on radiation dose and setting (eg, head and neck cancer vs. hematopoietic cell transplantation). Effective preventive strategies include dilute rinses (eg, saline, sodium bicarbonate, benzydamine, dexamethasone, and honey), low-level laser therapy, cryotherapy, and palifermin.[166] In patients with breast cancer receiving everolimus, oral dexamethasone swish-and-spit preparation decreased mucositis markedly compared with placebo.[167] Only institutions familiar with low-level laser therapy should provide this treatment in adults receiving high-dose chemotherapy in preparation for hematopoietic cell transplantation with or without irradiation.[166] Oral cryotherapy (ie, sucking on ice chips during chemotherapy administration) produces temporary vasoconstriction and reduces the delivery of bolus dose FU chemotherapy to the oral mucosa. Data indicate that cryotherapy reduces oral mucositis by approximately 50%. A recent multi-institutional study randomized patients receiving chemotherapy to a reusable self-contained cryotherapy delivery device or best supportive care. The patients on the cryotherapy arm developed less oral pain and had less use of analgesics in the first two cycles.[168] The keratinocyte growth factor palifermin decreases severe mucositis for patients undergoing autologous hematopoietic cell transplantation with total-body irradiation conditioning regimens.[166] Palifermin c was superior to placebo in preventing FU-associated mucositis, but it has not been widely adopted because of cost. A phase 2 study in peripheral T-cell lymphoma and cutaneous T-cell lymphoma patients using oral leucovorin 25 mg three times a day for 48 hours starting 24 hours after pralatrexate reduced rates of grade 2/3 mucositis.[169] Sucralfate, allopurinol, chamomile tea, glutamine, and vitamin E are not more effective than placebo. Sucralfate also does not prevent radiotherapy-associated esophagitis. Although evidence suggests that amifostine, a cytoprotective adjuvant, can mildly decrease radiotherapy-induced esophagitis, inconvenience and expense limit its widespread use.

MUCOSITIS TREATMENT

Effective oral mucositis management includes general measures such as oral hygiene and dietary modification, topical local anesthetics, and systemic analgesics. Empirical clinical practices include gently brushing teeth with a soft-bristled toothbrush and fluoride toothpaste two to three times daily. Gentle flossing daily is encouraged to remove food and bacteria buildup. Dentures should be removed, particularly at night. When patients have mucositis-induced severe pain, adequate pain relief often requires systemic opioids, including parenteral opioids and patient-controlled analgesia.

Investigators have evaluated multiple types of mouthwash in the palliation of mucositis. A mouthwash made of doxepin, a tricyclic antidepressant, has demonstrated improved palliation of radiotherapy-associated oral mucosal pain.[170,171] A randomized study evaluated different mouthwashes consisting of saline, sodium bicarbonate, or chlorhexidine and so-called magic mouthwash (ie, lidocaine, diphenhydramine, aluminum hydroxide, magnesium hydroxide) and found decreased signs and symptoms of mucositis within 12 days without any significant differences among the groups. Given the comparable effectiveness of the mouthwashes, the least costly was the mouthwash containing salt and sodium bicarbonate.[166] Alcohol-based mouthwashes and spicy foods or beverages should be avoided.

XEROSTOMIA

Xerostomia can be seen up to 80% of the head and neck patients receiving RT.[172] Salivary functions can continue to decline for several weeks after completion of radiation therapy more so Xerosotmia can cause QoL impairment and multiple long-term

oral complications.[173] Lack of saliva also cause dyguesia and difficulty in chewing and swallowing foods, speech changes.[174] A retrospective study of 91 patients found grade 2 or higher xerostomia was associated with tumors located in the nasopharynx, oropharynx, floor of mouth, or oral cavity, while grade 3 or higher was associated with age >61 years.[175] ISOO/MASCC/ASCO Guidelines on Xerostomia induced by non-surgical modalities recommend tissue-sparing intensity-modulated radiation therapy (IMRT) to decrease injury to salivary glands. Patients who develop xerotomia can use topical mucosal lubricants or saliva substitutes can be used. Transient relief can be obtained by stimulating the residual gland capacity using sugar-free acidic or non-acidic gums/lozenges or muscarinic agonist, for example, pilocarpine or Cevimeline.[176]

KEY POINTS

- Evidence-based prevention strategies of mucositis include oral rinses, low-dose laser therapy, cryotherapy, and palifermin.
- Dexamethasone rinse improves the prevention of everolimus-induced stomatitis. Doxepin mouthwash improves mucositis-related pain.
- There are no differences in effectiveness for palliation of oral mucositis among mouthwashes consisting of saline, sodium bicarbonate, chlorhexidine, or so-called magic mouthwash.

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

CIPN may develop after treatment with platinum analogs (eg, cisplatin, oxaliplatin, carboplatin), taxanes (eg, paclitaxel, docetaxel, nab-paclitaxel), vinca alkaloids (eg, vincristine), proteasome inhibitors (eg, bortezomib), and immunomodulators (eg, thalidomide, lenalidomide). The clinical presentation reflects an axonal peripheral neuropathy with glove-and-stocking distribution sensory loss, combined with features suggestive of nerve hyperexcitability, including paresthesia, dysesthesia, and pain. These symptoms may be disabling, adversely affecting activities of daily living and QoL.

The incidence of CIPN seems to be related to cumulative dose and infusion duration; individual risk factors may also influence the development and severity of neurotoxicity. Substantial work has evaluated genetic predispositions for CIPN, but no genetic

Table 8-11 **Mechanisms of Chemotherapy-Induced Peripheral Neuropathy**

Chemotherapy	Neurotoxicity	Incidence	Cumulative Dose	Recovery
Cisplatin	Long-lasting cumulative distal sensory neuropathy	50%-90% of patients receiving ≥500 mg/m^2	Beginning at 300 mg/m^2	Incomplete
Carboplatin	Mild sensorimotor neurotoxicity	Uncommon; mild in 25% of patients; severe in 5%	More common with high doses: 800-1,600 mg/m^2	Not fully described
Oxaliplatin	Acute cold–associated neurotoxicity and chronic sensory neuropathy	Acute symptoms in 95%; severe chronic toxicity in 10%-20% at 750-850 mg/m^2	Acute symptoms at all doses, severe at >540-700 mg/m^2	May persist for a long time; in 10% of patients at 2 years post-treatment
Paclitaxel	Distal sensory neuropathy with pain and motor symptoms at high doses	Severe dose dependence in 10%-30% of patients	>300 mg/m^2 but can occur at lower doses	May persist, although reversibility is reported
Docetaxel	Distal sensory neuropathy with pain	Less severe neurotoxicity than paclitaxel, severe in 6%-10% of patients	>100 mg/m^2; severe toxicity >600 mg/m^2	Not fully described
Vincristine	Distal sensorimotor painful neuropathy	60% of patients, dose dependent	4-10 mg	≤33% of patients report persistent symptoms
Bortezomib	Sensory axonal neuropathy, occasionally demyelinating	≥35%-50% of patients	1.3 mg/m^2	Resolution in 3 months; may persist
Thalidomide	Sensorimotor painful neuropathy	25%-75% of patients	At dose ≥20 g	Not fully described

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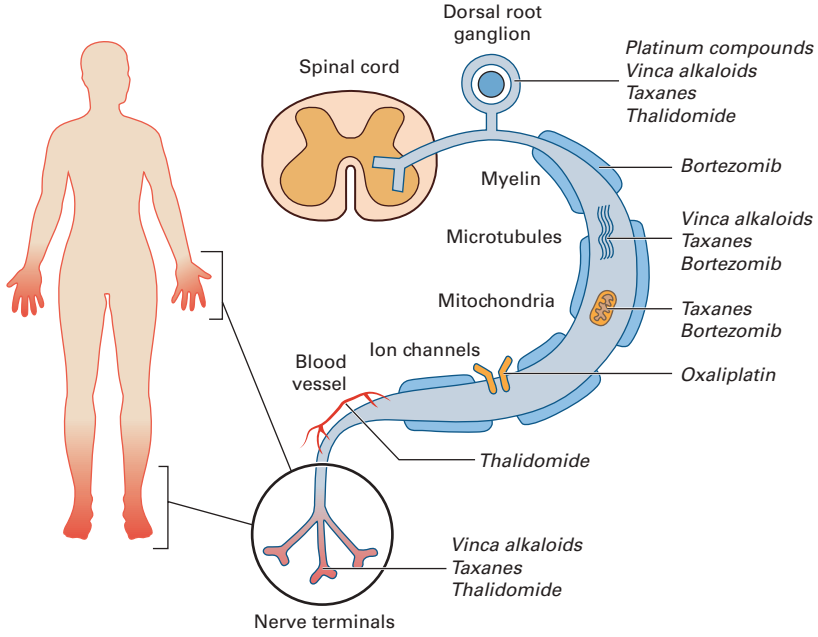
tests have been established for use in clinical practice. However, patients who have family members with Charcot-Marie-Tooth–associated neuropathies may be predisposed to CIPN from neurotoxic chemotherapy.[177] CIPN develops more often in patients who have obesity, diabetes, or a history of alcoholism. Exercise and increased blood to the peripheral nerves might mitigate this toxicity.[178-180]

Differences in structural properties between chemotherapies further contribute to variations in clinical presentation. The mechanisms underlying CIPN are diverse and, when present in combination, additive (Table 8-11). Different chemotherapy classes target different components of the peripheral nervous system, including dorsal root ganglia neuronal cell bodies, axonal transport pathways, mitochondrial operation, calcium ion regulation systems, and axonal membrane ion channels (Fig. 8-5). In addition, data strongly support that the acute pain syndrome caused by paclitaxel, which classically has been identified as arthralgias and myalgias, is not from an injury to muscles or joints; rather, it seems to be a manifestation of an acute neuropathy.[181]

Figure 8-5 Mechanisms of CIPN



Abbreviation: CIPN, chemotherapy-induced neurotoxicity.
Proposed targets of CIPN in the peripheral nervous system include damage to dorsal root ganglion neuronal cell bodies (platinum compounds, vinca alkaloids, taxanes, thalidomide), demyelination (bortezomib), microtubule-associated toxicity (vinca alkaloids, taxanes, bortezomib), mitochondrial dysfunction (taxanes, bortezomib), axonal membrane ion channelopathy (oxaliplatin), peripheral vasculature impairment (thalidomide), and distal axonal injury (vinca alkaloids, taxanes, thalidomide).
Adapted from Park SB, Goldstein D, Krishnan AV, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. *CA Cancer J Clin*. 2013;63:419-437. doi:10.3322/caac.21204

The 2020 ASCO CIPN guideline reviewed the value of strategies for preventing CIPN and treating patients with it.[182] Amifostine, amitriptyline, calcium and magnesium, glutathione, and vitamin E were all found to be ineffective in preventing CIPN. Per this guideline, no agents are recommended for preventing CIPN. However, there is one preventive strategy specific to the administration of bortezomib. Patients with multiple myeloma treated with subcutaneous versus intravenous bortezomib experienced less CIPN and had similar overall response rates.[183] Consequently, subcutaneous administration of bortezomib to patients with multiple myeloma is now the standard of care.[184,185] Cryotherapy is also emerging as an option to help prevent taxane-induced peripheral neuropathy and is supported by recent meta-analyses, given its relative safety.[184] Duloxetine is the only agent with proven efficacy for treating established CIPN.[139,186] Gabapentinoids (gabapentin and pregabalin), helpful for many peripheral neuropathies of other etiologies, are not effective for CIPN. Limited data do not support the use of acetyl-L-carnitine, tricyclic antidepressants, or topical treatments (eg, baclofen, amitriptyline hydrochloride, ketamine) to treat patients with CIPN.[182] A recent observational study in breast cancer patients with painful CIPN showed that a high-concentration topical capsaicin patch caused a significant reduction in neuropathic pain and improvement in CIPN-related QoL.[187] This agent will need further validation in large-scale studies. In addition, meta-analysis suggests exercise interventions are associated with improved patient CIPN symptoms and QoL, though higher-quality trials are needed.[188]

KEY POINTS

- There are no established methods to prevent CIPN other than limiting exposure to the offending drugs.
- Patients at higher risk for developing CIPN include those with a history of inherited neuropathy, obesity, diabetes, and alcoholism.
- The best-established drug for treating painful CIPN is duloxetine, but its efficacy is limited.

DYSPNEA

Dyspnea is the subjective experience of breathlessness. In patients who have advanced cancer, the prevalence is 21% to 79%, with moderate to severe dyspnea in 10% to 63% of patients. The respiratory center, located in the medulla oblongata and pons of the brainstem, controls breathing homeostasis. Chemoreceptors detect blood oxygenation, and mechanoreceptors detect stretching and congestion. Alterations in blood pH and blood gases increase the demand for respiratory signaling by the brain through activation of chemoreceptors and mechanoreceptors, resulting in dyspnea.

Dyspnea is a subjectively measured outcome. Objective measurements of compromised respiratory status (eg, respiratory rate, peripheral oxygen saturation) may or may not correlate with a patient's subjective report.[189] In appropriate patients, a short walking test with or without oxygen monitoring should be considered. Although there can be many unrelated cancer etiologies and comorbid disease states causing dyspnea (eg, chronic obstructive pulmonary disease, asthma, congestive heart failure), common causes in patients who have advanced cancer are pleural effusions, lymphangitic tumor spread, and pulmonary embolism. Treatment-related causes include infectious pneumonitis and pneumonitis caused by molecularly targeted agents, checkpoint inhibitors, cytotoxic chemotherapy, and radiotherapy.

NON-PHARMACOLOGICAL APPROACHES

ASCO published guidelines on the management of dyspnea in patients with advanced cancer in 2021.[189] Limited evidence exists on the effectiveness of non-pharmacological management of dyspnea in patients who have cancer, but clinicians may offer supplemental oxygen for patients who have hypoxemia and psychoeducational self-management, a room air fan, or room air delivered by nasal cannula.[190,191] A room air fan positioned to target the patient's maxillary ridge is often effective.[189,192] The proposed mechanism is facial cooling of the trigeminal cranial nerve branches. In a phase 3 trial of nasal cannula oxygen versus room air in patients who did not have hypoxia, oxygen provided no additional symptomatic benefit for the relief of refractory dyspnea compared with room air.[191] The flow of either oxygen or room air activates nasal mechanoreceptors and decreases dyspne.

PHARMACOLOGICAL APPROACHES

For patients who have dyspnea for whom non-pharmacological interventions do not provide relief, clinicians may offer systemic opioids and consider corticosteroids and benzodiazepines.[193] Opioids may relieve dyspnea by reducing ventilation and the central-mediated perception of dyspnea through the same receptors that relieve pain. For opioid-naive patients, low-dose oral morphine at 5 to 10 mg every 3 to 4 hours or intravenous morphine at 2 to 5 mg (or equivalent) every 2 hours typically provides relief. Patients receiving long-term opioid treatment should be given the same rescue opioid dose (ie, 10%-20% of the total 24-hour opioid dose) that is given for intermittent pain relief. Evidence does not support nebulized morphine use.[193] Given the interrelatedness of dyspnea and anxiety, limited evidence supports short-acting benzodiazepines for patients who experience dyspnea-related anxiety refractory to opioids and non-pharmacological measures. If airway obstruction or inflammation is a likely contributor to dyspnea, systemic corticosteroids should be considered. Bronchodilator use should be limited to patients with dyspnea resulting from obstructive pulmonary disorder or bronchospasm. Evidence does not support the use of antidepressants, neuroleptics, or inhaled furosemide for the palliation of dyspnea. For patients with a life expectancy of days and refractory dyspnea, continuous palliative sedation, ideally in collaboration with hospice clinicians or palliative care specialists, will provide relief.[193]

KEY POINTS

- Dyspnea is a subjective experience that may or may not correlate with objective findings.
- Any reversible causes of dyspnea should be identified and treated when possible.
- In the absence of hypoxemia, oxygen provides no additional symptomatic benefit for dyspnea compared with room air.
- Limited evidence supports the use of systemic opioids to palliate dyspnea.

CUTANEOUS TOXICITIES OF CANCER THERAPIES

EGFR INHIBITORS

Up to 50% of patients with cancer who receive EGFR inhibitors experience a prominent skin rash.[194,195] This rash has acne-like characteristics but is not considered acne. Other targeted drugs associated with a similar rash include mammalian target of rapamycin (eg, everolimus and temsirolimus) and multikinase inhibitors (eg, sorafenib and sunitinib). Prophylactic and treatment

guidelines describe the prevention and treatment of patients with EGFR inhibitor–associated rash (Table 8-12).[85] EGFR inhibitor rash prevention includes topical corticosteroids and moisturizers or oral minocycline or doxycycline. EGFR inhibitor rash treatment includes topical corticosteroids, clindamycin, oral minocycline, doxycycline, or low-dose isotretinoin. Patients with moderate to severe rash may benefit from a consultation with a dermatologist. In addition to the acneiform rash, these drugs can also cause many other dermatological problems, including periungual disease, photosensitivity, pruritus, xerosis, Stevens-Johnson syndrome, and skin cancer. Of note, data support the development of an EGFR inhibitor–induced rash as a pharmacodynamic marker of antitumor activity.[153,196,197]

Table 8-12 Strategies for EGFR-Associated Acneiform Rash

Strategy	Recommended	Not Recommended
Topical preventive	Hydrocortisone	Pimecrolimus
		Tazarotene
		Sunscreen as a single agent
Systemic preventive	Minocycline	Tetracycline
	Doxycycline	
Topical treatment	Alclometasone	
	Fluocinonide	
	Clindamycin	
Systemic treatment	Doxycycline, 100 mg twice daily	Photosensitizing agents
	Minocycline, 100 mg daily	
	Low-dose isotretinoin, 20-30 mg daily	

Abbreviation: EGFR, epidermal growth factor receptor.
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HAND-FOOT SYNDROME

One of the dose-limiting toxicities of capecitabine is a prominent rash called palmar-plantar erythrodysesthesia, also known as hand-foot syndrome.[198] Patient symptoms usually begin with erythema and proceed to pain, swelling, desquamation, and rarely ulceration. With prolonged capecitabine use, hand-foot syndrome can lead to substantial morbidity to the point that patients may be unable to use their hands and feet. Predictors of hand-foot syndrome include increased serum folate and red blood cell folate levels as well as genomic variants linked to wound healing and cytoskeletal anchoring.[52]

Celecoxib prevented moderate to severe and all-grade hand-foot syndrome in RCTs.[53,199,200] A single-center, double-blind, placebo-controlled trial using topical diclofenac gel for hand-foot syndrome prevention in patients with breast and gastrointestinal cancers treated with capecitabine showed a reduction in grade 2/3 hand-foot syndrome from 18.1% to 6.1%. In the same study, the rates of capecitabine dose reduction because of hand-foot syndrome were 13.5% (placebo) versus 3.8% (topical diclofenac).[200] The current mainstay of treatment is interruption of therapy and, if necessary, dose reduction. Placebo-controlled studies demonstrated no benefit from vitamin B6, urea–lactic acid cream, topical emollients or creams, systemic or topical corticosteroids, nicotine patches, or vitamin E.[52,85,201]

ALOPECIA

Chemotherapy-induced alopecia is a common concern for patients undergoing cancer-directed therapies and is such a feared complication that nearly 10% of women would consider refusing chemotherapy to avoid it.[202] Thinning of the hair shaft, leading to breakage, and inhibition of dividing hair matrix cells, resulting in hair separation from the bulb, are likely responsible. Risks for alopecia include the type of chemotherapy, higher chemotherapy doses, shorter infusion times, certain non-Western European hair, female sex, and older age. Hair loss generally occurs 2 to 4 weeks after chemotherapy initiation, and regrowth occurs 3 to 6 months after cessation of therapy, although, rarely, irreversible hair loss occurs. Available evidence suggests that regional hypothermia decreases alopecia without increasing the incidence of scalp metastasis in patients with solid tumors.[202-207] However, there are no data to suggest the safety of regional hypothermia for patients with hematological malignancies.[85]

KEY POINTS

- Prevention of patients with EGFR inhibitor–associated rash includes topical corticosteroids and moisturizers, or oral minocycline or doxycycline.

- Treatment of patients with EGFR inhibitor–associated rash includes topical corticosteroids, clindamycin, oral minocycline, doxycycline, or low-dose isotretinoin.
- No evidence supports the use of vitamin B6 supplementation, urea–lactic acid cream, topical emollients or creams, systemic or topical corticosteroids, nicotine patches, or vitamin E to prevent or treat hand-foot syndrome.
- Scalp cryotherapy is effective for select patients with solid tumors, but safety data are lacking for patients with hematological malignancies.

HORMONE-DEPRIVATION SYMPTOMS

Androgen-deprivation treatment is often used to treat patients with prostate cancer but is associated with multiple adverse effects, including weight gain, osteoporosis and bone fractures, and hot flashes (see "Hot Flashes" section). Although a recent prospective study showed that androgen-deprivation treatment was not associated with a cognitive decline, after 1 year of treatment, androgen-deprivation treatment was associated with increased depressive symptoms, fatigue, and more sleep disturbances. Increased insomnia symptoms explained the relationship between taking androgen-deprivation treatment and perceived cognitive function and satisfaction with cognition.[208-210]

HOT FLASHES

Hot flashes are highly prevalent among patients with breast cancer and other premenopausal women who undergo ovarian function suppression. In addition, approximately 75% of men undergoing androgen-deprivation treatment will have substantial discomfort because of hot flashes. Non-pharmacological approaches to prevent hot flashes in healthy postmenopausal women include electroacupuncture, paced respiration, cognitive behavioral therapy, and hypnosis.[211]

Estrogens and androgens can alleviate hot flashes for women and men, respectively; however, there is concern about administering exogenous hormones to patients with hormonally driven cancers. Alternative agents, therefore, should be used to control hot flashes for patients who are refractory to non-pharmacological approaches.

Evidence supports the use of antidepressants to treat hot flashes. Use venlafaxine, citalopram, or escitalopram for patients receiving tamoxifen, because these agents do not alter tamoxifen metabolism. Paroxetine, fluoxetine, and sertraline, however, should be avoided in patients taking tamoxifen, because they can decrease the metabolism of tamoxifen to its active metabolite endoxifen by the enzyme CYP2D6.

The results from placebo-controlled RCTs indicate that clonidine inhibits hot flashes more than placebo but carries a higher risk of anticholinergic adverse effects.[212] Gabapentin is also effective in controlling hot flashes at a dose of 900 mg per day, but not at a dose of 300 mg per day. Randomized placebo-controlled trials demonstrated that oxybutynin decreased hot flashes in men, with mouth dryness being the most common adverse effect.[212]

A recent phase 3 study demonstrated that elinzanetant (dual NK-1/NK-3 antagonist) caused a significant decrease in hot flash frequency, severity, and sleep disturbance, along with improved QoL in patients with breast cancer on endocrine therapy.[213]

Oxybutnin has shown promising results in the management of hot flashes in men on androgen deprivation therapy (ADT) for prostate cancer. A phase 2 study using high-, low-dose oxybutynin, and placebo showed daily hot flash score reduction of 13.95, 9.94, and 4.85, respectively, from an average daily hot flash of 18.23.[214]

Results from large placebo-controlled clinical trials do not demonstrate any benefit from a phytoestrogen product for breast cancer survivors.[215] Black cohosh, flaxseed, magnesium oxide, and vitamin E were similarly ineffective.[216-218]

VAGINAL DRYNESS, DYSPAREUNIA, AND LOW LIBIDO

More than 60% of people treated for cancer have long-term sexual dysfunction. However, fewer than 25% of those with sexual problems get professional help.[219] Although cancer-related sexual problems usually begin with physiological damage from cancer treatment, a patient's coping skills and the quality of the sexual relationship are crucial in sexual rehabilitation. Barriers to care for patients with cancer with sexual dysfunction include a lack of discussion of this problem with the oncology team.

Vaginal dryness from urogenital atrophy is a major symptom of estrogen depletion for some women. It can contribute to pain during intercourse as well as itching and irritation. Aqueous lidocaine preparation, used topically at the introitus before sexual activity, can decrease dyspareunia. Non–estrogen-containing vaginal lubricants help to alleviate symptoms.[220] These products, however, are less efficacious than topical estrogen therapy.[221]

Despite evidence showing rare persistent estradiol elevation among patients who have breast cancer receiving aromatase inhibitors,[222] clinicians continue to report concern about the systemic absorption of topical estrogens and testosterone. However, data presented at ASCO 2025 demonstrated no increased risk from vaginal estrogen tablets in breast cancer survivors,[223] and their use decreases the incidence of urinary tract infections.

Data in women who do not have cancer show that vaginal dehydroepiandrosterone can decrease vaginal dryness and reduce discomfort during sexual activity without increasing systemic estrogen levels. RCTs involving patients who have a history of cancer support the safe use of dehydroepiandrosterone, an estradiol-releasing vaginal ring, and intravaginal testosterone cream

for dyspareunia.[224] A double-blind, randomized, placebo-controlled trial of transdermal testosterone in women with cancer, however, did not show any improvement in libido.[13] A potential explanation for the negative results in patients with cancer is that the women involved in this trial were postmenopausal and did not receive supplemental estrogen. In most previous trials in other patient groups, women were premenopausal and had also been receiving estrogen-replacement therapy (Table 8-13).

Table 8-13 Approaches to Hormone-Related Symptoms in Patients With Cancer

Symptom	Evidence-Based Therapy	Non-Evidence-Based Therapy
Hot flashes	Antidepressants	Phytoestrogen product (soy)
	Clonidine	Black cohosh
	Gabapentin	Flaxseed
	Oxybutynin	Magnesium oxide
	Cognitive behavioral therapy	
	Hypnosis	
	Elinzanetant (dual NK-1/NK-3 antagonist)	
Vaginal dryness	Dehydroepiandrosterone	
	Vaginal estrogen tablets	
Dyspareunia	Lidocaine	
	Vaginal estrogen tablets	
Low libido		Transdermal testosterone

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KEY POINTS

- Sexual health concerns are common in patients who have cancer, but oncologists do not commonly discuss them with patients.
- Non-hormonal therapies to decrease hot flashes include antidepressants, gabapentin, clonidine, oxybutynin, and elinzanetant.
- For patients receiving tamoxifen, paroxetine, fluoxetine, and sertraline should be avoided, because they can decrease the metabolism of tamoxifen by CYP2D6 to its active metabolite.
- Hormonal therapy for hot flashes can include the use of progesterone analogs.
- Dehydroepiandrosterone, vaginal laser therapy, and vaginal estrogen tablets can help to alleviate vaginal dryness.
- Topical dehydroepiandrosterone, an estradiol-releasing vaginal ring, intravaginal testosterone cream, vaginal estrogen tablets, and topical lidocaine can ease dyspareunia.
- Testosterone, without the addition of estrogen-replacement therapy, does not seem to help increase libido in postmenopausal women who have cancer.

HIGH-YIELD TAKEAWAYS

- No pharmacological intervention is supported by evidence to treat cancer-related fatigue.
- Low-dose olanzapine can be used to improve weight and appetite in patients with advanced cancer.
- Opioids can be considered for patients with advanced cancer to relieve dyspnea.
- In patients with painful chemotherapy-induced peripheral neuropathy, duloxetine should be considered.

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

PAIN AND SYMPTOM MANAGEMENT

8

CHAPTER SUMMARY GUIDE

KEY POINTS

- Clinicians may inadvertently miss or underestimate the severity of patient symptoms.
- Symptom monitoring using PROs improves QoL and overall survival for patients who have advanced cancer.
- Daily patient-reported global symptom monitoring is feasible in hospitalized patients and outpatient settings who have advanced cancer.
- A multimodal approach to managing the pain of cancer patients that includes pharmacological and non-pharmacological interventions is strongly recommended.
- Non-steroidal anti-inflammatory agents are first-line therapies for mild pain and can minimize the need for opioids in patients with somatic pain, including pain from bone metastases.
- Morphine is the most studied, evidence-based, cost-efficient opioid for the treatment of patients with cancer who have pain.
- Methadone is a mu agonist and *N*-methyl-D-aspartate receptor antagonist effective in treating neuropathic pain. Methadone is a complex drug that requires expert oversight in its prescribing and monitoring.
- TDF and buprenorphine patches are approved for opioid-tolerant patients.
- Methadone, buprenorphine, and fentanyl are the safest opioids in the setting of renal failure; however, they are not intended to be first-line options in those for whom other opioids can be considered or used.
- Avoid defining anticipated and transient opioid-associated adverse effects (eg, nausea, pruritus) as true allergies (eg, hives, shortness of breath).
- When prescribing opioids to patients who have cancer, it is important to anticipate expected adverse effects and develop strategies to prevent them.
- Stimulant laxatives (eg, senna, bisacodyl), not stool softeners, are the most effective approach to prevent and treat OIC. Polyethylene glycol is also effective.
- Consideration of interventional approaches for cancer pain should be discussed.
- Oncologists must use accurate terminology to describe OUD.
- Universal precautions describe an opioid-prescribing practice in which clinicians assess all patients for history or risk of opioid misuse regardless of demographic, social, or disease-related variables.
- Effective use of adjuvant agents for bone and neuropathic pain can provide more effective pain control with fewer adverse effects than opioids alone.
- There are four types of CINV: acute, delayed, breakthrough, and anticipatory.
- Chemotherapy is classified into four emetic risk categories: highly emetogenic (>90% risk), moderately emetogenic (30%-90% risk), low emetogenic (10%-30% risk), and minimally emetogenic (<10% risk).
- Prevention of CINV is key because patients who experience CINV during the first cycle of chemotherapy are up to five times more likely to experience CINV in subsequent cycles.
- Olanzapine significantly reduces nausea and emesis in highly emetogenic chemotherapy regimens when combined with neurokinin-1 receptor antagonists, $5HT_3$ receptor antagonists, and dexamethasone.
- Cancer fatigue is widespread and often multifactorial.
- In patients experiencing cancer-related fatigue, clinicians should evaluate and treat coexisting conditions, such as depression, anemia, thyroid dysfunction, and electrolyte disorders, and discontinue fatigue-inducing medications when possible.
- In patients who have cancer fatigue, moderate-intensity exercise, psychological interventions, and Tai Chi–based interventions can improve symptoms.
- National guidelines do not support the use of psychostimulants, antidepressants, or wakefulness agents to treat cancer-related fatigue.
- Two phase 3 studies demonstrated improved cancer-related fatigue with ginseng compared with placebo for patients undergoing cancer treatment.

- Categories of cachexia include precachexia, cachexia, and refractory cachexia.
- Cachexia is associated with increased treatment-related toxicity, decreased QoL, and poor survival.
- Overall, studies demonstrate a net harm when providing parenteral nutrition to patients who have cancer.
- There are no FDA-approved pharmacological treatments for weight loss associated with cancer cachexia.
- The weight gain associated with the use of megestrol acetate, dronabinol, and dexamethasone is primarily adipose tissue and fluid, not skeletal muscle.
- Deep vein thrombosis and adrenal suppression are two notable adverse effects of megestrol acetate.
- Clinicians must support caregivers given the paucity of effective treatment options and the distress cachexia causes when caregivers witness anorexia, weight loss, weakness, and decreased QoL in their loved ones.
- Pancreatic exocrine insufficiency is common in patients who have pancreatic cancer. Clinicians should treat patients with exogenous enzyme replacement and titrate to control abdominal symptoms and steatorrhea.
- FU and topoisomerase I inhibitors (irinotecan, topotecan) commonly cause diarrhea.
- Irinotecan causes acute diarrhea because of a cholinergic mechanism, as well as subsequent, more severe diarrhea because of its active metabolite SN38.
- In addition to supportive measures, loperamide can be used effectively to treat chemotherapy-induced diarrhea. Second-line approaches include diphenoxylate and atropine, deodorized tincture of opium, and octreotide.
- In addition to supportive measures, radiotherapy-induced diarrhea should be treated with octreotide.
- Diarrhea is common with targeted therapy and is best treated with antimotility agents and withdrawal of the offending drug.
- Checkpoint inhibitors can cause life-threatening colitis that is best treated with corticosteroids and, rarely, infliximab.
- Graft-versus-host disease–associated diarrhea should be treated with corticosteroids, optimal immunosuppression, and octreotide.
- Evidence-based prevention strategies of mucositis include oral rinses, low-dose laser therapy, cryotherapy, and palifermin.
- Dexamethasone rinse improves the prevention of everolimus-induced stomatitis. Doxepin mouthwash improves mucositis-related pain.
- There are no differences in effectiveness for palliation of oral mucositis among mouthwashes consisting of saline, sodium bicarbonate, chlorhexidine, or so-called magic mouthwash.
- There are no established methods to prevent CIPN other than limiting exposure to the offending drugs.
- Patients at higher risk for developing CIPN include those with a history of inherited neuropathy, obesity, diabetes, and alcoholism.
- The best-established drug for treating painful CIPN is duloxetine, but its efficacy is limited.
- Dyspnea is a subjective experience that may or may not correlate with objective findings.
- Any reversible causes of dyspnea should be identified and treated when possible.
- In the absence of hypoxemia, oxygen provides no additional symptomatic benefit for dyspnea compared with room air.
- Limited evidence supports the use of systemic opioids to palliate dyspnea.
- Prevention of patients with EGFR inhibitor–associated rash includes topical corticosteroids and moisturizers, or oral minocycline or doxycycline.
- Treatment of patients with EGFR inhibitor–associated rash includes topical corticosteroids, clindamycin, oral minocycline, doxycycline, or low-dose isotretinoin.
- No evidence supports the use of vitamin B6 supplementation, urea–lactic acid cream, topical emollients or creams, systemic or topical corticosteroids, nicotine patches, or vitamin E to prevent or treat hand-foot syndrome.
- Scalp cryotherapy is effective for select patients with solid tumors, but safety data are lacking for patients with hematological malignancies.
- Sexual health concerns are common in patients who have cancer, but oncologists do not commonly discuss them with patients.
- Non-hormonal therapies to decrease hot flashes include antidepressants, gabapentin, clonidine, oxybutynin, and elinzanetant.
- For patients receiving tamoxifen, paroxetine, fluoxetine, and sertraline should be avoided, because they can decrease the metabolism of tamoxifen by CYP2D6 to its active metabolite.
- Hormonal therapy for hot flashes can include the use of progesterone analogs.
- Dehydroepiandrosterone, vaginal laser therapy, and vaginal estrogen tablets can help to alleviate vaginal dryness.
- Topical dehydroepiandrosterone, an estradiol-releasing vaginal ring, intravaginal testosterone cream, vaginal estrogen tablets, and topical lidocaine can ease dyspareunia.
- Testosterone, without the addition of estrogen-replacement therapy, does not seem to help increase libido in postmenopausal women who have cancer.

CHAPTER TABLES AND IMAGES

Table 8-1 Examples of Validated Pain Instruments in Cancer Patients[12]

Instrument Name	Constructs Measured	Estimated Completion Time
Brief Pain Inventory Short Form	Pain severity, pain interference with physical and affective functioning, pain location	5 minutes
Edmonton Symptom Assessment System–Revised	Current pain severity, pain location	1 minute
Short-Form McGill Pain Questionnaire	Pain quality, pain location, pain severity	5-10 minutes
Verbal analog scales	Pain level	1 minute
Verbal rating scales	Pain level	1 minute
Wong-Baker FACES Pain Rating Scale[a]	Pain level	1 minute

[a]Validated in pediatric care; age 3 years or older.

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Table 8-2 **Pain Terminology**[15]	
Term	**Definition**
Acute pain	Pain occurring over hours up to weeks, characterized by a well-defined temporal pattern of onset with subjective and objective physical signs and hyperactivity of the autonomic nervous system
Subacute pain	Pain present for between 6 weeks and 3 months
Chronic pain	Pain present more than 3 months, cause often not easily identified, usually multifactorial, may be nociceptive and/or neuropathic; characterized by vegetative signs (eg, anorexia, anhedonia, sleep disturbance) as well as physical and mental withdrawal
Nociceptive pain	Somatic or visceral pain associated with actual or potential tissue damage caused by ongoing activation of intact nociceptors
Neuropathic pain	Pain resulting from injury to the peripheral or central nervous system, causing pain described as burning, shooting, tingling, stabbing, scalding, crawling, or painful numbness
Somatic pain	Localized pain causing activation of the μ-receptors and described as aching, stabbing, or throbbing
Visceral pain	Poorly localized pain resulting from activation of nociceptors in the viscera by obstruction, infiltration, ischemia, stretching, compression, and/or inflammation
Baseline pain	Average pain intensity experienced for 12 hours during a 24-hour period
Breakthrough pain	Transient increase in pain to greater than moderate intensity, occurring in addition to baseline pain
Incident pain	Specific experience of pain associated with an event or movement (eg, wound care)
Episodic pain	Transient exacerbation or recurrence of pain
Allodynia	Pain from light touch or mild pressure
Hyperalgesia	Increased pain response to a noxious stimulus
Dysesthesia	Unpleasant, abnormal sense of touch
Paresthesia	Abnormal dermal sensation (eg, tingling, pricking, chilling, burning, or numb sensation on the skin) with no apparent physical cause
Opiates	Natural substances that come from opium, including morphine and codeine
Opioid	Semisynthetic or synthetic products that bind to the same receptors as opiates but do not occur naturally; used broadly to include both natural or synthetic (or semisynthetic) substances acting on one of the three main opioid receptor systems (μ, κ, δ)
Adjuvant	Non-opioid medications used to enhance analgesia and minimize adverse effects, including anticonvulsants and antidepressants
End-of-dose failure	Predictable return of pain before the next scheduled dose of medication
Incomplete cross tolerance	Different levels of tolerance to an opioid of a different class

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Table 8-3 **Non-Pharmacological Approaches to Treating Cancer Pain**[8]

Category	Treatment Type
Alternative, complementary, or integrative strategies	Acupuncture, art therapy, massage, music therapy, physical/movement, aromatherapy
Interventional	Injection therapies, implant therapy, neural blockade, surgical neuroablation, orthopedic procedures
Rehabilitative	Hydrotherapy, occupational therapy, physical modalities such as ultrasound, therapeutic exercise, and therapy for specific disorders such as lymphedema
Psychological	Hypnotherapy, cognitive behavioral therapy, guided imagery, other forms of psychotherapy, psychoeducational interventions, relaxation therapy, stress management
Neurostimulation	Dorsal column stimulation, intrathecal drug delivery

The IMPACT trial recently showed that both acupuncture and massage improved pain, fatigue, insomnia, and quality of life over 26 weeks in advanced cancer patients, highlighting the importance of integrating non-pharmacological approaches to pain and symptom management when possible.[17]
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Table 8-4 **Non-Opioid Pharmacological Agents Targeting Neuropathic Pain**

Pharmacological Agent Targeting Neuropathic Pain	Mode of Action	Starting Dose/Max Dose	Adverse Effect
Anticonvulsants	Decreased release of glutamate, norepinephrine, and substance P affects calcium channels		Sedation and dizziness should not be abruptly stopped
Gabapentin		100-300 mg 1-3× per day/1,200 mg 3× per day[a]	
Pregabalin		50 mg 3× per day/200 mg 3× per day	
Antidepressants			
TCAs: nortriptyline, desipramine	Inhibition of serotonin/norepinephrine reuptake, sodium channel blocking, and anticholinergic	25 mg/150 mg daily	Sedation, anticholinergic effect, cardiac arrhythmias, and nausea
SNRISs: duloxetine, venlafaxine	Inhibition of serotonin/norepinephrine reuptake	Duloxetine: 30 mg daily/60 mg 2× daily; venlafaxine: 37.5 mg daily or twice daily/225 mg daily	Nausea, insomnia, appetite loss, weight gain
Topical agents			
5% Lidocaine patch	Sodium channel blocking	1-3 patches/3 patches daily	Rash, local erythema
Capsaicin: cream, 8% patch	Highly selective agonist for TRPV1 receptors expressed in afferent neuronal C fibers and some Aδ fibers	Cream: 0.025%, 0.075%, and 0.1% creams; apply 3-4 times per day; 8% patch: 1 patch/4 patches applied for 60 minutes every 3 months[b]	Erythema and uncomfortable burning, stinging, or itching

Abbreviations: SNRIS, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.
[a]Need to adjust in those with renal insufficiency, especially those on renal replacement therapy.
[b]8% patch is applied by a medical provider only. Consideration of cost.
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Table 8-5 **Opioids, Active Metabolites, and Pharmacokinetics**[25-27]

Opioid	Active Metabolites	Half-Life (Hours)	Equianalgesic	
			Parental	Oral
Morphine	Yes	2-4	10	30
Oxycodone	Yes	3-4	Not available in the United States	20
Hydrocodone	No	3-4	NA	30
Hydromorphone	Yes	2-3	1.5	7.5
Fentanyl	No	Transmucosal: 1-2 Transdermal: 48-72	Variable conversion methods available; may consider using ratio of 2.5-1 (oral morphine per day: TDF per hour); should not initiate in opioid-naive patients or patients receiving less than 60 mg MEDD	
Methadone	No	2-3 (distribution phase); 15-60 (elimination phase)	[a]	

Abbreviations: MEDD, morphine equivalent daily dose; NA, not applicable; TDF, transdermal fentanyl.
There is no clear consensus on opioid conversions; these serve as guidelines only.
[a]Methadone conversions should be supervised by a pain expert (palliative care specialist or acute/chronic pain management specialist).
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Table 8-6 **Opioid Aberrancy Terminology**[33,50-53]

Term	Definition
Aberrant	Actions departing from accepted, medically appropriate drug-taking behaviors
Abuse	A maladaptive pattern of prescription opioid use leading to clinically significant impairment and distress
Addiction	A primary, chronic, and neurobiological disease with manifestations influenced by genetic, psychosocial, and environmental factors, characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving
Chemical coping	Behaviors focused on obtaining opioids to relieve psychosocial distress rather than pain
Dependence	A state of adaptation indicated by a medication class-specific withdrawal syndrome produced by abrupt cessation, rapid dosage reduction, decreasing blood level of the drug, or administration of an antagonist
Misuse	The inappropriate use of a prescription opioid agent, whether intentional or unintentional, and regardless of motivation
Pseudo-addiction	An iatrogenic syndrome with behaviors that mimic addiction, driven by unrelieved pain
Substance abuse	Use of a substance in a manner outside of sociocultural conventions
Tolerance	Diminution of one or more drug effects caused by exposure to the drug that may require higher doses for effect
Withdrawal	An uncomfortable but non–life-threatening reaction that occurs after the abrupt cessation of opioids or use of naloxone, characterized by the presence of one or more of a variable group of symptoms and signs, including tremulousness, anxiety, insomnia, tachycardia, tachypnea, hypertension, nausea and vomiting, diarrhea, piloerection, and sweating

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Table 8-7 **Selection of Antiemetics Based on Neurotransmitters Involved**[84]

Anatomic Location	Neurotransmitter Involved	Drug Class
Cortex	Unknown	Dexamethasone
		Lorazepam
		Cannabinoids
	Dopamine	Haloperidol
Chemoreceptor trigger zone	Serotonin	Metoclopramide
		Prochlorperazine
		Ondansetron
		Oral granisetron
		Transdermal granisetron
	Dopamine	Metoclopramide
		Prochlorperazine
	Endocannabinoid	Cannabinoids
	Substance P inhibitors	Aprepitant
		Fosaprepitant
		Netupitant
		Rolapitant
Vomiting center/vestibular apparatus	Histamine	Cetirizine (preferred)
		Diphenhydramine
		Meclizine
		Hydroxyzine
	Acetylcholine	Scopolamine

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Table 8-8 **CINV Types**

Types of CINV	Time Frame
Acute	Within 24 hours of chemotherapy administration
Delayed	2-5 days after chemotherapy administration
Breakthrough	Anytime, despite adequate prophylaxis
Anticipatory	Before the next treatment

Abbreviation: CINV, chemotherapy-induced nausea and vomiting.
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Table 8-9 **CINV Prophylaxis Based on Emetic Risk**	
Risk	**Recommended Prophylaxis**
High	NK-1 + $5HT_3$ + dexamethasone + olanzapine
Moderate	$5HT_3$ + dexamethasone
Low	$5HT_3$ or dexamethasone
Minimal	None

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Table 8-10 **Emetic Risk in Adults by Site of Radiation Therapy**		
Risk Level	**Site**	**Therapy Options**
High (>90%)	Total body irradiation	5-HT_3 antagonist with dexamethasone
Moderate (30%-90%)	Upper abdomen, craniospinal irradiation	5-HT_3 antagonist with or without dexamethasone
Low (10%-30%)	Brain, head and neck, thorax, pelvis	Brain: dexamethasone; head and neck, thorax, pelvis: $5HT_3$ antagonist or dexamethasone or dopamine receptor antagonist (use as rescue)
Minimal (<10%)	Extremities, breast	$5HT_3$ antagonist, dexamethasone, or dopamine receptor antagonist (use as rescue)

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Table 8-11 **Mechanisms of Chemotherapy-Induced Peripheral Neuropathy**

Chemotherapy	Neurotoxicity	Incidence	Cumulative Dose	Recovery
Cisplatin	Long-lasting cumulative distal sensory neuropathy	50%-90% of patients receiving ≥500 mg/m^2	Beginning at 300 mg/m^2	Incomplete
Carboplatin	Mild sensorimotor neurotoxicity	Uncommon; mild in 25% of patients; severe in 5%	More common with high doses: 800-1,600 mg/m^2	Not fully described
Oxaliplatin	Acute cold–associated neurotoxicity and chronic sensory neuropathy	Acute symptoms in 95%; severe chronic toxicity in 10%-20% at 750-850 mg/m^2	Acute symptoms at all doses, severe at >540-700 mg/m^2	May persist for a long time; in 10% of patients at 2 years post-treatment
Paclitaxel	Distal sensory neuropathy with pain and motor symptoms at high doses	Severe dose dependence in 10%-30% of patients	>300 mg/m^2 but can occur at lower doses	May persist, although reversibility is reported
Docetaxel	Distal sensory neuropathy with pain	Less severe neurotoxicity than paclitaxel, severe in 6%-10% of patients	>100 mg/m^2; severe toxicity >600 mg/m^2	Not fully described
Vincristine	Distal sensorimotor painful neuropathy	60% of patients, dose dependent	4-10 mg	≤33% of patients report persistent symptoms
Bortezomib	Sensory axonal neuropathy, occasionally demyelinating	≥35%-50% of patients	1.3 mg/m^2	Resolution in 3 months; may persist
Thalidomide	Sensorimotor painful neuropathy	25%-75% of patients	At dose ≥20 g	Not fully described

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Table 8-12 **Strategies for EGFR-Associated Acneiform Rash**

Strategy	Recommended	Not Recommended
Topical preventive	Hydrocortisone	Pimecrolimus
		Tazarotene
		Sunscreen as a single agent
Systemic preventive	Minocycline	Tetracycline
	Doxycycline	
Topical treatment	Alclometasone	
	Fluocinonide	
	Clindamycin	
Systemic treatment	Doxycycline, 100 mg twice daily	Photosensitizing agents
	Minocycline, 100 mg daily	
	Low-dose isotretinoin, 20-30 mg daily	

Abbreviation: EGFR, epidermal growth factor receptor.
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Table 8-13 **Approaches to Hormone-Related Symptoms in Patients With Cancer**

Symptom	Evidence-Based Therapy	Non-Evidence-Based Therapy
Hot flashes	Antidepressants	Phytoestrogen product (soy)
	Clonidine	Black cohosh
	Gabapentin	Flaxseed
	Oxybutynin	Magnesium oxide
	Cognitive behavioral therapy	
	Hypnosis	
	Elinzanetant (dual NK-1/NK-3 antagonist)	
Vaginal dryness	Dehydroepiandrosterone	
	Vaginal estrogen tablets	
Dyspareunia	Lidocaine	
	Vaginal estrogen tablets	
Low libido		Transdermal testosterone

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Figure 8-1 Characterization of Pain by Temporality and Type

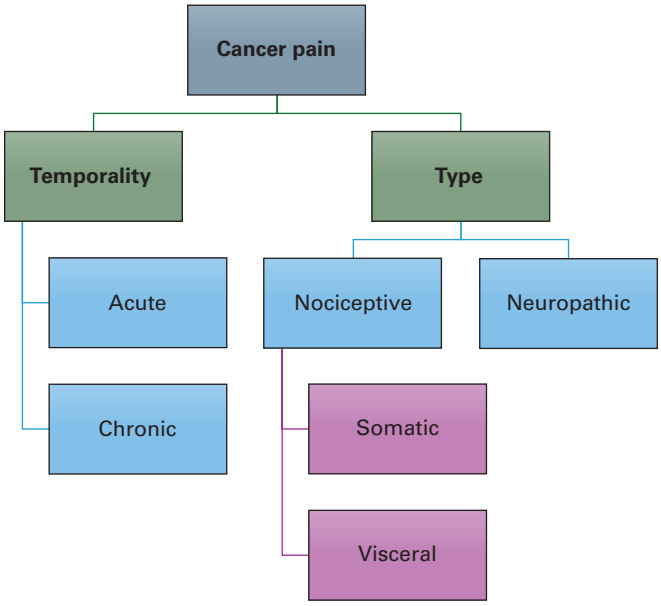

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Figure 8-2 The Revised World Health Organization Analgesic Ladder

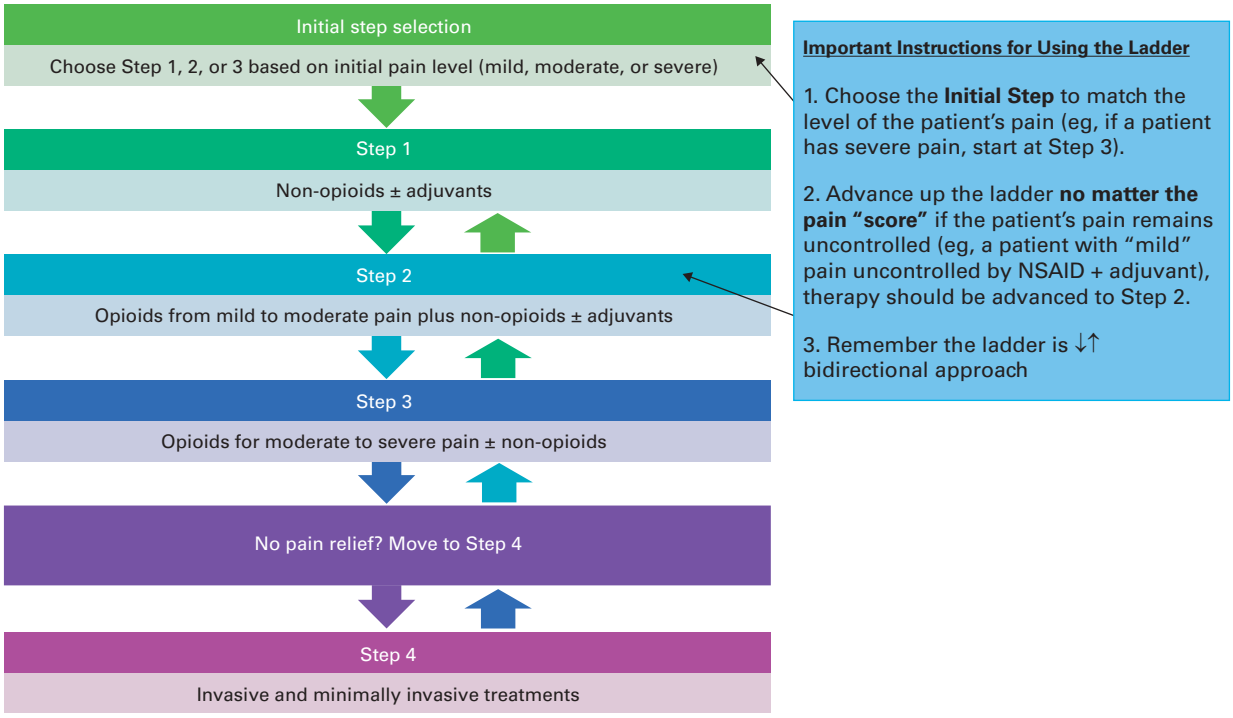

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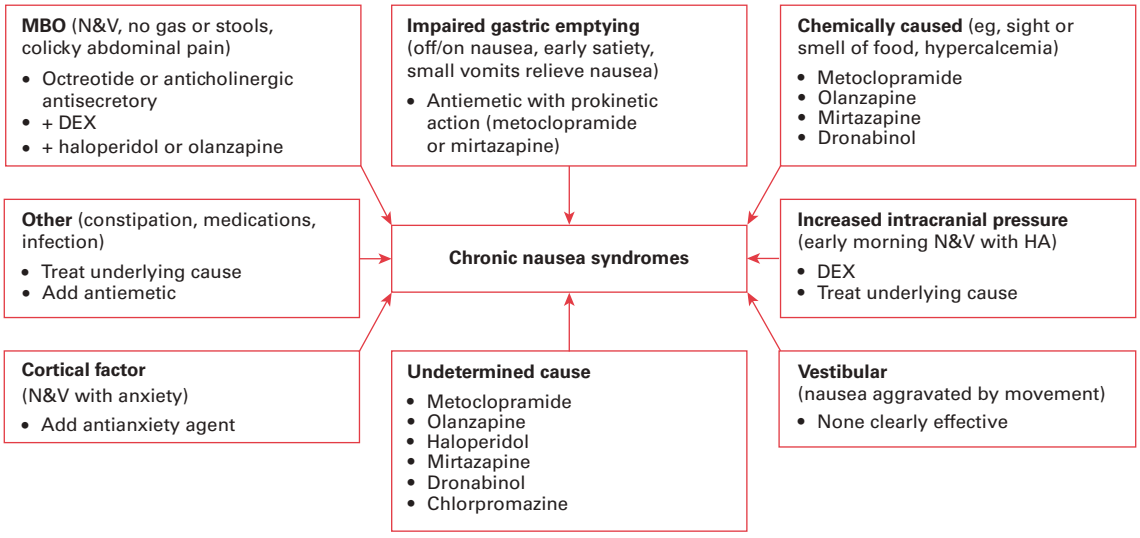
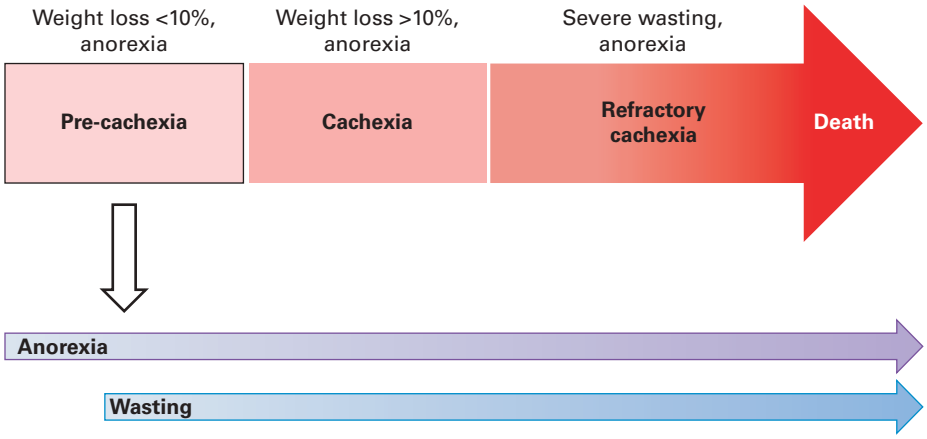
Figure 8-3 Nausea Management Options



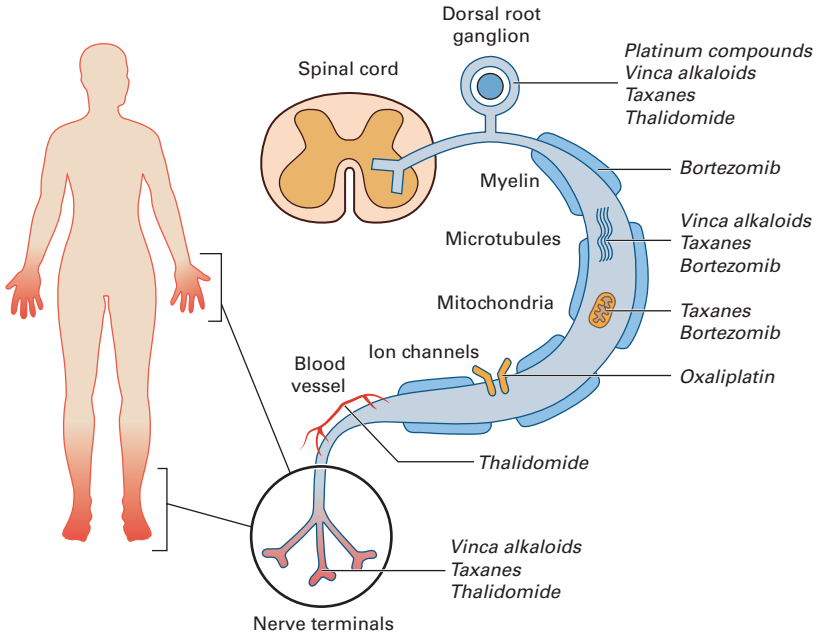
Abbreviations: DEX, dexamethasone; HA, headache; MBO, malignant bowel obstruction; N&V, nausea and vomiting.
Adapted under Creative Commons license. Source: Wickham R. Nausea and vomiting not related to cancer therapy: intractable problem or clinical challenge? *J Adv Pract Oncol*. 2020;11(5):476-488. doi:10.6004/jadpro.2020.11.5.4

Figure 8-4 Stages of Cachexia: Precachexia, Cachexia, and Refractory Cachexia



Reprinted under Creative Commons license. Source: Yeom E and Yu K. Understanding the molecular basis of anorexia and tissue wasting in cancer cachexia. *Exp Mol Med*. 2022;54:426-432. doi:10.1038/s12276-022-00752-w

Figure 8-5 Mechanisms of CIPN



Abbreviation: CIPN, chemotherapy-induced neurotoxicity.
Proposed targets of CIPN in the peripheral nervous system include damage to dorsal root ganglion neuronal cell bodies (platinum compounds, vinca alkaloids, taxanes, thalidomide), demyelination (bortezomib), microtubule-associated toxicity (vinca alkaloids, taxanes, bortezomib), mitochondrial dysfunction (taxanes, bortezomib), axonal membrane ion channelopathy (oxaliplatin), peripheral vasculature impairment (thalidomide), and distal axonal injury (vinca alkaloids, taxanes, thalidomide).
Adapted from Park SB, Goldstein D, Krishnan AV, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. *CA Cancer J Clin*. 2013;63:419-437. doi:10.3322/caac.21204

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PALLIATIVE CARE AND CARE AT THE END OF LIFE

9

Kathryn DeCarli, MD, MBE, and Frederick J. Meyers, MD, MACP

RECENT UPDATES

- Inpatient palliative care for patients hospitalized for intensive chemotherapy treatment of acute myeloid leukemia or for hematopoietic stem cell transplantation led to better quality of life and less psychological distress than for patients receiving standard oncology care.[1-3]
- Delivery of early palliative care follow-up visits virtually versus in person demonstrated equivalent effects on quality of life in patients with advanced non–small cell lung cancer, underscoring the potential to improve access to timely palliative care through telehealth delivery.[4]
- A stepped-care model resulted in fewer palliative care visits without diminishing the benefits for patients' quality of life.[5] In this model, palliative care follow-up visits occur only at key disease transitions or acute episodes during patients' cancer trajectories, with the recognition that a decrement in quality of life should trigger more intensive palliative care exposure.

OVERVIEW

Palliative care is an interdisciplinary medical specialty centered around preventing or relieving suffering and improving quality of life (QoL) for patients with serious illness and their caregivers. Palliative care is an essential component of high-quality cancer care throughout the cancer journey. The 2024 ASCO Guideline Update states that oncologists should refer patients with advanced cancer to specialized interdisciplinary palliative care teams early in the course of the disease, alongside active treatment of their cancer.[6] As outlined in the National Consensus Project clinical practice guidelines for quality palliative care,[7] high-quality palliative care includes eight domains:

1. Structures and processes of care (eg, the nature of palliative care services available, such as the presence of a truly interdisciplinary team or the availability of a bereavement program)
2. Physical aspects of care (eg, regular symptom assessment and appropriate management)
3. Psychological (emotional) and psychiatric aspects of care (eg, screening and management of mood disorders, distress, and grief)
4. Social aspects of care (eg, comprehensive interdisciplinary assessment of patient and family social needs and development of a care plan to address them)
5. Spiritual, religious, and existential aspects of care (eg, attention to issues such as faith, meaning, identity, and control)
6. Cultural aspects of care (eg, attention to cultural values, beliefs, and preferences)
7. Care of the patient nearing the end of life (eg, attention to issues specific to end-of-life care)
8. Ethical and legal aspects of care (eg, methods to assess values and preferences and implement goal-concordant care, including but not limited to advance directives)

Some cancer centers in the United States have rebranded specialist palliative care as the "Supportive Care" team. Studies show that clinicians and patients are more likely to engage with a supportive care team due to misperceptions about the name "Palliative Care" and conflation with hospice or end-of-life care.[8-10] Indeed, even this chapter treats palliative care and hospice together. While palliative care and hospice share a focus on comfort, they are distinct and distinguished by the goals of care. Hospice care is appropriate for patients who are not receiving cancer-directed care and have a prognosis of <6 months. On the other hand, palliative or supportive care can be given to any patient with a serious illness, concurrently with cancer-directed care. This includes patients undergoing curative-intent treatment and patients with long life expectancy. For this chapter, we will use

the nomenclature "Palliative Care," but acknowledge the benefits of using "Supportive Care" to name the services provided by specialist palliative care clinicians.

This chapter focuses on the timely delivery and implementation of specialist palliative care, topics in communication, patient and caregiver distress, and an overview of hospice and end-of-life (EOL) care. Pain and symptom management, which are key components of high-quality palliative care, are covered separately in Chapter 8. Symptoms that can be particularly impactful at EOL are discussed in the last portion of this chapter. This chapter aims to outline the scope of palliative care for patients with cancer and their caregivers and to prepare the oncologist to effectively collaborate with palliative care specialists.

SCOPE OF PALLIATIVE CARE IN ONCOLOGY

Simply stated, palliative care aims to help patients and their loved ones live life to the fullest when faced with serious or life-threatening illness. Palliative care is ideally integrated at diagnosis, extending throughout the course of cancer care regardless of prognosis. This is consistent with the American Society of Clinical Oncology (ASCO) position, as outlined in a 2024 guideline update on integrating palliative care into standard oncology care.[6,11]

To understand the role of palliative care specialists, it is helpful to differentiate primary or generalist palliative care from secondary or specialist palliative care. Primary or generalist palliative care encompasses the basic skills and competencies to support patients' QoL that all oncology clinicians should possess, whereas secondary or specialist palliative care refers to the complex skills and services provided by specialists with additional palliative care training. Specialist palliative care is provided by an interdisciplinary team that includes physicians, advanced practitioners, nurses, chaplains, social workers, and others (Table 9-1). The provision of specialist palliative care in dedicated inpatient palliative care units and academic medical centers, where research and education focus on patients with more complex needs, is sometimes also referred to as tertiary palliative care.

Oncologists and other cancer care clinicians provide most of the primary palliative care for their patients, including assessment and management of symptoms, leading and coordinating patient family conferences on discussions about prognosis and goals of care, and support for the patient and caregiver(s) in coping with serious illness. Referral to or consultation with a palliative care specialist can help provide additional expertise regarding management of difficult-to-control symptoms, existential distress, or complex medical decision-making.

It is important to recognize that specialist palliative care does not duplicate or replace care by the cancer care team; instead, it augments that care in areas of complex patient and caregiver needs. Specialist palliative care enhances the care delivered by the primary oncology team, providing an added layer of support not only to the patient and family but also to the cancer care team.[12] Lack of access to on-site palliative care was associated with lower job satisfaction among chemotherapy-prescribing physicians globally.[12]

In one study, oncologists were more likely to endorse certain palliative care skills than others as fundamental to routine oncology, including communication, shared decision-making, advance care planning, and end-of-life care.[13] Spiritual and cultural assessment, psychosocial assessment, and second-line management of pain, depression, and anxiety were least endorsed by oncologists, and therefore conferred the highest potential for referral to specialty palliative care.

Table 9-1 Primary Versus Secondary Palliative Care

Primary	Management of cancer-related pain, including basic opioid regimens
	Basic non-pain symptom management, including nausea, constipation, and mood
	Advance care planning, eliciting patient values to provide goal-concordant care
	Ongoing prognostic awareness assessment
Secondary	Management of cancer-related pain, including complex opioid regimens
	High-touch and refractory non-pain symptom management
	Advanced communication strategies to augment advanced care planning and serious illness conversations with complex dynamics
	Enhanced prognostic awareness assessment and discussions with key stakeholders (eg, patient, treating team, family members)

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These findings mirror those from randomized trials of integrated palliative care in patients with advanced solid tumors and acute leukemia, wherein palliative care specialists were noted to focus more on coping and psychosocial care during consultations than the oncologists seeing those same patients.[2,14]

IMPLEMENTING EARLY PALLIATIVE CARE

EVIDENCE SUPPORTING EARLY INTEGRATION OF SPECIALIST PALLIATIVE CARE

Palliative care should be delivered concurrently with cancer-directed therapy and integrated early in the disease course.[15,16] Randomized trials have shown that, compared with primary palliative care provided by oncologists, early integrated specialist palliative care improves QoL, symptom intensity, patient and caregiver satisfaction, mood, illness understanding, quality of end-of-life care, and survival.[14,16-19] Importantly, no study to date has shown any harm caused by integrating palliative care into standard oncology care.[19]

Given the rapidly expanding evidence base, ASCO released a provisional clinical opinion in March 2012[20] that was updated and published as a clinical practice guideline update in 2016,[11] and again in 2024.[6] The guideline recommends that "[o]ncology clinicians should refer patients with advanced solid tumors and hematologic malignancies to specialized interdisciplinary palliative care teams that provide outpatient and inpatient care beginning early in the course of the disease, alongside active treatment of their cancer."[2,3,21] Other national and international professional societies also now endorse integrated palliative care as a routine practice, including the American College of Surgeons Commission on Cancer,[22] the Oncology Nursing Society,[23] the National Comprehensive Cancer Network (NCCN),[24] and the European Society for Medical Oncology (ESMO).[25]

Evidence from several new trials in solid tumors demonstrated that early referral to specialized palliative care of patients with advanced cancer led to improved QoL, mood, and a higher likelihood of discussing or documenting end-of-life preferences. In addition, there were two trials of early palliative care for inpatients with hematological malignancies, specifically for patients admitted for treatment of acute myelogenous leukemia and those receiving hematopoietic stem cell (HSC) transplantation, which reported benefits of early palliative care for outcomes of QoL, depression, anxiety, and posttraumatic stress disorder (PTSD).[2,3,26] The same authors recently reported a multi-institutional randomized study of the benefits of palliative care in patients undergoing HSC transplantation. Significant benefit was seen in QoL, depression symptoms, and PTSD, underscoring the need to integrate routine palliative or supportive care in these patients. One note of interpretation, in this study and others, the "improvement in QoL" is often a reduction in the decline in QoL, understandable as many of the QoL instruments include the physical domains, which will decline in patients receiving intensive therapy.

CHALLENGES IN IMPLEMENTING EARLY PALLIATIVE CARE

Despite the abundance of data supporting the benefits of palliative care early in the patient's cancer journey, its incorporation remains markedly underutilized.[27,28] Studies suggest that this is not a uniquely American concern but rather seen in other countries with more robust systems of universal health coverage, including the UK, Australia, and Canada. Over the last decade, there have been many studies documenting this phenomenon as well as the challenges that contribute to the underutilization of palliative care involvement. These include healthcare team factors such as limited time and competing priorities at work, gaps in clinician knowledge and education, lack of access to services, and personal discomfort; as well as patient factors including negative perceptions of palliative care, family and cultural values, and communication barriers. These are summarized in Table 9-2. Even in a research setting at academic sites that met the requirements for integrated palliative care, 14% of patients randomized to receive monthly early palliative care in one study had not received any palliative care by 24 weeks.[28] This discrepancy highlights the challenges of providing early integrated palliative care even in highly resourced settings. The bulk of cancer care in the United States is provided at community sites, many of which lack access to specialty palliative care. Telehealth and policy changes may offer opportunities to enhance palliative care delivery in low-resource settings.[29]

Table 9-2 Barriers and Facilitators to Early Integration of Palliative Care

Factors Impacting Delayed Referral to Palliative Care	Potential Solutions to Improve Early Palliative Care Engagement[30]
• Patient's negative perceptions of palliative care • Family's negative perceptions of palliative care • Physician reluctance to discuss prognosis/EOL issues, including loss of hope • Physician perception of overlapping skill sets with palliative care • Lack of the medical team's recognition of the terminal phase of disease	• Education regarding the benefits of early palliative care for patients and caregivers as part of public health policy strategy • Using the term Supportive Care to name the services offered by the palliative care team • Adequate staffing, training, and resources to accommodate early palliative care referrals • Screening mechanism to help prioritize early palliative care referrals • Effective communication and collaboration among palliative care and oncology teams

Factors Impacting Delayed Referral to Palliative Care	Potential Solutions to Improve Early Palliative Care Engagement[30]
• Lack of integration between oncology and palliative care, including perceived conflict in goals of care that is, disease-directed therapy versus palliative care • Lack of clearly defined responsibilities between oncology and palliative care • Limited palliative care resources and a lack of clearly defined consensus referral criteria • Inadequate systems support and timely actionable data	• Clarifying the roles and responsibilities of oncology and palliative care teams in a collaborative delivery model • Concurrent or simultaneous care models of integration • Bridge programs • Health system support for leadership, access to actionable data, financial support for multidisciplinary team organization, and care delivery • Regulatory amendments that support palliative care services billing separately from disease-directed therapy • Follow-up palliative care visits via virtual care and/or using a stepped-care model, with palliative care visits occurring only at key points in patients' cancer trajectories[4,5]

Abbreviation: EOL, end of life.
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Another well-recognized challenge is the integration of palliative care for patients enrolled on early-phase clinical trials. The rapid development of new cancer-directed therapies offers great promise at the population level. However, in a phase 1 trial setting, by definition, there is no guarantee that a particular drug will help a particular patient.[31,32] Patients with advanced cancer who have exhausted standard therapies and are enrolled on phase 1 clinical trials demonstrate high levels of psychological distress.[33] This warrants even more integration between oncology and palliative care. A growing body of literature supports structured specialty palliative care intervention for patients with advanced cancer on phase 1 clinical trials.[34-37]

SOLUTIONS TO THE CHALLENGES OF EARLY INTEGRATION OF PALLIATIVE CARE

Recently reported strategies address some of these challenges (Table 9-2). The experience of an inpatient specialized palliative care team for HSC transplantation noted above is emphasized.

- A recent randomized controlled trial showed that a stepped-care model, with palliative care follow-up visits occurring only at key points in patients' cancer trajectories and using a decrement in QoL to trigger more intensive palliative care exposure, resulted in fewer palliative care visits without diminishing the benefits for patients' QoL.[5]
- Another recently developed model, Symptom Screening with Targeted Early Palliative care (STEP), includes routine symptom monitoring at each oncology visit with referral to palliative care upon reaching a prespecified threshold score.[38] This model, which showed promise in a phase 2 trial, depends on the routine collection and availability of patient-reported outcomes (PROs) with infrastructure that allows the scores to become actionable. This risk-stratified approach to early palliative care referral is especially important in resource-constrained settings. Recognition and agreement between palliative care and oncology teams as to the time frame considered early is important, as it will vary with the disease. When possible, it is important to integrate palliative care and oncology clinical teams in the same space to facilitate communication and patient care. There may also be opportunities in leveraging telehealth to improve access to palliative care consultations, especially considering emerging data showing comparable efficacy. Delivery of early palliative care follow-up visits virtually versus in person demonstrated equivalent effects on QoL in patients with advanced non–small cell lung cancer.[4] This will need to be coupled with regulations supporting telehealth services in palliative care.[4]
- Oncologists can apply lessons from trials of early palliative care when providing primary palliative care for their patients. The TEAM approach (Time, Education, Assessment, and Management) is helpful in this regard[21] (Table 9-3).
- Quality improvement plays an important role in enhancing palliative care delivery. An excellent example is embedded palliative care consultation services. Palliative care consultation teams have expanded rapidly into cancer hospitals and clinics, with 90% of National Cancer Institute–designated cancer centers having both inpatient and outpatient specialty palliative care services.[39] However, despite clinical guidelines recommending that all patients with advanced cancer or high-risk hematological malignancies receive dedicated palliative care services within 8 weeks of diagnosis, referral to specialty palliative care teams typically occurs late in the disease course, if at all. Prognosis-, needs-, and trigger-based models of palliative care integration have been proposed, with trigger-based approaches thought to best capture patients most likely to benefit from consultation.[40] Triggers may include clinical characteristics, symptoms, performance status, prognosis, or a combination of these.[18]

Sustainable improvements in palliative care need systematic and systems-based interventions. Clinical research programs to assess systems and implement and measure change include implementation science and a learning healthcare system (LHCS). The systematic study of how to design and evaluate a set of activities to facilitate the successful uptake of an evidence-based health intervention is implementation science.[41] Implementation science frameworks emphasize multifactorial causes for the successful and sustainable implementation of interventions, such as organizational and patient perspectives, policies, and health system characteristics. A much higher level of training is one aspect of sustainable change that includes teamwork, systems thinking, and a patient/family/community focus, synthesized under the model of an LCHS. LHCS may be seen as one mechanistic approach to not only integrate sustainable change but also to overcome the deficits in workforce and resources cited as foundational to the challenge of palliative care delivery.[42] A frontline oncologist and palliative care specialist might be expected to understand there are many implementation science frameworks and perhaps some of the vocabulary. Behavioral psychologists, sociologists, systems engineers, social workers, and doctoral-trained health outcomes faculty, trained and expert in information system are likely better suited for leadership of such efforts. Oncologists and palliative care clinicians must be present and willing to work in these teams to identify core challenges and promote solutions.

Table 9-3 **The Components of TEAM-Based Palliative Care**

Component	In the Trials	What Is Known
Time	A structured palliative care visit of at least one extra hour per month; repeated at regular intervals (ie, monthly); not once	These assessments can be conducted by a physician or APN with specific training in conducting such assessments.
Education	Structured, prospective, and recurrent discussions about symptoms, goals, and preferences for care, prognosis understanding, advance care planning, and communication with the healthcare team	Education that is done prospectively and regularly, rather than during a crisis, is more effective. Usual topics include, on a recurring basis: • Medically appropriate options for treatment; patients should know they have or have not left any medical stones unturned; this is best done by listing the treatments used and their outcomes, especially with recurrent disease; if appropriate, reinforce patient and family work as advocates • Advance care planning should be started early and revisited along the disease trajectory; documented components may include power of attorney documents, healthcare proxies, living wills or advance directives, and do-not-resuscitate orders • Use of hospice for the best possible care, and arranging a hospice information visit once it is evident the disease is going to take the person's life
Assessment	Formal assessments for: • Symptoms (ESAS, MSAS-C, CAPC rounding tool) • Spirituality (FICA, or "Are you a religious or spiritual person?") • Distress (Distress Thermometer, others) • Psychosocial (PHQ-2) • Caregiver strain It is not sufficient to just ask "How are you?"; patients and families are sometimes reluctant to share their problems for fear that nothing can be done, or that it is not in the clinician's remit, or that the oncologist will stop treating their cancer, or that they will be labeled a complainer.	After these formal symptom assessments, move on to goal setting. Questions may include: • How do you like to get medical information? • What is your understanding of your disease? • What is important to you? • What are you hoping for? • Have you thought about a time when you might become sicker, such that you would need an advance directive or living will? (some motivational interviewing) The authors of the table have incorporated this into a temporary tattoo that gives oncologists a script to start the most difficult discussions (Fig. 9-1). If progressive disease is evident, it is time to revisit goals of care, prognosis understanding, and advance care planning.

Component	In the Trials	What Is Known
Management	By setting protocols and an interdisciplinary team (APNs, social workers, chaplains, doctors)	Interdisciplinary care and referrals were common elements of all studies. Giving people knowledge of their realistic options and a plan of action was shared across all the studies. Establishing ties with social work or chaplaincy is as important as developing ties with surgeons, radiation oncologists, or other medical professionals.

Abbreviations: APN, advance practice nurse; CAPC, Center to Advance Palliative Care; ESAS, Edmonton Symptom Assessment Scale; FICA, Faith and Belief, Importance, Community, Address in Care; MSAS-C, Memorial Symptom Assessment Scale Condensed; PHQ-2, Patient Health Questionnaire-2.
From Bakitas MA, El-Jawahri A, Farquhar M, et al. The TEAM approach to improving oncology outcomes by incorporating palliative care in practice. *J Oncol Pract*. 2017;13(9):557-566. doi:10.1200/JOP.2017.022939
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PALLIATIVE CARE SPECIALIST TRAINING AND WORKFORCE

The American Board of Medical Specialties (ABMS) first recognized Hospice and Palliative Medicine (HPM) as a subspecialty in 2006. From 2008 to 2012, physicians could sit for the HPM board examination after fulfilling certain clinical competencies. The first ACGME-approved HPM fellowship was launched in 2012. Since then, ABMS has required candidates to complete a formal fellowship training program (12 months) to be eligible for board certification.[43] There are more than 100 fellowship programs today in the United States. Between 2008 and 2022, 8,328 physicians received subspecialty board certification in HPM through the ABMS; between 2008 and 2018, an additional 419 physicians were certified through the American Osteopathic Association (AOA).[44] Clinicians from 10 different primary fields can train and certify in HPM, including family medicine, anesthesiology, pediatrics, obstetrics and gynecology, emergency medicine, surgery, neurology, psychiatry, internal medicine, radiology, and physical medicine and rehabilitation. Some programs specialize in pediatric palliative care; however, there is only one board certification examination, which includes adult and pediatric content. Dual training has garnered increased interest in recent years, with approximately 630 physicians board-certified in both Hematology/Oncology and HPM as of 2021.[45] In 2023, the inaugural class matriculated to an integrated fellowship in Hematology/Oncology and HPM. This pathway consists of combined ACGME-accredited training over a period of 36 months, resulting in clinical competency and board examination eligibility in both fields. A cohort of dual-trained physicians is projected to effect change in clinical care, palliative care delivery models within cancer centers, and research at the intersection of oncology and palliative care. Fellowship training programs in HPM emphasize the core skills of serious illness care, including comprehensive symptom assessment and management, prognostication and prognostic disclosure, serious illness communication and goals-of-care discussions, conflict management and resolution, advance care planning, psychosocial distress assessment and management, assessment and management of existential distress, family and caregiver support, and end-of-life care. Although these topics are often part of what cancer care clinicians do in caring for their patients with advanced disease, palliative care specialists receive advanced training in these areas and therefore possess expert, high-level skills in these domains. Given that these topics are of central importance to the practicing oncologist as well, they are highlighted briefly in the latter half of this chapter.

Overall, cancer care is facing a looming workforce crisis, with projections forecasting significant shortages of oncologists across the United States. This problem is also affecting the palliative care workforce; there are simply not enough palliative care specialists to see all the patients who would benefit from their services.[46] In this vein, it is important to recognize the important role that advanced practice nurses (APNs) play in providing primary palliative care.[47] Nonphysician clinicians may also train and become certified in palliative care, with various certification programs available through professional societies like the Hospice and Palliative Nurses Association and the National Association of Social Workers, among others. There is also a growing number of fellowship programs available to advanced practitioners and pharmacists providing advanced palliative care training.

Oncologists themselves are also important providers of primary palliative care, which can be provided via the TEAM approach (Table 9-3).[21] Board-certified palliative care specialists with complementary training in leadership, teamwork, and change management lead and participate in the teams responsible for the Implementation Sciences and Learning Health Care System strategies noted above.

PROCESS AND OUTCOME METRICS FOR ASSESSING QUALITY

As oncology practices face mounting financial constraints, quality assessment becomes important to align services with metrics established by healthcare systems and insurers. It is difficult to assess the success of a palliative care program in oncology, as there is limited evidence-based literature on consensus quality metrics to define success. While the benefit of early palliative care is well established in the literature, its widespread adoption and integration nationally lags.[48] Certainly, one of the main goals of palliative care is to improve QoL. However, in practice, improvement in QoL is difficult to benchmark and measure routinely, as assessment generally relies on surveys, which are not routinely administered. QoL questionnaires such as EORTC-QLQ-C30,

McGill QoL questionnaire, and EQ-5D have been validated in the palliative care setting. However, these may not help assess the magnitude of clinically meaningful change. In the United States, surrogate metrics have been used to assess QoL, including some used by the Centers of Medicare and Medicaid Services within the Merit-based Incentive Payment System (MIPS) Quality Measures 2024 for Oncology.[49] These include the following:

- Percentage of patients who died from cancer receiving systemic cancer-directed therapy in the last 14 days of life (lower score—better). A recent report reviewed current outcomes of this metric, a metric previously endorsed by ASCO and the National Quality Forum, NCCN, with similar indicators by ESMO and the Cancer Quality Control Council of Ontario. They reported a rise in the use of systemic therapy at EOL, correlated largely with increased use of immunotherapy.[50]
- Percentage of patients who died from cancer admitted to hospice for less than 3 days (lower score—better).
- Medical and radiation—pain intensity quantified: percentage of patient visits, regardless of patient age, with a diagnosis of cancer currently receiving chemotherapy or radiation therapy, in which pain intensity is quantified.
- Medical and radiation—plan of care for pain.

A study evaluating these metrics in a community academic hospital setting found that among patients referred to and seen by palliative care 30 days before death, the rates of admission to emergency departments (EDs), hospital, and intensive care units (ICUs) in the last 30 days of life were notably lower.[51] Studies such as this can provide a real-world assessment of the impact of palliative care intervention as well as provide areas for growth. A systematic review of the literature on the effectiveness of community-based palliative care programs showed improved outcomes among patients receiving palliative care.[52] Sixty-one studies were included in the review, with half from the United States or Canada and only three from lower-income countries. Hospital utilization was consistently lower in palliative care patients compared with the general population. Patients cared for in a palliative care program also generally have a lower length of stay when admitted to the hospital, and most, but not all, studies reported a decrease in ED visits. Similarly, most studies showed a decrease in healthcare costs for patients enrolled in palliative care programs. The authors note that further research is needed to understand the reasons for mixed results across several metrics. This systematic review emphasizes the importance of creating standard benchmarks for quality and effectiveness in palliative care. Establishing an initial baseline with such metrics and then evaluating the impact of early palliative care can provide tangible improvements in clinical outcomes.

Another study recently synthesized evolving evidence that guides the care of patients with malignant bowel obstruction.[50] Clinical epidemiology and quality outcomes show high rates of perioperative morbidity and mortality for patients who undergo palliative surgery, and improved population-based outcomes in patients who are managed with medical and palliative support. Early identification of patients at risk can be aided by easily available information.[53] The use of intensive at-home palliative care is associated with reduced hospitalizations and days at home, equated with "good days."

These studies support the importance of quality metrics to assess the impact of palliative and supportive care. PROs offer another underutilized avenue for assessing the quality and impact of palliative care interventions among patients with advanced cancer. Patients who are unsheltered or who have insufficient support in the home may need to utilize inpatient palliative care services to achieve similar outcomes.

KEY POINTS

- Oncologists provide primary palliative care—the common and foundational services promoting QoL among patients and families facing cancer—and should refer those with advanced cancer, high-risk hematological malignancies, patients enrolled on phase 1/2 clinical trials, or significant symptom burden to specialists who provide secondary and tertiary palliative care via interdisciplinary teams with specialty training.
- Randomized trials have shown that, compared with primary palliative care provided by oncologists, early integrated specialist palliative care improves QoL, symptom intensity, patient and caregiver satisfaction, mood, illness understanding, quality of end-of-life care, and survival.
- ASCO has released an updated formal guideline recommending that oncology clinicians refer patients with advanced solid tumors and hematological malignancies to specialized interdisciplinary palliative care teams that provide care alongside active cancer treatment beginning early in the disease course.
- Palliative care consultation is the standard of care for patients with advanced cancer and/or significant symptoms, per ASCO guideline recommendations.
- Palliative care specialists are experts in complex symptom management and communication surrounding serious illness.
- Barriers to early palliative care exist but can be addressed through education of oncologists, close collaboration between oncology and palliative care teams, and systems-based research and quality improvement.[4,5]
- APNs play an important role in delivering primary palliative care.[13,21,30,47-49,52,54]

- Stepped palliative care models and virtual palliative care have been demonstrated as being equivalent to routine in-person palliative care follow-up and hold promise for improving palliative care access while reducing resources.
- There is a need for standard metrics for measuring the effectiveness of palliative care programs to identify key interventions.

PALLIATIVE CARE COMMUNICATION IN ONCOLOGY

PROGNOSTIC AWARENESS AND COMMUNICATION

Prognostic awareness is an essential component of informed medical decision-making in oncology and is associated with higher-quality end-of-life care.[55-57] As such, it is critically important for clinicians to routinely assess prognostic understanding throughout the illness course, honestly and empathically convey accurate prognostic information to patients and families, particularly during illness transitions, elicit patient goals and values in the context of this prognosis, and provide clear goal-concordant recommendations.[58]

Many patients with advanced cancer have a poor understanding of their prognosis, estimated survival, or intent of cancer-directed treatment.[59-61] Patients' caregivers similarly often have poor prognostic understanding; in one study of 390 caregivers of adults with incurable cancer, more than half of caregivers had misperceptions about the patients' likelihood of cure, and one-third of patient-caregiver dyads had discordant perceptions.[62]

Relatedly, in a cross-sectional analysis of 236 patients and 38 oncologists, 68% of patients had discordant expectations from their oncologist regarding survival, and only 11% of these patients were aware that their expectations differed from those of their oncologist.[63] Similarly, a secondary analysis of a cluster randomized trial involving patients with incurable solid tumor malignancy or lymphoma and their oncologists found that 60% of patient-oncologist dyads were discordant with respect to cancer curability, and 72% of dyads were discordant with respect to life expectancy estimates.[55,64] Studies show that prognostic misunderstanding is common among patients with hematological malignancies as well.[65,66]

Discussing the intent and potential benefits of cancer-directed therapies should be considered an integral component of the informed consent process, alongside the usual conversations about the risk and potential adverse effects of antineoplastic therapy. In the era of immunotherapies, prognostication is increasingly challenging; although exceptional responders to such therapies remain the exception rather than the rule, robust responses are common enough to raise more uncertainty in discussions about the future with patients who previously would have been said to have clearly incurable metastatic disease with a life expectancy of weeks to months.

Even when accurate prognostic estimates are communicated, patients' interpretations of this information may be affected by the manner in which the information is communicated. For example, a recent study found that the interpretation of estimated survival (25% at 3 years vs 10% at 5 years) was affected more by the chosen timeframe than by the survival probability.[67] Similarly, prognostic estimates that are framed using positive language (eg, survival) are often interpreted differently from the same information framed using negative language (eg, mortality).[68] Furthermore, patients may not believe that the prognosis communicated by their oncologist applies to them because they perceive intrinsic characteristics (eg, fighting spirit or will to live) or faith as having the potential to affect clinical outcomes.[69,70]

Studies show that a vast majority of patients with cancer want to talk about prognosis. Patients desire an honest prognostic disclosure from their oncologist, without sugar-coating. Contrary to oncologists' traditionally held fears, prognostic awareness is not associated with negative outcomes, including sadness, anxiety, or worse patient-physician relationship ratings.[71,72] Rather, prognostic disclosure is associated with maintained hope and increased trust in the oncologist.[73,74] In the setting of serious illness, physicians can help patients redefine hope and establish achievable goals, such as alleviation of distress, improved pain control, and meaningful interactions with loved ones. The challenge is to deliver difficult news with compassion, support, and empathy.[75]

COMMUNICATION PRACTICES AND TECHNIQUES

Serious illness conversations are a critical, challenging, and rewarding aspect of caring for patients with cancer. Communication skills are like physical examination skills in that they can be taught but must be practiced and honed over time. Several educational platforms are successful in improving communication skills in a variety of settings.[76-83] Effective communication in serious illness care should begin not with cancer-related information, but rather with patient-related attributes, including the following:

- Assessment of the patient's capacity for decision-making or need for a surrogate medical decision-maker
- Clarification of the patient's information and communication preferences
- Evaluation of the patient's and family's prognostic awareness
- Discussion of the patient's core values, goals, and priorities that inform medical decision-making, often summarized as "shared goals of care."

This approach emphasizes asking permission before embarking on a difficult discussion or addressing an important topic, an important step in building respect, anchoring rapport, and maintaining open, honest communication. One might conceptualize

this approach as establishing an effective team. It should initiate an ongoing process of clear and consistent discussion with the patient and family regarding treatment, changes in clinical status, prognosis, EOL, and patient and family needs, Timely discussions during disease transitions are associated with less use of acute care and ICU care at the EOL and greater use of hospice, further reinforcing the role of these conversations in optimizing appropriate, patient-centered, advanced cancer care.

A formal ASCO patient-clinician communication guideline[84] outlines best practices for communication in cancer care, including the following:

- Participate in communication skills training programs
- Hold regular discussions of goals of care with patients and their caregivers/families, at the time of diagnosis and at decision points, including a change in clinical status
- Partner with patients actively in their care
- Initiate conversations about goals, values, and end-of-life preferences early in serious illness and often thereafter
- Discuss costs of care
- Discuss with patients all options for their care, including the early initiation of concurrent palliative care
- Endorse the value of and refer patients and families to psychosocial team members (eg, social workers, counselors, psychologists, psychiatrists, and clergy) when appropriate

Figure 9-1 outlines key steps in communicating prognostic information.[85]

Figure 9-1 The AEGIS Model of Patient Communication

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Recommended frameworks for communicating difficult news are described elsewhere.[75,84,86] Whenever possible, difficult news should be communicated in a private setting free from distractions, and the oncologist should be seated. Before communicating new clinical information, it is important to first explore the patient's and family's current understanding. Information should be communicated clearly and succinctly, with frequent pauses to listen for and verify understanding, and allow for questions. The use of silence also allows the patient and family to reflect upon and process the new information. Throughout the conversation, the clinician should respond to emotional cues with empathic statements and nonverbal affective communication. At the end of the discussion, the clinician should confirm that the patient and family have a sound understanding, for example, by asking them to summarize the information in their own words. This approach is often termed ask-tell-ask and is rooted in research and teaching about high-quality communication in serious illness care. Finally, next steps should be established, covering what the patient and family will do, what the physician will do, and when the next contact will occur.

CULTURAL HUMILITY ENHANCES COMMUNICATION AND OUTCOMES

Cultural humility is a lifelong process of self-reflection to identify and examine biases. By contrast, cultural competency is the ability to interact with individuals with different belief systems. Clinicians should consider that patients and families hold different views about who should participate in serious illness conversations, what information should be included, the appropriate setting, and who should convey the information. Cross-cultural reviews have helped expand the literature related to communication and are particularly relevant to clinicians treating diverse populations.[87] Cultural norms with respect to medical

decision-making, prognostic disclosure, and withholding of information may affect communication preferences. Taking the time to explain and discuss the communication plan with the patient and family before delivering serious news can help clinicians navigate these potentially challenging conversations. By remaining curious and avoiding assumptions, clinicians can build trust by supporting each patient's specific communication preferences and needs. When a language barrier exists, professional medical interpreters should be used to communicate with the patient and family.

EQUITABLE ACCESS TO PALLIATIVE CARE

Disparities in access to oncology care and cancer outcomes have been well documented.[88-90] There is also an emerging body of evidence showing that there are differences in access to palliative care for underrepresented patients with cancer.[91,92] Disparities in symptom management, including access to medications and symptom relief, exist among non-White/Hispanic patients compared with their White counterparts.[93,94] Improved understanding of patient-level, clinician-level, and structural barriers to the equitable dissemination of palliative care for patients with cancer, coupled with active efforts to address these inequities, is critical. Telemedicine may present an avenue to close the gap in access to specialty palliative care services in rural and underserved areas of the United States.[95]

ADVANCE CARE PLANNING—AN IMPORTANT CHALLENGE IN PALLIATIVE CARE COMMUNICATION

Advance care planning is a process whereby individuals consider their wishes for future care and end-of-life treatment preferences and make them known to loved ones and healthcare professionals in the event of decisional incapacity. Introducing advanced care planning can be a helpful starting point for conversations with patients with advanced and potentially life-limiting diseases. Normalization of the process, that is, routinely raising the issue, can reduce anxiety and negative reactions. Advance care planning should be done in advance—hence the term—and revisited along the clinical trajectory. Documented components of advance care planning may include advance directives for healthcare, healthcare proxies or powers of attorney for healthcare documents, living wills, do-not-resuscitate orders, and forms that communicate a patient's treatment preferences. These documents vary by state in accordance with local policy.

An advance directive is a legal document representing a person's preferences regarding their medical care and appointed durable power of attorney for healthcare. The percentage of individuals with a completed advance directive remains low, even in the setting of serious illness, such as advanced cancer. There are online advance care planning tools available that are effective at increasing rates of advance directive completion by 25% to 35% and are easily completed via free online resources, such as the PREPARE website.[96,97]

There are ICD-10 codes for documented palliative care discussions, for example, Z51.5 and current procedural terminology (CPT) codes for advanced care planning. Documentation of palliative care needs and planning is a quality-of-care outcome. Such documentation by any member of the care team elevates the appropriate referral to hospice at key transitions in illness.

KEY POINTS

- Although often equated with estimated survival, prognosis can refer to a variety of consequences of the disease and its treatment along a patient's clinical trajectory (eg, cognitive decline, functional status, symptom burden).
- Although most patients with advanced cancer desire prognostic disclosure from their oncologists, many patients have a poor understanding of their prognosis, estimated survival, or intent of cancer-directed treatment.
- The ASCO communication guideline outlines principles of good communication in cancer care, including assessment and discussion of prognosis, elicitation of preferences and values, and discussion about the role of early integrated palliative care.
- Coordinated efforts are needed to effectively address disparities in access to specialty palliative care.

PSYCHOLOGICAL DISTRESS, DEPRESSION, SPIRITUAL SUFFERING, AND CAREGIVER DISTRESS

IDENTIFYING AND ADDRESSING PATIENT DISTRESS

Distress is defined as a multifactorial, unpleasant experience of a psychological, social, spiritual, and/or physical nature that may interfere with the ability to cope effectively with cancer, its symptoms, and its treatment.[98] All patients with cancer have some degree of distress related to the cancer diagnosis, its associated symptoms, and its treatment, regardless of the stage of disease. It is estimated that more than 50% of patients with cancer have high levels of psychological distress.[99] Risk factors for distress in patients with cancer include cognitive impairment, communication barriers (eg, language, literacy), history of psychiatric disorder, history of substance use disorder, history of depression or suicidality, psychosocial issues (eg, family conflict, young or dependent children, limited social support, living alone), financial concerns, and uncontrolled symptoms. In addition to leading to poorer QoL, distress is a risk factor for nonadherence to cancer treatment and surveillance and is associated with

increased emergency room visits and longer hospital stays.[98,100] Despite the high prevalence of distress in patients with cancer, it can be difficult to detect or diagnose. Many patients do not tell their oncologist about their distress, and oncologists often do not ask about distress during outpatient visits due to competing priorities and time limitations. Routine screening for distress is therefore important and has been required as an accreditation standard for hospital cancer programs since 2015 (https://www.facs.org/quality-programs/cancer/coc/standards). In Canada, distress screening has been endorsed as the sixth vital sign.[101]

NCCN guidelines recommend routine screening for distress, while ASCO guidelines recommend routine screening specifically for symptoms of depression and anxiety.[98,100] At a minimum, patients should be screened at the initial visit, at appropriate intervals, and as clinically indicated, especially with changes in disease status (eg, remission, recurrence, or progression). Distress can be identified using a simple screening tool, such as the NCCN Distress Thermometer, which asks patients to rate their distress on a 0-to-10 visual scale, from "no distress" (0) to "extreme distress" (10). Although the Distress Thermometer is not a screening tool for psychiatric disorders, it has concordance with the Hospital Anxiety and Depression Scale and the Depression Anxiety and Stress Scale.[98] NCCN also recommends using a 39-item Problem List, which is on the same page as the Distress Thermometer[98]; both are freely available for noncommercial use. The Problem List asks patients to identify their problems in five distinct categories: practical, family, emotional, spiritual/religious, and physical. Problem-based interventions are a validated approach to the reduction of distress in a patient—family-focused strategy. The NCCN patient website includes a patient-friendly description of distress with a copy of the Distress Thermometer.[102]

Moderate to severe distress (Distress Thermometer score of 4 or higher) should prompt referral to a mental health professional, social worker, spiritual counselor, or palliative care team, depending on the problems identified in the Problem List. Such elevated distress scores are not diagnostic but should trigger further evaluation with validated measures for depression and/or anxiety.

Alternatively, screening can occur directly with measures for depression or anxiety. Screening should be done using validated measures that have established cut-offs to ensure that they are clinically meaningful. The Patient Health Questionnaire-9 for depression (cut-off score of 8 or higher for moderate to severe depression) and the Generalized Anxiety Disorder-7 (cut-off score of 10 or higher for moderate to severe anxiety) are in the public domain and recommended for this purpose, but many other validated measures are available.

Studies demonstrate that medical encounters are shorter when the physician explicitly acknowledges the patient's emotions.[103] In addition, emerging data that demonstrate the beneficial effects of specialty-level palliative care suggest this benefit is at least in part mediated through improved coping, a critical skill that oncology clinicians can incorporate into everyday practice.[104] Problem-based assessment and interventions can reduce distress, improve coping, and can be initiated by the primary team, including the oncologist.

DEPRESSION AND ANXIETY

Depression and anxiety are common in patients with cancer, and often co-occur.[105] Using self-reported measures with specific cut-off points, 13% to 27% of patients with cancer have moderate to severe depressive symptoms, with variability depending on cancer diagnosis; prevalence using self-report instruments with specific cut-offs is 4% to 48%, while, in diagnostic interviews, the prevalence is approximately 10%.[106] In one study, 31% of patients with cancer with an anxiety disorder also had major depressive disorder.[107]

ASCO guidelines state that all patients with cancer and their family caregivers should be offered information regarding depression and anxiety, as well as available resources for further evaluation and treatment, within or external to the hospital.[105] All patients with cancer should be re-evaluated for depression and anxiety throughout their course of illness, and both integrative and pharmacological interventions should be implemented when appropriate.[108]

Clinicians should use a stepped-care model, that is, selecting the most effective and least resource-intensive intervention based on symptom severity.

- For patients with mild depression or anxiety, referral to available support services should be offered.
- Patients with moderate to severe depression or anxiety should be offered culturally informed and linguistically appropriate information such as their prevalence among patients with cancer, common associated symptoms, signs of worsening, and indications to call the treatment team. In addition, those with moderate depression or anxiety should be offered individual or group therapy with evidence-based psychosocial interventions (eg, cognitive behavioral therapy, behavioral activation, structured physical activity and exercise, or mindfulness-based stress reduction).
- For a patient with severe symptoms of depression or anxiety, clinicians should offer individual psychotherapy with evidence-based psychosocial interventions (eg, cognitive behavioral therapy, behavioral activation, mindfulness-based stress reduction, or interpersonal therapy). Pharmacological treatment may be offered for those expressing a preference for pharmacotherapy, or those who do not improve following first-line psychological or behavioral management. Pharmacotherapy should also be considered for patients with a history of treatment response to medications, severe symptoms, or depression with accompanying psychotic features.

Differentiating between grief and depression in patients with serious illness can be difficult, even for experienced clinicians.[108] Patients with depression experience sadness, hopelessness, and anhedonia sustained over a period longer than 2 weeks, often accompanied by physical symptoms of decreased appetite and energy. By contrast, patients with normal grief reactions experience improvement in symptoms over time, can maintain a realistic view of themselves, and can modify their healthcare goals to maintain hope. Complicated grief lasts longer than 6 months and impacts normal function, whereas anticipatory grief can affect both the patient and their loved ones as they prepare for the patient's death.

Diagnosing depression in patients with serious illness is of paramount importance. Studies show that untreated depression results in an increase in morbidity and sequelae, including suicide. Depression, as well as hopelessness, loss of meaning in life, and loss of interest in activities, ranks among the risk factors for the desire to hasten death. Patients whose psychosocial needs are acknowledged as less likely to persist in their desire for death. When a patient expresses a desire to hasten death, requests should be addressed explicitly and should prompt a reassessment of symptom control, psychosocial issues such as relationship strain or fear of caregiver burden, spiritual or existential suffering, and psychological issues such as depression. The care plan should be clarified, with renewed attention to how best to relieve physical, psychological, interpersonal, and spiritual suffering. A detailed discussion of Medical Aid in Dying is beyond the scope of this chapter.

Referral should be made to an appropriate clinician, ideally a palliative care expert, psychiatrist, or psychologist with expertise in the management of psychological disorders who can tailor care to the stage of illness. Pharmacological therapies should be considered in the context of a patient's comorbidities and prognosis. For example, a serotonin-norepinephrine reuptake inhibitor may be used to treat depression and chemotherapy-induced peripheral neuropathy, whereas olanzapine may be used to manage both anxiety and chemotherapy-related nausea and vomiting. Notably, for a patient who has a limited life expectancy, selective serotonin reuptake inhibitors may not exert an effect quickly enough; psychostimulants, such as methylphenidate, may offer a more realistic treatment strategy in this setting.

SPIRITUAL OR EXISTENTIAL SUFFERING

Most patients have a spiritual or religious belief system that is important to them and their family, and is an important resource for effective coping with cancer. Attention to a patient's spiritual and existential needs is an essential component of high-quality palliative care and underscores why palliative care teams include chaplaincy members. Up to 50% of patients with cancer and 25% of long-term survivors experience spiritual distress.[109] Existential suffering may arise through questions that include "Why me?," "Why now?," "How did this happen?," "What is the meaning of life?," "Why am I here?," "What have I achieved in my life?," "How do I fit into the universe?," and "What will happen to 'me' after my death?" The spiritual belief systems of all parties concerned, as well as their personal belief systems regarding our spiritual nature, will influence how they react to these broad existential questions. Of note, spirituality and religion are different, and everyone's experience is unique. Although eliciting information about a patient's belief system (eg, religious affiliation) may help oncologists gain understanding of the patient's religious or spiritual framework, it does not determine the interpretations or beliefs that apply. In addition, a patient need not adhere to any system of belief to experience or successfully resolve existential or spiritual issues.

Experiencing a serious illness and confronting mortality can manifest in a variety of emotions, such as anger, fear, or powerlessness. At times, these feelings can be directed toward clinical staff or toward family members. Although physicians typically are not trained to provide spiritual care, patients and families often assume clinicians will be able to adequately introduce and discuss these issues. To help structure an approach to the assessment and care of patients, the NCCN recommends screening for psychosocial distress, including spiritual/existential distress, in all patients with cancer via the NCCN Distress Thermometer and Problem List.[110] Alternatively, semi-structured interviews for spiritual assessment can be used. Common screening questions include the following[111]:

- "Do you have spiritual or religious beliefs?"
- "Have your beliefs been affected by your cancer diagnosis, and if so, how?"
- "Have your spiritual beliefs influenced your healthcare decisions, and if so, how?"

For patients who are experiencing spiritual distress, a more complex tool, such as FICA (Faith, Importance, Community, Address), can guide a comprehensive spiritual assessment by a chaplain or spiritual care provider.[112]

Cancer care at the EOL, perhaps more than in any other phase of the illness, involves multidisciplinary efforts. During spiritual conversations with patients, clinicians should seek to understand the depths and nuances of the patient's orientation toward this potentially complex area of life. This understanding will assist clinicians in identifying needs that other professionals (eg, chaplains, psychotherapists) should address; the oncologist's responsibility is to guide the delivery of compassionate care and incorporate insights about the patient's spiritual or existential status into clinical decisions to best treat the patient as a whole person.

CAREGIVER/FAMILY DISTRESS

Family caregivers are partners, relatives, or friends who provide care that requires substantial time over months to years and involves performing a wide range of physically, socially, emotionally, or financially demanding tasks.[113] Studies show that 32% to 70% of family caregivers of patients with advanced cancer experience a level of distress or depressive symptoms high enough to suggest clinical depression.[114-116] Caregivers often feel unprepared for the various commitments (eg, financial, emotional, physical) that are involved in caring for a loved one.[117] Furthermore, many caregivers lack the medical knowledge and skills necessary to anticipate the needs of the patient. Because of the multiple demands of caregiving, family members often are forced to leave their jobs or work part-time, which adds financial stress at a time that is already emotionally challenging. Moreover, by attending to the needs of their loved ones, caregivers may neglect their own physical or mental health.

Certain characteristics of caregivers are associated with the negative effects of caregiving. These include caregiver age, ethnicity, sex, socioeconomic status, and health and functional status. Younger, non-White, female, and less affluent individuals tend to experience greater negative effects, such as distress or depressive symptoms. Other factors associated with negative effects include the duration and intensity of caregiving, the mood and physical health of the caregiver, a recurrence of the patient's illness, and the caregiver's subjective sense of burden.[113]

Interventions to support caregivers can be categorized into those that target caregivers themselves, those targeting caregiver-patient dyads, and those targeting mainly patients (the latter are mostly palliative care interventions). In a recent meta-analysis, these interventions all led to improvements in QoL, mental well-being, depression, and anxiety.[118] A growing body of evidence suggests that integrated palliative care can yield significant, often underrecognized, benefits in caregiver well-being, particularly regarding mood.[119,120] Care for caregivers in oncology settings can be improved through the CARES framework: Considering caregivers as part of the unit of care; Assessing the caregiver's situation and needs; Referring to appropriate services and resources; Educating about practical aspects of caregiving; and Supporting caregivers through bereavement.[113]

In offering high-quality primary palliative and supportive care, the clinician exerts a powerful therapeutic effect simply by being present. By being available, communicating openly about difficult topics, and addressing symptoms that are causing distress, the physician can provide significant support. Caregivers particularly value the support and respect of clinicians; those who report that physicians listen to their opinions and concerns are less likely to report depressive symptoms. Good communication, which includes anticipatory guidance and clear explanations of what to expect, is an essential therapeutic tool. By providing appropriate referrals to assistance agencies, such as hospice, physicians can greatly support family members. In all cases, effective communication, listening, and availability contribute substantially to alleviating suffering at the EOL.

KEY POINTS

- Most patients who are dying experience psychological distress. Physicians must be prepared to address this via medical and psychosocial support and to encourage patients and families to leverage the expertise of other members of the interdisciplinary oncology team (eg, social work, behavioral health, etc.).
- Oncology practices should systematically screen for psychological and spiritual distress using available validated tools. Patients with moderate to severe distress should be referred to a specialist, while mild distress may be managed by the primary oncology team.
- ASCO guidelines state that all patients with cancer and their family caregivers should be offered information regarding depression and anxiety, as well as internal or external resources for evaluation and treatment.
- Differentiating between illness-related grief and depression is important. Depression is characterized by a persistent set of emotional symptoms, worthlessness, hopelessness, and anhedonia. Identifying and treating depression and its sequelae are essential for reducing end-of-life morbidity as well as the desire for hastened death.
- Caregiver distress is common and can be reduced with simple interventions.

HOSPICE CARE

Hospice is one of the most effective yet underused resources for patients, families, and clinicians as patients with advanced cancer approach the EOL, although use in the United States is increasing annually. Data consistently demonstrate the benefits of hospice for patients and caregivers, including effects on symptom relief and patient goal attainment. In addition, hospice increases quality of care near the EOL, reduces overall healthcare costs, and can directly improve outcomes. Despite the existence and availability of hospice across most of the United States for approximately 35 years, referrals to hospice are underutilized for patients near the EOL, and, when referrals are made, they are often late. In one study, patients spent a median of 10 days in hospice, and 71% (n = 161) of patients were in hospice 30 days or less.[121] Data from the National Hospice and Palliative Care Organization (NHPCO) reveal that 50% of patients were enrolled for 18 days or less, and the median length of stay has been 2.5 to 3 weeks for the last few decades.[122]

Late referrals to hospice stem from both patient factors, oncologist factors, and system barriers. A study of patients with advanced lung cancer revealed that only 53% of patients had discussed hospice with their oncologists 4 to 7 months after

diagnosis; predictors of not having the discussion included patients having overly optimistic assessments of prognosis and lacking moderate to severe pain or dyspnea.[123] In other words, patients with poor understanding of prognosis who feel well often do not bring up hospice with their oncologists, and, likewise, the topic is not broached by their care team, ultimately leading to delayed referrals.

HOSPICE ELIGIBILITY

The key difference between palliative care and hospice care for patients living with cancer is that palliative care can be given concurrently with disease-directed therapy, whereas hospice care typically entails stopping cancer-directed care.

Patients with cancer are eligible for the Medicare hospice benefit if they are determined by a physician to have a terminal diagnosis wherein the average life expectancy is less than 6 months if the disease runs its usual course. The latter part of this statement is important because the usual course of any disease is variable. The patterns of hospice referral noted above dispel any concerns about premature referral to hospice. In addition, given the inherent uncertainty in prognostication, patients may receive hospice services for longer than 6 months if there is clear documentation of the expected trajectory of illness and decline. Of note, hospice enrollment also generally entails the cessation of disease-modifying treatments aimed at extending life, in exchange for a focus on comfort, patient-focused goals equivalent to QoL, and, most often, death at home.[124,125] Regulatory barriers exist for patients who wish to receive hospice care and also participate in early-phase clinical research, or for patients with hematological malignancies who are transfusion-dependent. Encouragingly, Medicare and healthcare delivery systems are increasingly testing models to improve hospice use via concurrent care, offering opportunities to better meet the needs of people living with serious illness and their families.[125]

Up to 90% of hospice participants elect to use the Medicare hospice benefit, an earned benefit as part of Medicare Part A, to pay for hospice services, including pharmacy costs, nurse and social work support, coordination of care, and more. Patients who use their Part A benefit for other purposes, such as acute hospitalization or active rehabilitation within a skilled nursing facility, cannot simultaneously be enrolled in hospice. This leads to quandaries when patients are seeking an approach focused on comfort care near the EOL, but are reliant on 24-hour caregiving services or are interested in the intensive physical rehabilitation provided in skilled nursing facilities.

There remains a common misperception regarding the need for patients to have a do-not-attempt-resuscitation order in place before referral to hospice. In fact, there is no stipulation for this to participate in residential hospice under Medicare, although some hospice care agencies may strongly discourage enrollment of patients without a do-not-attempt-resuscitation order. In fact, the coercion of patients into a particular resuscitation status can lead to significant penalties for individual clinicians and their organizations and can threaten the therapeutic bond between the patient and the clinician. That said, performing cardiopulmonary resuscitation on a patient with terminal disease is highly ineffective[126] and largely incompatible with the philosophy of hospice care and high-quality cancer care, both of which aim at the promotion and maintenance of comfort and QoL rather than treatment of disease. As such, it is critical to understand, to respectfully explore, and to reexamine the issue at intervals, the rationale for maintaining a full-code status in a patient who elects to receive hospice care, to ensure that the patient and family do not harbor significant misconceptions or unrealistic expectations about the likely outcome.

HOSPICE CARE PROVISION

There are more than 6,000 hospices in operation in the United States, covering all 50 states and most territories. Most are independent and free-standing agencies not restricted to serving patients of any particular nursing home, hospital, or home health agency. Hospices are required to provide six foundational services to participate in the Medicare hospice benefit, including a physician medical director, nursing services, social work services, spiritual support, bereavement support, and volunteers. These services are provided along the spectrum of hospice care, often beginning with a comprehensive assessment of needs during the admission process, with frequent reevaluations of needs along the trajectory of care. Integral to this care is the role of the oncology team, whose members are considered partners in the patient's care. As an example of this, with the right billing and coding approach, oncology practices can still be paid for seeing patients in the clinic who are also receiving hospice care, truly reflecting a concurrent care approach. Often, the primary oncologist serves as the hospice physician of record as well, recognizing that many oncologists view care at the EOL as an important aspect of the primary palliative care that they provide to their patients with cancer.

Many patients with cancer hold an incorrect understanding of hospice as a place to go (ie, a physical destination) instead of a type of care optimized to patient and family needs near the EOL. However, recent data from the NHPCO highlight that more than 90% of hospice care is provided at home or in long-term care facilities in which patients reside.

LEVELS OF HOSPICE CARE

Hospice is generally provided within one of four levels of care: routine home care, continuous home care, general inpatient care, and inpatient respite care. As mentioned, most patients receive routine home care, remaining in their usual place of residence with a focus on preventing crises and being in familiar surroundings. Within continuous home care, the hospice team comes

to the residence to provide crisis-directed care, make the patient comfortable, and avoid visits to the ED or hospital. General inpatient care is used when acute symptom crises, often in the last few weeks of life, cannot be managed at home and require admission to a dedicated inpatient hospice facility or through contracted beds in an acute care hospital. This care is focused on acute symptom management with transition back home once symptoms can be managed outside the acute inpatient setting. Last, inpatient respite care is a time-limited admission to an approved facility to allow caregivers some time away and rest from continuous caregiving.

KEY POINTS

- Hospice care is the best mechanism for providing high-quality care near the EOL in the United States and greatly enhances the ability of patients to die at home in comfort, surrounded by family and friends.
- Patients with an expected prognosis of 6 months or less are eligible for hospice.
- More than 90% of hospice care is provided at home or in long-term care facilities in which patients reside.

PRESENTING CASE STUDY

A 48-year-old man is admitted to the hospital for failure to thrive with wild-type *KRAS/NRAS/BRAF*, nonamplified HER2, microsatellite-stable metastatic rectal adenocarcinoma diagnosed 2 years ago. He previously received treatment with 5-fluorouracil, oxaliplatin, irinotecan, bevacizumab, and panitumumab and ultimately progressed. He achieved stable disease with trifluridine and tipiracil hydrochloride (TAS-102), but, after 6 months, repeat imaging indicates progressive disease in his lungs, liver, and peritoneum. Next-generation sequencing does not reveal any actionable mutations. The patient's Eastern Cooperative Oncology Group (ECOG) performance status is 3. He spends most of his time in a chair but is able to walk to the bathroom using a walker, attributing his decreased mobility to fatigue. Liver function tests are two times the upper reference limit, aside from his bilirubin level, which is within the reference range. The patient remains treatment-focused, hoping to gain enough strength to be considered for additional treatment options.

With this patient's advanced, refractory cancer and poor performance status, what treatment approach would you recommend, balancing his wishes with his limited potential for benefit?

The patient's functional status is compromised. While additional treatment options such as regorafenib are available in the United States, Canada, and the European Union, this patient's ECOG status suggests poor tolerance, with studies demonstrating an improvement in mean overall survival of 1.4 months. At this point in the patient's disease course, it is reasonable to discuss alternative options, including best supportive care and hospice. This discussion should include other members of his care team so that the patient's motivation to be considered for treatment can be explored. Most patients will express concerns not directly linked to longevity for example, family concerns, unresolved conflict, financial issues, etc. Despite the longstanding existence and availability of hospice care across most of the United States, hospice referrals are underutilized for patients near the end of life, and, when referrals are made, they are often late. In one study, for example, patients spent a median of 10 days in hospice, and 71% were in hospice for 30 days or less.[121] Data from the NHPCO reveal that approximately 50% of patients are enrolled for 18 days or less, with a median length of stay of 2.5 to 3 weeks.[122]

Late hospice referrals stem from factors related to the patient, their oncologist, and regulatory barriers restricting concurrent hospice care and early-phase clinical research. Initiating a discussion about best supportive care and hospice would allow this patient and his family to consider their options and weigh the risks and benefits of all approaches.

MANAGEMENT OF THE LAST DAYS OF LIFE

SIGNS AND SYMPTOMS OF THE ACTIVE DYING PROCESS

Clinicians should recognize the process of dying as a part of the trajectory of advanced malignancies and sharpen the focus of goals of care to intensive symptom management and family support. The dying process generally manifests in the continued deterioration of a person's overall condition, with increasing lethargy, progressive asthenia, decreasing levels of consciousness, and, at times, increasing confusion, increasing time asleep, less spontaneous movement, decreased urinary output, inability to regulate body temperature, and changes in patterns of respiratory effort (eg, Cheyne-Stokes breathing). For many people, systemic signs

can include progressive hypotension, diminishing oxygenation, and progressive loss of peripheral perfusion, causing mottling of the skin. A large multicenter study determined that 3-day mortality can be predicted in patients with a Palliative Performance Scale (PPS) value of 20 or lower (ie, bedbound, completely dependent) by a simple diagnostic model with three easily evaluable clinical signs (P3did-DT): decreased urine output, decreased response to verbal stimuli, and decreased consciousness.[127]

In contrast to the usual slow decline described above, the terminal phase of cancer may sometimes be signaled by a sudden change in condition: intracerebral bleeding, pulmonary embolus, perforated viscus, or overwhelming sepsis. When this change is superimposed on an already moribund condition, continued symptom control becomes the primary goal. Understanding patients' wishes, often through conversations they have had with their families throughout the course of their illness or life, will help determine the best course of action. Catastrophic decline can be effectively managed with a palliative care team in place, a continued focus on effective communication and symptom goals of care, and well-described patient wishes expressed by a designated caregiver. In this situation, most patients will remain at home or out of the ICU.

Whether the EOL approaches as an expected deterioration or as an unexpected catastrophic decline, the issue of comfort is paramount. Clinicians should ensure that all clinical actions contribute to the comfort of the person who is dying. Given the unfamiliarity of caregivers with the signs and symptoms of the dying process, it is critical to share information and educate them to minimize fear and anxiety. Frequently, hospice programs will have an informational brochure or handout that can be shared with loved ones who are interested. Caregivers can be supported by underscoring that successful care is defining goals of care, and, in this situation, goals of care are focused on comfort and relief of suffering.

BEDSIDE CARE AT THE EOL

Attention to the bedside care of the dying patient is crucial. Regular checking of vital signs should be replaced, at this stage, with regular checking of symptoms. Good bedside care includes the following:

- Mouth care, to ensure that the dying person's mouth is clean and moist, will aid comfort.
- Eyes can also become dry and painful and may require additional supportive measures, such as eye lubricants and/or drops.
- Proper skin care includes regular repositioning of the patient to relieve musculoskeletal pain from inertia and avoid the excruciating (and difficult to control) pain of skin tears and pressure sores. Use of a pressure-relieving mattress is advised. An air mattress will facilitate the shifting of the person's weight.
- The head of the bed can be elevated, or patients can be gently repositioned, to help reduce noisy upper respiratory tract secretions through postural drainage.
- Urinary retention and fecal impaction should be evaluated and treated if present.

TERMINAL SECRETIONS

Noisy ventilation (often referred to as death rattle or terminal secretions), caused by oscillatory movements of accumulated bronchial mucosa and salivary secretions, is common among patients who are dying and are unable to clear secretions by coughing or swallowing.[128] The symptom usually occurs after patients are unconscious, and it may cause considerable distress to families and caregivers. The reported prevalence varies between 12% and 80% in the final 3 days of life.[129]

Intervention to reduce secretions is often instituted to alleviate the distress of attendant family members, even when the patient seems settled. The primary intervention should be to explain the source of this sound to the patient's family or other caregiver(s), with reassurance that it is not associated with any discomfort. Standard nonpharmacological practices for alleviating terminal secretions should be initiated first. These include gentle positioning (reverse Trendelenburg or lateral decubitus), towels placed appropriately to absorb secretions, and reducing parenteral and enteral fluids.

Anticholinergic agents are often used to reduce sputum volume and salivary secretions and alleviate the noise, despite a lack of strong evidence to support their efficacy.[130] These drugs include scopolamine, hyoscyamine, glycopyrrolate, and atropine. The primary difference in these drugs is whether they are tertiary amines that cross the blood-brain barrier (eg, scopolamine, atropine) or quaternary amines, which are less likely to do so (eg, hyoscyamine, glycopyrrolate). However, all these drugs have the potential for central and peripheral anticholinergic adverse effects, including sedation, confusion, delirium, paradoxical excitation, and urinary retention. These medications are especially high risk in older patients, who should be monitored closely for side effects. Atropine, a widely available drug, is frequently used in home care; a common approach is 1% atropine ophthalmic solution, one to two drops sublingually every 4 hours as needed. Scopolamine (hyoscyamine hydrobromide), a muscarinic receptor antagonist, is given transdermally every 72 hours. Glycopyrrolate or hyoscyamine are preferred due to their lower potential for central anticholinergic effects, though use is limited by cost and poor oral absorption.

Best evidence supports prophylactic administration of scopolamine butylbromide in patients close to death, which reduces the number who develop death rattle (13% vs 27% with placebo[131]). Evidence supporting treatment of the death rattle once it has begun is less clear, with no evidence that one antimuscarinic is clearly superior to another.[132] Discussing terminal secretions

with family members to reduce their distress is the most important intervention; these conversations should address the cause, implications, and caregivers' fears and concerns.

DEPRESCRIBING ANCILLARY INTERVENTIONS INCLUDING MEDICATIONS

As the patient nears the EOL, the clinician should review all medications and continue only those that contribute to increased comfort. Long-term medications aimed at reducing late effects, such as statins for cardiovascular risk reduction (primary prevention), should be discontinued in most cases. Deprescribing medications not aimed at comfort and symptom management can significantly reduce pill burden for patients and caregivers.[133] Implanted defibrillators should be deactivated to prevent painful shocks at EOL, though pacemakers may remain active and do not interfere with natural death. Diagnostic tests and functions (eg, transfusions, needle sticks, measurement of intake and output, blood glucose monitoring, oxygen saturation monitoring, suctioning) can and should be discontinued if deemed unnecessary for symptom control and comfort.

In deciding which medications to discontinue, all medications should be reconsidered for their benefit to the patient, not only those that were introduced for symptom control in the palliative phase of the illness. For example, for type 1 diabetes, insulin is necessary to prevent hyperglycemia to spare the patient unquenchable thirst, and it is common to continue such interventions as comfort measures even at the EOL. Essential medications should be obtained in a form that can be administered to someone who may not able to swallow predictably. Alternative formulations include sublingual, subcutaneous, intravenous, transdermal, intranasal, and rectal. Doses of medications retained for symptom management should be increased as necessary to optimize comfort. It is important to discuss deprescribing as a comfort measure near the EOL and individualize this approach with each patient and family, while carefully considering the balance between adverse reactions and benefits and potential withdrawal risk for each medication.[134]

OTHER INTERVENTIONS

Nutrition and Hydration

As patients are actively dying, any nutritional supplements or parenteral hydration should be reviewed. Almost always, parenteral hydration should be stopped, with appropriate advice to the family, because overhydration will worsen respiratory symptoms, and enteral fluids will potentially cause secretions and distention in the gut that may cause vomiting. At worst, ongoing hydration can even prolong or worsen difficult symptoms during the dying process, thus worsening the patient's and family's discomfort.[135] This requires in-depth conversations with and education of the family and caregivers, emphasizing the natural progression of the anorexia-cachexia syndrome at the EOL. It is important to recognize that stopping nutrition and/or hydration can be an emotionally charged issue for loved ones, which may require time to process and extra support from nonmedical colleagues, such as those in social work and chaplaincy, to address cultural, emotional, and existential sources of distress.

Management of Terminal Delirium

Characterized by a disturbance of consciousness, cognition, and perception, delirium is most highly prevalent in the days and hours immediately preceding before death, with rates reported as high as 88%.[136] It often provokes considerable distress among patients, caregivers, and medical providers who are witnessing the patient's transition toward death.[137] Delirium is generally an indirect result of various factors associated with the patient's underlying cancer, such as adverse treatment effects, metabolic disorders, nutritional deficiencies, or infection. Adverse effects of medications are also a common cause of delirium for patients near the EOL.[138]

Terminal delirium (also known as terminal agitation), delirium that occurs in the setting of the active dying process, requires a different approach from that of hyperactive or hypoactive delirium. The clinician should first ensure that this agitation is not a result of pain, urinary retention, or constipation. There is a paucity of studies in this setting, but benzodiazepines are often used. One study suggested that neuroleptics, such as haloperidol and chlorpromazine, can help reduce refractory agitation.[139] When symptoms are severe, sedation may be required through the use of continuous infusion of a benzodiazepine or barbiturate (midazolam or pentobarbital are most commonly used). Sometimes called palliative sedation, this intervention can be controversial and is associated with significant misconceptions about hastening death.[140]

Communication with the Family and/or Caregivers

Communication with the family or other loved ones involved in the last stages of caregiving should be a key focus for health professionals as a patient nears death. What does the family expect? How well do they understand the patient's condition and the dying process? A trusted clinician should clearly, but compassionately, describe the process of dying. The clinician should emphasize that, at this important phase, the sole focus of care is the dying person's comfort and that current medical practice has multiple strategies to optimize comfort.

Many family members have a strong desire to be present at the time of death. This specific time can be difficult to predict. The need to be present varies from family to family and, within families, from one individual to another. If family members have a particular wish to be present at the patient's time of death, the clinician may recommend a vigil roster to ensure that one member of the family is always present during the patient's last days.

Management of Care for the Unconscious Patient

Even when a patient is unconscious, clinical staff should carefully assess him or her to ensure comfort. Evaluation cannot be done from the door of the patient's room. An examination is required, with special attention to the face (is it relaxed?), respiration (is it regular and unlabored?), and positioning (is the patient positioned comfortably?). Available tools to assess nonverbal signs of pain include the following[141]:

- Behavioral Pain Scale (BPS), Checklist of Nonverbal Pain Indicators (CNPI)
- Critical Care Pain Observation Tool (CPOT)
- Faces, Legs, Activity, Cry, Consolability (FLACC) pain tool
- Multidimensional Observational Pain Assessment Tool (MOPAT)
- Nociception Coma Scale (NCS)
- Nonverbal Pain Scale (NVPS)

The clinician should continue to explain to the patient what is happening in the clinical examination, as if he or she were conscious; it is important for family members to understand that people, even when unconscious, may still recognize their voices and their touch. The clinician should also reassure the family that symptom-control medications will be continued to ensure the patient's comfort even though consciousness has been lost. There is no concern that these medications will hasten death, especially if continued at the same dose.

CARE AFTER DEATH

The clinician's role does not end immediately upon the death of the patient. Follow through with the patient's body, logistic considerations, and attention to family members and other caregivers are the crucial last steps in end-of-life care.

Immediately after the patient's death, the clinician should allow the family to spend time with the body, if they so desire. Treatment of the body should be respectful and culturally sensitive. If not addressed previously, plans for eye donation (allowable in many cases of cancer, except some leukemias and eye malignancies) and autopsy are discussed, addressing any family member or caregiver concerns. The clinician files a death certificate, completes any other required forms, and conveys information to the funeral director as needed. In addition, the clinician should inform the patient's other healthcare providers of the death.

Attention should be directed to family members and other caregivers. The normal bereavement process should be described to them; information regarding available bereavement support should be provided, and referral can be made to appropriate services. If the patient and family were receiving support from a hospice team, bereavement support may be obtained through the same agency. Palliative care clinicians can help the oncologist identify family members who may be at risk for complicated bereavement, and they can follow through with requisite care. Formal expressions of condolence on the patient's death, such as a card, phone call, or brief letter, can be immensely meaningful and supportive to family members and caregivers. Amid busy clinical practices, we sometimes forget to pause for a moment to reflect on the privilege of caring for a patient and their family during the patient's last days. Sharing memories, talking with colleagues and staff about the patient, and reflecting on the experience may be helpful in the prevention of burnout, an issue rising in prevalence among oncologists.

KEY POINTS

- At the EOL, the patient's comfort should be the primary focus. Unconscious patients should be treated with the same degree of care, concern, and communication as conscious patients.
- Physical care should address mouth care and musculoskeletal positioning, with attention given to maintaining skin integrity and comfort.
- Terminal secretions can be addressed with the careful administration of anticholinergic agents, as well as with attentive nursing care, positioning, and, most importantly, education of family caregivers.
- As the patient nears the EOL, all medications, medical interventions, nutritional supplements, and hydration efforts should be reviewed to continue only those that directly contribute to comfort.
- Delirium is frequently a source of great distress for the patient, their loved ones, and the care team. The clinician should screen for and treat any underlying reversible causes. If agitation occurs, clinicians should determine the source, if possible, and address it appropriately. Specialist palliative care consultation is recommended in cases of difficult and/or refractory symptoms.
- The wishes of family members with regard to being present at the time of death and aftercare of the patient's body should be respected and facilitated to the greatest degree possible.

HIGH-YIELD TAKEAWAYS

- Hospice referral is often delayed and/or underutilized at the EOL, stemming from patient, physician, and regulatory factors.
- A "Do-Not-Resuscitate" order is not required for enrollment in hospice.
- Clinicians should routinely assess prognostic understanding, honestly and empathically convey accurate prognostic information to patients and families, elicit patient goals and values in the context of this prognosis, and provide clear goal-concordant recommendations.

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PALLIATIVE CARE AND CARE AT THE END OF LIFE

9

CHAPTER SUMMARY GUIDE

KEY POINTS

- Oncologists provide primary palliative care—the common and foundational services promoting QoL among patients and families facing cancer—and should refer those with advanced cancer, high-risk hematological malignancies, patients enrolled on phase 1/2 clinical trials, or significant symptom burden to specialists who provide secondary and tertiary palliative care via interdisciplinary teams with specialty training.
- Randomized trials have shown that, compared with primary palliative care provided by oncologists, early integrated specialist palliative care improves QoL, symptom intensity, patient and caregiver satisfaction, mood, illness understanding, quality of end-of-life care, and survival.
- ASCO has released an updated formal guideline recommending that oncology clinicians refer patients with advanced solid tumors and hematological malignancies to specialized interdisciplinary palliative care teams that provide care alongside active cancer treatment beginning early in the disease course.
- Palliative care consultation is the standard of care for patients with advanced cancer and/or significant symptoms, per ASCO guideline recommendations.
- Palliative care specialists are experts in complex symptom management and communication surrounding serious illness.
- Barriers to early palliative care exist but can be addressed through education of oncologists, close collaboration between oncology and palliative care teams, and systems-based research and quality improvement.[4,5]
- APNs play an important role in delivering primary palliative care.[13,21,30,47-49,52,54]
- Stepped palliative care models and virtual palliative care have been demonstrated as being equivalent to routine in-person palliative care follow-up and hold promise for improving palliative care access while reducing resources.
- There is a need for standard metrics for measuring the effectiveness of palliative care programs to identify key interventions.
- Although often equated with estimated survival, prognosis can refer to a variety of consequences of the disease and its treatment along a patient's clinical trajectory (eg, cognitive decline, functional status, symptom burden).
- Although most patients with advanced cancer desire prognostic disclosure from their oncologists, many patients have a poor understanding of their prognosis, estimated survival, or intent of cancer-directed treatment.
- The ASCO communication guideline outlines principles of good communication in cancer care, including assessment and discussion of prognosis, elicitation of preferences and values, and discussion about the role of early integrated palliative care.
- Coordinated efforts are needed to effectively address disparities in access to specialty palliative care.
- Most patients who are dying experience psychological distress. Physicians must be prepared to address this via medical and psychosocial support and to encourage patients and families to leverage the expertise of other members of the interdisciplinary oncology team (eg, social work, behavioral health, etc.).
- Oncology practices should systematically screen for psychological and spiritual distress using available validated tools. Patients with moderate to severe distress should be referred to a specialist, while mild distress may be managed by the primary oncology team.
- ASCO guidelines state that all patients with cancer and their family caregivers should be offered information regarding depression and anxiety, as well as internal or external resources for evaluation and treatment.
- Differentiating between illness-related grief and depression is important. Depression is characterized by a persistent set of emotional symptoms, worthlessness, hopelessness, and anhedonia. Identifying and treating depression and its sequelae are essential for reducing end-of-life morbidity as well as the desire for hastened death.
- Caregiver distress is common and can be reduced with simple interventions.
- Hospice care is the best mechanism for providing high-quality care near the EOL in the United States and greatly enhances the ability of patients to die at home in comfort, surrounded by family and friends.
- Patients with an expected prognosis of 6 months or less are eligible for hospice.
- More than 90% of hospice care is provided at home or in long-term care facilities in which patients reside.

- At the EOL, the patient's comfort should be the primary focus. Unconscious patients should be treated with the same degree of care, concern, and communication as conscious patients.
- Physical care should address mouth care and musculoskeletal positioning, with attention given to maintaining skin integrity and comfort.
- Terminal secretions can be addressed with the careful administration of anticholinergic agents, as well as with attentive nursing care, positioning, and, most importantly, education of family caregivers.
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- The wishes of family members with regard to being present at the time of death and aftercare of the patient's body should be respected and facilitated to the greatest degree possible.

CHAPTER TABLES AND IMAGES

Table 9-1 **Primary Versus Secondary Palliative Care**	
Primary	Management of cancer-related pain, including basic opioid regimens
	Basic non-pain symptom management, including nausea, constipation, and mood
	Advance care planning, eliciting patient values to provide goal-concordant care
	Ongoing prognostic awareness assessment
Secondary	Management of cancer-related pain, including complex opioid regimens
	High-touch and refractory non-pain symptom management
	Advanced communication strategies to augment advanced care planning and serious illness conversations with complex dynamics
	Enhanced prognostic awareness assessment and discussions with key stakeholders (eg, patient, treating team, family members)

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Table 9-2 **Barriers and Facilitators to Early Integration of Palliative Care**

Factors Impacting Delayed Referral to Palliative Care	Potential Solutions to Improve Early Palliative Care Engagement[30]
• Patient's negative perceptions of palliative care • Family's negative perceptions of palliative care • Physician reluctance to discuss prognosis/EOL issues, including loss of hope • Physician perception of overlapping skill sets with palliative care • Lack of the medical team's recognition of the terminal phase of disease • Lack of integration between oncology and palliative care, including perceived conflict in goals of care that is, disease-directed therapy versus palliative care • Lack of clearly defined responsibilities between oncology and palliative care • Limited palliative care resources and a lack of clearly defined consensus referral criteria • Inadequate systems support and timely actionable data	• Education regarding the benefits of early palliative care for patients and caregivers as part of public health policy strategy • Using the term Supportive Care to name the services offered by the palliative care team • Adequate staffing, training, and resources to accommodate early palliative care referrals • Screening mechanism to help prioritize early palliative care referrals • Effective communication and collaboration among palliative care and oncology teams • Clarifying the roles and responsibilities of oncology and palliative care teams in a collaborative delivery model • Concurrent or simultaneous care models of integration • Bridge programs • Health system support for leadership, access to actionable data, financial support for multidisciplinary team organization, and care delivery • Regulatory amendments that support palliative care services billing separately from disease-directed therapy • Follow-up palliative care visits via virtual care and/or using a stepped-care model, with palliative care visits occurring only at key points in patients' cancer trajectories[4,5]

Abbreviation: EOL, end of life.
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Table 9-3 **The Components of TEAM-Based Palliative Care**

Component	In the Trials	What Is Known
Time	A structured palliative care visit of at least one extra hour per month; repeated at regular intervals (ie, monthly); not once	These assessments can be conducted by a physician or APN with specific training in conducting such assessments.
Education	Structured, prospective, and recurrent discussions about symptoms, goals, and preferences for care, prognosis understanding, advance care planning, and communication with the healthcare team	Education that is done prospectively and regularly, rather than during a crisis, is more effective. Usual topics include, on a recurring basis: • Medically appropriate options for treatment; patients should know they have or have not left any medical stones unturned; this is best done by listing the treatments used and their outcomes, especially with recurrent disease; if appropriate, reinforce patient and family work as advocates • Advance care planning should be started early and revisited along the disease trajectory; documented components may include power of attorney documents, healthcare proxies, living wills or advance directives, and do-not-resuscitate orders • Use of hospice for the best possible care, and arranging a hospice information visit once it is evident the disease is going to take the person's life
Assessment	Formal assessments for: • Symptoms (ESAS, MSAS-C, CAPC rounding tool) • Spirituality (FICA, or "Are you a religious or spiritual person?") • Distress (Distress Thermometer, others) • Psychosocial (PHQ-2) • Caregiver strain It is not sufficient to just ask "How are you?"; patients and families are sometimes reluctant to share their problems for fear that nothing can be done, or that it is not in the clinician's remit, or that the oncologist will stop treating their cancer, or that they will be labeled a complainer.	After these formal symptom assessments, move on to goal setting. Questions may include: • How do you like to get medical information? • What is your understanding of your disease? • What is important to you? • What are you hoping for? • Have you thought about a time when you might become sicker, such that you would need an advance directive or living will? (some motivational interviewing) The authors of the table have incorporated this into a temporary tattoo that gives oncologists a script to start the most difficult discussions (Fig. 9-1). If progressive disease is evident, it is time to revisit goals of care, prognosis understanding, and advance care planning.
Management	By setting protocols and an interdisciplinary team (APNs, social workers, chaplains, doctors)	Interdisciplinary care and referrals were common elements of all studies. Giving people knowledge of their realistic options and a plan of action was shared across all the studies. Establishing ties with social work or chaplaincy is as important as developing ties with surgeons, radiation oncologists, or other medical professionals.

Abbreviations: APN, advance practice nurse; CAPC, Center to Advance Palliative Care; ESAS, Edmonton Symptom Assessment Scale; FICA, Faith and Belief, Importance, Community, Address in Care; MSAS-C, Memorial Symptom Assessment Scale Condensed; PHQ-2, Patient Health Questionnaire-2.

From Bakitas MA, El-Jawahri A, Farquhar M, et al. The TEAM approach to improving oncology outcomes by incorporating palliative care in practice. *J Oncol Pract*. 2017;13(9):557-566. doi:10.1200/JOP.2017.022939

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Figure 9-1 The AEGIS Model of Patient Communication

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BREAST CANCER 10

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RECENT UPDATES

- In patients with node-positive, hormone receptor–positive and HER2-negative early-stage breast cancer, the addition of abemaciclib to adjuvant endocrine therapy improved the secondary endpoints of overall survival (OS) and distant relapse-free survival (DRFS) compared to endocrine therapy alone (7-year OS 86.8% vs 85%; 7-year DRFS 80% vs 74.9%).[1-4]

- OS was significantly improved with inavolisib, a PI3K inhibitor, in combination with fulvestrant and palbociclib (median overall survival [mOS] 34 months) versus fulvestrant, palbociclib, and placebo (mOS 27 months) in patients with PIK3CA-mutated, hormone receptor–positive and HER2-negative advanced breast cancer with endocrine-resistant disease that had progressed during or within 12 months of adjuvant endocrine therapy.[5] Imlunestrant, an estrogen receptor 1 (ESR1) antagonist, was FDA approved in individuals with advanced hormone receptor–positive and HER2-negative breast cancer with an ESR1 mutation after receipt of at least one prior line of endocrine therapy.

OVERVIEW

In the United States, breast cancer is the most common cancer among women. Since 1990, mortality rates have consistently declined, primarily as a result of advances in systemic therapy. For early-stage breast cancer, advances in surgery and radiation oncology have led to the de-escalation of locoregional therapy. Substantial progress has been made toward the approval of new agents for patients who have early-stage and metastatic breast cancers (MBCs). However, more effective therapeutic options are still needed, as are biomarkers, to select patients in whom therapy can be optimized. Advances in supportive care have reduced serious complications of breast cancer treatment and improved both symptom management and quality of life.

EPIDEMIOLOGY

Breast cancer is the most common malignancy among women, with approximately 2.3 million women diagnosed worldwide in 2020, accounting for 11.7% of all new cancer cases.[6] The incidence rates are higher in economically developed regions and lower in economically developing areas, such as sub-Saharan Africa and parts of Asia.

Breast cancer remains the second most common cause of cancer-related death among women (beside lung cancer), with estimated deaths of 42,680 in the United States 2025.[7]

The incidence and mortality rates of breast cancer in the United States differ according to age, race, and ethnicity. The incidence rate of breast cancer has increased by 1% per year since 2012, but this increase is higher in women younger than 50 years (1.4% per year) versus women older than 50 years (0.7% per year). The increased incidence in younger women may be due to decreased number of births, older age at first birth, and increased body weight. The overall incidence of breast cancer is highest among White women and lowest among Asian American/Pacific Islander and Hispanic women, although the annual incidence among these two groups has increased recently.[8]

Although the overall incidence has increased, the overall breast cancer mortality has decreased by 44% in the last three decades. This decline is likely due to earlier detection and improvement in treatments. Although Black women have a 5% lower incidence of breast cancer compared to White women, mortality among Blacks is 38% higher. Multiple factors play a role in this observation. Breast cancer is more likely to develop before the age of 40 years in Black women than in White women; Black women are also more likely to be diagnosed with a more advanced stage of breast cancer and to have high-grade triple-negative tumors. Nonbiologic factors, such as patterns of care and underuse of treatment, likely contribute to the higher mortality rate.[9]

KEY POINTS

- The incidence rate of breast cancer in the United States has been slowly increasing at a rate of 1% annually overall since 2012. By contrast, the mortality rate has consistently declined, primarily as a result of advances in systemic therapy.

- The incidence rate has been steeper among women under 50 years.
- The incidence rate of breast cancer is increasing in nonindustrialized countries, in part due to changing lifestyle patterns (eg, rising rates of obesity and decreased physical activity).
- Compared with non-Hispanic White women in the United States, Black women now have a similar rate of incidence but a higher rate of mortality for breast cancer. The causes behind this significant disparity are not fully understood and are likely multifactorial.

NONMODIFIABLE RISK FACTORS

AGE AND SEX

In the United States, older age and female sex are the most important risk factors for the development of breast cancer (Table 10-1). The lifetime risk of breast cancer among US women is estimated at one in eight (12%), with multiple risk factors identified.[10]

Table 10-1 Established Risk Factors for Breast Cancer: Fixed Factors (Excluding Genetic Mutations)[10]

Factor	Relative Risk
Sex (female vs male)	100
Age (older than 50 vs younger than 50 years)	6.7
Endocrine factors	
Age at first birth (older than 30 years) or nulliparity	1.2-1.7
Age at menarche (younger than 12 years) or age at menopause (older than 55 years)	1.2-1.3
Benign breast disease	
ADH, LCIS	4.0-5.0
Family history (no known mutation)	
One first-degree relative	1.5-2.0
Ashkenazi Jewish ethnicity	1.4
Therapeutic radiation to the chest before age 30 years	7.0-17.0

Abbreviations: ADH, atypical ductal hyperplasia; LCIS, lobular carcinoma in situ.
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Breast cancer in men is uncommon, accounting for approximately 1% of all breast cancers.[11] Men are usually diagnosed after the age of 60 years; the specific risk factors for this disease among men include the following:

- Genetic predisposition associated with *BRCA2* or *PALB2* mutations
- Klinefelter syndrome
- Testicular alterations that result in testosterone deficiency (eg, undescended testes and testicular injury)
- Syndromes that increase the estrogen-to-testosterone ratio (eg, obesity and cirrhosis)

FAMILIAL RISK FACTORS

Approximately 5% to 10% of all breast cancers are hereditary and are associated with mutations in highly or moderately penetrant genes. An additional 15% to 20% of women diagnosed with breast cancer have a family history of breast cancer. Having first-degree relatives with breast cancer portends a twofold higher risk of breast cancer.[10] This risk can increase three- to fourfold if a first-degree relative is diagnosed at an age younger than 50 years or when two first-degree relatives are affected.[12,13] Having a history of breast cancer is also associated with a higher risk of developing contralateral breast cancer, which can be compounded if a family history of breast cancer is present.

GENETIC RISK FACTORS

The inherited risk of breast cancer can result from alterations in highly (*BRCA1*, *BRCA2*, *PALB2*, *TP53*, *CDH1*, *STK11*, and *PTEN*) or moderately (*CHEK2*, *ATM*, and *NF1*) penetrant genes (Table 10-2). Pathogenic or likely pathogenic alterations in highly or moderately penetrant genes may be associated with other malignancies.[14-22] High-penetrance alterations (relative risk ≥ 5) are associated with a recognizable autosomal dominant predisposition. Moderate-penetrance alterations (relative risk, 2-5) may be more challenging to identify because of incomplete penetrance. Multigene panel testing is now offered to most patients; however, the panel composition and interpretation vary based on the specific commercial or private test.[23] The challenges of using these panels include uncertainties about the actionability of moderate-penetrance genes and the higher likelihood of detecting variants of uncertain significance.[24,25]

Table 10-2 **Lifetime Cancer Risk for People Who Have High- and Moderate-Penetrance Mutations in Selected Genes**[14-22]

Gene (Associated Disease)	Cumulative Lifetime Risk of Breast Cancer Development (%)	Other Tumors
High penetrance		
BRCA1	55-70	Ovarian cancer
BRCA2	45-70	Prostate cancer Pancreatic cancer Malignant melanoma Gallbladder and bile duct cancer Stomach cancer
TP53 (Li-Fraumeni syndrome)	90	Soft tissue sarcoma and osteosarcoma Brain tumors Leukemia Adrenocortical cancer
PTEN (Cowden syndrome/*PTEN* hamartoma tumor syndrome)	Poorly characterized	Follicular thyroid cancer Endometrial cancer Colon cancer Renal cancer
STK11 (Peutz-Jeghers syndrome)	Poorly characterized	Colon cancer Pancreatic cancer Stomach and small bowel cancer
CDH1 (hereditary diffuse gastric cancer)	50-60 (mainly lobular)	Diffuse gastric cancer
PALB2	40-50	Pancreatic cancer
Moderate penetrance		
ATM	20-30	Pancreatic cancer
BRIP1	Insufficient evidence	Ovarian cancer
BARD1	Insufficient evidence	
CHEK2	20-30	Colorectal cancer
MSH2, MLH1, MSH6, PMS2, EPCAM (Lynch syndrome)	Insufficient evidence	Endometrial cancer, Ovarian cancer
NBN	Insufficient evidence	
NF1	18	
RAD51C	Insufficient evidence	
RAD51D	Insufficient evidence	

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The most common mutations are localized in the *BRCA1* and *BRCA2* genes. The characteristics of carriers of *BRCA1* and *BRCA2* pathogenic variants (PVs) include the following:

- Among women who have a *BRCA1* PV, the risk of breast cancer up to the age of 70 years ranges from 55% to 70%; it ranges between 45% and 70% in women who have a *BRCA2* PV.[26-29]
- The risk of developing ovarian cancer during a lifetime is higher with a *BRCA1* PV (40%-45%) than with a *BRCA2* PV (15%-20%).[26-29]
- The development of contralateral or second primary breast cancer is increased (*BRCA1* relative risk, 4.5; *BRCA2* relative risk, 3.4). The absolute risk after 10 years is higher for women diagnosed at younger than 30 years (28.2%) than for women older than 50 years (10.8%).[30]
- The risk of breast cancer in men before the age of 80 years is approximately 7% among *BRCA2* PV carriers.[31]

- Approximately 2.5% of people of Ashkenazi Jewish ancestry carry one of three founder variants: 185delAG and 5382insC in *BRCA1* or 6174delT in *BRCA2*. These three mutations account for 12% of breast cancers and 35% of ovarian cancers in this population. An additional 2% to 4% of Ashkenazi Jewish women who have breast cancer have a nonfounder PV, which is similar to the prevalence of alterations in non–Ashkenazi Jewish women.[32]
- *BRCA1* PV carriers are more likely to develop triple-negative breast cancer (TNBC) than *BRCA2* PV carriers or non-*BRCA* PV carriers. Approximately 80% of breast cancers in *BRCA1* carriers are TNBC, whereas the distribution of breast cancer subtypes in *BRCA2* mirrors the general population, being predominantly hormone sensitive. The risk of pancreatic cancer and prostate cancer is higher in *BRCA2* carriers than in *BRCA1*.

The characteristics of other high-penetrance genes include the following:

- Li-Fraumeni syndrome, a rare hereditary cancer predisposition syndrome of multiple cancer types that occur at an early age, is associated with PVs in *TP53*. Carriers have a 90% lifetime risk of developing cancer, with breast cancer being the most common. There is a particular predilection for very–early-onset breast cancer, in addition to other types of malignancies.[14-22] HER2–positive breast cancer is more prevalent in women with a *TP53* germline PV than in women without a *TP53* PV.[33] In addition, patients with Li-Fraumeni syndrome are at an increased risk of secondary malignancies developing in a radiation field.[34] (Note that the HER2 gene is also called the ERBB2 gene.)
- Cowden syndrome is a rare autosomal dominant syndrome; 80% of cases are caused by variants in the *PTEN* tumor suppressor gene (10q23). In this syndrome, breast cancer can occur in conjunction with other cancers, such as thyroid, endometrial, colon, and renal. Specific physical findings among patients with Cowden syndrome include macrocephaly, hamartomas, autism, and trichilemmomas of the face, hands, and feet.[35]
- Germline PVs in *CDH1* are associated with an increased risk of diffuse gastric cancer and invasive lobular carcinoma.
- *PALB2* (partner and localizer of *BRCA2*) has emerged as a relevant gene associated with predisposition to breast cancer. Loss-of-function mutations in *PALB2* are observed in 0.6% to 3.9% of families with a history of breast cancer.[14]
- Germline PVs in *STK11* are associated with Peutz-Jeghers syndrome, a rare syndrome with 55% to 85% lifetime risks of cancer. Individuals with PVs have an increased risk for breast cancer in the range of 32% to 54%.[36]

Multigene panel testing identifies PVs in several moderate-penetrance genes in a significant number of women who have breast cancer. Taken together, PVs in moderately penetrant genes such as *ATM* and *CHEK2* are as common as alterations in *BRCA1* and *BRCA2*.[37] Criteria such as those published by the National Comprehensive Cancer Center Network are less sensitive for the detection of PVs in these genes than they are for high-penetrance variants.[38] Some advocate that multigene panel testing is offered at the time of breast cancer diagnosis to all women and men, regardless of family history.[39] American Society of Clinical Oncology (ASCO), working with the Society of Surgical Oncology, has published guidelines suggesting testing for women diagnosed at age younger than 65 years.[40]

Second cancer risks for women with PVs in *BRCA1* and *BRCA2* are significantly higher than for women with PVs in *PALB2*, *ATM*, and *CHEK2*.[41]

The identification of a PV or likely PV in highly penetrant genes has important therapeutic implications.[41] Women with *BRCA* mutations may choose bilateral mastectomies at the time of a breast cancer diagnosis. In addition, women with *TP53* mutations might be offered mastectomy to avoid radiation therapy (and risk of second cancers). Furthermore, patients with germline *BRCA1* and *BRCA2* PVs or likely PVs and either early-stage or metastatic HER2-negative breast cancer may benefit from PARP inhibitors. Based on therapeutic implications, genetic testing for patients with MBC is recommended.[42]

Guidelines from ASCO and the Society of Surgical Oncology recommend *BRCA1/2* mutation testing to all newly diagnosed patients 65 years or younger and in select patients older than 65 years based on personal and family history, ancestry, or eligibility for PARP inhibitor therapy, as mentioned. Additional gene panel testing should be offered to those who have a supportive family history.[40]

REPRODUCTIVE AND ENDOGENOUS HORMONES

Endogenous and exogenous estrogen plays a well-established role in breast cancer risk and development. Increased levels of premenopausal endogenous hormones are associated with an increased risk of disease among postmenopausal women. Terminal differentiation of breast epithelium occurs after a full-term pregnancy. This histologic change in breast parenchyma seems to be protective and associated with a reduction in breast cancer risk when the first full-term pregnancy occurs at a younger age (less than 30 years). Lactation may also convey protection; however, the duration of lactation required for this benefit is not well defined.

The role of endogenous hormonal risk factors is not the same in all breast cancer subtypes. Early onset of menarche, late age at menopause, and nulliparity, all of which connot extended estrogen exposure, confer an elevated risk of hormone receptor–positive disease.[43] By contrast, TNBC is associated with an increasing number of births and is not associated with nulliparity or age at first full-term delivery.[44]

BENIGN PROLIFERATIVE BREAST DISEASE

Pathologic nonmalignant changes found at biopsy can be associated with an increased risk of breast cancer. Findings such as atypical ductal or lobular hyperplasia or lobular carcinoma in situ convey an increased risk of breast cancer, approximately fourfold for atypical hyperplasia and 10-fold for lobular carcinoma in situ and thus can be termed "high-risk lesions." These lesions are not innately precancerous.[45] Benign proliferative lesions without atypia do not seem to significantly increase breast cancer risk.

Atypical hyperplasia is associated with an approximately 15% to 30% risk of breast cancer developing over 25 years.[46] After a diagnosis of atypical ductal hyperplasia (ADH) using core needle biopsy, it is recommended that most individuals undergo an excisional procedure to exclude the possibility of an associated invasive carcinoma. On the other hand, for atypical lobular hyperplasia (ALH) and lobular carcinoma in situ, given the low reported risk of upgrade to ductal carcinoma in situ (DCIS) or invasive carcinoma, incidental radiologic-pathologic concordant cases diagnosed on core needle biopsy no longer require surgical excision.[47]

MODIFIABLE RISK FACTORS

EXOGENOUS HORMONES

The use of contemporary hormonal contraceptives has been associated with a higher risk of breast cancer compared with never use of hormonal contraceptives; however, the absolute increase in risk is low (Table 10-3).[48]

Table 10-3 Established Risk Factors for Breast Cancer: Modifiable Factors

Factor	Relative Risk
Oral contraceptive pill	0.9-1.0
Estrogen replacement (more than 10 years)	1.1
Estrogen and progesterone	1.4-3.0
Postmenopausal obesity (BMI higher than 30 kg/m^2)	2.5
Alcohol use	1.1-2.2
Diet	1

Abbreviation: BMI, body mass index.

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Menopausal hormone therapy in the form of a combination of estrogen and progesterone is associated with an increased risk of invasive breast cancer (hazard ratio [HR], 1.26)[49]; however, the risk returns to normal within 2 years after discontinuation of menopausal hormone therapy.[50] Women who take combined menopausal hormone therapy also have a more advanced stage of breast cancer at the time of diagnosis. The global cessation of combined menopausal hormone therapy in 2002 was associated with an 8.6% reduction in the annual incidence of invasive breast cancer, primarily observed in hormone receptor–positive disease and in women older than 50 years. Interestingly, the use of estrogen alone does not appear to increase the risk of breast cancer,[51] and there are data to support a small (about 20%) reduction in risk.[52]

RADIATION EXPOSURE

Survivors of Hodgkin lymphoma and other malignancies who received therapeutic mediastinal or mantle field radiation have a higher risk of breast cancer development, depending on the dose of radiation and radiation field volume. The risk is greatest when treatment occurs during active proliferation of the breast tissue (ie, between ages 10 and 30 years). The median time for the development of breast cancer after treatment is approximately 18 years; however, increased risk can start as early as 8 years after treatment. Use of lower doses of therapeutic radiation involving smaller volumes has resulted in lower risks of breast cancer.[53-55] For patients who have a history of thoracic radiation received between ages 10 and 30 years, it is recommended that annual screening mammograms and annual breast MRI start at the age of 25 years.[56]

MAMMOGRAPHIC DENSITY

There is a linear trend associated with increasing mammographic density and risk of breast cancer, wherein women with greater than 75% breast density have a four- to six-fold higher risk of disease than those whose breasts are almost entirely fatty.[57] Exogenous hormone use, such as postmenopausal hormone replacement therapy or oral contraceptives, may result in increased mammographic density. Lower mammographic density may be a reflection of involution of the terminal ductal-lobular units, a natural aging process of the breast that is associated with lower breast cancer incidence.[58,59]

Mammographic density is a principal factor in the failure of mammography to detect cancer, which leads to interval cancers (ie, cancers presenting as clinical findings during the interval after a normal mammogram).[60] Digital breast tomosynthesis is

increasingly used as a primary screening examination rather than a supplemental imaging tool and has been shown to detect an additional 1.5 to 2 additional cancers per 1,000 women.[61] Screening breast MRI has been shown in one study to improve cancer detection rates and is recommended by some societies for women with extremely dense breast tissue.[62,63] Contrast-enhanced mammography is also a newer technology with improved sensitivity in women at an increased risk of breast cancer, particularly in women with dense breasts. In a small series, cancer detection rates approached 16 per 1,000, similar although not equivalently sensitive to MRI.[64]

BEHAVIORAL FACTORS

Several modifiable risk factors are associated with an increased risk for breast cancer. Consumption of one alcoholic beverage per day is associated with a 12% increased risk of breast cancer, and a further 10% increase in risk occurs with every additional 10 g per day of alcohol (or 0.75 to one alcoholic beverage per day) consumed. The risk is independent of the type of alcohol consumed and may be related to an increase in serum hormone levels and systemic inflammation.[65-67]

Obesity (body mass index [BMI] more than 30 kg/m^2) increases the risk of breast cancer in postmenopausal women by more than 63% but is inversely correlated with risk in premenopausal women.[68] Larger waist circumference is also associated with a greater incidence of premenopausal estrogen receptor (ER)–negative breast cancer.[69] Waist circumference and BMI are markers of visceral adiposity associated with metabolic syndrome. Several underlying mechanisms contribute to the association of obesity with increased breast cancer risk and mortality, including inflammation, increased bioavailable estrogens, insulin and insulin-like growth factor signaling, and activation of tumor growth factor programs.[70,71]

Smoking tobacco is associated with a moderate increase in breast cancer risk, and there is also evidence for a moderate increase in risk with passive smoking.[72] Physical activity is inversely related to breast cancer risk (see "Lifestyle Modifications" section). Isoflavones (ie, phytoestrogens most often found in soy), dairy products, and high-fat diets have unclear relationships with the incidence of breast cancer, whereas fiber consumption appears to be protective.[73]

RISK DETERMINATION MODELS

Several models are available to predict the risk of breast cancer based on family history and/or the probability of carrying a *BRCA* mutation. The Claus model includes first- and second-degree relatives with breast and/or ovarian cancer and incorporates the age at diagnosis. BRCAPRO, the Tyrer-Cuzick model (also called the International Breast Cancer Intervention Study [IBIS] trial), and the BOADICEA model all calculate risk based on the probability of carrying a genetic mutation.[74-77]

The modified Gail model[78] is the most widely used risk assessment tool; it incorporates nongenetic factors such as the following:

- Current age
- Age at menarche and first full-term pregnancy or nulliparity
- Number of breast biopsies and the presence of atypical hyperplasia
- Number of first-degree relatives with breast cancer
- Race

The original Gail model was modified and validated to incorporate race as a risk factor, specifically assessing breast cancer risk in Black women (the Contraceptive and Reproductive Experience model).[79] The modified Gail model is an excellent tool to determine risk on a population basis; however, the 5-year or lifetime risk of disease calculated for an individual woman is not robust.[80] This model will also underestimate risk if there is a significant genetic predisposition. Prevention strategies are often considered when the modified Gail model calculates a 5-year risk greater than 1.67%; however, this calculation does not take into account factors such as breast density or the presence of lobular carcinoma in situ and may also underestimate the risk associated with atypia.

KEY POINTS

- Menopausal hormone replacement therapy in the form of a combination of estrogen and progesterone (but not estrogen alone) is associated with an elevated risk of invasive breast cancer and correlates with duration of use.
- Patients who received therapeutic mediastinal or mantle field radiation have a higher risk of breast cancer, most pronounced when treatment occurred during active proliferation of breast tissue (ie, between ages 10 and 30 years).
- Atypical ductal or lobular hyperplasia and lobular carcinoma in situ are high-risk, nonmalignant lesions associated with a 30% risk of breast cancer development over 25 years.
- *BRCA1* and *BRCA2* mutations are associated with a 50% to 70% lifetime risk of development of breast cancer.
- Other highly (*PALB2*, *CDH1*, *TP53*, *PTEN*, and *STK11*) and moderately (*ATM*, *CHEK2*, and *NF1*) penetrant genes are associated with a significant risk for breast cancer.

- Postmenopausal obesity and alcohol use are associated with a higher risk of breast cancer.
- Increased breast density is associated with a higher risk of breast cancer.
- Several risk models are available to predict the risk of developing breast cancer on the basis of family history, prior atypia, and other factors.

PREVENTION

The goal of breast cancer prevention is to reduce the risk of the development of the disease with minimal toxicity. Women with a high-penetrance genetic mutation or a strong family history of breast cancer not associated with a pathogenic mutation in a breast cancer susceptibility gene may consider risk-reducing surgery. Lifestyle and medical risk-reducing strategies can be discussed with women with any degree of breast cancer risk.

RISK-REDUCING SURGERY

Prophylactic surgeries for high-risk patients reduce the risk of breast cancer development and include risk-reducing bilateral salpingo-oophorectomy (BSO) and bilateral risk-reducing mastectomy.

Risk-reducing BSO has been associated with the following:

- Decrease in the risk of ovarian cancer (which includes primary peritoneal and fallopian tube cancers) by approximately 85% (HR, 0.14).
- Reduction in the risk of a first diagnosis of breast cancer by 40% and 60% among *BRCA1* and *BRCA2* mutation carriers, respectively (HRs, 0.63 and 0.36, respectively).
- Lower breast cancer–specific mortality (HR, 0.44), lower all-cause mortality (HR, 0.40), and lower ovarian cancer–specific mortality (HR, 0.21) rates.[81]

BSO is recommended for *BRCA1* carriers between the ages of 35 and 40 years when childbearing is complete, and for *BRCA2* carriers between the ages of 40 and 45 years. The concern about the adverse effect of mortality from inducing early menopause may be safely mitigated with short-term menopausal hormone therapy given until age 50 years without an apparent compromise in the overall benefit of risk-reducing BSO on breast cancer risk reduction.[82]

Bilateral risk-reducing mastectomy reduces the risk of breast cancer by more than 90% in women with hereditary breast and ovarian cancer syndromes, with most studies focusing on *BRCA* mutation carriers.[83] Prophylactic risk-reducing mastectomy should be offered to these patients, although the decision should be based on personal preference, given that effective screening is available. Women at a high or moderate risk of breast cancer (ie, known genetic linkage or significant family history without known genetic predisposition) should also have a discussion with their physicians about prevention.

Skin-sparing mastectomy with reconstruction is increasingly being used and seems to be as effective as total mastectomy.[84] Reconstructive surgery after mastectomy does not seem to increase breast cancer risk. Even after prophylactic surgery, residual at-risk breast tissue remains on the chest wall, and new primary breast cancers can arise, although the risk is low.

MEDICAL RISK REDUCTION (CHEMOPREVENTION)

Selective ER Modulators

The observation that adjuvant tamoxifen used to treat invasive breast cancer led to a significant reduction in the development of new primary breast cancers[85] prompted several randomized trials examining the efficacy of selective ER modulators (SERMs) in reducing the risk of breast cancer among high-risk women. The benefit of tamoxifen for chemoprevention has been evaluated in several trials and consistently shows a reduction in the risk of invasive breast cancer between 30% and 50% compared with placebo.[86-89] This reduction is exclusively limited to ER-positive breast cancers. No effect on ER-negative incidence is seen. A meta-analysis of four studies led by the US Preventive Services Task Force[90] concluded that, when compared with placebo, tamoxifen led to the following:

- Reduction in the incidence of invasive breast cancer by 30%
- Significant reduction in the incidence of nonvertebral fractures by 34%
- No effect on breast cancer–specific or all-cause mortality

Tamoxifen and other SERMs have both estrogenic and antiestrogenic activity depending on the tissue, resulting in the following:

- Increased incidence of endometrial cancers (risk ratio, 3.28), which translates to a 1.6% risk with tamoxifen compared with a baseline 0.7% risk over 7 years.[91] Typically presenting with postmenopausal bleeding, adenocarcinomas are commonly

detected at an early stage and affect women older than 50 years. No data support routine screening for endometrial cancer using transvaginal ultrasonography or biopsy unless abnormal vaginal bleeding is present.

- Increased incidence of venous thromboembolic events (deep venous thrombosis: risk ratio, 1.44; pulmonary embolism: risk ratio, 2.15). The risk of stroke was not consistently increased among the tamoxifen studies, and this association is not supported by large population studies. Risks of endometrial cancer and venous thromboembolic events increase with advancing age.
- Increased incidence of cataracts as well as gynecologic (vaginal discharge) and vasomotor symptoms (VMS; hot flashes).
- Bone loss in premenopausal women.[92] However, in the Breast Cancer Prevention Trial P1, a reduction in the incidence of osteoporotic bone fractures (of the hips, spine, or radius) by 29% was seen among women aged 50 years or older.[91]

Tamoxifen at a dose of 5 mg per day for 3 years, compared with placebo (not compared with the standard tamoxifen 20 mg per day for 5 years program), decreased the risk of disease recurrence by half in postmenopausal women with ADH, lobular carcinoma in situ, or DCIS with a favorable toxicity profile.[93,94] The effect in premenopausal women was not significantly improved.[95] Low-dose tamoxifen may be an alternative for women who have intraepithelial neoplasia.

Raloxifene, a second-generation SERM, can also be used for chemoprevention in postmenopausal women. The NSABP P-2 STAR trial compared the efficacy of 5 years of tamoxifen with that of raloxifene.[86] After an extended follow-up of nearly 8 years, raloxifene retained only 76% of the effectiveness of tamoxifen in reducing the risk of invasive cancer.[86] There was no difference in mortality outcome between the two SERMs. Raloxifene use was associated with significantly less toxicity than tamoxifen, specifically, fewer endometrial cancers and thromboembolic events. Raloxifene is approved only for preventing breast cancer and not as a treatment after diagnosis.

A meta-analysis of the individual participant data from all randomized prevention trials involving SERMs (nine trials; 83,399 participants) demonstrated a 10-year cumulative incidence of breast cancer of 4.2% in patients receiving SERMs versus 6.3% in those receiving placebo.[96] The reduction in breast cancer was evident during years 0 to 5 (42%) and during years 5 to 10 (25%). The increased risk of endometrial cancer (HR, 1.64) was confined to years 0 to 5, coinciding with tamoxifen, and was not sustained in years 5 to 10. Although the number of venous thromboembolic events increased overall, there was no effect on the incidence of myocardial infarction, stroke, or transient ischemic attack. SERM use had no effect on the risk of ER–negative breast cancer or on overall mortality.

Aromatase Inhibitors

Similar to tamoxifen, aromatase inhibitor (AI) use in the adjuvant setting was shown to decrease the risk for second primary breast cancers (Fig. 10-1). Subsequently, two large trials have shown the efficacy of AIs in the prevention of invasive breast cancer among postmenopausal women at an elevated risk:

- The NCIC-CTG MAP.3 demonstrated a 65% reduction in the incidence of invasive breast cancer, including a 73% reduction in the incidence of ER–positive invasive breast cancer, among women receiving exemestane for 5 years, compared to placebo.[97]
- In the IBIS-II trial, 5 years of anastrozole reduced the risk of hormone receptor–positive invasive breast cancer and DCIS by more than 50% among postmenopausal women at an elevated risk of developing breast cancer compared with placebo.[98] Anastrozole neither conveyed a risk reduction for ER–negative breast cancer nor improved survival.

Few women with *BRCA* mutations have been specifically evaluated in prevention trials; therefore, the role of primary medical prevention in these women is not well understood. However, data suggest that tamoxifen can reduce the development of contralateral breast cancers in carriers of *BRCA1* (42% risk reduction) or *BRCA2* (52% risk reduction) mutations after the diagnosis of breast cancer.[99] An adjuvant trial of metformin versus placebo failed to demonstrate any beneficial effects in preventing second breast cancers.[100] The use of other medications for breast cancer prevention (eg, aspirin, statins, and vitamin D) remains investigational.

LIFESTYLE MODIFICATIONS

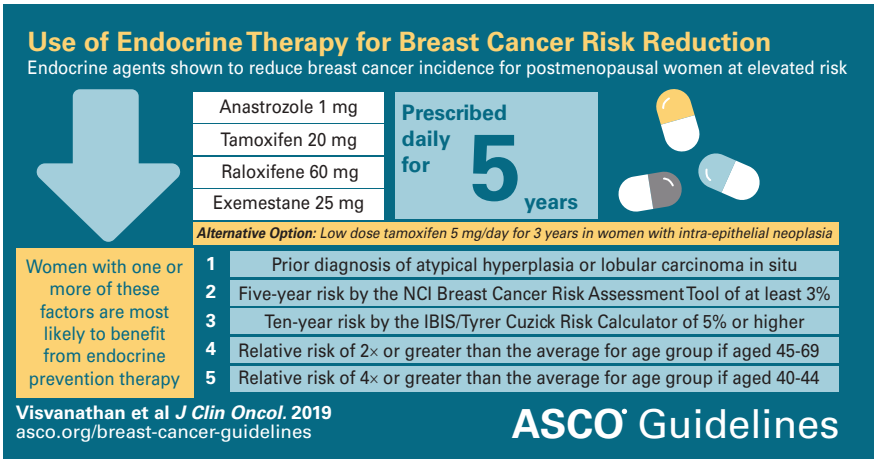
Physical Activity

Prospective cohort studies demonstrated that current total or recreational exercise can reduce the incidence of breast cancer by 20% to 30%, primarily among premenopausal women.[101]

Diet and Weight Change

The correlation among significant alcohol consumption, obesity, and risk of breast cancer is well established.[102] Data are lacking regarding whether moderate alcohol use after a diagnosis of breast cancer influences mortality risk.[103,104] In terms of diet, most studies have not conclusively supported a reduction in risk with increased consumption of fruits and vegetables. Although a study from the Women's Health Initiative suggested a 9% reduction in risk when women consumed a low-fat diet, prospective studies evaluating dietary changes and their effect on breast cancer risk have not been conclusive.[105,106] Vitamin and mineral

Figure 10-1 Use of Endocrine Therapy for Breast Cancer Risk Reduction



Abbreviations: IBIS, International Breast Cancer Intervention Study; NCI, National Cancer Institute.
Reproduced from Visvanathan K, Fabian CJ, Bantug E, et al. Use of endocrine therapy for breast cancer risk reduction: ASCO clinical practice guideline update. *J Clin Oncol*. 2019;37:3152-3165. doi:10.1200/JCO.19.01472
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supplements, specifically vitamin D and calcium, respectively, have not been shown to date to affect the development of breast cancer, although vitamin D deficiency may correlate with worse survival outcomes after a breast cancer diagnosis.[107,108]

KEY POINTS

- Risk-reducing BSO in *BRCA1* and *BRCA2* carriers is associated with lower breast cancer–specific mortality, lower all-cause mortality, and lower ovarian cancer–specific mortality rates.
- Bilateral risk-reducing mastectomy reduces the risk of breast cancer by more than 90% in *BRCA1* and *BRCA2* carriers.
- Tamoxifen in premenopausal or postmenopausal women and raloxifene, anastrozole, or exemestane in postmenopausal women all reduce the risk of development of ER–positive breast cancer.
- Significant alcohol consumption is associated with an increased risk of breast cancer, and there seems to be a significant dose–response relationship.

SCREENING

AVERAGE RISK

Screening has been shown to have a favorable effect on breast cancer–related mortality given that early-stage disease is associated with a more favorable prognosis. Published randomized trials have been criticized for variable quality of imaging, flawed study design or execution, insufficient duration of follow-up, and problems regarding lead time bias. However, these studies, including a meta-analysis of randomized controlled trials of screening mammography performed predominantly in the 1960s to 1970s, reported a 22% relative reduction in breast cancer mortality; patients in this analysis ranged in age from 39 to 74 years.[109]

The benefit of screening mammography varies with age. The Pan-Canadian Study of Mammography Screening and Mortality demonstrated a 44% reduction in mortality in women aged 40 to 49 years undergoing screening mammography, a 40% reduction in women aged 50 to 59 years, and a 42% reduction in women aged 60 to 69 years. The effect of screening mammography on breast cancer mortality for women aged 70 years or older is less robust.[101]

Harms from screening include anxiety provoked by false-positive findings, unnecessary biopsies, overdiagnosis, and increased detection of DCIS, which may not proceed to invasive cancer.[110]

Frequency of Screening

The optimal frequency for mammographic screening is not known. The advantage of shorter intervals is an increased chance of detecting faster-growing cancers at an earlier stage, but this advantage comes with the disadvantage of a higher false-positive rate. The American Cancer Society updated guidelines from 2015 support annual imaging beginning at the age of 40 years and

strongly recommend annual screening from age 45 to 54 years, followed by biennial or annual screening that continues as long as a woman's overall health is good, and she has a life expectancy of 10 years or more.[111] The National Comprehensive Cancer Center Network, Society of Surgical Oncology, and American College of Radiology recommend annual mammography beginning at the age of 40 years. In 2024, the US Preventive Services Task Force revised their recommendations to initiate biennial screening at the age of 40 years and continue until the age of 74 years on the basis of modeling that estimated benefits, risks, and use of resources and estimated that biennial screening still achieved 81% of the benefit of annual screening with nearly half the number of false-positive results.[112] Although the optimal age to begin screening and optimal interval remain unclear, annual mammography beginning at the age of 40 years prevents the most deaths as a result of breast cancer.

Different Screening Modalities

There has been a gradual and now nearly complete conversion to digital from film screening technology in the United States. Although digital imaging provides only a small increase in sensitivity compared with optimally performed film imaging, the move to digital imaging has greatly improved and standardized image quality across all sites.

Digital breast tomosynthesis mammography enables three-dimensional imaging of the breast, similar to computed tomography (CT).[113] Digital breast tomosynthesis results in slightly greater sensitivity and a significant reduction in recall rates. It is unknown whether digital breast tomosynthesis leads to a reduction in the number of advanced breast cancers because of earlier detection. Interpretation times are longer with digital breast tomosynthesis than with digital imaging, but the amount of radiation exposure is now equivalent to that of standard mammography when a synthesized two-dimensional technology is used.

Breast self-examination has not been found to improve the detection of early-stage breast cancer on a population basis.[114,115] Clinical breast examinations also do not seem to have affected breast cancer detection or mortality rates from a population perspective.[116] However, many groups encourage breast self-examination as a method of increasing breast self-awareness to seek medical attention if abnormalities are detected.[117-119]

Breast MRI screening has been widely studied but remains controversial. It is clearly more sensitive than mammography but results in more subsequent evaluations, including biopsies. It is generally recommended for high-risk women and those with very dense breasts. Among patients with *BRCA* mutations, supplementing mammography with MRI improves the sensitivity to 80% to 100% compared with 25% to 59% with mammography alone; however, the specificity of combined mammography and MRI is lower (73%-93%).[120] Adding annual MRI screening to mammography has been shown to significantly reduce the incidence of larger or lymph node–positive breast cancers and is associated with a survival advantage over mammography alone in individuals with germline *BRCA* mutations.[121]

Annual breast MRI screening as an adjunct to mammography is usually recommended in the following situations:[111,122]

- People with mutations in *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *PALB2*, and *STK11*, and may be considered in individuals with *CDH1*, *CHEK2*, *ATM*, *NF1*, or *BARD1*.
- First-degree relative of a person with mutations *BRCA1*, *BRCA2*, *TP53*, *PALB2*, or *STK11*, who is untested for the presence of a mutation.
- Lifetime risk of 20% or greater as defined by a model that largely depends on family history.
- Radiation to the chest between the ages of 10 and 30 years.

In general, screening for these high-risk individuals begins at the age of 25 years and includes annual breast MRI with biannual clinical breast examinations. Annual mammography should begin at the age of 30 years or be individualized if the earliest onset in the family is in a member younger than 25 years. Women will often have their breast imaging (mammogram and MRI) alternate every 6 months coincidently with their clinical breast examination, although no data support that this screening schedule is superior to that of concurrent breast imaging.[123]

Women who have received chest radiation at an early age are screened with a mammogram and MRI either concurrently or alternating every 6 months, beginning approximately 8 to 10 years after completing radiation therapy.[124] For women at high risk because of familial (nonhereditary) reasons, initiation of screening should begin approximately 10 years earlier than the age of the youngest woman in the family diagnosed with breast cancer but not later than the age of 40 years.

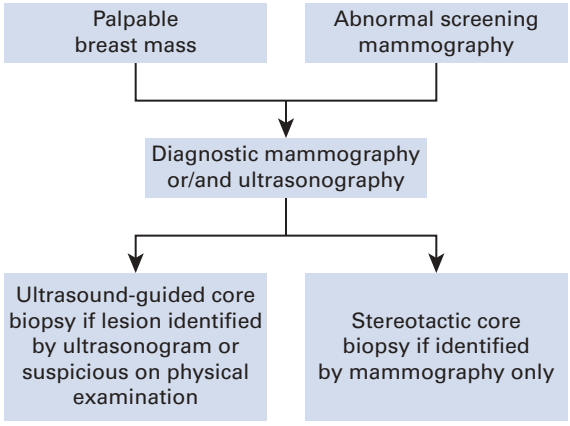
Women with extremely dense breasts may consider breast MRI screening. In the DENSE trial of over 40,000 women aged 50 to 75 years with extremely dense breast tissue and normal screening mammogram, one group was invited to undergo supplemental breast MRI (assigned 1:4 to breast MRI). Fifty-nine percent of those invited for supplemental MRI accepted. The primary outcome of interval cancers in a 2-year period decreased from 5 per 1,000 screenings with a mammogram only to 2.5 per 1,000 screenings with MRI. Importantly, the MRI cancer detection rate was 16.5/1,000 screenings; the positive predictive value was 17.4% for recall for additional testing and 26.3% for biopsy. The false-positive rate was 79.8/1,000 screenings. The optimal screening MRI frequency is not known. To date, not enough evidence supports routine MRI screening for women with scattered fibroglandular density or heterogeneously dense breast or the diagnosis of lobular carcinoma in situ, ADH, or DCIS. In addition, data are insufficient to support routine MRI screening for all women whose only risk factor is a history of invasive cancer.[62]

DIAGNOSIS

Algorithms for imaging evaluation of a palpable breast mass are stratified according to the age of the woman. Ultrasonography is usually the first diagnostic procedure performed to evaluate palpable breast masses in women younger than 30 years, as the incidence of breast cancer is low in this age group.[125] Diagnostic mammography is used for palpable masses in women older than 30 years. Diagnostic mammography differs from screening mammography in that it adds images to the standard two-view imaging used with screening (ie, craniocaudal and mediolateral oblique). If a suspicious finding is seen on a diagnostic mammogram or if the palpable breast mass is mammographically occult, a targeted ultrasonogram is used to obtain specific characteristics that will differentiate a suspicious solid mass from a benign cyst.

In a patient with suspicious imaging findings or a suspicious palpable breast mass after appropriate imaging workup, the next step is biopsy (Fig. 10-2). Although a fine needle aspiration biopsy of a palpable breast mass is less invasive than a core needle biopsy, fine needle aspiration specimens often yield insufficient tissue for analysis and cannot differentiate invasive from noninvasive carcinomas.[126] Fine needle aspiration of suspicious palpable axillary lymph nodes is often acceptable, given the limited variability of tissue present within a lymph node. It is also appropriate to use fine needle aspiration in the evaluation of a simple cyst detected by ultrasound, because drainage of the cystic fluid without re-accumulation can imply a benign etiology and eliminate the need for additional evaluation.

Figure 10-2 Workup of Palpable Breast Mass or Screening Abnormality



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Core needle biopsy specimens can be obtained through ultrasound guidance or stereotactically when suspicious calcifications are seen on mammography and do not have an associated density. The amount of tissue obtained by a core needle biopsy is usually sufficient to characterize the lesion and, when cancer is identified, to perform quantitative immunohistochemical analysis of ER, progesterone receptor (PR), and HER2 protein status. These results provide sufficient information about the cancer to allow the initiation of neoadjuvant systemic therapy if needed without compromising future treatment. The need to identify the site of biopsy is crucial, so a radiolucent clip is commonly placed in the lesion as a locator.

MRI can also be used to evaluate the extent of disease within the breast after the detection of invasive breast cancer. A meta-analysis of 19 studies assessing the role of MRI in revealing multifocal or multicentric disease found a 16% incidence of additional disease within the affected breast.[127] This was associated with an 8.1% conversion from breast conservation to mastectomy and an 11.3% need for additional surgery after wide excision. MRI can also be used to detect multicentric DCIS, but it is not accurate in assessing noninvasive tumor size. Caution must be used when assessing the contralateral breast with MRI after the diagnosis of breast cancer, because MRI detects an occult contralateral malignancy in approximately 3% of patients. This results in a high rate of biopsies and contralateral mastectomies despite a lack of evidence that these procedures result in a survival advantage.[128]

KEY POINTS

- Mammographic screening results in a 14% to 32% reduction in breast cancer–related mortality among women aged 50 to 70 years. The effect on mortality for women aged 40 to 49 years or older than 70 years is less robust.
- For women with *BRCA* mutations who have not undergone risk-reducing surgery, annual MRI of the breasts is recommended beginning at the age of 25 years, and annual mammography is recommended beginning at the age of 30 years. For women who have received therapeutic mantle field radiation, beginning 10 years after the completion of radiation

therapy, annual screening mammography (not before the age of 30 years) and annual breast MRI (not before the age of 25 years) are recommended.

- For breast cancer diagnosis, a core needle biopsy of a suspicious breast or lymph node finding is preferable to fine needle aspiration to accurately assess the histology of the tissue and the status of ER, PR, and HER2.

PROGNOSTIC INDICATORS

TNM STAGING

The eighth edition of the American Joint Committee on Cancer (AJCC) staging manual[129] for breast cancer includes biologic features, such as tumor grade, HER2, ER, PR, and genomic assays (when appropriate) as elements required to assign stage in conjunction with the anatomic information provided by the TNM (tumor, node, metastasis) classification. Three stage groups are defined: an anatomic stage solely based on the T, N, and M categories and intended for use when biomarkers are not available; a clinical prognostic stage; and a pathologic prognostic stage. The clinical prognostic stage is used to assign a stage for all patients. It is determined by the clinical T, N, M, and markers, including tumor grade, HER2, ER, and PR status. The pathologic prognostic stage is used to assign a stage for patients who have surgical resection as the initial treatment of their cancer before any systemic or radiation therapy. It is based on the pathologic T, N, M, and biomarker information. Multigene panels are not required for staging but may provide additional prognostic and predictive information. In the eighth edition of the AJCC staging manual, the prognostic stage group is preferred for patient care and should be used for reporting on all patients with breast cancer in the United States.

Additional important updates in the eighth edition of the AJCC staging manual include the removal of lobular carcinoma in situ from TNM staging (lobular carcinoma in situ is now treated as a benign entity) and the determination that the presence of cancer within blood vessels, lymph vessels (lymphovascular invasion), or lymph nodes precludes post-treatment classification as a complete pathologic response.

The prognostic features of breast cancer can be divided into two categories: anatomic and biologic. Recent technologies are leading to an increased understanding of the role of biologic features in determining outcomes, and treatment strategies will continue to evolve as our knowledge increases.

ANATOMIC PROGNOSTIC INDICATORS

Lymph Node Involvement

The most important anatomic prognostic indicator for localized breast cancer is the nodal burden of disease. Ipsilateral axillary lymph nodes are often the first site of invasion. Intramammary lymph nodes are found within the breast parenchyma and are included in the axillary lymph node category when they contain breast cancer metastases. The clinical detection of ipsilateral internal mammary or supraclavicular lymph node involvement is associated with a greater risk of local recurrence and distant metastasis. Regardless of other characteristics of breast cancer, having more axillary lymph nodes involved with the disease is related to increased risk of systemic recurrence and decreased disease-specific survival.

The size of the metastatic component within the axillary lymph node is also important for prognosis. Lymph nodes with macrometastases (more than 2 mm) or micrometastases (more than 0.2 mm or more than 200 cells, but none more than 2 mm) are counted as nodal involvement. There is a greater risk of disease recurrence and death with macrometastases compared with micrometastases.[130] Isolated tumor cell clusters (clusters of cells or single tumor cells less than 0.2 mm or less than 200 cells) found within a sampled axillary lymph node seem to be associated with a prognosis comparable to that of lymph node–negative disease, and the use of immunohistochemistry (IHC) to detect these cells is not recommended.

Lymphovascular Invasion

The presence of tumor emboli within lymphatic or vascular channels is associated with a less favorable prognosis, mainly because of a higher risk of ipsilateral breast recurrence. The presence of lymphovascular invasion does not preclude breast conservation but often factors into determining the need for radiation therapy.

Tumor Size

Tumor size (which refers to the size of the invasive component) is one of the most important prognostic indicators for breast cancer. The size of associated DCIS does not influence the risk of systemic disease but may contribute to the risk of ipsilateral recurrence after breast conservation. A multifocal (ie, two or more foci of disease within one quadrant of the breast) or multicentric (ie, two or more foci of disease in separate quadrants) disease is associated with a higher frequency of positive lymph nodes and risk of ipsilateral breast recurrence after breast conservation therapy. Tumor staging is based on the size of the largest tumor and does not take into account other smaller foci. The sizes of multiple tumors should not be added. The presence of multiple tumors is noted by adding the (m) modifier to the T category.

Histology

A majority of invasive mammary carcinomas (75%) are of no special type, commonly referred to as infiltrating ductal carcinomas. Infiltrating lobular carcinoma is the second most common type of breast cancer (15%). Compared with infiltrating ductal carcinoma, infiltrating lobular carcinoma is characterized by the following:

- More challenging to detect with mammography
- Increased frequency of multifocality and indistinct borders
- Older age at onset
- Larger tumor size
- Lower grade
- Higher incidence of bilateral involvement at the time of diagnosis
- Greater likelihood of late recurrence

Most infiltrating lobular carcinomas are ER-positive and HER2-negative. Infiltrating lobular carcinoma frequently displays mutations in the *CDH1* gene and loss of the adhesion molecule E-cadherin, resulting in a more discohesive and infiltrative growth. Infiltrating lobular carcinomas can have a distinct pattern of metastasis with involvement of serosas, ovaries, meninges, and the gastrointestinal tract.[131]

Rarer subtypes of breast cancer include but are not limited to tubular, mucinous, adenoid cystic, medullary, micropapillary, and metaplastic tumors. The tubular and mucinous subtypes are associated with a favorable prognosis. Although adenoid cystic carcinomas of the breast usually lack hormone receptors and HER2, this rare subtype of TNBC, characterized by alterations in MYB, generally behaves indolently.[132] On the other hand, metaplastic carcinomas, characterized by epithelial and mesenchymal differentiations, have an unfavorable outcome.[133]

BIOLOGIC PROGNOSTIC INDICATORS

Tumor Grade

The histologic grading system for breast cancer is a semiquantitative evaluation of morphologic features consisting of the percentage of tubular formation, degree of nuclear pleomorphism, and mitotic count within a predefined area. On the basis of the scoring of these characteristics, three grades reflect breast cancer differentiation: low (grade 1), intermediate (grade 2), and high (grade 3). The histologic grade is an independent prognostic indicator that has been closely linked to the molecular features of breast cancer.[134]

Hormone Receptors: ER and PR

ER functions as a ligand-dependent transcriptional factor that, when activated by estrogen, regulates gene expression and activates oncogenic pathways.[135] The two isoforms of ER are ER-α and ER-β. The precise role of ER-β is currently unclear, and the term "ER" usually applies to ER-α, a product of the ESR1 gene.[136] IHC measures ER-α levels and is the method currently used to assess ER expression. ER positivity is predictive of response to endocrine therapy. PR is a marker of ER-α signaling. The 2020 ASCO/College of American Pathologists (CAP) guideline defines a tumor as ER or PR positive if 1% or more of the tumor cell nuclei are immunoreactive, but categorizes tumors with ER staining of 1% to 9% as ER low positive, and these tumors may be less sensitive to endocrine therapy.[137] ER-α is expressed in approximately 70% of invasive breast cancers, a majority of which also express PR. Cancers that are ER positive, PR negative also respond to endocrine therapy, but they tend to have a less favorable biology. ER-negative, PR-positive cancers are uncommon, and lack of ER expression can often be attributed to false-negative assay results. Patients with these cancers should still receive endocrine therapy.

Strong hormone receptor expression is frequently associated with older age, lower tumor grade, and negative lymph nodes. ER-positive, PR-positive disease is associated with a modestly superior disease-free interval, local recurrence rate, and overall survival (OS) compared with ER-negative, PR-negative disease, particularly within the first 5 to 10 years after diagnosis. However, in hormone receptor–positive breast cancer, only half of all relapses occur within the first 5 years after diagnosis, and there is a persistent significant risk of late recurrence (up to 20 years after diagnosis), despite therapy.[138,139]

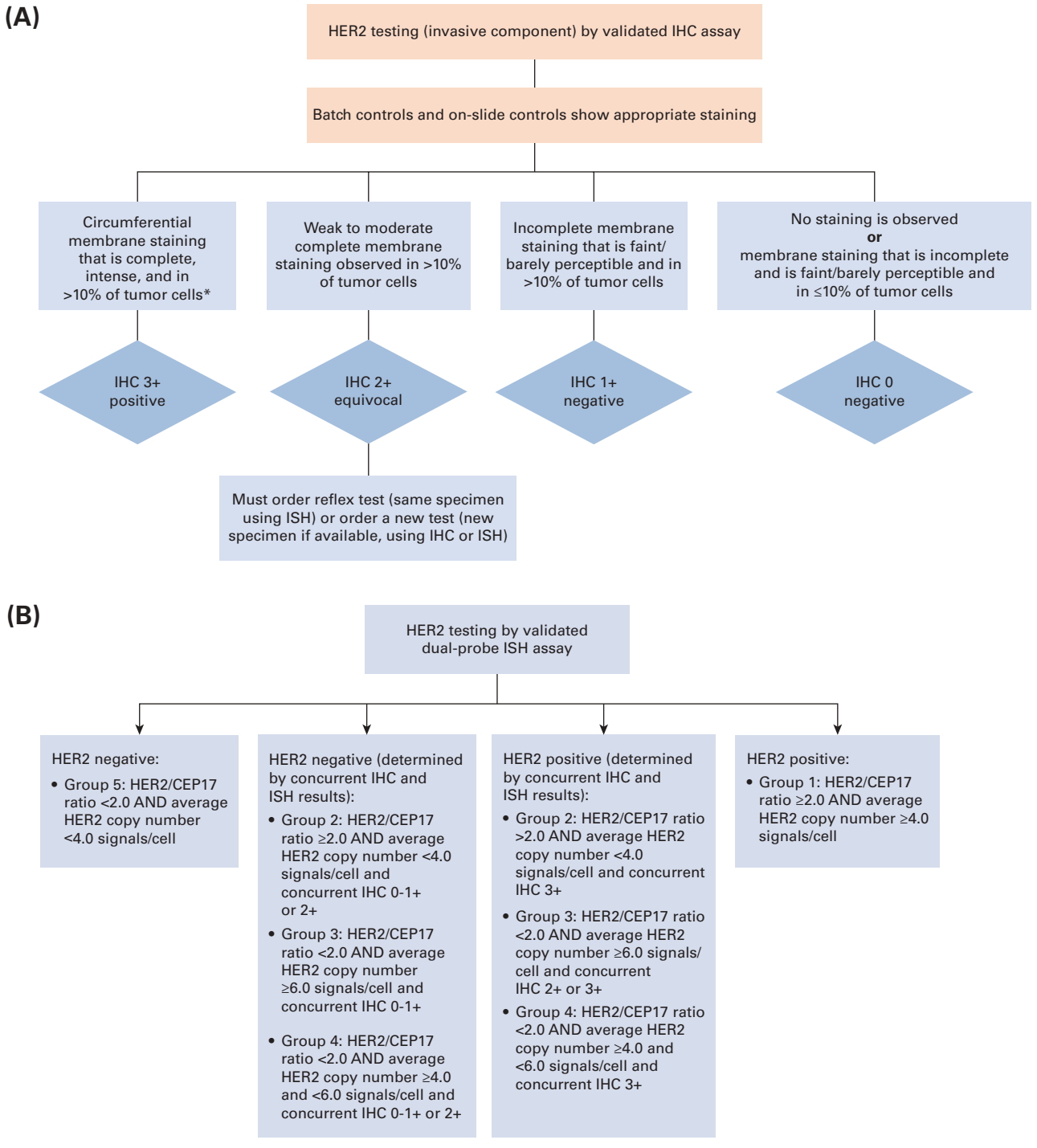
Approximately 25% of breast cancers are hormone receptor–negative, and 15% of breast cancers are triple negative. Risk of TNBC recurrence is greatest within the first 5 years and significantly declines afterward.[140]

HER2 Overexpression

HER2 is a member of the epidermal growth factor receptor (EGFR) tyrosine kinase family, which includes four transmembrane receptor proteins: HER1 (EGFR-1), HER2, HER3, and HER4. Receptor activation, through either ligand binding or ligand-independent effects, results in homodimerization or heterodimerization of the receptor proteins, which stimulate cellular growth, cell survival, migration, and angiogenesis. HER2 is overexpressed or amplified in approximately 20% of all breast cancers. HER2 overexpression is correlated with high proliferation, demonstrated by high-grade histology and a higher incidence of lymph node involvement.[141] In the absence of anti-HER2 therapy, HER2-positive disease is associated with a poor prognosis, independently

of other prognostic indicators, including tumor size, lymph node involvement, and hormone receptor status. HER2 is measured by IHC, often in conjunction with in situ hybridization. HER2 status is defined by the ASCO/CAP guideline,[142] which was updated in 2023 (Fig. 10-3A and B).

Figure 10-3 Summary of the ASCO/College of American Pathologists Guidelines



(A) HER2 testing by validated IHC assay. (B) HER2 testing by validated dual-probe ISH assay.
Abbreviations: IHC, immunohistochemistry; ISH, in situ hybridization.
*Readily appreciated using a low-power objective and observed within a homogeneous and contiguous invasive cell population.
Reproduced from Wolff AC, Hammond MEH, Allison KH, Harvey BE, McShane LM, Dowsett M. HER2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update summary. *J Oncol Pract.* 2018;14:437-441. doi:10.1200/JOP.18.00206

The updated ASCO/CAP guidelines address metastatic tumors that are not HER2 overexpressed or amplified but may respond to the HER2 antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd). HER2 overexpression or amplification is a strong predictive factor for response to HER2-directed therapy. The degree of HER2 positivity is not directly associated with prognosis, although higher HER2-to-CEP17 ratios may correlate with higher rates of pathologic complete response (pCR) after neoadjuvant chemotherapy and HER2-targeted therapy.[143]

Proliferation Rate: Ki67

The nuclear antigen Ki67 is currently the most used marker of proliferation rate in breast cancer. Increased proliferation correlates with adverse prognostic indicators, such as tumor size, nodal involvement, and histologic grade. Changes in Ki67, particularly after neoadjuvant therapy, have been associated with clinical outcomes and incorporated into multiple research studies. The routine use of Ki67 in clinical management has been limited by the variability of the assay, lack of reproducibility of results among pathologists, and inconsistent value as a predictive marker in clinical trials.[144]

Intrinsic Molecular Subtypes

Gene expression analysis has enabled the classification of breast cancer into distinct groups or intrinsic subtypes,[145] which have specific characteristics and prognoses. Molecular classification according to these intrinsic subtypes is not routinely used for clinical purposes, but the definition of intrinsic subtypes and their applications in research continue to further our understanding of breast cancer biology. Four main breast cancer intrinsic subtypes have been defined: luminal A, luminal B, basal, and HER2-enriched. The general characteristics of these subtypes are summarized in Table 10-4. There is a substantial but not complete overlap between classification according to intrinsic subtypes and routine immunostains for ER, PR, and HER2.

Table 10-4 Molecular Subtypes

Subtype	Characteristic
Luminal A	Favorable prognosis High ER/PR Low proliferation rate Grade 1/2 Lower sensitivity to chemotherapy
Luminal B	Less favorable prognosis Lower ER and PR High proliferation rate Grade 2/3 Higher sensitivity to chemotherapy
HER2 enriched	HER2 positive Hormone receptor positive or negative High proliferation rate Grade 2/3
Basal	ER, PR, and HER2 negative High proliferation rate Grade 3

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
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GENE EXPRESSION SIGNATURES

There are several validated tests to assess the risk of breast cancer recurrence, particularly in early-stage hormone receptor–positive breast cancer.

MammaPrint is a 70-gene signature that classifies tumors as having either a high or low risk of recurrence.[146] MammaPrint was prospectively validated in the MINDACT trial.[147] In this phase 3 study of women with early-stage breast cancer and up to three positive lymph nodes, genomic risk (according to MammaPrint) and clinical risk (according to a modified version of Adjuvant! Online) were determined. Most patients had node-negative and ER–positive tumors.

- Women at low clinical and genomic risk did not receive adjuvant chemotherapy, and those at high clinical and genomic risk received chemotherapy.
- Patients with discordant clinical and genomic risk results were randomly assigned to chemotherapy. Women with high clinical risk but low genomic risk who did not receive chemotherapy had a 5-year survival rate without distant metastases 1.5% lower than those with chemotherapy (this was not a significant difference).
- There was no benefit of chemotherapy in patients with low clinical risk and high genomic risk.
- ASCO guidelines state that the MammaPrint assay may be used to guide decisions on withholding adjuvant systemic chemotherapy in patients with hormone receptor–positive, node-negative breast cancer and in select patients with node-positive breast cancer. MammaPrint should only be used in patients with high clinical risk.[148]

The 21-gene expression assay known as Oncotype DX[149] is the most widely used prognostic and predictive genomic recurrence score test in the United States. The Oncotype recurrence score is reported as a continuous function to assess the risk of systemic recurrence among women with ER-positive breast cancer treated with tamoxifen for 5 years.[150] The risk of recurrence was initially defined as low (recurrence score, less than 18), intermediate (recurrence score, 18-30), and high (recurrence score, greater than or equal to 31) on the basis of prespecified cutoffs. In the initial retrospective validation studies, node-negative tumors with a high recurrence score derived the greatest benefit from chemotherapy.[150] Chemotherapy was not beneficial in women who had a low recurrence score, and its role in women with an intermediate-range recurrence score was unclear. In addition, postmenopausal women who had one to three involved lymph nodes and a recurrence score of less than 18 did not benefit from the addition of chemotherapy to tamoxifen.[151]

The TAILORx trial was a prospective trial to clinically validate the prognostic and predictive value of the 21-gene expression assay in hormone receptor–positive, HER2-negative, and lymph node–negative breast cancer. Patients who had a recurrence score of 0 to 10 received endocrine therapy alone and had a low rate of distant relapse at 5 years.[152] Patients who had a recurrence score of 11 to 25 were randomly assigned to receive either adjuvant chemotherapy and endocrine therapy or endocrine therapy alone, whereas patients who had a recurrence score higher than 25 received chemotherapy in addition to endocrine therapy.

- In general, there was no benefit with the addition of chemotherapy in patients who had a recurrence score of 11 to 25.
- However, the benefit of chemotherapy varied according to age for those with intermediate recurrence scores; women 50 years or younger who received chemotherapy and had a recurrence score of 16 to 20 had a 1.6% lower rate of distant recurrence at 9 years, which increased to 6.5% in women with a recurrence score of 21 to 25. Exploratory analysis has suggested that this benefit may be mediated by the hormonal effect of chemotherapy, inducing menopause in pre/perimenopausal women rather than its direct cytotoxic effects; however, this hypothesis is not yet validated.
- The risk of recurrence and the benefit of chemotherapy were further influenced by tumor size and grade.[153] These factors are integrated into the RSClin score, which estimates recurrence risk with and without chemotherapy, and with tamoxifen versus an AI on the basis of recurrence score, age, tumor grade, and size.[154]

The RxPONDER trial prospectively assessed whether women with low-volume, node-positive breast cancer (one to three nodes) and a recurrence score of 25 or lower could safely avoid chemotherapy.

- This study showed no benefit of chemotherapy in postmenopausal women.[155]
- By contrast, in premenopausal women, the addition of chemotherapy to endocrine therapy was associated with a 5.2% benefit in the invasive disease-free survival (iDFS) rate, regardless of recurrence score.

Although biologically plausible, it is unknown whether chemotherapy-induced amenorrhea played a role in this observation. In the prospective West German Study PlanB trial,[156] women who had fewer than three lymph nodes involved and a recurrence score of 11 or lower had a good outcome with endocrine therapy alone, again supporting the omission of chemotherapy in women who had high clinical risk but favorable biology.

Other signatures, including the PAM50 risk of recurrence (a gene signature derived from the original intrinsic subtype classification), EndoPredict, and the Breast Cancer Index, were retrospectively validated to assess the risk of recurrence, including after 5 years of treatment (late recurrence). Patients with hormone receptor–positive, HER2-negative cancer, and a low Breast Cancer Index score are at lower risk of distant recurrence and derive less benefit from extended endocrine therapy (beyond 5 years). Patients who have a high Breast Cancer Index score have a higher risk of late distant recurrence, and disease-free survival (DFS) seems to improve with extended endocrine therapy.[157,158]

In summary, gene signatures are now commonly used to inform adjuvant chemotherapy in hormone receptor–positive, node-negative and low-volume, node-positive breast cancers, along with other factors. For patients who have node-negative disease, ASCO guidelines recommend the addition of chemotherapy for those who have a recurrence score of 26 or higher, or higher than 16 if younger than 50 years may also be offered chemotherapy.[148,159] For patients who have one to three positive lymph nodes,

chemotherapy should be discussed with premenopausal patients, who derive benefit regardless of recurrence score, and can be omitted in postmenopausal women who have a recurrence score of 25 or lower. Chemotherapy should be discussed with postmenopausal women who have one to three positive lymph nodes and a recurrence score higher than 25, and with any patient who has four or more positive lymph nodes, because there are insufficient data at this time on the role of recurrence score for N2 disease.

KEY POINTS

- Pathologic features associated with a favorable prognosis include small tumor size, negative lymph node status, low tumor grade, absence of lymphovascular invasion, and positive hormone receptor status.
- Quantitative ER expression is predictive of response to endocrine therapy.
- HER2 overexpression/amplification is predictive of benefit from HER2-directed therapy.
- The 21-gene recurrence score and 70-gene signature have been validated prospectively in large trials and may guide the use of adjuvant chemotherapy in addition to endocrine therapy in hormone receptor–positive and HER2-negative breast cancer patients who have either no nodal involvement or one to three lymph nodes involved.

INITIAL EVALUATION

The initial evaluation of patients diagnosed with breast cancer includes a physical examination and breast imaging with diagnostic mammography with or without ultrasonography. Additional diagnostic testing should be individualized, especially the use of breast MRI (see "Diagnosis" section). Baseline laboratory tests, such as a complete blood count and liver function tests, can be obtained for women who will need chemotherapy and/or for those in whom clinical symptoms or signs are suggestive of metastatic disease. In the absence of symptoms, imaging studies to evaluate for metastasis are not routinely recommended for patients who have stage I. It could be considered in patients with stage II to III disease based on clinical concern, particularly those with node-positive disease and high-risk histologies such as HER2-positive or TNBC. Systemic staging consists of either CT imaging of the chest and abdomen (with or without a CT scan of the pelvis) and a bone scan or a fluorodeoxyglucose (FDG) PET scan. PET/CT may reduce the false-positive risk by half compared with CT and bone scan and allow neoadjuvant treatment to start earlier.[160-163] Brain MRIs are not part of routine staging in the absence of symptoms, although a lower threshold should be considered for HER2–positive breast cancer.

Additional considerations for patients who have a new diagnosis of breast cancer include the following:

- Genetic counseling for patients who have a family history positive for cancer or other characteristics that may suggest an inherited predisposition, as outlined in "Risk Factors" section. The American Society of Breast Surgeons and ASCO have recommended that genetic testing be offered to all patients who have a personal history of breast cancer.
- Premenopausal women who use a hormonal method of contraception should be counseled about nonhormonal alternatives. In such cases, referral to a gynecologist or a women's health specialist is indicated.
- All patients of reproductive age should be counseled regarding the risks of infertility (as a result of chemotherapy) and/or delayed childbearing (as a result of adjuvant endocrine therapy). Consultation with a reproductive specialist should occur early for those interested in fertility preservation.[164]

Oocyte, sperm, and embryo cryopreservation are established methods of fertility preservation. Several trials have evaluated suppression of ovarian function with gonadotropin-releasing hormone (GnRH) agonists administered concurrently with chemotherapy as a method of fertility preservation. These trials have yielded conflicting results. However, in the randomized POEMS study, women who had hormone receptor–negative breast cancer who received goserelin starting 1 week before initiation of chemotherapy had a higher likelihood of a successful pregnancy.[165] In a meta-analysis including hormone receptor–positive and hormone receptor–negative breast cancers, the use of GnRH agonists decreased the rate of premature ovarian failure and did not affect breast cancer outcome.[166] The ASCO fertility preservation guideline states that a GnRH agonist may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRH agonists should not be used in place of proven fertility preservation methods.[164]

TREATMENT OF DCIS

DCIS is a neoplastic proliferation of epithelial cells confined to the mammary ductal-lobular system and characterized by subtle to marked cytologic atypia and risk of progression to invasive breast cancer.[167] In TNM staging, DCIS is designated as Tis/stage 0. Although DCIS occasionally may present as a mass or nipple discharge, 80% to 85% of the time, DCIS is detected by a screening mammogram and presents without clinical findings. Calcifications are the most common mammographic presentation of DCIS, and, because of mammographic screening, DCIS accounts for approximately 20% of all breast cancers in the United States.

DCIS is a heterogeneous entity. Pathologic features used to describe DCIS include the following:

- Nuclear grade (low, intermediate, or high)
- Presence of necrosis
- Architectural pattern (comedo, solid, cribriform, micropapillary, or papillary)
- Size or extent of the lesion

DCIS can be associated with a microinvasive tumor (tumor size less than 1 mm), which is staged as T1mi. An estimated 15% to 50% of DCIS tumors will ultimately progress to invasive disease if left intact by either direct transformation or development in parallel from a single progenitor cell.[168] The exact biologic mechanism is not well understood, and we cannot predict which subset of DCIS will progress to invasive breast cancer. ER testing of DCIS is recommended, but there are no current data to support HER2 testing.

Paget's disease of the breast is an unusual form of breast cancer, which begins as adenocarcinoma cells within the epidermis of the nipple-areola complex and extends into the surrounding areola. It frequently presents as eczematous changes of the nipple-areola complex. Surgical treatment usually requires excision of the nipple/areolar complex. Further appropriate local and systemic treatment of Paget's disease depends on the underlying cancer, which may either be completely in situ or may have progressed to invasive disease.

Although surgical excision (lumpectomy or mastectomy) is a current standard of care, surgery leads to potential overtreatment in many cases. Recognizing this risk, studies to compare surgery with active surveillance in cases of low-risk DCIS are ongoing.[169]

The goal of treatment in DCIS is to prevent local recurrence, because approximately half of local recurrences of DCIS are invasive.[170] The risk of local recurrence after a simple mastectomy is 1% to 2%. Based on the data on invasive breast cancer, breast-conserving surgery and radiation therapy (also called breast conservation therapy) were adopted as an appropriate option for treating DCIS. Breast conservation therapy or mastectomy provides equivalent long-term disease-specific survival.[171] The most current guidelines establish 2 mm as the standard for an adequate margin for pure DCIS treated with radiation therapy.[172] If the DCIS is associated with invasive carcinoma, then "no ink on tumor" is considered adequate. Axillary node dissection or sentinel node biopsy is not routinely performed in DCIS. However, sentinel lymph node biopsy (SLNB) should be considered in situations with a higher likelihood of finding invasive cancer in the surgical specimen (large or palpable lesions) or in patients undergoing mastectomy (because SLNB is not feasible after mastectomy if invasive cancer is identified on surgical pathology review).[173]

RADIATION THERAPY

After a margin-negative lumpectomy for DCIS, patients remain at modest risk of local recurrence within the breast. The addition of adjuvant radiation therapy to surgical excision has been evaluated by several randomized trials, revealing that the relative local control benefit of radiation therapy ranges from approximately 30% to 60%, depending on baseline risk.[174,175] Although recent studies have shown low overall recurrence rates (likely because of the concomitant use of endocrine therapy along with improvements in imaging and surgical technique), the relative benefit of radiation therapy persists when studied in a randomized controlled manner. A large body of literature supports both conventional (5-6 weeks) and hypofractionated (3-4 weeks) whole-breast radiation therapy as equivalent options for DCIS.[176,177] Accelerated partial breast irradiation is also a suitable option among appropriately selected patients.[178] Factors associated with increased risk of local recurrence include margins smaller than 2 mm, large tumor size, younger patient age, high nuclear grade, and presence of necrosis, among other histologic features.

Studies have yet to identify a subset of patients who do not benefit from radiation therapy with respect to local control.[177,178] However, although radiation therapy improves local outcomes, no reports to date have demonstrated a survival benefit for adjuvant radiation therapy for DCIS. Given limited absolute rates of recurrence in contemporary practice, some patients may forgo radiation therapy, assuming modest absolute increases in local recurrence risk without impinging on OS outcomes.[179]

ENDOCRINE THERAPY

The long-term outcomes are excellent for noninvasive breast cancer. Therefore, endpoints of adjuvant trials were to lower ipsilateral and contralateral events. In the NSABP B-24 trial, adjuvant tamoxifen at 20 mg for 5 years after breast-conserving surgery and whole-breast irradiation for DCIS resulted in a 32% relative reduction in the risk of local recurrence (from 9% to 6.6%) and a 53% relative reduction in the risk of contralateral disease over 15 years.[170] Premenopausal and postmenopausal women were included. The benefit of tamoxifen was seen only in ER–positive DCIS and was not associated with improved OS.[180] In the NSABP B-35 trial of postmenopausal women who received breast conservation therapy for ER–positive DCIS, adjuvant anastrozole was associated with a small improvement in breast cancer–free interval at 10 years versus tamoxifen (93.5% vs 89.2%), with the benefit mainly limited to women younger than 60 years.[181] Therefore, both adjuvant tamoxifen and anastrozole are appropriate options for postmenopausal women with DCIS, and considerations regarding toxicities should influence treatment choices for individual women. There is no role for endocrine therapy for risk reduction in women who undergo bilateral

mastectomy. Women who have a unilateral mastectomy for ER–positive DCIS may consider endocrine therapy for the prevention of contralateral breast cancer.

The TAM-01 study was a randomized placebo-controlled trial of 500 women who had DCIS, lobular carcinoma in situ, or ADH and evaluated the benefit of tamoxifen 5 mg for 3 years versus placebo. The 10-year follow-up data show a roughly 50% risk reduction in invasive cancer events, similar to the standard tamoxifen 20 mg for 5 years. There was no significant change in menopausal symptoms, such as hot flashes or vaginal dryness, between the two groups. Rates of venous thromboembolic events were the same in the tamoxifen and placebo arms, and one patient receiving tamoxifen developed endometrial cancer (0.4%).[93]

KEY POINTS

- DCIS (stage 0) accounts for approximately 20% of breast cancers in the United States.
- Most cases of DCIS are detected on screening mammograms.
- Whole-breast irradiation decreases the risk of local recurrence after breast-conserving surgery.
- DCIS treated with mastectomy or breast conservation therapy results in equivalent breast cancer–related 5-year survival rates.
- Current guidelines establish 2 mm as an adequate margin of resection in DCIS treated with breast conservation therapy.
- For women with ER–positive DCIS who elect to undergo breast conservation therapy, adjuvant endocrine therapy reduces the risk of ipsilateral and contralateral recurrences with no established survival benefit. For those patients who undergo bilateral mastectomy for DCIS, there is no role for endocrine therapy for prevention.
- Adjuvant tamoxifen (for premenopausal and postmenopausal women) and AIs (for postmenopausal women only) are appropriate options for decreasing subsequent invasive breast cancers in women with ER–positive DCIS treated with breast conservation therapy.

TREATMENT OF NONMETASTATIC OR EARLY-STAGE INVASIVE BREAST CANCER (STAGES I, II, AND III)

Treatment of early-stage invasive breast cancer focuses on reducing the risks of locoregional (breast and regional lymph nodes) and systemic recurrences. The decision to add systemic therapy to the local treatment of breast cancer is based on the risk of development of distant metastasis and the relative and absolute benefit of therapies to reduce that risk. For each patient, a multidisciplinary evaluation should occur at diagnosis to determine the optimal treatment modalities (local and systemic) and their sequencing.

Historically, surgery was typically performed first, followed by chemotherapy (and concurrent anti-HER2 therapy if HER2 positive), and then radiation to the remaining breast or chest wall and endocrine therapy for many subsequent years. The decisions to recommend each (breast preserving therapy vs mastectomy; chemotherapy or not, radiation or not, and targeted nonchemotherapy systemic therapy [endocrine therapy, targeted therapy, and anti-HER2 therapy]) have been based on staging (T, N) and expression of ER and HER2.

Over the last two to three decades, several studies have investigated the benefits of administering systemic therapy before rather than after surgery—termed "neo-adjuvant" therapy. Neo-, compared with classic postsurgical, adjuvant systemic therapy, has several potential advantages:[182,183]

- Possible higher efficacy because of two hypothetical advantages: (1) giving the therapy a few months sooner rather than waiting for surgery and healing, thus minimizing cellular mutation to therapy resistance and (2) giving the therapy before surgery to avoid the growth factor "storm" related to wound healing.
- Downstaging the tumor and permitting more effective surgery or equally effective but less disfiguring surgery.
- Identifying patients for whom the applied systemic therapy is less effective (based on residual disease after the surgery) and who might benefit from additional systemic treatments.
- Investigational studies of the efficacy of novel therapies.

In regard to the first bullet, a meta-analysis showed that preoperative (neoadjuvant) and postoperative (adjuvant) chemotherapies were similarly effective in lowering the risk of distant disease recurrence or breast cancer mortality.[184] Other potential benefits of neoadjuvant chemotherapy are discussed in subsequent sections.

Endocrine therapy and HER2-targeted therapy can safely be administered concurrently with radiation therapy; however, chemotherapy is usually completed before starting radiation therapy. Neoadjuvant endocrine therapy can be used in select patients, although it is uncommon (see "Neoadjuvant Endocrine Therapy" section).

Stage III disease was originally defined as tumors that were either too big (IIIa) or too locally extensive (IIIb) for surgery to be considered effective, and, therefore, these cancers were deemed "inoperable" as defined as follows:

1. IIIa: Patients who have large tumors (T3; 5 cm or larger) or multiple palpable positive lymph nodes, who have disease that can be resected.
2. IIIb: Patients who have inoperable disease (T4) because of skin involvement (nodules or ulcers), disease attachment to the chest wall, inflammatory carcinoma, or extensive nodal involvement that precludes initial surgical resection (eg, matted axillary lymph nodes and supraclavicular lymph node involvement).

Patients who have inoperable disease require neoadjuvant systemic therapy, followed by surgery and radiation therapy.

Locoregional treatment includes decisions regarding breast surgery (breast conservation or mastectomy), surgical management of axillary lymph nodes, and radiation therapy.

BREAST SURGERY

The past decades of research regarding breast and axillary surgery have focused on minimizing interventions to lower morbidity while maintaining equivalence in outcomes.

- The NSABP B-04 study established that there is no difference in OS between a Halsted radical mastectomy (ie, removal of the breast, chest wall muscles, and regional lymph nodes) and total (or simple) mastectomy (ie, removal of the breast).[185]
- The NSABP B-06 trial established that there are no differences in OS between total mastectomy and lumpectomy, either with or without radiation therapy.[185] Patients who received radiation therapy after lumpectomy had fewer local recurrences than those treated with lumpectomy alone, with no difference in local recurrence rates between lumpectomy and radiation therapy compared with mastectomy.

Optimal characteristics for breast conservation therapy include the ability to resect the entire tumor with negative surgical margins and achieve an acceptable cosmetic outcome. If these conditions are not met at diagnosis, neoadjuvant systemic therapy may be favored to downstage the disease in the breast and/or axilla. The current definition of adequate negative surgical margins for invasive breast cancer, according to the Society of Surgical Oncology as well as the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer, is no tumor present in the inked margin, whereas a margin of 2 mm is considered adequate for DCIS.[186,187] Patients with invasive cancer with DCIS, including those with an extensive intraductal component (defined as DCIS occupying at least 25% of invasive carcinoma or a lesion that is predominantly DCIS with one or more foci of invasive disease), should be treated according to the invasive breast cancer guidelines. Individual judgment, however, is important, particularly in patients thought to be at higher risk of residual disease after breast-conserving surgery.

Patients who are not candidates for breast conservation therapy should undergo a total mastectomy. Relative contraindications to breast conservation therapy for operable disease include the following:

- Multicentric disease (see below)
- Diffuse suspicious calcifications
- Persistently positive margin(s) after re-excision
- Pregnancy in the first or second trimester (women in the second to third trimester might be candidates for breast conservation therapy if radiation therapy is delayed until delivery)
- Prior radiation therapy and autoimmune connective tissue diseases involving the skin are considered relative contraindications.[188] In recent years, breast conservation and reirradiation have gained wider acceptance.[189]

In the case of multicentric disease, treatment can be individualized. The ACOSOG Z11102 trial prospectively evaluated lumpectomies for two to three biopsy-proven foci of ipsilateral N0/1 breast cancer. Patients underwent two to three margin-negative lumpectomies and radiation to each lumpectomy bed. At a median follow-up of 66.4 months, the 5-year local recurrence rate was 3.1%, below the prespecified threshold of 8%. In motivated patients for whom cosmesis would not be significantly compromised, multiple lumpectomies for multicentric tumors are considered a safe approach, provided preoperative MRI does not show evidence of intervening disease between biopsy-proven sites.[190]

SURGICAL MANAGEMENT OF THE AXILLA

Surgical management of the axilla is an integral part of the local treatment of breast cancer. The extent of and even indications for axillary surgery have decreased over time, resulting in less morbidity and similar breast cancer outcomes. The following are some key findings guiding current surgical management of the axilla in patients not receiving neoadjuvant therapy (Fig. 10-4A and B)[191]:

- Women who have a clinically negative axilla are candidates for SLNB at the time of their breast surgery, which results in substantially less morbidity compared with axillary lymph node dissection. Routine immunohistochemical staining

of the sentinel lymph node for cytokeratins is not recommended, and most therapeutic decisions should be based on assessment of tumor presence in the sentinel lymph node as determined by hematoxylin and eosin staining. In women with a negative SLNB specimen, the likelihood of additional nodal involvement is small, and no additional surgery is indicated.[192,193]

- The Society of Surgical Oncology Choosing Wisely Guidelines recommend no axillary surgery in women ≥70 years with early-stage, hormone receptor–positive breast cancer.
- A substantial proportion of women with limited axillary nodal involvement no longer require an axillary lymph node dissection (complete level 1 and level 2 dissection). The ACOSOG Z0011 study showed that, in patients who have clinical T1 or T2 tumors, a clinically negative axilla (N0), and one or two positive sentinel lymph nodes treated with lumpectomy, tangential whole-breast irradiation, and adjuvant therapy, sentinel lymph node dissection was noninferior to axillary lymph node dissection.[194] Axillary lymph node dissection is still usually performed in patients whose tumors do not fit the Z11 criteria (including those undergoing mastectomy), in patients who will not receive radiation therapy, or if the sentinel lymph node is not identified.
- IBCSG 23-01[195,196] showed noninferiority of no axillary dissection compared with axillary dissection in patients with micrometastatic sentinel nodal disease (with most patients in this study treated with lumpectomy and radiation therapy and a minority treated with mastectomy).
- In the AMAROS study, patients who had a T1 to T2 tumor and clinically negative axilla but positive sentinel lymph node were randomly assigned to either axillary surgery or radiation therapy. Most patients had one positive sentinel lymph node. Both patients treated with lumpectomy (82%) and those undergoing mastectomy were enrolled. In this study, local control was excellent in both the radiation therapy and surgical arms, but the rate of lymphedema was lower in the radiation therapy arm. Therefore, omission of axillary lymph node dissection can be considered if radiation to the axilla is planned.[197]
- Data from several randomized trials of SLNB versus observation have identified a group of patients for whom no SLNB is recommended. Postmenopausal women ≥50 to 69 years undergoing breast-conserving surgery for a unifocal grade 1 to 2, hormone receptor–positive and HER2-negative tumor <2 cm and who had a negative axillary ultrasound had excellent iDFS rates and low rates of axillary recurrence without SLNB. Patients received breast radiation.[198,199]

Patients who are candidates for neoadjuvant chemotherapy who present with a clinically negative axilla can undergo sentinel lymph node surgery after completion of neoadjuvant chemotherapy.[200] If the sentinel lymph nodes are negative, no additional axillary surgery is indicated. If any sentinel lymph node is positive, complete axillary lymph node dissection is recommended.[201]

Patients presenting with clinically node-positive disease by physical exam will need axillary lymph node dissection unless they receive neoadjuvant systemic therapy with a favorable response in the lymph node. The likelihood of downstaging the axilla with neoadjuvant chemotherapy is higher in patients presenting with TNBC or HER2-positive breast cancer for whom this approach is particularly favored.[202] Several studies have examined the feasibility of SLNB after neoadjuvant chemotherapy.[203-205] In ACOSOG 1071, the use of dual-tracer mapping and retrieval of at least three sentinel lymph nodes resulted in clinically acceptable false-negative rates of less than 10%, which is similar to the sentinel lymph node false-negative rate in patients who have clinically node-negative disease undergoing up-front SLNB, suggesting that axillary lymph node dissection can be omitted in select cases. Targeted axillary dissection, in which a lymph node is biopsied and clipped before neoadjuvant surgery, is removed in addition to any sentinel lymph nodes, also decreases the false-negative rate, although occasional technical challenges are encountered with this approach.

Ongoing clinical trials are also exploring the optimal locoregional management of the axilla after neoadjuvant chemotherapy. Alliance A011202 randomly assigns patients who have a positive sentinel lymph node after neoadjuvant chemotherapy to axillary dissection or axillary radiation therapy to evaluate which modality provides the best local control and survival. NSABP B-51 examined whether adjuvant nodal radiation therapy is required in patients who convert from biopsy-proven node-positive disease to pathologically node-negative disease after neoadjuvant chemotherapy by randomly assigning them to nodal radiation therapy or no radiation therapy. Evaluable patients (n = 1,556) had similar outcomes whether they received adjuvant regional nodal irradiation or not: 91.8% of patients without radiation and 92.7% of those with radiation were free of invasive breast cancer recurrences 5 years after surgery. Distant recurrence and OS rates were also similar between the arms, with 93.4% of patients in each arm free from distant recurrence 5 years after surgery, and 94% of those without radiation and 93.6% of those with radiation alive after 5 years.[206] Therefore, in cT1-3N1 patients who convert to ypT0-1N0 after neoadjuvant chemotherapy, adjuvant postmastectomy radiation therapy (PMRT)/regional nodal irradiation may be omitted.

ADJUVANT RADIATION THERAPY AFTER BREAST-CONSERVING SURGERY

Radiation to the Breast

Adjuvant breast radiation therapy is recommended for most patients who have invasive breast cancer after breast-conserving surgery. This includes patients treated with neoadjuvant therapy, regardless of clinical or pathologic response. A landmark meta-analysis revealed that radiation therapy after breast-conserving surgery reduced the rate of locoregional recurrences by

Figure 10-4 Suggested Axillary Management for Clinically Node-Negative Axilla

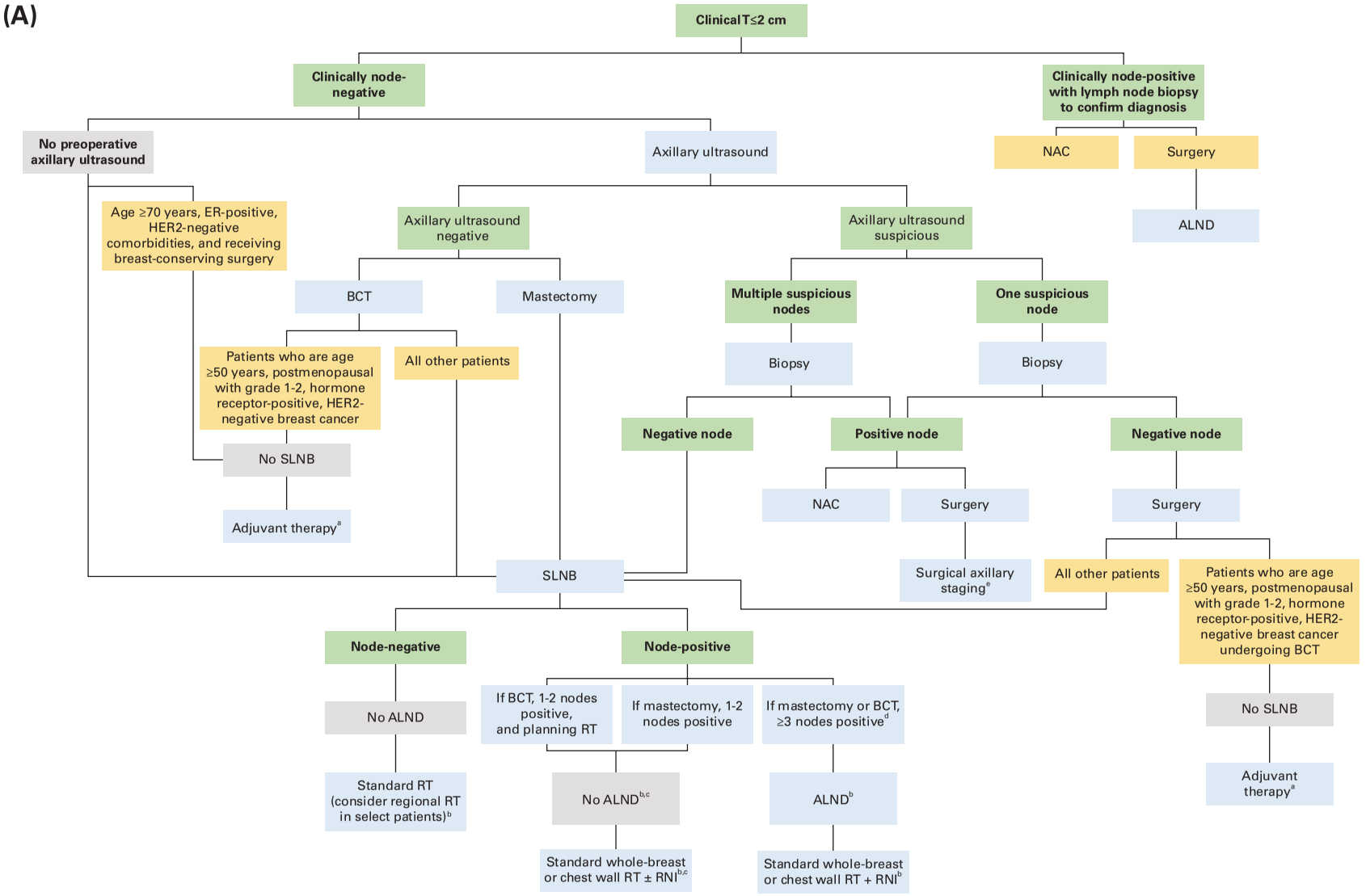
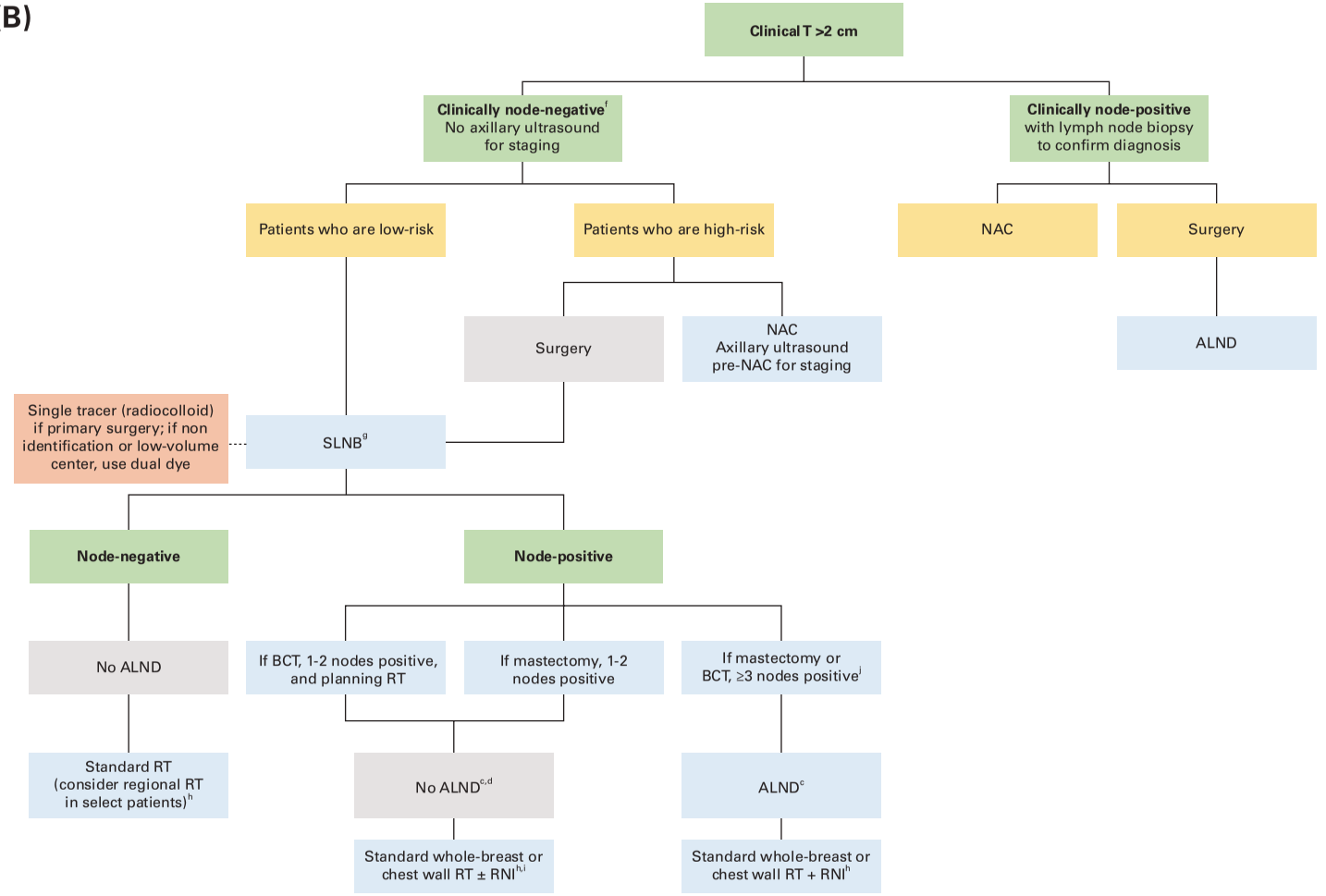


Figure 10-4 Continued

(B)



(A) Management of the axilla for patients with clinical T ≤2 cm breast cancer. (B) Management of the axilla for patients with clinical T >2 cm breast cancer.
Abbreviations: ALND, axillary lymph node dissection; BCT, breast-conserving therapy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NAC, neoadjuvant chemotherapy; PMRT, postmastectomy radiation therapy; RNI, regional nodal irradiation; RT, radiation therapy; SLNB, sentinel lymph node biopsy; T, tumor.
[a]Refers to all patients with no palpable axillary nodes on physical examination, including those who may have had an ultrasound that was equivocal, abnormal, or even biopsy-proven positive.
[b]Do not recommend SLNB before chemotherapy except in special circumstances after multidisciplinary discussion.
[c]Decision making should be made on a case-by-case basis, and include a patient-centered approach; that is, consider and discuss pros and cons of various options in light of patient's specific circumstances, values, and preferences.
[d]Full lymph node dissection may mitigate the need for RT in select patients.
[e]Patients with three positive nodes were underrepresented in trials evaluating the omission of completion ALND.
[f]Refers to all patients with no palpable axillary nodes on physical examination, including those who may have had an ultrasound that was equivocal, abnormal, or even biopsy-proven positive.
[g]Do not recommend SLNB before chemotherapy except in special circumstances after multidisciplinary discussion.
[h]Decision making should be made on a case-by-case basis, and include a patient-centered approach; that is, consider and discuss pros and cons of various options in light of patient's specific circumstances, values, and preferences.
[i]Full lymph node dissection may mitigate the need for RT in select patients.
[j]Patients with three positive nodes were underrepresented in trials evaluating the omission of completion ALND.
Adapted from Park KU, Somerfield MR, Anne N, et al. Sentinel lymph node biopsy in early-stage breast cancer: ASCO guideline update. *J Clin Oncol*. 2025;43(14):1720-1741. doi:10.1200/jco-25-00099
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approximately half (from 35.0% to 19.3%) and decreased the absolute risk of death as a result of breast cancer by one-sixth (from 25.2% to 21.4%) at 10 and 15 years, respectively.[207] Although the proportional benefit was similar across subgroups, the absolute benefit of radiation therapy differed significantly as a function of patient age, disease stage, tumor grade, ER status, tamoxifen use, and extent of surgery.

Contemporary systemic therapy, along with advances in imaging, surgical, and irradiation techniques, has contributed to improved local control after breast conservation therapy across all tumor types. Recent randomized controlled trials in patients with early-stage breast cancer have reported 10-year local recurrence rates as low as 2% to 7% under favorable circumstances.[208-210]

Hypofractionated whole-breast irradiation, in which the breast receives 40 to 42.5 Gy over 3 weeks (15-16 fractions), is now an established option for most patients undergoing whole-breast treatment. This dosing is based on randomized trials demonstrating equivalent local control and favorable toxicity compared with the more traditional approach of 25 fractions over 5 to 6 weeks.[208-210] A boost to the tumor bed is typically recommended, except in patients at lower risk of recurrence.[211]

In contrast to whole-breast irradiation, accelerated partial breast irradiation targets the region of the tumor bed while sparing more distant breast tissue and is typically administered over 1 to 2 weeks, either once or twice daily. Accelerated partial breast irradiation is an option for appropriately selected patients, and trials over the past decade have increasingly expanded the breadth of suitable indications.[176]

Older patients with favorable tumor characteristics (eg, small, node-negative, ER–positive tumors) who receive endocrine therapy may undergo breast-conserving surgery alone and omit radiation therapy in select circumstances. This approach is based on several studies showing that although radiation therapy decreased the rate of locoregional failure, the absolute risk of locoregional recurrence in the absence of radiation therapy may remain low with no effect on OS, provided endocrine therapy is taken.[209,212] Several studies are ongoing to evaluate whether radiation therapy may be feasibly omitted in younger patients, based on risk stratification using molecular biomarkers.[213]

Regional Nodal Radiation Therapy After Breast Conservation Therapy or Mastectomy

Regional nodal irradiation typically refers to comprehensive targeting of the axilla (levels 1, 2, and 3), supraclavicular fossa, and internal mammary nodal basin (interspaces 1-3), although each case is individualized based on the extent of disease, presenting clinicopathologic features, and type of axillary surgery. Regional nodal irradiation is generally indicated for patients who have three or more involved lymph nodes and may be considered in those who have one to three involved nodes and other risk factors for recurrence. Those without nodal involvement sometimes also qualify for regional nodal irradiation if the risk of recurrence is high based on a constellation of clinicopathologic risk factors. This personalized approach is largely based on the results of two contemporary studies among patients with node-positive or high-risk node-negative breast cancer: NCIC-CTG MA.20[214] and EORTC 22922/10925.[215] These trials evaluated adjuvant radiation to the breast/chest wall versus radiation to the breast/chest wall and regional nodal irradiation. Notably, both studies showed significant improvements in locoregional control, distant metastasis–free survival, and DFS; however, no significant OS benefits were observed.

Landmark surgical studies evaluating the omission of axillary lymph node dissection (in favor of SLNB) have shown excellent outcomes without regional nodal irradiation for select node-positive situations.[194,197] This has led to several randomized trials that allow for differing radiation therapy approaches to be applied in those cases with fewer than three involved nodes. Indeed, axillary nodal management, particularly among patients with a low burden of nodal disease, remains among the most controversial decisions in contemporary locoregional breast treatment.

KEY POINTS

- The goal of systemic therapy in nonmetastatic disease is to reduce the risk of local recurrence and distant metastasis.
- Randomized trials have demonstrated equivalent survival, regardless of whether neoadjuvant or adjuvant chemotherapy is used.
- Patients who present with inoperable disease require neoadjuvant therapy.
- pCR after neoadjuvant systemic therapy is a strong prognostic factor for reduced risk of recurrence, particularly in TNBC and HER2-positive disease.
- The presence of residual disease after neoadjuvant systemic therapy guides adjuvant systemic therapy choices.
- Treatment of operable breast cancer with mastectomy or breast conservation therapy results in equivalent survival in stages I and II breast cancer, with the following exceptions.
- Positive margins. The definition of an adequate margin of resection for invasive breast cancer treated with breast conservation therapy is no tumor present in the inked margin.
- Inability to remove the tumor with adequate margins and a favorable cosmetic outcome.
- Multicentric disease.
- Contraindications to radiation therapy.
- Patients presenting with a clinically negative axilla can undergo SLNB but axillary staging may be omitted in certain populations with low-risk hormone receptor–positive and HER2-negative tumors.

- Patients with clinical T1 to T2 N0 tumors and up to two involved sentinel lymph nodes treated with up-front breast conservation therapy and whole-breast irradiation can avoid axillary lymph node dissection.
- Patients with clinical T1 to T2 N0 tumors with one to two SLN metastases treated with up-front mastectomy may omit axillary lymph node dissection, provided PMRT is indicated based on additional risk factors.
- Patients presenting with clinically positive lymph nodes require axillary lymph node dissection unless neoadjuvant therapy is used, and their approach must be individualized.
- Hypofractionated radiation therapy is now an established option for most patients requiring adjuvant radiation therapy.
- Accelerated partial breast irradiation is a suitable option for appropriately selected patients.
- Adjuvant breast radiation therapy may be omitted in older patients who have favorable tumor characteristics under select conditions.
- Regional nodal irradiation after breast-conserving surgery or mastectomy is typically indicated in patients who have three or more positive lymph nodes and can be considered in patients who have zero to three positive lymph nodes and additional risk factors.

SYSTEMIC THERAPY: GENERAL PRINCIPLES

One of the hallmarks of cancer is genetic instability with increasing clonal evolution, with mutations that confer sensitivity and resistance to systemic therapies. Few, if any, trials have demonstrated long-term OS or cure in patients with established macrometastases. The major objective of adjuvant systemic therapy is to treat micrometastases before they evolve into macrometastases. Multiple clinical trials have demonstrated the benefit of adjuvant systemic therapy in reducing the incidence of distant metastatic disease and mortality.

However, not all patients need or will respond to adjuvant systemic therapy. Stage and biology are used to determine the risk of distant recurrence and guide the choice of adjuvant treatment. Other factors are also considered when making treatment decisions. Age is an independent prognostic feature. Women younger than 35 years have a worse 5-year OS compared with women aged 35 to 69 years (74.7% vs 83.8%-88.3%)[216,217]; therefore, the threshold for offering adjuvant therapy is often reduced in younger women.[218] On the other hand, relatively few clinical trials have included a substantial number of women older than 70 years. Patient preferences, treatment toxicity, and comorbidities are also important treatment considerations (Fig. 10-5).

In general, breast cancers with a tumor size larger than 0.5 cm have a high enough risk of systemic recurrence to warrant consideration of adjuvant treatment. Patients with a tumor size of 0.5 cm or smaller and negative nodes may not gain sufficient benefit from systemic chemotherapy or HER2-directed therapy to justify the expected toxicities. For hormone receptor–positive breast cancers, risk assessment using genomic assays can identify a group of patients who may avoid chemotherapy. Adjuvant endocrine therapy is recommended for hormone receptor–positive breast cancers to reduce the risk of distant and local recurrences and as a secondary prevention, given its favorable safety profile.

The following are general principles regarding adjuvant chemotherapy:

- Full-dose chemotherapy is administered based on height and actual weight. The Hematology/Oncology Pharmacy Association recommends that cytotoxic agents be considered independently for dose rounding within 10% of the prescribed dose.
- Combination chemotherapy is superior to single-agent chemotherapy.
- In general, anthracycline- and taxane-containing regimens are appropriate for higher-risk disease, whereas non–anthracycline-containing regimens can be used for node-negative tumors and select node-positive tumors with more favorable disease biology.
- The absolute benefit of chemotherapy is greater for women with higher-risk disease based on either anatomy (ie, node positive) or biology (ie, high recurrence score or hormone receptor–negative disease).

The choice of regimen depends on the overall risk of disease recurrence and the relative reduction of risk with the administration of chemotherapy, weighed against the toxicity of the regimens, patient comorbidities, and patient preferences.[85,219] Compared with methotrexate-containing regimens, the use of anthracyclines in adjuvant therapy improved the proportional reduction in the risk of breast cancer recurrence by 12% and death by 15%.[85] These data support the use of anthracyclines for adjuvant treatment, with the most used combination being doxorubicin and cyclophosphamide (AC) for four cycles. A meta-analysis of 13 randomized trials involving 22,453 women showed that the addition of taxanes to anthracycline-containing regimens resulted in a 17% reduction in the relative risk of relapse and an 18% reduction in the relative risk of death at 5 years. This translated into a 5% absolute improvement in DFS and a 3% improvement in OS.[220] This benefit was observed regardless of the type of taxane used (paclitaxel or docetaxel) and whether taxanes were used in sequence (ie, doxorubicin/cyclophosphamide, followed by paclitaxel or docetaxel or in combination such as docetaxel/doxorubicin/cyclophosphamide).

Schedule optimization trials next proved that a dose-dense chemotherapy schedule administered every 2 weeks with growth factor support was associated with improved clinical outcomes compared with chemotherapy administration on a conventional

Figure 10-5 Suggested Guidelines for (Neo)Adjuvant Systemic Therapy for Four Main Breast Cancer Subtypes if No Germline *BRCA* Mutation

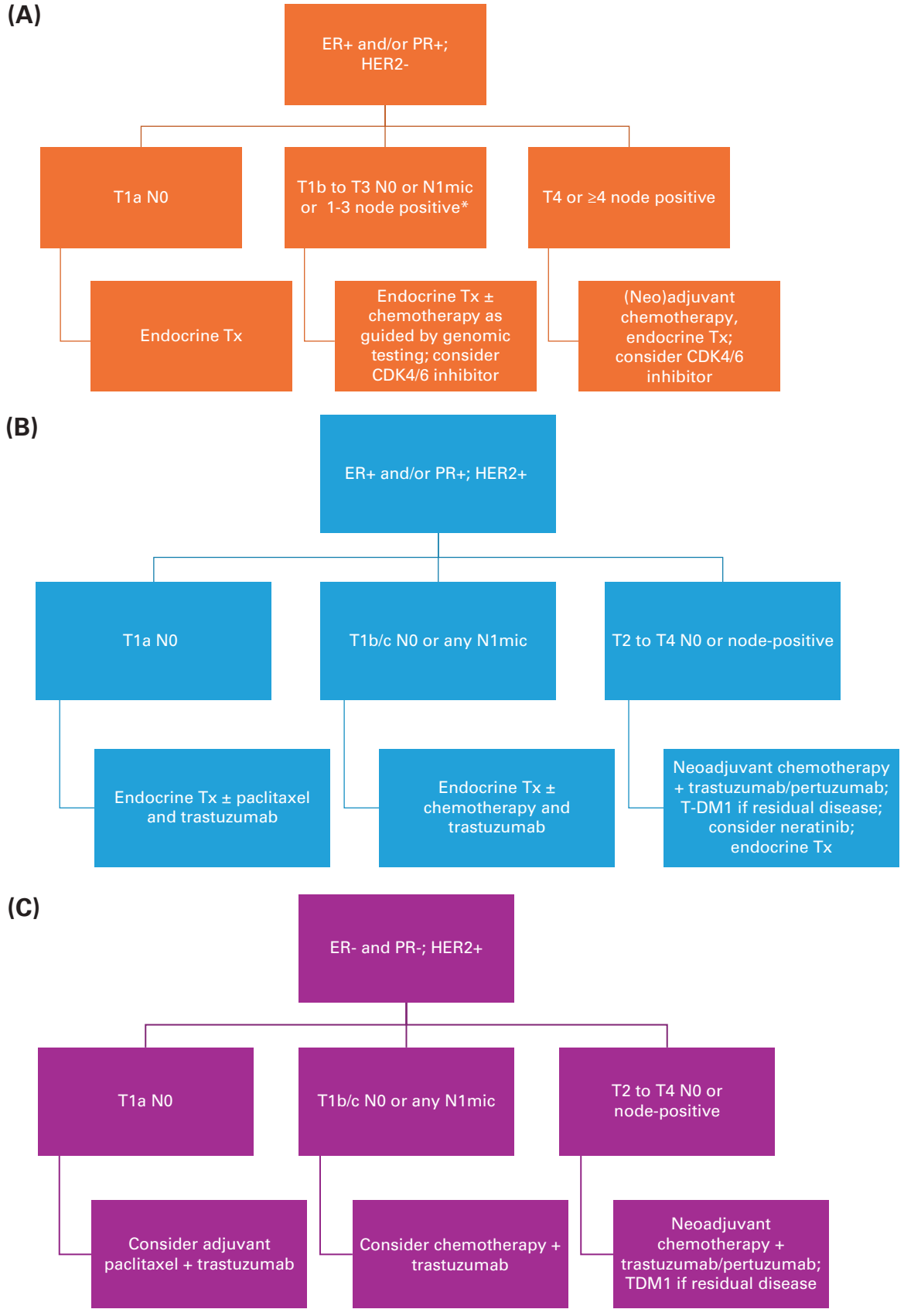
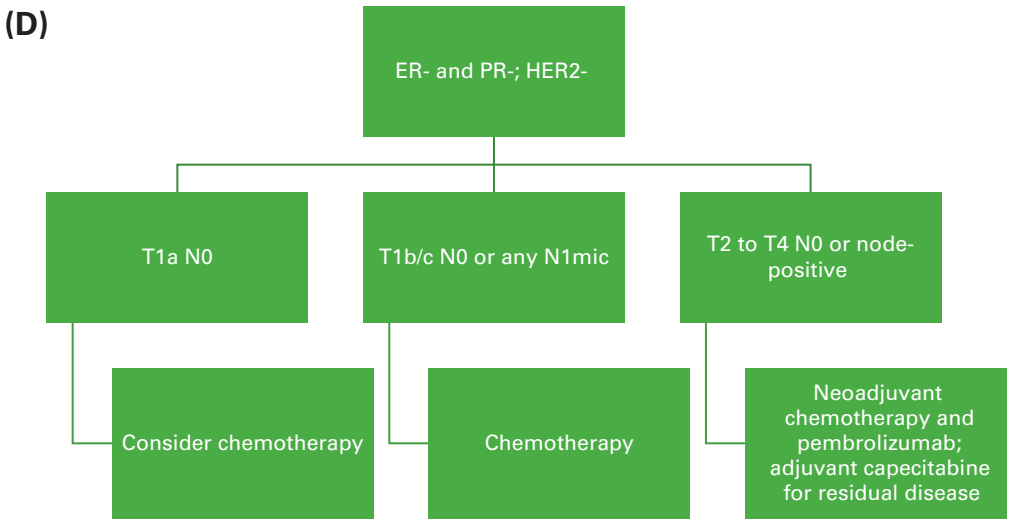


Figure 10-5 Continued



(A) Hormone receptor–positive, HER2-negative disease. (B) Hormone receptor–positive, HER2–positive disease. (C) Hormone receptor–negative, HER2–positive disease. (D) Hormone receptor–negative, HER2–negative disease.
Abbreviations: ER, estrogen receptor; PR, progesterone receptor; Tx, therapy.
*Gene signatures may help with decision-making in appropriate patients. Clinical trials did not include T1c, N0.
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every-3-week schedule. In CALGB 9741, 2,005 women with lymph node–positive disease were randomly assigned to receive similar doses of AC for four cycles, followed by paclitaxel for four cycles, administered on a dose-dense or conventional schedule.[221] The dose-dense regimen resulted in a 26% reduction in the relative risk of recurrence and a 31% reduction in the relative risk of death. A meta-analysis of 26 trials with more than 37,000 women compared dose-dense with standard dosing and confirmed the CALGB 9741 findings of a 14% relative reduction in risk of recurrence and a 13% relative reduction in the risk of death.[222]

The optimal schedule and type of taxane were examined in ECOG 1199, which randomly assigned patients with stage II to III breast cancer to either every-3-week docetaxel or paclitaxel for four cycles or weekly docetaxel or paclitaxel for 12 weeks (after four cycles of AC). At a median follow-up of 12 years, compared with every-3-week paclitaxel, weekly paclitaxel improved DFS with a trend toward improved OS.[223]

Given the potential for long-term cardiotoxicity associated with the use of anthracyclines, identifying who can be safely treated with non–anthracycline-containing regimens is an important question. A randomized trial compared four cycles of AC with four cycles of another two-drug regimen, docetaxel and cyclophosphamide (TC), among women with stage I to III breast cancer.[224] After a 7-year follow-up, there was a 6% improvement in the DFS rate and a 5% improvement in the OS rate with the TC regimen. However, this trial compared TC with non–dose-dense every-3-week AC, shown to be inferior to dose-dense AC (ddAC) in other trials. An analysis of the ABC trials[225] showed that a regimen containing taxanes and anthracyclines, compared with a taxane-only regimen for six cycles, improved iDFS, although the benefit was seen particularly in patients with TNBC and those with hormone receptor–positive breast cancer and a higher number of involved axillary lymph nodes. In the West German Study Group PlanB trial, patients with HER2-negative node-positive or high-risk node-negative breast cancer who received six cycles of TC had noninferior 5-year DFS compared with those who received an anthracycline-containing regimen (four cycles of epirubicin and cyclophosphamide, followed by four cycles of docetaxel). A majority of patients had hormone receptor–positive cancer (TC, 82.2%; epirubicin, cyclophosphamide, and docetaxel, 81.4%) and N0 to N1 disease (TC, 92.6%; epirubicin, cyclophosphamide, and docetaxel, 93.1%).[156]

In summary, the choice of regimen depends on the overall risk of breast cancer recurrence and the relative and absolute reduction of risk with the administration of chemotherapy, all balanced by the toxicity of the regimen, patient comorbidities, performance status, and preferences.

Major considerations associated with the most commonly used adjuvant chemotherapy regimens include the following:

- ddAC followed by paclitaxel
  - AC is considered highly emetogenic.
  - Hematopoietic growth factors are required to maintain dose density.
  - Anthracyclines are associated with cardiac toxicity; doxorubicin-associated cardiac dysfunction is related to cumulative dose. Relatively acute (in the first few years after treatment) congestive heart failure is less than 1% to 2% at cumulative doses of doxorubicin up to approximately 400 mg/m^2 (HD1). Most doxorubicin-containing adjuvant

breast cancer regimens administer less than 300 mg/m^2 total. Risk factors for cardiac toxicity include underlying heart disease, use of anthracyclines concurrently with other cardiotoxic agents or radiation therapy, and previous treatment with mediastinal or chest wall irradiation.[226] A baseline assessment of left ventricular ejection fraction is recommended.
    - Paclitaxel can cause severe hypersensitivity reactions and, therefore, requires premedication with steroids and antihistamines.
    - Alopecia is common with this regimen. Scalp cooling may mitigate some of the risk of alopecia.
    - Sensory peripheral neuropathy is common with paclitaxel and docetaxel. Neuropathy is more likely in patients who are older, have existing neuropathy, or who have previously received taxane chemotherapy.
    - Dose adjustment of doxorubicin or paclitaxel is not required in cases of renal impairment. The need for cyclophosphamide dose reduction in renal insufficiency is controversial.
    - Dose adjustment of doxorubicin, cyclophosphamide, and paclitaxel may be needed in cases of hepatic impairment. It is recommended to administer 50% of the doxorubicin dose if serum bilirubin is 1.2 to 3 mg/dL and 25% if serum bilirubin is 3.1 to 5 mg/dL; doxorubicin is contraindicated if the bilirubin level is higher than 5 mg/dL or in cases of Child-Pugh class C. It is also advised to avoid cyclophosphamide if the serum bilirubin level is higher than 5 mg/dL. Paclitaxel dose should be adjusted on the basis of aminotransferase and bilirubin levels, and paclitaxel should be avoided if aminotransferase levels are 10 times the upper level of normal or higher or if bilirubin level is more than five times the upper level of normal.
- Four cycles of TC
    - Emesis risk is moderate.
    - Steroid treatment before and after docetaxel administration reduces the incidence of docetaxel-induced fluid retention.
    - Alopecia is common with this regimen. Rare cases of permanent alopecia have been reported with docetaxel. Scalp cooling may mitigate some of the risk of alopecia.
    - Sensory peripheral neuropathy is common with paclitaxel and docetaxel. Neuropathy is more likely in patients who are older, have existing neuropathy, or who have previously received taxane chemotherapy.
    - Dose adjustment of docetaxel is not required in cases of renal impairment. The need for cyclophosphamide dose reduction in renal insufficiency is controversial.
    - Regarding hepatic impairment, docetaxel should not be administered when the serum bilirubin level is higher than the upper limit of normal or with aminotransferase elevations more than 1.5 times the upper limit of normal in conjunction with an alkaline phosphatase level more than 2.5 times the upper limit of normal.

PRESENTING CASE STUDY

A 52-year-old woman with mild hypertension presents with persistent lower back pain despite intermittent physical therapy and use of over-the-counter analgesics. Her primary care doctor took plain radiographs of the spine. These revealed questionable lytic lesions in her lumbar spine and the patient was advised to see her oncologist. Her history is notable for a T2N0 estrogen receptor (ER)–positive (90%) and HER2-negative (1+ by immunohistochemistry [IHC]) cancer of the right breast diagnosed 6 years ago. She underwent breast conservation and completed 5 years of adjuvant tamoxifen. She did not receive adjuvant chemotherapy, based on a tumor recurrence score of 12.

As her oncologist, you order a computed tomography (CT) of the chest, abdomen, and pelvis, which is notable for several sclerotic and lytic lesions in the axial skeleton as well as enlarged right hilar, mediastinal, and intra-abdominal lymph nodes. There are two pulmonary nodules in the right lung; the largest measures 1.5 cm. Lymph node biopsy confirms recurrent metastatic breast cancer (MBC).

Which biomarkers do you need to know to develop her treatment plan?

IHC to determine ER, progesterone receptor (PR), and HER2 status is essential to select appropriate first-line therapy for metastatic disease. Discordance in receptor status between the primary tumor and a distant metastatic site can occur in around 15% of cases. Germline genetic testing is important because the presence of a *BRCA1* or *BRCA2* mutation is actionable, with PARP inhibitors such as olaparib and talazoparib showing superiority to cytotoxic chemotherapy. Finally, tissue or circulating tumor DNA (ctDNA) sequencing can identify important alterations in *ESR1*, *PI3K*, *AKT*, or *PTEN*, which can guide use of targeted therapies in combination with endocrine therapy for ER-positive tumors.

Her tumor tests as follows: ER 80%, PR 20%, and HER2 1+ by IHC. Germline genetic testing is negative for pathogenic mutations, and her somatic sequencing lacks *ESR1* and *PI3K* mutations. She is now postmenopausal. Her pain has improved with consistent use of nonsteroidal anti-inflammatory drugs.

What is the preferred approach for first-line treatment of ER-positive HER2-low MBC that is wild type for *ESR1* and *PI3K*?

Endocrine therapy with an aromatase inhibitor (AI) and cyclin-dependent kinase 4/6 (CDK4/6) inhibitor is a preferred first-line therapy option for patients with ER-positive MBC who are not in visceral crisis (see "Hormone Receptor–Positive Disease" section). Ribociclib is the only CDK4/6 inhibitor that has shown a statistically significant overall survival (OS) benefit in the first-line setting. Bisphosphonates and the RANK ligand inhibitor denosumab reduce the incidence of skeletal-related events and the time to occurrence of skeletal-related events in patients with bone metastases.

After 2.5 years on first-line endocrine therapy and a CDK4/6 inhibitor, the patient's disease progresses in her bones and lungs, and new liver lesions appear. Her complete blood count and comprehensive panel are within the reference range. She reports fatigue but is otherwise asymptomatic. You send a ctDNA sample and find that her tumor has an *AKT* mutation.

What therapeutic options are available for patients who progress on a CDK4/6 inhibitor and whose tumors contain an *AKT* mutation?

In November 2023, the FDA approved the AKT inhibitor capivasertib in combination with fulvestrant for patients with ER-positive MBC whose tumors have a *PI3K* mutation, *AKT* mutation, or *PTEN* loss. This is based on the phase 3 CAPitello-291 study, which showed a significant improvement in median progression-free survival (PFS) with the addition of capivasertib to fulvestrant compared with fulvestrant alone (7.3 vs 3.1 months) in those with AKT pathway alterations. If ctDNA sequencing revealed an *ESR1* mutation, the patient would be a candidate for single-agent elacestrant. If her tumor had a *PI3K* mutation, she would be a candidate for either combination therapy with capivasertib or alpelisib, the PI3K inhibitor. Choices based on tolerability and toxicity are reasonable in that setting, as no head-to-head data are available to guide decision-making.

The patient begins fulvestrant and capivasertib. Seven months later, she has additional liver lesions and mild transaminitis. No new mutations have emerged on repeat ctDNA sequencing. She begins first-line chemotherapy with capecitabine. After dose adjustment for hand-foot syndrome, she tolerates treatment well and remains progression-free for about 12 months. However, her most recent CT of the chest, abdomen, and pelvis confirms disease progression with increasing and new bone and liver lesions. Lung nodules are stable, and she has no respiratory symptoms.

Given her disease progression following endocrine therapy and one line of chemotherapy, what would you recommend for the treatment of this patient's HER2-low MBC?

The DESTINY-Breast04 trial randomized patients with HER2-low MBC who had received two or fewer lines of chemotherapy to trastuzumab deruxtecan (T-DXd) or a physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel). Most patients (88.7%) had hormone receptor–positive disease. Among patients who had hormone receptor–positive cancer, median PFS was 10.1 months and median OS was 23.9 months with T-DXd compared with median PFS of 5.4 months and median OS of 17.5 months with chemotherapy (PFS HR, 0.51; $P < .001$; OS HR, 0.64; $P = .003$). Based on these data, the FDA approved fam-T-DXd in 2022 for adult patients with unresectable or metastatic HER2-low breast cancer who received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant treatment.

Would your recommendation be any different if she were symptomatic from a large burden of lung metastases with chronic cough and dyspnea on exertion?

In the DESTINY-Breast04 trial, drug-related interstitial lung disease (ILD) occurred in 12.1% of patients, with 0.8% experiencing grade 5 ILD. However, the percentage of patients with a confirmed objective response in the hormone receptor–positive cohort was 52.6% (95% CI, 47.0-58.0) in the T-DXd group and only 16.3% (95% CI, 11.0-22.8) in the physician's choice group. Therefore, the risk–benefit balance favors using T-DXd to most effectively treat the underlying cause of this patient's symptoms, namely, MBC to the lung. There are clear guidelines for the monitoring and managing of T-DXd-related ILD.[227]

SYSTEMIC THERAPY FOR EARLY-STAGE BREAST CANCER

TRIPLE-NEGATIVE BREAST CANCER

Triple-negative breast cancer refers to tumors that test ER 0%, PR 0%, and HER2 0 or low (1+/2+ and fluorescence in situ hybridization [FISH] not amplified). TNBC generally has a higher risk of distant recurrence and a more aggressive phenotype. These tumors do not derive benefit from adjuvant endocrine therapy. In fact, tumors that test ER and PR low (1%-10%) behave biologically more like TNBC than estrogen-dependent cancers and are sometimes included in clinical trials for TNBC. As a result, even small (less than 5 mm) node-negative tumors are considered for adjuvant chemotherapy based on the benefit/risk balance. The introduction of the checkpoint inhibitor pembrolizumab to the neoadjuvant treatment of early-stage TNBC and the effect of adjuvant therapy on those patients who have residual disease following preoperative chemotherapy have driven more of a preoperative systemic therapy approach to the treatment of early-stage TNBC.

Neoadjuvant Chemotherapy

KEYNOTE-522 examined the addition of the checkpoint inhibitor pembrolizumab to anthracycline, taxane, and platinum-based chemotherapy for localized TNBC. Patients who had tumors larger than 2 cm or involved axillary lymph nodes were randomly assigned to neoadjuvant paclitaxel and carboplatin followed by epirubicin or AC, all with pembrolizumab or with a placebo. Pembrolizumab (or placebo) was continued for nine cycles in the adjuvant setting after surgery, regardless of response. The addition of pembrolizumab to chemotherapy demonstrated a statistically and clinically significant improvement in both pCR (64.8% vs 51.2%) and 5-year event-free survival (EFS) rates (81.3% vs 72.3%).[228] The median EFS was not reached in either treatment arm (HR, 0.63; 95% CI, 0.49-0.81). Recently, the final analysis for OS was reported after 75 months median follow-up. The estimated OS at 60 months was 86.6% (95% CI, 84.0-88.8) with pembrolizumab-chemotherapy compared with 81.7% (95% CI, 77.5-85.2) in the placebo-chemotherapy arm ($P = .002$). These data have established the KEYNOTE-522 regimen as standard of care for high-risk, early-stage TNBC.[229]

Monitoring for immune-related adverse events is important, particularly screening for thyroid disease and adrenal insufficiency before surgery (Fig. 10-5).

Neoadjuvant therapy can be considered for T1cN0 TNBC using preferred chemotherapy regimens containing anthracycline, cyclophosphamide, and a taxane to help prognosticate based on residual cancer burden and to escalate therapy in the adjuvant setting for those at greatest risk of recurrence. For patients who have a contraindication to anthracycline, TC-alternate regimens such as taxane and carboplatin may be considered.

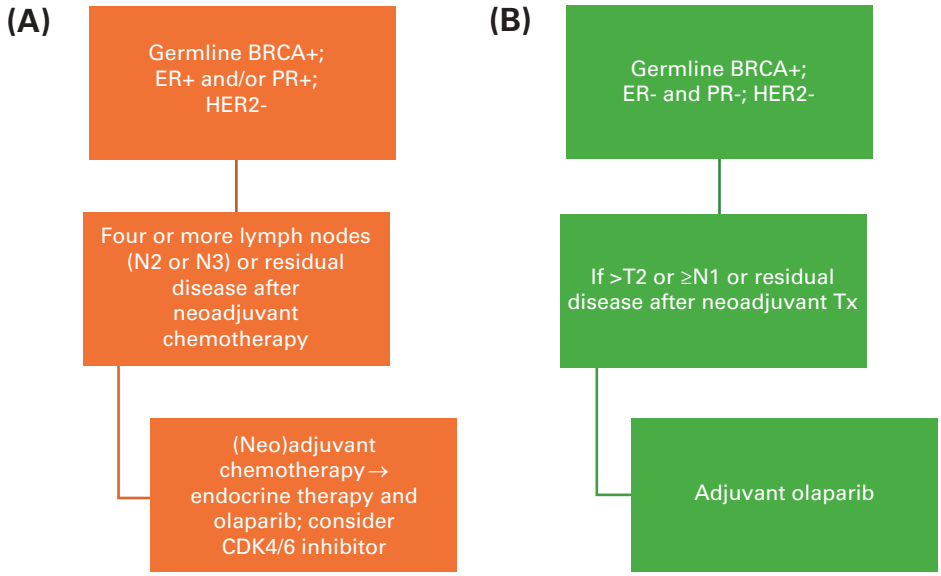
Improved adjuvant treatment options are needed for patients with TNBC who do not achieve pCR with neoadjuvant therapy, as these patients are at high risk of distant recurrence. For example, in KEYNOTE-522, those patients who failed to achieve pCR had a 5-year EFS of 69% and 47% for stage II and III disease, respectively, despite pembrolizumab. The CREATE-X[230] trial randomly assigned 910 patients with HER2-negative breast cancer who received neoadjuvant chemotherapy (containing anthracycline, taxane, or both) and had residual disease at the time of surgery to receive six to eight cycles of capecitabine or placebo. There was an improvement in OS in the capecitabine group compared with placebo (89.2% vs 83.6% at 5 years; HR, 0.59). Patients with TNBC derived the largest benefit, with a DFS rate at 5 years of 69.8% in the capecitabine group versus 56.1% in the control group (HR, 0.58) and an OS rate of 78.8% versus 70.3% (death HR, 0.52; 95% CI, 0.30-0.90). Although KEYNOTE-522 did not allow for adjuvant capecitabine in patients who had residual disease, safety data exist for the combination of capecitabine and pembrolizumab in MBC, and the combination is often used for patients with residual disease. The ASCO guideline update from 2018 recommends that patients with early-stage HER2-negative breast cancer with invasive residual disease at surgery after standard anthracycline- and taxane-based preoperative therapy may be offered up to six to eight cycles of adjuvant capecitabine.[231] The EA1131 trial did not demonstrate noninferiority of adjuvant carboplatin or cisplatin compared with adjuvant capecitabine in patients with stage II to III basal-type TNBC and residual disease of 1 cm or more. Three-year iDFS for patients who received platinum was 42% versus 49% for those who received capecitabine (HR, 1.94; 95% CI, 0.69-5.45).[232]

Adjuvant Chemotherapy

For those patients with TNBC who have up-front surgery, chemotherapy is a consideration for tumors measuring at least 6 mm. Following the principles outlined earlier, an anthracycline- and taxane-based adjuvant regimen is generally preferred for high-risk patients, although non–anthracycline-containing combinations such as TC, taxane/carboplatin, or even cyclophosphamide/methotrexate/fluorouracil may be considered based on personalized risk/benefit assessment.

The OlympiA trial examined the role of PARP inhibitors in patients with germline *BRCA1* and *BRCA2* mutations and high-risk HER2-negative breast cancer. For TNBC, high risk was defined as either residual disease after neoadjuvant therapy or at least T2 or N1 disease in the adjuvant setting. The addition of 1 year of adjuvant olaparib improved iDFS from 77.1% to 85.9% at 3 years (HR, 0.58; 99.5% CI, 0.41-0.82). At the second planned interim analysis with a 3.5-year median follow-up, 3-year OS was 92.0% in the olaparib arm versus 89.1% in the placebo arm (HR, 0.68; 98.5% CI, 0.47-0.97).[233,234] Adjuvant olaparib is recommended for patients with germline *BRCA1* and *BRCA2* mutations and high-risk HER2-negative breast cancer (Fig. 10-6).

Figure 10-6 Suggested Guidelines for (Neo)Adjuvant Systemic Therapy for HER2-Negative Breast Cancer With Germline *BRCA* Mutation



(A) Hormone receptor–positive, HER2-negative disease. (B) Hormone receptor–negative, HER2-negative disease.
Abbreviation: Tx, therapy.
Gene signatures may help with decision-making in appropriate patients. Clinical trials did not include T1c, N0.Created for ASCO. Copyright © 2026 by American Society of Clinical Oncology.

HORMONE RECEPTOR–POSITIVE BREAST CANCER

Recommendations for the use of gene expression signatures to guide adjuvant chemotherapy decisions in hormone receptor–positive disease are discussed in "Gene Expression Signatures" section. General principles regarding chemotherapy in early-stage breast cancer were addressed in "Triple-Negative Breast Cancer" section (also see Fig. 10-5). When both chemotherapy and endocrine therapy are recommended, chemotherapy is administered before endocrine therapy.

Endocrine Therapy

The majority of invasive breast cancers are hormone receptor positive. Endocrine therapy reduces the risk of systemic recurrence and death by approximately one-third among women with hormone receptor–positive (ER and/or PR) breast cancer regardless of age, menopausal status, nodal involvement, tumor size, HER2 status, or use of chemotherapy. For this reason, adjuvant endocrine therapy should be recommended for all women who have hormone receptor–positive disease.[235,236]

There are two endocrine therapy options with distinct mechanisms of action and side effects. Tamoxifen is a SERM that binds to the ER but has tissue-specific ER antagonist and agonist properties. ER antagonist side effects include hot flashes and vaginal dryness. However, there is a less than 1% risk of venous thromboembolism and of uterine cancer because of the ER agonist properties in those tissues. In postmenopausal women, tamoxifen is an estrogen agonist regarding bone mineral density (BMD).

AIs block aromatization of androgens into estrogens, which is the primary means of estrogen production in postmenopausal women. As a result, side effects and risks include hot flashes, vaginal dryness, and the potential to decrease BMD, among others. In addition, up to 40% of patients complain of musculoskeletal aches and joint stiffness. Depending on the severity and effect on quality of life, these musculoskeletal symptoms may contribute to noncompliance in 10% to 15% of women. There are three FDA-approved AIs—anastrozole, letrozole (nonsteroidal AIs), and exemestane (steroidal AI)—and they are equivalent in efficacy and side effect profiles.[237,238]

Tamoxifen

Tamoxifen is effective in premenopausal and postmenopausal women. The Early Breast Cancer Trialists' Collaborative Group meta-analysis showed that 5 years of tamoxifen reduced the relative risk of distant recurrence by approximately 41% and the relative risk of death by 34%.[239] Two large studies support extending the duration of tamoxifen treatment to 10 years.[240] In the ATLAS trial, tamoxifen for 10 years compared with 5 years reduced the rate of recurrence by 3.2% and improved the mortality

rate by 2.8%. The difference between the arms of the study did not emerge until year 10, likely because of the carryover protective effect in years 5 to 10 conferred by 5 years of tamoxifen. Prolonged tamoxifen use was associated with an increased incidence of pulmonary embolism and endometrial cancer, with a 3.1% cumulative risk of endometrial cancer after 5 years of tamoxifen therapy, translating into an absolute increase in the endometrial cancer mortality rate of 0.2%. There was no increase in the risk of stroke or cardiovascular events with prolonged treatment. These results were replicated in the aTTom trial, which had a similar design.[241] Although these data support the efficacy of prolonged use of tamoxifen, longer treatment duration must be weighed against potential adverse outcomes on an individual basis, particularly for patients with early-stage disease at low risk of recurrence.

Cytochrome P450 2D6 (CYP2D6) is the primary hepatic enzyme responsible for tamoxifen metabolism to its active metabolite. A CYP2D6 polymorphism can result in a decreased active metabolite, potentially resulting in decreased efficacy. Currently, ASCO guidelines do not recommend the use of testing for CYP2D6 polymorphisms to guide the selection of adjuvant endocrine therapy.[242]

Role of Ovarian Function Suppression

The SOFT and TEXT trials evaluated the role of ovarian function suppression (OFS) as adjuvant therapy for hormone receptor–positive breast cancer.[243] In TEXT, premenopausal women were randomly assigned to receive 5 years of tamoxifen or exemestane with concurrent OFS. In SOFT, women were randomly assigned to receive 5 years of tamoxifen, tamoxifen and OFS, or exemestane and OFS. In both studies, chemotherapy was administered per the physician's choice. The comparisons of exemestane and OFS and tamoxifen and OFS in both trials were analyzed together. At a median follow-up of 13 years, the combination of OFS and exemestane improved 12-year DFS by 21% and distant recurrence-free interval by 17% compared with OFS and tamoxifen.[244] The differences in OS were not statistically significant. For premenopausal women with higher-risk disease, for example, those requiring adjuvant chemotherapy, OFS and AI should be offered.

A consistent finding in these studies was that patients who had low-risk disease did equally well with tamoxifen alone. For these patients, tamoxifen alone remains an appropriate choice, which is particularly important given the added toxicities of OFS and AI therapy, including hot flashes, musculoskeletal symptoms, loss of bone density, and sexual dysfunction.

On the basis of the initial report of the SOFT and TEXT trials, the 2016 ASCO guideline recommends the following:

- For premenopausal women at higher risk of cancer recurrence because of tumor stage (II and III) or biologic features, OFS, in addition to adjuvant endocrine therapy, is recommended, particularly in women younger than 35 years. On the other hand, women who have stage I disease for whom chemotherapy is not deemed necessary should not receive OFS.
- OFS and an AI are favored for patients at higher risk and for younger women.

Aromatase Inhibitors

Although tamoxifen is effective in postmenopausal women, AIs are usually preferred on the basis of data from multiple studies comparing both agents in postmenopausal women. AIs alone are not effective in premenopausal or perimenopausal women and, therefore, should not be used in this group of patients in the absence of concurrent OFS. It is important to remember that chemotherapy-induced amenorrhea can be transient; therefore, the choice of endocrine therapy should be based on menopausal status before treatment, and hormone laboratories should be serially monitored.

Multiple studies have addressed the efficacy of AIs compared with tamoxifen, either evaluating 5 years of tamoxifen versus an AI or switching to an AI after 2 to 3 years of tamoxifen. Data from an Oxford meta-analysis showed that, compared with 5 years of tamoxifen, the use of an AI in postmenopausal women reduced the 10-year risk of recurrence by approximately 30% and the breast cancer mortality rate by approximately 15%.[245]

Although an AI is generally preferred to tamoxifen in postmenopausal women because of efficacy, the absolute difference in risk reduction is small, particularly for early-stage cancers. Therefore, women who are unable to tolerate an AI should be switched to tamoxifen.[246]

AI treatment after 5 years of endocrine therapy was also studied. Switching to an AI after 5 years of treatment with tamoxifen demonstrated an additional reduction in disease recurrence in postmenopausal women.[247] Several other studies have examined the continuation of an AI after 5 years of treatment that included an AI.[248-251] The optimal duration of extended therapy after year 5 was also evaluated.[252,253] These studies are listed in Table 10-5.[254] Taken together, these data show a modest improvement in DFS in patients who continued an AI after an AI treatment, largely driven by prevention of contralateral breast cancer. The Breast Cancer Index (see "Gene Expression Signatures" section) was retrospectively validated to identify patients at higher risk of late distant relapse who may benefit most from extended endocrine therapy. In light of the modest activity of extended AI treatment and added toxicity, patients who have higher-risk disease are the most suitable candidates for extended endocrine therapy.

Table 10-5 **Extended Endocrine Therapy With AI**[255]	
Trial	**Intervention**
Extended adjuvant AI after 5 years of tamoxifen	
MA.17	Letrozole for 5 years or placebo
NSABP B-33	Exemestane for 5 years or placebo
ABCSG 6	Anastrozole for 3 years or placebo
Extended AI after 5 years of therapy that included an AI	
MA.17R	Letrozole or placebo for 5 years after 5 years of letrozole (preceded by 5 years of tamoxifen in most patients)
NSABP B-42	Letrozole or placebo for 5 years after 5 years of endocrine therapy with 5 years of an AI or 3 or fewer years of tamoxifen
DATA	Anastrozole for 6 years, 3 years after 2 to 3 years of tamoxifen
Optimal duration or dosing of AI in years 5-10	
IDEAL	Letrozole for 2.5 vs 5 years after tamoxifen, AI, or both for 5 years
ABCSG-18	Anastrozole for 2 vs 5 years after tamoxifen, AI, or both for 4 to 6 years

Abbreviation: AI, aromatase inhibitor.
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ASCO Guidelines recommend that postmenopausal women with node-positive disease be offered extended (10 years) AI therapy.[256] The benefits are likely lower for those with node-negative disease. As the major benefit of extended AI therapy is contralateral breast cancer, and there are risks and side effects with longer therapy, treatment decisions need to be individualized and incorporate patient preferences.

NEOADJUVANT ENDOCRINE THERAPY

Neoadjuvant endocrine therapy is an acceptable treatment for postmenopausal women with hormone receptor–positive disease to either achieve breast conservation or downstage disease that is inoperable at presentation. This approach is particularly valuable in women who have tumors with low chemosensitivity or who are poor candidates for chemotherapy. At least five randomized trials (including patients with stage II disease) have demonstrated superiority with a neoadjuvant AI compared with tamoxifen.[254,255,257] Despite low pCR rates associated with neoadjuvant endocrine therapy, surrogate markers of response can offer prognostic information about long-term clinical outcomes, including the expression of Ki67 in residual tumors (a low value or a decrease compared with baseline is favorable),[258] and prospective validation of these biomarkers is ongoing.

Neoadjuvant endocrine therapy is usually administered for no less than 4 to 6 months to allow maximum response before surgery. Patients who have a clinical response to neoadjuvant endocrine therapy should continue to receive endocrine therapy after surgery. Those who do not have a clinical response should be considered for adjuvant chemotherapy, followed by adjuvant endocrine therapy. Neoadjuvant endocrine therapy in premenopausal women and in men remains investigational.

ADJUVANT CDK4/6 INHIBITORS

Because of their efficacy in the treatment of hormone receptor–positive MBC, the role of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors added to endocrine therapy for localized breast cancer has been the subject of large randomized clinical trials. All three CDK4/6 inhibitors have been studied.

In the monarchE trial, patients who had high-risk node-positive hormone receptor–positive and HER2-negative breast cancer were randomly assigned to standard adjuvant endocrine therapy with or without abemaciclib for 2 years.[259] The addition of abemaciclib resulted in a 3.5% improvement in iDFS at 2 years (92.2% vs 88.7%; HR, 0.75; 95% CI, 0.6-0.93). Based on these data, in 2021, the US FDA approved abemaciclib as adjuvant therapy for patients who have hormone receptor–positive and HER2-negative breast cancer with four or more positive nodes or one to three nodes and a tumor size of 5 cm or larger or a grade 3 tumor. With longer follow-up, the iDFS was maintained, and the 7-year absolute difference was 6.5% (77.4% vs 70.9%; HR, 0.74). In addition, the secondary endpoints to OS and distant relapse-free survival (DRFS) were statistically improved with a median follow-up of 76 months. The 7-year OS was 86.8% with abemacilib and endocrine therapy versus 85% with endocrine therapy alone. The 7-year DRFS was 80% versus 74.9%, respectively.[4]

The NATALEE trial evaluated ribociclib in the adjuvant setting. In addition to node-positive disease, node-negative tumors larger than 2 cm with high-risk features, including grade and high risk based on genomic profiling, were eligible. Ribociclib was dose-reduced and given for 3 years with endocrine therapy. iDFS was improved by 25% with a 3-year iDFS rate of 90.4%

associated with ribociclib and an AI versus 87.1% with an AI alone. Ribociclib was FDA approved in September 2024 for node-positive and high-risk node-negative hormone receptor–positive and HER2-negative breast cancer.

By contrast, the PALLAS trial of adjuvant palbociclib and the PENELOPE-B trial of adjuvant palbociclib after neoadjuvant chemotherapy both failed to meet their primary endpoint of DFS.[260,261]

KEY POINTS

- Adjuvant tamoxifen has efficacy in premenopausal and postmenopausal women.
- OFS improves DFS and freedom from recurrence when combined with 5 years of adjuvant tamoxifen or exemestane in premenopausal women who have high-risk disease.
- Compared with 5 years, 10 years of adjuvant tamoxifen is associated with a small improvement in DFS and breast cancer–specific survival, and extended-duration tamoxifen is an option in premenopausal or postmenopausal patients at high risk.
- AIs are the first-choice adjuvant endocrine treatment in postmenopausal women.
- Administering AIs for 5 years results in similar outcomes as initial tamoxifen for 2 to 3 years, followed by an AI for a total of 5 years.
- An extended duration of AI therapy beyond 5 years should be considered in postmenopausal women who have high-risk disease.
- Neoadjuvant endocrine therapy is an acceptable treatment approach for postmenopausal women who have stage II or III hormone receptor–positive breast cancer, but it infrequently results in pCR.
- Two years of adjuvant abemaciclib in combination with endocrine therapy improves DFS and OS and is an option for patients with node-positive disease. Three years of dose-reduced ribociclib in combination with an AI improves iDFS in patients with high-risk node-negative and node-positive disease.

(NEO)ADJUVANT CHEMOTHERAPY IN HORMONE RECEPTOR–POSITIVE BREAST CANCER

Adjuvant Chemotherapy

A course of adjuvant chemotherapy in addition to endocrine therapy is considered for patients at a higher risk of recurrence, including patients who have four or more positive axillary lymph nodes (N2/N3) or one to three lymph nodes or node-negative disease with a high risk by tumor gene expression assays. See the discussion on adjuvant chemotherapy section in the "Systemic Therapy for Stage IV (Metastatic) Disease."

Neoadjuvant Chemotherapy

For patients receiving preoperative chemotherapy, both KEYNOTE-756 and CheckMate 7 FL revealed improved pCR rates with the addition of pembrolizumab (24.3% vs 15.6%) and nivolumab (24.5% vs 13.8%) to standard neoadjuvant chemotherapy, respectively, versus neoadjuvant chemotherapy alone.[261,262] However, no EFS (the coprimary endpoint in the KEYNOTE trial) has been reported, and neither of these PD-1 inhibitors is FDA approved in early-stage hormone receptor–positive breast cancer.

PARP Inhibitors in Adjuvant Therapy

The OlympiA trial examined the role of PARP inhibitors in patients with germline *BRCA1* and *BRCA2* mutations and high-risk HER2-negative breast cancer. For hormone receptor–positive disease, high risk was defined as four or more positive lymph nodes or non-pCR and clinical pathologic staging-ER grading score of 3 or higher. The addition of 1 year of adjuvant olaparib improved iDFS from 77.1% to 85.9% at 3 years (HR, 0.58; 99.5% CI, 0.41-0.82). At the second planned interim analysis with a 3.5-year median follow-up, 3-year OS was 92.0% in the olaparib arm versus 89.1% in the placebo arm (HR, 0.68; 98.5% CI, 0.47-0.97).[233] Adjuvant olaparib is recommended for patients with germline *BRCA1* and *BRCA2* mutations and high-risk HER2-negative breast cancer (Fig. 10-6).

HER2–POSITIVE BREAST CANCER

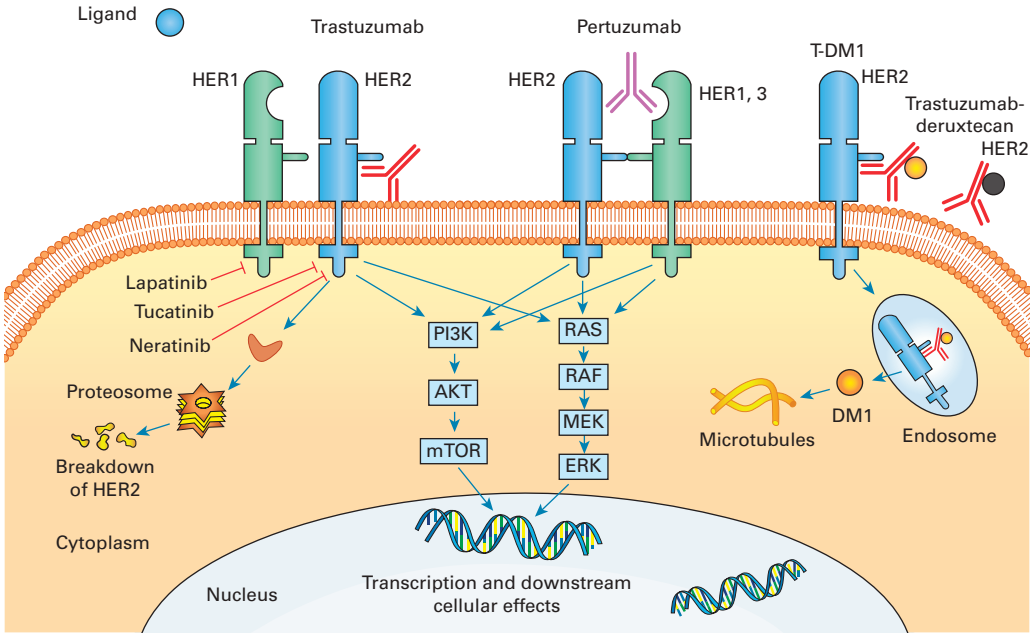
Most women diagnosed with early-stage HER2-positive breast cancer receive HER2-targeted therapy and chemotherapy as adjuvant systemic therapy. Exceptions are those with very small tumors (smaller than 0.5 cm; this should not be considered a strict cutoff, and other factors need to be considered) or with significant comorbidities.

Four HER2-targeted therapies are currently used in the adjuvant setting: trastuzumab, pertuzumab, neratinib, and ado-trastuzumab emtansine (T-DM1) (Fig. 10-7).

- Monoclonal antibodies trastuzumab and pertuzumab (HP) both target the extracellular domain of HER2; trastuzumab binds to subdomain IV and disrupts ligand-independent downstream signaling, whereas pertuzumab binds to subdomain II, which blocks dimerization of HER2 and subsequent ligand-dependent signaling.

- Neratinib is an oral irreversible tyrosine kinase inhibitor that blocks signal transduction through the EGFR family, including HER2.
- T-DM1 is an ADC that consists of trastuzumab linked to maytansinoid DM1, a potent microtubule-disrupting agent, joined by a nonreducible stable linker.

Figure 10-7 Targets for HER2-Targeted Therapy



Abbreviation: T-DM1, ado-trastuzumab emtansine.
Adapted under Creative Commons license CC BY-NC-SA 3.0. Source: Singh JC, Jhaveri K, Esteva FJ. HER2-positive advanced breast cancer: optimizing patient outcomes and opportunities for drug development. *Br J Cancer*. 2014;111:1888-1898. doi:10.1038/bjc.2014.388

Trastuzumab-Based Adjuvant and Neoadjuvant Therapy Regimens

When added to chemotherapy, trastuzumab substantially improves DFS and OS compared with chemotherapy alone.[263,264] A meta-analysis of five adjuvant therapy studies demonstrated a 38% reduction in the relative risk of recurrence and a 34% reduction in the relative risk of death as a result of any cause.[265] Concurrent administration of chemotherapy and trastuzumab seems to confer greater benefit compared with sequential treatment. This concept was supported by the NCCTG N9831 study, which showed that the concurrent administration of trastuzumab with paclitaxel was associated with a 23% reduction in the risk of an event compared with sequential trastuzumab administration. Concomitant administration of trastuzumab is supported by ASCO clinical practice guidelines. Trastuzumab is continued as a single agent after chemotherapy, commonly administered every 3 weeks and concurrently with endocrine therapy for hormone receptor–positive disease.[266]

The currently accepted duration of adjuvant trastuzumab is 1 year. The HERA trial evaluated combination chemotherapy followed by observation or 1 or 2 years of adjuvant trastuzumab.[267,268] Trial results showed that 1 year of trastuzumab significantly reduced the risk of a DFS event and death compared with observation. Two years of adjuvant trastuzumab did not improve DFS outcomes compared with 1 year of therapy[265,268] and was associated with greater cardiac toxicity.[265,268] Other studies examined the question of the duration of trastuzumab.[269-273] Of these, only the PERSEPHONE trial showed that 6 months of trastuzumab was not inferior to 12-month treatment and was associated with fewer severe adverse events and less cardiac toxicity.[274] Differences in the results of these trials can be explained, at least partially, by the different prespecified statistical analysis plan and patients in each study. At this point, 12 months of adjuvant therapy continues to be the standard for most patients who have HER2-positive disease.

The most used trastuzumab-based regimens in the neoadjuvant or adjuvant setting are the following:

- Combination docetaxel, carboplatin, and trastuzumab with or without pertuzumab
- ddAC followed by paclitaxel and trastuzumab with or without pertuzumab
- Paclitaxel and trastuzumab (in the adjuvant setting only)

The efficacy of the combination of trastuzumab with a non–anthracycline-containing regimen was evaluated in the BCIRG 006 trial. In this study, patients were randomly assigned to a combination of docetaxel, carboplatin, and trastuzumab, administered every 3 weeks for six cycles, or to four cycles of AC every 3 weeks, followed by four cycles of docetaxel with or without trastuzumab. The results of adding trastuzumab to chemotherapy led to improved DFS and OS. There was a non–statistically significant 3% absolute difference in the DFS rate and a 1% difference in the OS rate at 5 years, favoring the arm receiving AC with docetaxel and trastuzumab over the combination of docetaxel, carboplatin, and trastuzumab arm. However, the study was not designed to compare the two trastuzumab-containing arms, and any conclusions about the benefits of one regimen over another should be considered exploratory.[275] The combination of docetaxel, carboplatin, and trastuzumab was associated with less cardiac toxicity and risk of secondary leukemia compared with the AC and docetaxel arms, making it an acceptable treatment alternative.

Additional formulations of trastuzumab are available for patients. Two randomized trials, HannaH and SafeHER, showed comparability between a subcutaneous formulation of trastuzumab and the intravenous version, leading to US FDA approval.[276,277] A subcutaneous formulation of the combination of HP (HP hyaluronidase-oysk) has also received FDA approval. Finally, the FDA has also approved several biosimilar formulations of trastuzumab and noted no difference in safety or efficacy between biosimilars and the original biologic.

HER2-positive breast cancer is associated with a high response rate to neoadjuvant chemotherapy, which is increased substantially with the addition of HER2-directed treatment. Two studies evaluated neoadjuvant trastuzumab-containing regimens in which trastuzumab was administered with an anthracycline.[278,279] Both studies demonstrated that the addition of trastuzumab improved the pCR rate and reduced the risk of recurrence and death. Neoadjuvant HER2-directed therapy is most often used in patients with lymph node–positive disease or tumors larger than 2 cm in combination with pertuzumab (see next section).

Neoadjuvant/Adjuvant Pertuzumab

The NeoSphere trial was an open-label phase 2 study that randomly assigned 417 patients to receive four cycles of docetaxel combined with trastuzumab, pertuzumab, or both agents versus a combination of pertuzumab and trastuzumab without docetaxel (a nonchemotherapy arm).[280] The combination of pertuzumab and trastuzumab with docetaxel achieved the highest pCR rate of 39.3% compared with the other groups. All patients in the NeoSphere trial also received adjuvant treatment with three cycles of combined fluorouracil, epirubicin, and cyclophosphamide chemotherapy administered concomitantly with trastuzumab, followed by completion of 1 year of trastuzumab therapy. The TRYPHAENA trial studied the safety of neoadjuvant pertuzumab in combination with either docetaxel/carboplatin/trastuzumab or fluorouracil, epirubicin, and cyclophosphamide, followed by docetaxel in combination with HP or in sequence. Cardiac safety was acceptable for HP in sequence after anthracycline. pCR rates in breast and nodes were highest for docetaxel/carboplatin/trastuzumab with pertuzumab at 64%.

In the phase 3 APHINITY trial, 4,805 patients with HER2-positive, node-positive breast cancer or high-risk node-negative breast cancer were randomly assigned to adjuvant chemotherapy with trastuzumab and placebo or pertuzumab.[281] With a median follow-up of 74 months, the addition of pertuzumab to chemotherapy and trastuzumab was associated with a modest benefit, resulting in a 6-year iDFS rate of 91% compared with the placebo arm rate of 88% (HR, 0.76; 95% CI, 0.64-0.91). Treatment was effective in all subgroups; however, those who had node-positive and/or hormone receptor–negative disease seemed to derive the most benefit. Diarrhea was increased in the pertuzumab arm, predominantly during chemotherapy and with the combination docetaxel, carboplatin, and trastuzumab regimen. Cardiac toxicity was low and not different between the two arms.

As a result of these data, patients with tumors larger than 2 cm or nodal involvement are recommended to receive a neoadjuvant trastuzumab- and pertuzumab-based chemotherapy regimen, followed by adjuvant HER2-directed therapy; the type of adjuvant HER2 therapy will depend upon the presence of residual disease. The ASCO 2018 clinical practice guidelines state that clinicians may add 1 year of adjuvant pertuzumab to trastuzumab-based combination chemotherapy in patients with high-risk, early-stage, HER2–positive breast cancer for those who did not receive neoadjuvant therapy.[231,282]

Recently, a large neoadjuvant study tested fam-T-DXd, an ADC composed of trastuzumab conjugated to deruxtecan, a derivative of the camptothecin analog exatecan, a DNA topoisomerase 1 inhibitor in early-stage HER2+ breast cancer. In DESTINY-Breast11[264] patients with high-risk early-stage HER2+ breast cancer were randomized to T-DXd ×8 cycles, T-DXd-THP (4 + 4 cycles), or ddAC followed by paclitaxel + trastuzumab + pertuzumab (ddAC-THP; 4 + 4 cycles). The primary endpoint was pCR; pCR rates were 43.0% (T-DXd, *n* = 123), 67.3% (T-DXd-THP, *n* = 216), and 56.3% (ddAC-THP, *n* = 180). EFS data are immature, and the study is not powered for EFS. All-grade drug-related interstitial lung disease (ILD) rates were low and similar across arms (T-DXd-THP, 4.4%). The T-DXd containing arms had lower grade 3 or greater adverse events and fewer serious adverse events as well.

Residual Disease After Completion of Neoadjuvant Therapy

Patients who receive neoadjuvant chemotherapy with HER2 therapy and have residual disease at the time of surgery are at a higher risk of recurrence. In KATHERINE, a study of 1,486 patients who had residual invasive breast cancer after receiving neoadjuvant chemotherapy and HER2 therapy,[283] the use of T-DM1 after surgery was associated with improved DFS and a lower risk of distant recurrence compared with trastuzumab. Updated results after a median of 8.4 years of follow-up revealed a 4.7%

absolute benefit in OS at 7 years with T-DM1.[284] However, there were more serious adverse events with T-DM1 than with trastuzumab (13% vs 8%, respectively). This regimen has been adopted by many as the treatment of choice for patients who have residual disease. If the disease is also hormone receptor positive, adjuvant endocrine therapy is administered concurrently with T-DM1. Radiation may be delivered concurrently with T-DM1.

DESTINY-Breast05[285] reported results for patients who had either inoperable HER2+ breast cancer or residual nodal disease following neoadjuvant therapy. Participants were randomized to receive either T-DXd or T-DM1 for 14 cycles. The primary endpoint, iDFS, significantly favored T-DXd (9% absolute improvement in 3-year iDFS over T-DM1, reflecting a 53% reduction in risk (HR, 0.47; $P < .0001$). Efficacy endpoints, including distant DFS and central nervous system (CNS) recurrence, favored T-DXd. OS is immature, but a favorable trend was seen at this first interim analysis, with rates of 97.4% and 95.7%, respectively (HR, 0.61; 95% CI, 0.43-1.10). Rates of grade 3 or greater treatment-related AEs were comparable between arms; treatment-related ILD occurred in ~9% of patients receiving T-DXd.

Adjuvant Neratinib

In the ExteNET trial, which included 2,840 patients who had early-stage HER2-positive breast cancer who were within 2 years of completing adjuvant trastuzumab therapy, the 2-year iDFS rate was 94.2% among those who received adjuvant neratinib for 1 year compared with a rate of 91.9% in those receiving placebo. The most common adverse events were diarrhea, fatigue, rash, and stomatitis, with 16.8% of patients discontinuing treatment because of diarrhea.[286] These results led to FDA approval of neratinib for the extended adjuvant treatment of patients who have early-stage HER2-positive breast cancer after adjuvant trastuzumab-based therapy. After 8 years of follow-up, the benefit of iDFS was most pronounced in patients with hormone receptor–positive cancers who began neratinib within 1 year of trastuzumab; there is no observed difference in OS.[287] Concurrent administration of antidiarrheal prophylaxis is recommended with initiation of neratinib and is supported by the ASCO 2018 clinical practices guidelines.

Small, Node-Negative Tumors

Retrospective data suggest that small, node-negative, HER2-positive breast cancers have a small but tangible risk of distant recurrence. However, most patients with these cancers were not eligible for enrollment in the pivotal adjuvant trastuzumab clinical trials. The phase 2 APT trial explored the efficacy of a trastuzumab-containing adjuvant therapy regimen with a de-escalation of chemotherapy. The APT trial enrolled 406 patients with node-negative, HER2-positive breast cancer tumor size smaller than 3 cm.[288] In this single-arm study, patients received 12 weeks of paclitaxel (80 mg/m^2) and concurrent trastuzumab, followed by 9 months of single-agent trastuzumab therapy. The 7-year DFS rate was 93.3%, with only four DFS events (1%) being distant metastases. The regimen was well tolerated, with minimal neuropathy and cardiac compromise, and has become a common choice in patients who have node-negative, HER2-positive breast cancers smaller than 2 cm.

Adverse Events With HER2-Directed Therapies

Major toxicities associated with HER2-targeted therapies used in early breast cancer include the following:

- Cardiac toxicity: The addition of trastuzumab in the adjuvant studies resulted in a less than 4% difference in incidence of congestive heart failure or death between the treatment arms. However, up to 18% of patients experienced asymptomatic decreases in ejection fraction that prompted discontinuation of trastuzumab.[289] The risk of cardiac compromise was associated with advanced age, hypertension, preexisting cardiac dysfunction, and high BMI. Cardiac monitoring with echocardiography or multigated acquisition scan is recommended every 3 months during adjuvant trastuzumab treatment. Among patients with asymptomatic low ejection fraction, the decision to use HER2-targeted therapy must be made on an individual basis, assessing the relative risk of cardiac dysfunction from a specific regimen versus disease progression, and in collaboration with a cardiologist.[290] Concurrent administration of anthracyclines with HER2-targeted therapy increases the risk of heart failure and should be avoided.
- Diarrhea: The incidence of all-grade diarrhea across various studies with pertuzumab ranged from 28% to 72%, with grade 3 diarrhea in 0% to 12% of cases.[291] Diarrhea was common, occurred mainly during the first treatment cycle, and was manageable with antidiarrheal medications. Diarrhea is an important adverse effect of neratinib (21% of patients in the TBCRC 022 study had grade 3 diarrhea with low-dose loperamide prophylaxis). Prophylactic antidiarrheal medications should be started concurrently with neratinib.
- Rash: Overall, 22% of patients treated with HER2-targeted therapies,[292] including lapatinib and pertuzumab, experienced rash. Most dermatologic toxicities in patients receiving lapatinib present early and rarely require dose reduction or lead to treatment discontinuation.[293] Rash associated with EGFR inhibitors is typically acneiform, accompanied by pruritus and tenderness in 62% of patients, and can be managed with topical hydrocortisone and oral doxycycline or minocycline in most situations. In a meta-analysis with data from 1,726 patients, pertuzumab increased the risk of rash compared with control (relative risk, 1.53).[294]

KEY POINTS

- The recommended total duration of adjuvant trastuzumab is 12 months.
- The addition of 1 year of adjuvant pertuzumab concurrently with trastuzumab can be considered for high-risk patients because it provides a small absolute improvement in DFS.
- Pertuzumab, when administered concurrently with trastuzumab and taxane-based chemotherapy, is associated with a significantly increased pCR rate.
- In patients with residual disease after neoadjuvant chemotherapy, switching to T-DM1 after surgery is recommended.

INFLAMMATORY BREAST CANCER

Inflammatory breast cancer accounts for up to 2% of all breast cancers in the United States. Inflammatory breast cancer (T4d in TNM staging) is a clinical diagnosis in the setting of documented invasive breast cancer and is characterized by a rapid onset of clinical changes in the breast, including skin erythema, warmth, edema (peau d'orange), breast enlargement, and pain. These clinical criteria differentiate inflammatory breast cancer from a neglected locally advanced breast cancer with secondary inflammatory characteristics, which is associated with a more favorable prognosis.

Pathologically, tumor emboli are seen within dermal lymphatics in 75% of cases.[295] The classic physical findings of the breast are a result of damage to the dermal lymphatics caused by tumor emboli.[296] Breast imaging with mammography usually reveals asymmetrically increased density throughout the affected breast associated with skin thickening and axillary adenopathy. MRI is more sensitive and specific in detecting breast masses and confirming disease response to neoadjuvant chemotherapy compared with mammography.[297] Staging scans to rule out distant metastasis are recommended, given the locally advanced and aggressive behavior of inflammatory breast cancer.

Although all subtypes are seen in inflammatory breast cancer, HER2-positive or triple-negative subtypes are common.

Inflammatory breast cancer is treated with neoadjuvant chemotherapy, followed by mastectomy with axillary lymph node dissection and PMRT with comprehensive regional nodal irradiation.

Standard neoadjuvant chemotherapy, including combination anthracycline and taxane-based regimens, is recommended for inflammatory breast cancer. The combination of chemotherapy and HER2-directed therapy is recommended for HER2-positive inflammatory breast cancer. If the tumor is triple negative, then pembrolizumab and chemotherapy are offered as discussed earlier in this chapter. Adjuvant endocrine therapy and HER2-directed therapy are given as appropriate.

Breast conservation is contraindicated, as is SLNB in inflammatory breast cancer. A total mastectomy with levels 1 and 2 axillary lymph node dissection improves surgical control compared with surgery of lesser extent. Given the elevated risk of local recurrence, reconstruction of the breast is best deferred to avoid delays in the initiation of radiation therapy. Radiation therapy to the chest wall and regional lymph nodes (supraclavicular, infraclavicular, and internal mammary) is included in the treatment field.

If a patient is still not able to undergo surgery after completing an initial course of neoadjuvant chemotherapy, additional treatments should be pursued, including additional chemotherapy using different agents or radiation therapy.[298] For patients who present with metastatic disease or who develop metastatic disease during the initial course of therapy, treatment is similar to that for noninflammatory breast cancer.

KEY POINTS

- Inflammatory breast cancer is treated with neoadjuvant chemotherapy, followed by mastectomy with axillary lymph node dissection, PMRT, and adjuvant endocrine, anti-HER2, immunotherapy, and PARP inhibitor therapy, when indicated.
- Despite optimal multimodality care, DFS is worse in inflammatory breast cancer compared with noninflammatory breast cancer, even for patients who achieve pCR.

TREATMENT OF RECURRENT OR METASTATIC (STAGE IV) DISEASE

LOCOREGIONAL RELAPSE

Locoregional disease relapse can be defined as cancer recurrence in the ipsilateral breast, chest wall, or regional lymph nodes. In breast and even in chest wall, recurrence can be difficult to distinguish from a new primary cancer. Development after 5 years and/or in sites distant from the original site and the presence of in situ cancer, especially in chest wall lesions of normal breast tissue, are all indicators that the lesion may be a new, de novo primary cancer rather than a locoregional recurrence. Nodal recurrence in the contralateral axilla can occur as a result of aberrant drainage patterns, and breast imaging should be performed to exclude a new primary. These should be treated as new primary cancers.

Locoregional recurrences are frequently associated with distant metastases, and, therefore, full-body evaluation for metastases should be performed. If metastases are identified, a patient should be treated as per any patient with metastatic disease.

Although the prognosis for a locoregional recurrence is worse than for a new primary breast cancer, it is superior to that with distant metastases, and isolated locoregional recurrences are treated with curative intent.[299] Ipsilateral breast tumor recurrence

after breast conservation therapy has been associated with a three- to fourfold increase in the risk of developing systemic metastases.[300] Patients who experienced a chest wall recurrence after mastectomy fared worse, with a 6.68-fold greater risk of distant recurrence at 5 years and a 5.85-fold greater risk of death.

The treatment of locoregional recurrences requires a multidisciplinary approach. The standard treatment of ipsilateral in breast tumor recurrences that occur after breast conservation therapy usually occurs in the setting of prior radiation therapy and systemic therapy. Therefore, the standard of care is a total mastectomy, although excision and reirradiation can be considered for select patients.[301] In patients without prior radiation therapy, breast conservation therapy can be considered. If the axilla is clinically negative after assessment by clinical examination and ultrasonography, sentinel lymph node surgery can be attempted; however, it has a lower sentinel lymph node identification rate.[302] Axillary lymph node dissection should be considered in cases in which sentinel lymph nodes are not identified. In cases with clinically positive nodes or positive sentinel lymph nodes, axillary lymph node dissection should be performed.

Chest wall recurrences after mastectomy are more likely to be true recurrences rather than new primary cancer, and they occur most frequently within the first 5 years after treatment and rarely occur after 10 years. A majority of chest wall recurrences develop near the mastectomy incision, whereas fewer recurrences develop in the regional lymph node areas (in order of decreasing frequency: supraclavicular, axillary, and internal mammary). The treatment of an isolated chest wall recurrence requires surgical excision, if feasible, to obtain negative margins. The chest wall and supraclavicular lymph nodes should then receive standard radiation therapy if not administered previously.

Systemic therapy is often administered after completion of local treatment of a locoregional recurrence, although the data supporting its use are limited. The international CALOR (BIG 1-02/IBCSG 27-02/NSABP B-37) trial only enrolled 162 of planned 977 patients with invasive breast cancer in whom an isolated local and/or regional ipsilateral recurrence developed after mastectomy or breast conservation therapy.[303] Patients received radiation therapy and endocrine therapy as appropriate and were randomly assigned to receive chemotherapy of the physicians' choice or not. The 5-year DFS rate was improved with chemotherapy (69%) compared with no chemotherapy (57%). However, the benefits of chemotherapy were limited to ER–negative tumors, a finding confirmed after 9 years of follow-up.[304] Although highly underpowered, this study supports consideration of chemotherapy after local or regional disease recurrence in patients with triple-negative disease.

Patients who have ER–positive breast cancer should receive endocrine therapy. The precise type should be guided by the timing of the recurrence. If the patient was still taking or recurred soon after taking one type, her therapy should be switched to a different type. If the recurrence was many years after stopping prior adjuvant endocrine therapy, physicians can consider restarting that therapy or switching. There are no trial guidelines for this issue. Ongoing trials are addressing the benefits of adding CDK4/6 inhibition to the endocrine therapy after locoregional recurrence and local treatment. There are no trial data assessing the treatment of HER2-positive disease in this setting, but it is reasonable to initiate an effective anti-HER2 treatment.

KEY POINTS

- Locoregional recurrences require a multidisciplinary approach.
- Local recurrence is associated with a high rate of distant metastasis, and systemic imaging is recommended for these patients.
- After breast conservation therapy, the standard treatment of local recurrences involves a total mastectomy.
- The addition of chemotherapy after surgical management of a locoregional recurrence may benefit some patients, primarily those with ER–negative disease.

SYSTEMIC THERAPY FOR STAGE IV (METASTATIC) DISEASE

Treatment options for MBC depend on tumor characteristics, previous treatments, concern for organ failure as a result of metastatic disease (visceral crisis), disease burden, patient performance status, preferences, and comorbidities.[305,306]

The incorporation of new therapies over recent decades has resulted in a gradual improvement in OS rate by 1% to 2% per year.[307] The overall goals of treating MBC are to delay the progression of disease, improve quality of life, and prolong survival while minimizing treatment-associated toxicity. MBC is a chronic disease; sequential therapy is a mainstay of treatment.

Once metastatic disease is diagnosed, its extent should be determined by radiographic imaging. The most common initial sites of metastasis include bone, liver, and lung, which can be imaged by conventional CT and bone scan. FDG PET imaging can complement these studies, especially in the setting of lytic bone metastases, which may be underestimated on bone scan. Fluoroestradiol PET was FDA approved in 2021 for the detection of ER–positive lesions as an adjunct to biopsy in patients with recurrent or MBC. Appropriate use criteria for fluoroestradiol PET have been published.[308] CNS disease is less likely to be present at the initial appearance of metastatic disease, and MRI of the brain is not necessary in the absence of symptoms. Bone metastases are more common in the hormone receptor–positive subtype (68%), whereas TNBC is associated with a high frequency of metastasis to the lungs (40%). HER2-positive disease and TNBC are associated with a higher frequency of brain metastasis compared with the hormone receptor–positive subtype.[309]

Discordance of hormone receptor and HER2 status between the primary tumor and the metastatic disease can occur in 10% to 15% of patients. A biopsy of the metastatic disease at initial presentation is indicated to confirm the presence of MBC rather than another malignancy, either primary or metastatic, and to determine hormone receptor and HER2 status.

Biopsy of a metastatic lesion can also be sent for next-generation sequencing (NGS). NGS of tumors for alterations with a therapeutic target may identify additional therapies or eligibility in a clinical trial. Serum markers, such as cancer antigen 27.29 or 15-3, and carcinoembryonic antigen levels can complement the interpretation of imaging studies in metastatic disease but should not be used alone for monitoring response to treatment.[310] Despite promising data, the use of circulating tumor cells or circulating tumor DNA (ctDNA) in the interpretation of disease response and management remains investigational at this time.

HORMONE RECEPTOR–POSITIVE DISEASE

In hormone receptor–positive and HER2-negative advanced breast cancer, sequential endocrine therapy is preferred over cytotoxic chemotherapy as initial treatment, as endocrine-based therapy can be highly effective and well tolerated. NGS of tumor or of circulating tumor cells can identify tumor alterations for which there are increasing numbers of targeted therapies for patients with hormone receptor–positive and HER2-negative advanced breast cancer who were previously treated with AI therapy with/without CDK4/6 inhibitors for their advanced disease.

First-Line Therapy

CDK4/6 Inhibitors

The addition of CDK4/6 inhibitors to endocrine therapy is a major advance in the treatment of women with metastatic hormone receptor–positive breast cancer.[311] CDK4/6 inhibitors interfere with progression from the G1 to S phase of the cell cycle. When CDK4 and CDK6 are activated by d-type cyclins, they phosphorylate the retinoblastoma-associated protein, releasing its suppression of the E2F transcription factor family. The CDK4/6 inhibitors prevent progression through this checkpoint, leading to cell cycle arrest.[312]

Four prospective trials compared first-line AI therapy to the combination of an AI and a CDK4/6 inhibitor, as summarized in Table 10-6. All four trials revealed a consistent benefit in PFS with the three FDA-approved CDK4/6 inhibitors palboclib, ribociclib, and abemaclicilb. Trials of ribociclib revealed an OS benefit as well. Importantly, the CDK4/6 inhibitors have not been directly compared with one another.[313-324]

Despite extensive research, ER expression remains the only known predictive biomarker of response to CDK4/6 inhibitors. The CDK4/6 inhibitors, as a class, are generally well tolerated. The most common adverse effects of these agents include nausea, diarrhea, fatigue, neutropenia, anemia, and thrombocytopenia. Neutropenia is more common with palbociclib and ribociclib (although febrile neutropenia is rare), whereas diarrhea is the most common adverse effect of abemaciclib. Neutropenia is a common reason for dose reduction. Importantly, dose reduction does not seem to decrease the efficacy of palbociclib.[327] Other potential toxicities, including QT prolongation with ribociclib or elevation of aminotransferase levels, can occur and should be monitored in accordance with the agent chosen.

SONIA was an investigator-initiated trial that questioned the use of first-line CDK4/6 in combination with a nonsteroidal AI.[328] In this phase 3 trial, patients were randomly assigned to the control arm of an AI and a CDK4/6 inhibitor (91% received palbociclib) or an AI alone. Upon disease progression, those who received an AI alone received fulvestrant and the CDK4/6 inhibitor, whereas the control arm received fulvestrant alone. The primary endpoint was PFS after two lines of therapy (PFS2). Although median PFS was improved with up-front combination therapy, consistent with the prior phase 3 studies, there was no difference in median PFS2 at the median follow-up of 37 months. There was no difference in OS. Given the significant and consistent benefit of a first-line AI and a CDK4/6 inhibitor, the combination remains the standard of care as first-line treatment.

The phase 3 INAVO120 study randomized patients with endocrine-resistant hormone receptor–positive and HER2-negative breast cancer to first-line fulvestrant and palbociclib in combination with the PI3K inhibitor inavolisib or placebo. Eligible patients had tumors with a PIK3CA mutation by ctDNA, and patients experienced metastatic recurrence during or within 12 months of completing adjuvant endocrine therapy. The primary endpoint of PFS was improved from 7.3 months with fulvestrant, palbociclib, and placebo to 15 months with the triplet.[329] As will be elaborated further with similar drugs, the inavolisib arm experienced more adverse events of hyperglycemia, diarrhea, stomatitis, and rash. In October 2024, the FDA approved inavolisib in combination with fulvestrant and palbociclib as first-line therapy in patients described above. OS has been reported with a median OS of 34 months with the triplet therapy versus 27 months with fulvestrant and palbociclib.

Although endocrine therapy is recommended as first-line treatment in metastatic hormone receptor+ breast cancer, cytotoxic chemotherapy has been considered for those with visceral metastases. The phase 4 PADMA trial randomized previously untreated patients with hormone receptor+ and HER-negative MBC with an indication for mono-chemotherapy to endocrine therapy and palbociclib or mono-chemotherapy of the physician's choice (paclitaxel, capecitabine, epirubicin, or vinorelbine). The primary endpoint of median time to treatment failure was 17.2 months with endocrine therapy and palbociclib compared to 6.1 months with chemotherapy, and median PFS was 18.7 months versus 7.8 months, respectively. The results of PADMA have not been published, but provide reassuring evidence that first-line endocrine therapy and a CDK4/6 inhibitor remain the standard treatment.[330]

Table 10-6 **Trials With CDK4/6 Inhibitors**

Treatment	Study	Phase	Description	Median PFS, Months (HR, 95% CI)	Median OS, Months (HR, 95% CI)
First line	PALOMA-2	3	Palbociclib/letrozole vs placebo/letrozole	24.8 vs 14.5 (0.58, 0.46-0.72)	53.9 vs 51.2 (0.96, 0.777-1.177)[313]
	MONALEESA-2	3	Ribociclib/letrozole vs placebo/letrozole	25.3 vs 16.0 (0.56, 0.43-0.72)[314]	63.9 vs 51.4 (0.76, 0.63-0.93)[315]
	MONALEESA-7	3	Ribociclib/OFS/AI or tamoxifen vs placebo/OFS/AI or tamoxifen	23.8 vs 13.0 (0.55, 0.44-0.69)[316]	58.7 vs 40.9 (0.76, 0.61-0.96)[317]
	MONARCH-3	3	Abemaciclib/AI vs placebo/AI	28.2 vs 14.7 (0.54, 0.41-0.72)[325]	66.8 vs 53.7 (0.80, 0.64-1.01)[326]
First or second line	MONALEESA-3	3	Ribociclib/fulvestrant vs placebo/fulvestrant	20.5 vs 12.8 (0.59, 0.48-0.73)[318]	67.6 vs 51.8 (0.67, 0.50-0.90)[319]
Second line	PALOMA-3	3	Palbociclib/fulvestrant vs placebo/fulvestrant	9.5 vs 4.6 (0.46, 0.36-0.59)[320]	34.9 vs 28.0 (0.81, 0.65-0.99)[321]
	MONARCH-2	3	Abemaciclib/fulvestrant vs placebo/fulvestrant	16.4 vs 9.3 (0.55, 0.45-0.66)[322]	46.7 vs 37.3 (0.757, 0.61-0.94)[324]
Later line	MONARCH-1	2	Abemaciclib	6[323]	17.7[323]

Abbreviations: AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; HR, hazard ratio; OFS, ovarian function suppression; OS, overall survival; PFS, progression-free survival.
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Second-Line Therapy and Beyond

All three CDK4/6 inhibitors have also been evaluated after disease progression on endocrine therapy, as summarized in Table 10-6. The addition of a CDK4/6 inhibitor to fulvestrant improved PFS and OS compared with fulvestrant alone.

PI3K-AKT-PTEN Signaling Pathway

Overactivation of this signaling pathway through activating mutations in *PIK3CA* or *AKT1* or inactivation of *PTEN* occurs in 40% to 50% of hormone receptor–positive and HER2-negative breast cancers. The phase 3 CAPItello-291 trial randomized patients to capivasertib, the oral AKT inhibitor, and fulvestrant or to placebo and fulvestrant.[6] Forty percent of patients had a tumor AKT pathway alteration. Median PFS was significantly improved in the capivasertib versus placebo arms in the overall population (7.2 vs 3.6 months) and in the group with AKT pathway alterations (7.3 vs 3.1 months). The most common adverse event in the capivasertib arm was diarrhea in 72%, with 9.3% grade 3 and no grade 4 diarrhea. Rash was seen in 38%, including 12% with grade 3, followed by grades 1 and 2 nausea in 35%. Hyperglycemia was reported in 16%, with only 2% grade 3. In November 2023, the FDA approved capivasertib for patients with previously treated hormone receptor–positive and HER2-negative advanced breast cancer with alterations in the AKT pathway.

Similarly, the addition of the PIK3CA inhibitor alpelisib to fulvestrant improved median PFS compared with placebo and fulvestrant in the phase 3 SOLAR-1 trial.[331] The incidence of grades 3 and 4 hyperglycemia was 36%; 58% reported diarrhea, 6.7% was grade 3. Alpelisib was FDA approved in 2019 for PIK3CA-mutated hormone receptor–positive and HER2-negative advanced breast cancer. Subjects who had received prior alpelisib were excluded from the CAPItello trial, and the optimal sequencing to target the PI3K-AKT-PTEN pathway is unknown.

Estrogen Receptor 1

Mutations in estrogen receptor 1 (ESR1) result in estrogen-independent ER activation and potential resistance to AIs but not ER inhibitors. Elacestrant is an oral selective estrogen receptor degrader (SERD). In the phase 3 EMERALD trial,[332] patients with previously treated MBC, including a prior CDK4/6 inhibitor, were randomized to endocrine monotherapy or elacestrant. Approximately 48% of the study population had a tumor ESR1 mutation, and PFS was significantly improved in both the overall population and those with tumor ESR1 mutations. The most common adverse event with elacestrant was nausea in 35%, 2.5% with grade 3 or 4. Elacestrant was FDA approved in 2023 for ESR1-mutated hormone receptor–positive and HER2-negative advanced breast cancer. Patients with previously treated MBC, including a prior CDK4/6 inhibitor, were randomized to endocrine monotherapy or elacestrant. Approximately 48% of the study population had a tumor ESR1 mutation, and PFS was significantly improved in both the overall population and those with tumor ESR1 mutations. The most common adverse event with elacestrant was nausea in 35%, 2.5% with grade 3 or 4. Elacestrant was FDA approved in 2023 for ESR1-mutated hormone receptor–positive and HER2-negative advanced breast cancer.

The EMBER 3 trial compared the SERD imlunestrant to standard endocrine monotherapy or to the combination of imlunestrant and abemaciclib after progression on first-line endocrine therapy with/without a CDK4/6 inhibitor. The median PFS was significantly improved with imlunestrant compared with endocrine monotherapy among patients with ESR1 mutations (5.5 vs 3.8 months).[3] The combination of imlunestrant and abemaciclib was associated with improved median PFS compared to imlunestrant alone (9.4 vs 5.5 months). Imlunestrant was FDA-approved in patients with metastatic hormone receptor–positive and HER2-negative breast cancer with an ESR1 mutation after one line of endocrine therapy.

Mammalian Target of Rapamycin Inhibitors

The phosphoinositide-3 kinase–AKT–mammalian target of rapamycin (mTOR) pathway is associated with the development of endocrine resistance.[333] The addition of everolimus, an oral mTOR inhibitor, to endocrine therapy was hypothesized to reverse endocrine resistance. In the phase 3 BOLERO-2 trial, 724 postmenopausal women whose disease progressed or recurred while receiving a nonsteroidal AI were randomly assigned to receive everolimus and exemestane or exemestane alone.[334] The median PFS was improved with combination therapy from 4.1 to 10.6 months. Everolimus is associated with a relatively common risk of stomatitis and a small but potentially serious risk of pneumonitis. Use of a steroidal mouthwash reduces the incidence of stomatitis.[335] A combination of everolimus and exemestane is an option for patients with disease progression after a nonsteroidal AI.

Sequencing of Endocrine Therapy

There is little guidance regarding the optimal sequencing of endocrine therapy in MBC. In patients who do not receive CDK4/6 inhibitors as first-line therapy, the PALOMA-3, MONALEESA-3, and MONARCH 2 trials support the use of these agents in the second line. However, given the efficacy and favorable toxicity profile, almost all patients will receive a CDK4/6 inhibitor for first-line treatment of hormone receptor–positive breast cancer. Select patients may be treated with endocrine therapy alone because of comorbidities and/or indolent low-burden disease (Fig. 10-8).

Patients who experience progression after treatment that includes a CDK4/6 inhibitor can be offered appropriate targeted therapy based on NGS, such as capivasertib, alpelisib, elacestrant, or imlunestrant. There are no data on the optimal sequencing of targeted therapies if a tumor harbors an alteration in both ESR1 and PIK3CA. Likewise, there are no robust data on treatment with another ESR1 antagonist or PID3CA inhibitor after prior treatment.

If no targeted alterations are identified, results of the phase 3 postMONARCH trial suggest changing endocrine therapy and continuing treatment with the CDK4/6 inhibitor abemaciclib.[336] Ninety percent of subjects had received either palbociclib or ribociclib in combination with an AI as first-line therapy for metastatic hormone receptor–positive and HER2-negative breast cancer. Upon progression, patients were randomly assigned to fulvestrant alone or in combination with abemaciclib. Median PFS improved from 5.3 months with fulvestrant to 6 months with fulvestrant and abemaciclib. The FDA has not approved abemaciclib in this setting. Other options include the combination of everolimus and exemestane or tamoxifen.[337] Patients are given sequential endocrine therapy regimens before switching to palliative chemotherapy. Olaparib or talazoparib is an option for patients with germline BRCA mutations (see discussion in "Biomarker-Guided Approach to Metastatic TNBC: Germline BRCA1 and BRCA2 Mutation Carriers" section).

Cytotoxic Chemotherapy

Despite these advances and new agents, patients with hormone receptor–positive breast cancer may either exhaust endocrine therapy options or experience tumor resistance. Cytotoxic chemotherapy and, more recently, ADCs are options. Single-agent therapies are sequenced based on patient preference and side effect profiles. (See discussion in "Triple-Negative Breast Cancer" section.)

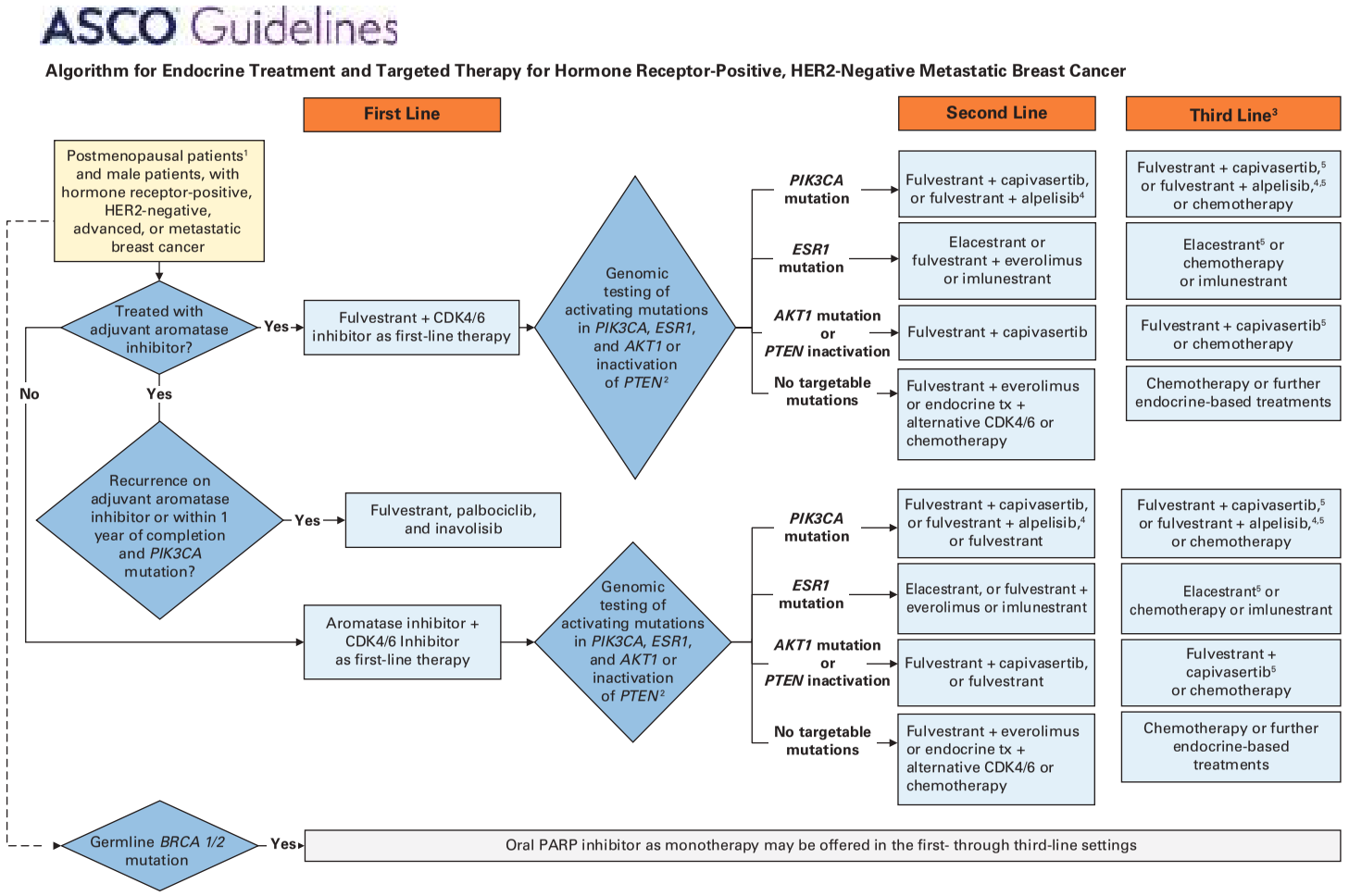
Antibody-Drug Conjugates

T-DXd is a HER2 monoclonal antibody linked to a topoisomerase inhibitor. It is approved in metastatic HER2-positive breast cancer (see discussion in "HER2-Positive Breast Cancer" section). However, T-DXd has demonstrated efficacy in breast cancers with low levels of HER2 (either 1+ staining by IHC or 2+ by IHC and FISH negative). The DESTINY BREAST-04 trial randomized patients with "HER2-low" previously treated advanced breast cancer to T-DXd or the physician's choice of chemotherapy (PCC), which included capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.[338] Notably, 90% of patients had tumors that were hormone receptor positive. Both PFS and OS were significantly improved with T-DXd compared with PCC. T-DXd was FDA approved in 2022 for previously treated "HER2-low" advanced breast cancer.

DESTINY BREAST-06 included patients with hormone receptor–positive and "HER2-low" breast cancer, as defined above, as well as "HER2-ultra low" breast cancer, defined as HER2 0 or 1+ by IHC with some membrane staining. Patients had received more than one line of endocrine therapy but no prior chemotherapy for MBC. They were randomized to T-DXd or PCC, including capecitabine, nab-paclitaxel, or paclitaxel. Median PFS was significantly improved to 13.2 months with T-DXd compared to 8.1 months with PCC. Trastuzumab dertuxtecan was FDA approved in this setting in January 2025.[339]

Sacituzumab govitecan is a Trop-2 monoclonal antibody conjugated to SN-38, the active metabolite of irinotecan. TROPiCS-02 randomized patients with previously treated hormone receptor–positive and HER2-negative advanced breast cancer to sacituzumab govitecan or PCC, which included eribulin, vinorelbine, capecitabine, or gemcitabine.[340] In this phase 3 trial, PFS and,

Figure 10-8 Suggested Treatment Sequencing in Hormone Receptor–Positive and HER2–Negative MBC



Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CLIA, Clinical Laboratory Improvement Amendments; ESR1, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; OFS, ovarian function suppression; PARPi, poly-ADP-ribose polymerase inhibitor; PTEN, phosphatase and tensin homolog protein.

BRCA mutation options: olaparib or talazoparib.

[1]If patient is premenopausal, initiate ovarian suppression and continue as postmenopausal.

[2]Tumor genomic testing includes sequencing for targetable mutations, accomplished through large panel tumor genomic testing in a CLIA-certified laboratory performed on tissue or plasma obtained either at the time of progression or from archival tissue. In addition to selecting patients whose tumors have increased PIK3CA or AKT1 activity because of the presence of activating mutations, it is also important to identify those whose tumors have inactivation of phosphatase and tensin homolog (PTEN) protein. PTEN inactivation can be identified based on the presence of premature stop codons, frameshift alterations, splice site mutations, PTEN homozygous deletion, PTEN rearrangements that disrupt protein function, or specific missense mutations (*C124R*, *C124S*, *G129E*, *G129V*, *G129R*, *R130Q*, *R130G*, *R130L*, *R130P*, *C136R*, *C136Y*, *S170R*, and *R173C*), on next-generation sequencing.

[3]There are few data on the value of older endocrine treatment options after therapy with modern treatment regimens such as AIs, SERDs, CDK4/6 inhibitors and/or other targeted agents. In select patients—typically those with indolent cancers, limited disease burden or symptoms, and demonstrated clinical benefit from prior endocrine treatments—therapies such as tamoxifen, megestrol acetate, or reintroduction of previously administered treatments may be of clinical value.

[4]Alpelisib is an option for patients with tumors harboring PIK3CA activating mutations but not AKT1 activating mutations or PTEN inactivation.

[5]If not previously given.

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subsequently, OS were improved with sacituzumab govitecan compared with PCC (median 5.5 vs 4 months and median 14.4 vs 11.2 months, respectively).[341] Sacituzumab govitecan was FDA approved in 2023 for patients with previously treated hormone receptor–positive and HER2-negative breast cancer.

Datopotamab deruxtecan (Dato-DXd) is a Trop-2 monoclonal antibody conjugated to a topoisomerase inhibitor payload. TROPION-Breast 01 randomized patients with previously treated hormone receptor–positive and HER2-negative advanced breast cancer, who had received up to two lines of chemotherapy in the metastatic setting, to Dato-DXd or to the investigator's choice of chemotherapy (ICC; eribulin, capecitabine, vinorelbine, or gemcitabine). The dual primary endpoints were PFS and OS. PFS was significantly improved on Dato-DXd compared with ICC (median 6.9 vs 4.9 months, respectively). OS data were not mature at this analysis.[342] Dato-DXd was FDA approved in January 2025 for patients previously treated with endocrine therapy or chemotherapy.

TRIPLE-NEGATIVE BREAST CANCER

Patients who have TNBC generally have a worse prognosis than those with either hormone receptor or HER2-positive cancers. Until recently, the only option was standard chemotherapy. However, over the last decade, several new treatments for metastatic TNBC have been introduced, many of them targeted to specific biomarkers present in the cancer.

General Principles of Chemotherapy in MBC

Chemotherapy, in some cases with immunotherapy, has generally been the treatment of choice for metastatic hormone receptor–negative breast cancer. It is also indicated in hormone receptor–positive breast cancer in the setting of rapidly progressing or symptomatic disease, disease associated with visceral crisis, or development of endocrine resistance. Sequential use of single-agent chemotherapy is recommended instead of combination chemotherapy regimens. Although combination chemotherapy is associated with a higher chance of response, it is also associated with more toxicity without a survival benefit. The exception to this rule is the presence of visceral crisis or rapidly progressive disease that would benefit from prompt cytoreduction.

The duration of treatment must be tailored to each patient, considering the toxicity of treatment, control of disease-related symptoms, and patient goals for treatment and quality of life. Patients whose disease is responding well to chemotherapy without significant toxicity may remain on treatment, whereas chemotherapy holidays are appropriate for patients who require time to recover from toxicity and whose disease may be responsive to less toxic targeted therapy.

Biomarker-Guided Approach to Metastatic TNBC: Immunotherapy

The first-line treatment of advanced TNBC is guided by the PD-L1 status of the tumor and influenced by the disease-free interval from any prior adjuvant therapy. Pembrolizumab in combination with chemotherapy has been, until recently, the preferred treatment of patients with previously untreated locally recurrent, unresectable, or metastatic TNBC whose tumors express PD-L1, defined by a combined positive score (CPS) of 10 or higher, based on the results of the KEYNOTE-355 trial.[343] This double-blind phase 3 trial randomly assigned 847 patients to pembrolizumab or placebo in combination with chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine, and carboplatin). In patients with CPS of 10 or higher, the addition of pembrolizumab to chemotherapy improved PFS from 5.6 to 9.7 months. The median OS was 23.0 months (95% CI, 19.0-26.3) in the pembrolizumab-chemotherapy group and 16.1 months (95% CI, 12.6-18.8) in the placebo-chemotherapy group (HR for death, 0.73; 95% CI, 0.55-0.95; two-sided $P = .0185$). The benefit of checkpoint inhibition with chemotherapy is uncertain upon recurrence after neoadjuvant and adjuvant pembrolizumab (Fig. 10-9).

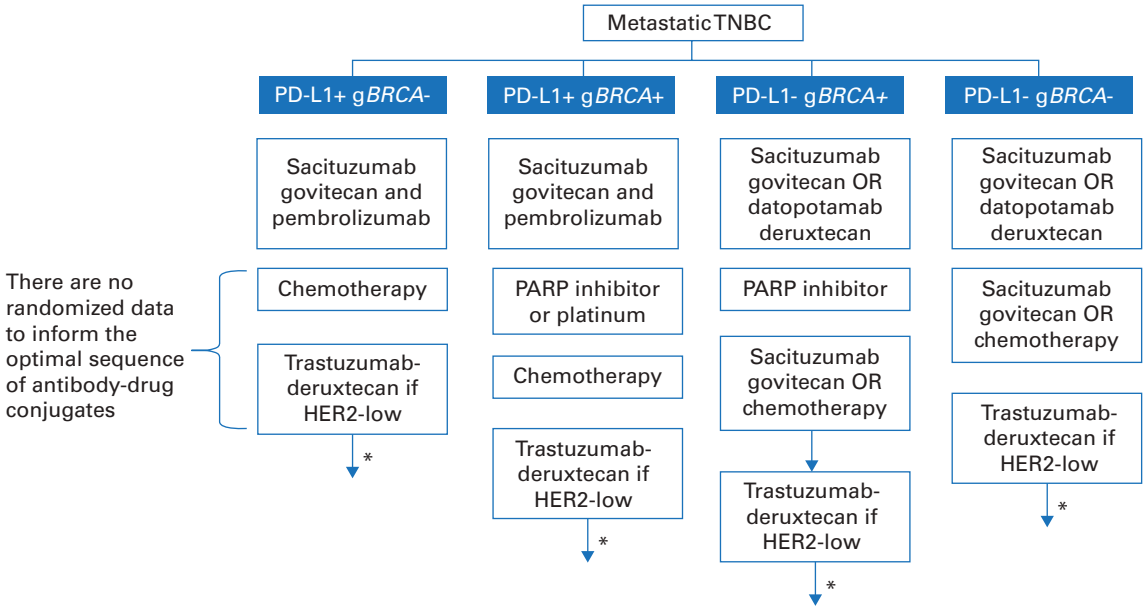
More recently, the phase 3 ASCENT-04 trial evaluated the combination of sacituzumab govitecan plus pembrolizumab versus chemotherapy plus pembrolizumab in the first-line setting. This study demonstrated a clinically meaningful improvement in progression-free survival (median 11.2 vs 7.8 months) and supports the integration of antibody-drug conjugate–based combinations with immunotherapy. As a result, sacituzumab govitecan plus pembrolizumab is emerging as a preferred first-line option for patients with PD-L1-positive metastatic triple negative breast cancer (TNBC).[344]

Single-agent immunotherapy with pembrolizumab may also be appropriate. In the Keynote-119 trial, patients who had MBC and who had received one or more prior chemotherapies were randomly assigned to receive either pembrolizumab (312 [50%]) or chemotherapy of the physician's choice. Median OS was similar in the two groups. Toxicities were as expected in each of the two arms, with one toxicity-related death in the pembrolizumab group and two in the chemotherapy group. Furthermore, pembrolizumab has received an "agnostic" (tumor nonspecific) approval by the FDA for cancers in which the tumor mutational burden is 10 or higher.[345,346]

Biomarker-Guided Approach to Metastatic TNBC: Germline *BRCA1* AND *BRCA2* Mutation Carriers

Patients who have germline *BRCA1* and *BRCA2* mutations seem to derive specific benefit from platinum compared with non-*BRCA1* and non-*BRCA2* mutation carriers. For those patients with germline *BRCA1* and *BRCA2* mutations and a PD-L1–negative tumor, either a platinum or PARP inhibitor is preferred.

Figure 10-9 Approach to Metastatic TNBC



Abbreviation: TNBC, triple negative breast cancer.
*Subsequent lines of therapy should be considered based on performance status and patient goals and values; options include single-agent cytotoxic therapy and select biomarker-driven therapies. Clinical trials may be considered at each decision point.
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In the phase 3 TNT trial,[347] patients who had metastatic TNBC were randomly assigned to carboplatin or docetaxel, and carboplatin was not more active than docetaxel in the unselected population. By contrast, in the group of patients with germline *BRCA1* and *BRCA2* mutations, carboplatin had double the objective response rate of docetaxel (68% vs 33%; $P = .01$).

Two PARP inhibitors, olaparib and talazoparib, are approved for patients who have HER2-negative advanced breast cancer with germline *BRCA1* and *BRCA2* mutations. The phase 3 OlympiAD trial evaluated olaparib as monotherapy compared with chemotherapy (physician choice of capecitabine, eribulin, or vinorelbine) in patients who had germline *BRCA*-mutated HER2-negative advanced breast cancer.[348] Olaparib was associated with an objective response rate of 60% and a superior median PFS of 7.0 months compared with an objective response rate of 29% and a median PFS of 4.2 months for patients receiving chemotherapy (HR, 0.58; $P = .0009$). More low-grade adverse events occurred in those receiving olaparib (primarily nausea and vomiting), whereas there were more high-grade adverse events in those receiving chemotherapy (primarily neutropenia). In the phase 3 EMBRACA trial,[349] 431 patients with advanced breast cancer and a germline *BRCA1* or *BRCA2* mutation were assigned, in a two-to-one ratio, to receive talazoparib (1 mg once daily) or a physician's choice of standard single-agent therapy. The median PFS was significantly longer in the talazoparib group (8.6 vs 5.6 months; HR, 0.54; $P < .001$). Talazoparib caused more grades 3 and 4 anemias than standard chemotherapy (55% vs 38%), although patient-reported outcomes favored talazoparib.

The role of platinum after progression during PARP inhibitor treatment and vice versa is currently unclear, given the concern for similar mechanisms of resistance. The optimal sequencing of therapies for patients with germline *BRCA1* and *BRCA2* mutations and HER2-negative MBC also remains unclear.

Biomarker Negative: BRCA-Wild Type and PD-L1-Negative

For those patients who do not have *BRCA1* or *BRCA2* mutations and a PD-L1–negative tumor, the use of cytotoxic chemotherapy has been the standard of care until recently. Anthracyclines and taxanes are active chemotherapies for MBC. Capecitabine, an antimetabolite, is also commonly used for the treatment of metastatic disease, given that it is an oral drug and has a favorable toxicity profile with little alopecia. However, most patients with TNBC have already received anthracycline, taxane, platinum, and capecitabine in the curative intent setting; when disease recurs, the preferred choice of first-line therapy is an antibody-drug conjugate (ADC). ADCs are a class of therapeutic agents that combine monoclonal antibodies with highly potent anticancer agents through a chemical linker.

Two trials have recently tested the use of anti-TROP2 ADCs in the first-line setting for the treatment of patients with TNBC who are not candidates for immunotherapy. The ASCENT03 trial[350] compared sacituzumab govitecan to investigator choice chemotherapy (taxane or gemcitabine/carboplatin) in patients who had at least a 6-month disease-free interval from adjuvant therapy. The primary endpoint of PFS favored sacituzumab (median PFS 9.7 vs 6.9 months [HR, 0.62, $P < .001$]). The TROPION-Breast 02[351] trial tested Dato-DXd compared to investigator choice chemotherapy (taxane, carboplatin, eribulin, or capecitabine) in patients with advanced TNBC; this study population allowed for rapid progressors with 15% having a disease-free interval

of <6 months. The primary endpoint was powered for both PFS and OS. Dato-DXd was found to have statistically significant superiority of PFS (10.8 months vs 5.6 months, HR, 0.57) and OS (23.7 months vs 18.7 months, HR, 0.79). Although neither study included a significant portion of patients progressing after exposure to checkpoint inhibitors in the (neo)adjuvant setting, they will likely become the new standard of care for first-line metastatic TNBC.

As described, T-DXd was associated with longer PFS and OS in patients who had HER2-low advanced breast cancer in the DestinyBreast-04 trial. This trial was primarily for patients who had hormone receptor–positive breast cancer; however, about 10% of the study included patients with ER/pR–negative HER2-low disease (N = 58). In this hypothesis-generating subset, T-DXd improved median PFS (8.5 vs 2.9 months) and OS (18.2 vs 8.3 months) compared with standard of care chemotherapy. As a result, this ADC is a preferred option for second-line or later treatment of patients with TNBC that is HER2 low.

Tumor sequencing may reveal actionable somatic mutations to allow for third-line and later targeted therapies. For example, a high tumor mutational burden or MSIH is an indication for a single-agent checkpoint inhibitor even if CPS is lower than 1. NTRK fusion allows for larotrectinib or entrectinib therapy, and RET fusion is an indication for selpercatinib. However, these alterations are unfortunately uncommon in breast cancer.

Sacituzumab govitecan-hziy is a monoclonal antibody against Trop-2 conjugated via a cleavable linker to SN-38, the active metabolite of irinotecan. The randomized phase 3 ASCENT trial compared single-agent sacituzumab to treatment of PCC in more than 500 patients with metastatic TNBC who had received at least two previous therapies (inclusive of adjuvant treatment). Sacituzumab demonstrated a median PFS of 5.6 months compared with 1.7 months with chemotherapy (HR, 0.39; 95% CI, 0.31-0.49, $P < .0001$). Median OS was significantly longer with sacituzumab as well (12.1 vs 6.7 months, HR, 0.48; 95% CI, 0.39-0.59, $P < .0001$). The most common adverse reactions (25% or more of patients) associated with sacituzumab govitecan-hziy were nausea, neutropenia, diarrhea, fatigue, anemia, vomiting, alopecia, constipation, rash, decreased appetite, and abdominal pain. There are no prospective randomized data to inform the optimal sequence of ADCs.

HER2+ BREAST CANCER

The introduction of HER2-targeted therapy led to an unprecedented survival gain in metastatic disease compared with the benefit historically reported with chemotherapy alone. The OS of patients who have HER2-positive MBC has increased from 20.3 months reported with chemotherapy alone to 57.1 months seen with the addition of HER2-targeted therapy (trastuzumab, pertuzumab, and docetaxel in the CLEOPATRA trial).[352-355] Given this survival benefit, most patients who have HER2-positive MBC will initiate treatment with chemotherapy in addition to one or more HER2-targeted therapies. The next sections present a summary of the relevant studies in patients who have advanced HER2-positive breast cancer (Fig. 10-10).

The CLEOPATRA trial randomly assigned 808 patients with HER2-positive MBC to receive placebo, trastuzumab, and docetaxel or pertuzumab, trastuzumab, and docetaxel as first-line treatment. The primary endpoint was independently assessed PFS. The addition of pertuzumab led to an improvement of 6.1 months (from 12.4 to 18.5 months) in PFS and 16.3 months (from 40.8 to 57.1 months) in OS. The 8-year landmark OS rates were 37% for the pertuzumab group and 23% for the control group.[352,353] The combination of trastuzumab, pertuzumab, and a taxane is considered optimal first-line therapy per ASCO guidelines.[306,356] The PERUSE trial demonstrated equivalent outcomes, regardless of the specific taxane (docetaxel, paclitaxel, or nab-paclitaxel) combined with HP.[357]

With this regimen, chemotherapy is recommended for at least 4 to 6 months or until maximum response, whereas HER2 therapy is continued until disease progression. For patients who have hormone receptor–positive and HER2-positive disease, endocrine therapy may be added when chemotherapy is discontinued. If a patient completed trastuzumab-based adjuvant treatment in the last 6 months before recurrence (ie, treatment-free interval less than 6 months), second-line therapy should be adopted.

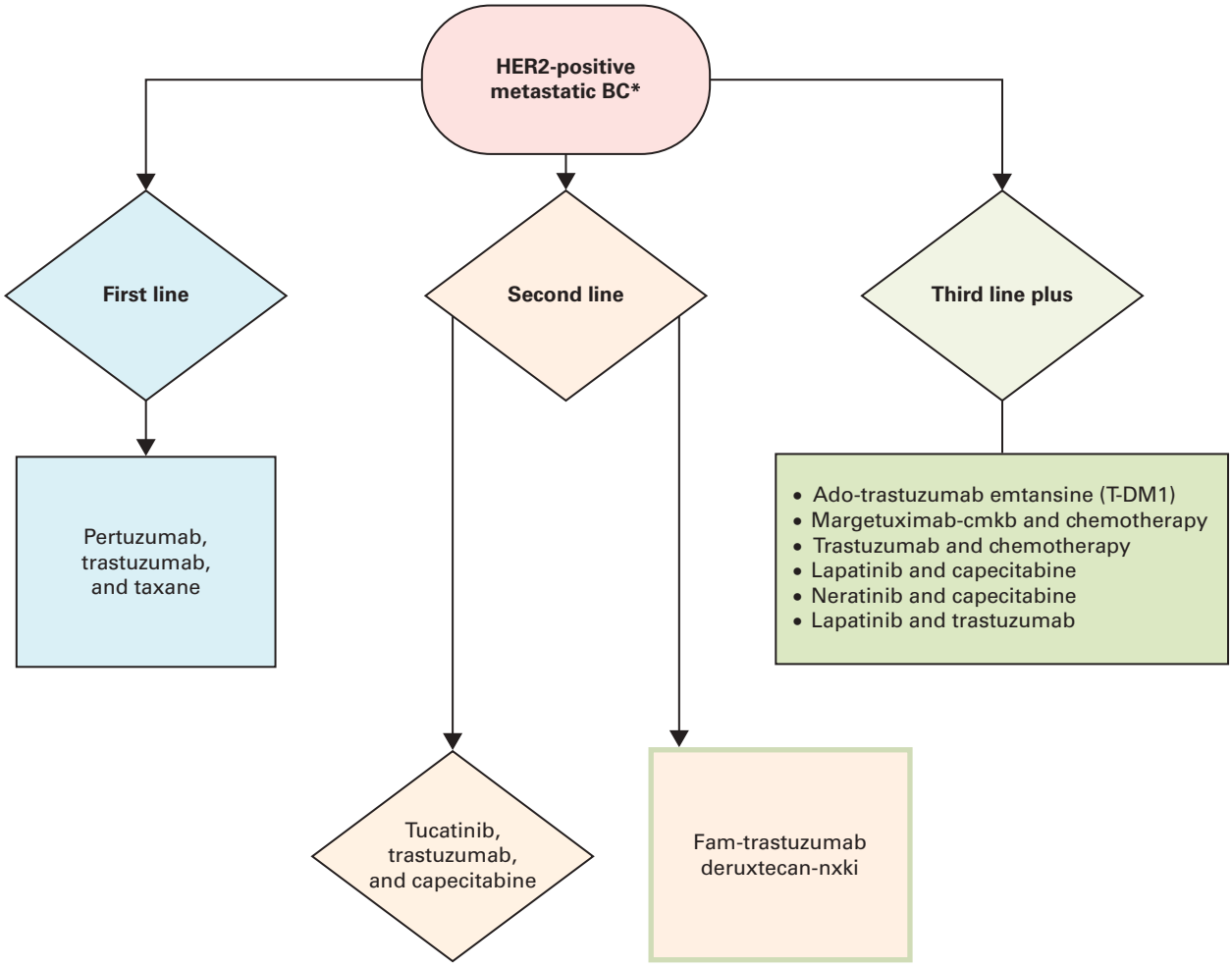
For patients with hormone receptor-positive, HER2-positive breast cancer, the PATINA trial recently demonstrated that adding the CDK4/6 inhibitor palbociclib to standard anti-HER2 and endocrine therapy significantly extended PFS in those who had not progressed following induction chemotherapy with HER2-directed therapy (median PFS 44.3 vs 29.1 months). This may offer a less toxic maintenance approach for certain patients.[358]

Recently, the results of DESTINY-Breast09 were presented at ASCO 2025.[359] This global phase 3 trial randomized patients with HER2+ MBC in the first-line setting to taxane, HP versus Pertuzumab with fam-trastuzumab deruxtecan-nxki, an ADC composed of trastuzumab conjugated to deruxtecan, a derivative of the camptothecin analog exatecan, a DNA topoisomerase 1 inhibitor. The study has met its primary endpoint for PFS with a median PFS of 40.7 months for T-DXd with pertuzumab compared to 26.9 months with THP (HR, 0.56, $P < .00001$). There were no new safety signals. OS data are immature at this time.

Second-Line Therapy: Fam-Trastuzumab Deruxtecan-nxki

In DESTINY-Breast01, a multicenter, open-label, single-arm phase 2 trial, patients with HER2-positive advanced breast cancer previously treated with two or more anti-HER2 therapies were enrolled. The objective response rate was 60.3%, and the median duration of response was 14.8 months. Fatal outcomes because of ILD occurred in 2.2% of patients.[360] The median OS was 24.6 months, and the 18-month OS rate was 74%.[361]

Figure 10-10 Suggested Treatment Sequencing in HER2-Positive Metastatic Breast Cancer



*For select patients with hormone receptor–positive, HER2-positive tumors, endocrine therapy and trastuzumab ± pertuzumab may be considered.
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The DESTINY-Breast03 trial compared T-DXd and T-DM1 in the second-line setting. At the first interim analysis with a median follow-up of 16 months, the median PFS was 6.8 months with T-DM1 and not yet reached with T-DXd (HR, 0.2840; $P = 7.8 \times 10^{-22}$).[362] In the second interim analysis, the median PFS was 28.8 months for T-DXd and 6.8 months for T-DM1 (HR, 0.33; 95% CI, 0.26-0.43; nominal $P < .0001$) with 28.4 and 26.5 months of follow-up, respectively. Two-year OS was 77.4% with T-DXd and 69.9% with T-DM1.[363] Based on these data, T-DXd is recommended as second-line therapy for patients who have experienced progression with trastuzumab and a taxane.

Second-Line Therapy: Tucatinib

Tucatinib is an oral tyrosine kinase inhibitor with selective inhibition of HER2 enzymatic activity and reduced potency against EGFR, which differentiates it from lapatinib and neratinib. The phase 3 HER2CLIMB trial enrolled participants who had HER2-positive MBC previously treated with trastuzumab, pertuzumab, and T-DM1. Patients were randomly assigned to receive tucatinib and trastuzumab and capecitabine or placebo and trastuzumab and capecitabine. The addition of tucatinib led to improvements in PFS (5.6-7.8 months; HR, 0.54) and OS (17.4-21.9 months; HR, 0.66).[364] Overall, 48% of patients had brain metastases at baseline, including patients with untreated brain metastases. In the tucatinib-containing arm, there was a 68% reduction in the risk of CNS PFS and a 42% reduction in the risk of death overall.[365] Tucatinib in combination with capecitabine and trastuzumab is a reasonable second-line treatment option, particularly in patients who have CNS metastases or in patients with contraindication to T-Dxd (such as clinically significant lung disorders).

Third-Line Therapy and Beyond

The EMILIA study compared T-DM1 with lapatinib and capecitabine in patients who had previously received trastuzumab and a taxane. Treatment with T-DM1 resulted in a 3-month improvement in PFS and a 32% reduction in the risk of death compared with lapatinib and capecitabine, with less toxicity. The TH3RESA study demonstrated the superiority of T-DM1 compared with treatment of physician choice, with approximately 30% of the patients enrolled having received more than five prior regimens for recurrent disease.[366]

Lapatinib is an oral dual tyrosine kinase inhibitor selective for the inhibition of EGFR and HER2 and can be administered either in combination with trastuzumab or in combination with capecitabine.[367,368] Neratinib is an irreversible oral pan-HER2 tyrosine kinase inhibitor, whereas lapatinib and tucatinib are both reversible tyrosine kinase inhibitors. The phase 3 NALA trial evaluated the efficacy of neratinib for patients with metastatic HER2–positive breast cancer who received at least two prior anti-HER2–based regimens in the metastatic setting.[369] Patients were randomly assigned to neratinib and capecitabine compared with lapatinib and capecitabine. Neratinib was associated with a statistically significant improvement in PFS (8.8 vs 6.6 months; HR, 0.76; 95% CI, 0.63-0.93) and a non-statistically significant improvement in OS (21 vs 18.7 months; HR, 0.88; 95% CI, 0.72-1.07).

The GBG 26/BIG 3-05 study confirmed the benefit of continuing trastuzumab with alternative chemotherapy after disease progression with combination chemotherapy and trastuzumab. Based on these data, continuing trastuzumab beyond progression is considered standard of care.[370]

Margetuximab is a chimeric Fc-engineered monoclonal antibody that targets HER2. Margetuximab was engineered with an Fc domain to enhance the engagement of the immune system and has HER2 binding and antiproliferative effects similar to trastuzumab. In the SOPHIA study, a phase 3 open-label trial including 536 patients, margetuximab and chemotherapy were associated with an improved median PFS (5.8 vs 4.9 months) and median OS (21.6 vs 19.8 months) compared with trastuzumab with chemotherapy.[371] Exploratory PFS analysis by CD16A genotype suggested that the CD16A-158F allele may predict a benefit of margetuximab over trastuzumab.

Approximately 45% of HER2-positive breast cancers are also hormone receptor positive, and targeted therapy for both receptors is indicated. Cross-talk exists between HER2 and ER, resulting in relative resistance to endocrine therapy alone in HER2-positive disease. In clinical trials, the addition of trastuzumab to anastrozole and lapatinib to letrozole resulted in a significant but modestly improved PFS and clinical benefit compared with endocrine treatment alone in patients with hormone receptor–positive, HER2-positive metastatic disease. However, an OS advantage was not seen, possibly because of the crossover study designs.[372]

BRAIN METASTASES

Brain metastases are diagnosed in approximately 15% of patients with metastatic disease[373] and have become more common with the improvement in systemic therapies. The risk of brain metastases is greater in patients with TNBC and HER2-positive breast cancer. Recommendations regarding presentation, diagnosis, symptomatic control, and supportive care of brain metastases are discussed in Chapter 18: Central Nervous System Tumors.

The approach to brain metastases in breast cancer is determined by tumor subtype, number and size of lesions, the presence or absence of obstruction of cerebrospinal fluid flow, and overall prognosis. Patients with good performance status and controlled systemic disease benefit from aggressive treatment with the goal of optimal local control. Options for local treatment include surgery, stereotactic radiation, and whole-brain radiation therapy, with the following recommendations:

- Surgery should be strongly considered in patients presenting with a single metastasis and stable or absent extracranial disease.[374]
- Surgery has a limited role in patients with more than one brain metastasis, except when a large symptomatic lesion is also present.
- In the presence of multiple lesions, either stereotactic radiosurgery, whole-brain radiation therapy, or the combination is usually preferred.

Whole-brain radiation therapy decreases the risk of intracranial recurrence but does not seem to increase survival, and stereotactic radiosurgery is often preferred to decrease the risk of neurocognitive impairment associated with whole-brain radiation therapy.[375] There are no FDA-approved systemic therapies at this time specifically for the treatment of breast cancer brain metastases.

Brain metastases are common in HER2-positive MBC.[309] They often occur despite optimal systemic control, likely because trastuzumab does not cross an intact blood-brain barrier. Historically, patients with HER2-positive systemic disease not progressing at the time of diagnosis of brain metastases would continue to receive the same systemic therapy.[376] Recent trials suggest that certain HER2-targeted therapies may have more CNS activity, which has led to this paradigm being reexamined.

In the HER2CLIMB trial, patients receiving tucatinib, trastuzumab, and capecitabine had a median CNS PFS of 9.9 months compared with 4.2 months in patients receiving placebo, trastuzumab, and capecitabine (HR, 0.39; 95% CI, 0.27-0.56; $P < .001$).[377]

The use of tucatinib, trastuzumab, and capecitabine was associated with a 68% reduction in the risk of CNS PFS and a 42% reduction in the risk of death overall compared with placebo, trastuzumab, and capecitabine.[365]

In the phase 3 NALA trial, the combination of neratinib and capecitabine resulted in fewer interventions for CNS metastases compared with lapatinib and capecitabine (22.8% vs 29.2%; $P = .043$).[367] The DESTINY-Breast03 trial compared T-DXd and T-DM1 in the second-line setting. In patients who had brain metastases, the median PFS and CNS response were improved for those treated with T-DXd (15 vs 3 months; objective response rate, 67.4% vs 20.5%). The TUXEDO-1 trial[378] found that T-DXd resulted in an intracranial objective response rate (ORR-IC) of 73.3% and a median PFS of 21 months in 15 HER2-positive breast cancer patients with active brain metastases. The DEBBRAH trial demonstrated T-DXd activity in HER2-positive and HER2-low advanced breast cancer with CNS involvement, achieving a 46.2% ORR-IC in patients with active brain metastases and a 13.3-month median OS in a cohort of seven patients with leptomeningeal disease. Given the availability of multiple systemic therapies with effect in the CNS, the development of CNS progression may prompt a change in systemic therapy in HER2-positive MBC.

KEY POINTS

- MBC is incurable; therefore, the goal of treatment is to control disease progression and improve quality of life.
- The choice of systemic therapy is based on hormone receptor and HER2 status as well as on the extent of metastatic disease, the effect of disease on quality of life (eg, symptoms, performance status), and the pace of metastatic disease.
- Germline *BRCA1/2* status, tumor PD-L1 staining, and alterations in tumor PIK3CA and AKT pathways or ESR1 can influence treatment options.
- Endocrine therapy with a CDK4/6 inhibitor is the preferred initial treatment of hormone receptor–positive and HER2-negative metastatic disease unless visceral crisis or extensive visceral involvement is present.
- Sequential single-agent chemotherapy is preferable to combination chemotherapy unless a rapid disease response is required.
- Combined treatment with pertuzumab, trastuzumab, and taxane is the recommended first-line therapy for HER2-positive metastatic disease.
- Pembrolizumab with chemotherapy is approved for use in patients with advanced PD-L1–positive TNBC.
- Patients with brain metastases and good performance status benefit from local control with either surgery, whole-brain radiation therapy, or stereotactic radiosurgery.

BONE-MODIFYING AGENTS

METASTATIC TREATMENT

Approximately 65% to 80% of patients who have MBC will develop bone metastases. Although bone involvement is associated with a more favorable prognosis than visceral metastases, patients are at higher risk of skeletal-related events, including pain, pathologic fracture, hypercalcemia, and spinal cord compression. Breast cancer that metastasizes to bone is treated with appropriate systemic therapy. Palliative radiation to specific disease sites can reduce the morbidity associated with pain and fracture and control disease that may compromise the spinal cord.

Metastases to the bone can produce osteoblastic or osteolytic lesions, both of which are associated with activation of osteoclasts. Breast cancer cells involving the bone can also secrete cytokines that stimulate receptor activator of nuclear factor kB ligand (RANKL) secretion by osteoblasts, which mediates osteoclast maturation and activation. Bisphosphonates are pyrophosphate analogs that are internalized by osteoclasts, which disrupt their function and result in apoptosis. Bisphosphonates (eg, pamidronate and zoledronate) reduce the incidence of skeletal-related events and the time to occurrence of skeletal-related events. Denosumab is a fully human monoclonal antibody that impairs the binding of RANKL to RANK, inhibiting the development and activity of osteoclasts, leading to suppression of bone resorption, and reducing skeletal-related events and time to occurrence of skeletal-related events.[379,380]

Zoledronic acid is associated with renal compromise, whereas hypocalcemia is more common with denosumab. Zoledronic acid is favored over pamidronate because of its ease of infusion. Calcium and vitamin D supplementation should be used for patients receiving all bone-modifying agents, and renal function should be monitored in patients receiving bisphosphonates.

Both bisphosphonates and denosumab are associated with about 2% incidence of osteonecrosis of the jaw; ideally, physicians should avoid administering these agents to patients before or after any invasive dental procedure that involves manipulation of the bone, such as extractions and placement of dental implants.

Dosing interval studies for bone-modifying agents were reported. A randomized trial compared up-front zoledronic acid at monthly versus quarterly intervals for 2 years and demonstrated equivalence.[381] The REaCT trial demonstrated equivalent rates of symptomatic skeletal events for 4- and 12-week dosing schedules of denosumab, zoledronic acid, and pamidronate in 263 patients with metastatic breast cancer or prostate cancer with bone metastases.[382] Final results from the Swiss REDUSE trial, in

which denosumab every 12 weeks was compared with every 4 weeks after an induction phase, which included four doses administered every 4 weeks in patients with metastatic solid tumors, are awaited.[383]

According to ASCO guidelines, bone-modifying agents (eg, bisphosphonates and RANKL inhibitors) are recommended for patients who have evidence of bone destruction. Options include the following[379]:

- Denosumab at 120 mg subcutaneously every 4 weeks
- Pamidronate at 90 mg intravenously every 3 to 4 weeks
- Zoledronic acid at 4 mg intravenously every 12 weeks or every 3 to 4 weeks

The optimal duration of treatment with either a bisphosphonate or denosumab is unknown because the therapeutic intervals in published studies vary from 3 months to indefinitely. The ASCO guideline recommends indefinite use of bone-modifying agents until evidence of a substantial decline in a patient's general performance status.[379]

ADJUVANT TREATMENT

Multiple clinical trials have been conducted to determine the role of bone-modifying agents in the adjuvant setting to decrease the development of metastatic disease. Data are conflicting, as evident in the following:

- The AZURE trial showed no overall effect of zoledronic acid on iDFS among 3,360 patients with stage II or III disease who received chemotherapy. However, zoledronic acid reduced the development of bone metastases and improved iDFS in women who were postmenopausal for at least 5 years before enrollment.[384]
- In the ABCSG-12 trial, use of zoledronic acid was associated with a 36% reduction in risk of disease recurrence among 1,803 premenopausal women who had stage I or II disease who received ovarian suppression and endocrine therapy.[385]
- A meta-analysis of 17 trials with more than 21,000 patients demonstrated a 3.5% absolute reduction in the risk of distant relapse, predominantly bone metastatic relapse, as well as a 2.3% absolute improvement in all-cause mortality (ie, OS), among postmenopausal women who received adjuvant bisphosphonate.[386]
- In the D-CARE phase 3 trial, 4,509 premenopausal and postmenopausal women who had high-risk early breast cancer were randomized to receive denosumab 120 mg subcutaneously every 3 to 4 weeks for 6 months and then every 12 weeks for up to 5 years versus placebo in combination with standard neoadjuvant/adjuvant treatment. No significant difference between bone metastasis–free survival in patients treated with denosumab compared with placebo was reported.[387]
- In the ABCSG-18 trial, postmenopausal women with early-stage hormone receptor–positive breast cancer were randomly assigned to receive subcutaneous denosumab (60 mg) or a matching placebo every 6 months during AI therapy. In the final protocol-defined analysis, there were 309 versus 368 DFS events (HR, 0.83; 95% CI, 0.71-0.97) in the denosumab versus the placebo group, respectively, resulting in an absolute 9-year DFS benefit of 3.5 percentage points (79.4% vs 75.9%).[388]

In 2022, Cancer Care Ontario and ASCO published an updated evidence-based guideline informed by a systematic review of the literature.[389,390] The guideline recommends that bisphosphonates (intravenous zoledronic acid, oral clodronate, or oral ibandronate) be considered for adjuvant therapy for postmenopausal patients (natural or induced menopause) who are deemed candidates for systemic therapy. This panel did not recommend adjuvant denosumab to prevent breast cancer recurrence, because studies did not show a consistent reduction of breast cancer recurrence risk.

KEY POINTS

- Bisphosphonates or denosumab decreases skeletal-related events when bone metastases are present.
- Adjuvant bisphosphonates have been associated with a reduction in risk of recurrence and improvement in OS. Adjuvant denosumab has been associated with improvement in DFS. These agents may be considered for postmenopausal patients who are candidates for adjuvant systemic therapy.
- Renal function should be monitored with bisphosphonate use.
- Calcium and vitamin D supplementation should be strongly encouraged for patients receiving bone-modifying agents.

SURVEILLANCE AND SURVIVORSHIP

There are more than 3.1 million breast cancer survivors in the United States. The primary goal of surveillance after completion of adjuvant therapy is to detect a new and curable cancer at an early stage. ASCO recommendations for surveillance include[391] the following (Table 10-7):

- History and physical examination every 3 to 6 months for the first 3 years and then every 6 to 12 months for the next 2 years.
- For women with remaining breasts, mammography should be performed yearly. Patients should wait 6 to 12 months after the completion of radiation therapy to start annual mammogram surveillance.

Table 10-7 **ASCO Recommendations for Follow-Up Care of Patients Who Have Primary Breast Cancer**[112,392]	
Mode of Surveillance	**Summary of Recommendations**
Breast cancer surveillance: recommended	
History/physical examination	Every 3 to 6 months for the first 3 years after primary therapy, every 6 to 12 months for years 4 and 5, and then annually
Patient education regarding symptoms of recurrence	Physicians should counsel patients about the symptoms of recurrence, including new lumps, bone pain, chest pain, abdominal pain, dyspnea, or persistent headaches; helpful websites for patient education include www.cancer.net and www.cancer.org
Referral for genetic counseling	*BRCA1/2* mutation testing should be offered to all patients diagnosed at the age of 65 years or earlier, or select patients older than 65 years based on personal and family history, ancestry, or eligibility for a PARP inhibitor; further gene panel testing depends on personal and family history
Breast self-examination	All women should be counseled to perform monthly breast self-examination
Mammography	First post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis, but no earlier than 6 months after definitive radiation therapy; subsequent mammograms should be obtained as indicated for surveillance of abnormalities
Coordination of care	Continuity of care is encouraged and should be performed by a physician experienced in surveilling patients with cancer and in breast examination, including the examination of irradiated breasts; if follow-up is transferred to a PCP, the PCP and the patient should be informed of the long-term options regarding adjuvant hormone therapy for the particular patient; this may necessitate referral for oncology assessment at an interval consistent with guidelines for adjuvant hormone therapy
Pelvic examination	Regular gynecologic follow-up is recommended for all women; patients who receive tamoxifen should be advised to report any vaginal bleeding to their care team
Breast cancer surveillance testing: not recommended	
Routine blood tests	CBC and liver function tests are not recommended
Breast MRI	Breast MRI is not recommended for routine breast cancer surveillance; MRI may be considered on an individual basis for high-risk patients
Systemic imaging studies	Chest radiograph, bone scans, liver ultrasonograms, CT scans, and FDG PET scans are not recommended
Tumor markers	CA 15-3, CA 27-29, and carcinoembryonic antigen testing are not recommended

Abbreviations: CA, cancer antigen; CBC, complete blood count; FDG, fluorodeoxyglucose; PCP, primary care provider.
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Additional breast imaging is not usually indicated except for women with hereditary breast cancer syndromes and those who had significant medical radiation exposure. The use of other imaging, tumor markers, or laboratory tests among asymptomatic patients has not been found to be beneficial and has been shown to adversely affect quality of life and increase downstream healthcare use.[393] Thus far, the use of ctDNA is not routinely recommended, given the lack of improved clinical outcomes. Surveillance time should also be used to ensure that appropriate referrals for genetic counseling are made. Patients with genetic risks should be screened for second primary cancers as outlined in the "Screening" section.

Most breast cancer recurrences are identified between office visits; therefore, it is crucial to focus on patient education about the signs and symptoms of disease recurrence. Once symptoms occur, appropriate imaging should be performed.

- Clinical outcomes are identical when patients continue their post-treatment surveillance with either their oncologist or primary care provider. However, understanding potential long-term complications of treatment is important.
- Use of AIs can adversely affect bone density, which should be closely monitored. Potential cardiac toxic effects from anthracyclines and trastuzumab may require the involvement of cardiologists.[394]
- Focusing on healthy activities, such as exercise and maintaining a normal BMI, seems to favorably affect the risk of disease recurrence and improve well-being. Moderate exercise (2-3 hours per week) has been associated with reductions in breast cancer recurrence and improved all-cause mortality.[395,396] Ongoing studies are addressing the role of weight loss in breast cancer recurrence. The BWEL study has enrolled approximately 3,200 overweight women with early-stage breast cancer to test whether weight loss decreases the risk of breast cancer recurrence.[397]
- Cognitive dysfunction associated with cancer therapy is a subject of ongoing investigation.[398]
- The psychosocial ramifications of the diagnosis and treatment of breast cancer cannot be minimized and may require ongoing support and therapy.

VASOMOTOR SYMPTOMS

Chemotherapy-induced amenorrhea or ovarian suppression can result in the onset of menopausal symptoms at an earlier-than-expected age.

Hot flashes may be relieved with venlafaxine or gabapentin. Oxybutynin has also been found to be superior to a placebo for the management of hot flashes.[399] In 2025, the OASIS trial randomized patients on adjuvant endocrine therapy and moderate-to-severe VMS to placebo or to elizanetant, a neurokinin (NK)1 and NK3 inhibitor.[400] Both the frequency and severity of VMS significantly decreased on elizanetant; this drug is not yet FDA approved. Fezolinetant, an NK1 inhibitor, was FDA approved in 2023 for postmenopausal women with VMS but was not specifically studied in women with breast cancer. Notably, breast cancer outcomes were not a study outcome in OASIS.

Intravaginal application of estrogens to improve vaginal dryness and sexual dysfunction can be considered but requires a discussion with patients, particularly in patients who have hormone receptor–positive disease because the safety of intravaginal estrogens is not clearly established. Recently, a meta-analysis of eight retrospective observational studies did not demonstrate an increase in breast cancer recurrence.[401] A cancer registry study that used pharmacy records in Scotland and Wales likewise found no increased risk of breast cancer-specific mortality among women with breast cancer who used vaginal estrogens. However, only 5% of the breast cancer patients had a prescription. The details of the cancer and the actual use of the vaginal estrogen are unknown.[402]

AI-ASSOCIATED MUSCULOSKELETAL SYMPTOMS

A common cause for noncompliance with AIs is the musculoskeletal pain associated with their use. A randomized trial of acupuncture versus sham acupuncture in women taking adjuvant AIs demonstrated a significant decrease in pain at 6 weeks with acupuncture.

In 2016, ASCO and the American Cancer Society developed a comprehensive set of recommendations that extend beyond cancer surveillance recommendations to further address symptom management, surveillance, and management of late toxicities of cancer therapy as well as general wellness (eg, weight management, nutrition, and activity).[403]

KEY POINTS

- The primary schedule of disease monitoring after the completion of therapy includes an annual mammogram and a complete history and physical examination every 3 to 6 months for the first 3 years and then every 6 to 12 months for the next 2 years.
- Routine breast imaging is not needed after mastectomy.
- Anthracyclines and trastuzumab are associated with a risk of cardiac toxicity.
- AIs are associated with decreased bone density and musculoskeletal symptoms. Acupuncture may help with the latter.
- Chemotherapy and OFS can result in premature amenorrhea, resulting in menopausal symptoms, such as hot flashes, vaginal dryness, and sexual dysfunction, and affect bone health.

SPECIAL CIRCUMSTANCES

MALE BREAST CANCER

Male breast cancer is rare, accounting for approximately 1% of all breast cancers.[404] Most cases of breast cancer in men are invasive ductal carcinomas, and other histologic subtypes are rare. Presentation as DCIS is also uncommon. Male breast cancer is almost always ER-positive. In a large series study of male breast cancers, only 9% of cancers were HER2-positive.[405] Risk factors for male breast cancer are discussed in the "Risk Factors" section.

Most men with breast cancer present with a retroareolar mass, but nipple changes and axillary adenopathy are also common. Because of the lack of awareness and early detection, men often present with larger tumors and nodal involvement.

The optimal local and systemic treatments of male breast cancer have not been studied in randomized clinical trials. Mastectomy is often performed, as breast cosmesis may not be an issue. However, breast conservation therapy can be offered if standard criteria for breast conservation therapy are met. In general, recommendations for local disease treatment, including adjuvant radiation therapy, should be governed by the same criteria outlined for breast cancer in women.

Adjuvant chemotherapy should also be administered using the same criteria as for women. Tamoxifen is the mainstay of endocrine therapy in hormone receptor–positive male breast cancer. The efficacy of AIs in men is not well established and may be lower than in women, because of incomplete estradiol suppression.[404] In men with contraindications for tamoxifen, AIs should be combined with GnRH analogs to ensure estradiol suppression.[406] There are limited data on the activity of AIs with or without GnRH agonists and fulvestrant in men with hormone receptor–positive MBC. However, guidelines for systemic therapy of advanced disease are the same as for women.

In addition, the 2020 ASCO Guidelines recommend the following[407]:

- Extended adjuvant endocrine therapy (up to 10 years) if the patient has high-risk disease and is tolerating treatment.
- Ipsilateral annual mammogram after breast conservation therapy can be offered, as well as contralateral screening, in men with a history of breast cancer and genetic predisposition. The data on screening in men are limited.
- All men with breast cancer should be offered genetic counseling and testing.

PREGNANCY-ASSOCIATED BREAST CANCER

Cancer during pregnancy is rare, affecting approximately 1 in every 1,000 pregnancies. Breast cancer is responsible for approximately 25% of cases.[408] Two studies that compared women with breast cancer who received chemotherapy during pregnancy with women who were not pregnant at the time of diagnosis found no negative effect on outcome for women diagnosed during pregnancy.[409,410]

In general, the same treatment recommendations apply as for nonpregnant women, with some exceptions to protect the fetus. Perhaps the most important strategies are to minimize exposure to diagnostic and therapeutic radiation and to limit chemotherapy, if indicated, to the second and third trimesters. The selected strategy should also plan for optimal timing and sequencing of local and systemic therapies to avoid delays in treatment and optimize outcomes. The appropriate treatment should be determined with an obstetrician who specializes in high-risk cases.

These recommendations are summarized as follows:

- Breast-conserving surgery or mastectomy is a reasonable option for pregnant women with breast cancer. There is controversy regarding axillary node evaluation, and the use of blue dye is discouraged, making sentinel lymph node surgery difficult.
- If radiation therapy is recommended, it should be administered after delivery.
- Chemotherapy, if indicated, can be safely administered from week 14 and until 3 to 4 weeks before delivery.
- The use of anthracyclines, cyclophosphamide, and taxanes seems feasible and safe during the second and third trimesters of pregnancy with minimal maternal, fetal, or neonatal toxicity.[411,412]
- Trastuzumab is contraindicated during pregnancy (category D), and labeling contains a black box warning about the risk for oligohydramnios and related pulmonary hypoplasia, skeletal abnormalities, and neonatal death. T-DM1 is also contraindicated in pregnancy.
- Pembrolizumab should not be used during pregnancy (category D).
- Administration of granulocyte colony-stimulating factor during pregnancy seems to be safe based on a retrospective review in a limited number of patients.[413]
- Antiemetic and other supportive medicines, including steroids, should be reviewed with the patient's obstetrician.
- Neonatal morbidity seems to be mainly related to prematurity; therefore, if possible, delivery should not be induced before 37 weeks.
- Endocrine therapy should start after delivery.

Interruption of Endocrine Therapy to Become Pregnant

Fertility preservation and future childbearing are important issues facing young women diagnosed with early-stage breast cancer. Pregnancies are challenging given the 5- to 10-year length of endocrine therapy.

The POSITIVE trial prospectively enrolled 516 women with early-stage hormone receptor–positive breast cancer who desired pregnancy.[414] Endocrine therapy was temporarily interrupted for up to 2 years to allow for pregnancy, delivery, and breastfeeding if desired. Eligible patients had been on endocrine therapy for 18 to 30 months before interruption and were strongly encouraged to resume endocrine therapy after interruption to complete 5 to 10 years total. The primary endpoint was the number of breast cancer events deemed acceptable compared with an external cohort of similar patients in the SOFT and TEXT trials (discussed in "Hormone Receptor–Positive Breast Cancer" and "Role of Ovarian Function Suppression" sections).

At a median follow-up of 41 months, the 3-year incidence of breast cancer events was 8.9% (95% CI, 6.3-11.6) in the treatment interruption group compared with 9.2% (95% CI, 7.6-10.8) in the control cohort. This observation did not exceed the safety threshold. Seventy-four percent of participants had at least one pregnancy, and 63.8% had at least one live birth. Although encouraging, the results should be interpreted with caution, given the short follow-up for hormone receptor–positive breast cancer. However, a balanced discussion is recommended to support young women on endocrine therapy who desire pregnancy after breast cancer.

OLDER PATIENTS

Increasing age is a risk factor for breast cancer. Comorbidities are more common in older adults and are independent predictors of worse survival. However, among healthy older women, chemotherapy regimens administered without dose reduction impart the same relative benefit as that in younger women.[415] Older women can be more susceptible to some toxicities associated with chemotherapy, including hematologic and cardiac toxicities.[416]

An adequate interpretation of chemotherapy benefit among high-risk older women is difficult to make, given that women older than 65 years make up only 8% of enrollment in clinical trials. The CALGB 49907 trial randomly assigned 633 women older than 65 years to receive adjuvant therapy with capecitabine or the standard AC or cyclophosphamide, methotrexate, and fluorouracil regimen.[417] Two-thirds of the women were older than 70 years, and 5% were older than 80 years. The standard regimens of AC and cyclophosphamide, methotrexate, and fluorouracil were associated with a 50% lower risk of recurrence or death compared with the less toxic oral capecitabine regimen. These data continue to support the benefit of standard chemotherapy in healthy elderly women who do not have substantial comorbidities.

Similarly, Japanese investigators compared treatment de-escalation in older women with early and advanced HER2-positive breast cancer. In RESPECT, women aged 70 to 80 years were randomized to adjuvant trastuzumab monotherapy or trastuzumab and chemotherapy.[418] Trastuzumab monotherapy failed to meet its noninferiority DFS endpoint, although more toxicities were reported with chemotherapy. The HERB TEA study randomized women over 65 years with advanced, untreated HER2–positive breast cancer to standard docetaxel, trastuzumab, and pertuzumab or the ADC trastuzumab emtansine. The study was terminated early when the interim analysis exceeded the noninferiority margin for the primary endpoint of OS.[419]

To better understand their overall health status, ASCO recommends performing a geriatric assessment in all older patients with cancer.[420] The geriatric assessment is a multidimensional evaluation that can help unravel the functional, nutritional, psychological, cognitive, and social characteristics of older adults and identify deficits undetected by usual oncologic evaluations.[420] This information can help guide treatment by allowing for an estimation of non–cancer-specific life expectancy as well as the risk of chemotherapy toxicity.[421,422] Ongoing efforts to tailor treatment of older women with breast cancer include the design of a breast cancer–specific chemotherapy toxicity calculator, which uses geriatric assessment variables to predict the risk of grade 3 to 4 toxicity.[423]

KEY POINTS

- The treatment of male breast cancer is extrapolated from information about female breast cancer, with tamoxifen as the preferred agent for adjuvant endocrine therapy.
- There are limited data supporting the use of AIs for the treatment of metastatic disease in men.
- Breast cancer during pregnancy should be treated to minimize fetal harm while ensuring the best oncologic outcome.
- Temporary interruption of adjuvant endocrine therapy can be discussed with young women desiring pregnancy, but longer follow-up is needed to assess long-term safety.
- Performance status, comorbidities, and life expectancy, but not age, should be the deciding factors for adjuvant therapy recommendations for breast cancer.
- Additional studies are needed to balance efficacy and toxicities of treatment in the elderly.

HIGH-YIELD TAKEAWAYS

Premalignant Conditions

- High-risk histologies (ALH, ADH)
  - Atypia on breast biopsy confers an increased risk of developing in situ or invasive breast cancer.
  - ADH on biopsy should be followed by excision to exclude in situ or invasive disease.
  - ALH or classic lobular carcinoma in situ can be managed without immediate excision and with continued imaging follow-up. Excision can be performed for high-risk features.
  - In general, re-excision for negative margins is not necessary for atypia.
- Genetic predispositions
  - Consider genetic counseling/testing for all women diagnosed who are 65 years or younger and all men with breast cancer.
  - Consider testing for patients eligible for PARP inhibitors.
- DCIS
  - Local treatment includes lumpectomy followed by radiation or mastectomy.
  - Adjuvant endocrine therapy for ER-positive DCIS after lumpectomy can decrease ipsilateral and contralateral breast events with no established DFS or OS benefits.

- Early Stage
  - All newly diagnosed breast cancer patients should have their hormone receptor and HER2 status determined.
- HER2-positive
  - Neoadjuvant chemotherapy and anti-HER2 monoclonal antibodies (docetaxel, carboplatin, trastuzumab, and pertuzumab [TCHP]) are offered for larger than T2 and/or node-positive disease.
  - For tumors smaller than T2N0, adjuvant weekly paclitaxel and trastuzumab can be offered.
  - The standard duration of anti-HER2 therapy is 1 year.
  - If there is residual disease after neoadjuvant therapy, adjuvant therapy should switch from trastuzumab to trastuzumab emtansine.
  - Adjuvant radiation therapy and endocrine therapy should be offered if appropriate.
- Hormone receptor–positive, HER2-negative
  - Adjuvant endocrine therapy should be offered to hormone receptor–positive breast cancer.
  - Gene tumor expression assays can identify patients with node-negative and low-volume (N1) node-positive disease who do not benefit from adjuvant chemotherapy.
  - Adjuvant abemaciclib or ribociclib can be offered with endocrine therapy for high-risk disease.
  - Adjuvant olaparib can be offered to high-risk patients with germline *BRCA* mutations.
- TNBC
  - Neoadjuvant therapy with AC-taxol/carboplatin and pembrolizumab improves event-free and OS in patients with T2 or larger or node-positive TNBC.
  - Adjuvant olaparib for 1 year following adjuvant chemotherapy improved OS for patients with pathogenic germline *BRCA* mutations.
- Inflammatory
  - Inflammatory breast cancer is a clinical diagnosis characterized by the rapid onset of breast erythema, skin changes, including peau d'orange, edema, and warmth.
  - There is a high incidence of nodal involvement at presentation and worse DFS compared to noninflammatory breast cancer.
  - Neoadjuvant chemotherapy (and, if appropriate, anti-HER2 therapy or pembrolizumab) followed by mastectomy with axillary lymph node dissection and PMRT should be offered.
  - Adjuvant endocrine, anti-HER2, pembrolizumab, and PARP inhibitor should be offered when indicated.

Locally Recurrent

- In-breast recurrence
  - Imaging to rule out distant metastasis is recommended at the time of an in-breast recurrence.
  - If a patient had a prior lumpectomy, radiation, a completion mastectomy is standard, although treatment can be individualized.
  - Tumor hormone receptor and HER2 status should be repeated.
  - Prognosis is worse for locoregional recurrences compared with primary breast cancers, but they should be treated with curative intent.
  - Systemic therapy should be individualized depending on hormone receptor and HER2 status.
- Chest wall recurrence
  - Imaging to rule out distant metastasis is recommended at the time of chest wall recurrence; if no distant metastasis, then excision is recommended.
  - Tumor hormone receptor and HER2 status should be repeated.
  - Radiation should be offered but needs to be individualized based on prior radiation.
  - Systemic therapy should be individualized depending on hormone receptor and HER2 status.
  - Prognosis is worse for locoregional recurrences compared with primary breast cancers, but they should be treated with curative intent.

Metastatic Disease

- HER2-positive
  - First-line treatment of HER2-positive MBC is a taxane with the dual HER2-targeted combination of trastuzumab with pertuzumab.

- T-DXd is a preferred second-line treatment for HER2-positive MBC.
- Tucatinib with capecitabine and trastuzumab is a standard-of-care third-line regimen and may be used in the second-line setting, particularly in patients with CNS metastases.

- Hormone receptor–positive HER2-negative
  - First-line treatment includes endocrine therapy in combination with a CDK4/6 inhibitor.
  - All patients should undergo tumor NGS to identify alterations for which there are subsequent FDA-approved targeted therapies, including ESR1 and PIK3CA.
- TNBC
  - Neoadjuvant therapy with AC-taxol/carboplatin and pembrolizumab improves event-free and OS in patients with T2 or larger or node-positive TNBC.
  - Adjuvant olaparib for 1 year following adjuvant chemotherapy improved OS for patients with pathogenic germline *BRCA* mutations.

Less Common Clinical Scenarios

- Male breast cancer
  - Male breast cancer accounts for about 1% of all breast cancer. Risk factors include germline *BRCA2* or *PALB2* mutations, Klinefelter syndrome, testicular alterations resulting in testosterone deficiency, and conditions that increase the estrogen-to-testosterone ratio (eg, obesity, cirrhosis).
  - Diagnosis, testing, and treatment for men with breast cancer are extrapolated from studies of female breast cancer.
  - Nearly all male breast cancers are ER–positive, and tamoxifen is the mainstay of endocrine therapy. If AIs are used, a GnRH agonist must be used in combination to ensure estradiol suppression.
- Pregnancy-associated breast cancer
  - Workup and treatment for breast cancer during pregnancy follow that for nonpregnant women but should minimize risk to the fetus, especially in the first trimester.
  - Surgery can be offered, but radiation should be given after delivery.
  - If appropriate, neoadjuvant chemotherapy with anthracycline- and/or taxane-based therapies can be safely administered in the second and third trimesters.
  - Trastuzumab and pembrolizumab are contraindicated during pregnancy (category D).
  - Endocrine therapy should start after delivery.

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

BREAST CANCER 10

CHAPTER SUMMARY GUIDE

KEY POINTS

- The incidence rate of breast cancer in the United States has been slowly increasing at a rate of 1% annually overall since 2012. By contrast, the mortality rate has consistently declined, primarily as a result of advances in systemic therapy.
- The incidence rate has been steeper among women under 50 years.
- The incidence rate of breast cancer is increasing in nonindustrialized countries, in part due to changing lifestyle patterns (eg, rising rates of obesity and decreased physical activity).
- Compared with non-Hispanic White women in the United States, Black women now have a similar rate of incidence but a higher rate of mortality for breast cancer. The causes behind this significant disparity are not fully understood and are likely multifactorial.
- Menopausal hormone replacement therapy in the form of a combination of estrogen and progesterone (but not estrogen alone) is associated with an elevated risk of invasive breast cancer and correlates with duration of use.
- Patients who received therapeutic mediastinal or mantle field radiation have a higher risk of breast cancer, most pronounced when treatment occurred during active proliferation of breast tissue (ie, between ages 10 and 30 years).
- Atypical ductal or lobular hyperplasia and lobular carcinoma in situ are high-risk, nonmalignant lesions associated with a 30% risk of breast cancer development over 25 years.
- *BRCA1* and *BRCA2* mutations are associated with a 50% to 70% lifetime risk of development of breast cancer.
- Other highly (*PALB2*, *CDH1*, *TP53*, *PTEN*, and *STK11*) and moderately (*ATM*, *CHEK2*, and *NF1*) penetrant genes are associated with a significant risk for breast cancer.
- Postmenopausal obesity and alcohol use are associated with a higher risk of breast cancer.
- Increased breast density is associated with a higher risk of breast cancer.
- Several risk models are available to predict the risk of developing breast cancer on the basis of family history, prior atypia, and other factors.
- Risk-reducing BSO in *BRCA1* and *BRCA2* carriers is associated with lower breast cancer–specific mortality, lower all-cause mortality, and lower ovarian cancer–specific mortality rates.
- Bilateral risk-reducing mastectomy reduces the risk of breast cancer by more than 90% in *BRCA1* and *BRCA2* carriers.
- Tamoxifen in premenopausal or postmenopausal women and raloxifene, anastrozole, or exemestane in postmenopausal women all reduce the risk of development of ER–positive breast cancer.
- Significant alcohol consumption is associated with an increased risk of breast cancer, and there seems to be a significant dose–response relationship.
- Mammographic screening results in a 14% to 32% reduction in breast cancer–related mortality among women aged 50 to 70 years. The effect on mortality for women aged 40 to 49 years or older than 70 years is less robust.
- For women with *BRCA* mutations who have not undergone risk-reducing surgery, annual MRI of the breasts is recommended beginning at the age of 25 years, and annual mammography is recommended beginning at the age of 30 years. For women who have received therapeutic mantle field radiation, beginning 10 years after the completion of radiation therapy, annual screening mammography (not before the age of 30 years) and annual breast MRI (not before the age of 25 years) are recommended.
- For breast cancer diagnosis, a core needle biopsy of a suspicious breast or lymph node finding is preferable to fine needle aspiration to accurately assess the histology of the tissue and the status of ER, PR, and HER2.
- Pathologic features associated with a favorable prognosis include small tumor size, negative lymph node status, low tumor grade, absence of lymphovascular invasion, and positive hormone receptor status.
- Quantitative ER expression is predictive of response to endocrine therapy.
- HER2 overexpression/amplification is predictive of benefit from HER2-directed therapy.
- The 21-gene recurrence score and 70-gene signature have been validated prospectively in large trials and may guide the use of adjuvant chemotherapy in addition to endocrine therapy in hormone receptor–positive and HER2-negative breast cancer patients who have either no nodal involvement or one to three lymph nodes involved.
- DCIS (stage 0) accounts for approximately 20% of breast cancers in the United States.

- Most cases of DCIS are detected on screening mammograms.
- Whole-breast irradiation decreases the risk of local recurrence after breast-conserving surgery.
- DCIS treated with mastectomy or breast conservation therapy results in equivalent breast cancer–related 5-year survival rates.
- Current guidelines establish 2 mm as an adequate margin of resection in DCIS treated with breast conservation therapy.
- For women with ER–positive DCIS who elect to undergo breast conservation therapy, adjuvant endocrine therapy reduces the risk of ipsilateral and contralateral recurrences with no established survival benefit. For those patients who undergo bilateral mastectomy for DCIS, there is no role for endocrine therapy for prevention.
- Adjuvant tamoxifen (for premenopausal and postmenopausal women) and AIs (for postmenopausal women only) are appropriate options for decreasing subsequent invasive breast cancers in women with ER–positive DCIS treated with breast conservation therapy.
- The goal of systemic therapy in nonmetastatic disease is to reduce the risk of local recurrence and distant metastasis.
- Randomized trials have demonstrated equivalent survival, regardless of whether neoadjuvant or adjuvant chemotherapy is used.
- Patients who present with inoperable disease require neoadjuvant therapy.
- pCR after neoadjuvant systemic therapy is a strong prognostic factor for reduced risk of recurrence, particularly in TNBC and HER2-positive disease.
- The presence of residual disease after neoadjuvant systemic therapy guides adjuvant systemic therapy choices.
- Treatment of operable breast cancer with mastectomy or breast conservation therapy results in equivalent survival in stages I and II breast cancer, with the following exceptions.
- Positive margins. The definition of an adequate margin of resection for invasive breast cancer treated with breast conservation therapy is no tumor present in the inked margin.
- Inability to remove the tumor with adequate margins and a favorable cosmetic outcome.
- Multicentric disease.
- Contraindications to radiation therapy.
- Patients presenting with a clinically negative axilla can undergo SLNB but axillary staging may be omitted in certain populations with low-risk hormone receptor–positive and HER2-negative tumors.
- Patients with clinical T1 to T2 N0 tumors and up to two involved sentinel lymph nodes treated with up-front breast conservation therapy and whole-breast irradiation can avoid axillary lymph node dissection.
- Patients with clinical T1 to T2 N0 tumors with one to two SLN metastases treated with up-front mastectomy may omit axillary lymph node dissection, provided PMRT is indicated based on additional risk factors.
- Patients presenting with clinically positive lymph nodes require axillary lymph node dissection unless neoadjuvant therapy is used, and their approach must be individualized.
- Hypofractionated radiation therapy is now an established option for most patients requiring adjuvant radiation therapy.
- Accelerated partial breast irradiation is a suitable option for appropriately selected patients.
- Adjuvant breast radiation therapy may be omitted in older patients who have favorable tumor characteristics under select conditions.
- Regional nodal irradiation after breast-conserving surgery or mastectomy is typically indicated in patients who have three or more positive lymph nodes and can be considered in patients who have zero to three positive lymph nodes and additional risk factors.
- Adjuvant tamoxifen has efficacy in premenopausal and postmenopausal women.
- OFS improves DFS and freedom from recurrence when combined with 5 years of adjuvant tamoxifen or exemestane in premenopausal women who have high-risk disease.
- Compared with 5 years, 10 years of adjuvant tamoxifen is associated with a small improvement in DFS and breast cancer–specific survival, and extended-duration tamoxifen is an option in premenopausal or postmenopausal patients at high risk.
- AIs are the first-choice adjuvant endocrine treatment in postmenopausal women.
- Administering AIs for 5 years results in similar outcomes as initial tamoxifen for 2 to 3 years, followed by an AI for a total of 5 years.
- An extended duration of AI therapy beyond 5 years should be considered in postmenopausal women who have high-risk disease.
- Neoadjuvant endocrine therapy is an acceptable treatment approach for postmenopausal women who have stage II or III hormone receptor–positive breast cancer, but it infrequently results in pCR.
- Two years of adjuvant abemaciclib in combination with endocrine therapy improves DFS and OS and is an option for patients with node-positive disease. Three years of dose-reduced ribociclib in combination with an AI improves iDFS in patients with high-risk node-negative and node-positive disease.

- The recommended total duration of adjuvant trastuzumab is 12 months.
- The addition of 1 year of adjuvant pertuzumab concurrently with trastuzumab can be considered for high-risk patients because it provides a small absolute improvement in DFS.
- Pertuzumab, when administered concurrently with trastuzumab and taxane-based chemotherapy, is associated with a significantly increased pCR rate.
- In patients with residual disease after neoadjuvant chemotherapy, switching to T-DM1 after surgery is recommended.
- Inflammatory breast cancer is treated with neoadjuvant chemotherapy, followed by mastectomy with axillary lymph node dissection, PMRT, and adjuvant endocrine, anti-HER2, immunotherapy, and PARP inhibitor therapy, when indicated.
- Despite optimal multimodality care, DFS is worse in inflammatory breast cancer compared with noninflammatory breast cancer, even for patients who achieve pCR.
- Locoregional recurrences require a multidisciplinary approach.
- Local recurrence is associated with a high rate of distant metastasis, and systemic imaging is recommended for these patients.
- After breast conservation therapy, the standard treatment of local recurrences involves a total mastectomy.
- The addition of chemotherapy after surgical management of a locoregional recurrence may benefit some patients, primarily those with ER–negative disease.
- MBC is incurable; therefore, the goal of treatment is to control disease progression and improve quality of life.
- The choice of systemic therapy is based on hormone receptor and HER2 status as well as on the extent of metastatic disease, the effect of disease on quality of life (eg, symptoms, performance status), and the pace of metastatic disease.
- Germline *BRCA1/2* status, tumor PD-L1 staining, and alterations in tumor PIK3CA and AKT pathways or ESR1 can influence treatment options.
- Endocrine therapy with a CDK4/6 inhibitor is the preferred initial treatment of hormone receptor–positive and HER2-negative metastatic disease unless visceral crisis or extensive visceral involvement is present.
- Sequential single-agent chemotherapy is preferable to combination chemotherapy unless a rapid disease response is required.
- Combined treatment with pertuzumab, trastuzumab, and taxane is the recommended first-line therapy for HER2-positive metastatic disease.
- Pembrolizumab with chemotherapy is approved for use in patients with advanced PD-L1–positive TNBC.
- Patients with brain metastases and good performance status benefit from local control with either surgery, whole-brain radiation therapy, or stereotactic radiosurgery.
- Bisphosphonates or denosumab decreases skeletal-related events when bone metastases are present.
- Adjuvant bisphosphonates have been associated with a reduction in risk of recurrence and improvement in OS. Adjuvant denosumab has been associated with improvement in DFS. These agents may be considered for postmenopausal patients who are candidates for adjuvant systemic therapy.
- Renal function should be monitored with bisphosphonate use.
- Calcium and vitamin D supplementation should be strongly encouraged for patients receiving bone-modifying agents.
- The primary schedule of disease monitoring after the completion of therapy includes an annual mammogram and a complete history and physical examination every 3 to 6 months for the first 3 years and then every 6 to 12 months for the next 2 years.
- Routine breast imaging is not needed after mastectomy.
- Anthracyclines and trastuzumab are associated with a risk of cardiac toxicity.
- AIs are associated with decreased bone density and musculoskeletal symptoms. Acupuncture may help with the latter.
- Chemotherapy and OFS can result in premature amenorrhea, resulting in menopausal symptoms, such as hot flashes, vaginal dryness, and sexual dysfunction, and affect bone health.
- The treatment of male breast cancer is extrapolated from information about female breast cancer, with tamoxifen as the preferred agent for adjuvant endocrine therapy.
- There are limited data supporting the use of AIs for the treatment of metastatic disease in men.
- Breast cancer during pregnancy should be treated to minimize fetal harm while ensuring the best oncologic outcome.
- Temporary interruption of adjuvant endocrine therapy can be discussed with young women desiring pregnancy, but longer follow-up is needed to assess long-term safety.
- Performance status, comorbidities, and life expectancy, but not age, should be the deciding factors for adjuvant therapy recommendations for breast cancer.
- Additional studies are needed to balance efficacy and toxicities of treatment in the elderly.

CHAPTER TABLES AND IMAGES

Table 10-1 Established Risk Factors for Breast Cancer: Fixed Factors (Excluding Genetic Mutations)[10]

Factor	Relative Risk
Sex (female vs male)	100
Age (older than 50 vs younger than 50 years)	6.7
Endocrine factors	
Age at first birth (older than 30 years) or nulliparity	1.2-1.7
Age at menarche (younger than 12 years) or age at menopause (older than 55 years)	1.2-1.3
Benign breast disease	
ADH, LCIS	4.0-5.0
Family history (no known mutation)	
One first-degree relative	1.5-2.0
Ashkenazi Jewish ethnicity	1.4
Therapeutic radiation to the chest before age 30 years	7.0-17.0

Abbreviations: ADH, atypical ductal hyperplasia; LCIS, lobular carcinoma in situ.
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Table 10-2 **Lifetime Cancer Risk for People Who Have High- and Moderate-Penetrance Mutations in Selected Genes**[14-22]

Gene (Associated Disease)	Cumulative Lifetime Risk of Breast Cancer Development (%)	Other Tumors
High penetrance		
BRCA1	55-70	Ovarian cancer
BRCA2	45-70	Prostate cancer Pancreatic cancer Malignant melanoma Gallbladder and bile duct cancer Stomach cancer
TP53 (Li-Fraumeni syndrome)	90	Soft tissue sarcoma and osteosarcoma Brain tumors Leukemia Adrenocortical cancer
PTEN (Cowden syndrome/*PTEN* hamartoma tumor syndrome)	Poorly characterized	Follicular thyroid cancer Endometrial cancer Colon cancer Renal cancer
STK11 (Peutz-Jeghers syndrome)	Poorly characterized	Colon cancer Pancreatic cancer Stomach and small bowel cancer
CDH1 (hereditary diffuse gastric cancer)	50-60 (mainly lobular)	Diffuse gastric cancer
PALB2	40-50	Pancreatic cancer
Moderate penetrance		
ATM	20-30	Pancreatic cancer
BRIP1	Insufficient evidence	Ovarian cancer
BARD1	Insufficient evidence	
CHEK2	20-30	Colorectal cancer
MSH2, MLH1, MSH6, PMS2, EPCAM (Lynch syndrome)	Insufficient evidence	Endometrial cancer, Ovarian cancer
NBN	Insufficient evidence	
NF1	18	
RAD51C	Insufficient evidence	
RAD51D	Insufficient evidence	

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Table 10-3 **Established Risk Factors for Breast Cancer: Modifiable Factors**

Factor	Relative Risk
Oral contraceptive pill	0.9-1.0
Estrogen replacement (more than 10 years)	1.1
Estrogen and progesterone	1.4-3.0
Postmenopausal obesity (BMI higher than 30 kg/m^2)	2.5
Alcohol use	1.1-2.2
Diet	1

Abbreviation: BMI, body mass index.
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Table 10-4 **Molecular Subtypes**	
Subtype	**Characteristic**
Luminal A	Favorable prognosis High ER/PR Low proliferation rate Grade 1/2 Lower sensitivity to chemotherapy
Luminal B	Less favorable prognosis Lower ER and PR High proliferation rate Grade 2/3 Higher sensitivity to chemotherapy
HER2 enriched	HER2 positive Hormone receptor positive or negative High proliferation rate Grade 2/3
Basal	ER, P High proliferation rate Grade 3

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
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Table 10-5 **Extended Endocrine Therapy With AI**[255]	
Trial	**Intervention**
Extended adjuvant AI after 5 years of tamoxifen	
MA.17	Letrozole for 5 years or placebo
NSABP B-33	Exemestane for 5 years or placebo
ABCSG 6	Anastrozole for 3 years or placebo
Extended AI after 5 years of therapy that included an AI	
MA.17R	Letrozole or placebo for 5 years after 5 years of letrozole (preceded by 5 years of tamoxifen in most patients)
NSABP B-42	Letrozole or placebo for 5 years after 5 years of endocrine therapy with 5 years of an AI or 3 or fewer years of tamoxifen
DATA	Anastrozole for 6 years, 3 years after 2 to 3 years of tamoxifen
Optimal duration or dosing of AI in years 5-10	
IDEAL	Letrozole for 2.5 vs 5 years after tamoxifen, AI, or both for 5 years
ABCSG-18	Anastrozole for 2 vs 5 years after tamoxifen, AI, or both for 4 to 6 years

Abbreviation: AI, aromatase inhibitor.
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Table 10-6 **Trials With CDK4/6 Inhibitors**

Treatment	Study	Phase	Description	Median PFS, Months (HR, 95% CI)	Median OS, Months (HR, 95% CI)
First line	PALOMA-2	3	Palbociclib/letrozole vs placebo/letrozole	24.8 vs 14.5 (0.58, 0.46-0.72)	53.9 vs 51.2 (0.96, 0.777-1.177)[313]
	MONALEESA-2	3	Ribociclib/letrozole vs placebo/letrozole	25.3 vs 16.0 (0.56, 0.43-0.72)[314]	63.9 vs 51.4 (0.76, 0.63-0.93)[315]
	MONALEESA-7	3	Ribociclib/OFS/AI or tamoxifen vs placebo/OFS/AI or tamoxifen	23.8 vs 13.0 (0.55, 0.44-0.69)[316]	58.7 vs 40.9 (0.76, 0.61-0.96)[317]
	MONARCH-3	3	Abemaciclib/AI vs placebo/AI	28.2 vs 14.7 (0.54, 0.41-0.72)[325]	66.8 vs 53.7 (0.80, 0.64-1.01)[326]
First or second line	MONALEESA-3	3	Ribociclib/fulvestrant vs placebo/fulvestrant	20.5 vs 12.8 (0.59, 0.48-0.73)[318]	67.6 vs 51.8 (0.67, 0.50-0.90)[319]
Second line	PALOMA-3	3	Palbociclib/fulvestrant vs placebo/fulvestrant	9.5 vs 4.6 (0.46, 0.36-0.59)[320]	34.9 vs 28.0 (0.81, 0.65-0.99)[321]
	MONARCH-2	3	Abemaciclib/fulvestrant vs placebo/fulvestrant	16.4 vs 9.3 (0.55, 0.45-0.66)[322]	46.7 vs 37.3 (0.757, 0.61-0.94)[324]
Later line	MONARCH-1	2	Abemaciclib	6[323]	17.7[323]

Abbreviations: AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; HR, hazard ratio; OFS, ovarian function suppression; OS, overall survival; PFS, progression-free survival.

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Table 10-7 **ASCO Recommendations for Follow-Up Care of Patients Who Have Primary Breast Cancer**[112,392]

Mode of Surveillance	Summary of Recommendations
Breast cancer surveillance: recommended	
History/physical examination	Every 3 to 6 months for the first 3 years after primary therapy, every 6 to 12 months for years 4 and 5, and then annually
Patient education regarding symptoms of recurrence	Physicians should counsel patients about the symptoms of recurrence, including new lumps, bone pain, chest pain, abdominal pain, dyspnea, or persistent headaches; helpful websites for patient education include www.cancer.net and www.cancer.org
Referral for genetic counseling	*BRCA1/2* mutation testing should be offered to all patients diagnosed at the age of 65 years or earlier, or select patients older than 65 years based on personal and family history, ancestry, or eligibility for a PARP inhibitor; further gene panel testing depends on personal and family history
Breast self-examination	All women should be counseled to perform monthly breast self-examination
Mammography	First post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis, but no earlier than 6 months after definitive radiation therapy; subsequent mammograms should be obtained as indicated for surveillance of abnormalities
Coordination of care	Continuity of care is encouraged and should be performed by a physician experienced in surveilling patients with cancer and in breast examination, including the examination of irradiated breasts; if follow-up is transferred to a PCP, the PCP and the patient should be informed of the long-term options regarding adjuvant hormone therapy for the particular patient; this may necessitate referral for oncology assessment at an interval consistent with guidelines for adjuvant hormone therapy
Pelvic examination	Regular gynecologic follow-up is recommended for all women; patients who receive tamoxifen should be advised to report any vaginal bleeding to their care team
Breast cancer surveillance testing: not recommended	
Routine blood tests	CBC and liver function tests are not recommended
Breast MRI	Breast MRI is not recommended for routine breast cancer surveillance; MRI may be considered on an individual basis for high-risk patients
Systemic imaging studies	Chest radiograph, bone scans, liver ultrasonograms, CT scans, and FDG PET scans are not recommended
Tumor markers	CA 15-3, CA 27-29, and carcinoembryonic antigen testing are not recommended

Abbreviations: CA, cancer antigen; CBC, complete blood count; FDG, fluorodeoxyglucose; PCP, primary care provider.
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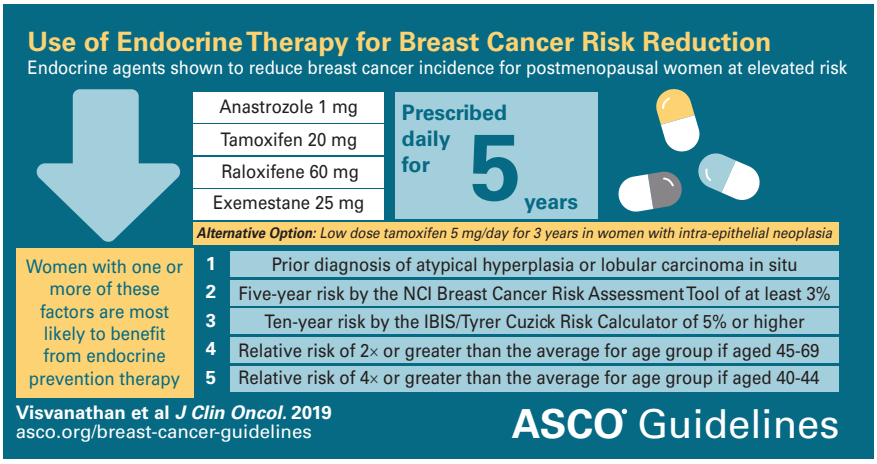
Figure 10-1 Use of Endocrine Therapy for Breast Cancer Risk Reduction



Abbreviations: IBIS, International Breast Cancer Intervention Study; NCI, National Cancer Institute.
Reproduced from Visvanathan K, Fabian CJ, Bantug E, et al. Use of endocrine therapy for breast cancer risk reduction: ASCO clinical practice guideline update. *J Clin Oncol*. 2019;37:3152-3165. doi:10.1200/JCO.19.01472
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Figure 10-2 Workup of Palpable Breast Mass or Screening Abnormality

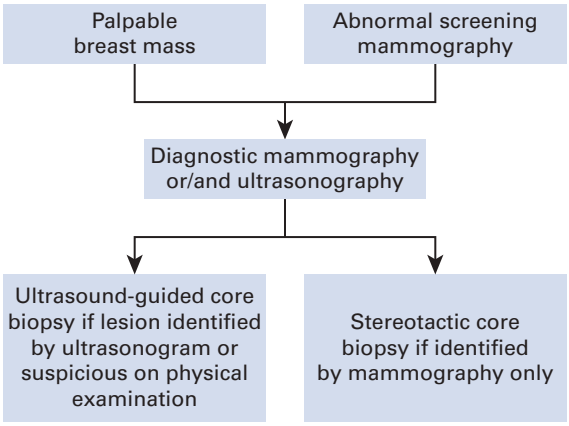

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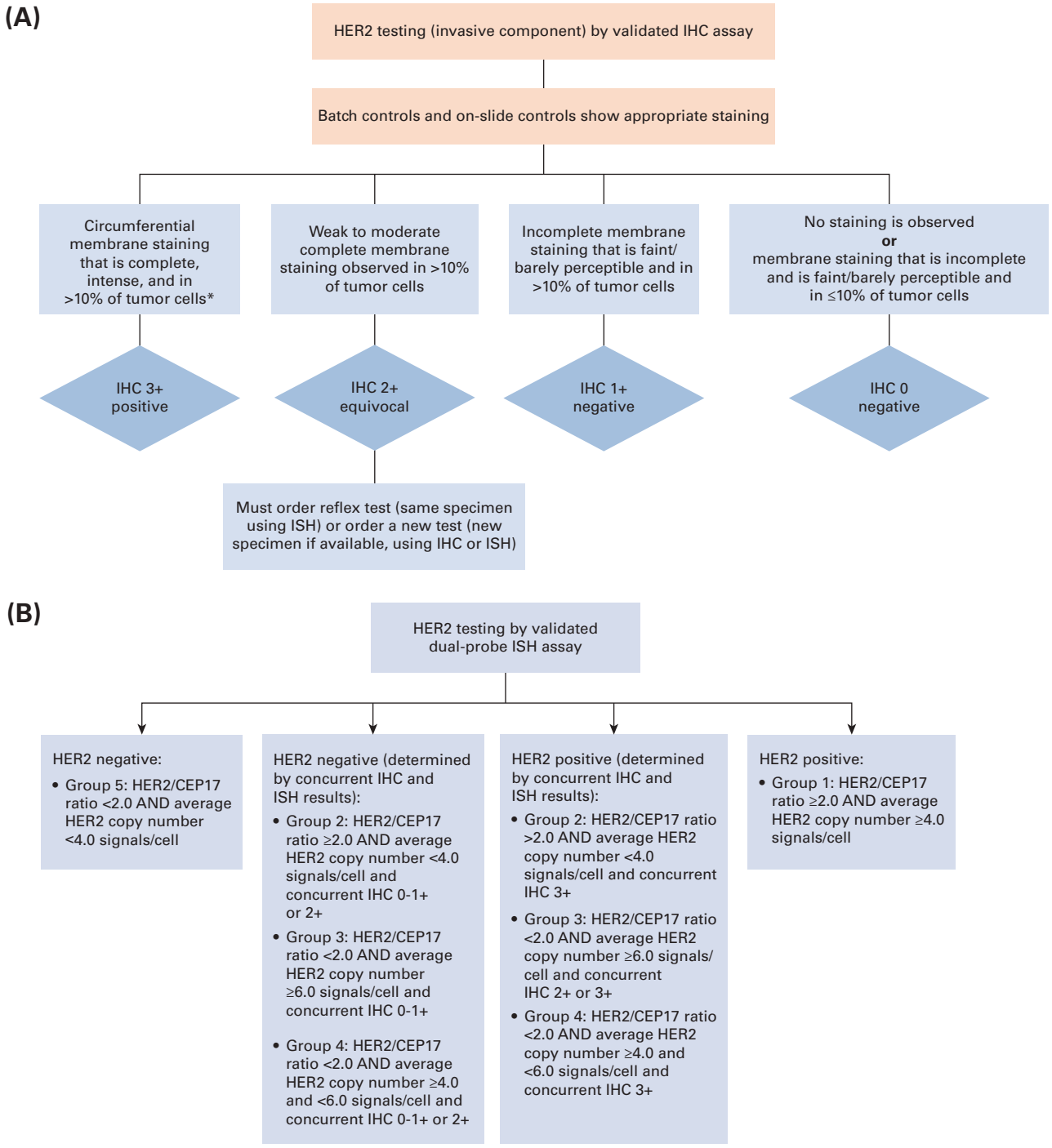
Figure 10-3 Summary of the ASCO/College of American Pathologists Guidelines



(A) HER2 testing by validated IHC assay. (B) HER2 testing by validated dual-probe ISH assay.
Abbreviations: IHC, immunohistochemistry; ISH, in situ hybridization.
*Readily appreciated using a low-power objective and observed within a homogeneous and contiguous invasive cell population.
Reproduced from Wolff AC, Hammond MEH, Allison KH, Harvey BE, McShane LM, Dowsett M. HER2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update summary. *J Oncol Pract.* 2018;14:437-441. doi:10.1200/JOP.18.00206

Figure 10-4 Suggested Axillary Management for Clinically Node-Negative Axilla

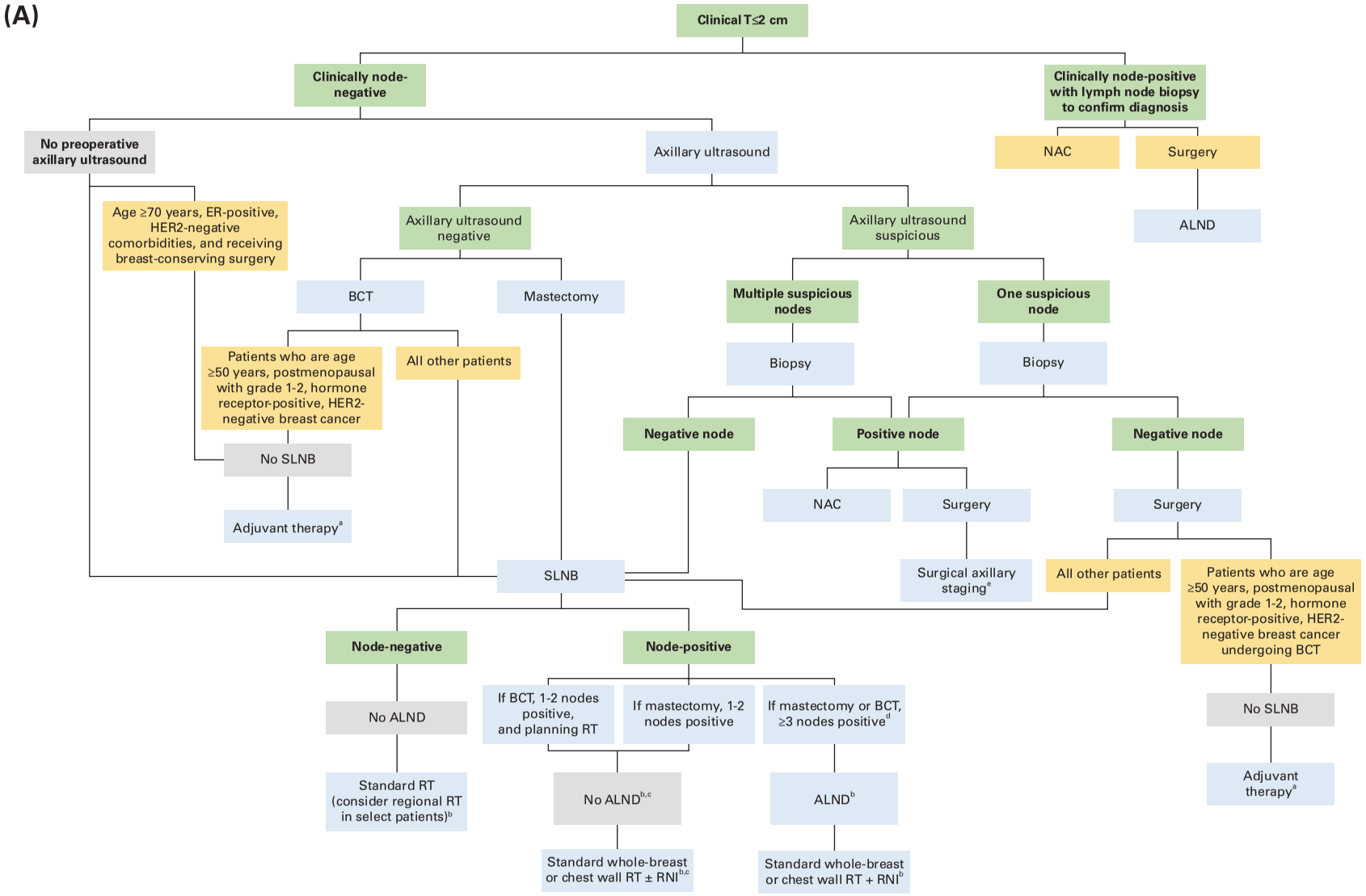
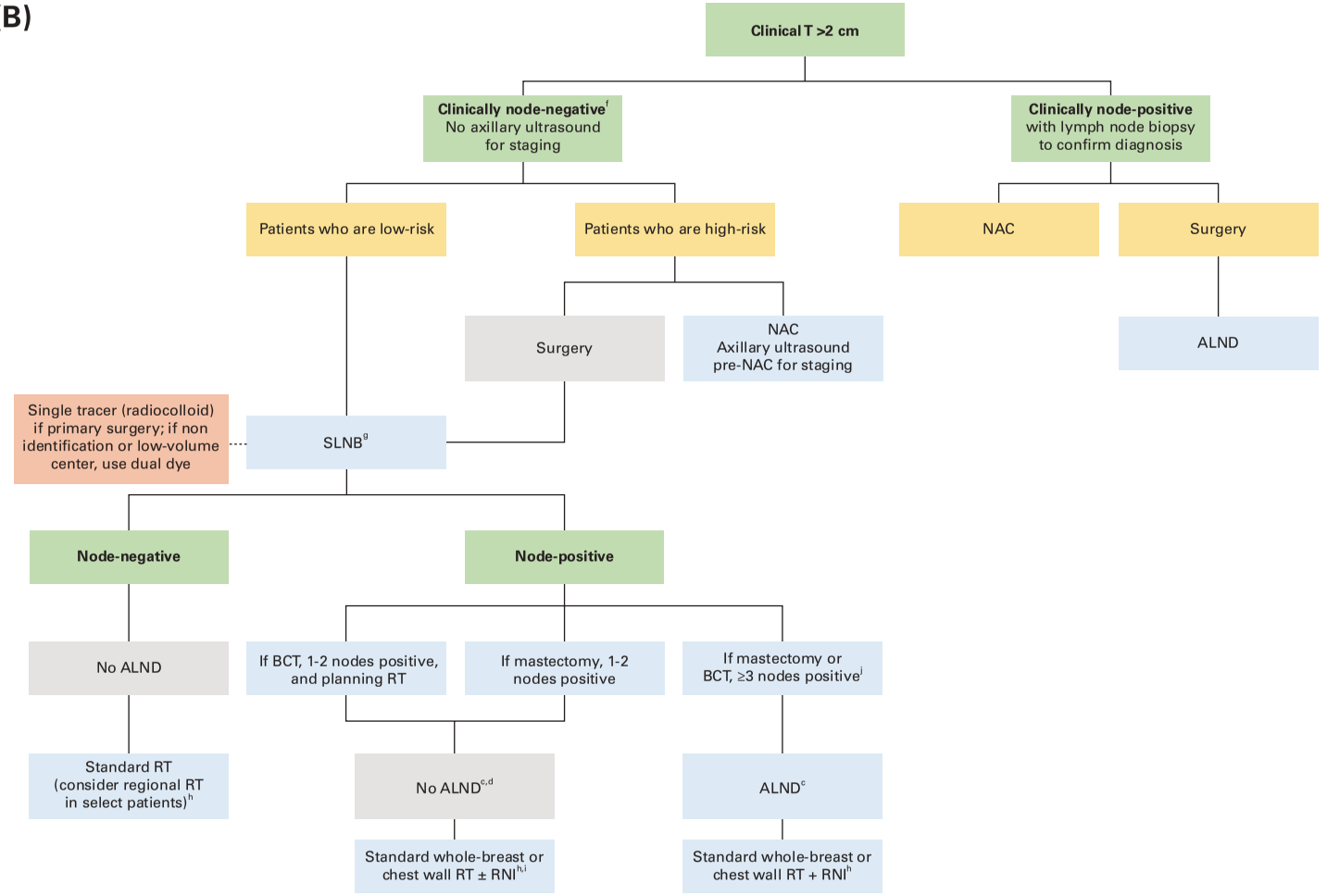


Figure 10-4 Continued

(B)



(A) Management of the axilla for patients with clinical T ≤2 cm breast cancer. (B) Management of the axilla for patients with clinical T >2 cm breast cancer.
Abbreviations: ALND, axillary lymph node dissection; BCT, breast-conserving therapy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NAC, neoadjuvant chemotherapy; PMRT, postmastectomy radiation therapy; RNI, regional nodal irradiation; RT, radiation therapy; SLNB, sentinel lymph node biopsy; T, tumor.
[a]Refers to all patients with no palpable axillary nodes on physical examination, including those who may have had an ultrasound that was equivocal, abnormal, or even biopsy-proven positive.
[b]Do not recommend SLNB before chemotherapy except in special circumstances after multidisciplinary discussion.
[c]Decision making should be made on a case-by-case basis, and include a patient-centered approach; that is, consider and discuss pros and cons of various options in light of patient's specific circumstances, values, and preferences.
[d]Full lymph node dissection may mitigate the need for RT in select patients.
[e]Patients with three positive nodes were underrepresented in trials evaluating the omission of completion ALND.
[f]Refers to all patients with no palpable axillary nodes on physical examination, including those who may have had an ultrasound that was equivocal, abnormal, or even biopsy-proven positive.
[g]Do not recommend SLNB before chemotherapy except in special circumstances after multidisciplinary discussion.
[h]Decision making should be made on a case-by-case basis, and include a patient-centered approach; that is, consider and discuss pros and cons of various options in light of patient's specific circumstances, values, and preferences.
[i]Full lymph node dissection may mitigate the need for RT in select patients.
[j]Patients with three positive nodes were underrepresented in trials evaluating the omission of completion ALND.
Adapted from Park KU, Somerfield MR, Anne N, et al. Sentinel lymph node biopsy in early-stage breast cancer: ASCO guideline update. *J Clin Oncol*. 2025;43(14):1720-1741. doi:10.1200/jco-25-00099
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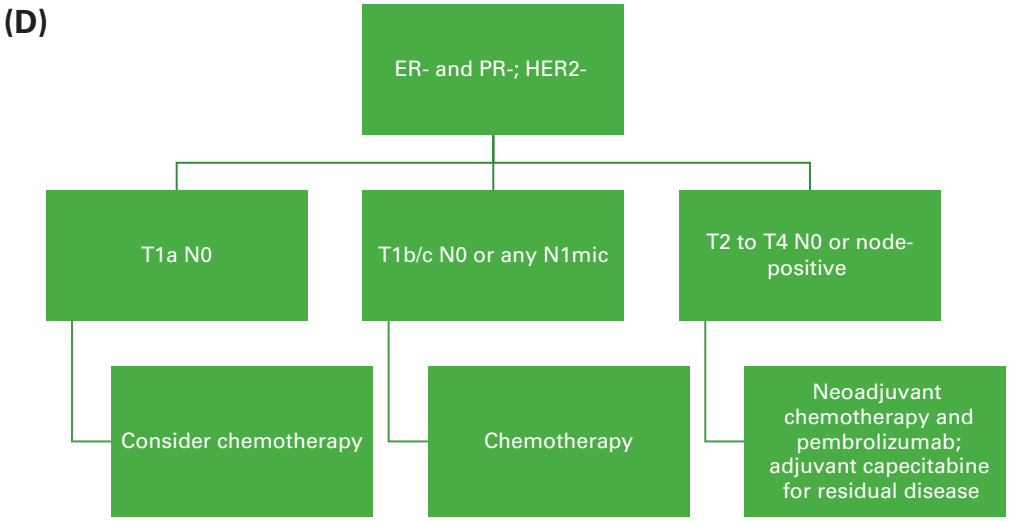
Figure 10-5 Suggested Guidelines for (Neo)Adjuvant Systemic Therapy for Four Main Breast Cancer Subtypes if No Germline *BRCA* Mutation

Figure 10-5 Continued



(A) Hormone receptor–positive, HER2-negative disease. (B) Hormone receptor–positive, HER2–positive disease. (C) Hormone receptor–negative, HER2–positive disease. (D) Hormone receptor–negative, HER2–negative disease.
Abbreviations: ER, estrogen receptor; PR, progesterone receptor; Tx, therapy.
*Gene signatures may help with decision-making in appropriate patients. Clinical trials did not include T1c, N0.
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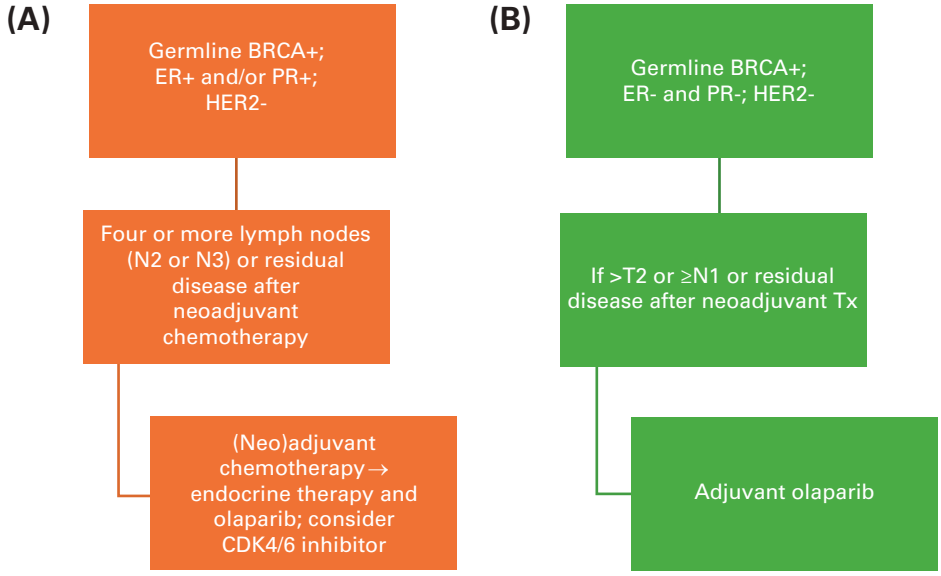
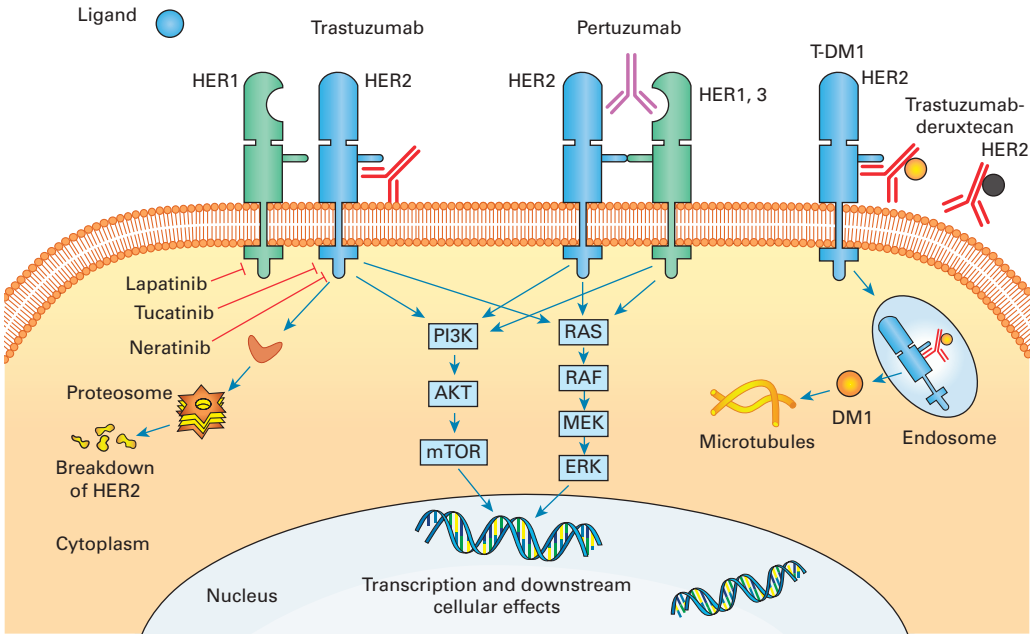
Figure 10-6 Suggested Guidelines for (Neo)Adjuvant Systemic Therapy for HER2-Negative Breast Cancer With Germline *BRCA* Mutation



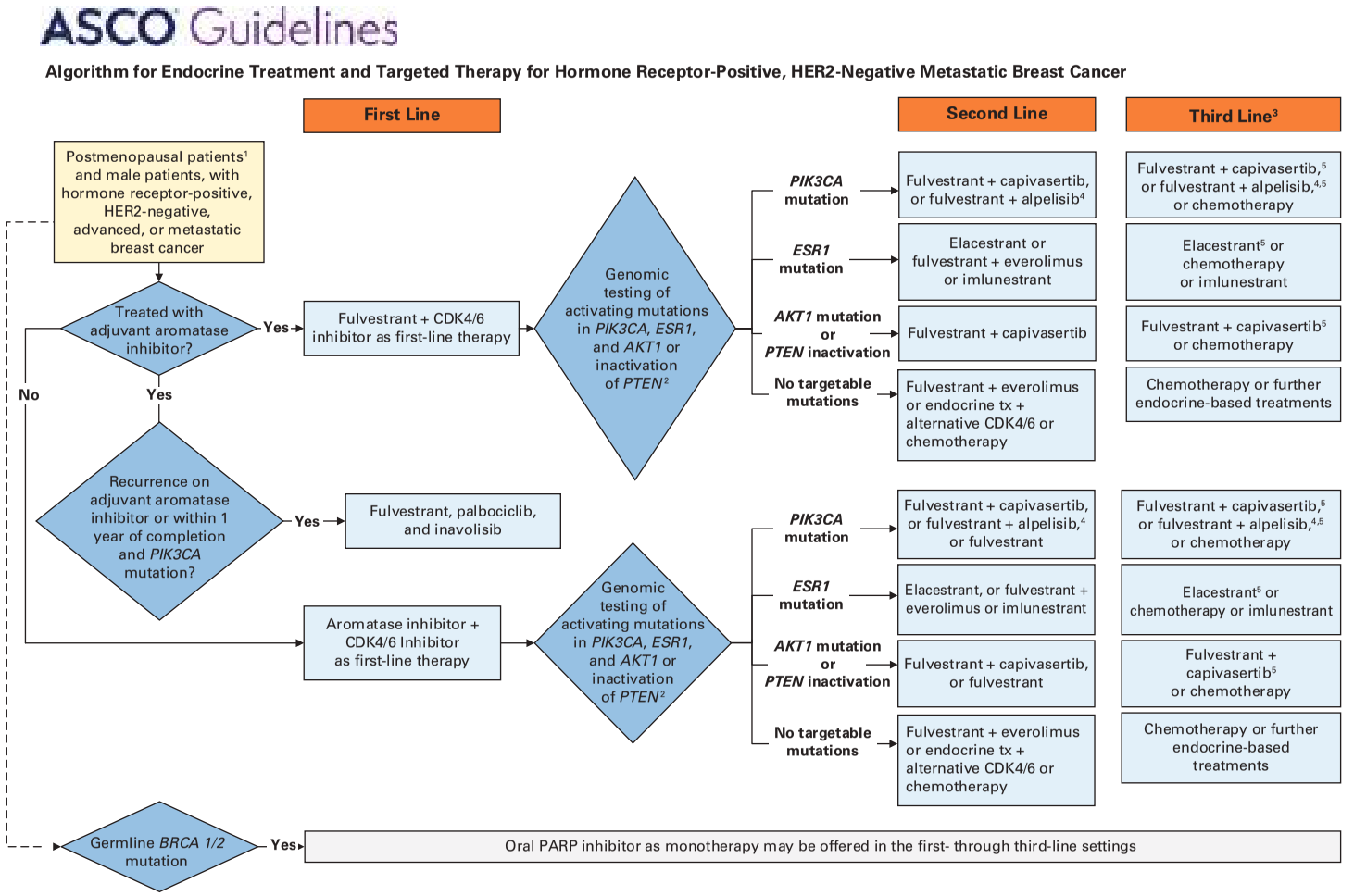
(A) Hormone receptor–positive, HER2-negative disease. (B) Hormone receptor–negative, HER2-negative disease.
Abbreviation: Tx, therapy.
Gene signatures may help with decision-making in appropriate patients. Clinical trials did not include T1c, N0.Created for ASCO. Copyright © 2026 by American Society of Clinical Oncology.

Figure 10-7 Targets for HER2-Targeted Therapy



Abbreviation: T-DM1, ado-trastuzumab emtansine.
Adapted under Creative Commons license CC BY-NC-SA 3.0. Source: Singh JC, Jhaveri K, Esteva FJ. HER2-positive advanced breast cancer: optimizing patient outcomes and opportunities for drug development. *Br J Cancer*. 2014;111:1888-1898. doi:10.1038/bjc.2014.388

Figure 10-8 Suggested Treatment Sequencing in Hormone Receptor–Positive and HER2–Negative MBC



Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CLIA, Clinical Laboratory Improvement Amendments; ESR1, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; OFS, ovarian function suppression; PARPi, poly-ADP-ribose polymerase inhibitor; PTEN, phosphatase and tensin homolog protein.
BRCA mutation options: olaparib or talazoparib.
[1]If patient is premenopausal, initiate ovarian suppression and continue as postmenopausal.
[2]Tumor genomic testing includes sequencing for targetable mutations, accomplished through large panel tumor genomic testing in a CLIA-certified laboratory performed on tissue or plasma obtained either at the time of progression or from archival tissue. In addition to selecting patients whose tumors have increased PIK3CA or AKT1 activity because of the presence of activating mutations, it is also important to identify those whose tumors have inactivation of phosphatase and tensin homolog (PTEN) protein. PTEN inactivation can be identified based on the presence of premature stop codons, frameshift alterations, splice site mutations, PTEN homozygous deletion, PTEN rearrangements that disrupt protein function, or specific missense mutations (*C124R*, *C124S*, *G129E*, *G129V*, *G129R*, *R130Q*, *R130G*, *R130L*, *R130P*, *C136R*, *C136Y*, *S170R*, and *R173C*), on next-generation sequencing.
[3]There are few data on the value of older endocrine treatment options after therapy with modern treatment regimens such as AIs, SERDs, CDK4/6 inhibitors and/or other targeted agents. In select patients—typically those with indolent cancers, limited disease burden or symptoms, and demonstrated clinical benefit from prior endocrine
treatments—therapies such as tamoxifen, megestrol acetate, or reintroduction of previously administered treatments may be of clinical value.
[4]Alpelisib is an option for patients with tumors harboring PIK3CA activating mutations but not AKT1 activating mutations or PTEN inactivation.
[5]If not previously given.
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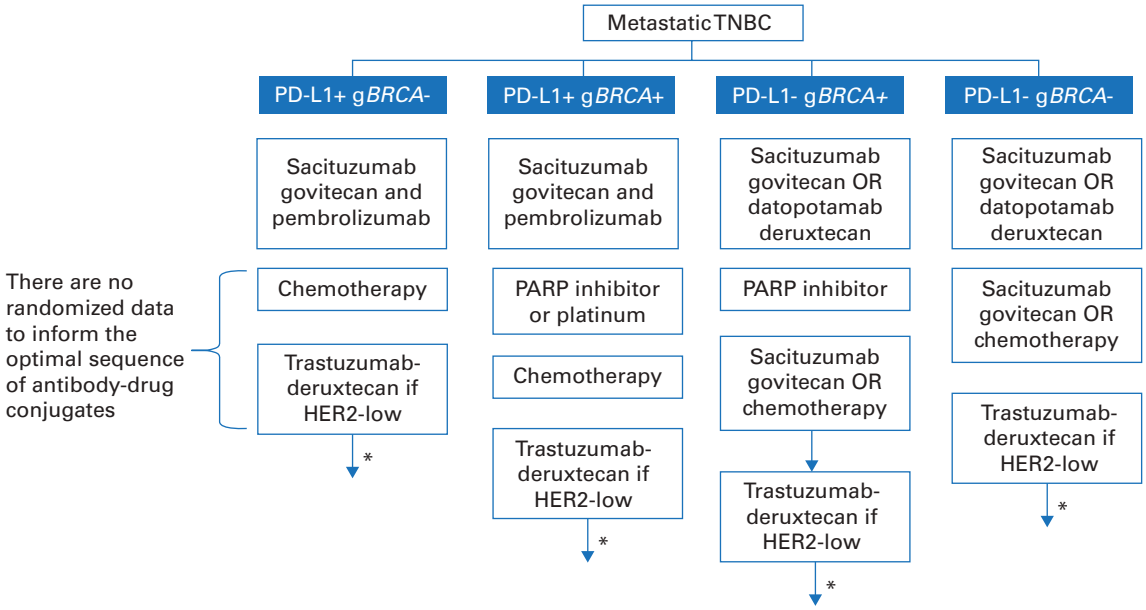
Figure 10-9 Approach to Metastatic TNBC



Abbreviation: TNBC, triple negative breast cancer.
*Subsequent lines of therapy should be considered based on performance status and patient goals and values; options include single-agent cytotoxic therapy and select biomarker-driven therapies. Clinical trials may be considered at each decision point.
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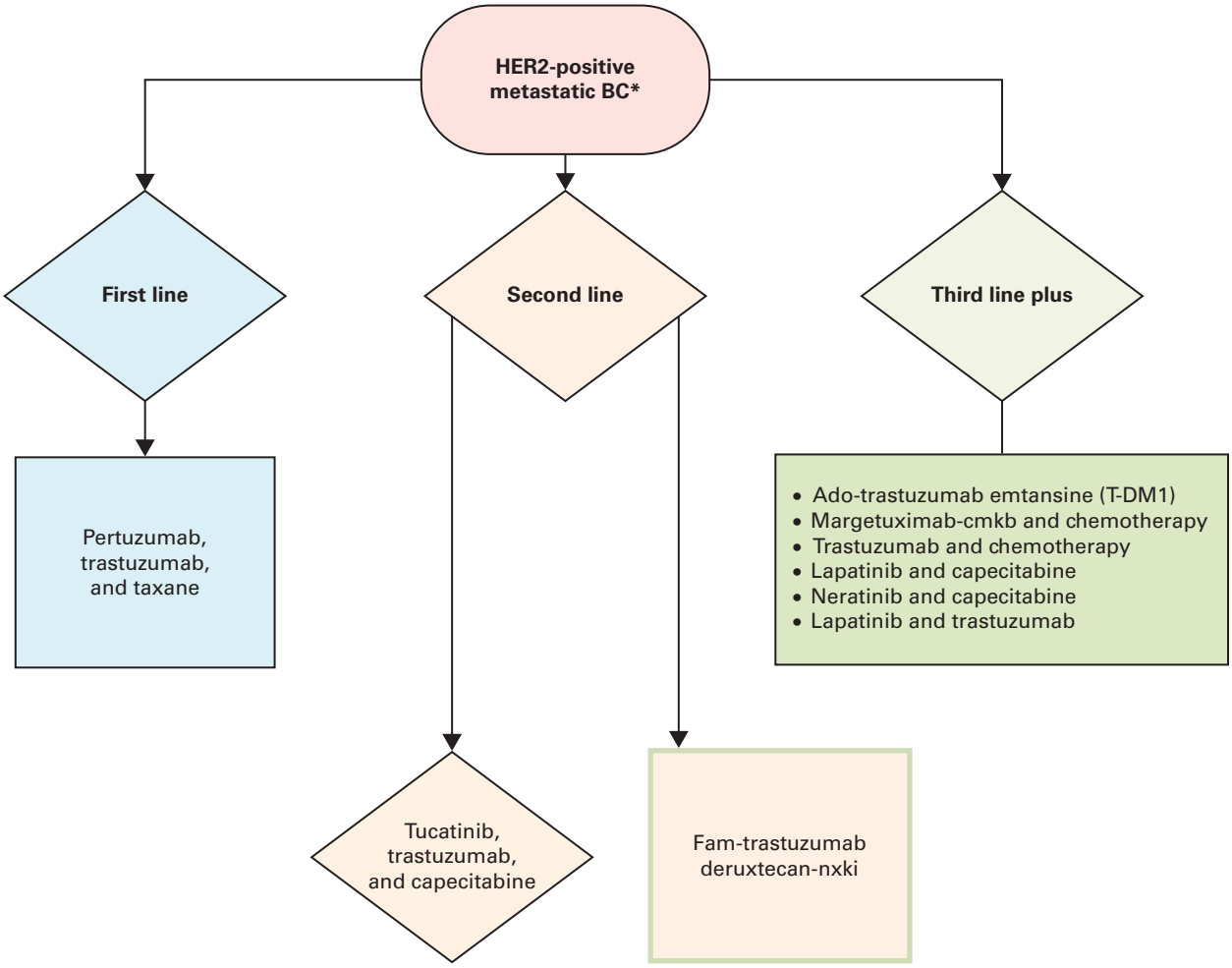
Figure 10-10 Suggested Treatment Sequencing in HER2-Positive Metastatic Breast Cancer



*For select patients with hormone receptor–positive, HER2-positive tumors, endocrine therapy and trastuzumab ± pertuzumab may be considered.
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LUNG CANCER 11

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RECENT UPDATES

- Tarlatamab improves overall survival when compared with standard second-line chemotherapy in patients with extensive-stage small cell lung cancer whose cancer has progressed after initial chemotherapy and immunotherapy.[1]
- Datopotamab deruxtecan is approved for patients with locally advanced or metastatic epidermal growth factor receptor (EGFR)-mutated non–small cell lung cancer (NSCLC) who have received prior EGFR-directed therapy and platinum-based chemotherapy.[2]
- Zongertinib is approved for patients with unresectable or metastatic non–squamous NSCLC whose tumors have HER2 (*ERBB2*) tyrosine kinase domain (TKD) activating mutations.[3]
- Sunvozertinib is approved for patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.[4]
- Telisotuzumab vedotin-tllv is approved for patients with locally advanced or metastatic, non–squamous NSCLC with high c-Met protein overexpression (immunohistochemistry [IHC] 3+ > 50%) who have received a prior systemic therapy.[5]
- Taletrectinib is approved for patients with locally advanced or metastatic *ROS-1* fusion–positive NSCLC.[6]

OVERVIEW

An estimated 226,650 new cases of lung cancer were diagnosed in the United States in 2024, making it the second most common cancer in men (following prostate cancer) and women (following breast cancer).[7] It is also the most lethal cancer in the United States, with approximately 124,730 deaths annually or approximately 20% of all US deaths resulting from cancer. Since 2006, the incidence of lung cancer has decreased by 2.6% annually in men and 1.1% annually in women. This reduction is attributed almost entirely to a reduction in smoking rates. The 3-year relative survival rate for lung cancer has also improved, from 22% in patients diagnosed from 2004 to 2006 to 33% in those diagnosed from 2016 to 2018. Possible reasons for this improvement include improved surgical and medical therapies (eg, targeted therapies and immunotherapies) and earlier detection because of lung cancer screening.[8] There is real hope that these trends will continue with additional improvements in therapy as well as the stage migration that results from the increased use of low-dose chest computed tomography (CT) for lung cancer screening.

KEY POINT

- Lung cancer is the most common cause of cancer-related death in the United States in both men and women.

RISK FACTORS

Although the biology of lung cancer is complex, the link between lung cancer and tobacco use is clear. Numerous epidemiologic and laboratory studies, as well as in vitro data, have tied lung cancer to the carcinogenic effects of tobacco smoke. It is important to recognize, however, that each year in the United States, there are 17,000 to 26,000 deaths resulting from lung cancer in individuals with limited/no tobacco use history, with an even higher proportion in some geographic areas.[9] Other environmental and occupational exposures have also been linked to the development of lung cancer, with varying levels of evidence.

The main risk factors for lung cancer are the following:

- Tobacco smoke[10]
- Environmental exposures (radon, asbestos, arsenic, chromium, and nickel)[11]

- Radiation[12]
- Family history[11,3,14]

TOBACCO

Cigarette smoking is the most common cause of lung cancer and is associated with approximately 85% of all cases. The risk of lung cancer in those who use cigarette tobacco increases with the number of cigarettes smoked and the duration of smoking history; the latter is a stronger risk factor than the former. Tripling of the number of cigarettes smoked per day is estimated to triple the risk of lung cancer, whereas tripling of the duration of smoking is estimated to increase the risk by 100-fold.[15] The risk of lung cancer decreases with smoking cessation and approaches that of the non–smoking population after 10 to 15 years of abstinence. However, one study among women reported that even after 30 years, the risk was not as low as that for the population who had never smoked.[10]

Cigarette smoke contains thousands of constituents, many of which are carcinogenic. Two of the major classes of nicotine-related inhaled carcinogens include polycyclic aromatic hydrocarbons and *N*-nitrosamines, which are metabolized to nitrosamine ketone and N^0-nitrosonornicotine. Both compounds are activated by the cytochrome P450 enzyme system and exert carcinogenic effects through the formation of DNA adducts.

ENVIRONMENTAL EXPOSURES

Radon is a naturally occurring chemically inert gas that is a decay product of uranium. The relative risk of lung cancer is increased for underground miners who are exposed to high levels of radon. For underground miners who smoke, the risk may exceed 10 times the risk for a non–smoking miner. The relationship between indoor residential radon exposure and lung cancer risk is less well defined, although it is estimated that 2% to 10% of lung cancers may be caused by exposure to residential radon.[11] Exposure to asbestos combined with smoking increases the risk of lung cancer. Other occupational or environmental exposures associated with a risk of lung include air pollution and environmental (ie, secondhand) tobacco smoke.[15]

RADIOTHERAPY

High doses of radiation have also been associated with an increased risk of lung cancer. For example, an increased risk has been observed in patients with breast cancer, as well as in long-term survivors of Hodgkin and non–Hodgkin lymphomas, particularly if patients continue to smoke after completing radiation therapy.[15]

FAMILY HISTORY AND GENETIC PREDISPOSITION

Epidemiologic studies have shown that a family history of lung cancer is a predictor of increased risk. Familial aggregation of lung cancer has led to the hypothesis of a genetic susceptibility to lung cancer.[13] This may be related to inherited differences in carcinogen metabolism and DNA repair capacity. Germline polymorphisms in genes with products that activate (eg, cytochrome P450 1A1 [*CYP1A1*]) or detoxify (eg, glutathione *S*-transferases M1 [*GSTM1*] and T1 [*GSTT1*]) chemical carcinogens found in tobacco smoke have been associated with a risk of lung cancer from environmental tobacco smoke that is substantially greater than the risk for individuals who are heterozygous or homozygous carriers of the wild-type *GSTM1* allele. However, some results from these studies are conflicting, suggesting that particular polymorphisms may predict increased risks in specific ethnic populations, limiting generalizability. The *EGFR* T790M mutation, most frequently associated with resistance to first- or second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), can also be present as a germline risk allele for lung cancer. The germline inheritance of *EGFR* T790M usually occurs in an autosomal dominant pattern, and the presence of an *EGFR* T790M mutation at diagnosis (before treatment) should trigger consideration for referral for genetic counseling and germline testing and CT-based screening.[16]

KEY POINT

- Most cases of lung cancer (85%) are caused by carcinogens in tobacco smoke.

PATHOLOGY

More than 95% of lung cancers consist of one of the four major histologic types: adenocarcinoma, squamous cell carcinoma, large cell carcinoma (three subtypes of non–small cell lung cancer [NSCLC]), or small cell lung cancer (SCLC; Table 11-1).[8,17] Histologic subtype influences treatment selection based on the differences in chemotherapy sensitivity and safety profiles in squamous versus non–squamous tumors.

Table 11-1 **Characteristics of Major Subtypes of Lung Cancer**			
Histology	**Frequency (%)**	**Immunohistochemistry**	**Clinical Features/Comments**
Non–small cell			
Adenocarcinoma	50	TTF-1, Napsin-A, CK7	Most common histology to have actionable driver mutations
Squamous cell carcinoma	25	P63, p40, CK5/6	Often central tumors; may develop cavitation; more commonly seen in those with heavy smoking history
Large cell carcinoma	5	—	Poorly differentiated tumors that do not meet the criteria for adenocarcinoma or squamous cell carcinoma
Pulmonary neuroendocrine tumors			
Typical carcinoid	1-2	Synaptophysin, chromogranin, INSM-1	<2 mitoses/2 mm^2 (10 HPF); lacking necrosis
Atypical carcinoid	1-2	Synaptophysin, chromogranin, INSM-1	2-10 mitoses/2 mm^2 (10 HPF) or necrosis
Large cell neuroendocrine carcinoma	5	Synaptophysin, chromogranin, INSM-1	High mitotic rate (>10 mitoses/2 mm^2; may show organoid nesting and rosettes
Small cell carcinoma	12-13	Synaptophysin, chromogranin, INSM-1	High mitotic rate (>10 mitoses/2 mm^2); small cells; nuclear molding; often crush artifact noted

Abbreviations: CK, cytokeratin; HPF, high-power fields; INSM-1. insulinoma-associated protein 1.
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In the United States, the most common form of lung cancer was squamous cell cancer (SCC) until approximately 1987, when it was supplanted by adenocarcinoma. This is largely thought to be because of the introduction of filtered and low-tar cigarettes. SCLC once accounted for approximately 20% of all lung cancer diagnoses, but because of the changes in smoking rates, its incidence has declined to 14%.[18,19] Additional uncommon neuroendocrine tumors that occur in the lung are carcinoid, atypical carcinoid, and large cell neuroendocrine cancer.[17] Rare primary tumors in the lung include sarcomas, cancers with sarcomatoid or sarcomatous elements (eg, giant cell cancer, carcinosarcoma, and pulmonary blastoma), and cancers of the salivary gland (eg, mucoepidermoid cancer and adenoid cystic cancer).[20]

ATYPICAL ADENOMATOUS HYPERPLASIA

Atypical adenomatous hyperplasia is considered as a precursor to adenocarcinoma and is usually identified incidentally, often at the time of resection. Lesions are typically small (a few millimeters) and consist of discrete but ill-defined bronchoalveolar proliferation in which the alveoli are lined by monotonous slightly atypical cuboidal to low-columnar epithelial cells.

ADENOCARCINOMA IN SITU

Adenocarcinoma in situ, previously referred to as bronchioalveolar carcinoma, is defined as an adenocarcinoma of the lung that grows lepidically, along the alveolar septa.[17] Histologically, pure adenocarcinoma in situ is rare; more common is adenocarcinoma, mixed subtype, with both adenocarcinoma in situ features and invasive components. The natural history of both atypical adenomatous hyperplasia and adenocarcinoma in situ is not well characterized. Radiographically, both atypical adenomatous hyperplasia and adenocarcinoma in situ may be initially detected as ground-glass lesions on cross-sectional chest imaging; an increasingly solid or more solid component to a mixed-density nodule often signals evolution of invasive disease.

ADENOCARCINOMA

Adenocarcinoma accounts for approximately 50% of all new lung cancer cases, has been associated with scarring (fibrosis), and is more likely to be peripherally located than squamous cell lung cancer or SCLC. Lung adenocarcinoma typically stains positive by immunohistochemistry (IHC) for cytokeratin (CK) 7 and negative for CK20. Accepted markers for identification of pulmonary adenocarcinoma are TTF-1 and Napsin-A, both of which have a sensitivity of approximately 80%.[20] Adenocarcinoma is the most common lung cancer histology seen in individuals with limited or no tobacco use history. Similarly, the most currently actionable molecular drivers, discussed later in this chapter, are commonly seen in adenocarcinomas (as opposed to other NSCLC subtypes), and NSCLCs occurring in individuals with limited/no tobacco use history tend to be enriched with cancers harboring these actionable oncogenic driver events.

SQUAMOUS CELL CANCER

SCCs account for approximately 25% of lung cancers and occur almost exclusively in patients with a heavy smoking history. These lesions tend to be located centrally in segmental bronchi, involve lobar and main-stem bronchi by extension, and may cavitate, leading to hemoptysis. Histologic features of SCC include intercellular bridging, squamous pearl formation, and individual cell keratinization. Squamous cell lung cancer often overexpresses the squamous histology marker p63 and its isoform p40, as well as CK5/6, all detectable by IHC. The primary site for squamous cell carcinoma cannot typically be determined pathologically, and therefore, review of the clinical and radiographic features of the tumor is required to determine that it is a primary lung cancer as opposed to a metastatic lesion.

LARGE CELL CANCER

Pure large cell lung cancer accounts for fewer than 5% of new lung cancer cases. This diagnosis is restricted to fully resected tumors where any differentiation morphologically or immunohistochemically to squamous cell carcinoma or adenocarcinoma has been excluded.[21] These tumors are typically poorly differentiated and are composed of large cells with abundant cytoplasm and large nucleoli.

PULMONARY NEUROENDOCRINE TUMORS

Neuroendocrine lung tumors represent a spectrum of pathologic entities, including typical carcinoid, atypical carcinoid, large cell neuroendocrine cancer, and SCLC. SCLC and large cell neuroendocrine cancer are high-grade tumors, whereas typical carcinoid and atypical carcinoid are low- and intermediate-grade cancers, respectively. These tumors demonstrate evidence of neuroendocrine differentiation through IHC expression of at least one of the following: chromogranin, synaptophysin, CD56 (neural cell adhesion molecule), or insulinoma-associated protein 1 (INSM-1). Methods for detecting cell turnover, including mitotic count, ki67, and the presence of necrosis, are used to distinguish between these diagnoses. Approximately 20% to 40% of patients with typical or atypical carcinoid have no history of tobacco use, whereas virtually all patients with SCLC and large cell neuroendocrine cancer have a history of smoking. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a syndrome often seen in middle-aged women with no history of tobacco use that consists of abnormal proliferations of neuroendocrine cells that are not yet invasive and is considered a precancerous lesion with the risk of progression to carcinoid tumors.[22]

Carcinoid Tumors

Carcinoid tumors are low-grade malignant neoplasms of neuroendocrine cells, which are divided into typical and atypical types. Compared with typical carcinoids, atypical carcinoids tend to be larger, have more mitoses per high-power field, and are associated with necrosis. Patients are also more likely to have nodal or distant metastases at presentation, and survival is reduced.

Large Cell Neuroendocrine Cancer

Large cell neuroendocrine cancer is defined as a tumor with neuroendocrine morphologic characteristics, including organoid nesting, palisading, a trabecular pattern, and rosette-like structures. It is differentiated from SCLC on the basis of histologic characteristics, including larger cell size, more abundant cytoplasm, and less prominent nuclear molding.[23]

SMALL CELL LUNG CANCER

SCLC is characterized by small cells with scant cytoplasm, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. Nuclear molding and smearing of the nuclear chromatin may be present because of crush artifact. Mitotic figures are common, necrosis can be extensive, and ki67 often stains more than 80% of cells.[17,23]

KEY POINT

- The four most common histologic subtypes of lung cancer are adenocarcinoma, squamous cell carcinoma, large cell carcinoma (collectively referred to as NSCLC), and SCLC.

STAGING

Accurate staging of lung cancer is critical for proper clinical management and assessment of prognosis. Staging of lung cancer follows the American Joint Committee on Cancer (AJCC) criteria (version 9),[24] which provide a standard classification with three components: the extent of the primary tumor (T), lymph node involvement (N), and distant metastases (M).

MOLECULAR BIOLOGY

A more sophisticated understanding of the biology of lung cancer has led to further subclassification based on molecular characteristics, most notably in lung adenocarcinoma. The presence of specific oncogenic drivers informs biology and prognosis. Importantly, it also guides systemic therapy. In fact, for patients with advanced non–squamous NSCLC, optimal systemic therapy should not be selected without the results of comprehensive tumor molecular profiling. As a result, it is imperative to assess the molecular profile of NSCLC at diagnosis in all treatment-eligible individuals.

GENOMIC PROFILING

Actionable genomic alterations in NSCLC are more commonly identified in tumors with non–squamous histology in patients with limited or no tobacco use history.[25] These include both mutations (single-nucleotide variants and deletions) as well as translocations and gene fusions; to date, amplification of genetic drivers has not proven predictive for therapeutic selection in NSCLC.[26] The current National Comprehensive Cancer Network (NCCN) guideline recommends testing for mutations in *EGFR, BRAF, HER2, KRAS, NRG1*, and *MET* and for translocations/fusions in *ALK, ROS-1, NTRK*, and *RET* in all advanced non–squamous NSCLCs.[26] For each of these alterations, there are targeted agents approved for therapeutic use (described later in this chapter). Per the NCCN guideline, molecular testing should also be considered in those with advanced squamous cell histology (especially patients with little/no tobacco use history), small biopsy specimens that may preclude comprehensive histologic assessment, or mixed histology tumors. Selected molecular testing for *EGFR* and *ALK* is indicated for patients with stage IB to IIIA non–squamous NSCLC for whom surgery is planned because the presence of those alterations can guide perioperative and adjuvant treatment (as detailed below). In addition, as discussed later in the chapter, testing for *EGFR* and *ALK* is indicated for patients with inoperable stage III non–squamous NSCLC because patients with those molecular aberrations do not benefit from immunotherapy as part of their treatment regimen. In addition, patients with an *EGFR* mutation may be considered for EGFR-targeted therapy after chemotherapy and radiation.

BLOOD-BASED GENOMIC TESTING

Circulating tumor DNA (ctDNA) from peripheral blood can be used for molecular analysis of NSCLC, particularly if the available tissue is sufficient to establish a histopathologic diagnosis of NSCLC but insufficient for molecular testing.[27,28] Molecular testing can be performed on blood using various nucleic acid sequencing methods to examine a panel of genes. Assays that use next-generation sequencing (NGS) of DNA and RNA are preferred when available.

A positive blood test is generally specific for the presence of the molecular aberration; however, a negative test should be interpreted with caution, given the known limits of sensitivity (ie, false-negative result). In addition, currently available blood-based assays are limited by the inability to provide validated results for programmed cell death ligand 1 (PD-L1) expression, which is often used for treatment planning for stage IV NSCLC. The absence of validated results for the latter significantly precludes meaningful use of ctDNA for therapeutic selection of palliative systemic therapy in advanced squamous cancers. When possible, uninformative ctDNA testing should be followed by a tissue biopsy to determine the presence or absence of a genomic aberration more conclusively.

IMMUNOHISTOCHEMICAL TESTING

In NSCLC, the presence of PD-L1 can be detected with immunohistochemical staining and is generally expressed as a percentage of tumor cells (Tumor Proportion Score [TPS]) or as a percentage of tumor cells and hematopoietic cells within the tumor (Combined Proportion Score [CPS]). In general, in NSCLC, a higher amount of staining for PD-L1 predicts a greater likelihood of response to PD-1/PD-L1–directed therapies.[29] The utility of PD-L1 staining will be discussed later in this chapter when discussing specific immunotherapies. With the approval of antibody-drug conjugates targeting HER-2 and c-MET for advanced NSCLC that has progressed on prior lines of therapy (discussed later in the chapter), immunohistochemical testing for these proteins is indicated in this population.

KEY POINTS

- Guidelines recommend testing for *EGFR*, *KRAS*, *HER2*, *BRAF*, and *MET* mutations and *ALK*, *ROS-1*, *NTRK*, *RET*, and *NRG1* translocations/fusions in all treatment-eligible patients with stage IV non–squamous NSCLC, with the consideration of testing in select treatment-eligible individuals with stage IV squamous NSCLC.

- *EGFR* and *ALK* testing is indicated for patients with resectable stage IB to IIIA non–squamous NSCLC and patients with inoperable stage III NSCLC who will receive concurrent chemotherapy and radiation.
- When tissue is not available for genomic testing, a blood-based "liquid biopsy" can be utilized for molecular testing; there are limitations to its sensitivity, and uninformative results may need to be confirmed with tissue-based testing.

CLINICAL PRESENTATION

Most patients with lung cancer present with symptomatic disease. The most common symptoms are anorexia, fatigue, weakness, and cough (Fig. 11-1). Metastatic disease at presentation is common in SCLC (75%) and adenocarcinoma (50%), and many metastatic sites are possible, with the most common being brain, bone, liver, and adrenal gland.[30]

Figure 11-1 Signs and Symptoms Associated With Lung Cancer

Key Symptoms	Other Common Symptoms	Less Frequent, but Important Symptoms	Rare/Severe Symptoms
1. Cough 2. Increased sputum production 3. Shortness of breath	1. Fatigue 2. Weight loss 3. Anorexia 4. Low-grade fever	1. Chest pain 2. Hemoptysis 3. Hoarseness (recurrent laryngeal nerve) 4. Bone pain	1. Superior vena cava obstruction 2. Superior sulcus/Pancoast tumor 3. Pericardial tamponade 4. Paraneoplastic syndromes 5. Brain metastases

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SUPERIOR VENA CAVA SYNDROME

Superior vena cava (SVC) syndrome occurs when the SVC becomes obstructed by either a tumor, a thrombus, or metastases to regional lymph nodes and is considered an oncologic urgency. SVC syndrome is seen in 10% of SCLC cases and 2% to 4% of NSCLC cases, but given the high prevalence of NSCLC, it accounts for approximately 50% of SVC syndrome cases, with SCLC accounting for 25% to 30%.[31] Hospitalization and urgent biopsy should be considered so that prompt treatment may be initiated. Common symptoms include distension of the collateral veins over the anterior chest wall and neck; swelling and puffiness of the neck, face, throat, eyes, and arms; headache; and cyanosis (known as Pemberton sign).

PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes (PNS) are caused by humoral factors produced by cancer cells that act at a site distant from the primary site and its metastases or by cross-reactivity between host antitumor antibodies and normal tissues.[32,33] For all PNS, treatment of the underlying cancer is recommended. In addition, syndrome-specific therapies may be used.

Two common PNS in patients with NSCLC are hypercalcemia and hypertrophic pulmonary osteoarthropathy (HPOA). Although hypercalcemia is most often caused by diffuse skeletal metastases, it can be the result of ectopic production of a parathyroid hormone-related peptide or other humoral substances. HPOA is seen more commonly in adenocarcinoma[34] and is characterized by clubbing of the digits and, when severe, painful periostitis of the long bones. HPOA may also occur with other non–malignant pulmonary diseases.

Although neurologic PNS are rare and can occur in various cancer types, they are predominately seen in SCLC. Up to 3% of patients with SCLC develop the most common syndrome, known as Lambert-Eaton myasthenic syndrome (LEMS).[35] This syndrome is especially important to recognize because amifampridine is an approved effective therapy for LEMS. Other observed central nervous system (CNS) paraneoplastic disorders include cerebellar degeneration, dementia, limbic encephalopathy, and visual PNS with optic neuritis and retinopathy. Paraneoplastic sensory neuropathy is often associated with the presence of anti-Hu antibody (also known as type 1 antineuronal nuclear antibodies [ANNA1]) and can lead to subacute distal sensory loss and the absence of deep tendon reflexes with normal muscle strength.

In patients with SCLC, ectopic production of ACTH may result in Cushing syndrome with excess cortisol production, resulting in muscle weakness, weight loss, hypertension, hyperglycemia, and profound hypokalemia. As a result of rapid tumor growth,

the classic physical manifestations of Cushing syndrome are often absent. The syndrome of inappropriate antidiuretic hormone (SIADH) leads to euvolemic hypo-osmolar hyponatremia. Most malignancy-associated SIADH cases are seen in SCLC, and symptoms are related to the degree and speed of development of the hyponatremia.

KEY POINTS

- Common symptoms of lung cancer include local symptoms, such as cough, pain, and shortness of breath, and constitutional symptoms, such as fatigue, weakness, anorexia, and weight loss.
- The most common sites for metastatic disease in lung cancer are the lungs (ipsilateral and contralateral), adrenal glands, liver, bone, and brain.
- PNS are commonly seen in patients with lung cancer, notably, hypercalcemia, SIADH, ectopic ACTH production, and neurologic syndromes.

SCREENING

Most patients with lung cancer present with advanced disease, which is associated with a poor prognosis. This has led to great interest in screening to detect lung cancer at an earlier, and therefore theoretically more curable, stage. Although the role of screening patients at high risk of the development of early-stage disease was debated for many years, screening with low-dose CT (LDCT) scan of the chest results in a clear reduction in lung cancer mortality in the screened population.

In LDCT, only the pulmonary parenchyma is examined, negating the use of intravenous contrast medium. This type of scan can usually be performed quickly (within one breath) and involves low doses of radiation. The National Lung Screening Trial (NLST) was a randomized multicenter study comparing annual LDCT with chest x-ray (CXR) for the screening of current and former heavy smokers for lung cancer. LDCT led to more cancer diagnoses and a 20% relative reduction in lung cancer mortality (P = .004) and a 6% decrease in all-cause mortality.[36] As a result of these data, the US Preventive Services Task Force issued recommendations for annual lung cancer screening with LDCT for adults of age 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the last 15 years. Similar results were seen in the NELSON trial conducted in Belgium and the Netherlands.[37] With 10 years of follow-up, use of LDCT at baseline and years 1, 2, 4, and 6.5 led to a 24% reduction in lung cancer mortality compared with no screening; the benefit was seen in men and women, and cancers detected by screening were primarily early stage (59% stage I cancers). The American Lung Association's 2024 "State of Lung Cancer Report" noted that in 2022, only 16% of eligible patients in the United States were screened for lung cancer.

KEY POINT

- Screening for lung cancer with annual LDCT of the chest is recommended for patients of age 50 to 80 years who have a smoking history of 20 or more pack-years and who are currently smoking or have quit within the last 15 years.

NSCLC MANAGEMENT

DIAGNOSIS AND STAGING WORKUP

Lung cancer is typically detected on chest imaging, either CXR or chest CT. For those with suspected lung cancer, biopsy for confirmation of the diagnosis is required. Based on the size and location of the suspected cancer, biopsy through one of the following procedures is typically pursued:

- Bronchoscopy with or without endobronchial ultrasound (EBUS)
- CT-guided biopsy by interventional radiology
- Surgical biopsy

Once a diagnosis is confirmed, a positron emission tomography (PET) scan is necessary to evaluate local extent and distant disease to common metastatic sites, such as liver and adrenal glands. Magnetic resonance imaging (MRI) of the brain is recommended for patients with clinical stage II or greater NSCLC. PET scans are more sensitive than CT scans and therefore may detect occult nodal or metastatic (especially skeletal) disease not readily seen on CT. Limitations of PET include cost, availability, inability to detect small lesions (<0.5-1 cm), and lack of specificity, particularly in patients with inflammatory or granulomatous disease and in the assessment of intrathoracic nodal involvement, which may be over- or underestimated by PET. Considering these limitations, PET does not replace invasive mediastinal staging (see below) for patients with potentially resectable lung cancer and is not a substitute for brain MRI.

Invasive Mediastinal Staging

Accurate staging of the mediastinum is critical in patients with radiographic evidence of early-stage or locally advanced NSCLC to assign precise tumor stage, guide optimal therapy selection/sequencing, and identify appropriate candidates for surgical

resection. Therefore, invasive mediastinal staging (either before or at the time of surgery) should be considered in all patients with clinical stage I to III NSCLC. The one possible exception is patients with clinical stage IA NSCLC with peripheral tumors who have no evidence of pathologic mediastinal lymphadenopathy by CT and PET because the combined negative predictive value of CT and PET for mediastinal nodal involvement in that setting is greater than 90%.[38] As discussed below, patients with extensive N2 or N3 nodal disease are often not considered for surgery. Transthoracic, transbronchial, and EBUS–guided needle aspirations or biopsy specimens is a minimally invasive method utilized at high-volume centers. Mediastinoscopy is a more invasive historic standard, which has a higher predicative value.[39]

STAGE I AND II NSCLC

SURGERY

Approximately one-third of all patients with lung cancer present with stage I or II disease. The treatment of choice for fit patients is anatomic surgical resection, which can result in cure for many patients. As discussed below, these patients may also be considered for neoadjuvant or perioperative treatment with chemotherapy and immunotherapy. The preferred surgical procedure is lobectomy, although for patients in whom disease crosses a major fissure or involves the proximal main-stem bronchus, bilobectomy or pneumonectomy may be required. Minimally invasive surgery (including robotic or video-assisted approaches) should be performed when feasible and where expertise in those techniques exist as it has been shown to result in increased functional outcomes, decreased pain, and fewer adverse events without compromising cancer outcomes when compared with traditional open lobectomy.[40]

Historically, lobectomy has been the procedure of choice, even for patients with small peripheral lesions, because prior studies suggested that sublobar resections are associated with increased local recurrence and decreased survival.[41] Lobectomy should include resection of bronchial, hilar, and selected mediastinal nodes, on the basis of published guidelines (at least nodes 4R and 7 for right-sided tumors; at least nodes 5/6 and 7 for left-sided tumors). Patients with peripheral chest-wall invasion (T3) should undergo en bloc resection of the involved ribs and underlying lung.

Importantly, a recent randomized trial of sublobar resection (including wedge resection and segmentectomy) versus lobectomy for patients with T1A (<2 cm) node-negative NSCLC demonstrated that sublobar resection was not inferior to lobectomy with respect to disease-free survival (DFS), and overall survival (OS) was similar between the two arms.[41] As a result, this approach should be considered in patients with tumors 2 cm or smaller that are clinically node negative and appropriate for a sublobar resection.

Preoperative Evaluation

The suitability of a patient for a definitive resection depends on two factors: the stage of the lesion and the ability of the patient to undergo surgery. A detailed discussion of the preoperative evaluation and comorbid conditions is beyond the scope of this chapter; however, assessment of pulmonary reserve is important. It should be emphasized that a certified thoracic surgeon, working as part of a multidisciplinary thoracic oncology team, is best qualified to determine whether a patient is a surgical candidate. The key pulmonary function tests are FEV1 and diffusing capacity. Predicted postoperative FEV1 and diffusing capacity should be calculated (based on the number of pulmonary segments to be resected) and expressed as a percentage of normal. A predicted postoperative FEV1 or diffusing capacity percentage of 30% or lower suggests an increased risk of postoperative morbidity or mortality.[42]

RADIATION THERAPY

Stereotactic ablative radiation therapy (SABR), also known as stereotactic body radiation therapy (SBRT), delivers high-dose radiation in a few fractions to small targets with limited toxicity. For patients with NSCLC who are not candidates for surgery, or who decline surgery, and have tumors smaller than 5 cm and no evidence of regional nodal disease, SABR is the preferred alternative therapy and has good local disease control and better OS than conventional radiation therapy. Numerous prospective series of SABR in medically inoperable patients with T1/T2 N0 NSCLC report local control rates of 86% to 97% at 2 to 5 years, with some noting 5-year survival approaching 40%.[43] Although randomized trials comparing SBRT with surgery in medically operable patients with T1/T2 NSCLC have been attempted, they have been challenging to complete, and therefore, there are insufficient data to recommend SABR for patients who are able to undergo surgery.

Other locally ablative treatments, including radiofrequency ablation and microwave ablation, are used in specific clinical situations and may be considered in medically inoperable patients with appropriately sized tumors at centers with expertise or when SABR is not an option.

PANCOAST TUMORS

Pancoast, or superior sulcus, tumors in the upper lobe adjoining the brachial plexus are frequently associated with Horner syndrome (ptosis, miosis, and anhidrosis) or shoulder and arm pain; the latter is caused by rib destruction, involvement of

the seventh cervical vertebra or T1 nerve roots, or both. The SWOG Intergroup phase 2 trial involving patients with T3-4, N0-1, M0 superior sulcus NSCLC established the current standard of care, which consists of a combination of cisplatin and etoposide and concomitant radiation therapy (45 Gy) followed by surgical resection and then two cycles of consolidation chemotherapy after surgery. The 2-year survival rate was 55% for all eligible patients and 70% for patients who had complete resection.[44] This treatment paradigm was developed well before the use of immunotherapy and molecularly targeted therapy in NSCLC, and, therefore, studies are currently evaluating the incorporation of these therapies into the treatment of superior sulcus tumors. Unresectable Pancoast tumors are generally approached similarly to cases of unresectable stage III NSCLC (as discussed below).

ADJUVANT CHEMOTHERAPY

The rationale for adjuvant chemotherapy for patients with resected early-stage lung cancer is based on the observation that distant metastases are the most common sites of failure after potentially curative surgery. Several randomized trials have evaluated the role of adjuvant chemotherapy after surgical resection of early-stage NSCLC. In a meta-analysis of five of these trials, there was a 5.4% absolute survival benefit at 5 years (hazard ratio [HR], 0.89).[45] Importantly, the benefit of adjuvant chemotherapy varied considerably by disease stage, and staging in these trials was per AJCC staging version 7, not the current version 8. In stage IA NSCLC, adjuvant chemotherapy was associated with a trend toward worse survival (HR for death, 1.40), and a nonsignificant trend toward a survival benefit was observed in stage IB disease (HR for death, 0.93). A substantial survival benefit was seen in stage II and III disease (HR for each, 0.83). In the CALGB 9633 trial, patients with resected stage IB NSCLC were randomly assigned to receive postoperative chemotherapy or undergo standard observation. Although the overall study results were negative, an unplanned retrospective subset analysis of patients with tumors 4 cm or larger demonstrated a substantial survival difference in favor of adjuvant chemotherapy (HR, 0.69).[46] Based on these trials, the role of adjuvant chemotherapy for resected stage IIB and III (using AJCC version 8) NSCLC is well established, and adjuvant chemotherapy is not recommended for patients with stage IA disease. In patients with stage IB/IIA NSCLC, the major US guidelines differ in their recommendations, with ASCO recommending against the routine use of adjuvant chemotherapy and the NCCN giving the option of observation or use of adjuvant chemotherapy.[47] ASCO does include a careful discussion of the risks and benefits of adjuvant chemotherapy with a medical oncologist in its recommendations. Some advocate consideration of adjuvant chemotherapy in this population in patients with other high-risk features, such as tumors 4 cm or larger, high-grade histology, lymphovascular invasion, wedge resection, and pleural invasion, although there are no prospective trials demonstrating a survival benefit with chemotherapy in these groups. Cisplatin was combined with vinca alkaloids or etoposide in the adjuvant trials, but it is common practice to use more modern agents along with cisplatin, such as docetaxel, gemcitabine (in squamous histology), or pemetrexed (in non–squamous histology). Despite the fact that treatment with these agents is included in current guidelines, data demonstrating a survival benefit with them are lacking. Carboplatin is often substituted for cisplatin in patients who are not candidates for cisplatin, but again, there are no trials to support a benefit of carboplatin-based adjuvant chemotherapy in resected NSCLC.

ADJUVANT IMMUNOTHERAPY

The IMpower 010 trial revealed that the addition of 1 year of atezolizumab after adjuvant chemotherapy significantly improved DFS (HR, 0.66) in patients with stage II to IIIA NSCLC expressing PD-L1 on 1% or more of tumor cells, and atezolizumab is a US Food and Drug Administration (FDA)–approved option for this population. OS data with atezolizumab remain immature, but a recent update demonstrated an improvement in OS for patients whose tumors had at least 50% PD-L1 expression (HR, 0.43).[48] KEYNOTE-091 led to the FDA approval of 12 months of pembrolizumab after adjuvant chemotherapy significantly improved DFS for PD-L1–unselected patients with completely resected stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC (median DFS in the pembrolizumab group, 53.6 months vs 42.0 months in the placebo group; HR, 0.76; 95% CI, 0.63-0.91; $P = .0014$).[49] Although there has been a shift toward perioperative therapy (discussed below) for patients with clinical stage II or III disease, adjuvant chemotherapy followed by adjuvant immunotherapy remains an important consideration in patients who have not received preoperative systemic therapy and those upstaged at the time of surgery.

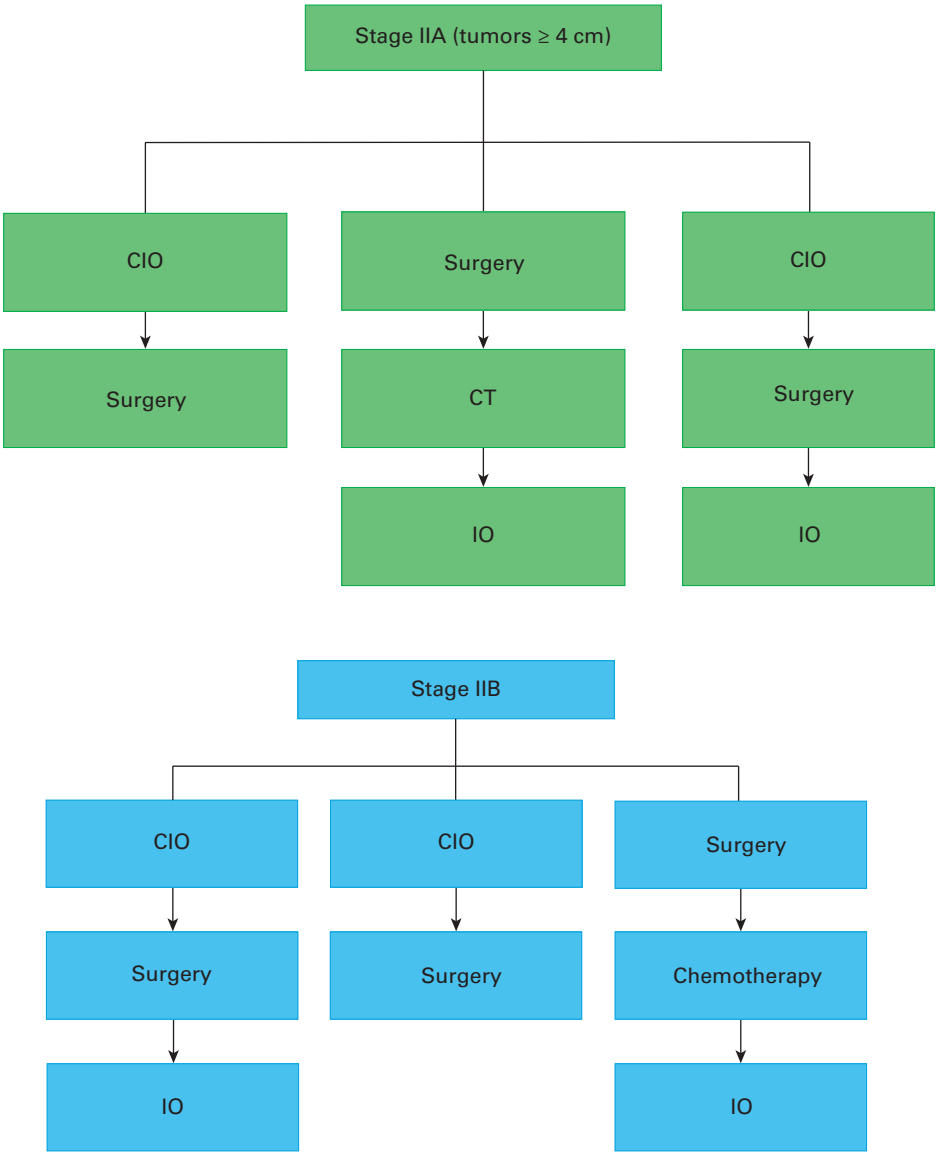
MOLECULARLY TARGETED AGENTS

The phase 3 ADAURA trial randomly assigned patients with completely resected stage IB, II, or IIIA (per AJCC version 7 staging) NSCLC with *EGFR* exon 19 deletions or L858R to 3 years of the third-generation EGFR TKI osimertinib versus placebo. Use of adjuvant chemotherapy was not mandated but was similar between the two arms (~60% of patients in both arms received adjuvant chemotherapy). Osimertinib improved DFS for patients with resected stage IB to IIIA NSCLC, with a 2-year DFS rate of 89% with osimertinib versus 52% with placebo and a DFS HR of 0.20. In patients with stage IB to IIIA disease, the 5-year OS rate was 88% in the osimertinib group and 78% in the placebo group (overall HR for death, 0.49; 95.03% CI, 0.34-0.70; $P < .001$).[50]

One potential criticism of the trial is that only 43% of patients assigned to the placebo arm received osimertinib on recurrence of disease. Osimertinib is currently recommended as adjuvant therapy after chemotherapy for patients with completely resected stage IB to IIIA NSCLC harboring a sensitizing *EGFR* mutation.[51]

The phase 3 ALINA trial randomized patients with completely resected *ALK*-positive NSCLC of stage IB (tumors ≥4 cm), II, or IIIA (per AJCC version 7 staging) to receive alectinib for 2 years or four cycles of platinum-based chemotherapy. Of note, the patients receiving alectinib did not receive adjuvant chemotherapy. The primary endpoint was DFS in the stage II and IIIA population, and this endpoint was met, with 93.8% of patients receiving alectinib and 63% of patients receiving chemotherapy alive and disease free at 2 years (DFS HR, 0.24). Based on these data, alectinib was approved for use in the United States for patients with stage II to IIIA *ALK*-positive NSCLC undergoing complete resection. The current trial does not answer the question of whether these patients should also receive adjuvant chemotherapy before alectinib (Fig. 11-2).[51]

Figure 11-2 Approved Options for Resectable *ALK* and *EGFR*–Wild-Type Stage IIA and IIB NSCLC



Abbreviations: CIO, chemotherapy with immunotherapy; CRT, chemotherapy and radiation therapy; EGFR, epidermal growth factor receptor; IO, immunotherapy; NSCLC, non–small cell lung cancer.
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PRESENTING CASE STUDY

A 66-year-old woman was diagnosed with non–small cell lung cancer (NSCLC) after having a low-dose screening computed tomography (CT) of the chest 3 months ago. She now presents to an oncologist 6 weeks after undergoing a minimally invasive right lower lobectomy. Final lobectomy pathology identifies a 2.6-cm adenocarcinoma and no pleural invasion. Surgical margins are negative for tumor. Two of the five sampled 11R lymph nodes contain cancer. Three 4R lymph nodes and a level 7 lymph node are negative for cancer. The programmed cell death ligand 1 (PD-L1) tumor proportion score is 60. *EGFR* and *ALK* analyses show no *EGFR* mutation or *ALK* rearrangement. The patient has recovered from thoracotomy; her incisions are well healed, and her Eastern Cooperative Oncology Group (ECOG) performance status is 1. Her medical history is significant for hypertension and no autoimmune disease. Laboratory studies, including complete blood count and comprehensive metabolic panel, are within reference ranges.

Given this patient's stage, medical history, molecular testing, and performance status, what additional treatment options are most appropriate?

This patient has completely resected stage IIB NSCLC, and her tumor is positive for PD-L1 staining. Her functional status is good, and she has no apparent contraindication to chemotherapy or immunotherapy. There is level I evidence to support four cycles of adjuvant cisplatin-based chemotherapy followed by immunotherapy (atezolizumab or pembrolizumab) for 12 months. Given that molecular testing for *EGFR* and *ALK* was negative, there is no indication for *EGFR*- or *ALK*-targeted therapy. For patients with a positive surgical margin following resection, re-resection or radiation therapy is recommended. With this patient undergoing a complete resection with negative surgical margins, there is no role for additional surgery or radiation therapy.

Following completion of four cycles of cisplatin and pemetrexed and 3 months of immunotherapy, the patient develops right upper quadrant abdominal pain. CT of the abdomen reveals multiple new liver lesions concerning for metastases. FGD/PET (positron emission tomography) confirms the liver lesions to be avid along with two new PET-avid pulmonary nodules in the right lung. Biopsy of a liver lesion confirms recurrent adenocarcinoma, and broad panel molecular testing does not reveal any targetable molecular changes. Other than the pain, which is controlled with occasional analgesics, the patient reports no other symptoms, and her ECOG performance status remains at 1.

What management options are most appropriate in this setting?

The patient now has biopsy-proven stage IV NSCLC. Given that she recently received platinum-based chemotherapy and was on immunotherapy at the time of recurrence, there is likely limited benefit to a re-trial of platinum-based treatment and immunotherapy. Given her lack of significant co-morbidities and preserved functional status, second-line chemotherapy with docetaxel (with or without ramucirumab) can be considered. With the development of stage IV disease, it is also reasonable to perform an MRI of the brain to exclude the presence of metastatic disease. Referral to palliative care for symptom management and to initiate goals of care discussions is also appropriate.

NEOADJUVANT AND PERIOPERATIVE IMMUNOTHERAPY AND CHEMOIMMUNOTHERAPY

In patients with surgically resectable NSCLC, there are now multiple approved approaches for sequencing of chemotherapy and immunotherapy: (1) neoadjuvant therapy alone, (2) perioperative (both neoadjuvant and adjuvant therapy), and (3) adjuvant therapy alone. CheckMate 816 was a randomized phase 3 study of three cycles of neoadjuvant nivolumab and platinum-doublet chemotherapy versus chemotherapy alone in resectable stage IB (with tumors >4 cm) to IIIA NSCLC.[52] The study met its primary endpoint, demonstrating a significantly improved pathologic complete response (pCR) rate of 24% with neoadjuvant nivolumab and chemotherapy, compared with only 2% with chemotherapy alone. Nivolumab and chemotherapy also led to significant improvements in event-free survival (median 31.6 vs 20.8 months; HR, 0.63; $P = .005$) and OS (median not reached vs 73.7 months; HR, 0.72; $P = .048$).[53] In the KEYNOTE-671 trial, 797 patients with resectable stage II to IIIB (N2 nodal stage) NSCLC were randomized to neoadjuvant pembrolizumab or placebo for up to four cycles along with cisplatin-based chemotherapy followed by surgical resection and either adjuvant pembrolizumab or placebo for up to 13 cycles. The primary endpoints were DFS and OS.[54] The DFS rate was significantly improved in the group receiving pembrolizumab (62.4% at 24 months vs 40.6%; HR, 0.58; $P < .001$). OS had not reached maturity at this analysis. The similarly designed AEGEAN trial randomized patients with resectable

stage IIA to IIIB (N2 nodal stage) NSCLC to receive durvalumab or placebo with platinum-based chemotherapy for four cycles followed by surgery and then durvalumab or placebo for up to 12 cycles.[55] The primary endpoints were pCR and DFS. The pCR rate was improved in the group receiving durvalumab (17.2% vs 4.3%; $P < .001$), as was the DFS rate at 12 months (73.4% vs 64.5%; HR, 0.68; $P = .004$). The CheckMate 77T trial evaluated the addition of perioperative nivolumab versus placebo to neoadjuvant platinum-based chemotherapy followed by surgical resection and either adjuvant nivolumab or placebo for up to 12 cycles and demonstrated significant improvements in pCR and event-free survival.[56] Note that for all the studies discussed above, the AJCC version 7 staging system was utilized. As a result of these trials, multiple strategies for neoadjuvant and perioperative systemic therapy are now FDA approved and guideline concordant in patients with surgically resectable stage IB (≥4 cm) to IIIA NSCLC without *EGFR*/*ALK* alterations: (1) neoadjuvant platinum-based chemotherapy with nivolumab or (2) perioperative platinum-based chemotherapy with pembrolizumab, durvalumab, or nivolumab. Many unanswered questions remain, such as what to do with patients with a suboptimal response to neoadjuvant treatment and whether a neoadjuvant, perioperative, or adjuvant approach is the most effective (2). Ongoing trials are attempting to answer some of these questions.

KEY POINTS

- The KEYNOTE-091 trials demonstrated that 12 months of pembrolizumab after adjuvant chemotherapy significantly improves DFS for PD-L1–unselected patients with completely resected stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC.
- The IMpower 010 trial revealed that the addition of 1 year of atezolizumab after adjuvant chemotherapy significantly improves DFS in patients with stage II to IIIA NSCLC expressing PD-L1 on 1% or more of tumor cells.
- Adjuvant osimertinib improves DFS and OS for patients with resected stage IB to IIIA *EGFR*-mutated NSCLC.
- Adjuvant alectinib improves DFS for patients with resected stage II to IIIA *ALK*-rearranged NSCLC.

STAGE III NSCLC

Treatment of stage III NSCLC is one of the most controversial issues in the management of lung cancer. In large part, this is because of the heterogeneity of the disease and the patient population. Treatment of stage III NSCLC should be managed by an experienced multidisciplinary team and could include consultation with thoracic surgery, medical oncology, and radiation oncology, with the consideration of systemic therapies (chemotherapy, immunotherapy, targeted therapy), radiation therapy, and surgery, in various combinations and sequences (Fig. 11-3). Interpretation of the results of clinical trials involving patients with locally advanced disease has been clouded by several issues, including changing diagnostic techniques, different staging systems, and the heterogeneity of stage III lung cancer. For example, a patient with bulky, symptomatic, unresectable NSCLC and a patient with resectable NSCLC and incidental lymph node involvement can have the same TNM stage.

MICROSCOPIC STAGE IIIA NSCLC

Occasionally, despite appropriate preoperative staging, patients thought to have stage I or II disease are found to have N2 nodal involvement at the time of surgery. As outlined in the previous section, there is a survival benefit with adjuvant cisplatin-based chemotherapy and immunotherapy for patients with completely resected stage III NSCLC. Postoperative radiation therapy (PORT) is no longer standard of care. In a meta-analysis, PORT reduced locoregional recurrence but did not prolong survival.[57] The randomized phase 3 Lung-ART trial was the first prospective trial to explore the role of PORT. In this study, 501 patients with completely resected NSCLC with confirmed N2 nodal involvement were randomly assigned to PORT or observation after adjuvant chemotherapy.[58] Use of PORT was not associated with a significant improvement in either PFS or OS, with no difference in the 3-year OS rate (66.5% with PORT vs 68.5% with observation), and therefore, its use has fallen out of standard practice.

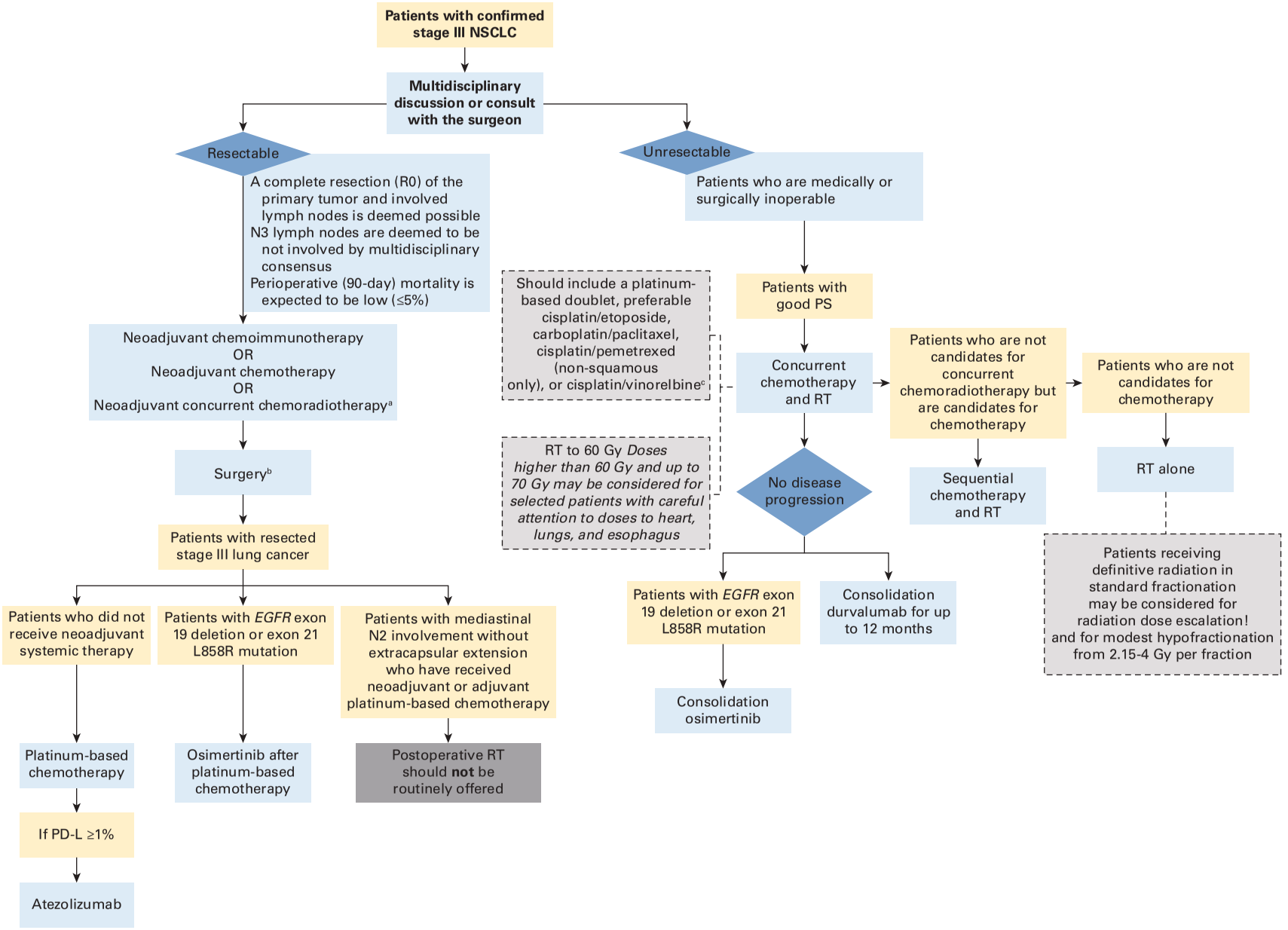
RESECTABLE STAGE III NSCLC

The optimal treatment of resectable, non–bulky stage IIIA NSCLC generally consists of systemic treatment (see Adjuvant Treatment and Neoadjuvant and Perioperative Chemotherapy and Immunotherapy sections above) combined with a local approach (radiation therapy and/or surgery).[59] Strategies include surgery followed by adjuvant therapy, neoadjuvant chemoimmunotherapy followed by surgery, perioperative chemoimmunotherapy and surgery, or concurrent or sequential chemotherapy with definitive radiation therapy followed by immunotherapy or targeted therapy (Fig. 11-3). For patients who cannot receive immunotherapy, neoadjuvant chemotherapy or chemotherapy and radiation therapy are sometimes used.

UNRESECTABLE STAGE III NSCLC

The standard treatment of unresectable, locally advanced stage III NSCLC is concurrent chemoradiation therapy. This population often includes patients with bulky stage IIIA or IIIA disease with multistation mediastinal lymph node involvement and those with stage IIIB or IIIC NSCLC, although the definition of unresectable is not universally agreed upon. Randomized studies

Figure 11-3 Management of Stage III NSCLC Algorithm



Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; NSCLC, non–small cell lung cancer; PET, positron emission tomography; PS, performance status; RT, radiation therapy.
Arrows with dotted lines indicate that the level of obligation is a "may" (moderate) recommendation.
[a]Resectable superior sulcus tumors.
[b]Patients with stage III NSCLC generally should not be excluded from consideration for surgery by nonsurgical physicians.
[c]Carboplatin may be substituted for cisplatin in patients with contraindications to or deemed ineligible for cisplatin.
Reprinted from Daly ME, Singh N, Ismaila N, et al., Management of stage III non–small cell lung cancer: ASCO guideline rapid recommendation update. *J Clin Oncol*. 2024;42(25):3058-3060. doi:10.1200/JCO-24-01324

have demonstrated an improvement in median and long-term survival with chemotherapy and radiation therapy compared with radiation therapy alone.[60] Delivery of concurrent chemoradiation therapy is associated with a survival benefit over sequential chemotherapy and radiation therapy, although this is also associated with greater toxicity.

In the United States, the two chemotherapy regimens most commonly administered with definitive radiation therapy for NSCLC are a combination of cisplatin and etoposide (at full doses) and a combination of carboplatin and paclitaxel (at low weekly doses). The combination of cisplatin and etoposide was studied in a multicenter phase 2 study of patients with stage IIIB NSCLC. In this study, the 5-year survival rate was 15%, and treatment was notable for myelosuppression and a relatively high rate of radiation esophagitis (grades 3-4, 20%).[61] A randomized phase 3 trial compared cisplatin and etoposide with weekly carboplatin and paclitaxel.[62] In this study, 200 patients with stage III NSCLC received 60 to 66 Gy of thoracic irradiation and were randomly assigned to receive either concurrent full-dose cisplatin and etoposide or weekly carboplatin and paclitaxel. There was no significant difference in the median OS between the two arms. The 3-year survival rate was notably higher with cisplatin and etoposide (41.1% vs 26%), although the toxicity rates were also higher, including the incidence of grade 2 or worse radiation pneumonitis (33.3% vs 18.9%) and grade 3 or worse esophagitis (20% vs 6.3%).

Additional platinum doublets have also been explored. In the phase 3 PROCLAIM trial, 598 patients with stage IIIA to IIIB non–squamous NSCLC were randomly assigned to receive thoracic irradiation (60-66 Gy) with either concurrent cisplatin and etoposide for two cycles followed by two cycles of consolidation platinum-based doublet chemotherapy or concurrent cisplatin and pemetrexed for three cycles followed by four cycles of pemetrexed consolidation. This superiority study did not meet its primary endpoint. The combination of cisplatin and pemetrexed did not improve survival over cisplatin and etoposide (HR, 0.98; median, 26.8 vs 25.0 months), although the cisplatin and pemetrexed arm had a lower incidence of any drug-related grades 3 to 4 adverse events (64.0% vs 76.8%), including neutropenia (24.4% vs 44.5%).[63]

The optimal chemotherapy to deliver with radiation therapy remains unclear. Escalating radiation dose, however, does not improve outcomes. Results of a phase 3 trial showed that standard 60-Gy thoracic irradiation is superior to a 74-Gy radiation dose with chemotherapy in terms of OS and locoregional control for treatment of stage III NSCLC.[64] These results were not explained simply by an increase in toxicity.

IMMUNOTHERAPY IN STAGE III NSCLC

Although definitive chemoradiation is a potentially curative approach, long-term survival is unfortunately only achieved in a minority of patients. Based in part on the preclinical evidence demonstrating a synergy between radiation therapy and the use of checkpoint inhibitors, the randomized phase 3 PACIFIC study explored the role of durvalumab as consolidation therapy after concurrent chemoradiotherapy. In this trial, 713 patients with unresectable stage III NSCLC who had completed definitive thoracic irradiation (54-66 Gy) with at least two cycles of concurrent platinum-based chemotherapy and had not experienced progression were randomly assigned at a 2:1 ratio to receive 10 mg/kg of durvalumab or placebo every 2 weeks for up to 12 months. After a median follow-up of 34.2 months, the use of durvalumab significantly improved PFS from 5.6 to 16.9 months (HR, 0.55) and also led to a significant improvement in OS (HR, 0.72).[65] The incidence of new lesions was lower with durvalumab, including the development of new brain metastases (6.3% with durvalumab vs 11.8% with placebo). The incidence of grade 3 or 4 adverse events was slightly higher with durvalumab (30.5% vs 26.1%), with similar rates of pneumonitis (4.8% vs 2.6%). Given the acceptable tolerability and a clear improvement in survival, incorporation of durvalumab in appropriate patients has emerged as standard of care in this setting.[66]

TARGETED THERAPY IN STAGE III NSCLC

The LAURA trial recently established a role for osimertinib in the treatment of patients with unresectable, *EGFR*-mutated stage III NSCLC receiving concurrent chemotherapy and radiation. After completion of chemotherapy and radiation therapy, patients were randomly assigned to osimertinib or placebo until progression or unacceptable toxicity. Patients in the osimertinib arm had a statistically significant improvement in median PFS (39.1 vs 5.6 months).[66] On the basis of this trial, osimertinib is an FDA- and guideline-approved option for *EGFR*-mutated, unresectable stage III NSCLC after completion of concurrent chemoradiation therapy. Ongoing trials are addressing this approach in patients with less common actionable genetic alterations.

KEY POINTS

- Treatment options for stage III NSCLC are complex and varied and generally include some combination of systemic therapy (chemotherapy, immunotherapy, and targeted therapy), radiation therapy, and surgery; treatment decisions should be made in discussion with a multidisciplinary team.
- If microscopic N2 (or N1) disease is detected at surgery in a patient who did not receive neoadjuvant therapy, adjuvant therapy should be administered.
- For patients with *EGFR*-mutated, unresectable stage III NSCLC, osimertinib is an approved option after completion of concurrent chemoradiation therapy.

STAGE IV NSCLC

Most patients with NSCLC present with stage IV disease; the goal of treatment in such patients is typically palliative. Systemic therapy can prolong survival and improve quality of life. Historically, a similar treatment approach was used for all patients with advanced NSCLC; however, current treatment recommendations are guided by performance status (PS), histology, the presence or absence of actionable oncogenic driver alterations, and tumor PD-L1 status.[26] When present, targeted therapy may be the preferred frontline therapy, although the level of evidence for each specific target will vary. For some targets, such as *EGFR*, *ALK*, *RET*,[67] *MET*, and *ROS-1*, FDA-approved agents offer superior outcomes to chemotherapy and/or immunotherapy. For other targets, the evidence supporting targeted therapy is still evolving, but identification of these alterations may influence later lines of therapy or facilitate involvement in a clinical trial.[68] When no actionable alterations are identified, early incorporation of immunotherapy improves outcomes. For all patients, optimizing palliation and supportive measures remains an important consideration.

OLIGOMETASTATIC NSCLC

Although the presence of distant metastases confirms stage IV lung cancer, the extent of disease may play a role in management. Stage IV lung cancer still represents a spectrum of disease, and some advanced cancers can still have a more indolent course.[69] The current AJCC staging system provides for identification of patients with a single extrathoracic metastasis in a single organ (M1b). For patients with NSCLC who have a limited number of metastases, or oligometastatic NSCLC, the potential benefit with definitive therapy at all sites of disease in addition to metastatic systemic therapy was suggested by small trials in the preimmunotherapy era. In a randomized phase 2 study, 49 patients with oligometastatic NSCLC, defined here as three or fewer sites of metastasis, were randomly assigned to receive definitive local consolidative therapy, either surgery or radiation therapy, to the isolated involved sites after receiving first-line systemic therapy.[70] The median PFS favored the local consolidative arm (14.2 vs 4.4 months), as did the median OS (41.2 vs 17.0 months). NRG LU002 randomly assigned patients to receive maintenance systemic therapy and local consolidative therapy or maintenance systemic therapy alone after completing four cycles of first-line systemic therapy and had at least stable disease for metastatic NSCLC with limited metastatic sites. The addition of local consolidative therapy did not provide additional benefit to maintenance systemic therapy with a PFS HR of 0.93 (95% CI, 0.66-1.31) and an OS HR (95% CI, 0.70-1.56) of 1.05 between both arms.[71] The optimal definition of oligometastatic disease and the importance of specific sites of disease involvement will require additional refinement. Although more studies are required, local consolidation is a consideration for a subset of patients with limited sites of disease and good PS.

TARGETED THERAPY IN NSCLC

EGFR MUTATION–POSITIVE NSCLC

EGFR belongs to the HER/erbB family of growth factor receptors, which includes EGFR (HER1 or erbB1), HER2/neu (erbB2), HER3 (erbB3), and HER4 (erbB4). These cell surface proteins consist of an extracellular ligand-binding domain, a transmembrane structure, and an intracellular tyrosine kinase domain. The binding of ligand to receptor activates receptor dimerization and tyrosine kinase autophosphorylation, initiating a cascade of intracellular events and leading to increased cell proliferation, angiogenesis, and metastasis and decreased apoptosis. Inappropriate pathologic activation of this receptor-signal transduction pathway can be caused by specific *EGFR*-activating mutations.[72,73]

In NSCLC, activating mutations in the *EGFR* tyrosine kinase domain are seen in approximately 10% to 30% of lung adenocarcinomas, depending on the region of the world, and are centered around exons 18 to 21.[74] At diagnosis, these mutations are typically mutually exclusive of other driver alterations and are associated with certain clinicopathologic features (eg, female sex, East Asian race, never or light smoking history, and adenocarcinoma histology), although *EGFR* mutations can regularly be detected in patients without these characteristics. Exon 19 deletions, commonly in-frame deletions of amino acids 746 to 750, and L858R in exon 21 (ie, classic activating *EGFR* mutations) account for approximately 90% of *EGFR* mutations. Other *EGFR* mutations exist as well, although with variable responsiveness to available EGFR TKIs. When a TKI-sensitizing *EGFR* mutation is identified in advanced NSCLC, EGFR-directed TKIs are the preferred initial therapy.

There are currently seven different EGFR TKIs FDA approved for the initial treatment of *EGFR*-mutated NSCLC. In this setting, EGFR TKI therapy has been consistently superior to platinum-doublet chemotherapy, with markedly higher response rates and significantly improved PFS and OS. EGFR TKI therapy can be associated with rash, diarrhea, and paronychia, related to wild-type *EGFR* expression in nontumor tissue such as the gastrointestinal tract and skin, but consistently has lower rates of grade 3 or worse toxicity than chemotherapy.

First-generation EGFR TKIs (erlotinib and gefitinib) have an average 9-month benefit, often limited by the development of the resistance mutation T790M. Second-generation TKIs (eg, afatinib and dacomitinib) have increased toxicity associated with irreversible binding and target wild-type *EGFR, HER2*, and *HER4*. The RELAY trial explored the addition of ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor receptor 2 (VEGFR2), to erlotinib. The combination led to a significant improvement in PFS from 12.4 to 19.4 months (HR, 0.59),[75] leading to its FDA approval. Importantly, this study excluded patients with brain metastases.

The third-generation TKI osimertinib was compared with first-generation TKI therapy in the randomized FLAURA trial.[76] Osimertinib had a superior PFS of 18.9 months compared with 10.2 months in the control arm (HR, 0.46). Duration of response (DoR) was greater with osimertinib (17.2 vs 8.5 months), and the incidence of grade 3 or worse adverse events was lower with osimertinib (34% vs 45%). Osimertinib also has greater activity in the CNS, supported by a decreased incidence of CNS progression with osimertinib (6%) compared with the control arm (15%). With longer follow-up, a survival advantage was seen with osimertinib (HR, 0.80), where the median survival was 38.6 months compared with 31.8 months with erlotinib or gefitinib.[77] Osimertinib is approved as a single-agent initial therapy for *EGFR*-mutated NSCLC.

The phase 3 FLAURA2 study,[73] which explored the addition of platinum and pemetrexed to osimertinib in 557 treatment-naive patients with *EGFR*-positive (exon 19 deletion or L858R mutation) NSCLC, reported a significant improvement in median investigator-assessed PFS (HR, 0.62; 95% CI, 0.49-0.79; $P < .001$), with no new safety concerns, although there was an increased incidence of grade 3 or higher adverse events driven by chemotherapy. The objective response rate (ORR) was 83% in the combination arm compared with 76% in the osimertinib arm, with median DoRs of 24 (95% CI, 20.9-27.8) and 15.3 months (95% CI, 12.7-19.4), respectively. There is a significant OS benefit with the combination: median OS 47.5 versus 37.6 months for osimertinib alone HR for death, 0.77; 95% confidence interval, 0.61 to 0.96; $P = .02$.[78] Patients with brain metastases were included; in fact, the median PFS was longer among patients with untreated asymptomatic CNS metastases (24.9 vs 13.8 months) and those with the L858R mutation (24.7 vs 13.9 months) who received osimertinib and chemotherapy than among those who received osimertinib monotherapy. Dose interruption and discontinuation rates were higher in the combination arm (43% and 11%, respectively) compared with the osimertinib monotherapy arm (19% and 6%, respectively). The safety profile of this combination was consistent with the established profile of each individual drug.

MARIPOSA, a randomized phase 3 study, showed that the combination of amivantamab with lazertinib improved median PFS (23.7 vs 16.6 months; HR, 0.70), the primary endpoint, and response rate (86% vs 85%) in treatment-naive patients with *EGFR*-mutated (exon 19 deletion or L858R) NSCLC compared with osimertinib monotherapy. The regimen also showed a significant OS advantage: median OS was not yet reached (95% CI, 42.9 months-not reported [NR]) with amivantamab + lazertinib versus 36.7 months (95% CI, 33.4-41.0) with osimertinib (HR, 0.75; 95% CI, 0.61-0.92; $P < .005$), with 3.5-year survival rates of ~56% and ~44%, respectively.[79] The median PFS was longer among patients with CNS metastases (27.5 vs 18.4 months). Dose interruption and discontinuation rates were higher in the combination arm (83% and 35%, respectively) compared with the osimertinib monotherapy arm (39% and 14%, respectively). There was an increased risk of venous thromboembolism, so prophylactic anticoagulation is required. Additionally, there are increased adverse effects associated with amivantamab (infusion reactions and skin toxicities), which have limited the use of this regimen in the frontline setting.[80] Taken together, these data support combination therapy in frontline classical *EGFR* mutant NSCLC, with singe-agent osimertinib still reasonable for patients with contraindications or objections to this intensified approach. Despite an initial dramatic response to EGFR inhibitors in patients with *EGFR*-mutated NSCLC, resistance generally develops after a median of 1 to 2 years.[81] After the initial use of first- or second-generation EGFR TKIs, approximately half of cases that develop resistance to these inhibitors are associated with a secondary *EGFR* T790M mutation in exon 20, which results in steric hindrance to EGFR TKI binding and altered ATP handling.[82,83] Acquired resistance to EGFR TKIs may also be driven by histologic transformation to SCLC and may respond to chemotherapy regimens active in that disease.[84] An increased incidence of this is seen in those tumors harboring inactivated *RB1* and *TP53* at initial diagnosis.[85] Additional mechanisms of resistance to third-line EGFR TKIs include *MET* amplification, *HER2* amplification, acquired translocation such as *ALK* or *RET*, and *EGFR* C797S mutation.[86,87] In addition to encouraging patients' participation in clinical trials, re-biopsy and repeat NGS are warranted to detect mechanisms of resistance to osimertinib after progression. For patients with *EGFR*-mutated NSCLC with T790M mutation after progression during prior first- or second-generation EGFR TKI therapy, osimertinib is the standard of care. In the randomized phase 3 trial,[88] Osimertinib was associated with a longer PFS (8.5 vs 4.2 months; HR, 0.42), a higher response rate (71% vs 31%), and fewer grade 3 or higher adverse events (23% vs 47%) than carboplatin-pemetrexed chemotherapy.

Patients now receive osimertinib in the first-line setting, making acquired drug resistance to this third-generation agent an area of active investigation. In the MARIPOSA-2 phase 3 study, 657 patients whose *EGFR*-mutated (exon 19 or exon 21 L858R) NSCLC progressed with osimertinib were randomly assigned at a 2:2:1 ratio to receive amivantamab and lazertinib and chemotherapy, chemotherapy, or amivantamab and chemotherapy. The combination, later approved, of amivantamab and carboplatin pemetrexed significantly improved PFS (6.3 vs 4.2 months; HR, 0.48; $P < .001$), the primary endpoint, ORR (64% vs 36%; $P < .001$), and median intracranial PFS (12.5 vs 8.3 months; HR, 0.55) compared with carboplatin pemetrexed. Dose interruption and discontinuation rates were higher in the combination arm (65% and 18%, respectively) compared with the chemotherapy arm (33% and 4%, respectively). The safety profile in the combination was dominated by hematologic EGFR and MET inhibition–related toxicities. Treatment-related adverse events leading to death were infrequent (2% vs 0.4%, respectively).[89] Updated results from CHRYSALIS-2 showed that amivantamab and lazertinib achieved an ORR of 35% with a median DoR of 8.3 months, a median PFS of 4.5 months, and a median OS of 14.8 months in patients with *EGFR* exon 19 deletion or L858R NSCLC after osimertinib and platinum chemotherapy. Activity was seen across resistance mechanisms and in patients with baseline CNS disease.[90,91]

Datopotamab Deruxtecan (Dato-DXd) received accelerated FDA approval in June 2025 for patient with *EGFR*-mutated NSCLC who have progressed after EGFR-directed therapy and platinum-based chemotherapy. This approval was based on pooled efficacy data from the TROPION-Lung05 (phase 2, single-arm) and TROPION-Lung01 (phase 3, randomized) trials involving 114 patients. Dato-DXd achieved a confirmed overall response rate of ~45% (95% CI, 35-54) and a median DoR of 6.5 months (95% CI, 4.2-8.4). Notable adverse events included interstitial lung disease/pneumonitis, ocular adverse reactions, stomatitis, and embryo-fetal toxicity.[92]

EGFR Exon 20 Insertion–Positive NSCLC

Activating insertions in *EGFR* exon 20 are less common and generally resistant to the currently approved EGFR TKIs for the classic mutations, likely because of the homology between exon 20–mutated *EGFR* and wild-type *EGFR*. Amivantamab is an EGFR-MET–bispecific antibody with immune cell–directing activity, binding to the extracellular domain of each receptor and bypassing resistance at the TKI binding site.[89,93] Amivantamab was initially approved following platinum-doublet chemotherapy based on the phase 1 chrysalis trial, which has been supplanted by frontline combination with carboplatin and pemetrexed.[94]

In the PAPILLON study, 308 patients with *EGFR* exon 20 insertion–positive NSCLC were randomly assigned to first-line treatment with chemotherapy with or without amivantamab. The combination of amivantamab with chemotherapy provided a superior median PFS than chemotherapy (11.4 vs 6.7 months; HR, 0.40). Treatment was discontinued in 7% of patients because of adverse events.

Sunvozertinib received FDA-accelerated approval in July 2025, for adults with locally advanced or metastatic NSCLC harboring *EGFR* exon 20 insertion mutations who have progressed on or after platinum-based chemotherapy. The approval was based on the results from the WU-KONG1B phase 1/2 trial, in which 85 evaluable patients achieved a confirmed overall response rate of approximately 46% and a median DoR of 11.1 months. This marks an important addition to the treatment landscape for patients with *EGFR* exon 20 insertion–positive NSCLC but is not yet commercially available.[95]

Less Common *EGFR* Mutations

Less common *EGFR* mutations were included in three trials of afatinib: LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6.[96] Several rare *EGFR* mutations did confer sensitivity, including S768I, L861Q, and G719X. These uncommon *EGFR* mutations can also be responsive to the third-generation EGFR inhibitor osimertinib.[97] Afatinib is FDA approved for NSCLCs harboring nonresistant *EGFR* mutations, including these less common variants. Recent studies have shown that lazertinib monotherapy in treatment-naive NSCLC patients and amivantamab and lazertinib combination therapy either frontline or in previously treated NSCLC harboring uncommon *EGFR* mutations such as G719X, S768I, and L861Q have encouraging results.[98,99]

ALK REARRANGEMENT–POSITIVE NSCLC

Rearrangements in the *ALK* gene can lead to a fusion oncogene with transforming potential and are detected in approximately 2% to 7% of NSCLCs. Although there are multiple described fusion partners, the most common involves a chromosome 2p inversion that results in fusion of the protein encoded by the *EML4* gene with the intracellular signaling portion of the ALK receptor tyrosine kinase. Analogous to *EGFR* mutations, the *EML4::ALK* fusions result in constitutive tyrosine kinase activity, dependence of the cancer cell on activated downstream mitogenic pathways, and sensitivity to ALK inhibition.[100] *ALK* fusions are more common in patients with adenocarcinoma histology, younger age, and a history of light or never smoking.[101] *ALK*-rearranged NSCLC can be identified using IHC, fluorescence in situ hybridization, or NGS.[102]

The first TKI approved for NSCLCs harboring an *ALK* gene rearrangement was crizotinib, now largely supplanted by next-generation inhibitors with better CNS efficacy. Multiple agents have demonstrated efficacy, including ceritinib, alectinib, lorlatinib,[103,104] brigatinib, and ensartinib in the post–crizotinib and frontline setting.[105-107] In the ALEX trial, 303 *ALK*-positive patients were randomly assigned to first-line alectinib or crizotinib.[108] Investigator-assessed PFS was notably longer with alectinib (HR, 0.43), with a median PFS of 34.8 months compared with 10.9 months with crizotinib therapy.[109] In the ALTA-1L study, 275 *ALK*-positive patients were randomly assigned to treatment with first-line brigatinib or crizotinib.[110] Brigatinib had a superior PFS (HR, 0.49), with a much higher intracranial response rate (78% vs 29%). Because of an increased risk of pneumonitis with brigatinib on loading, during the first week of treatment, patients receive a dose of 90 mg followed by an increase to 180-mg dosing if tolerated. Similarly, ensartinib was compared with crizotinib in the eXALT3 trial, leading to the recent FDA approval of ensartinib in frontline treatment of *ALK*-altered NSCLC. In the CROWN study, 296 *ALK*-positive patients were randomly assigned to treatment with first-line lorlatinib or crizotinib. Lorlatinib had a superior PFS (HR, 0.27), with a much higher intracranial response rate in the lorlatinib arm (82% vs 23%).[104] Lorlatinib was associated with a higher rate of grade 3 or 4 adverse events than crizotinib (76% vs 57%), and dose reductions with lorlatinib were often necessary because of neurocognitive adverse effects. After 5 years of follow-up, the median PFS was not reached (>60 months) with frontline lorlatinib, making this a preferred frontline approach.[111]

Acquired resistance is still a significant clinical challenge with all ALK TKIs, given the heterogeneity of resistance mechanisms to ALK TKIs. Secondary *ALK* resistance mutations are seen in approximately 30% of patients whose tumors develop resistance to crizotinib, with the most common being non–G1202R mutations. Lorlatinib is the only approved drug with activity in this

mutation. Solvent-front point mutations in *ALK* have been described in a subset of cases, although other mechanisms have also been identified.[112] Lorlatinib has in vitro activity against a broad spectrum of *ALK* TKI resistance mutations and is approved for the treatment of *ALK*-rearranged NSCLC in patients whose disease has progressed during treatment with crizotinib and another ALK inhibitor or during treatment with first-line alectinib or ceritinib.[104,113] For patients who had received two or more ALK TKIs, the response rate was 42% (n = 11 of 26 patients).

ROS-1 REARRANGEMENT–POSITIVE NSCLC

ROS-1 gene rearrangements are oncogenic drivers present in approximately 1% of NSCLC tumors.[114] *ROS-1* is an orphan tyrosine kinase of the insulin receptor family located on chromosome 6 and with notable sequence homology to *ALK*. Gene rearrangements of *ROS-1* lead to constitutive activation of this tyrosine kinase. Like many oncogene-addicted lung cancers, *ROS-1*–rearranged tumors commonly arise in younger individuals with limited/no tobacco use history and lung adenocarcinoma histology. Crizotinib, entrectinib, repotrectinib, and taletrectinib are all FDA-approved options for initial therapy. Crizotinib was approved after a single-arm study showed a high response rate (72%), with a median PFS of 19.2 months.[115] Entrectinib was approved based on an analysis of 161 patients across three separate phase 1/2 trials; the overall response rate was 67.1%, with a median PFS of 15.7 months.[116] Repotrectinib was recently FDA approved for the treatment of advanced NSCLC with an *ROS-1* fusion after the lung cohort of a single-arm study, TRIDENT-1, showed a high response rate of 79%, with a median DoR of 34.1 months and a median PFS of 35.7 months in ROS-1 TKI–naive patients (n = 71) and a response rate of 38% with a median DoR of 14.8 months and a median PFS of 9.0 months in chemotherapy-naive patients exposed to a prior ROS-1 TKI (n = 56).[117] Most recently, taletrectinib was FDA approved in June 2025 in locally advanced or metastatic ROS-1-positive NSCLC, including after prior ROS-1 TKI therapy. In the phase 2 TRUST-I/II trials, taletrectinib achieved ORRs of ~85 to 90% in TKI-naive patients and ~50 to 60% in previously treated patients, with durable responses and meaningful intracranial activity, offering another option across lines of therapy.[6]

KRAS MUTATION–POSITIVE NSCLC

Dysregulation of the RAS family of GTPases is responsible for driving nearly 30% of all cancer types. Of the three major RAS family isoforms, mutated *KRAS* comprises 84% of all RAS-driven diseases and propagates many aggressive tumor types, including lung, colorectal, and pancreatic cancers. Discovered nearly four decades ago as the oncogenes *NRAS, KRAS*, and *HRAS*, the RAS family has expanded to include approximately 150 members involved in important cellular processes such as cell division, differentiation, migration, and apoptosis. Although long regarded as undruggable because of the unique structure and surface topology of KRAS, recent advances in medicinal chemistry have identified a binding pocket in the glycine-to-cysteine missense-mutated KRAS protein at amino acid 12 (G12C), which comprises the most common *KRAS* mutation in lung adenocarcinoma. Covalent binders to the mutant cysteine were developed that extend into the binding pocket containing the switch II region, generating a selective response in *KRAS* G12C–mutated tumors. In the CodeBreaK100 phase 2 trial, heavily pretreated patients with *KRAS* G12C–mutated NSCLC were treated with sotorasib and had an ORR of 37% and a median PFS of 6.8 months.[118] Treatment was generally well tolerated, and only 20% of patients experienced grade 3 or worse adverse events. In the phase 2 KRYSTAL-1 registration trial, another KRAS G12C inhibitor, adagrasib, showed a 43% ORR, a median PFS of 6.5 months, and a similar toxicity profile.[119] The rates of discontinuation of sotorasib and adagrasib were 7.1% and 6.9%, respectively. The results of these studies led to the FDA approval of sotorasib and adagrasib for patients with NSCLC with *KRAS* G12C mutations in the second-line setting.[120]

To date, many heterogeneous mechanisms of resistance have already emerged and largely converge on reactivation of the downstream mitogen-activated protein kinase pathway, as well as alterations in the tumor microenvironment.[121,122] In the CodeBreaK200 phase 3 trial, sotorasib showed improvement in PFS (primary endpoint), with no difference in OS (secondary endpoint), compared with docetaxel in patients with *KRAS* G12C metastatic NSCLC who experienced progression with platinum chemotherapy and immunotherapy.[123] Many combination strategies with these inhibitors are being actively investigated in trials.

BRAF MUTATION–POSITIVE NSCLC

BRAF mutations are present in 2% to 4% of lung adenocarcinomas. Unlike *EGFR*-mutated or *ALK*-rearranged disease, *BRAF*-mutated lung adenocarcinoma is frequently seen in patients with a smoking history.[124] Unlike melanoma, in which a majority of *BRAF* mutations are V600E, only approximately half of the *BRAF* mutations in NSCLC are the targetable V600E. In a phase 2 trial of combination dabrafenib and trametinib, in 57 patients with previously treated *BRAF* V600E–positive NSCLC, the response rate was 63.2%, and the median PFS was 9.7 months.[125] In a subsequent cohort of treatment-naive *BRAF* V600E–positive patients, the combination of dabrafenib and trametinib had similar outcomes, with a response rate of 64% (including two patients with a CR) and a PFS of 10.9 months.[126] The combination of encorafenib and binimetinib is also FDA approved for the treatment of advanced NSCLC with *BRAF* V600E mutation based on the single-arm PHAROS study, which showed a high response rate (75%), with a median DoR not reached, in BRAF TKI–naive patients (n = 59) and a response rate of 46%, with a median DoR of 16.7 months, in previously treated patients (n = 39).[127] Less pyrexia was reported with this combination compared with other BRAF/MEK combinations. Of note, *BRAF*-mutated lung cancers are associated with high levels of PD-L1 expression and can have a favorable response to immunotherapy.[128]

OTHER DRIVER ALTERATIONS

NTRK1/2/3 Gene Fusion–Positive NSCLC

NTRK fusions have been described in fewer than 1% of lung cancers, but when present, they predict response to NTRK inhibitors. Larotrectinib is a selective NTRK inhibitor approved in a tumor-agnostic manner for use in advanced cancers harboring an *NTRK* fusion. In a report of 55 patients with *NTRK* fusion–positive cancer (n = 4 with lung cancer), the response rate was 75%, with no drug-related grade 3 or 4 adverse events.[129] Entrectinib is another potent NTRK inhibitor with efficacy across tumor types and approval for a tumor-agnostic indication. In an analysis of 54 *NTRK*-positive patients (n = 10 with NSCLC), the response rate was 57%, with a median PFS of 11 months.[130] Entrectinib is also highly CNS penetrant, with an intracranial response rate of 55%.

RET Rearrangement–Positive NSCLC

RET gene fusions have been identified in 1% to 2% of NSCLCs and are more frequently seen in younger patients with no smoking history.[131] Selpercatinib is a selective RET inhibitor that received FDA-accelerated approval for NSCLCs harboring a *RET* fusion. In the phase 1/2 LIBRETTO trial, after showing response rates of 64% overall and 85% in treatment-naive patients,[132] the median DoR was 17.5 months, and only 2% of patients stopped therapy for drug-related adverse events. A second selective RET inhibitor, pralsetinib, also received accelerated approval after efficacy was observed in the phase 1/2 ARROW trial.[133] In *RET* fusion–positive NSCLC, pralsetinib offered a response rate of 65%; the median DoR was not reached, and only 4% of patients receiving pralsetinib discontinued therapy because of treatment-related adverse events.

MET Exon 14 Skipping Mutation–Positive NSCLC

Capmatinib is a MET kinase inhibitor that has received approval in NSCLC with a *MET* exon 14 skipping mutation based on the activity seen in the GEOMETRY trial. In previously treated patients, capmatinib had a response rate of 41%, with a PFS of 5.4 months.[134] In the first-line setting, outcomes were better, with a response rate of 68% and a median PFS of 9.7 months. Tepotinib was also granted accelerated approval based on the efficacy seen in the VISION trial, which enrolled patients with NSCLC harboring an *MET* exon 14 skipping mutation detected by either liquid or tissue biopsy. The response rate was similar, regardless of the method of detection (48% in the liquid cohort and 50% in the tissue cohort), and the median DoR was 11.1 months.[135]

c-MET Protein High NSCLC

A recent advance in lung cancer therapy is the development of agents targeting tumors with high c-MET protein expression. In May 2025, the US FDA granted accelerated approval to telisotuzumab vedotin in previously treated, non–squamous NSCLC characterized by high MET overexpression, defined as strong (3+) immunohistochemical staining in at least 50% of tumor cells and without *EGFR*-activating mutations. Approval was supported by the phase 2 LUMINOSITY trial, which showed an overall response rate of approximately 35% and a median DoR of 7.2 months in patients with MET IHC-high tumors. The most common adverse effects were peripheral neuropathy, fatigue, decreased appetite, and edema. This agent represents the first FDA-approved therapy directed specifically at MET IHC-high NSCLC, broadening treatment options for patients whose tumors do not harbor *MET* exon 14 skipping alterations but display high protein overexpression.[5]

HER2 Mutation–Positive NSCLC and *HER2*-Positive (IHC3+) NSCLC

HER2 mutations have been described in approximately 1% to 2% of NSCLCs. *HER2* can be amplified in lung cancer, as it is in breast cancer, but the *HER2* mutations found in NSCLC are distinct from *HER2* amplification and most commonly are insertions in exon 20.[136] The antibody-drug conjugate ado-trastuzumab emtansine was initially used off label[137] In the phase 2 DESTINY-Lung01 study, 91 patients with *HER2*-mutated NSCLC who progressed on *chemotherapy* were treated with trastuzumab deruxtecan. Based on a response rate of 55% and a median DoR of 9.3 months, trastuzumab deruxtecan was granted accelerated approval for patients with *HER2*. Noteworthy toxicities of this drug included grade 3 or worse drug-related adverse events in 46% of patients, which included neutropenia (19%) and interstitial lung disease (26%). Trastuzumab deruxtecan also showed a response rate between 26% and 34% in the *HER2*-positive (IHC3+) NSCLC cohorts (n = 90) after progression during prior therapy.[138] This study and others in different solid tumors led the FDA to grant accelerated approval of trastuzumab deruxtecan as a tissue agnostic option for refractory *HER2*-positive (IHC3+) solid tumors.

In the phase 1b Beamion LUNG-1 trial, zongertinib produced robust activity in previously treated HER2-mutant NSCLC leading to accelerated FDA approval in August 2025. Among patients with tyrosine kinase domain mutations, the ORR was 71% with a median DoR of 14.1 months and a median progression-free survival of 12.4 months. Responses were also seen in patients with brain metastases, and activity was retained after prior HER2-directed ADC therapy (ORR 48%). Treatment was generally well tolerated, with grade ≥3 drug-related adverse events in 17%, most commonly elevated liver enzymes, and importantly no drug-related interstitial lung disease was observed.[3]

NRG1 Fusion–Positive NSCLC

NRG1 fusions are rare molecular aberrations described in a variety of tumors, including NSCLC and pancreatic cancer. Their detection is likely to be doubled if both DNA- and RNA-NGS methods are used. In NSCLC, *NRG1* fusions have been identified in

0.2% to 0.3% of cases and specifically in the invasive mucinous lung adenocarcinoma histology subtype. Patients with *NRG1* fusion NSCLC have a poor prognosis when treated with chemotherapy and/or immunotherapy.

Zenocutuzumab is an *HER2* × *HER3* bispecific antibody that was granted accelerated approval in previously treated patients with recurrent or metastatic *NRG1* fusion NSCLC. In the phase 2 eNRGy study, 64 patients with NSCLC achieved an ORR of 33% and a median DoR of 7.4 months. PFS and OS data are not yet known.[139,140]

KEY POINTS

- For *EGFR* exon 19–deleted and *EGFR* L858R–mutated NSCLC, the preferred first-line option is osimertinib with or without chemotherapy or amivantamab with lazertinib.
- Amivantamab with chemotherapy is an option for *EGFR* exon 19–deleted and exon 21 L858R–mutated NSCLC after progression during treatment with osimertinib.
- Acquired resistance to first- and second-generation EGFR TKIs is often mediated by the T790M resistance mutation, and osimertinib is indicated in this setting.
- For *EGFR* exon 20 insertion mutations: Amivantamab and chemotherapy are approved as frontline therapy (PAPILLON). Sunvozertinib received FDA-accelerated approval (July 2025) for patients who progressed on platinum-based chemotherapy.
- For *ALK*-rearranged NSCLC, the preferred first-line options include alectinib, brigatinib, and lorlatinib.
- For ROS-1-rearranged NSCLC, taletrectinib was FDA approved (June 2025) and joins crizotinib, entrectinib, and repotrectinib.
- For *KRAS* G12C–mutated advanced NSCLC, both sotorasib and adagrasib are approved treatments in the second-line setting.
- For advanced NSCLC with *BRAF* V600E mutation, a combination of either dabrafenib and trametinib or encorafenib and binimetinib is approved; the latter has less reported pyrexia.
- For advanced NSCLC with *NTRK* fusion, larotrectinib and entrectinib are approved treatments. For advanced NSCLC with *RET* fusion, selpercatinib and pralsetinib are approved treatments. For advanced NSCLC with *MET* exon 14–skipping mutation, capmatinib and tepotinib are approved treatments.
- For MET IHC–high EGFR–wild-type NSCLC, the antibody-drug conjugate telisotuzumab vedotin-tllv (Emrelis) received accelerated approval.
- For advanced NSCLC with *HER2* mutation, zongertinib and trastuzumab deruxtecan are approved in the second-line setting; trastuzumab deruxtecan may also be used as second-line treatment for *HER2*-positive (IHC3+) advanced NSCLC.
- For advanced NSCLC with *NRG1* fusion, zenocutuzumab is approved as treatment in the second-line setting.

IMMUNOTHERAPY

FIRST-LINE IMMUNOTHERAPY

Anti–PD-(L)1 Monotherapy

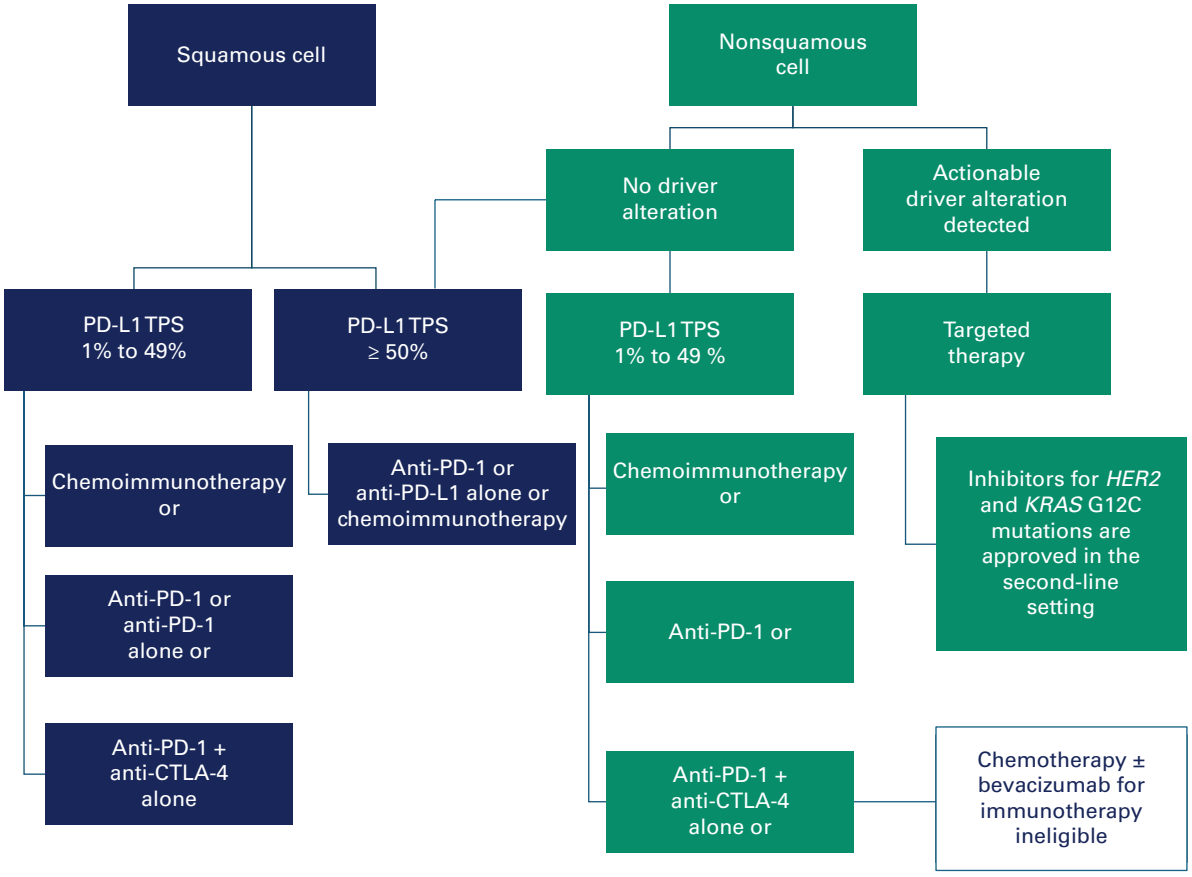
The introduction of checkpoint inhibitors, specifically antibodies targeting PD-1 and PD-L1, has dramatically changed the treatment paradigm for NSCLC (Fig. 11-4). Although initial studies were conducted in previously treated patients, immunotherapy has now become part of first-line treatment for NSCLC. There are now several validated strategies that incorporate immunotherapy for NSCLC, but the first was the use of PD-1 inhibitor monotherapy (Table 11-2).

In the KEYNOTE-024 trial, 305 patients with PD-L1 expression of at least 50% of tumor cells (ie, TPS, 50%) and wild-type *EGFR* and *ALK* were randomly assigned to receive either pembrolizumab, a PD-1 inhibitor, or platinum-based chemotherapy.[141] The primary endpoint of PFS was superior in the pembrolizumab arm compared with the chemotherapy arm, with a median PFS of 10.3 versus 6.0 months (HR, 0.50). Even with crossover, survival was significantly improved in the pembrolizumab arm, with a median survival of 26.3 versus 13.4 months (HR, 0.62).[142] The 5-year OS rate was 31.9% with pembrolizumab and 16.3% with chemotherapy. Treatment-related adverse events of any grade were less frequent with pembrolizumab (73.4% vs 90.0% of patients). Pembrolizumab was initially FDA approved as first-line treatment for stage IV NSCLC with a PD-L1 TPS of at least 50%.

KEYNOTE-042 compared first-line pembrolizumab monotherapy with chemotherapy for patients with PD-L1–positive NSCLC using a PD-L1 TPS cutoff of 1%.[143] The study met its primary endpoint of improved OS in the pembrolizumab arm, with a median OS of 16.7 versus 12.1 months (HR, 0.81). The benefit was driven, however, by patients with a PD-L1 TPS of 50% or higher. This study provides rationale for frail patients with a PD-L1 TPS of 1% to 49%, who may not be candidates for chemotherapy combinations.

Other PD-L1 and PD-1 antibodies demonstrated comparable results. In the phase 3 IMpower 110 trial of atezolizumab, 572 patients with advanced NSCLC with at least 1% PD-L1 expression were randomly assigned to atezolizumab or platinum-based chemotherapy.[144] For patients with PD-L1–high NSCLC, survival favored atezolizumab, with a median survival of 20.2 versus 13.1 months with chemotherapy (HR, 0.59). Atezolizumab received FDA approval as initial treatment for disease with PD-L1

Figure 11-4 Treatment Paradigms for Advanced Non–Small Cell Lung Cancer by Cancer Subtype and PD-L1 TPS



Abbreviations: PD-L1, programmed cell death ligand 1; TPS, Tumor Proportion Score.
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Table 11-2 **PD-(L)1 Inhibitor Monotherapy in PD-L1–High NSCLC**

Study	Agent	Median Survival vs Chemotherapy (Months)	Survival HR	Response Rate (%)
KEYNOTE-024	Pembrolizumab	26.3 vs 13.4	0.62	44.8
KEYNOTE-042	Pembrolizumab	20.0 vs 12.2	0.69	39.0
IMpower 110	Atezolizumab	20.2 vs 13.1	0.59	38.3
EMPOWER-Lung01	Cemiplimab	NR vs 14.2	0.57	39.0
CheckMate 026	Nivolumab	15.9 vs 13.9	0.9	34.0

Abbreviations: HR, hazard ratio; NR, not reported; NSCLC, non–small cell lung cancer; PD-L1, programmed cell death ligand 1.
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expression of 50% or greater. Similarly, cemiplimab was also approved for PD-L1–high NSCLC based on the phase 3 EMPOWER-Lung01 trial. In this study, 710 patients with advanced NSCLC and a smoking history (never smokers were ineligible) were randomly assigned to cemiplimab or platinum-doublet chemotherapy. In the PD-L1–high subset (n = 563), survival favored cemiplimab (HR, 0.57), despite the high crossover rate (74%).[142]

Not all trials of first-line immunotherapy in metastatic NSCLC have had positive results. In the CheckMate 026 trial, 541 patients whose tumors were PD-L1 positive (defined as expression in 1% of cells using the Dako 28-8 PD-L1 IHC clone) were randomly assigned to receive the PD-1 inhibitor nivolumab or platinum-based chemotherapy.[144] The primary endpoint was PFS for patients with a PD-L1 expression of 5% or greater was not reached, and there was no difference in survival (median, 14.4 months for nivolumab vs 13.2 months for chemotherapy; HR, 1.02).

Dual-Checkpoint Blockade

CTLA-4 is another immune checkpoint, the blockade of which has been associated with immune-mediated antitumor responses across multiple cancer types. Combined blockade of PD-1 with nivolumab and CTLA-4 with ipilimumab is another FDA-approved first-line strategy for PD-L1–positive NSCLC. In the CheckMate 227 trial, patients with advanced *EGFR* and *ALK* wild-type NSCLC with at least PD-L1 TPS 1% were randomly assigned at a 1:1:1 ratio to receive nivolumab and ipilimumab, nivolumab monotherapy, or chemotherapy.[145] The primary endpoint of improved survival with nivolumab and ipilimumab compared with chemotherapy was met (17.1 vs 14.9 months; HR, 0.79). The response rate with nivolumab and ipilimumab was 35.9%, with a median DoR of 23.2 months. For patients with PD-L1–negative NSCLC, a benefit was also observed (17.2 vs 12.2 months; HR, 0.62), although this analysis was exploratory.

Chemoimmunotherapy Combinations

Combinations of checkpoint inhibitors with cytotoxic chemotherapy have also shown great promise for patients across the strata of PD-L1 expression. Concurrent administration of chemotherapy and immunotherapy has several potential advantages.[146] Chemotherapy can lead to the depletion of immunosuppressive cells and promote neoantigen presentation to facilitate an immune-mediated antitumor response. Data also show that pemetrexed administration can induce an immune activation gene expression signature.[147] Early trials of combined chemotherapy with PD-L1 inhibitors demonstrated the potential for long-term survival, with no significant increase in the toxicity profile.[148]

The first approved chemoimmunotherapy combination for NSCLC was carboplatin, pemetrexed, and pembrolizumab in non–squamous NSCLC. In the confirmatory phase 3 KEYNOTE-189 study, 616 patients with treatment-naive non–squamous NSCLC were randomly assigned at a 2:1 ratio to platinum (carboplatin or cisplatin), pemetrexed, and pembrolizumab (with pembrolizumab and pemetrexed maintenance) or platinum, pemetrexed, and placebo (with placebo and pemetrexed maintenance).[149] The response rate was higher with pembrolizumab in the overall study population (48% vs 19%) and in all PD-L1 subsets (61% vs 23% with PD-L1 TPS ≥ 50%, 48% vs 21% with PD-L1 TPS 1% to 49%, and 32% vs 14% in PD-L1–negative tumors). Survival also favored chemoimmunotherapy, with an HR of 0.49, also seen across PD-L1 subsets.

A four-drug regimen of carboplatin, paclitaxel, bevacizumab, and atezolizumab was approved based on the IMpower 150 study; this regimen was compared with carboplatin, paclitaxel, and bevacizumab.[150] Unlike KEYNOTE-189, IMpower 150 included some patients with *EGFR* or *ALK* alterations, after progression during the appropriate TKI therapy. The addition of atezolizumab to the backbone of carboplatin, paclitaxel, and bevacizumab led to an improvement in PFS (8.3 vs 6.8 months; HR, 0.62) as well as a significant increase in OS (19.2 vs 14.7 months; HR, 0.78). This combination has also been approved for treatment-naive non–squamous NSCLC, independent of PD-L1 expression. Its FDA approval does not include the exploratory subset of *EGFR*- or *ALK*-positive NSCLC, although some approvals outside of the United States do include this subset.

Atezolizumab also has improved outcomes when added to carboplatin and nab-paclitaxel. In the IMpower 130 trial,[151] 724 patients were randomly assigned to carboplatin, nab-paclitaxel, and atezolizumab or placebo. The addition of atezolizumab improved survival from 13.9 to 18.6 months (HR, 0.79), leading to its FDA approval for patients with advanced non–squamous NSCLC.

Chemoimmunotherapy also has improved outcomes in squamous NSCLC. In KEYNOTE-407, 559 patients with untreated stage IV squamous NSCLC were treated with carboplatin and either paclitaxel or nab-paclitaxel (investigator's choice) and were randomly assigned to receive either pembrolizumab or placebo, with pembrolizumab or placebo maintenance for up to 31 cycles.[152] The response rate was higher with pembrolizumab in the overall study population (58% vs 38%) and in PD-L1–high (60% vs 33%), PD-L1–low (50% vs 41%), and PD-L1–negative (63% vs 40%) subsets. Survival also favored the addition of pembrolizumab (HR, 0.64). This regimen has been approved as initial therapy for squamous NSCLC regardless of PD-L1 expression.

Adding chemotherapy to dual-checkpoint blockade has also improved outcomes. In the CheckMate 9LA trial, 719 patients were randomly assigned to receive a four-drug regimen of nivolumab, ipilimumab, and platinum-doublet chemotherapy or chemotherapy alone.[153] In the chemoimmunotherapy arm, chemotherapy was limited to only two cycles. The investigational arm was superior, with an improvement in median survival (15.6 vs 10.9 months; HR, 0.66) that was observed in both non–squamous (HR, 0.69) and squamous (HR, 0.62) histologic subtypes and across PD-L1 strata, although 19% of patients discontinued part of therapy because of treatment-related adverse events.

Similarly, in the phase 3 POSEIDON study, 1,013 patients were randomly assigned (1:1:1) to receive a platinum-based doublet for four cycles in combination with durvalumab and tremelimumab, just durvalumab, or chemotherapy alone.[154] In the chemoimmunotherapy arms, chemotherapy was limited to four cycles, whereas in the chemotherapy arm, up to six cycles of therapy could be administered. Although the median OS improvement with the addition of durvalumab to chemotherapy was nonsignificant (HR, 0.86), adding tremelimumab and durvalumab to chemotherapy reached statistical significance (14.0 vs 11.7 months; HR, 0.77). Treatment-related adverse events led to discontinued treatment in 15.5% of patients receiving chemotherapy and dual-checkpoint inhibitor blockade, compared with 9.9% receiving chemotherapy alone.

IMMUNOTHERAPY AS SECOND-LINE THERAPY IN PATIENTS WITH ACTIONABLE GENOMIC ALTERATIONS

The role of immunotherapy in patients with certain actionable genomic alterations is associated with inferior efficacy as well as excess toxicity. Immunotherapy should not supplant first-line TKI therapy for several molecularly defined subgroups (ie, EGFR and ALK); this may be particularly true for those molecular aberrations that more commonly occur in individuals with limited/no tobacco use history (Table 11-3).[155] In a retrospective analysis of patients with *EGFR* mutations or *ALK* rearrangements, the response to PD-(L)1 inhibition was reported as only 3.6%, compared with 23.3% in an *EGFR* and *ALK* wild-type population.[156] Patients with *EGFR* and *ALK* alterations were excluded from the first-line randomized trials of pembrolizumab and the combination of pembrolizumab, carboplatin, and pemetrexed.[141,148] In KEYNOTE-789, the addition of pembrolizumab to platinum-pemetrexed in patients with *EGFR*-mutated metastatic non–squamous NSCLC who experienced progression during targeted therapy did not significantly prolong PFS or OS compared with placebo and platinum-pemetrexed.[157] Similarly, in CheckMate 722, the addition of nivolumab to chemotherapy did not improve PFS compared with chemotherapy alone in the same population.[158] A phase 2 study explored the role of first-line pembrolizumab for patients with *EGFR*-mutated PD-L1–positive NSCLC and reported no responses.[159] In addition, the use of TKIs, such as osimertinib, after a PD-1 or PD-L1 inhibitor was associated with a high rate of immune-related adverse events, including some cases of fatal pneumonitis. Immunotherapy after TKI therapy was not associated with this risk.[160] For this reason, all patients with non–squamous NSCLC must have molecular testing results before starting immunotherapy. Chemotherapy may be started if patients need treatment during the waiting period.

Table 11-3 Targeted Therapy for Unresectable or Metastatic NSCLC With Targetable Molecular Aberration

Target	Preferred Targeted Therapy
EGFR exons 19 and 21	Osimertinib, osimertinib and chemotherapy, amivantamab and lazertinib
EGFR exon 20	Amivantamab[a]
ALK fusions	Lorlatinib; alectinib, brigatinib, ensartinib
ROS-1 fusions	Crizotinib, entrectinib, repotrectinib, taletrectinib
KRAS G12C	Sotorasib,[b] adagrasib[b]
BRAF V600E	Dabrafenib + trametinib, encorafenib + binimetinib
RET	Selpercatinib, pralsetinib
MET exon 14 skipping mutation	Capmatinib, tepotinib
MET IHC high (3+)	Telisotuzumab vedotin-tllv
HER2 mutation	Zongertinib, trastuzumab deruxtecan[b]
HER-2 IHC high (3+)	Trastuzumab deruxtecan
NTRK1/2/3 fusions	Larotrectinib, entrectinib
NRG fusions	Zenocutuzumab

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer.
[a]Preferred in first line in combination with carboplatin and pemetrexed.
[b]Approved after progression during first-line systemic therapy.
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KEY POINTS

- NSCLC without an activating alteration in *EGFR* or *ALK* and with high PD-L1 expression (TPS ≥ 50%) can be treated with pembrolizumab, atezolizumab, or cemiplimab, all of which confer an improvement in survival over platinum-doublet chemotherapy.
- Dual-checkpoint blockade with nivolumab and ipilimumab improved survival compared with chemotherapy in PD-L1–positive (TPS ≥ 1%) NSCLC and is also a first-line treatment option. It may be used in the PD-L1–negative squamous NSCLC population as well.
- The combination of an immune checkpoint inhibitor with platinum-doublet chemotherapy improves PFS and survival in patients with squamous and non–squamous NSCLC (*EGFR* and *ALK* wild type) across all PD-L1 subsets.
- The combination of nivolumab and ipilimumab with two cycles of platinum-doublet chemotherapy, or durvalumab and tremelimumab with four cycles of platinum-doublet chemotherapy, is also approved across histologies and PD-L1 levels.
- Use of immunotherapy is not appropriate for certain molecular subtypes of advanced NSCLC (ie, EGFR/ALK), regardless of tumor PD-L1 expression; use of immune checkpoint inhibitors in these subgroups can be associated with both inferior efficacy and excess toxicity.

FIRST-LINE PLATINUM-DOUBLET CHEMOTHERAPY

Most patients with advanced NSCLC without actionable molecular alterations should receive immunotherapy (alone or with chemotherapy) as their initial therapy. For patients who are not candidates for immunotherapy, platinum-doublet chemotherapy remains a relevant option. The landmark ECOG 1594 study randomly assigned 1,207 patients with treatment-naive NSCLC to cisplatin and paclitaxel, cisplatin and gemcitabine, cisplatin and docetaxel, or carboplatin and paclitaxel.[161] The response rate and survival were similar across all arms. Data now support different treatment approaches for specific histologic subtypes of NSCLC, based on efficacy (pemetrexed and gemcitabine) and safety (bevacizumab). A phase 3 trial of more than 1,700 patients with chemotherapy-naive disease compared combination pemetrexed and cisplatin and combination gemcitabine and cisplatin.[162] Although OS was similar in the two arms, in a prespecified subset analysis, survival was statistically superior for cisplatin and pemetrexed compared with cisplatin and gemcitabine for patients with adenocarcinoma (12.6 vs 10.9 months) and large cell carcinoma histologies (10.4 vs 6.7 months). Conversely, patients with squamous cell histology experienced a significant improvement in survival with cisplatin and gemcitabine compared with cisplatin and pemetrexed (10.8 vs 9.4 months). In a phase 3 trial of 1,052 patients with NSCLC comparing carboplatin combined with either paclitaxel or nab-paclitaxel, patients with squamous histology had a significantly higher response rate with carboplatin and nab-paclitaxel (41% vs 24%; $P < .001$), although the OS in each arm was not different. Taken together, for adenocarcinoma histology, the preferred regimen is platinum with pemetrexed; for squamous histology, the preferred regimen is platinum with either gemcitabine, paclitaxel, or nab-paclitaxel.

In advanced-stage disease treated with palliative intent, carboplatin is an appropriate alternative to cisplatin because of the adverse effects of the latter on quality of life.

The phase 3 clinical trial (PARAMOUNT) explored continuation maintenance pemetrexed. Patients with advanced non–squamous NSCLC were randomly assigned to four cycles of cisplatin and pemetrexed followed by observation compared with continuation maintenance pemetrexed every 3 weeks until progression or intolerable toxicity-related effects occurred.[163] Continuation maintenance with pemetrexed improved PFS and OS, with a median OS of 16.9 months compared with 14 months after induction.

BEVACIZUMAB

Bevacizumab is a monoclonal antibody that targets VEGF and inhibits the process of angiogenesis. Bevacizumab was approved for the management of non–squamous NSCLC based on the ECOG 4599 phase 3 trial of 878 patients randomly assigned to chemotherapy (paclitaxel and carboplatin) or chemotherapy and 15 mg/kg of bevacizumab every 3 weeks.[164] The median survival for patients who received chemotherapy and bevacizumab was 12.3 months compared with 10.3 months for patients who received chemotherapy alone. Bevacizumab also improved both PFS (6.2 vs 4.5 months) and the response rate (35% vs 15%). However, because of grades 3 to 4 bleeding episodes observed in a phase 2 study,[165] use of bevacizumab is restricted to patients with non–squamous histology (because of higher levels of severe hemoptysis observed in squamous NSCLC).

A second randomized study of bevacizumab involving more than 1,000 patients was conducted (the AVAIL trial).[166] Unlike the ECOG 4599 study, this study involved gemcitabine and cisplatin, and patients were randomly assigned to chemotherapy and placebo, chemotherapy with 7.5 mg/kg of bevacizumab every 3 weeks, or chemotherapy with 15 mg/kg of bevacizumab every 3 weeks. The study met its primary endpoint of PFS; however, the absolute benefit was modest (median PFS, 6.7 and 6.5 vs 6.1 months), with no improvement in survival. It is unclear whether the lack of survival benefit was a result of the differences in chemotherapy doublets between the ECOG 4599 study and the AVAIL trial, differences in bevacizumab dose, or differences in study design, of which there were many.

CHEMOTHERAPY IN OLDER PATIENTS

The median age of patients with lung cancer is approximately 70 years, and treatment of patients aged 65 years or older tends to be complicated by comorbid conditions and polypharmacy. However, studies show that fit older patients are likely to benefit as much from chemotherapy as their younger counterparts. Despite an increase in toxicity-related effects, platinum-based doublet chemotherapy yields superior outcomes to single-agent chemotherapy in fit older individuals. In a phase 3 trial, 451 previously untreated patients aged 70 to 89 years (median, 77 years) with Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2 were randomly assigned to carboplatin and paclitaxel or monotherapy with vinorelbine or gemcitabine.[167] In each arm of the study, 27% of patients had an ECOG PS of 2. The median survival was 10.3 months in the carboplatin and paclitaxel arm compared with 6.2 months in the monotherapy arm. Subset analyses of other randomized trials showed the response rate, toxicity, and survival for fit older patients receiving platinum-based treatment for NSCLC seemed to be similar to the same variables for younger patients. For patients aged 70 years or older, however, comorbidity is greater, and the frequencies of leukopenia and neuropsychiatric toxicity are higher. Therefore, advanced age alone should not preclude appropriate treatment, but upfront dose reduction and or granulocyte colony-stimulating factor (GCSF) support may be considered.

SECOND- AND THIRD-LINE THERAPIES

For patients whose disease progresses during platinum-doublet therapy and immunotherapy (administered concurrently or sequentially), docetaxel with or without ramucirumab remains the current standard of care.

In two randomized trials, second-line docetaxel was evaluated for patients who did not respond to first-line platinum-doublet chemotherapy. Docetaxel significantly prolonged survival compared with best supportive care.[168] Moreover, docetaxel also improved quality of life and reduced weight loss and the need for pain medication. Previous exposure to paclitaxel did not affect response to docetaxel, suggesting non–cross-resistance between the two agents.

Ramucirumab is a monoclonal antibody that targets VEGFR2. This antiangiogenesis agent, in combination with docetaxel, has been approved for the treatment of metastatic NSCLC with progression of disease during or after platinum-based treatment. Unlike bevacizumab, which is contraindicated in squamous histology NSCLC, ramucirumab is approved and has shown benefit in both squamous and non–squamous subtypes. Approval was based on the results from the randomized phase 3 REVEL trial, in which 1,253 patients with stage IV NSCLC after progression during platinum-based chemotherapy were randomly assigned to docetaxel therapy with or without ramucirumab.[169] Survival (10.5 vs 9.5 months), PFS (4.5 vs 3.0 months), and response rates (23% vs 14%) were all improved with the addition of ramucirumab.

Ramucirumab with pembrolizumab showed an improvement in OS compared with single-agent chemotherapy (HR, 0.69) after progression with platinum and immunotherapy in the phase 2 trial Lung-Map nonmatch substudy S1800A.[170] However, the confirmatory phase 3 study Pragmatica-Lung was negative.

Tumor treating fields (TTFields) are approved to use in combination with immune checkpoint inhibitors or docetaxel based on the improved outcomes noted in the phase 3 LUNAR trial of patients with metastatic NSCLC after progression during platinum-based chemotherapy.[171] The TTFields were delivered to the thorax at continuous frequencies of 150 kHz for at least 18 hours per day, which in preclinical models enhanced antitumor immune response by disrupting the mitosis and downstream induction of immunogenic cell death. There was a statistically significant improvement in the primary endpoint, median OS, with the addition TTFields therapy to standard systemic therapy (13.2 vs 9.9 months, respectively; $P = .04$). Most treatment-related adverse events were mild. Six patients (4%) experienced grade 3 skin toxicity that required a break from treatment.

The improvement in median OS was statistically significant ($P = .02$) in 70 patients who received TTFields therapy with an immune checkpoint inhibitor (19 months; 95% CI, 10.6-28.2) compared with 71 patients who received an immune checkpoint inhibitor alone (10.8 months; 95% CI, 8.3-17.6). Of note, this trial was performed before the incorporation of immunotherapy into the frontline setting, which limits the interpretation of the potential benefit for this approach in ICI-exposed patient populations.

KEY POINTS

- Pemetrexed is an appropriate platinum partner in non–squamous histology; gemcitabine is appropriate for treatment of tumors with squamous histology. Paclitaxel or nab-paclitaxel is a reasonable choice for either histology.
- Fit older patients tolerate chemotherapy and derive the same survival benefit as their younger counterparts.
- The addition of the VEGFR2 antibody ramucirumab to second-line docetaxel improves survival.
- TTFields in combination with immune checkpoint inhibitors or docetaxel have improved outcomes in NSCLC after progression during platinum-based chemotherapy.

SMALL CELL LUNG CANCER

EPIDEMIOLOGY

SCLC most often occurs in patients with significant tobacco use history and is typically centrally located with bulky lymphadenopathy. SCLC accounts for approximately 13% of new lung cancer diagnoses in the United States. The incidence has decreased over the last few decades, with a peak in the early 1990s, when it represented as many as 25% of lung cancer diagnoses. In the 1970s, only 28% of patients with SCLC were female, whereas in the early 2000s, 50% of patients were female. These changes in incidence and demographics are most likely related to tobacco use, as are geographic variations in the incidence of SCLC, which has a strong dose-response relationship with smoking. As noted earlier in this chapter, SCLC is also characterized by a high incidence of PNS.

ESTABLISHING A DIAGNOSIS

Staging

Staging of SCLC uses the same AJCC TNM staging system used in NSCLC. The staging system has been validated in SCLC and carries prognostic value. However, because of the aggressive nature of this disease and the limited role of surgery, the Veterans Affairs Lung Study Group staging system is often applied in clinical practice. In this staging schema, patients with limited stage SCLC (LS-SCLC) are those with tumor limited to one hemithorax, with regional nodes that can be included in a single tolerable radiation therapy port, and patients with extensive-stage SCLC (ES-SCLC) are those with tumor that does not meet the criteria for LS, including those with distant metastases or malignant pericardial or pleural effusions.

SCLC TREATMENT

SCLC is a chemotherapy- and radiation therapy–sensitive tumor with remarkably high response rates to multiple regimens. Unfortunately, it is characterized by rapid relapse, and after recurrence, it is a much more refractory disease. For those with LS-SCLC, definitive therapy offers a chance for cure in a small subset of patients. For those with ES disease, treatment is largely palliative. For those patients with poor PS, there may still be a palliative role for systemic therapy, given the high response rates with chemotherapy, although it is important to discuss the limitations of therapy with patients.

Treatment of LS-SCLC

There is a limited role for surgical resection in SCLC, which is often disseminated or locally advanced at the time of diagnosis. For stage I to IIA (T1/T2, N0) SCLC, limited retrospective series demonstrate good outcomes with surgical resection. Stage I or IIA (T1/T2, N0) SCLC, however, is exceedingly rare (<5% of patients), and before pursuing surgery, extensive staging, including invasive mediastinal staging, is appropriate. If proper staging workup does confirm stage I or IIA SCLC, surgery may be considered. After surgery, adjuvant chemotherapy is recommended regardless of stage, although not on the basis of high-level evidence. Commonly, despite proper staging, histopathologic analysis of the surgical specimen upstages the disease by identifying involved lymph nodes, in which case chemoradiation therapy (as discussed in the next paragraph) is an appropriate consideration.

For most patients with LS-SCLC, the recommended treatment is definitive concurrent chemoradiation.[172] Chemotherapy administered concurrently with thoracic irradiation is more effective than sequential chemoradiation therapy with a median OS of 27.2 months compared with 19.7 months in the sequential arm (P = .097); however, it was associated with substantially more frequent esophagitis and hematologic toxicity. To decrease the morbidity associated with such treatment, as well as to improve overall outcome, investigative efforts have focused on optimizing radiation fields, fractionation, and schedule. In one randomized study, twice-daily hyperfractionated radiation therapy to 45 Gy was compared with a once-daily schedule to 45 Gy; both were administered concurrently with four cycles of cisplatin and etoposide. Survival was significantly higher with the twice-daily regimen (median survival, 23 vs 19 months; 5-year survival, 26% vs 16%), although at the expense of more frequent grade 3 esophagitis.[173] A shortcoming of this trial is that the radiobiologic dose of 45 Gy twice daily was significantly higher than once daily to 45 Gy. Therefore, it was thought that daily radiation administered to a higher dose may produce comparable results. However, a European randomized phase 3 trial (the CONVERT trial) failed to demonstrate a survival advantage for once-daily radiation to 66 Gy over twice daily to 45 Gy, although numeric outcomes and toxicity between the two arms were similar.[165] Both approaches are currently used in clinical practice. Cisplatin and etoposide for four cycles is the current standard regimen used in combination with radiation therapy for LS-SCLC.

With concurrent chemoradiation therapy, response rates are high; 97% of patients achieve a response, and 40% achieve a CR. Long-term survival, however, is uncommon, and the 5-year survival rate is lower than 25%. This discordance between initial sensitivity and frequent relapse has been the subject of intense research. Despite the high risk of recurrence, prolonged or maintenance therapy has not improved outcomes, and until recently, radiographic observation remained standard of care after definitive chemoradiation therapy.[174] This paradigm changed with the presentation of the ADRIATIC trial. In this trial, patients with LS-SCLC received standard chemoradiation and were then randomized to receive the combination of durvalumab and tremelimumab, durvalumab alone, or placebo for 24 months. At the first interim analysis, patients in the durvalumab alone arm experienced significantly improved OS (median, 55.9 vs 33.4 months) and PFS (median, 16.6 vs 9.2 months). Results in the durvalumab-tremelimumab group remain blinded.[174] This study establishes durvalumab as an effective therapy after chemoradiation for eligible patients.

First-Line Treatment of ES-SCLC

Most patients with SCLC will present with ES disease, and most patients with LS-SCLC will experience disease relapse. For ES-SCLC, the cornerstone of treatment is platinum-based chemotherapy in combination with etoposide. The COCIS meta-analysis of individual patient data compared patients with SCLC who received cisplatin and those who received carboplatin. There was no difference in response rate, PFS, or survival based on the choice of platinum, although the toxicity profiles of these two drugs include important differences.[175] Cisplatin remains the standard of care in LS-SCLC; however, carboplatin and cisplatin are both appropriate options in the treatment of patients with ES-SCLC.

The first study to demonstrate an improvement in OS in the first-line treatment of ES-SCLC in several decades was IMpower 133, a randomized phase 3 trial of carboplatin and etoposide with the PD-L1 inhibitor atezolizumab.[176] In this global study, 403 patients with ES-SCLC received four cycles of carboplatin and etoposide and were randomly assigned at a 1:1 ratio to receive either concurrent atezolizumab or placebo followed by atezolizumab or placebo maintenance. The addition of atezolizumab led to a significant improvement in survival (12.3 vs 10.3 months; HR, 0.70) as well as an improvement in PFS (HR, 0.77). The survival benefit was independent of PD-L1 expression. The CASPIAN trial explored durvalumab with first-line chemotherapy and produced strikingly similar results. In this open-label trial, the addition of durvalumab to platinum and etoposide improved survival from 10.3 to 13.0 months (HR, 0.73).[177] Both atezolizumab and durvalumab are FDA approved with chemotherapy as initial treatment for ES-SCLC. In contrast, a phase 3 trial of first-line pembrolizumab with chemotherapy (KEYNOTE-604) improved PFS but failed to demonstrate a survival benefit.[178]

The addition of chemotherapy with lurbinectedin to maintenance atezolizumab was recently approved based on the phase 3 IMFORTE trial. This study randomized patients with ES-SCLC who responded to initial carboplatin, etoposide, and atezolizumab and had a PS of 0-1 to lurbinectedin and atezolizumab or atezolizumab alone as maintenance. Both PFS (HR, 0.54) and OS (HR, 0.73) improved in the combination arm.

Prophylactic Cranial Irradiation

Brain metastases comprise the first site of relapse for approximately one-third of patients who have relapsing SCLC. Another third of such patients will have both brain and systemic metastases as the first sites of relapse, and the remaining one-third will have systemic-only disease. Because of the morbidity and cognitive decline associated with brain metastases, the role of prophylactic cranial irradiation (PCI) to prevent the development of brain metastases has been studied in numerous randomized trials. A meta-analysis of patients with SCLC in complete remission (primarily those with LS disease) concluded that PCI was associated with a 5.4% increase in survival at 3 years.[179] A typical course of PCI is 25 Gy to the whole brain in 10 fractions.

A study from the European Organisation for Research and Treatment of Cancer also showed a survival benefit for patients with ES disease who had any response to induction chemotherapy.[180] Patients with ES-SCLC who had a response to chemotherapy were randomly assigned to undergo PCI or receive no additional therapy. Irradiation was associated with an increase in median survival from 5.4 to 6.7 months and an improvement in the 1-year survival rate (27.1% vs 13.3%), in addition to a lower risk of brain metastases (risk of metastases at 1 year, 14.6% vs 40.4%). One limitation of the study was the lack of baseline brain imaging and MRI surveillance. A recent trial mirrored this study design but required brain imaging at baseline and during surveillance. In that randomized trial of 224 patients with ES-SCLC, there was no difference in survival between patients who underwent PCI and those who were radiographically observed, with a median survival of 11.6 months with PCI and 13.7 months with observation.[181] With no survival advantage with PCI and a risk of neurocognitive toxicity, PCI in ES-SCLC is not typically recommended if MRI for surveillance of the brain is available.

Consolidative Thoracic Irradiation

SCLC is a radiosensitive tumor, and given the high local recurrence rates after initial chemotherapy for ES-SCLC, the role of thoracic irradiation after chemotherapy has been explored. A randomized clinical trial of 498 patients with ES-SCLC with a response to platinum-based induction chemotherapy showed that thoracic irradiation, when added to PCI, significantly increased the PFS.[182] The primary endpoint of the study was an improvement in survival at 1 year. The study did not meet its primary endpoint; survival at 1 year was not significantly prolonged (33% vs 28%; $P = .066$), and the median survival was the same in both arms (8 months). However, in a secondary analysis, there was a significant improvement in 2-year survival (13% vs 3%; $P = .04$). Some of the features of the overall patient population were atypical for ES-SCLC, such as a 46% rate of isolated intrathoracic progression in the control group. Although these studies predate the use of immunotherapy, consolidative radiation therapy may be considered in ES patients who respond to initial chemotherapy and immunotherapy but have residual thoracic disease and limited extrathoracic disease.

Second-Line Therapy

The response rate to second-line agents correlates with the timing of relapse after induction chemotherapy. Patients who experience relapse more than 3 months after completing first-line chemotherapy are considered to have platinum-sensitive disease and are more likely to have a response. Patients who experience disease progression during or within 3 months after receiving a first-line regimen are considered to have resistant disease.

For those with sensitive disease, revisiting platinum and etoposide is an option, especially if the interval from completion of first-line chemotherapy is at least 6 months. For decades, the only drug approved as second-line therapy for SCLC in the United States was topotecan, which is associated with a response rate of approximately 25% and survival of approximately 6 months.[183]

Lurbinectedin, a marine-derived transcription inhibitor, received accelerated approval by the FDA in this setting based on promising single-agent activity in a single-arm phase 2 study.[184] In 105 patients with relapsed SCLC, lurbinectedin achieved a response rate of 35.2%. For patients with a chemotherapy-free interval of less than 90 days (chemotherapy resistant), the response rate was 22.2%, and in those with an interval of at least 90 days, the response rate was 45.0%.[185]

Tarlatamab, a bispecific T-cell engager (BITE) immunotherapy targeting delta-like ligand 3 and CD3, was studied at two doses (10 and 100 mg) in a phase 2 trial in patients with ES-SCLC who had experienced progression during prior platinum-based chemotherapy. The study reported an ORR of 55% in the 10-mg group and 57% in the 100-mg group and a median PFS of 4.9 months in the 10-mg group and 3.9 months in the 100-mg group. Encouragingly, in patients with an objective response, the DoR was longer than 6 months in 59%.[185] The FDA granted tarlatamab at 10 mg fast-track approval for patients with ES-SCLC who have experienced progression during platinum-based therapy. A randomized phase 3 trial of tarlatamab compared with second-line chemotherapy (topotecan, lurbinectedin, or amrubicin) demonstrated that patients who received tarlatamab had a superior median OS (13.6 vs 8.3 months; HR, 0.60, $P < .001$), confirming[1] tarlatamab as the second-line treatment of choice for ES patients who progress after chemotherapy and immunotherapy. Of note, as a BITE therapy, tarlatamab can have significant toxicity,

including cytokine-release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), which were seen in 56% and 6% of the 10-mg group, respectively. Therefore, centers using tarlatamab must be prepared for and experienced in the management of these adverse effects, which may limit the availability of this treatment to all patients.

KEY POINTS

- SCLC is characterized by high response rates to systemic therapy and high relapse rates.
- The AJCC TNM staging system is appropriate, but the functional staging system proposed by the Veterans Authority Lung Study Group is often used clinically. LS-SCLC can be encompassed in a tolerable radiation therapy port; ES disease cannot.
- For LS-SCLC, the standard approach is cisplatin and etoposide with definitive radiation therapy followed by consideration of PCI and durvalumab for 24 months.
- For ES-SCLC, the standard approach is platinum with etoposide and either atezolizumab or durvalumab, with immunotherapy continued as maintenance after four cycles of chemoimmunotherapy.
- For relapsed SCLC, tarlatamab is the preferred agent for eligible patients.

PALLIATION FOR PATIENTS WITH LUNG CANCER

For patients with good PS, systemic therapy can play an important palliative role by reducing symptoms and improving quality of life. This is particularly the case in highly responsive tumors, such as previously untreated SCLC or NSCLC with an actionable driver alteration. Other ways to offer palliation for patients with lung cancer merit consideration.

PALLIATIVE CARE

Palliative care specialists can provide valuable insight into and guidance on symptom management and psychosocial support but are often involved late in the disease course. In a landmark trial, 151 patients with newly diagnosed metastatic NSCLC were randomly assigned to early integration with a palliative care team or standard oncologic care alone.[186] Early referral to palliative care led to improvements in quality of life and fewer patients with depressive symptoms. Although there were fewer patients who received aggressive end-of-life care in the palliative care arm (33% vs 54%), survival was longer for patients with an early referral to palliative care (11.6 vs 8.9 months).

BONE-TARGETED AGENTS

Bone metastases are common in NSCLC and SCLC and are an important potential cause of patient morbidity. Supportive medications have been effective at preventing complications associated with bone metastases. Bisphosphonates (eg, zoledronate) have resulted in the reduction of skeletal-related complications, such as pain, hypercalcemia, pathologic fractures, and spinal cord and nerve compression, as well as improvements in the quality of life for patients with metastatic bone disease who are likely to have a prolonged clinical course.[187] However, a small risk of osteonecrosis of the jaw is seen. Denosumab, a monoclonal antibody to the receptor activator of nuclear factor-kappa B ligand, was noninferior to zoledronate in delaying or preventing skeletal-related complications for patients with advanced cancer, including patients with lung cancer, in a randomized double-blind study in the treatment of bone metastases for patients with advanced cancer (excluding breast and prostate cancers) or multiple myeloma.[188] The incidence of osteonecrosis is similar to that with bisphosphonates.

RADIATION THERAPY

Palliative radiation therapy is often helpful for controlling pain related to bone metastases or for improving neurologic function for patients with brain metastases. Irradiation of the thorax may also help control hemoptysis, SVC syndrome, airway obstruction, laryngeal nerve compression, and other local complications. Different modalities of radiation therapy, such as SBRT, may have relative advantages over conventional radiation therapy, but dose and modality will vary by specific clinical situation.

MANAGEMENT OF PLEURAL EFFUSION

Palliative thoracentesis should be performed for patients with symptomatic pleural effusion, and management with intermittent thoracentesis can frequently be effective if the effusion does not reaccumulate quickly. When reaccumulation is rapid, pleurodesis may be considered. The two most common methods of pleurodesis are through a chest tube or via thoracoscopy. Common sclerosing agents include doxycycline, talc, and bleomycin, with talc being the most effective. Unfortunately, the procedure is effective in only approximately 50% of cases and is associated with discomfort and a prolonged hospital stay. For these reasons, long-term drainage through a semipermanent catheter is used more frequently.[189] Effective systemic therapy may also reduce malignant effusions.

KEY POINTS

- Early integration with palliative medicine specialists improves quality of life for patients with metastatic lung cancer and may help extend survival.
- Every attempt should be made to palliate the symptoms of patients with lung cancer. In addition to systemic anticancer therapies, approaches include administering antiresorptive agents for bone metastases, incorporating palliative radiation therapy when appropriate, and addressing dyspnea caused by pleural effusions.

THYMIC MALIGNANCIES

Several different tumors can arise in the anterior mediastinum, including thymomas, Hodgkin and non–Hodgkin lymphomas, carcinoid tumors, and germ cell neoplasms. Thymomas are malignant neoplasms originating within the epithelial cells of the thymus, which often contain admixtures of lymphocytes.[190] Thymic carcinomas also are tumors of the thymic epithelium, but they are associated with a paucity of lymphocytes and are more aggressive and have a worse prognosis. Approximately 400 new cases of thymic malignancies are diagnosed annually in the United States. They affect men and women equally, have no known risk factors, and can be found incidentally on imaging.

Thymomas are the most common (~20%-30%) of all anterior mediastinal tumors in adults. Most thymomas are well encapsulated, but they are considered malignant because of their invasive potential. Cytokeratin is a useful diagnostic marker to distinguish thymomas from nonepithelial cell malignancies. Although they usually present in the fourth and fifth decades of life, cases have been reported from infancy into the ninth decade. At presentation, one-third of patients have local symptoms, such as cough, SVC syndrome, and dysphagia. Distant metastases are uncommon, with the most common metastatic site being the pleura. Definitive diagnosis requires tissue evaluation while avoiding a transpleural approach. Complete resection of thymomas is preferred over biopsy to avoid seeding and upstaging by violating the capsule. In the case of thymic carcinomas, consider open biopsy if core biopsy is not feasible or not diagnostic. Several PNS have been associated with thymoma. Myasthenia gravis, an autoimmune disorder caused by circulating acetylcholine receptor antibodies resulting in acetylcholine receptor deficiency at the motor end plate, occurs in approximately one-third of patients with thymoma, although it is rarely seen with thymic carcinoma. Interestingly, thymomas associated with myasthenia gravis tend to be less aggressive, and histologically, they tend to have a larger ratio of lymphocytes to epithelial cells. Surgical removal of all thymic tissue, not just tumor tissue, usually results in an attenuation of the severity of myasthenia gravis, although not all patients achieve resolution of all symptoms. Patients should have their serum anti–acetylcholine receptor antibody levels measured before surgery to determine whether they have myasthenia gravis, thus allowing proper management and avoiding respiratory failure during surgery.

Other PNS include pure red cell aplasia, vasculitis, hypogammaglobulinemia, and other autoimmune disorders. Thymectomy may result in normalization of the bone marrow for 40% or fewer of patients with pure red cell aplasia, although the procedure rarely results in a return to normal immunoglobulin levels for patients with immunodeficiency. The Masaoka staging for thymoma is based on encapsulation of the tumor and invasion into surrounding organs and distant sites outside the chest (Table 11-4).[191] Although the TNM staging provides more clinically relevant differentiation, it does not provide any therapeutic implication because a majority of studies supporting treatment decisions in thymic malignancies were based on Masaoka staging. Important prognostic factors include WHO histologic grade, complete resection status, and size.[190,192] Negative prognostic factors include tumor size larger than 10 cm, tracheal or vascular compromise, age younger than 30 years, the presence of hematologic PNS, incomplete surgical resection, and thymic carcinoma histology.

Table 11-4 Modified Masaoka Clinical Staging of Thymoma

Masaoka Stage	Diagnostic Criteria
I	Macroscopically and microscopically completely encapsulated
II	(A) Microscopic transcapsular invasion
	(B) Macroscopic invasion into the surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organs (ie, pericardium, great vessels, and lung)
	(A) Without invasion of great vessels
	(B) With invasion of great vessels
IV	(A) Pleural or pericardial dissemination
	(B) Lymphatic or hematogenous metastasis

Data adapted from Wright CD. Management of thymomas. *Crit Rev Oncol Hematol*. 2008;65:109-120.
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All patients with thymic malignancies should be treated by an experienced multidisciplinary team. The treatment of choice for thymoma is surgical resection of the thymus and contiguous and noncontiguous disease (eg, pericardium, pleura, lung, phrenic nerve, and major vessels). Surgical clips should be placed at the site of close margin and residual disease to guide the radiation field if needed. Pleural surface should be examined and metastases removed to aim for a pCR (no active cancer in the resected tumor). Minimally invasive procedures are not routinely recommended because of a lack of long-term data. Long-term survival for patients with encapsulated noninvasive (stage I) tumors is excellent, approaching 90% to 95% at 10 years. The role played by PORT after a complete (R0) resection is controversial, but sometimes, the procedure is used for completely resected stage II to IV thymoma. If R0 is uncertain to be achieved, preoperative chemotherapy should be considered. Adjuvant radiation therapy with or without chemotherapy is often recommended for patients with remaining microscopic (R1) or macroscopic (R2) residual disease.[193]

The optimal management of incompletely resected or unresectable thymic malignancies is controversial. Achieving an R0 resection is an important prognostic indicator. Therefore, debulking with chemotherapy for locally advanced disease to attempt to increase the potential for an R0 resection should be considered. Surveillance for recurrence is performed with CT chest with intravenous contrast every 6 to 12 months for 2 years, then annually for 5 years for thymic carcinoma and 10 years for thymoma.

Given the small number of affected patients, no randomized trials have been performed to identify the best chemotherapy regimen for inoperable or recurrent thymoma. Commonly used regimens in the first-line metastatic or unresectable setting include combined cisplatin, doxorubicin, and cyclophosphamide[193]; combined cisplatin and etoposide; and combined carboplatin and paclitaxel.[194]

Thymic carcinomas are aggressive and characterized by a high degree of histologic anaplasia and architectural atypia. The preferred first-line regimen for unresectable or metastatic disease is carboplatin and paclitaxel for up to six cycles with or without ramucirumab; the latter will be continued until progression of disease or unacceptable toxicity.[195] Rarely, these tumors have activating *c-KIT* mutations and can be responsive to sunitinib after progression during a platinum-based regimen.[196] Several different subtypes have been described, although more than half are undifferentiated. These tumors often metastasize to regional lymph nodes and distant sites; therefore, they have a worse prognosis than thymomas, with 5-year survival rates of 20% to 30%. Phase 2 studies of pembrolizumab have shown promising activity, with response rates greater than 20%, but immune-related toxicity was also noted and at a higher incidence than in some other cancers, such as NSCLC; specifically, severe myocarditis was reported in 5% to 9% of patients with thymic carcinoma who were treated with pembrolizumab. Post–platinum therapy: Lenvatinib shows maturing benefit in the phase 2 REMORA study—updated analyses report a median OS ≈28.3 months, reinforcing lenvatinib as an active option after platinum.[197] In pretreated disease, the phase 2 CAVEATT trial of avelumab + axitinib in heavily pretreated thymic carcinoma/WHO B3 thymoma demonstrated a median OS of 23.4 months, with durable benefit in select subgroups (eg, those without liver metastases).[198]

KEY POINTS

- Thymomas are often encapsulated, well differentiated, and associated with PNS such as myasthenia gravis.
- The optimal treatment of thymoma is thymectomy and complete surgical resection, in which case survival is excellent.
- The most important prognostic factors after resection are Masaoka stage, histology, complete resection status, and size.
- Thymic carcinomas are more aggressive than thymomas.
- Platinum-based chemotherapy remains standard therapy for unresectable or recurrent thymoma or thymic carcinoma.
- Immunotherapy is not indicated in the treatment of thymoma.
- The incidence of immune-related adverse events with immunotherapy is higher with thymic carcinoma than with other cancers.

MESOTHELIOMA

Mesothelioma arises from mesothelial cells, which form the serosal lining of the pleura, pericardium, and peritoneal cavities.[199] Although benign mesotheliomas have been described, most are malignant, have an aggressive clinical course, and are difficult to cure. Malignant mesotheliomas are rare, with approximately 2,500 new cases diagnosed annually in the United States. Although approximately 80% are associated with exposure to asbestos, only approximately 5% of asbestos workers are diagnosed with mesothelioma. In contrast to lung cancer and asbestosis, smoking does not increase the risk of mesothelioma.

Carcinogenic effects of asbestos seem to result from its physical properties rather than from its chemical structure, with long rod-like fibers of narrow diameter being more likely to induce tumors in laboratory animals. Pathology remains the most prognostic factor. Three histologic variants of mesothelioma have been described: (1) epithelial, the most common form, which is chemosensitive and associated with the best prognosis; (2) sarcomatoid, associated with the worst prognosis; and (3) mixed (or biphasic).

To distinguish mesotheliomas from metastatic adenocarcinomas, the periodic acid–Schiff stain is frequently used before and after diastase digestion. Neutral mucopolysaccharides that are strongly positive on periodic acid–Schiff staining are found in

intracellular secretory vacuoles and in intra-acinar vacuoles in most adenocarcinomas but are rarely found in most mesotheliomas. In addition, IHC staining for CD15, Ber-EP-4, TTF1, and carcinoembryonic antigen is usually absent in mesotheliomas but is positive in most adenocarcinomas, whereas mesothelioma is characterized by staining for calretinin, Wilms tumor antigen (WT1), vimentin, CK5/6, mesothelin, or HBME-1 (an anti–mesothelial cell antibody).[200]

Mesothelioma most commonly develops in the fifth to seventh decade and affects men and women at a 5:1 ratio. The onset of disease occurs 20 to 50 years after exposure. Family members are also at higher risk of mesothelioma, presumably because of exposure to asbestos fibers brought home on the clothing and bodies of individuals who work with asbestos. The typical presentation consists of B symptoms and dyspnea secondary to a pleural effusion or chest-wall pain. Most mesotheliomas (60%) occur on the right side, and bilateral involvement of the chest wall is present at the time of diagnosis in fewer than 5% of cases. Cytologic examination of pleural fluid may be negative, necessitating either diagnostic thoracoscopy or pleural biopsy.

Mesothelioma tends to be locally invasive. For approximately 20% of patients, a chest-wall mass develops over biopsy tracts, resulting from thoracentesis, chest tubes, or thoracotomy. Therefore, single-port thoracoscopy on the line of potential incision is recommended to prevent seeding and can be excised during definitive surgery. Direct involvement of the ribs, diaphragm, pericardium, and vertebrae is common. Although various staging classifications have been described, the TNM staging system adopted by the AJCC is most used, and its prognostic value was confirmed by the International Association for the Study of Lung Cancer and the International Mesothelioma Interest Group.[201]

The choice of surgical resection for mesothelioma is controversial and has not been shown conclusively to improve survival. Surgical approaches include extrapleural pneumonectomy (EPP) and pleurectomy with decortication (P/D). EPP includes en bloc resection of the parietal pleura, lung, pericardium, and diaphragm. P/D involves careful resection of only the visceral and parietal pleura.[202] In resectable pleural mesothelioma, adding extended pleurectomy/decortication (EPD) to platinum–pemetrexed did not improve outcomes and was associated with worse OS versus chemotherapy alone (median ~19.3 vs 24.8 months) and worse quality of life; perioperative morbidity contributed, and fewer patients in the surgery arm received postoperative chemotherapy. These results do not support routine EPD outside trials.[203]

The prognosis is poor for patients who have unresectable disease at presentation. A phase 3 study demonstrated a 9.3-month median survival for patients treated with cisplatin alone and 12.1-month survival for patients treated with cisplatin and pemetrexed (HR, 0.77; $P = .02$).[204] The response rate with cisplatin and pemetrexed was 41.3% compared with 16.7% with cisplatin alone. This trial led to the first FDA-approved treatment with cisplatin and pemetrexed for unresectable malignant pleural mesothelioma (MPM) in 2004. A similar time to progression (7 vs 6.9 months) and 1-year OS rate (63.1 vs 64%) were found in chemotherapy-naive patients with MPM who received pemetrexed with cisplatin or carboplatin under an international expanded access program (EAP).[205] Based on these data, carboplatin can be considered an alternative to cisplatin in patients who would not be eligible to receive cisplatin. In a randomized phase 3 trial (MAPS), bevacizumab added to cisplatin and pemetrexed improved survival (18.8 vs 16.1 months).[206] More grade 3 or worse hypertension (23% vs 0%) and thrombotic events (6% vs 1%) were noted with bevacizumab. Cisplatin and pemetrexed with bevacizumab should be considered for patients with unresectable MPM who are bevacizumab eligible, although bevacizumab is not FDA approved in this setting. Pemetrexed rechallenge can be considered in patients with MPM who had a response to pemetrexed-based therapy more than 6 months earlier.

Immunotherapy has emerged as a potential new standard of care for eligible patients with advanced mesothelioma. In the CheckMate 743 trial, 605 patients with unresectable pleural mesothelioma were randomly assigned to the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab or standard platinum and pemetrexed chemotherapy.[207] Survival was greater with nivolumab and ipilimumab than with chemotherapy (median OS, 18.1 vs 14.1 months; HR, 0.74). The benefit was more profound in the nonepithelioid subtype (n = 149; OS HR, 0.46) than in the epithelioid subtype (n = 456; OS HR, 0.86). The combination of nivolumab and ipilimumab was approved as first-line therapy for unresectable MPM. In the previously treated setting, single-agent immunotherapy has also shown activity for patients who did not receive it in the first line. In the CONFIRM trial, a randomized placebo-controlled phase 3 study, nivolumab improved the median survival (10.2 vs 6.9 months; HR, 0.69; $P = .009$), median PFS (3.0 vs 1.8 months; HR, 0.67; $P = .001$), and overall response rate (11% vs 1%; OR 14.0; $P = .0008$).[208]

CCTG IND.227 (or KEYNOTE-483), a randomized phase 3 study, showed that the combination of chemoimmunotherapy with a platinum agent, pemetrexed, and pembrolizumab improved the OS (16.1 vs 17.3 months; HR, 0.79; $P = .03$) and response rate (62% vs 38%; $P < .0001$) in treatment-naive patients with MPM compared with chemotherapy across all subgroups, with no new safety signals.[209,210] This combination was approved as first-line therapy for unresectable MPM in 2024.

KEY POINTS

- Approximately 80% of pleural mesotheliomas are associated with exposure to asbestos, including indirect exposure.
- The epithelial histologic form of mesothelioma is associated with a better prognosis than the sarcomatoid or mixed histology form.
- Surgical options are not curative and include EPP and P/D.

- First-line chemotherapy for patients with unresectable mesothelioma consists of cisplatin and pemetrexed with or without bevacizumab.
- The combination of nivolumab and ipilimumab had a survival advantage over chemotherapy for patients with unresectable pleural mesothelioma, specifically with nonepithelioid histology, and is an approved first-line option.
- Combination chemotherapy and immunotherapy in first-line treatment of MPM is a promising strategy.

HIGH-YIELD TAKEAWAYS

Important Clinical Presentation

- SVC syndrome is an oncologic urgency seen in patients with lung cancer. Because of the compression of the SVC by surrounding tumor, patients present with facial, neck, and upper-extremity swelling. It requires prompt diagnosis and treatment.

Staging of NSCLC

- Staging for patients with NSCLC typically includes CT scan of the chest and abdomen as well as a PET scan.
- MRI of the brain is also recommended for patients with clinical stage II or greater NSCLC.
- Mediastinal staging is recommended for most patients with stage IB to III NSCLC.

Resectable NSCLC

- Treatment for stage I and II NSCLC is surgical resection (if the patient is a candidate) or radiation therapy (preferably stereotactic radiation therapy) if the patient is not a surgical candidate.
- Anatomic resection such as lobectomy is preferred, although recent data indicate that sublobar resection is acceptable for patients with tumors 2 cm or smaller and negative lymph nodes.
- Adjuvant chemotherapy consisting of a cisplatin-based combination is indicated for patients with stage IIB to III disease after surgical resection. Adjuvant chemotherapy can be considered for patients with stage IIA disease or higher.
- Adjuvant atezolizumab improves DFS for resected stage II to IIIA NSCLC with PD-L1 of 1% or greater.
- The KEYNOTE-091 trial demonstrated that 12 months of pembrolizumab after adjuvant chemotherapy significantly improves DFS for PD-L1–unselected patients with completely resected stage IB (T2a $\geq$ 4 cm), II, or IIIA NSCLC.
- Adjuvant osimertinib improves DFS and OS for resected stage IB to IIIA *EGFR*-mutated NSCLC; similarly, adjuvant alectinib improves PFS in *ALK* fusion–positive NSCLC.

Stage III NSCLC

- Treatment options for stage III NSCLC are complex and varied and generally include some combination of chemotherapy, radiation therapy, surgery, and immunotherapy; treatment decisions should be made in discussion with a multidisciplinary team.
- If microscopic N2 (or N1) disease is detected at surgery in a patient who did not receive neoadjuvant therapy, adjuvant therapy should be administered.
- The current standard treatment of unresectable stage III *ALK* and *EGFR*–wild-type NSCLC is concurrent platinum-based chemoradiation therapy followed by immunotherapy with durvalumab.

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

LUNG CANCER 11

CHAPTER SUMMARY GUIDE

KEY POINTS

- Lung cancer is the most common cause of cancer-related death in the United States in both men and women.
- Most cases of lung cancer (85%) are caused by carcinogens in tobacco smoke.
- The four most common histologic subtypes of lung cancer are adenocarcinoma, squamous cell carcinoma, large cell carcinoma (collectively referred to as NSCLC), and SCLC.
- Guidelines recommend testing for *EGFR, KRAS, HER2, BRAF*, and *MET* mutations and *ALK, ROS-1, NTRK, RET*, and *NRG1* translocations/fusions in all treatment-eligible patients with stage IV non–squamous NSCLC, with the consideration of testing in select treatment-eligible individuals with stage IV squamous NSCLC.
- *EGFR* and *ALK* testing is indicated for patients with resectable stage IB to IIIA non–squamous NSCLC and patients with inoperable stage III NSCLC who will receive concurrent chemotherapy and radiation.
- When tissue is not available for genomic testing, a blood-based "liquid biopsy" can be utilized for molecular testing; there are limitations to its sensitivity, and uninformative results may need to be confirmed with tissue-based testing.
- Common symptoms of lung cancer include local symptoms, such as cough, pain, and shortness of breath, and constitutional symptoms, such as fatigue, weakness, anorexia, and weight loss.
- The most common sites for metastatic disease in lung cancer are the lungs (ipsilateral and contralateral), adrenal glands, liver, bone, and brain.
- PNS are commonly seen in patients with lung cancer, notably, hypercalcemia, SIADH, ectopic ACTH production, and neurologic syndromes.
- Screening for lung cancer with annual LDCT of the chest is recommended for patients of age 50 to 80 years who have a smoking history of 20 or more pack-years and who are currently smoking or have quit within the last 15 years.
- The KEYNOTE-091 trials demonstrated that 12 months of pembrolizumab after adjuvant chemotherapy significantly improves DFS for PD-L1–unselected patients with completely resected stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC.
- The IMpower 010 trial revealed that the addition of 1 year of atezolizumab after adjuvant chemotherapy significantly improves DFS in patients with stage II to IIIA NSCLC expressing PD-L1 on 1% or more of tumor cells.
- Adjuvant osimertinib improves DFS and OS for patients with resected stage IB to IIIA *EGFR*-mutated NSCLC.
- Adjuvant alectinib improves DFS for patients with resected stage II to IIIA *ALK*-rearranged NSCLC.
- Treatment options for stage III NSCLC are complex and varied and generally include some combination of systemic therapy (chemotherapy, immunotherapy, and targeted therapy), radiation therapy, and surgery; treatment decisions should be made in discussion with a multidisciplinary team.
- If microscopic N2 (or N1) disease is detected at surgery in a patient who did not receive neoadjuvant therapy, adjuvant therapy should be administered.
- For patients with *EGFR*-mutated, unresectable stage III NSCLC, osimertinib is an approved option after completion of concurrent chemoradiation therapy.
- For *EGFR* exon 19–deleted and *EGFR* L858R–mutated NSCLC, the preferred first-line option is osimertinib with or without chemotherapy or amivantamab with lazertinib.
- Amivantamab with chemotherapy is an option for *EGFR* exon 19–deleted and exon 21 L858R–mutated NSCLC after progression during treatment with osimertinib.
- Acquired resistance to first- and second-generation EGFR TKIs is often mediated by the T790M resistance mutation, and osimertinib is indicated in this setting.
- For *EGFR* exon 20 insertion mutations: Amivantamab and chemotherapy are approved as frontline therapy (PAPILLON). Sunvozertinib received FDA-accelerated approval (July 2025) for patients who progressed on platinum-based chemotherapy.
- For *ALK*-rearranged NSCLC, the preferred first-line options include alectinib, brigatinib, and lorlatinib.
- For ROS-1-rearranged NSCLC, taletrectinib was FDA approved (June 2025) and joins crizotinib, entrectinib, and repotrectinib.
- For *KRAS* G12C–mutated advanced NSCLC, both sotorasib and adagrasib are approved treatments in the second-line setting.

- For advanced NSCLC with *BRAF* V600E mutation, a combination of either dabrafenib and trametinib or encorafenib and binimetinib is approved; the latter has less reported pyrexia.
- For advanced NSCLC with *NTRK* fusion, larotrectinib and entrectinib are approved treatments. For advanced NSCLC with *RET* fusion, selpercatinib and pralsetinib are approved treatments. For advanced NSCLC with *MET* exon 14–skipping mutation, capmatinib and tepotinib are approved treatments.
- For MET IHC–high EGFR–wild-type NSCLC, the antibody-drug conjugate telisotuzumab vedotin-tllv (Emrelis) received accelerated approval.
- For advanced NSCLC with *HER2* mutation, zongertinib and trastuzumab deruxtecan are approved in the second-line setting; trastuzumab deruxtecan may also be used as second-line treatment for *HER2*-positive (IHC3+) advanced NSCLC.
- For advanced NSCLC with *NRG1* fusion, zenocutuzumab is approved as treatment in the second-line setting.
- NSCLC without an activating alteration in *EGFR* or *ALK* and with high PD-L1 expression (TPS $\geq$ 50%) can be treated with pembrolizumab, atezolizumab, or cemiplimab, all of which confer an improvement in survival over platinum-doublet chemotherapy.
- Dual-checkpoint blockade with nivolumab and ipilimumab improved survival compared with chemotherapy in PD-L1–positive (TPS $\geq$ 1%) NSCLC and is also a first-line treatment option. It may be used in the PD-L1–negative squamous NSCLC population as well.
- The combination of an immune checkpoint inhibitor with platinum-doublet chemotherapy improves PFS and survival in patients with squamous and non–squamous NSCLC (*EGFR* and *ALK* wild type) across all PD-L1 subsets.
- The combination of nivolumab and ipilimumab with two cycles of platinum-doublet chemotherapy, or durvalumab and tremelimumab with four cycles of platinum-doublet chemotherapy, is also approved across histologies and PD-L1 levels.
- Use of immunotherapy is not appropriate for certain molecular subtypes of advanced NSCLC (ie, EGFR/ALK), regardless of tumor PD-L1 expression; use of immune checkpoint inhibitors in these subgroups can be associated with both inferior efficacy and excess toxicity.
- Pemetrexed is an appropriate platinum partner in non–squamous histology; gemcitabine is appropriate for treatment of tumors with squamous histology. Paclitaxel or nab-paclitaxel is a reasonable choice for either histology.
- Fit older patients tolerate chemotherapy and derive the same survival benefit as their younger counterparts.
- The addition of the VEGFR2 antibody ramucirumab to second-line docetaxel improves survival.
- TTFields in combination with immune checkpoint inhibitors or docetaxel have improved outcomes in NSCLC after progression during platinum-based chemotherapy.
- SCLC is characterized by high response rates to systemic therapy and high relapse rates.
- The AJCC TNM staging system is appropriate, but the functional staging system proposed by the Veterans Authority Lung Study Group is often used clinically. LS-SCLC can be encompassed in a tolerable radiation therapy port; ES disease cannot.
- For LS-SCLC, the standard approach is cisplatin and etoposide with definitive radiation therapy followed by consideration of PCI and durvalumab for 24 months.
- For ES-SCLC, the standard approach is platinum with etoposide and either atezolizumab or durvalumab, with immunotherapy continued as maintenance after four cycles of chemoimmunotherapy.
- For relapsed SCLC, tarlatamab is the preferred agent for eligible patients.
- Early integration with palliative medicine specialists improves quality of life for patients with metastatic lung cancer and may help extend survival.
- Every attempt should be made to palliate the symptoms of patients with lung cancer. In addition to systemic anticancer therapies, approaches include administering antiresorptive agents for bone metastases, incorporating palliative radiation therapy when appropriate, and addressing dyspnea caused by pleural effusions.
- Thymomas are often encapsulated, well differentiated, and associated with PNS such as myasthenia gravis.
- The optimal treatment of thymoma is thymectomy and complete surgical resection, in which case survival is excellent.
- The most important prognostic factors after resection are Masaoka stage, histology, complete resection status, and size.
- Thymic carcinomas are more aggressive than thymomas.
- Platinum-based chemotherapy remains standard therapy for unresectable or recurrent thymoma or thymic carcinoma.
- Immunotherapy is not indicated in the treatment of thymoma.
- The incidence of immune-related adverse events with immunotherapy is higher with thymic carcinoma than with other cancers.
- Approximately 80% of pleural mesotheliomas are associated with exposure to asbestos, including indirect exposure.
- The epithelial histologic form of mesothelioma is associated with a better prognosis than the sarcomatoid or mixed histology form.

- Surgical options are not curative and include EPP and P/D.
- First-line chemotherapy for patients with unresectable mesothelioma consists of cisplatin and pemetrexed with or without bevacizumab.
- The combination of nivolumab and ipilimumab had a survival advantage over chemotherapy for patients with unresectable pleural mesothelioma, specifically with nonepithelioid histology, and is an approved first-line option.
- Combination chemotherapy and immunotherapy in first-line treatment of MPM is a promising strategy.

CHAPTER TABLES AND IMAGES

Table 11-1 Characteristics of Major Subtypes of Lung Cancer

Histology	Frequency (%)	Immunohistochemistry	Clinical Features/Comments
Non–small cell			
Adenocarcinoma	50	TTF-1, Napsin-A, CK7	Most common histology to have actionable driver mutations
Squamous cell carcinoma	25	P63, p40, CK5/6	Often central tumors; may develop cavitation; more commonly seen in those with heavy smoking history
Large cell carcinoma	5	—	Poorly differentiated tumors that do not meet the criteria for adenocarcinoma or squamous cell carcinoma
Pulmonary neuroendocrine tumors			
Typical carcinoid	1-2	Synaptophysin, chromogranin, INSM-1	<2 mitoses/2 mm^2 (10 HPF); lacking necrosis
Atypical carcinoid	1-2	Synaptophysin, chromogranin, INSM-1	2-10 mitoses/2 mm^2 (10 HPF) or necrosis
Large cell neuroendocrine carcinoma	5	Synaptophysin, chromogranin, INSM-1	High mitotic rate (>10 mitoses/2 mm^2; may show organoid nesting and rosettes
Small cell carcinoma	12-13	Synaptophysin, chromogranin, INSM-1	High mitotic rate (>10 mitoses/2 mm^2); small cells; nuclear molding; often crush artifact noted

Abbreviations: CK, cytokeratin; HPF, high-power fields; INSM-1. insulinoma-associated protein 1.

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Table 11-2 **PD-(L)1 Inhibitor Monotherapy in PD-L1–High NSCLC**

Study	Agent	Median Survival vs Chemotherapy (Months)	Survival HR	Response Rate (%)
KEYNOTE-024	Pembrolizumab	26.3 vs 13.4	0.62	44.8
KEYNOTE-042	Pembrolizumab	20.0 vs 12.2	0.69	39.0
IMpower 110	Atezolizumab	20.2 vs 13.1	0.59	38.3
EMPOWER-Lung01	Cemiplimab	NR vs 14.2	0.57	39.0
CheckMate 026	Nivolumab	15.9 vs 13.9	0.9	34.0

Abbreviations: HR, hazard ratio; NR, not reported; NSCLC, non–small cell lung cancer; PD-L1, programmed cell death ligand 1.
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Table 11-3 **Targeted Therapy for Unresectable or Metastatic NSCLC With Targetable Molecular Aberration**	
Target	**Preferred Targeted Therapy**
EGFR exons 19 and 21	Osimertinib, osimertinib and chemotherapy, amivantamab and lazertinib
EGFR exon 20	Amivantamab[a]
ALK fusions	Lorlatinib; alectinib, brigatinib, ensartinib
ROS-1 fusions	Crizotinib, entrectinib, repotrectinib, taletrectinib
KRAS G12C	Sotorasib,[b] adagrasib[b]
BRAF V600E	Dabrafenib + trametinib, encorafenib + binimetinib
RET	Selpercatinib, pralsetinib
MET exon 14 skipping mutation	Capmatinib, tepotinib
MET IHC high (3+)	Telisotuzumab vedotin-tllv
HER2 mutation	Zongertinib, trastuzumab deruxtecan[b]
HER-2 IHC high (3+)	Trastuzumab deruxtecan
NTRK1/2/3 fusions	Larotrectinib, entrectinib
NRG fusions	Zenocutuzumab

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer.
[a]Preferred in first line in combination with carboplatin and pemetrexed.
[b]Approved after progression during first-line systemic therapy.
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Table 11-4 **Modified Masaoka Clinical Staging of Thymoma**	
Masaoka Stage	**Diagnostic Criteria**
I	Macroscopically and microscopically completely encapsulated
II	(A) Microscopic transcapsular invasion
	(B) Macroscopic invasion into the surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organs (ie, pericardium, great vessels, and lung)
	(A) Without invasion of great vessels
	(B) With invasion of great vessels
IV	(A) Pleural or pericardial dissemination
	(B) Lymphatic or hematogenous metastasis

Data adapted from Wright CD. Management of thymomas. *Crit Rev Oncol Hematol*. 2008;65:109-120.
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Figure 11-1 Signs and Symptoms Associated With Lung Cancer

Key Symptoms	Other Common Symptoms	Less Frequent, but Important Symptoms	Rare/Severe Symptoms
1. Cough 2. Increased sputum production 3. Shortness of breath	1. Fatigue 2. Weight loss 3. Anorexia 4. Low-grade fever	1. Chest pain 2. Hemoptysis 3. Hoarseness (recurrent laryngeal nerve) 4. Bone pain	1. Superior vena cava obstruction 2. Superior sulcus/Pancoast tumor 3. Pericardial tamponade 4. Paraneoplastic syndromes 5. Brain metastases

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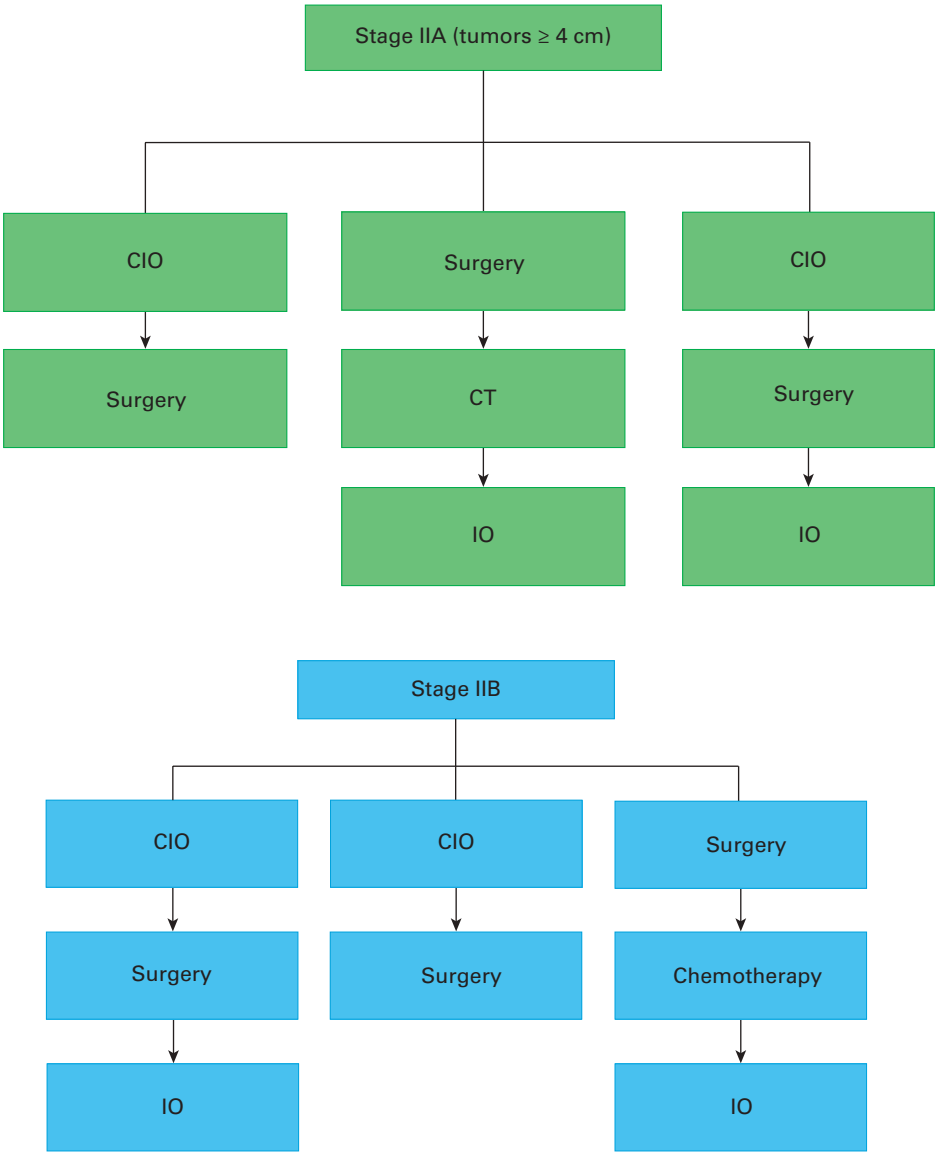
Figure 11-2 Approved Options for Resectable *ALK* and *EGFR*–Wild-Type Stage IIA and IIB NSCLC



Abbreviations: CIO, chemotherapy with immunotherapy; CRT, chemotherapy and radiation therapy; EGFR, epidermal growth factor receptor; IO, immunotherapy; NSCLC, non–small cell lung cancer.
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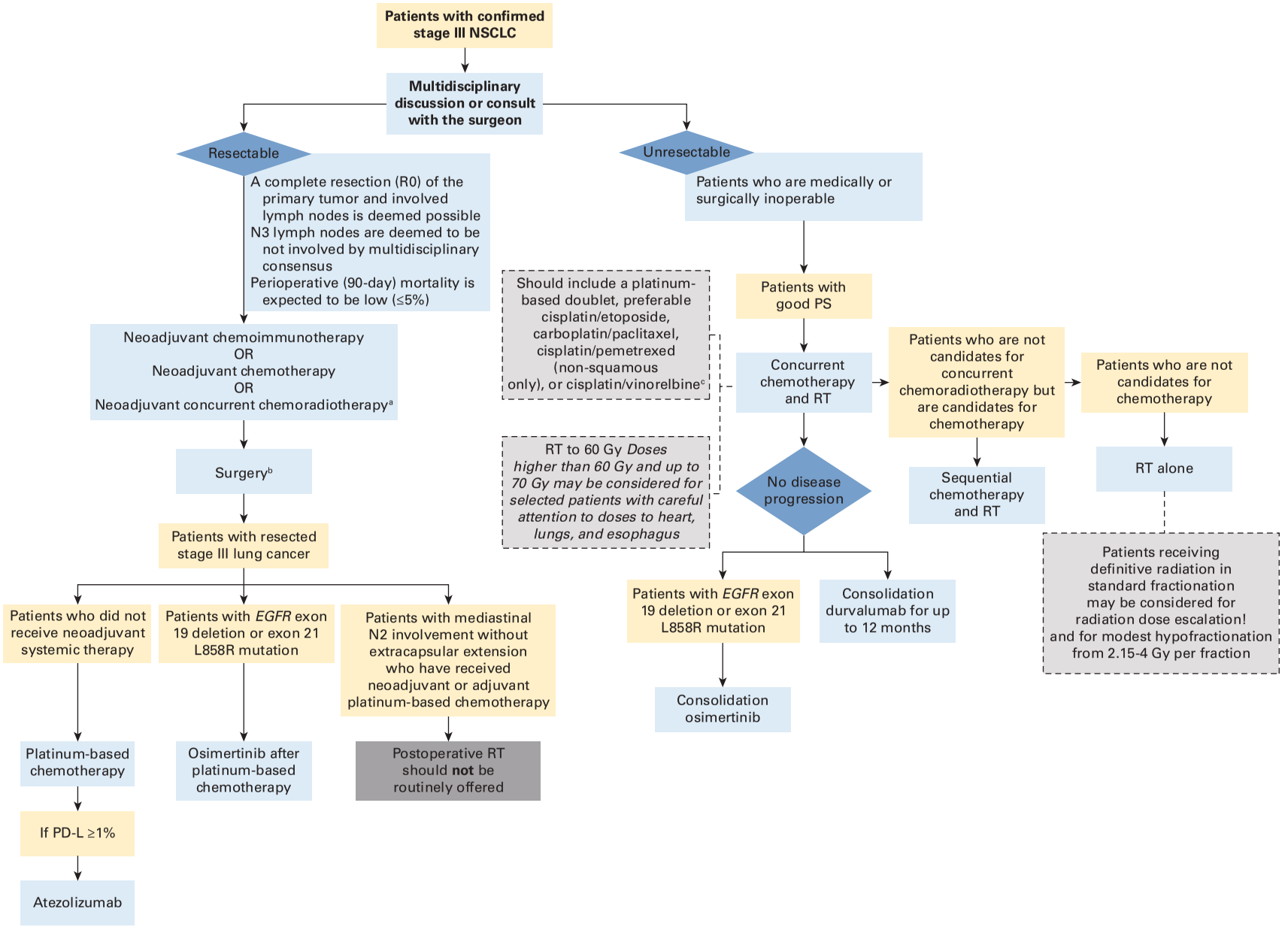
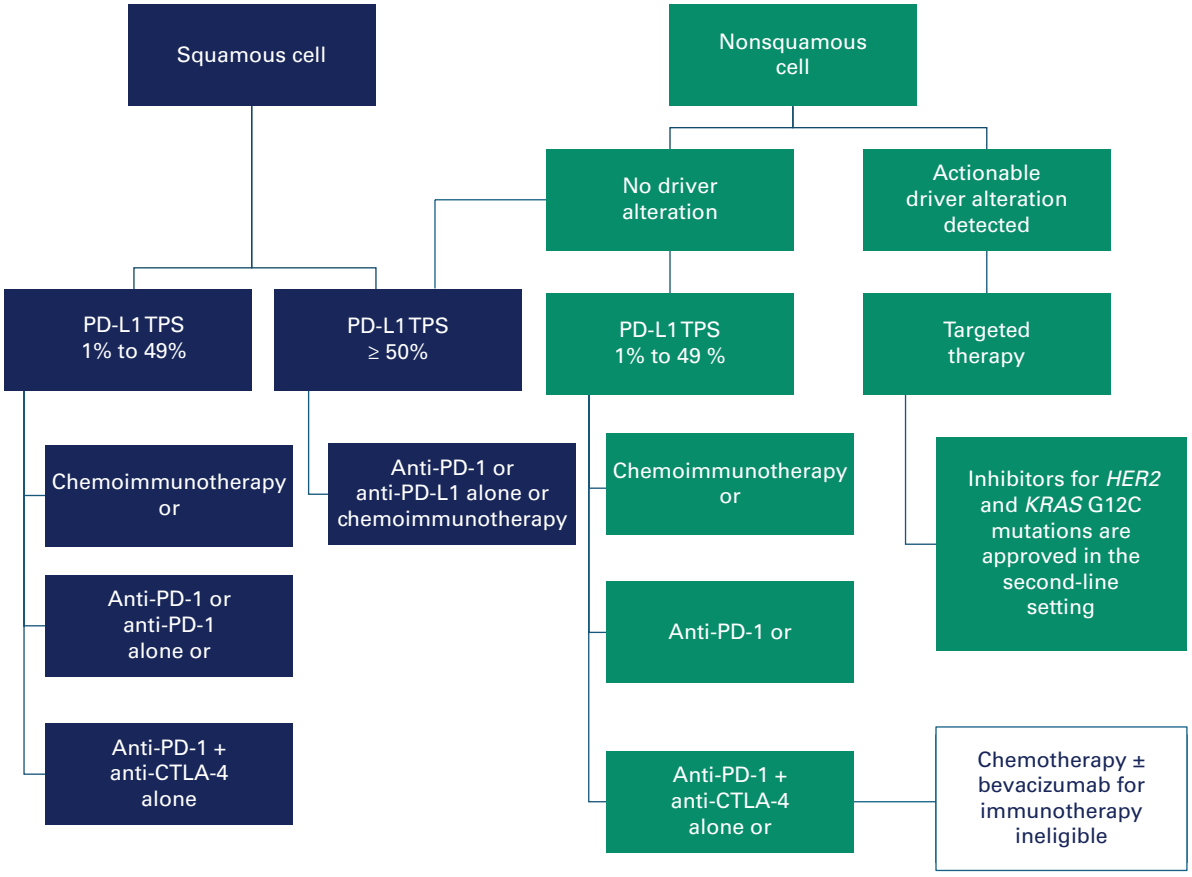
Figure 11-3 Management of Stage III NSCLC Algorithm



Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; NSCLC, non–small cell lung cancer; PET, positron emission tomography; PS, performance status; RT, radiation therapy.
Arrows with dotted lines indicate that the level of obligation is a "may" (moderate) recommendation.
[a]Resectable superior sulcus tumors.
[b]Patients with stage III NSCLC generally should not be excluded from consideration for surgery by nonsurgical physicians.
[c]Carboplatin may be substituted for cisplatin in patients with contraindications to or deemed ineligible for cisplatin.
Reprinted from Daly ME, Singh N, Ismaila N, et al., Management of stage III non–small cell lung cancer: ASCO guideline rapid recommendation update. *J Clin Oncol*. 2024;42(25):3058-3060. doi:10.1200/JCO-24-01324

Figure 11-4 Treatment Paradigms for Advanced Non–Small Cell Lung Cancer by Cancer Subtype and PD-L1 TPS



Abbreviations: PD-L1, programmed cell death ligand 1; TPS, Tumor Proportion Score.
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HEAD AND NECK CANCERS 12

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RECENT UPDATES

- The FDA recently approved penpulimab with cisplatin or carboplatin and gemcitabine for the first-line treatment of adults with recurrent or metastatic nonkeratinizing nasopharyngeal carcinoma (NPC). FDA also approved penpulimab-kcqx as a single agent for adults with metastatic nonkeratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.
- The FDA-approved pembrolizumab for adults with resectable locally advanced head and neck squamous cell carcinoma whose tumors express PD-L1 (combined positive score [CPS] ≥1) as determined by an FDA-approved test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without cisplatin after surgery, and then as a single agent.

OVERVIEW

Head and neck cancers are a heterogeneous group of malignant tumors arising from the epithelial lining of the upper aerodigestive tract. The specific primary sites are subdivided by anatomic boundaries: lip and oral cavity, pharynx (comprising the nasopharynx, oropharynx, and hypopharynx), larynx, nasal cavity, and paranasal sinuses (Table 12-1). Squamous cell cancer is the most common histologic type, accounting for 85% to 95% of head and neck cancers. Other cancers in the head and neck region are often lumped together under the generic "head and neck cancers" umbrella, and they include neoplasms of the salivary glands and thyroid and tumors of the skull base, such as esthesioneuroblastoma, sinonasal undifferentiated carcinomas, and NUT midline carcinomas. These are biologically distinct and will be covered separately.

Table 12-1 **Head and Neck Cancer: Primary Sites**

Anatomic Area	Primary Cancer Site
Oral cavity and lip	Floor of mouth
	Oral tongue
	Buccal mucosa
	Alveolar ridges
	Hard palate
	Retromolar trigone
Pharynx	Nasopharynx (includes the superior surface of the soft palate)
	Oropharynx (includes the inferior surface of the soft palate, uvula, base of the tongue, tonsil, posterior pharyngeal wall)
	Hypopharynx (pyriform sinus, postcricoid, posterior wall)
Larynx	Supraglottic larynx (false cords, arytenoids, epiglottis)
	Glottic larynx (includes commissures)
	Subglottic larynx
Nasal cavity and paranasal sinuses	Nasal cavity
	Maxillary sinuses
	Ethmoid sinuses
	Frontal sinuses
	Sphenoid sinuses

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Etiologic factors include tobacco and alcohol use and viruses such as human papillomavirus (HPV) and Epstein-Barr virus (EBV). Less common risk factors include exposures from betel nut chewing and occupational exposure (eg, formaldehyde, Agent Orange). Head and neck cancers are generally categorized as early-stage disease (localized to the primary site without neck nodal involvement), locoregionally advanced disease (large, bulky tumors [T3 or T4] with or without nodal involvement or smaller primary tumors with nodal involvement), or metastatic disease beyond the neck lymph nodes. Involvement of the neck nodes is prognostically substantial in HPV-negative disease, which reduces the cure rate for patients with a given tumor stage by approximately 50%. Patients with HPV-positive oropharyngeal tumors and multiple ipsilateral neck nodes smaller than 6 cm in size still maintain a favorable prognosis. This is reflected in the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, 8th edition, and subsequent versions of the staging system, which have separated staging for p16-positive oropharyngeal squamous cell carcinomas (OPSCCs or oropharyngeal cancers [OPCs]) from p16-negative OPCs. Note that, while p16 immunohistochemistry (IHC) is generally taken as a validated surrogate for HPV-related OPC, this surrogate is not synonymous with HPV-related OPC. Because HPV-specific treatments are emerging, it will be important for clinicians to understand that the gold standard for HPV testing remains either in situ hybridization (ISH) or polymerase chain reaction (PCR) in this situation. Early-stage disease, at times, may be treated with single-modality therapy (ie, surgery, radiation), whereas locally advanced disease is generally treated with multimodality therapy.

Within the aerodigestive tract, second primary malignancies (SPMs) occur most frequently in the lung, followed by the esophagus. SPMs occur as a result of the carcinogenic effect on the upper aerodigestive tract mucosa of chronic exposure to environmental carcinogens (tobacco and alcohol), putting the entire mucosa at risk for forming multiple, independent tumors. The risk and distribution of SPMs vary substantially based on the subsite of the index cancer and are highest for hypopharyngeal cancers. When solitary distant lesions are identified on imaging, patients with early-stage cancers (ie, with no involved neck nodes) are more likely to have an SPM than to have metastases, and treatment should be with curative intent for both the SPM and head and neck cancer. Systemic therapy by itself is palliative and is the mainstay for distant metastatic or recurrent head and neck squamous cell carcinomas (HNSCCs) not amenable to curative approaches.

The other disease sites included in the head and neck region are uncommon base-of-skull and sinonasal tumors and thyroid and salivary gland malignancies. Surgical resection is the standard of care for surgically resectable early-stage or locoregionally advanced salivary gland tumors, followed by radiation when indicated. These diseases are composed of numerous histologies that are associated with differing natural histories. For instance, adrenocortical carcinomas (ACCs) tend to be more indolent, whereas salivary ductal cancers may be more aggressive. For metastatic or recurrent salivary gland cancers, molecular analysis may inform treatment selection in a minority of cases, such as neurotrophic receptor tyrosine kinase (NTRK)-targeting agents for *ETV6::NTRK3* fusion–positive cancers (mammary analog secretory carcinoma [MASC]). In addition, salivary ductal cancers that express either human epidermal growth factor receptor 2 (HER2) or androgen receptor may be treated with HER2-targeting therapies or androgen deprivation therapy (ADT), respectively.

Thyroid cancers include the subtypes of differentiated thyroid cancers (DTCs) such as papillary, follicular, oncocytic, or medullary (MTC), as well as poorly differentiated and anaplastic thyroid carcinomas. Surgical treatment remains the primary modality for patients with DTC who have locoregional disease, and cure rates are very high. Patients with well-differentiated papillary or follicular thyroid cancer typically receive radioactive iodine (RAI) in the postoperative setting for locally advanced disease, and this is the first treatment of choice for metastatic disease if radiolabeled thyroid imaging is positive. Tyrosine kinase inhibitors (TKIs) are approved for the treatment of RAI-refractory disease, regardless of mutation status. Poorly differentiated and anaplastic thyroid cancers (ATCs) often arise from dedifferentiation of DTCs and are associated with a poor prognosis, but data on targeting *BRAF*-mutated ATC with a BRAF and MEK inhibitor combination have been encouraging. MTCs arise from the parafollicular C cells of the thyroid gland and do not respond to RAI. For MTC with known actionable molecular targets such as NTRK and rearrangement during transfection (RET) receptor fusions, targeted agents with remarkably high anticancer activity are FDA-approved agents in the recurrent/metastatic setting. In addition, two multitargeted vascular endothelial growth factor (VEGF)-targeting TKIs are approved for the management of recurrent/metastatic MTC. For both differentiated and medullary thyroid cancers, active surveillance is often appropriate before systemic therapy initiation, even in the metastatic setting, as these cancers can display indolent behavior.

EPIDEMIOLOGY

In 2025, head and neck cancers were expected to account for approximately 4% of all cancers in the United States. It is estimated that 72,700 people will develop carcinomas of the head and neck.[1] The median age at diagnosis is approximately 60 years, and it is also estimated that 16,680 people will die as a result of their disease. Worldwide, head and neck cancer accounts for more than 550,000 cancer cases and 380,000 deaths annually.

Head and neck cancers affect men and women at a ratio of 2.5:1, although the ratio varies according to the primary site (eg, 4:1 for cancer of the oropharynx, 7:1 for cancer of the larynx). OPC incidence has increased substantially since the 1980s, more so in developing countries and often in younger individuals. This increase is related to the rise in HPV-related OPCs, particularly

among men. The prognosis for patients who have HPV-related OPC is much better than for those who have HPV-unrelated OPC. Site-specific cure rates vary, but, in general, environmental carcinogen-induced cancers have a worse prognosis than viral-induced cancers. Overall, the age-adjusted incidence and mortality rates for head and neck cancer are highest among Black men, and the stage-specific survival rates are lowest for this group.

RISK FACTORS

Tobacco and Alcohol

Epidemiologic data document a multiplicative risk relationship between tobacco and alcohol. Those who begin to smoke when they are younger than 18 and who have a cumulative smoking duration of more than 35 pack-years are at the highest risk. In addition, immunosuppression, such as secondary to chronic lymphocytic leukemia, HIV, or immunosuppression after solid organ transplantation, contributes to an increased risk of developing head and neck cancer. Smokeless tobacco and other chewed carcinogens (eg, betel quid, a combination of betel leaf, lime, and areca nut, commonly used in India and parts of Asia) are associated with the development of cancers of the oral cavity. Black air-cured tobacco (used in cigars and pipe tobacco) is more irritating to the respiratory mucosa than blonde or flue-cured tobacco (used in cigarettes) and is associated with a higher risk for head and neck cancer. Preclinical data suggest that, in HPV-related tumors, when tetrahydrocannabinol (THC) is absorbed into the bloodstream, it activates the p38 mitogen-activated protein kinase pathway, which ultimately prevents apoptosis, leading to uncontrolled growth of cancer cells; this is a possible explanation for the epidemiologic observation that the risk of HPV-related OPC is higher in marijuana users.[2,3]

Diet and Genetic Syndromes

Diets low in vitamins A and B and poor oral and dental hygiene are believed to elevate the risk for head and neck cancer. Plummer-Vinson syndrome, which is most commonly seen in postmenopausal women older than 50 years, is associated with iron deficiency anemia, hypopharyngeal webs, dysphagia, and a higher risk for squamous cell carcinomas (SCCs) in the postcricoid region of the hypopharynx, oral cavity, and esophagus. Two inherited syndromes, Fanconi anemia and dyskeratosis congenita, are also linked with the development of head and neck cancers.

Occupational Exposures

Tumors of the sinonasal tract are associated with various occupational toxin exposures (eg, nickel, radium, mustard gas, and chromium, which are byproducts of leather tanning and woodworking).

Viruses

Human Papillomavirus

In the United States between 1984 and 1989, 16% of OPCs were related to HPV; between 2000 and 2019, this increased to 70% of OPCs, predominantly HPV serotypes 16 or 18, revealing a fourfold increase within two decades. This trend was striking, given the decrease in tobacco use in the United States. The incidence of OPCs among men younger than 60 years who have no or minimal use of alcohol or tobacco continues to increase. Although it is clear that HPV can lead to the development of OPCs, the vast majority of humans with evidence of oral HPV exposure do not develop HPV-related OPC, and the latency between HPV exposure and development of HPV-related OPC seems to be in the order of decades. Effective multivalent vaccines against HPV have been developed that provide near-complete immunity against oral and oropharyngeal infection with the highest risk strains of the virus, and they are FDA-approved agents for eligible preteens and young adults up to age 45 years.[4]

The transforming potential of HPV is thought to be from viral proteins E6 and E7, which inactivate the tumor suppressors p53 and pRB and result in loss of cell cycle regulation, cellular proliferation, and chromosome instability.[5]

Expression of p16 is upregulated when HPV E7 oncoprotein degrades the retinoblastoma protein, whereas p16 expression in HPV-negative tumors is silenced by epigenetic promoter methylation or genetic mutation. IHC analysis of tumoral p16 protein expression in OPC serves as a surrogate for determining HPV-related SCC. Thus, the AJCC staging manual, in conjunction with the College of American Pathologists and ASCO guidelines,[6] adopted p16 overexpression by IHC, defined as 70% or higher tumor expression with at least a moderate staining intensity marker, as a surrogate for HPV positivity in OPCs. Because the same survival benefit does not extend to HPV-positive or p16-positive tumors from non-oropharyngeal head and neck sites, p16 IHC staining is not recommended for any other squamous cell head and neck cancers. There is a small risk of discordance between p16 and high-risk HPV testing; 5% of patients with OPC are noted to be HPV DNA–positive but p16-negative.[7] Therefore, confirmatory testing for high-risk HPV should be performed if available. Because more experimental approaches to HPV-related OPC are specific to HPV, and because the prognoses for p16-positive HPV-negative tumors are worse than for HPV-positive OPC, many now consider direct testing for HPV with ISH or PCR to be the gold standard for testing. Patients with HPV-related OPCs have strikingly better survival rates than those with HPV-negative tumors; there is a 3-year progression-free survival (PFS) rate of greater than 90% among low-risk tumors, but, as of 2025, treatment recommendations for the two remain analogous in the curative setting.

Clinical trials attempting to reduce morbidity while preserving cure rates for HPV-associated OPC have, to date, been discordant and not uniformly practice-changing. Therefore, confirmatory testing for high-risk HPV should be performed if available. Because more experimental approaches to HPV-related OPC are specific to HPV, and because the prognoses for p16-positive but HPV-negative tumors are worse than for HPV-positive OPC, many now consider direct testing for HPV with ISH or PCR to be the gold standard for testing. Patients with HPV-related OPCs have strikingly better survival rates than those with HPV-negative tumors; there is a 3-year PFS rate of greater than 90% among low-risk tumors, but, as of 2025, treatment recommendations for the two remain analogous in the curative setting. Clinical trials attempting to reduce morbidity while preserving cure rates for HPV-associated OPC have, to date, been discordant and not uniformly practice-changing.

Detection of circulating tumor HPV DNA (ct HPV DNA) has recently been demonstrated to have a high positive predictive value for relapse after curative treatment of patients with locoregional HPV-associated OPC. The role of this biomarker in the clinical care of these patients remains to be defined because it is not yet known to what extent the use of ct HPV DNA in this or other settings will have an impact on clinically meaningful patient outcomes or decision-making.

Epstein-Barr Virus

Nasopharyngeal carcinoma (NPC) is strongly associated with EBV. However, although the vast majority of humans have serological evidence of EBV exposure as infants or young adults, only a small fraction of those exposed to EBV develop NPC. NPC is common among individuals from endemic areas in southern China and northern Africa, where World Health Organization (WHO) type 2 (nonkeratinizing) and type 3 (undifferentiated carcinoma) NPCs are more common and EBV-driven (Table 12-2). Epstein-Barr-encoding region (EBER) ISH on tumor biopsy is the method of choice for the detection of EBV. WHO type 1 (keratinizing) NPC is more common in Western countries and seems to be more likely related to tobacco exposure or HPV. EBV-associated NPC has a better prognosis than non-EBV-related NPC. A large body of data suggests that, for patients with EBV-related locoregional NPC, baseline ct EBV DNA level is a prognostic biomarker independent of anatomically based AJCC staging parameters. Several studies have also demonstrated that detectable ct EBV DNA after definitive chemoradiation therapy (CRT) for NPC is an independent predictor of poor prognosis. Epidemiologic modeling studies suggest that ct EBV DNA or NPC serological markers might be a cost-effective NPC screening tool in regions of the world with the highest incidence of NPC.[8] Lack of standardization and harmonization of ct EBV DNA assays has substantially restricted the widespread adoption of ct EBV DNA as a tool in the detection and treatment of NPC.[9] Many routinely available assays for EBV DNA in the blood were developed for the study of EBV as an infectious disease or as a marker in EBV-related post-transplantation proliferative disorders. These assays, in general, do not perform at the same levels as those ct EBV DNA assays developed specifically for the study of NPC.

Table 12-2 **WHO Classification Criteria of Nasopharyngeal Carcinoma**

WHO Classification	Former Terminology
Type I: Keratinizing squamous cell carcinoma	Squamous cell carcinoma
Type II: Nonkeratinizing carcinoma Without lymphoid stroma With lymphoid stroma	Transitional cell carcinoma Intermediate cell carcinoma Lymphoepithelial carcinoma (Regaud)
Type III: Undifferentiated carcinoma Without lymphoid stroma With lymphoid stroma	Anaplastic carcinoma Clear-cell carcinoma Lymphoepithelial carcinoma (Schminke)

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KEY POINTS

- Tobacco and alcohol use are the major risk factors for non-viral-associated HNSCC, and the use of both results in a multiplicative increase in risk.
- There is a causal association between high-risk oncogenic HPV and cancers of the oropharynx (tonsil, base of the tongue, soft palate) and a causal association between EBV and NPCs, but, in most humans, neither HPV nor EBV exposure results in the development of cancer.
- The prognosis is substantially better for HPV-related OPCs and EBV-related NPCs than for HPV-negative and EBV-negative cancers, respectively, at these sites.
- The incidence of second primary cancers for patients with a history of non-viral-associated HNSCC is 3% to 7% annually; common sites include the head and neck, lung, and esophagus. This high rate of second primaries seems related to a field cancerization effect of tobacco, alcohol, and other toxins.

HEAD AND NECK CARCINOGENESIS

MOLECULAR PROGRESSION MODEL

Among carcinogen-induced cancers, a molecular progression model of multistep carcinogenesis in toxin-related HNSCC has been elucidated for the transformation of normal mucosa to invasive SCC. The earliest genetic alteration noted during transition from normal mucosa to hyperplastic mucosa is the loss of genetic material containing tumor suppressor genes (ie, loss of heterozygosity, allelic imbalance) from chromosome region 9p21 and inactivation (promoter hypermethylation) of the *pl6* tumor suppressor gene.

The next step during the transition from hyperplastic mucosa to dysplasia is the loss of genetic material containing tumor suppressor genes (ie, loss of heterozygosity, allelic imbalance) 3p and 17p, with inactivation (promoter hypermethylation) of the *p53* gene.

Transition from dysplasia to carcinoma in situ is associated with loss of chromosome regions 11q, 13q, and 14q. During the transition to invasive SCC, there is a loss of chromosome regions 6p, 8p, and 4q.

More than half of all patients with tobacco- and alcohol-associated HNSCC have a *TP53* gene mutation and downregulation of p16 protein. By contrast, HPV-associated HNSCC characteristically demonstrates the downregulation of wild-type *TP53* and *RB1* genes and upregulation of p16 protein levels.

ORAL PREMALIGNANCY (INTRAEPITHELIAL) NEOPLASIA

Leukoplakia

Leukoplakia is the most common precancerous lesion in the oral mucosa; the majority (approximately 80%) of leukoplakia lesions are benign.[5] The clinical presentation of these lesions includes white plaques distributed on the patient's lips, buccal mucosa, floor of the mouth, hard palate, tongue, and soft palate.

Erythroplakia

Erythroplakia lesions are associated with a 90% incidence of severe dysplasia, carcinoma in situ, or invasive disease. The clinical presentation of these lesions includes a mucosal red, velvety patch that is separated from the surrounding normal tissue by a distinct interface that occasionally has a pebbled or granular appearance.

KEY POINTS

- The earliest genetic alteration during the transition from normal mucosa to hyperplastic mucosa is the loss of genetic material containing tumor suppressor genes, known as a loss of heterozygosity or allelic imbalance.
- Erythroplakia and leukoplakia lesions are premalignant lesions that can be associated with severe dysplasia, carcinoma in situ, or invasive SCCs.

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

In general, cancers of the oral cavity, pharynx, and larynx are characterized by disease confined to the primary site with or without spread to regional lymph nodes at the time of diagnosis, and, for most primary sites, less than 10% of patients have distant disease (beyond regional lymph nodes) at presentation. NPC (see "Nasopharyngeal Cancer" section of this chapter) is an exception. Thus, initial disease staging and management focus on the extent of locoregional involvement and the effect of the choice of treatment on speech and swallowing function, as well as on the risk for recurrence.

PRESENTING SIGNS AND SYMPTOMS

Clinical signs and symptoms vary with the anatomic site affected. The discovery of a painless lump in the neck is a common presenting symptom for a patient with head and neck cancer. The location of cervical adenopathy, denoted by dividing the neck into levels, may direct the physician to the primary site. Higher-level nodes (eg, level 5) may indicate a nasopharyngeal primary, whereas level 2 or 3 nodal involvement more likely dictates a primary from the oral cavity, larynx, or oropharynx. HPV+ OPC may present with occult/small primary with large neck nodes.

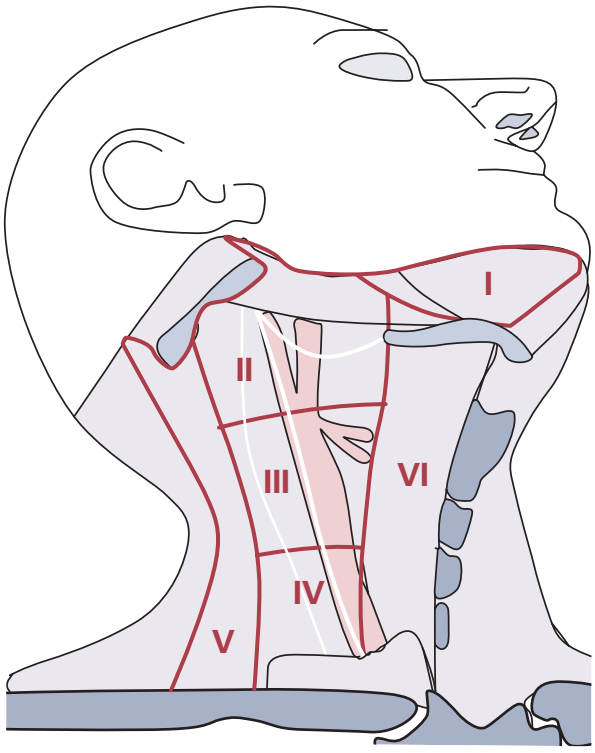
DIAGNOSTIC EVALUATION

Because lymph nodes track along the internal jugular vein, examination of the neck for enlarged lymph nodes is facilitated by rotating the head to the side during examination to promote relaxation of the sternocleidomastoid muscle on that side (Fig. 12-1).

ENDOSCOPY

A comprehensive examination of the head and neck with the assistance of mirrors or fiberoptic scopes is central to the evaluation. Examination under anesthesia may be important for patients with tumors of the larynx or pharynx that are not well

Figure 12-1 Cervical Lymph Node Levels



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visualized with fiberoptic endoscopic examination. Triple endoscopy (ie, laryngoscopy or pharyngoscopy plus bronchoscopy and esophagoscopy) to rule out synchronous tumors is primarily indicated for patients with evidence of diffuse mucosal abnormalities in the setting of a malignant neck node, especially in levels IV, Vb, and VI without a clear primary site (ie, lower neck nodes), which increases the likelihood of lung or esophageal primary tumors.

IMAGING

High-quality CT scans performed with contrast medium or MRI scans with contrast are the standards for imaging of head and neck cancers. MRI is particularly useful for skull-based tumors and those arising from the sinuses and nasopharynx. CT is thought to be more sensitive for cortical bone erosion evaluation, whereas MRI is the preferred mode to evaluate involvement of extrinsic tongue or pterygoid muscles, nerve involvement, spread to prevertebral fascia, and bone marrow infiltration. In some cases, both CT and MRI are recommended to optimally define the tumor extent, lymph node involvement, and the presence of extracapsular spread.[10]

Thoracic imaging for all but the earliest-stage head and neck cancers is indicated, and for all patients whose tobacco exposure history suggests an increased risk of second primary from field cancerization. Chest radiographs are considered inadequate as screening tests in patients with head and neck cancer. Although both high-resolution thoracic CT with intravenous contrast and PET/CT can be valuable, NCCN guidelines recommend FDG-PET/CT as the preferred modality to evaluate for distant metastatic disease and neck lymph node involvement, even in patients with cN0 disease.[11-13]

Body CT scans and bone scans or FDG-PET/CT imaging scans are also appropriate parts of the workup for patients with NPC, because of the increased incidence of distant metastases for patients with high T and N stages. Bone is the most common site of metastasis in patients with NPC. FDG-PET is also appropriate when the primary site is unknown, to evaluate an equivocal finding on cross-sectional imaging. In approximately 30% of unknown primaries presenting in the neck, the primary site of disease can be located with PET imaging. PET scans should be ordered with cross-sectional imaging of the primary site and neck with contrast, which may be useful for identifying spread to regional nodes in the clinically N0 neck. Identification of the primary site can alter radiation fields or the choice of neck dissection to be performed. FDG-PET is also used to establish a baseline for evaluating response after definitive treatment with CRT (eg, oropharyngeal and nasopharyngeal primaries).

TISSUE DIAGNOSIS

Fine-needle aspiration (FNA) biopsy of a neck lymph node is frequently used to establish tissue diagnosis. Histological examination of needle biopsies with appropriate special stains (eg, p16 IHC or EBER or HPV ISH or PCR) and/or transoral biopsy remains the gold standard for diagnosing head and neck cancer because of their high diagnostic accuracy and ability to be performed in the clinic. In patients with cystic or necrotic lymph nodes whose initial needle biopsy is nondiagnostic, a repeat biopsy under ultrasound or CT guidance, with attention to sampling of the non-necrotic rim of the lymph node, can often establish the diagnosis without a more invasive neck procedure or the need for examination under anesthesia. In patients for whom an alternative definitive pathologic diagnosis, such as lymphoma, is considered, an excisional lymph node biopsy may be preferred. As described above, when SCC of the head and neck is identified in a lymph node, it is important to identify the primary site, but often clinical examination and/or imaging can establish this without the need for a biopsy of a mucosal lesion. A specimen from either the primary site of disease or a clinically involved lymph node is acceptable, depending upon relative feasibility and safety. A biopsy of a primary site is usually preferable to a neck dissection for diagnostic purposes, because open surgical neck procedures for diagnostic purposes can contaminate the field and complicate subsequent treatment plans. It is common for FNAs of cystic lymph nodes to be nondiagnostic because central, necrotic material is obtained. As discussed above, for an initially nondiagnostic needle aspiration of a neck lymph node or transoral biopsy of a suspicious primary site, repeat needle biopsy under ultrasound guidance with attention to sampling of non-necrotic rind material or repeat biopsy of a primary mucosal site is almost always preferable to an open neck procedure performed for diagnostic purposes.

GENERAL RULES FOR CLINICAL STAGING

The stage groupings for all primary sites are based on the TNM classification of the Union for International Cancer Control/AJCC system. The TNM system is based on clinical examination, radiographic information, and pathologic findings. Staging in head and neck cancer is complex and differs according to the primary site of disease as well as p16 or HPV status (in the case of OPC).

For p16-negative tumors, the following is a general summary of the TNM staging guidelines for HNSCC:

- T0 does not apply.
- Oral cavity T stage incorporates primary tumor size and sites of local invasion and depth of invasion (not tumor thickness).
- Primary tumors of the oral cavity and oropharynx that are 4 cm or larger are classified as T3; those with local invasion of adjacent structures are classified as T4.
- Vocal cord paralysis in the setting of a primary tumor of the larynx or hypopharynx indicates a stage of no less than T3.
- Nodal staging system incorporates extranodal extension (ENE) into the N staging (N3b) to reflect the poorer prognosis associated with tumors clinically (skin invasion, dense tethering to adjacent structures, nerve invasion with dysfunction [eg, cranial nerve, brachial plexus]) or pathologically determined to have extension outside the lymph nodes into surrounding connective tissue with or without stromal reaction. Pathologically, it is classified as microscopic (less than 2 mm) or macroscopic (more than 2 mm) and increases the N stage. Radiographic evidence of ENE supports the clinical evidence of ENE but is insufficient alone to upstage N status, according to the AJCC, 8th edition, but this may be incorporated in subsequent AJCC staging manuals.

For p16-positive (HPV-associated) OPC:

- T0 refers to an unidentified primary; other T staging is similar to p16-negative tumors.
- N1 disease refers to any number of involved ipsilateral neck nodes if they are smaller than 6 cm, N2 refers to bilateral or contralateral neck disease, and N3 refers to lymph nodes larger than 6 cm.
- Stage IV is not subdivided into A, B, and C and refers to distant metastatic disease.

For NPCs:

- T2 disease typically involves adjacent muscles, and T4 disease involves prevertebral soft tissue.
- Unilateral or bilateral metastases in cervical lymph nodes larger than 6 cm in greatest dimension are considered N3.
- For all primary sites except the nasopharynx and for p16-positive OPCs, the TNM stage grouping is the same.

Cancers of unknown primary origin for patients who are HPV or EBV positive (ie, p16 positive or EBER positive from cervical nodal biopsy) are regarded as OPCs or NPCs, respectively, and are staged as T0, N-appropriate disease; Tx has been eliminated.

For p16-negative disease, the term early-stage disease refers to stage groups I and II disease and to low-volume stage group III disease (ie, T1 or T2, N0 or N1); the terms locally or locoregionally advanced disease refer to M0 stage groups III and IV disease, specifically a large primary tumor (T3 or T4) or the presence of multiple or bulky neck nodes (N2 or N3).

PRESENTING CASE STUDY 1

A 67-year-old man presents with hoarseness and dysphagia lasting for 2 to 3 weeks. He is a former smoker with a 35 pack-year history of smoking. The patient has a medical history significant for well-controlled hypertension and hypothyroidism. Otolaryngologic evaluation reveals an ulcerative lesion on the right true vocal cord, which is also immobile. He undergoes direct laryngoscopy, and pathology from a biopsy of the lesion shows keratinizing p16-negative SCC. CT of the neck shows two enlarged level 2 lymph nodes on the right side, concerning for metastatic spread. There is no extralaryngeal spread and no thyroid cartilage involvement. PET/CT does not indicate distant spread. The patient completes a medical oncology evaluation; baseline laboratory testing and hearing evaluation findings are unremarkable.

What information would you use in determining the stage of this patient's tumor?

This patient has a glottic larynx tumor. Cord immobility without extralaryngeal spread or thyroid cartilage involvement implies a T3 primary. Multiple involved ipsilateral neck nodes indicate N2b disease, and the absence of distant disease is denoted as M0. This makes the overall stage IVA (cT3N2bM0).

What treatment should you recommend based on the staging?

The three-arm randomized Radiation Therapy Oncology Group (RTOG) 91-11 trial evaluated radiation therapy (RT); induction cisplatin and 5-fluorouracil (5-FU), followed by RT; and concurrent cisplatin and RT. Findings from RTOG 91-11 established the superiority of concurrent chemo RT as a larynx-sparing curative treatment approach. Carboplatin is a less effective radiosensitizer compared with cisplatin, and cetuximab was proven inferior to cisplatin as a radiosensitizer in multiple phase 3 trials in patients with HPV-positive oropharyngeal cancers.[14]

HUMAN PAPILLOMAVIRUS–RELATED OPCS

The AJCC staging system was updated in the eighth edition to account for p16 status, used as a practical but imperfect surrogate for HPV staging of oropharyngeal tumors, given the marked difference in prognosis between patients with p16-positive and p16-negative tumors. The staging system for p16-positive oropharyngeal tumors combines T4a and T4b into a single T4 category. N1 disease indicates one or more ipsilateral lymph nodes with none larger than 6 cm, N2 disease indicates contralateral or bilateral nodal disease, and N3 nodes are those larger than 6 cm.

This p16-positive staging system has three stage groupings for nonmetastatic disease: (1) early stage or stage group I (T0-T2, N0-N1), (2) locally advanced disease or stage group II (T0-T2, N2 or T3, N0-N2), or (3) locoregionally advanced-stage group III (T4 or N3). Stage IV grouping is reserved for M1 disease. Unknown primary cancers that are HPV or EBV positive are treated as OPCs or NPCs with a T0 stage, respectively.

KEY POINTS

- Many presenting signs and symptoms are associated with a particular primary site (eg, hoarseness may refer to the larynx or hypopharynx, and a unilateral otitis media may refer to the nasopharynx).
- The location of pathologic lymph nodes in the neck may suggest the primary site.
- The initial evaluation for head and neck cancer includes a comprehensive examination of the head and neck, including endoscopic examination; imaging of the primary site, neck, and chest; and routine laboratory screenings.
- Early-stage disease is primarily defined as disease limited to a small primary tumor (T1 or T2) with low-risk (N1, one node smaller than 3 cm with no high-risk features) nodal involvement. Locally or locoregionally advanced disease is generally defined as the presence of a large primary tumor (T3 or T4) or the presence of large, multiple, or contralateral regional node involvement (N2 or N3).
- Criteria for unresectable disease include base-of-skull involvement, fixation to the prevertebral fascia, carotid encasement, and involvement of the pterygoid musculature.
- M1 disease is typically not curable and is approached with systemic therapy, although some patients with oligometastatic disease can have long-term remissions using combined modality treatment.

PRINCIPLES OF DISEASE MANAGEMENT

TNM stage groupings help define prognosis and treatment options. Because of their curative potential, surgery and radiation therapy (RT) are the central treatment modalities for head and neck cancers. Chemotherapy may enhance the effects of RT, but, in most cases, by itself, it is not usually considered curative. Although there have been a number of situations in which cures

have been achieved with systemic therapy alone (eg, early-stage larynx cancer),[15] these cure rates are far below what surgery or radiation-based approaches can achieve; therefore, systemic therapy alone is not recommended for HNSCC when a curative option exists.

Management of the primary site and management of the neck are often considered independently, but the overall strategy of minimizing the use of multimodality therapy while maximizing cure potential is used to avoid unnecessary treatment morbidity. Management of head and neck cancer is best served by multidisciplinary treatment planning that involves not only a head and neck surgeon, medical oncologist, and radiation oncologist but also, in certain cases, dentists, prosthodontists, dieticians, pharmacists, audiologists, speech and swallow therapists, physical and occupational therapists, social workers, tobacco cessation support, and psychiatrists.

UNRESECTABLE T4 LESIONS

Primary criteria for unresectability include base-of-skull involvement, fixation to the prevertebral fascia, carotid encasement, and involvement of the pterygoid musculature. Additional criteria include an inability to perform an adequate reconstruction for a functional result and a low likelihood of achieving negative margins.

For p16-negative disease, assignment to the stage group IVB category has implications for prognosis (ie, less favorable) and treatment (ie, primary surgical management not planned, except for oral cavity cancers in which primary surgical resection is the standard upfront approach for resectable disease). For these primary sites, stage group IVB disease includes patients with T4b, any N category, and no metastasis (M0) or any T category and N3 (any neck node larger than 6 cm in greatest diameter). Stage group IVC includes any T and N category as well as M1 disease.

DECISION-MAKING BASED ON PRIMARY SITE OF DISEASE

The primary site of disease, along with stage, dictates initial management decisions. Oral cavity cancers are often initially resected, sometimes with preceding neoadjuvant immunotherapy, followed by appropriate adjuvant therapy. However, for oral cavity tumors, when surgery is not possible, cure rates with CRT are less favorable. Data from randomized trials support integrated chemotherapy and RT as standard treatment options for patients with locally advanced, resectable cancers of the larynx and hypopharynx (with the intent of avoiding total laryngectomy) and for patients with p16-negative or p16-positive cancers of the oropharynx when a nonsurgical approach is chosen. Principles that guide the treatment of laryngeal cancers focus on the ability to provide nonsurgical organ preservation therapy when appropriate. With the increasing use of TransOral Robotic Surgery (TORS) and neoadjuvant immunotherapy, decision-making for OPCs often takes into account stage, functional outcome, and surgical resectability when choosing between surgery and nonsurgical approaches. Once initial management pathways are determined, the stage guides whether to incorporate single or multiple treatment modalities. General guidelines based on the stage are discussed below.

NEWLY DIAGNOSED HPV-NEGATIVE STAGES I, II, AND LOW-BULK III (P16-NEGATIVE T1 OR T2, N0 OR N1, AND M0) OR HPV-POSITIVE STAGE I (NONBULKY DISEASE)

Single-modality treatment with surgery or radiation is typically used for previously untreated early-stage tumors (Fig. 12-2). For T1-2 N1 single lymph node smaller than 3 cm, single-modality surgery or RT should be considered.

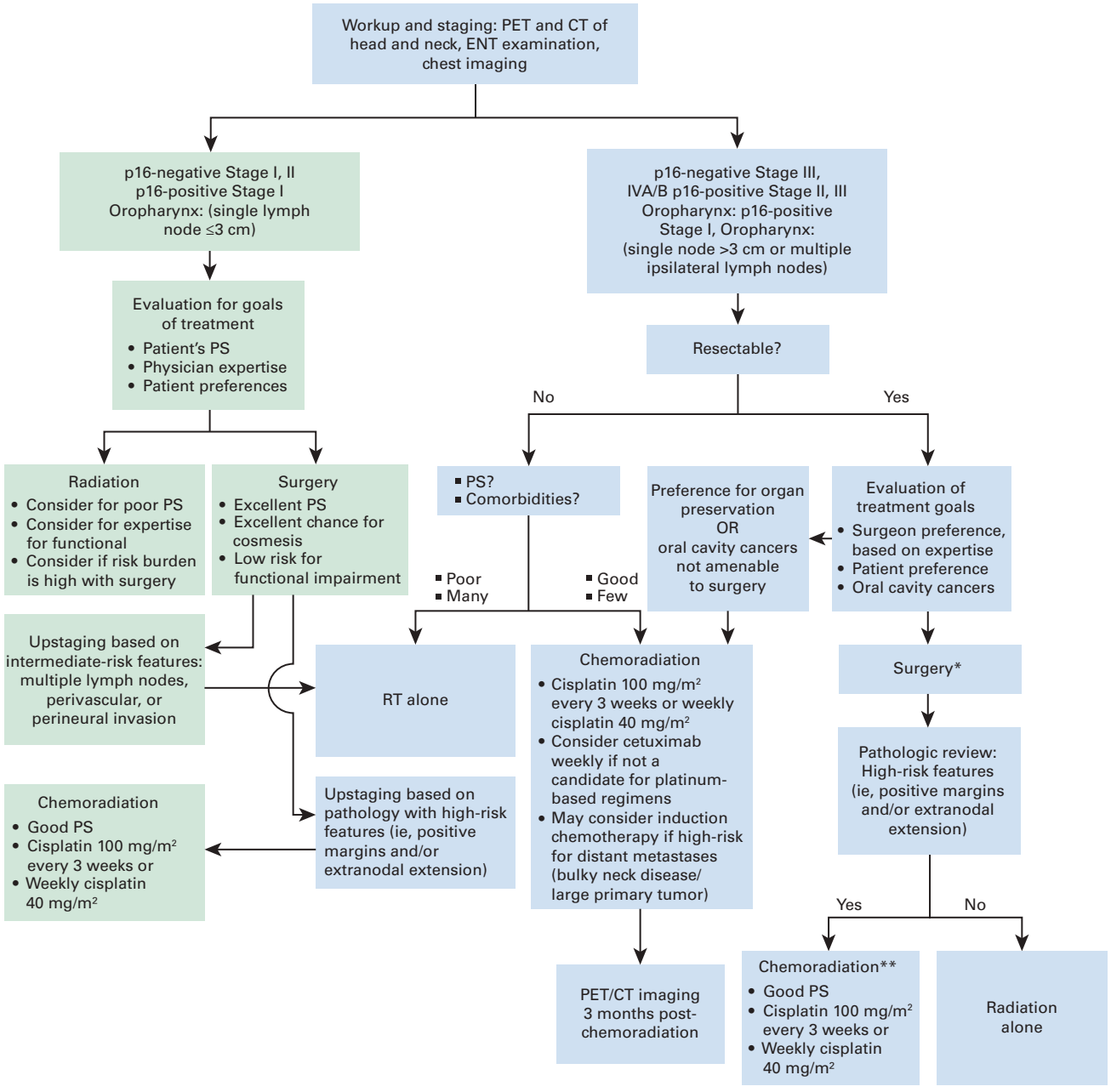
This includes p16-negative stages I, II, or low-bulk (T1-2 N1) III disease (essentially a small primary tumor with or without a single ipsilateral node measuring less than 3 cm in diameter and without clinical or radiographic evidence of ENE) and for p16-positive stage I disease of the oropharynx with a single ipsilateral node measuring less than 3 cm in diameter and without clinical or radiographic evidence of ENE.[16] Based on the Surveillance, Epidemiology and End Results Program (SEER) data, approximately 20% to 30% of head and neck cancers are diagnosed at an early stage. Cure rates for this group range from 52% to 100%, depending on the primary site. Tumors that are upstaged or have positive margins or ENE pathologically typically require additional surgery or adjuvant radiation with or without chemotherapy.

The chosen modality depends on local expertise, anticipated functional outcome, and patient preference. Randomized clinical trials (RCTs) have failed to demonstrate a definite advantage of either an initial surgical or radiation-based approach in terms of survival or quality of life. Because of more favorable survival outcomes and technical concerns of radiation toxicity to the mandible, oral cavity cancers are typically treated surgically. For early-stage larynx cancers, an organ function–sparing strategy is preferred, which may be definitive radiation or organ-sparing laryngeal surgery when feasible.

NEWLY DIAGNOSED, HIGHER-VOLUME HPV-NEGATIVE STAGES III AND IVA/IVB DISEASE OR P16-POSITIVE STAGES I, II, AND III

This group comprises approximately 60% of patients with head and neck cancers at diagnosis, all T3 or greater, all N with more than one lymph node or a lymph node larger than 3 cm. The standard approach is multimodality treatment, often incorporating definitive CRT or surgery followed by radiation or CRT based on pathologic risk factors.

Figure 12-2 Treatment Algorithm for Localized and Locally Advanced HNSCC



Abbreviations: CPS, combined positive score; ENT, ear, nose, and throat; HNSCC, head and neck squamous cell carcinoma; PS, performance status; RT, radiation therapy.
*If PD-L1 CPS ≥1, consider perioperative pembrolizumab.
**If no neoadjuvant immunotherapy, consider adjuvant nivolumab.
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When primary CRT is used, surgery is reserved for persistent disease or for recurrence of resectable disease. For locally advanced, resectable cancers of the oral cavity, primary surgical management with appropriate reconstruction and risk-stratified postoperative RT with or without chemotherapy and peri-operative immunotherapy is the mainstay of treatment because anticipated functional and survival outcomes are favorable, even for more advanced tumors, with this treatment approach. KEYNOTE-689 was a phase 3 open-label trial that randomized 714 patients with locally advanced, resectable HNSCC to receive two cycles of neoadjuvant pembrolizumab and 15 cycles of adjuvant pembrolizumab (both at a dose of 200 mg every 3 weeks) in addition to standard care (pembrolizumab group) or standard care alone (control group). Standard care was surgery and adjuvant radiotherapy with or without concomitant cisplatin. The primary endpoint was event-free survival (EFS).[17] EFS at 36 months was 57.6% and 46.4%, respectively (hazard ratio,

0.73; 95% CI, 0.58-0.92; two-sided P = .008), in the total population, almost exclusively HPV negative, and with increasingly diluted benefit with inclusion of lower PD-L1 expressors. Potentially immune-mediated adverse events of grade 3 or higher occurred in 10.0% of the participants in the pembrolizumab group. Based on these results, the FDA-approved pembrolizumab for adults with resectable locally advanced HNSCC whose tumors express PD-L1 (combined positive score [CPS] ≥1) as determined by an FDA-approved test, as neoadjuvant treatment, and continued as adjuvant treatment in combination with RT with or without cisplatin after surgery, and then as a single agent. Thus, neoadjuvant immunotherapy is increasingly used before primary surgical resection for locally advanced HPV-negative and PD-L1-positive HNSCC.

For p16-positive OPC, there is considerable regional variation concerning patterns of treatment and preference for transoral resection and lymph node dissection versus initial CRT. Although two RCTs have been conducted in relatively early-stage p16-positive OPC, neither has been able to definitively answer which approach is superior.[18]

In general, patients who have disease presenting as M1 or recurrent unresectable disease are thought to be incurable, and the standard approach is palliative systemic treatment. An exception to this is patients presenting with low-bulk oligometastatic disease (three or fewer small foci of M1 disease) with a high likelihood of sensitivity to systemic therapy, such as p16-positive OPC and EBV-positive NPC. These patients are often approached with systemic treatment upfront and may be considered for definitive curative therapies in selected cases.[19]

KEY POINTS

- Single-modality treatment with surgery or RT is typically used with curative intent for previously untreated p16-negative stage I, II, or low-bulk III (T1-2, N0, N1: single node smaller than 3 cm) disease or p16-positive stage I (T1-2, N0-1) disease with a single ipsilateral node measuring less than 3 cm in diameter and without clinical or radiographic evidence of ENE.
- Combined modality treatment of surgery and RT or CRT is used with curative intent for previously untreated, higher-volume, p16-negative stage III (T3, N0-1) and stage IVA/B disease or p16-positive stages I (multiple nodes or single node larger than 3 cm), II, and III disease.
- Neoadjuvant and adjuvant pembrolizumab, in addition to risk-stratified standard adjuvant therapy, is associated with improvement in EFS in patients with locally advanced PD-L1-positive (CPS ≥1) HNSCC, where surgery is the initial therapy.
- Metastatic disease below the clavicle and locoregional recurrent disease without a surgical or RT option are generally incurable and are treated with palliative intent. However, there are some patients with oligometastatic disease who are highly sensitive to systemic therapy and for whom curative paradigms of treatment should be considered.

SURGICAL MANAGEMENT OF HEAD AND NECK CANCER

SURGERY OF THE PRIMARY TUMOR

Surgery is used as a definitive modality as well as a salvage option in many types of head and neck cancer. Complete extirpation of the primary tumor with negative margins defines an adequate surgical resection. Nodal surgery (typically a neck dissection) is also required for most head and neck cancers, but it depends on numerous patient factors and tumor characteristics. Recent surgical advances have been made, particularly with TORS. This approach can provide improved visualization and may decrease the morbidity and functional sequelae of surgery. Despite recent advances, surgery in the head and neck anatomic region may lead to significant morbidity and affect a patient's quality of life, particularly when considering operations that necessitate the removal of critical functional structures, like the larynx, tongue, eye, or mandible. The potential adverse effects on cosmesis and function underscore the importance of optimal reconstruction and associated postoperative rehabilitation as part of the treatment strategy. The anticipated adverse effects are also important to consider when discussing surgery with the patient as a possible definitive treatment approach. For example, when considering treatment options for a patient with advanced p16-positive OPC, the decision to choose surgery followed by adjuvant therapy or upfront CRT, for which both options have equivalent survival outcomes, may depend on which modality will lead to better functional outcomes; however, there remain significant regional differences in practice patterns in this area, and there is no consensus on which approach is less morbid.

Improvements in reconstructive techniques have enabled large extirpations with good functional results. A variety of free flaps, frequently composed of skin, muscle, and/or bone (and, occasionally, multiple flaps in the same patient), can successfully address many defects that arise from surgery. In addition, customized obturators and prosthetics can be used alone or in combination with free-flap reconstruction to optimize function.

SURGERY OF THE NECK

Neck dissection plays an integral role in the surgical management of head and neck cancers. The extent of neck dissection depends on a variety of factors, including the location of the primary tumor, extent of clinically positive lymph nodes, and extracapsular extension of nodal disease into surrounding structures (eg, the sternocleidomastoid muscle, internal jugular vein) (Table 12-3).

The use of sentinel lymph node biopsy as part of staging to help guide the need for further treatment has become more common, but has not been widely adopted as a standard of care, replacing lymph node dissection. Neck dissections are typically classified as either radical, modified radical, or selective. A radical or comprehensive neck dissection includes the en bloc removal of all five lymph node levels along with the resection of the sternocleidomastoid muscle, the internal jugular vein, and the spinal accessory nerve. If any or all these structures are preserved, the procedure is considered a modified radical neck dissection. A selective neck dissection removes only specific nodal levels. For example, larynx cancer is typically addressed with a bilateral level 2 to 4 selective neck dissection.

Table 12-3 Lymph Nodal Drainage in Head and Neck Cancers

Primary Cancer	Lymph Nodes
Oral cavity	Submental and submandibular areas (level I), upper and midneck (levels II and III) after level I
Oropharyngeal	Upper and midneck (levels II and III)
Laryngeal (except glottis)	Upper and midneck (levels II and III)
Nasopharyngeal	Upper neck and posterior triangle (levels II and V)
Primary lesion below the clavicle or in the thyroid	Disease confined to the lower part of the neck or supraclavicular area (levels IV and V)
Glottic larynx	Spread to the neck is uncommon
Paranasal sinuses	Spread to the neck is uncommon

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Neck dissection is frequently indicated for patients, even those who have no clinically apparent neck disease, given the high risk (20%-35%) of occult nodal metastases, particularly in the oral cavity, and in pharyngeal and supraglottic tumors.[20] In a randomized controlled trial, D'Cruz et al[21] evaluated whether surgeons should treat early-stage oral cavity cancers (cT1-2N0) with elective neck dissection or wait until relapse and then conduct a therapeutic neck dissection at the time of nodal relapse. At 3 years, elective nodal dissection with initial surgery resulted in a better overall survival (OS) rate (80% vs 67.5%) and disease-free survival (DFS) rate (69.5% vs 45.9%). Thus, elective lymph node dissection has been adopted as the standard of care in this scenario.[12]

Sentinel lymph node biopsy could also be used to identify patients with early-stage clinically N0 oral cavity cancer who may benefit from neck dissection, although randomized trials of this approach are ongoing. Reconstruction is frequently required for surgery involving advanced-stage disease.

KEY POINTS

- Function-conserving procedures are applicable for select patients in whom negative margins can be achieved with preservation of structures important for function.
- Debulking surgery is not part of routine clinical practice for head and neck cancer.
- Comprehensive neck dissections involve the removal of all five lymph node levels and are usually performed with therapeutic intent. Selective neck dissections involving the removal of fewer than all five levels are generally done electively to improve staging precision.

PRINCIPLES OF RADIATION THERAPY

The curability of head and neck cancer with RT is inversely related to tumor bulk. HPV- and EBV-positive cancers have higher radiosensitivity compared with HPV- and EBV-negative tumors. The rate of disease control with RT alone decreases with increasing T stage, which explains why RT can be used as a single modality to treat early-stage disease but is generally applied as an adjunct to surgery or combined with chemotherapy for more advanced tumors.

RADIATION DOSE AND FRACTIONATION

Adjuvant Radiation Therapy

Adjuvant RT doses are typically 60 Gy delivered in standard, once-per-day fractionations after surgery and neck dissection and should begin no later than 6 weeks from the postoperative date. Areas of positive margin or nodal extracapsular extension are boosted to 66 Gy, and concurrent radiosensitizing chemotherapy is typically recommended in these high-risk situations.

Uninvolved, nondissected nodal regions considered at risk are typically treated with 50 to 56 Gy. The advantage of locoregional control (LRC) and OS has been demonstrated with adjuvant RT started within 6 weeks of surgery and completed with minimal treatment interruptions. Of note, the ECOG3311 study was a randomized phase 2 trial that tested 60 gray versus 50 gray in the adjuvant setting for intermediate-risk HPV-positive OPC, demonstrating no inferiority, but adoption into clinical practice outside of clinical trials remains controversial.[22]

Technical Aspects of Radiation Therapy

Intensity-modulated radiation therapy (IMRT) is regularly used in the treatment of head and neck cancer and is considered the standard of care. This therapy delivers therapeutic radiation doses specifically to the sites of gross tumor, around the tumor, and the at-risk lymph nodes, with improved conformality defined as the ratio of the dose to the tumor relative to the dose to normal tissues. Advantages of IMRT compared with traditional 2D RT include increased normal tissue-sparing and preservation of anatomic structures (eg, the pharyngeal constrictor muscles necessary for swallowing and the salivary glands). Patients treated with IMRT have a lower incidence of xerostomia than those treated with conventional RT, but they experience higher rates of fatigue during treatment.

Another more recent development is the use of proton beam therapy. In proton beam therapy, the particle delivering the dose of energy is a proton, rather than traditional radiographs or electron therapy. In proton beam therapy, the Bragg peak refers to the physical properties of a proton beam that allow a rapid decrease in RT dose beyond the tumor, leading to lower doses to some normal tissue distal to the radiation source relative to the tumor targeted. Phase 2 data demonstrated efficacy, safety, and favorable toxicity profiles in base-of-skull malignancies, periorbital tumors, NPC, and reirradiation. However, there are no well-controlled data establishing a preferred role for proton beam radiation in most HNSCC situations. Without such data to suggest improved tumor control or decreased toxicity associated with the use of proton beam therapy, its use and cost remain controversial.

Radiation-Related Toxicity

Radiation at the doses previously outlined is associated with predictable acute mucosal and skin toxicities, including mucositis, desquamation, pain, odynophagia, dysgeusia, and thick phlegm or mucus. More aggressive dosing and fractionation schedules, and the addition of concomitant chemotherapy generally increase the severity of these acute toxicities. Rates of any acute and late toxicities higher than grade 3 of 70% to 85% and 40% to 50%, respectively, are associated with a 20% feeding tube dependence at 1 year for patients with HPV-negative disease and 5% for those with HPV-positive disease.[23,24] Feeding tubes will be needed by a subset of patients to get through treatment, especially those who present with swallowing dysfunction and substantial weight loss. Although institutional practices vary, most centers have moved away from prophylactic feeding tubes, given that approximately 50% of patients will never use them.[25] Xerostomia can be a late sequela of RT. Adequate saliva is an important component of oral hygiene; thus, careful dental assessment is recommended before the start of RT, followed by ongoing dental prophylaxis and fluoride treatments. Pain management, nutritional support, swallowing evaluation and therapy, and aggressive oral care are recommended during therapy.

Definitive Radiation

Standard, once-per-day fractionation consists of 2 Gy/d with a total dose of 70 Gy or more to the primary site and gross adenopathy and 50 to 60 Gy to uninvolved nodal stations at risk. Other biologically equivalent fractionation schemes may be used. Altered fractionation schedules consist of more RT doses with a lower dose per fraction, with the goals of improving LRC and widening the therapeutic index. Altered fractionation RT alone is associated with improvements in OS compared with conventional, single-fraction RT alone, but this advantage is not seen when combined with systemic cancer treatment, which is discussed below.

Hyperfractionation refers to twice-per-day treatment, and accelerated fractionation (AF) typically refers to six fractions per week separated by more than 6 hours to allow for normal tissue repair. RTOG 0129 was designed to test the efficacy and toxicity of cisplatin plus AF with a concomitant boost versus standard fractionation (SF). Patients with locally advanced HNSCC were randomly assigned to 70 Gy in 35 fractions over 7 weeks (SF) or 72 Gy in 42 fractions over 6 weeks (AF). Cisplatin doses were 100 mg/m^2 once every 3 weeks for two (AF) or three (SF) cycles. The clinical trial established no benefit from combined concurrent CRT with SF or AF in OS rate (hazard ratio [HR], 0.96; $P = .37$; 5-year rate: 57% vs 60%; 8-year estimated rate: 48% vs 48%), PFS rate (HR, 1.02; $P = .52$; 5-year rate: 49% vs 50%; 8-year estimated rate: 42% vs 41%), or locoregional failure rate (HR, 1.08; $P = .78$; 5-year rate: 31% vs 34%; 8-year estimated rate: 37% vs 39%).[26]

KEY POINTS

- Head and neck RT commonly causes acute toxicities, including mucositis, edema, dermatitis, dysgeusia, and xerostomia. Other potential toxicities include osteoradionecrosis of the mandible.
- IMRT delivers radiation around the tumor and high-risk lymph nodes conformally. It is associated with less dry mouth after treatment than that seen with conventionally planned RT.

PRINCIPLES OF CHEMOTHERAPY

Cisplatin is the most widely used cytotoxic drug in the curative treatment of HNSCC. Other drugs with activity include carboplatin, fluorouracil and related oral analogs, taxanes (ie, paclitaxel, docetaxel, nab paclitaxel), methotrexate, and cetuximab. The reported response proportions with chemotherapy vary with the setting (untreated or pretreated) and with the drugs used (single agent or combination).

Platinum-based regimens are most commonly used as first-line therapy with CRT, with induction regimens, and with disease that is metastatic or incurable. The anticipated major response rate for patients with previously untreated disease is 60% to 90%, with clinical complete responses in 20% to 50% of patients. By contrast, the activity of platinum-based drug combination therapy for patients with recurrent disease is 30% to 40%, and complete responses are rare. Rates of complete and partial responses from single-agent therapy are approximately half the rate of those observed with combination chemotherapy.

When the goal for therapy is to control or cure locoregional disease, the chemotherapy literature can be divided into the following four groups:

- Induction or neoadjuvant chemotherapy administered before definitive local therapy (surgery, RT, or CRT)
- Concurrent CRT in the setting of locally advanced disease
- Adjuvant CRT after definitive surgery
- Adjuvant chemotherapy after definitive CRT or sequential CRT

INDUCTION CHEMOTHERAPY

Historically, induction chemotherapy has not provided improvements in LRC or survival compared with standard concurrent CRT treatments for HNSCC; currently, it is often reserved for patients who are not ideal candidates for upfront concurrent treatment (Table 12-4). However, cisplatin and 5-FU (PF) in one subset analysis demonstrated potential survival benefit. Subsequent induction studies compared the addition of taxanes to cisplatin and 5-FU (docetaxel, cisplatin, 5-FU [TPF]) versus PF followed by definitive RT or CRT. Results from three phase 3 RTCs compared three or four cycles of induction TPF with standard PF.[24] These three trials, along with a meta-analysis of five randomized trials of 1,772 patients comparing PF induction therapy with the TPF regimen, established TPF as the standard of care for HNSCC when induction chemotherapy followed by definitive RT or CRT is elected following a multidisciplinary discussion; however, there is no consensus concerning which patients should be offered induction.[27]

Table 12-4 Induction Chemotherapy Clinical Trials Followed by Definitive Radiation for Patients With HNSCC

Study	No. of Patients	Population	Study Arm	Primary Outcome	Secondary Outcome
GORTEC9 2000-01	213	Larynx and hypopharynx (requiring laryngectomy) for organ preservation	IC with TPF vs IC with PF followed by definitive radiation	3-year laryngeal preservation: 70.3% vs 57.5% (P = .03)	Overall response rate: 80% vs 59.2% (P = .002)
TAX 32310	358	Unresectable oropharynx, hypopharynx, oral cavity, and larynx	IC with TPF vs IC with PF, both followed by definitive radiation	Median PFS, 11 months vs 8.2 months; median OS, 18.8 months	CRR: 33% vs 19.9% (P = .004)
TAX 32411	501	Oropharynx, larynx, hypopharynx, and oral cavity for organ preservation (T3-T4, N2-N3 disease only)	IC with TPF vs IC with PF, both followed by weekly carboplatin (AUC 1.5) with radiation	5-year OS: 52% vs 42% (P = .014)	Median PFS: 38.1 months vs 13.2 months (HR, 0.75; 95% CI, 0.60-0.94)

Abbreviations: AUC, area under the curve; CRR, complete response rate; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; IC, induction chemotherapy; OS, overall survival; PF, cisplatin, fluorouracil; PFS, progression-free survival; TPF, docetaxel, cisplatin, fluorouracil.
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SEQUENTIAL THERAPY

To test whether induction chemotherapy followed by CRT improved survival compared with CRT alone, three phase 3 randomized trials comparing TPF followed by CRT versus initial CRT alone were conducted; they demonstrated no survival benefit.[28-30] With the exception of treatment of nasopharyngeal and laryngeal primary tumors, induction chemotherapy is considered a category 3 recommendation guideline per the NCCN.[31] Outside of NPC, no sequential CRT or induction CRT regimen has demonstrated an improvement in OS in patients with HNSCC (Table 12-5). However, studies have established that TPF induction carries an OS

benefit relative to PF induction as discussed above. Therefore, if there is a clinical situation in which induction chemotherapy followed by sequential CRT is indicated, TPF should be used if feasible. There is no expert consensus concerning when to use induction instead of starting concurrent CRT initially. The most common scenario for induction chemotherapy outside of NPC is when a change in tumor bulk would have a significant impact on subsequent radiation planning and toxicity from large radiation fields. A specific exception is in patients with NPC. Induction chemotherapy followed by sequential CRT is the standard of care for patients with locoregionally advanced NPC based on RCTs that demonstrate improved OS[32-34] and is discussed in more detail below.

Table 12-5 Sequential Therapy Clinical Trials for Patients With HNSCC

Study	No. of Patients	Population	Study Arm	Primary Outcome	Secondary Outcome	Grades 3 to 4 Toxicity (%)
PARADIGM[28]	145 (study terminated early owing to poor accrual)	Unresectable or T3-T4 or N2-N3 (except for T1, N2), or candidates for organ preservation	IC with TPF for three cycles: response evaluation; NR: weekly docetaxel with RT; PR: weekly carboplatin with RT vs high-dose cisplatin every 3 weeks with RT	3-year OS: 73% vs 78% (HR, 1.09; *P* = .77)	Febrile neutropenia in the IC followed by chemoradiation (16 patients) compared with the chemoradiation arm	Mucositis IC: 47 CRT: 16
						Febrile neutropenia IC: 23 CRT: 1
						PEG tube placement IC: 79 CRT: 85
DeCIDE[33]	280 (planned: 400)	N2-N3 disease	Docetaxel/FU/hydroxyurea and radiation vs TPF three cycles followed by docetaxel/FU/hydroxyurea and radiation	3-year OS 75% vs 73% (*P* = NS)	3-year distant failure: 10% vs 19% (*P* = .025)	Mucositis IC: 9 CRT: 47
						Neutropenia IC: 11 CRT: 2
						PEG tube placement IC: 79
Hitt et al[30]	439	Unresectable; primary sites: oropharynx, oral cavity, larynx, hypopharynx; greater than measurable lesion	IC with TPF or PF three cycles followed by high-dose cisplatin every 3 weeks with radiation vs high-dose cisplatin every 3 weeks with radiation	Median PFS: 14.6 months/14.4 months vs 13.8 months (*P* = .56) TTF 7.9 months/7.9 months vs 8.2 months (*P* = .90)	No statistically significant differences for OS	Stomatitis IC: 44 CRT: 37
						Febrile neutropenia IC: 10 CRT: 1

Abbreviations: CR, complete response; CRR, complete response rate; CRT, concomitant chemoradiation; FU, fluorouracil; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; IC, induction chemotherapy; NR, nonresponse; NS, not significant; OS, overall survival; PEG, percutaneous endoscopic gastrostomy; PF, cisplatin, fluorouracil; PFS, progression-free survival; PR, partial response; RT, radiation therapy; TPF, docetaxel, cisplatin, fluorouracil; TTF, time to treatment failure.

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CONCOMITANT SYSTEMIC THERAPY AND RADIATION THERAPY

Chemotherapy

A major role of chemotherapy in patients with nonmetastatic disease is a radiation sensitizer. Therefore, priority has focused on agents that show activity against the disease and radiation enhancement properties (eg, cisplatin, carboplatin, cetuximab, taxanes, and 5-FU). Combined modality therapy with chemotherapy and RT is considered standard treatment for patients who have locally advanced, unresectable HNSCC who can tolerate the anticipated added treatment-related toxicity; in some cases, it may preserve organ function.

CRT, typically with concurrent cisplatin, is considered standard of care in organ preservation of locoregionally advanced larynx and hypopharynx cancers and OPCs and NPCs.[35] Toxicities, including hearing loss, protracted nausea and vomiting, renal

dysfunction, and peripheral neuropathy, may preclude patients from receiving all planned cisplatin doses. Based on retrospective data, a cumulative minimum cisplatin dose of 200 mg/m^2 appears optimal. Schedules of 40 mg/m^2 once per week or 100 mg/m^2 once every 21 days are most commonly used. Data from an ongoing prospective RCT comparing cisplatin every 21 days to cisplatin once per week are not yet available, and either administration schedule is considered an acceptable standard of care. It is noteworthy that most phase 3 trials comparing definitive CRT versus RT for locoregionally advanced HNSCC have used 100 mg/m^2 once-every-21-days dosing.

An option for patients who are not eligible for cisplatin is carboplatin and 5-FU, based on improvement in OS and DFS seen in a phase 3 trial when administered in combination with RT versus RT alone (3-year OS: 51% vs 31%, respectively; P = .02; 3-year DFS: 42% vs 20%; P = .04).[36] Another option is docetaxel once per week, based on phase 2/3 data from a trial that randomly assigned patients to docetaxel-RT versus RT alone. Toxicities in the concurrent arm included mucositis, dysphagia, and odynophagia. Compared with RT alone, the addition of docetaxel resulted in an improvement in DFS (30.3% vs 42%) and median OS (15.3 months vs 25.5 months).[37] Weekly carboplatin and paclitaxel remains a commonly utilized concurrent regimen in the cisplatin-ineligible population based on single-arm studies. As discussed below, cetuximab combined with RT is superior to RT alone in HNSCC, but cetuximab is also known to be inferior to cisplatin combined with RT in patients with p16-positive OPC.

When possible, with the exception of advanced laryngeal cancers, which were excluded from landmark organ preservation studies, large, bulky (T4 or N3) tumors should be treated with combined cisplatin and RT.[37,38] A published meta-analysis demonstrated that CRT regimens are associated with an 8% absolute survival benefit at 5 years compared with RT alone (HR, 0.81; 95% CI, 0.76-0.88; P < .0001).[39] An updated analysis of 87 trials involving more than 16,000 patients showed the same absolute benefit for survival with concomitant treatment (HR, 0.81; P < .0001), and multiagent chemotherapy (eg, cisplatin and 5-FU) does not offer an advantage over single-agent cisplatin when combined with RT.[40]

Cetuximab

Epidermal growth factor receptor (EGFR) is highly expressed in HNSCC, and the expression is inversely associated with prognosis. In a multicenter trial, the EGFR inhibitor cetuximab, when administered once per week with RT, demonstrated improvements in locoregional failure-free survival (FFS) and OS compared with RT alone for patients with advanced head and neck cancers.[36] The updated median OS for patients with disease treated with cetuximab and RT was 49.0 months (95% CI, 32.8-69.5) compared with 29.3 months (95% CI, 20.6-41.4) in the RT-alone group (HR, 0.73; 95% CI, 0.56-0.95; P = .018). The 5-year OS rate was 45.6% in the cetuximab and RT group and 36.4% in the RT-alone group. Survival was improved for patients who experienced at least a grade 2 acneiform rash compared with patients with grade 0 or 1 rash (HR, 0.49; 95% CI, 0.34-0.72; P = .002).[41] Unlike cisplatin, cetuximab, when administered with RT, has no effect on distant metastases. Three different randomized trials—RTOG 1016, De-ESCALaTE, and TROG 12.01—established the superiority of cisplatin over cetuximab for HPV-related OPC.[38,42,43] The only indication for cetuximab with RT instead of platinum-based chemotherapy is in the treatment of patients with good performance status for whom the use of platinum-based chemotherapy is precluded (eg, severe hearing loss, creatinine clearance less than 30 mL/min, severe peripheral neuropathy) or because of patient preference, because of a concern for platinum-related toxicities. It is unknown whether docetaxel, carboplatin/paclitaxel, or cetuximab is preferable in this situation.

The addition of cetuximab to cisplatin and RT is not beneficial. RTOG 0522 directly evaluated the addition of cetuximab to standard treatment with cisplatin and RT and did not find a PFS or OS benefit.[44]

Checkpoint Inhibitors in the Curative Setting

As outlined above, KEYNOTE-689 has established the role of pembrolizumab in the perioperative treatment of resectable locally advanced HNSCC with CPS ≥1 disease, while NIVOPOSTOP has shown benefit for nivolumab in combination with CRT in patients with high-risk HNSCC in the adjuvant setting.

To date, numerous phase 3 trials have not supported the use of immune checkpoint inhibitors (ICIs) when administered concurrently with CRT.[45] Both avelumab and pembrolizumab did not improve PFS and EFS, respectively, when added to standard-of-care cisplatin and RT in patients with locally advanced HNSCC, although pembrolizumab did trend toward positivity with longer follow-up, and atezolizumab did not improve EFS when administered after multimodality definitive treatment. In addition, NRG-HN004 was a randomized phase 2 trial that randomized cisplatin-ineligible patients with stages III to IVB p16-negative HNSCC or unfavorable stages I to III p16-positive OPC or unknown primary carcinoma to cetuximab versus durvalumab in combination with curative-intent RT. The trial was suspended following an interim futility analysis after 190 patients were enrolled. Two-year PFS was 50.6% (95% CI 41.5-59.8) in the durvalumab group versus 63·7% (51.3-76.1) in the cetuximab group (HR 1.33, P = 0.89).[46-49] Therefore, this approach is considered investigational.

Adjuvant Chemoradiation Therapy

Adjuvant CRT applies mainly to patients with advanced, resectable oral cavity or larynx, oropharynx, or hypopharynx cancers for whom organ-sparing CRT as the initial modality of treatment is not appropriate.

Two phase 3 RCTs have clarified the role of CRT in the postoperative adjuvant setting. The RTOG[50] and the European Organization for Research and Treatment of Cancer (EORTC)[51] trials addressed the question of whether the addition of high-dose cisplatin to standard postoperative RT (based on pathologic criteria) would improve the outcome for patients compared with postoperative RT alone. In both studies, toxicity was greater with concomitant CRT.[50,51] Although the treatment was similar in these two studies, the high-risk pathologic features were not uniform, and the study populations differed. The RTOG trial high-risk criteria included more than two positive lymph nodes, extracapsular extension of nodal disease, or positive margins. The EORTC trial high-risk criteria included positive margins, ENE, vascular embolism, or perineural disease; for oral cavity or oropharynx primary sites, high risk was defined as positive nodes at level 4 or 5.

Survival differences were statistically significant in the EORTC trial but not in the RTOG trial, partly because of the differences in entry criteria. A pooled analysis of both studies indicated that the subsets of patients in both trials who experienced a substantial benefit from cisplatin with RT had either microscopically involved margins or extracapsular extension of disease in neck nodes.[52] The presence of either or both of these risk factors is considered an absolute indication for adjuvant CRT. The presence of one or more intermediate pathologic risk factors in the absence of involved margins or extracapsular extension, such as close (less than 5 mm) resection margin(s), pathologic T3 or T4a tumor, pathologic N2 disease, lymphovascular, and/or perineural invasion, adjuvant CRT can be considered.[53]

A reanalysis of the RTOG trial, with a median follow-up of 9.4 years, demonstrated a substantial advantage for CRT with LRC of disease and DFS for patients with either positive margins or extracapsular nodal extension, but with only a trend for OS benefit.[54] Cisplatin (100 mg/m^2) administered on days 1, 22, and 43 during RT is one CRT regimen for adjuvant therapy. The phase 2/3 JCOG 1008 trial randomly assigned patients with high-risk (microscopically positive margin and/or ENE) locally advanced HNSCC to cisplatin once every 3 weeks (100 mg/m^2) or once per week (40 mg/m^2) concurrently with adjuvant RT. A total of 261 patients were enrolled, and, at a median follow-up of 2.2 years, CRT with cisplatin once per week was noninferior to 3-weekly cisplatin in terms of OS, with an HR of 0.69 (99.1% CI, 0.374-1.273 [<1.32]; one-sided *P* for noninferiority = .0027 [<.0043]). The once-per-week cisplatin arm was associated with less frequent infection, neutropenia, hearing loss, and renal impairment.[55] For concerns related to poor compliance because of toxicities related to high dose, the NCCN guidelines for head and neck cancer note that once-per-week cisplatin (40 mg/m^2) with RT may be considered in an adjuvant setting.

The NIVOPOST-OP trial was a phase 3, open-label trial that randomized 666 patients with high-risk pathologic features to adjuvant nivolumab before, during, and after cisplatin-RT versus adjuvant cisplatin-RT alone. The 3-year DFS was 63.1% in the nivolumab and CRT arm versus 52.5% in the CRT-alone arm, with an HR of 0.76, and is a treatment option for high-risk resected patients who did not receive neoadjuvant immunotherapy.[56]

KEY POINTS

- For patients with unresectable HNSCC, CRT with concurrent cisplatin improves survival compared with RT alone and is the standard of care.
- The optimal dosing regimen (40 mg/m^2 once per week or 100 mg/m^2 once every 21 days) for concurrent cisplatin remains to be defined. A cumulative dose of 200 mg/m^2 should be prioritized.
- In locally advanced laryngeal cancer (T2 to low-volume T4), LRC and larynx preservation are substantially improved with concomitant cisplatin and RT compared with induction chemotherapy followed by RT or RT alone.
- Cetuximab added to RT improves survival compared with RT alone in locally advanced head and neck cancer, but it is inferior to cisplatin with RT.
- Docetaxel combined with RT in patients who are not candidates for treatment with cisplatin is superior to RT alone in patients with locoregionally advanced disease.[57]
- CRT with cisplatin is the standard of care for postoperative adjuvant treatment of patients with positive resection margins and/or ENE of disease, with an emerging role for immunotherapy.
- The role of induction chemotherapy before CRT has yet to be defined. Several clinical trials have failed to demonstrate an advantage to induction other than for NPC (discussed below).

COMBINED MODALITY TREATMENT: ORGAN PRESERVATION

For patients with locally advanced SCC of the larynx, hypopharynx, or oropharynx, CRT yields better disease control compared with RT alone, although acute toxicities are greater. Successful applications of chemotherapy and RT strategies (ie, management of mucositis, weight loss, hematologic toxicities, swallowing dysfunction necessitating the need for a feeding tube) for organ preservation often use a team approach that may include the head and neck surgeon, radiation oncologist, and medical oncologist, as well as a dietician, swallowing therapist, oncology nurses, advanced care practitioners, pharmacists, and social workers. Close monitoring with comprehensive head and neck examinations and timely integration of salvage surgery, when necessary, are part of the treatment plan and are necessary to avoid compromising survival.

PET imaging 3 months after treatment is useful in the assessment of patients with node-positive disease who were treated with CRT. Rather than having all patients proceed to neck dissection, given the high negative predictive value of FDG-PET, observation can be considered for patients who achieve a complete metabolic response. Premature FDG-PET/CT imaging is associated with a high rate of false-positive incomplete metabolic response, so FDG-PET imaging should not be obtained within 12 weeks after RT completion. For HPV-positive OPC, cancer-specific ct HPV DNA has a high positive predictive value and negative predictive value for relapse after definitive CRT. However, the exact role of ct HPV DNA for routine posttreatment surveillance has not yet been specifically defined. Evaluation of functional and quality-of-life outcomes[58] is also required to assess the overall benefit of organ preservation therapies.

LARYNX AND HYPOPHARYNX

The US Department of Veterans Affairs Laryngeal Cancer Study Group (VALCSG) RCT demonstrated that organ-sparing CRT could substitute for laryngectomy with no significant difference in survival between CRT and surgery.[59] In this trial, patients with locally advanced, resectable T2-T4 laryngeal cancers were randomly assigned to induction chemotherapy with three cycles of cisplatin and 5-FU (PF) followed by RT for chemotherapy-responsive disease or total laryngectomy followed by RT. Total laryngectomy was avoided for approximately two-thirds of survivors who received CRT. Although OS was suboptimal in both arms, long-term follow-up of more than 10 years continued to demonstrate no significant difference in survival between the groups. On multivariable analysis, T4 and N2 disease were both significant predictors of treatment failure, with 56% of patients who had T4 tumors eventually requiring laryngectomy.

The EORTC performed a similar study involving patients with advanced, resectable (T2-T4) cancer of the hypopharynx.[60] No difference in survival between the two groups was noted, and the 5-year estimated rate of successful larynx functional preservation (ie, local control and no tracheostomy or feeding tube) was 35%.

In follow-up to the VALCSG study, the Intergroup RTOG 91-11 trial addressed two unresolved issues: the optimal sequencing of chemotherapy and RT (induction chemotherapy followed by RT or concomitant chemotherapy and RT) and the precise contribution of chemotherapy added to RT.[14] Patients with locally advanced SCC of the larynx were randomly assigned to one of three treatment arms: RT alone (70 Gy), concomitant cisplatin (100 mg/m^2 once every 21 days × 3 and RT [70 Gy]), or three cycles of induction PF followed by 70 Gy RT. Both chemotherapy regimens significantly improved locoregional FFS compared with RT alone. OS did not differ significantly, although there was a possibility of a worse outcome with concomitant relative to induction chemotherapy.[14] For patients who fit the inclusion criteria for this study, concomitant cisplatin and RT or induction followed by RT remain the standard treatment options for preservation of organ function. It is important to note that this strategy was not used in T4 tumors or tumors that had already significantly compromised laryngeal function.[61]

OROPHARYNX

CRT was standard practice for most resectable, advanced oropharynx cancers before the increasing use of transoral surgical techniques. Randomized data between the two modalities are limited, and patient selection for nonsurgical treatment depends on T/N stage and functional preservation.

A retrospective multivariable analysis of patients who received treatment in the RTOG 0129 trial revealed significantly improved 3-year survival rates among patients who were HPV positive compared with those who were HPV negative (84% vs 57%, respectively).[24] Per the ASCO Radiation Oncology Evidence-Based Clinical Practice Guidelines,[62] intermittent bolus dose of cisplatin (100 mg/m^2) delivered with definitive RT (70 Gy) is considered standard of care for locally advanced OPCs. Although it was the intention to deliver three cycles of cisplatin with RT in the control arm, a retrospective analysis of RTOG 0129 established that at least 200 mg/m^2 cisplatin (total dose) was required to attain maximum survival benefit.[24] Alternatively, concurrent cisplatin 40 mg/m^2 once per week with definitive RT may be delivered, based on preliminary noninferiority data in a mostly non-HPV-associated population.[63]

Three studies have reaffirmed that combined modality therapy with cisplatin and RT is the standard of care for most patients with p16-positive OPCs. The RTOG 1016 trial[38] randomly assigned patients with p16-positive OPCs of all stages to RT with concurrent cetuximab or cisplatin. The study was designed as a noninferiority trial; the hypothesis was that cetuximab would reduce toxicity while maintaining survival rates. The 5-year OS, PFS, and locoregional failure rates all favored patients who were treated in the cisplatin arm, and the rates of overall acute and late-grade 3 to 4 toxicities were similar between the two groups. Similar to RTOG 1016, the De-ESCALaTE HPV trial[43] randomly assigned the same population (but included only those with smoking histories of 10 pack-years or less) to cisplatin and RT versus cetuximab and RT. The 2-year OS rate also favored the cisplatin arm (97.5% vs 89.4%; HR, 5.0; 95% CI, 1.7-14.7; P = .001). Finally, the TROG 12.01 study randomly assigned 189 patients with HPV-positive OPC to once-per-week cisplatin versus cetuximab with RT. The 3-year FFS rate favored cisplatin (93% vs 80%), and the use of cetuximab did not improve the toxicity profile.[64]

Concomitant bolus doses of carboplatin (70 mg/m^2 once per day for 4 days) and 5-FU (600 mg/m^2 as a once-per-day 24-hour infusion for 4 days) on days 1, 22, and 43 with RT (70 Gy; 35 fractions) may be administered as an alternative to cisplatin.[37]

This randomized trial treated only patients with OPCs and compared CRT to RT alone. Carboplatin and 5-FU with RT improved 3-year OS (51% vs 31%). The incidence of severe, late (grade 3-4) toxicities was higher (14%) in the combined arm than in the RT-alone arm (9%), with cervical fibrosis being more severe in those receiving chemotherapy. Cetuximab should be considered only when patients are not eligible to receive either cisplatin or carboplatin-based regimens, and as discussed above, concurrent docetaxel is also an option for this platinum-ineligible population. CRT is considered an evidence-based standard treatment option and is particularly applicable for the management of T3-T4 or N2-N3 disease located at the base of the tongue or tonsils.

Given the low volume and favorable prognosis of early-stage disease, radical surgery (total glossectomy) or CRT should be avoided, in general, for patients with T1-T2, N0-N1 HPV-negative disease or for patients with T1-T2, N0-N1 HPV-positive disease when N1 is a single node smaller than 3 cm. Preservation of speech and swallowing function can be attained with RT or organ-sparing surgery. Per the NCCN guidelines, RT, TORS, or open resection at T1 or T2 oropharyngeal primary sites without neck nodal involvement is appropriate. For N0 disease, strong consideration for neck dissection should be given because oropharyngeal tumors often harbor disease in the neck, with a risk of up to 20% of occult metastases noted in observational studies. For patients with HPV-positive N1 disease limited to a single node smaller than 3 cm or HPV-negative disease, a neck dissection should be performed along with surgery to the primary site. Bilateral neck dissections are required for tumors arising from the midline.

Multiple trials are ongoing to evaluate the role of TORS in OPC,[18,65] but no large phase 3 randomized trial data exist to evaluate surgery compared with definitive CRT. Two small studies comparing transoral resection with an RT-based approach to limited stage HPV-positive OPC did not demonstrate substantial differences in functional or cancer outcomes, but one of the trials was closed prematurely because of unexpected early deaths in the transoral surgical patients.[65]

Given the favorable prognosis of HPV-related OPC, recent efforts have focused on attempts to deintensify the definitive standard modalities of RT and chemotherapy. Studies selecting patients for lower doses of RT with concomitant systemic therapy if they demonstrate complete responses to induction chemotherapy remain promising, yet these data are considered exploratory. At this time, any deintensification approach, although potentially attractive for reducing long-term toxicities, should be considered investigational, because no trials have demonstrated improved quality of life with noninferior cancer control.

ct HPV DNA is a potential biomarker that can be followed posttreatment, with a negative predictive value of 93% to 95% for 2-year locoregional failure and PFS, but there is no consensus on how, when, or in which patients to incorporate blood HPV DNA testing, either at baseline or after treatment. Future prospective studies will need to establish the role of ct HPV DNA in this setting.

KEY POINTS

- No definitive data demonstrate that induction chemotherapy followed by CRT leads to better survival compared with CRT alone.
- Induction chemotherapy with TPF is considered the standard induction regimen when induction is recommended because it has been shown to improve both OS and LRC compared with PF.
- For patients with unresectable locally advanced HNSCC, CRT with cisplatin significantly improves survival compared with RT alone and is the standard of care.
- In locally advanced laryngeal cancer, LRC and larynx preservation are best achieved with concomitant cisplatin and RT, although induction chemotherapy followed by RT is a reasonable alternative because long-term data show no difference in laryngectomy-free survival for either treatment paradigm.
- Cetuximab added to RT improves survival compared with RT alone in locally advanced head and neck cancer, as does docetaxel in platinum-ineligible patients, but neither should replace CRT with cisplatin therapy as the standard of care in patients who are candidates for it.
- CRT with cisplatin is the standard of care for postoperative adjuvant treatment of patients with positive resection margins and/or extracapsular extension of nodal disease.

NASOPHARYNGEAL CANCER

OVERVIEW

WHO type 1 (keratinizing) SCC of the nasopharynx has a locoregional behavior more similar to that of other smoking-related head and neck cancers. WHO type 2 (nonkeratinizing, differentiated) and type 3 (undifferentiated) cancers, both of which can occur with lymphoid stroma (previously called lymphoepithelioma), predominate in endemic areas (eg, southern China, southeast Asia, northern Africa) and have a higher propensity for distant metastases. More than 90% of patients who have WHO type 2 or type 3 disease have a disease associated with EBV. If tumors are EBV positive, the presence of HPV is rarely, if ever, seen. However, many EBV-negative NPCs are often HPV positive. Because the overwhelming majority of all clinical trials for patients with NPC have been conducted where NPC is endemic and therefore EBV related, it is unclear to what extent results from these trials can be applied to patients with EBV-unrelated NPC. There is a lack of expert consensus on whether treatment decisions should be made by extrapolation from EBV-related NPC paradigms or by extrapolation from non-EBV HNSCC at other anatomic sites.

RT is the historic mainstay of treatment of M0 NPC. Active agents include cisplatin, taxanes, 5-FU, capecitabine, gemcitabine, cetuximab, and ICI targeting programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1). The clinical behavior of NPC varies somewhat according to its histologic subtype and biomarkers. Patients who have WHO type 2 or type 3 respond more favorably to definitive CRT than those who have WHO type 1.

THERAPY

Chemoradiation Therapy

Numerous randomized studies and multiple meta-analyses have established that cisplatin-based CRT is the cornerstone of therapy for newly diagnosed, advanced, locoregional NPC. Current guideline-based standards of care for curative treatment of NPC include induction therapy before CRT for patients with locoregionally very advanced disease. RCTs have confirmed that induction chemotherapy followed by CRT improves OS relative to concurrent CRT alone with or without adjuvant PF chemotherapy. The two most commonly used regimens are gemcitabine and cisplatin (GC) and dose-attenuated TPF. CRT with concurrent cisplatin remains the standard for patients with intermediate-risk locoregional NPC, but there is no consensus on whether a subgroup of these patients also benefits from adjuvant PF. RT alone is used for patients with highly curable early T- and N-stage tumors.

Sequential Chemotherapy With Induction

Sequential therapy, defined as induction chemotherapy with either GC or dose-attenuated TPF followed by CRT, is now accepted as the standard for treatment of locoregionally advanced NPCs (Table 12-6). The GC induction regimen followed by concurrent CRT is used more frequently, but RCTs also support dose-attenuated docetaxel, cisplatin, and 5-FU (TPF) in this setting.[32] A phase 3 randomized trial reported by Zhang et al[66] found that the addition of induction GC to CRT improved recurrence-free survival (85% vs 77% at 3 years) and OS (95% vs 90% at 3 years) compared with CRT alone. Approximately half the patients enrolled had N2, N3A, or N3B disease, and thus were at risk for developing distant metastases. Data incorporating immunotherapy in curative-intent NPC are evolving, with some studies suggesting a benefit.[67]

There remain challenges concerning the identification of which patients are most appropriate for this very aggressive sequential therapy approach, but, in general, it is reserved for patients who have T3-T4 and N2-N3 tumors. Substantial data suggest that markedly elevated levels of baseline ct EBV DNA are an independent risk factor for poor prognosis in patients with EBV-associated NPC. Lack of harmonization of ct EBV DNA has prevented a uniform definition that could be used to define high-risk patients beyond TNM staging.

Cisplatin, on either a once-per-week or once-per-21-days schedule combined with curative dose radiation, typically 70 Gy to all sites of clinical and radiologic disease with lower doses to at-risk areas of the skull and neck, remains the standard CRT paradigm for locoregional NPC. IMRT is the standard because it is associated with the highest rates of LRC. Although there are advocates for the prioritization of proton-based RT treatments for NPC, evidence supporting this approach remains limited to small case series and anecdotal; therefore, although the scientific rationale for proton beam treatment seems valid, there are insufficient data to support claims of superiority to IMRT in terms of OS, LRC, or adverse effects.

Carboplatin is an acceptable substitute for cisplatin with concurrent RT in NPC for patients who are unfit for cisplatin. One randomized trial of carboplatin versus cisplatin with RT in locoregional NPC failed to demonstrate an OS advantage to cisplatin, a finding unique to NPC in HNSCC. Unlike other HNSCC sites, the role of cetuximab or taxanes concurrently with RT has not been defined.

Adjuvant Chemotherapy

The use of adjuvant chemotherapy after CRT in NPC remains highly debated. A phase 3 trial was reported by Al-Sarraf et al[68] in 1998. The design of that RCT incorporated both concurrent cisplatin and adjuvant PF together in the experimental arm compared with RT alone.[69] This relatively small trial in the United States did not shed light on the contribution of adjuvant PF to OS superiority. Subsequent studies, including a trial by Chen et al,[70] have challenged the routine use of adjuvant chemotherapy after CRT. They compared once-per-week CRT with or without adjuvant chemotherapy in 251 patients with nonmetastatic stage III or IV NPC. The primary endpoint was FFS. After a median follow-up of 37.8 months, the estimated 2-year FFS rate was 86% in the CRT plus adjuvant chemotherapy arm and 84% in the CRT-only arm ($P = .13$). However, critics believe that the study was not designed as a noninferiority study against the standard of care (ie, high-dose cisplatin and RT).

A meta-analysis of 20 trials suggested that there is a benefit of adjuvant chemotherapy after concurrent CRT, which led NRG Oncology to conduct an international study (NRG HN001), which unfortunately closed in 2023 before completing accrual. That trial used post-radiation ct EBV DNA as a randomization factor: patients with undetectable ct EBV DNA were randomly assigned to adjuvant PF or to no adjuvant treatment, whereas patients with detectable ct EBV DNA were randomly assigned to adjuvant PF or gemcitabine plus paclitaxel. Given the premature closure of that study, it is not clear whether the questions that the trial set out to ask will be answered.

Table 12-6 **Summary of Clinical Studies for Patients With Locally Advanced Nasopharyngeal Cancer**

Study (Location)	No. of Patients	AJCC Stage (Year)	Study Arm	Median Follow-Up (Months)	Primary Outcome	Secondary Outcome	Grades 3 to 4 Toxicity (%)
Al-Sarraf et al[68] (United States)	147	III to IV (1992)	Cisplatin (100 mg/m^2) every 3 weeks with radiation and adjuvant chemotherapy, cisplatin (80 mg/m^2) and FU (1,000 mg/m^2) for three cycles vs radiation alone	60	OS: 67% vs 37% (P = .001)	PFS 58% vs 29% (P = .001)	RT alone: Stomatitis: 28 Leukopenia: 1 Nausea/vomiting: 10
							CRT: Stomatitis: 37 Leukopenia: 36 Nausea/vomiting: 31
Chan et al[69] (Hong Kong)	350	Ho's N2-N3 or node larger than 4 cm	Weekly cisplatin (40 mg/m^2) with radiation vs radiation alone (no adjuvant chemotherapy)	66	OS: 90% vs 80% (P = .049)	PFS 60% vs 52% (P = .16)	RT alone: Stomatitis: 36 Leukopenia: 0 Nausea/vomiting: 0
							CRT: Stomatitis: 49 Leukopenia: 13 Nausea/vomiting: 12
Zhang et al[66]	480		Compared gemcitabine and cisplatin as induction chemotherapy and concurrent chemoradiotherapy with concurrent chemoradiotherapy alone	42.7	OS: 94.6% vs 90.3%		RT alone: Stomatitis: 76 Leukopenia: 132 Nausea/vomiting: 66
							CRT: Stomatitis: 69 Leukopenia: 63 Nausea/vomiting: 109

Abbreviations: AJCC, American Joint Committee on Cancer; CRT, concomitant chemoradiation; DFS, disease-free survival; FU, fluorouracil; OS, overall survival; PFS, progression-free survival; RT, radiation therapy.
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Recently, two RCTs incorporated adjuvant capecitabine as part of a sequential CRT plan for high-risk locoregionally advanced NPC. One trial used low-dose uninterrupted capecitabine for a year, and the other used a higher-dose intermittent regimen for 6 months. Both studies demonstrated improved recurrence-free survival, and one study demonstrated improved OS; tolerability was acceptable, with most patients completing these adjuvant treatments. In one of these trials, the PFS and OS advantage was also seen in the subgroup of patients treated with either GC or TPF induction.[71,72] Therefore, in patients who have high-risk locoregionally advanced NPC, adjuvant capecitabine is recommended after induction and concurrent CRT.

RECURRENT OR METASTATIC NASOPHARYNGEAL CANCER

First-line treatment of recurrent or metastatic (R/M) NPC uses a platinum-based doublet combined with immunotherapy. GC is the preferred doublet over PF on the basis of one randomized study that demonstrated a PFS of 7 months versus 5.6 months, respectively.[73] One difficulty in interpreting these data is that the use of GC in this trial was in an era when GC was not widely used as induction treatment, and, therefore, the superiority in patients with previous exposure to GC is uncertain.

Monoclonal antibodies that interrupt the PD-1/PD-L1 interaction, when added to GC, have demonstrated a meaningful PFS advantage over GC alone for patients with metastatic NPC. In a phase 3 trial, patients were randomly assigned to GC with or without the addition of toripalimab, a PD-1 inhibitor. The outcomes favored the addition of immunotherapy, with a median PFS of 11.7 months versus 8.0 months (HR, 0.52; 95% CI, 0.36-0.74; two-sided $P = .0003$) and 1-year PFS rates of 49% and 28%, respectively.[74] Toripalimab also improved OS relative to placebo (HR 0.63, two-sided $P = .008$). Median OS was not reached in the toripalimab group, while it was 33.7 months in the placebo group.[74] Similar median PFS improvement (9.7 months vs 6.9 months) was seen with the addition of PD-1 inhibitor camrelizumab to GC, penpulimab to GC, and tislelizumab to GC. It seems that this effect is robust across PD-1 inhibitors, and therefore, the combination of GC and a PD-1-targeted ICI is recommended in this setting. A single-arm phase 2 trial tested toripalimab in 190 chemorefractory patients with metastatic NPC and demonstrated an objective response rate (ORR) of 20.5%. Based on cumulative evidence from these trials, toripalimab was FDA-approved treatment in late 2023 for R/M NPC, both as a single agent and in combination with GC.[75] Subsequently, in April 2025, penpulimab received similar FDA approval in combination with GC in the first-line treatment of adults with recurrent or metastatic nonkeratinizing NPC. FDA also approved penpulimab-kcqx as a single agent for adults with metastatic nonkeratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

Many chemotherapeutic agents are active against NPC, including cisplatin, carboplatin, nedaplatin, docetaxel, paclitaxel, nab paclitaxel, 5-FU, capecitabine, cetuximab, and methotrexate. Many ICIs targeting the PD-1/PD-L1 interaction have demonstrated anticancer activity, occasionally with durable remissions. Fit patients who have relapsed or progressed after the curative or first-line R/M disease regimens can experience significant prolonged benefit from palliative systemic treatments.

Patients with oligometastatic disease, typically having fewer than three metastatic sites, either at presentation or in relapse, may benefit from a multimodality approach that can include definitive CRT to the head and neck region with subsequent focal RT or surgical resection of oligometastatic sites. A typical approach is to begin with systemic treatment and consolidate with locoregional treatments for metastatic sites for patients with demonstrated responses and lack of progression while receiving systemic therapy.

KEY POINTS

- The standard of care (according to stage) is RT alone for limited stage (typically T1-2 N0M0).
- Concurrent cisplatin-based CRT with or without adjuvant PF for intermediate-risk locoregional disease, and sequential CRT including induction GC or TPF, concurrent CRT, and adjuvant capecitabine for patients with the highest-risk locoregionally advanced disease remain the standards of care.
- NPC is a very chemotherapy-sensitive disease. Patients with metastatic disease often experience prolonged benefit from systemic chemotherapy. GC and ICI are the widely accepted first-line treatments of R/M disease, but other platinum-based chemotherapies combined with immunotherapy are also acceptable systemic treatment options.
- For patients with oligometastatic disease, a potentially curative treatment paradigm that includes systemic chemotherapy and local definitive treatment of the head and neck and oligometastatic sites is associated with some long-term survival.
- All treatment paradigms for NPC are largely based on data from EBV-associated NPC.

CANCER OF UNKNOWN PRIMARY SITE

Although a malignant neck lymph node without a clear primary tumor is a common presentation of HNSCC, for most patients, the primary site is found after comprehensive examination of the head and neck, endoscopy, and diagnostic imaging. The location of the lymph node in the neck directs the examiner toward the likely potential primary sites. FDG-PET imaging should be part of the standard evaluation for SCC of unknown primary site; it can help identify the primary site in approximately 30% of cases.

FNA of the lymph node is the first choice for initial biopsy. If negative, repeating FNA with consideration of a core needle biopsy, if feasible, is appropriate. Often, with cystic lymph nodes, ultrasound can facilitate sampling of the viable rind of the tumor instead of the central necrotic debris. Viral testing of the nodal specimen (HPV and EBV) should be performed. If positive, their tumors should be treated as oropharyngeal or primary nasopharyngeal, respectively. The tumor staging classification becomes T0 if subsequent inquiries fail to identify a primary site. If viral staining is negative, the tumor staging classification becomes Tx. If the histologic diagnosis remains inconclusive, a subsequent excisional biopsy should be performed in such a way that the incision can be incorporated into an appropriate neck dissection. Open biopsy may contaminate the surgical field and lead to seeding of tumor cells, and is usually not necessary, because repeat needle biopsy or directed mucosal biopsies can often identify the cancer.

If pathologic findings from the neck indicate a diagnosis of SCC, and a primary lesion above the clavicle is suggested (in particular, if the lymph node is high in the neck), assuming an in-office endoscopy and imaging have not revealed anything, a comprehensive head and neck examination under anesthesia is the next step. Directed biopsies should be performed for suspicious mucosal areas as well as for locations known to be a source of occult tumors, such as the hypopharynx, base of the tongue, and nasopharynx. In addition, bilateral simple tonsillectomies are recommended based on the increasing incidence of tonsillar cancers associated with HPV. Transoral resection of lingual and pharyngeal wall tissues can often uncover occult primary sites in these cases.

The skin, the upper part of the esophagus, and the lung are other potential sources of SCC spread to the neck. If the findings on biopsy specimen of a cervical lymph node indicate an adenocarcinoma, the thyroid gland, salivary gland, or sites below the clavicle should be considered.

Lymphoma is another important diagnostic possibility and may require a core needle biopsy. Similarly, distinguishing lymphoma from anaplastic and undifferentiated or poorly differentiated cancers can be difficult based on the cytologic analysis alone and may require additional IHC studies or more tissue.

The choice of treatment of patients with SCC in a neck node of unknown primary site is controversial and evolving. Historically, either surgery or RT was used to treat patients with low-bulk disease in a single lymph node, whereas both modalities were necessary for patients with more advanced disease. The extent of RT to the potential primary sites requires clinical judgment with regard to the likely source of the tumor, because a larger portal will increase the morbidity associated with treatment. Findings from clinical series indicate that, with longitudinal follow-up, the primary site ultimately is found for approximately 30% of patients. Long-term survival is better for patients in whom the primary lesion remains occult than for those in whom it does not.

The mainstay of treatment is still neck dissection followed by RT with concomitant cisplatin when extracapsular extension of nodal disease is present. However, the majority of these cases are now p16-positive tumors arising from the oropharynx, and definitive CRT is considered another standard treatment option.

KEY POINTS

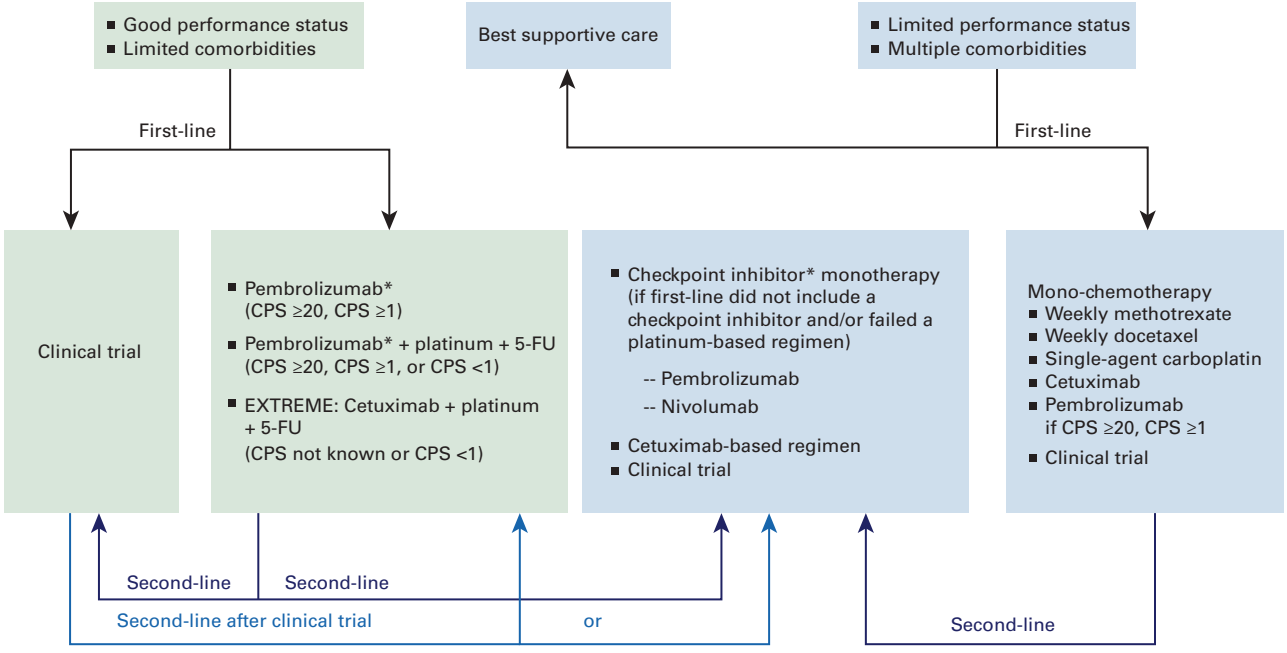
- The search for the primary site should include FDG-PET/CT imaging and an examination under anesthesia with directed biopsies of the base of the tongue, nasopharynx, and hypopharynx, and bilateral, simple tonsillectomies.
- After an FNA biopsy of the lymph node, HPV and EBV testing should be performed. If the tumors are positive, they should be treated as oropharyngeal or primary nasopharyngeal, respectively.
- Standard treatment consists of neck dissection followed by RT to include the likely primary sites, and concurrent cisplatin is added if extracapsular extension of nodal disease is present.
- In selected patients, CRT is another primary treatment option.

INCURABLE RECURRENT OR DISTANT METASTATIC DISEASE

SYSTEMIC THERAPY

Recurrent or persistent disease that is not appropriate for additional surgery or RT after definitive therapies have been delivered or disease that involves distant organs is considered incurable. Cisplatin, carboplatin, docetaxel, paclitaxel, 5-FU, methotrexate,

Figure 12-3 Treatment Algorithm for Metastatic HNSCC



Abbreviations: 5-FU, fluorouracil; CPS, combined positive score; HNSCC, head and neck squamous cell carcinoma.
*For second-line, do not use a checkpoint inhibitor if given as 1st line under clinical trial.
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and capecitabine are the most commonly used cytotoxic agents to treat R/M HNSCC in the first- and second-line settings. Cetuximab is an active targeted agent that is also commonly used as a second- or third-line regimen (Fig. 12-3).

Pembrolizumab and nivolumab, monoclonal antibodies directed at the PD-1 protein, were first approved by the FDA for the treatment of platinum-refractory R/M HNSCC based on the results of large clinical trials; pembrolizumab was subsequently approved for first-line R/M HNSCC based on KEYNOTE-048.

Historically, randomized trials comparing combination chemotherapy and single-agent therapy show a near doubling of the response rate with platinum-based combinations, but, unless a clinical complete response is achieved, the duration of response is brief (2-4 months) and does not have a substantial effect on OS. Toxicity is generally greater when combination chemotherapy is used. Combination chemotherapy should be limited to patients with a good performance status (eg, Eastern Cooperative Oncology Group [ECOG] performance status of 0-1), who are better able to tolerate the added toxicity.

FIRST-LINE THERAPY

KEYNOTE-048 was a multicenter, three-arm, randomized trial of 882 patients with newly diagnosed R/M HNSCC. Patients were randomly assigned 1:1:1 to pembrolizumab alone, pembrolizumab with chemotherapy (cisplatin or carboplatin in combination with 5-FU), or cetuximab in combination with chemotherapy (aka, the EXTREME regimen). Each experimental pembrolizumab arm was compared independently with the EXTREME arm. The principal outcomes consisted of noninferiority for OS for pembrolizumab versus EXTREME and superiority for pembrolizumab plus chemotherapy versus EXTREME in the study populations whose tumors had a CPS higher than 20 and a CPS higher than 1. CPS is defined as the number of PD-L1-positive cells among tumors, lymphocytes, or macrophages divided by the total number of tumor cells times 100 in evaluable samples (with a minimum of 100 viable tumor cells) as measured by the PD-L1 IHC 22C3 pharmDx kit.

Pembrolizumab and chemotherapy significantly improved OS versus the EXTREME regimen in the CPS 20 or higher population (HR, 0.60; $P = .004$), the CPS 1 or higher population (HR, 0.65; $P < .0001$), and the overall study population (HR, 0.77; $P = .0086$).[76] Updated 5-year survival data have highlighted that some patients have an extension of survival with immunotherapy; up to 24% of the patients were alive at the 5-year landmark for both immunotherapy arms of the trial.[77]

The decision of whether to treat with pembrolizumab monotherapy versus the combination of chemotherapy and immunotherapy depends on PD-L1 expression, the patient's performance status, overall disease burden, and symptoms.

Among patients who have contraindications to immunotherapy, the EXTREME regimen is still an option in the first-line setting. In the phase 3 EXTREME trial, 440 patients with R/M HNSCC were randomly assigned to either the intervention arm (cisplatin or carboplatin with 5-FU and cetuximab) or the standard arm (cisplatin or carboplatin with 5-FU) as first-line treatment of R/M disease.[78] Cetuximab and the platinum and 5-FU combination significantly prolonged the median OS from 7.4 months to 10.1 months (HR for death, 0.80; 95% CI, 0.64-0.99; $P = .04$), significantly prolonged the median PFS from 3.3 months to 5.6 months (HR for progression, 0.54; $P < .001$), and increased the response rate from 20% to 36% ($P < .001$).

Although 5-FU has been partnered with platinum in these trials, it can be associated with increased toxicity and requires the use of an infusion pump. Therefore, taxane doublets are another option instead of PF therapy. Results from an ECOG study showed that survival with paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2) treatment did not differ significantly (9 months vs 8 months) from standard cisplatin (100 mg/m^2) and 5-FU (1,000 mg/m^2 by continuous infusion over 4 days); the 1-year survival rate was 30% versus 41%, respectively, although the paclitaxel regimen was generally better tolerated.[79] A phase 2 RCT of four cycles of docetaxel plus cisplatin (TPEx) versus six cycles of PF, both arms with cetuximab, suggests that TPEx is an acceptable alternative to the EXTREME regimen. Many oncologists in the United States[80] use a platinum agent plus taxane plus an ICI for PD-L1-positive patients, extrapolating from the KEYNOTE-B10, KEYNOTE-048, TPEx, and ECOG data discussed above. On the basis of data from these trials, the NCCN guidelines provide the option of platinum doublet therapy with taxanes in the first-line setting with pembrolizumab.[34,81]

PRESENTING CASE STUDY 2

A 63-year-old man presents to your clinic following surveillance chest radiograph findings of new bilateral lung nodules. He has a history of T2N1 HPV-associated right tonsil cancer, treated with definitive cisplatin and radiation therapy 2 years ago. He has never smoked. CT of the chest confirms the new lung nodules, the largest measuring 2.4 cm in the right midlung. Pathology from a CT-guided lung biopsy indicates p16-positive (100%), metastatic SCC. PET imaging shows no other sites of disease. The patient is asymptomatic and in otherwise good health.

What additional biomarker information do you need in this patient with treatment-naive metastatic head and neck SCC to guide systemic therapy selection?

PD-L1 testing would inform first-line systemic therapy in this patient with asymptomatic, metastatic head and neck SCC. Pembrolizumab monotherapy is an FDA-approved agent for patients with a PD-L1 CPS of 1 or higher. Pembrolizumab combined with platinum-based chemotherapy is approved regardless of PD-L1 CPS score.

This patient's PD-L1 CPS is 25. What treatment should you initiate? How would your management differ if the PD-L1 CPS were 0?

Both pembrolizumab and pembrolizumab with platinum-based chemotherapy would be appropriate choices if the PD-L1 CPS were 25; however, for this patient with a high PD-L1 CPS score and asymptomatic, small-volume disease, pembrolizumab monotherapy would be the least toxic treatment.[73]

If the PD-L1 CPS were 0, pembrolizumab alone would be unlikely to have significant clinical activity, and platinum-based chemoimmunotherapy would be a more appropriate choice.

SECOND-LINE THERAPY

Both nivolumab and pembrolizumab were originally studied and approved in the platinum-refractory setting without prior immunotherapy. KEYNOTE-040 and CheckMate 141 enrolled patients primarily with a performance status of 0 to 1 in whom platinum-based therapies failed. Both trials randomly assigned immunotherapy versus single-agent standard-of-care therapy with cetuximab, methotrexate, or cetuximab. The number of grade 3 to 4 adverse effects, however, was much higher with the standard-of-care chemotherapy arms (36% in chemotherapy vs 13% pembrolizumab and 35% in chemotherapy vs 13% nivolumab).[82] In general, factors associated with poor response to systemic therapy include poor performance status, the presence of comorbidities, bulky locoregional disease or high tumor volume, and previous treatment of recurrent disease. PD-1 inhibitors are associated with immune-related toxicities. The most common adverse effects in both studies were fatigue, rash, and skin-related toxicities. In addition, the CheckMate study reported stability in several quality-of-life measures in those receiving nivolumab and declines in measures in those receiving chemotherapy.

What is most remarkable about the use of pembrolizumab, nivolumab, and other ICIs for patients with R/M HNSCC is not response rates, which are typically 15% to 20% in this population.[83] Rather, it is the tail on the survival curve, suggesting that a minority of the patients treated seem to benefit from long-term remission of their cancers, an effect not commonly seen with cytotoxic chemotherapy treatments.

Cetuximab is the only molecularly targeted drug to be approved for use in the United States for platinum-refractory metastatic or recurrent head and neck cancer in combination with chemotherapy or as monotherapy. In a randomized trial in which the combination of cisplatin and placebo was compared with cisplatin and cetuximab in 123 patients, no significant difference was found in median PFS (2.7 months vs 4.2 months; $P = .27$), although the rate of major response (complete plus partial) was significantly higher for patients who received cisplatin and cetuximab (10% vs 26%; $P = .03$).[84]

Cetuximab as a single agent demonstrated a response rate of 11% and a disease control rate of 46% for patients with metastatic or recurrent head and neck cancers who experienced progression while receiving platinum therapy, and 19% in patients who received prior immunotherapy. Grades 1 to 4 acneiform rash and dry skin were the most bothersome adverse effects of this agent, occurring in more than 50% of all of patients. Hypomagnesemia is not uncommon and must be monitored, especially in those with a history of cardiac arrhythmias. Because cetuximab is not a fully humanized antibody, care must be taken to monitor for acute and delayed anaphylactic reactions that could lead to cardiopulmonary arrest.

Overall, treatment options beyond the first- or second-line setting are limited. Patients who progress on platinum doublets and immunotherapy overall have a poor prognosis, and monotherapy with taxanes or cetuximab is usually associated with low response rates. Patients who are taxane naive are often treated with paclitaxel or docetaxel monotherapy before cetuximab or other single agents with lower activity. Palliative and supportive care are key tools for patients with recurrent refractory disease. Ongoing trials are studying new immunotherapy combinations, bispecific antibodies targeting EGFR, and antibody-drug conjugates.

KEY POINTS

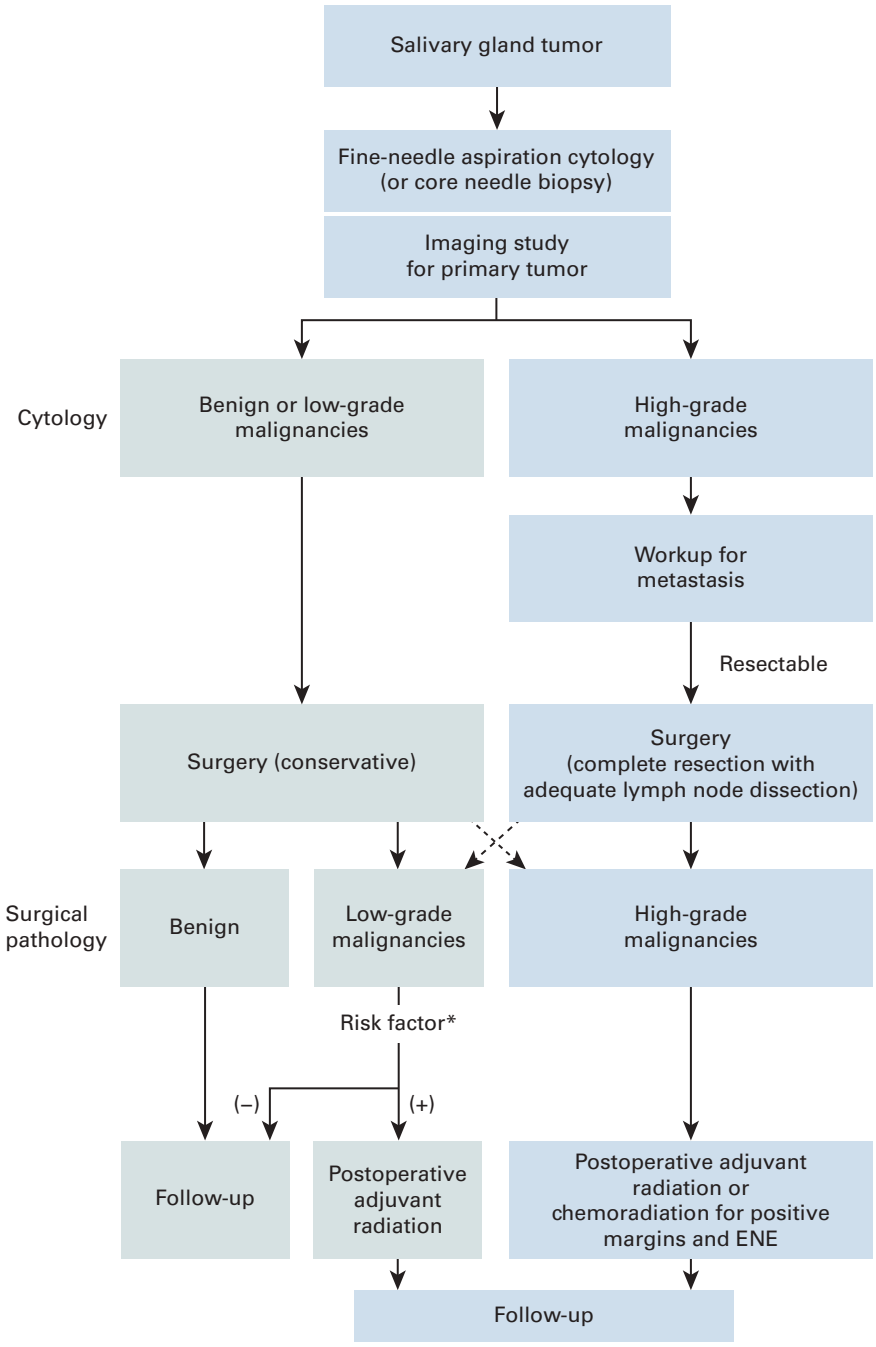
- Pembrolizumab (if PD-L1 CPS is 1 or higher and preferably 20 or higher) and pembrolizumab combined with platinum and 5-FU or platinum plus taxane are now considered the first-line standard of care for R/M HNSCC. For patients with PD-L1 CPS lower than 1, PF or TP with either cetuximab or pembrolizumab is used.
- Cetuximab combined with PF or TP (or cetuximab with carboplatin and paclitaxel) should be considered in the R/M setting when patients are not candidates for immunotherapy.

- Nivolumab and pembrolizumab are indicated as the second-line therapy for patients in whom platinum-based chemotherapy failed in the R/M setting.
- Taxanes, capecitabine, cetuximab, and methotrexate may be useful as single agents in patients with R/M HNSCC who have not had previous exposure to these agents, but, in general, response rates are low, and the duration of responses is limited.

SALIVARY GLAND TUMORS

Cancers of the major salivary glands (parotid, submandibular, sublingual) and the minor salivary glands are uncommon, accounting for about 5% of epithelial head and neck tumors. Tobacco and alcohol use are not risk factors for tumors of the salivary

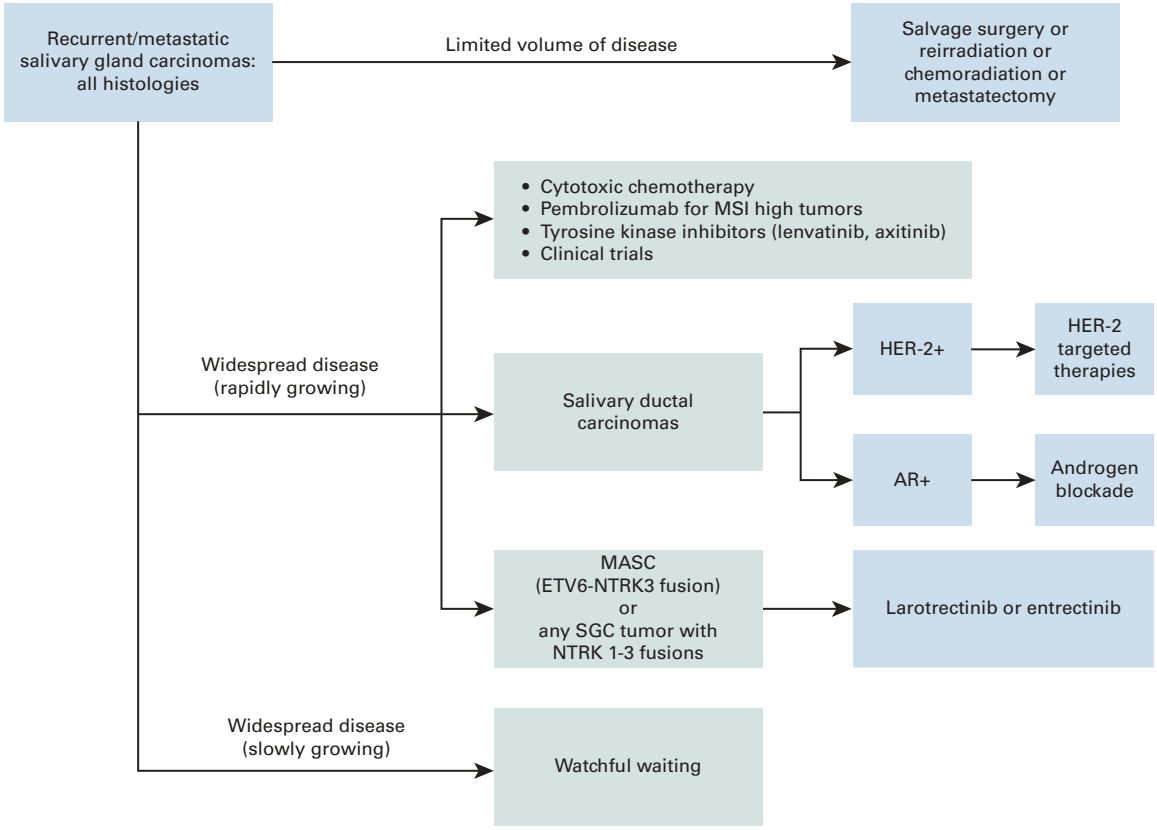
Figure 12-4 Treatment Algorithm of Local and Locally Advanced Salivary Gland Tumors



Abbreviation: ENE, extranodal extension.
*Multiple lymph nodes, perineural spread.
Reproduced under Creative Commons license. Source: Jang JY, Choi N, Ko Y, et al. Treatment outcomes in metastatic and localized high-grade salivary gland cancer: high chance of cure with surgery and postoperative radiation in T1-2 N0 high-grade salivary gland cancer. *BMC Cancer*. 2018;18:672. doi: 10.1186/s12885-018-4578-0

glands, but there may be an association with previous exposure to RT. The WHO classification lists 24 histologic subtypes of malignant epithelial salivary tumors. Their small numbers and their histologic and prognostic heterogeneity make them difficult to study (Figs. 12-4 and 12-5).

Figure 12-5 Management of R/M Salivary Gland Tumors



Abbreviations: AR, androgen receptor; MASC, mammary analog secretory carcinoma; MSI, microsatellite instability; R/M, recurrent/metastatic; SGC, salivary gland carcinoma.
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Pleomorphic adenomas are the most common salivary gland tumors. They have a variable appearance architecturally. Pleomorphic adenomas are diagnosed by FNA, and surgery is the treatment of choice because these tumors can transform into carcinomas (carcinoma ex pleomorphic adenoma).

The most common types of malignant salivary gland cancers are ACC and adenocarcinoma, which originate from the intercalated ducts, and mucoepidermoid carcinoma, which originates from the secretory ducts. A histologic reading of high-grade mucoepidermoid or adenocarcinoma correlates with aggressive behavior and a greater likelihood of eventual metastasis, whereas low-grade cancers of these histologies are more likely to be cured with initial local therapies. An ongoing cooperative group trial is attempting to answer whether cisplatin added to adjuvant RT in high-risk postsurgical patients is beneficial.

ACC, most commonly found in the minor salivary glands, is prone to neurotropic spread. It has the highest propensity of all histologic subtypes for distant metastases, yet it can grow indolently. Therefore, palliative chemotherapy should be attempted only for a symptomatic patient or when substantial tumor growth can be appreciated on serial imaging. In this setting, combinations of cyclophosphamide, doxorubicin, and cisplatin or those drugs as single agents can be considered. Antiangiogenic agents, such as lenvatinib and axitinib, have also been studied. Although these agents demonstrated low response rates in phase 2 trials, they remain a viable treatment option until agents with more efficacy or a better toxicity profile are studied.[85-87] Some providers advocate metastatectomy for patients who have ACC with oligometastatic pulmonary disease, but the benefit of this approach is neither validated nor widely accepted.

Salivary duct carcinoma is an aggressive subtype of adenocarcinoma with a rapid appearance of metastases. Microscopically, it looks similar to ductal breast cancer and frequently overexpresses HER2 and androgen receptors on IHC analysis. Substantial and durable responses in many patients to antiandrogen blockade or HER2 cytotoxic conjugate therapies have been reported in

small phase 2 clinical trials. However, a recent randomized phase 2 trial compared first-line platinum-based chemotherapy versus androgen blockade therapy in these patients demonstrated a numerically superior ORR and PFS in the chemotherapy group (ORR 35% vs 23% with ADT, median PFS 6.5 months vs 4 months with ADT).[88] Dual checkpoint inhibition with ipilimumab and nivolumab has also been studied in non-ACC salivary gland cancers, and preliminary data indicate activity.[89]

Often mistaken for acinic cell carcinoma, the now-classified secretory carcinoma (previously known as MASC) harbors an ETV6::NTRK3 fusion protein. Larotrectinib and entrectinib, both inhibitors of tropomyosin kinase receptors TrkA, TrkB, and TrkC, were recently approved by the FDA for patients with *NTRK* gene fusions. Results from three multicenter, open-label, single-arm clinical trials with larotrectinib demonstrated an overall response rate of 75%, with a 22% complete response rate, and a longer-than-6-month duration of response rate of 73% for patients with *NTRK* fusions. Entrectinib was studied in 57 patients, all with *NTRK* fusions among 10 different tumor types, and produced an ORR of 57% with a complete response rate of 7%. The median duration of response was 10 months (95% CI, 7.1-not estimable). The most common grade 3 or 4 treatment-related adverse effects were increased weight in 10% and anemia in 12%. The most common serious treatment-related adverse effects were nervous system disorders (4%).[90] All metastatic salivary gland tumors should be considered for testing for *NTRK* fusions, especially if the histology is uncertain.[91]

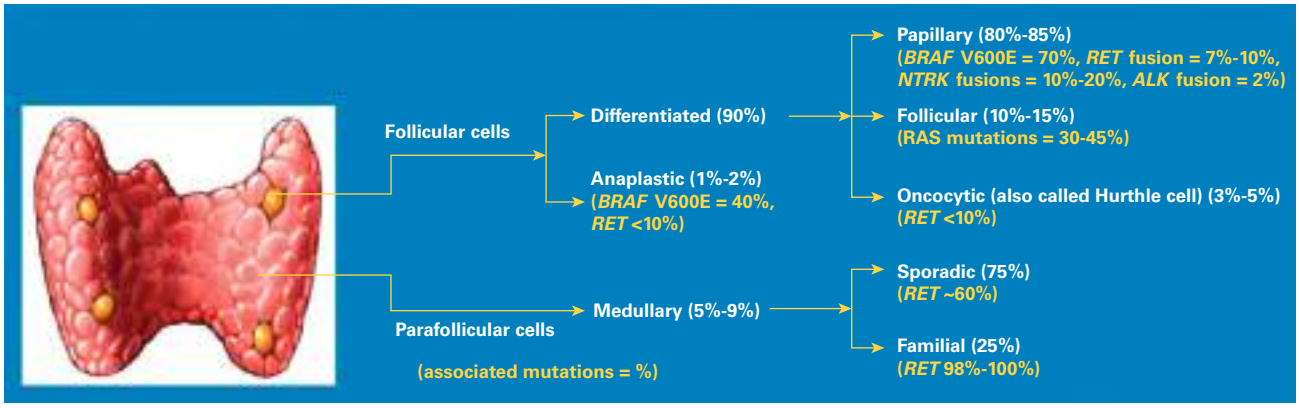
KEY POINTS

- Surgery is the mainstay treatment of salivary gland tumors, followed by RT for those tumors with high-risk features; pleomorphic adenomas should be surgically resected because of their potential for malignant transformation.
- Metastatic ACC and selected other salivary gland cancers are often characterized by an indolent natural history and have no known effective treatments; therefore, they are often followed without systemic treatment.
- For most slow-growing salivary gland cancers, systemic treatment should be delayed until substantial tumor growth can be appreciated on serial imaging studies within 6 months or if the disease is located such that symptom development is imminent (eg, bronchial obstruction). Comprehensive testing, including next-generation sequencing to evaluate for actionable molecular targets and appropriate immunotherapy biomarkers, should be performed for patients with metastatic disease.
- Salivary ductal tumors are histologically similar to breast cancer and can overexpress androgen receptors and HER2. Such tumors are often treated effectively with antiandrogen blockade or HER2-targeted cytotoxic conjugate therapies. Chemotherapy can also be an effective option.
- Secretory carcinomas, formerly known as MASCs, are characterized by the presence of ETV6-NTRK3 fusion proteins; larotrectinib or entrectinib is the treatment of choice for secretory carcinomas that are metastatic or for tumors for which surgery is likely to result in severe morbidity.

THYROID CANCER

Until recently, thyroid cancer was the most rapidly increasing cancer diagnosis among the US population. This increase was believed to be associated with highly sensitive diagnostic tests that could detect very small cancers (Fig. 12-6). The increase has now dropped from 7% annually during the 2000s to 1.5% annually from 2011 to 2015. In 2023, an estimated 43,720 adults (12,540 men and 31,180 women) received a diagnosis of thyroid cancer, with an estimated resultant 2,120 deaths.[92] It is the

Figure 12-6 Classification of Thyroid Cancers



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most common cancer in women aged 20 to 34 years. Women are three times more likely to have thyroid cancer than men, but women and men die at similar rates, suggesting that male patients have a worse prognosis than female patients. The 5-year OS rate for thyroid cancer is 98.5%, depending on the type and stage of disease. Thyroid cancers are classified based on the two main parenchymal cells of origin: the follicular cells involved in thyroid hormone production and the parafollicular cells that produce calcitonin.

DIFFERENTIATED THYROID CANCER

Etiology

The only well-documented etiologic factor for DTC is exposure to RT, with an inverse relationship between age at exposure and risk for development of thyroid malignancy. The thyroid glands of children younger than 10 are highly vulnerable to developing thyroid cancer if they are exposed to ionizing radiation. The risk for the development of thyroid cancer is much higher for individuals who have been exposed to RAI isotopes from nuclear reactor accidents and atomic bomb testing, as well as for children and young adults who have received external RT for other cancers (eg, Hodgkin lymphoma, neuroblastoma, Wilms tumor). More than 90% of well-differentiated thyroid cancers, however, are unrelated to radiation exposure. Approximately 5% of DTCs are associated with hereditary syndromes such as Gardner syndrome (familial adenomatous polyposis), Cowden syndrome, Pendred syndrome, Werner syndrome, and Carney complex.

Clinical Presentation and Workup

The sporadic DTCs are usually asymptomatic for a long time and present as a solitary nodule. The familial papillary thyroid cancers (PTCs) seem to be clinically more aggressive than the sporadic ones. The familial DTCs are usually multifocal and bilateral and have a tendency to recur both locoregionally and in distant sites.

PTC and its variants tend to recur locally in the regional lymph nodes, whereas follicular and Hurthle cell cancers tend to recur distantly, especially in bone and lung. Several factors have been widely accepted as being associated with a poor prognosis, including age older than 55 years, male sex, poorly differentiated histology, tumor size larger than 1.5 cm, and extrathyroidal extension at diagnosis. Involvement of the regional lymph nodes is associated with a greater risk for nodal recurrence but does not confer a worse prognosis for survival. The 10-year survival rate for DTC is 90%. The median age at diagnosis is 45 years, and the median age at death is 75 years.

Most thyroid cancers are detected as incidental thyroid nodules found on physical examination or by the patient presenting to the physician with a neck mass. The diagnostic evaluation should include high-resolution ultrasonography to aid in performing an FNA biopsy and to assess the number and characteristics of the nodules, including whether the nodules are solid or cystic. FNA has high sensitivity and specificity and is the test of choice when evaluating solitary thyroid nodules.

Routine thyroid scanning with ^{123}I or technetium-99 is not recommended. These tests provide information on whether a nodule is functional; however, the majority of benign and malignant nodules are "cold" or nonfunctioning, meaning that the test is nonspecific and not cost-effective. However, all patients with a thyroid nodule and suspected familial MTC should have calcitonin level testing.

Treatment

Surgery

The mainstay of treatment for DTC is surgery. The extent of initial surgical therapy is controversial. Some experts recommend removal of the entire thyroid gland, with the caveats that removal of only the affected lobe and the isthmus is necessary for patients with better risk (eg, young patients with small tumors) and that total thyroidectomy is associated with a greater risk for complications, such as recurrent laryngeal nerve injury leading to vocal cord paralysis and hypocalcemia secondary to hypoparathyroidism. After surgery, levothyroxine suppression of thyroid-stimulating hormone (TSH) is the standard of care. Postoperative RAI is used for patients whose disease has high-risk features, which typically include large tumors, those with vascular invasion or extrathyroidal extension, bulky or numerous involved lymph nodes, or postsurgically elevated thyroglobulin. Treatments with external beam RT for localized disease and antiangiogenic agents for widespread, metastatic disease are reserved for the palliative setting.

Radioactive Iodine

A single dose of RAI is usually recommended to ablate any normal thyroid remnant and destroy any microscopic deposits of the remaining thyroid cancer after a total thyroidectomy for patients who are at high risk of recurrence or persistence. In addition to treating residual iodine–avid thyroid cancer, RAI also eliminates residual normal thyroid tissue, which facilitates surveillance by means of thyroglobulin detection. Use of iodinated contrast medium, an iodine-rich diet, and inadequate elevation of the level of TSH (thyrotropin) can all undermine the effectiveness of RAI treatment, and human recombinant thyrotropin has replaced the need for a patient to be put into a hypothyroid state.

Dosing strategies for RAI ablation are determined by the patient's prognostic risk, and they range from 30 to 75 mCi for ablation of remnants after total thyroidectomy for low-risk patients, to 100 to 150 mCi for the treatment of locoregional lymph nodes, to 150 to

250 mCi for the treatment of lung and bone metastases. Ablation of remnants enables improved surveillance because normal thyroid cells are also removed, which could cause false-positive results on whole-body iodine scans or false-positive elevations of serum thyroglobulin. In the absence of all normal thyroid tissue, the serum thyroglobulin is a highly sensitive and specific tumor marker for most patients. After total thyroidectomy and ablation of remnants, the serum TSH level generally should be suppressed to below normal levels with levothyroxine, because TSH is a potential growth factor for microscopic cancer deposits.

Six to 12 months after initial therapy, serum thyroglobulin should be measured while the patient is receiving suppressive doses of levothyroxine. If the serum thyroglobulin is undetectable and the findings of ultrasound imaging of the neck are negative, an annual analysis of thyroglobulin levels and physical examination are sufficient for most low-risk patients. With no detectable level of serum thyroglobulin during treatment with suppressive doses of levothyroxine at 1 year after surgery and ablation, the thyroglobulin level should be determined after two doses of recombinant human TSH. If the level increases to more than 2 ng/mL, a search for remaining disease is warranted. Diagnostic whole-body imaging with iodine scanning should be performed. If this is negative, recombinant human TSH-stimulated FDG-PET helps localize disease in more than 60% of such cases.

If metastases develop, RAI is the treatment of choice. Complete response to treatment has been observed for 45% of patients with distant metastases, although a higher complete response rate has been noted for younger patients and those with small pulmonary metastases. Patients with bulky metastatic disease and FDG-avid disease are less likely to respond to RAI because of dilution of the radiation dose in the former case and lower tumor uptake secondary to sodium/iodine symporter downregulation in the latter case.

Radioactive Iodine–Refractory Differentiated Thyroid Cancer

If DTC no longer takes up iodine on diagnostic scanning, or patients have received a maximum of 600 mCi of RAI, or patients develop recurrent DTC within a year of the last dose of RAI, such tumors are deemed RAI refractory (RAIR). Some thyroid tumors grow slowly, so a period of careful observation is reasonable before committing to treatment. Interest in targeted therapies has been stimulated by the discovery of activating point mutations of the *BRAF* gene that occur early, are associated with more advanced disease at diagnosis, and independently predict recurrence. Point mutations of the *BRAF* gene are found in 45% of PTCs. BRAF serine-threonine kinase can lead to activation of the mitogen-activated protein kinase signaling pathway. Three multitargeted TKIs—lenvatinib, cabozantinib, and sorafenib—have been approved by the FDA for the treatment of RAIR DTC independent of mutational status. It is important to note that the response rate to lenvatinib (approximately 60%) far exceeds that of sorafenib (approximately 10%). Cabozantinib is an FDA-approved agent as a second-line TKI, based on an 18% response rate and 11-month PFS in this setting.[93] Alternative TKIs that have demonstrated robust activity in phase 2 trials include pazopanib and axitinib.

With the advent of newly targeted therapeutic agents for a variety of solid tumors, genetic profiling should be considered for patients with RAIR PTC, poorly differentiated thyroid cancer (PDTC), and ATC. Such patients can harbor *BRAF* mutations (37%-50% of PTCs, 25%-45% of ATCs, and 90%-95% of mixed PTCs and ATCs), RET fusions (10%-20% of PTCs), NTRK fusions (5%-25% of PTCs), and anaplastic lymphoma kinase (ALK) fusions (9% of PDTCs, 4% of ATCs, and 1.6% of PTCs). When treatments with standard multikinase inhibitors are no longer options, patients with *BRAF* mutations may be amenable to treatment with dabrafenib with or without trametinib or vemurafenib. For *BRAF* V600E–mutant DTC, VEGF-targeting TKIs such as lenvatinib remain the first-line choice; although some of these patients respond to BRAF inhibition, the activity of the VEGF TKIs is superior. Larotrectinib and entrectinib are highly effective in tumors with NTRK fusions. Similarly, selpercatinib and pralsetinib have strong affinity for tumors driven by RET fusions. Thyroid cancers with ALK fusions have shown responses to crizotinib, ceritinib, and entrectinib, which are inhibitors of NTRK, reactive oxygen species, and ALK. Finally, cytotoxic chemotherapy has no role in the treatment of this disease.[94]

Lenvatinib

Lenvatinib inhibits VEGFR 1 to 3, fibroblast growth factor receptor 1 to 4, platelet-derived growth factor-A, RET, and KIT. It was approved by the FDA based on the positive results of the phase 3 SELECT trial.[94] In a 2:1 design, 261 patients were randomly assigned to lenvatinib 24 mg once per day, and 131 patients were randomly assigned to placebo. Patients receiving a placebo were allowed to receive lenvatinib upon disease progression. The median PFS was 18.3 months versus 3.6 months, favoring lenvatinib with an HR for progression or death of 0.21 (95% CI, 0.14-0.31; $P < .001$). The response rate to lenvatinib was 64.8%, with four complete responses and 165 partial responses. Treatment-related adverse effects (grade 3 or higher) occurred in 75.9% of patients receiving lenvatinib versus 9.9% receiving a placebo. The most common toxicities included hypertension (68%), diarrhea (59%), fatigue (59%), anorexia (50%), and weight loss (46%). Despite the FDA package insert dose of 24 mg once per day, most patients can tolerate only 20 mg or less per day, and lower doses have demonstrated efficacy.

ANAPLASTIC THYROID CANCER

ATC or giant cell variant thyroid cancer is associated with an extremely poor prognosis; the best available therapy produces a median survival of less than 1 year. Well-differentiated thyroid cancer precedes ATC or coexists with approximately 50% of ATC. Patients with ATC are older (generally in their 60s or 70s), and the distribution between the sexes is balanced. 20% to 50% of ATCs harbor activating *BRAF* V600 mutations.[95]

Distinguishing the tumor from a large-cell lymphoma of the thyroid is of fundamental importance. Clinically, ATC is characterized by a rapidly growing mass in the thyroid that invades the trachea or larynx and causes symptoms of dysphagia, hoarseness, or hemoptysis. Between 20% and 50% of patients have distant metastases at the time of presentation (most often pulmonary), and the remainder usually manifest metastases within 1 or 2 months of diagnosis. Most deaths are a result of aggressive locoregional spread and upper airway respiratory failure.

The treatment of choice is surgical resection if feasible, although these tumors are typically unresectable at presentation, and the patient often requires an urgent tracheostomy. Initial external beam RT, for definitive treatment and as an adjuvant (often with paclitaxel sensitization), is commonly used and considered the standard of care, but a durable response to RT alone is uncommon. Use of radiosensitizing chemotherapy is common, including paclitaxel, paclitaxel plus carboplatin, or doxorubicin. The use of doxorubicin in this setting has fallen out of favor because of severe CRT toxicity. Chemotherapy alone has limited efficacy, and RAI generally plays no role in the treatment of these tumors.

The combination of dabrafenib, a BRAF inhibitor, and trametinib, an MEK inhibitor, has been FDA approved for the treatment of *BRAF* V600E-mutated ATCs. In an open-label, phase 2 study, this combination produced a 69% response rate and estimated 12-month PFS and OS rates of 79% and 80%, respectively.[96] The most significant adverse effects included fatigue (38%), pyrexia (37%), and nausea (35%). A phase 2 trial of neoadjuvant pembrolizumab in combination with dabrafenib and trametinib for BRAF V600E-mutated anaplastic thyroid cancer showed substantial clinical benefit, with improved PFS and OS.[96-98]

MEDULLARY THYROID CANCER

MTC is a neoplasm of the calcitonin-producing cells that reside in the thyroid. It constitutes approximately 5% to 9% of all thyroid cancers and is associated with a mutation in the *RET* proto-oncogene. Both sporadic and familial types occur. The 10-year survival rate for patients with MTC ranges from 75% to 85%. Approximately half of patients with MTC present with disease localized to the thyroid gland, whereby total thyroidectomy often results in a complete cure. The 10-year survival rate for these patients is 95.6%. PET/CT imaging is useful for detecting nodal and distant metastases in this disease, but RAI scans are not useful.

The sporadic form is more common (75% of cases) and tends to occur in an older age group (age 40-45 years). The clinical presentation of the sporadic type of MTC is usually a painless thyroid mass; however, high calcitonin levels may result in a watery, secretory diarrhea as the primary symptom. The diagnosis is made based on a constellation of a thyroid mass, a high calcitonin level, and an FNA specimen that stains positive for calcitonin.

Three distinct familial syndromes account for the remaining 25% of cases. They tend to occur in a younger age group (age 15-25 years). The RET mutation is transmitted in the germline, and familial MTC may be part of multiple endocrine neoplasia type 2A (MTC, pheochromocytoma, and parathyroid hyperplasia) or type 2B (MTC, pheochromocytoma, and intestinal and mucosal ganglioneuromatosis with characteristic marfanoid habitus); it may also be a familial form of MTC not associated with multiple endocrine neoplasia. For the familial syndromes, a dominant inheritance pattern has been recognized, and family members of patients with newly diagnosed cases of the disease should be screened for *RET* mutations, because germline mutations are substantially higher than might be expected based on family history alone. Screening for pheochromocytoma (catecholamine excess) is important for excluding a familial syndrome, and all patients with germline mutations should be referred for a genetic counseling evaluation. Prophylactic total thyroidectomy will prevent MTC in young, at-risk family members (based on *RET* gene testing), even in the absence of clinically detectable thyroid abnormalities.

The treatment of choice for MTC is total thyroidectomy with bilateral central compartment node dissection and unilateral neck dissection (at the least). RT has disappointing efficacy for macroscopic disease, and postoperative RT is not routinely used.

After resection of all disease in the neck, patients should be monitored for two tumor markers: calcitonin and carcinoembryonic antigen levels. Patients whose calcitonin levels double within 6 months have a worse prognosis.

Local recurrences are usually treated surgically. Metastatic disease (commonly to the mediastinum, lung, bone, and liver) often follows an indolent course, and, in this case, observation is reasonable. MRI is required to monitor liver disease, because metastases may be small and not readily visualized with CT scans. Palliative surgery, including tumor debulking, or RT may be used as indicated for symptom control or to manage tumor encroachment on critical structures.

Vandetanib and cabozantinib are FDA-approved agents for the treatment of patients with locally advanced MTC that is not amenable to surgery or for those with metastatic disease. No data exist comparing these agents head-to-head; thus, the choice of which agent to use first may depend on expected adverse effects, and the indications for starting therapy will need to be individualized and balanced with toxicity profiles and quality-of-life outcomes.

Vandetanib is an oral inhibitor that targets VEGFR, RET, and EGFR. Vandetanib was an FDA-approved agent based on the positive results of a phase 3 placebo-controlled trial for patients with symptomatic or progressive unresectable, locally advanced, or metastatic MTC.[99] In the trial, 331 patients with advanced MTC were randomly assigned 1:1 to receive vandetanib 300 mg once per day versus placebo. The primary endpoint was PFS. There was a statistically significant improvement in PFS with vandetanib compared with placebo (HR, 0.46; 95% CI, 0.31-0.69; $P < .001$). The ORR, disease control rate, and biochemical response were also favorable with vandetanib. Common adverse effects of any grade included diarrhea (56%), rash (45%), nausea (33%),

hypertension (32%), and headache (26%). QT prolongation (14%), torsades de pointes, and sudden death are serious adverse effects that have resulted in a black box warning for this drug.

Cabozantinib is an oral TKI that targets MET, VEGFR2, and RET. Cabozantinib was approved for patients with progressive MTC based on the positive results of a phase 3, randomized, double-blind, placebo-controlled trial.[27] In the trial, 330 patients were enrolled and randomly assigned 2:1 to cabozantinib (140 mg/d) or placebo. The primary endpoint was PFS. Response rates were 28% for cabozantinib and 0% for placebo ($P < .001$). Common adverse effects of cabozantinib include diarrhea (63%), palmar-plantar erythrodysesthesia (50%), decreased weight (48%), appetite (46%), nausea (43%), and fatigue (41%), prompting dose reductions in 79% of patients. Patients assigned to cabozantinib therapy achieved a statistically significant improvement in PFS of 11.2 months compared with 4.0 months for the placebo arm ($P < .001$). This drug has black box warnings for serious adverse effects of gastrointestinal perforations (3%) and fistula formation (1%).

For patients who have MTC and whose tumors harbor *RET* mutations known to be sensitive to new, more selective RET inhibitors (selpercatinib, pralsetinib), these agents have displaced vandetanib and cabozantinib as first-line treatments.

Selpercatinib is an FDA-approved selective RET kinase inhibitor for *RET*-altered MTC and *RET* fusion–positive RAIR thyroid cancer in patients who have advanced or metastatic disease. In the LIBRETTO-001 phase 1/2 trial, 143 patients who had MTC (age 12 years or older) and advanced or metastatic disease who also harbored *RET* mutations were treated. Fifty-five of these patients had been previously treated with cabozantinib, vandetanib, or both. The ORR in the previously treated group was 69%, with 76% of these responses lasting for at least 6 months. The median duration of response was not reached. In the treatment-naive MTC group, the ORR was 73%, and 61% of these patients maintained their response for at least 6 months; the median duration of response was 22 months.[100] Common adverse effects with selpercatinib included increased aspartate transaminase (AST) and alanine transaminase (ALT) enzymes in the liver, increased blood sugars, and leukopenia.

Pralsetinib is a selective RET kinase inhibitor for *RET*-altered MTC and *RET* fusion–positive, RAIR thyroid cancer with advanced or metastatic disease. The multicohort, open-label, phase 1/2 ARROW trial included 55 patients with *RET*-mutant MTC previously treated with cabozantinib or vandetanib and had an ORR of 60%.[101] Almost 80% have had responses lasting for at least 6 months. Twenty-nine patients were treatment naive and achieved an ORR of 66%, 84% of whom had responses lasting for at least 6 months. The median duration of response had not yet been reached. Common adverse effects included constipation, hypertension, fatigue, musculoskeletal pain, and diarrhea. Common grades 3 and 4 laboratory abnormalities included lymphopenia, neutropenia, thrombocytopenia, anemia, hypocalcemia, and elevations in liver function tests (ie, AST, ALT, and alkaline phosphatase).

KEY POINTS

- For DTCs, poor prognostic features include age older than 45 years, male sex, poorly differentiated histology, a tumor size larger than 1.5 cm, and extrathyroidal extension at diagnosis. By contrast, involvement of the regional lymph nodes does not confer a worse prognosis for survival. Postoperative suppression of TSH with levothyroxine supplementation is done to decrease recurrence risk.
- RAI is the first-line treatment of metastatic RAI-sensitive disease. RAI generally has no role in the treatment of ATC or MTC.
- Lenvatinib, cabozantinib, and sorafenib are FDA-approved agents for the treatment of locally R/M progressive DTC that no longer responds to RAI treatment.
- All RAIR PTC, PDTC, MTC, and ATC tumors should undergo next-generation sequencing to evaluate for the presence of alterations (*BRAF*, *RET*, *ALK*, *NRTK*) that may be actionable to treatments with targeted therapies.
- Screening for germline *RET* gene mutation in patients who have MTC is recommended because total thyroidectomy, based on the results of genetic testing, often results in complete cures for young, at-risk family members.
- Vandetanib and cabozantinib are FDA-approved agents for the treatment of symptomatic or progressive locally advanced or metastatic MTCs, but, with the emergence of highly active RET inhibitors, use of these agents is now limited to patients without *RET* mutations.
- Selpercatinib is an FDA-approved treatment option for *RET*-altered advanced solid tumors, including MTC.
- The combination of dabrafenib and trametinib is approved for the treatment of *BRAF* V600E-mutated ATCs. Consideration of neoadjuvant TKIs and immunotherapy for patients who have ATC is emerging as a new standard based on multiple case series and a phase 2 trial, and some patients experience long-term survival with multimodality treatment.

MANAGEMENT OF DISEASE IN OLDER PATIENTS

Older patients present with age-specific problems such as multiorgan dysfunction, depression, alteration of mental status, reduced nutritional status, and limited social support, all of which can interfere with the diagnosis and treatment of cancer. A multidisciplinary team with both oncologic and nononcologic providers is needed to optimize a treatment strategy in older patients. Biologic age is more important than chronologic age and takes into account comorbid illnesses and performance status. In a large, single-institution study, 21% of patients with head and neck cancer had moderate to severe comorbidity, and there was a significant relationship between the severity of comorbidity and OS. A comprehensive geriatric assessment can be used to evaluate functional status, mental status,

medications, nutritional status, social support, and comorbid illnesses to provide physicians with a better sense of a patient's life expectancy and tolerance to different treatment modalities when making therapeutic decisions.

Surgery remains an appropriate option for the management of head and neck cancer in older patients, once a full risk assessment is completed and medical optimization is initiated. Postsurgical mortality is associated with older age, severity of comorbid illnesses, and length of the operation.

RT is a potentially curative option for patients diagnosed with early-stage disease or those with nonmetastatic disease who are deemed ineligible for surgical resection. RT can be safely administered in an older population, and most patients can complete their planned treatment. No data demonstrate poorer tolerance or the need to reduce radiation dose because of age.

Based on previous data, patients aged 70 years or older derive little or no incremental survival benefit from adding chemotherapy to RT; however, the use of CRT for patients aged 65 years or older has steadily increased recently. This trend has further increased with the use of cetuximab with RT. However, the OS benefit in an older patient population is not clear.[41] The use of aggressive CRT regimens should still be administered if patients are potential candidates. In some patients, the benefit of CRT may be offset by acute, often severe, treatment-related toxicities. Older patients often have limitations in performance status because they have multiple comorbidities and a lack of physiologic fitness, which makes them more susceptible to the toxic effects of chemotherapy, because of potential delayed clearance from renal or hepatic impairment, decreased bone marrow reserve, malnutrition, and cognitive impairment.

KEY POINTS

- Older patients can safely be treated with RT-based therapy for head and neck cancer, but require additional attention for management of comorbid illnesses.
- Measures of biologic rather than chronologic age are relevant when determining appropriate treatment of patients with locally advanced head and neck cancer.

SURVIVORSHIP

Studies involving survivors of head and neck cancer have mainly focused on social supports, tobacco and alcohol use, the risk for second primary cancers, functional status, and depression, and how these factors influence quality of life. Chronic pain, xerostomia, lymphedema, impairments of speech and swallowing, alterations of taste and smell, and poor cosmesis are some of the long-term sequelae associated with the treatment of head and neck cancer. These variable, long-term toxicities can have a profound psychosocial effect on cancer survivors and their families. Suicide rates for patients with head and neck cancer, including survivors, are three times higher than those of the general population. Advances in reconstructive techniques and organ preservation strategies are having a positive effect on quality of life relative to the functional and cosmetic consequences of the radical local therapies of the past. Nevertheless, quality-of-life and survivorship issues must continue to be a focus of future research.

KEY POINT

- Survivors of head and neck cancer can experience issues with swallowing, breathing, pain, and neck mobility that require ongoing management.

HIGH-YIELD TAKEAWAYS

- Smoking and alcohol exposure remain the commonest etiology for HNSCC, although HPV-related OPCs are on the rise.
- The majority of the patients with HNSCC are diagnosed with locally advanced disease, where multimodality therapy incorporating surgery, radiation, and chemotherapy is the standard of care.
- Definitive chemoradiation is the curative treatment of choice when a critical organ is at risk, for example, the base of the tongue and larynx. Cisplatin is the radiosensitizer of choice for eligible patients and was superior to cetuximab in multiple phase 3 clinical trials.
- Perioperative immunotherapy is an FDA-approved treatment option for resectable head and neck cancer that expresses PD-L1.
- For patients with recurrent or metastatic HNSCC, either pembrolizumab monotherapy or platinum, 5-FU, and pembrolizumab is the first-line treatment of choice.
- For patients with R/M nasopharyngeal cancers, toripalimab, in addition to platinum and gemcitabine, was recently approved by the FDA for first-line treatment based on improvement in PFS and OS.

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

HEAD AND NECK CANCERS 12

CHAPTER SUMMARY GUIDE

KEY POINTS

- Tobacco and alcohol use are the major risk factors for non-viral-associated HNSCC, and the use of both results in a multiplicative increase in risk.
- There is a causal association between high-risk oncogenic HPV and cancers of the oropharynx (tonsil, base of the tongue, soft palate) and a causal association between EBV and NPCs, but, in most humans, neither HPV nor EBV exposure results in the development of cancer.
- The prognosis is substantially better for HPV-related OPCs and EBV-related NPCs than for HPV-negative and EBV-negative cancers, respectively, at these sites.
- The incidence of second primary cancers for patients with a history of non-viral-associated HNSCC is 3% to 7% annually; common sites include the head and neck, lung, and esophagus. This high rate of second primaries seems related to a field cancerization effect of tobacco, alcohol, and other toxins.
- The earliest genetic alteration during the transition from normal mucosa to hyperplastic mucosa is the loss of genetic material containing tumor suppressor genes, known as a loss of heterozygosity or allelic imbalance.
- Erythroplakia and leukoplakia lesions are premalignant lesions that can be associated with severe dysplasia, carcinoma in situ, or invasive SCCs.
- Many presenting signs and symptoms are associated with a particular primary site (eg, hoarseness may refer to the larynx or hypopharynx, and a unilateral otitis media may refer to the nasopharynx).
- The location of pathologic lymph nodes in the neck may suggest the primary site.
- The initial evaluation for head and neck cancer includes a comprehensive examination of the head and neck, including endoscopic examination; imaging of the primary site, neck, and chest; and routine laboratory screenings.
- Early-stage disease is primarily defined as disease limited to a small primary tumor (T1 or T2) with low-risk (N1, one node smaller than 3 cm with no high-risk features) nodal involvement. Locally or locoregionally advanced disease is generally defined as the presence of a large primary tumor (T3 or T4) or the presence of large, multiple, or contralateral regional node involvement (N2 or N3).
- Criteria for unresectable disease include base-of-skull involvement, fixation to the prevertebral fascia, carotid encasement, and involvement of the pterygoid musculature.
- M1 disease is typically not curable and is approached with systemic therapy, although some patients with oligometastatic disease can have long-term remissions using combined modality treatment.
- Single-modality treatment with surgery or RT is typically used with curative intent for previously untreated p16-negative stage I, II, or low-bulk III (T1-2, N0, N1: single node smaller than 3 cm) disease or p16-positive stage I (T1-2, N0-1) disease with a single ipsilateral node measuring less than 3 cm in diameter and without clinical or radiographic evidence of ENE.
- Combined modality treatment of surgery and RT or CRT is used with curative intent for previously untreated, higher-volume, p16-negative stage III (T3, N0-1) and stage IVA/B disease or p16-positive stages I (multiple nodes or single node larger than 3 cm), II, and III disease.
- Neoadjuvant and adjuvant pembrolizumab, in addition to risk-stratified standard adjuvant therapy, is associated with improvement in EFS in patients with locally advanced PD-L1-positive (CPS $\geq$1) HNSCC, where surgery is the initial therapy.
- Metastatic disease below the clavicle and locoregional recurrent disease without a surgical or RT option are generally incurable and are treated with palliative intent. However, there are some patients with oligometastatic disease who are highly sensitive to systemic therapy and for whom curative paradigms of treatment should be considered.
- Function-conserving procedures are applicable for select patients in whom negative margins can be achieved with preservation of structures important for function.
- Debulking surgery is not part of routine clinical practice for head and neck cancer.
- Comprehensive neck dissections involve the removal of all five lymph node levels and are usually performed with therapeutic intent. Selective neck dissections involving the removal of fewer than all five levels are generally done electively to improve staging precision.

- Head and neck RT commonly causes acute toxicities, including mucositis, edema, dermatitis, dysgeusia, and xerostomia. Other potential toxicities include osteoradionecrosis of the mandible.
- IMRT delivers radiation around the tumor and high-risk lymph nodes conformally. It is associated with less dry mouth after treatment than that seen with conventionally planned RT.
- For patients with unresectable HNSCC, CRT with concurrent cisplatin improves survival compared with RT alone and is the standard of care.
- The optimal dosing regimen (40 mg/m^2 once per week or 100 mg/m^2 once every 21 days) for concurrent cisplatin remains to be defined. A cumulative dose of 200 mg/m^2 should be prioritized.
- In locally advanced laryngeal cancer (T2 to low-volume T4), LRC and larynx preservation are substantially improved with concomitant cisplatin and RT compared with induction chemotherapy followed by RT or RT alone.
- Cetuximab added to RT improves survival compared with RT alone in locally advanced head and neck cancer, but it is inferior to cisplatin with RT.
- Docetaxel combined with RT in patients who are not candidates for treatment with cisplatin is superior to RT alone in patients with locoregionally advanced disease.[57]
- CRT with cisplatin is the standard of care for postoperative adjuvant treatment of patients with positive resection margins and/or ENE of disease, with an emerging role for immunotherapy.
- The role of induction chemotherapy before CRT has yet to be defined. Several clinical trials have failed to demonstrate an advantage to induction other than for NPC (discussed below).
- No definitive data demonstrate that induction chemotherapy followed by CRT leads to better survival compared with CRT alone.
- Induction chemotherapy with TPF is considered the standard induction regimen when induction is recommended because it has been shown to improve both OS and LRC compared with PF.
- For patients with unresectable locally advanced HNSCC, CRT with cisplatin significantly improves survival compared with RT alone and is the standard of care.
- In locally advanced laryngeal cancer, LRC and larynx preservation are best achieved with concomitant cisplatin and RT, although induction chemotherapy followed by RT is a reasonable alternative because long-term data show no difference in laryngectomy-free survival for either treatment paradigm.
- Cetuximab added to RT improves survival compared with RT alone in locally advanced head and neck cancer, as does docetaxel in platinum-ineligible patients, but neither should replace CRT with cisplatin therapy as the standard of care in patients who are candidates for it.
- CRT with cisplatin is the standard of care for postoperative adjuvant treatment of patients with positive resection margins and/or extracapsular extension of nodal disease.
- The standard of care (according to stage) is RT alone for limited stage (typically T1-2 N0M0).
- Concurrent cisplatin-based CRT with or without adjuvant PF for intermediate-risk locoregional disease, and sequential CRT including induction GC or TPF, concurrent CRT, and adjuvant capecitabine for patients with the highest-risk locoregionally advanced disease remain the standards of care.
- NPC is a very chemotherapy-sensitive disease. Patients with metastatic disease often experience prolonged benefit from systemic chemotherapy. GC and ICI are the widely accepted first-line treatments of R/M disease, but other platinum-based chemotherapies combined with immunotherapy are also acceptable systemic treatment options.
- For patients with oligometastatic disease, a potentially curative treatment paradigm that includes systemic chemotherapy and local definitive treatment of the head and neck and oligometastatic sites is associated with some long-term survival.
- All treatment paradigms for NPC are largely based on data from EBV-associated NPC.
- The search for the primary site should include FDG-PET/CT imaging and an examination under anesthesia with directed biopsies of the base of the tongue, nasopharynx, and hypopharynx, and bilateral, simple tonsillectomies.
- After an FNA biopsy of the lymph node, HPV and EBV testing should be performed. If the tumors are positive, they should be treated as oropharyngeal or primary nasopharyngeal, respectively.
- Standard treatment consists of neck dissection followed by RT to include the likely primary sites, and concurrent cisplatin is added if extracapsular extension of nodal disease is present.
- In selected patients, CRT is another primary treatment option.
- Pembrolizumab (if PD-L1 CPS is 1 or higher and preferably 20 or higher) and pembrolizumab combined with platinum and 5-FU or platinum plus taxane are now considered the first-line standard of care for R/M HNSCC. For patients with PD-L1 CPS lower than 1, PF or TP with either cetuximab or pembrolizumab is used.
- Cetuximab combined with PF or TP (or cetuximab with carboplatin and paclitaxel) should be considered in the R/M setting when patients are not candidates for immunotherapy.

- Nivolumab and pembrolizumab are indicated as the second-line therapy for patients in whom platinum-based chemotherapy failed in the R/M setting.
- Taxanes, capecitabine, cetuximab, and methotrexate may be useful as single agents in patients with R/M HNSCC who have not had previous exposure to these agents, but, in general, response rates are low, and the duration of responses is limited.
- Surgery is the mainstay treatment of salivary gland tumors, followed by RT for those tumors with high-risk features; pleomorphic adenomas should be surgically resected because of their potential for malignant transformation.
- Metastatic ACC and selected other salivary gland cancers are often characterized by an indolent natural history and have no known effective treatments; therefore, they are often followed without systemic treatment.
- For most slow-growing salivary gland cancers, systemic treatment should be delayed until substantial tumor growth can be appreciated on serial imaging studies within 6 months or if the disease is located such that symptom development is imminent (eg, bronchial obstruction). Comprehensive testing, including next-generation sequencing to evaluate for actionable molecular targets and appropriate immunotherapy biomarkers, should be performed for patients with metastatic disease.
- Salivary ductal tumors are histologically similar to breast cancer and can overexpress androgen receptors and HER2. Such tumors are often treated effectively with antiandrogen blockade or HER2-targeted cytotoxic conjugate therapies. Chemotherapy can also be an effective option.
- Secretory carcinomas, formerly known as MASCs, are characterized by the presence of ETV6-NTRK3 fusion proteins; larotrectinib or entrectinib is the treatment of choice for secretory carcinomas that are metastatic or for tumors for which surgery is likely to result in severe morbidity.
- For DTCs, poor prognostic features include age older than 45 years, male sex, poorly differentiated histology, a tumor size larger than 1.5 cm, and extrathyroidal extension at diagnosis. By contrast, involvement of the regional lymph nodes does not confer a worse prognosis for survival. Postoperative suppression of TSH with levothyroxine supplementation is done to decrease recurrence risk.
- RAI is the first-line treatment of metastatic RAI-sensitive disease. RAI generally has no role in the treatment of ATC or MTC.
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- Vandetanib and cabozantinib are FDA-approved agents for the treatment of symptomatic or progressive locally advanced or metastatic MTCs, but, with the emergence of highly active RET inhibitors, use of these agents is now limited to patients without *RET* mutations.
- Selpercatinib is an FDA-approved treatment option for *RET*-altered advanced solid tumors, including MTC.
- The combination of dabrafenib and trametinib is approved for the treatment of *BRAF* V600E-mutated ATCs. Consideration of neoadjuvant TKIs and immunotherapy for patients who have ATC is emerging as a new standard based on multiple case series and a phase 2 trial, and some patients experience long-term survival with multimodality treatment.
- Older patients can safely be treated with RT-based therapy for head and neck cancer, but require additional attention for management of comorbid illnesses.
- Measures of biologic rather than chronologic age are relevant when determining appropriate treatment of patients with locally advanced head and neck cancer.
- Survivors of head and neck cancer can experience issues with swallowing, breathing, pain, and neck mobility that require ongoing management.

CHAPTER TABLES AND IMAGES

Table 12-1 **Head and Neck Cancer: Primary Sites**	
Anatomic Area	**Primary Cancer Site**
Oral cavity and lip	Floor of mouth
	Oral tongue
	Buccal mucosa
	Alveolar ridges
	Hard palate
	Retromolar trigone
Pharynx	Nasopharynx (includes the superior surface of the soft palate)
	Oropharynx (includes the inferior surface of the soft palate, uvula, base of the tongue, tonsil, posterior pharyngeal wall)
	Hypopharynx (pyriform sinus, postcricoid, posterior wall)
Larynx	Supraglottic larynx (false cords, arytenoids, epiglottis)
	Glottic larynx (includes commissures)
	Subglottic larynx
Nasal cavity and paranasal sinuses	Nasal cavity
	Maxillary sinuses
	Ethmoid sinuses
	Frontal sinuses
	Sphenoid sinuses

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Table 12-2 **WHO Classification Criteria of Nasopharyngeal Carcinoma**

WHO Classification	Former Terminology
Type I: Keratinizing squamous cell carcinoma	Squamous cell carcinoma
Type II: Nonkeratinizing carcinoma Without lymphoid stroma With lymphoid stroma	Transitional cell carcinoma Intermediate cell carcinoma Lymphoepithelial carcinoma (Regaud)
Type III: Undifferentiated carcinoma Without lymphoid stroma With lymphoid stroma	Anaplastic carcinoma Clear-cell carcinoma Lymphoepithelial carcinoma (Schminke)

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Table 12-3 **Lymph Nodal Drainage in Head and Neck Cancers**	
Primary Cancer	**Lymph Nodes**
Oral cavity	Submental and submandibular areas (level I), upper and midneck (levels II and III) after level I
Oropharyngeal	Upper and midneck (levels II and III)
Laryngeal (except glottis)	Upper and midneck (levels II and III)
Nasopharyngeal	Upper neck and posterior triangle (levels II and V)
Primary lesion below the clavicle or in the thyroid	Disease confined to the lower part of the neck or supraclavicular area (levels IV and V)
Glottic larynx	Spread to the neck is uncommon
Paranasal sinuses	Spread to the neck is uncommon

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Table 12-4 **Induction Chemotherapy Clinical Trials Followed by Definitive Radiation for Patients With HNSCC**

Study	No. of Patients	Population	Study Arm	Primary Outcome	Secondary Outcome
GORTEC9 2000-01	213	Larynx and hypopharynx (requiring laryngectomy) for organ preservation	IC with TPF vs IC with PF followed by definitive radiation	3-year laryngeal preservation: 70.3% vs 57.5% (*P* = .03)	Overall response rate: 80% vs 59.2% (*P* = .002)
TAX 32310	358	Unresectable oropharynx, hypopharynx, oral cavity, and larynx	IC with TPF vs IC with PF, both followed by definitive radiation	Median PFS, 11 months vs 8.2 months; median OS, 18.8 months	CRR: 33% vs 19.9% (*P* = .004)
TAX 32411	501	Oropharynx, larynx, hypopharynx, and oral cavity for organ preservation (T3-T4, N2-N3 disease only)	IC with TPF vs IC with PF, both followed by weekly carboplatin (AUC 1.5) with radiation	5-year OS: 52% vs 42% (*P* = .014)	Median PFS: 38.1 months vs 13.2 months (HR, 0.75; 95% CI, 0.60-0.94)

Abbreviations: AUC, area under the curve; CRR, complete response rate; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; IC, induction chemotherapy; OS, overall survival; PF, cisplatin, fluorouracil; PFS, progression-free survival; TPF, docetaxel, cisplatin, fluorouracil.
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Table 12-5 **Sequential Therapy Clinical Trials for Patients With HNSCC**

Study	No. of Patients	Population	Study Arm	Primary Outcome	Secondary Outcome	Grades 3 to 4 Toxicity (%)
PARADIGM[28]	145 (study terminated early owing to poor accrual)	Unresectable or T3-T4 or N2-N3 (except for T1, N2), or candidates for organ preservation	IC with TPF for three cycles: response evaluation; NR: weekly docetaxel with RT; PR: weekly carboplatin with RT vs high-dose cisplatin every 3 weeks with RT	3-year OS: 73% vs 78% (HR, 1.09; *P* = .77)	Febrile neutropenia in the IC followed by chemoradiation (16 patients) compared with the chemoradiation arm	Mucositis IC: 47 CRT: 16 Febrile neutropenia IC: 23 CRT: 1 PEG tube placement IC: 79 CRT: 85
DeCIDE[33]	280 (planned: 400)	N2-N3 disease	Docetaxel/FU/hydroxyurea and radiation vs TPF three cycles followed by docetaxel/FU/hydroxyurea and radiation	3-year OS 75% vs 73% (*P* = NS)	3-year distant failure: 10% vs 19% (*P* = .025)	Mucositis IC: 9 CRT: 47 Neutropenia IC: 11 CRT: 2 PEG tube placement IC: 79
Hitt et al[30]	439	Unresectable; primary sites: oropharynx, oral cavity, larynx, hypopharynx; greater than measurable lesion	IC with TPF or PF three cycles followed by high-dose cisplatin every 3 weeks with radiation vs high-dose cisplatin every 3 weeks with radiation	Median PFS: 14.6 months/14.4 months vs 13.8 months (*P* = .56) TTF 7.9 months/7.9 months vs 8.2 months (*P* = .90)	No statistically significant differences for OS	Stomatitis IC: 44 CRT: 37 Febrile neutropenia IC: 10 CRT: 1

Abbreviations: CR, complete response; CRR, complete response rate; CRT, concomitant chemoradiation; FU, fluorouracil; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; IC, induction chemotherapy; NR, nonresponse; NS, not significant; OS, overall survival; PEG, percutaneous endoscopic gastrostomy; PF, cisplatin, fluorouracil; PFS, progression-free survival; PR, partial response; RT, radiation therapy; TPF, docetaxel, cisplatin, fluorouracil; TTF, time to treatment failure.

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Table 12-6 **Summary of Clinical Studies for Patients With Locally Advanced Nasopharyngeal Cancer**

Study (Location)	No. of Patients	AJCC Stage (Year)	Study Arm	Median Follow-Up (Months)	Primary Outcome	Secondary Outcome	Grades 3 to 4 Toxicity (%)
Al-Sarraf et al[68] (United States)	147	III to IV (1992)	Cisplatin (100 mg/m^2) every 3 weeks with radiation and adjuvant chemotherapy, cisplatin (80 mg/m^2) and FU (1,000 mg/m^2) for three cycles vs radiation alone	60	OS: 67% vs 37% (P = .001)	PFS 58% vs 29% (P = .001)	RT alone: Stomatitis: 28 Leukopenia: 1 Nausea/vomiting: 10 CRT: Stomatitis: 37 Leukopenia: 36 Nausea/vomiting: 31
Chan et al[69] (Hong Kong)	350	Ho's N2-N3 or node larger than 4 cm	Weekly cisplatin (40 mg/m^2) with radiation vs radiation alone (no adjuvant chemotherapy)	66	OS: 90% vs 80% (P = .049)	PFS 60% vs 52% (P = .16)	RT alone: Stomatitis: 36 Leukopenia: 0 Nausea/vomiting: 0 CRT: Stomatitis: 49 Leukopenia: 13 Nausea/vomiting: 12
Zhang et al[66]	480		Compared gemcitabine and cisplatin as induction chemotherapy and concurrent chemoradiotherapy with concurrent chemoradiotherapy alone	42.7	OS: 94.6% vs 90.3%		RT alone: Stomatitis: 76 Leukopenia: 132 Nausea/vomiting: 66 CRT: Stomatitis: 69 Leukopenia: 63 Nausea/vomiting: 109

Abbreviations: AJCC, American Joint Committee on Cancer; CRT, concomitant chemoradiation; DFS, disease-free survival; FU, fluorouracil; OS, overall survival; PFS, progression-free survival; RT, radiation therapy.

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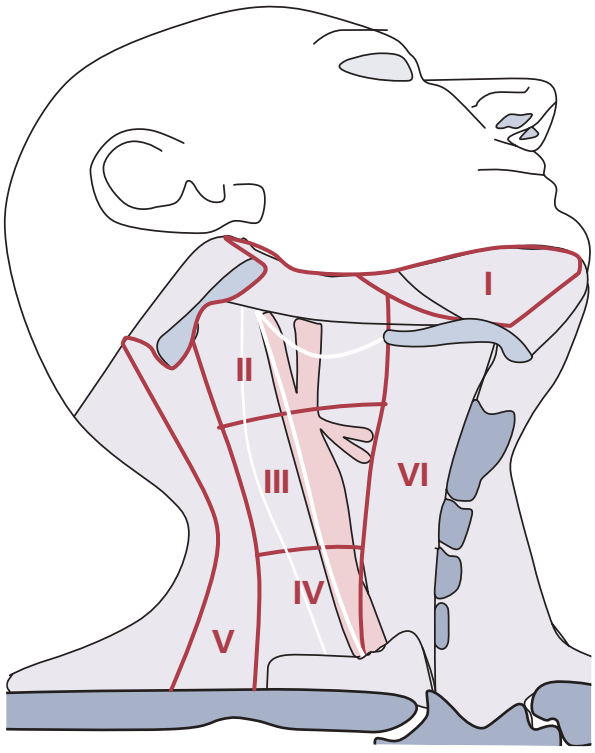
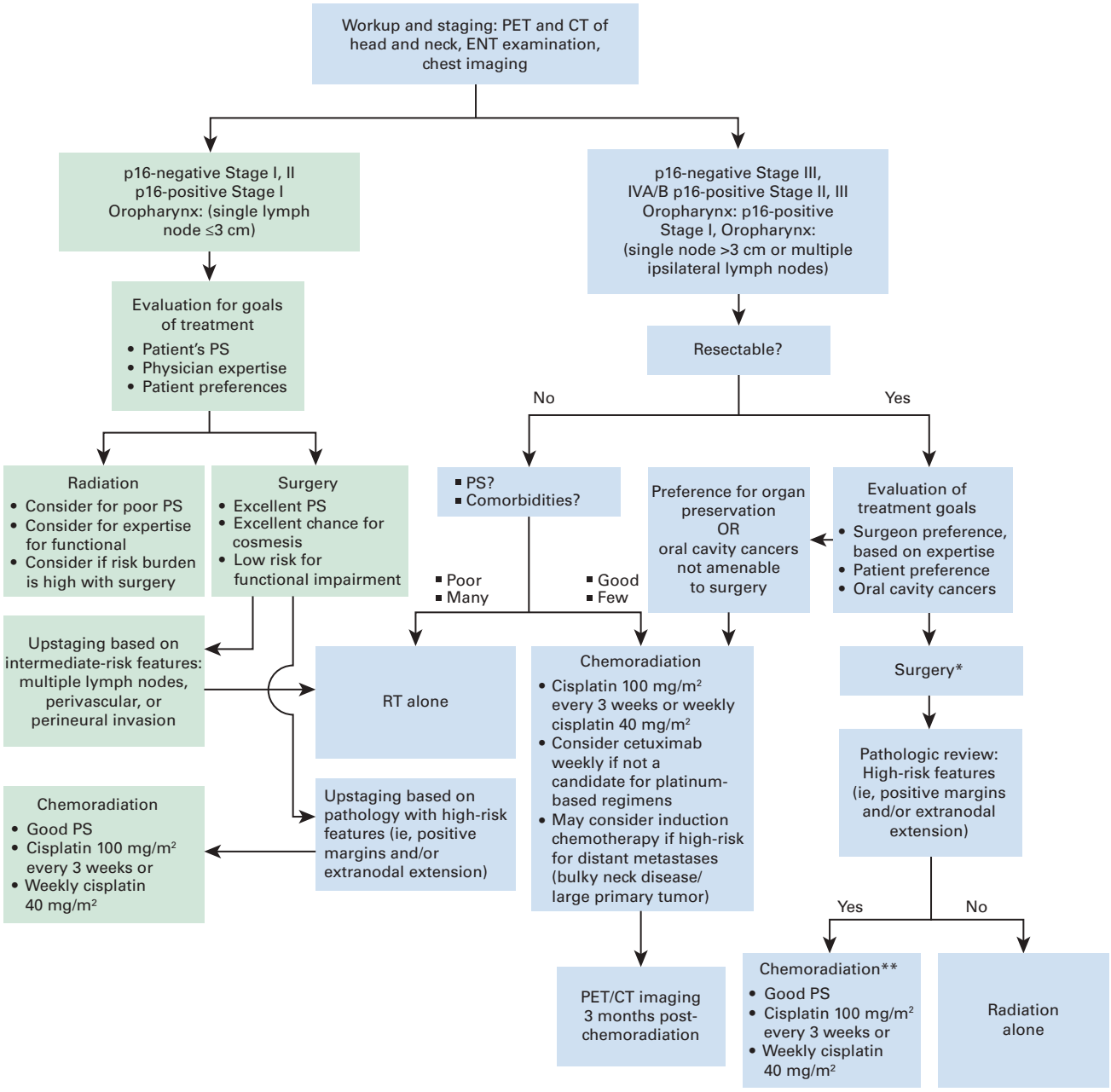
Figure 12-1 Cervical Lymph Node Levels



Reproduced under Creative Commons license. Source: Moergel M, Jahn-Eimermacher A, Krummenauer F, et al. Effectiveness of adjuvant radiotherapy in patients with oropharyngeal and floor of mouth squamous cell carcinoma and concomitant histologic verification of singular ipsilateral cervical lymph node metastasis (pN1-state)-a prospective multicenter randomized controlled clinical trial using a comprehensive cohort design. *Trials*. 2009;10:118. doi: 10.1186/1745-6215-10-118

Figure 12-2 Treatment Algorithm for Localized and Locally Advanced HNSCC



Abbreviations: CPS, combined positive score; ENT, ear, nose, and throat; HNSCC, head and neck squamous cell carcinoma; PS, performance status; RT, radiation therapy.
*If PD-L1 CPS ≥1, consider perioperative pembrolizumab.
**If no neoadjuvant immunotherapy, consider adjuvant nivolumab.
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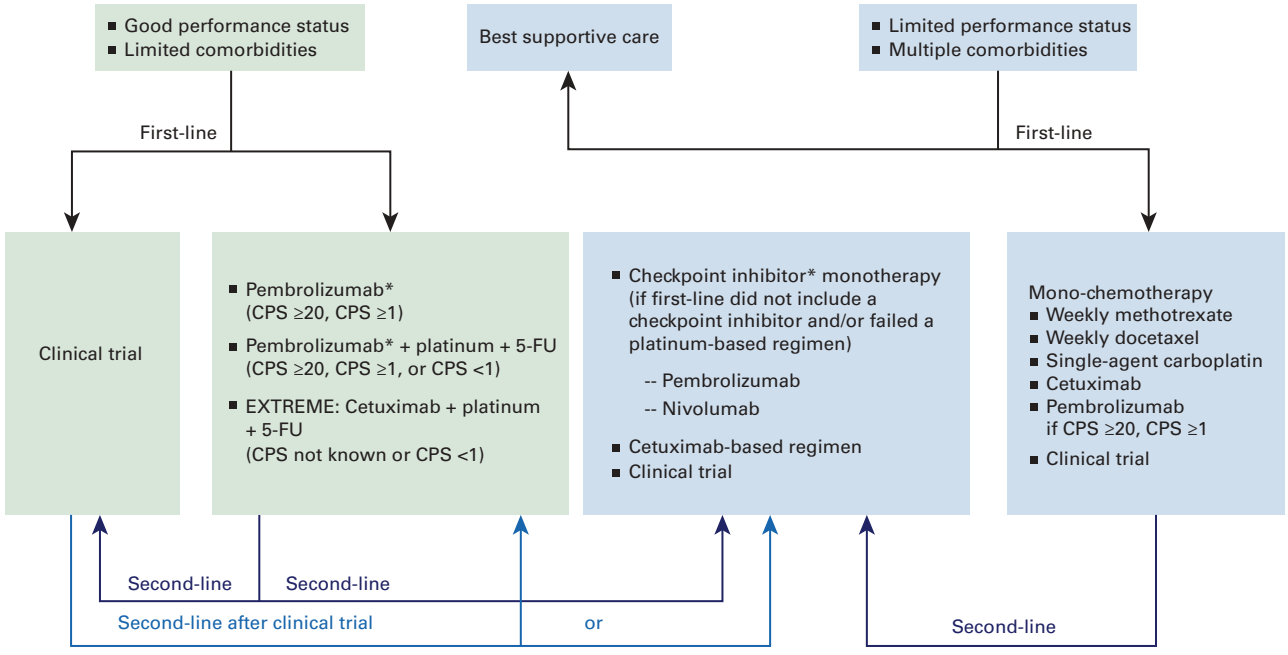
Figure 12-3 Treatment Algorithm for Metastatic HNSCC



Abbreviations: 5-FU, fluorouracil; CPS, combined positive score; HNSCC, head and neck squamous cell carcinoma.
*For second-line, do not use a checkpoint inhibitor if given as 1st line under clinical trial.
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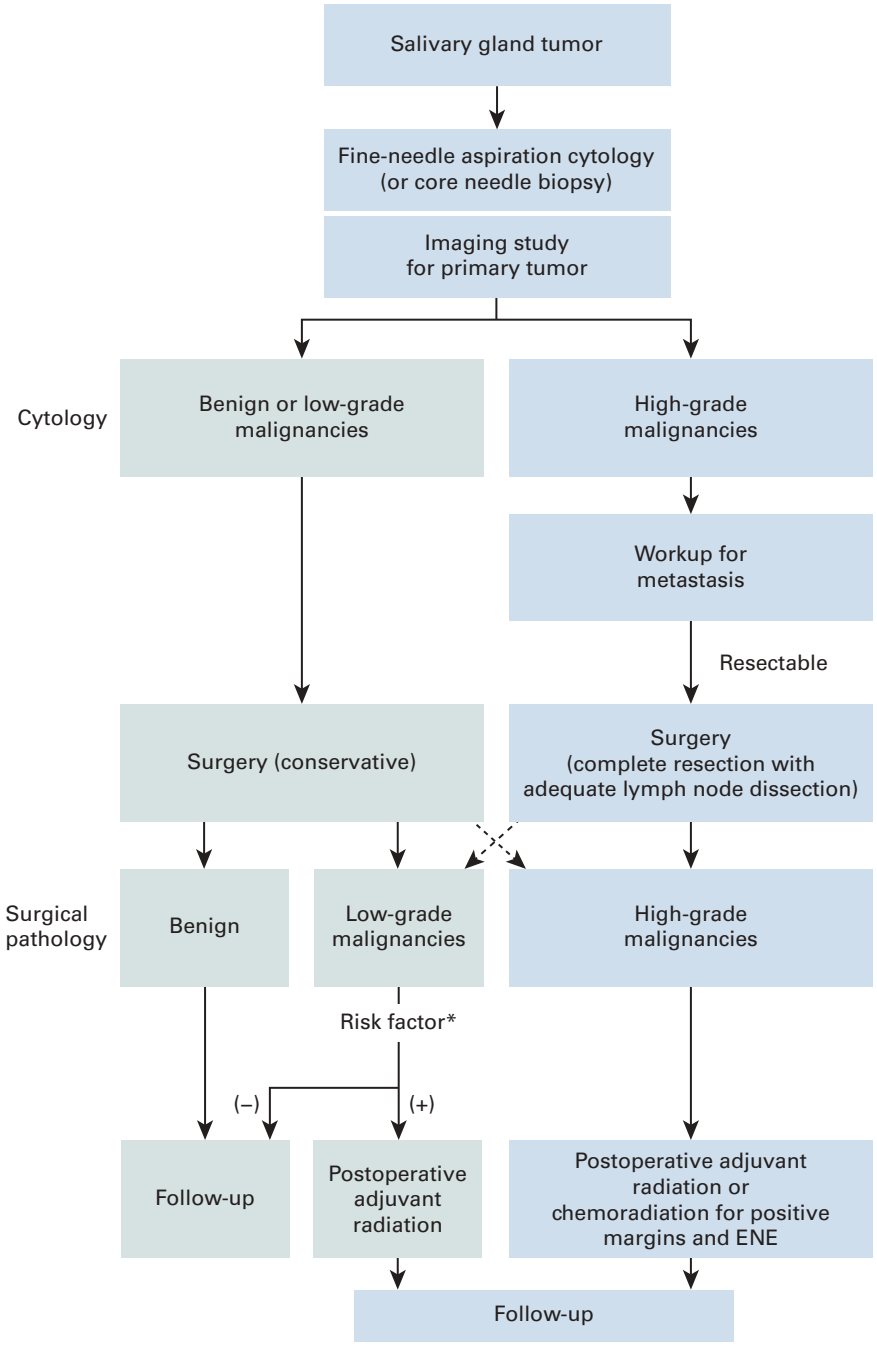
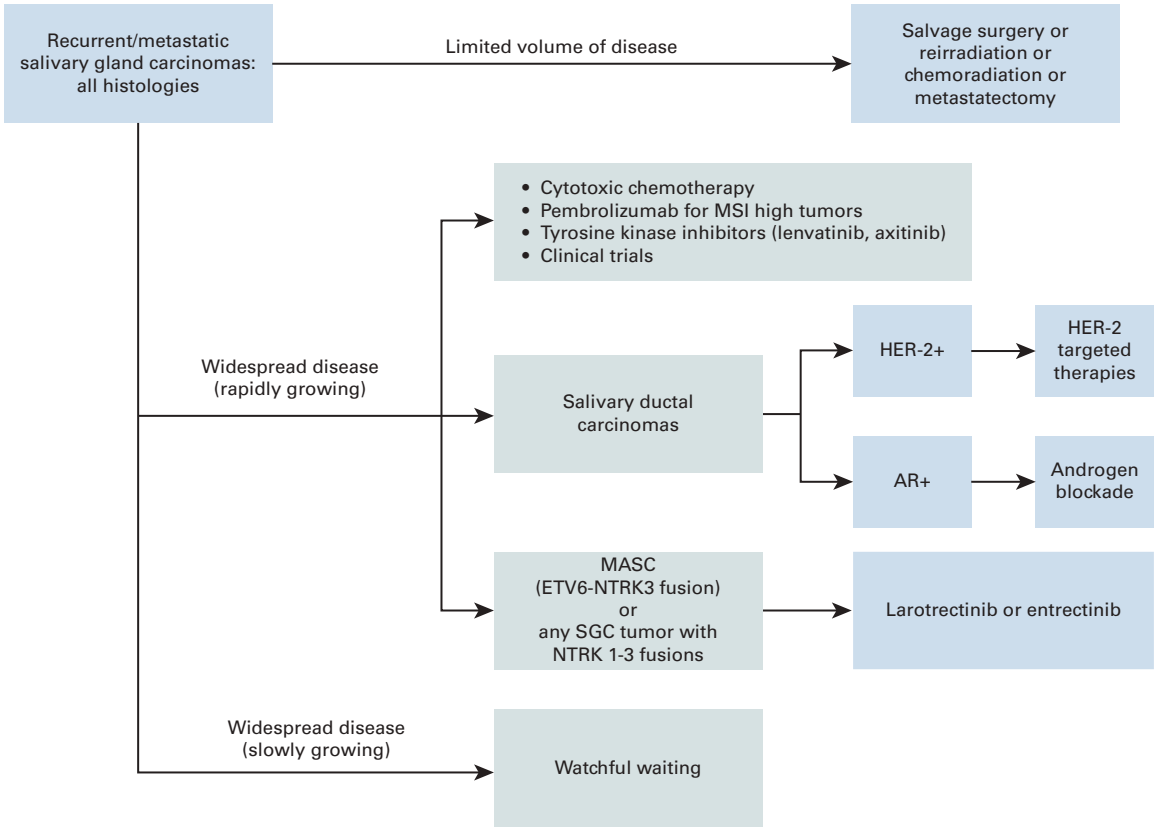
Figure 12-4 Treatment Algorithm of Local and Locally Advanced Salivary Gland Tumors



Abbreviation: ENE, extranodal extension.
*Multiple lymph nodes, perineural spread.
Reproduced under Creative Commons license. Source: Jang JY, Choi N, Ko Y, et al. Treatment outcomes in metastatic and localized high-grade salivary gland cancer: high chance of cure with surgery and postoperative radiation in T1-2 N0 high-grade salivary gland cancer. *BMC Cancer*. 2018;18:672. doi: 10.1186/s12885-018-4578-0

Figure 12-5 Management of R/M Salivary Gland Tumors



Abbreviations: AR, androgen receptor; MASC, mammary analog secretory carcinoma; MSI, microsatellite instability; R/M, recurrent/metastatic; SGC, salivary gland carcinoma.

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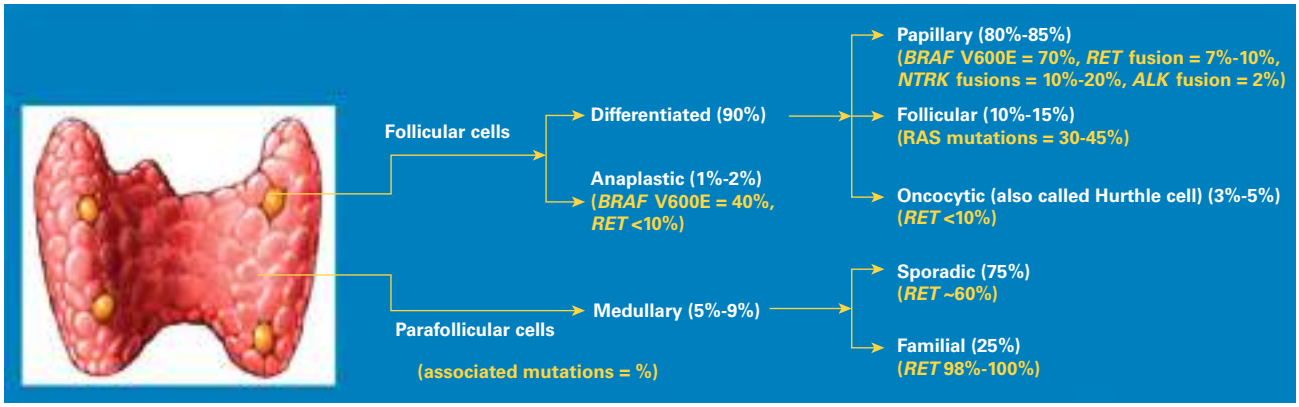
Figure 12-6 Classification of Thyroid Cancers



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UPPER GASTROINTESTINAL CANCERS 13.1

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RECENT UPDATES

Esophageal Squamous Cell Carcinoma

- RATIONALE 306[1] was a global trial randomizing unresectable, locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) regardless of PD-L1 expression to receive tislelizumab or placebo in combination with a chemotherapy doublet of investigator's choice in the first-line setting. In patients with PD-L1 expression of 1 or higher, the median overall survival (OS) in the tislelizumab arm was 16.8 versus 9.6 months in the chemotherapy alone arm (hazard ratio [HR], 0.66, 95% CI 0.53-0.82). The US FDA-approved tislelizumab plus platinum-containing chemotherapy for the frontline treatment of adult patients with unresectable or metastatic ESCC with a tumor PD-L1 expression of 1 or higher on March 4, 2025.
- RATIONALE 302 was a global phase 3 study that compared tislelizumab with investigator's choice of chemotherapy as second-line treatment of patients with unresectable, locally advanced, or metastatic ESCC. The primary endpoint of OS was significantly improved in the tislelizumab arm; OS was 8.6 months (95% CI, 7.5-10.4) versus 6.3 months (95% CI, 5.3-7.0) in the chemotherapy arm (HR, 0.70; 95% CI, 0.57-0.85; $P = .0001$). However, given that current standard treatments include immune anti-PD1/anti-CTLA-4 agents in the first-line setting, the FDA approval of this agent for immunotherapy-naive ESCC (granted on March 14, 2024) will likely have limited impact on clinical practice.[2]

Esophagogastric Adenocarcinoma

- The approaches to treating patients with high-risk resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma (cT1 cN+, cT2–4a cN+, or cT2–4a cN0 disease) who are candidates for surgery has changed significantly over the last few years which now include neoadjuvant chemoradiation per the CROSS trial versus perioperative systemic treatment (FLOT plus durvalumab). This is supported by positive results from the ESOPEC and MATTERHORN trials.[3]
- Perioperative FLOT is a standard approach for patients with resectable gastric or GEJ adenocarcinomas who are candidates for surgery based on the positive results from the FLOT4-AIO study. The MATTERHORN trial,[4] reported in 2025, extended that approach by defining the role of immune checkpoint inhibitor. This phase 3 multinational trial randomized resectable gastric or GEJ adenocarcinoma to receive perioperative durvalumab plus FLOT followed by durvalumab for additional 10 cycles versus placebo plus FLOT. The 2-year OS was 75.7% in the durvalumab group versus 70.4% in the placebo group (HR, 0.67 for month 12 onwards; $P < .0001$).
- NCCN guidelines on esophageal and esophagogastric junction cancers list durvalumab plus FLOT as category 1 recommendation for the treatment of resectable GEJ and gastric adenocarcinoma. Although not included in the MATTERHORN trial, the NCCN guideline lists durvalumab plus FLOT as category 2A recommendation for resectable esophageal adenocarcinoma with PD-L1 combined positive score (CPS) ≥1 or tumor area positivity (TAP) ≥1.
- In patients with resected esophageal or GEJ adenocarcinoma who received neoadjuvant chemoradiation, 12 months of adjuvant nivolumab are recommended for those who have residual pathologic disease at the time of resection per CheckMate 577.[5] With a median follow-up of 78.3 months,[6] adjuvant nivolumab achieved superior disease-free survival (DFS) versus placebo (HR, 0.76; 95% CI, 0.63-0.91), and median OS was numerically longer with nivolumab versus placebo (51.7 vs 35.3 months). This is an alternative for patients who are not a candidate for perioperative FLOT +/− durvalumab.[6]

- On October 28, 2024, the FDA-approved zolbetuximab, a claudin 18.2 directed antibody, in combination with fluoropyrimidine and platinum-containing chemotherapy for the first-line treatment of advanced gastric and GEJ adenocarcinoma. This approval was based on the results from two phase 3 studies (SPOTLIGHT and GLOW) that demonstrated that the addition of zolbetuximab improves OS in patients whose tumors are positive for claudin 18.2 (as determined by an FDA-approved test) and negative for HER2. The median OS were 18.2 versus 15.5 months (HR, 0.750) in the zolbetuximab plus FOLFOX6 arm compared with the control in the SPOTLIGHT trial; and 14.4 versus12.2 months (HR, 0.771) in the zolbetuximab plus capecitabine and oxaliplatin (CAPOX) compared with the control in the GLOW trial.[7,8]
- On December 27, 2024, the FDA-approved tislelizumab in combination with chemotherapy for first-line treatment of HER2-negative gastric or GEJ adenocarcinoma with PD-L1 1% or greater. This approval was based on the results of the randomized phase 3 RATIONALE-305 trial, which demonstrated significant improvement in OS with tislelizumab's addition. In patients with a PD-L1 TAP score of 1 or greater, tislelizumab improved OS compared with placebo plus chemotherapy with HR of 0.78 (median OS, 15.0 vs 12.8 months).[9]

Hepatocellular Carcinoma

- The phase 3 open-label HIMALAYA study of single-dose tremelimumab and monthly durvalumab versus sorafenib showed improved OS (median OS, 16.43 vs 13.77 months; HR, 0.78; 96.02% CI, 0.65-0.93; $P = .0035$) but not PFS in the first-line treatment of patients with advanced hepatocellular carcinoma (HCC).[10] Tremelimumab and durvalumab received FDA approval on October 21, 2022, for the first-line treatment of unresectable HCC.
- The phase 3 open-label CheckMate-9DW study of combination nivolumab plus ipilimumab versus investigator's choice of sorafenib or lenvatinib showed improved OS (median OS, 23/7 vs 20.6 months; HR, 0.79; 95% CI, 0.65-0.96; $P = .018$) but not PFS in the first-line treatment of patients with advanced HCC.[11] Nivolumab and ipilimumab received FDA approval on April 11, 2025, for the first-line treatment of unresectable HCC.

Biliary Tract Carcinoma

- The phase 2 HERIZON-BTC-01 study assessed the safety and efficacy of zanidatamab, a bispecific HER2-directed antibody, in patients with unresectable or metastatic HER2-amplified biliary tract cancer (BTC), who had previously received gemcitabine-based therapy. The objective response was 41% with a duration of response of 12.9 months. Based on these results, the FDA granted accelerated approval of zanidatamab in previously treated HER2-positive (IHC 3^+) advanced BTC on November 20, 2024.[12]

Pancreatic Adenocarcinoma

- The phase 3 randomized open-label NAPOLI-3[13] study of liposomal irinotecan combined with 5-fluorouracil (5-FU) and oxaliplatin (NALIRIFOX) versus nab-paclitaxel and gemcitabine demonstrated improved OS (median OS, 11.1 vs 9.2 months; HR, 0.83; 95% CI 0.70-0.99; $P = .036$) and PFS (median PFS, 7.4 vs 5.6 months; HR, 0.69; 95% CI 0.58-0.83; $P < .0001$) with NALIRIFOX in the first-line treatment of patients with previously untreated metastatic pancreatic adenocarcinoma, which led to FDA approval of NALIRIFOX on February 13, 2024.[14]
- Zenocutuzumab, a bispecific antibody that targets HER2/HER3 dimerization and NRG1 protein binding, has received accelerated FDA approval for patients with advanced or metastatic pancreatic cancer harboring a *NRG1* gene fusion and disease progression after a prior systemic therapy. In the phase 2 study, objective responses were seen in 44% of pancreatic cancer cases.[15]

OVERVIEW

In 2025,[16] approximately 174,660 new cancers of the upper digestive system (gastroesophageal, hepatobiliary, and pancreatic) were diagnosed in the United States. About 113,500 patients would die annually because of upper gastrointestinal (GI) cancers, including 51,980 patients with pancreatic cancer, 34,490 patients with hepatobiliary cancer, and 27,030 patients with gastroesophageal cancer.

Many upper GI cancers are aggressive,[17-22] with survival measured in months. While some cancers, including gastroesophageal and pancreatic, may have a hereditary component,[23-25] the majority of upper GI cancers are sporadic. Systemic treatments for upper GI cancers include immunotherapy-based regimens, targeted therapies, and chemotherapy. Biomarkers[17-22] to assess disease prognosis and response to treatment are available for many upper GI cancers; however, their validity and reliability are lacking in certain diagnoses, particularly hepatocellular carcinoma (HCC). The majority of upper GI cancers require multidisciplinary

management. To provide patients with the best possible care, medical oncologists may need to collaborate with surgeons, radiation oncologists, interventional radiologists, gastroenterologists, and pathologists. A key role of the medical oncologist is coordinating the various members of a patient's care team to determine which treatment strategies to recommend.

GASTROESOPHAGEAL CANCER

Gastroesophageal cancers (GECs) are a group of heterogeneous diseases that exhibit great variation in histology, geographic distribution, clinical behavior, and molecular classification. The esophageal squamous cell carcinoma (ESCC) molecular profile resembles those of squamous cell carcinoma (SCCs) of other organs. Meanwhile, gastric and gastroesophageal junction (GEJ) adenocarcinomas comprise four molecularly defined subtypes based on gene copy alteration, point mutations, gene expression patterns, and changes in DNA methylation: tumors positive for Epstein–Barr virus, microsatellite instability-high (MSI-H) tumors, genomically stable tumors, and tumors with chromosomal instability (CIN). Esophageal adenocarcinoma resembles the CIN subtype found in the gastric cardia and gastric carcinoma.[26-28]

Despite the noted differences between esophageal, GEJ, and gastric adenocarcinomas, these tumor types are often grouped together as esophagogastric adenocarcinomas (EGAs) especially in metastatic settings when considering therapy. Numerous histological subtypes have been described, particularly pertinent to EGA, including histological differentiation (ie, well, moderate, or poor), Lauren classification (ie, intestinal, diffuse, or mixed type), presence of signet-ring cells, and a host of other subtypes in the WHO criteria.[29] However, tumor classification has now evolved beyond location and histology and relies on molecular biomarkers to guide treatment selection.

KEY POINTS

- Beyond known histopathologic and epidemiological distinctions, molecular features differentiate ESCC from esophageal adenocarcinoma with SCC resembling SCCs of other organs more than it does esophageal adenocarcinoma, whereas esophageal adenocarcinoma predominantly resembles the CIN type found in gastric adenocarcinoma.
- The Cancer Genome Atlas project proposed a molecular classification dividing esophageal and GEJ adenocarcinomas and gastric adenocarcinoma (together, gastroesophageal adenocarcinoma (GEA)) into four subtypes: tumors positive for Epstein–Barr virus, MSI-H unstable tumors, genomically stable tumors, and tumors with CIN.

EPIDEMIOLOGY, ETIOLOGY, AND PREVENTION

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Worldwide, ESCC is a significant health issue and the most common esophageal malignancy. As the eighth most common cancer globally, ESCC is the sixth most common cancer–related death. In the United States, ESCC is infrequent (~20% of esophageal cancer), constituting approximately 1% of all cancers and approximately 6% of GI malignancies. ESCC is more likely to occur in Black patients.[30] The primary risk factors are cigarette smoking and excessive alcohol consumption, but others include achalasia, caustic injury, tylosis, and Plummer–Vinson syndrome. Infection with human papillomavirus (HPV) has been correlated with an increased incidence of SCC of the upper cervical esophagus.[31] Patients with ESCC are at risk for synchronous or metachronous head and neck or lung SCC, which are molecularly more similar to ESCC than to esophageal and GEJ adenocarcinomas. With increased awareness and decreased exposure to the primary risk factors of smoking and alcohol use, the incidence of ESCC has decreased substantially in recent decades in the United States. However, worldwide, there remains a high incidence, particularly in areas of Iran, Russia, and northern China.

ESOPHAGEAL ADENOCARCINOMA AND GEJ ADENOCARCINOMA

For the last three decades, the incidence of esophageal and GEJ adenocarcinomas has increased significantly in Western countries, including the United States.[32] It is one of the fastest-growing cancers, typically diagnosed after age 60 years and affecting men at least five times more often than women. Esophageal and GEJ adenocarcinomas typically arise in the metaplastic epithelium.[33] Murine carcinogenesis models suggest migration of precursor cells from the gastric cardia proximally into the distal esophagus.[34,35] This premalignant condition is characterized by the replacement of the stratified squamous epithelium by the columnar epithelium, which develops as a consequence of chronic gastroesophageal reflux disease (GERD). The incidence of Barrett esophagus is 10% to 20% among symptomatic patients who undergo endoscopy and 30% to 50% among patients with peptic strictures. Risk factors associated with Barrett esophagus include GERD, White or Hispanic race, male sex, advanced age, smoking, diabetes, Western diet, and obesity.[36,37] However, there is heterogeneity in carcinogenesis, and not all tumors arise within a Barrett esophagus background. Approximately 60% of esophageal and GEJ adenocarcinomas have evidence of the precursor Barrett esophagus.

Detection of low-grade dysplasia on index endoscopy was associated with an adenocarcinoma incidence of 5.1 cases per 1,000 person-years. Risk estimates for patients with high-grade dysplasia (HGD) are slightly higher. In contrast, the incidence among patients without dysplasia was one case per 1,000 person-years.[38]

There is an inverse association between *Helicobacter pylori* infection and esophageal and GEJ adenocarcinomas, potentially as a result of the reduced acidity associated with atrophic gastritis.[39] Whether rigorous medical management of GERD with long-term use of proton-pump inhibitors can affect the natural history of the disease or the development of malignancy has long been debated.

A large randomized preventive study, AspECT, evaluated this question for patients with Barrett esophagus ≤1 cm and no HGD or esophageal adenocarcinoma.[40] A total of 2,563 patients were randomly assigned to high-dose (40 mg twice daily) or low-dose (20 mg once daily) esomeprazole alone or combined with 300 mg of aspirin per day. The primary composite endpoint was time to all-cause mortality, esophageal adenocarcinoma, or HGD. The use of a high-dose proton-pump inhibitor, especially in combination with aspirin, substantially improved outcomes for patients with Barrett esophagus.[40]

Another recent large population-based retrospective analysis in Nordic countries evaluating 942,906 patients with GERD reported that medical and surgical treatments for GERD were associated with a similar reduced esophageal adenocarcinoma risk with the risk decreasing to the same level as that in the background population over time, supporting the hypothesis that effective treatment of GERD might prevent esophageal adenocarcinoma.[41] Other than antiacid medication[40] and antireflux surgery,[41] typical treatment of patients with Barrett esophagus is surveillance using upper endoscopy and biopsy to evaluate for dysplasia.[37] HGD is an indication for more aggressive management, including surgical resection.[42,43]

GASTRIC ADENOCARCINOMA

In the United States, gastric adenocarcinoma is seen twice as often in men as in women and more frequently in Black men than in White men, and its incidence increases with age, starting at 50 years.[44] The incidence of gastric adenocarcinoma has varied considerably during the last century. In the United States, the incidence of gastric adenocarcinoma has decreased by approximately 75% during the last few decades.[36] Although gastric adenocarcinoma rates have declined worldwide, it is still prevalent in regions of the world where the storage of fresh food and the quality of water are poor and in some industrialized nations as well (eg, Japan).[45] Gastric adenocarcinoma is a major health issue in Japan and Korea, and both countries have nationwide screening programs. In Japan and Korea, gastric adenocarcinoma is associated with a better prognosis than in Western cultures. When controlling baseline tumor characteristics, patient demographics, and surgical factors, there is a difference in survival that remains unexplained.[46] Studies of migrant populations support evidence for the effect of environmental influences on the development of gastric adenocarcinoma.[47,48] Factors associated with an increased risk of gastric adenocarcinoma include nutritional factors, such as high salt and nitrate intake, a diet low in vitamins A and C, consumption of large amounts of smoked or cured foods, lack of refrigerated foods, and poor-quality drinking water.[49] Occupational exposure to rubber and coal also increases the risk. Cigarette smoking, *H. pylori* infection,[50,51] Epstein–Barr virus,[52] radiation exposure, and prior gastric surgery for benign ulcer disease are also implicated as risk factors. Together, these data support the belief that gastric adenocarcinoma is strongly influenced by nutritional, socioeconomic, and medical factors rather than dominated by genetic predisposition. Awareness of and decreased exposure to these factors have contributed to a decline in the incidence and mortality rate of gastric adenocarcinoma in the United States.

Genetic risk factors include type A blood, pernicious anemia, family history of gastric adenocarcinoma, Lynch syndrome, Li–Fraumeni syndrome, and hereditary diffuse gastric cancer (HDGC) caused by mutations in the E-cadherin gene, *CDH1*. HDGC is a genetic predisposition syndrome characterized by a family history of gastric adenocarcinoma with poorly cohesive diffuse-type histology, often with early onset of disease (generally age <40 years). The cumulative risk of the development of diffuse gastric adenocarcinoma by age 80 years for *CDH1* mutation carriers is 70% for men and 56% for women. Women who have germline *CDH1* mutations are also at higher risk of developing lobular breast cancer with a cumulative risk of 42% by age 80 years.[53] Individuals with a germline *CDH1* mutation should undergo risk-reducing prophylactic gastrectomy to prevent future development of HDGC.[54] The optimal timing of prophylactic gastrectomy is unknown and is usually highly individualized. The current consensus is that the procedure should be discussed with and offered to carriers of pathogenic germline *CDH1* mutation in early adulthood, generally between ages 20 and 30 years.

Results from several studies demonstrate an increased likelihood of gastric cancer, especially cancer originating in the distal stomach, in association with *H. pylori* infection.[50,51] Although cancer does not develop in most people with *H. pylori* infections, the increased risk in infected patients led to the hypothesis that *H. pylori* treatment might decrease the risk of gastric adenocarcinoma. Indeed, several population studies demonstrate that *H. pylori* eradication in at-risk individuals reduces the incidence of gastric cancer. All patients with evidence of *H. pylori* infection should be treated.[55]

KEY POINTS

- Individuals who carry a germline *CDH1* mutation are at substantial lifetime risk of developing gastric cancer and should undergo risk-reducing prophylactic gastrectomy as early as in their 20s.
- All patients with *H. pylori* infection should undergo treatment.

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

The most common clinical presentation of esophageal and GEJ cancers is dysphagia resulting from the obstructive nature of the tumor and subsequent weight loss. Additional presenting symptoms include occult or frank bleeding (usually manifested by melena, iron-deficiency anemia, and fatigue) and treatment-refractory heartburn.[45] Patients with more proximal tumors can have tracheobronchial invasion and may present with laryngeal nerve paralysis, cough, and/or postobstructive pneumonia.[56] In contrast, patients with gastric adenocarcinoma commonly experience anorexia and early satiety leading to weight loss as their presenting symptom in addition to iron-deficiency anemia.

Because of vague symptoms that go unaddressed for some time, it is unfortunately common for patients with upper GI cancers to present with synchronous metastatic disease when symptoms become more severe, persistent, and compounded by metastatic spread. Common sites of disseminated disease are liver, lung, distant lymph nodes (LNs), bone, and peritoneum. Peritoneal carcinomatosis is seen in approximately 30% of patients with gastric adenocarcinoma and 10% to 15% of those with esophageal or GEJ adenocarcinoma (particularly those with diffuse or mixed-type histology or tumors with signet-ring features) and results in the development of ascites and abdominal pain, culminating in severe anorexia, dysfunctional bowel, and in many cases partial or complete bowel obstruction.[45]

An upper endoscopic examination should be performed to obtain a diagnostic biopsy. Diffuse-type gastric adenocarcinoma may be elusive during routine upper endoscopy because there is no obvious mass. Therefore, repeated endoscopy with endoscopic ultrasound (EUS) and other specialized endoscopic techniques may be required to arrive at a confirmed diagnosis if there is still high clinical suspicion of gastric adenocarcinoma. CT imaging of the chest, abdomen, and pelvis should be performed with tomographic slices through the liver to evaluate the extent of disease in the upper abdomen. A thorough clinical examination with careful attention paid to the LNs in the supraclavicular regions is essential.

For patients without obvious metastatic disease by CT scan, additional staging should include EUS, which is a standard component when evaluating patients with GEC eligible for locoregional therapy to determine the depth of invasion of the primary tumor (T stage) and locoregional LN involvement (N stage).[57,58] PET, preferably as a PET-CT scan, is part of the routine pretreatment diagnostic workup for patients with esophageal or GEJ cancer for detecting occult metastatic disease. PET allows for the detection of occult sites of distant metastatic spread; therefore, it may spare a patient the morbidity of aggressive locoregional treatments.[59-61] PET may not be sensitive to diagnose occult peritoneal spread in gastric cancer and staging laparoscopy should also be considered. Given the similar risk factors for lung and ESCCs, consideration of two separate primaries is important for patients with a primary ESCC and a solitary lung lesion at staging. It should be noted that diffuse-type gastric adenocarcinoma tumors can be negative on PET staging scans.[58] Given the similar risk factors for lung and ESCCs, consideration of two separate primaries is important for patients with a primary ESCC and a solitary lung lesion at staging. Staging laparoscopy is essential in the workup of locoregional gastric adenocarcinoma and should be offered to all patients without radiologically evident metastatic disease and who have at least T2 or node-positive disease on EUS. Diagnostic laparoscopy can identify up to 20% to 30% of occult peritoneal metastases in these cases; therefore, this is considered a standard staging procedure for these patients, which should be performed before initiating therapy.[61,62] The biology of Siewert III GEJ cancer is similar to gastric cancer and should be staged similarly to gastric cancer.

Staging has evolved through various editions of the American Joint Committee on Cancer (AJCC) manual, but three distinct staging systems have been maintained for ESCC, esophageal and GEJ adenocarcinomas, and gastric adenocarcinoma, respectively, based on the extent of involvement of the esophagus and stomach. Within esophageal and GEJ adenocarcinomas, subdivision into three Siewert types (type I, esophageal adenocarcinoma; type II, GEJ; and type III, gastric cardia), largely for surgical anatomic planning, was named after the German surgeon who defined these.[63] The Siewert types are now often used as criteria for enrollment in clinical trials. However, practically speaking, these distinctions are difficult to accurately characterize by upper endoscopy because tumors often span these artificial boundaries. The eighth edition of the AJCC staging manual incorporated consideration of clinical staging at diagnosis before any therapy or surgery (c stage), pathologic stage after neoadjuvant therapy (yp stage), and pathologic stage in those not receiving neoadjuvant therapy (p stage) and the prognostic estimates by stage for each scenario.[64-70]

KEY POINTS

- Common presenting symptoms for GEC include dysphagia, anorexia, early satiety, nausea, dyspepsia, pain, bleeding, and hematemesis.
- Cross-sectional imaging including PET, EUS, and laparoscopic staging for patients with gastric and Siewert III GEJ tumors are critical to determine the location and stage of the tumor.

TREATMENT

LOCAL DISEASE

Surgery plays a critical role in managing patients with early-stage esophagogastric tumors except for patients with proximal ESCC that are treated with definitive concurrent chemotherapy plus radiation therapy (chemoRT). Aside from very early-stage disease, multimodality approaches are essential.

Patients who have GEC limited to the mucosa (HGD or tumors invading the lamina propria or muscularis mucosae; T1a) may be managed with endoscopic resection (endoscopic mucosal resection or endoscopic submucosal dissection) because there is a relatively low risk (2%) of occult regional LN metastasis.[71-73] For lesions that have penetrated the submucosa without LN involvement on staging studies (tumor invading the submucosa; T1b), surgical resection with lymphadenectomy is recommended because of the approximately 15% to 40% risk of occult LN involvement.[74]

Unfortunately, most patients are diagnosed with more advanced disease for which surgery alone is insufficient. For any lesions that are at least T3 (tumor invading through the muscularis propria) and/or node-positive disease amenable to surgical resection, multimodal management with chemotherapy or chemotherapy with concurrent radiation therapy before and/or after surgery has become the standard given the high risk of micrometastatic dissemination.[3,21,40] It is controversial whether all patients who have T2N0 GEC (ie, tumor invading the muscularis propria; T2) should receive perioperative or neoadjuvant therapy and surgery versus surgery alone because some studies have included such patients as eligible and other studies have not, and some reports suggest a lack of benefit in the setting of adequate surgery.[75-78] Currently, a discussion of potential risks and benefits of perioperative therapy and surgery versus surgery alone with the patient and family is prudent, and a personalized approach for patients with T2N0 disease is recommended, including enrollment in a clinical trial if available. The NCCN guideline[79] recommends T2N0 GEC with high-risk lesions, defined as presence of lymphovascular invasion, ≥3 cm and/or poorly differentiated histology) to be considered for neo-adjuvant or perioperative therapy then surgery. The identification and treatment of patients who have minimal residual disease postresection are emerging areas of investigation to reduce the risk of recurrence and improve long-term outcomes for high-risk patients.[80]

SURGERY

The optimal curative treatment approach for patients who have locally advanced GEC includes surgical resection with preoperative chemotherapy or concurrent chemoradiation.[81] For distal ESCC and esophageal and GEJ adenocarcinomas, the two most commonly used surgical techniques are transhiatal esophagectomy and a transthoracic approach (eg, an Ivor–Lewis resection). The results associated with the two approaches are similar.[82-84] Reports suggest a higher retrieval rate of LNs with an Ivor–Lewis approach.[85,86] The surgical approach is determined by the experienced surgeon on the basis of the tumor location and patient details, including transthoracic esophagectomy with two-field lymphadenectomy; transhiatal esophagectomy with lower mediastinal and upper abdominal lymphadenectomy; and proximal, subtotal, or total gastrectomy. Minimally invasive approaches via laparoscopy and robotic surgeries are becoming more common in GEC without evidence of detriment in efficacy.[87]

For gastric cancer, the number of LNs removed is important.[88-90] D2 lymphadenectomy is defined as the contiguous resection of the second tier of LNs along the branches of the celiac trunk (eg, common hepatic artery, left gastric artery, and splenic artery). After 15-year follow-up of a randomized Dutch trial that included 1,078 patients with distal gastric adenocarcinoma, D2 lymphadenectomy was associated with lower locoregional recurrence (12% vs 22%) and gastric cancer–related death rates (37% vs 48%) than D1 surgery (fewer LNs removed).[91] Although D2 dissection was associated with higher operative morbidity, these data suggest D2 lymphadenectomy should be considered the surgical standard of care. Larger meta-analyses confirm the benefit of D2 lymphadenectomy, particularly in patients who have undergone D2 resection without resection of the spleen or distal pancreas or nodal stations around these (ie, modified D2) as well as in patients who have higher risk T3 to T4 or node-positive cancer.[92,93] The NCCN guideline recommends that gastric resection should include regional D1 and D2 lymph node dissection with a goal of examining ≥16 LNs. Operative mortality rates for GEC should be <5% when surgery is performed by an experienced surgeon at a high-volume center.[94] Historically, survival has been poor for patients with GEC treated with surgery alone with 5-year survival rates ranging from 5% to 34%,[56] leading to several studies evaluating the benefit of perioperative therapies.

NEOADJUVANT, ADJUVANT, OR PERIOPERATIVE TREATMENT

Various neoadjuvant, adjuvant, or perioperative (a course of both neoadjuvant and adjuvant therapies) combined-modality approaches for the treatment of GEC have been evaluated because of the poor outcomes observed with surgery alone. Combined-modality treatment involves surgery, chemotherapy with or without radiation therapy, or both. The interpretation of the results from these clinical trials is complicated by EGA classification and differential incidence of upper GI cancer subtypes based on geographic distribution, making cross-trial comparisons challenging and potentially misleading. Similarly, the different makeup of ESCC and adenocarcinoma within different esophageal studies makes comparison across studies challenging because these subtypes have a different biology, natural history, and sensitivity to perioperative therapies. This ultimately led to a fragmented treatment approach with each approach deemed to be more effective than surgery alone, and until recently, it remained unclear which, if any, is superior.[3,80,95] The positive results of the phase 3 CROSS trial established neoadjuvant concurrent chemoradiation followed by surgical resection as a standard for localized resectable esophageal cancer. Then recent positive results from two prospective phase 3 studies evaluating perioperative treatments in EGA support perioperative chemotherapy as another standard approach to the management of these patients.[3,95] Neoadjuvant chemoradiation remains the optimal therapeutic approach for patients who have resectable ESCC, followed by adjuvant nivolumab for those who have residual pathologic disease at resection.

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Local recurrence rates of muscle-invasive or node-positive ESCC are high with surgery alone, similar to other SCC tumor sites.[56,81] Data from the phase 3 CROSS trial, which enrolled patients who had ESCC (25%) and adenocarcinoma (75%), confirmed the superiority of a neoadjuvant CRT approach (with weekly carboplatin and paclitaxel) compared with surgery alone for patients who have localized ESCC.[5] These results confirm CRT as the standard of care option for patients who have locally advanced ESCC.[96]

With 10-year follow-up, the OS survival benefit continued with perioperative treatment per CROSS; however, systemic recurrences were similar between the control (surgery alone) and CRT arms across all enrolled patients,[97] suggesting the need for better systemic treatments for micrometastatic disease. The positive results from the CheckMate 577 trial[5] established adjuvant nivolumab as standard adjuvant therapy in patients who did not have pathological complete response (pCR) after preoperative CRT. The phase 3 randomized placebo-controlled global study evaluated adjuvant nivolumab or placebo for patients who have esophageal cancer (including SCC and adenocarcinoma) who received neoadjuvant CRT followed by surgery with residual disease (T+ and/or N+; R0 resection).[98] The first report[6] of survival following 24.4 month median follow-up, the median OS for the adjuvant nivolumab arm is numerically superior to the placebo arm, though not reaching statistical significance (51.7 vs 35.3 months; HR, 0.85; 95% CI 0.70-1.03; P = .1064). Long-term follow-up to confirm the survival benefit is ongoing. Nivolumab is approved by FDA for use as adjuvant therapy for patients who have ESCC with residual pathological disease after chemoradiation and resection.[99]

Given the favorable pCR rate (approximately 49%)[5] with CRT in ESCC, definitive CRT (without surgical resection) is considered a standard option for patients who have localized ESCC, or those with or locally advanced disease who are not appropriate surgical candidates.[5,100,101] Decisions regarding surgical appropriateness involve several factors, including but not limited to tumor location, patient age, comorbidities, performance status (PS), and need for laryngectomy. Patients who have T4b disease (tumors invading other adjacent structures, such as aorta, vertebral body, and trachea), tracheoesophageal fistula, or cervical ESCC are not candidates for curative-intent surgery.

Patients who achieve clinical complete response after CRT may choose not to proceed to resection immediately, opting for close monitoring with the goal of avoiding esophagectomy altogether. Salvage esophagectomy at recurrence is associated with similar survival compared with proceeding directly to esophagectomy following completion of chemoRT but has a higher surgical morbidity, including a risk of anastomotic leak of 25% (for salvage esophagectomy) versus 3% if performed shortly after completion of combined-modality therapy.[101,102] Notably, there are ongoing clinical trials evaluating the benefit of immunotherapy in patients treated with definitive CRT for locoregional disease.[103] While the positive CROSS trial established carboplatin and paclitaxel as radiosensitizer of choice to be given concurrently with radiation, fluoropyrimidine plus oxaliplatin (FOLFOX, capecitabine/oxaliplatin) are alternatives for patients who are not candidates for the CROSS regimen.[104-106]

ESOPHAGOGASTRIC ADENOCARCINOMA

In the past, treatment of EGA was driven primarily by tumor location. Historically, patients with esophageal cancers received preoperative chemoRT, whereas patients with gastric cancer were treated with perioperative chemotherapy. For years, management of distal esophageal and GEJ adenocarcinomas has been an area of contention as patients who have tumors arising at GEJ have been included in clinical trials for esophageal cancer (and grouped together with patients with ESCC) as well as in trials for patients who have gastric cancer proper. Therefore, interpreting past data has been challenging.

Until recently, the standard approach to patients who have esophageal adenocarcinoma, including Seiwert I and II GEJ tumors, mirrored those of ESCC. The rationale to support this approach included improved (R0) resection rates with preoperative CRT and improved OS compared with resection alone. The CROSS study with doublet chemotherapy (carboplatin and paclitaxel) was the first stand-alone phase 3 study to support this approach with 75% of patients enrolled having esophageal or GEJ adenocarcinoma (type I or II Siewert tumors) and the other 25% having ESCC. For patients who have esophageal or GEJ adenocarcinoma, the pCR rate was 23% (21% intention to treat), and median OS was 43.2 months with CRT followed by surgery versus 27.1 months with surgery alone. However, the results of the ESOPEC[3] and MATTERHORN[4] trials changed that practice, and the NCCN guideline[79] recommends perioperative systemic chemotherapy as the preferred approach for patients with adenocarcinoma of the esophagus and GEJ who are medically fit for surgery.

The phase 3 randomized ESOPEC trial evaluated perioperative FLOT compared with neoadjuvant ChemoRT with carboplatin and paclitaxel (the CROSS regimen) for patients who have proximal esophageal or GEJ adenocarcinoma.[108] This trial demonstrated a superior 3-year OS for perioperative chemotherapy compared with chemoradiation (57.4% vs 50.7%; HR, 0.70, P = 0.01). The PFS and pathological outcomes were similarly better in the FLOT arm, whereas rates of R0 resection were similar in patients who were treated with radiation and chemotherapy. Notably, patients in the neoadjuvant CRT group did not receive adjuvant nivolumab as the trial was conducted before the results of CheckMate 577 were available.

It is important to acknowledge that not all patients are candidates for triplet FLOT chemotherapy. Dosage modifications should be considered in those who are too frail to tolerate this regimen. Preoperative chemoradiation per CROSS study remains an appropriate approach for patients who are not candidates for intensive chemotherapy and/or surgery, or decline surgery.

Adjuvant nivolumab should be considered for patients who do not achieve complete pathological response following resection based on the positive results from the CheckMate 577 trial described above.

In contrast, patients who have gastric adenocarcinomas are treated with perioperative chemotherapy, and standard treatment consists of perioperative (neoadjuvant and adjuvant) triplet chemotherapy with FLOT (United States,[107] United Kingdom, and much of Europe) or adjuvant chemotherapy alone after D2 resection (Asia).[109] The FLOT regimen is a standard perioperative treatment based on the results of the FLOT4-AIO study.[107] The strategy in the perioperative FLOT4 study was to proceed with four more adjuvant cycles as tolerated. However, it should be noted that, in the perioperative studies, only approximately 50% of patients received all the intended adjuvant chemotherapy.[107,110,111] Despite improvement in outcomes, there are remaining unsettled issues regarding perioperative therapy. It is unclear how to approach patients postoperatively who, on the basis of poor pathological response, did not benefit from neoadjuvant therapy. Further investigation is necessary to better direct an optimal approach in the scenarios of excellent response and poor response to the neoadjuvant component whether it is to continue more FLOT, change to other therapy, or observe only. For now, the standard approach is to complete adjuvant therapy, if possible, in all scenarios (or consider a clinical trial to address these issues).

The use of immune checkpoint inhibitor with perioperative therapy in EGA is established by the positive results from the pivotal MATTERHORN[4] trial. This phase 3 multinational trial randomized resectable gastric or GEJ adenocarcinoma to receive perioperative durvalumab plus FLOT followed by durvalumab for additional 10 cycles versus placebo plus FLOT. The 2-year OS was 75.7% in the durvalumab group versus 70.4% in the placebo group (HR, 0.67 for month 12 onwards; $P < .0001$). The NCCN guideline lists durvalumab plus FLOT as category 1 recommendation for the treatment of resectable GEJ and gastric adenocarcinoma, and category 2A for resectable esophageal adenocarcinoma.

Although neoadjuvant therapy is preferred before surgery in the United States, large studies from Asia have demonstrated the benefit of adjuvant chemotherapy after D2 resection without neoadjuvant treatment.[109,112-114] The Korean CLASSIC study, which included 1,035 patients who had D2-resected stage II or III distal gastric adenocarcinoma, identified adjuvant therapy with CAPOX (capecitabine and oxaliplatin) as superior to surgery alone with substantial improvement in OS.[109] The superior outcomes of patients in Eastern countries are clearly highlighted in the CLASSIC study compared with outcomes in Western countries, but one should not compare perioperative FLOT as studied in the West with adjuvant CAPOX as studied in the East.[107,109] In addition to these individual trials supporting adjuvant chemotherapy, a meta-analysis of 17 trials with 3,838 patients confirmed that adjuvant chemotherapy without radiation therapy after gastric adenocarcinoma resection was associated with a substantial survival benefit.[115] Adjuvant oxaliplatin and fluoropyrimidine is an option for patients who had upfront surgery based on the CLASSIC study. Adjuvant CRT is an option for patients with inadequate surgery, most often the case in patients who have had surgery first in the United States.[116]

EARLY-STAGE MSI-H/DMMR GEJ ADENOCARCINOMA

MSI-H gastric and GEJ adenocarcinoma represent a subtype of tumors with differential biological behavior and response to therapy.[117] A recent meta-analysis demonstrated that MSI-H tumors have a good prognosis compared with microsatellite stable tumors.[118] Importantly, this meta-analysis, including several perioperative phase 3 studies, also demonstrated that patients with MSI-H tumors seem to have a poor outcome with chemotherapy compared with surgery alone, similar to observations in stage II MSI-H colorectal cancer.[117]

The NEONIPIGA phase 2 study evaluated the role of perioperative nivolumab and ipilimumab in 32 patients who have MSI-H, T2-T4, NxM0 resectable gastric adenocarcinoma/GEJ adenocarcinoma.[119] In this study, 29 patients had an R0 resection, and 17 (58.6%; 90% CI 41.8-4.1) had a pCR. The other three patients had a complete clinical response and did not undergo surgery. With a median follow-up of 14.9 months, no patients experienced recurrent disease during this study.

Similar results were seen in the phase 2 INFINITY trial,[120] which enrolled 18 patients. These data demonstrate a potential role for immunotherapy in patients who have MSI-H tumors, but the optimal management of these patients is evolving.

KEY POINTS

- Combined-modality CRT followed by resection is the standard neoadjuvant approach in the treatment of locally advanced ESCC.
- Definitive CRT (without surgery) is a valid treatment option for patients who have ESCC, especially if patients are high-risk surgical candidates.
- One year of adjuvant nivolumab for patients who have esophageal cancer (both SCC and adenocarcinoma) who received neoadjuvant CRT followed by surgery with residual pathological disease (T+ and/or N+; R0 resection) is the standard of care based on the improved DFS observed in CheckMate 577.[95,107]
- The positive results from ESOPEC, FLOT4-AIO, and MATTERHORN established perioperative systemic therapy as the preferred approach for patients with resectable esophageal, GEJ, and gastric cancers who are candidates for surgery and intensive systemic therapy.

- Perioperative FLOT plus durvalumab is a standard for patients with resectable esophageal, GEJ, or gastric cancers who are candidates for surgery.
- Adjuvant nivolumab for 1 year is the standard for patients with resected esophageal or GEJ tumors who received preoperative chemoradiation and have residual pathological disease after surgical resection.
- Adjuvant CAPOX without radiation therapy was superior for tumors with at least muscle invasive (≤T2) and/or node-positive disease (≤N1) in patients with an adequate D2 lymphadenectomy compared with surgery alone based on the CLASSIC study. This should be considered in patients who do not receive preoperative systemic chemotherapy or preoperative chemoradiation.
- Immune checkpoint inhibitor(s) should be considered for patients with resectable MSI-H/mismatch repair (MMR)-deficient esophageal or GEJ adenocarcinoma in either neoadjuvant or perioperative approaches.

TREATMENT OF METASTATIC DISEASE

Unfortunately, many patients present with metastatic disease at initial diagnosis. This risk of recurrence is high after curative-intent therapy; >50% of patients recur within 2.5 to 3 years. There is no role for routine resection of the primary tumor without resection of the metastatic disease even when there is limited single-site metastasis.[121]

As such, the goals of treatment for metastatic GEC are to control the disease, prolong life, and provide palliation while limiting toxicities from therapy. Palliative systemic therapy is associated with improved quality-of-life as well as improved survival. Ancillary support including palliative radiation therapy for symptomatic localized metastases such as bone lesions as well as radiation therapy and/or endoluminal stenting for refractory or symptomatic primary tumors also contributes to improvement in patient outcomes.

SYSTEMIC THERAPY

Many systemic agents have shown anti-cancer activity in GEC, including cytotoxic (eg, fluoropyrimidines, platinum agents, taxanes, irinotecan, and trifluridine and tipiracil), molecularly targeted drugs (eg, trastuzumab, zolbetuximab, and ramucirumab), immune checkpoint inhibitors (ipilumumab, nivolumab, pembrolizumab, and tislelizumab) and antibody-drug conjugates such as trastuzumab deruxtecan.

First-line treatment typically involves doublet chemotherapy as the backbone of combination regimens. The utility of cytotoxic regimens is similar across gastroesophageal subtypes and studies in the West have focused predominantly on EGA due to the higher prevalence in these countries.

Doublet chemotherapy regimens have yielded response rates as high as 40% to 50% and are associated with increased OS when compared with single-agent therapies.[122] Standard contemporary doublet regimens such as FOLFOX and FOLFIRI (5-fluorouracil [5-FU], leucovorin, and irinotecan) achieve similar outcomes with convenient dosing schedules and acceptable toxicity.[123-126] Triplet regimens, using older generation cytotoxics such as epirubicin and cisplatin, in contrast, are not widely used in the United States due to unacceptable toxicity profile and unclear superiority over FOLFOX and FOLFIRI.[127] However, there is an ongoing phase 3 trial AO22102 evaluating FOLFIRINOX compared with FOLFOX chemotherapy in the first-line setting for advanced GEA treatment.[128] The AO22102 trial Alliance[124] cooperative group is ongoing to compare the triplet FOLFIRINOX to doublet FOLFOX regimen (+/− nivolumab) in the first-line treatment of metastatic HER2-negative GEA.[128]

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

First-Line Therapy

Chemo-immunotherapy is the standard as first-line treatment of advanced, metastatic ESCC. The phase 3 randomized, placebo-controlled, global KEYNOTE-590 study evaluated first-line therapy for the treatment of newly diagnosed metastatic esophageal cancer with 5-FU and cisplatin with either pembrolizumab or placebo. Median OS was superior in ESCC with chemotherapy and pembrolizumab versus chemotherapy (median, 12.6 vs 9.8 months; HR, 0.72; 95% CI 0.60-0.88; P = .0006). Median PFS was also significantly longer in patients with ESCC treated with chemotherapy and pembrolizumab as compared with chemotherapy alone (median PFS 6.3 vs 5.8 months; HR, 0.65; 95% CI 0.54-0.78; P < .0001). This benefit was more pronounced in patients who had PD-L1 combined positive score (CPS) ≥10 tumors. Pembrolizumab is currently listed in the NCCN guideline as category 1 recommendation for use in CPS ≥1 tumors in combination with platinum and fluoropyrimidine. The FDA-approved pembrolizumab for all tumors irrespective of histology or PD-L1 level on March 22, 2021.[129] Oxaliplatin may be used interchangeably for cisplatin based upon the findings from the REAL-2 study.[130]

CheckMate 648 tested the role of nivolumab as a component of chemoimmunotherapy in the first-line setting for patients with metastatic ESCC.[131] This phase 3 study randomly assigned patients (N = 970) irrespective of PD-L1 expression to receive treatment with 5-FU and cisplatin alone or in combination with nivolumab (240 mg) every 2 weeks or to a chemotherapy-free combination of nivolumab (3 mg/kg) every 2 weeks and ipilimumab (1 mg/kg) every 6 weeks. The coprimary endpoints were OS and PFS for patients with PD-L1 CPS ≥1% tumors. Median OS in the overall population was 13.2 months with chemotherapy and nivolumab versus 10.7

months with chemotherapy (HR, 0.74; 95% CI 0.61-0.89; *P* = .002). Similarly, the median OS in the overall population was 12.7 months for ipilimumab/nivolumab versus 10.7 months for chemotherapy (HR, 0.78; 95% CI 0.65-0.94; *P* = .01). Median PFS in the overall population was not significantly longer with chemotherapy/nivolumab compared with chemotherapy alone. In the nivolumab and ipilimumab arm, OS was also improved compared with chemotherapy alone (12.7 vs 10.7 months with HR of 0.77). Patient-specific characteristics should be considered during therapy selection, and priority should be given to chemotherapy with nivolumab in the treatment of patients who have bulky disease or with significant symptomatic disease burden. Ipilimumab plus nivolumab, a cytotoxic free regimen, is a reasonable consideration for patients with tumor PD-L1 CPS ≥1 and who are not candidates for combination cytotoxic regimen.

RATIONALE 306 was a double-blind global phase 3 trial in which patients with advanced ESCC with no prior treatment were randomized in a 1:1 manner to chemotherapy (platinum agent combined with either a fluoropyrimidine or paclitaxel plus either tislelizumab or placebo). The addition of tislelizumab to chemotherapy significantly improved OS in both the intent-to-treat population (17.2 vs 10.6 months, HR, 0.66) and in several prespecified subgroups based on the level of PD-L1 expression (tumor area positivity score, TAP ≥ 5). Notably, tislelizumab in patients who have tumors with low PD-L1 level (TAP < 1%) appeared to have a potential detrimental effect with HR of 1.34 on OS. Tislelizumab, in combination with platinum-containing chemotherapy, was approved by FDA on March 4, 2025 for the frontline treatment of patients with unresectable or metastatic ESCC with a tumor PDL1 TAP score ≥1.

The benefit of adding other checkpoint inhibitors to first-line chemotherapy in Asian patients with ESCC has been demonstrated in several phase 3 studies. In the ORIENT-15 study, sintilimab combined with chemotherapy improved OS compared with chemotherapy alone (median, 16.7 vs 12.5 months; HR, 0.63; 95% CI 0.51-0.78; *P* < .001). In the JUPITER-06 study, toripalimab combined with chemotherapy improved OS compared with chemotherapy alone (median, 17.0 vs 11.0 months; HR, 0.58; 95% CI 0.43-0.78; *P* = .0004). In the ESCORT-1 study, the addition of camrelizumab to chemotherapy improved OS compared with chemotherapy alone (median, 15.3 vs 12.0 months; HR, 0.70; 95% CI, 0.56-0.88; *P* = .001). In the RATIONALE-306 study, the addition of tislelizumab to chemotherapy also improved OS compared with chemotherapy alone (median, 17.2 vs 10.6 months; HR, 0.66; 95% CI, 0.54-0.80; *P* < .0001).

In aggregate, these studies established PD-1–based chemoimmunotherapy as the standard first-line therapy for unresectable, metastatic ESCC.

ESOPHAGEAL, GEJ, AND GASTRIC ADENOCARCINOMAS

Biomarker testing, including HER2, PD-L1, Claudin 18.2 (CLDN18.2), and MMR, should be routine and standard when developing treatment plans for patients with unresectable, metastatic esophageal, GEJ, or gastric adenocarcinoma (Table 13.1-1). Next-generation sequencing (NGS) is highly recommended for all cases of advanced-stage disease to identify potentially actionable alterations.

Table 13.1-1 First-line Treatment Options for Advanced Esophago-Gastric Adenocarcinoma

Tumor Characteristics	Treatment
HER2+[a] and PDL1 CPS ≥1	Chemotherapy, trastuzumab, and pembrolizumab
HER2+[a] and PDL1 CPS <1	Chemotherapy and trastuzumab
HER2–[a] and PDL1 CPS ≥1	Chemotherapy and anti-PD1 ab[b]
CLAUDIN 18.2+[c]	Chemotherapy and zolbetuximab
HER2– and PDL1 CPS <1, CLAUDIN 18.2–	Chemotherapy
dMMR/MSI-H	Anti-PD1 ab +/– anti-CTLA4 ab[d] OR chemotherapy + anti-PD1[e]

Abbreviations: CPS, combined positive score; dMMR, deficient DNA mismatch repair; MSI-H, microsatellite instability-high.
[a]HER2+: IHC 3 + or IHC2+/ISH+; HER2-: IHC 1+ or IHC2+/ISH–
[b]Nivolumab, tislelizumab, or pembrolizumab.
[c]Claudin 18.2 moderate or strong expression by IHC in ≥75% tumor cells.
[d]Pembrolizumab, dostarlimab, nivolumab + ipilumumab.
[e]Nivolumab, pembrolizumab.
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First-Line Therapy

Since 2021 there have been several regulatory approvals for chemoimmunotherapy in the first-line setting for esophageal, GEJ, and gastric adenocarcinomas.

HER2 Overexpression–Negative Adenocarcinomas

The combination of fluoropyrimidine (5-FU or capecitabine), oxaliplatin, and nivolumab represents the standard of care for HER2 overexpression–negative EGA. The phase 3 randomized open-label global CheckMate 649 study evaluated first-line therapy for newly diagnosed metastatic HER2-negative GEA (gastric cancers, 70%; GEJ cancer, ~17%; and esophageal adenocarcinoma, ~13%) with fluoropyrimidine and oxaliplatin and either nivolumab or placebo. Dual primary endpoints were OS

and PFS in patients with PD-L1 CPS ≥5. A total of 1,581 patients were randomly assigned into these two arms. After a minimum follow-up of 3 years, there was a statistically significant improvement in OS in the chemotherapy and nivolumab arm when compared with the chemotherapy alone arm in patients with PD-L1 CPS ≥5 (median OS, 14.4 vs 11.1 months; HR, 0.70; 95% CI, 0.61-0.81) as well as in all randomly assigned patients (median OS, 13.7 vs 11.6 months; HR, 0.79; 95% CI, 0.71-0.88). There was also an improvement in PFS in patients treated with chemotherapy and nivolumab compared with chemotherapy alone in those with PD-L1 CPS ≥5 (median PFS, 8.3 vs 6.1 months; HR, 0.70; 95% CI, 0.60-0.81) as well as in all randomly assigned patients (median PFS, 7.7 vs 6.9 months; HR, 0.79; 95% CI, 0.71-0.89). Combination fluoropyrimidine/oxaliplatin and nivolumab is currently listed in the NCCN guidelines as a category 1 recommendation for use in CPS ≥5 EGA. It is important to note that, in a subgroup analysis of OS based on CPS score, patients who have PD-L1 CPS <1 (n = 265) experienced no survival benefit with the addition of nivolumab to chemotherapy (median OS, 13.1 months with chemotherapy and nivolumab vs 12.5 months with chemotherapy alone; HR, 0.95; 95% CI, 0.73-1.24).[132-134]

Pembrolizumab is also approved in combination with chemotherapy for patients who have esophageal or GEJ adenocarcinoma tumors based on the KEYNOTE-590 study as described previously.[129] In a subgroup analysis for OS and PFS in adenocarcinoma (approximately 27% of the study population), the arm receiving chemotherapy and pembrolizumab had better OS (11.6 vs 9.9 months; HR, 0.74; 95% CI, 0.55-0.99) and PFS (6.3 vs 5.7 months; HR, 0.61; 95% CI, 0.45-0.84) compared with the chemotherapy alone arm. Pembrolizumab is approved for use in gastric and GEJ adenocarcinoma based on the results of a phase 3 randomized study, KEYNOTE-859, which demonstrated improvement in OS with pembrolizumab in addition to chemotherapy compared with placebo and chemotherapy (median OS, 12.9 vs 11.5 months; HR, 0.78; 95% CI, 0.70-0.87). The NCCN guidelines recommend chemotherapy and pembrolizumab in esophageal, GEJ, and gastric adenocarcinomas with the strongest support for use in patients who have PD-L1 CPS ≥10 tumors.

Tislelizumab, another anti-PD1 antibody, also demonstrated activity in a similar setting, but it is not yet approved for use in the United States. In the phase 3 study, RATIONALE-305, addition of tislelizumab to chemotherapy improved OS (median OS, 17.2 vs 12.6 months; HR, 0.74; 95% CI, 0.59-0.94) and PFS (median PFS, 7.2 vs 5.9 months; HR, 0.67; 95% CI, 0.55-0.83) in PD-L1–positive patients (TAP score of ≥5) As of December 27, 2024, the FDA approved tislelizumab in combination with chemotherapy for first-line treatment of HER2-negative gastric or GEJ adenocarcinoma with PD-L1 1% or greater based on improvement in OS with HR of 0.78 (median OS of 15.0 vs 12.8 months) in patients with TAP 1 or greater.[7,8]

Special note must be made of MSI-H/dMMR GEA tumors. These account for 5% to 20% of all GEAs but show high response rates to checkpoint inhibitors.[135-137] In the CheckMate 649 study, after a minimum follow-up of 24 months, median OS with chemotherapy and nivolumab was significantly longer (38.7 months) than with chemotherapy alone (12.3 months; HR, 0.38; 95% CI, 0.17-0.84) in the MSI-H subgroup of patients. Similarly, ipilimumab/nivolumab significantly prolonged median OS compared with chemotherapy alone in this subgroup of patients (median OS, not reached vs 10 months; HR, 0.28; 95% CI, 0.08-0.92).[132] In a post hoc analysis of the KEYNOTE-062 study, which was a first-line study with three arms (pembrolizumab alone, chemotherapy and pembrolizumab, and chemotherapy), median OS was not reached for both pembrolizumab and chemotherapy and pembrolizumab arms in patients who have dMMR/MSI-H tumors. The 12-month OS rate for the pembrolizumab arm was 79%, and that for chemotherapy and pembrolizumab was 71% (compared with 47% with chemotherapy alone).[138] Based on these data, NCCN guidelines recommend the use of checkpoint inhibitors or chemotherapy and checkpoint inhibitors as first-line treatment of MSI-H GEAs. Recently, zolbetuximab was approved in combination with chemotherapy in the first-line setting as well. Zolbetuximab is a chimeric IgG1 monoclonal antibody (mAB) that binds to the extracellular loop of CLDN18.2, tight junction protein, on the tumor cell surface. Over a third of advanced GEA have upregulated CLDN18.2 expression.[7] In the phase 3 SPOTLIGHT trial, patients with locally advanced, previously untreated, HER2-negative, CLDN18.2-positive GEA (defined as ≥75% of tumor cells showing moderate-to-strong membranous CLDN18 staining) were randomized to either modified 5-FU, leucovorin, and oxaliplatin chemotherapy (mFOLFOX6) plus zolbetuximab or mFOLFOX6 plus placebo.[8] The study met its primary endpoint of median PFS improvement with zolbetuximab addition (10.61 vs 8.67 months, HR, 0.75). Median OS was also significantly improved with zolbetuximab addition (18.23 vs 15.54 months, HR, 0.75). Notably, the objective response rate (ORR) was similar between the two groups. The randomized phase 3 GLOW study had a similar design but used CAPOX as a chemotherapy backbone.[7] Similar to the SPOTLIGHT trial, PFS (8.21 vs 6.80 months, HR, 0.687) and OS (14.39 vs 12.16 months, HR, 0.771) were improved with zolbetuximab in addition to chemotherapy in a biomarker-select patient population. There were no differences in ORR (42.5% in the zolbetuximab arm versus 40.3% in the control arm) in the GLOW trial as well. In both studies, zolbetuximab demonstrated a similar safety profile with nausea and vomiting being the only adverse events (AEs) with more than 10% difference between the treatment arms. These toxicities are likely due to on-target effects of zolbetuximab related to normal expression of CLDN18.2 in gastric mucosa. In both studies, these GI toxicities were more prominent during the first treatment cycle and decreased with subsequent treatments. Based on the results of these trials, the FDA approved zolbetuximab in combination with chemotherapy for the treatment of CLDN18.2 positive GEA in the first-line setting. The infusion-related reactions (IRRs) ranged from 7% to 9% in these trials consisting of flushing, fever, chills and mild hypotension though true hypersensitivity reactions were infrequent. Most IRRs were manageable with anti-emetics and infusion rate adjustments.

KEY POINTS

- The addition of anti-PD1, pembrolizumab, nivolumab, or tislelizumab to combination chemotherapy is considered a standard in the first-line treatment of unresectable, metastatic ESCC. The benefit increases with increasing tumor PD-L1 expression. The NCCN guideline recommends the addition of anti-PD1 to chemotherapy in patients with tumor PD-L1 composite score ≥1.
- In the CheckMate 648 study, ipilumumab plus nivolumab achieved better OS than chemotherapy alone and was numerically shorter than nivolumab plus chemotherapy. Ipilimumab plus nivolumab may be considered for patients with tumor PD-L1 CPS ≥1 who are not candidates for anti-PD1 and chemotherapy combination.
- The CheckMate 649 study established that nivolumab when combined with fluoropyrimidine and platinum improved both PFS and OS compared with chemotherapy alone in patients who have GEAs with pronounced benefit seen in patients with tumors PD-L1 CPS ≥5.
- The KEYNOTE-590 and KEYNOTE-859 studies demonstrated PFS and OS benefit with the addition of pembrolizumab to fluoropyrimidine/platinum chemotherapy when compared with chemotherapy alone in GEAs. This benefit was pronounced in tumors PD-L1 CPS ≥10.
- Zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy is indicated for the treatment of CLDN 18.2 positive, HER-2 negative GEA.

HER2-POSITIVE GEA

HER2 EXPRESSION TESTING

Current clinical diagnostic testing requires evaluation by a combination of immunohistochemistry (IHC; membranous reactivity in >10% of cancer cells in a surgical specimen or a cluster of at least five cells in a biopsy specimen) and fluorescence in situ hybridization (FISH; with an HER2-to-CEP17 ratio ≤2).[139] IHC 0/1$^+$ should be considered negative irrespective of FISH positivity, and IHC3$^+$ is considered positive, whereas IHC2$^+$ requires reflex to FISH assessment. Higher throughput assays, including NGS, have emerged with the potential to refine diagnostic accuracy as well as to assess for other relevant aberrations via multiplexing capability.[140,141] Assessment of amplification by cell-free DNA is also emerging as a potential noninvasive strategy, with additional potential for the serial assessment of HER2 status over time in a noninvasive manner.[142] Intra-patient molecular heterogeneity is becoming a well-recognized phenomenon in these tumors with obvious implications for targeted therapy, including anti-HER2 therapy.[143,144] Consideration of biopsy of a metastatic lesion may assist with optimal targeted-therapy decisions.[143] Similarly, molecular evolution over time after anti-HER2 therapy in the first-line setting may be best identified by repeated testing via tissue or blood biopsy at the time of progression to determine whether HER2 directed therapy in a late line setting remains appropriate.[145]

Approximately 10% to 20% of GEA are HER2-positive GEAs.[146] The first targeted therapy to demonstrate benefit in GEA was trastuzumab, the humanized monoclonal antibody against HER2, added to standard cisplatin and fluoropyrimidine chemotherapy in *ERBB2* gene–amplified and HER2-overexpressing tumors. In the pivotal phase 3 ToGA (trastuzumab for gastric cancer) trial, 584 patients were randomly assigned to receive fluoropyrimidine in combination with 80 mg/m^2 of cisplatin on day 1 with or without trastuzumab.[147] The addition of trastuzumab to cisplatin and a fluoropyrimidine increased the median OS from 11.1 to 13.8 months (P = .0046). In addition, secondary endpoints such as PFS and ORR were also improved in the trastuzumab arm. There were no substantial differences in toxicity between the two treatment arms. An asymptomatic decrease in ejection fraction occurred in 4.6% and 1.1% of patients in the trastuzumab and chemotherapy alone arms, respectively. It is common practice in the United States to use the FOLFOX chemotherapy backbone with trastuzumab, again with routine exclusion of 5-FU bolus, given the better tolerability compared with cisplatin and more convenient 5-FU dosing schedule.[148]

In a randomized phase 3 study, KEYNOTE-811, 698 patients with HER2-positive (IHC 3$^+$ or IHC 2$^+$ and amplified by ISH) GEJ or gastric adenocarcinoma were randomly assigned to fluoropyrimidine (5-FU or capecitabine), platinum (oxaliplatin or cisplatin), or trastuzumab with or without pembrolizumab. In both arms, 85% of the patients were also PD-L1 positive (CPS ≥ 1). The dual primary endpoints were PFS and OS. The ORR favored the pembrolizumab arm (72.6% vs 60.1%). Median PFS was longer in the pembrolizumab arm (10 vs 8.1 months; HR, 0.72; 95% CI, 0.60-0.87; P = .0002). Median OS was improved in the pembrolizumab arm. In patients with PD-L1 CPS ≥1, median OS in the pembrolizumab arm was 20.1 months versus 15.7 months in the placebo arm (HR, 0.79, P = .006). The combination of fluoropyrimidine, platinum, trastuzumab, and pembrolizumab is now FDA approved for first-line treatment of HER2-positive and PD-L1–positive (CPS ≥ 1) EGA. However, there was no survival benefit in PD-L1–negative patients (PD-L1 CPS < 1), and pembrolizumab is not indicated with chemotherapy and trastuzumab for that patient population.

Other attempts to target HER2 in the first-line setting have not been successful. High-dose trastuzumab failed to demonstrate improved survival in comparison with standard dosing in the HELOISE study.[149] In contrast to the positive results observed with trastuzumab in the first-line setting, the addition of oral HER2 inhibitor lapatinib (LOGIC trial) or another anti-HER2 antibody pertuzumab (JACOB trial) to trastuzumab and chemotherapy failed to improve outcomes versus trastuzumab and

chemotherapy.[150,151] Of note, in a single-arm phase 2 study, zanidatamab, a novel bispecific antibody targeting two distinct HER2 epitopes, was studied in combination with first-line fluoropyrimidine/platinum in HER2-expressing GECs. The confirmed ORR was 79%, and the disease control rate was 92%. Median PFS was 12.5 months (95% CI, 7.1 months to not estimable), and median OS has not yet been reached (95% CI, 23.6 months to not estimable). The 12-month OS rate was 88% (95% CI, 73%-95%).

HERIZON-GEA-01 is an ongoing global phase 3 study for patients who have HER2-overexpressing GEA who are randomized between chemotherapy and trastuzumab versus chemotherapy and zanidatamab versus chemotherapy, zanidatamab, and tislelizumab (ClinicalTrials.gov identifier: NCT05152147).

EMERGING TARGETS

FGFR2-β is emerging as another important target in GEA. In a phase 2 study of 155 patients who have tumors selected for FGFR2-β overexpression, FOLFOX and bemarituzumab, a humanized IgG1 monoclonal antibody against FGFR2-β, showed encouraging efficacy with improvement in median PFS and OS in the bemarituzumab arm compared with placebo arms. This agent is currently being evaluated in two large phase 3 trials, FORTITUDE-101 and FORTITUDE-102 (NCT05111626, NCT05052801).

KEY POINTS

- The addition of trastuzumab and pembrolizumab to platinum and fluoropyrimidine is the standard of care in HER2-positive ($IHC3^+$ or $IHC2^+/FISH^+$) and PD-L1–positive (CPS ≥ 1) metastatic GEAs.
- In patients who have tumors that are HER2 positive but PD-L1 negative, the standard treatment is platinum with fluoropyrimidine and trastuzumab.

SECOND-LINE AND SUBSEQUENT THERAPY

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

The phase 3 randomized KEYNOTE-181 sec-line study evaluated the anti-PD-1 antibody pembrolizumab versus paclitaxel for the treatment of esophageal cancer. Substantial improvement in survival was noted only in ESCCs with tumors having a PD-L1 CPS ≥10, which led to FDA approval for this subgroup of patients on July 30, 2019.[152] Within the CPS ≥10 population, median OS was 10.3 versus 6.7 months in favor of pembrolizumab compared with monotherapy taxane/irinotecan, respectively. In contrast, in patients with CPS <10 tumors, median OS was 7.3 versus 7.5 months, respectively. The phase 3 randomized open-label ATTRACTION-3 study, conducted mostly in Asia, compared nivolumab with paclitaxel or docetaxel monotherapy for the treatment of second-line ESCC, which improved median OS to 10.9 months from 8.5 months and led to FDA approval on June 10, 2020. This was not evaluated by PD-L1 CPS scoring.[153]

In the setting of chemoimmunotherapy now being the standard first-line treatment, there is no role for monotherapy checkpoint inhibitor use in subsequent treatment lines for patients who have received initial immunotherapy in first line.

HER2-NEGATIVE ADENOCARCINOMA

Ramucirumab, a VEGFR-2 antibody, demonstrated benefit as monotherapy or in combination with paclitaxel in the second-line setting for advanced or metastatic gastric or GE junction adenocarcinoma.[154,155] In the REGARD trial, 472 patients whose disease had not responded to first-line fluoropyrimidine and platinum therapy were randomly assigned in a 2:1 fashion to receive single-agent ramucirumab or placebo.[154] Median OS was 5.2 months for the ramucirumab group and 3.8 months for the placebo group. Aside from a higher rate of hypertension, no relevant differences were seen in recorded adverse effects between ramucirumab and placebo. Combination ramucirumab and paclitaxel is the standard of care for second-line therapy in adenocarcinomas that do not overexpress HER2 based on the results of the RAINBOW trial. The RAINBOW trial (N = 665) compared second-line therapy with paclitaxel and placebo with paclitaxel and ramucirumab for those in whom disease had progressed after exposure to a platinum and fluoropyrimidine–based regimen.[155] OS was 9.6 months in the ramucirumab arm compared with 7.4 months with paclitaxel alone. Patients in the ramucirumab arm had a substantially higher response rate (28% vs 16%; $P = .001$) and improved PFS (4.4 vs 2.9 months; $P < .0001$) than patients in the paclitaxel and placebo arm.

Despite the activity of ramucirumab seen in these second-line setting therapies in which this was an approved standard option, studies in the first-line setting, including the phase 3 RAINFALL study and others, did not show a benefit to adding ramucirumab to first-line chemotherapy.[156-158] Similarly, the phase 3 AVAGAST study, in which combination bevacizumab and standard chemotherapy was evaluated versus chemotherapy alone in the first-line setting, was negative for OS.[159,160]

In patients who are not candidates for taxanes, combination FOLFIRI and ramucirumab is an acceptable option[161]; retrospective analyses of patients with GEA[162] led to the inclusion of this regimen as a category 2A recommendation in this setting in the NCCN guidelines for gastric cancer and esophageal and GEJ cancers. The RAMIRIS phase 2/3 study of FOLFIRI and ramucirumab versus paclitaxel and ramucirumab reported similar efficacy in the phase 2 part of the study with better efficacy for patients who had prior exposure to taxanes.[163]

Although anti-VEGFR-2 therapy with ramucirumab is the standard of care in second-line treatment, alternative chemotherapy options exist for second-line therapy based on studies evaluating chemotherapy versus best supportive care in which improvement in OS was clearly demonstrated with either irinotecan or taxane after failure of first-line combination fluoropyrimidine and platinum therapy.[164-168] Head-to-head comparison between two commonly used second-line therapies, paclitaxel and irinotecan, demonstrated similar efficacy, and each is a reasonable option.[166,167] There is a drop off in the number of eligible patients proceeding to second-line therapy. Even in modern studies, such as SPOTLIGHT, CheckMate 649, among others, there are only approximately 50% of patients who have preserved PS who remain candidates for continued treatment.[3,9,133,135,169] Similarly, the utility of chemotherapy in third-line and later treatment settings was debatable for the approximately 20% to 30% of patients still otherwise eligible for palliative therapy with preserved PS, but there is now support for continued therapy for these patients. A large phase 3 placebo-controlled randomized study, TAGS, evaluated oral trifluridine/tipiracil versus best supportive care and reported a modest survival advantage (median OS, 3.6-5.7 months) in a third-line (27% of patients) or higher setting (63% of patients); oral trifluridine/tipiracil is an option for therapy in these settings and gained FDA approval on February 25, 2019.[170]

For all patients with advanced disease, NGS testing should be performed in a CLIA-approved laboratory for identification of other biomarkers that can influence treatment selection.

Molecular characterization of EGA has identified mutations and copy-number variations in a number of readily targetable genes, including *ERBB2*, *EGFR*, *FGFR2*, *MET*, and *PI3K*/*mTOR*, along with other oncogenes, biomarkers, and immune oncological checkpoints that may serve as actionable therapeutic targets.[26,27,140,171]

- EGFR monoclonal antibodies added to chemotherapy in unselected patients did not improve patient survival, including in the two first-line GEA studies, EXPAND with cetuximab and REAL-3 with panitumumab, and the COG study of second-line or higher treatment of GEC with gefitinib.[172-174] The consistently negative data from these trials confirm there is no role for EGFR inhibitors in GEC, at least in unselected patients.[175,176]

Similarly, MET tyrosine kinase (hepatocyte growth factor [HGF] receptor) pathway inhibitors were assessed by selecting MET-expressing tumors in two large first-line GEA studies. Each study used different diagnostic antibodies and scoring systems, but both evaluated HGF ligand–blocking antibodies.[177,178] The RILOMET-1 study, in which the combination of the anti-HGF antibody rilotumumab and first-line epirubicin, cisplatin, and 5-fluorouracil (ECF) therapy was evaluated versus ECF and placebo, was negative despite a previous positive randomized phase 2 study.[179] The single-arm METGastric study evaluated the anti-MET antibody onartuzumab, which is another ligand–blocking antibody, and was also negative, confirming the lack of efficacy of this strategy for GEA.[178] Tumors with *MET* gene amplification remain a small subset that may derive benefit from MET-directed therapies, but these require additional investigation.[180]

HER2-POSITIVE ADENOCARCINOMA

Trastuzumab deruxtecan is now FDA approved in second and later lines of therapy for HER2-overexpressing gastric adenocarcinoma based on the results of the DESTINY-GASTRIC01 study. The phase 2 DESTINY-GASTRIC01 study included Asian patients with metastatic HER2-positive GEA who had received two or more prior lines of therapy and were randomly assigned in a 2:1 fashion to receive either trastuzumab deruxtecan (6.4 mg/kg every 3 weeks) or chemotherapy with irinotecan or paclitaxel. The study met its primary endpoint by demonstrating an improved ORR of 51% in the trastuzumab deruxtecan group compared with 14% in the physician's choice chemotherapy group ($P < .001$). Furthermore, OS was longer for patients treated with trastuzumab deruxtecan versus chemotherapy at 12.5 versus 8.4 months (HR, 0.59; 95% CI, 0.39-0.88; $P = .01$). Treatment with trastuzumab deruxtecan was associated with increased grade 3 toxicity bone marrow suppression and trastuzumab deruxtecan–induced interstitial lung disease and pneumonitis. DESTINY-GASTRIC02 was a single-arm study conducted in the Western part of the world that required confirmation of HER2 positivity postprogression during trastuzumab-based treatment before receiving trastuzumab deruxtecan. In the study, 89 patients were enrolled, and the confirmed ORR was 42%. Median PFS was 5.6 months, and median OS was 12.1 months. This drug is FDA approved for patients with HER2-positive GEA as second-line therapy or beyond. Therapy options in the second-line setting and beyond for HER2-negative patients are also used in the HER2-positive setting. Optimal sequencing of therapy remains to be determined.

PALLIATIVE CARE FOR PATIENTS WITH ADVANCED GEC

It is important to monitor and maintain patients' nutritional status in light of weight loss and continued difficulty with alimentation before and during perioperative treatment and surgery, as well as in the advanced metastatic setting. For tumor-related esophageal or gastric outlet obstruction in the advanced setting, several palliative options exist, including radiation therapy, esophageal stents, laser therapy, endoscopic dilation, and/or gastric or jejunal tube feeding. However, >80% of patients derive benefit from systemic palliative chemotherapy. Therefore, chemotherapy could be administered first, followed by radiation therapy. Stenting can be considered when the obstructive symptoms did not improve with chemotherapy and/or radiation.

For refractory bleeding from the primary tumor, endoscopic cautery, interventional radiology embolization, and radiation therapy are all options to address this common issue. Because thromboembolic events are common in advanced disease, balancing anticoagulation and intact primary tumors is often challenging, and clinical discretion as to the more pressing issue is recommended. Oral anticoagulants lead to a higher risk of bleeding compared with subcutaneous low-molecular-weight heparin if the primary tumor is in place, and this should be considered when treating thromboembolic events. Carcinomatosis and ascites are common in GEC, particularly gastric adenocarcinoma, and partial or complete bowel obstruction is frequently experienced by patients with these conditions. Venting gastrostomy tubes, peritoneal drain placement, and somatostatin analogs can be palliative in this subset of patients, particularly if symptoms are refractory to a trial of palliative first-line chemotherapy.[181] Having patients see palliative care physicians to manage the diverse set of these cancer–related symptoms and pain is encouraged as is seeing a nutritionist to assist with dietary issues. Oxaliplatin-induced neuropathy is common, and duloxetine has demonstrated palliative benefit. The OPTIMOX strategy (ie, intermittently adding and stopping oxaliplatin over time to limit cumulative neuropathy) as described in colon cancer is often routinely used for patients with GEA. Recent approvals of immune checkpoint blockade require consideration of all potential toxicities and treatments related to them.

KEY POINTS

- Nivolumab is FDA-approved second-line therapy for all ESCCs based on results from the ATTRACTION-3 study.
- Pembrolizumab is FDA-approved second-line therapy for patients who have metastatic ESCC with PD-L1 expression levels of CPS ≥10 based on results from KEYNOTE-181. In patients who have not received checkpoint inhibitor therapy as part of their first-line treatment, nivolumab or pembrolizumab monotherapy might be a viable option.
- The VEGFR antibody ramucirumab has shown efficacy in second-line phase 3 trials in advanced GEA and is now a standard-of-care option either alone or with paclitaxel therapy, leading to an NCCN guideline listing (category 1). Retrospective and prospective analyses show historically similar efficacy for FOLFIRI and ramucirumab compared with paclitaxel and ramucirumab with a potentially better toxicity profile, particularly for patients previously treated with taxanes, leading to an NCCN guideline listing (category 2A). However, no randomized controlled studies evaluating agents targeting angiogenesis in the first-line setting have shown an OS benefit.
- Approximately 50% of patients have preserved PS and derive benefit from continued treatment with palliative therapy in the second-line setting.
- Third-line chemotherapy has demonstrated a benefit compared with best supportive care or placebo, including with trifluridine and tipiracil (TAS-102), and should be considered for patients with preserved PS after two or more lines of therapy.
- The phase 2 randomized open-label DESTINY-GASTRIC01 study in Asian patients showed an improved ORR as well as PFS and OS for trastuzumab deruxtecan in comparison with chemotherapy as third-line or higher therapy for metastatic HER2-positive GEA, which led to FDA approval on January 15, 2021.

CANCERS OF THE LIVER AND BILIARY TREE

HEPATOCELLULAR CARCINOMA

Epidemiology and Etiology

Primary HCCs represent the highest global incidence of solid-organ tumors and are responsible for approximately 1 million deaths annually; although they are less common in the West, HCC is the cancer with the fastest-growing incidence rate in the United States[182] The risk factors for HCC are well known and include cirrhosis of any etiology. Hepatitis B virus infection accounts for approximately 60% of all liver cancer incidence in developing countries and approximately 23% of liver cancers in developed countries; the corresponding percentages for hepatitis C virus infection are 33% and 20%. Hepatitis B infection can be decreased by vaccination. Effective therapy to eradicate hepatitis C viral infection may lead to fewer cases of HCC in the coming years. The overall incidence of HCC in the Western world has been increasing, mostly as a result of alcohol-related cirrhosis and nonalcoholic steatohepatitis (NASH) associated with obesity. NASH is now referred to as MASH (metabolic dysfunction-associated steatohepatitis) to better reflect its etiology.

Clinical Presentation and Diagnosis

There are a number of presentations of HCC from asymptomatic disease found at screening to decompensated cirrhosis or paraneoplastic syndromes. Guidelines disseminated from several consensus conferences and professional organizations recommend HCC surveillance for patients with cirrhosis who are at high risk of development of HCC.[177] Ultrasound and serum alpha-fetoprotein (AFP) are the most commonly used modalities for HCC surveillance. Data suggest that an elevated subfraction of AFP, the lens culinaris agglutinin-reactive fraction of AFP (AFP-L3%), is a more reliable indicator of the presence of HCC in combination with CT scan or MRI for patients with hepatitis C–related cirrhosis than total AFP.[181] Making an HCC diagnosis with imaging alone versus a confirmatory biopsy has long been deliberated, and debate remains over whether to routinely incorporate biopsy into standard diagnostic practices.[183-185]

HCC is graded as well differentiated, moderately differentiated, and poorly differentiated. The most important pathological issue is the distinction between the fibrolamellar variant and the more traditional HCC. Fibrolamellar cancer is generally seen in younger patients, much more likely to be resectable, and less commonly associated with infection or cirrhosis.[186] In contrast, traditional HCC is found more often in men age >65 years.

Treatment

Localized HCC

The Barcelona Clinic Liver Cancer staging classification and treatment schedule have served as a paradigm on how to stage and treat HCC.[187] The treatment of choice for patients with localized HCC is surgical resection or transplantation. However, resection is not possible in most cases (often because of underlying cirrhosis), and transplantation is limited by organ availability and tumor burden. Fewer than 25% of tumors are resectable, often because of underlying liver disease and inadequate hepatic reserve.[188] HCC commonly presents as unresectable late-stage disease because of the multifocal nature of the disease in the liver, detection late in the disease course, and long asymptomatic latency until diagnosis. Attempts at administration of traditional cytotoxic systemic chemotherapy have been unsuccessful in demonstrating improvement in survival for patients with localized disease. Nonetheless, local ablative options have proven to be useful and have been associated with improved outcomes. Local ablative treatments are generally reserved for unresectable localized disease. In selected patients, local ablative therapy may also be used as bridging for liver transplantation candidates. These approaches include transcatheter arterial chemoembolization (TACE), transarterial radioembolization (TARE), alcohol injection, radiofrequency ablation, microwave ablation, and external-beam radiation therapy or stereotactic body radiation therapy (SBRT). In a recent meta-analysis of three randomized studies, TARE and TACE resulted in similar outcomes in unresectable HCC.[189] Percutaneous ablation achieves complete remission in >80% of tumors <3 cm in diameter but in only 50% of tumors 3 to 5 cm.[190] The single-center randomized phase 2 TRACE study[191] of patients with unresectable HCC treated with TARE or TACE reported prolonged time to progression and OS patients who received TARE; response rates were similar between treatment arms. Although response rates are relatively high, it is unclear whether these techniques result in a significant survival benefit. Meta-analyses[192,193] have supported the superiority of TARE compared to TACE in terms of response to treatment and time to progression, although conclusions regarding potential OS benefit of TARE vary.

Multimodality therapies combining systemic therapy with locally ablative therapies represent evolving therapeutic strategies that are under investigation in multiple studies. The randomized phase 3 NRG/RTOG 1112 study[194,195] demonstrated improvement in PFS and OS with the addition of SBRT to sorafenib treatment, with no significant increase in AEs; the trial was closed due to changes in the HCC treatment landscape. EMERALD-1[196] is a phase 3 randomized placebo-controlled study of TACE combined with durvalumab with or without bevacizumab in patients who have intermediate-stage HCC. The study met its primary endpoint of PFS for superiority of TACE, durvalumab, and bevacizumab versus TACE and placebos with OS data still pending. LEAP-012[197] is another study that combined TACE with systemic treatment in patients with locally advanced HCC. This phase 3 randomized, double-blind study compared patients receiving TACE plus lenvatinib with patients receiving TACE plus placebo. The co-primary endpoint of PFS for superiority of TACE plus lenvatinib over TACE plus placebo was met; however, the study was closed after an interim analysis (https://www.merck.com/news/merck-and-eisai-provide-update-on-phase-3-leap-012-trial-in-unresectable-non-metastatic-hepatocellular-carcinoma/) revealed that the study was unlikely to meet the co-primary OS endpoint. Previous data failed to show a benefit for patients undergoing systemic therapy after resection or ablation. The STORM trial tested whether patients would benefit from sorafenib after resection or ablation; there were no differences in recurrence-free survival or OS.[198] More recently, updated data from the IMbrave 050 trial, a randomized phase 3 study assessing the role of atezolizumab and bevacizumab versus active surveillance in patients with HCC undergoing resection and with a high risk of recurrence (>5 cm, more than three nodules, (micro)vascular invasion, or poorly differentiated), demonstrated that adjuvant treatment did not improve the primary endpoint of relapse-free survival nor did it improve OS.[199] Similarly, a prespecified interim analysis (https://www.merck.com/news/merck-co-inc-rahway-n-j-usa-announces-second-quarter-2025-financial-results/) of the phase 3 KEYNOTE-937 study reported that there was no improvement in the primary endpoint of recurrence-free survival with adjuvant pembrolizumab versus placebo.

Liver transplantation represents the ultimate local therapy for non-metastatic or liver-only unresectable HCC in the presence of liver cirrhosis. In this subgroup of patients, liver transplantation provides an excellent option for early-stage tumors because the procedure is therapeutic for both the cancer and the underlying pathology. Once patients have passed the high-risk peritransplantation phase, the prognosis is similar to that for patients who have had resection of localized disease.[200] Patients with known extrahepatic disease and gross vascular invasion are not candidates for liver transplantation.

Systemic Therapy For Advanced HCC

There seems to be no meaningful role for systemic cytotoxic chemotherapy in HCC although all randomized controlled trials (RCTs) have focused on Child–Pugh class A disease (CPA). Beyond CPA, there have been no clear standard options examined in the RCT setting, and concerns regarding the tolerability and safety of various standard systemic options in HCC remain. Combination

immunotherapy now represents the standard first-line treatment option for eligible patients with advanced HCC with no contraindications for immunotherapy, such as patients undergoing solid-organ transplantation or those with uncontrolled and severe autoimmune disease. Three immunotherapy combinations considered standard in the first-line setting for those eligible include combination atezolizumab and bevacizumab, single tremelimumab regular interval durvalumab (STRIDE), and combination nivolumab and ipilimumab. Atezolizumab plus bevacizumab and STRIDE demonstrated improved OS in comparison with the historical first-line therapy, sorafenib, while nivolumab plus ipilimumab demonstrated improved OS in comparison with investigator's choice of sorafenib or lenvatinib. PFS, however, was improved only with atezolizumab plus bevacizumab and not with STRIDE or nivolumab plus ipilimumab.

Historically, first-line therapy for advanced unresectable HCC with sorafenib was approved by the FDA in 2007 on the basis of results from the SHARP trial.[201] Similar findings were observed in the parallel Asian study.[202] Diarrhea, weight loss, hand-foot skin reaction, and hypophosphatemia were more common in patients receiving sorafenib than in control participants receiving placebo in these studies.

In the last decade, contemporary trials focusing on targeted therapies, including inhibitors of angiogenesis, signal transduction, and immune checkpoint inhibitors in combination, have shown promising results. Interestingly, several other multitargeted tyrosine kinase inhibitors (TKIs) with antiangiogenic activity have failed to achieve superiority to sorafenib in head-to-head studies, including sunitinib,[203] brivanib in the BRISK-FL study,[204] and linifanib.[205] Combinations of sorafenib with erlotinib (an anti-EGFR tyrosine kinase) in the SEARCH study or with everolimus were also negative.[206,207] In the REFLECT study, lenvatinib proved to be noninferior to sorafenib, thus establishing it as another option versus sorafenib.[208] As such, lenvatinib and sorafenib are considered reasonable treatment options for first-line treatment of HCC in patients who are not candidates for immunotherapy.[203,209]

Initial evidence for combination immunotherapy in the management of advanced HCC in the first-line setting was demonstrated in the IMbrave 150 study. IMbrave 150 was an open-label global phase 3 study in which patients with unresectable HCC were randomly assigned at a 2:1 ratio to receive atezolizumab and bevacizumab (n = 336 patients) or sorafenib (n = 165 patients). This study excluded patients who had untreated or incompletely treated esophageal or gastric varices (assessed with esophagogastroduodenoscopy and treated according to local clinical practice) with bleeding or high risk of bleeding. However, this study included patients with main portal vein tumor thrombus (Vp4). The coprimary endpoints were OS and PFS in the intention-to-treat population as assessed at an independent review facility according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1). The HR for death of atezolizumab and bevacizumab compared with sorafenib was 0.58 (95% CI, 0.42-0.79; $P < .001$),[199] with a 12-month OS rate for atezolizumab and bevacizumab of 67.2% (95% CI, 61.3-73.1) and 54.6% (95% CI, 45.2-64.0) for sorafenib. Median PFS was 6.8 months (95% CI, 5.7-8.3) for atezolizumab and bevacizumab and 4.3 months (95% CI, 4.0-5.6) for sorafenib (HR, 0.59; 95% CI, 0.47-0.76; $P < .001$). The results of this study resulted in FDA approval of the combination of atezolizumab and bevacizumab as first-line therapy in patients with advanced HCC.

The HIMALAYA trial provided the second level of evidence for combined immunotherapy, in this case combining dual immune checkpoint blockade targeting CTLA-4 and PD-L1. This phase 3 study randomly assigned patients who had previously untreated unresectable HCC to receive durvalumab and a single priming dose of tremelimumab (STRIDE regimen; n = 393 patients), durvalumab (n = 389), or sorafenib (n = 389) as first-line therapy. Of note, this study excluded patients with Vp4. The study met its primary endpoint, demonstrating a reduced risk of death in patients treated with the STRIDE regimen compared with sorafenib (HR, 0.78; 95% CI, 0.65-0.092; $P = .0035$). STRIDE-treated patients achieved a median OS of 16.4 versus 13.8 months. The study failed to show an improvement in median PFS, which was similar between the two groups, at 3.8 months for the STRIDE regimen and 4.1 months for sorafenib (HR, 1.02; 95% CI, 0.88-1.99). Serious treatment-related AEs occurred in 17.5% of patients treated with STRIDE, 8.2% of those in the durvalumab arm and 9.4% of those treated with sorafenib. STRIDE treatment-related deaths resulted from immune-mediated toxicity. The results of this study led to FDA approval of the STRIDE regimen for the treatment of unresectable HCC.

In the CheckMate-9DW[11] study first-line combination nivolumab and ipilimumab (NIVO + IPI) improved median OS versus investigator's choice of lenvatinib or sorafenib (LEN/SOR) in patients with untreated unresectable HCC. In total, 668 patients were randomized to NIVO + IPI (n = 335) or LEN/SOR (n = 333); among 325 patients treated in the LEN/SOR arm, 275 (85%) received LEN. After a median (range) follow-up of 35.2 (26.8-48.9) months, median OS was 23.7 months with NIVO + IPI versus 20.6 months with LEN/SOR (HR, 0.79; 95% CI, 0.65-0.96; $P = .0180$) with respective 24-month OS rates (95% CI) of 49% (44-55) versus 39% (34-45). ORR was higher with NIVO + IPI (36%) versus LEN/SOR (13%; $P < .0001$); complete response was observed in 7% of patients with NIVO + IPI versus 2% with LEN/SOR. Median duration of response (DOR) was 30.4 months with NIVO + IPI versus 12.9 months with LEN/SOR. Treatment-related adverse events (TRAEs) were reported in 84% of the NIVO + IPI arm and 91% of the LEN/SOR arm, and grade 3 or 4 TRAEs were 41% and 42%, respectively. Any-grade TRAEs led to treatment discontinuation in 18% of patients receiving nivolumab and ipilimumab and 10% receiving lenvatinib or sorafenib. Combination atezolizumab and bevacizumab, tremelimumab and durvalumab, or ipilimumab and nivolumab are considered first-line therapy for appropriately fit patients with unresectable HCC and preserved liver function. Several phase 3 studies evaluating other

combination therapies in the first-line setting, including atezolizumab in combination with cabozantinib (COSMIC-312)[210] and pembrolizumab in combination with lenvatinib (LEAP-002),[211] showed no improvement over sorafenib and lenvatinib, respectively. CARES-310[212] assessed the role of camrelizumab in combination with rivoceranib, which proved superior to sorafenib; this regimen has not received FDA approval for use in the United States.

With the recent simultaneous approvals of several therapies in the same second-line indication, the optimal sequencing of these therapies post-immunotherapy is not well established. Regorafenib proved superior to placebo in the second-line treatment of patients with advanced HCC who experienced progression during or were intolerant to sorafenib in the RESORCE study.[213] Patients treated with regorafenib experienced a median OS of 10.6 months versus 7.8 months with placebo (HR, 0.63; 95% CI, 0.5-0.79; $P < .0001$), which led to FDA approval on April 27, 2017.[213] The REACH phase 3 study evaluating the efficacy of ramucirumab for patients with HCC whose disease had progressed during prior sorafenib therapy was negative; however, the follow-up REACH-2 phase 3 study confirmed the benefit of ramucirumab for patients with an AFP level ≥400 ng/mL, which led to approval in this indication on May 10, 2019. A pooled analysis of patients with an AFP level ≥400 ng/mL (n = 542) from the REACH and REACH-2 studies demonstrated improved median survival to 8.1 from 5.0 months with placebo (HR, 0.694; 95% CI, 0.571-0.842; $P = .0002$).[214] The CELESTIAL phase 3 study evaluated 707 patients who were randomly assigned (2:1) to receive cabozantinib or placebo, which led to FDA approval of cabozantinib on January 14, 2019.[215] Eligible patients had received previous treatment with sorafenib, had disease progression after at least one systemic treatment of HCC, and could have received up to two previous systemic regimens for advanced HCC. At the second planned interim analysis, median OS was 10.2 months with cabozantinib versus 8.0 months with placebo (HR, 0.76; 95% CI, 0.63-0.92; $P = .005$). Most patients had received only one prior systemic therapy (72%) compared with two prior systemic therapies (27%) with more pronounced OS benefit in the second line (HR, 0.74; 95% CI, 0.59-0.92) compared with the third line (HR, 0.9; 95% CI, 0.63-1.29). The appropriate sequencing of second-line therapy with a TKI or ramucirumab is complicated by the fact that all the studies were conducted after sorafenib failure with no data available post-immunotherapy. Finally, pembrolizumab remains the only anti-PD-1 immune checkpoint inhibitor approved for use in the second-line setting after sorafenib failure. In the follow-up randomized phase 3 KEYNOTE-240 study, pembrolizumab did not significantly improve survival compared with placebo.[216] In that study, 413 patients were randomly assigned at a 2:1 ratio (n = 278 patients received pembrolizumab; n = 135 received placebo). The HR for OS was 0.78, and the HR for PFS was 0.78, in favor of pembrolizumab; however, these differences did not meet significance per the prespecified statistical plan. The double-blind phase 3 KEYNOTE-394[217] study investigated patients from Asia with metastatic HCC who had experienced progression with sorafenib and were randomly assigned to receive pembrolizumab or best supportive care. Pembrolizumab treatment resulted in a 21% reduction in death (HR, 0.79; 95% CI, 0.63-0.99) and median OS of 14.6 months (95% CI, 12.6-18.0) in comparison with 13.0 months (95% CI, 10.5-15.1) for best supportive care. These results support the continued approval for use of pembrolizumab in second-line treatment of HCC although its potential applicable use is complicated by the fact that the first-line landscape has changed dramatically over the years.[218] Conditional FDA approval has been granted for nivolumab and ipilimumab used after first-line TKI therapy in fit patients based on CheckMate 040 (Table 13.1-2).

Table 13.1-2 Current Clinical Trials Paradigm for Hepatocellular Carcinoma

Treatment Line	Outcome	Notes	Study
First			
Sorafenib vs placebo	Superiority study	First approved first-line therapy, December 1, 2007	SHARP study[201]
Lenvatinib vs sorafenib	Noninferiority study	Approved August 16, 2018	REFLECT study[208]
Atezolizumab and bevacizumab vs sorafenib	Superiority study	Approved May 29, 2020	IMbrave 150 study[199]
Durvalumab and tremelimumab vs sorafenib	Superiority study	Approved October 21, 2022	HIMALAYA study[10]
Nivolumab and ipilimumab vs investigator's choice of sorafenib or lenvatinib	Superiority study	Approved April 11, 2025	CheckMate 9DW study[11]
Second			
Regorafenib vs placebo	Superiority study	First approved second-line therapy, April 27, 2017	RESORCE study[213]
Ramucirumab vs placebo	Superiority study	AFP ≥400 ng/mL eligible; approval May 10, 2019	REACH-2 study[219]

Treatment Line	Outcome	Notes	Study
Pembrolizumab		Conditional approval December 17, 2018; has not been removed	KEYNOTE-224 study,[220,221] KEYNOTE-240 study,[216] KEYNOTE-394 study[218]
Nivolumab and ipilimumab		Accelerated approval March 10, 2020	CheckMate 040 study[222]
Second and third			
Cabozantinib vs placebo	Superiority study	Approved January 14, 2019	CELESTIAL study[215]

Abbreviation: AFP, alpha-fetoprotein.
FDA approval of second-line nivolumab is revoked because of lack of efficacy in confirmatory study.
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BILIARY CANCERS

Epidemiology, Etiology, and Clinical Presentation

BTCs comprise a diverse group of cancers, including intrahepatic cholangiocarcinoma (IHCC), hilar cholangiocarcinoma, extrahepatic cholangiocarcinoma (EHCC), and gallbladder cancer. Historically, these were considered a uniform entity, but they now are recognized to be quite distinct in terms of etiology, molecular biology, and most recently treatment.[220,224-227] In Western countries, cholangiocarcinoma is associated with metabolic syndrome, inflammatory bowel disease, primary sclerosing cholangitis, and hepatolithiasis, whereas liver fluke and hepatitis B viral infections are important risk factors in Asian countries.[228-231] Cholangiocarcinoma is most common in women age >50 years, and long-term survival is highly dependent on the effectiveness of surgical therapy. A number of risk factors for gallbladder cancer have been described and include the following:[230,231]

- Obesity
- Female sex
- Family history
- Middle age
- Gallstones causing chronic inflammation
- Porcelain gallbladder (ie, hardened gallbladder as a result of calcium deposits)
- Ethnicity (highest in Mexican, Latin American, and Native American individuals)
- Choledochal cysts (ie, bile-filled sacs along the common bile duct)
- Gallbladder polyps
- Abnormalities of the bile ducts causing backflow
- Primary sclerosing cholangitis

Recent molecular studies demonstrate distinct molecular profiles between anatomic sites and geographic or etiologic subsets.[232-235] Cancers of the extrahepatic bile duct and gallbladder are relatively rare with only 12,610 cases diagnosed annually in the United States, resulting in approximately 4,400 deaths annually.[15,236] Approximately 50% of gallbladder cancers are incidental findings on cholecystectomy. Unfortunately, the United States statistics do not provide specific data for IHCC incidence but classify them under hepatobiliary tumors; the actual incidence of biliary cancers as a whole is definitely higher, perhaps approaching the incidence of esophageal cancers, with approximately 15,000 cases per year.[237] Adenocarcinomas of unknown primary site involving the liver are increasingly recognized as primary IHCCs, which has also led to an increase in incidence of the disease.[238]

Typical presentation of cholangiocarcinoma includes jaundice, pain, anorexia, abnormal laboratory test results, or a mass evident on CT scan or ultrasound or visualized endoscopically. Gallbladder cancer often presents as vague postprandial right-upper quadrant pain and is often initially diagnosed as gallstones with incidental finding of gallbladder cancer at the time of resection and/or in the pathology specimen. The location of the primary tumor often dictates which of these symptoms predominantly occur, such as painless jaundice with EHCC, which is quite similar to that seen with pancreatic cancer.

Treatment of Localized Disease

The primary treatment is surgical resection if localized and technically feasible. Because of the location of these tumors, they are frequently difficult to resect; therefore, specialized surgical intervention should always be sought. The cure rate for patients with early-stage disease ranges from 60% to 70%; however, for patients with more advanced-stage disease, the 5-year survival rate is only 10% to 25%.[227,239,240] Prognostic factors associated with decreased relapse-free survival and OS include LN positivity and R1 resection. It is important to note that, when gallbladder cancer is found after laparoscopic cholecystectomy, reresection of the adjacent liver segment and lymphadenectomy are indicated for all disease stages except T1a (limited to the lamina propria).[241,242]

The role of adjuvant therapy continues to be an emerging field with only a few randomized studies. In the phase 3 PRODIGE 12-ACCORD 18 trial, GEMOX (gemcitabine and oxaliplatin) was evaluated and compared with observation in 196 patients randomly assigned after curative-intent resection of BTC, showing no significant difference in relapse-free survival between the two groups.[243] In the BILCAP study,[244] patients with completely resected cholangiocarcinoma or gallbladder carcinoma were randomly assigned to capecitabine at 1,250 mg/m^2 per day (capecitabine administered twice daily on days 1-14 of 21-day cycles) or observation. In the intention-to-treat analysis, median OS was 51.1 months (95% CI, 34.6-59.1) in the capecitabine group compared with 36.4 months (95% CI, 29.7-44.5) in the observation group (adjusted HR, 0.81; 95% CI, 0.63-1.04; *P* = .097). In a protocol-specified sensitivity analysis, adjusting for minimization factors, nodal status, grade, and sex, the OS HR was 0.71 (95% CI, 0.55-0.92; *P* = .010).[244] These data helped establish capecitabine as an acceptable standard for patients with resected cholangiocarcinoma. Additional studies are under way to assess the role of adjuvant gemcitabine and cisplatin with or without immunotherapy in this setting.

The role of radiation therapy in the adjuvant setting is less clear, with an absence of randomized studies evaluating CRT in resected BTCs.[245] The single-arm Intergroup S0809 study evaluated the role of adjuvant chemotherapy comprising four cycles of gemcitabine and capecitabine every 21 days followed by concurrent capecitabine and radiation therapy in EHCC. For all patients, the 2-year survival rate was 65% (95% CI, 53%–74%); it was 67% and 60% for patients who underwent R0 and R1 surgery, respectively. Median OS was 35 months for all patients (R0, 34 months; R1, 35 months). Local, distant, and combined relapses occurred in 14, 24, and 9 patients, respectively. A recent meta-analysis demonstrated that the greatest benefit with adjuvant therapy was in patients with biliary cancers who had LN-positive disease (odds ratio (OR), 0.49; *P* = .004) and in those who had a positive microscopic resection margin (OR, 0.36; *P* = .002).[246] A number of web-based nomograms predicting the benefit of adjuvant chemotherapy and CRT have been developed for BTCs as well as for specific subsets (IHCC, hilar cholangiocarcinoma, EHCC, and gallbladder), which can serve as guidelines in the absence of definitive phase 3 data in this setting.[247-251]

Treatment of Advanced Disease

The efficacy of systemic chemotherapy alone in advanced BTCs has been limited with response rates ranging from 10% to 40% for single-agent and combination chemotherapy regimens.[239] The phase 3 ABC-02 (advanced biliary cancer) trial represented the first RCT assessing the role of systemic therapy in advanced BTC. The study randomly assigned 410 patients who had advanced BTC to receive first-line gemcitabine at 1,000 mg/m^2 on days 1, 8, and 15 every 4 weeks for six cycles or 1,000 mg/m^2 of gemcitabine and 25 mg/m^2 of cisplatin on days 1 and 8 every 3 weeks for eight cycles.[252] The addition of low-dose cisplatin did not result in substantial differences in grade 3 or 4 toxicities. PFS was 8.4 months in the gemcitabine and cisplatin arm and 6.5 months in the gemcitabine only arm (HR, 0.72; 95% CI, 0.57-0.90; *P* = .003). This translated into an OS benefit with a median OS of 11.7 months in the gemcitabine and cisplatin arm compared with 8.3 months in the gemcitabine only arm (HR, 0.70; 95% CI, 0.54-0.89; *P* = .002). AEs were similar in the two groups with the exception of more neutropenia in the cisplatin and gemcitabine group. This trial established combination gemcitabine and cisplatin as a new standard of care in the treatment of advanced biliary cancers. GEMOX has also been studied, and oxaliplatin may be substituted for patients who are not candidates for cisplatin therapy.[253]

The TOPAZ-1 trial established chemoimmunotherapy with durvalumab as a standard first-line treatment of patients with unresectable, recurrent, or metastatic BTC. Six hundred eighty-five previously untreated patients who had unresectable, recurrent, or metastatic BTCs were randomly assigned to receive durvalumab or placebo in addition to gemcitabine and cisplatin.[254] Patients received 1,500 mg of durvalumab every 3 weeks or placebo combined with standard gemcitabine and cisplatin every 3 weeks for up to eight cycles followed by 1,500 mg of durvalumab or placebo every 4 weeks until disease progression. The estimated 24-month OS rate for patients treated with durvalumab and chemotherapy was 24.9% versus 10.4% for chemotherapy alone with an HR for OS of 0.80 (95% CI, 0.66-0.97; *P* = .021), favoring durvalumab and chemotherapy. In addition, there was a significant improvement in PFS (HR, 0.75; 95% CI, 0.63-0.89; *P* = .001) and higher ORR (26.7% vs 18.7%).[254] More recently, another chemoimmunotherapy approach showed benefit in biliary tract tumors. The phase 3 KEYNOTE-966 trial randomly assigned patients with untreated locally advanced or metastatic BTC to receive gemcitabine and cisplatin with pembrolizumab or gemcitabine and cisplatin with placebo.[255] Median OS increased from 10.9 to 12.7 months with the addition of pembrolizumab (HR, 0.83; 95% CI, 0.72-0.95; *P* = .0034). More patients had an ongoing response at 24 months in the pembrolizumab group than in the placebo group (18% vs 6%). In KEYNOTE-966, patients who had IHCC seemed to derive greater survival benefit from pembrolizumab than those who had tumors at other primary locations (HR, 0.76; 95% CI, 0.64-0.91), whereas in TOPAZ-1, the benefit was also seen in EHCC. In both studies, patients who had gallbladder cancer seemed to have less benefit, and there was no significant relationship between higher PD-L1 expression and improved outcomes with chemoimmunotherapy. The results of KEYNOTE-966 support the use of pembrolizumab with gemcitabine and cisplatin as another treatment option for patients who had previously untreated metastatic or unresectable BTC. It is important to note that, in TOPAZ-1 and KEYNOTE-966, PD-L1 expression was not an eligibility criterion and should not be used to select patients for immunotherapy with biliary cancer.

The ABC-06 randomized phase 3 study compared modified FOLFOX chemotherapy versus active symptom control for second-line treatment of BTCs.[256] Median OS was 6.2 months for the chemotherapy arm versus 5.3 months for active symptom control

(adjusted HR, 0.69; 95% CI, 0.50-0.97, P = .031). The role of liposomal irinotecan in the second-line setting of BTC remains unclear. The phase 2b NIFTY trial showed that 5-FU, leucovorin, and liposomal irinotecan had superior outcomes compared with 5-FU and leucovorin in South Korean patients who had disease progression during gemcitabine and cisplatin therapy.[257] However, the recently published phase 2 AIO NALIRICC trial showed that the addition of liposomal irinotecan to FU and leucovorin failed to improve outcomes and worsened toxicity in European patients.[258]

Recently, molecular profiling has revealed targeted therapeutic options for patients with cholangiocarcinoma, particularly IHCC with MSI-H, *FGFR2* fusions (10% of patients with IHCC), *BRAF* V600E mutations (5% of patients), *HER2* amplifications (5% of patients), or *IDH1* mutations (15% of patients with IHCC).[235,259] Thus, molecular profiling of newly diagnosed advanced biliary cancers is essential to ensure potential therapeutic targets are not missed. The randomized phase 3 ClarIDHy study with the IDH1 inhibitor ivosidenib versus placebo for *IDH1*-mutated cholangiocarcinoma met its primary endpoint of PFS and reported improved quality-of-life, leading to FDA approval on August 25, 2021.[260] Targeting *FGFR2* fusions in IHCC has yielded recent accelerated approvals by the FDA.[261,262] First, on the basis of the FIGHT-202 study, pemigatinib obtained accelerated approval for patients with chemorefractory cholangiocarcinoma harboring *FGFR2* fusions on April 20, 2020.[261] The single-arm phase 2 study FOENIX-CCA2 demonstrated the role of futibatinib in FGFR inhibitor–naive patients with unresectable or metastatic *FGFR2* fusion–positive or *FGFR2* rearrangement–positive IHCC who developed disease progression after one or more previous lines of systemic therapy. Treatment with futibatinib demonstrated a response in 43 (42%) of 103 patients (95% CI, 32-52) and was associated with a median PFS of 9.0 months and OS of 21.7 months, leading to the FDA approval of futibatinib. Second-generation FGFR inhibitors such as RLY 4008 are being developed with promising early results.[263,264] The combination of dabrafenib and trametinib has shown activity in patients who have *BRAF* V600E–mutated BTC. In the phase 2 multicenter ROAR (rare oncology agnostic research) basket trial, 43 patients with *BRAF* V600E–mutated BTC were enrolled. Overall response[265] was achieved by 20 (47%) of 43 patients (95% CI, 31.2-62.3). The most common grade ≥3 AE was increased γ-glutamyl transferase in five patients (12%); 17 patients (40%) had serious AEs, and nine (21%) had treatment-related serious AEs, the most frequent of which was pyrexia (eight [19%]). No treatment-related deaths were reported.[266] SGNTUC-019 was an open-label phase 2 basket study evaluating the efficacy and safety of tucatinib and trastuzumab in patients with HER2-altered solid tumors, including a BTC cohort with HER2-overexpressing or *HER2*-amplified (HER2$^+$) tumors. The confirmed ORR was 46.7% (90% CI, 30.8-63.0) with a median DOR and PFS of 6.0 months (90% CI, 5.5-6.9) and 5.5 months (90% CI, 3.9-8.1), respectively. The two most common treatment-emergent AEs were pyrexia (43.3%) and diarrhea (40.0%).[267] A previous study with pertuzumab and trastuzumab suggested similar favorable outcomes.[268]

The phase 2 single-arm HERIZON-BTC-01 assessed the safety and efficacy of zanidatamab, a bispecific antibody targeting two distinct HER2 epitopes, in patients who have unresectable or metastatic *HER2*-amplified BTC who had previously received gemcitabine-based therapy. Patients received zanidatamab 20 mg/kg intravenously every 2 weeks Among patients with HER2-positive disease (IHC 2$^+$ and 3$^+$), confirmed ORR was 41.3%. In the subgroup of IHC 3$^+$, ORR was 51.6%, and median DOR increased to 14.9 months (95% CI, 7.4 not reached). The most common TRAEs included diarrhea (any grade, 36.8%), infusion-related reaction (33.3%), decreased ejection fraction (10.3%), and nausea (9.2%). Based on these results, the FDA granted accelerated approval of zanidatamab in HER2-positive (IHC 3$^+$) advanced BTC on November 20, 2024.[12,269] An open-label randomized phase 3 trial evaluating the addition of zanidatamab to combination treatment with gemcitabine and cisplatin, with or without pembrolizumab or durvalumab, is ongoing (ClinicalTrials.gov ID NCT06282575).

KEY POINTS

- HCC is an important cancer, and global incidence can be reduced by vaccination against hepatitis B virus; treatment of hepatitis C is curative, which may lead to reduced incidence of HCC in the coming years. Alcohol abuse, obesity, and metabolic syndrome represent modifiable risk factors, the moderation of which could also reduce worldwide incidence of the disease.
- The Barcelona Clinic Liver Cancer staging classification and treatment schedule have served as a main paradigm on how to broadly stage and treat HCC.
- Local ablative treatments are generally reserved for intermediate disease. These approaches include TACE, TARE, alcohol injection, radiofrequency ablation, microwave ablation, and external-beam radiation therapy or stereotactic radiation therapy.
- Combination locoregional plus systemic therapy options show promise in the intermediate stage of the disease and require further optimization.
- There is no role for adjuvant treatment in patients with resected HCC.
- The SHARP study established the first standard systemic therapy in HCC with sorafenib.[201]
- The IMbrave 150 study confirmed the benefit of atezolizumab and bevacizumab in first-line treatment compared with sorafenib for advanced HCC.[199]
- The HIMALAYA study demonstrated the role of tremelimumab and durvalumab as a first-line treatment option compared with sorafenib for advanced HCC.[10]

- CHECKMATE 9DW demonstrated the role of ipilimumab and nivolumab as a first-line treatment option compared with investigator's choice of sorafenib or lenvatinib for advanced HCC.[11]
- The REFLECT study confirmed the noninferiority of lenvatinib in first-line treatment compared with sorafenib for advanced HCC.[208]
- The RESORCE study confirmed the benefit of regorafenib in second-line treatment compared with placebo for advanced HCC.[213]
- The CELESTIAL study confirmed the benefit of cabozantinib in second- and third-line treatment compared with placebo for advanced HCC after sorafenib.[215]
- The REACH-2 study confirmed the benefit of ramucirumab in the second-line treatment of patients with AFP level ≥400 ng/mL compared with placebo for advanced HCC.[219,223]
- Immune checkpoint blockade has great promise in HCC with improved response rates and meaningful DOR in select patients with response to anti-PD-1 monotherapy. However, to date, treatment with monotherapy checkpoint blockade has not demonstrated definitive survival benefit in any patients in larger phase 3 randomized studies compared with sorafenib in the first-line setting or placebo in the second-line setting. Biomarker studies to identify those who may derive the most benefit are ongoing.
- The treatment paradigm of advanced HCC is in flux with the addition of all these agents relatively simultaneously without direction on the best sequencing approach.
- Resection, when feasible, is the mainstay of treatment of hepatobiliary tumors.
- The randomized phase 3 BILCAP study of adjuvant capecitabine versus observation in resected BTCs demonstrated improved OS in the prespecified per-protocol analysis and can be considered a standard of care.
- There is limited clinical evidence supporting the adoption of concurrent radiation therapy in the adjuvant setting, but this could be considered for patients who have high risk of relapse, such as patients who have positive LN disease and positive microscopic margins.
- Chemoimmunotherapy comprising durvalumab with gemcitabine and cisplatin as well as pembrolizumab with gemcitabine and cisplatin is a new standard of care option for first-line treatment of patients with advanced BTCs.
- The combination of 5-FU with oxaliplatin represents an appropriate second-line therapy for patients lacking an actionable somatic mutation who have developed progressive disease during gemcitabine and platinum combination therapy based on the ABC-06 trial.
- NGS should be incorporated into routine standard of care for patients who have advanced BTC to identify actionable molecular abnormalities (*FGFR2* fusions, *IDH1* mutations, *HER2* amplification, *BRAF* V600E, and MSI-high).
- The phase 3 ClarIDHy trial with the IDH1 inhibitor ivosidenib versus placebo for *IDH1*-mutated cholangiocarcinoma met its primary endpoint of PFS with the added benefit of improved quality-of-life.
- The FGFR inhibitors pemigatinib and futibatinib have received accelerated FDA approval for the treatment of *FGFR2* fusion–positive or *FGFR2* rearrangement–positive cholangiocarcinoma. The ROAR basket study using the combination of dabrafenib and trametinib showed benefit for patients who have BTC harboring *BRAF* V600E–mutations.
- Zanidatamab is a new bispecific antibody targeting HER2 that has been FDA-approved to treat unresectable or metastatic HER2-positive (IHC3+) BTC previously treated with gemcitabine-based chemotherapy.

PANCREATIC CANCER

EPIDEMIOLOGY AND ETIOLOGY

Pancreatic ductal adenocarcinoma (PDAC) is a substantial health problem in the United States with an annual incidence of 67,440 cases and death occurring in 51,980 patients annually[16] with only 13% surviving 5 years.[270,271] Survival rates are better for those who have localized disease with a 5-year survival rate of >35%, but remain dismal for those with metastatic disease with a 5-year survival of only 3%.[272] The nonhereditary risk factors for pancreatic cancers include older age, long-standing diabetes, chronic pancreatitis, intraductal pancreatic mucinous neoplasms, cigarette smoking, obesity, physical inactivity, and a diet high in saturated fats.[273] Diabetes can also be a paraneoplastic syndrome in pancreatic cancer although in some cases this may simply be a coincident diagnosis. Patients with new-onset diabetes have a fivefold- to eightfold-increased risk of being diagnosed with pancreatic cancer within 1 to 3 years. It is also not uncommon for patients who have well-controlled long-standing diabetes to develop unexplained poor control of their diabetes and subsequently be diagnosed with pancreatic cancer. More recent data suggest pathogenic germline alterations may be present in up to 20% of unselected exocrine pancreatic cancers and have led to the recommendation for universal testing of patients with pancreatic cancer for germline mutations regardless of family history.[274,275] There is no agreed-on approach for screening patients for pancreatic cancer who have an identified germline mutation, but screening typically involves alternating magnetic resonance cholangiopancreatography and EUS procedures. Several ongoing trials are attempting to define the best screening algorithms.

There is no standard surveillance or screening for pancreatic cancer. Pancreatic intraepithelial neoplasias, which are microscopic lesions of the pancreas, and intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, which are both macroscopic lesions often found incidentally during imaging for other reasons, are thought to be precursors of invasive pancreatic cancer, especially those involving the main pancreatic duct.[276,277] The American Gastroenterological Association has issued management guidelines for these lesions.[278] More than 90% of pancreatic cancers harbor activating genetic mutations of the oncogene *KRAS*, which is integrated in signaling pathways of various receptor kinases, such as EGFR and insulin-like growth factor receptor I. In addition, >50% of pancreatic cancers harbor mutations in at least one of three tumor suppressor genes: *p16/CDKN2A*, *TP53*, and *SMAD4*. *BRCA* mutations are less common and found in approximately 5% of pancreatic cancers, but they have recently been found to have therapeutic implications as is discussed in more detail in this section under "First-Line Therapy."[275,277] The advent of drugs targeting these genetic mutations supports the practice of complete germline and somatic genetic analyses of patients upon diagnosis of pancreatic adenocarcinoma (Table 13.1-3).

Table 13.1-3 Germline Mutations Associated With Pancreatic Cancer

Mutated Gene	Syndrome
BRCA1, *BRCA2*	Hereditary breast and ovarian syndrome
ATM	Ataxia-telangiectasia
PALB2	Hereditary breast cancer
PRSS1	Hereditary pancreatitis
STK11	Peutz-Jeghers syndrome
CDKN2A	Familial atypical multiple mole and melanoma syndrome
MLH1, *MLH2*, *MSH6*, *PMS2*	Lynch syndrome

Abbreviations: *ATM*, *ATM* serine/threonine kinase; *BRCA1/2*, *BRCA1/2* DNA repair–associated protein; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *MLH1/2*, DNA mismatch repair protein *MLH1/2*; *MSH6*, MutS homolog 6; *PALB2*, partner and localizer of *BRCA2*; *PRSS1*, protease, serine 1; *STK11*, serine/threonine protein kinase 11.
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CLINICAL PRESENTATION AND DIAGNOSIS

Symptoms associated with pancreatic cancer at the time of presentation commonly include abdominal pain with or without back pain, cachexia, and/or jaundice. Initial symptoms are often vague and can vary based on location with pancreatic head lesions more likely to cause jaundice and tail lesions often asymptomatic and, thus, diagnosed at a later stage. When evaluating patients who have adult-onset diabetes without other risk factors or worsening diabetes without an obvious cause, physicians should consider pancreatic cancer as a possible diagnosis.[275]

The most common diagnostic tests used for pancreatic cancer are triple-phase pancreatic protocol CT scan (so arterial and venous structures are clearly evaluable and differences between enhancement of pancreatic parenchyma and lack of enhancement of tumor are emphasized), MRI, EUS, and endoscopic retrograde cholangiopancreatography. Tissue is best obtained by EUS-guided biopsy and, for those patients presenting with biliary obstruction and for whom immediate surgery is not planned, placement of a biliary stent. Although pancreatic cancer is staged using the standard TNM methodology, in practice, it is often classified as resectable, borderline resectable, locally advanced/unresectable, or metastatic. Degree of vascular involvement, particularly of the superior mesenteric artery and celiac artery, is a criterion in distinguishing resectable and borderline resectable from locally advanced unresectable disease. Additional criteria used in determining unresectability include significant encasement of the common hepatic artery or unreconstructable venous involvement. Levels of serum carbohydrate antigen 19.9 (CA 19-9) may provide limited benefit in predicting resectability and/or surgical outcomes, and should be considered in combination with other criteria when making surgical decisions.[279-282]

TREATMENT

General Principles

The most important component in the management of a patient newly diagnosed with non-metastatic pancreatic cancer is the involvement of a multidisciplinary team at a center with high-volume experience with this cancer. The continuum is complex and often requires the opinions of surgeons and expert radiologists, endoscopists, and radiation oncologists. Although surgery has been the mainstay of treatment of pancreatic cancer and remains an essential component of a curative approach, cure rates with surgery alone remain dismal. This has led to the incorporation of more highly active chemotherapy regimens, such as FOLFIRINOX, into the adjuvant setting and, increasingly, into the neoadjuvant setting. The duration and sequence of these therapies and their role in converting previously unresectable cancers into resectable cancers are the subjects of multiple studies, and the field is rapidly evolving.[283]

Resectable Pancreatic Cancer: Adjuvant Therapy

The appropriate adjuvant treatment of resectable pancreatic cancer has come into clearer focus over the last several years although some controversy remains regarding the role of radiation therapy. A German phase 3 trial (CONKO-001) including 364 patients demonstrated the superiority of adjuvant chemotherapy with gemcitabine compared with surgery alone for patients with resected pancreatic cancer regardless of whether a tumor-free resection margin could be obtained.[284,285] An update of this study demonstrated a substantial improvement in 5-year OS at 20.7% (95% CI, 14.7%–26.6%) for gemcitabine compared with 10.4% (95% CI, 5.9%–15.0%) for surgery alone.[286] Building on CONKO-001, the ESPAC-4 study compared adjuvant gemcitabine with gemcitabine and capecitabine in a large phase 3 study of 732 patients.[287] This study demonstrated a modest improvement in survival with combination adjuvant therapy; median survival was 28.0 versus 25.5 months with gemcitabine alone (HR, 0.82; 95% CI, 0.68-0.98; *P* = .032) with a 5-year OS rate of 29% (95% CI, 22.0%–35.2%) versus 16% (95% CI, 10.2%–23.7%). To date, the most important and practice-changing adjuvant clinical trial was the phase 3 PRODIGE-24 trial,[288] which compared 6 months of adjuvant FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) with gemcitabine therapy; median disease-free survival (DFS) and OS with adjuvant FOLFIRINOX were 21.6 and 53.5 months, respectively. To date, this is the longest median survival seen in a phase 3 trial of adjuvant therapy for pancreatic cancer. As a result, FOLFIRINOX is the preferred adjuvant therapy for patients who are fit enough and have recovered adequately from surgery to receive this regimen.

The phase 3 APACT (adjuvant therapy for patients with resected pancreatic cancer) study compared gemcitabine with gemcitabine plus nab-paclitaxel in the adjuvant setting and did not meet its primary endpoint of improved median DFS; however, long-term follow-up demonstrated persistent improved OS for patients treated with gemcitabine and nab-paclitaxel with median OS of 41.8 versus 37.7 months with gemcitabine alone (HR, 0.80; 95% CI, 0.678-0.947; *P* = .0091).[289] At this point, the role of gemcitabine plus nab-paclitaxel in the adjuvant setting remains unclear.

The role of CRT in the adjuvant treatment setting for pancreatic cancer remains controversial and has been made more difficult by the results seen in the PRODIGE-24 trial described above. The ESPAC-1 study was a complex trial (2 × 2 design) that compared adjuvant chemotherapy and adjuvant CRT each with no such therapy. The trial showed no benefit (and perhaps harm) with CRT but a benefit for chemotherapy.[290] The RTOG 0848 trial of gemcitabine versus gemcitabine and erlotinib followed by either additional chemotherapy or CRT was recently reported at ASCO, 2024.[291] For the entire patient population, there was no benefit to the addition of postoperative radiation therapy. However, in the subset of patients who had node-negative disease, there appeared to be a potential benefit with postoperative radiation therapy. This may be related to less chance of systemic recurrence and greater potential benefit of a local treatment modality. Interestingly, the subgroup of patients who had positive margins (who would be considered at higher risk for local recurrence) did not benefit from postoperative radiation therapy. Whether to offer postoperative radiation therapy to node-negative patients or at all remains controversial.[292,293]

Neoadjuvant Therapy: Resectable and Borderline Resectable Pancreatic Cancers

Several recent trials have shed light on the role of neoadjuvant therapy in this setting: SWOG 1505, ESPAC5, PREOPANC, PREOPANC-2,[294] and ALLIANCE A021501.[295-298] In the resectable pancreatic cancer setting, the SWOG 1505 trial of perioperative mFOLFIRINOX versus gemcitabine and nab-paclitaxel demonstrated no substantial differences in patients who underwent surgery (72%) or in median survival with median OS for mFOLFIRINOX of 23.2 months (95% CI, 17.6-45.9) versus 23.6 months (95% CI, 17.8-31.7) for gemcitabine and nab-paclitaxel.[295] The primary endpoint of achieving a 58% 2-year survival was not met. One cautionary note from this trial, which emphasizes the importance of having these patients evaluated at high-volume centers in a multidisciplinary setting, was that nearly one third of the patients thought to have resectable disease were not deemed to have resectable disease on central review.[299] The ESPAC5 trial compared surgery versus a short course (8 weeks) of several perioperative regimens (CRT, mFOLFIRINOX, and gemcitabine and capecitabine) in the borderline resectable setting.[296] There was no significant difference in R0 resection rates between neoadjuvant therapy groups versus immediate surgery; although 1-year OS rates were higher among the neoadjuvant therapy groups compared to immediate surgery, the trial was not powered for formal comparison of the different neoadjuvant arms.[296]

The Dutch study PREOPANC provides further support for neoadjuvant CRT in patients who have either resectable or borderline resectable disease. Patients were randomly assigned to receive three cycles of neoadjuvant gemcitabine with the addition of radiation therapy at 15 × 2.4 Gy in cycle two followed by surgical resection and four cycles of adjuvant gemcitabine versus up-front surgical resection followed by six cycles of adjuvant gemcitabine. The R0 resection rate was 71% versus 40%, favoring patients receiving neoadjuvant therapy.[297] The updated survival analysis showed that the 5-year OS rate was 20.5% with neoadjuvant CRT and 6.5% with up-front surgery. The beneficial effect of neoadjuvant CRT was consistent across the prespecified subgroups, including resectable and borderline resectable pancreatic cancer.[300] The subsequent phase 3 PREOPANC-2[294] study compared neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer. There was no significant difference in OS between FOLFIRINOX and gemcitabine-based chemoradiotherapy (median OS 21.9 vs 21.3 months; HR, 0.88; 95% CI 0.69-1.13; *P* = .32). Additionally, there were no significant differences in PFS, (R0) resection percentage, complete pathological response, and adverse event incidence. The authors conclude that both regimens can be considered in the (neo)adjuvant setting for this patient population.

The phase 2 randomized ALLIANCE A021501[301] study compared neoadjuvant FOLFIRINOX with or without hypofractionated radiotherapy. Patients who received neoadjuvant FOLFIRINOX alone reported significant improvements in OS (29.8 vs 17.1 months) and 18-month OS rate (66.7% vs 47.3%) compared to patients who received FOLFIRINOX plus radiotherapy although the radiotherapy arm did not meet target accrual and conclusions regarding efficacy could not be made. We await the results of the phase 3 ALLIANCE A021806 study (ClinicalTrials.gov identifier: NCT04340141), a randomized trial for patients who have resectable pancreatic cancer designed to evaluate the role of perioperative FOLFIRINOX versus up-front resection followed by adjuvant FOLFIRINOX.

Recently, the phase 3 CASSANDRA–PACT-21 trial evaluated neoadjuvant PAXG (cisplatin, nab-paclitaxel, capecitabine, and gemcitabine) versus neoadjuvant mFOLFIRINOX in patients with stage I to III resectable or borderline resectable pancreatic ductal adenocarcinoma. The primary endpoint of event-free survival was met; median event-free survival was 16.0 months for the PAXG arm and 10.2 months for the mFOLFIRINOX arm (HR, 0.64, 95% CI 0.48-0.86, $P = 0.003$); 3-year event-free survival rates were 31% and 13%, respectively. Of note, after patients had received 4 months of neoadjuvant treatment, there was a second randomization event in which patients received either surgery followed by 2 months of the same treatment in the adjuvant setting or two more months of the same neoadjuvant treatment followed by surgery. Consequently, the median duration of neoadjuvant therapy was longer in the PAXG arm compared to the mFOLFIRINOX arm (162 vs 132 days), which may have influenced efficacy outcomes.

Locally Advanced Unresectable Pancreatic Cancer

For patients who have locally advanced unresectable disease, current ASCO guidelines recommend 6 months of initial systemic chemotherapy with a combination regimen with consideration of CRT in those who do not experience progression after induction therapy.[302] As in the case of those with resectable disease, the role of CRT in this setting remains controversial. The international LAP07 phase 3 trial randomly assigned patients with locally advanced unresectable pancreatic cancer to treatment with gemcitabine with or without erlotinib. Patients who had at least stable disease after 4 months were randomly assigned a second time to either continue with the same chemotherapy as in the first phase or proceed to CRT with capecitabine as a radiation sensitizer. This study closed at the first planned interim analysis because of a lack of efficacy. No OS or PFS benefit was observed with the switch from chemotherapy to consolidating CRT. A subsequent analysis to evaluate the effect of radiation therapy on locoregional tumor control found that patients in the radiation therapy arm had substantially less local tumor progression (34% vs 65%; $P < .0001$) and a longer time before reintroduction of chemotherapy (159 vs 96 days; $P = .05$).[303] The NEOLAP trial compared a continuous gemcitabine and nab-paclitaxel regimen with a sequential regimen of gemcitabine and nab-paclitaxel followed by FOLFIRINOX in the preoperative setting. In this trial, roughly two thirds of patients underwent surgical exploration and more than one third had a complete macroscopic resection, much higher than the 4% observed in the LAP07 trial, underscoring the evolution of neoadjuvant chemotherapy and improved surgical expertise.[298] However, no difference in median OS between the two arms was seen in this phase 2 trial, and comparisons between these trials should consider the differences between patient populations, definitions of locally advanced disease, and treatment modalities.[298]

Although previously published studies have not reported a clinical benefit with the addition of radiotherapy, recent prospective and retrospective data suggest that optimization of radiation amounts and administration techniques may be required to significantly improve clinical benefit in this patient population. A retrospective study[304] of 119 patients treated with ablative radiation therapy reported a median OS of 26.8 months, and a single-arm phase 2 trial[305] of 136 patients treated with stereotactic magnetic resonance–guided adaptive radiation therapy reported a median OS of 22.8 months and 2-year OS rate of 53.6%. Ongoing randomized trials include LAP100 (ClinicalTrials.gov ID NCT06958328) and LAPSTAR (ClinicalTrials.gov ID NCT06272162). While both trials are investigating modified radiotherapy (dose-escalated radiotherapy in LAP100 and stereotactic magnetic resonance–guided radiotherapy in LAPSTAR), the primary endpoint for LAP100 is OS; in contrast, LAPSTAR's primary endpoint is health-related quality-of-life deterioration-free survival, with OS as a secondary endpoint. LAPSTAR's choice of primary outcome serves as a reminder that prolonged survival at the cost of significantly impaired quality-of-life may not be acceptable to patients, and their goals of treatment should be considered in trial design and treatment planning.

The recently published phase 3 PANOVA-3[306] trial investigated the use of tumor treating fields (TTFields) in combination with gemcitabine and nab-paclitaxel versus gemcitabine and nab-paclitaxel alone. This is the first trial to demonstrate improved OS over gemcitabine and nab-paclitaxel alone in patients with locally advanced unresectable pancreatic cancer. Median OS for TTFields plus gemcitabine/nab-paclitaxel was 16.2 months versus 14.2 months for gemcitabine/nab-paclitaxel alone (HR, 0.82, 95% CI 0.68-0.99, $P = 0.039$); median 1-year survival rates were 68.1% and 60.2%, respectively. A premarket approval application has been submitted to the FDA, with a decision expected in the second half of 2026 (https://www.businesswire.com/news/home/20250820419511/en/Novocure-Submits-Premarket-Approval-Application-to-FDA-for-Tumor-Treating-Fields-Therapy-in-Locally-Advanced-Pancreatic-Cancer).

In general, after completion of planned chemotherapy, patients should be reevaluated by a multidisciplinary team with high-volume expertise in pancreatic cancer to determine whether they could be candidates for surgical resection. If the disease is deemed non-metastatic at that time, then CRT should be considered.

PRESENTING CASE STUDY

A 66-year-old woman presents to the oncology clinic for management of her recently diagnosed metastatic pancreatic cancer. Her medical history includes obesity, hypertension, hypercholesterolemia, and a bilateral hip replacement. She was diagnosed with diabetes mellitus approximately 2 years ago that has become difficult to control over the last 6 months, resulting in a 30-pound (13.6-kg) unintentional weight loss and gnawing post-prandial discomfort that lasts for a few hours. Subsequent imaging reveals numerous liver and lung lesions and a mass in the pancreas tail. Biopsy of a liver lesion confirms moderately differentiated adenocarcinoma. The patient's family history is notable for ovarian cancer in a maternal aunt; germline testing identifies a pathogenic *BRCA2* mutation. The patient's family has observed functional decline over several years; her Eastern Cooperative Oncology Group (ECOG) PS is 2.

How would this patient's comorbidities, ECOG PS, and *BRCA2* mutation status inform your decisions regarding first-line treatment?

This patient has metastatic pancreatic cancer with a confirmed germline *BRCA2* mutation. Results from the pivotal POLO trial support the use of maintenance olaparib monotherapy for individuals with an ECOG PS of 0 or 1 who have achieved disease response or stability after at least 16 weeks of induction platinum-based chemotherapy.[307] Most study subjects received 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) variants, while a very small minority were treated with gemcitabine and cisplatin. The US Food and Drug Administration has approved olaparib for first-line maintenance in patients with germline BRCA-mutated metastatic pancreatic cancer following 16 weeks of platinum-based chemotherapy.

As such, platinum-containing chemotherapy should be considered for this patient, followed by olaparib maintenance should she achieve disease stabilization/benefit following induction chemotherapy. However, she has multiple comorbidities and an intermediate ECOG PS of 2. The treatment recommendation should be personalized after discussing the risks and benefits. The intensive triplet therapy FOLFIRINOX and variant is highly likely to result in unacceptable toxicities and should be avoided. Platinum doublets (eg, gemcitabine and cisplatin, 5-fluorouracil, leucovorin, and oxaliplatin [FOLFOX]) may be more appropriate with cautious monitoring and support during treatment. To mitigate the risk of toxicities during initial treatment, one approach includes starting with gemcitabine alone and adding the platinum agent if she tolerates monotherapy with an improvement in PS.

TREATMENT OF METASTATIC PANCREATIC CANCER

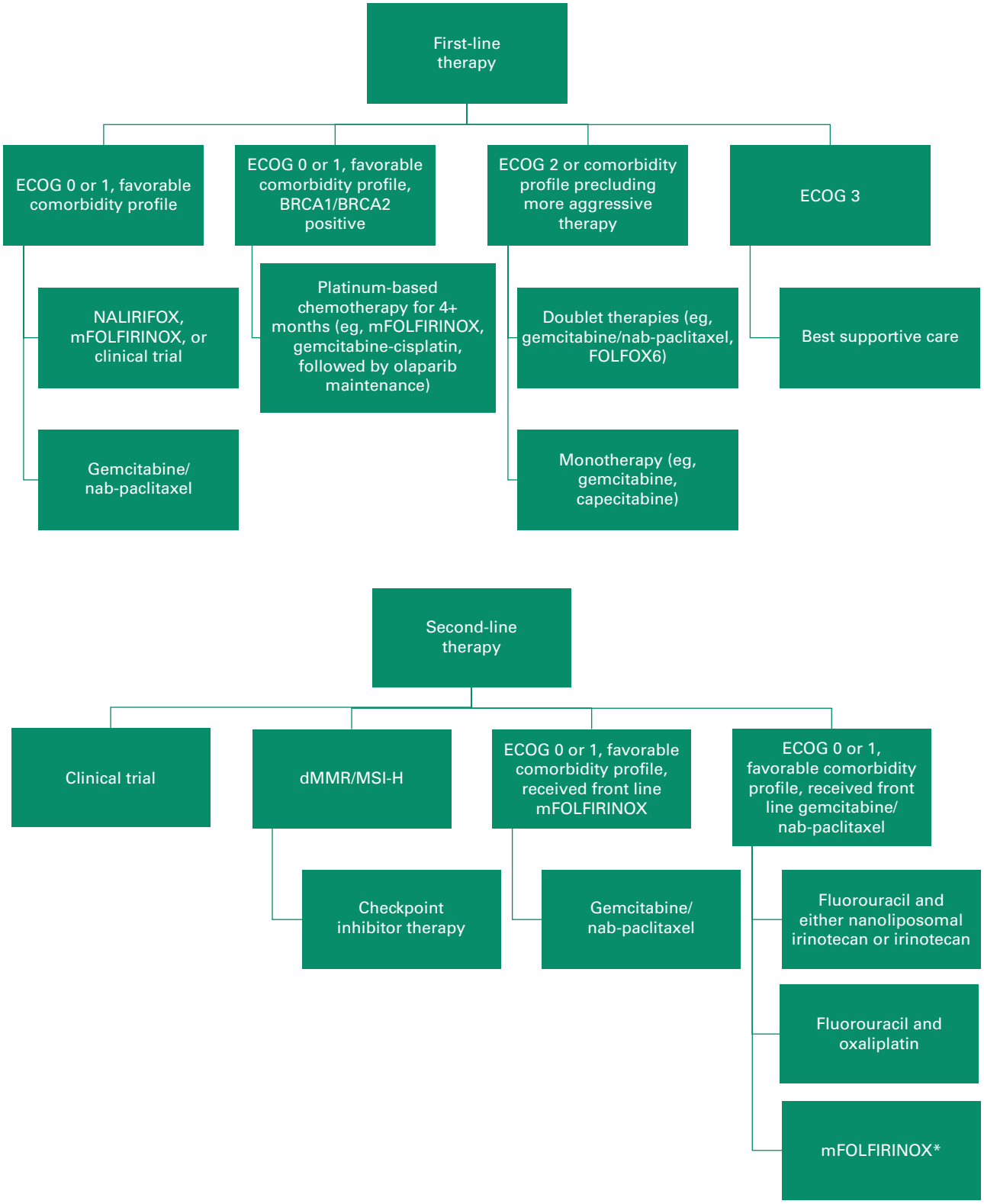
First-Line Therapy

All patients who have metastatic pancreatic cancer should be considered for early referral to a palliative care specialist if available. Because these patients often have symptoms that are due to direct involvement of the celiac plexus, biliary obstruction, and gastric outlet obstruction, involvement of specialists in interventional pain management and interventional endoscopy is also often required (Fig. 13.1-1).

Historically, single-agent gemcitabine was considered the standard of care for patients who have metastatic pancreatic cancer when it was approved by the FDA in 1997.[308,309]

A present standard of care in the treatment of metastatic pancreatic cancer was defined in 2011 by the results of the French PRODIGE trial of 342 patients comparing gemcitabine with FOLFIRINOX.[310] Median OS was an unprecedented 11.1 months in the FOLFIRINOX group compared with 6.8 months in the gemcitabine group (HR, 0.57; 95% CI, 0.45-0.73; $P < .001$); median PFS was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (HR, 0.47; 95% CI, 0.37-0.59; $P < .001$), and the ORR was 31.6% for FOLFIRINOX compared with 9.4% for gemcitabine ($P < .001$). More AEs were noted in the FOLFIRINOX group, but despite this, overall quality-of-life scores were superior in the FOLFIRINOX arm. These results established FOLFIRINOX as the new standard of care for patients who have advanced pancreatic cancer, good PS, absence of biliary obstruction, and no infectious complications. It should be noted that the trial excluded patients who had an ECOG PS of ≥2 and patients aged >75 years. More recent trials with FOLFIRINOX in pancreatic cancer have modified the original regimen by eliminating the 5-FU bolus and reducing the irinotecan dose from 180 to 150 mg/m^2 without seeming to compromise effectiveness. This mFOLFIRINOX regimen was used in the practice-changing PRODIGE-24 adjuvant study.[311] An alternative first-line therapy for advanced pancreatic cancer was established in 2013 when the addition of nab-paclitaxel to gemcitabine was found to be superior to gemcitabine alone in the phase 3 MPACT trial.[312] In this study, median OS was 8.5 months in the nab-paclitaxel and gemcitabine group compared with 6.7 months in the gemcitabine alone group (HR, 0.72; 95% CI, 0.62-0.83; $P < .001$); the response rate, according to independent

Figure 13.1-1 Treatment Algorithm for Metastatic Pancreatic Cancer



Abbreviations: dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; FOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; mFOLFIRINOX, modified regimen of leucovorin, fluorouracil, irinotecan, and oxaliplatin; MSI-H, microsatellite instability high; NALIRIFOX, liposomal irinotecan, 5-fluorouracil, leucovorin, and oxaliplatin.
*Only for those patients deemed medically fit.
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review, was 23% compared with 7% ($P < .001$). Rates of neutropenia, febrile neutropenia (3% vs 1%), neuropathy, and fatigue were substantially higher in the nab-paclitaxel arm. Notably, unlike the FOLFIRINOX study, the nab-paclitaxel and gemcitabine trial included patients with ECOG PS of 2 and older patients.

More recently, the NAPOLI-3 trial evaluated the role of NALIRIFOX (triplet 5-FU, liposomal irinotecan, and oxaliplatin) compared with gemcitabine and nab-paclitaxel. This open-labeled randomized phase 3 study assigned 770 treatment-naive patients who had de novo metastatic pancreatic adenocarcinoma to receive NALIRIFOX versus nab-paclitaxel and gemcitabine. Median OS was 11.1 months with NALIRIFOX versus 9.2 months with nab-paclitaxel and gemcitabine (HR, 0.83; 95% CI, 0.70-0.99; $P = .036$). The most common grade 3 to 4 treatment-emergent AEs were neutropenia, diarrhea, and hypokalemia in the NALIRIFOX group and neutropenia, anemia, and peripheral neuropathy in the nab-paclitaxel and gemcitabine group. The FDA approved the NALIRIFOX regimen for first-line treatment of metastatic PDAC.[12]

In the POLO study,[313] 154 patients with metastatic pancreatic cancer and a germline *BRCA1* or *BRCA2* mutation who had received, but not experienced progression during, at least 16 weeks of a platinum-containing regimen were randomly assigned to receive maintenance therapy with the PARP inhibitor olaparib or placebo. Median PFS was substantially longer in the olaparib group than in the placebo group (7.4 vs 3.8 months; HR, 0.53; 95% CI, 0.35-0.82; $P = .004$).[313] The final OS data did not demonstrate a benefit for olaparib treatment (median, 19.0 vs 19.2 months; HR, 0.83; 95% CI, 0.56-1.22; $P = .3487$). Olaparib has received FDA approval for metastatic germline *BRCA*-mutated pancreatic adenocarcinoma as maintenance therapy without disease progression on at least 16 weeks of platinum-based chemotherapy. For patients with germline *BRCA* or *PALB2* mutations, the combination of cisplatin and gemcitabine demonstrated high response rates as initial therapy for advanced disease in a phase 2 study. The addition of a PARP inhibitor to cisplatin/gemcitabine did not improve outcomes further. The combination of maintenance PARP inhibition with immune checkpoint blockade is a promising avenue of ongoing investigation.

mFOLFIRINOX, NALIRIFOX, and gemcitabine/nab-paclitaxel are appropriate initial treatment options for patients who have metastatic pancreatic cancer. Platinum-based regimens, which also include gemcitabine/cisplatin, are preferred options for patients with *BRCA1/2* or *PALB2* mutations. We caution against the tendency for cross-trial comparisons in general given potential differences in the underlying populations. Decisions regarding first-line treatment, therefore, depend on patient factors and clinician preferences. It could be reasonable to establish a three-tiered approach toward metastatic pancreatic cancer; otherwise healthy, medically fit patients with good ECOG PS (0 or 1) and those with a germline *BRCA1/2* mutation could preferentially be treated with FOLFIRINOX or NALIRIFOX as first-line therapy. A small randomized phase 2 trial also suggested that first-line gemcitabine and cisplatin could be an effective regimen for patients who have germline *BRCA* or *PALB2* mutations with a median OS of 16.4 months and 3-year OS rate of 17.8%.[314] Patients who have poor PS, advanced age, and substantial comorbidities could still be considered candidates for single-agent gemcitabine or 5-FU therapy. In between these extremes, given that NALIRIFOX improved outcomes compared with gemcitabine/nab-paclitaxel, lies a group of patients who could be considered for nab-paclitaxel and gemcitabine as first-line therapy.

Second-Line Therapy and Beyond

There is no agreed-on standard-of-care regimen for patients who experience progression during first-line treatment of metastatic pancreatic cancer. In general, the treatment choice for the second line is often based on the first-line regimen, PS, and organ function. These patients should always be considered for enrollment in a clinical trial. The NAPOLI-1 trial evaluated nanoliposomal irinotecan for patients with metastatic pancreatic cancer refractory to gemcitabine.[315] Patients in the combination nanoliposomal irinotecan with 5-FU and leucovorin arm had a substantially improved OS compared with patients in the 5-FU and leucovorin arm at 6.1 months compared with 4.2 months (HR, 0.67; 95% CI, 0.49-0.92; $P = .012$). Second-line therapy continues to be characterized by poor outcomes and short median survivals.

Neuregulin 1 (*NRG1*) fusions have been shown to enhance HER2/HER3 dimerization and downstream activation. Therefore, targeting HER2 and HER3 in patients with *NRG1* fusions may be beneficial. Zenocutuzumab[14] is a first-in-class bispecific antibody targeting HER2 and HER3. The phase 2 eNRGy study evaluated zenocutuzumab in patients with *NRG1* fusion–positive solid tumors, including 36 patients with pancreatic cancer. Of note, all 36 patients had *KRAS* wild-type disease. Objective responses were observed in 16 of 36 patients per BICR; the ORR (95% CI) was 44% (28-62) and the DCR (95% CI) was 81% (64-92). Median PFS (95% CI) was 7.4 months (5.5-10.2); median DOR was 9.1 months. On December 4, 2024, the FDA granted accelerated approval (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zenocutuzumab-zbco-non-small-cell-lung-cancer-and-pancreatic) for the use of zenocutuzumab-zbco in patients with advanced pancreatic adenocarcinoma with an *NRG1* gene fusion with disease progression during or after prior systemic therapy.

Additional rare alterations in pancreatic cancer include rearranged during transfection (*RET*) fusions, V-RAF murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E mutations, neurotrophic tropomyosin kinase receptors (*NTRK*) fusions, and MSI-high.

On September 21, 2022, the FDA granted accelerated approval for the use of selpercatinib[316] in patients with locally advanced or metastatic pancreatic adenocarcinoma with an *RET* gene fusion with disease progression during or after prior systemic therapy. This accelerated approval was based on data from the LIBRETTO-1[317] phase 1/2 open-label basket trial, which included 11 patients with *RET* fusion–positive pancreatic cancer. The ORR was 54.5%, and the median DOR was not reached.

Dabrafenib plus trametinib received accelerated approval by the FDA (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dabrafenib-combination-trametinib-unresectable-or-metastatic-solid) on June 22, 2022, for patients with advanced solid tumors with a *BRAF* V600E mutation who had progressed on prior systemic therapy. Of note, of the two trials used as evidence for this accelerated approval, ROAR[265] and NCI-MATCH Subprotocol H,[318] ROAR did not include patients with pancreatic cancer; NCI-MATCH included two patients with pancreatic adenocarcinoma, of whom only one was included in efficacy analyses.

The tropomyosin receptor kinase inhibitors larotrectinib and entrectinib are two FDA-approved treatment options for patients with advanced solid tumors with a *NTRK* gene fusion and no known acquired resistance mutations. A pooled analysis of three phase 1 or 2 studies[319] (LOXO-TRK-14001, SCOUT, and NAVIGATE) in 55 pediatric and adult patients treated with larotrectinib reported an overall response rate (95% CI) of 75% (61-85); one patient with pancreatic cancer was included and achieved a partial response to treatment. Long-term efficacy and safety data of an expanded 150-patient cohort[320] reported an ORR (95% CI) of 57% (50-65). Seven adult patients with pancreatic cancer were included; of six evaluable patients, one patient achieved a partial response.

FDA approval of entrectinib was based on a pooled analysis of three phase 1 or 2 clinical trials[321] (ALKA-372-001, STARTRK-1, and STARTRK-2). Of 121 patients total, the efficacy-evaluable population included four patients with pancreatic cancer. The ORR for this subgroup was 75%, with a median PFS of 12.8 months and median OS of 22.0 months; these statistics are comparable to those of the total study population, which reported an ORR of 74%, median PFS of 13.8 months, and median OS of 33.8 months.

Among patients with MSI-high disease, the FDA has approved the immune checkpoint inhibitor pembrolizumab for patients with advanced MSI-high solid tumors who have progressed on prior systemic therapy. The phase 2 KEYNOTE-158[322,323] study enrolled 22 patients with pancreatic cancer and reported an ORR of 18.2% (one complete response and three partial responses). Although the median DOR was not reached, PFS and OS remained low (2.1 and 3.7 months, respectively).

EMERGING THERAPIES

The acquisition of activating mutations in *KRAS* is the single most common genetic abnormality associated with pancreatic adenocarcinoma, accounting for >95% of patients. The recent development of KRAS inhibitors represents a new area of promise for treating patients with this disease. Initial evidence of the promise of this approach was observed in *KRAS* G12C–mutated pancreatic adenocarcinoma, which accounts for 1% to 2% of pancreatic cancers. The KRYSTAL-1 study treated 63 patients who had *KRAS* G12C–mutated cancer with adagrasib, 21 of whom had pancreatic cancer. Seven (33.3%) of 21 evaluable patients achieved a partial response. Median PFS was 5.4 months (95% CI, 3.9-8.2), and median OS was 8.0 months (95% CI, 5.2-11.8).[324]

The CodeBreaK study was a phase 1/2 study of the KRAS G12C inhibitor sotorasib for patients who have *KRAS* G12C–mutated pancreatic cancer. Thirty-eight patients were treated in the study with 21% having a confirmed objective response (95% CI, 10-37). Median PFS was 4.0 months (95% CI, 2.8-5.6), and median OS was 6.9 months (95% CI, 5.0-9.1).

Daraxonrasib has received FDA breakthrough designation (https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-announces-fda-breakthrough-therapy) for patients with previously treated metastatic cancer with *KRAS* G12 mutations. This approval is based on data from the ongoing phase 1 RMC-6236-001 trial.[325] The phase 3 RASolute 302[326] trial of daraxonrasib versus investigator's choice of standard of care chemotherapy in patients with metastatic PDAC who experienced disease progression on first-line chemotherapy (5-FU–based or gemcitabine-based) is ongoing, with results expected in 2026. Together, these data demonstrate promise for *KRAS* mutation–targeted therapy in this disease.[327]

KEY POINTS

- Exocrine pancreatic cancer is an aggressive disease with an incidence nearly equaling the mortality rate and a 5-year survival rate of 13%.
- Several lifestyle risk factors are associated with the risk of pancreatic cancer.
- Genetic testing for inherited mutations is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes.
- Best surveillance screening for affected relatives continues to be the subject of ongoing trials, and family members should be referred to centers with expertise in this area.
- Presenting symptoms of pancreatic cancer are vague but often include abdominal or back pain, jaundice, and cachexia.
- Staging should include CT scans of chest, abdomen, and pelvis with appropriate arterial phasing to assess the abdominal vasculature.
- Pathologic diagnosis is best obtained by EUS biopsy for patients who have localized disease, and patients who have biliary obstruction for whom immediate surgery is not planned should undergo biliary stenting.
- Although formal TNM staging exists, in practice, tumors are best classified as resectable, borderline resectable, locally advanced unresectable, and metastatic disease.
- Six months of modified FOLFIRINOX (mFOLFIRINOX) treatment is the standard of care for fit patients with resected pancreatic cancer.

- For those patients not felt to be candidates for mFOLFIRINOX, 6 months of treatment with gemcitabine and capecitabine or gemcitabine alone can be considered.
- The optimal preoperative regimen for patients with pancreatic cancer remains debated. For patients with resectable pancreatic cancer, resection followed by adjuvant chemotherapy or perioperative chemotherapy are both appropriate and being compared in an ongoing trial.
- For borderline resectable patients, initial chemotherapy with either FOLFIRINOX or gemcitabine/nab-paclitaxel are reasonable options with reevaluation for resection.
- For locally advanced unresectable patients, initial chemotherapy with either FOLFIRINOX or gemcitabine/nab-paclitaxel is reasonable with reevaluation for local radiation therapy in select patients. There are numerous active studies testing neoadjuvant chemotherapy and CRT for resectable and borderline resectable pancreatic cancers, and although the data are early and based on relatively small trials, there is a suggestion of a survival advantage with a neoadjuvant approach compared with surgery and adjuvant chemotherapy in the borderline resectable pancreatic cancer population.
- Although the exact definition of locally advanced unresectable disease differs by guideline, contraindications to successful surgical resection often include: >180° encasement of the superior mesenteric artery or portal vein or direct involvement of the celiac axis or common hepatic artery deemed unreconstructable.
- Determination of unresectability must be made in conjunction with a multidisciplinary team at a high-volume pancreatic cancer center.
- Treatment should include initial multiagent chemotherapy with consideration of CRT in those who do not experience progression. The exact duration of therapy is not well defined.
- After definitive therapy, the patient should be reevaluated by the multidisciplinary team to determine if the cancer is now potentially resectable.
- All patients with metastatic pancreatic cancer should be referred to a palliative care specialist if available.
- mFOLFIRINOX, NALIRIFOX, and gemcitabine/nab-paclitaxel are considered appropriate first-line regimens. Choice should be based on the patient's PS, underlying organ dysfunction, and presence or absence of germline *BRCA1/2* mutations.
- Patients with *BRCA1/2* germline mutations who do not experience progression during at least 16 weeks of a platinum-containing regimen could be considered for olaparib maintenance therapy. A less toxic gemcitabine and cisplatin chemotherapy regimen can also be considered for initial chemotherapy in these patients.
- Second-line treatment should be based on first-line treatment and the patient's overall functional status. These patients should be considered for a clinical trial if available. Liposomal irinotecan and 5-FU can be considered for those who experience progression with gemcitabine and nab-paclitaxel based on the NAPOLI-1 data.

HIGH-YIELD TAKEAWAYS

- Common presenting symptoms for GEC include dysphagia, anorexia, early satiety, nausea, dyspepsia, pain, bleeding, and hematemesis. Individuals who carry a germline *CDH1* mutation are at substantial lifetime risk of developing gastric cancer and should undergo risk-reducing prophylactic gastrectomy as early as in their 20s. Nivolumab is a standard-of-care adjuvant treatment of patients with esophageal and GEJ adenocarcinoma with residual disease after preoperative chemoradiation.
- Perioperative FLOT chemotherapy is the standard treatment of patients with resectable microsatellite stable esophageal, GEJ, and gastric adenocarcinoma.
- Patients with advanced E/GEJ/G adenocarcinoma should have their tumor tested for the following biomarkers for optimal first-line treatment selection: HER2, PD-L1 CPS, CLAUDIN 18.2, and MMR expression/microsatellite status.
- Immunotherapy-based regimens are standard of care first-line systemic treatment for patients with HCC.
- Chemoimmunotherapy comprising gemcitabine and cisplatin with either durvalumab or pembrolizumab is a new standard of care option for first-line treatment of patients with advanced BTCs regardless of PD-L1 expression.
- NGS should be incorporated into routine standard of care of patients with advanced BTC to identify actionable molecular abnormalities (*FGFR2* fusions, *IDH1* mutations, *HER2* amplification, *BRAF* V600E, and *MSI*-high).
- mFOLFIRINOX, NALIRIFOX, and gemcitabine/nab-paclitaxel are considered appropriate first-line regimens for patients with metastatic pancreatic cancer. Choice should be based on the patient's PS, underlying organ dysfunction, and presence or absence of germline *BRCA1/2* mutations, for which platinum-containing regimen is preferred.
- Patients with pancreatic cancer and *BRCA1/2* germline mutations who do not experience progression on a platinum-containing regimen could be considered for olaparib maintenance therapy.

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We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

UPPER GASTROINTESTINAL CANCERS 13.1

CHAPTER SUMMARY GUIDE

KEY POINTS

- Beyond known histopathologic and epidemiological distinctions, molecular features differentiate ESCC from esophageal adenocarcinoma with SCC resembling SCCs of other organs more than it does esophageal adenocarcinoma, whereas esophageal adenocarcinoma predominantly resembles the CIN type found in gastric adenocarcinoma.
- The Cancer Genome Atlas project proposed a molecular classification dividing esophageal and GEJ adenocarcinomas and gastric adenocarcinoma (together, gastroesophageal adenocarcinoma (GEA)) into four subtypes: tumors positive for Epstein–Barr virus, MSI-H unstable tumors, genomically stable tumors, and tumors with CIN.
- Individuals who carry a germline *CDH1* mutation are at substantial lifetime risk of developing gastric cancer and should undergo risk-reducing prophylactic gastrectomy as early as in their 20s.
- All patients with *H. pylori* infection should undergo treatment.
- Common presenting symptoms for GEC include dysphagia, anorexia, early satiety, nausea, dyspepsia, pain, bleeding, and hematemesis.
- Cross-sectional imaging including PET, EUS, and laparoscopic staging for patients with gastric and Siewert III GEJ tumors are critical to determine the location and stage of the tumor.
- Combined-modality CRT followed by resection is the standard neoadjuvant approach in the treatment of locally advanced ESCC.
- Definitive CRT (without surgery) is a valid treatment option for patients who have ESCC, especially if patients are high-risk surgical candidates.
- One year of adjuvant nivolumab for patients who have esophageal cancer (both SCC and adenocarcinoma) who received neoadjuvant CRT followed by surgery with residual pathological disease (T+ and/or N+; R0 resection) is the standard of care based on the improved DFS observed in CheckMate 577.[95,107]
- The positive results from ESOPEC, FLOT4-AIO, and MATTERHORN established perioperative systemic therapy as the preferred approach for patients with resectable esophageal, GEJ, and gastric cancers who are candidates for surgery and intensive systemic therapy.
- Perioperative FLOT plus durvalumab is a standard for patients with resectable esophageal, GEJ, or gastric cancers who are candidates for surgery.
- Adjuvant nivolumab for 1 year is the standard for patients with resected esophageal or GEJ tumors who received preoperative chemoradiation and have residual pathological disease after surgical resection.
- Adjuvant CAPOX without radiation therapy was superior for tumors with at least muscle invasive (≤T2) and/or node-positive disease (≤N1) in patients with an adequate D2 lymphadenectomy compared with surgery alone based on the CLASSIC study. This should be considered in patients who do not receive preoperative systemic chemotherapy or preoperative chemoradiation.
- Immune checkpoint inhibitor(s) should be considered for patients with resectable MSI-H/mismatch repair (MMR)-deficient esophageal or GEJ adenocarcinoma in either neoadjuvant or perioperative approaches.
- The addition of anti-PD1, pembrolizumab, nivolumab, or tislelizumab to combination chemotherapy is considered a standard in the first-line treatment of unresectable, metastatic ESCC. The benefit increases with increasing tumor PD-L1 expression. The NCCN guideline recommends the addition of anti-PD1 to chemotherapy in patients with tumor PD-L1 composite score ≥1.
- In the CheckMate 648 study, ipilumumab plus nivolumab achieved better OS than chemotherapy alone and was numerically shorter than nivolumab plus chemotherapy. Ipilimumab plus nivolumab may be considered for patients with tumor PD-L1 CPS ≥1 who are not candidates for anti-PD1 and chemotherapy combination.
- The CheckMate 649 study established that nivolumab when combined with fluoropyrimidine and platinum improved both PFS and OS compared with chemotherapy alone in patients who have GEAs with pronounced benefit seen in patients with tumors PD-L1 CPS ≥5.
- The KEYNOTE-590 and KEYNOTE-859 studies demonstrated PFS and OS benefit with the addition of pembrolizumab to fluoropyrimidine/platinum chemotherapy when compared with chemotherapy alone in GEAs. This benefit was pronounced in tumors PD-L1 CPS ≥10.

- Zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy is indicated for the treatment of CLDN 18.2 positive, HER-2 negative GEA.
- The addition of trastuzumab and pembrolizumab to platinum and fluoropyrimidine is the standard of care in HER2-positive ($IHC3^+$ or $IHC2^+/FISH^+$) and PD-L1–positive (CPS ≥ 1) metastatic GEAs.
- In patients who have tumors that are HER2 positive but PD-L1 negative, the standard treatment is platinum with fluoropyrimidine and trastuzumab.
- Nivolumab is FDA-approved second-line therapy for all ESCCs based on results from the ATTRACTION-3 study.
- Pembrolizumab is FDA-approved second-line therapy for patients who have metastatic ESCC with PD-L1 expression levels of CPS ≥10 based on results from KEYNOTE-181. In patients who have not received checkpoint inhibitor therapy as part of their first-line treatment, nivolumab or pembrolizumab monotherapy might be a viable option.
- The VEGFR antibody ramucirumab has shown efficacy in second-line phase 3 trials in advanced GEA and is now a standard-of-care option either alone or with paclitaxel therapy, leading to an NCCN guideline listing (category 1). Retrospective and prospective analyses show historically similar efficacy for FOLFIRI and ramucirumab compared with paclitaxel and ramucirumab with a potentially better toxicity profile, particularly for patients previously treated with taxanes, leading to an NCCN guideline listing (category 2A). However, no randomized controlled studies evaluating agents targeting angiogenesis in the first-line setting have shown an OS benefit.
- Approximately 50% of patients have preserved PS and derive benefit from continued treatment with palliative therapy in the second-line setting.
- Third-line chemotherapy has demonstrated a benefit compared with best supportive care or placebo, including with trifluridine and tipiracil (TAS-102), and should be considered for patients with preserved PS after two or more lines of therapy.
- The phase 2 randomized open-label DESTINY-GASTRIC01 study in Asian patients showed an improved ORR as well as PFS and OS for trastuzumab deruxtecan in comparison with chemotherapy as third-line or higher therapy for metastatic HER2-positive GEA, which led to FDA approval on January 15, 2021.
- HCC is an important cancer, and global incidence can be reduced by vaccination against hepatitis B virus; treatment of hepatitis C is curative, which may lead to reduced incidence of HCC in the coming years. Alcohol abuse, obesity, and metabolic syndrome represent modifiable risk factors, the moderation of which could also reduce worldwide incidence of the disease.
- The Barcelona Clinic Liver Cancer staging classification and treatment schedule have served as a main paradigm on how to broadly stage and treat HCC.
- Local ablative treatments are generally reserved for intermediate disease. These approaches include TACE, TARE, alcohol injection, radiofrequency ablation, microwave ablation, and external-beam radiation therapy or stereotactic radiation therapy.
- Combination locoregional plus systemic therapy options show promise in the intermediate stage of the disease and require further optimization.
- There is no role for adjuvant treatment in patients with resected HCC.
- The SHARP study established the first standard systemic therapy in HCC with sorafenib.[201]
- The IMbrave 150 study confirmed the benefit of atezolizumab and bevacizumab in first-line treatment compared with sorafenib for advanced HCC.[199]
- The HIMALAYA study demonstrated the role of tremelimumab and durvalumab as a first-line treatment option compared with sorafenib for advanced HCC.[10]
- CHECKMATE 9DW demonstrated the role of ipilimumab and nivolumab as a first-line treatment option compared with investigator's choice of sorafenib or lenvatinib for advanced HCC.[11]
- The REFLECT study confirmed the noninferiority of lenvatinib in first-line treatment compared with sorafenib for advanced HCC.[208]
- The RESORCE study confirmed the benefit of regorafenib in second-line treatment compared with placebo for advanced HCC.[213]
- The CELESTIAL study confirmed the benefit of cabozantinib in second- and third-line treatment compared with placebo for advanced HCC after sorafenib.[215]
- The REACH-2 study confirmed the benefit of ramucirumab in the second-line treatment of patients with AFP level ≥400 ng/mL compared with placebo for advanced HCC.[219,223]
- Immune checkpoint blockade has great promise in HCC with improved response rates and meaningful DOR in select patients with response to anti-PD-1 monotherapy. However, to date, treatment with monotherapy checkpoint blockade has not demonstrated definitive survival benefit in any patients in larger phase 3 randomized studies compared with sorafenib in the first-line setting or placebo in the second-line setting. Biomarker studies to identify those who may derive the most benefit are ongoing.

- The treatment paradigm of advanced HCC is in flux with the addition of all these agents relatively simultaneously without direction on the best sequencing approach.
- Resection, when feasible, is the mainstay of treatment of hepatobiliary tumors.
- The randomized phase 3 BILCAP study of adjuvant capecitabine versus observation in resected BTCs demonstrated improved OS in the prespecified per-protocol analysis and can be considered a standard of care.
- There is limited clinical evidence supporting the adoption of concurrent radiation therapy in the adjuvant setting, but this could be considered for patients who have high risk of relapse, such as patients who have positive LN disease and positive microscopic margins.
- Chemoimmunotherapy comprising durvalumab with gemcitabine and cisplatin as well as pembrolizumab with gemcitabine and cisplatin is a new standard of care option for first-line treatment of patients with advanced BTCs.
- The combination of 5-FU with oxaliplatin represents an appropriate second-line therapy for patients lacking an actionable somatic mutation who have developed progressive disease during gemcitabine and platinum combination therapy based on the ABC-06 trial.
- NGS should be incorporated into routine standard of care for patients who have advanced BTC to identify actionable molecular abnormalities (*FGFR2* fusions, *IDH1* mutations, *HER2* amplification, *BRAF* V600E, and MSI-high).
- The phase 3 ClarIDHy trial with the IDH1 inhibitor ivosidenib versus placebo for *IDH1*-mutated cholangiocarcinoma met its primary endpoint of PFS with the added benefit of improved quality-of-life.
- The FGFR inhibitors pemigatinib and futibatinib have received accelerated FDA approval for the treatment of *FGFR2* fusion–positive or *FGFR2* rearrangement–positive cholangiocarcinoma. The ROAR basket study using the combination of dabrafenib and trametinib showed benefit for patients who have BTC harboring *BRAF* V600E–mutations.
- Zanidatamab is a new bispecific antibody targeting HER2 that has been FDA-approved to treat unresectable or metastatic HER2-positive (IHC3+) BTC previously treated with gemcitabine-based chemotherapy.
- Exocrine pancreatic cancer is an aggressive disease with an incidence nearly equaling the mortality rate and a 5-year survival rate of 13%.
- Several lifestyle risk factors are associated with the risk of pancreatic cancer.
- Genetic testing for inherited mutations is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes.
- Best surveillance screening for affected relatives continues to be the subject of ongoing trials, and family members should be referred to centers with expertise in this area.
- Presenting symptoms of pancreatic cancer are vague but often include abdominal or back pain, jaundice, and cachexia.
- Staging should include CT scans of chest, abdomen, and pelvis with appropriate arterial phasing to assess the abdominal vasculature.
- Pathologic diagnosis is best obtained by EUS biopsy for patients who have localized disease, and patients who have biliary obstruction for whom immediate surgery is not planned should undergo biliary stenting.
- Although formal TNM staging exists, in practice, tumors are best classified as resectable, borderline resectable, locally advanced unresectable, and metastatic disease.
- Six months of modified FOLFIRINOX (mFOLFIRINOX) treatment is the standard of care for fit patients with resected pancreatic cancer.
- For those patients not felt to be candidates for mFOLFIRINOX, 6 months of treatment with gemcitabine and capecitabine or gemcitabine alone can be considered.
- The optimal preoperative regimen for patients with pancreatic cancer remains debated. For patients with resectable pancreatic cancer, resection followed by adjuvant chemotherapy or perioperative chemotherapy are both appropriate and being compared in an ongoing trial.
- For borderline resectable patients, initial chemotherapy with either FOLFIRINOX or gemcitabine/nab-paclitaxel are reasonable options with reevaluation for resection.
- For locally advanced unresectable patients, initial chemotherapy with either FOLFIRINOX or gemcitabine/nab-paclitaxel is reasonable with reevaluation for local radiation therapy in select patients. There are numerous active studies testing neoadjuvant chemotherapy and CRT for resectable and borderline resectable pancreatic cancers, and although the data are early and based on relatively small trials, there is a suggestion of a survival advantage with a neoadjuvant approach compared with surgery and adjuvant chemotherapy in the borderline resectable pancreatic cancer population.
- Although the exact definition of locally advanced unresectable disease differs by guideline, contraindications to successful surgical resection often include: >180° encasement of the superior mesenteric artery or portal vein or direct involvement of the celiac axis or common hepatic artery deemed unreconstructable.
- Determination of unresectability must be made in conjunction with a multidisciplinary team at a high-volume pancreatic cancer center.

- Treatment should include initial multiagent chemotherapy with consideration of CRT in those who do not experience progression. The exact duration of therapy is not well defined.
- After definitive therapy, the patient should be reevaluated by the multidisciplinary team to determine if the cancer is now potentially resectable.
- All patients with metastatic pancreatic cancer should be referred to a palliative care specialist if available.
- mFOLFIRINOX, NALIRIFOX, and gemcitabine/nab-paclitaxel are considered appropriate first-line regimens. Choice should be based on the patient's PS, underlying organ dysfunction, and presence or absence of germline *BRCA1/2* mutations.
- Patients with *BRCA1/2* germline mutations who do not experience progression during at least 16 weeks of a platinum-containing regimen could be considered for olaparib maintenance therapy. A less toxic gemcitabine and cisplatin chemotherapy regimen can also be considered for initial chemotherapy in these patients.
- Second-line treatment should be based on first-line treatment and the patient's overall functional status. These patients should be considered for a clinical trial if available. Liposomal irinotecan and 5-FU can be considered for those who experience progression with gemcitabine and nab-paclitaxel based on the NAPOLI-1 data.

CHAPTER TABLES AND IMAGES

Table 13.1-1 First-line Treatment Options for Advanced Esophago-Gastric Adenocarcinoma

Tumor Characteristics	Treatment
HER2+[a] and PDL1 CPS ≥1	Chemotherapy, trastuzumab, and pembrolizumab
HER2+[a] and PDL1 CPS <1	Chemotherapy and trastuzumab
HER2−[a] and PDL1 CPS ≥1	Chemotherapy and anti-PD1 ab[b]
CLAUDIN 18.2+[c]	Chemotherapy and zolbetuximab
HER2− and PDL1 CPS <1, CLAUDIN 18.2−	Chemotherapy
dMMR/MSI-H	Anti-PD1 ab +/− anti-CTLA4 ab[d] OR chemotherapy + anti-PD1[e]

Abbreviations: CPS, combined positive score; dMMR, deficient DNA mismatch repair; MSI-H, microsatellite instability-high.
[a]HER2+: IHC 3 + or IHC2+/ISH+; HER2-: IHC 1+ or IHC2+/ISH−
[b]Nivolumab, tislelizumab, or pembrolizumab.
[c]Claudin 18.2 moderate or strong expression by IHC in ≥75% tumor cells.
[d]Pembrolizumab, dostarlimab, nivolumab + ipilumumab.
[e]Nivolumab, pembrolizumab.
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Table 13.1-2 **Current Clinical Trials Paradigm for Hepatocellular Carcinoma**

Treatment Line	Outcome	Notes	Study
First			
Sorafenib vs placebo	Superiority study	First approved first-line therapy, December 1, 2007	SHARP study[201]
Lenvatinib vs sorafenib	Noninferiority study	Approved August 16, 2018	REFLECT study[208]
Atezolizumab and bevacizumab vs sorafenib	Superiority study	Approved May 29, 2020	IMbrave 150 study[199]
Durvalumab and tremelimumab vs sorafenib	Superiority study	Approved October 21, 2022	HIMALAYA study[10]
Nivolumab and ipilimumab vs investigator's choice of sorafenib or lenvatinib	Superiority study	Approved April 11, 2025	CheckMate 9DW study[11]
Second			
Regorafenib vs placebo	Superiority study	First approved second-line therapy, April 27, 2017	RESORCE study[213]
Ramucirumab vs placebo	Superiority study	AFP ≥400 ng/mL eligible; approval May 10, 2019	REACH-2 study[219]
Pembrolizumab		Conditional approval December 17, 2018; has not been removed	KEYNOTE-224 study,[220,221] KEYNOTE-240 study,[216] KEYNOTE-394 study[218]
Nivolumab and ipilimumab		Accelerated approval March 10, 2020	CheckMate 040 study[222]
Second and third			
Cabozantinib vs placebo	Superiority study	Approved January 14, 2019	CELESTIAL study[215]

Abbreviation: AFP, alpha-fetoprotein.
FDA approval of second-line nivolumab is revoked because of lack of efficacy in confirmatory study.
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Table 13.1-3 **Germline Mutations Associated With Pancreatic Cancer**	
Mutated Gene	**Syndrome**
BRCA1, *BRCA2*	Hereditary breast and ovarian syndrome
ATM	Ataxia-telangiectasia
PALB2	Hereditary breast cancer
PRSS1	Hereditary pancreatitis
STK11	Peutz-Jeghers syndrome
CDKN2A	Familial atypical multiple mole and melanoma syndrome
MLH1, *MLH2*, *MSH6*, *PMS2*	Lynch syndrome

Abbreviations: *ATM*, *ATM* serine/threonine kinase; *BRCA1/2*, *BRCA1/2* DNA repair–associated protein; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *MLH1/2*, DNA mismatch repair protein *MLH1/2*; *MSH6*, MutS homolog 6; *PALB2*, partner and localizer of *BRCA2*; *PRSS1*, protease, serine 1; *STK11*, serine/threonine protein kinase 11.

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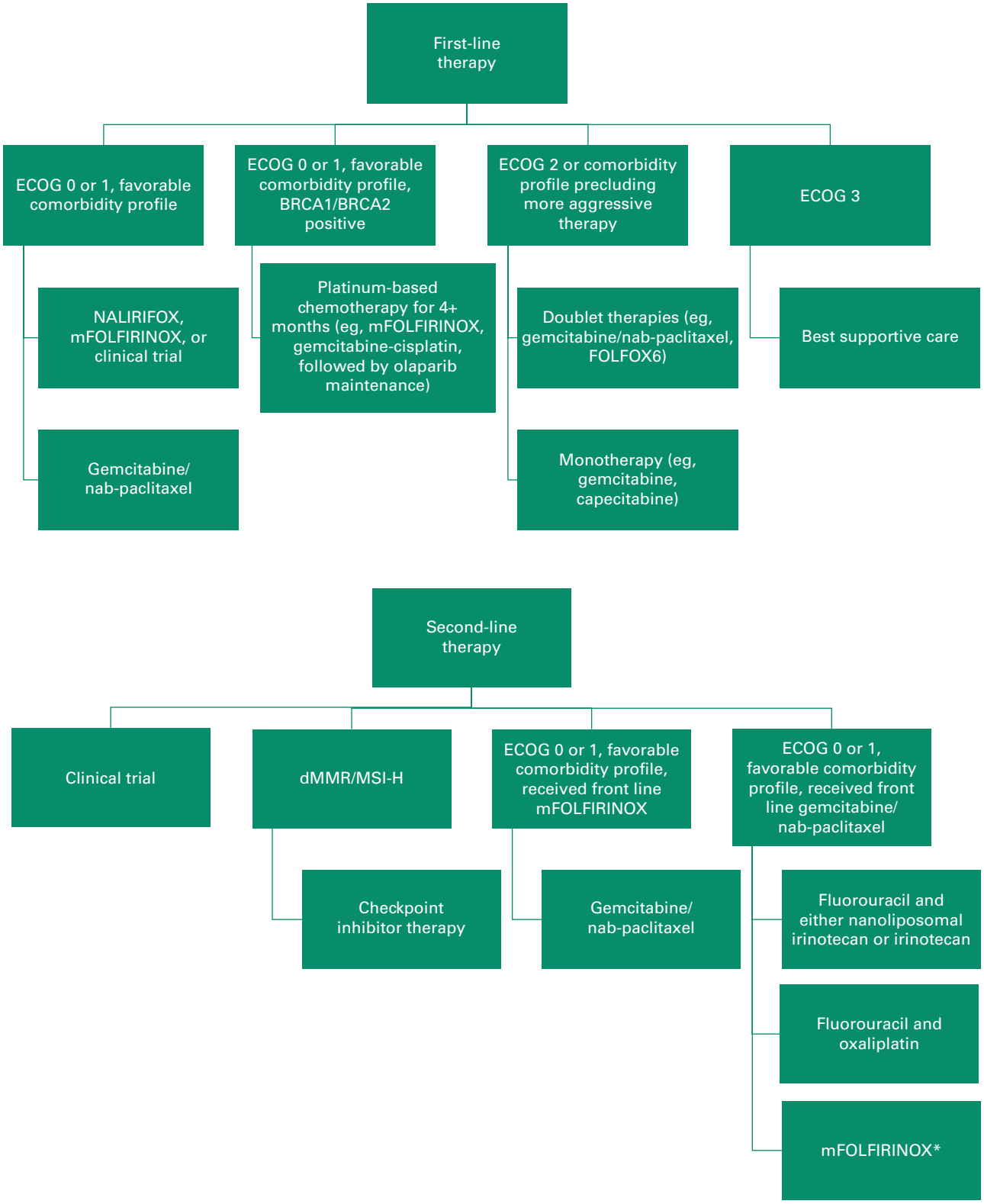
Figure 13.1-1 Treatment Algorithm for Metastatic Pancreatic Cancer



Abbreviations: dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; FOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; mFOLFIRINOX, modified regimen of leucovorin, fluorouracil, irinotecan, and oxaliplatin; MSI-H, microsatellite instability high; NALIRIFOX, liposomal irinotecan, 5-fluorouracil, leucovorin, and oxaliplatin.
*Only for those patients deemed medically fit.
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LOWER GASTROINTESTINAL CANCERS 13.2

Steven J. Cohen, MD, and Katrina S. Pedersen, MD, MS

RECENT UPDATES

Colorectal Cancer

- In the ALASCCA randomized clinical trial, 626 patients with stage 1 to 3 rectal cancer or stage 2 to 3 colon cancer with alterations in the PI3K pathway were randomized to receive aspirin 160 mg or placebo for 3 years. For the primary outcome measure, the use of aspirin was associated with a significantly decreased risk of colorectal cancer recurrence whether the tumor had a *PIK3CA* exon 9/20 mutation (3-year recurrence 7.7% vs 14.1%, HR, 0.49, P = 0.044) or other PI3K pathway alteration (3-year recurrence 7.7% vs 16.8%, HR, 0.42, P = .013). For the secondary outcome measure of 3-year disease-free survival, the use of aspirin was also associated with an improvement in the other PI3K pathway group (89.1% vs 78.7%, HR = 0.51, P = .017). These data have been incorporated into guidelines, with implications for testing all early-stage colorectal cancer tumors for alterations in the PI3K pathway.[328]
- Exercise has long been associated with improved colon cancer-specific survival. The Canadian Cancer Trials Group (CCTG) CO.21 CHALLENGE trial was the first randomized trial to evaluate whether a structured exercise program could improve colon cancer survival. In this trial, 889 patients primarily from Canada or Australia with resected stage 3 or high-risk stage 2 colon cancer after 2-6 months of adjuvant therapy were randomized to a 3-year structured exercise program and given health education materials or only given health education materials. The goal of the structured exercise program was to increase physical activity by 10 MET/hours/week above baseline, with 1 hour of brisk walking equivalent to 4 MET-hours. The primary endpoint of 3-year disease-free survival (DFS) was improved in the structured exercise arm from 73.9% to 80.3%, HR 0.72, P = 0.017. The secondary endpoint of 8-year overall survival (OS) was also improved, from 83.2% to 90.3%, HR, 0.63, P = .022. While there are questions about the applicability in everyday practice, these data support recommendations to colorectal cancer survivors for increasing physical activity.[329]
- *BRAF* V600E mutations are present in 5% to 10% of metastatic colorectal cancer and have been associated with poor prognosis. The BREAKWATER built upon demonstration of benefit of the encorafenib/cetuximab combination in second-line therapy from the BEACON trial and investigated encorafenib/cetuximab (EC) plus mFOLFOX6 (modified FOLFOX regimen: 5-fluorouracil, leucovorin, and oxaliplatin) versus standard of care chemotherapy as initial therapy for untreated metastatic *BRAF* V600E colorectal cancer. The initial report demonstrated that EC + mFOLFOX6 had increased ORR, 60.9% versus 40.0% with SOC chemotherapy. Median duration of response was 13.9 versus 11.1 months. A subsequent presentation and manuscript extended the analysis and follow-up, reporting a statistically significant improvement in progression-free survival for the addition of EC (median, 12.8 vs 7.1 months; hazard ratio for progression or death, 0.53; 95% confidence interval [CI], 0.41 to 0.68; P < .001). An interim analysis also demonstrated improved OS with the addition of EC to FOLFOX (median, 30.3 vs 15.1 months; hazard ratio for death, 0.49; 95% CI, 0.38-0.63; P < .001). Side effects were modestly increased but consistent with known profiles of these agents. These data highlight the importance of testing for *BRAF* mutations with initial diagnosis of metastatic disease.[330] As a result of this trial, NCCN guidelines were updated as well as the FDA approval for encorafenib and cetuximab in combination with mFOLFOX6 for treatment of patients with metastatic colorectal cancer (CRC) with a *BRAF* V600E mutation.

Anal Squamous Cell Cancer

- For many years, there was no standard treatment for recurrent or metastatic anal squamous cell cancer (ASCC). This changed with the presentation and publication of the POD1UM-303/InterAACT 2 trial, which was a phase 3,

double-blind, controlled trial. The trial enrolled and randomized 303 patients with treatment-naive locally recurrent or metastatic ASCC to receive either first-line carboplatin, paclitaxel, and a placebo or carboplatin, paclitaxel, and retifanlimab, a PD-1 inhibitor In this study, patients were randomly assigned to six cycles of standard-dosage carboplatin and paclitaxel plus placebo (P arm) or retifanlimab (PD-1 inhibitor) 500 mg q4w (R arm) for up to 1 year with possibility of crossover. The trial met its primary endpoint with the median progression-free survival (PFS) improving from 7.4 months in the placebo arm to 9.30 months in patients receiving retifanlimab (HR, 0.63 [95% CI], 0.63 [0.47-0.84]; *P* = .0006). Follow-up remains immature, though currently suggests retifanlimab with chemotherapy despite crossover is trending toward improved mOS (29.2 vs 23.0 months, HR, 0.70 [95% CI, 0.49-1.01]. As a result of these data, in May 2025, the FDA approved carboplatin/paclitaxel/retifanlimab for first-line treatment of advanced, anal squamous cell cancer, and is the current standard of care for patients eligible to receive immunotherapy.

OVERVIEW

The management of lower gastrointestinal cancers has evolved significantly, increasingly leveraging molecular profiling to guide clinical decision-making. For colorectal cancer (CRC), adjuvant therapy in stage II disease requires risk stratification and shared decision-making; notably, patients with stage IIA dMMR/MSI-H tumors have an excellent prognosis and do not require adjuvant chemotherapy. For stage III colon cancer, 6 months of FOLFOX or CAPOX remains a standard, though 3 months of CAPOX is a reasonable alternative for T1–3 and N1 disease to reduce neurological toxicities. In the metastatic setting, treatment is guided by extended *RAS*, *BRAF*, *MSI*, and *HER2* mutation testing. First-line management for MSI-H/dMMR metastatic CRC is centered on immunotherapy, such as single-agent pembrolizumab or the combination of nivolumab and ipilimumab. For *BRAF* V600E–mutated metastatic CRC, current standards support the use of encorafenib and cetuximab in combination with mFOLFOX6. Circulating tumor DNA (ctDNA) is also emerging as a highly specific prognostic tool for monitoring minimal residual disease (MRD), which may soon refine adjuvant therapy intensity.

For anal squamous cell cancer (ASCC), definitive chemoradiation remains the standard for localized disease. As of May 2025, the FDA-approved regimen of carboplatin, paclitaxel, and retifanlimab serves as the standard of care for first-line treatment of advanced ASCC in patients eligible for immunotherapy. Regarding neuroendocrine tumors (NETs), management is dictated by tumor site, histological grade, and functional status. Somatostatin analogs like octreotide and lanreotide are utilized as first-line therapy for advanced well-differentiated NETs. Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu is indicated for progressive disease, with recent data supporting its activity in the first-line setting for specific grade 2 and 3 tumors. Targeted options for pancreatic NETs include sunitinib, everolimus, and cabozantinib, with cabozantinib also approved for extrapancreatic GI NETs. Surgical resection remains the primary curative approach for isolated or oligometastatic disease, necessitating multidisciplinary evaluation.

Regarding rectal cancer, current treatment of locally advanced rectal cancer (LARC) is centered on total neoadjuvant therapy (TNT) strategies, in which chemotherapy and radiation therapy are used neoadjuvantly before total mesorectal excision (TME). Selected patients who achieve a clinical complete response after TNT or immunotherapy may be considered for nonoperative management (NOM) with "watch & wait" surveillance.

COLORECTAL CARCINOMA

EPIDEMIOLOGY AND ETIOLOGY

In 2025, colorectal cancer (CRC) was estimated to affect approximately 154,270 patients in the United States.[331] Among all cancers, it is the second leading cause of death in the United States (n = 52,900) and affects men and women equally (second only to lung cancer).[254] The incidence of CRC is higher in developed countries than in developing countries. In the last two decades, there have been decreases in the incidence and mortality rate of CRC in the United States in the overall population, likely due to improved adherence to screening recommendations.[22] Findings from epidemiologic studies indicate that, during the last two decades, the anatomic distribution of CRC may have shifted from the distal to the proximal colon, but alarmingly, there has also been a particularly sharp increase in the incidence of distal colon and rectal cancers among persons under 50 years (early-onset) that are mostly not associated with germline mutations and high inherited cancer risk.[332] These results indicate strong environmental associations for CRC. For colorectal cancer as a whole, data from prospective interventional studies indicating an association among dietary fiber, calcium, fat intake, and CRC are not clear.[333,334] Additional environmental factors include the intake of alcohol and tobacco, antibiotics, hormone replacement in women (protective), total calorie consumption, and physical activity as it relates to obesity.[335]

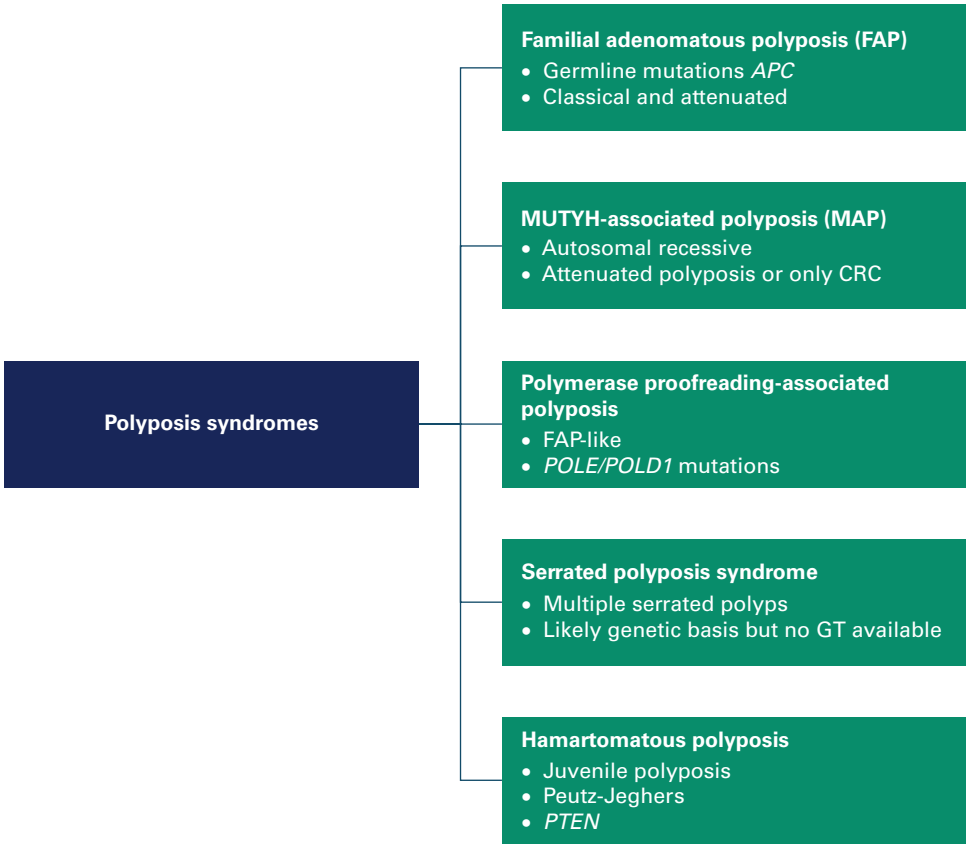
FAMILIAL SYNDROMES

The two most common inherited forms of CRC are those associated with Lynch syndrome and the familial adenomatous polyposis (FAP) syndrome. These two recognized genetic syndromes are distinct in their molecular biology and clinical characteristics.

FAP Syndrome

The first syndrome to be recognized was familial adenomatous polyposis (FAP) (Fig. 13.2-1). FAP syndrome is caused by an inherited germline mutation in the adenomatous polyposis coli (*APC*) gene, a key regulator of the Wnt signaling pathway. Mutations in the *APC* gene lead to the formation of a dysfunctional protein, which cannot bind to β-catenin; thus, β-catenin can then activate the transcription of various oncogenes. Patients who have a germline *APC* mutation have hundreds to thousands of colonic polyps, predisposing them to malignant tumors at a young age. Although FAP represents a small percentage (~0.5%-1%) of the overall number of cases of CRC, somatic *APC* (or β-catenin) mutations activating the Wnt signaling pathway have been found in a majority (80%-85%) of sporadic CRCs. Additional gene expression studies along the adenoma-to-carcinoma sequence (Fig. 13.2-2) provide an important genetic model in which specific genetic mutations, leading to invasive CRCs, have been clearly elucidated.[336]

Figure 13.2-1 Polyposis Syndromes



Abbreviations: CRC, colorectal cancer; GT, genetic testing.
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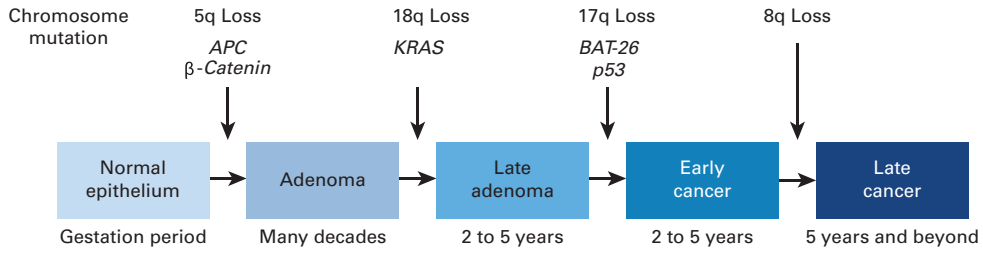
Figure 13.2-2 Adenoma-to-Carcinoma Sequence



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Lynch Syndrome

Lynch syndrome (previously known as hereditary nonpolyposis colorectal cancer [HNPCC]) is an inherited autosomal dominant disease with high penetrance. It is the most common hereditary colorectal syndrome, accounting for approximately 5% of CRCs (Table 13.2-1). CRC generally develops at an early age in these patients (median age, 45 years) and most commonly in the proximal colon. Other malignancies associated with the genetic syndrome include endometrial, ovarian, pancreatic, breast, biliary, gastric, bladder, prostate, cutaneous squamous cell carcinomas, and small bowel adenocarcinomas. Although the Amsterdam and Bethesda criteria have traditionally been used to identify patients who should be considered for genetic testing, there is a push for universal germline testing in all patients diagnosed with CRC. Due to its prevalence and now the predictive nature of high microsatellite instability in the immunotherapeutic treatment of colorectal cancers, all newly diagnosed colorectal cancers should have at least DNA mismatch repair (MMR) genes assessed via IHC, or microsatellite instabity established by PCR or NGS.

Table 13.2-1 Clinical Criteria to Determine Likelihood of Lynch Syndrome

Amsterdam II criteria (all criteria must be met)
At least three relatives with Lynch syndrome–associated cancer (CRC, cancer of endometrium, small bowel, ureter, or renal pelvis)
One relative should be a first-degree relative of the other two
Malignancies should include at least two successive generations
At least one family member should have been diagnosed at age <50 years
Familial adenomatous polyposis is excluded
Tumors should be verified by pathological examination
Revised Bethesda criteria to identify patients with CRC who should undergo pathological examination for Lynch syndrome (any criterion is sufficient)
Synchronous or metachronous CRC or associated with another Lynch syndrome–associated tumor (ie, endometrial, stomach, small intestine, ovarian, pancreatic, biliary tract, ureter or renal pelvis, brain, sebaceous gland adenoma, or keratoacanthoma)
Pathological features of MSI-H cancer (eg, tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern) in patient age <60 years
Development of CRC in individual who has a first-degree relative with CRC and/or Lynch syndrome–related extracolonic cancer and/or colorectal adenoma, with one of the cancers diagnosed before the patient reaches age 50 years or an adenoma diagnosed at age <40 years
CRC in two or more first- or second-degree relatives with Lynch syndrome–related tumors, regardless of age

Abbreviations: CRC, colorectal cancer; MSI-H, microsatellite instability-high.
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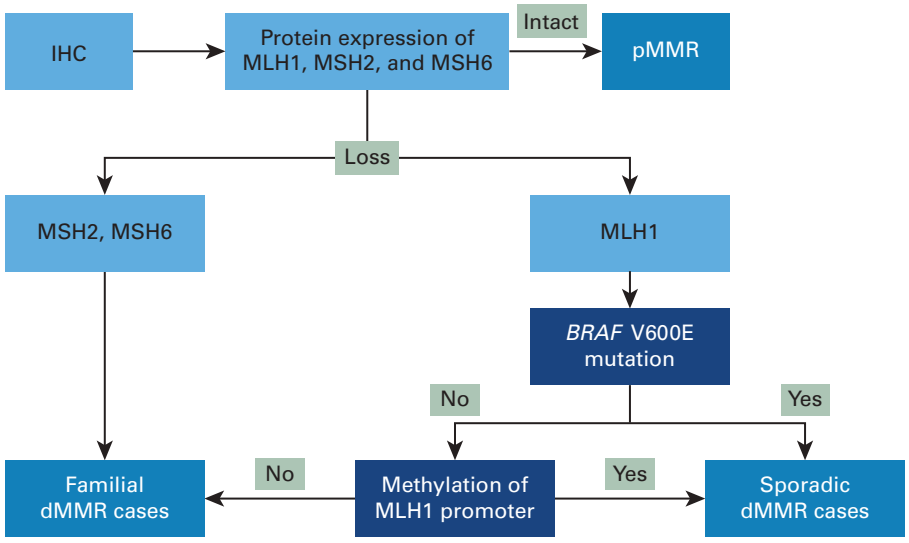
Lynch syndrome is caused by mutations in a group of genes that code for DNA MMR enzymes, including *MSH2*, *MLH1*, *PMS2*, *MSH6*, and *EPCAM* (deletion causes loss of expression of MSH2).[337] The defect in MMR allows spontaneous genetic mutations to accumulate in the colonic mucosa, which predispose to the development of dysplasia and, eventually, for invasive cancers. Tumor testing can be performed in one of two ways, and this often creates confusion in terminology. Microsatellite instability (MSI) designation is derived from a polymerase chain reaction–based tumor test in which a panel of microsatellite markers (so-called Bethesda markers) is used to test for MSI, and tissue is classified as microsatellite instability-high (MSI-H) if two or more of five core markers show instability. A second, and now more common, test is to perform IHC analysis of the four MMR proteins listed at the beginning of this paragraph. If any one of them is not expressed on IHC, the tumor is classified as dMMR (mismatch repair deficient). Although dMMR and MSI-H are often used interchangeably, this is technically not accurate.

Approximately 20% of patients with dMMR or MSI-H CRC have Lynch syndrome (ie, germline mutations); the rest have sporadic alterations in the MMR mechanism confined to the tumor. Approximately 10% to 15% of sporadic colon cancers have aberrations in the MMR enzymes, and the prevalence is approximately 15% in stage II, 8% in stage III, and 4% to 5% in stage IV CRCs.[338] These sporadic cases are generally caused by epigenetic silencing of *MLH1*.[339] These patients also often lack expression of PMS2 and usually have a mutation in *BRAF*.

Regardless of whether universal germline screening is performed for patients with CRC, routine testing for dMMR by IHC or for MSI by polymerase chain reaction should be performed on the tumors of all patients with CRC (Fig. 13.2-3) because this has implications for the treatment of early-stage cancers and is the basis of the FDA approval of checkpoint inhibitor use in both early-stage and more advanced-stage disease.

Figure 13.2-3 Mismatch Repair Testing Algorithm



Abbreviations: dMMR, mismatch repair deficient; IHC, immunohistochemistry; pMMR, mismatch repair proficient.
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OTHER POLYPOSIS AND COLORECTAL CARCINOMA SYNDROMES

There are other polyposis and CRC syndromes. Inflammatory bowel disease (IBD), particularly ulcerative colitis, is associated with an increased risk of colon cancer, estimated to be 5% to 10% by 20 years after the time of diagnosis of IBD. IBD is also associated with a high incidence of synchronous cancers, affecting 10% to 20% of cases. Crohn's disease also may have a role in increasing the risk of CRC, particularly cancer in the ileocolic region. However, in the absence of colonic involvement by Crohn's disease, there is no increased risk of colon cancer. The risk of developing a subsequent cancer is 3% for patients who have a history of adenomatous polyps.

COLORECTAL CARCINOMA GENETIC ABERRATIONS

CRC is driven by three key carcinogenic pathways, including chromosomal instability (CIN), MSI, and CpG island methylator phenotype (CIMP). The CIN pathway is characterized by early mutations in key genes, including *APC*, *TP53*, and *KRAS*, and constitutes most CRCs (85%).[340] The CIMP pathway involves hypermethylation of promoter regions of tumor suppressor genes such as *MGMT* and may overlap with MSI through hypermethylation of *MMR* genes such as *MLH1*.[341] The MSI pathway is the result of loss of function of MMR genes, resulting in instability of lengths of microsatellites, which are short sequences of DNA distributed throughout the genome. In 2015, a consensus statement was released evaluating data from 18 colorectal data sets, including the TCGA and other public and proprietary sources. Four consensus molecular subtypes (CMSs) were described: CMS1 (MSI immune, 14%) with hypermutated MSI and strong immune activation, CMS2 (canonical, 37%) with marked WNT and MYC activation, CMS3 (metabolic, 13%) with metabolic dysregulation, and CMS4 (mesenchymal, 23%) with transforming growth factor-β activation and angiogenesis.[342] With the exception of CMS1, which has clear prognostic and predictive implications for cancer treatment, as is discussed later in this section, the other three CMSs have not yet been incorporated into clinical decision making but form the basis for continued attempts to personalize therapy for CRC.

SCREENING

Screening recommendations from the US Preventive Services Task Force (see also Chapter 1: Epidemiology and Prevention) are in alignment with the American Cancer Society recommendations, which propose starting screening for CRC in average-risk individuals at age 45 years instead of 50 years. Fecal immunochemical test (FIT) or fecal DNA tests for screening is now included as an option for patients every 1 to 3 years.[3] The sensitivity for detecting CRC is 92.3% with fecal DNA testing and 73.8% with FIT ($P = .002$). The sensitivity for detecting advanced precancerous lesions is 42.4% with fecal DNA testing and 23.8% with FIT ($P < .001$) and represents a weakness in potentially preventing evolution of precursor lesions, including adenomatous polyps, into invasive colorectal adenocarcinomas. Direct visualization tests included in the guidelines are colonoscopy, CT colonography, and flexible sigmoidoscopy, with emphasis that, for average-risk patients, colonoscopy every 10 years or CT colonography every 5 years have greater estimated life years gained than flexible sigmoidoscopy every 5 years.[343,344]

Screening should occur at shortened intervals for patients at high risk, including those who have inherited syndromes, IBD, previous adenomatous polyps or CRC, and strong family history of CRC. Individuals who have Lynch syndrome should have screening by total colonoscopy every 1 to 3 years beginning between ages 20 and 25 years because of the lack of a visible premalignant lesion in this population and the higher risk of right-sided colon cancers.[345] Individuals who have FAP should start screening colonoscopies as early as age 10 years. If colon cancer or severe dysplasia is found for patients with IBD, the general recommendation is for near total or subtotal colectomy because of the high incidence of synchronous and metachronous cancers in this population.[346] Surgery can be less extensive for patients who have sporadic cancers. For patients who have Lynch syndrome, more extensive surgery can be recommended, particularly for women beyond childbearing age, for whom hysterectomy and oophorectomy should be considered. Finally, patients with a strong family history (one first-degree relative diagnosed before age 60 years or two first-degree relatives diagnosed at any age) of colon cancer or advanced adenomatous polyps (>1 cm or high-grade dysplasia [HGD] or with villous elements) should start screening with colonoscopy no later than age 40 years or 10 years younger than the youngest first-degree relative and should undergo screening every 5 years. Several blood-based biomarkers for screening are under development, but their role is unclear; none are approved by the FDA, and currently, none are included in any major consensus guidelines.

KEY POINTS

- Screening for CRC is underutilized. Screening colonoscopy and fecal DNA/FIT reduce CRC-associated death over the long term.
- All individuals who have CRC should have their tumors evaluated for MMR or MSI status. Those with dMMR/MSI-H tumors suggestive of germline origin should be referred for genetic screening.
- If universal screening for germline mutations is not performed in all patients who have colon cancer, clinicians should follow the revised Bethesda criteria to determine who should be recommended for germline genetic testing.
- Early-onset CRC patients are more likely to have cancer-associated germline mutations compared to standard-onset patients, but the rapidly increasing incidence of CRC in young-adults (<50 years old) is not associated with genetic causes but rather yet-to-be-identified environmental hazards.

STAGING

In the eighth edition of the AJCC manual (2017), important areas to note that are included in the seventh and eighth editions but differ from the sixth edition are the T4b category (invasion or adherence to other organs or structures) and the N1c category (tumor deposits in subserosa, mesentery, or nonperitonealized pericolic and perirectal tissues without regional lymph nodes [LNs]). In effect, T4b places a patient in the very high-risk IIC or IIIC category, depending on nodal status, and N1c (recorded as present or absent and not counted) is considered a risk equivalent to that of N1 LNs (one to three regional LNs). The eighth edition also includes nodal micrometastases (tumor clusters >0.2 mm in diameter) as being LN positive and has added the M1C category (peritoneal metastases), creating a stage IVC category. Proposed changes to the forthcoming AJCC version 9 staging criteria were previewed at the ASCO 2025 Annual Meeting and will likely place greater emphasis on tumor deposits in assigning stage.[347]

TREATMENT OF COLORECTAL CARCINOMA

Early-Stage Colon Cancer (Stages 0 and 1)

Nearly all patients who have stage 0 disease (carcinoma in situ or intramucosal cancer) are cured by endoscopic resection alone; note, however, that LNs are not adequately assessed by this technique. The primary treatment of virtually all invasive nonmetastatic CRCs is surgery. For stage I cancers, surgical resection alone is often recommended and frequently curative. For select T1 cancers without other high-risk features (low grade, no angiolymphatic invasion, and negative margin) diagnosed in a polyp, endoscopic resection alone may be sufficient.[348]

Stage II Colon Cancer

For patients who have stage II disease, the role of adjuvant chemotherapy remains controversial because of the heterogeneity of this disease stage. ASCO recommendations suggest that routine adjuvant chemotherapy is not recommended for most patients who have stage II tumors A discussion should be held with patients about their individual benefit-to-risk ratio when using adjuvant chemotherapy in stage II colon cancer.[349] The identification of prognostic factors might help distinguish patients at high risk of relapse and identify patients who have high-risk stage II disease who may be more likely to benefit from adjuvant treatment. In addition to T4 status, all major groups (ASCO, NCCN, and European Society of Medical Oncology) consider inadequate LN sampling (<12 or 13 nodes), lymphovascular invasion, perineural invasion, and clinical obstruction or perforation to be high-risk stage II disease that may warrant chemotherapy. Poorly differentiated tumors must be evaluated in the context of their MSI/dMMR status.

Apart from the aforementioned clinical risk factors, molecular determinants of prognosis such as MSI have been evaluated. Remarkably consistent results from retrospective analyses of large adjuvant trials and pooled data sets confirm that patients with

stage IIA colon cancers that are dMMR/MSI-H have excellent prognosis (>95% long-term DFS) and may be harmed from treatment with single-agent fluoropyrimidine adjuvant chemotherapy.[349-353] For patients who have dMMR/MSI-H stage IIB, stage IIC, or stage III disease, adjuvant therapy with a fluoropyrimidine, oxaliplatin, and immunotherapy should be considered. Duration of such treatment is discussed in more detail in the following paragraphs. Efforts to develop a molecular profile of predictive variables that could potentially guide adjuvant treatment decisions in stage II colon cancer have not proven useful clinically.[350,354,355] These tests include gene expression signatures, such as Oncotype DX Colon[356] and ColoPrint,[354] as well as molecular detection assays of micrometastases in morphologically unaffected LNs.[355] At this time, none of these assays is routinely recommended for use in clinical practice as a decision tool for adjuvant therapy in stage II colon cancer because they remain prognostic tests but are not able to predict which patients derive benefit from chemotherapy.

Emerging Role of Circulating Tumor DNA

Circulating tumor DNA (ctDNA) comprises fragments of DNA that are 130- to 150-bp long released into circulation by cancer cells undergoing apoptosis or necrosis or via secretion with a short half-life of up to 2.5 hours.[357] Given the short half-life, ctDNA is a real-time marker of tumor burden and is rapidly emerging as a prognostic tool across the continuum of cancer care, including in CRC. In the adjuvant setting, the detection of ctDNA after completion of curative-intent treatment—that is, minimal residual disease (MRD)—is highly specific and has high positive predictive value (90% to 100% for both) for occult micrometastatic disease that may result in eventual clinical recurrence. For instance, in the observational GALAXY trial (n = 3,034 stage II-IV resectable CRC), ctDNA positivity postsurgery was associated with higher risk of recurrence (HR, 15.75; $P < .0001$). In MRD-positive patients who received adjuvant therapy, 73% had ctDNA clearance. However, with longer follow-up, only 54% had sustained ctDNA clearance with much better outcomes compared with those with transient clearance (HR, 32.57; $P < .0001$).[358] Because the sensitivity of detection of ctDNA directly correlates with the underlying tumor volume, the sensitivity of such assays for detecting MRD is limited but improving over time and currently provides a median lead time of nearly 8 to 9 months.[356,359-361] Ongoing trials are aiming to establish the clinical utility of postoperative ctDNA-defined MRD in determining the intensity of adjuvant therapy. These trials are evaluating the role of adjuvant therapy for patients with clinically low-risk but MRD-positive stage II disease and also escalation/de-escalation of standard-of-care adjuvant therapy for patients who have stage III disease depending on postoperative MRD status.[361-363] The DYNAMIC trial randomly assigned 455 patients who had stage II colon cancer 2:1 to adjuvant therapy guided by either ctDNA results or standard clinicopathological features with a primary endpoint of recurrence-free survival at 2 years and showed that ctDNA-guided management was noninferior to standard management (93.5% and 92.4%, respectively; absolute difference, 1.1 percentage points; 95% CI, −4.1 to 6.2; noninferiority margin, −8.5 percentage points). A key secondary endpoint was adjuvant chemotherapy use with the results showing that a lower percentage of patients in the ctDNA-guided group than in the standard management group received adjuvant chemotherapy (15% vs 28%; relative risk, 1.82; 95% CI, 1.25-2.65). Thus, the utilization of ctDNA as opposed to traditional pathological features could spare nearly half of patients from receiving unnecessary chemotherapy and is being increasingly utilized in clinical practice for stage 2 colon cancer. In the phase 2/3 COBRA trial, patients who had resected stage II colon cancer without high-risk features deemed appropriate for surveillance were randomly assigned to observation versus ctDNA assay–guided therapy (a blood-only assay evaluating mutations and methylation changes); patients who were MRD-positive were treated with 6 months of adjuvant chemotherapy. The trial was stopped early because it crossed the futility boundary for the phase 2 endpoint of ctDNA clearance, likely related to the specificity of the assay.[364]

KEY POINTS

- Stage II colon cancer is a heterogeneous disease, and there is no one-size-fits-all answer for which patients should receive chemotherapy.
- The role of adjuvant therapy in stage II colon cancer should involve risk stratification and shared decision making.
- Patients who have stage IIA colon cancer that is dMMR/MSI-H have an excellent prognosis and do not require adjuvant therapy.
- Patients who have stage IIB or IIC dMMR/MSI-H colon cancer should be considered for adjuvant oxaliplatin-based therapy and potentially immunotherapy.
- Patients who have stage IIA disease without any risk factors do not typically benefit from adjuvant chemotherapy and should be counseled about the low absolute benefit of chemotherapy.
- Patients who have stage IIA disease and high-risk features and those who have stage IIB (T4a) or IIC disease should be counseled regarding their higher risk of tumor recurrence and the potential benefit of fluoropyrimidine and oxaliplatin-based chemotherapy.
- Accumulating data suggest that, for patients with resected colon cancer, postoperative ctDNA-defined MRD status is strongly prognostic, and prospective trials show that ctDNA-guided management is noninferior to standard-of-care management and that it also results in lesser use of adjuvant therapy. While awaiting additional data from ongoing trials, whether to incorporate ctDNA into adjuvant therapy decisions for stage II colon cancer outside of clinical trials should be a shared discussion between patients and their providers.

Stage III Colon Cancer

Adjuvant Chemotherapy

The initial trial presented in the early 1990s that established adjuvant chemotherapy as a standard of care in stage III colon cancer used a combination of 5-FU and levamisole administered for 12 months.[365] A 10% to 20% absolute improvement in 5-year survival was documented for patients receiving postoperative adjuvant 5-FU–based chemotherapy. Evidence from subsequent trials demonstrated that 5-FU combined with leucovorin provides superior outcomes with 6 months of therapy being adequate to achieve this survival benefit.[366] For more than a decade, the standard in adjuvant therapy remained unchanged because of the lack of novel agents with relevant activity in CRC. This changed when oxaliplatin, irinotecan, and the oral 5-FU prodrug capecitabine were used for the treatment of advanced CRC with combination regimens of 5-FU and either irinotecan or oxaliplatin demonstrating high antitumor efficacy.

Worldwide, six phase 3 trials were conducted to evaluate the value of these three novel chemotherapeutic agents in the adjuvant setting. The results of the pivotal MOSAIC (Multicenter International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial clearly demonstrated that FOLFOX is superior to 5-FU with leucovorin in terms of 3-year DFS and ultimately OS with longer follow-up.[367] Results of the National Surgical Adjuvant Breast and Bowel Project C-07 trial and XELOXA trial confirmed the role of oxaliplatin and intravenous or oral 5-FU–based regimens in adjuvant therapy for colon cancer.[368,369]

Although irinotecan- and oxaliplatin-based regimens are thought to be equally effective as palliative therapy for advanced CRC, for unknown reasons, none of the three phase 3 trials using combination regimens of irinotecan, 5-FU, and leucovorin demonstrated substantially superior efficacy regarding 3-year DFS when compared with 5-FU and leucovorin alone.[370-372] Similarly, despite their activity in the metastatic setting, several trials examining the addition of bevacizumab in an unselected population and cetuximab in a *KRAS* wild-type (WT) population did not show benefit when adding these agents to standard 6-month 5-FU– and oxaliplatin-based regimens.[373-376]

To mitigate the long-term neurotoxic adverse effects of oxaliplatin-based adjuvant therapy (10%-15% of patients can develop grade 3 neuropathy, resulting in, for example, an inability to button shirts or walk without difficulty), the IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration was established to prospectively combine and analyze data from six randomized trials conducted around the world to answer the question of whether a 3-month course of oxaliplatin-based adjuvant therapy is noninferior to the current standard 6-month treatment in patients with stage III colon cancer.[377] The final combined published analysis included 12,834 patients from 12 countries. The primary endpoint of noninferiority overall was not met (HR, 1.07; 95% CI, 1.00-1.15); however, the absolute difference in 3-year DFS was only 0.9% (75.5% vs 74.6%). Importantly, grade ≤ 2 neurotoxicity during therapy and in the month after treatment was substantially lower in the 3-month group than in the 6-month group. Preplanned subgroup analyses included specific tumor penetration, nodal status groups, and chemotherapy regimen (FOLFOX or capecitabine and oxaliplatin [CAPOX]).[378] For patients who have stage III colon cancer, after a median follow-up of 72 months, updated DFS results confirmed prior findings (HR, 1.08; 95% CI, 1.02-1.15) but with minimal 5-year OS differences: 82.4% (95% CI, 81.4-83.3) with 3 months of therapy and 82.8% (95% CI, 81.8-83.8) with 6 months of therapy (HR, 1.02; 95% CI, 0.95-1.11). The 5-year OS results according to the regimen were as follows (3 vs 6 months of therapy): CAPOX, 82.1% (95% CI, 80.5-83.6) vs 81.2% (95% CI, 79.2-82.9; HR, 0.96; 95% CI, 0.85-1.08) and FOLFOX, 82.6% (95% CI, 81.3-83.8) vs 83.8% (95% CI, 82.6-85.0; HR, 1.07; 95% CI, 0.97-1.18).

Current ASCO clinical guidelines recommend that patients who have T4 or N2 disease receive 6 months of therapy and that, for all other patients, either 6 months of adjuvant chemotherapy or a shorter duration of 3 months may be offered on the basis of a potential reduction in AEs and no substantial difference in DFS with the 3-month regimen.[379] On the basis of the subgroup analyses, many expert panels, including the NCCN, favor CAPOX over FOLFOX if 3 months of therapy is chosen. The ASCO guideline panel also favored CAPOX over FOLFOX but chose not to make it a formal recommendation. Data presented at the ASCO 2019 Annual Meeting revealed the same findings of 3 versus 6 months for stage II cancers with high-risk features when an oxaliplatin regimen was chosen.[380] These results were reaffirmed in the subsequent publication, which included high-risk stage II patients from 4 of the 6 IDEA studies.[381] Five-year DFS was 80.7% for 3 months of therapy and 83.9% for 6 months of therapy, HR 1.17, *P* for noninferiority .39). While a formal test of interaction by chemotherapy regimen (FOLFOX vs capeox) was negative, the duration effect did appear related to choice of regimen and for this reason and convenience most favor 3 months of capeox for the high-risk stage 2 adjuvant pMMR population for whom chemotherapy is selected. Additional analyses regarding early therapy discontinuation (ETD; <75% of planned doses) or early oxaliplatin discontinuation (EOD) for patients with stage III disease initially intending to receive 6 months of therapy revealed worse outcomes with ETD for both DFS and OS (HR, 1.40; 95% CI, 1.23-1.58; $P < .001$ and HR, 1.51; 95% CI, 1.31-1.74; $P < .001$, respectively) but not with EOD (HR, 1.10; 95% CI, 0.77-1.58; $P = .6$ and HR, 0.97; 95% CI, 0.62-1.52; $P = .9$, respectively). Overall, these data suggest that, for patients treated with 6 months of therapy, it is reasonable to discontinue oxaliplatin while continuing fluoropyrimidine in individuals who have significant neurotoxicity having received >50% of the planned 6-month chemotherapy. These data indicate that fluoropyrimidines remain the mainstay of adjuvant chemotherapy.[382]

The ATOMIC trial randomized patients with dMMR/MSI-H stage 3 colon cancer to 6 months of FOLFOX chemotherapy alone or with 1 year of the checkpoint inhibitor atezolizumab.[383] The addition of atezolizumab improved 3-year disease-free survival (primary endpoint) from 76.6% to 86.4%, HR, 0.5, $P < 0.0001$. Whether these results can be extrapolated to higher risk stage

II dMMR colon cancer is unclear, but in practice this is a reasonable approach. The other key unanswered question from the ATOMIC trial is whether checkpoint inhibitor therapy alone would result in similar benefit in this patient population, as the relative benefit of chemotherapy for dMMR colon cancer is significantly less.

A further emerging area of investigation for patients with dMMR primary colon cancer is whether neoadjuvant immunotherapy may be beneficial in a similar manner to the dMMR rectal cancer paradigm described below. Theoretical benefits include enhanced efficacy of immunotherapy in the preoperative setting (when target antigens are present with the intact primary tumor) and the potential to downstage cancers. It remains less clear whether this may potentially create opportunities to pursue nonoperative management. In a phase 2 single-arm NICHE-2 study, investigators treated 115 patients with clinical stage 2/3 dMMR locally advanced colon cancer with one dose of ipilimumab/nivolumab followed 2 weeks later with one dose of nivolumab monotherapy followed by surgical resection 2 to 4 weeks after the second immunotherapy dose. Impressively, approximately two-thirds of patients (68%) had a complete pathological response (pCR) and no tumor recurrences had been detected at a median follow-up of over 2 years.[384] While encouraging, challenges in implementing neoadjuvant immunotherapy strategies include a need to change cancer referral patterns (so that medical oncologists see localized colon cancer preoperatively), the need for timely MMR testing on initial colonoscopy biopsies, and the limitations of preoperative radiographic staging leading to potential overtreatment of some patients with reactive rather than malignant LNs, which are commonly seen in dMMR colon cancers.

SURVIVORSHIP

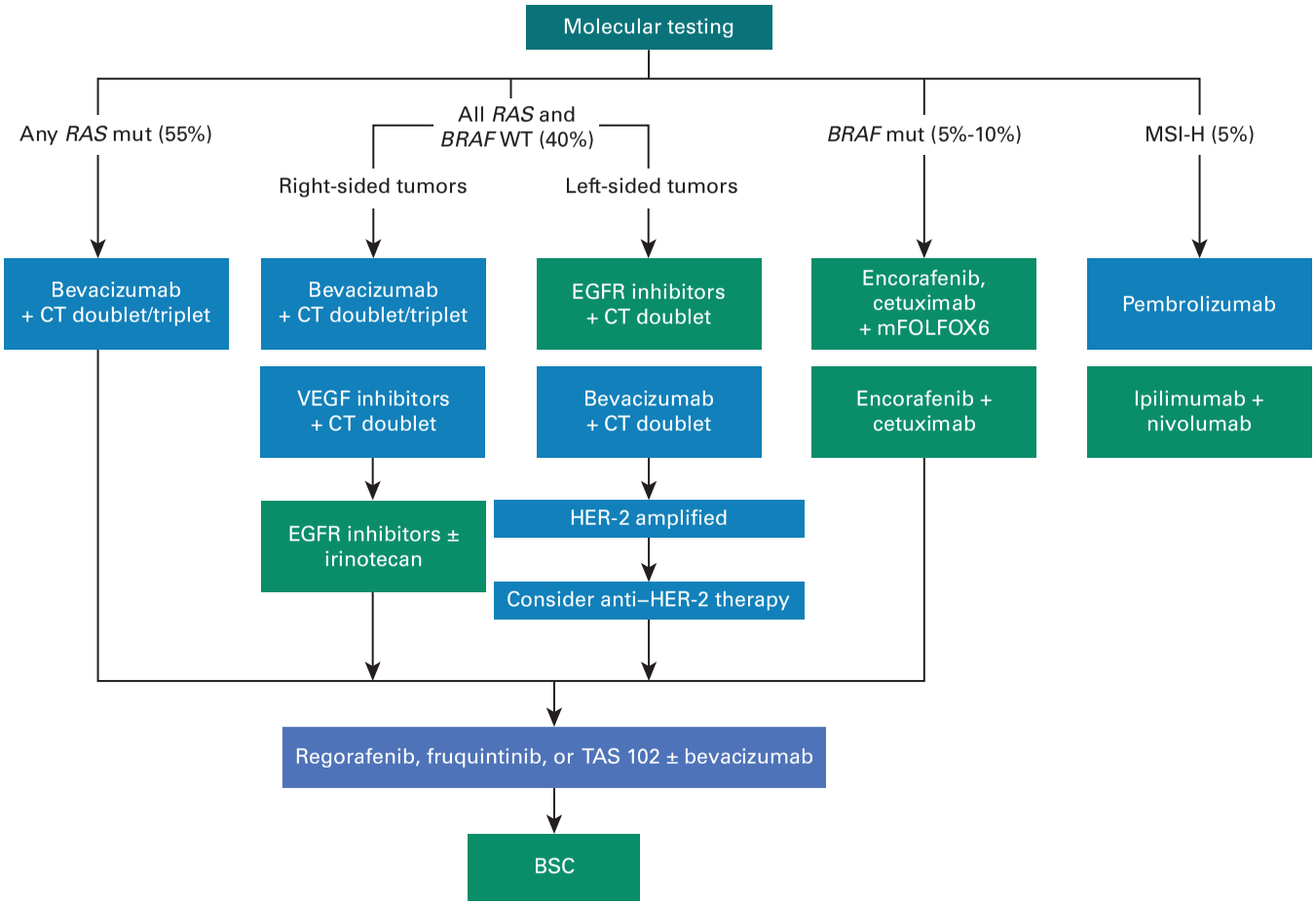
In addition to adjuvant chemotherapy, recent data demonstrate the benefit of intensive exercise programs and aspirin use for patients whose tumors have alterations in the *PIK3CA* pathway. The CHALLENGE Trial was the first randomized trial to evaluate whether a structured exercise program could improve colon cancer survival. In this trial, 889 patients primarily from Canada or Australia with resected stage III or high-risk stage II colon cancer after 2 to 6 months of adjuvant therapy were randomized to a 3-year structured exercise program and given health education materials, or only given health education materials. The goal of the structured exercise program was to increase physical activity by 10 MET/hours/week above baseline, with 1 hour of brisk walking equivalent to 4 MET-hours. The primary endpoint of 3 year disease-free survival was improved in the structured exercise arm from 73.9% to 80.3%, HR, 0.72, $P = 0.017$. The secondary endpoint of 8 year overall survival was also improved, from 83.2% to 90.3%, HR 0.63, $P = 0.022$. While there are questions about the applicability of this intense approach to exercise in everyday practice, these data support recommendations to colorectal cancer survivors for increasing physical activity.[329]

Alterations in PI3K pathway genes are noted in approximately one-third of colorectal cancers. Aspirin has been demonstrated to reduce the rate of colonic adenomas and cancers among high-risk patients and there have been suggestions of improved outcomes among patients with resected colorectal cancers with *PIK3CA* mutations. In the ALASCCA randomized clinical trial, 626 patients with stage 1-3 rectal cancer or 2-3 colon cancer with alterations in the PI3K pathway were randomized to receive aspirin 160 mg or placebo for 3 years. For the primary outcome measure, the use of aspirin was associated with a significantly decreased risk of colorectal cancer recurrence whether the tumor had a *PIK3CA* exon 9/20 mutation (3-year recurrence 7.7% vs 14.1%, HR 0.49, $P = .044$) or other PI3K pathway alteration (3-year recurrence 7.7% vs 16.8%, HR 0.42, $P = .013$). For the secondary outcome measure of 3-year disease-free survival, the use of aspirin was also associated with an improvement in the other PI3K pathway group (89.1% vs 78.7%, HR = 0.51, $P = .017$). These data have been incorporated into guidelines, with implications for testing all early-stage colorectal cancer tumors for alterations in the PI3K pathway.[328]

KEY POINTS

- By strict scientific criteria, 6 months of adjuvant CAPOX or FOLFOX remains a standard of care for stage III colon cancer.
- Emerging clinical consensus suggests 3 months of adjuvant therapy, particularly with capeox, is a reasonable alternative for patients who have T1-3 and N1 disease given the small absolute difference in DFS and the substantial decrease in clinically substantial neurological and other toxicities. The data are also similar for high-risk stage III colon cancer.
- If 3 months of therapy is chosen, many expert panels favor CAPOX over FOLFOX.
- Six months of therapy with FOLFOX or 3 to 6 months with CAPOX are recommended for those with T4 or N2 disease. It is reasonable to discontinue oxaliplatin while continuing fluoropyrimidine in individuals with significant neurotoxicity having received >50% of the planned 6-month chemotherapy.
- For dMMR (MSI-H) stage 3 colon cancer, the addition of atezolizumab to adjuvant chemotherapy improves outcome. Whether this can be extrapolated to high-risk stage 2 dMMR(MSI-H) colon cancer is unknown but a reasonable extension.
- For patients with stage 2/3 colorectal cancer, data now support a focus and recommendation for exercise the intensity of which should likely be individualized.
- For patients with stage 2/3 colorectal cancer with alterations in the PIK3CA pathway, after adjuvant therapy, the use of low-dose aspirin for 3 years is now recommended.
- Irinotecan, anti-VEGF agents such as bevacizumab, and anti-EGFR antibodies such as cetuximab, regardless of *RAS* status, should not be used in the adjuvant setting.

Figure 13.2-4 Treatment Algorithm for Metastatic Colorectal Cancer



Abbreviations: BSC, best supportive care; CT, chemotherapy; mFOLFOX6, modified regimen of 5-fluorouracil, leucovorin, and oxaliplatin; MSI-H, microsatellite instability high; mut, mutation; TAS-102, trifluridine and tipiracil; WT, wild type.

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ADVANCED COLORECTAL CARCINOMA (STAGE IV)

Stage IV CRC (colon and rectal cancers are managed similarly in the metastatic setting) is generally not considered curable with the exception of a small subset of patients who have isolated sites of metastasis (see the section "Oligometastatic CRC" later in the chapter). For decades, standard first-line therapy consisted of 5-FU and leucovorin with a response rate of approximately 20% and median survival of approximately 1 year. In the late 1990s and early 2000s, the addition of oxaliplatin and irinotecan to the backbone of 5-FU and leucovorin resulted in an improvement in median OS to nearly 24 months when patients received active first- and second-line treatment. The introduction of biological agents, such as bevacizumab, ziv-aflibercept, ramucirumab, cetuximab, and panitumumab, has further enhanced the efficacy of systemic medical therapy. The emphasis of current advances in medical therapy is on the development of predictive biomarker signatures, which can help guide treatment decisions for specific patient subpopulations.

The availability of various active agents for the treatment of mCRC has resulted in an abundance of therapeutic options that now demand a goal-oriented strategic approach to therapy to maximize patient benefit (Fig. 13.2-4). When treating a patient who has mCRC, the first determination is whether stage IV disease is potentially curable by surgical resection of metastases either at the time of diagnosis or after downsizing initially unresectable metastases by neoadjuvant chemotherapy. This will guide the choice and timing of chemotherapy because, in this scenario, the most appropriate treatment is conceivably the one that generates the highest response rate and carries the greatest potential to downsize metastases. If the patient's disease does not seem potentially curable, the main goals of systemic chemotherapy are to extend the duration of the patient's life and to maintain quality of life for as long as possible. In this scenario, treatment regimens that offer the longest PFS and OS as well as a favorable toxicity profile are preferred.

Irinotecan and Oxaliplatin

In the late 1990s and early 2000s, several trials established the benefit of oxaliplatin- and irinotecan-containing regimens in the first-line metastatic setting (eg, FOLFOX, FOLFIRI [5-fluorouracil, leucovorin, and irinotecan], IFL [irinotecan, bolus 5-FU, and leucovorin], and CAPOX).[382,385-392] The main lessons learned over time were that an infusional or oral fluoropyrimidine-based regimen was superior to a bolus 5-FU–based regimen, especially when combined with irinotecan, and that oxaliplatin was ineffective as a single agent and needed to be combined with other chemotherapy agents such as a fluoropyrimidine or irinotecan.

In the 2000s, several trials established the superiority of FOLFOX and FOLFIRI over bolus 5-FU regimens in the metastatic setting, and smaller trials suggested an equivalency between FOLFOX and FOLFIRI.[393-395] The choice between FOLFOX and FOLFIRI in the clinic should be based mainly on the expected adverse effect profile although recently published work using tumor molecular profiling, clinical data, and artificial intelligence suggests that an algorithm may be used to determine who is most likely to benefit from up-front FOLFOX chemotherapy.[396] These results still must be validated in a prospective fashion. Because the benefit of subsequent-line therapy in CRC has been well established, patients should receive all active cytotoxic drugs in the course of their therapy to optimize outcome.[397]

Bevacizumab

Bevacizumab, a recombinant humanized monoclonal antibody to VEGF-A, demonstrates clinical efficacy in the treatment of mCRC. In a large, phase 3 placebo-controlled trial with 813 patients, the IFL protocol was compared with IFL and bevacizumab (5 mg/kg every 2 weeks) as first-line therapy for advanced CRC.[398] The addition of the anti-VEGF antibody led to a substantially increased response rate (45% vs 35%; $P = .0036$), PFS (10.6 vs 6.2 months; HR, 0.54; $P < .00001$), and median OS (20.3 vs 15.6 months; HR, 0.66; $P = .00004$). This trial was the first phase 3 validation of an antiangiogenic agent as an effective treatment option in a human malignancy. Subsequently, bevacizumab was also shown to enhance the efficacy of oxaliplatin-based regimens in first- and second-line treatment as well as in combination with 5-FU and leucovorin alone or with irinotecan.[399-401] It also improved survival when administered with trifluridine-tipiracil in the SUNLIGHT trial in patients who received up to 2 prior chemotherapy regimens (10.8 months vs 7.5 months for trifluridine-tipiracil alone).[402]

It is important to note that bevacizumab does not seem to have substantial single-agent activity in mCRC.[403]

The main adverse effects observed with bevacizumab consist of hypertension (a class effect of all agents targeting VEGF signaling), bleeding, GI perforations (1.5%-2% of patients), and poor wound healing as well as arterial thrombotic events in approximately 4%-5% of patients.[403] In addition to arterial thrombotic events, a meta-analysis identified a 33% higher incidence of venous thrombotic events for patients receiving bevacizumab compared with the nonbevacizumab control arm in randomized trials[404] although another more recent analysis refuted this claim.[405] Bevacizumab should be used with extreme caution, if at all, for patients who have a strong history of a recent arterial thrombotic event. Bevacizumab should also be used with caution for patients who have recent surgery or for whom surgery is planned (at least 4 weeks between bevacizumab and surgery is recommended if possible) and those who have obstructing primary tumors. History of a venous thromboembolic event is not considered an absolute contraindication to bevacizumab therapy and patients on stable therapeutic anticoagulation can also receive bevacizumab without an increase in severe bleeding risk.[406]

On the basis of its well-documented efficacy and relative moderate toxicity, bevacizumab has emerged as a standard component of first-line chemotherapy for advanced CRC. Its use in right- versus left-sided tumors is discussed in the section titled "Head-to-Head Comparison between EGFR Monoclonal Antibodies and Bevacizumab."

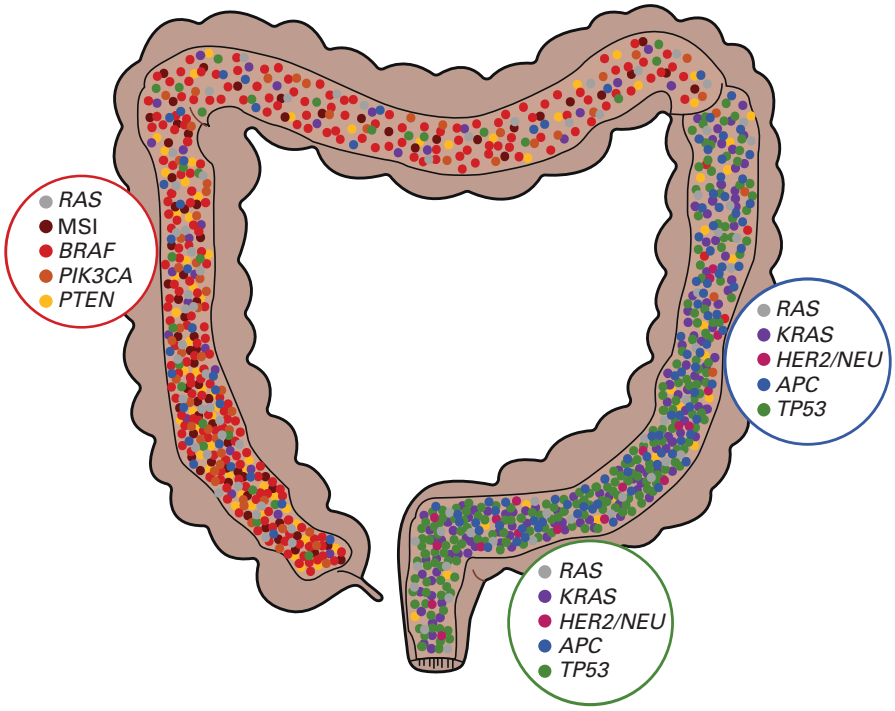
Anti-EGFR Antibodies: Cetuximab and Panitumumab

Data from various clinical trials and translational studies have opened the door to individualized treatment approaches in CRC by identifying patients who are most likely to benefit from monoclonal antibodies against EGFR, namely, cetuximab and panitumumab. It is increasingly clear that patients who have advanced CRC must have a tumor that is WT for *KRAS* exons 2, 3, and 4 and *NRAS* exons 2, 3, and 4 (referred to as extended RAS) for EGFR monoclonal antibodies to be effective.[407-412] Mutations in *RAS* (~55% of tumors) result in constitutively active signaling downstream from EGFR, thereby negating the effect of blocking the receptor. The CRYSTAL trial was a large phase 3 trial of 1198 patients with untreated metastatic colon cancer that compared FOLFIRI and cetuximab with FOLFIRI alone. In patients with pan-*RAS* WT tumors, response rate (57% vs 40%), median PFS (9.9 vs 8.4 months), and OS (23.5 vs 20 months) were all improved with the addition of cetuximab.[411] The PRIME trial of FOLFOX with or without panitumumab yielded similar results. NCCN guidelines call for expanded *RAS* mutation testing before EGFR monoclonal antibodies are used in patients with CRC, and all patients who have metastatic colon cancer should have extended *RAS* and *RAF* testing performed at the time of diagnosis if active therapy is being considered.[412] Use of either agent with either chemotherapy backbone (FOLFOX or FOLFIRI) is an acceptable standard of care for the first-line treatment of extended *RAS* WT tumors. Additional negative predictive biomarkers for first-line anti-EGFR therapy include *BRAF* V600E–mutated and *HER2*-amplified tumors as well as right-sided tumors.

The main toxic effects of anti-EGFR monoclonal antibodies are acneiform skin rash, hypomagnesemia, diarrhea, and hypersensitivity reactions, the latter of which is particularly relevant for the chimeric antibody cetuximab. Prophylactic treatment of the skin rash with oral doxycycline and topical corticosteroids was investigated in the randomized phase 2 STEPP trial,[413] and skin toxicities were reduced from 62% in the reactive group to 29% in the preemptive group. Preemptive therapy should be considered for all patients receiving anti-EGFR therapies. Recent ESMO guidelines for prevention and treatment of dermatologic toxicity from EGFR antibodies have been published.[414]

Initial reports suggested synergistic activity when bevacizumab was combined with cetuximab in salvage therapy.[415] Results of subsequent larger randomized first-line trials, however, demonstrated an antagonistic effect of the combination of EGFR monoclonal antibodies with bevacizumab in the context of concurrent chemotherapy.[416,417] Therefore, combinations of bevacizumab and EGFR monoclonal antibodies should generally not be used in clinical practice outside of a clinical trial at this time.

Figure 13.2-5 Molecular Alterations by Tumor Sidedness in Colorectal Cancer



Abbreviation: MSI, microsatellite instability.
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The choice of anti-EGFR therapy versus bevacizumab in the first-line metastatic setting for patients with extended *RAS* WT tumors has been addressed by several phase 3 trials. The FIRE-3 trial randomly selected 592 patients who had conventionally assessed *KRAS* exon 2 WT CRC to receive FOLFIRI and cetuximab or FOLFIRI and bevacizumab. The primary endpoint of investigator-assessed response rate was not reached. In addition, no difference in PFS was noted (10.0 vs 10.3 months); in fact, the PFS curves were almost completely superimposable. Surprisingly, however, a statistically substantial difference was found in OS with a difference in median OS of 3.7 months in favor of FOLFIRI and cetuximab.[418] An updated analysis that accounted for additional mutations in *KRAS* and *NRAS* demonstrated an even larger difference in median OS (33.1 vs 25.0 months; HR, 0.70; $P = .0059$), again without a statistically substantial difference in response rate or PFS.[418]

The US Intergroup study CALGB/SWOG 80405 compared investigator's choice of chemotherapy (FOLFOX or FOLFIRI) with cetuximab or bevacizumab as first-line therapy for 1,137 patients who had *KRAS* exon 2 WT mCRC.[419] In contrast to the FIRE-3 trial, no difference in OS was noted between the two treatment arms, not even when any *RAS*-mutated cancers were excluded. Both treatment arms showed long median OS: 31.2 months for chemotherapy and bevacizumab and 32.0 months for chemotherapy and cetuximab (HR, 0.9; $P = .40$). Note that the outcome parameters of FIRE-3 and CALGB/SWOG 80405 were more similar than different with the exception of poor performance in the bevacizumab arm in FIRE-3.

Colorectal tumors present with substantial heterogeneity in molecular features, which is strongly associated with tumor location (Fig. 13.2-5). Left-sided tumors (splenic flexure to rectum) often present with WT *BRAF*, *KRAS* point mutations (codons 12, 13, and 61), and extensive copy-number alterations as well as other structural genomic aberrations, including CIN and loss of heterozygosity. Right-sided tumors (cecum to hepatic flexure) are enriched for *BRAF* V600E point mutations; are WT for *KRAS*; and have a diploid copy number, MSI, DNA hypermutation, and extensive DNA hypermethylation associated with the CIMP phenotype.

On the basis of these molecular differences, left- and right-sided colon tumors are now becoming increasingly recognized as two unique cancer types that may benefit from different therapeutic strategies. A post hoc analysis of the CALGB 80405 data found sidedness to be prognostic; median survival of patients with left- versus right-sided tumors was 31.4 versus 24.2 months, respectively ($P = .01$).[420,421] The trial also suggested that sidedness was predictive of response to cetuximab versus bevacizumab ($P_{int} = .05$) with cetuximab having an OS advantage for left-sided tumors ($P = .01$) and a suggestion of improved survival with bevacizumab for right-sided tumors ($P = .08$). An analysis of the CRYSTAL and FIRE-3 studies similarly showed a survival advantage for chemotherapy and cetuximab over chemotherapy alone or chemotherapy and bevacizumab for left-sided tumors.[422] The PARADIGM trial randomly assigned 802 patients who had *RAS* WT metastatic CRC (604 with left-sided tumors) to first-line mFOLFOX6 with bevacizumab or panitumumab with OS as the endpoint to be tested hierarchically in left-sided tumors followed by the full analysis set (FAS) population. These results showed that panitumumab substantially improved OS in both groups: left-sided (HR, 0.82; 95.798% CI, 0.68-0.99; $P = .031$, which crossed the boundary of significance [.042]) and in the overall population (HR, 0.84; 95% CI, 0.72-0.98; $P = .030$, with <.05 as the boundary). Although PFS was comparable between the arms, response rates (80.2%; 95% CI, 75.3-84.5% vs 68.6%; 95% CI, 62.9-74.0) were higher with panitumumab. NCCN and ESMO guidelines currently recommend either anti-EGFR therapy or bevacizumab as the biological choice in combination with chemotherapy for left-sided extended *RAS* WT tumors; anti-EGFR antibodies should not be used as first-line therapy for patients with right-sided extended *RAS* WT tumors. Data on response to EGFR antibodies for patients with transverse colon (hepatic to splenic flexure) primaries are currently lacking.

5-Fu, Oxaliplatin, and Irinotecan Regimens

The FOLFIRINOX regimen (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; also called FOLFOXIRI) has high activity but also increased toxicity. The largest trial evaluating FOLFIRINOX in this setting was the TRIBE trial, in which FOLFIRINOX and bevacizumab were compared with FOLFIRI and bevacizumab alone.[423] The triplet combination improved median OS (29.8 vs 25.8 months; HR, 0.8; 95% CI, 0.65-0.98; $P = .03$), and 5-year survival was doubled to 25% vs 12.5%. There was also a suggestion that patients with *BRAF*-mutated tumors had improved median OS (19 vs 10.7 months; HR, 0.54; 95% CI, 0.24-1.20) that did not reach statistical significance, likely secondary to the small number of patients with this mutation (n = 28). A subsequent phase 2 trial, OLIVIA, testing FOLFIRINOX with bevacizumab versus FOLFOX with bevacizumab also showed higher response rates and longer PFS and improved rates of liver resection.[424] Another phase 3 trial, STEAM, confirmed the benefit of the triplet regimen for PFS and liver resection rates, and the TRIBE2 study of FOLFIRINOX with bevacizumab versus FOLFOX with bevacizumab suggested an OS advantage with early results.[425,426] The TRIPLETE study compared FOLFOX versus FOLFIRINOX in combination with panitumumab for patients who have advanced *RAS* and *BRAF* WT mCRC (88% left-sided) and failed to show an improvement in the primary endpoint of ORR (76% vs 73%; OR, 0.87; 95% CI, 0.56-1.34; $P = .526$) or secondary endpoint of PFS (median PFS, 12.3 vs 12.7 months; HR, 0.88; 95% CI, 0.70-1.11; $P = .277$). Given the increased efficacy at the cost of potentially increased toxicities, the triplet regimen may be a potential option for patients with aggressive tumors (eg, right-sided tumors, *BRAF* V600E mutated) or in those needing rapid clinical response but with overall excellent clinical status.

Stop-and-Go Strategies

Because the treatment-limiting toxicity of oxaliplatin-based first-line therapy is cumulative neurotoxicity, proactive strategies must be used to maximize treatment duration for patients who start palliative therapy with fluoropyrimidine and oxaliplatin.

Initial trials such as OPTIMOX1 and CONCePT, which randomly assigned patients to continuous versus intermittent oxaliplatin therapy while continuing fluoropyrimidine, showed lower toxicity for intermittent dosing, especially for peripheral neuropathy.[427,428] However, subsequent trials, such as OPTIMOX-2 and MRC COIN, suggested that complete discontinuation of therapy without careful patient selection may be detrimental.[428,429] The results of these trials have paved the way toward the current approach of induction maintenance with a limited number of oxaliplatin-containing treatment cycles up front and maintenance therapy with a fluoropyrimidine and targeted agent combination now considered standard of care. Maintenance therapy with a fluoropyrimidine and bevacizumab is supported by several prospective trials and most prominently by the Dutch CAIRO3 study.[430] In this trial, 558 patients who had achieved at least stable disease after 18 weeks (six cycles) of induction therapy of capecitabine and oxaliplatin with bevacizumab were randomly assigned to a completely chemotherapy-free interval or maintenance therapy with low-dose continuous capecitabine (625 mg/m^2 twice daily) and bevacizumab (7.5 mg/kg every 3 weeks). All prospectively defined outcome parameters in this strategy trial were in favor of the maintenance therapy arm with a strong trend toward improvement in OS. Similarly, in eligible patients who are started on oxaliplatin and anti-EGFR monoclonal antibody regimens, maintenance therapy with a fluoropyrimidine and anti-EGFR monoclonal antibody is recommended over either single agent. In the TRIBE 2 trial, patients were randomly assigned to receive two different strategies: first-line FOLFOX plus bevacizumab (bev) followed by FOLFIRI plus bev after disease progression (arm A, standard treatment) or first-line FOLFIRINOX plus bev followed by reintroduction of FOLFIRINOX plus bev after disease progression (arm B, experimental strategy). All treatments are administrated up to eight cycles followed by 5-FU/LV plus bev randomized to receive two different strategies: first-line FOLFOX plus bev followed by FOLFIRI plus bev after disease progression (arm A, standard treatment) or first-line FOLFIRINOX plus bev followed by reintroduction of FOLFIRINOX plus bev after disease progression (arm B, experimental strategy). All treatments are administrated up to eight cycles followed by 5-FU/LV plus bev maintenance until disease progression or unacceptable adverse events. In this study, up-front FOLFIRINOX plus bevacizumab followed by the reintroduction of the same regimen after disease progression seems to be a preferable therapeutic strategy to sequential administration of chemotherapy doublets in combination with bevacizumab. The phase 2 VALENTINO study showed inferior outcomes in the primary endpoint of 10-month PFS with maintenance panitumumab (49%) versus 5-FU and leucovorin with panitumumab (59%) after induction with FOLFOX and panitumumab (HR, 1.51; 95% CI, 1.11-2.07. A combination maintenance approach in this setting was also supported by the phase 3 PANAMA study. After induction with FOLFOX and panitumumab, this trial randomly assigned patients to maintenance therapy with 5-FU versus 5-FU and panitumumab and showed improvement in PFS with the combination (8.8 vs 5.7 months; HR, 0.72. Therefore, an induction maintenance approach with a limited duration of oxaliplatin-based therapy and prolonged fluoropyrimidine and monoclonal antibody therapy may be considered an option to minimize toxicity for patients who have advanced CRC. Importantly, these and other trials established that oxaliplatin could be reintroduced at the time of progression and still yield acceptable response rates as demonstrated in the OPTIMOX1 trial.

Benefit in Older Patients

Although most patients who have mCRC tolerate and receive bevacizumab in the context of an irinotecan- or oxaliplatin-based combination regimen, it is unclear whether specific subgroups such as older patients benefit from a bevacizumab and fluoropyrimidine combination alone. This question was addressed in the AVEX phase 3 trial.[431] In this study, 280 patients age ≥ 70 years (median age, 76 years) who were not deemed to be candidates for oxaliplatin- or irinotecan-based first-line chemotherapy regimens were randomly selected to receive capecitabine alone or bevacizumab and capecitabine every 3 weeks. PFS, the primary endpoint, was substantially longer with bevacizumab and capecitabine than with capecitabine alone (median, 9.1 vs 5.1 months; HR, 0.53; 95% CI, 0.41-0.69; $P < .0001$). Although the study was underpowered to demonstrate a statistically significant improvement in OS, the median survival in the bevacizumab arm of 20.7 months (compared with 16.8 months for capecitabine alone) is remarkable given the age of the patient population and the limited postprogression therapies patients received. The combination of fluoropyrimidine and bevacizumab can be considered an acceptable standard of care for older patients who are not eligible for irinotecan or oxaliplatin but have no contraindication to receiving bevacizumab.

KEY POINTS

- All patients with metastatic colon cancer being considered for multiagent chemotherapy should have their tumors undergo extended *RAS* and *BRAF* mutation testing. In addition, all tumors should be tested for dMMR/MSI-H status and should undergo HER2 testing for overexpression or amplification as this may be a marker of resistance to anti-EGFR therapy as well as a potential target for therapies discussed subsequently.
- Either FOLFOX or FOLFIRI with a biological agent is an appropriate first-line chemotherapy backbone for patients who have mCRC.
- Eventual exposure to all appropriate agents is what is most important. Triplet regimens (FOLFIRINOX) with bevacizumab may be an option for patients who have aggressive tumors.

- For patients who have left-sided extended *RAS* WT tumors, anti-EGFR therapy should be preferentially considered, and anti-EGFR therapy should be avoided as initial therapy for patients who have right-sided tumors for which bevacizumab is preferred.
- Induction maintenance approaches with a limited number of oxaliplatin-containing treatment cycles up front and maintenance therapy with a fluoropyrimidine and bevacizumab combination can be considered standard of care. Those whose disease progresses during maintenance therapy can still have oxaliplatin reintroduced.
- For patients who are not candidates for either oxaliplatin- or irinotecan-containing regimens, the combination of a fluoropyrimidine and bevacizumab can be considered an acceptable standard of care.

ANTI-VEGFR ANTIBODY THERAPY BEYOND FIRST-LINE PROGRESSION

It has been suggested that prolonged inhibition of the VEGF-mediated proangiogenic system is required to maximize the treatment benefit for patients who are receiving anti-VEGF therapy, particularly because the mechanism and onset of secondary resistance could differ between chemotherapy and bevacizumab.[432] Additional evidence supporting the concept of prolonged VEGF inhibition as an optimized treatment approach in CRC comes from the ML18147 phase 3 trial, which tested the efficacy of bevacizumab beyond progression added to chemotherapy in mCRC.[433] A total of 820 patients who had received first-line palliative therapy with a bevacizumab-based combination were randomly assigned at progression to either continue bevacizumab with another standard chemotherapy backbone or stop bevacizumab. The primary endpoint of the study, improvement in OS, was reached with an HR of 0.81 (95% CI, 0.69-0.94) and median improvement of 1.4 months (11.2 vs 9.8 months; $P = .0062$). This effect was confirmed in all evaluated subgroups and supported by the PFS results, which demonstrated superiority for the bevacizumab beyond progression arm (HR, 0.68; median, 5.7 vs 4.1 months; $P < .0001$). No increase in response rate was seen in the bevacizumab beyond progression group, and the response rates seen in both arms in second-line therapy were low, approximately 4% to 5%. No new or unexpected safety issues emerged for bevacizumab. Confirmatory results were seen with two alternative anti-VEGF therapies: ziv-aflibercept (formerly known as VEGF-Trap), a VEGF receptor decoy fusion protein, and ramucirumab, a human monoclonal antibody directed against VEGFR-2.[154,434] It should be noted that there is no role for bevacizumab as a single agent as either maintenance or subsequent-line therapy. Further support for the efficacy of bevacizumab in patients who have previously received bevacizumab is provided by the randomized SUNLIGHT clinical trial which demonstrated improved survival for the addition of bevacizumab to trifluridine-tipiracil in previously treated patients. Approximately 3/4 of patients in both treatment arms had received prior bevacizumab. While a subgroup analysis of overall survival demonstrated what appeared to be a greater benefit to the addition of bevacizumab in the group who hadn't received bevacizumab compared to those who had (0.4 and 0.72 respectively), the benefit was statistically significant in both groups.[402]

Oral Agents in Salvage Therapy for CRC

Regorafenib, a small-molecule inhibitor of multiple cell-signaling kinases (eg, VEGFR-1 to -3, KIT, RET, FGFR1-2, PDGFR-β, and BRAF), has documented efficacy as salvage therapy in advanced CRC. Regorafenib was investigated in a placebo-controlled randomized phase 3 trial in a salvage therapy setting. Efficacy results of the trial demonstrated a benefit in OS for patients receiving regorafenib compared with placebo (6.4 vs 5.0 months).[435] The activity of regorafenib was also reflected in an improvement of PFS (1.9 vs 1.7 months). The most common severe toxicities observed with regorafenib were hand-foot syndrome, fatigue, diarrhea, and hypertension. Regorafenib is FDA approved as a salvage therapy option for patients with advanced CRC who have previously been treated with fluoropyrimidine, oxaliplatin, irinotecan, a VEGF inhibitor, and, if pan-*RAS* WT, an anti-EGFR monoclonal antibody. Given that approximately two-thirds of patients assigned to regorafenib in the pivotal required dose modification due to toxicity, and that clinical practice generally deemed the 160 mg daily dose approved by the FDA as intolerable for many patients, the randomized phase 2 ReDOS trial was performed.[436] Toxicities necessitating dose modification were primarily dermatologic, gastrointestinal, and constitutional. The ReDOS trial ultimately compared a starting dose of 80 mg/day and dose increases as tolerated versus a starting dose of 160 mg/day. The primary endpoint of essentially making it to start cycle 3 was met, with 43% in the dose escalation group versus 26% in standard dosing. Thus, in clinical practice, a ReDOS strategy is generally recommended for regorafenib use.

Trifluridine and tipiracil (TAS-102) comprise a novel oral anticancer agent consisting of trifluorothymidine as the antitumor component, which is incorporated into and retained in the DNA of cancer cells, and tipiracil hydrochloride, which prevents the degradation of trifluorothymidine. An international phase 3 study of 800 patients was launched in the same setting with random assignment at a 2:1 ratio favoring trifluridine and tipiracil.[437] The primary endpoint of the trial was met with an improvement in OS (median OS, 7.1 vs 5.3 months) with trifluridine/tipiracil compared with placebo. The most common grade 3 to 4 AE was neutropenia, seen in approximately 40% of patients with 4% having febrile neutropenia. Trifluridine and tipiracil received FDA approval in September 2015 for the treatment of patients with mCRC who have previously been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological product, and an anti-EGFR monoclonal antibody, if pan-*RAS* WT. Trifluridine and tipiracil and regorafenib have distinctly different adverse effect profiles (trifluridine and tipiracil,

myelosuppression; regorafenib, hand-foot skin reaction and fatigue) but similar efficacy data. A phase 2 trial of 93 patients with refractory mCRC randomly assigned to trifluridine and tipiracil with or without bevacizumab showed improvement in the primary endpoint of PFS (median PFS, 4.6 vs 2.6 months). The follow-up phase 3 SUNLIGHT trial randomly selected patients with pretreated mCRC in the third-line setting to receive trifluridine and tipiracil with or without bevacizumab and showed an improvement in the primary endpoint of OS from 7.5 to 10.8 months (HR, 0.61; 95% CI, 0.49-0.77) and improvement in PFS from 2.4 to 5.6 months (HR, 0.44; 95% CI, 0.36-0.54) with the combination of trifluridine/tipiracil and bevacizumab, and this combination is included as an option in NCCN guidelines.[438]

Fruquintinib is a selective inhibitor of VEGFR-1, -2, and -3. It was evaluated in the placebo-controlled phase 3 FRESCO trial conducted in China for patients who have pretreated CRC (≤2 lines) that showed improvement in the primary endpoint of OS (9.3 vs 6.6 months; HR, 0.65; 95% CI, 0.51-0.83; $P < .001$), which led to its approval in China in the third- or later-line setting. The FRESCO-2 trial was a global placebo-controlled phase 3 trial that randomly selected 691 patients with refractory CRC, including prior trifluridine and tipiracil and/or regorafenib, that showed an improvement in the primary endpoint of OS (7.4 vs 4.8 months; HR, 0.66; 95% CI, 0.55-0.80; $P < .001$). The most common grade 3+ adverse events in the pivotal trials were hypertension, asthenia, and hand/foot syndrome. This drug gained FDA approval in November 2023.

With the approvals of trifluridine/tipiracil, regorafenib, and fruquintinib, these serve as reasonable subsequent treatment options for patients with metastatic colon cancer who have received prior fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and anti-EGFR inhibitor if RAS/RAF wild-type. The key missing data are direct comparisons between the agents. Thus, in practice, selection of an oral agent is often based on prior toxicities experienced by patients as well as patient preferences as the dose schedules differ as well.

PD-1/PD-L1 Immune Checkpoint Inhibitors in CRC

Immune checkpoint inhibitors targeting the PD-1 pathway by binding to PD-1 or its ligand (PD-L1 or PD-L2) have shown proof of efficacy in various malignancies since 2014, and several antibodies targeting this system have already received FDA approval in noncolorectal malignancies, such as melanoma and non-small-cell lung cancer.[439] PD-1/PD-L1 inhibitors allow the patient's immune system to recognize cancer cells by blocking immunosuppressive mechanisms generated by tumor cells, particularly when these tumor cells carry a high DNA mutational burden with consecutive expression of many neoantigens. MSI-H/dMMR CRCs carry 10 to 100 times as many somatic mutations as microsatellite stable/MMR-proficient (pMMR) tumors.[440] In addition, MSI-H/dMMR colon cancers are commonly characterized by dense lymphocytic infiltrates, indicating a potential activation of the host's immune system.[441] On the basis of these observations, a pivotal pilot study was initiated that investigated the role of pembrolizumab, an antibody against PD-1, in heavily pretreated patients with advanced CRC, with cohorts identified by their MSI status (MSI-H/dMMR vs microsatellite stable/pMMR).[442] In addition, a cohort of patients who have MSI-H/dMMR non-CRC was included in the study. Single-agent pembrolizumab showed remarkable activity only in patients who have MSI-H/dMMR cancer, independent of histological origin. In MSI-H/dMMR CRCs, patients experienced a response rate >60% and a disease control rate >90% with some experiencing durable response for >1 year.[443] These findings led to the initiation of several studies with PD-1/PD-L1 antibodies, targeting the approximately 4% to 5% of mCRCs characterized as MSI-H/dMMR. Furthermore, for the first time, the FDA granted organ site–agnostic approval of pembrolizumab for any dMMR solid tumor. For CRC, pembrolizumab was approved for MSI-H/dMMR tumors after prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Similarly, the FDA approved both nivolumab and combination nivolumab and ipilimumab for the treatment of patients with metastatic colon cancer with MSI-H/dMMR tumors. This was based on the results of the CheckMate 142 study, which showed an ORR of 34% (complete response [CR], 9%) and disease control rate of 62% in the single agent nivolumab arm.[444] In the 119 patients treated with the combination of ipilimumab and nivolumab, the ORR was 55% and disease control rate was 80%.[445] The two arms were not randomly assigned, so caution is required when comparing the results. At this point, there is no specific guidance on which PD-1 inhibitor should be used or whether it should be used in combination with ipilimumab or as a single agent.

The landmark phase 3 KEYNOTE-177 study randomly assigned patients who had first-line treatment-naive metastatic MSI-H/dMMR CRC to pembrolizumab or investigator's choice of chemotherapy; crossover to pembrolizumab was allowed at disease progression for patients in the chemotherapy arm. Median PFS was 16.5 months for pembrolizumab versus 8.2 months for chemotherapy (HR, 0.60; 95% CI, 0.45-0.80). The 24-month PFS rate was 48% for pembrolizumab versus 19% for chemotherapy. Overall response was 43.8% for pembrolizumab versus 33.1% for chemotherapy with 11% of patients in the pembrolizumab arm achieving a CR ($P = .0275$). In an updated analysis, after a median follow-up of 44.5 months, although the HR for OS favored pembrolizumab, it did not reach statistical significance (HR, 0.74; 95% CI, 0.53-1.03; $P = .0359$). This likely was related to 60% of patients in the chemotherapy arm subsequently receiving anti–PD-1/PD-L1 therapies on or off study.[446] This study, however, established pembrolizumab as the standard-of-care first-line therapy for patients with MSI-H/dMMR tumors and is now FDA approved for this indication. Additional trials are examining combinations with CTLA-4 inhibitors and combinations of chemotherapy with immunotherapy. CheckMate 8HW, which is a randomized phase 3 study comparing nivolumab and ipilimumab with nivolumab or chemotherapy in patients with MSI-H/dMMR mCRC, initially reported results only for the nivolumab and ipilimumab arm. This arm demonstrated superior PFS versus chemotherapy in previously untreated patients who have MSI-H/

dMMR mCRC.[447] The trial subsequently reported data for the comparison between combination ipilimumab/nivolumab and nivolumab monotherapy across all lines of therapy.[448] There was a statistically significant improvement in PFS (median 54.1 months vs 18.4 months, HR 0.64 [0.52-0.79], with a 13% increase in response rate (58%-71%, $P = .0011$). Of equal importance, treatment-related adverse events of grade 3/4 were only modestly increased from 14 to 22%, with 9% discontinuing the combination due to adverse events compared to 4% with nivolumab monotherapy. Based on these data, combination therapy with ipilimumab/nivolumab may be considered the standard initial therapy for patients with dMMR/MSI-H metastatic colorectal cancer with good performance status. Single-agent checkpoint inhibitor therapy can also be considered in select patients. It is reasonable to consider dual immunotherapy for patients who have progressed on single-agent checkpoint inhibitor, although data addressing the degree of benefit (if any) are lacking. It must be emphasized again that, for all of the immunotherapy trials discussed in this section, these agents should not be used in patients who have pMMR tumors outside of a clinical trial.

BRAF-Mutated Tumors

BRAF encodes a protein GTPase, downstream of RAS. *BRAF* V600E mutations can be found in approximately 5% to 10% of patients with advanced CRC.[449] They are mutually exclusive with *RAS* mutations and have been consistently found to be associated with a poor prognosis.[411,450,451] Even in the era of modern combination therapy, median survival of patients with *BRAF*-mutated stage IV CRC is only 12 to 14 months.[411] Whether activating *BRAF* mutations can be considered negative predictive markers for the activity of anti-EGFR antibodies has long been unclear because of their strong negative prognostic effect and their low prevalence. A meta-analysis of nine phase 3 trials and one phase 2 trial, which all randomly assigned patients to treatment with or without EGFR inhibitors, showed no benefit for the use of EGFR antibodies with regard to PFS, OS, or response rate.[452] Therefore, the use of EGFR inhibitors (without combining with a BRAF inhibitor) for patients with tumors containing activating *BRAF* mutations should not be considered a first choice if at all.

The phase 3 BEACON trial evaluated second- or third-line cetuximab and the BRAF inhibitor encorafenib with or without the MEK inhibitor binimetinib compared with irinotecan (with or without 5-FU) and cetuximab.[453] Both experimental arms showed improved efficacy over the control, but the doublet regimen of cetuximab and encorafenib showed lower toxicity rates. Updated results of this trial showed improvement in median OS for triplet over control (9.3 vs 5.9 months; HR, 0.60; 95% CI, 0.47-0.75) and for doublet over control (9.3 months; HR, 0.61; 95% CI, 0.48-0.77). Confirmed response rates were 26.8% (95% CI, 21.1-33.1) for triplet, 19.5% (95% CI, 14.5-25.4) for doublet, and 1.8% (95% CI, 0.5%-4.6%) for control. Based on these encouraaging second-line data, the phase 3 BREAKWATER trial investigated encorafenib/cetuximab (EC) plus mFOLFOX6 versus standard-of-care chemotherapy for untreated metastatic BRAFV600E colorectal cancer.[454] The initial report demonstrated that EC + mFOLFOX6 had increased ORR, 60.9% versus 40.0% with SOC chemotherapy. Median duration of response was 13.9 versus 11.1 months. A subsequent presentation and manuscript extended the analysis and follow-up, reporting a statistically significant improvement in progression-free survival for the addition of EC (median, 12.8 vs 7.1 months; hazard ratio for progression or death, 0.53; 95% confidence interval [CI], 0.41 to 0.68; $P < .001$). An interim analysis also demonstrated improved OS with the addition of EC to FOLFOX (median, 30.3 vs 15.1 months; hazard ratio for death, 0.49; 95% CI, 0.38 to 0.63; $P < .001$). Side effects were modestly increased but consistent with known profiles of these agents. These data highlight the importance of testing for *BRAF* mutations with initial diagnosis of metastatic disease.[370] As a result of this trial, NCCN guidelines were updated as well as the FDA approval for encorafenib and cetuximab in combination with mFOLFOX6 for treatment of patients with metastatic CRC with a *BRAF* V600E mutation. In practice, many substitute panitumumab for cetuximab. It also should be noted that nearly all patients in the BREAKWATER trial had MSS cancers. While patients with dMMR (MSI-H) tumors and concomitant *BRAF* V600E mutations would technically be eligible for encorafenib/cetuximab combination therapy, most would favor initial immunotherapy given the degree and durability of benefit, and reserving BRAF-targeted therapy for progression.

Non-V600E mutations in *BRAF* (atypical *BRAF* mutations) represent a rare subset (2%-3% of all patients with CRC) and are divided into classes II (RAS independent; intermediate to high kinase activity) and III (RAS dependent; low kinase activity); such patients may have limited response to anti-EGFR antibodies.[455] Other studies show that their OS may be better than that of patients with *BRAF* V600E–mutated or *BRAF* WT tumors.[456]

HER2 Overexpression/Amplification

HER2 is overexpressed in approximately 5% of metastatic colon cancers and this overexpression occurs more in left-sided tumors. The HERACLES trial treated patients with mCRC with *KRAS* WT/*HER2*-amplified disease (IHC 3^+ or IHC 2^+ with FISH ratio >2.0) with trastuzumab and lapatinib. Despite 74% of these patients receiving more than four lines of therapy, the ORR was 30%, and the disease control rate was 60%.[456] Similar findings were seen in the MyPathway trial, in which patients who had HER2-positive disease were treated with trastuzumab and pertuzumab therapy.[457] In the 37 patients who had colon cancer, most of whom had received more than four prior therapies, 38% had tumor response, and the disease control rate was 49% with a median DOR of >11 months. The MOUNTAINEER trial treated 84 patients who had *RAS* WT/*HER2*-amplified disease with tucatinib and trastuzumab and showed an ORR of 38%, (95% CI, 28-49); median DOR was 12.4 months (95% CI, 8.5-20.5).[458] Based on these data, the FDA granted accelerated approval of tucatinib in combination with trastuzumab for *RAS* WT/*HER2*-amplified unresectable

or metastatic colorectal cancer that has progressed after fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. The ongoing phase 3 MOUNTAINEER-03 trial is comparing tucatinib, trastuzumab, and mFOLFOX6 versus mFOLFOX6 with or without bevacizumab or cetuximab in the first-line setting for these patients. The DESTINY-CRC02 trial of the antibody-drug conjugate trastuzumab-deruxtecan (T-DXd) was conducted in two stages. In stage 1, 80 patients were randomly assigned 1:1 to 5.4 (n = 40) or 6.4 mg/kg (n = 40) of T-DXd once every 3 weeks. In stage 2, an additional 42 patients received 5.4 mg/kg of T-DXd. The confirmed ORR was 37.8% (95% CI, 27.3%-49.2%) in the 5.4 mg/kg arm and 27.5% (95% CI, 14.6%-43.9%) in the 6.4 mg/kg arm. Grade ≥ 3 TEAEs were observed in 41 (49.4%) of 83 patients and 23 (59.0%) of 39 patients in the 5.4 and 6.4 mg/kg arms, respectively. Serious AEs were observed in 20 (24.1%) of 83 patients and 12 (30.8%) of 39 patients in the 5.4 and 6.4 mg/kg arms, respectively. Independently adjudicated drug-related interstitial lung disease occurred in seven (8.4%) of 83 patients with 5.4 mg/kg of T-DXd and five (12.8%) of 39 patients with 6.4 mg/kg of T-DXd. This study suggests that the 5.4 mg/kg dose may be preferable over the 6.4 mg/kg dose with similar efficacy but an improved toxicity profile. Additionally, antitumor efficacy was observed irrespective of *RAS* mutation status at 5.4 mg/kg of T-DXd and in those with prior anti-HER2 therapy although no meaningful activity was observed in those with low HER2 expression.[459] Thus in practice, the MOUNTAINEER regimen of tucatinib/trastuzumab may be preferred for patients with *HER2* amplified, RAS wild-type cancers and is not approved for patients whose tumors have *RAS* mutations. Trastuzumab-deruxtecan is preferred for patients with HER2-positive (HER2 3+) cancers and concomitant *RAS* mutations.

KRAS G12C–Mutated Tumors

Although *KRAS* mutations have been long thought to be undruggable, recently developed small molecules that covalently bind to the mutant cysteine in the *KRAS* switch II binding pocket of *KRAS* G12C have shown activity. *KRAS* G12C mutations are seen in 3% to 4% of CRCs and are associated with worse survival outcomes than other *KRAS* mutations in retrospective studies. The nonrandomized phase 1 to 2 KRYSTAL study assigned 44 heavily pretreated patients who had *KRAS* G12C–mutated CRC to receive adagrasib and 32 to receive combination therapy of adagrasib and panitumumab. Both the response rate (19% vs 46%) and median response duration seemed to be higher with the combination (4.3 vs 7.6 months). Updated data on 94 patients receiving adagrasib and cetuximab with a median follow-up of 11.9 months suggested an ORR of 34.0%, disease control rate of 85.1%, and median duration of response of 5.8 months (95% confidence interval [CI], 4.2-7.6). Median progression-free survival was 6.9 months (95% CI, 5.7-7.4), and median overall survival was 15.9 months (95% CI, 11.8-18.8). Treatment-related adverse events (TRAEs) occurred in all patients; grade 3-4 in 27.7% and no grade 5. No TRAEs led to adagrasib discontinuation. This combination was provided an accelerated approval by the FDA in June 2024.[460] Sotorasib, another *KRAS* G12C inhibitor, was evaluated as a single agent in 62 patients in the phase 2 CODEBREAK trial and in combination with cetuximab in 40 patients in the CODEBREAK101 trial. Although the single agent seemed to have modest activity with a response rate of 9.7%, the combination showed better results with a response rate of 30%. The combination of sotorasib and panitumumab was ultimately evaluated in a phase 3 randomized trial at one of two doses of sotorasib (960, 240 mg) or investigator's choice of lonsurf or regorafenib in patients with previously treated metastatic colorectal cancer with a *KRAS* G12C mutation.[461] After a median follow-up of 7.8 months (range, 0.1-13.9), the median progression-free survival was 5.6 months (95% confidence interval [CI], 4.2-6.3) and 3.9 months (95% CI, 3.6-5.7) in the 960-mg sotorasib–panitumumab and 240-mg sotorasib–panitumumab groups, respectively, compared with 2.0 months (95% CI, 1.9-3.9) in the standard-care group. The hazard ratio for disease progression or death in the 960-mg sotorasib–panitumumab group compared with the standard-care group was 0.48 (95% CI, 0.30-0.78; $P = .005$), and the hazard ratio in the 240-mg sotorasib–panitumumab group was 0.59 (95% CI, 0.37-0.95; $P = .036$). The objective response was 26.4% (95% CI, 15.3-40.3), 5.7% (95% CI, 1.2-15.7), and 0% (95% CI, 0.0-6.6) in the 960-mg sotorasib–panitumumab, 240-mg sotorasib–panitumumab, and standard-care groups, respectively. In the era of G12C-targeted therapy, it is of utmost importance to recognize the specific *RAS* mutation that may be present in each patient's tumor.

KEY POINTS

- Continuing anti-VEGF therapy beyond first-line progression with bevacizumab and second-line chemotherapy is supported by data.
- Patients who have *BRAF* V600E–mutated tumors should be considered for encorafenib/cetuximab/mFOLFOX6 for the front line or, in the second line and beyond, treatment with the doublet regimen of encorafenib and anti-EGFR antibody.
- For patients who have MSI-H/dMMR tumors, the use of single-agent pembrolizumab or the combination of nivolumab/ipilimumab is considered a preferred standard of care over multiagent chemotherapy as first-line therapy based on the KEYNOTE-177 trial and CheckMate 8HW, respectively.
- Patients who have *HER2*-amplified or HER2-overexpressed colorectal cancers should be considered for treatment with agents directed against HER2 after initial therapy with consideration of RAS status.
- Patients with colorectal cancer with *KRAS* G12C mutations should be considered for targeted therapy after initial chemotherapy with sotorasib or adagrasib alone or with anti-EGFR antibody therapy.

- Regorafenib, fruquintinib, or trifluridine/tipiracil with or without bevacizumab should be considered for patients who have disease refractory to all other approved agents. The decision of how to best sequence these agents is based on the adverse effect profile and individual preferences.

PRESENTING CASE STUDY

A 55-year-old man presents with a 10-pound unintentional weight loss over a few months and newly discovered iron-deficiency anemia. Subsequent evaluation with colonoscopy identifies a mass in the ascending colon; biopsy confirms invasive adenocarcinoma of the colon. Staging imaging reveals numerous metastatic lesions in both lobes of the liver and the right lung and periportal and retroperitoneal lymphadenopathy. Hepatic lesion biopsy confirms adenocarcinoma of likely colonic origin. Baseline carcinoembryonic antigen level is 278 ng/mL. The patient has well-controlled hyperlipidemia and is otherwise in good health. His Eastern Cooperative Oncology Group performance status is 1. Further testing of the biopsy samples shows that the tumor is RAS and BRAF wild type with proficient mismatch repair proteins. HER2 is not overexpressed. He visits the oncology clinic to discuss systemic treatment.

How would this patient's symptoms, primary tumor site, baseline comorbid conditions, and RAS/BRAF status inform your choice of initial front-line systemic therapy?

For patients with previously untreated metastatic colon cancer, the site of the primary tumor, presenting symptoms and baseline comorbid conditions, and the RAS/BRAF status influence the choice of biological agent added to chemotherapy in the front line.

Cumulative data from randomized trials indicate that right-sided tumors that are RAS and BRAF wild type derive relatively more benefit when standard-of-care chemotherapy (eg, FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (5-fluorouracil, leucovorin, and irinotecan), or FOLFIRINOX) is combined with bevacizumab. On the other hand, patients with left-sided tumors that are similarly RAS and BRAF wild type derive relatively more benefit when chemotherapy is combined with epidermal growth factor receptor inhibitors (eg, cetuximab and panitumumab). In general, bevacizumab may need to be approached with caution on initial cycle(s) if there is threatened obstruction, recent surgery or radiation, active GI bleeding, or other relative contraindications that may improve on subsequent treatment dates. Thus, chemotherapy plus bevacizumab would be the most appropriate initial treatment selection for this patient.

OLIGOMETASTATIC CRC

All patients who have potentially resectable metastatic disease, most frequently presenting with few lesions limited to liver and/or lung, should be evaluated by a multidisciplinary team at a center with high-volume expertise in treating oligometastatic disease. If there is any question about potential resectability, a referral is appropriate. When pooling data for all patients who have a hepatic resection, the average 5-year survival rate is approximately 30% with a less favorable prognosis for patients with multiple lesions, a short interval between the diagnosis of the primary tumor and recurrence, and the presence of stage 3 disease at the time of initial diagnosis.[462-464]

Preoperative chemotherapy can be used to downsize initially unresectable metastases to increase potential resectability. Patients who undergo successful neoadjuvant therapy with subsequent R0 resection of liver metastases may achieve a median OS approaching that of patients with initially resectable metastases.[462,465] Therefore, the initial therapeutic approach for a patient who has limited metastatic disease should always include consideration of a potentially curative option.

The benefit of chemotherapy in the setting of clearly resectable hepatic disease either in the adjuvant or the neoadjuvant setting is low with no clear survival advantage. In a European phase 3 trial of resectable liver-limited mCRC, 364 patients were randomly assigned to either proceed directly to surgery or receive FOLFOX chemotherapy for 3 months followed by resection and then followed by three additional months of FOLFOX.[466] Patients meeting the eligibility criteria of the trial who received perioperative chemotherapy had a significant improvement in 3-year PFS compared with patients in the surgery alone arm (36.2% vs 28.1%; HR, 0.77; $P = .041$). After a median follow-up of 8.5 years, no difference in OS was seen in this study.[467] It is important to note that 5-year survival in this group of patients with resectable metastatic disease was approximately 50%, which is significantly better than historically expected for all-comers with stage IV colorectal cancer. The small phase II/phase III JCOG 0603 study examined the role of observation alone versus adjuvant FOLFOX for 6 months after resection of colorectal liver metastases in approximately 300 total patients (280 deemed eligible after randomizing). The study similarly found that, while DFS improved (HR, 0.67; 95% CI, 0.5-0.9), OS did not (HR, 1.25; 95% CI, 0.78-2.00) in the adjuvant chemotherapy cohort after nearly 5 year

median follow-up. Notably, patients in the adjuvant FOLFOX cohort did not start treatment until 56 to 84 days after hepatectomy, which is generally considered a window of significantly less adjuvant benefit in earlier cancer stages,[468,469] and of 146 FOLFOX patients deemed eligible, only 91 patients completed chemotherapy.[470]

The role of biological agents (eg, EGFR and VEGF inhibitors) in the context of preoperative or perioperative therapy for potentially resectable liver metastases is unclear. Initial data suggest some benefit with the addition of cetuximab to chemotherapy (FOLFOX or FOLFIRI) in this setting,[471] but later results from the randomized new EPOC trial conducted in the United Kingdom suggested an unexplained detrimental effect on OS when cetuximab was added to perioperative FOLFOX or FOLFIRI, though initially the study did not exclude *RAS*-mutated cancers, but was amended to include only KRAS wild type tumors beginning 1 year into the 5 years of enrollment to this study, by which point 12 *RAS/RAF*-mutated cancers had been enrolled in each arm.[472] No randomized trial, to our knowledge, has tested the role of chemotherapy with or without bevacizumab in the context of liver resection. If bevacizumab is used in the preoperative setting, it must be discontinued approximately 6 to 8 weeks before planned abdominal surgery to reduce the risk of wound-healing complications.[473]

Colorectal oligometastasis to only the lung has been associated with better progression free and overall survival compared to colorectal cancer liver metastasis (CRCLM). It is important to note that there are substantial data to support disease resection outside of the liver with the lung being the next most common site for secondary resection.[474]

The randomized TransMet trial recently assessed the role of liver transplantation plus chemotherapy compared to palliative chemotherapy alone in select patients with unresectable liver-only metastases. Patients aged 18 to 65 years, with unresectable colorectal liver metastases from resected *BRAF*-nonmutated colorectal cancer responsive to systemic chemotherapy (≥3 months, ≤3 lines), and no extrahepatic disease were eligible for enrollment. Patients were randomized to liver transplantation plus chemotherapy or chemotherapy alone. In the intention-to-treat population, 5-year OS was 56.6% (95% CI, 43.2-74.1) for liver transplantation plus chemotherapy and 12.6% (5.2-30.1) for chemotherapy alone (HR, 0.37 [95% CI, 0.21-0.65]; *P* = .0003) and 73.3% (95% CI, 59.6-90.0) and 9.3% (3.2-26.8), respectively, for the per-protocol population. Serious adverse events occurred in 32 (80%) of 40 patients who underwent liver transplantation (from either group), and 69 serious adverse events were observed in 45 (83%) of 54 patients treated with chemotherapy alone.[474]

Liver-Directed Therapies

Hepatic arterial infusion pumps have been evaluated in multiple prospective trials. Although excellent response rates and control of hepatic metastases have been achieved, a meta-analysis of 10 randomized trials enrolling >1000 patients found no differences in OS.[475] Similarly, radioembolization using ^{90}Y and systemic chemotherapy was evaluated in three parallel multinational trials for patients with CRCLM, and despite improved response rates and liver-specific PFS, no improvement in OS, PFS, or hepatic resection rates was seen.[476] The recent phase III COLLISION[477] trial compared overall survival between patients receiving surgical metastasectomy versus thermal ablation for liver metastases ≤3 cm. While median OS has not yet been reached for either group, the study found survival outcomes for ablation were noninferior to surgery. Combinations of surgical resection and radiofrequency ablation are used at some specialty centers as is external-beam stereotactic radiation therapy (RT). Histotripsy, a device used to sonicate liver lesions, was cleared by the FDA in 2023 for use with liver metastases from any primary site on the basis of reasonably safe application in small early HOPE4LIVER trials[478] (n = 44); however, there are no trials specific to CRCLM, no long-term survival outcomes, nor comparative trials against other liver-directed modalities to determine if this should be utilized over other established options. This again emphasizes the importance of evaluation at centers with high-volume expertise in treating such patients.

Peritoneal-Only Metastases

An older randomized Dutch trial that compared cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) with systemic 5-FU chemotherapy for patients with CRC with peritoneal-only disease reported improved survival for the cytoreductive surgery and HIPEC group.[479] The relevance of the trial was questioned because of the use of the older, less aggressive systemic chemotherapy (ie, 5-FU alone) and because the relative value of HIPEC added to cytoreductive surgery could not be determined. The results from the PRODIGE-7-ACCORD-15 trial comparing the outcomes between patients with peritoneal-only colorectal metastases who were randomly assigned to either CRS with 6 months of systemic chemotherapy, or the same with HIPEC using oxaliplatin, showed no difference in OS between the two groups with a median OS of >41 months in both groups and a 5-year survival rate of 40%.[480] Overall, this did represent better than expected mOS for patients in both cohorts compared to mOS in all-comers with stage IV CRC, suggesting CRS itself may improve mOS. Subgroup analyses found a trend toward HIPEC survival benefit in those with intermediate-volume peritoneal disease. CAIRO6 is a phase 3 trial, presented at ASCO Annual Meeting 2025, that randomized 358 patients with treatment-naive CRC with peritoneal-only metastases, to receive CRS-HIPEC alone versus perioperative doublet-chemotherapy (CAPOX, FOLFOX, or FOLFIRI) with CRS-HIPEC, to determine if perioperative chemotherapy improved OS from CRS-HIPEC at 3 years.[481] While there was numeric improvement of mOS and OS-3 year in the perioperative group compared to the CRS-HIPEC only cohort, this was not statistically significant. At this time, HIPEC, at least that with oxaliplatin, which does not traditionally exhibit systemic single-agent activity in CRC, cannot be universally recommended

for patients who have CRC with peritoneal-only metastases. CRS is an option, but patients should be seen at centers with specialization in assessing patients for this type of procedure.

KEY POINTS

- All patients who have isolated metastatic disease should be considered for surgical resection or other locoregional therapies, and discussion should take place in a multidisciplinary setting conducted at a center with high-volume expertise in treating these cancers.
- Patients who have initially unresectable disease can be considered for conversion therapy with multiagent neoadjuvant chemotherapy.
- The benefit of neoadjuvant, perioperative, or adjuvant chemotherapy for patients who have clearly resectable metastatic disease, although often used, has not been substantiated by randomized clinical trials to improve OS.
- Liver-directed therapies with either intrahepatic chemotherapy or radioembolization have not shown a survival advantage in multi-institution trials and should not be considered standard of care outside of careful patient selection in experienced centers.
- Liver transplantation is an option for highly select patients with permanently unresectable liver-only metastases and where the primary tumor was previously resected.
- Patients who have peritoneal-only CRC should be evaluated at specialized centers for cytoreductive surgery, but HIPEC remains controversial.

NONMETASTATIC RECTAL CANCER

Cancers arising in the rectum are associated with a higher overall risk of recurrence than those associated with similar stages of colon cancer. The reason for local recurrence in rectal cancer is believed to be the anatomic location of the rectum and the challenge this presents to the surgeon to achieve clear circumferential resection margins. Traditionally, clinical stage II and III rectal cancers, unlike colon cancer, are treated with trimodality therapy of chemotherapy, radiation therapy, and surgery, though a number of recent trials have been shifting the treatment paradigm.

STAGING

Staging of rectal cancer consists of either rectal MRI or transrectal ultrasound (TRUS) to determine clinical tumor (T) and N (lymph node) staging. Both are considered appropriate, but more recent data suggest more information can be gleaned from rectal MRI, including more precise T staging and better evaluation of the likely circumferential resection margin.[482] Both approaches are contingent on the technical competence of the endoscopist or the reading radiologist and on the availability of modern MRI equipment. Cross-sectional imaging, preferably with CT of the chest and abdomen (contrast-enhanced), should be performed to rule out metastatic disease. There is no role for routine PET scan in the staging of rectal cancer. DNA mismatch repair (MMR) IHC or microsatellite instability (MSI) PCR/NGS testing needs to be conducted on the initial biopsy tissue confirming malignancy, as subsequent treatment may vary significantly depending on whether the cancer is pMMR/microsatellite stable (MSS) or deficient (dMMR)/microsatellite instability-high (MSI-H).

TREATMENT

There is increasing evidence to suggest that local excision (ie, transanal endoscopic microdissection [TEM]) should be restricted to patients who have stage T1 rectal cancer without high-risk factors.[483] For all other stages, total mesorectal excision (TME) has emerged as the preferred surgical technique. This technique honors natural tissue planes alongside the mesorectal fascia (MRF) and decreases the chances of local seeding and subsequent recurrence.[484] TME is most frequently performed as a sphincter-preserving low anterior resection (LAR) in mid-to-proximal rectal tumors, or as permanent sphincter excision with an anterior peritoneal resection (APR) in distal rectal cancers that arise too closely to the anorectal junction. In combination with preoperative (neoadjuvant) or postoperative (adjuvant) chemoradiation therapy (CRT), 5-year local recurrence rates of less than 5% to 10% can be achieved.[485-488]

Due to significant morbidity and higher disease-specific mortality associated with local relapse, neoadjuvant and adjuvant pelvic radiation strategies were designed to reduce local recurrence in locally advanced (stage II and stage III). Two different approaches have been used in this regard: short-course, high-dose radiation therapy commonly delivered as 5 Gy daily for 5 days (5 × 5) or long-course combined-modality CRT with radiosensitizing systemic chemotherapy (ie, capecitabine, 5-FU) administered concurrently with radiation therapy to a total dose of 50.4 Gy (45 + 5.4 Gy local boost) over 5 to 5.5 weeks (25-28 fractions), followed by an 8- to 10-week treatment break before curative surgery.[486,488,489]

Of note, only the longer CRT approach has repeatedly been demonstrated to downstage tumors, which might allow sphincter preservation. Both treatment approaches, however, have been associated with a decrease in locoregional failure. Prevention of

local recurrence has not uniformly been associated with improved OS. However, one Swedish trial, in which 1,168 patients were randomly assigned to either short-course RT (5 Gy × 5 days to 25 Gy) in the week before surgery versus surgery alone, demonstrated both a reduction in local recurrences (11% vs 27%; $P < .001$) and a survival advantage at 5 years (58% vs 48%; $P = .004$) for those receiving neoadjuvant RT.[488] A subsequent Dutch trial, using the same short-course RT regimen in combination with quality-controlled TME surgery, confirmed a low rate of local recurrence (at 2 years, 2.4% vs 8.4%; $P < .001$) but did not demonstrate a survival benefit.[486] Of note, however, the local recurrence rate of tumors >10 cm above the anal verge was not significantly improved, suggesting more proximal/upper rectal tumors may not all benefit from radiation.

Although the short-course neoadjuvant RT strategy is most commonly used in Scandinavia and other European countries, most US oncologists have historically preferred neoadjuvant or adjuvant combined long-course CRT. Findings from two studies of adjuvant CRT demonstrated that combination 5-FU-based chemotherapy and RT were more effective than RT or surgery alone in preventing both local and distant recurrences.[490,491] Results from NSABP R-01 showed that 5-FU in a continuous IV infusion (CIVI) was superior to 5-FU bolus administration during adjuvant radiation therapy, providing a 3-year DFS advantage.[492] This finding confirms that protracted delivery of chemotherapy-sensitizing agents concomitant with long-course RT regimens is the best option for CRT. Two randomized phase 3 studies confirmed the noninferiority of oral capecitabine (825 mg/m^2 twice daily on days of RT) as a radiosensitizer compared with 5-FU CIVI during neoadjuvant therapy in rectal cancer.[493,494] Clinically, either 5-FU CIVI or capecitabine is an acceptable choice to administer with RT, and the choice depends on patient preferences for convenience and the clinical team's determination of potential adverse effects and whether the patient is likely to adhere to an oral regimen.

The long-standing question about whether neoadjuvant or adjuvant CRT results in improved outcomes was definitively answered by the results of a large German randomized trial that compared standard long-course CRT with 5-FU CIVI either before or after quality-controlled TME.[488] Patients undergoing neoadjuvant CRT had a lower rate of local recurrence (6% vs 13% at 5 years), a lower rate of acute and chronic toxicities, and a significantly higher rate of sphincter preserving TME compared with those receiving adjuvant CRT ($P = .006$), but there was no survival advantage to the neoadjuvant approach. This trial established neoadjuvant CRT with 5-FU CIVI as a new standard of care for stage II and III rectal cancers. It is important to note that, for those patients who undergo up-front surgery (because of clinical stage I disease) and are found to have pathological stage II or III disease, postoperative chemotherapy and CRT should be considered.

Subsequent studies have tried to further improve the local control rate by incorporating additional radiosensitizing agents, such as oxaliplatin, and biological agents into the preoperative treatment phase.[495-498] Data call into question the potential role of oxaliplatin as a radiosensitizer when added to fluoropyrimidines in neoadjuvant CRT for rectal cancer.[499-501] Consistent results from Italian, French, and US phase 3 trials have shown the addition of oxaliplatin to fluoropyrimidine (5-FU or capecitabine) as a component of neoadjuvant CRT does not increase the rate of pCR with the use of oxaliplatin, but it significantly increases toxic effects, mainly diarrhea. Only a German trial, which used a slightly different schedule of oxaliplatin administration, showed superiority in the oxaliplatin arm in terms of pathological response.[497] However, the overwhelming body of evidence at this time suggests oxaliplatin should not be used as part of neoadjuvant CRT for rectal cancer outside of a clinical trial.

Two smaller phase 3 trials (Polish I, TTOG 01.04) compared neoadjuvant CRT, following the German rectal protocol, with short-course radiation therapy (5 × 5 Gy) as neoadjuvant treatment of localized rectal cancer. The two trials demonstrated that both treatment approaches are valid options in the preoperative setting of rectal cancer with similar rates of local recurrence and OS.[502,503] The more complex Chinese STELLAR trial enrolled 599 patients with mid/distal clinical stage II or III rectal cancer to receive either neoadjuvant treatment with short-course RT and consolidation CAPOX x4 cycles or long-course CRT with capecitabine.[504] In both groups, this followed by surgery (though this was not pursued in 63 patients in each cohort) and adjuvant CAPOX for either two cycles in the short-course group (erroneously labeled "TNT" in the study paper, as patients were intended to receive adjuvant therapy), or six cycles in the long-course CRT group. Despite this more heterogeneous treatment course in both cohorts and more prevalent severe acute toxicity during neoadjuvant therapy (26.5% vs 12.6%, $P < .01$), DFS at 3 years was noninferior (64.5% vs 62.2%, $P < .01$ for noninferiority) and OS at 3 years was improved (86.5% vs 75.1%, $P = .33$) in the short-course group.

Role of Adjuvant Chemotherapy

The role of adjuvant chemotherapy, particularly after neoadjuvant radiation therapy, has been disputed by the results of individual trials and by a meta-analysis of four studies.[505] The meta-analysis included subgroups of patients from trials, two of which were completed a decade ago. The trials used 5-FU-based adjuvant chemotherapies administered according to outdated regimens no longer considered standard of care, such as the Mayo Clinic regimen (5-FU/LV) and its variations. Neoadjuvant therapy was heterogeneous and included CRT and radiation therapy alone. The authors found no difference in distant relapse or OS associated with the use of adjuvant therapy. A consistent problem in many of these studies and in clinical practice is that it is difficult for patients to complete chemotherapy after surgery; completion rates of ≤50% are often seen. The more recent Korean ADORE trial randomly assigned patients who had received neoadjuvant CRT and had pathological stage II or III cancer to either adjuvant bolus 5-FU/LV or FOLFOX for 4 months (16 weeks). The 6-year DFS rate was 68.2% in the FOLFOX arm versus 56.8% in

the bolus 5-FU arm (HR, 0.63; 95% CI, 0.43-0.93; $P = .018$).[506] Although some experts advocate that those who achieve a pathological complete response (pCR) following neoadjuvant CRT do not need adjuvant chemotherapy, this is not standard of care, and NCCN guidelines currently recommend all such patients receive adjuvant chemotherapy, though this clinical scenario is becoming uncommon in the era of TNT.

Total Neoadjuvant Therapy (TNT) Approach

Currently, the most widely used treatment for locally advanced rectal cancer is TNT, in which all intended systemic chemotherapy and CRT (or short-course RT) are completed before surgery. The theoretical advantage to this approach is that micrometastatic disease is treated earlier, tumor downstaging is enhanced, and delivery of the full chemotherapy regimen (ie, FOLFOX for 4 months) may be increased in the absence of patients having complications from surgery or reduced drug tolerance after surgery, leading to greater dose intensity of treatment.

In one phase II trial, 108 patients were randomly assigned to CRT with CAPOX followed by TME followed by four cycles of adjuvant CAPOX or assigned to a TNT approach of four cycles of neoadjuvant CAPOX followed by CRT with CAPOX followed by surgery. pCR rates did not differ between the groups, but grade 3 toxicity was much lower in the TNT arm (19% vs 54%), and compliance with all four cycles of chemotherapy was higher with TNT (94% vs 57%).[507]

The multicenter "Timing" trial included 259 patients who were administered neoadjuvant CRT with 5-FU CIVI followed by sequential assignment to cohorts receiving either zero, two, four, or six cycles of FOLFOX before TME. Patients who received six cycles of neoadjuvant FOLFOX (ie, TNT) experienced 38% pCR, significantly greater than the 18% pCR experienced by the group receiving standard CRT alone ($P = .0036$).[470] Chemotherapy was also completed by 98% of the patients in the six-cycle group.

Two phase II trials have examined the sequencing order of neoadjuvant modalities, with chemotherapy being given either before (induction) or after (consolidation) CRT. CAO/ARO/AIO-12, a randomized phase II trial, compared patients receiving CRT with either induction or consolidation neoadjuvant FOLFOX chemotherapy, who then went on to TME. The study found increased pCR rates in the consolidation chemotherapy arm (25% vs 17% in the induction group).[508] The OPRA trial also examined the question of optimal sequence of chemotherapy in the TNT approach in a randomized fashion, but additionally allowed "nonoperative management" with close "watch & wait" for patients who achieved a clinical complete response (cCR) to TNT.[509] This trial demonstrated that the 3-year TME-free survival rate was 41% (95% CI, 33-50) in the induction group and 53% (95% CI, 45-62) in the consolidation group. The three-year DFS rates did not seem to be compromised by this nonoperative approach compared to historical controls, though DFS was the same whether patients received either induction or consolidation chemotherapy.

On the question of long-course CRT versus short-course RT having the best outcomes with TNT, several randomized phase III trials have been performed. The Polish II trial randomized 541 patients to receive either neoadjuvant short-course RT with FOLFOX4 x3 cycles or long-course CRT (bolus 5-FU/LV on weeks 1 and 5 with or without weekly oxaliplatin x5 weeks) followed by surgical resection, though the trial was subsequently amended during enrollment to allow omission of oxaliplatin in both groups.[510,511] While this makes the study more difficult to contextualize, those on the short-course TNT regimen had significantly less acute toxicity and improved OS rate at 3 years (73% vs 65%, $P = 0.046$), though no improvement in R0 resection rates (77% vs 71%, $P = 0.07$), pCR rates (16% vs 12%, $P = 0.17$), local failure (22% vs 21%, $P = 0.82$), or DFS rates at 3 years (53% vs 52%, $P = 0.85$). The European RAPIDO trial (n = 920) compared short-course RT followed by consolidation CAPOX or FOLFOX for 4.5 months followed by TME versus CRT, TME, and optional adjuvant FOLFOX or CAPOX chemotherapy strictly in rectal cancers with one or more high-risk features for metastasis (ie, cT4, cN2, MRF+, EMVI+, pelvic sidewall LN+).[512] The results demonstrated a significantly higher pCR rate with the TNT approach (28% vs 14%; $P < .001$) and a lower rate of distant metastases at 3 years (20% vs 27%; $P = .005$). No difference in OS was seen. However, after longer follow-up, the short-course radiation therapy arm had higher rates of locoregional failure particularly at the anastomosis and presacral space (10% vs 6%; $P = .027$) that has dampened uptake of short-course RT in the United States, especially in the high-risk tumors that were included on RAPIDO, but has not reduced enthusiasm for TNT.[513]

Optimal drug combinations for neoadjuvant chemotherapy are also being investigated. The phase III PRODIGE 23 trial examined CRT followed by 3 months of neoadjuvant mFOLFIRINOX and TME followed by 3 months of adjuvant FOLFOX or CAPOX versus the standard-of-care approach of CRT followed by TME and adjuvant chemotherapy for 6 months. The experimental arm showed improvement in pCR rate (27.5% vs 11.7%), 3-year DFS (HR, 0.69; 95% CI, 0.49-0.97; $P = .034$), and metastasis-free survival (HR, 0.64; 95% CI, 0.44-0.93; $P < .02$). OS data are not yet mature.[514] Triplet versus doublet TNT chemotherapy superiority is currently being evaluated in the JANUS trial, though results will not be mature for several years.

Removing a Modality of Therapy in Locally Advanced Rectal Cancer

Retrospective and prospective data have prompted the question of whether all patients who have locally advanced rectal cancer (LARC) need surgery and whether all need radiation therapy. In terms of nonoperative management (NOM), data from Brazil suggest high rates of rectal preservation and excellent DFS and OS in patients who have a cCR to neoadjuvant therapy compared with a population of patients who have pCR who underwent surgery.[515] These findings were confirmed in a meta-analysis of 23 studies[516] including 867 patients and in the large multicenter International Watch & Wait (IWW) registry, which suggested

local regrowth rates of 15% to 25% in the NOM group, most of which could be successfully treated with salvage resection.[517] A subsequent analysis of this registry showed that the probability of two additional years of local recurrence-free survival after remaining disease free for 1, 3, and 5 years was 88.1%, 97.3%, and 98.6%. For distant (metastatic) recurrence-free survival, these proportions were 93.8%, 97.8%, and 96.6%, respectively. Together, these data suggest that recurrence risk is highest in the first two years, supporting enhanced posttreatment surveillance during this period though studies have not been performed to inform the optimal schedule and currently mostly follow the protocol used in the OPRA trial (Table 13.2-2).

Table 13.2-2 Surveillance Survivorship for Colorectal Cancer

	Recommendations	
	Resected (Standard)	**Unresected (NOM)[#]**
Testing schedule	H&P with laboratory tests including CEA every 3 months for 2 years, then every 6 months for years 3-5 from surgical resection	H&P and labs with CEA every 4 months for 2 years, then every 6 months years 3-5 from end of treatment and cCR determination
	CT CAP every 12 months for 5 years	Rectal MRI every 6 months and CT CAP every 12 months for 2 years, then CT CAP and rectal MRI once every 12 months for years 3-5
	Colonoscopy 1 year after initial diagnosis, then at 3 years if findings are normal, and then every 5 years for life if findings remain normal	Flexible sigmoidoscopy and digital rectal examination every 4 months for 2 years and every 6 months years 3-5 (consider switching one endoscopic evaluation for colonoscopy annually years 0-2, then as indicated per standard schedule)
	In families without an identified familiar risk syndrome, all first-degree relatives should undergo screening colonoscopy starting 10 years younger than when the patient was diagnosed but no later than age 40 years and should undergo screening colonoscopy every 5 years	
	Chemo prophylaxis	ALASCCA and consideration daily ASA for 3 years for PI3K altered rectal cancer
Lifestyle changes	• Increased exercise after diagnosis and avoidance of a Western-style diet; diets with a low glycemic load are associated with a reduced risk of cancer recurrence and improved OS[287,518,519] • Patients with class II or III obesity (BMI >35 kg/m^2) have a modestly increased risk of recurrence[332] • Lower serum vitamin D levels have been associated with an increased risk of recurrence, but prospective studies are lacking to show that increasing vitamin D to normal levels can improve outcomes in the adjuvant setting[363]	

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CT CAP, computed tomography of chest, abdomen, pelvis; H&P, history and physical examination; OS, overall survival.
[#]Surveillance regimen per OPRA trial[509] as published in Scott et al.[520]
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Another approach being tested is whether radiation therapy can be eliminated in a subset of patients with LARC. The phase 3 PROSPECT trial assessed a primary endpoint of DFS and randomized >1,100 patients with cT2N$^+$ or cT3N$^{+/-}$ (provided ≤4 mesorectal lymph nodes were >1 cm in short-axis diameter) rectal cancer eligible for sphincter-sparing surgery (ie, LAR) to receive either neoadjuvant CRT followed by surgery and adjuvant FOLFOX or CAPOX (given to 77.9% for up to 4 months) or to receive neoadjuvant FOLFOX for 3 months with selective CRT only if the primary tumor decreased <20%, followed by TME and optional adjuvant FOLFOX for 3 months, of which 79.5% of patients opted in. In the neoadjuvant FOLFOX arm, only 10.5% received CRT (9% preoperatively; 1.5% postoperatively). Five-year DFS was noninferior with FOLFOX despite the omission of CRT for the majority of patients (HR, 0.92; 90% CI, 0.74-1.14), and OS and local recurrence were similar in both groups.[521] The NCCN guidelines recommend this approach as an alternative to CRT for patients without cT4 disease and who are eligible for sphincter-sparing surgery. Also, the phase 3 FOWARC trial conducted in China compared FOLFOX alone with FOLFOX and radiation therapy or 5-FU and radiation therapy followed by surgery and demonstrated similar rates of local recurrence, 3-year DFS, and OS.[522]

Role of Immunotherapy in dMMR/MSI-H Rectal Tumors

Approximately 1% to 5% of rectal adenocarcinomas are MSI-H/dMMR, and retrospective studies have suggested that they respond poorly to chemotherapy regimens. Several studies show the activity of immunotherapy for patients who have localized tumors. A single-institution phase 2 study of dostarlimab, a PD-1 inhibitor, in 47 patients with locally advanced dMMR tumors, 100% of patients who completed all 6 months of immunotherapy had a clinical complete response (cCR) with a median follow-up of >12 months.[523,524] Based on these and other data showing the efficacy of immunotherapy in dMMR tumors, the preferred neoadjuvant therapy for locally advanced dMMR rectal cancer is currently checkpoint inhibitor monotherapy for up to 6 months with those achieving a cCR being appropriate for surveillance without further chemotherapy, radiation, or surgery.[523] Ongoing studies are exploring the utility of doublet immunotherapy in MSI-H LARC, as well as attempting to reproduce the single-institution dostarlimab trial in a global population (AZUR-1).

Role of Biologics

Several studies have sought to enhance the efficacy of preoperative radiation therapy by adding biological agents to a fluoropyrimidine backbone. Results with bevacizumab suggest improved response rates in some studies but at the cost of perineal wound and anastomotic healing complications.[525,526] Results with anti-EGFR therapy (cetuximab and panitumumab) have been disappointing with respect to pCR rates and toxicity.[527,528] As a result, adding a biological to fluoropyrimidine chemotherapy during radiation therapy is not recommended.

KEY POINTS

- Rectal cancer should be staged preferably with rectal MRI or in certain cases with endorectal ultrasound (ERUS) on the basis of local availability and technical competence of the endoscopist or reading radiologist.
- Imaging of chest and upper abdomen should also be performed to rule out metastatic disease. There is no role for routine PET scan in the staging of rectal cancer.
- Neoadjuvant CRT using either infusional 5-FU or capecitabine followed by TME and adjuvant FOLFOX or CAPOX is the historical standard treatment approach for stage II and III rectal cancers.
- Current treatment of LARC (clinical stage II or III rectal cancer) is centered on TNT strategies, in which chemotherapy and radiation therapy (in either order) are used neoadjuvantly before TME. Although short-course RT is a reasonable alternative to long-course CRT, it may be associated with higher risk of local recurrence in patients with high-risk disease.
- A subset of patients who have non-cT4 disease who are eligible for sphincter-sparing surgery may be treated with neoadjuvant FOLFOX with selective use of CRT in those who have ≤ 20% tumor regression. Adjuvant chemotherapy was offered in the trial.
- Selected patients who have a complete clinical response after TNT or immunotherapy may be considered for nonoperative management with watch & wait surveillance in lieu of surgery.
- Patients with dMMR/MSI-H locally advanced rectal cancer may be considered for TNT with PD-1 immune checkpoint inhibitor treatment for 6 months and avoid surgery, radiation, and chemotherapy if cCR is achieved.
- Oxaliplatin, bevacizumab, cetuximab, or panitumumab should not be added to the CRT backbone for patients with rectal cancer.

ANAL SCC

EPIDEMIOLOGY AND ETIOLOGY

Cancers of the anus are relatively uncommon in the United States. The male-to-female ratio is approximately 2:3.5. The clearest causal relationship for anal cancer is infection with HPV (mainly HPV-16); >90% of anal cancers are associated with HPV infection.[529] One large study found a strong positive correlation between the amount of sexual activity and the risk of anal cancer.[530] The association between HIV infection and anal cancer has been known for some time, but the exact etiologic relationship has not been elucidated. The incidence of anal cancer in patients infected with HIV is increased >40 times compared with the general population and, unlike other HIV-associated cancers, has not decreased since the introduction of highly active antiretroviral therapy (HAART).[531] Additional risk factors for anal cancer are smoking, immunosuppression, chronic inflammation or fistulas in the context of IBD, and extramammary Paget's disease in the perianal region (adenocarcinoma).

The efficacy of a quadrivalent HPV vaccine (HPV-6, -11, -16, and -18) against anal intraepithelial neoplasia was prospectively investigated in a double-blind randomized study of 602 healthy homosexual men aged 16 to 26 years.[532] The rate of grade 2 or 3 anal intraepithelial neoplasia related to infection with HPV-6, -11, -16, or -18 was reduced by 54.2% (95% CI, 18.0%-75.3%) in the intention-to-treat population and by 74.9% (95% CI, 8.8%-95.4%) in the per-protocol efficacy population. These intriguing findings, which could lead to a decrease in the incidence of anal cancer through HPV vaccination, prompted the Advisory Committee on Immunization Practices (ACIP) to recommend routine HPV vaccination for girls aged 11 to 12 and catch up

vaccination for women through age 26 years since 2007 and routine HPV vaccination in boys aged 11 to 12 years with catch up vaccination in men up to age 21 and high-risk populations through age 26 since October 2011.[533] Catch up vaccination was amended in 2019 to include all persons through 26 years, and suggested consideration with shared medical decision making in all adults aged 27 to 45 years.

Most anal cancers are squamous cell carcinomas (ASCC) or cloacogenic cancers, and the rare anal adenocarcinomas should be treated as rectal cancers. Inguinal lymph nodes (LNs) are locoregional in ASCC and may be involved in as many as 63% of cases. The most important prognostic factors are tumor (T) stage (T1, <2 cm; T2, 2-5 cm; T3, >5 cm; T4, invasion into adjacent organs) and lymph node (N) status. In a pooled analysis of four randomized trials with a total of 644 patients, tumor diameter >5 cm and LN involvement were associated with poorer 5-year DFS ($P < .0001$) and 5-year OS ($P = .0001$). In stratified analyses, LN involvement had more adverse influence on DFS and OS than did tumor diameter. Patients with tumors >5 cm and LN metastases had the worst DFS (only 30% at 3 years compared with 74% for the best group, which had <5 cm primary and N0 status) and OS (only 48% at 4 years compared with 81% for the best group, which had <5 cm primary and N0 status). Men had worse DFS ($P = .02$) and OS ($P = .016$).[534]

STAGING

In general, staging involves physical examination and biopsy to determine the size of the primary and the presence of inguinal lymphadenopathy. Cross-sectional (ie, CT) imaging of the chest and abdomen should be performed to rule out metastatic disease, especially in those with T3 to T4 or N+ disease, as well as CT or MRI of the pelvis in all patients to assess regional LNs. PET-CT scan should be strongly considered for anal cancer because a meta-analysis suggested PET imaging changed nodal staging in nearly 30% of the patients.[535] Because the presence of inguinal or pelvic LNs change the radiation therapy strategy, information provided by PET is important in treatment planning. Women with anal cancer should also be evaluated for cervical cancer, which is also mostly induced by HPV infection with oncogenic viral strains.

TREATMENT OF LOCALIZED DISEASE

In the distant past, treatment of patients who have anal cancers was surgical, entailing an abdominal perineal resection (APR). This treatment option was curative for only approximately 50% of patients and was associated with a high morbidity rate. Today, the standard approach to treatment of ASCC is definitive CRT. Local excision is reserved for patients with small node-negative tumors (T1N0) that are well differentiated. Even here, long-term efficacy data are lacking.

In initial CRT trials, combinations of 5-FU and mitomycin C with RT, still referred to today as the "Nigro protocol" after Dr. Norman Nigro who developed the definitive approach in the 1970s, yielded high response rates, including pCR.[531,536] Eventually, it was recognized that surgical resection was not necessary for many patients, and APR is used today only as salvage therapy for patients who have local recurrence after CRT. The expectation is that the cCR rate with combined-modality CRT therapy will be between 70% and 80% with a 5-year OS rate >65%, but this is highly dependent on stage at diagnosis. More recently, capecitabine with mitomycin has been explored and appears to be well tolerated across several prospective trials and one retrospective report with one small trial reporting a cCR of 100% and treatment failure rate of 90% at 3 years.[537-539] Overall, though, a substantial number of patients still experience either local recurrence or metastatic disease.

Strategies to improve survival outcomes on the existing 5-FU/mitomycin CRT standard beyond the likely equivalent shift from 5-FU CIVI to capecitabine, have not been successful. The phase III RTOG 98-11 trial (n = 682 patients) assessed an intensified regimen with induction 5-FU/cisplatin followed by CRT with 5-FU/cisplatin compared against the standard CRT with 5-FU/mitomycin C.[540] Both the 5-year locoregional recurrence rate (25% vs 33%) and the distant metastasis rate (15% vs 19%) trended in favor of the mitomycin-based (Nigro) treatment. The cumulative rate of colostomy was significantly better for mitomycin C–based than for cisplatin-based therapy (10% vs 19%; $P = .02$). An updated analysis with long-term follow-up identified the standard mitomycin C–based arm as significantly superior in OS.[541] Results of a more recent phase 3 ACT II 2 × 2 randomized trial comparing between 5-FU/mitomycin or 5-FU/cisplatin with RT with second randomization to receive either no further treatment or "maintenance" treatment with two subsequent weeks (weeks 11 and 14) of 5-FU/cisplatin chemotherapy found no substantial difference in outcome,[542] so the inferior results of the RTOG 98-11 intensified arm could be related to the delay in RT because of the initial induction chemotherapy component. The ACT II trial also did not show the benefit of post-RT maintenance 5-FU/cisplatin chemotherapy; therefore, neither induction nor consolidation chemotherapy has a role in locally advanced anal cancer. Currently, clinical research (ie, EA2165) is investigating the role of immune checkpoint inhibitors in locoregional ASCC after activity was recently shown in the metastatic setting, though data awaits maturation.

As described above, the well-established definitive combined-modality approach using 5-FU/mitomycin/RT remains the standard of care. Mitomycin C carries an FDA black-box warning for severe bone marrow suppression that is often delayed (nadir occurs often at 4 weeks) and can be prolonged. Patients' blood cell counts should be carefully monitored during and after the completion of therapy, including CD4 T cell levels in patients with HIV+ who despite HAART adherence may experience CD4 nadirs that require prophylaxis for opportunistic infections until recovery. Combination cisplatin and 5-FU can be used

for patients with contraindications to mitomycin C, usually those related to baseline bone marrow deficiency, though should be applied with caution due to enhanced toxicity seen in recent 5-FU/cisplatin trials.

Intensity-modulated radiation therapy (IMRT) for anal cancer is being evaluated in an effort to reduce short- and long-term toxicities from radiation therapy.[385] Intensity-modulated radiation therapy should only be used by radiation oncologists experienced in delivering this therapy for anal cancer to avoid undertreatment of the cancer (ClinicalTrials.gov identifier: NCT04166318). EA2182 (DECREASE), an ongoing randomized phase 2 clinical trial is comparing standard of care versus lower dosage CRT in early (cT1-2N0) anal cancer, has completed accrual though results are maturing.

The treatment of anal cancer for patients with HIV+ is somewhat more complex. Standard aggressive combined-modality therapies should be used for patients who have a CD4 count >200 × 10^9/mm^3 who have no signs or symptoms of other HIV-related diseases. For patients who have more severe HIV-related problems, reduced doses of radiation, chemotherapy, or both should be considered to maintain local disease control.[543]

FOLLOW-UP AFTER TREATMENT

Evaluation of ASCC response to treatment too early after the completion of CRT can result in premature declaration of treatment failure and unnecessary APRs. The most recent data from the aforementioned ACT II trial suggest tumor regression can be seen up to 26 weeks after therapy completion[544]; therefore, persistent disease before 26 weeks should not be deemed a treatment failure as long as the tumor does not appear to be progressing (Table 13.2-3).

Table 13.2-3 Anal Cancer Follow-Up

Years	Tests	Interval	Patients
0-5	Digital rectal examination	Every 3-6 months starting 12 weeks after completion of chemoradiation therapy	All
	Anoscopy		
	History and physical examination with inguinal LN palpation		
	CBC with differential at least until count recovery. Consider CD4 T cell levels in HIV+ patients until count recovery		
0-3	CT scan of chest, abdomen, and pelvis	Annually	cT3/T4 disease or cN+ disease or with positive disease on 12 week examination

Abbreviation: LN, lymph node.

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TREATMENT OF RECURRENT AND METASTATIC DISEASE

For those patients who have locally recurrent disease at the 26-week post-CRT evaluation or progressive nonmetastatic disease at any time after end of treatment, surgical resection is preferred with evidence of 5-year survival rates of nearly 50%.[545]

Patients with newly diagnosed metastatic disease are currently recommended to receive first-line carboplatin/paclitaxel based palliative chemotherapy (CT CAP every 3 months in patients with non progressing incomplete responders until cCR is achieved or progression is confirmed). Prior to the phase 2 InterAACT trial, 5-FU/cisplatin was the standard first-line recommendation, primarily on the basis of the regimen's activity in other squamous cell carcinomas. InterAACT randomized 91 patients with untreated advanced anal cancer to either 5-FU/cisplatin or carboplatin/paclitaxel with a pick-the-winner design and primary endpoint of ORR. Although ORR was not different between the regimens (57% vs 59%), combination 5-FU/cisplatin was associated with significantly more serious adverse effects (62% vs 36%; $P = .016$). Furthermore, carboplatin/paclitaxel achieved higher median PFS (8.1 vs 5.7 months) and OS (20 vs 12.3 months; HR, 2; $P = .014$). These results provide strong evidence for the use of carboplatin and paclitaxel as first-line treatment of patients with metastatic anal cancer.[546]

Recently published and ongoing studies also suggest a role for immunotherapy in metastatic ASCC. In NCI9673, originally a single-arm second- or later-line trial of 37 patients treated with nivolumab, results showed ORR 24%, including two patients achieving CR, disease control rate (DCR) 70%, median PFS 4.1 months, and median OS 11.5 months.[534] This led to a part B expansion of the original NCI9673 study to the randomized phase II cohorts of nivolumab +/− ipilimumab in 100 patients with refectory metastatic ASCC that showed ipilimumab/nivolumab did not significantly improve outcomes compared to nivolumab alone (mPFS 3.7 vs 2.9 months ($P = .16$), ORR 21.5% vs 17.4% ($P = .89$), DCR 47.7% vs 43.5%, mOS 20.0 vs 15.4 months ($P = .59$)).[547] Currently, dual immunotherapy targets are not recommended for refractory metastatic ASCC.

The activity of checkpoint inhibitors in later-line palliative treatment led to first-line chemo/immunotherapy investigations. POD1UM-303/InterAACT 2 was a phase 3, double-blind, controlled trial that randomized 303 patients with treatment-naive locally recurrent or metastatic ASCC to receive either first-line carboplatin/paclitaxel/placebo or carboplatin/paclitaxel/retifanlimab, a PD-1 inhibitor, with possibility of crossover. The trial met its primary endpoint with the median PFS improving from 7.4 months in the placebo arm to 9.3 months in patients receiving retifanlimab (HR 0.63 [95% CI, 0.47, 0.84]; $P = .0006$). Follow-up remains immature, though currently suggests retifanlimab with chemotherapy despite crossover is trending toward improved mOS (29.2 vs 23.0 months, HR 0.70 [95% CI 0.49, 1.01]. As a result of this data, in May 2025, the FDA approved carboplatin/paclitaxel/retifanlimab for first-line treatment of advanced ASCC, and is the current standard of care for patients eligible to receive immunotherapy. Results from EA2176, the randomized phase 3 trial (ClinicalTrials.gov identifier: NCT04444921) evaluating carboplatin/paclitaxel with or without nivolumab for patients with newly diagnosed metastatic anal cancer, are awaited.

KEY POINTS

- HPV vaccination reduces the incidence of anal intraepithelial neoplasia and will, it is hoped, reduce the incidence of anal cancer as well.
- Combination 5-FU/mitomycin with RT remains the standard approach for localized anal squamous cell cancers, but 5-FU/cisplatin or capecitabine/mitomycin C can be considered for those at risk for bone marrow or other toxicity.
- Responses to definitive CRT can be seen up to and occasionally beyond 26 weeks after treatment completion, so early declaration of failure should be avoided.
- Salvage surgery (APR) is the treatment of choice for those with locally recurrent or progressive disease at or beyond the 26-week evaluation.
- There is no role for induction or consolidation chemotherapy in locally advanced disease.
- Standard chemotherapy for first-line treatment of metastatic anal cancer is carboplatin and paclitaxel per the InterAAct study.
- Retifanlimab added to carboplatin and paclitaxel represents a new standard of care option in the first-line treatment of locally recurrent/metastatic ASCC.
- In the refractory metastatic setting, treatment with nivolumab or pembrolizumab can be considered. CTLA-4 inhibitors have not shown significant additive benefit.

APPENDICEAL MUCINOUS NEOPLASMS, ADENOCARCINOMAS, AND GOBLET CELL ADENOCARCINOMAS

Appendiceal mucinous neoplasms and cancers and goblet cell adenocarcinoma (GCA, formerly goblet cell ex carcinoid) have their own terminology and a recently updated WHO diagnostic grading system (Table 13.2-4).[548,549] AJCC recently updated their staging guidelines to version 9 for appendiceal malignancies, with a significantly enhanced importance given to tumor grade.[550] These malignancies most frequently metastasize along peritoneal surfaces with cellular lesions (ie, peritoneal carcinomatosis) more frequently seen in higher grade appendiceal cancers, or with acellular mucinous deposits (ie, pseudomyxoma peritonei (PMP)) that is frequently seen in low-grade mucinous histologies. Patients who have appendiceal neoplasms, adenocarcinomas, or goblet cell adenocarcinomas, should have tumor pathology reviewed by expert pathologists and should be seen by multidisciplinary teams specializing in these cancers.

Table 13.2-4 **Appendicular Mucinous Cancers and Goblet Cell Carcinoids**

Diagnostic Terminology	Histological Criteria
Serrated polyp with or without dysplasia	Serrated crypt profiles confined to the mucosa with intact muscular is mucosae; when present, dysplasia can be classified as low or high grade
Low-grade appendiceal mucinous neoplasm (LAMN)	Mucinous neoplasm with low-grade cytology and any of the following:
	Loss of lamina propriety and muscular is mucosae
	Fibrosis of submucosa
	Pushing diverticulum-like growth into the wall
	Dissection of acellular mucin in the wall
	Mucin and/or neoplastic cells outside of appendix
High-grade appendiceal mucinous neoplasm (HAMN)	Mucinous neoplasm with high-grade cytology present (at least focally) and lacking infiltrative invasion

Diagnostic Terminology	Histological Criteria
Mucinous adenocarcinoma	Mucinous neoplasm with infiltrative invasion; patterns of infiltrative invasion include:
	Infiltrative glands, incomplete glands, or single infiltrative tumor cells associated with extracellular mucin and desmoplastic stroma
	Small cellular mucin pool pattern characterized by small dissecting pools of mucin containing floating nests, glands, or single neoplastic cells
	Grade assessment is based on AJCC criteria
Mucinous adenocarcinoma with signet-ring cells	Mucinous neoplasm with signet-ring cell component accounting for ≤50% of tumor cells
	Mucinous neoplasm with signet-ring cell component accounting for >50% of tumor cells

Abbreviations: AJCC, American Joint Committee on Cancer; HAMN, high-grade appendicular mucinous neoplasm; LAMN, low-grade appendicular mucinous neoplasm.
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Recent molecular characterization suggests unique patterns of genomic alterations are seen across the low- to high-grade histological spectrum of appendiceal malignancies.[551] This includes *GNAS* and *KRAS* being mutated in the majority of patients with low-grade mucinous appendiceal adenocarcinomas and PMP, whereas high grade adenocarcinomas (ie, signet ring) and GCA most frequently appear driven by *TP53* mutations. Unsurprisingly in a disease characterized by peritoneal patterns of metastatic spread, circulating tumor DNA (ctDNA) is less frequently detected from appendiceal adenocarcinoma (38% detectable) compared to other GI adenocarcinomas.[552] These observations suggest potential roles for targeted therapies, particularly against GNAS and KRAS alterations.

Treatment usually consists of surgical cytoreduction (CRS) with consideration of HIPEC, although the use of HIPEC is not universally accepted, it appears to have more impact in lower grade, mucinous histologies and several expert groups have recommendations on how to apply CRS/HIPEC for appendiceal malignancies. Systemic therapy, primarily extrapolated from colorectal cancer studies, is usually recommended for high-grade and poorly differentiated tumors, although prospective clinical trials are lacking to guide therapy. One small observational study (n = 20) assessing patients with PMP (60% low grade, 40% high grade) receiving FOLFOX4 after progression from prior CRS/HIPEC found ORR 20%, DCR 65%, median duration of response 14.2 months, mPFS 8 months with 6 month PFS rate 50%, and median OS 26.3 months.[553] A more recent attempt at a randomized trial of patients with low-grade appendiceal adenocarcinoma to observation for 6 months followed by investigator's choice of chemotherapy for 6 months versus upfront chemotherapy followed by observation unfortunately closed early due to slow accrual (n = 24, enrollment goal had been 30 patients), but suggest from the data available that there was no benefit in either tumor response or bowel obstructions in patients on fluoropyrimidine-based chemotherapy phases compared to observation phases.[554] Intriguingly, despite the historical approach to treating appendiceal adenocarcinomas as colorectal cancers, recent retrospective data leveraged knowledge of infrequent APC alterations in appendiceal adenocarcinoma, and found that taxane-based chemotherapy given to a small number of patients (n = 13) in the metastatic refractory setting, was associated with ORR 30%, DCR 50%, and an mOS 8.3 months.[555] Compare this to multiple taxane-based trials in metastatic CRC that have consistently shown no responses, and it appears that trials dedicated to the various appendiceal malignancies are of urgent need to improve outcomes of patients with these rare cancers.

Two recent trials have explored the efficacy of targeted therapy or immunotherapy in patients with advanced appendiceal malignancies. This includes the small (n = 16), single-institution, single-arm phase II trial of the CDK4/6 tyrosine kinase inhibitor, palbociclib, in patients with *GNAS*-mutated peritoneal mucinous carcinomatosis.[556] The primary endpoint was CEA biomarker reduction and was achieved in 13 of 16 patients, and DCR at 12 months was 50% with mOS not reached after median follow-up of 17.6 months. Atezolizumab/bevacizumab was studied in a small (n = 16), single institution, single arm with synthetic case-matched historical cohort, phase II study as well, though in any-grade appendiceal adenocarcinoma patients.[557] Despite the biological heterogeneity, atezo/bev achievied DCR 100%, mPFS 18.3 months, mOS not reached after median follow-up of 40 months. This was compared to the synthetic control cohort of mPFS 4.4 months (P = .041). While these treatments require further prospective validation before entering standard of care globally, they again further highlight the need to focus research on orphan diseases or risk continued suboptimal outcomes.

GASTROENTEROPANCREATIC NETS

EPIDEMIOLOGY, CLASSIFICATION, AND STAGING

The gastroenteropancreatic (GEP) NET incidence rate is 3.56 per 100,000 individuals in the United States and has increased substantially over the last >40 years as has median OS. Five-year survival rates for metastatic grade 1 and 2 GEP NETs range from 28% for rectal to 69% for small-intestine NETs.[255] Although there are many different historical classification systems for GEP NETs, in practice and in the recent clinical trial literature, they tend to be divided between pancreatic and extrapancreatic

NETs. They are then additionally classified into low-, intermediate-, and high-grade tumors on the basis of either mitotic rate per 10 high-power fields or Ki-67 labeling. A recent change in the 2017 WHO classification system for pancreatic NETs created a category of well-differentiated grade 3 tumors, which are tumors that have a high-grade proliferation index but a more well-differentiated appearance on histology. They are treated more in line with the well-differentiated than the poorly differentiated small cell and large cell subtypes. Staging is slightly different for each location but follows general TNM AJCC principles.

CLINICAL GENETICS

Although most pancreatic NETs are sporadic, they have been clearly associated with multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau disease (VHL), neurofibromatosis 1 (NF1), and tuberous sclerosis.

CLINICAL PRESENTATION AND WORKUP

A majority of NETs are nonfunctional; therefore, patients often exhibit few symptoms, and the NETs are often found incidentally at the time of imaging for unrelated reasons. Workup for metastatic GEP NETs typically involves dotatate PET (gallium [^{68}Ga] or copper [^{64}Cu]) imaging, which has largely replaced somatostatin receptor scintigraphy (octreotide scan) because of its superior sensitivity and specificity. CT imaging with arterial phase (multiphase) contrast for improved liver visualization of what are typically hyperenhancing metastases (compared to metastatic GEP adenocarcinomas that tend to have hypoenhancing liver lesions) or MRI with gadoxetate disodium is the preferred anatomic imaging. If the primary is not identified with these modalities, then upper and lower endoscopy, pancreatic EUS, and/or CT or MRI enterography can be used to better identify pancreatic, gastric, or small-bowel (duodenal, jejunal, ileal) origin. Laboratory workup can include measuring 24-hour urine 5-hydroxyindoleacetic acid (HIAA) or serum chromogranin A levels, but these are often nonspecific or prone to artifact. In pancreatic NETs, additional functional markers, such as glucagon, gastrin, vasoactive intestinal peptide (VIP), and insulin levels, can be determined depending on the clinical presentation. Pathological findings should be reviewed by pathologists with expertise in evaluating these tumors and should include degree of tumor differentiation (ie, well vs poorly differentiated), tumor grade (G1-G3), and either Ki-67 labeling (preferred) and/or mitotic rate per 10 high-power fields.

TREATMENT

Locoregional Therapies

Surgery is the primary treatment of patients who have nonmetastatic tumors. There is no role for adjuvant therapy in these patients. For patients who have advanced disease, palliative cytoreductive surgery (debulking) is controversial and may be considered for patients who have refractory hormone-producing tumors (decreasing the amount of hormone-producing tissue). Such surgery includes hepatic resection or resection of other intra-abdominal and thoracic metastases. Surgical palliation of bowel obstruction from tumor masses or mesenteric fibrosis associated with carcinoid tumors may substantially improve quality of life.

Liver-directed therapy, such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and radiofrequency ablation (RFA), are particularly useful for reducing symptoms caused by local growth of the tumor or by hormone production and should be regarded as nonsurgical debulking. These procedures are also associated with a greater likelihood of prolonged tumor regression.

Somatostatin Analogs

Somatostatin analogs have been used for many years to control the secretion of 5-HIAA and other peptides.[558,559] Although octreotide has long been used and is indicated for the palliation of symptoms related to excess hormone secretion, more recently, the analogs have been assessed for their antitumor activity despite their poor tumoricidal effect, resulting in few regressions. In the PROMID study, a prospective placebo-controlled randomized trial of 85 patients with midgut NETs, the use of long-acting octreotide (30 mg intramuscular injection monthly) was associated with substantial delay in tumor progression and a trend toward improvement in OS.[560] An alternative long-acting somatostatin analog, lanreotide, was evaluated in the randomized, placebo-controlled CLARINET trial of advanced NETs.[561] In contrast to the PROMID study, which included mainly patients who had low-grade midgut NETs, CLARINET enrolled 204 patients who had NETs from the pancreas, midgut, hindgut, or unknown origin, that were well-differentiated or moderately differentiated and had a Ki-67 <10%. PFS was not reached in the lanreotide arm, compared with PFS 18 months in the placebo arm (HR, 0.47; 95% CI, 0.30-0.73; $P < .001$). The 2-year PFS rates were 65.1% and 33.0% for the lanreotide and placebo arms, respectively. OS was not different between the arms, likely because crossover was allowed in the study and because of potential differences in subsequent treatments. Lanreotide was approved by the FDA in December 2014. The excellent PFS of 18 months in the placebo group should be noted from the CLARINET study as should the finding that lanreotide was associated with increased rates of diarrhea, abdominal pain, and cholelithiasis. This argues that, in asymptomatic patients with a low burden of metastatic disease, watchful waiting is an appropriate option.

Somatostatin analogs are the first-line therapy for all patients who have advanced well-differentiated NETs in need of systemic therapy. The indication to start therapy in asymptomatic patients is not well defined but should be strongly considered in those who have progressive disease on interval imaging or those who have a large baseline burden of disease.

Treatment of Carcinoid Syndrome

In addition to the use of surgical and nonsurgical debulking and somatostatin analogs for carcinoid syndrome, patients who have carcinoid syndrome symptoms refractory to standard therapy may benefit from telotristat etiprate, which targets an enzyme involved in excess serotonin production, tryptophan hydroxylase. In a phase 3 trial, patients with carcinoid syndrome uncontrolled by somatostatin analog treatment experienced a 35% reduction in the number of bowel movements with telotristat etiprate compared with placebo (17%; $P < .001$).[562] Patients in the telotristat etiprate arm also had a lower frequency of flushing episodes and less intense abdominal pain compared with those receiving placebo although these differences were not statistically significant.

Radioligand Therapy

^{177}Lu-DOTA0-Tyr3-octreotate (^{177}Lu) is a peptide receptor radionuclide therapy (PRRT) that has been available in Europe since 2000 and was approved by the FDA in 2018. This therapy was tested in the randomized phase 3 trial NETTER-1, in which patients who had progressive somatostatin receptor–positive midgut well-differentiated NETs with Ki67 <20% were randomly assigned to receive four doses of ^{177}Lu every 8 weeks followed by 30 mg of octreotide compared with octreotide alone at 60 mg every 28 days.[563] With a median follow-up of 30 months, median PFS was not reached in the ^{177}Lu/octreotide arm and was 8.4 months in the octreotide alone arm (HR, 0.21; 95% CI, 0.13-0.34; $P < .0001$). Serious AEs include renal failure, irreversible myelotoxicity, a 2% to 3% rate of myelodysplastic syndrome, and a 0.5% rate of acute leukemia. Acute events include nausea related to the amino acid infusion required for renal protection, which has improved with new amino acid formulations. Updated results show that median PFS was 28.4 and 8.4 months (HR, 0.21; 95% CI, 0.14-0.33) and median OS was 48 and 36.3 months (HR, 0.84; $P = .30$) in the ^{177}Lu arm and the octreotide arm, respectively. The OS difference was likely not substantial in large part because of the 36% crossover from the octreotide to the ^{177}Lu arm.[564] PRRT was approved by the FDA for all patients with well-differentiated GEP NETs based on these data in conjunction with retrospective data from the Netherlands.[565] The recently reported phase 3 NETTER-2 trial randomly assigned patients with GEP NETs with Ki-67 10% to 55% diagnosed within 6 months to receive either ^{177}Lu for 4 doses once every 8 weeks followed by 30 mg of monthly octreotide versus monthly octreotide monotherapy at 60 mg. The primary endpoint of PFS improved from 8.5 to 22.8 months (HR, 0.28; 95% CI, 0.18-0.42) along with improvement in response rate (43% vs 9.3%) with the addition of ^{177}Lu compared to monthly depot octreotide alone.[566] Ongoing trials are evaluating novel radioligands, including those with alpha particle emitters, such as ^{225}Ac and ^{212}Pb.

Additional Systemic Treatment of Pancreatic NETs

Pancreatic NETs (pNETs) are more sensitive to cytotoxic chemotherapy compared with other GEP NETs and respond to alkylating agents such as streptozocin, dacarbazine, and temozolomide. Single-arm studies with temozolomide-based regimens show response rates up to 50%.[567-569] In an important phase 2 trial by the ECOG-ACRIN group (study E2211), 144 patients who had metastatic or unresectable pNETs were randomly assigned to temozolomide alone or capecitabine/temozolomide (CAPTEM) combination. Median PFS was 22.7 months in the combination arm versus 14.4 months in the temozolomide arm (HR, 0.58; 95% CI, 0.36-0.93) with a response rate of 33% in the combination arm.[570]

Novel biologics, including VEGF inhibitors, such as sunitinib, and signal transduction inhibitors, such as mTOR inhibitors, also show efficacy in pNETs.[571] Data from a placebo-controlled phase 3 trial with sunitinib (37.5 mg per day) versus best supportive care for 169 patients who had advanced pancreatic NETs, all of whom had experienced progression in the last 12 months,[571] demonstrated that PFS increased from 5.5 months with placebo to 11.4 months in the sunitinib group (HR, 0.42; 95% CI, 0.26-0.66; $P < .001$). Median OS favored sunitinib but was not statistically significant (38.6 vs 29.1 months).[572] In a parallel placebo-controlled phase 3 trial of 410 patients with advanced low- to intermediate-grade pNETs, the mTOR inhibitor everolimus (10 mg per day) likewise improved median PFS from 4.6 to 11.0 months (HR, 0.35; 95% CI, 0.27-0.45; $P < .001$).[573] OS data showed a nonsignificant improvement in median OS of 44.0 months in the everolimus arm and of 37.7 months in the placebo arm (HR, 0.94; 95% CI, 0.73-1.20; $P = .300$).[574] These trials also show that the ORR with these agents are low at approximately 5%. Based on these positive trial results, sunitinib and everolimus gained FDA approval in 2011 for the treatment of pancreatic NETs. The placebo-controlled phase 3 SANET-p trial of surufatinib conducted in China in 264 patients with pNETs showed improvement in the primary endpoint of PFS from 3.7 to 10.9 months (HR, 0.49; 95% CI, 0.32-0.76; $P = .0011$).[575] The randomized placebo-controlled phase 3 CABINET trial enrolled 290 patients with progressive well-differentiated NETs during at least one prior therapy other than somatostatin analogs into two separate cohorts: pNETs and extrapancreatic NETs (epNETs). Patients were randomly assigned 2:1 to receive cabozantinib versus placebo in both cohorts, with a primary endpoint of PFS. The study was stopped early after an interim analysis and showed significant PFS benefit with cabozantinib in both cohorts (11.4 vs 3 months; HR, 0.25; 95% CI, 0.12-0.54 in the pNET cohort).[111]

Multiple systemic therapy options now exist for patients who have metastatic pNETs. The correct sequencing of these agents remains unknown at this time and will require shared decision making regarding the differing toxicities and response rates associated with each of the agents. For instance, for patients who have a need for radiographic response, temozolomide-based regimens would be reasonable given the high rates as noted above.

EXTRAPANCREATIC GI NETs

Everolimus added to octreotide initially demonstrated only modest activity for patients with epNETs with only a borderline statistically significant improvement in PFS.[576] The RADIANT-4 study was a randomized phase 3 trial of everolimus versus placebo for patients who have advanced progressive well-differentiated nonfunctional lung and GI epNETs.[577] Patients in the everolimus arm had a median PFS of 11.0 months compared with 3.9 months with placebo ($P < .001$). There were few partial responses (2% and 1% for everolimus and placebo, respectively). OS favored everolimus but this was not significant (HR, 0.73; 95% CI, 0.48-1.11). Based on these results, the FDA approved everolimus for these tumors in February 2016. The epNET cohort from the abovementioned CABINET showed improved PFS with cabozantinib to 8.3 months compared with 3.2 months with placebo (HR, 0.45; 95% CI, 0.30-0.66).[111] As a result of the CABINET findings, the FDA approved cabozantinib for use in epNETs in March 2025.

Unlike pNETs, well-differentiated grade 1 nonpancreatic GEP tumors are not as responsive to cytotoxic chemotherapy. For patients whose disease is refractory to somatostatin analogs, the clinician has the choice among everolimus, cabozantinib, or ^{177}Lu. Many are choosing ^{177}Lu because of its long PFS, but this is not based on clear level I evidence. As mentioned, shared decision making regarding the different toxicities and costs of these agents is needed.

POORLY DIFFERENTIATED GEP NETs

For patients who have poorly differentiated or for many well-differentiated grade 3 GEP tumors, the selection of chemotherapy is similar to that for small-cell lung cancer with the most consistent regression observed using combination etoposide and platinum agents.[578,579] A trial comparing CAPTEM with platinum/etoposide for these tumors was stopped because of a lack of CAPTEM benefit based on an interim futility analysis, and should be reserved for more medically frail patients who are likely unable to tolerate platinum/etoposide. The success of immunotherapy in small-cell lung cancers has led to an interest in these poorly differentiated tumors as well. Ongoing trials are evaluating the role of adding anti–PD-1/PD-L1 agents to first-line chemotherapy; other trials suggest modest activity for dual checkpoint inhibitor regimens in the salvage setting.[578]

KEY POINTS

- GEP NETs are a heterogeneous group of tumors leading to a variable course of illness depending on stage, site of origin, and histological grade based on Ki-67 index labeling and/or mitotic rate.
- Surgery is the primary treatment of tumors amenable to resection. There is no role for adjuvant therapy in patients undergoing complete surgical resection.
- The oral tryptophan hydroxylase inhibitor telotristat ethyl is an option for patients who have somatostatin-refractory carcinoid syndrome–related diarrhea.
- For asymptomatic patients who have metastatic low-grade tumors and low tumor burden, a watch-and-wait strategy may be appropriate.
- Somatostatin analogs octreotide and lanreotide are standard first-line treatment options for most well or moderately differentiated NETs that exhibit uptake on functional imaging.
- PRRT with ^{177}Lu dotatate is an approved treatment of patients with GEP NETs whose disease has progressed with somatostatin analogs, and recent data also suggest robust activity in first-line therapy for patients with GEP NETs with Ki-67 10-55%.
- Combination capecitabine and temozolomide is a systemic chemotherapy option for patients who have pancreatic NETs. Nonpancreatic NETs do not seem to be as responsive to cytotoxic chemotherapy.
- Everolimus, cabozantinib, and sunitinib are targeted therapy options in pancreatic NETs, and everolimus and cabozantinib are approved for extrapancreatic GI NETs. Recent data show that cabozantinib has activity in patients with NETs irrespective of primary site. The optimal sequencing of these agents, however, has not been established.

HIGH-YIELD TAKEAWAYS

- The role of adjuvant therapy in stage II colon cancer should involve risk stratification and shared decision making.
- Three months of adjuvant therapy is a reasonable alternative for patients with pMMR stage III T1-3 N1 disease given the small absolute difference in DFS and the substantial decrease in neurological and other toxicities with 3 months. If 3 months of therapy is chosen, many expert panels favor CAPOX over FOLFOX.

- All patients with localized colorectal cancer should have tumor testing for MMR/MSI and consideration of testing for PI3K pathway mutations (ie, PIK3CA, PIK3R1, loss of PTEN).
- All patients with metastatic CRC being considered for multiagent chemotherapy should have their tumors tested for extended *RAS* and *BRAF* mutations, dMMR/MSI-H and *HER2* amplifications.
- FOLFOX, FOLFIRI, or FOLFIRINOX with a biological agent is an appropriate first-line chemotherapy backbone for patients with pMMR, BRAF wild type mCRC.
- For patients with left-sided extended *RAS* WT tumors, anti-EGFR therapy may be preferentially considered, and anti-EGFR therapy should be avoided with initial chemotherapy for patients with right-sided tumors, for which bevacizumab is preferred, or in combination with FOLFOXIRI/FOLFIRINOX.
- For patients with newly diagnosed pMMR, *BRAF* V600E–mutated mCRC, the new standard of care for first-line therapy is FOLFOX + encorafenib + cetuximab (panitumumab) due to superior mOS compared to first-line combination chemotherapy and later-line encorafenib/cetuximab.
- For patients with newly diagnosed dMMR mCRC, the first-line standard of care is immunotherapy only (ipilimumab + nivolumab, or anti-PD1 monotherapy).

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

LOWER GASTROINTESTINAL CANCERS 13.2

CHAPTER SUMMARY GUIDE

KEY POINTS

- Screening for CRC is underutilized. Screening colonoscopy and fecal DNA/FIT reduce CRC-associated death over the long term.
- All individuals who have CRC should have their tumors evaluated for MMR or MSI status. Those with dMMR/MSI-H tumors suggestive of germline origin should be referred for genetic screening.
- If universal screening for germline mutations is not performed in all patients who have colon cancer, clinicians should follow the revised Bethesda criteria to determine who should be recommended for germline genetic testing.
- Early-onset CRC patients are more likely to have cancer-associated germline mutations compared to standard-onset patients, but the rapidly increasing incidence of CRC in young-adults (<50 years old) is not associated with genetic causes but rather yet-to-be-identified environmental hazards.
- Stage II colon cancer is a heterogeneous disease, and there is no one-size-fits-all answer for which patients should receive chemotherapy.
- The role of adjuvant therapy in stage II colon cancer should involve risk stratification and shared decision making.
- Patients who have stage IIA colon cancer that is dMMR/MSI-H have an excellent prognosis and do not require adjuvant therapy.
- Patients who have stage IIB or IIC dMMR/MSI-H colon cancer should be considered for adjuvant oxaliplatin-based therapy and potentially immunotherapy.
- Patients who have stage IIA disease without any risk factors do not typically benefit from adjuvant chemotherapy and should be counseled about the low absolute benefit of chemotherapy.
- Patients who have stage IIA disease and high-risk features and those who have stage IIB (T4a) or IIC disease should be counseled regarding their higher risk of tumor recurrence and the potential benefit of fluoropyrimidine and oxaliplatin-based chemotherapy.
- Accumulating data suggest that, for patients with resected colon cancer, postoperative ctDNA-defined MRD status is strongly prognostic, and prospective trials show that ctDNA-guided management is noninferior to standard-of-care management and that it also results in lesser use of adjuvant therapy. While awaiting additional data from ongoing trials, whether to incorporate ctDNA into adjuvant therapy decisions for stage II colon cancer outside of clinical trials should be a shared discussion between patients and their providers.
- By strict scientific criteria, 6 months of adjuvant CAPOX or FOLFOX remains a standard of care for stage III colon cancer.
- Emerging clinical consensus suggests 3 months of adjuvant therapy, particularly with capeox, is a reasonable alternative for patients who have T1-3 and N1 disease given the small absolute difference in DFS and the substantial decrease in clinically substantial neurological and other toxicities. The data are also similar for high-risk stage III colon cancer.
- If 3 months of therapy is chosen, many expert panels favor CAPOX over FOLFOX.
- Six months of therapy with FOLFOX or 3 to 6 months with CAPOX are recommended for those with T4 or N2 disease. It is reasonable to discontinue oxaliplatin while continuing fluoropyrimidine in individuals with significant neurotoxicity having received >50% of the planned 6-month chemotherapy.
- For dMMR (MSI-H) stage 3 colon cancer, the addition of atezolizumab to adjuvant chemotherapy improves outcome. Whether this can be extrapolated to high-risk stage 2 dMMR(MSI-H) colon cancer is unknown but a reasonable extension.
- For patients with stage 2/3 colorectal cancer, data now support a focus and recommendation for exercise the intensity of which should likely be individualized.
- For patients with stage 2/3 colorectal cancer with alterations in the PIK3CA pathway, after adjuvant therapy, the use of low-dose aspirin for 3 years is now recommended.
- Irinotecan, anti-VEGF agents such as bevacizumab, and anti-EGFR antibodies such as cetuximab, regardless of *RAS* status, should not be used in the adjuvant setting.
- All patients with metastatic colon cancer being considered for multiagent chemotherapy should have their tumors undergo extended *RAS* and *BRAF* mutation testing. In addition, all tumors should be tested for dMMR/MSI-H status and

should undergo HER2 testing for overexpression or amplification as this may be a marker of resistance to anti-EGFR therapy as well as a potential target for therapies discussed subsequently.

- Either FOLFOX or FOLFIRI with a biological agent is an appropriate first-line chemotherapy backbone for patients who have mCRC.
- Eventual exposure to all appropriate agents is what is most important. Triplet regimens (FOLFIRINOX) with bevacizumab may be an option for patients who have aggressive tumors.
- For patients who have left-sided extended *RAS* WT tumors, anti-EGFR therapy should be preferentially considered, and anti-EGFR therapy should be avoided as initial therapy for patients who have right-sided tumors for which bevacizumab is preferred.
- Induction maintenance approaches with a limited number of oxaliplatin-containing treatment cycles up front and maintenance therapy with a fluoropyrimidine and bevacizumab combination can be considered standard of care. Those whose disease progresses during maintenance therapy can still have oxaliplatin reintroduced.
- For patients who are not candidates for either oxaliplatin- or irinotecan-containing regimens, the combination of a fluoropyrimidine and bevacizumab can be considered an acceptable standard of care.
- Continuing anti-VEGF therapy beyond first-line progression with bevacizumab and second-line chemotherapy is supported by data.
- Patients who have *BRAF* V600E–mutated tumors should be considered for encorafenib/cetuximab/mFOLFOX6 for the front line or, in the second line and beyond, treatment with the doublet regimen of encorafenib and anti-EGFR antibody.
- For patients who have MSI-H/dMMR tumors, the use of single-agent pembrolizumab or the combination of nivolumab/ipilimumab is considered a preferred standard of care over multiagent chemotherapy as first-line therapy based on the KEYNOTE-177 trial and CheckMate 8HW, respectively.
- Patients who have *HER2*-amplified or HER2-overexpressed colorectal cancers should be considered for treatment with agents directed against HER2 after initial therapy with consideration of RAS status.
- Patients with colorectal cancer with *KRAS* G12C mutations should be considered for targeted therapy after initial chemotherapy with sotorasib or adagrasib alone or with anti-EGFR antibody therapy.
- Regorafenib, fruquintinib, or trifluridine/tipiracil with or without bevacizumab should be considered for patients who have disease refractory to all other approved agents. The decision of how to best sequence these agents is based on the adverse effect profile and individual preferences.
- All patients who have isolated metastatic disease should be considered for surgical resection or other locoregional therapies, and discussion should take place in a multidisciplinary setting conducted at a center with high-volume expertise in treating these cancers.
- Patients who have initially unresectable disease can be considered for conversion therapy with multiagent neoadjuvant chemotherapy.
- The benefit of neoadjuvant, perioperative, or adjuvant chemotherapy for patients who have clearly resectable metastatic disease, although often used, has not been substantiated by randomized clinical trials to improve OS.
- Liver-directed therapies with either intrahepatic chemotherapy or radioembolization have not shown a survival advantage in multi-institution trials and should not be considered standard of care outside of careful patient selection in experienced centers.
- Liver transplantation is an option for highly select patients with permanently unresectable liver-only metastases and where the primary tumor was previously resected.
- Patients who have peritoneal-only CRC should be evaluated at specialized centers for cytoreductive surgery, but HIPEC remains controversial.
- Rectal cancer should be staged preferably with rectal MRI or in certain cases with endorectal ultrasound (ERUS) on the basis of local availability and technical competence of the endoscopist or reading radiologist.
- Imaging of chest and upper abdomen should also be performed to rule out metastatic disease. There is no role for routine PET scan in the staging of rectal cancer.
- Neoadjuvant CRT using either infusional 5-FU or capecitabine followed by TME and adjuvant FOLFOX or CAPOX is the historical standard treatment approach for stage II and III rectal cancers.
- Current treatment of LARC (clinical stage II or III rectal cancer) is centered on TNT strategies, in which chemotherapy and radiation therapy (in either order) are used neoadjuvantly before TME. Although short-course RT is a reasonable alternative to long-course CRT, it may be associated with higher risk of local recurrence in patients with high-risk disease.
- A subset of patients who have non-cT4 disease who are eligible for sphincter-sparing surgery may be treated with neoadjuvant FOLFOX with selective use of CRT in those who have ≤ 20% tumor regression. Adjuvant chemotherapy was offered in the trial.
- Selected patients who have a complete clinical response after TNT or immunotherapy may be considered for nonoperative management with watch & wait surveillance in lieu of surgery.

- Patients with dMMR/MSI-H locally advanced rectal cancer may be considered for TNT with PD-1 immune checkpoint inhibitor treatment for 6 months and avoid surgery, radiation, and chemotherapy if cCR is achieved.
- Oxaliplatin, bevacizumab, cetuximab, or panitumumab should not be added to the CRT backbone for patients with rectal cancer.
- HPV vaccination reduces the incidence of anal intraepithelial neoplasia and will, it is hoped, reduce the incidence of anal cancer as well.
- Combination 5-FU/mitomycin with RT remains the standard approach for localized anal squamous cell cancers, but 5-FU/cisplatin or capecitabine/mitomycin C can be considered for those at risk for bone marrow or other toxicity.
- Responses to definitive CRT can be seen up to and occasionally beyond 26 weeks after treatment completion, so early declaration of failure should be avoided.
- Salvage surgery (APR) is the treatment of choice for those with locally recurrent or progressive disease at or beyond the 26-week evaluation.
- There is no role for induction or consolidation chemotherapy in locally advanced disease.
- Standard chemotherapy for first-line treatment of metastatic anal cancer is carboplatin and paclitaxel per the InterAAct study.
- Retifanlimab added to carboplatin and paclitaxel represents a new standard of care option in the first-line treatment of locally recurrent/metastatic ASCC.
- In the refractory metastatic setting, treatment with nivolumab or pembrolizumab can be considered. CTLA-4 inhibitors have not shown significant additive benefit.
- GEP NETs are a heterogeneous group of tumors leading to a variable course of illness depending on stage, site of origin, and histological grade based on Ki-67 index labeling and/or mitotic rate.
- Surgery is the primary treatment of tumors amenable to resection. There is no role for adjuvant therapy in patients undergoing complete surgical resection.
- The oral tryptophan hydroxylase inhibitor telotristat ethyl is an option for patients who have somatostatin-refractory carcinoid syndrome–related diarrhea.
- For asymptomatic patients who have metastatic low-grade tumors and low tumor burden, a watch-and-wait strategy may be appropriate.
- Somatostatin analogs octreotide and lanreotide are standard first-line treatment options for most well or moderately differentiated NETs that exhibit uptake on functional imaging.
- PRRT with ^{177}Lu dotatate is an approved treatment of patients with GEP NETs whose disease has progressed with somatostatin analogs, and recent data also suggest robust activity in first-line therapy for patients with GEP NETs with Ki-67 10-55%.
- Combination capecitabine and temozolomide is a systemic chemotherapy option for patients who have pancreatic NETs. Nonpancreatic NETs do not seem to be as responsive to cytotoxic chemotherapy.
- Everolimus, cabozantinib, and sunitinib are targeted therapy options in pancreatic NETs, and everolimus and cabozantinib are approved for extrapancreatic GI NETs. Recent data show that cabozantinib has activity in patients with NETs irrespective of primary site. The optimal sequencing of these agents, however, has not been established.

CHAPTER TABLES AND IMAGES

Table 13.2-1 **Clinical Criteria to Determine Likelihood of Lynch Syndrome**
Amsterdam II criteria (all criteria must be met)
At least three relatives with Lynch syndrome–associated cancer (CRC, cancer of endometrium, small bowel, ureter, or renal pelvis)
One relative should be a first-degree relative of the other two
Malignancies should include at least two successive generations
At least one family member should have been diagnosed at age <50 years
Familial adenomatous polyposis is excluded
Tumors should be verified by pathological examination
Revised Bethesda criteria to identify patients with CRC who should undergo pathological examination for Lynch syndrome (any criterion is sufficient)
Synchronous or metachronous CRC or associated with another Lynch syndrome–associated tumor (ie, endometrial, stomach, small intestine, ovarian, pancreatic, biliary tract, ureter or renal pelvis, brain, sebaceous gland adenoma, or keratoacanthoma)
Pathological features of MSI-H cancer (eg, tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern) in patient age <60 years
Development of CRC in individual who has a first-degree relative with CRC and/or Lynch syndrome—related extracolonic cancer and/or colorectal adenoma, with one of the cancers diagnosed before the patient reaches age 50 years or an adenoma diagnosed at age <40 years
CRC in two or more first- or second-degree relatives with Lynch syndrome–related tumors, regardless of age

Abbreviations: CRC, colorectal cancer; MSI-H, microsatellite instability-high.
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Table 13.2-2 **Surveillance Survivorship for Colorectal Cancer**		
	Recommendations	
	Resected (Standard)	**Unresected (NOM)[#]**
Testing schedule	H&P with laboratory tests including CEA every 3 months for 2 years, then every 6 months for years 3-5 from surgical resection	H&P and labs with CEA every 4 months for 2 years, then every 6 months years 3-5 from end of treatment and cCR determination
	CT CAP every 12 months for 5 years	Rectal MRI every 6 months and CT CAP every 12 months for 2 years, then CT CAP and rectal MRI once every 12 months for years 3-5
	Colonoscopy 1 year after initial diagnosis, then at 3 years if findings are normal, and then every 5 years for life if findings remain normal	Flexible sigmoidoscopy and digital rectal examination every 4 months for 2 years and every 6 months years 3-5 (consider switching one endoscopic evaluation for colonoscopy annually years 0-2, then as indicated per standard schedule)
	In families without an identified familiar risk syndrome, all first-degree relatives should undergo screening colonoscopy starting 10 years younger than when the patient was diagnosed but no later than age 40 years and should undergo screening colonoscopy every 5 years	
	Chemo prophylaxis	ALASCCA and consideration daily ASA for 3 years for PI3K altered rectal cancer
Lifestyle changes	• Increased exercise after diagnosis and avoidance of a Western-style diet; diets with a low glycemic load are associated with a reduced risk of cancer recurrence and improved OS[287,518,519] • Patients with class II or III obesity (BMI >35 kg/m^2) have a modestly increased risk of recurrence[332] • Lower serum vitamin D levels have been associated with an increased risk of recurrence, but prospective studies are lacking to show that increasing vitamin D to normal levels can improve outcomes in the adjuvant setting[363]	

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CT CAP, computed tomography of chest, abdomen, pelvis; H&P, history and physical examination; OS, overall survival.
[#]Surveillance regimen per OPRA trial[509] as published in Scott et al.[520]
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Table 13.2-3 **Anal Cancer Follow-Up**			
Years	**Tests**	**Interval**	**Patients**
0-5	Digital rectal examination	Every 3-6 months starting 12 weeks after completion of chemoradiation therapy	All
	Anoscopy		
	History and physical examination with inguinal LN palpation		
	CBC with differential at least until count recovery. Consider CD4 T cell levels in HIV+ patients until count recovery		
0-3	CT scan of chest, abdomen, and pelvis	Annually	cT3/T4 disease or cN+ disease or with positive disease on 12 week examination

Abbreviation: LN, lymph node.
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Table 13.2-4 **Appendicular Mucinous Cancers and Goblet Cell Carcinoids**

Diagnostic Terminology	Histological Criteria
Serrated polyp with or without dysplasia	Serrated crypt profiles confined to the mucosa with intact muscular is mucosae; when present, dysplasia can be classified as low or high grade
Low-grade appendiceal mucinous neoplasm (LAMN)	Mucinous neoplasm with low-grade cytology and any of the following:
	Loss of lamina propriety and muscular is mucosae
	Fibrosis of submucosa
	Pushing diverticulum-like growth into the wall
	Dissection of acellular mucin in the wall
	Mucin and/or neoplastic cells outside of appendix
High-grade appendiceal mucinous neoplasm (HAMN)	Mucinous neoplasm with high-grade cytology present (at least focally) and lacking infiltrative invasion
Mucinous adenocarcinoma	Mucinous neoplasm with infiltrative invasion; patterns of infiltrative invasion include:
	Infiltrative glands, incomplete glands, or single infiltrative tumor cells associated with extracellular mucin and desmoplastic stroma
	Small cellular mucin pool pattern characterized by small dissecting pools of mucin containing floating nests, glands, or single neoplastic cells
	Grade assessment is based on AJCC criteria
Mucinous adenocarcinoma with signet-ring cells	Mucinous neoplasm with signet-ring cell component accounting for ≤50% of tumor cells
	Mucinous neoplasm with signet-ring cell component accounting for >50% of tumor cells

Abbreviations: AJCC, American Joint Committee on Cancer; HAMN, high-grade appendicular mucinous neoplasm; LAMN, low-grade appendicular mucinous neoplasm.

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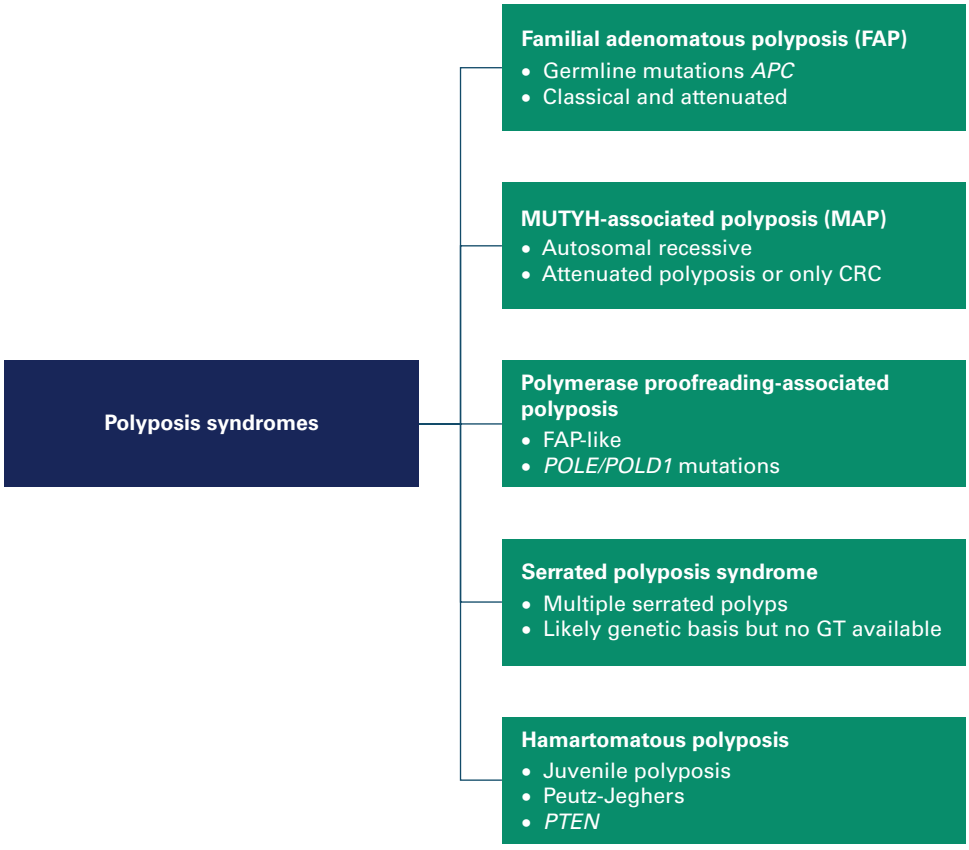
Figure 13.2-1 Polyposis Syndromes



Abbreviations: CRC, colorectal cancer; GT, genetic testing.
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Figure 13.2-2 Adenoma-to-Carcinoma Sequence

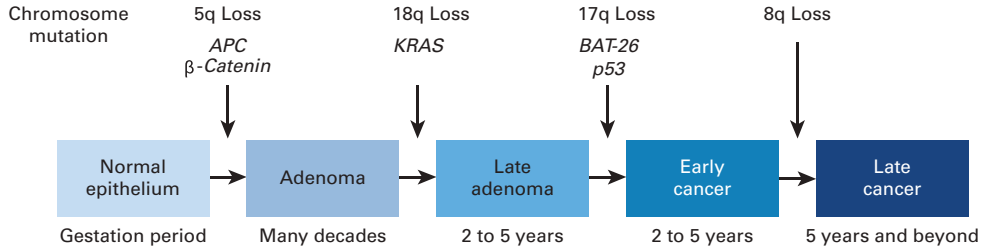

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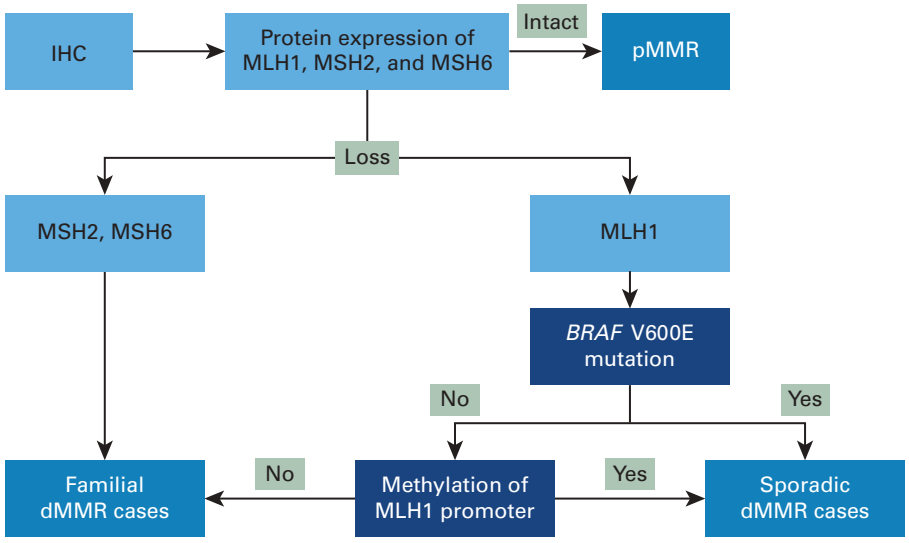
Figure 13.2-3 Mismatch Repair Testing Algorithm



Abbreviations: dMMR, mismatch repair deficient; IHC, immunohistochemistry; pMMR, mismatch repair proficient.
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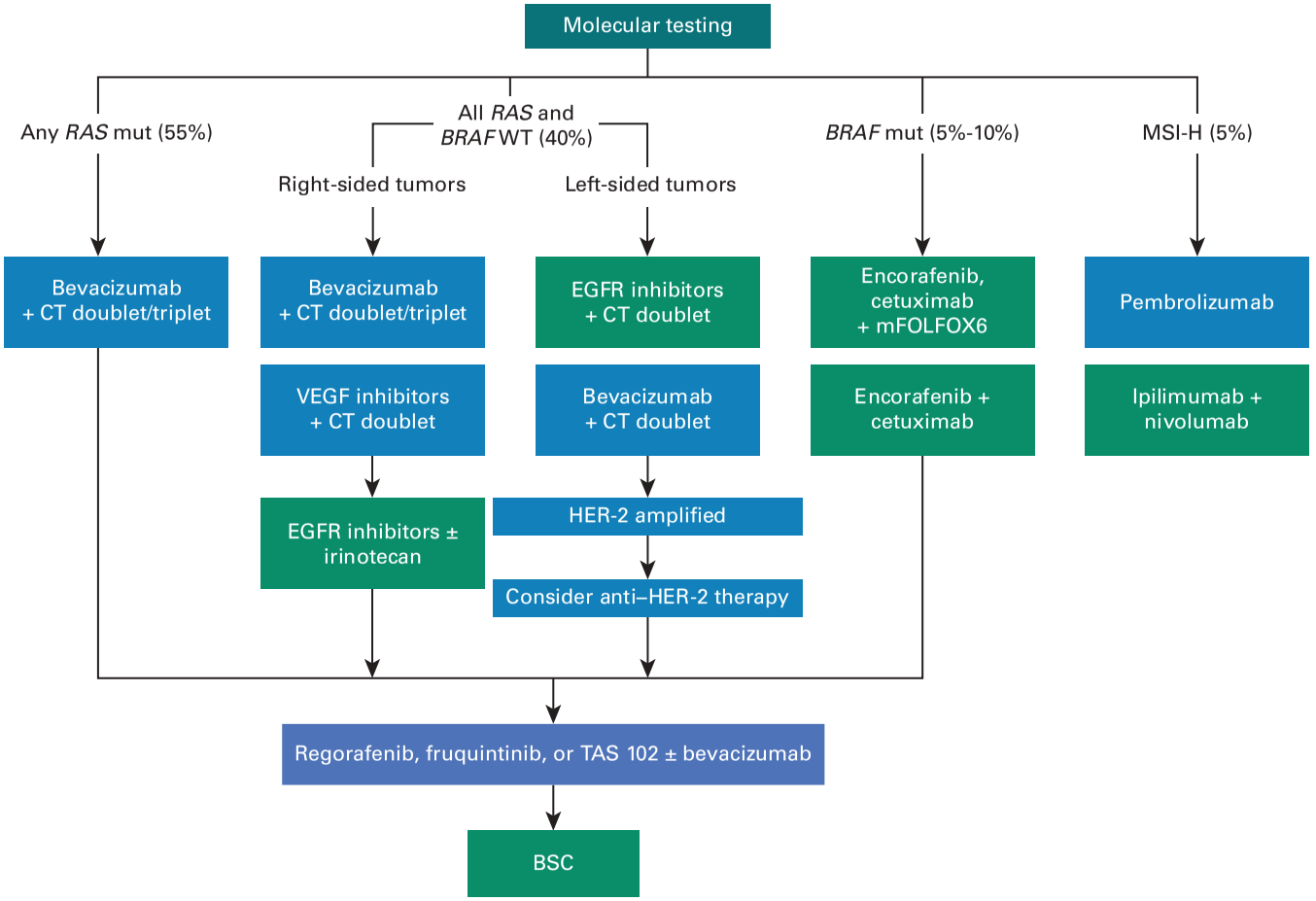
Figure 13.2-4 Treatment Algorithm for Metastatic Colorectal Cancer



Abbreviations: BSC, best supportive care; CT, chemotherapy; mFOLFOX6, modified regimen of 5-fluorouracil, leucovorin, and oxaliplatin; MSI-H, microsatellite instability high; mut, mutation; TAS-102, trifluridine and tipiracil; WT, wild type.

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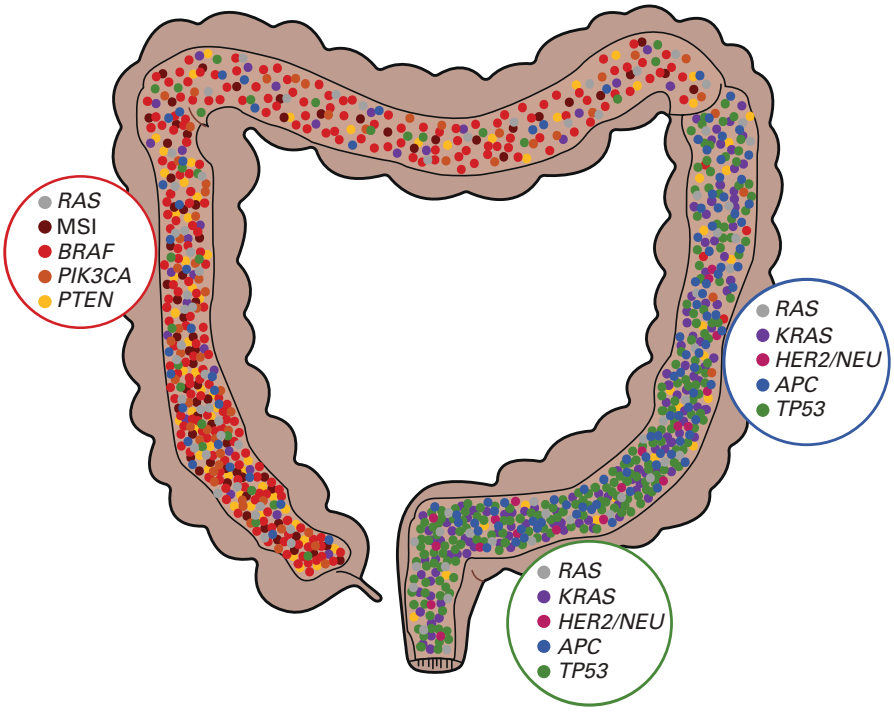
Figure 13.2-5 Molecular Alterations by Tumor Sidedness in Colorectal Cancer



Abbreviation: MSI, microsatellite instability.
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GENITOURINARY CANCERS 14

David Einstein, MD, and Daniel Fein, MD

RECENT UPDATES

Prostate Cancer

- In June 2025, darolutamide with androgen deprivation therapy (ADT) was FDA approved for patients with metastatic castration-sensitive prostate cancer (mCSPC). This was approved based on a progression-free survival (PFS) benefit compared to ADT + placebo demonstrated in the ARANOTE study.[1] Darolutamide, enzalutamide, apalutamide, and abiraterone + prednisone with ADT are now all FDA-approved options for treatment of mCSPC.
- In March 2025, lutetium Lu 177 vipivotide tetraxetan (Lu177PSMA) was FDA approved for patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who previously received an androgen receptor pathway inhibitor (ARPI). Previously, this radioligand was approved only for patients who had received ARPI and docetaxel chemotherapy, but it is now approved for patients who have not yet received docetaxel and are considered appropriate to delay taxane-based chemotherapy. This was based on the PSMAfore study,[2] which demonstrated a PFS benefit with Lu177PSMA compared to switching to an alternative ARPI.
- The combination of Radium-223 and enzalutamide was shown in the PEACE-3 study to improve PFS compared to enzalutamide alone for patients receiving first-line therapy for mCRPC with no prior ARPI exposure.[3]

Bladder Cancer

- In March 2025, the combination of neoadjuvant gemcitabine, cisplatin, and durvalumab, followed by adjuvant durvalumab after cystectomy, was FDA approved for patients with muscle-invasive bladder cancer (MIBC). This was approved based on the NIAGARA trial,[4] which demonstrated improvements in event-free survival and overall survival (OS) for the combination compared to standard perioperative cisplatin-based chemotherapy. The option of "sandwich" chemo-immunotherapy with gemcitabine, cisplatin, and durvalumab or cisplatin-based chemotherapy followed by risk-adapted adjuvant PD-1 immunotherapy is now a preferred option for perioperative systemic therapy for MIBC.
- The FDA approved two additional local therapies for the treatment of Bacillus Calmette-Guérin (BCG)–refractory non-muscle-invasive bladder cancer: the gemcitabine instillation system TAR-200 device (based on the SUNRISE-01 study[5]) and nogapendekin alfa inbakicept-pmln in combination with BCG (based on the QUILT-3.032 study).
- EV-303 demonstrated an OS benefit with perioperative enfortumab vedotin + pembrolizumab compared to cystectomy alone in cisplatin-ineligible patients with MIBC, resulting in FDA approval.[6]

Renal Cancer

- Long-term results from CheckMate-214 confirmed the benefit of ipilimumab/nivolumab over sunitinib across subgroups, including favorable International Metastatic Renal-Cell Carcinoma Database Consortium risk.[7]
- Long-term results from Keynote-564 confirmed the benefit of adjuvant pembrolizumab across all subgroups.

OVERVIEW

Genitourinary malignancies, including cancers of the prostate, bladder, ureters, kidneys, testes, and penis, are a heterogeneous group of tumors with major public health implications.[8] Prostate cancer is the second most common cancer among men worldwide and the fourth most common cancer overall. Bladder cancer incidence is increasing in developing nations, reflecting increased rates of tobacco smoking decades ago. In this chapter, we discuss the medical oncologist's approach to genitourinary malignancies. We discuss risk stratification and, in some cases of low-risk cancers, active surveillance (AS) instead of intervention. In more advanced settings, we discuss established treatment protocols as well as emerging biomarkers and therapies. The spectrum of treatments for genitourinary malignancies is wide and includes not only chemotherapy but also hormonal therapies, molecularly targeted therapies, and immunotherapies, in addition to local therapies, such as surgery and radiation therapy (RT).

EPIDEMIOLOGY OF PROSTATE CANCER

Approximately one in eight American men will be diagnosed with prostate cancer during his lifetime, and it is the most common cancer in American men other than skin cancer.[9] It has been estimated that approximately 15% to 17% of men older than age 50 years harbor occult prostate cancer, and this percentage increases with each decade of advancing age.[10] Autopsy series show that nearly 70% of men older than age 80 years have occult prostate cancer.[11] Only approximately 1 in 41 will die as a result of prostate cancer, but this incidence still makes it the second leading cause of death resulting from cancer in American men. In the United States in 2023, there were an estimated 288,300 new cases of prostate cancer and 34,700 associated deaths.[12] The 8:1 ratio of incidence to mortality demonstrates that, although the disease is lethal for some men, a majority of men with prostate cancer die of other causes. These data highlight the variable biology and clinical course of prostate cancer. Many prostate cancers do not require immediate intervention because the risk of death from non–cancer related causes exceeds that from the cancer; other prostate cancers require multimodality approaches to both eradicate the tumor locally and eliminate micrometastases.

Although the frequency of histological cancers at autopsy is similar throughout the world, the clinical incidence is significantly higher in Western countries, suggesting a role for environmental factors. High consumption of dietary fats, in particular the fatty acid α-linoleic acid, is believed to increase risk by two-fold to three-fold. Several potentially protective dietary factors for prostate cancer incidence have been proposed, including tomatoes (which contain lycopene), cruciferous vegetables, carotenoids, fish, long-chain marine omega-3 fatty acids, soy, and polyphenols. The association with dietary animal fat intake is most robust.

KEY POINT

- Prostate cancer is a common diagnosis, and although metastatic disease develops in only a small percentage of affected patients, this translates into a large absolute number of deaths resulting from prostate cancer.

PROSTATE CANCER: FAMILY HISTORY AND HEREDITY

Prostate cancer is among the most heritable human cancers.[13] Several population-based studies, including a Nordic twin study and others, have shown family history of prostate or breast cancer, especially in a first-degree relative, is a strong risk factor.[14-17] Although family history is a strong risk factor, not all familial cancers are correlated with inheritable germline pathogenic mutations. One study found that, among patients with prostate cancer with a first-degree relative with prostate cancer, approximately 12% of cases are hereditary with germline pathogenic mutations in DNA-repair genes.[18] An interesting finding was that the frequency of this mutation was the same (12%) for those without a first-degree relative with prostate cancer. This observation suggests that approximately 90% of all prostate cancers are sporadic without detectable germline pathogenic mutations, and family history is not an enriching factor for detecting germline pathogenic mutations, at least in DNA-repair genes.[19]

Examples of germline alterations in prostate cancer are the following:

- A rare but recurrent mutation (G84E) in *HOXB13* (rs138213197), a homeobox transcription factor, is strongly associated with early-onset familial prostate cancer, suggesting that rare genetic variants exist that contribute to familial clustering of prostate cancer.
- Germline alterations in DNA-repair genes (*BRCA2*, *BRCA1*, and *MSH2*) are more common and are especially enriched in metastatic disease.

The Prostate Cancer Consensus Conference discussed the role and implementation of genetic testing for inherited prostate cancer risk.[20] Based on these findings, along with available therapeutic options (eg, PARP inhibitors for *BRCA1*, *BRCA2*, or other homologous recombination repair [HRR] gene mutations and PD-L1/PD-1 inhibitors for mismatch repair [MMR]-deficient solid tumor, including in patients with Lynch syndrome), National Comprehensive Cancer Network (NCCN) prostate cancer guidelines recommend routine germline testing in patients with a personal history of prostate cancer in the following scenarios[21,22]:

1. By the patient's prostate cancer stage/risk group:
   a. Any patient with metastatic or node-positive prostate cancer
   b. Any patient with a very high-risk or high-risk disease
   c. May be considered for a patient with intermediate-risk prostate cancer with intraductal/cribriform histology or a patient diagnosed at age ≤55 who would otherwise not meet criteria for testing.
2. By family history/ancestry:
   a. Ashkenazi Jewish ancestry
   b. One or more first-, second- or third-degree relative with ANY:

i. Breast cancer at age ≤50
ii. Male breast cancer
iii. Ovarian cancer
iv. Pancreatic cancer
v. Metastatic, node-positive, or very high-risk or high-risk prostate cancer

c. Three or more first-, second-, or third-degree relatives with prostate cancer (any grade) and/or breast cancer on the same side of the family, including the patient with prostate cancer.
d. A first- or second-degree blood relative who meets any of the criteria above.

KEY POINTS

- Prostate cancer is one of the most hereditary cancers. Clinicians should take a full history of malignancies in the family and be familiar with the link between prostate cancer and germline alterations in *BRCA2* and MMR genes, which are enriched among men with metastatic prostate cancer.
- Clinicians should offer genetic counseling for all patients with high-risk or very high-risk localized, regional node-positive, or metastatic prostate cancer, regardless of family history; those with localized prostate cancer and strong family history as outlined in the preceding paragraphs; and those with alterations in DNA damage repair or MMR genes identified from tumor sequencing.

ANATOMY OF PROSTATE CANCER

The peripheral zone is palpable by digital rectal examination (DRE) and is the site of origin of 70% of prostate cancers. The transition zone surrounds the urethra and cannot be assessed by DRE. Up to 20% of all prostate cancers develop in the transition zone; however, benign prostatic hypertrophy is more common than prostate cancer in the transition zone. The anterior portion of the prostate gland is especially important because this area is generally not biopsied as part of a routine prostate needle biopsy. It should be evaluated by either MRI or targeted directed biopsy in cases in which the prostate-specific antigen (PSA) level continues to rise in the setting of continued negative biopsy specimens, often harboring, in these circumstances, high-grade cancers.

When counseling men considering treatment options with either a surgical approach or RT, the anatomic location of the positive biopsy specimen is instructive. In the standard 12-core biopsy, generally two biopsy cores are obtained from the base of the gland, the midportion, and the apical regions. The possibility of seminal vesicle involvement with a preponderance of positive biopsy specimens in the base of the gland is a concern, especially because the base is in the anatomic region of the seminal vesicle. Therefore, a clinician should carefully review the MRI of the prostate, if available, to look for seminal vesicle involvement if the bulk of positive biopsy specimens are from the base. If seminal vesicle involvement is suspected, primary RT and androgen deprivation therapy (ADT) are typically used in lieu of prostatectomy.

Likewise, apical disease poses the problem of having a higher rate of positive surgical margins, harboring an anterior tumor (not necessarily biopsied during a standard biopsy procedure), and incontinence resulting from the necessity of creating an anastomosis between the bladder neck and the penile urethra, near the external urinary sphincter. Therefore, patients with a bulk of positive biopsy specimens from the apex may not be optimal candidates for prostatectomy. In addition, the possibility of an anterior tumor in this instance may prompt an MRI to investigate for undersampled disease via standard transrectal ultrasound (TRUS) biopsy. These considerations may aid decision-making regarding the initial treatment approach.

Although TRUS biopsy has been the most widely used method, a transperineal approach may reduce the chances of biopsy-related infection, although data have been mixed. Typically, this approach is done in an operating room instead of an office setting, potentially limiting accessibility, although some centers are now offering this in the office. The transperineal approach may be preferred for patients with anterior and apical tumors not easily accessible by TRUS, or for those at higher risk of infection.

ROLE OF MULTIPARAMETRIC MRI IN DIAGNOSTIC WORKUP IN SUSPECTED PROSTATE CANCER

There is mounting evidence to support the use of multiparametric MRI and multiparametric MRI-guided biopsy combined with systematic TRUS biopsy in men with suspected prostate cancer. For decades, a TRUS-guided 12-core prostate biopsy has been used as a standard procedure to ensure that biopsy specimens encompass all portions of the gland. However, there are several limitations with TRUS biopsy, including undersampling of anterior tumors and the detection of clinically insignificant prostate cancer.

Multiparametric MRI provides detailed visualization of the prostate gland and potentially significant prostate cancer, and facilitates direct targeting of suspicious lesions during biopsy and to select patients who may not need a prostate biopsy.

A study called PRECISION accrued 500 men with elevated PSA who had not yet undergone biopsy.[23] Men with suspected prostate cancer were randomly assigned to undergo MRI, with or without targeted biopsy, or standard TRUS-guided 10 to 12 core biopsy. Men in the MRI-targeted biopsy group underwent a targeted biopsy without standard biopsy cores if the MRI was

suggestive of prostate cancer. Men whose MRI results were not suggestive of prostate cancer were not offered a biopsy. The investigators found that when MRI was used for guidance, there was higher detection of clinically significant cancer (38% vs 26% with TRUS biopsy) and a lower chance of detecting low-grade cancers that were not clinically significant. In addition, 28% of patients could avoid biopsy given the absence of MRI abnormalities.

Similarly, The PAIREDCAP study and other large trials show that while MRI-targeted biopsies detect more cancer per core than systematic biopsies, the overall detection rates are similar when each is used alone (about 52%-60%). Combining MRI-targeted and systematic approaches, however, provides the highest detection rate (around 62%-70%), ensures fewer clinically significant cancers are missed (about 9% if MRI-guided biopsy alone without systematic biopsies), and reduces upgrading at prostatectomy (3.5% vs 8.7% with MRI and 16.8% with systematic alone).

These data are prompting the increased use of MRI as the first diagnostic step in the evaluation of PSA-suspected prostate cancer, but longer follow-up is needed to determine the safety of eliminating standard template biopsies based on MRI and to determine the cost-effectiveness of this strategy.

Most recently, the PRIME study[24] investigated the utility of a "Bi-parametric" prostate MRI (ie, MRI without gadolinium contrast) in comparison to the standard multiparametric MRI for initial diagnosis. The investigators found that biparametric MRI was non-inferior to the multiparametric MRI for the detection of clinically significant prostate cancer. This data may lead to a change in the standard of care to allow for more biparametric MRI use, which could allow for greater MRI availability for patients and reduce worldwide healthcare costs.

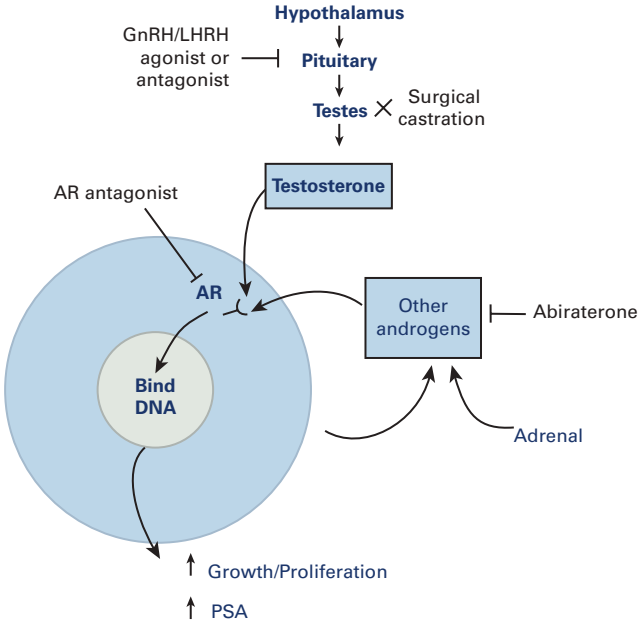
KEY POINTS

- Prostate cancer is typically diagnosed via TRUS or transperineal biopsy using a standard 12-core template to sample the posterior peripheral zone. MRI-guided biopsy combined with a standard TRUS biopsy has been shown to lessen the likelihood of missing clinically significant cancers and should be used when available.
- Among men undergoing evaluation for elevated PSA, a prebiopsy multiparametric or biparametric MRI may help triage those who require biopsy, limiting biopsies to those with a greater likelihood of clinically significant cancer. Anatomic location can help predict the pattern of spread and treatment-related risks. Disease near the base of the gland may extend into the seminal vesicles. Disease in the apex may increase the risk of positive surgical margins and urinary incontinence.

PROSTATE CANCER PATHOLOGY AND MOLECULAR PATHOGENESIS

Androgens are the primary drivers of prostate cancer cell growth and proliferation. Prostate cancer rarely develops in castrated men or in those who have hypopituitarism before the age of 40 years.[25] The androgen receptor (AR), located on chromosome Xq11-13, is a member of a superfamily of ligand-dependent transcription factors that have a similar structure with different

Figure 14-1 Basic Schematic of Androgen Receptor–Directed Therapies



Abbreviations: AR, androgen receptor; GnRH, gonadotropin-releasing hormone; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.
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functional domains. The development of prostate cancer involves a multistep process in which AR signaling plays a key role (Fig. 14-1). The cornerstone of systemic therapy is inhibition of AR signaling, which can be accomplished through direct inhibition of AR with AR antagonists, and/or depleting androgen ligands. Androgens include testicular testosterone, which can be inhibited with ADT, and androgens synthesized in the adrenal glands and/or intratumorally, which can be blocked with abiraterone. Collectively, AR antagonists and abiraterone are referred to as androgen receptor pathway inhibitors (ARPIs) in this chapter, although elsewhere they may also be referred to as androgen signaling inhibitors (ASIs), androgen receptor signaling inhibitors (ARSIs), androgen receptor inhibitors (ARIs), or novel hormonal agents (NHAs).

Specific genetic changes have been identified in tumors representing different clinical states. Gene expression profiling has identified numerous molecular abnormalities that may differ between primary, metastatic, and castration-resistant prostate cancers (CRPCs). As such, the targets relevant for the treatment of early-stage disease may not be the same as those for late-stage tumors.

The typical immunohistochemistry profile of prostate cancer is as follows:

- Negative for cytokeratins 7 and 20
- Positive for AR and PSA
- Positive for the NKX 3.1 homeobox protein

Figure 14-2 Gleason Scoring

A

A Gleason score is assigned by adding the two most common grades of prostate cancer cells in a tissue sample.

How is it calculated?

Formula for Gleason scoring

Primary pattern (>50%) + Secondary pattern (<50%) = GS

Example:

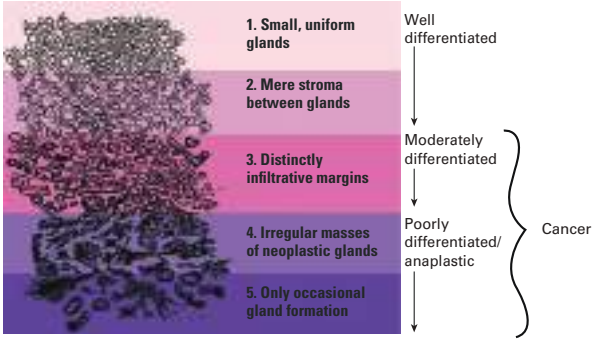
Primary pattern = 3

Secondary pattern = 4

Total GS = 7

This means that most of the tumor is grade 3 (aka dominant pattern), and a smaller portion is grade 4.

B



C

Gleason score Formula: GS = Primary pattern (>50%) + Secondary pattern (<50%)	ISUP Grade Groups derived from GS; Cancer grading
6 (</3 + 3)	Grade Group I (GS = </6)
7 (3 + 4)	Grade Group II
7 (4 + 3)	Grade Group III
8 (4 + 4)	Grade Group IV
9 (4 + 5)	Grade Group V
9 (5 + 4)	Grade Group V
10 (5 + 5)	Grade Group V

The Gleason score is a scale that helps with the staging of prostate cancer (by aggressiveness and prognosis) based on the microscopic examination of the sample tissue in the prostate biopsy. The grades in the score compare the pattern of the cancerous tissue with that of normal tissue in regard to aspects including shape, disposition, and spread. There are two grades that are awarded, each on a scale from 1 to 5. The primary grade is given to the most commonly observed type of cancerous cell; the secondary grade is given to the second most commonly observed type of cancerous cell.
(A) Calculating the Gleason score. (B) Gleason Pattern. (C) Deriving ISUP grade groups from GS.
Abbreviations: GS, Gleason score; ISUP, International Society of Urological Pathology.
Sources: (A, C) Created for ASCO. Copyright © 2026 by American Society of Clinical Oncology. (B) Reprinted from Wikimedia Commons, https://commons.wikimedia.org/wiki/Category:Gleason_grading_system#/media/File:Gleasonscore.jpg

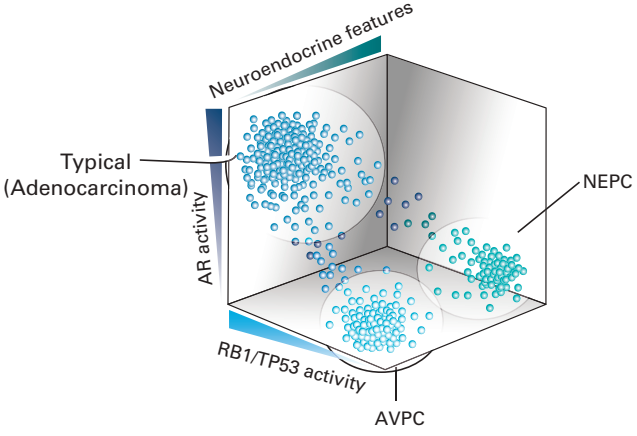
NKX 3.1 positivity is retained even in some advanced treatment-resistant prostate cancers that have lost AR and/or PSA expression (although loss in neuroendocrine prostate cancer, discussed subsequently, can occur). In cases of a mass involving both prostate and bladder, this profile can help differentiate prostate cancer from urothelial cancer, which is typically positive for cytokeratins 20 and (usually) 7 as well as GATA3 and negative for PSA and NKX 3.1 (and typically, but not always, negative for AR). The Gleason grading system is used to describe the morphology of adenocarcinomas of the prostate. It can be applied to prostate biopsies (each core graded separately) or entire radical prostatectomy specimens; it should not be applied to metastatic biopsies or after preceding hormone therapy. In general, the higher the Gleason pattern, the less well differentiated (gland-forming) the histology (Fig. 14-2).

During the 2014 International Society of Urological Pathology Consensus Conference, a new prostate grade system was developed.[25] This new system provides more accurate stratification with simplified grading categories. Many experts believe that this stratification helps patients understand the risk of their cancer and limits overtreatment. As shown in Figure 14-2, the new system assigns grade groups from 1 through 5, derived from the Gleason score. This new system has been validated in two separate studies.[26] Both studies found that grade groups predicted the risk of recurrence after primary treatment.[27]

Prostatic intraepithelial neoplasia is an epithelial cellular proliferation within benign-appearing glands and acini. Approximately 50% of men with prostatic intraepithelial neoplasia, as demonstrated in prostate biopsy specimens, will be diagnosed with prostate cancer in 5 years, depending on the frequency of biopsy procedures. More than 99% of prostate cancers are adenocarcinomas; <1% are pure ductal and mucinous variants. Other histological subtypes include small-cell carcinoma and rare mesenchymal tumors (ie, rhabdomyosarcomas in younger patients and leiomyosarcomas in older patients). Urothelial carcinomas of the prostate are confined to the periurethral ducts and are more common among patients who have been successfully treated for non-muscle-invasive bladder cancer (NMIBC). Though cases are rare, lymphomas and leukemias may occur in the prostate gland.

During the course of treatment of advanced prostate cancer, multiple genomic and transcriptomic alterations can occur as mechanisms of treatment resistance. Despite resistance to castration and ARPIs, most prostate cancers remain dependent on AR signaling, but a subset may become androgen-independent and are generally characterized by alterations in *RB1*, *PTEN*, and *p53* (Fig. 14-3).[28] According to a multi-institutional prospective series of 202 consecutive patients with metastatic castration-resistant prostate cancer (mCRPC), 17% of patients with mCRPC developed treatment-associated small-cell/neuroendocrine histology on metastatic tumor biopsies.[29] Some, but not all, of these tumors may exhibit neuroendocrine differentiation with positive synaptophysin and/or chromogranin A staining. The extreme of neuroendocrine differentiation is small-cell morphology. A patient with rapid visceral progression in the absence of significant PSA change should prompt rebiopsy to exclude the emergence of a neuroendocrine or aggressive variant histology.

Figure 14-3 Relationship Between AR Signaling, Tumor-Suppressor Genes, and Neuroendocrine Features in Metastatic Castration-Resistant Prostate Cancer



This depicts a conceptual representation of the spectrum of profiles that include AR signaling, loss of tumor-suppressor genes, and development of neuroendocrine features during prostate cancer progression. Individual dots represent hypothetical patients, but different subclones may also be present within one individual.

Abbreviations: AR, androgen receptor; AVPC, aggressive variant prostate cancer; NEPC, neuroendocrine prostate cancer.

Reprinted with permission from Wolters Kluwer. Source: Einstein DJ, Arai S, Balk SP. Targeting the androgen receptor and overcoming resistance in prostate cancer. *Curr Opin Oncol*. 2019;31(3):175–182; figure 1. doi: 10.1097/CCO.0000000000000520

KEY POINTS

- Prostate cancer can be characterized by its typical immunohistochemistry profile: cytokeratin 7/20 negative, PSA positive, AR positive, and NKX 3.1 positive.
- As treatment resistance occurs, different phenotypes may emerge. Most CRPCs are still driven by AR signaling even after developing resistance to subsequent AR-directed therapies.
- Some advanced CRPCs may become androgen-independent, often harboring alterations in *RB1*, *PTEN*, and *p53.* These may be admixed with AR-driven tumors. A subset of these cases may have neuroendocrine features, with the most extreme exhibiting small-cell morphology.
- There are two kinds of small-cell/neuroendocrine prostate cancer: (1) de novo small-cell prostate cancer, which is a very rare disease subset and presents admixed with adenocarcinoma (more common) or pure, (2) treatment-associated small-cell/neuroendocrine prostate cancer, which occurs in about 15% to 20% of patients who have mCRPC. Small-cell/neuroendocrine prostate cancer should be suspected in patients with a rapid radiographic progression or new hepatic metastases without PSA increase. It is characterized primarily by morphology, but it can also be positive for synaptophysin and/or chromogranin A staining.

PROSTATE CANCER PREVENTION

A number of chemoprevention strategies have been studied in prostate cancer, including the Prostate Cancer Prevention Trial (PCPT)[9] and REDUCE trials, both using 5-α reductase inhibitors.[30]

In 2011, a US Food and Drug Administration (FDA) advisory committee analysis of both trials confirmed a relative reduction of approximately 25% in the overall incidence of prostate cancer. The authors of the analysis noted, however, that this reduction was limited to tumors with a modified Gleason score of 6 or below and that many of the detected cancers were diagnosed by prostate biopsy in response to an elevated PSA level or an abnormal DRE. The reassessment of the PCPT and REDUCE trials confirmed a significantly increased incidence of high-grade prostate cancers, and the committee estimated that the use of a 5-α reductase inhibitor for the prevention of prostate cancer would result in one additional high-grade cancer to avert three to four potentially clinically relevant lower-grade cancers. The advisory committee concluded that finasteride and dutasteride do not have a favorable risk–benefit profile for chemoprevention of prostate cancer in healthy men. In a recent population-based cohort study, the all-cause and prostate cancer–specific mortality rates were increased in patients treated with 5-α reductase inhibitors, possibly related to a delay in diagnosis resulting from the decrease in PSA level that occurs with treatment; importantly, PSA is expected to fall by approximately one-half on 5-α reductase inhibitors, so more stringent criteria must be used to trigger a workup for cancer.[29]

Trials of vitamin supplementation have also not demonstrated benefit in reducing the risk of prostate cancer, and the Selenium and Vitamin E Cancer Prevention (SELECT) trial actually demonstrated a 17% increased risk of prostate cancer in the vitamin E group but not in the selenium and vitamin E group, suggesting that vitamin E supplementation at 400 IU daily significantly increases the risk of prostate cancer development.[31,32]

PROSTATE CANCER SCREENING AND EARLY DETECTION

PSA is a single-chain glycoprotein that functions as a kallikrein-like serine protease, causing liquefaction of seminal coagulum. It is prostate-specific, but not prostate cancer–specific, and an elevated PSA concentration may occur as a result of prostatitis, nonmalignant enlargement of the gland, biopsy of the prostate, ejaculation, and prostate cancer. A DRE does not alter PSA levels appreciably. The half-life of PSA is estimated to be 2 to 3 days, and levels should remain undetectable if the prostate has been removed.[33]

A screening procedure, by definition, is intended to be performed in asymptomatic patients with no signs or symptoms of the organ being evaluated. The PSA blood test was first introduced in the early 1990s as a screening test for prostate cancer. Three large randomized controlled trials failed to demonstrate any overall survival (OS) benefit conferred by PSA with or without DRE screening, and cancer–specific survival benefit has been inconsistent and modest at best. However, there are methodological issues, including significant "contamination" of the control arm of one trial, and benefits on prevention of distant metastatic disease have been observed in some trials.

- A PSA level >4 ng/mL has predictive value for the diagnosis of prostate cancer; however, lower PSA values may also be associated with prostate cancer as well as with high-grade cancers, as demonstrated in the PCPT.[10]
- For men with a PSA value between 4 and 10 ng/mL, a PSA velocity of at least 0.75 ng/mL per year is suspicious for cancer.

PSA measurements should be made on at least three to four consecutive occasions, usually separated by 6 months over at least 12 to 18 months because of variability.

- A variety of additional modifications to PSA testing have been developed to help improve its sensitivity and specificity, especially when PSA values are between 4 and 10 ng/mL. The proportion of free/bound PSA can help suggest a higher chance of cancer if <10%. PSA density (value divided by volume of gland) >0.15 is associated with prostate cancer. The SelectMDx, Prostate Health Index, and 4K scores are commercially available platforms that have been proposed to help decide whether to biopsy, but may be increasingly superseded by prebiopsy MRI.

US PREVENTIVE SERVICES TASK FORCE GUIDELINE

In 2018, the US Preventive Services Task Force issued a grade C evaluation (balance of risks and benefits is too close to make a recommendation) of prostate cancer screening in average-risk men aged 55 to 69 years, revised from a grade D recommendation previously (harms outweigh benefits) in light of increasing use of active surveillance to decrease harms and not from any new known benefits. Men at higher risk by virtue of family history, African ancestry, or known germline predisposition may be more strongly advised to undergo screening, but not based on any high-level data. If screening is beneficial in these patients, it is likely to be in younger men (eg, 40-45 years of age), and screening is generally unlikely to be beneficial in older populations (eg, 75 years of age and older), given the natural history of prostate cancer.

The US Preventive Services Task Force summarized the risks and benefits of PSA testing for the early diagnosis of prostate cancer as follows[34]:

Benefits

- In men aged 55 to 69 years, PSA testing may prevent approximately 1.3 deaths resulting from prostate cancer over approximately 13 years per 1,000 men screened.
- Screening may prevent approximately three cases of metastatic prostate cancer per 1,000 men screened.

Harms

- Erectile dysfunction, urinary incontinence, and bowel symptoms are associated with definitive therapies, and occasionally, some erectile dysfunction is associated with biopsies.
- Harms of screening in men older than 70 years of age are at least moderate and greater than in younger men.

KEY POINTS

- There are no universally accepted protocols for prostate cancer prevention or screening.
- Two 5-α reductase inhibitors (eg, finasteride and dutasteride) were evaluated in large phase 3 chemoprevention trials. Although these agents decreased the overall incidence of prostate cancer by approximately 25%, this decrease was limited to low-grade tumors. The use of these agents was associated with a significantly increased incidence of high-grade prostate cancer.
- PSA-based prostate cancer screening has shown, at most, a small reduction in prostate cancer–specific mortality rate and no convincing effect on overall mortality. Screening could be more effective if targeted to men with a higher risk and to the age groups most likely to benefit (ie, younger men rather than older men), but additional studies evaluating this possibility are underway. DRE for screening does not significantly add to PSA.

PROSTATE CANCER STAGING

The American Joint Committee on Cancer (AJCC) *Cancer Staging Manual, 8th Edition* (2017), TNM system describes the extent of the primary tumor (T), status of the regional nodes (N), and presence or absence of T4 distant metastases (M).[33,35,36] For more information, visit https://www.cancer.org/cancer/types/prostate-cancer/detection-diagnosis-staging/staging.html.

Clinical T stage is assigned by DRE. Radiographic evidence of extracapsular extension is not formally part of the staging guidelines, but clinicians may opt to intensify therapy for patients with radiographically advanced tumors. As discussed in the earlier section above, there has been increased use of multiparametric MRI in staging, which incorporates T2-weighted, diffusion-weighted, and dynamic contrast–enhanced MRI imaging for the detection, staging, and management of prostate cancer. The Prostate Imaging Reporting and Data System (PI-RADS) assessment uses a 5-point scale based on the multiparametric MRI findings to determine the likelihood of a clinically significant cancer (International Society of Urological Pathology grade 2+) in the prostate gland; importantly, higher PI-RADS scores do not indicate higher-grade disease. MRI can also provide a likelihood of extraprostatic extension (EPE), sometimes graded from 0 to 3, where 3 is frank EPE (closest to clinical T3 staging by digital rectal exam), whereas 1 to 2 indicate some probability of microscopic EPE.

Pathological T stage is assigned based on examination of a radical prostatectomy specimen for patients who undergo surgery. Margin positivity, which is influenced by surgical technique and the anatomic extent of disease, should be specified in the pathology report. Nodal involvement can also be assessed.

Tumors detected in a biopsy specimen based on an elevated PSA level, and no palpable disease detected by DRE are designated T1c. T2 disease is confined to the prostate (pathological substaging to T2a, T2b, or T2c is no longer performed). In T3 disease, the tumor extends through the prostate capsule (T3a) or invades the seminal vesicles (T3b), whereas tumors are considered T4 if they invade adjacent structures or organs.

RISK STRATIFICATION

Localized prostate cancer is clinically heterogeneous. Many groups have developed prognostic models based on the combination of the initial T stage, Gleason score, and baseline PSA level. These algorithms are used to predict disease extent (ie, organ-confined versus non-organ-confined), node status (negative or positive), and the probability of success using a PSA-based definition of failure specific to the local therapy under consideration. Specific nomograms have been developed for radical prostatectomy, external-beam radiation therapy (EBRT), and brachytherapy (ie, radioactive seed implantation). The eighth edition of the *AJCC Cancer Staging Manual* includes prognostic groupings that incorporate anatomic stage and PSA.[36]

Using T stage, Gleason score, and PSA value, discrete risk categories have been defined and form the basis for treatment decision-making (Fig. 14-4).[35] ASCO guidelines differ slightly from NCCN criteria but are broadly similar. Historically, patients were categorized as low, intermediate, or high risk. However, these categories have been subdivided in more recent updates using additional factors, such as PSA density and the number of involved cores.

There are several tissue-based molecular biomarkers (genomic risk classifiers) that have been developed to refine clinical risk stratification, although none have been prospectively validated to improve decision-making. In 2019, ASCO published a guideline with recommendations for these tissue-based assays to help clinicians select patients for active surveillance versus definitive therapy and to choose between adjuvant RT versus surveillance/salvage RT (although adjuvant RT is increasingly not used outside of pathological node positivity).[37] The Decipher test may have a role in determining the benefit of ADT in combination with salvage RT for patients with low PSAs, as is increasingly common in modern practice, although this is still being prospectively validated. In the future, pathology artificial intelligence platforms may be used in some of these settings.

ROLE OF IMAGING IN STAGING

Prostate cancers spread by local extension through the capsule and seminal vesicles, the lymphatic system to regional nodes, or hematogenously to bone and visceral sites. Imaging studies play a key role in staging. Generally, evaluation of the extent of the local disease is done by a combination of DRE and multiparametric MRI. Although there is no consensus on which patients should undergo MRI, multiparametric MRI is commonly used in centers with available resources. See "Role of Multiparametric MRI in Diagnostic Workup in Suspected Prostate Cancer" section for further reading.

For all men with unfavorable intermediate-, high-, or very high-risk disease, the ASCO, the American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology, and the NCCN recommend cross-sectional imaging with CT or MRI and conventional ^{99m}Tc methylene diphosphonate bone scan to evaluate regional and distant metastases. No routine staging imaging study is recommended for low-risk or favorable intermediate-risk patients.

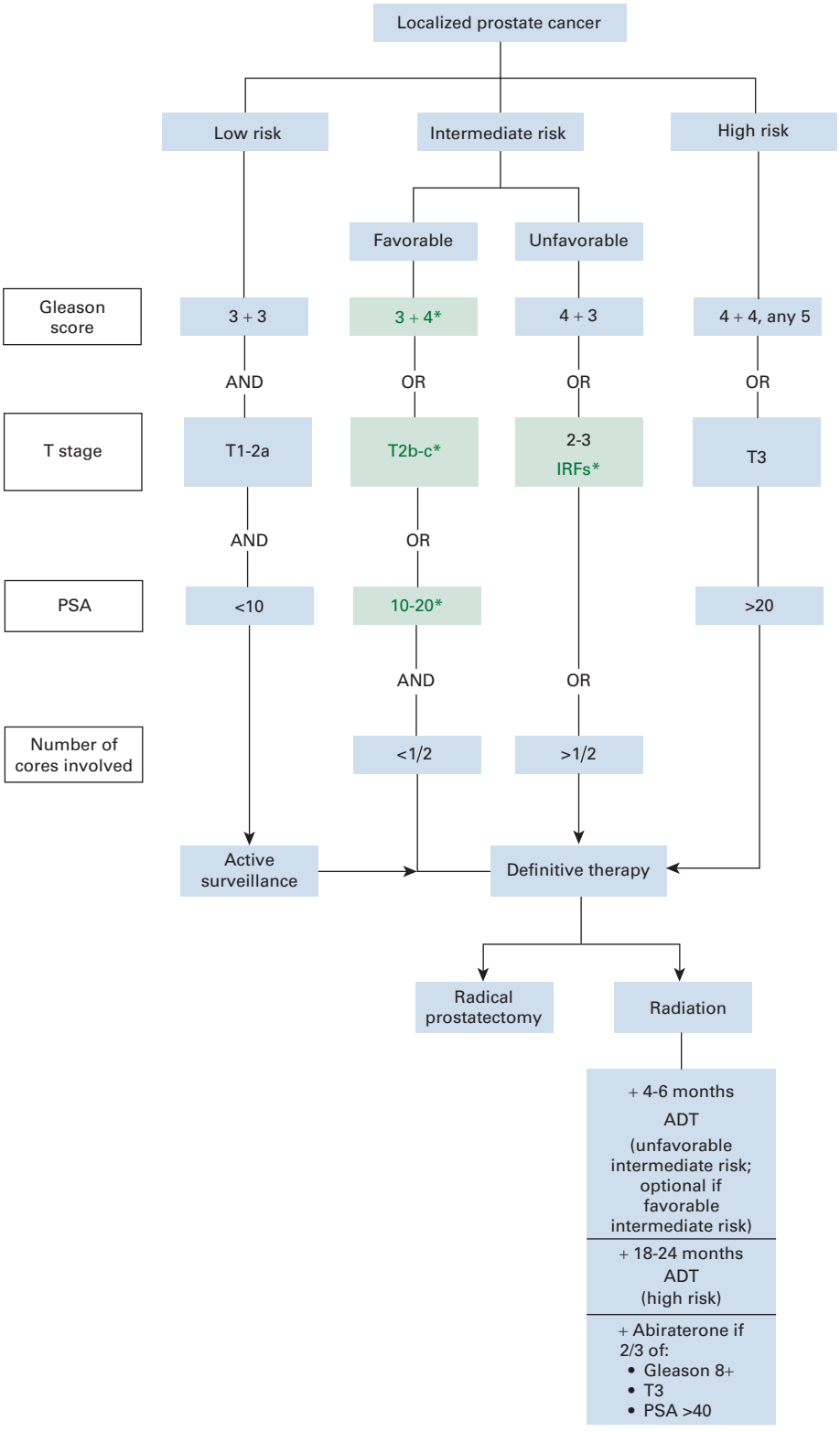
There are emerging roles of next-generation imaging with PET scan using prostate cancer–specific tracers such as ^{18}F fluciclovine,^{11}Ccholine, ^{68}Ga PSMA-11, and ^{18}F piflufolastat.[38] Although all four of these are FDA approved for evaluation of biochemically recurrent prostate cancer, the last two are also FDA approved for initial staging in men who have high-risk or very high-risk prostate cancer with suspected metastases. The trials that led to the approval of ^{68}Ga PSMA-11 and piflufolastat tracers as initial staging for newly diagnosed high-risk prostate cancer showed a sensitivity of 40% and specificities of 95% and 98% for detecting pelvic lymph node metastases.[36,38] Importantly, specificity is higher than sensitivity; thus, negative scans do not exclude nodal metastases, but positive scans are likely to represent true nodal metastases and provide valuable information that may affect management decisions. To date, there are no prospective data supporting a validated approach for changing the treatment of these patients compared with those who undergo staging using conventional imaging. Nevertheless, the use of prostate-specific membrane antigen (PSMA) PET/CT scans is recommended for staging of men with high- and very high-risk disease. Some data also suggest the use of PSMA PET/CT in unfavorable intermediate-risk patients, although the yield is likely lower, and this is a controversial area.

MANAGEMENT OF PROSTATE CANCER BY RISK

Localized prostate cancers are those confined to the prostate gland without nodal involvement or metastases. Treatment selection considers whether the disease can be eradicated by a treatment directed solely at the prostate, whether a combined local and systemic approach is necessary for cure, or whether therapy is not needed or can be deferred because of a low risk of progression. In general, therapy is aimed at complete local control to decrease the potential for recurrence while preserving optimal bowel, bladder, and sexual function.

Tumors confined to the prostate are generally managed by radical prostatectomy, RT, or, in some cases, AS. An assessment of the patient's life expectancy, overall health status, and tumor characteristics should be undertaken before a treatment decision

Figure 14-4 Approach to Treatment Options in Newly Diagnosed Localized Prostate Cancer According to Risk Stratification



Various forms of radiation are discussed in the text. Short course of ADT (4–6 months) is recommended for intermediate-risk category (especially if unfavorable) and long course (18–24 months) for high-risk category.
Abbreviations: ADT, androgen deprivation therapy; EBRT, external-beam radiation therapy; IRF, intermediate risk factor; PSA, prostate-specific antigen.
*IRFs.
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is made. Life expectancy can be estimated with nomograms, including one from the Social Security database. Patients with a life expectancy of <5 years do not benefit from treatment of low-risk prostate cancer and therefore should undergo watchful waiting and additional workup only if the patient becomes symptomatic.

The general approach to treatment of prostate cancer by risk category is described here, with further details of the treatment modalities of radical prostatectomy and radiation described in the following sections.

LOW RISK

For patients with very low-risk localized prostate cancer, AS is the preferred management option. AS is also generally preferred for patients with low-risk localized prostate cancer, but depending on patient preferences, interstitial prostate brachytherapy, EBRT, and radical prostatectomy can also be offered. Prostate brachytherapy should not be offered to men who have significant lower urinary tract symptoms or who have had repeated episodes of prostatitis or urinary infections, because brachytherapy may be more likely to exacerbate these symptoms. The American Urological Association symptom score index for assessment of urinary symptoms (developed to assess urinary symptoms of benign prostatic hyperplasia) or the EPIC-26 instrument can be used to quantify the current symptom burden a patient is experiencing. This information can then be incorporated into initial therapy decisions for men opting for localized treatment with EBRT or prostatectomy, and these instruments can be used to track changes in symptoms after treatment. Subtotal approaches such as focal ablation or high-intensity focused ultrasound are still being evaluated and may not have a favorable risk/benefit profile pending longer-term results but can sometimes be offered for patients with very focal, low- or intermediate-grade disease with the understanding that recurrences are still possible and may be more difficult to manage with conventional definitive therapy and that quality of life is not necessarily improved.

INTERMEDIATE AND HIGH RISK

For patients with intermediate-, high-, or very high-risk localized prostate cancer, definitive therapy with either prostatectomy or RT (+/− ADT, dependent on risk category) is recommended as long as the patient's life expectancy is 10 years or more (intermediate risk) or 5 years or more (high and very high risk) or if the patient is symptomatic. Patients with favorable intermediate-risk prostate cancer may be considered for active surveillance, especially those with small proportions of Gleason pattern 4 disease. The rate of subsequent upgrading may be increased for favorable intermediate-risk patients compared with low-risk patients under active surveillance, but it is not clear whether OS or cancer–specific survival is affected.

With few randomized trials, comparisons among treatments have been limited by selection bias and differences in outcome reporting with respect to both cancer control and quality of life. The best available data suggest that long-term cancer control is equivalent between surgery and radiation. This is supported by the ProtecT study, which was a large phase 3 trial in the UK that randomized patients with newly diagnosed localized prostate cancer to undergo (1) active monitoring, (2) surgery, or (3) radiation for first-line treatment. At 15 years of follow-up, the risk of metastasis was similar between intervention groups and was higher in the inactive monitoring group, but the overall prostate cancer mortality risk was low regardless of treatment group assigned (61% of patients in the active monitoring group eventually received treatment).[39] Given this apparent equipoise, the treatment decision is guided primarily by adverse effect profiles.

- Overall, prostatectomy is primarily associated with urinary incontinence and erectile dysfunction, with the incontinence typically improving in the months after surgery and erectile function dependent on baseline function as well as surgical approach (nerve-sparing versus non–nerve-sparing surgery).
- Radiation therapy is more associated with irritative urinary and bowel symptoms in the days/weeks after treatment (acute) or months to years later (chronic).[40]

Reported complication rates for each modality vary widely in the literature. The differences are related to the different definitions used, whether the patient or physician is reporting, and the time from treatment to assessment of symptoms. Health-related quality of life studies are more accurately defining patient satisfaction with the different treatments for localized prostate cancer. For example, in one study, adjuvant hormone therapy was associated with worse quality of life outcomes among patients receiving brachytherapy or external RT; prostatectomy was associated with worse urinary incontinence, but urinary irritation and obstruction improved, particularly in patients with a large prostate.[35] Thus, prostatectomy may be the preferred modality in patients with significant baseline urinary obstructive symptoms; RT may worsen obstructive symptoms in the short term.

Erectile dysfunction can occur as a result of both RT and radical prostatectomy. The risk is generally greater with radical prostatectomy. Of note, all patients experience decreases in erectile function over time related to reasons other than prostate cancer treatment. This was observed in the ProtecT study as referenced above. These analyses have led to the development of health-related quality of life nomograms that may help guide treatment choice in an individual patient with localized prostate cancer.

ROLE OF ADT WITH RADIATION FOR LOCALIZED PROSTATE CANCER

ADT has a clearly established role for use with radiation for the treatment of localized prostate cancer. It does not yet have an established role in the perioperative setting for patients undergoing surgery, but this is currently under investigation.

Common modalities of ADT with radiation include luteinizing hormone-releasing hormone (LHRH) agonists (leuprolide, goserelin, triptorelin) and LHRH antagonists (relugolix, degarelix). ADT is typically started approximately 2 months before RT, although earlier or later timing of RT relative to ADT does not seem to affect long-term outcomes. It is uncertain whether the addition of bicalutamide to ADT improves outcomes for localized prostate cancer, but based on analyses in more advanced disease (see "Therapy for Metastatic Prostate Cancer" section), some clinicians will add bicalutamide for the first 4 to 6 months of ADT or until after RT is completed.

For patients with intermediate-risk disease, the addition of 4 to 6 months of ADT to RT has been shown to improve biochemical-free survival and progression-free survival (PFS) in several trials.[41-43] Importantly, the addition of ADT here has not been shown to improve OS for intermediate-risk disease. A secondary analysis of the RTOG 9408 study found that patients categorized with "unfavorable" intermediate-risk disease receiving ADT had a reduction in distant metastases and prostate cancer–specific mortality. This benefit was not seen for patients categorized to have "favorable" intermediate-risk disease. Based on these data, NCCN guidelines support a short course of ADT for 4 to 6 months together with RT for patients with "unfavorable" intermediate-risk prostate cancer.

In contrast to intermediate risk disease, the addition of ADT to radiation in high-risk disease has been clearly demonstrated to improve OS in addition to prostate cancer–specific mortality. The optimal duration of ADT with EBRT for high-risk disease has been evaluated in several randomized, controlled trials.[44-48] Longer ADT courses resulted in improved long-term survival, with an optimal duration in the range of 18 to 24 months. Two studies showed superiority of prolonged ADT, whereas one showed comparable outcomes with medium-course versus prolonged ADT (although not powered as a noninferiority study). The recommended duration can be customized depending on patient tolerability and comorbidities.

For patients with very high-risk disease and those with regional lymph node involvement, the addition of an AR pathway inhibitor (such as abiraterone) to ADT for 2 years should be considered, based on data from the STAMPEDE protocol described below. This is endorsed by the NCCN guidelines. The role of adding docetaxel to ADT and RT in this setting has been evaluated in several clinical trials, but is not recommended as it has not shown a definitive OS benefit.[38,49,50]

- A meta-analysis of pooled data from two randomized controlled trials of the STAMPEDE protocol indicated metastasis-free survival (MFS) and OS benefit from the addition of 2 years of abiraterone to ADT and standard-of-care RT for men with newly diagnosed "high-risk" or relapsing with high-risk features non-metastatic prostate cancer.[51] Newly diagnosed high-risk non-metastatic prostate cancer was defined as node positive (Tx N1) or, if node negative, having at least two of the following: tumor stage T3 or T4, Gleason score of 8 to 10, and PSA concentration of 40 ng/mL or more. Notably, these are not the same as NCCN high-risk criteria but instead represent a particularly high-risk subset. The results of similar studies with second-generation AR antagonists are awaited.

REGIONAL RISK PROSTATE CANCER (CN1) (STAGE IVA)

Some aggressive local tumors may have already metastasized to pelvic lymph nodes at the time of diagnosis. These may be diagnosed clinically, by suspicious appearance on a CT scan, MRI, and/or PSMA PET/CT. The treatment of patients with positive lymph nodes found at the time of prostatectomy with lymph node dissection (ie, surprise positive lymph nodes) is discussed under the "Pathologic Node-Positive Disease" section of the chapter. Suspicious nodes located above the aortic bifurcation are considered outside of the pelvis and, therefore, are staged as M1 disease (stage IVB) rather than N1 (stage IVA).

Some nodes may be borderline. In this case, the clinician may choose to obtain a biopsy specimen for clarification. Alternatively, treatment with neoadjuvant ADT may be started before planned definitive RT. Then, if a repeated CT scan or MRI after approximately 3 months of ADT shows that any suspicious nodes have decreased in response to ADT, this strongly implies the presence of prostate cancer and may be treated as such. Finally, PSMA PET may be helpful, although, as noted, negative results do not rule out nodal involvement.

Men with clinical evidence of regional lymph node metastases (stage IVA) without distant metastases are not necessarily precluded from definitive (ie, curative-intent) therapy. Although no randomized trials have established the role of definitive local therapy in men with regional lymph node metastases, retrospective analyses[52] from the National Cancer Database,[53] the SEER database,[54] have suggested a survival benefit from definitive EBRT to prostate and pelvic nodes with ADT in men with clinical node-positive prostate cancer.

The meta-analysis of two randomized controlled trials of the STAMPEDE protocols, which included patients with TxcN1M0, showed the MFS and OS benefited from adding 2 years of abiraterone to ADT and standard-of-care EBRT and ADT.[55] Currently, the NCCN recommends EBRT plus ADT plus 2 years of abiraterone for regional lymph node-positive prostate cancer. Alternatively, prostatectomy and extended lymphadenectomy may be performed, but with a likely plan for adjuvant RT and ADT after surgery (trimodality therapy) for selected patients. The increased toxicity of trimodality therapy may only be justified if a patient has significant obstructive urinary symptoms that could actually be palliated by surgery.

KEY POINTS

- Patients with localized prostate cancer can be risk-stratified based on three clinical factors: T stage, Gleason score, and PSA level. Genomic testing of the cancer specimen may provide additional information about risk and progression, but this has not yet been prospectively validated for decision-making.
- Patients with low-risk disease may be offered active surveillance, which uses serial PSA measurements, DREs, and biopsy specimens to detect any presence of higher-risk disease, at which point definitive therapy can be offered. Sequential MRI may also be helpful. This strategy results in less treatment-associated morbidity and similar long-term cancer survival compared with immediate therapy.
- Patients with intermediate- or high-risk disease typically should receive definitive therapy, assuming a life expectancy of at least 5 (high risk) to 10 (intermediate risk) years (or if symptomatic). Definitive therapies include radical prostatectomy and RT. Long-term cancer survival is similar with either strategy, but adverse effect profiles differ.
- For patients who have intermediate- or high-risk disease undergoing RT, the addition of ADT improves biochemical disease-free survival (DFS) (intermediate risk) and OS (high risk). Duration is typically 4 to 6 months for unfavorable intermediate-risk disease and 18 to 24 months for high-risk disease.
- Patients with clinical evidence of pelvic lymph node involvement (cN1) are typically treated with definitive RT to the prostate and pelvis with long-course ADT. Although no randomized data exist, prostatectomy followed by adjuvant RT and ADT may also be an option.
- For patients who are very high-risk or regional risk (cN1) undergoing definitive EBRT and ADT, the addition of 2 years of abiraterone has been shown to improve MFS and OS.

PROSTATE CANCER TREATMENT MODALITIES

WATCHFUL WAITING AND ACTIVE SURVEILLANCE

Watchful waiting is a policy of no therapeutic intervention after a diagnosis has been established until symptomatic disease progression is evidenced by changes in symptoms, local tumor growth, or development of symptomatic metastases. In contrast with active surveillance, watchful waiting involves no monitoring of PSA levels or scheduled serial biopsies. Watchful waiting is most appropriate for men with limited life expectancy based on age and/or comorbid conditions. The approach evolved from studies of predominantly older men who had well-differentiated tumors in whom tumor progression occurred over a protracted time, and among whom, during the follow-up interval, a substantial proportion died as a result of illnesses unrelated to prostate cancer.

Active surveillance (with delayed intention to treat) is a recommended option for men with low-risk prostate cancer; no immediate treatment interventions are initiated in an effort to reduce overtreatment and the resulting adverse effects of therapy. These protocols include scheduled PSA testing, DREs, and periodic repeated prostate needle biopsies (or more recently, use of repeat multiparametric MRIs after the initial prostate biopsies). Most protocols require a repeated biopsy at 1 year to account for the sampling error of a 12-core biopsy. Treatment is offered if or when changes in Gleason score, volume of tumor, or serum PSA suggest increasing disease activity.

The largest randomized trial to evaluate immediate versus delayed primary therapy was the ProtecT trial, as referenced earlier, which randomized a population of mostly low-risk patients in the United Kingdom to active monitoring (no serial biopsies mandated, unlike AS), radical prostatectomy, or EBRT with or without ADT. Overall, there was no OS advantage to immediate definitive therapy, and there was an adverse effect of definitive therapies on several quality of life metrics. There was a slight increase in distant metastases. Importantly, some higher-risk patients who would not otherwise be offered AS by current guidelines were included, and approximately half of the active monitoring group eventually did receive primary therapy. Thus, this trial was not a study of doing "nothing" versus "something."

RADICAL PROSTATECTOMY

The goal of radical prostatectomy is to completely excise the cancer while maintaining urinary control and preserving potency. After the prostate has been removed, PSA should decline to undetectable levels; any detectable or increasing PSA levels after prostatectomy are an indication of recurrent or residual cancer. Cancer control is assessed by PSA relapse-free survival, time to objective progression (local or systemic), cancer–specific survival, and OS.

Robotic prostatectomy has become common, with a majority of procedures using robot-assisted laparoscopic prostatectomy rather than the historically more common open or laparoscopic radical prostatectomy. Despite initial enthusiasm and widespread acceptance of this technique by community and academic urological centers, few data exist to suggest improvements in oncological or functional outcomes when compared with the more traditional approaches. In fact, the skill of the operating surgeon in the surgeon's specific modality should be a major determinant in which approach is selected.

Management of Erectile Dysfunction

As discussed earlier, most men will experience erectile dysfunction after radical prostatectomy, even in settings where one neurovascular bundle is spared during surgery. Less frequent loss of erectile function may occur when both neurovascular bundles are spared. Methods for treating this include the use of PDE-5 inhibitors (eg, sildenafil and tadalafil), sometimes administered in the immediate postoperative period to help minimize penile shortening. Some experts advocate daily doses ("penile rehab") with increases in dosing before anticipated sexual activity, although data supporting this practice are limited. Use of vacuum pumps is often effective, but these must be judiciously used, especially in the immediate postoperative period, because disruption of the bladder neck–penile anastomosis can occur. Direct injections of alprostadil or insertion of drug pellets containing alprostadil into the penis or penile urethra may result in more effective erections. When regaining, erectile function is not achieved by these methods, patients may be considered for implantation of a penile prosthesis, of which several varieties are available, each with advantages and disadvantages. Patients will find it helpful to understand these potential options before surgery and set appropriate expectations, because this adverse effect is likely to occur and can be irreversible without intervention.

Management of Urinary Incontinence

Development of urinary incontinence after radical prostatectomy is an adverse effect that can more commonly result in patient-reported poorer quality of life and regret. Performing Kegel exercises of the pelvic floor muscles can speed recovery if routinely practiced. Most of the improvement after prostatectomy tends to happen within the first year, with typically no major changes after that point. After prostatectomy, many men use a male diaper to maintain their current lifestyle without being limited by incontinence. Surgical approaches to reduce incontinence should be considered when the difficulty tolerating symptoms is high, as a result of leakage itself or urinary odor, which can be particularly bothersome to patients. Procedures include bulbourethral sling surgery, which may have only modest and temporary effects, and the implantation of an artificial urinary sphincter, often more effective than a sling if the amount of urinary leakage is interfering with normal daily activities and is not controllable with diapers or pads, or is accompanied by urinary odor. As with erectile dysfunction, urinary incontinence must be recognized as a potential complication before surgery to ensure that patient expectations are aligned with possible outcomes.

RADIATION THERAPY

Radiation therapy can be administered using external-beam techniques, an implant of radioactive seeds, or a combination of the two. Contemporary EBRT incorporates three-dimensional conformal treatment planning with intensity modulation to maximize the administered dose to the tumor while minimizing the exposure of surrounding normal structures. These techniques allow for the safe administration of higher doses, which, in turn, have resulted in improved outcomes. Most EBRT protocols involve approximately 5 to 8 weeks of treatment, five times per week. Stereotactic radiosurgery (eg, CyberKnife) offers a more condensed schedule of only five treatments (hypofractionation) and otherwise seems comparable with standard EBRT.[56] Protons are heavier than the photons emitted by standard EBRT and, therefore, discharge their energy over a shorter distance, thereby limiting damage to surrounding normal tissue (ie, a narrow Bragg peak). In theory, this would optimize delivery of radiation to the tumor and prevent toxicity to nearby organs, but the technique has not improved clinical outcomes or quality of life[57] and is significantly more costly.

Radiation therapy administered to pelvic lymph nodes in addition to the prostate can be considered for patients with a substantial risk of lymph node involvement, although including nodes in the radiation field was not associated with superior outcomes in two randomized trials. For patients with radiographically evident lymph node involvement, the radiation field should include the pelvic lymph nodes and may still offer a chance of long-term disease control or, at a minimum, decreased chance of symptomatic local relapse.

The use of interstitial radiation or implantation of radioactive seeds, also known as brachytherapy, is typically used either as monotherapy for gland-confined, low- to intermediate-risk disease or as a boost together with EBRT for gland-confined, high-risk disease. An acute toxicity associated with implantation is irritative urinary symptoms, including urinary frequency. Long-term complications, including stricture and irritative symptoms, can be bothersome, especially in men who had symptoms of lower urinary tract symptoms before receiving treatment. Four prospective randomized trials have demonstrated that RT doses <70 Gy are inadequate for the curative treatment of clinically localized prostate cancer, and doses of 78 to 79 Gy provide improved cancer control. Studies that have evaluated the addition of ADT to RT (with or without a brachytherapy boost) suggest some improvements in local control and biochemical freedom from relapse.

Compared with surgery, RT is associated with a higher frequency of bowel complications, mainly loose stools and diarrhea, as well as irritative urinary symptoms, but lower rates of urinary incontinence and sexual dysfunction. Because urinary symptoms may worsen with RT, patients with significant baseline urinary obstructive symptoms may be better candidates for

prostatectomy; if they do undergo RT, symptoms can be improved with a combination of several months of neoadjuvant ADT, standard therapies such as α-blockers, and transurethral resection of the prostate in refractory cases.

Management of Proctitis

The development of rectal proctitis commonly occurs throughout the lifetime of patients who have had curative doses of radiation for prostate cancer. Proctitis can be accompanied by sporadic rectal bleeding, which can occur months to years after completion of RT and is often self-limited in duration. Increased dietary fiber or fiber supplements can help in mild, clinically suspected cases. Endoscopic findings include telangiectasias in the distal rectum that are often cauterized at the time of endoscopic examination using argon plasma coagulation. Administration of rectal suppositories containing steroids or mesalamine can also lessen the effects of proctitis. For refractory cases, hyperbaric oxygen or formalin injections can be used. Judicious evaluations of the distal rectal mucosa should be performed routinely, especially because a small but finite increase in the incidence of rectal cancers after RT has been observed.

Management of Radiation Cystitis

Cystitis can manifest as hematuria and/or dysuria. It can be diagnosed symptomatically and treated with nonsteroidal anti-inflammatories in mild cases; in more severe cases, a cystoscopy may be indicated. Intractable cases may respond to the use of hyperbaric oxygenation. Suspicion for urothelial cancer should be raised in the setting of persistent hematuria and urinary irritative symptoms, and cystoscopy and urine cytology should be strongly considered if these symptoms develop after the first few months to years after RT.

KEY POINTS

- Prostatectomy, RT, and ADT have unique adverse effect profiles. Prostatectomy can lead to urinary incontinence and erectile dysfunction, but it can help improve significant obstructive symptoms.
- Short-term side effects of RT include irritative urine and bowel symptoms. Radiation cystitis or proctitis may occur months to years after the completion of prostate RT. Endoscopic evaluation is warranted if the symptoms persist to rule out a second malignancy (eg, urothelial carcinoma) or telangiectasias.
- Patients with preexisting urinary symptoms should avoid brachytherapy and may experience symptomatic benefit from radical prostatectomy.
- There is little to no advantage to treatment with robotic prostatectomy versus other surgical approaches or to treatment with proton therapy versus conventional RT for clinically localized prostate cancer.

THERAPY FOR RECURRENT OR ADVANCED PROSTATE CANCER

PATHOLOGICAL NODE-POSITIVE DISEASE (PN1)

This section refers to a clinical scenario in which patients undergo radical prostatectomy and pelvic lymph node dissection for a localized prostate cancer and are found to have pathological nodal involvement (pN1) and undetectable PSA (<0.1 ng/mL) post-prostatectomy.

The risks of biochemical and radiographic recurrence are high for this group of patients. Adjuvant ADT is an option justified by a small multi-institutional randomized trial demonstrating improved OS and prostate cancer–specific survival in patients with positive lymph nodes at the time of prostatectomy and lymphadenectomy.[58,59] Unfortunately, this OS benefit of immediate over delayed ADT for pN1 patients could not be confirmed by another similar phase 3 study trial, EORTC 30846,[60] population-based study,[61] and meta-analysis.[62] In fact, the ASCO practice guideline in 2007 did not recommend immediate ADT for pathologically node-positive prostate cancer.[62] Adjuvant RT is often considered. However, only retrospective data are available on the use of adjuvant RT combined with ADT in such patients.[63-65] Alternatively, salvage EBRT with ADT at the time of biochemical recurrence (BCR) is an alternative option.

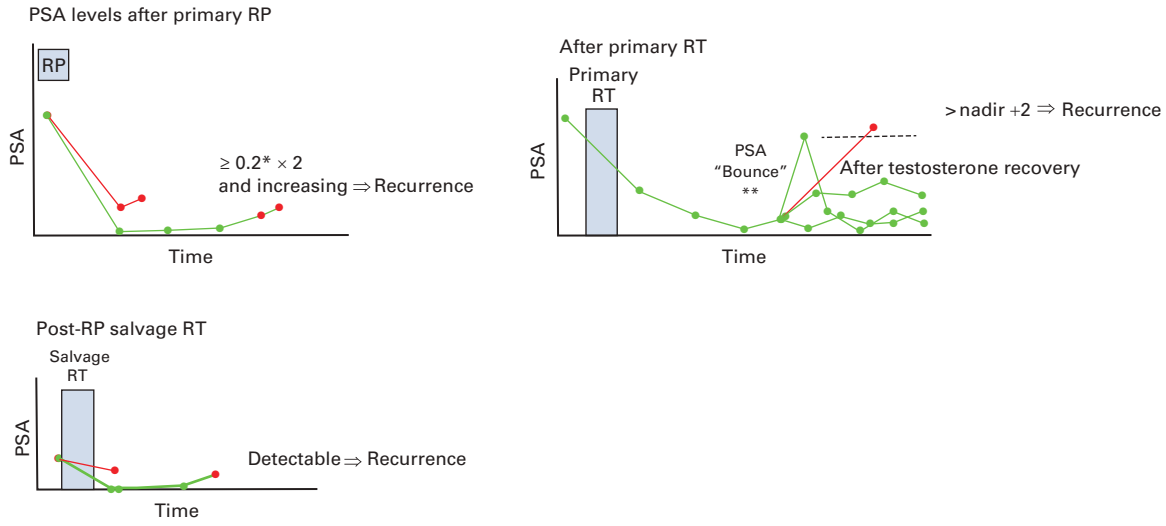
BIOCHEMICAL RECURRENCE

BCR refers to the disease status in which patients have rising PSA levels only without radiographic evidence of recurrence or metastatic disease after radical prostatectomy, RT, or both (Fig. 14-5). It does not refer to an increase in PSA level for patients in whom the disease is managed by watchful waiting. BCR is generally defined by the absence of metastases on conventional imaging (eg, CT scans and Tc99 bone scan) with either of the following:

- In patients who received primary radical prostatectomy (regardless of adjuvant or salvage RT), serum PSA 0.2 ng/mL or more, which is confirmed by a second determination (American Urological Association definition). Although a successful radical prostatectomy should remove the source of PSA from both the cancer and the normal prostate tissue, some patients may have a persistently detectable PSA <0.2 ng/mL, particularly when an ultrasensitive PSA immunoassay is used.

- In patients who received primary RT, a serum PSA level that has increased by 2 ng/dL above the nadir PSA value after RT (Phoenix criteria). Of note, PSA level may transiently increase after RT because of recovery of testosterone after ADT and/or the so-called "PSA bounce" that may be induced by prostate inflammation in the months after RT (18-24 months). Issues in management include whether the increasing PSA value represents local recurrence that could be eliminated with additional treatment to the prostate bed, metastatic disease, or both.

Figure 14-5 PSA Outcomes After Primary Therapies for Localized Prostate Cancer-Defining Biochemical Recurrence



Abbreviations: PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.
*Ultrasensitive PSA assays define biochemical recurrence as any measurable PSA value after radical prostatectomy.
**PSA "bounce" observed only in the absence of ADT.
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In most cases, an increasing PSA level represents micrometastatic disease that is not detectable on conventional imaging studies. The time to the development of metastases is highly variable. Prostate-specific antigen doubling time (PSADT), time to biochemical progression, and Gleason score can be used to prognosticate regarding time to development of metastases. PSADTs of <3 to 6 months are generally associated with development of metastases within months, whereas PSA doubling times of 1.5 to 2 years are generally associated with many years of MFS. Therefore, treatment is often targeted to those with the short PSA doubling times (<3-6 months), although it is not clear that these prognostic markers can be used to predict benefit from treatment versus surveillance (Figs. 14-6 and 14-7).

Figure 14-6 Management Options After Primary Therapy for Prostate Cancer

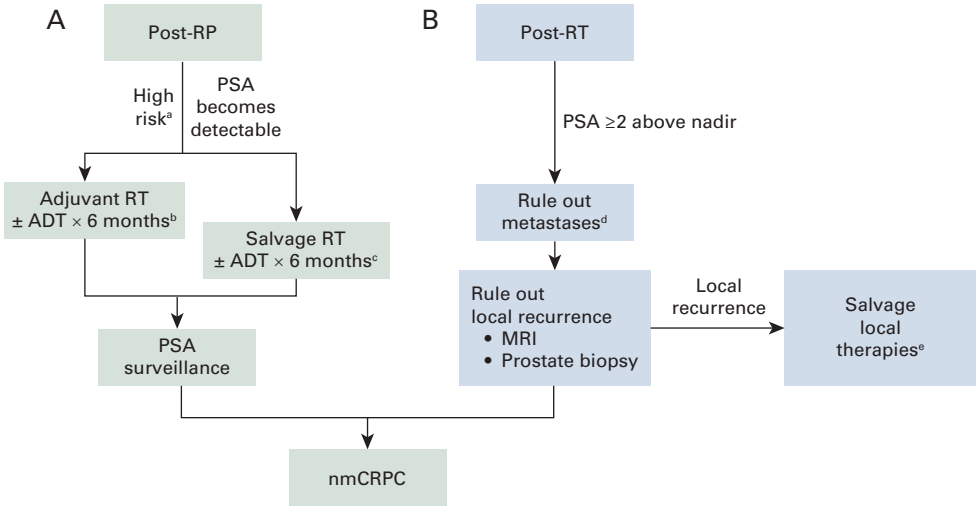

Figure 14-6 Continued

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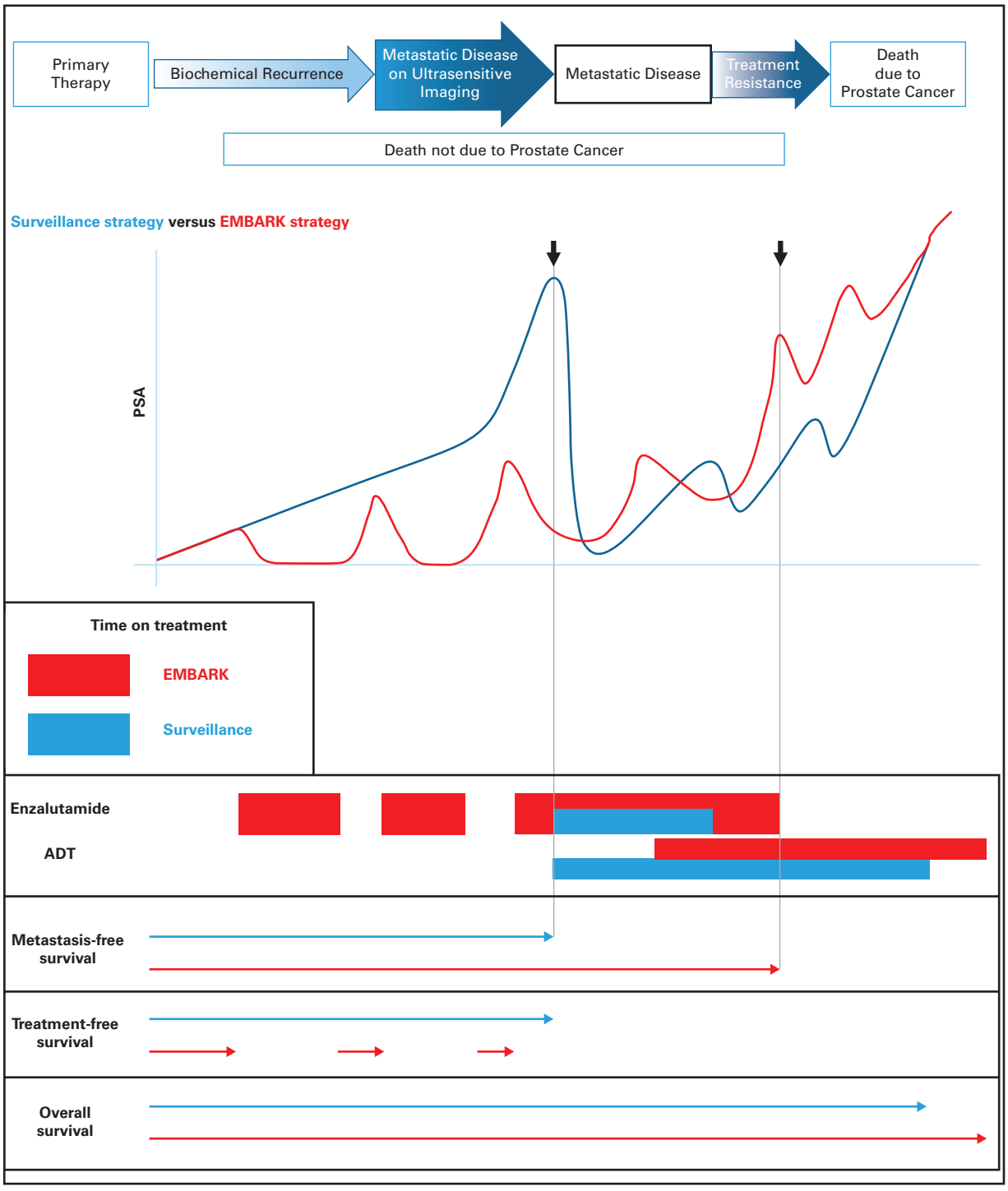


Panel (A) illustrates options following radical prostatectomy. Panel (B) illustrates options following radiation therapy. Panel (C) illustrates the hypothetical comparison of a surveillance strategy for biochemically recurrent prostate cancer to the EMBARK strategy with enzalutamide monotherapy. For options regarding recurrence after maximal local therapy, see Figure 14-7.

Abbreviations: ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mCSPC; metastatic castration-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiation therapy.

[a]High risk defined as pT3b or R1 (positive margin).

[b]Use and duration of ADT are variable; 6 months is common, but patients with low PSA may not benefit.

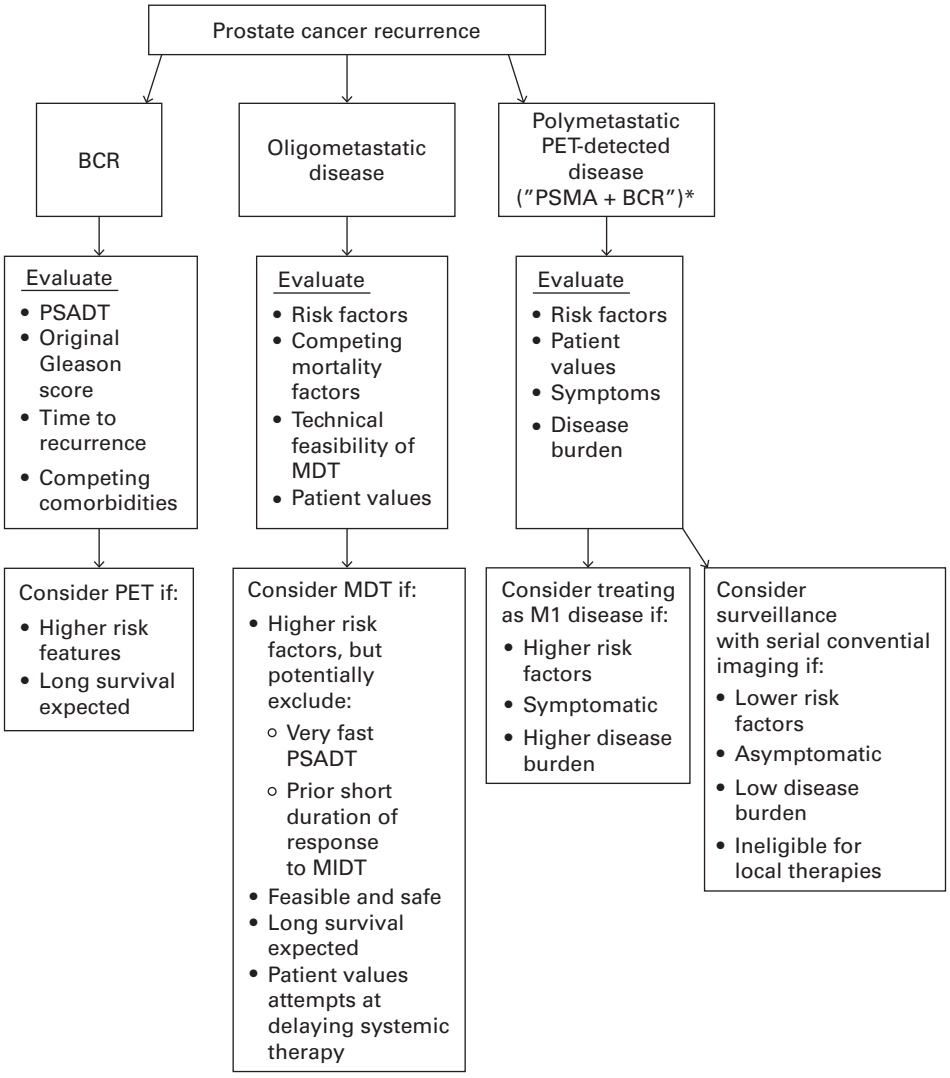
[c]Enzalutamide ± ADT. Previously, ADT, continuous or intermittent.

[d]Consider using ultrasensitive diagnostic imaging if available (eg, PET using PSMA tracers; eg, ^{68}Ga PSMA or ^{18}F[^{18}F] piflufolastat, ^{18}F fluciclovine, or ^{11}C choline); if not available, use conventional imaging modalities.

[e]Salvage local therapies may include brachytherapy, cryotherapy, radiofrequency ablation, high-intensity focused ultrasound, or salvage prostatectomy.

Panels (A, B) were created for ASCO. Copyright © 2026 by American Society of Clinical Oncology. Panel (C) was originally published in: David J. Einstein; Meredith M. Regan; Julia S. Stevens; David F. McDermott; Ravi A. Madan. JCO 2024 05-16. doi: 10.1200/JCO.24.00279

Figure 14-7 Recurrent Prostate Cancer After Maximal Local Therapy



Abbreviations: BCR, biochemical recurrence; MDT, metastasis-directed therapy; PET, positron emission tomography; PSADT, PSA doubling time.
*For discussion of "PSMA+BCR," see Einstein DJ, Abel ML, Aragon-Ching JB, et al. National Cancer Institute's Working Group on Biochemically Recurrent Prostate Cancer: clinical trial design considerations. *J Clin Oncol*. 2025;43(34):3672-3683. doi: 10.1200/jco-25-01693
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Role of Next-Generation Imaging in Evaluation of Patients With Biochemical Recurrence

In men with BCR considered for local salvage therapies, the most common treatment failure occurs with undetected metastatic disease. Therefore, detection of occult metastatic disease is critical and affects disease management in these patients. Historically, ^{99}T radionucleotide bone scan and CT scans have been considered conventional imaging studies to diagnose bone and pelvic metastases, respectively, despite their limited sensitivity at low levels of PSA <10 ng/mL.[66,67]

However, in recent years, newer imaging studies (eg, ^{68}Ga PSMA PET/CT, ^{18}F fluciclovine, or ^{11}C choline PET/CT) have significantly improved the sensitivity to detect recurrent disease at lower PSA levels. The rate of detection using these novel tracers depends on the PSA level and the type of tracer. A review of the literature showed the average rates of detection with ^{68}Ga PSMA PET/CT were 51.5%, 74%, and 90.5% of patients with PSA levels of <1.0, 1.0 to 2.0, and >2.0 ng/mL, respectively. The average rates of detection with fluciclovine PET/CT were 38%, 74%, and 78% of patients with PSA levels of <1.0, 1.0 to 2.0, and >2.0 ng/mL, respectively. The rates of detection with ^{11}C choline were somewhat lower: 19.5%, 44.5%, and 76% of patients with PSA levels of <1.0, 1.0 to 2.0, and >2.0 ng/mL, respectively.[68]

As noted, PSMA PET/CT may increasingly be used as part of the staging of high-risk localized prostate cancer and perhaps for unfavorable intermediate risk. For patients who have early BCR post-prostatectomy, who are increasingly offered early salvage radiation at PSAs around 0.2 ng/mL, the yield of PSMA PET/CT imaging is typically low. However, for a patient with PSA

persistence post-prostatectomy who did not undergo initial staging PSMA PET/CT or for a patient presenting for salvage radiation evaluation at higher PSAs, PSMA PET/CT may help guide the radiation treatment field and intensification of both radiation doses and potentially systemic therapy.

PSMA PET/CT restaging should generally not be performed in patients with rising PSA after primary radiation until PSA reaches 2.0 ng/mL above nadir, the Phoenix criterion. However, patients who have high initial risk and rapidly rising PSAs may be considered for PSMA PET/CT if there is a consistent, rapid rise across multiple checks.

PSMA PET/CT may have false positives, especially noted with benign rib lesions and some other malignancies, such as renal cell carcinoma and salivary gland tumors. Whether to confirm findings with biopsy depends on the overall level of suspicion and how closely any findings mirror the typical pattern of prostate cancer spread.[69]

PROSTATE CANCER: LOCAL FAILURE

ADJUVANT AND SALVAGE RADIATION THERAPY

- Adjuvant RT to the prostatic bed is considered for patients with certain high-risk features at the time of radical prostatectomy, especially pathologically positive lymph nodes.
- Salvage RT is similar but refers to RT at the time of PSA recurrence (BCR) after prostatectomy, thus limiting RT to only those patients with definitive evidence of recurrence.

Three randomized trials comparing immediate (adjuvant) versus early salvage RT indicated that early salvage is likely equally effective in the represented patient populations (ie, excluding node-positive patients). In practice, some physicians might choose to use adjuvant RT (while PSA undetectable) for very high-risk pathology (eg, seminal vesicle involvement or positive lymph nodes) and use early salvage RT (when PSA becomes detectable and rising or PSA >0.1 ng/mL in more ambiguous cases (eg, high Gleason score, EPE, or positive margins) to avoid the risk of overtreatment. Early salvage RT at low PSA levels seems to be superior to later RT at higher PSA levels. Importantly, salvage RT should not be delayed until there are positive findings on PSMA PET/CT, as this is not fully sensitive for lymph node involvement. Salvage RT may increase prostate cancer–specific survival, but one study suggested the benefit was limited to men with a PSA doubling time of <6 months.

The role of hormone therapy with RT in the salvage or adjuvant setting has also been studied by several multicenter international cooperative group randomized phase 3 studies:

- RTOG 9601: 24 months of high-dose bicalutamide (150 mg orally daily) provided an OS benefit relative to placebo but with increased cardiac toxicity and gynecomastia.[63]
  - No benefit was seen in patients who had a PSA <0.6 ng/mL, as is common in modern practice with early salvage RT.
  - An ancillary study suggested that a high score on the Decipher test, a 22-gene expression assay developed to estimate the risk of distant metastasis and prostate cancer–specific mortality post-radical prostatectomy, was associated with the benefit of ADT even in the low-PSA subgroup. This association is being prospectively validated with more modern systemic therapies.
- GETUG-AFU16, an open-label study, showed 6 months of ADT with GnRH agonist added to salvage RT improved 10-year PFS rate from 49% to 64% (hazard ratio [HR], 0.54; 95% CI, 0.43-0.68, $P < .0001$), but because this endpoint included PSA progression as "progression," this may have been artificially prolonged by the comparison of PSA-lowering ADT versus no ADT. There was no effect on the 12-year OS rate.[63]
- SPPORT is another multicenter trial that showed PFS benefit with 4 to 6 months of ADT and extending the RT field to pelvic lymph node RT compared with salvage RT only to the prostate bed.[70] It did not specifically parse out whether nodal RT without ADT would have been equally effective.
- RADICALS-HD evaluated the optimal duration of the ADT for postoperative RT, either immediate or salvage.[69] Patients were offered randomization to either (1) 6 versus 0 months of ADT or (2) 24 versus 6 months of ADT. Patients randomized within the first comparison had more favorable characteristics, and there was no difference found between short-course versus no ADT. Within the second comparison, long-course ADT had prolonged MFS versus short-course ADT. Thus, patients with higher risk factors (eg, pT3b/4) could be considered for longer-course ADT, but this study raises further questions about which patients even benefit from any ADT.

There are also questions about whether to intensify hormone therapy. An abstract from the FORMULA-509 phase 2 study suggested an MFS benefit with the addition of ARPIs in patients with higher PSAs, although not in the entire study population or in patients with other high-risk features. The STAMPEDE M0 cohort study testing the addition of abiraterone to ADT, in theory, included salvage RT patients, but few such patients were actually enrolled.

In summary, a course of ADT (4-6 months) should be considered in most patients receiving salvage RT. The RADICALS-HD study suggests that certain patients may not benefit from ADT and could be omitted in some patients (eg, older age with higher

toxicity risk, Gleason score 7 or lower, no T3/T4 disease, low PSA with long PSADT). This and other studies also suggest that intensification of ADT by prolonging the duration or adding an AR pathway inhibitor could be beneficial for patients with the highest risk features.

SALVAGE PROSTATECTOMY

Patients treated initially with RT may be considered for salvage prostatectomy if they were surgical candidates at the time of diagnosis, have a life expectancy of more than 10 years, and have no metastatic disease. Biopsy-specimen confirmation of persistent disease in the gland and no evidence of spread are essential before surgery is considered. Despite refinements in case selection, incontinence rates remain high, and virtually all patients are impotent after the procedure. Salvage treatments, including cryotherapy and brachytherapy for post-RT recurrent prostate cancer, may be considered for select patients. MRI is most useful for detecting recurrence in the prostate after RT, and a confirmatory diagnosis is then made via prostate biopsy specimen. Of note, biopsies should not be done for several months after RT because the effect of radiation is prolonged, and residual cancer cells may persist at these earlier time points.

SYSTEMIC THERAPY FOR BIOCHEMICALLY RECURRENT PROSTATE CANCER

Once local therapies have been exhausted, the two approaches to persistent BCR are surveillance or systemic (noncurative intent) therapy. Notably, BCR has a highly heterogeneous natural history. Initial Gleason score, time to recurrence, and especially PSADT are prognostic factors, but they do not necessarily predict who will most benefit from intervention versus surveillance.

Although PSA level almost always declines in response to hormone therapy, the clinical benefit in this setting is still unclear. One trial attempted to answer this question by randomly assigning patients who had BCR (as well as those ineligible for curative treatment because of age, comorbidities, or locally advanced disease) to early ADT at the time of BCR versus delayed ADT at the time of metastatic disease.[65] Although OS was improved with early ADT in the entire cohort, there was no OS benefit in the BCR-only group. In addition, the trial was under-enrolled, with too few events to allow definitive conclusions. NCCN guidelines currently recommend observation as the preferred management of non-metastatic castration-naive disease (ie, BCR), but with ADT as another option. Therefore, the decision of when to start ADT for BCR is a difficult one and must factor in patient preferences in the absence of clear evidence-based guidelines.

Historically, intermittent androgen suppression (for 8 months in each cycle, restarting ADT when PSA is >10 ng/mL) has often been used if a decision is made for systemic therapy. Randomized trials suggested this was a reasonable alternative to continuous androgen suppression, but only in the setting of non-metastatic disease. The goal is to minimize the adverse effects of chronic ADT, including hot flashes, loss of libido, bone loss, and muscle atrophy, but it is not clear to what extent this strategy, in fact, does improve patients' quality of life overall.

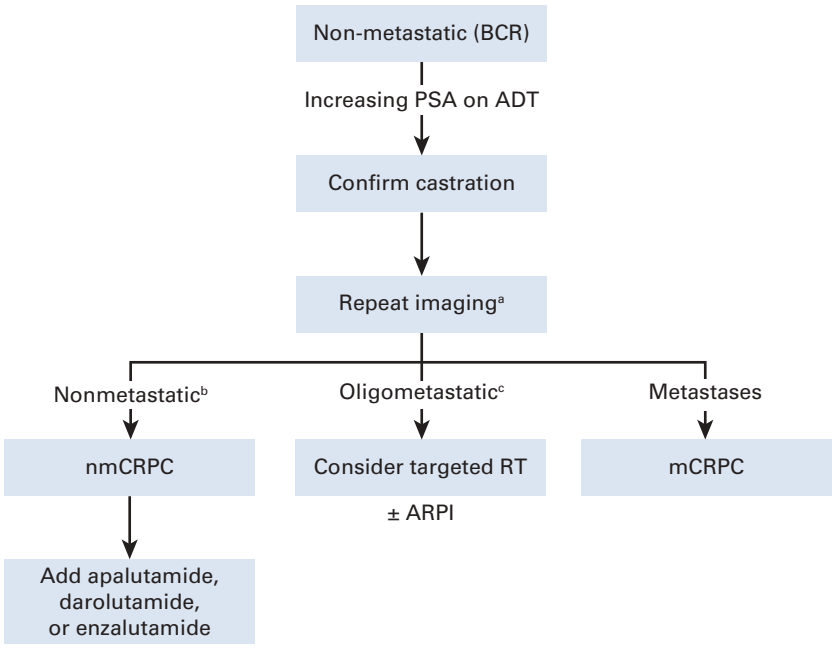
More recently, the EMBARK study randomized patients with BCR and PSADT <9 months as well as absolute PSA >1.0 ng/mL post-prostatectomy or more than 2.0 ng/mL above nadir post-primary RT to receive ADT only, enzalutamide only, or the combination.[66] A one-time treatment break was built into the protocol on all arms. Both enzalutamide alone and with ADT showed superior MFS (and a recent update showing improved OS) compared with ADT alone, resulting in FDA approval. Combination treatment had the largest MFS benefit. Nonetheless, the benefit of delaying metastases must be weighed against the alternative of starting delayed intensive hormone therapy at the first sign of radiographic recurrence (not tested in the study), and/or using oligometastasis-directed therapies; this is an individualized decision based on patient preferences. Importantly, all arms had high rates of toxicity and treatment discontinuation because of toxicity. Enzalutamide monotherapy may help avoid ADT side effects, but with increased rates of gynecomastia due to increased testosterone, which is converted to estrogen; this effect can be mitigated with prophylactic breast radiation or low-dose tamoxifen if symptoms develop. In addition, the study was conducted before the widespread availability of PSMA PET/CT, and many of the included patients would have been expected to have some degree of metastatic disease visible on ultrasensitive imaging, although the natural history of PET-detected disease may not be equivalent to that of conventional metastatic disease.

NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

If patients are started on ADT for BCR, some will go on to develop non-metastatic CRPC (nmCRPC), meaning increasing PSA levels despite castration-level testosterone values but without overt radiographic evidence of metastases by conventional bone scan and CT imaging (Fig. 14-8). Several randomized trials have demonstrated that the addition of second-generation AR antagonists in this setting delays the onset of radiographic metastatic disease (MFS) and OS compared with ongoing ADT alone.[71-73] The FDA approved enzalutamide, apalutamide, and darolutamide for patients who have nmCRPC with a PSA doubling time of 10 months or fewer. The novel endpoint of MFS had been established to be a strong surrogate of OS in localized prostate cancer.[74]

However, as previously discussed, it is not yet clear that starting men on early ADT and then proceeding to one of these agents before the development of metastatic disease will prolong survival relative to starting ADT (and additional therapies) only at the time of metastatic disease. The potential benefit needs to be weighed against toxicity for these non-metastatic patients who have

Figure 14-8 Treatment Options for nmCRPC



Abbreviations: ADT; androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BCR, biochemical recurrence; mCRPC, metastatic castration-resistant prostate cancer; NGI, next-generation imaging; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; RT, radiation therapy.
[a]Consensus from the ASCO Expert Panel is that NGI may be considered only if a change in clinical care is contemplated. Assuming patients have received or are ineligible for local salvage treatment options, NGI may clarify the presence or absence of metastatic disease, but the data on the detection capabilities of NGI in this setting and its impact on management are limited.
[b]In nmCRPC studies, patients were included who had pelvic lymph nodes up to 2 cm in diameter.
[c]Oligometastatic disease is variably defined as one to five metastases.
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no disease-related symptoms. Apalutamide was associated with an increased risk of rash, hypothyroidism, and fracture; enzalutamide was associated with an increased risk of hypertension, myocardial infarction, fatigue, falls, and fractures; darolutamide was associated with an increased risk of fatigue.

However, patient-reported outcomes were mostly similar in these trials between the active treatment and placebo arms. In addition, these drugs carry high financial costs (to patients, insurers, and society). In addition, the proper interpretation of these studies is complicated by the inclusion of node-positive (<20 mm by short axis) patients in the ARAMIS (darolutamide, 17% vs placebo, 29%) and SPARTAN (apalutamide, 16.5% vs placebo, 16.2%) studies, whereas the PROSPER study allowed node positivity only if the lymph node was <15 mm by short axis and below aortic bifurcation, and as in the discussion of EMBARK, many included patients would have been expected to have more widespread disease visible by ultrasensitive imaging. Indeed, one study demonstrated that, in 200 patients with nmCRPC who would have been eligible for ARAMIS, PROSPER, and SPARTAN, 96% had detectable disease on PSMA PET.[75]

ROLE OF LOCAL THERAPY OUTSIDE THE PROSTATE FOR BIOCHEMICAL RECURRENCE

Patients with BCR at some point may develop oligometastatic recurrence, in which case local therapies such as targeted RT, cryoablation, or radiofrequency ablation may be used to delay the need for systemic therapy (Fig. 14-8). This strategy was demonstrated to delay the need for ADT in a randomized trial[76] although more objective measures and survival data are needed. In conjunction with this approach, more sensitive imaging modalities have been developed to detect oligometastatic disease earlier in the disease course. PSMA PET/CT may be particularly helpful for detecting early oligometastatic recurrences.

KEY POINTS

- Detectable PSA (>0.2 ng/mL) after radical prostatectomy or an increase in PSA concentration by 2 ng/mL or more above PSA nadir after RT is an indicator of recurrent prostate cancer. In the absence of evidence of metastatic disease on standard bone scan and CT imaging, this is termed BCR.

- Salvage RT may be used for patients who experience BCR after radical prostatectomy, typically combined with 6 months of ADT. Conversely, salvage prostatectomy is less commonly performed after primary RT because of high rates of urinary incontinence and impotence. Other local salvage therapies may be possible.
- The optimal timing of systemic therapy for BCR is unclear. ADT will lower PSA level in this setting and delay time to metastatic disease, but its effect on OS relative to ADT at the time of metastatic disease is unknown.
- Patients with BCR who are treated with ADT and whose PSA levels increase without evidence of metastases on standard bone scan and CT imaging have disease that has progressed to nmCRPC. The addition of the second-generation AR antagonist apalutamide, darolutamide, or enzalutamide prolongs MFS and OS in this setting.

PRESENTING CASE STUDY 1

A 70-year-old man is referred to your clinic for management of a rising PSA level following primary therapy. Five years ago, he underwent a radical prostatectomy, with pathology showing Gleason 4+3 disease confined to the prostate, with negative margins. Three years later, his PSA level rose again, prompting salvage radiation to the prostate fossa and pelvic lymph nodes along with 6 months of androgen deprivation therapy (ADT). Now, 2 years later, his PSA level has risen from undetectable while on ADT to 0.1 ng/mL after testosterone recovery, with the most recent values increasing from 0.2 ng/mL to 0.4 ng/mL to 0.8 ng/mL over the course of 16 months.

How would you assess this patient's risk of recurrent prostate cancer?

This patient is experiencing biochemical recurrence (BCR), given that his PSA level is detectable after prostatectomy (regardless of salvage radiation) and is rising with a doubling time (PSADT) of 7 months. However, the natural history of BCR is heterogeneous, and before recommending any diagnostic or therapeutic steps, it is important to first factor in patient life expectancy and comorbidities, as well as BCR prognostic details: time to recurrence, original Gleason score, and PSADT. Nomograms can be helpful for comparing the estimated time to metastases given these BCR prognostic details versus patient life expectancy.

This patient has intermediate prognostic factors for BCR. His time to initial recurrence and original Gleason score are favorable, and his current PSADT is intermediate. The MSKCC nomogram[77] would estimate an approximate 10-year risk of death from prostate cancer of 33%. Patients with a very long time to recurrence, slow PSADT (approximately >1 year), or limited life expectancy may not benefit from early use of ultrasensitive restaging imaging and most likely do not benefit from systemic therapy.

For patients in whom initial restaging seems reasonable, a prostate-specific membrane antigen (PSMA) PET scan is an option to identify oligometastatic and/or pelvic recurrence. MRI of the prostate can also be useful for local restaging in patients who did not undergo prostatectomy, especially if there are suspicious findings revealed by PET scan.

PSMA PET shows a rib lesion, SUVmax 2, without a CT correlate, and no other findings.

How do you interpret this finding?

False-positive rib findings are common with PSMA PET, especially if they are isolated, low avidity, and have no sclerotic correlate on CT. Typically, these can simply be followed.

One should initiate a nuanced discussion on surveillance versus systemic therapy. Overall, this patient's long-term prognosis is likely to be very good regardless of intervention. Systemic therapy could include enzalutamide with or without ADT as per the EMBARK trial.[78] However, the benefit in delay of metastases (and possibly a small increase in overall survival) needs to be weighed against the increased time on treatment and associated toxicity.

The patient opts for surveillance. After a subsequent PSA level rise to 2.0 ng/mL, a PSMA PET shows two aorto-caval PSMA-avid lymph nodes (SUVmax 20), both measuring <1 cm.

How do you approach this scenario?

An important consideration is to recalculate PSADT. PET findings do not always require action, especially if other prognostic factors (especially PSADT) are favorable. For a patient who wishes to defer systemic therapy until metastases, serial imaging with conventional imaging can help determine the optimal timing of treatment initiation.

The two very suspicious lesions support a diagnosis of oligometastatic recurrence. Per the STOMP and ORIOLE phase 2 trials,[79] metastasis-directed therapy (MDT) can also be considered in the hopes of delaying the need for systemic therapy. Risks of MDT can include damage to adjacent structures, such as the bowel.

The patient opts for stereotactic body radiation (SBRT) as MDT to these two areas. Do you recommend hormonal therapy along with MDT?

This is unclear. The RADIOSA phase 2 trial suggested a progression-free survival benefit with the addition of 6 months of ADT to MDT, but post hoc analysis showed that this was primarily attributable to the known suppressive effects of ADT, without any clear synergistic increase in the effect of radiation.[80]

The patient receives SBRT alone with good effect, but PSA subsequently rises about a year later. After a period of surveillance, PSMA PET at PSA 5 ng/mL (PSADT 1 year) shows widespread PSMA-avid lymph nodes, all measuring <1 cm. What do you recommend?

While it can be tempting to start intensive lifelong hormonal therapy when PSMA PET reports describe multiple sites of "metastatic" disease, one must remember that such disease is not necessarily equivalent to metastatic disease defined by conventional imaging; it can be labeled "PSMA+ BCR".[81] Those with favorable BCR prognostic factors can sometimes be monitored with conventional imaging until the latter shows evidence of metastases.

METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

ADT FOR METASTATIC PROSTATE CANCER

ADT (ie, castration therapy) is the backbone of systemic therapy for metastatic prostate cancer. It is now the standard of care to incorporate an AR pathway inhibitor (eg, abiraterone, apalutamide, enzalutamide, darolutamide) together with ADT for the treatment of metastatic prostate cancer, as they have clearly demonstrated significant benefits in PFS, time to castration resistance, time to skeletal events, and OS. The use of an AR pathway inhibitor in this setting remains inconsistent across the United States, so the benefits of these inhibitors should be emphasized.

The critical role of androgens in prostate cancer growth was established by Huggins and Hodges in the 1940s. Their findings led to the development of ADT as the treatment of advanced prostate cancer. ADT is palliative and results in PSA decline or objective tumor responses in more than 90% of patients with advanced prostate cancer. Thus, this disease status is termed metastatic "hormone-sensitive" or "castration-sensitive" prostate cancer.

Despite this almost universal initial response, the duration of response to ADT is highly variable and depends on various clinical and biological factors. Generally speaking, the median time to castration resistance or PSA progression on ADT monotherapy is about 7 to 12 months.[82-84] Almost all patients with metastatic castration-sensitive prostate cancer (mCSPC) experience treatment resistance as evidenced by rising PSAs or radiographic progression despite a castrated level of testosterone (lower than 50 ng/dL), that is, mCRPC. Despite resistance to castration therapy, treatments that target androgen biosynthesis or AR confer additional clinical benefit, indicating an androgen-dependent biology of CRPC. This benefit is a part of the reason ADT remains the backbone of systemic therapy and should be kept continuously, even if patients develop castration resistance.

There are two forms of ADT: surgical and medical castration. The goal is to keep the testosterone level below 50 ng/dL. Surgical castration can be achieved by bilateral orchiectomy. Medical castration can be achieved by either luteinizing hormone-releasing hormone (LHRH) agonist (eg, leuprolide and goserelin) or LHRH antagonist (eg, degarelix and relugolix).

Medical or surgical castration is associated with significant side effects: impotence, loss of libido, weakness, fatigue, hot flashes, loss of muscle mass, anemia, depression, cardiovascular toxicity, and loss of bone over time. Resistance and aerobic exercises can improve muscle mass, strength, and physical function. There have been conflicting data regarding the risk of dementia in patients with prostate cancer who are receiving ADT. Prolonged castration can result in osteoporosis or osteopenia; thus, monitoring with dual-energy X-ray absorptiometry (DEXA) scans can be used to screen for osteopenia or osteoporosis (see "Supportive Care for Metastatic Castration-Sensitive Prostate Cancer" section below). Response to ADT can be measured by a decline in PSA values, a decrease in the size of nodal or visceral metastases, and improvement in cancer-related symptoms. Overall, 60% to 70% of patients with abnormal PSA levels will have normalization of the value to <4 ng/mL after castration, 30% to 50% of measurable tumor masses will regress by 50% or more, and approximately 60% of patients will have palliation of symptoms. Serial bone scans will show improvement in only 30% to 40% of patients, and a scintigraphic flare on serial bone scans can occur after ADT between 3 and 6 months after initiation of therapy; this flare should not be confused with progression of skeletal metastases. The PSA value measured at 7 months after initiating therapy is prognostic, with dramatically shorter median survival for patients with a PSA concentration >4 ng/mL and dramatically longer median survival for those with a PSA concentration <0.2 ng/mL at this point.[85]

Treatment with an LHRH agonist initially increases serum testosterone level for up to a few weeks after treatment initiation, although the clinical relevance of this is debatable. Because of this, an AR antagonist (eg, bicalutamide 50 mg daily) is sometimes used concurrently to block potential effects of the testosterone surge, especially if a patient has high-risk metastatic lesions (eg, imminent spinal cord compression or urinary obstruction). Alternatively, an LHRH antagonist or surgical castration could be used to avoid testosterone flare.

An AR antagonist as monotherapy is not a standard-of-care choice for systemic treatment of metastatic prostate cancer, but they can be used in patients who decline or do not tolerate castration therapy or in patients who are significantly debilitated and have other life-limiting comorbidities.

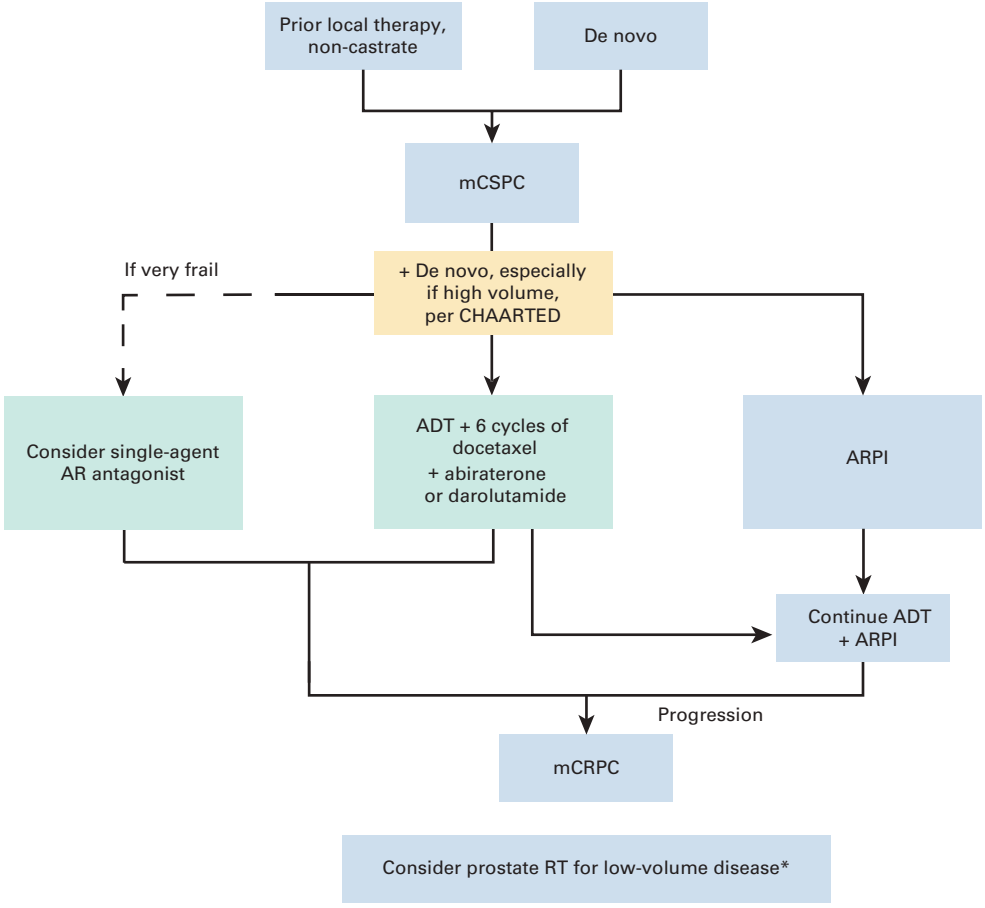
SECONDARY THERAPIES FOR mCSPC

Building on the backbone of ADT as a systemic therapy for advanced prostate cancer, several clinical trials examined intensification of systemic therapy for mCSPC by adding a secondary therapy to improve the clinical outcomes and OS. Examples include docetaxel chemotherapy and AR synthesis/pathway inhibitors such as abiraterone, apalutamide, enzalutamide, and darolutamide. There are other new agents under clinical development.

DOCETAXEL FOR mCSPC

Two randomized controlled trials, CHAARTED and STAMPEDE, showed improvement in OS with the addition of docetaxel to ADT backbone. With these data, docetaxel/ADT became one of the standards of care for mCSPC.

Figure 14-9 Standards of Care for mCSPC by Disease Volume



High volume is defined as the presence of ≥4 bone metastases with one or more lesions in the extra-axial skeleton or the presence of visceral metastasis. Abiraterone is always administered with prednisone.

Abbreviations: ADT, androgen deprivation therapy; AR, androgen receptor; ARPI, androgen receptor pathway inhibitor; mCRPC, metastatic castration-resistant prostate cancer; mCSPC; metastatic castration-sensitive prostate cancer; RT, radiation therapy.

*Supported by a prespecified subgroup analysis from STAMPEDE, but the comparison arm was ADT alone. Efficacy in the setting of intensified therapy (ADT and docetaxel or ARPI) is unknown.

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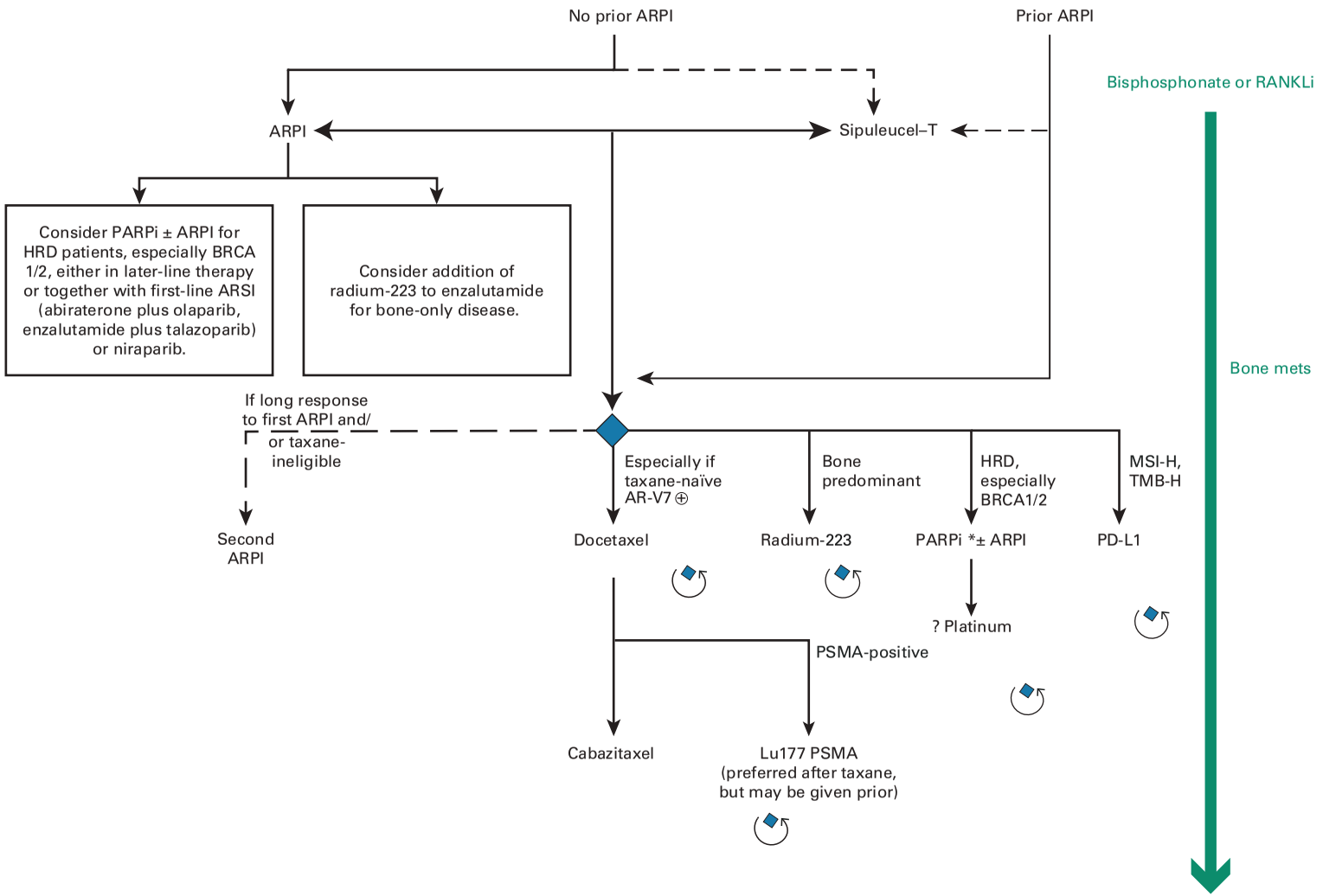
Figure 14-10 Treatment Options for mCRPC



Abiraterone is always administered with prednisone.
Abbreviations: ARPI, androgen receptor pathway inhibitor; HRD, homologous recombination deficiency; mCRPC, metastatic castration-resistant prostate cancer; MSI-H, high microsatellite instability; PARPi, poly ADP-ribose polymerase inhibitor; PSMA, prostate-specific membrane antigen; TMB-H, high tumor mutational burden.
*Consider PARPi ± ARPI for HRD patients, especially BRCA1/2, either in later-line therapy or together with first-line ARSI (abiraterone plus olaparib, enzalutamide plus talazoparib) or niraparib.
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- The subgroup analyses of the CHAARTED study by extent or "volume" of metastatic disease (high vs low) as determined by CT and bone scans showed that the benefit of docetaxel is most clear in patients with high-volume metastatic disease, which was defined as the presence of four or more bone metastases with at least one outside the axial skeleton (ie, skull, ribs, or extremities) or presence of visceral metastases.
- Similar benefits were not seen in the CHAARTED trial in patients with low-volume metastatic disease, even with longer follow-up or in the prior GETUG study.
- By contrast, the stratified subgroup analysis of the primary results from STAMPEDE by tumor volume did not show a difference in benefit between high and low metastatic burden subgroups for OS or failure-free survival,[72] using the CHAARTED definition.

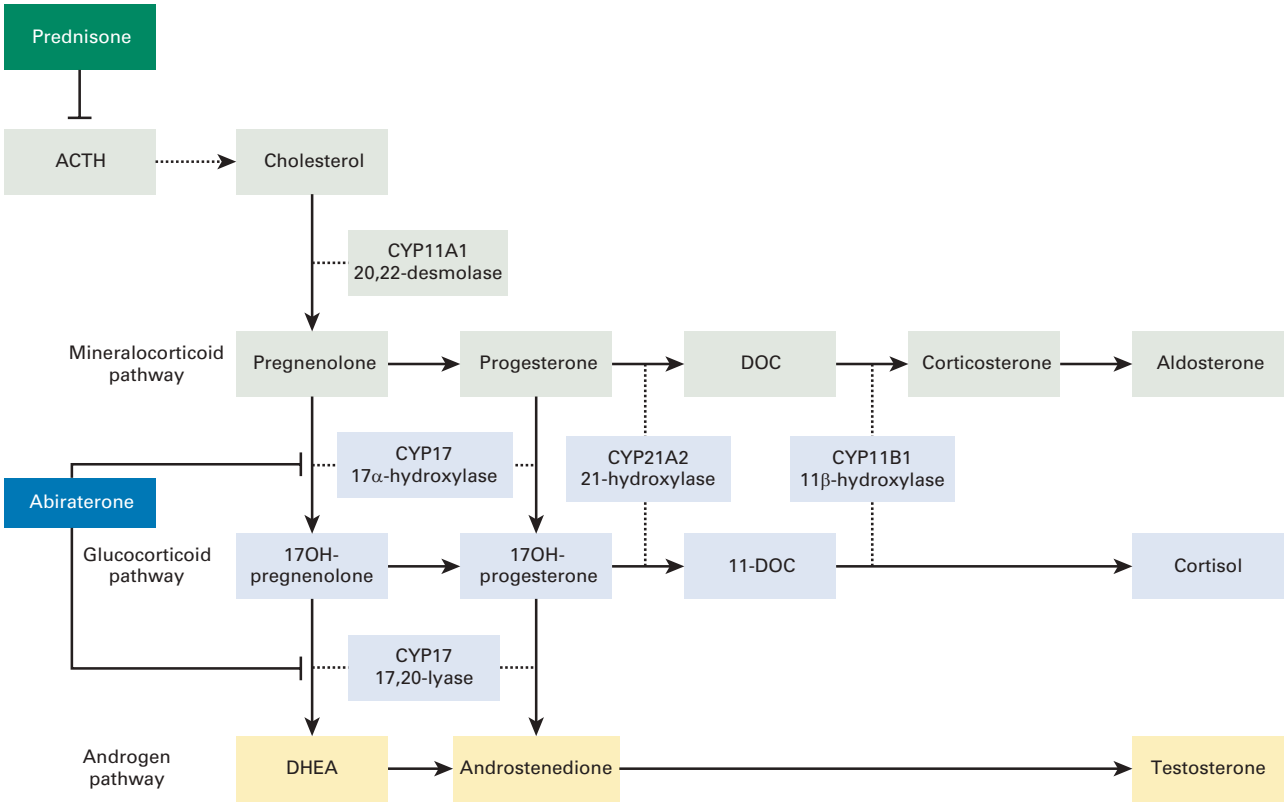
How can these differing results be reconciled? One major difference between the two trials was the relative percentage of patients with recurrent versus de novo metastatic disease. Recurrent metastatic disease may carry a better prognosis. A substantial proportion (approximately 16%) of patients with low-volume metastases in the CHAARTED trial had recurrent disease, versus a few (approximately 5%) patients in the STAMPEDE trial. Therefore, the potential benefit of docetaxel in low-volume disease may be limited to those with de novo low-volume disease, not recurrent low-volume disease (Figs. 14-9 and 14-10).

Febrile neutropenia can occur with docetaxel, although routine primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was left to the investigator discretion in clinical trials. Docetaxel is considered an intermediate-risk regimen, so by NCCN guidelines, patients with additional risk factors (eg, prior chemotherapy, persistent neutropenia, bone marrow involvement by tumor, liver or renal dysfunction, and older age) could be considered for primary prophylaxis. Docetaxel can also cause edema that is refractory to diuresis; this effect is prevented with steroid prophylaxis. In the CHAARTED trial, quality of life decreased during docetaxel treatment but was similar or better in patients treated with ADT alone at later points.

TRIPLET THERAPY FOR mCSPC

Building on this new backbone of ADT/docetaxel, two studies addressed the question of whether the addition of ARPI would result in further improvements. Notably, no trial has addressed the question of whether docetaxel is beneficial when added to

Figure 14-11 Biochemical Pathways Resulting From Abiraterone Administration and Prednisone



Administration of prednisone prevents a compensatory ACTH surge and thus decreases downstream symptoms of excess mineralocorticoid production (eg, hypertension, hypokalemia, and edema).
Abbreviations: ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone.
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an ADT/ARPI backbone, as is modern practice. Thus, in the absence of randomized data addressing this issue, the question of whether to use triplet therapy (including taxane) or ADT and ARPI is guided by older data reviewed earlier. The PEACE-1 study, a multicenter European study, examined the benefit of adding abiraterone and/or local RT to the prostate with a 2 × 2 study design (Fig. 14-11).[86] The mechanism of action for abiraterone is discussed under the "Abiraterone for mCSPC" section. The study showed that abiraterone added to ADT/docetaxel significantly improves median radiographic PFS in men with mCSPC by 2.5 years.[86] The PFS benefit of abiraterone added to ADT with docetaxel was seen in both high- and low-burden metastatic disease. The results from OS analyses also showed that the addition of abiraterone resulted in an 18% reduction in the risk of death and an improvement in median OS by 1 year in the overall population, as well as in the ADT with docetaxel cohort. The OS benefit was clearly seen in the subgroup with the high metastatic disease burden. However, the OS data were immature for the low-burden subgroup. The role of triple therapy in mCSPC is being established.

Darolutamide is a potent AR antagonist that first showed efficacy in patients with nmCRPC. The ARASENS study evaluated the efficacy of adding darolutamide in an international placebo-controlled randomized phase 3 trial with OS as a primary endpoint. In this trial involving 1,306 men, darolutamide lowered the risk of death by 32.5% compared with placebo in patients receiving ADT and docetaxel, with a similar incidence of serious adverse events in the two treatment groups. The patients had to be appropriate candidates for docetaxel and ADT based on the judgment of the investigators. The baseline characteristics indicated 3% of patients had M1a disease (distant lymph node only), 79.4% had M1b (bone metastases with or without lymph node metastases), and 17.5% had M1c (visceral metastases with or without lymph node or bone metastases) at screening. Importantly, a significant majority of patients in this study were diagnosed with high-risk (LATITUDE criteria) or high-volume (CHAARTED criteria) and de novo metastatic disease. Within this trial, there was a suggestion of benefit with the addition of darolutamide regardless of volume or risk status at diagnosis, but as discussed, the benefit of docetaxel in low-volume or low-risk disease is less clear.[87] Darolutamide was approved by the FDA in combination with docetaxel for patients with mCSPC in August 2022 and is an option for patients with mCSPC and deemed appropriate candidates for docetaxel.[1] The ARANOTE trial, discussed further below, led to an approval for darolutamide in mCSPC with ADT but without docetaxel.[1]

ABIRATERONE FOR mCSPC

Abiraterone acetate is an oral CYP17 (17α hydroxylase and 17,20 lyase) inhibitor that inhibits androgen and glucocorticoid biosynthesis. Feedback loops during treatment result in adrenocorticotropic hormone-mediated excess mineralocorticoid activity, including hypertension, fluid retention, and hypokalemia. Low-dose prednisone (starting at 5 mg daily) is administered concurrently to prevent this. Potassium level, blood pressure, and liver function should be monitored during treatment. Hepatotoxicity is managed with dose holds and resumption at lower dose levels. Hypertension may be treated with standard antihypertensive mineralocorticoid receptor antagonists such as eplerenone if standard agents are ineffective. Cardiac symptoms should be monitored in patients with preexisting cardiovascular disease.

After the publication of trials demonstrating the efficacy of adding docetaxel to ADT for first-line treatment of mCSPC, two other studies, LATITUDE and STAMPEDE-G, demonstrated an improvement in OS with the addition of abiraterone and prednisone to ADT for mCSPC. The LATITUDE study included only patients with de novo mCSPC with high-risk features as defined by having two or three of the following: visceral disease, at least three bone metastases, and a Gleason score of 8 or

Table 14-1 Randomized Trials of ADT Plus Abiraterone and Prednisone for mCSPC

Trial	No. of Participants	Study Population	Design	Outcome	Notes
LATITUDE	1,199	De novo high-risk mCSPC	ADT plus placebo vs ADT plus abiraterone and prednisone	Improved OS with the addition of abiraterone and prednisone (53.3 vs 36.5 months)[89]	High risk based on 2 of 3: Gleason 8+, 3 + bone lesions, visceral metastases
STAMPEDE	1,917	High-risk localized or high-risk BCR or mCSPC (recurrent or de novo)	ADT plus placebo vs ADT plus abiraterone and prednisone (plus RT for localized or N + disease)	Improved 3-year OS with the addition of abiraterone and prednisone (83% vs 76%)	Benefit was seen across subsets, including M0 tumors, although there were few events in this group

Abbreviations: ADT, androgen deprivation therapy; BCR, biochemical recurrence; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; RT, radiation therapy.

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higher (Table 14-1). After a median follow-up of 51.8 months, the LATITUDE study showed an improvement of median OS by 16.8 months (53.3 vs 36.5 months) with an HR of 0.65. The STAMPEDE-G study similarly showed an improvement of 5-year survival rate from 41% to 60% with an HR of 0.60.[88]

At the time of PSA progression on abiraterone, one study suggested that switching from prednisone to dexamethasone could produce durable PSA responses.[88]

ARPIs FOR mCSPC

Multiple trials have demonstrated benefits with the addition of the ARPIs enzalutamide, apalutamide, and darolutamide to ADT for treatment of mCSPC (Table 14-2). On the basis of these studies, apalutamide, enzalutamide, and darolutamide all have received FDA approval for use in mCSPC treatment. In addition, some of these trials were the first to evaluate intensification of AR-directed therapy together with docetaxel, although none were specifically designed to answer the question of whether docetaxel and ARPI are more effective than either alone or in combination with ADT.

Table 14-2 Randomized Trials of ADT Plus Androgen Receptor Pathway Inhibitors for mCSPC

Trial	No. of Participants	Study Population	Design	Outcome	Notes
ARANOTE[1]	669	mCSPC (recurrent or de novo)	ADT + placebo vs ADT + darolutamide	Improved radiographic PFS with the addition of darolutamide (not reached vs 25 months)	rPFS benefit seen regardless of disease volume. OS data immature
ARCHES	1,150	mCSPC (recurrent or de novo)	ADT versus ADT plus enzalutamide. Docetaxel is allowed at the investigator's discretion in either trial arm	Improved radiographic PFS with addition of enzalutamide (not reached vs 19 months)	rPFS benefit seen regardless of docetaxel use and/or disease volume. OS data immature
ENZAMET	1,125	mCSPC (recurrent or de novo)	ADT versus ADT plus enzalutamide. Docetaxel is allowed at the investigator's discretion in either trial arm	Improved OS with the addition of enzalutamide (median OS not yet estimable; 80% versus 72% OS at 3 years)	Possibly limited benefit of enzalutamide in docetaxel-treated patients. Possible increased docetaxel toxicity with the addition of enzalutamide
TITAN	1,052	mCSPC (recurrent or de novo)	ADT versus ADT plus apalutamide. Docetaxel is allowed at the investigator's discretion in either trial arm	Improved OS and radiographic PFS with apalutamide (82% vs 74% OS; 68% vs 48% rPFS)	rPFS benefit seen regardless of docetaxel use and/or disease volume. Possibly limited OS benefit of apalutamide in docetaxel-treated patients

Abbreviations: ADT, androgen deprivation therapy; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; PFS, progression-free survival; rPFS, radiography progression-free survival; RT, radiation therapy.

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SELECTING AN AR SIGNALING PATHWAY INHIBITOR FOR mCSPC

There are no high-quality randomized studies comparing the efficacy of these ARPIs in the first-line mCSPC setting. When selecting an ARPI in combination with ADT for treatment of mCSPC, the first decision point should be if the patient would benefit from the addition of docetaxel for upfront "triplet therapy" treatment, as described in the sections above and below. If so, then darolutamide (see ARASENS study) or abiraterone (see STAMPEDE and PEACE-1 studies) should be considered. If the patient is

not a candidate for or would decline docetaxel chemotherapy, then all ARPIs would be potential options as a pair with ADT, and selection can be made based on administration, monitoring, side effect profile, drug interaction risk, and patient preferences.

Enzalutamide, apalutamide, and abiraterone are all once-daily medications. Darolutamide is taken twice daily. Apalutamide offers a "single pill once daily" option that can be dispersed in water for patients unable to swallow tablets whole. Enzalutamide and apalutamide are very similar in chemical structure and carry similar risks of fatigue, hypertension, falls, and rarely, seizures. Both have the potential to cause rash, but apalutamide has a greater risk for rash as well as thyroid disease. Non-randomized post-marketing studies have suggested slightly different rates of these side effects. Importantly, enzalutamide and apalutamide are significant CYP3A4 inducers and can result in significant drug-drug interactions with medications metabolized via this pathway (eg, direct oral anticoagulants, statins, fentanyl).

Darolutamide, in comparison, has been associated with lower rates of fatigue and seizures as its chemical structure leads to less penetration into the central nervous system (CNS). Darolutamide is a much weaker CYP3A4 inducer compared to enzalutamide and apalutamide, and thus may be a preferred option for patients with significant drug-drug interaction risk. Data on OS in the ARANOTE study, which led to its FDA approval in this setting, remain immature.

Abiraterone is associated with generally lower rates of fatigue, drug-drug interaction, and seizures compared to the alternative ARPIs above. It does carry the risks of liver function test elevation and mineralocorticoid excess (eg, hypertension, hypokalemia, edema) requiring concomitant low-dose prednisone use, with frequent lab and blood pressure monitoring as previously described. These cardiac side effects make abiraterone a less preferred option for those with significant cardiovascular disease. In addition, preliminary data from a recent meta-analysis suggested no OS benefit with abiraterone added to ADT in patients aged 75 and older, so it may be a less preferred option in this patient population.[90]

EMERGING CLINICAL QUESTIONS

Although it is encouraging to see further improvement of OS with intensification of the systemic therapy for mCSPC, the role of docetaxel in this triple regimen remains unknown. We know that ADT + docetaxel is superior to ADT alone, especially for high-volume mCSPC. We also know ADT + ARPI is superior to ADT alone. However, we do not know if docetaxel or an ARPI is superior as a secondary therapy. Only limited data are available comparing docetaxel with ARPI from the multi-arm STAMPEDE study. Because the study was neither designed nor powered to make a comparison between these two arms, there was no discernible difference in OS between the docetaxel cohort (n = 5,189) and abiraterone cohort (n = 5,377) of the multi-arm STAMPEDE trial.[91] Although we know the "triplet" of ADT + docetaxel + abiraterone or darolutamide is superior to ADT + docetaxel, we do not know whether the "triplet" regimen is indeed superior to ADT + ARPI or whether ADT + ARPI is just as good or not inferior to the triplet regimen. The role of docetaxel in this triple regimen is yet to be examined. Numerous translational biomarker studies are ongoing in efforts to improve patient selection for the "triplet" therapy regimen.

A key takeaway, as emphasized throughout the chapter, is that all patients with mCSPC should be treated with ADT and an ARPI. That is, a standard of care for a high-volume mCSPC patient includes ADT + abiraterone or darolutamide or apalutamide or enzalutamide with or without the addition of docetaxel. The standard of care for low-volume mCSPC is ADT + abiraterone or darolutamide or apalutamide or enzalutamide, with consideration of radiation therapy to the prostate. For older, frail patients at high risk for toxicity, ARPI monotherapy can be considered, but ADT + ARPI (with consideration of an initial dose reduction of the ARPI) should be considered for all.

PROSTATE-DIRECTED THERAPY FOR METASTATIC PROSTATE CANCER

Historically, the presence of metastatic disease excluded consideration for radical prostatectomy or definitive prostate RT. However, interest in prostate-directed therapy is growing even in the setting of metastatic disease. Some reports have described long-term remissions using prostate-directed therapy with targeted RT and ADT for oligometastatic prostate cancer. The definition of oligometastatic disease is likely to evolve as increasingly sensitive imaging techniques are used in this setting, and this disease state is defined by a different number of metastatic sites in different studies (see "Biochemical Recurrence" section). The HORRAD and STAMPEDE trials assessed the efficacy of prostate RT in more diffuse metastatic disease treated with ADT alone.[82,92] Neither trial demonstrated an increase in OS in the population overall, but there was an increase in OS in patients with low-volume disease (per the CHAARTED criteria) in STAMPEDE in a preplanned subgroup analysis. Therefore, there may be a role for definitive prostate RT in the setting of low-volume mCSPC. Additional data from the PEACE-1 study demonstrated an increase in OS for certain patients with high-volume disease as well, perhaps relating to patients with highly symptomatic bulky primary tumors.[93] Ongoing studies are evaluating whether patients with mCSPC should undergo treatment of the primary tumor with surgery or RT and whether treatment with docetaxel, abiraterone, or other systemic therapies or metastasis-directed RT will improve survival.

SUPPORTIVE CARE FOR mCSPC

Cardiovascular Health

As described in localized prostate cancer, long-course (or lifelong, in the case of most metastatic disease) ADT has been associated with cardiovascular (CV) risks and metabolic syndrome in patients for whom cardiovascular disease and metabolic syndrome

are already prevalent. The addition of any ARPI raises the risk of CV disease compared to ADT alone. The oral GnRH antagonist relugolix may decrease major adverse cardiovascular events compared with GnRH agonists (small event rate in a secondary endpoint of the HERO trial), though a similar agent (degarelix) was not clearly superior to GnRH agonists in another trial designed to look primarily at cardiovascular health (although this finding may also have been a result of under-enrollment and decreased power) in the context of aggressive management of baseline cardiovascular risk factors. Thus, relugolix is a consideration, particularly in patients with prior major cardiovascular events, but, as described, aggressive management of baseline risk factors is probably most critical. Surgical castration may also be considered, and it is quite cost-effective and entails fewer injections and less financial toxicity for patients; although surgical castration is often not preferred by patients, testicular implants can decrease the cosmetic effects.

It is most important that oncologists work closely with primary care physicians to ensure that baseline risk factors are well managed and that regular surveillance for the emergence of new cardiovascular conditions and metabolic syndrome is performed. A cancer diagnosis may provide a psychological cue to patients to begin regular health management if this had not previously occurred; importantly, oncologists can tell patients that this is "worth it," because even patients with metastatic disease may have a life expectancy of many years, during which cardiovascular health can certainly become a source of morbidity and mortality. For such patients, the increased frequency of oncology visits can also provide opportunities for blood pressure checks, hemoglobin A1c measurements, assessment of medication adherence, even with nononcological medications, etc.

Bone Health

Many years of ADT with possible intensification and concomitant prednisone may pose a threat to bone health, particularly in patients with baseline osteopenia/osteoporosis or risk factors for these (eg, excessive alcohol use, smoking, prior prednisone use). DEXA scans can be used at baseline and over time to screen for the development of osteopenia and osteoporosis, although there are no high-quality data to guide who should be screened or how frequently. NCCN guidelines recommend using the National Osteoporosis Foundation guidelines for screening and treatment in the general population but also mention a recommendation from the International Society for Clinical Densitometry to obtain DEXA scans at baseline and after 1 year of ADT.[94] Again, there are no high-level data to guide treatment recommendations in this population, but the Fracture Risk Assessment Tool (FRAX) score can be used with ADT, which would be considered secondary osteoporosis in this algorithm.

In practice, some clinicians might obtain a baseline bone mineral density scan at the start of long-term ADT (typically in conjunction with primary RT for high-risk localized or regional disease), especially for patients aged 70 years or older and those with additional risk factors for osteoporosis, and repeat this scan after 1 year of ADT. Any patient who had a FRAX score justifying treatment would then be treated unless testosterone recovery was imminent. FRAX score is calculated with several clinical factors and estimates the 10-year probability of fracture.[95]

Interestingly, two randomized trials of early use of zoledronic acid in the setting of mCSPC failed to show an improvement in skeletal-related events or OS, raising the hypothesis that hormone therapy was so effective for cancer control that antiresorptive therapy could not improve on this. However, there may be a role for antiresorptive therapy for the prevention of fragility fractures, especially in those with baseline or treatment-induced osteopenia/osteoporosis, and this is the subject of active research. There are no data to support using denosumab for mCSPC unless there is concomitant osteopenia/osteoporosis warranting antiresorptive therapy with the Prolia formulation (as opposed to the Xgeva formulation used for mCRPC). Denosumab has only been compared with zoledronic acid in the mCRPC setting. In addition, denosumab carries higher financial toxicity and may have a risk of increased bone turnover if discontinued, an important consideration for patients with mCSPC who may be receiving long-term therapy and may choose to hold therapy intermittently.

Sexual Health

Unfortunately, most men with metastatic disease will require lifelong ADT or, at a minimum, long periods on ADT. ADT almost always removes any libido (the "spark") present at baseline, and therefore, interventions for erectile dysfunction (the "machinery") are typically ineffective (PDE5 inhibitors) or unhelpful (intracorporeal injections, penile prostheses). Moreover, there may be lingering effects of prior local therapies on erectile function. Single-agent AR antagonist therapy preserves testosterone and libido but is not the standard of care for metastatic disease. When treating with standard ADT-based therapy, counseling is needed regarding the expectation for minimal libido. Thus, patients should be encouraged to be open about their concerns with their sexual partners and may explore alternative forms of intimacy that do not require sexual intercourse. Sexual health counselors and support groups can be very helpful in helping discuss these issues and reducing stigma.

Mental Health

A diagnosis of cancer is always life-changing. Use of ADT may further contribute to depression and other mood disturbances. Although patients with mCSPC should be reassured that their disease can be controlled for many years, most will have their lives shortened considerably by this illness. Oncology social workers, psychiatrists, and support groups can be very helpful in

managing the emotional difficulties that come along with this journey. Early involvement of palliative care—concurrently with cancer-directed care—is also recommended, although it is unclear whether this is best done at diagnosis or at the time of more resistant disease and is likely dependent on individual patients' needs. The effects of sexual health discussed earlier can be quite impactful on mental health and relationships. Financial toxicity and concerns about the ability to perform work functions can also play into mental health and should be addressed. In sum, it is important for oncologists counseling patients with mCSPC to simultaneously emphasize that this diagnosis is a serious and likely life-limiting one, but also one that can be managed as a chronic illness for many years.

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

The treatment of patients with a disease that progresses during ADT requires documentation that the patient is medically castrated (defined as a serum testosterone level <50 ng/dL). Despite castration resistance, castration is continued during all subsequent therapies because this decreases the availability of AR ligand and possibly direct antagonism of tumor LHRH receptors. Despite the development of mCRPC, AR signaling continues to play a major role in many prostate cancers. Mechanisms leading to persistent AR activation despite castrate testosterone levels include AR overexpression, ligand-independent activation, de novo synthesis of intratumoral androgens, and alterations in the AR, including splice variants and circulating subcastrate levels of androgens.

Multiple classes of therapy that improve OS are available in mCRPC, including immunotherapy (sipuleucel-T), taxane chemotherapy (docetaxel, cabazitaxel), radiopharmaceuticals (radium-223, lutetium-617), and AR signaling inhibitors. All of the ARPIs described in the mCSPC sections above first demonstrated their efficacy through improvements in survival in the castration-resistant setting. This second generation of ARPIs, as described in the mCSPC section above, includes abiraterone acetate, enzalutamide, apalutamide, and darolutamide. These agents have replaced the use of first-generation antiandrogens such as flutamide, nilutamide, bicalutamide, and ketoconazole.

For patients who have previously received primary localized therapy and present with overt symptomatic metastatic disease (after PSA and radiological progression) at the time of initiating ADT, characterization of the anatomic location and symptoms is important. The presence of new-onset back pain should raise concern for possible spinal cord or cauda equina disease, and if clinically indicated, an MRI of the spine should be performed. In approximately 10% to 15% of patients, the disease will relapse with aggressive local or distant metastases. In circumstances in which the PSA level seems to be disproportionately low for the tumor burden present or the presence of visceral metastases, a repeated biopsy of a metastatic site may indicate a neuroendocrine or small-cell phenotype. PSMA PET imaging remains a mainstay imaging modality in this setting.

ARPIs FOR mCRPC

The ARPIs abiraterone, enzalutamide, apalutamide, and darolutamide remain effective even after the onset of castration resistance. Abiraterone and enzalutamide are the two ARPIs that carry an FDA approval for use in mCRPC, as mentioned below. Enzalutamide, apalutamide, and darolutamide are also approved for use in nmCRPC, as described in the sections above.

Abiraterone acetate was FDA approved in 2011 for men with mCRPC after docetaxel treatment based on OS benefit relative to placebo. It was subsequently FDA approved in 2012 as a treatment before docetaxel therapy based on improved OS.

As discussed under abiraterone mCSPC, abiraterone acetate shuts down androgen and glucocorticoid biosynthesis by inhibiting CYP17 (17α hydroxylase and 17,20 lyase) (Fig. 14-16). Feedback loops during treatment result in adrenocorticotropic hormone-mediated excess mineralocorticoid activity, including hypertension, fluid retention, and hypokalemia, and low-dose prednisone is administered concurrently to prevent this. The FDA label includes directions to administer concurrent prednisone at 5 mg twice daily in the setting of castration-resistant disease but only 5 mg daily in the setting of castration-sensitive disease, which was studied later than mCRPC. However, given the potential adverse effects of higher-dose steroids, another off-label option is to start treatment in mCRPC at 5 mg daily (as in mCSPC) and then increase to twice daily if adrenocorticotropic hormone-mediated adverse effects develop.

Abiraterone is taken on an empty stomach because fatty food may increase absorption. Food effects on abiraterone were investigated in a randomized phase 2 noninferiority study comparing 1,000 mg of abiraterone per day after an overnight fast versus 250 mg per day after a low-fat meal in 75 patients with mCRPC.[83] The primary endpoint was a log change in PSA as a pharmacodynamic biomarker for efficacy, with second endpoints of PSA response (≥50%) and PFS. The study investigators found that there was a greater effect on PSA in the low-fat meal arm with a mean log change of −1.59 compared with the overnight fast arm with a mean log change of −1.19. The PSA response rate was 58% in the low-fat meal arm and 50% in the overnight fast arm, and the median PFS was 9 months in both arms. No difference was seen in PSA response or PFS despite higher abiraterone concentrations noted in the overnight fast arm. Taken together, the noninferiority of low-dose abiraterone (250 mg per day with a low-fat meal) to standard dosing was established with respect to PSA metrics. From a financial toxicity perspective, this alternative dosing may be considered for those who cannot afford the cost of the standard dose, though studies confirming this approach using validated endpoints such as MFS or OS are currently lacking.

Enzalutamide was FDA approved in 2012 for the treatment of mCRPC after docetaxel treatment and in 2014 for use in patients with mCRPC before docetaxel treatment. As ARPIs are increasingly used in the castrate-sensitive setting, the role of ARPIs in the castrate-resistant setting is becoming less clear. Although abiraterone and enzalutamide have changed the landscape for the management of CRPC, approximately 15% to 25% of patients have primary resistance and a high degree of cross-resistance. Starting with abiraterone and then administering enzalutamide is associated with a better time to PSA progression with second-line therapy than enzalutamide followed by abiraterone, but OS is similar between the two sequences.[84]

It must be noted that there is limited efficacy of a switch to an alternative ARPI after progression on a prior ARPI. Given an increasing number of superior alternative agents, the strategy of an "ARPI switch" in mCRPC should generally be discouraged except in certain clinical scenarios (eg, patients who have had long prior responses, have clinically indolent disease, or are ineligible for alternative therapies). Commercially available assays can be used to look for the presence of an AR splice variant (AR-v7) and inform a choice between ARPI switch (which is particularly unlikely to help in patients with detectable AR-v7) versus taxane chemotherapy, but these assays are seldom used in current practice.

As a primarily historical note, treatment-induced AR mutations could result in first-generation AR antagonists acting instead as partial agonists; thus, in the setting of PSA progression on bicalutamide, withdrawal of bicalutamide could result in a PSA decrease in a subset of patients, typically temporary. This is very infrequent with second-generation AR antagonists.

CHEMOTHERAPY FOR mCRPC

In 2004, two randomized trials were reported that compared docetaxel-based therapy with mitoxantrone and prednisone in patients with mCRPC. A significant improvement in OS was demonstrated for patients who received docetaxel, with a median survival of >18 months. Docetaxel was also superior to mitoxantrone with respect to pain response rate, PSA response rate, and quality of life indices. Based on these study results, the FDA approved the use of docetaxel (75 mg/m^2 every 21 days) together with prednisone as frontline therapy for men with mCRPC.

Cabazitaxel is a microtubule-stabilizing taxane that was FDA approved after prior docetaxel therapy based on the results of a phase 3 trial in patients who had received treatment with docetaxel and demonstrated improved OS with cabazitaxel (25 mg/m^2) versus mitoxantrone. Grade 3 to 4 neutropenic fever was the major serious toxicity in patients who received cabazitaxel, and primary prophylaxis with G-CSF should be administered routinely for patients using standard dosing. A subsequent study demonstrated that cabazitaxel at 20 mg/m^2 is noninferior in terms of survival and is less toxic.[95] In the third-line setting, the CARD trial demonstrated that cabazitaxel resulted in improved OS versus a second ARPI for patients who had mCRPC previously treated with docetaxel and a first ARPI.[85] It is important to note that progression within 12 months of first ARPI therapy was required for eligibility, so this trial may have selected for the so-called worst actors, and results may not be generalizable to patients with longer responses to hormone therapy.

Mitoxantrone and other regimens that have demonstrated activity in mCRPC may be beneficial as possible additional therapies for patients with good performance status if they have used all other available treatment options and cannot enroll in a clinical trial.

In patients with small-cell histologies, platinum-containing chemotherapy combination regimens such as cisplatin or carboplatin with etoposide or carboplatin with taxane (cabazitaxel or docetaxel) are recommended. ADT should be continued during the treatment of small-cell carcinoma because of intratumoral and intertumoral heterogeneity.

PARP INHIBITORS FOR mCRPC

The DNA-repair pathway has emerged as a validated target for cancer therapy. Although a critical defect in this DNA-repair pathway allows mutagenesis and eventually cancer development, some of these defects present themselves as targets for cancer therapy. For example, tumors with defective HRR caused by deleterious mutations in the *BRCA2* gene can be exquisitely sensitive to inhibition of PARP, a critical enzyme in initiating repair machineries for single-strand DNA breaks. PARP inhibition leads to the accumulation of single-strand DNA breaks, stalling and disrupting the replication fork, and leading to double-strand DNA breaks. Cancer cells with deleterious *BRCA2* mutations cannot repair double-strand DNA breaks via the HRR pathway.

PARP inhibitors have demonstrated their efficacy in tumors harboring somatic or germline deleterious mutations in *BRCA1* or *BRCA2* or other HRR-related genes. For patients with mCRPC, both olaparib and rucaparib received FDA approval in May 2020. The approval of olaparib was based on the results from the PROfound study, a phase 3 trial comparing olaparib versus second-line ARPI (switching to abiraterone or enzalutamide after progression on the other ARPI) in patients with mCRPC harboring deleterious mutations in any of 15 prespecified HRR-related genes. The study showed that olaparib resulted in radiographic PFS and OS in the primary analysis cohort consisting of *BRCA1*, *BRCA2*, and *ATM* alterations and in the secondary analysis cohort, which combined the primary cohort mutations with 12 other HRR gene alterations.[96] This resulted in FDA approval for olaparib in this setting (except those with *PPP2R2A* alteration). However, there are some caveats:

- Although benefits were demonstrated in the combined analysis of patients with the 14 prespecified HRR alterations, the benefit of olaparib over a second-line ARPI was most clear in patients with a *BRCA2* alteration. Exploratory analyses by individual HRR gene subgroup were limited by small sample size (eg, fewer than five cases of *BARD1*, *BRIP1*, *CHEK1*, and

RAD51D mutations). Even for groups with a sizable number of mutation cases (eg, *ATM*, *CDK12*, and *CHEK2*), the benefit seemed underwhelming. It is unclear whether patients with these mutations would still benefit from olaparib over taxane-based chemotherapy, which is an option for those who experience progression after the first-line ARPI.

Similarly, the FDA granted accelerated approval to rucaparib in patients with mCRPC after prior ARPI and taxane-based therapy on the overall response rate (ORR) of 44% seen in the TRITON2 single-arm study of patients with *BRCA*-altered mCRPC.[97] TRITON3 is currently evaluating the efficacy of rucaparib in men with mCRPC with *BRCA1*, *BRCA2*, or *ATM* alteration against chemotherapy.

The addition of platinum chemotherapy to docetaxel may also be effective in patients with alterations in DNA-repair genes because their tumors are less able to repair the platinum-induced double-strand breaks. It is hoped that ongoing research will clarify biomarkers of response to either PARP inhibition or platinum therapy (Fig. 14-13).

PARP INHIBITOR–BASED COMBINATION

Given the encouraging results from PARP inhibitor trials in prostate cancer, several combination approaches have been examined. The PROPEL study, a double-blinded phase 3 study of abiraterone and olaparib versus abiraterone and placebo in patients with mCRPC in the first-line setting, showed abiraterone combined with olaparib improved imaging-based PFS by 8.2 months over the control arm irrespective of HRR gene mutation status (HR, 0.66; 95% CI, 0.54-0.81; $P < .001$).[1] A planned radiographic PFS analysis by blinded independent central review confirmed showing improvement of median radiographic PFS by 11.2 months. Based on exploratory subgroup analysis suggesting that the radiography PFS (rPFS) benefit from the combination was driven by patients with BRCA1/2-altered tumors, the FDA approved the combination of abiraterone and olaparib only for patients with BRCA1/2-altered CRPC. Indeed, the OS analysis across the entire study population showed no difference between abiraterone alone or in combination with olaparib.[51]

The MAGNITUDE study was another study that evaluated a PARP inhibitor combined with abiraterone.[98] This was a double-blinded, phase 3 study of abiraterone and niraparib versus abiraterone and placebo in two cohorts of patients with mCRPC: (1) with specified HRR biomarker (deleterious mutations in *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *HDAC2*, *PALB2*) and (2) without the biomarker (BM-), in the first-line setting. Unlike the PROPEL study, the MAGNITUDE study took an a priori approach to examine the outcomes in HRR BM1 and HRR BM cohorts separately with preplanned futility analysis. The study showed abiraterone combined with niraparib improved radiographic PFS compared with abiraterone and placebo in patients with the HRR biomarker but not in patients without the HRR biomarker.[99] The final analysis did not show a statistically significant OS improvement but did show trends favoring longer OS with the niraparib + AAP combination. This data led to the approval of the niraparib + AAP combo.[100]

Talazoparib is approved in combination with enzalutamide for CRPC with alterations in one of 12 homologous recombination genes (ATM, ATR, BRCA1/2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C).[101] The TALAPRO-2 study compared enzalutamide monotherapy with talazoparib and enzalutamide in first-line mCRPC. Patients were stratified into two cohorts: (1) HRR gene alteration and (2) HRR gene status unknown or not altered. This study demonstrated improved rPFS overall as well as within each cohort. The FDA approved talazoparib and enzalutamide for first-line mCRPC treatment in patients with alterations in the tested HR genes.

Many questions remain regarding the combination of PARP inhibition and ARPI. Perhaps most critical, given the varied and limited numbers of patients in the control arms who received subsequent PARP inhibitor (PARPi) therapy, it is unclear whether men with HRR gene mutation benefit from a combination of PARPi and abiraterone as opposed to sequential therapy. Most of the study populations included in the trials above were ARPI-naive, which is an increasingly rare circumstance in CRPC, so relevance in the modern era is less clear. Given discordant results in the non–HRR altered populations from MAGNITUDE and TALAPRO-2, the role of PARP inhibitor combinations in this population remains unknown. Emerging data highlight that improved biomarkers may refine patient selection for PARP inhibitor mono- and combination therapy.

At ASCO Annual 2025, data from the AMPLITUDE study[102] were presented, investigating the efficacy of the niraparib + AAP + ADT combination compared to AAP + ADT in the metastatic castrate-SENSITIVE setting. Patients with germline or somatic HRR gene alterations (*BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *PALB2*, *RAD51B*, *RAD54L*) were included. This study showed a significant radiographic PFS benefit favoring the PARP inhibitor combination (HR 0.63), even more so for the BRCA1/2 subgroup (HR 0.52). The majority of patients had high-volume de novo metastatic disease. There was a non-significant OS trend favoring the PARP inhibitor combination. As of this writing, this PARP + ARPI combination is not yet FDA approved in the mCSPC setting. This highlights the importance of germline and somatic testing for all patients with metastatic disease at initial diagnosis.

PSMA-TARGETED THERAPY

PSMA is another exciting target for both imaging and therapeutics. ^{177}Lu PSMA-617 (also ^{177}Lu vipivotide tetraxetan, or LuPSMA) is a radioligand therapy that delivers β-particle radiation to PSMA-expressing cells and the surrounding microenvironment.

The TheraP trial,[103] a randomized phase 2 study, evaluated the clinical activity of LuPSMA compared with cabazitaxel in men with PSMA-positive mCRPC by PET imaging. LuPSMA resulted in a superior PSA50 response rate and fewer grade 3 or 4 adverse events. A pivotal phase 3 trial, the VISION study,[104] evaluated the efficacy of LuPSMA and standard care versus standard care alone in men with mCRPC. Eligibility criteria included progression after an AR pathway inhibitor and at least one taxane chemotherapy with the presence of at least one PSMA-positive lesion and no PSMA-negative lesions as assessed by ^{68}Ga-PSMA-11 PET–CT. The treatment was administered intravenously once every 6 weeks for a total of four to six infusions. LuPSMA and standard care resulted in superior OS and radiographic PFS in men with previously treated PSMA-positive mCRPC. ^{177}Lu vipivotide tetraxetan was approved by the FDA in March 2022 for mCRPC with PSMA-positive lesions by a PET scan using Ga-68 gozetotide or another approved PSMA-11 imaging agent.[2]

Several phase 3 trials are underway to test the efficacy of LuPSMA in earlier disease settings. PSMAfore is examining the efficacy in patients with progressive mCRPC after one ARPI versus switching to a different ARPI. The study met its primary endpoint and demonstrated improvement in radiographic PFS in PSMA-positive mCRPC.[2] This led to FDA approval in 2025 of LuPSMA for patients with mCRPC who have progressed after at least one ARPI and have not yet received docetaxel, and would be considered appropriate to delay taxane-based chemotherapy. LuPSMA carries the risk of myelosuppression, especially in patients with high-volume bone involvement and xerostomia, given that the salivary glands also express PSMA. Due to renal excretion of the beta-emitting payload, patients with incontinence are given special instructions about frequent diaper changes after LuPSMA infusion, and all patients are cautioned about close exposure to household members, especially children.

IMMUNOTHERAPY

Sipuleucel-T is the first FDA-approved immunotherapy for the treatment of mCRPC. It is a therapeutic cancer vaccine composed of activated autologous dendritic cells loaded with an engineered fusion protein of prostatic acid phosphatase and the granulocyte-macrophage CSF, PAP-GMCSF, also called PA2024. This cellular product is prepared in three steps:

1. Leukapheresis to isolate CD541 dendritic cells.
2. Cell harvest and culture with PA2024 ex vivo.
3. Reinfusion of the activated dendritic cells into the original patient.

The preparation and administration of this autologous cellular product are performed every 2 weeks for a total of three infusions and are designed to elicit an immune response to prostatic acid phosphatase. Two small, randomized, placebo-controlled phase 3 trials, D9901 (N = 5,127) and D9902A (N = 598),[86,105] showed that sipuleucel-T resulted in a difference in median OS in asymptomatic patients with mCRPC without any effect on time to progression, which was the primary endpoint. Therefore, a third phase 3 study, IMPACT, was designed with OS as the primary endpoint. The study showed sipuleucel-T resulted in a 22% relative reduction in the risk of death compared with the placebo group. This translated into a 4.1-month improvement in median survival without any effect on time to progression. These data eventually led to FDA approval in 2010.

Other immune-based therapies have been assessed in mCRPC and have not been effective. Checkpoint inhibitors, such as inhibitors of CTLA-4 and PD-1/PD-L1, have had limited efficacy in advanced CRPC after failure of standard therapies. However, a small percentage of patients with metastatic prostate cancer have MSI-high/MMR-deficient status. The FDA approved the PD-1 inhibitor pembrolizumab for such patients regardless of primary tumor type in 2017, and some patients have had dramatic responses to pembrolizumab when no other treatment options were available.[106] In addition, the FDA approved pembrolizumab for second-line treatment of any unresectable or metastatic tumor with high tumor mutational burden (TMB), defined as 10 or more mutations per megabase. Of the small number of patients with mCRPC and high TMB, most have MSI/MMRd (microsatellite instability/mismatch repair deficiency); rarer still are TMB-high microsatellite-stable tumors (potentially as a result of DNA polymerase epsilon, or POLE, mutations), which are now also eligible for PD-1 therapy under this new approval. Responses to PD-1/PD-L1 inhibition have also been seen in a small number of patients with prostate cancer without MSI-high/MMR-deficient status, sometimes in combination with other agents, and this is an active area of research.

BONE-TARGETED THERAPY

Involvement of bone occurs at some point in the disease course in a vast majority of patients with metastatic prostate cancer. In some patients, metastatic disease is confined to or predominantly involves bone. Bone metastases may be asymptomatic or painful, and they can eventually lead to pathological fracture, spinal cord compression, need for RT, or need for surgery to the bone, all of which are collectively termed skeletal-related events (SREs).

The α-emitter radium-223 (^{223}Ra) is a bone-seeking radionuclide that has been approved by the FDA for treatment of patients with mCRPC and symptomatic bone metastases with no known visceral metastatic disease based on results of the ALSYMPCA trial.[107] Patients included in the study had received treatment with docetaxel, were unfit for docetaxel, or refused docetaxel, and toxicity included myelosuppression and gastrointestinal symptoms. This study led to the FDA approval in 2013 of ^{223}Ra

dichloride. Notably, the ERA 223 trial randomly assigned men with mCRPC with no prior treatment of mCRPC to treatment with abiraterone with or without radium-223.[108] The study was unblinded early because of an increased fracture risk and poorer OS in the combination arm. An updated analysis demonstrated that the treatment arms had similar survival, but there was an increased risk of fragility fractures in the combination arm and a low rate of treatment in the study overall, with bone-targeting agents to prevent SREs. The FDA subsequently recommended avoiding concurrent treatment with ^{223}Ra and abiraterone plus prednisone. Most recently, PEACE-3 tested enzalutamide with or without radium-223 in patients with ARPI-naive mCRPC, an increasingly rare situation in modern practice, but demonstrated prolongation in rPFS and OS, suggesting that radium-223 may have a role beyond palliation of multifocal bone pain.[109] In contrast with ^{177}Lu-PSMA-617 as described above, radium-223 targets lesions located in bone only and is not effective for the treatment of extraosseous disease.[109] The optimal sequence of these novel radioligand therapies currently remains unclear and is under investigation.

Bisphosphonates or denosumab, a fully humanized anti-RANKL monoclonal antibody, were approved by the FDA in two situations:

- Men receiving long-course ADT in combination with RT for localized prostate cancer who are found to have baseline or treatment-induced osteopenia or osteoporosis: In this case, the goal is to increase bone mineral density and prevent osteoporosis-related fractures (see note about denosumab dosing).
- Men with mCRPC and bone metastases: in this case, the goal is to prevent SREs. Notably, use of bisphosphonates in mCSPC did not improve SREs or OS in the STAMPEDE trial or CALGB 90202.[53]

Renal insufficiency, osteonecrosis of the jaw, and hypocalcemia are potential adverse effects of bisphosphonates. Patients with significant dental disease or who require dental procedures should not be treated with bisphosphonates until after dental clearance. Monthly dosing or dosing every 3 months with zoledronic acid is indicated for bone metastases, whereas yearly infusions can be used for the treatment of osteoporosis.

In a phase 3 trial, denosumab, a RANKL inhibitor, was superior to zoledronic acid for the prevention of SREs. Hypocalcemia was more common in patients treated with denosumab, and osteonecrosis of the jaw occurred infrequently in both arms. Denosumab can be used in patients with renal impairment. Of note, the approved dose and schedule of denosumab for prevention of SREs in patients with mCRPC (120 mg every month) differ from those approved for fragility fracture prevention (60 mg every 6 months). Extrapolating from data showing equivalence of zoledronic acid administered every 3 months versus monthly in preventing SREs in patients with bone metastases from any cancers,[110] some clinicians may use denosumab every 3 months off-label instead of monthly for mCRPC with bone metastases. Bisphosphonates may be stopped or administered less frequently after 2 years of therapy because of an increased risk of atypical femoral fractures and osteonecrosis of the jaw. Denosumab may be continued indefinitely, given the increase in bone turnover markers after stopping therapy, especially in the metastatic setting, although the clinical significance of this is unclear.

Both denosumab and zoledronic acid are administered with calcium to mitigate the risk of hypocalcemia, and typically, this is also administered in combination with vitamin D (especially in patients being treated for osteoporosis).

PALLIATION

An important aspect of patient care is the palliation of pain. Durable relief in selected sites can be achieved with EBRT delivered via a focal or hemibody technique. Systemic therapies can also provide palliation, especially nonsteroidal anti-inflammatory medications or steroids. Bone-seeking radiopharmaceutical agents, such as ^{223}Ra or ^{177}Lu-PSMA-617, reduce the pain of skeletal metastases, as discussed previously.

KEY POINTS

- Although not curative, ADT is palliative and results in clinical response in most patients with mCSPC.
- The addition of docetaxel, abiraterone with prednisone, or an AR pathway inhibitor (eg, apalutamide, enzalutamide, darolutamide) to ADT improves OS for patients with mCSPC.
- Recent studies indicate that the OS efficacy of triple therapy (ADT/docetaxel/NHT [eg, abiraterone or darolutamide]) was superior to ADT/docetaxel. The benefit was clear, especially for high-volume mCSPC with the addition of abiraterone to ADT/docetaxel. High-volume metastasis is defined by the presence of four or more bone metastases with one or more outside the spine and pelvis or the presence of visceral metastasis using CT and bone imaging.
- It is unknown whether the triple therapy is superior to ADT/NHT or whether they are equivalent, or whether the ADT/NHT doublet is not inferior to the triplet.
- In the setting of mCRPC, abiraterone, enzalutamide, sipuleucel-T, docetaxel, ^{223}Ra, ^{177}Lu-PSMA-617, and cabazitaxel all prolong OS. Unfortunately, cross-resistance to AR-directed therapies occurs after exposure to abiraterone or enzalutamide for a prolonged period, and the efficacy of enzalutamide after abiraterone or abiraterone after enzalutamide is limited.

- The role of PARP inhibitors is actively evolving. Two PARP inhibitors, olaparib and rucaparib, are FDA approved as monotherapy in mCRPC. Niraparib is approved in combination with abiraterone for mCRPC and BRCA1/2 alterations. Talazoparib is approved in combination with enzalutamide as first-line treatment in mCRPC for patients with selected HRR gene alterations. Although the benefit of PARP inhibitors in diseases with *BRCA2* mutations is most clear, their benefit in the setting of some other HRR gene alterations is debatable. Clinical context and alternative treatment options should be considered.

PROSTATE CANCER SURVIVORSHIP AND CONSIDERATIONS IN ELDERLY PATIENTS

With early detection and treatment, many men will be cured of prostate cancer by RT or surgery. A variety of adverse effects may develop in these patients who are related to therapy, including urinary incontinence, erectile dysfunction, and post-treatment psychosocial issues. Prostate cancer is predominantly a disease of older men with coexisting medical issues, and ADT is associated with numerous adverse effects that may be particularly pronounced in older men, including decreased libido, impotence, decreased lean body mass and muscle strength, increased fat mass, decreased quality of life, and osteoporosis. It has also been recognized that metabolic complications, such as insulin resistance, hyperglycemia, and metabolic syndrome, can occur in patients receiving long-term ADT (more than 12 months), potentially contributing to an increased risk of cardiovascular events. Men receiving long-term ADT may be monitored for the development of diabetes, and those in whom an adverse lipid profile develops should be treated according to the established guidelines for hyperlipidemia. It has been suggested that men (especially those with preexisting cardiovascular diseases) who receive as little as 6 months of ADT with RT may have an increased risk of cardiovascular-related mortality, but this observation was not confirmed in other retrospective analyses or in a meta-analysis. Other studies have suggested that men with previous cardiovascular disease may be at increased risk of cardiovascular morbidity while receiving ADT. One report suggested that cardiovascular disease risk may be highest in the first 6 months of ADT in men who experienced two or more cardiovascular events before therapy. Data are conflicting regarding the association of ADT and dementia, including Alzheimer's disease, in men with prostate cancer, and there is evidence to suggest an association between ADT and the development of depression.[108] None of these studies has established a causal link, and no randomized trials have demonstrated a significantly increased risk of cardiovascular mortality, dementia, or depression, although they have not been powered for these outcomes. In practice, the potential risks of ADT are likely justified for patients with intermediate- to high-risk localized or metastatic disease in which clear survival advantages have been established, and clinicians should be judicious about the use of ADT in lower-risk prostate cancer and low-risk BCR prostate cancer.

PRESENTING CASE STUDY 2

A 70-year-old man is admitted to the hospital with urinary retention and a several-month history of weight loss and vague back pains. He has no significant medical history in his normal state of health 1 year ago. He does report a family history of prostate cancer in his father, who died as a result, and a paternal aunt who had breast cancer in her 40s. He has never undergone screening for prostate cancer. Chest, abdominal, and pelvic CT reveals a prostate tumor causing bilateral hydronephrosis and suspicious pelvic and retroperitoneal lymphadenopathy. His PSA level is 500 ng/mL.

Should you pursue tissue diagnosis or treat it as metastatic prostate cancer based on clinical suspicion?

Tissue diagnosis is always preferred and will provide samples for genomic sequencing to inform future targeted therapies. In this case, a biopsy of the prostate or an accessible lymph node would be appropriate. It is important to note that for a patient with significant frailty with a high risk of procedural complications, or a patient who prefers to defer biopsy, the classic pattern of spread and highly suggestive tumor marker could reasonably lead to a clinical diagnosis and hormone therapy initiation.

What is your first-line therapeutic approach?

The standard of care includes androgen deprivation therapy (ADT) and, especially once out of the hospital, intensification with an androgen receptor pathway inhibitor (eg, abiraterone) or a second-generation AR antagonist. Some clinicians prefer to give luteinizing hormone-releasing hormone (LHRH) antagonists at least upfront. Alternatively, an AR antagonist (eg, bicalutamide) and LHRH agonist can be combined in patients with relatively high-volume disease owing to concerns for initial testosterone flare with an LHRH agonist. This approach is controversial, and there is some debate about the clinical consequences of testosterone flare in this setting. It is important to note that symptomatic/radiographic response will take weeks to months, so temporizing measures should be used in the meantime (eg, Foley catheter placement). In very frail patients or those who prefer a supportive approach, bicalutamide monotherapy can

be offered as it is likely to aid symptom management and is minimally toxic. For this patient, who was otherwise healthy before this illness, ADT initiation would be appropriate. After biopsy, bicalutamide could be started in the hospital or upon discharge, concurrent with LHRH agonist (eg, Leuprolide). Alternatively, an LHRH antagonist (eg, relugolix, degarelix) could be used if available.

Does the patient's family history affect treatment decision-making at this point? Is there any other lab or imaging testing that should be pursued right now?

Although it will not affect immediate treatment decisions (pending mature data from recent genomically selected trials in mHSPC), germline and somatic testing should be conducted to inform future treatment decisions and determine family members' cancer risk. Although most cases of prostate cancer are sporadic, this patient has a family history of breast and prostate cancer, which was demonstrated by BRCA2 syndrome, the most common inherited prostate cancer syndrome. Consider assessing baseline bone mineral density to inform decisions regarding antiresorptive therapy and ensure adequate calcium and vitamin D intake through diet or supplementation. Patients should be counseled on the need for aerobic/cardio exercise to address fatigue and metabolic syndrome, and weight/resistance training to address sarcopenia and osteopenia.

Are there any other systemic therapies or other treatments you would consider adding to his first-line hormone therapy?

Some patients with metastatic prostate cancer are eligible to receive docetaxel chemotherapy in addition to first-line hormone therapy. Currently, the best available evidence gathered from studies such as CHAARTED, ARASENS, and PEACE-1 suggests that patients who benefit most from adding docetaxel chemotherapy are those with de novo and/or high-volume bone disease (four or more bone lesions with one bone lesion outside of the axial skeleton) and/or visceral involvement. Since this patient has lymph node disease only, docetaxel would not routinely be used in this circumstance.

Prostate radiation may be offered to this patient. Patients in Arm H of the STAMPEDE study were found to have an overall survival benefit with radiation to the prostate, but only if they had low-volume disease by CHAARTED criteria, like this patient. There is an evolving role of using radiation to the prostate for certain patients with high-volume disease as well. If used, prostate radiation should be delayed until after resolution of urinary obstruction through alpha blockers, hormonal therapy, and/or surgical intervention, as radiation may worsen obstructive symptoms in the short term.

BLADDER CANCER

EPIDEMIOLOGY

In 2024, it is estimated that there will be 83,190 new cases of bladder cancer (n = 63,070 in men and n = 20,120 in women) and 16,840 deaths from bladder cancer (about 12,290 in men and 4,550 in women).[108] The incidence of bladder cancer is three to four times higher in men than in women, and the median age at diagnosis is 73 years. The approximate five-to-one ratio of incidence to mortality reflects the high frequency of noninvasive tumors compared with muscle-invasive tumors and metastatic disease. Although White Americans have a two-fold higher incidence of bladder cancer, Black Americans have a higher mortality rate with a higher incidence of high-grade and muscle-invasive tumors.

Risk factors for bladder cancer include the following:

- Tobacco use
- Occupational exposures
- Urinary tract diseases
- Pharmaceutical drug use

Cigarette smoking is strongly associated with an increased risk of bladder cancer among men and women. In the United States, the risk of bladder cancer in former and current smokers compared with the risk in never-smokers has increased over time. Although smoking cessation is associated with a reduced risk of bladder cancer, the risk in comparison with that in never-smokers remains elevated for those who have quit, even after 10 or more years of not smoking. This risk increases in proportion to the amount and duration of cigarette exposure with heavy smokers (>20 cigarettes smoked per day and/or greater than 40 years of smoking), resulting in up to a five-fold higher relative risk compared with nonsmokers.

Occupational exposure to aromatic amines (particularly 2-naphthylamine, benzidine, and polycyclic aromatic hydrocarbons) is associated with an increased incidence of bladder cancer (eg, workers in dyestuff manufacturing and rubber and aluminum industries).

Infection with the trematode *Schistosoma haematobium* leads to chronic irritation of the urothelium and to an increased risk of both squamous and urothelial carcinomas. Other chronic urinary tract infections, including stones and cystitis, may lead to chronic inflammation and to an increased risk of bladder cancer.

Heavy use of phenacetin-containing analgesics is associated with tumors of the renal pelvis and ureter, and cyclophosphamide also has been associated with an increased risk of urothelial carcinoma.

These myriad risk factors lead to field changes within the urothelium that predispose individuals to the development of recurrent tumors as well as to the involvement of new locations in the urothelial tract (polychronotropism). Hereditary nonpolyposis colon cancer syndrome, also known as Lynch syndrome, is associated with an increased risk for the development of bladder and other urothelial cancers, most notably upper-tract tumors. Cowden disease, characterized by *PTEN* mutations (breast and thyroid cancers), is associated with a higher incidence of urothelial carcinoma.

The three general categories of disease (ie, non-muscle-invasive, muscle invasive, and metastatic) differ in tumor biology, clinical phenotype, management, and prognosis, as follows:

- For non-muscle-invasive tumors, the goal is to prevent recurrence and progression to muscle-invasive disease or metastases.
- For muscle-invasive disease, the goal is to maximize the chance for cure using a multimodality approach incorporating systemic therapy with surgery or RT.
- For metastatic disease, the goal is palliation to improve overall quality of life and prolong survival with systemic therapies.

KEY POINTS

- Urothelial carcinoma is predominantly a disease of older men and is most associated with smoking. Additional risk factors include certain occupational exposures, chronic catheters, and chronic bladder infections, including schistosomiasis in endemic areas. Upper-tract (ureteral and renal pelvis) urothelial carcinoma may be associated with Lynch syndrome.
- The entire urothelial tract is at risk from these carcinogenic exposures (field cancerization), so patients with urothelial carcinoma in one area are at risk for separate primaries in other areas and at other times.

PATHOLOGY

Urothelial carcinoma may occur throughout the urinary tract (ie, any structure lined by the urothelium), with more than 90% of tumors originating in the bladder. Upper urinary tract tumors, including the renal pelvis and ureter, account for 5% to 7% of urothelial carcinomas, with renal pelvis tumors constituting the majority. Urothelial carcinomas usually stain positive for uroplakin III, GATA-3, p63, and cytokeratin 7.

Lesions of mixed histology generally are variants of urothelial carcinoma. Such variants include micropapillary, sarcomatoid, rhabdoid, and plasmacytoid differentiation of urothelial cancer and exhibit more aggressive behavior. Tumors with plasmacytoid differentiation may often have lepidic growth (ie, proliferation along tissue planes without invasion), appearing as infiltrative processes on imaging rather than discrete metastatic deposits.

In the United States, 92% of lower urinary tract tumors are urothelial carcinomas, 5% are squamous cell cancers, 2% are adenocarcinomas, and 1% are small-cell carcinomas. High-grade urothelial carcinomas can also be associated with other histological features, such as squamous, glandular, and small-cell or neuroendocrine differentiation. Pure adenocarcinomas may be of urachal origin, occurring at the junction of the urachal ligament and bladder dome. In Northern Africa and the Middle East, where there is a high prevalence of infection with *S. haematobium*, up to 75% of tumors are pure squamous cell carcinomas, although urothelial carcinomas are becoming more prevalent in those regions as well.

KEY POINTS

- Most bladder and ureter cancers are of urothelial (transitional cell) histology. There are several variants of urothelial carcinoma, most of which are treated similarly to pure urothelial carcinoma but may exhibit more aggressive behavior.
- Rare bladder cancers can have pure adenocarcinoma, squamous cell, or small-cell histology. These are generally more aggressive and usually present with advanced disease.

BIOLOGY

Molecular profiling has demonstrated that urothelial tumors evolve through divergent pathways, corresponding to the clinical phenotypes of recurrent non-muscle-invasive lesions, muscle-invasive lesions, and metastatic disease. Although approximately

70% of these low-grade lesions will recur, only 10% to 15% will progress to invasive lesions. The progression of low-grade lesions to invasive disease is characterized by structural and functional alterations in the tumor suppressors *TP53* and *Rb* in addition to chromosome aberrations. Alterations in *TP53* and *Rb* are also frequently seen in high-grade muscle-invasive tumors. Despite radical cystectomy and the use of perioperative chemotherapy, up to 50% of muscle-invasive tumors will progress to local and distant metastases. This ability to invade and metastasize is not only a function of alterations in the tumor cells but also involves the interactions of the tumor cells with the local microenvironment.

However, the role of *TP53* status as a prognostic or predictive biomarker remains limited. A phase 3 study of adjuvant chemotherapy after cystectomy guided by *TP53* status failed to confirm either the prognostic value of *TP53* or the benefit of chemotherapy in *p53*-positive tumors, but it was limited by methodological issues.[111]

Data suggest mutations in DNA damage-repair genes in urothelial cancers may predict response to platinum-based chemotherapy as well as to immune checkpoint inhibitors but generally do not predict benefit from poly-ADP ribose inhibitors.[112] TMB also seems to enrich for responses to immune checkpoint inhibitors.[113,114] Bladder cancer has one of the highest mutational burdens among cancers. Approximately 8% to 20% of patients who have locally advanced or metastatic bladder cancer can have alterations of the fibroblast growth factor receptor (*FGFR*) gene, with their disease associated with the luminal subtype. *FGFR* alterations are more common in non-muscle-invasive disease and upper-tract urothelial cancer. Erdafitinib, an oral FGFR inhibitor, is FDA approved for locally advanced or metastatic urothelial carcinoma with susceptible FGFR3 genetic alterations after at least one line of prior systemic therapy.

DIAGNOSIS AND STAGING

The most common presenting symptom is hematuria. Irritative voiding symptoms, including dysuria in a patient with risk factors such as tobacco use, may be related to carcinoma in situ (CIS) or a bladder tumor. Less frequently, patients present with symptoms related to distant metastases. Urine cytology can help evaluating patients with irritative symptoms (especially heavy smokers).

The diagnosis is established by cystoscopy and biopsy. As of 2011, the US Preventive Services Task Force concluded there was insufficient evidence to make a recommendation on screening for bladder cancer in asymptomatic adults.

The T staging for bladder cancer is as follows:

- Papillary urothelial neoplasms of low malignant potential.
- Ta tumors are noninvasive papillary lesions that tend to recur but not invade.
- Tis, or CIS, is the precursor of a more aggressive and potentially lethal invasive variant.
- T1 tumors invade the subepithelial connective tissue, including lamina propria or muscularis mucosa.
- T2 tumors invade the muscle.
- pT2a tumors invade superficial muscle.
- pT2b tumors invade deep muscle.
- T3 tumors invade the perivesical tissue.
- pT3a are evident microscopically.
- pT3b are evident macroscopically (extravesical mass).
- T4 tumors invade the prostate, seminal vesicles, uterus, vagina, pelvis, and/or abdominal wall.

The major problem with staging is that the correlation of depth of invasion determined by cystoscopy and transurethral resection of bladder tumor (TURBT) with the results of cystectomy is only about 60%. A TURBT specimen is mainly useful for determining the presence or absence of muscle-invasive (T2) disease but cannot give information about more advanced invasion because the urologist must avoid bladder perforation during the procedure. Muscularis propria must be present in the TURBT specimen; if it is not, then a repeated TURBT is recommended, balancing the risk of understaging with the risk of bladder perforation in aggressive TURBT. Noninvasive imaging with CT or MRI can identify extravesical or nodal disease and is more reliable if done before the transurethral resection with a distended bladder; immediately after TURBT, local adenopathy may be inflammatory. Fluorodeoxyglucose (FDG) PET/CT imaging may have a role in the staging of muscle-invasive disease and in the detection of metastatic bladder cancer,[113] but the urinary excretion of FDG limits its usefulness in local staging, and it may actually be inferior to CT for the detection of pathological presacral nodes.[115] The histological grading system of low grade and high grade is more relevant for non-muscle-invasive tumors; all muscle-invasive neoplasms are high grade.

UROTHELIAL CANCERS IN BLADDER DIVERTICULA

Urothelial cancers arising in bladder diverticula, although uncommon, pose diagnostic and therapeutic challenges. Because of the limited presence of a muscularis propria layer, bladder perforation is a potential complication if a transurethral resection is contemplated. The traditional pathological stage T2 is often eliminated, and the cancer is staged clinically as Ta, Tis, T1, or

T3, indicating extradiverticular extension. A conservative approach for disease without extradiverticular extension has been recommended and includes diverticulectomy or, in lesions that are anatomically amenable, partial cystectomy. Partial or radical cystectomy is often recommended for extradiverticular extension.

KEY POINTS

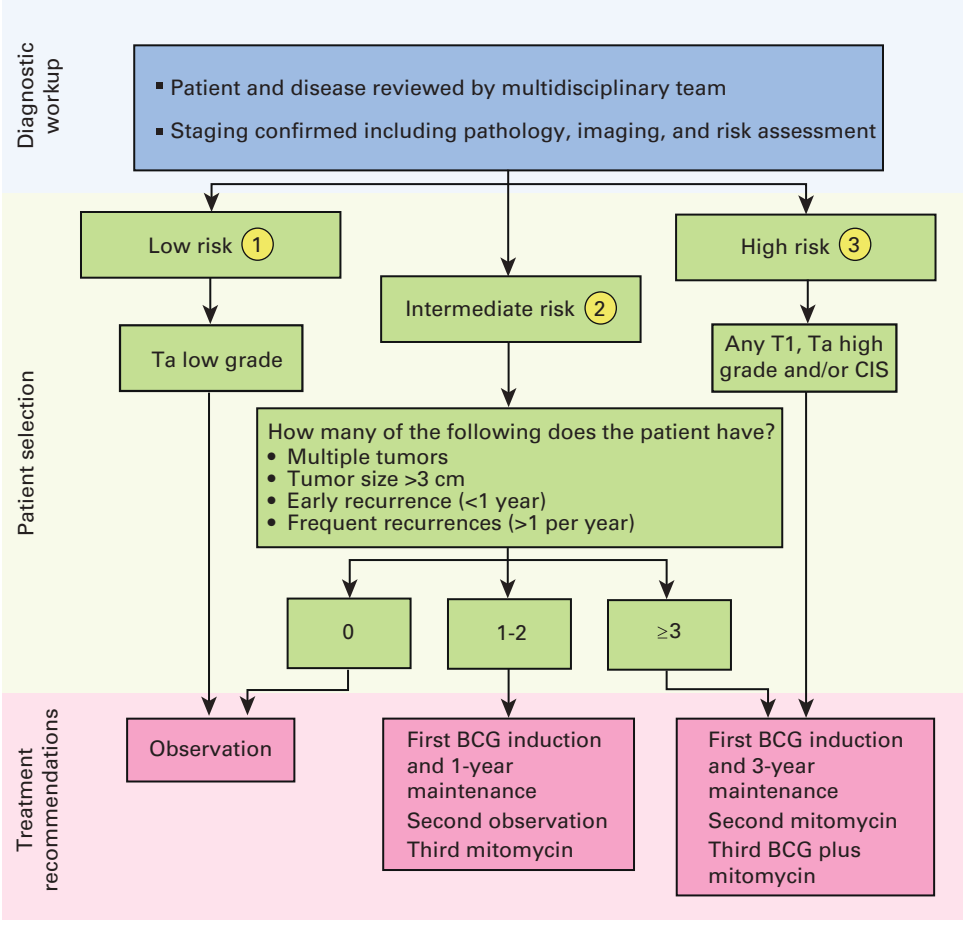
- Bladder cancer may present as painless hematuria or irritative urinary symptoms, and it is typically diagnosed via TURBT.
- Based on TURBT pathology, bladder cancer is broadly divided into non-muscle-invasive tumors and muscle-invasive tumors. Muscularis propria must be present in the TURBT specimen to enable this assessment; otherwise, a repeat TURBT is recommended.

THERAPY FOR NMIBC

The following section is specifically provided to the medical oncologist to enhance the understanding of the management issues that patients face with the diagnosis of NMIBC because most medical oncologists may not actively treat these patients until muscle-invasive disease is detected.

Up to 80% of patients with newly diagnosed bladder cancer present with non-muscle-invasive disease (which includes papillary urothelial neoplasm of low malignant potential, CIS, and low- and high-grade urothelial cancers) with 70% confined to the

Figure 14-12 Treatment Algorithm for Non-Muscle-Invasive Bladder Cancer



All of the treatment options shown may be appropriate. The selection of therapy should be individualized based on patient eligibility and the availability of the therapy at the discretion of the treating physician. These algorithms are meant to provide advice as the consensus recommendations of the Task Force. (1) The Task Force defines low risk as a solitary, primary low-grade Ta tumor. (2) Intermediate risk is defined as histologically confirmed multiple and/or recurrent low-grade Ta tumors. (3) High risk is defined as any T1, high grade, and/or carcinoma in situ.
Abbreviations: BCG, Bacillus Calmette-Guerin; CIS, carcinoma in situ.
Reprinted under Creative Commons Attribution 4.0 International License from Kamat AM, Bellmunt J, Galsky MD, et al. Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma. *J Immunother Cancer*. 2017;5:68. doi:10.1186/s40425-017-0271-0

mucosa (Ta or Tis) and 30% involving the submucosa (T1). Patients initially will be diagnosed by positive urinary cytology or after an evaluation for hematuria or dysuria. The initial evaluation is via flexible cystoscopy performed during an office visit to allow the urologist to systematically evaluate the entire urothelial surface and identify abnormal and erythematous areas. This procedure is then followed by a formal TURBT as well as random bladder biopsies in areas that do not look abnormal to the urologist on visual inspection. The urologist may use imaging techniques such as blue light fluorescent cystoscopy or narrow band imaging to enhance the identification of bladder lesions. This imaging is performed under general or spinal anesthesia and enables bladder resection, including muscle specimens to be obtained, random biopsies of both normal and erythematous-appearing areas, prostatic urethral evaluation, and assessment for determination of the need for upper-tract evaluations. Patients receive constant bladder irrigation after this procedure and are discharged home with a catheter for approximately 1 week. The determination of the presence or absence of muscle-invasive disease is made by pathologists and requires the presence of muscle in the biopsy specimen to enable accurate assessment. For non-muscle-invasive disease, an assessment of risk is performed on the basis of clinical and pathological features. American Urological Association guidelines suggest a treatment algorithm according to this risk assessment (Fig. 14-12).

A single dose of intravesical chemotherapy (mitomycin C or epirubicin) within 24 hours of TURBT may decrease tumor recurrence, and this is recommended for patients with suspected or known low- or intermediate-risk bladder cancer (unless there was extensive resection or suspected perforation). The greatest effect seems to be in patients with single small low-grade tumors, and the risk of recurrence may be decreased even when additional adjuvant intravesical therapy is administered.

Low-risk disease includes small (≤3 cm) solitary low-grade Ta lesions without CIS. Treatment typically involves a single dose of intravesical therapy just after the resection.

High-risk lesions include CIS, high-grade lesions, T1 lesions, or large (larger than 3 cm) or multiple lesions. Intermediate risk is any lesion not meeting low- or high-risk criteria. Very high-risk disease is defined as large or multiple T1 high-grade lesions, co-occurring T1 high-grade lesions with CIS or involving the prostatic urethra, or micropapillary histology. This may require early consideration of cystectomy rather than intravesical therapy.

The diagnosis of intermediate- or high-risk disease at the time of TURBT is then followed (usually within 4 weeks) with the so-called induction course of intravesical *Bacillus* Calmette-Guerin (BCG). This consists of 6 weekly instillations of BCG vaccine (alone or with the addition of intravesical interferon [IFN]). A repeated TURBT, again obtaining specimens involving muscularis propria, is then performed approximately 4 weeks after, during which biopsy specimens are collected again from the previously identified lesions along with repeated urinary cytology.

Patients in whom a complete remission is achieved (ie, negative cytological results and no evidence of residual cancer in the biopsy specimens of previous disease) may begin a 3-year program of maintenance BCG therapy. The first such treatment starts approximately 3 months after the second TURBT and then every 6 months thereafter. In contrast to the induction program, maintenance treatments are administered weekly for 3 weeks. Approximately 1 month after each maintenance program, repeated cytology and office cystoscopies are performed for continued surveillance. The maintenance program continues for 3 years if possible. Unfortunately, both the local and systemic adverse effects of intravesical BCG (with or without IFN) are significant, such that nearly 75% of patients are unable to tolerate or complete the entire program.

Regarding the management of noninvasive bladder cancer with intravesical BCG, it is not uncommon for relapse to occur at the ureteral orifices, ureter, or urethral areas that are less accessible for intravesical treatment. As such, monitoring must include periodic evaluations of the remaining urothelium with cytology and imaging to ensure relapses or new primary tumors are identified and treated when diagnosed.

Potential adverse effects of intravesical BCG include the following:

- Cystitis, including urinary frequency, dysuria, hematuria, and/or fever
- Systemic complications, including arthralgia, osteomyelitis, sepsis, and multiorgan dysfunction resulting from granulomatous involvement.

Patients who do not achieve a complete response (CR) after induction BCG and second TURBT may be considered BCG unresponsive. If muscle-invasive disease is detected, definitive bladder-directed therapy is considered. In those with persistent but non-muscle-invasive disease, cystectomy is standard treatment for patients with high-grade disease, but a second induction course of BCG or other bladder-sparing therapies can also be considered. Second-line intravesical therapies include gemcitabine, docetaxel, valrubicin, or other investigational agents. The combination of intravesical gemcitabine and docetaxel resulted in 46% recurrence-free survival in a retrospective study.[110]

There have been several approvals for novel intravesical therapies in recent years, broadening treatment options for patients with BCG-refractory NMIBC, described below.

- In December 2022, intravesical nadofaragene firadenovec-vncg, a nonreplicating adenoviral vector with a gene copy of IFN alfa-2b, was approved by the FDA to treat patients with BCG unresponsive NMIBC with CIS. This was based on the results of

a large phase 3 clinical study with 157 subjects. Nearly 53.4% of patients had a CR with a median duration of response of 9.7 months with treatment once every 3 months for 12 months or until treatment intolerance. Bladder spasms, discharge, fatigue, and fever with chills were the most common side effects.[116]

- In April 2024, Nogapendekin alfa inbakicept-pmln, an IL-15 superagonist, with BCG in combination, was FDA approved for patients with BCG-unresponsive NMIBC with CIS with or without papillary tumors. This was based on a single-arm, multicenter trial of 82 patients receiving the intravesical combination once weekly for 6 weeks as induction, followed by a shorter course every 3 months. The CR rate was 62% and 58% of patients with a CR had a duration of response over 12 months and 40% over 24 months.[117]

In September 2025, the TAR-200 device, an intravesical system for slow gemcitabine delivery, was FDA approved for patients with BCG-unresponsive NMIBC with CIS with or without papillary tumors. This was based on a single-arm multicenter trial of 83 patients receiving the intravesical system every 3 weeks for 6 months, followed by a maintenance insertion every 12 weeks up to 18 months.[5] The CR rate was 82%, and 51% of patients with a CR had a duration of response over 12 months.

Systemic therapy with intravenous pembrolizumab is also a treatment option for patients with BCG-unresponsive NMIBC. In cohort A of the single-arm phase 2 trial KEYNOTE-057, patients receiving pembrolizumab 200 mg IV every 3 weeks demonstrated a 41% CR rate at 3 months with a median duration of response of 16.2 months.[118] The risk of immune-related adverse effects with pembrolizumab (including those that are life-threatening) should be considered when discussing this option with the patient, given that only <10% of patients in this study maintained a complete response for more than 24 months.[119]

KEY POINTS

- NMIBC is stratified according to risk of recurrence.
- For low-risk tumors, surveillance (cystoscopy and urine cytology) is most appropriate.
- For intermediate- and high-risk tumors, intravesical BCG decreases the risk of recurrence, and surveillance is also crucial. Definitive bladder therapy (cystectomy) is considered in situations of very high-risk non-muscle-invasive tumors or BCG-refractory tumors.
- Intravenous pembrolizumab is currently an FDA-approved treatment option for patients with BCG-unresponsive NMIBC, in addition to several novel intravesical immune-based therapies.

UROTHELIAL CARCINOMA IN PROSTATE URETHRA AND PROSTATE GLAND

The diagnosis of carcinoma or CIS of the prostatic urethra poses diagnostic and therapeutic challenges. Increased morbidity follows resection of the prostatic urethra; however, it is important for appropriate staging. In addition, it is more challenging to treat the prostatic urethra with intravesical therapies because these are administered via Foley catheter, essentially bypassing exposure of the drug to the prostatic urethra. Patients may undergo a transurethral resection of the prostate with the expectation that more accurate staging may result, and the prostate will be exposed to optimal concentrations of BCG. If prostatic stromal invasion is found, surgical management would include cystoprostatectomy.

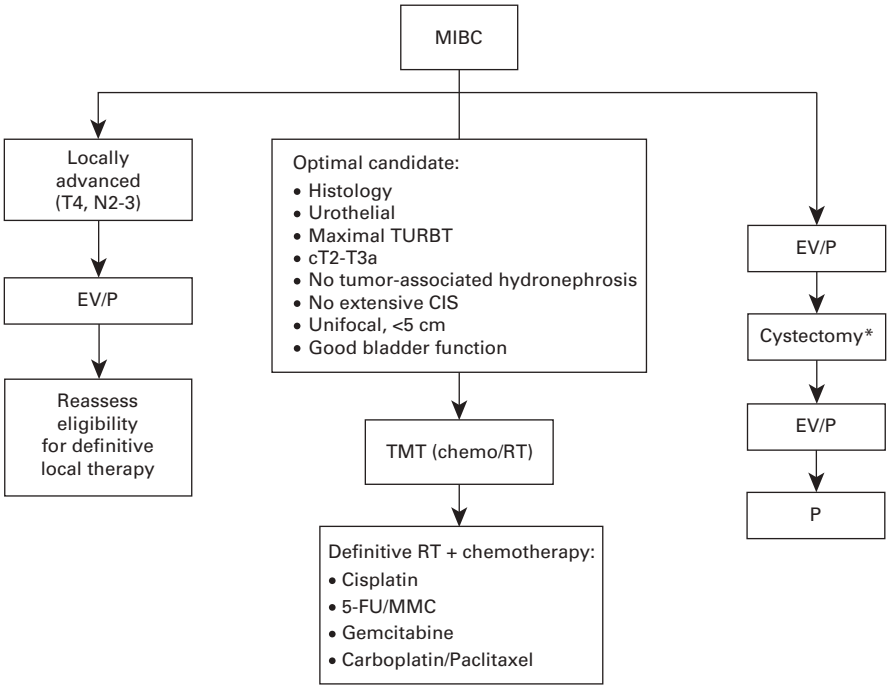
TREATMENT OF MUSCLE-INVASIVE BLADDER CANCER

Although most patients present with non-muscle-invasive disease, approximately 20% to 40% of patients either present with more advanced disease or experience disease progression after therapy for non-muscle-invasive disease (Fig. 14-13).[107] Staging for patients with muscle-invasive disease includes a CT scan of the abdomen and pelvis, chest imaging (CT preferred), and, if clinically indicated, a bone scan. FDG PET can be used to evaluate distant metastases, but because FDG is excreted through the urinary tract, FDG PET is less helpful for evaluating bladder masses, local extension, and local nodal involvement.[120,121]

Cystectomy

The standard treatment of a muscle-invasive bladder cancer (MIBC) is a radical cystectomy with bilateral pelvic lymphadenectomy that includes removal of the bladder, prostate, seminal vesicles, and proximal urethra for men and removal of the bladder, urethra, and uterus (including bilateral salpingo-oophorectomy) as well as possible excision of a portion of the anterior vaginal wall for women. Pelvic lymph node dissection is a necessary part of the radical cystectomy surgery, with a more extended lymph node dissection associated with an improvement in outcome. The three main types of urinary diversions include an ileal conduit that drains to an appliance on the anterior abdominal wall, a continent cutaneous reservoir constructed from detubularized bowel segments, and an orthotopic neobladder. More men are candidates for continent urethral reservoirs than women because of anatomic considerations. It is not clear that continent reconstruction after radical cystectomy is associated with an improvement in quality of life as compared with conduit diversion. In fact, most patients report a favorable quality of life regardless of the type of diversion used. Of note, urinary diversion may result in hypokalemic hyperchloremic metabolic acidosis due to

Figure 14-13 Treatment Options for Muscle-Invasive Bladder Cancer



Abbreviations: 5-FU, 5-fluorouracil; CIS, carcinoma in situ; ddMVAC, dose-dense methotrexate/vinblastine/doxorubicin/cisplatin; EV/P, enfortumab vedotin and pembrolizumab; GC, gemcitabine/cisplatin; MMC, mitomycin C; P, pembrolizumab; RT, radiation therapy; TMT, trimodality therapy; TURBT, transurethral resection of bladder tumor.
*If N + disease is established or suspected before scheduled radical cystectomy, and the patient has not received neoadjuvant therapy, radical cystectomy plus pelvic lymphadenectomy is still a treatment option. There is no level I evidence for adjuvant chemotherapy in the post-cystectomy node-positive setting, but many clinicians would consider its use based on results of the Advanced Bladder Cancer Collaborative meta-analysis.
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reabsorption of urinary solutes by the intestinal segment, and use of ileum for a conduit may result in malabsorption of vitamin B_{12}, requiring parenteral supplementation.

Prognosis varies inversely with higher T stage, lymphatic or vascular invasion in the primary tumor, and lymph node involvement. Approximately two-thirds of patients remain recurrence-free after cystectomy with long-term follow-up, but prognosis worsens with non–organ-confined disease and/or nodal involvement. Multivariate nomograms have been developed to predict outcome after radical cystectomy. A partial cystectomy can provide adequate local control of invasive bladder cancer in highly selected patients (eg, solitary tumor with no evidence of CIS on random biopsies). Less invasive surgical techniques, including laparoscopic and robotic radical cystectomy, have been evaluated, and robot-assisted techniques may be similar to standard open surgery in terms of operative, pathologic, oncologic, complication, and most functional outcomes. The use of bladder-sparing protocols as alternatives to surgery in the management of MIBC is reviewed in the "Bladder Preservation" section.

Perioperative Chemotherapy

The use of perioperative chemotherapy in the management of invasive and locally advanced bladder cancer has been studied in the neoadjuvant and adjuvant settings. Neoadjuvant cisplatin-based chemotherapy is the standard of care for cisplatin-eligible patients. The potential advantages of neoadjuvant chemotherapy include evaluation of response to therapy in vivo with assessment of the pathological response in the cystectomy specimen, tumor downstaging to allow for a less complicated surgery, and delivery of full-dose chemotherapy without the potential problems associated with postoperative recovery. The major advantages of the use of adjuvant chemotherapy include treatment based on an exact pathological staging with the ability to select those patients at higher risk who are most likely to benefit from chemotherapy and to avoid the unnecessary treatment of patients with lower-risk disease.

Platinum Eligibility

Cisplatin is the backbone of perioperative and palliative chemotherapy regimens. However, medical comorbidities, especially renal dysfunction, may pose a challenge to treating with cisplatin-based therapy. Cisplatin ineligibility has been defined by expert consensus[122] as patients with any of the following:

- World Health Organization (WHO) or Eastern Cooperative Oncology Group performance status 2 or higher
- Estimated creatinine clearance <60 mL per minute
- Audiometric hearing loss—grade 2 or higher by the Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.0)
- Peripheral neuropathy—grade 2 or higher by CTCAE v4.0
- New York Heart Association class III heart failure

However, these criteria are not based on prospective data. Renal impairment poses a particular problem because 30% to 50% of patients undergoing radical cystectomy have an estimated creatinine clearance below the threshold of 60 mL per minute,[123] meaning that the standard of care would not be offered to almost half of all patients. In addition, different equations for estimating creatinine clearance or glomerular filtration rate may result in different estimates, and the commonly used Cockroft-Gault equation, in particular, may result in lower estimates of renal function than alternative equations. A 24-hour creatinine clearance may provide a more accurate estimate of renal function in patients with borderline renal function. Second, cisplatin-based therapy may be feasible in patients with borderline renal function, as shown in observational studies, and some clinicians will use split-dose cisplatin regimens. In addition, the risk of cisplatin nephrotoxicity may be related to factors other than calculated creatinine clearance, including albumin and performance status, so these should be taken into account.[4]

Indeed, reflecting current practices, modern clinical trials are now beginning to tolerate lower creatinine clearance boundaries for cisplatin[4] eligibility—in the NIAGARA study, a study of perioperative durvalumab and neoadjuvant chemotherapy (as further discussed below), nearly 20% of patients enrolled had creatinine clearance in the range of 40 to 60 mL/min/1.73 m^2, allowing cisplatin to be given in a split-dosing strategy. This strategy was found to be safe with no perceived compromise on treatment efficacy.

Regarding the use of carboplatin, retrospective and prospective studies have evaluated carboplatin-based regimens in the neoadjuvant setting for cisplatin-ineligible patients with inferior complete response rates and OS.[124] Because of this, patients considered "cisplatin-ineligible and cystectomy eligible" should be referred for upfront cystectomy followed by adjuvant immunotherapy or consider trimodality therapy, as described below. The greater uptake of the split-dosing cisplatin strategy for patients with CrCl 40-60 will, in turn, lead to fewer patients considered "cis-ineligible."

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is the standard of care for patients with MIBC who are eligible for both cystectomy and cisplatin-based therapy (Table 14-3). A US phase 3 Intergroup trial randomly assigned patients with T2-4aN0M0 bladder cancer to neoadjuvant methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) and cystectomy (n = 5,153 patients) or to cystectomy alone (n = 5,154 patients).[125] Median survival of patients assigned to surgery alone was 46 months compared with 77 months among patients assigned to MVAC and cystectomy. The survival benefit of neoadjuvant MVAC was associated with tumor downstaging to pT0 (38% in those patients who received MVAC compared with 15% of those who received cystectomy), with an 85% 5-year survival for patients who experienced a pathological CR to neoadjuvant chemotherapy. A meta-analysis of neoadjuvant chemotherapy showed a significant OS benefit for platinum-based combination chemotherapy with a 14% reduction in the risk of death and 5% absolute survival benefit at 5 years (OS increasing from 45% to 50%). This effect did not vary between subgroups of patients or the type of local treatment.

Table 14-3 Standard Neoadjuvant Chemotherapy Regimens

Classic MVAC (28-Day Cycle)	Dose-Dense MVAC (14-Day Cycle)	Gemcitabine and Cisplatin
Methotrexate on days 1, 15, and 22	Methotrexate on day 1	21-day regimen
Vinblastine on days 2, 15, and 22	Vinblastine on day 2	Cisplatin on day 1 or 2
Doxorubicin on day 2	Doxorubicin on day 2	Gemcitabine on days 1 and 8
Cisplatin on day 2	Cisplatin on day 2	28-day regimen:
	G-CSF on days 4-10 or pegylated	Cisplatin on day 1 or 2
	G-CSF after chemotherapy	Gemcitabine on days 1, 8, and 15

Abbreviations: G-CSF, granulocyte colony-stimulating factor; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin.
For classic MVAC and dose-dense MVAC, all four chemotherapy agents (methotrexate, vinblastine, doxorubicin, and cisplatin) may be given together on day 1.
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Two single-arm, phase 2 studies using dose-dense MVAC (ddMVAC) with pegfilgrastim support demonstrated promising pathological response rates in patients with cT2-cT4a N0-1 M0 MIBC,[126,127] with much less myelotoxicity than seen with the classic MVAC regimen. In addition, the dose-dense regimens reduced the time needed to deliver neoadjuvant chemotherapy before definitive surgery.

The combination of GC is frequently used instead of MVAC; an extrapolation of evidence in the metastatic setting shows that GC offers equivalent response rates and less toxicity compared with classic MVAC.[126] In the randomized phase 2 clinical trial SWOG 1314, CR rates were seen in 30% patients receiving GC and 28% patients receiving dose-dense MVAC, and downstaging was achieved in 47% and 40%, respectively.[128]

The phase III VESPER clinical study compared the perioperative use of six cycles of ddMVAC every 2 weeks to four cycles of gemcitabine with cisplatin (GC) every 3 weeks.[129] Patients received neoadjuvant or adjuvant chemotherapy. Fewer patients completed all six cycles of ddMVAC compared with all four cycles of GC (60% vs 84%). The 3-year PFS in the intention-to-treat (ITT) population was 64% in the ddMVAC arm compared with 56% for GC but did not meet statistical significance. The 5-year follow-up reported no significant difference in OS in the ITT population.[130] However, OS was improved in the neoadjuvant ddMVAC group versus neoadjuvant GC group (66% vs 57%; HR, 0.71 [95% CI, 0.52-0.97]), and time to death because of bladder cancer was also improved in the ddMVAC group (27% vs 40%; HR, 0.61 [95% CI, 0.45-0.84]). More patients in the ddMVAC group achieved an equivalence of four cycles of cisplatin in comparison with patients in the GC group, suggesting the importance of optimal cisplatin dosing.[4] Thus, in patients eligible for anthracyclines, ddMVAC may be preferable to GC, although it may be reasonable to aim for four cycles rather than six.

The NIAGARA trial recently tested neoadjuvant GC with or without the addition of durvalumab as perioperative (neoadjuvant and adjuvant) therapy, showing an improvement in event-free survival and OS. This treatment led to the FDA approval for durvalumab in this setting, but unfortunately, many questions remain. Given that this trial was primarily conducted before the availability of adjuvant PD-1 inhibitors as standard of care (see below), it is unclear whether the strategy of adding durvalumab before and after cystectomy in all MIBC patients is superior to using adjuvant PD-1 inhibitors in a risk-adapted manner in the adjuvant setting for those patients with suboptimal pathological response to chemotherapy alone. The forthcoming results of EV-302 and EV-303 may make these questions less relevant if the combination of enfortumab vedotin and pembrolizumab ends up supplanting cisplatin-based chemotherapy (see further discussion of enfortumab vedotin and pembrolizumab in the advanced systemic therapy section below).[4]

When selecting a strategy of perioperative systemic therapy, the provider must now determine whether a "sandwich" approach with immunotherapy will be used (ie, using perioperative durvalumab with cisplatin-based chemotherapy in the neoadjuvant setting followed by adjuvant durvalumab) or if a traditional risk-adapted approach will be used (ie, forgoing the addition of neoadjuvant immunotherapy and considering the addition in the adjuvant setting, as further discussed below). NCCN guidelines currently endorse either approach as a category 1 recommendation.

In late 2025, the combination of enfortumab vedotin and pembrolizumab (EVP), the current preferred first-line treatment of advanced urothelial cancer, was FDA approved for perioperative therapy in patients who are deemed ineligible for cisplatin but eligible for cystectomy. This approval was on the basis of the phase 3 KEYNOTE-905/EV-303 study,[6] presented at ESMO 2025, which demonstrated that perioperative EVP significantly improved event-free survival (HR 0.40; 95% CI 0.28-0.57; $P < .001$), OS (not reached vs. 41.7 months, HR 0.50; 95% CI 0.33-0.74; $P < .001$), pathological complete response (pCR) rate (57.1% vs 8.6%). This pCR is significantly higher than previous studies, even with platinum-based chemotherapy.

The phase 3 KEYNOTE-B15/EV-304 study is currently ongoing and is investigating the efficacy of EVP in comparison to standard cisplatin-based chemotherapy in the perioperative setting for cisplatin-eligible patients. These are landmark studies that are expected to change the standard of care for patients with MIBC.

Some neoadjuvant trials described above included patients with cN1 disease, but optimal management of these patients and those with more extensive nodal involvement is not well defined. Based on the results of EV-304 described below, it is reasonable to apply the best available systemic therapy with a combination of enfortumab vedotin and pembrolizumab in this setting, especially for those with disease deemed unresectable, and then consider consolidative local therapy in those with good radiographic response.

Adjuvant Systemic Therapy

For patients who have not received neoadjuvant chemotherapy and have nodal involvement or extravesical tumor extension on surgical pathology, many physicians favor the use of adjuvant chemotherapy. However, definitive trials are lacking, with most of the completed adjuvant studies harboring major limitations, including suboptimal statistical methodology as a result of underpowered trials and early termination, as well as the use of older chemotherapy programs that did not include cisplatin. In addition, cystectomy is a major surgery entailing substantial postoperative recovery for many patients. These circumstances may limit or delay the ability to deliver adjuvant chemotherapy in a timely manner.

The largest adjuvant chemotherapy phase 3 study published to date, EORTC 30994, randomly assigned patients with pT3-pT4 or N1 M0 bladder cancer after radical cystectomy to immediate chemotherapy (four cycles of GC, dose-dense MVAC, or classic MVAC) compared with six cycles of chemotherapy at relapse.[131] The trial was closed after recruitment of only 284 of 660 planned patients. Although no significant improvement in OS with immediate treatment compared with deferred treatment was observed, median PFS was prolonged from 0.99 to 3.11 years with the addition of adjuvant chemotherapy. Several meta-analyses

have concluded there is an OS benefit with adjuvant chemotherapy, but the validity of the meta-analyses is clearly limited by the flawed trials from which the analyses are derived. In sum, adjuvant chemotherapy may be offered to high-risk patients who have not received neoadjuvant chemotherapy with the caveat that prospective evidence is lacking.

As in the neoadjuvant setting, patients who are not eligible for cisplatin are generally not treated with adjuvant chemotherapy. Randomized trials of adjuvant immune checkpoint inhibitors have reported some evidence of efficacy. In the large phase 3 clinical study CheckMate-274, patients with T3-T4a or N1 bladder cancer without cisplatin-based neoadjuvant chemotherapy or residual T2-T4a or N1 bladder cancer after cisplatin-based neoadjuvant chemotherapy were randomly assigned to adjuvant nivolumab versus placebo for 1 year.[132] At median follow-up of 3 years, median DFS was significantly longer in the nivolumab-treated group versus the placebo group (22.0 vs 10.9 months, HR, 0.71 [95% CI, 0.58-0.86]), At this interim analysis, median OS was longer in the nivolumab group compared with placebo (69.5 vs 50.1 months; HR, 0.76 [95% CI, 0.61-0.96]). Although OS benefit was observed for both the ITT and PD-L1 over 1% group (about 40% of the total population), at the time of this interim analysis, median OS had yet to be reached in the PD-L1 over 1% group.[132]

Based on these results, adjuvant nivolumab is FDA approved to treat high-risk MIBC post-cystectomy.[107] Similarly, the AMBASSADOR trial of adjuvant pembrolizumab reported DFS benefit in a high-risk MIBC population post-cystectomy, whereas OS was not different at interim analysis.[133] Finally, the IMvigor010 trial did not show a DFS benefit with adjuvant atezolizumab versus observation,[134] although patients with post-cystectomy detectable circulating tumor DNA did seem to benefit.[134,135] Given the trial findings described above, the role of PD-L1 testing to assist with decision-making for adjuvant immunotherapy is not routinely performed.

In sum, patients who are eligible for neoadjuvant cisplatin-based therapy should still receive this. In patients who did not receive neoadjuvant chemotherapy but are eligible and who have adverse pathological characteristics, adjuvant cisplatin-based treatment is reasonable. If patients received neoadjuvant chemotherapy and still have adverse pathological characteristics or if they did not receive perioperative chemotherapy, then adjuvant nivolumab should be considered.

Bladder Preservation

Although neoadjuvant chemotherapy leads to CRs in a subset of patients (30%-40%), radical cystectomy is currently recommended for all patients with muscle-invasive disease to evaluate and confirm pathological responses and remove any residual disease. The role of chemotherapy alone in bladder preservation is problematic because of the inability to definitively determine which bladders are truly without residual tumors. Chemotherapy alone cannot replace definitive treatment of the bladder by surgery or RT.

Radical cystectomy following neoadjuvant chemotherapy remains a standard of care for MIBC. Many patients are either ineligible for cystectomy, based on medical comorbidities, or prefer a bladder-sparing approach. For select patients with small solitary tumors, partial cystectomy may be considered.

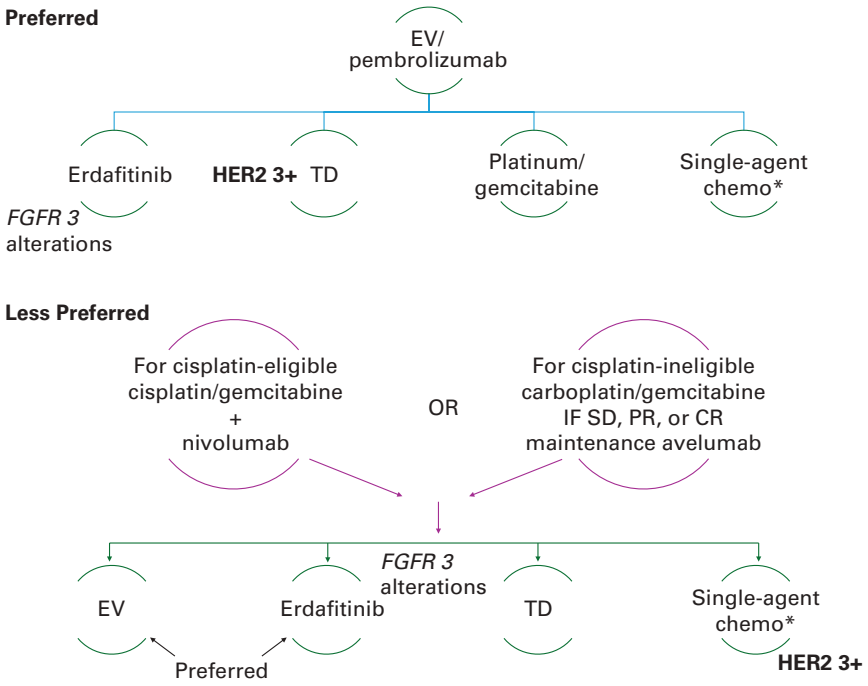
For appropriately selected patients, a trimodality treatment consisting of maximal transurethral resection (as complete as safely possible) followed by definitive RT and radiosensitizing chemotherapy has resulted in long-term DFS and OS rates approaching those seen in radical cystectomy series (Fig. 14-14). Trimodality treatment is now included as a category 1 recommendation in the NCCN guidelines alongside cystectomy.[136] Optimal patients for trimodality therapy include the following:

- Unifocal urothelial carcinoma <5 cm
- Visibly complete TURBT
- No extensive CIS
- No T4 disease or tumor-associated hydronephrosis
- Good bladder function and capacity.

An analysis of long-term outcomes of selective bladder preservation in 348 patients at the Massachusetts General Hospital from 1986 to 2013 demonstrated 5-year disease-specific survival and OS rates of 64% and 52%, respectively, with preservation of the bladder in more than 70% of patients.[137] In the years 2005 to 2013, 5-year DFS and OS improved to 88% and 84%, respectively.

The optimal radiosensitizing regimen is unclear. Current NCCN guidelines endorse cisplatin alone, low-dose gemcitabine, or 5-FU with mitomycin as preferred options. A majority of trimodality protocols have used cisplatin-based chemotherapy (typically weekly cisplatin monotherapy); however, other agents, such as paclitaxel and gemcitabine, have been used as well. In the largest randomized study to compare chemoradiation therapy using fluorouracil and mitomycin with RT alone in MIBC, the chemoradiation therapy arm was associated with an improvement in 2-year locoregional DFS from 54% to 67%.[138] It is unknown which radiosensitizing chemotherapy is optimal and whether induction therapy with standard systemic doses of chemotherapy (eg, GC) before chemoradiation therapy is beneficial. Many bladder-sparing protocols include an early evaluation of response to treatment with cystoscopy after RT; patients who show less than a CR may go on to consider salvage cystectomy.

Figure 14-14 Systemic Therapy for Advanced Urothelial Cancer



*In cases of progression after prior treatments.
Abbreviations: CR, complete response; EV, enfortumab vedotin; *FGFR*, fibroblast growth factor receptor; PR, partial response; SD, stable disease; TD, trastuzumab deruxtecan.
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Quality of life is another important consideration. Radiation therapy can induce disturbances in the function of the bladder, anal sphincter, and large bowel. The morbidity of RT has decreased with imaging and radiation advances, allowing for a boost to the primary tumor and a reduction in fraction size. An evaluation of late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer who received treatment in four prospective Radiation Therapy Oncology Group protocols showed low rates of substantial late pelvic toxicity (7% of patients with late grade 3 or higher pelvic toxicity: genitourinary, 5.7%; gastrointestinal, 1.9%) at a median follow-up of 5.4 years. The disadvantages of bladder preservation are the requirement for lifelong cystoscopy surveillance as a result of the risk of intrabladder recurrence and the surgical and post-surgical challenges of post-radiation salvage cystectomy if needed. Nonetheless, many of these new or recurrent tumors are noninvasive and can be treated endoscopically with or without intravesical therapies.

KEY POINTS

- The most established standard of care for MIBC is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy and lymph node dissection. The optimal neoadjuvant chemotherapy regimens are GC and dose-dense MVAC. The addition of durvalumab in the perioperative setting to chemotherapy is now an approved option.
- For cisplatin-ineligible patients undergoing cystectomy, perioperative EVP is now an FDA-approved option. For those ineligible for EVP, no other perioperative chemotherapy is currently recommended, and carboplatin should not be substituted for cisplatin. Recent data suggest good safety and efficacy of a cisplatin split-dosing strategy for those with CrCl 40 to 60 mL/min; thus, cisplatin should be considered for this population.
- Adjuvant nivolumab or pembrolizumab immunotherapy for 1 year significantly improves DFS in patients with high-risk MIBC and is FDA approved for this indication.
- Maximal transurethral resection of the bladder tumor followed by concurrent definitive RT with radiosensitizing chemotherapy, also known as bladder-sparing or trimodality therapy, may offer similar long-term disease control for appropriately selected patients. Historically, this has been considered only for patients ineligible for or declining cystectomy, but based on nonrandomized data, it is now considered a reasonable alternative to cystectomy in all eligible patients.

THERAPY FOR METASTATIC BLADDER CANCER

FIRST-LINE THERAPY

Patients may develop either de novo metastatic bladder cancer or metastatic recurrence after prior therapy for localized disease. Gemcitabine and cisplatin have been the most commonly used first-line therapies for metastatic bladder cancer for many years, with de novo metastatic disease or recurrence more than 1 year following prior neoadjuvant therapy, but recent randomized clinical trials are changing the treatment paradigm. Gemcitabine and cisplatin have been the preferred therapies for cisplatin-eligible patients based on a phase 3 study of GC versus MVAC demonstrating similar response rates (approximately 50%) and median OS of approximately 14 to 15 months but less toxicity with GC.[126]

More recently, enfortumab vedotin (Nectin-4 targeting antibody-drug conjugate with a monomethyl auristatin E payload) with pembrolizumab showed significantly improved OS (HR, 0.47; median OS 31.5 vs 16.1 months), PFS (HR, 0.45; median PFS 12.5 vs 6.3 months), and objective response rates (67.7% vs 44.4%) as compared with gemcitabine and cisplatin or carboplatin in the randomized phase 3 EV-302 trial.[139] All patient subgroups analyzed appeared to benefit regardless of PD-L1 expression, cisplatin-eligibility, or primary site of disease (upper tract or lower tract). The marked efficacy benefits in EV-302 led to regulatory approval of enfortumab vedotin and pembrolizumab as first-line therapy for patients with locally advanced or metastatic urothelial cancer in late 2023. Common treatment-related adverse events in patients receiving enfortumab vedotin and pembrolizumab include peripheral sensory neuropathy, pruritus, alopecia, rash, fatigue, diarrhea, decreased appetite, nausea, cytopenias, dry eye, and hyperglycemia.

Around the same time, the randomized phase 3 CheckMate 901 trial showed the addition of nivolumab to gemcitabine and cisplatin significantly improved OS (HR, 0.78; median 21.7 vs 18.9 months), PFS (HR, 0.72; median 7.9 vs 7.6 months), and ORR (57.6% vs 43.1%).[140] This led to FDA approval of nivolumab in combination with cisplatin and gemcitabine for first-line treatment of unresectable or metastatic urothelial carcinoma. Based on the totality of the data and magnitude of benefit seen in EV-302, enfortumab vedotin and pembrolizumab are the preferred first-line therapies for most patients with locally advanced or metastatic urothelial bladder cancer, although no direct comparisons are available with the combination of nivolumab, gemcitabine, and cisplatin.

For patients who are not candidates for immunotherapy, gemcitabine and platinum remain standard-of-care first-line systemic therapies. Cisplatin is preferred for cisplatin-eligible patients because multiple phase 2 trials have suggested an improvement in outcome with cisplatin-based compared with carboplatin-based chemotherapy. However, in contrast to neoadjuvant therapy, it is acceptable in the metastatic setting to substitute carboplatin for patients with renal impairment that precludes cisplatin treatment. For patients who had stable disease or response following four to six cycles of gemcitabine and platinum, maintenance avelumab should be considered based on data from the phase 3 JAVELIN Bladder 100 study.[141] At a planned interim analysis, there was a significant OS benefit with maintenance avelumab regardless of PD-L1 status. This led to FDA approval for avelumab as maintenance therapy following gemcitabine and cisplatin. However, with the recent positive data with both enfortumab vedotin with pembrolizumab and nivolumab, gemcitabine, and cisplatin combinations, patients who are eligible for immunotherapy should start it in the upfront first-line setting.

SECOND- AND SUBSEQUENT-LINE THERAPIES

With the recent improvements in first-line treatment options, there is a lack of data to guide the optimal second- and subsequent-line therapies. Decisions on subsequent treatments will depend on the first-line therapy administered (Fig. 14-14). Options include platinum with gemcitabine (for patients who received first-line enfortumab vedotin and pembrolizumab), enfortumab vedotin monotherapy (for patients who received first-line platinum and gemcitabine with nivolumab or maintenance avelumab), erdafitinib (for tumors with susceptible FGFR3 alterations), trastuzumab deruxtecan (for HER2 IHC3-positive tumors), and single-agent chemotherapies (eg, pemetrexed, paclitaxel). Sacituzumab govitecan, an antibody-drug conjugate directed against Trop-2, had previously been granted accelerated approval in this space, but this indication was withdrawn after the confirmatory phase 3 trial failed to demonstrate an OS benefit relative to the physician's choice of single-agent chemotherapy, as well as increased toxicity, primarily neutropenic infections.

Erdafitinib is a tyrosine kinase inhibitor (TKI) of FGFR. FGFR genetic alterations are seen in approximately 20% of patients with advanced or metastatic urothelial carcinoma, with many acting as oncogenic driver mutations or fusions.[138] Erdafitinib initially showed promising activity in a single-arm phase 2 trial in patients with advanced urothelial carcinoma and prior chemotherapy (with or without prior PD-1/PD-L1 treatment) and *FGFR3 or FGFR2* alterations, demonstrating a confirmed response rate of 40% (CR, 3%).[142] The efficacy of erdafitinib was confirmed in the randomized phase 3 THOR trial in which patients with advanced or metastatic urothelial carcinoma with susceptible FGFR3 or FGFR2 alterations and progression after prior therapy were randomized to erdafitinib or investigator's choice of chemotherapy (docetaxel or vinflunine).[143] Erdafitinib significantly improved OS (HR, 0.64; median 12.1 vs 7.8 months), PFS (HR, 0.58; median 5.6 vs 2.7 months), and objective response rate (45.6% with 6.6% CR vs 11.5%). Common adverse events with erdafitinib include hyperphosphatemia, skin and nail changes, stomatitis, dry mouth, dry eye, palmar-plantar erythrodysesthesia, asthenia, and fatigue. Regular ophthalmological examination

is recommended. Initially, erdafitinib was granted accelerated approval by the FDA for patients with susceptible *FGFR2* or *FGFR3* mutations, but because the THOR study showed little activity of erdafitinib in *FGFR2* mutations, the FDA approval was amended in 2024. Erdafitinib is currently FDA approved for patients with metastatic urothelial carcinoma with susceptible *FGFR3* genetic alteration who have previously progressed on at least one prior line of systemic therapy.

Finally, trastuzumab deruxtecan is another antibody-drug conjugate that gained FDA accelerated approval in April 2024 for patients with unresectable or metastatic HER2-positive (IHC3 positive) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. A total of 41 patients with advanced urothelial carcinoma were treated in the phase 2 trial DESTINY-PanTumor02.[144] ORR was 56.6% in the 16 response-evaluable patients with HER2 IHC3 positive (ORR 35.0% in HER2 IHC2 positive). Median duration of response in urothelial patients with cancer (IHC3 positive or 2 positive) was 8.7 months. No confirmatory randomized study data are available. Common drug-related adverse events include nausea, diarrhea, anemia, fatigue, vomiting, neutropenia, decreased appetite, asthenia, alopecia, and thrombocytopenia. Drug-related pneumonitis occurred in 10.5% of patients, with the majority being grade 1 to 2, but there was one grade 3 and three fatal adjudicated drug-related cases of pneumonitis. HER2 positivity occurs in a minority of urothelial cancers, with a systematic literature review reporting HER2-positive prevalence of 13.0% in locally advanced or metastatic urothelial cancers.[145]

SUBSEQUENT THERAPY

Small studies of single-agent chemotherapy, such as ifosfamide, docetaxel, gemcitabine, paclitaxel, nab-paclitaxel, and pemetrexed, have demonstrated response rates between 9% and 27% with a PFS in the range of 2 to 3 months and no documented improvement in OS. Although multidrug regimens have been associated with higher response rates, this does not seem to translate into an improvement in survival. Clinical trial participation should be considered in this treatment-refractory setting for eligible patients.

KEY POINTS

- The preferred first-line therapy for patients with metastatic bladder cancer is combination EVP. Alternatively, less preferred regimens are cisplatin-based chemotherapy with or without nivolumab, followed by PD-1/PD-L1 checkpoint inhibitor maintenance. For patients who are not eligible for immunotherapy, gemcitabine and cisplatin remains a standard treatment option. In contrast with perioperative chemotherapy, carboplatin may be substituted for cisplatin-ineligible patients.
- Optimal second- and subsequent-line therapies are not well defined in the setting of the recent changes in first-line therapy. HER2 IHC and genomic testing for the *FGFR3* mutation should be requested. Options include platinum with gemcitabine, enfortumab vedotin monotherapy, erdafitinib, trastuzumab deruxtecan, and single-agent chemotherapies, depending on the prior systemic therapies used.

OTHER UROTHELIAL TRACT CANCERS

UPPER-TRACT AND URETHRAL UROTHELIAL CARCINOMA

Cancers of the renal pelvis, ureter, and proximal urethra are also typically of urothelial origin and should be treated based on primary histology. Upper urinary tract tumors may have a worse outcome in comparison with urothelial carcinomas that arise in the bladder. They can also arise in the setting of Lynch syndrome. Comprehensive genomic profiling of upper-tract tumors has revealed novel mutations, differing mutational frequencies, and expression subtypes with unique molecular profiles in comparison with bladder cancer, including a higher incidence of FGFR genetic alterations.

Upper-tract urothelial carcinomas may first be detected by imaging or retrograde pyelogram. Selective ureter cytology and/or brushing of lesions may be performed during the pyelogram. Unfortunately, unlike bladder cancer, great difficulty exists in the clinical staging of upper-tract urothelial carcinomas, and management decisions generally rely on tumor grade. Ultimately, the definitive diagnosis is made after nephroureterectomy. Lymph node dissection is not performed routinely for clinically node-negative patients, but it may be performed in the presence of radiographically suspicious lymphadenopathy. Node-positive disease is considered stage IV, but resection is still performed if possible because long-term remission is still possible.

No definitive data were available on the role of perioperative chemotherapy until the randomized POUT study evaluated the same.[146] Patients who had undergone nephroureterectomy for high-risk upper-tract urothelial carcinoma (pT2-4 and/or node positive) were randomly assigned to adjuvant GC or carboplatin and gemcitabine versus surveillance. Disease-free survival was significantly prolonged with adjuvant chemotherapy compared with no adjuvant chemotherapy. The 3-year event-free estimate was 71% for the chemotherapy arm compared with 46% for surveillance. Longer-term follow-up reported that the 3-year OS data trended toward improvement but was nonstatistically significant (79% with adjuvant chemotherapy vs 67% with surveillance).[147] The benefit was less clear in those with T2 disease, with caveats of underpowered subgroup analyses. Adjuvant nivolumab may also be considered for patients who decline or are unfit for adjuvant chemotherapy. CheckMate-274 included

21% of patients with upper-tract disease, although (underpowered) subgroup analyses suggested a lack of benefit with adjuvant nivolumab in such patients.

Neoadjuvant chemotherapy may also be reasonable, extrapolating from bladder cancer, but there are no randomized data in this setting. In addition, upper-tract disease may be diagnosed simply based on the suspicious imaging and/or cytology, so pathological information on risk may not be available until resection is performed.

Because approximately 20% to 50% of patients with resected upper-tract urothelial carcinoma will eventually develop bladder cancer, surveillance cystoscopy is necessary. The two theories for the multifocal nature of urothelial carcinoma include the field cancerization effect and monoclonality (ie, tumor cells spreading from their origin to multiple sites). Therefore, simultaneous or metachronous primary tumors of the urothelium at multiple sites may occur, and monitoring is required, including follow-up cystoscopies and imaging of the upper tracts.

NONUROTHELIAL BLADDER CANCER

It is not uncommon for urothelial carcinomas to be associated with minor components of nonurothelial histologies, and management is typically the same as for pure urothelial carcinoma. Fewer than 5% of bladder cancers in the United States have pure nonurothelial histology, including squamous cell carcinoma, adenocarcinoma, and small-cell or neuroendocrine carcinoma. Squamous cell carcinoma of the bladder is typically related to chronic urinary tract infections, RT, prior cyclophosphamide therapy, and, possibly, chronic indwelling catheters. In endemic areas, schistosomiasis can cause urothelial carcinoma as well as squamous and adenocarcinoma bladder cancers. Pure adenocarcinomas may originate from remnant urachal tissue, especially if they are located in the bladder dome. Small-cell or neuroendocrine carcinomas often behave aggressively with a propensity for distant metastases and a higher potential for brain metastasis. Plasmacytoid variant is an aggressive form of urothelial carcinoma associated with a somatic *CDH1* gene mutation with an aggressive course.[148]

The primary treatment modality for all localized nonurothelial bladder cancers is cystectomy, and the role of chemotherapy and/or RT as neoadjuvant or adjuvant therapy is not well defined. Chemotherapy regimens used for urothelial carcinoma have been considered to be less effective in non-urothelial histology tumors. Tumors with <90% variant histology are typically treated as standard urothelial carcinoma, although the optimal regimens for pure variant histologies are not well defined either. Neoadjuvant RT may have a role for squamous cell carcinomas, which have a greater tendency for local recurrence than metastatic spread.

Various strategies for the treatment of pure small-cell carcinoma of the bladder have arisen, primarily extrapolated from the treatment paradigms in small-cell lung cancer, including chemoradiation with or without induction chemotherapy with cisplatin and etoposide. Perioperative cisplatin/etoposide and surgery have been considered as well. This is a rare diagnosis with an associated poor prognosis, similar to other pure variant histology bladder tumors.

KEY POINTS

- Upper-tract (ureteral and renal pelvis) urothelial carcinoma may be diagnosed initially by imaging, urine cytology, and/or biopsy via retrograde ureteroscopy, but often a nephroureterectomy is required for pathological diagnosis as well as treatment.
- Perioperative chemotherapy should be considered for high-risk tumors based on extrapolation from bladder cancer or from one randomized trial of adjuvant platinum-based chemotherapy. For patients with high-risk disease who are unfit for or decline chemotherapy, adjuvant nivolumab may be considered as an alternative, although the supporting data are not as robust.
- Pure nonurothelial bladder cancers are typically treated with cystectomy; the role of perioperative chemotherapy and/or RT is not well defined.

BLADDER CANCER SURVIVORSHIP AND CONSIDERATIONS IN ELDERLY PATIENTS

Bladder cancer is predominantly a disease of older individuals (median age, 73 years) with coexisting medical issues, strongly affecting management decisions. Although most patients are diagnosed with non-muscle-invasive disease, lifelong surveillance, including urine cytology, cystoscopy, and periodic imaging, is required. Among those with muscle-invasive disease, the requirement for a radical cystectomy for most patients necessitates a urinary diversion procedure, and in patients receiving neoadjuvant cisplatin-based chemotherapy, the potential for short- and long-term chemotherapy-related adverse effects, including peripheral neuropathy, hearing loss, and renal dysfunction as well as others, exists. Although life expectancy is limited in patients with metastatic disease, chemotherapy-related adverse effects can have a substantial effect on quality of life. Many older patients are not candidates for perioperative chemotherapy secondary to the normal physiological decline in renal function with aging, baseline hearing loss, and other comorbidities such as cardiac disease. Additional advancements in immune-oncology, and antibody-drug conjugates may enable treatment of older patients who otherwise would be unable to receive conventional chemotherapy.

PRESENTING CASE STUDY 3

A 70-year-old man presents with hematuria. In-office cystoscopy reveals a large bladder mass, measuring approximately 6 × 4 cm. Abdominal CT shows no disease outside the bladder. His calculated creatinine clearance is 80 mL/min, and he has no major comorbidities. Transurethral resection of bladder tumor (TURBT) is performed with maximal resection. Pathology indicates muscle-invasive high-grade urothelial carcinoma.

How do the TURBT findings guide the definitive therapies you offer, and what systemic treatment would complement each approach?

Standard definitive therapies for muscle-invasive bladder cancer include radical cystectomy (with urinary diversion or neobladder creation) or definitive bladder radiation. For a cisplatin-eligible patient, as in this scenario, neoadjuvant cisplatin-based chemotherapy should be offered (gemcitabine and cisplatin for four cycles or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin [ddMVAC] for four to six cycles). One could also consider adding durvalumab to gemcitabine and cisplatin as neoadjuvant and adjuvant therapy, or alternatively, use a risk-adapted approach to PD-1 inhibition in the adjuvant setting.

If the patient opts for radiation therapy, it is important to first perform maximal TURBT. Radiosensitizing chemotherapy regimens vary and could include weekly cisplatin, once or twice weekly gemcitabine, 5-fluorouracil, and mitomycin C, or carboplatin and paclitaxel. It is unclear whether a systemic dose "induction" phase should be included.

It is important to note that treatment paradigms for patients considered "cisplatin-ineligible" are evolving. There is no role for carboplatin-based neoadjuvant therapy, and it should not be substituted for cisplatin in this setting. Of note, the NIAGARA trial demonstrated that cisplatin in a split-dosing strategy (ie, 35 mg/m^2 day 1 and day 8) can be used safely and successfully in patients with borderline renal function, CrCl 40 to 60 mL/min. Patients otherwise eligible for cisplatin with CrCl 40 to 60 mL/min should be considered for cisplatin if possible.

The patient opts for cystectomy and completes four cycles of cisplatin, gemcitabine, and durvalumab, followed by a radical cystoprostatectomy with an ileal conduit creation. Pathology revealed residual T3 disease and no lymph node involvement. How do you approach postoperative treatment?

This patient received the newest standard-of-care neoadjuvant therapy with chemo-immunotherapy as established by the NIAGARA study. He should receive adjuvant immunotherapy with durvalumab for 8 months, a strategy known as "sandwich immunotherapy." The pathological features would not change the plan for adjuvant durvalumab in this circumstance.

It is important to mention that if this patient elected to receive chemotherapy alone without immunotherapy before surgery (such as 4 cycles of ddMVAC or gemcitabine and cisplatin alone), then the patient would now be eligible instead to receive immunotherapy with either nivolumab or pembrolizumab for 1 year owing to adverse pathological findings.

If the patient had imaging evidence of metastatic disease, how would that affect the choice of systemic therapy?

The combination of enfortumab vedotin and pembrolizumab (EVP), established by the EV-302 study, is now the preferred first-line treatment of metastatic urothelial carcinoma. This regimen has been associated with the highest response rates and the most promising duration of response. Alternative options include nivolumab with gemcitabine and cisplatin, followed by nivolumab maintenance (Checkmate 901 study) and ddMVAC or gemcitabine and cisplatin, followed by avelumab maintenance therapy (JAVELIN Bladder 100 study).

Following disease progression on EVP, how do you think about next-line options?

Tumor genomic sequencing should be requested to identify a targetable *FGFR3* mutation, which would make the patient eligible for oral erdafitinib. HER2 immunohistochemistry (IHC) testing should be performed to determine trastuzumab deruxtecan eligibility, which currently has a pan-tumor approval for all HER2-overexpressing solid tumors. Platinum-based chemotherapy doublet may be offered after EVP, but data are lacking in this setting. Single-agent chemotherapies can be used as later lines of therapy (eg, pemetrexed, paclitaxel).

KEY POINTS

- Bladder cancer is predominantly a disease of older patients and frequently occurs in patients with other comorbidities. Therefore, a significant portion of patients are not candidates for many standard therapies such as cisplatin and cystectomy.
- Bladder-sparing or trimodality therapy is now considered an equal alternative to cystectomy and is increasingly offered to appropriately selected patients who wish to preserve their bladders and avoid urinary diversion; previously, it was reserved primarily for patients ineligible for cystectomy because of comorbidities.
- Cisplatin should be offered to any eligible patient regardless of age, but this requires careful assessment of baseline neuropathy, hearing, and kidney function, and serial assessment during and after treatment. Split-dosing of cisplatin should be considered for patients with CrCl 40 to 60 mL/min. Newer systemic treatment modalities (eg, immune checkpoint inhibitors, antibody-drug conjugates, and targeted therapies) are rapidly improving treatment options for patients with locally advanced or metastatic disease and those not eligible for conventional chemotherapy.

RENAL CANCER

EPIDEMIOLOGY

Renal cell carcinomas account for 90% of all malignant neoplasms of the kidney. An estimated 81,610 new cases of kidney cancer (n = 52,380 in men and n = 29,230 in women) will be diagnosed, and approximately 14,390 people (n = 9,450 men and n = 4,940 women) will die of this disease.[149,150] Renal cancers were historically called the internist's tumors based on their protean clinical presentations, including fatigue, weight loss, and anemia. Today, <10% of patients present with the classic triad of hematuria, abdominal pain, and a palpable mass. Between 1993 and 2004, the proportion of patients diagnosed with stage I renal cell carcinoma increased from 43.0% to 57.1%, whereas the proportion of patients diagnosed with stage IV disease decreased from 27.4% to 18.7%, indicating an increase in incidental diagnoses as a result of the increased use of imaging for other diagnostic purposes. Risk factors for renal cell carcinoma include smoking, obesity, hypertension, and acquired cystic kidney disease, which is associated with end-stage renal disease. Tobacco use (longer duration and exposure) is associated with an increased risk of advanced renal cell carcinoma. Environmental toxins, such as cadmium and asbestos, have also been associated with increased risk of renal cell carcinoma. Approximately 2% of cases are associated with inherited syndromes.

KEY POINTS

- Renal cell carcinoma is the most common type of kidney tumor. The classic triad of hematuria, abdominal pain, and a palpable mass is rarely seen in modern practice. Incidental diagnoses are increasing.
- Risk factors include smoking, obesity, hypertension, environmental exposures, hereditary kidney cancer syndromes, and acquired cystic kidney disease leading to end-stage renal disease.

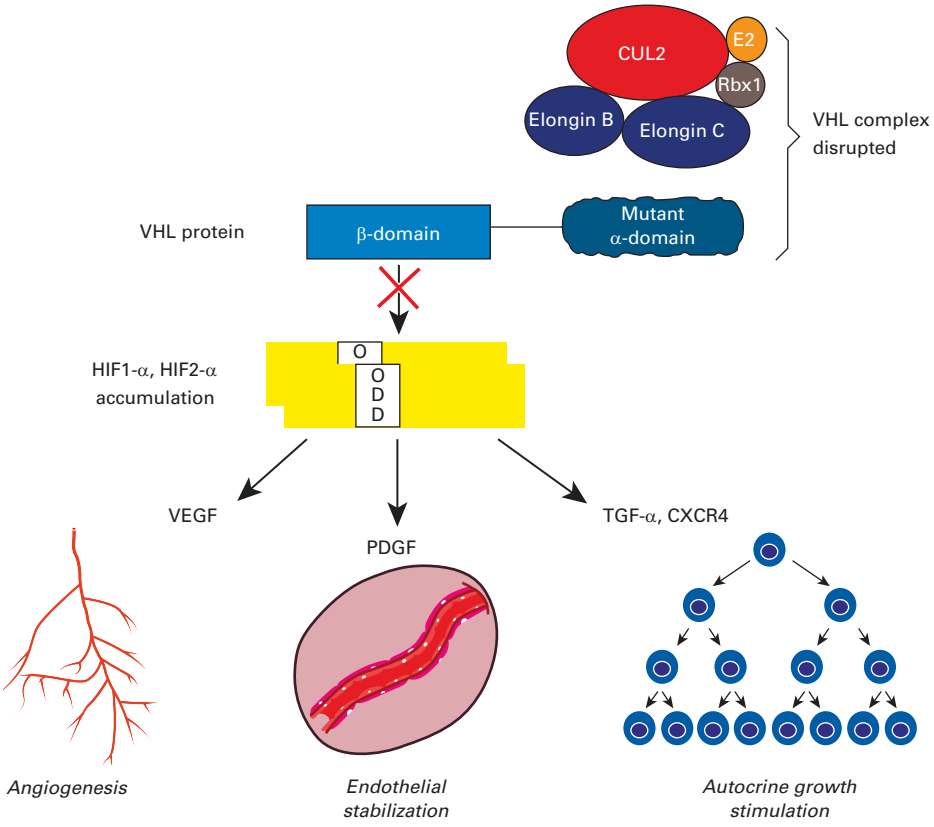
PATHOLOGY AND MOLECULAR PATHOGENESIS

The most recent WHO classification in 2022 incorporates histological and molecular subtypes of kidney cancers.[151] The classification of adult epithelial kidney tumors has expanded to include numerous histologies and molecularly defined tumors that are associated with distinct clinical outcomes. The most common types of renal cancer in adults are clear cell (75%-80% of cases) and papillary (15% of cases) renal cell carcinomas. More rare types include chromophobe (~5% of cases), collecting-duct and renal medullary (each in ~1% of cases), and translocation (<1% of cases) carcinomas. Oncocytomas consist of neoplastic cells and can grow similarly to renal cell carcinomas, but they have benign behavior and are not considered truly malignant. However, the presence of oncocytoma should prompt thorough evaluation for coexisting renal cell carcinoma, and patients should have ongoing surveillance despite a relatively low risk of subsequent renal cell carcinoma development. Sarcomatoid or rhabdoid differentiation, which is associated with a worse prognosis, can occur with any major histological subtype.

Renal cell carcinomas can have a variable natural history that reflects the biology of the histological tumor type. The clinical course of clear–cell carcinomas, which make up most renal tumors, is typically aggressive, although some patients can have an indolent course with stable metastases for years or metastases occurring decades after complete resection of a primary tumor. Molecular studies are attempting to identify markers that may predict prognosis. Papillary tumors were previously divided into type I and type II lesions according to architectural, cytologic, and genetic features, but the latest update to the WHO classification has removed the subclassification of papillary renal cell carcinomas. Chromophobe carcinomas are also typically indolent and uncommonly result in metastases and cancer-related death, although tumor necrosis and sarcomatoid differentiation predict a more aggressive phenotype versus chromophobes lacking these characteristics. Collecting-duct carcinomas have an aggressive clinical course, with more than half of patients presenting with metastases and a median survival of only a few months for patients with metastatic disease.

Von Hippel-Lindau (VHL) disease is an autosomal dominant familial cancer syndrome that predisposes individuals to clear–cell renal cancers, retinal angiomas, pancreatic cysts and neuroendocrine tumors, hemangioblastomas of the spinal cord and cerebellum, and pheochromocytomas, as well as to other rare neoplasms. Frequent loss of at least one allele on chromosome 3p in renal tumors from patients with VHL disease led to the identification of the *VHL* tumor-suppressor gene. This gene encodes a protein that promotes the ubiquitination and degradation of hypoxia-inducible factor-a (HIF-α; Fig. 14-15). Several proteins encoded by HIF-α are involved in angiogenesis, such as VEGF and platelet-derived growth factor B chain. When the VHL protein is lost in renal cancers, VEGF, platelet-derived growth factor B chain, and other proteins are overexpressed, promoting angiogenesis and tumor cell growth. Defects in the *VHL* gene, including mutation or gene silencing through methylation, also occur in a majority of tumors from patients with sporadic clear–cell renal cell carcinomas. Tumor angiogenesis is also stimulated by other growth factors that activate AKT and mTOR signaling, which also increases HIF-α expression. Therapies that target VHL-regulated and AKT-signaling pathways have demonstrated substantial antitumor activity. A novel inhibitor of HIF-2α, belzutifan, has gained FDA approval for treatment of VHL syndrome-associated cancers as well as in treatment-refractory advanced clear–cell renal cell carcinomas.

Figure 14-15 VHL Pathways for Oncogene Activation



Abbreviations: HIF, hypoxia inducible factor; PDGF, platelet-derived growth factor; TGF-α, transforming growth factor α; VEGF, vascular endothelial growth factor.
Pathways of oncogene activation in any loss of VHL function with emphasis on HIF activation.
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Several other genetic syndromes may be associated with renal cell carcinoma (Table 14-4). Genetic counseling is recommended for patients with renal cancer who are aged 46 years or younger and may be considered in patients with multifocal or bilateral renal masses and/or if personal or family history is potentially consistent with an inherited renal cancer (Table 14-5).

- The most common type of renal cell carcinoma is clear cell, accounting for approximately 80% of all renal cell cancers. Papillary renal cell carcinoma is the most common non–clear-cell type.
- Clear–cell renal cell carcinoma is driven by loss of VHL tumor-suppressor activity and increased angiogenesis mediated in part by VEGF, which provides the rationale for inhibition of VEGF as a key treatment modality in renal cell carcinoma.

Table 14-4 **Genomic Alterations in Inherited and Sporadic Renal Tumors**		
Genomic Alteration	**Type of Renal Tumor**	**Syndrome**
VHL	ccRCC	Von Hippel-Lindau (autosomal dominant): • Hemangioblastomas of CNS • Retinal angiomas • Pheochromocytomas • Pancreatic serous cystadenomas and neuroendocrine tumors
Chromosome 3 translocations or *BRCA1*-associated protein 1 (*BAP1* gene)	ccRCC	Familial ccRCC
MET (germline and somatic)	Hereditary or sporadic type I papillary RCC	Hereditary papillary renal carcinoma (autosomal dominant): • Bilateral multifocal papillary renal tumors
Fumarate hydratase (germline)	Type II papillary RCC	Hereditary leiomyomatosis and RCC: • Autosomal dominant • Uterine fibroids
Succinate dehydrogenase (germline)	ccRCC or chromophobe RCC	Hereditary paraganglioma and pheochromocytoma (autosomal dominant): • Paragangliomas • Pheochromocytomas • Bilateral and/or multifocal kidney tumors
Xp11.2 (*TFE* gene)	ccRCC or papillary RCC	Early-onset RCC
Folliculin (*FLCN* gene)	Chromophobe RCC or mixed chromophobe-oncocytoma renal tumors	Birt-Hogg-Dube syndrome: hair-follicle hamartomas of the face and neck: • Renal and pulmonary cysts • Slow-growing bilateral kidney tumors
Hamartin (*TSC1*) or tuberin (*TSC2*)	Angiomyolipomas, rare ccRCC	Tuberous sclerosis complex: • Bilateral multifocal kidney tumors
SMARCB1 (germline)	Medullary carcinoma	

Abbreviations: ccRCC, clear–cell renal cell carcinoma; CNS, central nervous system; RCC, renal cell carcinoma.
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Table 14-5 **Factors More Common in Hereditary RCC Useful for Referral for Genetic Evaluation**
Early age at RCC diagnosis (46 years or younger)
Bilateral renal cancer
Multifocal renal cancer
Strong family history of RCC (two or more relatives in the same bloodline)
RCC with personal or family history of one or more tumor type[a]
Unusual skin conditions (eg, leiomyomas, fibrofolliculomas, angiofibromas)
Family history of kidney cancer syndrome

Abbreviation: RCC, renal cell carcinoma.
[a]Pheochromocytoma, brain/spinal hemangioblastoma, pancreatic neuroendocrine tumor, retinal tumor, papillary cystadenoma, endolymphatic sac tumor, gastrointestinal stromal tumor, uterine fibroid (age ≤35 years), uveal and cutaneous melanomas, and solid cancer occurring in childhood.
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SCREENING

Certain populations may be eligible for kidney cancer screening. Patients with end-stage renal disease who have been on dialysis for three or more years may be screened for acquired cystic disease, which can be a premalignant condition. Screening is

indicated for some inherited renal carcinoma syndromes. Patients with known hereditary kidney cancer syndromes may be screened, but the screening protocol depends on the syndrome and the nature of the anticipated kidney tumors.

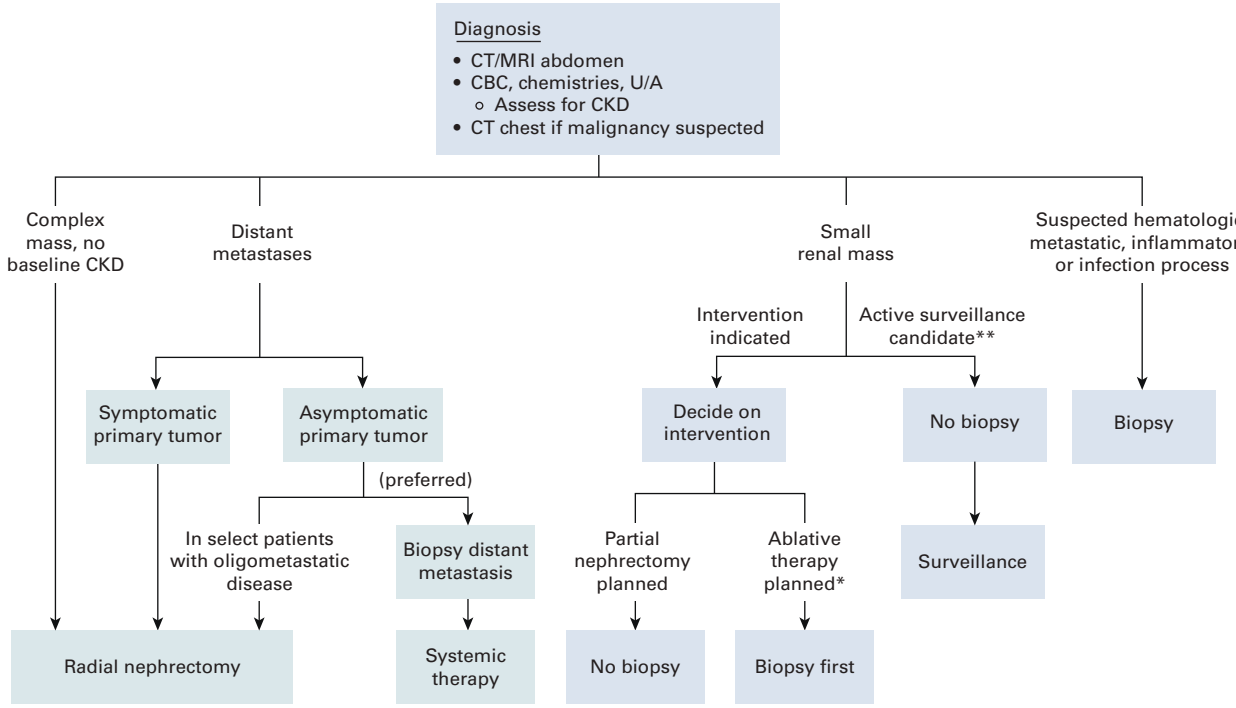
STAGING

A CT scan with contrast medium is a reliable method for detecting and staging renal cancers. MRI is useful when renal function is poor, as well as when evaluating for local invasion or assessing the renal vein and inferior vena cava for thrombus. MRI can also help distinguish a benign tumor known as an angiomyolipoma, which contains fat. Staging is performed using the AJCC staging classification.

MANAGEMENT OF LOCALIZED RENAL CANCER

Surgical excision by open or laparoscopic nephrectomy is the primary treatment of patients with localized disease by either radical nephrectomy or nephron-sparing partial nephrectomy for small tumors (Fig. 14-16). The role of lymphadenectomy remains controversial and does not clearly improve OS. Tumor extension into the renal vein or inferior vena cava, indicating stage III disease, does not preclude resection, and cardiopulmonary bypass may be required for some cases; approximately 50% of such patients have prolonged survival with a successful resection. There is no benefit to postoperative RT for patients with locally advanced disease. Signs and symptoms of hepatic dysfunction may occur in patients with localized renal cancer (ie, without evidence of metastatic disease). This is a paraneoplastic phenomenon referred to as Stauffer syndrome. Although it is rare, patients with this syndrome should undergo resection, which leads to reversal of the hepatic dysfunction.

Figure 14-16 Diagnostic and Treatment Approaches to the Patient With a Kidney Mass



Abbreviations: CBC, complete blood cell; CKD, chronic kidney disease; U/A, urinalysis.
*Criteria for observation of small renal masses. Ablative approaches include catheter embolization, radio frequency ablation, and radiation therapy.
**Consideration in favorable risk.
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Small renal masses are defined as incidentally image-detected contrast-enhancing renal tumors 4 cm or less in diameter that are generally consistent with stage T1a renal cell carcinoma. Historically, small renal masses did not require biopsy, but biopsy should be considered with suspicion of hematologic, metastatic, inflammatory, or infectious etiology.[152] Active surveillance is used for patients with significant comorbidities and limited life expectancy, especially for those with lesions smaller than 2 cm. No validated protocols for active surveillance exist, but serial imaging is generally performed every 3 to 6 months for the first 2 years to establish growth rate and then every 6 to 12 months afterward. Triggers for intervention are unclear but may include a size larger than 3 cm, median growth rate greater than 5 mm per year, or increased stage.[152]

Focal therapy (eg, partial nephrectomy or cryotherapy) is preferred for patients in whom a nonsurgical intervention is indicated and with a tumor amenable to this approach. Focal therapy is associated with less risk of renal dysfunction than radical nephrectomy in patients with baseline normal renal function. Percutaneous thermal ablation or radiofrequency ablation may be considered as an alternative to partial nephrectomy in patients with cT1a masses smaller than 3 cm, although these techniques may have an increased likelihood of tumor persistence or local recurrence compared with surgery.[153]

By contrast, radical nephrectomy should be considered for complex masses that would make partial nephrectomy technically challenging in a patient with no baseline renal dysfunction or proteinuria and a normal contralateral kidney.

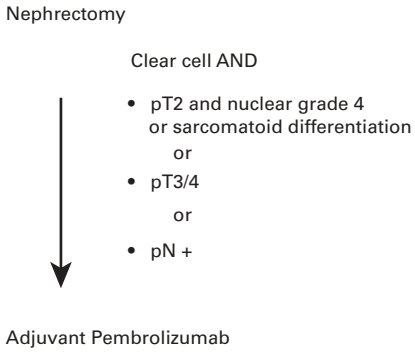
KEY POINTS

- After radiographic evaluation of a localized kidney mass, the decision whether to biopsy or to perform partial or radical nephrectomy depends on the level of suspicion of malignancy, the size of the lesion, and the age and comorbidities of the patient.
- Small renal masses are often incidentally detected as contrast-enhancing tumors <4 cm. Options for management include active surveillance, partial nephrectomy, and percutaneous ablation.
- Complex masses may require radical nephrectomy with some increased subsequent risk of renal impairment.

Adjuvant Therapy

In the phase 3 *S*-TRAC study, 615 patients with high-risk clear cell–type renal cell carcinoma after nephrectomy received 1 year of adjuvant sunitinib or placebo (Fig. 14-17).[154] The median DFS was significantly longer in patients receiving sunitinib versus placebo at 6.8 versus 5.6 years, respectively. *S*-TRAC resulted in FDA approval of sunitinib as adjuvant therapy. However, sunitinib also increases toxicity, and no data demonstrating OS benefit are available. Furthermore, four additional phase 3 studies of adjuvant TKIs have all failed to meet their primary DFS endpoints, including studies with axitinib, pazopanib, and sorafenib, as well as the ASSURE trial that included sunitinib.

Figure 14-17 Adjuvant Pembrolizumab for High-Risk Localized RCC



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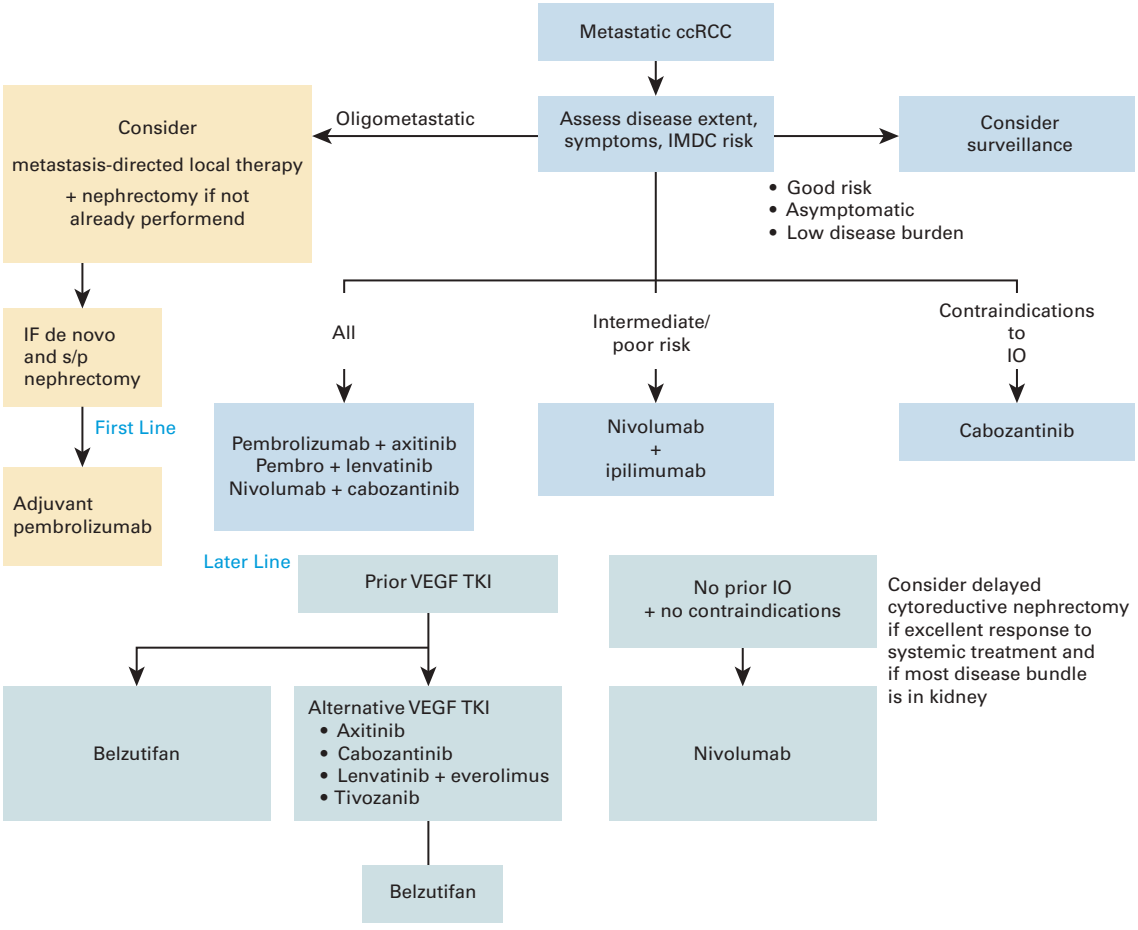
A large phase 3 randomized clinical study, KEYNOTE-564, evaluated the role of adjuvant pembrolizumab 200 mg intravenously every 3 weeks for 1 year versus placebo in patients with clear–cell kidney cancer with intermediate high or high risk of recurrence after prior nephrectomy with or without metastasectomy. At prespecified interim analysis, the use of pembrolizumab had resulted in significant improvement in DFS (HR, 0.68; 24-month DFS 77.3% vs 68.1%).[155] Further follow-up showed an OS benefit with adjuvant pembrolizumab (HR, 0.62), which was maintained with further follow-up.[156] Common adverse effects with pembrolizumab were fatigue, diarrhea, rash, itching, hypothyroidism, and muscle aches. Based on these results, pembrolizumab is FDA approved as adjuvant therapy for renal cell carcinoma at intermediate high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

METASTATIC RENAL CELL CARCINOMA

Patients with metastatic renal cell carcinoma may have a varied, unpredictable, and in some cases protracted clinical course. One prospective phase 2 study of patients with treatment-naive asymptomatic metastatic renal cell carcinoma with a primary endpoint of time to initiation of systemic therapy made at the discretion of the treating physician and patient-reported a median time of surveillance of 14.9 months.[157] Having variant features, more adverse risk factors, and more metastatic sites was associated with a shorter surveillance time. Therefore, a select subset of patients with metastatic renal cell carcinoma may be managed on a

surveillance program before systemic therapy. One nomogram used to predict survival based on patients treated in the cytokine era (Memorial Sloan-Kettering Cancer Center prognostic model) includes the following as poor prognostic variables: time from diagnosis to systemic treatment <1 year, low Karnofsky performance status (<80%), low hemoglobin level, high corrected serum calcium level, and high serum lactate dehydrogenase (LDH) level. Newer prognostic models for patients with metastatic renal cell carcinoma treated with contemporary targeted therapies have generally included these prognostic factors in addition to others, such as platelet count, alkaline phosphatase, and number and sites of metastases, although the International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) model (risk factors: anemia, thrombocytosis, neutrophilia, hypercalcemia, Karnofsky performance status <80%, and <1 year from diagnosis to treatment) has been externally and prospectively validated in patients treated with first-line VEGF-targeted treatment and also validated with first-line combination immunotherapy treatment (Fig. 14-18). This risk-stratification scheme has been used to define eligibility and stratify patients for multiple studies evaluating immunotherapy or immunotherapy/TKI combinations in frontline treatment.

Figure 14-18 Treatment Options for Metastatic ccRCC



Abbreviations: ccRCC, clear–cell renal cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immunotherapy; TKI, tyrosine kinase inhibitor.
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Role of Surgery In Metastatic Disease

Cytoreductive nephrectomy may be considered as an initial treatment of patients with metastatic disease to relieve local symptoms or control bleeding. In the era of cytokine therapies, two prospective randomized studies demonstrated improved survival for patients subsequently treated with IFNα-2b. With improved systemic therapies in the era of VEGF TKIs as standard first-line treatment, the role of cytoreductive nephrectomy was addressed in the CARMENA trial, which randomly assigned patients with confirmed de novo metastatic clear–cell renal cell carcinoma and intermediate or poor risk by the Memorial Sloan-Kettering Cancer Center prognostic model to standard care (nephrectomy followed by sunitinib) versus sunitinib without nephrectomy.[158] OS in the sunitinib-only group was statistically noninferior (although numerically superior) to that in the standard care group at the planned interim analysis. This trial was limited by unequal allocation of T3/4 tumors to the surgery arm, failure of some

patients in both arms to undergo assigned interventions, and selection bias with particularly poor-risk patients enrolled in the study. There was also concern that patients who have symptomatic primary tumors might have been preferentially selected to undergo nephrectomy rather than be enrolled in the study, thus limiting generalizability to these patients. In the era of combination checkpoint inhibitor-based frontline therapy, the role of cytoreductive nephrectomy is not well defined. Patient selection is key, and nephrectomy may still be appropriate for some patients, especially those without poor-risk disease or patients experiencing symptoms (eg, hematuria and pain) from the renal mass, or in patients who achieve excellent response to initial systemic therapy and have minimal metastatic disease burden. In general, immediate systemic therapy is preferred over upfront nephrectomy based on the results from CARMENA, unless immediate local palliation is needed. Delayed cytoreductive nephrectomy may be considered in select cases exhibiting a favorable response to systemic therapy.

The use of neoadjuvant systemic therapies in patients with locally advanced renal cell carcinoma has demonstrated tumor downsizing as well as treatment with partial nephrectomy in a subset of patients who would otherwise have required a radical nephrectomy, but this is not standard. Use of embolization may be recommended preoperatively for large primary tumors and for the resection of metastatic lesions because of the highly vascular nature of renal cell carcinoma. Surgical excision of oligometastatic disease at presentation or after prolonged disease-free intervals may be appropriate in select patients, especially those with non–clear cell histologies.

Systemic Therapies

Available systemic therapies for renal cell carcinoma include the following:

- Agents targeting VEGF receptor (VEGFR), including monoclonal antibodies and TKIs
- Agents targeting mTOR
- Immune-based therapies, including cytokines and checkpoint inhibitors
- Inhibitor of HIF-2α

FRONTLINE THERAPY FOR METASTATIC RENAL CELL CARCINOMA (CLEAR CELL)

Immune Checkpoint Inhibitor Combination

The combination of PD1-inhibitor nivolumab with the CTLA-4 inhibitor ipilimumab demonstrated improved OS in comparison with sunitinib in treatment-naive patients with intermediate- or poor-risk advanced renal cell carcinoma (per IMDC criteria described previously) in the phase 3 Checkmate 214 trial.[159] Nivolumab was administered 3 mg/kg IV and ipilimumab 1 mg/kg IV once every 3 weeks for four doses, followed by nivolumab monotherapy every 2 weeks. Primary endpoints were OS, PFS, and ORR in IMDC intermediate- or poor-risk patients. Nivolumab and ipilimumab significantly improved OS and ORR compared with sunitinib in the primary study analyses. The safety profiles of nivolumab and ipilimumab were manageable, with fewer grade 3 to 5 adverse events seen with the combination (46%) in comparison with sunitinib (63%). However, systemic corticosteroids were required in 40% of patients treated with nivolumab and ipilimumab. This is higher than the approximately 15% to 20% of patients receiving VEGF TKI and immunotherapy combinations requiring glucocorticoids. Long-term follow-up shows that the combination of ipilimumab and nivolumab was associated with durable responses in IMDC intermediate- and poor-risk patients with a median duration of response of 75 months and a median OS of 47 months. Because combined CTLA-4 and PD-1/PD-L1 blockade is associated with significant immune-related adverse events, other trials (HCRN GU16-260 and OMNIVORE)[160] have tested a strategy of first-line PD-1/PD-L1 inhibitor monotherapy followed by the addition of CTLA-4 blockade as salvage only for those patients who have a suboptimal response to PD-1/PD-L1 monotherapy. Response rates to salvage combination therapy were modest, and some patients experienced progression too rapidly to receive it, so this strategy is currently recommended only for patients with borderline performance status that may preclude upfront CTLA-4 with PD-1 or VEGF with PD-1/PD-L1 inhibitor combinations or select patients with favorable-risk disease interested in minimizing treatment toxicity.

VEGF TKI and Immunotherapy Combinations

Several recent trials have also tested the combination of VEGF-targeted agents with PD-1/PD-L1 inhibitors because VEGF-targeted agents are active in kidney cancer and may also have immunomodulatory effects. There are no head-to-head data to inform which combination of VEGF/IO to use, so most clinicians choose the regimen with which they are most familiar.

The phase 3 KEYNOTE-426 trial demonstrated improved OS and PFS with the combination of pembrolizumab and axitinib versus sunitinib in previously untreated advanced or metastatic kidney cancer.[161] Improvement in PFS and OS was observed in the ITT patients who included all IMDC risk groups, and was irrespective of PD-L1 expression. The most common adverse effects were hypertension, diarrhea, fatigue, and transaminase elevations in the axitinib pembrolizumab arm.[161] Similarly, the phase 3 CheckMate-9ER trial demonstrated improvement in PFS and OS as well as quality of life with the combination of nivolumab and cabozantinib versus sunitinib in the frontline setting for the ITT population encompassing all IMDC risk groups.[162] Common treatment-related serious adverse effects included hand-foot syndrome, hypertension, hypothyroidism, and fatigue. The CLEAR

trial compared lenvatinib (20 mg daily) with pembrolizumab versus lenvatinib (18 mg daily) and everolimus (5 mg daily) versus sunitinib and demonstrated a prolonged PFS with both lenvatinib-containing arms; in addition, OS was improved with lenvatinib and pembrolizumab versus sunitinib in the ITT patients. Complete responses were seen in 16.1% patients on lenvatinib with pembrolizumab compared with 4% with sunitinib alone.[163] Serious side effects were more common with the lenvatinib with pembrolizumab combination compared with sunitinib. Most common side effects were diarrhea, hypertension, hypothyroidism, and fatigue.

The phase 3 JAVELIN Renal 101 trial demonstrated improved PFS with the combination of axitinib and avelumab relative to sunitinib regardless of PD-L1 status.[162] However, in contrast to the prior 3 anti–PD-1/TKI regimens, no OS benefit has been reported to date for avelumab and axitinib, and consequently, other immunotherapy combinations are preferred. The FDA approved avelumab with axitinib, pembrolizumab with axitinib, cabozantinib with nivolumab, and lenvatinib with pembrolizumab for first-line therapy of kidney cancer based on these trials. Therefore, the standard frontline treatment of locally advanced or metastatic renal cell carcinoma now includes either combined CTLA-4/PD-1 blockade or combination anti-VEGFR and anti–PD-1 therapy. Of note, FDA approval for the anti–PD-1/TKI combinations includes all treatment-naive advanced renal cell carcinoma patients regardless of IMDC risk group, whereas nivolumab and ipilimumab are approved for IMDC intermediate- and poor-risk patients, adhering to the primary endpoint population of the respective studies. However, the IMDC favorable-risk subgroup has consistently demonstrated favorable and relatively little difference in efficacy outcomes in all of these studies comparing sunitinib and immunotherapy combinations; moreover, this approach may be best for patients who value the possibility of treatment-free survival.

The role of triplet combination therapy with anti–CTLA-4/PD-1 blockade and VEGFR TKI was evaluated in the phase 3 COSMIC-313 study, in which advanced clear–cell renal cell carcinoma with IMDC intermediate- or poor-risk disease were randomized to receive first-line therapy with ipilimumab and nivolumab with either cabozantinib or placebo.[164] The addition of cabozantinib was associated with an improvement in the primary endpoint with a significantly prolonged PFS (HR, 0.73) as well as a higher ORR of 43% versus 36%. However, the toxicity of the triplet regimen also appeared to be substantially higher, and data regarding OS benefit were immature. The triplet regimen of ipilimumab, nivolumab, and cabozantinib is not currently approved by any regulatory authority, but OS follow-up is ongoing.

Single-Agent Tyrosine Kinase Inhibitors

The data from multiple phase 3 trials demonstrate that immunotherapy-based combinations involving ipilimumab with nivolumab or anti–PD-1/TKI combinations should be the preferred first-line therapy for most patients. However, some patients may be poor candidates for immune checkpoint inhibitors because of comorbidities (eg, history of orthotopic transplant or significant autoimmune disease). TKI monotherapy is a preferred option for patients who are not eligible to receive immunotherapy.

Multiple TKIs have been developed to target the kinase domain of VEGFR and were the standard of care first-line treatment for many years until the recent advancement of immune checkpoint inhibitor combinations described. The multikinase TKIs sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib, and tivozanib have been approved by the FDA as either monotherapy or in combination with other treatments for advanced renal cell carcinoma (Table 14-6). Sunitinib, pazopanib, and cabozantinib are preferred first-line options based on clinical data and prior FDA approvals as first-line therapy. However, sunitinib monotherapy has been a standard comparator arm in several recent first-line trials, and TKI monotherapy is now considered an inferior therapy compared with any of the modern immune checkpoint inhibitor combination options.

The major toxicities of sunitinib are fatigue, oral lesions, hand-foot syndrome (also known as palmar-plantar erythrodysesthesia), hypertension, and diarrhea. Alternative dosing schedules, including 2 weeks on and 1 week off, may be associated with improved tolerability and similar efficacy as standard dosing. A randomized phase 3 noninferiority trial compared the efficacy and safety of pazopanib and sunitinib as first-line therapy. The PFS for patients treated with pazopanib was noninferior to that for those treated with sunitinib, and the OS was similar.[165] The safety profile favored pazopanib with less fatigue (55% vs 63%), hand-foot syndrome (29% vs 50%), and thrombocytopenia (41% vs 78%). A higher incidence of increased alanine aminotransferase level was seen with pazopanib (60% vs 43%). Health-related quality of life measures favored pazopanib with less fatigue and soreness of the mouth, hands, and feet. However, this trial did not allow dose reductions or alternative dosing schedules frequently used to ensure tolerability of sunitinib, as discussed previously. Other toxicities from this class of drugs include rash, myelosuppression (including thrombocytopenia), hypothyroidism, and congestive heart failure. Pazopanib therapy may also be associated with serious hepatotoxicity. Sunitinib-associated hypertension, defined as a maximum or mean systolic blood pressure greater than 140 mm Hg, was associated with an improvement in clinical outcome, suggesting that the development of hypertension during therapy may be a biomarker of response to sunitinib.

The randomized phase 2 CABOSUN trial showed that cabozantinib improved PFS relative to sunitinib in treatment-naive patients, although the difference in OS was not statistically significant.[166] Based on these trials, cabozantinib is FDA approved as first-line therapy for metastatic renal cell carcinoma or after failure of prior antiangiogenic therapy. Cabozantinib may have particular efficacy in patients with bone metastases.

Table 14-6 **Combination Therapies for Frontline Treatment of Metastatic Renal Cell Carcinoma**

	Ipilimumab + Nivolumab	Axitinib + Pembrolizumab	Axitinib + Avelumab	Cabozantinib + Nivolumab	Lenvatinib + Pembrolizumab
Randomization (control arm)	1:1 (sunitinib)	1:1 (sunitinib)	1:1 (sunitinib)	1:1 (sunitinib)	1:1:1 (lenvatinib with everolimus, sunitinib)
No. of subjects	1,096	861	886	651	1,069
IMDC risk (%)	23	31.2	21.4	23	31
Favorable	61	56.2	61.8	58	59.2
Intermediate poor	17	12.6	16.2	19	9.3
PD-L1 >1% (%)	24	60.5	63.2	26	30.1
OS	0.68	0.53	0.78	0.60	0.66
HR 95% CI	0.49-0.95	0.38-0.74	0.55-1.08	0.40-0.89	0.49-0.88
Median PFS (months)	12.4	15.1	13.8	16.6	23.9
Combination sunitinib	12.3	11.1	8.4	8.3	9.2
Objective RR	39%	59.3%	51.4%	55.7%	71%
Complete RR	10.20%	5.8%	3.4%	8%	16.1%
Median DoR (months)	76.2	23.6	19.4	20.2	25.8

Abbreviations: DoR, duration of response; IMDC, International Metastatic Renal-Cell Carcinoma Database Consortium; OS, overall survival; PFS, progression-free survival; RR, response rate.
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First-line VEGF TKI therapy is reasonable to consider in patients who have metastatic renal cell carcinoma who have a contraindication to receiving immune checkpoint inhibitors or in selected patients with favorable risk and low burden of disease.

Cytokines

Until 2006, immunotherapy had represented the primary treatment of patients with advanced renal cancer, as conventional chemotherapy had little clinical activity. The most extensively studied agents were IFN-α and aldesleukin (human recombinant interleukin-2 [IL-2]). IFN-α demonstrated low but reproducible response rates of 10% to 20% with occasional durable responses. Increased expression of VEGF in clear–cell renal carcinomas led to investigations of bevacizumab, a humanized VEGF-neutralizing antibody, in metastatic renal cell carcinoma before and after cytokine therapy. The addition of bevacizumab to IFN for first-line therapy significantly improved ORR and PFS in two phase 3 randomized trials.[167,168] Hypertension and asymptomatic proteinuria were the most common adverse events.

Therapy with IL-2 results in responses in approximately 20% of patients of patients who have clear–cell histology, with durable responses in 4% to 5% of cases.[169] Prolonged and durable responses occur more commonly in patients with good performance status and younger age. Toxicity associated with high-dose bolus IL-2 is related to increased vascular permeability and often necessitates treating patients in an intensive-care setting. IL-2 has been associated with a 4% incidence of treatment-related death. IL-2 is associated with durable CRs and may be most appropriate for younger, good-risk patients. With advances in immune checkpoint inhibitor combinations, cytokine therapies are now used primarily in select cases, typically in treatment-refractory settings and younger patients with excellent performance status and minimal comorbidities.

mTOR Inhibitors

The mTOR pathway is frequently activated in renal cell carcinoma, which can result in increased production of HIF-1α and HIF-2α. Consequently, agents that inhibit mTOR have been studied in patients with metastatic renal cell carcinoma. The mTOR inhibitor temsirolimus improved OS compared with IFN (10.9 vs 7.3 months) in treatment-naive patients with poor-risk metastatic renal cell carcinoma. This led to FDA approval of single-agent temsirolimus in 2007. Because of the improved efficacy of immunotherapy and VEGF with immunotherapy combinations in intermediate- and poor-risk metastatic renal cell carcinoma, single-agent temsirolimus is rarely used as a frontline single agent.

SECOND AND SUBSEQUENT LINES OF THERAPY

Previous studies have shown that patients whose disease progresses while undergoing VEGF-targeted therapy can experience a response to another VEGF-targeted therapy. The phase 3 AXIS trial compared the VEGFR selective TKI axitinib with sorafenib in patients whose disease had progressed during first-line therapy.[170] The overall median PFS was 6.7 months for patients who received axitinib compared with 4.7 months for patients treated with sorafenib. Therefore, axitinib was FDA approved in 2012 for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

Key Phase 3 Trials of Antiangiogenic Therapy in Treatment-Refractory Metastatic Renal Cell Carcinoma

The PD-1 inhibitor nivolumab prolonged OS in comparison with everolimus in patients with metastatic renal cell carcinoma after prior angiogenic therapy (25.0 vs 19.6 months),[171] and it received FDA approval for this indication, but it is now rare for patients to be PD-1-inhibitor-naive in later-line settings (Table 14-7).

Table 14-7 Key Phase 3 Trials of Antiangiogenic Therapy in Metastatic RCC

Trial	No. of Participants	Study Population	Design	Outcome	Notes
Motzer et al[172]	750	Treatment-naive metastatic RCC	Sunitinib vs interferon-α	Improved PFS with sunitinib (11 vs 5 months)	Improved OS with sunitinib in long-term follow-up (26.4 vs 21.8 months)
Sternberg et al[173]	435	Treatment-naive and cytokine-treated metastatic RCC	Pazopanib vs placebo	Improved PFS with pazopanib (9.2 vs 4.2 months)	PFS benefit seen regardless of prior treatment
AXIS[174]	723	Previously treated metastatic RCC	Axitinib vs sorafenib	Improved PFS with axitinib (6.7 vs 4.7 months)	OS did not differ in long-term follow-up (20.1 vs 19.2 months)
METEOR[175]	658	VEGFR-treated metastatic RCC	Cabozantinib vs everolimus	Improved PFS with cabozantinib (7.4 vs 3.8 months)	More toxicity with cabozantinib. Improved OS with cabozantinib in long-term follow-up
CABOSUN[176]	157	Treatment-naive intermediate-/high-risk metastatic RCC	Cabozantinib vs sunitinib	Improved PFS with cabozantinib (8.6 vs 5.3 months)	No significant OS difference in long-term follow-up
Motzer et al[177]	153	VEGFR-treated metastatic RCC	Lenvatinib plus everolimus vs lenvatinib versus everolimus	Improved PFS with lenvatinib plus everolimus (14.6 months) or lenvatinib (7.4 months) vs everolimus (5.5 months)	Marginally improved OS with lenvatinib plus everolimus vs everolimus, but underpowered. Increased toxicity with combination therapy

Abbreviations: OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; VEGFR, vascular endothelial growth factor receptor.
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Targeted therapies have also been directed against several identified mechanisms of resistance to VEGF-directed therapy. Cabozantinib is a TKI that targets MET and AXL in addition to VEGFR. The phase 3 METEOR trial demonstrated that cabozantinib was superior to everolimus in OS and PFS in previously treated patients with metastatic renal cell carcinoma.[178] Lenvatinib is a TKI that inhibits FGFR in addition to VEGF. Lenvatinib combined with everolimus improved PFS versus everolimus alone in patients previously treated with antiangiogenic therapy.[177] This combination was approved by the FDA in 2016 for the treatment of advanced renal cell carcinoma after one prior antiangiogenic therapy. In the third-line setting, another VEGF-directed TKI, tivozanib, demonstrated improved PFS and less toxicity in comparison with sorafenib after prior

VEGF-directed therapy,[179] earning FDA approval for relapsed or refractory advanced renal cell carcinoma following two or more prior systemic therapies. Based on results of a large phase 3 clinical study (Tivo-3), tivozanib, an oral VEGF inhibitor, is FDA approved for relapsed or refractory metastatic renal cell carcinoma after progression with two or more prior lines of systemic therapy, including at least one VEGF inhibitor. Common adverse effects associated with tivozanib include fatigue, hypertension, proteinuria, and diarrhea.

In practice, clinicians may switch between VEGF inhibitors if other options are exhausted and clinical trials are not available, and it may be reasonable to alternate between TKIs with broad-spectrum (cabozantinib, lenvatinib) and narrow-spectrum (axitinib, tivozanib) activity.

For patients who progress on prior immune checkpoint inhibitor therapy, there is unlikely to be a benefit from continuing or switching anti–PD-1/L1 therapy along with a TKI. The phase 3 CONTACT-03 study randomized patients with advanced renal cell carcinoma with progression on or after a prior jPD-(L)1i-based therapy to receive either cabozantinib monotherapy or cabozantinib and atezolizumab. There was no difference in any major efficacy outcome (OS, PFS, and ORR), and the addition of atezolizumab was associated with increased toxicity.[180] Similarly, the phase 3 TiNivo-2 study showed no benefit of nivolumab in addition to tivozanib in patients with progression post-PD-(L)1i.[180] These results are not applicable to patients who discontinued prior PD-(L)1i due to toxicity or reasons other than progression.

HIF Inhibitor

As described, the transcription factor HIF is a major element in clear–cell renal cell carcinoma pathogenesis. Belzutifan is an orally bioavailable inhibitor of HIF-2α. Belzutifan demonstrated clinical efficacy compared with everolimus in the phase 3 LITESPARK-005 study of advanced clear–cell renal cell carcinoma patients with progression after prior anti–PD-1/L1 and VEGFR TKI.[181] Coprimary endpoints of PFS and OS were evaluated, and belzutifan improved PFS in comparison with everolimus, but OS was not statistically different at the time of the initial data report. Belzutifan was associated with an objective response rate of 22.7% in comparison with 3.5% with everolimus. Common adverse events with belzutifan included fatigue, anemia, hypoxia, dyspnea, and nausea. Based on the PFS benefit, the FDA approved belzutifan in December 2023 for advanced renal cell carcinoma patients following prior anti–PD-1/L1 and VEGFR TKI.

Other Therapies

Everolimus is an orally administered mTOR inhibitor. In comparison with placebo, everolimus improved PFS in previously treated patients with metastatic renal cell carcinoma (4.0 vs 1.9 months). This study was the first phase 3 randomized trial to demonstrate the efficacy of second-line therapy for patients whose disease progressed during treatment with a VEGF inhibitor, and it led to FDA approval of everolimus in 2009 for the treatment of advanced renal cell carcinoma after failure of either sunitinib or sorafenib. However, everolimus monotherapy is infrequently used, given the availability of more active therapies described already, including combination therapy with lenvatinib and everolimus. Adverse reactions from mTOR inhibitors include rash, asthenia, mucositis, nausea, edema, myelosuppression, hyperlipidemia, hypercholesterolemia, hyperglycemia, and drug-induced pneumonitis.

Finally, based on the known activity of cytokine therapy and retrospective data of clinical responses in patients following anti–PD-1/PD-L1 therapy, high-dose IL-2 may be considered for select clear–cell renal cell carcinoma patients in the treatment-refractory setting.[182]

Chemotherapy

In general, renal cell carcinoma is highly resistant to conventional chemotherapy, which does not have a role in the treatment algorithm. One exception is collecting-duct carcinoma, a rare and aggressive subtype of kidney cancer that originates from medullary collecting ducts. Small studies show that gemcitabine plus platinum has activity in metastatic collecting-duct carcinoma, analogous to the treatment of upper-tract urothelial carcinoma.[183] Renal medullary carcinoma is another rare, aggressive subtype of collecting-duct carcinomas, most commonly occurring in patients with the sickle cell trait associated with SMARCB1 loss. Platinum-based chemotherapy combinations have also reported clinical activity in a small case series of patients with renal medullary carcinoma.[184]

SARCOMATOID RENAL CELL CARCINOMA

Sarcomatoid histology represents tumor dedifferentiation and can be associated with any major histological subtype of renal cell carcinoma. Sarcomatoid features are associated with aggressive tumor biology as well as relatively limited benefit from VEGFR TKIs. However, immune checkpoint inhibitors have demonstrated promising clinical activity. Nivolumab and ipilimumab demonstrated a high ORR of 61% (23% CR) in patients with sarcomatoid clear–cell renal cell carcinomas, along with significantly improved OS and PFS compared with sunitinib.[185]

Similarly, the phase 3 studies of anti–PD-1 and TKI combinations included a subset of patients with sarcomatoid histology and reported clinical benefit with these combinations over sunitinib. However, the long-term follow-up and overall data with nivolumab and ipilimumab appear more robust than the data currently available for anti–PD-1 and TKI combinations for sarcomatoid variant disease.

KEY POINTS

- Adjuvant pembrolizumab for 1 year improves DFS and OS in intermediate- and high-risk resected localized clear–cell renal cell carcinoma.
- First-line systemic therapy for metastatic clear–cell renal cell carcinoma includes combination immune checkpoint blockade with ipilimumab and nivolumab or combination of PD-1/PD-L1 inhibition and VEGFR TKIs.
- The role of cytoreductive nephrectomy in the setting of metastatic disease remains undefined in the era of immune checkpoint inhibitor combinations. For patients without symptomatic primary tumors who are eligible for first-line systemic therapy, immediate cytoreductive nephrectomy may not provide significant benefit. The role of deferred nephrectomy is being evaluated in prospective clinical trials.
- Second-line therapy for metastatic disease includes VEGFR TKIs, belzutifan, mTOR inhibitors, and cytokine therapy in select patients, with the choice of therapy dependent on prior treatment. Alternate antiangiogenesis inhibitors may still be active after prior antiangiogenic therapy.

NON–CLEAR CELL RENAL CELL CARCINOMA

Most treatment strategies in renal cell carcinoma have been tested primarily or exclusively in clear–cell renal cell carcinoma, and high-level evidence for treatment of rare non–clear cell renal cell carcinoma histologies is lacking. Importantly, non–clear cell renal cell carcinoma (RCC) is not one disease, and the biology of different histological subtypes is quite different; unfortunately, many trials have lumped these patients together, given the rarity of individual subtypes. For localized disease, the standard treatment remains nephrectomy. No adjuvant therapy has proven benefit for non–clear cell disease. For advanced disease, targeted therapies or immunotherapy may be offered (Table 14-8); chemotherapy is generally ineffective but may have

Table 14-8 Targeted Agents for Non–Clear Cell RCC

Agent	Primary Target	Histology	Outcome
Sunitinib	*VEGFR*	Papillary, chromophobe, translocation	Improved PFS with sunitinib vs everolimus (8.3 vs 5.6 months), but poor-risk patients may have better PFS with everolimus
Temsirolimus	*mTOR*	Papillary, chromophobe	Improved OS with temsirolimus vs IFN (11.6 vs 4.3 months)
Everolimus	*mTOR*	Papillary, chromophobe, translocation	See above comments on sunitinib. No clear difference between sequencing sunitinib followed by everolimus vs everolimus followed by sunitinib
Crizotinib	*MET*	Type I papillary RCC	In 4 of 23 patients with *MET* alteration, 2 had PR
Foretinib	*MET*, *VEGF*	Papillary RCC	In 10 patients with germline *MET* alteration, 5 had PR. Overall, RR was 13.5%; median PFS was 9 months
Savolitinib	*MET*	Papillary RCC	In the phase 3 SAVOIR trial, compared savolitnib vs sunitinib in *MET*-driven papillary RCC. Enrollment was closed early when new data suggested longer-than-anticipated PFS of patients with papillary RCC treated with sunitinib. PFS numerically improved, not statistically significant (with early termination). Savolitinib arm of PAPMET closed early for futility
Cabozantinib	*MET*, *VEGF*	Papillary RCC	Improved ORR and PFS were seen in comparison with sunitinib in the frontline setting in PAPMET (see above)

Abbreviations: IFN, interferon; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; RR, response rate; VEGFR, vascular endothelial growth factor receptor.
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some benefit for collecting-duct renal cell carcinoma or renal medullary carcinomas. Ipilimumab with nivolumab was recently evaluated versus the investigator's choice (primarily VEGF inhibitor monotherapy) in non–clear cell histologies in the phase two SUNNIFORECAST trial.[186] Across all histologies, OS at 12 months was improved with ipilimumab/nivolumab versus investigator's choice (86.9% vs 76.8%), with no clear differences emerging in papillary versus nonpapillary histologies in an underpowered comparison. Nonrandomized data suggest that single-agent PD-1 inhibitors may result in objective responses in patients with papillary tumors.[12,187] Combination of VEGF and PD-1 inhibition may also be a reasonable option, especially in papillary RCC, based on single-arm data.[12,187] Better therapies are needed for patients with non–clear cell renal cell carcinoma, and clinical trials are preferred when available.

Activation of the c-MET signaling pathway in papillary renal cell carcinomas has led to trials with agents that target the c-MET tyrosine kinase receptor or its ligand, hepatocyte growth factor, in patients with metastatic papillary renal cell carcinoma. MET-driven disease can be defined by chromosome 7 copy gain, focal *MET* or *HGF* gene amplification, or MET kinase domain mutations. Several MET inhibitors have been investigated in this disease. The PAPMET trial investigated the optimal therapy for patients with metastatic papillary renal cell carcinoma treated with up to one previous therapy (excluding VEGF- and/or MET-targeted agents), comparing sunitinib, cabozantinib, crizotinib, and savolitinib. Crizotinib and savolitinib arms were halted for futility; ORR and PFS were significantly improved with cabozantinib versus sunitinib.[188]

SPECIAL CONSIDERATIONS FOR PATIENTS WITH METASTATIC RENAL CELL CARCINOMA

Approximately one-third of patients with advanced renal cell carcinoma have bone metastases, and these are predominantly osteolytic. Treatment with bone-targeting agents, such as zoledronic acid (which requires dose adjustment for renal impairment) or denosumab, has been shown to decrease the risk of SREs in patients with bone metastases. As discussed in the "Prostate Cancer" section, dosing schedules may vary.

Brain metastases are a frequent complication in patients with metastatic clear–cell renal cancer. Surgical resection or stereotactic radiosurgery is a feasible alternative to whole-brain irradiation and may result in long-term survival. Patients with treated brain metastases may safely receive systemic therapy. Limited studies have also suggested that patients with severe renal impairment or end-stage renal disease who are receiving hemodialysis may safely be treated with selected targeted therapies.

TREATMENT OF CANCERS ASSOCIATED WITH VHL DISEASE

Von Hippel-Lindau disease is a rare condition characterized by a mutation of the *VHL* gene. VHL is commonly associated with the development of bilateral renal cell carcinomas, CNS, pancreatic, and retinal hemangioblastomas and other tumors. Impressive responses to oral belzutifan, an HIF-2α inhibitor, were demonstrated in renal cell carcinomas (49%), pancreatic tumors (77%), and CNS hemangioblastomas (30%) associated with VHL. Based on the results of this phase 2 single-arm study, oral belzutifan was FDA approved for the treatment of VHL-associated disease manifestations, including primitive neuroectodermal tumors, renal cell carcinomas, and hemangioblastomas.

SURVIVORSHIP AND CONSIDERATIONS IN ELDERLY PATIENTS

Radical nephrectomy is a significant risk factor for chronic kidney disease. With the normal physiological decline in renal function attributed to aging, older patients have a greater decline in kidney function compared with younger patients. Nephron-sparing approaches should be considered in appropriately selected patients in an effort to preserve renal function; however, despite having similar tumor sizes, fewer older patients are treated with a partial nephrectomy. Although checkpoint inhibitors and agents targeting the VEGF and mTOR pathways have substantially improved the outcome for patients with advanced kidney cancer, these drugs are associated with a wide spectrum of adverse effects, including immune-related adverse events, hypertension, hand-foot syndrome, thyroid dysfunction, hyperglycemia, hyperlipidemia, dysphonia, and pneumonitis, as well as others, compared with conventional cytotoxic chemotherapy. Monitoring for and management of these new toxicities are critical to ensure patients tolerate treatment and derive the greatest benefit from these effective therapies. With the substantial improvement in survival associated with targeted therapies in renal cell carcinoma, special attention to long-term adverse effects, including cardiac disease, thyroid dysfunction, renal insufficiency, and infection risk, among others, is needed. Older patients with preexisting medical issues, such as hypertension or heart disease, must be monitored closely for worsening hypertension and left ventricular function decline during treatment. For example, patients with a history of hypertension and coronary artery disease are at increased risk of cardiotoxicity related to sunitinib. An analysis of age and efficacy and toxicity from phase 3 trials of sorafenib, sunitinib, temsirolimus, and bevacizumab, and from an expanded-access experience with sunitinib and sorafenib, suggests that outcomes and major toxicities are similar for patients aged 65 years or older and younger patients. Prospective studies of immune-based and targeted agents in elderly patients with advanced renal cell carcinoma with particular attention to adverse effects are needed.

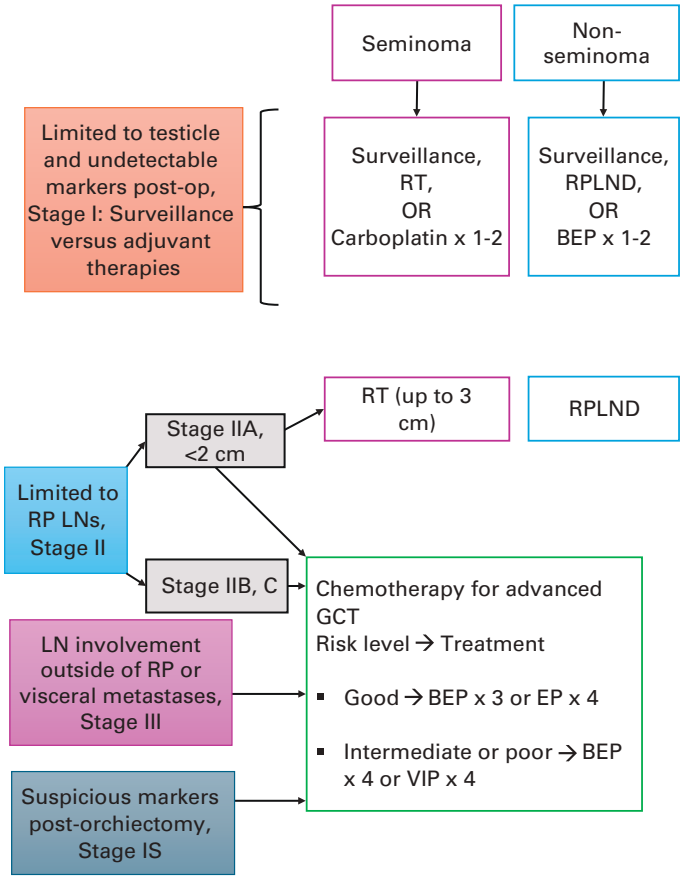
KEY POINTS

- Non–clear cell renal cell carcinomas have been underrepresented in clinical trials, and the optimal treatment strategy is not well defined. Targeted agents include standard anti-VEGF TKIs as well as an emerging role for *MET* inhibition in papillary renal cell carcinoma, especially using the dual VEGF/MET inhibitor cabozantinib.
- Bone metastases may be treated with systemic therapy and bone-protective agents such as bisphosphonates or denosumab. Brain metastases and oligometastases can be treated with local therapies (eg, surgery, RT, or ablation) followed by systemic therapy, sometimes with long-term disease control.
- Elderly patients with comorbidities may benefit from active surveillance of appropriate renal cell carcinomas or nephron-sparing approaches (eg, partial nephrectomy or stereotactic body RT) when treatment is required. For those being treated for advanced renal cell carcinoma, attention must be paid to the unique toxicities of checkpoint inhibitors and/or targeted therapies in the setting of concomitant hypertension, diabetes, chronic kidney disease, and thyroid disease, among others.

GERM CELL TUMORS

Germ cell tumors are the most common malignancies among men between ages 15 and 35 years, although there is a second peak in patients older than age 60 years (primarily seminomas).[189] Germ cell tumors most frequently originate in the gonads (testis or ovary) and less commonly in the retroperitoneum and mediastinum or CNS (primary extragonadal germ cell tumors; for a discussion of germ cell tumors in women, see Chapter 15: Gynecological Cancers). Retroperitoneal tumors in the absence of primary testicular cancer may represent pure extragonadal germ cell tumors. Occasionally, an orchiectomy in these circumstances may show no distinct cancer but rather remnants of a scar (ie, scar carcinoma or burnt-out primary), which has been attributed to rapidly proliferating testicular cancer that metastasized, leaving only a scar at its site of origin. Primary mediastinal germ cell tumors arise in the anterior mediastinum and are not associated with testicular involvement. Primary extragonadal germ cell neoplasms also

Figure 14-19 Treatment Options for Germ Cell Tumors



Abbreviations: BEP, bleomycin/etoposide/cisplatin; EP, etoposide/cisplatin; GCT, germ cell tumor; LN, lymph node; RP, retroperitoneal; RPLND, retroperitoneal lymph node dissection; RT, radiation therapy; VIP, etoposide/ifosfamide/cisplatin.
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arise rarely in the sacrum, pineal gland, paranasal sinuses, and liver and may be associated with several concomitant hematological abnormalities, including idiopathic thrombocytopenia or acute megakaryocytic (M7) leukemia. Regardless of the stage or extent of disease, the therapeutic objective is cure, which requires an integrated multidisciplinary approach (Fig. 14-19).[190]

EPIDEMIOLOGY

Risk factors include both abdominal and inguinal cryptorchidism (which is associated with cancer in both the affected and, to a lesser extent, unaffected testis), spermatic or testicular dysgenesis, and family history, which confers a 4- to 10-fold increase in risk. Orchidopexy or surgical correction of abdominal cryptorchidism results in an improved ability to monitor the testis but does not affect the risk of cancer diagnosis; treatment of an undescended testis before puberty or during infancy decreases the risk of testicular cancer compared with correction after puberty. Factors associated with increased risk for testicular cancer mortality include age older than 40 years, non-White race, and lower socioeconomic status. Testicular seminoma occurs more frequently in men with HIV, and the treatment is the same as that for the HIV-negative population. Klinefelter syndrome (XXY) is a risk factor for the development of mediastinal germ cell tumors. CIS (intratubular germ cell neoplasia) is a common finding when testicular germ cell tumors are diagnosed. Men in whom in situ disease is identified during a testicular biopsy as part of an infertility evaluation have a 50% risk of an invasive tumor within 5 years. Asynchronous testicular primary germ cell tumors occur in 2% of patients with seminoma as the most common histology and should be treated as a separate entity from the first testicular primary.

BIOLOGY

Germ cell tumors are derived from the malignant transformation of premeiotic germ cells. To create a pluripotential tumor, these transformed germ cells must be able to differentiate like the totipotent zygote without the reciprocal genetic information that results from fertilization. An isochromosome of the short arm of chromosome 12 (i[12p]) is present in 80% of all histological subtypes, including CIS and primary extragonadal tumors. The remaining 20% of cases have an excess 12p genetic copy number, tandem duplication, or transposition, which indicates that one or more genes on 12p are involved in malignant transformation. Most germ cell tumors are marked by aneuploidy and reciprocal loss of heterozygosity, though whether these are passenger or driver events remains to be elucidated. I(12p) can be detected by fluorescence in situ hybridization and helps identify germ cell tumors from other malignancies.

KEY POINTS

- The most well-known risk factor for testicular cancer is the history of undescended testis (cryptorchidism). Early surgical correction can help mitigate this risk.
- Genes on chromosome arm 12p seem to be involved with germ cell tumor pathogenesis, and i(12p) is a common finding that may help differentiate germ cell tumors from other tumor types in ambiguous situations or cancers with unknown primary.

DIAGNOSIS

Most patients diagnosed with testicular cancer initially present with a painless testicular mass, though patients can also present with diffuse testicular swelling, induration, hardness, discomfort, pain, or some combination of these findings. For patients who present with scrotal or testicular pain, the initial therapy prescribed is often antibiotics for presumed infectious epididymitis or orchitis. Scrotal ultrasonography (specificity of 89%-90% and sensitivity of 98%-99% for testicular cancer) should be performed when any concern is present about the possibility of a testicular tumor. If the ultrasonogram is abnormal and a testicular tumor is suspected, levels of tumor markers (human chorionic gonadotropin [hCG], α-fetoprotein [AFP], and LDH) should be obtained. This should be followed by a radical inguinal orchiectomy with removal of the testis and ligation of the spermatic cord at the level of the internal ring. Because the testes originate in the genital ridge and migrate through the abdomen and inguinal canal into the scrotum, the vascular and lymphatic drainage of the testes is to the renal or great vessels and the retroperitoneal nodes, respectively. A testicular biopsy or transscrotal orchiectomy is contraindicated because the normal vascular and lymphatic drainage is disturbed. Levels of AFP, β-hCG, and LDH should also be determined before and after orchiectomy. Less common presentations include unilateral or bilateral gynecomastia (as a result of elevated levels of β-hCG), hyperthyroidism resulting from homology between β-hCG and thyroid-stimulating hormone, persistent back pain related to retroperitoneal nodal disease, superior vena cava syndrome from primary mediastinal tumors, supraclavicular adenopathy, and hemoptysis from extensive pulmonary metastases.

KEY POINTS

- Suspicious testicular symptoms or findings should be evaluated by ultrasonography. If the results are suggestive, diagnosis is made via inguinal orchiectomy, never via percutaneous biopsy. Tumor marker levels should be determined beforehand, and if elevated, measurement must be repeated after surgery.

- For patients who present with life-threatening symptoms (eg, bleeding brain metastases or pulmonary metastases causing respiratory failure), highly elevated AFP or β-hCG levels, and a typical pattern of spread, systemic therapy should be started immediately. Resection of a suspicious testicular lesion can be delayed until after starting or completing chemotherapy, but should still be performed to establish a pathological diagnosis and remove a potential chemotherapy sanctuary site.

PATHOLOGY

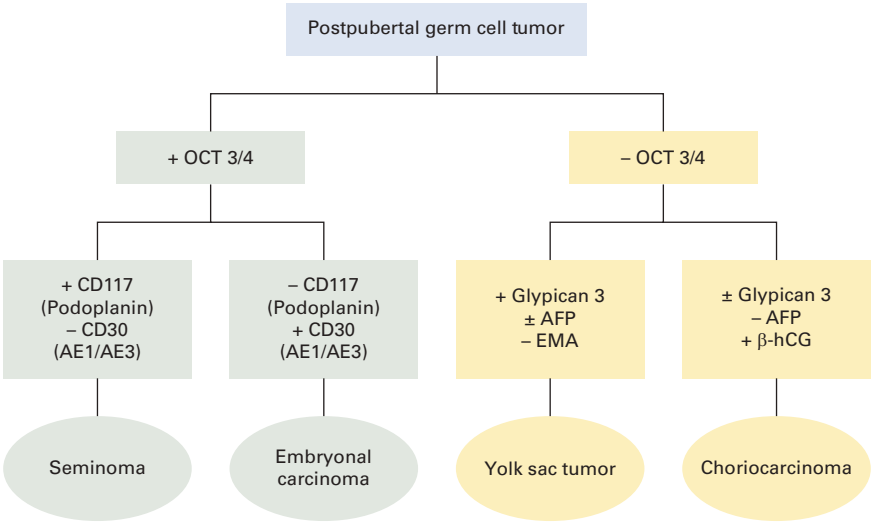
Germ cell tumors are classified histologically into seminomas and nonseminomas. Seminomas, which account for approximately half of testicular germ cell tumors, retain totipotentiality and are exquisitely sensitive to RT and chemotherapy. Nonseminomas are composed of one or more of the following cell types: embryonal carcinoma, teratoma, choriocarcinoma, and yolk sac tumors.

Classification for germ cell tumors can be found via the *AJCC Cancer Staging Manual, 8th Edition*. For more information, visit https://www.cancer.org/cancer/types/testicular-cancer/detection-diagnosis-staging/staging.html. Embryonal carcinoma is the most undifferentiated with totipotential capacity to differentiate into extraembryonic malignant cell types. Teratoma is composed of somatic cells from two or more germ cell layers (ie, ectoderm, mesoderm, or endoderm) and, thus, can differentiate into tissue types, such as cartilage, muscle, mucinous glandular epithelium, and others. Teratomas do not respond to chemotherapy or RT, and treatment primarily involves surgical resection. Yolk sac tumors are the most common testicular cancers seen in infants and children. They are associated with high AFP levels and are chemotherapy sensitive. Choriocarcinomas are frequently seen with other subtypes, are more likely to metastasize to the lungs and brain, and are sometimes associated with elevated β-hCG levels as well as a risk of hemorrhage. In patients with high-volume choriocarcinoma and marked elevation of β-hCG, a condition known as choriocarcinoma syndrome, the extent of hemorrhage can be life-threatening.

The presence of any component of nonseminoma with seminoma is treated as a nonseminomatous germ cell tumor. In addition, an abnormal serum AFP (>20-25) level is not seen in seminoma and should be treated as nonseminomatous because of either sampling error or not identifying the nonseminomatous component in the orchiectomy specimen or the nonseminomatous component being present in metastatic foci. Borderline AFP elevations can be caused by liver disease, but an occult nonseminomatous component must be considered and ruled out, especially if AFP levels climb. Most nonseminomas show mixed histologies, including embryonal carcinoma, yolk sac tumor, teratoma, and choriocarcinoma. When reporting histology, all subtypes present must be noted, starting with the most prevalent and ending with the least common component.

Seminomas are positive for placental alkaline phosphatase, CD117 (c-kit), OCT-4, and SALL-4 (Figs. 14-20 and 14-21). They are negative for cytokeratins and CD30. Embryonal carcinoma, however, almost universally expresses cytokeratins, epithelial membrane antigen, CD30, OCT-4, and SALL-4; approximately 50% express placental alkaline phosphatase. Yolk sac tumors are positive for cytokeratins, AFP, and SALL-4 but negative for CD117 and CD30. Immunohistochemical analysis and testing for i(12p) may be useful in the evaluation of patients with midline tumors of uncertain histogenesis. Serum markers consistent with germ cell tumors may also be helpful, although the elevation of β-hCG level is more specific than elevated levels of AFP or LDH.

Figure 14-20 Pathologic and Immunohistochemical Classifications of Testicular Germ Cell Tumors



Abbreviations: AFP, α-fetoprotein; EMA, epithelial membrane antigen; hCG, human chorionic gonadotropin.
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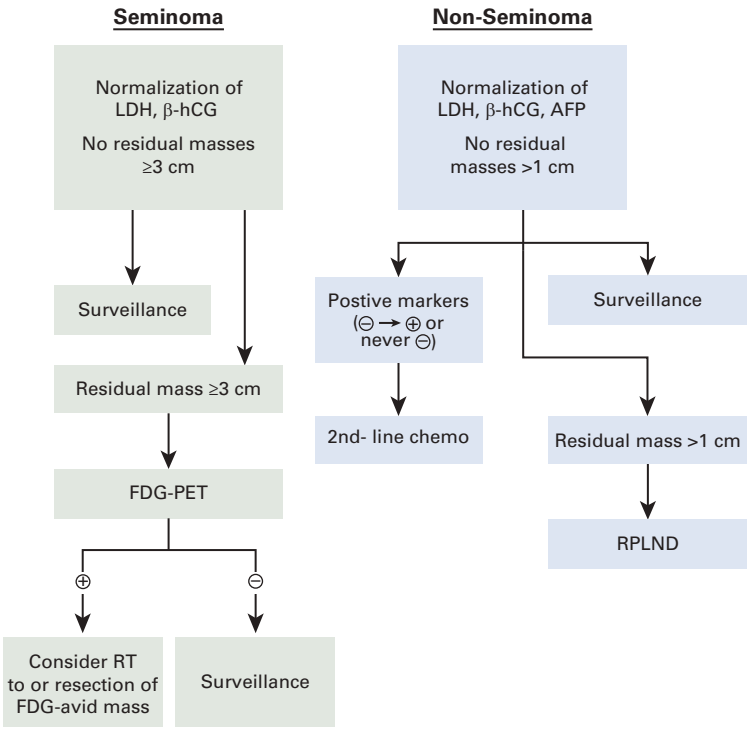
Figure 14-21 Recommended Follow-Up Post-chemotherapy in Advanced Testicular Cancer



Abbreviations: AFP, α-fetoprotein; FDG, fluorodeoxyglucose; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; RPLND, retroperitoneal lymph node dissection; RT, radiation therapy.
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KEY POINTS

- Germ cell tumors are divided into seminomas and nonseminomas. Seminomas must be composed entirely of seminoma; any component of other histology results in a diagnosis of nonseminoma, and an elevated AFP level (>20-25) should be treated as nonseminoma.
- Seminomas are highly sensitive to chemotherapy and RT. This has implications for therapy and evaluation of residual masses after therapy.
- Nonseminomas can be mixes of multiple histologies, including malignant germ cell tumors (embryonal carcinoma, yolk sac tumor, and choriocarcinoma) and teratomas. Malignant nonseminomatous germ cell tumors are generally chemotherapy sensitive. Teratoma is neither chemotherapy nor RT sensitive. By itself, teratoma does not usually metastasize, but it can dedifferentiate over time into malignant histologies, including (but not limited to) teratocarcinoma or certain sarcomas.

PATTERNS OF SPREAD

The primary lymphatic drainage for testicular germ cell tumors is to the retroperitoneal lymph nodes (primary landing zones). The right testicular artery originates from the aorta, and the right testicular vein drains into the inferior vena cava. The left testicular artery originates near the left renal artery, and the left testicular vein terminates in the left renal vein. Right-sided tumors spread to the interaortocaval lymph nodes immediately below the renal blood vessels, and left-sided tumors spread to the paraaortic lymph nodes immediately below the left renal artery and vein. Cross-metastases are more commonly seen from right to left but may occur in either direction if there has been a prior inguinal surgery, such as hernia repair. Invasion of the epididymis or spermatic cord may be associated with iliac nodal involvement, and inguinal metastases may be seen with scrotal invasion or disturbance of the normal lymphatic drainage related to prior surgery, such as a vasectomy or orchiopexy. A full understanding of lymphatic drainage has informed the development of retroperitoneal templates for right- and left-sided tumors that are often used when a retroperitoneal lymphadenectomy is performed, and helps minimize fertility consequences of the surgery. Additional metastatic sites include retrocrural, mediastinal, and supraclavicular lymph nodes; the lungs; and, less commonly, the liver, CNS, and bone.

KEY POINTS

- The testicles descend from the retroperitoneum embryologically; therefore, the lymphatic drainage is to the retroperitoneal lymph nodes rather than the inguinal or pelvic lymph nodes. This has implications for surveillance and treatment.
- If prior inguinal or transscrotal surgeries have been performed, the lymphatic drainage may be disrupted; therefore, the pattern of metastasis can be less predictable, and more caution is needed if considering adjuvant retroperitoneal lymph node dissection (RPLND) or radiation.
- From the retroperitoneal lymph nodes, testicular cancer may spread to mediastinal and other lymph nodes. Pulmonary metastases are much more common than other visceral metastases and do not carry as poor a prognosis as other visceral involvement.

STAGING

Pretreatment Evaluation

The extent of disease evaluation for patients with newly diagnosed germ cell tumors includes a chest radiograph, CT scan of the abdomen and pelvis, and measurement of tumor-marker levels (Table 14-9). Indications for a CT scan of the chest include an abnormal chest radiograph, known mediastinal disease, and risk for pulmonary metastases. A bone scan and MRI of the brain are indicated if related symptoms are present or patients are high risk for intracranial metastases by virtue of the presence of bone or pulmonary metastases, high β-hCG (eg, >5,000 IU/L), or choriocarcinoma-predominant histology. Measurement of tumor markers, including AFP, hCG, and LDH, is used to establish the diagnosis and may assist in determining histological subtype (Table 14-10). Sperm banking should be performed before treatment is pursued when practical, but also with an appreciation that many men with testicular cancer will have low sperm counts associated with their disease.

Table 14-9 Risk Stratification According to the International Germ Cell Consensus Classification[167]

Germ Cell Tumor	Risk Stratification
Seminoma	Good risk: • Any primary and any markers and no nonpulmonary visceral metastases
	Intermediate risk: • Any primary and any markers and nonpulmonary visceral metastases
Nonseminoma	Good risk: • Testis or retroperitoneal primary and good-risk markers, and no nonpulmonary visceral metastases
	Intermediate risk: • Testis/retroperitoneal primary and intermediate-risk markers and no nonpulmonary visceral metastases
	Poor risk: • Mediastinal primary site or testis or retroperitoneal primary with either nonpulmonary visceral metastases or poor-risk markers

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Table 14-10 Serum Markers in Germ Cell Tumors

Histology	Serum Marker		
	AFP[a]	β-hCG[b]	LDH[c]
Seminoma	Never	+/− (Typically <100)	+/−
Nonseminoma			
Choriocarcinoma	+/−	+++	+/−
Embryonal carcinoma	+/−	++	+/−
Teratoma	—	—	—
Yolk sac tumor	+++	+/−	+/−

Abbreviations: AFP, alpha fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.
[a]Half-life: 5 to 7 days.
[b]Half-life: 1 to 2 days.
[c]Half-life: varies by isoform.
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Stage Groupings

A TNM staging classification system was developed by the AJCC and incorporates clinical features as well as serum tumor markers, including AFP, β-hCG, and LDH. For testicular germ cell tumors, it is useful to delineate between localized (clinical stage 1, tumor markers normal after orchiectomy) and metastatic (clinical stage 2 or 3 regardless of tumor markers, or clinical stage 1 with elevated tumor markers).[183] Adverse prognostic factors for germ cell tumors include mediastinal primary site; degree of elevation of AFP, β-hCG, and LDH; and presence of nonpulmonary visceral metastases. Regardless of the initial risk stratification, patients with advanced germ cell tumors who survive and remain without disease more than 2 years after their diagnosis have an excellent chance of remaining disease-free in subsequent years, although relapses after the 2-year mark (termed "late relapse") can occur. Late relapses after 3 or more cycles of platinum-based chemotherapy tend to be more chemorefractory, and surgery is the preferred approach for management.

Tumor Markers

Tumor-marker levels are measured before, during, and after treatment. An initial increase in tumor-marker levels may occur with chemotherapy, particularly in the setting of bulky advanced disease. The serum half-lives of AFP and β-hCG are 5 to 7 days and 24 to 48 hours, respectively, and a slow decline in marker level after orchiectomy or during chemotherapy may imply residual active disease. In the absence of radiographic metastases, markers should be checked approximately 4 to 5 weeks (five AFP half-lives) after orchiectomy to assess for residual disease (stage IS) that would require systemic treatment. Elevated or increasing AFP and/or β-hCG levels that occur without radiological or clinical findings can imply micrometastatic disease and should, at a minimum, trigger imaging and close follow-up. Other conditions associated with elevated AFP levels include hepatocellular carcinoma, liver damage, and other gastrointestinal malignancies. β-hCG elevations may occur as a result of hypogonadism or cross-reactivity with pituitary hormones, including luteinizing hormone, as well as some gastrointestinal tumors, including gastric cancer. This cross-reactivity is generally less of an issue with current assays specific for the β subunit of hCG. Hyperthyroidism may be associated with elevated levels of β-hCG related to homology between β-hCG and thyroid-stimulating hormone. A spurious elevation in hCG has also been associated with marijuana use. With these exceptions, increased levels of AFP are pathognomonic of nonseminoma and not seen in seminoma, whereas elevated levels of β-hCG may be seen in both seminoma and nonseminoma. AFP elevation in the setting of a diagnosis of seminoma should prompt re-evaluation of the pathology and often treatment of presumed nonseminoma, regardless of the official histological diagnosis; a low level of AFP elevation (<20 ng/mL) that does not change should not change management on its own. Lactate dehydrogenase levels can increase in patients with advanced seminoma or nonseminoma and are used for staging and assessment of outcome. However, LDH is a nonspecific biomarker, and as a result, a rise in LDH alone must be further evaluated before attributing this finding to germ cell tumor. Furthermore, low-level elevation (ie, three times the upper limit of normal) should not, on its own, influence treatment decisions.

KEY POINTS

- Before orchiectomy, tumor-marker levels should be measured, and patients should undergo cross-sectional imaging of the abdomen and pelvis as well as chest imaging. MRI of the head and a bone scan are indicated only for patients with suspicious symptoms or in the setting of specific risk factors.
- Advanced (metastatic) germ cell tumors are risk-stratified according to primary site, pattern of spread, and degree of serum tumor-marker elevation.

SEMINOMA

Stage I

Approximately 70% of patients with seminoma have stage I disease. After radical inguinal orchiectomy, standard treatment options include surveillance, adjuvant infradiaphragmatic RT to include the para-aortic nodes, and single-agent carboplatin, recognizing that approximately 85% of clinical stage 1 patients will never relapse and that the long-term survival is nearly 100% regardless of the initial option chosen. Observational studies of patients with clinical stage I seminoma indicate a 15% to 20% likelihood of disease relapse, mostly in the retroperitoneum, and the median time to relapse is 12 to 14 months, which is longer than that for clinical stage I nonseminomatous tumors. Given the relatively indolent course of seminoma, late relapses may occur, but as discussed, if chemotherapy-naive, then these tumors can be treated using standard approaches. A contralateral tumor in the remaining testis should be considered when relapses occur.

Based on the excellent outcomes for patients with stage I seminoma and the potential for long-term RT-related toxicity, including secondary malignancies, active surveillance represents the preferred strategy for the management of patients with clinical stage I disease.

Adjuvant RT or single-agent chemotherapy reduces recurrence risk but increases late toxicity, and patients whose disease is managed with active surveillance can almost always be cured with deferred treatment at the time of relapse. Adjuvant radiation

therapy and carboplatin are considered equally effective for risk reduction based on a randomized noninferiority study[191] but have different considerations around their use. Radiation therapy should be avoided in the setting of inflammatory bowel disease or horseshoe kidney and is associated with a small risk of secondary cancers. Inclusion of a pelvic field should be considered for men with a history of scrotal surgery (eg, vasectomy) because out-of-field recurrences can occur if the possibility of aberrant lymphatic drainage is not addressed. One to two cycles of carboplatin have clear short-term toxicity and poorly quantified long-term side effects but also reduce the risk of a second primary germ cell tumor.

In seminoma, stage IS disease is rare, and low levels of LDH or β-hCG may be attributable to other causes. In cases of ambiguously low but elevated tumor-marker levels, patients should receive ongoing surveillance to monitor for the development of radiographically apparent metastases or persistent tumor-marker rise, and alternative explanations for tumor marker elevation should be sought.

Stage IIA/B

Patients with stage IIA and nonbulky IIB disease (2-3 cm) can be treated with chemotherapy or 30 to 36 Gy of radiation to the para-aortic and ipsilateral iliac lymph nodes. There is a small risk of recurrence outside of the radiated field, although these patients can be effectively salvaged with chemotherapy. Chemotherapy is preferred for patients with clinical stage IIB seminoma with bulkier disease (>3 cm). There is emerging research as to the role of retroperitoneal lymph node dissection in stage IIA or nonbulky stage IIB disease, but given varying results in small prospective studies, this approach is generally considered investigational.

Advanced Seminoma

Patients with retroperitoneal masses >5 cm (stage IIC), supradiaphragmatic lymphadenopathy, visceral disease, bulky retroperitoneal tumors, tumor-related back pain, and mediastinal extragonadal presentations are treated with primary chemotherapy. At least 90% of patients with advanced seminoma will be classified as having a good prognosis and receive treatment with good-risk chemotherapy, which is associated with a 96% 5-year survival rate, whereas fewer than 10% of patients have intermediate-risk disease because of metastases outside lymph nodes and the lung. Pure seminomas are never classified as poor risk (see "Management of Advanced Germ Cell Tumors by Risk Classification" section and refer to NCCN guidelines for seminomas).

Post-Chemotherapy Residual Masses

Surgery after chemotherapy is technically more difficult for patients with seminoma because of a dense desmoplastic reaction after chemotherapy in seminoma that occurs less frequently in patients with nonseminoma. Post-chemotherapy residual masses usually represent fibrosis rather than persistent seminoma and may continue to shrink in the absence of any additional interventions over months to years. Residual masses smaller than 3 cm very rarely contain viable seminoma, and thus, surveillance is indicated in this context. Residual masses larger than 3 cm present more than 6 weeks after the last cycle of chemotherapy can be further evaluated by FDG PET imaging.

Though the positive predictive value of PET in seminoma for post-chemotherapy masses larger than 3 cm has been questioned,[192] guidelines recommend further intervention with serial imaging, biopsy, or surgical resection if a residual seminoma mass larger than 3 cm demonstrates FDG avidity.

KEY POINTS

- Stage I seminomas are generally managed with active surveillance. Alternatives include adjuvant chemotherapy (one to two cycles of carboplatin) or RT, which decreases the risk of recurrence but results in some degree of overtreatment and has long-term toxicities. OS is excellent regardless of immediate versus delayed intervention. Therefore, adjuvant treatment is typically offered only to patients who are eager to reduce their chance of recurrence (and the need for more intensive therapy) or who may have difficulty adhering to a surveillance schedule, with the understanding that OS will not likely be improved.
- Stage IIA and nonbulky IIB seminomas can be treated with RT to the retroperitoneal lymph nodes or chemotherapy.
- Stage IIB and advanced seminomas (stages IIC and III) are treated according to the risk stratification scheme for advanced germ cell tumors, with most falling into the good-risk category and a minority being intermediate risk because of nonpulmonary visceral metastases. Seminomas are never considered poor risk.

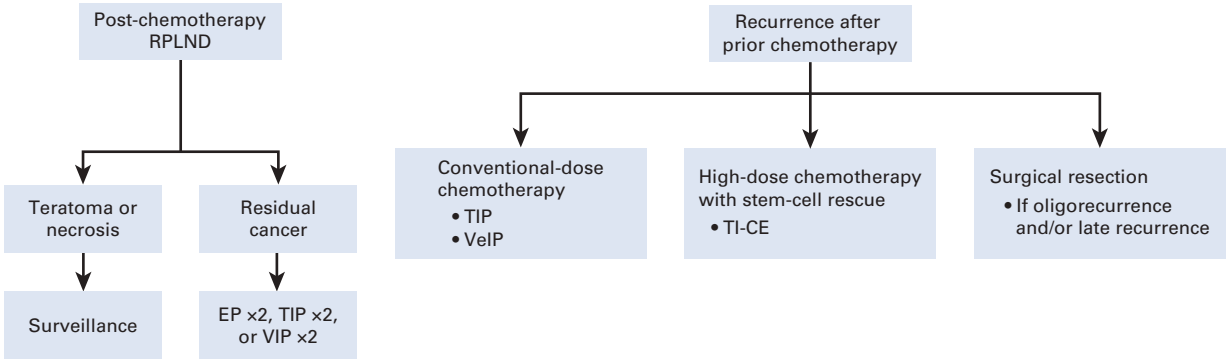
NONSEMINOMATOUS GERM CELL TUMORS

Stage I

Approximately 30% to 40% of patients with nonseminomatous germ cell tumors present with stage I disease. Management options include surveillance or adjuvant risk reduction with RPLND or chemotherapy.

Surveillance is a preferred option for patients who have stage IA disease (pT1 tumors; ie, those with no vascular or lymphatic invasion or with invasion into the tunica vaginalis, spermatic cord, or scrotum) who have a low risk of recurrence and are likely to return for follow-up (Fig. 14-22). Absence of a predominant (>50%) embryonal carcinoma component in the primary tumor is also favorable, although rarely seen without the accompanying risk factor of lymphovascular invasion (LVI). Approximately 20% to 30% of patients will experience a recurrence of the disease (most commonly in the retroperitoneum) and will need chemotherapy or primary RPLND. Most recurrences of nonseminomatous germ cell tumors will occur within 2 years of orchiectomy, and these patients must have meticulous follow-up that includes history, physical examination, and measurement of serum tumor markers every 2 to 3 months as well as a chest radiograph at months 4 and 12 and an abdominal and pelvic CT scan every 4 to 6 months during the first year (see NCCN guidelines for nonseminomas). Although the intervals for follow-up increase during subsequent years, it is important to remember that late recurrences can occur. Compliance with this surveillance schedule and with salvage therapy as indicated produces cure rates of 98% to 99%. Surveillance spares the 70% to 80% of patients without micrometastatic disease from additional therapy and associated complications. The potential long-term risk of secondary cancers associated with exposure to low-dose ionizing radiation with surveillance imaging has generated particular concern for young patients with germ cell tumors. The lifetime attributable risk of fatal secondary cancers from the current recommended surveillance schedule with modern CT techniques is challenging to estimate (one recent study suggested approximately 0.2% as a likely overestimate).[193] To minimize radiation exposure from these repeated radiographic evaluations, MRI evaluations of the abdomen and pelvis can be substituted for CT imaging.

Figure 14-22 Management After Pathology From RPLND



Abbreviations: EP, etoposide/cisplatin; RPLND, retroperitoneal lymph node dissection; TI-CE, paclitaxel/ifosfamide/carboplatin/etoposide; TIP, paclitaxel/ifosfamide/cisplatin; VeIP, vinblastine/ifosfamide/cisplatin; VIP, etoposide/ifosfamide/cisplatin.
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Patients with stage I dis\ease for whom the risk of disease recurrence is high (>50%) based on pathological features, including embryonal carcinoma predominance (>50%) and/or presence of lymphatic, vascular, scrotal, or spermatic cord invasion (stage IB), may be considered for adjuvant risk reduction with nerve-sparing RPLND or one cycle of combination bleomycin/etoposide/cisplatin (BEP). RPLND should be performed by a high-volume urological oncology surgeon and may be especially considered for patients with a substantial teratoma component in the primary tumor. In a nerve-sparing RPLND, the sympathetic chains, postganglionic sympathetic nerve fibers, and hypogastric plexus are identified and spared as feasible to increase the likelihood of preserved antegrade ejaculation (non–nerve-sparing techniques may result in retrograde ejaculation and, therefore, impaired fertility). Low recurrence rates have been demonstrated in studies evaluating the use of short-course primary chemotherapy with one or two cycles of combination BEP in patients with clinical stage I nonseminomatous germ cell tumors; however, some experts have concerns regarding the many men exposed to unnecessary chemotherapy, resulting in a potential for long-term adverse effects. The decision to recommend adjuvant chemotherapy after RPLND is made based on pathological findings as described for patients who have pathological stage II disease. Surveillance in a compliant patient with stage IB is an accepted option and is preferred by some experts in the field. Patients without evidence of clinical disease and persistently elevated levels of tumor markers, including β-hCG, AFP, or both after orchiectomy (stage IS), should receive standard chemotherapy for metastatic disease rather than surgery.

Stage II

The standard treatment of a patient with stage IIA disease (retroperitoneal nodes <2 cm in diameter) is a modified bilateral RPLND. Experience with the technique is essential because, depending on the location of the tumor, an ejaculatory nerve-sparing procedure can be performed.

Approximately 20% to 25% of patients who have undergone a primary RPLND will have pathological N1 disease (metastases with node diameter ≤2 cm or five or fewer involved nodes, ie, an occult nodal metastasis that was not detected on preoperative imaging). In these patients, the risk of relapse is low; therefore, surveillance is preferred in an adherent patient. With modern CT imaging, it would be rare to have occult N2 or N3 disease discovered at the time of primary RPLND (radiographic N2 or N3 disease would be treated with chemotherapy). The likelihood of micrometastatic disease outside the templated dissection is ≤50% for patients with pathological N2 disease (an involved node diameter >2 cm, more than five involved nodes, or any extranodal extension). Assuming that serum tumor-marker levels return to normal after surgery, these patients should receive two cycles of adjuvant chemotherapy, which results in a 98% to 99% likelihood of cure. It is unusual to have patients with pathological N3 disease (node diameter >5 cm) because such evidence guiding their management is limited, but guidelines recommend three to four cycles of adjuvant chemotherapy. In circumstances in which the disease recurs or if the serum tumor-marker levels do not normalize, indicating residual active disease, three to four cycles of chemotherapy and subsequent surgical excision of residual macroscopically documented disease are recommended. Most patients with clinical stage IIB disease (nodes >2 cm but not >5 cm in diameter) are advised to receive primary chemotherapy rather than undergo RPLND.

Advanced Nonseminoma

Clinical stage IIC disease (nodes >5 cm in diameter) and stage III disease should be treated with upfront chemotherapy (see "Management of Advanced Germ Cell Tumors by Risk Classification" section). Approximately 70% to 80% of patients with metastatic disease will be cured with cisplatin-based chemotherapy combined with surgery to resect residual disease as an integral part of management. The therapeutic objective is cure with distinct approaches for disease deemed good risk (ie, high probability of cure at approximately 90%) and poor risk (ie, lower probability of cure, which is as low as 50%). For patients with good-risk disease, the goal is to minimize toxicity without compromising cure, whereas management of poor-risk disease focuses less on minimizing toxicity and more on increasing the probability of cure.

MANAGEMENT OF ADVANCED GERM CELL TUMORS BY RISK CLASSIFICATION

The treatment of germ cell tumors is based on the International Germ Cell Consensus Classification, developed in 1996 and updated in 2020, as well as 2021.[192,194]

Good Risk

Approximately 60% of patients with nonseminomatous germ cell tumors present with good-risk disease. Patients with good risk include those with stage II or III disease with testis or primary extragonadal retroperitoneal primary tumors, no nonpulmonary visceral metastases, and good-risk tumor markers. Most patients with advanced seminoma have good-risk disease. According to the results of clinical studies, more than 90% of these patients will be cured with the use of combination chemotherapy, including cisplatin and etoposide with or without bleomycin.[195-199]

Summaries of the trials are as follows:

- Four cycles of etoposide and cisplatin or three cycles of BEP lead to a durable CR in more than 90% of patients with good-risk disease.
- The elimination of bleomycin can compromise the cure if only three cycles of therapy with etoposide and cisplatin are administered or if adequate doses of etoposide are not administered. Three cycles of BEP are considered the standard therapy for good-risk germ cell tumors, but four cycles of etoposide and cisplatin without bleomycin are considered an acceptable alternative, especially for patients with risk factors for lung toxicity based on two randomized trials suggesting similar OS but higher CR rates with BEP.
- Although carboplatin has less toxicity, it cannot be substituted for cisplatin because it is less effective.

Bleomycin is associated with Raynaud phenomenon and skin and pulmonary toxicity, although clinically significant pulmonary toxicity is rare.[76] Risk factors for bleomycin-induced lung toxicity include older age, history of smoking, cumulative dose of bleomycin, subsequent exposure to high-flow oxygen, and impaired renal function. Pulmonary function tests can be obtained at baseline, and some clinicians repeat these every one to two cycles. Notably, diffusing capacity of the lungs for carbon monoxide (DLCO; adjusted for hemoglobin) is neither 100% sensitive nor specific for pulmonary toxicity. Bleomycin should be held in patients with new dry cough or dyspnea without alternative explanations. Guidance for asymptomatic drop in DLCO is variable, but some will hold bleomycin for asymptomatic drops by ≥25% from baseline, though published data suggests that DLCO will improve over time post-chemotherapy.[199]

Although bleomycin is not myelosuppressive, the combination of etoposide and cisplatin does have significant myelosuppressive effects, and the risk of febrile neutropenia with etoposide and cisplatin may exceed 20%. It is generally considered intermediate risk for febrile neutropenia, so primary prophylaxis with granulocyte growth factors could be considered based on the presence of other risk factors and/or considerations. Concerns about growth factors increasing the risk of bleomycin

pulmonary toxicity have not been validated by research to date. Though variability exists in practice about treatment modification for myelosuppression, some advocate for no delays in treatment regardless of myelosuppression because neutrophil counts will often improve through the 5 days of therapy with steroids that are administered as side-effect prophylaxis. There is also variability in practice about the use of granulocyte growth factors; some prefer to use them only if febrile neutropenia or dose delays resulting from neutropenia occur during therapy, whereas others use them as primary prophylaxis to minimize the risk of delays and dose modification.

Etoposide carries a small risk of secondary leukemia, and cisplatin carries well-known risks of renal toxicity, neuropathy, ototoxicity, metabolic syndrome, and some increase in thrombotic risk and long-term increase in cardiovascular events because of vascular irritation. Long-term survivorship care, either through specialized oncology survivorship clinics or through regular primary care, is essential for maximizing the long-term quality of life from curative chemotherapy.

Intermediate Risk

The intermediate-risk group includes patients with nonseminomatous tumors with intermediate-risk tumor markers, as well as patients with seminoma who have nonpulmonary visceral metastases. These patients comprise 20% to 30% of those with germ cell tumors and have a 5-year survival rate of approximately 89%. Intermediate risk disease is treated with four cycles of triplet cisplatin-based chemotherapy with either BEP or etoposide/ifosfamide/cisplatin (VIP) if there is a contraindication to bleomycin. Ifosfamide is commonly associated with gastrointestinal toxicity and lower blood counts and can also cause encephalopathy, cardiac arrhythmias, and hemorrhagic cystitis.

Poor Risk

Patients with poor-risk disease include those with nonseminomatous germ cell tumors with nonpulmonary visceral metastases, poor-risk tumor markers, or a primary mediastinal site. These patients comprise 10% to 20% of those with nonseminomas and have a 5-year survival of approximately 67%. For patients with poor-risk disease, the standard of care is also four cycles of cisplatin-based triplet combination chemotherapy. This may include BEP or VIP if there is a contraindication to bleomycin. In patients with primary mediastinal nonseminomatous germ cell tumors, a report from Indiana University demonstrated a high rate of postoperative pulmonary failure and mortality after BEP with a suggestion to substitute ifosfamide for bleomycin (ie, the VIP regimen) in the treatment of these patients who will undergo a major thoracic surgery,[200] but many experts still use BEP and may omit the last two doses before surgery. In this case, the anesthesiologist should be made aware of the history of bleomycin treatment and should use a low fraction of inspired oxygen (Fio_2) during the surgery because of the risk of acute respiratory distress syndrome in patients previously treated with bleomycin who have diminished pulmonary function (decrease in DLCO) and receive copious hydration in the operative period.

KEY POINTS

- Good-risk advanced germ cell tumors are treated with three cycles of BEP or four cycles of etoposide and cisplatin.
- Intermediate- and poor-risk advanced germ cell tumors are treated with four cycles of BEP or four cycles of VIP. Omission of bleomycin is not acceptable unless the patient is receiving VIP.

SECOND-LINE THERAPY FOR GERM CELL TUMORS

In 20% to 30% of patients with advanced germ cell tumors, a durable response to first-line chemotherapy regimens, including cisplatin and etoposide with or without bleomycin, will not be achieved. These patients remain curable, although, unfortunately, the chance of cure is lower. Most relapses occur within 2 years of first-line chemotherapy. Late relapses (after 2 years) may also occur. Nonseminomatous late relapses are best treated with an approach that involves maximal surgical resection of the disease.

Paclitaxel/ifosfamide/cisplatin (TIP) was evaluated as second-line therapy for patients with favorable prognostic features for response, including testis primary tumor site and a prior CR to a first-line chemotherapy program.[201] Four cycles of TIP as second-line therapy resulted in a 70% complete response rate, a 5-year PFS rate of 70%, and a 5-year OS rate of 72%. The high level of activity with TIP as salvage therapy is related, in part, to the criteria used to select patients who are more likely to benefit from conventional-dose second-line therapy (relapse >6 months after induction therapy). Ifosfamide-based therapy has been associated with significant hematologic, renal, and neurological toxicities, and the use of granulocyte growth factors is standard. An alternative second-line regimen is vinblastine, ifosfamide, and cisplatin (VeIP).

The use of high-dose chemotherapy with peripheral stem cell rescue may be considered as second-line therapy, especially for patients with incomplete response to induction chemotherapy or rapid relapse (<6 months) after first-line therapy, or as third-line therapy (Table 14-11).

Table 14-11 **Selected Treatment Regimens for Relapsed Germ Cell Tumors After First-Line Bleomycin, Etoposide, and Cisplatin Combination or Etoposide and Cisplatin**

Chemotherapy	Regimen	Agents	Results
Standard dose	TIP[91]	Paclitaxel (Taxol)	Limited to patients with favorable prognostic factors
		Ifosfamide plus mesna	ORR, 63%; 2-year PFS, 65%
		Cisplatin	
	VeIP	Vinblastine	Disease-free rate, 36% (including patients undergoing subsequent resection of masses); median survival, 12.7 months
		Ifosfamide plus mesna	
		Cisplatin	
High-dose with autologous stem cell rescue	TI-CE[103]	Two cycles of conventional-dose paclitaxel (Taxol) and ifosfamide plus mesna, followed by G-CSF, followed by stem cell collection (leukapheresis)	Limited to patients with unfavorable prognostic factors
		3 cycles of high-dose carboplatin and etoposide, followed by stem cell rescue, each cycle	5-year DFS, 47%; OS, 52%

Abbreviations: DFS, disease-free survival; G-CSF, granulocyte colony-stimulating factor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Tl-CE, paclitaxel/ifosfamide/carboplatin/etoposide; TIP, paclitaxel/ifosfamide/cisplatin; VelP, vinblastine/ifosfamide/cisplatin.
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There are two accepted regimens for high-dose chemotherapy. One, developed by the Indiana group, involves stem cell mobilization followed by high-dose carboplatin and etoposide, and this process is repeated after recovery. The overall 2-year PFS was 60%, with improved outcomes in patients who received this regimen as second-line therapy. The second regimen, developed at Memorial Sloan-Kettering Cancer Center, involved two cycles of paclitaxel and ifosfamide followed by stem cell collection, then high-dose carboplatin and etoposide for three cycles with stem cell rescue after each cycle. Outcomes are comparable between the two regimens; thus, the choice is usually institution-dependent.

Patients with primary mediastinal (extragonadal) germ cell tumors treated with high-dose chemotherapy and stem cell rescue represent a unique clinical challenge as they tend to be more chemorefractory, perhaps in part related to *TP53* mutations. High-dose chemotherapy can be effective in up to 25% of patients with relapsed primary mediastinal disease, and these patients should be managed at specialized centers.

It is unclear whether standard-dose or high-dose chemotherapy should be used for patients whose disease recurs after prior chemotherapy. Two prospective phase 3 trials that evaluated the role of high-dose chemotherapy versus standard-dose salvage therapy demonstrated mixed results. An important phase 3 trial of initial salvage chemotherapy for patients with germ cell tumors (TIGER) has randomly assigned patients with relapsed disease to TIP for four cycles (standard-dose chemotherapy) versus a paclitaxel, ifosfamide, carboplatin, and etoposide (high-dose chemotherapy) regimen; accrual has been completed, but results are not yet available.

In patients who relapse after high-dose chemotherapy, unfortunately, there are no further curative options. Palliative chemotherapy regimens including combinations of gemcitabine, paclitaxel, and oxaliplatin can be used, but resistance is inevitable, and novel treatment approaches are desperately needed.

KEY POINTS

- Germ cell tumors refractory to first-line chemotherapy are still curable, but the prognosis is worse.
- Options for second-line chemotherapy include standard-dose regimens such as TIP and high-dose chemotherapy with autologous stem cell rescue. Which strategy is superior is unknown, but high-dose chemotherapy is generally preferred for patients with poor-prognosis features or as third-line therapy.
- Residual masses after second-line chemotherapy in nonseminomas should still undergo resection as in the first-line setting.
- Pulmonary toxicity must be managed in patients treated with bleomycin by continued monitoring of symptoms and DLCO. Bleomycin should be discontinued if there are suggestive symptoms. Small asymptomatic drops in DLCO are common, but discontinuation is generally recommended for drops of ≥25%. For bleomycin-treated patients who subsequently require surgery, low intraoperative Fio_2 and minimal hydration should be used.

ASSOCIATED MALIGNANT DISEASE

Malignant transformation of a teratoma to a somatic malignancy, including rhabdomyosarcoma, adenocarcinoma, embryonic-type neuroectodermal tumor (previously referred to as primitive neuroectodermal tumor), and leukemia, as well as others, has been well described. The presence of i(12p) or excess 12p copy number in these tumors establishes the clonal germ cell tumor origin. The finding of i(12p) or excess 12p genetic material by either molecular or cytogenetic studies correlates with response to cisplatin therapy. Mediastinal nonseminomatous germ cell tumors are also associated with the presence of myeloproliferative disorders, including acute nonlymphocytic leukemia and acute megakaryocytic leukemia, and idiopathic thrombocytopenia. A minority of patients with poorly differentiated carcinomas of unknown primary origin have a CR to cisplatin-based chemotherapy. The presence of additional clinical features, including male sex, midline tumor, relatively young age, and elevated levels of serum tumor markers, has suggested that a minority of patients with poorly differentiated carcinomas of unknown primary origin may have germ cell tumors. Clinical features, as well as molecular and cytogenetic studies, are important in the management of carcinomas of unknown primary or midline tumors of uncertain histogenesis.

SEX CORD STROMAL TESTICULAR TUMORS

Non–germ cell testicular tumors are rare and comprise sex cord stromal tumors, including Leydig cell tumors, Sertoli cell tumors, granulosa cell tumors, and other extremely rare histologies. Leydig cell tumors are the most common among sex cord and stromal tumors. Unlike the more common germ cell varieties, Leydig cell tumors arise from interstitial cells of Leydig, one of the cell types that make up the interstitium, along with cells of the seminiferous tubules. Two peaks of incidence are observed, in young childhood (age 3-9 years) and mid to later adult life (age 30-60 years). The clinical presentation is a painless testicular mass and can be accompanied by gynecomastia and other endocrine abnormalities. Ultrasonography shows a hypoechoic mass with areas of hypervascularity. Mutations in the luteinizing hormone receptor may be associated with Leydig cell hyperplasia. Levels of the common germ cell markers (serum and immunohistochemistry), AFP, LDH, and hCG are normal. Specific diagnosis is established by immunohistochemistry staining with inhibin and melan-A. Staining for calretinin and vimentin is sometimes positive. Treatment is surgical removal, and long-term survival is generally good. In the rare circumstance of metastatic disease, chemotherapy and RT are of limited utility.

SURVIVORSHIP

Cardiovascular Disease and Myocardial Infarctions

Long-term testicular cancer survivors have a moderately increased risk of myocardial infarction associated with cisplatin-containing chemotherapy and/or infradiaphragmatic radiation. Short-term risk of venous thrombotic disease may also increase as a result of increased plasma von Willebrand factor levels and endothelial damage. The Khorana score can be used to guide prophylactic anticoagulation; testicular cancer is one of several cancer types that result in a +1 point. In addition to chemotherapy-induced endothelial damage, cardiovascular toxicity is also likely related to metabolic syndrome and gonadal dysfunction.

Secondary Malignancies

Patients with testicular cancer treated with RT or chemotherapy have an increased risk of secondary malignancies for at least 35 years after treatment. Increased risks have been seen for cancers of the stomach, gallbladder, bile ducts, pancreas, bladder, kidney, and thyroid, as well as for soft-tissue sarcoma, nonmelanoma skin cancer, and myeloid leukemia.

Decreased Sperm Count and Other Late Effects

Patients with newly diagnosed testicular cancer are at risk for decreased sperm counts or impaired sperm motility even before any treatment. With treatment, infertility can result from retrograde ejaculation after RPLND or as a result of RT or chemotherapy. Some but not all patients will have long-standing chemotherapy-induced oligospermia or azoospermia. Patients who are scheduled to undergo RPLND, RT, or chemotherapy are advised to bank sperm. Other late effects of treatment include ototoxicity, chronic neurotoxicity, renal impairment, pulmonary toxicity, and anxiety disorder. Considering a young age at diagnosis and high cure rates, patients with testicular cancer require specialized follow-up care with close attention to monitoring for late effects of cancer and cancer therapy.

KEY POINTS

- Teratoma may undergo malignant transformation into teratocarcinoma, adenocarcinoma, or other histologies, generally as a late complication of unresected teratomatous components of nonseminoma.
- In a situation of diagnostic uncertainty, the presence of i(12p) points to a likely germ cell tumor origin.
- Non–germ cell testicular cancers are rare and include sex cord tumors, the most common being Leydig cell tumors. These can cause endocrinopathies and are typically cured via orchiectomy.

- Most patients with testicular cancer have long-term survival and are treated relatively early in life, so monitoring for and intervening in early and late complications of treatment are important, especially those complications related to the cardiovascular system. Cisplatin-based chemotherapy and/or RT may increase cardiovascular risk, risk of secondary malignancies, and risk of infertility, among others. Patients treated with chemotherapy and/or RT should monitor and treat other cardiovascular risk factors, including hypertension, and adhere to age-appropriate cancer screening. These risks further justify the avoidance of adjuvant therapies for most patients with stage I disease.

PRESENTING CASE STUDY 4

A 25-year-old man presents to your clinic after noticing a painless left testicular mass. Ultrasonogram reveals a solid, 4-cm mass with increased vascularity. Pathology from a transinguinal orchiectomy reveals a mixed germ cell tumor with embryonal, yolk sac, and choriocarcinoma components. Lymphovascular invasion (LVI) is present with no spermatic cord invasion. Serum alpha fetoprotein (AFP) and human chorionic gonadotropin levels were slightly elevated before surgery but decreased to within the reference range after surgery.

How would staging chest, abdominal, and pelvic CT with no evidence of metastatic disease inform your choice of next steps?

This patient has a stage I non-seminomatous germ cell tumor (NSGCT) of the testis. Options after resection of a stage I NSGCT with or without risk factors include surveillance, adjuvant chemotherapy (bleomycin, etoposide, and cisplatin [BEP] for one to two cycles), or retroperitoneal lymph node dissection (RPLND). LVI with or without an increasing percentage of embryonal carcinoma (>40%-50%) correlates with higher relapse risk, approaching 50% if both risk factors are present. Although this increased relapse risk does not mean that surveillance is not reasonable, such patients may be more likely to benefit from adjuvant therapies than those with lower risk nonseminoma. RPLND is advantageous because it can diagnose and treat any teratoma while avoiding long-term toxicities from chemotherapy.

The high-risk pathological feature of LVI characterizes this patient's case as a stage I NSGCT with risk factors. This categorization necessitates a discussion of the options for adjuvant BEP chemotherapy or RPLND. Surveillance would be the preferred initial approach for stage I NSGCT without risk factors.

What if the patient is instead found on pathology with pure seminoma, 6 cm in size, with rete testis involvement? Staging CT chest and and/pelvis again shows no evidence of metastatic disease. What is the best next step?

The approach to management of testicular pure seminoma after resection is slightly different, as pure seminoma is generally more sensitive to chemotherapy and radiation compared to NSGCT. Since these treatments are very effective for patients with recurrent disease, surveillance is the preferred approach for most patients with stage I pure seminoma. Surveillance is recommended as a preferred approach even for high-risk pathological factors such as tumor size >5 cm, LVI, and rete testis invasion, as shown in this patient. For those electing for adjuvant treatment, radiation to the retroperitoneal lymph nodes or carboplatin chemotherapy for one to two cycles is a standard-of-care option.

If this patient has a mixed (nonseminomatous) germ cell tumor but also is noted to have left retroperitoneal (RP) lymphadenopathy, how would you proceed? How would the size of the involved lymph node affect your decision-making?

Suspicious adenopathy in the "landing zone" would be diagnostic of stage II disease. Stage IIA disease (<2 cm) could be treated as advanced disease with chemotherapy, but RPLND is also an option with IIA disease, assuming serum markers are negative. Borderline radiographically suspicious lymph nodes may not actually contain cancer, so close monitoring of borderline lymph nodes is an option. Biopsies are generally not helpful owing to the potential for sampling errors and technical challenges. There is no role for FDG PET because it is neither sensitive nor specific.

Larger RP lymph nodes above the IIA cutoff would be treated as advanced disease with chemotherapy. Once the patient is determined to have advanced disease requiring chemotherapy, and *only* then, use the risk-stratification scheme to distinguish good, intermediate, or poor risk and decide on appropriate chemotherapy regimens. The risk-stratification

scheme does not apply to patients with stage I disease who are being offered adjuvant therapy. (A patient who has stage IS nonseminoma is not offered adjuvant therapy and is treated as having advanced disease.)

What do you recommend if the patient's serum markers remain outside the reference range after orchiectomy?

This scenario would be concerning for stage IS disease (treated as advanced disease), but there are a few caveats. Persistent borderline AFP elevation that does not change over many months may be caused by benign biliary processes. Borderline lactate dehydrogenase (LDH) elevation that does not significantly change over time should not be used on its own to indicate micrometastatic disease because LDH is relatively nonspecific.

If the patient has a seminoma and a 1.7 cm left retroperitoneal lymph node, what should you do next? What if the lymph node is 4 cm?

As in nonseminoma, patients who have seminoma and stage IIA disease have an option other than chemotherapy. In this case, the option is radiation rather than surgery, because seminoma is highly radiation-sensitive and does not carry a risk of teratoma. There is an evolving role of RPLND in certain patients with stage IIA seminoma. For patients with bulkier disease (>3 cm RP lymph nodes or metastases elsewhere), chemotherapy per the risk-classification schema is the only option.

What would you be looking for after chemotherapy to determine whether a patient with advanced nonseminoma is in remission and requires no further treatment? Or, in a patient with advanced seminoma?

Residual masses may simply indicate fibrosis and can often be followed for some time, especially if they are approaching the cutoffs used to determine the need for additional therapy. Following chemotherapy, there is a relatively stringent cutoff of 1 cm for any residual disease to determine the need for additional treatment. For patients with negative markers and residual disease larger than 1 cm, resection should be considered to diagnose and treat any teratoma. For patients with seminoma, the cutoff is less stringent (3 cm) because the disease is much more chemosensitive and there is no risk for teratoma. For residual masses larger than 3 cm, consider FDG PET (the *only* circumstance in which FDG PET is useful for germ cell tumors) and radiation to any residual disease that is FDG-avid.

For a patient with nonseminoma, poor initial risk, and markers that never normalize or normalize briefly before rising again, second-line chemotherapy may be considered. Conventional-dose chemotherapies, such as paclitaxel, ifosfamide, and cisplatin (TIP), or tandem high-dose chemotherapy with stem cell rescue (eg, TI-CE) are used in this setting.

PENILE CANCER

EPIDEMIOLOGY, RISK FACTORS, AND HISTOLOGY

Penile cancer is rare in industrialized nations, with fewer than one case per 100,000 men per year; in the United States, approximately 2,210 new cases and 460 deaths occurred in 2021. It is more prevalent in developing nations, and it is also more common among the elderly.

Positive associations have been described between penile cancer and human papillomavirus (HPV) infection, as have negative associations between penile cancer and circumcision that could be mediated by decreased rate of HPV infection in circumcised men. Phimosis, HIV infection, and tobacco exposure have also been described as risk factors, among others.

A vast majority of penile cancers are of squamous cell histology, although a few subtypes are identified, including verrucous carcinoma, papillary carcinoma, warty carcinoma, basaloid carcinoma, and sarcomatoid carcinoma. Warty and basaloid carcinomas may be more associated with HPV infection, especially HPV 16.

STAGING

A deep biopsy is necessary to obtain a specimen for adequate diagnosis and staging. Staging is according to AJCC criteria.[36] Invasiveness (increased T stage) or high-risk features (ie, LVI, perineural invasion, and high grade) are classified as stage II, whereas clinical node involvement is classified as at least stage III.

Although many cases present with inguinal adenopathy, only approximately half will be due to nodal metastases. Infection and/or inflammation, often with an odiferous component, can commonly cause adenopathy in conjunction with penile cancer. Clinical staging is performed based on physical examination, although imaging can be helpful in the absence of overt adenopathy on examination, and PET imaging can be used in node-positive patients to evaluate for distant spread. Pathological staging should be performed for men with high-risk features in the primary tumor. The standard method is with inguinal lymph node

dissection, but this carries significant potential for morbidity, including lymphedema. Alternatives include fine-needle aspiration of any palpable lymphadenopathy or dynamic sentinel node biopsy (with lymphoscintigraphy or fluorescent dye labeling) at experienced centers.

For men with a negative clinical examination, the NCCN recommends lymph node staging based on pathologic features in the primary tumor as follows:

- Low risk (pTis, Ta, or T1a; grade 1): surveillance
- Intermediate risk (pT1a; grade 2): sentinel node biopsy or inguinal lymph node dissection with close surveillance is also reasonable
- High risk (pT1b): sentinel node biopsy or inguinal lymph node dissection. For men with palpable lymphadenopathy, strategies include the following:
  - Empirical antibiotics followed by re-evaluation
  - Fine-needle aspiration; if negative, an excisional biopsy or inguinal node dissection can be used in patients with sufficiently high risk

Because distant metastases occur rarely and typically late in the disease course, if at all, imaging for the detection of distant metastases may only be needed in patients with bulky regional nodal metastases or concerning symptoms.

TREATMENT BY STAGE

Stage 0: Tis or Ta, N0, M0

Also known as erythroplasia of Queyrat on the glans or Bowen disease on the shaft, penile CIS is a precursor lesion to invasive disease. There are no high-level data to guide decision-making, but treatment options include Mohs surgery, laser surgery, cryosurgery, and topical fluorouracil cream or imiquimod cream.

Stages I and II: T1a, N0, M0 or T1b-T3, N0, M0

Treatment options include circumcision for tumors limited to the foreskin or, for more infiltrating tumors, surgical resection or RT.

Stage III: T1-3, N1-2, M0

As noted, inguinal adenopathy may be due to infection or inflammation rather than cancer involvement. In the event of confirmed inguinal lymph node metastases without distant metastases, bilateral ilioinguinal dissection is appropriate. If two or more nodes are involved, additional pelvic lymph node dissection may be considered.

Stage IV: T4 or N3 or M1

Distant metastases are rare and occur late in the disease course. There is no standard treatment for advanced penile cancer. Surgery and/or RT may be used for local palliation, especially for bulky or symptomatic nodal disease; some consider the addition of radiosensitizing cisplatin. Neoadjuvant chemotherapy has also been used for patients with advanced tumors and/or adenopathy. A regimen of neoadjuvant TIP was tested in a phase 2 study of patients with node-positive penile cancer and demonstrated a 50% response rate.

ADJUVANT THERAPY

There are no high-level studies to guide treatment in the setting of high-risk resected penile cancer. Adjuvant chemotherapy may be considered for patients who did not receive neoadjuvant chemotherapy and have high-risk features, including pelvic lymph node involvement, extranodal extension, bilateral inguinal node involvement, or four or more nodes involved. TIP or other cisplatin-based therapy may be used. For patients who have received neoadjuvant TIP and have residual disease with extranodal extension or bilateral lymph node involvement, adjuvant RT to the inguinal/pelvic area may be considered.

RECURRENT DISEASE

Local recurrence may be treated with penectomy if not already performed or, in some circumstances, with a second penis-preserving treatment. Inguinal recurrence may be treated with neoadjuvant chemotherapy followed by node dissection or chemoradiation therapy, but the prognosis is poor. For distant metastatic disease, cisplatin-based treatment may be used; the described neoadjuvant TIP regimen is considered the standard first-line therapy for patients with adequate performance status and renal function, despite a lack of high-level data in the metastatic setting.

The addition of pembrolizumab to 5-FU and cisplatin/carboplatin was investigated in a phase 2 single-arm multicenter trial in Brazil.[202] Of the 37 patients enrolled in this study, the ORR was 39.4% with a median PFS of 5.4 months and a median OS of 9.6 months. Four patients (10%) had a duration of response >12 months. ORR and PFS were improved for those with HPV-positive

disease and high TMB. There was no association between PD-L1 expression and response. Based on this data, 5-FU + cisplatin/carboplatin + pembrolizumab followed by pembrolizumab maintenance therapy is an alternative option endorsed by NCCN guidelines.

Clinical activity of pembrolizumab monotherapy was reported in patients with high TMB and MSI-high metastatic penile cancer. Pembrolizumab should be considered in those with metastatic penile cancer with MSI-high status, MMR deficiency, or high TMB.

HER2 testing can be performed to determine the eligibility for trastuzumab deruxtecan, given pan-tumor approval, but HER2 overexpression in penile cancer is exceedingly rare (<1%).

KEY POINTS

- Penile cancer is a rare disease associated with age, lack of circumcision, HPV and/or HIV infection, and tobacco use.
- Penile cancer is typically of squamous histology.
- The primary pattern of spread is local invasion followed by inguinal lymph node metastasis. However, inguinal nodes may frequently be enlarged as a result of concomitant inflammation and infection. Evaluation of the inguinal nodes depends on the invasiveness of the primary tumor and whether the nodes are palpable.
- Penile cancer is managed according to the degree of tumor invasion and lymph node involvement. The primary treatment modality is surgery.
- Patients with intermediate- or high-risk penile cancers should undergo assessment for lymph node involvement.
- Perioperative chemotherapy (eg, TIP regimen) and/or RT with or without radiosensitizing chemotherapy may be used for advanced tumors, but high-level evidence is lacking.

MALIGNANT ADRENAL TUMORS

Malignant adrenal tumors are extremely rare cancers with only limited information to guide specific treatment recommendations. Malignant adrenal cortical carcinoma is derived from the adrenal cortex, with approximately 60% of cases associated with hormone secretion leading to symptoms and signs of hypercortisolism, virilization, and mineralocorticoid excess. Localized disease is managed with surgery. The overall prognosis is poor, particularly in patients with larger tumors (>5 cm) and/or evidence of local invasion. The adrenocortical agent mitotane is commonly used for patients with metastatic disease; however, response rates are low, with no clear survival benefit. Although several studies have suggested higher response rates with chemotherapy and mitotane, it is not at all clear that this translates into an improvement in outcome. There may be a benefit for mitotane in the adjuvant setting, and it is commonly used in patients at high risk of recurrence after surgery. In the advanced setting, the FIRM-ACT study compared mitotane with a combination of etoposide, doxorubicin, and cisplatin every 4 weeks or streptozocin every 3 weeks and demonstrated significant improvements in response and PFS with etoposide, doxorubicin, and cisplatin plus mitotane but no difference in OS (although with a built-in crossover design). A phase 1b study of the PD-L1 inhibitor avelumab in previously treated adrenal cortical carcinoma demonstrated limited ORR but a disease control rate of approximately 50%.[108]

Malignant pheochromocytomas arise from chromaffin tissue of the adrenal medulla and are extremely rare, accounting for approximately 10% of all pheochromocytomas. Functional pheochromocytomas secrete catecholamines and lead to an array of clinical symptoms, including the classic triad of headache, diaphoresis, and tachycardia (and episodic hypertension). The typical initial diagnostic test is either a 24-hour urine collection for fractionated metanephrines and catecholamines or plasma-fractionated metanephrines (collected through an intravenous catheter placed 20 to 30 minutes before and with the patient supine), being sure to stop all antiadrenergic medications beforehand. If abnormal, localization is performed with dedicated adrenal imaging. No curative therapy exists for malignant pheochromocytoma, and the mainstay of management includes surgical resection of the tumor with preoperative α- and β-adrenergic blockade. Close collaboration with endocrinologists is essential. Data are limited, and no definitive recommendations regarding systemic therapy can be made; however, the association of pheochromocytomas with VHL has led to the use of VEGFR-targeted agents in this disease.

KEY POINTS

- Malignant adrenal tumors are extremely rare.
- After resection of localized adrenal cortical carcinoma, patients at high risk of recurrence may be considered for adjuvant mitotane.
- Adding mitotane to chemotherapy in the advanced setting increases response rates but not survival.
- Malignant pheochromocytoma is treated surgically, similarly to nonmalignant pheochromocytoma.

HIGH-YIELD TAKEAWAYS

Prostate Cancer

- Consider a diagnosis of metastatic prostate cancer in an older male presenting with lower urinary obstruction, diffuse bone pain, progressive anemia, and/or weight loss/failure to thrive.
- Immediately life-threatening complications include urinary obstruction leading to kidney injury and electrolyte abnormalities, pathological fracture, spinal cord compression, and hypercalcemia. Any high-risk bone lesions—those larger than or equal to 2 cm; involving hip, shoulder, or sacroiliac joints; in long bones with one-third to two-thirds of cortical thickness; or in junctional spine (C7-T1, T12-L1, L5-S1) and/or with posterior involvement—should be evaluated for possible prophylactic radiation.
- ADT is the cornerstone of systemic therapy, although it will not result in immediate clinical benefit. Intensification within the first several months of therapy with an androgen signaling inhibitor is standard. Taxane therapy can also be considered, especially in those with de novo high-volume (per CHAARTED) disease, and radiation to the prostate can be offered to most low-volume de novo patients and possibly in high-volume de novo patients, especially those with bulky primary lesions.

Bladder Cancer

- In patients with muscle-invasive but localized disease, systemic therapy is used as neoadjuvant treatment before radical cystectomy or concurrently with radiation as a radiosensitizer. Cisplatin-based regimens are standard for those who are eligible, although eligibility is not strictly defined.
- In patients with metastatic disease, platinum-based therapy was the standard first-line treatment of those eligible but has now been supplanted by enfortumab vedotin/pembrolizumab. This approach can also be considered in patients with node-positive disease with subsequent definitive therapy pending response, although treatment here is less well defined.
- Later-line therapies include trastuzumab deruxtecan, single-agent chemotherapies, and, for those with targetable FGFR alterations, erdafitinib.

Kidney Cancer

- Small renal masses are common incidental diagnoses and may not require intervention if they have low-risk features and slow growth rates; active surveillance is often a safe approach.
- Higher-risk lesions are typically resected, and adjuvant pembrolizumab can be considered for those with T2 grade 4, T3/T4, N positive, or fully resected M1 disease.
- First-line systemic therapy involves PD-1 blockade with either CTLA-4 blockade or VEGF blockade; there are pros and cons to each strategy that should be discussed with the patient.
- Later-line therapy can include VEGF TKIs with different spectrums of activity and, newly, the HIF-2α inhibitor belzutifan.

Testicular Cancer

- Seminomas are highly chemo- and radiation-sensitive. Nonseminomas can be chemosensitive but can be associated with teratoma. Teratoma on its own is not malignant and also neither chemo- nor radiation-sensitive, and if left in place over the long term, it can transform into aggressive malignant histologies. Thus, seminoma treatment typically incorporates chemotherapy and/or radiation, whereas nonseminomas are typically treated with chemotherapy and/or surgery.
- Stage I disease (except stage IS, defined by residual suspicious serum markers) is limited to the testicles. Active surveillance is the preferred initial approach for most patients, but adjuvant treatment can be considered for those with high-risk nonseminoma. Options for adjuvant treatment include radiation or chemotherapy for seminoma and surgery or chemotherapy for nonseminoma.
- Stage II disease involves retroperitoneal lymph nodes, which are the local draining lymph nodes of the testicles. Stage IIA disease (smaller than 2 cm) may be treated with radiation for seminoma or surgery for nonseminoma or chemotherapy for either.
- Stage IIB-C disease, stage III disease (defined by metastases outside the RP lymph nodes), and stage IS disease are all treated as advanced germ cell tumors with chemotherapy per the risk-stratification approach. ONLY use the risk-stratification algorithm for these patients and NOT for patients receiving adjuvant therapy.
- Following chemotherapy, the threshold for additional action is higher in seminoma (3 cm), given that these are typically quite chemosensitive and do not harbor teratoma compared with nonseminoma (1 cm). For seminoma, residual large masses that are FDG-avid may be radiated. For nonseminoma, residual masses larger than 1 cm should be resected to diagnose and treat any residual teratoma.

Acknowledgments

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GENITOURINARY CANCERS 14

CHAPTER SUMMARY GUIDE

KEY POINTS

- Prostate cancer is a common diagnosis, and although metastatic disease develops in only a small percentage of affected patients, this translates into a large absolute number of deaths resulting from prostate cancer.
- Prostate cancer is one of the most hereditary cancers. Clinicians should take a full history of malignancies in the family and be familiar with the link between prostate cancer and germline alterations in *BRCA2* and MMR genes, which are enriched among men with metastatic prostate cancer.
- Clinicians should offer genetic counseling for all patients with high-risk or very high-risk localized, regional node-positive, or metastatic prostate cancer, regardless of family history; those with localized prostate cancer and strong family history as outlined in the preceding paragraphs; and those with alterations in DNA damage repair or MMR genes identified from tumor sequencing.
- Prostate cancer is typically diagnosed via TRUS or transperineal biopsy using a standard 12-core template to sample the posterior peripheral zone. MRI-guided biopsy combined with a standard TRUS biopsy has been shown to lessen the likelihood of missing clinically significant cancers and should be used when available.
- Among men undergoing evaluation for elevated PSA, a prebiopsy multiparametric or biparametric MRI may help triage those who require biopsy, limiting biopsies to those with a greater likelihood of clinically significant cancer. Anatomic location can help predict the pattern of spread and treatment-related risks. Disease near the base of the gland may extend into the seminal vesicles. Disease in the apex may increase the risk of positive surgical margins and urinary incontinence.
- Prostate cancer can be characterized by its typical immunohistochemistry profile: cytokeratin 7/20 negative, PSA positive, AR positive, and NKX 3.1 positive.
- As treatment resistance occurs, different phenotypes may emerge. Most CRPCs are still driven by AR signaling even after developing resistance to subsequent AR-directed therapies.
- Some advanced CRPCs may become androgen-independent, often harboring alterations in *RB1*, *PTEN*, and *p53.* These may be admixed with AR-driven tumors. A subset of these cases may have neuroendocrine features, with the most extreme exhibiting small-cell morphology.
- There are two kinds of small-cell/neuroendocrine prostate cancer: (1) de novo small-cell prostate cancer, which is a very rare disease subset and presents admixed with adenocarcinoma (more common) or pure, (2) treatment-associated small-cell/neuroendocrine prostate cancer, which occurs in about 15% to 20% of patients who have mCRPC. Small-cell/neuroendocrine prostate cancer should be suspected in patients with a rapid radiographic progression or new hepatic metastases without PSA increase. It is characterized primarily by morphology, but it can also be positive for synaptophysin and/or chromogranin A staining.
- There are no universally accepted protocols for prostate cancer prevention or screening.
- Two 5-α reductase inhibitors (eg, finasteride and dutasteride) were evaluated in large phase 3 chemoprevention trials. Although these agents decreased the overall incidence of prostate cancer by approximately 25%, this decrease was limited to low-grade tumors. The use of these agents was associated with a significantly increased incidence of high-grade prostate cancer.
- PSA-based prostate cancer screening has shown, at most, a small reduction in prostate cancer–specific mortality rate and no convincing effect on overall mortality. Screening could be more effective if targeted to men with a higher risk and to the age groups most likely to benefit (ie, younger men rather than older men), but additional studies evaluating this possibility are underway. DRE for screening does not significantly add to PSA.
- Patients with localized prostate cancer can be risk-stratified based on three clinical factors: T stage, Gleason score, and PSA level. Genomic testing of the cancer specimen may provide additional information about risk and progression, but this has not yet been prospectively validated for decision-making.
- Patients with low-risk disease may be offered active surveillance, which uses serial PSA measurements, DREs, and biopsy specimens to detect any presence of higher-risk disease, at which point definitive therapy can be offered. Sequential MRI may also be helpful. This strategy results in less treatment-associated morbidity and similar long-term cancer survival compared with immediate therapy.

- Patients with intermediate- or high-risk disease typically should receive definitive therapy, assuming a life expectancy of at least 5 (high risk) to 10 (intermediate risk) years (or if symptomatic). Definitive therapies include radical prostatectomy and RT. Long-term cancer survival is similar with either strategy, but adverse effect profiles differ.
- For patients who have intermediate- or high-risk disease undergoing RT, the addition of ADT improves biochemical disease-free survival (DFS) (intermediate risk) and OS (high risk). Duration is typically 4 to 6 months for unfavorable intermediate-risk disease and 18 to 24 months for high-risk disease.
- Patients with clinical evidence of pelvic lymph node involvement (cN1) are typically treated with definitive RT to the prostate and pelvis with long-course ADT. Although no randomized data exist, prostatectomy followed by adjuvant RT and ADT may also be an option.
- For patients who are very high-risk or regional risk (cN1) undergoing definitive EBRT and ADT, the addition of 2 years of abiraterone has been shown to improve MFS and OS.
- Prostatectomy, RT, and ADT have unique adverse effect profiles. Prostatectomy can lead to urinary incontinence and erectile dysfunction, but it can help improve significant obstructive symptoms.
- Short-term side effects of RT include irritative urine and bowel symptoms. Radiation cystitis or proctitis may occur months to years after the completion of prostate RT. Endoscopic evaluation is warranted if the symptoms persist to rule out a second malignancy (eg, urothelial carcinoma) or telangiectasias.
- Patients with preexisting urinary symptoms should avoid brachytherapy and may experience symptomatic benefit from radical prostatectomy.
- There is little to no advantage to treatment with robotic prostatectomy versus other surgical approaches or to treatment with proton therapy versus conventional RT for clinically localized prostate cancer.
- Detectable PSA (>0.2 ng/mL) after radical prostatectomy or an increase in PSA concentration by 2 ng/mL or more above PSA nadir after RT is an indicator of recurrent prostate cancer. In the absence of evidence of metastatic disease on standard bone scan and CT imaging, this is termed BCR.
- Salvage RT may be used for patients who experience BCR after radical prostatectomy, typically combined with 6 months of ADT. Conversely, salvage prostatectomy is less commonly performed after primary RT because of high rates of urinary incontinence and impotence. Other local salvage therapies may be possible.
- The optimal timing of systemic therapy for BCR is unclear. ADT will lower PSA level in this setting and delay time to metastatic disease, but its effect on OS relative to ADT at the time of metastatic disease is unknown.
- Patients with BCR who are treated with ADT and whose PSA levels increase without evidence of metastases on standard bone scan and CT imaging have disease that has progressed to nmCRPC. The addition of the second-generation AR antagonist apalutamide, darolutamide, or enzalutamide prolongs MFS and OS in this setting.
- Although not curative, ADT is palliative and results in clinical response in most patients with mCSPC.
- The addition of docetaxel, abiraterone with prednisone, or an AR pathway inhibitor (eg, apalutamide, enzalutamide, darolutamide) to ADT improves OS for patients with mCSPC.
- Recent studies indicate that the OS efficacy of triple therapy (ADT/docetaxel/NHT [eg, abiraterone or darolutamide]) was superior to ADT/docetaxel. The benefit was clear, especially for high-volume mCSPC with the addition of abiraterone to ADT/docetaxel. High-volume metastasis is defined by the presence of four or more bone metastases with one or more outside the spine and pelvis or the presence of visceral metastasis using CT and bone imaging.
- It is unknown whether the triple therapy is superior to ADT/NHT or whether they are equivalent, or whether the ADT/NHT doublet is not inferior to the triplet.
- In the setting of mCRPC, abiraterone, enzalutamide, sipuleucel-T, docetaxel, ^{223}Ra, ^{177}Lu-PSMA-617, and cabazitaxel all prolong OS. Unfortunately, cross-resistance to AR-directed therapies occurs after exposure to abiraterone or enzalutamide for a prolonged period, and the efficacy of enzalutamide after abiraterone or abiraterone after enzalutamide is limited.
- The role of PARP inhibitors is actively evolving. Two PARP inhibitors, olaparib and rucaparib, are FDA approved as monotherapy in mCRPC. Niraparib is approved in combination with abiraterone for mCRPC and BRCA1/2 alterations. Talazoparib is approved in combination with enzalutamide as first-line treatment in mCRPC for patients with selected HRR gene alterations. Although the benefit of PARP inhibitors in diseases with *BRCA2* mutations is most clear, their benefit in the setting of some other HRR gene alterations is debatable. Clinical context and alternative treatment options should be considered.
- Urothelial carcinoma is predominantly a disease of older men and is most associated with smoking. Additional risk factors include certain occupational exposures, chronic catheters, and chronic bladder infections, including schistosomiasis in endemic areas. Upper-tract (ureteral and renal pelvis) urothelial carcinoma may be associated with Lynch syndrome.
- The entire urothelial tract is at risk from these carcinogenic exposures (field cancerization), so patients with urothelial carcinoma in one area are at risk for separate primaries in other areas and at other times.

- Most bladder and ureter cancers are of urothelial (transitional cell) histology. There are several variants of urothelial carcinoma, most of which are treated similarly to pure urothelial carcinoma but may exhibit more aggressive behavior.
- Rare bladder cancers can have pure adenocarcinoma, squamous cell, or small-cell histology. These are generally more aggressive and usually present with advanced disease.
- Bladder cancer may present as painless hematuria or irritative urinary symptoms, and it is typically diagnosed via TURBT.
- Based on TURBT pathology, bladder cancer is broadly divided into non-muscle-invasive tumors and muscle-invasive tumors. Muscularis propria must be present in the TURBT specimen to enable this assessment; otherwise, a repeat TURBT is recommended.
- NMIBC is stratified according to risk of recurrence.
- For low-risk tumors, surveillance (cystoscopy and urine cytology) is most appropriate.
- For intermediate- and high-risk tumors, intravesical BCG decreases the risk of recurrence, and surveillance is also crucial. Definitive bladder therapy (cystectomy) is considered in situations of very high-risk non-muscle-invasive tumors or BCG-refractory tumors.
- Intravenous pembrolizumab is currently an FDA-approved treatment option for patients with BCG-unresponsive NMIBC, in addition to several novel intravesical immune-based therapies.
- The most established standard of care for MIBC is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy and lymph node dissection. The optimal neoadjuvant chemotherapy regimens are GC and dose-dense MVAC. The addition of durvalumab in the perioperative setting to chemotherapy is now an approved option.
- For cisplatin-ineligible patients undergoing cystectomy, perioperative EVP is now an FDA-approved option. For those ineligible for EVP, no other perioperative chemotherapy is currently recommended, and carboplatin should not be substituted for cisplatin. Recent data suggest good safety and efficacy of a cisplatin split-dosing strategy for those with CrCl 40 to 60 mL/min; thus, cisplatin should be considered for this population.
- Adjuvant nivolumab or pembrolizumab immunotherapy for 1 year significantly improves DFS in patients with high-risk MIBC and is FDA approved for this indication.
- Maximal transurethral resection of the bladder tumor followed by concurrent definitive RT with radiosensitizing chemotherapy, also known as bladder-sparing or trimodality therapy, may offer similar long-term disease control for appropriately selected patients. Historically, this has been considered only for patients ineligible for or declining cystectomy, but based on nonrandomized data, it is now considered a reasonable alternative to cystectomy in all eligible patients.
- The preferred first-line therapy for patients with metastatic bladder cancer is combination EVP. Alternatively, less preferred regimens are cisplatin-based chemotherapy with or without nivolumab, followed by PD-1/PD-L1 checkpoint inhibitor maintenance. For patients who are not eligible for immunotherapy, gemcitabine and cisplatin remains a standard treatment option. In contrast with perioperative chemotherapy, carboplatin may be substituted for cisplatin-ineligible patients.
- Optimal second- and subsequent-line therapies are not well defined in the setting of the recent changes in first-line therapy. HER2 IHC and genomic testing for the *FGFR3* mutation should be requested. Options include platinum with gemcitabine, enfortumab vedotin monotherapy, erdafitinib, trastuzumab deruxtecan, and single-agent chemotherapies, depending on the prior systemic therapies used.
- Upper-tract (ureteral and renal pelvis) urothelial carcinoma may be diagnosed initially by imaging, urine cytology, and/or biopsy via retrograde ureteroscopy, but often a nephroureterectomy is required for pathological diagnosis as well as treatment.
- Perioperative chemotherapy should be considered for high-risk tumors based on extrapolation from bladder cancer or from one randomized trial of adjuvant platinum-based chemotherapy. For patients with high-risk disease who are unfit for or decline chemotherapy, adjuvant nivolumab may be considered as an alternative, although the supporting data are not as robust.
- Pure nonurothelial bladder cancers are typically treated with cystectomy; the role of perioperative chemotherapy and/or RT is not well defined.
- Bladder cancer is predominantly a disease of older patients and frequently occurs in patients with other comorbidities. Therefore, a significant portion of patients are not candidates for many standard therapies such as cisplatin and cystectomy.
- Bladder-sparing or trimodality therapy is now considered an equal alternative to cystectomy and is increasingly offered to appropriately selected patients who wish to preserve their bladders and avoid urinary diversion; previously, it was reserved primarily for patients ineligible for cystectomy because of comorbidities.
- Cisplatin should be offered to any eligible patient regardless of age, but this requires careful assessment of baseline neuropathy, hearing, and kidney function, and serial assessment during and after treatment. Split-dosing of cisplatin should be considered for patients with CrCl 40 to 60 mL/min. Newer systemic treatment modalities (eg, immune

checkpoint inhibitors, antibody-drug conjugates, and targeted therapies) are rapidly improving treatment options for patients with locally advanced or metastatic disease and those not eligible for conventional chemotherapy.

- Renal cell carcinoma is the most common type of kidney tumor. The classic triad of hematuria, abdominal pain, and a palpable mass is rarely seen in modern practice. Incidental diagnoses are increasing.
- Risk factors include smoking, obesity, hypertension, environmental exposures, hereditary kidney cancer syndromes, and acquired cystic kidney disease leading to end-stage renal disease.
- After radiographic evaluation of a localized kidney mass, the decision whether to biopsy or to perform partial or radical nephrectomy depends on the level of suspicion of malignancy, the size of the lesion, and the age and comorbidities of the patient.
- Small renal masses are often incidentally detected as contrast-enhancing tumors <4 cm. Options for management include active surveillance, partial nephrectomy, and percutaneous ablation.
- Complex masses may require radical nephrectomy with some increased subsequent risk of renal impairment.
- Adjuvant pembrolizumab for 1 year improves DFS and OS in intermediate- and high-risk resected localized clear–cell renal cell carcinoma.
- First-line systemic therapy for metastatic clear–cell renal cell carcinoma includes combination immune checkpoint blockade with ipilimumab and nivolumab or combination of PD-1/PD-L1 inhibition and VEGFR TKIs.
- The role of cytoreductive nephrectomy in the setting of metastatic disease remains undefined in the era of immune checkpoint inhibitor combinations. For patients without symptomatic primary tumors who are eligible for first-line systemic therapy, immediate cytoreductive nephrectomy may not provide significant benefit. The role of deferred nephrectomy is being evaluated in prospective clinical trials.
- Second-line therapy for metastatic disease includes VEGFR TKIs, belzutifan, mTOR inhibitors, and cytokine therapy in select patients, with the choice of therapy dependent on prior treatment. Alternate antiangiogenesis inhibitors may still be active after prior antiangiogenic therapy.
- Non–clear cell renal cell carcinomas have been underrepresented in clinical trials, and the optimal treatment strategy is not well defined. Targeted agents include standard anti-VEGF TKIs as well as an emerging role for *MET* inhibition in papillary renal cell carcinoma, especially using the dual VEGF/MET inhibitor cabozantinib.
- Bone metastases may be treated with systemic therapy and bone-protective agents such as bisphosphonates or denosumab. Brain metastases and oligometastases can be treated with local therapies (eg, surgery, RT, or ablation) followed by systemic therapy, sometimes with long-term disease control.
- Elderly patients with comorbidities may benefit from active surveillance of appropriate renal cell carcinomas or nephron-sparing approaches (eg, partial nephrectomy or stereotactic body RT) when treatment is required. For those being treated for advanced renal cell carcinoma, attention must be paid to the unique toxicities of checkpoint inhibitors and/or targeted therapies in the setting of concomitant hypertension, diabetes, chronic kidney disease, and thyroid disease, among others.
- The most well-known risk factor for testicular cancer is the history of undescended testis (cryptorchidism). Early surgical correction can help mitigate this risk.
- Genes on chromosome arm 12p seem to be involved with germ cell tumor pathogenesis, and i(12p) is a common finding that may help differentiate germ cell tumors from other tumor types in ambiguous situations or cancers with unknown primary.
- Suspicious testicular symptoms or findings should be evaluated by ultrasonography. If the results are suggestive, diagnosis is made via inguinal orchiectomy, never via percutaneous biopsy. Tumor marker levels should be determined beforehand, and if elevated, measurement must be repeated after surgery.
- For patients who present with life-threatening symptoms (eg, bleeding brain metastases or pulmonary metastases causing respiratory failure), highly elevated AFP or β-hCG levels, and a typical pattern of spread, systemic therapy should be started immediately. Resection of a suspicious testicular lesion can be delayed until after starting or completing chemotherapy, but should still be performed to establish a pathological diagnosis and remove a potential chemotherapy sanctuary site.
- Germ cell tumors are divided into seminomas and nonseminomas. Seminomas must be composed entirely of seminoma; any component of other histology results in a diagnosis of nonseminoma, and an elevated AFP level (>20-25) should be treated as nonseminoma.
- Seminomas are highly sensitive to chemotherapy and RT. This has implications for therapy and evaluation of residual masses after therapy.
- Nonseminomas can be mixes of multiple histologies, including malignant germ cell tumors (embryonal carcinoma, yolk sac tumor, and choriocarcinoma) and teratomas. Malignant nonseminomatous germ cell tumors are generally chemotherapy sensitive. Teratoma is neither chemotherapy nor RT sensitive. By itself, teratoma does not usually metastasize,

but it can dedifferentiate over time into malignant histologies, including (but not limited to) teratocarcinoma or certain sarcomas.

- The testicles descend from the retroperitoneum embryologically; therefore, the lymphatic drainage is to the retroperitoneal lymph nodes rather than the inguinal or pelvic lymph nodes. This has implications for surveillance and treatment.
- If prior inguinal or transscrotal surgeries have been performed, the lymphatic drainage may be disrupted; therefore, the pattern of metastasis can be less predictable, and more caution is needed if considering adjuvant retroperitoneal lymph node dissection (RPLND) or radiation.
- From the retroperitoneal lymph nodes, testicular cancer may spread to mediastinal and other lymph nodes. Pulmonary metastases are much more common than other visceral metastases and do not carry as poor a prognosis as other visceral involvement.
- Before orchiectomy, tumor-marker levels should be measured, and patients should undergo cross-sectional imaging of the abdomen and pelvis as well as chest imaging. MRI of the head and a bone scan are indicated only for patients with suspicious symptoms or in the setting of specific risk factors.
- Advanced (metastatic) germ cell tumors are risk-stratified according to primary site, pattern of spread, and degree of serum tumor-marker elevation.
- Stage I seminomas are generally managed with active surveillance. Alternatives include adjuvant chemotherapy (one to two cycles of carboplatin) or RT, which decreases the risk of recurrence but results in some degree of overtreatment and has long-term toxicities. OS is excellent regardless of immediate versus delayed intervention. Therefore, adjuvant treatment is typically offered only to patients who are eager to reduce their chance of recurrence (and the need for more intensive therapy) or who may have difficulty adhering to a surveillance schedule, with the understanding that OS will not likely be improved.
- Stage IIA and nonbulky IIB seminomas can be treated with RT to the retroperitoneal lymph nodes or chemotherapy.
- Stage IIB and advanced seminomas (stages IIC and III) are treated according to the risk stratification scheme for advanced germ cell tumors, with most falling into the good-risk category and a minority being intermediate risk because of nonpulmonary visceral metastases. Seminomas are never considered poor risk.
- Good-risk advanced germ cell tumors are treated with three cycles of BEP or four cycles of etoposide and cisplatin.
- Intermediate- and poor-risk advanced germ cell tumors are treated with four cycles of BEP or four cycles of VIP. Omission of bleomycin is not acceptable unless the patient is receiving VIP.
- Germ cell tumors refractory to first-line chemotherapy are still curable, but the prognosis is worse.
- Options for second-line chemotherapy include standard-dose regimens such as TIP and high-dose chemotherapy with autologous stem cell rescue. Which strategy is superior is unknown, but high-dose chemotherapy is generally preferred for patients with poor-prognosis features or as third-line therapy.
- Residual masses after second-line chemotherapy in nonseminomas should still undergo resection as in the first-line setting.
- Pulmonary toxicity must be managed in patients treated with bleomycin by continued monitoring of symptoms and DLCO. Bleomycin should be discontinued if there are suggestive symptoms. Small asymptomatic drops in DLCO are common, but discontinuation is generally recommended for drops of ≥25%. For bleomycin-treated patients who subsequently require surgery, low intraoperative Fio_2 and minimal hydration should be used.
- Teratoma may undergo malignant transformation into teratocarcinoma, adenocarcinoma, or other histologies, generally as a late complication of unresected teratomatous components of nonseminoma.
- In a situation of diagnostic uncertainty, the presence of i(12p) points to a likely germ cell tumor origin.
- Non–germ cell testicular cancers are rare and include sex cord tumors, the most common being Leydig cell tumors. These can cause endocrinopathies and are typically cured via orchiectomy.
- Most patients with testicular cancer have long-term survival and are treated relatively early in life, so monitoring for and intervening in early and late complications of treatment are important, especially those complications related to the cardiovascular system. Cisplatin-based chemotherapy and/or RT may increase cardiovascular risk, risk of secondary malignancies, and risk of infertility, among others. Patients treated with chemotherapy and/or RT should monitor and treat other cardiovascular risk factors, including hypertension, and adhere to age-appropriate cancer screening. These risks further justify the avoidance of adjuvant therapies for most patients with stage I disease.
- Penile cancer is a rare disease associated with age, lack of circumcision, HPV and/or HIV infection, and tobacco use.
- Penile cancer is typically of squamous histology.
- The primary pattern of spread is local invasion followed by inguinal lymph node metastasis. However, inguinal nodes may frequently be enlarged as a result of concomitant inflammation and infection. Evaluation of the inguinal nodes depends on the invasiveness of the primary tumor and whether the nodes are palpable.
- Penile cancer is managed according to the degree of tumor invasion and lymph node involvement. The primary treatment modality is surgery.

- Patients with intermediate- or high-risk penile cancers should undergo assessment for lymph node involvement.
- Perioperative chemotherapy (eg, TIP regimen) and/or RT with or without radiosensitizing chemotherapy may be used for advanced tumors, but high-level evidence is lacking.
- Malignant adrenal tumors are extremely rare.
- After resection of localized adrenal cortical carcinoma, patients at high risk of recurrence may be considered for adjuvant mitotane.
- Adding mitotane to chemotherapy in the advanced setting increases response rates but not survival.
- Malignant pheochromocytoma is treated surgically, similarly to nonmalignant pheochromocytoma.

CHAPTER TABLES AND IMAGES

Table 14-1 Randomized Trials of ADT Plus Abiraterone and Prednisone for mCSPC

Trial	No. of Participants	Study Population	Design	Outcome	Notes
LATITUDE	1,199	De novo high-risk mCSPC	ADT plus placebo vs ADT plus abiraterone and prednisone	Improved OS with the addition of abiraterone and prednisone (53.3 vs 36.5 months)[89]	High risk based on 2 of 3: Gleason 8+, 3 + bone lesions, visceral metastases
STAMPEDE	1,917	High-risk localized or high-risk BCR or mCSPC (recurrent or de novo)	ADT plus placebo vs ADT plus abiraterone and prednisone (plus RT for localized or N + disease)	Improved 3-year OS with the addition of abiraterone and prednisone (83% vs 76%)	Benefit was seen across subsets, including M0 tumors, although there were few events in this group

Abbreviations: ADT, androgen deprivation therapy; BCR, biochemical recurrence; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; RT, radiation therapy.

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Table 14-2 **Randomized Trials of ADT Plus Androgen Receptor Pathway Inhibitors for mCSPC**					
Trial	**No. of Participants**	**Study Population**	**Design**	**Outcome**	**Notes**
ARANOTE[1]	669	mCSPC (recurrent or de novo)	ADT + placebo vs ADT + darolutamide	Improved radiographic PFS with the addition of darolutamide (not reached vs 25 months)	rPFS benefit seen regardless of disease volume. OS data immature
ARCHES	1,150	mCSPC (recurrent or de novo)	ADT versus ADT plus enzalutamide. Docetaxel is allowed at the investigator's discretion in either trial arm	Improved radiographic PFS with addition of enzalutamide (not reached vs 19 months)	rPFS benefit seen regardless of docetaxel use and/or disease volume. OS data immature
ENZAMET	1,125	mCSPC (recurrent or de novo)	ADT versus ADT plus enzalutamide. Docetaxel is allowed at the investigator's discretion in either trial arm	Improved OS with the addition of enzalutamide (median OS not yet estimable; 80% versus 72% OS at 3 years)	Possibly limited benefit of enzalutamide in docetaxel-treated patients. Possible increased docetaxel toxicity with the addition of enzalutamide
TITAN	1,052	mCSPC (recurrent or de novo)	ADT versus ADT plus apalutamide. Docetaxel is allowed at the investigator's discretion in either trial arm	Improved OS and radiographic PFS with apalutamide (82% vs 74% OS; 68% vs 48% rPFS)	rPFS benefit seen regardless of docetaxel use and/or disease volume. Possibly limited OS benefit of apalutamide in docetaxel-treated patients

Abbreviations: ADT, androgen deprivation therapy; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; PFS, progression-free survival; rPFS, radiography progression-free survival; RT, radiation therapy.
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Table 14-3 **Standard Neoadjuvant Chemotherapy Regimens**

Classic MVAC (28-Day Cycle)	Dose-Dense MVAC (14-Day Cycle)	Gemcitabine and Cisplatin
Methotrexate on days 1, 15, and 22	Methotrexate on day 1	21-day regimen
Vinblastine on days 2, 15, and 22	Vinblastine on day 2	Cisplatin on day 1 or 2
Doxorubicin on day 2	Doxorubicin on day 2	Gemcitabine on days 1 and 8
Cisplatin on day 2	Cisplatin on day 2	28-day regimen:
	G-CSF on days 4-10 or pegylated	Cisplatin on day 1 or 2
	G-CSF after chemotherapy	Gemcitabine on days 1, 8, and 15

Abbreviations: G-CSF, granulocyte colony-stimulating factor; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin.
For classic MVAC and dose-dense MVAC, all four chemotherapy agents (methotrexate, vinblastine, doxorubicin, and cisplatin) may be given together on day 1.
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Table 14-4 **Genomic Alterations in Inherited and Sporadic Renal Tumors**

Genomic Alteration	Type of Renal Tumor	Syndrome
VHL	ccRCC	Von Hippel-Lindau (autosomal dominant): • Hemangioblastomas of CNS • Retinal angiomas • Pheochromocytomas • Pancreatic serous cystadenomas and neuroendocrine tumors
Chromosome 3 translocations or *BRCA1*-associated protein 1 (*BAP1* gene)	ccRCC	Familial ccRCC
MET (germline and somatic)	Hereditary or sporadic type I papillary RCC	Hereditary papillary renal carcinoma (autosomal dominant): • Bilateral multifocal papillary renal tumors
Fumarate hydratase (germline)	Type II papillary RCC	Hereditary leiomyomatosis and RCC: • Autosomal dominant • Uterine fibroids
Succinate dehydrogenase (germline)	ccRCC or chromophobe RCC	Hereditary paraganglioma and pheochromocytoma (autosomal dominant): • Paragangliomas • Pheochromocytomas • Bilateral and/or multifocal kidney tumors
Xp11.2 (*TFE* gene)	ccRCC or papillary RCC	Early-onset RCC
Folliculin (*FLCN* gene)	Chromophobe RCC or mixed chromophobe-oncocytoma renal tumors	Birt-Hogg-Dube syndrome: hair-follicle hamartomas of the face and neck: • Renal and pulmonary cysts • Slow-growing bilateral kidney tumors
Hamartin (*TSC1*) or tuberin (*TSC2*)	Angiomyolipomas, rare ccRCC	Tuberous sclerosis complex: • Bilateral multifocal kidney tumors
SMARCB1 (germline)	Medullary carcinoma	

Abbreviations: ccRCC, clear–cell renal cell carcinoma; CNS, central nervous system; RCC, renal cell carcinoma.
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Table 14-5 **Factors More Common in Hereditary RCC Useful for Referral for Genetic Evaluation**
Early age at RCC diagnosis (46 years or younger)
Bilateral renal cancer
Multifocal renal cancer
Strong family history of RCC (two or more relatives in the same bloodline)
RCC with personal or family history of one or more tumor type[a]
Unusual skin conditions (eg, leiomyomas, fibrofolliculomas, angiofibromas)
Family history of kidney cancer syndrome

Abbreviation: RCC, renal cell carcinoma.
[a]Pheochromocytoma, brain/spinal hemangioblastoma, pancreatic neuroendocrine tumor, retinal tumor, papillary cystadenoma, endolymphatic sac tumor, gastrointestinal stromal tumor, uterine fibroid (age ≤35 years), uveal and cutaneous melanomas, and solid cancer occurring in childhood.
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Table 14-6 **Combination Therapies for Frontline Treatment of Metastatic Renal Cell Carcinoma**

	Ipilimumab + Nivolumab	Axitinib + Pembrolizumab	Axitinib + Avelumab	Cabozantinib + Nivolumab	Lenvatinib + Pembrolizumab
Randomization (control arm)	1:1 (sunitinib)	1:1 (sunitinib)	1:1 (sunitinib)	1:1 (sunitinib)	1:1:1 (lenvatinib with everolimus, sunitinib)
No. of subjects	1,096	861	886	651	1,069
IMDC risk (%)	23	31.2	21.4	23	31
Favorable	61	56.2	61.8	58	59.2
Intermediate poor	17	12.6	16.2	19	9.3
PD-L1 >1% (%)	24	60.5	63.2	26	30.1
OS	0.68	0.53	0.78	0.60	0.66
HR 95% CI	0.49-0.95	0.38-0.74	0.55-1.08	0.40-0.89	0.49-0.88
Median PFS (months)	12.4	15.1	13.8	16.6	23.9
Combination sunitinib	12.3	11.1	8.4	8.3	9.2
Objective RR	39%	59.3%	51.4%	55.7%	71%
Complete RR	10.20%	5.8%	3.4%	8%	16.1%
Median DoR (months)	76.2	23.6	19.4	20.2	25.8

Abbreviations: DoR, duration of response; IMDC, International Metastatic Renal-Cell Carcinoma Database Consortium; OS, overall survival; PFS, progression-free survival; RR, response rate.

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Table 14-7 **Key Phase 3 Trials of Antiangiogenic Therapy in Metastatic RCC**

Trial	No. of Participants	Study Population	Design	Outcome	Notes
Motzer et al[172]	750	Treatment-naive metastatic RCC	Sunitinib vs interferon-α	Improved PFS with sunitinib (11 vs 5 months)	Improved OS with sunitinib in long-term follow-up (26.4 vs 21.8 months)
Sternberg et al[173]	435	Treatment-naive and cytokine-treated metastatic RCC	Pazopanib vs placebo	Improved PFS with pazopanib (9.2 vs 4.2 months)	PFS benefit seen regardless of prior treatment
AXIS[174]	723	Previously treated metastatic RCC	Axitinib vs sorafenib	Improved PFS with axitinib (6.7 vs 4.7 months)	OS did not differ in long-term follow-up (20.1 vs 19.2 months)
METEOR[175]	658	VEGFR-treated metastatic RCC	Cabozantinib vs everolimus	Improved PFS with cabozantinib (7.4 vs 3.8 months)	More toxicity with cabozantinib. Improved OS with cabozantinib in long-term follow-up
CABOSUN[176]	157	Treatment-naive intermediate-/high-risk metastatic RCC	Cabozantinib vs sunitinib	Improved PFS with cabozantinib (8.6 vs 5.3 months)	No significant OS difference in long-term follow-up
Motzer et al[177]	153	VEGFR-treated metastatic RCC	Lenvatinib plus everolimus vs lenvatinib versus everolimus	Improved PFS with lenvatinib plus everolimus (14.6 months) or lenvatinib (7.4 months) vs everolimus (5.5 months)	Marginally improved OS with lenvatinib plus everolimus vs everolimus, but underpowered. Increased toxicity with combination therapy

Abbreviations: OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; VEGFR, vascular endothelial growth factor receptor.
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Table 14-8 **Targeted Agents for Non–Clear Cell RCC**

Agent	Primary Target	Histology	Outcome
Sunitinib	*VEGFR*	Papillary, chromophobe, translocation	Improved PFS with sunitinib vs everolimus (8.3 vs 5.6 months), but poor-risk patients may have better PFS with everolimus
Temsirolimus	*mTOR*	Papillary, chromophobe	Improved OS with temsirolimus vs IFN (11.6 vs 4.3 months)
Everolimus	*mTOR*	Papillary, chromophobe, translocation	See above comments on sunitinib. No clear difference between sequencing sunitinib followed by everolimus vs everolimus followed by sunitinib
Crizotinib	*MET*	Type I papillary RCC	In 4 of 23 patients with *MET* alteration, 2 had PR
Foretinib	*MET*, *VEGF*	Papillary RCC	In 10 patients with germline *MET* alteration, 5 had PR. Overall, RR was 13.5%; median PFS was 9 months
Savolitinib	*MET*	Papillary RCC	In the phase 3 SAVOIR trial, compared savolitnib vs sunitinib in *MET*-driven papillary RCC. Enrollment was closed early when new data suggested longer-than-anticipated PFS of patients with papillary RCC treated with sunitinib. PFS numerically improved, not statistically significant (with early termination). Savolitinib arm of PAPMET closed early for futility
Cabozantinib	*MET*, *VEGF*	Papillary RCC	Improved ORR and PFS were seen in comparison with sunitinib in the frontline setting in PAPMET (see above)

Abbreviations: IFN, interferon; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; RR, response rate; VEGFR, vascular endothelial growth factor receptor.
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Table 14-9 **Risk Stratification According to the International Germ Cell Consensus Classification**[167]	
Germ Cell Tumor	**Risk Stratification**
Seminoma	Good risk: • Any primary and any markers and no nonpulmonary visceral metastases
	Intermediate risk: • Any primary and any markers and nonpulmonary visceral metastases
Nonseminoma	Good risk: • Testis or retroperitoneal primary and good-risk markers, and no nonpulmonary visceral metastases
	Intermediate risk: • Testis/retroperitoneal primary and intermediate-risk markers and no nonpulmonary visceral metastases
	Poor risk: • Mediastinal primary site or testis or retroperitoneal primary with either nonpulmonary visceral metastases or poor-risk markers

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Table 14-10 **Serum Markers in Germ Cell Tumors**			
	Serum Marker		
Histology	**AFP[a]**	**β-hCG[b]**	**LDH[c]**
Seminoma	Never	+/− (Typically <100)	+/−
Nonseminoma			
Choriocarcinoma	+/−	+++	+/−
Embryonal carcinoma	+/−	++	+/−
Teratoma	—	—	—
Yolk sac tumor	+++	+/−	+/−

Abbreviations: AFP, alpha fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.
[a]Half-life: 5 to 7 days.
[b]Half-life: 1 to 2 days.
[c]Half-life: varies by isoform.
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Table 14-11 **Selected Treatment Regimens for Relapsed Germ Cell Tumors After First-Line Bleomycin, Etoposide, and Cisplatin Combination or Etoposide and Cisplatin**

Chemotherapy	Regimen	Agents	Results
Standard dose	TIP[91]	Paclitaxel (Taxol)	Limited to patients with favorable prognostic factors
		Ifosfamide plus mesna	ORR, 63%; 2-year PFS, 65%
		Cisplatin	
	VeIP	Vinblastine	Disease-free rate, 36% (including patients undergoing subsequent resection of masses); median survival, 12.7 months
		Ifosfamide plus mesna	
		Cisplatin	
High-dose with autologous stem cell rescue	TI-CE[103]	Two cycles of conventional-dose paclitaxel (Taxol) and ifosfamide plus mesna, followed by G-CSF, followed by stem cell collection (leukapheresis)	Limited to patients with unfavorable prognostic factors
		3 cycles of high-dose carboplatin and etoposide, followed by stem cell rescue, each cycle	5-year DFS, 47%; OS, 52%

Abbreviations: DFS, disease-free survival; G-CSF, granulocyte colony-stimulating factor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TI-CE, paclitaxel/ifosfamide/carboplatin/etoposide; TIP, paclitaxel/ifosfamide/cisplatin; VeIP, vinblastine/ifosfamide/cisplatin.
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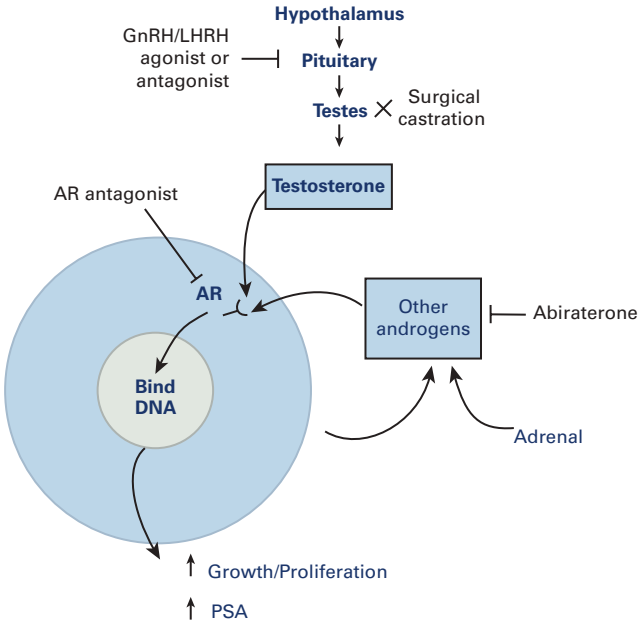
Figure 14-1 Basic Schematic of Androgen Receptor–Directed Therapies



Abbreviations: AR, androgen receptor; GnRH, gonadotropin-releasing hormone; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.

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Figure 14-2 Gleason Scoring

A

A Gleason score is assigned by adding the two most common grades of prostate cancer cells in a tissue sample.

How is it calculated?

Formula for Gleason scoring

Primary pattern (>50%) + Secondary pattern (<50%) = GS

Example:

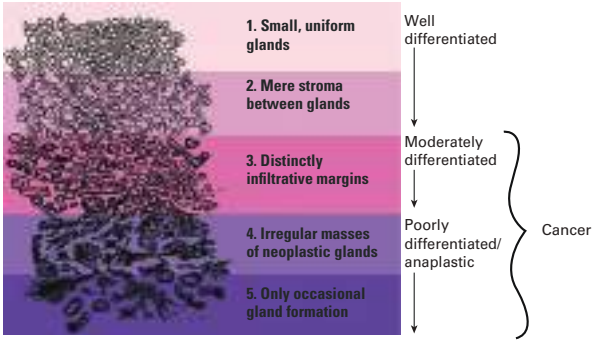
Primary pattern = 3

Secondary pattern = 4

Total GS = 7

This means that most of the tumor is grade 3 (aka dominant pattern), and a smaller portion is grade 4.

B



C

Gleason score Formula: GS = Primary pattern (>50%) + Secondary pattern (<50%)	ISUP Grade Groups derived from GS; Cancer grading
6 (</3 + 3)	Grade Group I (GS = </6)
7 (3 + 4)	Grade Group II
7 (4 + 3)	Grade Group III
8 (4 + 4)	Grade Group IV
9 (4 + 5)	Grade Group V
9 (5 + 4)	Grade Group V
10 (5 + 5)	Grade Group V

The Gleason score is a scale that helps with the staging of prostate cancer (by aggressiveness and prognosis) based on the microscopic examination of the sample tissue in the prostate biopsy. The grades in the score compare the pattern of the cancerous tissue with that of normal tissue in regard to aspects including shape, disposition, and spread. There are two grades that are awarded, each on a scale from 1 to 5. The primary grade is given to the most commonly observed type of cancerous cell; the secondary grade is given to the second most commonly observed type of cancerous cell.

(A) Calculating the Gleason score. (B) Gleason Pattern. (C) Deriving ISUP grade groups from GS.

Abbreviations: GS, Gleason score; ISUP, International Society of Urological Pathology.

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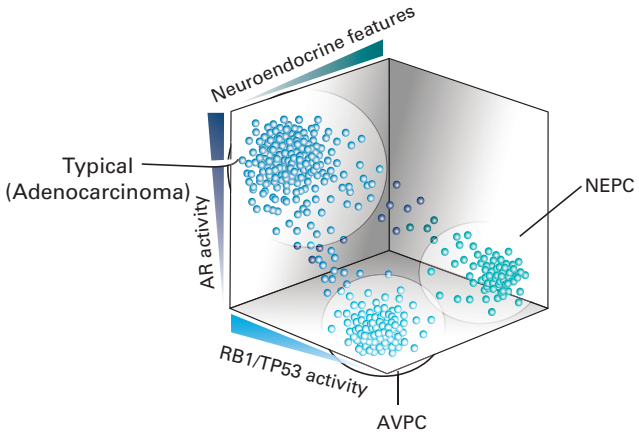
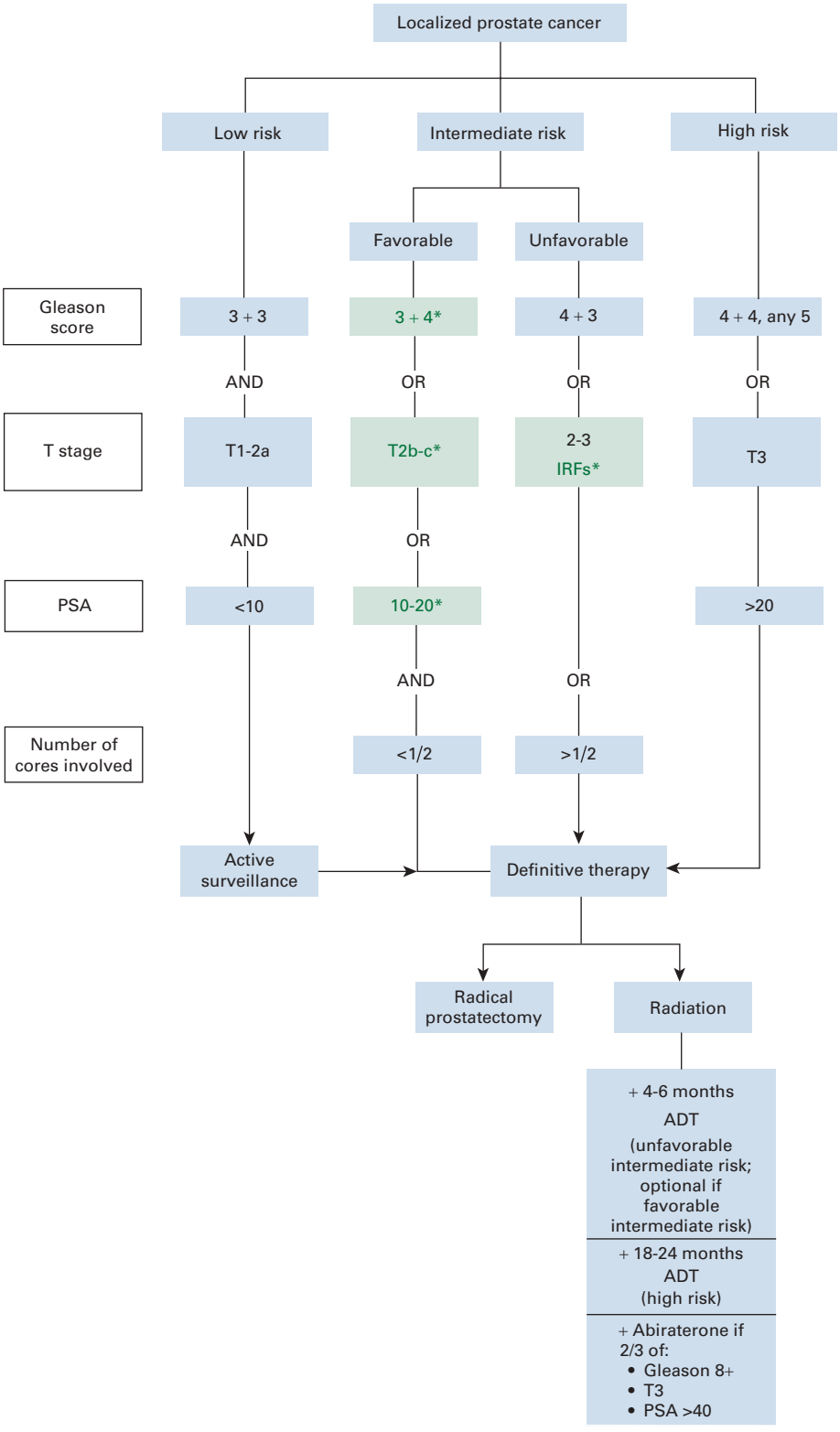
Figure 14-3 Relationship Between AR Signaling, Tumor-Suppressor Genes, and Neuroendocrine Features in Metastatic Castration-Resistant Prostate Cancer



This depicts a conceptual representation of the spectrum of profiles that include AR signaling, loss of tumor-suppressor genes, and development of neuroendocrine features during prostate cancer progression. Individual dots represent hypothetical patients, but different subclones may also be present within one individual.
Abbreviations: AR, androgen receptor; AVPC, aggressive variant prostate cancer; NEPC, neuroendocrine prostate cancer.
Reprinted with permission from Wolters Kluwer. Source: Einstein DJ, Arai S, Balk SP. Targeting the androgen receptor and overcoming resistance in prostate cancer. *Curr Opin Oncol*. 2019;31(3):175–182; figure 1. doi: 10.1097/CCO.0000000000000520

Figure 14-4 Approach to Treatment Options in Newly Diagnosed Localized Prostate Cancer According to Risk Stratification



Various forms of radiation are discussed in the text. Short course of ADT (4–6 months) is recommended for intermediate-risk category (especially if unfavorable) and long course (18–24 months) for high-risk category.
Abbreviations: ADT, androgen deprivation therapy; EBRT, external-beam radiation therapy; IRF, intermediate risk factor; PSA, prostate-specific antigen.
*IRFs.
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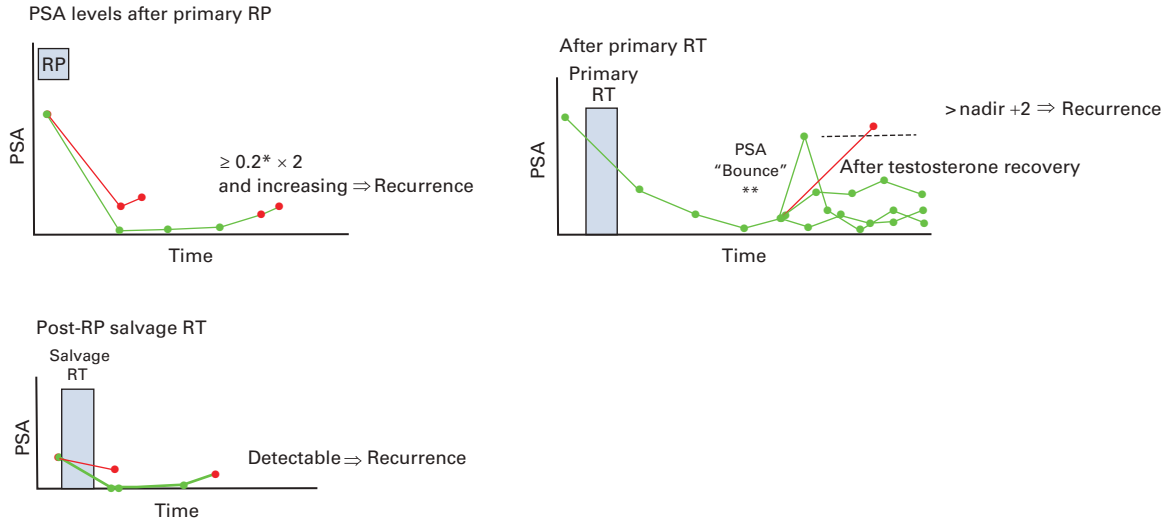
Figure 14-5 PSA Outcomes After Primary Therapies for Localized Prostate Cancer-Defining Biochemical Recurrence



Abbreviations: PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.
*Ultrasensitive PSA assays define biochemical recurrence as any measurable PSA value after radical prostatectomy.
**PSA "bounce" observed only in the absence of ADT.
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Figure 14-6 Management Options After Primary Therapy for Prostate Cancer

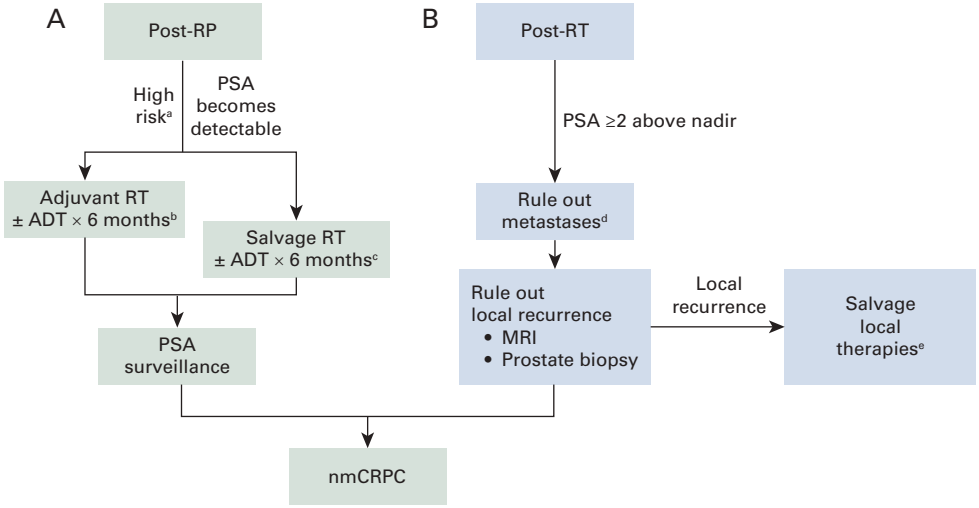
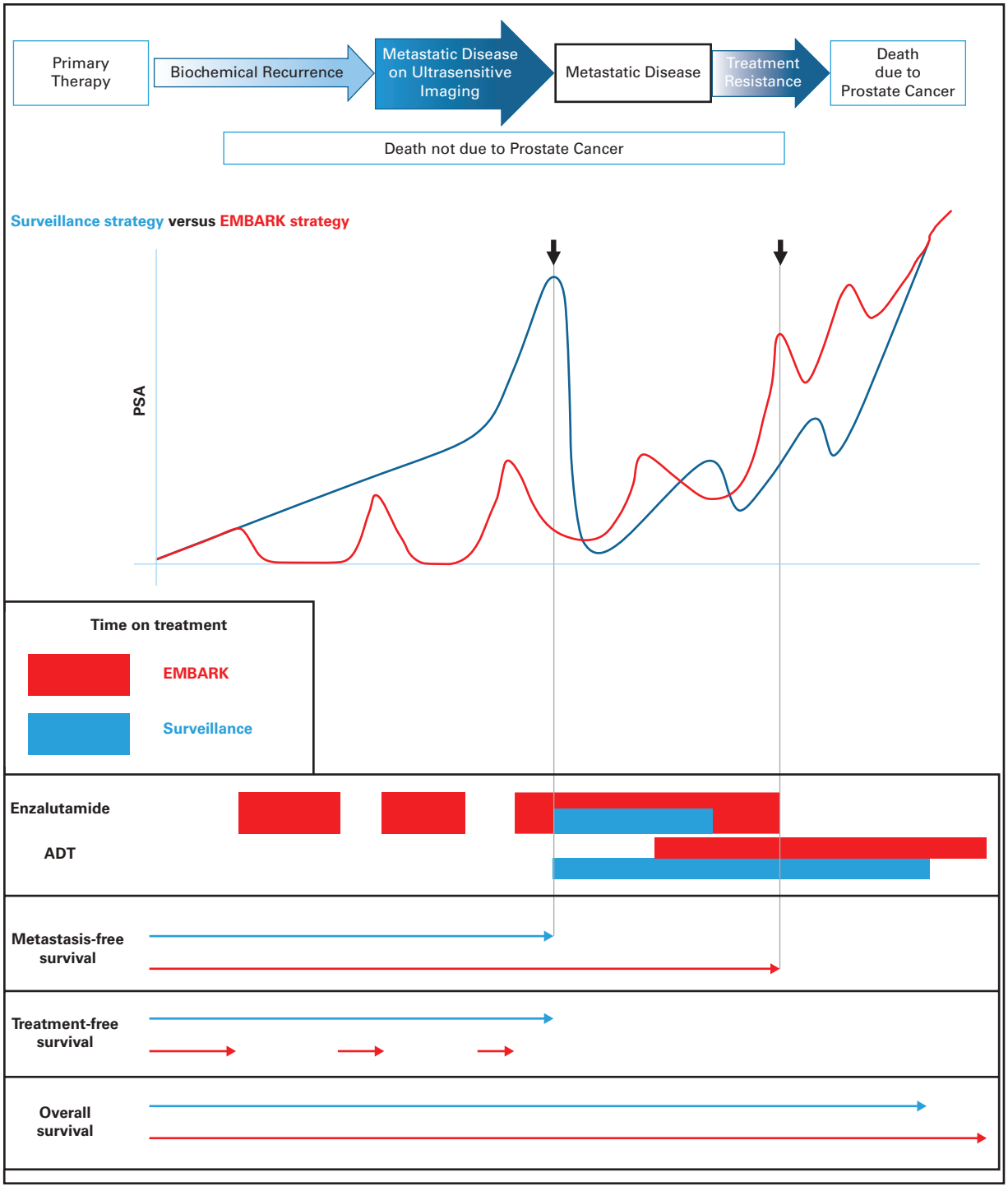


Figure 14-6 Continued

C



Panel (A) illustrates options following radical prostatectomy. Panel (B) illustrates options following radiation therapy. Panel (C) illustrates the hypothetical comparison of a surveillance strategy for biochemically recurrent prostate cancer to the EMBARK strategy with enzalutamide monotherapy.For options regarding recurrence after maximal local therapy, see Figure 14-7.

Abbreviations: ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mCSPC; metastatic castration-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiation therapy.

[a]High risk defined as pT3b or R1 (positive margin).

[b]Use and duration of ADT are variable; 6 months is common, but patients with low PSA may not benefit.

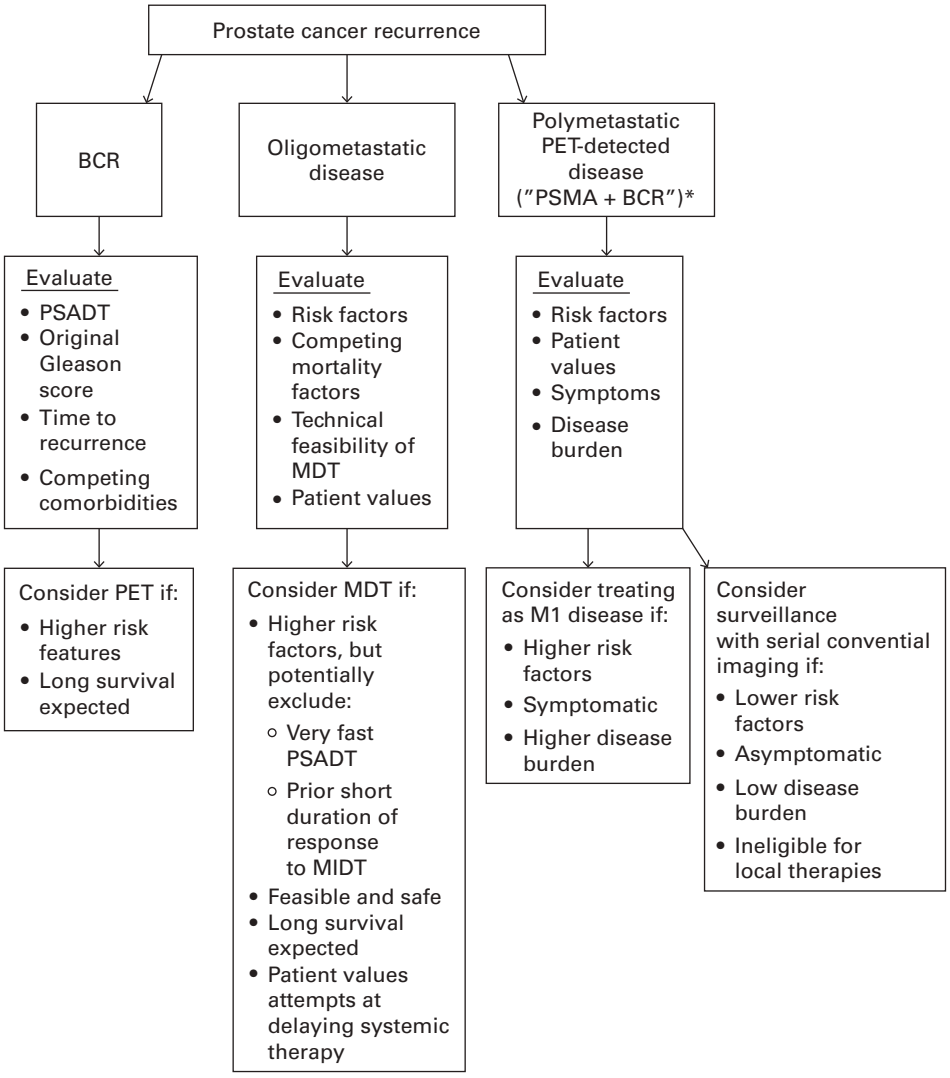
[c]Enzalutamide ± ADT. Previously, ADT, continuous or intermittent.

[d]Consider using ultrasensitive diagnostic imaging if available (eg, PET using PSMA tracers; eg, ^{68}Ga PSMA or ^{18}F[^{18}F] piflufolastat, ^{18}F fluciclovine, or ^{11}C choline); if not available, use conventional imaging modalities.

[e]Salvage local therapies may include brachytherapy, cryotherapy, radiofrequency ablation, high-intensity focused ultrasound, or salvage prostatectomy.

Panels (A, B) were created for ASCO. Copyright © 2026 by American Society of Clinical Oncology. Panel (C) was originally published in: David J. Einstein; Meredith M. Regan; Julia S. Stevens; David F. McDermott; Ravi A. Madan. JCO 2024 05-16. doi: 10.1200/JCO.24.00279

Figure 14-7 Recurrent Prostate Cancer After Maximal Local Therapy



Abbreviations: BCR, biochemical recurrence; MDT, metastasis-directed therapy; PET, positron emission tomography; PSADT, PSA doubling time.
*For discussion of "PSMA+BCR," see Einstein DJ, Abel ML, Aragon-Ching JB, et al. National Cancer Institute's Working Group on Biochemically Recurrent Prostate Cancer: clinical trial design considerations. *J Clin Oncol*. 2025;43(34):3672-3683. doi: 10.1200/jco-25-01693
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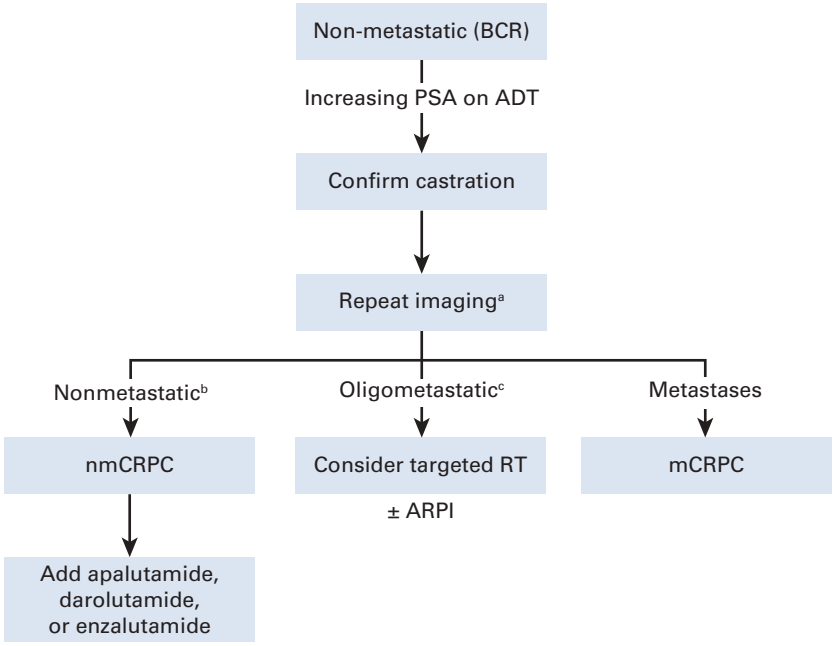
Figure 14-8 Treatment Options for nmCRPC



Abbreviations: ADT; androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BCR, biochemical recurrence; mCRPC, metastatic castration-resistant prostate cancer; NGI, next-generation imaging; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; RT, radiation therapy.

[a]Consensus from the ASCO Expert Panel is that NGI may be considered only if a change in clinical care is contemplated. Assuming patients have received or are ineligible for local salvage treatment options, NGI may clarify the presence or absence of metastatic disease, but the data on the detection capabilities of NGI in this setting and its impact on management are limited.

[b]In nmCRPC studies, patients were included who had pelvic lymph nodes up to 2 cm in diameter.

[c]Oligometastatic disease is variably defined as one to five metastases.

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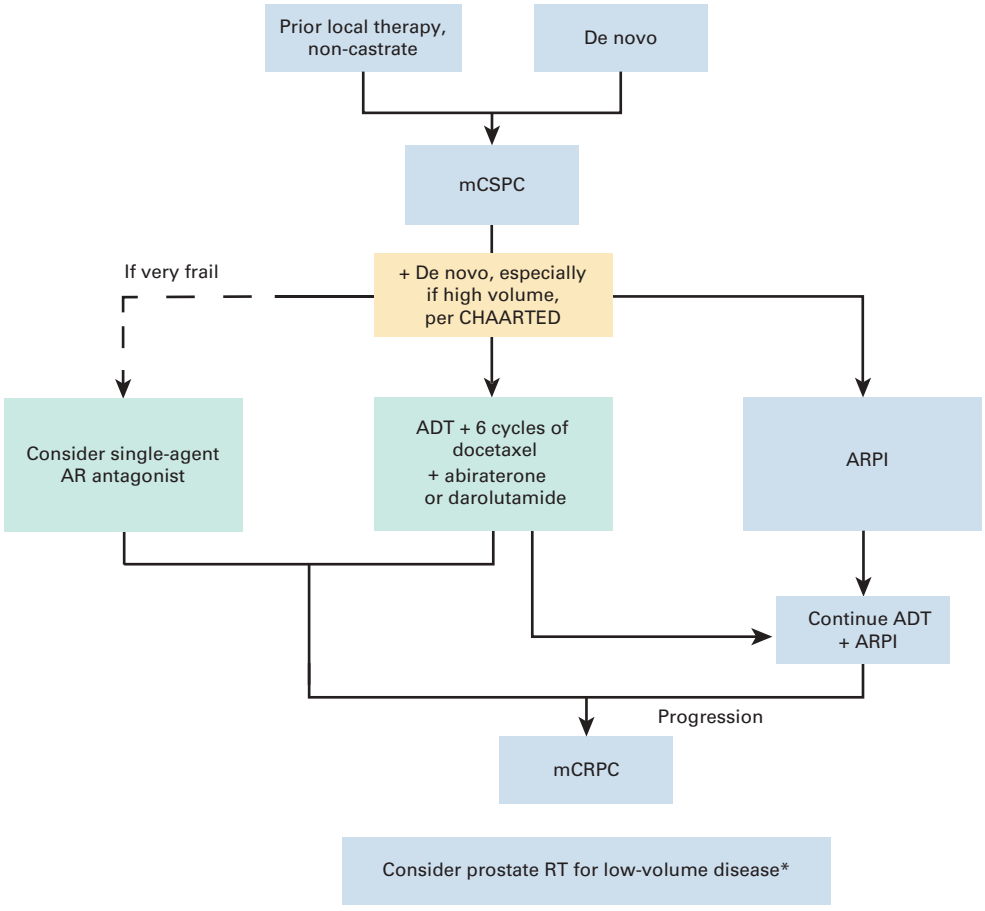
Figure 14-9 Standards of Care for mCSPC by Disease Volume



High volume is defined as the presence of ≥4 bone metastases with one or more lesions in the extra-axial skeleton or the presence of visceral metastasis.
Abiraterone is always administered with prednisone.
Abbreviations: ADT, androgen deprivation therapy; AR, androgen receptor; ARPI, androgen receptor pathway inhibitor; mCRPC, metastatic castration-resistant prostate cancer; mCSPC; metastatic castration-sensitive prostate cancer; RT, radiation therapy.
*Supported by a prespecified subgroup analysis from STAMPEDE, but the comparison arm was ADT alone. Efficacy in the setting of intensified therapy (ADT and docetaxel or ARPI) is unknown.
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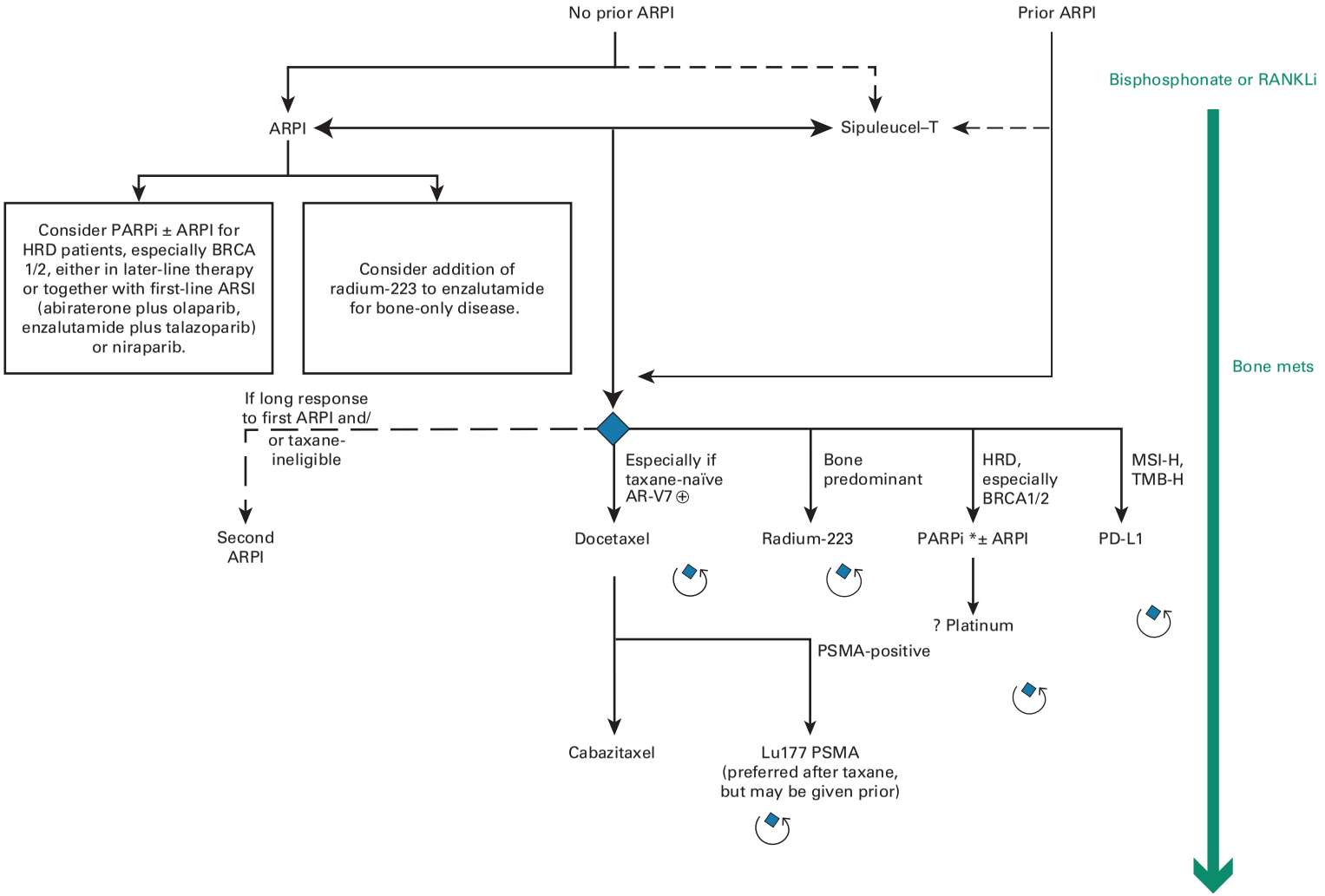
Figure 14-10 Treatment Options for mCRPC



Abiraterone is always administered with prednisone.
Abbreviations: ARPI, androgen receptor pathway inhibitor; HRD, homologous recombination deficiency; mCRPC, metastatic castration-resistant prostate cancer; MSI-H, high microsatellite instability; PARPi, poly ADP-ribose polymerase inhibitor; PSMA, prostate-specific membrane antigen; TMB-H, high tumor mutational burden.
*Consider PARPi ± ARPI for HRD patients, especially BRCA1/2, either in later-line therapy or together with first-line ARSI (abiraterone plus olaparib, enzalutamide plus talazoparib) or niraparib.
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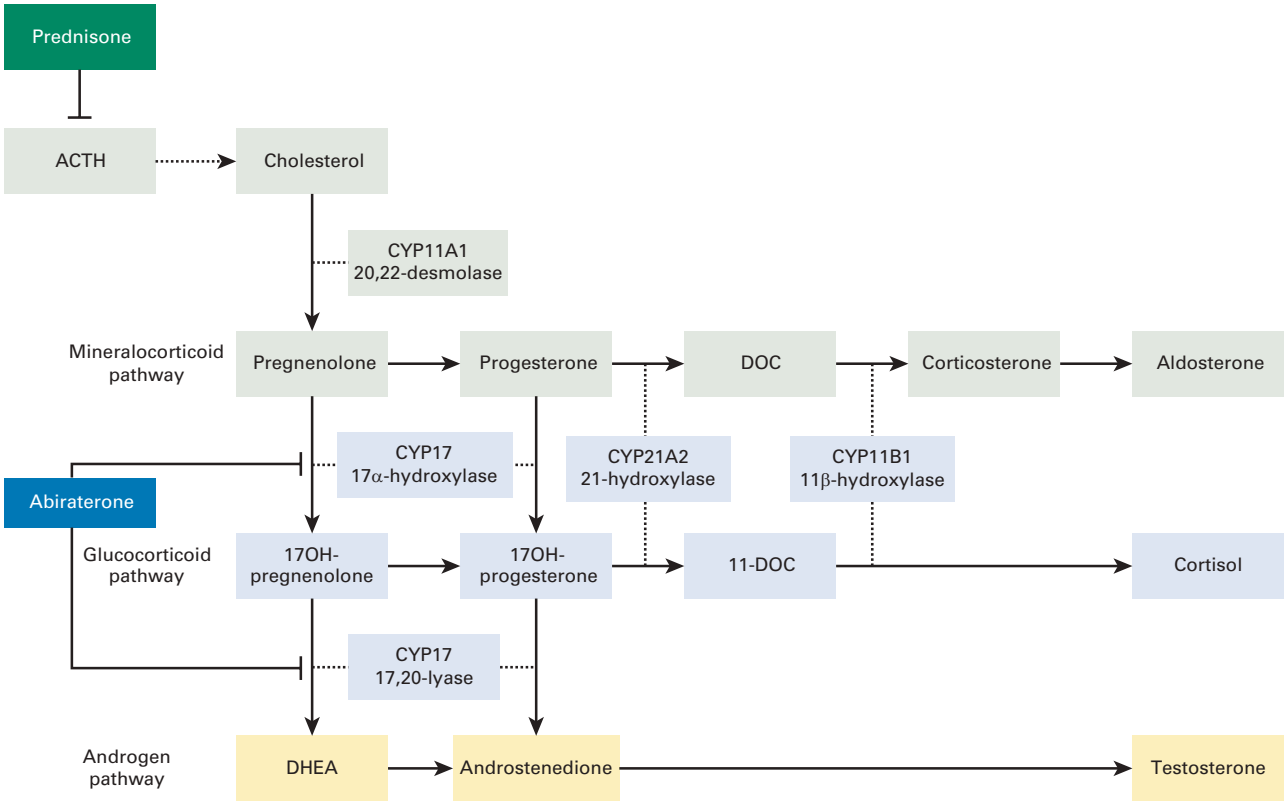
Figure 14-11 Biochemical Pathways Resulting From Abiraterone Administration and Prednisone



Administration of prednisone prevents a compensatory ACTH surge and thus decreases downstream symptoms of excess mineralocorticoid production (eg, hypertension, hypokalemia, and edema).
Abbreviations: ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone.
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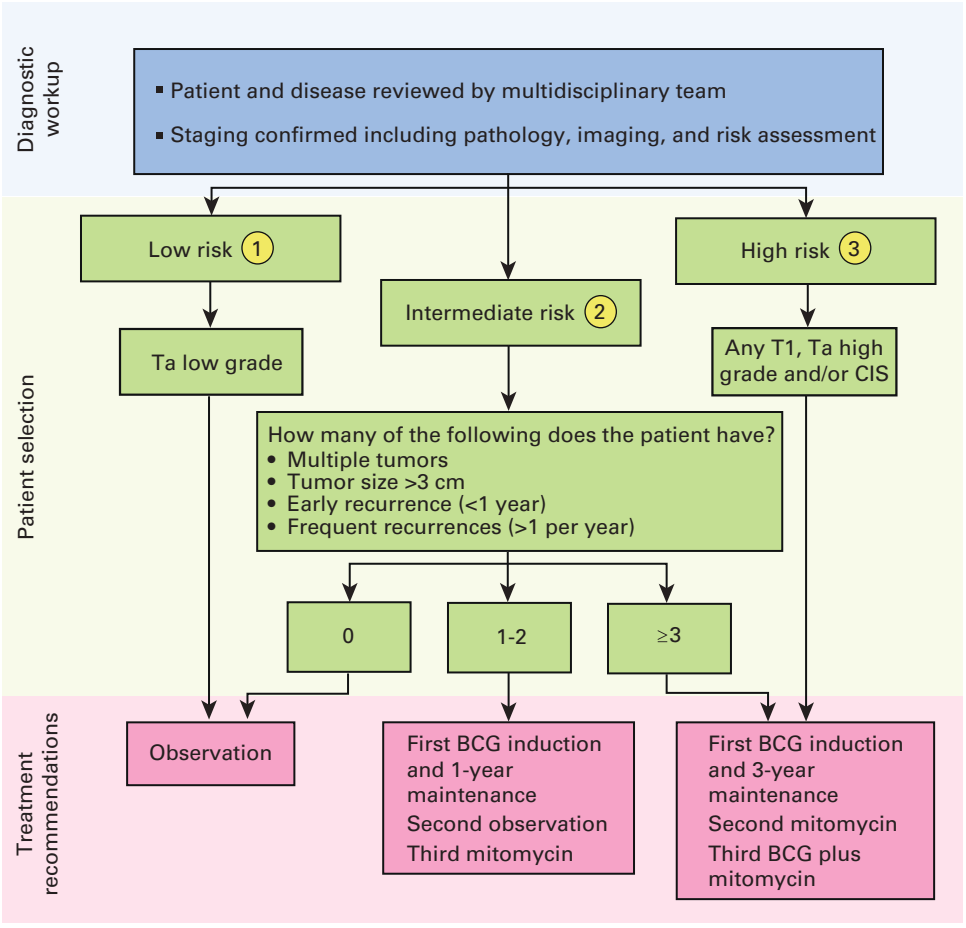
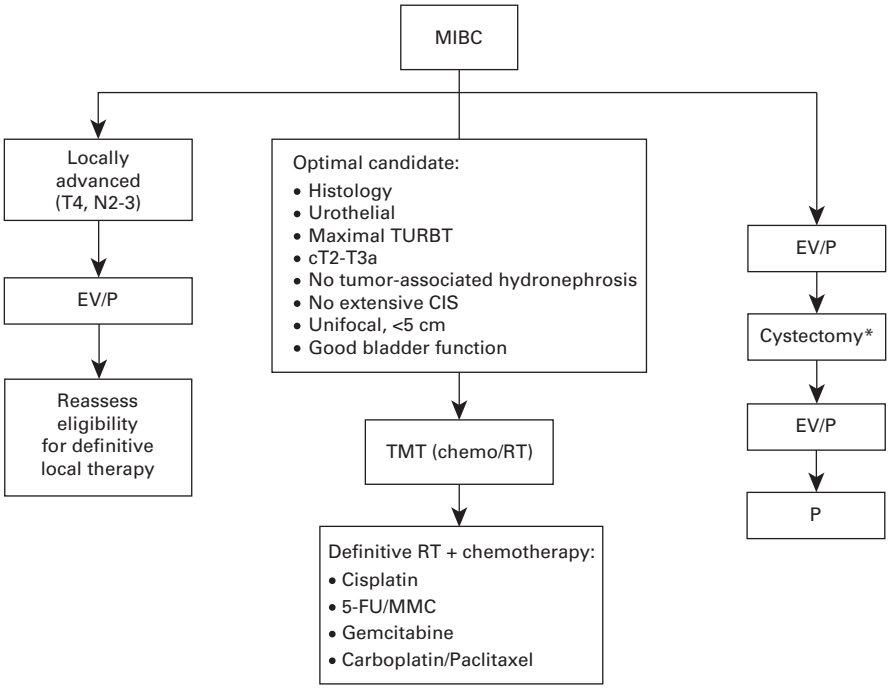
Figure 14-12 Treatment Algorithm for Non-Muscle-Invasive Bladder Cancer



All of the treatment options shown may be appropriate. The selection of therapy should be individualized based on patient eligibility and the availability of the therapy at the discretion of the treating physician. These algorithms are meant to provide advice as the consensus recommendations of the Task Force. (1) The Task Force defines low risk as a solitary, primary low-grade Ta tumor. (2) Intermediate risk is defined as histologically confirmed multiple and/or recurrent low-grade Ta tumors. (3) High risk is defined as any T1, high grade, and/or carcinoma in situ.
Abbreviations: BCG, Bacillus Calmette-Guerin; CIS, carcinoma in situ.

Reprinted under Creative Commons Attribution 4.0 International License from Kamat AM, Bellmunt J, Galsky MD, et al. Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma. *J Immunother Cancer*. 2017;5:68. doi:10.1186/s40425-017-0271-0

Figure 14-13 Treatment Options for Muscle-Invasive Bladder Cancer



Abbreviations: 5-FU, 5-fluorouracil; CIS, carcinoma in situ; ddMVAC, dose-dense methotrexate/vinblastine/doxorubicin/cisplatin; EV/P, enfortumab vedotin and pembrolizumab; GC, gemcitabine/cisplatin; MMC, mitomycin C; P, pembrolizumab; RT, radiation therapy; TMT, trimodality therapy; TURBT, transurethral resection of bladder tumor.

*If N + disease is established or suspected before scheduled radical cystectomy, and the patient has not received neoadjuvant therapy, radical cystectomy plus pelvic lymphadenectomy is still a treatment option. There is no level I evidence for adjuvant chemotherapy in the post-cystectomy node-positive setting, but many clinicians would consider its use based on results of the Advanced Bladder Cancer Collaborative meta-analysis.

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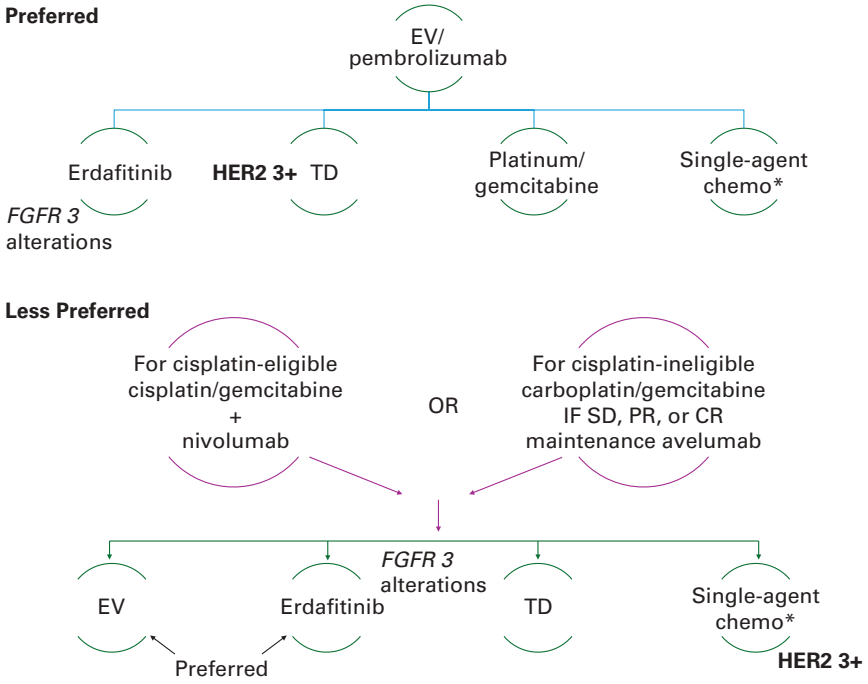
Figure 14-14 Systemic Therapy for Advanced Urothelial Cancer



*In cases of progression after prior treatments.
Abbreviations: CR, complete response; EV, enfortumab vedotin; *FGFR*, fibroblast growth factor receptor; PR, partial response; SD, stable disease; TD, trastuzumab deruxtecan.
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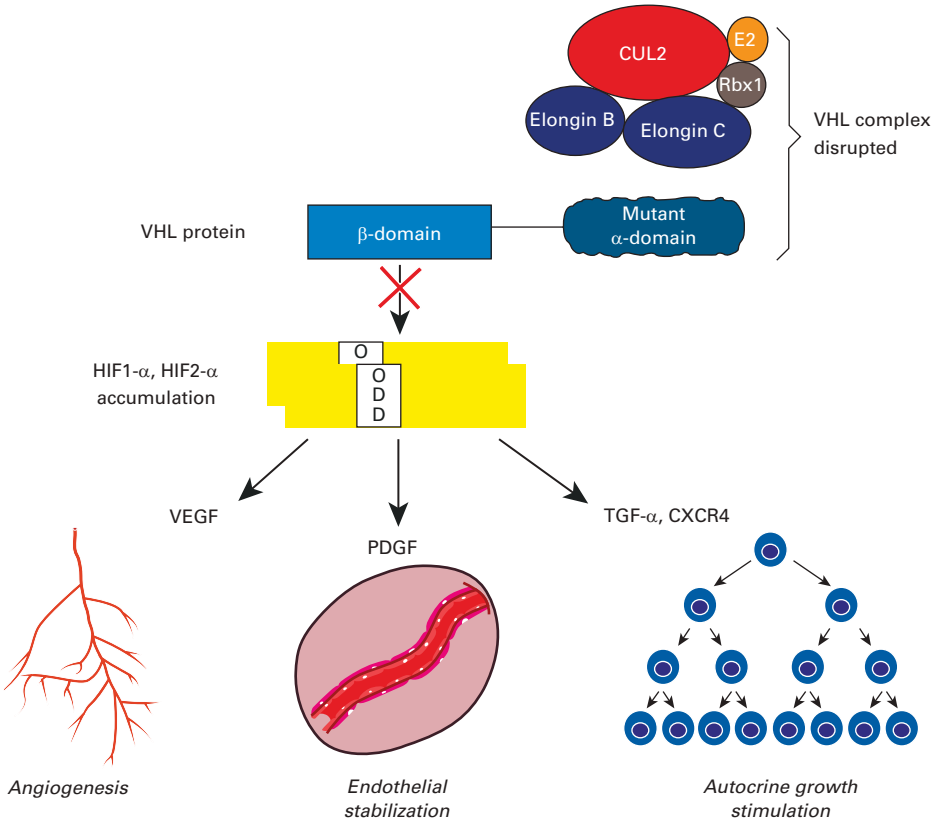
Figure 14-15 VHL Pathways for Oncogene Activation



Abbreviations: HIF, hypoxia inducible factor; PDGF, platelet-derived growth factor; TGF-α, transforming growth factor α; VEGF, vascular endothelial growth factor.
Pathways of oncogene activation in any loss of VHL function with emphasis on HIF activation.
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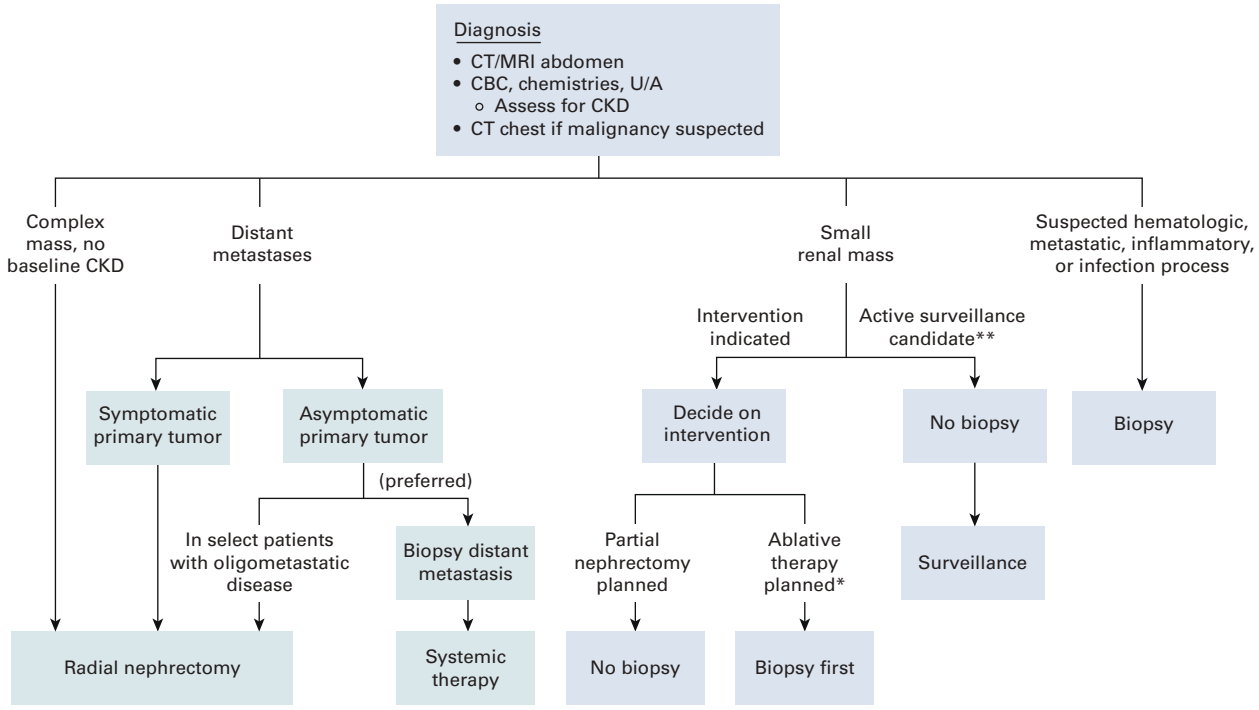
Figure 14-16 Diagnostic and Treatment Approaches to the Patient With a Kidney Mass



Abbreviations: CBC, complete blood cell; CKD, chronic kidney disease; U/A, urinalysis.
*Criteria for observation of small renal masses. Ablative approaches include catheter embolization, radio frequency ablation, and radiation therapy.
**Consideration in favorable risk.
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Figure 14-17 Adjuvant Pembrolizumab for High-Risk Localized RCC

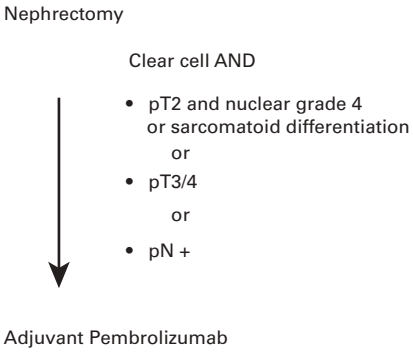

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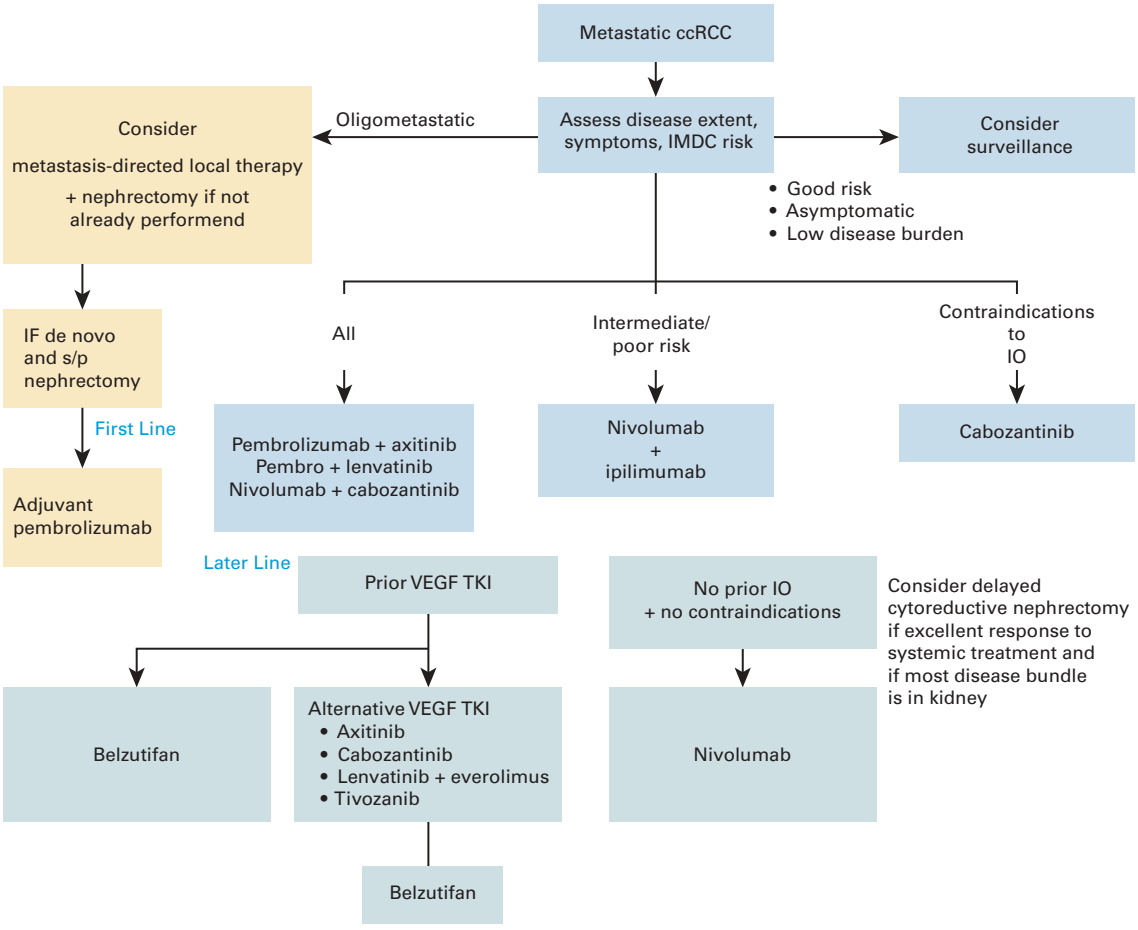
Figure 14-18 Treatment Options for Metastatic ccRCC



Abbreviations: ccRCC, clear–cell renal cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immunotherapy; TKI, tyrosine kinase inhibitor.

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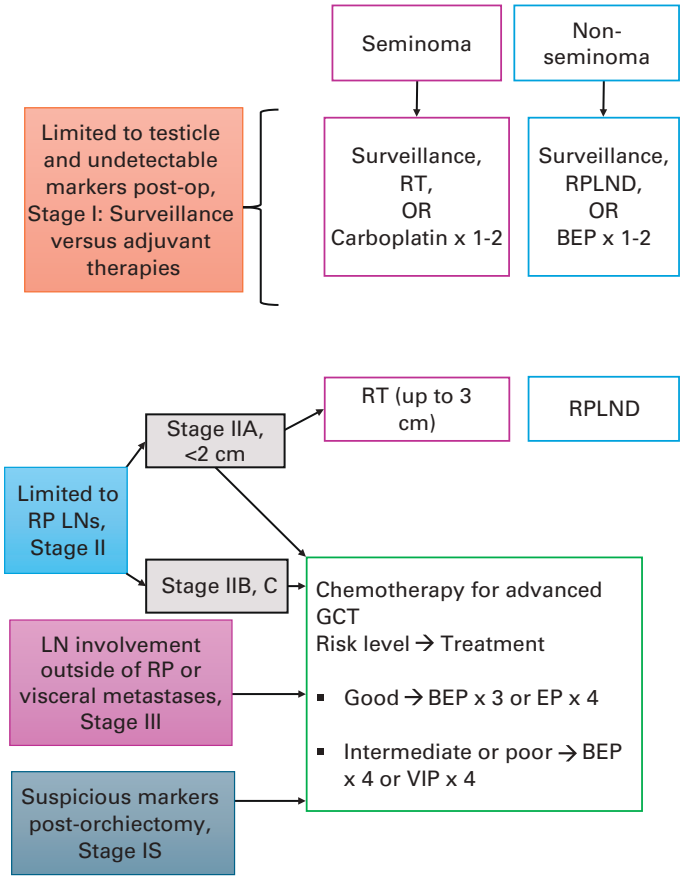
Figure 14-19 Treatment Options for Germ Cell Tumors



Abbreviations: BEP, bleomycin/etoposide/cisplatin; EP, etoposide/cisplatin; GCT, germ cell tumor; LN, lymph node; RP, retroperitoneal; RPLND, retroperitoneal lymph node dissection; RT, radiation therapy; VIP, etoposide/ifosfamide/cisplatin.
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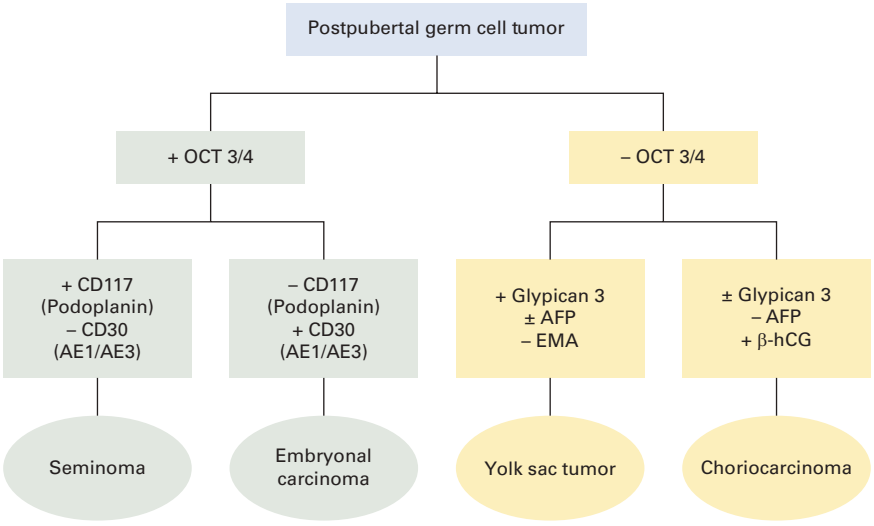
Figure 14-20 Pathologic and Immunohistochemical Classifications of Testicular Germ Cell Tumors



Abbreviations: AFP, α-fetoprotein; EMA, epithelial membrane antigen; hCG, human chorionic gonadotropin.
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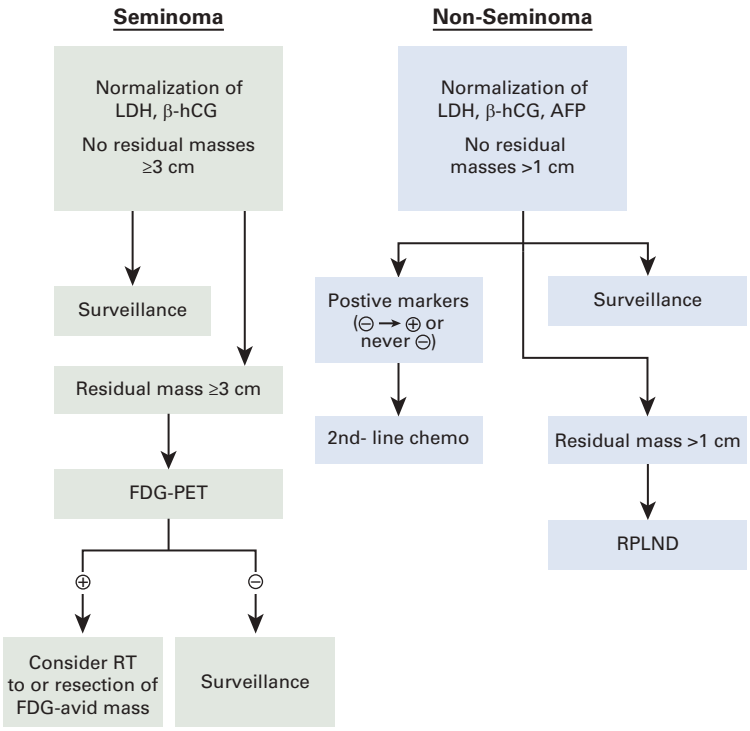
Figure 14-21 Recommended Follow-Up Post-chemotherapy in Advanced Testicular Cancer



Abbreviations: AFP, α-fetoprotein; FDG, fluorodeoxyglucose; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; RPLND, retroperitoneal lymph node dissection; RT, radiation therapy.

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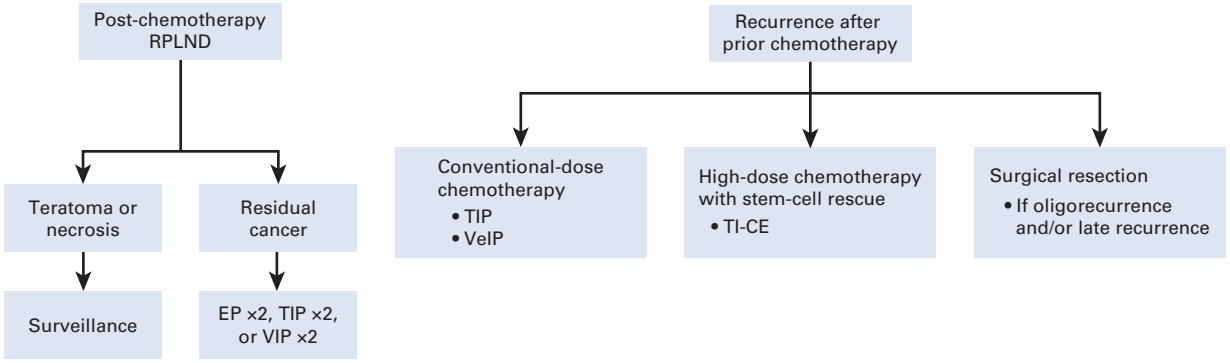
Figure 14-22 Management After Pathology From RPLND



Abbreviations: EP, etoposide/cisplatin; RPLND, retroperitoneal lymph node dissection; TI-CE, paclitaxel/ifosfamide/carboplatin/etoposide; TIP, paclitaxel/ifosfamide/cisplatin; VeIP, vinblastine/ifosfamide/cisplatin; VIP, etoposide/ifosfamide/cisplatin.
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GYNECOLOGIC CANCERS 15

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RECENT UPDATES

Ovarian Cancer

- The combination of avutometinib and defactinib was granted accelerated approval by the FDA on May 5, 2025, for adult patients with *KRAS*-mutated recurrent low-grade serous ovarian cancer who have received prior systemic therapy. The approval was based on the RAMP 201 study, a phase 2 trial of the oral RAF/MEK clamp avutometinib, combined with defactinib, a selective inhibitor of FAK. This combination attempts to block the compensatory upstream reactivation of MEK by RAF, seen with the use of standard MEK inhibitors, as well as inhibit FAK, which is a key adaptive resistance mechanism to the RAS/MAPK pathways.[1-3] RAMP 201 evaluated avutometinib and defactinib versus avutometinib alone and demonstrated the superiority of the combination. The trial then moved into an expansion phase of the combination in both *KRAS*mut and *KRAS* wild-type low-grade ovarian cancer. In total, 115 patients were included: 58 with *KRAS*mut and 57 with *KRAS* wild type. Overall, 22% had prior MEK inhibitor treatment. The overall response rate (ORR) was 31%. Among patients with *KRAS*mut tumors, the ORR was 44%, and among *KRAS* wild-type tumors, it was 17%.[4] The confirmatory trial RAMP 301 is currently ongoing.
- Trastuzumab deruxtecan-nxki (T-DXd) was granted accelerated approval by the FDA on April 5, 2024, based on the results of the DESTINY-PanTumor02,[5] DESTINY-Lung01,[6] and DESTINY-CRC02[7] trials for any solid tumor with *HER2* immunohistochemistry (IHC) of 3+. In this basket trial, 40 patients with recurrent ovarian cancer and 2+ or 3+ IHC per *HER2* gastric scoring were enrolled. The ORR for all 40 patients was 45%. The ORR was 63.6% for centrally confirmed 3+ IHC, and it was 36.8% for centrally confirmed 2+ IHC.[8,9] The NCCN listed T-DXd for *HER2*-positive tumors (IHC 3+ or 2+) as a category A recommendation under Useful in Certain Circumstances on July 15, 2024.
- On July 14, 2025, a new drug application for relacorilant was submitted to the FDA based on results from the phase 3 ROSELLA trial (GOG-3073). ROSELLA evaluated relacorilant in combination with nab-paclitaxel versus nab-paclitaxel monotherapy in patients with advanced, platinum-resistant high-grade epithelial ovarian cancer. Relacorilant is a novel selective glucocorticoid receptor antagonist that restores the sensitivity of cancers to cytotoxic chemotherapy. Presented at ASCO in 2025, the study showed a significant improvement in progression-free survival with a hazard ratio of 0.70 in favor of the experimental arm and a trend toward improved overall survival (OS).

Endometrial Cancer

- Dostarlimab-gxly and carboplatin plus paclitaxel in recurrent/metastatic endometrial cancer: The FDA-approved dostarlimab-gxly in combination with carboplatin and paclitaxel, followed by single-agent dostarlimab-gxly for the treatment of patients with primary advanced or recurrent endometrial cancer on August 1, 2024. This approval was based on the randomized phase 3 RUBY trial,[10] which first led to the approval of this combination in mismatch repair–deficient (dMMR) tumors or tumors with microsatellite instability (MSI) in July 2023. In 2024, the indication was expanded to all tumors (dMMR and MMR proficient) on the basis of demonstrated OS benefit across the study population.[11]
- Full FDA approval for pembrolizumab and carboplatin plus paclitaxel in recurrent/metastatic endometrial cancer: The FDA-approved pembrolizumab in combination with carboplatin and paclitaxel, followed by single-agent pembrolizumab for the treatment of patients with primary advanced or recurrent endometrial cancer on June 17, 2024. This approval was based on results from the NRG-GY018/KEYNOTE-868,[12] and the indication applies to all patients, irrespective of MMR protein status.[13] A separate phase 3 double-blind, randomized, controlled trial evaluated carboplatin and paclitaxel with pembrolizumab versus placebo administered concurrently with chemotherapy and as maintenance for up to 2 years in 816 patients with measurable stage III or IVA, stage IVB, or recurrent endometrial

cancer. Previous adjuvant chemotherapy was permitted if the treatment-free interval was at least 12 months. The median progression-free survival (PFS) was 18.8 months versus 8.5 months with pembrolizumab versus placebo, respectively. In 218 patients with dMMR high MSI (MSI-H) tumors, the median PFS was not reached with pembrolizumab versus 7.6 months with placebo, and the 12-month PFS rate was 74% versus 38% (HR, 0.30).[14]

- Pembrolizumab and carboplatin plus paclitaxel as adjuvant therapy in tumors considered high risk for recurrence: The MK-3475-B21/KEYNOTE-B21/ENGOT-en11/GOG-3053 study (GOG, Gynecologic Oncology Group)[15] was presented and published in 2024. This study evaluated the addition of pembrolizumab to tumors that were International Federation of Gynecology and Obstetrics (FIGO) stage I/II of non-endometrioid histology and that also had a *TP53* alteration or stage III/IVA of any histology. All patients had surgery with curative intent followed by random assignment to paclitaxel and carboplatin with or without pembrolizumab, followed by pembrolizumab maintenance for six cycles (6-week dosing). The primary endpoints were disease-free survival (DFS) and OS in the intent-to-treat population. This study failed to show a benefit for the addition of pembrolizumab, with an HR of 1.02 (95% CI, 0.79-1.32; *P* = .570). Subgroup analysis showed that the HR for DFS was 0.31 (95% CI, 0.14-0.69) in the dMMR population and 1.20 (95% CI, 0.91-1.57) in the MMR-proficient population.[16] Regulatory decisions regarding these analyses are pending at the time of this update.
- T-DXd was granted accelerated approval by the FDA on April 5, 2024, based on the results of the DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 trials for any solid tumor with *HER2* 3+ immunohistochemistry (IHC). In this basket trial, 40 patients with recurrent endometrial cancer and 2+ or 3+ IHC for *HER2* (gastric scoring) were enrolled. The ORR for all 40 patients was 57.5% (95% CI, 9.9-NE). The ORR for centrally confirmed 3+ IHC was 84.6% (95% CI, 9.6-NE), and the ORR for centrally confirmed 2+ IHC was 47.1% (95% CI, 3.0-NE). In addition, the ORR for 1+ IHC (only four patients) was 25%, and the ORR for centrally confirmed *HER2* 0 IHC (five patients) was 60%. The NCCN listed T-DXd for *HER2*-positive tumors (3+ or 2+ IHC) as a category A recommendation under Useful in Certain Circumstances in the July 15, 2024, update.[17]

Cervical Cancer

- The FDA granted fast-track designation to ADRX-0706 for the treatment of advanced cervical cancer in May 2025. ADRX-0706 is a Nectin-4 targeted antibody-drug conjugate that is being evaluated in a phase 1a/b clinical trial for the treatment of advanced solid tumors. Preliminary safety and antitumor activity were reported at ASCO in 2025.
- The FDA approved the Teal Wand on May 9, 2025, as the first at-home vaginal self-collection device for cervical cancer screening.
- Pembrolizumab plus cisplatin and radiation: On January 12, 2024, the FDA-approved pembrolizumab with chemoradiation therapy and as maintenance therapy for patients with FIGO 2014 stage III to IVA cervical cancer based on the results of MK-3475-A18/KEYNOTE-A18/ENGOT-cx11/GOG-3047,[18] a multicenter, randomized, double-blind, placebo-controlled phase 3 trial that evaluated pembrolizumab versus placebo with chemoradiation therapy and also as maintenance therapy in 1,060 patients with cervical cancer who had not previously undergone treatment. Pembrolizumab, 400 mg intravenously once every 6 weeks for maintenance therapy, is continued for 15 cycles after completion of cisplatin plus pembrolizumab therapy plus radiation therapy.
- Neoadjuvant chemotherapy: In 2024, the INTERLACE trial[19] was published and provided new options for planning treatment of locally advanced cervical cancer. The trial included 596 patients with stage III to IVA disease and 462 patients with stage IB2 to IIB node-positive disease.[20] A statistically significant improvement in PFS was demonstrated in the overall population. In an exploratory subgroup analysis, in patients with stage III to IVA disease, the PFS HR estimate was 0.59 (95% CI, 0.43-0.82), and 21% of patients in the pembrolizumab arm experienced PFS compared with 31% of patients in the placebo arm. By contrast, in an exploratory subgroup analysis in the 462 patients with FIGO 2014 stage IB2 to IIB disease, the PFS HR estimate was 0.91 (95% CI, 0.63-1.31). Five-year OS rates were 80% in the induction chemotherapy with chemoradiotherapy group and 72% in the chemoradiotherapy alone group, with an HR of 0·60 (95% CI, 0·40-0·91; *P* = .015).[20-24]
- T-DXd was granted accelerated approval by the FDA on April 5, 2024, based on the results of the DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 trials for any solid tumor with *HER2* 3+ IHC. In this basket trial, 40 patients with recurrent cervical cancer and 2+ or 3+ IHC for *HER2* (gastric scoring) were enrolled. The ORR for all 40 patients was 50%. The ORR in patients with centrally confirmed 3+ IHC was 75%, and the ORR for patients with centrally confirmed 2+ IHC was 40%.[8] The NCCN listed T-DXd for *HER2*-positive tumors (3+ or 2+ IHC) as a category A recommendation under Useful in Certain Circumstances in the July 15, 2024.

▶ Tisotumab vedotin-tftv was approved by the FDA on April 29, 2024, based on the results of innovaTV 301.[25] This randomized phase 3 trial evaluated tisotumab vedotin-tftv versus investigator choice of chemotherapy in patients with cervical cancer that had recurred after 1 to 2 previous lines of systemic therapy and who had demonstrated a statistically and clinically relevant improvement in OS.[26] Tisotumab vedotin-tftv had previously received accelerated approval in September 2021 for the same population.[9,27]

OVERVIEW

Each year, more than 110,000 people are diagnosed with a gynecologic cancer, with a death rate of more than 32,000.[28,29] Although ovarian cancer continues to have a high fatality rate, endometrial cancer now has the highest mortality rate and is the most common gynecologic cancer.[28,30,31] Most gynecologic cancers are treated in the metastatic setting with carboplatin- and paclitaxel-based therapies that have high efficacy but few cures. For many years, significant advances in survival outcomes for gynecologic cancers have been elusive. This trend seems to be changing with the identification of druggable targets, the development of highly active novel therapies, and innovation in clinical trial design toward the evaluation of target-based endpoints. In this chapter, the epidemiology and clinical characteristics of the major gynecologic cancers are reviewed; established approaches to prevention are described; and updates in management, increasingly biomarker directed, are discussed. Areas of ongoing controversy in the management of these diseases are also reviewed.

CERVICAL CANCER

EPIDEMIOLOGY AND PREVENTION

Within the United States, cervical cancer is the third most common gynecologic malignancy, where approximately 13,360 new cases of cervical cancer are diagnosed, with 4,320 deaths.[28] This cancer is more common worldwide, particularly in resource-poor regions, where screening and prevention programs have not been fully established[32] and where cervical cancer is the leading cause of death resulting from cancer in women. The relatively slow growth rate of most cancers of the cervix, along with the causal association with high-risk human papillomavirus (HPV) infection, means that HPV vaccination, HPV testing, and Papanicolaou smear screening offer opportunities for cancer prevention or early detection of preinvasive changes in the cells of the surface of the cervix, and thus can prevent the development of invasive cancer.[33]

Risk factors for the development of cervical cancer include smoking (which increases the risk of persistent cervical dysplastic changes) and immunocompromised status (eg, HIV infection). Use of an intrauterine device (IUD) has been associated with a lower risk of cervical cancer, independent of HPV status.

A majority of cervical cancers are either squamous cell carcinomas or adenocarcinomas, although there are rare subtypes, including clear-cell and neuroendocrine cancers. These rare histologic types confer a worse prognosis, and treatment often requires a specialized multidisciplinary approach.

PATHOGENESIS

HPV infection is the leading cause of cervical cancer, accounting for more than 90% of all cases in the United States annually (Fig. 15-1). Approximately 70% of all cervical cancers are caused by infection with high-risk HPV strain 16 or 18. The development of cervical cancer requires four major steps. Notably, progression from persistent infection to preinvasive disease often takes up to 5 years. Cervical cancer does not affect most people with an HPV infection. Persistent infections and precancer are established in less than 10% of new infections. Invasive cancer arises over many years in a minority of people with precancer.[32]

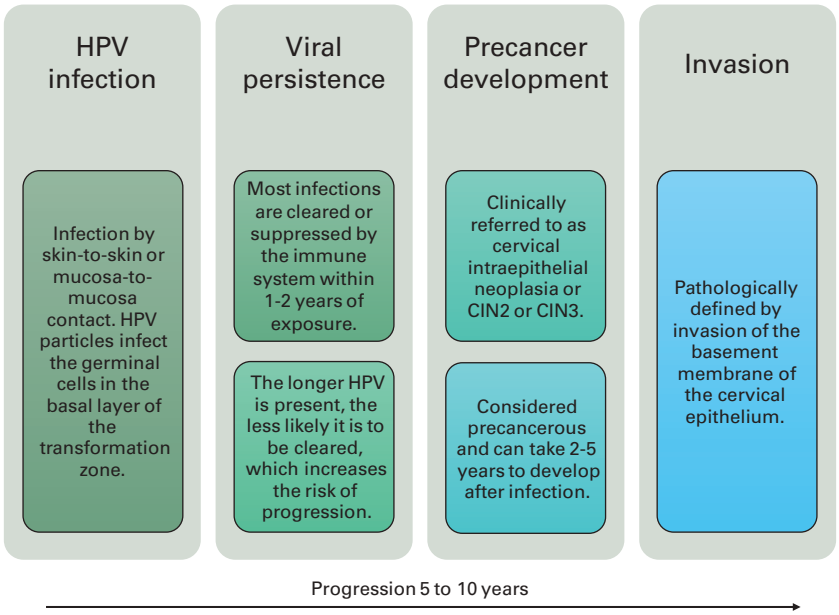
It is widely recommended that people who are eligible for HPV vaccination receive it. The recombinant 9-valent HPV vaccine received expanded approval to include people aged 9 through 45 years (it was initially approved for those aged 26 years or younger) based on the data from a randomized trial showing efficacy against HPV vaccination in people aged 26 years or older[34] and effective prevention of other conditions, including vulvar intraepithelial neoplasia, anal disease, and oral HPV infection. Whether and to what degree the vaccine is effective in people with active HPV infection or cervical dysplasia is not clear, but vaccination is still recommended.

CLINICAL PRESENTATION AND STAGING

Most people are asymptomatic in the early stages of cervical cancer. Symptoms of vaginal bleeding (ie, intermenstrual, postcoital), pelvic pain, and vaginal discharge typically suggest the presence of more advanced disease.

Cervical cancer is staged by the FIGO system, which was updated in October 2018. This version incorporates nodal involvement as stage IIIC disease, with clarification whether the disease was detected radiologically or pathologically.[32] In clinical practice in the United States, advanced imaging with MRI or PET is often used for staging (including nodal assessment), which yields important information for treatment planning.

Figure 15-1 Stepwise Progression From HPV Infection to Cervical Carcinoma



Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.
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CURRENT TREATMENT PRACTICE

Early Invasive Cervical Cancer

A discussion of the treatment of early invasive cervical cancer must start with an understanding of current versus past staging definitions. Currently, FIGO 2018 defines stage IA tumors as microscopic invasive carcinomas with a maximum depth of invasion (DOI) of less than 5 mm. Within stage IA, tumors are subclassified as follows: stage IA1 indicates DOI less than 3 mm, while stage IA2 represents DOI of 3 mm or more but less than 5 mm. Stage IB is now divided into three categories based on tumor size: stage IB1 for DOI greater than 5 mm and less than 2 cm in greatest dimension; stage IB2 for tumors 2 cm or greater but less than 4 cm; and stage IB3 for tumors 4 cm or larger.[26]

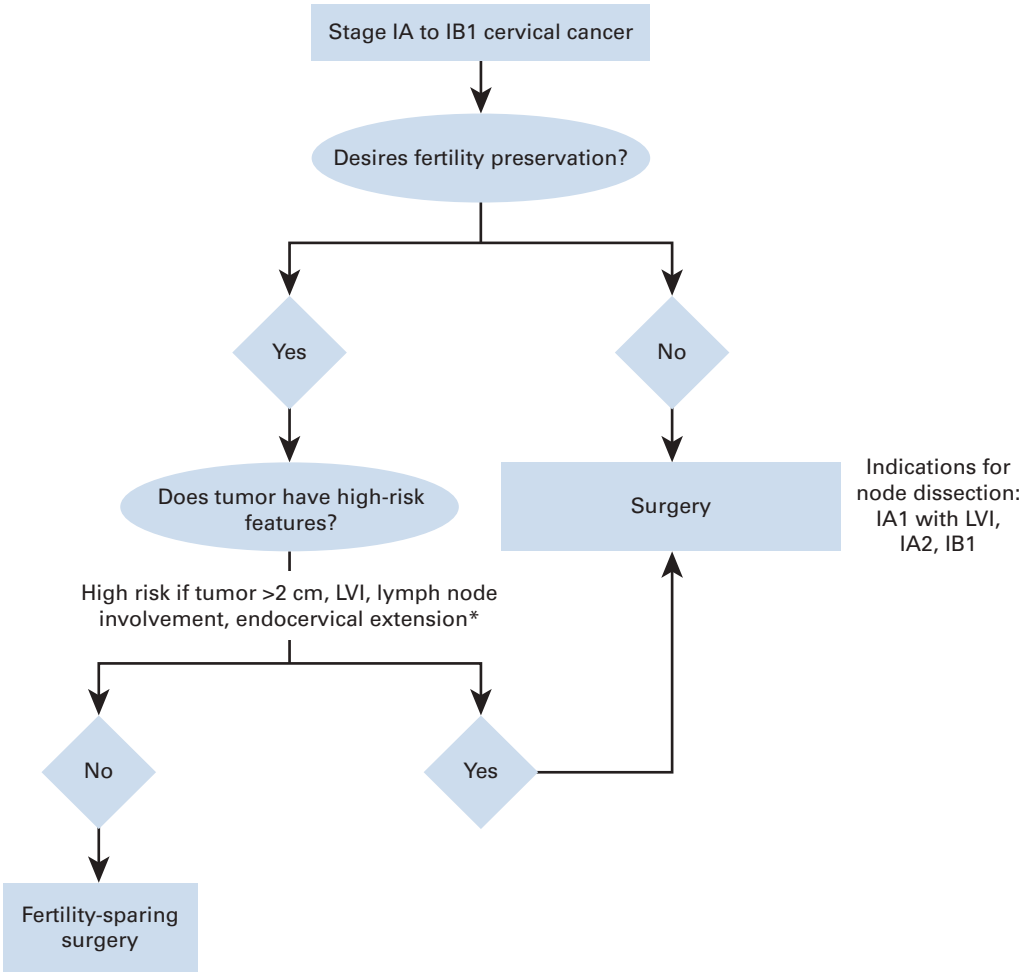
Early invasive cervical cancer is defined as stage IA or IB1 disease (Fig. 15-2). Patients diagnosed with stage IA or IB1 cervical cancer have an excellent prognosis, with 5-year relative survival rates exceeding 90%.

Early invasive cervical cancer is managed surgically. The radicality and approach for surgery are important for survival, quality of life, and preservation of fertility. The need for radical resection was challenged by the Simple Versus Radical Hysterectomy in Women with Low-risk Cervical Cancer (SHAPE) (NCT01658930) clinical trial.[35] In this trial, a subset of patients with stage I cervical cancer was deemed so low risk (based on historical data on parametrial and lymph node involvement) that de-escalation of the surgical approach was warranted. Low-risk tumors were defined as FIGO 2009 stage IA2 or IB1 with lesions less than 2 cm, DOI less than 10 mm, and MRI showing invasion of less than 50% of cervical stromal tissue (required for stage IB1 only). Preoperative imaging also had to show no evidence of lymph node metastasis. Patients were randomly assigned to a radical hysterectomy versus a simple hysterectomy; both procedures included lymph node evaluation. The primary endpoint was pelvic recurrence within 3 years after random assignment.

In all, 700 patients were randomly assigned, the majority of whom had stage IB1 tumors. With a median follow-up of 4.5 years, the incidence of pelvic recurrence was 2.17% in the radical hysterectomy arm and 2.52% in the simple hysterectomy arm, which demonstrated no loss in oncologic control with de-escalation to simple hysterectomy. Importantly, rates of urinary incontinence and urinary retention were lower in the simple hysterectomy group.[36] This study is one of the most important advances in cervical cancer because it de-escalates the radicality of surgery for a substantial number of patients with low-risk, early-stage cervical cancer and makes access to appropriate surgical care more feasible across the global landscape. It is important to emphasize that the selection criteria for this study must be followed accurately to identify patients appropriate for a simple hysterectomy.

For patients with early-stage tumors that do not meet SHAPE criteria but are still deemed appropriate for radical hysterectomy, the surgical approach may impact survival. Results of two important clinical trials indicated that people undergoing surgery for early-stage cervical cancer should undergo an open laparotomy rather than a minimally invasive approach.[37,38] In the Laparoscopic Approach to Cervical Cancer (LACC) trial, more than 600 people with FIGO 2009 stage IA1, IA2, or IB1 cervical cancer were randomly assigned to minimally invasive radical hysterectomy or an open abdominal radical hysterectomy.

Figure 15-2 Approach to Early-Stage Cervical Cancer



Abbreviation: LVI, lymphovascular invasion.
*In previous American Joint Committee on Cancer staging manuals, nodes were not considered; however, the eighth edition specifically defines nodal involvement as stage III disease.
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The 2009 FIGO stages IA1 and 1A2 were very similar to the FIGO 2018 staging, with the exception that FIGO 2009 required the horizontal dimension of the tumor to be 7 mm or less. However, FIGO 2009 stage IB1 included tumors with clinically visible lesions of 4 cm or less in greatest dimension. Therefore, stage IB1 tumors in the LACC trial may have been larger than what is currently classified as IB1 under FIGO 2018 criteria. Compared with open surgery, minimally invasive surgery was associated with lower rates of disease-free survival (DFS) (HR, 3.74; 95% CI, 1.63-8.58) and overall survival (OS; HR, 6.0; 95% CI, 1.77-20.3).[38] There has been much discussion about why a minimally invasive approach led to worse outcomes, and the leading hypothesis centers on tumor containment during the surgery. This hypothesis is being tested in the ongoing ROCC trial,[39] which enrolls patients with FIGO 2018 stage IA2 to IB2 tumors and mandates proper tumor containment and no transcervical uterine manipulators.[40] If these modifications reverse the survival detriment seen in LACC, minimally invasive approaches may become available again for those requiring radical hysterectomy. At this time, open radical hysterectomy is the standard of care. In patients who want to maintain fertility and who have an early-stage and low-risk cervical cancer, radical trachelectomy may be an option.[36,41]

The use of sentinel node dissection at the time of radical hysterectomy has been enthusiastically adopted by most providers. The SENTICOL I study was a prospective multicenter study that evaluated the diagnostic value of sentinel lymph node (SLN) biopsy in patients with early-stage cervical cancer and found no false-negative cases in patients who had bilateral SLN detection.[42] The subsequent SENTINEL II trial confirmed reduced lymphedema, reduced surgical morbidity, and better quality of life in those patients who underwent SLN mapping.[43] However, there is a paucity of data regarding survival and oncologic safety of SLN biopsy. A post hoc analysis of SENTICOL I and II showed no differences between SLN biopsy and full node dissection for

DFS and DSS.[44] In 2025, the PHENIX trial was presented at ASCO. In all, 908 patients with at least one SLN detected were randomized intraoperatively to undergo SLN biopsy alone or full lymphadenectomy, with no differences in the two groups seen with respect to 3-year DFS or 3-year cancer-specific survival rate.

Early Invasive Cervical Cancer With High-Risk Features

Adjuvant treatment may be recommended based on final pathologic findings. For patients with stage IB or IIA disease, there is a higher risk of surgicopathologic findings that may result in the need for adjuvant therapy; there is a high rate of morbidity, and careful patient selection for surgical intervention is indicated in this setting.[26,45] When adjuvant therapy is indicated after radical hysterectomy, the standard of care is pelvic radiotherapy with or without cisplatin-based chemotherapy, depending on surgicopathologic risk factors. GOG-92 randomized patients with a combination of risk factors, including tumor size, presence of lymphovascular invasion, and depth of cervical stromal invasion, to either no adjuvant therapy or adjuvant pelvic radiotherapy.[46] Results demonstrated a significant reduction in the risk of recurrence with radiotherapy (relative risk, 0.53; $P = .008$, one-tailed) with a recurrence rate of 88% versus 79% at 2 years in the radiotherapy versus no adjuvant therapy groups, respectively. With longer follow-up, there was also a significant reduction in the risk of progression or death with adjuvant radiotherapy versus no adjuvant therapy (HR, 0.58; $P = .009$), with fewer recurrences in patients with adenocarcinoma or adenosquamous histology who received radiotherapy.[47]

Patients with high-risk factors, including positive lymph nodes, positive margins, or the presence of parametrial extension, were not eligible for GOG-92. Instead, those patients were randomized to pelvic radiotherapy with or without concurrent and adjuvant bolus cisplatin 70 mg/m^2 and 96-hour infusion of 5-fluorouracil (5FU) 1,000 mg/m^2/day with two every three-week cycles delivered with radiotherapy and two cycles after radiotherapy. In this intergroup study, there was a significant improvement in PFS and OS in the group that received radiotherapy with concurrent and adjuvant chemotherapy, HR 2.01 ($P = .003$) and 1.96 (P=.007), respectively. In this study, it was not possible to determine whether the survival benefit was obtained from the addition of radiosensitizing concurrent cisplatin/5FU or adjuvant cisplatin/5FU or both. However, improved progression-free survival (PFS) and OS were noted ($P = .03$) in patients who received 3 to 4 cycles of chemotherapy. As a result, the randomized phase 3 RTOG-0724 trial was designed to test the value of four cycles of additional systemic carboplatin and paclitaxel to follow concurrent weekly cisplatin and radiotherapy compared with cisplatin and radiotherapy alone. This study enrolled patients with FIGO 2009 stage IA2, IB, or IIA with high-risk factors after surgery. Here again, it is important to convert this to the current FIGO 2018 staging. Stage II cervical cancer staging did not change dramatically between 2009 and 2018 and includes tumors that extend to the upper vagina without (IIA) and with (IIB) parametrial involvement. Stage IIIA also did not change between 2009 and 2018 and includes tumors that invade the lower third of the vagina; stage IIIB has extension of the tumor to the pelvic side wall. FIGO 2018 stage IIIC is a new stage category and includes involvement of pelvic lymph nodes (stage IIIC1) and para-aortic lymph nodes (stage IIIC2). These two categories may be annotated with r (imaging) and p (pathology) to designate how the lymph node involvement is determined.[26] If the patients in the RTOG-0724 trial were converted to FIGO 2018 staging, 50% of them would be upstaged largely on the basis of the new IIIC1 and IIIC2 stages. There was no benefit to the addition of adjuvant systemic paclitaxel and carboplatin to the treatment of patients with high-risk features after radical hysterectomy. The HR for PFS was 1.05 (90% CI, 0.65-1.68), and the HR for OS was 0.91 (90% CI, 0.49-1.69).[45]

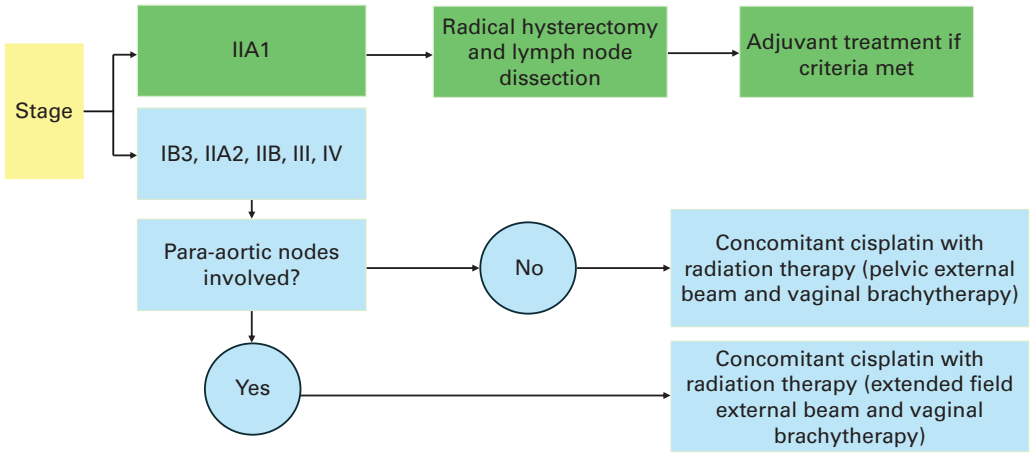
Early Invasive Cervical Cancer With Intermediate-Risk Features

The results of GOG-263 were very recently published and show the use of adjuvant therapy in intermediate-risk early-stage cervical cancer. GOG-263 was a randomized phase 3 trial of adjuvant radiation versus chemoradiation in intermediate-risk, early-stage cervical cancer following radical hysterectomy.[48] Intermediate-risk factors included combinations of lymphovascular space invasion, stromal invasion, and tumor size. Patients received conformal radiation therapy (RT) or intensity modulated radiation therapy (IMRT). In the chemoradiation (CRT) arm, six cycles of weekly cisplatin at a dose of 40 mg/m^2 were given. The primary endpoint of the trial was recurrence-free survival (RFS). The 3-year RFS was 88.5% in the CRT arm and 85.4% in the RT arm, with an HR of 0.698 (95% CI, 0.408-1.192; $P = .09$). Notably, CRT increased grade 3 and 4 adverse events with a transient decline in the quality of life.

Locally Advanced Cervical Cancer

Locally advanced cervical cancer is defined as FIGO 2018 stage IB3 or IIA2 to IVA disease (Fig. 15-3). (It should be noted that FIGO 2018 stage IIA1 may be a candidate for definitive radical surgery.) If the need for definitive chemoradiation is anticipated at diagnosis, surgery should not be performed, and chemoradiation (now with the addition of immunotherapy) should be pursued with curative intent. In locally advanced disease, concurrent chemoradiation therapy is preferred based on a series of studies that demonstrated improved outcomes with the addition of radiosensitizing chemotherapy.[49] A typical treatment protocol includes weekly administration of cisplatin 40 mg/m^2 per week during the course of external radiation therapy and continuing through brachytherapy.

Figure 15-3 Approach to Locally Advanced Cervical Cancer



People with stage IIA1 disease are candidates for primary surgery.
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For women with more advanced disease, imaging (typically with PET/CT scanning) is required to evaluate nodal involvement. The presence of para-aortic nodal involvement (either suspected or pathologically confirmed) warrants the use of extended-field external beam radiation therapy (EBRT).[20,50-53] MR imaging may help determine the extent of local disease, particularly parametrial or vaginal extension, which may help determine subsequent brachytherapy.[54] Radiotherapy is the cornerstone of treatment for women with locally advanced cervical cancer. Treatment consists of a combination of EBRT and brachytherapy with concurrent cisplatin-based chemotherapy. Based on several phase III randomized studies comparing 3D conformal radiotherapy (3DCRT) versus IMRT in both the adjuvant and definitive setting, the preference is to treat with IMRT if resources are available.[55-57] Collectively, these studies have demonstrated a reduction in acute and late toxicities, particularly genitourinary and gastrointestinal toxicities. In addition, image-guided brachytherapy incorporating MR imaging for treatment planning allows for improved identification of residual disease and response after initial EBRT compared to CT imaging.[58]

After many decades of no change in the standard of care for locoregionally advanced disease, several randomized trials have resulted in a modified standard that uses cisplatin-based radiotherapy with improvements in OS.

The first hypothesis was whether systemic carboplatin and paclitaxel would improve OS in addition to standard cisplatin-based radiation in locoregionally advanced cervical cancer. The OUTBACK GOG-274[59] trial evaluated the addition of four cycles of paclitaxel and carboplatin to follow standard cisplatin-based radiation in FIGO 2009 stage IB1 disease with positive lymph nodes (FIGO 2018 stage IIIC1 or stage IB2, II, IIIB, or IVA disease). Similar to the RTOG-0724 trial, the addition of systemic chemotherapy after definitive cisplatin-based radiotherapy did not improve OS; the HR was 0.90 (95% CI, 0.70-1.17; $P = .81$). Of interest is the fact that 27% of the patients randomly assigned to the experimental arm received either no or only one cycle of planned adjuvant therapy.[50] It is noteworthy that the same trend was seen in the RTOG-0724 trial, in which 26% of patients received no adjuvant chemotherapy in the experimental arm. This suggested that new strategies were needed.

The INTERLACE trial also evaluated the addition of systemic paclitaxel and carboplatin given as neoadjuvant therapy *before* planned cisplatin-based radiation. This study enrolled patients with FIGO 2009 stage IB1 disease with nodal involvement (FIGO 2018 stage IIIC1) or stage IB2, IIA, IIB, IIIB, or IVA disease. Patients were randomly assigned to cisplatin-based radiotherapy alone versus neoadjuvant chemotherapy (NACT) followed by cisplatin-based radiotherapy. In this study, the primary endpoints were both PFS and OS. Use of NACT led to an improvement in PFS with an HR of 0.65 (95% CI, 0.46-0.91; $P = .013$) as well as an improvement in OS with an HR of 0.60 (95% CI, 0.40-0.91; $P = .015$). It is important to note that the majority of patients enrolled in this study (50%) were FIGO 2018 stage I or II, and 40% were stage IIIC (node positive).[20]

The second hypothesis tested whether the addition of an immune checkpoint inhibitor (ICI) would improve outcomes in locoregionally advanced cervical cancer. This hypothesis is derived from the HPV-driven nature of cervical cancer and clinical evidence in the advanced and metastatic setting of efficacy. The first study evaluated the addition of the PD-L1 inhibitor durvalumab to cisplatin-based radiotherapy to follow as maintenance every 4 weeks for up to 24 cycles versus standard cisplatin-based radiotherapy. The CALLA study[60] had a primary endpoint of PFS, and it enrolled patients with FIGO 2009 stage IB2 to IIB with lymph node positivity or any stage III or higher tumor. The addition of durvalumab failed to improve PFS; the HR was 0.84 (95% CI, 0.65-1.08; $P = .17$). However, the results of the ENGOT-cx11/GOG-3047/KEYNOTE-A18[18] trial confirmed the benefit of adding an ICI (pembrolizumab) to standard cisplatin-based radiotherapy and for 15 cycles of maintenance (6-week dosing intervals). Enrolled patients had FIGO 2014 stage IB2 to IIB with node-positive tumors or any stage III to IVA disease. The HR for PFS was

0.70 (95% CI, 0.55-0.89; *P* = .0020), and the HR for OS was 0.67 (95% CI, 0.50-0.90; *P* = .0040).[51,52] In this study, stage IB2 to IIB (node positive) versus stage III to IVA was a stratification factor. The margin of benefit in these subgroups led the FDA to approve the addition of pembrolizumab to cisplatin-based radiotherapy and as maintenance for 15 cycles only in FIGO 2014 stage III to IV disease. This includes patients with disease that extends to the pelvic sidewall (IIIB) and/or extends to the lower third of the vagina (IIIA), whereas stage IVA involves spread to distant organs.[53] This would not include FIGO 2018 stage IIIC1 or IIIC2 unless those tumors had extended to the side wall or involved distal vaginal tissue.[52]

Therefore, given current data and regulatory approvals, pembrolizumab should be added to cisplatin and radiation and be given as maintenance for patients with FIGO 2014 stage IIIA, IIIB, and IVA, and could be considered for patients with IIIC1 or IIIC2 disease if the primary tumor had extended to the sidewall or involved lower vaginal tissue. Otherwise, patients who have FIGO 2018 stage IB3, IIA2, IIB, IIIC1, or IIIC2 should be considered for the INTERLACE regimen.

There are currently no data to support combining the INTERLACE regimen with the A18 regimen in high-risk LACC. The NCI is prospectively studying the combination in the GY-037 trial (NCT07061977).

Metastatic or Recurrent Cervical Cancer

The prognosis is poor for patients with de novo metastatic (stage IVB) cervical cancer and for those who have disease recurrence after primary treatment (Table 15-1). For patients who have an isolated pelvic recurrence within a previously irradiated field, an en bloc resection that requires bowel and/or bladder resection (ie, pelvic exenteration) can be considered with potentially curative intent, although careful patient selection is key, and morbidity can be substantial. All other patients with advanced or recurrent cervical cancer should be treated with systemic therapy. The results of GOG-240 demonstrated that compared with chemotherapy alone, the addition of bevacizumab to chemotherapy increased OS by nearly 4 months.[61,62] For patients who have tumors that express PD-L1, pembrolizumab can be incorporated with combination platinum-based chemotherapy with or without bevacizumab based on the results of KEYNOTE-826, which showed that the addition of pembrolizumab in this population improved both PFS and OS. The assessment of PD-L1 is determined by the combined positive score, which represents the number of PD-L1-stained tumor cells, lymphocytes, or macrophages relative to all viable tumor cells. A combined positive score of 1 or higher is considered positive. In the KEYNOTE-826 trial, the PD-L1 IHC 22C3 pharmDx quantitative assay (Agilent Technologies, Santa Clara, CA, USA) was used. It is reasonable to substitute carboplatin for cisplatin because of its more tolerable toxicity profile, particularly in patients who were previously treated with cisplatin and RT.[63] A subsequent subset analysis of Keynote 826 verified the role of bevacizumab in achieving the best OS in this population. Patients who received bevacizumab and pembrolizumab experienced the best median OS (37.6 months for all comers).[64] Based on this subset analysis, all patients eligible for bevacizumab should receive this as part of this regimen.

Table 15-1 Clinical Features and Postoperative Surgical and Pathological Risk Factors to Assess the Risk of Recurrence in Cervical Cancer

Intermediate Risk (Sedlis Criteria)	High Risk (Peters Criteria)
LVSI and deep stromal invasion (outer third)	Positive surgical margins
LVSI and middle stromal invasion (one-third) and tumor size ≥2 cm	Detection of pathologically confirmed lymph node metastases
LVSI and superficial stromal invasion (inner third) and tumor size ≥5 cm	Extension into the parametrial tissue
No LVSI but deep or middle stromal invasion and tumor size ≥4 cm	

Abbreviation: LVSI, lymph-vascular space invasion.
Adapted from Fleischmann M, Chatzikonstantinou G, Fokas E, et al. Molecular markers to predict prognosis and treatment response in uterine cervical cancer. *Cancers*. 2021;13(22):5748. doi:10.3390/cancers13225748
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The BEATcc study confirmed the results of Keynote 826 in a biomarker-agnostic population. In this randomized, open-label phase 3 trial, patients with advanced or recurrent cervical cancer (first-line setting) were enrolled and randomized to receive taxane, platinum, bevacizumab, and atezolizumab versus taxane, platinum, and bevacizumab alone. Patients were not required to have a PD-L1-positive tumor, and all patients were required to receive bevacizumab. The study met its primary endpoints of PFS and OS with a median OS of 32·1 months (95% CI, 25.3-36.8) versus 22·8 months (20.3-28.0), respectively (HR, 0.68; 95% CI 0.52-0.88; *P* = .0046). Data regarding PD-L1 status were not reported.[65]

After patients have progressed with combination chemotherapy, pembrolizumab is approved by the FDA for those who have not already received immune checkpoint blockade and who have PD-L1-positive disease or are found to have MSI-H/dMMR tumors.[66] The approval for treatment of PD-L1-positive cervical cancer in this setting was based on the results of the

KEYNOTE-158 phase 1 trial, in which more than 90 people were enrolled and were treated with pembrolizumab for up to 2 years.[67] The overall response rate (ORR) was 12%, and in women with PD-L1-positive tumors, it was 14.6%. The PFS rate at 6 months was 25%, and the median OS was 9.4 months. Similar to KEYNOTE-826, the KEYNOTE-158 trial used the PD-L1 IHC 22C3 pharmDx quantitative assay.

In 2021, the FDA granted accelerated approval of tisotumab vedotin-tftv, a tissue factor–directed antibody and microtubule inhibitor–drug conjugate, for patients with previously treated recurrent or metastatic cervical cancer. This approval was based on the innovaTV 204/GOG-3023/ENGOT-cx6 clinical trial, which demonstrated an ORR of 24% and a median DOR of 8.3 months (95% CI, 4.2-not reached).[68] Results of the confirmatory innovaTV 301/ENGOT-cx12/GOG-3057 trial, which randomly assigned 502 patients to receive tisotumab vedotin-tftv versus the physician's choice of chemotherapy, showed a statistically significant and clinically meaningful improvement in OS favoring tisotumab vedotin-tftv, with 48.7% of patients in the treatment arm alive at 12 months versus 35.3% in the physician's choice of chemotherapy arm (HR, 0.70; 95% CI, 0.54-0.89).[69] This study led to full approval of tisotumab vedotin-tftv on April 24, 2024. EMA approval for tisotumab vedotin-tftv is pending at the time of this review. T-DXd is also an option in this patient population.

Approach to Rare Cervical Cancers

Clear-cell and neuroendocrine tumors (including large- and small-cell carcinomas) account for 4% and up to 2% of all cervical cancers in the United States, respectively.[70] Thus, there are no large prospective trials to inform treatment. In clinical practice, treatment that consists of platinum-based therapy is extrapolated from the treatment of squamous cell cancer, adenocarcinoma, and small-cell lung cancer. These patients are typically younger, are more likely to have metastatic disease, and have poorer survival outcomes at all stages. It is noteworthy to mention the Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) SWOG S1609 effort to study these rare tumors. Clear-cell cervical cancer was included in cohort 42, and five patients were treated with ipilimumab and nivolumab. There were zero responses, and the median PFS was dismal at one disease assessment cycle, which emphasizes the need for continued focus on these rare tumors.[71]

Reports from centers with extensive experience with neuroendocrine tumors of the cervix help guide therapies for this rare group of patients.[72]

SURVIVORSHIP

The prognosis for people treated for cervical cancer is good for those diagnosed with localized disease; 5-year survival estimates are 66% for all stages and 91% for localized disease.[73] Among those with regional nodal involvement, however, more than 40% will die within 5 years.[73] Regardless of their risk of recurrence, all patients who complete curative-intent treatment should be observed for recurrent disease with serial pelvic examinations every 3 to 6 months for 5 years and then annually.[73] Guidelines support imaging if it is clinically indicated. The general tenets of survivorship care in the Institute of Medicine report[74] are relevant for people with gynecologic cancers. Specific issues related to symptoms and follow-up recommendations depend on the primary treatment modality. Women treated with chemoradiation therapy often develop premature genitourinary symptoms of menopause. Hormone replacement therapy may be offered in an age-appropriate context.[74] The choice of agent must take into account whether the uterus is present, in which case combined hormone therapy should be prescribed. Vaginal dilators are often offered as a tool to prevent and treat vaginal tightening, adhesions, and shortening.

Patients undergoing a pelvic and/or para-aortic lymph node dissection are also at risk for lower-extremity lymphedema, even years after surgery. Education and prompt referral for decongestive therapy are important aspects of management.[74]

SPECIAL POPULATIONS

Patients With Renal Insufficiency

All patients with renal insufficiency require a workup to rule out correctable causes of renal dysfunction, including ureteral obstruction resulting from cervical cancer. This can often be improved by placing a ureteral stent; occasionally, nephrostomy may be required. It is important for obstruction to be addressed before treatment begins to allow for cisplatin therapy. For people with chronic renal insufficiency, consultation with a nephrologist is helpful to determine appropriate therapy and to follow-up with the patient. If cisplatin cannot be administered, the use of an alternative agent such as carboplatin can be considered. Other agents, such as gemcitabine or fluorouracil, could also be considered on the basis of published guidelines.

KEY POINTS

- Cervical cancer is a sexually transmitted disease associated with a chronic infection of oncogenic types of HPV. HPV strains 16 and 18 account for 70% of cervical cancers. HPV vaccination represents an opportunity to reduce the worldwide occurrence of cervical cancer. The 9-valent vaccine available in the United States can be administered to people aged 9 to 45 years.
- Although vaccination against HPV is available, cervical cancer screening remains an important part of health maintenance.

- The approach to invasive cervical cancer depends on whether a patient presents with early-stage, locally advanced, or metastatic disease. The FIGO 2018 staging of cervical cancer is defined by tumor characteristics and nodal involvement.
- For people with early-stage cervical cancer, treatment is primarily surgical. New data define tumors at such low risk that radical surgery may be de-escalated. For those who require a radical hysterectomy, the open approach is the current standard of care. Sentinel node dissection seems to be oncologically safe in this population, but more prospective data are needed.
- The indications for adjuvant treatment after radical surgery using RT with or without concomitant chemotherapy depend on final pathologic findings, including tumor grade, presence of lymphovascular invasion, and depth of stromal invasion, as well as whether there are positive surgical margins and parametrial or nodal involvement. Use of adjuvant systemic chemotherapy is not supported in this setting.
- For most people with locally advanced cervical cancer, cisplatin and RT are administered as curative treatment without surgery.
- For patients with FIGO 2018 stages sIB3 to IIB, IIIC1, or IIIC2 without side wall involvement or distal vaginal involvement, NACT should be considered with an OS advantage from the INTERLACE trial.
- For patients with FIGO 2018 stages IIIA, IIIB, IIIC1, or IIIC2 with side wall or distal vaginal involvement or IVA, the addition of pembrolizumab to chemotherapy and radiation therapy can now be considered the standard of care, with the advantage of both PFS and OS. For women with de novo metastatic (stage IVB) or recurrent cervical cancer, first-line treatment consists of platinum-based doublet chemotherapy and bevacizumab, with the addition of pembrolizumab in patients whose tumors express PD-L1.
- The first-line recurrent/metastatic regimen should include paclitaxel, platinum, pembrolizumab, and bevacizumab for patients whose tumor is PD-L1 IHC positive by CPS score or atezolizumab, regardless of PD-L1 status. Strong consideration should be given to including bevacizumab in all settings if not contraindicated for medical reasons.
- Patients whose disease progresses after first-line therapy and who have not previously received pembrolizumab may receive pembrolizumab, provided that their tumor is positive for PD-L1 expression or they are found to have an MSI-H tumor.
- Tisotumab vedotin-tftv or T-DXd (for biomarker-positive tumors) can be considered in patients who have recurrent disease after previous chemotherapy with or without immunotherapy.
- Patients with advanced or recurrent disease should have their tumors tested for *HER2* IHC via gastric scoring to assess eligibility to receive T-DXd.

ENDOMETRIAL CANCER

EPIDEMIOLOGY AND PREVENTION

Endometrial cancer is the fourth most common cancer in the United States.[75,76] At the time of this review, it is one of the only solid tumors that is increasing in incidence and mortality, mainly at the expense of Black patients. Among Black patients, the mortality rate is approximately 50% higher, and Black patients often present with advanced-stage or more aggressive histology, such as serous histology or carcinosarcoma.[75] The cause of this mortality discrepancy is largely unknown. Data from the American Cancer Society show that the incidence of endometrial cancer has increased by 1% per year in white patients and 2% to 3% per year in all other racial and ethnic groups. In addition, the death rate has increased by 1.7% per year since the mid-2000s.[75,76] In 2025, there will be 69,120 new cases of endometrial cancer and approximately 13,860 deaths.[28,76] It is notable that the number of deaths as a result of endometrial cancer now eclipses that from ovarian cancer.

Most people diagnosed with endometrial cancer (75%) are postmenopausal, the average age at diagnosis is 60 years, and approximately 70% of patients present with early-stage uterine-confined disease. There are some known genetic and environmental risk factors for endometrial cancer. Lynch syndrome results from pathogenic germline variants in *MMR* genes *MLH1, MSH2, MSH6*, and *PMS2*. Lynch syndrome can confer an increased risk of developing endometrial cancer of up to 60%.[77] Thus, all patients with newly diagnosed endometrial cancer should undergo MMR IHC testing with reflexive germline genetic testing when indicated; if there is a family history and MMR tests are normal, patients should have germline genetic testing.[75] High body mass index is a risk factor for the development of endometrial cancer. Although women receiving tamoxifen face a three- to seven-fold greater risk of endometrial cancer, its benefits for the treatment and prevention of breast cancer outweigh this risk in appropriate patients. Routine pelvic (or transvaginal) ultrasonographic surveillance in otherwise asymptomatic women who receive tamoxifen is not recommended. Prevention strategies have focused on the importance of a healthy lifestyle and a reduction in obesity as an independent risk factor. Interception strategies emphasize early recognition and appropriate workup via endometrial biopsy of abnormal uterine bleeding, especially among Black patients. Movements such as Spot Her aim to educate women as broadly as possible regarding the early symptoms of endometrial cancer, which will hopefully promote more timely diagnosis and treatment among vulnerable populations.[78]

Histologic subtypes of endometrial cancer include endometrioid adenocarcinoma, serous endometrial cancer, carcinosarcoma, clear-cell carcinoma, adenosquamous carcinomas, and other rare types such as neuroendocrine cancers and cancers with

small-cell histology. The staging and treatment of these tumors use an approach similar to that used for more typical endometrial cancers. IHC testing for MMR should be performed for all newly diagnosed patients. Patients whose tumors show loss of MMR protein expression should be referred for genetic screening for Lynch syndrome; there is also an elevated risk of germline *BRCA1* mutations in patients with serous endometrial cancers. MMR deficiency is also predictive of the potential benefit related to treatment with ICIs as monotherapy or in combination in the setting of recurrence.

There has been a transition toward the use of molecular features to classify endometrial cancer (Table 15-2). An integrated genomic analysis of endometrial cancer was conducted as part of The Cancer Genome Atlas (TCGA); based on the mutation frequencies, tumors could be stratified into the following four groups:

1. *POLE*-ultramutated
2. Tumors with MSI (hypermutated)
3. Low copy number (endometrioid)
4. High copy number (serous-like)[79]

Table 15-2 Molecular Classification for Endometrial Cancer

TransPORTEC Classification (TCGA Classification)	Prognosis	Treatment Approach	Other Molecular Features
POLE mut (ultramutated)	>90%; 5 years, OS	Candidate for de-escalation of therapy	
MMRd (hypermutated)	Very good	Checkpoint inhibitor therapy	Can occur as a germline or somatic mutation or through methylation of the *MLH1* gene promoter in the tumor
NSMP (copy number low)	Very good for most patients, but a subset with worse outcomes	May have functional hormonal receptors and can consider hormonal therapy	More likely to have ER/PR. Most common associated mutations: *PTEN*, *ARID 1A*, *PIK3CA*, *CTNNB1*, *PIK3R1*, *KRAS*
*P53*abn (copy number high)	Poor <50%; 5 years, OS	Recommend an aggressive approach with chemotherapy	Can look for *HER2* overexpression/ amplification, HRD

Abbreviations: abn, abnormal; ER, estrogen receptor; HRD, homologous recombination–deficient; MMRd, mismatch repair–deficient; mut, mutated; NSMP, no specific molecular profile; OS, overall survival; PR, progesterone receptor; TCGA, The Cancer Genome Atlas.
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The FDA approval of trastuzumab deruxtecan-wxki for *HER2* 3+ IHC and NCCN listing for 2+ and 3+ IHC has also prompted more widespread testing of *HER2* IHC either at diagnosis for advanced-stage tumors or at the time of recurrence, although these recommendations may change with emerging clinical trial data.

PATHOGENESIS

Historically, endometrial cancers are classified on the basis of features that define the underlying genetics as proposed by TCGA.

These subgroups are associated with PFS; patients with *POLE*-type tumors have the best prognosis, and those with high copy number (serous-like) tumors have the worst prognosis. Subsequent work has refined these categories into subtypes that parallel the TCGA subtypes; a combination of IHC and next-generation sequencing (NGS) clinical tests can be performed rapidly to determine these molecular subtypes according to the following categories: *POLE*-mutated, mismatch repair–deficient (dMMR), no specific molecular profile, and abnormal expression of *p53*.[80,81] Because additional IHC markers (such as *HER2*) are validated as predictive biomarkers, these subgroups may be defined further for both prognosis and treatment planning, as will be described below. The World Health Organization (WHO) and the Society of Gynecologic Oncology (SGO) have recommended incorporating molecular classification into pathology reports on endometrial cancers.[82,83]

CLINICAL PRESENTATION AND STAGING

The most common symptom associated with endometrial cancer is postmenopausal bleeding or blood-tinged discharge from the vagina. Therefore, all postmenopausal women with abnormal uterine bleeding or discharge require evaluation by their

gynecologist along with endometrial sampling. Some endometrial cancers may or may not present with bleeding; for these patients, the presence of nonspecific symptoms (eg, abdominal pain, bloating, sexual dysfunction, changes in bowel or bladder habits) often heralds more advanced disease.

The FIGO staging system for endometrial cancer was revised in 2023, and greater emphasis was placed on histology, tumor grade, and the presence of lymphovascular invasion.[84] The TCGA molecular categorization was also incorporated. Endometrial cancer is surgically staged, and all patients should be evaluated by and receive surgery from a gynecologic oncologist. The standard surgical staging procedure for endometrial cancer includes hysterectomy, bilateral salpingo-oophorectomy, pelvic washings (possibly), and examination of the entire abdominal cavity. Nodal evaluation may not be necessary for all patients, but many gynecologic oncologists recommend nodal staging for patients with newly diagnosed endometrial cancer using SLN identification and biopsy. Patients with advanced unresectable disease may be candidates for chemotherapy before surgery.

PRESENTING CASE STUDY

A 64-year-old woman presents with 6 months of vaginal bleeding and 2 months of vague abdominal discomfort. Pelvic ultrasound shows a thickened endometrial stripe and small-volume ascites. Endometrial biopsy confirms endometrial serous carcinoma. Chest CT is unremarkable, and abdominal/pelvic CT indicates small-volume ascites and pelvic adenopathy. The patient undergoes surgery and is found to have endometrial serous cancer with 40% myometrial invasion, enlarged pelvic lymph nodes with metastases to both ovaries, and two out of three positive pelvic nodes. Based on the 2023 endometrial cancer staging system, the cancer is stage IIICii. Further testing reveals mismatch-repair proficiency (MMRp), *HER2* positivity (2+ on IHC), and a *p53* mutation.

She begins adjuvant chemotherapy with carboplatin and paclitaxel. During the second cycle, NGS returns as MMRp, *TP53* mutated, *CCNE1* amplified, and *HER2* positive (2+ on IHC) with no *ERBB2* amplification. Because the patient does not qualify for the addition of trastuzumab to her chemotherapy regimen due to the lack of ERBB2 amplification, and recent data demonstrate no benefit to adding ICIs to nonmeasurable adjuvant therapy, she continues with six cycles of paclitaxel and carboplatin.

Ten months later, she presents with shortness of breath and is found to have new lung and liver metastases.

Based on the patient's clinical history, endometrial cancer histology, and known specific biomarkers, how would you proceed with further workup and treatment?

Endometrial serous carcinoma is an aggressive endometrial cancer that is typically MMRp, with a low tumor mutational burden and high copy number changes. This patient's cancer is also *HER2* positive (2+ on IHC [immunohistochemistry]) and meets gastric cancer criteria. Higher levels of *HER2* expression are associated with this histologic subtype. If the cancer was 3+ on IHC, she would be eligible to receive Trastuzumab deruxtecan-nxki (T-DXd) per the FDA label. *HER2* positivity of 2+ and 3+ is both listed on the National Comprehensive Cancer Network uterine cancer guidelines as category 2A T-DXd in the second-line metastatic or subsequent-line setting.

Another option would be a therapy that includes ICIs. KEYNOTE-775, a phase 3, randomized trial, enrolled patients with recurrent endometrial cancer of any histology to either chemotherapy (paclitaxel or doxorubicin) or pembrolizumab and lenvatinib (20 mg/day). Median PFS and OS were both significantly longer with lenvatinib and pembrolizumab compared to chemotherapy; this regimen is FDA approved for advanced MMRp endometrial cancer. Toxicities with this regimen are quite significant, with nearly 66% of patients needing to have the dose of lenvatinib reduced and approximately 33% of patients needing to discontinue treatment.

Other possible treatments include returning to carboplatin or a carboplatin doublet, such as carboplatin and paclitaxel. FDA approvals have been granted for the addition of either dostarlimab or pembrolizumab combined with carboplatin and paclitaxel, regardless of MMR status.

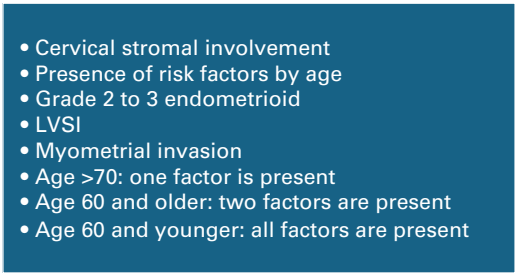
Clinical trials should be considered for novel ADCs. Endometrial serous cancers on NGS may have cyclin E1 amplification, and several trials targeting CCNE1 amplification, such as Wee1 and CDK2 inhibitors, are ongoing. Endometrial serous tumors also express *FOLR1*, and several camptothecin payload ADCs are enrolling endometrial cohorts.

CURRENT TREATMENT PRACTICE

Adjuvant Treatment

For patients who undergo surgery with curative intent, there is no single approach to adjuvant therapy, and the approach should consider the presence or absence of high-risk pathologic factors (Fig. 15-4). Patients without these features have low-risk disease that does not require additional treatment. However, the approach in patients with stage I, high-intermediate risk, or high-risk disease continues to evolve, and an individualized approach is often recommended.

Figure 15-4 High- to Intermediate-Risk Factors in Early-Stage Endometrial Cancer



Abbreviation: LVSI, lymphovascular space invasion.
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The role of radiotherapy in the adjuvant setting for stage I/II endometrial cancer was investigated in multiple randomized studies, which examined the role of radiotherapy for intermediate-risk endometrial adenocarcinoma. GOG-99 was a prospective study that randomized women with "intermediate-risk" endometrioid adenocarcinoma after surgical staging (hysterectomy, bilateral salpingo-oophorectomy, and selective bilateral pelvic and para-aortic lymph node dissection) to either pelvic radiotherapy or observation. PORTEC-1, which was a multinational study led by Dutch investigators, had similar randomization post-surgery: observation versus pelvic radiotherapy. Important differences in the studies include the absence of a requirement for nodal evaluation in PORTEC and exclusion of the highest risk stage I patients from randomization (FIGO Stage IC grade 3[1988]1988]).[85,86] The two studies reached similar conclusions: pelvic radiotherapy reduced locoregional recurrences without any differences in OS. An important finding in both studies was that approximately two-thirds of the locoregional recurrences in patients who were randomized to observation were located in the upper vagina. As a result of this finding, PORTEC-2 investigated whether vaginal cuff brachytherapy could be sufficient adjuvant therapy for women with high-intermediate risk endometrioid adenocarcinoma (which included women with stage IA grade 3 disease, stage IB grade 3 without LVSI or stage IB, grade 1 or 2 with age ≥60 years and/or lymphovascular invasion, stage IB, grade 3 without lymphovascular invasion or stage II grade 1[2009]).[87,88] Patients were randomized to pelvic radiotherapy or vaginal cuff brachytherapy. A 10-year isolated pelvic recurrence was 2.5% versus 0.5% (P = .10) for patients who received vaginal brachytherapy versus pelvic radiotherapy, respectively. Rates of grade 1 to 2 gastrointestinal toxicity were significantly lower with vaginal brachytherapy versus pelvic radiotherapy, 12.6% versus 53.8%, respectively. Thus, depending on risk factors, vaginal brachytherapy may be the preferred adjuvant therapy for women with high-intermediate risk endometrioid carcinoma.[89]

Three trials sought to clarify the appropriate adjuvant systemic therapy for endometrial cancer. GOG-249 was a prospective phase 3 study of patients with GOG-defined high-intermediate risk, stage II (any histology), or stage I to II serous or clear-cell cancer. Patients were randomly assigned to whole-pelvis irradiation with or without vaginal brachytherapy versus adjuvant paclitaxel and carboplatin chemotherapy with intravaginal brachytherapy.[90] With a median follow-up of 24 months, RFS was the same in both treatment arms (82% with pelvic irradiation vs 84% with vaginal brachytherapy and chemotherapy). GOG-258 enrolled people with stage III or IVA endometrial cancer and randomly assigned them to six cycles of paclitaxel and carboplatin chemotherapy or an investigational regimen consisting of chemoradiation therapy (cisplatin and tumor volume–directed RT) followed by paclitaxel and carboplatin for four cycles.[91] There were no differences in RFS between the two arms; with a median of 112 months of follow-up, Matei et al reported no difference in OS between the two arms.[92] Although local relapse rates were lower in the investigational arm, distant relapse rates were higher. In an ancillary study of GOG-258, Clements et al examined whether molecular classification using MMR and p53 protein expression predicts RFS and OS in this cohort. They observed worse RFS for patients with *p53*abn tumors. Furthermore, *p53*wt predicted improved RFS with chemoradiotherapy versus chemotherapy (77% vs 60%; HR, 0.54; 95% CI, 0.32-0.94), while OS was similar.[93] PORTEC-3 enrolled patients with stage I, grade 3, and clear-cell or serous histology and myometrial invasion or stage II or III cancer and randomly assigned them to a standard treatment of pelvic irradiation (and vaginal brachytherapy if there was cervical involvement) or cisplatin and RT followed by paclitaxel and carboplatin for four cycles.[94] There were no differences in RFS or OS between the two arms. However, on subset analysis[95] for stage III disease, there was a significant difference in RFS favoring the investigational arm.[95]

The results of PORTEC-3 and GOG-258 supported the role of chemotherapy generally being reserved for advanced endometrial cancer; exceptions to this would be consideration of chemotherapy for early-stage, high-risk histologies such as serous endometrial cancers or carcinosarcoma; expert opinion from pathologists and oncologists specializing in gynecologic oncology is warranted in these cases. The role of RT in endometrial cancer remains unclear, although there may be a benefit in reducing local recurrences. RT modalities include intravaginal radiation therapy (IVRT) and/or pelvic radiation therapy.

Medically Inoperable Uterine Cancer

Surgery is the cornerstone of therapy for patients with uterine cancer. For those patients with medical comorbidities, a thorough assessment should be performed by their gynecologic oncologists as well as other medical professionals to determine whether the patient is medically inoperable. For women with medically inoperable uterine cancer, definitive radiotherapy should be considered as an option. Initial staging should include a pelvic MRI to determine the extent of myometrial invasion (greater or less than ½) and the presence of cervical stromal invasion, as this may impact the risk of nodal metastases. For patients with well-differentiated grade 1 endometrioid carcinoma with limited myometrial invasion and without cervical stromal invasion or pelvic/para-aortic nodal metastases, oral progestins or levonorgestrol (LNG)-releasing IUDs can be considered. In the morbidly obese patient group, LNG-IUDs may serve as a bridge while weight loss interventions can be pursued with surgery as an ultimate goal. Brachytherapy alone may be considered for women with well to moderately differentiated carcinoma without deep myometrial invasion, cervical stromal invasion, or lymph node metastases on MR imaging. For all others, a combination of EBRT 45 to 50.4 Gy in 1.8 Gy fractions to the pelvis and brachytherapy (2-5 fractions 5-8.5 Gy) is typically recommended.[96]

Advanced-Stage, Recurrent, or Metastatic Disease

For patients with pelvic recurrence (either vaginal or nodal), GOG-238 tested whether the addition of cisplatin weekly 40 mg/m^2 to fractionated EBRT and brachytherapy as appropriate could improve PFS. Median PFS was longer in patients who received radiotherapy alone versus chemoradiotherapy (median not reached vs 73 months, respectively, HR, 1.25; 95% CI, 0.75-2.07). PFS at 3 years was 73% versus 62% for the radiotherapy alone versus the chemoradiotherapy group, respectively.

Immune Checkpoint Inhibitors GY018: In this phase 3 study, pembrolizumab was added to carboplatin and paclitaxel and then given as maintenance for 2 years versus carboplatin and paclitaxel alone; eligibility included measurable stage III to IVA or measurable/nonmeasurable stage IVB or recurrent endometrial cancer. The primary endpoint was PFS as assessed by the investigator. The addition of pembrolizumab to carboplatin and paclitaxel improved PFS in both the MMR-proficient (pMMR) and dMMR populations. In the pMMR population, median PFS was 11.7 months for the pembrolizumab arm and 8.7 months for the placebo arm (HR, 0.57; 95% CI, 0.44-0.74); $P < .0001$). In the dMMR population, median PFS was not reached for the pembrolizumab arm and was 7.6 months for the placebo arm (HR, 0.3; 95% CI, 0.19-0.48; $P < .0001$). OS was a secondary endpoint, and there were favorable trends for the addition of pembrolizumab to chemotherapy in both pMMR and dMMR populations. On June 17, 2024, the FDA-approved pembrolizumab with carboplatin and paclitaxel for primary advanced or recurrent endometrial cancer, regardless of the MMR status.

RUBY study: The RUBY study was a phase 3 study of dostarlimab-gxly added to carboplatin and paclitaxel, followed by 3 years of dostarlimab maintenance versus carboplatin and paclitaxel alone. This trial had dual primary endpoints of PFS by the investigator and OS. PFS was improved in both dMMR and pMMR populations, with a statistically significant OS benefit in the overall population. On July 31, 2023, the FDA-approved dostarlimab-gxly with carboplatin and paclitaxel with dostarlimab-gxly maintenance, and on August 1, 2024, this approval was extended to patients with primary advanced or recurrent endometrial cancer, regardless of MMR status.

DUO-E: The results of this trial led to the FDA approval of durvalumab on June 14, 2024, combined with carboplatin and paclitaxel, followed by single-agent durvalumab for patients with newly diagnosed advanced or recurrent endometrial cancer with dMMR tumors. In DUO-E, patients were randomly assigned to carboplatin and paclitaxel with durvalumab followed by durvalumab maintenance, carboplatin and paclitaxel with placebo followed by placebo maintenance, and a third arm that tested olaparib maintenance. FDA-approved durvalumab for use in patients with dMMR tumors because median PFS was not reached in the durvalumab arm and was 7 months for placebo in the placebo arm (HR, 0.42; 95% CI, 0.22-0.80).

For patients with serous endometrial carcinoma or those in whom a *p53* mutation was identified,[97,98] testing for *HER2*/neu overexpression is recommended, because a multicenter phase 2 randomized clinical trial showed that the addition of trastuzumab to chemotherapy improved PFS and OS in patients with *HER2* 3+ or 2+ IHC and amplification.[99] Phase 3 clinical trials are ongoing to substantiate the use of trastuzumab with carboplatin and paclitaxel.

For patients requiring second-line therapy after previous systemic chemotherapy with a platinum-based regimen, the results of KEYNOTE-775 support the use of pembrolizumab and lenvatinib. In this trial, more than 820 volunteers were randomly assigned to pembrolizumab and lenvatinib or to single-agent chemotherapy of the physician's choice (doxorubicin or paclitaxel).[100] Treatment with pembrolizumab and lenvatinib resulted in a significant improvement in ORR, PFS, and OS compared with single-agent chemotherapy. Benefits were seen in those with pMMR disease as well as in all comers, although single-agent approval for pembrolizumab at this time is limited to patients with dMMR disease. Treatment with pembrolizumab and

lenvatinib was associated with a higher rate of serious adverse events compared with traditional chemotherapy, including hypertension and hypothyroidism. KEYNOTE-775 enrolled patients who had not received previous checkpoint inhibition, so for those patients who received an ICI with carboplatin and paclitaxel, there are no data for the use of an ICI after an ICI.

Pembrolizumab is FDA approved for patients who have tumors with dMMR or MSI-H after first-line therapy has failed, based on the KEYNOTE-158 study. The data regarding additional benefits with the addition of lenvatinib in these patients are limited. Another FDA-approved option for patients who have tumors with dMMR or MSI-H is dostarlimab-gxly, based on the GARNET study. Multiple other agents are available and appropriate for use (see NCCN guidelines).

ADCs: As mentioned above, T-DXd was granted accelerated approval by the FDA on April 5, 2024, based on the results of the DESTINY-PanTumor02 trial for any solid tumor with *HER2* 3+ IHC. This basket study enrolled 40 patients with recurrent endometrial cancer and 2+ or 3+ IHC for *HER2* (gastric scoring). The ORR for all 40 patients was 57.5%. The ORR in patients with tumors having centrally confirmed 3+ IHC was 84.6%, and the ORR for those with tumors having centrally confirmed 2+ IHC was 47.1%.[8] The NCCN listed T-DXd for *HER2*-positive tumors (3+ or 2+ IHC) as a category A recommendation under Useful in Certain Circumstances in the 2024 update.[17]

Hormonal Therapy: Clinical features that are predictors of response to endocrine therapy, with responses of up to 38%, include grade 1 or 2 histology, a long disease-free interval from diagnosis, and the presence of estrogen or progesterone receptors on the tumor cells. Strategies include the use of megestrol acetate, tamoxifen, aromatase inhibitors, or fulvestrant. Another approach combines the mammalian target of rapamycin inhibitor everolimus with letrozole. This was evaluated in a phase 2 trial conducted by NRG Oncology.[101,102] In 38 patients, the ORR was 32%; no patients stopped treatment because of toxicity. In addition, CDK4/6 inhibitors and aromatase inhibitors, ribociclib, and abemaciclib, have been studied in phase 2 trials in recurrent endometrial cancer with promising results and incorporation into NCCN guidelines.

SURVIVORSHIP

People treated for endometrial cancer should be observed, with pelvic examination as part of routine surveillance, using a risk-based strategy. For people who experience premature menopause related to treatment, estrogen therapy can be provided with no significant risk within appropriate age ranges. This was shown in a randomized trial that included more than 1,200 people with stage I or II endometrial cancer[103]; there was no difference in recurrence rates in those who received estrogen compared with those treated with a placebo preparation. Guidance discussed previously in this chapter for people treated for cervical cancer remains relevant for this population as well.

Patients with advanced or recurrent disease who are receiving immuno-oncology (IO) maintenance should undergo serial scans to confirm no progression while on treatment. The role of routine surveillance scans in the post-treatment setting remains unclear. The most up-to-date recommendations for surveillance can be found in the SGO white paper.[104]

In addition, some patients with endometrial cancer are morbidly obese and/or too ill to proceed with surgery. Diagnosis via endometrial sampling and obtaining pathology is critical. Patients who cannot receive surgical treatment and who have cancer confined to the uterus may be managed by a gynecologic oncologist with hormone therapy or with RT and other systemic treatments. Fertility preservation may be appropriate in certain selected patients, which would be explored with a gynecological oncology team.

KEY POINTS

- Endometrial carcinoma is the most common gynecologic cancer in the United States. The major risk factors for endometrioid endometrial carcinoma are those typically associated with increased estrogen exposure. More aggressive subtypes are often estrogen independent and associated with older age and non-white race.
- For people who receive surgical treatment, adjuvant therapeutic options include RT (pelvic irradiation with or without IVRT) and/or chemotherapy, typically with paclitaxel and carboplatin, and RT should be determined using an individualized approach. Postoperative risk factors can help determine who should be offered adjuvant treatment.
- All patients with endometrial adenocarcinoma should undergo MMR and/or MSI assessments. This information will identify patients who are appropriate for treatment with pembrolizumab, dostarlimab-gxly, or durvalumab. It is also important to identify patients with Lynch syndrome. Patients whose tumors show dMMR expression should be referred for genetic screening for Lynch syndrome.
- Pembrolizumab and lenvatinib combination therapy represents an important advance for patients with MMRp recurrent disease after treatment with paclitaxel and carboplatin.
- The combination of chemotherapy and immunotherapy (pembrolizumab or dostarlimab-gxly) is considered the standard of care in the treatment of patients with advanced-stage or recurrent dMMR endometrial cancer. The addition of IO to the chemotherapy backbone may also be appropriate for patients with pMMR tumors; we await mature data from GY018 and RUBY to further determine recommendations.

UTERINE SARCOMAS

EPIDEMIOLOGY AND PREVENTION

Uterine sarcomas make up less than 10% of all uterine cancers. The most common of these are leiomyosarcoma and low-grade endometrial stromal sarcoma. Other variants include undifferentiated sarcoma and adenosarcomas. Unfortunately, there are no preventive strategies against these mesenchymal tumors. Of note, carcinosarcomas are not considered true sarcomas but rather dedifferentiated carcinomas. They are staged and treated as endometrial adenocarcinomas, and their treatment should be followed as such.

PATHOGENESIS

Little is known about the pathogenesis of uterine sarcomas.

CLINICAL PRESENTATION AND STAGING

Uterine sarcomas typically present with nonspecific symptoms, including abnormal uterine bleeding, a pelvic mass, or abdominal pain or pressure. However, these are not pathognomonic of sarcoma and are also commonly reported among people ultimately diagnosed with leiomyomas. Uterine sarcomas are staged differently from endometrial adenocarcinoma, with separate staging for adenosarcoma and all other sarcomas.

CURRENT TREATMENT PRACTICE

Leiomyosarcoma

Leiomyosarcoma is a high-risk cancer of the uterine smooth muscle with a propensity for early hematogenous dissemination. Patients with uterus-limited disease have a 50% to 70% risk of recurrence. Despite this high risk of recurrence, there are no data to suggest that adjuvant treatment affords a survival advantage. As a result, the standard of care is surgical resection. Tumor size is a prognostic indicator, and a cutoff of 5 cm is used; nodal involvement is rarely encountered if the disease is confined to the uterus. Adjuvant radiation therapy can be considered to decrease the rate of pelvic recurrence but has no effect on survival outcomes.

For patients with advanced, recurrent, or metastatic leiomyosarcoma, an anthracycline-based regimen is used, with gemcitabine and docetaxel as a typical alternative. In a randomized phase 3 trial that included 150 patients with metastatic leiomyosarcoma of both uterine and nonuterine origin, doxorubicin and trabectedin, followed by trabectedin, improved PFS and ORRs over doxorubicin alone, and these same benefits were seen when restricted to the uterine leiomyosarcoma population of 67 patients.[105] However, the combination is associated with a higher toxicity rate. If not used in the initial regimen, other active agents include doxorubicin, gemcitabine, ifosfamide, trabectedin, pazopanib, and dacarbazine.

Endometrial Stromal Sarcoma

Endometrial stromal sarcomas may be high or low grade. High-grade endometrial sarcomas are referred to as undifferentiated endometrial sarcomas. Histopathologic features and molecular alterations can help differentiate low-grade from high-grade tumors. Low-grade tumors nearly always express estrogen and progesterone receptors. Although the risk of recurrence is approximately 30% for women with disease limited to the uterus at the time of diagnosis, 10-year survival rates exceed 90% because of the indolent pace of progression. The treatment of choice is surgery, and recurrence rates seem to be lower in women who undergo bilateral oophorectomy at the time of diagnosis. For patients who require medical therapy for recurrence, endocrine therapy, such as aromatase inhibition, is typically administered. There are limited data that support a preferred chemotherapy approach for advanced metastatic high-grade endometrial stromal sarcoma, but regimens used in the treatment of leiomyosarcoma are typically considered.

Adenosarcoma

Adenosarcomas are tumors of mixed histology in which the sarcomatous portion seems similar to low-grade endometrial stromal sarcoma, and the adeno portion seems to be benign. Prognosis and management are similar to those for endometrial stromal sarcoma unless there is evidence of sarcomatous overgrowth. Adenosarcomas with sarcomatous overgrowth are high-risk cancers, the prognosis and treatment of which are driven by the high-grade portion of the tumor. Surgery is the primary treatment of choice, with systemic or RT reserved for recurrent or metastatic disease.

Undifferentiated Uterine Sarcoma

Undifferentiated uterine sarcomas are hormone receptor–negative and behave aggressively. Because of their rarity, there are no prospective studies that address active agents for these tumors. Retrospective data and sarcoma treatment guidelines support doxorubicin-based treatment or gemcitabine and docetaxel treatment. Enrollment in clinical trials for soft tissue sarcomas is encouraged.

SURVIVORSHIP

The approach to treating women who have uterine sarcoma is similar to that for women being treated for endometrial cancer. For patients with endometrial stromal sarcoma, hormone therapy should not be offered because these tumors express estrogen

and progesterone receptors. Follow-up may include routine chest radiographs and periodic imaging, as is performed for other soft tissue sarcomas.

KEY POINTS

- Sarcomas are a heterogeneous group of diseases that account for 4% of all uterine cancers.
- Surgery is the mainstay of treatment for uterine sarcoma. There is no evidence that adjuvant treatment improves survival outcomes, and adjuvant treatment is typically not recommended.

EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER, AND PRIMARY PERITONEAL CANCER

Epithelial cancers arising from the ovary, fallopian tube, or peritoneum (collectively referred to as ovarian cancer for the remainder of this section) are one of the leading causes of death resulting from gynecologic cancer in the United States. Epithelial adenocarcinomas can be histologically subclassified into several categories, the most common of which is high-grade serous ovarian cancer (HGSOC), which comprises ~80% of ovarian cancers. Other rarer subtypes include low-grade serous, endometrioid (low grade or high grade), mucinous, or clear cell. Ovarian carcinosarcomas are considered epithelial cancers and are considered high-grade epithelial ovarian cancer. A rare variant, small-cell carcinoma of the ovary (hypercalcemia type), is highly malignant and typically affects women in their second decade. In 2014, mutations in *SMARCA4*, which plays a role in chromatin modification, were identified as critical drivers of these tumors. Subsequent research also found loss of *SMARCA2*.

EPIDEMIOLOGY AND PREVENTION

In the average-risk population, ovarian cancer will develop in approximately one person in 70 in the United States (Figs. 15-5 and 15-6). The mean age at diagnosis is 63 years. Risk factors have implications for both treatment and cancer prevention. Carriers of deleterious mutations in *BRCA1* or *BRCA2* have a high lifetime risk of HGSOC, estimated at ~16% and up to 50% to 60%. Other germline mutations in genes related to homologous recombination are also associated with a moderately increased risk of ovarian cancer and include *BRIP1, RAD51C, RAD51D*, and *PALB2*. People with genetic mutations that are part of Lynch syndrome are also at increased risk of endometriosis-associated ovarian cancer, although the lifetime risk likely varies depending on the specific *MMR* gene mutation. Emerging data are elucidating whether there is a clinically relevant increased risk of epithelial ovarian cancer associated with other germline mutations. However, a person without a known germline mutation but with at least one first-degree relative with ovarian cancer has a relative risk of ~2 to 3 for the development of ovarian cancer, meaning that their lifetime risk of ovarian cancer is approximately 3% to 5%. Regardless of risk factors, all patients with a new diagnosis of ovarian, fallopian tube, or primary peritoneal cancer should be offered genetic testing.[106]

Figure 15-5 Protective and Associated Risk Factors for Ovarian Cancer

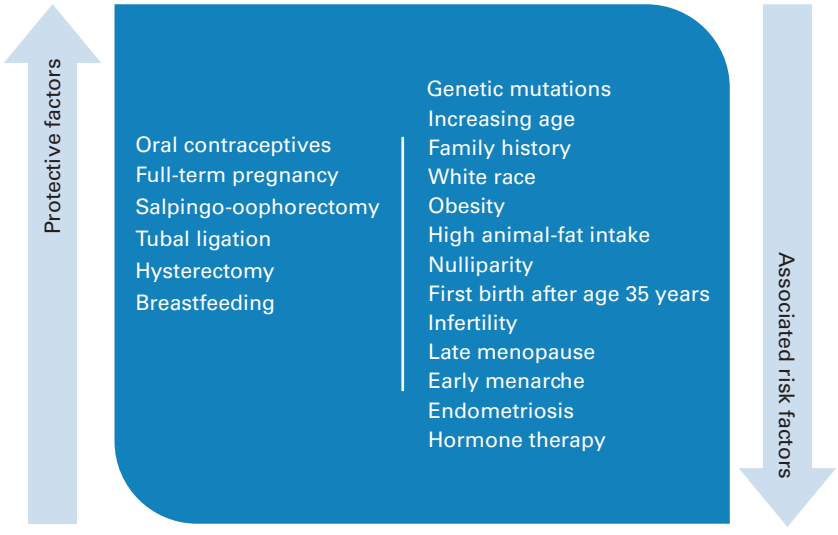

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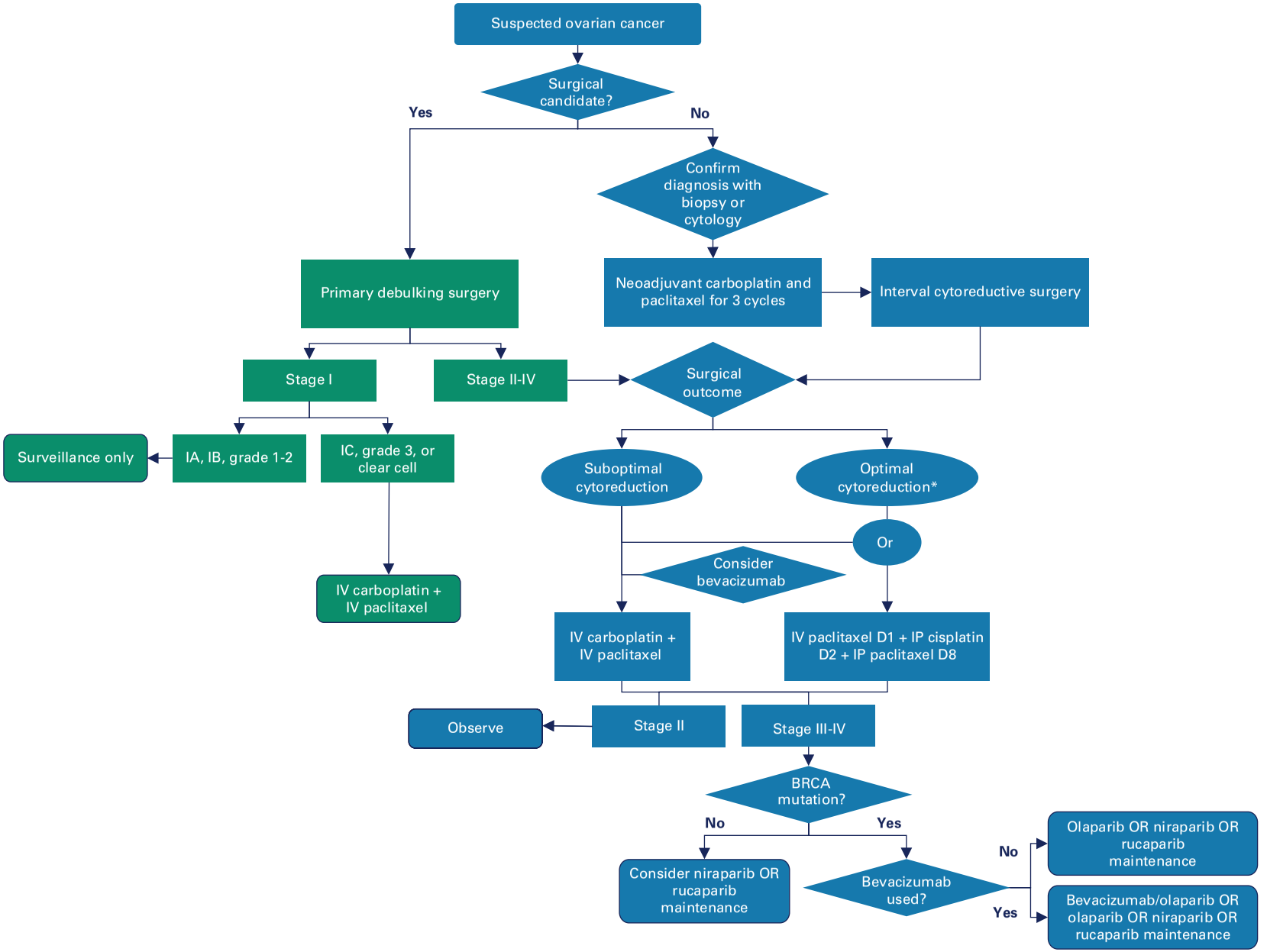
Figure 15-6 Treatment Algorithm for Ovarian Cancer



Abbreviations: IP, intraperitoneal; IV, intravenous.
*In people receiving neoadjuvant chemotherapy and who achieve an optimal cytoreduction at interval surgery, a phase 3 trial in the Netherlands demonstrated that hyperthermic intraperitoneal chemotherapy (HIPEC) delivered at the time of surgery and then followed by IV carboplatin and paclitaxel was associated with a survival advantage compared with IV chemotherapy alone.
Data from NCCN. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 1.2023. Available at: https://www.nccn.org
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At this time, there is no effective ovarian cancer screening strategy. People with known genetic mutations that increase the risk of ovarian cancer are recommended for prophylactic bilateral salpingo-oophorectomy, with or without hysterectomy, for risk reduction. Several studies indicate that performing a bilateral risk-reducing salpingo-oophorectomy (RRSO) may substantially reduce the risk of ovarian cancer and improve mortality for women who are carriers of deleterious *BRCA1* or *BRCA2* mutations (an approximately 80% lower risk of ovarian, fallopian tube, and peritoneal cancers, with an average follow-up of 5.6 years from surgery, and 77% reduction in all-cause mortality). Opportunistic salpingectomies can also be considered in women at average risk for ovarian cancer when other procedures for benign conditions are performed. However, removal of the tubes (or even both tubes and ovaries) does not completely negate the risk of ovarian or primary peritoneal cancer. Ongoing studies are testing risk-reducing salpingectomy (rather than bilateral salpingo-oophorectomy) in those at high genetic risk for ovarian cancer.

PATHOGENESIS

Contemporary data implicate the fallopian tubes as the origin of HGSOC, b3ecause high-grade intraepithelial carcinomas have been identified in the fimbria of people with a *BRCA1* or *BRCA2* mutation who have undergone bilateral salpingo-oophorectomy.[107] These precursor lesions include *p53* signature, secretory cell outgrowths (SCOUT), serous tubular intraepithelial lesions (STIL), and serous tubular intraepithelial carcinoma (STIC) and are thought to have clonal relationships to invasive HGSOCs.

Management of STIC is challenging, as there are limited data available to guide management. Currently, risk-reducing salpingectomy is recommended for all women undergoing surgery, particularly pelvic surgery. For average-risk (most) women, opportunistic salpingectomy is recommended during routine procedures such as hysterectomy or cesarean section, with an increased push for opportunistic salpingectomy at any surgery.[108,109] This intervention has demonstrated significant potential in reducing ovarian cancer incidence while maintaining safety and feasibility.[110]

For high-risk individuals, particularly *BRCA* mutation carriers, RRSO remains the gold standard. Alternative approaches, such as salpingectomy alone, are under investigation to preserve ovarian function in younger patients (NCT04251052). To improve STIC detection, the SEE-FIM pathology protocol is recommended when patients are undergoing risk-reducing surgery to prevent ovarian cancer, but challenges such as diagnostic variability and limited data persist.

When STIC is detected incidentally, management varies based on risk factors and lesion characteristics. Genetic counseling and testing are recommended when STIC is identified, as hereditary predisposition may guide further management. Chemotherapy is not routinely recommended for the treatment of STIC. Surveillance is suggested when STIC has been diagnosed, but there are no set guidelines as to the frequency and type of monitoring.

Older case-control studies reported that endometriosis is associated with a threefold increased risk of clear-cell carcinoma of the ovaries and a twofold increase in the risk of low-grade or endometrioid carcinomas.[111]

CLINICAL PRESENTATION AND STAGING

Patients with early-stage ovarian cancer often have nonspecific symptoms, including irregular menses (if premenopausal), urinary frequency, persistent bloating, and constipation.[112] Most patients with advanced disease will present with symptoms reflecting advanced disease, including abdominal pain, bloating, dyspnea, emesis, early satiety, anorexia, and constipation.

The definitive diagnosis of ovarian, fallopian tube, or primary peritoneal cancer is made by preoperative biopsy or surgical exploration, with stage assigned based on the FIGO system. Prognosis is linked to the amount of residual tumor after surgical cytoreduction (debulking surgery). Optimal cytoreduction has been defined as no residual tumor measuring larger than 1 cm at the end of the surgical procedure, although a more contemporary definition is no gross residual disease (R0 cytoreduction). People with a tumor larger than 1 cm at the end of surgery are deemed to have had a suboptimal cytoreduction, which confers a worse prognosis.

ASCO and SGO practice guidelines recommend that all patients with suspected epithelial ovarian cancer undergo evaluation by a gynecologic oncologist to determine whether the patient is a candidate for upfront cytoreductive surgery or will require a biopsy to confirm ovarian cancer, followed by NACT.[113]

CURRENT TREATMENT PRACTICE

The approach to treating people with ovarian cancer is guided by whether patients are surgical candidates at presentation and, ultimately, by disease stage. All women with ovarian cancer, regardless of stage, age, family history, and ovarian cancer histology, should be referred for genetic counseling and testing at diagnosis to assess the risk of other cancers and familial risk, and because the information can affect treatment in the first and/or subsequent line of treatment in advanced disease or recurrence. Other recommendations include somatic (tumor) testing to look for tumor *BRCA1/2* and other mutations, and testing for homologous recombination deficiency (HRD) to confirm eligibility for PARP inhibitor (PARPi) maintenance therapies.

Early-Stage Ovarian Cancer

Patients with stage I ovarian cancer are classified as having early-stage ovarian cancer. Historically, women with stage II disease were included in this category, but contemporary data show that stage II disease is associated with a less favorable prognosis.

As a result, these patients are often considered to be in the same group as patients who have advanced ovarian cancer and are treated the same way.

Not all patients with early-stage ovarian cancer require adjuvant treatment. Patients with stage IA or IB grade 1 or 2 tumors have 5-year DFS rates greater than 90% with surgery alone, and the risks of adjuvant chemotherapy likely outweigh the benefits. For patients with stage IA or IB grade 3 tumors, stage IC disease, or clear-cell carcinoma, adjuvant chemotherapy is recommended. An analysis of data from more than 900 patients with high-risk early-stage disease showed that adjuvant platinum-based chemotherapy led to an 11% improvement in the 5-year PFS rate and an 8% improvement in the 5-year OS rate compared with a strategy of observation. Although patients are often recommended to undergo six cycles of therapy, the optimal duration of therapy is not clear. One randomized trial of patients with stage I to II ovarian cancer showed that those who received three cycles of therapy had a trend toward a higher risk of recurrence compared with those who received six cycles, particularly in HGSOC, although there was no difference seen in OS.[114]

Advanced Ovarian Cancer

For people with stage II or higher ovarian cancer who undergo primary surgical cytoreduction, a series of randomized phase 3 trials have established combination intravenous platinum (cisplatin or carboplatin) and taxane (paclitaxel or docetaxel) chemotherapy as the standard of care in first-line treatment. Results generally have shown a significant improvement in OS with a combination of platinum and taxane regimens. The angiogenesis inhibitor bevacizumab, in combination with platinum and taxane chemotherapy and then used as single-agent maintenance treatment, has been approved by the FDA on the basis of an improvement in PFS, although no OS benefit was seen.[115,116]

For patients who undergo optimal cytoreduction (ie, residual disease of less than 1 cm), intraperitoneal chemotherapy can be offered with OS improvement on the basis of the results of the GOG-172 trial. However, toxicities were higher in the intraperitoneal arm, and a careful risk:benefit assessment needs to be discussed with the patient. Lowering the cisplatin dose to 75 mg/m^2 intraperitoneally was tested in the GOG-252 trial; in this study, one arm with intraperitoneal treatment was compared with two arms of intravenous treatment (although all patients received bevacizumab), with no improvement in outcomes.

The typical schedule of administration of intravenous carboplatin and paclitaxel is every 3 weeks for six cycles. Alternative approaches use a dose-dense schedule, as compared in the ICON8 phase 3 trial,[117,118] which showed no difference in PFS among the three arms. Compared with carboplatin and paclitaxel every 3 weeks, carboplatin every 3 weeks with weekly paclitaxel and weekly carboplatin and paclitaxel both had a higher frequency of grade 3 or 4 toxicities (63% and 53% vs 42%, respectively).

The use of NACT in advanced ovarian cancer is favored in patients for whom a complete cytoreduction seems unlikely or when other circumstances are present that make patients poor candidates for surgery at the time of diagnosis; these patients should be assessed by a gynecologic oncology surgeon before initiation of NACT. ASCO and the SGO have published clinical practice guidelines on the role of NACT that support its use in appropriate candidates.[113]

There have been multiple historical randomized trials designed to determine the superior surgical approach to advanced ovarian cancer (upfront vs interval cytoreductive surgery) (the interested reader is referred to these studies).[119-122] The Trust trial is the most modern of these, presented at ASCO in 2025. Trust is an international randomized multicenter phase 3 trial in patients with stage IIIB-IVB OC and good performance status comparing primary cytoreductive surgery (PCS) followed by six cycles of IV chemotherapy to neoadjuvant IV chemotherapy (NACT) followed by interval cytoreduction and three further IV cycles. The primary endpoint was OS. The study demonstrated an improvement in PFS (a secondary endpoint) for patients who underwent upfront surgery. But there was no benefit seen in the OS. Median PFS was 22.2 months in the PCS group and 19.7 months in the interval cytoreductive surgery (ICS) group (HR, 0.80; 95% CI: 0.66-0.96; P = .02). Median OS was 54.3 months in the PCS group and 48.3 months in the ICS group (HR, 0.89l; 95% CI, 0.74-1.08; P = 0.24). Patients with complete cytoreduction after PCS had the most favorable outcome, with a median PFS and OS of 27.9 and 67.0 months, respectively.

For those who undergo surgery after neoadjuvant therapy (ie, an interval cytoreduction), the optimal treatment in the adjuvant setting is not clear. For women who have an optimal cytoreduction, limited data suggest intraperitoneal treatment; one randomized trial reported an OS advantage with heated intraperitoneal chemotherapy.[123] Otherwise, the current approach for treatment of these patients is to continue platinum and taxane therapy (with or without bevacizumab), typically for a total of six cycles. Regardless, bevacizumab should be held for the treatment before and immediately after the interval surgery to allow optimal postoperative healing.

Regarding maintenance therapy after initial chemotherapy, the optimal choice of treatment should be based on careful assessment of ovarian cancer genetic markers. Bevacizumab is approved in this setting because of a PFS benefit, but randomized trials do not show an OS benefit. PARPis are another option for maintenance treatment in advanced ovarian cancer, with the magnitude of benefit depending on *BRCA* or HRD status; PRIMA and ATHENA monotherapy have both shown neither OS benefit nor detriment in any population treated with a PARPi. In the SOLO1 and PAOLA-1 trials, there was a trend toward improved OS for the PARPi arm. For those who present with advanced ovarian cancer, PARPis have demonstrated PFS and/or OS benefit as single agents or, in one instance, in combination with bevacizumab maintenance therapy. [124-128] Knowledge of germline or somatic *BRCA* mutations or HRD status is also relevant for optimizing treatment in the setting of recurrent disease.

The effect of maintenance olaparib after completion of a platinum-based regimen was demonstrated in the SOLO1 trial, which included 391 volunteers with advanced-stage III or IV high-grade endometrioid or serous carcinoma and a known genetic or somatic *BRCA1* or *BRCA2* mutation. The volunteers were randomly assigned in a 2:1 ratio to olaparib (300 mg twice daily) or placebo to be taken for a maximum of 2 years. Compared with placebo, maintenance olaparib significantly reduced the risk of disease progression or death at 3 years (27% vs 60%, respectively; HR, 0.30; $P < .001$). Data from this study led to FDA approval of olaparib in this setting. The benefit of maintenance olaparib in this setting was confirmed in a 5-year follow-up of SOLO1 trial participants. Compared with those in the placebo arm, patients in the maintenance olaparib arm had a median PFS of 56 months versus 13.8 months.[126] OS showed a clinically meaningful trend toward improved OS with olaparib.

In the PAOLA-1 trial, 806 volunteers were randomly assigned to maintenance olaparib and bevacizumab versus bevacizumab alone. Compared with bevacizumab alone, the combination with olaparib significantly improved PFS (median, 22.1 months vs 16.6 months, respectively; HR, 0.59; 95% CI, 0.49-0.72), with benefits seen in subgroups with a known *BRCA1* or *BRCA2* mutation and those with HRD tumors. In patients with HRD-negative tumors (n = 277), the median PFS was 16.6 months in the olaparib group and 16.2 months in the bevacizumab group (HR, 1.00; 95% CI, 0.75-1.35).[127] OS showed a clinically meaningful trend toward improvement with olaparib and bevacizumab compared with bevacizumab alone in patients with *BRCA* mutations and those with HRD tumors, but not in those with homologous recombination–proficient (HRP) tumors.

In the PRIMA trial, 733 volunteers were randomly assigned to maintenance niraparib therapy or placebo.[129] Compared with placebo, niraparib treatment resulted in significant improvement in PFS in those with HRD tumors (median, 21.9 vs 10.4 months; HR, 0.43; 95% CI, 0.31-0.59), in those without HRD tumors (8.1 vs 5.4 months; HR, 0.68; 95% CI, 0.49-0.94), and in the entire population (median, 13.8 vs 8.2 months; HR, 0.62; 95% CI, 0.50-0.76). Based on the initial PRIMA PFS results, niraparib received FDA approval on April 29, 2020, for use as maintenance treatment of patients with advanced ovarian cancer who are in a complete or partial response to first-line platinum-based chemotherapy. OS results were recently reported by ESMO 2024 in the overall population; median OS for the niraparib group was 46.6 months, and median OS for the placebo group was 48.8 months (HR, 1.01; 95% CI, 0.84-1.23; $P = .8834$).[130] Because this was not a significant difference, the HRD group was not formally tested. However, median OS results were provided per group: HRD, niraparib 71.9 months and placebo 69.8 months (HR, 0.95; 95% CI, 0.71-1.29), HRP, 36.6 months (niraparib) versus 32.2 months (placebo) (HR, 0.93; 95% CI, 0.69-1.26). The specific results for patients who had HRD/*BRCA*-mutated tumors were not reported, but the OS curves were provided in the Supplementary section of the manuscript,[131] and the HR was 0.94 (95% CI, 0.63-1.41). There was 57.7% crossover PARPi use for the placebo arm. In 2025, the first-line maintenance indication for niraparib (approved in 2020) was restricted to HRD-positive tumors.

ATHENA is a phase 3 trial testing four maintenance arms after first-line treatment with platinum and taxane chemotherapy for advanced ovarian cancer; patients were randomly assigned at 4:4:1:1, and the arms consisted of rucaparib plus nivolumab, rucaparib, nivolumab, and placebo. The primary endpoint was investigator-assessed PFS in the intention-to-treat population. In the intention-to-treat population of ATHENA-MONO, median PFS was 20.2 months for the rucaparib arm versus 9.2 months for the placebo arm (HR, 0.52; 95% CI, 0.40-0.68; $P < .0001$). In the HRD group, median PFS was 28.7 months for the rucaparib arm versus 11.3 months for the placebo arm (HR, 0.47; 95% CI, 0.31-0.72; $P = .0004$); for the HRD-negative group, median PFS was 12.1 months for the rucaparib arm and 9.1 months for the placebo arm (HR, 0.65; 95% CI, 0.45-0.95). Interim OS showed for the HRD population,[132] median OS for both the rucaparib and placebo arms was not reached (HR, 0.84; 95% CI, 0.44-1.58). For the intention-to-treat population, median OS for rucaparib was not reached, and for the placebo arm, it was 46.2 months (HR, 0.83; 95% CI, 0.58-1.17). For the exploratory subgroup of non–tumor tissue *BRCA*/loss of heterozygosity-low, OS was 42.9 months for the rucaparib arm and 32.4 months for the placebo arm (HR, 0.75; 95% CI, 0.48-1.17). OS results were recently presented; for the overall intention-to-treat group, median PFS was 15.0 months for the rucaparib and nivolumab arm and 20.2 months for the rucaparib and placebo arm (HR, 1.29; 95% CI, 1.08-1.53). For the placebo-alone arm, median PFS was 9.2 months. Interim OS results at 46.5% maturity showed a median OS of 49.4 months for the rucaparib and nivolumab arm versus 58.0 months for the rucaparib alone arm (HR, 1.13; 95% CI, 0.93-1.38).[132] To date, the addition of ICIs to chemotherapy has not added any benefit and should not be used in this setting.

Recurrent Ovarian Cancer

The approach to recurrent ovarian cancer is often based on whether the recurrent disease is platinum resistant (defined as progression within less than 6 months of first-line platinum-based therapy completion) or platinum sensitive (defined as recurrence more than 6 months after completion of first-line platinum-based therapy).

For women with a platinum-sensitive disease recurrence, the typical recommendation is to offer retreatment with carboplatin in combination with paclitaxel, liposomal doxorubicin, or gemcitabine, with or without bevacizumab, which can then be continued as maintenance therapy.[133] For patients with recurrent disease who respond to second-line platinum-based therapy and have a *BRCA* mutation, there are three FDA-approved PARPis that have demonstrated consistent and statistically significant benefits in PFS when used as maintenance therapy in the PARPi-naive setting; one trial has shown PFS benefit with retreatment with a PARPi in the setting of previous use of a PARPi. The SOLO2 trial specifically evaluated the magnitude of benefit of maintenance

PARP inhibition among women with *BRCA* mutation–positive recurrent ovarian cancer. Compared with placebo, olaparib (dosed in tablet formulation) significantly improved PFS (5.5 months vs 19.1 months, respectively; HR, 0.30; $P < .0001$) and time to first subsequent treatment or death (7.1 months vs 27.9 months, respectively; HR, 0.28; $P < .0001$). Updated data from the SOLO2 trial showed that for those with a known *BRCA* mutation, maintenance olaparib conferred a statistically nonsignificant OS advantage compared with placebo (51.7 months vs 38.8 months; HR, 0.74; $P = .054$).

Long-term OS results show that the HRs of the populations with HRD and HRP tumors are not in favor of PARPi for NOVA and ARIEL3. The OS data for patients with non-germline *BRCA*-mutated tumors from NOVA and ARIEL3 and from Study 19 led to the withdrawals of niraparib (in September 2022),[131] rucaparib (in December 2022; Clovis filed for bankruptcy in 2023), and olaparib (in September 2023) as maintenance treatment for patients who had ovarian cancer with platinum-sensitive recurrent *BRCA* wild-type tumors. The FDA indication for use in maintenance for patients with *BRCA*-mutated tumors remains for all three drugs (germline or somatic for rucaparib and olaparib; germline for niraparib). The EMA has not withdrawn any of the PARPi approvals in the recurrent maintenance setting, and thus, the standard of care differs between the United States and Europe. As a result, approval for niraparib, rucaparib, and olaparib is now limited to use in patients with a germline *BRCA* mutation, and rucaparib approval is granted only for patients with either a germline or somatic *BRCA* mutation.[124] The primary adverse effects are similar to all the commercially available agents and include gastrointestinal toxicities (eg, diarrhea, nausea, anorexia) and myelosuppression (eg, neutropenia, anemia, thrombocytopenia). In addition, the risk of acute myeloid leukemia or myelodysplastic syndrome is higher with PARPi use in the recurrent platinum-sensitive setting compared with use in the newly diagnosed upfront setting. Risk factors include the number of previous lines of therapy, duration of PARPi use (set duration vs given until either disease progression or toxicities), and presence of a *BRCA* mutation, which allows for more treatment to be used.

Data from three phase 3 trials demonstrated PFS benefit in recurrent platinum-sensitive disease for secondary cytoreduction, particularly when complete gross surgical cytoreduction was achieved. An OS benefit was seen in one trial, but not in another, and OS data are immature in the third trial. In these trials, there was a trend toward worse OS if surgery was performed and optimal cytoreduction was not achieved.[134-136] Evaluation by a gynecologic oncologist for consideration of secondary cytoreduction in the setting of recurrent platinum-sensitive disease is recommended.

For women with platinum-resistant disease recurrence, use of sequential single-agent chemotherapy with or without bevacizumab, on the basis of data from the AURELIA study, is advised, and enrollment in clinical trials is strongly encouraged. Data from a randomized trial showed that compared with single-agent therapy (ie, weekly paclitaxel, liposomal doxorubicin, or topotecan), the combination of bevacizumab and chemotherapy improved PFS, which led to the approval of bevacizumab in this setting.

Antibody-drug conjugates: The antibody-drug conjugate (ADC) mirvetuximab soravtansine-gynx has been tested in a single-arm phase 2 study (SORAYA) and a randomized phase 3 study (MIRASOL). Mirvetuximab soravtansine-gynx is an ADC that targets *FOLR1* with a tubulin targeting agent as the payload (DM4). The FDA granted accelerated approval of mirvetuximab soravtansine-gynx in November 2022 based on the data from the global single-arm phase 3 study of the ADC in 106 patients who had platinum-resistant ovarian cancer with high folate receptor alpha expression, defined as 75% or more tumor cells staining with 2+ intensity. All patients had received bevacizumab and up to three previous lines of systemic therapy. The ORR was 31.7%, and the median DOR was 6.9 months.[28] A randomized phase 3 trial was subsequently conducted comparing mirvetuximab soravtansine-gynx with the physician's choice of chemotherapy in platinum-resistant ovarian cancer; it demonstrated an improvement in median PFS from 3.98 months to 5.62 months, an objective response in 42.3% versus 15.9% of patients, and an improvement in median OS from 12.75 to 16.46 months with mirvetuximab soravtansine-gynx compared with standard-of-care chemotherapy; mirvetuximab soravtansine-gynx received full FDA approval in March 2024. In addition, patients receiving mirvetuximab soravtansine-gynx experienced fewer grade 3 or higher adverse events (41.7% vs 54.1%) and a lower rate of treatment discontinuation (9.2% vs 15.9%).[137] These data led to full FDA approval of mirvetuximab soravtansine-gynx in March 2024.

Mirvetuximab soravtansine-gynx has also been studied as a single agent in patients with platinum-sensitive recurrent ovarian cancer, yielding a response rate of 51.9%, median DOR of 8.25 months, and median PFS of 6.93 months.[138]

T-DXd was granted accelerated approval by the FDA in April 2024, based on the results of the DESTINY-PanTumor02 trial for any solid tumor with *HER2* 3+ IHC. In this basket trial, 40 patients who had recurrent ovarian cancer and 2+ or 3+ IHC for *HER2* (gastric scoring) were enrolled. The ORR for all 40 patients was 45%; the ORR in centrally confirmed 3+ IHC was 63.6%, and the ORR for centrally confirmed 2+ IHC was 36.8%. The NCCN listed T-DXd as a 2A recommendation for *HER2*-positive tumors (3+ or 2+ IHC) under Useful in Certain Circumstances in the 2024 update.[9,17] Somatic testing should be performed that includes hotspot testing for dMMR, *NTRK* fusions, and other rare mutations for which there are disease-agnostic FDA-approved agents, such as pembrolizumab and Larotrectinib, for such targets.

The data from the Rosella study were presented at ASCO in 2025. These data demonstrated a PFS advantage for the combination of weekly nab-paclitaxel and relacorilant versus nab-paclitaxel alone. The OS data are not yet mature.

For women who have previously received chemotherapy and have a known genetic or somatic mutation in *BRCA* or other evidence of HRD tumors, olaparib, rucaparib, and niraparib no longer carry approvals as single-agent treatment strategies and should not be used. SOLO3 and ARIEL4 trials that compared PARPis to chemotherapy all demonstrated poorer OS outcomes with

PARPis used as treatment compared with chemotherapy. The QUADRA trial was a single-arm trial, and the FDA indications for all three agents as treatment in this setting have been withdrawn. The updated ASCO guideline on the use of PARPis in ovarian cancer reflects these updates.[124]

Low-Grade Serous Ovarian Cancer

Low-grade serous ovarian cancer (LGSOC) is a less common subtype of ovarian cancer with molecular features different from those of high-grade ovarian cancer.[139] Mutations in *p53* are much less common and are seen in less than 10% of patients. This disease more commonly harbors mutations in genes of the mitogen-activated protein kinase pathway. Abnormalities in *HER2* mutation and expression can also be seen.[140]

LGSOC is typically characterized by an indolent clinical course and a longer 5-year OS compared with HGSOC. Of concern is that this disease is relatively resistant to chemotherapy. Although chemotherapy is considered the standard of care in newly diagnosed disease, hormone therapy is used as a maintenance therapy in this setting and as an active treatment of recurrent disease.[141] A phase 3 randomized trial (NRG-GY019) is currently evaluating the use of hormone therapy alone compared with chemotherapy with carboplatin and paclitaxel followed by maintenance with hormone therapy.[142] In the setting of recurrence, hormone therapy and targeted therapy with MEK inhibitors can be used, although in some cases, chemotherapy can provide periods of disease control. It is recommended that molecular testing of tumors be performed in the setting of recurrent disease to assess the presence of molecular targets for disease-agnostic approved agents.

The combination of the RAF-MEK clamp avutometinib with the FAK inhibitor defactinib was tested in a phase 2 study of patients with recurrent LGSOC, either *KRAS*-mutated or *KRAS* wild-type tumors; mature results were presented at a meeting of the International Gynecologic Cancer Society in 2024.[4] ORR was 31% in all evaluable patients; ORR was 44% in patients with *KRAS*-mutated tumors, and the ORR was 17% in patients with *KRAS* wild-type tumors. A longer PFS of 22 months was seen in patients with *KRAS* mutations, and a PFS of 12.8 months was seen for patients with *KRAS* wild-type tumors. This drug combination received accelerated FDA approval on May 8, 2025. This is the first-ever FDA-approved treatment for LGSOC.

SURVIVORSHIP

Despite standard treatment, women with ovarian cancer are at high risk of cancer relapse. Whether a cancer antigen-125 (CA-125) value is determined as part of follow-up can be individualized, but CA-125 levels are usually followed closely. One randomized trial showed no survival or quality-of-life advantage to routine monitoring of CA-125 for relapse detection, because early treatment based on increasing CA-125 levels in the absence of measurable disease or symptomatic recurrence did not improve survival. Women treated for ovarian cancer may experience physical and emotional adverse effects, even months after treatment has ended. These include fear of recurrence, depression, paclitaxel-induced neuropathy, and fatigue. Prompt evaluation and referral are necessary to help women adjust to survivorship.

KEY POINTS

- Gynecologic oncologists play a key role in the management of patients with ovarian cancer, particularly as it relates to surgical cytoreduction.
- Risk factors for ovarian cancer include genetics, increasing age, nulliparity, family history, early menarche, and late menopause.
- Oral contraceptive use, tubal ligation, breastfeeding, and higher parity are protective.
- For women who are not candidates for surgery because of tumor burden or morbidity, NACT is a reasonable option.
- Women who undergo an optimal cytoreduction should receive six cycles of intravenous platinum and taxane adjuvant therapy. Exceptions to this include women with stage IA or IB disease, grade 1 or 2 cancer, or non-clear-cell histology. Maintenance therapy should be discussed.
- Women whose disease relapses can be stratified as having platinum-sensitive or platinum-resistant disease. This can help in devising treatment strategies, with retreatment using a platinum-based doublet regimen favored for women with platinum-sensitive disease and the use of a nonplatinum single agent, or in combination with bevacizumab, for those with platinum-resistant disease.
- All women should undergo genetic testing for hereditary risk at diagnosis. Patients with stage III or IV high-grade serous or endometrioid tumors are candidates for maintenance with a PARPi after primary therapy. Benefit is most often seen in those with *BRCA1* or *BRCA2* mutation, followed by those with HRD versus HRP tumor status. Alternatively, patients with wild-type *BRCA* status who started with bevacizumab as part of the primary regimen may continue with bevacizumab maintenance.
- PARPis are also indicated as maintenance therapy after a response to retreatment with platinum-based therapy in women with a *BRCA* mutation.

OTHER TUMORS OF THE OVARY

TUMORS OF LOW-MALIGNANT POTENTIAL

Low-malignant-potential tumors of the ovary (also referred to as borderline ovarian tumors) are noninvasive ovarian cancers. The primary approach is surgical, because most women have early-stage disease at diagnosis. Because their outcomes are excellent (ie, 5-year OS rates are more than 95%) and because chemotherapy has no role in this tumor, adjuvant chemotherapy is not recommended in these patients.

SEX CORD–STROMAL CELL TUMORS

Sex cord–stromal tumors are subclassified as granulosa cell tumors and androgen-producing tumors, such as Sertoli-Leydig cell tumors. Adult-type granulosa cell tumors are generally stage I at diagnosis and are classically diagnosed in women between the ages of 40 and 70 years. Most granulosa cell tumors have a somatic mutation in *FOXL2*, which may be useful in diagnosis. Serum inhibin B levels may be elevated in granulosa cell tumors and can be measured as part of the disease evaluation. Treatment for granulosa cell tumors is surgical resection. Adjuvant therapy is not generally recommended. For those whose disease relapses, surgical resection is strongly favored. For those who are not candidates for surgery or who have residual disease after surgery, a platinum-based combination is often administered as treatment. Bevacizumab, as well as hormonal options including leuprolide, also has activity. Sertoli-Leydig tumors commonly present before 40 years. More than 90% of patients have stage I disease at diagnosis and, as with granulosa cell tumors, surgery is the preferred treatment. Platinum-based chemotherapy may be considered for patients with poorly differentiated tumors and for patients with advanced or recurrent disease.

GERM CELL TUMORS

Germ cell tumors of the ovary account for 2% to 3% of ovarian cancers and usually affect adolescent and young women; 50% are dysgerminomas (Table 15-3). Other histologic types include yolk sac tumors (endodermal sinus tumors), teratomas (immature, mature, and monodermal types), embryonal cell tumors, polyembryoma, nongestational choriocarcinomas, and mixed germ cell tumors. These cancers typically can be followed with serum tumor markers (Table 15-4). Dysgerminomas are more likely to be confined to one ovary at diagnosis and carry a favorable prognosis. Adjuvant chemotherapy is typically not administered to patients with stage I dysgerminomas who have undergone complete staging surgery and those with stage I grade 1 immature teratomas because they can generally be cured with surgery. For all others, adjuvant treatment is indicated, which includes three to four cycles of bleomycin, etoposide, and cisplatin based on the risk.[143] For patients with germ cell tumors that relapse after initial chemotherapy, platinum-based chemotherapy can be repeated (as paclitaxel, ifosfamide, and cisplatin or cisplatin, ifosfamide, and either etoposide or vinblastine), and in patients with platinum-resistant tumors, high-dose chemotherapy with stem cell rescue may offer a cure. Given the typically young age of these patients, fertility concerns should be discussed, and appropriate referrals should be made to tertiary care centers where germ cell tumor expertise exists for these patients.

Table 15-3 **Seminal Phase 3 Trials of Maintenance PARP Inhibitors in First-Line Treatment of Advanced Ovarian Cancer**

Characteristic	PAOLA-1	PRIMA	SOLO1	ATHENA
Volunteers	All comers	All comers	*BRCA* mutation associated	All comers
Intervention	Olaparib and bevacizumab	Niraparib	Olaparib	Rucaparib
Comparator	Bevacizumab	Placebo	Placebo	Placebo
HR for PFS (vs comparator)				
All comers	0.59	0.62	NR	0.52
BRCA1/2 positive	0.31	0.4	0.31	0.40
HRD (any)	0.33	0.43	NR	
HRD positive (no *BRCA*)	0.43	0.5	NR	0.47
HRD negative/unknown	0.92	NR	NR	
HRD proficient	NR	0.68	NR	
HRD unknown	0	0.85		

Abbreviations: HR, hazard ratio; HRD, homologous recombination–deficient; NR, results not reported; PFS, progression-free survival.
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Table 15-4 **Serum Tumor Markers in Ovarian Germ Cell Tumors**	
Marker	**Tumor Type**
hCG	Embryonal cell carcinoma
	Choriocarcinoma
	Mixed germ cell tumors
	Dysgerminoma
AFP	Yolk sac tumors
	Embryonal cell carcinoma
	Polyembryoma carcinoma
	Mixed germ cell tumors
	Immature teratomas
LDH	Dysgerminoma

Abbreviations: *AFP*, alpha fetoprotein; *hCG*, human chorionic gonadotropin; *LDH*, lactate dehydrogenase.
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KEY POINTS

- Sex cord–stromal tumors are rare gynecologic malignancies that typically affect younger women.
- The primary treatment of sex cord–stromal tumors is surgical excision. Medical therapy is often reserved for patients with tumors that are not resectable at diagnosis (either initially or at relapse).
- For women with germ cell tumors, systemic treatment with platinum-based chemotherapy is often recommended after surgery. Exceptions to this rule include stage I dysgerminomas after complete staging surgery and stage I grade 1 immature teratomas, because they rarely relapse.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease (GTD) comprises diseases of the human placenta that occur in women of childbearing age. There is a spectrum of malignant potential, from lesions with very low-malignant potential (ie, complete and partial hydatidiform moles) to invasive tumors with metastatic potential (ie, invasive moles) to tumors with an exceedingly high risk of systemic metastases (ie, gestational choriocarcinoma, epithelioid trophoblastic tumors [ETT], and placental type trophoblastic tumors [PSTT]). Despite the risk of metastatic disease, nearly all women with GTD can be cured with the appropriate use of chemotherapy, careful monitoring for treatment response, and surveillance for relapse using sensitive beta human chorionic gonadotropin (hCG) assays. Given the rarity of this disease and the highly curative nature with appropriate treatment, all patients should be referred to a specialized center.[144]

Malignant GTD is also referred to as gestational trophoblastic neoplasia (GTN). All patients with GTN require FIGO staging and WHO risk assessment, with the exception of ETT/PSTT, which is always treated with platinum-based multi-agent chemotherapy regimens. Treatment for GTN is then based on risk classification. For patients requiring chemotherapy, response is evaluated by longitudinal assessment of the quantitative level of serum hCG. Treatment is continued for several cycles after a negative hCG level is achieved. The finding of a plateau or increase in hCG while receiving treatment indicates relapse, and if an increase is observed, all patients require restaging and additional treatment.[145]

SURVIVORSHIP

After hCG levels have been normalized, patients should have their levels rechecked at monthly intervals for 12 months, and physical examination should be performed every 6 to 12 months. Most women who require chemotherapy will resume menses during surveillance. It is strongly recommended that women use contraception to avoid pregnancy during the first year after treatment. Beyond that, patients can be counseled that pregnancy after GTN is typically uncomplicated, although there is a 1% to 2% risk of GTD developing again. Survivorship issues after treatment of GTD should follow the principles in place for patients receiving curative treatment of other solid tumors, because their prognosis is typically excellent.

KEY POINTS

- GTNs are the malignant tumors within the category of GTD. If suspected or diagnosed, all patients require FIGO staging and WHO scoring.
- Medical treatment of GTN is based on the WHO score. Patients with low-risk disease (WHO score: 0-6) have a good prognosis and can be treated with single-agent chemotherapy. Both methotrexate and actinomycin D are used in this situation.

- For patients with high-risk disease, combination chemotherapy is preferred. The most commonly used regimen is EMA/CO, a sequential treatment using etoposide, methotrexate, and actinomycin D during week 1, followed by cyclophosphamide and vincristine during week 2 of a 14-day cycle.
- ETT/PSTT are considered high risk, and treatment is surgery for early-stage disease and multi-agent platinum-containing chemotherapy for more advanced disease or disease with long latency from antecedent pregnancies.
- GTN is a highly curable group of diseases. However, given the rarity of this disease, referral to a specialty center is highly advised.

VULVAR CANCER

Most vulvar cancers are squamous cell carcinomas. There are approximately 6,000 cases annually in the United States, and these occur mostly in older postmenopausal women (median age, 68 years). Risk factors include smoking, vulvar dystrophy, HPV infection, history of cervical cancer, and previous immunodeficiency syndrome. The primary approach to vulvar cancer is surgical. Patients with lymph node involvement are at greater risk of recurrence and death (5-year survival rate, 25%-41%) and are often treated with adjuvant EBRT with or without concomitant sensitizing cisplatin. There may be other indications for adjuvant radiotherapy after surgical excision, particularly if margins are close or positive, but the close observation is also an option, as vulvar recurrences can be re-resected. For patients with locally advanced disease that cannot be completely resected, primary chemoradiation therapy with weekly cisplatin is used; patients who have an excellent clinical response to chemoradiation therapy may subsequently be considered for resection of residual disease.[146] For those who experience a local recurrence, surgical re-excision should be considered. If the disease is unresectable, RT is administered, provided that the patients were not previously treated with RT. For all other patients (including those with metastatic disease), palliative chemotherapy can be used, although there are no prospective data that evaluate the efficacy of systemic chemotherapy for metastatic vulvar cancer. Agents such as cisplatin, carboplatin, paclitaxel, vinorelbine, and erlotinib are reasonable options for patients who are fit for chemotherapy. Pembrolizumab can also be used in this setting for PD-L1-positive disease or MSI-H/dMMR disease, as can cemiplimab (although cemiplimab is not approved in the US).

SURVIVORSHIP

After patients are treated for vulvar cancer, all of them should be observed by using serial physical examinations, including pelvic examinations. The schedule is similar to that for cervical cancer.

KEY POINTS

- Most vulvar cancers are squamous cell carcinomas. The primary treatment is surgical.
- For patients with locally advanced disease that cannot be completely resected, primary chemoradiation therapy with weekly cisplatin is used.

VAGINAL CANCER

Primary cancers arising from the vagina are rare and represent 1% to 2% of vaginal malignancies. Most vaginal carcinomas are squamous cell carcinomas and affect women in the sixth or seventh decade of life. Because of the increase in the incidence of HPV infections, there has been an increase in the number of women diagnosed with vaginal cancer before 40 years. Other risk factors include smoking, early age at first intercourse, multiple lifetime sexual partners, previous sexually transmitted diseases, and a history of cervical cancer. Other vaginal cancer histologic types are extremely rare and include clear-cell carcinoma, melanoma, sarcoma, and adenocarcinoma. It is important to consider metastatic or recurrent disease from other sites (eg, cervix, vulva, ovary, breast, endometrium, or uterus) in the evaluation of a new vaginal lesion, because metastatic disease is more common than primary vaginal carcinoma. There are no prospective studies on which to base treatment recommendations for vaginal carcinomas. As with vulvar cancers, primary treatment is surgical; if surgery is not feasible, treatment using RT with or without concomitant cisplatin is used. Although there are no prospective comparison data showing chemoradiation therapy to be superior to RT alone, many physicians extrapolate the data from randomized trials in cervical cancer and interpret data from retrospective studies in vaginal cancer to support the recommendation of chemoradiation therapy. Patients with unresectable metastatic disease may be offered palliative cytotoxic chemotherapy, but there are no prospective data to establish which agents are active. Once again, incorporation of ICIs in this setting is based on disease site–agnostic approvals and extrapolation from cervical carcinoma treatment paradigms.

SURVIVORSHIP

As with vulvar cancer, after treatment for vaginal cancer, all patients should be observed by using serial physical examinations, including pelvic examinations, following a schedule similar to that for cervical cancer.

KEY POINTS

- Vaginal cancers are typically squamous cell carcinomas and should be considered for definitive surgical resection.
- For patients with a history of another primary cancer, it is important to consider that the vaginal lesion may be metastatic from another site.
- For patients who are not candidates for surgical treatment, RT affords palliation.

HIGH-YIELD TAKEAWAYS

- Surgery by a board-certified gynecologic oncologist has been shown to improve outcomes. The importance of multidisciplinary consultation at the diagnosis stage should not be understated.
- Regardless of stage, histology, age, or family history, all patients with epithelial ovarian cancer need to undergo germline genetic testing.
- For HGSOC, regardless of stage, all patients should receive platinum and taxane chemotherapy.

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

GYNECOLOGIC CANCERS 15

CHAPTER SUMMARY GUIDE

KEY POINTS

- Cervical cancer is a sexually transmitted disease associated with a chronic infection of oncogenic types of HPV. HPV strains 16 and 18 account for 70% of cervical cancers. HPV vaccination represents an opportunity to reduce the worldwide occurrence of cervical cancer. The 9-valent vaccine available in the United States can be administered to people aged 9 to 45 years.
- Although vaccination against HPV is available, cervical cancer screening remains an important part of health maintenance.
- The approach to invasive cervical cancer depends on whether a patient presents with early-stage, locally advanced, or metastatic disease. The FIGO 2018 staging of cervical cancer is defined by tumor characteristics and nodal involvement.
- For people with early-stage cervical cancer, treatment is primarily surgical. New data define tumors at such low risk that radical surgery may be de-escalated. For those who require a radical hysterectomy, the open approach is the current standard of care. Sentinel node dissection seems to be oncologically safe in this population, but more prospective data are needed.
- The indications for adjuvant treatment after radical surgery using RT with or without concomitant chemotherapy depend on final pathologic findings, including tumor grade, presence of lymphovascular invasion, and depth of stromal invasion, as well as whether there are positive surgical margins and parametrial or nodal involvement. Use of adjuvant systemic chemotherapy is not supported in this setting.
- For most people with locally advanced cervical cancer, cisplatin and RT are administered as curative treatment without surgery.
- For patients with FIGO 2018 stages sIB3 to IIB, IIIC1, or IIIC2 without side wall involvement or distal vaginal involvement, NACT should be considered with an OS advantage from the INTERLACE trial.
- For patients with FIGO 2018 stages IIIA, IIIB, IIIC1, or IIIC2 with side wall or distal vaginal involvement or IVA, the addition of pembrolizumab to chemotherapy and radiation therapy can now be considered the standard of care, with the advantage of both PFS and OS. For women with de novo metastatic (stage IVB) or recurrent cervical cancer, first-line treatment consists of platinum-based doublet chemotherapy and bevacizumab, with the addition of pembrolizumab in patients whose tumors express PD-L1.
- The first-line recurrent/metastatic regimen should include paclitaxel, platinum, pembrolizumab, and bevacizumab for patients whose tumor is PD-L1 IHC positive by CPS score or atezolizumab, regardless of PD-L1 status. Strong consideration should be given to including bevacizumab in all settings if not contraindicated for medical reasons.
- Patients whose disease progresses after first-line therapy and who have not previously received pembrolizumab may receive pembrolizumab, provided that their tumor is positive for PD-L1 expression or they are found to have an MSI-H tumor.
- Tisotumab vedotin-tftv or T-DXd (for biomarker-positive tumors) can be considered in patients who have recurrent disease after previous chemotherapy with or without immunotherapy.
- Patients with advanced or recurrent disease should have their tumors tested for HER2 IHC via gastric scoring to assess eligibility to receive T-DXd.
- Endometrial carcinoma is the most common gynecologic cancer in the United States. The major risk factors for endometrioid endometrial carcinoma are those typically associated with increased estrogen exposure. More aggressive subtypes are often estrogen independent and associated with older age and non-white race.
- For people who receive surgical treatment, adjuvant therapeutic options include RT (pelvic irradiation with or without IVRT) and/or chemotherapy, typically with paclitaxel and carboplatin, and RT should be determined using an individualized approach. Postoperative risk factors can help determine who should be offered adjuvant treatment.
- All patients with endometrial adenocarcinoma should undergo MMR and/or MSI assessments. This information will identify patients who are appropriate for treatment with pembrolizumab, dostarlimab-gxly, or durvalumab. It is also important to identify patients with Lynch syndrome. Patients whose tumors show dMMR expression should be referred for genetic screening for Lynch syndrome.
- Pembrolizumab and lenvatinib combination therapy represents an important advance for patients with MMRp recurrent disease after treatment with paclitaxel and carboplatin.

- The combination of chemotherapy and immunotherapy (pembrolizumab or dostarlimab-gxly) is considered the standard of care in the treatment of patients with advanced-stage or recurrent dMMR endometrial cancer. The addition of IO to the chemotherapy backbone may also be appropriate for patients with pMMR tumors; we await mature data from GY018 and RUBY to further determine recommendations.
- Sarcomas are a heterogeneous group of diseases that account for 4% of all uterine cancers.
- Surgery is the mainstay of treatment for uterine sarcoma. There is no evidence that adjuvant treatment improves survival outcomes, and adjuvant treatment is typically not recommended.
- Gynecologic oncologists play a key role in the management of patients with ovarian cancer, particularly as it relates to surgical cytoreduction.
- Risk factors for ovarian cancer include genetics, increasing age, nulliparity, family history, early menarche, and late menopause.
- Oral contraceptive use, tubal ligation, breastfeeding, and higher parity are protective.
- For women who are not candidates for surgery because of tumor burden or morbidity, NACT is a reasonable option.
- Women who undergo an optimal cytoreduction should receive six cycles of intravenous platinum and taxane adjuvant therapy. Exceptions to this include women with stage IA or IB disease, grade 1 or 2 cancer, or non-clear-cell histology. Maintenance therapy should be discussed.
- Women whose disease relapses can be stratified as having platinum-sensitive or platinum-resistant disease. This can help in devising treatment strategies, with retreatment using a platinum-based doublet regimen favored for women with platinum-sensitive disease and the use of a nonplatinum single agent, or in combination with bevacizumab, for those with platinum-resistant disease.
- All women should undergo genetic testing for hereditary risk at diagnosis. Patients with stage III or IV high-grade serous or endometrioid tumors are candidates for maintenance with a PARPi after primary therapy. Benefit is most often seen in those with *BRCA1* or *BRCA2* mutation, followed by those with HRD versus HRP tumor status. Alternatively, patients with wild-type *BRCA* status who started with bevacizumab as part of the primary regimen may continue with bevacizumab maintenance.
- PARPis are also indicated as maintenance therapy after a response to retreatment with platinum-based therapy in women with a *BRCA* mutation.
- Sex cord–stromal tumors are rare gynecologic malignancies that typically affect younger women.
- The primary treatment of sex cord–stromal tumors is surgical excision. Medical therapy is often reserved for patients with tumors that are not resectable at diagnosis (either initially or at relapse).
- For women with germ cell tumors, systemic treatment with platinum-based chemotherapy is often recommended after surgery. Exceptions to this rule include stage I dysgerminomas after complete staging surgery and stage I grade 1 immature teratomas, because they rarely relapse.
- GTNs are the malignant tumors within the category of GTD. If suspected or diagnosed, all patients require FIGO staging and WHO scoring.
- Medical treatment of GTN is based on the WHO score. Patients with low-risk disease (WHO score: 0-6) have a good prognosis and can be treated with single-agent chemotherapy. Both methotrexate and actinomycin D are used in this situation.
- For patients with high-risk disease, combination chemotherapy is preferred. The most commonly used regimen is EMA/CO, a sequential treatment using etoposide, methotrexate, and actinomycin D during week 1, followed by cyclophosphamide and vincristine during week 2 of a 14-day cycle.
- ETT/PSTT are considered high risk, and treatment is surgery for early-stage disease and multi-agent platinum-containing chemotherapy for more advanced disease or disease with long latency from antecedent pregnancies.
- GTN is a highly curable group of diseases. However, given the rarity of this disease, referral to a specialty center is highly advised.
- Most vulvar cancers are squamous cell carcinomas. The primary treatment is surgical.
- For patients with locally advanced disease that cannot be completely resected, primary chemoradiation therapy with weekly cisplatin is used.
- Vaginal cancers are typically squamous cell carcinomas and should be considered for definitive surgical resection.
- For patients with a history of another primary cancer, it is important to consider that the vaginal lesion may be metastatic from another site.
- For patients who are not candidates for surgical treatment, RT affords palliation.

CHAPTER TABLES AND IMAGES

Table 15-1 Clinical Features and Postoperative Surgical and Pathological Risk Factors to Assess the Risk of Recurrence in Cervical Cancer

Intermediate Risk (Sedlis Criteria)	High Risk (Peters Criteria)
LVSI and deep stromal invasion (outer third)	Positive surgical margins
LVSI and middle stromal invasion (one-third) and tumor size ≥2 cm	Detection of pathologically confirmed lymph node metastases
LVSI and superficial stromal invasion (inner third) and tumor size ≥5 cm	Extension into the parametrial tissue
No LVSI but deep or middle stromal invasion and tumor size ≥4 cm	

Abbreviation: LVSI, lymph-vascular space invasion.
Adapted from Fleischmann M, Chatzikonstantinou G, Fokas E, et al. Molecular markers to predict prognosis and treatment response in uterine cervical cancer. *Cancers*. 2021;13(22):5748. doi:10.3390/cancers13225748
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Table 15-2 **Molecular Classification for Endometrial Cancer**

TransPORTEC Classification (TCGA Classification)	Prognosis	Treatment Approach	Other Molecular Features
POLE mut (ultramutated)	>90%; 5 years, OS	Candidate for de-escalation of therapy	
MMRd (hypermutated)	Very good	Checkpoint inhibitor therapy	Can occur as a germline or somatic mutation or through methylation of the *MLH1* gene promoter in the tumor
NSMP (copy number low)	Very good for most patients, but a subset with worse outcomes	May have functional hormonal receptors and can consider hormonal therapy	More likely to have ER/PR. Most common associated mutations: *PTEN*, *ARID 1A*, *PIK3CA*, *CTNNB1*, *PIK3R1*, *KRAS*
*P53*abn (copy number high)	Poor <50%; 5 years, OS	Recommend an aggressive approach with chemotherapy	Can look for HER2 overexpression/amplification, HRD

Abbreviations: abn, abnormal; ER, estrogen receptor; HRD, homologous recombination–deficient; MMRd, mismatch repair–deficient; mut, mutated; NSMP, no specific molecular profile; OS, overall survival; PR, progesterone receptor; TCGA, The Cancer Genome Atlas.
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Table 15-3 **Seminal Phase 3 Trials of Maintenance PARP Inhibitors in First-Line Treatment of Advanced Ovarian Cancer**

Characteristic	PAOLA-1	PRIMA	SOLO1	ATHENA
Volunteers	All comers	All comers	*BRCA* mutation associated	All comers
Intervention	Olaparib and bevacizumab	Niraparib	Olaparib	Rucaparib
Comparator	Bevacizumab	Placebo	Placebo	Placebo
HR for PFS (vs comparator)				
All comers	0.59	0.62	NR	0.52
BRCA1/2 positive	0.31	0.4	0.31	0.40
HRD (any)	0.33	0.43	NR	
HRD positive (no *BRCA*)	0.43	0.5	NR	0.47
HRD negative/unknown	0.92	NR	NR	
HRD proficient	NR	0.68	NR	
HRD unknown	0	0.85		

Abbreviations: HR, hazard ratio; HRD, homologous recombination–deficient; NR, results not reported; PFS, progression-free survival.
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Table 15-4 **Serum Tumor Markers in Ovarian Germ Cell Tumors**

Marker	Tumor Type
hCG	Embryonal cell carcinoma
	Choriocarcinoma
	Mixed germ cell tumors
	Dysgerminoma
AFP	Yolk sac tumors
	Embryonal cell carcinoma
	Polyembryoma carcinoma
	Mixed germ cell tumors
	Immature teratomas
LDH	Dysgerminoma

Abbreviations: *AFP*, alpha fetoprotein; *hCG*, human chorionic gonadotropin; *LDH*, lactate dehydrogenase.
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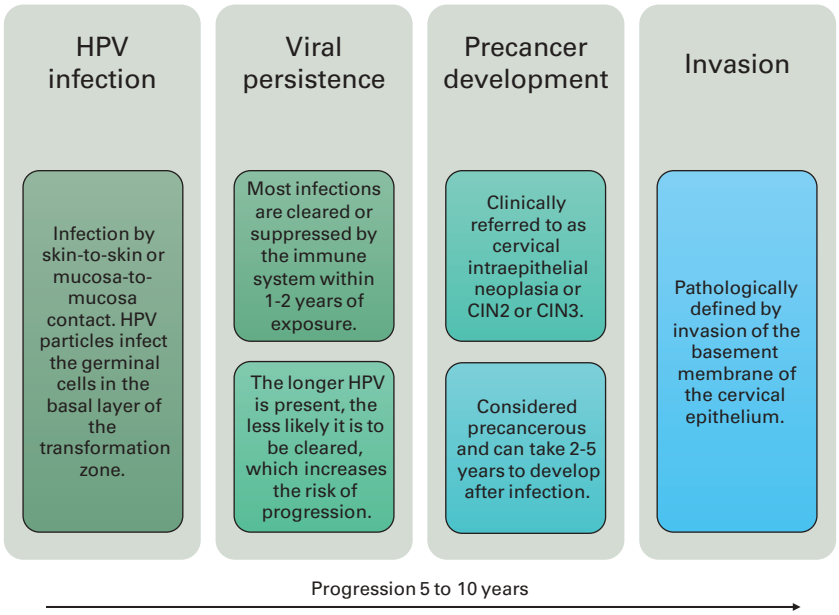
Figure 15-1 Stepwise Progression From HPV Infection to Cervical Carcinoma



Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.
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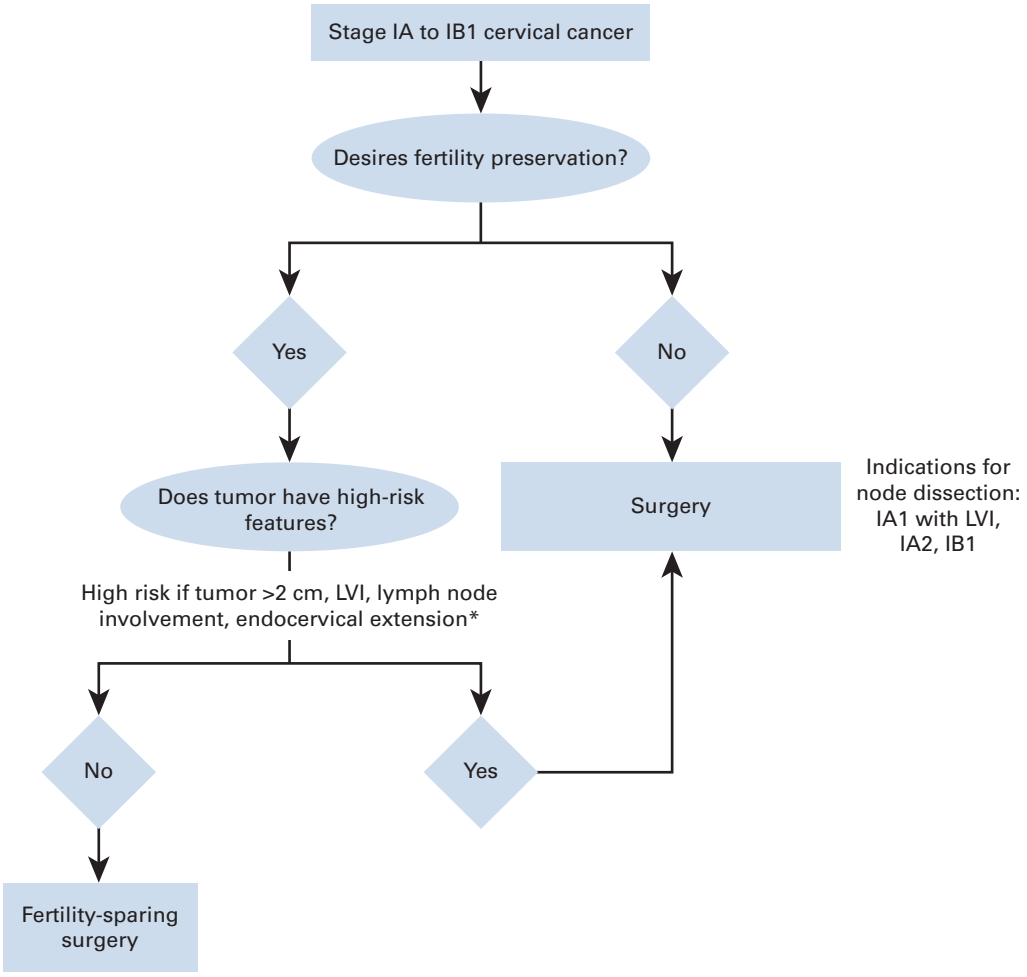
Figure 15-2 Approach to Early-Stage Cervical Cancer



Abbreviation: LVI, lymphovascular invasion.
*In previous American Joint Committee on Cancer staging manuals, nodes were not considered; however, the eighth edition specifically defines nodal involvement as stage III disease.
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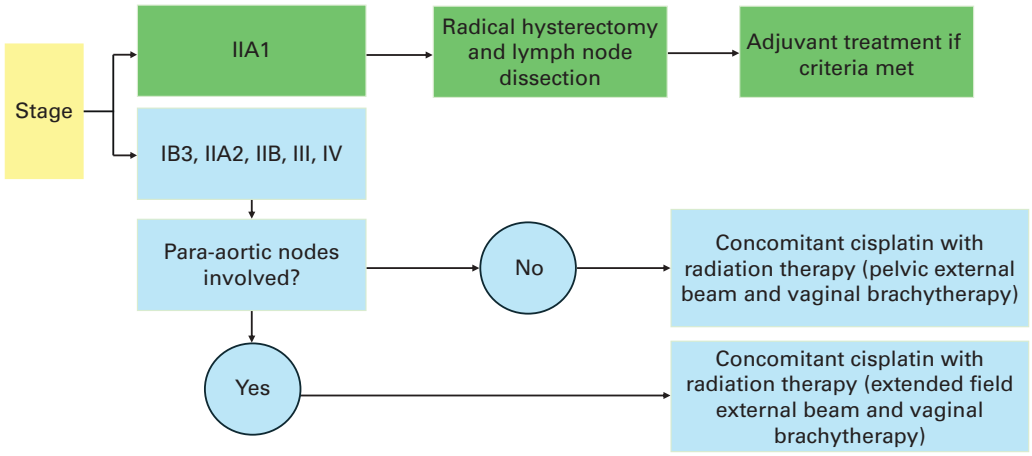
Figure 15-3 Approach to Locally Advanced Cervical Cancer



People with stage IIA1 disease are candidates for primary surgery.
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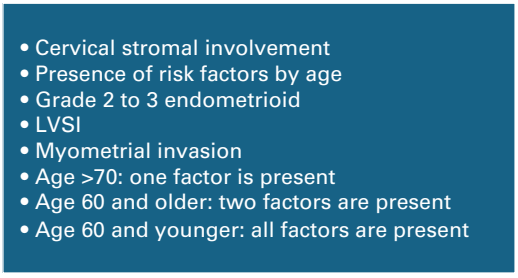
Figure 15-4 High- to Intermediate-Risk Factors in Early-Stage Endometrial Cancer



Abbreviation: LVSI, lymphovascular space invasion.
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Figure 15-5 Protective and Associated Risk Factors for Ovarian Cancer

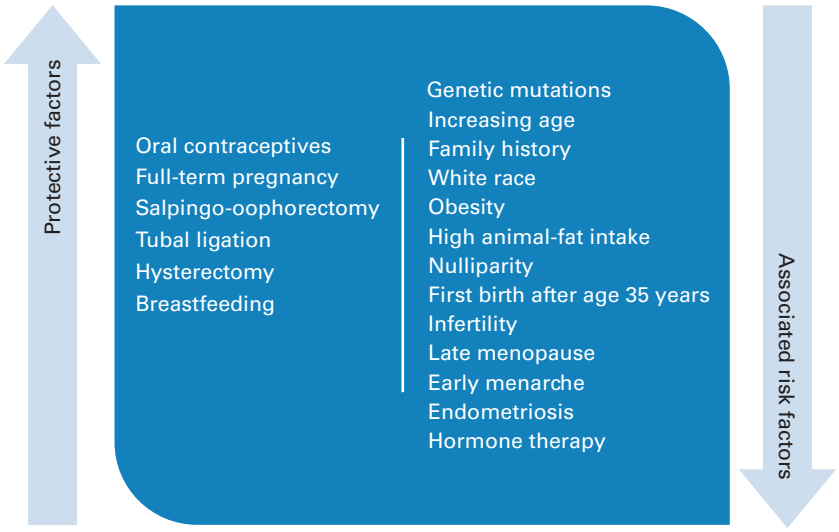

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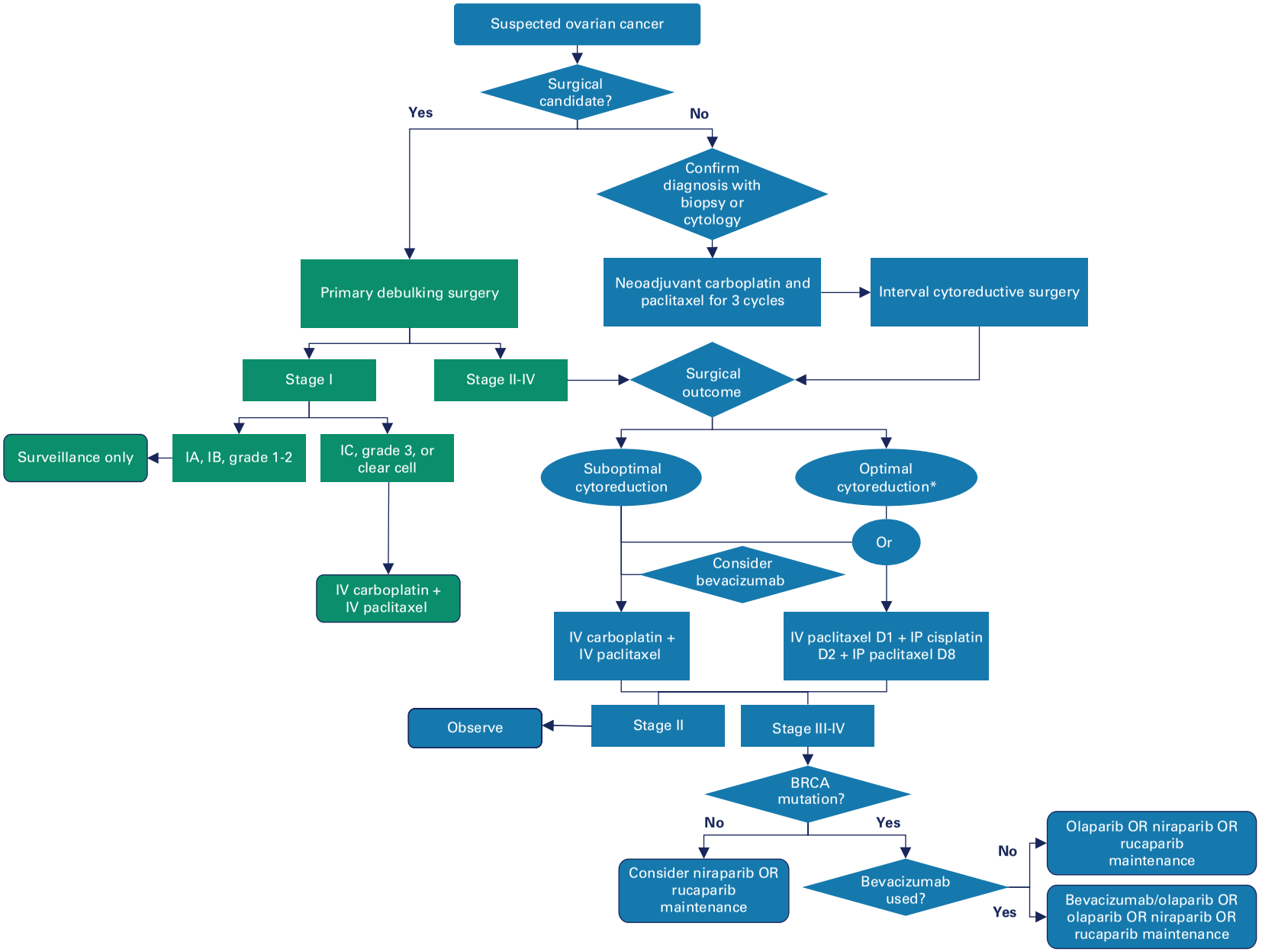
Figure 15-6 Treatment Algorithm for Ovarian Cancer



Abbreviations: IP, intraperitoneal; IV, intravenous.
*In people receiving neoadjuvant chemotherapy and who achieve an optimal cytoreduction at interval surgery, a phase 3 trial in the Netherlands demonstrated that hyperthermic intraperitoneal chemotherapy (HIPEC) delivered at the time of surgery and then followed by IV carboplatin and paclitaxel was associated with a survival advantage compared with IV chemotherapy alone.
Data from NCCN. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 1.2023. Available at: https://www.nccn.org
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MELANOMA AND OTHER SKIN CANCERS

16

Jacob S. Choi, MD, PhD, and Upendra P. Hegde, MD

RECENT UPDATES

- In SWOG S1801, a randomized phase 2 study of adjuvant versus neoadjuvant-adjuvant therapy with pembrolizumab for patients with resectable stage IIIB to IV melanoma, neoadjuvant pembrolizumab followed by adjuvant pembrolizumab significantly improved event-free survival compared with adjuvant pembrolizumab only.[1] Further supporting evidence for neoadjuvant immunotherapy for resectable, macroscopic stage III melanoma was observed in the phase 3 trial (NADINA study),[2] which demonstrated superior event-free survival for neoadjuvant ipilimumab and nivolumab when compared to adjuvant nivolumab therapy alone.
- In a non–randomized phase 2 trial (C-144-01), lifileucel, an autologous tumor-infiltrating lymphocyte (TIL) adoptive cell therapy, demonstrated a meaningful clinical benefit with a durable response in patients with unresectable or metastatic melanoma who were refractory to anti–PD-(L)1 therapy.[3] On the basis of this study, lifileucel was the first TIL therapy approved by the US Food and Drug Administration (FDA) in February 2024 for adult patients with advanced melanoma refractory to PD-1 blockade and BRAF/MEK inhibitor therapy if *BRAF* mutated.
- In a randomized phase 3 trial (C-POST) of adjuvant cemiplimab versus placebo for patients with resected, high-risk cutaneous squamous cell carcinoma, adjuvant cemiplimab achieved significantly longer disease-free survival.[4]

OVERVIEW

This chapter primarily focuses on cutaneous melanoma, with sections dedicated to nonmelanoma skin cancers, including basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (CSCC), and Merkel cell carcinoma (MCC), as well as mucosal melanoma and uveal melanoma.

CUTANEOUS MELANOMA

EPIDEMIOLOGY

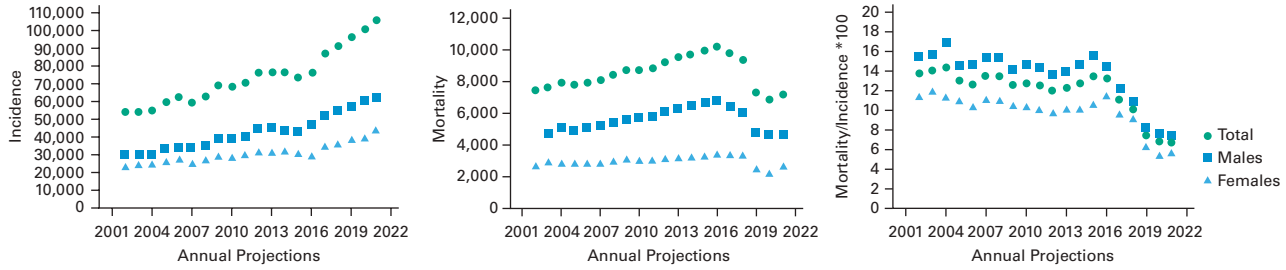
Cutaneous melanoma accounts for 232,100 of all new cancer cases worldwide (1.7%). However, the melanoma-specific mortality rate is only 0.7% of all cancer-related deaths[5] because of screening, early detection, and adequate surgical management of early-stage disease. In the United States, cutaneous melanoma is the fifth most common cancer in men and women[6] with an estimated lifetime risk of developing invasive melanoma in white, Black, and Hispanic people of about 1 in 33, 1 in 1,000, and 1 in 200, respectively. In 2025, about 104,960 new cases of invasive melanoma are expected to be diagnosed in the United States with about 8,430 subjects projected to die from it. At the time of new melanoma diagnosis, 84% of cutaneous melanomas are localized (stages I and II), 8% are regional (stage III), and only 4% are distant metastatic (stage IV). Therefore, most early-stage cutaneous melanomas are highly treatable and do not cause death.

After decades of increase, invasive melanoma incidence rates declined from 2005 to 2018 in patients younger than 50 years (by approximately 1% per year). Incidence rates seem to have stabilized for men aged 50 years or older but are continuing to increase by approximately 1% per year for women aged 50 years or older.[6] Melanoma-specific mortality has dropped steeply from 2015 to 2019 (by approximately 4% per year) because of advances in systemic treatment. Figure 16-1 shows annually projected incidence, mortality, and mortality-to-incidence ratios from American Cancer Society Annual Surveillance and Health Services Research for cutaneous melanoma.

RISK FACTORS

Geography and ethnicity play a role in the risk of cutaneous melanoma development. Australians and New Zealanders have the highest incidence of cutaneous melanoma development (42 per 100,000 person-years for males and 31 per 100,000 person-years

Figure 16-1 Melanoma Incidence, Mortality, and Mortality-to-Incidence Ratios



Data adapted from the American Cancer Society. Annual Cancer Facts and Statistics. Accessed June 26, 2023. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures.html

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for females), followed by Western Europeans (19 per 100,000 person-years for males and females) and North Americans (18 per 100,000 person-years for males and 14 per 100,000 person-years for females).[7] In the United States, approximately one-half (48%) of patients with newly diagnosed cutaneous melanoma are aged 55 to 74 years. In addition, within the United States, non–Hispanic white people have a 25-fold higher risk of cutaneous melanoma development than Black people and an approximately six-fold higher risk than Hispanic white people. Melanoma outcomes are significantly worse for Black Americans. Of all cancers, melanoma exhibits the largest differential in survival rates between Black and white people, with an observed absolute difference of 24% in overall survival. While a higher incidence of acral melanoma has been observed in Black Americans, worse survival outcomes are observed in this population even after accounting for stage and histology, with differences in survival partly due to diagnosis occurring at later stages and less access to health care.[8]

The most important risk factors for cutaneous melanoma are as follows:

- UV light exposure is the most well-characterized risk factor for cutaneous melanoma. A higher number of tanning bed sessions and sunburns increase the risk of development of cutaneous melanoma.
- Various forms of immunosuppression increase the risk of cutaneous melanoma, including immune senescence of older age, malignancy-associated immunosuppression (eg, non–Hodgkin lymphoma and chronic lymphocytic leukemia), virally induced immunosuppression (eg, HIV infection), and iatrogenic immunosuppression as in recipients of a solid organ transplant.
- Skin phenotype, a polygenic trait with various polymorphisms among pigment-associated genes (eg, *MC1R, TYR, TYRP1*, and *ASIP*) regulating the amount and type of melanin present in the skin, has also been associated with cutaneous melanoma development. For example, people with light skin (Fitzpatrick skin types I and II), red hair, and light eye color have an increased risk of cutaneous melanoma.
- Precursor melanoma lesions known to harbor cancer-associated mutations, such as atypical or common nevi (odds ratios [ORs], 17.40 and 1.02, respectively), personal history of melanoma (OR, 12.78), personal history of nonmelanoma skin cancer (relative risk, 4.28), and family history of cutaneous melanoma are also associated with increased risk of cutaneous melanoma.
- Familial atypical mole melanoma syndrome
- Xeroderma pigmentosum (caused by mutations in UV damage repair genes)
- Certain genes bearing germline mutations or gene variants are associated with a higher risk of development of familial melanoma, as discussed in the Familial Melanoma section of this chapter.

KEY POINTS

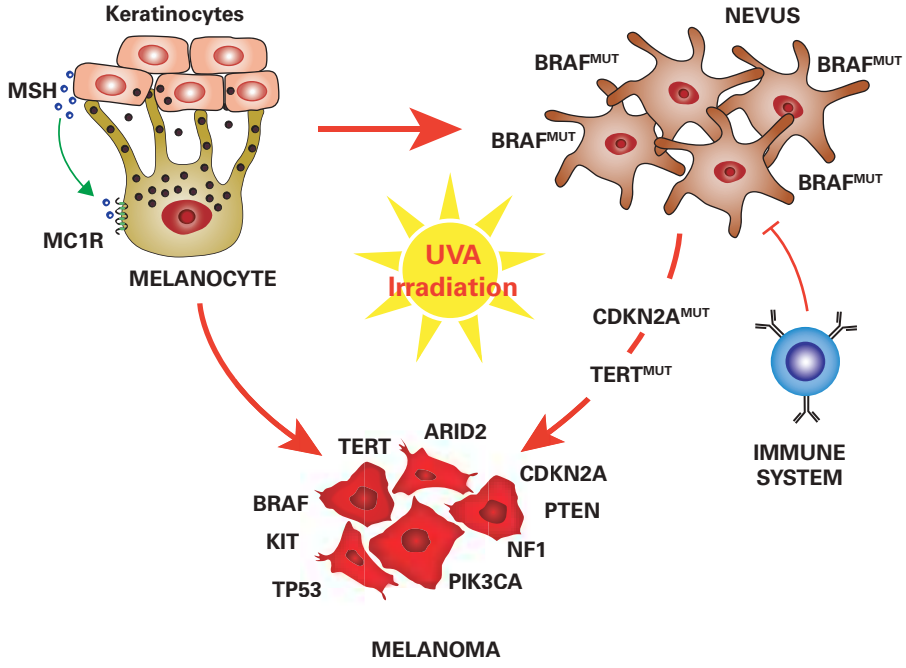
- Cutaneous melanoma accounts for 1.7% of all new cancer diagnoses annually worldwide; 0.7% of all cancer-related deaths are a result of cutaneous melanoma.
- Projected melanoma-specific mortality rates have been declining since 2016; overall incidence rates seem to have stabilized for men after decades of increase while continuing to increase for women.
- In 2025, about 104,960 new cases of invasive melanoma are expected to be diagnosed in the United States with about 8,430 projected deaths.
- Both cutaneous melanoma incidence and mortality rates are higher in men than in women.
- UV light exposure is the most well-characterized risk factor for cutaneous melanoma.
- Australia and New Zealand have the highest incidence of melanoma but relatively better survival outcomes, while Black Americans experience low melanoma incidence but relatively worse survival.

BIOLOGY

Melanocytes are derived from neural crest cells, and they resemble dendritic cells and neurons. Their dendritic shape, along with the vesicles (ie, melanosomes) and molecules they secrete, implies that melanocytes have a prominent function within their microenvironment. Melanoma cells share several common antigens with melanocytes (eg, MAGE family, melan A-MART-1, and GAGE family).[9] Antigens from these shared proteins can stimulate a strong immune response.

Melanin is the principal multiprotein pigment structure within melanosomes and has complex physicochemical properties that protect against UV radiation–induced DNA damage. The primary function of the melanocyte is to respond to UV radiation–induced damage that occurs within keratinocytes by activating the production of melanin. However, the intermediate enzymatic steps leading up to melanin production are pro-oxidative and, therefore, lead to higher levels of oxidative stress and reactive oxygen species within melanocytes. Conditions such as high UV radiation exposure and p16 deficiency, which generate more reactive oxygen species within melanocytes, can lead to melanocyte transformation. High oxidative stress and defects in DNA repair may lead to genomic instability and can account for the high somatic mutation burden seen in cutaneous melanoma compared with other cancers[9,10] (Fig. 16-2).

Figure 16-2 Melanocyte to Melanoma Transition



Abbreviations: ARID2, AT-rich interaction domain 2; BRAF, B-Raf proto-oncogene; CDKN2A, cyclin-dependent kinase inhibitor 2A; KIT, KIT proto-oncogene receptor tyrosine kinase; MC1R, melanocortin 1 receptor; MSH, melanocyte-stimulating hormone; NF1, neurofibromin 1; PTEN, phosphatase and tensin homolog; TERT, telomerase reverse transcriptase; TP53, tumor protein p53.
Reproduced under Creative Commons license. Source: Leonardi et al. Cutaneous melanoma: from pathogenesis to therapy (review). *Int J Oncol.* 2018;52:1071-1080. Fig. 1. PMID: 29532857.

The production of melanin, which is packaged within melanosomes (Fig. 16-2, filled black circles) and secreted to nearby keratinocytes in response to UV radiation, is highly regulated in part through the *MC1R* gene, which activates the master melanocyte transcriptional regulator MITF. In response to UV exposure or skin repair, melanocytes also respond to growth factors (eg, human growth factor, platelet-derived growth factor, and stem cell factor) through growth factor receptors (eg, epidermal growth factor receptor, platelet-derived growth factor receptor, KIT, and vascular epidermal growth factor receptor) by means of a highly regulated process. Growth factor–mediated stimuli signal through the Ras-Raf-Mek-Erk pathway and, to a lesser extent, others, including the phosphatidylinositol 3-kinase-Akt-mammalian target of rapamycin pathway.

Aggressive melanomas have several unique characteristics, including the ability to (1) increase proliferative capacity (eg, *CDKN2A* locus genetic, or epigenetic aberrations), (2) escape senescence (eg, telomerase transcriptase [*TERT*] gene promoter mutations), (3) upregulate autonomous cell growth independently of membrane receptor signaling (eg, *PTEN* loss, *NRASQ61* mutation, *BRAF* V600 mutations, and *NF1* highly functional mutations), (4) exhibit deficiencies in DNA repair and alter melanin production (mutations or polymorphisms in the *MC1R* gene [*MC1R**]), and (5) accumulate epigenetic changes with altered patterns of gene expression that affect immunogenicity (expression of major histocompatibility complex [MHC] class 1, β2-microglobulin) and interaction with cell partners from keratinocytes to melanoma cells themselves (eg, loss of E-cadherin and P-cadherin, upregulation of N-cadherin, MelCam, and αVβ integrins).

Progression from benign nevi to dysplastic nevi, to melanoma in situ, and to invasive melanoma is associated with increases in the numbers of somatic mutations and copy number alterations in melanomas arising from nevi. *BRAF* V600 is the most frequent somatically mutated gene codon identified in benign nevi. More genetic events (eg, NRAS, Q61, mutations in the promoter for *TERT*,[11] and mutations or gene copy number deletions of the *CDKN2A* locus[12]) occur even before invasive melanoma is detected (ie, melanoma in situ). Invasive melanomas are associated with a higher frequency of activating mutations in oncogenes (*BRAF* V600E, *NRAS* Q61, *CDK4* K22, *RB1* Y498, *PPP6C* R264, and *PIK3CA*), genetic aberrations in tumor suppressor genes (*CDKN2A* locus, *PTEN*, and *TP53*), genes encoding for chromatin remodeling complexes (*ARIDs*, *SMARCA4, PBRM1*, and *EZH2*), and increased expression of genes encoding for proteins involved in the mitogen-activated protein kinase (MAPK) signaling pathway.[13]

SPORADIC MELANOMA

The Cancer Genome Atlas project in cutaneous melanoma (N = 333) confirmed the mutational landscape of cutaneous melanoma that had been previously reported (ie, 52% *BRAF* V600 codon, 31% *CDKN2A* gene loss, 28% *RAS* oncogenic mutations, 15% *TP53*, 14% *NF1* mutations, and 13% *CDKN2A* gene locus mutations).[14] Genetic or epigenetic aberrations in melanoma cells have consequences regarding the host immune response. Decreased protein expression of tumor suppressor genes (eg, *PTEN, CDKN2A*, and *APC*/*CTNNB1*) or mutations in distinct oncogenes (eg, *NRAS* Q61) are associated with a decreased incidence of tumor-infiltrating lymphocytes (TILs), poor response to systemic therapies, and worse prognosis. Coexistence of these genetic aberrations, or lack thereof, along with other more frequently mutated genes,[14] may enable more personalized combination therapy strategies in the future. More recently, additional (secondary) driver genes that are somatically mutated and involve the transforming growth factor-β pathway, chromatin remodeling, and histone modification were identified. Interestingly, these new mutation driver genes are rarely shared among the different genetic subgroups (*BRAF* V600 mutated, *NRAS* Q61 mutated, *NF1* mutated, and triple wild type) and may be associated with overall prognosis and response to immune checkpoint blockade.[15]

Of therapeutic relevance, The Cancer Genome Atlas in cutaneous melanoma showed that MEK1/2 proteins are activated in both *BRAF* and *RAS* hotspot mutation subtypes.[9] The high level of activation of MEK1/2 accounts for the clinical benefit with concurrent BRAF and MEK inhibition in *BRAF* V600–mutated melanoma.

The approximate 50% incidence of cutaneous melanoma–bearing TILs (ie, inflamed) at least partially accounts for the high incidence of antitumor responses to immunotherapies.

FAMILIAL MELANOMA

Approximately 10% of patients with cutaneous melanoma have familial melanoma.[16] The *CDKN2A* gene locus is the most well-studied and strongest genetic factor for familial cutaneous melanoma. Carriers of *CDKN2A* germline mutations have a 60-fold higher risk of cutaneous melanoma development, partly because of high penetrance of gene mutations (60%-90%). Carriers of germline mutations in the *BAP1* gene are also at high risk of developing cutaneous melanoma (OR, 17.3), as well as uveal melanoma. Carriers of the *MITF* Mi-E318K variant, the master regulator of melanocyte development, have a higher risk of development of either multiple primary melanomas or renal cell carcinoma. Carriers of the *MC1R* gene variant have a moderate risk of cutaneous melanoma; variants corresponding to red hair color confer a higher risk than non–red hair variants (OR, 2.4 vs 1.2). Furthermore, the number of *MC1R* variants increases the relative risk of cutaneous melanoma in *CDKN2A* mutation carriers. Mutations in the telomere-related genes such as POT1, shelterin complex genes, and TERT have been identified in families with clusters of cutaneous melanomas.

Patients with multiple primary melanomas, a personal history of melanoma and another noncutaneous cancer, a family history of at least two relatives with cutaneous melanoma, a family history of cancers, and/or early age (35 years or younger) at onset should be offered genetic counseling, given a recent study showing that germline genetic testing in these individuals resulted in the diagnosis of clinically impactful hereditary cancer predisposition for 15% of patients who met these criteria. Emerging evidence suggests that more common cancer predisposition genes involving DNA repair genes, such as *BRCA1/2* and Lynch syndrome genes, are also involved in hereditary melanoma.[17]

KEY POINTS

- Familial cutaneous melanomas represent approximately 10% of melanomas.
- Germline mutations in the *CDKN2A* and *BAP1* gene locus are associated with an increased risk of developing cutaneous and uveal melanoma.
- All patients with melanoma and a personal history or family history of cancer should be referred to genetics.
- *BRAF* V600E is the most frequent somatic mutation in sporadic melanomas, followed by mutations in *NRAS*, *CDKN2A*, *TERT*, and *NF1*.

SCREENING AND PREVENTION

The broad availability of smartphones with high-resolution cameras is changing the early evaluation of atypical, pigmented skin lesions, with technology now supplementing, but not replacing, routine skin screening. The question of whether skin examination

for cutaneous melanoma detection increases melanoma-specific overall survival has been investigated. The SCREEN project was a massive population-based skin cancer screening program conducted in the German state of Schleswig-Holstein. More than 1,700 physicians and more than 360,000 participants older than 20 years participated for the duration of the intervention (2003-2004). In the years before the start of the project, the feasibility of physician training, screening test performance, and documentation of screening examinations was evaluated. The mortality rate before (1998-2000) and after (2007-2008) the intervention was calculated for Schleswig-Holstein, three neighboring German states (Hamburg, Mecklenburg-Vorpommern, Lower Saxony), and the neighboring country of Denmark. Schleswig-Holstein, the only state where the intervention was applied, was the only state with an almost 50% decline in melanoma-specific mortality in the period after intervention.[18] Atypical nevi, a personal history of melanoma, and multiple (≥40) nevi were associated with an increased risk of melanoma detection. A screening strategy that focused on only three risk factors (age ≥35 years, family history, and congenital nevi) reduced the number of people needed to screen to detect one melanoma from the originally screened 360,000 participants to 178 participants.[19]

Apart from early detection, sunscreens, antioxidants, anti-inflammatory drugs, vitamins, and supplements have been considered for chemoprevention in cutaneous melanoma.[20] Only regular sunscreen use has the highest level of clinical evidence for melanoma prevention. A prospective study in Queensland, Australia, of 1,621 participants who were randomly assigned to daily use of sunscreen versus any other sun protective factor at the discretion of investigators showed that sunscreen use significantly reduced the development of invasive melanomas (hazard ratio [HR], 0.27; 95% CI, 0.08-0.97).[21]

KEY POINTS

- Population-based skin cancer screening programs have identified risk factors that can render melanoma screening cost efficient to select high-risk patients.
- The use of sunscreens has the highest level of clinical evidence for melanoma prevention.

CLINICAL PRESENTATION

STAGING SYSTEM

Stage at diagnosis, as defined in the American Joint Committee on Cancer 2018 staging system, is the most significant predictor of overall survival.[22] The Surveillance, Epidemiology, and End Results (SEER) program 5-year overall survival rates for localized (stages I and II), regional (stage III), and distant metastatic melanoma (stage IV) diagnosed between 2009 and 2015 were 99%, 65%, and 25%, respectively. The current eighth edition of the American Joint Committee on Cancer staging system is distinguished from the previous seventh edition because it

- Retains the major histopathologic parameters of the primary melanoma (Breslow depth of invasion for thin [T1], intermediate [T2, T3], or thick [T4] melanoma; ulceration) and regional lymph node status (N) staging (number of metastasis-containing regional lymph nodes; the presence of satellite, microsatellite, or in-transit lesions)
- Simplifies reporting of Breslow depth of invasion value to the nearest 0.1 mm
- Reclassifies thin melanomas (T1a and T1b) by Breslow depth of invasion of either less than 0.8 mm versus 0.8 mm or greater and the presence or absence of ulceration (T1a melanomas have <0.8 mm Breslow depth of invasion and are also nonulcerated)
- Simplifies the terminology of locoregional (satellite and in-transit disease) or regional lymph node involvement (clinically occult vs clinically detected)
- Introduces the fourth substage for stage III, identified by D
- Refines distant metastatic disease (M) by introducing a D substage (central nervous system metastases) and takes into consideration biochemical changes (by elevated serum lactate dehydrogenase [LDH]) across each M1 subcategory designated as "[0]" for not elevated LDH and "[1]" for elevated LDH)

The eighth edition of the American Joint Committee on Cancer staging system provides more accurate prognostic information for patients with stage III melanoma without any significant loss of prognostic value for stages I and II.[23]

OTHER PROGNOSTIC FACTORS

Younger women, white patients, and immunocompetent patients have an overall better prognosis than older men, Black patients, and patients with immunosuppression, respectively. Several histopathologic features not included in the 2018 American Joint Committee on Cancer staging system remain important prognostic factors, such as the mitotic rate of the primary cutaneous melanoma and density of TILs, whether measured in the primary cutaneous melanoma, regional lymph nodes,[9] or distant metastatic sites.

An increasing number of molecular assays have been used to evaluate the prognosis of patients with stage I to II cutaneous melanoma. However, they still lack validation in prospective studies. DecisionDx-Melanoma (Castle Biosciences) is based on a

retrospective analysis of RNA extracted from archival formalin-fixed paraffin-embedded primary melanoma tissue and tested for a 31-gene expression profiling signature. This test categorizes patient risk as class 1 (A or B) or 2 (A or B). In a retrospective analysis of 259 patients with cutaneous melanoma who had negative sentinel lymph node (SLN) mapping, those whose disease was classified as class 2 by the DecisionDx-Melanoma test had worse relapse-free survival and overall survival than patients in any other class. In patients with stage I or IIA cutaneous melanoma, the 31-gene expression test predicted relapse-free survival independently of Breslow thickness. However, Breslow thickness and SLN status remain the stronger prognostic indicators.[24] Therefore, the clinical utility of the DecisionDx-Melanoma test is not yet clear, and its application in stage I to II melanoma is not considered routine at this time.

PATIENT EVALUATION

Clinical

The initial evaluation of a patient with a recent diagnosis of cutaneous melanoma involves obtaining a thorough history and performing a physical examination. To investigate the need for further genetic risk evaluation, the patient history should document a family history of melanoma or other noncutaneous cancers (eg, breast cancer, prostate cancer, renal cell carcinoma, and mesothelioma). A personal history of (1) multiple cutaneous melanomas (two or more); (2) regressing pigmented skin lesions, raising the possibility of melanoma of unknown primary; or (3) nonmelanoma skin cancers should also be documented. Younger patients diagnosed with cutaneous melanoma have a higher incidence of *BRAF* V600 somatic mutations.

Constitutional symptoms can be a sign of advanced melanoma, and new-onset headaches or other neurologic symptoms can be a sign of central nervous system metastases.[25] New-onset pulmonary or neurologic symptoms should elicit radiologic workup in patients with a history of early-stage melanoma.[25] The physical examination can be remarkable for the presence of chronically sun-damaged skin (eg, actinic keratosis, solar elastosis, and lentigines) or other nonmelanoma skin cancers. Alternatively, multiple atypical, pigmented lesions suggest that cutaneous melanoma may have arisen from nevi. Blood tests have little prognostic significance for patients with stage I to III melanoma. However, high white blood cell count, neutrophilia, monocytosis, low absolute lymphocyte count, and elevated serum LDH have been associated with worse prognosis in patients with stage IV melanoma.[22]

Surgical Staging

A patient with a recently diagnosed primary cutaneous melanoma should undergo wide excision and, when indicated, concurrent SLN mapping and biopsy. Wide excision with 1- to 2-cm margins decreases the incidence of a local recurrence.[26] SLN mapping is the recommended method to complete the regional surgical staging by assessing the incidence of regional lymph node metastases for patients at risk of regional nodal involvement (≥T1b). SLN biopsy should be offered to all patients with at least T2 lesions. SLN biopsy could also be considered for patients with thinner lesions, in particular, young patients whose diseases also bear aggressive histopathologic features (eg, high mitotic rate and the presence of ulceration).[27] In experienced hands, the use of standardized probes (eg, technetium-99 sulfur colloid and intraoperative vital blue dye around the primary tumor) results in an overall SLN identification rate of 95% and low morbidity. SLN status is an independent prognostic factor for overall survival. At a median follow-up of 20 months, 15% of patients with positive SLNs who did not undergo complete lymph node dissection had a nodal recurrence. MSLT-I was a prospective phase 3 study in which 2001 patients with at least T2 cutaneous melanoma, but no patients with clinically detectable nodal disease, were enrolled. Patients were randomly assigned to undergo immediate complete lymph node dissection if SLN biopsy was positive versus nodal observation at the time of study entry. MSLT-I showed no difference in the 10-year overall survival rate.[28] These data suggest that SLN mapping provides only prognostic information, and control of regional clinically undetectable disease may not have an effect on overall survival.

Radiographic Staging

Radiographic staging in cutaneous melanoma has considerably lower sensitivity and specificity compared with SLN mapping because it cannot detect microscopic (ie, ≤3 mm) lymph node involvement. Cross-sectional imaging should be considered for the initial staging of higher-risk patients (stage ≥IIB).[29]

SURVEILLANCE AFTER ORIGINAL DIAGNOSIS AND THERAPY

Any surveillance strategy should consider patterns of recurrence after resection of the primary lesion and/or nodal staging or resection. Approximately one-half of recurrences are within the regional lymph node bed, 20% are locoregional, and 30% involve distant metastases. Most recurrences occur within the first 2 years of cutaneous melanoma diagnosis, with a decreasing risk between the second and fourth years. All patients should undergo follow-up with a medical history and physical examination, including skin and lymph node examinations every 3 to 6 months for the first 3 to 5 years and then annually for their lifetime. Patients should have skin screening for additional primary melanomas and other nonmelanoma skin cancers at least annually for their lifetime.

Radiographic cross-sectional imaging with either whole-body PET/CT scans or CT scans and MRI of the brain is recommended for patients with stage III disease to screen for locoregional and distant metastases and can be considered in patients with high-risk stage II disease (stages IIB and IIC) as well.

KEY POINTS

- Clinical evaluation of a patient with newly diagnosed cutaneous melanoma should include a full medical history, including family and personal histories of melanoma and other cancers.
- Physical examination should include skin and lymph node examinations every 3 to 6 months for the first 3 to 5 years and then annually for their lifetime.
- Surgical management includes wide local excision concurrent with SLN biopsy when indicated. SLN status is an independent prognostic factor for overall survival.

SURGICAL TREATMENT OF TIS TO T4 (STAGE 0-II) MELANOMA

The standard for definitive treatment of localized melanoma is complete removal with adequate margins (Table 16-1). Several large randomized controlled trials have established optimal wide-excision margins for Tis to T4 melanoma. Surgical margins are clinically defined from the edges of the primary tumor, or primary melanoma scar, to the edges of the gross resection specimen and are not based on the histopathologic margins reported by the pathologist. Fewer standardized criteria are available regarding the optimal depth of wide excision. A phase 3 randomized trial (MelMarT-II) of 1-cm versus 2-cm margin of excision in patients with stage II (Breslow thickness >2 mm or 1-2 mm with ulceration) primary cutaneous melanoma is currently ongoing to evaluate for difference in risk of melanoma recurrence (ClinicalTrials.gov identifier NCT03860883).

Table 16-1 Recommended Wide and Deep Excision Margins for Tis to T4 Melanoma

Breslow Depth of Invasion (mm)	Wide Surgical Margin (cm)	Deep Surgical Margin
In situ	0.5-1	Excised to the depth within the adipose layer
≤1.0	1	
>1.0 and ≤2.0	1-2	Excised to the depth immediately above muscle fascia
>2.0	2	

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KEY POINT

- Melanoma with deep Breslow thickness (ie, ≥4.0 mm) and ulceration, even without positive regional lymph nodes (stage IIC), has a high risk of recurrence.

ROLE OF SURGERY

CLINICALLY OCCULT (NON-PALPABLE) REGIONAL LYMPH NODE METASTASES

On the basis of the results of the Multicenter Selective lymphadenectomy Trial (MSLT-II) and the German Dermatologic Cooperative Oncology Group Sentinel Lymph Node Trial (DeCOG-SLT), completion lymph node dissection is no longer considered the standard recommended treatment of all patients with positive SLN biopsy specimens (ie, nonclinically detected).

MSLT-II, a phase 3 randomized study (N = 1,939 patients), aimed to address the question of whether immediate completion lymph node dissection versus surveillance ultrasonograms of the affected nodal basin after positive SLN mapping in patients without clinical evidence of regional lymphadenopathy increased the rate of regional disease control and/or prolonged overall survival. This was an important question because complete lymph node dissection could identify additional positive lymph nodes (21%) after positive SLN mapping at the cost of surgical morbidities (eg, pain, lymphedema, seroma, and infection). Although regional disease control was improved with complete lymphadenectomy in patients with SLN-positive disease, melanoma-specific overall survival was not prolonged in this group.[30]

The German DeCOG-SLT study also reported a lack of an overall survival benefit of complete lymphadenectomy in patients with occult reginal lymph node metastases in a phase 3 multicenter randomized trial that included 483 patients.[31] Lack of an overall survival benefit after control of regional disease implies that a patient's outcome is not solely influenced by eradication of the regional clones. Regional nodal disease might not be the launchpad for the development of distant metastatic disease, as was previously thought.

In cutaneous melanoma patients with clinically occult, SLN-positive stage III disease, the new-generation FDA-approved adjuvant therapy with anti–PD-1 agents (pembrolizumab and nivolumab) and BRAF-directed treatment in *BRAF* mutation–positive

melanoma has improved relapse-free survival and shown trend toward overall survival with longer follow-up. Complete lymph node dissection can be discussed and offered to select patients with positive SLNs. ASCO guidelines recommend a balanced discussion about the risks and benefits of foregoing complete lymph node dissection in favor of watchful observation with serial nodal ultrasonograms.[27] Many centers have primarily adopted the observation approach, given the lack of an overall survival benefit with complete lymph node dissection, followed by adjuvant anti–PD-1 therapy. Also important to note is that staging will be influenced by the decision to avoid complete lymph node dissection in these patients.

CLINICALLY DETECTED REGIONAL LYMPH NODE METASTASES

Therapeutic Lymph Node Dissection and Role of Adjuvant Radiation Therapy

Therapeutic lymph node dissection (TLND; level I-III dissection in the axilla, superficial groin dissection in the groin, and level II-V radical lymph node dissection in the neck) is the historical treatment standard for patients with clinically detected stage III melanoma and no radiographic evidence of distant metastases because it offers the best opportunity for locoregional control. However, patients with sizable nodal tumor burden or extracapsular nodal extension of tumor still have a high risk of regional and distant relapse after complete lymph node dissection.

The role of adjuvant radiation therapy after complete lymph node dissection for patients presenting with palpable lymph node involvement was examined in the phase 3 multicenter ANZMTG 01.02/TROG 02.01 trial, in which patients were randomly assigned to regional adjuvant radiation therapy versus observation. Compared with those receiving observation only, radiation therapy–treated patients had a significantly lower incidence of lymph node in-field relapse (HR, 0.52; 95% CI, 0.31-0.88).[32] Of note, however, this trial did not demonstrate an overall survival benefit (HR, 1.27; 95% CI, 0.89-1.79; $P = .21$) or relapse-free survival benefit (HR, 0.89; 95% CI, 0.65-1.22; $P = .51$) for the adjuvant radiation therapy group.

Recent SWOG 1801[1] and NADINA[2] trials provide emerging data for consideration of neoadjuvant treatment approaches typically with either anti–PD-1 monotherapy or a preferred neoadjuvant combination of anti–PD-1 and anti–CTLA-4 checkpoint blockade, while other combined regimens incorporating LAG-3 inhibitors or BRAF-directed treatment in *BRAF* mutation–positive melanoma have also shown benefit prior to lymph node dissection (see "Neoadjuvant Therapy" section).

Although adjuvant radiation therapy to the locoregional or regional lymph node site may no longer be standard for all patients in this era of immune checkpoint inhibitors and BRAF-directed treatment in *BRAF*-mutated melanoma patients, it can be considered in select patients at high risk of local or regional recurrence identified on index lymph node specimen or lymphadenectomy specimen following neoadjuvant treatment such as no pathologic response or minimal pathologic response. Additionally, patients with high-risk features such as metastases in multiple lymph nodes, matted lymph nodes, or the presence of extracapsular extension of the tumor should also be considered for adjuvant radiation.

Isolated Limb Infusion and Perfusion

Therapeutic isolated limb perfusion (ILP) and isolated limb infusion (ILI) are surgical techniques that achieve temporal regional vascular isolation to enable regional delivery to the tumor of chemotherapeutic agents at doses many-fold higher than those administered systemically without causing irreversible organ and bone marrow toxicity.

ILP involves hyperthermia and oxygenation of the circulation that potentiates tumoricidal effects of chemotherapeutic agents.

ILI is a low-flow ILP procedure performed via percutaneous catheters without oxygenation.

Patients with advanced locoregional cutaneous melanoma involving an extremity are eligible. The most frequently used cytotoxic agent is melphalan (10 mg/L in lower-limb tissue perfused and 13 mg/L in upper-limb tissue perfused), and the usual perfused time is 60 to 90 minutes. Local complications include myotoxicity, neuropathy, erythema, edema, blistering, and desquamation. Systemic complications depend on the level of systemic drug leakage and include nausea, vomiting, and bone marrow toxicity. Other agents used include Thiotepa, Mechlorethamine with or without tumor necrosis factor alpha, and Interferon gamma. Experienced academic institutions achieve high overall response rates (81% for heated ILP and 43% for ILI) and low mortality rates.[33] The procedure requires a hospital stay. Both these procedures may help shrink the tumor and improve patient's quality of life by controlling local pain that may not be possible with surgery. An overall survival benefit was not demonstrated in clinical trials that were largely conducted before the modern era of targeted therapies and immune checkpoint inhibitors. Although ILI use has largely fallen out of favor, it can be a useful option in select patients.[33]

KEY POINTS

- Completion lymph node dissection did not improve overall survival after a positive SLN biopsy specimen in two randomized clinical trials and is not considered standard of care for all patients with clinically occult stage III melanoma. Completion lymph node dissection decreases the incidence of regional lymph node recurrence and can be considered in select patients.
- For patients with clinical stage III melanoma (clinically palpable regional lymph nodes), neoadjuvant treatment approaches preferably containing combination immunotherapy is recommended. Total lymph node dissection with or without external

radiation therapy to the lymph node basin should be reserved for patients who are refractory to neoadjuvant treatment (ie, no pathologic response or minimal pathologic response) of the regional nodal basin.

- Although adjuvant radiation decreased the risk of in-field recurrence, there was no significant decrease in relapse-free survival or overall survival. Adjuvant radiation can be considered for select patients with a high risk for locoregional recurrence.

ROLE OF SYSTEMIC THERAPY IN THE ADJUVANT SETTING

ADJUVANT THERAPY FOR STAGE II MELANOMA

Historically, systemic adjuvant therapy for completely resected stage IIB/IIC disease consisted of high-dose interferon alpha-2b (IFN-alpha-2b). Given the frequent dosing schedule and high burden of toxicities in administering adjuvant high-dose IFN-alpha-2b, as well as the unclear overall survival benefit in stage IIB/IIC melanoma in the era of more effective and less toxic immune checkpoint inhibitors for stage III/IV melanoma, high-dose IFN-alpha-2b is no longer used in patients with high-risk stage II melanoma.

There are recently published phase 3 studies regarding the use of adjuvant immune checkpoint inhibitors (anti–PD-1 monotherapy) in patients with stage IIB/IIC melanoma that led to FDA approvals: one with pembrolizumab and the other with nivolumab (KEYNOTE-716 and CheckMate 76K, respectively).

The KEYNOTE-716 phase 3 trial randomly assigned 976 patients with completely resected stage IIB/IIC melanoma to pembrolizumab or placebo for up to 1 year. At a median follow-up of 20.9 months, patients receiving pembrolizumab had significantly prolonged relapse-free survival compared with patients receiving placebo (HR, 0.61; 95% CI, 0.45-0.82; median not reached for both).[34] This trial led to FDA approval in December 2021 of pembrolizumab as adjuvant treatment of adult and pediatric (age >12 years) patients with completely resected stage IIB/IIC melanoma. Longer-term follow-up at a median follow-up of 27.4 months showed that adjuvant pembrolizumab also significantly improved distant metastasis–free survival (HR, 0.64; 95% CI, 0.47-0.88; $P = .0029$) versus placebo.[35] Treatment-related grade 3 or worse toxicities were experienced by 17.2% of patients in the pembrolizumab arm, and immune-mediated adverse events were experienced by 37.7%.

Nivolumab also earned FDA approval for adjuvant therapy in resected, stage IIB/IIC melanoma based on the evidence of CheckMate 76K, which demonstrated superior relapse-free survival of nivolumab when compared with placebo (HR, 0.42: 95% CI, 0.30-0.59).[36] Treatment-related grade 3 or 4 adverse events occurred in 10.3% of patients who received nivolumab, including one treatment-related death (0.2%). The decision to pursue adjuvant therapy in a population with a high surgical cure rate should include a careful discussion of potential risks versus benefits, particularly when there is not yet evidence of an overall survival benefit (Fig. 16-3).

ADJUVANT THERAPY FOR STAGE III MELANOMA

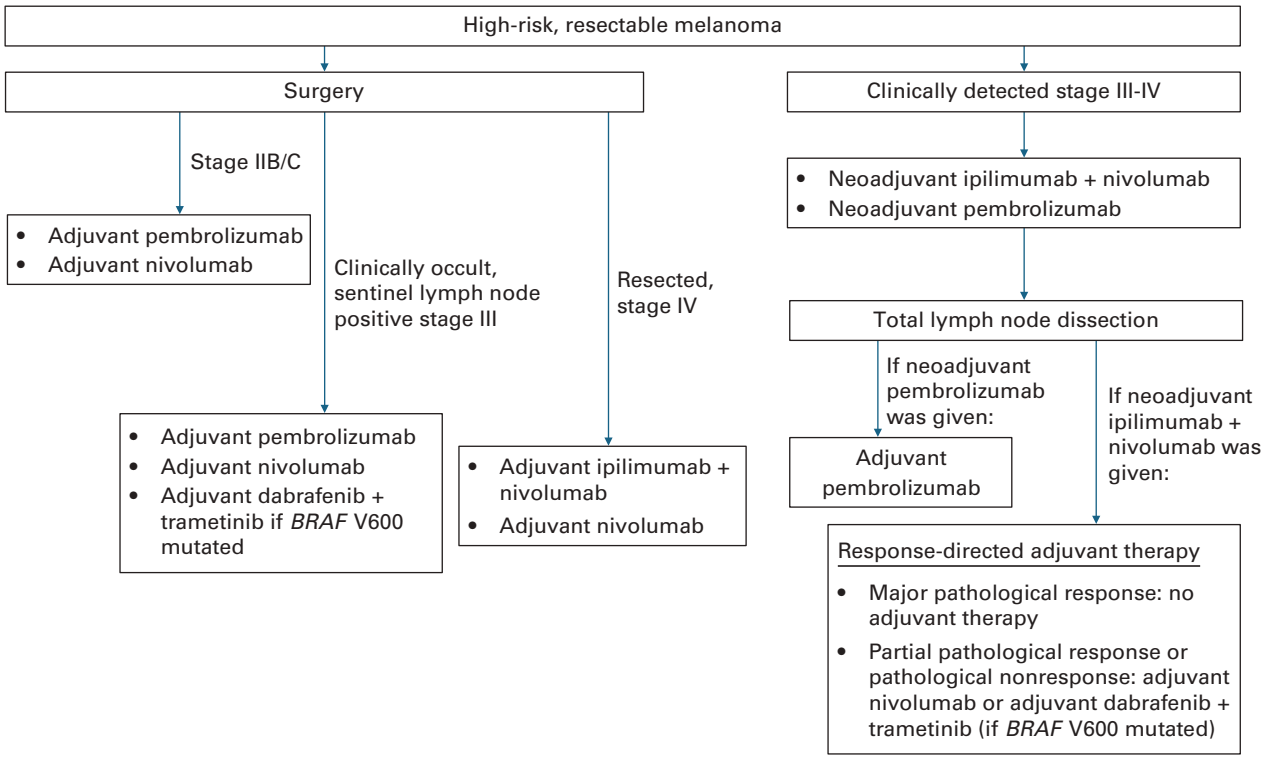
Seminal studies have also changed standard-of-care treatments for patients with stage III melanoma. All FDA-approved adjuvant therapies are administered for up to 1 year. Experimental drugs in most adjuvant clinical trials were tested in patients with stage III melanoma and compared against placebo, with the exceptions of CheckMate 238 and SWOG 1404. CheckMate 238 compared adjuvant nivolumab to adjuvant ipilimumab in patients with resected stage III and IV melanoma. SWOG 1404 compared pembrolizumab against either ipilimumab or high-dose IFN-alpha-2b in the adjuvant setting.[37,38]

Adjuvant pembrolizumab (200 mg administered intravenously every 3 weeks for 18 doses or 400 mg every 6 weeks) was approved based on KEYNOTE-054 showing relapsed-free survival benefit compared with placebo (HR, 0.56; 95% CI, 0.47-0.68). Similarly, adjuvant nivolumab (240 mg administered intravenously every 2 weeks or 480 mg every 4 weeks) gained FDA approval based on improved relapse-free survival compared with adjuvant ipilimumab (high dose; 10 mg/kg administered intravenously every 3 weeks for up to four doses and then every 12 weeks) for up to 1 year observed in CheckMate 238 (HR, 0.65; 95% CI, 0.51-0.83) (Fig. 16-3). With a minimum follow-up of 4 years (CheckMate 238), no overall survival benefit was observed in favor of nivolumab over ipilimumab.[39,40] Although a significant improvement in recurrence-free survival was observed with adjuvant pembrolizumab in SWOG 1404 (HR, 0.77; 95% CI, 0.59-0.99), there was again no significant difference in the primary endpoint of overall survival between pembrolizumab and adjuvant high-dose IFN-alpha-2b/ipilimumab at a median follow-up of 47.5 months.[39] It is unclear whether with longer follow-up in KEYNOTE-054, overall survival will be significantly improved by pembrolizumab (vs placebo).

If the longer follow-up studies in patients with anti–PD-1 adjuvant therapy show no overall survival benefit, such a finding might imply that patients could be equally effectively treated at the time disease recurs rather than with adjuvant therapy.

BRAF-directed adjuvant therapy of *BRAF*-mutated stage III cutaneous melanoma: In the COMBI-AD clinical trial, adjuvant dabrafenib (150 mg administered orally twice daily), a BRAF inhibitor, and trametinib (2 mg administered orally once daily), a MEK inhibitor, showed improved relapse-free survival compared with placebo in patients with stage III melanoma, leading to the FDA approval of this combination for patients with completely resected stage III *BRAF* V600–mutated melanoma (Fig. 16-3). The COMBI-AD trial had a minimum follow-up duration of 59 months and relapse-free survival HR, 0.51 (95% CI, 0.42-0.61).[41] As in studies of adjuvant immunotherapy, an overall survival difference was not observed to be statistically significant in the final

Figure 16-3 Perioperative Treatment Options for High-Risk, Resectable Melanoma



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10-year analysis of adjuvant BRAF/MEK inhibition in comparison with placebo (median follow-up 8.33 years; HR for death, 0.80; 95% CI, 0.62-1.01; $P = .06$).[42]

Adjuvant ipilimumab and nivolumab (attenuated dosing schedule) for cutaneous melanoma in stage IIIB-IIID compared with nivolumab monotherapy. In a large phase 3 randomized study (CheckMate 915) of resected stage IIIB to IIID melanoma, combination immunotherapy with attenuated dosing schedule of ipilimumab at 1 mg/kg every 6 weeks and nivolumab at 480 mg every 4 weeks versus nivolumab monotherapy at 480 mg every 4 weeks did not significantly prolong relapse-free survival.[43]

In patients with surgically resected stage IV melanoma without any evidence of disease, the role of systemic immunotherapy versus watchful observation was evaluated in IMMUNED, a phase 2, placebo-controlled trial. A total of 167 patients were randomly assigned (1:1:1) to receive ipilimumab and nivolumab at the FDA-approved dosing schedule (3 and 1 mg/kg, respectively, every 3 weeks for four doses; group A) versus nivolumab monotherapy (3 mg/kg every 2 weeks and ipilimumab-matching placebo during weeks 1-12; group B) versus double-matching placebo (group C). At a median follow-up of 28.4 months, the 1-year relapse-free survival rate was 75% for group A versus 52% for group B and 32% for group C. Both nivolumab-treated groups had significantly longer relapse-free survival compared with the placebo group (HR point estimate, 0.23 and 0.56, respectively). In the 2022 final analysis, overall survival was significantly improved in patients who received adjuvant ipilimumab/nivolumab (HR, 0.41; 95% CI, 0.71-0.99) in comparison with those who received placebo; no survival benefit over placebo was seen in the group receiving adjuvant nivolumab monotherapy (HR, 0.75; 95% CI, 0.36-1.56). Notably, the incidence of grade 3 to 4 treatment-related adverse events was 71% in the nivolumab and ipilimumab group and 29% in nivolumab alone.

IMMUNED is the only reported randomized trial in patients with stage IV melanoma with no evidence of disease to show that a nivolumab-based treatment is superior to observation for this patient population.[44]

In summary, given the higher clinical benefit and significantly lower toxicity of pembrolizumab, nivolumab, dabrafenib, and trametinib in the adjuvant setting, ipilimumab (at any dose) and high-dose IFN are no longer recommended as adjuvant therapy options. Recurrence-free survival and distant metastasis–free survival are significantly improved with pembrolizumab, nivolumab, dabrafenib, and trametinib, but overall survival benefit has not yet been observed. The role of ipilimumab and nivolumab in the adjuvant setting requires further study regarding the most appropriate dosing schedule, patient population, and toxicity profile versus clinical benefit, although a survival benefit in the resected stage IV setting has been observed. Certainly, given the increased incidence and severity of potential immune-related adverse events (irAEs) with combination ipilimumab and nivolumab compared with pembrolizumab or nivolumab monotherapy, the role of combination immunotherapy in the adjuvant setting remains to be investigated.

KEY POINTS

- Adjuvant pembrolizumab and nivolumab are FDA approved for patients with resected stage IIB/C melanoma because of improved relapse-free survival; however, the decision to pursue adjuvant therapy should include a careful discussion of risks and benefits.
- Combination dual targeted therapy with dabrafenib and trametinib (in *BRAF* V600–mutated disease), as well as nivolumab and pembrolizumab, is an adjuvant treatment option for patients with completely resected stage III melanoma based on improved relapse-free survival and reasonable tolerability.
- Active surveillance alone, without adjuvant therapy, is an equally acceptable option for patients with high-risk resected melanoma, given that there is no clear overall survival benefit with adjuvant anti–PD-1 monotherapy or adjuvant targeted therapy. The decision between treatment and observation requires shared decision-making between the patient and provider, including a detailed discussion of risk and potential benefit.
- Adjuvant ipilimumab and nivolumab at attenuated doses showed no clinical benefit in resected stage IIIB-IIID melanoma patients and is not a recommended adjuvant therapy of melanoma.
- The combination of nivolumab and ipilimumab in the adjuvant setting has shown overall survival benefit in the resected stage IV setting with a significantly higher immune-related adverse event rate than definitive treatment for stage IV melanoma.

NEOADJUVANT THERAPY

Neoadjuvant treatment approach of locally advanced cancer incorporates presurgical use of effective anti–cancer agent/agents as it is expected to shrink the tumor enabling complete surgical resection while reducing the risk of delayed tumor recurrence by eliminating systemic micrometastases. Historically, melanoma did not attract neoadjuvant treatment approaches due to the lack of effective systemic therapies to potentially transform a patient's melanoma from unresectable to resectable tumor. With the availability of effective treatment options of melanoma such as immune checkpoint inhibitors and BRAF-directed therapy for *BRAF*-mutated melanoma, trials to explore neoadjuvant treatment approaches became logical and received support. Additional advantages with neoadjuvant use of immune checkpoint inhibitor therapy of melanoma included expansion and activation of in situ tumor–exposed antigen-specific effector T cells and the opportunity to review available tumor tissue obtained at surgery offering several immune and histologic correlates as well as biomarkers of treatment response (or lack of) to help plan future treatments.

The potential risk of neoadjuvant treatment approaches includes tumor progression both locally or systemically if the tumor did not respond to the neoadjuvant treatment or if definitive surgery is delayed due to the management of toxicity from systemic therapy.

Patients with clinically detected stage III and resectable stage IV melanoma became ideal candidates to trial neoadjuvant approaches since this group of patients represent the high-risk population with poor long-term outcomes when treated with upfront surgery alone or with surgery, followed by adjuvant treatment.

Early neoadjuvant studies in melanoma enrolled modest sample sizes and were heterogeneous in design with regard to the type of neoadjuvant therapy, number of preoperative doses administered, and whether/what kind of adjuvant therapy was administered postoperatively. To show that pathologic response from neoadjuvant therapy correlated with clinical outcomes, data were pooled from six neoadjuvant clinical trials in clinical stage III melanoma for patients with nodal metastases who underwent definitive surgery as part of the International Neoadjuvant Melanoma Consortium. Of the 189 patients whose data were analyzed, 138 received immunotherapy, and 51 received targeted therapy. Despite differences between neoadjuvant immunotherapy and BRAF/MEK inhibitor therapy trials in terms of stage (IIIB vs IIIC), anatomic location of involvement (axilla vs groin), treatment duration of the neoadjuvant strategy, median time to surgery, and median follow-up after surgery, the incidence of complete pathologic response was high (37%-47%). Across all patients, 2-year relapse-free survival rates were higher for those who achieved complete pathologic response (89% vs 50%, respectively). Radiologic response had a moderate correlation with pathologic response; for example, 38% of patients who received immunotherapy and had stable disease by Response Evaluation Criteria in Solid Tumors (RECIST) preoperatively also had complete or near-complete pathologic response at the time of surgery.[45]

According to the International Melanoma Neoadjuvant Consortium recommendations, a 6- to 8-week duration of preoperative neoadjuvant therapy is recommended followed by surgery and possible use of additional adjuvant component postsurgery for a total duration of treatment of 1 year. However, assessment of pathologic response in the index lymph node (largest metastatic lymph node in the lymph node basin at the baseline) after initial preoperative treatment has been a reliable biomarker of response and determines postsurgery treatment.

Neoadjuvant immune therapy protocols include standard dose combined ipilimumab and nivolumab or altered dose ipilimumab (1 mg/kg) and nivolumab (3 mg/kg), single-agent anti–PD-1 agent either nivolumab or pembrolizumab, fixed-dose relatlimab and nivolumab or BRAF and MEK inhibitor agents in patients with *BRAF* mutation–positive melanoma where the upfront immune checkpoint inhibitor is not favored. Altered dose ipilimumab (1 mg/kg) and nivolumab (3 mg/kg) confer similar response rates, but the toxicity is lower compared to the standard dose of combined therapy and hence is the preferred treatment regimen.

Combined immune checkpoint inhibitor therapy with the standard dose confers high response rates but also high rates of immune-related adverse effects while single-agent anti–PD-1 agents confer lower response rate but lower risk of immune-related adverse events. The decision to choose upfront treatment depends upon patient conditions such as comorbidities and autoimmune disease history.

Typically, two cycles of combined immune checkpoint inhibitors or three cycles of single-agent anti–PD-1 agents were administered about 3 weeks later by surgical resection of the index lymph node or involved lymph node/nodes. Postsurgery treatment is decided by pathologic response and the status of systemic metastases as assessed by imaging studies.

Recent notable updates supportive of the clinical benefit of neoadjuvant therapy include the SWOG S1801 and NADINA trials.

SWOG S1801 was a phase 2 study that randomly assigned 313 patients with stage IIIB to resectable stage IVC melanoma to three doses of neoadjuvant pembrolizumab, followed by surgery and 15 doses of postsurgery adjuvant pembrolizumab (neoadjuvant-adjuvant group) or surgery, followed by pembrolizumab (200 mg intravenously every 3 weeks for a total of 18 doses) for approximately 1 year until disease recurred or unacceptable toxic effects developed (adjuvant-only group). The primary endpoint was event-free survival, defined as documented tumor progression rendering the patient unable to receive planned surgery, no initiation of pembrolizumab within 84 days of surgery, tumor relapse after surgery, or death resulting from any cause. With a median follow-up of 14.7 months, event-free survival was significantly higher with the neoadjuvant-adjuvant group compared with the adjuvant-only pembrolizumab group (Cox HR, 0.59; 95% CI, 0.40-0.86; one-sided log-rank P = .0015). The benefit of neoadjuvant over adjuvant therapy was consistent across age, sex, performance status, stage, LDH, ulceration, and BRAF status. Notably, the same proportion of patients made it through surgery to adjuvant pembrolizumab in both arms, and the rates of adverse events attributed to pembrolizumab or surgery were similar in both arms. The improved event-free survival in the neoadjuvant over the adjuvant arm is striking and provides strong rationale for the neoadjuvant approach.[2]

The NADINA study demonstrated further support for neoadjuvant immunotherapy. The rationale for the NADINA trial was based on analysis from the prior PRADO trial, which suggested that two doses of neoadjuvant ipilimumab 1 mg/kg and nivolumab 3 mg/kg may have significant clinical efficacy and that there may be an opportunity to personalize treatment after neoadjuvant immunotherapy based on the pathologic response.[46] In the NADINA trial, 423 patients with resectable (clinical), macroscopic stage III melanoma was randomized to either neoadjuvant ipilimumab (80 mg) and nivolumab (240 mg) every 3 weeks for two cycles or the adjuvant nivolumab group. Patients in both groups underwent TLND. Patients in the neoadjuvant group who had major pathologic response (≤10% residual viable tumor) did not receive any adjuvant therapy, and the patients who had either pathologic partial (11%-50% residual viable tumor) or nonresponse (>50% residual viable tumor) received additional 11 cycles of nivolumab or, if *BRAF* V600E or V600K mutated, received adjuvant dabrafenib and trametinib for 46 weeks. The primary endpoint was event-free survival, defined as disease progression to unresectable melanoma before surgery, melanoma recurrence, or melanoma or treatment-related death. After a median follow-up of 10.6 months in the neoadjuvant group and 9.9 months in the adjuvant group, event-free survival at 12 months was significantly longer in the neoadjuvant arm (83.7% vs 57.2%; HR, 0.32; 95% CI 0.15-0.66).[1] On pathologic review of surgically resected tissue, 59.0%, 8.0%, and 26.4% of patients treated with neoadjuvant ipilimumab and nivolumab had major, partial, and no response, respectively; 2.4% of patients had disease progression prior to surgery. The estimated recurrence-free survival at 12 months was 95.1% in patients with major pathologic response (importantly, these patients did not receive adjuvant therapy), 76.1% in patients with partial pathologic response, and 57.0% in patients with pathologic nonresponse. These results taken together with data from the SWOG S1801 trial have strengthened the rationale for a neoadjuvant approach in clinical practice for patients with clinically palpable/resectable, stage III-IV melanoma (Fig. 16-3).

Neoadjuvant-adjuvant relatlimab and nivolumab in clinical stage III and stage IV (M1a) melanoma: In a multi-institutional clinical trial, 30 patients with stages IIIB, IIIC, IIID, and IV (M1a) received neoadjuvant relatlimab 160 mg and nivolumab 480 mg for two cycles administered intravenously every 4 weeks (Q4W), followed by response assessment and surgery (at week 9) for evaluation of pathologic response. Postsurgery, patients received additional 10 adjuvant doses (total of 1 year) of relatlimab and nivolumab combination. A major pathologic response (complete pathologic response or near-complete responses) was seen in 63% patients. At a median follow-up of 24.4 months, 1- and 2-year event-free survival rates were 90% and 81%, respectively, and 1- and 2- year relapse-free survival rates were 97% and 82%, respectively. Patients with high pathologic responses showed higher rates of event-free and relapse-free survival with 1- and 2-year overall survival rates for all patients at 93% and 88%, respectively.[47]

KEY POINTS

- Neoadjuvant approach is relevant and effective in high-risk clinically palpable stage III and resectable stage IV melanoma.
- Status of pathologic response in an index lymph node helps determine the need for lymph node dissection and additional adjuvant treatment in high-risk stage III disease.
- Neoadjuvant and adjuvant pembrolizumab improved event-free survival compared with adjuvant pembrolizumab in a randomized phase 2 trial.
- In a phase 3 trial, neoadjuvant ipilimumab and nivolumab had superior event-free survival compared with adjuvant nivolumab. The patients who achieved major pathologic responses after two doses of neoadjuvant ipilimumab and

nivolumab did not receive adjuvant therapy and had an estimated 12-month recurrence-free survival of 95.1%, highlighting the potential role of pathologic response as a predictive biomarker to personalize adjuvant therapy.

- In a smaller multi-institutional study, neoadjuvant relatlimab and nivolumab regimen was found to be effective and safe option in melanoma patients with stages IIIB, IIIC, IIID, and IV (M1a) disease.

STAGE IV MELANOMA

BIOLOGY

Few studies with matched (ie, same patient) primary and metastatic melanoma tumors are available to investigate what makes advanced melanomas biologically distinct from their primary lesion. Beyond the well-described frequently mutated *BRAF, NRAS, PTEN, CDKN2A*, and *TP53* genes, infrequent mutations in a few other genes (eg, *RAC1* and *SPEN*) may have prognostic significance in metastatic melanoma.[48] Whereas important mutated oncogenes that are present early in melanoma development (eg, *BRAF* V600E and *NRASQ61*) are retained at a high frequency between primary and metastatic tumors in the same patient, other somatically mutated tumor suppressor genes (eg, *CDKN2A*) are more frequent in distant metastases. The finding that the *BRAF* V600E mutation is also present in metastases is the molecular basis for targeting a protein present in earlier stages of melanoma development, such as mutant *BRAF* V600.[13] Considerable intratumoral genetic heterogeneity of large metastatic melanoma lesions provides a molecular explanation for the lower responses seen with all systemic therapies in advanced melanomas with high tumor burden.[49]

Two reports that analyzed at least two metastatic melanoma tumors from the same patient, using gene expression profiling and targeted panel sequencing, showed that intertumoral (ie, molecular differences between different metastatic lesions) homogeneity and heterogeneity are both seen in advanced melanoma.[50] Molecular homogeneity between extracranial and intracranial metastases may account for concordance in extracranial and intracranial responses seen with combination ipilimumab and nivolumab administration in patients with active brain metastases (CheckMate 204).[51] Intratumoral heterogeneity (ie, molecular differences between different locations of the same tumor) is an adverse prognostic factor as well as a predictor of poor response to available systemic therapies. Epigenetic heterogeneity, which is not only driven by genetic aberrations but also influenced by physicochemical factors, such as pH, hypoxia, and cues derived from the metastatic organ-specific niche, is poorly understood at this time. The recent discovery of distinct bacteria in both melanoma and tumor-infiltrating immune cells and their association with response to immunotherapies adds another level of complexity to the intratumoral microbiome that may shape biologic behavior, prognosis, and response to systemic treatments.[52] Even more intriguing is the role of the gut microbiome as a predictor of response to PD-1/PD-L1 inhibitors.[53,54] Knowledge about the biology of metastatic melanoma has tremendous implications in the treatment approach to advanced melanoma, as discussed in the next sections.

SURGERY

In appropriately selected patients (eg, those with oligometastatic melanoma), curative-intent metastasectomy was a standard treatment option before 2010. Analysis of the SEER database for patients diagnosed with advanced melanoma between 1986 and 2006 (N = 4,229) showed that approximately one-third of patients underwent metastasectomy. These patients were usually younger and had more recently diagnosed advanced melanoma. Patients who underwent metastasectomy had longer overall survival compared with patients who did not undergo metastasectomy, irrespective of M1 substage (M1a vs all others). Selection bias to perform a metastasectomy was a limitation of the study. It also implied, however, that patients with oligometastatic melanoma might have an inherently better prognosis than patients with multiple distant metastases. A single-institution study conducted at the Royal Marsden Hospital NHS Foundation Trust showed that since 2011, there have been fewer excisions for in-transit melanoma and more abdominal metastasectomies.[55] Surgery continues to have a treatment role in selected patients with advanced melanoma, both for palliative intent and for disease control.

RADIATION THERAPY

Palliative management of melanoma metastases: hypofractionated radiation therapy (≥2.5 Gy per fraction) is a standard treatment option in the palliative care of patients with advanced melanoma who have symptomatic lesions (eg, pain, mass effect, hemorrhage, and bone destruction) that are not amenable or responsive to systemic treatment or surgery. Advances in imaging techniques, patient mobilization, and instrumentation have enabled radiation oncologists to provide even higher doses per fraction, sparing adjacent normal tissues from toxicity through a variety of radiation delivery methods (eg, external-beam radiation therapy, stereotactic radiosurgery, and intensity-modulated radiation therapy).

Radiation therapy in melanoma brain metastases: stereotactic radiosurgery should be considered in patients with limited parenchymal brain metastases who are candidates for systemic therapy with immune checkpoint inhibitor agents or BRAF-directed therapy in *BRAF* mutation–positive melanoma.

Adjuvant whole-brain radiation is not routinely recommended in newly diagnosed melanoma brain metastases. A phase 3 multicenter randomized trial of patients with melanoma brain metastases who had local treatment (surgery or stereotactic

radiosurgery) for one to three brain metastases showed that follow-up adjuvant whole-brain radiation therapy did not significantly improve distant intracranial failure compared with observation, and it was associated with earlier decline in performance status and higher toxicity.[56] Therefore, the use of whole-brain irradiation should be reserved for patients with refractory e central nervous system disease and for palliation in patients who fail standard treatment.

Concurrent administration of MAPK inhibitors with radiation therapy can significantly worsen radiation therapy–related toxicities; therefore, concomitant use of MAPK inhibitors and radiation therapy should be avoided.[57,58]

Radiation can induce immunogenic cell death, and the resulting release of tumor-associated antigens may expand anti–melanoma activity of immune checkpoint inhibitor-activated T cells. In small phase 2 trials, the combination of radiation and immune checkpoint inhibitors seemed to be well tolerated[59]; however, the synergism in the antitumoral effect of the two therapies is being further investigated in several clinical trials.

KEY POINTS

- Surgical resection can be considered in select patients with symptomatic melanoma brain metastases and for disease control (ie, oligometastatic disease) or with palliative intent.
- Systemic therapy with immune checkpoint inhibitor-based or BRAF-directed therapy in BRAF mutation–positive melanoma should be considered for primary treatment of melanoma brain metastases.
- Stereotactic radiosurgery is a standard palliative treatment option in advanced melanoma and can be considered for disease control in select patients with oligometastatic disease or limited central nervous system disease or when the tumor is inaccessible for surgery.
- Whole-brain irradiation did not reduce distant intracranial failure and was associated with earlier decline in performance status and hence not routinely recommended.
- Concurrent administration of MAPK inhibitors with radiation therapy worsens radiation therapy–related toxicities.
- Concurrent use of immune checkpoint inhibitor treatment and stereotactic radiosurgery of melanoma brain metastases is found to be safe in retrospective studies. However, optimal sequencing of immune checkpoint inhibitor treatment and radiation therapy is under clinical investigation in patients with melanoma brain metastases.

SYSTEMIC THERAPY FOR UNRESECTABLE/METASTATIC MELANOMA

Effective systemic treatments for advanced melanoma have prolonged overall survival and reduced melanoma-specific mortality over the last several years (Fig. 16-1). In 2010, there were only two systemic treatment options for advanced melanoma: dacarbazine and high-dose bolus interleukin-2 (IL-2). Since 2011, three treatment combinations targeting the MAPK signaling pathway (vemurafenib and cobimetinib, dabrafenib and trametinib, and encorafenib and binimetinib), five immune checkpoint inhibitors (ipilimumab, fixed combination of relatlimab and nivolumab, pembrolizumab, and atezolizumab), and one oncolytic virotherapy administered intratumorally (talimogene laherparepvec [TVEC]) have been FDA approved. In 2024, a first-in-class TIL therapy, lifileucel, was approved for patients who were refractory to anti–PD-1-based therapy, and BRAF/MEK inhibitors if *BRAF* mutated (Fig. 16-4). The increasing number of options has generated questions about their comparative safety and efficacy, optimal combinations and sequences, and rational combination with a growing number of investigational drugs currently in clinical development. The following sections elaborate on the essential data from pivotal clinical trials that led to the FDA approval of these drugs and provide recommendations regarding optimal use and sequence, as well as discussing mechanisms of resistance and the potential for rechallenge.

IMMUNOTHERAPY—T-CELL ACTIVATION

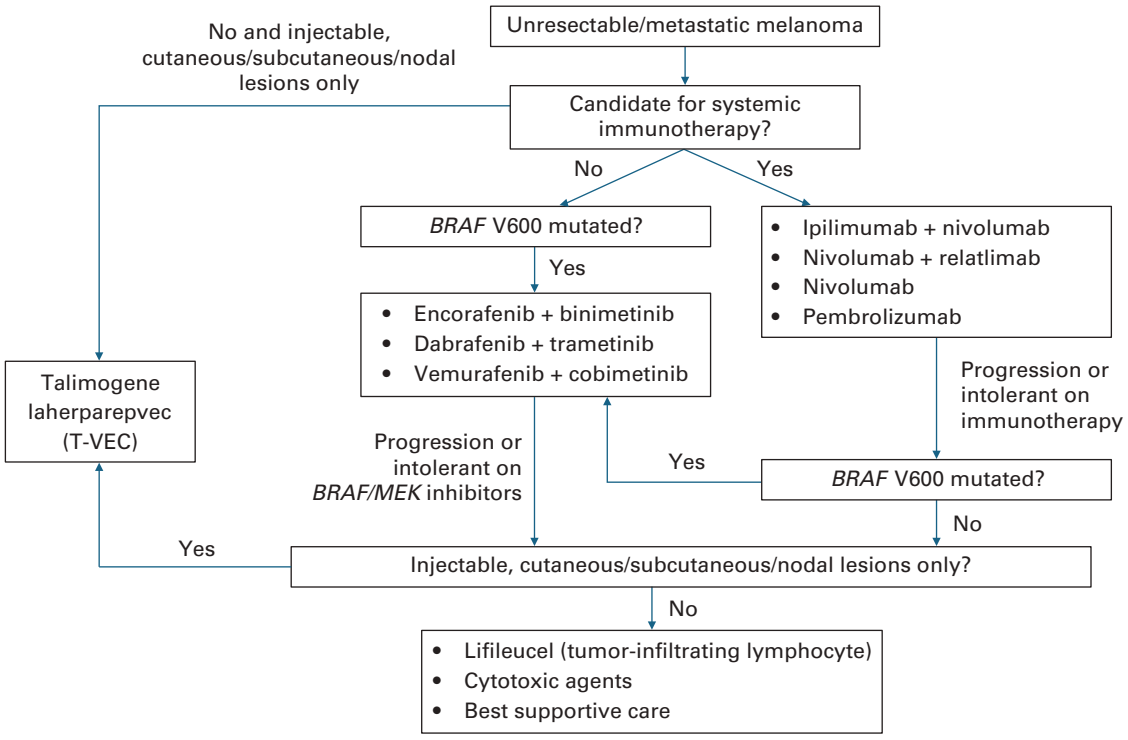
Historically, patients with metastatic melanoma exhibited spontaneous regressions of tumors, raising suspicion of anti–melanoma immune responses as an underlying mechanism of this clinical observation. Pathologic assessment of melanoma revealed tumor infiltration by numerous T lymphocytes (TIL) aiding the discovery of multiple melanoma antigenic epitopes used as vaccine candidates. In order to activate a T cell when presented with a tumor antigen, two signals are required:

- Signal 1. T-cell priming: First, the antigen is required to be presented by the antigen presenting cells (APC) in the tumor microenvironment at their MHC molecules (class 1 for CD8 and class 2 for CD4 T cells) to the T-cell receptors of T cells.
- Signal 2. T-cell activation: The binding of the costimulatory molecules between APC (CD80 and CD86) and T cell (CD28 molecule) brings the antigen on APC closest to the TCR on T cells resulting in transmission of signal to T-cell nucleus and activation of the T cell.

Successful transmission of the signal and T-cell activation results in the expansion of antigen-specific T cells, cytokine generation, and induction of T-cell memory against the presented tumor antigen.

The use of systemic therapies to augment host immune response to melanoma has been ongoing since at least the 1960s.[60] In retrospect, high-throughput and histopathologic analyses of cutaneous melanoma samples as part of The Cancer Genome

Figure 16-4 Treatment Options for Metastatic Melanoma



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Atlas and other projects have explained the immunogenicity of this tumor in terms of the high somatic mutation burden, the aberrant expression of various melanoma-associated and other cancer/testis antigens, and the increased frequency of TILs.[16] Various cytokines, growth factors, and melanoma vaccines constituted the early immunotherapies that were tested in metastatic melanoma, with overall low success before the advent of immune checkpoint inhibitors.[60]

HIGH-DOSE IL-2

High-dose IL-2 was the second treatment to be FDA approved in advanced melanoma after dacarbazine in 1975. IL-2, previously known as T-cell growth factor, plays an essential role in T-cell survival, proliferation, and activation. High-dose IL-2 was approved in 1988 on the basis of the durability of antitumor responses (6% and 10% incidence of complete and partial responses, respectively) from several phase 2 non–randomized single-arm studies.[61,62] The median overall survival of 11.4 months was the new bar set for any new systemic treatments in advanced melanoma, and approximately two-thirds of patients who experienced complete responses following high-dose IL-2 treatment remained alive and progression free even decades after receiving therapy. Given the severe adverse effects of high-dose IL-2, its safe use is limited to select fit patients diagnosed with metastatic melanoma, and strict guidelines for its administration have been developed.[58] Use of high-dose IL-2 has largely been supplanted by use of immune checkpoint inhibitors, given their more favorable efficacy and toxicity profiles.

The identity of melanoma antigens and demonstration of antigen-specific T-cell responses following exposure of effector T cells to diverse melanoma antigens led to trial of therapeutic melanoma vaccines in humans. Although the concept was successful in mice, its results in humans were unpredictable and lacked efficacy. Also, elicitation of antigen-specific T-cell response following melanoma vaccination did not translate to clinical responses in patients.

Research showed that although effector T cells against melanoma are generated and documented, its therapeutic efficacy is compromised by T-cell expression of inhibitory molecules called checkpoints. T-cell checkpoints serve to prevent excessive inflammation and maintain immune homeostasis but remain a barrier to effective anti–cancer T-cell activity.

Cytotoxic T lymphocyte antigen 4 (CTLA-4) was the first T-cell checkpoint to be studied in mice blockade of which by a monoclonal antibody led to successful anti–melanoma T-cell effects. Ipilimumab was the first humanized monoclonal antibody against CTLA-4 that was tested successfully in melanoma patients and approved by the FDA for treatment of melanoma.

Additional T-cell checkpoint discovered on an activated effector T cell and responsible for interference with anti–tumor activity is the PD-1 molecule (programmed death-1) binding of which to the PD-L1 molecule expressed on tumor cells result in effector T-cell exhaustion. Reactivation of the effector T cell against melanoma has become successful with therapeutic use of monoclonal antibodies to PD-1 (nivolumab and pembrolizumab) or PD-L1 (atezolizumab) approved by the FDA in melanoma treatment.

IPILIMUMAB

MDX-020-010 was the first phase 3 randomized trial (N = 676) in advanced melanoma that tested the clinical benefit of ipilimumab (3 mg/kg administered intravenously every 3 weeks for up to four infusions) alone and in combination with an HLA-A*0201–restricted gp100 vaccine.[63] Both ipilimumab-treated arms had longer relapse-free survival and overall survival compared with the gp100 vaccine–treated arm. Although the median overall survival seen in the ipilimumab-treated arms from this trial was comparable with that seen with high-dose IL-2, the outpatient administration of the ipilimumab regimen every 3 weeks and its less severe acute toxicities compared with those of high-dose IL-2 broadened the use of ipilimumab to a far larger group of medical oncologists. Interestingly, a randomized trial of ipilimumab (10 mg/kg administered intravenously every 3 weeks for up to four infusions) versus lower-dose ipilimumab (3 mg/kg administered intravenously every 3 weeks for up to four infusions) for patients with advanced melanoma resulted in prolonged overall survival in favor of the high dose (median overall survival, 15.7 vs 11.5 months; HR, 0.84; 95% CI, 0.70-0.99) but at the expense of higher incidence of treatment-related toxicities (37% vs 18%).[63] Despite the higher clinical benefit of high-dose ipilimumab in stage IV melanoma and given the fact that this trial was conducted before the advent of PD-1 inhibitors, standard lower-dose ipilimumab remains the FDA-approved standard of care. Ipilimumab monotherapy is not recommended as standard first-line therapy because of the superiority of anti–PD-1 agents, as detailed in the next section.

PD-1 INHIBITORS

Pembrolizumab was the first PD-1 inhibitor to be approved by the FDA in September 2014 for ipilimumab-refractory advanced melanoma (and MAPK inhibitor–refractory advanced melanoma, if *BRAF* V600 mutated) on the basis of the results of the KEYNOTE-002 study.[64] Pembrolizumab was subsequently approved by the FDA as a first-line treatment of patients with advanced melanoma on the basis of results from the randomized KEYNOTE-006 trial (N = 834) that compared pembrolizumab (10 mg/kg administered intravenously either every 2 or every 3 weeks) versus ipilimumab (3 mg/kg administered intravenously every 3 weeks). Based on dosing data from KEYNOTE-002 and KEYNOTE-006, the FDA-approved dose of pembrolizumab was 2 mg/kg administered intravenously every 3 weeks. On the basis of pharmacokinetic analysis, dosing was subsequently updated to flat dosing of either 200 mg every 3 weeks or 400 mg every 6 weeks.

Nivolumab was FDA approved in December 2014 as a result of data from CheckMate 037, a randomized (2:1) study that compared the efficacy of single-agent nivolumab (3 mg/kg administered intravenously every 2 weeks) with investigator's choice of chemotherapy in a similar patient population to that enrolled in the KEYNOTE-002 study. The study met its primary endpoint of significantly higher durable antitumor responses with nivolumab.[65] Nivolumab was similarly approved in the first-line setting on the basis of the CheckMate 066 trial, a phase 3 randomized study of patients without *BRAF* V600 codon mutations. As part of this trial, nivolumab significantly prolonged progression-free survival and overall survival compared with dacarbazine.[65] Nivolumab also demonstrated an improved overall survival benefit over ipilimumab in the CheckMate 067 trial in the first-line setting. The dosing was subsequently updated to flat dosing of either 240 mg every 2 weeks or 480 mg every 4 weeks.

CTLA-4 AND PD-1 INHIBITOR COMBINATION

CheckMate 067 was tested in treatment-naive advanced melanoma patients, the efficacy and toxicity profile of the combination of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) every 3 weeks for four doses followed by nivolumab maintenance dosing at 3 mg every 2 weeks; nivolumab at a dose of 3 mg/kg every two weeks and placebo; or ipilimumab at 3 mg/kg dose every 3 weeks for four doses and placebo, until tumor progression, the occurrence of unacceptable toxic effects, or withdrawal of consent. Randomization was stratified by PD-L1 status, *BRAF* mutation status, and metastases stage. The two primary endpoints were progression-free survival and overall survival in the nivolumab and ipilimumab group and in the nivolumab groups versus the ipilimumab group.

At a minimum follow-up of 10 years from last patient random assignment, the median overall survival was 71.9 months with nivolumab and ipilimumab, 36.9 months with nivolumab, and 19.9 months with ipilimumab (the HR for death was 0.53 for nivolumab and ipilimumab as compared to ipilimumab and 0.63 for nivolumab as compared to ipilimumab).

Median melanoma-specific survival was more than 120 months with nivolumab and ipilimumab (not reached) compared to 49.4 months with nivolumab and 21.9 months for ipilimumab. Among patients who had been alive and progression free at 3 years, a 10-year melanoma-specific survival was 96% with nivolumab and ipilimumab, 97% with nivolumab, and 88% with ipilimumab. The 10-year melanoma-specific survival for combination ipilimumab and nivolumab, nivolumab alone, and ipilimumab alone was 52%, 44%, and 23%, respectively.[66] Of note, this study was powered to detect a difference between the ipilimumab and nivolumab arm versus the ipilimumab alone arm, not between the two nivolumab-containing arms. Post hoc analysis of the systemic treatments after exit from the trial showed that patients in the nivolumab alone arm received salvage ipilimumab-containing regimens more frequently than patients who were randomly assigned to the combination arm (28% vs 6%).[66] This implies that ipilimumab may potentially be a salvage treatment of patients who receive nivolumab alone, such that the overall survival may not be significantly different.

S1616, a phase 2 study, addressed this question by randomly assigning 92 patients at a 3:1 ratio who had primary resistance to first-line PD-1 blockade to receive either combination ipilimumab and nivolumab or ipilimumab alone. Patients in the

combination therapy arm had significantly longer progression-free survival (HR, 0.63; 90% CI, 0.41-0.97) and a greater objective response rate (28% vs 9%) compared with those receiving ipilimumab monotherapy. As expected, there was an increased incidence of grade 3 or worse toxicity (57% vs 35%) with the combination therapy. No difference in overall survival was observed; however, this study was not powered to detect a difference in overall survival.[67]

Therefore, this study supports the use of combination ipilimumab and anti–PD-1 in patients who experience progression with single-agent anti–PD-1 and suggests that primary resistance to PD-1 inhibitors can be reversed in select patients with dual CTLA-4 and PD-1 blockade. Caution must be exercised, nonetheless, because there was increased toxicity associated with the combination therapy, and its impact on overall survival remains unknown.

Flipped-dose regimen of nivolumab and ipilimumab was tested in CheckMate 511, a phase 3b/4 study comparing standard-dose ipilimumab and nivolumab (3 and 1 mg/kg, respectively) versus alternative doses of 1 mg/kg of ipilimumab and 3 mg/kg of nivolumab, often referred to as a flipped-dose regimen.[68] The study met its primary endpoint, which measured grade 3 to 5 treatment-related adverse events, and found a lower incidence of serious adverse events with the alternative doses (48% vs 34%; $P = .006$). This study was not powered to measure noninferiority for treatment efficacy outcomes.

PD-1 AND LAG-3 INHIBITOR COMBINATION

Although checkpoint inhibition with anti–CTLA-4 and anti–PD-1 agents have revolutionized treatment of patients with advanced melanoma, novel combinations are needed to optimize the risk/benefit profile of combination therapy.

LAG-3 is a negative regulator of T-cell activity and is upregulated in melanoma, among other tumor types. The RELATIVITY047 study tested a novel immune checkpoint inhibitor combination of relatlimab, a human immunoglobulin G4 LAG-3–blocking antibody, and nivolumab in a phase 2/3 randomized double-blind study. Treatment-naive patients ($N = 714$) were randomly assigned 1:1 to receive relatlimab and nivolumab in a fixed-dose combination of 160 and 480 mg every 4 weeks or nivolumab monotherapy at 480 mg every 4 weeks. At a median follow-up of 13.2 months, the median progression-free survival in the fixed relatlimab and nivolumab combination group was significantly prolonged as compared to nivolumab alone arm (10.1 vs 4.6 months; HR, 0.75; 95% CI, 0.62-0.92; $P = .006$). The toxicity profile of the combination was promising, with incidence of grade 3 to 4 treatment-related adverse events noted to be 18.9% in the combination arm and without unexpected safety signals (compared with a grade 3-4 treatment-related adverse event incidence of 59% with nivolumab and ipilimumab in CheckMate 067).[69] Updated data included a confirmed overall response rate of 43.1% (95% CI, 37.9-48.4) in the fixed-dose relatlimab and nivolumab combination arm versus 32.6% (95% CI, 27.8-37.7) in the nivolumab-only arm.[70] These results are the first from a phase 3 study showing clinical benefit of dual LAG-3 and PD-1 pathway inhibition. On the basis of these data, relatlimab and nivolumab in a fixed-dose combination were approved by the FDA in March 2022 for patients with previously untreated unresectable and metastatic melanoma.

TARGETED THERAPIES

BRAF represents a central oncogene of the MAPK signaling pathway that is critical for growth and differentiation of melanocytes and the most frequently mutated oncogene detected in about 50% of cutaneous melanoma patients. Single point mutation of the codon 600 (mostly V600 E) in exon 15 is the most frequently detected mutation accounting for about 70 to 88% of cases while V600K, V600R, and V600D make up for about 12% of cases.

Oncogenic *BRAF* mutations result in constitutive activation of the MAPK signaling pathway resulting in uncontrolled cellular proliferation and survival of melanocytes and is linked to the etiology and progression of melanoma. Although *BRAF*-mutated melanoma exhibits aggressive growth patterns and metastases, it offers opportunities for molecular therapy with agents targeting BRAF. However, resistance to BRAF inhibition eventually develops in the majority of patients.

Although not mutated, BRAF-independent hyperactivity is detected in the downstream MEK protein in patients harboring *BRAF* mutation promoting acquired resistance to BRAF inhibition treatment of melanoma. Combining BRAF with MEK inhibitors improved the progression-free and overall survival of *BRAF*-mutated cutaneous melanoma, indicating clinical relevance of enhanced inhibition of the MAPK signaling pathway.

Vemurafenib and dabrafenib were the first two BRAF inhibitors to be FDA approved for patients with *BRAF* V600–mutated advanced melanoma on the basis of results from the BRIM-3 and BREAK-3 phase 3 randomized studies, which tested each BRAF inhibitor against dacarbazine.[71,72]

Single-agent MEK inhibitors were clinically developed because direct inhibition of a downstream effector of an oncogenic protein, such as BRAF V600, adds clinical benefit to BRAF inhibitors, especially in distinct subgroups of patients with *BRAF* V600 mutation. In line with this, early clinical studies using single-agent MEK inhibitors showed that although MEK inhibition alone had activity in *BRAF* V600–mutated melanoma, all clinical endpoints (ie, antitumor responses, progression-free survival, and overall survival) seemed inferior to those obtained with single-agent BRAF inhibitors.[73] Part of the explanation for the inferior results is the inherent weakness of a drug that targets a downstream effector of an oncogenic protein, MEK, which is usually nonmutated in melanoma.[10] This, along with the essential physiologic role of MEK signaling in normal cells, makes dose escalation of even high-affinity MEK inhibitors challenging because of frequent toxicities.

COMBI-d, COMBI-v, and coBRIM were three phase 3 randomized clinical studies that tested the dabrafenib and trametinib combination (150 mg administered orally twice daily and 2 mg administered orally once daily, respectively) and the vemurafenib and cobimetinib combination (960 mg administered orally twice daily and 60 mg administered orally daily, respectively, on a 21-days-on, 7-days-off schedule) versus a single-agent BRAF inhibitor in patients with advanced *BRAF* V600–mutated melanoma. All three studies showed higher activity of the combination strategy over single-agent BRAF inhibition across all clinical endpoints (ie, relative risk, progression-free survival, and overall survival).[74-76] A landmark 4-year analysis of longer follow-up for COMBI-d and COMBI-v (N = 563) showed that approximately 34% of patients who received the dabrafenib and trametinib combination treatment were still alive at 5 years after treatment initiation, and approximately 13% remained free of progression.[77]

Combination encorafenib and binimetinib is the most recent FDA-approved BRAF/MEK inhibitor combination for *BRAF* V600–mutated melanoma. Encorafenib is a novel ATP-competitive inhibitor that binds its target at least 15 times longer than dabrafenib and vemurafenib (the dissociation half-life from the target for encorafenib was 30 hours; for dabrafenib, 120 minutes; and for vemurafenib, 30 minutes, in a biochemical assay). Binimetinib is a selective allosteric ATP-noncompetitive inhibitor of MEK1/2 with a shorter half-life than those of the other two FDA-approved MEK inhibitors. Paradoxically, concurrent administration of encorafenib and binimetinib allowed for higher dosing of encorafenib (450 mg administered orally once daily [E450]) compared with the maximum tolerated dose identified in the phase 1 study of encorafenib (ie, 300 mg administered orally once daily [E300]).

A phase 3 randomized study, COLUMBUS part 1, tested concurrent E450 and binimetinib (45 mg administered orally twice daily) against E300 and against vemurafenib alone (960 mg administered orally twice daily) in patients with *BRAF* V600–mutated BRAF inhibitor–naive advanced melanoma.[78] E450 and binimetinib showed a superior antitumor response, progression-free survival, and overall survival compared with vemurafenib alone. At 99.7-month follow-up, the median overall survival for the E450 and binimetinib combination was 33.6 months. When compared with E300, the E450 and binimetinib combination resulted in higher antitumor responses and significantly longer progression-free survival, but no significant difference in overall survival was observed.[79] A secondary analysis showed that E300 was superior to vemurafenib alone across all important clinical endpoints (ie, relative risk, progression-free survival, and overall survival).[78]

A number of phase 3 randomized studies are under way to address the question of whether PD-1/PD-L1 pathway inhibition in addition to BRAF/MEK inhibition results in superior clinical benefit compared with BRAF/MEK inhibition alone in patients with *BRAF* V600–mutated melanoma.

IMspire150 was the first of these studies to report on its progression-free survival endpoint, testing atezolizumab, an anti–PD-L1 antibody, and vemurafenib and cobimetinib combination against vemurafenib and cobimetinib combination alone as first-line therapy for patients with *BRAF* V600–mutated unresectable stage IIIC or IV melanoma[80]; this resulted in FDA approval of this triplet therapy. Patients (N = 514) were randomly assigned 1:1 to each arm. At a median follow-up of 18.9 months, the addition of atezolizumab significantly prolonged the median progression-free survival compared with vemurafenib and cobimetinib combination alone (15.1 vs 10.6 months; $P = .025$). The addition of atezolizumab did not significantly increase the incidence of grade 3 to 4 adverse events compared with vemurafenib and cobimetinib combination alone (79% vs 73%, respectively). Other triplet combination trials (COMBI-I, a phase 3 study of spartalizumab, dabrafenib, and trametinib combination compared with placebo, dabrafenib, and trametinib combination; KEYNOTE-022, a phase 2 study of pembrolizumab, dabrafenib, and trametinib combination) have shown negative results with regard to their primary endpoint of progression-free survival, emphasizing the importance of longer follow-up to assess whether the triplet combination significantly prolongs overall survival parameters.

There are no FDA-approved targeted treatments for patients with somatic mutations other than *BRAF* V600. Of note, melanomas with mutations other than non–*BRAF* V600 comprise 50% to 60% of cutaneous melanomas.[9] A high proportion of melanomas in this group have hotspot mutations in the *NRASQ61* codon (15%-20%). Constitutive activation of RAS, a signaling molecule upstream from RAF proteins, involves more than one signaling pathway, in contrast to BRAF V600, which predominantly dysregulates a single pathway (ie, MAPK).[9] Several approaches have indirectly targeted constitutively activated NRAS by blocking distinct downstream signaling pathways, such as the MAPK pathway.

NEMO was a phase 3 randomized (2:1) study that tested the efficacy of binimetinib (45 mg administered orally twice daily) compared with dacarbazine (1,000 mg/m^2 administered intravenously every 3 weeks) in patients with advanced *NRASQ61*-mutated melanoma. Although the study met its primary endpoint, showing that binimetinib significantly prolongs progression-free survival compared with dacarbazine, the difference (2.8 vs 1.5 months) was not clinically meaningful; furthermore, no overall survival difference was observed.[81] The results emphasize the challenges when the target cannot be directly pharmacologically inhibited; therefore, the alternative approach of blocking only one of the several downstream effectors of RAS signaling does not lead to a meaningful clinical benefit.

ADOPTIVE CELL THERAPY

TILs represent an adoptive cell therapy in which tumor-resident T lymphocytes are harvested from a patient's tumor for ex vivo expansion for intravenous infusion after lymphodepleting chemotherapy. After the transfer of cells to the patient, IL-2 is administered to induce the growth of TILs in vivo and promote their antitumoral activity. The clinical activity of TILs in melanoma was first reported in 1994 by Rosenberg et al.[82] More recently, lifileucel, a one-time autologous TIL therapy, was evaluated in the

C-144-01 study. In this non–comparative phase 2 trial, lifileucel achieved an objective response rate of 31.4%, with eight complete responses and 40 partial responses in patients with unresectable or metastatic melanoma who had experienced progression with anti–PD-1 therapy.[3] With a median follow-up of 27.6 months, the median progression-free and overall survival were 4.1 and 13.9 months, respectively. Based on these findings, lifileucel became the first TIL product to gain FDA approval in February 2024; this therapy is indicated for adult patients with advanced melanoma for whom PD-1 blocking antibody therapy or, if *BRAF* V600 mutation–positive, therapy with a BRAF inhibitor with and without a MEK inhibitor has failed. With a 5-year follow-up, the median duration of response was 36.5 months, and 31.8% of the responses were ongoing at the 5-year assessment demonstrating a clinically meaningful durability of lifileucel.[83] Recently, a Dutch randomized phase 3 trial compared a regionally distributed TIL product against ipilimumab at 3 mg/kg as first- or second-line treatment.[84] 168 patients (84 in each arm) with stage IIIC or IV melanoma were randomized in a 1:1 ratio to receive TIL or Ipilimumab. Infusion of at least 5×10^9 TILS was preceded by non–myeloablative lymphodepleting chemotherapy consisting of cyclophosphamide and fludarabine, followed by high-dose interleukin-2. The primary endpoint was progression-free survival. In 86% of patients who were refractory to anti–PD-1 therapy, this TIL product demonstrated significant improvement in median progression-free survival (7.2 vs 3.1 months; HR, 0.50; 95% CI, 0.35-0.72). A phase 3 trial is under way to examine the efficacy and safety of lifileucel in combination with PD-1 blockade in the first-line setting for unresectable or metastatic melanoma (ClinicalTrials.gov identifier NCT05727904).

TALIMOGENE LAHERPAREPVEC

TVEC is a type 1 herpes simplex virus that has been genetically modified to attenuate viral pathogenicity (through deletion of the neurovirulence factor ICP34.5) in favor of greater immunogenicity through insertion and expression of the gene encoding for the human granulocyte-macrophage colony-stimulating factor. In line with an immune-mediated mechanism of action, analysis of TVEC-injected and non–injected distant lesions from patients with melanoma showed that TVEC was able to break local immune tolerance in the microenvironment of injected lesions by suppressing regulatory T cells and myeloid-derived suppressor cells and activating melanoma antigen-specific effector T cells. The effect of TVEC in distant non–injected melanoma lesions was also present but was much weaker.

A phase 3 randomized (2:1) study tested the clinical benefit of intralesional TVEC injections versus systemic granulocyte-macrophage colony-stimulating factor injections for patients with lesions 1 cm or larger amenable to direct or ultrasonography-guided injection. In this heterogeneous patient group (IIIB-M1c), incidence of antitumor responses lasting at least 6 months was significantly higher in patients in the TVEC-treated arm compared with those in the systemic granulocyte-macrophage colony-stimulating factor–treated arm (19.3% vs 1.4%). At a median follow-up of 49 months, both the median time to treatment failure and overall survival were significantly longer in the TVEC-treated arm as opposed to the granulocyte-macrophage colony-stimulating factor–treated arm. From these results, the FDA-approved TVEC for patients with unresectable stage IIIB to IV melanoma.[85]

This drug has since been evaluated in combination with various immune checkpoint inhibitors. Despite promising early trial results, the phase 3 MASTERKEY-265 study that randomly assigned patients with advanced melanoma to TVEC and pembrolizumab versus pembrolizumab monotherapy did not show a progression-free survival benefit in the combination arm. Although there was a 5.8-month numeric difference in progression-free survival between arms favoring the combination arm, the results were not statistically significant (HR, 0.86; 95% CI, 0.71-1.04; $P = .013$). Furthermore, no difference in overall survival was observed.[86]

CHEMOTHERAPY

Before 2010, cytotoxic chemotherapy, along with high-dose IL-2, was a mainstay in the treatment of advanced melanoma. After the initial FDA approval of dacarbazine in 1975, subsequent trials using combination chemotherapy regimens or biochemotherapy did not show any overall survival benefit, although higher toxicity rates were reported.[87] European Organisation for Research and Treatment of Cancer (EORTC) 18,032 tested the efficacy and toxicity of escalated-dose temozolomide (150 mg/m^2 once daily for 7 days, followed by 7 days off) against those of standard-dose dacarbazine (1,000 mg/m^2 administered intravenously every 3 weeks) in patients with advanced melanoma. No significant differences in progression-free survival or overall survival were seen between the two arms. However, antitumor responses were significantly higher with temozolomide compared with dacarbazine (14.5% vs 10%).[88] Although the FDA never approved temozolomide for the treatment of advanced melanoma, the convenience of administering a pill over an infusion, the ability of temozolomide to better penetrate the blood-brain barrier, and the significantly higher antitumor responses with temozolomide favor its use in patients whose quality of life may depend on antitumor response.

At present, chemotherapies are primarily used as salvage treatment in patients whose disease has progressed with immunotherapies or targeted therapies (if *BRAF* V600 mutated) and who are not eligible for clinical trial participation, although early data suggest that the clinical benefit is small.[89]

KEY POINTS

- Dual checkpoint blockade is the preferred first-line immunotherapy treatment option in unresectable/advanced melanoma.

- Concurrent ipilimumab and nivolumab should be considered for patients with small asymptomatic central nervous system metastases; both topics are discussed later in the chapter.
- Four phase 3 randomized clinical studies in patients with *BRAF* V600–mutated metastatic melanoma have shown significant progression-free survival and overall survival benefits favoring concurrent BRAF/MEK inhibition compared with a single-agent BRAF inhibitor.
- Oncolytic viral therapy such as TVEC represents a reasonable option to control local tumor in selected patients and showed superior responses lasting at least 6 months when compared to the granulocyte-macrophage colony-stimulating factor-treated arm. However, its combination with anti–PD-1 agent did not improve progression-free or overall survival.
- Lifileucel, a one-time autologous TIL therapy, is approved by the FDA for patients with anti–PD-1 refractory melanoma and can have clinically meaningful durable effect.
- Although systemic chemotherapy is not recommended as a first-line treatment of melanoma, it may be used in selected clinical scenarios as a bridge to future treatments.

ROLE OF SYSTEMIC TREATMENT IN THE MANAGEMENT OF MELANOMA BRAIN METASTASES

Historically, the mainstay of treatment of melanoma brain metastases included consideration for upfront surgery and/or stereotactic radiation therapy. Since the approval of immune checkpoint inhibitors and molecularly targeted therapy options, results of several phase 2 trials have shown that systemic therapy can achieve meaningful intracranial (as well as extracranial) responses.

Targeted therapy has intracranial activity in patients with *BRAF* V600–mutated melanoma, demonstrating intracranial response rates of 25% to 40% with BRAF inhibitor monotherapy and up to 58% with combined BRAF and MEK inhibition.[90-95]

Immune checkpoint inhibitors have shown activity against melanoma brain metastases as well, with intracranial response rates of 24% with ipilimumab alone,[96] approximately 20% with anti–PD-1 monotherapy,[97] and greater than 55% with combination nivolumab and ipilimumab.[51]

CheckMate 204 results were practice changing in solidifying combination nivolumab and ipilimumab as standard of care for the treatment of a select group of patients with melanoma metastatic to the brain. CheckMate 204 was a phase 2 single-group study designed to investigate the efficacy and safety of treating patients with untreated melanoma brain metastases with combination nivolumab and ipilimumab at standard dosing (1 and 3 mg/kg, respectively); patients were eligible if they were neurologically asymptomatic, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, were not receiving steroids, and presented with intracranial metastases measuring no larger than 3 cm in diameter.[51] This study met its primary endpoint of intracranial clinical benefit rate; longer-term results for the original asymptomatic cohort (cohort A) of CheckMate 204, at a median follow-up of 34.3 months, confirmed an intracranial clinical benefit rate (percentage of patients with stable disease for at least 6 months, partial response, or complete response) in 58 (57.4%; 95% CI, 47.2-67.2) of 101 patients in cohort A.[98] Results were also reported for a smaller cohort of symptomatic patients (cohort B) with an ECOG PS of 0 to 2 who could receive low-dose dexamethasone. An intracranial clinical benefit was observed in only three (16.7%; 95% CI, 3.6-41.4) of 18 patients in cohort B. For patients in cohort A, the 36-month intracranial progression-free survival and overall survival rates were 54.1% (95% CI, 42.7-64.1) and 71.9% (95% CI, 61.8-79.8), respectively. For patients in cohort B, the 36-month intracranial progression-free survival and overall survival rates were 18.9% (95% CI, 4.6-40.5) and 36.6% (95% CI, 14.0-59.8), respectively.

In the ABC clinical trial, an open-label randomized phase 2 study, patients diagnosed with asymptomatic, treatment-naive melanoma brain metastases (ECOG PS 0-2) were randomized to receive intravenous ipilimumab 3 mg/kg and nivolumab 1 mg/kg every 3 weeks for four doses, then nivolumab 3 mg/kg every 2 weeks (cohort A), or nivolumab 3 mg/kg every 2 weeks (cohort B). A third cohort, C, included patients with previous brain-directed treatment, symptomatic brain metastases, or those with leptomeningeal disease assigned to receive nivolumab 3 mg/kg dose. The primary endpoint was best intracranial response (complete or partial response) from week 12. Secondary survival endpoints included intracranial progression-free survival and overall survival. Out of 79 eligible patients enrolled into the study, 36 patients were assigned to cohort A, 27 patients to cohort B, and 16 patients to cohort C. At a median follow-up of 7.6 years, the overall intracranial response occurred in 18 patients (51%) of cohort A, five (20%) from cohort B, and one (6%) from cohort C. The 7-year intracranial progression-free survival was 42%, 15%, and 6% in cohorts A, B, and C, respectively. The 7-year overall survival was 48%, 26%, and 13%, respectively, in cohort A, B, and C, respectively.[99]

In an Italian multicenter study of asymptomatic melanoma brain metastases patients, patients (age 18 years or above, ECOG status 0-1, asymptomatic brain metastases measuring between 5 and 20 mm, a life expectancy of more than or equal to 12 weeks) were randomized 1:1:1 to fotemustine 100 mg/m^2 (arm A) or ipilimumab 10 mg/kg and fotemustine 100 mg/m^2 (arm B), or ipilimumab 3 mg/kg and nivolumab 1 mg/kg (arm C). Treatment was continued until progressive disease, unacceptable toxicity, or patient refusal. The primary endpoint was overall survival; the secondary endpoint was progression-free survival, best overall response, and duration of response. Surveys for health-related quality of life were collected at weeks 1, 4, 7, 12, 24, and 36 and at end of treatment using the EORTC Quality of life Questionnaire (QLQ)-C30 V.3 and the QLQ-Brain neoplasm (BN20).

At a median follow-up of 67 months, the median overall survival was 8.5, 8.2, and 29.2 months for arm A, B, and C, respectively. The 7-year overall survival was 10%, 10.3%, and 42.8% in arm A, B, and C, respectively.

Quality of life was preserved in all three arms. Most functional scales evaluated from baseline to week 12 were preserved, with a lower mean score for EORTC QLQ-C30 and an increase for EORTC QLQ-Brain neoplasm (BN20) in patients receiving ipilimumab and nivolumab.

Although data directly comparing nivolumab and ipilimumab with combinations of BRAF/MEK inhibitors in patients with *BRAF* V600–mutated melanoma brain metastases are lacking, intracranial responses have been shown to be more durable in patients with asymptomatic parenchymal brain metastases who were treated with nivolumab and ipilimumab as opposed to dabrafenib and trametinib; disease in patients with *BRAF* V600–mutated melanoma who receive concurrent dabrafenib and trametinib tends to relapse earlier in the brain as opposed to at extracranial sites.[51,92]

Understanding that *BRAF*-mutated melanoma can behave more aggressively and that symptomatic patients with melanoma brain metastases specifically harbor poor prognosis, the TRICOTEL study results are particularly notable. This single-arm phase 2 study was designed to have two cohorts: a *BRAF* wild-type cohort and a *BRAF* V600–mutated cohort. Patients in the *BRAF* wild-type cohort received atezolizumab and cobimetinib. Patients in the *BRAF* V600 mutation–positive cohort received atezolizumab with oral vemurafenib and oral cobimetinib. The *BRAF* wild-type cohort was closed early; however, the intracranial objective response rate was 42% (95% CI, 29-54) by independent review committee assessment in the *BRAF* V600 mutation–positive cohort and 27% (95% CI, 8-55) by investigator assessment in the wild-type cohort.[100] Survival data with longer follow-up are required to better assess the effect of the combination of atezolizumab, vemurafenib, and cobimetinib in this population.

The question of concordance between intracranial and extracranial responses has also been explored. Overall, intracranial antitumor responses are similar to same-patient extracranial antitumor responses and are overall higher in patients who receive either combination targeted therapies or immunotherapies.[51,89-91,94] The similar response seen in extracranial and intracranial disease is supported by translational studies showing that same-patient intracranial and extracranial lesions are biologically similar.[50]

It is important to note, however, that the clinical benefit for patients with leptomeningeal disease or with symptomatic parenchymal brain metastases was disappointingly low, irrespective of whether concurrent BRAF/MEK blockade, single-agent PD-1 inhibitors, or combination PD-1 and CTLA-4 inhibitors were administered.[98]

Overall, data from these studies have provided evidence to support upfront systemic therapy in a select population of patients with metastatic melanoma to the brain. Asymptomatic patients who do not require urgent local treatment with surgery or stereotactic radiation therapy for small central nervous system metastases (<3 cm) can be treated with ipilimumab and nivolumab, with a high rate of durable intracranial response. However, close monitoring is required for early detection of progressing brain metastases, which would require surgery or stereotactic radiation therapy.

KEY POINTS

- Patients with small untreated asymptomatic parenchymal brain metastases can be safely and effectively treated with concurrent ipilimumab and nivolumab, without local surgery or radiation therapy.
- Intracranial responses are durable in patients with asymptomatic parenchymal brain metastases treated with concurrent ipilimumab and nivolumab; the combination of dabrafenib and trametinib results in less durable intracranial responses.
- The care of patients with symptomatic melanoma brain metastases remains challenging. Coordination of multidisciplinary care, including expertise in surgery and radiation therapy, is recommended for this population.

TOXICITIES FROM SYSTEMIC TREATMENTS IN ADVANCED MELANOMA

Immune checkpoint inhibitor treatment and toxicity: Immune checkpoint inhibitors can result in a novel class of toxicities called immune-related adverse effects or irAEs. These toxicities mimic autoimmune diseases in their clinical presentation; however, both diagnosis and treatment of irAEs differ from those of their naturally occurring autoimmune counterparts. ASCO, the European Society for Medical Oncology, the Society for Immunotherapy of Cancer, and the National Comprehensive Cancer Network have published clinical practice guidelines for the management of immune-mediated adverse events in patients treated with immune checkpoint inhibitors.[101] These guidelines provide recommendations for specific organ-based toxicities. Similar guidelines exist for the management of toxicities from high-dose IL-2.[62]

Overall incidence of serious treatment-related adverse events increases with combination versus single-agent immunotherapy (Table 16-2); the incidence was 55.4% versus 9.9% in a pooled analysis from all phase 3 trials that tested single-agent nivolumab versus standard-dose ipilimumab and nivolumab (3 and 1 mg/kg, respectively).

The timing and number of treatment-related adverse events have been associated with overall response rates to immunotherapy; higher response rates were associated with longer time to adverse event development (>12 vs ≤12 weeks from treatment initiation) and more adverse events (one or more vs no adverse events).[102] A lower dose of ipilimumab (1 mg/kg), compared with the FDA-approved dose of 3 mg/kg, concurrently administered with PD-1 inhibitors significantly reduced serious adverse

events in patients with advanced melanoma in two studies, KEYNOTE-029 and CheckMate 511. However, in both studies, clinical outcome was not a primary study endpoint.[103,104] The use of ipilimumab at 1 mg/kg in combination with PD-1 blockade is not a currently approved regimen.

Table 16-2 Incidence and Timing of Organ-Specific Adverse Events From Combination Therapy With Ipilimumab and Nivolumab Versus Nivolumab Alone

	Median Onset (weeks; %)	
Affected System	**Combination Therapy**	**Single-Agent Nivolumab**
Skin	2; 64	5; 33
Gastrointestinal	5; 47	7.3; 14
Hepatic	6.1; 29	7.7; 4
Endocrine	7.4; 30	10.4; 8
Pulmonary	10.6; 8	8.9; 2
Renal	10.2; 4	15.1; 2

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A detailed medical history and clinical examination followed by appropriate laboratory tests and imaging studies help diagnosis of irAEs. Attention to severity of adverse events graded using Common Terminology Criteria for Adverse Events (CTCAE) on a scale from 1 to 5 (1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = death related to toxicity) (National Cancer Institute, 2009) offers effective approach to treatment. Clinical judgment of patient symptoms often complements an objective grading system in managing irAE. Steroids are the cornerstone of immune suppressive treatment of irAEs with biologic agents reserved in specific clinical circumstances.

With expanded use of immune checkpoint inhibitor therapy and growing body of clinical experience of irAEs, there was an increasing need felt to develop a common terminology to describe heterogeneity of natural history, clinical patterns, and response to treatment.

The Society for Immunotherapy of Cancer (SITC) convened expert panel offers such guidance that may be used in managing irAE in patients. This includes terminology for:

- Natural history: onset of irAE such as acute versus chronic (persisting beyond 3 months), delayed onset (occur more than 3 months after immune checkpoint inhibitor treatment), recurrent irAE—occurring in the same organ at least twice after discontinuation of immune checkpoint inhibitor treatment.
- Patterns of irAEs: such as multisystem irAEs occurring in the same or different organ system or occurring concomitantly with another irAE or during treatment for the first irAE.
- Response to steroids: such as steroid-responsive versus steroid-unresponsive irAE, steroid-resistant irAEs or steroid dependent irAEs.

irAEs are generally reversible with corticosteroids and other immunosuppressive agents, with the exception of endocrinopathies. Corticosteroid doses and tapers vary by toxicity but generally are initially dosed between 1 and 2 mg/kg and are continued until toxicities diminish to grade 1 or lower, after which a taper should occur over 4 to 6 weeks.[101] Autoimmune endocrinopathies, such as immune-mediated hypothyroidism and/or adrenal insufficiency (primary or secondary), can be managed with hormone replacement therapy. Grade 3 toxicities generally warrant suspension of immune checkpoint inhibitors. For grade 4 toxicities (with the exception of endocrine-related toxicities that are controlled with appropriate therapy), permanent discontinuation is generally recommended. Steroid-refractory gastrointestinal irAEs may require infliximab or vedolizumab treatment, whereas steroid-refractory hepatic adverse events may require mycophenolate mofetil, budesonide, azathioprine, or tacrolimus.

Discontinuation of immunotherapy because of treatment-related toxicity did not significantly diminish treatment efficacy in a pooled analysis of phase 2 and 3 trials using concurrent ipilimumab and nivolumab.[105] Resumption of anti–PD-1 alone in patients who experienced high-grade toxicity with combination PD-1 and CTLA-4 blockade was often well tolerated, although 18% had recurrent toxicities, and another 21% had onset of distinct toxicities.[106] Rechallenge with anti–PD-1 after cessation for toxicity resulted in a 30% to 50% rate of recurrent toxicities.[107-110] Patients with preexisting autoimmune disorders who were treated with PD-1 inhibitors frequently experienced a flare of their underlying autoimmune disorder; the type of flare was usually an exacerbation of their preexisting symptoms that could be managed with corticosteroids as opposed to an extension of their underlying autoimmune disorder. Although response rates were comparable to those in patients without preexisting autoimmune diseases (ie, 33%), patients receiving immunosuppressant therapy had a lower frequency of response compared with those not receiving immunosuppressants (15% vs 44%).[106]

Steroid use has improved outcomes of irAE in patients, but the decisions about its dose and duration require consideration of affected organ and grade of irAE. Inadequate dosing of steroids results in relapse of irAE while indiscriminate and excessive dose of steroid may adversely affect clinical outcome in patients.[107,108]

A small proportion of immune-related toxicities may be fatal. An international multicenter pharmacovigilance database from seven centers demonstrated a 0.6% fatality rate from immunotherapy. Colitis and myocarditis were the most common causes of death resulting from combination CTLA-4/PD-1 inhibition, and pneumonitis, hepatitis, and neurotoxicities were the most common reasons for fatality resulting from anti–PD-1 monotherapy.[107,111] Classes of irAEs with the highest rates of mortality include myocarditis, neurotoxicities (eg, Guillain-Barre syndrome, myasthenia gravis, aseptic meningitis, encephalitis, and transverse myelitis), and pneumonitis.[107,111] The overlap syndrome of myocarditis, myositis, and myasthenia gravis, sometimes called triple M or triple M overlap syndrome (TMOS), has particularly high fatality rates, with estimates of up to 60% mortality in those who develop this presentation.[54]

Targeted therapy of melanoma and toxicity: Targeted therapy has a more consistent toxicity spectrum; however, there are class-specific differences in treatment-related toxicities between combinations of BRAF and MEK inhibitors (Table 16-3). Irrespective of the choice of doublet therapy, common adverse events of any grade include nausea (30%-41%), diarrhea (24%-36%), skin rashes (23%-39%), fatigue (29%-32%), and arthralgias (24%-32%). Uncommon adverse events associated with MEK inhibitors that warrant careful and timely assessment are cardiac toxicity (decreased left ventricular ejection fraction), ocular toxicity (central serous retinopathy due to fluid accumulation in the retina and may increase risk of serous neuroretinal detachment, retinal vein thrombosis, uveitis, and conjunctivitis), pulmonary toxicity (interstitial lung disease and pneumonitis), and fever.[73] Within each drug class, there are differences in the incidence of certain adverse events. For example, vemurafenib tends to cause diarrhea, transaminitis, photosensitivity, secondary nonmelanoma skin cancers, and hypertension more frequently than the other BRAF inhibitors. Encorafenib not only tends to cause vomiting, alopecia, palmar-plantar erythrodysesthesia, and myalgias more frequently than dabrafenib or vemurafenib but also tends to cause photosensitivity, fatigue, and pyrexia less frequently. Trametinib not only tends to cause rash, dry skin, and alopecia more frequently than binimetinib but also can cause acneiform dermatitis, peripheral edema, nausea, vomiting, and serum creatinine kinase elevation less frequently. The treating physician must have a balanced discussion with the patient regarding the specific adverse events of each drug, given that certain options may be more favorable for some patients than for others. Pretreatment assessment of cardiac function, ophthalmologic exam, and assessment of lung function is recommended with close clinical monitoring of symptoms and surveillance of toxicity in patients. Concurrent treatment with BRAF and MEK inhibitors has toxicity profiles distinct from either agent as monotherapy.

Table 16-3 Differences in Treatment-Related Adverse Effects of Any Grade Between Combinations of BRAF Inhibitors and MEK Inhibitors

Adverse Effect	BRAF Inhibitors (%)	MEK Inhibitors (%)
Diarrhea	12-34	40-43
Alopecia	26-37	17 (trametinib only)
Palmar-plantar erythrodysesthesia	14-47	NR
Hyperkeratosis	29-39	NR
Skin papilloma	9-18	NR
Secondary nonmelanoma skin cancer	9-18	NR
Photosensitivity	4-30	NR
Fatigue	26-35	22-26
Headache	19-26	NR
Arthralgia	27-45	NR
Myalgia	22-27	NR
Acneiform dermatitis	3-4	19-36
Peripheral edema	5	26-36

Abbreviation: NR, not reported.

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Irrespective of the treatment combination, certain adverse events warrant particular attention, such as pyrexia, decreased left ventricular ejection fraction, hypertension, and QTc prolongation. Pyrexia (≥38°C) can occur in more than 50% of patients in the early course of combined treatment with dabrafenib and trametinib (median time to onset, 19 days), can last longer than 1 week (median duration, 9 days), and can recur. Early treatment can involve non–steroidal anti-inflammatory drugs and hydration;

however, high-grade and prolonged pyrexias may require the use of dose interruption and systemic corticosteroids. Excellent reviews regarding the optimal management of other adverse events in patients who receive MAPK inhibitors are available.[112] Knowledge about class-specific, drug-specific, and regimen-specific adverse events is key to the selection of the most appropriate doublet therapy and the decision of whether to interrupt, modify, or reduce the dose or even switch to another doublet if toxicity, but not disease progression, is the issue.

KEY POINTS

- Toxicities from immune checkpoint inhibitors are generally reversible with dose suspension and use of corticosteroids and/or other immunomodulatory agents. The exception is endocrine toxicities, which may require permanent hormone replacement. For serious adverse events, suspension or discontinuation of immune checkpoint inhibitors is recommended.
- Discontinuation of immunotherapy because of severe adverse events has not been shown to affect overall clinical benefit.
- Physicians should be aware of drug- and class-specific adverse events of the three currently FDA-approved BRAF/MEK combinations (vemurafenib and cobimetinib, dabrafenib and trametinib, and encorafenib and binimetinib), as well as appropriate dose reductions, delays, or even treatment discontinuations, if necessary.

SEQUENCING OF THERAPY, INITIAL TREATMENT SELECTION, AND STOPPING OF THERAPY

After the approval of immunotherapy and BRAF/MEK inhibitors for frontline therapy in advanced, unresectable melanoma, a major question in the field was the sequencing of therapy for patients with *BRAF* V600–mutated melanoma. The DREAMseq ECOG-ACRIN EA 6134 study has provided the first prospective data regarding clinical outcomes in this patient population.[113,114] This phase 3 trial randomly assigned treatment-naive patients with *BRAF* V600–mutated metastatic melanoma to first-line therapy (step 1) with nivolumab and ipilimumab (arm A) or dabrafenib and trametinib (arm B). At disease progression, patients enrolled in step 2 and received the alternative therapy of dabrafenib and trametinib (arm C) or nivolumab and ipilimumab (arm D), respectively. At the time of the fourth interim analysis (59% of patients being 2 years from enrollment), available data led the data safety monitoring committee and National Cancer Institute Cancer Therapy Evaluation Program to recommend halting accrual and releasing data. The 2-year overall survival rate significantly improved for those starting with combination immunotherapy (arm A) was 72% (95% CI, 62%-81%) compared with 52% for those starting with targeted therapy (arm B) (95% CI, 42%-62%; log-rank $P = .0095$). Progression-free survival showed a trend in favor of arm A (log-rank $P = .054$). The objective response rates in each arm were 46% (52 of 113 patients) for arm A, 43% (49 of 114 patients) for arm B, 48% (11 of 23 patients) for arm C, and 30% (8 of 27 patients) for arm D. The final update with nearly 5 years of follow-up confirmed the superior overall survival for patients with *BRAF* V600–mutated metastatic melanoma receiving nivolumab and ipilimumab first-line compared with those receiving the treatment sequence beginning with dabrafenib and trametinib with nearly doubling of the overall survival rate (63.3% vs 33.9%, $P \leq 0.01$).[115] Thus, combination immunotherapy is preferred over targeted therapy in the first-line setting for stage IV *BRAF* mutant melanoma.

Another question is whether first-line concurrent PD-1/CTLA-4 blockade should be a universal strategy for any patient with advanced melanoma or whether PD-1/LAG-3 blockade is sufficient. The optimal upfront combination regimen should consider patient preferences and perceptions about the severity of life-threatening treatment-related toxicities, total tumor burden, requirement for a prompt response if tumor volume and location of metastatic tumors (eg, CNS) cause life-threatening symptoms, and overall performance status. Although a combination immunotherapy regimen is favored as the first-line treatment of patients with metastatic melanoma, single-agent anti–PD-1 therapy may be considered as an alternative treatment option when the risks of irAE is high, or in those who decline combination treatment, if the patient has oligometastatic disease (low burden/small volume disease and 1-2 organ involvement), normal LDH, PD-L1 expressive melanoma, and good performance status of 0-1. In these clinical scenarios, single-agent anti–PD-1 treatment has comparable outcomes as combined immune checkpoint inhibitor treatment with lower risks of irAE.

Once secondary resistance to MAPK inhibitors develops, rechallenge after several months after the end of initial MAPK inhibitor treatment can be beneficial. A multicenter retrospective analysis of patients (N = 116) who had previously received MAPK inhibitors and whose disease subsequently progressed showed that rechallenge with MAPK inhibitors was associated with a high antitumor response rate (42%). Of interest, responses on rechallenge were usually higher in patients who had longer intervals between the first treatment and rechallenge.[116]

PD-1 inhibitors may result in long-lasting durable responses after stopping treatment. An analysis of patients who received at least one dose of pembrolizumab as part of the phase 1 pembrolizumab study (KEYNOTE-001; N = 655) and stopped treatment after a complete response after 2 years (n = 67) showed that responses were durable after stopping.[117] Less is known about outcomes after rechallenging patients with metastatic disease progression whose disease had previously responded to PD-1 inhibitors, but treatment was stopped; however, patients can respond again after resuming immunotherapy.

KEY POINTS

- In treatment-naive patients with advanced *BRAF* V600–mutated melanoma, intermediate-term data show significantly improved overall survival for those who start with nivolumab and ipilimumab and then switch to dabrafenib and trametinib at the time of disease progression rather than the reverse treatment sequence.
- Although anti–PD-1 monotherapy remains a first-line option, the decision to treat with single or dual checkpoint blockade (PD-1/CTLA-4 vs PD-1/LAG-3) should be individualized on the basis of risk for immune-related toxicities, tumor burden, central nervous system disease status, performance status, tumor-associated symptoms, and patient preference.
- Immunotherapy can result in durable complete responses after stopping therapy. Treatment discontinuation of immunotherapy should be discussed with patients who have a confirmed complete response.

PRESENTING CASE STUDY

A 59-year-old woman with past medical history significant for hypertension and type 2 diabetes mellitus presents to her dermatologist for an "ugly mole" on her left forearm that has been getting larger in the past 3 months. It began to intermittently bleed 1 month ago, prompting a visit to a dermatologist. A shave biopsy demonstrated a nodular melanoma with a Breslow depth of 3.4 mm without ulceration, four mitoses per mm^2, and positive deep margins. She is referred to surgical oncology for excision, and further evaluation reveals a 3.5-cm palpable, enlarged left axillary node. A core needle biopsy of the lymph node is consistent with melanoma. She has no prior personal or family history of skin cancer or autoimmune disease. The patient's Eastern Cooperative Oncology Group performance status is 0.

Based on the information gathered from the skin and lymph node biopsies, what are your next steps to complete staging? What other information about this patient's melanoma would have potential treatment implications?

This patient's melanoma is at least stage IIIB (pT3aN1bMx) based on the Breslow depth, absence of ulceration, and clinically detected regional lymph node involvement. The first step would be to complete staging with chest, abdominal, and pelvic CT with intravenous contrast (or PET/CT) and brain MRI with and without intravenous contrast. Tumor testing for *BRAF* should be performed to assess for *BRAF* V600E/K mutation.

The result of the molecular test performed on tumor for *BRAF* V600E/K mutation status are positive for *BRAF* V600E.

Scenario 1

There is no evidence of distant spread on imaging. How does this finding affect your choice of next steps?

Neoadjuvant-adjuvant immunotherapy demonstrated improved event-free survival compared to adjuvant-only immunotherapy in clinically detected, resectable stage III melanoma; therefore, a neoadjuvant approach, followed by surgical resection should be considered for this patient. One option is neoadjuvant pembrolizumab monotherapy (200 mg) for 9 weeks (3 cycles), followed by total lymph node dissection per SWOG 1801. All patients would receive 15 cycles of postoperative adjuvant pembrolizumab. For this patient, a more preferrable approach could be combination neoadjuvant immunotherapy with ipilimumab (80 mg) and nivolumab (240 mg) for 6 weeks (2 cycles), followed by total lymph node dissection per the NADINA trial. In this option, the decision for adjuvant therapy is guided by pathologic response. Patients who achieve major pathologic or complete response (≤10% residual viable tumor) would be allowed to omit adjuvant therapy. Patients who have partial or no pathologic response (≥11% residual viable tumor) would receive either adjuvant nivolumab for 44 weeks (11 cycles) if *BRAF* wild type or adjuvant dabrafenib and trametinib daily for 46 weeks if *BRAF* V600E/K mutated.

Scenario 2

Three pulmonary nodules and two hepatic lesions, all measuring between 1 and 3 cm in size, suspicious of metastases, are discovered on preoperative staging. Biopsy of the liver lesion confirms metastatic melanoma. How would your choice of treatment differ from the first scenario?

Combination immunotherapy with standard-dose ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) or nivolumab and relatlimab should be considered in the frontline setting for this patient. Of note, there may be a select group of patients

for whom anti-PD-1 monotherapy is appropriate based on their disease status, comorbidities, performance status, and preference. For patients with *BRAF* V600E/K-mutated melanoma, including the patient for this particular case study, combination immunotherapy is still the preferred upfront therapy rather than BRAF/MEK inhibitor therapy based on the results of DREAMSeq and SECOMBIT trials, which showed superior overall survival in patients who received immunotherapy before switching to BRAF/MEK inhibitor therapy at progression compared to patients who started with BRAF/MEK inhibitor therapy before switching to immunotherapy at progression.

SURVIVORSHIP

The number of melanoma survivors living in the United States has increased over the last few years (Fig. 16-1). As of 2022, cutaneous melanoma is the second and fourth most common tumor among male and female survivors, respectively.[118] Patients with previously diagnosed cutaneous melanoma have a 1% to 8% lifetime risk of developing another invasive melanoma. Melanoma survivors also tend to be diagnosed with nonmelanoma skin cancers more frequently. Patients with lymphedema had significantly lower scores on a majority of health-related quality-of-life measures. Younger patients reported financial issues, ranging from poor performance at work requiring a career change to financial difficulties associated with the cost of lymphedema therapy, whereas young men and women reported worse social functioning and poorer body image scores. Female long-term melanoma survivors had a higher frequency of fatigue, nausea, insomnia, appetite loss, and constipation. In the modern era of immunotherapy and targeted therapy, survivorship care must include management of long-term and chronic adverse effects, which are characteristic, in particular, of immunotherapy-based regimens.[119]

MELANOMA IN OLDER ADULTS

Of patients diagnosed with cutaneous melanoma, 30.7% are older than the age of 60 years.[120] In fact, the gradual increase in cutaneous melanoma incidence over the last 20 years shown in Figure 16-1 is predominantly attributable to men older than 70 years and to a lesser extent to women older than 70 years.[121] Older men have significantly higher cutaneous melanoma incidence and mortality rates than older women. Cutaneous melanoma occurring in patients older than 60 years is biologically and clinically different from the cutaneous melanoma occurring in younger patients. Melanoma in older adults usually has greater Breslow thickness of invasion, has a lower incidence of positive SLNs, and is less frequently of the superficial spreading melanoma histologic subtype. The incidence of positive SLNs is lower in older patients. Melanomas in older adults have a higher incidence of somatic mutations of the UV radiation signature type, implying chronically sun-damaged skin. In this patient population, *BRAF* V600K and *NRASQ61* mutations are more frequently seen. Despite the under-representation of older patients with melanoma in the pivotal studies that led to the FDA approval of various systemic treatments, older patients respond at least as well as younger patients and do not experience worse toxicities.[122] Nevertheless, the incidence of severe adverse events from targeted therapies tends to be higher in older than in younger patients. Data are mixed regarding whether the incidence of irAEs from checkpoint inhibition changes with age,[123,124] although generally, cancer-related outcomes are similar in older and younger patients.[125]

In the treatment of older patients with advanced melanoma, geriatric assessments may be considered to determine the level of fitness and, therefore, eligibility for the potentially higher-risk higher-benefit combined-modality treatment. In cases of oligometastatic melanoma, upfront surgery (ie, metastasectomy), if possible, is a reasonable approach as an attempt to delay initiation of systemic treatments, given the possibility of their administration for the patient's remaining lifespan and their association with adverse events. Overall, immunotherapy is relatively safe to use in this cohort; however, further research is warranted to understand optimal decision-making.[126]

NONCUTANEOUS MELANOMA

EPIDEMIOLOGY AND RISK FACTORS

Although most prevalent in the skin, melanocytes can be found in other organs of the body and can give rise to noncutaneous melanomas. Noncutaneous melanomas comprise 5% of all melanomas. Approximately 3% to 5% are uveal, and the remaining 1% to 2% are mucosal. Mucosal melanomas represent a heterogenous disease based on primary anatomic origin, which include head and neck (55%; conjunctival, sinonasal, and oropharyngeal), anorectal (24%), and vulvovaginal (18%) areas.

HISTOPATHOLOGY, BIOLOGY, AND PROGNOSIS

Mucosal Melanoma

Oncogenic *BRAF* and *NRAS* mutations are less frequent in mucosal melanomas (6.4% and 13.8%, respectively) than in cutaneous melanomas, although the incidence of *KIT* mutations is higher; these tumors have a much lower somatic mutation burden than cutaneous melanoma.[127] Two large mucosal melanoma cohorts from Germany (N = 444) and China (N = 706)[128] have provided significant insight into the prognostic significance of various histopathologic factors. These cohorts showed that the depth of the

primary lesion, number of positive regional lymph nodes, and sites of distant metastases are important prognostic factors for overall survival.

Uveal Melanoma

The human adult choroid tissue does not have the classic lymphatic system drainage seen in other tissues. The transformation of choroidal melanocytes to melanoma leads to two possible uveal melanoma subtypes with respect to their propensity to metastasize distantly. These two types are classified as low risk (class 1) or high risk (class 2) for metastatic disease by gene expression profiling.[129] DecisionDx-UM (Castle Biosciences) is a commercially available 15-gene expression profiling diagnostic assay used for risk stratification in uveal melanoma. Another independent biomarker that was identified was *PRAME* expression, and the combination of the 15-gene expression profile and *PRAME* status has been validated in a multicenter prospective study as an integrated prognostic test for uveal melanoma.[130] Risk stratification can aid clinically in tailoring the frequency/modality of long-term surveillance in this patient population.[130]

Activating mutations in any of the two G-protein pathway–associated *GNAQ* and *GNA11* genes are present in a majority of uveal melanomas and are thought to be early events in tumorigenesis. Genetic aberrations of BAP1, an enzyme that removes single ubiquitin moieties from various substrates, including histones, are associated with the more aggressive class 2 type.[131] Gene expression analysis of 80 uveal melanomas as part of The Cancer Genome Atlas project has also shown low (ie, <15%) incidence of tumors bearing T cells expressing immune exhaustion markers. These molecular characteristics have provided the basis for several clinical trials, as discussed next in the "Treatment" section.

Once uveal melanoma becomes metastatic, the prognosis is poor, with the median overall survival ranging between 11.3 and 13.4 months.[132,133] Multivariable analysis has shown that ECOG PS of 1 or higher, high serum LDH level, and short time from primary tumor diagnosis to metastasis are poor prognostic factors for survival.

TREATMENT

Mucosal Melanoma

Management of this rare subtype often requires a multidisciplinary approach. Resection of the primary lesion with negative surgical margins is an important prognostic factor and can be curative in select cases. The utility of SLN mapping is controversial. Lymph node dissection is considered if there is clinical or radiologic evidence of nodal involvement. Postoperative radiotherapy can reduce the risk of local-regional recurrence and is considered in high-risk disease (close and positive margins, multifocal lesions, or extracapsular extension); however, it has not affected the rate of distant metastasis or overall survival.[134-136] There is a paucity of data for adjuvant immunotherapy in resected mucosal melanoma. An international retrospective study included 55 patients with resected mucosal melanoma who completed adjuvant anti–PD-1 therapy and found no statistical difference in recurrence-free survival (HR, 1.36; 95% CI, 0.69-2.68), distant metastasis–free survival (HR, 0.53; 95% CI, 0.24-1.17), or overall survival (HR, 1.1; 95% CI, 0.45-2.65) when compared with the matched historical cohort.[137] Adjuvant nivolumab and ipilimumab was tested in the multicenter phase 2 single-arm SALVO trial. Thirty-five patients with resected mucosal melanoma who received ipilimumab at 1 mg/kg and nivolumab at 3 mg/kg (flipped-dose regimen) for 4 cycles every 3 weeks, followed by maintenance nivolumab had 2-year recurrence-free survival and overall survival rates of 37% and 68%, respectively.[138]

The prognosis for patients with metastatic mucosal melanoma is poor. Even though the treatment for metastatic mucosal melanoma is largely extrapolated from randomized trials for cutaneous melanoma, the efficacy of immunotherapy in mucosal melanoma is consistently suboptimal compared to cutaneous melanoma. In a pooled analysis of six clinical trials that recruited patients with advanced mucosal melanoma, treatment with combination ipilimumab and nivolumab, nivolumab alone, and ipilimumab alone showed objective response rates of 37.1%, 23.3, and 8.3%, compared to 60.4%, 40.9%, and 21.2% for cutaneous melanoma.[139] This finding was supported by a large, international retrospective study which reported that a single-agent anti–PD-1 and or combination PD-1 and CTLA-4 blockade may result in antitumor response rates of 29% and 31%, respectively.[140] The decreased efficacy of conventional immunotherapies may be, in part, explained by the lower tumor mutation burden, lower rates of oncogenic driver mutations, and decreased PD-L1 positivity seen in these tumors.

Prospective studies have been mostly conducted in China, where there is an increased prevalence of mucosal melanoma. In a phase 2 trial, 114 Chinese patients with previously untreated advanced mucosal melanoma were randomly assigned to carboplatin and paclitaxel with bevacizumab or carboplatin and paclitaxel alone.[141] The addition of bevacizumab moderately improved the median progression-free survival (4.8 vs 3.0 months; HR, 0.461; 95% CI, 0.306-0.695) and overall survival (13.6 vs 9.0 months; HR, 0.611; 95% CI, 0.407-0.917). More recently, combination anti–PD-1 and antiangiogenic therapies were examined in two separate prospective single-arm studies in China. Both combination toripalimab (anti–PD-1 antibody) and axitinib (a vascular endothelial growth factor receptor inhibitor) and atezolizumab and bevacizumab regimens achieved an objective response rate of 45% to 48%, a median progression-free survival of 8.0 to 8.2 months, and a 1-year overall survival rate of 62.1% to 76.0% in Chinese patients with unresectable or metastatic mucosal melanoma.[142,143] Despite these promising results, these combinations remain investigational. Currently, a phase 2 study exploring the efficacy of a combination of anti–PD-1 therapy and a vascular endothelial growth factor receptor inhibitor in the United States is in progress (NCT05384496).

KIT-targeted therapies have been investigated in melanomas bearing *KIT* genetic aberrations, including the mucosal subtype. In a 25-patient phase 2 study, imatinib (400 mg administered orally once daily) was associated with a 21% incidence of confirmed antitumor response rates. All responses occurred in patients with mutations as opposed to gene amplifications. However, most responses were short (median time to progression, 3.7 months), and the median overall survival was 12.5 months.[144]

Uveal Melanoma

Historically, enucleation had been the standard-of-care treatment of select patients with uveal melanoma. The Collaborative Ocular Melanoma Study is the largest trial of patients (N = 1317) with uveal melanoma to address whether local radiation therapy is noninferior to eye enucleation. Patients with no evidence of metastatic disease were randomly assigned to eye-preserving[133] I-plaque radiation therapy versus enucleation; there was no difference in melanoma-specific overall survival.[145]

Molecular assays have enabled better identification of patients at high risk of distant metastatic uveal melanoma. Adjuvant clinical trials in this high-risk group are under way; at this time, only results from non–randomized single-arm studies are available.

Metastatic uveal melanoma has a poor prognosis. A single-institution retrospective analysis of 521 patients who were diagnosed with metastatic uveal melanoma and observed until 2011 showed poor overall survival, irrespective of whether the patient received treatment (median overall survival, 6.3 vs 1.7 months, respectively).[146] In a selected patient population, adoptive cell therapies have shown proof-of-principle efficacy, suggesting that immunotherapies can have a role in this aggressive disease.[147] Retrospective studies have shown the overall response rate of metastatic uveal melanoma to combination nivolumab and ipilimumab to be low (11.6%),[148] although higher than with single-agent PD-1/PD-L1 therapy (3.6%).[149] An increased benefit of combination immunotherapy was confirmed by two phase 2 prospective single-arm multicenter studies in patients with metastatic uveal melanoma, showing that concurrent CTLA-4/PD-1 blockade was associated with a clinical benefit inferior to that seen in cutaneous melanoma and mucosal melanoma.[150,151] Despite advances in knowledge about the biology of uveal melanoma, little clinical benefit has been demonstrated so far with targeted therapies, including MEK inhibitors.[152,153]

The first FDA-approved drug for metastatic uveal melanoma, tebentafusp, is a first-in-class bispecific fusion protein. This engineered T-cell receptor therapeutic detects the gp100 peptide presented by HLA*02:01, with the other end fused to an anti-CD3 chain that binds and activates T cells. The phase 3 IMCgp100-202 trial randomly assigned 378 patients (2:1) to tebentafusp versus investigator's choice of therapy (pembrolizumab, ipilimumab, or dacarbazine), with a primary endpoint of overall survival. A recent update with a median follow-up of 36 months showed that the median overall survival was 21.6 months for the tebentafusp arm versus 16.9 months for the investigator's choice arm (HR, 0.68; 95% CI, 0.54-0.87).[154] Tebentafusp was FDA approved for HLA-A*02:01–positive patients with unresectable or metastatic uveal melanoma in January 2022.

Liver-directed therapies can be considered for patients with liver-dominant or isolated metastatic uveal melanoma. The FOCUS trial evaluated the efficacy of HEPZATO, a percutaneous hepatic perfusion (PHP) with melphalan, in a phase 3 multicenter study of 144 patients with unresectable metastatic uveal melanoma predominantly in the liver.[155] Although this study began as a randomized trial, the control arm of best alternative care (investigator's choice of transarterial chemoembolization, pembrolizumab, ipilimumab, or dacarbazine) was stopped after accruing 42 patients because of enrollment concerns, and 59 patients were then added to the PHP arm only. Melphalan at 3 mg/kg ideal body weight, infused into the hepatic artery every 6 to 8 weeks for up to six total infusions, demonstrated a superior objective response rate (35.2% vs 12.5%; $P = .0154$) and median progression-free survival (9.03 vs 3.12 months; $P = .0007$) when compared with the control arm. The median overall survival was numerically improved in the PHP arm (20.53 vs 14.06 months) compared with best alternative care but has yet to fully mature. Subsequently, isolated hepatic perfusion with melphalan in patients with isolated uveal melanoma liver metastases showed similar clinical benefit, with an improved objective response rate (40% vs 4.5%, $P < .0001$) and median progression-free survival (7.4 vs 3.3 months, $P < .0001$), against investigator's choice of treatment in the phase 3 randomized SCANDIUM trial.[156] PHP with melphalan gained FDA approval for liver-directed therapy for patients with liver-dominant uveal melanoma in August 2023; however, its availability is restricted to programs participating in the HEPZATO KIT Risk Evaluation and Mitigation Strategy (REMS) because of the risk of periprocedural complications, including hemorrhage, thromboembolic events, and liver injury.

KEY POINTS

- Noncutaneous melanomas account for 5% of all melanomas and consist of uveal and mucosal melanomas.
- *KIT* mutations are more frequent in mucosal melanomas compared with cutaneous melanomas; the incidence of oncogenic *BRAF* and *NRAS* mutations is low.
- A commercially available 15-gene expression profile (DecisionDx-UM) and *PRAME* RNA expression were validated in a prospective study as an integrated prognostic biomarker for uveal melanomas based on their propensity to metastasize and melanoma-specific survival. Genomic information assists in tailoring surveillance plans for patients after definitive treatment of their uveal melanomas.[130]
- *GNAQ* and *GNA11* mutations are present in a majority of uveal melanomas and are thought to be early events in tumorigenesis; genetic aberrations of *BAP1* are associated with the more aggressive class 2 type.

- A novel bispecific fusion protein, tebentafusp, is the first T-cell receptor therapeutic drug developed and the first drug to significantly improve overall survival in patients with metastatic uveal melanoma who are positive for HLA*02:01. Tebentafusp has been FDA approved for HLA-A*02:01–positive patients with unresectable or metastatic uveal melanoma.
- Combination ipilimumab and nivolumab is associated with higher response rates in both uveal and mucosal melanomas compared with single-agent PD-1 inhibitors; however, the clinical benefit from immunotherapy is much lower in these rare subtypes when compared with cutaneous melanoma.

NONMELANOMA SKIN CANCERS

Nonmelanoma skin cancer can arise from any skin cell subtype. BCCs and CSCCs comprise nearly 99% of nonmelanoma skin cancers and are by far the most frequently diagnosed skin cancers. Less common (1%) skin cancer types include MCC, Kaposi sarcoma, cutaneous lymphoma, skin adnexal tumors, and various types of sarcomas (eg, carcinosarcoma and fibrosarcoma). Approximately 5.4 million BCCs and CSCCs are diagnosed each year in the United States, affecting 3.3 million Americans; an increase in diagnoses and treatments represents an increasing public health challenge.

BCC, CSCC, and MCC share common risk factors (Table 16-4), such as high UV radiation exposure, skin phototype (low Fitzpatrick skin type), male sex, advanced age, and immunosuppression. In MCC, Merkel cell polyomavirus also plays a pathogenic role. Several histopathologic analyses across the three nonmelanoma skin cancers have detected a high incidence of PD-1–positive lymphocytes that infiltrate PD-L1–expressing tumors; these studies have established the translational rationale for the successful use of PD-1/PD-L1 pathway inhibitors in each of these three cancers.[157-159] Because of the high frequency of these cancers and the increasing costs of diagnostics and treatments, considerable research on chemoprevention is ongoing. Apart from large public health care campaigns to encourage the use of broad-spectrum (UV radiation types A and B) sunscreens and adoption of sun-safe practices, large randomized clinical trials have identified a handful of chemopreventive agents that reduce the incidence of skin cancer development compared with standard-of-care practices, but those agents still have not been incorporated into routine clinical use.[160,161]

Table 16-4 **Important Characteristics of the Three Most Frequent Nonmelanoma Skin Cancers**

Characteristic	Squamous Cell Carcinoma	Basal Cell Carcinoma	Merkel Cell Carcinoma
New diagnoses	>1 million per year	Approximately 4.3 million per year	Approximately 2000 per year
Cell origin	Stem cells in the hair follicle bulge and basal layer of interfollicular epidermis	Undifferentiated $CD200^+$ basal cells of the hair follicle outer root sheath	Merkel cells in the basal epidermal layer of skin
Precursor lesion	Solar keratosis, Bowen disease, and keratoacanthoma	Not known	Not known
Risk factors	UV radiation exposure, skin phototype, ionizing radiation, chronic wounds/scars, immunosuppression, HPV infection, smoking, and genetic defects in DNA repair	UV radiation exposure, tanning bed use, skin phototype, male sex, age >50 years, immunosuppression, and basal cell nevus syndrome	UV radiation exposure, skin phototype, age >70 years, male sex, immunosuppression, and MCPyV
Biology	High somatic mutation burden (*TP53, NOTCH1/2/4, CDKN2A*, and *EGFR*), high degree of PD-1–positive tumor-infiltrating lymphocytes	Mutations in *PTCH1*, smoothened homolog, high degree of PD-1–positive tumor-infiltrating lymphocytes	Low somatic mutation burden if MCPyV positive, high somatic mutation burden if MCPyV negative, high degree of PD-1–positive tumor-infiltrating lymphocytes
Prevention	Broad-spectrum sunscreens, nicotinamide, and acitretin	Broad-spectrum sunscreens, nicotinamide, and calcipotriol + 5-fluorouracil	Broad-spectrum sunscreens
Propensity to metastasize, %	41[162]	0.0029-0.55[163]	33[164]
Median OS, if distant metastatic	2.2 years[165]	24.1 months[166]	12-17.2 months[167,168]

Abbreviations: HPV, human papillomavirus; MCPyV, Merkel cell polyomavirus; OS, overall survival.
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Newly diagnosed CSCC and BCC can be stratified on the basis of relapse risk and metastatic potential according to the National Comprehensive Cancer Network guidelines. Large size (>20 mm for trunk and extremities and 10 mm for face), poorly defined borders, prior recurrence, immunosuppression, and poor histology are associated with a high risk of relapse and distant metastasis. In cases of CSCC and MCC, which have a higher propensity for metastasis, SLN mapping should be considered for complete staging. MCC staging is assigned based on tumor, node, and metastasis assessment according to the eighth edition of the American Joint Committee on Cancer staging system. CSCC staging can be assigned by American Joint Committee on Cancer staging. Of note, American Joint Committee on Cancer staging applies only to CSCC in the head and neck region because these guidelines were developed within the American Joint Committee on Cancer Head and Neck Committee and thus represent a major change from the seventh edition. The Brigham and Women's Hospital tumor staging system for CSCC was developed with the goal of providing an alternative T staging system for better risk stratification.[169-171]

Nonmelanoma skin cancers include BCC, CSCC, and MCC that are seen in older subjects and linked to excessive skin damage from sun exposure. Nonmelanoma skin cancers show infiltration by activated T lymphocytes and exhibit high tumor mutation load (except in Merkel cell polyoma virus associated MCC). Nonmelanoma skin cancers are highly curable with complete surgical resection conferring reduced risk of local relapse compared to alternative options such as cryotherapy, photodynamic therapy, radiation therapy, or local application of 5-fluorouracil and imiquimod. For lesions located on the face, Mohs micrographic surgery can provide the best cosmetic outcome. There are no standards for optimal wide-excision margins, although the National Comprehensive Cancer Network recommends excision of low-risk CSCC and BCCs with 4- to 6-mm and 4-mm clinical margins, respectively.

Radiation therapy is recommended for patients who are at high risk of local relapse following surgery and in cases in which surgery did not achieve negative margins. Radiation therapy can also be considered in patients with CSCC and MCC who have positive lymph nodes and cannot be considered for systemic chemotherapy or radical lymph node surgery.

Considerable advances in the systemic management of nonmelanoma skin cancers have been achieved since 2012; these advances have challenged the use of cytotoxic chemotherapies for these cancers, which was common practice before 2012.

BCC is a tumor arising from the keratinocyte in the basal layer of epidermis that is increasingly diagnosed in older subjects linked to cumulative sun exposure, particularly to ultraviolet radiation. Although highly curable when diagnosed early, locally advanced surgically unresectable and metastatic BCC are incurable and often result in poor outcomes with historical treatments such as radiation. Driven by the unique biology of BCC, in which constitutive activation of the hedgehog signaling pathway is seen secondary to mutations in hedgehog pathway–associated genes, eg, *PTCH1* (mutation in 90%) and *SMO* (mutation in 10%), molecularly targeted therapy is possible. Vismodegib (first-in-class) and sonidegib are two FDA-approved small-molecule inhibitors of SMO for locally advanced surgically unresectable or metastatic BCC. The approval was based on large phase 2 non–placebo-controlled clinical trials (BOLT and STEVIE).[172,173] Both targeted therapies, sonidegib (200 mg) and vismodegib (150 mg), are orally available and are administered once daily. Antitumor responses were greater than 50% for both drugs, and they are higher in patients with locally advanced disease compared with those with metastatic disease. Class-specific adverse event rates for hedgehog inhibitors are muscle spasms (49%-64%), alopecia (43%-62%), dysgeusia (38%-54%), weight loss (27%-33%), asthenia (8%-28%), appetite loss (19%-25%), diarrhea (17%-24%), nausea (16%-33%), and fatigue (16%-29%). Given the cumulative constitutional symptoms, treatment with hedgehog inhibitors is frequently interrupted or discontinued. Nevertheless, the median overall survival for the metastatic BCC cohort for vismodegib was 33.4 months, whereas it was not reached for sonidegib.

In February 2021, FDA-approved cemiplimab-rwic at a dose of 350 mg every 3 weeks for patients with locally advanced surgically unresectable or metastatic BCC who had progressed on HHI therapy, had not had an objective response after 9 months on HHI therapy, or were intolerant of prior HHI therapy or are not candidates for curative surgery or radiation therapy. The incidences of confirmed objective antitumor response in patients with metastatic BCC (n = 28) and locally advanced BCC (n = 84) were 21% and 29%, respectively. At median follow-ups of 9.5 (metastatic BCC) and 15.1 months (locally advanced BCC), the duration of response had not been reached (range, 9 to ≥23 and 2 to ≥21 months, respectively).[174,175]

CSCC: Although highly cured by surgery in early-stage disease, locally advanced surgically unresectable or metastatic CSCC is life threatening and not cured with historical treatments such as chemotherapy or epidermal growth factor antagonist cetuximab or radiation therapy. Due to exhibition of favorable biomarkers for response to immune checkpoint inhibitor therapy (such as high tumor mutation burden, increased TILs, and PD-L1 expression), locally advanced and surgically unresectable CSCC patients underwent clinical trials with anti–PD-1 agents. PD-1 inhibitors, cemiplimab, pembrolizumab, and cosibelimab were granted FDA approval for treatment of locally advanced surgically unresectable and distant metastatic CSCC on the basis of high antitumor responses and longer durability of responses. EMPOWER-CSCC-1 was a phase 1/2 study of cemiplimab (3 mg/kg administered intravenously every 2 weeks or 350 mg every 3 weeks) in patients with locally advanced and metastatic squamous cell carcinoma, reporting overall response rates of 44% and 49%, respectively.[176] At a median follow-up of 9 (locally advanced disease) and 17 months (metastatic disease), the median overall survival had not been reached.[177,178] In the KEYNOTE-629 phase 2 study, single-agent pembrolizumab led to a 34% response rate in patients with recurrent or metastatic

CSCC. At a median follow-up of 11.4 months, the median progression-free survival was 6.9 months, whereas the median overall survival had not been reached.[179] In the CARSKIN trial, single-agent pembrolizumab had a slightly higher response rate in patients with unresectable CSCC (41%). At a longer median follow-up of 22.4 months, the median progression-free survival was 6.7 months, and the overall survival had not been reached.[180] CK-301-101 was a phase 1 trial of cosibelimab, a fully humanized monoclonal antibody against PD-L1. Unique to this drug molecule is the potential for a dual function of triggering antibody-dependent cellular cytotoxicity (ADCC) in addition to the conventional mechanism of action of PD-1/PD-L1 blockade. ADCC function is mediated through the Fc region of the antibody engaging with natural killer (NK) cells to promote direct tumor lysis. Seventy-eight patients with metastatic (defined as nodal and/or distant) CSCC received cosibelimab 800 mg every 2 weeks until confirmed complete response, progressing disease, or intolerant toxicity. The primary endpoint of objective response rate was 47.4% with ongoing response in 73.0% of patients with a median follow-up of 15.4 months. Grade 3 or higher treatment-related adverse events occurred in 10.3% of participants. Overall, this study demonstrated a meaningful clinical activity without any new safety signals.[181]

There is also now emerging evidence of clinical benefit of perioperative immunotherapy for high-risk CSCC.

After surgical resection and postoperative radiotherapy, cemiplimab administered at a dose of 350mg for the first 12 weeks and then switched to 700mg every 6 weeks for additional 36 weeks demonstrated superior disease-free survival compared to placebo (HR 0.32, 95% CI 0.20 to 0.51, $P < 0.001$) in high-risk CSCC in a randomized phase 3 trial.[182] The trial defined high-risk disease as patients with in-transit metastases, radiologic or clinical evidence of perineural invasion of named nerves, T4 primary tumor (with bone invasion), or local recurrence with poorly differentiated history, nodal stage ≥N2b, ≥T3 lesion (diameter >4.0 cm). Patients with high-risk nodal disease defined as extracapsular extension with at least one node measuring at least 20 mm in diameter or at least three involved nodes regardless of extracapsular extension were also eligible for the study.

Neoadjuvant cemiplimab, administered for a maximum of four cycles at a 350-mg fixed dose, showed a promising pathologic complete response rate of 51% and radiologic RECIST response rate of 68% in an international phase 2 single-arm trial that enrolled 71 patients with resectable stage II to IV CSCC; all 15 patients who had either a pathologic complete or a major response were disease free at a median follow-up of 37.4 months.[183] A phase 3 randomized trial to evaluate neoadjuvant cemiplimab with or without adjuvant cemiplimab (pathologic response guided) compared to standard-of-care surgical resection is in progress (NCT 06568172).

PD-1/PD-L1 inhibitors were also approved by the FDA in 2017 (avelumab), 2018 (pembrolizumab), and 2023 (retifanlimab) for the treatment of metastatic MCC.[184] Although antitumor responses have been similar to those seen with metastatic melanoma and squamous cell carcinoma, overall survival has been shorter. In the JAVELIN Merkel 200 study, avelumab (10 mg/kg administered intravenously every 2 weeks) in the first-line setting was associated with a 33% confirmed overall response rate. At a median follow-up of 40.8 months, the median overall survival was 12.6 months, and the 42-month overall survival rate was 31%.[185] The clinical benefit was not significantly different when avelumab was administered to patients who had previously experienced progression after prior chemotherapy for metastatic MCC.[186] In the smaller study of pembrolizumab for patients with treatment-naive metastatic disease, MCC antitumor responses were higher (56%), and the 24-month overall survival rate was 69%.[187] Lastly, retifanlimab, a PD-1 blocking antibody (500 mg administered intravenously every 4 weeks) achieved an overall response rate of 46.2% with a disease control rate of 53.8%.[184]

KEY POINTS

- Nonmelanoma skin cancers are by far the most frequently diagnosed cancers. This has implications for increasing health care costs, particularly for BCC and squamous cell carcinoma.
- Surgery is the cornerstone therapy for management of most nonmelanoma skin cancers.
- Unlike MCC, squamous cell carcinoma and BCC have low metastatic potential.
- PD-1/PD-L1 inhibitors have been approved for patients with locally advanced or distant metastatic nonmelanoma skin cancers: pembrolizumab and cemiplimab for CSCC, avelumab and pembrolizumab for MCC, and cemiplimab for BCC.
- Neoadjuvant cemiplimab showed a high pathologic complete response rate in a phase 2 trial of stage II to IV resectable CSCC.
- In a phase 3 trial which randomized patients with resected high-risk CSCC to either adjuvant cemiplimab or placebo, the adjuvant cemiplimab group achieved significantly longer disease-free survival.
- Two hedgehog inhibitors, sonidegib and vismodegib, are approved for the treatment of advanced BCC. In practice, both can be used interchangeably, although notably, sonidegib was studied in patients with locally advanced BCC, whereas vismodegib was studied both in patients with locally advanced disease and in those with metastatic disease.

HIGH-YIELD TAKEAWAYS

Triple M overlap syndrome

- TMOS, characterized by myocarditis, myositis, and myasthenia gravis, is an oncologic emergency that can occur in patients treated with single or combination immunotherapy. Although rare, it carries a particularly high mortality rate and requires a multidisciplinary team (cardiology, neurology, and rheumatology) effort for prompt diagnosis and treatment.

Melanoma and brain metastases

- Combination nivolumab and ipilimumab at standard dosing (1 and 3 mg/kg, respectively) should be considered when deciding the upfront treatment option for patients with brain metastases as it has demonstrated meaningful intracranial and extracranial responses, particularly in patients who are neurologically asymptomatic, not receiving steroids, and have intracranial metastases 3 cm in diameter or smaller.

Resectable melanoma and treatment

- Adjuvant immunotherapy is approved for resected stage IIB/C, III, and IV melanoma.
- Adjuvant BRAF/MEK inhibitor therapy is approved for resected stage III melanoma.
- There is emerging data for neoadjuvant immunotherapy, followed by surgery for patients with resectable, macroscopic stage III or IV melanoma.

Unresectable metastatic melanoma and treatment

- Combination immunotherapy (ipilimumab and nivolumab, relatlimab and nivolumab) and anti–PD-1 monotherapy (nivolumab and pembrolizumab) are approved therapies for metastatic or unresectable melanoma.
- For patients with *BRAF* V600–mutated melanoma, combination targeted therapy (encorafenib + binimetinib, dabrafenib + trametinib, or vemurafenib + cobimetinib) is also approved.
- For patients with *BRAF* V600–mutated melanoma, combination immunotherapy is preferred over the combination targeted therapy for the first-line setting based on the improved overall survival demonstrated in the DREAMseq study.

ANTI–PD-1 refractory melanoma and treatment

- Lifileucel, TIL therapy, was recently approved for patients who have progressed on anti–PD-1 therapy and, if *BRAF* V600 mutated, BRAF/MEK inhibitors.

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MELANOMA AND OTHER SKIN CANCERS 16

CHAPTER SUMMARY GUIDE

KEY POINTS

- Cutaneous melanoma accounts for 1.7% of all new cancer diagnoses annually worldwide; 0.7% of all cancer-related deaths are a result of cutaneous melanoma.
- Projected melanoma-specific mortality rates have been declining since 2016; overall incidence rates seem to have stabilized for men after decades of increase while continuing to increase for women.
- In 2025, about 104,960 new cases of invasive melanoma are expected to be diagnosed in the United States with about 8,430 projected deaths.
- Both cutaneous melanoma incidence and mortality rates are higher in men than in women.
- UV light exposure is the most well-characterized risk factor for cutaneous melanoma.
- Australia and New Zealand have the highest incidence of melanoma but relatively better survival outcomes, while Black Americans experience low melanoma incidence but relatively worse survival.
- Familial cutaneous melanomas represent approximately 10% of melanomas.
- Germline mutations in the *CDKN2A* and *BAP1* gene locus are associated with an increased risk of developing cutaneous and uveal melanoma.
- All patients with melanoma and a personal history or family history of cancer should be referred to genetics.
- *BRAF* V600E is the most frequent somatic mutation in sporadic melanomas, followed by mutations in *NRAS, CDKN2A, TERT*, and *NF1*.
- Population-based skin cancer screening programs have identified risk factors that can render melanoma screening cost efficient to select high-risk patients.
- The use of sunscreens has the highest level of clinical evidence for melanoma prevention.
- Clinical evaluation of a patient with newly diagnosed cutaneous melanoma should include a full medical history, including family and personal histories of melanoma and other cancers.
- Physical examination should include skin and lymph node examinations every 3 to 6 months for the first 3 to 5 years and then annually for their lifetime.
- Surgical management includes wide local excision concurrent with SLN biopsy when indicated. SLN status is an independent prognostic factor for overall survival.
- Melanoma with deep Breslow thickness (ie, ≥4.0 mm) and ulceration, even without positive regional lymph nodes (stage IIC), has a high risk of recurrence.
- Completion lymph node dissection did not improve overall survival after a positive SLN biopsy specimen in two randomized clinical trials and is not considered standard of care for all patients with clinically occult stage III melanoma. Completion lymph node dissection decreases the incidence of regional lymph node recurrence and can be considered in select patients.
- For patients with clinical stage III melanoma (clinically palpable regional lymph nodes), neoadjuvant treatment approaches preferably containing combination immunotherapy is recommended. Total lymph node dissection with or without external radiation therapy to the lymph node basin should be reserved for patients who are refractory to neoadjuvant treatment (ie, no pathologic response or minimal pathologic response) of the regional nodal basin.
- Although adjuvant radiation decreased the risk of in-field recurrence, there was no significant decrease in relapse-free survival or overall survival. Adjuvant radiation can be considered for select patients with a high risk for locoregional recurrence.
- Adjuvant pembrolizumab and nivolumab are FDA approved for patients with resected stage IIB/C melanoma because of improved relapse-free survival; however, the decision to pursue adjuvant therapy should include a careful discussion of risks and benefits.
- Combination dual targeted therapy with dabrafenib and trametinib (in *BRAF* V600–mutated disease), as well as nivolumab and pembrolizumab, is an adjuvant treatment option for patients with completely resected stage III melanoma based on improved relapse-free survival and reasonable tolerability.

- Active surveillance alone, without adjuvant therapy, is an equally acceptable option for patients with high-risk resected melanoma, given that there is no clear overall survival benefit with adjuvant anti–PD-1 monotherapy or adjuvant targeted therapy. The decision between treatment and observation requires shared decision-making between the patient and provider, including a detailed discussion of risk and potential benefit.
- Adjuvant ipilimumab and nivolumab at attenuated doses showed no clinical benefit in resected stage IIIB-IIID melanoma patients and is not a recommended adjuvant therapy of melanoma.
- The combination of nivolumab and ipilimumab in the adjuvant setting has shown overall survival benefit in the resected stage IV setting with a significantly higher immune-related adverse event rate than definitive treatment for stage IV melanoma.
- Neoadjuvant approach is relevant and effective in high-risk clinically palpable stage III and resectable stage IV melanoma.
- Status of pathologic response in an index lymph node helps determine the need for lymph node dissection and additional adjuvant treatment in high-risk stage III disease.
- Neoadjuvant and adjuvant pembrolizumab improved event-free survival compared with adjuvant pembrolizumab in a randomized phase 2 trial.
- In a phase 3 trial, neoadjuvant ipilimumab and nivolumab had superior event-free survival compared with adjuvant nivolumab. The patients who achieved major pathologic responses after two doses of neoadjuvant ipilimumab and nivolumab did not receive adjuvant therapy and had an estimated 12-month recurrence-free survival of 95.1%, highlighting the potential role of pathologic response as a predictive biomarker to personalize adjuvant therapy.
- In a smaller multi-institutional study, neoadjuvant relatlimab and nivolumab regimen was found to be effective and safe option in melanoma patients with stages IIIB, IIIC, IIID, and IV (M1a) disease.
- Surgical resection can be considered in select patients with symptomatic melanoma brain metastases and for disease control (ie, oligometastatic disease) or with palliative intent.
- Systemic therapy with immune checkpoint inhibitor-based or BRAF-directed therapy in BRAF mutation–positive melanoma should be considered for primary treatment of melanoma brain metastases.
- Stereotactic radiosurgery is a standard palliative treatment option in advanced melanoma and can be considered for disease control in select patients with oligometastatic disease or limited central nervous system disease or when the tumor is inaccessible for surgery.
- Whole-brain irradiation did not reduce distant intracranial failure and was associated with earlier decline in performance status and hence not routinely recommended.
- Concurrent administration of MAPK inhibitors with radiation therapy worsens radiation therapy–related toxicities.
- Concurrent use of immune checkpoint inhibitor treatment and stereotactic radiosurgery of melanoma brain metastases is found to be safe in retrospective studies. However, optimal sequencing of immune checkpoint inhibitor treatment and radiation therapy is under clinical investigation in patients with melanoma brain metastases.
- Dual checkpoint blockade is the preferred first-line immunotherapy treatment option in unresectable/advanced melanoma.
- Concurrent ipilimumab and nivolumab should be considered for patients with small asymptomatic central nervous system metastases; both topics are discussed later in the chapter.
- Four phase 3 randomized clinical studies in patients with *BRAF* V600–mutated metastatic melanoma have shown significant progression-free survival and overall survival benefits favoring concurrent BRAF/MEK inhibition compared with a single-agent BRAF inhibitor.
- Oncolytic viral therapy such as TVEC represents a reasonable option to control local tumor in selected patients and showed superior responses lasting at least 6 months when compared to the granulocyte-macrophage colony-stimulating factor-treated arm. However, its combination with anti–PD-1 agent did not improve progression-free or overall survival.
- Lifileucel, a one-time autologous TIL therapy, is approved by the FDA for patients with anti–PD-1 refractory melanoma and can have clinically meaningful durable effect.
- Although systemic chemotherapy is not recommended as a first-line treatment of melanoma, it may be used in selected clinical scenarios as a bridge to future treatments.
- Patients with small untreated asymptomatic parenchymal brain metastases can be safely and effectively treated with concurrent ipilimumab and nivolumab, without local surgery or radiation therapy.
- Intracranial responses are durable in patients with asymptomatic parenchymal brain metastases treated with concurrent ipilimumab and nivolumab; the combination of dabrafenib and trametinib results in less durable intracranial responses.
- The care of patients with symptomatic melanoma brain metastases remains challenging. Coordination of multidisciplinary care, including expertise in surgery and radiation therapy, is recommended for this population.
- Toxicities from immune checkpoint inhibitors are generally reversible with dose suspension and use of corticosteroids and/or other immunomodulatory agents. The exception is endocrine toxicities, which may require permanent hormone replacement. For serious adverse events, suspension or discontinuation of immune checkpoint inhibitors is recommended.

- Discontinuation of immunotherapy because of severe adverse events has not been shown to affect overall clinical benefit.
- Physicians should be aware of drug- and class-specific adverse events of the three currently FDA-approved BRAF/MEK combinations (vemurafenib and cobimetinib, dabrafenib and trametinib, and encorafenib and binimetinib), as well as appropriate dose reductions, delays, or even treatment discontinuations, if necessary.
- In treatment-naive patients with advanced *BRAF* V600–mutated melanoma, intermediate-term data show significantly improved overall survival for those who start with nivolumab and ipilimumab and then switch to dabrafenib and trametinib at the time of disease progression rather than the reverse treatment sequence.
- Although anti–PD-1 monotherapy remains a first-line option, the decision to treat with single or dual checkpoint blockade (PD-1/CTLA-4 vs PD-1/LAG-3) should be individualized on the basis of risk for immune-related toxicities, tumor burden, central nervous system disease status, performance status, tumor-associated symptoms, and patient preference.
- Immunotherapy can result in durable complete responses after stopping therapy. Treatment discontinuation of immunotherapy should be discussed with patients who have a confirmed complete response.
- Noncutaneous melanomas account for 5% of all melanomas and consist of uveal and mucosal melanomas.
- *KIT* mutations are more frequent in mucosal melanomas compared with cutaneous melanomas; the incidence of oncogenic *BRAF* and *NRAS* mutations is low.
- A commercially available 15-gene expression profile (DecisionDx-UM) and *PRAME* RNA expression were validated in a prospective study as an integrated prognostic biomarker for uveal melanomas based on their propensity to metastasize and melanoma-specific survival. Genomic information assists in tailoring surveillance plans for patients after definitive treatment of their uveal melanomas.[130]
- *GNAQ* and *GNA11* mutations are present in a majority of uveal melanomas and are thought to be early events in tumorigenesis; genetic aberrations of *BAP1* are associated with the more aggressive class 2 type.
- A novel bispecific fusion protein, tebentafusp, is the first T-cell receptor therapeutic drug developed and the first drug to significantly improve overall survival in patients with metastatic uveal melanoma who are positive for HLA*02:01. Tebentafusp has been FDA approved for HLA-A*02:01–positive patients with unresectable or metastatic uveal melanoma.
- Combination ipilimumab and nivolumab is associated with higher response rates in both uveal and mucosal melanomas compared with single-agent PD-1 inhibitors; however, the clinical benefit from immunotherapy is much lower in these rare subtypes when compared with cutaneous melanoma.
- Nonmelanoma skin cancers are by far the most frequently diagnosed cancers. This has implications for increasing health care costs, particularly for BCC and squamous cell carcinoma.
- Surgery is the cornerstone therapy for management of most nonmelanoma skin cancers.
- Unlike MCC, squamous cell carcinoma and BCC have low metastatic potential.
- PD-1/PD-L1 inhibitors have been approved for patients with locally advanced or distant metastatic nonmelanoma skin cancers: pembrolizumab and cemiplimab for CSCC, avelumab and pembrolizumab for MCC, and cemiplimab for BCC.
- Neoadjuvant cemiplimab showed a high pathologic complete response rate in a phase 2 trial of stage II to IV resectable CSCC.
- In a phase 3 trial which randomized patients with resected high-risk CSCC to either adjuvant cemiplimab or placebo, the adjuvant cemiplimab group achieved significantly longer disease-free survival.
- Two hedgehog inhibitors, sonidegib and vismodegib, are approved for the treatment of advanced BCC. In practice, both can be used interchangeably, although notably, sonidegib was studied in patients with locally advanced BCC, whereas vismodegib was studied both in patients with locally advanced disease and in those with metastatic disease.

CHAPTER TABLES AND IMAGES

Table 16-1 Recommended Wide and Deep Excision Margins for Tis to T4 Melanoma

Breslow Depth of Invasion (mm)	Wide Surgical Margin (cm)	Deep Surgical Margin
In situ	0.5-1	Excised to the depth within the adipose layer
≤1.0	1	
>1.0 and ≤2.0	1-2	Excised to the depth immediately above muscle fascia
>2.0	2	

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Table 16-2 **Incidence and Timing of Organ-Specific Adverse Events From Combination Therapy With Ipilimumab and Nivolumab Versus Nivolumab Alone**

Affected System	Median Onset (weeks; %)	
	Combination Therapy	**Single-Agent Nivolumab**
Skin	2; 64	5; 33
Gastrointestinal	5; 47	7.3; 14
Hepatic	6.1; 29	7.7; 4
Endocrine	7.4; 30	10.4; 8
Pulmonary	10.6; 8	8.9; 2
Renal	10.2; 4	15.1; 2

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Table 16-3 **Differences in Treatment-Related Adverse Effects of Any Grade Between Combinations of BRAF Inhibitors and MEK Inhibitors**

Adverse Effect	BRAF Inhibitors (%)	MEK Inhibitors (%)
Diarrhea	12-34	40-43
Alopecia	26-37	17 (trametinib only)
Palmar-plantar erythrodysesthesia	14-47	NR
Hyperkeratosis	29-39	NR
Skin papilloma	9-18	NR
Secondary nonmelanoma skin cancer	9-18	NR
Photosensitivity	4-30	NR
Fatigue	26-35	22-26
Headache	19-26	NR
Arthralgia	27-45	NR
Myalgia	22-27	NR
Acneiform dermatitis	3-4	19-36
Peripheral edema	5	26-36

Abbreviation: NR, not reported.
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Table 16-4 **Important Characteristics of the Three Most Frequent Nonmelanoma Skin Cancers**

Characteristic	Squamous Cell Carcinoma	Basal Cell Carcinoma	Merkel Cell Carcinoma
New diagnoses	>1 million per year	Approximately 4.3 million per year	Approximately 2000 per year
Cell origin	Stem cells in the hair follicle bulge and basal layer of interfollicular epidermis	Undifferentiated $CD200^+$ basal cells of the hair follicle outer root sheath	Merkel cells in the basal epidermal layer of skin
Precursor lesion	Solar keratosis, Bowen disease, and keratoacanthoma	Not known	Not known
Risk factors	UV radiation exposure, skin phototype, ionizing radiation, chronic wounds/scars, immunosuppression, HPV infection, smoking, and genetic defects in DNA repair	UV radiation exposure, tanning bed use, skin phototype, male sex, age >50 years, immunosuppression, and basal cell nevus syndrome	UV radiation exposure, skin phototype, age >70 years, male sex, immunosuppression, and MCPyV
Biology	High somatic mutation burden (*TP53, NOTCH1/2/4, CDKN2A*, and *EGFR*), high degree of PD-1–positive tumor-infiltrating lymphocytes	Mutations in *PTCH1*, smoothened homolog, high degree of PD-1–positive tumor-infiltrating lymphocytes	Low somatic mutation burden if MCPyV positive, high somatic mutation burden if MCPyV negative, high degree of PD-1–positive tumor-infiltrating lymphocytes
Prevention	Broad-spectrum sunscreens, nicotinamide, and acitretin	Broad-spectrum sunscreens, nicotinamide, and calcipotriol + 5-fluorouracil	Broad-spectrum sunscreens
Propensity to metastasize, %	41[162]	0.0029-0.55[163]	33[164]
Median OS, if distant metastatic	2.2 years[165]	24.1 months[166]	12-17.2 months[167,168]

Abbreviations: HPV, human papillomavirus; MCPyV, Merkel cell polyomavirus; OS, overall survival.
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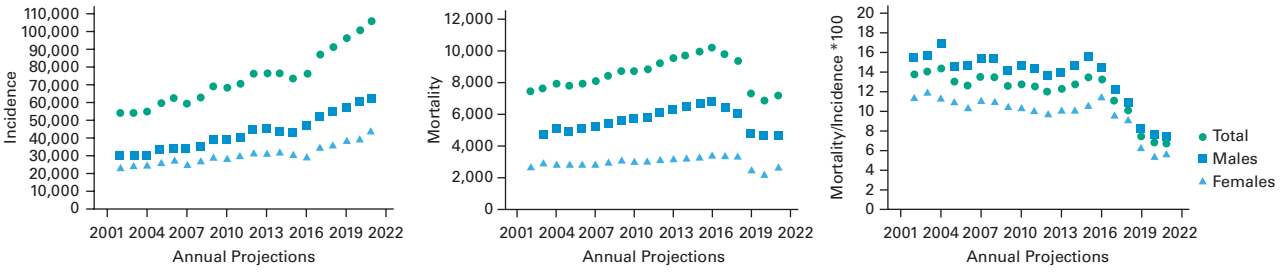
Figure 16-1 Melanoma Incidence, Mortality, and Mortality-to-Incidence Ratios



Data adapted from the American Cancer Society. Annual Cancer Facts and Statistics. Accessed June 26, 2023. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures.html

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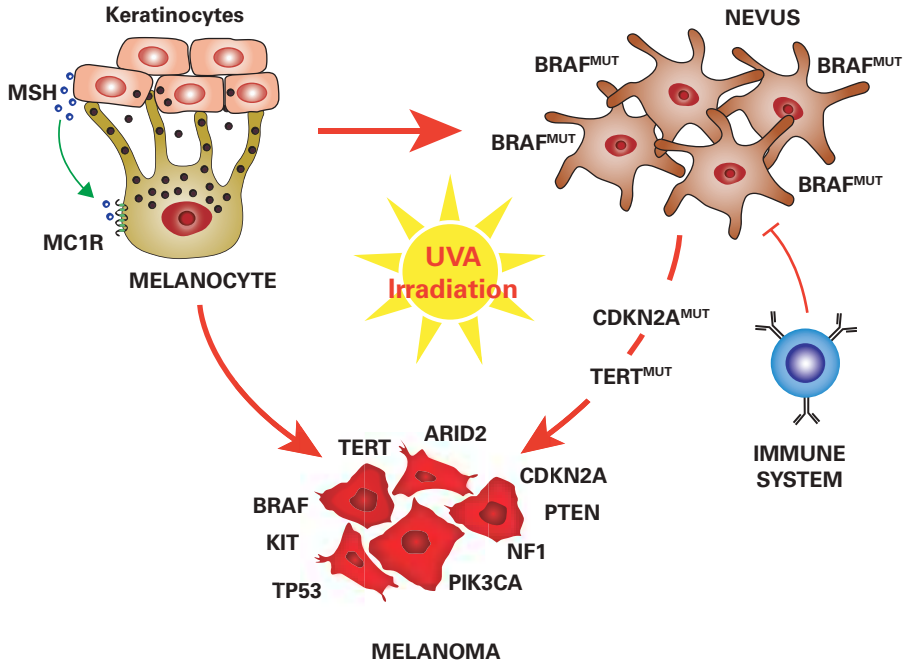
Figure 16-2 Melanocyte to Melanoma Transition



Abbreviations: ARID2, AT-rich interaction domain 2; BRAF, B-Raf proto-oncogene; CDKN2A, cyclin-dependent kinase inhibitor 2A; KIT, KIT proto-oncogene receptor tyrosine kinase; MC1R, melanocortin 1 receptor; MSH, melanocyte-stimulating hormone; NF1, neurofibromin 1; PTEN, phosphatase and tensin homolog; TERT, telomerase reverse transcriptase; TP53, tumor protein p53.
Reproduced under Creative Commons license. Source: Leonardi et al. Cutaneous melanoma: from pathogenesis to therapy (review). *Int J Oncol.* 2018;52:1071-1080. Fig. 1. PMID: 29532857.

Figure 16-3 Perioperative Treatment Options for High-Risk, Resectable Melanoma

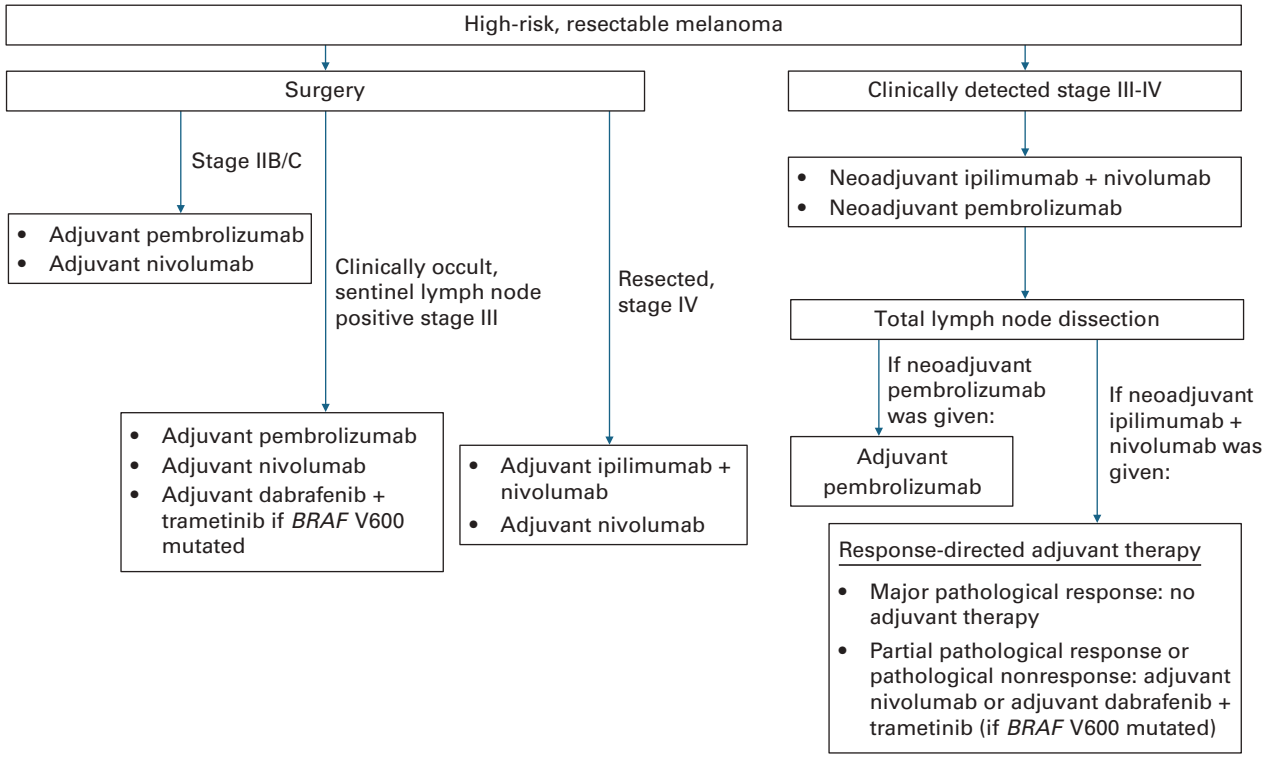


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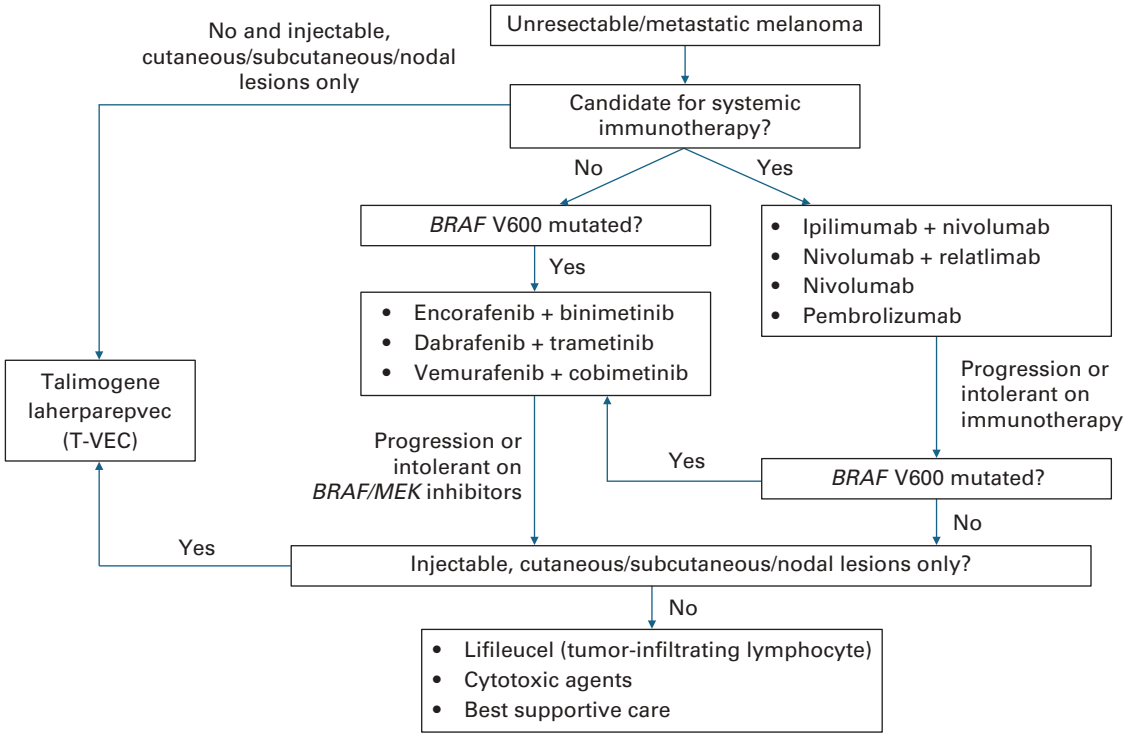
Figure 16-4 Treatment Options for Metastatic Melanoma



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SARCOMA 17

Ravin Ratan, MD, and Richard F. Riedel, MD

RECENT UPDATES

- Afamitresgene autoleucel, an engineered autologous T-cell receptor product targeting melanoma-associated antigen A4 (MAGE-A4), was FDA approved for adults who have select HLA-A*02 serotypes and have unresectable or metastatic MAGE-A4-expressing synovial sarcoma and have received prior chemotherapy.[1]
- The addition of neoadjuvant and adjuvant pembrolizumab to radiation therapy and surgery was shown to significantly improve disease-free survival for patients who have stage III undifferentiated pleomorphic sarcoma and pleomorphic or dedifferentiated liposarcoma of the extremity and limb girdle.[2]
- Vimseltinib, an oral colony-stimulating factor (CSF)-1R inhibitor, showed improved overall response rate and meaningful improvements in symptoms and function when compared with placebo in a randomized phase 3 trial for patients with symptomatic tenosynovial giant cell tumor.[3]
- Nirogacestat, a gamma-secretase inhibitor, demonstrated improved progression-free survival (PFS) and patient-reported outcomes over placebo for patients who have progressive desmoid fibromatosis and was FDA approved.[4]
- The combination of doxorubicin with trabectedin, followed by trabectedin single-agent therapy, improved PFS and overall survival over patients receiving doxorubicin alone for unresectable or metastatic leiomyosarcoma in a randomized phase 3 trial.[5,6]
- In March 2026, there was a voluntary manufacturer recall of tazemetostat, previously used to treat epithelioid sarcoma. This was based on emerging data from the ongoing Phase Ib/III SYMPHONY-1 trial on secondary hematologic malignancies.

OVERVIEW

Sarcomas are rare cancers that can originate in bone and soft tissues. Most sarcomas arise from mesoderm-derived cells. These cancers are uncommon, constituting less than 1% of cancers occurring in adults and approximately 15% of cancers in children. Sarcomas are heterogeneous, with more than 150 subtypes recognized in the World Health Organization classification of tumors of soft tissue and bone, with further subtyping commonplace based on modern molecular phenotyping.[7] In adults, soft tissue sarcomas (STSs) are approximately four times more common than sarcomas of bone (13,400 vs. 3,970 projected cases, respectively, in the United States in 2023).[8] Approximately 42% of patients diagnosed with sarcoma will die of their disease, with a majority dying from metastatic disease.[7]

Appropriate multidisciplinary treatment is essential for patients presenting with sarcoma. In most cases of localized sarcoma, complete surgical removal of the primary tumor is required for cure. Surgery is also used when feasible in the management of oligometastatic disease, particularly in the lung, and for diseases with more indolent growth patterns. Radiation therapy (RT) is important in many sarcoma subtypes to reduce the risk of local tumor recurrence after surgery for localized disease or for palliation of tumor-related symptoms. Stereotactic body radiotherapy also plays an increasingly important role in the treatment of oligometastatic disease. Chemotherapy in the neo/adjuvant setting plays a more controversial role in most soft tissue histologic subtypes but is critically important and well established in selected subtypes, such as osteosarcoma, Ewing sarcoma, and nonpleomorphic rhabdomyosarcoma. The role of chemotherapy in the adjuvant setting for the remaining sarcomas is determined based on patient- and disease-specific considerations, such as histology sensitivity to chemotherapy in the metastatic setting, and survival rate based on risk factors such as size, grade, location, and age. For patients who have metastatic disease, histology-guided systemic therapy is generally the primary treatment, with other modalities used in specific circumstances.

Recently, there have been important advances in the treatment of sarcoma. With appropriate multidisciplinary management, long-term survival rates of localized osteosarcoma and Ewing sarcoma have improved from less than 20% to more than 70%. Similar gains in cure rates have occurred in patients who have nonpleomorphic rhabdomyosarcoma, mostly as a result of large multicenter histology-specific cooperative group studies. Significant improvements in long-term survival rates of patients who

have metastatic gastrointestinal (GI) stromal tumor (GIST) have occurred since the introduction of tyrosine kinase inhibitor (TKI) therapy, with 20% to 30% of patients surviving 9 to 10 years after initiation of treatment.[9] However, improvements in outcomes have been less impressive in most other STS subtypes. Historically, large phase 3 trials of novel therapies have included multiple subtypes of STS and/or bone sarcoma, which has caused difficulty in interpreting subtype-specific results. Recognizing that a one-size-fits-all approach is unlikely to be feasible given the biologic and genetic heterogeneities of sarcomas, there has also been a shift toward conducting clinical trials for specific sarcoma subtypes or molecularly defined markers. This approach has led to the approval of a number of new therapies, including albumin-bound sirolimus for perivascular epithelioid cell tumor (PEComa) in 2021, atezolizumab for alveolar soft part sarcoma (ASPS) in 2022, nirogacestat for desmoid tumors in 2023, afamitresgene autoleucel for synovial sarcoma in 2024, and both pexidartinib and vimseltinib for tenosynovial giant cell tumor (TGCT) in 2019 and 2025, respectively.

EPIDEMIOLOGY AND ETIOLOGY

The most common subtypes of STS include GIST, leiomyosarcoma, liposarcoma (LPS), and undifferentiated pleomorphic sarcoma (UPS). Osteosarcoma and chondrosarcoma are the two most common bone sarcomas in adults. Although osteosarcoma can arise in soft tissue (extraskeletal osteosarcoma), it is important to note that this is a different entity and is generally treated following STS paradigms. Ewing sarcoma can arise in either bone or soft tissue, but is typically classified as a bone sarcoma and is treated identically regardless of primary location.

The most common cause of sarcoma is unknown. However, known causes are hereditary cancer predisposition syndromes or exposures to specific environmental factors. The incidence of sarcoma generally increases with age, although there are exceptions for some subtypes. Ewing sarcoma, nonpleomorphic rhabdomyosarcoma (embryonal and alveolar subtypes), and osteosarcoma occur more frequently in children and young adults.

Many hereditary syndromes are associated with sarcoma (Table 17-1). In an international genomic study of more than 1,000 patients who have sarcoma, recognized pathogenic germline variants were detected in approximately 10% of patients, and a large minority had multiple genomic variants, suggesting an interacting contribution of rare mutations to sarcoma risk.[10] People who have Li-Fraumeni syndrome are at great risk for the development of osteosarcoma or STS. In one large study of patients who have sarcoma, germline tumor protein p53 (*TP53*) mutations were present in approximately 3% of cases.[11]

Table 17-1 Genetic Syndromes Associated With Sarcoma

Syndrome	Genetic Abnormality	Associated Sarcoma Types
Li-Fraumeni syndrome	*TP53* mutation	Various types of STS and bone sarcomas
Retinoblastoma	*RB1* gene deletion	Leiomyosarcoma, osteosarcoma
Neurofibromatosis type I	*NF-1* mutation	MPNST, GIST
Gardner syndrome	*APC* mutation	Desmoid tumor
McCune-Albright syndrome	*GNAS1* mutation	Osteosarcoma
Bloom syndrome	*RECQL3* mutation	Embryonal RMS, osteosarcoma
Rothmund-Thomson syndrome	*RECQL4* mutation	Osteosarcoma
Werner syndrome	*WRN* mutation	Osteosarcoma
Costello syndrome	*HRAS* mutation	Embryonal RMS
Nijmegen breakage syndrome	*NBS1* mutation	Embryonal RMS
Carney-Stratakis syndrome	*SDH* mutation	GIST
Noonan syndrome	*PTPN11* mutation	Embryonal RMS, giant cell tumor, PVNS

Abbreviations: *APC*, APC regulator of WNT signaling pathway; GIST, gastrointestinal stromal tumor; *GNAS1*, GNAS complex locus; *HRAS*, HRAS protooncogene, GTPase; MPNST, malignant peripheral nerve sheath tumor; *NBS1*, nibrin; *NF-1*, neurofibromin-1; *PTPN11*, protein-tyrosine phosphatase, nonreceptor-type 11; PVNS, pigmented villonodular synovitis; *RB1*, RB transcriptional corepressor 1; *RECQL3/4*, RECQ protein-like 3/4; RMS, rhabdomyosarcoma; *SDH*, succinate dehydrogenase; STS, soft tissue sarcoma; *TP53*, tumor protein p53; *WRN*, Werner syndrome.
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Referral for genetic counseling and testing should be considered in individuals younger than 46 years who have STS or osteosarcoma, who also have a family history of STS, osteosarcoma, breast cancer, CNS tumor, or adrenocortical carcinoma in a first- or second-degree relative occurring before 56 years.[12] Referral for genetic counseling and testing should also be considered for patients who have multiple cancers of the listed types, regardless of age at diagnosis.

Some epidemiologic evidence indicates an association between occupational exposure to vinyl chloride, pesticides, or herbicides (including Agent Orange) or exposure to the imaging agent thorotrast and development of hepatic angiosarcoma, but few other environmental exposures are linked to sarcoma.[13] A recent meta-analysis suggested an association between a woodworking occupation and STS incidence.[14]

There is also a small but measurable long-term risk of STS or bone sarcoma after exposure to therapeutic radiation, well less than 1% overall.[15] Despite their rarity, it is important to recognize symptoms concerning radiation-associated sarcoma, particularly in breast cancer survivors, as well as sarcomas occurring in pediatric patients with cancer.[16,17] It is estimated that radiation-associated sarcomas make up approximately 3% to 6% of all new sarcoma diagnoses.[18] The median latency in one series was 8.6 years (range, 6 months to 44 years).[19] Analysis of sarcoma incidence in survivors of atomic bomb blasts suggested that moderate levels of ionizing radiation, lower than typically administered for therapy, also increased the risk of bone sarcoma and STS.[20]

Other risk factors for the development of STS include lymphedema (angiosarcoma) and human herpesvirus-8 (HHV-8; Kaposi sarcoma [KS]) infection. KS is causally associated with HHV-8 and occurs in the setting of immune dysregulation—most notably HIV infection—but also classically in older Mediterranean men ("classic"), in certain parts of Africa ("endemic"), and in chronically immunosuppressed patients, including transplant recipients, in the absence of HIV.

GENETIC CHARACTERISTICS

Sarcomas exhibit a wide range of genetic abnormalities, including complex chromosomal aberrations, chromosomal translocations involving transcription factors, overexpression of ligands to receptor kinases, and gene mutations resulting in activated cellular kinases, gene amplification, and regulatory protein inactivation, among others (Table 17-2).[7] Many sarcomas have defined, recurring, specific genetic alterations that contribute to pathogenesis. These alterations are important for diagnostic purposes, especially in cases in which histologic findings do not point to a definite diagnosis.

Table 17-2 Representative Genetic Alterations in Sarcoma

Class of Alteration	Sarcoma Subtype	Genetic Change	Frequency, %
Activating mutation	GIST	*KIT* or *PDGFRA* mutation	>90
	Desmoid fibromatosis	*Beta-catenin* or *APC* mutations	85-90
	Chondrosarcoma	*IDH1/2* mutations	≥50
	PEComa	*TSC1/2* mutations	~50
Ligand expression	Dermatofibrosarcoma protuberans	*COL1A1-PDGFB* gene fusion	~100
	Giant cell tumor of the bone	*RANK* ligand	~100
Inactivation/deletion	Myxofibrosarcoma	*NF-1* mutation, *NF-1* deletion	~10-20, >90
	Malignant peripheral nerve sheath tumor		
	Epithelioid sarcoma, rhabdoid tumors	*INI1* loss	81
Gene amplification	Well-differentiated and dedifferentiated liposarcoma	CDK4, MDM2	>90
Translocation	Synovial sarcoma	*t*(*X*;18) SYT-SSX1 or SYT-SSX2	>90
	Ewing sarcoma	*t*(11;22) EWSR1-FLI1	>85
		t(21;22) *EWSR1-ERG*	5-10
	Alveolar rhabdomyosarcoma	*t*(2;13) PAX3-FOXO1	~70
		t(1;13) PAX7-FOXO1	~15
	Inflammatory myofibroblastic tumors	*ALK* fusions	50

Abbreviations: *ALK*, anaplastic lymphoma kinase; *APC*, APC regulator of WNT signaling pathway; *CDK4*, cyclin-dependent kinase 4; *EWRSR1-ERG*, fusion of EWS RNA-binding protein 1 and ETS transcription factor ERG; *EWSR1-FLI1*, fusion of EWS RNA-binding protein 1 and FLI1 protooncogene, ETS transcription factor; *FOXO1*, forkhead box O1; GIST, gastrointestinal stromal tumor; *IDH1/2*, isocitrate dehydrogenase 1/2; *INI1*, integrase interactor 1; *KIT*, KIT protooncogene, receptor tyrosine kinase; *MDM2*, MDM2 protooncogene; *NF-1*, neurofibromin-1; *PAX3/7*, paired box gene 3/7; *PDGFRA*, platelet-derived growth factor receptor, alpha; PEComa, perivascular epithelioid cell tumor; *RANK*, receptor activator of nuclear factor-kappa B; *SYT-SSX1/2*, synovial sarcoma, X-chromosome-related 1/2; *TSC1/2*, TSC complex subunit 1/2.[7,11]

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Tumor genome sequencing identifies potentially actionable mutations in less than 20% of patients with STS, and the impact on survival is yet to be defined.[21] Two important low-frequency actionable genetic alterations occasionally seen in sarcoma are *NTRK* fusions and high microsatellite instability (MSI). Although most sarcomas exhibit low tumor mutational burden (TMB), identifying the subset of sarcomas with high TMB may support treatment with immunotherapy in the metastatic or relapsed setting.[22]

KEY POINTS

- Sarcomas account for approximately 1% of cancers in adults.
- STSs are three to four times more common than those of bone.
- Individuals who have certain hereditary cancer susceptibility syndromes, such as Li-Fraumeni, have an increased risk of sarcoma.
- Therapeutic radiation confers a small but definite risk for the development of sarcoma.
- HHV-8 infection is associated with KS.
- Approximately 30% to 40% of sarcomas have defined, recurring, specific genetic alterations such as chromosomal translocations, gene amplifications, or mutations that contribute to pathogenesis.

CLINICAL PRESENTATION AND DIAGNOSIS

STSs generally present as growing masses that are sometimes associated with pain, whereas bone sarcomas are often associated with pain in the region of bone involvement, with or without an associated soft tissue mass. STSs may be clinically suspected by either their clinical characteristics on physical exam (generally firm) and/or their location (typically deep to subcutaneous fat). Regardless of the clinical impression, soft tissue masses that are increasing in size, associated with symptoms, or larger than 5 cm warrant imaging before attempts at surgical resection.

Dermal vascular neoplasms, such as angiosarcoma and KS, often appear as indistinct red, purple, blue, or brown discoloration in the skin. Often, a mass-like lesion is not present. Angiosarcomas, occurring in the dermis in older adults, and KS, occurring in the setting of HIV/AIDS, frequently involve the head-and-neck region and are often multicentric. KS occurring mostly in Mediterranean men in the absence of HIV infection (often referred to as classic KS) frequently involves the legs and feet. Advanced KS (usually in the setting of AIDS) may involve the lymph nodes (resulting in severe edema), oropharynx, GI tract, or respiratory tract.

Ultrasound and cross-axial imaging (MRI or CT imaging) are useful in the evaluation of suspected sarcomas and can help differentiate benign lesions from potentially malignant masses. Core needle biopsy is the preferred method of biopsy when sarcoma is suspected, ideally in consultation with an orthopedic or surgical oncologist, to ensure an approach that can ultimately allow for resection. Fine-needle aspiration is not adequate because it does not allow for accurate assessment of subtype or grade. When diagnostic material cannot be obtained by core needle biopsy, incisional biopsy is performed with the understanding that the subsequent oncologic resection must encompass the prior biopsy site and scar.

KEY POINTS

- STSs often present as enlarging masses and may be painful or painless.
- Bone sarcomas are usually associated with pain.
- A core needle or incisional biopsy is required to obtain sufficient tumor material for definitive diagnosis and sarcoma subtype classification.
- Angiosarcoma and KS can present as dermal-only or visceral disease.

PATHOLOGIC FEATURES, STAGING, AND PROGNOSTIC FACTORS

Because of the diversity of sarcoma subtypes and their differential diagnoses, such as sarcomatoid carcinoma (which is treated as a carcinoma, not a sarcoma), uterine carcinosarcoma, melanoma, and lymphoma, the pathologist is a critical contributor to patient care. Expert review of a patient's biopsy or resection by an expert bone and soft tissue pathologist is critical for optimal outcome. Retrospective analyses report a change in diagnosis from the original reference center approximately 40% of the time with expert review.[23,24]

Important considerations for sarcoma staging include sarcoma subtype (bone or soft tissue), site, size, and tumor grade. It is important to recognize that pathologists have historically used different grading systems; however, the American Joint Committee on Cancer (AJCC) staging guidelines (ninth edition) use a three-grade classification, including 1 (low grade), 2 (intermediate to high grade), and 3 (high grade), based on degree of differentiation, mitoses, and necrosis.[25] The presence of nodal disease and distant metastases also factor into AJCC TNM staging. Nodal metastatic disease is an unfavorable prognostic feature, but it is associated with better overall survival (OS) than distant metastatic disease. Nodal metastatic disease is observed in less than 10% of patients

with STS; however, several subtypes do have a propensity for nodal spread in addition to hematologic sites, including epithelioid sarcoma, dedifferentiated liposarcoma, pediatric rhabdomyosarcoma, ASPS, angiosarcoma, myxofibrosarcoma, synovial sarcoma, clear-cell sarcoma, and myxoid liposarcoma. Sentinel-node biopsy can be considered on a case-by-case basis for specific subtypes but is not considered standard for any sarcoma. In the current staging system, lymph node metastasis is considered stage IV.

Evaluation of the local extent of sarcoma is generally accomplished by MRI or CT imaging of the primary site. For patients who have high-grade sarcoma, a chest CT scan should be performed to evaluate for the presence of lung metastases and to serve as a baseline for future comparison. A CT scan of the abdomen and pelvis is needed for the aforementioned subtypes that can spread via lymphatics in addition to the bloodstream. Myxoid liposarcoma may also spread to the spine or other bones, and additional imaging, such as whole-body MRI and total spine MRI, should be considered to fully stage the disease. In the absence of symptoms, the yield from routine imaging of the brain for patients who have tumors originating outside the head-and-neck region is low apart from high-risk histologies, including visceral angiosarcoma, ASPS, and left-sided cardiac sarcomas. For high-grade bone sarcomas, radionuclide bone scan or positron emission tomography (PET)/CT is recommended to evaluate for the presence of bone metastases. PET/CT can also be used to stage STS and evaluate response to neoadjuvant therapy, as well as to assess early response to TKI treatment of patients who have GIST, and help distinguish well-differentiated liposarcoma from dedifferentiated liposarcoma. A PET scan is notoriously not helpful for myxoid liposarcoma.

Histology, grade, size, and completeness of resection are the most important factors in determining the risk of relapse. Of primary importance in determining OS is tumor grade; OS also depends on the initial size and location of the tumor. Multiple nomograms that include factors such as tumor histology, size, location, and patient age have been developed and found to be prognostic with respect to survival outcomes.[26,27]

KEY POINTS

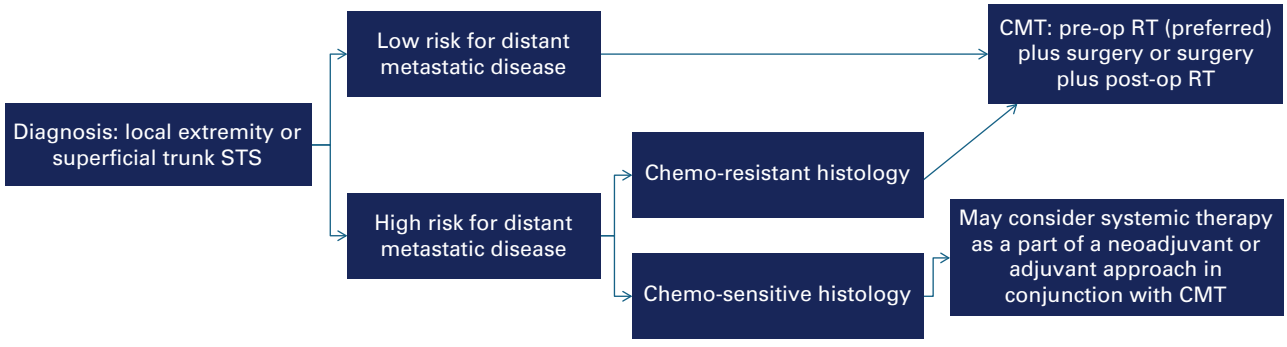
- Tumor grade is a key factor in sarcoma staging, treatment, and patient prognosis.
- Staging of extremity STSs or bone sarcomas should include the lungs, as they are the most common site for distant metastases.

TREATMENT OF LOCALIZED STS: GENERAL PRINCIPLES

SURGERY

The primary curative treatment modality for most sarcomas is surgery (Fig. 17-1). A planned oncologic resection to remove the tumor intact with a rim of normal tissue at the surgical margin (R0 resection) results in a lower risk of local relapse and better long-term patient survival than removal in which sarcoma touches the surgical margin (R1 resection) or in which gross disease remains (R2 resection).

Figure 17-1 Treatment Paradigm for Extremity and Superficial Trunk STS



Abbreviations: CMT, combined modality therapy; RT, radiation therapy; STS, soft tissue sarcoma.
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RADIATION THERAPY

Radiation to the site of the primary tumor is the standard of care for all intermediate- and high-grade STS of the extremities or body wall that are larger than 5 cm (Fig. 17-1). RT greatly improves the rates of local control and reduces the need for amputation for patients who have extremity STS. RT may be considered in select cases of low-grade STS, such as situations in which reoperation for recurrence would result in substantial morbidity or for locally recurrent low-grade STS. Patients who have an STS less than 5 cm occurring in an extremity or body wall do not uniformly require adjuvant RT after an R0 resection, although it can be used to prevent local recurrence in an area that would be difficult to manage with surgery in the event of local recurrence.

For intermediate- and high-grade STS, RT can be administered either before or after surgery. Preoperative RT allows for treatment of a smaller field using a lower dosage. This is because the tumor defines the target volume rather than the entire operative bed. A Canadian randomized study of preoperative RT compared with postoperative RT demonstrated similar rates of local disease control.[28] The risk of early wound complications (eg, delayed healing, infection, or need for reoperation) was increased (most often in the leg) with preoperative RT, but the treatment field was smaller, and the radiation dosage was lower than with postoperative RT. The risk of late complications, including fibrosis and lymphedema, seems greater with postoperative RT. The timing of RT should be decided in conjunction with the orthopedic or surgical oncologist. Recently, hypofractionated courses have been reported with encouraging results.[29,30]

In contrast to the benefit of RT for STS of the extremities or body wall, the role of RT for retroperitoneal or visceral STS resected with clear or microscopically positive margins remains controversial and, historically, has not been recommended. The dosages that can be administered postoperatively for abdominal STS generally are limited by normal tissue (eg, bowel) tolerance. Although preoperative RT may be considered for high-grade or large abdominal or retroperitoneal STS, it does not clearly improve survival in these patients but may improve local control.[31]

Intraoperative RT has been used for improved local control when an STS extends to the surgical margin adjacent to critical structures or after resection of local recurrence in a previously irradiated field. Its use, however, is not widely available. Proton radiation can be useful as treatment of STS in anatomic areas with little tolerance for radiation scatter, such as the spine, sacrum, and base of the skull.

Stereotactic body RT, which provides ablative doses of radiation, is frequently used in the setting of recurrent or metastatic disease.[32] Dosage and fractionation should be determined by an experienced radiation oncologist in the setting of a multidisciplinary team.

ADJUVANT CHEMOTHERAPY

The role of chemotherapy in the curative setting for patients who have localized STS (nonrhabdomyosarcoma) has continued to evolve in recent years. Because of the rarity of this group of diseases, older studies enrolled patients who had a variety of STS histologies and were often underpowered to detect a survival benefit. The prolonged periods of time required to accrue meant that treatment regimens were often outdated at the time of study analysis and publication. Despite various conclusions being reached in individual studies, meta-analyses of conducted studies using anthracycline and later anthracycline- and ifosfamide-based regimens have suggested a small but potential survival benefit.[33,34] Modern prospective studies have reached variable conclusions, further fueling debate.

Two large, adequately powered studies prospectively studied the impact of neoadjuvant or adjuvant chemotherapy in localized STS since the most recent meta-analysis. The first, conducted by the European Organization for Research and Treatment of Cancer (EORTC), enrolled intermediate- or high-grade STSs of any size and a wide range of histologies. Patients were randomized after surgery to receive either adjuvant doxorubicin and ifosfamide or no chemotherapy. The study failed to show an OS benefit to adjuvant chemotherapy.[35] A key critique was the inclusion of intermediate-grade and smaller tumors, as both size and grade are important risk factors for the subsequent development of metastatic disease.

A subsequent study attempted to address concerns regarding heterogeneity of risk factors and potential lack of comfort with randomization to placebo, using a different design. In the neoadjuvant setting, patients with five specific sarcoma subtypes (myxoid liposarcoma, leiomyosarcoma, synovial sarcoma, UPS, and malignant peripheral nerve sheath tumor) were randomized to receive either neoadjuvant epirubicin and ifosfamide for three cycles or an active, histology-specific, nonanthracycline-based regimen, which varied for each subtype. Tumors were required to be at least 5 cm in size, high grade, and with a deep anatomic location. The study demonstrated an OS benefit for patients receiving anthracycline (epirubicin) and ifosfamide (AI) over a histology-tailored approach.[36] A critique of this study, however, was that it was not specifically designed to answer whether adjuvant chemotherapy provided a benefit compared with no chemotherapy; rather, it addressed whether a histotype-specific regimen improved outcomes of a more generic anthracycline-based regimen. In this context, it was a negative study. Of note, however, a separate analysis of these patients found that those deemed to be high risk (10-year predicted OS <60%) as determined by a sarcoma-specific nomogram had greater OS when receiving AI compared with predicted OS rates, whereas those predicted to be lower risk (10-year predicted OS ≥60%) and those who received histotype-tailored chemotherapy did not.[37]

Taken together, these studies indicate that adjuvant anthracycline and ifosfamide chemotherapy is likely associated with little benefit in low-risk groups but can potentially impact survival in patients at higher risk of mortality and those with chemotherapy-sensitive histologies. The potential benefit must be balanced against the substantial toxicity associated with these regimens, including high rates of grades 3 and 4 hematologic toxicity as well as substantial risk of nonhematologic toxicity. Although tools such as the nomogram or specific risk factors, such as size and subtype, can assist in risk assessment and selection of patients for adjuvant treatment, the heterogeneity of sarcoma subtypes and anatomic locations is not fully captured by these tools. As such, the judgment of treating physicians and local practice patterns often impact the decision to offer perioperative chemotherapy with curative intent.

More recently, in the setting of reported responses to checkpoint blockade in the metastatic setting of select histologic subtypes and high pathologic response rates with neoadjuvant radiation and checkpoint blockade, the SU2C-SARC032 clinical trial examined the role of neoadjuvant pembrolizumab in combination with preoperative RT, followed by surgical resection and adjuvant pembrolizumab compared with radiation and surgery alone in patients with UPS and pleomorphic or dedifferentiated LPS of the extremity and limb girdle.[2] The addition of pembrolizumab resulted in a significant improvement in 2-year disease-free survival (DFS) for patients who have stage III UPS and pleomorphic or dedifferentiated LPS. Notably, the majority of patients in the study had UPS, and based on subgroup analysis, the benefit appeared to be limited to those patients with grade 3 disease. Although radioimmunotherapy likely represents a significant improvement in tolerability over anthracycline- and ifosfamide-based neoadjuvant systemic therapy, the relative efficacy of the two approaches is not well understood and has not been explicitly studied. Practice patterns are more consistent for specific sarcoma subtypes that are resistant to conventional cytotoxic-based, chemotherapy-based regimens. These include ASPS, clear-cell sarcoma, extraskeletal myxoid chondrosarcoma, and solitary fibrous tumor, among others, for which adjuvant chemotherapy is not offered. By contrast, adjuvant or neoadjuvant chemotherapy has greatly improved OS for patients who have nonpleomorphic rhabdomyosarcoma (eg, embryonal and alveolar rhabdomyosarcoma) and extraskeletal Ewing sarcoma. Although these types of sarcomas are typically seen in the pediatric population and are found less frequently in adults, treatment of adults typically follows the same schedule of therapy as that for pediatric patients when feasible.

KEY POINTS

- Surgical resection remains the standard of care for most patients who have localized STS when treating with curative intent.
- Preoperative or postoperative external-beam RT is used for large (>5 cm in greatest dimension), intermediate- to high-grade STS arising in the extremity or body wall.
- The addition of neoadjuvant and adjuvant pembrolizumab to RT and surgery is shown to significantly improve 2-year DFS for patients who have stage III UPS and pleomorphic or dedifferentiated LPS of the extremity and limb girdle.
- Adjuvant RT is not routinely recommended after resection of retroperitoneal or visceral STS.
- Adjuvant or neoadjuvant chemotherapy with an anthracycline (doxorubicin or epirubicin) and ifosfamide reduces the risk of sarcoma recurrence and may improve OS in patients who have chemotherapy-sensitive STS subtypes that have a high risk for the development of metastasis.
- Patients who have localized extraskeletal Ewing sarcoma should be treated with chemotherapy as administered to patients who have skeletal Ewing sarcoma if not medically contraindicated.
- Embryonal and alveolar rhabdomyosarcomas are aggressive cancers with a propensity for nodal and distant metastases. Depending on clinical group and staging, they are typically managed using surgery, adjuvant RT, and multiagent chemotherapy at centers with experience in treating these STS.

TREATMENT OF METASTATIC STS: SYSTEMIC THERAPY OPTIONS

ANTHRACYCLINES

As single drugs or in combination, anthracyclines, such as doxorubicin and epirubicin, yield the best response rates for metastatic non-GIST STSs (rates of 10%-25% in various studies).[37] PEGylated liposomal doxorubicin has also been studied and is active in the treatment of metastatic STS.[38] Studies show varying degrees of efficacy associated with this agent. It is generally administered at lower dosages and, thus, better tolerated than conventional doxorubicin. Liposomal doxorubicin is commonly used in the treatment of older patients and those with sensitive histologies, such as those who have KS, in which higher dosages of doxorubicin are not likely to be beneficial.

IFOSFAMIDE

Ifosfamide demonstrates single-agent activity in the treatment of advanced STS. Based on available studies, it seems to have a similar degree of activity as doxorubicin. Similar to doxorubicin, there is a dosage-response relationship in the treatment of metastatic STS with increased responses seen at dosages in excess of 10 g/m^2, particularly in chemotherapy-sensitive histologies, such as synovial sarcoma.[39,40] Continuous infusional schedules may be less toxic than bolus administration with conserved activity. There is no direct evidence that such dosages improve survival compared with lower dosages administered conventionally. Ifosfamide is challenging to use and is associated with substantial side effects, including nephrotoxicity, neurologic toxicity, and hemorrhagic cystitis requiring concomitant administration of mesnaand careful monitoring.

DOXORUBICIN-BASED COMBINATIONS

A randomized EORTC trial of doxorubicin at 75 mg/m^2 combined with ifosfamide at 10 g/m^2 per cycle demonstrated an improved objective response rate (26% with the combination and 14% with doxorubicin alone) and progression-free survival (PFS; 7.4

vs. 4.6 months) in patients with advanced sarcoma, but showed OS similar to that with single-agent doxorubicin.[41] Because of toxicity, 18% of patients receiving the combination discontinued treatment before completing six cycles compared with 3% of patients receiving doxorubicin alone. The rate of death resulting from toxic effects was low (<2%) and similar in the two treatment arms. Based on these results, the authors recommended sequential single-agent therapy in the palliative setting when the patient has minimal symptoms from STS and consideration of combination therapy if sarcoma regression would relieve acute symptoms or improve the likelihood of tumor control with surgery or RT.

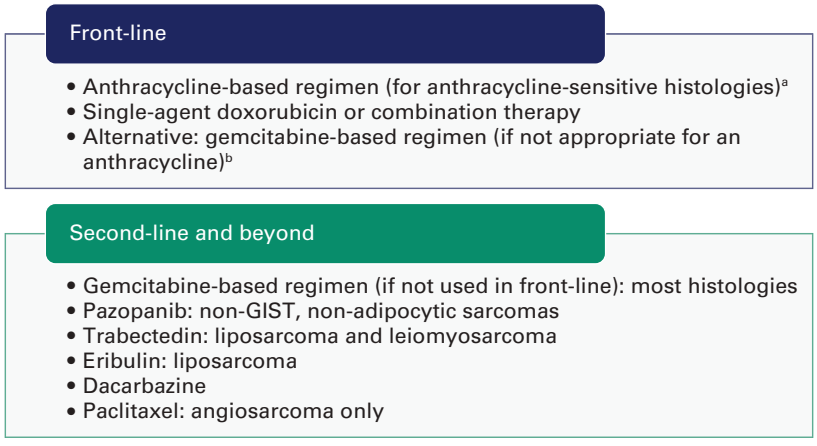
For patients who require a response and for whom ifosfamide is not appropriate, other doxorubicin-based combinations, including doxorubicin and dacarbazine, have been studied and are listed in national guidelines. Recently, a phase 3 trial demonstrated improved PFS (12.2 vs 6.2 months), response rate (36% vs 13%), and OS with doxorubicin and trabectedin, followed by trabectedin maintenance versus doxorubicin alone for patients with leiomyosarcoma.[5,6]

GEMCITABINE AND DOCETAXEL

Multiple phase 2 studies have evaluated and confirmed the activity of single-agent gemcitabine as well as gemcitabine and docetaxel for patients with STS. To investigate whether docetaxel (an agent with little single-agent activity against sarcoma) had synergistic activity with gemcitabine and improved activity of the regimen, a randomized study was conducted, enrolling patients who had multiple sarcoma subtypes and demonstrated improved PFS and OS for the combination of gemcitabine and docetaxel compared with gemcitabine alone. Because of the novel Bayesian statistical design, the study enrolled only 122 patients across multiple sarcoma subtypes.[42] A second randomized study was conducted in patients specifically who have soft tissue and uterine leiomyosarcoma comparing gemcitabine with gemcitabine and docetaxel. In contrast to the prior study, this second histotype-specific trial failed to demonstrate a PFS or OS benefit with the combination but did reveal a 3-month PFS of 40% for each.[43] The combination remains a treatment option for STS patients, particularly in the United States. Given conflicting data regarding the benefit and the acknowledgment that docetaxel adds substantial toxicity to the regimen, interest remains in evaluating other gemcitabine-based combinations, with examples including vinorelbine, pazopanib, and dacarbazine.[44-47]

Finally, gemcitabine and docetaxel were compared with single-agent doxorubicin in the first-line treatment of unresectable or metastatic STS in the randomized phase 3 GeDDis trial.[48] This study found no difference in the proportion of patients alive and free of disease progression at 24 weeks, but did find that gemcitabine and docetaxel were less convenient to give and associated with more toxicity when compared with doxorubicin. As a result, doxorubicin is most often used in the frontline setting for anthracycline-responsive disease (Fig. 17-2).

Figure 17-2 Treatment Paradigm for Metastatic Soft Tissue Sarcomas^



Abbreviations: GIST, gastrointestinal stromal tumor; LMS, leiomyosarcoma.
^Excluding GIST, pediatric rhabdomyosarcoma, and most indolent histologies.
[a]Doxorubicin/ifosfamide (most histologies), doxorubicin/dacarbazine (most histologies), doxorubicin/trabectedin (LMS only).
[b]Gemcitabine/docetaxel (preferred), gemcitabine/dacarbazine, gemcitabine/vinorelbine.
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DURATION OF FRONTLINE THERAPY

No consensus is available as to the duration of frontline therapy for metastatic disease. Some physicians treat until progression or toxicity, whereas others administer a defined number of cycles or to maximum response (clinical or tumor) and then closely

observe patients after therapy for signs or symptoms of tumor progression. The use of traditional doxorubicin has historically been limited to six to eight cycles or a cumulative anthracycline dose of 450 mg/m^2 because of concerns for cardiac toxicity. Although specific guidelines and practices vary, dexrazoxane, a cardioprotectant, should be considered in patients expected to receive high cumulative doses (>250 to 300 mg/m^2) of doxorubicin. If dexrazoxane is unavailable, doxorubicin may be administered as a continuous infusion over 48 to 72 hours as an alternative way to decrease the risk of cardiotoxicity.

SECOND-LINE AND LATER CHEMOTHERAPY

Trabectedin

Trabectedin is a cytotoxic agent that was approved by the US FDA for use in patients who have unresectable or metastatic leiomyosarcoma or liposarcoma after prior treatment with an anthracycline-based chemotherapy regimen. Treatment with trabectedin led to a 45% reduction ($P < .001$) in risk of sarcoma progression or death compared with dacarbazine in a randomized, open-label, international phase 3 study.[49] Trabectedin was administered via a 24-hour infusion. The median PFS was 4.2 months with trabectedin compared with 1.5 months with dacarbazine, with no substantial difference in OS. Objective response rates were less than 10% and not substantially different between the two arms. Principal adverse effects of trabectedin are neutropenia, anemia, thrombocytopenia, increased transaminase levels, increased creatine kinase levels, fatigue, and nausea. Treatment with trabectedin led to a 1.2% incidence of rhabdomyolysis and a 2.1% incidence of treatment-related death; this did not occur in the dacarbazine-treated arm. Therefore, it is important to monitor patients with weekly CPK levels in addition to standard laboratory tests. Older patients (aged >70 years) did not have increased adverse event rates with trabectedin compared with younger individuals. Although not FDA approved for this indication, trabectedin can be considered for translocation-associated sarcomas based on a Japanese study that randomized 76 patients with translocation-associated sarcomas (one-third with myxoid liposarcoma) after progression on standard chemotherapy to receive either trabectedin or best supportive care. Patients receiving trabectedin had a median PFS of 5.6 months compared with 0.9 months in the placebo group.[50]

Eribulin

Eribulin is an antimitotic agent that inhibits microtubule function and, in a phase 3, randomized, open-label trial, improved OS compared with dacarbazine for patients who had previously treated locally advanced or metastatic leiomyosarcoma or liposarcoma.[51] A planned subgroup analysis stratified by sarcoma subtype identified a statistically significant improvement in PFS and OS for patients with liposarcoma treated with eribulin as compared with dacarbazine. There was a 1.2-month difference in median PFS and a 7-month difference in OS in favor of eribulin. No difference in PFS or OS was seen for patients who had leiomyosarcoma. Based on these results, the FDA-approved eribulin for the treatment of unresectable or metastatic liposarcoma in patients who previously received an anthracycline. Patients treated in the phase 3 study had previously received at least an anthracycline and one other chemotherapy. The most frequent adverse events were neutropenia, fatigue, nausea, alopecia, and constipation. Importantly, dacarbazine is likely a more active drug in leiomyosarcoma than liposarcoma, and the lack of benefit seen in the leiomyosarcoma cohort is best interpreted as eribulin and dacarbazine having similar efficacy rather than eribulin being inactive in leiomyosarcoma. On this basis, it is currently considered a standard agent for subsequent treatment of advanced STS beyond just liposarcoma by the National Comprehensive Cancer Network (NCCN), regardless of histology.

MOLECULARLY TARGETED THERAPY, INCLUDING TKIs

Pazopanib, an oral multikinase inhibitor that targets vascular endothelial growth factor (VEGF) receptors, platelet-derived growth factor receptor, alpha (PDGFRA), and PDGFRB, among others, is FDA approved as a treatment for patients with locally advanced or metastatic non-adipocytic STS after treatment with standard chemotherapy. This approval was based on the results of the phase 3, randomized, placebo-controlled PALETTE trial that demonstrated substantial improvement in median PFS involving patients receiving pazopanib as compared with placebo (20 vs 7 weeks).[52] The objective response rate was only 6% in the group receiving pazopanib. The median OS was not substantially different between patients receiving pazopanib compared with those receiving placebo (12.5 vs 10.7 months). Importantly, patients who had liposarcoma or GIST were not included in this trial. Notable severe toxicities associated with pazopanib included fatigue, anorexia, nausea, mucositis, hypertension, diarrhea, rash or desquamation, hypopigmentation, and decline in cardiac ejection fraction. In addition, a boxed warning exists for severe and fatal hepatotoxicity, requiring close monitoring of liver function tests. The target dose is 800 mg daily, although many patients cannot tolerate that dose. Many physicians opt for starting at a lower dose, such as 400 mg daily, with close monitoring of liver enzymes and blood pressure and titration to the full dose as tolerated.

Larotrectinib is a highly selective inhibitor of the three tropomyosin receptor kinases (TRK1, TRK2, and TRK3). The genes (*NTRK1, NTRK2*, and *NTRK3*) encoding these kinases can be constitutively activated by chromosomal translocations, which can be seen in a variety of different cancers, including a rare subset of sarcomas. Larotrectinib was FDA approved for the treatment of solid tumors with a known *NTRK* fusion without a resistance mutation. This approval was made on the basis of a 55-patient study that found this agent was associated with a 75% response rate in these cancers. Notably, this study included 18 patients

with STS.[53] Both larotrectinib and entrectinib are included in the NCCN guidelines as treatment options for sarcomas exhibiting *NTRK* fusions.[54]

Cyclin-dependent kinase 4 (*CDK4*) is frequently amplified along with *MDM2* (MDM2 protooncogene) in well-differentiated and dedifferentiated liposarcomas. Treatment of patients with well-differentiated or dedifferentiated liposarcoma using the selective CDK4 inhibitor palbociclib resulted in one objective tumor response and a median PFS of 18 weeks in a single-arm, open-label, phase 2 trial.[55] The most common adverse events were neutropenia, anemia, and thrombocytopenia. Promising activity was also observed in a phase 2 trial of abemaciclib for dedifferentiated liposarcomas,[56] which is being evaluated in an ongoing placebo-controlled phase 3 trial.[57]

Nab-sirolimus, a formulation of protein-bound particles for injectable suspension, was FDA approved for adult patients who have locally advanced unresectable or metastatic malignant PEComa after completion of a multicenter single-arm clinical trial involving 31 patients. The overall response rate was 39%, with an additional 52% of patients achieving stable disease. The median duration of response was not reached after a median follow-up for response of 2.5 years. The median PFS was 10.6 months, and the median OS was 40.8 months. Responses were seen preferentially in tumors with a *TSC2* mutation.[58] Adverse events observed were similar to those of other commercially available mTOR inhibitors.

In July 2022, the anaplastic lymphoma kinase (ALK) inhibitor crizotinib was approved by the FDA for the treatment of unresectable, recurrent, or refractory ALK-positive inflammatory myofibroblastic tumors. In 12 ALK-positive evaluable patients treated in a prospective single-arm protocol, the objective response rate was 66.7% with a median PFS of 18 months.[59]

IMMUNOTHERAPY

Immune checkpoint inhibitors blocking PD-1, PD-L1, and CTLA-4 have been studied in the treatment of advanced bone and STS. Pembrolizumab was found in a small phase 2 trial to have activity against UPS and dedifferentiated liposarcoma. This trial enrolled a total of 40 patients who had advanced STS. The response rate was 40% in the UPS cohort and 20% in the liposarcoma cohort.[60] Subsequent expansion cohorts for UPS and liposarcoma evaluated 40 patients for each subtype; the final response rates were 23% in UPS and 10% in liposarcoma.[61] There was minimal activity against synovial sarcoma, leiomyosarcoma, and bone sarcomas in this trial. Similar results were observed in a noncomparative phase 2 study of 85 patients with bone sarcomas and STS who received nivolumab (n = 43) or the combination of ipilimumab and nivolumab (n = 42).[62] Response rates were 5% for nivolumab monotherapy and 16% for ipilimumab and nivolumab. Subsequent expansion cohorts for this study included patients who had GIST (n = 18), dedifferentiated liposarcoma (n = 24), and UPS (n = 24). Final 6-month response rates were 0% for patients who have GIST, 14% for those with dedifferentiated liposarcoma, and 14% for those with UPS treated with combination ipilimumab and nivolumab.[63] Finally, a study examining the combination of durvalumab and tremelimumab showed encouraging response rates in cutaneous angiosarcoma (20%), UPS (20%), chordoma (20%), and, importantly, in 40% of patients with ASPS.[64]

A checkpoint blockade with various agents is effective in the treatment of ASPS, either alone or in combination with axitinib.[65,66] Atezolizumab, as a single agent, demonstrated activity against ASPS in a dedicated phase 2 trial with a response rate of 37%, ultimately leading to FDA approval in 2022.[66]

Cutaneous angiosarcomas often exhibit high TMB, and recently, the combination of ipilimumab and nivolumab showed a response rate of 25% in angiosarcoma, with three of five patients who had cutaneous angiosarcomas of the scalp and face achieving partial response.[67] NCCN guidelines currently list pembrolizumab as an appropriate treatment under certain circumstances for advanced or metastatic myxofibrosarcoma, UPS, cutaneous angiosarcoma, ASPS, and undifferentiated sarcomas.

Pembrolizumab is also FDA approved for the treatment of advanced cancers with high MSI or defects in mismatch repair.[68] In addition, it was recently FDA approved for the treatment of advanced cancers with high TMB. Therefore, the small subset of sarcomas that exhibit MSI, defects in mismatch repair, or high TMB should be considered for immunotherapy either as standard of care or in clinical trials. Numerous ongoing clinical trials are exploring checkpoint inhibitors in various combinations with cytotoxic chemotherapies, as well as TKIs for bone sarcomas and STS, to further improve outcomes and further elucidate uncommon subtypes that may respond. Importantly, a correlative analysis from completed trials suggests that tumor PD-L1 expression is not a reliable biomarker for potential response to checkpoint blockade, unlike in other cancers.[69]

Afamitresgene autoleucel, an engineered autologous T-cell receptor product, targeting melanoma-associated antigen A4 (MAGE-A4), was FDA approved for adults who are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive, and have unresectable or metastatic MAGE-A4-expressing synovial sarcoma treated with prior chemotherapy. This was based on the single-arm, open-label, phase 2 SPEARHEAD-1 study showing an overall response rate of 39% for patients with synovial sarcoma.[1] Cytokine release syndrome and cytopenias were the most common adverse events observed.

HISTOLOGY-SPECIFIC TREATMENT

Because sarcomas are a biologically heterogeneous group of diseases, it is not surprising that specific sarcoma subtypes may be preferentially sensitive to certain agents (Table 17-3). Ifosfamide is particularly active against synovial sarcoma and seems to be less active against nonuterine soft tissue leiomyosarcomas. Dacarbazine consistently demonstrates modest activity against

leiomyosarcoma, and paclitaxel, as well as PEGylated liposomal doxorubicin, are active against cutaneous or breast angiosarcoma.[70] Studies demonstrate activity of sunitinib, pazopanib, and cediranib against ASPS.[71-73] The combination of temozolomide and bevacizumab, as well as sunitinib and pazopanib, has activity in malignant solitary fibrous tumors.[74-76] As previously noted, immunotherapy has varying activity based on histologic type.

Table 17-3 Select Histology-Specific Treatments and FDA-Approved Agents

Histology	FDA Approved	NCCN Compendia Listed Agents
Angiosarcoma		Paclitaxel; checkpoint inhibitors
ASPS	Atezolizumab	Sunitinib; pazopanib; pembrolizumab ± axitinib
Desmoid tumor	Nirogacestat	Sorafenib; pazopanib
Giant cell tumor of bone	Denosumab	
GIST	Imatinib (first line)	
	Sunitinib (second line)	
	Regorafenib (third line)	
	Ripretinib (fourth line)	
	Avapritinib (PDGFR exon 18 mutations, including D842V)	
Liposarcoma	Trabectedin	
	Eribulin	
LMS	Trabectedin	
Synovial sarcoma	Afamitresgene autoleucel	
TGCT	Pexidartinib	
UPS		Checkpoint inhibitors

Abbreviations: ASPS, alveolar soft part sarcoma; GIST, gastrointestinal stromal tumor; LMS, leiomyosarcoma; NCCN, National Comprehensive Cancer Network; TGCT, tenosynovial giant cell tumor; UPS, undifferentiated pleomorphic sarcoma.
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KEY POINTS

- Doxorubicin and ifosfamide are the most active single-agent drugs for metastatic (non-GIST, non-rhabdomyosarcoma) adult STS.
- Anthracycline-based combinations have not consistently improved OS for patients who have metastatic disease, but are reasonable to consider in select patients.
- Sequential single-agent treatment of metastatic disease is a reasonable approach for many patients who have metastatic disease.
- Gemcitabine and docetaxel, as a combination, are active in advanced or metastatic STS with efficacy similar to doxorubicin but with more toxicity.
- Trabectedin is FDA approved in patients with leiomyosarcoma or liposarcoma who have received prior treatment with an anthracycline.
- Eribulin is FDA approved for the treatment of advanced liposarcoma after prior treatment with an anthracycline.
- Pazopanib is FDA approved for non-GIST, non-adipocytic STS patients who have received prior chemotherapy.
- Afamitresgene autoleucel, an engineered autologous T-cell receptor product, targeting MAGE-A4, was FDA approved for adults with select HLA-A*02 serotypes, who have unresectable or metastatic MAGE-A4-expressing synovial sarcoma and have received prior chemotherapy.
- Immune checkpoint inhibitors, for patients with metastatic disease, are under active exploration but appear to have activity in UPS and angiosarcoma, and atezolizumab is FDA approved in ASPS.
- The addition of neoadjuvant and adjuvant pembrolizumab to RT and surgery was shown to significantly improve DFS for patients with stage III UPS and pleomorphic or dedifferentiated LPS of the extremity and limb girdle.
- Treatments are becoming increasingly histology-specific.

SPECIAL CONSIDERATIONS: OTHER SOFT TISSUE NEOPLASMS

DESMOID TUMOR

Desmoid tumor, also known as aggressive fibromatosis, is a locally aggressive soft tissue tumor with no metastatic potential that can occur in the setting of familial adenomatous polyposis (FAP) or sporadically. It is important to refer desmoid patients to genetics, evaluate for somatic mutations, and/or refer for colonoscopy to rule out FAP. It follows an unpredictable course with spontaneous regressions seen in 20% of patients in one recently reported phase 3 trial[77] and 8% in another randomized study of previously progressing patients.[4] Given this unpredictable behavior, global consensus statements recommend a watch-and-wait approach ("active surveillance") with treatment reserved for patients with symptomatic and/or rapidly progressive disease.[78] Given their lack of metastatic potential, symptom palliation and prevention of anatomic complications are the key goals in the treatment of desmoid tumors, with radiographic resolution being a secondary consideration.

Surgical resection of desmoid tumors is problematic because of the high risk of recurrence and morbidity associated with surgery at some sites, and is recommended only for selected patients, generally after multidisciplinary discussion. RT is effective; however, it is associated with a small but concerning risk of secondary malignancies and seems less effective in younger patients, limiting its use for patients younger than 30.[79] Novel interventional approaches, such as cryoablation and high-intensity frequency ultrasound, are also being explored for desmoid tumors.

Until recently, the evidence supporting the activity of individual systemic agents was limited to small and/or uncontrolled case series. More recently, however, two randomized controlled trials confirmed the benefit associated with both sorafenib and pazopanib in the treatment of this disease. Sorafenib, a multitargeted tyrosine kinase targeting both RAF kinases and cell-surface kinase receptors (including VEGF receptors, among others), improved PFS compared with placebo for patients with progressive, symptomatic, or recurrent disease.[77] The study enrolled 87 patients; the median PFS was 9.4 months for placebo, and it had not yet been reached for patients treated with sorafenib. Common adverse effects associated with sorafenib included rash, hypertension, fatigue, palmar-plantar erythrodysesthesia, and pain. Of the patients treated with sorafenib, 18% had to stop treatment due to toxicity. In another clinical trial, pazopanib was compared with methotrexate and vinblastine chemotherapy in a randomized trial and improved the 6-month non-progression rate from 50% to 86%.[80]

Most recently, the results of the international, randomized, placebo-controlled, phase 3 DeFi study evaluating the use of the gamma-secretase inhibitor nirogacestat for patients with progressive desmoid tumor demonstrated a 71% decrease in the risk of tumor progression with nirogacestat, with an overall response rate of 41% versus 8% for placebo.[4] Commonly observed toxicities included diarrhea, hypokalemia, hypophosphatemia, rash, and ovarian dysfunction in women of childbearing age. Other effective agents with varying levels of evidence available in support of their efficacy include liposomal doxorubicin, doxorubicin-based combination chemotherapy, pazopanib, and the combination of methotrexate and vinblastine or vinorelbine.

TENOSYNOVIAL GIANT CELL TUMOR

Tenosynovial giant cell tumor (TGCT), previously known as pigmented villonodular synovitis and giant cell tumor (GCT) of tendon sheath, is a non-malignant, but locally aggressive neoplasm, most commonly affecting joint spaces, and is driven by translocations leading to overexpression of colony-stimulating factor (CSF) 1. It consists of a localized type, which is treated with surgery, and a diffuse type, which is characterized by multiple recurrences despite attempts at surgical resection. Pexidartinib, a selective inhibitor of CSF-1R, was approved by the FDA for the treatment of TGCT not amenable to surgical resection. This agent, in the randomized phase 3 ENLIVEN study, had a 25-week RECIST v1.1 response rate of 39% compared with 0% for placebo.[81] It is a reasonable option for selected patients but has been associated with a small risk of severe hepatotoxicity in the phase 3 clinical trial, and currently can only be prescribed via a risk evaluation and mitigation strategy program. Vimseltinib, another oral CSF-1R antagonist, has also demonstrated a significant improvement in objective response rate (40% for vimseltinib vs 0% in placebo) and clinically meaningful improvements in symptoms and function for patients who have TGCT in the recently published randomized phase 3 MOTION clinical trial (NCT 05059262).[3]

KEY POINTS

- Sorafenib, pazopanib, and nirogacestat are effective in the treatment of desmoid tumors requiring treatment based on disease progression or tumor-related symptoms. Active surveillance is recommended for most patients who are asymptomatic, have minimal symptoms, or are not at risk for anatomic complications from further progression. Nirogacestat is FDA approved for this indication.
- Strategies targeting CSF-1R, such as pexidartinib (FDA approved) and vimseltinib, are effective in TGCT that is not amenable to surgical resection.

SPECIAL CONSIDERATION: KAPOSI SARCOMA

Treatment of KS is aimed at disease control and alleviation of tumor-related symptoms and complications. No treatment is clearly curative. Specific treatment recommendations vary based on the disease extent and the presence or absence of concurrent HIV

infection. Asymptomatic lesions may be observed without direct therapy. In patients who have HIV infection and KS, introduction of antiretroviral therapy (ART), resulting in a decline in viral load and an increase in CD4 cell count, frequently leads to regression in Kaposi lesions with durable clinical response rates greater than 50%.[82] This is standard for all patients who have HIV/AIDS and is the only treatment needed in some cases. Occasionally, and sometimes dramatically, patients with KS who subsequently receive ART experience a sudden flare or burst in KS lesion growth.[83] This phenomenon, known as immune reconstitution inflammatory syndrome, resulting from immune response against pathogens, may occur within weeks to a few months after initiation of ART. In a cohort study of 150 patients who had HIV-associated KS who began ART as the sole treatment of KS, 10 (6.6%) had progressive immune reconstitution inflammatory syndrome–associated KS. In such instances, ART usually can be successfully continued, although chemotherapy may also be required for a time to control KS growth.[84] In HIV-negative patients, classic KS is often an indolent disease that is limited to the skin and managed with local therapies except in advanced cases. The decision to provide specific antitumor local or systemic treatment of KS should be based on several factors, including assessment of disease extent, site of the disease, rate of disease progression, patient-specific psychological factors, and presence of organ dysfunction.[83]

LOCAL TREATMENT

Local treatment may be possible for patients who have limited, nonbulky, and accessible lesions. Alitretinoin gel (0.1%) is the only topical patient-administered therapy approved by the FDA for the treatment of AIDS-related KS.[85]

Other local treatments for KS include alternative topicals such as imiquimod and timolol, intralesional chemotherapy, RT, laser therapy, and cryotherapy, all of which can be effective at controlling local tumor growth. RT has a role in the treatment of KS, particularly when the disease is bulky and symptomatic and when rapid tumor shrinkage is required.

SYSTEMIC THERAPY

Patients who have KS-associated edema, extensive mucocutaneous disease, or symptomatic pulmonary or GI disease need a rapid response, which is best achieved with systemic therapy. Liposomal formulations of doxorubicin and daunorubicin are the standard frontline treatments for patients who have extensive or advanced disease or for those who require rapid tumor shrinkage. For HIV-related KS, each of the two available liposomal anthracyclines proved superior to conventional chemotherapy (bleomycin and vincristine with or without non-liposomal doxorubicin) in terms of response rate and toxicity profile based on the results of randomized prospective clinical trials.[86-88] Liposomal doxorubicin also has substantial activity in classic KS.[88] Patients who have KS whose tumors initially respond well to this treatment may require additional therapy. Low-dose weekly paclitaxel is an established second-line therapy for KS and shows efficacy even for patients who have HIV-associated KS and anthracycline-resistant disease.[89] Pomalidomide is shown to be effective for both HIV-positive and -negative patients. In one representative study, it was administered at a dose of 5 mg once daily on days 1 through 21 of a 28-day cycle. The overall response rate was 73% in the HIV-positive cohort and 100% in the HIV-negative cohort.[90] Based on the results of this trial and other studies, pomalidomide was FDA approved for the treatment of adult patients who have AIDS-related KS after failure of highly active ART, and also for the treatment of KS in adult patients who are HIV negative. More recently, pembrolizumab has demonstrated activity for patients who have classic or endemic KS with a best overall response rate of 71% in a single-arm, phase 2 trial.[91] Oral etoposide, vinorelbine, gemcitabine, bevacizumab, and imatinib have also been evaluated individually for patients who have anthracycline-treated KS and have demonstrated objective responses.

KEY POINTS

- KS may be observed without the use of antineoplastic therapy when the disease burden is limited and asymptomatic.
- ART is the standard frontline treatment of all patients who have HIV-associated KS.
- Immune reconstitution after introduction of ART for patients who have HIV-associated KS may result in tumor flare in 5% to 10% of cases.
- Liposomal anthracycline is the standard first-line chemotherapy for patients requiring systemic treatment of KS because of tumor growth, symptoms, or involvement of visceral organs.
- Paclitaxel is active in anthracycline-resistant KS.
- Pomalidomide is FDA approved for the treatment of advanced KS in both HIV-positive and -negative patients.

SPECIAL CONSIDERATION: GIST

BIOLOGY AND PRESENTATION

GISTs are the most common sarcoma subtype and are characterized by the presence of the CD117 (KIT protooncogene, receptor tyrosine kinase [*KIT*]) and/or DOG-1 (discovered on GIST-1) immunohistochemical markers; most express the stem cell marker CD34. Most GISTs have activating mutations in the *KIT* or *PDGFRA* gene. Approximately 10% to 15% of GISTs use alternative mechanisms for pathogenesis, including loss of function of the succinate dehydrogenase (*SDH*) complex, inactivating mutations

in neurofibromin-1 (*NF-1*), and activating mutations in *BRAF*.[92] Rarely, *NTRK* fusions can also be seen in these tumors.[93] These latter three types of GIST, those without *KIT* or *PDGFRA* mutations, were previously referred to as wild-type GIST.

GISTs are thought to arise from the interstitial cells of Cajal, the pacemaker cells of the GI tract. Approximately 65% of GISTs occur in the stomach, 25% in the small bowel, and the remainder in other sites along the GI tract or in the abdomen. GISTs occurring in the setting of neurofibromatosis predominantly appear in the small intestine, including the duodenum, as multifocal tumors and frequently exhibit a low mitotic rate.[94]

In some cases, GISTs are found unexpectedly during an endoscopy study in the absence of symptoms. Often, symptoms are nonspecific, such as bloating and early satiety. They can also present with bleeding, causing substantial anemia, and less commonly can cause frank bowel obstruction. CT is the imaging study of choice, and an endoscopic biopsy for localized disease is the standard of care for determining a diagnosis, particularly if neoadjuvant therapy is planned.

The primary treatment of localized GIST is surgery, although surveillance with periodic endoscopic ultrasound can be considered for gastric GISTs less than 2 cm in size that do not have high-risk features by endoscopic ultrasound. High-risk features include irregular borders, cystic spaces, ulceration, echogenic foci, or internal heterogeneity.[95] The most common sites for metastatic recurrence are the peritoneum and liver. Nodal, bone, and pulmonary metastases from GIST have been described but are rare.

Tumors are staged on the basis of size, location in the GI tract, mitotic rate, involvement of lymph nodes, and presence of metastasis. The involvement of lymph nodes (rare) or the presence of metastasis is classified as stage IV disease. GIST is graded by mitotic rate. A low mitotic rate is 5 or fewer mitoses per 5 mm^2 (50 microscopic fields using 40× magnification); a high mitotic rate is more than 5 mitoses per 5 mm^2. The occurrence of tumor rupture before or during surgery is associated with a high risk of GIST recurrence.

LOCALIZED DISEASE

Adjuvant Therapy

Imatinib is a standard adjuvant treatment for patients who have resected GIST at an elevated risk of recurrence. It was initially FDA approved based on the Z9001 study, which showed improved recurrence-free survival (RFS) when administered for 1 year in comparison with no adjuvant treatment.[96] The SSG XVIII trial, a large, randomized, open-label trial, examined the use of imatinib administered for 1 year compared with 3 years after complete resection of high-risk GIST.[97,98] High risk was defined by a tumor size larger than 10 cm, a mitotic count of more than 10 per 50 high-power field (hpf), a tumor size larger than 5 cm with a mitotic count of more than 5 per 50 hpf, or tumor rupture. The study revealed improvements in both RFS and OS. Most recently, the multicenter, open-label, randomized phase 3 IMADGIST study explored the use of 6 years of adjuvant imatinib compared to 3 years in patients with a recurrence risk of at least 35%. An improvement in RFS was observed, but data on OS were premature.[98]

Imatinib therapy can be associated with intolerable adverse effects, and one-quarter of the patients assigned to take imatinib for 3 years discontinued treatment early for reasons other than disease recurrence. Periorbital edema, muscle cramps, leukopenia, and elevation in serum creatinine level were more common in patients assigned to 3 years of imatinib. Based on the information currently available, it is reasonable to discuss adjuvant imatinib therapy for at least 3 years with patients who are at high risk of tumor relapse. Importantly, adjuvant imatinib is not recommended for patients with imatinib-insensitive disease, including wild-type (non-*KIT*, non-*PDGFRA* mutated) GIST or those with a *PDGFRA* exon 18 D842V mutation.

Neoadjuvant Therapy

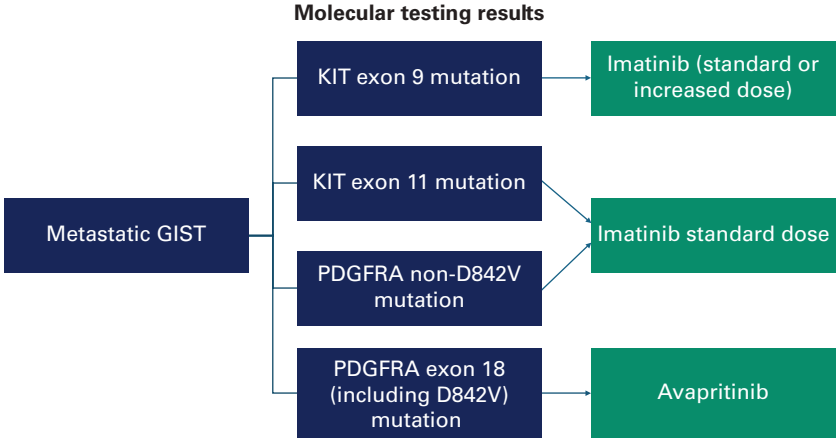
The primary treatment of localized GIST is surgery. Imatinib can be considered as neoadjuvant therapy for patients who have high predicted morbidity associated with primary surgery, though this has not been prospectively studied. In that setting, optimal response to imatinib can take up to 12 months based on data in advanced disease. No evidence is available that neoadjuvant imatinib improves outcomes compared with adjuvant imatinib, but it may help extent of surgery eventually required. If neoadjuvant or adjuvant therapy is considered, mutation testing to confirm the presence of a responsive *KIT*/*PDGFRA* mutation is recommended beforehand to ensure the tumor is likely to respond. If neoadjuvant therapy is pursued, risk stratification for further adjuvant therapy should be done based on the pretreatment biopsy, as treatment with imatinib is likely to lower the observed mitotic rate.

Advanced Disease

Cytotoxic chemotherapy is ineffective for the treatment of GIST. However, imatinib has remarkable activity against most *KIT* or *PDGFRA* mutation-positive GISTs. In early-phase studies of imatinib therapy for metastatic GIST, response rates were approximately 54%, with an additional 28% of patients achieving stable disease.[99] In randomized phase 2 and 3 studies, a once-daily dose of 400 mg was as effective as 600 or 800 mg of imatinib daily.[99,100] As a result, 400 mg daily of oral imatinib is the standard treatment of metastatic GIST (Fig. 17-3). The *KIT* genotype of a GIST predicts the responsiveness of the tumor to imatinib. Patients who have mutations in exon 11 of *KIT* have a greater chance of response to imatinib than patients with exon 9 *KIT* mutations or wild-type *KIT*.[101] Tumors that harbor the *PDGFRA* mutation D842V are particularly insensitive to imatinib, although other mutations in *PDGFRA* are imatinib sensitive. Avapritinib is a TKI directed against the *PDGFRA* D842V mutation.

In the phase 1 NAVIGATOR clinical trial, this agent yielded an impressive 88% response rate in the treatment of patients with this previously highly resistant mutation.[102] Based on these data, avapritinib was FDA approved for the treatment of unresectable or metastatic GIST harboring a *PDGFRA* exon 18 mutation, including the D842V mutation.

Figure 17-3 GIST Treatment Options Algorithm in the First-Line Setting



Abbreviation: GIST, gastrointestinal stromal tumor.
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Patients with GIST harboring an activating mutation in exon 9 of *KIT* may benefit from a higher starting dose of imatinib (400 mg twice daily). A meta-analysis of two large, randomized trials comparing 400 mg of imatinib daily with 400 mg twice daily in the treatment of advanced or metastatic GIST confirmed a small PFS advantage and detected a higher objective response rate associated with the higher dose for patients with exon 9 *KIT* mutations.[103] However, with a median follow-up of more than 40 months, there was no improvement in OS. There was no difference in outcome between the standard and high-dose groups among patients who had the more common exon 11 *KIT* mutations.

After disease progression with 400 mg of imatinib daily, a conventional approach is to increase the dosage to a total daily dose of 800 mg (or 600 mg if the higher dose is not tolerated). Approximately one-third of patients may have some degree of tumor control after escalation of imatinib dosage.[99,104]

For patients with imatinib-refractory disease or patients intolerant to imatinib, sunitinib is the standard second-line therapy based on a randomized, phase 3 study, showing improved PFS compared with placebo.[105] The median duration of PFS in the sunitinib arm was 24 weeks compared with 6 weeks for patients treated with placebo. OS was superior in the sunitinib arm. Objective tumor responses, however, were infrequent (less than 10% of patients). The most frequently reported adverse effects of sunitinib were fatigue, diarrhea, skin discoloration, and nausea, each occurring in more than 20% of patients. Patients with *KIT* exon 9 mutations appear to have more clinical benefit in terms of response rate and PFS with sunitinib compared with those with *KIT* exon 11 mutations.[106] Hypertension and hypothyroidism are also known toxicities of sunitinib and should be closely monitored and treated immediately when identified. Rare cases of fatal liver and cardiac events have been reported.

Regorafenib, at a dose of 160 mg daily for 3 of every 4 weeks, is approved for the treatment of GIST after the development of resistance to imatinib and sunitinib based on the results of a randomized, blinded, placebo-controlled trial.[107] The median PFS was 5 months for patients receiving regorafenib compared with 1 month for patients receiving placebo. The most common severe adverse events related to regorafenib were hypertension and hand-foot skin reaction, which occurred in 24% and 20% of patients, respectively.

Ripretinib is a novel TKI that targets not only *KIT* but also *PDGFRA* mutations commonly found in advanced GIST. In the phase 3 INVICTUS trial, this agent was compared with placebo for patients with metastatic GIST who had been previously treated with imatinib, sunitinib, and regorafenib.[108] Patients treated with ripretinib had a median PFS of 6.3 months compared with 1.6 months in the placebo group. Based on these data, it was FDA approved in May 2020 for the treatment of advanced GIST for patients who have received three or more TKIs. Given that ripretinib is active against mutations in the activation loop of *KIT*, it was hoped that earlier-line use of this agent would yield improved PFS compared with sunitinib. Unfortunately, this was not demonstrated in the recent phase 3 randomized INTRIGUE study despite patients on ripretinib experiencing fewer severe adverse events.[109] However, an exploratory subgroup analysis indicated that certain resistance mutations (*KIT* exon 11 with secondary 17/18 mutations) were associated with longer PFS in patients who received ripretinib. Of note, an increase from standard dose ripretinib (150 mg daily) to dose-escalated (150 mg twice daily) therapy can be considered upon progression.[110,111]

Surgery and Other Local Therapies

Surgery and other local therapies can play a potential role in the setting of limited, progressive, metastatic disease.[112] In some patients who have multifocal metastatic disease, progression is identified in a limited number of sites with other sites remaining under control. Patients with this pattern of disease progression can be treated successfully with resection of progressing sites coupled with continued TKI therapy. In the liver—the most common site of metastasis—ablation and other types of liver-directed therapy can be considered for oligoprogression when surgery is not feasible. It is essential to continue TKI therapy in such patients because of the risk of rapid progression without systemic treatment. Patients who have multiple sites of disease progression, indicative of generalized resistance to systemic therapy, are not appropriate candidates for local therapies because they almost universally experience additional progression soon afterwards.

PRESENTING CASE STUDY

A 60-year-old woman presents to her primary care physician with a long-standing history of persistent iron-refractory iron-deficiency anemia and ongoing fatigue; she has no other pertinent past medical history. Gastrointestinal testing reveals a 4.8-cm submucosal small bowel tumor associated with ulceration but without stigmata of recent bleeding. Endoscopic biopsy identifies a spindle cell tumor that is positive for *KIT* (CD117) and DOG-1, consistent with a diagnosis of gastrointestinal stromal tumor (GIST). The patient undergoes primary surgical resection with partial small bowel resection. Pathology confirms GIST with 18 mitoses/50 hpf. *KIT* gene sequencing demonstrates a mutation in exon 11. She is referred to medical oncology for consideration of adjuvant therapy.

Based on the characteristics of this patient's tumor, what is the next best step?

Surgical resection is the standard of care for patients with localized GIST. This patient exhibits high-risk features for recurrent disease, including a non-gastric primary location and a mitotic rate greater than 10 mitoses/50 hpf. Based on the SSGXVIII/AIO study, 3 years of adjuvant imatinib improved both recurrence-free and OS compared to 1 year of adjuvant therapy. *KIT* exon 11 mutations are predicted to be sensitive to imatinib. As a result, adjuvant imatinib is the next best step. Although the optimal duration of adjuvant therapy is unknown, data would currently support at least 3 years. Recently published data from the IMADGIST study, comparing 6 years to 3 years of adjuvant imatinib, revealed an improvement in recurrence-free survival, while data for OS were premature.

Two years after completing therapy, imaging reveals multifocal hepatic disease; biopsy indicates metastatic GIST. Molecular testing again reveals a *KIT* exon 11 mutation with no evidence of secondary mutations. How would you proceed based on these findings?

Resumption of systemic therapy with imatinib (400 mg, once daily) would be the most appropriate next step. Lifelong therapy with a KIT-targeted tyrosine kinase inhibitor (TKI) is now recommended, as trials exploring discontinuation have universally shown more rapid progression of metastatic disease off TKI-based therapy.

KEY POINTS

- Most GISTs have activating mutations in the *KIT* or *PDGFRA* gene.
- Surgery is the best curative treatment of primary GIST, although surveillance is an option for small gastric GISTs without high-risk features on endoscopic ultrasound.
- For patients who have localized GIST at high risk of recurrence, 400 mg of imatinib daily for at least 3 years after surgery delays time to recurrence and improves OS.
- Imatinib at a dosage of 400 mg daily is the standard of care in first-line therapy for metastatic GIST with sensitive mutations. Dose escalation can be considered upon progression.
- Patients with *KIT* exon 9–mutated GISTs may benefit from a higher initial starting dose of imatinib (eg, 400 mg twice daily).
- GISTs with *PDGFRA* exon 18 D842V mutations are resistant to imatinib but highly responsive to avapritinib.
- Sunitinib is FDA approved as a second-line therapy for patients with imatinib-refractory GIST or who cannot tolerate imatinib.
- Regorafenib is FDA approved for third-line treatment of GIST after failure of imatinib and sunitinib.
- Ripretinib is FDA approved for fourth-line treatment of GIST after treatment with at least three prior TKIs. Dosage escalation can be considered upon progression.
- Local therapies (eg, surgery, liver-directed therapy) may be appropriate in conjunction with continued TKI therapy for patients with limited progression of metastatic disease.

BONE SARCOMAS

OSTEOSARCOMA

Osteosarcomas are the most common primary tumors of bone, with two peaks of incidence: one between ages 10 and 20 years and a smaller peak between ages 60 and 80 years. Disease in the latter age group is sometimes associated with Paget's disease of bone. Osteosarcomas generally arise in the metaphysis of the bone (between the bone end [epiphysis] and the shaft [diaphysis]). They are characterized by lytic and blastic features in admixed bone. If the tumors extend to soft tissue, they can cause both a periosteal reaction and ossification in a pattern perpendicular to the surface of the bone (Fig. 17-4).

Figure 17-4 Osteosarcoma of the Right Distal Femur With Characteristic Cortical Destruction and Bone Formation

(A) At diagnosis. (B) After three cycles of neoadjuvant doxorubicin and cisplatin with coarsening of calcification consistent with response to therapy.
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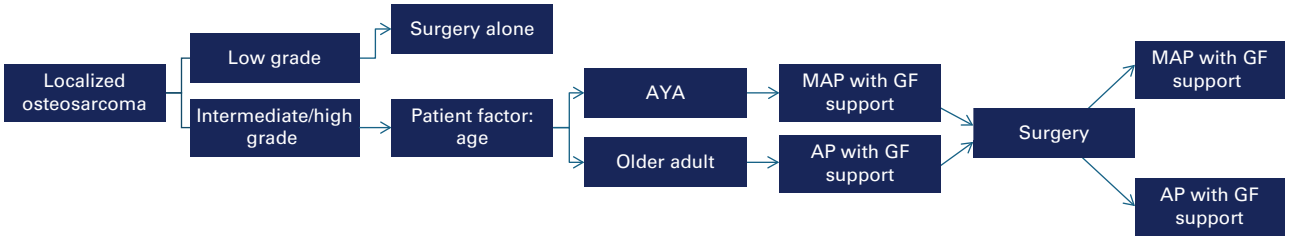
Neoadjuvant and adjuvant chemotherapy are the standard of care for most patients who have osteosarcomas (Fig. 17-5). It has resulted in significant improvement in 5-year survival rates from approximately 20% with surgery alone to as high as 80% in patients with responsive disease. Neoadjuvant chemotherapy is often preferred because it allows for assessment of histologic response, which is a major prognostic factor in localized high-grade osteosarcoma. Nearly all patients with localized osteosarcoma benefit from chemotherapy. The exception is superficial low-grade osteosarcomas for which adjuvant chemotherapy is not indicated. For conventional osteosarcomas, six cycles of cisplatin and doxorubicin were found to be as effective as a more complex seven-drug regimen in one randomized multicenter study.[113]

Figure 17-5 Treatment Paradigm for Localized Osteosarcoma



Abbreviations: AP, doxorubicin, cisplatin; AYA, adolescent and young adult; GF, growth factor; MAP, methotrexate, doxorubicin, cisplatin.
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Data regarding the use of methotrexate remains somewhat controversial in adult patients. However, the combination of doxorubicin, cisplatin, and high-dose methotrexate (methotrexate, doxorubicin, cisplatin [MAP] chemotherapy) is a standard therapy in young patients who have normal cardiac and renal function based on pediatric osteosarcoma studies. In older adults,

high-dose methotrexate is associated with delayed clearance, increased risk of nephrotoxicity, and acute lung injury. Given these risks and the unclear benefit associated with this agent, methotrexate is not routinely considered a standard component of the treatment of adults.

The response of osteosarcomas to neoadjuvant chemotherapy is best assessed by pathologic examination at the time of surgery. This examination assesses the percentage of viable tumor in the total volume of the resection specimen. Presently, there is no evidence that changing therapy improves OS for patients who have osteosarcoma and have a poor response to preoperative chemotherapy. EURAMOS-1, a large, international, randomized, phase 3 trial, evaluated the addition of ifosfamide and etoposide (IE) for patients with ≥10% viable tumor (poor histologic response) after two cycles of MAP. Of note, the addition of IE resulted in increased toxicity with no improvement in event-free survival (EFS). The 3-year EFS rate was 55% in the control group and 53% in the group receiving IE.[114] Because patients with poorly responding osteosarcoma treated with full-course chemotherapy have higher survival rates than patients who do not receive additional chemotherapy, all patients should be offered adjuvant chemotherapy for treatment of primary osteosarcoma, regardless of histologic response.

RT is not commonly used as an adjuvant or neoadjuvant treatment of localized high-grade osteosarcoma. It can, however, be considered for patients who have undergone positive-margin surgery (such as a head-and-neck osteosarcoma) for whom additional surgery may result in significant morbidity. Of note, it has no role for those who have undergone negative-margin surgery.

Osteosarcomas typically metastasize to the lung. Resection of pulmonary metastases (stage IVA disease) can be curative in a substantial minority of patients.[115] Patients with fewer than three pulmonary metastases who are more than 2 years from diagnosis to the development of lung metastasis have the best survival rates after metastasectomy.

IE has activity in relapsed osteosarcoma.[116,117] Gemcitabine (with or without docetaxel) also has some activity in this setting.[118] More recently, TKIs have demonstrated activity in the treatment of advanced osteosarcoma. Regorafenib was compared with placebo in two randomized, phase 2 clinical trials for patients with known progressive disease, many of whom had previously been treated with chemotherapy for metastatic disease. In the REGOBONE study, the median PFS was 16.4 weeks in the regorafenib group compared with 4.1 weeks for those on placebo.[119] In the SARC024 study, the median PFS was 3.6 months with regorafenib compared with 1.7 months for placebo.[120] The most common toxicities encountered were hypertension, hand-foot syndrome, asthenia, and diarrhea. Sorafenib and cabozantinib have also shown activity in osteosarcoma.[121,122]

EWING SARCOMA

Ewing sarcoma typically occurs in the bones of children and less commonly in adults. Radiographically, skeletal Ewing sarcoma usually affects the shaft of the bone in an infiltrative pattern called onion skinning, which is easily visible on CT scans and X-rays (Fig. 17-6). On microscopy, Ewing sarcoma appears as monotonous sheets of small, round, blue cells that express high levels of a cell-surface glycoprotein (CD99) and the nuclear factor FLI-1, which can be detected using immunohistochemistry. However, expression of CD99 and FLI-1 is not specific for Ewing sarcoma, and molecular studies may be performed to detect the characteristic chromosome translocations present in the disease. Most Ewing sarcomas have reciprocal translocation involving *EWSR1* and *FLI-1*, with a small minority involving *EWSR1* and *ERG* or other less commonly seen partners. A small percentage have alterations that do not involve *EWSR1*.

Recently, other undifferentiated round cell sarcomas, specifically those harboring *CIC-DUX4* and *BCOR-CCNB3* translocations, have been identified. These tumors, although previously grouped within the Ewing sarcoma family of tumors (ESFT) and often treated similarly to Ewing sarcoma, likely have their own distinct biology, responsiveness to treatment, and prognosis.[123]

Localized Disease

Multimodality therapy with surgery, chemotherapy, and RT is the standard of care for localized ESFT and results in greater than 50% cure rates (Fig. 17-7). Local treatment of the primary site of disease is usually performed after an initial 12 to 18 weeks of multiagent chemotherapy. Complete resection of the tumor is preferred when feasible. RT is administered as an adjuvant for the treatment of microscopic residual tumor or as definitive local therapy if surgery cannot be performed with acceptable morbidity.

The combination of vincristine, doxorubicin, and cyclophosphamide (VDC) with IE is the current standard chemotherapy regimen used and showed improvements in relapse-free survival and OS when compared with VDC alone in a study performed primarily in pediatric patients with nonmetastatic Ewing sarcoma.[124] Of note, a randomized trial of VDC alternating with IE every 2 weeks (known as interval-compressed therapy) for a total of 14 cycles, as compared with the standard every 3-week dosing schedule in patients aged younger than 50 years with localized Ewing sarcoma, demonstrated an improvement in RFS.[125] The toxicity profile and frequency did not differ between arms, and secondary malignancies, including acute leukemia, osteosarcoma, and lymphoma, occurred in approximately 3% of patients. Whereas interval-compressed therapy has become a reasonable standard for adolescent and young adult patients, a minority of adult patients (12% of the study population) were enrolled in this study.

Figure 17-6 Characteristic Changes in Tibial Ewing Sarcoma

Onion skin changes are seen along the tibial diaphysis in this radiograph in the area of the associated soft tissue mass.
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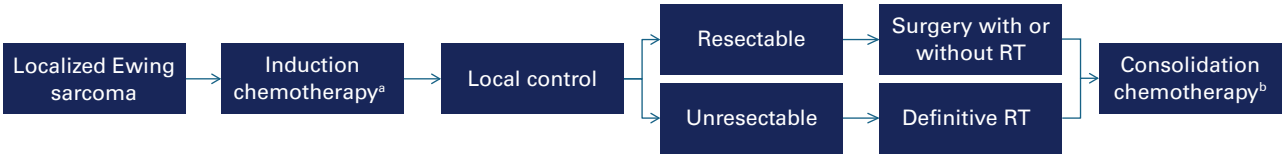
Figure 17-7 Treatment Paradigm for Localized Ewing Sarcoma



Abbreviations: GF, growth factor; IE, ifosfamide and etoposide; RT, radiation therapy; VDC, vincristine, doxorubicin, and cyclophosphamide.
[a]Four to six cycles of interval compressed (Q2W) VDC/IE with GF support.
[b]Complete a total of 14 cycles of interval compressed VDC/IE, as tolerated.
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Late recurrence of Ewing sarcoma, more than 5 years after initial diagnosis, occurs in approximately 10% to 15% of children and adolescents, with approximately 25% of the late recurrences developing more than 10 years after diagnosis.[126] As a result, long-term surveillance is recommended.

Metastatic Disease

For metastatic Ewing sarcomas, the addition of IE to VDC in the upfront setting did not appear to improve survival outcomes over VDC alone, although the study was likely underpowered to identify a survival difference in the metastatic patient population.[124] In the relapsed setting, the phase 3 rEECur study examined the activity of several frequently used salvage regimens, including high-dose ifosfamide, cyclophosphamide in combination with topotecan, irinotecan in combination with temozolomide, and gemcitabine in

combination with docetaxel, using a Bayesian approach and multiple pairwise comparisons. Among the regimens examined, gemcitabine in combination with docetaxel appears to be the least favored, whereas high-dose ifosfamide appeared to be the most favored.[127]

CHONDROSARCOMA

Chondrosarcomas are the second most common primary tumor of bone and usually affect patients aged 60 years or older. On radiographs, chondrosarcomas generally appear as a radiolucent area with obvious bony destruction and a moderate number of discrete calcified areas. They most often involve the medullary cavity and have scalloped edges consistent with a multinodular growth pattern. Metastases from conventional chondrosarcoma often involve the lung, follow a relatively indolent growth rate, and may be managed by surgery if limited in number.

There is no role for traditional chemotherapy in the management of most conventional chondrosarcomas, as they are highly resistant to chemotherapy. Patients who have unresectable metastatic or recurrent chondrosarcoma are best served by clinical trial participation when available. Chondrosarcomas may have activating mutations in different receptor tyrosine kinases as well as mutations in isocitrate dehydrogenase 1 (*IDH1*) and isocitrate dehydrogenase 2 (*IDH2*). The NCCN guidelines list the IDH1 inhibitor ivosidenib as a potential option for *IDH1*-mutated chondrosarcomas.[128] Pazopanib is additionally listed based on a phase 2 prospective study revealing a disease control rate at 16 weeks of 43%, a median PFS of 7.9 months, and a median OS of 17.6 months.[129] Finally, dasatinib can be considered based on more limited data.

Dedifferentiated chondrosarcoma is generally a high-grade variant and occasionally responds to chemotherapy used for osteosarcoma. Patients who have mesenchymal chondrosarcoma, another high-grade variant that resembles Ewing sarcoma on routine staining, may benefit from chemotherapy used for the treatment of Ewing sarcoma. Extraskeletal myxoid chondrosarcoma is not a cartilaginous tumor, but rather a soft tissue malignancy that often occurs in deep soft tissue and is characterized by chromosomal translocations involving *NR4A3*. It has a relatively indolent growth rate, a high risk of dissemination, and is relatively resistant to chemotherapy.[130,131]

GCT OF BONE

GCT of bone is a rare, primary tumor of bone composed of malignant stromal cells that secrete receptor activator of nuclear factor-kappa B (RANK) ligand and recruit multinucleated osteoclast-like cells that result in bone lysis. Although considered largely benign, metastatic disease can occur in a small number of cases (primarily to the lungs).

Patients usually present with lytic bone destruction, pain, and restricted mobility of the joint adjacent to the lesion. Management of primary disease typically involves complete curettage of the lesion, often followed by intralesional adjuvant therapy with heat, freezing, or chemicals (eg, phenol). Approximately 10% to 20% of tumors recur locally, often necessitating joint resection and replacement; metastasis occurs in approximately 1% of cases. The use of denosumab, an inhibitory monoclonal antibody to RANK ligand, administered subcutaneously during the first month on days 1, 8, and 15, followed by day 1 monthly dosing thereafter, resulted in a lack of tumor progression in the large majority of patients in a phase 2 trial.[132] Substantial adverse events that occurred during denosumab treatment included osteonecrosis of the jaw in 1% of patients, hypocalcemia in 5%, and hypophosphatemia in 3%. Based on the high rate of tumor control and relatively low rate of adverse effects from denosumab treatment of GCT of bone, the FDA-approved denosumab as treatment of patients with unresectable GCT of bone or in situations in which complete resection would result in severe morbidity in adults and skeletally mature adolescents.

KEY POINTS

- Chemotherapy is critical for curative intent treatment of localized osteosarcoma.
- Doxorubicin and cisplatin are commonly used as standard therapy in adult patients, and high-dose methotrexate (MAP chemotherapy) is added in the treatment of children and young adults with normal renal function.
- The addition of IE does not improve survival for individuals who have a poor response to initial MAP chemotherapy.
- Resection of lung metastases (metastasectomy) should be considered for patients with osteosarcoma.
- TKIs, such as regorafenib, show activity in patients with metastatic osteosarcoma.
- Multimodality therapy, including multiagent chemotherapy, surgery, and/or RT, is critical in the management of patients who have localized Ewing sarcoma.
- Interval-compressed VDC/IE is the standard treatment approach for adolescents and young adults who have localized disease.
- Conventional chondrosarcomas are generally low to intermediate grade and are resistant to chemotherapy. There is no currently FDA-approved therapy.
- Denosumab, a monoclonal antibody targeting RANK ligand, is FDA approved for the treatment of GCT of bone that is deemed unresectable or for which surgery would likely result in severe morbidity.

SURVIVORSHIP

Survivors of childhood cancer are at risk for the development of secondary cancers, including sarcomas. The Childhood Cancer Survivor Study identified a ninefold higher risk of a secondary sarcoma among survivors of childhood cancer compared with the general population.[133] Moreover, the great improvement in long-term survival rates of children and adults with sarcoma, especially Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma, from multimodality treatment comes at a high cost for a minority of patients. Serious late effects of treatment include secondary malignancy, infertility, cardiomyopathy, nephropathy, neuropathy, hearing impairment, and limb dysfunction. The cumulative incidence of secondary malignancy in children treated for sarcoma is approximately 1% to 3% at 10 to 20 years, with the highest risk for patients who received chemotherapy and RT. Children treated for sarcoma have a threefold to sixfold higher risk of secondary cancer than those in the age-matched general population.[134,135]

Adults who have sarcoma treated with chemotherapy and/or RT are also at risk for long-term complications, including secondary malignancies and radiation-induced fibrosis and lymphedema. Symptomatic cardiomyopathy develops in approximately 1% to 2% of patients treated for sarcoma with doxorubicin and ifosfamide, and renal tubular and/or glomerular dysfunction develops in 5% to 10%, with the risk related to the cumulative dose received. Infertility is most often related to exposure to alkylating agents and affects postpubescent men more often than women. The Children's Oncology Group has guidelines for the long-term follow-up of survivors of childhood, adolescent, and young adult cancers (http://www.survivorshipguidelines.org).

HIGH-YIELD TAKEAWAYS

- The treatment of metastatic GIST follows a clear sequence of sequential TKI-based therapy (see the following) based on drug approvals, although specific mutations may confer differential sensitivity to various agents. This applies to *KIT* and *PDGFRA* mutant GIST, with the exception of *PDGFRA* D842V mutant GIST, for which avapritinib is the only FDA-approved therapy.

Line of Treatment	Agent
First	Imatinib
Second	Sunitinib
Third	Regorafenib
Fourth	Ripretinib

- Patients who have localized GIST should be considered for adjuvant therapy with imatinib if their tumors are at high risk for recurrence. Risk factors that suggest high risk include a non-gastric primary location, a tumor size larger than 10 cm, a mitotic rate of more than 10 per 50 hpf, a tumor size larger than 5 cm with a mitotic rate of more than 5 per 50 hpf, or tumor rupture. The optimal duration of adjuvant therapy is unknown, but at least 3 years is recommended for high-risk disease. Given the extremely high risk for disease recurrence after tumor rupture, some advocate long-term therapy for this situation.
- Patients who have most subtypes of metastatic STS are generally treated with doxorubicin-based chemotherapy in the first line.
- Ewing sarcoma and osteosarcoma are both chemosensitive tumors with high metastatic potential. Nonmetastatic tumors are treated with chemotherapy both before and after local control interventions (surgery, RT, or both).

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SARCOMA 17

CHAPTER SUMMARY GUIDE

KEY POINTS

- Sarcomas account for approximately 1% of cancers in adults.
- STSs are three to four times more common than those of bone.
- Individuals who have certain hereditary cancer susceptibility syndromes, such as Li-Fraumeni, have an increased risk of sarcoma.
- Therapeutic radiation confers a small but definite risk for the development of sarcoma.
- HHV-8 infection is associated with KS.
- Approximately 30% to 40% of sarcomas have defined, recurring, specific genetic alterations such as chromosomal translocations, gene amplifications, or mutations that contribute to pathogenesis.
- STSs often present as enlarging masses and may be painful or painless.
- Bone sarcomas are usually associated with pain.
- A core needle or incisional biopsy is required to obtain sufficient tumor material for definitive diagnosis and sarcoma subtype classification.
- Angiosarcoma and KS can present as dermal-only or visceral disease.
- Tumor grade is a key factor in sarcoma staging, treatment, and patient prognosis.
- Staging of extremity STSs or bone sarcomas should include the lungs, as they are the most common site for distant metastases.
- Surgical resection remains the standard of care for most patients who have localized STS when treating with curative intent.
- Preoperative or postoperative external-beam RT is used for large (>5 cm in greatest dimension), intermediate- to high-grade STS arising in the extremity or body wall.
- The addition of neoadjuvant and adjuvant pembrolizumab to RT and surgery is shown to significantly improve 2-year DFS for patients who have stage III UPS and pleomorphic or dedifferentiated LPS of the extremity and limb girdle.
- Adjuvant RT is not routinely recommended after resection of retroperitoneal or visceral STS.
- Adjuvant or neoadjuvant chemotherapy with an anthracycline (doxorubicin or epirubicin) and ifosfamide reduces the risk of sarcoma recurrence and may improve OS in patients who have chemotherapy-sensitive STS subtypes that have a high risk for the development of metastasis.
- Patients who have localized extraskeletal Ewing sarcoma should be treated with chemotherapy as administered to patients who have skeletal Ewing sarcoma if not medically contraindicated.
- Embryonal and alveolar rhabdomyosarcomas are aggressive cancers with a propensity for nodal and distant metastases. Depending on clinical group and staging, they are typically managed using surgery, adjuvant RT, and multiagent chemotherapy at centers with experience in treating these STS.
- Doxorubicin and ifosfamide are the most active single-agent drugs for metastatic (non-GIST, non-rhabdomyosarcoma) adult STS.
- Anthracycline-based combinations have not consistently improved OS for patients who have metastatic disease, but are reasonable to consider in select patients.
- Sequential single-agent treatment of metastatic disease is a reasonable approach for many patients who have metastatic disease.
- Gemcitabine and docetaxel, as a combination, are active in advanced or metastatic STS with efficacy similar to doxorubicin but with more toxicity.
- Trabectedin is FDA approved in patients with leiomyosarcoma or liposarcoma who have received prior treatment with an anthracycline.
- Eribulin is FDA approved for the treatment of advanced liposarcoma after prior treatment with an anthracycline.
- Pazopanib is FDA approved for non-GIST, non-adipocytic STS patients who have received prior chemotherapy.
- Afamitresgene autoleucel, an engineered autologous T-cell receptor product, targeting MAGE-A4, was FDA approved for adults with select HLA-A*02 serotypes, who have unresectable or metastatic MAGE-A4-expressing synovial sarcoma and have received prior chemotherapy.

- Immune checkpoint inhibitors, for patients with metastatic disease, are under active exploration but appear to have activity in UPS and angiosarcoma, and atezolizumab is FDA approved in ASPS.
- The addition of neoadjuvant and adjuvant pembrolizumab to RT and surgery was shown to significantly improve DFS for patients with stage III UPS and pleomorphic or dedifferentiated LPS of the extremity and limb girdle.
- Treatments are becoming increasingly histology-specific.
- Sorafenib, pazopanib, and nirogacestat are effective in the treatment of desmoid tumors requiring treatment based on disease progression or tumor-related symptoms. Active surveillance is recommended for most patients who are asymptomatic, have minimal symptoms, or are not at risk for anatomic complications from further progression. Nirogacestat is FDA approved for this indication.
- Strategies targeting CSF-1R, such as pexidartinib (FDA approved) and vimseltinib, are effective in TGCT that is not amenable to surgical resection.
- KS may be observed without the use of antineoplastic therapy when the disease burden is limited and asymptomatic.
- ART is the standard frontline treatment of all patients who have HIV-associated KS.
- Immune reconstitution after introduction of ART for patients who have HIV-associated KS may result in tumor flare in 5% to 10% of cases.
- Liposomal anthracycline is the standard first-line chemotherapy for patients requiring systemic treatment of KS because of tumor growth, symptoms, or involvement of visceral organs.
- Paclitaxel is active in anthracycline-resistant KS.
- Pomalidomide is FDA approved for the treatment of advanced KS in both HIV-positive and -negative patients.
- Most GISTs have activating mutations in the *KIT* or *PDGFRA* gene.
- Surgery is the best curative treatment of primary GIST, although surveillance is an option for small gastric GISTs without high-risk features on endoscopic ultrasound.
- For patients who have localized GIST at high risk of recurrence, 400 mg of imatinib daily for at least 3 years after surgery delays time to recurrence and improves OS.
- Imatinib at a dosage of 400 mg daily is the standard of care in first-line therapy for metastatic GIST with sensitive mutations. Dose escalation can be considered upon progression.
- Patients with *KIT* exon 9–mutated GISTs may benefit from a higher initial starting dose of imatinib (eg, 400 mg twice daily).
- GISTs with *PDGFRA* exon 18 D842V mutations are resistant to imatinib but highly responsive to avapritinib.
- Sunitinib is FDA approved as a second-line therapy for patients with imatinib-refractory GIST or who cannot tolerate imatinib.
- Regorafenib is FDA approved for third-line treatment of GIST after failure of imatinib and sunitinib.
- Ripretinib is FDA approved for fourth-line treatment of GIST after treatment with at least three prior TKIs. Dosage escalation can be considered upon progression.
- Local therapies (eg, surgery, liver-directed therapy) may be appropriate in conjunction with continued TKI therapy for patients with limited progression of metastatic disease.
- Chemotherapy is critical for curative intent treatment of localized osteosarcoma.
- Doxorubicin and cisplatin are commonly used as standard therapy in adult patients, and high-dose methotrexate (MAP chemotherapy) is added in the treatment of children and young adults with normal renal function.
- The addition of IE does not improve survival for individuals who have a poor response to initial MAP chemotherapy.
- Resection of lung metastases (metastasectomy) should be considered for patients with osteosarcoma.
- TKIs, such as regorafenib, show activity in patients with metastatic osteosarcoma.
- Multimodality therapy, including multiagent chemotherapy, surgery, and/or RT, is critical in the management of patients who have localized Ewing sarcoma.
- Interval-compressed VDC/IE is the standard treatment approach for adolescents and young adults who have localized disease.
- Conventional chondrosarcomas are generally low to intermediate grade and are resistant to chemotherapy. There is no currently FDA-approved therapy.
- Denosumab, a monoclonal antibody targeting RANK ligand, is FDA approved for the treatment of GCT of bone that is deemed unresectable or for which surgery would likely result in severe morbidity.

CHAPTER TABLES AND IMAGES

Table 17-1 Genetic Syndromes Associated With Sarcoma

Syndrome	Genetic Abnormality	Associated Sarcoma Types
Li-Fraumeni syndrome	*TP53* mutation	Various types of STS and bone sarcomas
Retinoblastoma	*RB1* gene deletion	Leiomyosarcoma, osteosarcoma
Neurofibromatosis type I	*NF-1* mutation	MPNST, GIST
Gardner syndrome	*APC* mutation	Desmoid tumor
McCune-Albright syndrome	*GNAS1* mutation	Osteosarcoma
Bloom syndrome	*RECQL3* mutation	Embryonal RMS, osteosarcoma
Rothmund-Thomson syndrome	*RECQL4* mutation	Osteosarcoma
Werner syndrome	*WRN* mutation	Osteosarcoma
Costello syndrome	*HRAS* mutation	Embryonal RMS
Nijmegen breakage syndrome	*NBS1* mutation	Embryonal RMS
Carney-Stratakis syndrome	*SDH* mutation	GIST
Noonan syndrome	*PTPN11* mutation	Embryonal RMS, giant cell tumor, PVNS

Abbreviations: *APC*, APC regulator of WNT signaling pathway; GIST, gastrointestinal stromal tumor; *GNAS1*, GNAS complex locus; *HRAS*, HRAS protooncogene, GTPase; MPNST, malignant peripheral nerve sheath tumor; *NBS1*, nibrin; *NF-1*, neurofibromin-1; *PTPN11*, protein-tyrosine phosphatase, nonreceptor-type 11; PVNS, pigmented villonodular synovitis; *RB1*, RB transcriptional corepressor 1; *RECQL3/4*, RECQ protein-like 3/4; RMS, rhabdomyosarcoma; *SDH*, succinate dehydrogenase; STS, soft tissue sarcoma; *TP53*, tumor protein p53; *WRN*, Werner syndrome.
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Table 17-2 **Representative Genetic Alterations in Sarcoma**

Class of Alteration	Sarcoma Subtype	Genetic Change	Frequency, %
Activating mutation	GIST	*KIT* or *PDGFRA* mutation	>90
	Desmoid fibromatosis	*Beta-catenin* or *APC* mutations	85-90
	Chondrosarcoma	*IDH1/2* mutations	≥50
	PEComa	*TSC1/2* mutations	~50
Ligand expression	Dermatofibrosarcoma protuberans	*COL1A1-PDGFB* gene fusion	~100
	Giant cell tumor of the bone	*RANK* ligand	~100
Inactivation/deletion	Myxofibrosarcoma	*NF-1* mutation, *NF-1* deletion	~10-20, >90
	Malignant peripheral nerve sheath tumor		
	Epithelioid sarcoma, rhabdoid tumors	*INI1* loss	81
Gene amplification	Well-differentiated and dedifferentiated liposarcoma	CDK4, MDM2	>90
Translocation	Synovial sarcoma	*t*(*X*;18) SYT-SSX1 or SYT-SSX2	>90
	Ewing sarcoma	*t*(11;22) EWSR1-FLI1	>85
		t(21;22) *EWSR1-ERG*	5-10
	Alveolar rhabdomyosarcoma	*t*(2;13) PAX3-FOXO1	~70
		t(1;13) PAX7-FOXO1	~15
	Inflammatory myofibroblastic tumors	*ALK* fusions	50

Abbreviations: *ALK*, anaplastic lymphoma kinase; *APC*, APC regulator of WNT signaling pathway; *CDK4*, cyclin-dependent kinase 4; *EWRSR1-ERG*, fusion of EWS RNA-binding protein 1 and ETS transcription factor ERG; *EWSR1-FLI1*, fusion of EWS RNA-binding protein 1 and FLI1 protooncogene, ETS transcription factor; *FOXO1*, forkhead box O1; GIST, gastrointestinal stromal tumor; *IDH1/2*, isocitrate dehydrogenase 1/2; *INI1*, integrase interactor 1; *KIT*, KIT protooncogene, receptor tyrosine kinase; *MDM2*, MDM2 protooncogene; *NF-1*, neurofibromin-1; *PAX3/7*, paired box gene 3/7; *PDGFRA*, platelet-derived growth factor receptor, alpha; PEComa, perivascular epithelioid cell tumor; *RANK*, receptor activator of nuclear factor-kappa B; *SYT-SSX1/2*, synovial sarcoma, X-chromosome-related 1/2; *TSC1/2*, TSC complex subunit 1/2.[7,11]

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Table 17-3 **Select Histology-Specific Treatments and FDA-Approved Agents**		
Histology	**FDA Approved**	**NCCN Compendia Listed Agents**
Angiosarcoma		Paclitaxel; checkpoint inhibitors
ASPS	Atezolizumab	Sunitinib; pazopanib; pembrolizumab ± axitinib
Desmoid tumor	Nirogacestat	Sorafenib; pazopanib
Giant cell tumor of bone	Denosumab	
GIST	Imatinib (first line)	
	Sunitinib (second line)	
	Regorafenib (third line)	
	Ripretinib (fourth line)	
	Avapritinib (PDGFR exon 18 mutations, including D842V)	
Liposarcoma	Trabectedin	
	Eribulin	
LMS	Trabectedin	
Synovial sarcoma	Afamitresgene autoleucel	
TGCT	Pexidartinib	
UPS		Checkpoint inhibitors

Abbreviations: ASPS, alveolar soft part sarcoma; GIST, gastrointestinal stromal tumor; LMS, leiomyosarcoma; NCCN, National Comprehensive Cancer Network; TGCT, tenosynovial giant cell tumor; UPS, undifferentiated pleomorphic sarcoma.
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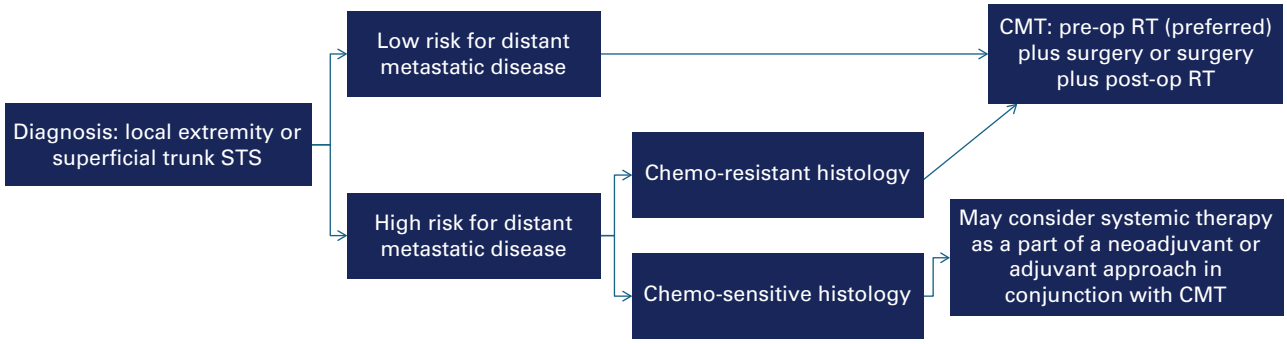
Figure 17-1 Treatment Paradigm for Extremity and Superficial Trunk STS



Abbreviations: CMT, combined modality therapy; RT, radiation therapy; STS, soft tissue sarcoma.
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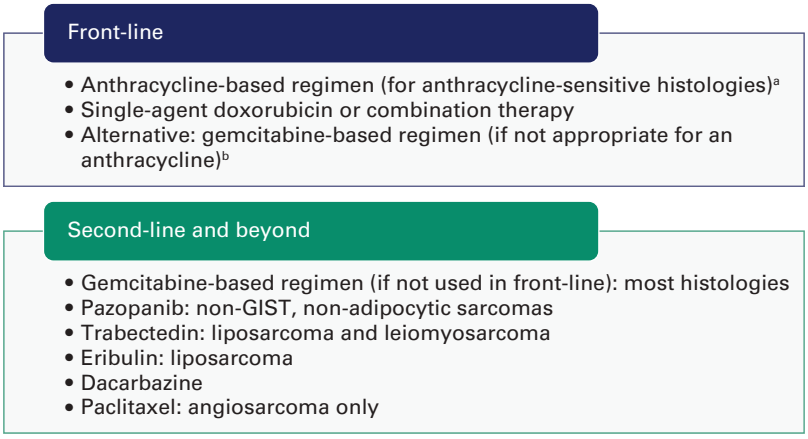
Figure 17-2 Treatment Paradigm for Metastatic Soft Tissue Sarcomas^



Abbreviations: GIST, gastrointestinal stromal tumor; LMS, leiomyosarcoma.
^Excluding GIST, pediatric rhabdomyosarcoma, and most indolent histologies.
[a]Doxorubicin/ifosfamide (most histologies), doxorubicin/dacarbazine (most histologies), doxorubicin/trabectedin (LMS only).
[b]Gemcitabine/docetaxel (preferred), gemcitabine/dacarbazine, gemcitabine/vinorelbine.
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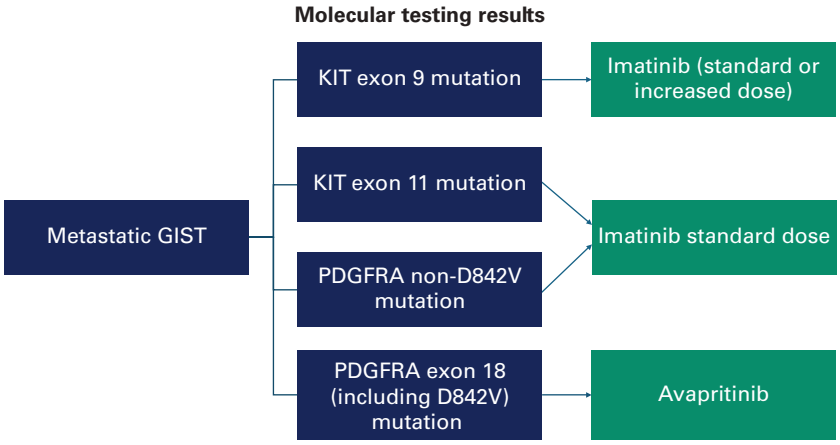
Figure 17-3 GIST Treatment Options Algorithm in the First-Line Setting



Abbreviation: GIST, gastrointestinal stromal tumor.
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Figure 17-4 Osteosarcoma of the Right Distal Femur With Characteristic Cortical Destruction and Bone Formation

(A) At diagnosis. (B) After three cycles of neoadjuvant doxorubicin and cisplatin with coarsening of calcification consistent with response to therapy.
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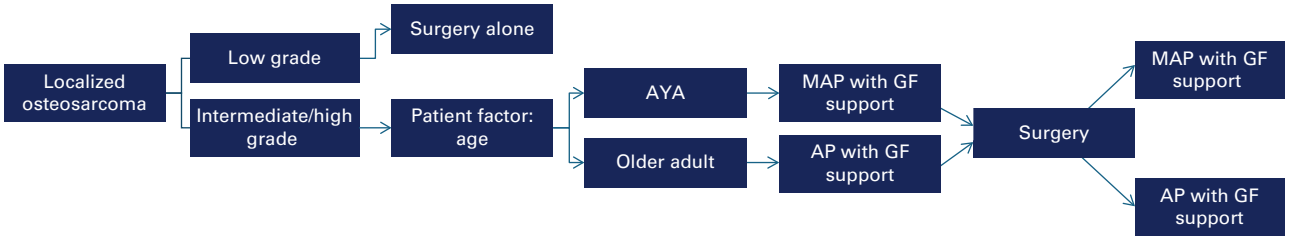
Figure 17-5 Treatment Paradigm for Localized Osteosarcoma



Abbreviations: AP, doxorubicin, cisplatin; AYA, adolescent and young adult; GF, growth factor; MAP, methotrexate, doxorubicin, cisplatin.
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Figure 17-6 Characteristic Changes in Tibial Ewing Sarcoma

Onion skin changes are seen along the tibial diaphysis in this radiograph in the area of the associated soft tissue mass.
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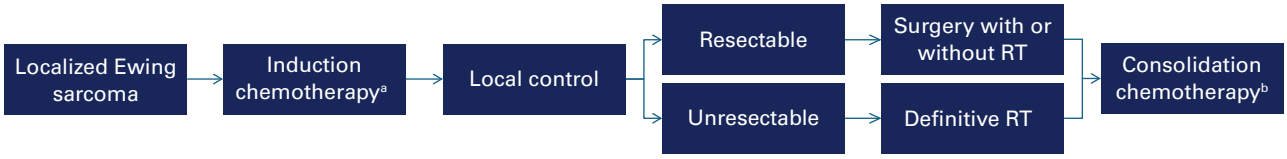
Figure 17-7 Treatment Paradigm for Localized Ewing Sarcoma



Abbreviations: GF, growth factor; IE, ifosfamide and etoposide; RT, radiation therapy; VDC, vincristine, doxorubicin, and cyclophosphamide.
[a]Four to six cycles of interval compressed (Q2W) VDC/IE with GF support.
[b]Complete a total of 14 cycles of interval compressed VDC/IE, as tolerated.
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CENTRAL NERVOUS SYSTEM TUMORS

18

Stephen J. Bagley, MD, MSCE, and Karisa C. Schreck, MD, PhD

RECENT UPDATES

- For patients who have grade 2 non-enhancing *IDH*-mutated astrocytoma or oligodendroglioma confirmed by biopsy or more extensive surgery, vorasidenib is an FDA-approved agent based on the randomized phase 3 INDIGO study, which demonstrated that it extends progression-free survival (27.2 months vs. 11.1 months in control) and time to next therapy.[1]
- For patients aged 6 months or older with relapsed/refractory pediatric low-grade glioma having a *BRAF* rearrangement or V600E alteration, tovorafenib is approved by the FDA (51% response rate and duration of response 13.8 months).[2]

OVERVIEW

Primary central nervous system (CNS) tumors consist of a diverse range of pathologic entities. Metastatic tumors represent the most common CNS tumor diagnosis. Among primary brain cancers, tumors of neuroepithelial tissue include most of the malignant primary CNS tumors, such as infiltrating glial tumors (including glioblastoma *IDH* wild type (*IDH*wt), astrocytoma *IDH* mutant, and oligodendroglioma) and embryonal tumors (eg, medulloblastoma). The last two editions of the World Health Organization Classification of Tumors of the Central Nervous System (WHO Classification of Tumors of the CNS) have included molecular diagnostics, with the most recent (fifth edition published in 2021) introducing major changes that advance the role of molecular diagnostics in CNS tumor classification.[3] The treatment of cancers within the CNS presents specific challenges, including relatively low incidence, drug delivery because of the blood-brain barrier, immunosuppressed tumor microenvironment, and highly infiltrative nature of many of these tumors. Surgery and radiation therapy have remained the mainstays in many CNS tumors; however, the role of systemic therapy has evolved in several of these cancers. The current understanding and evidence-based treatment of the most common cancers of the CNS as they are encountered in clinical oncology practice are outlined in this chapter.

EPIDEMIOLOGY

Primary malignant CNS tumors are the most common solid tumors in children and are the leading cause of death as a result of cancer in children. CNS tumors are the second leading cause of cancer-related death for those in the adolescent and young adult population (aged 15-39 years). The average age-adjusted incidence rate for primary brain tumors is 6.02 cases per 100,000 population per year in children and 11.8 and 43.7 cases per 100,000 population for individuals ages 15 to 39 years and 40 years or older, respectively. In all people, the average annual age-adjusted incidence rate of all malignant and non-malignant brain and other CNS tumors was 25.3 per 100,000 population. Of all primary CNS tumors, approximately one-third are meningiomas, one-third are gliomas, and the remainder are a variety of other benign and malignant tumors. Gliomas occur more frequently in men, whereas meningiomas are more common in women. Of all gliomas, approximately two-thirds are glioblastomas. In children, embryonal tumors, such as medulloblastoma, are the most common CNS tumors.[4]

It has been difficult to identify environmental factors associated with primary brain tumors. Ionizing radiation is the only environmental risk factor reliably considered to increase the risk of brain tumors, with young age at treatment and increased dosage conferring a higher risk.[5] The risk of primary CNS lymphoma but not other types of primary brain tumors is increased for patients who have immunodeficiency conditions, such as post-transplant immunosuppression or HIV infection.[6]

Genetic predisposition to primary CNS tumors is relatively uncommon, although they may be associated with several familial cancer syndromes.[7,8] For example, astrocytoma *IDH* mutant and glioblastoma *IDH*wt are associated with Li-Fraumeni syndrome, neurofibromatosis type 1, and Lynch syndrome. *IDH* mutant gliomas are associated with Maffucci syndrome and Ollier's disease. Medulloblastoma is associated with Li-Fraumeni syndrome, basal cell nevus syndrome, and familial

adenomatous polyposis. CNS hemangioblastomas are the most common manifestation of von Hippel-Lindau (VHL) disease. Recent genomic sequencing studies have identified an inheritable predisposition to the development of glioma in approximately 5% of patients who have glioblastoma.[9]

KEY POINTS

- Exposure to ionizing radiation is a well-established risk factor for primary CNS tumors.
- Most patients who have primary CNS tumors have no identifiable risk factor. The exceptions are patients who have a primary CNS tumor associated with one of the familial cancer syndromes, including neurofibromatosis type 1, Li-Fraumeni syndrome, Lynch syndrome, and familial adenomatous polyposis. Other, less common, inherited genomic risks are emerging.
- Immunodeficiency is a risk factor for primary CNS lymphoma.

PRESENTATION

The presenting symptoms of a brain tumor are related to mass effect, parenchymal infiltration, hydrocephalus, and/or tissue destruction. This may cause patients to present with seizures, altered mental status, focal neurologic deficits, or headache, among other symptoms.

DIAGNOSIS AND STAGING

DIAGNOSTIC IMAGING

MRI with and without contrast is more sensitive than CT imaging for confirming the presence of a brain tumor. Different types of brain tumors exhibit distinct imaging characteristics on MRI. The most crucial sequences for their evaluation are T1-weighted images with and without contrast, as well as T2-weighted and/or fluid-attenuated inversion recovery (FLAIR) sequences. Contrast enhancement is indicative of blood-brain barrier disruption and/or angiogenesis, and it usually increases with higher grades of malignant disease. However, there are a number of low-grade (WHO grade 1) tumors that are robustly enhancing as well. Heterogeneous enhancement is characteristic of glioblastoma and is a consequence, in part, of central tumor necrosis. Conversely, some high-grade tumors may not exhibit contrast enhancement. Contrast enhancement may not reflect the true extent of the disease because the blood-brain barrier may remain intact at the rim of the infiltrating tumor. Although MRI is generally much more helpful in evaluating brain tumors, non-contrast CT imaging can be useful in certain situations, such as evaluating hemorrhage, calcification, or tumor involvement of the bone.

DIAGNOSTIC PATHOLOGY

For nearly all patients, the definitive diagnosis of a CNS tumor requires a surgical biopsy or resection with histologic and molecular examination of the tissue. However, some patients, for example, those with brainstem gliomas, may not be optimal candidates for biopsy because of the operative risk, and imaging can be diagnostic in some cases. Minimally invasive methods that evaluate circulating tumor cells or DNA in plasma or cerebrospinal fluid (CSF) are yet to be validated for CNS tumors.

Primary CNS tumors typically remain localized to the brain and spinal cord, and a staging system, as is common in systemic cancers, does not exist, with medulloblastoma being an exception. Starting in 1993, the WHO classification system traditionally used a four-tiered histologic grading system based on degree of malignancy, with grade 1 tumors having the lowest proliferative potential and grade 4 tumors demonstrating the highest degree of cytologic malignancy and mitotic activity, often with necrosis and microvascular proliferation.

The 2021 WHO Classification of Tumors of the CNS incorporates both histologic and molecular features to generate a grade and integrated diagnosis for each patient.[3] This major update to brain tumor classification aims to group tumors based on biologic and molecular features rather than purely on histologic appearance, which enables clinicians to have a better understanding of the prognosis and optimal therapy for patients who have specific CNS tumors. Some of the most important changes involve the classification of gliomas, including differentiation of gliomas that occur primarily in adults from those that occur primarily in children, as well as the molecular criteria that define a glioblastoma, *IDH*wt. Key takeaways from the 2021 WHO classification system are discussed for each tumor type in the respective sections of this chapter. The following are techniques for assessing important CNS tumor biomarkers:

- Pathogenic point mutations
  - Immunohistochemistry (*IDH1* R132H; *BRAF* V600E; H3K27M)
  - Single-gene sequencing or next-generation sequencing (NGS)
- Chromosomal alterations (eg, 1p/19q codeletion, Chr. 7 gain, Chr. 10 loss)
  - Fluorescence in situ hybridization (FISH)
  - Single-nucleotide polymorphism arrays
  - NGS

- Pathogenic fusion alterations (KIAA-BRAF, FGFR-TACC, NTRK-fusions, etc.)
  - RNA sequencing
  - DNA or RNA fusion panels
  - FISH
- *MGMT* promoter methylation
  - Bisulfite sequencing
  - Methylation array

The 2021 WHO Classification includes tumors defined exclusively by their DNA methylation profile. This includes high-grade astrocytoma with piloid features and diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters.

PATHOGENESIS

CLINICALLY RELEVANT MARKERS IN GLIOMAS

Research in the past decade has rapidly increased understanding of the pathobiology of diffuse gliomas. Several molecular abnormalities have been discovered that play key roles in glioma development, and precise molecular characterization of diffuse gliomas is still subject to discussion and extensive research. The 2021 WHO Classification of Tumors of the CNS defines three broad categories of adult diffuse gliomas based on histopathology, mutational spectrum, and copy number alterations (Fig. 18-1).[3]

OLIGODENDROGLIOMA, *IDH* MUTANT, AND 1P/19Q CO-DELETED

These gliomas can be grade 2 or 3. The presence of both a pathogenic *IDH* mutation and codeletion of Chr. 1p and 19q is required for diagnosis. This category of tumors, compared with the other two groups of gliomas, is associated with a more favorable overall prognosis and better response to radiation therapy and chemotherapy. The 5-year survival rate of patients who have these tumors typically ranges from 50% to 80%, although, with aggressive treatment consisting of radiation therapy and chemotherapy, a median survival of ~12 to 18 years has been observed.

ASTROCYTOMA, *IDH* MUTANT

These gliomas can be grade 2, 3, or 4. The presence of a pathogenic *IDH1* or *IDH2* alteration is required, and *ATRX* is also frequently mutated.[3] The 5-year survival rate for patients who have these tumors typically ranges from 25% to 50%. In the 2021 WHO Classification of Tumors of the CNS, the grade 4 tumors in this category are no longer referred to as glioblastoma and are instead referred to as astrocytoma, IDH mutant, WHO grade 4. Some molecular features can impact grading, such as *CDKN2A*/B deletion, which portends an inferior prognosis and is sufficient to classify the tumor as grade 4, irrespective of microscopic features.

GLIOBLASTOMA, *IDH* WILD TYPE

Glioblastoma may be diagnosed by histopathologic criteria or by molecular criteria (Fig. 18-1). Tumors that appear to be low-grade glioma but lack *IDH1/2* or *BRAF* alterations should have molecular testing performed to evaluate for gain of chromosome (Chr) 7 and loss of Chr 10, *EGFR* amplification, or *TERT* promoter mutations.[10] Compared with the two categories above, these gliomas overall have a less favorable prognosis and are less responsive to chemotherapy. The 5-year survival rate for patients who have these tumors is approximately ~10% to 14%.

PEDIATRIC TYPE DIFFUSE HIGH-GRADE GLIOMA

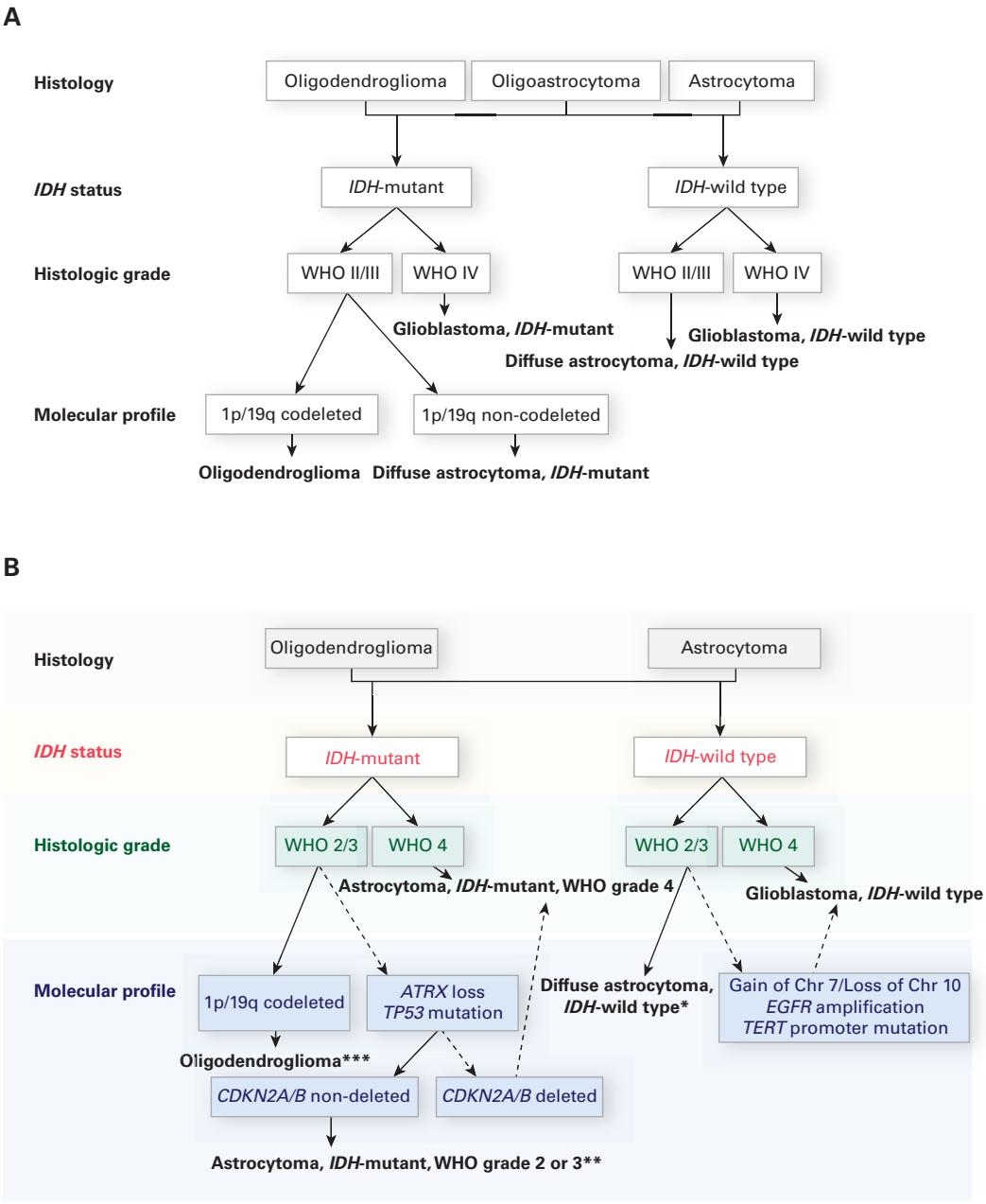
Diffuse midline gliomas (DMGs) are aggressive gliomas arising primarily from the pons and other midline sites in children and young adults. The presence of an H3K27 alteration is sufficient to make this diagnosis, which is classified as grade 4. Adults may present with DMG, often in the thalamus or diffuse hemispheric gliomas, having H3G34 alterations. In children, these gliomas are highly aggressive and poorly responsive to therapy.[11] In adults, the clinical course is more heterogeneous.[12] Standard treatment involves ionizing radiation, but the role of upfront systemic therapy is less clear. Dordaviprone (ONC201) recently received accelerated approval by the FDA for progressive disease in patients with *H3 K27M* mutations.[13]

IDH MUTATION

Mutations in the *IDH1* or *IDH2* genes are early genetic abnormalities in glioma development. *IDH* mutations result in the excess accumulation of 2-hydroxyglutarate, an oncometabolite, which contributes to the formation of and may participate in the progression of gliomas.[14,15] *IDH* mutations have been found in most WHO grade 2 and 3 gliomas and are a clear indicator of a favorable prognosis in high-grade glioma.[16]

In addition, *IDH* mutations have been demonstrated to independently predict survival benefit from the addition of chemotherapy to radiation therapy for patients who have grade 3 glioma.[17]

Figure 18-1 The Classification of Diffuse Gliomas



(A) WHO 2016. (B) WHO 2021.
Abbreviations: Chr, chromosome; CNS, central nervous system; *EGFR*, epidermal growth factor receptor.
Simplified diagnostic algorithm for adult diffuse gliomas based on the 2021 WHO classification of CNS tumors. Dashed lines denote changes compared with the 2016 WHO classification.
*Diffuse astrocytoma, *IDH* wild type without molecular features of glioblastoma, is a rare entity. Molecular testing for gain of *Chr* 7 and loss of Chr 10, *EGFR* amplification, and *TERT* promoter is required to exclude glioblastoma, *IDH* wild type, grade 4. In the absence of molecular features of glioblastoma, additional testing should be considered (eg, *BRAF* alterations, histone mutations, methylome profiling).
**Astrocytoma, *IDH* mutant, can be diagnosed as grade 2, 3, or 4 based on histopathologic grading criteria and *CDKN2A/B* status.
***Oligodendroglioma, *IDH* mutant with codeletion of the short arm of chromosome 1 and the long arm of chromosome (1p19q), can be diagnosed as grade 2 or 3 based on histopathologic features.
Reprinted by permission from Wiley Online Library: Gritsch S, Batchelor TT, Castro LN. Diagnostic, therapeutic, and prognostic implications of the 2021 World Health Organization classification of tumors of the central nervous system. *Cancer*. 2022;128(1):47-58. doi:10.1002/cncr.33918

1P/19Q CODELETION

Oligodendrogliomas show a combined loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) in addition to an *IDH* mutation. This codeletion of 1p/19q is secondary to an unbalanced pericentromeric translocation event and

seems to be instrumental in the development of oligodendrogliomas.[18] Several candidate genes have been identified, including *CIC* and *FUBP1*, which may represent the genetic alteration underlying the 1p/19q codeletion.[19]

Many studies demonstrate that 1p/19q codeletion is associated with a favorable prognosis in glioma.[18] 1p/19q codeletion has been determined to predict improved survival with the addition of combination chemotherapy (ie, procarbazine, lomustine, and vincristine [PCV]) to radiation therapy compared with radiation therapy alone.[20,21]

BRAF ALTERATIONS

Pathogenic alterations in the *BRAF* gene are probably early genetic abnormalities in glioma development. *BRAF* alterations result in increased signaling through the MAPK signaling cascade, resulting in proliferation, neovascularization, and increased survival. The most common *BRAF* alteration is a single-nucleotide variant p.V600E that enables *BRAF* to function as a single, aberrantly active protein molecule. *BRAF* V600E mutations are observed in a variety of non-CNS tumors, and in CNS tumors, primarily occurring in low-grade glioma, pleomorphic xanthoastrocytoma, ganglioglioma, and epithelioid glioblastoma, although they have been identified in many other CNS tumors of grades 1 to 4. The effect of *BRAF* V600E alterations on prognosis differs by grade and among pediatric and adult gliomas.[22-24] The FDA has approved targeted therapy for glioma with *BRAF* V600E alterations.

The second most common *BRAF* alteration is a rearrangement causing various gene fusions that result in increased activation through MAPK signaling dependent on dimerization. The FDA has approved a type II BRAF inhibitor, tovorafenib, for pediatric-type low-grade glioma with a *BRAF* fusion and V600 mutation.[2]

MGMT PROMOTER METHYLATION

MGMT (O6-methylguanine-DNA methyltransferase) is an enzyme that plays a crucial role in DNA repair. Alkylating agents, such as temozolomide, lead to methylation of nucleotide bases in genomic DNA. Although some of these lesions are fixed by base excision repair, O6-methylguanine requires MGMT for its repair.

Hypermethylation of the MGMT promoter–associated CpG island has been described in approximately 30% to 40% of glioblastomas. MGMT promoter methylation prevents transcription of the *MGMT* gene and subsequent expression of the DNA repair enzyme. Consequently, patients who have MGMT promoter–methylated tumors are expected to receive more benefit from temozolomide than those with tumors that lack it. The more favorable prognosis of patients who have MGMT promoter–methylated glioblastoma is well described, along with its association with a greater magnitude of benefit from temozolomide.[25] MGMT methylation has not been shown to be predictive of benefit from temozolomide in other grades of CNS tumors or in other tumor types.

KEY POINTS

- *IDH* mutations are central aspects of defining astrocytoma IDH mutant and oligodendroglioma, two types of adult diffuse gliomas.
- *IDH* mutations are most common in grade 2 and 3 gliomas but can also be seen in grade 4 astrocytomas.
- Regardless of grade, *IDH* mutations in glioma are associated with younger age, increased sensitivity to treatment, and comparatively favorable prognosis.
- Oligodendrogliomas are defined by the presence of both *IDH* mutation and 1p/19q codeletion and have improved response to chemotherapy and prognosis compared with other gliomas.
- Tumors that are *IDH* mutated without 1p/19q codeletion are referred to as astrocytoma, *IDH* mutant, and commonly harbor a mutation in *ATRX*.
- *BRAF* alterations, which may have an impact on available therapeutic options, occur in a range of CNS tumors, but at this time are not pathognomonic for any WHO CNS tumor type.
- According to the 2021 WHO Classification of Tumors of the CNS, glioblastoma is by definition *IDH* wild type.
- In glioblastoma, being MGMT promoter–methylated is both prognostic and predictive of the magnitude of benefit from temozolomide.

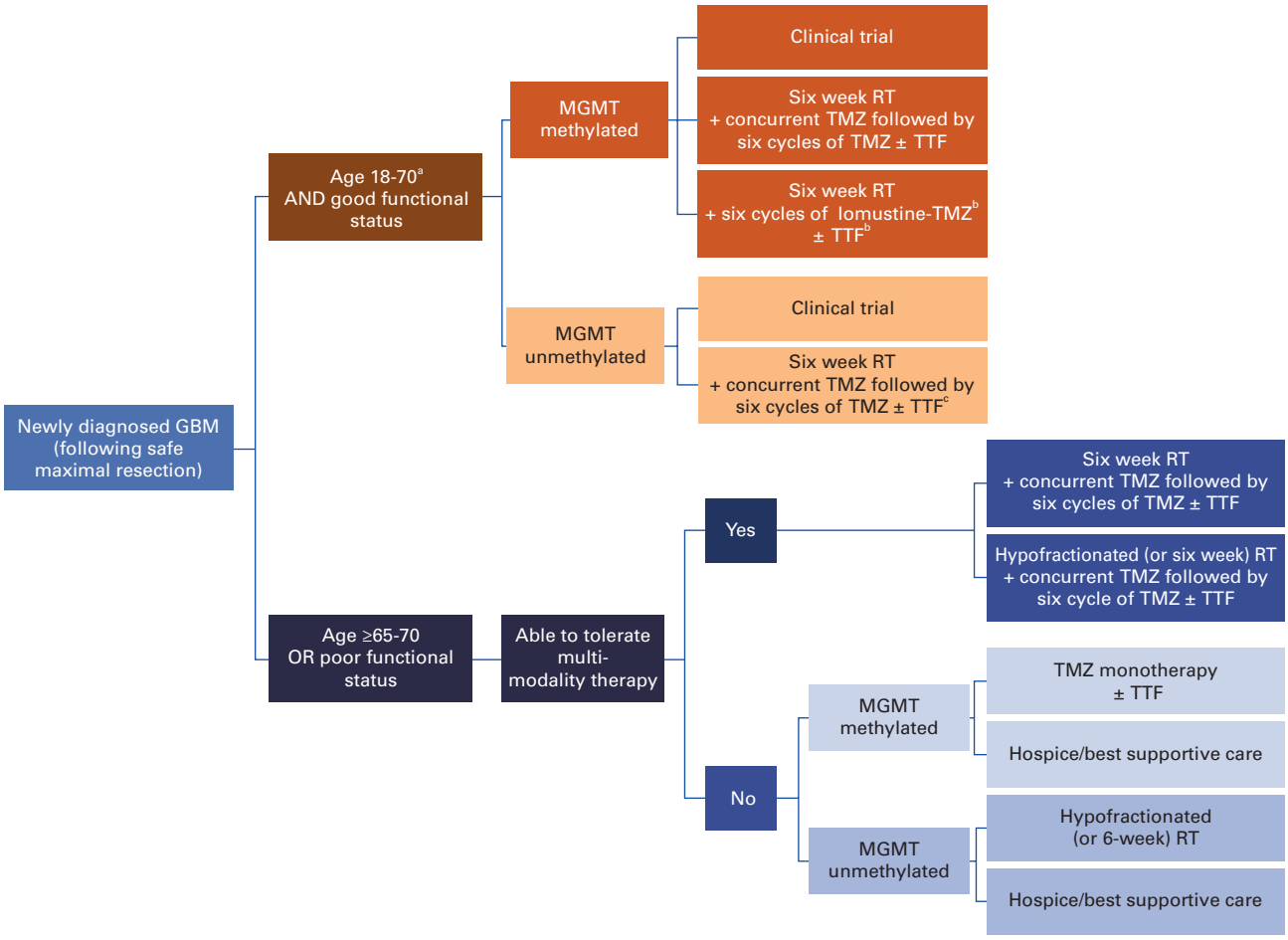
GLIOBLASTOMA, *IDH* WILD TYPE

Glioblastomas are the most common primary malignant brain tumors in adults. Histopathologic hallmarks include increased cellularity, nuclear pleomorphism, frequent mitoses, pseudopalisading necrosis, and neovascularization. The median age at diagnosis is approximately 65 years.[8] In the 2021 WHO Classification of Tumors of the CNS, glioblastoma is, by definition, *IDH* wild type and is formally referred to as glioblastoma, *IDH* wild type.[7] Traditionally, glioblastomas were diagnosed based on the histologic findings of microvascular proliferation and/or necrosis. Although these features continue to result in a diagnosis of glioblastoma under the 2021 classification system, the current classification also allows for a diagnosis of glioblastoma, *IDH* wild type, even in the absence of histologic features of glioblastoma if one or more of three genetic parameters are present in an *IDH* wild-type glioma: *TERT* promoter mutation, *EGFR* gene amplification, or combined gain of entire chromosome 7 and loss of entire chromosome 10 (+7/−10). This important change is based on several articles demonstrating that astrocytomas that appear

to be lower grade histologically but lack an *IDH* or *BRAF* alteration (eg, gliomas formerly referred to as *IDH* wild-type diffuse astrocytoma or *IDH* wild-type anaplastic astrocytoma) have similarly poor survival outcomes compared with histologically defined glioblastoma if any of these molecular alterations are present.[10,26]

Glioblastoma *IDH* wild type has a real-world median overall survival (OS) of approximately 12 to 15 months with standard treatment,[4,27,28] although recent phase 3 clinical trials suggest that the median OS may be closer to 18 to 21 months in selected populations with good performance status.[29,30] MGMT promoter methylation is associated with a prolonged survival of patients who have glioblastoma compared with those without methylation (18.2 months vs. 12.2 months; $P < .001$).[25] Guidelines for treatment of glioblastoma were released in 2021 by the ASCO and the Society for Neuro-Oncology.[31] Key elements of treatment are outlined in the following sections and are summarized in Figure 18-2.

Figure 18-2 Standard-of-Care Treatment Paradigm for Patients Who Have Newly Diagnosed or Recurrent Glioblastoma



Abbreviations: GBM, glioblastoma; MGMT, O6-methylguanine-DNA methyltransferase; RT, radiation therapy; TMZ, temozolomide; TTF, tumor-treating fields.
[a]In elderly patients with good performance status, standard 6-week daily radiation therapy plus TMZ can be considered.
[b]It is unclear whether lomustine plus TMZ is preferred over TMZ alone.
[c]Because MGMT methylation status is predictive of the efficacy of TMZ, TMZ can be withheld in select patients who have MGMT-unmethylated tumors, especially in the context of clinical trials or when the risks of TMZ outweigh the benefits.
Reprinted from Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol*. 2020;22(8):1073-1113, by permission of Society for Neuro-Oncology and Oxford University Press.

SURGERY

The initial step of treatment is the best possible safe neurosurgical resection. In general, the overall outcome is better in patients who can undergo a gross total resection (removal of all contrast-enhancing tissue assessed on an MRI scan performed within 48 hours after surgery), but because of tumor location and comorbidities, many tumors are amenable only to a partial resection or biopsy.[32] There are data to support a survival benefit from supramaximal resection (resection beyond the contrast enhancement) for newly diagnosed glioblastoma.[33] Unfortunately, even in the absence of residual contrast enhancement, the extremely

infiltrative nature of this tumor makes true complete surgical resection impossible, and all patients have residual cancer that requires additional therapy.

RADIATION THERAPY

Radiation therapy has remained the backbone of the treatment of newly diagnosed glioblastoma. Currently, focal brain radiation therapy (only to areas of tumor involvement, not the whole brain), consisting of 60 Gy delivered in 30 fractions, is considered standard. Shorter courses of hypofractionated radiation over 1 to 3 weeks have been evaluated in phase 3 clinical trials of older or frail patients who have glioblastoma because of the poorer prognosis of these patients. These trials demonstrate that a shorter course of radiation produces outcomes similar to or better than those seen with standard radiation (60 Gy in 30 fractions) in older or frail patients.[34-36] Multiple attempts to improve the therapeutic efficacy of radiation therapy by using altered fraction schemes have not produced substantially better results so far.

CHEMOTHERAPY

Temozolomide chemotherapy is the standard of care for newly diagnosed glioblastoma. A landmark phase 3 trial randomly assigned 573 patients aged 18 to 70 years to receive involved-field radiation therapy alone or radiation therapy plus concurrent once-per-day temozolomide (75 mg/m^2 per day) followed by up to six cycles of adjuvant temozolomide (cycle 1, 150 mg/m^2 once per day for 5 days of a 28-day cycle; cycles 2-6, 200 mg/m^2 once per day for 5 days of a 28-day cycle if blood counts are acceptable).[37] The addition of temozolomide to radiation therapy improved the median OS compared with radiation therapy alone (14.6 months vs. 12.1 months; hazard ratio [HR], 0.63; 95% CI, 0.53-0.75). With long-term follow-up, the survival rate continued to be superior in the temozolomide arm at 2 years (27% vs. 11%) and 5 years (10% vs. 2%).[38]

As described in the "MGMT Promoter Methylation" section, MGMT promoter methylation is predictive of benefit from temozolomide. Patients whose MGMT promoter is unmethylated may not benefit from temozolomide.[25] Subsequent trials have attempted to further improve outcomes in patients who have MGMT-methylated tumors by combining lomustine with temozolomide during and after radiation therapy in a randomized study.[39] In the modified intent-to-treat analysis (n = 129), the median OS was improved from 31.4 months (95% CI, 27.7-47.1) with temozolomide to 48.1 months (95% CI, 32.6 months to not assessable) with lomustine and temozolomide (HR, 0.60; 95% CI, 0.35-1.03). Grade 3 or 4 hematologic toxicity and nausea were more common with combination therapy. Although these results are intriguing, additional studies (such as the ongoing NRG BN011 phase 3 trial) are warranted to determine whether dual therapy with temozolomide and lomustine in combination with radiation therapy should be used routinely for patients who have MGMT-methylated glioblastoma.

Bevacizumab, an intravenous monoclonal anti-vascular endothelial growth factor (VEGF) antibody, has been evaluated for the treatment of patients with newly diagnosed glioblastoma with no improvement in survival, precluding routine use.[40,41] The effect on quality of life was mixed, but it may provide a benefit in select patients.[40] In contemporary practice, this agent is often used to treat symptomatic cerebral edema, often with shorter courses than what was described in the pivotal trials.

When considering chemotherapy in older patients who have glioblastoma, a careful assessment of the patient's overall clinical status and comorbidities is critical. For adults aged 65 years or older who have glioblastoma treated with hypofractionated radiation (40 Gy in 15 fractions), randomized phase 3 trial data demonstrate that OS is improved by the addition of concurrent and adjuvant temozolomide (median OS, 13.5 months vs. 7.7 months; HR, 0.53; 95% CI, 0.38-0.73).[42] For older patients who are not candidates for a combined-modality approach because of poor performance status or comorbidities, MGMT methylation status may be helpful for decision-making. In such patients who have MGMT-unmethylated tumors, a short course of radiation therapy without temozolomide may be reasonable. In such patients who have MGMT-methylated tumors, temozolomide alone (without radiation therapy) is supported by phase 3 data.[35,43]

TUMOR-TREATING FIELDS

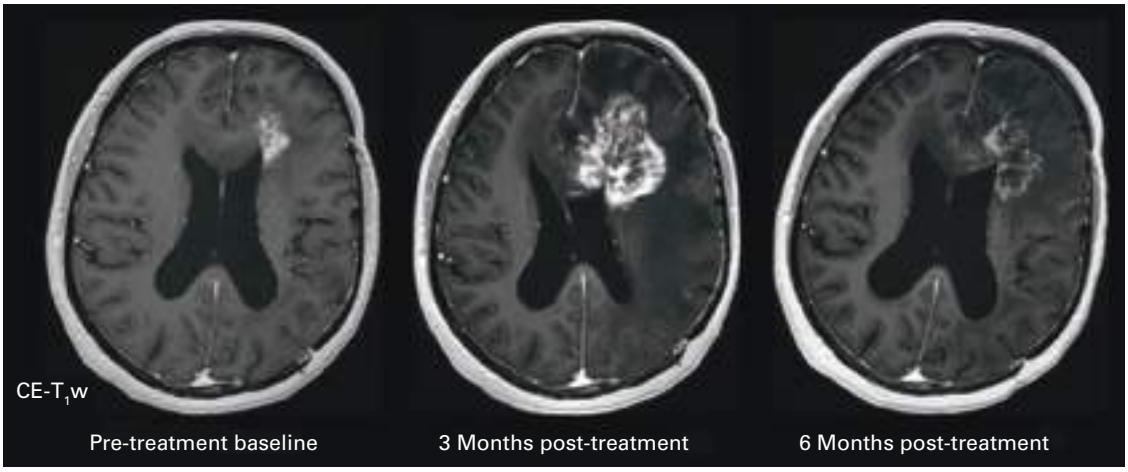
Tumor-treating fields are a form of treatment from a device that delivers alternating electromagnetic fields through electrodes placed on the shaved scalp. It is approved by the FDA for use in the treatment of patients who have newly diagnosed (as maintenance therapy in combination with temozolomide after concurrent chemoradiotherapy) and recurrent glioblastoma (as monotherapy), as well as some non-CNS malignancies. A randomized phase 3 trial of maintenance temozolomide cycles with or without tumor-treating fields enrolled 695 patients who had completed concurrent chemoradiotherapy and not yet experienced tumor progression. The final data demonstrated a significant increase in the median OS of patients treated concurrently with temozolomide and tumor-treating fields compared with patients treated with temozolomide alone (21 months vs. 16 months; $P < .00062$).[44] Although tumor-treating fields are part of the National Comprehensive Cancer Network guidelines, incorporation into routine clinical care has been mixed for a variety of reasons.

PSEUDOPROGRESSION

It is essential to consider so-called pseudoprogression before initiating alternative therapy. Pseudoprogression is best described in gliomas as a radiographic increase in enhancement or edema on MRI after chemoradiotherapy, often within a few months of

completing treatment, and this can raise concern for tumor progression. Pseudoprogression can mimic true tumor growth, especially in patients whose tumors exhibit MGMT promoter methylation.[45] On MRI, both progression and pseudoprogression are characterized by increased contrast enhancement, T2-weighted signal abnormality, and mass effect with or without clinical deterioration (Fig. 18-3). Advanced imaging techniques such as perfusion-weighted imaging, chemical exchange saturation transfer (CEST) imaging, or MR spectroscopy may be helpful, though not definitive. Amino acid PET shows high diagnostic accuracy for differentiating recurrence versus pseudoprogression, although it is not widely available.[46,47] Post-radiation therapy changes that are within the radiation treatment field can often be observed initially (typically for the first 3 months after radiation therapy) to assess whether the changes represent pseudoprogression rather than actual tumor growth.[48] Repeated tissue biopsy may be required to more definitively determine whether the patient has an active or progressive tumor or treatment effect or necrosis, but it can be challenging, and its value may be limited because tissues often comprise a mixture of treatment effect and necrosis of tumor, which can lead to significant interobserver variability in diagnosis.[49] Dexamethasone can be used for symptomatic relief from cerebral edema caused by treatment effect, generally with good responses. Bevacizumab may also be useful in this setting, particularly for patients who are symptomatic or intolerant of steroids.

Figure 18-3 Pseudoprogression Following Radiation in Glioblastoma



Abbreviations: CE, contrast-enhanced; T_1w, T_1-weighted.
Serial CE T_1w imaging showing an increase 3 months and spontaneous decrease 6 months after combined radiotherapy and temozolomide of contrast-enhancement, edema, and mass effect.
Reproduced under Creative Commons under the terms of the http://creativecommons.org/licenses/by-nc-nd/4.0/license. Source: Thust SC, van den Bent MJ, Smits M. Pseudoprogression of brain tumors. *J Magn Reson Imaging*. 2018;48(3):571-589. doi:10.1002/jmri.26171, figure 1.

PRESENTING CASE STUDY

A 49-year-old woman presents to the emergency room with 1 week of worsening headaches, and an MRI reveals a 4 cm × 4 cm contrast-enhancing mass in the right frontal lobe. Pathology from surgical resection identifies a glioma without necrosis or microvascular proliferation, and immunohistochemical staining is negative for the *IDH1* R132H mutation.

Given the patient's age, what is the most important next test to order?

Since this patient is under 55 years old, it is critical to determine whether this glioma harbors an *IDH* mutation. Although immunohistochemistry for *IDH1* R132H, the most common *IDH* mutation in glioma, is negative in this case, next-generation sequencing (NGS) is the gold standard for establishing *IDH* mutational status. It is imperative that NGS is performed on this tumor to confirm that there are no variants in *IDH1* or *IDH2*.

NGS revealed that this tumor was negative for any mutations in *IDH1* or *IDH2*. However, epidermal growth factor receptor (*EGFR*) amplification and a *PTEN* mutation were detected.

How do these results inform your decisions regarding next steps?

Although this patient's tumor did not exhibit histologic hallmarks of glioblastoma (ie, necrosis and/or microvascular proliferation), a diagnosis of glioblastoma was established because the tumor is *IDH* wild type and has *EGFR* amplification.

In an *IDH* wild-type glioma, the presence of any one of the following molecular alterations establishes a diagnosis of glioblastoma: *EGFR* amplification, *TERT* promoter mutation, or gain of chromosome (Chr) 7 and loss of Chr 10 (+7/−10).

Now that the diagnosis of glioblastoma has been established, are there any other tests to order on this tumor that could impact treatment and prognosis?

O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation can be very informative. MGMT is an enzyme that is responsible for DNA repair after alkylating-agent chemotherapy. In approximately 40% of glioblastomas, the *MGMT* gene is silenced by methylation of its promoter, thereby preventing DNA damage repair and increasing the potential effectiveness of alkylating-agent chemotherapy. Multiple clinical studies confirm that MGMT promoter methylation is prognostic of improved survival independent of established clinical factors. MGMT promoter methylation is also predictive of responsiveness to temozolomide in patients with glioblastoma. PD-L1 testing is not ordered routinely for patients who have glioblastoma because PD-1/PD-L1 immune checkpoint inhibitors have not demonstrated efficacy in this disease. Testing for tumor mutational burden (TMB) is also not indicated for most patients diagnosed with glioblastoma because TMB is almost uniformly low in this population. Rare exceptions include patients with Lynch syndrome or other inherited germline defects in DNA repair genes.

How would finding out that the patient's tumor is positive for MGMT promoter methylation affect further management?

Radiation with concomitant temozolomide chemotherapy, followed by six cycles of maintenance temozolomide, is the most appropriate treatment option for this patient. If the patient's tumor had been MGMT unmethylated, a clinical trial of radiation plus an experimental agent that does not include temozolomide chemotherapy could have been considered. Patients who have MGMT-unmethylated tumors have a poor prognosis and response to standard therapies and are encouraged to participate in clinical trials.

RECURRENCE

No uniform standard of care exists for the treatment of recurrent glioblastoma. Treatment options are tailored to the individual clinical setting. Participation in clinical trials should be considered. Unfortunately, all standard therapies have limited benefit, and a focus on symptom control with end-of-life care may be appropriate.

Of note, radiographic pseudoprogression may mimic tumor progression in patients who have glioblastoma treated with radiation therapy with or without temozolomide and should be considered before switching therapy, especially in patients who have MGMT promoter–methylated tumors (see the "Pseudoprogression" section).

For patients who have resectable disease with good neurologic function and performance status, a second resection may be reasonable.[50] Nitrosoureas, including lomustine and carmustine, which are FDA-approved agents for recurrent glioblastoma, may be used but have not demonstrated consistent efficacy and are associated with significant myelosuppresion.[51] Nonetheless, they form a cornerstone of non-clinical trial treatment of progressive glioblastoma *IDH*wt.[52] In 2009, the FDA approved bevacizumab for the treatment of recurrent glioblastoma after treatment with radiation therapy and temozolomide failed, although there were no data showing that bevacizumab improved OS.[53] A phase 3 clinical trial demonstrated that the addition of bevacizumab to lomustine did not improve survival compared with lomustine alone, although crossover may confound the results.[54] The use of bevacizumab can be of benefit to some patients who have significant symptomatic edema and mass effect, who have difficulty tolerating high doses or a long course of steroids. Because of these steroid-sparing and antiedema effects on the brain, tumor appearance on MRI can be dramatically improved for a period of time, and bevacizumab remains a key component of modern neuro-oncologic care. Bevacizumab in combination with reirradiation is also a viable option for select patients, although it does not improve survival over bevacizumab alone.[55] Complicating considerations for bevacizumab include that patients need a long washout period (ideally ≥4-6 weeks) after being considered for repeated surgery and that the drug increases the risks of hemorrhage, bowel perforation, venous thromboembolism, hypertension, and nephrotic syndrome. The initial bevacizumab patent (Avastin) expired several years ago, which resulted in the approval of several biosimilars with no known difference in safety or efficacy compared with bevacizumab.

Tumor-treating fields are also approved by the FDA for the treatment of recurrent glioblastoma. Results from a phase 3 randomized trial of tumor-treating fields compared with physician choice of chemotherapy for patients who have recurrent glioblastoma demonstrated no difference in OS. Although it did not provide a survival advantage, survival with tumor-treating fields was considered comparable to that with chemotherapy or bevacizumab and was associated with fewer serious adverse effects and

better quality of life.[56] However, the benefit of tumor-treating fields for recurrent glioblastoma remains uncertain because no evidence from phase 3 clinical trials is available to demonstrate that chemotherapy itself extends survival in this patient population.

Most recently, data from several phase 2 basket trials demonstrate benefit from targeted therapies in select patients with targetable biomarkers across numerous different solid tumors, including brain tumors. The benefit from the combination of dabrafenib and trametinib was shown in the phase 2 open-label ROAR trial,[57] which included 45 patients who had recurrent or progressive high-grade gliomas (69% had glioblastoma) who harbored *BRAF* V600E mutations and were previously treated with radiation therapy and first-line chemotherapy. With a median follow-up of 12.7 months, the objective response rate (ORR) was 31% (three complete responses and 11 partial responses), and the median duration of response was 13.6 months. The median progression-free survival (PFS) was 4.5 months, and the median OS was 17.6 months. Based on these and other data, the combination of dabrafenib plus trametinib was granted tissue-agnostic approval by the FDA in June 2022 in patients aged 6 years or older with unresectable or metastatic *BRAF* V600E–mutated solid tumors that had progressed with previous treatment. Similarly, basket trials of tropomyosin receptor kinase (TRK) inhibitors larotrectinib,[58] entrectinib,[59] and repotrectinib[60] have shown benefit in *TRK* fusion–positive solid tumors, and a basket trial of the RET (rearranged during transfection) kinase inhibitor selpercatinib showed benefit in solid tumors containing a *RET* fusion gene.[61] These studies led to tissue-agnostic, accelerated approvals of these agents by the FDA for patients who have any solid tumor with the appropriate molecular profile (ie, *TRK* fusion for larotrectinib, entrectinib, and repotrectinib; *RET* fusion for selpercatinib). Although additional studies are required to estimate the efficacy of these targeted agents more precisely in patients who have glioblastoma with targetable alterations and their optimal sequencing with standard-of-care therapies, these drugs represent FDA-approved treatment options for a small subset of patients who have glioblastoma.

It is important to note that immune checkpoint inhibitors have not demonstrated efficacy in the vast majority of patients who have glioblastoma, but two negative phase 3 trials have been completed in the first-line setting.[62,63] The anti-PD1 monoclonal antibody pembrolizumab is approved by the FDA for the treatment of adult and pediatric patients who have any unresectable or metastatic solid tumor that is microsatellite instability-high, mismatch repair deficient, and/or tumor mutational burden (TMB)-high as determined by an FDA-approved test.[64] Pembrolizumab is, therefore, an approved option for the rare cases of glioblastoma (approximately 1% or fewer) that harbor these phenotypes in the setting of a germline mutation related to DNA repair (eg, *MSH6, PMS2, POLE*, or others).[65]

KEY POINTS

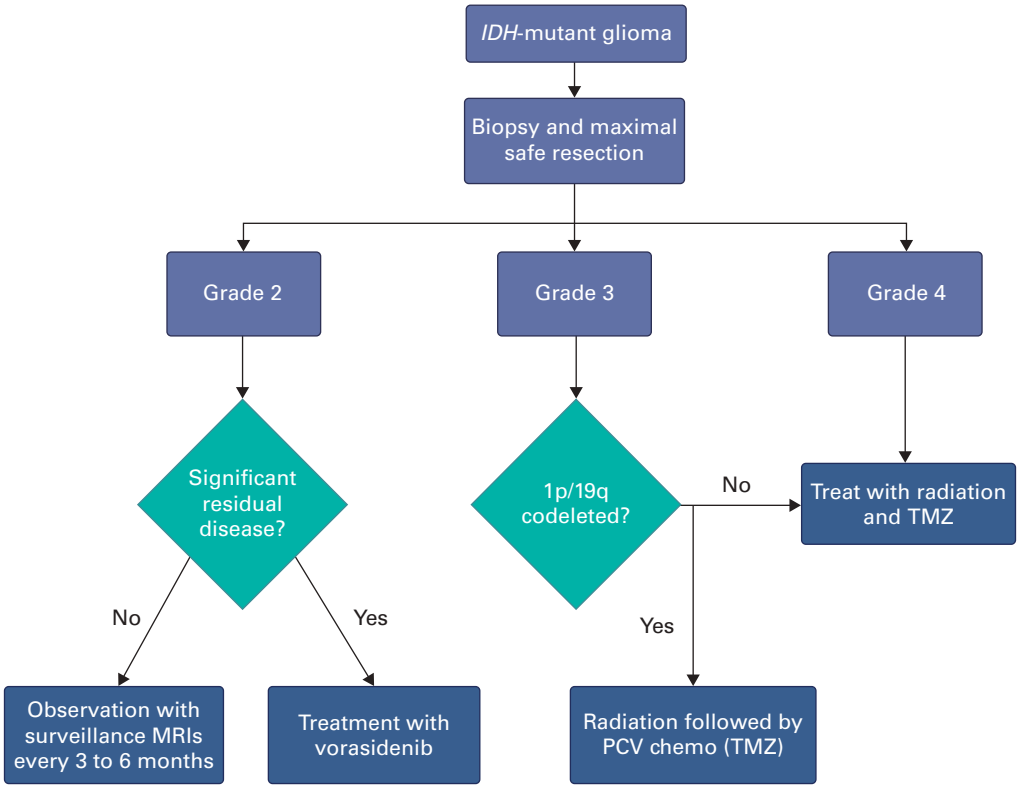
- The current standard of treatment of glioblastoma in patients younger than 70 years is maximal safe resection followed by radiation therapy with concurrent and adjuvant temozolomide, with consideration of tumor-treating fields.
- Phase 3 data also support the use of concurrent chemoradiotherapy in older adults based on the results of a trial with hypofractionated radiation therapy plus temozolomide versus treatment with hypofractionated radiation therapy alone.
- Pseudoprogression may mimic tumor progression in patients who have glioblastoma treated with radiation therapy and should be considered before switching therapy, especially in patients who have MGMT-methylated tumors.
- Tumor-treating fields are FDA approved for newly diagnosed and recurrent glioblastoma.
- Bevacizumab is effective as a steroid-sparing agent for symptom management in select patients who have glioblastoma, although evidence for improvement in OS is lacking.
- When detected in patients who have glioblastoma, *BRAF* V600E mutation, *TRK* fusion, and *RET* fusion are potentially actionable and can be targeted with drugs that have been granted accelerated approval by the FDA in a tissue-agnostic, genotype-specific manner.

ASTROCYTOMA, *IDH* MUTANT

In the current WHO Classification of Tumors of the CNS, all *IDH*-mutated diffuse astrocytic tumors are considered as a single type (*IDH*-mutant astrocytoma) and are then graded as WHO CNS grade 2, 3, or 4. Therefore, the terms "diffuse" and "anaplastic" are no longer used. Grade 2 *IDH*-mutant astrocytomas show an infiltrative diffuse growth pattern (perineuronal and/or perivascular satellitosis, subpial spread), have a variable degree of nuclear atypia and pleomorphism, and have no or few mitoses. Grade 3 *IDH*-mutant astrocytomas (formerly anaplastic) have increased cellularity and mitotic activity. Both these tumors have a high propensity to transform into higher grades over time. Grade 4 *IDH*-mutant astrocytomas may be diagnosed based on histologic findings of necrosis and/or microvascular proliferation. However, in the new 2021 classification system, the presence of *CDKN2A/B* homozygous deletion in an *IDH*-mutant astrocytoma automatically results in a CNS grade 4 classification even in the absence of histologic grade 4 features (microvascular proliferation or necrosis).

Prospective trials have yet to specifically study these molecularly defined groups based on the 2021 WHO integrated diagnostic criteria. All available clinical trial data on *IDH* mutation and 1p/19q codeletion status are either indirect or from subgroup analyses that incorporated post hoc categorization of patients. Within these limitations, guidelines for therapy for *IDH*-mutated astrocytoma were released in December 2021 by ASCO and the Society for Neuro-Oncology.[31] Key elements of treatment are outlined in the following sections and summarized in Figure 18-4.

Figure 18-4 Management of *IDH*-Mutant Glioma



Abbreviations: PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide.
For patients who have grade 2 *IDH*-mutant astrocytoma or oligodendroglioma, vorasidenib is approved in the first-line setting for patients following biopsy or resection. For patients who have oligodendroglioma (*IDH*-mutated, 1p/19q codeleted), radiation followed by PCV chemotherapy is also standard of care, but TMZ may be considered if toxicity is a concern. For patients who have grade 2 to 3 *IDH*-mutant astrocytoma, radiation with TMZ (12 cycles adjuvant, consider concurrent) can be used, although PCV may be considered. Patients who have grade 4 astrocytoma should be treated with radiation and concurrent TMZ as first-line therapy, followed by six cycles of adjuvant TMZ.
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SURGERY

As in glioblastoma, the initial step of treatment of a presumed grade 2 or 3 glioma is maximal safe neurosurgical resection. As with glioblastoma *IDH*wt, there appears to be a benefit from supramaximal resection in these tumors as well.[66] For tumors that enhance, removal of all contrast-enhancing tissue is a common goal. Grade 2 *IDH*-mutant astrocytomas can be indolent tumors; however, they tend to eventually progress to high-grade astrocytomas. Although the surgical management of small and asymptomatic grade 2 gliomas is more controversial, maximal safe surgical resection, when possible, is associated with improved survival.

IDH-INHIBITOR THERAPY

For patients who have grade 2 *IDH*-mutant glioma, the IDH1/2 inhibitor vorasidenib is approved by the FDA as a first-line therapy. The INDIGO phase 3 trial randomly assigned participants with residual or recurrent grade 2 *IDH*-mutant glioma who had received a surgical diagnosis between 1 and 5 years before enrollment, received no previous treatment, had no contrast-enhancing disease, and had a residual tumor measuring at least 1 cm × 1 cm in the two longest dimensions to be treated with vorasidenib 40 mg once per day or placebo.[1] PFS, the primary trial endpoint, was significantly improved to 27.7 months in the vorasidenib arm compared with 11.1 months for placebo (HR, 0.39; 95% CI, 0.27-0.56). Prespecified subgroup analysis demonstrated a benefit in patients who have 1p/19q codeleted and non-codeleted tumors. Grade 3 or higher toxicity was seen in 23% of patients, most commonly elevated liver function test results. Because the trial included patients who were 1 to 5 years beyond diagnosis, the optimal time to implement this therapy is still unclear; long-term survival data are not available, and it remains acceptable to monitor for radiographic or symptomatic tumor growth.

RADIATION THERAPY

As in patients who have glioblastoma, postoperative radiation therapy with chemotherapy is demonstrated to prolong survival in patients who have grade 3 astrocytoma and is a standard component of treatment.[67] Most practitioners currently treat with

54 to 60 Gy in 1.8- to 2.0-Gy fractions. Radiation therapy likely improves OS for grade 2 *IDH*-mutated astrocytoma as well, although the optimal timing for initiating treatment remains uncertain. A phase 3 clinical trial evaluated the role of immediate radiation therapy versus delayed radiation therapy in patients who have low-grade glioma and demonstrated no improvement in median OS with immediate treatment compared with delayed radiation therapy (7.4 years vs. 7.2 years; $P = .87$).[68] The study did demonstrate that early treatment extends the time to recurrence and reduces seizures compared with delayed radiation therapy at the time of tumor progression (median PFS, 5.3 years vs. 3.4 years; $P < .0001$). Thus, a rationale exists for delaying radiation therapy in an attempt to prevent radiation therapy–induced neurologic damage in patients who have grade 2 *IDH*-mutant astrocytoma, particularly in those with favorable prognostic factors (eg, complete resection, younger age). Importantly, however, the RTOG 9802 phase 3 trial of radiation therapy alone versus radiation therapy followed by chemotherapy with PCV demonstrated minimal long-term neurotoxicity. In fact, a majority of patients showed improvement in neurocognitive testing over time.[69] Therefore, for patients who have WHO grade 2 *IDH*-mutant astrocytoma and who have minimal symptoms, including well-controlled seizures, it is acceptable to either treat at the time of initial diagnosis or defer radiation therapy and chemotherapy until evidence of symptomatic tumor growth is observed. A trial of vorasidenib before treatment with radiation is considered appropriate in patients with low-grade *IDH* mutant astrocytoma or oligodendroglioma.

CHEMOTHERAPY

For patients who have WHO grade 3 *IDH*-mutant astrocytoma, the current standard of care is to offer adjuvant temozolomide after radiation therapy. Temozolomide can also be offered concurrently with radiation therapy. The EORTC 26053 (CATNON trial) phase 3 international trial randomly assigned patients who have grade 3 glioma without 1p/19q codeletion to either radiation therapy alone or radiation therapy with temozolomide during and/or after radiation therapy using a factorial design.[70] In the subgroup of 444 patients who have *IDH*-mutant tumors, concurrent temozolomide was not significantly associated with improved OS (HR, 0.80; 95% CI, 0.58-1.10), whereas adjuvant temozolomide showed an OS HR of 0.48 (95% CI, 0.35-0.67). Based on these data, it is considered standard to offer adjuvant temozolomide with or without concurrent temozolomide during radiation.

Observation is historically favored for patients who have low-risk, low-grade (WHO grade 2) glioma, loosely defined as patients aged younger than 40 years who have undergone surgical gross total resection. Such patients are, therefore, excluded from most clinical trials of chemotherapy. However, when the decision was made to treat patients who have WHO grade 2 *IDH*-mutant astrocytoma with radiation therapy, the preponderance of the evidence favored adding chemotherapy (either PCV or temozolomide). Although studies support improved survival with PCV in *IDH*-mutant 1p/19q non-codeleted tumors (5.5 years vs. 3.3 years), the survival advantage seems less pronounced than in 1p/19q codeleted tumors (ie, oligodendrogliomas)[17] (see the "Oligodendroglioma, *IDH* Mutant, and 1p/19q Codeleted" section for details). Given this observation, as well as the lower toxicity and probable efficacy of temozolomide in this setting (based on data from the CATNON study), adjuvant temozolomide rather than PCV is a reasonable treatment option for patients who have grade 2 *IDH*-mutant astrocytoma.

RECURRENCE

As with patients who have glioblastoma, no uniform therapy is available for patients who have *IDH*-mutant astrocytoma that has relapsed after radiation therapy and alkylating chemotherapy, and treatment options are tailored to the individual clinical setting. Repeated surgery may be considered in select cases for either diagnostic purposes (eg, possible progression to a higher grade, differentiation of active tumor vs. treatment effect) and/or for debulking. Retreatment with temozolomide or nitrosourea-based regimens may be an option. Bevacizumab is an option for recurrent high-grade disease with associated symptoms. In addition, repeated radiation therapy with or without concomitant temozolomide is considered in certain situations. IDH inhibitors may be considered for non-enhancing recurrent disease, although prospective randomized data that confirm a benefit are lacking.

KEY POINTS

- In the 2021 WHO Classification of Tumors of the CNS, all *IDH*-mutant diffuse astrocytic tumors are considered as a single entity (*IDH*-mutant astrocytoma) and are then graded as grade 2, 3, or 4. These tumors are 1p/19q non-codeleted.
- Initial treatment of grade 3 *IDH*-mutant astrocytomas is maximal safe resection followed by radiation therapy with chemotherapy. Adjuvant temozolomide provides a clear survival benefit, and concurrent temozolomide may be considered given the potential benefit and limited risk of harm.
- Grade 2 *IDH*-mutant astrocytomas can be indolent tumors; however, they tend to eventually progress to high-grade astrocytomas.
- Maximal safe resection is recommended, especially if a presumed glioma is large and/or symptomatic.
- The IDH inhibitor vorasidenib is an FDA-approved agent for grade 2, *IDH*-mutant astrocytomas following surgery.
- Radiation therapy with adjuvant chemotherapy (temozolomide or PCV) provides a clear survival benefit in grade 2 *IDH*-mutant astrocytoma regardless of whether treatment was administered just after diagnosis or at the time of tumor progression. Definitive therapy may be deferred until radiographic or symptomatic progression occurs in individuals with positive prognostic factors (eg, complete resection, younger age) or who elect first-line IDH-inhibitor therapy.

OLIGODENDROGLIOMA, *IDH* MUTANT, AND 1P/19Q CO-DELETED

Oligodendrogliomas are relatively uncommon, accounting for only ~8% of gliomas. Nevertheless, they are important to note because of their unique natural history, comparatively favorable prognosis, and sensitivity to chemotherapy. Key histologic features include monomorphic, rounded nuclei with artifactual, clear perinuclear halos on paraffin-processed tissues (fried-egg pattern), and delicate capillary vascular networks (chicken-wire vessels); requisite molecular features include *IDH* mutation and 1p/19q codeletion.

Grade 3 oligodendrogliomas typically demonstrate high cellularity, nuclear pleomorphism, and frequent mitoses. Abundant endothelial proliferation and tumor necrosis may also be seen, but these tumors are graded differently; a grade 4 does not exist for oligodendrogliomas. In the current WHO classifications, oligodendrogliomas, which are always *IDH* mutated, are also defined by the presence of a 1p/19q codeletion. Mass effect or seizures are typically seen at presentation. MRI scans reveal a variably contrast-enhancing mass in most patients. The disease course of grade 2 oligodendrogliomas is more indolent than that of grade 2 astrocytomas.

SURGERY

As previously described for *IDH*-mutant astrocytomas (see the "Astrocytoma, *IDH* Mutant" section), the initial step of treatment of a presumed grade 2 or 3 oligodendroglioma is the best-possible safe neurosurgical resection. For tumors that enhance, the removal of all contrast-enhancing tissue is performed as a common goal. The surgical management of small and asymptomatic gliomas is more controversial. Either first-line surgical resection or a watch-and-wait approach may be considered.

IDH INHIBITORS

The IDH1/2 inhibitor vorasidenib is an FDA-approved agent as first-line therapy for *IDH*-mutant astrocytomas and oligodendrogliomas based on the results of a double-blind randomized placebo-controlled phase 3 study as described in the "Astrocytoma, *IDH* Mutant" section.[71] For patients who have non-enhancing residual grade 2 oligodendroglioma who had received surgery within 1 to 5 years before enrollment, there was a clear improvement in PFS (HR, 0.32; 95% CI, 0.18-0.57) and time to next therapeutic intervention (HR, 0.14; 95% CI, 0.05-0.4). Given the indolent natural history of oligodendroglioma, it remains unclear at what point in the disease trajectory IDH inhibitor therapy should be implemented. Effects on OS, family planning, and quality of life are not yet clear. These factors should be considered with patients when initiating therapy.

RADIATION THERAPY AND CHEMOTHERAPY

For grade 3 oligodendrogliomas, surgical debulking is typically followed by radiation therapy with chemotherapy. Support for the use of chemotherapy and radiation therapy after resection of grade 3 (formerly anaplastic) oligodendrogliomas comes from two phase 3 trials, one conducted in North America (RTOG 9402) and one in Europe (EORTC 26951). In the North American trial, patients who had anaplastic oligodendrogliomas or anaplastic oligoastrocytomas were randomly assigned to receive PCV for four cycles before radiation therapy or radiation therapy alone.[20] Patients who have *IDH*-mutated 1p/19q co-deleted tumors benefited from the addition of PCV to radiation therapy (median survival, 14.7 years vs. 6.8 years).

In the European trial, patients received PCV after radiation therapy. Results were similar to those of the North American trial. Some long-term results demonstrated a longer median survival in patients who had 1p/19q co-deleted tumors who received both radiation therapy and PCV compared with those who received radiation therapy alone. Taken together, these two randomized trials support the standard use of radiation therapy and chemotherapy with PCV for patients who have grade 3 oligodendrogliomas.

In patients who have grade 2 oligodendroglioma, considerations regarding timing of therapy are similar to those for patients who have WHO grade 2 *IDH*-mutant astrocytoma (see the "Astrocytoma, *IDH* Mutant" section). If adjuvant therapy is chosen, the preponderance of the evidence is in favor of offering both radiation therapy and chemotherapy to patients who have WHO grade 2 *IDH*-mutant 1p/19q co-deleted oligodendroglioma. The phase 3 RTOG 9802 clinical trial defined patients as being at high risk of early progression if they were 40 years or older and/or if they were younger than 40 years and had undergone subtotal resection or biopsy instead of a gross total resection. Patients meeting these eligibility criteria were then randomly assigned to receive either radiation therapy alone or radiation therapy followed by chemotherapy with PCV. The study showed that the addition of chemotherapy with PCV significantly improved survival.[69] Subgroup analyses support trends that patients who have tumors with 1p/19q codeletion may, in fact, be the patients who derive the most benefit from chemotherapy.[72]

Radiation therapy with PCV may be superior to radiation therapy and concomitant temozolomide for patients who have grade 3 oligodendroglioma, based on a large retrospective cohort study.[71] Temozolomide is overall better tolerated, and patients are commonly treated with radiation therapy and temozolomide as well. The CODEL ongoing prospective trial is comparing radiation therapy followed by PCV with chemoradiotherapy with temozolomide followed by adjuvant temozolomide in patients who have oligodendrogliomas (both grade 2 and grade 3). This study will eventually answer the question of how the two regimens compare.

KEY POINTS

- Oligodendroglial tumors are characterized by both *IDH* mutation and 1p/19q codeletion and have a more indolent course than astrocytomas.
- After surgery for debulking and maximal safe resection, patients who have WHO grade 3 *IDH*-mutant 1p/19q co-deleted oligodendroglioma should be offered radiation therapy in combination with PCV because the addition of PCV after radiation therapy significantly improves OS compared with radiation therapy alone. TMZ is a reasonable alternative to PCV when toxicity is a concern.
- For patients who have WHO grade 2 *IDH*-mutant 1p/19q co-deleted oligodendroglioma, maximal safe resection is recommended if the tumor is large and/or symptomatic.
- The IDH inhibitor vorasidenib is an FDA-approved agent for grade 2 oligodendroglioma before radiation therapy, though the effect on survival is unknown.
- Radiation therapy and adjuvant PCV provide a clear survival benefit in grade 2 *IDH*-mutant 1p/19q co-deleted oligodendroglioma; however, no clear OS advantage is seen with immediate postoperative radiation therapy compared with delayed radiation therapy. Definitive therapy may be deferred until radiographic or symptomatic progression in individuals with positive prognostic factors (eg, complete resection, younger age) or who elect first-line IDH-inhibitor therapy.

RARE, TARGETABLE CNS TUMORS

DIFFUSE MIDLINE GLIOMA (H3K27M-MUTATED)

The role of chemotherapy in DMG has historically been unclear, given the lack of clinical trial data supporting efficacy. In 2025, the FDA granted accelerated approval of the protease activator dordaviprone for progressive disease following prior therapy in patients aged 1 year or older with DMG harboring an H3K27M mutation. This recommendation was based on a select subgroup of 50 patients from five non-randomized clinical trials in adults and children with gliomas.[13,73] In that select population, the overall response rate was 22% (including partial and minor responses) with a median duration of response lasting 10.3 months. It was well tolerated, with fatigue being the most common treatment-related grade 3 toxicity (10%; see Table 18-1).

Table 18-1 **Rare, Targetable CNS Tumors**

Rare, Targetable Nervous System Tumors	Grade	Tumor Characteristics	Common Alterations	Targeted Therapy	References
Pilocytic astrocytoma	1	Primarily pediatric. Frequently appear as a cyst with a mural nodule in the cerebellum. Can be cured by surgery if removed completely	*KIAA1549-BRAF* fusion	Tovorafenib	2,74
Subependymal giant cell astrocytoma	1	Periventricular, 1:10 in patients who have tuberous sclerosis	*TSC1* or *TSC2*	Everolimus	75
CNS hemangioblastoma	1	Highly vascular, 25% associated with VHL	*VHL*	Belzutifan (for VHL-associated)	76
Plexiform neurofibroma	1	Occur on peripheral nerves and can undergo malignant transformation	*NF1*	Selumetinib (for NF1-associated)	77
Pleomorphic xanthoastrocytoma	2 or 3	Primarily adolescent and young adult, predilection for cerebrospinal fluid dissemination	*BRAF*	Dabrafenib/ trametinib	78
Diffuse midline glioma	4	Primarily pediatric	*K3K27M*	Dordaviprone	13

Abbreviations: CNS, central nervous system; VHL, von Hippel-Lindau.
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KEY POINTS

- Grade 1 astrocytomas are more common in children and young adults. Surgical resection is often curative.
- Everolimus is an FDA-approved agent for the treatment of SEGAs.
- Low-grade astrocytomas with *BRAF* V600E or *BRAF* rearrangements may be amenable to *BRAF*- or *MEK*-targeted therapy.

MEDULLOBLASTOMA

Medulloblastoma is the most common malignant brain tumor in children, but young adults and older adults are also at risk, although at a lower frequency. Medulloblastomas develop in the posterior fossa. They may be located in either the cerebellar hemispheres or the vermis and may involve the fourth ventricle. Obstructive hydrocephalus is relatively common because of the proximity of the tumor to the fourth ventricle. Symptoms at presentation may include loss of balance, incoordination, diplopia, dysarthria, and signs of hydrocephalus such as headache, nausea, vomiting, and gait instability.

Molecular pathology studies demonstrate discrete subtypes of medulloblastoma that have variable prognoses. The following genetically defined subtypes are included in the WHO Classification of Tumors of the CNS[79]:

- WNT activated: best prognosis with long-term survival in more than 90% of patients
- Sonic hedgehog (SHH) activated: intermediate prognosis
- Group 3: overexpression of *MYC*; worst prognosis
- Group 4: intermediate prognosis

Although the molecular characterization has not yet resulted in specific therapies, the aberrant pathways identified may eventually lead to targeted treatments for the respective entities.

Maximal surgical resection is important because residual tumor after surgery confers a worse prognosis. A worse prognosis is also seen with positive CSF cytology or the presence of leptomeningeal metastases on MRI scans. Surgery alone is not curative; however, surgical resection followed by radiation to the craniospinal axis with a boost to the site of the primary tumor may be curative.

Post-radiation chemotherapy is a mainstay of treatment in children who have medulloblastoma, particularly because it limits the total dose of radiation required to treat the still-developing CNS. Based on this experience and data from retrospective studies in adults suggesting that adjuvant chemotherapy is associated with improved survival compared with craniospinal radiation alone, even after adjusting for potential confounders, adults with medulloblastoma are usually offered chemotherapy if post-radiation therapy blood cell counts permit. However, no prospective data show an added benefit from chemotherapy in adults who received full-dose craniospinal irradiation. Chemotherapy regimens for adult patients are often modeled after the experience in pediatric patients. Once-per-week treatment with vincristine during radiation therapy, frequently used in children, is often omitted in adults because of poor tolerability of the drug and concerns about lack of efficacy. Adjuvant chemotherapy regimens include cisplatin, cyclophosphamide, and vincristine[80] or cisplatin, lomustine, and vincristine,[80] but there is no unifying standard of care, and the role for chemotherapy after craniospinal irradiation remains controversial.

Vismodegib, a small-molecule inhibitor of the SHH pathway, has demonstrated activity in patients who have recurrent SHH-type medulloblastoma,[81] and high-dose chemotherapy with autologous stem cell transplantation may result in longer survival in some selected patients.[82,83] With appropriate initial therapy, 5-year event-free survival is achieved in more than 80% of patients who have average-risk medulloblastoma and in 36% of patients who have disseminated disease at diagnosis.[80]

KEY POINTS

- Medulloblastomas typically occur in the cerebellum in children, but they can also present in adults.
- Treatment of medulloblastoma includes maximal safe resection followed by irradiation of the craniospinal axis (with a boost to the tumor bed). Platinum-based chemotherapy regimens are considered, especially in higher-risk patients, if post-radiation therapy blood cell counts permit.

MENINGIOMA

Meningiomas are usually benign (grade 1) and originate in the dura covering the brain and spinal cord. Patients who have meningiomas may present with typical features of mass lesions in the brain, including seizures or focal neurologic deficits. Asymptomatic meningiomas may also be incidentally detected on CT or MRI scans that are obtained for other reasons. The tumors have a characteristic appearance on MRI scans, usually consisting of uniform contrast enhancement along the dura and distinct separation from brain parenchyma. Due to tumoral somatostatin receptor (SSTR) expression, there has been an increased use of DOTATATE-PET in the evaluation of these tumors though its optimal role has yet to be defined.

Many incidentally discovered meningiomas do not require treatment. For patients who have an asymptomatic presumed WHO grade 1 meningioma, observation may be appropriate. Epidemiologic evidence suggests that as many as two-thirds of these patients will not have symptoms over time.[84]

In cases of substantial mass effect and/or symptoms, the treatment of choice is usually complete resection. Surgery is often feasible if the meningioma is located over the cortical convexity, olfactory groove, anterior sagittal sinus, or posterior fossa. However, the possibility of resection may be limited for tumors in other sites, including sphenoid, parasagittal, orbital, tentorial, or clival locations. For those situations, external beam radiation therapy or focal stereotactic radiation therapy may be useful for tumor control.

Meningiomas may have more aggressive histologic or molecular features. Patients who have WHO grade 2 (previously atypical) meningiomas or WHO grade 3 (previously anaplastic) meningiomas are commonly treated with surgical resection followed by radiation therapy: either external beam radiation therapy or stereotactic radiosurgery. Those who experience relapse despite optimal surgery and radiation therapy often have progressive debilitation before death. Although several pharmaceutical approaches have been assessed, they have had limited, if any, efficacy.[85] Clinical trials should be considered for these patients.

KEY POINTS

- For many patients who have meningioma, observation is appropriate. For patients who are symptomatic, surgical removal of the tumor is the most common treatment.
- Meningiomas that are WHO grade 2 or 3 are rare but have a more aggressive course with recurrences that may require repeated resection and radiation therapy.
- Currently, systemic regimens have limited, if any, efficacy for the treatment of meningiomas.

HEMANGIOBLASTOMA

Hemangioblastoma is a rare, slow-growing tumor of the CNS that occurs most commonly in the posterior fossa or spinal cord. These tumors can occur sporadically or as a part of VHL disease, an inherited autosomal dominant syndrome characterized by numerous benign and malignant tumors, such as hemangioblastomas, retinal angiomas, endolymphatic sac tumors, renal cell carcinoma, pheochromocytomas, pancreatic cysts, and pancreatic neuroendocrine tumors.

Sporadic hemangioblastomas are typically solitary, whereas multiple tumors within the neuraxis should raise concern for VHL.[86] When hemangioblastomas are symptomatic, they typically result in local symptoms by compression of neural structures or as a result of bleeding. Surgical resection offers definitive therapy for sporadic, isolated hemangioblastomas. Radiation therapy is also an option in patients who have surgically inaccessible tumors. However, the role of surgery and/or radiation in patients who have VHL disease is less well defined because of the frequent occurrence of additional lesions. In these patients, the HIF2α inhibitor belzutifan is an additional treatment option.[87] In the LITESPARK-004 study, belzutifan demonstrated an ORR of 44% in the 50 patients with VHL disease who have CNS hemangioblastomas, with median duration of response and median PFS not reached after a median follow-up time of 38 months.[2] The drug is now FDA approved for adult patients who have VHL disease who require therapy for CNS hemangioblastoma and do not require immediate surgery. Patients must be monitored carefully for anemia and hypoxia.

KEY POINTS

- Surgery and/or radiation are definitive options for sporadic, isolated hemangioblastoma.
- For patients who have VHL-associated CNS hemangioblastoma, belzutifan represents an effective systemic treatment option.

PRIMARY CNS LYMPHOMA

Primary CNS lymphoma is a variant of non-Hodgkin lymphoma that involves the CNS without evidence of systemic disease. More than 95% of primary CNS lymphomas are diffuse large B-cell lymphomas with the remaining cases comprising T-cell lymphomas, low-grade lymphomas, or Burkitt lymphoma. Primary CNS lymphomas constitute approximately 2% to 3% of all brain tumors. The tumor is slightly more common in men, and the median age at diagnosis in immunocompetent patients is approximately 67 years.[88] Most patients diagnosed with primary CNS lymphoma are immunocompetent; however, patients who have a compromised immune system (eg, those who have undergone solid organ transplantation, have congenital immunodeficiency, or have HIV infection) are at increased risk of this disease. Epstein-Barr virus is frequently associated with primary CNS lymphoma in immunocompromised individuals, and Epstein-Barr virus DNA may be found within the tumor.

Patients present with a variety of symptoms characteristic of either focal or multifocal mass lesions. MRI scans usually show homogeneous contrast-enhanced tumors within the periventricular deep white matter. Multifocality is common because these tumors grow diffusely. Heterogeneous contrast enhancement is sometimes seen, especially in patients who have a compromised immune system or after exposure to immunosuppressant agents, such as corticosteroids. It is important to consider CNS lymphoma in the differential diagnosis of brain tumors because treatment of CNS lymphoma differs significantly from treatment of other primary brain cancers. Administration of corticosteroids may result in the complete disappearance of the contrast-enhancing lesion, making diagnosis difficult. Consequently, when CNS lymphoma is considered in the differential diagnosis, corticosteroids should be avoided unless mass effect is causing serious and immediate complications. Often, even in those settings, other means can be utilized to decrease intracranial pressure. Obtaining specimens of suspected lesions by biopsy is critically important because many malignant and non-malignant CNS conditions can mimic CNS lymphoma. As with systemic lymphoma, the role of surgery is restricted primarily to obtaining appropriate tissue for diagnosis.

Staging evaluation includes slit-lamp examination of the eyes (to assess for ocular lymphoma, which is present at diagnosis in approximately 25% of patients); MRI scans of the spine; PET/CT imaging or CT scan of the chest, abdomen, and pelvis; testicular ultrasound to rule out lymphoma; lumbar puncture if safe; and HIV testing. Primary CNS lymphomas typically do not involve the bone marrow, and the role of a bone marrow biopsy as part of the standard workup is controversial. Age and performance status are the strongest independent predictors of OS in patients who have primary CNS lymphoma.

High-dose methotrexate-based regimens with typical doses between 3.5 and 8 g/m^2 have remained the backbone of the treatment of CNS lymphoma. Several combination regimens are used in clinical practice, including high-dose methotrexate with rituximab; with rituximab plus temozolomide; with rituximab, vincristine, and procarbazine; or with rituximab, thiotepa, and high-dose cytarabine.[89-92] The different regimens have not been formally compared in prospective trials, and comparative efficacy cannot be conclusively defined. ORRs for the different regimens are reported to be between 35% and 95%. A substantial percentage of durable complete responses with many of these patients likely cured. However, late relapses, even after 10 years or more, can occur.

Controversy still remains regarding the role of consolidation therapy for patients who have responded to induction with high-dose methotrexate-based therapy. Encouraging data are reported with the use of thiotepa-based conditioning regimen followed by autologous stem cell transplantation, although prospective comparative trial data are sparse. A recently reported trial comparing autologous transplantation with high-dose chemotherapy as consolidation therapy in newly diagnosed primary CNS lymphoma (CALGB-51101) revealed that 2-year PFS was superior in the transplantation arm, although there was a statistically higher number of patients who had primary refractory disease on the high-dose chemotherapy arm during induction before consolidation. When comparing 2-year PFS from the start of consolidation, there was a trend toward improvement with transplantation (HR, 0.58; 95% CI, 0.25-1.36). The estimates of 3-year survival were similar between groups (83% for transplantation and 72% for high-dose chemotherapy).[93]

A possible role of low-dose whole-brain radiation therapy for consolidation in patients who have newly diagnosed primary CNS lymphoma has also been studied.[94] This approach is generally used only in patients who have responsive disease and preserved functional status but who are not candidates for high-dose chemotherapy based on organ dysfunction or patient preference.

A number of additional drugs show promising activity in primary CNS lymphoma, including ibrutinib and lenalidomide, and possibly immunotherapies, including chimeric antigen receptor (CAR) T cells and PD-1 inhibitors.[95] Additional research is needed to determine the best clinical use of these new agents.

Strategies for the treatment of recurrent disease include reinduction with high-dose methotrexate-based regimens and, in select cases, high-dose chemotherapy with autologous stem cell transplantation, temozolomide, ibrutinib, lenalidomide, CAR T cells, combinations with rituximab, and whole-brain radiation therapy.[96] Additional studies are needed to determine the optimal choice and sequence of these therapies for patients with recurrent disease.

The aforementioned doses of methotrexate (3.5-8.0 g/m^2) are potentially lethal if not followed by active measures to reduce associated toxicity. Multiple doses of leucovorin must be administered starting approximately 24 hours after treatment to minimize toxicity to normal cells (ie, leucovorin rescue), and hyperhydration with urinary alkalinization with intravenous fluids is used to enhance methotrexate excretion. Methotrexate levels must be monitored to confirm effective elimination. Prolonged exposure may be secondary to the accumulation of methotrexate in third-space fluid collections (eg, pleural effusions). Such fluid collections should be drained before treatment with methotrexate if possible. In patients who are unable to clear methotrexate quickly enough, administration of glucarpidase can be considered, which cleaves methotrexate and neutralizes its toxic effect.

KEY POINTS

- Primary CNS lymphomas are usually diffuse large B-cell lymphomas.
- Epstein-Barr virus is frequently associated with primary CNS lymphoma in immunocompromised individuals.
- When CNS lymphoma is considered in the differential diagnosis, corticosteroids should be held before biopsy, if clinically feasible, because they can lead to nondiagnostic biopsy results, which, in turn, can delay treatment.
- High-dose methotrexate-based chemotherapy has remained the backbone of therapy for newly diagnosed primary CNS lymphoma.
- Autologous stem cell transplantation can be considered for consolidation in patients who have good functional status and who respond to a methotrexate-based chemotherapy regimen.

METASTATIC DISEASE TO THE NERVOUS SYSTEM

BRAIN METASTASES

Brain metastases from systemic cancers are more common than those from primary brain tumors. The incidence of brain metastases has been reported as 9% to 17% in various studies; autopsy series suggest that the true incidence of brain metastases in adults may be greater than 20%, although these numbers may represent end-stage disease without direct clinical therapeutic relevance. Brain metastases are most associated with lung cancer, breast cancer, melanoma, or an unknown primary cancer. These lesions

generally result from hematogenous spread and are most common at the junction of the gray and white matter, at which the caliber of blood vessels narrows, thereby trapping tumor emboli. A total of 80% of brain metastases occur in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem.[97] It is reported that more than 80% of people with brain metastases have more than one, and approximately 50% have three or more brain metastases seen on MRI scans.[98] Interestingly, the incidence of metastases to the parenchyma of the spinal cord is low.

The management of brain metastases requires an individualized approach because these patients have highly heterogeneous primary disease processes. Considerations for therapy depend on multiple variables, such as the number and location of the brain metastases, histology of the primary cancer, tumor molecular characteristics, degree of extracranial disease, and performance status. Whole-brain radiation therapy remains a primary treatment modality for patients who have a high intracranial tumor burden, and the routine role of whole-brain radiation therapy as adjunctive therapy in patients who are candidates for stereotactic radiosurgery or surgical resection has evolved. Randomized trials show that, despite improved rates of intracranial disease control, adjunctive whole-brain radiation therapy does not improve OS and may decrease quality of life as a result of adverse effects and neurocognitive decline. Techniques such as hippocampal avoidance whole brain radiotherapy (WBRT; discussed below) or stereotactic radiosurgery (also discussed below) can mitigate the toxicity of radiation. In addition, the integration of systemic therapy into the management of brain metastases has increased considerably over the past decade because improved systemic therapies with significant brain penetration have begun to offer greater potential for intracranial disease control for certain cancer types and genotypes.[99]

SURGERY

For patients who have a single, surgically accessible metastasis that is large or associated with significant edema and mass effect, surgical resection achieves rapid symptom relief and local control. Surgery (or stereotactic biopsy for inaccessible tumors) is also favored for single lesions when there is uncertainty regarding the histologic diagnosis based on either clinical grounds or radiographic findings.

RADIATION THERAPY

For patients who receive surgery, radiation to the resection cavity with stereotactic radiosurgery is shown to decrease local recurrence compared with surgery alone. One phase 3 trial randomly assigned 132 patients who had undergone a complete resection of one to three brain metastases (maximum diameter of resection cavity <4 cm) to either stereotactic radiosurgery of the resection cavity or observation.[100] Freedom from local recurrence at 1 year was 43% in the observation group and 72% in the stereotactic radiosurgery group (HR, 0.46; $P = .015$), indicating that stereotactic radiosurgery significantly lowers local recurrence. Stereotactic radiosurgery may be preferred as an independent treatment in patients who have surgically inaccessible lesions and cannot undergo craniotomy because of the operative risk. Limitations include the inability to obtain tissue diagnosis or reduce mass effect; in addition, lesions must generally be less than 3 to 4 cm to be safely treated. Furthermore, stereotactic radiosurgery may increase cerebral edema, resulting in a mass effect that requires either corticosteroid treatment or resection of necrotic tissue.

Historically, stereotactic radiosurgery was used primarily in patients with 10 or fewer small (<3 cm) brain metastases.[101,102] However, recent practice has evolved such that patients with a greater number of small brain metastases are commonly managed with stereotactic radiosurgery. Local control rates with stereotactic radiosurgery are high, ranging from 80% to 90%.[103] In patients who have undergone stereotactic radiosurgery for up to 10 small brain metastases, there is no longer a role for adjunctive whole-brain radiation therapy. In a phase 3 clinical trial, patients who had one to three brain metastases were treated with either surgery or stereotactic radiosurgery and then randomly assigned to either whole-brain radiation therapy (30 Gy in 10 fractions) or observation. Whole-brain radiation therapy reduced the incidence of intracranial progression (48% vs. 78%; $P < .001$) and death resulting from neurologic factors (28% vs. 44%; $P < .002$); however, OS was similar in the two groups (10.97 months vs. 10.7 months; $P = .89$).[104] This study and many others also raise concerns regarding cognitive impairment with the addition of whole-brain radiation therapy. Nonetheless, whole-brain radiation remains the standard approach to initial treatment in most patients who have a very high overall tumor burden, including those with multiple large tumors. When whole-brain radiation therapy is used, data from a placebo-controlled phase 3 clinical trial suggest that concurrent use of memantine may delay cognitive decline.[105] A subsequent unblinded randomized phase 3 trial[106] shows that use of whole-brain radiation therapy with hippocampal avoidance led to an additional 26% relative reduction in risk of cognitive toxicity compared with conventional whole-brain radiation therapy; both groups received memantine during whole-brain radiation therapy and for 6 months afterward.

SYSTEMIC THERAPY

Classic chemotherapy plays a limited role in the treatment of brain metastases, in part because of poor drug delivery through the blood-brain barrier and blood-tumor barrier. However, chemotherapy may be curative in specific tumors, such as lymphoma and germ cell tumors; chemotherapy may be incorporated into the treatment plan for both brain tumors and systemic metastatic disease in these patients, often in combination with radiation therapy. Another unique situation is extensive-stage small-cell lung

cancer presenting with brain metastases; these patients may be treated with initial systemic therapy if their intracranial disease is asymptomatic and with whole-brain radiation therapy upon completion of induction therapy.

A growing body of evidence shows intracranial efficacy of molecularly targeted small molecules and/or immune checkpoint inhibitors in cancers in which the respective agents are known to be effective systemically. In select cases with small and asymptomatic or minimally symptomatic brain metastases, a closely monitored trial of systemic therapy with intracranial efficacy and deferral of locoregional CNS therapy is an increasingly acceptable treatment approach.[107] Key examples of effective systemic therapies across the solid tumors that most commonly metastasize to the CNS are displayed in Table 18-2.[108-127]

Table 18-2 Key Systemic Agents With Intracranial Activity in Patients With Brain Metastases

Primary Tumor	Drug(s)	Intracranial Response Rate(s) (95% CI) %	References
NSCLC, driver mutation negative, PD-L1 positive	Pembrolizumab	30 (16-47)	108
EGFR-mutant NSCLC	Osimertinib	91 (71-99)	109
ALK-rearranged NSCLC	Alectinib	81 (58-95)	110
	Brigatinib	78 (52-94)	111
	Lorlatinib	82 (57-96)	112
ROS1-positive NSCLC	Entrectinib	79 (60-93)	113
	Repotrectinib	89 (52-100)	60
RET-fused NSCLC	Selpercatinib	82 (57-96)	114
	Pralsetinib	70 (35-93)	115
MET exon-14 skipping mutation NSCLC	Capmatinib	54 (17-77)	116
	Tepotinib	55 (23-83)	117
KRAS G12C-mutant NSCLC	Adagrasib	42 (20-67)	118
	Sotorasib	25 (13-41)	119
Small cell lung cancer	Tarlatamab	63 (30-100)	128
HER2-positive breast cancer	Lapatinib and capecitabine	66 (50-80)	120
	Neratinib and capecitabine	49 (32-66)	121
	Tucatinib, capecitabine, and trastuzumab	47 (34-61)	122
	Fam-trastuzumab deruxtecan (T-Dxd)	46 (19-75)	123
Melanoma, *BRAF* V600E mutant	Dabrafenib and trametinib	58 (46-69)	124
Melanoma	Ipilimumab and nivolumab	54 (43-64)	125
	Pembrolizumab	22 (7-48)	126
	Nivolumab	20 (7-41)	127
Renal cell carcinoma	Cabozantinib	55 (36-73)	128
	Ipilimumab and nivolumab	32 (15-54)	129

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer.
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In addition, the FDA has approved the use of three TRK inhibitors, larotrectinib, entrectinib, and repotrectinib, for *NTRK* fusion–positive solid tumors regardless of tumor type.[60,61,130,131] The activity of these drugs has also been demonstrated in patients who have brain metastases. Entrectinib and repotrectinib are also FDA-approved agents for metastatic *ROS1*-positive non–small cell lung cancer, and there has been activity of these drugs for *ROS1*-positive non–small cell lung cancer brain metastases.

ANTIEPILEPTIC PROPHYLAXIS AND CORTICOSTEROIDS

A recently published guideline review by a panel of experts from ASCO and the Society for Neuro-Oncology focused on anticonvulsant prophylaxis and corticosteroid use in adults with metastatic brain tumors. Prophylactic antiepileptic drugs were not recommended for routine use in patients without a seizure history. Corticosteroids (dexamethasone) were recommended for symptomatic relief for patients who have signs of, and neurologic symptoms related to mass effect from their brain metastases.[132]

KEY POINTS

- Brain metastases as a group are the most common brain tumors.
- Stereotactic radiosurgery is increasingly being used in addition to or in place of surgery for patients with brain metastases.
- When whole-brain radiation therapy is used for the treatment of brain metastases, the use of hippocampal avoidance intensity-modulated radiation therapy and memantine together has been demonstrated in a randomized trial to decrease the risk of neurocognitive toxicity.
- Small molecules and immunotherapies are increasingly used in the treatment of brain metastases from cancers in which the respective medications are effective systemically.

LEPTOMENINGEAL METASTASES

Leptomeningeal metastases occur in approximately 5% of patients who have cancer and are more frequently recognized as patients who have cancer live longer, and as diagnostic studies improve.[133] Leptomeningeal disease is most common with breast cancer, lung cancer, and melanoma. The tumor may reach the leptomeninges by hematogenous spread or by direct extension from preexisting tumor deposits within the dura or brain parenchyma. Tumor cells are disseminated throughout the neuraxis by the flow of CSF. Patients present with signs and symptoms referable to one or more of the following: local injury to nerves traveling through the spinal fluid (cranial nerve palsies, weakness, paresthesias, or pain); direct invasion into the brain or spinal tissues or interruption of blood supply to those tissues (focal findings or seizures); obstruction of normal CSF flow pathways, increased intracranial pressure, and hydrocephalus (headache, nausea, vomiting, and dizziness); and interference with cognitive function (encephalopathy).

Diagnosis is made by MRI scanning or CSF analysis. Initial analysis of CSF demonstrates malignant cells in ~50% of affected patients; however, in nearly 10% of patients who have leptomeningeal involvement, the cytologic examination remains persistently negative.[134] Increasing the number of lumbar punctures (up to six) and the volume of CSF removed (10 mL per lumbar puncture) increases the yield of positive cytology. CSF analysis often demonstrates mild protein elevation, pleocytosis, and possible low glucose concentrations. Radiographic studies may demonstrate diffuse and/or nodular contrast enhancement of the leptomeninges or hydrocephalus without a mass lesion. More recently, the use of CSF advanced analyses (circulating tumor cells or cell-free DNA) is becoming incorporated into the assessment of patients. Their exact role is yet to be defined and validated.

In patients who have leptomeningeal disease from solid tumors, the median survival without therapy is typically short, often between 4 and 12 weeks, depending on the tumor type.[135] Death results from progressive neurologic dysfunction. Palliative care may be the most appropriate for patients who have poor performance status, significant neurologic dysfunction, and/or uncontrolled systemic disease. Corticosteroids and analgesics may offer limited temporary improvement. Radiation therapy, especially whole-brain radiation therapy, should be considered for the treatment of symptomatic sites. Ventriculoperitoneal shunting can be considered for palliative relief of refractory symptomatic hydrocephalus.

For patients who have minimal systemic disease, no significant neurologic deficits, and an acceptable performance status, a more aggressive approach may be considered. Unfortunately, no specific treatment has definitively demonstrated an improvement in OS. Imaging to assess for normal CSF flow should be considered before intrathecal therapy is given because blockage of flow by tumor deposits in the subarachnoid space reduces drug delivery and increases the risk of toxicity of intrathecal therapy. In the presence of CSF flow abnormalities, radiation therapy may be attempted to attain normal CSF flow. Radiation therapy may also be used to treat areas of bulky disease and other symptomatic sites. When available, proton craniospinal radiation therapy, which has an improved toxicity profile compared with photon craniospinal radiation therapy, is an option in selected patients who have a better prognosis and adequate functional status. This is based on a randomized phase 2 trial of proton craniospinal radiation therapy versus involved-field radiation therapy in 63 patients who have leptomeningeal disease from either breast cancer or non–small cell lung cancer, in which proton craniospinal radiation therapy improved both median CNS PFS (7.5 months vs. 2.3 months) and OS (9.9 months vs. 7.5 months) compared with involved-field radiation therapy with no difference in the rate of serious adverse effects.[136]

If CSF flow is normal, intrathecal chemotherapy or monoclonal antibodies, such as rituximab or trastuzumab, may provide some disease control in patients who have non-bulky leptomeningeal involvement of their cancer. Drugs can be administered intrathecally through an Ommaya reservoir or by repeated lumbar punctures, although certain drugs cannot be given by lumbar puncture because of toxicity.

For patients who have a systemic therapy option that has both efficacy against the primary tumor and a reasonable likelihood of CNS penetration or activity, systemic therapy can be offered. Key examples include osimertinib in *EGFR*-mutated non–small cell lung cancer or alectinib or lorlatinib in *ALK*-positive non–small cell lung cancer. Of note, leptomeningeal involvement

from hematologic malignancies may have a much better response to systemic (eg, high-dose methotrexate in secondary CNS lymphoma) and intrathecal chemotherapy.

KEY POINTS

- Leptomeningeal metastases are manifested by progressive symptoms and signs of injury to brain parenchyma, cranial nerves, and/or spinal nerves.
- Treatment of leptomeningeal metastases from solid tumors is often limited to symptom control. Radiation to symptomatic areas and, in select patient cases with symptomatic hydrocephalus, shunt placement may alleviate symptoms. Proton craniospinal radiation therapy, when available, should be considered for patients who have a better prognosis and adequate functional status.
- Intrathecal chemotherapy or systemic therapies can be offered to select patients.

COMPLICATIONS AND IMPORTANT SUPPORTIVE CARE AGENTS IN CNS TUMORS

CEREBRAL EDEMA

Corticosteroids, antiepileptic drugs, and anticoagulant drugs are important ancillary agents for the treatment of patients who have brain tumors. Corticosteroids are indispensable for controlling cerebral edema. Unfortunately, the long-term use of these agents can result in substantial toxic effects, including myopathy, hyperglycemia, peripheral edema, and Cushing syndrome. Dexamethasone is often the drug of choice because of its minimal mineralocorticoid activity and long half-life. Corticosteroids are generally recommended for temporary relief of symptoms and should be started at the minimum dose necessary and tapered as quickly as deemed possible, especially in asymptomatic patients. Patients on ≥4 mg of dexamethasone per day for at least 4 weeks should be given prophylaxis for pneumocystis jirovecii pneumonia. Bevacizumab may also be considered in select cases to control severe edema, including edema secondary to radiation necrosis.[137]

SEIZURES

Antiepileptic drugs are administered for the treatment of seizures. Clinical trials demonstrate that some antiepileptic agents, including phenytoin, phenobarbital, and carbamazepine, induce common hepatic enzyme systems, such as CYP450 enzymes. Induction of these enzymes results in decreased exposure to chemotherapy agents and other drugs metabolized by the same enzyme systems, including warfarin and small-molecule inhibitors. By contrast, valproate inhibits CYP450 and may reduce chemotherapy metabolism with a consequent increase in toxicity. Newer antiepileptic drugs, such as levetiracetam, zonisamide, lacosamide, lamotrigine, topiramate, and pregabalin, do not typically interact with current treatment regimens. These agents are preferred when feasible because they may help patients avoid the enzyme interactions previously noted.

Clinical trials have not demonstrated a discernible benefit for the use of routine prophylactic antiepileptic therapy for patients who have no history of seizures.[138] Similarly, no clear evidence supports the efficacy or lack of efficacy of antiepileptic therapy in the post-craniotomy setting.[138] Prospective randomized trials demonstrate a lack of efficacy of perioperative seizure prophylaxis[139]; however, the heterogeneity of included patients and the use of older antiepileptic agents in these trials have led to limited acceptance of these results. If antiepileptics are initiated perioperatively, current practice is to discontinue use after a few weeks. Patients who have had a seizure should generally continue to receive antiepileptic therapy indefinitely.

VENOUS THROMBOEMBOLISM

Clinically apparent venous thromboembolism or pulmonary emboli that require anticoagulation may occur in 20% to 30% of patients who have primary brain tumors. The reason for this high risk is likely multifactorial and includes hypercoagulability of malignancy as well as the immobility of many patients who have brain tumors. Presumably, the surgical injury of brain parenchyma also results in the release of procoagulant proteins that lead to a higher risk of thrombosis. Spontaneous bleeding during anticoagulation occurs in only 2% of patients who have malignant gliomas and does not seem to be higher than the rate seen in patients who are not treated with anticoagulants.[140] Low-molecular-weight heparin is generally considered more effective than warfarin in patients who have active malignancy.[141] Patients who have CNS tumors should receive anticoagulation for established venous thromboembolism as recommended for other patients who have cancer. Anticoagulation should be avoided in the setting of active intracranial bleeding (or especially hemorrhagic brain tumors), thrombocytopenia, or coagulopathy. Prospective clinical trials evaluating newer direct oral anticoagulants, including factor Xa inhibitors (eg, apixaban, edoxaban, rivaroxaban) and direct thrombin inhibitors (eg, dabigatran), have not yet conclusively assessed the safety of these drugs in patients who have brain tumors. However, accumulating retrospective data suggest that a direct oral anticoagulant is a reasonable alternative to low-molecular-weight heparin for patients who desire oral therapy; one large retrospective study demonstrated significantly lower rates of intracranial hemorrhage in patients who have glioblastoma-associated venous thromboembolism treated with direct oral anticoagulants compared with low-molecular-weight heparin.[142] Additional prospective clinical evaluation is warranted.

HIGH-YIELD TAKEAWAYS

- Surgical resection is the gold standard for diagnosis of primary CNS tumors, and testing for *IDH1/2* mutations and *MGMT* promoter methylation is critical for accurate diagnosis, treatment selection, and overall prognosis in glioma.
- Radiation and concomitant temozolomide followed by six cycles of temozolomide is the standard of care for *IDH*-WT glioblastoma and grade 4 *IDH*-mutant astrocytoma.
- Radiation followed by PCV is highly effective and is the standard of care for oligodendrogliomas (*IDH*-mutant, 1p/19q co-deleted) of all grades.
- A range of targeted therapies is increasingly available for metastatic CNS cancers and should be considered when appropriate.
- High-dose methotrexate-based chemotherapy has remained the backbone of therapy for newly diagnosed primary CNS lymphoma; autologous stem cell transplantation can be considered for consolidation in patients who have good functional status.
- Stereotactic radiosurgery is increasingly being used in addition to or in place of surgery for patients who have a single or a limited number of brain metastases.

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CENTRAL NERVOUS SYSTEM TUMORS

18

CHAPTER SUMMARY GUIDE

KEY POINTS

- Exposure to ionizing radiation is a well-established risk factor for primary CNS tumors.
- Most patients who have primary CNS tumors have no identifiable risk factor. The exceptions are patients who have a primary CNS tumor associated with one of the familial cancer syndromes, including neurofibromatosis type 1, Li-Fraumeni syndrome, Lynch syndrome, and familial adenomatous polyposis. Other, less common, inherited genomic risks are emerging.
- Immunodeficiency is a risk factor for primary CNS lymphoma.
- *IDH* mutations are central aspects of defining astrocytoma IDH mutant and oligodendroglioma, two types of adult diffuse gliomas.
- *IDH* mutations are most common in grade 2 and 3 gliomas but can also be seen in grade 4 astrocytomas.
- Regardless of grade, *IDH* mutations in glioma are associated with younger age, increased sensitivity to treatment, and comparatively favorable prognosis.
- Oligodendrogliomas are defined by the presence of both *IDH* mutation and 1p/19q codeletion and have improved response to chemotherapy and prognosis compared with other gliomas.
- Tumors that are *IDH* mutated without 1p/19q codeletion are referred to as astrocytoma, *IDH* mutant, and commonly harbor a mutation in *ATRX*.
- *BRAF* alterations, which may have an impact on available therapeutic options, occur in a range of CNS tumors, but at this time are not pathognomonic for any WHO CNS tumor type.
- According to the 2021 WHO Classification of Tumors of the CNS, glioblastoma is by definition *IDH* wild type.
- In glioblastoma, being MGMT promoter–methylated is both prognostic and predictive of the magnitude of benefit from temozolomide.
- The current standard of treatment of glioblastoma in patients younger than 70 years is maximal safe resection followed by radiation therapy with concurrent and adjuvant temozolomide, with consideration of tumor-treating fields.
- Phase 3 data also support the use of concurrent chemoradiotherapy in older adults based on the results of a trial with hypofractionated radiation therapy plus temozolomide versus treatment with hypofractionated radiation therapy alone.
- Pseudoprogression may mimic tumor progression in patients who have glioblastoma treated with radiation therapy and should be considered before switching therapy, especially in patients who have MGMT-methylated tumors.
- Tumor-treating fields are FDA approved for newly diagnosed and recurrent glioblastoma.
- Bevacizumab is effective as a steroid-sparing agent for symptom management in select patients who have glioblastoma, although evidence for improvement in OS is lacking.
- When detected in patients who have glioblastoma, *BRAF* V600E mutation, *TRK* fusion, and *RET* fusion are potentially actionable and can be targeted with drugs that have been granted accelerated approval by the FDA in a tissue-agnostic, genotype-specific manner.
- In the 2021 WHO Classification of Tumors of the CNS, all *IDH*-mutant diffuse astrocytic tumors are considered as a single entity (*IDH*-mutant astrocytoma) and are then graded as grade 2, 3, or 4. These tumors are 1p/19q non-codeleted.
- Initial treatment of grade 3 *IDH*-mutant astrocytomas is maximal safe resection followed by radiation therapy with chemotherapy. Adjuvant temozolomide provides a clear survival benefit, and concurrent temozolomide may be considered given the potential benefit and limited risk of harm.
- Grade 2 *IDH*-mutant astrocytomas can be indolent tumors; however, they tend to eventually progress to high-grade astrocytomas.
- Maximal safe resection is recommended, especially if a presumed glioma is large and/or symptomatic.
- The IDH inhibitor vorasidenib is an FDA-approved agent for grade 2, *IDH*-mutant astrocytomas following surgery.
- Radiation therapy with adjuvant chemotherapy (temozolomide or PCV) provides a clear survival benefit in grade 2 *IDH*-mutant astrocytoma regardless of whether treatment was administered just after diagnosis or at the time of tumor

progression. Definitive therapy may be deferred until radiographic or symptomatic progression occurs in individuals with positive prognostic factors (eg, complete resection, younger age) or who elect first-line IDH-inhibitor therapy.

- Oligodendroglial tumors are characterized by both *IDH* mutation and 1p/19q codeletion and have a more indolent course than astrocytomas.
- After surgery for debulking and maximal safe resection, patients who have WHO grade 3 *IDH*-mutant 1p/19q co-deleted oligodendroglioma should be offered radiation therapy in combination with PCV because the addition of PCV after radiation therapy significantly improves OS compared with radiation therapy alone. TMZ is a reasonable alternative to PCV when toxicity is a concern.
- For patients who have WHO grade 2 *IDH*-mutant 1p/19q co-deleted oligodendroglioma, maximal safe resection is recommended if the tumor is large and/or symptomatic.
- The IDH inhibitor vorasidenib is an FDA-approved agent for grade 2 oligodendroglioma before radiation therapy, though the effect on survival is unknown.
- Radiation therapy and adjuvant PCV provide a clear survival benefit in grade 2 *IDH*-mutant 1p/19q co-deleted oligodendroglioma; however, no clear OS advantage is seen with immediate postoperative radiation therapy compared with delayed radiation therapy. Definitive therapy may be deferred until radiographic or symptomatic progression in individuals with positive prognostic factors (eg, complete resection, younger age) or who elect first-line IDH-inhibitor therapy.
- Grade 1 astrocytomas are more common in children and young adults. Surgical resection is often curative.
- Everolimus is an FDA-approved agent for the treatment of SEGAs.
- Low-grade astrocytomas with *BRAF* V600E or *BRAF* rearrangements may be amenable to *BRAF*- or *MEK*-targeted therapy.
- Medulloblastomas typically occur in the cerebellum in children, but they can also present in adults.
- Treatment of medulloblastoma includes maximal safe resection followed by irradiation of the craniospinal axis (with a boost to the tumor bed). Platinum-based chemotherapy regimens are considered, especially in higher-risk patients, if post-radiation therapy blood cell counts permit.
- For many patients who have meningioma, observation is appropriate. For patients who are symptomatic, surgical removal of the tumor is the most common treatment.
- Meningiomas that are WHO grade 2 or 3 are rare but have a more aggressive course with recurrences that may require repeated resection and radiation therapy.
- Currently, systemic regimens have limited, if any, efficacy for the treatment of meningiomas.
- Surgery and/or radiation are definitive options for sporadic, isolated hemangioblastoma.
- For patients who have VHL-associated CNS hemangioblastoma, belzutifan represents an effective systemic treatment option.
- Primary CNS lymphomas are usually diffuse large B-cell lymphomas.
- Epstein-Barr virus is frequently associated with primary CNS lymphoma in immunocompromised individuals.
- When CNS lymphoma is considered in the differential diagnosis, corticosteroids should be held before biopsy, if clinically feasible, because they can lead to nondiagnostic biopsy results, which, in turn, can delay treatment.
- High-dose methotrexate-based chemotherapy has remained the backbone of therapy for newly diagnosed primary CNS lymphoma.
- Autologous stem cell transplantation can be considered for consolidation in patients who have good functional status and who respond to a methotrexate-based chemotherapy regimen.
- Brain metastases as a group are the most common brain tumors.
- Stereotactic radiosurgery is increasingly being used in addition to or in place of surgery for patients with brain metastases.
- When whole-brain radiation therapy is used for the treatment of brain metastases, the use of hippocampal avoidance intensity-modulated radiation therapy and memantine together has been demonstrated in a randomized trial to decrease the risk of neurocognitive toxicity.
- Small molecules and immunotherapies are increasingly used in the treatment of brain metastases from cancers in which the respective medications are effective systemically.
- Leptomeningeal metastases are manifested by progressive symptoms and signs of injury to brain parenchyma, cranial nerves, and/or spinal nerves.
- Treatment of leptomeningeal metastases from solid tumors is often limited to symptom control. Radiation to symptomatic areas and, in select patient cases with symptomatic hydrocephalus, shunt placement may alleviate symptoms. Proton craniospinal radiation therapy, when available, should be considered for patients who have a better prognosis and adequate functional status.
- Intrathecal chemotherapy or systemic therapies can be offered to select patients.

CHAPTER TABLES AND IMAGES

Table 18-1 Rare, Targetable CNS Tumors

Rare, Targetable Nervous System Tumors	Grade	Tumor Characteristics	Common Alterations	Targeted Therapy	References
Pilocytic astrocytoma	1	Primarily pediatric. Frequently appear as a cyst with a mural nodule in the cerebellum. Can be cured by surgery if removed completely	*KIAA1549-BRAF* fusion	Tovorafenib	2,74
Subependymal giant cell astrocytoma	1	Periventricular, 1:10 in patients who have tuberous sclerosis	*TSC1* or *TSC2*	Everolimus	75
CNS hemangioblastoma	1	Highly vascular, 25% associated with VHL	*VHL*	Belzutifan (for VHL-associated)	76
Plexiform neurofibroma	1	Occur on peripheral nerves and can undergo malignant transformation	*NF1*	Selumetinib (for NF1-associated)	77
Pleomorphic xanthoastrocytoma	2 or 3	Primarily adolescent and young adult, predilection for cerebrospinal fluid dissemination	*BRAF*	Dabrafenib/ trametinib	78
Diffuse midline glioma	4	Primarily pediatric	*K3K27M*	Dordaviprone	13

Abbreviations: CNS, central nervous system; VHL, von Hippel-Lindau.
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Table 18-2 **Key Systemic Agents With Intracranial Activity in Patients With Brain Metastases**

Primary Tumor	Drug(s)	Intracranial Response Rate(s) (95% CI) %	References
NSCLC, driver mutation negative, PD-L1 positive	Pembrolizumab	30 (16-47)	108
EGFR-mutant NSCLC	Osimertinib	91 (71-99)	109
ALK-rearranged NSCLC	Alectinib	81 (58-95)	110
	Brigatinib	78 (52-94)	111
	Lorlatinib	82 (57-96)	112
ROS1-positive NSCLC	Entrectinib	79 (60-93)	113
	Repotrectinib	89 (52-100)	60
RET-fused NSCLC	Selpercatinib	82 (57-96)	114
	Pralsetinib	70 (35-93)	115
MET exon-14 skipping mutation NSCLC	Capmatinib	54 (17-77)	116
	Tepotinib	55 (23-83)	117
KRAS G12C-mutant NSCLC	Adagrasib	42 (20-67)	118
	Sotorasib	25 (13-41)	119
Small cell lung cancer	Tarlatamab	63 (30-100)	128
HER2-positive breast cancer	Lapatinib and capecitabine	66 (50-80)	120
	Neratinib and capecitabine	49 (32-66)	121
	Tucatinib, capecitabine, and trastuzumab	47 (34-61)	122
	Fam-trastuzumab deruxtecan (T-Dxd)	46 (19-75)	123
Melanoma, *BRAF* V600E mutant	Dabrafenib and trametinib	58 (46-69)	124
Melanoma	Ipilimumab and nivolumab	54 (43-64)	125
	Pembrolizumab	22 (7-48)	126
	Nivolumab	20 (7-41)	127
Renal cell carcinoma	Cabozantinib	55 (36-73)	128
	Ipilimumab and nivolumab	32 (15-54)	129

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer.
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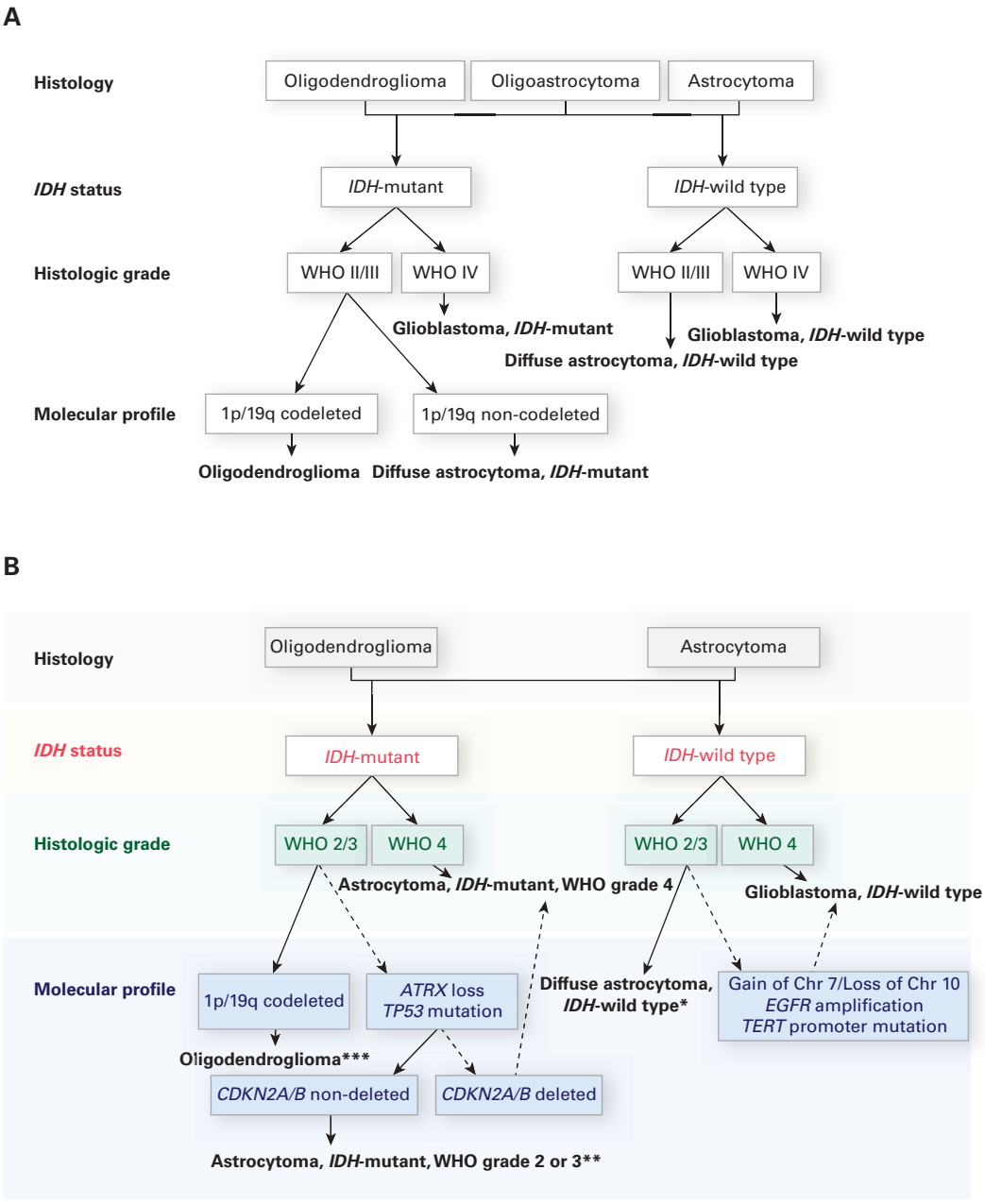
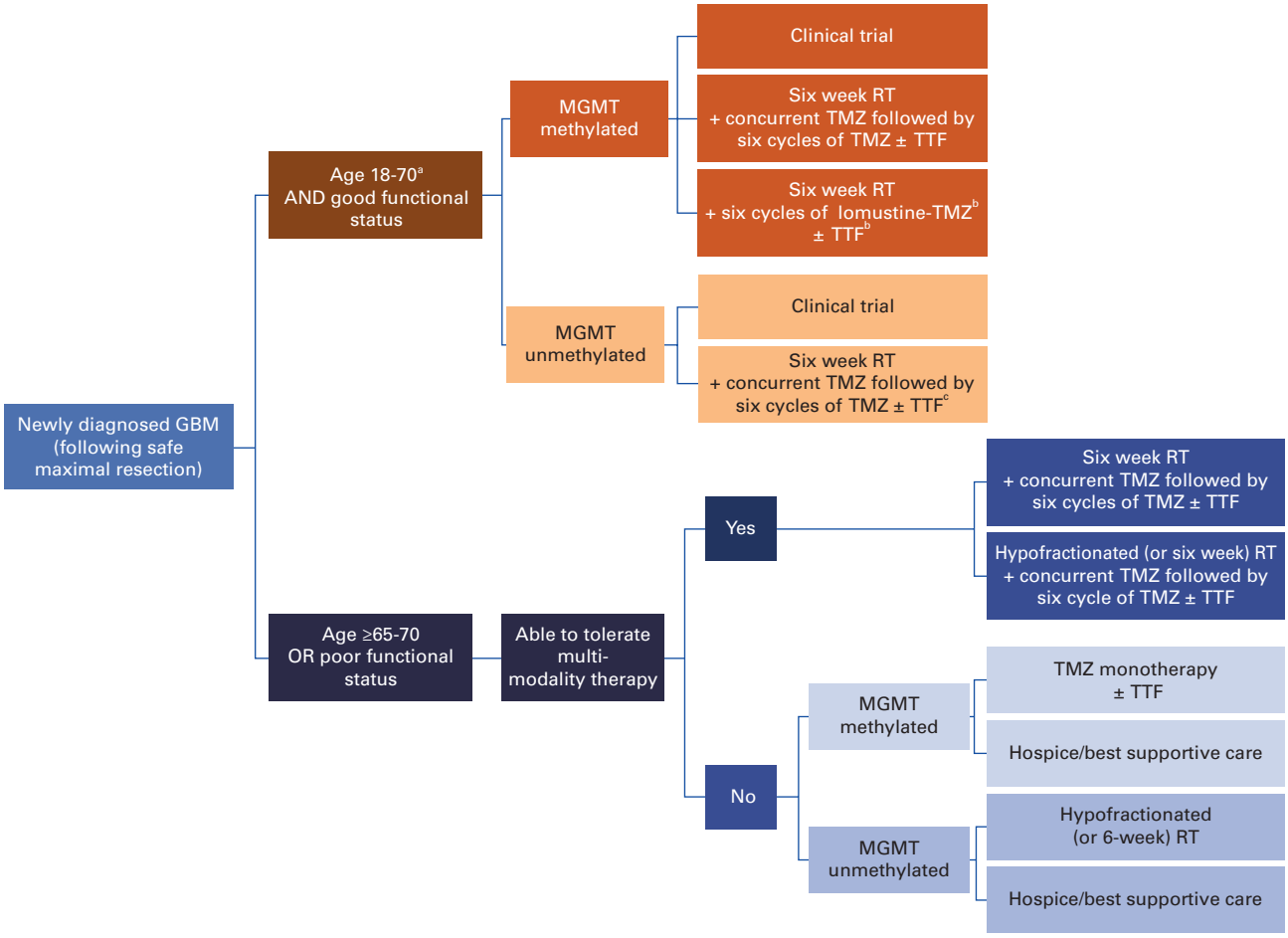
Figure 18-1 The Classification of Diffuse Gliomas



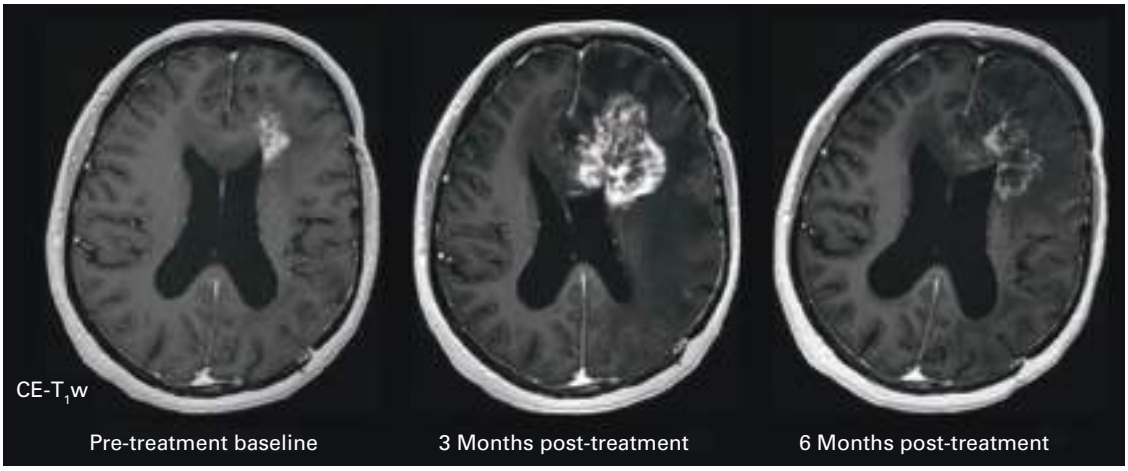
(A) WHO 2016. (B) WHO 2021.
Abbreviations: Chr, chromosome; CNS, central nervous system; *EGFR*, epidermal growth factor receptor.
Simplified diagnostic algorithm for adult diffuse gliomas based on the 2021 WHO classification of CNS tumors. Dashed lines denote changes compared with the 2016 WHO classification.
*Diffuse astrocytoma, *IDH* wild type without molecular features of glioblastoma, is a rare entity. Molecular testing for gain of *Chr* 7 and loss of Chr 10, *EGFR* amplification, and *TERT* promoter is required to exclude glioblastoma, *IDH* wild type, grade 4. In the absence of molecular features of glioblastoma, additional testing should be considered (eg, *BRAF* alterations, histone mutations, methylome profiling).
**Astrocytoma, *IDH* mutant, can be diagnosed as grade 2, 3, or 4 based on histopathologic grading criteria and *CDKN2A/B* status.
***Oligodendroglioma, *IDH* mutant with codeletion of the short arm of chromosome 1 and the long arm of chromosome (1p19q), can be diagnosed as grade 2 or 3 based on histopathologic features.
Reprinted by permission from Wiley Online Library: Gritsch S, Batchelor TT, Castro LN. Diagnostic, therapeutic, and prognostic implications of the 2021 World Health Organization classification of tumors of the central nervous system. *Cancer*. 2022;128(1):47-58. doi:10.1002/cncr.33918

Figure 18-2 Standard-of-Care Treatment Paradigm for Patients Who Have Newly Diagnosed or Recurrent Glioblastoma



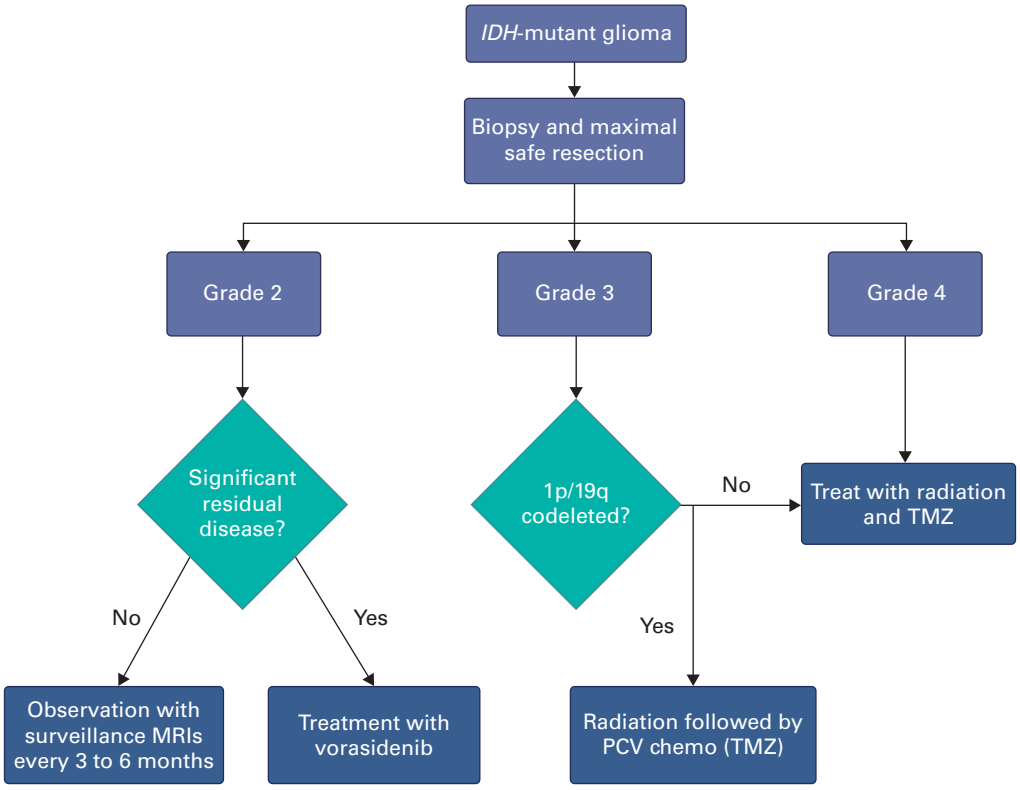
Abbreviations: GBM, glioblastoma; MGMT, O6-methylguanine-DNA methyltransferase; RT, radiation therapy; TMZ, temozolomide; TTF, tumor-treating fields.
[a]In elderly patients with good performance status, standard 6-week daily radiation therapy plus TMZ can be considered.
[b]It is unclear whether lomustine plus TMZ is preferred over TMZ alone.
[c]Because MGMT methylation status is predictive of the efficacy of TMZ, TMZ can be withheld in select patients who have MGMT-unmethylated tumors, especially in the context of clinical trials or when the risks of TMZ outweigh the benefits.
Reprinted from Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol*. 2020;22(8):1073-1113, by permission of Society for Neuro-Oncology and Oxford University Press.

Figure 18-3 Pseudoprogression Following Radiation in Glioblastoma



Abbreviations: CE, contrast-enhanced; T_1w, T_1-weighted.
Serial CE T_1w imaging showing an increase 3 months and spontaneous decrease 6 months after combined radiotherapy and temozolomide of contrast-enhancement, edema, and mass effect.
Reproduced under Creative Commons under the terms of the http://creativecommons.org/licenses/by-nc-nd/4.0/license. Source: Thust SC, van den Bent MJ, Smits M. Pseudoprogression of brain tumors. *J Magn Reson Imaging*. 2018;48(3):571-589. doi:10.1002/jmri.26171, figure 1.

Figure 18-4 Management of *IDH*-Mutant Glioma



Abbreviations: PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide.
For patients who have grade 2 *IDH*-mutant astrocytoma or oligodendroglioma, vorasidenib is approved in the first-line setting for patients following biopsy or resection. For patients who have oligodendroglioma (*IDH*-mutated, 1p/19q codeleted), radiation followed by PCV chemotherapy is also standard of care, but TMZ may be considered if toxicity is a concern. For patients who have grade 2 to 3 *IDH*-mutant astrocytoma, radiation with TMZ (12 cycles adjuvant, consider concurrent) can be used, although PCV may be considered. Patients who have grade 4 astrocytoma should be treated with radiation and concurrent TMZ as first-line therapy, followed by six cycles of adjuvant TMZ.
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LEUKEMIAS AND OTHER MYELOID NEOPLASMS

19

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RECENT UPDATES

The fifth edition of the World Health Organization (WHO) classification of hematolymphoid tumors and the first version of the International Consensus Classification (ICC) of myeloid neoplasms and acute leukemias were made available in 2022, and clinicians continue to optimize those classifications for diagnostic reporting and therapeutic decision-making.[1-3]

Acute Myeloid Leukemia

- Menin inhibition in patients who have acute myeloid leukemia (AML) with rearrangement of the *KMT2A (KMT2Ar)*, nucleoporin 98 (*NUP98r*) genes, or mutation of the nucleophosmin 1 gene (*NPM1*) was demonstrated to be safe and effective as monotherapy or in combination. Many menin inhibitor trials are ongoing in patients who have newly diagnosed and relapsed or refractory (relapsed/refractory) AML with *KMT2Ar*, *NUP98r*, or *NPM1* mutation.[4,5]
- Following the results of the AUGMENT-101 trial, the menin inhibitor revumenib was approved for relapsed or refractory acute leukemia with a *KMT2A* rearrangement or *NPM1* mutation.[6]
- Based on safety and efficacy demonstrated in the phase 1/2 KOMET-001 registration trial, ziftomenib was also approved for relapsed/refractory patients with *NPM1*-mutated AML.[7]
- The National Comprehensive Cancer Network (NCCN) guidelines now recommend gilteritinib, a *FLT3* inhibitor, as the preferred agent for post-transplant maintenance in patients with *FLT3*-ITD–mutated AML who are in first complete remission with measurable residual disease (MRD) by ultrasensitive peri-transplant assays. This recommendation is based on results from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1506 Morpho trial, which compared maintenance gilteritinib versus placebo post-transplantation and demonstrated a strong correlation between gilteritinib use and improved outcomes in patients with *FLT3*-ITD MRD detected by next-generation sequencing.[8]
- With observed limitations in European LeukemiaNet (ELN) genetic risk classifications from 2022 for older patients treated with less intensive therapies, new genetic risk classifications are offered by ELN 2024 for patients receiving less-intensive therapies, with *TP53* mutations defining the adverse risk group.[7,9]

Chronic Myeloid Leukemia

- Asciminib, an allosteric inhibitor of the myristoyl site of the BCR-ABL1 protein, was the first approved STAMP inhibitor for chronic-phase chronic myeloid leukemia (CP-CML) with resistance to at least two previous tyrosine kinase inhibitors (TKIs) and CP-CML with a *T315I* mutation.[10,11]
- Based on results of the ASC4FIRST trial, asciminib also received FDA approval for frontline use in newly diagnosed CP-CML.[12]

Myeloid Precursor Conditions (Clonal Hematopoiesis)

- With updates in the WHO 5th edition, clonal hematopoiesis is recognized for the first time as a category of precursor myeloid disease states, and clonal hematopoiesis of indeterminate potential and clonal cytopenia of undetermined significance are formally defined.[1]

- The clonal hematopoiesis risk score was published,[13] and it provided a simple and reproducible tool for assessing the risk of clonal hematopoiesis progressing to a myeloid malignancy. Based on clinical and molecular characteristics, patients with clonal hematopoiesis are categorized into three risk groups: low, intermediate, or high risk of progression to myeloid malignancy. Among clonal hematopoiesis risk score groups, the respective 5- and 10-year cumulative incidences of myeloid malignancy were 0.234% and 0.674% for low-risk, 2.59% and 7.34% for intermediate-risk, and 23.6% and 50.6% for high-risk myeloid malignancy, respectively.[13] Another score for clonal cytopenia of uncertain significance has also been developed.[14]

Myelodysplastic Syndromes

- Among the updates regarding myelodysplastic syndrome (MDS) classification is the novel entity MDS/AML in the ICC (but not recognized by the 2022 WHO classification), defined as 10% to 19% blasts in the peripheral blood and/or bone marrow in the absence of AML-defining recurrent genetic abnormalities. Specific emphasis is placed on genetically defined subtypes, such as MDS with deletion of 5q [del(5q)], MDS-SF3B1, and MDS with biallelic TP53 inactivation. Criteria for tp53 AML include blasts >10%, which is also not recognized by the classification system in the 2022 WHO. By contrast, hypoplastic MDS and MDS with fibrosis are formally included in the 2022 WHO but not recognized by the 2022 ICC.[1,3]
- A mutation-based risk assessment tool, the molecular International Prognostic Scoring System (IPSS-M), was published in 2022 and is the most accurate risk stratification tool.[15] It combines the prognostic impact of 31 gene mutations with traditional predictors (eg, blood counts, blast percentage, and karyotype) and improves prognostication compared with the revised IPSS (IPSS-R).
- In a phase 3 clinical trial in lower-risk MDS, decitabine given on days 1 to 3 of a 28-day cycle led to red blood cell transfusion independence and complete response (CR) in 41% and 36% of patients, respectively.[16] Luspatercept was approved as of August 28, 2023, for first-line treatment of anemia in adults with very low-risk to intermediate-risk MDS who are red cell transfusion-dependent. It had previously been approved in 2019 for use in patients with MDS after erythropoiesis-stimulating agents (ESA) failure, and or if there was a low likelihood of response due to erythropoietin level (>500). This expanded approval was based on results from the phase 3 COMMANDS trial. Luspatercept resulted in increased transfusion independence and increased hemoglobin levels compared with erythropoietin. This benefit was not demonstrated in MDS patients without ring sideroblasts (this subset showed equal response rates).[17]
- Hypomethylating-agent monotherapy with azacitidine or decitabine remains the standard of care for patients who have higher-risk MDS. To date, no phase 3 trials have demonstrated a benefit for adding an additional agent to azacitidine or decitabine. One of the most recent studies, the VERONA trial (NCT04401748), examined azacitidine with placebo versus azacitidine plus the Bcl-2 inhibitor, venetoclax, which fell short of meeting its primary clinical endpoint of overall survival (OS). Concerns about more frequent dose reductions of azacitidine in the combination arm as compared to the placebo arm may be a significant contributor to the outcome of this study (reference GGManero SOHO 2025).[18,19]
- On October 24, 2023, ivosidenib monotherapy was approved by the FDA for patients who have relapsed/refractory MDS based on data from the AG120-C-100 trial. The CR rate in 18 patients who had relapsed/refractory MDS was 38.9%, and the median duration of CR was not estimable (1.9-81 months).[20]
- Imetelstat, an oligonucleotide telomerase inhibitor, was approved by the FDA on June 6, 2024, for adults with low-to-intermediate-1 risk MDS for treatment of anemia in patients who had required four or more red cell transfusions over 2 months or who had not responded to ESAs. This was based on the IMerge randomized, double-blind, placebo-controlled trial in 178 patients. The rate of 8-week transfusion independence was 39.8% in the imetelstat group and 15% in the placebo group.[21]

Myeloproliferative Neoplasms

- In the WHO 5th edition, the main types of myeloproliferative neoplasms (MPNs) remain unchanged from the previous edition; however, there are several changes for the MDS/MPN overlap syndromes. Chronic myelomonocytic leukemia diagnostic criteria underwent major revisions, including lowering the cutoff for absolute monocytosis, adopting myelodysplastic and myeloproliferative subtypes, and eliminating the chronic myelomonocytic leukemia category 0. Atypical chronic myelomonocytic leukemia was renamed MDS/MPN with neutrophilia. MDS/MPN

with ring sideroblasts and thrombocytosis was redefined on the basis of an SF3B1 mutation and renamed MDS/MPN with SF3B1 mutation and thrombocytosis. Luspatercept is FDA approved for the treatment of anemia in adult patients with MDS/MPN-RS-T who require regular transfusions.[1]

- In November 2023, the FDA approved momelotinib for the treatment of intermediate- or high-risk myelofibrosis. This was based on the MOMENTUM study and a subset of patients who had anemia from the SIMPLY-1 phase 3 trial.[22,23]

Acute Lymphoblastic Leukemia

- The randomized phase 3 ECOG-ACRIN E1910 study demonstrated that blinatumomab added to conventional post-remission therapy significantly improved OS (median OS, not reached vs 71.4 months; hazard ratio [HR], 0.42; 95% CI, 0.24-0.75; two-sided $P = .003$) and recurrence-free survival (RFS) for patients who have newly diagnosed B-cell acute lymphoblastic leukemia (ALL) in MRD-negative first complete remission, leading to FDA approval for blinatumomab in this setting.[24]
- On March 19, 2024, the FDA approved ponatinib in adult patients who have newly diagnosed Philadelphia chromosome–positive (Ph+) ALL for use in combination with chemotherapy. This was based on the phase 3 PhALLCON trial.[25]
- Based on results of the FELIX trial, obecabtagene autoleucel is now approved for relapsed/refractory B-cell precursor ALL in adults.[25]
- With promising long-term results of the D-ALBA trial exploring dasatinib with blinatumomab and similarly positive results from a single institution phase 2 trial of ponatinib with blinatumomab, the chemotherapy-free regimen of tyrosine kinase inhibitor and blinatumomab is an offered induction strategy for Ph+ ALL in the NCCN guidelines.[26,27]

Chronic Lymphocytic Leukemia

- A phase 3 study comparing acalabrutinib with ibrutinib for patients who have treatment-naive chronic lymphocytic leukemia (CLL) showed acalabrutinib to be noninferior to ibrutinib for progression-free survival (PFS) but with reduced rates of atrial fibrillation (9.4% vs 16.0%; $P = .02$).[28] The acalabrutinib/enetoclax combination with or without obinutuzumab for 14 cycles was found to significantly prolong PFS compared with chemoimmunotherapy in fit patients who had not had prior CLL treatment in the AMPLIFY study.[29] A randomized trial of ibrutinib versus fixed-duration venetoclax and obinutuzumab or fixed-duration venetoclax and ibrutinib has now been published as an abstract, and this demonstrated noninferiority of the fixed-dose combinations.[30]
- The phase 3 SEQUOIA trial randomly assigned adults with treatment-naive CLL without del(17p)/*TP53* mutation to receive zanubrutinib or bendamustine and rituximab. PFS was superior for zanubrutinib (HR, 0.29 one-sided $P = .0001$). For the del(17p)/*TP53*-mutated arm that was not randomly assigned, 24-month PFS was 92% with zanubrutinib.[31,32]
- Update of a phase 3 study comparing zanubrutinib with ibrutinib for relapsed/refractory CLL showed zanubrutinib to be superior to ibrutinib for PFS and OS rates.[33]
- Lisocabtagene maraleucel (liso-cel), a CD19-directed chimeric antigen receptor T-cell therapy, was approved for use in patients who have CLL with previous exposure to both Bruton tyrosine kinase inhibitors and anti-BCL-2, based on the TRANSCEND CLL 004 study. The CR rate was 18%, and the median duration of response in all responders was 35.3 months.[34]

Hairy Cell Leukemia

- A phase 2 study of ibrutinib in relapsed classic and variant hairy cell leukemias showed a best overall response rate of 54% and 3-year PFS and OS rates of 73% and 85%, respectively.[35]
- A phase 2 study of the BRAF inhibitor vemurafenib and rituximab in relapsed/refractory hairy cell leukemia showed a complete response rate of 87% (65% MRD negative) and an RFS rate of 85% at a median follow-up of 34 months.[36]

OVERVIEW

The term *leukemia* describes a number of related cancers characterized by increased growth and/or impaired maturation of the blood-forming organs. Leukemias are classically defined by their rapidity of growth (acute vs chronic) and by the origin of the normal cell the leukemia most resembles (myeloid vs lymphoid). Thus, the four major forms of leukemia are acute myeloid

leukemia (AML), acute lymphoid leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphoid leukemia (CLL). Other leukemias include some of the mature B-cell, T-cell, or natural killer (NK)–cell neoplasms, such as hairy cell leukemia and chronic T-cell leukemias. Approximately 66,890 new cases of leukemia were expected in the United States in 2025, with 23,540 leukemia-related deaths.[37,38]

In addition to these four major forms of leukemia, in this chapter, we also discuss myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs), which, together with AML, encompass disorders the World Health Organization (WHO) has classified as myeloid neoplasms. MDS encompasses a heterogeneous group of clonal stem cell disorders characterized by peripheral blood cytopenias and an inherent tendency toward transformation to AML. MPNs are clonal stem cell diseases with excess proliferation of one or more hematopoietic cell lineages. In addition to CML, the classic MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (MF).[1] Chronic neutrophilic leukemia, chronic eosinophilic leukemia, and unclassifiable MPNs are other diseases currently recognized by WHO as MPNs.

In 2022, the WHO 5th edition classification of hematolymphoid tumors was released,[1,2] providing several key updates for leukemias and other myeloid neoplasms (Tables 19-1 and 19-2). Simultaneously, the International Consensus Classification (ICC) of myeloid neoplasms and acute leukemias was also published, providing mostly overlapping but occasionally conflicting disease definitions.[3] Updates to disease definitions are discussed in each respective disease section.

Table 19-1 2022 WHO Classification of AML[1,2]

Type of Leukemia	Classification
AML	
With defining genetic abnormalities	APL with *PML::RARA* fusion
	AML with *RUNX1::RUNX1T1* fusion
	AML with *CBFB::MYH11* fusion
	AML with *DEK::NUP214* fusion
	AML with *RBM15::MRTFA* fusion
	AML with *BCR::ABL1* fusion
	AML with *KMT2A* rearrangement
	AML with *MECOM* rearrangement
	AML with *NUP98* rearrangement
	AML with *NPM1* mutation
	AML with *CEBPA* mutation
	AML, myelodysplasia-related
	AML with other defined genetic alterations
Defined by differentiation	AML with minimal differentiation
	AML without maturation
	AML with maturation
	Acute basophilic leukemia
	Acute myelomonocytic leukemia
	Acute monocytic leukemia
	Acute erythroid leukemia
	Acute megakaryoblastic leukemia
Acute leukemia of ambiguous lineage	
With defining genetic abnormalities	Mixed-phenotype acute leukemia with *BCR::ABL1* fusion
	Mixed-phenotype acute leukemia with *KMT2A* rearrangement
	Acute leukemia of ambiguous lineage with other defined genetic alterations
	• Mixed-phenotype acute leukemia with *ZNF384* rearrangement
	• Acute leukemia of ambiguous lineage with *BCL11B* rearrangement
Immunophenotypically defined	Mixed-phenotype acute leukemia, B/myeloid
	Mixed-phenotype acute leukemia, T/myeloid

Type of Leukemia	Classification
	Mixed-phenotype acute leukemia, rare types
	Acute leukemia of ambiguous lineage, NOS
	Acute undifferentiated leukemia
B-lymphoblastic leukemia/lymphoma	
	B-lymphoblastic leukemia/lymphoma, NOS
	B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
	B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
	B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
	B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
	B-lymphoblastic leukemia/lymphoma with hyperdiploidy
	B-lymphoblastic leukemia/lymphoma with hypodiploidy
	B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*
	B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
	Provisional entity: B-lymphoblastic leukemia/lymphoma, *BCR-ABL1*-like
	Provisional entity: B-lymphoblastic leukemia/lymphoma with *iAMP21*

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocyte leukemia; NOS, not otherwise specified; WHO, World Health Organization.
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Table 19-2 **Tests and Procedures for Patients With AML**[39]

Test	Procedure
Diagnostic tests	CBC and differential count
	Bone marrow aspirate
	Bone marrow trephine biopsy
	Immunophenotyping, flow cytometry, next-generation sequencing for myeloid mutation panel, and RNA gene re-expression
Genetic analyses	Cytogenetics[a]
	Screening for these gene mutations[b]: *NPM1*, *CEBPA*, *IDH1*, *IDH2*, *FLT3*, *TP53*, *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*, *DDX41*
	Screening for these gene rearrangements: *PML-RARA*, *CBFB-MYH11*, *RUNX1-RUNX1T1*, *BCR-ABL1*, other fusion genes (if available)
Additional tests/procedures at diagnosis	Demographics and medical history[c]
	Detailed family history[d]
	Patient bleeding history[e]
	ECOG performance status
	Analysis of comorbidities
	Biochemistry, coagulation tests, urine analysis[f]
	Serum pregnancy test[g]
	Information on oocyte and sperm cryopreservation[h]
	Eligibility assessment for allo-SCT (including HLA typing)[i]
	Hepatitis A, B, C; HIV-1 testing
	Chest radiograph, 12-lead electrocardiogram, and echocardiography or MUGA (on indication)
	Lumbar puncture[j]
	Biobanking[k]

Test	Procedure
Sensitive assessment of response to treatment (MRD) by RT-qPCR or MFC[l]	RT-qPCR[m,n] for *NPM1* mutation, *CBFB-MYH11*, *RUNX1-RUNX1T1*, *BCR-ABL1*, other fusion genes (if available)
	MFC[n,o]

Abbreviations: allo-SCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; CBC, complete blood count; ECOG, Eastern Cooperative Oncology Group; HLA, human leukocyte antigen; MFC, multiparameter flow cytometry; MRD, measurable residual disease; MUGA, multigated acquisition (scan); RT-qPCR, reverse transcription quantitative polymerase chain reaction.
[a]Results from cytogenetics should be obtained preferably within 5 to 7 days. At least 20 bone marrow metaphases are needed to define a normal karyotype and are recommended to describe an abnormal karyotype. Abnormal karyotypes may sometimes be diagnosed from blood specimens.
[b]Results from *NPM1* and *FLT3* mutational screening should be available within 48 to 72 hours (at least in patients eligible for intensive chemotherapy), along with results from additional molecular genetics within the first treatment cycle. Screening for gene mutations is an evolving field of research; screening for single genes is now frequently replaced by gene panel diagnostics.
[c]Including race or ethnicity, previous exposure to toxic agents, previous malignancy, therapy for previous malignancy, and information on smoking.
[d]Thorough family history is needed to identify potential myeloid neoplasms with germline predisposition.
[e]History of bleeding episodes may inform cases of myeloid neoplasms with germline predisposition and preexisting platelet disorders.
[f]Biochemistry: levels of glucose, sodium, potassium, calcium, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin, urea, total protein, uric acid, total cholesterol, total triglycerides, and creatinine phosphokinase. Coagulation tests: prothrombin time; international normalized ratio, where indicated; activated partial thromboplastin time. Urine analysis: pH, and levels of glucose, erythrocytes, leukocytes, protein, and nitrite.
[g]In women with childbearing potential.
[h]Cryopreservation to be done in accordance with the wishes of the patient.
[i]HLA typing and cytomegalovirus testing should be performed in those patients eligible for allo-SCT.
[j]Required in patients who have clinical symptoms suspected of central nervous system involvement; the patient should be evaluated by an imaging study for intracranial bleeding, leptomeningeal disease, and mass lesion; lumbar puncture is considered optional in other settings (eg, high white blood cell count).
[k]Pretreatment leukemic bone marrow and blood samples for research studies are recommended.
[l]Sensitive assessment of response can be performed at early time points, for example, after induction and consolidation courses to assess remission status and determine kinetics of disease response, and sequentially beyond consolidation to detect impending morphologic relapse. No generally applicable time points can be defined because the kinetics of MRD response differ by treatment given, marker analyzed, and method used.
[m]Monitoring of response by RT-qPCR is recommended in clinical trials and clinical practice.
[n]Sensitivity of response assessment varies by method used and by marker tested; the test used and sensitivity of the assay should always be reported; analyses should be done in experienced laboratories (centralized diagnostics).
[o]Increasing evidence that response assessment by multiparameter flow cytometry qualitatively provides a better remission status than morphologic assessment and is of high prognostic value.
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ETIOLOGY

The cause of leukemia is usually unknown. However, in addition to a familial or genetic predisposition in some individuals, exposure to certain infectious pathogens, radiation, chemicals, and chemotherapeutic agents has been associated with an increased incidence of leukemia.

GENETIC PREDISPOSITION

Genetic predisposition for the development of leukemia is well established. Single germline mutations in several genes (eg, *GATA2*, *RUNX1*, *CEBPA*, *DDX41*, *TP53*, and *SRP72*) have been identified as causes of familial nonsyndromic MDS/AML predisposition syndromes.[40] Syndromes characterized by defective DNA repair, such as Fanconi anemia, ataxia telangiectasia, and Bloom syndrome, also have an increased incidence of acute leukemia. Similarly, bone marrow failure syndromes associated with ribosomal abnormalities, including Diamond-Blackfan anemia and Schwachman-Diamond syndrome, and disorders of telomere maintenance, such as dyskeratosis congenita, also have an increased incidence of AML and MDS. It seems that the prevalence of germline predisposition for AML and MDS has long been underestimated, given that only some patients present with typical syndromic findings on physical examination. For instance, a recent large analysis of adult patients who have MDS showed that 2.7% were found to have a mutation in the telomerase reverse transcription (*TERT*) gene without carrying a previous clinical diagnosis of a telomere biology disorder.[41]

RADIATION

Ionizing radiation is leukemogenic. The incidences of AML, CML, and ALL increased in individuals who received radiation therapy for ankylosing spondylitis and in survivors of the atomic bomb blasts at Hiroshima and Nagasaki.[42] The highest rates of leukemia were associated with higher doses of radiation, particularly if the radiation was absorbed over a shorter time. Younger individuals seem to be more susceptible to the leukemogenic effects of radiation. The incidence of leukemia peaks between 5 and 10 years after radiation exposure, regardless of patient age.

CHEMICALS

Extensive occupational exposure to benzene and benzene-containing compounds may lead to marrow damage that eventually can manifest as aplastic anemia, MDS, or AML. Benzene is widely used in industry, particularly as a starting material

for chemicals used to make plastics, resins, synthetic fibers, dyes, detergents, drugs, and pesticides, and it is a component of crude oil, gasoline, and cigarette smoke. Other associations between occupational exposure to chemicals and subsequent leukemia are not as persuasive. Most studies have found a small but consistent increase in the development of AML among cigarette smokers.[43]

THERAPY-RELATED LEUKEMIAS

Therapy with antineoplastic agents is a major identifiable cause of acute leukemia, with alkylating agents being most commonly associated with therapy-related leukemia. Among the various alkylating agents, melphalan (frequently used in autologous stem cell transplantation [ASCT]) and the nitrosoureas seem to be particularly associated with increased risk; however, all alkylating agents are likely leukemogenic, with an increased incidence of leukemia observed after prolonged exposure and dose-intensive regimens.

The leukemias associated with alkylating agents often present initially as MDS before progressing to AML; they have no other distinct morphologic features and, on cytogenetic examination, frequently exhibit whole or partial loss of chromosomes 5 or 7 or, less often, trisomy 8. These leukemias typically develop 5 to 7 years after chemotherapy.

Patients treated with topoisomerase II inhibitors are also at risk for therapy-related leukemia. In contrast to leukemias associated with alkylating agents, disease caused by topoisomerase II inhibitors tends to have a shorter latency period (1-3 years), lacks a myelodysplastic phase, carries a monocytic morphology, and frequently involves 11q23.3 abnormalities; less commonly, translocations of 21q22 are involved. Acute promyelocytic leukemia (APL) has been associated with previous exposure to leukemogenic agents as well. A growing body of evidence also suggests that some cases of ALL are related to previous treatments with chemotherapy or radiation therapy.[44] As the use of chimeric antigen receptor (CAR) T-cell therapy increases, some cases of second primary myeloid neoplasms have been identified,[45,46] although ongoing investigation is needed regarding the actual incidence or any identifiable risk factors.

ONCOGENIC VIRUSES

Human T-cell lymphotropic virus type 1 is a causative agent of adult T-cell leukemia and lymphoma. This enveloped single-stranded RNA virus is found in patients in geographic clusters in southwestern Japan, the Caribbean, intertropical Africa, the Middle East, South America, and Papua New Guinea. It spreads horizontally by sexual contact or through blood products or vertically from mother to fetus. Although it is endemic in these geographic areas, adult T-cell leukemia develops in only 3% to 5% of patients infected with the virus, and it has a long latency period, estimated to be 30 years or more.[47] Epstein-Barr virus is associated with the endemic African form of Burkitt lymphoma and leukemia.[48] The immunodeficiency-related type of Burkitt lymphoma is seen most often in patients who have HIV infection and is more common when the CD4 T-cell count is greater than 200/mcL, that is, early in the progression of HIV infection. The association of HIV with the endemic form of Burkitt lymphoma is less clear.[49]

Overall, approximately 50% of patients who have therapy-related neoplasms have adverse cytogenetics, and approximately one-third have *TP53* mutations, which partly explains why these neoplasms tend to have lower therapeutic response rates than *de novo* disease.[50]

KEY POINTS

- Leukemias, MDSs, and MPNs encompass a diverse group of clonal diseases of the hematopoietic system.
- Familial or genetic predisposition and exposure to certain infectious pathogens, radiation, chemicals, and therapeutic agents have been associated with an increased incidence of these hematopoietic neoplasms.

ACUTE MYELOID LEUKEMIA

PATHOGENESIS

AML is a clonally derived hematologic malignancy that originates from an aberrant hematopoietic stem cell that has an increased capacity for self-renewal and profoundly altered patterns of differentiation. The current understanding is that disturbed gene expression in hematopoietic stem cells causes a differentiation block and increased self-renewing capacity, which gives rise to a leukemic stem cell. The clonal evolution of AML starts from the leukemic stem cells, in which founder or so-called driver mutations arise that initiate the leukemogenesis process, but lack the entire arsenal of mutations required for leukemogenesis. Genes such as *DNMT3A*, *TET2*, and *ASXL1* involved in the regulation of DNA modification and the chromatin state are present in the preleukemic stem and progenitor cells.[51-53] Progression to AML is accompanied by a stepwise accumulation of additional mutations and sometimes chromosomal abnormalities, including those assumed to be part of the pathogenesis of the disease (the drivers) and random mutations (so-called passengers) that confer a strong proliferative advantage to the leukemic stem cells and the blasts derived therefrom. The acquisition of individual mutations and subsequent clonal evolution are highly dynamic

processes. This is indicated by studies of relapsed AML, in which typically either the founding clone gained additional mutations and evolved into the relapsed clone or a subclone present at diagnosis survived chemotherapy, acquired additional mutations, and expanded at relapse.[48,54] Although debulking chemotherapy helps reduce the percentage of blasts and may cure AML, newer targeted therapies are often directed toward the mutations that ensure the survival and proliferative advantage of the leukemic stem cells, possibly increasing cure rates.

Advancements in genomic profiling have expanded our understanding of AML and transformed treatment approaches.[55] These findings, along with the development of targeted therapy, allow for the reclassification of disease subgroups by AML-related genetic changes, inform treatment decisions (eg, use of FLT3 and IDH1/2 inhibitors), and provide clues for the ordinal nature of mutations (eg, *DNMT3A* followed by *NPM1* and another AML disease allele).

CLINICAL PRESENTATION AND DIAGNOSIS

Fatigue, bruising, bleeding, fever, and infection are common presentations reflecting a state of bone marrow failure. Ten percent of patients present with white blood cell (WBC) counts greater than 100×10^9/L and are at an increased risk of tumor lysis syndrome and leukostasis. Leukostasis may manifest as altered mental status, dyspnea, and chest pain.[56] These are medical emergencies that need to be recognized immediately, and treatment should be instituted promptly.

Other physical findings may include organomegaly, lymphadenopathy, and infiltration of extramedullary sites, including gingiva, skin (leukemia cutis), and soft tissue (chloromas or myeloid sarcomas), by leukemic cells, and this is more common in monocytic variants. A consumptive coagulopathy resembling disseminated intravascular coagulation is a common presentation in APL (see "Acute Promyelocytic Leukemia" section for more details), but may occur in other types of AML as well.

The major signs and symptoms of AML result from decreased normal hematopoiesis because of bone marrow involvement and infiltration of organs by leukemic blasts. The WBC count may be elevated, normal, or low, but most patients will have granulocytopenia, placing them at risk for severe bacterial and fungal infections.

Examination of the peripheral blood and a bone marrow aspirate are part of the routine diagnostic workup for a patient who has suspected AML and evaluation for morphology consistent with APL.[57] A lumbar puncture is required for patients who have clinical symptoms that suggest central nervous system (CNS) involvement. Before a lumbar puncture, brain imaging should generally be performed in patients who are symptomatic to assess for possible mass lesions. Cytogenetics and fluorescence in situ hybridization (FISH), as well as molecular studies, are essential for risk stratification. At a minimum, testing for mutations in *c-KIT*, *FLT3*-ITD/tyrosine kinase domain (TKD), *NPM1*, *CEBPA*, *IDH1*, *IDH2*, *ASXL1*, *RUNX1*, and *TP53* should be obtained. Multiplex gene panels and next-generation sequencing (NGS) analysis should be used to obtain a more comprehensive prognostic assessment when possible (Table 19-2).[58]

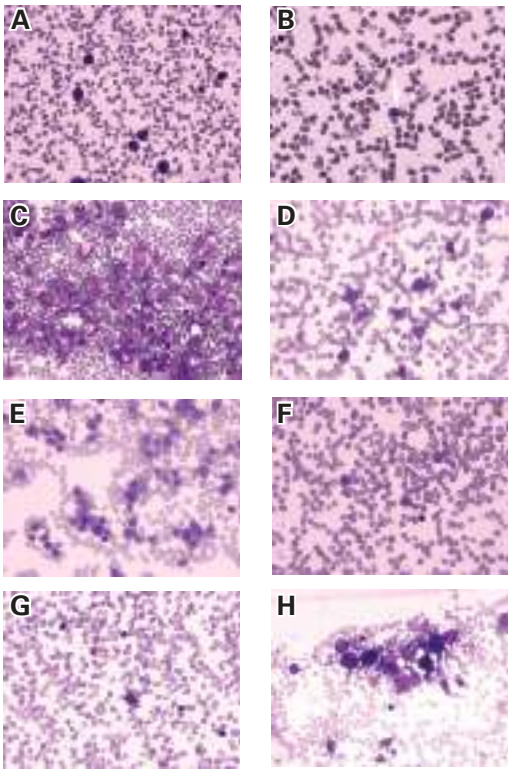
Historically, a myeloid neoplasm was classified as AML if 20% or more blasts were present in the peripheral blood or bone marrow.[59] The 2022 WHO classification and the 2022 ICC were recently introduced.[1,3,60] Although the 20% blast threshold was retained by the 2022 WHO classification, the 2022 ICC introduced a new category of MDS/AML with 10% to 19% blasts in the bone marrow or peripheral blood in recognition of the similarities in biology and prognosis between these patients and those with 20% or more myeloblasts.[1,3]

In the 2016 WHO classification, exceptions to the 20% or more blast cutoff rule included neoplasms with translocation of chromosomes 8 and 21 [t(8;21)](q22;q22.1)], inversion of chromosome 16 [inv(16)](p13.1q22), t(16;16)(p13.1;q22)], or APL, which are considered AMLs regardless of the blast percentage.[59] The 2022 WHO classification and 2022 ICC broadened the genetic abnormalities that define specific AML groups and recognized both *NPM1* and *CEBPA* as AML-defining mutations. Although ICC recognizes *TP53* (Variant allele frequency [VAF] > 10%)-mutated AML as a distinct entity, WHO does not.[1,3] In addition, AML with *BCR*::*ABL1* was added as a formal AML-defining lesion with the requirement of blasts of 20% or more, and not 10% or more, to differentiate it from CML in the accelerated phase. Importantly, the WHO classification and ICC use different blast thresholds to define AML. Although there is no minimum threshold in the 2022 WHO criteria for AML with defining genetic abnormalities (except 20% required for AML with *BCR*::*ABL1* and AML with a *CEBPA* bZIP [basic leucine zipper] mutation), the ICC requires at least 10% blasts in the bone marrow or peripheral blood for defining AML with recurrent genetic abnormalities (except 20% or more in AML with *BCR*::*ABL1*).[3]

Morphology and Immunohistochemistry

AML cells are typically 12 to 20 mm in diameter and have fine nuclear chromatin, multiple nucleoli, and azurophilic granules in the cytoplasm (Fig. 19-1). Specific patterns of reactivity with immunohistochemical stains, particularly myeloperoxidase (MPO) and nonspecific esterase, can be used to assign AML blasts to one (or more) cell lineage(s). Although the French-American-British Cooperative Group classified AML on the basis of morphology and immunohistochemistry, cytochemical stains have largely been replaced by immunophenotypic analyses of AML cells. Auer rods are coarse linear collections of cytoplasmic granules that sometimes obscure the nuclei that can be seen in AML blasts and are especially common in APL.

Figure 19-1 Morphologic Spectrum of AMLs



(A) Acute myeloblastic leukemia (AML) with minimal maturation. The cells are myeloblasts with dispersed chromatin and variable amounts of agranular cytoplasm; some display medium-sized, poorly defined nucleoli. (B) AML with maturation. Some of the blasts contain azurophilic granules, and there are promyelocytes. Note the Auer rod (arrow). (C) Acute promyelocyte leukemia. All of these cells are promyelocytes containing coarse cytoplasmic granules that sometimes obscure the nuclei. (D) Acute myelomonocytic leukemia. Promonocytes with indented nuclei are present with myeloblasts; the dense nuclear staining is unusual. (E) Acute monoblastic leukemia. These characteristic monoblasts have round nuclei with delicate chromatin and prominent nucleoli that stain intensely with nonspecific esterase (not shown); cytoplasm is abundant. (F) Acute monocytic leukemia. Most of the cells in this field are promonocytes; monoblasts and an abnormal monocyte are also present. (G) Acute erythroid leukemia. Dysplastic multinucleated erythroid precursors with megaloblastoid nuclei are present. (H) Acute megakaryoblastic leukemia. In this marrow biopsy specimen, there are large and small blasts as well as atypical megakaryocytes. Photographs and permission provided by Dr. Farid Barakat.
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Immunophenotype

Most cases of AML express antigens characteristic of neutrophilic or monocytic differentiation, including precursor cell markers, such as CD34, CD117, CD33, CD13, and HLA-DR, and granulocytic markers, such as MPO and CD65. Leukemias with monocytic features express CD14 together with other monocyte-associated antigens, such as CD36 and CD64. Erythroid leukemias frequently express CD36, CD71, and CD235a (glycophorin A), whereas megakaryocytic leukemias express CD41 and CD61. In 10% to 20% of cases, the AML blasts also express lymphoid antigens, which are usually restricted to B-, T-, or NK-cell lineages, especially CD2, CD7, CD19, and CD56.

PROGNOSTIC FACTORS

AML is heterogeneous, and responses to AML therapy vary substantially among individual patients. An accurate risk stratification of the patient's disease is essential to make an informed decision on the treatment strategy for each patient.

Multiple factors have been independently associated with not achieving remission with intensive chemotherapy and/or with experiencing shortened survival. These include older age, poor performance status, previous cytotoxic chemotherapy or radiation therapy (ie, therapy-related AML), and disease evolution from an antecedent hematologic disorder (ie, secondary AML). By contrast, extramedullary disease, although common, is not an independent prognostic factor.

In current clinical practice, AML is risk-stratified according to the European LeukemiaNet (ELN) risk classification into favorable-, intermediate-, and adverse-prognosis groups based on the cytogenetic and molecular profiles of the disease.[57] The 2017 ELN molecular risk classification was updated in 2022 and includes several new mutational characteristics with updates highlighted in Table 19-3.[57,60] In 2024, for older patients treated with less intensive therapies, new genetic risk classifications were

described by ELN, acknowledging prognostication may differ for patients managed with hypomethylating-based combinations. The adverse risk group was defined by patients harboring *TP53* mutations.[9]

Table 19-3 2022 ELN Cytogenetic and Molecular Risk Stratification of AML[39]

Risk Level	Subset
Favorable	t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*[a,b]
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*[a,b]
	Mutated *NPM1*[a,c] without *FLT3*-ITD
	bZIP in-frame mutated *CEBPA*[d]
Intermediate	**Mutated *NPM1*[a,c] with FLT3-ITD**
	Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*[a,e]
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23.3;q34.1)/*DEK::NUP214*
	t(v;11q23.3)/*KMT2A*-rearranged[f]
	t(9;22)(q34.1;q11.2)/*BCR::ABL1*
	t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM* (*EVI1*)
	t(3q26.2;v)/*MECOM* (*EVI1*)-rearranged
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,[g] monosomal karyotype[h]
	Mutated *ASXL1*, ***BCOR***, ***EZH2***, *RUNX1*, ***SF3B1***, ***SRSF2***, ***STAG2***, ***U2AF1***, and/or ***ZRSR2***[i]
	Mutated *TP53*[j]

Abbreviations: AML, acute myeloid leukemia; bZIP, basic leucine zipper; ELN, European LeukemiaNet.
Frequencies, response rates, and outcome measures should be reported by risk category and, if sufficient numbers are available, by specific genetic lesions indicated.
Bold text indicates the latest changes for AML.
[a]Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course on the basis of the results from analyses of measurable residual disease.
[b]Concurrent *KIT* and/or *FLT3* gene mutation does not alter risk categorization.
[c]AMLs with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse risk.
[d]Only in-frame mutations affecting the bZIP region of *CEBPA*, irrespective of whether they occur as monoallelic or biallelic mutations, have been associated with a favorable outcome.
[e]The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
[f]Excluding *KMT2A* partial tandem duplication.
[g]Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.
[h]Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).
[i]For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
[j]*TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.
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Response to treatment and long-term survival of patients are largely dependent on disease genetics, as described in the 2017 and 2022 ELN molecular risk classifications, and the age of the patient.[57,61] The 2017 ELN molecular risk classification was validated in a large cohort of 1,116 patients who had newly diagnosed AML treated with intensive induction chemotherapy during two phase 3 trials run by the German AML Cooperative Group.[61] Among patients younger than 60 years, 31% had ELN adverse-risk AML. By contrast, half the patients older than 60 years had adverse-risk AML. Although favorable-risk AML was associated with a complete remission rate of 72%, only 41% of patients who have adverse-risk AML achieved complete remission. The 5-year survival differed significantly based on ELN risk and was 54%, 31%, and 12% in patients who had favorable-, intermediate-, and adverse-risk AML, respectively. Importantly, patients older than 60 years had significantly worse 5-year survival rates than younger patients, with 37.4% versus 64.2% of patients who had favorable-risk AML and 6.4% versus 20.1% of patients who had adverse-risk AML and were alive at 5 years after treatment start. These data emphasize the poorer prognosis of older patients who have AML.

Outcomes for older patients treated with less intensive treatments for AML were difficult to discriminate using the 2017 and 2022 ELN risk classifications. Therefore, a bioinformatic algorithm was applied to a pooled analysis of the phase 3 VIALE-A trial and phase 1b study of venetoclax in combination with a hypomethylating agent in patients with AML ineligible for intensive induction, identifying new molecular signatures that were better able to differentiate survival outcomes for patients treated with azacitidine and venetoclax. This culminated in the ELN 2024 genetic risk classification incorporating a four-gene signature into three prognostic groups (favorable, intermediate, and adverse). The overall survival (OS) for the favorable-risk group was greater than 24 months, with those in the adverse-risk group, defined by mutations in *TP53*, having an OS of 5 to 8 months, and this prognostic tool applies to patients receiving hypomethylating monotherapy, hypomethylating agents with venetoclax, and azacitidine with ivosidenib for *IDH1*-mutated AML.[62]

Cytogenetics

Among patients younger than 60 years who have AML, core binding factor leukemias make up 10% to 15% of cases and have a favorable prognosis, along with APL.[63] Core binding factor leukemias consist of t(8;21) causing the fusion gene *RUNX1::RUNX1T1* and inv(16) or t(16;16), resulting in *CBFB::MYH11* fusion. The t(8;21) translocation is frequently accompanied by loss of a sex chromosome (particularly Y) or del(9q). Inv(16)/t(16;16) may be accompanied by trisomies, commonly involving chromosomes 22, 8, or 21.

Adverse cytogenetic features include inv(3)(q21;q26)/t(3;3)(q21;q26); *KMT2A* (*MLL)* rearrangements other than t(9;11), –5, –7, del(5q), del(7q); abnormalities involving chromosome 17; and a complex karyotype (three or more unrelated chromosomal abnormalities).[39] Patients who have complex or monosomal karyotypes (presence of two monosomies excluding X or Y loss or one monosomy with a structural chromosome abnormality) have a poor prognosis. Elucidation of the biological role of the menin-*KMT2A* interaction has facilitated the advent of menin inhibitors, now approved for patients with relapsed or refractory *KMT2A* rearranged AML.

In the 2022 ELN molecular risk classification, additional disease-defining cytogenetic abnormalities are considered adverse risk, including inv(3)/t(3;3) and t(3;21) involving the *MECOM* gene and t(8;16)(p11;p13), which is associated with *KAT6A*::*CREBBP*.[57,60] By contrast, hyperdiploid karyotypes with multiple trisomies (or polysomies) are no longer considered complex karyotypes and are excluded from the adverse-risk group.[39]

Mutations

Of patients aged 16 to 60 years who have AML, 35% to 40% have a normal karyotype at presentation. These patients may have accompanying mutations in *FLT3*, *NPM1*, *CEBPA*, *IDH1*, *IDH2*, *ASXL1*, and *TP53* in validated assays and a host of other mutations on comprehensive profiling.[64]

Biallelic mutations in *CEBPA* were previously reported as a favorable prognostic feature when patients were treated with chemotherapy alone.[65] In the 2022 ELN molecular risk classification, the good prognosis associated with *CEPBA* mutations was further defined as being limited to in-frame mutations affecting the bZIP region, irrespective of whether mono- or biallelic mutations were present.[57] *NPM1* mutations occur concurrently with *FLT3*-ITD in 60% of patients who have *FLT3* mutations. *NPM1* mutations occur by themselves in 30% of cytogenetically normal AMLs and are associated with a good prognosis. Although mutations in *NPM1* generally confer a favorable prognosis, patients with refractory or relapsed AML with *NPM1* mutations have poor outcomes. Advances in our understanding of the menin complex and its interaction with *NPM1* have enabled the FDA approval of menin inhibitors for patients with relapsed or refractory *NPM1*-mutated AML.

Approximately one-third of patients who have newly diagnosed AML have mutations in the *FLT3* gene. In all, 20% to 25% of patients who have AML harbor the *FLT3*-ITD gene, which is associated with a more proliferative phenotype, increased blast percentage, higher risk of relapse, and inferior OS compared with *FLT3* wild-type disease after combination chemotherapy. In all, 5% to 10% of patients who have newly diagnosed AML have a *FLT3*-TKD mutation. The prognostic impact of *FLT3*-TKD mutations is currently unclear. The presence of a coexisting *NPM1* mutation is associated with a decreased risk of relapse and improved survival in *FLT3*-ITD–mutated AML, especially in patients who have a low *FLT3*-ITD allele burden. The allelic ratio of *FLT3*-ITD:*FLT3* wild type strongly influences outcomes after induction chemotherapy that does not include an FLT3 inhibitor. A ratio of 0.5 or greater is associated with worse survival compared with a lower ratio. However, this is not the case any longer with the addition of FLT3 inhibitors to intensive chemotherapy.[66] Therefore, in the 2022 ELN molecular risk classification, *FLT3*-ITD allelic ratio is no longer incorporated into the risk classification, and all patients who have *FLT3*-ITD–mutated AML are included in the intermediate-risk group irrespective of their allelic ratio or presence of *NPM1* mutation.[57] *IDH1* and *IDH2* mutations occur in 6% to 10% and 9% to 13% of patients who have AML, respectively.[67] These mutations result in the accumulation of the oncometabolite 2-hydroxyglutarate. The prognostic relevance of these mutations is unclear, and other co-occurring mutations affect patient prognosis. Notably, drugs targeting IDH1 and IDH2 were recently approved by the FDA for first-line treatment of relapsed/refractory AML with an *IDH1* mutation or an *IDH2* mutation.

TP53 mutations are found in 70% of patients who have AML with complex cytogenetic abnormalities and are an independent poor prognostic factor in this AML subset. In addition, mutations in *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR*, or *STAG2*

were more than 95% specific for the diagnosis of a secondary ontogeny of AML, even if the morphologic bone marrow examination did not show evidence of previous MDS or MPNs.[68] Importantly, as in morphologically defined secondary AML, the presence of these mutations is associated with worse clinical outcomes, including a lower complete remission rate, more frequent need for reinduction, and decreased event-free survival (EFS). Therefore, in the updated 2022 ELN molecular risk classification, these mutations are included in the adverse-risk disease category.[57]

Measurable Residual Disease

Measurable residual disease (MRD) refers to residual disease that remains detectable after therapy with the help of highly sensitive techniques in the absence of morphologically detectable disease in the bone marrow. Detection of MRD at the time of remission after completion of induction chemotherapy, whether detected by multiparameter flow cytometry or molecular studies (eg, polymerase chain reaction [PCR] or NGS), is associated with increased rates of relapse and worse survival.[58,69-71] MRD detected concurrently by both flow cytometry and molecular studies confers the highest risk of disease relapse, whereas persistence of so-called DTA mutations (mutations in *DNMT3A*, *TET2*, and *ASXL1*), which are often present in individuals with age-related clonal hematopoiesis, is not correlated with an increased relapse rate.[69,70] Persistent MRD before allogeneic stem cell transplantation (allo-SCT) is associated with an increased risk of relapse and worse OS after transplantation, although this may be ameliorated by the use of myeloablative conditioning.[72,73] As maintenance strategies are explored after intensive induction or transplantation, MRD may be used to guide maintenance therapy. In the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1506 Morpho trial evaluating gilteritinib maintenance for patients who have *FLT3*-ITD–mutated AML post-transplant, the quantity of *FLT3*-ITD MRD by PCR was highly correlated with outcome, and MRD was eradicated with gilteritinib maintenance in some cases, resulting in inclusion in the National Comprehensive Cancer Network (NCCN) guidelines as the preferred agent in this clinical setting.[3,8]

TREATMENT

Overview of AML Treatment

Patient-related factors, such as age, comorbidities, and performance status, and disease-specific factors, such as the molecular profile of the disease, presence of preexisting MDS, and previous leukemogenic therapy, typically influence the induction strategy (Table 19-2). In clinical practice, physiologic age is the more important benchmark of overall fitness for induction compared with an absolute age cutoff, although age 75 years is often considered a differentiating point. The goal of treatment is the eradication of leukemia, which is known as remission. Once remission is achieved, consolidative approaches are attempted to maintain a long-term remission and potentially offer a chance for cure (such as high-dose chemotherapy consolidation in favorable-risk patients or allo-SCT in eligible patients who have intermediate- or adverse-risk disease). If consolidative approaches cannot be offered, non-curative maintenance regimens may be used to extend OS.

Treatment of fit patients who have AML typically involves an induction chemotherapy phase and a post-remission treatment phase. The post-remission treatment phase consists of consolidation chemotherapy alone (for patients who have ELN favorable risk), allo-SCT (for transplant-eligible patients who have ELN intermediate or adverse risk), or consolidation and maintenance therapy without transplantation (for transplant-ineligible patients who have ELN intermediate or adverse risk) (Fig. 19-2).

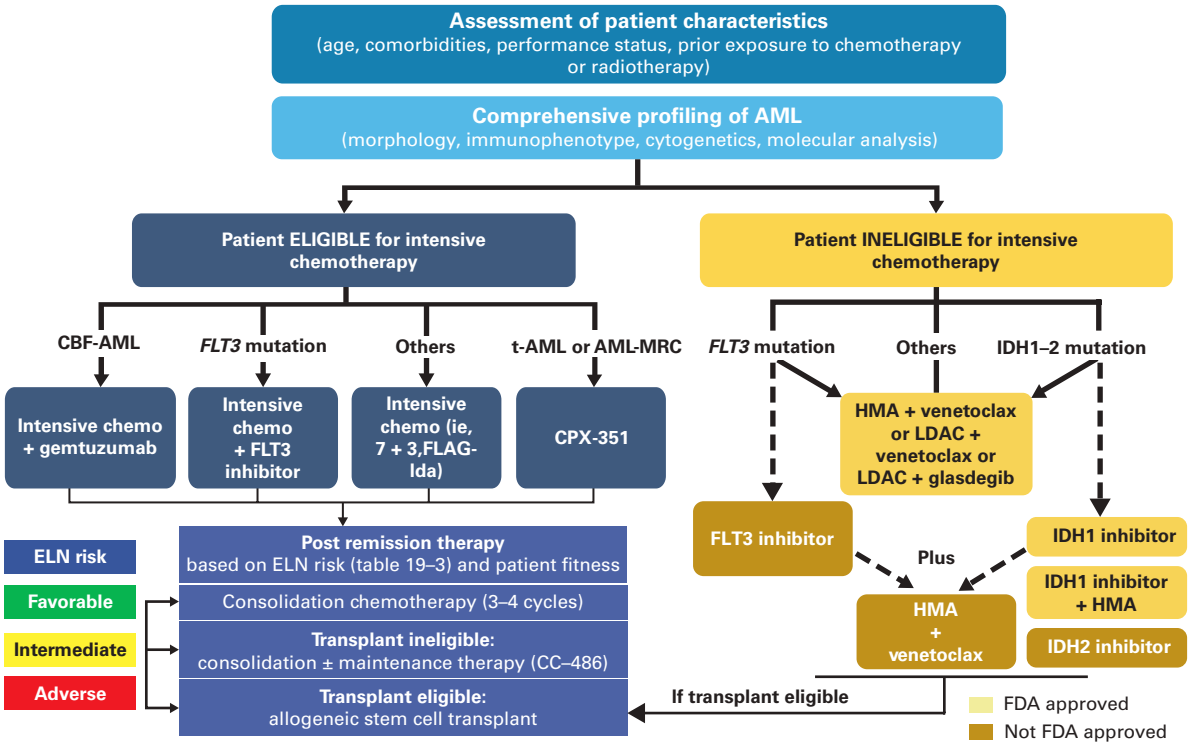
Treatment options for older patients or patients with comorbidities who are unfit for standard intensive induction therapy have improved. Treatment options now include the combination of the hypomethylating agents (HMAs, eg, azacitidine and decitabine) or low-dose cytarabine with the BCL-2 inhibitor venetoclax,[74-76] or targeted therapy.[77]

First-Line Treatment of Patients Eligible for Intensive Induction Chemotherapy

Standard intensive induction therapy uses an anthracycline for 3 days in combination with infusional cytarabine for 7 days (known as 3 + 7 or 7 + 3) with recent modifications based on cytogenetics, mutational profile, or cell-surface marker expression. ELN and NCCN consensus panels also recommend enrolling patients younger than 60 years who have AML in a clinical trial with curative intent.

Daunorubicin at 60 to 90 mg/m^2 and idarubicin at 12 mg/m^2 once per day for 3 days are the anthracyclines most used in combination with 7 days of continuously infused cytarabine at 100 to 200 mg/m^2 once per day. Daunorubicin and idarubicin at these dosage levels are comparable in terms of outcomes. A phase 3 Eastern Cooperative Oncology Group (ECOG) trial demonstrated an improved complete remission rate for daunorubicin at a dose of 90 mg/m^2 once per day for 3 days compared with 45 mg/m^2 once per day for 3 days; there was a survival benefit for patients who have a favorable- or intermediate-risk karyotype (median OS, 34 vs 21 months, respectively; $P = .004$) and for those aged younger than 50 years (median OS, 34 vs 19 months, respectively; $P = .004$). Patients aged 50 to 60 years with *FLT3*-ITD and *NPM1* mutations also had improved OS with daunorubicin at 90 mg/m^2 once per day.[39] In a randomized study based on a double-induction treatment strategy, however, no advantage was found for the 90 mg/m^2 once-per-day dose of daunorubicin compared with a dose of 60 mg/m^2 once per day in the first treatment cycle, except in patients who have *FLT3*-ITD–mutated AML.[78] Some experts recommend beginning a second cycle of chemotherapy in patients who still have more than 5% blasts in a more than 10% cellular marrow 7 to 10 days after the last dose of chemotherapy. The role of planned double induction in improving OS in AML is still not obvious, and more evidence from prospective studies is required in this regard.

Figure 19-2 First-Line Treatment Algorithm for AML



Abbreviations: AML, acute myeloid leukemia; AML-MRC, AML with myelodysplasia-related changes; CBF, core binding factor; CBF-AML, core binding factor AML; CC-486, oral azacitidine; chemo, chemotherapy; CPX-351, liposomal formulation of cytarabine and daunorubicin coencapsulated at a fixed molar ratio (5:1); ELN, European LeukemiaNet; FLAG-Ida, fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin; FL3, fms-like tyrosine kinase 3; HMA, hypomethylating agent; IDH, isocitrate dehydrogenase; LDAC, low-dose Ara-C (cytarabine); t-AML, therapy-related AML.
Dotted lines indicate alternative considerations.
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For patients who have *FLT3*-mutated AML, midostaurin or quizartinib is added to standard first-line induction chemotherapy. In a randomized phase 3 trial for patients who had AML with *FLT3* mutations, midostaurin, a multikinase inhibitor with activity against mutated *FLT3*-ITD and TKD, improved OS compared with placebo in patients up to age 60 (hazard ratio [HR], 0.77; 95% CI, 0.63-0.95; $P = .007$), leading to FDA approval of midostaurin for this indication.[66] In addition to midostaurin, based on the QuANTUM-First trial, quizartinib, an oral, highly potent, selective type 2 FLT3 inhibitor, was approved in combination with 7 + 3 for induction in *FLT3*-ITD–positive newly diagnosed AML based on OS improvement compared with placebo. Importantly, this trial enrolled patients up to age 75 years.[57]

Gemtuzumab ozogamicin is approved for newly diagnosed $CD33^+$ AML in combination with daunorubicin and cytarabine based on the reduced risk of relapse and improved OS compared with chemotherapy alone.[79] These benefits seem to be restricted to patients who have favorable- or intermediate-risk disease (median EFS, 17.3 vs 9.5 months for gemtuzumab ozogamicin and standard chemotherapy arms, respectively; HR, 0.56; $P < .001$). Gemtuzumab ozogamicin is associated with increased risk of hepatotoxicity, including possible severe and fatal hepatic veno-occlusive disease, especially in the allo-SCT setting.

In patients aged 60 to 75 who have untreated AML and a history of cytotoxic treatment, antecedent MDS, or chronic myelomonocytic leukemia, another therapeutic option is CPX-351. CPX-351 is a liposomal formulation of cytarabine and daunorubicin coencapsulated at a fixed molar ratio (5:1) to maximize synergy between these two agents at a dose of 100 mg/m^2 of cytarabine and 44 mg/m^2 of daunorubicin once per day on days 1, 3, and 5. In this patient population, CPX-351 significantly showed improved OS, EFS, and response rates without an increase in the 60-day mortality rate or adverse events compared with 7 + 3 therapy.[80] However, CPX-351 treatment was associated with a longer time to neutrophil and platelet count recovery. The survival benefit in the CPX-351 group was especially pronounced in patients undergoing allo-SCT because of lower nonrelapse mortality (NRM) compared with 7 + 3.

Patients who have underlying poor cardiac function can be treated with a nonanthracycline-based induction regimen, such as clofarabine, cladribine, or fludarabine with high-dose cytarabine with or without gemtuzumab ozogamicin (eg, granulocyte colony-stimulating factor [G-CSF] priming, clofarabine, and high-dose cytarabine [GCLAC], cladribine plus cytarabine plus G-CSF [CLAG], or fludarabine, arabinofuranosyl cytidine [cytarabine/ara-C], and G-CSF [FLAG]).

Consolidation and Maintenance Therapy

Most consensus panels recommend three or four cycles of high-dosage cytarabine consolidation for patients aged younger than 60 years with favorable-risk cytogenetics [t(8;21), inv(16)/t(16;16)] or favorable-risk mutational patterns. Results from a randomized study suggest that high-dose cytarabine at 3 g/m^2 once every 12 hours on days 1, 3, and 5 improves outcomes in patients aged younger than 60 years[81] in comparison with standard-dose cytarabine (100 or 400 mg/m^2 by continuous infusion for 5 days).[82] This benefit was not seen in patients older than 60 because of excess toxicity, particularly neurotoxicity. High-dose cytarabine carries an increased risk of chemical conjunctivitis (12.4%) compared with standard-dose cytarabine (0.5%). Alternative accelerated dosing schedules have been explored, including HiDAC administered on days 1, 2, and 3 (HiDAC-123) with comparable outcomes to conventional dosing and potentially reduced toxicity.[83] In addition, recently, intermediate-dose cytarabine (IDAC) was determined to be noninferior to high-dose cytarabine in AML patients between 18 and 60 years old.[81,84] High-dose cytarabine and midostaurin or quizartinib consolidation therapy is used for patients who have *FLT3*-mutation–positive AML.[57,66] By contrast, matched-sibling or alternate-donor allo-SCT should be considered for patients who have intermediate- or adverse-risk AML who are considered eligible to receive such therapy.[57,85]

Oral azacitidine (CC-486) was approved as maintenance therapy in patients who have AML and have achieved complete remission after intensive induction chemotherapy but who are not able to complete intensive consolidation therapy (eg, allo-SCT). In a randomized placebo-controlled phase 3 study, CC-486 showed improved OS (24.7 vs 14.8 months) and RFS (10.2 vs 4.8 months) compared with placebo.[86,87]

Allogeneic Stem Cell Transplantation for AML

Allo-SCT offers a strong antileukemic effect and continues to be the treatment of choice for medically fit patients younger than age 70 to 75 with an available donor except those with favorable cytogenetic or molecular risk profiles (ie, patients who have APL, core binding factor AML, biallelic *CEPBA* mutations, *NPM1* mutation without *FLT3*-ITD, or who achieve an early first complete remission and have no evidence of MRD after induction).[57] If no human leukocyte antigen (HLA)-matched related or unrelated donors are available, alternative donor sources (haploidentical donors, cord blood) are considered.

For patients who have intermediate-risk AML, the absolute benefit of allo-SCT in first complete remission is less marked than that for patients who have adverse-risk disease, and controversy remains regarding whether equivalent survival may be achieved by delaying transplantation until after the first relapse.[57,85]

The optimal intensity of pretransplantation conditioning chemotherapy for AML has been the subject of extensive study. Data from a major randomized trial showed significantly higher rates of relapse and shorter RFS with reduced-intensity conditioning compared with myeloablative conditioning in patients aged 18 to 65.[88] Myeloablative conditioning, therefore, should be prioritized if the patient is considered a suitable candidate. For patients older than age 40, the combination of busulfan and fludarabine is associated with lower transplantation-related mortality rates, but it retains antileukemic effects compared with busulfan and cyclophosphamide.[89] However, there continues to be a limited role for myeloablative regimens in treating older patients who have AML. Nonmyeloablative or reduced-intensity conditioning regimens have been developed to reduce the rate of NRM in older or less medically fit patients. Reduced-intensity conditioning in older patients has demonstrated a survival benefit and improved RFS.[90-92] The BMT CTN 1704 trial prospectively evaluated the Composite Health Risk Assessment Model (CHARM) in an effort to predict 1-year NRM for adults older than age 60 receiving an allo-SCT. The CHARM score, which comprises albumin, C-reactive protein, hematopoietic cell transplantation comorbidity index, and weight loss, predicted NRM within 1 year of transplantation, with each point increase in the CHARM score being associated with an HR of 2.83 (95% CI, 2.12-3.78; $P < .0001$) for NRM.[93]

Importantly, a study performed MRD analysis using ultra-deep error-corrected sequencing for 13 commonly mutated genes in blood samples before allo-SCT from patients treated in the BMT CTN 0901 phase 3 clinical trial. The trial randomly assigned adult patients who had AML in morphologic complete remission to myeloablative conditioning or reduced-intensity conditioning.[73] In patients who had detectable MRD before allo-SCT, reduced-intensity conditioning was significantly associated with increased relapse, decreased RFS, and decreased OS compared with myeloablative conditioning, whereas there was no difference between the two conditioning approaches for patients without detectable MRD. These data argue strongly for considering the pretransplantation MRD status of patients in making decisions about which conditioning regimen to use.

The low likelihood of response to salvage chemotherapy for patients for whom primary induction failed has led to attempts to use allo-SCT as first salvage therapy. Although the post-transplantation relapse rate is high, the 20% to 25% long-term OS rate with allo-SCT for patients who experience primary induction failure is better than what would be expected with additional chemotherapy.[94]

First-Line Treatment of Patients Ineligible for Intensive Induction Chemotherapy

Historically, patients who were not considered fit enough to receive intensive chemotherapy because of advanced age or comorbidities received either low-intensity therapy with HMAs or supportive care only. However, FDA approval of the BCL-2 inhibitor venetoclax has greatly improved the treatment of this patient population and is part of the standard of care in the current treatment era. Venetoclax in combination with HMAs or low-dose cytarabine has shown impressive activity in patients older than age

75 or unfit patients in clinical trials.[75,95] The landmark VIALE-A trial was a randomized phase 3 trial demonstrating improved OS with venetoclax plus azacitidine compared with azacitidine alone (14.7 vs 9.6 months; $P < .001$).[74] Long-term follow-up of VIALE-A demonstrated continued survival advantage with azacitidine/venetoclax-treated patients surviving 14.7 months (95% confidence interval [CI], 12.1-18.7) versus 9.6 months with azacitidine alone.[96]

The combination of venetoclax and HMAs or low-dose cytarabine is approved by the FDA as treatment for patients who have AML and are aged 75 years or older or patients who are unfit for standard induction therapy. In the VIALE-C phase 3 trial of venetoclax plus low-dose cytarabine (LDAC) versus LDAC alone, the combination resulted in numerically prolonged OS without reaching statistical significance (7.2 vs 4.1 months; $P = .11$).[75] Of note, an unplanned analysis with an additional 6 months of follow-up showed a statistically significantly longer OS with the combination treatment (7.2 vs 4.1 months; $P = .04$). Long-term follow-up of this trial demonstrated a persistent improvement in OS for the LDAC/venetoclax-treated patients versus those receiving LDAC alone (8.4 vs 4.1 months).

Venetoclax can cause tumor lysis syndrome, and appropriate preventive measures are required to avoid this complication. Venetoclax is metabolized by the CYP3A4 cytochrome system, and the dose needs to be adjusted when administered concurrently with CYP3A4 inhibitors, such as the antifungal agents, posaconazole and voriconazole. Given the FDA approval of gilteritinib, ivosidenib, and enasidenib for *FLT3*-, *IDH1*-, and *IDH2*-mutated relapsed/refractory AML (see "Treatment of Relapsed/Refractory AML or Persistent Disease" section), respectively, these targeted therapies have also been studied in the first-line treatment setting for patients who are ineligible for intensive chemotherapy either as monotherapy or in combination with HMAs.

The IDH1 inhibitor ivosidenib received FDA approval for the first-line treatment of *IDH1*-mutated AML in combination with azacitidine in patients older than 75 years or patients who are medically unfit for intensive induction.[77] By contrast, the IDH2 inhibitor enasidenib remains approved by the FDA only as treatment of *IDH2*-mutated relapsed/refractory AML. Recently, two phase 3 clinical trials directly compared the combination of the IDH inhibitor ivosidenib plus azacitidine or enasidenib plus azacitidine versus azacitidine monotherapy in the first-line treatment of *IDH1*- or *IDH2*-mutated AML, respectively. The AGILE trial showed both a higher overall response rate (ORR) (63% vs 19%; $P < .0001$) and improved median OS (24 vs 7.9 months; $P = .0005$) with the combination of ivosidenib and azacitidine compared with azacitidine alone.[97] By contrast, the AG221-AML-005 trial showed a higher ORR (74% vs 36%; $P = .0003$) but no improvement in OS with enasidenib plus azacitidine compared with azacitidine alone.[4] Likewise, the phase 3 LACEWING trial comparing gilteritinib plus azacitidine with azacitidine alone showed an improvement in the composite complete remission rate but no improvement in OS.[5]

Despite a high response rate, the absence of a survival advantage for enasidenib and gilteritinib in combination with azacitidine argues against using these combinations in routine clinical practice. Instead, venetoclax and an HMA or low-dose cytarabine is typically used in these patients instead. Whether to treat patients carrying an *IDH1* mutation with ivosidenib plus an HMA or venetoclax plus an HMA as first-line therapy remains an open question, given that both approaches are predicted to result in high response rates and improved OS. In frail patients who are thought to be potentially unable to tolerate the prolonged myelosuppression induced by venetoclax, single-agent ivosidenib (approved by the FDA for this indication) for *IDH1*-mutated AML, enasidenib for *IDH2*-mutated AML, or gilteritinib for *FLT3*-mutated AML may be considered. However, it is important to remember that enasidenib and gilteritinib are not approved in the first-line setting, and individual drug approval could depend on specific insurance coverage in the United States.

More encouraging results were reported recently from a phase 1/2 trial combining gilteritinib and azacitidine with venetoclax, with a median follow-up of 19.3 months, the median OS for patients who had newly diagnosed *FLT3*-mutated disease had not been reached, with an OS rate of 72%. Investigation of this triplet combination is ongoing.[98]

Treatment of Relapsed/Refractory AML or Persistent Disease

Relapsed/refractory AML may have new mutations or lose previous mutations at the time of relapse compared with the dominant clone at initial diagnosis, and in such cases, this information can be used to guide therapy. Therefore, genomic profiling should be repeated at the time of relapse. For those fit enough to receive intensive chemotherapy, regimens containing a purine analog (ie, fludarabine, cladribine, or clofarabine) have resulted in remission rates of 30% to 45% in the relapsed/refractory setting. Some common regimens for relapsed/refractory AML are mitoxantrone, etoposide, and cytarabine (MEC); FLAG or FLAG-Ida; and cladribine, cytarabine, and G-CSF with or without mitoxantrone (CLAG-M). High-dose cytarabine can also be administered in relapsed/refractory AML if it has not been given previously.

IDH1 mutations occur in 6% to 10% of patients, and *IDH2* mutations occur in 10% to 15% of patients who have relapsed/refractory AML. These mutations result in the accumulation of the oncometabolite 2-hydroxyglutarate, which alters the epigenetic profile of AML blasts. The IDH1 inhibitors ivosidenib and olutasidenib and the IDH2 inhibitor enasidenib block the enzymatic activity of mutated *IDH1* and *IDH2*, respectively, lowering the levels of the oncometabolite 2-hydroxyglutarate.

The IDH1 inhibitor ivosidenib has demonstrated an ORR of 42% at 500 mg taken orally once per day in relapsed/refractory AML.[99] Olutasidenib, which is another selective IDH1 inhibitor, was approved in 2022 for relapsed/refractory *IDH1*-mutated AML.[100] Based on the approval summary by the FDA,[98] the complete remission and complete remission with partial hematologic recovery rates among 147 patients who had relapsed/refractory *IDH1*-mutated AML was 35% (51 of 147). Because ivosidenib is

approved for the same patient population, and olutasidenib was not directly compared with ivosidenib, both IDH1 inhibitors can be used for relapsed/refractory *IDH1*-mutated AML. The IDH2 inhibitor enasidenib has demonstrated an ORR of 40.3% and OS of 9.3 months at a dose of 100 mg taken orally once per day.[101] Both ivosidenib and enasidenib are associated with a differentiation syndrome that occurs in 10% to 14% of all patients and is clinically characterized by fever, dyspnea, pulmonary infiltrates, and hypoxia. Leukocytosis often accompanies differentiation syndrome. Early recognition is important because it can be fatal if untreated. Patients for whom there is a clinical suspicion of differentiation syndrome should be treated with systemic corticosteroids and close monitoring of hemodynamic status.

Gemtuzumab ozogamicin is approved for the treatment of relapsed/refractory AML as monotherapy administered at 6 mg/m^2 once per day on days 1 and 3 mg/m^2 once per day on day 8. Patients who have no evidence of disease progression and no significant toxicities can continue receiving treatment of up to eight courses at a reduced dosage (2 mg/m^2 once every 4 weeks). Another regimen is single-agent gemtuzumab ozogamicin at 3 mg/m^2 administered intravenously once per day on days 1, 4, and 7.

Gilteritinib, a highly selective FLT3 inhibitor, has been approved for *FLT3*-ITD–positive relapsed/refractory AML at 120 mg taken orally once per day. In the phase 3 ADMIRAL trial, gilteritinib led to improved OS compared with salvage therapy in fit and unfit patients (9.3 vs 5.6 months; $P < .001$).[102]

After the discovery that menin is an essential oncogenic cofactor for *MLL*-associated leukemogenesis, menin inhibitors are promising targeted therapeutic agents for AML with rearrangement of the *KMT2A* gene (also known as *MLL*) and *NPM1*-mutated AML (with a gene expression profile similar to the *KMT2A* rearrangement [*KMT2Ar*]). Revumenib (SNDX-5613), a potent, selective small-molecule inhibitor of the menin-histone-lysine N-methyltransferase 2A (*KMT2A*) interaction, is safe and effective as monotherapy in patients who have relapsed/refractory *KMT2Ar* AML (investigated in the phase I/II AUGMENT-101 trial) and in combination in patients who have relapsed/refractory AML with *KMT2Ar* or *NPM1* mutation.[4,5] Revumenib has now been FDA approved as monotherapy in relapsed/refractory AML with *KMT2Ar* or *NPM1* mutations based on results from AUGMENT-101.[6] An alternative menin inhibitor, ziftomenib, is also now FDA approved for relapsed/refractory *NPM1*-mutated AML based on results of the phase 1/2 KOMET-001.[103]

Investigational Approaches for the Treatment of AML

The approval of venetoclax for first-line treatment of AML has paved the way for multiple ongoing trials evaluating the combination of venetoclax with chemotherapy and targeted therapy. Although response rates to combination approaches are promising, it remains to be seen whether this will also translate into improved survival. Currently, none of these trials has studied the addition of venetoclax in a randomized controlled design. Therefore, the addition of venetoclax to chemotherapy other than HMAs, low-dose cytarabine, or targeted therapy remains investigational.

Overall, the combination of venetoclax with various chemotherapy combinations shows promising results with high composite response rates. Venetoclax in combination with FLAG-Ida showed a high composite complete remission rate in both newly diagnosed and relapsed/refractory AML (90% and 67%, respectively).[104] Similarly, in the CAVEAT trial, the combination of cytarabine and idarubicin with venetoclax resulted in a complete remission for both combinations, with an incomplete recovery rate of 72% (97% in de novo AML and 43% in secondary AML).[105] In addition, venetoclax combined with alternating courses of cladribine and low-dose cytarabine and azacitidine resulted in a complete remission for both combinations, with an incomplete recovery rate of 94%.[106]

As with chemotherapy, the addition of targeted therapy (IDH1/2 and FLT3 inhibitors) to the azacitidine and venetoclax backbone results in high response rates, with some reports also demonstrating high MRD-negative response rates.[98,107-110] However, outcomes in these trials frequently include so-called composite complete remission rates, including complete remission and additional remission definitions with incomplete or complete absence of count recovery. It is currently unclear whether remission without complete count recovery will lead to an improvement in survival, given that complete remission remains the response most consistently associated with a survival advantage.

With success in treating relapsed/refractory AML with *KMT2Ar* or *NPM1* mutations, menin inhibition is currently being investigated in combination with intensive and less intensive treatment combinations for patients with newly diagnosed *KMT2Ar* or *NPM1*-mutated AML.

In an effort to offer a trial for every patient with AML, the National Cancer Institute is supporting a precision medicine clinical trial platform called MyeloMATCH, to match patients to targeted therapies based on the molecular profile of their disease. Currently, MyeloMATCH is enrolling with several studies in Tier 1, aimed at induction therapies for newly diagnosed patients stratified into younger and older age groups.[111]

Supportive Care During AML Therapy

Transfusions, tumor lysis syndrome prophylaxis, growth factor support, anti-infective prophylaxis, and correction of coagulopathies are the crux of supportive care during AML therapy. Leukocyte-depleted blood products are preferred for all transplantation-eligible candidates. Standard tumor lysis syndrome prophylaxis administered during treatment includes hydration, diuresis, and treatment with allopurinol and/or rasburicase. Rasburicase is a genetically engineered urate oxidase that can

rapidly decrease uric acid levels by conversion to the highly soluble allantoin and should be strongly considered for tumor lysis syndrome treatment and prophylaxis in the presence of a rapidly increasing blast count, high uric acid levels, and impaired renal function. Testing for glucose-6-phospate dehydrogenase deficiency is important to help prevent hemolysis associated with rasburicase in this population.

Monitoring for cerebellar and renal toxicities should be performed concurrently with treatment using high-dose cytarabine. If signs of neurologic toxicity are detected, high-dose cytarabine should be discontinued immediately, and only standard-dose cytarabine should be used from that point onward in treatment. Steroid eye drops are also provided while patients receive high-dose cytarabine to prevent conjunctivitis.

Growth factors such as G-CSF can decrease the duration of neutropenia and decrease the risk of life-threatening sepsis during treatment. Growth factors should be discontinued 1 week before a planned bone marrow biopsy, given that they can affect marrow interpretation and determination of remission status.

Although CNS leukemia is rare in AML, patients who have monocytic differentiation, biphenotypic leukemia, *FLT3* mutation, or WBC count greater than 40,000/mL at presentation should be screened for the presence of CNS leukemia with a lumbar puncture. Patients who have nerve palsies are presumed to have CNS involvement even in the absence of leukemic cells in the cerebrospinal fluid. Intrathecal chemotherapy should be incorporated into the treatment regimen if CNS leukemia is detected.[57,112]

PRESENTING CASE STUDY

A 60-year-old man presents to the emergency department with easy bruising and fevers for 2 weeks. Complete blood count revealed a leukocyte count of 120,000 cells/mcL, hemoglobin level of 7 g/dL, and platelet count of 8,000 cells/mcL. Peripheral blood differential reveals 80% blasts.

How do the observed circulating blasts and clinical presentation inform your decision on which tests to obtain?

The next best step is to order a bone marrow biopsy with aspirate. From the biopsy and aspirate, the following analyses should be performed, including morphology; immunophenotyping; cytogenetics; gene rearrangements in *PML-RARA*, *CBFB-MYH11*, *RUNX1-RUNX1T1*, *BCR-ABL1*, and other fusion genes; and a NGS panel.

These tests provide the necessary information to inform an acute myeloid leukemia (AML) diagnosis and allow for categorization by the 2022 WHO Classification and prognostication using ELN 2022 Risk Classification. Understanding the molecular characteristics of an AML diagnosis allows for appropriate therapeutic selection.

While awaiting bone marrow biopsy results, additional history can be obtained, and testing can be performed to determine family history, comorbidities, coagulation abnormalities, pulmonary and cardiovascular baseline testing, and Eastern Cooperative Oncology Group (ECOG) performance status to help inform appropriate therapy selection.

Additional testing revealed that the patient has AML with a mutation in *FLT3-ITD*. The patient reports a medical history of hypertension that is controlled with losartan. Echocardiogram revealed a normal ejection fraction of 60% with no other reported abnormalities. ECG demonstrated a corrected QT of 270 ms. No coagulopathy was identified on additional workup. His family history is significant for a father with prostate cancer at 80 years old. His ECOG performance status is 1.

Based on what you have learned thus far regarding this patient's characteristics, what treatment could be considered at this time?

There are now several targeted FLT3 inhibitors approved in combination with standard first-line intensive induction that should be offered to patients with *FLT3-ITD*–mutated AML who are fit for intensive chemotherapy. The patient in this case would be described as fit, with an ECOG of 1 and normal cardiac function with well-controlled comorbidities. Midostaurin, a multikinase inhibitor that has activity against FLT3-ITD and FLT3-TKD, was approved in combination with an intensive chemotherapy backbone (7 + 3) for patients with newly diagnosed *FLT3*-mutated AML. In addition, quizartinib, a selective type 2 FLT3 inhibitor, has also been approved for use in combination with 7 + 3 induction for patients with newly diagnosed *FLT3-ITD*–mutated AML. Both of these agents have been shown to improve OS in combination with intensive induction compared with intensive induction and placebo. It is now the standard of care to provide an FLT3 inhibitor in the frontline setting for patients with AML harboring an *FLT3* mutation.

SECONDARY AML AND THERAPY-RELATED MYELOID NEOPLASMS

Secondary AML evolves from a previous myeloid neoplasm, commonly MDS. Therapy-related myeloid neoplasms (MDS, AML) arise after previous chemotherapy and/or radiation therapy, typically for the treatment of a previous malignancy or autoimmune disorder. Previous exposure to alkylating agents predisposes patients to chromosome losses or deletions, commonly involving chromosomes 5 and 7. MDS or AML typically arises 5 to 7 years after exposure. Topoisomerase II inhibitors can cause balanced translocations commonly involving the *KMT2A* (*MLL*) gene at chromosome 11q23, leading to AML with a shorter latency period of 1 to 3 years. Mutations in *TP53* are particularly common in therapy-related myeloid neoplasms (21%-38%) and are associated with a poor prognosis. The presence of a mutation in *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR*, or *STAG2* is more than 95% specific for the diagnosis of secondary AML.[68]

The outcomes with standard therapy are poor, with an estimated median survival in the range of 8 to 16 months. Allo-SCT is currently the best treatment option for most patients who have therapy-related AML or MDS, although some with favorable-risk genetics may do well without SCT.[57,112] CPX-351 is approved for patients who have secondary or therapy-related AML.[80] The approval of the menin inhibitor revumenib in R/R *KMT2Ar* AML offers another treatment modality with promising outcomes and provides a potential bridge to transplantation.[6] With success in the relapsed/refractory setting, menin inhibitors are being investigated in the frontline setting in combination with intensive and less-intensive therapies.

ACUTE PROMYELOCYTIC LEUKEMIA

APL is a distinct subtype of AML with unique clinical, morphologic, and cytogenetic features. In more than 95% of patients, APL has the characteristic t(15;17) translocation. This translocation gives rise to the PML::RARA fusion product. As a result, an aberrant retinoic acid receptor recruits corepressor complexes that cause a differentiation arrest of the myeloid cells at the promyelocyte stage.

APL occurs more frequently in patients who are young, Hispanic, and obese. It has a typical morphology characterized by abnormal cytoplasmic granules and multiple Auer rods. Coagulopathy is a clinical hallmark of the disease, and it typically presents with hypofibrinogenemia, decreased coagulation factors, increased fibrin degradation products, and platelet consumption similar to disseminated intravascular coagulation. A unique feature of APL is its high sensitivity to treatment with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO).[113]

More than 80% to 90% of patients are expected to be cured with a combination of ATRA, ATO, and/or chemotherapy; however, early death, defined as death within the first 30 days of presentation, remains the major cause of treatment failure in APL. Early death is often caused by consumptive coagulopathy leading to intracerebral, gastrointestinal, and pulmonary hemorrhages and, less commonly, infection and differentiation syndrome.[114] Therefore, it is important to make an early diagnosis of APL and institute immediate treatment with ATRA without waiting for molecular or cytogenetic confirmation of the disease.[115]

The treatment of APL is informed by risk stratification based on WBC count at presentation. Patients who have an initial WBC count of 10×10^9/L or less are considered low risk (if platelets are >40,000/mcL) or intermediate risk (if platelets are ≤40,000/mcL), whereas patients who have a WBC count greater than 10×10^9/L are considered high risk.[116] Typically, low- and intermediate-risk groups are combined into a low-/intermediate-risk category for treatment choice.

Low- and Intermediate-Risk APL

The APL 0406 study demonstrated that patients who have low- or intermediate-risk APL can be treated with ATRA and ATO alone, with more sustained antileukemic efficacy and better survival than that seen with a regimen of ATRA plus chemotherapy.[117,118] Indeed, ATRA and ATO are the preferred regimens for induction and consolidation for low- and intermediate-risk APL. Maintenance therapy is not required after arsenic and ATRA therapy.

During induction therapy with either ATRA or ATO, it is important to monitor for the development of differentiation syndrome, which is manifested by fever, weight gain, respiratory distress, pulmonary infiltrates, episodic hypotension, and renal failure. This condition is believed to be related to the sudden maturation of promyeloblasts and usually responds to dexamethasone, which should be initiated immediately upon suspicion of this condition. Temporary discontinuation of ATRA or ATO is required for patients in poor clinical condition as a result of severe renal or pulmonary impairment. Prophylactic steroids to prevent differentiation syndrome are generally recommended for high-risk APL, whereas for low-risk APL, they are optional but have been used in some protocols even in lower-risk APL.[117]

Treatment with ATO can be complicated by QT-interval prolongation and, rarely, by sudden cardiac death. Therefore, before initiating treatment, any electrolyte imbalances should be corrected, especially hypomagnesemia and hypocalcemia, and other drugs that can prolong the QT interval should be discontinued.

High-Risk APL

The standard of care for patients who have high-risk APL is induction therapy using ATRA in combination with daunorubicin and cytarabine or ATRA in combination with ATO and idarubicin.[119,120] Induction treatment is then followed by consolidation therapy with ATRA plus daunorubicin or ATRA and ATO, which again is followed by maintenance therapy. If administered consistently,

these treatment regimens lead to excellent clinical outcomes. For instance, in the APML4 trial, the combination of ATRA, ATO, and idarubicin followed by ATRA and ATO consolidation and ATRA, 6-mercaptopurine, and methotrexate maintenance therapy led to excellent outcomes with a 5-year OS rate of 87%.[120] Recently, anthracycline-free regimens have shown excellent long-term outcomes for patients who have high-risk APL by adding gemtuzumab ozogamicin (an anti-CD33 monoclonal antibody conjugated to the anthracycline antibiotic calicheamicin) to ATRA and ATO.[121,122]

Molecular remission status is assessed during therapy and thereafter by reverse-transcription PCR monitoring for the PML-RARA transcript. A small fraction of patients who have APL morphology will have a different translocation and fusion partner for RARA, such as t(11;17), which is associated with a poor response to ATRA and ATO.[123]

KEY POINTS

- In 60% of patients who have AML, at least one clonal abnormality in chromosome number or structure can be found. These cytogenetic abnormalities, in combination with age and performance status, are the most important prognostic factors in AML and are indispensable in making therapeutic decisions.
- Genome-wide sequencing has identified more than 50 genes that are recurrently mutated in AML. Testing for mutations in *FLT3, NPM1, CEBPA, IDH1, IDH2, KMT2A, NPM1,* and *TP53*, among other genes, is important in making treatment decisions for patients who enter first remission.
- On the basis of cytogenetic and molecular markers, AML can be divided into several categories with distinct disease risk.
- Standard induction therapy for those eligible for intensive chemotherapy in AML involves the use of an anthracycline and cytarabine.
- All patients aged 70 to 75 years or younger who achieve complete remission, except those with a favorable-risk cytogenetic or molecular profile who achieve an early first complete remission and have no evidence of MRD after induction, should be considered for allo-SCT, particularly if the SCT comorbidity index score is low and a donor is available. Myeloablative conditioning is preferred for patients up to age 60 to 65 years.
- Patients who are considered unfit to receive chemotherapy because of age or medical comorbidities are treated with venetoclax in combination with an HMA or low-dose cytarabine. Studies of multiple novel combination therapies combining venetoclax with chemotherapy or targeted therapy are ongoing.
- The prognosis is poor for patients who have recurrent AML, and the likelihood of achieving a second remission is predicted by the length of the first remission. Individuals who have remained in remission for more than 1 year can be induced with the same chemotherapy administered for the first complete remission. Because of this poor outcome, transplantation should be considered for most patients who have recurrent AML and who are appropriate candidates.
- Genetic analysis should be repeated at the time of disease progression or relapse, given that multiple targeted therapies are currently approved in this setting. Gilteritinib is approved for relapsed/refractory *FLT3*-ITD–mutated AML, and ivosidenib, olutasidenib, and enasidenib are approved for *IDH1*- and *IDH2*-mutated relapsed/refractory AML. Revumenib is approved for relapsed/refractory AML with *KMT2Ar*. In addition, both revumenib and ziftomenib are approved for relapsed/refractory *NPM1*-mutated AML.
- The suspicion of APL in a patient who has newly diagnosed acute leukemia should trigger the immediate administration of ATRA to reduce the risk of early death resulting from hemorrhage.
- Patients who have APL should receive ATRA and ATO as part of induction and/or consolidation therapy.

CHRONIC MYELOID LEUKEMIA

CML accounts for approximately 15% of all adult leukemias with a median age at presentation of 67 years. The Ph chromosome created by t(9;22)(q34;q11) results in a fusion of two genes, *BCR* (on chromosome 22) and *ABL1* (on chromosome 9), creating the abnormal fusion oncoprotein BCR-ABL1, a dysregulated and constitutively active tyrosine kinase (p210). Another BCR-ABL1 fusion oncoprotein, p190, more common in the setting of Ph+ ALL, is detected in only 1% of patients who have CML. The BCR-ABL1 fusion protein manifests clinically with uncontrolled production of granulocytes (ie, neutrophils, eosinophils, and basophils) in various states of maturation.

CLINICAL PRESENTATION AND DIAGNOSIS

Historically, CML has been described as having three different phases—chronic phase, accelerated phase, and blast phase (blast crisis)—with the disease presenting in the chronic phase more than 90% of the time. Up to 50% of patients are diagnosed incidentally during routine blood testing. Untreated chronic-phase chronic myeloid leukemia (CP-CML) will progress to advanced-stage disease in 3 to 5 years.[124] Symptoms of CML include fatigue, night sweats, malaise, weight loss, bone aches, and abdominal discomfort from splenomegaly. Patients typically have leukocytosis, thrombocytosis, and moderate anemia at the time of presentation. The marrow is virtually always hypercellular with granulocytic hyperplasia. Ph positivity is observed in more than 90% of patients. In the remaining patients, cryptic or complex translocations leading to *BCR*::*ABL1* can be detected by FISH or PCR

assays. Both WHO and ELN have developed criteria to distinguish the phases of CML, with the most recent WHO update describing a biphasic scheme that recognizes only chronic and blast phases.[1,125] The blast cutoff value differs between WHO and ELN criteria, with the more commonly used WHO criteria defining blast phase as 20% blasts or more, whereas the ELN criteria define blast phase as 30% blasts or more.[1,125]

The recent WHO 2022 update for CML disease classification placed greater emphasis on high-risk features of progression and omitted the classification of accelerated phase. High-risk features of CML progression include, but are not limited to, the development of new additional chromosomal abnormalities, excess blasts (10%-19%) in the bone marrow or peripheral blood, and/or treatment failure in the effort to achieve complete hematologic response to the first tyrosine kinase inhibitor (TKI). The most common cytogenetic changes associated with CML evolution are additional Ph chromosomes, trisomy 8, isochromosome 17q, and trisomy 19.

In more than 60% of patients in blast crisis, the blasts are of myeloid lineage as determined by morphology and cell-surface markers. In 25% to 30% of patients, the blasts are of lymphoid lineage. In the remaining patients, blasts may be biphenotypic or undifferentiated. Determination of the blast lineage is useful for selecting appropriate therapy.

PROGNOSTIC FACTORS

With the advent of potent BCR-ABL1–selective TKIs, the prognosis of CML has improved dramatically compared with the pre-TKI era, with the life expectancy of patients who have CML now approaching that of the general population. Several prognostic models have been developed to assess prognosis and aid the selection of a TKI for the initial therapy for CML, including the Sokal, Euro (Hasford), and European Treatment Outcome Study scores. The most frequently used Sokal scoring system has been used to stratify risk for patients who have CML into low-, intermediate-, and high-risk groups for clinical trials evaluating TKIs. The Sokal score is based on the patient's age, spleen size, platelet count, and percentage of blasts in the peripheral blood.[126]

TREATMENT

Oral highly effective TKIs are now the first-line therapy for CML. Before the advent of TKIs, hydroxyurea, interferon alfa (IFN-α) with or without cytarabine, busulfan, omacetaxine, and allo-SCT were used in the management of CML. These therapies continue to be used in a limited manner. Omacetaxine was recently removed from the US drug market. Response to therapy in CML is assessed by measuring the hematologic, cytogenetic, and molecular responses to TKI treatment (Table 19-4).

Table 19-4 NCCN Criteria for Hematologic, Cytogenic, and Molecular Response and Relapse[127]

Complete hematologic response	Complete normalization of peripheral blood counts with a leukocyte count $<10 \times 10^9$/L
	Platelet count $<450 \times 10^9$/L
	No immature cells, such as myelocytes, promyelocytes, or blasts, in peripheral blood
	No signs or symptoms of disease with the disappearance of palpable splenomegaly
Cytogenetic response[a]	Complete cytogenetic response: no Ph+ metaphases
	Major cytogenetic response: 0%-35% Ph+ metaphases
	Partial cytogenetic response: 1%-35% Ph+ metaphases
	Minor cytogenetic response: >35%-65% Ph+ metaphases
Molecular response	Early molecular response: *BCR-ABL1* (IS) ≤ 10% at 3 and 6 months
	Major molecular response: *BCR-ABL1* (IS) ≤ 0.1% or a 3-log reduction in *BCR-ABL1* mRNA from the standardized baseline, if qPCR (IS) is not available
	Deep molecular response:
	MR4.0: *BCR-ABL1* (IS) ≤ 0.01% or
	MR4.5: *BCR-ABL1* (IS) ≤ 0.0032%
	Complete molecular response is variably described and is best defined by the assay's level of sensitivity (eg, MR4.5)
Relapse	Any sign of loss of hematologic response or loss of CCyR
	A 1-log increase in *BCR-ABL1* transcript levels with loss of MMR should prompt bone marrow evaluation for loss of CCyR, but is not itself defined as relapse (eg, hematologic or cytogenetic relapse)

Abbreviations: CCyR, complete cytogenic response; IS, International Scale; MMR, major molecular response; MR4.0, molecular response 4.0; mRNA, messenger RNA; NCCN, National Comprehensive Cancer Network; Ph+, Philadelphia chromosome–positive; qPCR, quantitative polymerase chain reaction.
[a]A minimum of 20 metaphases should be examined.
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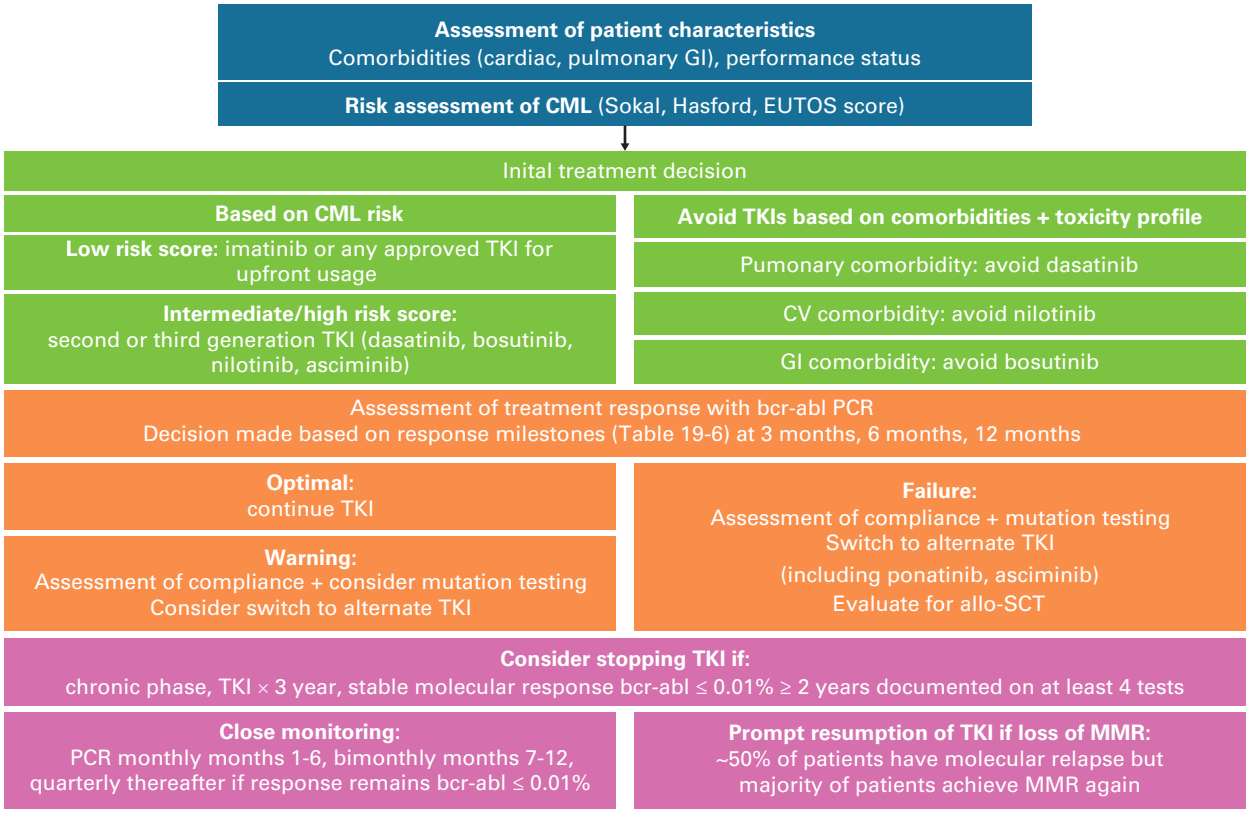
A simplified treatment algorithm for CP-CML based on the NCCN and ELN guidelines for the treatment of newly diagnosed CML is shown in Figure 19-3. The NCCN and ELN guidelines currently recommend initial therapy for CP-CML with the first-generation TKI imatinib (400 mg once per day) or a second-generation TKI, such as nilotinib (300 mg twice per day), dasatinib (100 mg once per day), or bosutinib (400 mg once per day). Recently, asciminib (80 mg once daily or 40 mg twice daily) has also been added to the NCCN guidelines as initial therapy.[125,128]

Figure 19-3 Treatment Algorithm for CP-CML Adapted From NCCN and ELN Guidelines[32,36,40]



Abbreviations: allo-SCT, allogeneic stem cell transplantation; CP-CML, chronic phase chronic myeloid leukemia; CV, cardiovascular; ELN, European LeukemiaNet; EUTOS, European Treatment Outcome Study; GI, gastrointestinal (tract); MMR, major molecular response; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.
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For the low- and intermediate-risk groups, imatinib remains an agent of choice, but for high-risk CML, the use of a second- or third-generation TKI is generally preferred. In addition, the specific toxicity profile of each TKI and the comorbidities of the patient help guide initial treatment selection. For instance, patients who have pulmonary comorbidities such as pleural effusion or pulmonary hypertension should avoid dasatinib, whereas patients who have significant cardiovascular comorbidities and hyperglycemia are advised to avoid nilotinib, and patients who have significant luminal gastrointestinal pathology are advised to avoid bosutinib.

Although most patients have an excellent response to initial TKI therapy, careful monitoring via blood cell counts, routine cytogenetic analysis of bone marrow, and FISH and quantitative PCR analyses of peripheral blood or bone marrow is critical for identifying treatment failures and considering making a change in therapy. The NCCN and ELN guidelines have established response criteria and clear milestones of response that need to be achieved with first-line TKI therapy.[125,128] Failure of treatment to achieve any of the goals of therapy at 3, 6, and 12 months or beyond should trigger an assessment of treatment compliance and testing for potential resistance mutations as well as consideration of a switch to an alternative TKI to limit the risk of progression and death (Table 19-5). Definitions of expected responses to second-line therapy have been developed, and they are relatively similar to those for first-line therapy. Failure of second-line therapy to achieve adequate disease response or a lack of response is an indication to proceed to allo-SCT. Patients who have accelerated-phase or blast-phase CML can respond to TKIs, but responses are generally short-lived, and the disease is relatively resistant to most types of therapy, with allo-SCT recommended for most eligible patients.

Table 19-5 **ELN Definitions of Response to TKIs as First-Line Therapy**[125,128]			
Time	**Optimal**	**Warning**	**Failure**
Baseline	NA	High risk or CCA/Ph+	NA
3 Months	*BCR-ABL1* ≤10% and/or Ph+ ≤ 35%	*BCR-ABL1* >10% and/or Ph+ 36%-95%	Non-CHR and/or Ph+ >95%
6 Months	*BCR-ABL1* <1% and/or Ph+ 0	*BCR-ABL1* >1%-10% and/or Ph+ 1%-35%	*BCR-ABL1* >10% and/or Ph+ >35%
12 Months	*BCR-ABL1* ≤0.1%	*BCR-ABL1* >0.1%-1%	*BCR-ABL1* >1% and/or Ph+ >0
After 12 months	*BCR-ABL1* ≤0.1%	Or loss of ≤0.1/% (MMR)	Loss of CHR, loss of CCyR, confirmed loss of MMR,[a] new mutations, or CCA/Ph+ changes

Abbreviations: CCA/Ph+, clonal chromosomal abnormalities in Philadelphia chromosome–positive cells; CCyR, complete cytogenetic response; CHR, complete hematologic response; ELN, European LeukemiaNet; MMR, major molecular response; NA, not applicable; TKI, tyrosine kinase inhibitor.
[a]MMR: *BCR-ABL1* ≤ 0.1% or ≥3-log reduction of *BCR-ABL1*.
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The ultimate confirmation of treatment efficacy is the ability to discontinue TKIs indefinitely without evidence of CML recurrence, which is referred to as treatment-free remission. Discontinuing TKI therapy seems to be safe in a select group of patients who have CML. For younger patients who are interested in reaching treatment-free remission as soon as possible, the use of a second-generation TKI instead of imatinib should be considered; second-generation TKIs induce a deeper response more rapidly than imatinib in a higher proportion of patients. However, the proportion of patients achieving deep molecular remissions beyond 8 years with first-line imatinib continues to increase, and long-term outcomes are similar between imatinib and second-generation TKIs.[129-131]

First-Generation TKI: Imatinib

Imatinib was the first TKI approved for the treatment of CML and has the longest record for safety and efficacy. At a dosage of 400 mg of imatinib once per day, a complete cytogenetic response has been achieved in 49% to 77% of patients, and a major molecular response after 1 year has been achieved in 18% to 58% of patients.[130,132] After 10 years of follow-up during the IRIS trial, 93% of patients had achieved a major molecular response, and 63% of patients had obtained a deep molecular response (MR4.5) (>4.5-log reduction in *BCR-ABL1*) with an OS of 84%.[130]

A better early response can also be obtained with higher doses of imatinib (600-800 mg once per day), but these are rarely used given the availability of alternative TKIs.[125,128] Chronic fatigue, musculoskeletal pain, and muscle cramps are common adverse effects of imatinib that are associated with a decreased quality of life. Skin hypopigmentation, bone pain, diarrhea, peripheral edema, elevated lipase and alanine transaminase (ALT) levels, and cytopenias are other reported adverse effects.

The most common identifiable reasons for resistance include poor compliance with therapy, mutations in the BCR-ABL1 kinase domain that interfere with imatinib binding, *BCR-ABL1* gene amplification or overexpression, decreased drug bioavailability, or increased drug efflux. ABL1 kinase domain mutations can be detected in samples collected before treatment, suggesting that the delayed failure of imatinib therapy may reflect the considerable amount of time required for outgrowth of these selected clones. Not all mutations in *BCR-ABL1* have the same significance; mutations causing T315I amino acid substitution and those affecting the phosphate-binding loop are believed to confer the greatest degree of imatinib resistance, whereas others can be overcome by a dose increase or are functionally irrelevant.[125,128]

Second- and Third-Generation TKIs

Compared with imatinib, second-generation TKIs, such as nilotinib, dasatinib, and bosutinib, lead to higher complete cytogenetic response and major molecular response rates after at least 1 year and sometimes later, and may slightly reduce the rate of progression or treatment failure. However, no differences in OS have been documented.[129,131] These drugs can also result in complete cytogenetic response rates in approximately 50% of patients whose disease is in the chronic phase and in whom resistance to imatinib develops; however, they are inactive against the *T315I* mutation.[125,128] Asciminib, which is also now approved for initial treatment, is active against the *T315I* mutation.

Ponatinib, a third-generation TKI, is approved for the treatment of patients who have *T315I*-mutated CML and for adults who cannot tolerate any other TKI. The adverse effect profiles of these TKIs are similar to those of imatinib, although with notable distinctions. All second- and third-generation TKIs have cardiac toxicity, and some reports highlight vascular safety issues with these agents.

Dasatinib and, less so, bosutinib can cause pleural effusions. Dasatinib has also been associated with pulmonary hypertension and significant but reversible inhibition of platelet aggregation, contributing to bleeding in some patients with accompanying

thrombocytopenia.[133] Nilotinib has been associated with QT-interval prolongation and sudden death, increased serum glucose levels and worsened diabetic control, and peripheral arterial occlusive disease.[134,135] Importantly, vascular complications, such as arterial and venous thrombosis and embolic events, have occurred with nilotinib and ponatinib. Ischemic arterial occlusive events can occur in 25% to 30% of patients or more with ponatinib at a 45 mg/day dosing schedule.[136]

Several studies have explored initiating lower dosages or dosage de-escalation of second-generation TKIs. There are several nonrandomized and retrospective analyses that detail successful efforts initiating TKIs such as bosutinib, nilotinib, or dasatinib at lower dosages or decreasing TKI dosing in closely monitored patients who have achieved optimal responses.[137] It is anticipated that these types of dosage adjustments will be used in practice to prevent and/or manage treatment-related adverse events and long-term toxicities. Newer TKIs such as olverembatinib are under investigation, and this also covers the *T315I* mutation. It can be dosed every other day.[138]

Stamp Inhibitor Asciminib

Asciminib is an allosteric BCR-ABL1 inhibitor that, instead of binding to the adenosine triphosphate (ATP) binding site, specifically targets the ABL myristoyl pocket of BCR-ABL1 (STAMP), which locks the protein in an inactive conformation. In October 2021, the FDA granted accelerated approval to asciminib for patients who have CP-CML that was previously treated with two or more TKIs (40 mg bid or 80 mg once per day) based on the ASCEMBL trial and for those who have CP-CML with a *T315I* mutation (200 mg twice daily) based on the CABL001X2101 trial.

In the ASCEMBL trial, patients who had CP-CML previously treated with two or more TKIs were randomly assigned to either asciminib or bosutinib. The primary endpoint was major molecular response at 24 weeks, which was achieved in 25.5% of patients treated with asciminib and 13.2% of patients treated with bosutinib (P = .029).[11] In the CABL001X2101 trial, asciminib was tested in patients who have CP-CML that carries a *T315I* mutation. Major molecular response was achieved in 42% of patients by 24 weeks and in 49% by 96 weeks.[139]

Several trials have evaluated asciminib in the frontline setting for newly diagnosed CP-CML. The Australasian Leukaemia and Lymphoma Group (ALLG) conducted the prospective phase 2 CML13 ASCEND-CML trial that evaluated asciminib as a first-line agent for CP-CML; enrollment was completed in December 2022. Major molecular responses at 12 months were comparable to those of other second-generation TKIs, although deeper responses seemed more rapid with asciminib.[140] Asciminib has now been FDA approved for use in newly diagnosed CP-CML based on results from the phase 3 ASC4FIRST trial, which demonstrated superior efficacy of asciminib with more frequent major molecular responses on the asciminib arm compared with investigator-selected TKI with less frequent grade 3 or higher adverse events.[12]

Allo-SCT

Allo-SCT is currently reserved for patients who have CP-CML that is resistant to TKIs, patients intolerant of all TKIs, those who have CML with a BCR-ABL1 *T315I* mutation, those who have accelerated-phase CML and poor response to TKIs, and those with blast-phase disease.[125,128] Three-year survival rates can be as high as 90%, and NRM rates lower than 10% when allo-SCT is used as second-line therapy after the failure of therapy with imatinib.[141] Patients who have accelerated-phase CML and poor response to TKIs or blast-phase CML should quickly undergo workup for allo-SCT because it is the only potentially curative therapy available to them. Results are somewhat better for patients whose disease is in the accelerated phase or blast crisis and responds to TKIs by entering a second chronic phase before SCT. Disease recurrence is the most common cause of transplantation failure in patients allografted for CML. Toxicity events from allo-SCT for CML have decreased over the last three decades, mainly because of a decrease in the number of transplantation-related deaths and, most notably, a reduction in the occurrence of chronic graft-versus-host disease. Post-transplantation maintenance therapy with TKIs is frequently used, although robust data supporting the use of TKIs in this setting are lacking.[142]

TREATMENT-FREE REMISSION

Patients may be considered for a TKI treatment-free remission attempt for multiple reasons, including TKI toxicity, cost of medication, convenience, and desire to become pregnant. However, patients need to meet strict criteria before TKI discontinuation can be considered (Table 19-6). Approximately half of patients who discontinue TKIs remain in long-term treatment-free remission.[143-145] Therefore, 10% to 15% of patients who have newly diagnosed CML are expected to achieve long-term treatment-free remission, given that half of the approximately one-third of patients who achieve sustained deep molecular remission and are eligible to attempt treatment-free remission remain in long-term treatment-free remission. Importantly, once a TKI is stopped, close monitoring of the BCR-ABL transcript by PCR is required (monthly for the first 6 months and then every 2 months for the next 18 months). If the major molecular response is lost at any time, a prompt restart of the TKI is recommended with monthly PCR monitoring until a major molecular response is recaptured. Fortunately, almost all patients who lose a molecular response are able to regain the response once TKI therapy is restarted.[143-145]

Table 19-6 **NCCN Criteria for TKI Discontinuation**[127]
Outside a clinical trial, all the following criteria should be met:
Age 18 years or older
Reliably taking TKI for ≥3 years
No previous resistance to a second-generation TKI that required switching to another agent
Previous evidence of a quantifiable *BCR-ABL1* transcript
Stable molecular response (ie, MR4; *BCR-ABL1* ≤0.01% by the IS) for ≥2 years, as documented by ≥4 separate tests performed ≥3 months apart
Access to a reliable qPCR test capable of detecting at least MR4.5, providing results within 2 weeks
Access to close monitoring: first 6 months, monthly measurement of *BCR-ABL1* by qPCR; next 18 months, measure every 2 months

Abbreviations: IS, International Scale; MR4, molecular response 4; NCCN, National Comprehensive Cancer Network; qPCR, quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.
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KEY POINTS

- TKIs such as imatinib, nilotinib, dasatinib, and bosutinib are remarkably effective in newly diagnosed CP-CML, leading to complete hematologic and cytogenetic responses for most patients with OS similar to that of age-matched controls. However, continued therapy and careful follow-up are necessary. Asciminib, an allosteric inhibitor of the myristoyl site of the BCR-ABL1 protein, is now also approved in the newly diagnosed setting.
- Second-generation TKIs (eg, dasatinib, nilotinib, and bosutinib) result in quicker cytogenetic and molecular responses compared with imatinib, with no differences in OS.
- Patients who have *T315I*-mutated CML may respond to ponatinib, although the duration of response is typically short.
- Asciminib is approved by the FDA for patients who have CP-CML with resistance to at least two previous TKIs or CP-CML with a *T315I* mutation.
- Patients who have accelerated or blast-phase CML can respond to TKIs, but responses are generally short, and the disease is relatively resistant to most types of therapy. Allo-SCT is potentially curative for these patients.

MYELOID PRECURSOR CONDITIONS

The steady increase in the use of relatively inexpensive high-throughput genetic sequencing has led to an increase in the detection of clonal myeloid precursor conditions, including clonal hematopoiesis and clonal cytopenia of undetermined significance (CCUS).[146] Clonal hematopoiesis and CCUS need to be distinguished from idiopathic cytopenia of undetermined significance (ICUS) and MDS based on the presence of clonality, cytopenias, dysplasia, and increased blasts (Table 19-7).[146] Clonal hematopoiesis with somatic mutations, sometimes called clonal hematopoiesis of indeterminate potential, is defined as the presence of a clonal blood cell population associated with a recognized hematologic neoplasm driver mutation at a VAF greater than 2% in the absence of cytopenias or a WHO-defined disorder. It is a common aging-associated biologic state (present in 20%-30% of patients older than 60 years) that further predisposes them to the development of cardiovascular disorders and hematologic malignancies such as MDS/AML. Although many clonal hematopoiesis–associated mutations are reported, *DNMT3A*, *TET2*, and *ASXL1* (so-called *DTA* mutations) are the acquired variants most often reported, which account for more than 80% of the cases, with mutations in *JAK2*, *TP53*, *SF3B1*, and *SRSF2* also seen.[147] Clonal hematopoiesis that occurs after chemotherapy or radiation therapy for a nonmyeloid malignancy is most often associated with the expansion of mutations in DNA damage response genes (*TP53*, *PPM1D*, *CHEK2*).[148] Clonal hematopoiesis–defining mutations confer a modest risk (0.5%-1%) of an increase in hematologic malignancies per year but are associated with a 40% increased risk of cardiovascular events and death as a result of myocardial infarction or stroke.[149] The current understanding regarding the causal relationship between clonal hematopoiesis and increased cardiovascular morbidity and mortality is that an accelerated development of atherosclerosis is driven by an altered function of the NLRP3 (nucleotide oligomerization domain [NOD]–like receptor pyrin domain)/interleukin-1β [IL-1β]) inflammasome in mutated monocytes and macrophages.[150]

More recently, clonal hematopoiesis was also found to be associated with and potentially to be a direct contributor to the pathophysiology of a multitude of other diseases, including chronic obstructive pulmonary disease,[151] osteoporosis,[152] gout,[153] chronic kidney disease,[154] and hemophagocytic lymphohistiocytosis.[155] In contrast to the negative association of clonal hematopoiesis with these diseases, clonal hematopoiesis is potentially beneficial in other clinical contexts. *DNMT3A* mutations detected in cells of allo-SCT donors were found to be associated with improved recipient survival as a result of a reduction in the risk of relapse after transplantation.[156] Interestingly, clonal hematopoiesis was found to be associated with a reduced risk of developing

Alzheimer's disease[157] and a reduced risk of mortality in a trial of patients who have metastatic colon cancer treated with chemotherapy (in particular, a pronounced effect was observed in those with *DNMT3A* mutations).[158] Clonal hematopoiesis has been reported after CAR T-cell therapy.[159]

Table 19-7 Myeloid Precursor Conditions

Characteristic	Myeloid Precursor Subtype			
	CHIP	ICUS	CCUS	MDS
Clonal	Yes	No	Yes	Yes
Dysplasia	No	No	No	Yes
Cytopenias	No	Yes	Yes	Yes

Abbreviations: CCUS, clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential; ICUS, idiopathic cytopenia of undetermined significance; MDS, myelodysplastic syndrome.
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ICUS is defined as single or multiple cytopenias that remain unexplained despite an appropriate evaluation, including bone marrow examination. The condition excludes patients who have a known clonal mutation. By contrast, CCUS is defined as the identification of a clonal mutation in a patient who has one or more clinically meaningful unexplained cytopenias who does not meet WHO-defined criteria for a hematologic neoplasm.[146,160] In a large study, patients who had CCUS were found to have a significantly higher probability of developing a myeloid neoplasm compared with patients who had ICUS (5- and 10-year cumulative probabilities of progression were 82% vs 9% and 95% vs 9%, respectively; $P < .001$).[160]

Clonal hematopoiesis risk scoring systems have been published,[13,14] which provide a simple and reproducible prognostic tool for assessing the risk of progressing to a myeloid malignancy over time. One study analyzed whole-exome sequencing data from 193,743 healthy volunteer participants in the United Kingdom and found that 11,337 (5.85%) had pathogenic variants in genes associated with myeloid malignancies and otherwise met criteria for clonal hematopoiesis of indeterminate potential or CCUS. Using conditional probability–based recursive partitioning analysis, the authors identified a set of variables critical for classifying patients who had CHIP or CCUS into groups with distinct risk of myeloid malignancy (mutations in *SF3B1*, *SRSF2*, *ZRSR2*, *JAK2*, *TP53*, *RUNX1*, *FLT3*, *IDH1*, and *IDH2* were classified as high-risk mutations). Based on these clinical and molecular characteristics, patients who have clonal hematopoiesis are categorized into three risk groups: low, intermediate, or high risk of progression to myeloid malignancy. This and other risk prediction models in myeloid precursor diseases continue to require real-world validation and refinement.[161] Experts currently do not recommend routine screening for clonal hematopoiesis because evidence is lacking regarding the management of cardiovascular and hematologic neoplasm risks associated with clonal hematopoiesis. Clinical trials are currently being developed that test early intervention for patients who have clonal hematopoiesis and CCUS; however, these patients should not be treated outside a clinical trial.[161] Anti-inflammatory agents such as canakinumab have been examined and have shown a reduction in cardiovascular events among patients who have *TET2*-mutated clonal hematopoiesis.[162] VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoimmune, somatic) is associated with *UBA1* mutations and can arise from existing clonal hematopoiesis. Treatments are designed to inhibit inflammatory manifestations.[163]

KEY POINTS

- Clonal hematopoiesis is defined by a hematologic neoplasm driver mutation at a VAF greater than 2% in the absence of cytopenia, dysplasia, or increased blasts. Cytopenia is present in both CCUS and ICUS; note that CCUS is associated with a clonal mutation in addition to cytopenia.
- The risk of progression to a myeloid malignancy (MDS or AML) is comparably lower for those with clonal hematopoiesis (approximately 0.5%-1% per year) or ICUS (approximately 1% per year) and higher for those with CCUS (approximately 10%-20% per year). Risk factors have now been validated, and a clonal hematopoiesis risk score can be determined.[13,14]

MYELODYSPLASTIC SYNDROMES

MDS comprises a heterogeneous group of malignant disorders characterized by disordered growth and differentiation of hematopoietic progenitors and a variable risk of transformation to AML. MDS generally affects older individuals (median age at diagnosis, 65-70 years); only 10% of patients are younger than 50 years.

PATHOGENESIS

MDS occurs as a result of the sequential acquisition of somatic mutations in hematopoietic stem cells. Clonal mutations with higher allele frequencies are more likely to be present in the disease-initiating cells of MDS. Clonal hematopoiesis and CCUS, discussed in the previous section, are now considered to be MDS precursor conditions.

Typically, early driver mutations occur in genes involved in RNA splicing and DNA methylation. Links between cytogenetic abnormalities and MDS phenotype are now well established. For example, patients who have del(5q33) (ie, the 5q-minus syndrome) generally have severe macrocytic anemia, a normal or elevated platelet count, and a relatively low rate of progression to AML. Disease in these patients frequently responds to treatment with lenalidomide. *RPS14* and casein kinase 1A1 (*CSNK1A1*) have been identified as likely candidate genes involved in the 5q-minus syndrome and its response to lenalidomide.[164]

Sequencing studies have revealed a number of recurrent point mutations beyond those involving cytogenetic abnormalities. These include, but are not limited to, RNA splicing machinery mutations (*SF3B1*, *SRSF2*, *ZRSR2*, *U2AF1*); DNA methylation genes (*TET2*, *DNMT3A*, *IDH1/2*); chromatin modulation (*ASXL1*, *EZH2*); RAS pathway genes such as *KRAS*, *NRAS*, *CBL*, *NF1*, and *PTN11*; and cohesin complex genes such as *STAG2*. *SF3B1* encodes a core component of the RNA splicing machinery and is frequently mutated in patients who have MDS with ring sideroblasts. These patients tend to have lower-stage disease and better prognosis overall.[165]

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical findings in MDS are nonspecific; are related to the reduction or dysfunction of blood cells present at diagnosis; and include fatigue, bleeding diathesis, and infections. Interestingly, concurrent systemic inflammatory and autoimmune diseases are observed in up to 25% of patients who have MDS. The diagnosis is based on the examination of the blood and bone marrow, which typically shows a hypercellular marrow with dysplastic features and, in some cases, increased numbers of blasts. The diagnostic classification of MDS was recently updated by the simultaneous publication of the 2022 WHO classification and the 2022 ICC.[1,3] The WHO classification renamed these disorders myelodysplastic neoplasms. A diagnosis of dysplasia requires morphologic dysplasia in at least 10% of cells in at least one lineage. In all, 50% to 60% of patients have an abnormal karyotype.

Although there is a generally strong consensus between the 2022 WHO classification and the ICC, there are several important and consequential differences.[166] One notable and clinically relevant difference between these two classifications is the creation of the novel entity MDS/AML in the ICC, which is applied to patients who have 10% to 19% blasts in the peripheral blood and/or bone marrow. The creation of this novel category by the ICC is supported by a growing body of evidence showing that the prognosis of patients who have oligoblastic (20%-30% blasts) AML and patients who have the WHO category of MDS-increased blast 2 (which is eliminated from the ICC but was retained by the WHO) are comparable.[1]

As the prognostic impact of mutations is increasingly appreciated, the 2022 WHO classification and the ICC define mutation-specific subtypes of MDS.[1,3,166] The presence of *SF3B1* mutations is associated with a relatively favorable prognosis; it is defined as MDS with low blasts and *SF3B1* mutation by the WHO and as MDS with mutated *SF3B1* in the ICC. The negative prognostic impact of *TP53* mutations is primarily driven by patients who have biallelic (WHO nomenclature) or multihit (ICC nomenclature) *TP53* alterations. Biallelic or multihit *TP53* loss can be caused by the presence of multiple mutations (presumably affecting both alleles), one mutation and a deletion of the *TP53* locus on 17p (often in the context of a complex karyotype), or one mutation combined with copy-neutral loss of heterozygosity. The 2022 WHO classification adds MDS, hypoplastic, and MDS with fibrosis as disease subtypes that must be distinguished from aplastic anemia and primary MF, respectively.[1]

PROGNOSIS

The most important independent prognostic factors identified in MDS were classically the percentage of bone marrow blasts, number of cytopenias, and karyotype, but more recently, attention has been given to the role of specific mutations. Monosomies 5 and 7 are associated with the shortest survival, whereas the longest survival is associated with a normal karyotype and –Y, del(11q), del(5q), or del(20q) as the sole abnormality.[167] These factors were used to develop the International Prognostic Scoring System (IPSS) and later the revised IPSS (IPSS-R), which categorizes patients who have primary MDS into five risk groups with differing survival and risk of progression to AML. Findings from additional studies suggest that the prognosis is worse for patients who have therapy-related MDS than for patients who have primary MDS. Examination for heritable germline mutations is important, particularly in younger patients. These include but are not limited to *GATA2* deficiency, Schwachman-Diamond syndrome, telomeropathies, and mutations of *DDX41*.[168]

Several mutations (*ASXL1*, *RUNX1*, *EZH2*, and *TP53*) are associated with shorter survival, whereas only one mutation, *SF3B1*, has been consistently demonstrated to confer a more favorable prognosis. *TP53* mutations are encountered in 5% to 10% of patients who have MDS, are enriched in patients who have therapy-related myeloid neoplasms, and are associated with particularly poor outcomes. Patients who have MDS who carry a *TP53* mutation have poor outcomes even if they undergo allo-SCT. In a study of 1,514 patients who had MDS, the presence of a *TP53* mutation was associated with a median OS of 0.7 years and a 3-year OS rate of only 20% after transplantation. Although younger patients who have *TP53* wild-type had significantly longer OS after transplantation compared with older patients, the presence of a *TP53* mutation predicted significantly shorter OS independent of age.[169] It is increasingly understood that not all *TP53* mutations carry equal prognostic weight and that distinct patient subpopulations exist even within the cohort of patients who have *TP53*-mutated MDS.[170] Patients who have MDS with a so-called multihit state of *TP53* mutations, defined as either two separate *TP53* mutations or loss of the remaining wild-type allele by

either chromosomal deletion or copy-neutral loss of heterozygosity, have significantly worse outcomes compared with patients who have only a single *TP53* mutation. Patients who have multihit targeting of *TP53* had a median OS of only 0.7 years with a dismal 3-year OS rate of 8%. Now, there is also evidence for nonmutational TP53 dysfunction in MDS, which is also associated with a poor prognosis.[171]

Several attempts have been made to refine prognostic scoring in MDS, with the most important systems being the WHO Prognostic Scoring System (WPSS)[172] and the revised IPSS.[167] Given the importance of mutations in the prognostication of MDS, the molecular IPSS (IPSS-M) mutation-based risk assessment tool is becoming the standard-of-care risk assessment model.[15] It combines the prognostic impact of 38 gene mutations with traditional predictors (eg, blood counts, blast percentage, and karyotype) and improves prognostication compared with the IPSS-R. Table 19-8 shows the clinical outcome based on IPSS-M risk stratification.

Table 19-8 Outcomes Based on IPSS-M Risk Stratification

Characteristic	Very Low	Low	IPSS-M Risk Category*		High	Very High
			Moderate Low	Moderate High		
Patients—No. (%)	381 (14)	889 (33)	302 (11)	281 (11)	379 (14)	469 (17)
Risk score	≤−1.5	>−1.5 to −0.5	>−0.5 to 0	>0 to 0.5	>0.5 to 1.5	>1.5
Hazard ratio (95% CI)†	0.51 (0.39-0.67)	1.0 (Reference)	1.5 (1.2-1.8)	2.5 (2.1-3.1)	3.7 (3.1-4.4)	7.1 (6.0-8.3)
Median LFS (25%-75% range)—years‡	9.7 (5.0-17.4)	5.9 (2.6-12.0)	4.5 (1.6-6.9)	2.3 (0.91-4.7)	1.5 (0.80-2.8)	0.76 (0.33-1.5)
Median OS (25%-75% range)—years	10.6 (5.1-17.4)	6.0 (3.0-12.8)	4.6 (2.0-7.4)	2.8 (1.2-5.5)	1.7 (1.0-3.4)	1.0 (0.5-1.8)
AML-t—%						
By 1 year	0	1.7	4.9	9.5	14.3	28.2
By 2 years	1.2	3.4	8.8	14	21.2	38.6
By 4 years	2.8	5.1	11.4	18.9	29.2	42.8
Death without AML—%						
By 1 year	2.2	8.5	12	18	19.3	30.6
By 2 years	7	16.2	19.8	31.1	39.8	45.6
By 4 years	15.9	29.5	33.6	51.1	54.2	51.3

Abbreviations: AML, acute myeloid leukemia; AML-t, acute myeloid leukemia transformation; CI, confidence interval; IPSS-M, International Prognostic Scoring System with Molecular; LFS, leukemia-free survival; OS, overall survival.
*Key metrics are presented across clinical endpoints per IPSS-M risk category.
†Hazard ratio is for the risk of leukemic transformation or death. Because the low category had the largest size, it was used as the reference level.
‡The 25% to 75% range represents the central interquartile interval. For example, for a 25% to 75% OS range from A to B years, 50% of patients lived longer than A years and died before B years.
Permission from NEJM Evidence, Elsa Bernard, Heinz Tuechler, Peter L. Greenberg, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes, Volume No 1, Issue 7, Table 2, Copyright © 2022 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

The evolution and important points regarding the following prognostic systems in MDS have been reviewed by DeZern and Greenberg.[173] An online calculator is available for clinicians to use at https://mds-risk-model.com/.

TREATMENT

The therapeutic strategy for MDS is based primarily on disease risk. The main goals for patients who have IPSS low- or intermediate-1–risk (lower risk) MDS are to reduce the consequences of cytopenias and improve quality of life, whereas for patients who have intermediate-2– or high-risk (higher risk) MDS, the focus is on disease modification with prevention of transformation into AML and prolongation of survival. Supportive care is crucial in all risk categories of MDS and encompasses transfusion support, growth factor support in select patients, management of iron overload in low-risk patients and before transplantation, and appropriate use of antibiotics for prophylaxis or treatment of infections. Deferoxamine and deferasirox are oral iron chelators that are available and can be used in those who have had 20 to 30 red blood cell (RBC) transfusions and have serum ferritin levels of 2,000 ng/mL or above, with the goal to keep the level at <1,000 ng/mL. Figure 19-4 shows a treatment algorithm for newly diagnosed MDSs.

Figure 19-4 Treatment Algorithm for Newly Diagnosed MDS

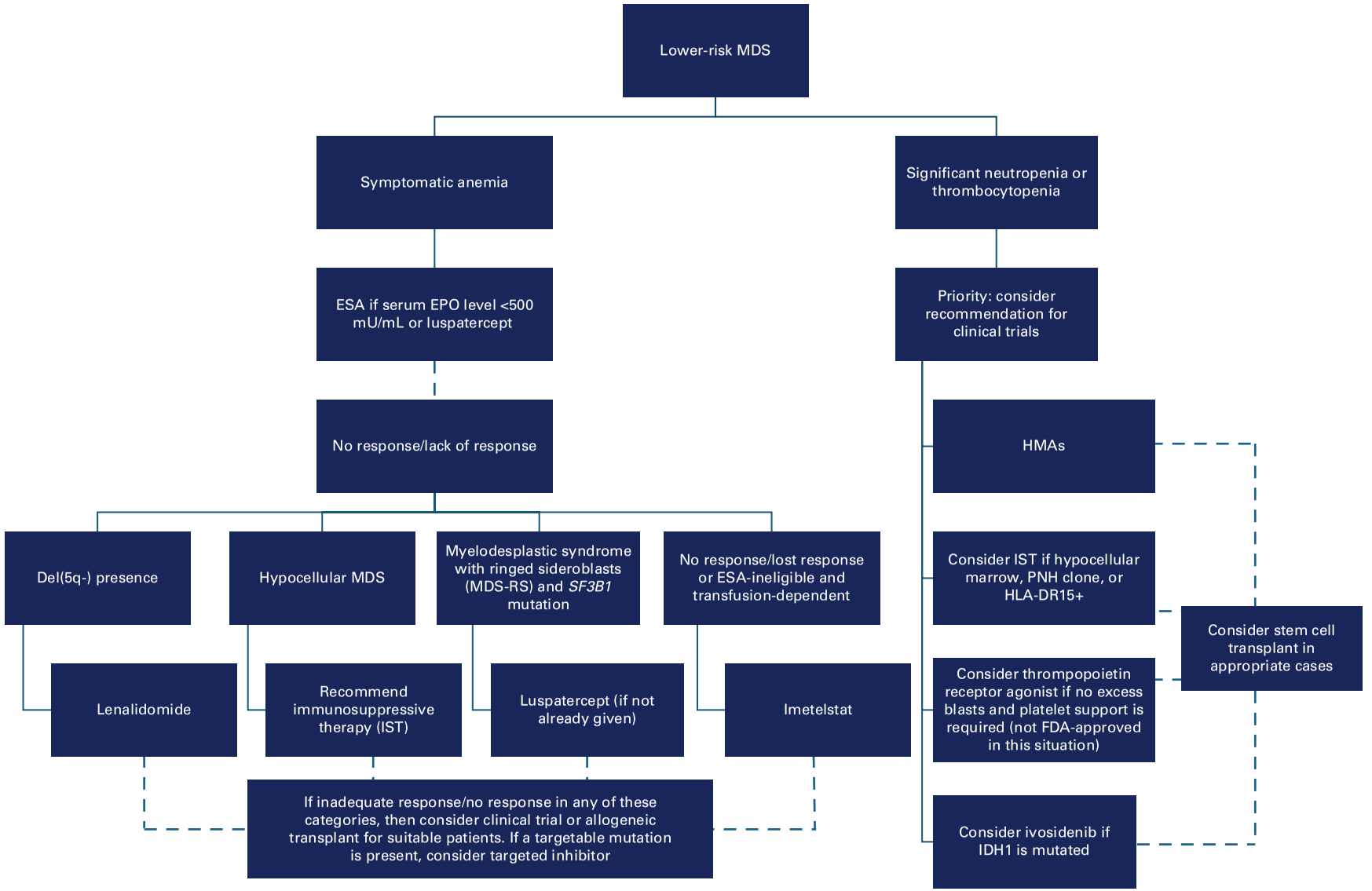
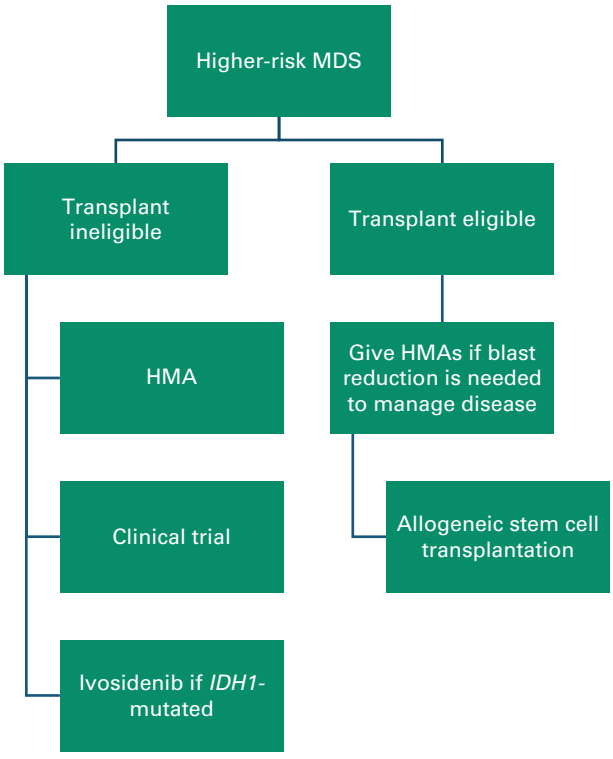


Figure 19-4 Continued



Abbreviations: EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; HMA, hypomethylating agent; IDH, isocitrate dehydrogenase; IST, immunosuppressive therapy; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal hemoglobinuria.
Dotted lines indicate alternative considerations.
Lower risk = very low and low by IPSS-R and very low, low, and moderate low by IPSS-M; higher risk = intermediate, high, and very high by IPSS-R and moderate high, high, and very high by IPSS-M.
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Lower-Risk MDS

To make the best treatment decisions for patients who have lower-risk MDS, it is helpful to know the endogenous erythropoietin level of the patient, the number of transfusions the patient required in the past, and whether an isolated 5q-minus abnormality or ring sideroblasts and/or an *SF3B1* mutation are present.

ESAs can improve the anemia associated with MDS and are most effective in patients who have low endogenous erythropoietin levels (<500 U/L and ideally <200 U/L) and relatively low transfusion burden (<2 units of packed RBCs in the last month). If these favorable prognostic factors are present, the response rate to ESAs is approximately 70%; however, in the absence of these favorable prognostic factors, the response rate to ESAs is only approximately 7% to 20%. The target hemoglobin should be no higher than 12 g/dL and, in most cases, 10 g/dL. The addition of a myeloid growth factor may result in additional responses for 20% of patients; however, myeloid growth factors alone, including G-CSF, have poor responses in MDS and are currently not recommended as single agents. Thrombopoietin receptor agonists such as eltrombopag are not approved for use in MDS, but they are sometimes used in cases of severe chronic thrombocytopenia in low-risk categories.

The introduction of lenalidomide revolutionized the treatment of patients who have MDS with a 5q-minus abnormality, which is present in approximately 10% to 20% of patients who have MDS. In the phase 2 MDS-003 trial, lenalidomide yielded RBC transfusion independence for more than 8 weeks during weeks 1 to 24 in 67% of patients who have lower risk 5q-minus MDS.[174] Lenalidomide clearly showed evidence of exerting a disease-modifying effect, with cytogenetic response being achieved in 50% to 73% of patients.[175]

For patients who do not respond to ESAs or are unlikely to respond, several additional treatment options exist. First, even if patients do not have a 5q-minus abnormality, they might derive benefit from adding lenalidomide to ESA therapy. A randomized phase 2 trial showed that the combination of lenalidomide and ESAs significantly improved the erythroid response rate (39.4% vs 23.1%) in patients who have ESA-resistant lower-risk MDS compared with lenalidomide alone.[176] A phase 3 trial confirmed that lenalidomide restores sensitivity to patients who have ESA-insensitive lower risk non–5q-minus MDS, yielding a significantly higher rate and duration of major erythroid response compared with lenalidomide alone (28.3% vs 11.5%) with a longer but not statistically significant duration of response (23.8 vs 13 months).[177]

The FDA approved luspatercept in April 2020 for patients who had low- to intermediate-risk MDS with ring sideroblasts, MDS with an *SF3B1* mutation, or MDS/MPN with ring sideroblasts and thrombocytosis who have not responded to ESAs and were RBC transfusion dependent. Luspatercept is a recombinant fusion protein that contains the modified extracellular domain of the activin receptor IIB, which blocks the transforming growth factor-beta superfamily inhibitors of erythropoiesis. A phase 3 randomized double-blind study (MEDALIST) comparing luspatercept with placebo in low- to intermediate-risk patients who had MDS-related anemia, ring sideroblasts, and/or *SF3B1* mutations showed that patients treated with luspatercept had a significantly reduced transfusion burden compared with those treated with placebo (37.9% vs 13.2% reached transfusion independence for 8 weeks or longer; $P < .0001$).[178] Luspatercept response is not dependent on erythropoietin levels, and it is now approved for up-front use even before ESAs are tried on the basis of the phase 3 COMMANDS trial, in which it outperformed erythropoietin in terms of hemoglobin increases and transfusion independence. In all, 59% of patients in the luspatercept group and 31% in the ESA group reached RBC transfusion independence for at least 12 weeks with an associated increase in hemoglobin by at least 1.5 g/dL during the first 24 weeks of the study. The best responses were seen in patients who had ring sideroblasts and *SF3B1* mutations, but responses were seen in patients who had other mutations as well. The FDA has now approved it in low- and intermediate-risk patients who have MDS and are transfusion dependent.[17]

Imetelstat, a first-in-class telomerase inhibitor, improved hemoglobin levels and led to transfusion independence in patients who had lower-risk MDS and were ineligible for, had relapsed with, or were refractory to ESAs. The phase 3 IMerge trial of imetelstat versus placebo for patients with lower-risk MDS who had required four or more red cell transfusions over 8 weeks and had not responded to ESAs or were ineligible to receive them met its primary efficacy endpoint of 8-week transfusion independence (40% vs 15%), and imetelstat was granted FDA approval in June 2024. The most common grade 3 to 4 adverse effect was neutropenia.[21] The optimal sequencing of ESAs, luspatercept, and imetelstat requires further investigation, as does their role in earlier use in anemic patients not yet needing transfusions.[179]

Patients who have MDS and are positive for HLA-DR15, which is characterized by bone marrow hypoplasia, normal cytogenetics, low-risk disease, and a paroxysmal nocturnal hemoglobinuria clone, have shown prolonged responses to antithymocyte globulin, cyclosporine, or the two agents in combination.[180]

For patients who do not respond to treatment with these agents, HMAs such as azacitidine, decitabine, and the oral decitabine and cedazuridine can be used. Although the standard regimens involve 7 days of azacitidine administration and 5 days of decitabine, in a phase 3 clinical trial in lower-risk MDS, decitabine dosed on days 1 to 3 of a 28-day cycle led to RBC transfusion independence and complete response in 41% and 36% of patients, respectively.[16] A shortened 5-day course of azacitidine has also been examined.[181] Up to six cycles of azacitadine may be needed before determining a response, and the optimal duration of therapy is not known, but HMAs are usually continued until relapse occurs or toxicity intervenes. Dosage and schedule adjustments are often required because of cytopenias. Those who have mutated *IDH1* may be treated with ivosidenib after four to six cycles of an HMA have been ineffective. This treatment was approved by the FDA in 2023. The IDH1 inhibitor, olutasidenib, is also being investigated in MDS.[182] Studies are also underway to examine the effects of enasidenib in those with *IDH2* mutations, but this treatment has not yet been approved.

Platelet counts have responded to the thrombopoietin mimetics romiplostim and eltrombopag, but concern regarding proliferation of leukemic blasts remains from in vitro studies. Ongoing clinical trials with these agents will help further elucidate leukemic risk.[183] Patients who have MDS and are receiving frequent RBC supportive transfusions are at risk for iron overload and resultant end-organ (ie, heart, liver, and pancreas) complications. Iron overload is a contributing factor to early mortality and morbidity in MDS.[184] As previously noted, the iron chelators deferoxamine and deferasirox are available to treat iron overload in MDS. Deferasirox has a black-box warning for potentially fatal acute renal failure and hepatic failure.

Higher-Risk MDS

The key question for the management of a patient with higher-risk MDS is whether the patient is eligible to undergo allo-SCT. Allo-SCT is currently the only curative therapy for MDS and can lead to long-term disease-free survival (DFS) for 35% to 50% of patients, with many patients alive without evidence of disease more than 5 years after transplantation and some for as long as 25 years.

Azacitidine and decitabine are both approved as treatment of MDS (although a survival advantage was demonstrated only with azacitidine). Both are thought to have utility in MDS through their DNA demethylating activity, which leads to re-expression of key genes otherwise inactivated in MDS by hypermethylation. The effects of azacitidine were demonstrated in a phase 3 trial in which researchers found improved OS compared with conventional care (ie, supportive care alone, low-dosage cytarabine, or intensive chemotherapy as selected by investigators before random assignment) for patients who have IPSS intermediate-2– to high-risk disease.[185] Compared with the best supportive care, treatment with decitabine was reported to significantly reduce the risk of AML transformation and improve progression-free survival (PFS) in a randomized phase 3 trial in patients who have intermediate-1–, intermediate-2–, and high-risk MDS, whereas OS was not statistically significantly prolonged. Neither azacitidine nor decitabine is curative.[186]

In an oral formulation, decitabine is combined with the cytidine deaminase inhibitor cedazuridine, which prevents deactivation of decitabine by cytidine deaminase, leading to a prolonged half-life and potentially greater efficacy. Decitabine at 35 mg

plus cedazuridine at 100 mg once per day for 5 days yielded pharmacokinetic equivalence to standard decitabine at 20 mg/m^2 intravenously once per day for 5 days in patients who have MDS and chronic myelomonocytic leukemia; clinical responses were observed in 60% of treated patients with 21% of patients achieving a complete response (CR).[187] Decitabine and cedazuridine were approved by the FDA in July 2020 for the treatment of intermediate- and high-risk MDS.

Although isocitrate dehydrogenase (*IDH*) mutations are rare in MDS, ivosidenib has been approved for patients who have relapsed/refractory MDS that expresses this mutation. Eighteen adult patients received 500 mg once per day on 28-day cycles, and the CR rate was 28.9%, with all responses being CRs. Of the nine patients who were transfusion dependent, six became transfusion independent in a 56-day window after starting ivosidenib. The treatment was well-tolerated, with gastrointestinal toxicities being the most common type reported, with only rare cases of QTc prolongation noted.[20] Olutasidenib is also being studied in patients with *IDH1*-mutated MDS.

Patients who have higher-risk MDS have, in some cases, been treated with AML-like induction chemotherapy. Although response rates are lower than the rates seen in de novo AML, CRs have been reported in 40% to 60% of patients in some studies, but it is unknown whether this results in an improvement in OS. Patients who have higher risk MDS whose disease does not respond to HMAs have a poor prognosis with a median OS of 4 to 6 months, and investigational therapies should be promptly explored for this group of patients.[188]

A proposal for a revised International Working Group response criterion for higher-risk MDSs has been put forward. This will aid in the standardization of response criteria in this heterogeneous group of diseases.[189]

Allo-SCT

The BMT CTN 1102 study showed, in a biologic assignment trial, that reduced-intensity allo-SCT improved the survival rate of patients who have IPSS intermediate-2– or high-risk MDS who were aged 50 to 75 years compared with pharmacologic therapy. At 3 years, 48% of patients for whom donors were identified were alive compared with 27% of patients without donors who were treated with pharmacologic therapy alone. Similarly, leukemia-free survival was significantly higher in the donor arm (35.8%) than in the no-donor arm (20.6%; $P < .003$).[190] *ASXL1*, *RUNX*, *TP53*, and *Ras* mutations had a higher incidence of relapse and mortality, but post hoc analysis showed improved survival of *TP53* single and multihit cases. It is important to check for germline mutations because the results can impact conditioning regimens and donor selection. Allo-SCT should be considered an integral part of disease management for all patients who have advanced MDS and are fit enough to receive a transplant. There is controversy about whether treatment to reduce blasts before SCT is required.

Investigational Approaches to the Treatment of MDS

A multitude of novel therapeutics are in development in late-phase clinical trials for both lower- and higher-risk MDS. In transfusion-dependent low-risk MDS, investigators are examining the most effective sequential use of ESAs, luspatercept, and imetelstat. Several combination therapies that add novel agents to an HMA backbone have been examined in higher-risk MDS. For example, the combination of the BCL-2 inhibitor venetoclax with azacitidine, which is already approved for the treatment of AML, has also shown high response rates in MDS. In MDS, venetoclax is given for only 14 days compared with 28 days to avoid severe cytopenias. Results of the phase 3 VERONA trial (NCT04401748) have now been presented in abstract form, and this trial did not meet its primary endpoint of OS with the addition of vernetoclax to azacitidine versus azacitidine alone.[191,192] Full reports are awaited, but this would suggest that venetoclax does not improve outcomes in MDS but may be effective in blast reduction for those who have a high burden of blasts and are transplant eligible. CPX-351, the liposomal preparation of daunorubicin and cytarabine, is being examined in MDS as well.

HMA monotherapy with azacitidine or decitabine or oral decitiabine/cedazuridine remains the standard of care for patients who have higher-risk MDS and are considered ineligible for allo-SCT.

KEY POINTS

- The important prognostic factors for patients who have MDS are percentage of marrow blasts, karyotype, number of peripheral blood cytopenias, and molecular mutations.
- The therapeutic strategy for MDS is based primarily on the disease risk, with the main goals of reducing consequences of cytopenias, improving quality of life for patients who have lower risk disease, preventing transformation into AML, and improving survival for patients who have higher risk disease.
- The 5q-minus subtype responds well to therapy with lenalidomide, and administration of lenalidomide early in the disease course can delay the onset of RBC transfusion dependence.
- Luspatercept can be used in low- and intermediate-risk transfusion-dependent patients who have MDS independent of erythropoietin level, either before or after a trial with an ESA. Imetelstat is also now approved for those MDS patients with low to intermediate-1 risk who are transfusion dependent and have not responded to ESAs.
- Allo-SCT is the only curative treatment for MDS.

MYELOPROLIFERATIVE NEOPLASMS

MPNs comprise a heterogeneous group of hematologic disorders currently recognized by the WHO: PV, ET, and primary MF; mastocytosis; myeloid or lymphoid neoplasms associated with eosinophilia; and myeloid neoplasms with clinical, laboratory, and morphologic features that overlap with MDS and MPN (Table 19-9). This section focuses on the classic MPNs: PV, ET, and primary MF.

Table 19-9 2022 WHO Classification of MPNs, Myeloid Neoplasms Associated With Eosinophilia, and MDS/MPNs

Neoplasm	Classification
MPN	Chronic myeloid leukemia
	Polycythemia vera
	Essential thrombocythemia
	Primary myelofibrosis
	Primary myelofibrosis, prefibrotic or early stage
	Primary myelofibrosis, overt fibrotic stage
	Chronic neutrophilic leukemia
	Chronic eosinophilic leukemia
	Juvenile myelomonocytic leukemia
	MPN, NOS
Mastocytosis	
Myeloid and lymphoid neoplasms associated with eosinophilia and tyrosine kinase gene fusions	*PDGFRA* rearrangement
	PDGFRB rearrangement
	FGFR1 rearrangement
	JAK2 rearrangement
	FLT3 rearrangement
	ETV6::ABL1 fusion
	Other defined tyrosine kinase fusions: *ETV6*::*FGFR2*, *ETV6*::*LYN*, *ETV6*::*NTRK3*, *RANBP2*::*ALK*, *BCR*::*RET*, *FGFR1OP*::*RET*
MDS/MPN	Chronic myelomonocytic leukemia
	MDS/MPN with neutrophilia
	MDS/MPN with *SF3B1* mutation and thrombocytosis
	MDS/MPN, NOS

Abbreviations: MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NOS, not otherwise specified; WHO, World Health Organization.
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PATHOGENESIS

MPNs are characterized by stem cell–derived clonal myeloproliferation that can evolve into AML or, in the case of PV or ET, into MF (secondary [after PV/ET] MF). Multiple recurrent somatic mutations have been identified in these disorders. Most prominent among these are the usually mutually exclusive mutations in *JAK2* (primarily in exon 14 [ie, V617F] and rarely in exon 12), calreticulin (*CALR*; primarily exon 9 deletions and insertions), and myeloproliferative leukemia virus oncogene (*MPL*; primarily exon 10 mutations). *JAK2* mutations are found in almost 100% of patients who have PV, 50% to 60% of patients who have ET, and 55% to 65% of patients who have primary MF. Generally, 20% to 25% of patients who have ET and primary MF harbor *CALR* mutations, whereas *MPL* mutations are present in 3% to 4% of patients who have ET and 6% to 7% of patients who have primary MF. Increasingly, characteristic differences (eg, age at diagnosis, blood cell counts, risk of thrombosis) are recognized among these three mutations. In approximately 10% to 15% of patients who have ET or primary MF, neither *JAK2*, *CALR*, nor *MPL* mutations are found (ie, triple-negative result).[193]

In addition to these three genes, mutations in many other genes such as *LNK*, *CBL*, *DNMT3A*, *TET2*, *IDH1/2*, *EZH2*, and *ASXL1* have been described in MPNs. Several of these mutations constitutively activate cell-signaling pathways and lead to a clonal growth advantage. Other mutations affect genes involved in epigenetic regulation and are believed to cooperate with the first class of mutations. Although activation of the JAK-STAT pathway is believed to be central for MPNs, the pathophysiologic role for many of the mutations found in these disorders has yet to be determined.[193] Similarly, it is not fully understood why a single

mutation such as *JAK2* V617F can result in different clinically distinct disorders, although differences in mutant allele burden, *STAT1* signaling, order of mutation acquisition, clonal heterogeneity, and microenvironmental background may play a role.[194]

In PV, there is increasing evidence that hepcidin, the inhibitor of the cellular iron exporter ferroportin, plays a role. Iron deficiency is common in PV and is related to increased use in the production of RBCs. This is supported by the fact that patients who have certain *HFE* genes that lead to hemochromatosis and increased iron absorption, with a reduction in hepcidin, have an increased incidence of PV.[195] These and other observations have led to studies examining the use of hepcidin mimetics in PV.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients may have fatigue, constitutional symptoms (eg, fever, weight loss, night sweats), microvascular symptoms (eg, headaches, erythromelalgias), pruritus, bone pain, thromboses at unusual sites (eg, portal vein, hepatic vein), early satiety, and abdominal discomfort. Subsets of patients present with a thrombotic event or have a history of thrombosis.

On physical examination, palpable splenomegaly and/or hepatomegaly can be present, and evidence of extramedullary hematopoiesis at other sites may be found. Peripheral blood studies are notable for blood counts that exceed the upper limit of normal, and changes consistent with hypermetabolism, such as elevated serum levels of lactate dehydrogenase (LDH) and uric acid, often occur. Leuko-erythroblastic changes on peripheral blood smear are characteristic of MF or primary MF. Secondary causes for erythrocytosis and thrombocytosis must be excluded.

Mutational screening is helpful to demonstrate the presence of clonal hematopoiesis. For example, with *JAK2* mutation screening and a serum erythropoietin level (below normal in PV), essentially all patients who have PV will be identified. However, the presence of a mutation alone is not required for, nor is it proof of, a diagnosis of MPN. In many cases, it is important to rule out a BCR/ABL translocation.

A bone marrow examination is important for accurate diagnosis of an MPN, but may not be necessary at diagnosis in all cases of PV and ET. Characteristic findings enable the clinician to distinguish between PV (trilineage hematopoiesis with pleomorphic megakaryocytes), ET (megakaryocyte proliferation with large and mature morphology), and primary MF (megakaryocyte proliferation and atypia as well as reticulin and/or collagen fibrosis). Marrow findings also help identify prefibrotic primary MF (bone marrow morphology consistent with primary MF but without marked fibrosis) or masked PV (bone marrow morphology consistent with PV but with blood cell counts that do not meet the criteria for PV). Table 19-10 outlines WHO diagnostic criteria for PV, ET, and MF.

PROGNOSTIC FACTORS

The median life expectancy varies considerably among patients who have ET (20 years), PV (14 years), or primary MF (6 years) because of varying risks of thrombosis, bleeding, and clonal evolution. The risk of leukemic transformation is substantially lower for PV and ET (at 20 years, <10% for PV and <5% for ET) than for primary MF. Once leukemic transformation has occurred, median survival is less than 6 months with a 3-year survival estimate of <5%.[197] An increasing number of risk factors have been recognized for shorter survival in various MPNs.

Prognostic Factors for PV

Thromboembolic events are the major cause of morbidity and mortality in PV. In the large ECLAP study of patients who had PV, two variables, being older than 65 years and having a history of previous thrombosis, were the most powerful predictors of recurrent thrombosis.[198] Although patients younger than 65 years and without previous thrombosis had an annual thrombosis risk of 2.5%, patients who had either one of the risk factors had an annual thrombosis risk of 5%, and patients who had both risk factors had an annual thrombosis risk of 11%. In the recently published REVEAL observational study of 2,510 patients who have PV, an elevated WBC count was associated with initial thromboembolic occurrence in both low-risk and high-risk patients, and this association was also found when hematocrit was controlled.[199] A prospective, multicenter study called PROSPERO is underway to validate other variables that may be associated with thromboembolic risk in PV.[200]

Prognostic Factors for ET

In the International Prognostic Score of Thrombosis scoring system for ET, patients are assigned a total score based on the following four features[201]: age older than 60 years (1 point), history of thrombosis (2 points), presence of cardiovascular risk factors (hypertension, diabetes, active tobacco use; 1 point), and presence of the *JAK2* V617F mutation (2 points). Using this model, three thrombosis risk groups were identified with different incidences of thrombosis per year: low risk (total score 0 or 1), 1% per year incidence of thrombosis; intermediate risk (total score 2), 2.4% per year incidence of thrombosis; and high risk (total score > 2), 3.6% per year incidence of thrombosis.

Prognostic Factors for Primary MF

The prognosis in primary MF is influenced by certain clinical factors (including older age, constitutional symptoms, anemia, leukocytosis, thrombocytopenia, circulating blasts, degree of bone marrow fibrosis, and transfusion dependence), specific

Table 19-10 **2016 WHO Diagnostic Criteria for PV, ET, and PMF**[196]	
Diagnosis	**Criteria Required for Diagnosis**
PV	Elevated hemoglobin concentration (men, >16.5 g/dL; women, >16.0 g/dL) or increased hematocrit (men, 49%; women, 48%) or increased red cell mass
	BM biopsy showing BM hypercellularity, trilineage hematopoiesis with prominent erythroid, granulocytic, and megakaryocyte proliferation with pleomorphic, mature megakaryocytes
	JAK2 V617F or *JAK2* exon 12 mutation; if such a mutation is absent, diagnosis of PV is still possible if there is a subnormal erythropoietin level
	Minor criterion: subnormal serum erythropoietin level
	Diagnosis of PV requires meeting either all three major criteria, or the first two major criteria and the minor criterion[a]
ET	Persistently elevated platelet count (≥450 × 10^9/L)
	BM with predominant proliferation of enlarged, mature megakaryocytes with hyperlobulated nuclei
	Not meeting diagnostic criteria for classic CML, PV, PMF, MDS, or other myeloid neoplasms
	JAK2 V617, *CALR*, or *MPL* mutation
	Minor criterion: presence of another clonal marker; if no clonal marker is present, there is no evidence of reactive thrombocytosis
	Diagnosis of ET requires meeting all four major criteria or the first three major criteria and the minor criterion
PMF	Megakaryocyte proliferation and atypia. For pre-PMF: no reticulin fibrosis grade >1, BM hypercellularity, granulocytic proliferation, and often decreased erythropoiesis. For overt PMF: grade 2-3 reticulin and/or collagen fibrosis
	Not meeting diagnostic criteria for classic CML, PV, ET, MDS, or other myeloid neoplasms
	JAK2 V617, *CALR*, or *MPL* mutation or other clonal marker; if no clonal marker is present, there is no evidence of minor reactive BM reticulin fibrosis (for pre-PMF) or reactive myelofibrosis (for overt PMF)
	Minor criteria: (1) anemia, (2) leukocytosis ≥11 × 10^9/L, (3) palpable splenomegaly, (4) LDH elevation, or (5), leuko-erythroblastosis (for overt PMF only)
	Diagnosis of overt PMF requires meeting all three major criteria and at least one minor criterion

Abbreviations: BM, bone marrow; CML, chronic myeloid leukemia; ET, essential thrombocythemia; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; MF, myelofibrosis; PMF, primary myelofibrosis; PV, polycythemia vera; WHO, World Health Organization.
[a]Criterion number 2 (BM biopsy) may not be required in patients with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial MF (present in up to 20% of patients) can be detected only by performing a BM biopsy; this finding may predict a more rapid progression to overt MF (post-PV MF).
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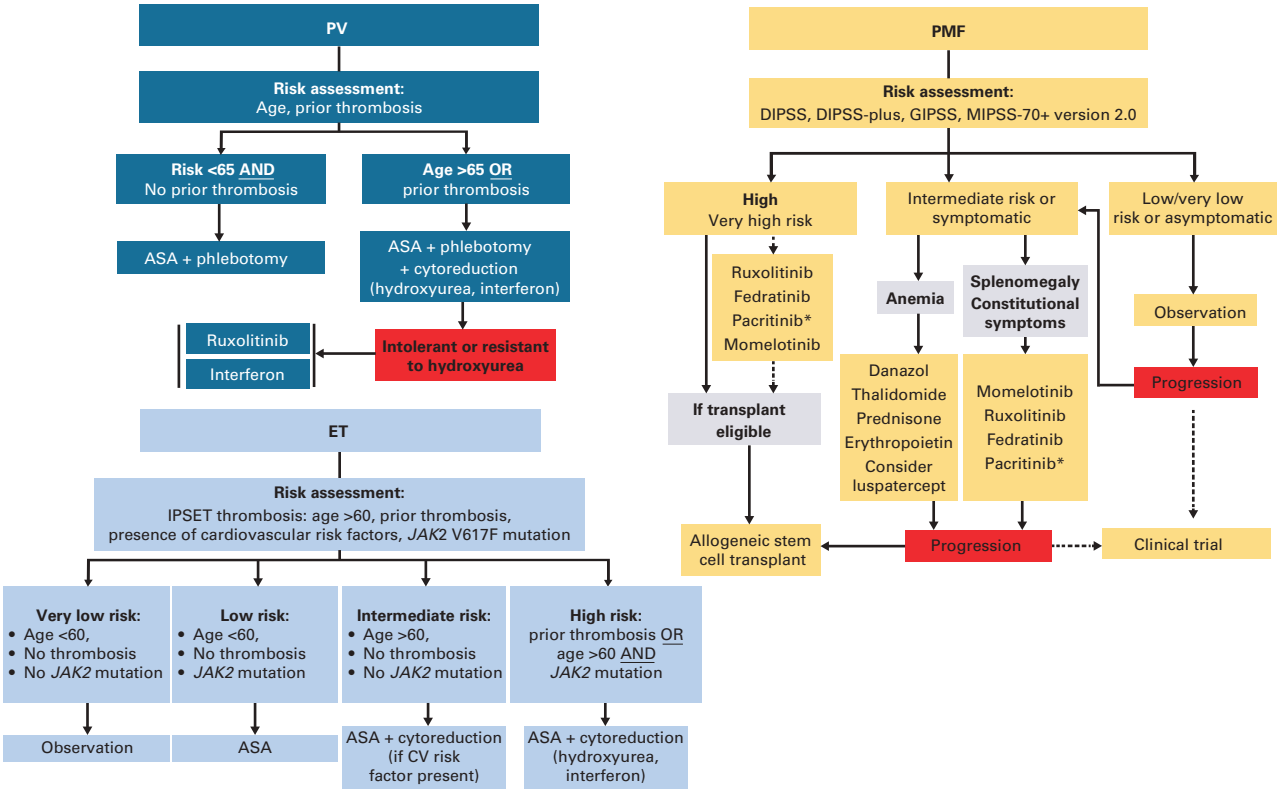
cytogenetic features, presence of driver mutations (*JAK2*, *CALR*, *MPL*), and certain high-risk molecular mutations (*ASXL1*, *SRSF2*, *U2AF1*, *EZH2*, *IDH1/2*).[202] Scoring systems are based on different combinations of these prognostic markers. The dynamic IPSS (DIPSS) is based on clinical information,[203] the DIPSS Plus is based on clinical and cytogenetic information,[204] and the mutation-enhanced IPSS and karyotype, MIPSS70 + v2.0, is based on clinical, cytogenetic, and mutational information.[205] The Genetically Inspired Prognostic Scoring System (GIPSS) is based on karyotype, absence of type 1–like *CALR* mutation, and the presence of *ASXL1*, *SRSF2*, or *U2AF1* mutations.[206] Karyotypic high-risk abnormalities include –7, inv(3), i(17q), and others, whereas +9, 20q–, and loss of the Y chromosome are some examples of favorable cytogenetics.[207] A prefibrotic early-stage MF has been defined, and in some patients, PV or ET transform to an MF state, so-called secondary MF, which can be prognosticated using the MySEC score or preferably the MIPSS70 + v2.0 score.[208]

TREATMENT

The general goals of therapy for MPNs are to alleviate symptoms, prevent thrombosis or bleeding, minimize the risk of progression to MF (for PV and ET), and, particularly in MF, reduce the risk of leukemic transformation and improve survival rates. Treatment is tailored on the basis of the individual patient's risk assessment for thrombosis and transformation into MF or AML (Fig. 19-5).

Figure 19-5 Treatment Algorithm for MPNs



Abbreviations: ASA, acetylsalicylic acid; CV, cardiovascular; DIPSS, Dynamic International Prognostic Scoring System; DIPSS Plus is based on clinical and cytogenetic information; ET, essential thrombocythemia; GIPSS, Genetically Inspired Prognostic Scoring System; IPSET, International Prognostic Score (of thrombosis) in Essential Thrombocythemia (IPSET-thrombosis); MIPSS70 + v2.0, mutation-enhanced IPSS plus karyotype is based on clinical, cytogenetic, and mutational information; MPN, myeloproliferative neoplasm; PMF, primary myelofibrosis; PV, polycythemia vera.
*If platelets <50 x 10^9/L
Dotted lines indicate alternative considerations.
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Therapy for PV

Patients aged 60 years or younger with no history of thrombosis are classified as low risk, whereas all others are considered high risk for a thrombotic event. Treatment for patients who have a lower risk is managed with aspirin and phlebotomy alone[209] to maintain a hematocrit target of less than 45%, but patients who have a higher risk are managed with additional cytoreductive therapy.[210] In the Cyto-PV trial, 365 patients who had PV were randomly assigned to more intensive treatment (target hematocrit, <45%) versus less intensive treatment (target hematocrit, 45%-50%). After a median follow-up of 31 months, more intensive therapy resulted in a decreased rate of cardiovascular mortality and major thrombotic events; such events were reported in 3% of the group that received more intensive treatment compared with 10% in the group that received less intensive therapy.[209] Attainment of a lower hematocrit value may be desirable in some cases, and treatment can be individualized (eg, <42% in female patients and those with progressive or residual vascular symptoms). For patients who have high-risk prognostic features and who require cytoreductive therapy, hydroxyurea is often used to lower the risk of thrombotic complications. Other reasons to consider cytoreductive therapy include symptomatic splenomegaly, constitutional symptoms, symptomatic thrombocytosis, leukocytosis, and poor compliance with or intolerance of phlebotomy.[210,211]

IFN offers an alternative to hydroxyurea as first-line cytoreductive therapy for patients who have PV, particularly for female patients who are considering becoming pregnant (teratogenicity can result from treatment with hydroxyurea). Two different formulations of IFN-α are available: pegylated IFN-α-2a and ropeginterferon-α-2b-njft. Pegylated IFN-α provides a more favorable toxicity profile than conventional IFN-α, and its prolonged activity is compatible with dosing once per week or dosing once every 2 weeks. A majority of patients treated with pegylated IFN-α-2a achieve a hematologic response with an ORR of 76.7% and a complete hematologic response rate of 48.5%.[212] In addition, pegylated IFN-α-2a has been shown to induce molecular responses with an overall molecular response rate of 54% and a complete molecular response rate of 14% shown in one study.[212] Typical adverse effects include fever, malaise, nausea, and vomiting; up to 35% of patients eventually

discontinue pegylated IFN-α therapy because of adverse effects. Ropeginterferon-α-2b-njft has an even longer duration of action and was approved by the FDA for the treatment of PV on the basis of results of the PROUD-PV/CONTINUATION-PV trial.[213] Patients were randomly assigned to receive ropeginterferon (subcutaneously once every 2 weeks) or hydroxyurea, and after 1 year, patients could opt to enter the extension part of the trial (CONTINUATION-PV). Although noninferiority to hydroxyurea was not demonstrated at the 12-month mark, response to ropeginterferon continued to increase over time, with improved responses compared with hydroxyurea at 36 months. In addition, the *JAK2* V617F variant allele fraction was decreased to a mean of 42.8% of the baseline value by month 36. In the ropeginterferon arm, there was an improvement in splenomegaly, microvascular disturbances, pruritus, and headache. After all patients on the study had been treated for 6 or more years, the EFS was significantly higher in the ropeginterferon-α-2b arm compared with the control arm. Reduction in *JAK2* V617F allele burden also continued to decrease, with 66% of ropeginterferon-α-2b patients still having 50% reduction in allele burden versus 19% in the control arm.[214,215]

Second-line treatments for individuals whose disease is resistant to or who cannot tolerate hydroxyurea include IFNs and the JAK inhibitor ruxolitinib. In the RESPONSE trial, 222 patients who had PV and were either resistant to or intolerant of hydroxyurea were randomly assigned to receive ruxolitinib (10 mg twice per day) or best available therapy.[216] Patients who received ruxolitinib showed improvement with a reduction in splenomegaly (38% vs 1%); there was also a reduction in the percentage of patients who required phlebotomy (20% vs 62%). An important limitation of this trial was the widespread use of hydroxyurea for patients assigned to best available therapy, even though documented resistance to or intolerance of this agent was an inclusion criterion for the trial. In older patients (age > approximately 75 years), oral busulfan can be used when other agents are ineffective or not tolerated. This is to be avoided in younger patients due to its leukemogenic potential.

In the phase 2 REVIVE study (NCT04057040), the hepcidin mimetic rusfertide (PTG-300) eliminated the need for phlebotomy in some patients and improved iron parameters and reduced constitutional symptoms that were a result of iron deficiency in nonerythroid compartments.[217] A phase 3 trial with this agent is underway, and preliminary results have been presented as plenary ASCO 2025 showing that 76.9% of patients on rusfertide versus 32.9% on placebo, no longer needed phlebotomy at 20 to 32 weeks[218] It is uncertain whether hepcidin modulators will have any effect on thromboembolic risk, which is intrinsic to the *JAK2* V617F mutation itself.[219]

Therapy for ET

For patients who have low-risk disease, aspirin is used to treat microvascular symptoms and may reduce the likelihood of vascular events in *JAK2*-mutated ET.[220] Younger patients who have a *CALR* or *MPL* mutation and triple-negative ET have relatively lower thromboembolic risks, and antiplatelet therapy may not affect the risk of thrombosis. If these patients are asymptomatic, their disease can be managed with observation alone. In patients who have high risk (age 60 years or older, history of vascular complications, or *JAK2* V617F mutation), hydroxyurea or IFN-α (for pregnant patients in whom hydroxyurea needs to be deferred) reduces the thrombotic risk.[220] In ET, the optimal platelet count is not known, but most treatments aim for a platelet count in the range of 400,000/mcL. Patients who have extreme thrombocytosis (eg, platelet count > 1,000,000/mcL) are not at a higher risk of thrombosis but instead might be at increased risk of hemorrhage, especially when treated with aspirin.[221] This increased risk of hemorrhage is because of the potential for development of von Willebrand syndrome as a result of the excessive adsorption of large von Willebrand multimers by platelets. Therefore, patients who have ET and extreme thrombocytosis should be screened for acquired von Willebrand syndrome, and if it is present, aspirin should be avoided, and cytoreduction should be administered to reduce the platelet count. Aspirin is relatively contraindicated if the ristocetin cofactor activity is <30%. In patients who are intolerant of hydroxyurea, anagrelide can be used; in younger patients, pegylated interferon can be used for platelet count and symptom control. IFN can cause flu-like symptoms, autoimmune disease, and psychological concerns after a long duration of therapy. Anagrelide may cause headache, fluid retention, and palpitations, and it has been suggested that it can lead to higher rates of myelofibrotic transformation.[222]

Therapy for Primary MF

Patients who have higher risk primary MF (DIPSS Plus, intermediate-2 and high risk; MIPSS70 + v2.0, high and very high risk) should be evaluated for allo-SCT; this is the only potentially curative option for primary MF. If the patient is not a candidate for allo-SCT, a JAK inhibitor can be used for symptom management or in those who are transplant eligible as a bridge to transplant. For patients who have lower risk primary MF (DIPSS Plus low and intermediate-1 risk; MIPSS70 + v2.0, very low, low, and intermediate risk), treatment decisions are guided by the nature and severity of symptoms, such as anemia, constitutional symptoms, and splenomegaly.[207] For those at low or intermediate-1 DIPSS Plus risk, observation or hydroxyurea (for constitutional symptoms or symptomatic splenomegaly) may be most appropriate. Androgens, prednisone, danazol, immunomodulatory agents (eg, thalidomide or lenalidomide), or splenectomy may be useful for symptomatic anemia, and some intermediate-1 patients may benefit from a JAK inhibitor, especially if they are not candidates for transplantation.[207]

Ruxolitinib is an inhibitor of *JAK2*, which is commonly mutated in primary MF, but its efficacy is independent of *JAK2* mutation status. The efficacy of ruxolitinib was demonstrated in two phase 3 trials, COMFORT-1 and COMFORT-2.[223,224] Ruxolitinib

significantly improved MF-related symptoms in up to half of patients and led to at least a 35% reduction in spleen volume in 28% to 42% of patients. There was also a trend in improvement in OS. However, ruxolitinib is not a specific inhibitor of the malignant clone, and it frequently results in myelosuppression, especially anemia and thrombocytopenia, as well as immunosuppression with risk of unusual infections. Ruxolitinib should not be discontinued abruptly, given that abrupt discontinuation can be associated with so-called ruxolitinib withdrawal symptoms that have potentially serious adverse effects, such as respiratory distress, shock, capillary leak, tumor lysis syndrome, splenic infarction, and/or disseminated intravascular coagulation. If ruxolitinib needs to be discontinued, it should be slowly tapered over a period of time.

Fedratinib, a JAK2-selective inhibitor, is also available for treatment of intermediate-2– or high-risk primary or secondary (post-ET, post-PV) MF. Fedratinib has been examined as both first-line (JAKARTA-1 trial)[225] and second-line (JAKARTA-2)[226] therapy for patients resistant to or intolerant of ruxolitinib. As first-line treatment, fedratinib was shown to achieve spleen volume reduction by at least 35% at week 24 in 36% of patients.[225] In patients who had MF and who were either resistant to or intolerant of ruxolitinib, a spleen response was seen in 30% of patients, and a reduction in symptoms was seen in 27%.[225,226] Wernicke encephalopathy was a rare and fatal complication of treatment. Thiamine levels should be checked before beginning treatment, and if Wernicke encephalopathy is suspected, treatment should be discontinued, and parenteral thiamine should be initiated instead. Hepatotoxicity can also be seen.

In February 2022, pacritinib received accelerated FDA approval for patients who have intermediate- or high-risk primary or secondary MF with severe thrombocytopenia (platelet count $<50 \times 10^9$/L). Pacritinib is a JAK2 and FLT3 inhibitor that also suppresses the IRAK-1 pathway but does not inhibit JAK1, resulting in less myelosuppression compared with ruxolitinib. The accelerated approval was based on results from the phase 3 PERSIST-2 study, which showed a reduction in spleen volume of at least 35% for 18% of patients treated with pacritinib versus 3% ($P < .001$) of patients who received the best available therapy, including ruxolitinib.[227] Pacritinib treatment also resulted in a statistically nonsignificant 25% reduction in total symptom score of 50% or more in the pacritinib arms versus 14% in the control group ($P = .08$). This approval of pacritinib is important because ruxolitinib is contraindicated for patients who have significant thrombocytopenia (<50,000/mcL).

In September 2023, momelotinib was approved for use in MF. It has erythropoiesis benefits because it inhibits activin A receptor type-1 (*ACVR1*) in addition to FLT3, Jak1, and Jak2. It decreases hepcidin production and mobilizes iron to improve erythroid production. It was examined in the phase 3 SIMPLIFY-1 trial in which it was compared with ruxolitinib in patients who had no previous exposure to JAK inhibitors. It was noninferior to ruxolitinib in spleen reduction potential, and it improved transfusion burden but not total symptom score.[210,228] In the phase 3 MOMENTUM trial, patients who had MF with DIPSS intermediate-1, intermediate-2, or high-risk prognostication scores were randomly assigned to momelotinib or danazol, and symptom relief, improvement in anemia, and spleen reduction were higher in the momelotinib arm.[23,209] Table 19-11 lists common adverse effects of the JAK inhibitors approved for treatment of MF.

Table 19-11 Major Adverse Effects of *JAK* Inhibitors Used in Myelofibrosis[196]

Drug	Adverse Effect
Ruxolitinib	Anemia and thrombocytopenia
	Herpes simplex and zoster reactivation (give recombinant vaccine before starting if possible)
	Tuberculosis reactivation
	Progressive multifocal leukoencephalopathy (rare)
	Reactivation of hepatitis B
	Nonmelanoma skin cancers
	Lymphoid neoplasms
	Withdrawal syndrome if stopped suddenly
	Hyperlipidemia and weight gain
Fedratinib	Diarrhea
	Liver function changes
	Wernicke encephalopathy (thiamine level should be tested before initiation)
Pacritinib	Anemia
	Thrombocytopenia (but less than with other *JAK2* inhibitors and approved in those with platelets $<50 \times 10^9$/L)
	Diarrhea
	Edema

Drug	Adverse Effect
Momelotinib	Anemia and thrombocytopenia, but less anemia and transfusion dependence with its use
	Abdominal pain
	Headache
	Neuropathy
	Asthenia
	A "first dose" effect with dizziness, hypotension, and flushing has been reported

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In addition to the use of JAK inhibitors, treatments that address patient symptoms and anemia management are important in MF.[229] The MPN-Symptom Assessment Form Total Symptoms Score (MPN-SAF TSS) is an important tool for assessing symptom burden in MF; it is used in clinical trial response assessment and is a valuable tool in all patient encounters.[230] Anemia can be managed with erythropoietin, danazol, luspatercept, and transfusions when required. In certain situations, immunomodulatory drugs (IMiDs) such as thalidomide, lenalidomide, and pomalidomide have been used to treat anemia in MF.

Allo-SCT

Allo-SCT is the only curative treatment modality available for MF therapy.[231] Both myeloablative and reduced-intensity approaches are used, the former to decrease relapse and the latter to reduce toxicity. The NRM rate is high in MF at about 20% at 1 year in some series. In general, 5-year EFS and OS are about 50%. Transplantation is thought to have the most benefit for those with intermediate-2 or high risk according to the IPSS or DIPSS Plus. In lower-risk patients, benefit is not seen until after many years of follow-up. Use of alternative donors, including haplo-matched donors, is feasible, but controversy persists regarding optimal conditioning, minimizing non- or poor engraftment, and management of splenomegaly pretransplantation.[231] Post-transplant cyclophosphamide has been safely used. A recent retrospective study from the Center for International Blood and Marrow Transplant Research (CIBMTR) showed that fludarabine-busulfan–based conditioning resulted in reduced early NRM and better OS in the reduced intensity settings.[232] Ruxolitinib is commonly used to reduce spleen size before allografting.

Investigational Approaches to the Treatment of MPNS

Despite management with phlebotomy and acetylsalicylic acid (ASA), patients who have lower-risk PV still experience a higher-than-normal rate of thrombosis because they may not always have an optimally controlled hematocrit less than 45% between phlebotomy visits and can also develop symptomatic iron deficiency over time. In this context, the self-injectable hepcidin mimetic rusfertide is being evaluated as an alternative medical phlebotomy agent. Rusfertide has shown impressive early results with excellent hematocrit control without the need for phlebotomy as well as an increase in ferritin and mean corpuscular volume, which suggests a reversal of preexisting iron deficiency.[219,233]

Ropeginterferon α-2b is being assessed in patients who have ET. Ruxolitinib was examined in ET in a randomized study (MAJIC-ET), but when it was compared with the best available therapy (usually hydroxyurea), it did not result in better control of platelet counts but did reduce symptoms.[234]

Intensive efforts are ongoing to develop new classes of drugs for primary MF, such as the BET inhibitor pelabresib,[235] the BCL-XL/BCL-2 inhibitor navitoclax, the telomerase inhibitor imetelstat, the LSD1 inhibitor bomedemstat, XPO1 inhibitors such as selinexor, and the TGF-β ligand trap luspatercept for anemia improvement.[236,237] PI3Kδ inhibitors such as parsaclisib are also being examined compared with ruxolitinib.[238] Some of these agents are being used singly, and some in combination with ruxolitinib. Some have demonstrated a degree of fibrosis regression. For those patients with ET or MF who have calreticulin mutations, antibodies to calreticulin are the subject of clinical trials.

Summary of Treatment Recommendations Based on Risk Stratification in MF

Low Risk

Observation if asymptomatic.

If symptomatic,

- Ruxolitinib or other appropriate JAK2 inhibitor; switch to an alternate JAK2 inhibitor for lack of response or intolerance
- Peginterferon α-2a
- Clinical trial
- Hydroxyurea if the disease has a proliferative nature
- Consider and prepare for allo-SCT (HLA typing, watch for transfusion needs and indications of disease progression to AML), and in certain patients, begin this process early based on an adverse mutational profile

Intermediate-2 or High Risk (and Certain Intermediate-1 Cases)

- Allo-SCT if the patient is a suitable candidate
- JAK inhibitor
- Clinical trial (Fig. 19-5)

MDS/MPN OVERLAP SYNDROMES

MDS/MPN overlap syndromes are characterized by ineffective or dysplastic hematopoiesis of one or more myeloid lineages with concurrent proliferation (with or without dysplasia) of one or more myeloid lineages. In the 2022 WHO classification, there were several changes for MDS/MPN overlap syndromes.[1] The diagnostic criteria for chronic myelomonocytic leukemia underwent major revisions, including lowering the cutoff for absolute monocytosis to 0.5×10^9/L or greater and adopting myelodysplastic (WBC $<13 \times 10^9$/L) and myeloproliferative (WBC $\geq 13 \times 10^9$/L) subtypes. Atypical CML was renamed MDS/MPN with neutrophilia. MDS/MPN with ring sideroblasts and thrombocytosis was redefined on the basis of an *SF3B1* mutation and renamed MDS/MPN with *SF3B1* mutation and thrombocytosis. Patients' diseases that do not meet criteria for any of these diseases are classified as MDS/MPN unclassifiable. Clinically, these diseases can present with cytopenias in one or more lineages or as a proliferative disease accompanied by splenomegaly, hepatosplenomegaly, and/or extramedullary hematopoiesis (skin, lymph nodes, liver, gastrointestinal tract, or lungs). Patients who have MDS/MPN with ring sideroblasts and thrombocytosis may present with thromboembolism.

Chronic myelomonocytic leukemia is characterized by persistent monocytosis of 3 months or longer. The triad of *TET2*, *ASXL1*, and *SRSF2* mutations is highly specific for this disease.[239] *TET2* mutations often appear early in the course of the disease. Patients who have increased blasts and adverse prognostic factors (*ASXL1* mutation) respond to treatment with HMAs (ie, azacitidine and decitabine), which is similar to results with MDS. Hydroxyurea can be used for count control. Allo-SCT is the only potentially curative therapy available for this disease.

MDS/MPN with neutrophilia (formerly atypical CML) is rare and usually presents with high WBC counts. It has a high rate of transformation to AML, and survival in the absence of SCT is short. *SETBP1* mutations are found in 25% to 40% of patients.[240]

Patients who have MDS/MPN with *SF3B1* mutation and thrombocytosis (formerly MDS/MPN-RS-T) with ring sideroblasts and thrombocytosis have marrow ring sideroblasts of 15% or more and a persistently elevated platelet count ($\geq 450 \times 10^9$/L). Classic hotspot mutations in *SF3B1* are found in more than 80% of the patients. In addition, patients may also have mutations in *JAK2*, *CALR*, and *MPL*. The treatment is generally supportive with ESAs and transfusions. Low-dose aspirin may be administered to those patients who have *JAK2* mutations and increased cardiovascular risk. In select patients, JAK inhibition is sometimes used in combination with hypomethylating agents.

KEY POINTS

- The treatment of PV, ET, and primary MF is tailored to the likelihood of the development of venous or arterial thrombosis, bleeding, or evolution to AML, the major life-threatening and limiting complications of these MPNs. In PV and ET, cytoreductive therapy is reserved for the high-risk disease categories.
- In MF, treatment is also based on risk stratification, and multiple prognostic scoring systems are available. By using the risk levels from the MIPSS70 + v2.0 for categorizing patients, those in low-risk categories can enter a period of observation, and for patients in the high-risk categories, allo-SCT is recommended for those who are appropriate candidates. Those in intermediate-risk categories must be individualized but may benefit from JAK inhibitors and treatments to improve anemia. Transplantation is indicated for some of these patients.
- Multiple JAK inhibitors are now available for treatment of MF (ruxolitinib, fedratinib, pacritinib, and momelotinib), and they can be selected on the basis of their adverse effect profiles.
- There is increased awareness of the MPN/MDS overlap syndromes, and classification based on clinical and molecular characteristics continues to evolve, as evidenced by the changes in the 2022 WHO and ICC classifications.

BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematopoietic neoplasm that originates from transformed plasmacytoid dendritic cells. It has a male predilection with a median age at presentation of 70 years. The disease most commonly presents with cutaneous tumors. Other sites of involvement are the spleen, bone marrow, lymph nodes, and extramedullary organs. Dual overexpression of IL-3 receptor subunit alpha (*IL3RA* or *CD123*) and *TCF4* occurs in almost all patients who have BPDCN.

The loss of multiple cell-cycle checkpoints leading to the altered G1/S transition seems to be important in the molecular pathogenesis of BPDCN. Loss-of-function mutations in *TET2* are the most commonly identified premalignant alterations in BPDCN and seem to confer resistance to UV-induced cell death in plasmacytoid dendritic cells.[241] The disease has a dismal

prognosis, with a median survival of less than 2 years without treatment. Younger age (younger than 60 years) and early allo-SCT predict superior outcomes.

Tagraxofusp-erzs, the first FDA-approved treatment of BPDCN, is a CD123-directed cytotoxin consisting of recombinant human IL-3 fused to a truncated diphtheria toxin. Given at the higher dosage of 12 mg/kg, the CR and clinical CR rate in previously untreated patients was 72% (95% CI, 53%-87%). The median time to response was 43 days (ORR, 90%). Of these patients, 45% underwent bridging treatment to allo-SCT while in complete remission. Among previously treated patients, the ORR was 67%; the median duration of response was 2.8 months, with a median time to response of 24 days.[242] Hypoalbuminemia, transaminitis, and thrombocytopenia are common adverse effects of this treatment. Tagraxofusp-erzs is also associated with capillary leak syndrome, with most cases occurring within the first cycle of treatment. Management of capillary leak syndrome includes close monitoring of volume status, necessitating aggressive intravenous fluid resuscitation or diuresis, glucocorticoids, and intravenous albumin. Other treatment strategies currently being explored in BPDCN include the combination of tagraxofusp-erzs with azacitidine and venetoclax or azacitidine plus venetoclax alone without tagraxofusp-erzs.[243]

ACUTE LYMPHOBLASTIC LEUKEMIA

ALL occurs in children and adults with a peak incidence between ages 2 and 5 years, which declines into early adulthood and increases again with older age. Relative to childhood ALL, in which cure rates are greater than 80%, the prognosis for adult ALL is significantly worse, particularly in older individuals. Current 5-year survival rates are approximately 50% for adults but only 10% to 15% for older patients. Numerous population-based studies in multiple countries have demonstrated improvements in survival over time in all age groups except in patients older than 60 or 70 years. The improvement in survival has been attributed to the increasing use of pediatric-intensive regimens in young adults, improved risk stratification with MRD testing, improved supportive care, the advent of BCR-ABL1–targeting TKIs, and increased use of allo-SCT in middle-aged and older adults. The addition of the anti-CD20 antibody rituximab for $CD20^+$ B-cell ALL and, more recently, the addition of blinatumomab for B-cell ALL to first-line therapy are further improving survival.

PATHOGENESIS

ALL is a clonal disorder caused by genetic lesions in hematopoietic progenitor cells committed to differentiate along the B-cell or T-cell pathway. The precise sequence of events that leads to ALL is unknown, and only a minority of patients have genetic predispositions (eg, familial abnormalities in *RUNX1*, *ETV6*, *PAX5*, *IKZF*, *TP53*) or exposure to exogenous factors, such as radiation therapy or chemotherapeutic agents.

CLINICAL PRESENTATION

Patients typically present with signs and symptoms of myelosuppression-related anemia, neutropenia, and/or thrombocytopenia. Fatigue, dyspnea, and pallor are common presentations, as well as infection and bleeding. Bone pain and joint pain are commonly reported by younger patients and patients who have highly proliferative disease. Approximately 50% of patients who have ALL present with enlarged lymph nodes, hepatomegaly, and/or splenomegaly. Approximately 5% of patients have CNS involvement at diagnosis, which is associated with a worse prognosis. T-cell ALL is associated with male sex, a mediastinal mass, and disseminated lymph node involvement. Lymphoblastic lymphoma is biologically similar to ALL but lacks blood and marrow involvement. Lymphoblastic lymphoma is typically treated as ALL with or without the use of mediastinal radiation therapy for those with mediastinal masses.

DIAGNOSIS

ALL is diagnosed and categorized using morphology, immunohistochemistry, flow cytometry, cytogenetics (karyotype and FISH), and molecular features (Table 19-12).

Morphology and Immunohistochemistry

The leukemia cells in ALL are typically smaller than AML blasts and are devoid of granules and Auer rods. The French-American-British Cooperative Group developed a morphology-based classification, which, although once widely used, has largely been replaced by immunophenotyping and cytogenetic classification. ALL blasts are typically negative for myeloid and monocytic markers, such as MPO and nonspecific esterase.

Immunophenotype

A majority of ALLs have the precursor B-cell immunophenotype with expression of CD10, CD19, CD22, HLA-DR, and TDT.[244] Approximately 25% of patients have ALL with a T-cell phenotype. In 40% to 50% of adult patients, the leukemia expresses CD10 (the common ALL antigen). In approximately 10% of patients, B-cell ALL expresses cytoplasmic immunoglobulin but not surface immunoglobulin. A subset of B-cell ALL expresses CD20. In some studies, CD20 expression has been associated with a worse

Table 19-12 **Summary of WHO Classification of Lymphoid Leukemia**[196]	
	B-Lymphoblastic Leukemia/Lymphoma, NOS
B-lymphoblastic leukemia/lymphoma	B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
	B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
	B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
	B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
	B-lymphoblastic leukemia/lymphoma with hyperdiploidy
	B-lymphoblastic leukemia/lymphoma with hypodiploidy
	B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*
	B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
	Provisional entity: B-lymphoblastic leukemia/lymphoma, *BCR-ABL1*-like
	Provisional entity: B-lymphoblastic leukemia/lymphoma with *iAMP21*
T-lymphoblastic leukemia/lymphoma	Provisional entity: early T-cell precursor lymphoblastic leukemia
	Provisional entity: NK-cell lymphoblastic leukemia/lymphoma

Abbreviations: NK, natural killer (cell); NOS, not otherwise specified; WHO, World Health Organization.
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outcome.[245] In 25% of patients who have ALL, a nondefinitive (ie, not MPO) myeloid antigen can be detected. As in AML, discordant combinations of antigens on leukemic blasts enable the detection of small numbers of abnormal blasts in a morphologically normal marrow using multiparameter flow cytometry. More sensitive methods for the detection of small numbers of ALL blasts involve the detection of clonally rearranged B-cell immunoglobulin genes or T-cell receptor genes by PCR or NGS.[246] PCR requires the development of individualized patient-specific probes. More recently, high-throughput NGS has been developed; it is as sensitive as PCR-based detection, but it is much less labor-intensive and more easily standardized. Unlike flow cytometry, molecular techniques require establishing the clone at diagnosis so it can be reliably followed later in therapy for the determination of MRD.

In 2% to 5% of acute leukemias, the definition of the disease as either myeloid or lymphoid is problematic because two or more distinct populations of cells exist in the same person (bilineage leukemias) or because a single population coexpresses definitive myeloid and lymphoid markers (biphenotypic leukemias). The current WHO classification combines these diseases into one diagnostic category called mixed-phenotype acute leukemia. Results of several studies suggest that patients who have this type of leukemia have a worse clinical outcome than those with either AML or ALL.[247]

Cytogenetic and Molecular Abnormalities

Cytogenetic and molecular characteristics have important prognostic significance in ALL.[248,249] In approximately 25% of patients, no cytogenetic abnormalities are found.[249] In approximately 10% of patients, an alteration in chromosome number is present without alteration in chromosome structure.[250] The most common translocation is the Ph-chromosome, seen in 20% to 30% of adults who have ALL. The Ph-chromosome results from a specific translocation, t(9;22)(q34.1;q11.2), which positions most of the *ABL1* proto-oncogene from chromosome 9 adjacent to the 5′ portion of the *BCR* gene on chromosome 22. The breakpoint on chromosome 9 is variable, whereas the breakpoints in the *BCR* gene on chromosome 22 occur within two regions: the major breakpoint cluster region (*M-bcr*) and the minor breakpoint cluster region (*m-bcr*). Rearrangements within the *M-bcr* region are transcribed into a chimeric messenger RNA that produces a hybrid 210-kd protein (p210 BCR-ABL1), whereas breaks within the *m-bcr* region express a chimeric messenger RNA that gives rise to a smaller 190-kd protein (p190 BCR-ABL1). In CML, virtually all breakpoints are mapped to the *M-bcr* region (p210 BCR-ABL1, known as CML-type Ph-chromosome). Conversely, in ALL, breakpoints are found within both the *M-bcr* and *m-bcr* regions, and those within the *m-bcr* region are called ALL-type Ph-chromosomes. The relative frequency of the two breakpoints in adult ALL has varied among studies, but overall, the two seem to be represented with equal frequency. Ph+ ALL with the CML type of *BCR-ABL1* translocation is not simply the lymphoid blast crisis phase of CML, although some cases of lymphoid blast crisis CML may mimic Ph+ ALL at diagnosis. Patients who have ALL rarely have a long prediagnostic prodrome and do not routinely have marked splenomegaly. However, an underlying CML could potentially be recognized in the patients who have p210-positive Ph+ ALL once the ALL is in remission after initial induction (ie, the lymphoblasts are no longer detected by flow cytometry, but a majority of the marrow cells still have evidence of BCR-ABL fusion by FISH or cytogenetics) or a patient develops CML after treatment of Ph+ ALL.

Another common poor-prognosis entity found in 20% to 25% of adolescents and adults is Ph-like B-cell ALL, which lacks the classic *BCR-ABL1* translocation but exhibits a gene expression profile similar to that of Ph+ ALL.[251] Kinase-activating genetic

rearrangements are characteristic of Ph-like ALL, including rearrangements of cytokine receptor–like factor 2 (*CRLF2*). *CRLF2* rearrangements are found in approximately 50% of all patients who have Ph-like ALL and are often associated with activating mutations in *JAK1/2*. In addition, ABL1/2 class fusions are seen in 10% of Ph-like ALLs. The presence of deletions or mutations in the transcription factor *IKAROS* (*IKZF1*), especially when combined with mutations in *CDKN2A*, *CDKN2B*, *PAX5*, or *PAR1* in the absence of *ERG* deletion (*IKZF1*$^{+}$), also confers a poor prognosis and is often seen in Ph+ and Ph-like ALLs.[252]

Another common translocation seen in adult B-cell ALL is t(4;11)(q21;q23), which is seen in 7% of B-cell ALLs. The translocation involves the *AF4* and *KMT2A* (formerly *MLL*) genes and is associated with a poor prognosis. Similarly, other translocations involving *KMT2A* may have a poor prognosis as well.

Disorders of chromosome copy number also have prognostic significance. Hyperdiploidy (51-65 chromosomes), especially with triploidy of chromosomes 4, 10, or 17, is a favorable risk and is much more common in children than adults. By contrast, hypodiploidy (<44 chromosomes) and near triploidy (56-78 chromosomes) have a poor prognosis and are highly associated with mutations in *TP53*.[253]

Other common cytogenetic changes seen in adult ALL involve del(9p) in 5% to 9% of patients, del(6q) in 5% to 7% of patients, del(13q) in 3% to 5% of patients, and t(1;19)(q23;p13) involving the *TCF3* and *PBX1* genes, which has an improved prognosis with current ALL therapy. T-cell ALLs often have translocations involving chromosome 7 or 14 at T-cell receptor enhancer gene sites.

An increasing number of genes in key signaling pathways (eg, regulation of lymphoid differentiation, tumor suppression and cell cycle, cytokine receptors, lymphoid signaling, epigenetic modification) are recognized to be recurrently mutated in ALL. Some of these are associated with prognosis. For example, alterations in the *IKAROS* gene family members confer a poor prognosis and are found selectively in different subtypes of high-risk ALL, such as Ph+ ALL or Ph-like ALL. *TP53* is commonly mutated in hypodiploid/near-triploid ALL. T-cell ALL is characterized by activating mutations in *NOTCH1* (seen in >50% of patients) and by rearrangement of transcription factors such as *TLX1* (also known as *HOX11*), *TLX3* (*HOX11L2*), *LYL1*, *TAL1*, and *KMT2A*.[254]

PROGNOSTIC FACTORS

Pretreatment Factors

Various pretreatment characteristics have been shown to affect CR rates and survival, including increasing age, elevated WBC counts, CNS involvement, obesity, and particularly cytogenetic and molecular abnormalities (Table 19-13).

Table 19-13 Prognostic Risk Factors in ALL

	Risk Factor
Pretreatment	Age
	Leukocyte count
	CNS involvement
	Cytogenetic abnormalities
	Molecular abnormalities
Post-treatment	Achievement of complete remission
	MRD state

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; MRD, measurable residual disease.
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Based on such factors, investigators have segregated patients who have ALL into standard-risk and high-risk disease groups. Although the exact schemas have inconsistencies, 5-year DFS averages are approximately 55% for patients who have standard-risk and 25% for those who have high-risk disease. With modern therapy, other factors such as immunophenotypic characteristics of leukemic blasts (eg, expression of T-cell or myeloid antigens by ALL blasts), which previously were associated with a worse prognosis, have lost their independent prognostic importance.

Cytogenetic characteristics have important prognostic and therapeutic significance.[249] Between 15% and 20% of all patients who have ALL are Ph+ (5% in childhood and 20% to 30% in adulthood), with an incidence that increases with age and can be seen in 40% to 50% of patients older than 60 years. In studies conducted before the availability of imatinib, the likelihood of complete remission was lower for patients who had Ph+ ALL, and the probability of remaining in complete remission was much lower.

Studies designed to find evidence of *BCR-ABL1* rearrangement by quantitative reverse-transcription PCR or FISH have shown that up to 10% of patients who are Ph− or are inadequately assessed by karyotype analysis will have *BCR-ABL1* rearrangement. The prognosis for these patients is the same as that for patients who are Ph+ by karyotypic analysis. Therefore, FISH and quantitative reverse-transcription PCR for the *BCR-ABL1* fusion should be conducted at diagnosis for all patients who have B-cell ALL. Although Ph+ ALL had a poor prognosis when treated with conventional ALL therapy alone, the use of BCR-ABL1–targeted TKIs,

especially second- (dasatinib, nilotinib) and third-generation (ponatinib) agents, in combination with chemotherapy, immunotherapy, or allo-SCT, has dramatically improved the prognosis for patients who have Ph+ ALL.

The responsiveness of Ph-like ALL to TKIs remains undefined, although in vitro studies suggest a potential benefit to targeting ABL1/2 or the JAK/STAT pathway in this subset of B-cell ALL. Other cytogenetic abnormalities of adult ALL that carry a poor prognosis (in terms of both achieving complete remission and remaining in complete remission) include t(4;11) and other *KMT2A* rearrangements, *IgH* translocations, low hypodiploidy/near triploidy, and complex cytogenetics with five or more abnormalities. By contrast, adults with high hyperdiploidy or del(9p) seem to have a more favorable prognosis. A higher risk of relapse is independently associated with *KMT2A* gene rearrangement, focal *IKZF1* gene deletion, and *TP53* mutations in B-cell ALL and with the absence of *NOTCH1*/*FBXW7* mutation, *NRAS* or *KRAS* mutation, and/or *PTEN* gene alterations in T-cell ALL.[255,256]

Post-Treatment Factors

Depth of early response to chemotherapy is a primary determinant of outcome in ALL. Several studies have shown that rapid clearance of blasts from the peripheral blood and bone marrow and an early complete remission after the first chemotherapy course are associated with improved outcomes. For those experiencing complete remission, the presence or absence of detectable MRD is a powerful prognostic factor. Many studies have demonstrated that the presence of MRD after induction, after consolidation, or before SCT can identify patients at high risk of disease recurrence.[246] These studies have provided the rationale for exploring novel interventions to eliminate persistent MRD and overcome intrinsic chemotherapy resistance to optimize patient outcomes.

TREATMENT

Induction Chemotherapy

Induction therapy for ALL aims to eliminate detectable ALL, restore bone marrow function, reverse any ALL-related organ damage, and begin the process of curing patients by achieving an MRD-negative state. Standard induction therapy for adult ALL most commonly involves combination chemotherapy with a backbone of vincristine, prednisone, or dexamethasone and an anthracycline. L-asparaginase is an important component of pediatric and younger adult ALL therapy. Adult regimens sometimes add cyclophosphamide to induction. With such regimens, 80% to more than 90% of patients achieve CR to induction. There are several variations among regimens, but no prospective randomized trial has identified a clearly superior regimen. Older patients who have ALL have lower rates of CR and tolerate standard chemotherapy regimens poorly, and treatment-related mortality rates are high.[257] Dose reductions with omission of some chemotherapy agents have shown promise in reducing treatment-related mortality and maintaining efficacy, although long-term results are still poor. Investigators have recently exploited preclinical evidence of BCL-2 dependence of lymphoblasts to support the inclusion of the BCL-2 inhibitor venetoclax to dose-reduced multiagent chemotherapy in older patients who have B-cell or T-cell ALL. Results from the recent phase 1b/2 trial in patients who have newly diagnosed ALL and are older than age 60 demonstrated safety and a promising MRD-negative CR rate of 83%.[258] Chemotherapy-free regimens are also being explored for patients who have newly diagnosed ALL; there is a phase 2 trial of the CD22 antibody-drug conjugate inotuzumab induction, followed by CD19/CD3 T-cell engager blinatumomab consolidation that demonstrates a 97% cumulative CR rate after two courses of therapy.[259] A number of investigators have explored the use of hematopoietic growth factors immediately after induction chemotherapy. Similar to the findings for AML, the results of such studies demonstrate accelerated myeloid recovery and a decrease in the incidence of febrile neutropenia. In some trials, the CR rate was improved, but no findings have indicated an improvement in DFS or OS.[260] For younger adults (younger than 60 years) with CD20[1] Ph-negative B-cell ALL, adding the CD20 antibody rituximab to combination chemotherapy improves EFS when it is part of induction and post-remission therapy.[261] For Ph+ disease, the addition of a BCR-ABL1–targeted TKI to first-line therapy improves remission rates and long-term survival with or without allo-SCT.

Post-Remission Therapy

If no additional therapy is administered after complete remission, the duration of remission is invariably short. Post-remission therapy aims to prevent relapse and cure patients who have ALL in first complete remission. Common non–cross-resistant agents used in post-remission therapy include those used in induction as well as methotrexate, cytarabine, and mercaptopurine. Recent randomized data in children and young adults who have T-cell ALL treated with a pediatric regimen showed that the addition of nelarabine improved PFS and CNS relapse rates but did not improve OS.[262] Allo-SCT is considered for eligible patients to maximize the chance of cure and long-term survival for those who have ALL and are at high risk of relapse with chemotherapy alone, such as those with positive MRD or potentially poor-risk genetic findings. Post-remission therapy includes CNS prophylaxis with intrathecal chemotherapy; otherwise, CNS relapse of ALL will develop in at least 35% of adults. Patients who have a high tumor burden at diagnosis, as evidenced by a high WBC count and elevated LDH levels, are at the highest risk. With CNS prophylaxis, the incidence of CNS relapse as an isolated event is approximately 5%. Post-remission regimens differ but generally include several cycles of intensive consolidation therapy administered over several months after achievement of complete remission, delayed intensification using a combination similar to induction therapy in some regimens, and less intensive maintenance therapy

(eg, mercaptopurine, vincristine, methotrexate, prednisone) administered for 2 to 3 years. The phase 3 ECOG1910 study randomly assigned adults who had Ph–B-cell ALL in first MRD-negative complete remission to receive a standard multiagent chemotherapy regimen or the same regimen with the CD19-CD3 bifunctional T-cell engager blinatumomab. MRD-negative patients receiving blinatumomab had superior OS and RFS compared with the control arm, which justifies the addition of blinatumomab to post-remission therapy as an FDA-approved new standard of care.[24]

Some data from randomized pediatric studies indicate that modifying post-remission treatment intensity on the basis of MRD status can optimize treatment outcomes.[263-265] In addition, the use of allo-SCT has been shown to improve outcomes of patients who are MRD positive in first complete remission.[266] No single optimal regimen for CNS prophylaxis, consolidation therapy, and maintenance has been identified. More intensive regimens, such as those used in pediatric ALL, are tolerable and may improve outcomes in adolescent and young adult ALL (patients younger than age 40), although randomized studies have not been conducted. One study suggested that patients aged 55 years or younger can also be considered for an intensive pediatric regimen if they are fit and are treated by experienced physicians; otherwise, the regimen was poorly tolerated with poor short- and long-term outcomes.[267] With current regimens, approximately 40% of adult patients who have ALL will remain alive and disease-free at 5 years after diagnosis. With pediatric-inspired therapies, studies have shown 5-year survival rates of 67% to 78% in adolescents and younger adults. For older patients who have ALL, the use of less-intensive regimens is appropriate to reduce therapy-related morbidity and mortality. Given the poor outcomes in older patients, enrollment in clinical trials of novel therapies is especially appropriate.

Treatment of Persistent or Recurrent Disease

Persistent ALL MRD after induction portends a high risk of relapse that can be overcome by myeloablative allo-SCT. For patients whose MRD does not clear with successive rounds of chemotherapy or recurs, blinatumomab is an FDA-approved agent to treat MRD. In adults who have B-cell ALL who were MRD positive after three or more cycles of chemotherapy, treatment with blinatumomab converted 78% of patients to MRD negativity. Patients who were MRD responders had improved RFS and OS compared with MRD nonresponders.[268]

Patients whose disease does not go into complete remission or subsequently relapses after complete remission have dismal outcomes with long-term survival at 5 years of less than 10%. Therefore, the current strategy is to achieve a second complete remission and then to proceed with allo-SCT. A variety of chemotherapeutic agents have been used in combinations similar to those used during first-line therapy, such as vincristine, corticosteroids, anthracyclines, L-asparaginase, methotrexate, and high-dose cytarabine. Newer purine analog drugs for relapsed/refractory ALL include clofarabine and nelarabine, the latter of which can achieve complete remission rates of 30% or higher in patients who have recurrent T-cell ALL, but it can have significant neurotoxic effects. In addition, dysregulation of BCL-2 family members has been reported in ALL, leading to evidence for the promising preclinical activity of the BCL-2 inhibitor venetoclax in ALL. Venetoclax combined with low-intensity chemotherapy in a phase 2 study of relapsed/refractory Ph– ALL was shown to be well tolerated and yielded a composite complete remission rate of 57%.[269]

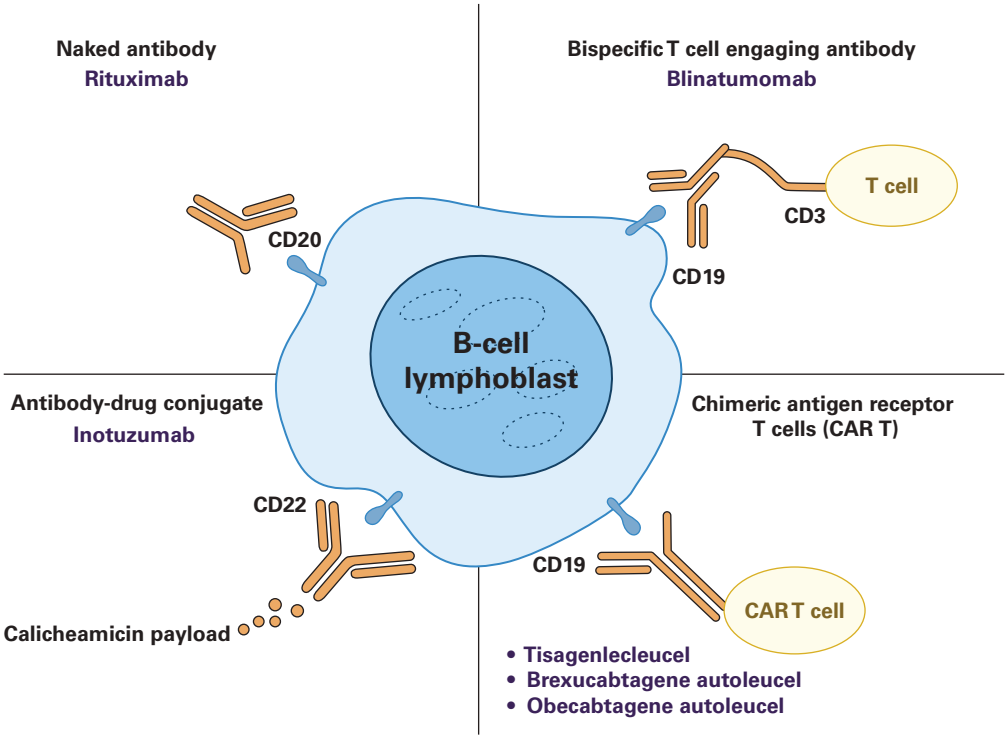
Newer targeted therapies have dramatically improved response rates in patients who have relapsed/refractory B-cell ALL and are now considered standard of care for most of them. Blinatumomab, a bispecific T-cell–engaging antibody that targets CD19 and CD3 in a single molecule, targets the patient's T cells to CD19-expressing cells, specifically, the malignant and normal B cells. Blinatumomab has been approved by the FDA as a treatment for relapsed/refractory Ph– B-cell ALL and for MRD eradication for B-cell ALL in first or second complete remission. A randomized phase 3 study reported an improved complete remission rate (44% vs 25%; $P < .001$) and improved median OS (7.7 vs 4.0 months) with blinatumomab compared with standard-of-care chemotherapy in adults who have relapsed/refractory B-cell ALL.[270] Notably, inferior response was seen in patients who have high bone marrow blast percentages at relapse. Unique toxicities of blinatumomab include neurologic events and, uncommonly, cytokine release syndrome.

A randomized phase 3 study of the anti-CD22 antibody-drug conjugate inotuzumab ozogamicin demonstrated higher CR rates (80% vs 30%) and longer PFS and OS compared with standard-of-care chemotherapy in adults who have relapsed/refractory B-cell ALL. Inotuzumab ozogamicin is associated with myelosuppression and hepatic sinusoidal obstruction syndrome (veno-occlusive disease) in approximately 10% of patients, mostly occurring among complete responders who went on to undergo allo-SCT using double-alkylator conditioning regimens.[271]

CR rates of 70% to 90% have been reported with adoptive cellular immunotherapy using autologous T cells that express CARs that recognize CD19 in pediatric and adult patients who have B-cell ALL, even after allo-SCT has failed (Fig. 19-6). Tisagenlecleucel is approved by the FDA as a treatment of B-cell ALL in patients aged 25 years or younger with refractory disease or at least two relapses.[272] Brexucabtagene autoleucel was approved for all adults who have relapsed/refractory B-cell ALL based on the data from a phase 2 study showing a complete remission/complete remission with incomplete recovery rate of 71% and a median duration of response of 12.8 months, which led to FDA approval of the drug in 2021.[25,273] More recently, another CD19-directed CAR T-cell therapy, obecabtagene autoleucel, was approved for adults with relapsed or refractory B-cell precursor ALL.[25] Cytokine release syndrome and neurologic toxicity are two key and common toxicities of cell therapy with T cells that express

CARs, which, at times, can be fatal. Cytokine release syndrome typically is managed successfully with anti–IL-6 antibody therapy (tocilizumab) and sometimes corticosteroids.

Figure 19-6 Mechanisms of Action of Immunotherapies for B-ALL



Abbreviation: B-ALL, B-cell acute lymphoblastic leukemia.
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Allo-SCT

Allo-SCT is an important post-remission treatment of ALL, but its curative potential must be balanced against transplantation-related morbidity and mortality, late complications, and associated reductions in quality of life. An evidence-based review of available trials led an expert panel to recommend the consideration of myeloablative allo-SCT for adults younger than 35 years with ALL in first complete remission after multiagent chemotherapy for all disease risk groups because of superior outcomes with regard to post-remission chemotherapy.[256] Currently, most ALL experts recommend reserving allo-SCT in first complete remission for those at high risk of relapse, especially those with MRD positivity after intensive induction. Comparative studies have not demonstrated a benefit from allo-SCT in patients achieving an early MRD-negative first complete remission.[266] In addition, allo-SCT has not yet been compared prospectively with pediatric-inspired chemotherapy regimens typically now used in younger adult patients who have ALL. Retrospective analyses find that this chemotherapy approach yields survival outcomes superior to those of allo-SCT because of lower nonrelapse-associated mortality rates and no increased risk of relapse.[274] With increasing age, the survival advantage of allo-SCT diminishes because of increased rates of nonrelapse-associated mortality. In the absence of a suitable HLA-matched related or unrelated donor, a haploidentical or cord blood donor can be considered as a stem cell source.[275] Conditioning that includes total body irradiation has consistently been shown to yield optimal outcomes in ALL.

For patients in second or later complete remission, allo-SCT is recommended versus chemotherapy alone if the patient did not receive a transplant in first remission. Myeloablative total body irradiation–based conditioning is generally preferred; there is limited data suggesting that reduced-intensity conditioning may produce reasonable outcomes in patients unfit for myeloablative regimens. Not surprisingly, the outcomes with SCT depend largely on the disease status of the patient. If allo-SCTs are performed during the first complete remission, long-term survival rates range from approximately 40% to 60%. If such transplantations are performed in patients who have disease resistant to conventional chemotherapy, long-term survival can be obtained in only 15% to 25% of patients.[276]

Efforts have been undertaken to use a risk-adapted approach to allo-SCT to spare patients from transplantation-related toxicities by allocating them to undergo chemotherapy if chemotherapy sensitivity was documented (eg, confirmed MRD-negative status after induction chemotherapy).[266,277] Conversely, MRD persistence after induction and/or consolidation signals a high risk

of relapse. MRD at the time of transplantation also indicates a higher risk of relapse, but outcomes are likely better than with chemotherapy alone. A recent study reported that, for patients who were MRD-positive after chemotherapy, treatment with blinatumomab converted 78% to MRD negativity, and patients who were MRD responders had improved RFS and OS compared with MRD nonresponders.[268] Based on this study, the FDA granted accelerated approval for the use of blinatumomab in late March 2018 to treat adults and children with B-cell precursor ALL who are in remission but still have MRD.

SPECIAL TYPES OF ADULT ALL

Ph+ ALL

As noted, ALL associated with t(9;22) translocations or BCR-ABL1 fusion has a poor prognosis when treated with conventional chemotherapy. However, the disease is sensitive to TKIs, such as imatinib, dasatinib, nilotinib, or ponatinib. When combined with induction chemotherapy or with corticosteroids alone, CR rates are 90% to 100%, and OS seems to be improved, especially with later-generation TKIs. In younger adults, less intensive chemotherapy combined with imatinib over the entire induction period is as effective as and less toxic than a more intensive regimen with imatinib administered only over the first 2 weeks.[278]

The role of allo-SCT, although it is a curative option particularly for younger adults, may be changing because the degree of improvement in outcome over TKI-containing combination chemotherapy is unclear, especially with regimens using ponatinib.[279,280] One retrospective study of patients who have Ph+ ALL in first molecular remission after chemotherapy with a TKI suggests that ASCT, although associated with substantially higher post-transplantation relapse risk, may yield similar survival outcomes for matched-sibling and unrelated-donor allo-SCTs.[281] If an MRD-negative remission is achieved early in Ph+ ALL, chemotherapy combined with a TKI may provide an alternative treatment strategy, particularly if patients are believed to be at high risk of death resulting from SCT.[282] Therapy with dasatinib and prednisone alone results in CRs in more than 90% of older patients who have Ph+ ALL without the need for concomitant chemotherapy, but disease in most patients ultimately relapses with the development of a *T315I* mutation in BCR-ABL1 being a major mechanism of resistance.

An exciting development in the treatment of Ph+ ALL has been the use of a BCR-ABL1–directed TKI in combination with blinatumomab to minimize the use of chemotherapy and minimize or eliminate treatment-related mortality and morbidity. In a phase 2 study of blinatumomab combined with dasatinib in 63 patients, a CR rate of 98% was achieved with a molecular response of 60% and an OS rate of 95% at a median follow-up of 18 months.[283] Recently, long-term follow-up was reported for this trial (D-ALBA trial), and with a median follow-up of 53 months, the OS was 80.7%.[26] Similar results have been reported from the SWOG 1318 phase 1/2 study.[284] In both studies, the *T315I* resistance mutation (which is sensitive to ponatinib) was commonly present at relapse. The single-center study of ponatinib and blinatumomab in adults who have newly diagnosed Ph+ ALL reported an MRD rate of 98% by next-generation clono-sequencing at a median follow-up of 24 months, and a 3-year OS of 91% and 3.[27] A randomized trial of chemotherapy plus dasatinib-ponatinib versus blinatumomab and dasatinib-ponatinib is currently enrolling in the United States (ECOG-ACRIN EA9181 study; NCT 04530565). Recently, based on data from the phase 3 PhALLCON trial of combination chemotherapy with ponatinib versus imatinib that demonstrated a median EFS that was not reached after 20 months of follow-up in the ponatinib arm, ponatinib was approved by the FDA for use in combination with chemotherapy in newly diagnosed Ph+ ALL.[285] Concerns remain about the long-term vascular toxicity associated with ponatinib reported from nonrandomized studies, although this may be ameliorated with planned dosage reductions.[279,280] Dasatinib has been explored in combination with STAMP inhibitor, asciminib, and prednisone in a phase I trial of Ph+ ALL, leading to 100% of patients achieving complete cytogenetic remission. Based on this data, dasatinib plus asciminib is an option for use in relapsed/refractory Ph+ ALL per NCCN guidelines.[286]

KEY POINTS

- Induction therapy for adult ALL generally should include vincristine, prednisone, and an anthracycline with or without L-asparaginase or cyclophosphamide. With such regimens, complete remission can be achieved in 80% to 90% of patients. Consideration of a pediatric-inspired regimen should be given for all patients aged 40 years or younger and possibly in select patients aged 55 years or younger.
- Patients who have CD20+ B-cell ALL should receive rituximab during induction and consolidation.
- Patients who have Ph+ ALL should receive a BCR-ABL1–directed TKI in combination with chemotherapy or blinatumomab.
- Recently, ponatinib was an FDA-approved agent in combination with chemotherapy for newly diagnosed Ph+ ALL.
- Blinatumomab can convert up to 80% of MRD-positive patients who have B-cell ALL and are in remission to an MRD-negative state and also improves outcomes.
- Allo-SCT is an important post-remission treatment except perhaps in patients who have highly chemotherapy-sensitive disease, as indicated by early MRD negativity.
- Salvage treatment options for patients who have relapsed/refractory B-cell ALL include blinatumomab, inotuzumab ozogamicin, and CAR T-cell therapy (tisagenlecleucel, brexucabtagene autoleucel, and obecabtagene autoleucel).
- Given the rarity of ALL and the complexity of its treatment, it is generally recommended that patients who have ALL be treated at high-volume centers (>10 new cases managed per year) with access to clinical trials, cell therapies, and SCT.

CHRONIC LYMPHOCYTIC LEUKEMIA

CLL is the most prevalent adult leukemia in Western countries. The disease is more common in men than women (ratio, 1.7:1) with a steeply climbing age-related incidence beginning after approximately age 40 years and peaking in the decade between ages 65 and 74 years. The incidence is higher in Jewish people of Russian or Eastern European ancestry and is rare in Asian countries. There are no known risk factors for CLL. It is one of the few leukemias that does not seem to be associated with exposure to ionizing radiation, chemicals, or drugs. However, a strong inherited component is well recognized, and genome-wide association studies have identified more than 40 susceptibility loci.[287]

CLINICAL PRESENTATION

Most patients who have CLL are asymptomatic at diagnosis, which is often made incidentally when lymphocytosis is noted during a routine evaluation. The findings on physical examination are normal for 20% to 30% of patients, whereas lymphadenopathy, hepatosplenomegaly, or both are observed in 40% to 50% of patients. However, as the disease progresses, generalized lymphadenopathy and splenomegaly become common features. Involvement of other organs and systemic symptoms such as fever and unexplained weight loss are unusual and should suggest the possibility of transformation (ie, Richter syndrome [see Aggressive Transformation (Richter Syndrome) section]) (Table 19-14).

Table 19-14 Clinical Features and Associations With CLL

Infections
Hypogammaglobulinemia
Reduced levels of complement
Impaired phagocytic killing of nonopsonized bacteria
Functional impairment of T-cell subsets
Autoimmunity
Autoimmune hemolytic anemia
Immune thrombocytopenia
Pure red cell aplasia
Aggressive transformation
Richter transformation
Secondary malignant disease
Skin cancers (including melanomas)
Colon cancers
Lung cancers
Myeloid neoplasms

Abbreviation: CLL, chronic lymphocytic leukemia.
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Infections

Increased susceptibility to infection reflects quantitative and qualitative defects seen within the innate and adaptive immune response (eg, hypogammaglobulinemia, reduced levels of complement, impaired phagocytic killing of nonopsonized bacteria, reduction in or functional impairment of T-cell subsets) that worsen with disease progression.[288] Historically, the most common pathogens have been those that require opsonization to kill bacteria, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae.* The use of immunosuppressive agents such as fludarabine, cladribine, pentostatin, and alemtuzumab to treat CLL markedly increases the number of infections by opportunistic organisms, such as *Candida* species, *Listeria*, *Pneumocystis jirovecii*, cytomegalovirus, *Aspergillus*, and herpes viruses. The prophylactic use of intravenous immunoglobulins or antimicrobial agents should be reserved for select patients who have documented repeated infections and a reduction in serum IgG levels. The use of prophylaxis for *P. jirovecii* pneumonia (PJP) or antiviral prophylaxis should be considered in patients at risk for these opportunistic infections. Live vaccines should be avoided in patients who have CLL; influenza vaccines, COVID-19 vaccinations, and zoster vaccine recombinant, adjuvanted, for those receiving Bruton tyrosine kinase inhibitors (BTKis) are recommended. It is anticipated that infection risk will diminish as the treatment of CLL continues to move away from adenosine deaminase inhibitors and steroids to more targeted therapies.

Autoimmunity

Autoimmune hemolytic anemia is noted in 10% to 15% of patients who have CLL and has been associated with fludarabine monotherapy.[289] Many additional patients have a positive direct antiglobulin test (direct Coombs) but no clinical evidence of hemolysis. The frequency of immune thrombocytopenia is approximately 2% to 15%. In most cases, antiplatelet antibodies are polyclonal and are not a product of the malignant B cells. Autoimmune anemia or thrombocytopenia generally responds to corticosteroids such as prednisone at 1 mg/kg once per day, which may be tapered after 1 or 2 weeks with evidence of response. Patients who have immune thrombocytopenia who do not experience a response to corticosteroids may respond to high-dose intravenous immunoglobulins. Rituximab and alternative immunosuppressants may also be used for patients who do not respond to steroids. CLL-associated immune thrombocytopenia may respond to thrombopoietin receptor agonists, such as romiplostim and eltrombopag. Splenectomy may be considered when systemic approaches fail. BTKis may also be of benefit when hemolysis is refractory to steroids or recurs after steroid use.

Pure Red Cell Aplasia

Pure red cell aplasia is uncommon in CLL (<1% of patient cases).[289] It is characterized by normochromic and normocytic anemia with an absolute reticulocyte count of <10,000/mL and an absence or near absence of erythroblasts in the marrow. WBC count, WBC differential count, and platelet counts are generally normal. Immunosuppressants, such as corticosteroids, as well as cyclosporine and rituximab, may be effective.

Aggressive Transformation (Richter Syndrome)

Annually, in approximately 0.5% of patients who have CLL, the disease will evolve into a more aggressive lymphoid malignant process termed Richter syndrome that characteristically presents with rapidly increasing lymphadenopathy, hepatosplenomegaly, fever, abdominal pain, weight loss, progressive anemia, and thrombocytopenia, often with an increased serum LDH level.[290]

This transformation is not clearly related to either the nature or extent of previous therapy. The WHO classification recognizes two distinct pathologic variants of Richter syndrome, namely, the diffuse large B-cell lymphoma (DLBCL) variant and the Hodgkin lymphoma (HL) variant. This is now classified under "high-grade transformation of indolent B-cell lymphomas." Molecular lesions in tumor suppression (*TP53*), cell cycle (*CDKN2A*), and cell proliferation (*NOTCH1*, *MYC*) genes are found in approximately 90% of patients who have Richter syndrome tumors. Approximately 80% of the variants (and 40% to 50% of the HL variants) are definitively clonally related to the preceding CLL phase. In the other patients, analyses of immunoglobulin heavy-chain variable domain (*IGHV*)-D-J genes show different rearrangements compared with the underlying CLL, likely indicating de novo lymphoma arising in a patient who has CLL. The prognosis of the DLBCL variant is usually unfavorable but not uniform, with outcomes being better in patients who have clonally unrelated Richter syndrome or in those with unmutated *TP53* who have not required treatment of CLL.[290] Outcomes with the HL variant of Richter syndrome are better than with the DLBCL variant but not as good as with de novo HL.[290,291] CLL may also have prolymphocytic progression, which is associated with progressive anemia and thrombocytopenia with 15% or more prolymphocytes in the peripheral blood and/or bone marrow. Clinical features include lymphadenopathy, hepatosplenomegaly, wasting syndrome, and increased resistance to therapy. This entity is no longer recognized in the WHO classification, 5th edition, because of heterogeneity. When this progression occurs in CLL, cells retain CD5 but do not express *IGH-CCND1* as would be seen in a prolymphocytic mantle cell variant.[2]

Secondary Malignant Diseases

Secondary malignant diseases occur with increased frequency in patients who have CLL, which are related to the immune defects of the disease and to the consequences of therapy. The most frequent tumors are skin cancers (including melanomas), colon cancers, lung cancers, and myeloid neoplasms.

DIAGNOSIS

Morphology

The diagnosis of CLL requires a sustained increase in mature-appearing B lymphocytes in the peripheral blood to more than 5,000/mm^3.[292] The presence of fewer clonal B cells without palpable lymphadenopathy in an asymptomatic individual is called monoclonal B lymphocytosis. In CLL, it is not unusual to find a small percentage of larger atypical cells, cleaved cells, or prolymphocytes. The bone marrow is usually infiltrated by at least 30% lymphocytes. Although a bone marrow aspirate and biopsy specimen are not needed to make the diagnosis, they can be useful in evaluating the etiology of cytopenias. Neither lymph node biopsy nor CT scanning is needed in the initial evaluation and should be performed only if clinically indicated, such as for suspicion of Richter syndrome.

Immunophenotype

The predominant CLL cell population expresses B-cell markers (CD19, CD20, and CD23) and CD5 but not other pan–T-cell markers. The B cells are monoclonal as evidenced by the presence of either κ or λ restricted light chains, and they characteristically express surface immunoglobulin, CD79b, CD22, and CD20 with low density (as opposed to mantle cell lymphoma, which usually

has higher expression of CD20 and surface immunoglobulin). Distinguishing CLL from mantle cell lymphoma is essential because both express CD5. CD23 is often helpful (often negative in mantle cell lymphoma), but the absence of cyclin D1 expression is critical for differentiation of CLL from mantle cell lymphoma.

Cytogenetic and Molecular Abnormalities

Conventional metaphase chromosome banding techniques and FISH detect cytogenetic abnormalities in more than 50% and more than 80% of patients who have CLL, respectively.[293] The most common abnormality, either alone or in combination with other abnormalities, is del(13q), which occurs in 55% of patients. The disease course is more benign for patients who have 13q14 abnormalities, and such patients often have a normal lifespan. The del(11q) abnormality is identified in 15% to 20% of patients and is associated with massive lymphadenopathy, often out of proportion to the increase in the peripheral blood lymphocyte count. Trisomy 12 can be detected in 15% to 20% of patients. Structural abnormalities of chromosome 17 occur in approximately 15% of patients when FISH testing is performed. The del(17p13) abnormality leads to loss of the *TP53* gene and is found more frequently in cases of atypical CLL that are associated with a higher likelihood of Richter transformation, more prolymphocytes, advanced stage, resistance to chemotherapy, and a poor prognosis with conventional chemoimmunotherapy. More than one-third of patients who have *TP53* loss have complex cytogenetic abnormalities (Table 19-15).

Table 19-15 Cytogenetic and Molecular Abnormalities of CLL

Deletion of 13q14
Deletion of 11q
Trisomy 12
Abnormalities of chromosome 17 (del(17p) with *TP53* gene disruption)
BCL2 gene overexpression
IgH variable domain mutations
ZAP70
Recurrent mutations involving *TP53*, *NOTCH1*, *SF3B1*, and *BIRC3*

Abbreviation: CLL, chronic lymphocytic leukemia.
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Translocations involving *BCL-2* [t(14;18)(q32;q21)] and *BCL-3* [t(14;19)(q32;q13.1)] have been detected in only 5% to 10% of patients, but overexpression of the *BCL-2* gene is present in more than 70% of patients. The expression ratio of the antiapoptotic gene *BCL-2* to the proapoptotic gene *BAX* is increased in CLL cells, supporting the concept that CLL is more a disorder of prolonged cell survival than a hyperproliferative disease, although both factors probably contribute.

Lymphocytes from approximately half of patients who have CLL are thought to develop from naive B cells and have unmutated *IGHV*; the other half contain mutated *IGHV*, indicating their CLL cells derive from post-germinal-center B cells. *IGHV* mutation status does not change over the course of the disease. These two subtypes are characterized by markedly different clinical outcomes, and survival is significantly shorter for the group with unmutated *IGHV*. Other unfavorable molecular prognostic markers, such as positive ZAP-70, positive CD38 expression, del(17p), and del(11q), are also more commonly found in patients who have unmutated *IGHV* than in those with mutated *IGHV*. Sequencing technologies have identified recurrent mutations in CLL involving *TP53*, *NOTCH1*, *SF3B1*, and *BIRC3z*,[294] and are used for risk prognostication. Among the many mutations identified in CLL, *TP53* mutation is an inferior prognostic and predictive marker, as shown in multiple studies demonstrating inferior PFS and OS in this molecular subgroup after conventional chemoimmunotherapy. Because the presence of a *TP53* mutation influences treatment decisions, testing for *TP53* mutation before treatment, alongside FISH analysis and *IGHV* mutation status, is recommended. Cytogenetic and molecular markers in CLL can change over time, requiring reassessment if the tempo of disease seems to be changing and new treatment interventions are required.

PROGNOSTIC FACTORS

Several characteristics can stratify patients who have CLL into groups according to different clinical outcomes that may require different therapeutic approaches. The five-stage Rai classification[295] is most commonly used in the United States, and the three-stage Binet system[296] is most often applied in Europe (Tables 19-16 and 19-17). The major difference between the two systems is that Rai stages 0 and I are mostly combined into Binet stage A, and Rai stages III and IV are combined into Binet stage C. Numerous cytogenetic and molecular markers have been found to have prognostic value. An internationally applicable prognostic index has been developed that is based on five independent prognostic factors: age, clinical stage, del(17p) and/or *TP53* mutation, unmutated *IGHV*, and β2-microglobulin level. This allows separation of patients into four different prognostic groups with substantially different 5-year OS.[297] More recently, an international prognostic score for patients who have asymptomatic

early-stage CLL was developed to predict time to first treatment. It relied on individual patient data from 11 international cohorts (a total of 4,933 patients) to build and validate the score with three covariates—unmutated *IGHV* gene, absolute lymphocyte count greater than 15 × 10^9/L, and presence of palpable lymph nodes—to robustly define three different risk groups.[298]

Table 19-16 Rai Classification for Clinical Staging of CLL[295]

Risk	Stage	Description	Median Survival (Years)[a]
Low	0	Lymphocytosis in blood or bone marrow	>12.5
Intermediate	I	Lymphadenopathy	8.5
	II	Splenomegaly and/or hepatomegaly with or without lymphadenopathy	6
High	III	Anemia (hemoglobin, <13 g/dL)[b]	1.5
	IV	Thrombocytopenia (platelet count <105/mcL)[b]	1.5

Abbreviation: CLL, chronic lymphocytic leukemia.
[a]Of historical significance because outcomes are changing with newer therapies.
[b]Anemia and thrombocytopenia cannot be immune-mediated.
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Table 19-17 Binet Classification for Clinical Staging of CLL[296]

Stage	Description	Median Survival (Years)[a]
A	<2 node-bearing areas[b]	>10
B	>3 node-bearing areas	5
C	Anemia (<10.0 g/dL) and/or thrombocytopenia (platelet count <100,000/mcL)	2

Abbreviation: CLL, chronic lymphocytic leukemia.
[a]Of historical significance because outcomes are changing with newer therapies.
[b]Five node-bearing areas are possible: cervical, axillary, inguinal-femoral, spleen, and liver.
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TREATMENT

With the possible exception of allo-SCT and a small percentage of favorable-prognosis patients treated with fludarabine, cyclophosphamide, and rituximab (FCR), most patients who have CLL are not curable with currently available therapies. Randomized studies have found no improvement in survival with early versus delayed treatment of patients who have early-stage disease (Rai 0-II or Binet A). A recent trial examining ibrutinib in early-stage disease did not show a survival advantage of ibrutinib monotherapy.[299] Therefore, asymptomatic patients should be monitored unless they are enrolled in a clinical trial. Indications to start therapy include evidence of progressive bone marrow failure (eg, anemia or thrombocytopenia not associated with autoimmune hemolytic anemia or immune thrombocytopenic purpura), symptomatic splenomegaly, massive or symptomatic lymphadenopathy, rapid lymphocyte doubling time of less than 6 months, steroid-refractory autoimmune anemia or thrombocytopenia, and constitutional B symptoms that limit activities of daily living (eg, weight loss, night sweats, fevers). Leukapheresis results in only transient reductions in circulating lymphocytes and is not recommended in CLL. Patients who have CLL rarely experience hyperleukocytosis symptoms; therefore, regardless of the number of circulating cells, systemic treatment is usually sufficient.

Initial Therapy

Before the advent of highly active targeted agents, the standard of care for patients who had treatment-naive CLL was chemoimmunotherapy. The addition of an anti-CD20 monoclonal antibody to chemotherapy (chemoimmunotherapy) prolongs survival in CLL compared with chemotherapy alone. Currently, chemotherapy regimens such as FCR are rarely used for first-line therapy except in rare younger patients who are fit have mutated IGHV, and are without del(17p)/*TP53* mutation. A subset of patients who have favorable genetic markers has been shown to achieve durable responses to chemoimmunotherapy lasting more than 10 years.[300]

- Currently, when deciding on first-line therapy in CLL, physicians and their patients must decide between single-agent targeted therapy, two-drug therapy that may be time-limited, or other investigational approaches. All regimens are associated with overall excellent PFS and OS.
- FDA-approved targeted agents for the initial treatment of CLL include ibrutinib, acalabrutinib, zanubrutinib, and venetoclax. BTKis (ibrutinib, acalabrutinib, zanubrutinib) were tested in randomized phase 3 trials and compared with conventional chemoimmunotherapy in treatment-naive CLL. A summary of first-line venetoclax combinations used in more

than 900 patients who have CLL has now been published.[301] The RESONATE-2 trial initially established the efficacy of ibrutinib compared with chlorambucil in older patients who have *TP53* mutations. The ECOG E1912 study compared ibrutinib and rituximab with FCR in younger treatment-naive patients who had CLL (younger than 70 years). The Alliance for Clinical Trials in Oncology study was a three-arm trial comparing bendamustine and rituximab with ibrutinib and rituximab or ibrutinib alone in older treatment-naive patients who had CLL (age 65 or older). Long-term outcome studies have now been published from each of these trials, and all continue to demonstrate superior PFS in the BTKi versus standard chemo(immunotherapy) arms with acceptable long-term toxicity profiles.[302-305] In patients on the ibrutinib arms in the A041201 trial, PFS was not inferior in those with a *TP53* mutation.[304]

- A phase 3 study comparing acalabrutinib with ibrutinib for treatment-naive CLL showed acalabrutinib to be noninferior to ibrutinib for PFS but with reduced rates of atrial fibrillation (9.4% vs 16.0%; $P = .02$).[28]
- The phase 3 SEQUOIA trial randomly assigned adults with treatment-naive CLL without del(17p)/*TP53* mutation to receive zanubrutinib or bendamustine and rituximab. PFS was superior for zanubrutinib (HR, 0.29; one-sided $P = .0001$). For the nonrandomized del(17p)/*TP53*-mutated arm D, 24-month PFS was 92% with zanubrutinib continuously and venetoclax for 24 months.[31,32]
- Venetoclax, a BCL-2 inhibitor, was initially approved for the treatment of relapsed/refractory disease and later received an expanded approval in treatment-naive CLL. The German CLL14 study reported a PFS benefit with venetoclax plus obinutuzumab compared with chlorambucil plus obinutuzumab in treatment-naive patients who had CLL with coexisting conditions.[306] This study has now been updated with a median observation period of 76.4 months, and PFS is 78.2 versus 36.4 months for venetoclax versus chlorambucil.[306] Venetoclax was stopped after 1 year in all patients, but a PFS benefit was still seen 2 years after completion of therapy.[307]

All of these studies demonstrated superior PFS in BTKi arms compared with conventional chemoimmunotherapy. It remains to be determined in which context the combination of an anti-CD20 antibody and a BTKi adds clinical benefit. There was no PFS difference between the two ibrutinib arms with or without rituximab in the Alliance study, whereas an exploratory analysis of ELEVATE-TN, a three-arm study of acalabrutinib plus obinutuzumab, acalabrutinib alone, or chlorambucil plus obinutuzumab did demonstrate improved PFS with the addition of obinutuzumab to acalabrutinib. Eighteen percent of patients receiving ibrutinib developed atrial fibrillation, and 55% had hypertension.[308] In a 6-year follow-up, OS was longer for acalabrutinib-obinutuzumab than for the cholorambucil-obinutuzumab arm (p0.0349).[309] In an update of the Alliance trial (A041202) in older patients, at 48 months, the PFS estimates were 47% for bendamustine and rituximab, 76% for ibrutinib, and 76% for ibrutinib plus rituximab.[302]

With the availability of BTKis and anti-Bcl-2 agents such as venetoclax, almost all patients who have CLL, especially those with del(17p)/*TP53* mutation and with more aggressive disease, are treated with these agents incorporated into first-line therapy. Ibrutinib, acalabrutinib, zanubrutinib, and venetoclax with or without an anti-CD20 monoclonal antibody are preferred first-line therapies.[32,292] In initial studies of BTKis such as ibrutinib and acalabrutinib, they were often continued indefinitely. Fixed-duration regimens have now been studied, and some of the many trials still ongoing are highlighted here:

- In the German CLL14 trial, patients were randomly assigned to receive venetoclax and obinutuzumab for 12 months compared with 6 months of chlorambucil and obinutuzumab. Those who received venetoclax and obinutuzumab had improved PFS (62.6% vs 27% at 5 years), but there was no effect on OS.[310]
- In the CAPTIVATE fixed-duration trial, patients received 3 months of ibrutinib and then ibrutinib plus venetoclax for 12 months. There was a 95% PFS at 2 years.[311]
- In the phase 3 GLOW study, patients were randomly assigned to ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab, with PFS at 30 months of 87% versus 36%, respectively.[312]
- In the AMPLIFY study, the PFS was 76.5% with acalabrutinib-venetoclas, 83.1! With acalabrutinib-venetoclax-obinutuzumab and 66.5% with chemoimmunotherapy.[29] In this study, fourteen 28-day cycles were administered. Longer follow-up is awaited for OS and EFS data.
- A randomized trial of ibrutinib versus fixed-duration venetoclax and obinutuzumab or fixed-duration venetocalx and ibrutinib has now been published as an abstract, and this demonstrated noninferiority of the fixed dose combinations.[30]

MRD detection has been implemented to guide the duration of therapy and to prognosticate the duration of response after various treatment regimens, but the impact it will have on long-term survival potential remains to be seen.[313] MRD can be measured with multiparameter flow cytometry, PCR to the *IGHV* gene, which requires allele-specific oligonucleotides, and NGS. All have been used in CLL and have varying degrees of sensitivity, ranging from detection of 1 in 10^4 to 1 in 10^6 aberrant cells. In continuous treatment regimens with BTKis or venetoclax, this can be examined as an indicator of PFS, but it is often not helpful because PFS is excellent even with positive MRD, given time to relapse, and the multitude of salvage regimens available. In first-line fixed-duration treatment of CLL, MRD can be measured 2 to 3 months after treatment ends, and its role in determining future treatment decisions is evolving.[313] Most relapses can be picked up at a molecular level, and this may make retreatment more effective, but longer

follow-up is desired. The use of venetoclax consolidation after more than 12 months of ibrutinib therapy was found to achieve a high rate of MRD at the 10^{-4} level.[314] It is also possible that using MRD may help define the duration of treatment in a personalized manner, as noted in the FLAIR study, in which MRD was used to direct how long ibrutinib and venetoclax were continued.[315]

Important adverse events associated with BTKis include bleeding, atypical infection (*P. jirovecii*, *Aspergillosis*, progressive multifocal encephalopathy), and atrial fibrillation. BTKis such as acalabrutinib are associated with improved toxicity profiles relative to ibrutinib, particularly in the reduction of the rate of atrial fibrillation to 7% from 13% of patients treated with ibrutinib.[316] Although BTKis are associated with atypical fungal infections, the incidence of these infections is low, and routine prophylaxis for fungal and viral organisms is generally not recommended. Tumor lysis syndrome can occur in patients treated with chemoimmunotherapy or venetoclax, especially those with high WBC counts, bulky lymphadenopathy, or impaired renal function. Tumor lysis syndrome may be fatal and is not consistently preventable with the use of prophylactic allopurinol and/or hydration. Patients at higher risk of developing tumor lysis syndrome should be monitored closely with laboratory testing and hydration during the initial period of venetoclax-based therapy or chemoimmunotherapy. A 5-week dosage ramp-up and inpatient or close outpatient monitoring is often recommended.

Fludarabine may be associated with autoimmune hemolytic anemia and immune thrombocytopenia; if such complications are seen, treatment should be stopped, and the patient should be switched to an alternative treatment. Despite the profound immunosuppression associated with fludarabine, the risk of secondary malignant disease does not seem to be increased with fludarabine alone, but there may be an increased incidence of myelodysplasia when fludarabine is combined with an alkylating agent, such as cyclophosphamide. This will likely be seen less frequently because regimens such as FCR have been replaced with BTKis and BH3-mimetics. Common toxicities of drugs used for first-line treatment of CLL are provided in Table 19-18. Diminished vaccine responses are seen with all targeted agents; in general, live vaccines are not recommended in CLL.

Table 19-18 Common Toxicities of Drugs Used for First-Line CLL Therapy

Drug	Adverse Effect
BTKis	Diarrhea
	Fatigue
	Arthralgias/cramps
	Infections
	Bleeding (with acalabrutinib and ibrutinib; warfarin should be avoided)
	Atrial fibrillation
	Hypertension - Acalabrutinib and zanubrutinib have more favorable toxicity profiles compared with ibrutinib because they are more specific inhibitors[292,316]
	PPIs are discouraged with acalabrutinib
Venetoclax	Tumor lysis syndrome (5-week ramp-up recommended)
	Neutropenia

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; PPI, proton pump inhibitor.
Diminished vaccine responses are seen with all targeted agents; in general, live vaccines are not recommended in CLL.
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The following summarizes first-line treatment of CLL[317]: There are multiple factors both disease and patient related such as comorbidities which are factored into these choices.

- For patients without del(17p)/*TP53* mutation:
  - BTKis with or without anti-CD20 monoclonal antibody; acalabrutinib or zanubrutinib are now usually recommended compared with ibrutinib on the basis of more favorable toxicity profiles
  - Venetoclax plus obinutuzumab (fixed-duration treatment)
- For patients with del(17p)/*TP53* mutation:
  - BTKis with or without obinutuzumab
  - Venetoclax plus obinutuzumab (fixed-duration treatment)

Treatment of Relapsed/Refractory Disease

The management of relapsed CLL depends on several factors, including age, performance status, presence of del(17p)/*TP53* mutation, previous therapies, response to and duration of last therapy, and time from last therapy. With many potential treatments

available, the best sequence and timing of salvage therapies are being addressed in clinical trials. The current standard of care for relapsed/refractory CLL includes acalabrutinib or zanubrutinib or venetoclax with anti-CD20 monoclonal antibody, ibrutinib, and duvelisib (currently approved as a third-line therapy).[318,319] In a randomized study, zanubrutinib was shown to yield superior PFS compared with ibrutinib in relapsed/refractory CLL.[320] This has now been finalized with a median follow-up of 42.5 months with PFS higher in the zanubrutinb arm and higher overall response rates with zanubrutinib versus ibrutinib (86% vs 75%). Median OS was not reached in either group.[32] Acalabrutinib is also a more selective BTKi and may provide a better safety profile than ibrutinib. Data from a head-to-head comparison trial of acalabrutinib and ibrutinib in previously treated patients showed acalabrutinib to be noninferior to ibrutinib for PFS and OS but with a significantly lower incidence of atrial fibrillation in those treated with acalabrutinib.[28] Acalabrutinib and zanubrutinib are not able to overcome resistance in patients who have ibrutinib-refractory CLL with BTK C481S mutations.[321] Pirtobrutinib can be tried in these situations. Pirtobrutinib is also now approved as second- or third-line therapy in those who are resistant or intolerant to other BTKis and have had two lines of previous therapy, including a BTKi and an anti-BCL-2 inhibitor.[322] This is a noncovalent (reversible) BTKi. In the BRUIN trial, the ORR in those previously treated with a BTKi was 73%, and the median PFS was 19.6 months in a heavily pretreated population.[323] Cytopenias, fatigue, bruising, musculoskeletal pain, and infections were among the most common adverse effects reported. In the BRUIN CLL-321 trial, pirtobrutinib versus idelalisib/rituximab or bendamustine/rituximab resulted in superior PFS and longer time to next treatment or death.[324] Venetoclax can be used as a monotherapy or in combination with an anti-CD20 monoclonal antibody in relapsed/refractory CLL. The MURANO study was a phase 3 trial in relapsed/refractory CLL in which 389 patients were randomly assigned to receive venetoclax for up to 2 years in combination with rituximab for the first 6 months or bendamustine and rituximab for 6 months. The study reported a PFS benefit in favor of venetoclax and rituximab over bendamustine and rituximab in the initial report and an OS benefit in a 5-year follow-up.[325] Clearance of MRD at 9 months was significantly better for venetoclax and rituximab at 62% versus 13% for bendamustine and rituximab, and OS was improved in the venetoclax and rituximab group. The following studies or agents have been examined in relapsed/refractory CLL: at 7 years of follow-up, the OS was 70% versus 51% in favor or pritobrutinib.[326]

- ASCEND—PFS 62% at 42 months with acalabrutinib[327]
- ELEVATE-RR—acalabrutinib noninferior to ibrutinib (PFS); median PFS was 38 months on both arms[28]
- RESONATE—ibrutinib versus ofatumumab; superior PFS with ibrutinib; median PFS was 44 versus 8 months[328]
- MURANO—venetoclax-rituximab versus bendamustine plus rituximab; venetoclax-rituximab was superior; median PFS was 54 months versus 17 months[325]
- ALPINE—zanubrutinib was more effective than ibrutinib with longer PFS; 78.4% versus 65.9% at 24 months[320]

Note that PI3 kinase inhibitors idelalisib and duvelisib met with safety concerns. Idelalisib is available in combination treatments, but duvelisib was withdrawn by the FDA on April 13, 2022, due to possible detriment in OS and safety concerns compared with ofatumumab.

CAR T-Cell Therapy

Encouraging results have also been reported with CD19-targeted autologous T cells expressing CARs. In one phase 1 study, the 6-year duration of response and OS were 26.4% and 31.2%, respectively.[329] Factors associated with durable responses are being examined. In March 2024, the FDA approved lisocabtagene maraleucel (liso-cel) for the treatment of adult patients who have relapsed/refractory CLL and who have received at least two previous lines of therapy, and these must include a BTKi and a BCL-2 inhibitor.[213]

Allo-SCT

Given that CLL is associated with advanced age and increased comorbidities, allo-SCT applies to a minority of patients for whom targeted agents have failed, who have a donor available, and who are relatively fit to undergo intensive therapy. Allo-SCT can provide long-term disease control and cure for a subset of patients. However, the NRM rate remains high in CLL.

Treatment of Richter Transformation

Treatment of Richter transformation is usually approached with regimens used for de novo DLBCL such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), dosage-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH), or other chemoimmunotherapy combinations.[291] BTKis can be used, and pirtobrutinib, in particular, has been examined in this setting. PD1-PD-L1 inhibitors, BCL-2 inhibitors, and anti-CD20-CD3 bispecifics are also being examined in patients who have Richter transformation to DLBCL. CAR T-cell therapies directed to CD19 may also be effective in these patients. A trial of liso-cel with nivolumab and ibrutinib (NCT05672173) is underway.

FUTURE DIRECTIONS IN CLL THERAPY

Trials with combinations of BTKis and venetoclax are underway. The addition of obinutuzumab to BTKis and venetoclax (triple therapy) is also being investigated. Whether a triplet regimen will be needed to obtain and maintain an undetectable MRD state

is still not understood. In the CLL2-GIVe trial, obinutuzumab, ibrutinib, and venetoclax were combined in patients who had untreated CLL with del(17p) or mutated *TP53*.[330] The 36-month PFS was 79.9%, and the 36-month OS was 92.6%.

Studies such as the ongoing MAJIC (NCT05057494) trial with obinutuzumab and venetoclax versus a fixed duration of acalabrutinib and venetoclax will help answer the question of whether an all-oral regimen might be as effective as a regimen with an anti-CD20 monoclonal antibody infusion.

Novel BH3-mimetics, BTK degraders, and new noncovalent BTKis are being examined in the treatment of CLL.[331] New roles for CAR T cells and bispecifics are also being examined in CLL.[332]

KEY POINTS

- Distinguishing CLL from other diseases, notably hairy cell leukemia or the leukemic presentations of marginal zone lymphoma or mantle cell lymphoma, is based on the morphologic appearance of the cells, the distinct immunophenotype of the malignant cells, and cytogenetic findings.
- Survival for patients who have CLL has improved with the introduction of highly active targeted agents.
- In patients who have treatment-naive CLL, five randomized phase 3 trials showed improved PFS in patients treated with BTKi-based regimens (ibrutinib, acalabrutinib, or zanubrutinib either as monotherapy or in combination with an anti-CD20 monoclonal antibody) compared with those treated with conventional chemoimmunotherapy. Another randomized phase 3 trial showed improved PFS with venetoclax plus obinutuzumab compared with chemoimmunotherapy. These results establish four targeted agents—ibrutinib, acalabrutinib, zanubrutinib, and venetoclax—as effective first-line therapy for CLL, regardless of the patient's age or cytogenetic status.
- In first-line therapy, a single-agent BTKi on a continuous basis is acceptable, especially in patients with *TP53* mutations.
- It is important to review the benefits of continuous versus fixed duration treatment with patients.
- In patients who have relapsed/refractory CLL, consider the type of first-line therapy, duration of response or remission to first-line therapy, and possible acquired resistance to therapy class.
- In the relapsed/refractory CLL setting, with many potential treatments available, the optimal sequence and timing of salvage therapies are being addressed in clinical trials. Current standards of care for relapsed/refractory CLL include ibrutinib, acalabrutinib, zanubrutinib, venetoclax with or without an anti-CD20 monoclonal antibody, or pirtobrutinib in those who have had at least two previous lines of therapy. The use of CAR T-cell therapy is evolving.
- The role that MRD will play in defining type and duration of therapy and whether resistance patterns emerge after time-limited therapies is still being investigated.[315]

PROLYMPHOCYTIC LEUKEMIA

T-cell prolymphocytic leukemia (T-PLL) is a rare lymphoid neoplasm that occurs predominantly in older adults. There is a slight male predominance. At presentation, the primary clinical features include rapidly increasing lymphocyte counts and splenomegaly. Lymphadenopathy, rashes, peripheral edema, and pleuroperitoneal effusions are relatively common in T-PLL.

T-PLL typically expresses CD2, $CD3^{+/-}$, CD5, CD7, and CD52 with variable expression of CD4 and CD8. It does not express DNA nucleotidylexotransferase or CD1a. Common cytogenetic abnormalities include complex karyotypes typically involving chromosome 14q32 or Xq26. T-cell clonality can be demonstrated by PCR, and there should be >5,000/mcL prolymphocytes in the blood or marrow. Patients who have T-PLL have T-cell leukemia 1 (TCL1) or MTCP1 overexpression and ATM loss (11q22.3).[333] T-PLL treatment can include alemtuzumab, pentostatin, or combinations of fludarabine, mitoxantrone, and cyclophosphamide.[334] Therapeutic activity of alemtuzumab and purine analogs tends to be transient. Allo-SCT should be considered for suitable patients in first remission. New therapeutic strategies may include BH3-mimetics, JAK inhibitors such as ruxolitinib, and epigenetic modulation.[334]

In the WHO 5th edition classification of lymphoid neoplasms,[2] B-cell PLL was eliminated as an entity because of its heterogeneity, some being mantle cell variants, some representing progression of chronic lymphocytic leukemia or small lymphocytic leukemia (CLL/SLL), and some being what others called "splenic B-cell lymphoma/leukemia with prominent nucleoli."[2]

HAIRY CELL LEUKEMIA

Approximately 1,000 new cases of hairy cell leukemia occur each year in the United States, primarily in middle-aged individuals, with a 4:1 male predominance.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients typically present with symptoms related to pancytopenia,[335,336] including infections, weakness or fatigue, shortness of breath, bleeding, or left upper quadrant abdominal pain related to splenomegaly. In addition to cytopenias and splenomegaly, the most common sign is the presence of circulating hairy cells. These cells generally have an eccentric spongiform kidney-shaped nucleus with characteristic filamentous cytoplasmic projections.

A bone marrow biopsy specimen is typically required to establish the diagnosis because an aspirate often cannot be obtained. The malignant cells in classic hairy cell leukemia are of B-cell origin; have no (or inconspicuous) nucleoli; and express CD19, CD20, CD123, and CD200 as well as the monocyte antigens CD11c, CD25, and VE1 (a *BRAF* V600E stain). The most specific marker is CD103. The cells stain positively with tartrate-resistant acid phosphatase, but this is rarely used diagnostically, given the availability of flow cytometry discrimination. Monocytopenia is a common feature of the disease. Mutations in *BRAF*, specifically V600E, have been found in virtually all cases of classic hairy cell leukemia. *BRAF* V600E is thought of as a causal genetic event, leading to the constitutive activation of the RAF-MEK-ERK signaling pathway, which represents the key event in the molecular pathogenesis of hairy cell leukemia.[337]

Hairy cell variant leukemia has biology and clinical behaviors that are distinct from those of classic hairy cell leukemia, and patients often present with significant leukocytosis. This entity is now called splenic B-cell lymphoma/leukemia with prominent nucleoli.[2] Cells are characterized by prominent nucleoli and a lack of CD200 expression. They also typically do not express CD25 or CD123, and molecularly, they lack the *BRAF* V600E mutation.

TREATMENT

Treatment is indicated in the setting of massive or progressive splenomegaly, worsening blood cell counts, recurrent infection, more than 20,000 hairy cells/mcL of peripheral blood, or bulky lymphadenopathy.

Classic hairy cell leukemia typically follows an indolent disease course and is now highly controllable. More than 80% of patients will experience a durable response to treatment with purine analogs cladribine or pentostatin with or without an anti-CD20 antibody such as rituximab.[338] The results with cladribine are equivalent to those with pentostatin. Rituximab can be given concurrently or sequentially; concurrent use is associated with a higher probability of achieving an undetectable MRD state.[338] The shorter duration of treatment makes cladribine somewhat more attractive. In patients who have renal impairment, purine analogs should be used with caution. Although IFN-α was the first systemic therapy to demonstrate activity in hairy cell leukemia, its current role is limited because the purine analogs are superior with regard to response duration, safety, and outcome. Likewise, splenectomy is no longer used to treat hairy cell leukemia. Some studies have examined the use of BRAF inhibitors along with obinutuzumab as initial therapy.[339]

Ultimately, approximately 30% to 40% of patients experience relapse after purine analog–based therapy. In many cases, relapse is characterized only by an increase in hairy cells in the bone marrow with no indication for treatment. Patients who develop symptomatic disease or progressive cytopenias as a result of relapse require retreatment. Selection of treatment at relapse is guided by the duration of remission after initial therapy.[340] A second durable response is achieved for most patients. Treatment options at relapse include a purine analog with rituximab for later relapses (>2-year remission). In those with shorter remissions, an alternate purine analog with rituximab or a BRAF inhibitor such as vemurafenib plus rituximab is an option.[36] For patients beyond first relapse, other options include the BTKi ibrutinib or other BRAF or MEK inhibitors, such as dabrafenib and trametinib, respectively.[35,341] The ideal sequence of these regimens is unknown.[342]

Variant hairy cell leukemia has a more aggressive disease course than does classic hairy cell leukemia.[343] Treatment results with purine analog monotherapy are substantially inferior (ORR, <50% vs 75% to 100% for the classic version; CR rate, <10% vs >50% to 70%), but the addition of rituximab or obinutuzumab seems to improve outcomes.[344] In relapsed/refractory disease, ibrutinib seems to have efficacy.[35]

KEY POINTS

- Classic hairy cell leukemia is highly responsive to treatment with purine analogs (eg, cladribine or pentostatin) administered alone or in combination with rituximab.
- Patients who have relapsed/refractory disease who require treatment may respond to retreatment with purine analog–based therapy, especially if they are in late relapse. In addition, anti-CD20 antibodies, a *BRAF* inhibitor, or ibrutinib are options for relapsed disease.

MATURE T-CELL/NK-CELL LEUKEMIAS

In the WHO 5th edition classification of lymphoid neoplasms, the mature T-cell and NK-cell neoplasms include T-PLL, T-large granular lymphocytic leukemia, NK-large granular lymphocytic leukemia, adult T-cell leukemia/lymphoma, Sezary syndrome, and aggressive NK-cell leukemia.[2] These diseases have phenotypic, genotypic, and clinical heterogeneity.[345,346]

Large granular lymphocytoses can be divided into two major subsets: T-cell large granular lymphocytosis ($CD3^+$, representing activated cytotoxic T cells) and NK-cell large granular lymphocytosis ($CD3^-$). T-cell large granular lymphocytosis tends to occur in older individuals, and most patients (60%) are symptomatic at diagnosis. Anemia and recurrent infections associated with neutropenia are common, and thrombocytopenia may also occur. Autoimmune hemolytic anemia and pure red cell aplasia can be associated. Diagnosis generally requires 2,000/mcL large granular lymphocytosis (LGL) cells and persistence for at least

6 months, but some series allow 500/mcL LGL cells for diagnosis with unexplained cytopenias. The immunophenotype includes positivity for CD3, CD8, and CD57. Clonal rearrangement of the T-cell receptor (*TCR*) gene is typically detected. There are also rare patients who have $CD4^+$ T-cell large granular lymphocytic leukemia (T-LGLL). In about 30% of patients, activating *STAT3* mutations are present, and other patients express mutations in *STAT5B* and *CCL22*.[347] The presence of these mutations helps further subclassify these disorders, and *STAT3* mutations can be associated with more severe neutropenia. The NK-cell variety accounts for approximately 15% of LGLs and includes aggressive NK-cell leukemia and a more indolent NK-cell lymphocytosis. The cells are negative for CD3; positive for CD8, CD16, and CD56; and may or may not be positive for CD57. *TCR* gene rearrangements are absent. Aggressive NK-leukemias are often associated with Epstein-Barr infections.

For the indolent forms of T-LGLL, a notable feature is their association with other diseases in up to 40% of patients, including rheumatoid arthritis; other autoimmune diseases, such as systemic lupus erythematosus; and other hematologic disorders, such as CLL, hairy cell leukemia, lymphoma, MDS, and monoclonal gammopathy of undetermined significance. With the indolent forms, treatment regimens vary and are not standardized. Generally, immunosuppressive therapy (eg, methotrexate, cyclophosphamide, cyclosporine) is the mainstay of initial treatment, and these drugs may be combined with corticosteroids in some patients.[348] Salvage therapies may include ruxolitinib or alemtuzumab.[349] G-CSF may be helpful in some cases to mitigate neutropenic complications.

Patients affected by the aggressive form of the disease tend to be younger and do not have rheumatoid arthritis. Infiltration of the gastrointestinal tract and bone marrow is common. Neutropenia is modest compared with the severity of anemia and thrombocytopenia. Patients often die as a result of multiorgan failure with a coagulopathy, generally within a few months of diagnosis, despite aggressive chemotherapy.

Approximately 5% of LGLs are a nonclonal expansion of $CD3^+$ LGL that is generally unaccompanied by lymphadenopathy or hepatosplenomegaly. The features of the cells are positivity for CD3, CD16, and CD56 and negativity for CD4 and CD8. The disease is indolent, rarely requiring intervention unless accompanied by neutropenia. Prednisone and immunosuppressive agents have been used. It is not clear whether this disorder is actually neoplastic.

KEY POINTS

- T- and NK-LGLL are a heterogeneous group of disorders, and it is important to obtain immunophenotyping and *STAT3* and *STAT5B* analysis at diagnosis.
- Some patients do not require treatment, but in those who have symptomatic neutropenia or require treatment of an underlying autoimmune disease, therapy should be started.
- Understanding mutational aberrancies in these disorders may suggest new treatment paradigms for the future, but none have been forthcoming thus far.

ADULT T-CELL LEUKEMIA/LYMPHOMA

Adult T-cell leukemia/lymphoma (ATLL) is endemic in certain geographic areas, including the southeastern United States, islands in southern Japan, the Caribbean basin (including Jamaica and Trinidad), northeast Iran, western Africa, and Peru. The disease is linked to human T-cell lymphotropic virus type 1 infection (HTLV-1). HTLV-1 carriers lose a balance between infected $CD4^+$ T cells and antiviral immunity in about 5% to 10% of patients and develop ATLL.[350]

Four clinical variants of ATLL are acute, chronic, smoldering, and lymphomatous disease. Elevated serum calcium and LDH are prognostic for poor outcomes. Patients who have the acute, lymphomatous, or unfavorable chronic type require multiagent chemotherapy with or without subsequent allo-SCT. The median survival without SCT is 7 to 13 months.[350] The addition of the anti-CC4 antibody mogamulizumab to the multiagent chemotherapy can improve the rate of overall response and PFS.[351] For the chronic or smoldering type, watchful waiting can be considered. Antiviral therapy with zidovudine plus IFN-α has also been examined, but has a controversial role. Retrospective studies demonstrated OS benefits in patients who have acute, chronic, and smoldering types but not the lymphomatous type. Approximately 10% to 25% of patients present with CNS involvement at diagnosis or relapse; therefore, patients who have an acute or aggressive presentation of the disease should be evaluated for CNS involvement and receive intrathecal chemotherapy for prophylaxis. Efforts to prevent mother-to-child or horizontal transmission are the subjects of current research efforts. Lenalidomide and PD-1 inhibitors are being examined in ATLL.

HIGH-YIELD TAKEAWAYS

- ATRA should be given right away when suspicious for APL; ATRA plus arsenic is a highly curable regimen.
- AML management can involve intensive or less intensive treatment regimens based on age, prognostic features, and other patient comorbidities.

- Tyrosine kinase inhibitors are the treatment of choice for chronic phase CML.
- Polycythemia vera and essential thrombocythemia are most often characterized by *the JAK2 V617F* variant.
- Treatment for Ph+ ALL should include TKI with chemotherapy or blinatumomab.

Acknowledgments

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LEUKEMIAS AND OTHER MYELOID NEOPLASMS

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CHAPTER SUMMARY GUIDE

KEY POINTS

- Leukemias, MDSs, and MPNs encompass a diverse group of clonal diseases of the hematopoietic system.
- Familial or genetic predisposition and exposure to certain infectious pathogens, radiation, chemicals, and therapeutic agents have been associated with an increased incidence of these hematopoietic neoplasms.
- In 60% of patients who have AML, at least one clonal abnormality in chromosome number or structure can be found. These cytogenetic abnormalities, in combination with age and performance status, are the most important prognostic factors in AML and are indispensable in making therapeutic decisions.
- Genome-wide sequencing has identified more than 50 genes that are recurrently mutated in AML. Testing for mutations in *FLT3, NPM1, CEBPA, IDH1, IDH2, KMT2A, NPM1,* and *TP53*, among other genes, is important in making treatment decisions for patients who enter first remission.
- On the basis of cytogenetic and molecular markers, AML can be divided into several categories with distinct disease risk.
- Standard induction therapy for those eligible for intensive chemotherapy in AML involves the use of an anthracycline and cytarabine.
- All patients aged 70 to 75 years or younger who achieve complete remission, except those with a favorable-risk cytogenetic or molecular profile who achieve an early first complete remission and have no evidence of MRD after induction, should be considered for allo-SCT, particularly if the SCT comorbidity index score is low and a donor is available. Myeloablative conditioning is preferred for patients up to age 60 to 65 years.
- Patients who are considered unfit to receive chemotherapy because of age or medical comorbidities are treated with venetoclax in combination with an HMA or low-dose cytarabine. Studies of multiple novel combination therapies combining venetoclax with chemotherapy or targeted therapy are ongoing.
- The prognosis is poor for patients who have recurrent AML, and the likelihood of achieving a second remission is predicted by the length of the first remission. Individuals who have remained in remission for more than 1 year can be induced with the same chemotherapy administered for the first complete remission. Because of this poor outcome, transplantation should be considered for most patients who have recurrent AML and who are appropriate candidates.
- Genetic analysis should be repeated at the time of disease progression or relapse, given that multiple targeted therapies are currently approved in this setting. Gilteritinib is approved for relapsed/refractory *FLT3*-ITD–mutated AML, and ivosidenib, olutasidenib, and enasidenib are approved for *IDH1*- and *IDH2*-mutated relapsed/refractory AML. Revumenib is approved for relapsed/refractory AML with KMT2Ar. In addition, both revumenib and ziftomenib are approved for relapsed/refractory *NPM1*-mutated AML.
- The suspicion of APL in a patient who has newly diagnosed acute leukemia should trigger the immediate administration of ATRA to reduce the risk of early death resulting from hemorrhage.
- Patients who have APL should receive ATRA and ATO as part of induction and/or consolidation therapy.
- TKIs such as imatinib, nilotinib, dasatinib, and bosutinib are remarkably effective in newly diagnosed CP-CML, leading to complete hematologic and cytogenetic responses for most patients with OS similar to that of age-matched controls. However, continued therapy and careful follow-up are necessary. Asciminib, an allosteric inhibitor of the myristoyl site of the BCR-ABL1 protein, is now also approved in the newly diagnosed setting.
- Second-generation TKIs (eg, dasatinib, nilotinib, and bosutinib) result in quicker cytogenetic and molecular responses compared with imatinib, with no differences in OS.
- Patients who have *T315I*-mutated CML may respond to ponatinib, although the duration of response is typically short.
- Asciminib is approved by the FDA for patients who have CP-CML with resistance to at least two previous TKIs or CP-CML with a *T315I* mutation.
- Patients who have accelerated or blast-phase CML can respond to TKIs, but responses are generally short, and the disease is relatively resistant to most types of therapy. Allo-SCT is potentially curative for these patients.

- Clonal hematopoiesis is defined by a hematologic neoplasm driver mutation at a VAF greater than 2% in the absence of cytopenia, dysplasia, or increased blasts. Cytopenia is present in both CCUS and ICUS; note that CCUS is associated with a clonal mutation in addition to cytopenia.
- The risk of progression to a myeloid malignancy (MDS or AML) is comparably lower for those with clonal hematopoiesis (approximately 0.5%-1% per year) or ICUS (approximately 1% per year) and higher for those with CCUS (approximately 10%-20% per year). Risk factors have now been validated, and a clonal hematopoiesis risk score can be determined.[13,14]
- The important prognostic factors for patients who have MDS are percentage of marrow blasts, karyotype, number of peripheral blood cytopenias, and molecular mutations.
- The therapeutic strategy for MDS is based primarily on the disease risk, with the main goals of reducing consequences of cytopenias, improving quality of life for patients who have lower risk disease, preventing transformation into AML, and improving survival for patients who have higher risk disease.
- The 5q-minus subtype responds well to therapy with lenalidomide, and administration of lenalidomide early in the disease course can delay the onset of RBC transfusion dependence.
- Luspatercept can be used in low- and intermediate-risk transfusion-dependent patients who have MDS independent of erythropoietin level, either before or after a trial with an ESA. Imetelstat is also now approved for those MDS patients with low to intermediate-1 risk who are transfusion dependent and have not responded to ESAs.
- Allo-SCT is the only curative treatment for MDS.
- The treatment of PV, ET, and primary MF is tailored to the likelihood of the development of venous or arterial thrombosis, bleeding, or evolution to AML, the major life-threatening and limiting complications of these MPNs. In PV and ET, cytoreductive therapy is reserved for the high-risk disease categories.
- In MF, treatment is also based on risk stratification, and multiple prognostic scoring systems are available. By using the risk levels from the MIPSS70 + v2.0 for categorizing patients, those in low-risk categories can enter a period of observation, and for patients in the high-risk categories, allo-SCT is recommended for those who are appropriate candidates. Those in intermediate-risk categories must be individualized but may benefit from JAK inhibitors and treatments to improve anemia. Transplantation is indicated for some of these patients.
- Multiple JAK inhibitors are now available for treatment of MF (ruxolitinib, fedratinib, pacritinib, and momelotinib), and they can be selected on the basis of their adverse effect profiles.
- There is increased awareness of the MPN/MDS overlap syndromes, and classification based on clinical and molecular characteristics continues to evolve, as evidenced by the changes in the 2022 WHO and ICC classifications.
- Induction therapy for adult ALL generally should include vincristine, prednisone, and an anthracycline with or without L-asparaginase or cyclophosphamide. With such regimens, complete remission can be achieved in 80% to 90% of patients. Consideration of a pediatric-inspired regimen should be given for all patients aged 40 years or younger and possibly in select patients aged 55 years or younger.
- Patients who have CD20+ B-cell ALL should receive rituximab during induction and consolidation.
- Patients who have Ph+ ALL should receive a BCR-ABL1–directed TKI in combination with chemotherapy or blinatumomab.
- Recently, ponatinib was an FDA-approved agent in combination with chemotherapy for newly diagnosed Ph+ ALL.
- Blinatumomab can convert up to 80% of MRD-positive patients who have B-cell ALL and are in remission to an MRD-negative state and also improves outcomes.
- Allo-SCT is an important post-remission treatment except perhaps in patients who have highly chemotherapy-sensitive disease, as indicated by early MRD negativity.
- Salvage treatment options for patients who have relapsed/refractory B-cell ALL include blinatumomab, inotuzumab ozogamicin, and CAR T-cell therapy (tisagenlecleucel, brexucabtagene autoleucel, and obecabtagene autoleucel).
- Given the rarity of ALL and the complexity of its treatment, it is generally recommended that patients who have ALL be treated at high-volume centers (>10 new cases managed per year) with access to clinical trials, cell therapies, and SCT.
- Distinguishing CLL from other diseases, notably hairy cell leukemia or the leukemic presentations of marginal zone lymphoma or mantle cell lymphoma, is based on the morphologic appearance of the cells, the distinct immunophenotype of the malignant cells, and cytogenetic findings.
- Survival for patients who have CLL has improved with the introduction of highly active targeted agents.
- In patients who have treatment-naive CLL, five randomized phase 3 trials showed improved PFS in patients treated with BTKi-based regimens (ibrutinib, acalabrutinib, or zanubrutinib either as monotherapy or in combination with an anti-CD20 monoclonal antibody) compared with those treated with conventional chemoimmunotherapy. Another randomized phase 3 trial showed improved PFS with venetoclax plus obinutuzumab compared with chemoimmunotherapy. These results establish four targeted agents—ibrutinib, acalabrutinib, zanubrutinib, and venetoclax—as effective first-line therapy for CLL, regardless of the patient's age or cytogenetic status.
- In first-line therapy, a single-agent BTKi on a continuous basis is acceptable, especially in patients with *TP53* mutations.

- It is important to review the benefits of continuous versus fixed duration treatment with patients.
- In patients who have relapsed/refractory CLL, consider the type of first-line therapy, duration of response or remission to first-line therapy, and possible acquired resistance to therapy class.
- In the relapsed/refractory CLL setting, with many potential treatments available, the optimal sequence and timing of salvage therapies are being addressed in clinical trials. Current standards of care for relapsed/refractory CLL include ibrutinib, acalabrutinib, zanubrutinib, venetoclax with or without an anti-CD20 monoclonal antibody, or pirtobrutinib in those who have had at least two previous lines of therapy. The use of CAR T-cell therapy is evolving.
- The role that MRD will play in defining type and duration of therapy and whether resistance patterns emerge after time-limited therapies is still being investigated.[315]
- Classic hairy cell leukemia is highly responsive to treatment with purine analogs (eg, cladribine or pentostatin) administered alone or in combination with rituximab.
- Patients who have relapsed/refractory disease who require treatment may respond to retreatment with purine analog–based therapy, especially if they are in late relapse. In addition, anti-CD20 antibodies, a *BRAF* inhibitor, or ibrutinib are options for relapsed disease.
- T- and NK-LGLL are a heterogeneous group of disorders, and it is important to obtain immunophenotyping and *STAT3* and *STAT5B* analysis at diagnosis.
- Some patients do not require treatment, but in those who have symptomatic neutropenia or require treatment of an underlying autoimmune disease, therapy should be started.
- Understanding mutational aberrancies in these disorders may suggest new treatment paradigms for the future, but none have been forthcoming thus far.

CHAPTER TABLES AND IMAGES

Table 19-1 **2022 WHO Classification of AML[1,2]**

Type of Leukemia	Classification
AML	
With defining genetic abnormalities	APL with *PML::RARA* fusion
	AML with *RUNX1::RUNX1T1* fusion
	AML with *CBFB::MYH11* fusion
	AML with *DEK::NUP214* fusion
	AML with *RBM15::MRTFA* fusion
	AML with *BCR::ABL1* fusion
	AML with *KMT2A* rearrangement
	AML with *MECOM* rearrangement
	AML with *NUP98* rearrangement
	AML with *NPM1* mutation
	AML with *CEBPA* mutation
	AML, myelodysplasia-related
	AML with other defined genetic alterations
Defined by differentiation	AML with minimal differentiation
	AML without maturation
	AML with maturation
	Acute basophilic leukemia
	Acute myelomonocytic leukemia
	Acute monocytic leukemia
	Acute erythroid leukemia
	Acute megakaryoblastic leukemia
Acute leukemia of ambiguous lineage	
With defining genetic abnormalities	Mixed-phenotype acute leukemia with *BCR::ABL1* fusion
	Mixed-phenotype acute leukemia with *KMT2A* rearrangement
	Acute leukemia of ambiguous lineage with other defined genetic alterations
	• Mixed-phenotype acute leukemia with *ZNF384* rearrangement
	• Acute leukemia of ambiguous lineage with *BCL11B* rearrangement
Immunophenotypically defined	Mixed-phenotype acute leukemia, B/myeloid
	Mixed-phenotype acute leukemia, T/myeloid
	Mixed-phenotype acute leukemia, rare types
	Acute leukemia of ambiguous lineage, NOS
	Acute undifferentiated leukemia
B-lymphoblastic leukemia/lymphoma	
	B-lymphoblastic leukemia/lymphoma, NOS
	B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
	B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
	B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
	B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
	B-lymphoblastic leukemia/lymphoma with hyperdiploidy
	B-lymphoblastic leukemia/lymphoma with hypodiploidy
	B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*

Type of Leukemia	Classification
	B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
	Provisional entity: B-lymphoblastic leukemia/lymphoma, *BCR-ABL1*-like
	Provisional entity: B-lymphoblastic leukemia/lymphoma with *iAMP21*

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocyte leukemia; NOS, not otherwise specified; WHO, World Health Organization.
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Table 19-2 **Tests and Procedures for Patients With AML**[39]

Test	Procedure
Diagnostic tests	CBC and differential count
	Bone marrow aspirate
	Bone marrow trephine biopsy
	Immunophenotyping, flow cytometry, next-generation sequencing for myeloid mutation panel, and RNA gene re-expression
Genetic analyses	Cytogenetics[a]
	Screening for these gene mutations[b]: *NPM1*, *CEBPA*, *IDH1*, *IDH2*, *FLT3*, *TP53*, *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*, *DDX41*
	Screening for these gene rearrangements: *PML-RARA*, *CBFB-MYH11*, *RUNX1-RUNX1T1*, *BCR-ABL1*, other fusion genes (if available)
Additional tests/procedures at diagnosis	Demographics and medical history[c]
	Detailed family history[d]
	Patient bleeding history[e]
	ECOG performance status
	Analysis of comorbidities
	Biochemistry, coagulation tests, urine analysis[f]
	Serum pregnancy test[g]
	Information on oocyte and sperm cryopreservation[h]
	Eligibility assessment for allo-SCT (including HLA typing)[i]
	Hepatitis A, B, C; HIV-1 testing
	Chest radiograph, 12-lead electrocardiogram, and echocardiography or MUGA (on indication)
	Lumbar puncture[j]
	Biobanking[k]
Sensitive assessment of response to treatment (MRD) by RT-qPCR or MFC[l]	RT-qPCR[m,n] for *NPM1* mutation, *CBFB-MYH11*, *RUNX1-RUNX1T1*, *BCR-ABL1*, other fusion genes (if available)
	MFC[n,o]

Abbreviations: allo-SCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; CBC, complete blood count; ECOG, Eastern Cooperative Oncology Group; HLA, human leukocyte antigen; MFC, multiparameter flow cytometry; MRD, measurable residual disease; MUGA, multigated acquisition (scan); RT-qPCR, reverse transcription quantitative polymerase chain reaction.

[a]Results from cytogenetics should be obtained preferably within 5 to 7 days. At least 20 bone marrow metaphases are needed to define a normal karyotype and are recommended to describe an abnormal karyotype. Abnormal karyotypes may sometimes be diagnosed from blood specimens.

[b]Results from *NPM1* and *FLT3* mutational screening should be available within 48 to 72 hours (at least in patients eligible for intensive chemotherapy), along with results from additional molecular genetics within the first treatment cycle. Screening for gene mutations is an evolving field of research; screening for single genes is now frequently replaced by gene panel diagnostics.

[c]Including race or ethnicity, previous exposure to toxic agents, previous malignancy, therapy for previous malignancy, and information on smoking.

[d]Thorough family history is needed to identify potential myeloid neoplasms with germline predisposition.

[e]History of bleeding episodes may inform cases of myeloid neoplasms with germline predisposition and preexisting platelet disorders.

[f]Biochemistry: levels of glucose, sodium, potassium, calcium, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin, urea, total protein, uric acid, total cholesterol, total triglycerides, and creatinine phosphokinase. Coagulation tests: prothrombin time; international normalized ratio, where indicated; activated partial thromboplastin time. Urine analysis: pH, and levels of glucose, erythrocytes, leukocytes, protein, and nitrite.

[g]In women with childbearing potential.

[h]Cryopreservation to be done in accordance with the wishes of the patient.

[i]HLA typing and cytomegalovirus testing should be performed in those patients eligible for allo-SCT.

[j]Required in patients who have clinical symptoms suspected of central nervous system involvement; the patient should be evaluated by an imaging study for intracranial bleeding, leptomeningeal disease, and mass lesion; lumbar puncture is considered optional in other settings (eg, high white blood cell count).

[k]Pretreatment leukemic bone marrow and blood samples for research studies are recommended.

[l]Sensitive assessment of response can be performed at early time points, for example, after induction and consolidation courses to assess remission status and determine kinetics of disease response, and sequentially beyond consolidation to detect impending morphologic relapse. No generally applicable time points can be defined because the kinetics of MRD response differ by treatment given, marker analyzed, and method used.

[m]Monitoring of response by RT-qPCR is recommended in clinical trials and clinical practice.

[n]Sensitivity of response assessment varies by method used and by marker tested; the test used and sensitivity of the assay should always be reported; analyses should be done in experienced laboratories (centralized diagnostics).

[o]Increasing evidence that response assessment by multiparameter flow cytometry qualitatively provides a better remission status than morphologic assessment and is of high prognostic value.

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Table 19-3 **2022 ELN Cytogenetic and Molecular Risk Stratification of AML**[39]

Risk Level	Subset
Favorable	t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*[a,b]
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*[a,b]
	Mutated *NPM1*[a,c] without *FLT3*-ITD
	bZIP in-frame mutated *CEBPA*[d]
Intermediate	**Mutated *NPM1*[a,c] with FLT3-ITD**
	Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*[a,e]
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23.3;q34.1)/*DEK::NUP214*
	t(v;11q23.3)/*KMT2A*-rearranged[f]
	t(9;22)(q34.1;q11.2)/*BCR::ABL1*
	t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM* (*EVI1*)
	t(3q26.2;v)/*MECOM* (*EVI1*)-rearranged
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,[g] monosomal karyotype[h]
	Mutated *ASXL1*, ***BCOR***, ***EZH2***, *RUNX1*, ***SF3B1***, ***SRSF2***, ***STAG2***, ***U2AF1***, and/or ***ZRSR2***[i]
	Mutated *TP53*[j]

Abbreviations: AML, acute myeloid leukemia; bZIP, basic leucine zipper; ELN, European LeukemiaNet.
Frequencies, response rates, and outcome measures should be reported by risk category and, if sufficient numbers are available, by specific genetic lesions indicated.
Bold text indicates the latest changes for AML.
[a]Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course on the basis of the results from analyses of measurable residual disease.
[b]Concurrent *KIT* and/or *FLT3* gene mutation does not alter risk categorization.
[c]AMLs with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse risk.
[d]Only in-frame mutations affecting the bZIP region of *CEBPA*, irrespective of whether they occur as monoallelic or biallelic mutations, have been associated with a favorable outcome.
[e]The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
[f]Excluding *KMT2A* partial tandem duplication.
[g]Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.
[h]Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).
[i]For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
[j]*TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.
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Table 19-4 **NCCN Criteria for Hematologic, Cytogenic, and Molecular Response and Relapse**[127]	
Complete hematologic response	Complete normalization of peripheral blood counts with a leukocyte count $<10 \times 10^9$/L
	Platelet count $<450 \times 10^9$/L
	No immature cells, such as myelocytes, promyelocytes, or blasts, in peripheral blood
	No signs or symptoms of disease with the disappearance of palpable splenomegaly
Cytogenetic response[a]	Complete cytogenetic response: no Ph+ metaphases
	Major cytogenetic response: 0%-35% Ph+ metaphases
	Partial cytogenetic response: 1%-35% Ph+ metaphases
	Minor cytogenetic response: >35%-65% Ph+ metaphases
Molecular response	Early molecular response: *BCR-ABL1* (IS) ≤ 10% at 3 and 6 months
	Major molecular response: *BCR-ABL1* (IS) ≤ 0.1% or a 3-log reduction in *BCR-ABL1* mRNA from the standardized baseline, if qPCR (IS) is not available
	Deep molecular response:
	MR4.0: *BCR-ABL1* (IS) ≤ 0.01% or
	MR4.5: *BCR-ABL1* (IS) ≤ 0.0032%
	Complete molecular response is variably described and is best defined by the assay's level of sensitivity (eg, MR4.5)
Relapse	Any sign of loss of hematologic response or loss of CCyR
	A 1-log increase in *BCR-ABL1* transcript levels with loss of MMR should prompt bone marrow evaluation for loss of CCyR, but is not itself defined as relapse (eg, hematologic or cytogenetic relapse)

Abbreviations: CCyR, complete cytogenic response; IS, International Scale; MMR, major molecular response; MR4.0, molecular response 4.0; mRNA, messenger RNA; NCCN, National Comprehensive Cancer Network; Ph+, Philadelphia chromosome–positive; qPCR, quantitative polymerase chain reaction.
[a]A minimum of 20 metaphases should be examined.
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Table 19-5 **ELN Definitions of Response to TKIs as First-Line Therapy**[125,128]

Time	Optimal	Warning	Failure
Baseline	NA	High risk or CCA/Ph+	NA
3 Months	*BCR-ABL1* ≤ 10% and/or Ph+ ≤ 35%	*BCR-ABL1* > 10% and/or Ph+ 36%-95%	Non-CHR and/or Ph+ > 95%
6 Months	*BCR-ABL1* < 1% and/or Ph+ 0	*BCR-ABL1* > 1%-10% and/or Ph+ 1%-35%	*BCR-ABL1* > 10% and/or Ph+ > 35%
12 Months	*BCR-ABL1* ≤ 0.1%	*BCR-ABL1* > 0.1%-1%	*BCR-ABL1* > 1% and/or Ph+ > 0
After 12 months	*BCR-ABL1* ≤ 0.1%	Or loss of ≤ 0.1/% (MMR)	Loss of CHR, loss of CCyR, confirmed loss of MMR,[a] new mutations, or CCA/Ph+ changes

Abbreviations: CCA/Ph+, clonal chromosomal abnormalities in Philadelphia chromosome–positive cells; CCyR, complete cytogenetic response; CHR, complete hematologic response; ELN, European LeukemiaNet; MMR, major molecular response; NA, not applicable; TKI, tyrosine kinase inhibitor.
[a]MMR: *BCR-ABL1* ≤ 0.1% or ≥3-log reduction of *BCR-ABL1*.
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Table 19-6 **NCCN Criteria for TKI Discontinuation**[127]
Outside a clinical trial, all the following criteria should be met:
Age 18 years or older
Reliably taking TKI for ≥3 years
No previous resistance to a second-generation TKI that required switching to another agent
Previous evidence of a quantifiable *BCR-ABL1* transcript
Stable molecular response (ie, MR4; *BCR-ABL1* ≤ 0.01% by the IS) for ≥2 years, as documented by ≥4 separate tests performed ≥3 months apart
Access to a reliable qPCR test capable of detecting at least MR4.5, providing results within 2 weeks
Access to close monitoring: first 6 months, monthly measurement of *BCR-ABL1* by qPCR; next 18 months, measure every 2 months

Abbreviations: IS, International Scale; MR4, molecular response 4; NCCN, National Comprehensive Cancer Network; qPCR, quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.
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Table 19-7 **Myeloid Precursor Conditions**

Characteristic	Myeloid Precursor Subtype			
	CHIP	**ICUS**	**CCUS**	**MDS**
Clonal	Yes	No	Yes	Yes
Dysplasia	No	No	No	Yes
Cytopenias	No	Yes	Yes	Yes

Abbreviations: CCUS, clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential; ICUS, idiopathic cytopenia of undetermined significance; MDS, myelodysplastic syndrome.
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Table 19-8 **Outcomes Based on IPSS-M Risk Stratification**

Characteristic	Very Low	Low	IPSS-M Risk Category*		High	Very High
			Moderate Low	Moderate High		
Patients—No. (%)	381 (14)	889 (33)	302 (11)	281 (11)	379 (14)	469 (17)
Risk score	≤−1.5	>−1.5 to −0.5	>−0.5 to 0	>0 to 0.5	>0.5 to 1.5	>1.5
Hazard ratio (95% CI)†	0.51 (0.39-0.67)	1.0 (Reference)	1.5 (1.2-1.8)	2.5 (2.1-3.1)	3.7 (3.1-4.4)	7.1 (6.0-8.3)
Median LFS (25%-75% range)—years‡	9.7 (5.0-17.4)	5.9 (2.6-12.0)	4.5 (1.6-6.9)	2.3 (0.91-4.7)	1.5 (0.80-2.8)	0.76 (0.33-1.5)
Median OS (25%-75% range)—years	10.6 (5.1-17.4)	6.0 (3.0-12.8)	4.6 (2.0-7.4)	2.8 (1.2-5.5)	1.7 (1.0-3.4)	1.0 (0.5-1.8)
AML-t—%						
By 1 year	0	1.7	4.9	9.5	14.3	28.2
By 2 years	1.2	3.4	8.8	14	21.2	38.6
By 4 years	2.8	5.1	11.4	18.9	29.2	42.8
Death without AML—%						
By 1 year	2.2	8.5	12	18	19.3	30.6
By 2 years	7	16.2	19.8	31.1	39.8	45.6
By 4 years	15.9	29.5	33.6	51.1	54.2	51.3

Abbreviations: AML, acute myeloid leukemia; AML-t, acute myeloid leukemia transformation; CI, confidence interval; IPSS-M, International Prognostic Scoring System with Molecular; LFS, leukemia-free survival; OS, overall survival.

*Key metrics are presented across clinical endpoints per IPSS-M risk category.

†Hazard ratio is for the risk of leukemic transformation or death. Because the low category had the largest size, it was used as the reference level.

‡The 25% to 75% range represents the central interquartile interval. For example, for a 25% to 75% OS range from A to B years, 50% of patients lived longer than A years and died before B years.

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Table 19-9 **2022 WHO Classification of MPNs, Myeloid Neoplasms Associated With Eosinophilia, and MDS/MPNs**

Neoplasm	Classification
MPN	Chronic myeloid leukemia
	Polycythemia vera
	Essential thrombocythemia
	Primary myelofibrosis
	Primary myelofibrosis, prefibrotic or early stage
	Primary myelofibrosis, overt fibrotic stage
	Chronic neutrophilic leukemia
	Chronic eosinophilic leukemia
	Juvenile myelomonocytic leukemia
	MPN, NOS
Mastocytosis	
Myeloid and lymphoid neoplasms associated with eosinophilia and tyrosine kinase gene fusions	*PDGFRA* rearrangement
	PDGFRB rearrangement
	FGFR1 rearrangement
	JAK2 rearrangement
	FLT3 rearrangement
	ETV6::ABL1 fusion
	Other defined tyrosine kinase fusions: *ETV6*::*FGFR2*, *ETV6*::*LYN*, *ETV6*::*NTRK3*, *RANBP2*::*ALK*, *BCR*::*RET*, *FGFR1OP*::*RET*
MDS/MPN	Chronic myelomonocytic leukemia
	MDS/MPN with neutrophilia
	MDS/MPN with *SF3B1* mutation and thrombocytosis
	MDS/MPN, NOS

Abbreviations: MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NOS, not otherwise specified; WHO, World Health Organization.
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Table 19-10 **2016 WHO Diagnostic Criteria for PV, ET, and PMF[196]**	
Diagnosis	**Criteria Required for Diagnosis**
PV	Elevated hemoglobin concentration (men, >16.5 g/dL; women, >16.0 g/dL) or increased hematocrit (men, 49%; women, 48%) or increased red cell mass
	BM biopsy showing BM hypercellularity, trilineage hematopoiesis with prominent erythroid, granulocytic, and megakaryocyte proliferation with pleomorphic, mature megakaryocytes
	JAK2 V617F or *JAK2* exon 12 mutation; if such a mutation is absent, diagnosis of PV is still possible if there is a subnormal erythropoietin level
	Minor criterion: subnormal serum erythropoietin level
	Diagnosis of PV requires meeting either all three major criteria, or the first two major criteria and the minor criterion[a]
ET	Persistently elevated platelet count (≥450 × 10^9/L)
	BM with predominant proliferation of enlarged, mature megakaryocytes with hyperlobulated nuclei
	Not meeting diagnostic criteria for classic CML, PV, PMF, MDS, or other myeloid neoplasms
	JAK2 V617, *CALR*, or *MPL* mutation
	Minor criterion: presence of another clonal marker; if no clonal marker is present, there is no evidence of reactive thrombocytosis
	Diagnosis of ET requires meeting all four major criteria or the first three major criteria and the minor criterion
PMF	Megakaryocyte proliferation and atypia. For pre-PMF: no reticulin fibrosis grade >1, BM hypercellularity, granulocytic proliferation, and often decreased erythropoiesis. For overt PMF: grade 2-3 reticulin and/or collagen fibrosis
	Not meeting diagnostic criteria for classic CML, PV, ET, MDS, or other myeloid neoplasms
	JAK2 V617, *CALR*, or *MPL* mutation or other clonal marker; if no clonal marker is present, there is no evidence of minor reactive BM reticulin fibrosis (for pre-PMF) or reactive myelofibrosis (for overt PMF)
	Minor criteria: (1) anemia, (2) leukocytosis ≥11 × 10^9/L, (3) palpable splenomegaly, (4) LDH elevation, or (5), leuko-erythroblastosis (for overt PMF only)
	Diagnosis of overt PMF requires meeting all three major criteria and at least one minor criterion

Abbreviations: BM, bone marrow; CML, chronic myeloid leukemia; ET, essential thrombocythemia; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; MF, myelofibrosis; PMF, primary myelofibrosis; PV, polycythemia vera; WHO, World Health Organization.

[a]Criterion number 2 (BM biopsy) may not be required in patients with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial MF (present in up to 20% of patients) can be detected only by performing a BM biopsy; this finding may predict a more rapid progression to overt MF (post-PV MF).

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Table 19-11 **Major Adverse Effects of *JAK* Inhibitors Used in Myelofibrosis**[196]

Drug	Adverse Effect
Ruxolitinib	Anemia and thrombocytopenia
	Herpes simplex and zoster reactivation (give recombinant vaccine before starting if possible)
	Tuberculosis reactivation
	Progressive multifocal leukoencephalopathy (rare)
	Reactivation of hepatitis B
	Nonmelanoma skin cancers
	Lymphoid neoplasms
	Withdrawal syndrome if stopped suddenly
	Hyperlipidemia and weight gain
Fedratinib	Diarrhea
	Liver function changes
	Wernicke encephalopathy (thiamine level should be tested before initiation)
Pacritinib	Anemia
	Thrombocytopenia (but less than with other *JAK2* inhibitors and approved in those with platelets $<50 \times 10^9$/L)
	Diarrhea
	Edema
Momelotinib	Anemia and thrombocytopenia, but less anemia and transfusion dependence with its use
	Abdominal pain
	Headache
	Neuropathy
	Asthenia
	A “first dose” effect with dizziness, hypotension, and flushing has been reported

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Table 19-12 **Summary of WHO Classification of Lymphoid Leukemia**[196]	
	B-Lymphoblastic Leukemia/Lymphoma, NOS
B-lymphoblastic leukemia/lymphoma	B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
	B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
	B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
	B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
	B-lymphoblastic leukemia/lymphoma with hyperdiploidy
	B-lymphoblastic leukemia/lymphoma with hypodiploidy
	B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*
	B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
	Provisional entity: B-lymphoblastic leukemia/lymphoma, *BCR-ABL1*-like
	Provisional entity: B-lymphoblastic leukemia/lymphoma with *iAMP21*
T-lymphoblastic leukemia/lymphoma	Provisional entity: early T-cell precursor lymphoblastic leukemia
	Provisional entity: NK-cell lymphoblastic leukemia/lymphoma

Abbreviations: NK, natural killer (cell); NOS, not otherwise specified; WHO, World Health Organization.
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Table 19-13 **Prognostic Risk Factors in ALL**	
	Risk Factor
Pretreatment	Age
	Leukocyte count
	CNS involvement
	Cytogenetic abnormalities
	Molecular abnormalities
Post-treatment	Achievement of complete remission
	MRD state

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; MRD, measurable residual disease.
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Table 19-14 **Clinical Features and Associations With CLL**
Infections
Hypogammaglobulinemia
Reduced levels of complement
Impaired phagocytic killing of nonopsonized bacteria
Functional impairment of T-cell subsets
Autoimmunity
Autoimmune hemolytic anemia
Immune thrombocytopenia
Pure red cell aplasia
Aggressive transformation
Richter transformation
Secondary malignant disease
Skin cancers (including melanomas)
Colon cancers
Lung cancers
Myeloid neoplasms

Abbreviation: CLL, chronic lymphocytic leukemia.
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Table 19-15 **Cytogenetic and Molecular Abnormalities of CLL**
Deletion of 13q14
Deletion of 11q
Trisomy 12
Abnormalities of chromosome 17 (del(17p) with *TP53* gene disruption)
BCL2 gene overexpression
IgH variable domain mutations
ZAP70
Recurrent mutations involving *TP53*, *NOTCH1*, *SF3B1*, and *BIRC3*

Abbreviation: CLL, chronic lymphocytic leukemia.
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Table 19-16 **Rai Classification for Clinical Staging of CLL**[295]

Risk	Stage	Description	Median Survival (Years)[a]
Low	0	Lymphocytosis in blood or bone marrow	>12.5
Intermediate	I	Lymphadenopathy	8.5
	II	Splenomegaly and/or hepatomegaly with or without lymphadenopathy	6
High	III	Anemia (hemoglobin, <13 g/dL)[b]	1.5
	IV	Thrombocytopenia (platelet count <105/mcL)[b]	1.5

Abbreviation: CLL, chronic lymphocytic leukemia.
[a]Of historical significance because outcomes are changing with newer therapies.
[b]Anemia and thrombocytopenia cannot be immune-mediated.
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Table 19-17 **Binet Classification for Clinical Staging of CLL**[296]

Stage	Description	Median Survival (Years)[a]
A	<2 node-bearing areas[b]	>10
B	>3 node-bearing areas	5
C	Anemia (<10.0 g/dL) and/or thrombocytopenia (platelet count <100,000/mcL)	2

Abbreviation: CLL, chronic lymphocytic leukemia.
[a]Of historical significance because outcomes are changing with newer therapies.
[b]Five node-bearing areas are possible: cervical, axillary, inguinal-femoral, spleen, and liver.
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Table 19-18 **Common Toxicities of Drugs Used for First-Line CLL Therapy**	
Drug	**Adverse Effect**
BTKis	Diarrhea
	Fatigue
	Arthralgias/cramps
	Infections
	Bleeding (with acalabrutinib and ibrutinib; warfarin should be avoided)
	Atrial fibrillation
	Hypertension - Acalabrutinib and zanubrutinib have more favorable toxicity profiles compared with ibrutinib because they are more specific inhibitors[292,316]
	PPIs are discouraged with acalabrutinib
Venetoclax	Tumor lysis syndrome (5-week ramp-up recommended)
	Neutropenia

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; PPI, proton pump inhibitor.
Diminished vaccine responses are seen with all targeted agents; in general, live vaccines are not recommended in CLL.
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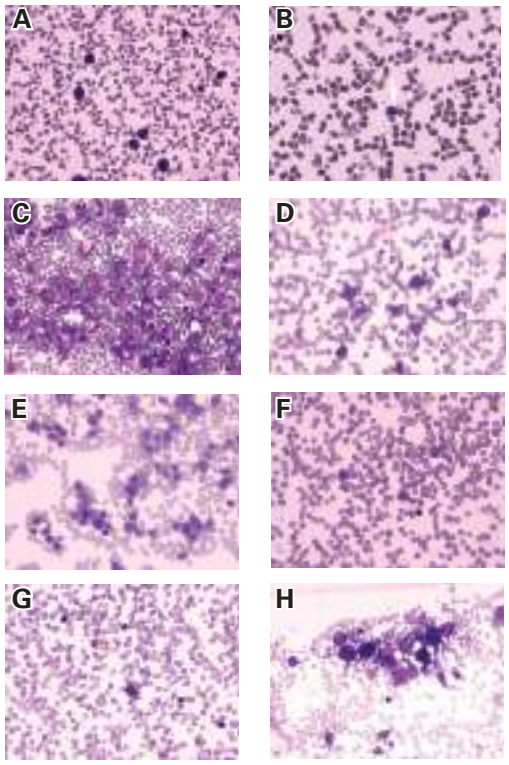
Figure 19-1 Morphologic Spectrum of AMLs



(A) Acute myeloblastic leukemia (AML) with minimal maturation. The cells are myeloblasts with dispersed chromatin and variable amounts of agranular cytoplasm; some display medium-sized, poorly defined nucleoli. (B) AML with maturation. Some of the blasts contain azurophilic granules, and there are promyelocytes. Note the Auer rod (arrow). (C) Acute promyelocyte leukemia. All of these cells are promyelocytes containing coarse cytoplasmic granules that sometimes obscure the nuclei. (D) Acute myelomonocytic leukemia. Promonocytes with indented nuclei are present with myeloblasts; the dense nuclear staining is unusual. (E) Acute monoblastic leukemia. These characteristic monoblasts have round nuclei with delicate chromatin and prominent nucleoli that stain intensely with nonspecific esterase (not shown); cytoplasm is abundant. (F) Acute monocytic leukemia. Most of the cells in this field are promonocytes; monoblasts and an abnormal monocyte are also present. (G) Acute erythroid leukemia. Dysplastic multinucleated erythroid precursors with megaloblastoid nuclei are present. (H) Acute megakaryoblastic leukemia. In this marrow biopsy specimen, there are large and small blasts as well as atypical megakaryocytes. Photographs and permission provided by Dr. Farid Barakat.
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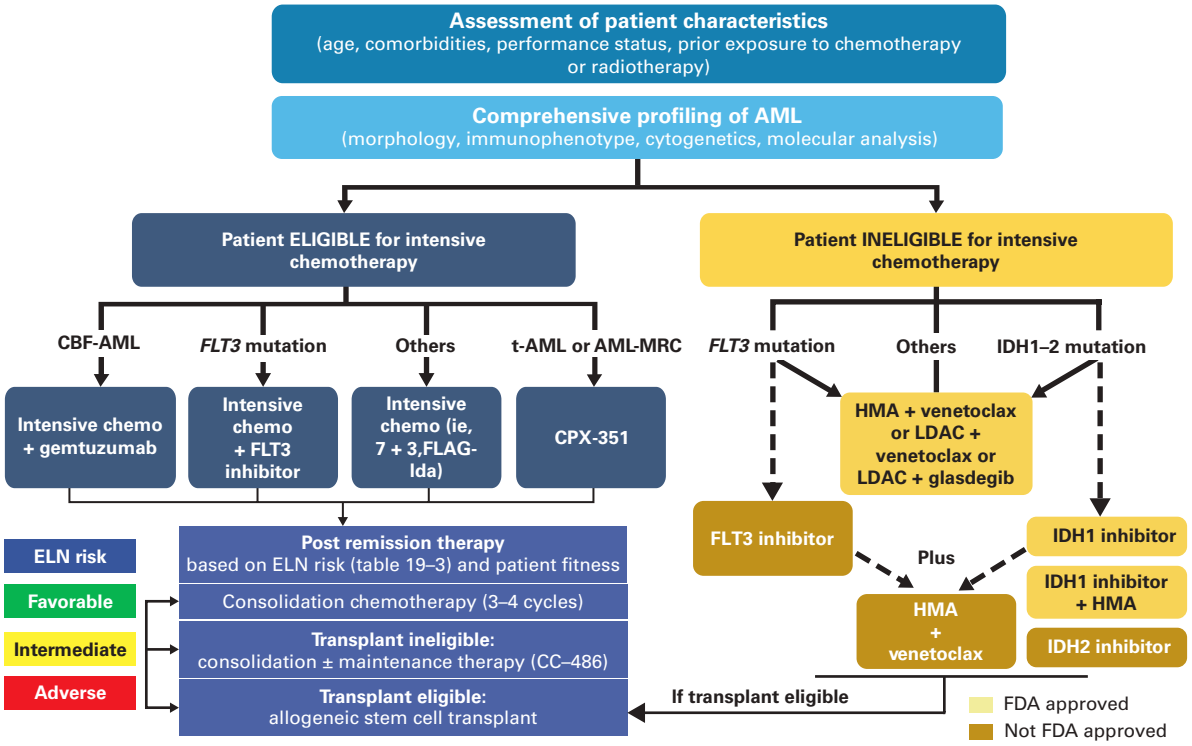
Figure 19-2 First-Line Treatment Algorithm for AML



Abbreviations: AML, acute myeloid leukemia; AML-MRC, AML with myelodysplasia-related changes; CBF, core binding factor; CBF-AML, core binding factor AML; CC-486, oral azacitidine; chemo, chemotherapy; CPX-351, liposomal formulation of cytarabine and daunorubicin coencapsulated at a fixed molar ratio (5:1); ELN, European LeukemiaNet; FLAG-Ida, fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin; FL3, fms-like tyrosine kinase 3; HMA, hypomethylating agent; IDH, isocitrate dehydrogenase; LDAC, low-dose Ara-C (cytarabine); t-AML, therapy-related AML.
Dotted lines indicate alternative considerations.
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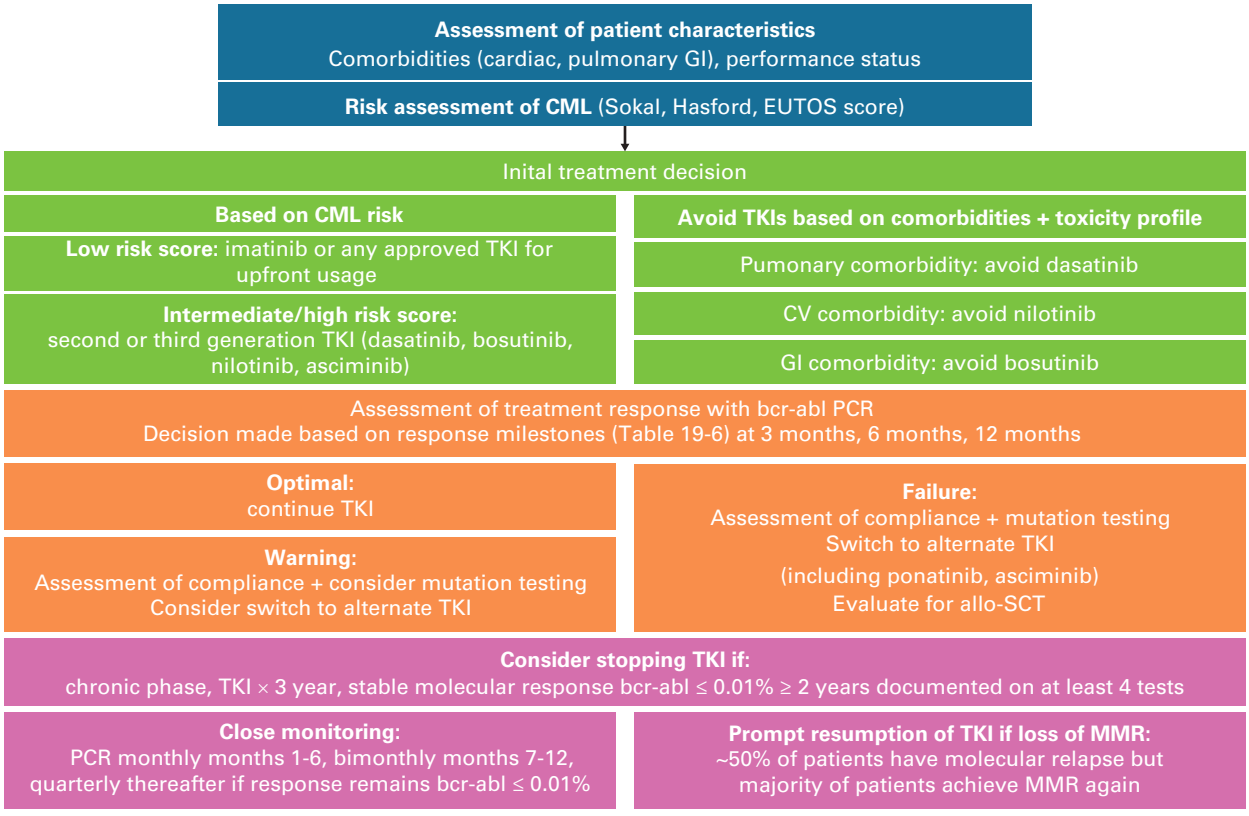
Figure 19-3 Treatment Algorithm for CP-CML Adapted From NCCN and ELN Guidelines[32,36,40]



Abbreviations: allo-SCT, allogeneic stem cell transplantation; CP-CML, chronic phase chronic myeloid leukemia; CV, cardiovascular; ELN, European LeukemiaNet; EUTOS, European Treatment Outcome Study; GI, gastrointestinal (tract); MMR, major molecular response; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.
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Figure 19-4 Treatment Algorithm for Newly Diagnosed MDS

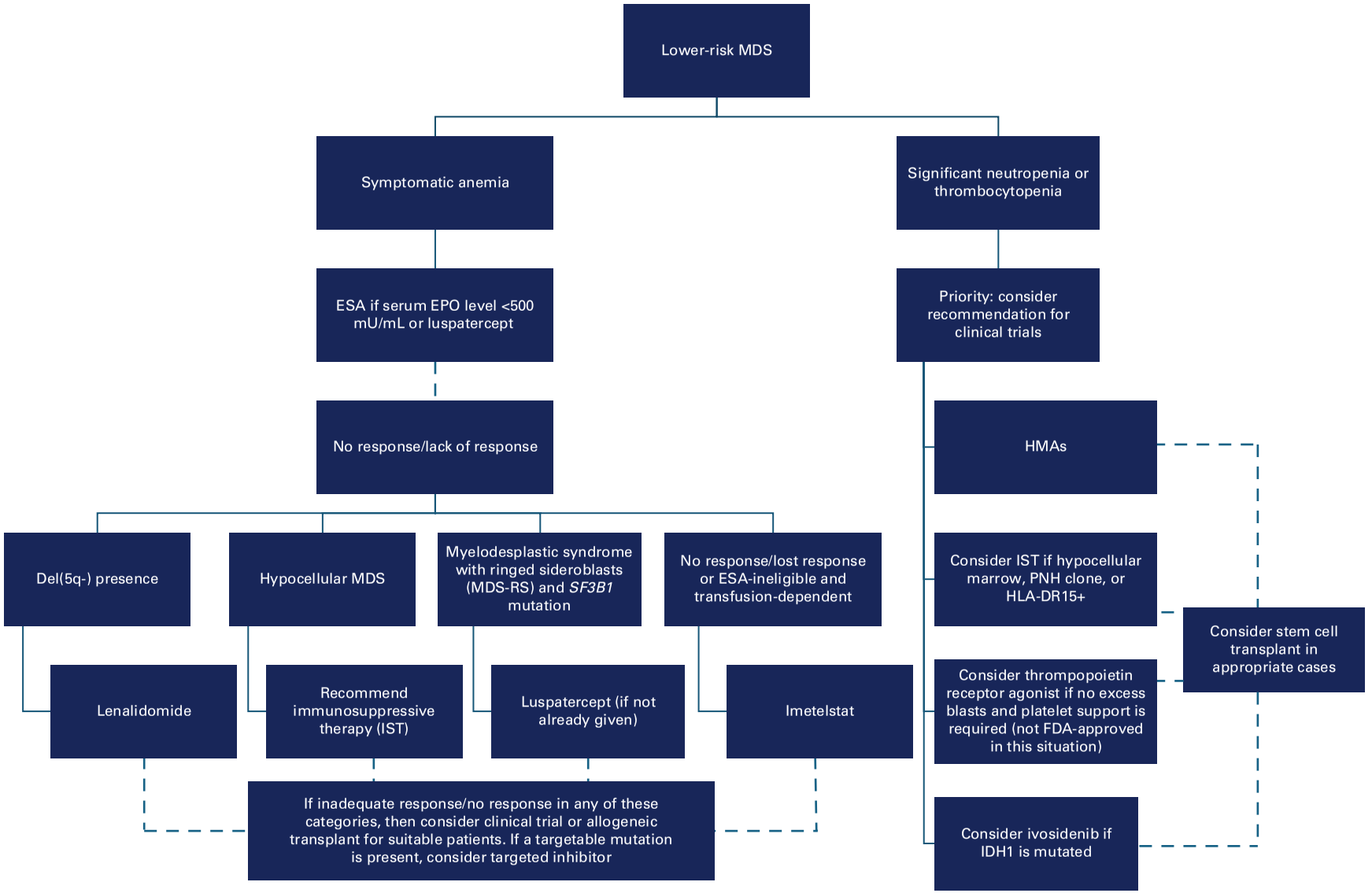
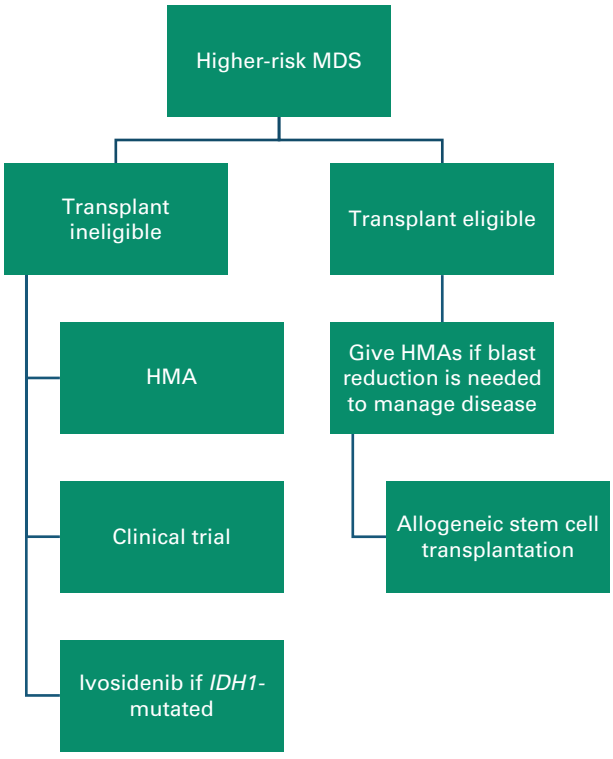


Figure 19-4 Continued



Abbreviations: EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; HMA, hypomethylating agent; IDH, isocitrate dehydrogenase; IST, immunosuppressive therapy; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal hemoglobinuria.
Dotted lines indicate alternative considerations.
Lower risk = very low and low by IPSS-R and very low, low, and moderate low by IPSS-M; higher risk = intermediate, high, and very high by IPSS-R and moderate high, high, and very high by IPSS-M.
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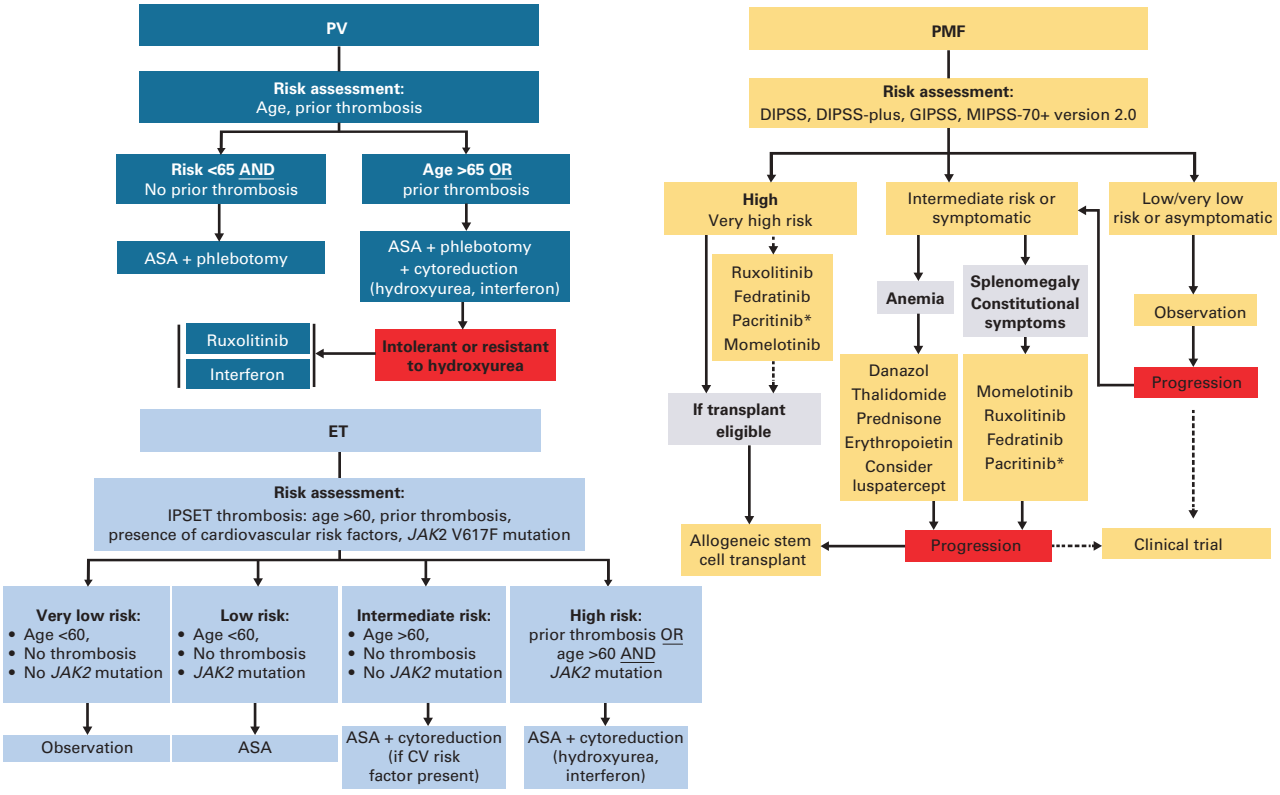
Figure 19-5 Treatment Algorithm for MPNs



Abbreviations: ASA, acetylsalicylic acid; CV, cardiovascular; DIPSS, Dynamic International Prognostic Scoring System; DIPSS Plus is based on clinical and cytogenetic information; ET, essential thrombocythemia; GIPSS, Genetically Inspired Prognostic Scoring System; IPSET, International Prognostic Score (of thrombosis) in Essential Thrombocythemia (IPSET-thrombosis); MIPSS70 + v2.0, mutation-enhanced IPSS plus karyotype is based on clinical, cytogenetic, and mutational information; MPN, myeloproliferative neoplasm; PMF, primary myelofibrosis; PV, polycythemia vera.
*If platelets <50 x 10^9/L
Dotted lines indicate alternative considerations.
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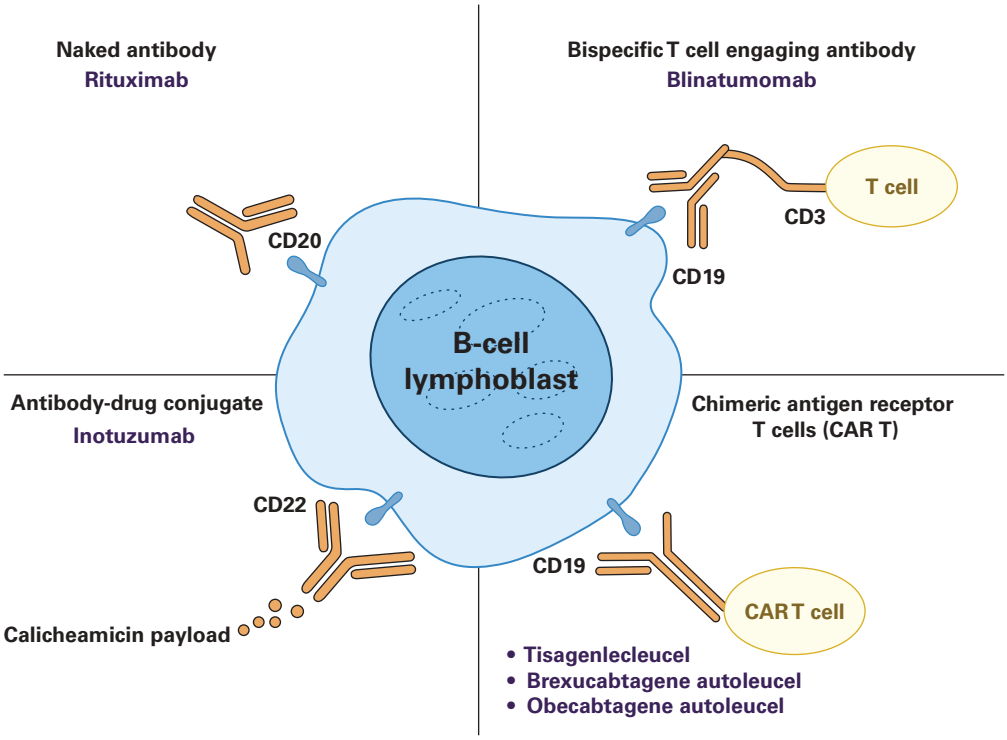
Figure 19-6 Mechanisms of Action of Immunotherapies for B-ALL



Abbreviation: B-ALL, B-cell acute lymphoblastic leukemia.
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LYMPHOMAS 20

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RECENT UPDATES

- The World Health Organization (WHO) released a new classification for lymphoid neoplasms, altering nomenclature and diagnostic criteria and introducing new subtypes.[1]
- Second-line chimeric antigen receptor T-cell therapies gained approval in diffuse large B-cell lymphoma (DLBCL), including the following:
  - Axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel): for patients refractory or relapsing within 12 months of first-line chemoimmunotherapy.[2]
  - Liso-cel for patients who have DLBCL relapsed/refractory to first-line therapy and not eligible for hematopoietic stem cell transplantation (HSCT) because of comorbidities or age.[3]
- Tisagenlecleucel and liso-cel are now approved for treatment of relapsed or refractory follicular lymphoma after two or more lines of systemic therapy, adding to axi-cel previously approved in this setting.
- Novel, bispecific T-cell engagers targeting CD20 and CD3 represent an important new class of therapy with recent approvals for both follicular lymphoma and DLBCL after two or more lines of therapy, and the combination of the Bruton tyrosine kinase (BTK) inhibitor zanubrutinib with obinutuzumab gained accelerated approval for relapsed/refractory follicular lymphoma.[4]
- Epcoritamab-bysp, now FDA approved both as monotherapy and in combination with lenalidomide and rituximab for relapsed or refractory follicular lymphoma, significantly improved progression-free survival and response rates compared with standard R^2 therapy in the EPCORE FL-1 trial.[5]
- The FDA approved the combination of tafasitamab with lenalidomide and rituximab for adults with relapsed or refractory follicular lymphoma, with demonstrated consistent benefit across all prespecified subgroups, including high-risk patients.[6]
- The STARGLO trial demonstrated an overall survival benefit of glofitamab plus gemcitabine and oxaliplatin (GemOx) over R-GemOx alone in patients with relapsed or refractory DLBCL ineligible for autologous stem cell transplant after at least one prior line of therapy.[7]
- An update of the ECHELON-1 trial showed that brentuximab and vedotin and doxorubicin, vinblastine, and dacarbazine (BV-AVD) showed a small but statistically significant overall survival benefit in first-line treatment of advanced-stage classic Hodgkin lymphoma (cHL) compared with standard doxorubicin, bleomycin, vinblastine, and dacarbazine at a cost of an increase in certain acute toxicities.[8]
- SWOG trial 1826 demonstrated a progression-free survival advantage of nivolumab in combination with AVD (N-AVD) over BV-AVD in newly diagnosed advanced-stage cHL, and N-AVD is considered a new standard-of-care option in this patient population.[9-11]
- Randomized trials in first-line treatment of mantle cell lymphoma (MCL) incorporating BTK inhibitors have been reported with a potential effect on the standard of care for transplant-eligible and transplant-ineligible older patients.[12]
- Brexucabtagene autoleucel and liso-cel are approved for relapsed/refractory MCL.
- In March 2026, there was a voluntary manufacturer recall of tazemetostat, previously used to treat follicular lymphoma. This was based on emerging data from the ongoing Phase Ib/III SYMPHONY-1 trial on secondary hematologic malignancies.

OVERVIEW

Lymphomas are a heterogeneous group of malignancies derived from mature B, T, and natural killer (NK) cells that encompass more than 100 distinct biologic entities, according to the latest version of the World Health Organization (WHO) classification.

This chapter covers indolent B-cell lymphomas (BCLs), aggressive BCLs, and T-cell lymphomas (TCLs). In the United States, approximately 85% to 90% of non-Hodgkin lymphomas (NHLs) are of B-cell origin, 10% to 15% are T-cell-derived, and less than 1% are NK-cell malignancies, but there is considerable worldwide variation, including higher rates of T- and NK-cell lymphomas in East Asian populations.

Hodgkin lymphoma, discussed in the final section of this chapter, is considered a mature B-cell malignancy with a deregulated B-cell program. The initial diagnostic approach and staging considerations for non-Hodgkin and Hodgkin lymphomas are similar and are discussed jointly. However, historically, treatment algorithms for these two groups have been distinct; therefore, management of non-Hodgkin and Hodgkin lymphomas is discussed separately. In this chapter, the term "lymphoma" is used whenever discussing issues pertinent to both non-Hodgkin and Hodgkin lymphomas. The WHO lymphoma classification, last published in 2008 and updated in 2022, is the reference standard for defining lymphoma subtypes.[1,13] Clinicians often classify NHL subtypes into indolent (slow growing) or aggressive (fast growing) to facilitate clinical decision-making regarding therapy and to estimate disease prognosis.

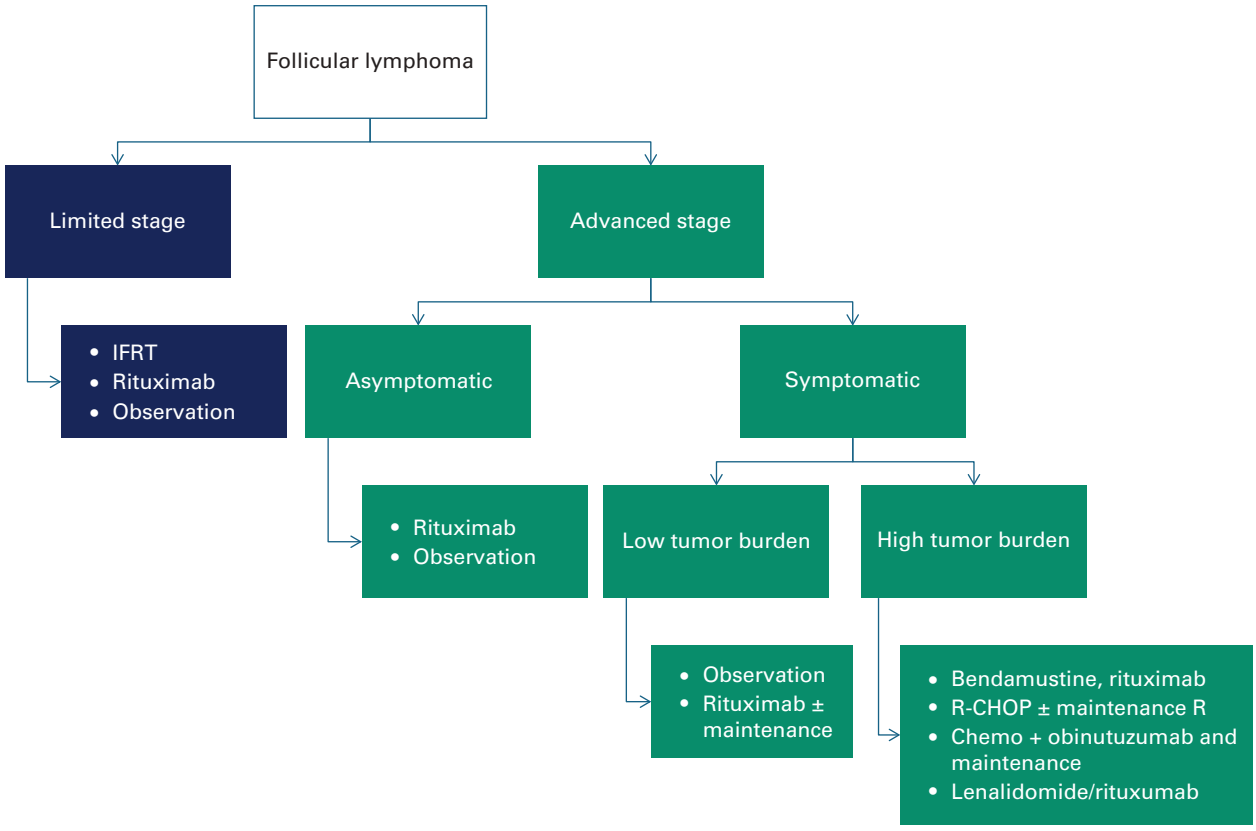
NON-HODGKIN LYMPHOMA

EPIDEMIOLOGY AND ETIOPATHOGENESIS

NHL is the seventh most common cause of cancer in men and the sixth most common cause in women. Annually, NHL accounts for approximately 80,000 new cancers and 20,000 deaths.[14] The median age of patients diagnosed with NHL varies by histologic subtype, although the incidence of most subtypes increases with age. In 2020, an estimated 790,000 people were living with lymphoma.[15] Many patients can expect to be cured of lymphoma or to live with it for a prolonged time. This is an important consideration when making management decisions because survivors are at increased risk of late toxicity and organ damage related to treatment.

The etiology of NHL in most patients is unknown beyond inherent genomic instability related to the B- and T-cell gene rearrangement process, but associations exist with chronic viral or bacterial infections, innate or acquired immunodeficiency, autoimmunity, environmental exposures, and rarely familial predisposition. Several viruses have been linked, either directly or indirectly, to specific lymphoma subtypes, including Epstein-Barr virus (EBV), hepatitis C virus, human herpesvirus 8, human

Figure 20-1 Treatment Algorithm for Follicular Non-Hodgkin Lymphoma



Abbreviations: Chemo, chemotherapy; IFRT, involved-field radiation therapy; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

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T-lymphotrophic virus 1, and human immunodeficiency virus (HIV), among others. Of note, the incidence of lymphoma subtypes associated with HIV has decreased in the era of antiretroviral therapy (ART). Bacterial infections, such as *Helicobacter pylori*, observed in association with gastric marginal zone lymphomas (MZLs), may result in lymphoma as a result of chronic antigenic stimulation. Autoimmune conditions (eg, Sjogren syndrome, systemic lupus erythematosus) are associated with an increased risk of lymphoma, including MZL and follicular lymphoma (FL). Support for an environmental contribution to lymphoma risk comes from observations that NHL incidence increases in industrialized regions, and several pesticides and chemical substances might contribute to lymphoma development.[16] Genetic predisposition plays a small role in lymphoma and remains an underexplored area. Whereas hereditary forms are rare, familial clustering is observed more frequently, and first-degree relatives of patients with lymphoma are at higher risk of developing a lymphoproliferative disorder.[17]

In terms of pathophysiology, B-cell NHL develops at various points during normal B-cell ontogeny (Fig. 20-1). A majority of BCLs are thought to originate from B cells undergoing the germinal center reaction.[13] After birth in the bone marrow, B cells undergo affinity maturation via exposure to antigenic stimuli, resulting in class-switch recombination and somatic hypermutation in the germinal center. These tremendous pressures and associated rapid proliferation likely increase the retention of adverse mutations and chromosomal errors, leading to malignancy and distinct diagnostic features.

DIAGNOSIS, STAGING, AND INITIAL EVALUATION

Diagnosis

The clinical presentation of NHL is variable. Most patients who have indolent disease present with incidentally noted, asymptomatic adenopathy, organomegaly, or occasionally peripheral blood abnormalities detected during a routine exam. By contrast, patients with aggressive lymphomas often present after noticing a rapidly growing mass or experiencing constitutional symptoms or pain associated with a site of disease. Symptoms may be related to compression of anatomic structures and may include cough, jaundice, ureteral obstruction, and neurologic compromise, among others. Constitutional symptoms may include classic B symptoms (eg, unexplained fevers, recurrent drenching night sweats, and ≥10% unintentional weight loss), which are more common in diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma, or may be asthenia or weakness. Pruritus, a classic paraneoplastic phenomenon associated with Hodgkin lymphoma, may occasionally occur in other B-cell malignancies.

Confirming a lymphoma diagnosis requires adequate tissue and appropriate preparation, permitting pathologic evaluation, which may include immunohistochemistry, flow cytometry, cytogenetic testing, and gene sequencing. An excisional lymph node biopsy yields the most tissue and is the gold standard for lymphoma diagnosis. It allows the hematopathologist to examine the nodal architecture, which is critical to adjudicating lymphoma subtypes. For example, in FL, morphologic analysis typically shows a preserved nodular pattern, whereas mantle cell lymphoma (MCL) or small lymphocytic lymphoma (SLL) is characterized by a diffuse infiltrate, and DLBCL causes a complete effacement of the lymph node architecture. When a lymph node or extranodal lesion is difficult to access, or a surgical biopsy would be unsafe, multiple core biopsies may be performed in lieu of an excision. Fine-needle aspiration (FNA) is rarely sufficient for diagnostic purposes.

Cytogenetic testing is routinely performed at most centers and can aid in ascertaining the lymphoma subtype (Table 20-1). These are especially helpful when the morphologic and immunohistochemical testing is inconclusive. These may also inform prognostication and guide the selection of therapy. For example, the t(11;14) leading to upregulation of cyclin D1 is a diagnostic hallmark of MCL and translocations involving the *MYC* gene (t(8;14)(q24;q32); t(2;8)(p11;q24), or t(8;22)(q24;q11)). On the other hand, the t(14;18) is a less specific marker as it is present in most patients with FL, some cases of DLBCL, and occasionally other subtypes[18] or even healthy individuals.[19] Concurrent rearrangements involving *MYC* and *BCL2* genes in a patient with DLBCL are diagnostic of so-called double-hit lymphoma (DHL) or DLBCL/HGBCL-MYC/BCL2 by the 2022 WHO classification.[1] This subtype is associated with a poor prognosis using standard therapy for DLBCL, warranting strong consideration for clinical trial or intensive treatment regimens.

Staging and Pretreatment Testing

The historical staging system for both Hodgkin and NHL has been the Ann Arbor classification, Cotswolds revision.[4] Typical staging involved CT scans of the chest, abdomen, and pelvis, along with a bone marrow biopsy. With the advent of functional imaging via PET, the Lugano classification was introduced and has several implications for the modern staging of lymphomas.[21] First, a staging bone marrow biopsy is no longer routinely required for the staging of Hodgkin lymphoma or DLBCL if PET/CT imaging has been performed. Second, PET/CT imaging should be used to assess response in consistently fluorodeoxyglucose (FDG)-avid histologies; interpretation of PET scans should be via the five-point scale,[22] also called the Deauville criteria. Third, the suffix notations for the absence (A) and presence (B) of B symptoms are required only for Hodgkin lymphoma, although many practitioners continue to use these as descriptive elements for NHL. For the most up-to-date staging information, please consult the NCCN guidelines.

Stage describes disease location (nodal vs. extranodal) and extent (limited vs. advanced) and may incorporate information on disease bulk. Stage may also have an effect on prognosis and treatment, although, typically, the specific subtype and its associated pathobiologic features have a greater influence on the choice of initial treatment.

Table 20-1 **Key Diagnostic Immunophenotypic and Cytogenetic Features of Non-Hodgkin Lymphomas**

Lymphoma Subtype	CD20	CD10	CD5	CD30	Other	Cytogenetics/ FISH Results	Genes
DLBCL: germinal center subtype	+++	+/−	Rare	Rare	*BCL6*$^+$ and MUM1$^-$	*BCL2* translocations (18q21)	*BCL6* and *EZH2* upregulation
DLBCL: nongerminal center subtype	+++	—	+/−	Rare	*BCL6* negative or *BCL6*$^+$, MUM1$^+$	*BCL6* translocations (3q27)	B-cell receptor signaling/*NFkB* activation
FL	+++	+	—	—		t(14;18)	*BCL2*
CLL/SLL	Dim	—	+	—	CD23$^+$		
MCL	+++	—	+	—	CD23$^-$, Cyclin D1$^+$, SOX11$^+$	t(11;14)	*Cyclin D1*
MZL	+++	—	Rare	—		t(11;18) (ENMZL) trisomy 3, 18 (NMZL) del 7q (SMZL)	*API2-MALT1*
LPL/WM	+++	—	Rare	—			*MYD88, CXCR4*[20]
Burkitt lymphoma	+++	+	—	—	TdT$^-$	t(8;14), t(8;22), t(2;8)	*MYC*
PMBL	+++	+/−	—	Occasional		t(16;X), 9p24.1 gain	*CIITA, PDL1/ JAK2/PDL2*
Hairy cell leukemia	+++	—	—	—	CD11c$^+$, CD25$^+$, CD103$^+$		
ALCL, ALK$^+$	—	—	—	+++		t(2; 5)	*ALK*
ALCL, ALK$^-$	—	—	—	+++		t(6;7)	*DUSP22*
AITL	—	+/−	+/−	—	At least three T_{FH} markers: PD-1, BCL6, CXCL13, ICOS, SAP, CCR5		*TET2, IDH2, DNMT3A, RHOA, ITK-SYK*
PTCL-NOS	—	+/−	+/−	—	Can have the same immunophenotype as AITL, often with dropped CD3 or CD7		

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; API2-MALT1, fusion of apoptosis inhibitor 2 and mucosa-associated lymphoid tissue lymphoma translocation 1; BCL2, B-cell CLL/lymphoma 2; BCL6, B-cell lymphoma 6; CCR5, chemokine, CC motif, receptor 5; CIITA, class II major histocompatibility complex transactivator; CLL, chronic lymphocytic leukemia; CXCL13, chemokine, CXC motif, ligand 13; DLBCL, diffuse large B-cell lymphoma; DNMT3A, DNA methyltransferase 3A; DUSP22, dual-specificity phosphatase 22; ENMZL, extranodal marginal zone lymphoma; FISH, fluorescence in situ hybridization; FL, follicular lymphoma; ICOS, inducible T-cell costimulator; IDH, isocitrate dehydrogenase 2; ITK-SYK, fusion of IL2-inducible T-cell kinase and protein-tyrosine kinase SYK; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MYC, MYC proto-oncogene, bHLH transcription factor; MYD88, MYD88 innate immune signal transduction adaptor; MZL, marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; PD-1, programmed cell death protein 1; PMBL, primary mediastinal B-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; RHOA, RAS homolog gene family, member A; SLL, small lymphocytic lymphoma; SMZL, splenic marginal zone lymphoma; TET2, TET methylcytosine dioxygenase 2; T_{FH}, T-follicular helper cell; WM, Waldenström macroglobulinemia.
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In addition to radiographic staging, screening for central nervous system (CNS) involvement, which may include leptomeningeal or parenchymal involvement, should be undertaken in all patients with suspicious neurologic findings, those with Burkitt lymphoma, and select people with high-grade lymphomas (eg, double-hit lymphoma [DHL], DLBCL of the testis, or very high CNS International Prognostic Index [CNS-IPI] risk score).[23] A lumbar puncture with cytologic and, ideally, flow cytometric analysis of cerebrospinal fluid (CSF) and imaging with MRI may identify CNS disease in high-risk patients and guide CNS-directed therapy.

Other tests performed at the time of initial evaluation may include cardiac function assessment (if treatment will include anthracyclines); pulmonary function testing (if treatment will include bleomycin); and laboratory testing including, at a minimum,

a complete blood count (CBC) with differential, comprehensive metabolic profile, serum lactate dehydrogenase (LDH), uric acid, hepatitis B screening, and a pregnancy test in women of childbearing age. Additional tests, including hepatitis C and HIV screening and b-2 microglobulin, may be helpful in selected patients. Testing for hepatitis B is required before the use of rituximab or other CD20-directed therapies because of the risks of viral reactivation and fatal hepatitis. Tests should include those for hepatitis B surface antigen and core antibody for patients who do not have risk factors. Patients who are seropositive for hepatitis B surface antigen or hepatitis core antibody must receive prophylactic therapy against hepatitis B with an antiviral during therapy and at least 12 months after completion.[24-26] Those who are HBV DNA positive may require therapeutic doses of anti–hepatitis B therapy and a hepatology consultation as appropriate. Similarly, hepatitis C treatment may be warranted in cases of lymphoma associated with hepatitis C, such as splenic marginal zone lymphoma.

SURVIVORSHIP AND SURVEILLANCE

Improved diagnostic and staging methods, improved treatments, and supportive care measures have led to an ever-increasing number of people who are either cured of their disease or are living with chronic NHL. Consequently, survivorship care plays an important role in the long-term management of lymphoma patients. The review of late effects of therapy is beyond the scope of this chapter and is offered elsewhere.[27,28]

Most patients who have Hodgkin lymphoma and a majority of those who have DLBCL can expect to be cured of their disease with standard therapy. The risk of recurrence is highest in the first 2 years after initial therapy and then decreases. Relapses are rare beyond 5 years, at which point follow-up with a lymphoma specialist is generally no longer required. The need for routine radiographic surveillance of asymptomatic patients has been questioned based largely on several retrospective analyses. Collectively, these studies found that recurrence was detected in only 2% to 5% of patients who were otherwise clinically and hematologically stable; furthermore, there was no difference in survival if relapse was detected radiographically or after the patient presented with signs or symptoms of disease recurrence.[29,30] Because of the increased exposure to radiation and contrast dye, associated cost and patient inconvenience, and potential test-related anxiety, routine surveillance scans after FDG PET–defined complete remission should be performed no more often than every 6 months for the first 2 years after completion of therapy per National Comprehensive Cancer Network (NCCN) guidelines. However, all patients should be observed clinically for disease monitoring and to address specific toxicities that may emerge later, such as hypothyroidism, infertility, premature menopause, and secondary malignancies. Guidelines for the surveillance of patients with indolent NHL are less defined, and practice varies among physicians.

INDOLENT NON-HODGKIN LYMPHOMA

Indolent lymphomas are characterized by slow growth, sometimes spanning decades, and by a waxing and waning course. With the exception of limited-stage disease treated with radiation therapy (RT), they are incurable with standard approaches. The most common indolent lymphomas include FL, MZL, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The lifetime risk of transformation of an indolent NHL to an aggressive B-cell NHL is approximately 30%; the transformation rate is approximately 2% per year but varies somewhat by tumor type.

KEY POINTS

- NHLs comprise a group of heterogeneous diseases that vary widely with respect to clinical presentation, therapy, and prognosis.
- Advances in the diagnosis and classification of these diseases are facilitated by immunophenotyping and by newer molecular and genetic approaches.
- Establishing a correct diagnosis at the time of initial presentation is critical to optimal management of NHL. Therefore, an adequately sized biopsy specimen is mandatory to permit rigorous classification. FNA is virtually never adequate for establishing the initial subtype of non-Hodgkin lymphoma.
- Indolent NHLs usually grow slowly and are also known as low-grade lymphomas. FL, MZL, LPL, and SLL are all indolent lymphomas.
- Transformation to a higher grade occurs at a rate of approximately 2% per year.

FOLLICULAR LYMPHOMA

FL is the second most common type of lymphoma and represents the paradigm for indolent NHL. FL typically presents with painless lymph node enlargement without systemic B-symptoms, though disseminated disease and marrow involvement are common. Symptoms of FL are often associated with high tumor burden and may include nodal enlargement alone, organ compression (eg, hydronephrosis) from nodes or conglomerates, cytopenias, splenomegaly, effusions, and, in a minority of cases, systemic "B" symptoms. Lymph node biopsy shows a mixture of centrocytes and centroblasts forming densely packed follicles (a follicular

growth pattern) in classic FL. Two other FL variants, based on the 2022 WHO classification, are defined by predominant centroblasts (known as follicular large B-cell lymphoma) or a diffuse growth pattern (FL with uncommon features).[1] The characteristic immunophenotype reflects a germinal center origin, including the B-cell markers CD20 and often CD10 without CD5. The protein BCL2 is overexpressed in >85% of patients, generally as a result of a t(14;18)(q32;q21) chromosome translocation, which can be detected by fluorescence in situ hybridization or standard cytogenetics (Table 20-1). Most patients who have FL have an indolent course with a median survival exceeding 10 years. However, not all patients have a long survival, and identifying patients with more aggressive disease relies on clinical prognostic scoring systems.

STAGING AND PROGNOSIS

At diagnosis, the main clinical tool for risk stratification at diagnosis is the Follicular Lymphoma International Prognostic Index (FLIPI), which includes five risk factors: (1) more than four nodal sites, (2) elevated LDH level, (3) age older than 60 years, (4) stage IV disease, and (5) hemoglobin level less than 12 g/dL (Table 20-2).[29] Although initially developed in the pre-rituximab era, the prognostic relevance of the FLIPI has been validated in modern clinical trials.

Table 20-2 Prognostic Indices for Non-Hodgkin Lymphomas

Risk Factors	Risk Group	No. of Factors	Patient Distribution (%)	Endpoint, OS (%)
IPI for patients treated with R-CHOP				
Age >60 years				3-year OS
PS >1	Low	0-1	52	91
Serum LDH > ULN	Low intermediate	2	21	81
1 EN Site	High intermediate	3	17	65
Stage III-IV	High	4-5	10	59
Stage-modified IPI for aggressive lymphoma[31]				
Age >60 Years				5-year OS
PS >1		0-1	71	82
Serum LDH >ULN		2	22	71
Stage II		3	14	48
FLIPI[30]				
Four nodal sites				5-year OS
Serum LDH > ULN	Low	0-1	36	91
Age >60 Years	Intermediate	2	37	78
Stage III-IV	High	3-5	27	36
Hemoglobin <12 g/dL				
MIPI[32]				
Age				5-year OS
Performance status	Low	0-3	44	60
LDH: ULN	Intermediate	4, 5	35	45
WBC count	High	6-11	21	20

Abbreviations: EN, extranodal; FLIPI, Follicular Lymphoma International Prognostic Index; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MIPI, Mantle Cell Lymphoma International Prognostic Index; OS, overall survival; PS, performance status; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ULN, upper limit of normal; WBC, white blood cell.
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A useful mnemonic is NoLASH[29]:

No = number of nodal sites of disease

L = LDH, lactate dehydrogenase

A = age

S = stage

H = hemoglobin

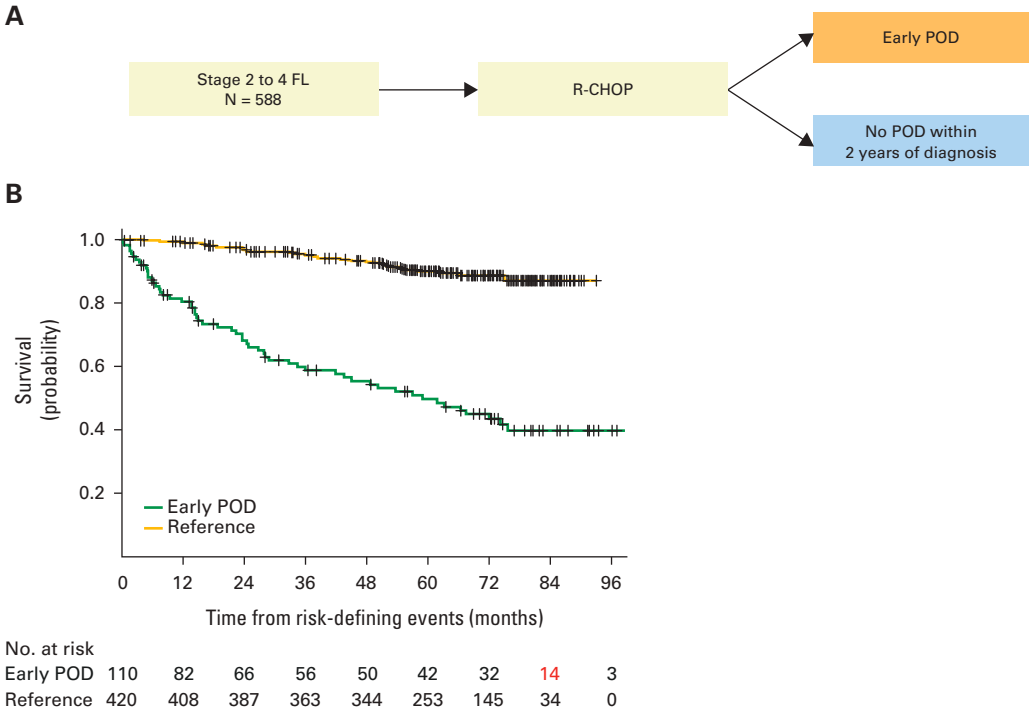
The FLIPI score stratifies patients into three groups with differing 5-year overall survival (OS) rates: (1) low risk (zero to one risk factor; OS, 91%), (2) intermediate risk (two risk factors; OS, 78%), and (3) high risk (three to five risk factors; OS, 53%).[30] Validating and comparing molecular predictive models in FL, which may assess pretreatment mutation status, epigenetic alterations, gene expression, and/or genomic aberrations, remains an active area of research.

FDG PET-CT is an essential study for initial staging and evaluation of FL, a routinely FDG-avid disease.[18] PET staging detects additional nodal and extranodal sites and permits accurate confirmation of localized FL (stage I/II) patients, who may be candidates for RT alone. Whereas early data suggested FDG PET-CT is prognostic in FL and can be used to predict transformation (or direct additional biopsies) based on maximum standardized uptake value, data from the randomized GALLIUM trial showed no such value.[30] Thus, the primary role of PET-CT remains for accurate staging and delineation of disease rather than guiding first-line therapy in FL (as reviewed by Trotman et al).[33]

The decision to initiate therapy for FL requires identifying symptomatic patients or those who have high tumor burden or risk of organ compromise (Fig. 20-2). Criteria used in clinical trials by the Groupe d'Etude des Lymphomes Folliculaires (GELF) can be useful in identifying such patients and include the following[34]:

- Involvement of three or more nodal sites >3 cm
- Any nodal or extranodal tumor mass >7 cm
- Systemic B symptoms
- Splenomegaly
- Cytopenias or leukemic blood involvement
- Pleural effusions or malignant ascites
- Impending organ dysfunction resulting from compression

Figure 20-2 Identification of a High-Risk Subgroup of FL Based on Early Relapse After Initial R-CHOP Chemoimmunotherapy



(A) Patients and methods in the National LymphoCare study. (B) Overall survival from a risk-defining event after diagnosis among patients receiving R-CHOP in the National LymphoCare study, demonstrating poor survival in those with early disease progression.
Abbreviations: FL, follicular lymphoma; POD, progression of disease; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.
Reprinted from Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: An analysis from the national lymphocare study. *J Clin Oncol.* 2015;33:2516-2522. doi: 10.1111/bjh.15718

Approximately 10% to 15% of patients who have FL present with stage I or nonbulky stage II disease. Involved-field radiation therapy (IFRT) or extended-field RT produces a 10-year failure-free survival (FFS) rate of 50% to 60% and a median OS rate of 60% to 80% and has traditionally been considered the standard of care in this setting. However, given the excellent prognosis of

stage I/II FL, selection of RT requires thorough staging with FDG PET-CT and bone marrow aspirate/biopsy to exclude advanced-stage disease and expert consideration of short-term and late risks (largely related to radiation dose and field).

The remaining 85% to 90% of FL patients have advanced-stage disease (bulky stage II or stage III or IV) at the time of presentation. Numerous randomized trials show no survival benefit with immediate treatment of asymptomatic FL even in advanced-stage disease. Thus, the decision to initiate treatment depends on the patient's symptoms and assessment of tumor burden based on GELF criteria discussed earlier.

KEY POINTS

- FL is the most common indolent lymphoma.
- Most patients with FL live for more than a decade.
- Prognostic scores using clinical risk factors can estimate OS.
- Defined treatment indications based on history, physical, imaging, and laboratory results are key to inform whether patients should receive treatment versus active surveillance without therapy (observation).

FIRST-LINE THERAPY

Patients who have symptomatic, low-tumor-burden FL can be treated with single-agent anti-CD20 monoclonal antibody therapy, primarily rituximab, the subject of the vast majority of clinical trials. When rituximab is used as monotherapy in the initial treatment of patients who have FL or low-grade NHL, the response rate ranges from 50% to 70% with a median duration of response (DoR) of 1.0 to 2.5 years.[35] In low-volume tumor settings, the median time to treatment failure is 3.9 or 4.3 years if maintenance rituximab follows induction.[36] Note that biosimilar CD20 antibodies with toxicity and drug exposure similar to rituximab are now in common use, depending on local insurance or center-specific policies on substitution for rituximab.

Patients who have high tumor burden disease are treated with chemoimmunotherapy, combining a CD20 monoclonal antibody and cytotoxic chemotherapy. The optimal chemoimmunotherapy regimen must be individualized and is informed by randomized trials and key findings related to safety. A randomized trial showed superior progression-free survival (PFS) with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) compared with nonanthracycline therapy in FL but no OS benefit.[37] The risk of cardiomyopathy with R-CHOP requires consideration, including pretreatment cardiac assessment.

Two subsequent trials compared bendamustine, a unique alkylating agent possessing a purine-like moiety, plus rituximab (BR) to either R-CHOP or the investigator's choice of rituximab, cyclophosphamide, vincristine, prednisone (R-CVP) or R-CHOP.[38,39] These trials found that BR was associated with improved PFS and lower rates of severe neutropenia, alopecia, and peripheral neuropathy. Of note, bendamustine has been associated with hypersensitivity reactions and an increased risk of opportunistic infections and secondary malignancies in the context of prolonged lymphopenia during and after therapy. None of these chemoimmunotherapy regimens has superior OS, although R-CVP) seems inferior, although less toxic in nearly all settings.

Recently, newer and second-generation anti-CD20 monoclonal antibodies have been tested. Obinutuzumab is a glycoengineered monoclonal antibody targeting CD20 with enhanced antibody-dependent, cell-mediated cytotoxicity compared with rituximab. The GALLIUM trial compared obinutuzumab and chemotherapy versus rituximab and chemotherapy in patients with treatment-naive FL and indolent lymphoma.[40] The trial demonstrated a significant PFS but no OS advantage of obinutuzumab and a chemotherapy arm, albeit with increased toxicity, leading to US FDA approval.

To replace first-line chemotherapy in FL, the RELEVANCE trial was designed to show the superiority of rituximab and lenalidomide in comparison with rituximab and chemotherapy in more than 1,000 previously untreated patients; both arms received rituximab maintenance. Three-year PFS was equivalent in both arms (77% and 78%, respectively).[41] Rituximab plus chemotherapy was associated with increased rates of high-grade neutropenia, febrile neutropenia, nausea, and peripheral neuropathy, whereas lenalidomide was associated with increased cutaneous reactions, diarrhea, and tumor flare reactions. Despite its efficacy, lenalidomide with rituximab lacks approval for first-line treatment of FL, in contrast to relapsed follicular and MZL.

MAINTENANCE THERAPY

Maintenance strategies after induction to partial response (PR) or complete response (CR) have been examined in FL to delay or prevent disease relapse. Trials consistently show an improvement in PFS without improvement in OS, and as expected, a substantial increase in rituximab use in the first years of therapy and an increased risk of infections. The largest study of maintenance in first-line therapy for FL (the PRIMA trial) randomly assigned patients who have high-tumor-burden disease treated with non-bendamustine immunochemotherapy to 2 years of maintenance versus placebo.[42] Maintenance improved PFS (75% vs. 58%; $P < .0001$) but did not affect OS, which was >90% in both arms; infections were more common in the maintenance group (39% vs. 24%). Highlighting important context-specific risks of maintenance, the randomized GALLIUM trial showed that patients older than 70 receiving bendamustine and obinutuzumab had the highest risk of fatal events and severe infection.[43] Thus, maintenance therapy with a CD20 antibody remains an option in first-line treatment of FL—to prolong remission—acknowledging risks and lack of survival benefit.

RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

Although FL and other low-grade lymphomas have an indolent natural history, they are predominantly incurable, and nearly all patients experience relapse. At the time of relapse, a similar approach considering tumor burden and symptoms is applied because not all patients with progression need immediate therapy. Many patients require numerous treatments over a period of many years. Thus, an individualized approach is required for R/R FL with attention to fast-evolving clinical trial data and drug approvals.

There are limited prognostic tools at the time of relapse, but a pivotal study found that the 15% to 20% of FL patients who progress within 24 months of first-line treatment (POD24) experience inferior survival, including a 5-year OS of only 50% (Fig. 20-2).[44] POD24—defined as progression of FL within 24 months of initiating first-line chemoimmunotherapy—identifies a biologically aggressive subset of patients with markedly inferior outcomes. In the pooled analysis by Casulo et al,[45] which included 5,225 patients across 13 randomized trials, POD24 was confirmed as a strong adverse prognostic factor, with affected patients experiencing significantly worse subsequent OS (adjusted hazard ratio [HR] ≈ 3-5) compared with those without early progression.

Group	Events/Total	Median OS, years (95% CI)	3-Year OS % (95% CI)	5-Year OS % (95% CI)
No POD	459/3,328	17.9 (17.5-NE)	93.6 (92.7-94.4)	85.6 (84.0-87.1)
POD within 24 months	422/1,095	11.4 (9.8-NE)	68.6 (64.6-72.5)	55.6 (49.4-61.4)
All patients	881/4,423	17.9 (17.5-NE)	89.5 (89.4-90.1)	87.9 (86.9-88.9)

Data from Casulo C, Dixon JG, Le-Rademacher J, et al. Validation of POD24 as a robust early clinical end point of poor survival in FL from 5225 patients on 13 clinical trials. Blood. 2022;139(11):1684-1693. doi: https://doi.org/10.1182/blood.2020010263

The analysis also identified baseline predictors of POD24, including male sex, poor performance status, elevated β2-microglobulin, and high FLIPI scores. This study firmly established POD24 as a validated early endpoint and clinically meaningful marker for risk stratification in FL. This subgroup is also at high risk of transformation to DLBCL, particularly among patients receiving BR as first-line therapy, emphasizing the need for full evaluation and rebiopsy for early R/R FL.[46,47] In nontransformed, relapsed FL, several factors may influence the selection of therapy:

- Duration of initiation remission (POD24): clinical trials, novel agents, and consideration of cellular therapies may be indicated in patients with POD24.
- Biopsy findings (confirmation of FL and exclusion of histologic transformation in selected patients).
- Composition of prior therapy and depth/DoR.
- Patient comorbidities.
- Patient preference.

The treatment landscape for R/R FL is diverse and includes CD20 monoclonal antibodies, chemotherapy, and novel agents (zanubrutinib and lenalidomide); bispecific T-cell-engaging antibodies; and cellular therapies, including chimeric antigen receptor (CAR)–modified T cells and hematopoietic stem cell transplantation (HSCT).

CD20-DIRECTED MONOCLONAL ANTIBODIES

Rituximab, a chimeric monoclonal antibody targeting CD20, was initially approved for R/R CD20 positive low-grade or follicular NHL in 1997 based on an initial pivotal trial showing responses in 48% of chemotherapy-treated patients and a median time to progression of 13 months.[48,49] In the modern era, given its frequent first-line use, the use of single-agent rituximab for R/R FL is relegated to rituximab-sensitive disease and those unable to tolerate other therapies.

The CD20-antibody obinutuzumab is also approved in combination with bendamustine in patients who have relapsed/refractory FL (R/R FL) after prior rituximab, based on the phase 3 GADOLIN trial.[50] This study compared obinutuzumab and bendamustine versus bendamustine alone in patients who were refractory to rituximab (failure to respond or progress within 6 months of therapy). Although the combined chemoimmunotherapy arm was superior in terms of PFS and OS, the pervasive use of bendamustine in first-line therapy and aspects of the study design (the comparator of bendamustine alone), and a study showing no benefit in PFS with single-agent obinutuzumab over rituximab render the role of obinutuzumab in R/R FL unclear.

BISPECIFIC T-CELL ENGAGERS

The class of agents known as bispecific T-cell engagers, including bispecific antibodies with B- and T-cell specificity, act by redirecting T cells toward malignant B cells, leading to their elimination. A number of agents are in development and represent an important emerging class of lymphoma therapy. Mosunetuzumab, a bispecific antibody targeting CD20 and CD3, was the first to receive accelerated approval (in December 2022) for the treatment of R/R FL after at least two prior therapies. In a phase 1/2 study of 90 patients with R/R FL, an 80% overall response rate (ORR) and CR rate of 60% were observed, and 70% of those

with a CR had continued remission at 18 months.[51] Treatment is administered for up to 17 cycles (given every 21 days), and patients with a CR after eight cycles can discontinue therapy. Cytokine release syndrome (CRS) was observed in 42% of patients, but was generally mild or moderate; only two patients experienced severe CRS. A step-up dosing regimen, premedications, and capability for immediate hospitalization are required to limit and mitigate the risk of CRS. Neurologic toxicity (mainly headache but also dizziness and confusional state), hypophosphatemia, infections, cytopenias, and tumor flare are other known toxicities, and intensive monitoring and recognition/management of toxicities of this novel class is paramount.[52] Subsequently, subcutaneous epcoritamab was approved by the US FDA in June 2024 for the same indication (R/R FL after two or more prior therapies). Epcoritamab, dosed until disease progression or unacceptable toxicity, is also efficacious (ORR 82%, and 63% CRs), but CRS was observed in 65% of patients.[53] The FDA has granted traditional approval to epcoritamab-bysp as monotherapy for relapsed or refractory FL after two or more prior lines of therapy and approved it in combination with lenalidomide and rituximab (R^2) based on the EPCORE FL-1 trial, who had received at least one line of therapy.[5] In this randomized study of 488 patients, epcoritamab-bysp plus R^2 significantly improved PFS and ORR compared with R^2 alone (PFS HR 0.21; ORR 89% vs. 74%). Safety findings included CRS in 24% of patients (serious in 12%), immune effector cell–associated neurotoxicity syndrome (ICANS) in 0.8%, and serious adverse reactions in 51%, predominantly infections.

These bispecific antibodies are, thus, an important therapeutic option but require experience in the prevention and management of unique toxicities such as CRS. Nonetheless, they are likely safer than intensive transplant or chimeric antigen receptor T (CAR-T) cell therapies, suggesting a role before these modalities in the third-line setting and beyond. Larger data sets, including more detail and follow-up, are needed to help inform the optimal choice and sequence of therapy for R/R FL. Bispecific T-cell engagers targeting other antigens, such as CD19, are currently being investigated.

NOVEL TARGETED AGENTS

Although there is a major need for improved, noncytotoxic therapies for FL because of its high prevalence and long natural history, relatively few agents are proven to be both safe and efficacious. Phosphoinositide 3-kinase inhibitors achieved initial approval for R/R FL but have been withdrawn from the US market in light of toxicity, including serious infections. Currently, the approved targeted small-molecule agents available for R/R FL is lenalidomide.[49]

Lenalidomide, which has a complex mechanism of action, including immunomodulatory, proapoptotic, and transcriptome-based antitumor properties, induces a response in approximately one-third of FL patients.[53] When combined with rituximab, the response rate is 76%, and CR is seen in approximately one-third of patients; PFS in the AUGMENT trial was 39 months, superior to PFS with rituximab alone.[54]

Inhibitors of Bruton's tyrosine kinase (BTK) have shown low single-agent efficacy in R/R FL, and biomarkers predicting patients most likely to benefit remain undefined. However, the combination of zanubrutinib and obinutuzumab (Z + O) was compared to obinutuzumab alone in R/R FL patients who have two or more prior treatments, including a response rate of 69% versus 46% and median PFS of 28 months versus 10.4 months.[55] This open-label, randomized study, which also involved long-term zanubrutinib administration (until progression or excess toxicity)—and obinutuzumab maintenance in both arms—showed more thrombocytopenia, pneumonia, zoster infections, and diarrhea in the Z + O arm and comparable OS. Nonetheless, these results led to accelerated approval of Z + O by the US FDA in 2024 for R/R FL after two or more prior lines of therapy.

The FDA recently approved tafasitamab in combination with lenalidomide and rituximab for adults with relapsed and refractory FL. This approval is based on a phase 3 randomized, double-blind, placebo-controlled study involving more than 500 patients with FL. Patients were stratified by POD24 status, refractoriness to prior therapy, and the number of prior lines of treatment. They were randomized to receive tafasitamab in combination with lenalidomide and rituximab for 12 cycles, versus lenalidomide and rituximab plus placebo every 4 weeks for up to 12 cycles. With a median follow-up of 14.1 months, PFS was 22.4 months in the tafasitamab arm, compared to 13.9 months in the placebo arm, corresponding to a 57% reduction in the risk of progression or death. Subgroup analysis demonstrated consistent benefit across all prespecified groups, including high-risk patients. The PET/CT CR rate increased from 40% in the placebo arm to 49% in the tafasitamab arm, and the ORR increased from 72% to 83%. The DoR was also improved, with the median not reached in the tafasitamab arm versus 28 months in the placebo arm. Adverse events were relatively similar between both treatment arms.[9]

HSCT AND CAR-T-CELL THERAPIES

Autologous stem cell transplantation (ASCT) may be useful for selecting patients who have high-risk disease and early relapse, but results are based on historical and nonrandomized trials. The potential efficacy of ASCT in R/R FL must be weighed against several risks, including secondary myelodysplasia and acute myeloid leukemia occurring in approximately 5% of patients. Allogeneic transplantation is associated with greater treatment-related risk but a lower likelihood of late relapse. In a registry study of 440 FL patients relapsing within 2 years of frontline therapy (POD24), ASCT and matched sibling allogeneic transplantation each achieved a 5-year OS of about 70% with nonrelapse mortality rates of 5% and 17%, respectively.[56] However, this study included patients undergoing HSCT from 2002 to 2014 and may have limited relevance in the modern therapeutic era as FL patients have an increasing array of immunotherapy options, including mosunetuzumab and CAR-T-cell therapies.

The first CAR-T-cell therapy approved (2021) was axicabtagene ciloleucel (axi-cel) for patients with R/R FL after at least two prior systemic therapies. The pivotal trial ZUMA-5 tested a single infusion of axictabtagene cilolecel in 148 patients who have R/R FL and MZL.[57] In a subset of 84 patients who have FL considered in the primary activity analysis, the ORR was 94%, including a 79% CR rate, and the 18-month PFS was 65%. The CR rates were similar in subgroups with high-risk baseline features, including those with relapse within 24 months of first-line rituximab-including therapy. However, CRS (7% grade ≥3), cytopenias, infections, and neurologic events (19% grade ≥3) were frequent toxicities in ZUMA-5, and half of the enrolled patients experienced serious adverse events. The 5-year update from the ZUMA-5 trial demonstrated that axi-cel provides durable and potentially curative responses in patients with relapsed or refractory FL. The 5-year PFS rate was approximately 50%, and the 5-year OS rate was 69%. In the FL cohort, the ORR was 94%, with a CR rate of 79%. More than half of the patients remained in remission due to ongoing responses. The median DoR in the FL group was approximately 60 months.[58] Subsequently, in 2022, tisagenlecleucel (tisa-cel) became the second CD19-directed CAR-T approved for FL, also after two or more lines of systemic therapy, based on a phase 2 trial of 94 efficacy-evaluable patients.[59] A single infusion of tisa-cel led to CR in 69% of patients and ORR in 86%; 12-month PFS was 85%, and instances of grade 3 CRS were seen. The 4-year follow-up data from the ELARA trial demonstrated a median PFS of 53.3 months, with a 4-year PFS rate of 50.2% and a 4-year OS rate of 79.3%. High-risk disease characteristics—such as being double refractory, having bulky disease, or experiencing progression within 2 years of prior therapy—did not predict inferior efficacy.[60] Responders also achieved higher rates of minimal residual disease negativity. Most recently, lisocabtagene maraleucel (liso-cel) was also approved in this setting—R/R after two or more lines of therapy—comprising the third CD19-directed CAR-T therapy available for FL.[61] Selection among these options is challenging as each carries significant risks, including CRS, neurologic toxicity, and infection. As a result, these agents are most appropriately considered for patients who have successive relapses of FL in a short time frame and limited comorbidities.

KEY POINTS

- Symptomatic patients who have progressive FL or other low-grade lymphomas have a number of treatment options without any evidence indicating a major survival advantage for any specific approach.
- Chemoimmunotherapy remains a standard for first-line FL treatment with high tumor burden, but the subset of patients relapsing within 2 years faces poor survival rates. In these cases, optimal therapy is unknown, but clinical trials, novel targeted therapies, and cellular therapies (HSCT, bispecific T-cell engagers, CAR-T-cell therapy) may be considered.
- The novel small-molecule therapy currently approved for relapsed FL is lenalidomide.
- Combination therapies currently approved for relapsed FL include Rituximab with lenalidomide, zanubrutinib with obinutuzumab, and tafasitamab in combination with lenalidomide and rituximab.
- Recently FDA-approved immunotherapies include the bispecific T-cell engager mosunetuzumab, epcoritamab, and CAR-T-cell therapies (axi-cel, tisa-cel, and liso-cel), representing an important new class of therapies in R/R FL.

HISTOLOGIC TRANSFORMATION OF FL TO AGGRESSIVE LYMPHOMA

Approximately one-third of patients who have FL undergo documented transformation to a more aggressive histology in their lifetime, typically DLBCL. The annual rate of transformation is 2% to 3%.

Confirming a diagnosis of transformed FL can be difficult. The gold standard is a biopsy specimen of a lymph node showing an aggressive BCL that is clonally related to the FL; biopsy of bulky, rapidly growing, or the most FDG-avid sites should be prioritized when safe. Clinical features associated with histologic transformation include rapid progression of nodal disease, increased LDH level, declining PS, hypercalcemia, new involvement in extranodal sites, and new-onset B symptoms. If a biopsy procedure is not safe or feasible, clinical symptoms and supportive laboratory abnormalities can justify the treatment of transformed disease.

Treatment of transformed FL depends on the extent and type of prior therapy, biologic features (eg, presence of *MYC* and *BCL2* rearrangement), and patient factors. For anthracycline-naive patients, R-CHOP or a similar regimen may be used; otherwise, regimens commonly used for relapsed DLBCL may be used (including platinum-based chemotherapy combinations). For eligible patients who have transformed lymphoma, consolidation with ASCT,[62-64] allogeneic transplantation,[63,65] RT, or CAR-T-cell therapy may be considered, but there are limited prospective, controlled data to support one strategy over another. In case of recurrent transformed lymphoma, therapies for relapsed DLBCL, such as bispecific antibodies, CAR-T-cell therapy[66] or less intensive regimens (tafasitamab and lenalidomide, loncastuximab tesirine, selinexor), can be considered.[67,68]

MARGINAL ZONE LYMPHOMA

MZLs constitute 10% of B-cell NHLs and have an indolent course. The three primary subtypes of MZL have varying incidence, biology, and prognosis (reviewed expertly by Rossi et al).[69]

The clinical presentation of MZL depends on the site of involvement. ENMZL arises from lymphoid tissue associated with epithelial tissues (mucosa-associated lymphoid tissue [MALT]), and most commonly involves the stomach or other gastrointestinal

sites as well as ocular adnexa, thyroid, lung, or skin. Nodal and splenic MZL typically present with node or spleen/peripheral blood/marrow involvement, respectively, but share histologic features with ENMZL; all arise from marginal zone B cells and express CD19/CD20, typically without CD10. Diagnosis of MZL requires adequate biopsy material to distinguish from chronic lymphocytic leukemia, MCL, LPL, and even DLBCL. Expert pathology review and consideration of surface markers, cytogenetic findings, and potentially sequencing-based analysis (*MYD88* mutations are typically absent in MZL but present in LPL).

The concept of lymphoma as an antigen-driven disease is best described for gastric ENMZL, formerly called gastric mucosa-associated lymphoid tissue, in which *H. pylori* consistently irritates the mucosal T and B cells that line the stomach, causing them to proliferate. At some point, the B cells become autoreactive and develop into an *H. pylori*–dependent lymphoma. Other examples of chronic antigenic stimuli associated with MZL include *Chlamydia psittaci* in ocular adnexal MZL; hepatitis C, leading to SMZL (treated successfully with elimination of hepatitis C); and *Borrelia burgdorferi* in cutaneous MZL. Autoimmune conditions associated with MZL include Hashimoto thyroiditis, leading to thyroid MZL, and Sjogren disease, leading to salivary gland MZL.

LOCALIZED GASTRIC ENMZL: FOCUS ON *H. PYLORI* ERADICATION

The most common MZL is gastric ENMZL in association with *H. pylori*. Patients typically present with nausea, abdominal discomfort, or GI bleeding. Patients should be evaluated for *H. pylori* by histopathology, and if negative, a stool antigen test or urea breath test should be performed. If *H. pylori* infection is present, fluorescence in situ hybridization or polymerase chain reaction testing for t(11;18) should also be performed to exclude *MALT1* translocation. The presence of t(11;18) is predictive of a lack of response to *H. pylori* eradication therapy.

H. pylori–positive gastric MZL is treated first with *H. pylori* eradication with either triple therapy (proton-pump inhibitor and two antimicrobials) or quadruple therapy (proton-pump inhibitor, bismuth, tetracycline, and metronidazole) for 14 days, which results in high rates of *H. pylori* eradication and histologic CR in more than half of patients.

Response assessment after *H. pylori* eradication requires repeated endoscopy, but this should not be performed sooner than 3 months after therapy because responses are often delayed. If repeated endoscopy is normal but biopsy specimens show lymphoid aggregates, asymptomatic patients may be kept under observation. Surveillance can stop after two sequential negative endoscopies.

Patients who have *H. pylori*–negative gastric ENMZL or relapse/refractoriness after *H. pylori* eradication are treated with RT or rituximab (if RT is contraindicated). RT offers excellent local control and is associated with high long-term survival rates, and rituximab monotherapy achieves responses in most patients, including those with t(11;18).[70,71]

SYSTEMIC THERAPIES FOR MZL: FIRST LINE AND BEYOND

First-line treatments for MZL prioritize eradication of infectious drivers such as *H. pylori* and hepatitis C and consideration of RT for localized disease because these modalities may result in long-term remission or cure. For advanced-stage disease, symptomatic patients often receive rituximab or chemoimmunotherapy. Single-agent rituximab is particularly effective in splenic MZL and represents a reasonable treatment option for many advanced-stage patients. Those who have bulky or high-risk disease may achieve deeper, longer remissions with combination chemoimmunotherapy (BR, R-CVP) at the cost of increased risk of infection and myelotoxicity. There is no proven role for anthracycline therapy (eg, R-CHOP) in MZL outside of defined histologic transformation. In the relapsed setting, akin to FL, factors including quality and duration of initial response, patient comorbidities, and goals must be considered during selection of therapy. Retreatment with rituximab is often feasible. Importantly, the oral BTK inhibitor zanubrutinib is available for relapsed MZL among patients who received prior anti-CD20–based therapy, based on phase 2 showing a response rate of 68% (35% CR) and PFS exceeding 80% at 15 months.[72] As in other B-NHL, zanubrutinib is dosed continuously until progression, and diarrhea, contusion, neutropenia, and infection are known risks.

NCCN guidelines also include combination with lenalidomide, specifically lenalidomide in combination with CD20 antibody therapy. Although FDA approved and supported by single-agent data, lenalidomide combined with rituximab failed to improve PFS, ORR, or the probability of 2-year OS compared with placebo and rituximab in the subset of patients with MZL of the AUGMENT trial.[54] Given its low incidence, clinical trials specific to MZL are challenging to conduct, but advances in oral targeted therapies and immunotherapies (CAR-T cells and bispecific antibodies are likely to benefit MZL patients and gain integration into standards of care in the relatively near future.

KEY POINTS

- Three types of MZL are EMZL, SMZL, and NMZL.
- MZLs are frequently antigen-driven diseases, and eradication of infection (eg, *H. pylori*) can result in regression of lymphoma without the need for additional therapy.
- RT for localized MZL, including persistence of gastric MZL after *H. pylori* eradication, is effective; systemic therapy for advanced-stage MZL incorporates rituximab and, for selected patients, chemotherapy with rituximab.
- R/R MZL requires individualized consideration of therapy, including additional rituximab, chemoimmunotherapy when appropriate, zanubrutinib, or lenalidomide-based therapy.

LYMPHOPLASMACYTIC LYMPHOMA/WALDENSTRÖM MACROGLOBULINEMIA

LPL is an uncommon and incurable indolent BCL. A vast majority of LPLs produce an IgM paraprotein, designated WM. Because less than 5% of cases produce IgG or IgA or are nonsecretory, most studies of LPL pertain to WM.

LPL/WM is typically diagnosed because of the presence of cytopenias or during the workup of a paraprotein. Less commonly, patients may have adenopathy or organomegaly at the time of diagnosis. Diagnosis requires a bone marrow biopsy specimen that shows infiltration by a spectrum of small lymphocytes, plasmacytoid cells, and plasma cells with associated B-cell and plasma cell markers.[1,73] However, this admixture of cell types renders accurate diagnosis challenging, and LPL/WM requires distinction from lymphoma, including MZL and MCL, among others. It has been found that >90% of WMs harbor a point mutation in the *MYD88* gene (L265P), aiding in diagnosis and differentiation from other lymphomas.

PRINCIPLES OF SYSTEMIC THERAPY FOR WM

As with other indolent lymphomas, treatment of LPL/WM is indicated only if the patient has disease-related symptoms, cytopenias related to marrow infiltration, bulky disease, or IgM-related complications. Elevated IgM may result in hyperviscosity as well as neuropathy, coagulopathies, or cryoglobulinemia syndromes/cold agglutinin disease.[74] Symptomatic hyperviscosity represents an emergent indication for plasmapheresis followed by systemic therapy and may be manifested by visual changes, neurologic symptoms (headache, confusion, or vertigo), or bleeding (retinal hemorrhage, epistaxis). In addition, rituximab can lead to an acute increase in IgM levels, leading to symptomatic hyperviscosity lasting several weeks.[74]

First-line treatment options include rituximab monotherapy, chemoimmunotherapy including bendamustine and rituximab, bortezomib-based treatment, or BTK inhibitors. A randomized trial demonstrated a trend toward improved depth of response and less toxicity with zanubrutinib compared with ibrutinib, leading to regulatory approval of this agent in 2021.[75] However, whereas associated with low risks of cardiac events or severe toxicities, zanubrutinib is administered continuously, and cumulative toxicities, including infection, hypertension, and bleeding, increase over time. Thus, fit patients should also be considered for fixed-duration regimens (such as BR) in first-line therapy. A 2021 French multicenter study of 69 WM patients treated with first-line BR reported an ORR of 97%, with 96% of patients achieving at least a 50% reduction in serum paraprotein.[76] Only six patients had progressed within 23 months of median follow-up.

Notably, in patients at high risk of hyperviscosity—generally, IgM 4,000 mg/dL or higher but with substantial interpatient variation—omission of rituximab from the first one to two cycles of chemoimmunotherapy or prophylactic plasmapheresis and close IgM monitoring should be considered.

KEY POINTS

- Despite its rarity and lack of comparative trials in WM, several key management aspects are evident from available data: An elevated paraprotein level alone is not an indication for therapy in asymptomatic patients.
- First-line therapy may include rituximab, chemoimmunotherapy, or a continuous BTK inhibitor, depending on goals and patient factors (disease burden, age, and comorbidities).
- Rituximab may result in a sudden increase in IgM levels, leading to symptomatic hyperviscosity.
- R/R WM is treated upon symptomatic progression, and selection of therapy depends on depth and DoR to initial therapy, as in other indolent NHL.
- BTK inhibitors, particularly zanubrutinib, are a mainstay of WM therapy.

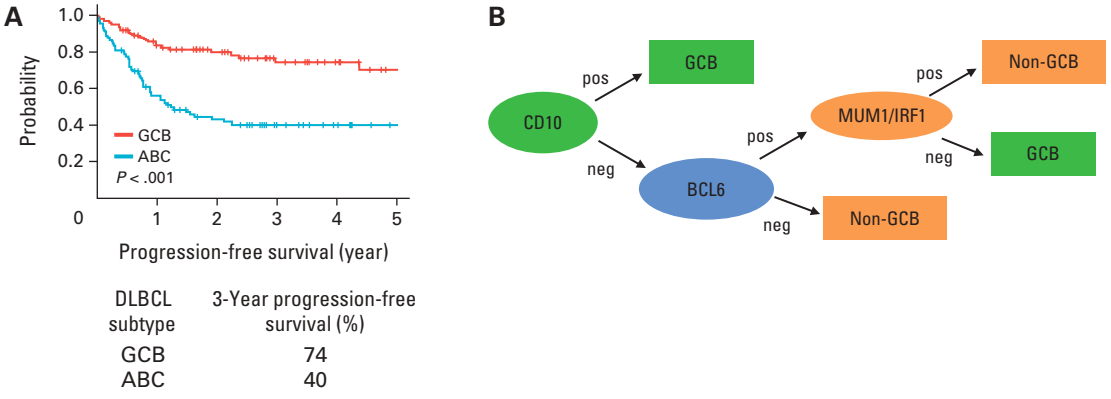
DLBCL AND OTHER AGGRESSIVE B-CELL LYMPHOMAS

Aggressive lymphomas are characterized by a rapid and usually symptomatic growth phase leading to clinical presentation. DLBCL not otherwise specified (NOS; heretofore referred to as DLBCL) is the prototype of aggressive B-cell NHL and constitutes 30% of all NHLs, although nomenclature has evolved as the heterogeneity of this disease has been better defined. Up to 40% of patients initially present with extranodal involvement, most commonly in the GI tract and also with involvement of the CNS, genitourinary or reproductive tract, lung, or other sites. Optimal diagnosis requires a sufficiently large tissue specimen to confirm histology and performance of important prognostic and predictive tests; FNA is never appropriate as the sole means of diagnosis and only serves to differentiate between solid tumors and lymphomas. The classic morphology is diffuse effacement of the normal lymph node architecture by intermediate to large cells expressing CD19, CD20, CD79a, and CD45. However, DLBCL is increasingly understood to be a heterogeneous disease with genetic, biologic, and clinical variants that have an important effect on clinical outcomes.

The International Prognostic Index (IPI) is the most used prognostic score that incorporates five clinical (Table 20-2) features that stratify patients into four risk categories: age >60 years, PS >1, increased LDH level, more than one extranodal site, and stage III to IV disease. The original IPI was developed before the advent of rituximab in DLBCL treatment, and several updates to the IPI have been developed, including the Revised-IPI and the NCCN-IPI[77,78]; however, the original IPI continues to be most widely used in clinical trials.

DLBCL is genetically heterogeneous. One way of classifying DLBCL is by the B cell of origin (COO) through gene-expression profiling (Fig. 20-3).[79] DLBCL specimens genetically resembling germinal center B cells are designated germinal center B-cell-like DLBCL (GCB-DLBCL), whereas those resembling activated B cells are called activated B-cell-like DLBCL (ABC-DLBCL); 10% to 15% of cases are unclassifiable by COO. GCB-DLBCL is characterized by common germinal center B-cell pathways, such as *BCL6* and *EZH2*, and ABC-DLBCL is characterized by chronic B-cell receptor signaling and activation of the NF-κB pathway.[79-81] New taxonomies of DLBCL based on in-depth genomic analyses have been proposed, including the LymphGen classification and DLBCL clusters, but they require further validation.[80,82,83] Testing for COO and performing genomic analysis is difficult in routine clinical practice because gene-expression profiling requires time and frozen material and is not widely available at this time. Several immunohistochemical algorithms are used as surrogates for COO, but there is an error rate of approximately 20%. One of the more common algorithms is the Hans method, which stains for CD10, MUM1, and *BCL6* to determine the COO as GCB versus non-GCB (akin to the ABC subtype and many unclassifiable cases). Despite similar clinical risk features, patients who have ABC-DLBCL have inferior survival compared with those who have GCB-DLBCL treated with CHOP or R-CHOP.[79]

Figure 20-3 Cell Origin Cultures



(A) Survival outcomes by genomic profiling determination of COO in patients treated with R-CHOP. (B) Hans algorithm for immunohistochemical determination of COO.
Abbreviations: ABC, activated B cell; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; neg, negative; pos, positive; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
Image (A) reprinted from Dunleavy K, Grant C, Wilson WH. *Ther Adv Hematol.* 4(1):43-57. Copyright © 2013 by Sage Publications. Reprinted by permission of Sage Publications.
Image (B) reproduced under Creative Commons license. Source: Reber R, Banz Y, Garamvölgyi E, et al. Determination of the molecular subtypes of diffuse large B-cell lymphomas using immunohistochemistry. *Swiss Med Wkly*. 2013;143:w13748. doi: 10.1016/S1470-2045(21)00591-X

MYC, a proto-oncogene and transcription factor classically rearranged in Burkitt lymphoma, is rearranged in up to 15% of cases of DLBCL and can be detected by fluorescent in situ hybridization (FISH). Because DLBCL is substantially more common than Burkitt lymphoma, many more patients with *MYC* rearrangements have DLBCL rather than Burkitt lymphoma in the United States. Of note, *MYC* rearrangement is diagnostic in Burkitt lymphoma, in which it is associated with upregulation of target genes of the c-myc transcription factor, whereas it is adversely prognostic in DLBCL.[83,84] In 5% to 7% of cases, the majority of which are GCB-DLBCL, *MYC* rearrangement may occur with *BCL2* and/or *BCL6*. These lymphomas are classified as high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, but are often commonly called DHL or triple-hit lymphoma. This is a clinically aggressive phenotype with poor long-term survival after R-CHOP, and there is considerable debate surrounding optimal management of high-grade BCL.

Both MYC and BCL2 proteins can be overexpressed as measured by immunohistochemical analysis, either with or without the underlying respective chromosomal rearrangements, in up to 30% of patients with DLBCL.[85,86] These are termed double-expressor lymphomas and can occur in either GCB-DLBCL or ABC-DLBCL. When DEL occurs without underlying DHL, outcomes are still poor but not quite as dismal. As discussed later in this chapter, it is unknown precisely how these patients should be treated.

PRESENTING CASE STUDY 1

A previously healthy 60-year-old man presents to his primary care physician with a 1-month history of swollen lymph nodes, night sweats, and unintentional weight loss. Core biopsy of an axillary node reveals sheets of large cells positive by immunohistochemistry for CD20, CD19, MUM1, *BCL2*, and *MYC*; *CD10* is negative. Fluorescent in situ hybridization (FISH) assessment is negative for *MYC*, *BLC2*, and *BCL6* rearrangement. PET/CT identifies diffusely FDG-avid lymphadenopathy

throughout the neck, axillae, chest, and abdomen. Kidney and liver function tests are within the upper reference limit. HIV test is negative. Complete blood count indicates a lactate dehydrogenase (LDH) level of 350 U/L (upper reference limit, 200 U/L). The patient's Eastern Cooperative Oncology Group (ECOG) performance status is 2.

How would this patient's disease presentation inform diagnosis and staging?

This patient's presentation and pathology are consistent with stage IIIB nongerminal center B-cell–like diffuse large B-cell lymphoma (DLBCL) based on the Hans algorithm. His International Prognostic Index (IPI) score is 4 (1 point each for age >60 years, ECOG performance score ≥2, elevated LDH, and stage III/IV disease), indicating high-risk disease with a 5-year overall survival rate around 26%.

If there are no feasible clinical trial options available to this patient, what are the treatment options you should consider?

Standard treatment options for this patient include six cycles of rituximab and cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP) or polatuzumab (a CD79b-directed antibody-drug conjugate) and rituximab in addition to cyclophosphamide, doxorubicin, and prednisone (pola-*R*-CHP). R-CHOP has been the standard of care for untreated DLBCL for several decades. In 2022, the phase 3 POLARIX trial randomized patients with an IPI score of 2 to 5 to receive either R-CHOP or pola-*R*-CHP. Patients in the pola-*R*-CHP arm had improved progression-free survival (PFS) over patients in the R-CHOP arm, with a 2-year PFS of 77% versus 70%, respectively, and pola-*R*-CHP is now FDA approved for untreated DLBCL. Like the patient in this case, study participants who were older than 60 years of age, those with an IPI score of 3 to 5, and those with the activated B-cell–like subtype of DLBCL seemed to benefit most from pola-*R*-CHP.

After discussing with the patient, the decision was made to treat his stage IIIB DLBCL with six cycles of pola-*R*-CHP. PET/CT at the end of treatment shows complete resolution of all previously noted, metabolically active lymph nodes. Three months after completing treatment, he presents for routine follow-up and reports feeling well. He continues to have mild peripheral sensory neuropathy in his fingertips; his ECOG performance status is 0, and he has returned to work. Physical examination demonstrates enlarged lymph nodes in the right axilla. Lymph node biopsy demonstrates relapsed DLBCL with the same immunophenotype as the original biopsy. Laboratory findings reveal a hemoglobin level of 10 g/dL; kidney and liver function tests are within the upper reference limit. The patient would like to be aggressive with the treatment of his lymphoma.

What factors should be taken into consideration when deciding the next treatment for this patient?

This patient has relapsed DLBCL less than 1 year after first-line treatment. He would be considered fit for autologous stem cell transplantation (ASCT) based on his age (<70 years), ECOG performance status, and organ function; before 2022, high-dose chemotherapy followed by ASCT in patients with chemosensitive disease was the standard treatment for relapsed/refractory DLBCL. ASCT is still the standard treatment for patients whose disease relapses more than 1 year after first-line treatment. However, in 2022, two phase 3 clinical trials randomized participants with refractory or relapsed DLBCL within 1 year of first-line treatment to either high-dose chemotherapy followed by ASCT in those with chemosensitive disease or anti-CD19 CAR-T-cell therapy. There was superior event-free survival of both axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) over ASCT as well as an overall survival advantage of axi-cel over ASCT, leading to the FDA approval of axi-cel and liso-cel in patients with early relapsed or refractory DLBCL in the second-line setting. Thus, this patient with early relapsed disease should be treated with either axi-cel or liso-cel.

TREATMENT OF NEWLY DIAGNOSED AGGRESSIVE LYMPHOMAS

Limited-Stage Disease

Approximately 30% of patients with DLBCL have limited-stage disease (stage I or nonbulky stage II) at the time of presentation and have a superior prognosis compared with patients with advanced-stage disease. Before the advent of rituximab, standard treatment of limited-stage DLBCL included three cycles of CHOP followed by IFRT. Because 5-year OS in limited-stage disease is 85% to 95%, prospective trials have focused on reducing toxicity through limiting the number of cycles of CHOP and omitting radiation. The randomized FLYER study enrolled patients younger than 60 years old with low risk by age-adjusted IPI and nonbulky (less than 7.5 cm) stage I and II DLBCL who received either six cycles of R-CHOP or four cycles of R-CHOP with two additional doses of rituximab.[87] The 3-year event-free survival (EFS) and 3-year OS were nearly identical in both treatment

arms. Another trial treated patients with nonbulky (<10 cm) stage I/II DLBCL based on interim PET.[88] All received three cycles of standard R-CHOP therapy followed by an interim PET. Those with a negative interim PET proceeded with one additional cycle of R-CHOP, whereas those with a positive interim PET received IFRT followed by ibritumomab tiuxetan radioimmunotherapy (RIT). The 5-year PFS estimate was 87% (95% CI, 79-92), and the OS estimate was 89% (95% CI, 82-94) with interim PET-positive and -negative patients having similar outcomes. Therefore, the routine use of RT may not be required in limited-stage DLBCL and is definitely not needed in younger patients lacking IPI risk factors. An important caveat to the discussion regarding limited-stage DLBCL is that none of these trials fully evaluated the effect of biology (eg, DHL, DEL, and high-grade morphology) or the specific extranodal site (eg, primary breast). An extension to this latter point is that primary testicular lymphoma, which is often stage I to II, constitutes a distinct clinicopathologic subset of DLBCL and has its own treatment approach, which is reviewed below.

Advanced-Stage Disease

In the early 2000s, rituximab added to CHOP chemotherapy demonstrated an advantage in not only PFS but also OS of approximately 15% in younger and older patients.[89,90] Importantly, most studies show a plateau after 5 years, supporting the curative potential of treatment of DLBCL. However, not all patients are cured, and there are a number of clinical and biologic factors affecting curability (reviewed by Sehn and Salles).[91] The standard of care is six cycles of R-CHOP, and additional cycles have shown no benefit in a randomized trial.[92] Attempts to improve on R-CHOP have taken several approaches, including dose-dense delivery, the addition of etoposide or novel agents to an R-CHOP backbone, the use of consolidative HSCT, maintenance therapy, and delivery of treatment by continuous infusion. Until recently, no major randomized trial had shown a clear benefit over full-course R-CHOP. In 2022, the POLARIX trial randomized 879 patients with an IPI 2 to 5 to receive either R-CHOP or polatuzumab vedotin (a CD79b-directed antibody-drug conjugate [ADC]) substituted for vincristine (pola-*R*-CHP). Patients in the pola-*R*-CHP arm had an improved PFS over patients in the R-CHOP arm, with a 2-year PFS of 77% versus 70%, respectively. Response rates, toxicity, including peripheral neuropathy, and OS were similar between the arms. Although the trial was not powered to evaluate subgroups, participants older than 60 years of age, those with IPI 3 to 5, and those with the activated B-cell–like subtype of DLBCL seemed to benefit most from pola-*R*-CHP. Pola-*R*-CHP is now FDA approved for untreated DLBCL, including high-grade DLBCL with an IPI of ≥2.

Patients who have high-grade B-cell lymphoma, including those with dual rearrangements of *MYC* and *BCL2* DLBCL/HGBCL-MYC/BCL2; high-grade BCL), probably need augmented approaches. Large retrospective series consistently show less than 20% long-term survival in high-grade BCL treated with R-CHOP.[85,93] Several retrospective reviews indicate that more-intensive regimens may have better outcomes, and the largest multicenter analysis showed R-CHOP to be inferior to almost any other regimen with a HR of 0.5.[94,95] Prospective data supporting the use of one regimen over another are limited, but a phase 2 trial showed promising activity of the 5-day infused regimen of dose-adjusted etoposide, doxorubicin, vincristine, and cyclophosphamide plus rituximab although not all patients in this trial had true high-grade BCL with dual translocations of both *MYC* and *BCL2*.[96]

For patients unlikely to tolerate standard R-CHOP, first-line regimens may incorporate attenuated dosing (eg, mini-R-CHOP for older patients[97]) or substitution of doxorubicin (eg, incorporating gemcitabine for patients with poor cardiac function).[98] Maximal supportive care, including growth factor support and attention to risk of neuropathy, infection, and cytopenias are required in these subgroups. Maximal supportive care, including growth factor support and attention to risk of neuropathy, infection, and cytopenias are required in these subgroups.

KEY POINTS

- Most patients with primary mediastinal BCL (PMBL) do well with chemoimmunotherapy (eg, R-CHOP) and RT or approaches that seek to eliminate RT (eg, dose-adjusted etoposide, doxorubicin, vincristine, and cyclophosphamide plus rituximab [DA-EPOCH-R]).
- The role of RT remains a controversial issue, and PET-adapted strategies are under investigation.
- CAR-T-cell therapy, high-dose chemotherapy (HDC) and ASCT, and pembrolizumab can be used in the relapsed setting.

Primary Mediastinal BCL

PMBL is a distinct, aggressive BCL derived from medullary thymic B cells and presents as a large and symptomatic mediastinal mass, often with superior vena cava syndrome and a predilection for extranodal organ involvement. The median age at onset is 30 years with a slight female predominance. Histopathology shows a diffuse infiltrate of large cells with CD20, CD79a, and *PAX5*, usually positive for CD10, BCL6, and CD23.7 CD30 can be expressed as well and is often weaker in intensity compared with that in Hodgkin lymphoma. Of interest, there are significant similarities in gene expression between PMBL and classic Hodgkin lymphoma (cHL) with deregulation of nuclear factor kB, Janus kinase 2, and programmed-death ligand 1 (PD-L1)/PD-L2.[99] Cases with intermediate histopathologic features between PMBL and Hodgkin lymphoma are termed gray-zone lymphomas, and these have a worse prognosis.[10,100]

The treatment of PMBL is not standardized, and prospective data are limited because of the rarity of PMBL. R-CHOP with consideration of radiation to bulky disease sites, borrowing from treatment of more common DLBCL-NOS subtypes, has emerged as a standard approach. However, this approach was associated with induction failure in 21%, and R-CHOP-like regimens achieve long-term disease control in only 60% to 70%.[101,102] On the other hand, a prospective international trial of rituximab plus various chemotherapy backbones followed by RT showed, in a majority of patients, 5-year PFS and OS rates >90% with the end-of-treatment PET being the most important discriminator of outcome.[103]

Investigators at the NCI and Stanford tested DA-EPOCH-R as a means to obviate the need for RT and reported a 5-year EFS rate of 93% with no relapses beyond 1 year.[104] Given the mediastinal location, avoiding RT is an appealing option, and it is omitted as part of planned therapy after DA-EPOCH-R. RT may also be avoided in patients with a negative FDG-PET scan after full-course therapy, although final results from a current randomized trial (International Extranodal Lymphoma Study Group-37[105]) are needed to ascertain whether this approach can be uniformly recommended.

Relapsed PMBL may occur in sites of initial disease bulk or in extranodal sites and generally occurs in the first 2 years.[101-103] Chemotherapy-sensitive, later relapses (more than a year from initial therapy) are treated similarly to DLBCL-NOS with salvage chemotherapy and consideration of ASCT. For R/R PMBL within a year of completing first-line therapy or in chemorefractory disease after second or later relapse, CAR-T-cell therapy is an approved option. Relapsed PMBL after two or more prior lines of therapy have another treatment option using the immune checkpoint inhibitor pembrolizumab.[106] At a median follow-up of 9.7 months, the ORR to single-agent pembrolizumab was 45% with a CR rate of 11% and a PR rate of 34%. The median time to initial objective response was 2.8 months (range, 2.1-8.5 months). The median DoR was not reached (range, <1.1 to <19.2 months).

Primary Testicular Lymphoma

Primary testicular lymphoma is usually an aggressive BCL limited to the testes. It is relatively rare and occurs most commonly in men in the sixth decade of life. Despite being localized (stages I to IIE) in most cases, outcomes are poor compared with those in other early-stage DLBCLs. In particular, there is a high risk of CNS recurrence (up to 25%) and a continuous risk of relapse persisting even 10 years after diagnosis.[107] Treatment should include R-CHOP for six cycles, CNS prophylaxis, and irradiation of the contralateral testis at the end of systemic therapy.[108]

CNS Prophylaxis

Aggressive BCLs can recur in the CNS with an extremely high risk of fatal outcome within 1 year. CNS recurrence typically occurs early, within 6 to 12 months after initial treatment, and is often parenchymal. Fortunately, the overall risk of secondary CNS involvement in the rituximab era is low at approximately 3% and 5% in all patients with DLBCL. Defining patients with a higher risk of recurrence and delivering CNS prophylaxis are essential, but these areas remain incompletely outlined. Extranodal areas confer increased risk of CNS involvement, although not all anatomic areas confer the same risk. Marrow, paranasal sinus, testis, and breast involvement confer a higher risk. One international collaboration evaluated 2,164 patients with aggressive BCLs and proposed a new CNS-IPI comprising kidney and/or adrenal gland involvement, age >60 years, LDH level higher than normal, Eastern Cooperative Oncology Group performance status (ECOG PS) >1, stage III to IV disease, or more than one extranodal site. Patients who had high-risk disease had a 10% to 12% risk of CNS relapse.

Unfortunately, prospective data are lacking to guide the best prophylactic regimen. Historically, CNS prophylaxis has involved four to eight doses of intrathecal methotrexate and/or cytarabine or systemic methotrexate (3-3.5 g/m^2) during or after the course of treatment.[109,110] There remains considerable debate, based on emerging data, surrounding the optimal role and value of CNS prophylaxis in DLBCL, summarized recently by Schmitz and Frontzek.[111]

Relapsed/Refractory Disease

Despite improved cure rates with chemoimmunotherapy, approximately 30% to 40% of patients who have DLBCL will have either primary refractory disease or experience relapse after a prior response. The treatment of R/R DLBCL is evolving with many recent and likely upcoming changes to the standard of care (Fig. 20-4). HDC and ASCT were the long-standing standard therapies for chemosensitive disease based on the randomized Parma trial conducted >20 years ago.[112] This trial randomly assigned 109 patients who were younger than 60 years and had relapsed aggressive BCL to either dexamethasone and cytarabine/platinum agent (DHAP) chemotherapy or ASCT, and ASCT was associated with superior EFS and OS rates of 46% versus 12% (P = .001) and 53% versus 32% (P = .038), respectively. Platinum chemotherapy is the backbone of common regimens. The CORAL trial randomly assigned patients with R/R DLBCL after either CHOP or R-CHOP to one of two salvage regimens (rituximab plus ifosfamide, carboplatin, and etoposide [ICE] or rituximab plus DHAP) before ASCT. Among 398 patients, the 3-year PFS rate was 37% overall, but it was 53% for those who had chemotherapy-sensitive disease who successfully underwent transplantation.[113] Patients with relapse within 12 months and having received prior R-CHOP therapy had worse outcomes with a 3-year PFS of 23%. Registry data suggest chemosensitivity remains an important predictor of ASCT outcomes with a 40% to 50% rate of durable remission among patients able to proceed to ASCT.[114]

However, chemotherapy and ASCT fail to cure at least half of patients with R/R DLBCL. CAR-T-cell therapy has emerged as a major treatment modality, first approved after two prior lines (or after ASCT) and more recently for primary refractory DLBCL or relapse within 1 year after first-line therapy. Initially, three CAR T-cell constructs targeting the B-cell receptor antigen CD19 were approved for patients receiving two prior lines of treatment. axi-cel demonstrated an ORR of 82% and a CR rate of 54%.[115] At 5 years, the OS was 42.6%, and with a median follow-up of 63 months, 31% of responses were ongoing.[116] Tisa-cel was the second CAR T-cell product approved after demonstration of an ORR of 54% and a CR rate of 32%. The median DoR was not reached in patients with CR.[117] A third construct, liso-cel, was approved in late 2020. It differs from the other two products in that the cell product contains a defined population of $CD4^+$ and $CD8^+$ T-cells. The ORR was 73% with a CR rate of 53%, similar to those of the first two constructs (46.8%-59.4%). After 2 years of follow-up, the estimated DoR, PFS, and OS rates of liso-cel were 49.5%, 40.6%, and 50.5%, respectively. The most common grade ≥3 adverse events were neutropenia in 161 patients (60%), anemia in 101 (37%), and thrombocytopenia in 72 (27%).[118] The long-term follow-up of these three agents demonstrates the curative potential of CAR T-cell therapy in a subset of patients.

Subsequently, in 2022, two randomized trials compared CAR-T therapy to ASCT in second-line therapy for patients with primary refractory disease to first-line therapy (R-CHOP) or relapse within a year, showing improved outcomes with CAR-T. In the Zuma-7 trial, patients were randomly assigned to axi-cel (N = 5,180) or standard care defined as two to three cycles of salvage chemotherapy then ASCT for those with chemosensitive disease (N = 5,179).[119] This study showed a superior CR rate with axi-cel versus standard care (65% vs. 32%) and superior EFS in accordance with the primary endpoint (2-year EFS 41% with axi-cel vs. 16% with standard care). Notably, 2-year OS was 61% with axi-cel versus 52% for standard care, even though 56% of patients in the standard care group subsequently received CAR T-cell therapy. The estimated OS benefit of axi-cel over standard care at 4 years was still significant.[120] A second randomized trial, TRANSFORM, included a similar patient population: 184 patients with primary refractory DLBCL or relapse within 12 months of first-line therapy randomized to either liso-cel or standard care (three cycles of salvage then ASCT in chemotherapy-sensitive disease).[121] Similar to Zuma-7, an improved EFS was observed with CAR-T therapy (10.1 months with liso-cel vs. 2.3 months after standard care), and at 3 years of follow-up, the median PFS was not reached for liso-cel and was 6.2 months for standard care.[122] Based on these data, CAR-T-cell therapy using axi-cel and liso-cel has gained approval for second-line use in refractory/early relapsing DLBCL, and it has emerged as an important option.

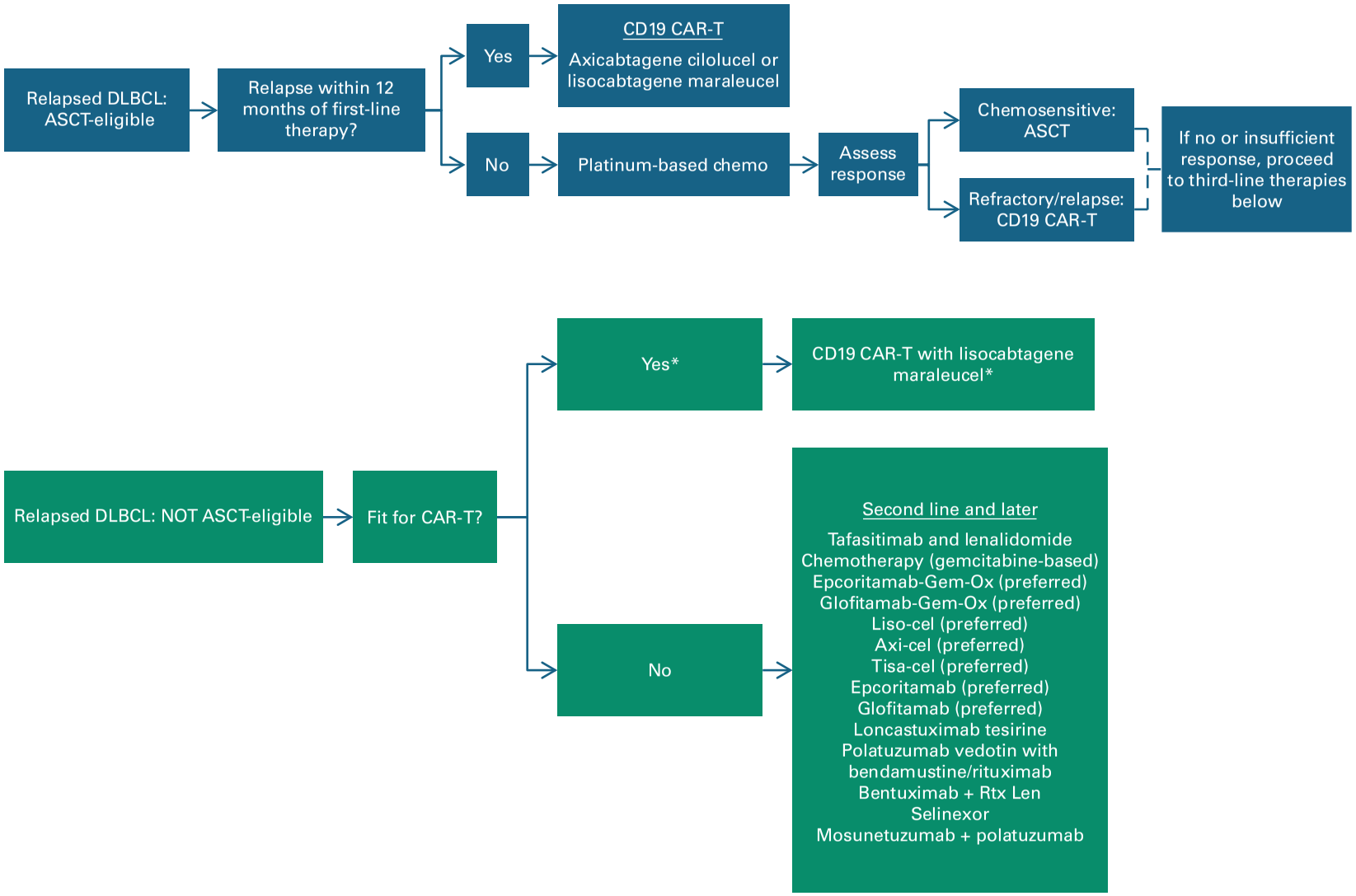
An additional second-line approval for CAR-T followed the PILOT trial, testing liso-cel specifically in patients who have DLBCL who were ineligible for ASCT based on prespecified criteria, including age 70 or older, ECOG 2, or impaired organ function.[123] This phase 2 study treated 61 patients with liso-cel, noting an 80% ORR (54% CR), median DoR 12 months, and only one case of grade 3 CRS with no treatment-related deaths. With a median follow-up of 18 months, the PFS and OS rates were 43% and 59%, respectively.[124] Thus, for patients ineligible for ASCT after second-line therapy who are eligible for CAR-T therapy, liso-cel is an effective treatment option.

Based on this rapidly evolving data, CAR-T therapy has become an important treatment option for relapsed DLBCL-NOS as well as DLBCL arising from FL, grade 3b FL, and PMBL. High-grade B-cell lymphomas (including DLBCL/HGBCL-MYC/BCL2) appear to achieve similar benefit from CAR-T therapies, though representing off-label use. Comparative studies between CAR-T-cell therapies are lacking, and critical questions remain related to their cost-effectiveness, efficacy in less common aggressive B-cell NHL subtypes (Richter transformation, secondary CNS lymphoma), the best measurement of tumor CD19 expression, and its relationship to CAR-T efficacy, and the best choice of bridging therapy to achieve disease control during cell manufacturing while avoiding T-cell depletion and excess myelotoxicity. Toxicities of CAR-T are significant and include CRS, neurologic toxicity (ICANS), cytopenias, infections, and potentially secondary malignancies; these require careful patient selection, monitoring, and prompt intervention based on defined algorithms at qualified centers.

The newest and most promising class of active agents in DLBCL is the bispecific antibodies (reviewed by Falchi et al.).[125] There are two bispecific CD20-directed CD3 T-cell engagers approved by the FDA in DLBCL, epcoritamab and glofitamab. These agents, as well as additional agents, are in development and represent an important emerging class of lymphoma therapy. The major toxicity of these agents is CRS, which occurs in 40% to 70% of patients, and various strategies have been used to decrease the risk of severe CRS with these agents. Corticosteroids, acetaminophen, and antihistamines should be administered before the agents during the first cycle of treatment, and the drugs are given in step-up dosages to reduce the risk of CRS. In addition, a dose of the anti-CD20 monoclonal antibody obinutuzumab is given before glofitamab to deplete circulating B cells and reduce the risk of severe CRS. Epcortamab and glofitamab were both granted accelerated approval by the FDA in 2023 for the treatment of DLBCL after two or more lines of prior therapy based on single-arm phase 2 studies.[126,127] These two agents have the same targets (CD20 and CD3) but differ in their dosing strategy and delivery. Epcoritamab is given subcutaneously until disease progression or unacceptable toxicity, whereas glofitamab is given as an intravenous infusion for a fixed duration of up to 12 cycles. In the phase 2 study, epcoritamab was given to 157 patients with an ORR of 63% with a CR rate of 39% and DoR of 12 months and a CRS rate of 50%. Quite similarly, glofitamab was given to 154 patients with an ORR of 56% and a CR rate of 43% with a median DoR of 18.4 months and a CRS rate of 63%.

Given the clear activity of bispecific antibodies in DLBCL, these agents are currently being tested alone and in combination with other agents in all lines of lymphoma therapy. The most important outcome so far has been the results of the randomized phase 3 STARGLO trial of glofitamab plus gemcitabine and oxaliplatin (GemOx) versus R-Gem-Ox in patients with relapsed or

Figure 20-4 Approach for Relapsed DLBCL



Abbreviations: ASCT, autologous stem cell transplantation; chemo, chemotherapy; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GemOx, gemcitabine-oxaliplatin.
*Patient features should mirror eligibility of the PILOT trial[123]: 70 years or older, ECOG 2, or impaired organ function.
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refractory DLBCL after at least one prior therapy who were not eligible for ASCT.[7] This study randomized 274 patients from Asia, Australia, Europe, and North America in a 2:1 fashion of glofitamab-GemOX for eight cycles plus four additional cycles of glofitamab monotherapy versus R-GemOx for eight cycles. The patients in the glofitamab-GemOx arm had a significantly better median OS of 25.5 months versus patients in the R-GemOx arm with a median OS of 12.9 months (HR = 0.62). Although not FDA approved in the United States, this regimen is a new option for patients with relapsed or refractory DLBCL who are ineligible for ASCT after at least one prior therapy. For patients with R/R DLBCL ineligible to receive intensive therapies, including ASCT and CAR T cells, there have been additional drug approvals in recent years. In June 2019, the FDA approved polatuzumab vedotin-piiq (pola) for the treatment of R/R DLBCL in combination with BR after at least two prior therapies. In a randomized comparison, pola and BR afforded an end-of-treatment ORR of 45% and a CR rate of 40%, superior to the control arm of BR (ORR, 17.5%).[128] After a median follow-up of 22.3 months, median PFS and median OS were also improved by the addition of pola compared with BR alone (9.5 and 12.4 months vs. 3.7 and 4.7 months, respectively). Infectious prophylaxis and growth factor support must be considered in patients treated with pola and BR. The combination of pola plus mosunetuzumab (mosun), a CD20-directed CD3 T-cell engager, was evaluated against R-GemOx in a randomized phase 3 trial in patients with relapsed DLBCL who were ineligible for autoHSCT, and pola-mosun demonstrated a significantly longer PFS of 11.5 months versus 3.8 months with R-GemOx. There were infrequent CRS events in the pola-mosun group along with fewer chemotherapy-associated toxicities.[129] Pola-mosun is now another option available for patients with relapsed disease who are ineligible for autoHSCT.

In July 2020, the FDA approved tafasitamab-cxix, a CD19-directed cytolytic antibody, indicated in combination with lenalidomide for adults who have R/R DLBCL-NOS, including DLBCL arising from low-grade lymphoma, who are not eligible for ASCT. Half of the patients had received only one prior line of therapy. The L-MIND study coadministered intravenous tafasitamab (12 mg/kg) and oral lenalidomide (25 mg/day) for up to 12 cycles (28 days each), followed by tafasitamab monotherapy (in patients with stable disease or better) until disease progression.[130] The ORR in 71 patients was 55% with CR and PR rates of 37% and 18%, respectively. Although the PR remission duration was short, 93% of CR patients sustained the remission at 18 months of follow-up.

In April 2021, the FDA approved the CD19-based ADC loncastuximab tesirine for relapsed DLBCL and high-grade BCL in which at least two prior therapies have failed, based on the LOTIS-2 trial.[131] This trial administered loncastuximab tesirine-lpyl, a novel ADC incorporating a pyrrolobenzodiazepine cytotoxic payload, every 3 weeks until progressive disease or unacceptable toxicity. The ORR was 48% with a CR rate of 24%; the trial included patients with refractory, transformed, or high-grade B-cell lymphoma. Loncastuximab tesirine-lpyl represents another option for treating R/R DLBCL and variants ineligible for cellular therapies (eg, CAR-T cells and ASCT) or when these therapies have failed. In the absence of comparative trials or definitive assays predicting response, careful consideration of toxicity profiles, disease features, prior therapies, patient preferences, medical comorbidities, and logistics is required when selecting among these options.

Whereas the oral exportin-1 inhibitor selinexor is approved for R/R DLBCL-NOS, its modest activity and toxicity may lead to a minimal clinical role alongside other options.[132]

KEY POINTS

- DLBCL is the most common and prototypical aggressive lymphoma.
- IPI is the most commonly used prognostic tool.
- Molecular classifications, including the most commonly used COO, currently provide prognostic information and may inform treatment strategies in the future.
- *MYC* rearrangement with or without *BCL2* is a poor prognostic feature in DLBCL.
- Early-stage DLBCL is increasingly treated with immunochemotherapy alone without RT, using PET scanning to tailor therapy.
- Patients with nonbulky disease and lacking IPI risk factors or with a negative PET/CT after three cycles of R-CHOP can be treated with four cycles of R-CHOP alone.
- Aggressive NHLs are potentially curable and require prompt initiation of therapy soon after the diagnosis to ameliorate symptoms, avert rapid progression of the disease, and optimize survival.
- Calculation of the IPI for a patient at the time of diagnosis with DLBCL permits estimation of projected survival on the basis of individual clinical characteristics.
- DLBCL is the most common aggressive NHL, and it is a heterogeneous disease with clinical and genomic variants. With a combination of anthracycline-containing chemoimmunotherapy, it has a cure rate of approximately 60% to 70%.[133,134] Current first-line options are R-CHOP or the newer combination of pola-*R*-CHP.
- The presence of dual *MYC* and *BCL2* rearrangements defines DLBCL/HGBCL-MYC/BCL2, a unique entity with poor prognosis when treated with standard R-CHOP treatment.
- CD-19-directed CAR-T-cell therapy is the treatment of choice for patients who have primary refractory or early relapsed DLBCL. If the patient is not transplant or CAR-T eligible, tafasitamab-cxix with lenalidomide (tafa-len) is a reasonable option.

- Patients who have relapsed more than 1 year following first-line treatment with chemosensitive disease are candidates for high-dose chemoimmunotherapy plus ASCT with curative intent, or if patients are not transplant-ineligible DLBCL, consider CD-19-directed CAR-T-cell therapy.
- Epcoritamab and glofitamab are bispecific CD20-directed CD3 T-cell engagers FDA approved for R/R DLBCL after two or more lines of prior therapy.
- Glofitamab plus gemcitabine and oxaliplatin and polatuzumab vedotin plus mosunetuzumab are new options for patients with relapsed or refractory DLBCL who are ineligible for ASCT, although not approved by the US FDA.
- Other FDA-approved regimens for R/R disease include polatuzumab vedotin (pola), tafa-len, loncastuximab tesirine, and selinexor; all have unique mechanisms of action and toxicity profiles but do not produce long-term disease control for most patients with R/R DLBCL.

MANTLE CELL LYMPHOMA

INTRODUCTION AND BACKGROUND

MCL is an uncommon NHL subtype that occurs in approximately 3,000 to 5,000 patients per year in the United States. For unclear reasons, there is a strong predilection for male sex at a ratio of three to one. The median age at onset is 70 years. The malignant cells characteristically express CD20 and CD5, features shared with CLL. However, MCL does not express CD23 (a feature of CLL) or CD10 (found in most cases of FL). Diagnosis is confirmed by the presence of mature $CD20^+$ $CD5^+$ B cells with cyclin D1 overexpression, most commonly resulting from t(11;14)(q13;q32).

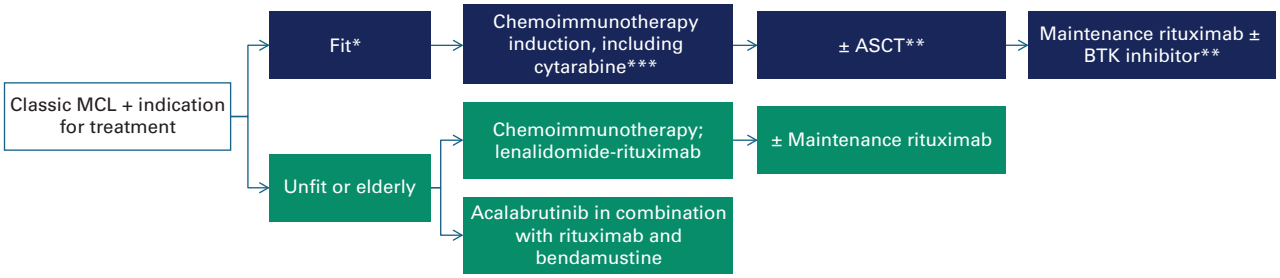
Three main clinicopathologic MCL variants have been described, including classic MCL, blastoid MCL, and indolent MCL. SOX11 is positive in classic and blastoid MCL but is frequently absent in indolent MCL, which presents with splenomegaly and lymphocytosis and has a better initial prognosis. Blastoid MCL presents with large and variable cell size and a high proliferation index, typically accompanied by complex cytogenetic abnormalities and abnormalities of *TP53* and an aggressive clinical course. Classic MCL is most common and presents with both adenopathy and extranodal involvement of the GI tract (lymphomatous polyposis) or with peripheral blood lymphocytosis. A vast majority of patients have bone marrow involvement at diagnosis.

Prognosis in MCL is affected by clinical and biologic features. The Mantle Cell Lymphoma International Prognostic Index (MIPI) stratifies patients into low-, intermediate-, and high-risk groups based on a calculation that involves age, PS, LDH level, and leukocyte count; the MIPI-c further incorporates a proliferation index based on Ki67 immunohistochemical staining, with ≥30% associated with poor prognosis.[135] Mutation of the *TP53* gene, although present in a minority of cases of newly diagnosed MCL, is associated with chemoresistance and poor outcomes even with intensive therapy, including ASCT, and genetic sequencing is now regarded as essential testing at the time of initial diagnosis.

FIRST-LINE SYSTEMIC THERAPY FOR MCL

Although MCL is highly heterogeneous, the majority of patients present with advanced-stage disease and symptoms related to lymphadenopathy, effusions, or extranodal disease. Patients who do not have any symptoms or the indolent MCL variant may safely undergo expectant management (observation) instead of receiving immediate therapy. Goals of first-line therapy in MCL include alleviation of symptoms and organ dysfunction and attainment of long-lasting remission, although even with highly effective therapy, relapses are inevitable for most patients. The MIPI prognostic index, although useful in discriminating high-risk

Figure 20-5 Treatment Algorithm for MCL



Abbreviations: ASCT, autologous stem cell transplantation; BR, bendamustine and rituximab; BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma; R-CHOP, rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone.
Chemoimmunotherapy includes BR; R-CHOP; and VR-CAP.
*"Fit" patients are generally aged 65 or younger, without comorbidities precluding myelotoxic chemoimmunotherapy and potential ASCT.
**Regimens are varied; see published treatment guidelines.
***Cytarabine chemotherapy with a BTK inhibitor for 2 years (and no ASCT) is supported by the randomized TRIANGLE study.[140]
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patients who may benefit from clinical trials or novel approaches, has not been validated in the context of first-line treatment selection (Fig. 20-5).

The standard approach to first-line therapy for classic MCL (without *TP53* mutation) depends on age and eligibility for intensive, myelotoxic therapy. Specific regimens are varied and best considered in the context of treatment guidelines[136] and/or tertiary lymphoma center consultation. The general strategies, with merits/disadvantages, are as follows:

1. Younger (generally age 65 or under) patients, fit/eligible for intensive therapy: cytarabine-containing chemoimmunotherapy, then consolidation ASCT, and 3 years of rituximab maintenance.
    a. Merits: High probability of CR; prolonged remissions often exceeding 5+ years depending on MIPI.
    b. Disadvantages: No conclusive long-term survival benefit from randomized trials. High-dose cytarabine is associated with severe myelotoxicity with risk of infection and potential transfusion requirements. Consolidation ASCT carries unique, additional risks of severe myelo- and organ toxicity, treatment-related MDS/AML, and treatment-related mortality.
2. Older patients >65 or ineligible for intensive therapy: lower intensity chemoimmunotherapy, consideration of rituximab maintenance.
    a. Merits: Lower risk of severe myelotoxicity/neutropenia and acute infections and treatment-related mortality.
    b. Disadvantages: Shorter remissions (median PFS about 5 years or less), risk of late infections after bendamustine and in the setting of rituximab maintenance.

Randomized clinical trial data on the selection of first-line treatment is scarce, but some key examples have demonstrated the following:

- Cytarabine-containing therapy improves depth of response and EFS over R-CHOP induction therapy in younger patients receiving ASCT, but at a cost of greater toxicity.[31]
- Three years of rituximab maintenance after ASCT improves both PFS (83% vs. 64%; $P < .001$) and OS (89% vs. 80%; $P = .04$).[137]
- In patients 65 or older with MCL, the SHINE trial demonstrated a PFS benefit with the addition of long-term ibrutinib therapy to BR induction (over BR alone). However, there was no survival benefit because of excess non-lymphoma deaths in the experimental arm, a finding that influenced the withdrawal of ibrutinib's indication for treatment of MCL in the United States.[138]
- On January 16, 2025, the FDA approved acalabrutinib combined with bendamustine and rituximab for adults with previously untreated MCL who are ineligible for autologous HSCT. This decision was based on the ECHO trial, which randomized ~600 patients aged 65 or older to receive either acalabrutinib + BR or BR + placebo. Adding acalabrutinib in this transplant-ineligible, older population significantly prolonged progression-free survival by approximately 16 to 17 months compared to BR alone, with slightly increased side effects that were generally manageable.[139]

This paradigm, in particular the role of ASCT for consolidation of response, is rapidly evolving as data from randomized trials testing first-line BTK inhibitors and novel, response-adapted strategies become available. In particular, although preliminary, the TRIANGLE trial tested the role of ibrutinib induction and the additive value of consolidative ASCT in a three-arm, randomized trial including 870 younger, fit MCL patients.[140] The three arms included cytarabine-containing chemoimmunotherapy then ASCT for patients with a response (arm A, the current standard of care); the same treatment and ibrutinib for 2 years (A + I); and chemoimmunotherapy and ibrutinib without ASCT (arm I). At 31 months of follow-up, the standard arm A was no better than arm I; in fact, it had numerically worse FFS than the ibrutinib-containing, nontransplant arm. The best 3-year FFS rate was achieved in the combination arm A + I (88%) compared with 72% in arm A ($P < .05$). Whereas arm A + I was also the most toxic during the maintenance phase, the authors conclude that BTK inhibition may benefit young, eligible patients with MCL as part of first-line therapy and call into question the universal application of ASCT. Further key details (outcomes based on induction response) and more follow-up are needed to better inform clinical decision-making using these results.

RELAPSED/REFRACTORY MCL

Patients who have MCL face a continual risk of relapse even after long-term remissions. Treatment options for R/R MCL range from chemoimmunotherapy to novel agents, including bortezomib, lenalidomide, and BTK inhibitors, to transplant or CAR-T cellular therapies. The BTK inhibitors acalabrutinib and zanubrutinib, administered on a continuous oral basis, represent the mainstay of second-line MCL therapy. Phase 2 trials with these agents demonstrate an ORR of approximately 80%, although a minority achieve CR, and median PFS is under 2 years.[141,142] Contusion/hemorrhage, infection, and neutropenia are well-described

risks. Notably, ibrutinib was withdrawn from the market due to its less favorable toxicity profile and data from the SHINE trial. Bortezomib and lenalidomide ± rituximab provide responses in a minority of R/R MCL patients and tend to be of shorter duration (PFS <1 year).

A noncovalent and highly specific BTK inhibitor, pirtobrutinib, was approved in January 2023 for relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor. Approval was based on demonstration of an ORR of 58% in a phase 1/2 trial of 90 patients with R/R MCL, the vast majority of whom had received another BTK agent with low rates of severe adverse events.[143]

Despite the efficacy of this class, most patients who have MCL ultimately experience disease progression and require additional therapy, and rapid progression has been reported on cessation of BTK inhibitors. CAR-T-cell therapy in MCL with brexucabtagene autoleucel, which targets CD19, resulted in an objective response rate of 87%, including a 62% CR rate, in 68 patients reported from the single-arm ZUMA-2 study.[144] Patients in this trial had a median age of 65 and three prior lines of therapy, and all had received treatment with a BTK inhibitor; toxicities included severe (grade 3 or higher) CRS and neurologic events in 15% and 31% of patients, respectively. After a median follow-up of 3 years, the objective response rate was 91%, including 61% CRs. The median DoR, progression-free survival, and OS were 28.2, 25.8, and 46.6 months, respectively.[145] In cohort 3 of ZUMA-2, which included patients with R/R MCL who were naive to BTK inhibitors, the efficacy was similar to that in cohort 1 of ZUMA-2 (which consisted of BTK-exposed patients).[146] High efficacy was also observed with liso-cel, including CR in 72% of patients and PFS of 15.3 months with lower observed rates of grade 3 or higher CRS and neurologic events (1% and 9%, respectively).[147] These CAR-T-cell therapies represent intensive but important options for patients with MCL, particularly with multiply relapsed disease, short remissions, and/or failure of BTK inhibitor-based therapy. Similarly, allogeneic HSCT remains an option for the highest risk, fit patients, including those with *TP53*-mutated, refractory MCL, but would generally be considered after CAR-T therapy, given the risk of complications and treatment-related mortality.

KEY POINTS

- MCL is a heterogeneous disease. Those with an indolent variant can often forgo initial therapy, although most will need treatment eventually.
- *TP53* sequencing is regarded as a standard component of biopsy evaluation in the workup of newly diagnosed MCL.
- Induction chemotherapy for classic MCL includes high-dose cytarabine and ASCT, followed by rituximab maintenance for young and eligible patients, but the advancement of BTK inhibitors into first-line therapy may soon change this paradigm.
- Older and ineligible patients have several first-line treatment options, including BR. If rituximab maintenance is used, attention to toxicity and particularly infections is required, particularly after bendamustine induction.
- Acalabrutinib in combination with rituximab and bendamustine is an option for transplant-ineligible older population with significant improvement in progression-free survival.
- R/R MCL is generally treated with a covalent BTK inhibitor with subsequent options, including the new noncovalent pirtobrutinib and CAR-T therapy.

LYMPHOBLASTIC LYMPHOMA

Lymphoblastic lymphoma is an aggressive neoplasm that typically presents in young men (median age, 16 years) with mediastinal masses. The tumor exhibits an immature T-cell immunophenotype with expression of CD7, cytoplasmic CD3, and TdT. Rearrangements of the T-cell receptor genes are virtually always present, and activating *NOTCH* mutations are present in a majority of cases. The clinical distinction between lymphoblastic lymphoma and T-cell acute lymphoblastic leukemia (ALL) is based on an arbitrary definition that assigns diagnosis as T-cell ALL if the bone marrow contains >25% lymphoblasts and lymphoblastic lymphoma if it contains less than 25%. The presence of an elevated serum LDH level and bone marrow or CNS involvement confers an unfavorable prognosis. The treatment of lymphoblastic lymphoma mirrors that of ALL; please refer to Chapter 19: Leukemias.

KEY POINT

- Lymphoblastic lymphoma is an aggressive lymphoma that expresses immature markers (ie, TdT) and is treated similarly to ALL.

BURKITT LYMPHOMA

Burkitt lymphoma is a highly aggressive tumor characterized by an exceptionally high proliferation rate (Ki67 score, approximately 100%), mature B-cell immunophenotype (monoclonal surface IgM and CD10, CD19, CD20, CD22, BCL6, CD38, and CD43 expression), and histologic appearance demonstrating diffuse infiltration with a starry sky pattern of macrophages phagocytosing apoptotic tumor cells. All cases of Burkitt lymphoma possess a translocation of the *MYC* oncogene at band 8q24, most commonly associated with a t(8;14) translocation, although t(2;8) and t(8;22) translocations involving k and l loci, respectively, also

occur. The three forms are endemic, sporadic, and HIV-associated. The endemic version occurs in certain parts of sub-Saharan Africa, typically presenting as jaw tumors in children, and is almost always associated with EBV. Sporadic cases occur elsewhere in the world, often presenting with ileocecal masses, and are associated with EBV in less than 30% of cases. Burkitt lymphoma is approximately 10 times more common in people who have HIV and occurs in patients who have long-term HIV viremia and relatively well-preserved $CD4^+$ T-cell counts. Despite its aggressive nature, more than 90% of children and 75% to 80% of adults are cured with highly dosage-intensive chemotherapy. Adult patients can be stratified into risk categories based upon the Burkitt Lymphoma International Prognostic Index (BL-IPI),[148] with patients given one point each for each factor:

- CNS involvement
- LDH is more than three times the institutional upper limit of normal
- ECOG PS score ≥2
- Age ≥40 years

According to the BL-IPI, patients who have no risk factors have low-risk disease, patients who have one risk factor have intermediate-risk disease, and patients who have two or more risk factors have high-risk disease.

Burkitt lymphomas are characterized by a rapid growth rate, and treatment may be associated with potentially fatal tumor lysis syndrome and renal failure. Biochemical abnormalities should be corrected, and patients should receive vigorous hydration as well as prophylactic rasburicase (in patients with LDH more than two times the upper limit of normal or bulky disease) or xanthine oxidase inhibitors (allopurinol) before treatment. Rasburicase is contraindicated in patients with G6PD deficiency. All variants of Burkitt lymphoma are treated with the same approach involving intensive chemotherapy regimens. The choice of treatment regimen may be based on risk category and the presence of CNS disease (reviewed in Roschewski et al).[149] The addition of rituximab to chemotherapy improved 3-year EFS in one randomized trial of adults with Burkitt lymphoma, and it is standard to include rituximab in the treatment of all patients with Burkitt lymphoma.[149] *R*-CODOX-M/IVAC, which is a highly intensive regimen with alternating courses of cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M) and courses of mesna and ifosfamide, etoposide, and cytarabine (IVAC) and intrathecal methotrexate and cytarabine, is a well-studied, highly intensive regimen in adults, including people who have HIV. *R*-CODOX-M/IVAC is associated with a 2-year 65% to 80% EFS in various series, depending on patient selection factors.[150-152] DA-EPOCH-R was studied in a prospective, multicenter trial in Burkitt lymphoma using a risk-adapted approach with a 4-year EFS survival rate of 85% regardless of age or HIV status.[153] In this study, patients who had low-risk disease received three cycles of DA-EPOCH-R without CNS prophylaxis, and patients who had high-risk disease received six cycles of treatment with intrathecal prophylaxis or active treatment. DA-EPOCH-R is not appropriate for patients who have parenchymal CNS disease. A randomized trial compared DA-EPOCH-R and *R*-CODOX-M/IVAC in patients with high-risk Burkitt lymphoma without CNS involvement. Although the study was closed prematurely because of slow accrual, there was no significant difference in 2-year PFS between the two regimens, but *R*-CODOX-M/IVAC was associated with more severe toxicity.[154]

Nearly all cases of relapsed or refractory Burkitt lymphoma are fatal. R/R disease is generally treated with aggressive second-line chemotherapy regimens followed by consideration of either autologous or allogeneic HSCT, but consideration for clinical trials is the best option.

KEY POINTS

- Burkitt lymphoma is an aggressive lymphoma characterized by *MYC* rearrangement, lack of *BCL2* expression, and extremely high proliferation index.
- Treatment consists of intensive chemotherapy regimens in combination with rituximab in a risk-adapted approach.
- Cure rates are high overall with intensive, multi-agent regimens, although regimens are associated with significant toxicity.
- Patients with relapsed or primary refractory disease have few treatment options and are rarely cured.

PRIMARY CNS LYMPHOMA

Primary CNS lymphomas (PCNSLs) are uncommon de novo lymphomas limited to brain structures, including brain parenchyma, leptomeninges, eyes, and spinal cord. Intraocular involvement is seen in 10% to 20% of cases. These are usually aggressive BCLs, with DLBCL being the most common. PCNSL can occur in both immunocompromised (eg, people who have HIV with very low CD4 T-cell counts, associated with EBV infection) and immunocompetent patients. Among immunocompetent patients, the median age is 60 years.

Patients typically present with symptoms related to mass effect or infiltration with neurologic compromise and symptoms. The diagnosis generally requires a tissue diagnosis, usually via a stereotactic biopsy or CSF analysis, although compatible magnetic resonance imaging findings in conjunction with expert consultation may support initiation of therapy for PCNSL without

histologic confirmation in some cases. If possible, it is important to avoid steroids, which are lympholytic, before planned biopsy because of the risk of a false-negative result/nondiagnostic biopsy with necrosis. If there is concern for irreversible neurologic compromise or impending herniation, avoiding steroids may not be possible. Histopathology shows a dense diffuse infiltrate of large B cells that are positive for CD20, CD19, and *PAX5* and often of a nongerminal center phenotype with MUM1 positivity.[10] Diagnostic and staging evaluation should also include a lumbar puncture (if safe to perform); slit-lamp eye examination; CT scan of the chest, abdomen, and pelvis; bone marrow biopsy; and an HIV test. For men aged >60 years, testicular examination and ultrasonography should also be performed.

The most frequently used regimens to treat PCNSL include high-dose methotrexate. High-dose methotrexate (minimum dose, 3 g/m^2) with or without high-dose cytarabine produces superior results compared with RT alone, with a median survival of 51 months.[155-157] In the setting of HIV-associated PCNSL, high-dose methotrexate along with ART can be used with curative intent, often without consolidation therapies, particularly if ART results in immune reconstitution.[158] Given the significant morbidity and long-term side effects of whole-brain radiation (WBRT), it is generally used only in the salvage setting.[159]

Radiation-sparing approaches include chemotherapy induction, high-dose methotrexate induction followed by either HDC or ASCT[160-162] and/or induction followed by chemotherapy consolidation.[163] Common induction regimens include methotrexate with temozolomide or rituximab with methotrexate, vincristine, and procarbazine. ASCT consolidation has impressive results with long-term PFS over 50%, similar to WBRT, but with less impairment in cognitive function as demonstrated by the randomized IELSG32 and PRECIS trials.[160,163] The addition of intravenous administration of rituximab may also improve outcomes and is standard in first-line therapy for PCNSL.[164]

The management options for R/R PCNSL are limited overall, but several exciting agents and approaches are in development. If patients have not undergone prior HDC and ASCT, this may be an option if salvage regimens can be safely delivered and if there is chemotherapy-sensitive disease.[165] WBRT is also used either with or without preceding salvage chemotherapy. Temozolomide, ibrutinib, lenalidomide, CAR-T-cell therapy, and intraventricular rituximab have also demonstrated activity in salvage settings.[166]

KEY POINTS

- PCNSL is a clinical variant of DLBCL that occurs exclusively in CNS structures, which may include the brain parenchyma, eyes, leptomeninges, and spinal cord.
- Treatment requires CNS-penetrating agents, usually high-dose methotrexate in the upfront setting.
- In the setting of HIV-associated PCNSL, high-dose methotrexate along with ART can be used with curative intent.

LYMPHOMAS ASSOCIATED WITH IMMUNODEFICIENCY

Acquired and iatrogenic immune suppression increases the risk of many types of lymphomas. Among people who have HIV, DLBCL, Burkitt lymphoma, plasmablastic, primary effusion lymphoma, primary CNS lymphoma, and cHL are the most common subtypes, but TCLs also occur at higher rates. Compared with the general population, people who have HIV typically present with more advanced-stage disease, including extranodal and leptomeningeal disease. In the era of effective ART, the incidence of lymphomas associated with profound immune suppression and low CD4$^+$ T-cell counts has significantly decreased, and the overall prognosis of HIV-associated lymphomas has substantially improved. Patients who have HIV-associated Hodgkin lymphoma, GCB-DLBCL, and Burkitt lymphoma tend to have higher CD4 counts compared with those with other subtypes; in particular, patients who have HIV-associated PCNSL have the lowest CD4 counts at diagnosis, and HIV-associated PCNSL is rare when ART is readily available.[167] There is a higher incidence of virus-associated lymphomas among people with HIV, including primary effusion lymphoma, which is caused by HHV8, and an increased association with EBV among HIV-associated plasmablastic, Hodgkin lymphoma, DLBCL, and Burkitt lymphoma compared with those without HIV.[168]

Treatment of HIV-associated lymphomas generally follows treatment of lymphoma in the general population, although DLBCL is typically treated with EPOCH-R based on the results of phase 2 trials[169] and metanalyses.[170] HIV-associated Burkitt lymphoma outcomes are similar to those of non-HIV-associated Burkitt lymphoma with a modified version of *R*-CODOX-M-IVAC or DA-EPOCH-R.[153,171] Despite initial concern over increased infectious toxicity with the use of rituximab, a meta-analysis and subsequent prospective trials conducted by the AIDS Malignancy Consortium have shown improved outcomes, and rituximab should be used as part of the treatment regimen for HIV-associated CD20$^+$ lymphomas.[170] Prophylaxis for neutropenic and opportunistic infections is standard, and attention to comorbid conditions (hepatitis B or C) is important. HIV-associated Hodgkin lymphoma can be managed with nivolumab in combination with doxorubicin, vinblastine, and dacarbazine (*N*-AVD) or brentuximab vedotin and AVD (BV-AVD).[172,173] Treatment of HIV-associated lymphomas should be delivered concurrently with ART with the assistance of an HIV specialist to avoid drug-drug interactions. Patients who have R/R disease are treated similarly to their HIV-negative counterparts based on a number of phase 2 trials demonstrating the feasibility of autologous and allogeneic transplantation.

Iatrogenic immunosuppression after solid organ transplantation or HSCT is associated with an increased risk of subsequent lymphomas, termed post-transplantation lymphoproliferative disorders (PTLDs). Iatrogenic T-cell suppression facilitates

EBV-driven B-cell proliferation and consequent PTLD, particularly in cases diagnosed within the first year after transplantation. Therefore, a vast majority of PTLDs are of B-cell origin, although other lymphomas can also occur. Risk factors for PTLD include recipient EBV-seronegative status and duration and intensity of immunosuppressive agents (reviewed by Dharnidharka et al.).[174] Early PTLDs (less than 1-2 years after transplantation) are usually EBV positive and may respond to reduced immunosuppression, whereas later PTLDs are more likely EBV negative and less amenable to reduced immunosuppression.

Confirming a diagnosis of PTLD requires a biopsy specimen. Histopathology can show early lesions (ie, plasmacytic hyperplasia and infectious mononucleosis-like lesions), polymorphic PTLD, monomorphic PTLD (which includes DLBCL and Burkitt lymphoma), or cHL-like PTLD.[10] A rising EBV titer and abrupt-onset adenopathy with constitutional symptoms increase the suspicion for PTLD. The general treatment approach to early-lesion PTLD is prompt reduction of immunosuppression followed by rituximab monotherapy. Phase 2 trials of rituximab monotherapy showed response rates of 40% to 60%.[175,176] The sequential addition of CHOP chemotherapy if there is an inadequate response to rituximab monotherapy improved the response rate to 90%; however, treatment-related mortality was increased by approximately 10%.[177] For patients who have advanced monomorphic PTLD, is it generally treated with standard chemotherapy for the specific subtype (eg, R-CHOP for DLBCL), similar to what is given in the immunocompetent setting. Another potential strategy to treat PTLD is to target EBV. Tabelecleucel is an off-the-shelf, allogeneic, EBV-specific T-cell immunotherapy that was studied in a phase 3 clinical trial in patients with EBV-positive relapsed or refractory PTLD after either HSCT or solid organ transplant, with an objective response rate of ~50%. Tabelecleucel is not currently FDA-approved.[178]

Finally, autoimmune diseases (eg, rheumatoid arthritis, Sjogren disease, and systemic lupus erythematosus) and treatment of autoimmune conditions with immunosuppressive agents are associated with an increased risk of lymphoma.[179,180] Both the specific risk and NHL subtype are variable, and the incidence may be up to sixfold higher compared with populations without autoimmune conditions. Methotrexate is the most common offending agent. Cessation of immunosuppression is the first step in treatment and can lead to regression of lymphoma without the requirement for additional treatment in a large proportion of patients.[181]

KEY POINTS

- Immune suppression (acquired, iatrogenic, or related to underlying autoimmunity) is associated with an increased risk of lymphoma.
- If possible, removing the cause of immune suppression can lead to lymphoma regression, particularly in early PTLD, leading to a stepwise approach. However, late PTLDs act like aggressive lymphomas.
- HIV-associated lymphomas should generally be treated in the same way as lymphoma in the general population, with the addition of ART. Oncologists should work with HIV specialists to help manage potential infectious complications and avoid drug-drug interactions between ART and cancer treatment.

T- AND NK-CELL LYMPHOMAS

OVERVIEW

Lymphomas arising from mature NK and T cells represent 10% to 15% of NHLs in the United States and nearly 30% of NHLs in Asian countries. The term peripheral TCL (PTCL) refers to a diverse group of post-thymic T-cell malignancies that have a mature T-cell phenotype. NK/TCLs are diverse and individually relatively rare entities with nearly 30 defined subtypes. In adult patients, the WHO classification identifies the following TCL groups: mature T/NK leukemias (covered in Chapter 19), primary cutaneous TCLs, intestinal T/NK lymphomas, hepatosplenic TCL, anaplastic large-cell lymphoma (ALCL), nodal T-follicular helper (T_{FH}) cell lymphoma, other PTCL (or PTCL-NOS), and EBV + NK/T lymphomas.[10] Compared with their B-cell counterparts, PTCLs are more often associated with higher risk features, including systemic symptoms and advanced-stage disease. In addition, patients who have PTCL generally have lower response rates to chemotherapy and a higher risk of relapse and death when treated with multi-agent chemotherapy regimens such as CHOP. A prognostic index specific for PTCL (known as the PIT) includes patient age, LDH level, PS, and presence of bone marrow involvement.[182] Poor prognosis is also associated with *p53* expression[183]; high Ki67 proliferation index (>25%); certain chemokine expression profiles (CXCR3 positive/CCR4 negative); and expression of CD56, *BCL2*, or *BCLXL*. A full exposition of the details of this diverse group of disorders is beyond the scope of this chapter and available elsewhere.[184] Given its rarity and clinical/biologic diversity, few trials have been dedicated to NK/TCL, and most treatment paradigms are extrapolated from treatment of aggressive BCLs. Brief descriptions of the most common entities and general treatment principles follow.

PERIPHERAL T-CELL LYMPHOMA NOT OTHERWISE SPECIFIED

PTCL-NOS is a provisional group encompassing mature aggressive TCLs not included in the other groups, and it is the most common PTCL (25%-30%). By nature, this category is subject to continuous revision as genetic and/or molecular markers allow

reclassification into known or newer entities. TCL usually presents with paracortical or diffuse nodal infiltration of malignant lymphoid cells expressing T-cell markers, including CD2, CD3, T-cell receptor, and usually CD4. Proving clonality can be difficult because oligoclonal or small clonal T-cell receptor populations can occur in nonmalignant tissue; however, loss or downregulation of T-cell lineage markers, such as CD5 or CD7, is characteristic of these neoplasms.[185] The median age of patients who have PTCL-NOS is 60 years, with a male-to-female ratio of 9:1. Clinically, it is characterized by frequent B symptoms, extranodal involvement, and advanced-stage presentation (69%).

ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

Angioimmunoblastic T-cell lymphoma (AITL) accounts for 18% of TCLs worldwide and typically presents with generalized lymphadenopathy with or without fever, weight loss, and rash with autoimmune phenomena, including hypergammaglobulinemia and a positive Coombs test.[186] The disease is derived from T_{FH} cells with malignant cells typically expressing CD10, *BCL6*, programmed cell death protein 1 (PD-1), and CXCL13 in addition to typical T-cell markers (ie, CD2, CD3, CD5, and CD4). The disease course is frequently complicated by serious, potentially life-threatening infections. AITL is frequently associated with EBV, which plays a pathogenetic role in a proportion of cases. EBV-associated BCL derived from EBV-infected B-cell blasts present in the tumor may also develop during the course of treatment. AITL exhibits frequent mutations in *RHOA* (70%) as well as epigenetic regulators such as *TET2* (82%), *IDH2* (30%), and *DNMT3A* (26%).[187,188]

ANAPLASTIC LARGE CELL LYMPHOMA

ALCL is a malignancy of large pleomorphic mature T lymphocytes that express T-cell surface markers such as CD2, CD4, and CD5, and almost invariably the CD30 antigen (Ki-1). Curiously, the pan T-cell antigen CD3 is negative in >75% of cases. There are two subtypes of ALCL based on the presence or absence of nucleophosmin-ALK t(2;5) translocation: ALK positive and ALK negative.[189] Patients who have ALK-positive ALCL are younger, with a median age at onset of 30 years, and the disease often occurs in pediatric patients. ALK-negative ALCL has a median age at onset of 55 years. ALCL is more common in men and often presents at an advanced stage with frequent extranodal involvement. ALK-positive ALCL has a more favorable prognosis with 5-year survival rates in the 70% to 90% range compared with 40% to 60% for ALK-negative ALCL after anthracycline-containing therapy. A subset of patients with ALK-negative ALCL harboring a *DUSP22* translocation may have outcomes similar to those in ALK-positive ALCL.[32]

GENERAL APPROACH TO NEWLY DIAGNOSED PTCL

Treatment of PTCL is challenging as CHOP is associated with ORRs of 60% to 70%, but long-term disease control of only 25% to 30%[190] and most of the benefit is in IPI low-risk groups. In a retrospective analysis of patients enrolled in sequential German trials, the addition of etoposide to CHOP (CHOEP) improved EFS in patients younger than 60 years, primarily those with ALK-positive ALCL (a subtype of PTCL associated with a more favorable prognosis). On the contrary, this regimen resulted in excessive toxicity in older patients, and ultimately, in neither cohort was an OS difference observed.[191] Despite the limitation of that analysis, CHOEP is sometimes used in younger, fit patients with newly diagnosed PTCL in clinical practice. Over the years, other clinical trials have explored the addition of novel agents (eg, romidepsin, alemtuzumab, lenalidomide)[192-194] to a CHOP-like backbone, largely without success. More recently, the ECHELON-2 randomized phase 3 trial compared CHOP with BV-CHP, in which vincristine in CHOP was replaced with the ADC brentuximab vedotin (BV-CHP).[195] In this 452-patient study, BV-CHP yielded a PFS of 48 months compared with 21 months with CHOP alone. OS and ORR were also significantly improved in the experimental arm. Although several subsets of PTCL were eligible for this trial and minimal CD30 positivity (the target of brentuximab vedotin) was required, 70% of the patients had ALCL (a subtype for which CD30 positivity is a diagnostic hallmark). The results of the ECHELON-2 trial led to US FDA approval of BV-CHP for all newly diagnosed $CD30^+$ PTCLs in November 2018.

Results of nonrandomized trials suggest an advantage to consolidative HDC and autologous stem cell support (HDT-ASCS) in patients who have newly diagnosed PTCL achieving CR to induction chemotherapy with a 60% PFS rate. Registry studies also suggest an advantage with this approach, with a 5-year OS of 48% versus 26% in favor of patients undergoing consolidative HDT-ASCS versus those who did not.[196,197] Similar benefits were seen in the ECHELON-2 study, with the caveat that only 16% of patients underwent HDT-ASCS, and this treatment was not randomly allocated.[198] It is important to note that achieving a CR to chemotherapy is the prerequisite for considering HDT-ASCS consolidation. Therefore, studies suggesting a benefit of this procedure generally carry a selection bias in that they only include chemosensitive patients (who inherently have a better prognosis than those with chemorefractory disease). In sum, although often considered in clinical practice, HDT-ASCS consolidation for patients with PTCL in first remission after induction chemotherapy is not supported by randomized controlled studies, and its clinical benefit remains uncertain.[198]

RELAPSED/REFRACTORY PTCL

Treatment options for patients who have R/R PTCL are limited, and the inability to offer effective salvage treatment to patients precludes opportunities for an allogeneic stem cell transplantation (alloSCT, the only curative therapy) in the majority of patients.

Historical population-based data show a median OS of less than 6 months for patients with relapsed PTCL,[199] though this notion may be changing in the era of new agents. Three agents are approved for use in relapsed PTCL based on the results of large phase 2 trials: pralatrexate, brentuximab vedotin (for CD30$^+$ disease), and belinostat. Pralatrexate is a competitive inhibitor of dihydrofolate reductase and inhibits polyglutamylation via the folylpolyglutamyl synthetase enzyme. A CR rate of 11% and a PR rate of 18% with a 10.1-month response duration were reported.[200] Belinostat is a histone deacetylase (HDAC) inhibitor and indicated response rates of 25% to 40%; despite a modest response rate, remissions can be durable. Brentuximab vedotin, an ADC against CD30, is highly active with single-agent response rates of 85% (CR >50%) in R/R ALCL and other CD30$^+$ TCLs, but it is less useful in the R/R setting if administered first line.[201] Romidepsin is another HDAC inhibitor with previous approval in R/R PTCL,[202] now only available through a restricted access program[203] because of failure to confirm efficacy in a randomized controlled trial.[192] Clinical trial enrollment should be prioritized for patients with R/R PTCL and HDT-ASCS (if not performed after first-line therapy), or alloSCT should be considered whenever feasible in patients who achieve a second or subsequent remission. Duvelisib is a dual PI3K-δ,γ inhibitor and was evaluated in a phase 2, open-label, multicenter, parallel cohort PRIMO trial in R/R PTCL.[204] The initial results of the dose-optimization phase (N = 33) demonstrated a 54% ORR in the 75 mg twice daily (N = 13) and 35% in the 25 mg twice daily (N = 20) cohorts.

Patients who have relapsed ALK + ALCL may be treated effectively with ALK inhibitors such as crizotinib or ceritinib (the latter is not FDA approved). In a small phase 2 study in 14 patients with ALK-positive lymphomas, crizotinib led to an objective response rate of 60%.[205] Recent long-term follow-up data support the preferential use of next-generation ALK inhibitors in relapsed or refractory ALK-positive lymphomas. In a 5-year, phase 2, single-center, open-label study, lorlatinib demonstrated rapid and strong anti-lymphoma activity in patients previously treated with chemotherapy, immunotherapy, and earlier-generation ALK inhibitors, including crizotinib. All participants responded within 1 month, with four of seven achieving CRs, two of which have been sustained for up to 56 months. Responses were especially durable in those achieving early complete remission, and lorlatinib was generally well tolerated, with mostly mild to moderate adverse events, highlighting its value as a salvage therapy and potential bridge to alloSCT.[206] Likewise, alectinib was evaluated in a phase 2, single-arm, open-label, multicenter trial in Japan in patients with relapsed or refractory ALK-positive ALCL. Given at standard oral doses, alectinib achieved a high ORR, with a significant proportion of patients attaining durable CRs. The therapy was well tolerated and formed the basis for its regulatory approval in Japan for this patient population.[207]

PRIMARY EXTRANODAL NK/TCL

Enteropathy-Associated TCL

Enteropathy-associated TCL (EATL) accounts for approximately 5% of TCLs and is more common in geographical areas with a higher incidence of celiac disease, including North America and Europe. Patients typically present with pain, weight loss, and bowel perforation.[208] Cases associated with celiac disease typically exhibit a pleomorphic histology and express CD3 and CD7, but not CD56, whereas patients who do not have celiac disease often display a monomorphic histology and express CD56. Up to 70% of cases of EATL contain gains at chromosome 9q33-q34.[209] Conventional therapy consists of CHOP with a median OS of only 10 months in one international series of 62 patients and a median FFS of only 6 months.[208] The presence of clinical sprue and an adverse PIT score both predicted poor survival independently. One study suggested that outcomes with EATL may be improved by inducing remission with a novel regimen of ifosfamide and etoposide and epirubicin alternating with intermediate-dose methotrexate followed by consolidation with ASCT.[210] This approach yielded a 5-year PFS rate of 52% and an OS rate of 60% among 26 patients who underwent transplantation. Monomorphic epitheliotropic intestinal TCL, formerly considered a variant of EATL, is now recognized as a distinct subtype of intestinal TCL[211] for which optimal treatment has not yet been identified.

Hepatosplenic Gamma-Delta TCL

Hepatosplenic gd TCL is a rare disease, predominantly affecting young men, derived from immature or nonactivated gd T cells. Recurrent genetic abnormalities include isochromosome 7q, trisomy 8, activating mutations of the JAK/STAT pathway (ie, STAT5B, STAT3), and chromatin-modifying genes (ie, *SETD2*, *INO80*, *ARID1B*).[212] This lymphoma typically infiltrates the liver, spleen, and marrow sinusoids with minimal adenopathy.[209] Patients often present with fever, chills, and other systemic symptoms. Cytopenias, especially thrombocytopenia, are typical and often accompanied by hemophagocytic syndrome. Outcome is generally poor, and the recommended induction regimen comprises aggressive multi-agent chemotherapy, such as ICE, followed by allogeneic HSCT in first remission.[213]

Cutaneous TCL

Cutaneous TCLs (CTCLs) are a heterogeneous group of lymphomas characterized by infiltration of the skin and other organs by malignant mature T cells. In the WHO classification, these disorders are considered indolent T-cell malignancies. The most common type of CTCL is mycosis fungoides (MF)/Sézary syndrome (SS), but other subtypes include primary cutaneous ALCL (not to be confused with systemic ALCL), subcutaneous panniculitis-like TCL, and many others.[10]

In most cases of MF, the diagnosis is made after a prolonged period of ill-defined skin disease or parapsoriasis. Subsequently, patches or plaques characteristic of MF develop. At the time of diagnosis, fewer than half of patients have limited plaques,

one-third have extensive plaques, and 10% to 15% have generalized erythroderma. The spleen, liver, and lymph nodes may also be involved, especially in patients with advanced skin disease and circulating malignant cells. Staging is performed using the T (skin) N (nodes) M (viscera) B (blood) system.[214] When the peripheral blood becomes extensively involved with the malignant T cells and erythroderma develops, the condition is called SS.

The treatment approach for MF/SS involves skin-directed therapy for skin-only disease, but may eventually require systemic agents.[215] Most patients who have CTCLs are initially treated with topical corticosteroids, photochemotherapy, and oral methoxypsoralen therapy followed by ultraviolet (UV) light, topical mechlorethamine, bexarotene, or electron-beam RT (either localized or total skin). Systemic therapy is required when these approaches fail or when major organ involvement, diffuse lymphadenopathy, or transformation to large-cell NHL develops. Treatment options for advanced CTCL include extracorporeal photopheresis, interferon-α, bexarotene, denileukin diftitox, liposomal doxorubicin, nucleoside analogs (eg, gemcitabine), alemtuzumab, mogamulizumab, and combination chemotherapy.[216] Mogamulizumab is an antibody against CCR4, a G protein-coupled receptor for CC chemokines that are involved in the trafficking of lymphocytes to various organs, and it showed improved ORR (28% vs. 5%) and DoR (13.0 months vs. 9 months) in a randomized trial leading to FDA approval.[217] Histone deacetylate inhibitors, such as vorinostat and romidepsin, have shown major activity in this condition, as has pralatrexate, and these drugs are being used increasingly earlier in the disease course. Brentuximab vedotin is highly active if there is CD30 expression.[218] Patients who have CTCL often die of infections, and as such, good skin care and oral antibiotics are important adjuncts to therapy. The only known curative therapy for MF is allogeneic HSCT, although a minority of patients are candidate to this approach.[219] The EBMT (European Society for Blood and Marrow Transplantation) guidelines recommend allogeneic hematopoietic cell transplantation as a potentially curative approach for patients with relapsed, refractory, or high-risk peripheral T-cell lymphoma. Patient selection should be individualized based on disease subtype, prior treatments, and overall fitness. Reduced-intensity conditioning is generally preferred to reduce toxicity, although myeloablative regimens may be considered for younger or fitter patients. Donor selection prioritizes matched siblings, followed by matched unrelated donors, with haploidentical or mismatched donors as alternatives. Routine post-transplant interventions, such as prophylactic donor lymphocyte infusions or measurable residual disease monitoring, are not strongly supported by current evidence, emphasizing the need for tailored clinical decisions and further research to optimize outcomes.[220]

Extranodal NK/TCL

Extranodal NK/TCL is an angioinvasive necrotizing lymphoma derived from cytotoxic NK or T cells that is almost invariably associated with EBV infection and typically presents in the nasal cavity, nasopharynx, or paranasal sinuses. It is divided into nasal and extranasal types and can affect skin, the GI tract, or testes. Nasal obstruction, bleeding, and ulceration are typical. The malignant lymphoid cells of nasal NK/TCL typically express CD2, CD56, and cytoplasmic CD3 Im (but not surface CD3) as well as cytotoxic molecules such as T-cell-restricted intracellular antigen, granzyme B, and perforin. The disease often presents at an early stage; RT is a critical therapeutic component of limited-stage disease, either concurrent or variably sequenced with chemotherapy.[221] The disease is relatively resistant to CHOP-type chemotherapy, but it is sensitive to asparaginase-containing regimens, such as SMILE, which contains dexamethasone, methotrexate, ifosfamide, *l*-asparaginase, etoposide, and DDGP (dexamethasone, cisplatin, gemcitabine, and pegaspargase).[133] Relapsed, chemorefractory disease remains a challenge. PD-1 blockers have shown promise in this setting.[222] Allogeneic HSCT should be considered when feasible, and clinical trials should be prioritized with attention to sequence and risk of overlapping toxicities.

KEY POINTS

- PTCL treatment is evolving; younger patients are typically treated with CHOP/CHOEP induction chemotherapy, and response is frequently consolidated with HDT-ASCS, largely based on the results of phase 2 and registry studies.
- Replacing vincristine in CHOP with the ADC brentuximab vedotin demonstrated dramatic improvement in PFS and improvement in OS in the ECHELON-2 randomized phase 3 trial of CD30 + PTCL, although the results are more clearly applicable to $CD30^+$ ALCL.
- Multiple agents are available as second line and beyond, with no clear advantage of one over the other; brentuximab vedotin should be used in patients with R/R $CD30^+$ PTCL if not previously used.
- TCLs are rare, heterogeneous, and aggressive diseases that are frequently chemotherapy resistant.
- Initial treatment of PTCLs without CD30 expression consists of multi-agent chemotherapy with CHOP or CHOEP for younger patients.
- The benefit of HDT-ASCS in first remission is frequently considered, but randomized controlled trials to support this approach are lacking.
- The ECHELON-2 trial showed a dramatic advantage of brentuximab vedotin substitution for vincristine in CHOP over CHOP alone.
- Patients who have R/R PTCL have limited treatment options, and their prognosis is poor, with only allogeneic HSCT representing a curative option in patients who achieve a response to therapy.

- Treatment options for less common TCL subtypes are not well defined, and outcomes are heterogeneous.
- MF is the most common type of CTCL and is an indolent disease in the majority of patients. Treatment is initially skin-directed.
- All patients with localized NK/TCL should have RT as part of their treatment.

HODGKIN LYMPHOMA

CLASSIFICATION

The WHO classification of lymphomas distinguishes two major types of Hodgkin lymphoma: cHL, which includes nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted subtypes, and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).[10] These two major categories of Hodgkin lymphoma, cHL and NLP, present differently and require different treatment paradigms.

EPIDEMIOLOGY AND ETIOLOGY

Hodgkin lymphoma is a mature B-lymphoid neoplasm that annually is diagnosed in approximately 9,050 individuals in the United States and causes approximately 1,150 deaths. cHL has a bimodal incidence distribution with respect to age at diagnosis, with an incidence peak in young adulthood and a second peak in older people, and NLPHL typically presents in middle-aged men. The etiology of Hodgkin lymphoma is not known, although a history of clinical EBV disease (mononucleosis) increases the likelihood of cHL threefold. cHL nodes show evidence of EBV DNA in the genome of the Reed–Sternberg cell in 30% to 80% of cases. HIV and allogeneic bone marrow transplantation increase the risk of cHL in people who have HIV, and cHL is almost always associated with EBV and tends to exhibit high-risk clinical features, such as advanced stage, extranodal involvement, and constitutional symptoms, although the outcomes with standard cHL therapy are similar to those in the general population.

CLASSIC HODGKIN LYMPHOMA

cHL typically presents with painless lymphadenopathy with or without splenomegaly, fever, drenching night sweats, weight loss, and pruritus or pain in a lymph node–bearing area that is associated with alcohol consumption. cHL represents 95% of all cases of Hodgkin lymphoma and is characterized pathologically by the presence of bizarre monoclonal lymphoid cells that may be either mononuclear (Hodgkin cells) or multinucleated (Reed–Sternberg cells). The diagnosis is best established by examination of an excisional lymph node biopsy specimen demonstrating large, atypical lymphocytes surrounded by a heterogeneous infiltrate of non-neoplastic inflammatory and accessory cells. The malignant Hodgkin and Reed–Sternberg (HRS) cells of cHL express CD15 and CD30 surface antigens but usually not typical B-cell markers, such as surface immunoglobulin, CD20, CD79a, or the common leukocyte antigen CD45.[15] The B-cell origin of HRS cells is nevertheless demonstrable by the expression of the B-cell-specific activator protein derived from the *PAX5* gene in 90% of cases.[10] The malignant (HRS) cells are typically surrounded by a heterogeneous infiltrate of reactive T and B lymphocytes, eosinophils, macrophages, fibroblasts, and variable amounts of collagen deposition (sclerosis). Chromosome 9p24.1 is frequently amplified in cHL, increasing the expression of PD-L1 and PD-L2 and promoting their induction through JAK-signal transducer and activator of transcription signaling.[223]

Four discrete histologic subtypes of cHL are recognized by the WHO classification based on the relative proportions of infiltrating small lymphocytes and HRS cells and the amount of collagen (sclerosis) in the biopsy specimen:

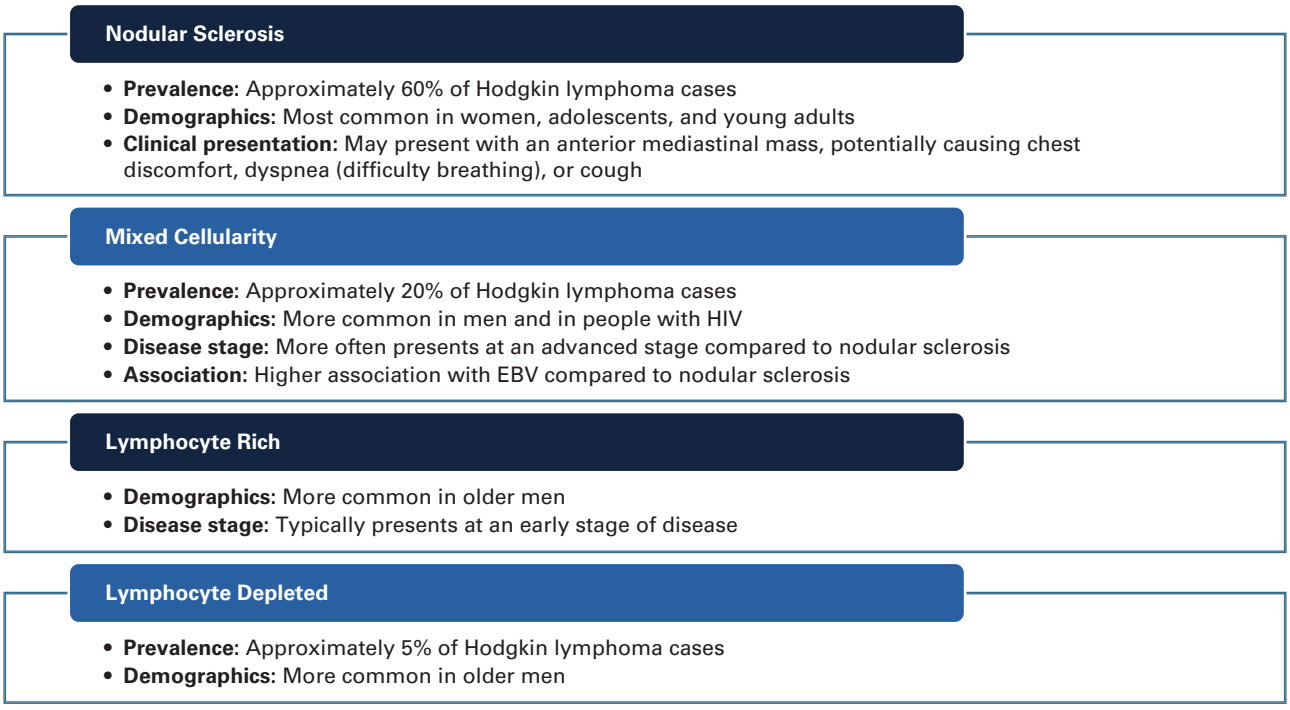
- Nodular sclerosis
- Mixed cellularity
- Lymphocyte-rich
- Lymphocyte-depleted

All four subtypes of cHL are evaluated and treated similarly, but the subtype may have an effect on prognosis, with mixed cellularity and lymphocyte-deplete subtypes having a worse prognosis. Figure 20-6 summarizes key points about the differences.

NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA

NLPHL is an indolent B-cell neoplasm that is distinguished from cHL by histologic and immunophenotypic features, including the presence of large neoplastic cells known as popcorn or lymphocytic and histiocytic cells (ie, L and H cells) residing in a large nodular meshwork of follicular dendritic cell processes filled with non-neoplastic lymphocytes. In marked contrast to the HRS cells of cHL, the malignant L and H cells of NLPHL express typical B-cell surface antigens, including CD20 and CD79a, as well as the common leukocyte antigen CD45, but do not express CD15 or CD30.[224] Fifty percent of NLPHL harbor *BCL6* rearrangements in contrast to cHL, in which this is a rare occurrence.[225] NLPHL is responsible for approximately 5% of all cases of Hodgkin

Figure 20-6 Subtypes of Classic Hodgkin Lymphoma



Abbreviations: EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.
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lymphoma, which typically affects men between the ages of 30 and 50 years, usually presents with localized lymphadenopathy (stages I to II), progresses slowly, and is associated with prolonged survival despite frequent relapses. There is a spectrum of associated pathologic entities (reviewed in Savage et al.).[226] Up to 15% of patients who have NLPHL can have a transformation to aggressive B-cell NHLs, frequently T-cell-rich DLBCL, and require aggressive treatment.

STAGING AND INITIAL EVALUATION

Recommended diagnostic tests include history, physical examination, excisional lymph node or core biopsy with specimen evaluation for histology and immunophenotype, CBC count with differential, chemistry panel including liver function test and albumin and LDH levels, erythrocyte sedimentation rate (ESR), HIV testing, chest radiography, FDG PET/CT, and fertility counseling. Other tests useful in selected cases include pulmonary function tests (before bleomycin therapy) and determination of the cardiac ejection fraction (before anthracycline therapy). Bone marrow biopsies are no longer routinely recommended for staging of cHL, provided FDG PET imaging is performed, as patients with early-stage disease rarely have bone marrow involvement in the absence of PET abnormalities, and bone marrow findings do not change treatment in patients with advanced-stage disease.[18] After completion of the diagnostic workup, the extent of involvement with Hodgkin lymphoma is designated using the Lugano staging system.

The clinical approach to Hodgkin lymphoma is based on the subtype (cHL or NLPHL) and initial stage and prognostic factors: early stage (stage I or IIA with favorable or unfavorable features) or advanced stage (stage IIB, III, or IV or bulky disease). Adverse prognostic factors for early-stage cHL include a large mediastinal mass, elevated sedimentation rate, involvement of three or more nodal sites, extranodal disease, age >50 years, or massive splenic disease.[227] Adverse prognostic factors for advanced-stage cHL include age >45 years, stage IV disease, male sex, leukocytosis (white blood cell count ≥15,000/mL), lymphopenia (absolute lymphocyte count <600/mL), low albumin level, or anemia (hemoglobin <10.5 g/dL).[228] As discussed, metabolic response reflected by FDG PET has emerged as one of the most important prognostic factors for survival, and it forms the rationale for response-adapted therapy.

TREATMENT OF HODGKIN LYMPHOMA

Early-Stage CHL

Patients with stage I and II cHL, also known as early-stage or limited-stage disease, have an excellent prognosis with long-term survival exceeding 90% to 95%. Early-stage disease is further split into two groups: favorable and unfavorable. Risk factors for

unfavorable disease are based upon age, bulky tumors (≥10 cm in size), presence of B symptoms, elevation in ESR, and the number of nodal sites, although cooperative groups vary in how they combine these prognostic factors, making it difficult to compare results across clinical trials. In the era of PET imaging, the interim and end-of-treatment PET results are the most important prognostic factors in cHL. Generally, early-stage cHL is treated with two to four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by IFRT, with the number of cycles of ABVD and the dose of radiation determined by interim PET results. Clinical trials focus on decreasing the amount of radiation and the number of cycles of chemotherapy required to decrease acute and late toxicities of treatment.

The German HD10 trial randomly assigned 1,370 patients with favorable prognostic factors to between two and four cycles of ABVD chemotherapy and IFRT at 20 and 30 Gy in an effort to reduce both chemotherapy cycles and total radiation dose.[229] Response, PFS, and OS were equivalent among the four arms, and two cycles of ABVD and IFRT at 20 Gy is now the recommended treatment of patients who have favorable early-stage disease, as it limits both chemotherapy and RT. Other studies have tested chemotherapy-only regimens. In general, omission of RT in nonbulky, early-stage cHL is associated with inferior disease control (EFS, PFS, and local relapse) on the order of 3% to 7% (reviewed in Engert et al.)[229]; however, long-term follow-up showed a 12-year OS rate of 94% among those receiving ABVD alone with fewer late toxicities.[230] Importantly, each of these trials was conducted before the incorporation of PET and response-adapted approaches. Two randomized trials in favorable-risk (UK RAPID and EORTC H10F) and one in unfavorable risk (EORTC H10U) disease[231,232] tested the omission of RT on the basis of a negative interim PET-CT, usually defined as a Deauville score less than or equal to two after two cycles of chemotherapy. EORTC H10F favored a combined-modality approach with respect to EFS; however, the 5-year OS rates were 96.7% versus 98.3% for the ABVD plus IFRT and ABVD-only arms, respectively.[231] Similar results were seen in the RAPID trial, which enrolled >600 patients who had stage IA to IIA Hodgkin lymphoma. Patients who had a negative PET scan after three cycles of ABVD (n = 426 patients, 74.6%) were randomly assigned to consolidative RT versus no additional therapy.[232] The 3-year PFS was 94.6% versus 90.8%, favoring RT, but with no difference in 3-year OS rates (97.1% vs. 99%; *P* = .27). Given the excellent outcomes, the RAPID approach without RT is now integrated into NCCN guidelines. Regimens incorporating brentuximab vedotin and PD-1 immune checkpoint inhibitors are under active study for initial treatment of early-stage Hodgkin lymphoma and are likely to further reduce dependence on cytotoxic chemotherapy and radiation.

Advanced-Stage CHL

Advanced-stage cHL is highly curable with combination chemotherapy. Clinical trials have refined the optimal systemic therapy (excellent and detailed reviews by Johnson and McKenzie[233] and Lynch and Advani[234]) with important questions revolving around early and late toxicity, role of intensification, role of RT, and response-adapted treatment. Today, the approach is based on several principles and observations.

ABVD was previously the treatment of choice in North America based on 7- or 10-year FFS rates of 70% to 75%, coupled with an excellent toxicity profile.[235-237] The risk of secondary malignancies is extremely low, and fertility is preserved in most patients. More intense regimens, such as the escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen developed in Germany, offer improved disease control but are associated with increased treatment-related mortality and significant infertility. An Italian intergroup study randomly assigned 331 patients who had advanced-stage Hodgkin lymphoma to ABVD or BEACOPP, and patients who had residual or progressive disease were treated with a uniform salvage program.[237] There was more progression in the ABVD arm (45 patients vs. 20 patients), but the 7-year freedom from second progression and OS results were similar in the two groups. Brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD) is an effective, targeted, and better-tolerated frontline regimen for advanced classical Hodgkin lymphoma, representing an evolution beyond escalated BEACOPP by maintaining efficacy while reducing toxicity. Second, response-adapted therapy is an important component of advanced-stage cHL treatment. The two approaches to integrate interim PET into the management of Hodgkin lymphoma are the following:

1. Treatment intensification based on positive interim PET (eg, escalation from ABVD to BrECADD).
2. Treatment de-escalation based on negative interim PET (eg, de-escalation from BEACOPP to ABVD).[234]

The RATHL study used the latter concept to reduce bleomycin from ABVD, a known pulmonary toxin and a cause of pneumonitis and death, particularly in older individuals.[238] The RATHL study enrolled 1,214 patients who had stage II bulky and advanced-stage cHL; 84% had a negative interim PET (Deauville score 1-3) after two cycles of ABVD. These patients were randomly assigned to continue ABVD or to de-escalate therapy to AVD for four additional cycles. With a median follow-up of 41 months, the 3-year PFS was 85.7% versus 84.4%, and the 3-year OS rate was 97% in both arms. Thus, bleomycin can be safely omitted from cycles three to six (ie, only administer bleomycin in the first two cycles) in patients with a negative interim PET.

When treating with ABVD, it is imperative to deliver treatment on time and without dose reduction to maximize efficacy. Although ABVD is associated with neutropenia, febrile neutropenia is uncommon in this generally young and healthy population.[233] The use of routine growth factors is not recommended because of concerns about an increase in bleomycin-induced lung injury, particularly in older patients, with growth factor support.[239,240]

Brentuximab vedotin is an ADC targeting CD30 with a toxic payload of monomethyl auristatin E. It was first shown to be effective in R/R cHL. In an attempt to improve outcomes and avoid the toxicity associated with bleomycin in the first-line setting, brentuximab vedotin was studied in combination with AVD (BV + AVD) and compared with standard ABVD in the randomized phase 3 ECHELON-1 study. In this study, six cycles of BV + AVD showed a PFS and OS benefit over six cycles of ABVD (6-year OS 93.9% vs. 89.4%, respectively) in untreated advanced-stage cHL, albeit BV + AVD was associated with increased neutropenia and peripheral neuropathy and requires the use of hematopoietic growth factor support.[8] BV + AVD was approved for the first-line treatment of advanced-stage cHL by the FDA based upon the ECHELON-1 study.

The German Hodgkin Study Group has also incorporated brentuximab vedotin into first-line treatment with the development of brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD). HD21 was a randomized, open-label phase 3 trial of 1,482 patients with stage IIB to IV untreated cHL who received either eBEACOPP or BrECADD guided by interim PET after two cycles, demonstrating similar 4-year PFS and OS rates between the two regimens but a significantly lower treatment-related morbidity rate of 42% with BrECADD versus 59% with eBEACOPP. These results have led to the adoption of BrECADD as the first-line treatment of advanced cHL in countries where eBEACOPP has previously been the standard treatment.[241]

More recently, monoclonal antibodies targeting PD-1 have been incorporated into first-line cHL treatment after showing excellent activity in the relapsed and refractory setting. SWOG trial 1826 was a phase 3 study in newly diagnosed advanced-stage cHL that randomized patients to receive either six cycles of the anti-PD-1 agent *N*-AVD or BV + AVD.[11] With a median follow-up of 2.1 years, the 2-year PFS was 92% in the *N*-AVD arm versus 83% in the BV-AVD arm. N-AVD was associated with less treatment discontinuation, and there were infrequent immune-related adverse events related to nivolumab. All adverse events were more common in the BV-AVD arm compared with the N-AVD arm, except for neutropenia and arthralgia. Neutropenia occurred in 56% of participants in the N-AVD arm versus 34% in the BV-AVD arm; however, growth factor support was required to be administered to participants in the BV-AVD arm and was optional in the N-AVD arm. Given the improvement in PFS, N-AVD is considered a new standard of care for advanced-stage cHL.

Bulky Hodgkin Lymphoma

Up to 25% of patients who have cHL will have bulky disease, which is a known negative prognostic factor. Bulky disease is defined as a mass 10 cm or larger on a CT scan or a mediastinal mass greater than 0.33 of the chest diameter on a chest radiograph at T5 to T6. Bulky disease may cause cough or chest pain, but more acute symptoms, such as superior vena cava syndrome, are more likely to be from aggressive lymphomas involving the mediastinum, such as PMBL. Bulky disease is described by its size (eg, 12 cm mediastinal mass), and the previous designation of "X" in the Lugano staging system for bulky disease is no longer used. The literature regarding bulky Hodgkin lymphoma is confounded by the general inclusion of bulky disease in early-stage trials in Europe versus inclusion in advanced-stage trials in North America.

Treatment of bulky cHL has traditionally been combined-modality therapy, but overall there is a strong move away from radiation for bulky mediastinal disease, particularly among patients with a CR by PET imaging and/or with historical risk factors (eg, young age and female sex) for late RT complications. Given the primarily mediastinal location of bulky cHL, RT is associated with secondary malignancies (especially medial breast cancer in young women), cardiovascular disease (which may be aggravated by concurrent use of anthracyclines), and pulmonary toxicity. After six cycles of ABVD, consolidative RT at 36 Gy is associated with a 5-year FFS rate of >80% in bulky Hodgkin lymphoma.[242] A German trial (HD15) used PET-directed RT in patients treated with escalated BEACOPP, and the researchers were able to reduce the use of RT to only 11% of patients.[243] The RATHL trial mentioned in the previous section did not administer RT to the small subset of patients with stage II bulky disease. A randomized trial of nearly 300 patients with advanced-stage Hodgkin lymphoma showed that consolidative RT could be omitted if interim and end-of-treatment PETs showed CR.[244] Overall, there is a strong move away from radiation for bulky mediastinal disease, particularly among patients with a CR by PET imaging and/or with historical risk factors (eg, young age and female sex) for late RT complications. Although retrospective data support the omission of RT in patients who have a negative PET scan, early results from prospective trials are more complex and controversial. A German trial (HD15) used PET-directed RT in patients treated with escalated BEACOPP, and the researchers were able to reduce the use of RT to only 11% of patients[243]; extrapolation to ABVD is controversial. The RATHL trial mentioned in the previous section did not administer RT to the small subset of patients with stage II bulky disease. A randomized trial of nearly 300 patients with advanced-stage Hodgkin lymphoma showed that consolidative RT could be omitted if interim and end-of-treatment PETs showed CR.[244] Overall, there is a strong move away from radiation for bulky mediastinal disease particularly among patients with a CR by PET imaging and/or with historical risk factors (eg, young age and female sex) for late RT complications.[173] A randomized trial of nearly 300 patients with advanced-stage Hodgkin lymphoma showed that consolidative RT could be omitted if interim and end-of-treatment PETs showed CR.[244] In addition, less than 1% of patients received radiation in the S1826 study of *N*-AVD versus BV-AVD in advanced cHL.

Relapsed CHL

Although most patients who have cHL are cured with initial treatment, approximately 10% to 20% have disease recurrence. The treatment approach at relapse is influenced by the time to relapse and the nature of the initial treatment, but generally

consists of a multistep process of second-line chemotherapy, hematopoietic stem cell mobilization, HDC with autologous stem cell rescue (ASCT), and consideration of consolidative brentuximab vedotin. In support of ASCT, two randomized trials showed superiority of ASCT over conventional chemotherapy. The historic British National Lymphoma Investigation randomly assigned 20 patients apiece with nonresponding or relapsed disease to either carmustine, etoposide, cytarabine, and melphalan (BEAM) alone or BEAM (augmented doses of the same agents) followed by ASCT. The 3-year EFS was 53% versus 10% in favor of the transplantation group.[245] A second trial, the German HD-R1 trial, randomly assigned 161 patients to either dexamethasone plus BEAM alone or BEAM followed by ASCT and showed an improved freedom from treatment failure for HDC (55% vs. 34%; $P = .019$).[246] Of interest, neither of these trials was powered to determine a survival advantage for transplantation, but a meta-analysis confirmed the benefit of transplantation with mature follow-up, and ASCT is now the standard of care.[247] The most important factors predicting outcome with ASCT are time to relapse and chemosensitivity. Trials show that there is little benefit from ASCT when relapse occurs early within 12 months of first-line chemotherapy, and patients do best when they have a negative PET before ASCT.[248,249] Second-line therapy for R/R cHL thus aims to achieve PET-negative CR to consider ASCT. In 2021, a phase 2 trial in PD-1 naive patients with R/R cHL reported pembrolizumab in combination with gemcitabine, vinorelbine, and liposomal doxorubicin (pembro-GVD), achieving CRs in 95% (36/38) of patients.[134] This outpatient regimen has emerged as an important treatment option for relapsed cHL. Although ASCT is an active and appropriate treatment for relapsed cHL, the long-term disease control rate is only 50% to 60% in randomized trials and registry analyses, with relapses occurring mainly in the first 3 years after ASCT. The AETHERA trial randomly assigned 329 BV-naive patients with high-risk R/R cHL to BV consolidation therapy or observation.[250] High risk was defined as primary refractory disease, relapse within 12 months after first-line treatment, or extranodal disease. Brentuximab vedotin consolidation was associated with improved PFS (42.9 months vs. 24.1 months; HR, 0.57; $P = .0013$), but to date, there is no difference in OS. Brentuximab vedotin is FDA approved for consolidation after ASCT.

Not all patients with relapsed Hodgkin lymphoma need ASCT, and controversy exists regarding the best approach for patients with limited relapse or those with minimal therapy in the first-line setting, particularly in the era of novel targeted agents. In addition, research is ongoing regarding nontransplantation options using newer agents.

The treatment options for multiply relapsed Hodgkin lymphoma, either after ASCT or in patients who are ineligible for ASCT, have greatly expanded in the past several years. Brentuximab vedotin has single-agent ORR and CR rates of 75% and 34%, respectively, with half of patients who have a CR remaining disease-free at 5 years.[251]

Brentuximab vedotin is administered at 1.8 mg/kg every 3 weeks and is well tolerated overall. The most common toxicity is sensory peripheral neuropathy, which occurs to some degree in most patients; >80% of patients in the pivotal trial reported eventual resolution of symptoms. Clearly, brentuximab vedotin would be of limited value if already administered in first-line treatment. A second new option is PD-1 blockade. Amplification of 9p24 in cHL leads to PD-L1 overexpression and activation of the JAK-signal transducer and activator of the transcription pathway, supporting the use of PD1/PD-L1 axis blockade and likely contributing to the highest response rate to PD-1 blockade among all tumor types when these agents are used. Nivolumab and pembrolizumab are FDA approved in the following settings:

- Nivolumab: relapsed or progressed after ASCT and brentuximab vedotin or after three lines of prior therapy including ASCT.[252]
- Pembrolizumab: refractory/relapsed after any prior therapy. This indication is based on a randomized trial of pembrolizumab versus brentuximab vedotin after at least one prior therapy. PFS was statistically significantly longer in the pembrolizumab arm. The median PFS was 13.2 months (95% CI, 10.9-19.4) in the pembrolizumab arm and 8.3 months (95% CI, 5.7-8.8) in the brentuximab vedotin arm with an HR of 0.65 (95% CI, 0.48-0.88; $P = .0027$).[253]

Allogeneic HSCT, usually with a reduced-intensity conditioning regimen, remains an option for eligible patients after failure of BV and/or PD-1 blockade.

Therapy for NLPHL

NLPHL treatment has followed a similar paradigm to cHL, as many clinical trials of cHL have included patients who have NLPHL despite the fact that NLPHL behaves as an indolent lymphoma. However, unlike cHL, rituximab may be added to treatment in NLPHL because of the expression of CD20. Early-stage NLPHL without risk factors (bulky disease, extranodal disease, elevated ESR, or ≥nodal areas) may be treated with excision, ISRT, or rituximab alone. In some cases, patients who have asymptomatic stage IA disease may undergo observation alone. Patients who have early-stage disease and risk factors can receive two to four cycles of ABVD, CHOP, or CVP with rituximab plus RT. Survival after early-stage disease is excellent and is approximately 90% with at least 10 years of follow-up. Patients with advanced-stage disease can be treated with six cycles of rituximab with ABVD, CHOP, or CVP (reviewed in Eichenauer and Engert).[254] Relapse is common in those with advanced-stage disease, although 10-year survival in one retrospective study of patients who had advanced-stage NLPHL who received ABVD or ABVD-like treatments was 83.5%. Suspected relapse should be investigated for transformation to an aggressive lymphoma with a biopsy. Patients who have a transformation to an aggressive B-cell lymphoma are treated with R-CHOP if not previously received or HDC with ASCT.

KEY POINTS

- cHL consists of four subtypes, but clinically is treated as one entity.
- NLPHL is an indolent B-cell neoplasm that progresses slowly and is associated with prolonged survival despite frequent relapses.
- The clinical approach to Hodgkin lymphoma is based on the initial stage and prognostic factors.
- Hodgkin lymphoma comprises cHL (nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted subtypes) and NLPHL, each of which has a distinctive clinical presentation, treatment paradigm, and prognosis.
- cHL of any stage is curable in most patients.
- In general, treatment with combined-modality therapy in early-stage cHL provides better PFS and fresh frozen plasma (FFP) but no difference in OS.
- Combination chemotherapy with ABVD or BV + AVD is the standard option for the treatment of advanced-stage cHL in North America, but Nivo-AVD was found to be superior to BV + AVD and represents a new first-line treatment option. The number of courses of chemotherapy varies with the stage of the disease.
- Low-dose IFRT is commonly administered after a short course of chemotherapy for the management of early-stage cHL, although the role of RT is undergoing reevaluation, and patients at higher risk of late RT complications may reasonably be treated with chemotherapy alone.
- PET-adapted therapy is now incorporated into treatment when ABVD is used.
- cHL expresses CD30, which can be targeted by the ADC brentuximab vedotin.
- Amplification of 9p24 is common in cHL and leads to overexpression of PD-L1, which is the basis for the use of PD-1 blockade.
- Patients with R/R cHL can be treated with a variety of therapies with the goal of PET negativity before consolidative autologous transplantation in eligible patients.
- NLPHL behaves similarly to indolent NHLs and expresses CD20. There is a risk of transformation to DLBCL, usually a T-cell-rich variant of DLBCL, which should be evaluated and confirmed via biopsy and treated as transformed aggressive BCL.

PRESENTING CASE STUDY 2

A 29-year-old man presented with a left-sided neck mass associated with significant unintentional weight loss of 40 pounds over 4 months and night sweats for the preceding 2 months. Initial laboratory evaluation revealed anemia and leukocytosis on complete blood count. His hemoglobin level was 9 g/dL, albumin was 3.5 g/dL, white blood cell count exceeded 15,000 cells/μL, and lymphocyte count was 1,500 cells/μL. His lactate dehydrogenase level was elevated at 400 U/L. Past medical history was notable only for lumbar radiculopathy following a motor vehicle accident.

An excisional biopsy of the cervical lymph node demonstrated lymphadenitis with sclerosing fibrosis.

Combined CT and PET/CT imaging revealed diffuse metabolically active lymphadenopathy throughout the neck, chest, abdomen, and pelvis; splenomegaly with numerous low-density, FDG-avid splenic lesions; and extensive FDG-avid osseous involvement of the axial and appendicular skeleton, including a dominant 5 × 4.5 cm lytic lesion in the left sacrum and posterior iliac bone. Metabolically active subcutaneous nodules were also noted. The patient's Deauville score was 5.

A CT-guided biopsy of the osseous lesion showed large, atypical cells with hyperchromatic nuclei in a background of small lymphocytes, eosinophils, plasma cells, and histiocytes.

Immunohistochemical staining demonstrated that the tumor cells were positive for CD15, CD30, *PAX5*, and MUM1. EBER1 was negative. Additional stains were negative for pancytokeratin, CD3, CD20, CD68, ALK1, and CD45.

This case highlights the importance of integrating clinical, pathologic, and imaging findings to diagnose and stage advanced Hodgkin lymphoma accurately. It underscores the need to tailor frontline therapy to individual patient factors, balancing efficacy and toxicity, as demonstrated by the use of nivolumab plus doxorubicin, vinblastine, and dacarbazine (AVD) in a patient at risk for neuropathy. Finally, the case emphasizes the value of PET-adapted response assessment to confirm remission and guide ongoing management.

How does this patient's presentation influence your determination of their risk level and choice of frontline treatment?

According to the International Prognostic Score, a score of 5 indicates high-risk advanced Hodgkin lymphoma, and the patient's presentation, pathology, and imaging findings were consistent with stage IVB classical Hodgkin lymphoma. Frontline treatment options for advanced disease include PET-adapted ABVD, which consists of two cycles of ABVD followed by interim PET and de-escalation to AVD for four additional cycles; this regimen is well studied but carries a risk of bleomycin-induced pulmonary toxicity. Another option is BV-AVD, which has been shown in the ECHELON-1 trial to improve progression-free survival (PFS) compared with ABVD, but is associated with an increased risk of peripheral neuropathy and febrile neutropenia. Nivolumab plus AVD (N-AVD) has demonstrated superior PFS and a more favorable toxicity profile compared with BV-AVD in the SWOG S1826 trial. Given the patient's pre-existing lumbar radiculopathy and the risk of neuropathy with BV-AVD, N-AVD was selected.

The SWOG S1826 trial, a phase 3 randomized multicenter study of 970 patients with stage III to IV classical Hodgkin lymphoma, compared N-AVD with BV-AVD. After a median follow-up of 2.1 years, N-AVD achieved a 2-year PFS of 92% versus 83% with BV-AVD. Treatment discontinuation due to toxicity (7.6% vs. 12%) and on-treatment mortality (0.6% vs. 1.7%) were also lower with N-AVD, and overall, it was better tolerated, including among older adults. These results established N-AVD as a more effective and safer frontline regimen, now recognized as an NCCN Category 1 preferred option, while BV-AVD remains useful for patients with contraindications to checkpoint inhibitors.

The patient completed six cycles of N-AVD without significant toxicity. End-of-treatment PET demonstrated a complete metabolic response according to Lugano criteria. Although sclerosis persisted in the dominant iliac bone lesion, there was no metabolic activity, and the repeat biopsy was negative for lymphoma.

Given this patient's pre-existing lumbar radiculopathy, nivolumab + AVD is the best option to maximize PFS and minimize the risk of worsening neuropathy.

The phase 3, randomized, multicenter SWOG S1826 trial enrolled 970 adolescents and adults with stage III or IV classical Hodgkin lymphoma. Patients received (BV-AVD). The primary endpoint was PFS, with secondary endpoints including OS, event-free survival, and toxicity. After a median follow-up of 2.1 years, the N-AVD group demonstrated superior outcomes, with a 2-year PFS of 92% compared to 83% in the BV-AVD group, reflecting a significantly lower risk of progression or death. Treatment discontinuation due to toxicity was also lower in the N-AVD arm (7.6% vs. 12%), as was mortality during treatment (0.6% vs. 1.7%). In addition, N-AVD was generally better tolerated, with fewer side effects overall, particularly among patients aged 60 years and older, who experienced reduced toxicity compared to those receiving BV-AVD. These findings establish N-AVD as a more effective and safer frontline treatment option for advanced-stage classical Hodgkin lymphoma, which is more effective and safer than BV-AVD. Recently, the NCCN updated the N-AVD regimen to a preferred Category 1 status due to its superior efficacy and reduced toxicity. In addition, BV-AVD is considered useful in certain circumstances for patients with contraindications to checkpoint inhibitors.

The patient above received N-AVD for six cycles and tolerated it well without any significant toxicities. The end-of-treatment PET demonstrated a complete metabolic response by the Lugano criteria. Although sclerosis was identified in the largest bone lesion in the ileum, there was no metabolic activity, and a repeat biopsy was negative for lymphoma.

HIGH-YIELD TAKEAWAYS

Diffuse large B-cell lymphoma

- The classic morphology of DLBCL is intermediate-to-large cells expressing CD19, CD20, CD79a, and CD45.
- Use the International Prognostic Index (IPI), presence of *MYC* rearrangements with or without *BCL2* rearrangements, and cell of origin to determine prognosis.
- Early-stage DLBCL with low-risk IPI and nonbulky disease is treated in the first line with four cycles of R-CHOP.
- Advanced-stage DLBCL is treated in the first line with six cycles of R-CHOP or pola-*R*-CHP.

- Refractory or early relapsed DLBCL (<1 year after first-line treatment) is treated with anti-CD19 CAR-T-cell therapy (axi-cel or liso-cel).
- Late-relapsed DLBCL (>1 year after first-line treatment) is treated with ASCT in patients who are fit for transplant.

Classical Hodgkin lymphoma

- CHL is characterized by large, multinucleated lymphocytes (Reed–Sternberg cells) that are CD15- and CD30-positive and negative for other typical B-cell markers, surrounded by reactive lymphocytes, macrophages, eosinophils, and collagen deposits (sclerosis).
- There are four subtypes: nodular sclerosis, mixed cellularity (worse prognosis), lymphocyte-rich, and lymphocyte-depleted (worse prognosis).
- Adverse prognostic factors for early-stage CHL include a large mediastinal mass, elevated sedimentation rate, involvement of three or more nodal sites, extranodal disease, age >50 years, or massive splenic disease.
- Adverse prognostic factors for advanced-stage cHL include age >45 years, stage IV disease, male sex, leukocytosis (white blood cell count ≥15,000/mL), lymphopenia (absolute lymphocyte count <600/mL), low albumin level, or anemia (hemoglobin <10.5 g/dL).
- Early-stage disease is treated with PET-adapted ABVD with or without IFRT.
- Advanced-stage CHL is treated with PET-adapted ABVD, six cycles of BV-AVD, or six cycles *N*-AVD.

Essential pathology workup of MCL

- Diagnosis of MCL involves immunohistochemistry (IHC), flow cytometry, potentially FISH testing, and molecular sequencing for *TP53* mutation.
- Cyclin D1 and/or translocation 11;14 are standard diagnostic findings; SOX11 by IHC can assist in uncertain cases. Ki67 index by IHC is prognostic.
- *TP53* mutation is unique from deletion 17p, and is associated with elevated p53 protein expression (>50%) and poor outcomes with standard chemotherapy.

Acknowledgments

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LYMPHOMAS 20

CHAPTER SUMMARY GUIDE

KEY POINTS

- NHLs comprise a group of heterogeneous diseases that vary widely with respect to clinical presentation, therapy, and prognosis.
- Advances in the diagnosis and classification of these diseases are facilitated by immunophenotyping and by newer molecular and genetic approaches.
- Establishing a correct diagnosis at the time of initial presentation is critical to optimal management of NHL. Therefore, an adequately sized biopsy specimen is mandatory to permit rigorous classification. FNA is virtually never adequate for establishing the initial subtype of non-Hodgkin lymphoma.
- Indolent NHLs usually grow slowly and are also known as low-grade lymphomas. FL, MZL, LPL, and SLL are all indolent lymphomas.
- Transformation to a higher grade occurs at a rate of approximately 2% per year.
- FL is the most common indolent lymphoma.
- Most patients with FL live for more than a decade.
- Prognostic scores using clinical risk factors can estimate OS.
- Defined treatment indications based on history, physical, imaging, and laboratory results are key to inform whether patients should receive treatment versus active surveillance without therapy (observation).
- Symptomatic patients who have progressive FL or other low-grade lymphomas have a number of treatment options without any evidence indicating a major survival advantage for any specific approach.
- Chemoimmunotherapy remains a standard for first-line FL treatment with high tumor burden, but the subset of patients relapsing within 2 years faces poor survival rates. In these cases, optimal therapy is unknown, but clinical trials, novel targeted therapies, and cellular therapies (HSCT, bispecific T-cell engagers, CAR-T-cell therapy) may be considered.
- The novel small-molecule therapy currently approved for relapsed FL is lenalidomide.
- Combination therapies currently approved for relapsed FL include Rituximab with lenalidomide, zanubrutinib with obinutuzumab, and tafasitamab in combination with lenalidomide and rituximab.
- Recently FDA-approved immunotherapies include the bispecific T-cell engager mosunetuzumab, epcoritamab, and CAR-T-cell therapies (axi-cel, tisa-cel, and liso-cel), representing an important new class of therapies in R/R FL.
- Three types of MZL are EMZL, SMZL, and NMZL.
- MZLs are frequently antigen-driven diseases, and eradication of infection (eg, *H. pylori*) can result in regression of lymphoma without the need for additional therapy.
- RT for localized MZL, including persistence of gastric MZL after *H. pylori* eradication, is effective; systemic therapy for advanced-stage MZL incorporates rituximab and, for selected patients, chemotherapy with rituximab.
- R/R MZL requires individualized consideration of therapy, including additional rituximab, chemoimmunotherapy when appropriate, zanubrutinib, or lenalidomide-based therapy.
- Despite its rarity and lack of comparative trials in WM, several key management aspects are evident from available data: An elevated paraprotein level alone is not an indication for therapy in asymptomatic patients.
- First-line therapy may include rituximab, chemoimmunotherapy, or a continuous BTK inhibitor, depending on goals and patient factors (disease burden, age, and comorbidities).
- Rituximab may result in a sudden increase in IgM levels, leading to symptomatic hyperviscosity.
- R/R WM is treated upon symptomatic progression, and selection of therapy depends on depth and DoR to initial therapy, as in other indolent NHL.
- BTK inhibitors, particularly zanubrutinib, are a mainstay of WM therapy.
- Most patients with primary mediastinal BCL (PMBL) do well with chemoimmunotherapy (eg, R-CHOP) and RT or approaches that seek to eliminate RT (eg, dose-adjusted etoposide, doxorubicin, vincristine, and cyclophosphamide plus rituximab [DA-EPOCH-R]).
- The role of RT remains a controversial issue, and PET-adapted strategies are under investigation.
- CAR-T-cell therapy, high-dose chemotherapy (HDC) and ASCT, and pembrolizumab can be used in the relapsed setting.

- DLBCL is the most common and prototypical aggressive lymphoma.
- IPI is the most commonly used prognostic tool.
- Molecular classifications, including the most commonly used COO, currently provide prognostic information and may inform treatment strategies in the future.
- *MYC* rearrangement with or without *BCL2* is a poor prognostic feature in DLBCL.
- Early-stage DLBCL is increasingly treated with immunochemotherapy alone without RT, using PET scanning to tailor therapy.
- Patients with nonbulky disease and lacking IPI risk factors or with a negative PET/CT after three cycles of R-CHOP can be treated with four cycles of R-CHOP alone.
- Aggressive NHLs are potentially curable and require prompt initiation of therapy soon after the diagnosis to ameliorate symptoms, avert rapid progression of the disease, and optimize survival.
- Calculation of the IPI for a patient at the time of diagnosis with DLBCL permits estimation of projected survival on the basis of individual clinical characteristics.
- DLBCL is the most common aggressive NHL, and it is a heterogeneous disease with clinical and genomic variants. With a combination of anthracycline-containing chemoimmunotherapy, it has a cure rate of approximately 60% to 70%.[133,134] Current first-line options are R-CHOP or the newer combination of pola-*R*-CHP.
- The presence of dual *MYC* and *BCL2* rearrangements defines DLBCL/HGBCL-MYC/BCL2, a unique entity with poor prognosis when treated with standard R-CHOP treatment.
- CD-19-directed CAR-T-cell therapy is the treatment of choice for patients who have primary refractory or early relapsed DLBCL. If the patient is not transplant or CAR-T eligible, tafasitamab-cxix with lenalidomide (tafa-len) is a reasonable option.
- Patients who have relapsed more than 1 year following first-line treatment with chemosensitive disease are candidates for high-dose chemoimmunotherapy plus ASCT with curative intent, or if patients are not transplant-ineligible DLBCL, consider CD-19-directed CAR-T-cell therapy.
- Epcoritamab and glofitamab are bispecific CD20-directed CD3 T-cell engagers FDA approved for R/R DLBCL after two or more lines of prior therapy.
- Glofitamab plus gemcitabine and oxaliplatin and polatuzumab vedotin plus mosunetuzumab are new options for patients with relapsed or refractory DLBCL who are ineligible for ASCT, although not approved by the US FDA.
- Other FDA-approved regimens for R/R disease include polatuzumab vedotin (pola), tafa-len, loncastuximab tesirine, and selinexor; all have unique mechanisms of action and toxicity profiles but do not produce long-term disease control for most patients with R/R DLBCL.
- MCL is a heterogeneous disease. Those with an indolent variant can often forgo initial therapy, although most will need treatment eventually.
- *TP53* sequencing is regarded as a standard component of biopsy evaluation in the workup of newly diagnosed MCL.
- Induction chemotherapy for classic MCL includes high-dose cytarabine and ASCT, followed by rituximab maintenance for young and eligible patients, but the advancement of BTK inhibitors into first-line therapy may soon change this paradigm.
- Older and ineligible patients have several first-line treatment options, including BR. If rituximab maintenance is used, attention to toxicity and particularly infections is required, particularly after bendamustine induction.
- Acalabrutinib in combination with rituximab and bendamustine is an option for transplant-ineligible older population with significant improvement in progression-free survival.
- R/R MCL is generally treated with a covalent BTK inhibitor with subsequent options, including the new noncovalent pirtobrutinib and CAR-T therapy.
- Lymphoblastic lymphoma is an aggressive lymphoma that expresses immature markers (ie, TdT) and is treated similarly to ALL.
- Burkitt lymphoma is an aggressive lymphoma characterized by *MYC* rearrangement, lack of *BCL2* expression, and extremely high proliferation index.
- Treatment consists of intensive chemotherapy regimens in combination with rituximab in a risk-adapted approach.
- Cure rates are high overall with intensive, multi-agent regimens, although regimens are associated with significant toxicity.
- Patients with relapsed or primary refractory disease have few treatment options and are rarely cured.
- PCNSL is a clinical variant of DLBCL that occurs exclusively in CNS structures, which may include the brain parenchyma, eyes, leptomeninges, and spinal cord.
- Treatment requires CNS-penetrating agents, usually high-dose methotrexate in the upfront setting.
- In the setting of HIV-associated PCNSL, high-dose methotrexate along with ART can be used with curative intent.
- Immune suppression (acquired, iatrogenic, or related to underlying autoimmunity) is associated with an increased risk of lymphoma.

- If possible, removing the cause of immune suppression can lead to lymphoma regression, particularly in early PTLD, leading to a stepwise approach. However, late PTLDs act like aggressive lymphomas.
- HIV-associated lymphomas should generally be treated in the same way as lymphoma in the general population, with the addition of ART. Oncologists should work with HIV specialists to help manage potential infectious complications and avoid drug-drug interactions between ART and cancer treatment.
- PTCL treatment is evolving; younger patients are typically treated with CHOP/CHOEP induction chemotherapy, and response is frequently consolidated with HDT-ASCS, largely based on the results of phase 2 and registry studies.
- Replacing vincristine in CHOP with the ADC brentuximab vedotin demonstrated dramatic improvement in PFS and improvement in OS in the ECHELON-2 randomized phase 3 trial of CD30 + PTCL, although the results are more clearly applicable to $CD30^+$ ALCL.
- Multiple agents are available as second line and beyond, with no clear advantage of one over the other; brentuximab vedotin should be used in patients with R/R $CD30^+$ PTCL if not previously used.
- TCLs are rare, heterogeneous, and aggressive diseases that are frequently chemotherapy resistant.
- Initial treatment of PTCLs without CD30 expression consists of multi-agent chemotherapy with CHOP or CHOEP for younger patients.
- The benefit of HDT-ASCS in first remission is frequently considered, but randomized controlled trials to support this approach are lacking.
- The ECHELON-2 trial showed a dramatic advantage of brentuximab vedotin substitution for vincristine in CHOP over CHOP alone.
- Patients who have R/R PTCL have limited treatment options, and their prognosis is poor, with only allogeneic HSCT representing a curative option in patients who achieve a response to therapy.
- Treatment options for less common TCL subtypes are not well defined, and outcomes are heterogeneous.
- MF is the most common type of CTCL and is an indolent disease in the majority of patients. Treatment is initially skin-directed.
- All patients with localized NK/TCL should have RT as part of their treatment.
- cHL consists of four subtypes, but clinically is treated as one entity.
- NLPHL is an indolent B-cell neoplasm that progresses slowly and is associated with prolonged survival despite frequent relapses.
- The clinical approach to Hodgkin lymphoma is based on the initial stage and prognostic factors.
- Hodgkin lymphoma comprises cHL (nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted subtypes) and NLPHL, each of which has a distinctive clinical presentation, treatment paradigm, and prognosis.
- cHL of any stage is curable in most patients.
- In general, treatment with combined-modality therapy in early-stage cHL provides better PFS and fresh frozen plasma (FFP) but no difference in OS.
- Combination chemotherapy with ABVD or BV + AVD is the standard option for the treatment of advanced-stage cHL in North America, but Nivo-AVD was found to be superior to BV + AVD and represents a new first-line treatment option. The number of courses of chemotherapy varies with the stage of the disease.
- Low-dose IFRT is commonly administered after a short course of chemotherapy for the management of early-stage cHL, although the role of RT is undergoing reevaluation, and patients at higher risk of late RT complications may reasonably be treated with chemotherapy alone.
- PET-adapted therapy is now incorporated into treatment when ABVD is used.
- cHL expresses CD30, which can be targeted by the ADC brentuximab vedotin.
- Amplification of 9p24 is common in cHL and leads to overexpression of PD-L1, which is the basis for the use of PD-1 blockade.
- Patients with R/R cHL can be treated with a variety of therapies with the goal of PET negativity before consolidative autologous transplantation in eligible patients.
- NLPHL behaves similarly to indolent NHLs and expresses CD20. There is a risk of transformation to DLBCL, usually a T-cell-rich variant of DLBCL, which should be evaluated and confirmed via biopsy and treated as transformed aggressive BCL.

CHAPTER TABLES AND IMAGES

Table 20-1 Key Diagnostic Immunophenotypic and Cytogenetic Features of Non-Hodgkin Lymphomas

Lymphoma Subtype	CD20	CD10	CD5	CD30	Other	Cytogenetics/ FISH Results	Genes
DLBCL: germinal center subtype	+++	+/−	Rare	Rare	*BCL6*$^{+}$ and MUM1^{-}	*BCL2* translocations (18q21)	*BCL6* and *EZH2* upregulation
DLBCL: nongerminal center subtype	+++	—	+/−	Rare	*BCL6* negative or *BCL6*$^{+}$, MUM1^{+}	*BCL6* translocations (3q27)	B-cell receptor signaling/*NFkB* activation
FL	+++	+	—	—		t(14;18)	*BCL2*
CLL/SLL	Dim	—	+	—	CD23^{+}		
MCL	+++	—	+	—	CD23^{-}, Cyclin D1^{+}, SOX11^{+}	t(11;14)	*Cyclin D1*
MZL	+++	—	Rare	—		t(11;18) (ENMZL) trisomy 3, 18 (NMZL) del 7q (SMZL)	*API2-MALT1*
LPL/WM	+++	—	Rare	—			*MYD88, CXCR4*[20]
Burkitt lymphoma	+++	+	—	—	TdT^{-}	t(8;14), t(8;22), t(2;8)	*MYC*
PMBL	+++	+/−	—	Occasional		t(16;X), 9p24.1 gain	*CIITA, PDL1/ JAK2/PDL2*
Hairy cell leukemia	+++	—	—	—	CD11c^{+}, CD25^{+}, CD103^{+}		
ALCL, ALK^{+}	—	—	—	+++		t(2; 5)	*ALK*
ALCL, ALK^{-}	—	—	—	+++		t(6;7)	*DUSP22*
AITL	—	+/−	+/−	—	At least three T_{FH} markers: PD-1, BCL6, CXCL13, ICOS, SAP, CCR5		*TET2, IDH2, DNMT3A, RHOA, ITK-SYK*
PTCL-NOS	—	+/−	+/−	—	Can have the same immunophenotype as AITL, often with dropped CD3 or CD7		

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; API2-MALT1, fusion of apoptosis inhibitor 2 and mucosa-associated lymphoid tissue lymphoma translocation 1; BCL2, B-cell CLL/lymphoma 2; BCL6, B-cell lymphoma 6; CCR5, chemokine, CC motif, receptor 5; CIITA, class II major histocompatibility complex transactivator; CLL, chronic lymphocytic leukemia; CXCL13, chemokine, CXC motif, ligand 13; DLBCL, diffuse large B-cell lymphoma; DNMT3A, DNA methyltransferase 3A; DUSP22, dual-specificity phosphatase 22; ENMZL, extranodal marginal zone lymphoma; FISH, fluorescence in situ hybridization; FL, follicular lymphoma; ICOS, inducible T-cell costimulator; IDH, isocitrate dehydrogenase 2; ITK-SYK, fusion of IL2-inducible T-cell kinase and protein-tyrosine kinase SYK; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MYC, MYC proto-oncogene, bHLH transcription factor; MYD88, MYD88 innate immune signal transduction adaptor; MZL, marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; PD-1, programmed cell death protein 1; PMBL, primary mediastinal B-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; RHOA, RAS homolog gene family, member A; SLL, small lymphocytic lymphoma; SMZL, splenic marginal zone lymphoma; TET2, TET methylcytosine dioxygenase 2; T_{FH}, T-follicular helper cell; WM, Waldenström macroglobulinemia.
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Table 20-2 **Prognostic Indices for Non-Hodgkin Lymphomas**				
Risk Factors	**Risk Group**	**No. of Factors**	**Patient Distribution (%)**	**Endpoint, OS (%)**
IPI for patients treated with R-CHOP				
Age >60 years				3-year OS
PS >1	Low	0-1	52	91
Serum LDH > ULN	Low intermediate	2	21	81
1 EN Site	High intermediate	3	17	65
Stage III-IV	High	4-5	10	59
Stage-modified IPI for aggressive lymphoma[31]				
Age >60 Years				5-year OS
PS >1		0-1	71	82
Serum LDH >ULN		2	22	71
Stage II		3	14	48
FLIPI[30]				
Four nodal sites				5-year OS
Serum LDH > ULN	Low	0-1	36	91
Age >60 Years	Intermediate	2	37	78
Stage III-IV	High	3-5	27	36
Hemoglobin <12 g/dL				
MIPI[32]				
Age				5-year OS
Performance status	Low	0-3	44	60
LDH: ULN	Intermediate	4, 5	35	45
WBC count	High	6-11	21	20

Abbreviations: EN, extranodal; FLIPI, Follicular Lymphoma International Prognostic Index; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MIPI, Mantle Cell Lymphoma International Prognostic Index; OS, overall survival; PS, performance status; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ULN, upper limit of normal; WBC, white blood cell.
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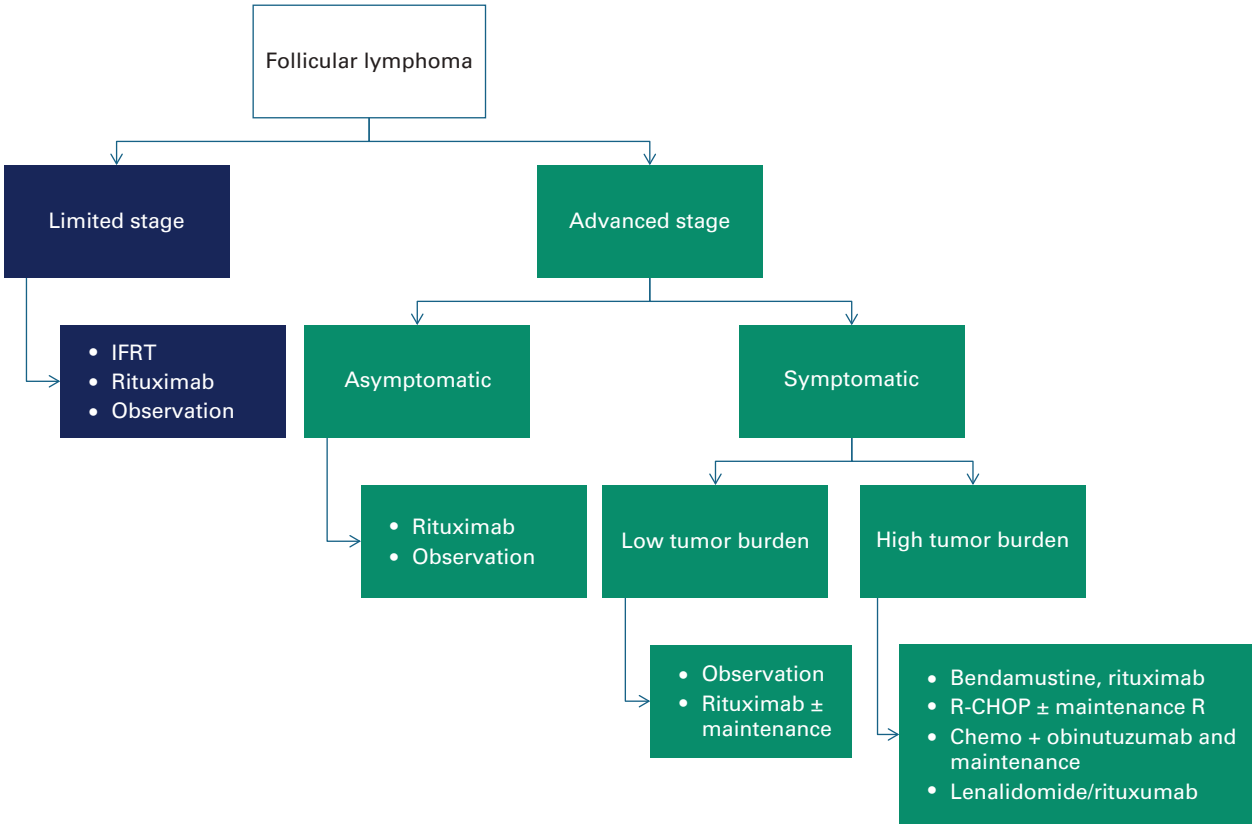
Figure 20-1 Treatment Algorithm for Follicular Non-Hodgkin Lymphoma



Abbreviations: Chemo, chemotherapy; IFRT, involved-field radiation therapy; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

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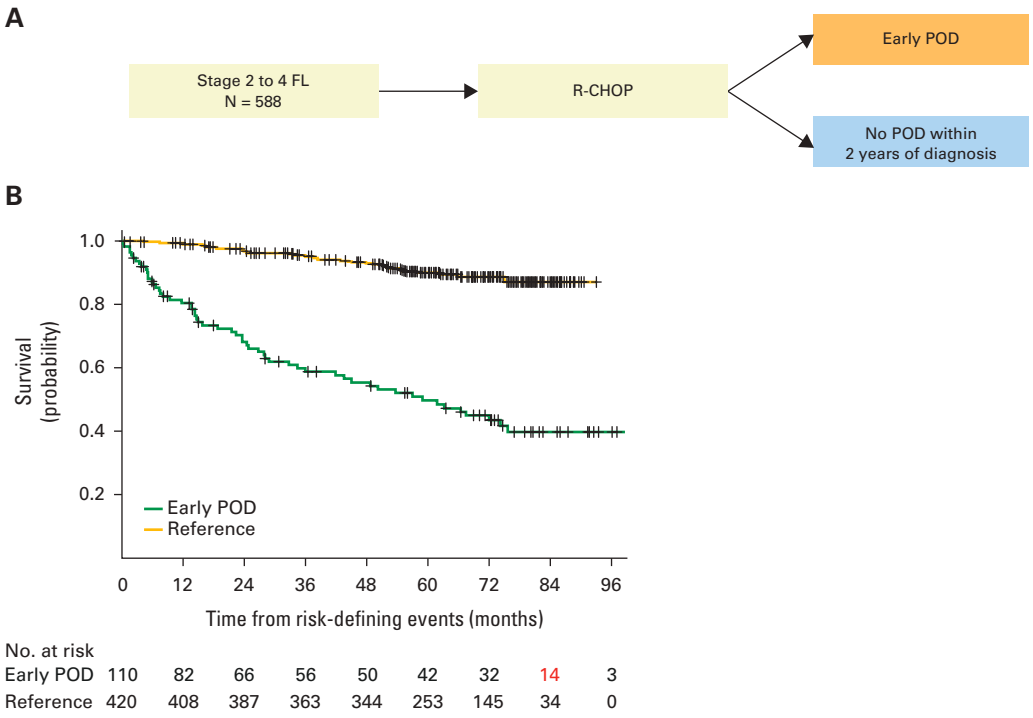
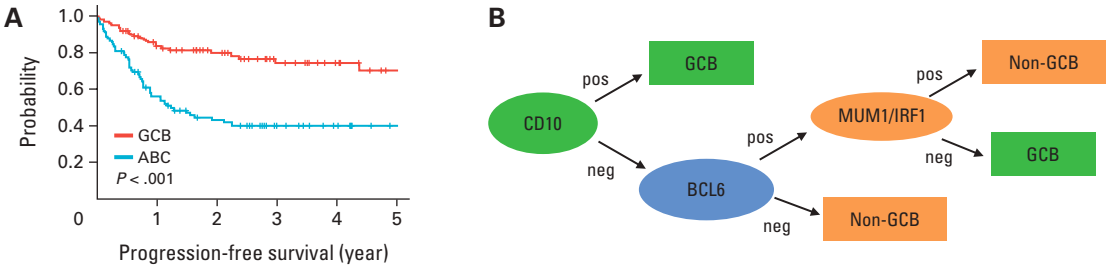
Figure 20-2 Identification of a High-Risk Subgroup of FL Based on Early Relapse After Initial R-CHOP Chemoimmunotherapy



(A) Patients and methods in the National LymphoCare study. (B) Overall survival from a risk-defining event after diagnosis among patients receiving R-CHOP in the National LymphoCare study, demonstrating poor survival in those with early disease progression.
Abbreviations: FL, follicular lymphoma; POD, progression of disease; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.
Reprinted from Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: An analysis from the national lymphocare study. *J Clin Oncol.* 2015;33:2516-2522. doi: 10.1111/bjh.15718

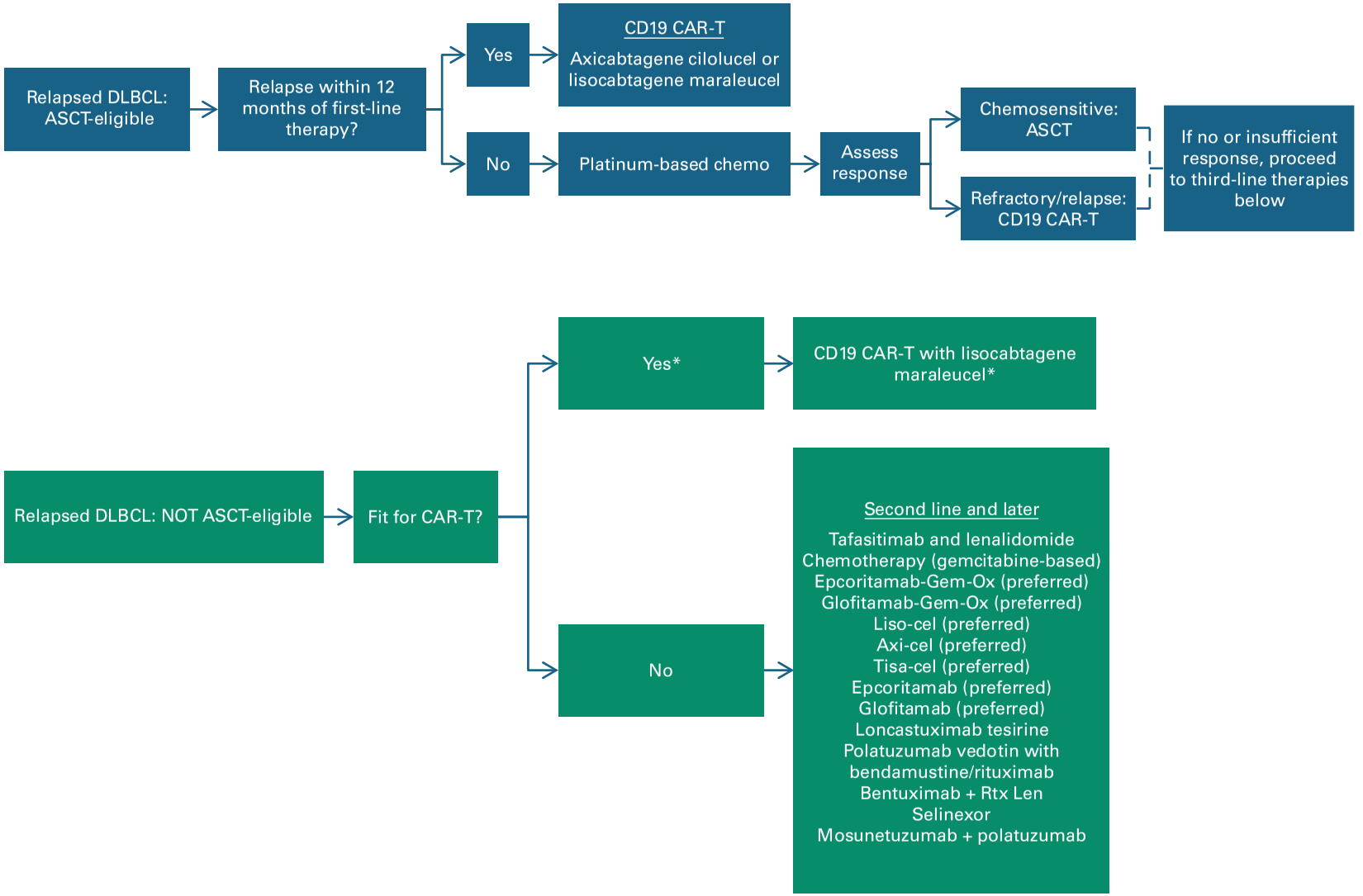
Figure 20-3 Cell Origin Cultures



DLBCL subtype	3-Year progression-free survival (%)
GCB	74
ABC	40

(A) Survival outcomes by genomic profiling determination of COO in patients treated with R-CHOP. (B) Hans algorithm for immunohistochemical determination of COO.
Abbreviations: ABC, activated B cell; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; neg, negative; pos, positive; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
Image (A) reprinted from Dunleavy K, Grant C, Wilson WH. *Ther Adv Hematol.* 4(1):43-57. Copyright © 2013 by Sage Publications. Reprinted by permission of Sage Publications.
Image (B) reproduced under Creative Commons license. Source: Reber R, Banz Y, Garamvölgyi E, et al. Determination of the molecular subtypes of diffuse large B-cell lymphomas using immunohistochemistry. *Swiss Med Wkly*. 2013;143:w13748. doi: 10.1016/S1470-2045(21)00591-X

Figure 20-4 Approach for Relapsed DLBCL



Abbreviations: ASCT, autologous stem cell transplantation; chemo, chemotherapy; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GemOx, gemcitabine-oxaliplatin.
*Patient features should mirror eligibility of the PILOT trial[123]: 70 years or older, ECOG 2, or impaired organ function.
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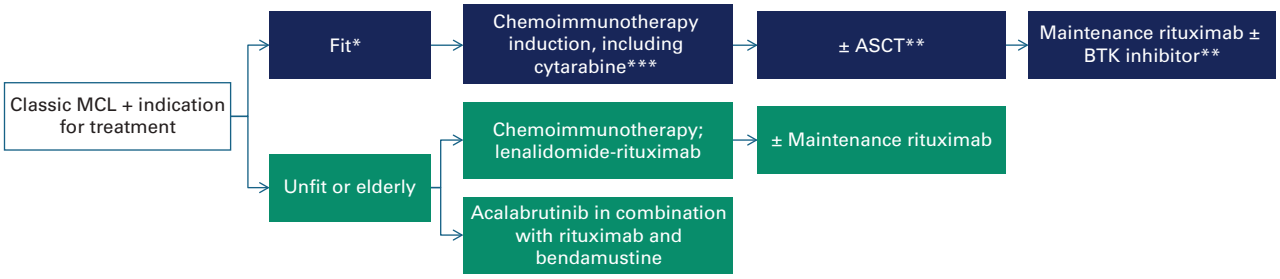
Figure 20-5 Treatment Algorithm for MCL



Abbreviations: ASCT, autologous stem cell transplantation; BR, bendamustine and rituximab; BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma; R-CHOP, rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone.
Chemoimmunotherapy includes BR; R-CHOP; and VR-CAP.
*"Fit" patients are generally aged 65 or younger, without comorbidities precluding myelotoxic chemoimmunotherapy and potential ASCT.
**Regimens are varied; see published treatment guidelines.
***Cytarabine chemotherapy with a BTK inhibitor for 2 years (and no ASCT) is supported by the randomized TRIANGLE study.[140]
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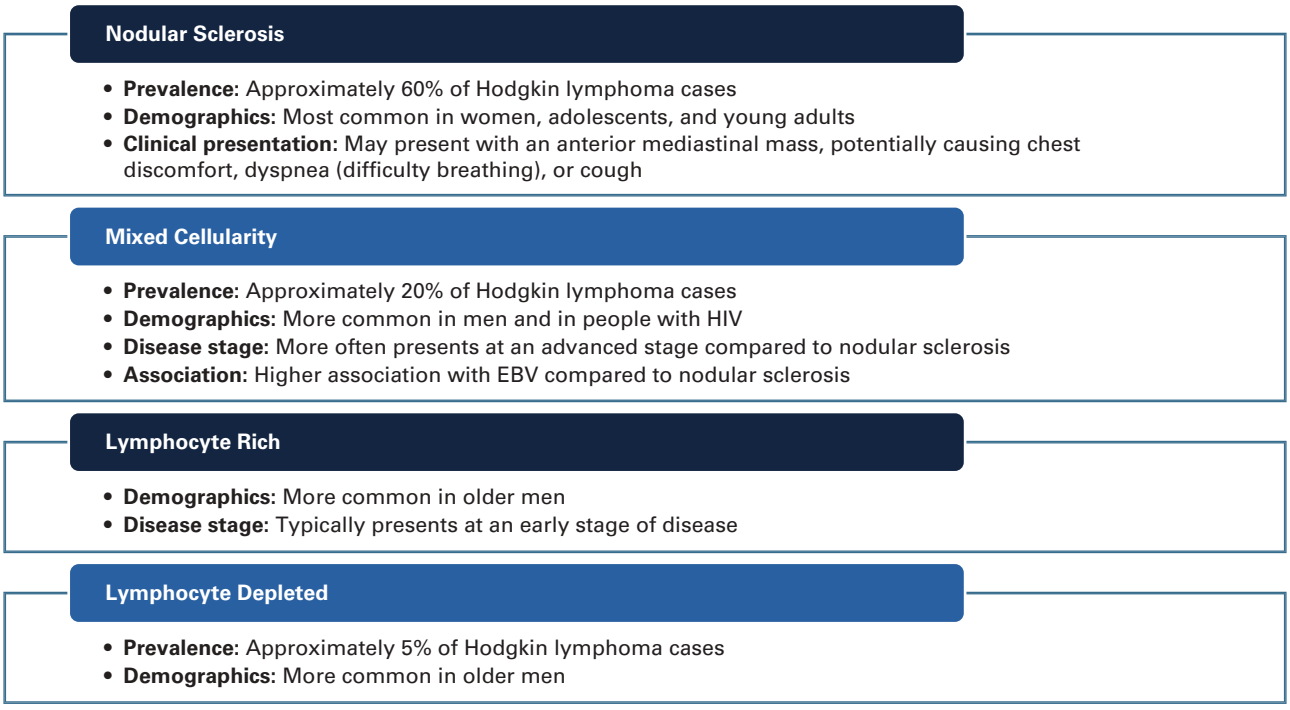
Figure 20-6 Subtypes of Classic Hodgkin Lymphoma



Abbreviations: EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.
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MULTIPLE MYELOMA 21

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RECENT UPDATES

- The International Myeloma Working Group definition of high-risk multiple myeloma, integrating cytogenetic and molecular markers, has been updated.[1]
- Several phase 3 randomized controlled trials (RCTs) are reaffirming the quadruplet induction regimens as a standard-of-care approach in newly diagnosed multiple myeloma (NDMM) patients. The GMMG-HD7 trial randomly assigned patients to bortezomib, lenalidomide, and dexamethasone (VRd) with or without isatuximab. The primary endpoint was minimal residual disease (MRD) negativity by next-generation flow cytometry to the 10^{-5} level. The addition of isatuximab improved MRD negativity (50% vs. 36%; $P < .001$).[2]
- The PERSEUS trial examined daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) induction and consolidation with daratumumab and lenalidomide maintenance versus VRd induction and consolidation, followed by maintenance with lenalidomide alone. After a median follow-up of 48 months, the DVRd group demonstrated a longer progression-free survival as well as response depth, which showed consistent benefits across various subgroups.[3]
- The IsKia trial was the first RCT to compare carfilzomib, lenalidomide, and dexamethasone (KRd)–based triplet therapy with isatuximab KRd quadruplet therapy in patients with transplant-eligible (TE) NDMM. The trial demonstrated the superiority of isatuximab and KRd in achieving a rate of MRD negativity less than 10^{-5} by next-generation sequencing (NGS) after consolidation in the intention-to-treat population.[4] Benefit was maintained with improvement consistent across all participant subgroups, including patients in high-risk categories.[5]
- The registrational IMROZ trial, an international, open-label, phase 3 trial, randomly assigned (in a 3:2 randomization) transplant-ineligible (TIE) NDMM patients to receive either isatuximab plus VRd or VRd alone. At a median follow-up of 59.7 months, PFS at the 60-month mark favored isatuximab plus VRd at 63.2% compared with 45.2% for VRd alone.[6]
- The registrational CEPHEUS study compared eight cycles of induction with dara-VRd (daratumumab and VRd) to VRd. Induction was followed by maintenance without bortezomib in both arms. Approximately 28% of patients had stage III, and 13% had high-risk cytogenetics. The primary endpoint of MRD negativity at 10^{-5} rate by NGS was met in favor of the quadruplet regimen with an OR of 2.37.[7]
- With the same endpoint, a non-registrational BENEFIT trial compared the isatuximab-Rd with and without bortezomib. Isa-bortezomib, lenalidomide, and dexamethasone improved the MRD-negativity rates and achieved higher rates of complete response (CR) or better, although survival data remain immature.[8]
- The GMMG-CONCEPT trials investigated Isa-KRd in TE and TIE patients with high-risk NDMM. Patients received this regimen in induction, consolidation, and maintenance therapy. However, maintenance therapy was given without dexamethasone. The trial met its primary endpoint with MRD-negativity rates of 67.7% after consolidation for TE patients and 54.2% after consolidation for TIE patients. Sustained MRD negativity for 1 year or longer was achieved in 62.6% of the patients.[9]
- For TE NDMM patients receiving proteasome inhibitor/immunomodulatory drug–based triplet induction, the phase 3 DETERMINATION trial—with a median follow-up of 76 months—demonstrated that incorporating autologous stem cell transplantation (ASCT) into first-line therapy conferred a statistically significant PFS benefit of 21.4 months compared with continued induction without transplant. After a median follow-up of 6.3 years, the median overall survival (OS) has not been reached in either arm of the study, necessitating additional follow-up (the study was not powered for OS).[10]

- The KarMMa-3 study was a phase 3 trial comparing idecabtagene vicleucel with one of five standard regimens in patients with relapsed and/or refractory multiple myeloma (RRMM) who had received two to four previous lines of therapy. After a median follow-up of 18.6 months, the idecabtagene vicleucel arm had superior mPFS and CR rate and overall response rates (ORRs). The toxicity profile in the idecabtagene vicleucel cohort reported no new toxicity concerns.[11]
- The CARTITUDE-4 trial was a phase 3, randomized, open-label trial that compared ciltacabtagene autoleucel with a physician's choice of standard care (pomalidomide, bortezomib, and dexamethasone [PVd] or daratumumab, pomalidomide, and dexamethasone [DPd]). After a median follow-up of 15.9 months, the mPFS was superior in the ciltacabtagene autoleucel arm.[12]
- A recent update of CARTITUDE-1 reported that 32/97 patients are alive and progression-free over 5 years after infusion.[13,14]
- Combination regimens employing belantamab mafodotin, an anti-B-cell maturation antigen (BCMA) antibody-drug conjugate, have demonstrated promising efficacy in RRMM. DREAMM-7 was a phase 3, open-label, randomized trial that evaluated belantamab mafodotin, bortezomib, and dexamethasone (BVd) to daratumumab, bortezomib, and dexamethasone (DVd), in patients after at least one line of therapy. The primary endpoint was PFS. At a median follow-up of 39.4 months, PFS was not reached in BVd versus 33.4 months in DVd.[15,16]
- DREAMM-8 was a phase 3, randomized, open-label trial that compared belantamab mafodotin, pomalidomide, and dexamethasone (BPd) with PVd in relapsed myeloma after the exposure of lenalidomide. The primary endpoint was PFS.[17] At a median follow-up of 28 months, mPFS was 32.6 months versus 12.5 months, favoring BPd. The estimated 18-month PFS rate was 63% compared with 41%. This benefit was maintained across key subgroups. Ocular events occurred in 89% of the BPd arm, grade 3 or 4 in 43%, and 30% in PVd, grade 3 or 4 in 2%. Belantamab mafodotin dose modification helped manage the increase in ocular events.[18] This drug was approved by the FDA on October 23, 2025.[19,20]
- Linvoseltamab-gcpt was approved on July 2, 2025, for patients after at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Linker-MM1 treated 117 patients with five median prior lines of therapy. The ORR was 71%, PFS was 70% at 12 months, and the median OS was 31.4 months.[21,22]
- The combination of teclistamab and talquetamab is being investigated as a novel dual–BsAb approach for relapsed or refractory multiple myeloma, aiming to enhance depth and durability of response through simultaneous targeting of BCMA and GPRC5D.[23,24]
- Anitocel (anitocaptagene autoleucel), a BCMA-directed CAR T therapy, demonstrated an ORR of 97% at a median follow-up of 12.6 months. The 12-month PFS and OS were 79% and 95%, respectively, with 93% achieved MRD negativity. Cytokine-release syndrome was seen in 15% neurotoxicity in 8%. Phase 3 trials are underway (presented at EHA 2025).[25]
- Although CAR T-cell and BsAb therapies have shown unprecedented efficacy in heavily pretreated patients who have RRMM, their use is associated with a significant risk of severe infections.[26] The combined expertise of hematologists and infectious disease specialists is required for proper management of the disease in patients who are recipients of T-cell–redirecting therapy and who have suspected infection.[27] Venous thromboembolism (VTE) at the time of diagnosis is associated with inferior survival in patients who have NDMM; therefore, risk-adapted strategies for prevention of VTE need to be used from the start to mitigate this preventable risk.[28]

OVERVIEW

Multiple myeloma (MM) is a plasma cell malignancy characterized by osteolytic bone lesions, anemia, hypercalcemia, and renal failure.[29,30] The disease is generally considered incurable, and the clinical course is characterized by remissions and relapses. The survival of patients with MM has improved with the advent and incorporation of therapies such as bortezomib, lenalidomide, carfilzomib, and pomalidomide, along with monoclonal antibodies (mAbs),[31,32] and most recently, T-cell–redirecting immunotherapies, into the overall treatment strategy. The use of autologous stem cell transplantation (ASCT) in selected patients remains an important modality in MM.

DISEASE DEFINITION

The definition of MM was last updated by the International Myeloma Working Group (IMWG) in 2014.[33] The revised definition incorporates specific biomarkers associated with a high risk of progression to symptomatic disease and signs revealed by advanced imaging

methods that help diagnose MM in patients who do not have standard features of end-organ damage. The new defining classification of MM results in patients with a higher risk of developing symptomatic disease being treated earlier. MM is currently determined by:

- Multiple myeloma: Diagnosis requires clonal bone marrow plasma cells (≥10% or plasmacytoma) plus either evidence of related end-organ damage (hypercalcemia, renal impairment, anemia, bone lesions) or specific biomarkers of malignancy (≥60% clonal plasma cells, involved: uninvolved free light chain (FLC) ratio ≥100, or >1 focal MRI lesion).
- Smoldering multiple myeloma: Diagnosis requires specific levels of serum or urine monoclonal protein and/or 10% to 59% clonal bone marrow plasma cells, without the presence of myeloma-defining events or amyloidosis.

Patients with MM must be differentiated from those with monoclonal gammopathy of undetermined significance (MGUS), smoldering MM (SMM), and other related plasma cell disorders.[33]

MGUS is an asymptomatic, premalignant phase of MM.[34] The risk of progression of MGUS to myeloma or a related disorder is fixed at approximately 1% per year. SMM is a more advanced, intermediate stage, defined by the presence of a serum monoclonal protein (M-protein) concentration greater than 3 g/dL or 10% to 59% clonal plasma cells in the marrow but without myeloma-defining events or light chain (AL) amyloidosis. SMM is a clonal expansion of plasma cells not associated with clinical manifestations and is at variable risk for progression on the basis of defined prognostic criteria.[35] In a study of 276 patients with SMM, the risk of progression to MM in the first 5 years after diagnosis[36] was 10% per year, 3% per year over the next 5 years, and 1% per year thereafter.[37] This trial was done before the advent of routine PET or MRI imaging and without the immunoglobulin FLC assay. Using modern staging techniques, one would anticipate the risk of progression to be lower. In another IMWG retrospective study evaluating 1,996 patients, incorporating cytogenetic abnormalities to the 2/20/20 model (M-protein >2 g/dL, free light-chain ratio >20, and marrow plasma cells >20%), the patients divided into four groups (low risk with 0, low intermediate risk with 1, intermediate risk with 2, and high risk with ≥3 risk factors) with 6%, 23%, 46%, and 63% risk of progression in 2 years, respectively.[36] Using genomic data from 374 patients, the cohort was divided into genomic MM and genomic MGUS. The genomic profile of the SMM group at biologic features is indistinguishable from MM, showing a high risk of progression. By contrast, 60% of MGUS patients showed genomic MGUS with no progression during follow-up. Integration of these features significantly improved the predictive value of the IMWG criteria for SMM.[38] Diagnosis of MM requires that myeloma-defining effects be attributable to the plasma cell neoplasm and not simply coexistent with MGUS or SMM, which is common and may occur in patients with renal insufficiency, anemia, hypercalcemia, or osteolytic lesions from other medical conditions. Care should be taken when considering alternative causes of myeloma-defining effects, particularly in patients with a low burden of neoplastic plasma cells.

KEY POINTS

- The diagnosis of MM requires evidence of one or more myeloma-defining effects: hypercalcemia, renal insufficiency, anemia, or bone lesions that can be attributed to the plasma cell proliferative disorder; clonal bone marrow plasma cells 60% or more; serum FLC ratio of involved to uninvolved at 100 or more, provided the involved FLC level is 100 mg/L or more; or more than one focal lesion on MRI scan.
- MGUS and SMM are asymptomatic plasma cell proliferative disorders that need to be distinguished from MM.

EPIDEMIOLOGY AND RISK FACTORS

MM accounts for 1.8% of all malignant diseases, and slightly greater than 10% of all hematologic malignancies. In 2024, it is estimated that there will be 36,110 new cases of myeloma, and an estimated 12,030 people will die of this disease.[39,40] There is a male-to-female predominance.[41] MGUS is about 1.6 times more common, and MM is twice as common in the Black population as in the White population.[42,43] The median age of patients at diagnosis is approximately 69 years. There is no known etiology. Exposure to radiation, benzene, other organic solvents, herbicides, or insecticides may play a role.[44-47] The Veterans Administration recognizes Agent Orange (dioxin) exposure in Vietnam Era veterans as a risk factor. If MM develops, it is considered a service-connected disability. There is a statistically significant risk for MM among firefighters, hairdressers, and employees exposed to engine exhaust.[48] The mortality is higher in firefighters and after low-level exposure to ionizing radiation in nuclear workers.[49,50]

There is an increased risk of MGUS in first-degree relatives.[51,52]

HEALTH DISPARITIES IN MM

Black patients are diagnosed with MM at a median age of 65, which is 5 years younger than the median age at diagnosis for White patients.[53] This difference may be partly due to population-specific variations in genomic makeup. There are also fundamental differences in the genetic and molecular signatures of the tumor itself. For example, there is a lower incidence of translocations such as t(11;14), t(4;14), and fewer monosomy 13/del13q and monosomy 17/del17p among Black patients in comparison with White patients.[54] Another study showed a significant difference in mutation frequency of TP53 and IRF4, with frequencies lower among

Black patients.[55] Notably, findings regarding t(11;14) have been inconsistent, with some smaller studies suggesting a higher incidence among Black patients, highlighting the heterogeneity of available data.[56] This higher incidence suggests that Black patients should do just as well as those of other races after anti-plasma cell therapy, but this has not been observed. The gains in survival among Black patients have not been as sizable compared with those of White patients, even with the advent of novel agents. Factors that account for this lag in survival may include socioeconomic determinants, such as access to cancer centers, structural racism, lack of private health insurance, mistrust of the medical community because of a history of previous injustices, and a shortage of Black healthcare workers who can help bridge the gap. Black patients are 50% less likely than White patients to undergo stem cell transplantation (SCT) and are less likely to receive first-line triplet induction therapy with a proteasome inhibitor and immunomodulatory agent.[57] Given the higher incidence of MM in the Black population, Black patients would especially benefit from participating in clinical trials, but currently, this group of patients accounts for only 4.5% of all trial participants.[58,59] The poor representation of Black patients in clinical trials only exacerbates outcome disparity by not considering the unique biology of this patient population when building treatment algorithms for patients with MM in the real world. Several studies have demonstrated that when Black patients are treated with appropriate and timely therapy, outcomes are at least similar and, in some studies, even superior to those of other races.[60]

Taken together, there is ample evidence to suggest that significant disparities still exist and are negatively affecting disease outcomes among Black people. The oncology community is addressing this issue of health inequality by implementing early screening initiatives, expanding the proportion of biospecimens from minority groups in established repositories, and developing study protocols that aim to increase participation by Black patients in clinical trials. These efforts will require a multistakeholder and community approach to overcome this unacceptable disparity.

PREVENTION

Prevention of MM is hampered by the low likelihood of progression in patients with the premalignant MGUS stage. Attempts to reduce the risk of transformation are being studied with ongoing trials of plant-based and ketogenic diets.[61] Investigations looking at potential modifications of the microbiology to prevent progression are also underway.[62]

The risk of MGUS progressing to MM increases by approximately 1% each year. In SMM, the highest risk of progression is in the first 5 years, with 2-, 5-, and 10-year risk of progression of 22%, 42%, and 64%, respectively.[36]

Recent screening efforts of note include the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) trial, which was a population-based screening study for MGUS and a randomized controlled trial (RCT) of follow-up strategies. In this study, more than 50% of the population (n = 80,759) provided informed consent, and 93.4% (n = 75,422) of enrolled individuals provided serum samples for the study.[63] Of the 75,422 screened individuals, 4.94% were found to have MGUS by diagnostic definitions, which is more common than previously reported (most cases were low- or low-intermediate risk in terms of progression). With 3 years of follow-up, iStopMM has identified a higher-than-expected number of individuals with SMM and MM. Although multiple meaningful and important findings were already reported by the iStopMM study, they represent population-based findings from one Nordic country.[64,65] Notably, the iStopMM study improved on the previously published Mayo Clinic criteria for risk of MGUS progression to MM. The Mayo Clinic model classifies MGUS into four risk groups based on the total score of laboratory values: IgG MGUS, M-protein concentration below 15 g/L, and FLC ratio between 0.26 and 1.65.[66] The new prediction model incorporates MGUS isotype, M-protein level, FLC ratio, and total concentrations of IgG, IgA, and IgM as predictors. Last, as FLCs are primarily cleared by the kidneys, the real prevalence of light chain MGUS is unknown in individuals with chronic kidney disease. Hence, iStopMM helped answer yet another significant question regarding defining new reference intervals for the FLC ratio based on kidney function. Abnormal FLC ratios were defined based on renal function: 0.46 to 2.62 for estimated glomerular filtration rate (eGFR) 45-50, 0.48 to 3.38 for eGFR 45-59, and 0.54 to 3.30 for eGFR less than 30 mL/min/1.73 m^2.[67] This suggests that published normal ranges for kappa FLC do not have the correct upper limit and isolated increases of kappa above published "ULN" should be approached cautiously.

The PROMISE study (NCT03689595) looked at the prevalence of monoclonal gammopathies and clinical outcomes in individuals aged ≥30 years within the high-risk US population, including those who self-identify as Black or with a family history of hematologic malignancy screened by mass spectrometry through a multicenter cohort study. This study detected a high prevalence of monoclonal gammopathies. By using the conventional serum protein electrophoresis/immunofixation (SPEP/IFX) method, the analysis revealed significantly higher rates of MGUS in high-risk individuals older than age 50 years (6%) than has been previously reported (3%); by using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, the detection rate was even higher (13% in individuals at high risk of disease), including rates of 17% among Black people and 13% among non-Black people with a family history of a close relative with a hematologic malignancy in comparison with 10% of non-Black people without such family history (the control group).[68]

Risk-stratification schemes have been developed to predict the risk of progression to active MM among patients who have SMM and to identify high-risk subsets of patients who might be suitable for earlier intervention. These schemes have included factors such as serum FLC ratio, immune paresis (defined by suppression of normal immunoglobulin levels or elimination of normal plasma cell populations), genetic or cytogenetic features, and other laboratory parameters. It was important to re-evaluate prognostic models after the 2014 revisions to the diagnostic criteria for active MM (discussed above), which reclassified the highest-risk patients with SMM as having active MM. The most useful scheme to be evaluated since then is the 2/20/20 rule developed by the

Mayo Clinic. M-protein greater than 2 g/dL, bone marrow plasmacytosis of greater than 20%, and FLC ratio greater than 20 can stratify patients into three groups with respect to risk of progression: (1) low risk (no factors), (2) intermediate risk (one factor), and (3) high risk (two or more factors). The median times to progression to active MM for low-, intermediate-, and high-risk groups were 110, 68, and 29 months, respectively.[35] The IMWG also added to the 2/20/20 rule by incorporating the presence of chromosomal abnormalities as an additional factor and allowed separation into four risk categories: low, low-intermediate, intermediate, and high. The risk of progression in 2 years for the high-risk group is 63%.[36] This risk of progression, however, has not been confirmed by other groups and may be significantly lower.[69]

Preventive strategies for MM have focused on preventing or delaying progression in high-risk patients with newly diagnosed SMM. A randomized trial conducted by the Spanish Myeloma Group in patients who had high-risk SMM found improved progression-free survival (PFS) and overall survival (OS) with early use of lenalidomide plus dexamethasone versus observation; however, participants in the observation arm may have been undertreated upon progression to active MM (only 11% of such participants received lenalidomide-based induction, which reflects its limited availability at the time); this possible undertreatment leaves uncertainty about whether the observed OS difference was due to early intervention per se.[70] In the long-term follow-up, the treatment arm continued to show a benefit on time to progression compared with the observation arm. Survival in patients who had received subsequent therapy at the time of progression did not differ between groups. The Eastern Cooperative Oncology Group (ECOG) E3A06 study found improved PFS when lenalidomide was used to prevent progression to symptomatic MM compared with observation among patients who had intermediate- to high-risk SMM. Subgroup analysis indicated that the benefit was restricted to the high-risk subset, according to the 2/20/20 rule; no OS difference has been reported.[71]

The AQUILA study randomized patients diagnosed with high-risk SMM to receive either 39 cycles of daratumumab or to undergo observation. With a median follow-up period of 65.2 months, results indicated that the risk of disease progression or death was reduced by 51% with daratumumab when compared with active monitoring (hazard ratio [HR], 0.49; 95% CI, 0.36-0.67; $P < .001$). PFS at 5 years was found to be 63.1% for the daratumumab group, in contrast to 40.8% for those undergoing active monitoring. Daratumumab demonstrated a low-grade safety profile among patients with SMM. A fixed duration of treatment provides patients with intervals free from daratumumab exposure, which may help prevent or delay the emergence of anti-CD38-refractory disease, thereby allowing for the subsequent use of anti-CD38-based quadruplet therapies following the progression to active MM.[72] Unfortunately, the observation group had limited access to daratumumab upon progression, with only 14% receiving this agent. This potential bias results in the comparison of patients receiving the drug to those patients not receiving the drug and may account for the survival difference.

On November 8, 2025, the FDA approved daratumumab for high-risk SMM. Patients with high-risk SMM should be monitored closely and considered for enrollment in clinical trials. With the recent FDA approval, daratumumab monotherapy represents an option to prevent or delay progression, following counseling on potential risks and uncertainties. Treatment with lenalidomide remains controversial because of uncertain OS implications, cost and toxicity concerns, and uncertain effects on outcomes with standard MM therapy in the event of disease progression. Ongoing trials are evaluating the effectiveness and safety of various regimens for treating high-risk SMM, ranging from doublet therapies to quadruplet therapies that incorporate ASCT.

KEY POINTS

- MM accounts for 1% of all cancers and approximately 10% of all hematologic cancers.
- Myeloma is twice as common in the Black population as in the White population.
- Early intervention with lenalidomide or daratumumab[72] prolongs time to progression to active MM and is now considered a possible treatment option for patients with high-risk SMM (participation in clinical trials is preferred).

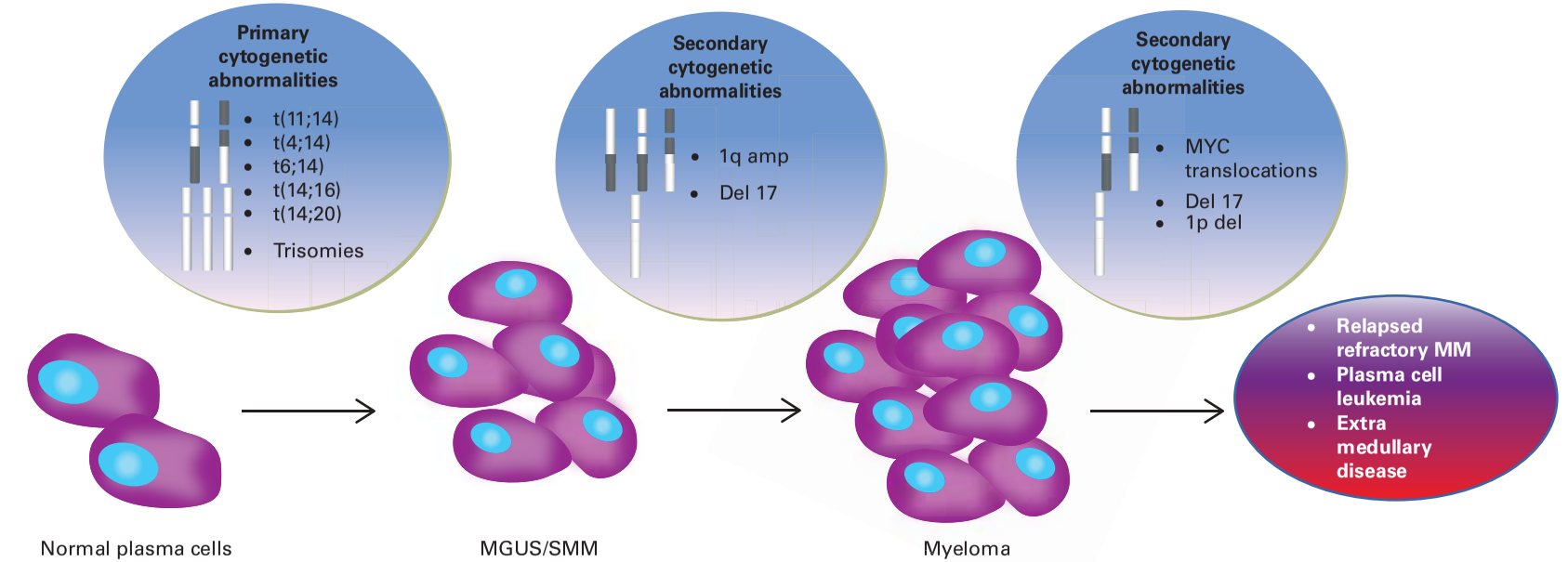
PATHOGENESIS

MM is almost always preceded by a premalignant phase referred to as MGUS. However, because MGUS is asymptomatic and can be detected only through specific laboratory testing, most patients diagnosed with MM do not have a history of MGUS. The pathogenesis of MM involves two initial steps.

The first step is the evolution of a normal plasma cell to an MGUS clone and is likely triggered by an abnormal response to antigenic stimulation. This results in the development of primary cytogenetic abnormalities in the affected plasma cells. In approximately 40% to 50% of patients who have MGUS, the primary cytogenetic abnormality is a reciprocal translocation involving the immunoglobulin heavy chain (IgH) locus on chromosome 14q32 (IgH-translocated MGUS) and one of five recurrent partner chromosome loci: 11q13 (cyclin D1 gene [*CCND1*]), 4p16.3 (*FGFR3* and *MMSET*), 6p21 (cyclin D3 gene [*CCND3*]), 16q23 (*c-Maf*), and 20q11 (*MAFB*). For more information on primary and secondary genetic events that can be identified by fluorescence in situ hybridization (FISH) data, see the IMWG report here.

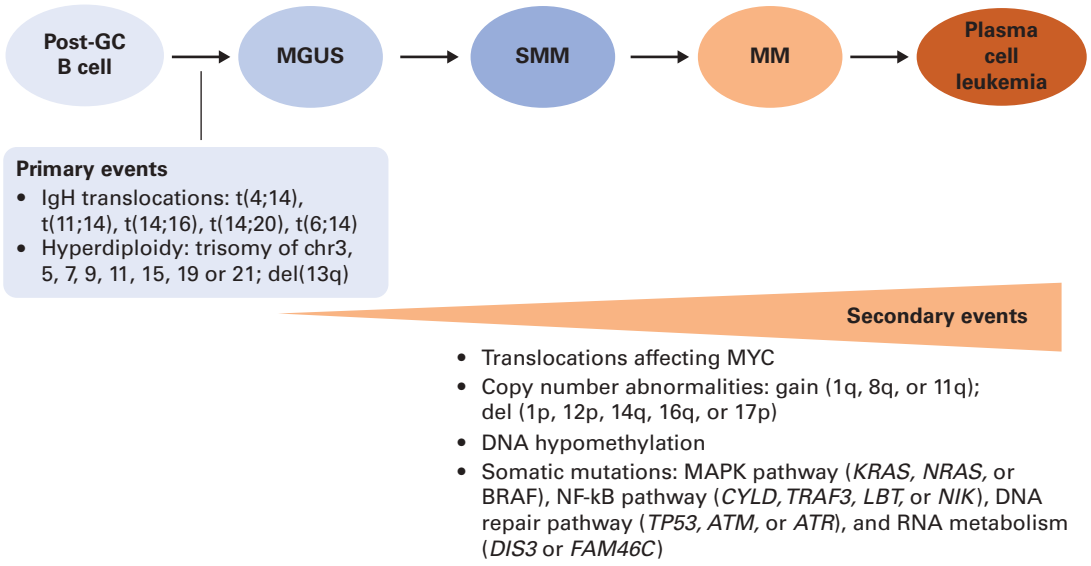
In most of the remaining patients with MGUS, the primary abnormality is the development of trisomies of one or more of the odd-numbered chromosomes, often resulting in hyperdiploidy (referred to as hyperdiploid MGUS or IgH-nontranslocated MGUS). In a small proportion of cases, neither trisomies nor IgH translocations are found, and in some patients, both types of abnormalities are found in the same clone (Figs. 21-1 and 21-2).

Figure 21-1 Cytogenetic Abnormalities in Multiple Myeloma



Primary cytogenetic abnormalities occur early when the normal plasma cell transitions to a clonal, premalignant stage. Most secondary cytogenetic abnormalities occur later in the disease course with malignant transformation or during progression of the malignancy. The effect of primary and secondary cytogenetic abnormalities on prognosis depends on the disease.
Abbreviations: IgH, immunoglobulin H; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.
Source: Rajan AM, Rajkumar SV. Interpretation of cytogenetic results in multiple myeloma for clinical practice. *Blood Cancer J*. 2015;5(10):e365, figure 1. PMID: 26517360. Reproduced under Creative Commons license.

Figure 21-2 Sequence of Genomic Events in the Molecular Pathogenesis of Multiple Myeloma



Abbreviations: GC, germinal center; IgH, immunoglobulin H; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.
Source: Awada H, Thapa B, Awada H, et al. A comprehensive review of the genomics of multiple myeloma: evolutionary trajectories, gene expression profiling, and emerging therapeutics. *Cells.* 2021;10(8):1961, figure 1. PMID: 34440730. Reproduced under Creative Commons license.

The second step is progression to MM, which occurs once an MGUS clone is established. Progression is often accompanied by additional genetic and transcriptional alterations, including abnormalities involving the *MYC* family of oncogenes; *RAS* mutations, *p16* methylation, and *p53* deletion or mutation; clonal diversification; perturbations of antimyeloma immunity; and permissive changes in the bone marrow microenvironment.

KEY POINTS

- MM is preceded by a premalignant phase that is clinically referred to as MGUS.
- The two principal pathogenetic steps are (1) transition from normal plasma cell to MGUS and (2) transition from MGUS to MM.
- The onset of MGUS is associated with IgH translocations (chromosome 14) in approximately 50% of cases and hyperdiploidy in the remaining 50%.

CLINICAL PRESENTATION AND DIAGNOSIS

Osteolytic bone lesions and/or compression fractures are hallmarks of the disease and can be detected on routine radiography, MRI scans, or CT scans in approximately 70% of patients. Anemia occurs in 70% of patients at diagnosis and is the primary cause of weakness and fatigue. Hypercalcemia is found in 15% of patients. Other symptoms may result from acute renal failure, radiculopathy, or recurrent infections.

When MM is suspected, patients should be tested for the presence of M-proteins by serum protein electrophoresis, serum immunofixation, urine protein electrophoresis, urine immunofixation, and serum FLC assay. The serum FLC assay and urine protein electrophoresis studies help identify the subset of patients with MM who lack M-protein heavy chain expression (ie, light chain MM). Only 82% of patients with MM have an M-protein that is detectable on serum protein electrophoresis, whereas serum immunofixation will identify an M-protein in 93% of patients. Combining serum studies with either urine studies or the serum FLC assay will reveal an M-protein in 97% to 98% of patients who have MM. Patients with serum M-protein concentration of less than 1 g/dL and urine M-protein of less than 200 mg/d are considered to have oligosecretory myeloma. In addition, approximately 2% to 3% of patients with MM have non-secretory disease with no evidence of an M-protein on serum immunofixation or urine immunofixation; a subset of these patients who also have a normal serum FLC ratio are considered to have true non-secretory myeloma.

Other tests considered essential for determining the presence of MM are complete blood cell count and serum creatinine, calcium, β_2 microglobulin, albumin, and lactate dehydrogenase levels. A unilateral bone marrow aspiration and biopsy are needed for the diagnosis. The monotypic nature of marrow plasma cells must be established by an abnormal κ:λ ratio found on immunohistochemistry or flow cytometry. Myeloma cells typically stain positive for CD38, CD56, and CD138. Bone marrow plasma

cells should also be studied with FISH and/or karyotyping to enable risk stratification (see the "Staging and Risk Stratification" section). FISH studies do not require dividing cells; hence, they are considerably more informative in MM than conventional karyotyping, which requires the presence of metaphases; however, conventional karyotyping can identify complex or unexpected abnormalities not detected by commonly used FISH probes.

Examination of all bones using whole-body, low-dose CT scans, whole-body MRI scans, or PET scans is required to detect lytic bone lesions[73] and can help differentiate SMM and solitary plasmacytoma from MM. PET/CT scans are especially useful in assessing extramedullary disease (EMD), whereas MRI scans can be used to visualize soft tissue and bones exceptionally well. Skeletal survey using plain radiography alone is considered inadequate, given that more sensitive testing is now available.

DIFFERENTIAL DIAGNOSIS

MM should be differentiated from some of the other plasmacytic or lymphoplasmacytic disorders, including but not limited to:

- MGUS
- SMM
- Solitary plasmacytoma (osseous or soft tissue)
- Waldenström macroglobulinemia
- Light chain or heavy chain deposition disease
- Systemic light chain (AL) amyloidosis
- Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome

MONITORING

Once MM is diagnosed, patients require periodic measurements of complete blood cell counts, serum creatinine, serum calcium, and M-protein levels by serum protein electrophoresis, serum FLC assay, and urine protein electrophoresis to assess treatment response and to monitor for relapse. In patients with oligosecretory myeloma (serum M-protein <1 g/dL and urine M-protein <200 mg/24 h) and in some patients with non-secretory myeloma, the serum FLC assay can be used to monitor response to therapy, provided that the FLC ratio is abnormal and the baseline level of the involved FLC is 100 mg/L or more.[74] In patients with oligosecretory myeloma who have lower levels of FLC and in patients with true non-secretory myeloma, monitoring is more difficult and requires periodic imaging studies and bone marrow examinations. Serum and urine tests for monitoring are done once per month during active therapy and once every 3 to 4 months thereafter. The widespread availability of the serum-FLC assay has reduced the need for frequent measurements of urinary light chain excretion. Bone marrow studies may be repeated to confirm a stringent complete response (CR), which is associated with a favorable prognosis, or when clinically indicated to assess relapse. In patients who experience CR, estimation of minimal residual disease (MRD) using next-generation flow cytometry or NGS with a sensitivity of 10^{-5} to 10^{-6} provides important prognostic information and may be a surrogate for PFS and OS. However, there is no data yet on the use of MRD results or CR status to guide therapy. Studies that assess MRD conversion from negative to positive have been found to be leading indicators of relapse by conventional M protein criteria, with 50% achieving traditional biochemical relapse criteria within 6 months.[75,76] Ongoing studies are using MRD for risk-adapted therapeutic decision-making. MRD can be checked annually through bone marrow studies, because MRD-negative sustainability is prognostic and is being explored as an endpoint to discontinue maintenance therapy. Response to therapy is assessed using the revised IMWG uniform response criteria.[77] For more information about the criteria for response and MRD assessment in MM, see the report here.

STAGING AND RISK STRATIFICATION

The two traditional methods of staging MM were the Durie-Salmon stage and the International Staging System (ISS). However, these staging systems have many limitations, and they do not account for the considerable variation in outcome that is dictated by the underlying cytogenetics of the disease. Previously, patients with del (17p13); translocations t(14;16), t(14;20), and t(4;14); and gain (three copies)/amplification (> 3 copies) (1q) are considered to have high-risk MM. Patients who do not have any of these abnormalities, typically those with trisomies, monosomy 13, or translocations t(11;14) and t(6;14), are considered to have standard risk.[78] The presence of concomitant trisomies may ameliorate the adverse prognosis associated with intermediate- and high-risk MM. This has been updated according to the latest modified version of the 2025 International Myeloma Society (IMS)/IMWG consensus criteria,[79] which require the presence of at least one of the following abnormalities: (1) del(17p), with a cutoff of >20% clonal fraction, and/or TP53 mutation; (2) an IgH translocation including t(4;14), t(14;16), or t(14;20) along with 1q+ and/or del(1p32); and (3) monoallelic del(1p32) along with 1q+ or biallelic del(1p32).

The revised ISS, introduced in 2015, is the current recommended staging system for MM, and it incorporates important markers of disease biology, including standard ISS, FISH for high-risk features (defined as presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16), and lactate dehydrogenase, a marker of increased proliferation), to provide a more accurate estimation of prognosis than previous staging systems did[80] (Table 21-1).

Table 21-1 **Revised International Staging System for Multiple Myeloma**

Publication Year	Stage	Criteria	Frequency (% of Patients)	Median Survival or 5-Year Survival Rate (%)
ISS stage	1	Serum albumin >3.5 g/dL, serum β2-microglobulin <3.5 mg/L	29	62 months
	2	Neither ISS stage I nor III	37.5	44 months
	3	Serum β2-microglobulin >5.5 mg/L	33.6	28 months
R-ISS stage	1	ISS-I	28	82%
		No high-risk cytogenetics		
		Normal LDH		
	2	Neither ISS stage I nor III	62	62%
	3	High-risk cytogenetics [t(4;14), t(14;16), or del17p13] or elevated LDH level	10	40%
R2-ISS stage*	1	0 points	19.2	Not reached
	2	0.5-1 points	30.8	109.2 months
	3	1.5-2.5 points	41.2	68.5 months
	4	3-5 points	8.8	37.9 months

Abbreviations: ISS, International Staging System; LDH, lactate dehydrogenase; R-ISS, revised ISS.
*ISS-III, 1.5 points; ISS-II, del17p13, high lactate dehydrogenase, or t(4;14), 1 point; and 1q1 0.5 points.
Reprinted from Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-2869. doi:10.1200/JCO.2015.61.2267

In a most recent study, the second revision of ISS (R2-ISS) investigated the prognostic value of adding 1q1 as a risk factor by collecting data from 10,843 newly diagnosed patients enrolled in 16 clinical trials. Using a training set (n = 7,072) and a validation set (n = 3,771), a value was assigned to each of the risk factors that had the highest impact on PFS and OS (ISS-III, 1.5; ISS II, 1; del17p13, 1; high lactate dehydrogenase, 1; t(4;14), 1; and 1q1, 0.5 points). Four independent risk groups were identified according to the total additive score: low risk (R-ISS I; 0 points), low-intermediate (R-ISS II; 0.5-1 point), intermediate-high (R-ISS-III, 1.5-2.5 points), and high (R-ISS IV, 3-5 points). Median OS was not reached versus 109.2, 68.5, and 37.9 months, respectively. Median PFS (mPFS) was 68, 45.5, 30.2, and 19.9 months, respectively.[81]

The Mayo Additive Staging System is another staging system that has been developed and validated; it incorporates additional FISH abnormalities not included in the R-ISS (eg, 1q gain/amplification) and reflects the additive effects of co-occurring high-risk disease features.[82]

KEY POINTS

- The most common presenting symptoms of MM are fatigue and bone pain; other presenting features are hypercalcemia, infection, and renal failure.
- When MM is suspected, patients should be tested for the presence of M-proteins by serum and urine protein electrophoresis, serum and urine immunofixation, and serum FLC assay.
- Full-body skeletal imaging studies and a bone marrow biopsy are required if MM is suspected.
- Patients are staged using the variations of ISS (R-ISS or R2-ISS).
- Patients are considered to have high-risk MM if at least one of the following abnormalities is present: (1) del(17p), with a cutoff of >20% clonal fraction, and/or TP53 mutation; (2) an IgH translocation including t(4;14), t(14;16), or t(14;20) along with 1q+ and/or del(1p32); (3) monoallelic del(1p32) along with 1q+ or biallelic del(1p32); or (4) β2 microglobulin ≥5.5 mg/L with normal creatinine (<1.2 mg/dL). Patients with trisomies or translocations t(11;14) and t(6;14) are considered to have standard-risk MM.

THERAPEUTIC MANAGEMENT

INITIAL THERAPY

Choice of initial induction therapy for MM should take into account the baseline comorbidity profile of a patient, specifically including the presence of peripheral neuropathy or cardiovascular comorbidities that may direct the choice of first-line induction regimen, as well as a patient's eligibility and preference for ASCT (Fig. 21-3). In general, eligibility for SCT is determined by performance status and comorbidities, although patients who are more fit and those of advanced age can still be considered. Age alone is not used in determining transplant eligibility. Patients who are not candidates for ASCT or those who choose not to pursue ASCT as first-line therapy are typically treated with an induction regimen for 6 to 12 months, followed by consideration of maintenance therapy, or they may simply continue triplet-based induction until disease progression, toxicity, or intolerance. Patients who are considered potential candidates for ASCT are first treated with three to four cycles of a quadruplet regimen (more recently considered a new standard) followed by stem cell collection. After stem cell harvest, many patients proceed to ASCT (the early ASCT approach), although some may choose to continue the initial treatment regimen if they have achieved a deep response and delay ASCT until relapse (the delayed ASCT approach). After initial treatment of patients who choose transplantation and those who choose not to receive transplantation, the standard treatment is risk-associated consolidation followed by indefinite maintenance until disease progression, unacceptable toxicity, or tolerance. Recent comparative meta-analysis of triplet versus quadruplet induction regimens in newly diagnosed, treatment-naive MM have all demonstrated four-drug induction regimens that include an anti-CD38 antibody improve anti-MM efficacy, although with higher rates of grade 3 or more infections and thrombocytopenia.[83]

TREATMENT OF PATIENTS WHO ARE NOT CANDIDATES FOR ASCT

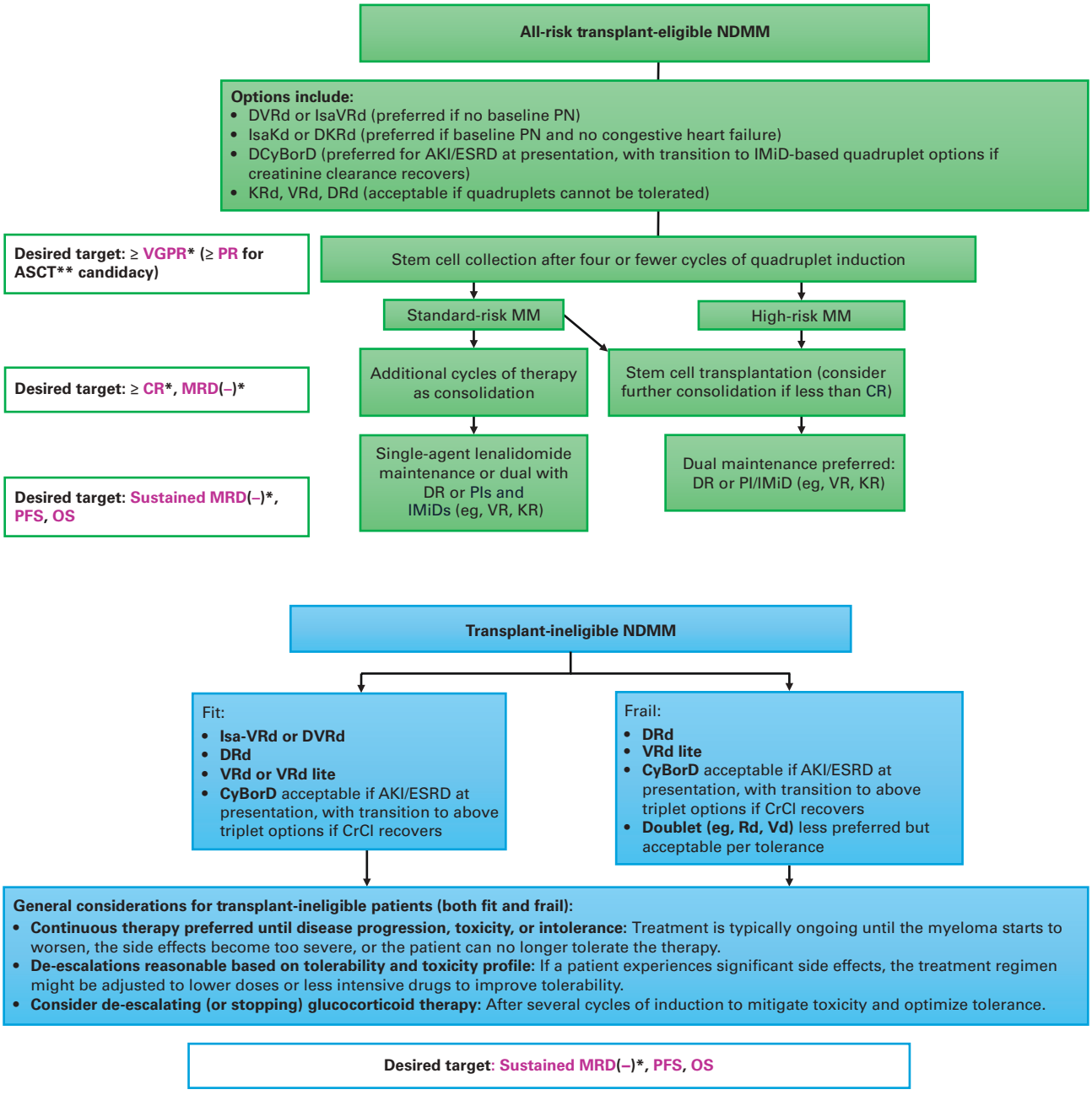
For patients with transplant-ineligible (TIE) newly diagnosed multiple myeloma (NDMM), melphalan-based regimens and doublet therapy are no longer preferred as first-line therapy. Even quadruplet therapies that do not incorporate immunomodulatory drug (IMiD) into the induction backbone, such as that commonly used in Europe based on the ALCYONE[84] data, are not common in the North American practice patterns. Until recently, the standard of care has been first-line therapy with either VRd or DRd triplets. The VRd data are based on superior PFS and OS compared with data for lenalidomide and dexamethasone (Rd) in the SWOG S0777 trial. The mPFS was 43 months versus 30 months (P = .0018); median OS was 75 months versus 64 months (P = .025). Although this study did not include SCT, the median age of the patients was only 63 years, with most intending to receive a transplant. A subgroup analysis suggested that VRd was not as beneficial in patients older than 65 years, and the VRd regimen as studied in this trial used doses and schedules that would be toxic in many older, frail patients. Conversely, the MAIA trial data with DRd were more representative of the TIE patients who had a median age of 73 years.[31] DRd was compared with Rd alone. The regimen was well tolerated, with improvement in deep responses and MRD-negativity rates. The PFS was superior for DRd compared with Rd. At 5 years, DRd reduced the risk of death by 32%, and the risk of progression or death was reduced by 47%. DRd is approved by the FDA for this indication.

Although quadruplet therapies based on triple backbone combinations with IMiDs and PIs added to anti-CD 38 monoclonal antibodies had previously been reserved for patients with transplant-eligible (TE) NDMM, several, recent, phase 3 RCTs and a recent FDA approval now support the use of similar quadruplet combinations in the frontline treatment of TIE, or transplant deferred, NDMM, ushering a new era of quadruplet therapies for all newly diagnosed patients regardless of transplant eligibility. Notable phase 3 RCTs in this space include the IMROZ, BENEFIT, and CEPHEUS trials.[6-8]

IMROZ was an international, open-label, phase 3 trial, which randomly assigned, in a 3:2 ratio, patients 18 to 80 years of age with TE NDMM to receive either isatuximab plus VRd or VRd alone. The median ages in the frail group were 75 and 76, respectively. The median age in the non-frail group was 71 years in both arms. The primary efficacy endpoint was PFS. At a median follow-up of 59.7 months, the estimated PFS at 60 months was 63.2% in the isatuximab-VRd group in comparison with 45.2% in the VRd group (HR for disease progression or death, 0.60; 98.5% confidence interval [CI], 0.41-0.88; P < .001). The percentage of patients with a CR or better was significantly higher in the isatuximab-VRd group than in the VRd group (74.7% vs. 64.1%, P = .01), as was the percentage of patients with MRD-negative status and a CR (55.5% vs. 40.9%, P = .003).[6] On September 20, 2024, the FDA approved isa-bortezomib, lenalidomide, and dexamethasone (Isa-VRd) for adults with NDMM who are not eligible for ASCT, making it the first anti-CD38 therapy available in this patient population plus VRd.[85]

BENEFIT was an Intergroupe Francophone of Myeloma phase 3 study (not a registrational study) that randomized 270 patients with TIE NDMM age 65 to 79 years, to IsaRd versus Isa-VRd. The median age in the two groups was 73.6 and 73.2 years, respectively. The primary endpoint was a MRD-negativity rate at 10^{-5} by NGS at 18 months from randomization. The 18-month MRD-negativity rates at 10^{-5} were reported in 35 patients (26%; 95% CI, 19-34) in IsaRd versus 71 (53%; 95% CI, 44-61) in Isa-VRd (odds ratio [OR] for MRD negativity 3.16; 95% CI, 1.89-5.28, P < .0001). The MRD benefit was consistent across subgroups at 10^{-5} and 10^{-6} and was observed at month 12. The proportion of patients with CR or better at 18 months was higher with Isa-VRd (58% vs. 33%; P < .0001), as was the proportion of MRD negativity and CR or better (37% vs. 17%; P = .0003). At a median follow-up of 23.5 months, no difference was observed for survival times (immature data).[8]

Figure 21-3 Treatment Approaches for Transplant-Eligible and Transplant-Ineligible Newly Diagnosed Multiple Myeloma



The primary goal of treatment for TE and TIE NDMM is to achieve a rapid, deep, and durable response. This aims to provide long-term disease control and ultimately improve patient prognosis.

Abbreviations: AKI, acute kidney injury; ASCT, autologous stem cell transplantation; CR, complete response; CrCl, creatinine clearance; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; DCyBorD, daratumumab, daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DKRd, daratumumab, carfilzomib, lenalidomide, and dexamethasone; DR, daratumumab and lenalidomide; DRd, daratumumab, lenalidomide, and dexamethasone; DVCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ESRD, end-stage renal disease; IMiD, immunomodulator (ie, lenalidomide or pomalidomide) drug; Isa-VRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Isa-KD, isatuximab, carfilzomib; and dexamethasone; KR, carfilzomib and lenalidomide; KRd, carfilzomib, lenalidomide, and dexamethasone; MM, multiple myeloma; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor (ie, bortezomib, ixazomib, carfilzomib); PN, peripheral neuropathy; PR, partial response; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone; VGPR, very good partial responses; VR; bortezomib and lenalidomide; VRd, bortezomib, lenalidomide, and dexamethasone.

*Target indicates the desired level of response, and not a failure of treatment if not achieved.

**For ASCT step: minimum PR and ideally VGPR. Standard risk includes all cytogenetics that are not considered high risk; high risk includes any patient with one high-risk cytogenetic mutation such as del(17p), t(14;16), t(14;20), t(4;14), del(1p), amp(1q) or gain(1q); ultra-high risk includes any patient with more than one high-risk cytogenetic mutation.

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The CEPHEUS trial[7] is a phase 3 study that compared the rates of MRD negativity at 10^{-5}, as determined by next-generation sequencing (NGS), following induction with the combination of VRd with or without daratumumab in myeloma patients who are either TE or have deferred transplantation. The trial also assessed response depth and OS as secondary endpoints. The median age of both arms was 70 years. Following eight cycles of induction, patients continued with maintenance therapy excluding bortezomib. A total of 395 patients were randomly assigned to the study. At baseline, approximately 28% of participants presented with high-risk cytogenetics, and 28% had ISS stage III myeloma. After a median follow-up of 58.7 months, 60.9% of patients in the daratumumab-VRd (DVRd) arm achieved MRD negativity, compared with 39.4% in the VRd arm, resulting in an OR of 2.37 (95% CI, 1.58-3.55); $P < .0001$. CR rates were significantly higher in the DVRd cohort at 81.2%, compared with 61.6% in the VRd group, yielding an OR of 2.73 (95% CI, 1.71-4.34); $P < .0001$. In addition, sustained MRD-negativity rates for 12 months or more were higher in the DVRd group at 48.7%, versus 26.3% for the VRd arm, with an OR of 2.63 (95% CI, 1.73-4.00; $P < .0001$). The 54-month PFS in the DVRd group was 68.1% compared with 49.5% in the VRd group, with an HR of 0.57; 95% CI, 0.41 to 0.79; $P = .0005$. No new safety concerns were reported with the addition of daratumumab to the VRd regimen.[7]

Other daratumumab regimens have been studied in combination with standard regimens in TIE candidates. The combination of daratumumab, bortezomib, melphalan, and prednisone was compared with bortezomib, melphalan, and prednisone alone in the ALCYONE trial. After the initial induction therapy, patients in the daratumumab arm continued to receive daratumumab as a single agent. In this study, the daratumumab arm was associated with a significant improvement in PFS in the entire population, and the OS was also superior in that arm.[86] In the subset of high-risk patients, there was no difference in PFS.[87] For extremely frail patients (ie, those who have multiple comorbidities and poor performance status), treatment with a doublet therapy or monotherapy daratumumab may be a consideration to add an agent based on tolerability. Frailty assessments and consultations with geriatric oncologists can be invaluable in the assessment of such a patient.

TREATMENT OF CANDIDATES FOR ASCT

Although three-drug combinations such as VRd and carfilzomib, lenalidomide, and dexamethasone (KRd; cyclophosphamide, bortezomib, and dexamethasone [CyBorD] in select patients who present with acute renal injury with light chain cast nephropathy) represented the previous standard of care, the availability of long-term follow-up data from the GRIFFIN trial and reports from phase 3 randomized trials, including GMMG-HD7, PERSEUS, and IsKia, have ushered in the new era of quadruplet-based induction for TE patients who have newly diagnosed MM.

Quadruplet therapy with DVRd in the randomized phase 2 GRIFFIN study was given in three weekly cycles (bortezomib on days 1, 4, 8, 11, and lenalidomide 14/21 days) and showed superior CR or greater (82% vs. 60%) and MRD-negativity rates (64.4% vs. 30.1%) in comparison with VRd alone in patients who received transplants. The median age for the DRVd arm was 59 years, and in the VRd arm, 61 years. mPFS (although it was not the primary endpoint of the trial) was ultimately improved at 50 months of median follow-up (4-year PFS was 87.2% for DVRd vs. 70.0% for VRd; HR, 0.45; $P = .032$).[88] The PERSEUS trial was a phase 3 counterpart of the GRIFFIN trial which delivered therapy in 28-day cycles (bortezomib on days 1, 4, 8, 11, and lenalidomide 21/28 days). Patients in the DVRd group also received subcutaneous daratumumab. The PERSEUS trial did not have a second randomization to maintenance therapy, allowing for a more precise interpretation of the benefit of adding daratumumab across the entire treatment regimen, compared with VRd induction therapy and lenalidomide maintenance therapy. Therefore, patients in the DVRd arm received at least 24 months of daratumumab before discontinuation if they achieved at least a CR and sustained MRD. After a median follow-up of 48 months, the DVRd group demonstrated a longer PFS than the VRd group (84.3% vs. 67.7%, respectively; HR, 0.42; $P < .001$). Prespecified subgroup analyses suggested a consistent benefit for PFS in the DVRd group compared with the VRd group across clinically relevant subgroups, including patients with ISS stage III disease and those with high cytogenetic risk [defined in this study as del (17p) and/or t(4;14), and/or t (14;16)].[3]

Several isatuximab-based phase 3 trials were also conducted that examined the quadruplet-versus-triplet question. The GMMG-HD7 was one such trial that randomly assigned patients to VRd with or without isatuximab. Median age in the isatuximab arm was 59 and 60 years in the control group. The primary endpoint was MRD negativity by next-generation flow cytometry to the 10^{-5} level. The addition of isatuximab improved MRD negativity (50% vs. 36%; $P < .001$).[2] More recently, the IsKia trial became the first RCT to compare a KRd-based triplet therapy with anti-CD38 antibody–containing KRd quadruplet therapy (isatuximab). The median age of both arms was 72 years. It demonstrated the superiority of isatuximab and KRd (Isa-KRd) in achieving a rate of MRD negativity less than 10^{-5} by NGS after consolidation in intention-to-treat patients (77% vs. 67%; OR, 1.67; $P = .049$). Benefit was maintained, and improvement was consistent across all participant subgroups, including high-risk categories [del(17p) and/or t(4;14) and/or t(14;16)].[5] Updated data[89] reported MRD negativity at 10^{-6} after full-dose consolidation was 67% versus 48% with Isa-KRd versus KRd (OR 2.29; $P < .001$), and 1-year sustained MRD at 10^{-6} after light consolidation was 52% versus 38% (OR 1.82; $P = .012$).

Anti-CD38 antibody quadruplets have become a preferred regimen for TE patients who have NDMM; it remains uncertain whether first-line daratumumab confers an OS benefit compared with its use in later lines of therapy because follow-up data are still premature.[90] As previously mentioned, CyBorD is an adequate alternative if it is used in the setting of acute renal failure with

light chain cast nephropathy (because lenalidomide is renally cleared). The metabolism of cyclophosphamide does not depend on adequate renal function.

Using lenalidomide for more than six cycles can impair the collection of peripheral blood stem cells in some patients when granulocyte colony-stimulating factor alone is used for stem cell mobilization. Stem cell mobilization in these patients is usually successful with a chemotherapy-containing mobilization regimen such as cyclophosphamide and granulocyte colony-stimulating factor, or by using plerixafor, a CXCR4 inhibitor. The influence of daratumumab on stem cell collection is a topic of ongoing debate, with several reports indicating a reduced yield in stem cell collection. Despite the impact of daratumumab on stem cell collection, patients are ultimately able to collect enough stem cells to proceed to transplantation.[91]

Anti-SLAMF7 antibody–containing induction regimens have also been attempted. Preliminary activity of elotuzumab in the frontline setting was suggested in a phase 2 trial[92] of Elo-KRd using an MRD-adapted design, which demonstrated MRD negativity rates (10^{-5} by NGS) of up to 70% and an estimated 3-year PFS of 72% overall (92% among patients achieving MRD negativity). However, in the GMMG-HD6 trial, elotuzumab-VRd was compared with VRd in TE patients who had NDMM, but the treatment arm that used quadruple therapy failed to show PFS or OS benefit.[2,93] Similarly, elotuzumab also failed to provide a PFS benefit when it was used in the same combination in the SWOG-1211 trial[94] in patients who had high-risk newly diagnosed MM. Overall, it seems that elotuzumab in combination with an immunomodulator performs better in the relapsed/refractory setting, in which an OS benefit was reported.[95,96]

HIGH-RISK PATIENTS

The 2025 IMS/IMWG consensus redefined high-risk MM criteria. The prior 2016 consensus had identified t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperdiploidy, and gain(1q) as poor prognostic factors.[97] High-risk MM is now defined by the presence of at least one of the following: (1) del(17p) with a cutoff of 20% clonal fraction or TP53 mutation; (2) an IgH translocation, including t(4;14), t(4;16) OR t(14;20) along with 1q+ and/or del(1p32); (3) monoallelic del (1p32) along with 1q+ or bialellic del(1p32), or (4) beta 2 microglolobulin ≥5.5 mg/L with creatinine ≤1.2 mg/dL.[1] For patients with high-risk myeloma, a combination of an immunomodulator and a proteasome inhibitor should be incorporated into first-line therapy for TE patients, and quadruplet therapy is preferred for delivery, if possible. Considering the high rate of deep responses observed on the GRIFFIN trial, DVRd is an acceptable option for high-risk patients. Some experts recommend a backbone of carfilzomib and an IMiD as initial therapy for high-risk patients based on high response rates observed with carfilzomib in several triplet and quadruplet studies. Of note, KRd has not been prospectively compared with VRd in high-risk patients, but no difference was seen in the ENDURANCE trial, which only included patients with standard-risk cytogenetics. However, a retrospective study in high-risk patients [defined as 1q+, t(4;14), t(14;16), t(14;20), and del(17p)] demonstrated a mPFS of 70.9 months with KRd, compared with 41 months with VRd, highlighting the potential benefit of KRd in this population. The open-label, phase 2 FORTE trial investigated carfilzomib-based induction and consolidation approaches (KRd × 12 cycles vs KRd plus ASCT vs carfilzomib, cyclophosphamide, and dexamethasone [KCd] plus ASCT). KRd plus ASCT showed superior response rates and MRD-negativity rates and significantly prolonged PFS, including among high-risk (defined as presence of one of the del(17p), t(4;14), t(14;16), del(1p), gain(1q), or amp(1q)), and ultra-high-risk (more than one high-risk mutation) groups. In the first published trial of high-risk MM, the addition of elotuzumab to VRd induction and maintenance did not improve patient outcomes. PFS in both study groups exceeded the original assumption, suggesting continuous two-drug maintenance therapy with a PI and IMiDs would be beneficial.[94] In the OPTIMUM/MUKnine OPTIMUM) trial, genetic screening was used to identify patients with high-risk MM. Patients were treated with daratumumab, bortezomib, lenalidomide, cyclophosphamide, and dexamethasone followed by ASCT. There was no control arm. Consolidation consisted of dara-VRd and a second consolidation with VRd and dara-R maintenance therapy. PFS estimates at 36, 48, and 60 months were 75%, 70%, and 61%, respectively. OS estimates at 60 months were 71%. This suggests that a clean triplet induction extended consolidation with the dara-VR group would be beneficial for this ultra-high risk.[98-100]

In the multicenter, single-arm, phase 2 MASTER trial, patients received four cycles of daratumumab, carfilzomib, lenalidomide, and dexamethasone (DKRd) as induction, ASCT, and zero, four, or eight cycles of DKRd consolidation according to MRD status. There was a planned enrichment for patients with high-risk cytogenetics (defined by the presence of del(17p), t(4;14), and/or t(14;16)). The primary endpoint was achievement of MRD negativity. Patients continued to receive therapy until they achieved two consecutive MRD-negative tests at a level less than 10^{-5}, and then they entered a treatment-free observation period with regular MRD testing. Although the odds of achieving two consecutive MRD-negative tests were similar across risk groups, patients with standard-risk or one high-risk mutation had excellent PFS and OS in the absence of maintenance therapy. Alternatively, the risk of progression was higher among patients with ultra-high-risk MM (two or more high-risk mutations); 2-year PFS from treatment cessation was 54% in this latter group. The results of the MASTER trial suggest that for many patients, an MRD-adapted treatment algorithm can provide durable disease control even off therapy, but for the ultra-high-risk patient, continued maintenance is still important regardless of MRD status.[101]

In another phase 2 trial (IFM 2018-04) using DKRd in high-risk disease (defined by the presence of del(17p), t(4;14), and/or t(14;16)), 50 previously untreated patients were treated with DKRd induction, followed by first ASCT, and DKRd consolidation,

followed by second ASCT followed by maintenance with daratumumab and lenalidomide. The overall response rate (ORR) was 96% (92% with a very good partial response [PR] or better) with an MRD-negativity rate by NGS at 64% at 10^{-5} and 62% at 10^{-6} before maintenance.[102] The 30-month PFS and OS rates were 80% and 91%, respectively.[99] This trial is ongoing, and long-term follow-up will be vital in determining whether this aggressive approach can be regarded as safe and efficacious over time.

By using a similar structure, the GMMG-CONCEPT trial investigated the efficacy of combining isatuximab, carfilzomib, lenalidomide, and dexamethasone in patients with high-risk myeloma, defined as ISS stage II to III along with del17p13, t(4;14), t(14;16), or more than three 1q21 copies (amplification 1q21). This category included primary plasma cell leukemia (PCL; oligosecretory or non-secretory disease), provided it was measurable by bone lesions. The trial enrolled patients irrespective of their transplant eligibility. The primary endpoint was achieving MRD negativity at a 10^{-5} level through next-generation flow cytometry. The treatment plan involved six cycles of the quadruplet induction (with stem cell collection after the third cycle), followed by an ASCT if the patient was TE or by two extra cycles otherwise. Consolidation included four cycles of the quadruplet chemotherapy, and maintenance comprised 26 cycles of the quadruplet therapy without dexamethasone. The GMMG-CONCEPT trial strategically integrated two beneficial approaches: quadruplet treatments and ongoing maintenance and treatment. Del17p13 emerged as the most prevalent high-risk cytogenetic feature. With a median age of 58 years, the trial met its primary endpoint with MRD negativity. After consolidation, MRD-negativity rates were 67.7% for TE patients and 54.2% for TIE patients. Significantly, MRD negativity sustained for at least 1 year was observed in 62.6% and 46.2% of TE and TIE patients, respectively.[100]

Other ongoing trial, that focused primarily on ultra-high-risk disease (defined as the presence of ≥2 genetic risk markers t(4;14)/t(14;16)/t(14;20), del(1p), gain(1q), and del(17p), and/or SKY92 gene expression risk signature) or PCL (defined by >20% circulating plasmablasts), include the UK-based OPTIMUM trial, a study using D-CVRd consolidation for 18 cycles after ASCT, followed by maintenance with daratumumab and lenalidomide. Patients with PCL were included in this study. The ORR after induction was 95.3%. The 30-month PFS of 77% compared favorably with that in the MASTER trial.[103]

The bone marrow transplant clinical trials network has not accruing trial for using T-cell–redirecting therapy in high-risk myeloma patients, which includes B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T and G protein–coupled receptor, class C, group 5, member D (GPRC5D) consolidation. The results of this trial have not been reported (NCT 05032820).

In patients with clinically aggressive disease (ie, PCL, extensive EMD), combination chemotherapy such as VTd plus cisplatin, doxorubicin, cyclophosphamide, and etoposide (PACE) can be used as initial therapy to achieve rapid disease control, although it is acceptable to treat these patients with potent triplet and quadruplet modern regimens, which may yield similar response rates.

KEY POINTS

- For TE patients, preferred regimens for initial MM treatment include PI, IMiD, and anti-CD38 antibody–containing quadruplet regimens such as DVRd, DKRd, Isa-VRd, Isa-KRd, and daratumumab, bortezomib, cyclophosphamide, and dexamethasone (DCybBorD; in case of inability to dose IMiDs optimally).
- CyBorD and VTd (less so) are alternatives, and may be preferred in the setting of acute renal failure with light chain cast nephropathy.
- For the TIE patients, recent FDA approval of Isa-VRd quadruplet with a category 1 recommendation, and availability of RCT phase 3 data with DVRd regimens adds these quadruplet combinations to the list of available, powerful induction combinations in this space. The triple combinations with either VRd or DRd remain category 1 options for those who are deemed unfit for frontline quadruplet therapy.

AUTOLOGOUS STEM CELL TRANSPLANTATION

Although ASCT is not curative for MM, it prolongs mPFS compared with conventional chemotherapy. The treatment-related mortality rate is low (1%-2%), and 40% to 50% of ASCTs can be performed entirely on an outpatient basis. Melphalan (at a dose of 200 mg/m^2) is used as the standard conditioning regimen, and trials are underway that are trying to improve its efficacy. ASCT can be performed immediately after initial therapy, or it can be delayed until the first relapse. In either case, stem cells must be collected early in the treatment course. Since the initial randomized studies of ASCT were performed, more recent studies have evaluated ASCT in the context of modern first-line and maintenance therapy. In the pivotal DETERMINATION trial, patients who had newly diagnosed MM received three cycles of VRd and underwent stem cell mobilization followed either by five additional VRd cycles (the VRd-alone group) or by ASCT followed by two additional VRd cycles (the ASCT group). Both groups received lenalidomide maintenance therapy until disease progression. After a median follow-up of 76 months, PFS was superior in the ASCT arm (median, 67.5 vs. 46.2 months; $P < .001$); OS was similar between the two arms, although median OS has not been reached, and the trial was not powered to detect differences in OS. Notably, only 22% of the VRd-alone group underwent ASCT at first relapse.[10] Other studies have highlighted the benefits of ASCT as first-line therapy. In the FORTE trial, KRd followed by ASCT provided higher PFS and MRD-negativity rates over KRd without transplantation.[102] In the EMN02 trial, which examined CyBorD induction followed by ASCT versus melphalan, bortezomib, and prednisone, ASCT reduced the risk of

disease progression by 27% and offered an OS advantage over no transplantation. In general, based on superior PFS, early ASCT is preferred. However, patient and physician preferences play an important role in deciding the timing of ASCT, especially in patients with standard risk. Although some earlier randomized trials showed a benefit with two ASCTs performed back-to-back (tandem ASCT), one randomized trial conducted in the United States (STAMINA trial) found no benefit with tandem ASCT in the context of modern therapy, with lenalidomide maintenance.[104] As such, there is no role for tandem ASCT in modern treatment paradigms for TE NDMM.[105]

The Midas trial randomized TE patients into post-induction (Isa-KRd) MRD+ or MRD− groups (MRD at 10^{-5}). MRD− groups post-induction randomized to consolidation versus ASCT, and no improvement of MRD negative at the more stringent 10^{-6} threshold was seen with ASCT. MRD+ patients randomized to single or tandem transplants and no increase in MRD− was seen.[106]

ALLOGENEIC STEM CELL TRANSPLANTATION

Allogeneic stem cell transplantation (allo-SCT) offers the potential benefit of a graft-versus-myeloma effect. However, conventional myeloablative allo-SCT has a limited role in MM because of high treatment-related mortality rates. One study found a significant OS advantage with allo-SCT followed by nonmyeloablative allo-SCT compared with allo-SCT alone. However, other trials have not shown such a benefit. Allo-SCT is safer, but nonmyeloablative allo-SCT is associated with a greater risk of relapse and has not shown a consistent benefit compared with allo-SCT alone. Currently, allo-SCT is generally not recommended for the treatment of MM outside of clinical trials.[107]

MAINTENANCE THERAPY

Myeloma maintenance after ASCT in patients who have newly diagnosed MM is considered standard treatment. Three randomized studies have shown superior PFS with lenalidomide maintenance after ASCT. All maintenance studies had PFS as the primary endpoint, and none were powered for assessment of their impact on OS. A meta-analysis of more than 1,200 patients from RCTs that assessed lenalidomide maintenance versus placebo or observation after ASCT demonstrated significant OS benefit and reaffirmed the PFS benefit with lenalidomide maintenance after ASCT.[108]

An increased risk of second cancers was seen in two randomized trials with lenalidomide maintenance (approximately 7% in the lenalidomide group vs. 3% in the placebo group; $P < .01$); this situation needs to be discussed with the patient and monitored during follow-up. Lenalidomide maintenance is recommended for patients with standard-risk MM after ASCT. In high-risk patients, the benefit of lenalidomide maintenance was shown in the Myeloma XI trial. Patients with high-risk disease benefited from lenalidomide maintenance compared with no maintenance, but the magnitude of that benefit was less.[109] Bortezomib maintenance (administered twice per month) after ASCT has also shown benefit and can be added to lenalidomide for patients with high- or intermediate-risk cytogenetics. Ixazomib, an oral proteasome inhibitor, has been shown to improve PFS compared with placebo as maintenance therapy for patients who have MM after induction therapy that included ASCT (TOURMALINE MM3) or excluded ASCT (TOURMALINE MM4). The PFS was improved from 21.3 months in the placebo group to 26.5 months in the ixazomib-after-transplantation group; however, the OS did not differ between the ixazomib versus placebo group. In the group of patients who did not receive a transplantation, there was a trend toward an inferior survival with ixazomib maintenance; however, the interim OS results may be skewed by early events in patients who did not benefit from maintenance, therefore, the final intention-to-treat outcomes remain uncertain.[110] The updated result showed ixazomib prolonged PFS in patients who were MRD+ before maintenance and at a 14-month landmark analysis.[111]

A combination of ixazomib and lenalidomide has demonstrated a PFS benefit in high-risk patients over lenalidomide alone in TE patients,[112] but in a post-transplant setting, ixazomib did not provide additional benefit to lenalidomide maintenance.[113] Ixazomib as a single-agent maintenance therapy is not FDA approved, and its specific role as maintenance remains unclear.

With the incorporation of daratumumab into first-line therapy, the safety and efficacy of an anti-CD38 mAb–lenalidomide maintenance strategy were evaluated. In the GRIFFIN trial, daratumumab and lenalidomide maintenance led to a doubling of the MRD-negativity rate after 2 years when compared with lenalidomide alone.[88]

The incorporation of anti-CD38 in conjunction with lenalidomide maintenance therapy yielded positive outcomes in the AURIGA trial. This trial is a phase 3 study that assesses the efficacy of daratumumab in combination with lenalidomide (D-R) compared with lenalidomide monotherapy (R) as maintenance treatment of NDMM patients who have attained a very good PR, exhibit positive MRD at a threshold of 10^{-5}, and are anti-CD38 naive following transplantation. The study successfully achieved its primary endpoint concerning MRD-negative (10^{-5}) conversion rates at the 12-month mark from the initiation of maintenance treatment. The addition of daratumumab significantly enhanced MRD-negativity rates (50.5% vs. 18.8%; OR, 4.51; 95% CI, 2.37-8.57; $P < .0001$). Furthermore, the rate of CRs or better rate improved (75.8% vs. 61.4%; OR, 2.00; 95% CI, 1.08-3.69; $P = .0255$) in comparison with maintenance with lenalidomide alone. The 30-month PFS rates were recorded at 82.7% for the D-R cohort and 66.4% for the R cohort.[114] The upcoming results from the SWOG S1803 trial (NCT04071457) are eagerly awaited to evaluate the advantages of implementing daratumumab with lenalidomide maintenance following prior exposure to daratumumab and to embrace an MRD-adapted strategy.

CASSIOPEIA is a two-part, open-label, randomized, phase 3 trial. In part 1 randomization, the trial demonstrated superiority in depth of response after adding daratumumab to VTd for induction and consolidation in patients who had newly diagnosed myeloma. In part 2, patients were randomly assigned to daratumumab once every 8 weeks or to observation-only for up to 2 years. At a median follow-up of 35.4 months from the second randomization, the mPFS was not reached with daratumumab compared with 46.7 months with observation only.[115] Furthermore, the PFS advantage with daratumumab maintenance was more pronounced in patients who did not receive daratumumab before ASCT. Interestingly, PFS was similar among all three arms that contained daratumumab, suggesting that exposure to daratumumab in either the induction or maintenance setting alone was adequate to confer benefit. More recently, an updated analysis showed that daratumumab-based maintenance improved MRD negativity both in patients who received daratumumab-containing induction and those who did not.[116] Daratumumab-VTd followed by daratumumab maintenance consistently produced the highest sustained MRD-negativity rates both at 10^{-5} and 10^{-6} at 77.3% and 60.7%, respectively.

The Atlas phase 3 trial was a randomized study of patients who had newly diagnosed myeloma after ASCT. Participants were assigned to either receive lenalidomide as standard care or to undergo a 36-cycle treatment with KRd, followed by lenalidomide maintenance. Carfilzomib was given at a dose of 20 mg/m^2 in cycle 1 on days 1 and 2 and then at 36 mg/m^2 on days 1, 2, 8, 9, 15, and 16 in cycles 1 to 4 and then at 36 mg/m^2 on days 1, 2, 15, and 16 from cycle 5 up to 36 cycles; lenalidomide was given at a dose of 25 mg on days 1 to 21; and dexamethasone was given at a dose of 20 mg on days 1, 8, 15, and 22 in 28-day cycles. Patients with standard-risk cytogenetics who achieved MRD negativity after six cycles were transitioned to standard lenalidomide maintenance. In the interim analysis, after a median follow-up of 33.8 months, the KRd group exhibited a mPFS of 59.1 months compared with 41.4 months in the lenalidomide group (P = .012).[117]

A comparable regimen was used in the previously mentioned FORTE trial, in which carfilzomib plus lenalidomide maintenance was compared with lenalidomide alone in patients who had newly diagnosed myeloma. In a preplanned analysis conducted after a median follow-up of 37 months, the 3-year PFS from the maintenance randomization was 80% in patients without high-risk cytogenetics, 68% in patients with one high-risk cytogenetic feature, and 53% in patients with two or more high-risk cytogenetic features.[118] It is important to note that the trial is still ongoing.

KEY POINTS

- Patients considered potential candidates for ASCT are typically treated with three to four cycles of quadruplet-based therapy (DVRd, DKRd, Isa-RVd, Isa-KRd, and DCyBorD), followed by a stem cell harvest. After stem cell harvest, patients with standard-risk disease can either proceed to early ASCT or continue the initial treatment regimen and delay ASCT until relapse.
- For patients with high-risk disease, ASCT should be pursued in the frontline setting and not deferred.
- After ASCT, patients can receive risk-adapted consolidation followed by maintenance therapy with lenalidomide; the addition of a proteasome inhibitor or anti-CD38 mAb is normally considered for high-risk patients.
- Even though it was incorporated in the post-induction approaches for TE NDMM, the role of the addition of anti-CD38 mAb to lenalidomide for maintenance after ASCT appears to be beneficial but requires confirmation from currently enrolling studies in daratumumab-exposed patients.

TREATMENT OF RELAPSED DISEASE

Almost all patients with MM eventually experience relapse. In general, patients can be retreated with regimens that have been effective in the past if the duration of the initial remission was more than 6 months. Alternatively, regimens that contain active drugs that the patient has not previously received can also be utilized.

In recent randomized trials, triplet combinations improved response rates and prolonged PFS compared with doublet backbone regimens. However, the newer triplet regimens have not been compared head-to-head in randomized trials, so the choice of a specific regimen at the time of relapse is based on many factors, such as response to previous therapy, aggressiveness of the relapse, patient characteristics, ease of use, and access to treatment.

Based on the effect size seen in randomized trials, reasonable options for the treatment of first relapse are anti-CD38 mAb with either pomalidomide and dexamethasone-based regimens[119] or with carfilzomib and dexamethasone-based regimens for patients whose disease is refractory to lenalidomide.[120] Carfilzomib once per week was compared with twice-per-week dosing in patients with relapsed disease. The mPFS was improved with the once-per-week dosing at 11.2 months compared with 7.6 months for the twice-per-week dosing.[121] Toxicity was similar between the two arms. Regimens combining carfilzomib with isatuximab have been approved by the FDA for use in the relapsed/refractory multiple myeloma (RRMM) setting. In an analogous fashion, the IKEMA trial tested isatuximab with carfilzomib and dexamethasone (Isa-Kd) versus Kd in previously treated patients who had MM and demonstrated excellent PFS benefit in early RRMM: mPFS was 35.7 months versus 19.2 months, respectively. PFS benefit was observed with Isa-Kd across subgroups, including patients with high-risk disease and poor prognosis.[122]

Combining mAbs (elotuzumab, isatuximab, and daratumumab) with immunomodulators has demonstrated impressive results. In the ICARIA trial, the combination of isatuximab with pomalidomide and dexamethasone compared with pomalidomide and dexamethasone alone in patients who had relapsed/refractory MM significantly improved PFS, with a manageable safety profile and a strong trend in OS benefit (24.6 months vs. 17.7 months).[123,124] Similarly, daratumumab combined with pomalidomide and dexamethasone significantly prolonged PFS compared with pomalidomide and dexamethasone alone in the APOLLO study.[119]

Daratumumab and isatuximab are similar CD38-directed mAbs. Although they have not been tested head-to-head, they seem to have similar efficacy and toxicity. Their differences are primarily in the route of administration, the length of infusions, and the degree of complement activation. It also seems that one agent does not overcome resistance to the other based on a study that used isatuximab after daratumumab resistance.[125] It is generally not recommended to sequence these agents immediately after each other. Resistance to CD38-targeted therapies is being investigated in depth.

CAR T-cell therapy is a novel treatment approach that is approved for patients who have MM and who have relapsed after two or more lines of therapy (idecabtagene vicleucel) or for those who have lenalidomide-refractory myeloma (ciltacabtagene autoleucel). This cellular therapy can be associated with substantial toxicity, and the manufacturing process can be time-consuming and laborious. CAR T-cells are made up of genetically engineered T cells that have been leukapheresed from the patient (ie, autologous T cells) and expanded ex vivo. The T cells are transfected with a gene that encodes for a receptor that recognizes an epitope on the myeloma cells and directs the engineered T cells to attack. The majority of existing myeloma CAR T-cell products target BCMA, a protein that is widely expressed on myeloma cells (Table 21-2). Patients receive lymphodepletion chemotherapy, usually with cyclophosphamide and fludarabine, before the infusion of CAR T-cells. The most common nonhematologic toxicity associated with CAR T-cells is cytokine-release syndrome (CRS), an acute systemic inflammatory syndrome that can be categorized by fever, hypoxia, hypotension, and multiorgan dysfunction. CRS typically arises within 1 to 2 weeks after CAR-T infusion and resolves within a few days to 2 to 3 weeks, depending on T-cell activation kinetics.[126] Although CRS is potentially life-threatening, it usually responds to tocilizumab, an interleukin-6 receptor antagonist, steroids, and aggressive supportive care (eg, intravenous fluids or vasopressors). Neurotoxicity represents another common adverse event. Neurotoxicity involving the central nervous system in a non-focal manner is called immune effector–associated neurotoxicity syndrome (ICANS), which can range from mild headaches to more severe presentations, such as encephalopathy, language deficits, hallucinations, tremors, seizures, and even cerebral edema with coma. ICANS typically develops within 1 to 3 weeks of infusion, often overlapping with CRS but sometimes occurring independently. Other neurotoxicities with more variable and wide-ranging symptoms, such as Parkinsonism, cranial nerve palsy, sensory loss, ataxia, peripheral motor or sensory neuropathy, altered mental status, and nystagmus, are often termed atypical neurotoxicity or "non-ICANS neurotoxicity."[127] The rate of Parkinsonism is overall low.[128]

Recipients have a higher incidence of second cancers; however, the real rate needs a longer follow-up. Patients can develop immune cell–associated hematotoxicity, hypogammaglobulinemia, infection, and immune effector cell–associated hemophagocytic lymphohistiocytosis-like syndrome. The rare case series of immune effector cell–associated entrocolitis[129] that can lead to intractable diarrhea. Non-relapsed mortality associated with this therapy ranges from 6% to 10%.[126,130]

Table 21-2 **T-Cell–Redirecting Therapies for Myeloma**

Modality	Target	Mechanism	Comments
Belantamab	BCMA	ADCC	DREAMM-7 Median PFS (BVd): 36.6 months
Teclistimab	BCMA	Bispecific CD3	MajesTEC-1 Median PFS: 11.3 months
Elranatamab	BCMA	Bispecific CD3	MagnetisMM-3 PFS at 15 months: 89%
Linvostelamab	BCMA	Bispecific CD3	LINKER-MM1 PFS at 12 months: 70%
Talquetamab	GPRC5D	Bispecific CD3	MonumenTAL-1 Median VGPR: 57%
Ide-cel	BCMA	CAR-T	KarMMa-3 Median PFS: 11.3 months
Cilta-Cel	BCMA	CAR-T	CARTITUDE-1 PFS at 60 months: 31% sCr: 82.5%

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; BCMA, B-cell maturation antigen; BVd, belantamab mafodotin, bortezomib, dexamethasone; CAR-T, chimeric antigen receptor T cell; GPRC5D, G protein–coupled receptor class C group 5 member D; PFS, progression-free survival; sCr, serum creatinine; VGPR, very good partial responses.

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The two most widely studied CAR T-cell products are idecabtagene vicleucel and ciltacabtagene autoleucel, both of which have received initial FDA approvals for use in patients with four or more previous lines of therapy, with subsequent approvals expanding their use to earlier lines. Common efficacy aspects of these two BCMA-targeting autologous CAR T products are outlined in Table 21-3, whereas their relevant toxicity and safety profiles are specified in Table 21-4. The KarMMa trial evaluated idecabtagene vicleucel in relapsed/refractory MM and reported that the ORRs and CR rates were 73% and 33%, respectively. CRS occurred in 84% of patients, but only 5% was high grade.[131] Neurotoxicity developed in 18% of patients, but only 3% were grade 3 or 4. Hematologic toxicity was also common after T-cell infusion. The mPFS was estimated to be 8.8 months.[131] Ciltacabtagene autoleucel, a second anti-BCMA CAR T-cell therapy, differs from idecabtagene vicleucel in that it comprises two BCMA-binding single-chain variable fragment domains. In the CARTITUDE-1 study, the ORR was 97% with a stringent CR rate of 65%, which is unprecedented in such a relapsed/refractory population (median of six previous lines of therapy) with responses deepening over time. The PFS at 12 months was 77%. At 60 months, PFS was 31%.[14,132]

Table 21-3 Approved CAR T-Cell and Bispecific Antibody Therapy Efficacy

Features	CAR T-Cell Therapies		Bispecific Antibody Therapies			
Agent	**Ide-cel[131]**	**Cilta-cel[132,133]**	**Teclistamab[19,134]**	**Elranatamab[20]**	**Talquetamab[22,135]**	**Linvostelamab[136]**
Phase of Study	**1**	**1b/2**	**1/2**	**2**	**1**	**2**
Target	**BCMA**		**BCMA**		**GPRC5D**	**BCMA**
Number of patients	128	97	165	123	130 SC 102 IV	177 (RP2D)
Median previous LOT, no. (range)	6 (3-16)	6 (4-8)	5 (2-14)	5 (2-22)	6 (2-17) (SC) 6 (3-20) (IV)	≥3 Required; median 5
Triple class refractory, %	84	88	78	96.7	75 (SC) 85 (IV)	82%
Penta-drug refractory, %	26	42	30	42.3	25 (SC) 35 (IV)	28.2%
Previous BCMA, %	NA		NA		32 (SC) 16 (IV)	6% (Belantamab)
High risk, %	35	24	26	25.2	16 (SC) 16 (IV)	39.3%
ORR, %	73	98	63	61	68 (SC)[a] 72 (IV)[a]	70.9
≥VGPR, %	53	95	58.8	56.1	53 (SC) 61 (IV)	63.2%
≥CR, %	33	82.5	39.4	35	21 (SC) 28 (IV)	49.6
Median PFS (months)	8.8	34.9	12.5[b]	NR	7.5 (qW) 11.9 (q2W)[c] 5.1[d]	70% @ 12 months
Median DoR (months)	10.7	33.9	24[b]	NR	NR	29.4
Median OS	19.4 months	63% at 3 years	21.9[b]	NR	NR	31.4

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; DoR, duration of response; GPRC5D, G protein–coupled receptor class C group 5 member D; IV, intravenous; LOT, line of therapy; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q2W, every 2 weeks; qW, weekly; SC, subcutaneous; VGPR, very good partial responses.

[a]At most active dose.

[b]Long-term follow-up data.

[c]61% censored.

[d]Prior T-cell redirection cohorts.

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Table 21-4 **Approved CAR-T and Bispecific Antibody Toxicity and Safety Profile**

	CAR T-Cells		Bispecific Antibodies			
	Idecabtagene Vicleucel[11,131,137]	**Ciltacabtagene Autoleucel**[132,133,138]	**Teclistamab**[19,134,139,140]	**Elranatamab**[20,140,141]	**Talquetamab**[22,140,142]	**Linvostelamab**[136]
	BCMA				**GPRC5D**	**BCMA**
Patients	**N = 349**	**N = 285**	**N = 165**	**N = 123**	**N = 102 (IV); N = 130 (SC)**	
Studies	KarMMa and KarMMa-3	CARTITUDE-1 and CARTITUDE-4	MajesTEC-1	MagnetisMM-3	MonumenTAL-1	Linker MM1
All grade CRS/≥G3, %	89/7	84/4	72/1	56/0	75/2	46/1%
Median (range) time to CRS onset, days	1 (1-27)	7 (1-23)	2 (1-6)	2 (1-9)	1 (0-7)	11 Hours
Median (range) time of CRS duration, days	5 (1-63)	4 (1-97)	2 (1-9)	2 (1-19)	1 (0-26)	15.6 Hours
Median (range) time to CRS resolution, days	NR	NR	NR	2 (1-19)	NR	NR
All grade NT/ICANS/≥G3, %	40/4	24/7	57/2	7	55/6	7.7/2.6%
Median (range) time to onset NT/ICANS, days	2 (1-148)	10 (1-101)	4 (2-8)	3 (1-4)	3 (1-16)	8/9 during step up dosing
Median (range) time of NT/ICANS duration, days	8 (1-720)	23 (1-544)	3 (1-20)	2 (1-18)	2 (1-22)	2 (1-11)
Median (range) time to NT/ICANS resolution, days	5 (1-245)	3 (1-143)*	NR	NR	NR	NR
Neutropenia ≥G3, %	40	27	64	49	35	26.9
Thrombocytopenia ≥G3, %	42	33	21	24	22	NR
Infections ≥G3, %	21	24	45	43	17	35.9%
Deaths from infection, %	5	4	7	7	2	2.5%
Hypogammaglobulinemia, %	13	36	75	75	87 @ 405-mcg qW	NA
iG prophylaxis, %	41	56	65	41	13	64.1% treated with IvIg
Dysgeusia (any grade), %	NR	NR	NR	NR	37-63	NR
Rash (any grade), %	11	7	NR	NR	15-47	NR
Nail-related (any grade), %	NR	NR	NR	NR	20-57	NR

Abbreviations: BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T; CRS, cytokine-release syndrome; G3, grade 3; GPRC5D, G protein–coupled receptor, class C group 5 member D; ICANS, Immune effector cell–associated neurotoxicity syndrome; iG, immune globulin; NR, not reported; NT, neurotoxicity; qW, weekly.
*For ICANS.
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CAR T-cells, idecabtagene vicleucel, and ciltacabtagene autoleucel were tested in an early relapse setting. KarMMa-3 was a phase 3 trial in which patients who had previously received two to four regimens were randomly assigned in a 2:1 ratio to receive either idecabtagene vicleucel or one of five standard regimens per physician discretion (daratumumab, pomalidomide, and dexamethasone [DPd], DVd, IRd, Kd, Elo-Pd). The disease was refractory to the last treatment before enrollment. At a median follow-up of 18.6 months, the mPFS was 13.3 months in the idecabtagene vicleucel group compared with 4.4 months in the standard regimen group ($P < .001$). All-grade infection rates were similar between groups. However, infections that were grade 3 or above were higher in the CAR T-cell arm (24% vs. 18%).[11] Similarly, the CARTITUDE-4 trial was a phase 3, randomized, open-label trial in which patients who had MM refractory to lenalidomide received ciltacabtagene autoleucel or standard-of-care therapy per the physician's choice (DPd, pomalidomide, bortezomib, and dexamethasone [PVd]). PFS at 12 months was better in the group that received ciltacabtagene autoleucel compared with those who received standard-of-care therapy (75.9% vs. 48.6%).[12] In addition, the CARTITUDE-4 trial demonstrated a substantial enhancement in OS following a median follow-up period of 34 months. The OS rate at 30 months was recorded at 76.4%, in comparison with 63.8%, yielding a HR of 0.55; 95% CI, 0.39-0.79; $P = .0009$. In addition, the 30-month PFS rate of 68.4% indicates that the utilization of cilta-cel in earlier treatment lines exhibited numerically superior overall and PFS rates.[13] It is noteworthy that ciltacabtagene autoleucel increased low-grade movement and neurocognitive symptoms in one patient, cranial nerve palsy in 9%, and CAR T-cell–related peripheral neuropathy in 2.8% of patients.

Research is ongoing to understand the occurrence of second primary malignancies after CAR T-cell therapy, especially in patients who have MM and who have received several previous treatments. Studies indicate that survivors have an increased risk of developing acute myeloid leukemia/myelodysplastic syndrome (AML/MDS). For instance, the CARTITUDE-1 trial reported six cases of MDS and three cases of AML out of 97 patients enrolled after a median follow-up of approximately 28 months.[133] Similarly, idecabtagene vicleucel was associated with MDS in two patients out of 62 enrolled in the CRB-401 trial after 18 months of follow-up. It is worth noting that both patients had previously received alkylating agents and had cytogenetic abnormalities (5q and 7q deletions) known to be associated with MDS after alkylating-agent chemotherapy.[143]

Given the success of CAR T-cell therapy in the relapsed setting, ongoing clinical trials (CARTITUDE-2, NCT04133636 and KarMMa-2, NCT03601078) are evaluating the role of CAR T cells earlier in the treatment paradigm when T-cell fitness may be superior. CARTITUDE-6 is a head-to-head comparison of quadruplet induction therapy followed by cilta-cel compared to quadruplet induction therapy followed by ASCT. The primary goal is to determine whether CAR-T therapy could replace ASCT.[144] Other myeloma targets are also being investigated, including GPRC5D and FcRH5. Natural killer CAR T cells are currently being developed as a strategy to mitigate CRS (ClinicalTrials.gov identifiers: NCT05008536 and NCT03940833).

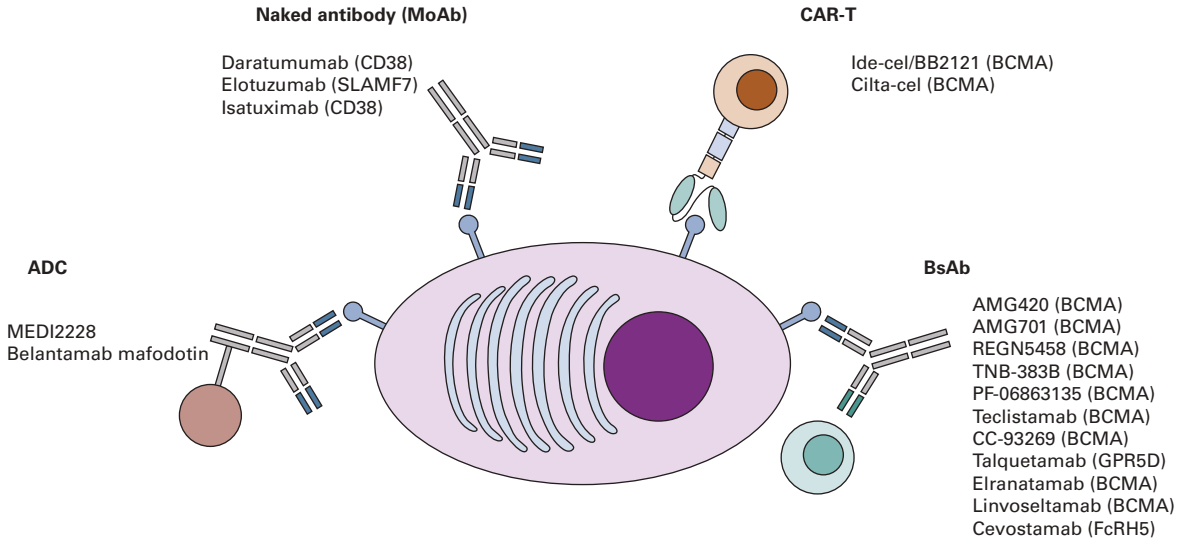
New targets for CAR T therapy are underway. Arlocabtagene autoleucel (BMS-986393) is an autologous CAR T-cell construct targeting GPRC5D that has been granted an FDA Regenerative Medicine Advanced Therapy designation for RRMM. A recent efficacy and safety update of a phase 1 study in patients with heavily pretreated RRMM after 15.1 months of median follow-up demonstrated high ORR (87%), CR (53%), mPFS of 18.3 months, and 1-year OS of 90% (ORR and/or PFS were not impacted by refractory status or exposure to previous BCMA-targeted therapy). Safety signals suggest skin, nail, and oral on-target/off-tumor adverse effects (AEs) as well as weight loss, though they appear to be of low frequency (19%-30%), low severity (all G1-2), and mostly self-resolving (70%-88%). There were no reports of cranial nerve palsy or Parkinsonism and a low incidence of high-grade infections (19% G3/4).[24]

Bispecific antibody (BsAb) represents another novel form of immunotherapy in relapsed/refractory MM. BsAb lacks an Fc region and contains only one variable domain. They can simultaneously bind to two different epitopes: CD3 present on T cells and a specific antigen on myeloma cells.

The function of the BsAb is to bring the patient's own T cells into proximity with the myeloma cells to allow for T-cell activation and destruction of the target cells. The advantage of BsAb therapy over CAR T-cell therapy is the distinct advantage of an off-the-shelf option because leukapheresis and gene modification are not required. Unlike CAR T-cell therapy, BsAb is currently given continuously. Of note, CRS and ICANS are also associated with BsAb therapy. Currently, there are four FDA-approved BsAb: teclistamab, elranatamab, and linvostelamab, which target BCMA, and talquetamab, which targets GPRC5D. Common efficacy aspects of these BsAb are outlined in Table 21-3, and their relevant toxicity and safety profiles are specified in Table 21-4. Teclistamab, an anti-BCMA-targeting BsAb, was granted accelerated FDA approval in October 2022 for patients who have RRMM and who have received at least four previous lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 mAb. This approval was based on the pivotal MajesTEC-1 phase 1/2 study. Patients received once-per-week subcutaneous injection of teclistamab after receiving two step-up doses to mitigate CRS and neurotoxicity. After a median follow-up of 14.1 months, the ORR was 63.0%, with a CR rate of more than 39.4%. The mPFS was 11.3 months (95% CI, 8.8-17.1). Most patients (72.1%) developed CRS, and most cases were low grade. In terms of toxicity, there was a high rate of grade 3 or 4 neutropenia (64%). Not surprisingly, infections were frequent (all-grade, 76.4%; grade 3 or 4, 44.8%), along with severe hypogammaglobulinemia and occasional opportunistic infections such as *Pneumocystis jirovecii* pneumonia and progressive multifocal leukoencephalopathy. Proactive use of intravenous immune globulin and prophylactic antibiotics against *P. jirovecii* pneumonia should be considered. Neurotoxic events occurred in 14.5% of the patients.[10]

Likewise, elranatamab secured accelerated approval in August 2023 as the second anti-BCMA BsAb for patients who have undergone a minimum of four previous lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 mAb. This approval was based on the results from the MagnetisMM-3 study, a multicenter, open-label, single-arm, phase 2 investigation into the efficacy and safety of elranatamab in relapsed/refractory MM. 32% of the enrolled patients reported the presence of EMD. Patients received two step-up priming doses of 12 and 32 mg subcutaneously on days 1 and 4 of cycle 1. Elranatamab was subsequently administered at 76 mg once per week in 28-day cycles. After six cycles, individuals with a PR or better that lasted at least 2 months transitioned to a dosing interval of once every 2 weeks. After a median follow-up of 14.7 months, the ORR was 61.0%; notably, CR or better was achieved in 35.0% of patients. As expected, the most common AEs leading to dose interruptions were infections (50.4%). Most patients received antiviral prophylaxis, and approximately half received anti-*P. jirovecii* prophylaxis. Six patients developed *P. jirovecii* pneumonia, but only one was receiving prophylaxis. Motor dysfunction and sensory neuropathy were observed in 17.1% and 13.8% of patients, respectively. Only grade 1 or 2 CRS was reported in 56.3% of patients (Fig. 21-4).[20]

Figure 21-4 Recent Immunotherapeutic Approaches to the Treatment of Myeloma



Abbreviations: ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T-cell; Cilta-cel, ciltacabtagene autoleucel; Ide-cel, idecabtagene vicleucel; MoAb, monoclonal antibody.
Source: Adapted from Mohan M, Hari P, Dhakal B. Immunotherapy in multiple myeloma—time for a second major paradigm shift. *JCO Oncol Pract.* 2021;17(7):405-413. doi:10.1200/op.21.00032
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Linvostelamab was approved based on the results of the Linker-MM1 trial. Step-up dosing was on days 1 and 8, followed by weekly dosing of 200 mg through weeks 13, every other week dosing through week 23, and then dosing every 4 weeks in those achieving a very good PR or better. The median age of patients was 70 years. EMD was reported in 14.5%. The ORR was 70.9% with an 18 month PFS of 68.8%. Eighteen-month OS is 69.8%.[136]

Talquetamab, a BsAb targeting GPRC5D, has also yielded impressive results. The phase 1 MonumenTAL-1 study evaluated talquetamab at various doses and frequencies by using subcutaneous or intravenous administration in patients who had heavily pretreated myeloma. After a median follow-up of 11.7 months for the 405-mcg dose and 4.2 months for the 800-mcg dose, the ORRs were 70% and 64%, respectively. The median duration of response was 10.2 and 7.8 months, respectively. Talquetamab has a unique toxicity profile; many patients experienced grade 1 or 2 oral AEs such as dysgeusia, dry mouth, and dysphagia, resulting in significant weight loss as well as nail changes.

Venetoclax is an oral BCL-2 inhibitor that is currently approved as a single agent or in combination with other medications for various leukemias and lymphomas. Venetoclax has demonstrated increased activity in patients whose MM harbors the t(11;14) mutation. The BELLINI phase 3 trial evaluated the combination of venetoclax, bortezomib, and dexamethasone compared with placebo, bortezomib, and dexamethasone in RRMM. The trial was stopped prematurely because of increased mortality in the venetoclax arm, mostly related to fatal infections. However, a subgroup analysis noted significantly improved PFS without a decrease in OS among patients with t(11;14).[145] Given these findings, venetoclax can be considered in patients who have RRMM with t(11;14) and have limited treatment options. These patients should be started on antibacterial and *P. jirovecii* pneumonia prophylaxis. Venetoclax and other BCL-2–targeted approaches are actively under investigation for relapsed/refractory MM.

Another therapy with a novel target that is approved for use in relapsed/refractory MM is XPO-1 inhibition. Selinexor (an XPO-1 inhibitor) was initially studied in penta-refractory MM and approved at an 80 mg twice weekly schedule, which carried significant toxicities.[146] Since then, it has also been approved with dexamethasone and once-per-week bortezomib and dexamethasone in the BOSTON study, which randomly assigned patients who had RRMM to once-per-week selinexor and bortezomib plus dexamethasone (Vd) (the selinexor dose was 100 mg weekly in 35-day cycles) versus Vd (bortezomib was given twice per week in 21-day cycles). The mPFS between selinexor-Vd versus Vd arms was 13.93 and 9.46 months, respectively.[147] Studies of selinexor combined with other novel agents such as daratumumab, carfilzomib, and pomalidomide have promising results.[148,149]

Selinexor has significant toxicity, including thrombocytopenia, neutropenia, nausea, vomiting, diarrhea, anorexia, and fatigue; however, these are milder and more easily managed when selinexor is given once per week at lower doses (40-100 mg). Prophylactic antinausea medications with two agents and careful monitoring, especially in the first month, are critical.

Belantamab mafodotin, an antibody-drug conjugate targeting BCMA, was withdrawn from the US market after the results of the DREAMM-3 trial (NCT04162210) were published. This phase 3 study assessed belantamab mafodotin versus pomalidomide plus low-dose dexamethasone to treat RRMM, but it did not meet its primary endpoint of PFS. This drug also had poorer outcomes in patients with EMD, and the high rates of keratopathy led to frequent treatment interruptions.[150] However, two new randomized clinical trials reported positive efficacy results of belantamab mafodotin. The DREAMM-7 trial was a phase 3, open-label, randomized study designed to evaluate the efficacy of belantamab mafodotin, bortezomib, and dexamethasone (BVd) versus daratumumab, bortezomib, and dexamethasone (DVd) following at least one line of therapy.[15] The study's primary endpoint was PFS, whereas secondary endpoints included OS and depth of response. At a median follow-up duration of 28.2 months, the mPFS was recorded at 36.6 months for the BVd cohort, compared with 13.4 months in the DVd cohort (PFS HR, 0.41; 95% CI, 0.31-0.53; $P < .001$). The percentage of patients achieving a ≥ CR was 84% for the BVd group and 42% for the DVd group. Notably, subgroup analyses revealed that BVd demonstrated superior outcomes over DVd among patients with high-risk cytogenetics, showing an HR of 0.36 (95% CI, 0.22-0.58). The OS rate at 18 months was 84% in the BVd group, in contrast to 73% in the DVd group. Furthermore, MRD-negative CR status was observed in 25% of patients in the BVd group compared with 10% in the DVd group. Higher incidences of grade 3 or above adverse events were reported in the BVd arm (95% versus 78% in the DVd group). In addition, ocular events were more prevalent in the BVd group (79% vs. 29%). Among patients with normal best-corrected visual acuity (BCVA: 20/25 or better in at least one eye) at baseline, a decline in BCVA to 20/50 or worse in both eyes was evidenced in 34% of cases, whereas a reduction to 20/200 in both eyes occurred in 2%. The median duration until BCVA deterioration was 73 days, with a median interval of 22 days to improvement. Such adverse events were managed through dose modifications, and declining visual acuity incidents proved reversible. The predominant reason for the discontinuation of belantamab mafodotin treatment was the progression of the disease.[15]

The DREAMM-8 trial constituted a phase 3, randomized, open-label study that assessed the efficacy of belantamab mafodotin, pomalidomide, and dexamethasone (BPd) in comparison with PVd for the treatment of relapsed or refractory myeloma in patients who had been previously exposed to lenalidomide.[17] At a median follow-up duration of 21.8 months, the 12-month PFS rates demonstrated an advantage for the BPd treatment group at 71%, in comparison with 51% in the PVd cohort (HR for PFS, 0.52; 95% CI, 0.37-0.73; $P < .001$). Furthermore, a subgroup analysis indicated that BPd exhibited superior efficacy with an HR of 0.57 and a 95% CI of 0.34-0.95. The percentage of patients with PR or above was 77% for the BPd group and 72% for the PVd group, and CR or better was noted in 40% of patients receiving BPd, in contrast with 16% of those receiving PVd. Notably, instances of grade 3 and above AEs were more prevalent in the BPd group, reported at 94%, compared with 76% in the PVd group. Ocular events were more frequently encountered in the BPd cohort, occurring at a rate of 89% (with grade 3 or 4 events noted in 43% of cases) versus 30% in the PVd group (with grade 3 or 4 events reported in 2%). The median duration until BCVA deterioration was 112 days, with a median interval of 29 days to resolution. Deterioration of BCVA to 20/200 or worse occurred at a median of 351 days. Ocular events within the BPd group were addressed through modifications to the dosing of belantamab mafodotin. Furthermore, ocular events necessitated treatment discontinuation in 9% of patients within the BPd group.[17] On October 23, 2025 FDA approved belantamab with bortezomib and dexamethasone for RRMM patients who have received at least two prior lines of therapy, including a proteasome inhibitor and IMiDs for use in the United States.[151] Cereblon E3 ligase modulators (CELMoDs) are a novel class of oral agents that recently entered the MM armamentarium, demonstrating enhanced tumoricidal and immune-stimulatory effects compared with IMiDs. In a multicohort, open-label, phase 1/2 trial in patients who had heavily pretreated IMiD RRMM, the combination of iberdomide and dexamethasone was found to be generally safe, with meaningful clinical activity (ORR, 26%). The most common toxicity profile included myelosuppression with grade 3 and above AEs that included neutropenia (45%), anemia (28%), infection (27%), and thrombocytopenia (22%).[152] Another recently tested CELMoD is mezigdomide, which was similarly tested as part of a dexamethasone doublet in a phase 1/2 trial in patients who had previously treated RRMM. After a median follow-up of 7.5 months, the ORR was 41%, and the mPFS was 4.4 months. The most common AEs included neutropenia (77% of the patients) and infections (65%; grade 3, 29%; grade 4, 6%). Currently, the combination of teclistimab and iberdomide is being tested in NCT 06465316.[153]

In patients with extramedullary plasmacytomas or PCL, multidrug regimens such as VTd and PACE for 1 to 2 months may be used to gain better disease control, but they are associated with greater toxicity.[154]

Other infusional chemotherapy regimens may be equally effective. These combinations are best used as a bridge to more definitive treatment that may be safely used for a longer period or may have a more durable response, such as a promising clinical trial or a second ASCT. A second ASCT is feasible, although remission durations are approximately 50% of what was achieved with the first ASCT. Because there have been no randomized trials, a second ASCT is used in patients who have had a reasonable duration of remission with the first ASCT. Thus, patients who obtain a remission duration of more than 36 months with maintenance therapy (or more than 18 months without maintenance therapy) after the first ASCT are potential candidates for a second ASCT as salvage therapy.[155] Novel immunotherapeutic approaches, such as BsAbs, are now being explored to improve outcomes in this high-risk population. In the phase 1b RedirecTT-1 trial, teclistamab plus talquetamab showed ORRs of 61% in EMD patients versus 92% in those without, with estimated 18-month PFS of 53% and 70%, respectively, highlighting its potential in these high-risk patients.[23]

Many currently used therapies, including bispecific T-cell engagers, CAR-T cells, and others, directly or indirectly depend on the anti-MM activity of T and other effector cells. Reduced T-cell fitness not only diminishes immune defenses, increasing patient susceptibility to opportunistic infections, but can also impact the effectiveness of anti-MM therapies.[156] Various studies have identified several factors that may compromise clinical outcomes following T-cell–redirecting therapies, such as age, performance status, cytogenetic abnormalities, the presence of EMD, prior treatments, and immunologic function, among others. Coupled with the rapid advancement of CAR T-cell and BsAb therapies into the earlier lines of treatment, the field is directing its focus on sequencing strategies that could modulate T-cell fitness and potentially optimize overall benefit and long-term clinical outcomes.[157,158]

KEY POINTS

- Daratumumab and isatuximab (targeting CD38) and elotuzumab (targeting SLAMF7) are the first mAbs approved for the treatment of RRMM.
- Typical first-relapse therapies involve using a CD38 antibody (in anti-CD38 mAb-naive or -sensitive patients) with the addition of an IMiD or a PI with dexamethasone.
- CAR T-cell and BsAb therapies are novel forms of immunotherapy that rely on T-cell–dependent destruction of MM cells through gene modification or the formation of a link between T cells and MM cells, respectively. Both technologies are associated with CRS and immune effector–associated neurotoxicity syndrome, which, in turn, must be carefully monitored for and urgently treated.
- Venetoclax is an oral BCL-2 inhibitor that is particularly effective in patients who have MM and harbor a t(11;14).
- Selinexor with either dexamethasone alone or bortezomib and dexamethasone is approved for patients with RRMM. Weekly dosing, where applicable and appropriate, is critical to toxicity mitigation.
- CELMoDs, including iberdomide and mezigdomide, represent a promising group of oral agents that are being investigated in all phases of MM treatment. Although CELMoDs are designed for superiority in terms of efficacy compared with IMiDs, their toxicity profile resembles the IMiD class with predominant myelosuppression signals.
- Considerations for sequencing and bridging therapies (particularly relating to CAR T and BsAb use) should incorporate strategies for the preservation of T-cell health and the avoidance of factors leading to T-cell exhaustion to maximize long-term outcomes.[159]

TREATMENT OF COMPLICATIONS AND PALLIATIVE CARE

TREATMENT OF DISEASE COMPLICATIONS

Patients who have MM should receive bone-modifying agents such as pamidronate, zoledronic acid, or denosumab to lower the risk of skeletal events. Typical treatment with pamidronate or zoledronic acid has been once per month for 1 to 2 years. In a randomized trial, OS was improved in MM with the use of zoledronic acid as prophylactic therapy. Results of a more recent randomized trial suggested that a reduced frequency of administration (once every 3 months) may be as effective as monthly administration.[160] A large, blinded, randomized study demonstrated that denosumab was noninferior to zoledronic acid for the prevention of skeletal-related effects. AEs were similar, except there was more renal toxicity with zoledronic acid and more hypocalcemia with denosumab. Rates of osteonecrosis of the jaw were similar.[160] Calcium supplementation and daily vitamin D supplementation are needed for patients receiving bisphosphonates. Surgical fixation of fractures or impending fractures of long bones can be performed as needed. Palliative local radiation should be limited to patients who have disabling pain that has not responded to analgesics and systemic therapy, or to treat tumors that threaten other organs by their location, that are not expected to regress quickly with systemic therapy. Radiation to vertebral compression fractures without MRI evidence of plasmacytomas compressing neural structures is not required, unless it is needed for palliative treatment for pain management. Vertebroplasty and kyphoplasty may be useful to decrease pain. Severe hypercalcemia can develop in some patients with MM. This is a medical emergency and requires treatment with hydration, corticosteroids, calcitonin, and either pamidronate (60-90 mg intravenously over 2-4 hours), zoledronic acid (4 mg intravenously over 15 minutes), or denosumab. Denosumab can be prioritized in patients with poor renal function, given its lack of renal toxicity.

Renal failure is common in MM and can be multifactorial. Volume depletion, nonsteroidal anti-inflammatory agents, infection, hypercalcemia, and radiographic contrast media may also contribute to renal failure. The most common cause of acute renal failure is light chain cast nephropathy, which requires prompt therapy to lower serum light chain levels. The role of plasmapheresis is controversial, but it may be incorporated in conjunction with CyBorD to treat patients who have MM and who also have proven or suspected acute light chain cast nephropathy with a goal of reducing the involved FLC level to less than 500 mg/L.[161]

Other disease-related complications include anemia, infections, and hyperviscosity syndrome. Anemia usually improves with treatment of the underlying MM, but some patients may require transfusions or erythropoietin. Recently, the TEAMM study has shown that the use of prophylactic levofloxacin for the first 12 weeks of treatment is associated with a lower risk of febrile infection and/or death.[162] Intravenous gamma globulin has generally been reserved for patients who have recurrent serious infections associated with severe hypogammaglobulinemia; intravenous gamma globulin should be considered even in the absence of infections in patients who have severe hypogammaglobulinemia after potent anti-BCMA immunotherapies, including BsAb, given the high risk of infection with these agents.[27] Hyperviscosity syndrome manifests with symptoms such as epistaxis, mucosal bleeding, headache, and blurred vision. Hyperviscosity syndrome requires emergent plasmapheresis.

Risk of venous thromboembolism (VTE) remains underrecognized in MM, yet it is one of the critically important and preventable causes of morbidity and mortality. It is ninefold higher in patients who have MM compared with the general population, likely driven by factors relating to malignancy, treatment agents, and other patient-related factors. Deep vein thrombosis in the first year after a new diagnosis of MM triples the risk of mortality compared with patients who have MM without VTE. Inferior OS associated with VTE has also been demonstrated in the context of modern induction triplet and quadruplet regimens commonly used in today's practice.[163,164] We currently lack data driven by RCTs in terms of the optimal prophylaxis strategies, and official recommendations for VTE prophylaxis in MM that are part of various national guidelines or multidisciplinary society panels are largely based on expert opinions.[28] Previous understanding of the risk timeline suggested that nearly all events usually occur within 6 months of treatment initiation, regardless of treatment regimen.[165] Most recent insights from analyses of VTE events in the GRIFFIN and MAIA trials suggest that median time to onset can be much longer than that (approximately 305 days for DVRd); events that occur during continuous DRd therapy have been recorded beyond 2 years of continuous therapy.[166,167] Until the gaps in RCT data are filled, simplified expert-based approaches to VTE prophylaxis at various stages of MM treated with various contemporary MM regimens can be considered.[28,168]

MANAGEMENT OF DRUG TOXICITY

The major AEs of thalidomide are sedation, constipation, and peripheral neuropathy. By contrast, the major AEs of lenalidomide are anemia, neutropenia, and thrombocytopenia. Both drugs cause fatigue. Because of the risk of teratogenicity, the use of any of the immunomodulatory agents (ie, thalidomide, lenalidomide, or pomalidomide) in pregnant patients is absolutely contraindicated. Furthermore, to prevent teratogenicity, there are strict requirements that must be met before these drugs can be prescribed. Patients who are receiving thalidomide, lenalidomide, or pomalidomide are also at significant risk of venous and arterial thrombotic events and require thromboprophylaxis with aspirin, low-molecular-weight heparin, a direct oral anticoagulant (DOAC), or warfarin.[169,170] Lenalidomide and pomalidomide can cause a skin rash that can be serious in a small proportion of patients. Medications such as sulfonamides and allopurinol may increase the risk and severity of skin toxicity and should be avoided if possible. Treatment with lenalidomide and pomalidomide can lead to thyroiditis and subsequent hypothyroidism. Thyroid function tests should be performed at baseline and every 3 to 4 months thereafter while a patient is receiving this therapy. Severe diarrhea can develop in approximately 10% to 15% of patients who receive lenalidomide treatment. The treatment is standard antimotility agents, and a bile acid sequestrant such as colestipol.

The major AEs of bortezomib are gastrointestinal toxicity, thrombocytopenia, and neuropathy. The best way to reduce the risk of neuropathy is to use bortezomib in a once-per-week schedule instead of a twice-per-week schedule[171] and administer the medication subcutaneously instead of intravenously. Neuropathy can be treated with drugs such as gabapentin or pregabalin, or antidepressants such as duloxetine. Scrambler therapy has been reported to benefit patients with chemotherapy-induced peripheral neuropathy. Patients who are being treated with bortezomib (and other proteasome inhibitors) are at high risk for reactivation of herpes zoster, and routine prophylaxis with acyclovir is recommended. Neuropathy is less of a risk with ixazomib and carfilzomib compared with bortezomib. The main AEs of ixazomib are nausea and diarrhea. Major AEs of carfilzomib include fatigue, nausea, cytopenias, and shortness of breath. Carfilzomib can also cause significant cardiac dysfunction in approximately 5% of patients; this effect must be considered carefully in the treatment of older patients.[172]

The main AEs of daratumumab, isatuximab, and elotuzumab are infusion-related reactions, which are mostly seen with the first dose. With intravenous daratumumab, approximately 50% of patients may have a grade 3 or above infusion reaction with the first dose, but this decreases to less than 5% with subsequent doses. Montelukast should be given before the first dose of daratumumab to reduce infusion reactions. Daratumumab, as a subcutaneous injection, was evaluated in a phase 3 study and found to be noninferior in terms of efficacy compared with the intravenous formulation. Subcutaneous administration also provided an improved safety profile with significantly fewer infusion-related reactions and was considered more convenient as a

treatment method.[173] Because steroids play a major role in the treatment of MM, patients often have major steroid-related AEs. These are best prevented by using the lowest possible dose of steroids. During the first few months of therapy, dexamethasone at 40 mg once per week is sufficient.[174] Some patients require a lower dose, even at the onset. After the first few months, an attempt should be made to rapidly reduce the dose of steroids. The ongoing IFM2017-03 Phase 3 trial[175] in frail patients with newly diagnosed MM compared a dexamethasone-sparing regimen of daratumumab plus lenalidomide (with dexamethasone only during the first two cycles) versus Rd, showing a 49% reduction in the risk of progression or death, along with a favorable safety profile and improved quality of life in the dexamethasone-sparing group.

We typically recommend ongoing prophylaxis for *P. jirovecii* pneumonia for patients receiving long-term steroid treatment.

Bisphosphonate therapy is associated with a risk of osteonecrosis of the jaw, and dental conditions should be assessed before initiation of bisphosphonate therapy. Other drug-induced complications include myelodysplastic syndrome and a risk of second primary malignancies.

KEY POINTS

- Patients with MM should receive bone-modifying agents prophylactically to prevent skeletal-related events.
- Severe hypercalcemia is a medical emergency and requires treatment with hydration, corticosteroids, and intravenous administration of bisphosphonates.
- The most common cause of acute renal failure is light chain cast nephropathy, which requires prompt therapy to lower SFLCs.
- Patients receiving IMiDs (thalidomide, lenalidomide, or pomalidomide) are at significant risk for venous and arterial thrombotic events and require routine thromboprophylaxis.
- When appropriate, modifications to reduce bortezomib-related neuropathy include a once-per-week schedule instead of a twice-per-week schedule; subcutaneous administration is always preferred to intravenous.
- The standard dose of steroids to be used in MM therapy usually should not exceed dexamethasone 40 mg once per week (or equivalent), unless there is an emergent need.

RELATED DISORDERS

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

MGUS is a premalignant precursor of MM.[34] It is defined by a serum M-protein concentration less than 3 g/dL, less than 10% clonal plasma cells in the bone marrow, and the absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency that can be attributed to a plasma cell disorder. The three subtypes of MGUS are nonimmunoglobulin M (non-IgM) MGUS, IgM MGUS, and light chain MGUS. MGUS is present in more than 3% to 4% of the population older than age 50.[34] The risk of MGUS is significantly higher in the Black population compared with the White population.[176,177] The risk of MGUS is also higher in first-degree relatives of patients with MGUS or MM[51] and in those exposed to certain pesticides.[177]

MGUS provides a lifelong risk of transformation to MM or related malignancy at a rate of 1% per year.[34] The size and type of the M-protein at diagnosis of MGUS and an abnormal serum FLC ratio are prognostic factors for progression. A bone marrow evaluation can be deferred in patients with low-risk MGUS and patients with IgM MGUS who have a normal FLC ratio and no anemia, lymphadenopathy, or organomegaly. It is generally indicated for patients with M protein ≥1.5 g/dL (15 g/L), all IgA MGUS cases, and most patients with an abnormal serum FLC ratio. Similarly, bone imaging at diagnosis can be deferred in patients with low-risk MGUS or IgM MGUS if there are no clinical concerns for MM or a related disorder.

No treatment is needed for MGUS. Patients with low-risk MGUS should be observed at 6 months, and subsequently when symptoms occur that may indicate progression. All other patients with MGUS should be observed at 6 months and, if they are stable, annually thereafter.

MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE

MGUS is asymptomatic, but in a small subset of patients, there may be complications directly related to the toxicity of the monoclonal immunoglobulin or to other mechanisms. In these cases, the diagnosis changes to monoclonal gammopathy of clinical significance (MGCS). This entity is poorly recognized and undertreated. Early suspicion and rapid intervention to preserve involved organ function are crucial.[178] Examples of organs affected by MGCS are the nervous system (cryoglobulinemia type I and II, IgM-related peripheral neuropathy, POEMS syndrome), skin (eg, scleredema, scleromyxedema, acquired cutis laxa, Schnitzler syndrome), kidneys (eg, amyloid nephropathy, light chain deposition disease, acquired Fanconi syndrome, immunotactoid glomerulopathy, C3 proliferative glomerulonephritis associated with monoclonal immune deposits), and various other target organs. When the kidneys are involved, the condition is called monoclonal gammopathy of renal significance[178] (Table 21-5). For more information on the pathophysiological classification of the main MGCS-related disorders, see the report here.

Table 21-5 **Current Classifications of the Main MGCS-Related Disorders by Mechanism**

Disorder	Mechanism	Main Characteristics of Monoclonal Gammopathy	Organs and Symptoms Involved
Autoantibody activity			
Type II mixed cryoglobulinemia[a]	Immune complex	IgM	Immune complex-mediated vasculitis; skin +++, kidney, peripheral nerve; may be systemic
C1 inhibitor deficiency	C1 inhibitor		Angioedema
von Willebrand disease	vW factor		Bleeding
Bullous skin disease	Dermoepidermal junction (collagen VII)		Skin
Xanthomatosis	Various lipoproteins	Usually IgG	Cholesterol accumulation in macrophages, skin and tendons, other localizations (necrobiotic xanthogranulomatous)
Cold agglutinin disease	Red blood cell (Ii)	IgM	Cold-induced skin manifestations + intravascular hemolysis
IgM-associated peripheral neuropathy	MAG +++	IgM	Peripheral nerve; ataxic polyneuropathy (anti-MAG)
	Gangliosides	IgM	CANOMAD
CAP[a] activation			
C3 glomerulonephritis atypical hemolytic-uremic syndrome	Mechanism to be determined; autoantibody activity against CAP regulator protein (factor H) in some cases	IgG	Kidney only; systemic
Cytokine mediated			
POEMS syndrome	VEGF	λ LC (~100%), IgA 50% Vλ1 (~100%); osteosclerotic bone lesions	Peripheral nerve (100%) and various other manifestations
Unknown mechanism			
Systemic capillary leak syndrome		IgG, IgA (rare)	Systemic
TEMPI syndrome		IgG	Systemic
Neutrophilic dermatosis[b]		IgA >80% (except Sweet syndrome)	Skin +++; different types and different associated manifestations
Acquired cutis laxa		Usually IgG; association with γ HCDD	Skin +++; other manifestations (lung, digestive tract)
Scleromyxedema		IgG with slow electrophoretic mobility	Skin +++; other localizations
Scleredema		IgG	Skin only
Schnitzler syndrome	Acquired autoinflammatory syndrome by IL-1 deregulation?	IgM	Skin +++; systemic symptoms; osteosclerotic bone lesions
Sporadic late-onset nemaline myopathy			Exclusively muscles (skeletal and possibly cardiac)

Abbreviations: +++, significant involvement; CANOMAD, chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies; CAP, complement alternative pathway; HCDD, heavy chain deposition disease; IgM, immunoglobulin M; IL-1, interleukin 1; MAG, myelin-associated glycoprotein; MGCS, monoclonal gammopathy of clinical significance; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; TEMPI, telangiectasias, elevated erythropoietin level and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting; VEGF, vascular endothelial growth factor; vW, von Willebrand (disease).

[a]Type II mixed cryoglobulinemia was observed in 10% of patients with chronic virus C infection.

[b]Including pyoderma gangrenosum, Sweet syndrome, subcorneal pustular dermatosis, and erythema elevatum diutinum.

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Some of the above paraprotein-mediated diseases can occur concomitantly with MM or in the presence of SMM. Note that patients with MGUS or SMM may have symptoms or manifestations of unrelated conditions that need to be excluded (eg, kidney damage from diabetes or hypertension). The spectrum of diagnoses that are associated with MGCS is rare and heterogeneous; some patients may benefit from therapy directed at the underlying plasma cell clone using regimens adapted from the MM literature.

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

Monoclonal gammopathy of renal significance can apply to a group of patients who harbor an M-protein produced by a B-cell or plasma cell clone that causes kidney injury. The underlying diagnosis may not meet the criteria for overt lymphoma or symptomatic myeloma, although myeloma or lymphoma may occur concomitantly. In fact, the clinical parameters (ie, M-spike size, serum light chain levels, extent of bone marrow involvement) may be identical to those of MGUS.[178] Monoclonal gammopathy of renal significance includes a wide array of pathologies, including light chain deposition disease, amyloid nephropathy, and C3 glomerulopathy with monoclonal gammopathy.[179] Light chain cast nephropathy is not a form of monoclonal gammopathy of renal significance but is rather a consequence of intratubular injury from the overproduction of light chains that have exceeded the resorptive capacity of the kidney and define active MM. Consequently, in monoclonal gammopathy of renal significance, the toxicity of the M-protein rather than the burden of disease is the defining feature. Patients with monoclonal gammopathy of renal significance often present with high-grade albuminuria or nephrotic syndrome rather than acute loss of glomerular filtration rate, which is more typical of light chain cast nephropathy. Monoclonal gammopathy of renal significance requires a renal biopsy to confirm the presence of monoclonal deposits in the kidney. Without treatment, patients may progress to end-stage renal disease. Treatment includes chemotherapeutic agents used to target plasma cell or B-cell neoplasms, depending on the type of clone present. Early recognition is critical, and thus clinicians must consider monoclonal gammopathy of renal significance in any patient with an M-protein who has unexplained and progressive renal failure or high-grade albuminuria.

MONOCLONAL GAMMOPATHY OF NEUROLOGIC SIGNIFICANCE

Peripheral neuropathy (PN) mediated by an M-protein in the serum and urine without any evidence of MM or Waldenström macroglobulinemia (WM) is defined as monoclonal gammopathy of neurologic significance (MGNS). We currently lack any definitive diagnostic methods that can reliably and causatively associate monoclonal paraproteinemia with the presence of PN, which is why the diagnosis of MGNS remains a diagnosis of exclusion.[180] One should consider whether MGNS is at play when PN occurs in the context of IgM-related paraprotein and the following clinical findings: it is sensory predominant, length dependent, slowly progressing (over months or years), bilateral and symmetrical, with MAG antibodies present, and demyelination confirmed by nerve conduction studies.[180] Essential aspects are excluding more common causes of PN, such as diabetes, chronic alcohol intake, cobalamin deficiency, autoimmune conditions, and infections such as HIV. Nerve conduction studies will typically reveal a hallmark feature in demyelination pattern of injury, whereas features commonly not associated with MGNS include purely axonal PN, short time to onset, and peak of symptoms (<6 months), whether PN is relapsing and remitting, if cranial nerve involvement is seen, if there is a nonsymmetrical distribution, or if there is a history of a viral infection 2 to 4 weeks before the onset of symptoms.[180] Pain and carpal tunnel syndrome are typically absent. Autonomic involvement is not seen in the absence of amyloidosis. Once identified, treatment of MGNS should follow the treatment guidelines for WM, with attention to avoiding neurotoxic therapies such as bortezomib or vincristine.

MONOCLONAL GAMMOPATHY OF THROMBOTIC SIGNIFICANCE

Monoclonal gammopathy of thrombotic significance is a newly recognized entity for which diagnostic and treatment criteria have not been established yet. This highly prothrombotic disorder is generally characterized by platelet-activating monoclonal antiplatelet factor 4 (PF4) antibodies, with or without associated persistent concurrent thrombocytopenia and a history of recurrent venous or arterial, micro- or macro-circulation thrombotic events.[181,182] Additional findings may also include reduced levels of natural anticoagulants and the presence of antiphospholipid antibody or cryoprotein activity.[183-185] It is usually accompanied by positive "heparin-induced thrombocytopenia-like" antibody assays such as the PF4/polyanion enzyme-linked immunosorbent assay (ELISA) and serotonin release assay (SRA), though presentations with ELISA/SRA-negative testing in the context of transient thrombocytopenia coincident with recurrent thrombotic episodes have also been described (cases with ELISA/SRA-negative testing require PF4-enhanced platelet-based testing for confirmation).[181,186] Presentations may be severe, despite anticoagulation therapy, suggesting that anticoagulant therapy alone is inadequate to control the underlying clotting.[187] Plasma cell-directed therapy aimed at reducing circulating monoclonal protein, with concurrent antithrombotic therapy is effective in mitigating long-term thrombotic risks.[181] Agents associated with increased thrombotic potential (ie, IMiDs) should be avoided in the context of any planned anti-plasma cell therapy.

SOLITARY PLASMACYTOMA

Solitary plasmacytoma is a localized plasma cell malignancy. It is defined by the presence of a single biopsy-proven plasmacytoma (bony or extramedullary) and a normal bone marrow examination. An M-protein may be present in serum or urine at

diagnosis. Treatment consists of radiation therapy (40-50 Gy) to the involved site. Patients with an apparent solitary plasmacytoma who have limited (<10%) clonal marrow involvement are considered to have solitary plasmacytoma with minimal marrow involvement; these patients are also treated similarly to patients with solitary plasmacytoma. The risk of recurrence or progression to MM within 3 years is approximately 10% in patients with solitary plasmacytoma versus 20% to 60% in patients with solitary plasmacytoma and minimal marrow involvement. Retrospective data demonstrate that patients with high-risk cytogenetic abnormalities by FISH—defined in this study as del(17p), t(14;16), t(4;14), or +1q (gain/amplification)—experience a shorter time to progression to multiple myeloma (8 months [95% CI, 6.3-26] vs. 42 months [95% CI, 25 to not reached]; $P < .001$).[188]

PLASMA CELL LEUKEMIA

PCL is a rare, highly aggressive variant of MM distinguished by the presence of ≥5% clonal plasma cells circulating in the peripheral blood, according to the revised IMWG criteria.[189] This threshold was lowered from the previous ≥20% based on evidence that patients with 5-20% circulating plasma cells have similar poor outcomes as those with higher levels.[190,191] PCL occurs as either primary (pPCL), arising de novo with no evidence of previous MM, or secondary (sPCL), emerging as leukemic transformation in RRMM. Secondary PCL carries a far worse prognosis, with recent cohorts showing median OS of only 3.2 to 3.5 months compared with 13 to 36.6 months in pPCL. Biologically, PCL is distinct from MM, characterized by frequent high-risk cytogenetics (del(17p), 1q gain, t(11;14), MAF translocations), elevated LDH, and EMD.[192-196] The t(11;14) is particularly common in pPCL and may confer a relatively better prognosis than other cytogenetic patterns.[195] Clinically, patients often present with cytopenias, high tumor burden, and rapidly progressive disease. Vigilant monitoring for clinical indications of central nervous system myeloma is crucial in patients diagnosed with PCL. Outcomes remain poor despite modern therapies. A reasonable strategy for initial treatment includes anti-CD38 plus VRd, anti-CD38 plus KRd, or a multidrug regimen such as VTd and PACE for two to three cycles followed by ASCT and subsequent maintenance therapy.[197-199] In the era of T-cell–directed therapy, the multicenter retrospective study[200] of 34 PCL patients treated with BCMA-directed CAR-T (19 ide-cel, 15 cilta-cel) showed mPFS of 9.0 months, and median OS of 13.0 months, with cilta-cel showing longer outcomes (mPFS 19.0 months vs. 6.0 months, median OS >23 months vs. 9.0 months), exceeding historical standards.

In this multicenter study of 122 PCL patients[201] treated with BsAbs, overall outcomes were poor (mPFS 3.2 months), but talquetamab showed superior activity compared with BCMA-directed BsAbs. Among the 60 patients with active PCL, prognosis was markedly worse, yet talquetamab (n = 29) achieved a mPFS of 6.9 months and OS of 12.2 months, substantially outperforming BCMA BsAbs (mPFS 0.7 months, mOS 1.4 months). Despite the relative benefit of T-cell–based therapies, prognosis remains dismal, underscoring the urgent need for dedicated prospective trials and novel therapeutic approaches for this high-risk population.

IMMUNOGLOBULIN LIGHT CHAIN (AL) AMYLOIDOSIS

Amyloid is a proteinaceous substance that consists of rigid, linear, nonbranching fibrils 7.5 to 10 nm in width, aggregated in a β-pleated sheet conformation.[202] It is detected on staining with Congo red and classic apple-green birefringence. Several types of amyloidosis are classified based on the major protein component of the amyloid. In systemic light chain amyloidosis (AL), the fibrils consist of the variable portion of a monoclonal light chain. All patients with a monoclonal gammopathy should be screened by using standard laboratory evaluation, careful history, and physical examination for evidence of amyloidosis if they have proteinuria, diastolic heart dysfunction, autonomic dysfunction, sensory-motor PN, hepatomegaly with elevated transaminases or alkaline phosphatase, or findings of macroglossia, periorbital purpura, or bleeding diathesis.

AL can affect numerous organs, including the tongue (macroglossia), heart, liver, kidneys, peripheral nerves, and lungs. To obtain an accurate diagnosis, four separate criteria must be satisfied: (1) the presence of an amyloid-related systemic syndrome (eg, renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement), (2) positive amyloid staining by Congo red in any tissue (eg, fat aspirate, bone marrow, or organ biopsy), (3) evidence that amyloid is light chain–related established by direct examination of the amyloid using mass spectrometry–based proteomic analysis or immuno-electron microscopy, and (4) evidence of a monoclonal plasma cell proliferative disorder (serum or urine monoclonal protein, abnormal FLC ratio, or clonal plasma cells in the bone marrow).[32] The primary aim in the management of systemic AL is the rapid achievement of deep hematologic response and ultimate reversal of any organ dysfunction caused by the deposition of amyloidogenic light chains.[203] The standard treatment has historically involved bortezomib-based therapy; however, patients who present with significant PN should avoid bortezomib-containing regimens because of the risk of further treatment-related exacerbation and toxicity.[204] The new standard in the management of systemic AL and the ability to achieve deep responses was established with the first FDA approval for the use of daratumumab in combination with CyBorD for newly diagnosed patients. In the pivotal ANDROMEDA study, which randomly assigned patients with newly diagnosed AL amyloidosis to receive six cycles of CyBorD either alone (control group) or with subcutaneous daratumumab followed by single-agent daratumumab once every 4 weeks for up to 24 cycles (daratumumab group); hematologic CR was significantly higher in the quadruplet compared with the triplet arm: 53.3% versus 18.1%, respectively.[205] After a median follow-up of 25.8 months, this response superiority deepened even further (60% vs. 19%, respectively).[206] Even though the ANDROMEDA trial had only two patients with Mayo 2004 stage IIIb disease on the quadruplet

arm, the International Society of Amyloidosis still recommends dose-modified (attenuated) DCyBorD for treating these patients who have the most advanced cardiac involvement.[204] Although patients who have systemic AL can also be considered for ASCT when appropriate, our ability to achieve an unprecedented level of responses with modern quadruplet regimens raises the question of whether ASCT consolidation can be obviated for patients achieving a deep hematologic response.[207]

When possible, patients who have systemic AL should be treated in the context of amyloidosis multidisciplinary programs that can ensure patients receive the full spectrum of multidisciplinary disease-directed and supportive care; this care focuses on symptoms of amyloid organ involvement, the AEs of the treatment directed at clonal plasma cells, and the psychosocial problems related to the treatment or disease. Two trials of fibril-directed therapy using anti-amyloid antibodies have failed to meet their primary endpoint.[203]

It should also be noted that amyloidosis can sometimes present in a localized, organ-specific fashion (eg, tracheobronchial tree, urinary tract, or skin) without evidence of systemic spread. In localized amyloidosis, the deposits are derived from monoclonal light chains, not because of an underlying systemic clonal plasma cell disorder, but sometimes from more than one light chain–variable family, and they may not be clonal in nature.[208] The clinical course is usually benign, and the most common recommendation is long-term follow-up. Surgical excision may be appropriate for patients with bladder, ureteral, or laryngeal deposits).[209]

WALDENSTRÖM MACROGLOBULINEMIA

WM is a lymphoplasmacytic lymphoma arising from post–germinal center B cells that have undergone somatic hypermutation but not immunoglobulin class-switch recombination, accounting for the persistent IgM paraprotein. The neoplastic cells secrete monoclonal IgM and display a lymphoplasmacytic morphology, with features intermediate between small lymphocytes and plasma cells.

The disease definition requires the presence of an IgM M-protein greater than or equal to 10% bone marrow involvement and a typical immunophenotype (eg, surface IgM-positive, CD10-negative, CD19-positive, CD20-positive, CD23-negative) that would exclude other lymphoproliferative disorders. Most patients with WM have a recurrent mutation of the *MYD88* gene (*MYD88* L265P). The main symptoms are weakness, fatigue, and hyperviscosity. Unlike in MM, lytic bone lesions are not seen in WM. Indications for therapy include symptomatic anemia, hyperviscosity, organomegaly, or other cytopenias. Initial treatment is typically with ibrutinib[210] with or without rituximab (eg, the iNNOVATE trial) or zanubrutinib (eg, the ASPEN trial)[211,212] or bendamustine plus rituximab or with bortezomib, dexamethasone, and rituximab. In selected patients with limited disease, single-agent rituximab may be an option but produces response rates under 50%, and there is a risk of a tumor flare if single-agent rituximab is used, resulting in a rapid rise in IgM levels. Therefore, combination therapy is preferred for patients with high IgM M-protein levels. Other active regimens for the treatment of WM are given with or without rituximab, including venetoclax,[213] rarely cladribine, or fludarabine, has been used as has the combination of lenalidomide and dexamethasone.

POEMS SYNDROME

The characteristics of POEMS are captured in its name: polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS).[214,215] Patients who have POEMS syndrome usually have osteosclerotic bone lesions or coexisting Castleman disease (a rare polyclonal lymphoproliferative disorder). The major clinical problem in POEMS syndrome is a severe, chronic, inflammatory-demyelinating polyneuropathy with predominantly motor features. If the osteosclerotic lesions are in a limited area, radiation therapy is the treatment of choice. If there are widespread osteosclerotic lesions or bone marrow involvement by a clonal plasma cell population, systemic therapy is pursued using anti-plasma cell agents already approved in MM. Most patients have an elevated vascular endothelial growth factor (VEGF), which can support the diagnosis. SCT is commonly used.

PRESENTING CASE STUDY

A 69-year-old man with a medical history significant for well-controlled diabetes and hypertension is found to have renal insufficiency (creatinine, 1.5 g/dL) during a routine primary care clinic check-up. Workup reveals 160 mg/day of proteinuria and an M spike of 0.4 g/dL. Serum immunofixation was positive for IgG kappa. The hematology team was consulted, and the initial workup identified hemoglobin level within the reference range, no hypercalcemia, and no other clinical complaints or concerns. Serum-free kappa light chain is 30 mg/L, and lambda light chain is 19 mg/L (K/L ratio, 1.57).

In an asymptomatic patient with low-level paraprotein and no CRAB features, what factors guide the decision to pursue advanced testing such as bone marrow biopsy or whole-body imaging?

Given the absence of risk factors for progression, advanced imaging and bone marrow evaluation were deferred. The patient was diagnosed with low-risk monoclonal gammopathy of undetermined significance (MGUS), with an estimated

5% chance of progression at 20 years. After confirmation of stable findings on 6-month follow-up, annual observation was recommended. The degree of proteinuria and kappa light chain burden was not sufficient to explain his mild renal impairment, which was attributed instead to comorbid conditions.

The patient, now 72 years old, presents to the emergency department with generalized fatigue and severe back pain. Lumbar spine MRI reveals multiple lytic lesions with an L4 compression fracture without cord compression or soft tissue mass. Other laboratory values are as follows: hemoglobin, 8.5 g/dL; calcium, 9.5 mg/dL; and creatinine, 3 g/dL (6 months prior, creatinine was 1.4 mg/dL). After consulting with the hematology team, the patient undergoes serum protein electrophoresis, which indicates an M spike of 1.5 g/dL. Serum-free kappa light chain level is now 1,100 mg/L, and lambda light chain is 5 mg/L (K/L ratio, 220). Follow-up whole-body PET/CT shows multiple focal bone lesions without extramedullary disease. Bone marrow biopsy confirms the presence of clonal kappa-restricted CD138 plasma cells, constituting about 70% of the total cellularity of the marrow (30% cellular). Fluorescence in situ hybridization (FISH) reveals del(17p13) with 1q amplification and 1 p deletion and no IgH translocations. The patient's Eastern Cooperative Oncology Group (ECOG) performance status is 3, owing mainly to his back pain and overall coexisting morbidities.

What are the key changes between this patient's original MGUS diagnosis and his current presentation that signal progression to active multiple myeloma? How do his high-risk cytogenetics influence treatment planning?

The patient was diagnosed with high-risk multiple myeloma. Because of acute renal failure, multiple lytic lesions, anemia (meeting several CRAB/SLiM criteria), and poor performance status, inpatient cytoreductive therapy with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) was initiated.

After a few days, his pain is better controlled with oxycodone, and he is cleared by physical therapy and discharged. Due to his poor performance status, he is regarded as a newly diagnosed, high-risk, autologous stem cell transplant (ASCT)-ineligible patient. After one cycle of CyBorD, he achieves a partial response; his M spike reduces to 0.7 g/dL, and serum creatinine level improves to near the reference range (creatinine clearance, 55 mL/min/1.73 m^2). Chemotherapy is switched to anti-CD38, carfilzomib, lenalidomide, and dexamethasone (anti-CD38-KRd), accompanied by the bone-modifying agent zoledronic acid, zoster prophylaxis with acyclovir, and adequate deep vein thrombosis prophylaxis with half-dose direct-acting oral anticoagulant. After an additional two cycles of anti-CD38-KRd therapy, he achieves a very good partial response with an unmeasurable M spike and only positive immunofixation electrophoresis (IFE) for IgG kappa. Daratumumab interference test is negative for IFE, and a complete response is suspected. His performance status greatly improves to 1.

Why might CyBorD be chosen as the initial regimen for this patient? How would you decide when to transition from a cytoreductive regimen to a more intensive induction strategy?

CyBorD is an adequate alternative in the setting of acute renal failure with light chain cast nephropathy, as the metabolism of cyclophosphamide does not depend on adequate renal function.

Because of renal recovery and high-risk cytogenetics, therapy was escalated to anti-CD38-KRd, supported by multiple trials in both transplant-eligible and -ineligible newly diagnosed myeloma.

How does improvement in functional status during therapy affect the decision of whether to pursue ASCT?

At this point, his improved ECOG performance status of 1 allowed safe administration of high-dose melphalan, making ASCT appropriate. Restaging confirmed a stringent complete response with MRD negativity at 10^{-6} by next-generation sequencing. He subsequently underwent ASCT, tolerating the procedure well aside from moderate mucositis.

Given the depth of response, consolidation was discussed but deferred.

For a patient with MRD negativity after ASCT and high-risk cytogenetics, what are the pros and cons of post-ASCT therapy?

Maintenance options mainly revolved around doublet maintenance choices due to high-risk disease and included:

- Carfilzomib and lenalidomide (FORTE trial[118])
- Carfilzomib, lenalidomide, and dexamethasone (Atlas trial[117])

- Isatuximab, carfilzomib, and lenalidomide (GMMG-CONCEPT and IsKia[5] trials)
- Daratumumab and lenalidomide (AURIGA trial[114]) (MRD-positive patients)

Considering that the patient underwent quadruplet induction therapy and harbored high-risk disease, single-agent maintenance options were not considered optimal. The patient was presented with several different options, including post-ASCT management strategies with carfilzomib and lenalidomide per FORTE trial; carfilzomib, lenalidomide, and dexamethasone per Atlas trial; and triplet maintenance with isatuximab, carfilzomib, and lenalidomide per GMMG-CONCEPT and IsKia trials. Applicability of daratumumab and lenalidomide per the AURIGA trial was also discussed, but the patient was deemed ineligible as the trial examined the role of dual versus single maintenance therapy in patients with MRD-positive disease post-ASCT. Ultimately, triplet maintenance with isatuximab, carfilzomib, and lenalidomide was selected for the initial post-ASCT period, with a likely plan to de-escalate therapy to the dual-drug maintenance approach with isatuximab and lenalidomide in an attempt to optimize convenience and personal quality-of-life goals.

HIGH-YIELD TAKEAWAYS

Monoclonal Gammopathy of Undetermined Significance

Diagnosis

- Serum M-protein <3 g/dL, <10% clonal plasma cells in marrow, no CRAB features (related end-organ damage)

Testing

- Low-risk IgG monoclonal gammopathy of undetermined significance (MGUS; M-protein <1.5 g/dL, normal FLC ratio): baseline marrow evaluation can be deferred
- Indications for marrow: M ≥1.5 g/dL, any IgA MGUS, or abnormal FLC ratio
- Bone imaging: can be deferred in low-risk MGUS or IgM MGUS if no clinical concerns

Treatment/Follow-Up

- No treatment is indicated.
- Low-risk MGUS should be observed at 6 months, and subsequently when symptoms occur that may indicate progression.
- All other MGUS patients should be observed at 6 months and, if stable, annually thereafter.

Smoldering Multiple Myeloma

Diagnosis

- Both of the following criteria must be met:
  1. Serum monoclonal protein (IgG or IgA) ≥30 g/L OR urinary monoclonal protein ≥500 mg per 24 hours AND/OR bone marrow clonal plasma cells 10% to 59%
  2. Absence of myeloma-defining events or amyloidosis

Monitoring (Risk-Stratified)

- Low/Intermediate risk: labs every 4 to 6 months (CBC, CMP, SPEP/UPEP/IFE, FLC); imaging annual MRI if no lesions, every 6 months if ≥1 focal lesion on MRI
- 7 labs every 2 to 3 months; imaging every 3 to 6 months; early intervention if progression

Multiple Myeloma

Diagnosis

- Essential Criterion: You need to have clonal bone marrow plasma cells ≥10% OR a biopsy-proven plasmacytoma, plus ≥ 1 myeloma-defining events

- CRAB criteria: hypercalcemia, renal insufficiency, anemia, and bone lesions
- Biomarkers of malignancy (≥1):
  - Clonal bone marrow plasma cells ≥60%
  - Involved/uninvolved serum FLC ratio ≥100
  - ≥1 focal lesion on MRI

Testing

- All suspected patients should be tested with complete blood count, complete metabolic profile, β2 microglobulin, lactate dehydrogenase, serum protein electrophoresis, serum immunofixation, 24-hour urine protein electrophoresis and urine immunofixation, serum FLC assay, bone marrow aspirate and biopsy with plasma-cell enriched FISH, and full body imaging with, whole-body low-dose computed tomography, whole-body MRI, or whole-body PET/CT (skeletal survey acceptable in limited resource environments).

Prognosis

- Driven by various staging systems at diagnosis, including International Staging System (ISS), revised-ISS (*R*-ISS), and R2-ISS
- Also driven by standard versus high-risk myeloma features that include cytogenetic abnormalities such as (1) del(17p) with a cutoff of 20% clonal fraction or TP53 mutation; (2) an IgH translocation including t(4;14), t(4;16) OR t(14;20) along with 1q+ and/or del(1p32); (3) monoallelic del (1p32) along with 1q+ or bialellic del(1p32), with all conferring poor prognosis

Treatment

- For TE NDMM, quadruplet regimens are the established frontline standard, with preferable early (vs. delayed) ASCT particularly in patients with high-risk features.
- For TIE NDMM, frontline quadruplet regimens, albeit triplet regimens such as DRd, remain the most frequently used regimen in frail patients.
- Treatment of RRMM is individualized based on patient and disease factors, prior exposures, and residual toxicities, as well as the patient's performance status and their personal preferences pertaining to logistics of therapy delivery and quality of life.
- CAR T-cell and bispecific antibody therapies have revolutionized our ability to treat multiclass refractory, previously treated MM, and patients who are not eligible for ASCT are frequently eligible for these T-cell–redirecting therapies.

Plasma Cell Leukemia

- Defined as ≥5% circulating plasma cells or absolute plasma cell count ≥5 × 10^9/L
- Primary plasma cell leukemia (PCL): arises de novo, aggressive
- Secondary PCL: evolves from MM, worse prognosis
- PCL is aggressive → treat with quad induction + ASCT when eligible; novel agents and CAR-T are increasingly used
- Prognosis: Poor overall; secondary PCL worse than primary

Solitary Plasmacytoma

- Localized plasma cell tumor (bone or extramedullary)
- Bone marrow plasma cells <10%, no systemic disease
- Treatment: definitive radiation therapy
- Follow-up/monitoring:
  - Risk of progression: ~10% within 3 years for solitary plasmacytoma alone
  - Higher risk if solitary plasmacytoma has minimal marrow involvement or HR cytogenetic
  - Periodic labs (CBC, CMP, SPEP/IFE, FLC) and imaging to monitor recurrence or progression

Primary Amyloidosis (Al Amyloidosis)

- Clonal plasma cell disorder → amyloid fibril deposition
- Clinical clues: nephrotic syndrome, restrictive cardiomyopathy, hepatomegaly, neuropathy
- Diagnosis: tissue biopsy with Congo red + mass spectrometry typing

- Treatment: similar to MM (eg, dara-CyBorD frontline)
- Prognosis: poor if cardiac involvement

Waldenström Macroglobulinemia (LPL/WM)

- IgM monoclonal gammopathy with marrow lymphoplasmacytic infiltration
- Clinical: hyperviscosity (visual changes, headache, bleeding), neuropathy, adenopathy, hepatosplenomegaly
- Diagnosis: IgM monoclonal protein + marrow infiltration by LPL
- Treatment: rituximab-based regimens (eg, BR, etc.); BTK inhibitors (ibrutinib, zanubrutinib)
- Plasmapheresis for acute hyperviscosity

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

MULTIPLE MYELOMA 21

CHAPTER SUMMARY GUIDE

KEY POINTS

- The diagnosis of MM requires evidence of one or more myeloma-defining effects: hypercalcemia, renal insufficiency, anemia, or bone lesions that can be attributed to the plasma cell proliferative disorder; clonal bone marrow plasma cells 60% or more; serum FLC ratio of involved to uninvolved at 100 or more, provided the involved FLC level is 100 mg/L or more; or more than one focal lesion on MRI scan.
- MGUS and SMM are asymptomatic plasma cell proliferative disorders that need to be distinguished from MM.
- MM accounts for 1% of all cancers and approximately 10% of all hematologic cancers.
- Myeloma is twice as common in the Black population as in the White population.
- Early intervention with lenalidomide or daratumumab[72] prolongs time to progression to active MM and is now considered a possible treatment option for patients with high-risk SMM (participation in clinical trials is preferred).
- MM is preceded by a premalignant phase that is clinically referred to as MGUS.
- The two principal pathogenetic steps are (1) transition from normal plasma cell to MGUS and (2) transition from MGUS to MM.
- The onset of MGUS is associated with IgH translocations (chromosome 14) in approximately 50% of cases and hyperdiploidy in the remaining 50%.
- The most common presenting symptoms of MM are fatigue and bone pain; other presenting features are hypercalcemia, infection, and renal failure.
- When MM is suspected, patients should be tested for the presence of M-proteins by serum and urine protein electrophoresis, serum and urine immunofixation, and serum FLC assay.
- Full-body skeletal imaging studies and a bone marrow biopsy are required if MM is suspected.
- Patients are staged using the variations of ISS (R-ISS or R2-ISS).
- Patients are considered to have high-risk MM if at least one of the following abnormalities is present: (1) del(17p), with a cutoff of >20% clonal fraction, and/or TP53 mutation; (2) an IgH translocation including t(4;14), t(14;16), or t(14;20) along with 1q+ and/or del(1p32); (3) monoallelic del(1p32) along with 1q+ or biallelic del(1p32); or (4) β2 microglobulin ≥5.5 mg/L with normal creatinine (<1.2 mg/dL). Patients with trisomies or translocations t(11;14) and t(6;14) are considered to have standard-risk MM.
- For TE patients, preferred regimens for initial MM treatment include PI, IMiD, and anti-CD38 antibody–containing quadruplet regimens such as DVRd, DKRd, Isa-VRd, Isa-KRd, and daratumumab, bortezomib, cyclophosphamide, and dexamethasone (DCybBorD; in case of inability to dose IMiDs optimally).
- CyBorD and VTd (less so) are alternatives, and may be preferred in the setting of acute renal failure with light chain cast nephropathy.
- For the TIE patients, recent FDA approval of Isa-VRd quadruplet with a category 1 recommendation, and availability of RCT phase 3 data with DVRd regimens adds these quadruplet combinations to the list of available, powerful induction combinations in this space. The triple combinations with either VRd or DRd remain category 1 options for those who are deemed unfit for frontline quadruplet therapy.
- Patients considered potential candidates for ASCT are typically treated with three to four cycles of quadruplet-based therapy (DVRd, DKRd, Isa-RVd, Isa-KRd, and DCyBorD), followed by a stem cell harvest. After stem cell harvest, patients with standard-risk disease can either proceed to early ASCT or continue the initial treatment regimen and delay ASCT until relapse.
- For patients with high-risk disease, ASCT should be pursued in the frontline setting and not deferred.
- After ASCT, patients can receive risk-adapted consolidation followed by maintenance therapy with lenalidomide; the addition of a proteasome inhibitor or anti-CD38 mAb is normally considered for high-risk patients.
- Even though it was incorporated in the post-induction approaches for TE NDMM, the role of the addition of anti-CD38 mAb to lenalidomide for maintenance after ASCT appears to be beneficial but requires confirmation from currently enrolling studies in daratumumab-exposed patients.
- Daratumumab and isatuximab (targeting CD38) and elotuzumab (targeting SLAMF7) are the first mAbs approved for the treatment of RRMM.

- Typical first-relapse therapies involve using a CD38 antibody (in anti-CD38 mAb-naive or -sensitive patients) with the addition of an IMiD or a PI with dexamethasone.
- CAR T-cell and BsAb therapies are novel forms of immunotherapy that rely on T-cell–dependent destruction of MM cells through gene modification or the formation of a link between T cells and MM cells, respectively. Both technologies are associated with CRS and immune effector–associated neurotoxicity syndrome, which, in turn, must be carefully monitored for and urgently treated.
- Venetoclax is an oral BCL-2 inhibitor that is particularly effective in patients who have MM and harbor a t(11;14).
- Selinexor with either dexamethasone alone or bortezomib and dexamethasone is approved for patients with RRMM. Weekly dosing, where applicable and appropriate, is critical to toxicity mitigation.
- CELMoDs, including iberdomide and mezigdomide, represent a promising group of oral agents that are being investigated in all phases of MM treatment. Although CELMoDs are designed for superiority in terms of efficacy compared with IMiDs, their toxicity profile resembles the IMiD class with predominant myelosuppression signals.
- Considerations for sequencing and bridging therapies (particularly relating to CAR T and BsAb use) should incorporate strategies for the preservation of T-cell health and the avoidance of factors leading to T-cell exhaustion to maximize long-term outcomes.[159]
- Patients with MM should receive bone-modifying agents prophylactically to prevent skeletal-related events.
- Severe hypercalcemia is a medical emergency and requires treatment with hydration, corticosteroids, and intravenous administration of bisphosphonates.
- The most common cause of acute renal failure is light chain cast nephropathy, which requires prompt therapy to lower SFLCs.
- Patients receiving IMiDs (thalidomide, lenalidomide, or pomalidomide) are at significant risk for venous and arterial thrombotic events and require routine thromboprophylaxis.
- When appropriate, modifications to reduce bortezomib-related neuropathy include a once-per-week schedule instead of a twice-per-week schedule; subcutaneous administration is always preferred to intravenous.
- The standard dose of steroids to be used in MM therapy usually should not exceed dexamethasone 40 mg once per week (or equivalent), unless there is an emergent need.

CHAPTER TABLES AND IMAGES

Table 21-1 Revised International Staging System for Multiple Myeloma

Publication Year	Stage	Criteria	Frequency (% of Patients)	Median Survival or 5-Year Survival Rate (%)
ISS stage	1	Serum albumin >3.5 g/dL, serum β2-microglobulin <3.5 mg/L	29	62 months
	2	Neither ISS stage I nor III	37.5	44 months
	3	Serum β2-microglobulin >5.5 mg/L	33.6	28 months
R-ISS stage	1	ISS-I No high-risk cytogenetics Normal LDH	28	82%
	2	Neither ISS stage I nor III	62	62%
	3	High-risk cytogenetics [t(4;14), t(14;16), or del17p13] or elevated LDH level	10	40%
R2-ISS stage*	1	0 points	19.2	Not reached
	2	0.5-1 points	30.8	109.2 months
	3	1.5-2.5 points	41.2	68.5 months
	4	3-5 points	8.8	37.9 months

Abbreviations: ISS, International Staging System; LDH, lactate dehydrogenase; R-ISS, revised ISS.
*ISS-III, 1.5 points; ISS-II, del17p13, high lactate dehydrogenase, or t(4;14), 1 point; and 1q1 0.5 points.
Reprinted from Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-2869. doi:10.1200/JCO.2015.61.2267

Table 21-2 **T-Cell–Redirecting Therapies for Myeloma**

Modality	Target	Mechanism	Comments
Belantamab	BCMA	ADCC	DREAMM-7 Median PFS (BVd): 36.6 months
Teclistimab	BCMA	Bispecific CD3	MajesTEC-1 Median PFS: 11.3 months
Elranatamab	BCMA	Bispecific CD3	MagnetisMM-3 PFS at 15 months: 89%
Linvostelamab	BCMA	Bispecific CD3	LINKER-MM1 PFS at 12 months: 70%
Talquetamab	GPRC5D	Bispecific CD3	MonumenTAL-1 Median VGPR: 57%
Ide-cel	BCMA	CAR-T	KarMMa-3 Median PFS: 11.3 months
Cilta-Cel	BCMA	CAR-T	CARTITUDE-1 PFS at 60 months 31% sCr: 82.5%

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; BCMA, B-cell maturation antigen; BVd, belantamab mafodotin, bortezomib, dexamethasone; CAR-T, chimeric antigen receptor T cell; GPRC5D, G protein–coupled receptor class C group 5 member D; PFS, progression-free survival; sCr, serum creatinine; VGPR, very good partial responses.
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Table 21-3 **Approved CAR T-Cell and Bispecific Antibody Therapy Efficacy**

Features	CAR T-Cell Therapies		Bispecific Antibody Therapies			
Agent	**Ide-cel**[131]	**Cilta-cel**[132,133]	**Teclistamab**[19,134]	**Elranatamab**[20]	**Talquetamab**[22,135]	**Linvostelamab**[136]
Phase of Study	**1**	**1b/2**	**1/2**	**2**	**1**	**2**
Target	**BCMA**		**BCMA**		**GPRC5D**	**BCMA**
Number of patients	128	97	165	123	130 SC 102 IV	177 (RP2D)
Median previous LOT, no. (range)	6 (3-16)	6 (4-8)	5 (2-14)	5 (2-22)	6 (2-17) (SC) 6 (3-20) (IV)	≥3 Required; median 5
Triple class refractory, %	84	88	78	96.7	75 (SC) 85 (IV)	82%
Penta-drug refractory, %	26	42	30	42.3	25 (SC) 35 (IV)	28.2%
Previous BCMA, %	NA		NA		32 (SC) 16 (IV)	6% (Belantamab)
High risk, %	35	24	26	25.2	16 (SC) 16 (IV)	39.3%
ORR, %	73	98	63	61	68 (SC)[a] 72 (IV)[a]	70.9
≥VGPR, %	53	95	58.8	56.1	53 (SC) 61 (IV)	63.2%
≥CR, %	33	82.5	39.4	35	21 (SC) 28 (IV)	49.6
Median PFS (months)	8.8	34.9	12.5[b]	NR	7.5 (qW) 11.9 (q2W)[c] 5.1[d]	70% @ 12 months
Median DoR (months)	10.7	33.9	24[b]	NR	NR	29.4
Median OS	19.4 months	63% at 3 years	21.9[b]	NR	NR	31.4

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; DoR, duration of response; GPRC5D, G protein–coupled receptor class C group 5 member D; IV, intravenous; LOT, line of therapy; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q2W, every 2 weeks; qW, weekly; SC, subcutaneous; VGPR, very good partial responses.

[a]At most active dose.

[b]Long-term follow-up data.

[c]61% censored.

[d]Prior T-cell redirection cohorts.

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Table 21-4 **Approved CAR-T and Bispecific Antibody Toxicity and Safety Profile**

	CAR T-Cells		Bispecific Antibodies			
	Idecabtagene Vicleucel[11,131,137]	**Ciltacabtagene Autoleucel**[132,133,138]	**Teclistamab**[19,134,139,140]	**Elranatamab**[20,140,141]	**Talquetamab**[22,140,142]	**Linvostelamab**[136]
	BCMA				**GPRC5D**	**BCMA**
Patients	**N = 349**	**N = 285**	**N = 165**	**N = 123**	**N = 102 (IV); N = 130 (SC)**	
Studies	KarMMa and KarMMa-3	CARTITUDE-1 and CARTITUDE-4	MajesTEC-1	MagnetisMM-3	MonumenTAL-1	Linker MM1
All grade CRS/≥G3, %	89/7	84/4	72/1	56/0	75/2	46/1%
Median (range) time to CRS onset, days	1 (1-27)	7 (1-23)	2 (1-6)	2 (1-9)	1 (0-7)	11 Hours
Median (range) time of CRS duration, days	5 (1-63)	4 (1-97)	2 (1-9)	2 (1-19)	1 (0-26)	15.6 Hours
Median (range) time to CRS resolution, days	NR	NR	NR	2 (1-19)	NR	NR
All grade NT/ICANS/≥G3, %	40/4	24/7	57/2	7	55/6	7.7/2.6%
Median (range) time to onset NT/ICANS, days	2 (1-148)	10 (1-101)	4 (2-8)	3 (1-4)	3 (1-16)	8/9 during step up dosing
Median (range) time of NT/ICANS duration, days	8 (1-720)	23 (1-544)	3 (1-20)	2 (1-18)	2 (1-22)	2 (1-11)
Median (range) time to NT/ICANS resolution, days	5 (1-245)	3 (1-143)*	NR	NR	NR	NR
Neutropenia ≥G3, %	40	27	64	49	35	26.9
Thrombocytopenia ≥G3, %	42	33	21	24	22	NR
Infections ≥G3, %	21	24	45	43	17	35.9%
Deaths from infection, %	5	4	7	7	2	2.5%
Hypogammaglobulinemia, %	13	36	75	75	87 @ 405-mcg qW	NA
iG prophylaxis, %	41	56	65	41	13	64.1% treated with Ivlg
Dysgeusia (any grade), %	NR	NR	NR	NR	37-63	NR
Rash (any grade), %	11	7	NR	NR	15-47	NR
Nail-related (any grade), %	NR	NR	NR	NR	20-57	NR

Abbreviations: BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T; CRS, cytokine-release syndrome; G3, grade 3; GPRC5D, G protein–coupled receptor, class C group 5 member D; ICANS, Immune effector cell–associated neurotoxicity syndrome; iG, immune globulin; NR, not reported; NT, neurotoxicity; qW, weekly.
*For ICANS.
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Table 21-5 **Current Classifications of the Main MGCS-Related Disorders by Mechanism**

Disorder	Mechanism	Main Characteristics of Monoclonal Gammopathy	Organs and Symptoms Involved
Autoantibody activity			
Type II mixed cryoglobulinemia[a]	Immune complex	IgM	Immune complex-mediated vasculitis; skin +++, kidney, peripheral nerve; may be systemic
C1 inhibitor deficiency	C1 inhibitor		Angioedema
von Willebrand disease	vW factor		Bleeding
Bullous skin disease	Dermoepidermal junction (collagen VII)		Skin
Xanthomatosis	Various lipoproteins	Usually IgG	Cholesterol accumulation in macrophages, skin and tendons, other localizations (necrobiotic xanthogranulomatous)
Cold agglutinin disease	Red blood cell (Ii)	IgM	Cold-induced skin manifestations + intravascular hemolysis
IgM-associated peripheral neuropathy	MAG +++	IgM	Peripheral nerve; ataxic polyneuropathy (anti-MAG)
	Gangliosides	IgM	CANOMAD
CAP[a] activation			
C3 glomerulonephritis atypical hemolytic-uremic syndrome	Mechanism to be determined; autoantibody activity against CAP regulator protein (factor H) in some cases	IgG	Kidney only; systemic
Cytokine mediated			
POEMS syndrome	VEGF	λ LC (~100%), IgA 50% Vλ1 (~100%); osteosclerotic bone lesions	Peripheral nerve (100%) and various other manifestations
Unknown mechanism			
Systemic capillary leak syndrome		IgG, IgA (rare)	Systemic
TEMPI syndrome		IgG	Systemic
Neutrophilic dermatosis[b]		IgA >80% (except Sweet syndrome)	Skin +++; different types and different associated manifestations
Acquired cutis laxa		Usually IgG; association with γ HCDD	Skin +++; other manifestations (lung, digestive tract)
Scleromyxedema		IgG with slow electrophoretic mobility	Skin +++; other localizations
Scleredema		IgG	Skin only
Schnitzler syndrome	Acquired autoinflammatory syndrome by IL-1 deregulation?	IgM	Skin +++; systemic symptoms; osteosclerotic bone lesions
Sporadic late-onset nemaline myopathy			Exclusively muscles (skeletal and possibly cardiac)

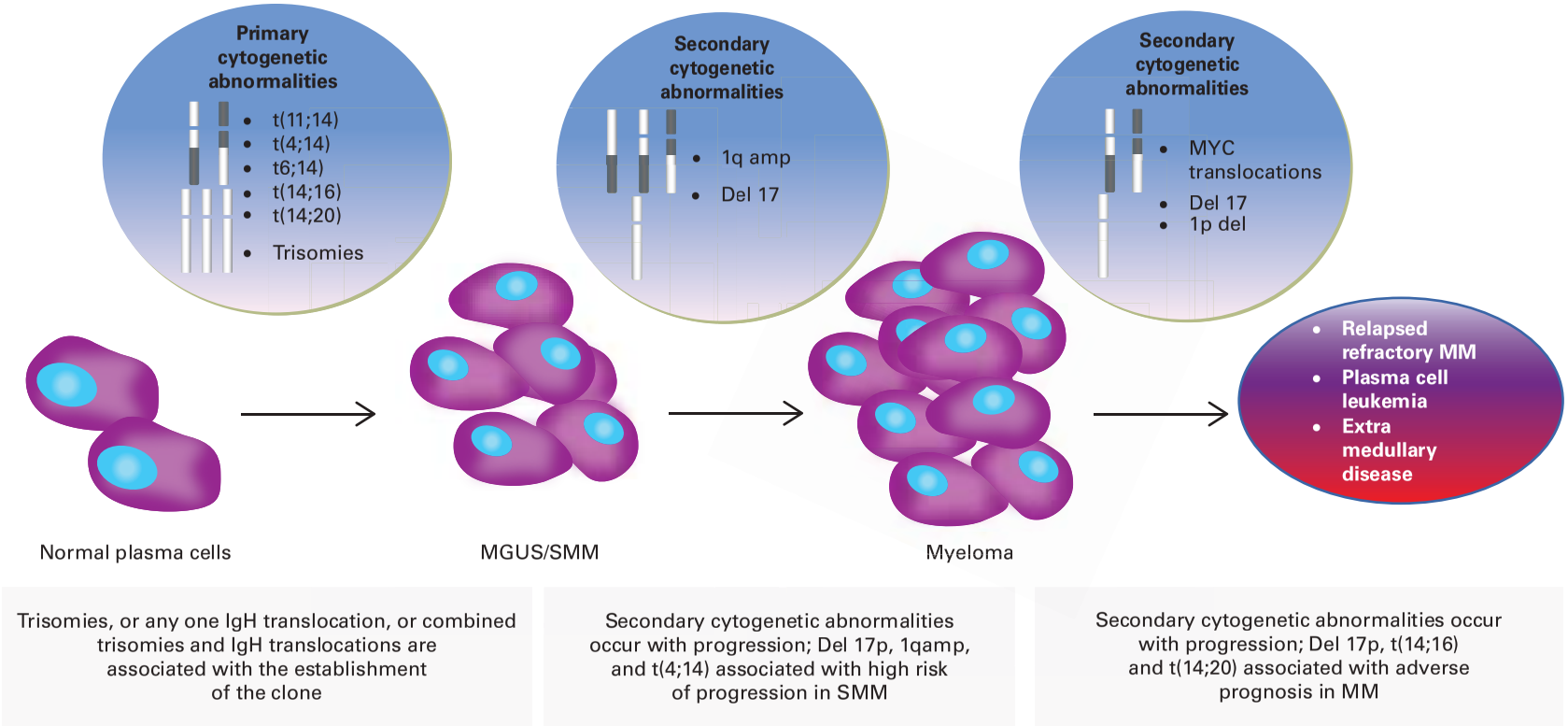
Abbreviations: +++, significant involvement; CANOMAD, chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies; CAP, complement alternative pathway; HCDD, heavy chain deposition disease; IgM, immunoglobulin M; IL-1, interleukin 1; MAG, myelin-associated glycoprotein; MGCS, monoclonal gammopathy of clinical significance; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; TEMPI, telangiectasias, elevated erythropoietin level and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting; VEGF, vascular endothelial growth factor; vW, von Willebrand (disease).

[a]Type II mixed cryoglobulinemia was observed in 10% of patients with chronic virus C infection.

[b]Including pyoderma gangrenosum, Sweet syndrome, subcorneal pustular dermatosis, and erythema elevatum diutinum.

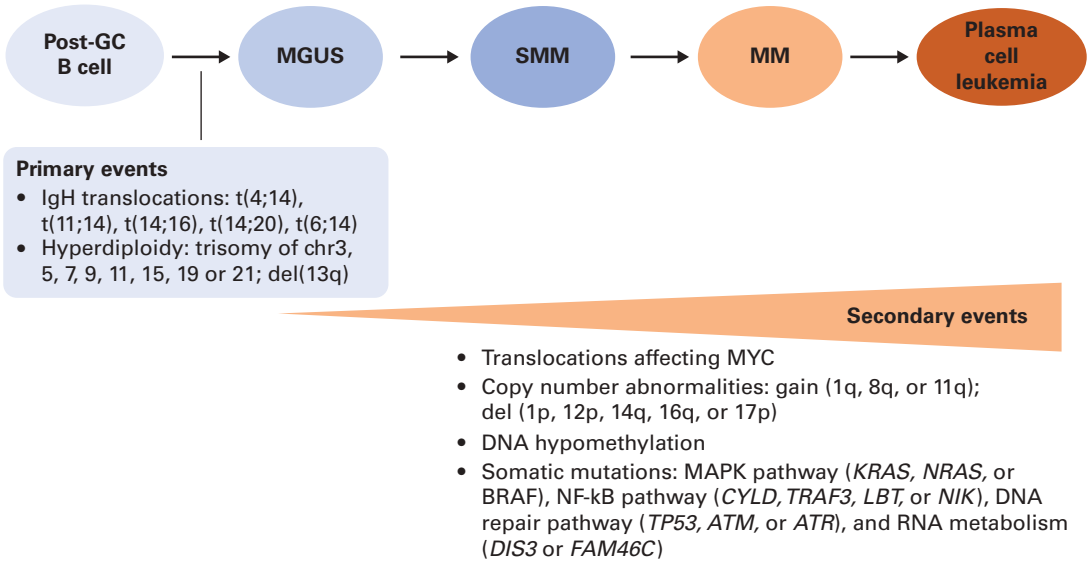
Reproduced under Creative Commons license. Source: Oganesyan A, Gregory A, Malard F, et al. Monoclonal gammopathies of clinical significance (MGCS): in pursuit of optimal treatment. *Front Immunol*. 2022;13:1045002. doi: 10.3389/fimmu.2022.1045002

Figure 21-1 Cytogenetic Abnormalities in Multiple Myeloma



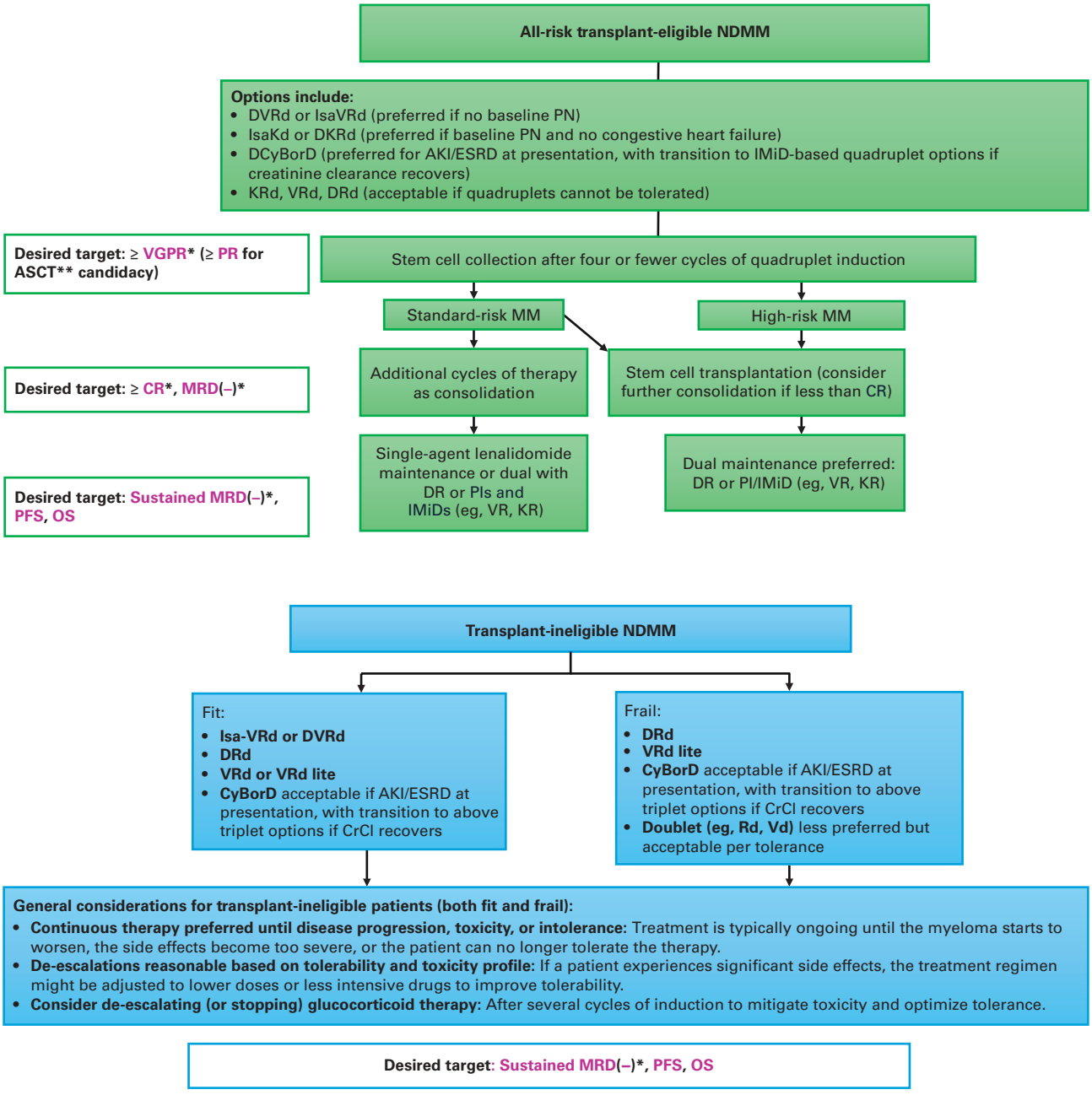
Primary cytogenetic abnormalities occur early when the normal plasma cell transitions to a clonal, premalignant stage. Most secondary cytogenetic abnormalities occur later in the disease course with malignant transformation or during progression of the malignancy. The effect of primary and secondary cytogenetic abnormalities on prognosis depends on the disease.
Abbreviations: IgH, immunoglobulin H; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.
Source: Rajan AM, Rajkumar SV. Interpretation of cytogenetic results in multiple myeloma for clinical practice. *Blood Cancer J*. 2015;5(10):e365, figure 1. PMID: 26517360. Reproduced under Creative Commons license.

Figure 21-2 Sequence of Genomic Events in the Molecular Pathogenesis of Multiple Myeloma



Abbreviations: GC, germinal center; IgH, immunoglobulin H; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.
Source: Awada H, Thapa B, Awada H, et al. A comprehensive review of the genomics of multiple myeloma: evolutionary trajectories, gene expression profiling, and emerging therapeutics. *Cells*. 2021;10(8):1961, figure 1. PMID: 34440730. Reproduced under Creative Commons license.

Figure 21-3 Treatment Approaches for Transplant-Eligible and Transplant-Ineligible Newly Diagnosed Multiple Myeloma



The primary goal of treatment for TE and TIE NDMM is to achieve a rapid, deep, and durable response. This aims to provide long-term disease control and ultimately improve patient prognosis.

Abbreviations: AKI, acute kidney injury; ASCT, autologous stem cell transplantation; CR, complete response; CrCl, creatinine clearance; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; DCyBorD, daratumumab, daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DKRd, daratumumab, carfilzomib, lenalidomide, and dexamethasone; DR, daratumumab and lenalidomide; DRd, daratumumab, lenalidomide, and dexamethasone; DVCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ESRD, end-stage renal disease; IMiD, immunomodulator (ie, lenalidomide or pomalidomide) drug; Isa-VRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Isa-KD, isatuximab, carfilzomib; and dexamethasone; KR, carfilzomib and lenalidomide; KRd, carfilzomib, lenalidomide, and dexamethasone; MM, multiple myeloma; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor (ie, bortezomib, ixazomib, carfilzomib); PN, peripheral neuropathy; PR, partial response; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone; VGPR, very good partial responses; VR; bortezomib and lenalidomide; VRd, bortezomib, lenalidomide, and dexamethasone.

*Target indicates the desired level of response, and not a failure of treatment if not achieved.

**For ASCT step: minimum PR and ideally VGPR. Standard risk includes all cytogenetics that are not considered high risk; high risk includes any patient with one high-risk cytogenetic mutation such as del(17p), t(14;16), t(14;20), t(4;14), del(1p), amp(1q) or gain(1q); ultra-high risk includes any patient with more than one high-risk cytogenetic mutation.

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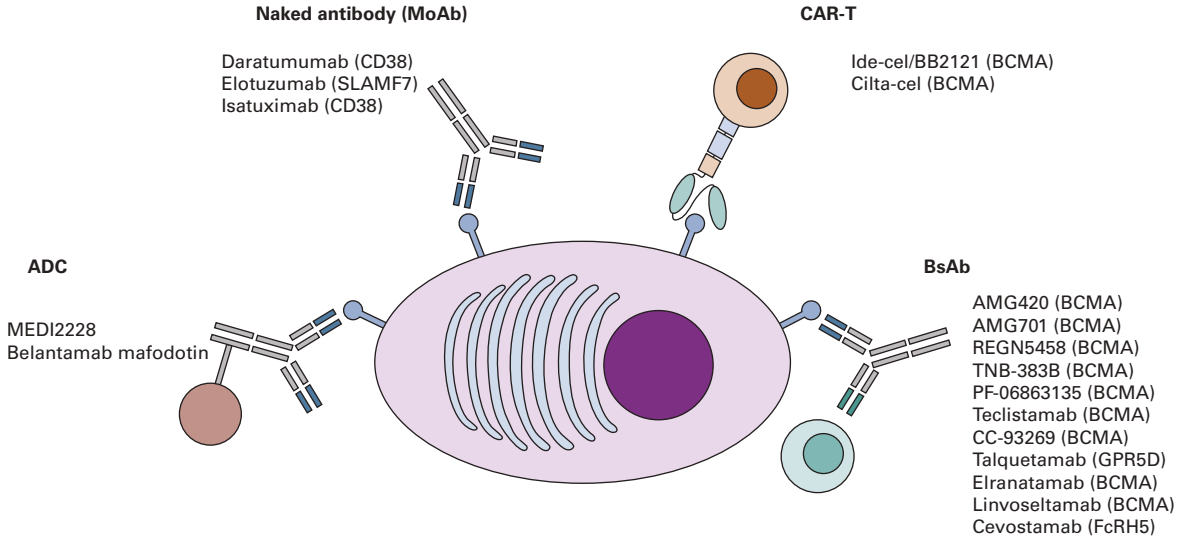
Figure 21-4 Recent Immunotherapeutic Approaches to the Treatment of Myeloma



Abbreviations: ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T-cell; Cilta-cel, ciltacabtagene autoleucel; Ide-cel, idecabtagene vicleucel; MoAb, monoclonal antibody.
Source: Adapted from Mohan M, Hari P, Dhakal B. Immunotherapy in multiple myeloma—time for a second major paradigm shift. *JCO Oncol Pract*. 2021;17(7):405-413. doi:10.1200/op.21.00032
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CELLULAR THERAPIES 22

Eric J. Huselton, MD, and Mohamad Hussein, MD

RECENT UPDATES

- The FDA approved CD19-directed chimeric antigen receptor (CAR) T-cell therapy obecabtagene autoleucel for relapsed/refractory B-cell acute lymphoblastic leukemia based on high rates of complete remission and median duration of remission.[1]
- The FDA approved CD19-directed CAR T-cell therapy lisocabtagene maraleucel for mantle cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia after at least two previous lines of therapy based on the response rate and duration of response.[2]
- Motixafortide, a CXCR4 inhibitor, was approved by the FDA for use in the mobilization of stem cells with granulocyte-colony stimulating factor for use in autologous transplantation for multiple myeloma.[3]
- Axatilimab, a CSF1R-blocking antibody, was approved by the FDA for chronic graft-versus-host disease that has not responded to other treatments.[4]

OVERVIEW

The term hematopoietic cell transplantation (HCT) encompasses the transfer of lymphohematopoietic progenitors from an individual to themselves (autologous transplantation) or to another individual (allogeneic transplantation).[5] HCT serves various purposes, from replacing abnormal yet nonmalignant hematopoietic systems, such as in aplastic anemia, to treating a spectrum of hematologic malignancies. It achieves this by facilitating the administration of myeloablative doses of chemotherapy and/or radiotherapy and establishing an immunologic graft-versus-tumor (GVT) effect, particularly in the setting of allogeneic HCT. By 2021, an estimated 1.5 million HCTs had been performed worldwide, with rates increasing due in part to the availability of alternative donor sources such as partially matched, haploidentical donors and mismatched unrelated donors.[6,7] The frequency of HCT procedures varies significantly across countries, often correlating closely with the gross national income per capita. Nevertheless, substantial differences persist among countries with similar income levels, varying by HCT referral and frequency, disease indications, and donor choices. Furthermore, racial disparities have been identified within these practices, including differences in referral patterns.[8]

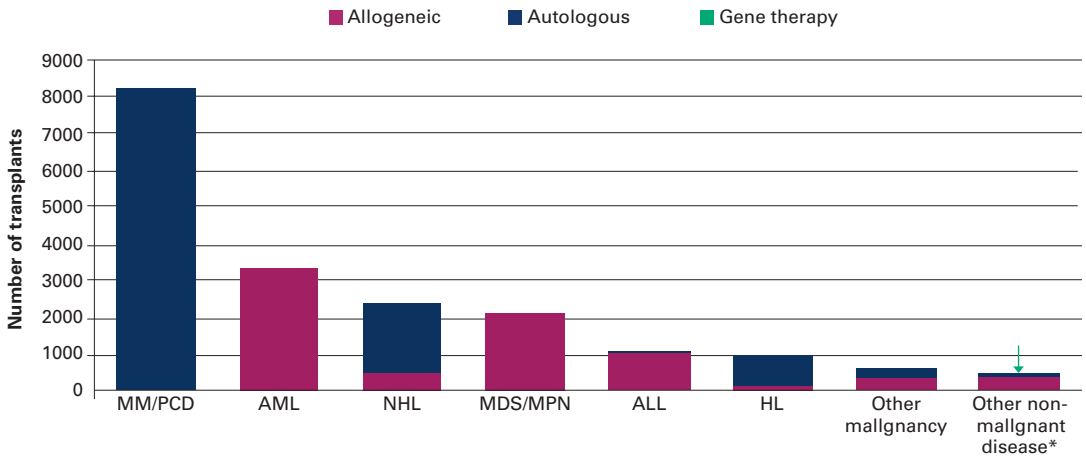
Chimeric antigen receptor (CAR) T-cell therapy shares similarities with HCT because both use cellular-based therapies to enhance immune responses against hematologic malignancies. Indeed, allogeneic donor lymphocyte infusion (DLI) in relapsed leukemia can be viewed as the first example of adoptive immune cell transfer. Subsequent advancements in gene-transfer techniques have enabled researchers to redirect T cells toward tumor-specific antigens. This chapter delves into the fundamental principles of cellular therapies, encompassing HCT, cell sources, preparative regimens, and associated complications. For a more comprehensive understanding of the role of HCT in treating specific diseases, further exploration is provided in dedicated chapters focusing on those ailments.

INDICATIONS

MALIGNANT DISEASES

The most frequent use of HCT has been for the treatment of malignant diseases.[9,10] The leading indication for autologous HCT in the United States is multiple myeloma (MM), followed by non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL; Fig. 22-1). Prospective randomized trials have shown that autologous HCT, when used as part of initial therapy, prolongs remission for patients with MM. This finding still holds true in the era of modern myeloma therapy.[11-13]

Figure 22-1 Number of Hematopoietic Cell Transplantations in US (2023) Adults



Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; MDS, myelodysplastic syndromes; MM, multiple myeloma; MPN, myeloproliferative neoplasms; NHL, non-Hodgkin lymphoma; PCD, plasma cell disorders.
*Includes 22 limited gene therapy events.
Reprinted with permission from Spellman SR, Xu S, Temitope O, et al. Current activity trends and outcomes in hematopoietic cell transplantation and cellular therapy—a report from the CIBMTR. *Transplant Cell Ther.* 2025;31(8):505-532. doi:10.1016/j.jtct.2025.05.014

Autologous HCT is curative for 40% to 50% of patients who have NHL or HL that recurred after first-line therapy; these results are superior to what would be expected with additional chemotherapy alone.[14-17] For patients who have diffuse large B-cell lymphoma (DLBCL) that is primary refractory to, or relapses within 12 months after initial chemotherapy, CD19-directed CAR T-cell therapies have shown superior event-free survival (EFS) and overall survival (OS) when compared with salvage chemotherapy and autologous transplantation in phase 3 trials.[18,19] Nonetheless, ongoing discussions persist regarding the role of high-dose chemotherapy with autologous HCT as part of initial therapy for patients who have high-risk NHL.[17-19] In addition, autologous HCT finds applications in primary central nervous system lymphoma and select chemotherapy-sensitive solid tumors with notable experiences in testicular cancer and neuroblastoma.[20] In the United States, the leading indications for allogeneic HCT are acute myeloid leukemia (AML; approximately 50% of cases), followed by myelodysplastic syndromes (MDS) and acute lymphoblastic leukemia (ALL).[10] HCT consistently yields 5-year disease-free survival (DFS) rates of 50% and 70% when performed during the first remission for AML and ALL, respectively.[21-23] Meta-analyses comparing matched-sibling allogeneic HCT versus conventional chemotherapy for adult patients who have these disorders have shown improved survival outcomes with HCT.[24-26] The benefits of HCT are most pronounced for patients who have higher-risk leukemia and are less so for those with lower-risk disease. Delaying HCT until the second remission in higher-risk patients results in less favorable outcomes, with cure rates limited to 25% to 40%. Relapse is the most common cause of post-transplantation mortality, and in general, patients who have better disease control and deeper remission before transplantation tend to experience better transplantation outcomes with less relapse. For patients who have MDS up to age 79 years, allogeneic HCT yields cure rates of 30% to 60% with improved OS compared with no HCT after hypomethylating agent therapy.[27-29] In patients with low-risk MDS who often live for long periods without treatment, HCT is typically reserved for those who have higher-risk disease.[30,31] Although more than 70% of patients who have chronic myeloid leukemia (CML) in the chronic phase can be cured with allogeneic HCT, it is usually restricted to patients whose disease has progressed after multiple tyrosine kinase inhibitor (TKI) therapies, those who cannot tolerate TKIs, or those with advanced disease states (ie, second chronic phase after blast crisis).[32] In addition, allogeneic HCT can reverse marrow fibrosis in primary myelofibrosis, serving as the sole potential curative option for these patients.[33] Allogeneic HCT is also used in the treatment of patients who have HL or NHL who have relapsed after autologous transplantation and/or CAR T-cell therapy, for recurrent chronic lymphocytic leukemia, and NHL with marrow involvement.[34] Although allogeneic HCT is used in a small subset of patients who have relapsed myeloma, considering the increased risk for transplant mortality in this setting, studies comparing reduced-intensity allogeneic transplantation with autologous transplantation have yielded conflicting results.[35,36]

NONMALIGNANT DISORDERS

The most prevalent data and best outcomes regarding allogeneic HCT for nonmalignant disorders of hematopoiesis are reported for severe aplastic anemia and thalassemia, with a growing experience in sickle cell anemia. Most patients who have severe aplastic anemia (90%) can be cured with allogeneic HCT from a matched sibling[37] or related haploidentical donor[38]; results are slightly less favorable if a matched unrelated donor (MUD) is used. Allogeneic HCT cures 70% to 90% of patients who have thalassemia

major, with the best results seen among patients who undergo transplantation before the development of hepatomegaly or portal fibrosis.[39] Although data on sickle cell disease are more limited, current reports document 5-year survival and DFS rates of 93% and 84%, respectively.[40,41] A recent Blood and Marrow Transplant Clinical Trials Network (BMT CTN) trial using reduced-intensity haploidentical bone marrow transplantation resulted in 2-year EFS of 88% and OS of 93%.[7] Cure has also been achieved in other nonmalignant disorders of hematopoiesis and immunodeficiency states, including Fanconi anemia, Diamond-Blackfan syndrome, chronic granulomatous disease, Kostmann syndrome, leukocyte adhesion deficiency, Wiskott-Aldrich syndrome, severe combined immunodeficiency disorders, and other immunodeficiency states. However, because allogeneic HCT has substantial and unpredictable complications, treatment recommendations should be based on identifying patients at high risk from their underlying diseases for whom the risk of HCT is justified.[42]

KEY POINTS

- All diseases of hematopoiesis, nonmalignant and malignant, are potentially curable with cellular therapy.
- The leading indication for autologous HCT in the United States is MM, followed by relapsed NHL and HL.
- Allogeneic HCT consistently leads to 5-year DFS rates of 50% to 70%, respectively, when performed for AML and ALL in first remission.

ELIGIBILITY

HCT is an intensive therapy with a high risk of adverse events and, in the case of allogeneic transplantation, transplantation-related nonrelapse mortality related to graft-versus-host disease (GVHD) and infectious complications. Patient evaluation for eligibility includes performance status, comorbidities, organ function, psychosocial status, social support, and disease status. Comorbidities can be associated increased risk of complications as scored by the HCT comorbidity index (HCT CI), which incorporates 14 comorbidities, including cardiac disease, arrhythmia, inflammatory bowel disease, diabetes, cerebrovascular disease, psychiatric conditions, hepatic dysfunction, obesity, active infection, rheumatologic disease, peptic ulcer, renal dysfunction, pulmonary dysfunction, and history of previous second cancer.[43] Having an HCT CI score of 3 or greater is associated with increased risk of treatment-related mortality following allogeneic transplant. Patients undergo assessment, including left ventricular function, pulmonary function testing, dental evaluation, infectious disease markers, social worker assessment, and laboratories assessing renal and hepatic function, as well as psychosocial factors such as the degree of caregiver support.

In earlier decades, various upper age limits of 65, 70, or 75 years were used for transplantation eligibility. With improvements in supportive care and use of reduced-intensity conditioning regimens, many centers no longer use an upper age cutoff, instead focusing on the aforementioned criteria for transplantation eligibility.

SOURCES OF STEM CELLS

Hematopoietic stem cells are $CD34^+$ progenitors used for HCT that can be categorized according to the relationship between the donor and the recipient or according to anatomic source (Table 22-1). In the rare instances in which the patient has an identical (syngeneic) twin, HCT can be conducted without the risk of graft rejection or GVHD because the individuals share genetic identity throughout the genome. However, these syngeneic HCTs confer fewer benefits of an immunologic effect, resulting in a higher risk of relapse of the underlying malignancy.[44]

Table 22-1 Cell and Donor Sources for Autologous and Allogeneic Hematopoietic Cell Transplantation

Type of Transplantation	Cell Source	Donor
Autologous	Bone marrow Peripheral blood	Recipient
Allogeneic	Bone marrow Peripheral blood Umbilical cord blood	Related Unrelated
Syngenic	Bone marrow Peripheral blood	Monochorionic twin

Reproduced under Creative Commons license. Source: HSCT: How does it work? In: Kenyon M, Babic A, eds. *The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT*. Springer; 2018:23-36, table 2.1.

BONE MARROW

Because bone marrow is rich in hematopoietic stem cells, it was historically used as the source of stem cells for HCT. Typically, marrow for HCT is obtained through multiple aspirations from bilateral posterior iliac crests. The harvested marrow is treated

with heparin or anticoagulant citrate dextrose solution or both and filtered through screens to remove osseous spicules and fat globules before either being infused into the patient or being cryopreserved for later use. Some studies have explored pretreating the marrow before cryopreservation or infusion to investigate whether the removal of T cells or T-cell subsets from allogeneic marrow can improve outcomes by reducing GVHD or whether tumor cells can be eliminated before autologous stem cell transplant (SCT), although these kinds of product manipulations are not routinely done.[45] Bone marrow remains the preferred graft source when transplanting for aplastic anemia and other nonmalignant disorders due to its association with less GVHD.[37]

PERIPHERAL BLOOD

Hematopoietic stem cells circulate in the peripheral blood, albeit in small numbers. However, during recovery from drug-induced cytopenia or after exposure to hematopoietic growth factors, such as granulocyte-colony stimulating factor (G-CSF), the number of hematopoietic progenitor cells in the peripheral blood significantly increases.

Stromal cell-derived factor 1 (SDF-1 or CXCL12) produced by marrow stromal cells plays a critical role in regulating hematopoietic stem cell homing and retention in the marrow by interacting with the chemokine receptor CXCR4 found on stem cells. Plerixafor and motixafortide, antagonists of CXCR4, induce rapid mobilization of CD34 cells into the peripheral blood. In patients who have MM and NHL, phase 3 trials of stem cell mobilization with plerixafor in combination with G-CSF compared with G-CSF alone have demonstrated favorable safety and improved efficacy in the combination arm with respect to reaching target collection goals.[46,47] Comparisons with conventional chemotherapy mobilization have also suggested that the cost and risk of complications with chemotherapy-mediated mobilization outweigh the cost of plerixafor.[48] Other cost-containment approaches include using plerixafor on demand if $CD34^{6}$ stem cell numbers are suboptimal with G-CSF alone.[49] Motixafortide with G-CSF also resulted in higher collection yields than G-CSF alone in patients with MM. Factors associated with poor stem cell mobilization and collection include increasing age, underlying marrow disease, previous extensive radiotherapy to the marrow, and exposure to chemotherapies, including melphalan, fludarabine, and prolonged use of immunomodulatory agents such as lenalidomide.[50]

With the use of these and other mobilizing techniques, followed by leukapheresis, it has become feasible to collect sufficient stem cells from the peripheral blood to permit successful HCT. Peripheral blood has largely supplanted marrow as the preferred source of stem cells because of its association with faster engraftment, reduced cost, and improved safety. In allogeneic HCT, peripheral blood stem cell grafts are associated with more rapid engraftment but with a higher incidence of chronic GVHD, similar rates of acute GVHD and DFS, and perhaps improved OS, particularly for patients who undergo transplantation for more advanced-stage disease.[51] In the setting of unrelated donor transplantation, a large randomized study comparing marrow with peripheral blood after myeloablative conditioning showed faster engraftment but more chronic GVHD with peripheral blood, although with equivalent OS. However, this trial encompassed various hematologic malignancies, and limited data are available regarding reduced-intensity allogeneic transplantation.[52] A retrospective European study of peripheral blood SCT compared with bone marrow with reduced-intensity conditioning regimens for acute leukemia also showed an increase in chronic GVHD with peripheral SCT but better leukemia-free survival and OS.[51] Despite the necessity for a prospective randomized trial, the preference for many centers is to use peripheral blood stem cells over bone marrow for allogeneic transplantation, particularly for treating hematologic malignancies.

Donor risks differ depending on the stem cell source requested, with incidences of serious adverse events after bone marrow and peripheral blood stem cell donation reported at 2.4% and 0.6%, respectively. Severe adverse events after peripheral blood donation include pain, fatigue, and numbness/tingling, whereas for bone marrow donation, they are mainly pain, anemia, and complications related to anesthesia. Extremely rare serious events, including cardiac arrest, pulmonary embolism, and subdural hematoma, have been reported after marrow donations, and pulmonary embolism, supraventricular tachycardia, and splenic rupture have been reported with peripheral blood donation.[53,54]

Peripheral blood stem cell donation is safe and is not associated with an increased risk of cancer, autoimmune illness, or stroke. Guidelines have been developed to ensure the safety and suitability of unrelated adult donors and for the hematopoietic cell collection process.[55]

KEY POINTS

- In the MUD setting, use of mobilized peripheral blood stem cells showed faster engraftment, but more chronic GVHD compared with bone marrow. Use of plerixafor and motixafortide, antagonists of CXCR4, with G-CSF results in mobilization of CD34+ cells into the peripheral blood and high stem cell collection yields for autologous HCT.

AUTOLOGOUS TRANSPLANTATION

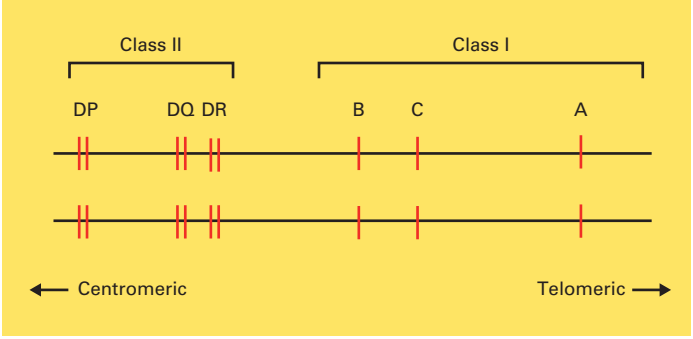
Over the past four decades, numerous clinical trials have been conducted to determine the suitability of high-dose therapy and autologous HCT for various diseases as well as the necessity for allogeneic HCT in certain cases. The use of a patient's own (ie, autologous) stem cells for HCT rescues them from the administration of myeloablative doses of chemotherapy. Approximately 60% of all HCTs are autologous. The leading indication for autologous HCT is MM[10] based on the studies dating back to the 1980s

that demonstrated the efficacy of high-dose melphalan conditioning followed by autologous HCT in achieving complete remission (CR). Subsequent trials in NHL have also shown superior progression-free survival (PFS) compared with traditional chemotherapy for relapsed disease, and that autologous transplant can be curative for a subset of patients with relapsed lymphoma.[56,57] Autologous HCT is also used in relapsed HL and occasionally in malignancies of nonhematopoietic origin, such as neuroblastoma and germ cell tumors.

ALLOGENEIC TRANSPLANTATION

Historically, the preferred source of allogeneic hematopoietic stem cells has been from a young human leukocyte antigen (HLA)-identical sibling, because greater HLA disparity and donor age are major drivers of post-HCT outcomes, specifically GVHD. HLA genes encode the major histocompatibility complex molecules that display exogenous peptides (eg, from an infecting organism) and endogenous peptides on nucleated cells, presenting them to T cells to initiate an immune response (Fig. 22-2). When two individuals are not HLA-identical, T cells from one person will vigorously react to the mismatched HLA molecules on the surface of cells from the other individual. Although non-twin siblings may be HLA matched, genetic polymorphisms in a wide range of genes can result in differences in the endogenous peptides presented by the HLA molecules. These differences lead to T-cell responses against minor HLA determinants, also known as minor histocompatibility antigens.

Figure 22-2 Genes Associated with HLA Typing on Chromosome 6



Abbreviation: HLA, human leukocyte antigen.
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SIBLING DONORS

The genes encoding HLA class I (*HLA-A, HLA-B*, and *HLA-C*) and class II (*HLA-DP, HLA-DQ*, and *HLA-DR*) are located on chromosome 6, tightly linked, codominantly expressed, and inherited as haplotypes with low recombination frequency. Therefore, for any given patient, the following are true:

- The likelihood that a full sibling will be HLA matched with the patient is 25%.
- The likelihood of finding a matched sibling for a patient can be calculated by the formula $x = 1 - 0.75^n$, where x equals the probability of finding a matched sibling and n equals the number of siblings.
- Given the size of families in the United States, the chance that a matched sibling can be identified for any patient is approximately 30%.

HAPLOIDENTICAL DONORS

Family members who are genotypically identical to the patient for only one HLA haplotype are considered haploidentical. Whereas the chance of finding a fully matched sibling donor is 25% per sibling, and the chance of finding an MUD varies by patient ethnicity, most patients will have haploidentical donor options because there is a 50% chance of a sibling being HLA haploidentical and because biologic parents and children will always be haploidentical. Haploidentical HCT initially relied on ex vivo T-cell depletion to combat higher rates of severe GVHD and graft rejection; however, in vivo T-cell depletion using post-transplantation high-dose cyclophosphamide allows the safe use of haploidentical related donors as well as related, matched unrelated, or mismatched unrelated donors.[58] Over the past decade, haploidentical HCT with post-transplantation high-dose cyclophosphamide has become widely adopted because of the ease of finding donors, low cost, and favorable outcomes.[6,59] Retrospective analyses show similar outcomes between haploidentical and matched-sibling donors for patients who have AML in remission, haploidentical and sibling donors for patients who have ALL, and haploidentical donors and MUDs for patients who have MDS and HL and NHL.[60-65]

Furthermore, studies comparing alternative donors have shown similar outcomes between haploidentical HCT and umbilical cord blood transplantation.[66] Despite the early closure of a randomized phase 3 trial comparing umbilical cord blood transplantation with haploidentical transplantation because of poor accrual, the trial revealed improved 2-year OS and lower nonrelapse mortality with haploidentical HCT.[67]

UNRELATED DONORS

Given that most patients will not have an age-appropriate matched sibling donor, the most commonly used donors for allogeneic HCT are completely unrelated to the patient but are matched for *HLA-A, -B, -C*, *-DRB1*, and *-DQB1.* Since the establishment of the National Marrow Donor Program in 1986 and other international registries, more than 25 million healthy individuals have volunteered to serve as stem cell donors. However, the likelihood of finding a fully matched, available, unrelated donor varies among racial and ethnic groups, ranging from 75% for White individuals of European descent to a low of 16% for Black individuals of South and Central American descent.[68]

When compared with the outcomes of matched-sibling transplantation, transplantations from unrelated donors matched with the patient at *HLA-A*, *-B*, *-C*, and *-DRB1* are associated with greater morbidity, mostly from GVHD, but survival at 3 to 5 years after HCT is similar.[69] Initial studies of MUD HCT did not consider *HLA-DPB1* matching, but retrospective analyses suggest that a mismatch at *HLA-DPB1* is associated with increased risk of GVHD and reduced risk of disease relapse.[70] Subsequent studies investigating T-cell epitope matching at *HLA-DPB1* define mismatch as permissive (ie, sharing T-cell epitope groups) or nonpermissive (ie, mismatched T-cell epitope groups). When compared with nonpermissive mismatch, permissive *HLA-DPB1* mismatch was associated with improved rates of survival, nonrelapse mortality, and severe GVHD.[71,72] With advancements in HLA matching and management of post-transplantation complications, recent analyses have suggested comparable outcomes between matched-sibling and MUD transplantations, and even better outcomes when choosing a younger MUD compared to an older matched-sibling.[73] However, a single-antigen HLA mismatch still correlates with higher rates of GVHD and treatment-related mortality, resulting in a lower survival rate.[74] Whereas HLA matching plays a significant role in transplantation outcomes, other donor factors, including age, sex, parity, and cytomegalovirus (CMV) serology, have a measurable effect.[75] The use of post-transplantation cyclophosphamide for GVHD prophylaxis results in lower rates of GVHD and improved survival outcomes for many transplantation types, including patients undergoing mismatched unrelated transplantations, with similar transplant outcomes between HLA 10/10 MUDs and less than 10/10 matches.[76,77]

UMBILICAL CORD BLOOD

Cord blood stem cell units have a paucity of mature T cells, which allows for less-stringent criteria for HLA matching and permits the use of units with one or two antigen mismatches in comparison with the recipient. Studies have shown cord blood to be a viable source of abundant stem cells for HCT. Given the small number of mature T cells, the risk of GVHD with cord blood seems to be somewhat lower than the risk associated with similarly matched marrow, although the risk of graft rejection or failure may be greater. Matched-related cord blood can be used as a source of stem cells to treat family members who have hemoglobinopathies with survival rates similar to those of matched-sibling bone marrow HCT.[78] By far, the most common use of cord blood has been in the treatment of unrelated recipients who lack a matched donor.

Improved survival after cord blood transplantation is associated with higher cell dose, younger patient age, and a greater degree of matching.[79] A low cord blood cell dose increases the risks of graft failure, delayed hematopoietic engraftment, and delayed immune recovery, which historically limited cord blood HCT to children and smaller adults.[80] Trials exploring the use of double-cord transplantation (which provides a greater cord blood cell dose) have demonstrated that, whereas only one cord ultimately engrafts, the use of two cords reduces the risk of graft failure and is associated with an enhanced GVT effect.[81,82] However, there seems to be no advantage to using two cords in cases in which a single cord provides a sufficient number of cells, at least in children and young adults.[83] A phase 3 trial comparing transplantation with the nicotinamide-expanded umbilical cord blood product omidubicel with standard cord blood transplantation showed improved, faster neutrophil and platelet engraftment.[84] This product was FDA approved in 2023.[85]

ABO BLOOD GROUPS

Hematopoietic stem cells do not express ABO, so HCT can be carried out across ABO blood group barriers by removing incompatible red blood cells (RBCs) and/or isoagglutinins from the donor graft. However, even with appropriate manipulation of the donor graft, a major ABO mismatch (eg, recipient O and donor A) can result in immediate or delayed hemolysis of donor RBCs or red cell aplasia by persistent recipient isohemagglutinins (Table 22-2). On the other hand, a minor mismatch (eg, recipient B and donor O) can result in immediate hemolysis of recipient RBCs by donor-derived isohemagglutinins in the graft or delayed hemolysis of recipient RBCs by newly generated isohemagglutinins from donor lymphocytes, also known as passenger lymphocytes.

Table 22-2 **Table of Donor-Recipient ABO Compatibility With Potential Complications and Interventions**

Donor-Recipient ABO Compatibility				
	Blood Type			
Mismatch Type	Recipient	Donor	Potential Complications	Interventions
Major	O	A, B, AB	Acute hemolysis of donor RBCs	RBC reduction of the stem cell product
	A	AB	Delayed engraftment	
	B	AB	Pure red cell aplasia from recipient anti-donor isohemagglutinins	
Minor	A	O	Acute hemolysis from donor isohemagglutinin	Plasma reduction of the stem cell product
	B	O	Delayed hemolysis from passenger lymphocyte syndrome	
	AB	O, A, B		
Bidirectional	A	B	A combination of major and minor	A combination of major and minor
	B	A		

Abbreviation: RBC, red blood cell.
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AVAILABILITY OF ALLOGENEIC STEM CELL SOURCES

With the availability of matched-related donors, MUDs, single-antigen mismatched related donors, haploidentical donors, and cord blood units, a suitable source of allogeneic stem cells can be identified for the vast majority of patients requiring transplantation. Notably, alternative donor types offer expanded options for ethnic groups with limited access to unrelated donors. For most patients, a haploidentical donor is accessible because all biologic parents and children of a patient are haploidentical. One limitation in using haploidentical donors and mismatched unrelated donors is the presence of anti-donor HLA antibodies, usually stemming from parous women against paternal HLA antigens in their children or from exposure to multiple transfusions. In instances where another donor cannot be found, regimens for donor-specific antibody desensitization have been used successfully.[86] Although matched-related donors are generally preferred, there is a scarcity of prospective randomized trials comparing alternative donors.[67] Emerging evidence suggests relatively similar survival after matched-unrelated cord blood, unrelated cord blood, and haploidentical donor HCT, and choosing a younger donor may result in the best outcomes.[87-92] Thus, donor selection is often guided by donor characteristics such as age, sex, parity, CMV serostatus, and the experience of the transplantation center.

KEY POINTS

- Although GVHD after HCT is more common with MUDs than with matched siblings, survival rates seem similar.
- Methods have been developed that allow for the selection of permissive single-antigen mismatched donors.
- HCT using either a haploidentical or HLA-mismatched unrelated donor is feasible; subsequently, an allogeneic donor can be found for most patients in need.
- Use of post-transplantation cyclophosphamide results in a low rate of GVHD and similar outcomes between donor types.

PREPARATIVE REGIMEN

The chemotherapy, with or without radiotherapy, administered to patients directly before HCT is known as a high-dose conditioning for autologous transplant or preparative regimen for allogeneic transplant. The selection of a conditioning regimen depends on the disease being treated, the source of the stem cells, and the patient's comorbidities. The primary objectives of conditioning are to eradicate disease, create space for engraftment, and, in the case of allogeneic transplantation, sufficiently immunosuppress the host to prevent graft rejection. Patients who have severe combined immunodeficiency diseases often require no preparative regimen before HCT because of the absence of an abnormal cell population requiring eradication; their severely compromised immune system rarely rejects infused hematopoietic cells if the donor is an HLA-matched sibling. By contrast, patients who have aplastic anemia are sufficiently immunocompetent to potentially reject allogeneic stem cells without pretransplantation immunosuppression. More recently, the Hopkins team and the BMT CTN have shown excellent outcomes when using a regimen of fludarabine, cyclophosphamide, and total body irradiation (TBI) followed by PTCy, likely replacing high-dose cyclophosphamide

and antithymocyte globulin (ATG) as the preferred preparative regimen for allogeneic HCT in aplastic anemia.[93] When HCT is used in the treatment of leukemia or other malignant diseases, the regimen must include myelosuppression as well as immunosuppression (in the setting of allogeneic HCT) to contribute to the eradication of the malignant disease. In the case of autologous HCT for lymphoma and myeloma, eradication of the malignant clone is the main goal of the high-dose conditioning regimen.

Conditioning regimens for allogeneic HCT are typically classified into three main categories: myeloablative, nonmyeloablative, and reduced intensity. Myeloablative regimens induce irreversible marrow aplasia and require replacement of the hematopoietic system; nonmyeloablative regimens cause minimal marrow suppression, and reduced-intensity conditioning results in cytopenias of intermediate duration.[94-96] Initially, high-dose myeloablative preparative regimens were the primary approach to HCT to treat malignant diseases. However, the recognition that antitumor effects occur after allogeneic HCT because of a GVT response prompted investigations into reduced-intensity regimens that might demonstrate comparable efficacy with less toxicity. Evidence supporting a GVT effect includes lower relapse rates after allogeneic marrow HCT when acute or chronic GVHD develops, higher rates of relapse in the absence of GVHD, and even higher rates with syngeneic or T-cell–depleted allogeneic marrow transplantation.[44,97] Additional evidence of a potent GVT effect comes from the use of viable DLIs. A simple transfusion of as few as 1×10^7 viable donor lymphocytes per kg as treatment for patients whose disease relapses after allogeneic HCT can result in CR for as many as 70% of patients who have CML and for a smaller portion of patients who have AML or MDS.[98]

Compared with high-dose preparative regimens, nonmyeloablative and reduced-intensity regimens result in less or minimal mucositis, fewer bacterial infections, and a lower incidence of direct toxicities to the lung and liver. However, these benefits are offset by generally higher relapse rates associated with reduced-dose regimens. A prospective randomized phase 3 trial demonstrated increased relapse rates and shortened survival with the use of reduced-intensity conditioning compared with myeloablative conditioning in patients who have AML or MDS.[99] Consequently, reduced-intensity conditioning is generally reserved for older patients and those who have substantial comorbidities, whereas high-dose regimens are preferred for younger, fit patients. Patients who have experienced relapse after autologous transplantation and are candidates for an allogeneic approach often receive reduced-intensity conditioning in an attempt to maximize efficacy and minimize organ toxicity. Suggested dose adjustments for patients with renal or hepatic impairment have been published.[100,101]

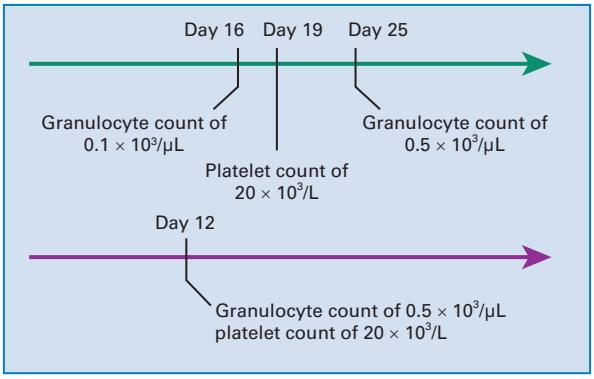
KEY POINTS

- The purpose of the high-dose regimen used before autologous HCT is to eradicate the underlying disease.
- The purpose of the preparative regimen in allogeneic HCT is to sufficiently immunosuppress the patient to prevent graft rejection and to eliminate residual disease.
- Evidence points to increased relapse rates and diminished survival with the use of reduced-intensity conditioning compared with myeloablative conditioning in patients with AML or MDS.

ENGRAFTMENT

After the administration of a preparative regimen and the infusion of stem cells, a period of profound myelosuppression ensues. Within 1 to 3 weeks after HCT, the peripheral neutrophil count begins to rise, indicating engraftment. When stem cells are procured from marrow without the use of hematopoietic growth factors after HCT, the granulocyte count typically reaches 0.1×10^3/mL by

Figure 22-3 Timeline of Granulocyte and Platelet Count Recovery After Hematopoietic Cell Transplantation Using Bone Marrow and Peripheral Blood Stem Cells



Graphical representation of a mechanism in which donor and recipient markers can mismatch (top) or match (bottom).
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approximately day 16 and 0.5 × 10^3/mL by day 25, and platelets reach 20 × 10^3/L by day 19 (Fig. 22-3). Administration of daily G-CSF can accelerate the recovery of peripheral granulocyte counts by up to 1 week. Platelet count recovery typically lags behind neutrophil engraftment, usually by several days but possibly by several weeks for some patients.

When peripheral blood is the source of stem cells, engraftment is faster, with a granulocyte count of 0.5 × 10^3/mL and a platelet count of 20 × 10^3/mL achieved by day 12, on average. Engraftment after cord blood HCT is typically delayed by approximately 1 week compared with marrow HCT. Engraftment of allogeneic stem cells can be documented using fluorescence in situ hybridization of sex chromosomes if the donor and recipient are of opposite sexes, and DNA-based assays of short tandem repeat loci allow for routine monitoring of donor-versus-recipient cell origin (chimerism) post-transplantation. Loss of chimerism is an indicator of graft failure and disease relapse.

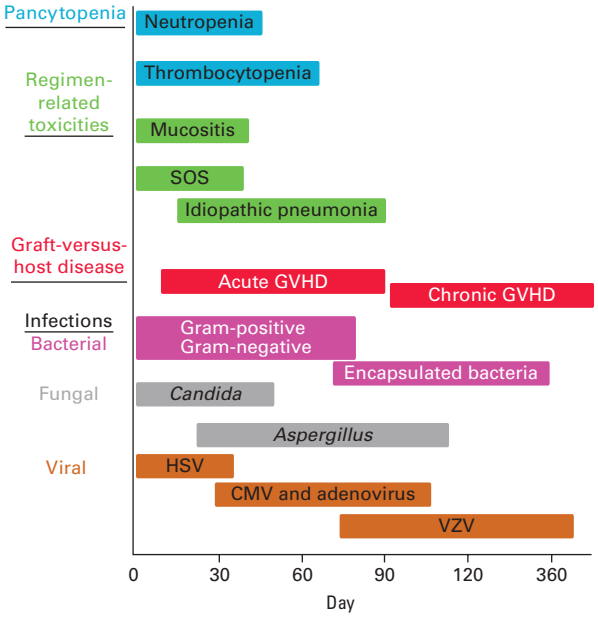
KEY POINTS

- By using in situ hybridization with sex chromosome–specific probes or typing of the variable number of tandem repeat polymorphisms, the donor-versus-recipient origin of populations of cells can be determined in virtually all cases in allogeneic HCT to assess engraftment and monitor for disease relapse.
- Loss of chimerism is an indicator of graft failure and/or disease relapse.

COMPLICATIONS OF HCT

The nature and the degree of complications associated with HCT depend on the age and health of the patient, the specific preparative regimen used, and the source of stem cells (Fig. 22-4). The frequency of complications is higher, and the rate of survival is lower for patients who have a Karnofsky performance score less than 80% and for patients who have substantial comorbidities.[102] GVHD is normally seen only after allogeneic HCT, although it can, in rare cases, be a complication of autologous transplantation, and subsequent infections related to the immunosuppression used to prevent or treat GVHD are leading causes of nonrelapse morbidity and mortality. The extent of other specific organ toxicities depends largely on the specific preparative regimen used. HCT-specific scoring systems have been developed that can predict the overall likelihood of GVHD and overall mortality after allogeneic HCT. Such systems are useful in the selection of preparative regimens for individual patients, allowing those who have few comorbidities to have the benefit of more intense regimens and selecting safer, less intense regimens for those with substantial comorbidities. The following sections discuss the major complications of HCT.

Figure 22-4 The Approximate Timing of Possible Toxicities After Allogenic Transplantation Using a Typical Intensive Preparative Regimen



Abbreviations: CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; SOS, sinusoidal obstruction syndrome; VZV, varicella zoster virus.

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GRAFT FAILURE

Failure to engraft occurs when there is no engraftment of donor cells. In some instances, the transplanted graft functions briefly, but after a period of days or weeks, marrow function is lost, and myeloid elements are absent on evaluation of marrow obtained by biopsy. In the setting of allogeneic HCT, failure of the graft is usually the result of residual host immune elements rejecting the donor marrow, a phenomenon termed graft rejection. After HCT involving an HLA-identical donor, graft rejection occurs most commonly when the patient has received multiple transfusions before HCT and little previous chemotherapy, and when the preparative regimen is less immunosuppressive. In general, the greater the disparity in HLA antigens between donor and recipient, the higher the chance of rejection. Donor-specific anti-HLA antibodies are found in approximately 10% of patients before partially matched cord blood HCT, in mismatched unrelated-donor HCT, and in haploidentical donor HCT, when their presence predicts a high rate of graft rejection, and use of such donors should be avoided.[103] Desensitization techniques can reduce these antibodies to levels permissible for donor engraftment.[104]

Because donor T cells help eliminate host immunocompetent cells not eradicated by the preparative regimen, T-cell depletion of donor stem cells before HCT can lead to persistence of host immunity, resulting in an increased chance of graft rejection.

Graft failure rarely occurs in recipients of autologous transplants.[105] A single cause is often difficult to identify, but several have been implicated, including the following:

- Previous exposure to stem cell poisons
- Marrow damage during in vitro processing and cryopreservation
- Drug toxicity after HCT
- Viral infections

Patients who have graft failure but not immunologically mediated graft rejection sometimes have a response to treatment with a hematopoietic growth factor, such as G-CSF, with an increase in the granulocyte count that may be sustained even after discontinuation of the growth factor. If persistent host lymphocytes are detected that document graft rejection, a second marrow transplantation after an immunosuppressive preparative regimen may be successful.

GRAFT-VERSUS-HOST DISEASE

GVHD is a complication mediated by allogeneic T and B cells, which are transfused with the graft, reacting against non-hematopoietic tissues on the genetically different host that they regard as foreign. The evolution of clinical immunology has brought additional insight into the pathogenesis of GVHD and identified, in addition to the genetic component (ie, HLA compatibility), an immunobiologic component, including the intestinal epithelium and gut microbiome. A National Institutes of Health consensus report recognizes two categories of GVHD, acute and chronic, each with two subcategories (Table 22-3).[106] Acute GVHD usually develops 2 to 42 weeks after allogeneic HCT and typically presents with an erythematous or maculopapular rash, nausea, vomiting, anorexia, diarrhea (sometimes profuse), ileus, and/or cholestatic jaundice. Sometimes, the diagnosis can be less straightforward, and a skin, liver, or gastrointestinal biopsy specimen may be required.

Table 22-3 Categories of Acute and Chronic GVHD

Category[107]	Time of Symptoms After HCT	Presence of Acute GVHD Features	Presence of Chronic GVHD Features
Acute GVHD			
Classic acute	≤100 days	Yes	No
Late onset	>100 days	Yes	No
Chronic GVHD			
Classic Chronic	No time limit	No	Yes
Overlap	No time limit	Yes	Yes

Abbreviations: GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation.
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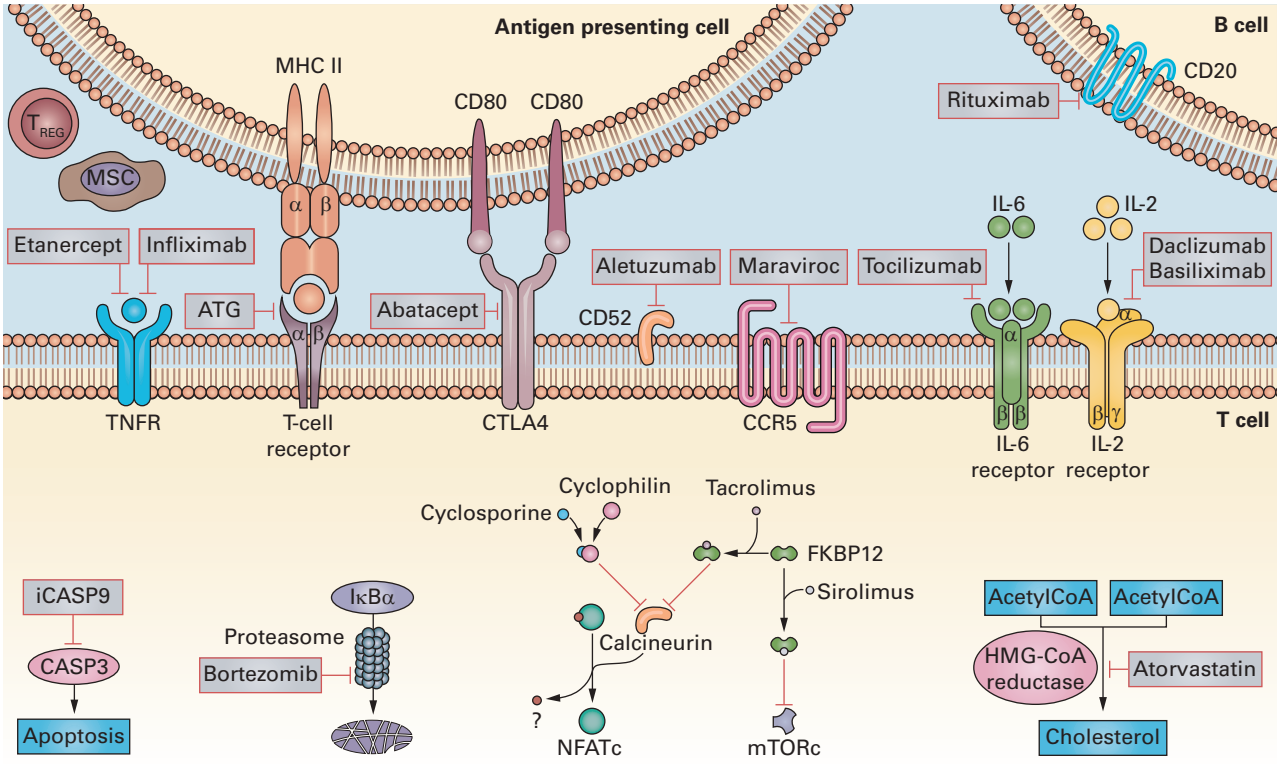
Factors associated with an increased risk of moderate or severe acute GVHD include the following:

- HLA mismatching
- Choice of GVHD prophylaxis regimen
- Older age of patient and donor
- A multiparous woman as the donor
- Exposure to more intensive conditioning regimens

GVHD PROPHYLAXIS

Immunosuppression remains the main prophylactic approach in GVHD (Fig. 22-5). The most commonly used regimens to prevent GVHD include a combination of a calcineurin inhibitor (cyclosporine or tacrolimus) and an antimetabolite (methotrexate [MTX] or mycophenolate mofetil) and/or post-transplantation cyclophosphamide.[108]

Figure 22-5 Standard and Emerging Therapies for the Prevention of Acute GVHD



Abbreviations: Acetyl CoA, acetyl coenzyme A; ATG, anti-thymocyte globulin; CCR5, C-C chemokine receptor 5; CLTA4, cytotoxic T lymphocyte antigen 4; FKBP12, FK506 binding protein 12; GVHD, graft-versus-host disease; HMG CoA reductase, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; iCasp9, inducible caspase 9; IkB, nuclear factor of kappa light polypeptide gene enhance in B cells inhibitor; IL, interleukin; MHC II, major histocompatibility class II; MSC, mesenchymal stem cell; mTORC, mammalian target of rapamycin complex; NFATc, nuclear factor of activated T cells cytoplasmic; TNFR, tumor necrosis factor receptor; TREG, regulatory T-cell.
The different medications and their targets against B cells and T cells are illustrated in this figure. MSC and TREG infusions are depicted extracellularly.
Reprinted from Choi SW, Reddy P. Current and emerging strategies for the prevention of graft-versus-host disease. *Nat Rev Clin Oncol*. 2014;11(9):536-547. doi:10.1038/nrclinonc.2014.102 [additional rights language TK].

Post-transplantation cyclophosphamide is increasingly used to target proliferating alloreactive T cells stimulated early after transplantation. Although initially developed for haploidentical transplantation, post-transplantation cyclophosphamide can serve as the only GVHD prophylaxis after HLA-matched HCT and is associated with a similar incidence of acute GVHD and OS and reduced chronic GVHD rates compared with traditional calcineurin-based prophylaxis.[109,110] In a randomized phase 3 trial of patients with AML or MDS who are undergoing transplantation from a closely matched donor with reduced-intensity conditioning, use of post-transplantation cyclophosphamide with tacrolimus and mycophenolate resulted in lower rates of severe acute and chronic GVHD when compared with tacrolimus and methotrexate.[111,112] A randomized phase 3 trial of patients receiving myeloablative conditioning with an HLA-matched marrow graft showed that single-agent post-transplantation cyclophosphamide resulted in rates of chronic GVHD and OS similar to rates achieved with tacrolimus and MTX with less relapse.[113] Three prospective randomized trials reported that the addition of ATG to standard prophylaxis led to lower rates of acute and chronic GVHD without affecting OS with myeloablative conditioning.[114] Although the European trials did not show a higher risk of relapse, the US prospective trial with reduced-intensity conditioning did.[115] Other approaches to preventing GVHD include the ex vivo removal of T cells from the donor marrow, but this approach is not widely used because of concerns of increased risk of relapse.[116] Abatacept, a CTLA-4 immunoglobulin that blocks T-cell costimulation, is an FDA-approved agent for GVHD prophylaxis in combination with calcineurin inhibitors and MTX based on the studies that show lower rates of severe acute GVHD.[117] Ongoing trials are evaluating the role of extended-dose abatacept in the prevention or treatment of steroid-refractory chronic GVHD.

ACUTE GVHD

With standard regimens, such as MTX plus tacrolimus, moderate acute GVHD requiring therapy occurs in approximately 30% of patients who have undergone HCT with a matched-sibling donor. Acute GVHD is usually staged and graded using a modification of the original Seattle system, which uses a four-stage system in which a higher stage is associated with worse mortality.[118]

Standard treatment of acute GVHD is prednisone at a daily dose of 2 mg/kg, although a lower dose of 1 mg/kg may be used for grades 1 to 2 acute GVHD; nonabsorbable steroids such as budesonide or beclomethasone for gastrointestinal GVHD and steroid ointments for skin GVHD are beneficial.[119] The optimal duration of steroid therapy is unknown, but it should be as limited as possible to avoid the adverse effects of prolonged therapy. However, approximately 35% to 45% of patients will be refractory to steroid therapy.[120] Steroid-refractory acute GVHD is defined as failure of GVHD to clinically respond to standard steroid therapy, and care of these patients remains a major challenge. Treatment options include secondary immunosuppressive agents, JAK inhibitors, or ATG. The JAK inhibitor ruxolitinib showed a greater overall response rate (ORR) with longer failure-free survival in a randomized phase 3 trial of steroid-refractory acute GVHD.[121] Other treatment options with limited data or that are currently in clinical trials include sirolimus, abatacept, etanercept, extracorporeal photopheresis, alpha 1 antitrypsin, and monoclonal antibodies.

In an effort to prognosticate acute GVHD at its onset and better risk-stratify treatment of patients with GVHD, a scoring system (Ann Arbor score) based on three biomarkers (TNFR1, ST2, and REG3a) was developed and validated.[122] The GVHD biomarker-based classification (Ann Arbor score 1-3), combined with a refined clinical risk score by one group,[123] has been incorporated into a few therapeutic clinical trials for newly diagnosed acute GVHD.

PRESENTING CASE STUDY

A 55-year-old woman was diagnosed with acute myeloid leukemia (AML) with a normal karyotype and mutations in ASXL1, IDH1, and SRSF2. She received 7+3 and achieved complete remission that was negative for measurable residual disease by flow cytometry. She subsequently received a cycle of high-dose cytarabine and a matched-unrelated donor allogeneic stem cell transplant with myeloablative conditioning. Her conditioning regimen includes busulfan and fludarabine, and graft-versus-host disease (GVHD) prophylaxis including tacrolimus, mycophenolate mofetil, and post-transplant cyclophosphamide. On day 30 after stem cell infusion, she develops abdominal discomfort, persistent nausea, and 10 episodes of watery diarrhea per day and presents to the hospital. Infection was ruled out, and sigmoidoscopy demonstrates erythema, aphthous lesions, and denudation of the mucosa. Biopsy is notable for crypt cell necrosis.

How would these findings inform your treatment decision?

Given the risks associated with GVHD therapy, making the correct diagnosis is critical. The patient's clinical history, combined with negative evidence of infection, physical examination, endoscopic evaluation, and histology confirm a diagnosis of gut GVHD. Her volume of diarrhea qualifies this as grade 3 acute GVHD of the gut. Corticosteroids, both topical and systemic, are first-line therapy for grade 3/4 acute GVHD. She is started on methylprednisolone 2 mg/kg/day and oral budesonide three times daily. Her symptoms failed to improve after 7 days.

How would her response influence your next treatment recommendations?

Many patients respond to corticosteroid therapy, in which case steroids can be gradually tapered. GVHD symptoms that worsen within 5 days or do not improve after 7 days are considered steroid-refractory disease. Based on the REACH2 trial, a randomized, open-label phase 3 trial that evaluated ruxolitinib versus the best available therapy in patients with steroid-refractory acute GVHD, ruxolitinib therapy led to significant improvements in overall response at day 28 and durable overall response at day 56 (40% vs 22%) with longer median failure-free survival and overall survival. Other treatment options include ATG, extracorporeal photopheresis, sirolimus, and abatacept, although data for these approaches are lacking.

CHRONIC GVHD

Chronic GVHD affects 20% to 40% of matched-sibling HCT recipients and manifests as a condition resembling collagen vascular disease involving skin, liver, eyes, mouth, upper respiratory tract, and esophagus, and, less frequently, serosal surfaces, female genitalia, and fascia.[124] A National Institutes of Health consensus project developed a detailed staging system for chronic GVHD

in which 12 organ systems are graded from 0 (no symptoms) to 3 (severe involvement), and these 12 scores are then combined into a severity score for chronic GVHD.[125]

Factors associated with increased risk of chronic GVHD include the following:

- Higher degree of HLA mismatching
- Use of peripheral blood stem cells instead of marrow
- Older patient age
- Increasing donor age
- Sex disparity between donor and recipient (especially a female donor to a male recipient)
- Previous donor alloimmunization through pregnancy or blood transfusion in the donor
- Previous episodes of acute GVHD

If chronic GVHD develops while the calcineurin inhibitor is being tapered, increasing the inhibitor to therapeutic levels may be effective in resolving GVHD. Mild chronic GVHD can sometimes be managed using local therapies alone (eg, topical steroids to the skin and cyclosporine eye drops). More severe diseases usually require prednisone alone or in combination with a calcineurin inhibitor, which can control chronic GVHD in 50% to 70% of cases. Steroid-refractory chronic GVHD remains a clinical challenge. A randomized controlled phase 3 trial comparing ruxolitinib with best available therapy for patients with moderate or severe chronic GVHD refractory to or dependent on steroids showed better ORR (50% vs 26%) and longer failure-free survival (>18.6 months vs 5.7 months) with ruxolitinib. The Bruton TKI ibrutinib is currently approved to treat refractory chronic GVHD based on a single-arm trial showing an ORR of 69% and a complete response rate of 31% in patients with steroid-refractory or -dependent GVHD.[126] The Rho-associated protein kinase 2 inhibitor belumosudil was approved to treat chronic GVHD that persists after two or more lines of treatment based on a phase 2 study showing an ORR of 74% with 44% of patients continuing to receive therapy for more than 1 year. Notably, responses were seen when treatment with ruxolitinib and ibrutinib failed.[127] Axatilimab, a monoclonal antibody targeting CSF-1R primarily on macrophages, was associated with an ORR of 74%, with 60% of the responses being durable for more than 12 months.[128] Other treatment options for patients who have multiply refractory chronic GVHD include mycophenolate mofetil, sirolimus, extracorporeal photopheresis, rituximab, or low-dose interleukin (IL)-2.[129,130]

Eventually, immunosuppression can be tapered and discontinued in 80% to 90% of patients. However, achieving tolerance may require many months to several years of immunosuppressive therapy, with the median duration of treatment typically ranging from 2 to 3 years. Bacterial infections frequently occur in patients with chronic GVHD who are receiving immunosuppressive therapy, thereby requiring the use of prophylactic antimicrobials. A commonly used regimen includes trimethoprim and sulfamethoxazole plus penicillin, which provides protection against both *Pneumocystis jirovecii* and encapsulated organisms. The choice of antifungal prophylaxis varies among medical centers but may include agents such as fluconazole, isavuconazole, posaconazole, or voriconazole. Invasive molds, predominantly aspergillosis, are a major cause of post-transplantation mortality in patients with chronic GVHD who require long-term steroids.

AUTOIMMUNE DISORDERS

After allogeneic HCT, an autoimmune disorder may develop in 3% to 5% of patients, most commonly in the form of autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura. Unrelated-donor source and chronic GVHD are risk factors. Treatment potentially involves cyclosporine, prednisone, or rituximab.

KEY POINTS

- T cells in the donor graft, combined with allogeneic targets on the genetically different host, are a major driver in the development of GVHD.
- Biomarker approaches for diagnosis and risk stratification are under study.
- Post-transplantation cyclophosphamide and ATG reduce rates of acute and chronic GVHD.
- Ruxolitinib is an effective treatment for steroid-refractory acute and chronic GVHD.

INFECTIOUS COMPLICATIONS

Infection is a major risk for nearly all transplant recipients. Recipients of autologous transplants are at risk for the early bacterial and fungal infections common to all patients who have granulocytopenia. Recipients of allogeneic hematopoietic grafts, particularly patients in whom GVHD develops, are also at risk for late-onset bacterial, fungal, and viral diseases. Use of prophylactic antimicrobials is an important part of managing infectious risks in these patients.[131]

BACTERIAL AND FUNGAL INFECTIONS

During the early neutropenic period after HCT, patients are likely to become febrile, and in approximately 50% of patients with febrile neutropenia, a bacterial source can be identified. Before engraftment, a fluoroquinolone is often administered if myeloablative conditioning regimens are used because they result in severe mucosal damage that facilitates bacterial translocation under profound immunosuppressive conditions. After engraftment, fluoroquinolone prophylaxis is typically discontinued, but patients who remain at risk for infection may receive antibiotics, including penicillin and trimethoprim plus sulfamethoxazole. Prophylaxis against fungal pathogens has been shown to reduce rates of fungal infection and improve OS. Prophylaxis with fluconazole is generally recommended for patients at standard risk, whereas prophylaxis with a mold-active agent should be considered for patients who have higher-risk disease, including patients who have had a previous fungal infection or recipients of a cord-blood or unrelated-donor transplantation. Although approaches vary, one standard approach is to continue fungal prophylaxis for 75 days after allogeneic HCT and until resolution of neutropenia after autologous HCT. Although having had a previous invasive fungal infection increases transplantation risk, with current methods of prophylaxis, it should not be considered a contraindication for HCT.[132] Patients who become or remain febrile despite treatment with broad-spectrum antibiotics and who have no obvious source of infection are usually treated with alternative antifungal agents (eg, voriconazole, isavuconazole, micafungin, or amphotericin lipid formulation, depending on the clinical situation).

With current methods of supportive care, the risk of death as a result of infection during the early granulocytopenic period after HCT is less than 3% for recipients of either allogeneic or autologous transplantations. Protective environment rooms incorporate the use of high-efficiency particulate air filters with 99.97% efficiency in removing particles larger than 0.3 mm to minimize the risk of infection from spores.

HERPES SIMPLEX INFECTION

Herpes simplex infection, which can contribute to the severity of oral mucositis, can be prevented with the use of systemic acyclovir, beginning during conditioning. At many centers, acyclovir is continued for up to 1 year to prevent late infection or reactivation with varicella zoster virus and is often continued even longer in patients receiving immunosuppression therapy. The new zoster vaccine containing varicella zoster virus glycoprotein E and the ASo1B adjuvant system was shown to be safe and effective in a phase 3 trial that included patients who had undergone autologous transplantation.[107] This finding led to the addition of this vaccine to the post-autologous HCT immunization schedule. Single-center cohort studies have suggested that it is safe to use after allogeneic HCT and does not increase the rate of GVHD, although its immunogenicity may be decreased.[133]

CMV INFECTION

In the past, symptomatic CMV infection, which typically involved either the gastrointestinal tract or the lungs, occurred in approximately 25% of patients who received allogeneic transplantations and led to death (typically resulting from CMV pneumonia) in 10% to 15% of patients. The improvement in control and prevention of CMV in HCT has had a substantial effect on the improvement in OS.

A randomized trial evaluated the prophylactic use of ganciclovir until day 100 after transplantation and demonstrated no difference in CMV infection by day 180 and similar OS. In addition, patients in the ganciclovir arm had a higher incidence of fungal and bacterial infections.[134] Therefore, preemptive therapy using blood polymerase chain reaction monitoring is standard practice rather than prophylactic therapy. However, even with this approach, early CMV reactivation remains associated with increased mortality.[135,136] Use of letermovir, an oral agent that inhibits CMV replication, led to a reduction in clinically significant CMV infection (37.5% vs 60.6% in the control group) in a placebo-controlled trial. It was well-tolerated and did not have the myelotoxic effects associated with ganciclovir; moreover, it offers a small survival advantage. Therefore, the use of letermovir was approved for prophylaxis in seropositive recipients after transplantation until day 100. Extended use may also be considered in high-risk patients.[137] Maribavir is approved for the treatment of CMV infections refractory to standard therapy.[138] Foscarnet is effective for some patients in the context of ganciclovir resistance, as well as for patients who cannot tolerate ganciclovir. Foscarnet, however, can be associated with severe electrolyte wasting and renal compromise.

PNEUMONIA

Pneumonia resulting from infection with *P. jirovecii*, previously seen in 5% to 10% of transplant recipients, can be prevented by treatment with oral trimethoprim and sulfamethoxazole for 1 week before HCT, with resumption of prophylaxis once the granulocyte count exceeds 0.5×10^3/mL. Treatment 2 days per week when patients are receiving immunosuppressive drugs after HCT is usually sufficient to prevent *Pneumocystis* infection. Allergic reactions to trimethoprim and sulfamethoxazole are common, and dapsone, atovaquone, or pentamidine can serve as a substitute for trimethoprim plus sulfamethoxazole.

COMMUNITY-ACQUIRED VIRAL INFECTIONS

Community-acquired viral infections, including COVID-19, respiratory syncytial virus (RSV), influenza virus, and parainfluenza virus, can cause lethal pneumonias in patients undergoing transplantation. Patients with upper respiratory symptoms before

HCT should be screened by nasopharyngeal lavage for viral infections before proceeding to HCT. If COVID-19, RSV, influenza virus, or parainfluenza virus is found, HCT should be delayed. Ribavirin and anti-RSV antibody, although unproven, are used by some centers in treating established RSV infection in patients undergoing transplantation.

VACCINE-PREVENTABLE DISEASE

Antibody titers to vaccine-preventable diseases decline after allogeneic or autologous HCT if the patient is not revaccinated. Therefore, post-transplantation revaccination against SARS-CoV-2, influenza, *Haemophilus influenzae*, Varicella Zoster, meningococcus, pneumococcus, polio, diphtheria, tetanus, pertussis, hepatitis A and B, and human papillomavirus, among others, is generally recommended.[139] Live-virus vaccines such as measles, mumps, and rubella (MMR) are usually given 2 years after HCT and when the patient has stopped receiving immunosuppression to avoid complications. The choice of vaccines and schedule may vary depending on patient age, underlying diagnosis, and degree of continuing immunosuppression. Therefore, although several guidelines have been written, decisions regarding whom, when, and how to vaccinate should be made in consultation with infectious disease experts and institutional transplantation guidelines.[131,140]

KEY POINTS

- Fungal infections can be prevented, and survival can be improved with the use of antifungal prophylaxis during the first few months after HCT.
- Letermovir prophylaxis can reduce the incidence of CMV infection.
- Patients should be screened for viral infections; a positive result may be cause for delaying HCT.
- Revaccination after HCT is generally recommended.

TOXICITIES RELATED TO THE PREPARATIVE REGIMEN

After most standard preparative regimens, patients commonly experience immediate toxic effects such as nausea, vomiting, fever, and mild skin erythema. Unusual toxic effects associated with high-dose cyclophosphamide include hemorrhagic cystitis and, rarely, acute hemorrhagic carditis. TBI commonly results in parotiditis.

Oral mucositis frequently results following conditioning containing melphalan, busulfan, and/or radiation. Cryotherapy, by having patients suck on ice chips, is an effective way to reduce mucositis following melphalan by restricting blood flow to the oropharynx, given the short half-life. Mucositis requiring narcotic analgesia typically develops 5 to 7 days after HCT that uses high-dose preparative regimens. Patient-controlled analgesia is preferred, providing superior patient satisfaction and minimizing cumulative narcotic doses.

Sinusoidal obstruction syndrome (formerly termed veno-occlusive disease) can develop within 1 to 4 weeks after treatment with many high-dose preparative regimens, as well as treatment with antibodies conjugated with calicheamicin (eg, inotuzumab ozogamicin and gemtuzumab ozogamicin); its symptoms include weight gain, ascites, tender hepatomegaly, and jaundice. The current overall incidence of sinusoidal obstruction syndrome is approximately 2%, but varies widely based on the patients, the preparative regimen, and the type of prophylaxis used.[141,142] In general, the incidence is higher for patients who have abnormal liver function tests before HCT and those with an active infection at the time of HCT. Defibrotide, a mixture of single-stranded oligonucleotides (not generally recognized as the dominant mechanism of action), has been approved by the FDA for treatment of sinusoidal obstruction syndrome based on retrospective controlled trials.[143] Prophylaxis with low molecular weight heparin and ursodeoxycholic acid may reduce the incidence of sinusoidal obstruction syndrome.[141]

Pulmonary complications after HCT pose significant risks to patient health, often leading to substantial morbidity and mortality and impacting long-term function. Idiopathic pneumonia syndrome, believed to stem directly from chemoradiotherapy toxicity, occurs 30 to 90 days after HCT in up to 5% of patients. As with other toxicities, the incidence of idiopathic pneumonia syndrome is influenced by various factors, including the preparative regimen; higher occurrences are observed after regimens involving elevated doses of TBI. Additional risk factors include preexisting lung conditions, previous thoracic irradiation, and advanced age, whereas the use of fractionated radiotherapy seems to lower the risk. Idiopathic pneumonia syndrome carries a mortality rate of approximately 50%, and currently available treatments lack clear effectiveness, although initial findings with tumor necrosis factor blockade show promise.[144]

Two categories of chronic pulmonary dysfunction are seen among patients who survive more than 3 months after allogeneic HCT: restrictive lung disease and obstructive lung disease. The most common cause of restrictive lung disease is cryptogenic organizing pneumonia, which presents with symptoms such as dry cough, shortness of breath, fever, and radiographic findings showing a diffuse, fluffy infiltrate. Histology shows patchy fibrosis, granulation tissue within alveolar spaces and small airways, and absence of identifiable infectious agents. Treatment with corticosteroids often yields a favorable response with the potential for complete reversal of the condition.[145] Conversely, bronchiolitis obliterans is an obstructive defect marked by progressive dyspnea, nonproductive cough, and radiologic evidence of airway trapping. Histology typically shows enhanced deposition of

collagen and granulation tissue in and around bronchial structures, ultimately leading to obliteration of small airways. This condition represents the pulmonary manifestation of chronic GVHD. Management generally involves increasing immunosuppression. Initially, promising results have been reported with a combination treatment comprising fluticasone, azithromycin, and montelukast. However, more recent updates, such as the ALLOZITHRO study, have raised concerns about an increased risk of hematologic malignancy relapse in the azithromycin arm, prompting an FDA alert against its use as prophylaxis for bronchiolitis obliterans.[146,147]

LATE EFFECTS AND LONG-TERM SURVIVORSHIP

The combined effects of therapeutic exposures before HCT and conditioning regimens during transplantation lead to cumulative damage to normal tissues. This damage contributes to the premature onset of various health conditions, including secondary neoplasms, infections, chronic GVHD, respiratory diseases, metabolic syndrome, cardiac and neurovascular diseases, and musculoskeletal abnormalities.[148-150] The 15-year cumulative incidence of chronic health conditions exceeds 40% in those who have undergone HCT, and a study by Martin et al[151] reported in 2010 demonstrated that the mortality rates of those undergoing HCT more than 5 years out from HCT are fourfold to ninefold higher than expected with an estimated 30% lower life expectancy compared with that of the general population regardless of current age. In addition, a study by Chow et al[152] in 2017 compared HCT survivors with a matched population of patients with cancer who did not undergo transplantation, revealing significantly higher rates of serious health outcomes among HCT survivors, including substantially greater rates of hospitalization (280 vs 173 episodes per 1,000 person-years), hospitalization or death resulting from infection (10-year cumulative incidence, 31% vs 22%), and respiratory complications (27% vs 20%).

Additional delayed complications include decreased growth velocity in children and delayed development of secondary sexual characteristics. Postpubescent women commonly experience ovarian failure, and few men regain spermatogenesis after HCT that uses high-dose preparative regimens. However, there are instances in which fertility is restored even after myeloablative conditioning, highlighting the importance of counseling patients about this possibility. Cataracts affect up to one-third of patients, with an increased risk among patients receiving high doses of TBI and those requiring steroids for treatment of GVHD. In addition, thyroid dysfunction and osteoporosis may occur, albeit usually well-compensated. Significant psychosocial difficulties accompany HCT, and survivors have increased rates of anxiety, depression, sleep and sexual disorders, and post-traumatic stress disorder.[153]

The Center for International Blood and Marrow Transplant Research and European Society for Blood and Marrow Transplantation have developed consensus guidelines to assist providers in screening and preventive care for infectious, cardiovascular, metabolic syndrome, and bone disease, as well as ocular, neurocognitive, and other late effects of HCT.[154] Collaboration between HCT providers and primary care physicians is crucial in using a patient-centered approach that considers individual risk factors and adheres to evidence-based screening, prevention, and intervention strategies for chronic conditions.

KEY POINTS

- Common chemoradiotherapy toxicities include nausea, vomiting, fever, and mild skin erythema. High-dose regimens, especially when combined with TBI, lead to more severe oral mucositis.
- Sinusoidal obstruction syndrome and idiopathic pneumonia syndrome are serious potential complications requiring careful clinical management.
- As survival improves for HCT recipients, additional attention should be paid to long-term complications, especially cardiovascular disease and endocrine effects.

RELAPSE AFTER TRANSPLANTATION

There is a substantial risk of recurrent malignant disease after HCT, particularly when HCT is performed after failure of conventional therapy rather than earlier in the course of the disease. The appropriate treatment of patients who experience relapse after HCT depends on the disease and type of transplantation. Patients with lymphoma whose disease recurs after autologous HCT may have a response to subsequent chemotherapy, and occasionally such responses are surprisingly complete and prolonged, particularly if the duration of remission after HCT was long. Newer agents, such as targeted antibody therapy or checkpoint inhibitors, can be used for relapses after autologous transplantation and may induce responses that then serve as a bridge to allogeneic transplantation.[155-157]

On occasion, patients who are receiving immunosuppressive drugs and have recurrent disease after allogeneic HCT will have a second CR after discontinuation of immunosuppressive therapy. Infusions of viable lymphocytes from the original stem cell donors (donor leukocyte infusion) can result in CR for many patients. In a European study involving 135 patients, the rate of CR was 70% for patients with chronic-phase CML, 12% for patients with advanced-phase CML, 29% for patients with AML or MDS, and 0% for

patients with ALL.[98] Results of a small study suggest better OS with TKIs than with donor leukocyte infusion, representing another option for CML relapse after allogeneic HCT.[158] Most experts recommend that patients who have recurrent acute leukemia undergo reinduction chemotherapy before donor leukocyte infusion to decrease the leukemia cell burden and provide sufficient time for a graft versus leukemia (GVL) effect to develop. Some form of GVHD develops in approximately 60% of patients after infusion of donor lymphocytes; of these patients, 50% require therapy for GVHD, and 15% experience life-threatening GVHD. In addition, marrow aplasia occurs in 35% of patients, and the overall mortality associated with the infusion of donor lymphocytes is 20%. Limiting the dose of $CD3^+$ lymphocytes to less than 10×10^7 can decrease the risk of GVHD and life-threatening complications without impairing the GVL effect.[159] CD19 CAR T-cells are effective in the treatment of patients with ALL who have experienced relapse after HCT (discussed in the next section).[160] Responses have also been seen after treatment with ipilimumab, but immune-mediated toxicity and GVHD flares were also seen.[161]

Patients with AML or MDS may undergo a second allogeneic HCT as treatment for relapse after the first HCT. Such HCTs, if performed within 1 year of the original HCT, have been associated with a high risk of severe or fatal transplantation-related toxicities, including sinusoidal obstruction syndrome and idiopathic interstitial pneumonia. Results are more favorable when the second HCT is performed more than 1 year after the original HCT, with prolonged subsequent remissions reported for as many as 25% of patients.[162]

APPROACHES TO REDUCE RELAPSE AFTER TRANSPLANTATION

In general, HCT is delivered with curative intent. However, relapse remains a leading cause of treatment failure after HCT, and the prognosis of hematologic malignancies that relapse after HCT is extremely poor, particularly after allogeneic HCT. Therefore, there have been a number of approaches used to prevent post-transplantation relapse, such as intensification of conditioning regimens, consolidation therapies, and maintenance therapies.

In an attempt to intensify conditioning regimens, novel conditioning therapies in allogeneic HCT have been evaluated, including the incorporation of newer chemotherapeutic agents (eg, clofarabine and bendamustine), CD45-targeting radioimmunotherapy, and dose-intensified total-marrow irradiation. A phase 3 study evaluating the radioimmunoconjugate Iomab-B in patients with relapsed/refractory (R/R) AML demonstrated that a higher percentage of patients receiving Iomab-B were able to proceed to transplantation and remained in remission at 6 months compared with patients who received conventional care, although Iomab-B does not have FDA approval.[163]

In MM, consolidation therapy and maintenance therapy have been extensively studied, partly because of the limitation of single autologous HCT with a high rate of relapse.[164] Nonmyeloablative allogeneic HCT as a consolidation therapy after standard autologous HCT was evaluated by a few groups with mixed results.[36,165,166] A recent large clinical trial supported by the Blood and Marrow Transplant Clinical Trial Network (trial 0702) demonstrated that second autologous HCT (tandem autologous) or a combination of lenalidomide, bortezomib, and dexamethasone consolidation was not associated with improved PFS or OS.[167] In myeloma, maintenance therapy after autologous HCT using lenalidomide improves PFS and OS and remains the standard therapy.[168] A phase III trial evaluating daratumumab and lenalidomide versus lenalidomide as maintenance in patients who are positive for minimal residual disease (MRD) after autologous HCT and are anti-CD38 naive showed higher rates of MRD negativity and improved PFS with daratumumab and lenalidomide.[13,169]

In lymphoma, the most commonly studied agent for post-HCT maintenance is rituximab. A phase 3 trial in recurrent large-cell lymphoma did not show an advantage in relapse-free survival (RFS) or OS,[170] and a study in follicular lymphoma (FL) demonstrated an improvement in PFS without a difference in OS.[171] Brentuximab vedotin was evaluated in high-risk HL after HCT, in which it substantially improved PFS compared with placebo.[172] More recently, checkpoint inhibitors have been evaluated in this setting with promising data.[173]

The role of maintenance therapy after allogeneic HCT has not been well-defined. Low-dose azacitidine, a hypomethylating agent, was evaluated in a phase 1 trial as maintenance therapy starting at 6 weeks after HCT, and it established an optimal dosing schedule with a promising 1-year OS rate of 77%.[174] Although TKIs have been widely used as maintenance after allogeneic HCT for Philadelphia chromosome-positive ALL, data supporting their use are conflicting and are largely from single-arm trials or retrospective registries.[175-177] For AML with FMS-like tyrosine kinase 3 (*FLT3*) internal tandem duplication, several *FLT3* TKIs have been evaluated as maintenance after allogeneic HCT, including sorafenib, quizartinib, and gilteritinib.[178,179] A randomized placebo-controlled phase 2 trial of sorafenib maintenance after allogeneic HCT showed an improved 2-year PFS rate (85% vs 53%). However, a randomized, placebo-controlled phase 3 trial of gilteritinib failed to show improvement in RFS, with benefit limited to patients who have detectable MRD.[180]

KEY POINT

- Patients who experience relapse after allogeneic HCT can potentially respond to subsequent immunologic manipulation, including withdrawal of immunosuppression, DLIs, and treatment with checkpoint inhibitors.

CAR T-CELLS FOR HEMATOLOGIC MALIGNANCIES

CAR T-cell therapy has revolutionized the management of many hematologic malignancies and provided long-lasting responses (Table 22-4). CAR T-cells are engineered T cells with receptors designed to target and eliminate cells that express a specific antigen. The foundation of CAR T-cell therapy comprises second-generation cells that include both the T-cell–activating domain and chimeric costimulatory receptors to enhance proliferation and expansion of T cells. The pioneering application of CAR T-cell therapy in hematologic malignancies was CD19 targeting for B-cell ALL. Subsequently, several trials demonstrated response rates of up to 90% in adults and children with relapsed ALL.[193,194] Trials in CLL and NHL have also yielded positive responses, including CRs in a substantial proportion of patients with lymphoma.[181,195] Subsequently, commercial CAR T-cell constructs have been approved in the United States for R/R B-cell ALL, R/R DLBCL, relapsed mantle cell lymphoma (MCL), relapsed FL, relapsed CLL, and relapsed MM.

Axicabtagene ciloleucel and lisocabtagene maraleucel were the first products approved for relapsed DLBCL. Phase 3 trials evaluating these CD19-directed CAR T-cell products for DLBCL that is primary refractory to initial therapy or with early relapse within 12 months both demonstrated improved EFS and OS when compared with standard salvage chemotherapy followed by autologous HCT.[18,19] In patients with FL for whom two or more lines of therapy failed, axicabtagene ciloleucel, lisocabtagene maraleucel, and tisagenlecleucel are approved for therapy based on the high rates of overall response.[186] Brexucabtagene autoleucel was approved for R/R MCL with an ORR of 87% in a single-arm trial, and it seemed to be effective even in patients with high-risk disease, including TP53 mutant and blastoid variant.[196] Data for all of the CAR-T products show long-term PFS is achieved in about 30% of patients with R/R NHL.

The success of CD19-directed CAR T-cell therapy led to the development of new constructs targeting other diseases, such as B-cell maturation antigen (BCMA) for MM.[197] Anti-BCMA–directed CAR T-cell therapies, idecabtagene vicleucel and ciltacabtagene autoleucel, were approved for patients with R/R MM after 1 or 2 lines of therapy, respectively, on the basis of trials showing higher rates of overall response when compared with standard therapies.[191,192]

CAR T-cell products have unique toxicities distinct from those associated with checkpoint inhibitors or other immune activators. Newer CAR T-cell products that use 4-1BB costimulatory domains seem to have less toxicity and better persistence in some studies. B-cell aplasia is an anticipated on-target effect of CD19-directed CAR T-cells, resulting in long-term compromised humoral immunity. Lymphodepletion given before CAR T-cell infusion can result in myelosuppression. An effect seen across all CAR T-cell therapies is a clinical syndrome termed cytokine-release syndrome (CRS), characterized by elevations in serum cytokine levels (eg, IL-6 and interferon gamma) and expansion of CAR T cells in the peripheral blood and clinically manifested as fevers, hypotension, and, in severe cases, capillary leakage and hypoxia.[198] To address CRS, the FDA-approved tocilizumab, an anti–IL-6 receptor antagonist, is used for treatment either alone or in combination with steroids.[199] Siltuximab (an anti–IL-6 antibody rather than one directed against the IL-6 receptor) and anakinra (IL-1 receptor antagonist) have been used in CRS refractory to tocilizumab and steroids.

Immune effector cell-associated neurotoxicity syndrome (ICANS) is another distinct complication of CAR T-cells across all targets. Early signs often include tremor, dysgraphia, and mild expressive aphasia, especially with reversible memory deficits. In addition, patients may experience decreased levels of consciousness, ranging from mild lethargy to complete obtundation. Management includes diagnostic workup to rule out seizures and imaging of the brain to rule out cerebral edema. The use of levetiracetam, either prophylactically or after the onset of ICANS, and high-dose dexamethasone is recommended for treatment. Tocilizumab is not effective for ICANS in the absence of accompanying CRS and may worsen symptoms.[200] The American Society for Transplantation and Cellular Therapy has provided instructive consensus grading for both CRS and ICANS.[199]

Hemophagocytic lymphohistiocytosis (HLH), also known as macrophage activation syndrome, is another complication of CAR T-cell therapy, characterized by proliferation of morphologically benign lymphocytes and macrophages that secrete high levels of inflammatory cytokines. Symptoms and laboratory findings can overlap with those of CRS. Monitoring ferritin and C-reactive protein (CRP) levels are key component of treatment. Emerging evidence supports ruxolitinib as a treatment of choice for HLH because of its immunosuppressive effects.[201-203] Prolonged cytopenias are common, likely related to ongoing CAR T-cell activity and direct immune effects on the bone marrow. This toxicity is managed with supportive care, including growth factors, transfusions, and antibiotic and antiviral prophylaxis. ASCO offers guidance on the recommended management of immune-related adverse events in patients treated with CAR T-cell therapy.[204,205] Finally, there have been reports of an increased rate in second primary malignancies after CAR T-cell therapy, particularly myeloid and T-cell neoplasms.[206]

In short, CAR T-cell therapy has led to a new array of treatment options for patients with relapsed hematologic malignancies. Although they offer promising outcomes, these therapies come with distinct toxicities, including risk of second primary malignancies, underscoring the need for oncologists to be well-versed in recognizing, grading, and managing these adverse effects. Looking ahead, it is expected that this transformative technology, including research into allogenic CAR T-cells, will have expanded applications to address a broader spectrum of malignancies in the future.

Table 22-4 **Summary of Clinical Trials of FDA-Approved CAR T-Cells in NHL**

Disease	Product (Costimulatory Domain, Target)	Indication (Approval Year)	Study: Phase (No. of Patients)	% ORR (% CR)	Median PFS (Months)	Median OS (Months)	% CRS (% Grade 3+)	% Neurologic Toxicity (% Grade 3+)	References
DLBCL	Axicabtagene ciloleucel (CD28, CD19)	DLBCL 3L (2017)	ZUMA-1: P1-2 (108)	83 (58)	5.9	NR	92 (11)	67 (33)	181
		DLBCL, HGBCL, PMBCL 2L (2022)	ZUMA-7: P3 (359)	83 (65)	14.7	NR	92 (6)	61 (21)	18
	Tisagenlecleucel (41BB, CD19)	DLBCL: 3L+ (2018)	JULIET: P2 (115)	53 (39)	2.9	11.1	35 (23)	20 (11)	182
	Lisocabtagene maraleucel (41BB, CD19)	DLBCL, HGBCL, PMBCL 3L (2021)	TRANSCEND: P2 (270)	73 (53)	6.8	27.3	42 (2)	0 (10)	183
		DLBCL, HGBCL, PMBCL 2L (2021)	TRANSFORM: P3 (92)	79 (61)	14.8	NR	49 (1)	11 (4)	19
FL	Lisocabtagene maraleucel (41BB, CD19)	FL 3L (2024)	TRANSCEND-FL: P2 (107)	97 (94)	NR	NR	59 (1)	15 (2)	184
	Axicabtagene ciloleucel (CD28, CD19)	FL 2L+ (2021)	ZUMA-5: P2 (104)	95 (76)	NR	NR	82(7)	59 (19)	185
	Tisagenlecleucel (41BB, CD19)	FL 3L (2022)	ELARA: P2 (97)	86 (69)	NR	NR	49 (0)	37 (3)	186
MCL	Brexucabtagene autoleucel (CD28, CD19)	MCL (2020)	ZUMA-2: P2 (68)	91 (68)	25.8	46.6	91 (18)	63 (31)	125
	Lisocabtagene maraleucel (41BB, CD19)	MCL 3L (2024)	TRANSCEND-MCL: P1 (88)	83 (72)	15.3	18.2	61 (1)	31 (1)	187
B-cell ALL	Tisagenlecleucel (41BB, CD19)	B-ALL 3L, up to age 25 years (2017)	ELIANA: P2 (79)	(82)	24	NR	77 (48)	40 (13)	125
	Brexucabtagene autoleucel (CD28, 41BB)	B-ALL (2021)	ZUMA-3: P2 (55)	(71)	11.6	18.2	89 (24)	60 (24)	188
	Obecabtagene autoleucel (41BB, CD19)	B-ALL 2L (2024)	FELIX: P1b-2 (127)	77 (55)	11.9	15.6	69 (2)	23 (7)	189
CLL	Lisocabtagene maraleucel (41BB, CD19)	CLL/SLL 3L (2024)	TRANSCEND-CL: Ph1-2 (89)	48 (18)	11.9	30.3	83 (9)	45 (18)	190
MM	Ciltacabtagene autoleucel (41BB, BCMA)	MM 2L (2022)	CARTITUDE-4: P3 (176)	84 (73)	NR	NR	76 (1)	21 (3)	191
	Idecabtagene vicleucel (41BB, BCMA)	MM 3L (2021)	KarMMa-3: P3 (225)	71 (39)	13.3	NR	88 (5)	15 (3)	192

Abbreviations: 2L, second line; 3L, third line; ALL, acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; CLL, chronic lymphocytic leukemia; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; NR, not reached; ORR, overall response rate; OS, overall survival; P, phase; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; SLL, small lymphocytic lymphoma.

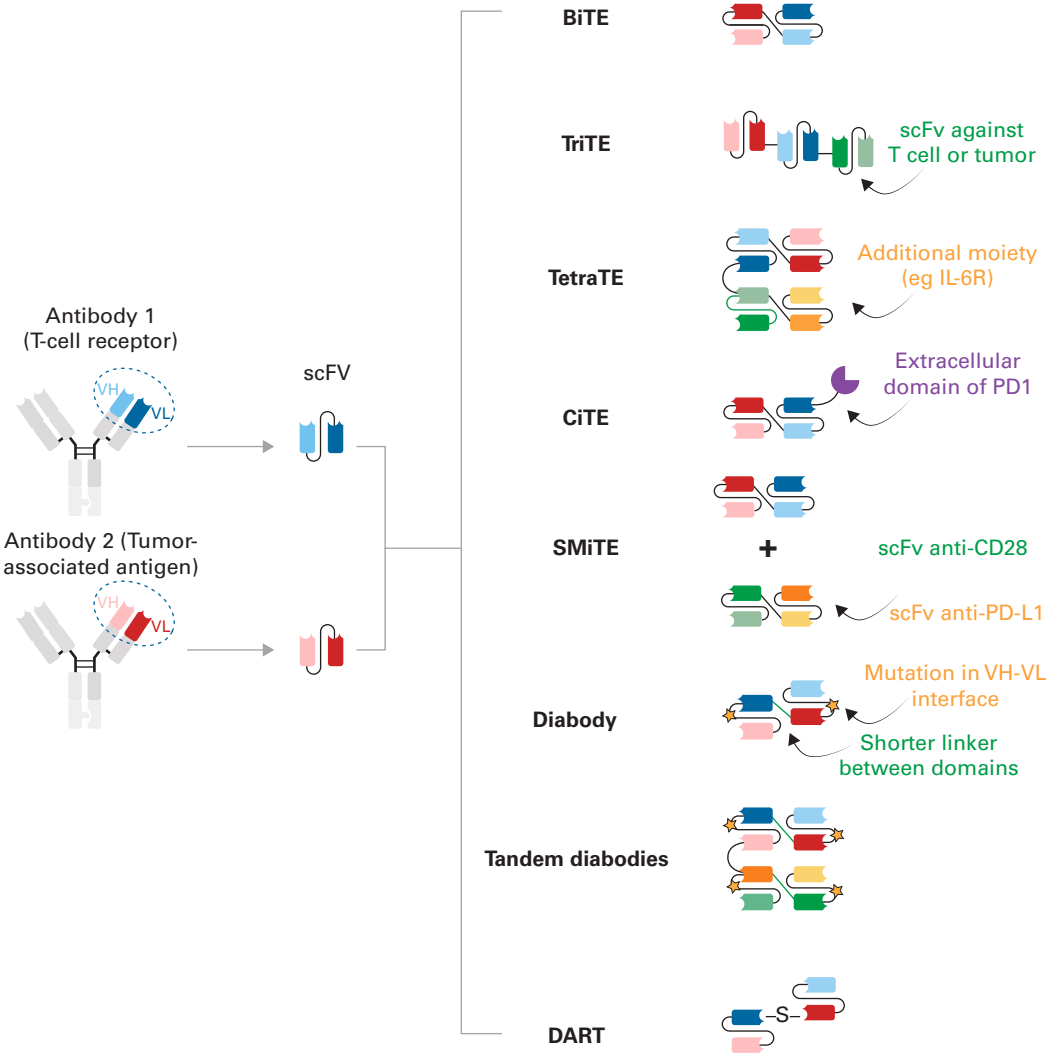
Source: Braunstein M, Main O. How do CAR T cells fit into the evolving non-Hodgkin lymphoma treatment landscape? *ASCO Daily News*. Published 2024. Accessed May 15, 2024. https://dailynews.ascopubs.org/do/do-car-t-cells-fit-into-evolving-non-hodgkin-lymphoma-treatment-landscape

IN VIVO CELLULAR THERAPY BY BISPECIFIC ANTIBODY AND IN VIVO CAR-T THERAPY

Historically, the development of bispecific antibodies (BsAbs) began in the early stages of antibody engineering with the first bispecific constructs described in the 1980s. The field has seen significant growth with advances in genetic engineering, leading to a variety of BsAb formats with different characteristics suited for specific applications.[207] BsAbs have emerged as a potent tool in cancer immunotherapy, providing the advantage of dual antigen recognition, which can be tailored to meet various therapeutic needs. This dual targeting approach allows for novel mechanisms of action, such as redirecting immune cells to cancer cells, dual inhibition of signaling pathways, and simultaneous blockade of immune checkpoints; in some bleeding disorders, they function as the inhibited or deficient factor.

Immune cell engagers are engineered antibodies with at least one arm binding a tumor-associated antigen and at least one other one directed against an activating receptor in immune effector cells: CD3 for recruitment of T cells and CD16a for natural killer (NK) cells.[208]

Figure 22-6 Various TCE Formats Described in Immuno-Oncology



Abbreviations: BiTE, bispecific T-cell engager; CiTE, checkpoint inhibitor T-cell engager; DART, dual affinity retargeting; scFv, single-chain variable fragment; SMiTE, simultaneous multiple interaction T-cell engager; TCE, T-cell engager; TetraTE, tetraspecific T-cell engager; TriTE, trispecific T-cell engager; VH-VL, variable heavy and variable light.

Various TCE formats described in immuno-oncology. scFvs derived from T-cell receptor antibodies (blue) and from tumor-associated antigen antibodies (red) can associate to form BiTEs. BiTEs can be combined with a third scFv (green) to form a TriTE and with an additional moiety to form a TetraTE. BiTEs can also be complemented with the extracellular domain of PD1 to form a CiTE or administered with a second molecule, such as an anti-CD28 × anti-PDL1, as in the SMiTE. Various molecular modifications, such as mutations of the VH-VL interface, shorter links between domains and the addition of disulfide bonds, have led to the development of additional formats, such as diabody, tandem diabody, and DART. Created with Biorender.

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BsAbs can be categorized by their structural format; for instance, bispecific T-cell engagers are characterized by their small size and lack of an Fc region, which allows for effective tumor penetration but necessitates continuous administration because of a short half-life (Fig. 22-6). Conversely, full-length immunoglobulin G–like (IgG-like) BsAbs maintain an Fc domain, providing a longer serum half-life and the capacity for antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, and phagocytosis. This format diversity is crucial for optimizing pharmacokinetics and efficacy.[209,210]

The first bispecific T-cell engager approved by the FDA was the anti-CD19 blinatumomab for the treatment of B-cell precursor ALL in 2014. A landmark in the field, this bispecific T-cell engager targets CD19 on B cells and CD3 on T cells, significantly enhancing T-cell–mediated cytotoxicity against cancer cells.[211]

SOLID TUMORS

Amivantamab, a bispecific monoclonal antibody targeting EGFR and MET, was approved for non–small cell lung cancer (NSCLC) in 2021. In 2022, tebentafusp—a bispecific T-cell engager targeting gp100 on uveal melanoma cells and CD3 on T cells—also received FDA approval.

Most recently, in 2025, the FDA approved ErbBicT (GEN1057/BNT327) for metastatic NSCLC with EGFR mutations following progression on osimertinib. By targeting both EGFR and c-MET, ErbBicT addresses key resistance pathways that develop after earlier EGFR inhibitor therapies, fulfilling a significant unmet need for this patient population.

HEMATOLOGIC MALIGNANCIES

T-cell engagers are revolutionizing the treatment of hematologic malignancies, with several agents approved since 2022. These BsAbs redirect a patient's own T cells to attack malignant cells, offering new options for difficult-to-treat diseases. Approved therapies include the following:

- Mosunetuzumab (CD20×CD3) for R/R FL.
- Teclistamab and Elranatamab (BCMA×CD3) for relapsed MM.
- Epcoritamab and Glofitamab (CD20×CD3) for DLBCL.
- Talquetamab (GPRC5D×CD3) for R/R MM.

Emerging agents like RO7616789 (CD123×CD3) are extending this approach to AML, particularly for patients with biomarkers such as FLT3 mutations or high CD123 expression, highlighting the expanding potential of this therapeutic class.

NONMALIGNANT DISEASES

Tibulizumab, which gained FDA approval in 2025, marks a therapeutic milestone as the first BsAb for an autoimmune disease. Targeting moderate-to-severe systemic lupus erythematosus (SLE) and lupus nephritis, its dual mechanism—simultaneously blocking BAFF and IL-6—provides coordinated control over pathogenic B-cell activity and the inflammatory response.[212]

T-cell engagers will likely revolutionize the treatment of hematologic malignancies, for which several have been approved since 2022. Mosunetuzumab targets CD20 and CD3 and is used for R/R FL, whereas teclistamab and elranatamab target BCMA and CD3 and are used for relapsed MM. Linvoseltamab-gcpt (Lynozyfic) was approved in July 2025 (anti-BCMA). Epcoritamab and glofitamab target CD20 and CD3 and are used for treating DLBCL. Talquetamab targeting GPRC5D and CD3 is used in R/R MM.[208,213,214]

INTRODUCTION TO IN VIVO CAR-T THERAPY

In vivo CAR-T therapy represents an innovative advancement in cancer treatment by streamlining the CAR-T cell manufacturing process. Instead of the traditional approach, which involves extracting a patient's T cells, genetically modifying them outside the body (ex vivo), and then reinfusing them, in vivo CAR-T therapy delivers the gene-editing components directly into the patient's bloodstream. This approach enables the patient's own T cells to be genetically reprogrammed within the body (in vivo) to express CARs. These CARs are designed to target myeloma cells, typically recognizing antigens such as BCMA or GPRC5D. By bypassing the ex vivo manufacturing process, this strategy significantly reduces complexity and cost.

At ASH 2025, a breakthrough presentation highlighted the first preliminary results of a novel in vivo CAR-T therapy, KLN-1010, in patients with R/R MM. KLN-1010 is administered intravenously and utilizes an improved lentiviral vector to generate fully human, anti-BCMA CAR-T cells inside the patient's body. This innovation eliminates the need for apheresis, ex vivo manufacturing, or lymphodepleting chemotherapy. Notably, removing the requirement for lymphodepleting therapy is a major advantage, alongside simplifying the logistical challenges historically associated with CAR-T therapy.

Key findings from the inMMyCAR study include the following:

- Promising Efficacy: All three initial patients achieved MRD negativity, with sensitivity levels of 10^{-5} or 10^{-6} at 1 month following treatment. Over time, these patients experienced deepening partial or very good partial responses, and no cases of disease progression were observed.

- Manageable Safety: The main adverse events reported were infusion-related reactions and Grade 2 CRS. Importantly, there were no instances of neurotoxicity or cytopenias graded 3 or higher. In addition, CAR-T cell expansion was observed without the need for preconditioning chemotherapy.

SUMMONING OTHER IMMUNE CELLS

Bispecific NK cell engagers are also in early-stage clinical studies and may offer efficacy similar to that of bispecific T-cell engagers with milder adverse effects. An attractive target for NK cells is CD16a, the receptor that recognizes the Fc fragment of IgG antibodies and confers to NK cells their ability to perform ADCC.[215] Bispecific and trispecific antibodies have been developed to target not only tumor and T or NK cells, but more recently, myeloid cells in cancer and infectious diseases, as well as macrophages.[213] Several bispecific NK cell engagers have been developed for hematologic malignancies and solid tumors.[216-221] This area has potential to grow not from the direct effect of the engagement but from learning about how to educate those NK cells to become guards against the recurrence of the tumor.

Altogether, these engineered molecules may change the paradigm of treatment for R/R hematologic malignancies. The clinical development of BsAbs has expanded significantly; there are now ongoing trials that explore their use in various cancers, including solid tumors, in which antigen heterogeneity and a complex tumor microenvironment present unique challenges. Despite their potential, challenges persist, such as immunogenicity, off-target effects, and production complexities because of the need for correct chain pairing. Innovations like the "knob-into-hole" method for stable heterodimer formation and the use of scFv or diabodies have been critical in overcoming these hurdles.[222]

Management of a Bispecific Therapy Adverse Effect Profile

Managing toxicities associated with BsAb therapies is critical, and physicians should familiarize their teams with that challenge, especially if this therapy becomes widespread and is used in the outpatient setting. Adverse effects, particularly CRS and neurotoxicity, could be minimized or totally alleviated by offering detailed recommendations on pretreatment evaluation, monitoring, and treatment strategies.[223]

The recommendations for mitigating toxicity associated with BsAbs, as highlighted by Crombie et al[223] include the following:

Cytokine-Release Syndrome

- Step-up dosing: Initiate treatment with gradually increasing doses to minimize the risk of CRS.
- Premedication: Administer corticosteroids (eg, dexamethasone), antipyretics, and antihistamines as prophylactic measures.
- Monitoring: Observe patients closely, especially after initial doses, and manage symptoms based on the severity (grade 1 to 4 CRS).
- Therapeutics: Use tocilizumab or other anti-cytokine agents for severe or refractory CRS.

Neurological Toxicities

- Educate patients and caregivers to recognize symptoms like headache, dizziness, and confusion.
- In severe cases, administer corticosteroids and consider a neurology consult.
- Use monitoring tools like immune effector cell-associated encephalopathy scores for assessment.

Tumor Flare Reaction

- Rare but severe cases require corticosteroids and possibly localized irradiation for bulky tumors near vital structures.

Cytopenias

- Monitor and provide growth factor support if necessary.
- Balance treatment continuation against the risk of neutropenia.

Infectious Complications

- Administer prophylaxis for *P. jirovecii* pneumonia and varicella zoster virus.
- Manage hypogammaglobulinemia with Ig replacement if infections are recurrent. Based on expert consensus, IV immunoglobulin (IVIg) is recommended during BsAb therapy when patients develop hypogammaglobulinemia (IgG <400 mg/dL) and experience recurrent or severe bacterial infections. Prophylactic use is often considered if IgG falls below 300 to 350 mg/dL. The standard regimen is 400 to 500 mg/kg every 3 to 4 weeks, maintaining a trough IgG level above 500 to 600 mg/dL. IVIg should be continued during therapy and typically for 6+ months after treatment ends, as immune suppression can be prolonged. Regular monitoring of IgG levels (every 4-8 weeks) is essential.

Patient and Facility Preparedness

- Educate patients on home monitoring for symptoms and provide contact points for emergencies.
- Ensure that necessary medications such as tocilizumab are available at treatment sites.
- Tailor the treatment location (outpatient vs inpatient) based on the patient's risk profile.

Other Precautions

- Screen for latent infections such as hepatitis B and ensure that standard vaccinations (eg, influenza, COVID-19) are available.
- Proactively manage tumor lysis syndrome based on the risk.

These strategies reflect a combination of prophylactic, monitoring, and reactive measures to ensure the safe administration of BsAbs and should be helpful in guiding healthcare teams in their management strategy.

In summary, BsAbs represent a dynamic and evolving field in cellular therapy and leverage the precision of dual targeting to enhance treatment outcomes. Although their efficacy in hematologic malignancies may not match the depth or response rates of CAR T-cell therapy, BsAbs offer the significant advantage of being available as an off-the-shelf treatment. This makes them a timely option, and they generally show better tolerability with lower severity and frequency of CRS, ICANS, and myelosuppression. However, they are associated with a higher rate of infections.[223-225]

Regulatory frameworks are also adapting to accommodate these complex molecules, with guidance that focuses on target selection, safety, and efficacy assessments to ensure that BsAbs can be brought to market efficiently while maintaining high safety standards.[207] Because of the ongoing research and clinical trials regarding BsAbs coupled with advancements in antibody engineering, BsAbs hold considerable promise for personalized, timely, and effective cancer treatments.

GENE THERAPY

The emergence and clinical application of cell-based gene therapy mark a significant advancement in the treatment of inherited diseases such as sickle cell disease and transfusion-dependent beta thalassemia. Current approaches in gene therapy involve using viral vectors to introduce new genes into stem cells or deleting suppressors for fetal hemoglobin. Both approaches involve collecting the patient's stem cells, which are subsequently edited with a lentivirus vector or by using CRISPR/CAS9 technology. After the gene modification process, patients undergo myeloablative conditioning. The gene-modified stem cell product is then infused, akin to an autologous SCT procedure. Clinical studies that evaluate these products demonstrate high levels of efficacy with notable resolution of severe veno-occlusive events. However, it is essential to recognize that patients treated with these gene therapy products may experience complications similar to those of patients undergoing traditional transplantations and could potentially face an increased risk of subsequent hematologic malignancies. Hence, ongoing monitoring and comprehensive management are crucial aspects of their care. The FDA-approved therapies for sickle cell and thalassemia should be discussed in more detail. The two therapies for sickle cell are exagamglogene autotemcel, which uses CRISPR/Cas9 gene-editing to modify the patient's hematopoietic stem cells to produce HbF and essentially generate HPFH to prevent sickling; and lovotibeglogene autotemcel, which uses a lentiviral vector to insert a norml copy of the beta-globin gene into the patient's hematopoietic stem cells. For thalassemia, exagamglogene autotemcel is also approved for patients age 12 years and older with transfusion-dependent beta thalassemia (TDBT). Betibeglogene autotemcel is approved for adult and pediatric patients with TDBT. It introduces a normal beta-globin gene to the patient's hematopoietic stem cells, which results in normal or almost normal levels of hemoglobin.

KEY POINTS

- CAR T-cell therapy results improved EFS and OS for patients with DLBCL refractory to first-line therapy or who relapse within 12 months when compared with standard salvage therapy and autologous transplantation.
- Bispecific T-cell engagers can be used to engage a host immune response against a target antigen, which has led to the development of many new products that can treat both hematologic and solid cancers.

HIGH-YIELD TAKEAWAYS

- Post-transplantation cyclophosphamide for GVHD prophylaxis results in comparable outcomes between haploidentical, matched sibling, MUD, and mismatched unrelated donor transplants.
- Ruxolitinib is effective for steroid-refractory acute and chronic GVHD.
- CAR T-cell therapy is effective for primary refractory or early relapsed DLBCL and lenalidomide refractory MM, with approximately 30% of patients having long-term PFS.
- BsAb therapy (T-cell and NK-cell engagers) provides the convenience of off-the-shelf accessibility and is slightly better tolerated compared with CAR T-cell therapy. However, the response rates are lower than what is expected with CAR T-cell–based modalities.

Acknowledgments

We acknowledge the valuable contributions of all individuals who helped shape previous iterations of this chapter.

CELLULAR THERAPIES 22

CHAPTER SUMMARY GUIDE

KEY POINTS

- All diseases of hematopoiesis, nonmalignant and malignant, are potentially curable with cellular therapy.
- The leading indication for autologous HCT in the United States is MM, followed by relapsed NHL and HL.
- Allogeneic HCT consistently leads to 5-year DFS rates of 50% to 70%, respectively, when performed for AML and ALL in first remission.
- In the MUD setting, use of mobilized peripheral blood stem cells showed faster engraftment, but more chronic GVHD compared with bone marrow. Use of plerixafor and motixafortide, antagonists of CXCR4, with G-CSF results in mobilization of CD34+ cells into the peripheral blood and high stem cell collection yields for autologous HCT.
- Although GVHD after HCT is more common with MUDs than with matched siblings, survival rates seem similar.
- Methods have been developed that allow for the selection of permissive single-antigen mismatched donors.
- HCT using either a haploidentical or HLA-mismatched unrelated donor is feasible; subsequently, an allogeneic donor can be found for most patients in need.
- Use of post-transplantation cyclophosphamide results in a low rate of GVHD and similar outcomes between donor types.
- The purpose of the high-dose regimen used before autologous HCT is to eradicate the underlying disease.
- The purpose of the preparative regimen in allogeneic HCT is to sufficiently immunosuppress the patient to prevent graft rejection and to eliminate residual disease.
- Evidence points to increased relapse rates and diminished survival with the use of reduced-intensity conditioning compared with myeloablative conditioning in patients with AML or MDS.
- By using in situ hybridization with sex chromosome–specific probes or typing of the variable number of tandem repeat polymorphisms, the donor-versus-recipient origin of populations of cells can be determined in virtually all cases in allogeneic HCT to assess engraftment and monitor for disease relapse.
- Loss of chimerism is an indicator of graft failure and/or disease relapse.
- T cells in the donor graft, combined with allogeneic targets on the genetically different host, are a major driver in the development of GVHD.
- Biomarker approaches for diagnosis and risk stratification are under study.
- Post-transplantation cyclophosphamide and ATG reduce rates of acute and chronic GVHD.
- Ruxolitinib is an effective treatment for steroid-refractory acute and chronic GVHD.
- Fungal infections can be prevented, and survival can be improved with the use of antifungal prophylaxis during the first few months after HCT.
- Letermovir prophylaxis can reduce the incidence of CMV infection.
- Patients should be screened for viral infections; a positive result may be cause for delaying HCT.
- Revaccination after HCT is generally recommended.
- Common chemoradiotherapy toxicities include nausea, vomiting, fever, and mild skin erythema. High-dose regimens, especially when combined with TBI, lead to more severe oral mucositis.
- Sinusoidal obstruction syndrome and idiopathic pneumonia syndrome are serious potential complications requiring careful clinical management.
- As survival improves for HCT recipients, additional attention should be paid to long-term complications, especially cardiovascular disease and endocrine effects.
- Patients who experience relapse after allogeneic HCT can potentially respond to subsequent immunologic manipulation, including withdrawal of immunosuppression, DLIs, and treatment with checkpoint inhibitors.
- CAR T-cell therapy results improved EFS and OS for patients with DLBCL refractory to first-line therapy or who relapse within 12 months when compared with standard salvage therapy and autologous transplantation.
- Bispecific T-cell engagers can be used to engage a host immune response against a target antigen, which has led to the development of many new products that can treat both hematologic and solid cancers.

CHAPTER TABLES AND IMAGES

Table 22-1 Cell and Donor Sources for Autologous and Allogeneic Hematopoietic Cell Transplantation

Type of Transplantation	Cell Source	Donor
Autologous	Bone marrow Peripheral blood	Recipient
Allogeneic	Bone marrow Peripheral blood Umbilical cord blood	Related Unrelated
Syngenic	Bone marrow Peripheral blood	Monochorionic twin

Reproduced under Creative Commons license. Source: HSCT: How does it work? In: Kenyon M, Babic A, eds. *The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT*. Springer; 2018:23-36, Table 2.1.

Table 22-2 **Table of Donor-Recipient ABO Compatibility With Potential Complications and Interventions**

Donor-Recipient ABO Compatibility				
	Blood Type			
Mismatch Type	**Recipient**	**Donor**	**Potential Complications**	**Interventions**
Major	O	A, B, AB	Acute hemolysis of donor RBCs	RBC reduction of the stem cell product
	A	AB	Delayed engraftment	
	B	AB	Pure red cell aplasia from recipient anti-donor isohemagglutinins	
Minor	A	O	Acute hemolysis from donor isohemagglutinin	Plasma reduction of the stem cell product
	B	O	Delayed hemolysis from passenger lymphocyte syndrome	
	AB	O, A, B		
Bidirectional	A	B	A combination of major and minor	A combination of major and minor
	B	A		

Abbreviation: RBC, red blood cell.
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Table 22-3 **Categories of Acute and Chronic GVHD**

Category[107]	Time of Symptoms After HCT	Presence of Acute GVHD Features	Presence of Chronic GVHD Features
Acute GVHD			
Classic acute	≤100 days	Yes	No
Late onset	>100 days	Yes	No
Chronic GVHD			
Classic Chronic	No time limit	No	Yes
Overlap	No time limit	Yes	Yes

Abbreviations: GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation.
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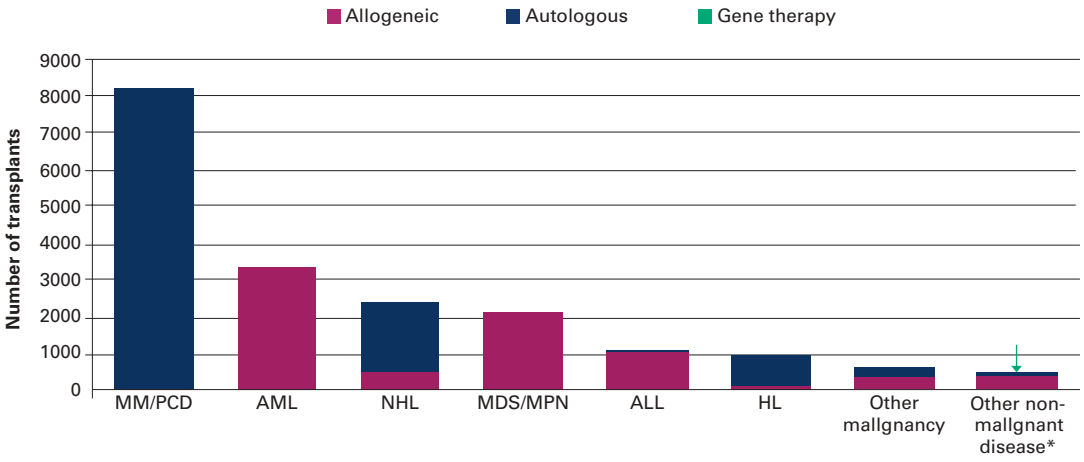
Table 22-4 **Summary of Clinical Trials of FDA-Approved CAR T Cells in NHL**

Disease	Product (Costimulatory Domain, Target)	Indication (Approval Year)	Study: Phase (No. of Patients)	% ORR (% CR)	Median PFS (Months)	Median OS (Months)	% CRS (% Grade 3+)	% Neurologic Toxicity (% Grade 3+)	References
DLBCL	Axicabtagene ciloleucel (CD28, CD19)	DLBCL 3L (2017)	ZUMA-1: P1-2 (108)	83 (58)	5.9	NR	92 (11)	67 (33)	181
		DLBCL, HGBCL, PMBCL 2L (2022)	ZUMA-7: P3 (359)	83 (65)	14.7	NR	92 (6)	61 (21)	18
	Tisagenlecleucel (41BB, CD19)	DLBCL: 3L+ (2018)	JULIET: P2 (115)	53 (39)	2.9	11.1	35 (23)	20 (11)	182
	Lisocabtagene maraleucel (41BB, CD19)	DLBCL, HGBCL, PMBCL 3L (2021)	TRANSCEND: P2 (270)	73 (53)	6.8	27.3	42 (2)	0 (10)	183
		DLBCL, HGBCL, PMBCL 2L (2021)	TRANSFORM: P3 (92)	79 (61)	14.8	NR	49 (1)	11 (4)	19
FL	Lisocabtagene maraleucel (41BB, CD19)	FL 3L (2024)	TRANSCEND-FL: P2 (107)	97 (94)	NR	NR	59 (1)	15 (2)	184
	Axicabtagene ciloleucel (CD28, CD19)	FL 2L+ (2021)	ZUMA-5: P2 (104)	95 (76)	NR	NR	82(7)	59 (19)	185
	Tisagenlecleucel (41BB, CD19)	FL 3L (2022)	ELARA: P2 (97)	86 (69)	NR	NR	49 (0)	37 (3)	186
MCL	Brexucabtagene autoleucel (CD28, CD19)	MCL (2020)	ZUMA-2: P2 (68)	91 (68)	25.8	46.6	91 (18)	63 (31)	125
	Lisocabtagene maraleucel (41BB, CD19)	MCL 3L (2024)	TRANSCEND-MCL: P1 (88)	83 (72)	15.3	18.2	61 (1)	31 (1)	187
B-cell ALL	Tisagenlecleucel (41BB, CD19)	B-ALL 3L, up to age 25 years (2017)	ELIANA: P2 (79)	(82)	24	NR	77 (48)	40 (13)	125
	Brexucabtagene autoleucel (CD28, 41BB)	B-ALL (2021)	ZUMA-3: P2 (55)	(71)	11.6	18.2	89 (24)	60 (24)	188
	Obecabtagene autoleucel (41BB, CD19)	B-ALL 2L (2024)	FELIX: P1b-2 (127)	77 (55)	11.9	15.6	69 (2)	23 (7)	189
CLL	Lisocabtagene maraleucel (41BB, CD19)	CLL/SLL 3L (2024)	TRANSCEND-CL: Ph1-2 (89)	48 (18)	11.9	30.3	83 (9)	45 (18)	190
MM	Ciltacabtagene autoleucel (41BB, BCMA)	MM 2L (2022)	CARTITUDE-4: P3 (176)	84 (73)	NR	NR	76 (1)	21 (3)	191
	Idecabtagene vicleucel (41BB, BCMA)	MM 3L (2021)	KarMMa-3: P3 (225)	71 (39)	13.3	NR	88 (5)	15 (3)	192

Abbreviations: 2L, second line; 3L, third line; ALL, acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; CLL, chronic lymphocytic leukemia; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; NR, not reached; ORR, overall response rate; OS, overall survival; P, phase; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; SLL, small lymphocytic lymphoma.

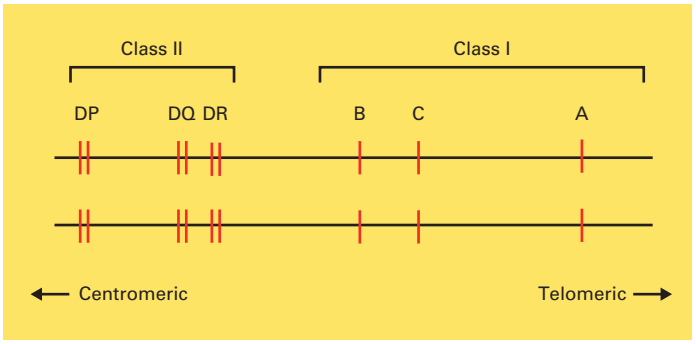
Source: Braunstein M, Main O. How do CAR T cells fit into the evolving non-Hodgkin lymphoma treatment landscape? *ASCO Daily News*. Published 2024. Accessed May 15, 2024. https://dailynews.ascopubs.org/do/do-car-t-cells-fit-into-evolving-non-hodgkin-lymphoma-treatment-landscape

Figure 22-1 Number of Hematopoietic Cell Transplantations in US (2023) Adults



Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; MDS, myelodysplastic syndromes; MM, multiple myeloma; MPN, myeloproliferative neoplasms; NHL, non-Hodgkin lymphoma; PCD, plasma cell disorders.
*Includes 22 limited gene therapy events.
Reprinted with permission from Spellman SR, Xu S, Temitope O, et al. Current activity trends and outcomes in hematopoietic cell transplantation and cellular therapy—a report from the CIBMTR. *Transplant Cell Ther.* 2025;31(8):505-532. doi:10.1016/j.jtct.2025.05.014

Figure 22-2 Genes Associated with HLA Typing on Chromosome 6



Abbreviation: HLA, human leukocyte antigen.
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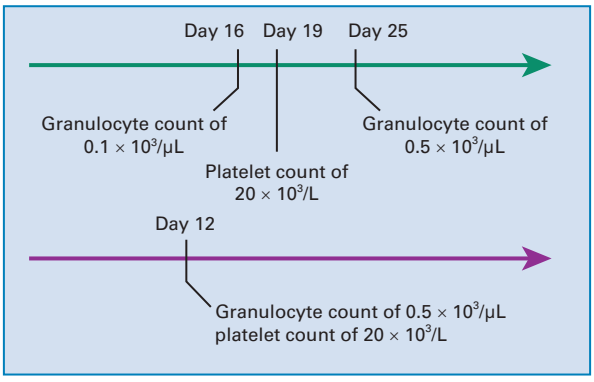
Figure 22-3 Timeline of Granulocyte and Platelet Count Recovery After Hematopoietic Cell Transplantation Using Bone Marrow and Peripheral Blood Stem Cells



Graphical representation of a mechanism in which donor and recipient markers can mismatch (top) or match (bottom).
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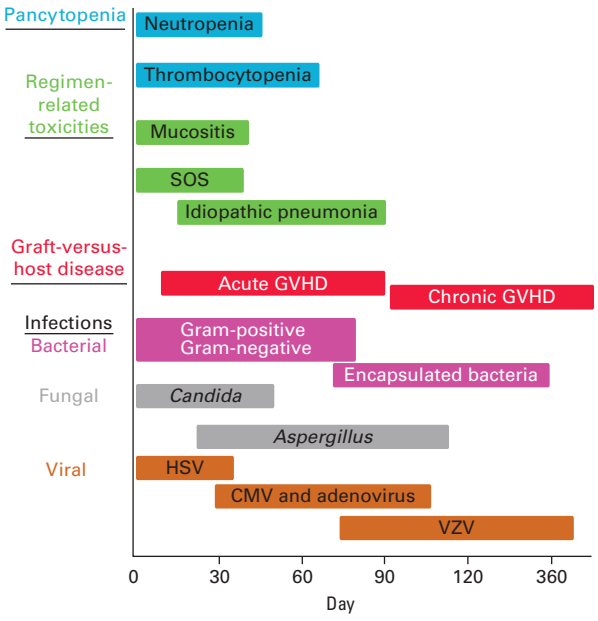
Figure 22-4 The Approximate Timing of Possible Toxicities After Allogenic Transplantation Using a Typical Intensive Preparative Regimen



Abbreviations: CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; SOS, sinusoidal obstruction syndrome; VZV, varicella zoster virus.

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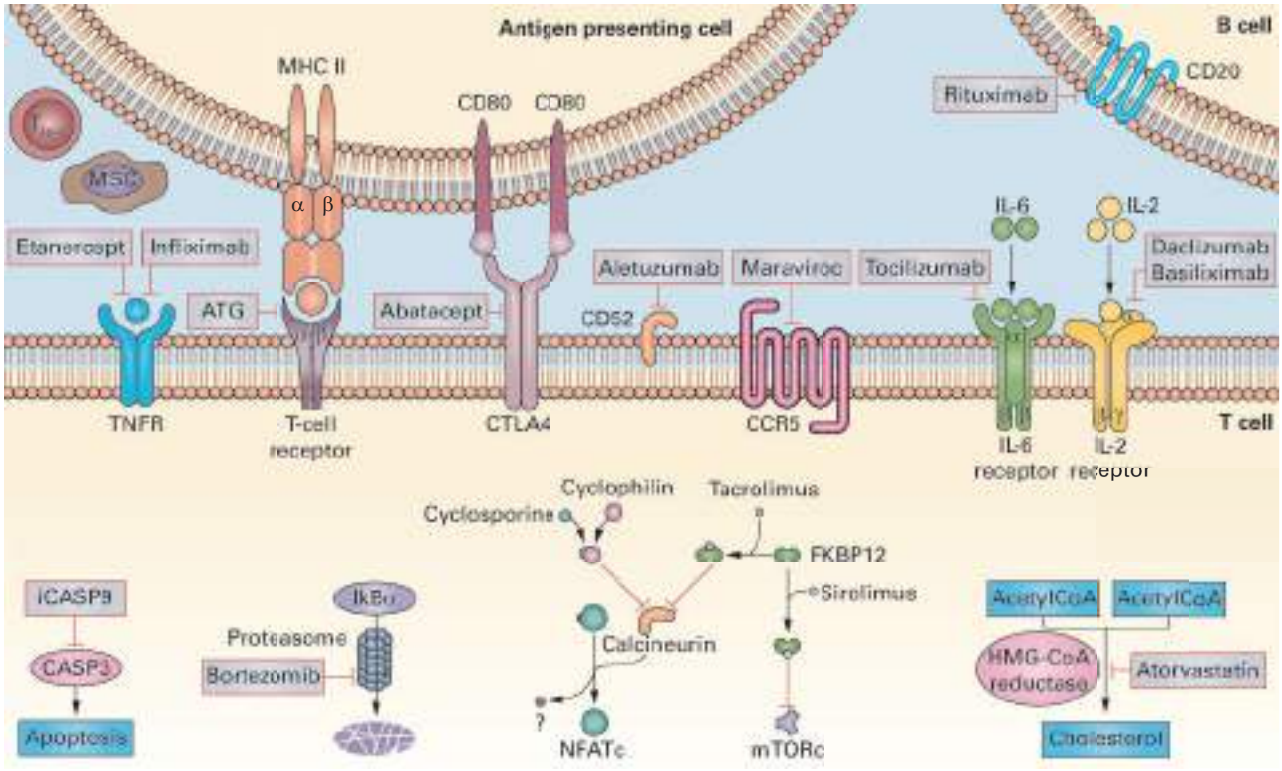
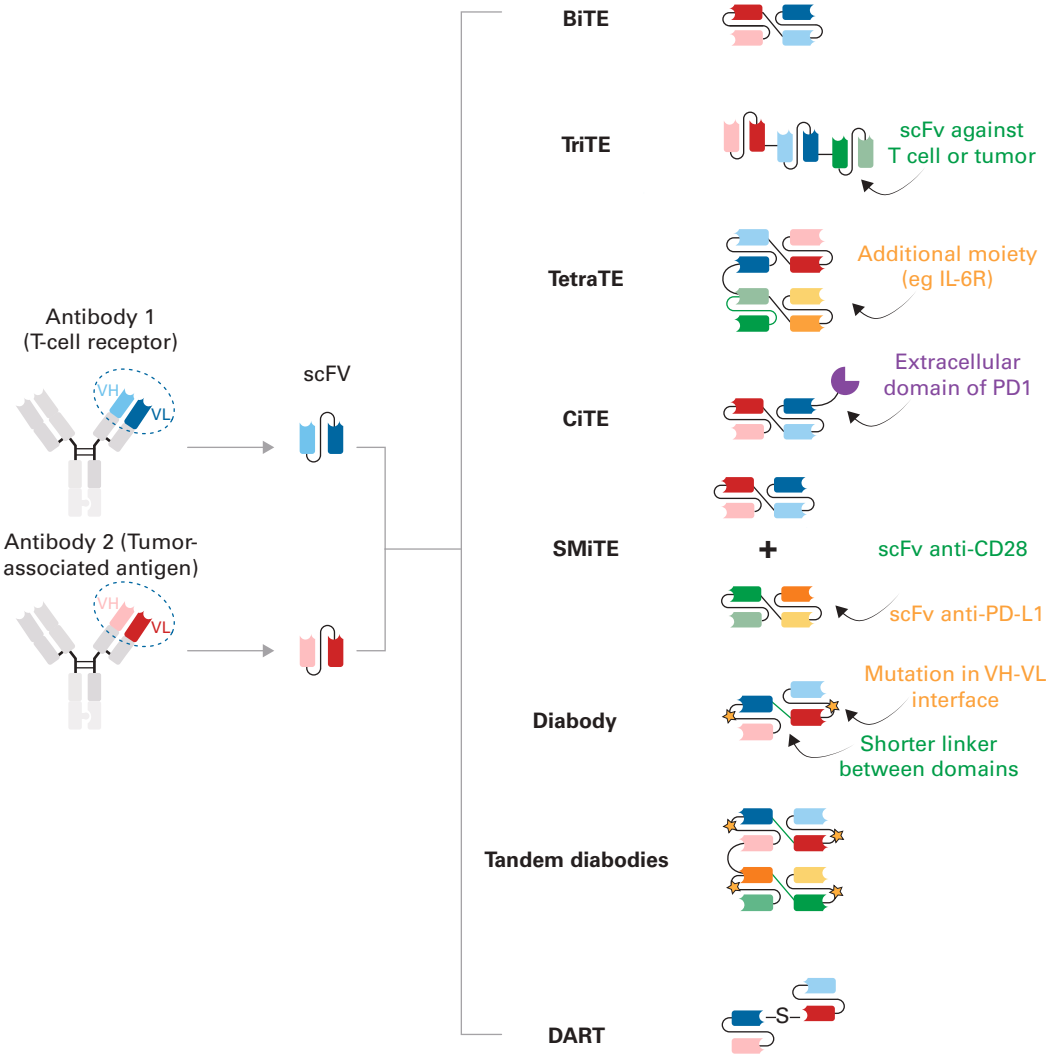
Figure 22-5 Standard and Emerging Therapies for the Prevention of Acute GVHD



Abbreviations: Acetyl CoA, acetyl coenzyme A; ATG, anti-thymocyte globulin; CCR5, C-C chemokine receptor 5; CLTA4, cytotoxic T lymphocyte antigen 4; FKBP12, FK506 binding protein 12; GVHD, graft-versus-host disease; HMG CoA reductase, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; iCasp9, inducible caspase 9; IkB, nuclear factor of kappa light polypeptide gene enhance in B cells inhibitor; IL, interleukin; MHC II, major histocompatibility class II; MSC, mesenchymal stem cell; mTORC, mammalian target of rapamycin complex; NFATc, nuclear factor of activated T cells cytoplasmic; TNFR, tumor necrosis factor receptor; TREG, regulatory T-cell.
The different medications and their targets against B cells and T cells are illustrated in this figure. MSC and TREG infusions are depicted extracellularly.
Reprinted from Choi SW, Reddy P. Current and emerging strategies for the prevention of graft-versus-host disease. *Nat Rev Clin Oncol*. 2014;11(9):536-547. doi:10.1038/nrclinonc.2014.102 [additional rights language TK].

Figure 22-6 Various TCE Formats Described in Immuno-Oncology



Abbreviations: BiTE, bispecific T-cell engager; CiTE, checkpoint inhibitor T-cell engager; DART, dual affinity retargeting; scFv, single-chain variable fragment; SMiTE, simultaneous multiple interaction T-cell engager; TCE, T-cell engager; TetraTE, tetraspecific T-cell engager; TriTE, trispecific T-cell engager; VH-VL, variable heavy and variable light.

Various TCE formats described in immuno-oncology. scFvs derived from T-cell receptor antibodies (blue) and from tumor-associated antigen antibodies (red) can associate to form BiTEs. BiTEs can be combined with a third scFv (green) to form a TriTE and with an additional moiety to form a TetraTE. BiTEs can also be complemented with the extracellular domain of PD1 to form a CiTE or administered with a second molecule, such as an anti-CD28 × anti-PDL1, as in the SMiTE. Various molecular modifications, such as mutations of the VH-VL interface, shorter links between domains and the addition of disulfide bonds, have led to the development of additional formats, such as diabody, tandem diabody, and DART. Created with Biorender.

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