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ONCOLOGY BOARD REVIEW

BLUEPRINT STUDY GUIDE AND Q&A

Third Edition

FRANCIS P. WORDEN
RAMI N. KHORIATY
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Oncology Board Review

ALGRAWANY

Oncology Board Review

Blueprint Study Guide and Q&A

Third Edition

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Preface

Preparation for board examinations can be a daunting and overwhelming process for many of us. As trainees, we are often busy with research projects, manuscripts, and a large clinical volume, making it difficult to find time to study for board examinations.

As practicing physicians, we find it hard to keep up on material needed for board recertification. Questions on the board examinations are drawn from well-established, validated medical literature and widely accepted clinical guidelines. With that being said, the University of Michigan Hematology/Oncology Fellowship Program designed this board review book to summarize information and facts that are most pertinent for testing. The *Oncology Board Review: Blueprint Study Guide and Q&A*, Third Edition also includes over 240 medical oncology board-style questions with all its chapters. This book is not intended to be an all-encompassing review. Rather, it is intended to help summarize the important facts that one might need to know for their examination, similar to taking notes of pertinent information that one would like to memorize. We created each chapter to cover all of the topics listed in the blueprint provided by the American Board of Internal Medicine as material one should know for the Medical Oncology Board Examination. The authors have endeavored to provide the most accurate and up-to-date information, including well-established chemotherapy regimens for a variety of malignancies.

We hope that hematology/oncology fellows and practicing medical oncologists preparing to certify or recertify will find *Oncology Board Review: Blueprint Study Guide and Q&A*, Third Edition a useful tool. Our goal is to help our readers summarize and solidify many important clinical facts and to help them build confidence during their exam preparation. As the hematology/oncology fellowship program director and faculty members from the University of Michigan (Ann Arbor, Michigan), we engaged our fellows and faculty to develop *Oncology Board Review: Blueprint Study Guide and Q&A*, Third Edition. Each chapter was written by a fellow and edited by an expert faculty member. We gratefully acknowledge the dedication of our fellows, faculty, and medical staff. The successful completion of this project was made possible by the editorial and publishing staff of Demos Medical Publishing, especially David D'Addona, senior editor, Jaclyn Shultz, associate editor, and Joseph Stubenrauch, the production editor who moved the project seamlessly through production. Finally, we dedicate this book to Michelle Reinhold for her continued devotion and immeasurable service to the University of Michigan Hematology/Oncology Fellowship Program as program coordinator.

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I

HEMATOLOGIC MALIGNANCIES

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1 Acute Myelogenous Leukemia

Morgan A. Jones, Lyndsey Runaas, Rami N. Khoriaty, and Dale Bixby

Acute Myeloid Leukemia

EPIDEMIOLOGY

1. What is the median age at diagnosis?

- Sixty-eight years

2. What is the incidence of acute myeloid leukemia (AML)?

- Twenty thousand new cases per year in the United States

ETIOLOGY AND RISK FACTORS

1. What are the common risk factors for AML?

- Older age
- Exposure to chemotherapeutic agents:
  - Topoisomerase II inhibitors: latency of 1 to 3 years, associated with rearrangement of the *mixed lineage leukemia* (*MLL*) gene (11q23)
  - Alkylating agents: latency period of 3 to 7 years, associated with the del 5q/-5 and/or del 7q/-7 chromosomal abnormalities as well as complex cytogenetic changes
- Bone marrow failure disorders like myelodysplastic syndrome (MDS) or aplastic anemia (AA)
- Myeloproliferative neoplasms
- Exposure to chemicals: benzene, pesticides, and petroleum products
- Radiation exposure
- Congenital disorders: Down syndrome, Bloom syndrome, Fanconi anemia, dyskeratosis congenita (Zinsser–Cole–Engman syndrome), GATA-2 deficiency, Shwachman–Diamond syndrome, Diamond–Blackfan anemia, and others

PATHOLOGY—CLASSIFICATION

1. Define the subtypes of AML according to the 2016 World Health Organization (WHO) classification.

- AML with recurrent genetic abnormalities
  - AML with t(8;21) (q22;q22.1); *RUNX1-RUNX1T1*
  - AML with inv(16) (p13.1;q22) or t(16;16) (p13.1;q22); *CBFB-MYH11*
  - Acute promyelocytic leukemia (APL) with t(15;17) (q24;q21); *PML-RARA*

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- AML with t(9;11) (p21.3;q23.3); *MLLT3-KMT2A*
- AML with t(6;9) (p23;q34.1); *DEK-NUP214*
- AML with inv(3) (q21.3;q26.2) or t(3;3) (q21.3;q26.2); *GATA2, MECOM*
- AML (megakaryoblastic) with t(1;22) (p13.3;q13.3); *RBM15-MKL1*
- AML with mutated *NPM1*
- AML with biallelic mutations of *CEBPA*
- Provisional entities:
  - AML with *BCR-ABL1*
  - AML with mutated *RUNX1*

- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, not otherwise specified (NOS)
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/monocytic leukemia
  - Pure erythroid leukemia
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis (TAM)
  - Myeloid leukemia associated with Down syndrome

SIGNS AND SYMPTOMS

1. What are the common signs and symptoms of AML?

- Fever and other constitutional symptoms of infections
- Bruising or bleeding (due to thrombocytopenia)
- Fatigue and other symptoms of anemia
- Leukostasis: central nervous system (CNS) manifestations, cardiopulmonary symptoms, retinal hemorrhage, priapism
- Disseminated intravascular coagulation (DIC)
- Tumor lysis syndrome

DIAGNOSTIC WORKUP

1. Define the diagnostic criteria for AML.

- Bone marrow and/or peripheral blood blasts greater than or equal to 20%
- The myeloid lineage is established if *any* of the following are identified:
  - Auer rods
  - Blasts are myeloperoxidase positive (by flow cytometry, immunohistochemistry, or cytochemistry)
  - Monocytic differentiation (with at least two of the following: nonspecific esterase, CD11c, CD14, CD64, lysozyme)
  - The presence of a balanced chromosomal translocation involving t(15;17)(q24;q21), t(8;21)(q22;q22.1); inv(16)(p13.1;q22) or t(16;16)(p13.1;q22) is diagnostic of AML regardless of the blast percentage.

PROGNOSTIC FACTORS

1. How are patients with AML stratified into different risk groups?

- Age, cytogenetics, and single gene mutations are independent prognostic factors (older age is a poor prognostic factor).

TABLE 1.1 ■ Risk Groups for AML

Risk Status	Cytogenetics/Molecular Abnormalities
Favorable risk	■ t(8;21)(q22;q22.1) ■ inv(16)(p13.1;q22) or t(16;16)(p13.1;q22) ■ Normal cytogenetics with *NPM1* mutation without *FLT3*-ITD or with *FLT*-3 ITD (low variant allele frequency) ■ Normal cytogenetics with biallelic *CEBPA* mutation
Intermediate risk	■ Normal cytogenetics without favorable risk or poor risk gene mutations ■ Mutated *NPM1* and *FLT3-ITD* (high variant allele frequency) ■ Normal cytogenetics with wild-type NPM without *FLT-3 ITD* mutation or with *FLT-3 ITD* (low variant allele frequency) ■ t(9;11)(p21.3;q11.2)(MLLT3-KMT2A)
Poor risk*	■ Complex cytogenetics† ■ Monosomal karyotype‡ ■ -5 or del(5q) ■ -7 ■ -17 or Abnormal 17(p) ■ t(v;11q23.3); KMT2A rearranged ■ inv(3)(q21.3q26.2) or t(3;3)(q21.3q26.2);GATA2,MECOM N(EVI1) ■ t(6;9)(p23;q34.1);DEK-NUP214 ■ t(9;22)(q34;q11.2); BCR-ABL1 ■ Normal cytogenetics with wild-type NPM and *FLT3-ITD* (high variant allele frequency) ■ *TP53* mutation ■ *RUNX1* mutation ■ *ASXL1* mutation

*Poor-risk AML: also includes patients with secondary AML—antecedent hematologic disease or treatment-related AML.

†Complex cytogenetics is defined as three or more chromosomal abnormalities.

‡ Monosomal karyotype is defined as the presence of at least 2 autosomal monosomies or a single autosomal monosomy associated with at least one structural abnormality.

AML, acute myeloid leukemia.

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2. How are the patients with acute promyelocytic leukemia (APL) risk-stratified?

TABLE 1.2 ■ Sanz Criteria

Low-risk APL	White blood cell (WBC) <10,000 and platelet >40,000
Intermediate-risk APL	WBC <10,000 and platelet <40,000
High-risk APL	WBC ≥10,000

APL, acute promyelocytic leukemia.

In most clinical circumstances, low risk APL and intermediate risk APL are treated similarly, so the clinical significance of these diagnostic subgroups is limited.

TREATMENT

Non-APL AML

1. What are the induction treatment options for younger, fit patients with non-APL AML?

In many publications, there are statements made about treatment algorithms based upon age, but for patients aged ≤75, overall performance status better dictates the choice of the intensiveness of chemotherapy and curative intent of the therapy choice.

TABLE 1.3 ■ Candidate for Intensive Induction Chemotherapy

Risk Category	Regimen
Favorable Risk	■ Anthracycline (daunorubicin or idarubicin or mitoxantrone) + cytarabine ■ Daunorubicin + cytarabine + gemtuzumab ozogamicin
Intermediate Risk	■ If *FLT3*-mutated: daunorubicin + cytarabine + midostaurin ■ Anthracycline (daunorubicin or idarubicin or mitoxantrone) + cytarabine ■ Daunorubicin + cytarabine + gemtuzumab ozogamicin
Poor Risk	■ Anthracycline (daunorubicin or idarubicin or mitoxantrone) + cytarabine ■ Venetoclax + a hypomethylating agent (azacitidine or decitabine) ■ Hypomethylating agent (azacitidine or decitabine) ■ If therapy related, can consider liposomal cytarabine and daunorubicin

Note: All patients should be considered for clinical trial enrollment.

2. How do we evaluate the efficacy of induction therapy?

- Obtain a bone marrow biopsy 7 to 14 days after completion of induction therapy (14–21 days after start) if providing an anthracycline and cytarabine combination treatment. Otherwise, most bone marrow assessments occur on/around day 28 from the start of chemotherapy.
  - Aplastic marrow (<5% cellular and <5% blasts): await count recovery and consider growth factor support

- Significant cytoreduction and a low percentage of blasts: consider repeating the bone marrow biopsy in 7 to 10 days
- Significant residual blasts: high-dose cytarabine-based regimen or standard-dose cytarabine + an anthracycline or venetoclax + a hypomethylating agent

- Obtain the next bone marrow biopsy at count recovery (see Question 5)

3. What are the induction treatment options for older or frail patients with non-APL AML?

TABLE 1.4 ■ Candidate for Less-Intensive Induction Chemotherapy

Scenario	Regimen
No actionable mutations	■ venetoclax + a hypomethylating agent (azacitidine or decitabine) ■ hypomethylating agent (azacitidine or decitabine) ■ venetoclax + low dose cytarabine ■ glasdegib + low dose cytarabine ■ gemtuzumab ozogamicin ■ low dose cytarabine ■ best supportive care
IDH1 mutation	■ ivosidenib ■ hypomethylating agent (azscitidine or decitabine) ■ venetoclax + a hypomethylating agent (azacitidine or decitabine)
IDH2 mutation	■ enasidenib ■ hypomethylating agent (azscitidine or decitabine) ■ venetoclax + a hypomethylating agent (azacitidine or decitabine)
FLT3 mutation	■ Sorafenib + azacitine or decitabine ■ venetoclax + a hypomethylating agent (azacitidine or decitabine)

4. When is complete remission (CR) evaluated for and how is it defined?

- Evaluation of CR requires that a bone marrow biopsy be performed after count recovery—absolute neutrophil count (ANC) ≥1,000, platelets ≥100,000 (independent of transfusions).
  - *Morphologic CR:* marrow blasts less than 5%, no Auer rods, no persistence of extramedullary disease
  - *Cytogenetic CR:* morphologic CR as well as normal cytogenetics in patients who had abnormal cytogenetics at the time of diagnosis
  - *Complete remission with incomplete count recovery (CRi):* CR with persistence of a single cytopenia

5. What is the post-remission treatment of choice for fit patients with non-APL AML in CR?

- Favorable-risk AML:
  - High-dose cytarabine
  - Clinical trial
- Intermediate-risk AML:
  - Allogenic hematopoietic stem cell transplant (patients may receive high-dose intermittent ARA-C [HIDAC] consolidation until donor is found)
    - High-dose cytarabine

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- The specific consolidation built into the treatment scheme of the induction therapy utilized
- Clinical trial

- Poor-risk AML:
  - Allogeneic hematopoietic stem cell transplant (patients may receive high-dose intermittent ARA-C [HIDAC] consolidation until donor is found)
  - The specific consolidation built into the treatment scheme of the induction therapy utilized
  - Clinical trial

6. What is the post-remission treatment of choice for unfit or older patients with non-APL AML in CR?

- Allogeneic hematopoietic stem cell transplant (patients may receive high-dose intermittent ARA-C [HIDAC] consolidation until donor is found) if their performance status improves
- Intermediate/high-dose cytarabine patients with favorable- or intermediate-risk AML with good performance status and organ function
- Standard-dose cytarabine ± anthracycline for one or two cycles
- If patients received a hypomethylating agent +/- venetoclax for induction: continue therapy until toxicity or disease progression
- For those receiving an IDH inhibitor, continue therapy until toxicity or disease progression
- Clinical trial
- Observation

7. What is the surveillance strategy for patients with AML in CR post-consolidation therapy?

- Complete blood count (CBC) every 1 to 3 months for 2 to 3 years, then every 3 to 6 months until 5 years
- Bone marrow aspirate and biopsy only if cytopenias or abnormalities are identified on peripheral smear

8. What is the treatment strategy for relapsed non-APL AML patients?

- The only chance for a cure is with allogeneic hematopoietic stem cell transplant, ideally in the second CR
  - Clinical trial followed by allogeneic hematopoietic stem cell transplant
  - Salvage chemotherapy followed by allogeneic hematopoietic stem cell transplant
- If a patient is not eligible for an allogeneic hematopoietic stem cell transplant, one can offer consolidation based upon the induction strategy used, but curative percentages are very low.
- Best supportive care

ACUTE PROMYELOCYTIC LEUKEMIA

1. What are the induction and consolidation treatment options for patients with *high-risk* APL?

- High risk APL is defined as a presenting white blood cell count >10,000 cells / microliter.
- Strategy is dependent on presence or absence of cardiac issues defined as decreased ejection fraction or prolonged QTc.

- Note that each regimen may have unique timing and dosing of the agents listed. Additionally, the regimens may contain maintenance therapy as indicated in the manuscript. Current NCCN guidelines also call for consideration for 4 to 6 doses of intrathecal prophylaxis in patients with high-risk APL.

TABLE 1.5 ■ Preserved Ejection Fraction and Normal QTc

APL-4	Induction	1. ATRA 2. Age adjusted idarubicin 3. Arsenic trioxide
	Consolidation / Maintenance	1. ATRA 2. Arsenic trioxide
C9710	Induction	1. ATRA 2. Daunorubicin 3. Cytarabine
	Consolidation	1. Arsenic 2. ATRA 3. Daunorubicin
LPA-99	Induction	1. ATRA 2. Idarubicin 3. Cytarabine
	Consolidation	1. Daunorubicin 2. Cytarabine
LPA-2005	Induction	1. ATRA 2. Idarubicin
	Consolidation	1. ATRA 2. Idarubicin 3. Cytarabine 4. Mitoxantrone
Reduced Ejection Fraction		
MD Anderson	Induction	1. ATRA 2. Arsenic trioxide 3. Gemtuzumab ozogamicin
	Consolidation/Maintenance	1. ATRA 2. Arsenic trioxide
AML-17	Induction	1. ATRA 2. Arsenic trioxide 3. Gemtuzumab ozogamicin
	Consolidation/Maintenance	1. ATRA 2. Arsenic trioxide
Prolonged QTc		
MD Anderson	Induction	1. ATRA 2. Gemtuzumab Ozogamicin
	Consolidation	1. ATRA 2. Gemtuzumab ozogammicin

(*continued*)

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TABLE 1.5 ■ Preserved Ejection Fraction and Normal QTc (*continued*)

LPA-99 and APL 2000	Induction	1. ATRA 2. Daunorubicin 3. Cytarabine
	Consolidation	1. Daunorubicin 2. Cytarabine
LPA-2005	Induction	1. ATRA 2. Idarubicin
	Consolidation	1. ATRA 2. Idarubicin 3. Cytarabine 4. Mitoxantrone

APL, acute promyelocytic leukemia.

2. What is the treatment of choice for patients *with low/intermediate–risk* APL?

- Low risk APL is defined as a presenting white blood cell count of ≤10,000 cells/microliter and a platelet count of >40,000/microliter.
- Intermediate risk APL is defined as a presenting white blood cell count of ≤10,000 cells/microliter and a platelet count of <40,000/microliter.
- Clinically, the therapies for both low and intermediate risk APL overlap, so the therapeutic significance of this prognostic distinction is limited.
- Note that each regimen may have unique timing and dosing of the agents listed. Additionally, the regimens may contain maintenance therapy as indicated in the manuscript. Patients started on an induction regimen according to one treatment protocol, should receive consolidation and maintenance following the same protocol. Switching from one protocol to another should not be done.

TABLE 1.6 ■ Therapy Regimens for Low and Intermediate APL

APL-0406	Induction	1. ATRA 2. Arsenic trioxide
	Consolidation	1. ATRA 2. Arsenic trioxide
AML-17	Induction	1. ATRA 2. Arsenic trioxide
	Consolidation	1. ATRA 2. Arsenic trioxide
LPA-2005	Induction	1. ATRA 2. Idarubicin
	Consolidation	1. ATRA 2. Idarubicin 3. Cytarabine 4. Mitoxantrone

MD Anderson	Induction	1. ATRA 2. Gemtuzumab Ozogamicin
	Consolidation	1. ATRA 2. Gemtuzumab ozogammicin

3. How are patients with APL monitored after consolidation and what is the post-consolidation therapy if polymerase chain reaction (PCR) is negative?

- Bone marrow biopsy should be performed to document cytogenetic/molecular remission after consolidation if not achieving these milestones after induction.
- If PCR is negative, patients should receive maintenance therapy as per the initial treatment protocol if indicated.
- PCR monitoring should be performed for up to 2 years after the completion of all therapy.

4. How should patients with PCR-positive disease (after consolidation or if PCR turns positive during post-consolidation therapy) be treated?

- PCR should be repeated in 2 to 4 weeks for confirmation and to rule out a false-positive result. If it is confirmed positive, patient are considered in first relapse.
  - No prior exposure to arsenic trioxide or late relapse (≥6 months) after arsenic trioxide containing regimen: arsenic trioxide +/− ATRA until count recovery with marrow confirmation of remission
  - Early relapse (<6 months) after ATRA or arsenic trioxide only (no anthracycline): consider ATRA + idarubicin + arsenic trioxide until count recovery with marrow confirmation of remission
  - Early relapse (<6 months) after arsenic trioxide/anthracycline containing regimen: arsenic trioxide +/− ATRA until count recovery with marrow confirmation of remission
- Those who achieve second morphologic remission should be strongly considered for CNS prophylaxis.
- If the PCR turns negative, patients should be consolidated with an autologous stem cell transplantation (autoSCT). Those who are not transplant candidates should undergo 6 cycles of arsenic consolidation.
- If the PCR stays positive, patients should be treated with an allogeneic hematopoietic stem cell transplant (or on a clinical trial if not transplant candidates).
- Patients who do not achieve second morphologic remission are treated on a clinical trial or with an allogeneic hematopoietic stem cell transplant.

Acute Lymphoblastic Leukemia

EPIDEMIOLOGY

1. What is the median age at diagnosis?

- Fifteen years
  - There is a bimodal age distribution of acute lymphoblastic leukemia (ALL), with peaks in children and then again in older adults.

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- 57% of patients are diagnosed at age less than 20 years, and 27% are diagnosed at age 45 years or older

2. What is the incidence of ALL?

- 6500 new cases per year in the United States

ETIOLOGY AND RISK FACTORS

1. What are the common risk factors for ALL?

- Hispanics > Whites > African Americans
- Men > women
- Intrauterine exposure to radiation
- Environmental exposure: nuclear radiation
- Chemical exposure: benzene
- Congenital disorders: Down syndrome, ataxia telangiectasia, Bloom syndrome

PATHOLOGY—CLASSIFICATION

1. What is the WHO classification of ALL?

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*

T-lymphoblastic leukemia/lymphoma:

- T-lymphoblastic leukemia/lymphoma, NOS
- Provisional entity: early T-cell precursor lymphoblastic leukemia
- Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma

SIGNS AND SYMPTOMS

1. What are the common signs and symptoms of ALL?

- Lymphadenopathy and/or hepatosplenomegaly
- Painless testicular swelling
- Fever and other constitutional symptoms of infections
- Bruising or bleeding from thrombocytopenia
- Fatigue and other symptoms of anemia
- Infections (due to neutropenia)
- Leukostasis: CNS manifestations, cardiopulmonary symptoms, retinal hemorrhage, priapism
- Tumor lysis syndrome
- Mediastinal mass
- Musculoskeletal pain

DIAGNOSTIC WORKUP

1. Define the diagnostic criteria for ALL.

- Marrow and/or peripheral blood and/or lymph node involvement with lymphoid blasts
  - Typically, there will be ≥20% lymphoblasts in the marrow at the time of diagnosis
- Phenotypic and genetic determination of the lymphoblasts to allow for appropriate subclassification as outlined earlier

PROGNOSTIC FACTORS

1. How are patients with ALL stratified into different risk groups?

TABLE 1.7 ■ Risk Groups for ALL

	Adverse Risk	Standard Risk
Age	<1 y or >35 y	>1 y but <35 y
Immunophenotype	- Early T precursor (ETP) -Pro-B (especially CD20+)	- T cell - Pre-B
WBC count	- >100,000 for T cell - >30,000 for B cell	- <100,000 for T cell - <30,000 for B cell
Genetic aberrations	- Complex (≥5 changes) - Hypodiploidy (<44 chromosomes) - t (9;22) or *BCR-ABL* -*KMT2A* (*MLL*) rearranged - Ph-like ALL	Hyperdiploidy (51–65 chromosomes) t(12;21)
CNS involvement	Present	Absent
Response to therapy	Minimal residual disease present after induction	

TREATMENT

1. How are adult patients with Philadelphia chromosome positive (Ph+) ALL treated?

- Patients who are less than 70 years old without major comorbidities: induction cytotoxic chemotherapy + tyrosine kinase inhibitors (TKIs).
  - If CR is achieved, patients should undergo an allogenic hematopoietic stem cell transplant in first remission followed by consideration for the use of a maintenance TKI for a period of time following the allogeneic transplant.
  - If no donor is available, they should be continued on consolidation multiagent chemotherapy + TKI followed by maintenance therapy + TKI.
- Examples of cytotoxic regimens include:
  - TKIs + hyper-CVAD

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- TKI + COG AALL-0031
- TKI + EsPhALL

- Patients who are 70 years old or older, or with significant comorbidities: induction therapy with TKI + steroids or TKI + low-dose chemotherapy. If they achieve CR, they should be continued on TKI as consolidation.
- Examples of regimens include:
  - LAL1205 protocol—TKI + corticosteroid
  - TKI + vincristine + dexamethasone
  - EWALL-PH-01 or EWALL-PH-02 protocol

2. How are adult patients with Ph (–) ALL treated?

- Patients less than 70 years old without major comorbidities: induction with multiagent chemotherapy (multiple regimens available—the backbone of these therapies is steroids + anthracycline + vincristine).
- For fit patients under age 39, strong consideration should be given for a pediatric-inspired regimen.
- If CR is achieved, patients should continue multiagent chemotherapy as consolidation followed by maintenance therapy or undergo an allogeneic hematopoietic stem cell transplant if a donor is available (typically in patients with high risk cytogenetic features or those with persistent morphologic or minimal residual disease).

  Examples of regimens include:
  - CALGB 10403
  - COG AALL0232
  - CALGB 8811
  - Linker regimen
  - Hyper-CVAD
  - MRC UKALLXII/ECOG2993
- Patients who are 70 years old or older, or with significant comorbidities: induction with dose limited chemotherapy and steroids.
  - If they achieve CR, they should receive consolidation with chemotherapy followed by maintenance therapy.

3. How are patients with relapsed/refractory ALL treated?

- Ph+ ALL: consider ABL kinase domain mutation testing to determine optimal TKI as a portion of the patient's therapy.
  - Treatment options include clinical trial, chemotherapy ± TKI, TKI ± steroids. Blinatumomab, or inotuzumab ozogamicin can be considered in patients who are TKI intolerant or who have refractory disease.
  - Allogeneic hematopoietic stem cell transplant is considered if a morphological remission is obtained.
  - Patients up to 25 years of age that is refractory or in second or later relapse may also be considered for treatment with CAR-T cell therapy (tisagenlecleucel).
- Ph (–) ALL: Treatment options include clinical trial or multiagent chemotherapy. Blinatumomab or inotuzumab ozogamicin are considered for B-ALL and nelarabine for T-ALL.
  - Allogenic hematopoietic stem cell transplant is considered if a morphological remission is obtained.

- For B-ALL in patients up to 25 years of age that is refractory or in second or later relapse, treatment with CAR-T cell therapy (tisagenlecleucel) may be considered.

SPECIAL CONSIDERATIONS IN ACUTE LEUKEMIAS

1. What are the medical emergencies in leukemias?

- Leukostasis: needs to be treated aggressively with IV hydration, cytoreduction with hydroxyurea (and steroids in case of lymphoid malignancies) and leukopheresis. Avoid red blood cell transfusions.
- Disseminated intravascular coagulopathy (DIC): needs to be treated aggressively with supportive blood and blood product transfusions and disease control. Suspect APL in patients with DIC and start ATRA before a cytogenetic or molecular diagnosis is established,
- APL: need to start ATRA immediately, even before diagnosis is genetically confirmed.
- Differentiation syndrome: develops in APL (ATRA and arsenic are risk factors).
  - Signs and symptoms are fever, weight gain, edema, dyspnea, hypoxia, worsening renal function, opacities on chest imaging, pleural/pericardial effusions, and hypotension.
  - Treat with dexamethasone 10 mg every 12 hours.
  - If differentiation syndrome is severe, ATRA (and arsenic) needs to be held and resumed only after it resolves. Starting cytotoxic chemotherapy (if not already done) is considered.
  - Consider prophylaxis for differentiation syndrome with dexamethasone when starting differentiating therapy, especially in those with high risk APL.
- Tumor lysis syndrome (TLS): could be spontaneous in aggressive hematologic malignancies or induced by therapy.
  - Typically, have elevated uric acid, potassium and phosphorus, low calcium, and worsening renal function (phosphorus is generally not elevated in spontaneous TLS).
  - Should be treated prophylactically with IV hydration, allopurinol or febuxostat, and monitoring for TLS through checking potassium, phosphorus, uric acid, and calcium 2 to 3 times a day during therapy.
  - Rasburicase can also be considered prophylactically in highly proliferative malignancies if the risk of TLS is elevated and particularly if the renal function is not normal.
  - Treatment of TLS includes aggressive IV hydration, aggressive measures to correct electrolyte abnormalities, allopurinol or febuxostat, and rasburicase in select cases. G6PD deficiency should be ruled out, if suspected, before administration of rasburicase.

Hairy Cell Leukemia

EPIDEMIOLOGY

1. What is the median age at diagnosis?

- 52 years of age

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2. What is the incidence of hairy cell leukemia (HCL)?

- There are about 600 to 800 new cases per year in the United States (2% of all leukemias)

ETIOLOGY AND RISK FACTORS

1. Is HCL more common in males or females?

- HCL is more common in males (with male to female ratio of 4:1)

SCREENING

Not applicable

PREVENTION

Not applicable

PATHOLOGY

1. What genetic mutation is seen in virtually all cases of HCL?

- *BRAF V600E*, though this is not known to be a disease initiating mutation.

SIGNS AND SYMPTOMS

1. What are the typical clinical manifestations of HCL?

- Pancytopenia, including monocytopenia
- Fever and other constitutional symptoms
- Infections
- Bleeding
- Fatigue and other symptoms of anemia
- Organomegaly (splenomegaly) is common

DIAGNOSIS

1. What is the common microscopic appearance of HCL?

- Hair-like projections from the leukemia cells
- Fried-egg appearance on bone marrow biopsy
- Leukemic cells stain brightly with CD20
- Bone marrow may be hypocellular (need to differentiate from aplastic anemia and hypoplastic MDS)
- Bone marrow fibrosis is often present

2. How is the diagnosis established?

- Typical clinical manifestations with immunophenotype by flow cytometry
- HCL immunophenotype: CD11c+, CD25+, CD103+, CD123+, CD20+, CD22+, CD52+, cyclin D1+, annexin A1+, BRAF V600E+
- Hairy cell variant immunophenotype: CD25−, CD123−, annexin A1−, BRAF V600E-

PROGNOSTIC FACTORS

1. Does the hairy cell variant respond better or worse to treatment?

- The hairy cell variant (immunophenotype CD25−, CD123−) tends not to respond as well to purine nucleoside analogue -based therapy. Consideration should be given to treatment with sequential purine nucleoside analogue-based therapy followed by rituximab.

TREATMENT

1. When do we initiate therapy in HCL?

- Watch and wait strategy is recommended unless one of the following criteria for starting therapy is met:
  - Symptomatic disease that interferes with daily activities (eg, fatigue with no other reason, symptomatic splenomegaly)
  - Anemia (Hb <11 g/dL)
  - Thrombocytopenia (plt <100,000/μL)
  - Neutropenia (ANC <1,000)

2. What are the treatment options for HCL?

- Cladribine (7-day continuous infusion, or 1–2-hour bolus IV daily for 5 days, or subcutaneously daily for 5–7 days, or weekly for 5–6 weeks)
- Alternative option: Pentostatin IV every 2 weeks until maximal response (every 3 weeks if neutrophil count falls far below the baseline)
- CR is achieved in about 70% to 90% of patients, with a relapse rate of approximately 30% to 40% (at 10–15 years).

3. How are patients followed after therapy?

- Improvement in peripheral blood counts may require weeks to months.
- Bone marrow to document CR should be done at 3 to 4 months.
- After CR, CBCs are typically obtained every 1 to 3 months.

4. How are patients with relapsed HCL treated?

- If initial remission was for more than 1 year, consider repeating therapy with the same agent.
- If the remission was for less than 1 year, consider the alternative purine nucleoside analog, combination of a purine nucleoside analog with rituximab, or vemurafenib.

5. How are patients with resistant HCL treated?

- Consider an alternative purine nucleoside analogue, the combination of a purine nucleoside analog with sequential rituximab, vemurafenib (though this remains off-label), or moxetumomab (in those who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog).

QUESTIONS

1. A 45-year-old man presents to his primary care physician (PCP) with symptoms of fatigue and easy bruising. A complete blood count (CBC) reveals a white blood cell (WBC) count of 68, hemoglobin of 9.8, and platelet count of 23. The WBC differential reveals 83% circulating blasts

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with Auer rods present. Bone marrow biopsy is performed and confirms the diagnosis of acute myeloid leukemia (AML). The patient begins induction chemotherapy with anthracycline and cytarabine in a standard 3 + 7 fashion using daunorubicin 90 mg/m2. Human leukocyte antigen (HLA) typing is sent on admission and he is found to have a 10/10 HLA matched sibling.

With which of the following genetic findings would you more strongly consider consolidation therapy with high-dose cytarabine in first complete remission (CR1)?

A. Normal male karyotype, *FLT3-ITD* (high variant allele frequency) mutation positive
B. Cytogenetics revealing a t(6;9)(p23;q34.1) translocation
C. Cytogenetics revealing a t(8;21)(q22;q22.1) translocation and c-KIT mutation negative
D. Cytogenetics revealing a del(5)(q13q33)

2. A 59-year-old woman presents to the emergency department with complaints of fatigue, dyspnea on exertion, vision changes, and headaches. Routine blood work reveals a white blood cell (WBC) count of 120, hemoglobin of 7, and platelet count of 73. Review of the peripheral smear shows 90% blasts with Auer rods. Physical exam confirms the presence of retinal hemorrhages bilaterally.

What is the next most important step in management?

A. Call for an urgent ophthalmology evaluation
B. Transfuse two units of packed red blood cells (PRBC)
C. Obtain an echocardiogram
D. Arrange for urgent leukapheresis, initiate fluids, and begin hydroxyurea

3. A 21-year-old woman completed multiagent chemotherapy including alkylating agents, etoposide, and radiation therapy for Ewing's sarcoma 2 years ago. She has been free of disease since but on routine blood work she was noted to have a white blood cell (WBC) count of 42, hemoglobin of 9, and platelet count of 77. Bone marrow biopsy confirms the diagnosis of acute myeloid leukemia (AML).

Which cytogenetic abnormality is she most likely to have?

A. 11q23 abnormality
B. t(8;21)(q22;q22.1)
C. t(15;17)(q24;q21)
D. Monosomy 7

4. A 52-year-old man is 10 days into therapy with all-trans retinoic acid (ATRA) and arsenic trioxide for a diagnosis of low-risk acute promyelocytic leukemia (APL) when he begins to develop hypoxia, dyspnea, and lower extremity edema. Chest x-ray reveals bilateral pulmonary infiltrates.

What is the most appropriate step in management?

A. Obtain a nasopharyngeal swab for presumed viral lower respiratory tract infection
B. Start dexamethasone 10 mg twice daily for presumed differentiation syndrome
C. Order a stat CT PE protocol and initiate a heparin drip
D. Perform a stat bedside transthoracic echocardiogram for suspected therapy-induced cardiomyopathy

5. A 58-year old man is transferred to your center for acute myeloid leukemia (AML). He has no known prior medical history. Initial laboratory assessment demonstrates a uric acid of 16, potassium of 7, calcium of 6.5, and a creatinine elevated to 4 from a normal baseline. His EKG is normal.

In addition to correcting the hyperkalemia and hypocalcemia, what are the next steps in management?

A. Initiate aggressive fluid resuscitation and give rasburicase (0.2 mg/kg) with plan to recheck labs in 6 to 8 hours
B. Obtain central venous access with plan to initiate leukapheresis
C. Initiate hydroxyurea for cytoreduction
D. Start dexamethasone

6. A 39-year-old woman is diagnosed with Philadelphia chromosome negative (Ph-) B-cell acute lymphoblastic leukemia (ALL). After undergoing intensive induction with multiagent chemotherapy, she achieves a complete remission (CR) but had evidence of minimal residual disease. She then underwent early intensification and interim maintenance therapy. A repeat bone marrow aspiration and biopsy continued to demonstrate a morphologic remission, but also continued to demonstrate minimal residual disease testing (0.7%). She has a human leukocyte antigen (HLA) matched related sibling.

What is the best strategy for additional therapy?

A. Immediate consolidation with an allogeneic hematopoietic stem cell transplant
B. Consolidation with maintenance chemotherapy
C. Consolidation with maintenance chemotherapy followed by an autologous stem cell transplant
D. Initiation of blinatumomab

7. A 57-year-old man presents to his primary care physician (PCP) for his annual exam. He is noted to have palpable splenomegaly but is otherwise asymptomatic. A complete blood count (CBC) demonstrates a white blood cell (WBC) count of 2.0 with an absolute neutrophil count (ANC) of 1.5, hemoglobin of 8, and platelets of 157. Additionally, monocytopenia is noted on differential. Review of peripheral smear demonstrates presence of lymphocytes with villous projections and a diagnosis of hairy cell leukemia is confirmed by flow cytometry.

What is the next step in management?

A. Initiate cladribine, IV daily for 5 days
B. Start BRAF-targeted therapy
C. Monitor symptoms and blood counts, no treatment at this time
D. Referral for bone marrow transplant

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ANSWERS

1. **C. Cytogenetics revealing t(8;21), c-KIT mutation negative.** The National Comprehensive Cancer Network (NCCN) identifies a number of adverse risk genetic changes including, but not limited to, a deletion of the long arm of chromosome 5 [del (5)(q)], the t(6;9) (p23;q34); DEK-NUP214 translocation, and a normal karyotype with a sole concomitant *FLT3-ITD* mutation with a variant allele frequency of greater than 50% as well validated poor risk prognostic factors in patients with AML. As such, the recommendation for standard post-remission therapy for these higher risk lesions would be an allogeneic hematopoietic stem cell transplant. Alternatively, the presence of the core binding factor leukemia beta translocation, t(8;21)(q22;q22.1), is a well validated favorable-risk group. As such, the recommendation for standard post-remission therapy is with high-dose cytarabine.

2. **D. Arrange for urgent leukapheresis, initiate fluids, and begin hydroxyurea.** This patient is suffering from life-threatening leukostasis as evidenced by complaints of dyspnea, vision changes, and headaches. She needs emergent leukapheresis, fluids, and initiation of a cytoreductive agent. Neither an urgent ophthalmologic exam nor an echocardiogram will alter your initial recommendations. Despite moderate anemia, transfusion of red cells in a patient with active leukostasis would be contraindicated at this time, due to concerns for exacerbating the stasis.

3. **A. An 11q23 abnormality.** The multiagent chemotherapy this patient received in treatment for her Ewing's sarcoma has put her at risk for a treatment-related myeloid neoplasm. The latency of 2 years between treatment and onset of AML and a lack of an intercedent MDS favors the topoisomerase II inhibitor (etoposide) as the culprit. Treatment-related myeloid neoplasms caused by topoisomerase II inhibitors are often associated with translocation 11q23 (KMT2A (previously known as the mixed lineage leukemia gene [MLL]). Alkylating agents, on the other hand, would be expected to have a longer latency period of 5 to 10 years, tend to be associated with antecedent treatment-related MDS, and are associated with complex cytogenetics as well as monosomy 5 or 7.

4. **B. Start dexamethasone 10 mg twice daily for presumed differentiation syndrome.** Differentiation symptom occurs in 2% to 30% of patients receiving ATRA or arsenic trioxide. Signs and symptoms include leukocytosis, dyspnea, fever, pulmonary edema or infiltrates, effusions, weight gain, and bone pain. Classically, it develops 10 to 12 days after initiation of therapy. Treatment includes prompt initiation of steroids as well as discontinuation of the differentiating agent, depending on the severity of symptoms.

5. **A. Initiate aggressive fluid resuscitation and give rasburicase (0.2 mg/kg) with plan to recheck labs in 6 to 8 hours.** The patient has evidence of tumor lysis syndrome (TLS) which has caused the hyperkalemia, hypocalcemi, and a decline in renal function. Given abnormalities in potassium and calcium, the former should be lowered and the latter should be

corrected. IV hydration is a cornerstone of therapy for hyperuricemia, and fluids should be used liberally in tolerant patients. In this case, since renal function is impaired with a high uric acid, rasburicase should be utilized. Given that this is an emergent situation, G6PD testing need not be completed, but evaluation for hemolysis should be included in laboratory assessment.

6. **D. Initiation of blinatumomab.** MRD positivity at the time of allogeneic hematopoietic stem cell transplant is associated with an increased risk of relapse. As such, additional therapy is needed with a goal of achieving an MRD negative state. In this case, blinatumomab, a bispecific T cell engager (BITE) targeting CD19, has demonstrated activity in, and has been FDA approved for patients achieving a morphologic remission with minimal residual disease. The FDA approval was based on the MT103-203 (BLAST) trial which was an open-label, multicenter, single-arm study that included patients with B-cell ALL who were ≥18 years of age, had received at least three chemotherapy blocks of standard ALL therapy (e.g., induction, intensification, and consolidation), were in morphologic CR, and had marrow MRD at a level of ≥0.1% using an assay with a minimum sensitivity of 0.01%. Providing additional cytotoxic chemotherapy in a patient who has already received 3 cycles of chemotherapy is unlikely to produce a significant response. Likewise, proceeding with a transplant with active disease, while not contraindicated, is likely to be associated with a higher risk of relapse.

7. **A. Initiate cladribine, IV daily for 5 days.** In this case, the patient has hairy cell leukemia and anemia with a hemoglobin <11. Indications for therapy in hairy cell leukemia include systemic symptoms, splenic discomfort, recurrent infection, anemia (hemoglobin **<**11), thrombocytopenia (platelet count **<**100), or neutropenia (ANC **<**1).

ALGRAWANY

Chronic Lymphocytic Leukemia

2

Jason C. Chen and J. Christine Ye

EPIDEMIOLOGY

1. What is chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)?

- CLL is the most common adult leukemia in the Western world (about 30% of all leukemias) and is characterized by lymphocytosis, with or without lymph node (LN) or organ involvement by clonal B-cells.
- SLL is similar, though no peripheral lymphocytosis, and mainly with LN or organ involvement by clonal B-cells.
- Median age at diagnosis: 70 years

SIGNS AND SYMPTOMS

1. What are the common signs and symptoms of CLL/SLL?

- Asymptomatic lymphocytosis, splenomegaly, or lymphadenopathy
- Fatigue and malaise associated with anemia
- Early satiety or abdominal discomfort secondary to splenomegaly
- B symptoms: fevers, night sweats, and weight loss
- Recurrent infections due to hypogammaglobulinemia (low IgG level) or neutropenia

2. What are the characteristic peripheral blood smear findings of CLL?

- Typical CLL smear: small mature lymphocytes (round, dark nucleus with minimal cytoplasm) and smudge cells (smeared broken lymphocytes)

DIAGNOSTIC CRITERIA

1. What are the main diagnostic criteria for CLL?

- Peripheral blood monoclonal B-lymphocyte count $\geq 5 \times 10^9/L$, lasting ≥3 months
- Characteristic lymphocyte flow cytometric immunophenotype (from blood or LN): positive for B-cell markers (CD19+, CD20 low/dim) and T-cell markers (CD5+, mostly CD23+). Restricted surface immunoglobulin expression suggesting clonality
- Needs to be t(11;14) and cyclin D1 negative to rule out mantle cell lymphoma
- Fluorescence in situ hybridization (FISH; tri12, del11q, del13q, del17p are most commonly seen), karyotyping, immunoglobulin heavy chain (IGHV) mutation, and TP53 mutation testing are recommended for prognostication or treatment decisions.
- A bone marrow biopsy is not needed to make the diagnosis of CLL, but should be considered when patient is cytopenic and other etiologies are ruled out.

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- Imaging: usually not needed for most patients. Can consider CT scan if starting treatment with significant adenopathy or splenomegaly. Consider PET/CT if suspecting Richter's transformation.

2. What are the diagnostic criteria for SLL?

- **LN biopsy showing CLL immunophenotypes (see Question 1)**

3. What is monoclonal B-cell lymphocytosis (MBL)?

- If monoclonal B-lymphocyte count is $<5 \times 10^9$/L in the setting of a characteristic flow cytometry pattern without end-organ involvement or cytopenias

4. What other B-cell disorders need to be ruled out?

- B-cell prolymphocytic leukemia: an aggressive leukemia with prolymphocytes comprised ≥55% of the lymphocytes in blood/marrow
- Mantle cell lymphoma: positive for t(11;14) and cyclin D1 expression, also commonly CD5+, CD23–
- Hairy cell leukemia (HCL): indolent B-cell disorder characterized by splenomegaly, cytopenias, distinct immunophenotype (CD103+, CD25+), and mononuclear cells with "hairy" projections that are tartrate-resistant acid phosphatase (TRAP) stain positive

STAGING

1. Define the staging for CLL/SLL.

TABLE 2.1 ■ Rai and Binet Staging for CLL/SLL

Rai Stage	Modified Rai Stage	Definition	Median Overall Survival
0	Low risk	Lymphocytosis only	>10 y
I	Intermediate risk	Lymphocytosis and lymphadenopathy	7 y
II	Intermediate risk	Lymphocytosis, lymphadenopathy with hepatomegaly and/or splenomegaly	7 y
III	High risk	Lymphocytosis and anemia (Hgb <11 g/dL)	<4 y
IV	High risk	Lymphocytosis and thrombocytopenia (platelets $<100 \times 10^9$/L)	<4 y

Binet Stage	Definition	Median Overall Survival
A	Hgb ≥10 g/dL and platelets $\geq 100 \times 10^9$/L with less than three nodal sites*	12 y
B	Hgb ≥10 g/dL and platelets $\geq 100 \times 10^9$/L with three or more nodal sites*	7 y

Binet Stage	Definition	Median Overall Survival
C	Anemia (Hgb <10 g/dL) and/or thrombocytopenia (platelets <100 × 10^9/L)	2–4 y

*The five nodal sites for Binet staging are head/neck (including Waldeyer ring), axillary, inguinal, spleen, and liver.

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; Hgb, hemoglobin.

- CT scans are not needed for staging. CT scans should only be obtained to follow and monitor disease progression in patients with new symptoms when peripheral adenopathy is not present.

PROGNOSTIC FACTORS

1. What are poor risk factors?

- Deletion 17p (FISH) or >10% *TP53* mutation
- Deletion 11q (FISH)
- Complex karyotype (karyotyping)
- Unmutated IGHV (≤2% mutation, DNA sequencing) portends a worse prognosis and less response to chemoimmunotherapy versus mutated IGHV (>2% mutation)
- CD38 ≥30%, ZAP-70 ≥20%, CD49d ≥ 0% (flow cytometry) predict higher risk, but IGHV mutation status is more important and relevant
- Elevated beta-2 microglobulin level

2. What are favorable risk factors?

- Deletion 13q (as a sole abnormality)
- Trisomy 12 and normal cytogenetics are intermediate/neutral features

3. Is there a scoring system to help determine prognosis?

TABLE 2.2 ■ International Prognostic Index for Chronic Lymphocytic Leukemia

Age	≤65 y old: 0 points >65 y old: 1 point
Clinical stage	Binet A or Rai 0: 0 points Binet B-C or Rai I-IV: 1 point
Serum beta-2-microglobulin (mg/L or mcg/mL)	≤3.5: 0 points >3.5: 2 points
IGHV mutational status	Mutated: 0 points Unmutated: 2 points
TP53 status	No abnormalities: 0 points Del(17p) or *TP53* mutation: 4 points

(*continued*)

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TABLE 2.2 ■ International Prognostic Index for Chronic Lymphocytic Leukemia (*continued*)

Five-year overall survival based on score:
Score 0–1 (low risk)—93.2%
Score 2–3 (intermediate risk)—79.3%
Score 4–6 (high risk)—63.3%
Score 7–10 (very high risk)—23.3%

CLL-IPI, International Prognostic Index for chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain; IV, intravenous.

INDICATIONS FOR TREATMENT

1. How do you manage asymptomatic CLL/SLL?

- Careful monitoring without therapy, typically with follow-up visits every 3, 6, or 12 months without surveillance imaging unless indicated for symptoms.

2. What are the indications for therapy?

- End-organ damage, refractory cytopenias, debilitating symptoms, or rapid disease progression
  - Anemia and/or thrombocytopenia not related to autoimmune or other causes (usually hemoglobin [Hgb] <10 or platelets <100)
  - Refractory autoimmune thrombocytopenia or hemolytic anemia not responding to steroids
  - Threatened end-organ function, massive or symptomatic adenopathy or splenomegaly, or symptomatic extranodal involvement (skin, kidney, lung, bone)
  - B symptoms: unexplained fevers, night sweats, unintentional weight loss, severe fatigue
  - Rapidly rising absolute lymphocyte count (ALC), either doubling time <6 months or an increase ≥50% over a 2-month period if ALC $\geq 30 \times 10^9/L$

TREATMENT

TABLE 2.3 ■ Overview of Novel Agents

Drug Name	Mechanism of Action	Indication	Notable Side Effects
Ibrutinib	BTK inhibitor *C481S* mutation: confers resistance	Initial treatment for del(17p) ± *TP53* mutation	Diarrhea, rash, myalgia, atrial fibrillation, HTN, bleeding
Acalabrutinib	BTK inhibitor	Initial treatment for del(17p) ± *TP53* mutation	Similar to ibrutinib, less overall toxicity, more headaches (caffeine helps), BID dosing, avoid PPI, need to take on empty stomach

(*continued*)

TABLE 2.3 ■ Overview of Novel Agents (*continued*)

Drug Name	Mechanism of Action	Indication	Notable Side Effects
Obinutuzumab	Anti-CD20 monoclonal antibody	Approved as initial treatment in combination with chemo or targeted agents	Similar to rituximab (infusion reactions, risk of hepatitis B reactivation)
Ofatumumab	Anti-CD20 monoclonal antibody	Approved as initial treatment and for relapsed/refractory disease	Similar to rituximab (infusion reactions, risk of hepatitis B reactivation)
Venetoclax	BCL2 inhibitor	Approved for ± del(17p) who received one prior therapy	**Risk of tumor lysis syndrome (higher risk in higher tumor burden), cytopenia, infection, GI issues.** Avoid strong CYP3A4 inhibitors/inducers
Idelalisib	PI3K inhibitor	Approved in combination with rituximab	Neutropenia, colitis, hepatotoxicity, pneumonitis, rash, increased infection risk
Duvelisib	PI3K inhibitor	Approved after failure of two lines of therapy	Similar to idelalisib

BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; HTN, hypertension; PI3K, phosphoinositide 3-kinase; PPI, proton pump inhibitor.

First-Line Therapy

1. What factors are important to consider when choosing a therapeutic regimen for CLL/SLL?

- Age
- Functional status and comorbidities
- Results of cytogenetic (FISH, karyotype) and TP53 mutation testing
- IGHV mutation status
  - IGHV unmutated status and presence of TP53 mutation or del(17p) are predictors of worse outcomes with chemotherapy-based regimens.

2. What are initial treatment options for CLL/SLL patients without del(17p) or *TP53* mutation?

- Preferred regimens: ibrutinib (RESONATE), acalabrutinib ± obinutuzumab (ELEVATE TN), venetoclax ± obinutuzumab (CLL14)
- Can consider chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) for young, fit patients who are IGHV mutation positive and prefer shorter fixed duration of therapy
  - Avoid in patients with autoimmune hemolytic anemia (AIHA); purine analogs are a risk factor in developing AIHA.

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- For elderly patients or young patients with comorbidities, can consider bendamustine + anti-CD20 antibody (e.g., rituximab), chlorambucil + obinutuzumab, high-dose steroids + rituximab, ofatumumab

3. What are initial treatment options for CLL/SLL patients with del(17p) or *TP53* mutation?

- Preferred regimens: ibrutinib, acalabrutinib ± obinutuzumab, venetoclax + obinutuzumab
- Can consider alemtuzumab ± rituximab, obinutuzumab, high-dose steroids + rituximab, ofatumumab

4. What type of transplant is preferred in CLL if transplant is indicated?

- Allogeneic stem cell transplants (SCTs) are now rarely used, but if needed, reduced intensity conditioning is preferred.

Response Criteria

1. How are complete response (CR) and partial response (PR) defined? How are progressive disease (PD) and stable disease (SD) defined?

TABLE 2.4 ■ Response Criteria for Progressive and Stable Disease

	CR	PR	SD	PD
Lymph nodes	None ≥1.5 cm	Decrease ≥50% from baseline	Not meeting other criteria	Increase ≥50% from baseline or prior response
Liver/spleen size	Spleen and liver size normal	Decrease ≥50% from baseline	Not meeting other criteria	Increase ≥50% from baseline or prior response
Constitutional symptoms	None	Any	Any	Any
Lymphocyte count	Normal	Decrease ≥50% from baseline	Not meeting other criteria	Increase ≥50% from baseline or prior response
Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% from baseline	Not meeting other criteria	Decrease ≥50% from baseline
Hemoglobin	≥11.0 g/dL	≥11 g/dL or increase ≥50% from baseline	Not meeting other criteria	Decrease of ≥2 g/dL from baseline
Marrow	Normocellular, no evidence of CLL	Presence of CLL cells	No change in marrow infiltrate	Increase in CLL cells by ≥50%

CLL, chronic lymphocytic leukemia; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

- Of note, the abovementioned criteria are only met if the findings are thought to be related to CLL/SLL and not other causes.

Second-Line Therapy

1. How are CLL/SLL patients managed following failure of first-line therapy?

- Asymptomatic patients at relapse: monitor closely and start therapy if one of the previously noted treatment criteria is met.
- Repeat LN biopsies as needed to rule out transformation prior to treatment reinitiation. PET is helpful to look for high fluorodeoxyglucose (FDG) uptake areas that would be higher yield targets for biopsy.
- If available, consider patients for clinical trial
- Patients with or without del(17p) have similar preferred regimens: acalabrutinib, ibrutinib, venetoclax + rituximab, duvelisib, idelalisib + rituximab
- Can also consider bendamustine-containing regimens (for fit patients), lenalidomide (watch for tumor flare: painful LN enlargement, fever, rash), ofatumumab

SPECIAL CONSIDERATIONS

1. What are causes of anemia in CLL/SLL patients?

- Differential diagnosis includes other causes of anemia (e.g., bleeding), autoimmune process, progressive marrow failure from CLL, pure red cell aplasia in cases of isolated anemia.
- **Cytopenia(s) from marrow failure secondary to CLL** should be documented by a bone marrow biopsy.
- **Pure red cell aplasia**: reduced reticulocytes and absence of erythroid precursors in the bone marrow. Exclude other causes including viral infections (Epstein–Barr virus [EBV], cytomegalovirus [CMV], parvovirus)
- **AIHA**: elevated lactate dehydrogenase (LDH), high unconjugated bilirubin, elevated reticulocyte count, low haptoglobin, and positive direct antiglobulin test (DAT). Peripheral smear showing spherocytes. Exclude other causes as well.

2. How is AIHA or idiopathic thrombocytopenic purpura (ITP) in patients with CLL/SLL treated?

- If indication for CLL therapy exists independent of the anemia, treat CLL.
- If no independent indication for CLL therapy: high-dose steroids with slow taper, folic acid supplementation. If inadequate response, can try other agents such as rituximab, intravenous immunoglobulin (IVIG), cyclophosphamide, and so on. A trial of rituximab and at least one immunosuppressive agent is generally recommended prior to consideration of splenectomy.
- Treatment refractory AIHA or ITP: treat underlying CLL.

3. Is worsening peripheral lymphocytosis on ibrutinib or idelalisib indicative of treatment failure or disease progression after initiation of treatment?

- No, the peripheral lymphocytosis that occurs after initiation of ibrutinib or idelalisib may vary among patients, can last for months up to a year, and is not indicative of progression of disease. This results from mobilization of lymphocytes from LNs to the peripheral blood.

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4. What is the treatment of patients with CLL/SLL and recurrent severe infections?

- Check serum IgG levels if recurrent infections. If <400 mg/dL, administer monthly IVIG for goal ≥500 mg/dL.
- Maintain up-to-date routine vaccinations

5. What anti-infective prophylaxis is indicated in patients receiving therapy?

- Purine analog (fludarabine)
  - Herpes prophylaxis with acyclovir
  - Pneumocystis jirovecii (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent
- PI3K inhibitors (idelalisib, duvelisib)
  - PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent

6. When is Richter's transformation suspected in CLL/SLL and how is it treated?

- Richter's transformation (transformation to diffuse large B-cell lymphoma [DLBCL] or Hodgkin lymphoma) is suspected in the following cases:
  - Patients with prominent B symptoms (fevers, night sweats, weight loss)
  - Rapidly enlarging LNs
  - If LDH is significantly elevated (in the absence of hemolysis)
  - Hypercalcemia ± lytic bone lesions can be seen
- PET/CT is useful to confirm or rule out Richter's transformation. Biopsy is required to confirm the transformation.
- Patients with DLBCL transformation should be treated with regimens developed for DLBCL. Patients should be considered for autologous or allogeneic SCT after CR or PR to initial therapy. Patients can also be considered for immunotherapy ± ibrutinib.
- Patients with Hodgkin lymphoma transformation should be treated with regimens used to treat Hodgkin lymphoma.

7. Is there an increased risk of second primary malignancies (SPM) in CLL/SLL patients?

- Yes, higher risk of both solid-organ and hematologic SPM. Routine age- and gender-appropriate cancer screening including skin cancer screening are recommended.

HAIRY CELL LEUKEMIA

1. How is HCL diagnosed?

- Symptoms: enlarged spleen, fatigue, weight loss, bruising, pancytopenia (particularly monocytopenia), abnormal lymphocytes with "fluffy" or indistinct cell membrane outline
- Often with dry tap (inability to obtain aspirate) on bone marrow biopsy
- Flow cytometry: CD5−, CD10−, CD103+, CD20+ CD11c+, Annexin A1+; + TRAP staining; classic HCL almost always carries a BRAF V600E mutation

2. How is newly diagnosed HCL treated?

- If no constitutional symptoms, recurrent infections, progressive splenomegaly/adenopathy, or significant cytopenia can consider observation

- Purine analogs are mainstay of initial therapy
  - Cladribine ± rituximab
  - Pentostatin

3. How is relapsed/refractory HCL treated?

- If relapse >2 years from prior therapy, can reattempt initial purine analog combination
- If relapse <2 years from prior therapy
  - Consider clinical trial
  - Can consider purine analog therapy but with a different agent
  - Vemurafenib for BRAF mutation positive disease
- For further progression after prior therapy for relapsed/refractory disease
  - Moxetumomab pasudotox-tdfk (a CD22-directed cytotoxin) is indicated for refractory HCL after failure of two prior systemic therapies. Watch for hemolytic uremic syndrome (HUS) and cytokine release syndrome (edema, weight gain, hypotension, and decreased albumin)
  - Can also consider vemurafenib ± rituximab

QUESTIONS

1. A 67-year-old male presents with white blood cell count of 87 × 10^9/L, hemoglobin of 13.1 g/dL, platelet count of 210 × 10^9/L. Peripheral blood flow cytometry reveals a clonal population of cells expressing CD5, CD20 (dim), CD19, and CD23. Immunohistochemistry staining was negative for cyclin D1.

Which of the following is NOT associated with an unfavorable prognosis for his diagnosis?

A. Deletion 11q
B. Deletion 17p
C. Elevated beta-2-microglobulin
D. Unmutated IGHV status
E. Deletion 13q

2. A 58-year-old female with chronic lymphocytic leukemia (CLL) presents with fevers, severe fatigue, and frequent night sweats. Her complete blood count (CBC) is significant for a white blood cell (WBC) count of 135 × 10^9/L, absolute lymphocyte count (ALC) of 110 × 10^9/L, hemoglobin of 9 g/dL, and platelet count of 97 × 10^9/L. Fluorescence in situ hybridization (FISH) testing positive for del(17p). She is initiated on ibrutinib 420 mg daily and has mild diarrhea but otherwise tolerates therapy in his first week. On her subsequent labs in 2 weeks, her WBC has increased to 160 × 10^9/L, ALC 135 × 10^9/L, with stable hemoglobin and platelet counts. In 1 month, her WBC has increased to 230 × 10^9/L, ALC 210 × 10^9/L, hemoglobin and platelet counts remain stable. Her fevers and night sweats have resolved.

What is the next appropriate step in management of her CLL?

A. Consider admission for urgent cytoreductive therapy
B. Switch therapy to venetoclax
C. Perform CT of chest/abdomen/pelvis to evaluate for bulky disease in areas that are not palpable by exam
D. Continue ibrutinib 420 mg daily
E. Increase ibrutinib to 560 mg daily

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3. A 45-year-old gentleman presents to clinic with fatigue, abdominal fullness, white blood cell (WBC) count of 1.5 × 10^9/L, hemoglobin of 7 g/dL, and platelet count of 34 × 10^9/L. Physical exam remarkable for splenomegaly without palpable adenopathy. Bone marrow biopsy with dry tap (unable to obtain aspirate sample). Core biopsy with abnormal-appearing cells that were negative for CD5 and CD10; cells were positive for CD20, CD103, CD11c, and annexin A1.

What would be the best initial management for this patient?

A. Observation
B. Cladribine
C. Ibrutinib
D. Rituximab
E. Repeat bone marrow biopsy

4. A 90-year-old gentleman with a history of poorly congestive heart failure with atrial fibrillation, history of gastrointestinal (GI) bleeding, hemorrhagic stroke, and uncontrolled diabetes presents for a follow-up appointment for his chronic lymphocytic leukemia (CLL). He also has severe gastroesophageal reflux disease, which is stable on proton pump inhibitor therapy. He has had progressively worsening fatigue and adenopathy in his groin over the last 5 weeks. His Eastern Cooperative Oncology Group (ECOG) performance status is 2. Labs show a white blood cell (WBC) count of 114 × 10^9/L, hemoglobin of 10 g/dL, and platelet count of 95 × 10^9/L without evidence of autoimmune-related anemia or thrombocytopenia. His hemoglobin was 14 g/dL at his appointment 6 months earlier.

Which of the following would be an appropriate first therapeutic option?

A. Ibrutinib
B. Venetoclax + obinutuzumab
C. Fludarabine, cyclophosphamide, and rituximab (FCR)
D. Duvelisib
E. Acalabrutinib

5. A 47-year-old woman with known chronic lymphocytic leukemia (CLL) presents to clinic with worsening lymphadenopathy, night sweats, and shortness of breath. Her white blood cell (WBC) count is 102 × 10^9/L, hemoglobin 8 g/dL, and platelet count 90 × 10^9/L. A CT scan of the chest/abdomen/pelvis demonstrates bulky lymphadenopathy in her cervical, axillary, retroperitoneal, and mesenteric lymph nodes. Fluorescence in situ hybridization (FISH) testing demonstrates a deletion 17p. She has not been previously treated for her CLL.

Which of the following would be the most appropriate frontline therapy option?

A. Fludarabine, cyclophosphamide, and rituximab (FCR)
B. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
C. Ibrutinib
D. Bendamustine and rituximab (BR)
E. Rituximab

6. A 67-year-old woman presents to clinic with a new diagnosis of chronic lymphocytic leukemia (CLL). She was incidentally found to have an elevated white blood cell (WBC) count of 23 × 10^9/L, absolute lymphocyte count (ALC) of 20 × 10^9/L, hemoglobin 13 g/dL, and platelet count of 175 × 10^9/L. She continues to work full time and is at her baseline state of health. On physical exam there are no appreciable palpable lymph nodes and no hepatosplenomegaly.

Which of the following is the most appropriate next step in the management of her disease?

A. Baseline CT scan of the chest, abdomen, and pelvis
B. Baseline PET scan
C. Bone marrow biopsy
D. No additional studies, follow-up in 3 months with labs only
E. No additional studies, follow-up as needed when symptomatic

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ANSWERS

1. **E. Deletion 13q.** This is associated with a better prognosis in chronic lymphocytic leukemia (CLL). (A), (B), (C), and (D) have all been associated with unfavorable prognosis in CLL.

2. **D. Continue ibrutinib 420 mg PO daily.** Increased peripheral lymphocytosis after initiating treatment with ibrutinib therapy is common and may last for several months. The development of peripheral lymphocytosis secondary to ibrutinib was due to mobilization of CLL cells from bone marrow and lymphoid organs. It has not been shown to be detrimental to long-term clinical outcomes.

3. **B. Cladribine.** This patient has splenomegaly, pancytopenia, and bone marrow biopsy immunophenotype consistent with hairy cell leukemia (HCL). Given severe cytopenia and symptoms, treatment should be considered rather than observation. First-line treatments include cladribine and pentostatin. Ibrutinib is not indicated for use in HCL. Rituximab is indicated in combination with a purine analog, not as a single agent in HCL. Repeating bone marrow biopsy to reattempt aspirate is not needed, as patients with HCL often have dry taps due to marrow fibrosis, and diagnosis was confirmed on the core biopsy.

4. **B. Venetoclax + obinutuzumab.** This is the best regimen given this patient's comorbidities. Ibrutinib may not be the best option given atrial fibrillation and bleeding risk. FCR is not a reasonable option for an elderly, frail patient. Duvelisib indicated for relapsed/refractory disease and not for previously untreated disease. Acalabrutinib would be a reasonable option though this medication cannot be taken with a proton pump inhibitor (PPI), which the patient requires for his severe gastroesophageal reflux disease (GERD).

5. **C. Ibrutinib.** This has been shown to have high overall response rates in deletion 17p patients and is currently a preferred first-line therapy. Deletion 17p and patients with TP53 mutations have poor outcomes with conventional chemoimmunotherapy regimens.

6. **D. No additional studies, follow-up in 3 months with labs only.** For an early-stage asymptomatic CLL patient, there is no indication for baseline CT scans or baseline bone marrow biopsy. Avoidance of baseline and serial CT scans in early-stage asymptomatic CLL patients was recently encouraged as a part of the American Society of Hematology Choosing Wisely Campaign. General follow-up every 3 to 6 months is the current standard of care.

Chronic Myelogenous Leukemia and Myeloproliferative Neoplasms

3

Charles E. Foucar and Rami N. Khoriaty

Chronic Myelogenous Leukemia

EPIDEMIOLOGY

1. What is the median age at diagnosis of chronic myelogenous leukemia (CML)?

- Sixty-seven years; incidence increases with age

ETIOLOGY AND RISK FACTORS

1. What is the one known causative factor?

- Ionizing radiation

2. What two genes are involved in the hallmark Philadelphia (Ph) chromosomal translocation of CML and what chromosomes are they on?

- *ABL1* proto-oncogene on chromosome 9 and *breakpoint cluster region* (*BCR*) on chromosome 22

3. What is the protein product of the balanced translocation between the long arms of chromosomes 9 and 22?

- The BCR-ABL1 oncoprotein

DIAGNOSTIC CRITERIA

1. What is required to make a diagnosis of CML?

- Identification of t(9;22) in cytogenetic analysis of bone marrow (BM)
- Identification of the *BCR-ABL1* fusion gene by fluorescence in situ hybridization (FISH)
- Identification of the BCR-ABL1 transcript with quantitative reverse transcription polymerase chain reaction (RT-PCR)

2. Name two other hematologic malignancies that can harbor t(9;22).

- Ph+ acute lymphoblastic leukemia
- Ph+ acute myeloid leukemia (AML)

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STAGING

1. What are the three phases of CML, and what characterizes each phase?

TABLE 3.1 ■ Phases of CML

CP	AP: Defined According to Modified MD Anderson Cancer Center Criteria	BP: defined According to International Bone Marrow Transplant Registry
No features of accelerated or blast phase	Peripheral blood myeloblasts ≥15% and <30%, peripheral blood myeloblasts and promyelocytes combined ≥30%, peripheral blood basophils ≥20%, platelets <100,000 unrelated to therapy, and additional clonal cytogenetic abnormalities in Ph+ cells.	Peripheral blood or bone marrow blasts ≥30%, extramedullary infiltrates of leukemic cells.

AP, accelerated phase; BP, blast phase; CML, chronic myelogenous leukemia; CP, chronic phase.

SIGNS AND SYMPTOMS

1. What is the classic presentation of CML?

- Asymptomatic neutrophilia (± left shift) on routine complete blood count (CBC), gradual onset of fatigue, weight loss, night sweats, splenomegaly, early satiety, gout, and leukocytosis

2. Are infections rare or common at presentation?

- Rare, because neutrophil function is preserved.

3. What is a typical CBC on presentation?

- Leukocytosis (20,000 to as high as 700,000) with left shift and circulating myeloblasts, myelocytes, metamyelocytes, and band forms
- Basophilia (± eosinophilia): a hallmark feature of CML
- Mild normochromic, normocytic anemia
- Normal or elevated platelet count

PROGNOSTIC FACTORS

1. What are two important poor prognostic factors?

- Disease status at diagnosis, with accelerated and blast phases (AP and BP) having poorer prognosis compared to chronic-phase disease.
- Failure to achieve (or loss of) hematologic, cytogenetic, and molecular responses (see Table 3.2)

2. What prognostic factors at diagnosis are associated with worse outcomes in CML?

- Age, spleen size, platelet count, and blast percentage in the peripheral blood (all included in the Sokal risk assessment score). Additionally, peripheral blood basophil and eosinophil percentages have prognostic values in the Hasford scoring system.

TREATMENT

1. How is newly diagnosed CML in chronic phase treated?

- Tyrosine kinase inhibitor (TKI) therapy: nilotinib (300 mg BID), dasatinib (100 mg daily), imatinib (400 mg daily), and bosutinib (400 mg daily) are the four Food and Drug Administration (FDA)-approved TKIs for first-line treatment of chronic phase CML.
- Consider hydroxyurea for patients with white blood cell (WBC) count greater than 100,000 (only temporarily until WBC goes down)
- Addition of allopurinol 300 mg daily until blood counts normalize

2. What should be taken into consideration when selecting one of the four TKIs (dasatinib, nilotinib, imatinib, or bosutinib) in the first-line treatment of chronic-phase CML?

- Sokal and Hasford prognostic scores: a second-generation TKI (nilotinib, dasatinib, or bosutinib) rather than imatinib is recommended in patients with intermediate- or high-risk scores. In patients with low-risk score, imatinib or one of the three second generation TKIs are acceptable options.
- Side effects of the different TKIs (see following Questions 3–6)
- Patient comorbidities
- Patient preference and cost/insurance coverage

3. What are some characteristic toxicities associated with nilotinib?

- QT prolongation, gastrointestinal (GI) upset, pancreatitis, hyperglycemia, hypercholesterolemia, liver toxicity
- Patients taking nilotinib also have increased risk of arterial adverse vascular events such as peripheral arterial occlusive disease.
- Nilotinib is the only TKI that needs to be taken twice a day. Patients cannot have PO intake for 2 hours before or 1 hour after each dose of nilotinib.

4. What are some characteristic toxicities associated with dasatinib?

- QT prolongation, thrombocytopenia, gastroesophageal reflux disease (GERD), pleural or pericardial effusion, bleeding from platelet dysfunction, pulmonary hypertension

5. What are some characteristic toxicities associated with imatinib?

- Skin rash, muscle cramps, diarrhea, periorbital swelling, edema, liver function test (LFT) abnormalities, hypophosphatemia, QT prolongation.

6. What are some characteristic toxicities associated with bosutinib?

- Diarrhea, nausea/vomiting, hepatotoxicity, rash, low incidence of pleural effusion, vascular events, and cardiac toxicity. In contrast to other TKIs, bosutinib has minimal QT prolongation.

7. Based on the toxicities of the different TKIs, which of the four TKIs approved in the first-line treatment setting (imatinib, dasatinib, nilotinib, bosutinib) should be avoided in the following conditions?

- History of pancreatitis: avoid nilotinib
- History of pericardial/pleural disease: avoid dasatinib
- History of (or significant risk factors for) arterial thrombotic events: avoid nilotinib
- Patients on anticoagulants: avoid dasatinib

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- Patient with pulmonary hypertension: avoid dasatinib
- Patients who are not able to fast for 3 hours twice a day (2 hours before and 1 hour after each dose of medication): avoid nilotinib
- History of irritable bowel syndrome or inflammatory bowel disease: consider alternative to bosutinib (due to diarrhea), although not strict contraindication

8. What are the treatment response goals and treatment failure criteria for CML patients treated with first-line TKIs?

TABLE 3.2 ■ Treatment Response Goals and Treatment Failure Criteria for CML Patients

Goal	Definition	Optimal Response	Treatment Failure*	Recommended Monitoring
Hematologic response	**CHR:** Normalization of counts with platelet count <450,000 and WBC <10,000, no peripheral blood myelocytes, promyelocytes, or blasts, no signs and symptoms of disease with resolution of palpable spleen	CHR by 3 months	No CHR by 3 months	CBC: every week for first 6 wks, then every 2 wks until CHR, then every 3 months
CyR	**Minor:** Ph+ cells 36%–65% **Partial (PCyR):** Ph+ cells 1%–35% **Complete (CCyR):** Ph+ cells 0%	At least PCyR at 3 months, and CCyR at 6 months	No PCyR at 6 months, no CCyR at 12 months	BM cytogenetics: at diagnosis; at 3 and 6 months if qPCR is not available; at 12 months if no CCyR documented prior or no MMR; if there is a 1 log increase in BCR-ABL transcript with loss of MMR

Goal	Definition	Optimal Response	Treatment Failure*	Recommended Monitoring
MR	**Major (MMR):** BCR-ABL1 (IS) ≤0.1% or ≥3-log reduction in BCR-ABL1 mRNA from baseline **Complete:** BCR-ABL1 transcripts undetectable in a lab where PCR sensitivity of at least 4.5 logs below standardized baseline	BCR-ABL ≤10% at 3 and 6 months, ≤1% at 12 months	BCR-ABL >10% at 6 months, BCR-ABL >1% at 15 months. One log increase in BCR-ABL transcript with loss of MMR is an indication for BM biopsy	qPCR: every 3 months until 2 y after either CCyR or BCR-ABL ≤1%, then every 3–6 months; perform mutational analysis only if response is suboptimal or if failure

*Treatment failure also includes loss of CHR or CCyR, and clonal chromosomal abnormalities.

BM, bone marrow; CBC, complete blood count; CCyR, complete cytogenetic response; CHR, complete hematologic response; CML, chronic myelogenous leukemia; MR, molecular response; MMR, measles, mumps, and rubella; PCyR, partial cytogenetic response; qPCR, quantitative polymerase chain reaction.

9. What is a practical approach to monitor chronic-phase CML after first-line TKI therapy?

- CBC every 1 to 2 weeks until complete hematologic response (CHR) then every 3 months. At 3 months: if no CHR, then this is treatment failure, and patients need to be treated as such. For patients in CHR by 3 months, further monitoring is as follows:
- At 3 months, perform quantitative polymerase chain reaction (qPCR; or BM cytogenetics if qPCR is not available):
  - If BCR-ABL transcripts ≤10% (or if partial cytogenetic response [PCyR] is achieved), this is optimal response. Continue the same treatment and monitor qPCR every 3 months.
  - If BCR-ABL transcripts >10% (or if no PCyR), this is suboptimal response, but not treatment failure. Evaluate for compliance, drug interactions, and check for ABL kinase mutation.
    - If patient was on imatinib, consider switching to second-generation TKI (recommended) or increasing the imatinib dose to a maximum of 800 mg a day if not a candidate for the second-generation TKIs. Consider evaluation for allogeneic stem cell transplant (ASCT).
    - If patient was on a second-generation TKI, consider switching to another second-generation TKI or keeping the same course. Do not switch from second-generation TKI to imatinib. Consider evaluation for ASCT.

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- At 6 months: perform qPCR (or BM cytogenetics if qPCR is not available):
  - BCR-ABL transcripts ≤10% constitutes optimal response.
  - If BCR-ABL transcripts ≤10% (or if PCyR is achieved), continue the same treatment and monitor qPCR in 3 months if available (or BM biopsy).
  - If BCR-ABL transcripts >10% (or if no PCyR), this is treatment failure.
- At 12 months, perform qPCR (or BM cytogenetics if qPCR is not available):
  - If BCR-ABL transcripts ≤1% (or if complete cytogenetic response [CCyR] is achieved), continue same treatment. Monitor qPCR every 3 months for 2 years post-CCyR (or post-BCR-ABL transcripts ≤1%) then every 3 to 6 months.
  - If BCR-ABL transcripts >1% to 10%: This represents a suboptimal response, but not necessarily treatment failure. Again, evaluate for patient compliance and possible drug–drug interactions. Consider ABL-kinase mutation testing and consider a BM biopsy to assess cytogenetics. Switching to an alternative TKI and evaluation for ASCT can also be considered.
    - If BCR-ABL transcripts >10%, this is treatment failure. Switch to an alternate TKI (see Question 2) and evaluate for ASCT.
- At 15 months, perform qPCR. If BCR-ABL transcripts >1%, this is treatment failure.
- Despite the ease of PCR monitoring, BM biopsy is typically still recommended at diagnosis, to document CCyR, and if there is suspicion of loss of response.

10. What are the management options for patients with TKI intolerance?

- Patients with intolerance to one TKI can be switched to one of the other TKIs approved in first-line treatment. An additional option is ponatinib, a third-generation TKI, FDA-approved for patients with a T315I ABL kinase mutation or for patients with resistance/intolerance to other TKIs.

11. What are the management options for patients with failure to first-line TKI therapy?

- Evaluate for compliance and drug interactions.
- Test for *ABL* kinase mutations to help guide the choice of the second-line TKI (see Question 2): approximately 50% of patients with treatment failure have mutations in the *ABL* kinase.
- If no mutations that guide therapy is identified, patients who received imatinib in the first line, switching to any second-generation TKI is appropriate (bosutinib, dasatinib, or nilotinib). For those who received a second-generation TKI as initial therapy, another second-generation TKI or ponatinib can be considered. Patients who initially received a second-generation TKI should not be switched to imatinib.
- Third-line treatment options include any of the remaining second-generation TKIs, ponatinib, and ASCT. Further options for patients not eligible for ASCT include ponatinib, omacetaxine, and clinical trials.
- Evaluate for ASCT (indications for ASCT are included in Question 15).
- Other possibilities include clinical trials, interferon (INF)-alpha.

12. What *ABL* kinase mutation confers resistance to all first- and second-generation TKIs: imatinib, nilotinib, dasatinib, and bosutinib?

- *T315I* mutation
- Patients with treatment failure due to *T315I* mutation should be treated with ponatinib. ASCT should be considered based on clinical context. Omacetaxine can be considered as a less favorable alternative to ponatinib.

13. What *ABL* kinase mutations help decide the choice of the second-line TKI therapy?

- Patients without the *T315I* can be switched to a second-generation TKI (dasatinib, nilotinib, or bosutinib).
- Mutations associated with resistance to nilotinib include: *Y253H, E255K/V, F359C/V/I, G250E*
- Mutations associated with resistance to dasatinib include: *F315A, F317L/V/I/C,* and *V299L*
- ABL kinase mutations conferring resistance to bosutinib include: *V299L, G250E*, or *F317L*

14. What are some characteristic toxicities associated with ponatinib?

- Arterial thrombotic events, heart failure, hepatotoxicity, QT prolongation, pancreatitis, fluid retention

15. What is the role of ASCT in CML?

- Reserved for patients with chronic phase CML that is resistant to sequential TKIs or who are intolerant of all TKIs.
- ASCT should be prioritized in patients with low probability of response to subsequent TKI therapy (patients with no cytogenetic response to imatinib or other second-generation TKIs or with mutations predicting low sensitivity to available second or third-generation TKIs).
- Indicated for AP or BP after best response to TKI is achieved (regardless of the depth of response) including those who progress to AP or BP from chronic phase.

16. How successful is ASCT for CML?

- Long-term cure rate of approximately 65% for patients transplanted in chronic phase
- Transplant-related mortality and relapse are higher in patients transplanted for AP or BP.

17. How should AP CML be treated?

- Patients in AP CML should be treated with dasatinib 140 mg daily, nilotinib 400 mg BID, bosutinib 500 mg daily, or ponatinib 45 mg daily (and less favorably imatinib 600 mg PO daily), followed by ASCT (if eligible) after best response is achieved with the TKI. Patients with optimal/deep response to the TKI might choose to be monitored very carefully with deferring ASCT until the first sign of disease progression. This relapse requires another TKI followed by ASCT.
- Omacetaxine can also be considered in patients with AP CML that is resistant to multiple TKIs. Additionally, omacetaxine can be used in patients with *T315I ABL* mutations as a less favorable option than ponatinib or in patients who are not candidates for ponatinib.

18. How are patients with BP CML treated?

- Patients with BP CML should undergo *ABL* kinase mutation analysis to help select the best TKI. All patients should be evaluated for ASCT.
- Patients with lymphoid blast crisis are treated with combination chemotherapy (ALL-type regimen) with second-generation TKI, followed by ASCT. Another option includes second-generation TKI and steroids, also followed by ASCT.

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- Myeloid blast crisis does not typically respond well to AML induction regimens. Patients with de novo myeloid blast crisis CML are treated with a second-generation TKI without chemotherapy until best response, followed by ASCT. Patients with blast crisis CML that develops on TKI therapy are treated with combination chemotherapy + more potent TKI, followed by ASCT.

MYELOPROLIFERATIVE NEOPLASMS (GENERAL)

1. What characterizes a myeloproliferative neoplasm (MPN)?
- Clonal hematopoietic stem cell disease with overproduction of one or more blood cell lines
- Normal maturation with effective hematopoiesis and extramedullary hematopoiesis
- Risk for leukemic transformation

2. What are the eight MPNs recognized by the World Health Organization (WHO) in 2016?
- BCR-ABL1-positive CML
- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Primary myelofibrosis (PMF)
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia, not otherwise specified
- MPNs, unclassifiable

3. What is the most common gene mutated in PV, ET, and PMF?
- *JAK2*

4. What is *JAK2*'s normal function?
- Tyrosine kinase, which is critical in intracellular signaling for the erythropoietin (EPO), thrombopoietin, interleukin-3, granulocyte colony-stimulating factor (G-CSF), and granulocyte macrophage colony-stimulating factor (GM-CSF) receptors

5. What *JAK2* mutations are tested for in MPN?
- *JAK2* V617F (most common) and *JAK2* exon 12 mutations
- *JAK2* V617F mutation causes constitutive activation of downstream messengers through the JAK–STAT, PI3K, and AKT pathways

6. In which MPN is *JAK2* mutation most prevalent?
- PV (98%–99%), ET (~60%), PMF (~55%)

7. Name two additional frequently mutated genes in ET and PMF?
- *MPL* (mutation in the transmembrane domain of the thrombopoietin receptor)
- *CALR*
- *JAK2*, *CALR*, and *MPL* mutations are generally mutually exclusive

8. What thrombophilic conditions should raise the suspicion of a *JAK2* mutation?
- Budd–Chiari syndrome
- Mesenteric venous thrombosis

9. Which gene is characteristically mutated in chronic neutrophilic leukemia?
- ***CSF3R***

Polycythemia Vera

EPIDEMIOLOGY

1. What is the median age at diagnosis of PV?

- Approximately 60 years old, but occurs in all age groups

2. What is the median survival of PV patients?

- Median survival is approximately 14 years (and ~24 years in patients <60 years).

3. What are prognostic factors for worse survival in PV?

- Risk factors predicting worsening survival in PV are age >57 (with age >67 being even higher risk), leukocytosis (WBC >15,000), venous thrombosis, and abnormal karyotype.

4. What are the risks of transformation to myelofibrosis (MF) and risk of leukemic transformation in PV?

- Transformation to MF occurs in 12% to 21% of PV patients.
- Risk of transformation to AML: ~8% at 20 years.

5. What characterizes PV pathophysiologically?

- Growth factor (EPO)–independent proliferation of erythroid cells, producing an elevated red cell mass.

DIAGNOSTIC CRITERIA

1. What are the WHO diagnostic criteria for PV?

TABLE 3.3 ■ 2017 WHO Criteria for PV

	2017 WHO Criteria*
Major	1. Hgb >16.5 g/dL (men) or Hgb >16.0 g/dL (women), OR Hct >49% in men or >48% in women, OR increased red cell mass.
	2. Bone marrow biopsy showing hypercellularity for age with trilineage growth and pleomorphic, mature megakaryocytes.
	3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation
Minor	1. Subnormal EPO level

*Diagnosis requires all three major criteria or first two major criteria and the minor criterion. Bone marrow biopsy may not be necessary if Hb >18.5 (or Hct >55.5) in men or if Hb >16.5 (or Hct >49.5) in women, if all other major and minor criteria are met.

EPO, erythropoietin; H**ct,** hematocrit; Hgb, hemoglobin; PV, polycythemia vera; WHO, World Health Organization.

2. What are the features of PV that help distinguish it from secondary polycythemia?

- Splenomegaly
- Leukocytosis
- Thrombocytosis
- Low EPO level

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- Panhyperplasia in BM
- Normal arterial oxygen saturation
- Increased vitamin B12 level

SIGNS AND SYMPTOMS

1. What are the common presenting signs/symptoms in patients with PV?

- Incidental polycythemia (± thrombocytosis ± leukocytosis) on CBC, pruritus aggravated by hot shower, erythromelalgia, gout, kidney stones, palpable splenomegaly (50%–70%), early satiety, joint pain, thrombosis symptoms (arterial or venous), and neurologic symptoms such as headache and confusion

TREATMENT

1. Which patients should be treated with aspirin?

- All patients with PV who do not have a contraindication should be treated with aspirin 81 mg daily.
- Additionally, all patients should have their cardiovascular risk factors strictly controlled.

2. In addition to aspirin, what are the treatment options for patients with PV, in the first-line setting?

- Phlebotomy and cytoreduction with either hydroxyurea or peginterferon-alpha-2a.

3. What is the goal hematocrit when the patient is getting phlebotomies or cytoreduction?

- The target hematocrit is always less than 45% in PV, regardless of the treatment modality.

4. How do we choose between phlebotomy alone versus a cytoreductive agent to achieve the hematocrit goal of <45%?

- Hydroxyurea or peginterferon-alpha-2a should be used in these situations:
  - Patients older ≥60 years of age
  - Patients with history of thromboembolism (consider in patients with strong risk factors for thromboembolic disease)
  - Patients with acquired von Willebrand disease (VWD) should also be considered for cytoreduction. Always check von Willebrand factor (VWF) activity if platelets are >1 million before administering aspirin (see Essential Thrombocythemia section).
  - Additional potential indications for cytoreductive therapy include frequent need for phlebotomy with poor tolerance of phlebotomy, symptomatic or progressive splenomegaly, symptomatic thrombocytosis, progressive leukocytosis, progressive disease-related symptoms (e.g., pruritus, night sweats, fatigue), disease-related major bleeding.
- Patients who do not have any of these criteria should be treated with aspirin and phlebotomies as needed (to keep hematocrit <45%).

5. When is peginterferon-alpha-2a considered instead of hydroxyurea?

- Hydroxyurea is the most commonly used (and generally preferred) cytoreductive agent in first line therapy for PV.

- Peginterferon-alpha-2a should be considered for younger patients in whom long-term exposure to hydroxyurea may confer a risk of secondary malignancy, in pregnant patients in need of cytoreductive therapy (risk category C), or in patients who defer hydroxyurea. Of note, it is debatable whether hydroxyurea is leukemogenic with recent data suggesting that the leukemia risk does not appear to be increased when hydroxyurea is used as a single agent.

6. In addition to aspirin, which therapy in PV has demonstrated the greatest reduction in thrombotic events?

- Hydroxyurea

7. What are the indications to change the cytoreductive agent to a second-line agent?

- Intolerance or resistance for first-line cytoreductive agent
- New thrombosis or disease-related major bleeding
- Frequent need for phlebotomy with poor tolerance of phlebotomy
- Symptomatic or progressive splenomegaly
- Symptomatic thrombocytosis
- Progressive leukocytosis
- Progressive disease-related symptoms (e.g., pruritus, night sweats, fatigue)

8. What are second-line treatment options for PV?

- Ruxolitinib (particularly if significant splenomegaly or constitutional symptoms)
- INF-alpha or peginterferon-alpha (if not previously used)
- Hydroxyurea (if not previously used)
- Clinical trial
- Busulfan (least favorable option)

9. Is allogeneic stem cell transplantation indicated for PV?

- Allogeneic stem cell transplantation is the only curative option, but is almost never indicated in PV, unless the disease progresses to MF or acute leukemia (for treatment of post-PV MF, please refer to the Myelofibrosis section)

Essential Thrombocythemia

EPIDEMIOLOGY

1. What is the typical age at presentation for ET?

- Age of presentation has bimodal distribution: one peak around age 30 with a second (larger) peak at age 50 to 60 years
- Women to men ratio is 1.5 to 2:1 in the early peak.

2. What is the median survival in ET patients?

- Median survival is approximately 20 years (and ~33 years in patients <60 years of age); in some reports, survival is comparable to that of the age-matched population.

3. What percent of ET patients have mutations in *JAK2*, *CALR*, or *MPL*?

- *JAK2* mutation (~60% of patients)
- *CALR* mutation (~22% of patients)
- *MPL* mutation (~3% of patients)

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4. What are prognostic factors for worse survival in ET?

- Risk factors predicting worse survival in ET are age >60 years, leukocytosis (WBC >11,000), and history of thrombosis

5. What percent of ET patients transform to MF of acute leukemia?

- Risk of transformation to MF: ~5% to 10% at 15 years.
- Risk of transformation to AML: ~5% at 20 years.

6. Does *CALR* mutation result in a similar risk compared to *JAK2* mutations in ET?

- Patients with *CALR* mutations have a lower risk of thrombosis compared to patients with *JAK2*-mutated ET.
- Patients with *CALR* mutations appear to have a comparable risk of transformation to MF or AML compared to patients with *JAK2*-mutated ET.

DIAGNOSTIC CRITERIA

1. What are the WHO diagnostic criteria for ET?

TABLE 3.4 ■ 2017 WHO Criteria for ET

	2017 WHO Criteria*
Major criteria	1. Platelet count >450,000
	2. Bone marrow showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged megakaryocytes with hyperlobulated nuclei. No significant increase in granulopoiesis or erythropoiesis and no left shift. Very rarely, minor (grade 1) increase in reticulin fibers can be found.
	3. Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasms
	4. Presence of *JAK2*, *CALR*, or *MPL* mutation.
Minor criteria	Presence of a clonal marker or absence of evidence for reactive thrombocytosis.

*Diagnosis requires four major criteria or the first three major criteria and minor criterion.

CML, chronic myelogenous leukemia; ET, essential thrombocythemia; MDS, myelodysplastic syndrome; PMF, primary myelofibrosis; PV, polycythemia vera; WHO, World Health Organization.

SIGNS AND SYMPTOMS

1. What are the most common presenting signs/symptoms in ET?

- Asymptomatic (50%)
- Vasomotor symptoms: visual changes, lightheadedness, headaches, palpitations, typical/atypical chest pain, erythromelalgia, livedo reticularis, acral paresthesias
- Palpable splenomegaly and related symptoms: early satiety or left upper quadrant abdominal pain
- Thrombosis (~15% at presentation)

2. In addition to the thrombosis risk and the risk of transformation to MF and AML, what are other complications of ET?

- Major hemorrhage (5%–10%) from acquired VWD
- Recurrent first trimester abortions

TREATMENT

1. How are patients in the different risk categories treated?

- Patients with very-low-risk disease (age ≤60, no *JAK2* mutation, and no prior history of thrombosis) and patients with low-risk disease (age ≤60 with *JAK2* mutation, and no prior history of thrombosis) are treated with aspirin 81 mg PO daily or observation. Of note, in one report, aspirin use didn't affect the risk of thrombosis in patients with *CALR*-mutated low-risk ET but was associated with higher bleeding risk. The latter has not been confirmed in a prospective clinical trial.
- Patients with intermediate-risk disease (age >60 with no *JAK2* mutation, and no prior history of thrombosis): aspirin 81 mg PO daily.
- Patients with high-risk disease (age >60 with *JAK2* mutation or history of thrombosis at any age): aspirin 81 mg PO daily + cytoreduction.
- All patients should have their cardiovascular risk factors monitored and strictly managed.
- Potential additional indications for cytoreductive therapy regardless of the ET risk group include symptomatic or progressive splenomegaly, symptomatic thrombocytosis, progressive leukocytosis, progressive disease-related symptoms (e.g., pruritus, night sweats, fatigue), disease-related major bleeding, vasomotor/microvascular disturbances not responsive to aspirin (e.g., headaches, chest pain, erythromelalgia).

2. In what situations should aspirin be avoided in ET?

- Aspirin should be avoided in patients with acquired VWD.
- In patients with platelets ≥1 million/μL, check VWD ristocetin cofactor activity before starting aspirin. Patients with VWD ristocetin activity ≤30% are at increased risk of bleeding and should undergo platelet cytoreduction to result in VWD ristocetin activity ≥30% prior to starting aspirin.

3. What are the first-line cytoreductive options in ET?

- Hydroxyurea (the most commonly used and preferred first-line treatment in ET)
- INF-alpha (or peginterferon-alpha) could be considered for younger patients, or in pregnant patients who require cytoreductive therapy (risk category C), or in patients who defer hydroxyurea
- Anagrelide

4. When is plateletpheresis indicated in ET?

- Plateletpheresis is indicated in patients with significantly elevated platelet counts in the setting of acute and serious thrombotic or hemorrhagic events (such as stroke, ischemic limb, significant hemorrhagic event due to acquired VWD).
- The effect of plateletpheresis on reducing platelet count is transient, and patient should be started at the same time on a cytoreductive agent.

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5. What are the indications to change the cytoreductive agent to a second line agent?

- Intolerance or resistance to first line cytoreductive agent
- New thrombosis, acquired VWD, or disease-related major bleeding
- Symptomatic or progressive splenomegaly
- Symptomatic thrombocytosis
- Progressive leucocytosis
- Progressive disease-related symptoms (e.g., pruritus, night sweats, fatigue)
- Vasomotor/microvascular disturbances not responsive to aspirin (e.g., headaches, chest pain, erythromelalgia)

6. What are second-line cytoreductive agents in ET?

- Hydroxyurea (if not previously used)
- INF-alpha (if not previously used)
- Anagrelide (if not previously used)
- Clinical trial
- Could consider ruxolitinib or busulfan (less favorable options than the ones given earlier)

7. What is the mechanism of action of anagrelide?

- Interferes with terminal differentiation of megakaryocytes

8. In what group of patients should anagrelide therapy be avoided and why?

- In those with cardiovascular comorbidities because it can cause fluid retention, palpitations, and pulmonary hypertension

9. Is allogeneic stem cell transplantation indicated for ET?

- Allogeneic stem cell transplantation is almost never indicated in ET, unless the disease progresses to MF or acute leukemia (for treatment of post-ET MF, please refer to the Myelofibrosis section).

Primary Myelofibrosis

EPIDEMIOLOGY

1. In addition to PMF, which two hematologic disorders most commonly lead to secondary MF?

- MF could be a primary disease (PMF) or secondary to ET or PV.
- Fibrosis in the BM could result from other etiologies such as hairy cell leukemia, metastatic solid tumor to the BM, autoimmune or chronic inflammatory conditions, and so on.

2. What is the median survival of patients with PMF?

- Median survival: ~6 years (but highly variable)

DIAGNOSTIC CRITERIA

1. What are the WHO 2017 diagnostic criteria for PMF?

TABLE 3.5 ■ 2017 WHO Criteria for PMF

	Prefibrotic PMF*	PMF†
Major*	1. Megakaryocyte proliferation and atypia without reticulin fibrosis > grade 1. Increased age-adjusted BM cellularity, granulocytic proliferation, and decreased erythropoiesis.	1. Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis (grades 2–3 on 0–3 scale).
	2. Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasms	2. Not meeting WHO criteria for CML, PV, ET, MDS, or other myeloid neoplasms
	3. Demonstration of *JAK2*, *CALR*, or *MPL* mutation or presence of another clonal marker or absence of minor reactive reticulin fibrosis.	3. Demonstration of *JAK2*, *CALR*, or *MPL* mutation or another clonal marker or no evidence of reactive myelofibrosis.
Minor‡	1. Anemia unrelated to medical comorbidities	1. Leukoerythroblastosis (absent in prefibrotic PMF)
	2. Leukocytosis ≥11 × 10^9/L	2. Increased serum LDH
	3. LDH above upper limit of normal	3. Anemia
	4. Palpable splenomegaly	4. Palpable splenomegaly
		5. Leukocytosis ≥ 11 × 10^9/L

*Diagnosis requires all three major criteria and one minor criterion.

†Diagnosis requires three major criteria and at least one minor criterion.

‡Confirmed on two sequential measurements.

BM, bone marrow; CML, chronic myelogenous leukemia; ET, essential thrombocythemia; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; PV, polycythemia vera; WHO, World Health Organization.

2. What are the three most commonly mutated genes in PMF?

- *JAK2* (~55% of patients)
- *CALR* (~27% of patients)
- *MPL* W515L (~7% of patients)
- ~10% of patients with PMF do not have any of the above mutations

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3. What are the diagnostic criteria of post-PV and post-ET MF?

TABLE 3.6 ■ Diagnostic Criteria of Post-PV and Post-ET Myelofibrosis

	Post-PV Myelofibrosis*	Post-ET Myelofibrosis†
Major*	1. Documentation of a prior diagnosis of PV	1. Documentation of a prior diagnosis of ET
	2. Bone marrow fibrosis (grade 2–3 on 0–3 scale or grade 3–4 on 0–4 scale)	2. Bone marrow fibrosis (grade 2–3 on 0–3 scale or grade 3–4 on 0–4 scale)
Minor	1. Anemia or lack of requirement of phlebotomies in absence of cytoreductive therapy	1. Anemia and ≥2 g/dL decrease from baseline Hgb
	2. Leukoerythroblastosis	2. Leukoerythroblastosis
	3. New splenomegaly or increase in palpable splenomegaly of ≥5 cm	3. New splenomegaly or increase in palpable splenomegaly of ≥5 cm
	4. One or more of these constitutional symptoms: unexplained fever (>37.5°C, night sweats, or >10% weight loss in 6 months)	4. One or more of these constitutional symptoms: unexplained fever (>37.5°C, night sweats, or >10% weight loss in 6 months)
		5. Increased LDH

*For diagnosis of post-PV myelofibrosis: two major and two minor criteria are required.

†For diagnosis of post-ET myelofibrosis: two major and two minor criteria are required.

ET, essential thrombocythemia; Hgb, hemoglobin; LDH, lactate dehydrogenase; PV, polycythemia vera.

SIGNS AND SYMPTOMS

1. Name several common presenting symptoms of PMF?

- Fatigue, anemia, abdominal discomfort and early satiety (from splenomegaly), fever, night sweats, weight loss, bone pain, pruritus, complications of portal hypertension (such as variceal bleed, ascites)

2. What are the two most common physical exam findings in patients with PMF?

- Palpable splenomegaly and hepatomegaly.

3. What does the classic peripheral blood smear of PMF show?

- Leukoerythroblastosis (immature cells of the granulocytic series and nucleated red blood cells [RBCs]) and teardrop-shaped RBCs (seen in fibrotic PMF).

PROGNOSTIC FACTORS

1. What are the factors associated with decreased survival in PMF based on the Dynamic International Prognostic Scoring System (DIPSS) plus?

- Age >65 years
- Presence of constitutional symptoms

- Anemia, hemoglobin (Hgb) ≤10 g/dL
- Leukocytosis, WBC greater than 25,000 × 106/L
- Presence of ≥1% circulating peripheral blasts
- Presence of unfavorable karyotype (complex karyotype, +8, −7/7q−, i(17q), inv(3), −5/5q, 12p−, or 11q23 rearrangement)
- Platelet count <100,000/μL
- RBC transfusion need (patients with RBC transfusion need will automatically get two points because their Hgb would be <10 g/dL)

2. How are patients with PMF divided into risk groups? What is the median survival in each risk group?

- Risk factors from the prior questions are added up:
  - Low risk: zero risk factors; median survival is approximately 15.4 years
  - Intermediate-1 risk: one risk factor; median survival is approximately 6.5 years
  - Intermediate-2 risk: two or three risk factors; median survival is approximately 2.9 years
  - High risk: at least four of the aforementioned risk factors; median survival is approximately 1.3 years

TREATMENT

1. What is the goal of treatment in PMF?

- Palliation in most cases, except in patients who are candidates for ASCT, where cure might be attained (see below)

2. How do you treat patients with low and intermediate-1-risk PMF?

- The mainstay of therapy is supportive care, symptom control, and improving quality of life.
- Assess symptom burden using myeloproliferative neoplasm symptom assessment form total symptom score (MPN-SAF TSS).
  - Asymptomatic patients: observation is reasonable
  - The treatment of symptomatic patients is highly individualized. Treatment options include ruxolitinib, INF (or peginterferon)-alpha, hydroxyurea, or a clinical trial. ASCT could be considered in patients with intermediate-1-risk PMF who have low platelet count, complex karyotype, or high-risk mutations.
  - Symptomatic splenomegaly
    - Hydroxyurea or ruxolitinib is reasonable as first-line therapy for symptomatic splenomegaly. The response of splenomegaly to ruxolitinib is superior to the response to hydroxyurea. Other less favorable options include splenectomy and splenic irradiation. Splenectomy is associated with significant risks, and the decision to proceed with splenectomy should be individualized. The risks of splenic irradiation include profound cytopenias and the benefit of this modality is only transient.
  - Cytoreduction in patients without significant/symptomatic splenomegaly
    - Hydroxyurea often considered first line for cytoreduction in these patients if cytoreduction is felt to be beneficial.
  - Patients with symptomatic anemia have generally higher risk disease (because symptomatic anemia is generally an indication for RBC transfusion, and transfusion requirement by itself puts patients immediately in at least the intermediate risk 2 group). See treatment for symptomatic anemia in the following question.

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3. How do you treat patients with intermediate-2- or high-risk PMF?

- Transplant candidates should undergo allogeneic stem cell transplantation.
- Nontransplant candidates with platelets ≥50K can be treated with ruxolitinib (certainly if symptomatic) or on a clinical trial. Fedratinib is generally reserved for patients who fail to respond or lose response to ruxolitinib. Patients with platelets <50K should be treated on a clinical trial.
- Nontransplant candidates with symptomatic anemia only should be worked up for other etiologies of anemia. If no other cause is identified, EPO levels should be obtained.
  - If EPO is <500 mU/mL, patients can be treated with an erythropoiesis-stimulating agent or on a clinical trial. Avoid erythropoiesis-stimulating agents in patients with significant splenomegaly, because they might worsen the splenomegaly.
  - If EPO is ≥500 mU/mL, the options include danazol, lenalidomide, or thalidomide ± prednisone, or a clinical trial. Use lenalidomide particularly in the presence of del 5q. Splenectomy can be considered in refractory cases with significant splenomegaly; however, this decision should not be taken lightly because of the morbidity and mortality associated with the procedure (~10% perisurgical mortality) and because a subset of patients develop compensatory hepatomegaly, some of whom might die of liver failure.

4. What is a contraindication to treatment with fedratinib or ruxolitinib?

- Platelet count $<50 \times 10^8$/L is a contraindication for both ruxolitinib and fedratinib.
- For platelet counts between 50 and 200×10^8/L, ruxolitinib (but not fedratinib) requires dose reduction.
- Fedratinib has been associated with serious and fatal encephalopathy (Wernicke's encephalopathy). Thiamine (vitamin B1) and nutritional status should be assessed in all patients before starting fedratinib and periodically. If a patient is deficient in thiamine, thiamine repletion should be confirmed before starting fedratinib.

5. What are some notable complications of ruxolitinib and fedratinib?

- Ruxolitinib toxicities: cytopenias; lipid elevation; infections including tuberculosis (TB), increase in hepatitis B viral load, PML, and herpes zoster; nonmelanoma skin cancer.
- Fedratinib toxicities: Wernicke's encephalopathy (as above); cytopenias; nausea and vomiting; hepatic toxicity; amylase and lipase elevation.
- Both medications can result in a cytokine storm if stopped immediately without a taper. Therefore, a slow taper is recommended when these medications need to be stopped.

6. How is MF-associated pulmonary hypertension diagnosed and treated?

- Diagnosis is confirmed by a technetium 99m sulfur colloid scintigraphy.
- Single fraction whole lung radiation (100 cGy) has been shown to be effective.

HYPEREOSINOPHILIC SYNDROMES

- Diagnosis: >1,500 eosinophils/mm^3 at least 6 months (r/o infections, parasites).
- Affects skin, lungs, GI tract, and nervous system.

- Most common mutation: FIP1L1/PDGFRA l; treatment if present: imatinib 100 mg daily.
- If translocation 5q33 leading to PDGFRB, treat with imatinib; increase to 400 mg/d if no response.

SYSTEMIC MASTOCYTOSIS

- Accumulation of abnormal mast cells in bone, liver, and spleen
- Symptoms: bone loss, flushing, headache, increased LFTs, cytopenias, and diarrhea
- BM biopsy: >20% mast cells; 90% harbor KITD816V mutation; CD 117+, CD25+
- Treatment
  - Indolent: H1/H2 blockers, steroids, cromolyn
  - Advanced or aggressive: midostaurin, INF-alpha, cladribine
  - May use Imatinib if NO presence of KITD816V mutation

QUESTIONS

1. A 70-year-old woman with a past medical history notable for hypertension, diabetes, and stroke is found to have leukocytosis (white blood cell [WBC] count of 25,000) on routine labs. Hemoglobin is mildly reduced at 11.5 g/dL and platelet count is mildly elevated at 500,000. She notes some mild fatigue but is otherwise asymptomatic. Examination is notable for a spleen tip palpable 3 cm below the left costal margin. Further testing reveals BCR-ABL by fluorescence in situ hybridization (FISH) to be positive. You calculate her Sokal score, and she is found to be high risk.

What is the next best step in management?

A. Initiation of ponatinib
B. Initiation of imatinib
C. Initiation of nilotinib
D. Initiation of dasatinib

2. A 55-year-old otherwise healthy man has been following with you for chronic phase chronic myelogenous leukemia (CML) for over a year. At diagnosis, he was found to have low-risk disease according to the Sokal score, and was started on imatinib 400 mg daily. He tolerated the medication well and had achieved a major molecular response 9 months into therapy. At his last visit, his BCR-ABL1 polymerase chain reaction (PCR) has increased to 0.4% international scale (IS). He is compliant with imatinib and has not started any other new medication. A follow-up PCR noted that the transcript level has further increased to 1% IS. ABL-kinase domain mutation testing was performed, revealing a T315I mutation, and a bone marrow biopsy was repeated and was consistent with chronic phase CML.

What is the next step in the patient's treatment plan?

A. Increase imatinib dose from 400 to 800 mg daily
B. Discontinue imatinib and switch to dasatinib
C. Discontinue imatinib and switch to bosutinib
D. Discontinue imatinib and switch to nilotinib
E. Discontinue imatinib and switch to ponatinib

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3. A 62-year-old otherwise healthy woman presents to her local ED with fatigue and abdominal pain. A CT scan of her abdomen and pelvis reveals splenomegaly (15 cm) without any other abnormalities. Labs are obtained and a complete blood count (CBC) shows a white blood cell count (WBC) of 95,000 with basophilia (14%), hemoglobin of 10.2, and platelets of 121,000. No peripheral blasts are observed. A bone marrow biopsy is performed with cytogenetics showing the Philadelphia chromosome in 20 out of 20 cells as well as a loss of chromosome 7 in 8 out of the 20 cells. Polymerase chain reaction (PCR) testing is positive for p210 BCR-ABL above the limit of quantification on the international scale (IS).

What is the next best step in management?

A. Admit to hospital for cytotoxic chemotherapy
B. Initiate imatinib
C. Initiate a second-generation tyrosine kinase inhibitor (TKI)
D. Refer for consideration of allogeneic stem cell transplant
E. Both C and D

4. A 55-year-old woman is referred to hematology for evaluation of a hemoglobin of 16.8/hematocrit of 51% found on routine labs. White blood cell (WBC) and platelet counts are normal. Upon further questioning she reports minimal pruritus following hot baths but denies burning and erythema of her hands. Her past medical history is otherwise notable for mild hypertension and tobacco dependency. She denies any family history of hematologic disorders. There is no personal or family history of thrombosis. Physical examination is unremarkable.

What is the next best step in management?

A. Initiate *JAK2* inhibitor therapy and evaluate for etiology
B. Immediately phlebotomize and evaluate for etiology
C. Evaluate for etiology
D. Initiate hydroxyurea and evaluate for etiology

5. A 46-year-old man presents with polycythemia (hemoglobin 18.7, hematocrit 56%). He does not have a history of prior thromboembolic events. Workup demonstrated negative *JAK2* V617F mutation. Bone marrow biopsy demonstrated increased cellularity with panmyelosis and pleomorphic mature megakaryocytes. Erythropoietin (EPO) level is low.

How should this patient be managed?

A. Initiate *JAK2* inhibitor therapy
B. Aspirin and phlebotomy
C. Aspirin only
D. Observation and optimizing risk factors for thrombosis
E. Aspirin and hydroxyurea

6. A 22-year-old woman presented to the ED with 2 days of severe right upper quadrant pain. A complete blood count (CBC) was performed and was notable for a white blood cell (WBC) count 17,000, hemoglobin of 13.9, and platelets of 340,000. An additional laboratory workup was

notable for aspartate transaminase (AST) of 1,100 and alanine transaminase (ALT) of 1,400 as well as a mildly elevated alkaline phosphatase. A right upper quadrant ultrasound revealed an occlusive hepatic vein **thrombosis** without collateral blood flow. The patient is not taking any medications, has a body mass index (BMI) of 23, and has never smoked cigarettes. She has no personal or family history of thrombosis.

Which of the following molecular tests is recommended?

A. JAK2V617F testing
B. CALR testing
C. MPL testing
D. Prothrombin 20210 Gene mutation testing
E. Factor V Leiden testing

7. A 78-year-old man with a past medical history of diabetes, coronary artery disease, heart failure (ejection fraction 35%), and hypertension presents for evaluation of fatigue, night sweats, unintentional weight loss, left upper quadrant abdominal pain, and early satiety. The patient developed these symptoms gradually over the past 6 months. Physical exam is notable for splenomegaly (spleen tip palpated about 15 cm below the left costal margin). Labs revealed a white blood cell (WBC) count of 14,000 (2% circulating blasts), hemoglobin of 9 g/dL, and platelet count of 75,000. These are similar to labs drawn in his PCP's office 2 months ago. Peripheral smear is notable for teardrop cells. A bone marrow biopsy reveals megakaryocytic proliferation and atypia, with grade 2 fibrosis and cytogenetics demonstrating 46, XY, inv(3) in 20/20 analyzed cells. JAK2 V617F and exon 12 mutations are negative, as is MPL mutation. The patient has a CALR mutation identified. Infections are ruled out. The patient reports that fatigue and abdominal pain are limiting his ability to perform his activities of daily living.

What is the best management option for this patient?

A. Supportive care with transfusions as needed
B. Hydroxyurea
C. Ruxolitinib
D. Cytotoxic chemotherapy followed by allogeneic bone marrow transplantation

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ANSWERS

1. **D. Initiation of dasatinib.** The patient is high risk based on her Sokal score; therefore, outcomes are improved with a second-generation tyrosine kinase inhibitor (TKI; nilotinib, dasatinib, or bosutinib) compared to imatinib. She has a history of arterial events (as well as multiple risk factors for arterial thrombosis), making nilotinib a less desirable option. Ponatinib is also not considered a first-line therapy in the absence of intolerance or failure of other TKIs. Therefore, the best option for this patient is dasatinib.

2. **E. Discontinue imatinib and switch to ponatinib.** The T315I mutation confers resistance to all first and second-generation tyrosine kinase inhibitors (TKIs). Patients with treatment failure due to T315I mutation should be switched to ponatinib. If ponatinib is contraindicated due to its high rate of vascular complications including risk of arterial thrombosis, then omacetaxine can be considered as a less favorable alternative.

3. **E. Both C and D.** This patient has accelerated phase chronic myelogenous leukemia (CML) because there is a population of cells that have both the Philadelphia chromosome and an additional clonal cytogenetic abnormality (in this case deletion of chromosome seven in eight out of 20 analyzed cells). Due to their historically poor outcomes, patients with accelerated phase CML should be treated with a second-generation tyrosine kinase inhibitor (TKI) and referred for consideration for allogeneic stem cell transplant. Allogeneic stem cell transplant is usually performed after best response is obtained with a second-generation TKI.

4. **C. Evaluate for etiology.** Patients who present with elevated hematocrit should be evaluated for the etiology prior to initiation of therapy directed at the etiology. If the patient has polycythemia secondary to hypoxemia, for example, an acute reduction of the hemoglobin/hematocrit with phlebotomy might result in respiratory compromise.

5. **B. Aspirin and phlebotomy.** Patients who present with polycythemia and exhibit typical bone marrow abnormalities for polycythemia vera (PV), as well as low EPO level, have a diagnosis of PV. *JAK2* V617F mutation is present in most patients with PV, but approximately 5% to 7% of patients with PV have the *JAK2* exon 12 mutation instead, while ~1% of patients with PV do not have either *JAK2* V617F or *JAK2* exon 12 mutations. In these patients, the typical bone marrow findings coupled with a low EPO level establish the diagnosis. This patient is <60 years of age and has no prior history of thromboembolic events; therefore, he is categorized as low risk and should be treated with aspirin and PRN phlebotomy (goal hematocrit <45%), instead of aspirin and hydroxyurea.

6. **A. JAK2V617F testing.** The patient in this question is presenting with newly diagnosed Budd–Chiari syndrome in the absence of any identifiable risk factors for thrombosis. Both Budd–Chiari syndrome and mesenteric venous thrombosis without any identified provoking factors should prompt testing for a *JAK2V617F* mutation, even in the absence of any abnormalities on the CBC to suggest the presence of an undiagnosed

myeloproliferative neoplasm. *CALR* and *MPL* mutations are not associated with increased risk of hepatic vein thrombosis. Hypercoagulable testing with Prothrombin 20210 Gene mutation and Factor V Leiden testing is not indicated as it is unlikely to change management in this clinical situation. Other etiologies for Budd–Chiari include paroxysmal nocturnal hemoglobinuria, inflammatory bowel disease, among others.

7. **C. Ruxolitinib.** This patient meets criteria for higher risk (intermediate-2-/high-risk) PMF according to Dynamic International Prognostic Scoring System (DIPSS) plus risk calculator. He is not a candidate for allogeneic stem cell transplantation given his age and comorbidities. He has symptomatic splenomegaly and fatigue as well as a platelet count >50,000; therefore, he would benefit from ruxolitinib therapy (or fedratinib as less favorable first-line option) as opposed to supportive care alone or Hydrea.

ALGRAWANY

4 Myelodysplastic Syndrome

Charles E. Foucar, Dale Bixby, and Rami N. Khoriaty

EPIDEMIOLOGY

1. What is the median age at diagnosis for myelodysplastic syndrome (MDS)?

- Seventy to 75 years old

2. What is the incidence of MDS?

- Ten thousand to 15,000 new cases per year in the United States (likely an underestimation)

ETIOLOGY AND RISK FACTORS

1. What is the etiology of MDS?

- Exact etiology is uncertain
- Ninety percent of MDS cases arise de novo, 5% to 10% cases are therapy related and 1% to 2% of cases have an inherited genetic predisposition

2. What are the common risk factors for MDS?

- Older age (incidence rises exponentially with age)
- Male sex
- Exposure to chemotherapeutic agents (alkylating agents, anthracyclines, and other topoisomerase II inhibitors)
- Radiation exposure
- Exposure to benzene and other organic solvents
- Congenital disorders: Down syndrome, neurofibromatosis type 1, Fanconi anemia, congenital neutropenic disorders, dyskeratosis congenita, *GATA-2* mutations, and others

CLASSIFICATION

1. What are the subtypes of MDS according to World Health Organization (WHO) classification?

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TABLE 4.1 ■ Subtypes of MDS

MDS Subtype	Blood	Bone Marrow
MDS-SLD	Single or bicytopenia, <1% blasts	<5% blasts, dysplasia in ≥10% of one cell line
MDS-RS†	Single or multiple cytopenias <1% blasts	≥15% of erythroid precursors with ring sideroblasts or ≥5% if *SF3B1* mutation present
MDS with isolated del(5q)	single or bicytopenia, often have normal or elevated platelets, <1% blasts	Isolated del(5q) ± other abnormality other than (7/del(7q), <5% blasts
MDS-MLD	Single or multiple cytopenias, <1% blasts	<5% blasts, dysplasia in ≥10% of cells in ≥2 lineages
MDS-EB-1	Single or multiple cytopenia(s), ≤4% blasts	5%–9% blasts, no Auer rods, dysplasia in ≥1 lineage
MDS-EB-2	Single or multiple cytopenia(s), Blasts 5%–19%	10%–19% blasts or presence of Auer rods, dysplasia in ≥1 lineage
MDS-U*	Single or multiple cytopenias, <1% blasts	<5% blasts, unilineage dysplasia or no dysplasia with MDS-associated cytogenetic changes

Note: Dysplasia is considered present if it involves at least 10% of a lineage.

*Pancytopenia with dysplasia in one lineage is classified as MDS-U.

†MDS with ringed sideroblasts can be MDS-RS with single lineage dysplasia or MDS-RS with multilineage dysplasia.

MDS, myelodysplastic syndrome; MDS-EB-1, MDS with excess blasts-1; MDS-EB-2, MDS with excess blasts-2; MDS-MLD, MDS with multilineage dysplasia; MDS-RS, MDS with ring sideroblasts; MDS-SLD, MDS with single lineage dysplasia; MDS-U, myelodysplastic syndrome, unclassified.

SIGNS AND SYMPTOMS

1. What are the common signs and symptoms of MDS?

- Incidental cytopenias
- Infections (due to neutropenia)
- Bleeding (due to thrombocytopenia)
- Fatigue and other signs/symptoms of anemia

DIAGNOSTIC CRITERIA

1. What are the diagnostic criteria for MDS?

- See above regarding specific WHO definitions and cutoffs. However, broadly speaking diagnosis is established with the following criteria.
- The patient must have one or more persistent cytopenias.
- The bone marrow examination may show dysplasia in one or more lineages.

- In the absence of dysplasia, the identification of an elevated blast percentage in the peripheral blood and/or bone marrow aspirate can also establish the diagnosis of MDS.
- A diagnosis of MDS may also be made in the correct clinical setting if MDS-specific karyotypic abnormalities are present.
- MDS-specific cytogenetic changes include –7/del(7q), –5/del(5q), –13/del(13q), del(11q), and i(17q) or t(17p) among many others. Note: –Y, del 20q, and +8 while commonly seen in patients with MDS are not MDS-defining cytogenetic changes.
- Treatment-related myeloid neoplasia, associated with **alkylating agents or radiation**, will have MDS with trilineage dysplasia about 5 to 7 years posttreatment. Chromosomal abnormalities are complex and monosomies involving deletion 5 and 7 (–5 or –7).

PROGNOSTIC FACTORS

1. How are patients with MDS stratified into different risk groups?

- The International Prognostic Scoring System (IPSS) stratifies MDS into four risk groups: low risk (IPSS score 0), intermediate-1 risk (IPSS score 0.5–1), intermediate-2 risk (IPSS score 1.5–2), and high risk (IPSS score 2.5–3.5). Patients with low, intermediate-1-, intermediate-2-, and high-risk MDS by IPSS have median overall survivals of 5.7, 3.5, 1.2, and 0.4 years, respectively.
- The IPSS scoring system should only be used at diagnosis in nontherapy-related MDS and, if the patient is referred to a tertiary care center, can only be calculated at the time of referral.

TABLE 4.2 ■ IPSS Scores

	0	0.5	1	1.5	2
Percentage of bone marrow blasts	<5	5–10	—	11–20	>20
Karyotype*	Good	Intermediate	Poor	—	—
Number of cytopenias†	0–1	2–3		—	—

*Good karyotype risk: normal, –Y, del(5q), del(20q); poor karyotype risk: complex karyotype (≥3 abnormalities), chromosome 7 abnormalities; intermediate karyotype risk: all others.

†Neutropenia: absolute neutrophil count <1,800; anemia: Hgb <10; thrombocytopenia: platelets <100,000.

Hgb, hemoglobin; IPSS, International Prognostic Scoring System.

- More recently, the IPSS has been updated and revised (IPSS-R) utilizing a larger patient cohort. It has additional risk groups of cytogenetic changes and has added the degree of anemia and thrombocytopenia into the model system. However, this still applies only to treatment naïve patients with de novo disease, though it may be recalculated throughout an untreated patient's course.
- Patients with very low (IPSS-R ≤2), low (>1.5–3), intermediate (>3–4.5), high (>4.5–6), and very high-risk (>6) MDS by IPSS-R have median overall survivals of 8.8, 5.3, 3.0, 1.6, and 0.8 years, respectively.

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TABLE 4.3 ■ Revised IPSS

	0	0.5	1	1.5	2	3	4
Bone marrow blasts	≤2		>2 to >5		5–10	>10	
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Hemoglobin	≥10		8 to <10	<8			
Platelets	≥100	50–100	<50				
Absolute neutrophil count	≥0.8	<0.8					

***Very good karyotype**: –Y or del(11q); **Good karyotype**: normal karyotype, del(5q), del(12p), del(20q), or a double abnormality including del(5q); **Intermediate karyotype**: del(7q), +8, +19, i(17q), and any other single or double independent clones; **Poor karyotype:** −7, inv(3)/t(3q)/del(3q), double abnormalities including −7/del(7q), or three abnormalities; **Very poor karyotype:** complex karyotype (≥3 abnormalities).

IPSS, International Prognostic Scoring System.

- A third score system for MDS, the WHO Prognostic Scoring System (WPSS), can be recalculated throughout disease course. However, it uses diagnostic criteria from the 2008 WHO classification of MDS and is therefore less commonly utilized.

INDICATIONS FOR TREATMENT

1. What are the indications of therapy in MDS?

- Transfusion dependence or symptoms related to cytopenias
- Intermediate-2- or high-risk MDS (based on IPSS)

TREATMENT

1. How is initial therapy chosen for MDS?

- Patient's should be risk stratified according to systems described earlier. Approach to treatment is dependent on risk score, indication for treatment, and associated cytogenetic changes such as del(5q).

2. What is the treatment of choice for patients with low or intermediate-1-risk MDS with symptomatic/transfusion-dependent anemia and del(5q) as the sole cytogenetic abnormality?

- Lenalidomide (10 mg a day) is the treatment of choice for these patients. Transfusion-dependent patients with low- or intermediate-1-risk MDS and del(5q) have an approximately 67% chance of becoming transfusion-independent (for medial duration of ~2–2.5 years) and approximately 62% chance of achieving complete cytogenetic response with lenalidomide.

3. Is lenalidomide indicated for patients with low-/intermediate-1-risk MDS with symptomatic or transfusion-dependent anemia but lacking del(5q)?

- Lenalidomide results in an overall response rate of 26% in patients with low-/intermediate-1-risk MDS without del(5q). This response rate is lower than that achieved with erythropoietin-stimulating agents (ESAs) in patient with an appropriate erythropoietin (EPO) level or with DNA methyltransferase inhibitors. Lenalidomide, as a single agent, is therefore not generally recommended as frontline therapy for MDS patients without del(5q) and is not currently Food and Drug Administration (FDA) approved for this indication.

4. What is the treatment of choice for patients with low- or intermediate-1-risk MDS with symptomatic/transfusion-dependent anemia but lacking del(5q)?

- The treatment of these patients is based on the EPO level and the number of red blood cell (RBC) transfusions per month.
- For patients with EPO ≤500 mU/mL:
  - Guidelines recommend treatment with an ESA in MDS with transfusion-dependent anemia with serum EPO ≤500 mU/mL.
  - The chance of responding to an ESA increases with lower EPO levels and fewer transfusions. For example, patients with an EPO level <100 and <2 transfusions per month have a 74% chance of responding to an ESA while patients with an EPO 100 to 500 and more than two transfusions per month have a 23% chance of responding to an ESA. Of note, patients with an EPO >500 have a 7% chance of responding to an ESA which underlies the recommendation against using ESAs in these patients.
  - It must be remembered that these percentages were calculated in patients receiving EPO 5 d/wk. Optimal dosing with less frequent administration of EPO has not been established nor has the optimal use of darbepoetin (Aranesp). Neither EPO nor darbepoetin is currently FDA approved in patients with MDS.
  - Most responses to ESAs occur within 8 weeks of treatment, though some patients might respond after 12 weeks of treatment. The median time of response is ~2 years.
  - Patients with serum EPO <500 mL/mL and MDS ring sideroblasts (MDS-RS) >15% benefit from ESAs along with granulocyte colony-stimulating factor (G-CSF) i.e., darbepoetin 150–300 mcg every other week and SQ G-CSF 1 mcg/kg 1–2 × per week.
  - Luspatercept-aamt is another option in patients with low- or intermediate-1-risk MDS-RS or in patients with MDS/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) who either have an elevated baseline EPO level (>200 U/L) or fail ESAs and require two or more RBC transfusions over 8 weeks.
- For patients with EPO ≥500 mU/mL:
  - Luspatercept-aamt can be considered as first-line treatment in patients with MDS-RS or MDS/MPN-RS-T with an EPO level >200.
  - Patients with EPO ≥ 500 mU/mL without a diagnosis of MDS-RS or MDS/MPN-RS-T could be treated with either DNA methyltransferase inhibitors (azacitidine or decitabine) and/or with RBC transfusions.

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5. When is iron chelation used in MDS?

- Currently, no iron chelation therapy is FDA approved for patients with myeloid neoplasms.
- Consider in patients with ferritin levels >1,000 ng/mL or evidence of iron overload (after ~ 20–30 units of packed red blood cells (PRBCs) and/or symptoms of congestive heart failure [CHF] or liver damage).
- Deferasirox or deferoxamine should be avoided if CrCl <40 mL/min.

6. What is the treatment of choice for patients with low- or intermediate-1-risk MDS with thrombocytopenia and/or neutropenia?

- Observation, if the thrombocytopenia and/or neutropenia are not severe
- Azacitidine or decitabine, two FDA-approved DNA methyltransferase inhibitors (hypomethylating agents), if the thrombocytopenia and/or neutropenia are significant.
- Interruption of hypomethylating agents is NOT recommended when patients are responding to therapy and is associated with a poor prognosis or early risk of relapse.
- Allogeneic stem cell transplant (ASCT) or a clinical trial can be considered in those who fail to respond or experience disease progression.

7. When is immunosuppressive therapy (antithymocyte globulin and cyclosporine) considered in MDS?

- Antithymocyte globulin and cyclosporine could be considered in a specific subgroup of patients with low-/intermediate-1-risk MDS with one or more of the following characteristics: younger age (age <60), hypocellular bone marrow, <5% blasts, presence of a paroxysmal nocturnal hemoglobinuria (PNH) clone, presence of an HLA-DR15 haplotype, or the presence of *STAT3*-mutated T-cell clones.

8. What are the treatment options for patients with intermediate-2-/high-risk MDS?

- ASCT is the only curative modality in MDS and should be strongly considered in this patient population. Administration of azacitidine or decitabine prior to ASCT is not routinely recommended because it has not been shown to add value in patients planning to proceed with ASCT; however, this should be considered in patients whose ASCT is expected to be delayed.
- Patients who are not candidates for or who decline ASCT should be considered for treatment with azacitidine or decitabine. Azacitidine is the only one of these two drugs that was shown in a randomized control trial to confer a survival benefit compared to best supportive care. However, this is felt to be due to the different designs of the azacitidine and decitabine trials, and both drugs are considered to have equal value in MDS.

9. For how many cycles should azacitidine or decitabine be given?

- Patients receiving azacitidine or decitabine who are not candidates for ASCT should continue receiving these drugs unless their MDS progresses or they develop side effects prohibiting their use if they are responding to therapy. Patients should receive a minimum or four to six cycles of azacitidine or decitabine before declaring the patient nonresponsive to therapy.

SPECIAL CONSIDERATIONS

1. What is chronic myelomonocytic leukemia (CMML)?

- CMML is an overlap syndrome between MDS and myeloproliferative neoplasms, and has features of both.
- MDS features: dysplasia, anemia, and/or thrombocytopenia
- Myeloproliferative features: leukocytosis, monocytosis, and splenomegaly)

2. How is CMML diagnosed?

- CMML is characterized by absolute monocytosis (≥1000/μL and ≥10% of the peripheral blood), persistent for more than 3 months (unless a clonal cytogenetic or molecular mutation is identified), and with no other etiologies identified.
- CMML can only be diagnosed after ruling out other myeloid neoplasms (such as chronic myelogenous leukemia [CML], polycythemia vera [PV], essential thrombocythemia [ET], or primary myelofibrosis [PMF]), and secondary causes of monocytosis.
- *PDGFRA*, *PDGFRB*, *FGFR*, and *PCM1-JAK2* rearrangements should be ruled out, particularly in cases with concomitant eosinophilia.
- Cytogenetic abnormalities are found in ~30% of patients with CMML and molecular mutations in multiple myeloid associated genes can be seen as well.
- In patients without cytogenetic abnormalities and without significant dysplasia on the bone marrow, other causes of monocytosis need to be carefully ruled out before a diagnosis of CMML can be made.

3. How is CMML classified?

- CMML can be subdivided into CMML-0 (dysplasia in ≥1 cell line, <5% blasts in marrow), CMML-1 (dysplasia in ≥1 cell line, 5%–9% blasts in marrow) and CMML-2 (dysplasia in ≥1 cell line, 10%–19% blasts in marrow or Auer Rods).

4. How is CMML treated?

- Asymptomatic patients with no significant anemia or thrombocytosis could be observed. Hydrea could be utilized in these patients if they have a significantly increased leukocyte count or symptomatic splenomegaly.
- The only curative option for CMML is ASCT. Patients who require therapy should be directed toward ASCT if clinically appropriate. CMML has its own prognostic scoring systems (CPSS, CPSS-mol, etc.) though the optimal prognostic tool remains unknown.
- Patients who require therapy but are not candidates for ASCT, or in whom ASCT has to be significantly delayed, should be treated with hypomethylating agents, azacitidine or decitabine.

5. What is clonal hematopoiesis of indeterminate potential (CHIP)?

- CHIP is characterized by the acquisition of a gene mutation in a population of myeloid cells that confers a survival advantage in the absence of a detectable hematologic malignancy.
- To diagnosis CHIP, a somatic mutation has to be present at >2% allelic frequency in the setting of normal blood counts and no clinical or pathologic evidence of hematologic malignancy.

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- CHIP does not include monoclonal B-cell lymphocytosis (MBL) or monoclonal gammopathy of undetermined significance (MGUS), which are precursors to chronic lymphocytic leukemia (CLL) and multiple myeloma (MM), respectively.
- The incidence of CHIP increases with age and it is present in ~10% of people >65 years old.
- The most common mutations associated with CHIP occur in *DNMT3A*, *TET2*, and *ASXL1*.
- Morphologic dysplasia is not present in CHIP.
- CHIP is associated with a small risk of transformation to a hematologic malignancy (MDS or acute myeloid leukemia [AML])
- The risk of transformation to AML is approximately 0.5% to 1% per year.
- CHIP is associated with increased risk of coronary artery disease.

6. What are the definitions of other indolent myeloid disorders on the same spectrum as CHIP?

TABLE 4.4 ■ Definitions of Other Indolent Myeloid Disorders

	ICUS	IDUS	CHIP	CCUS
Cytopenia	Yes	No	No	Yes
Dysplasia	No	Yes	No	No
Clonality*	No	No	Yes	Yes

*Clonality refers to a population of myeloid cells with an acquired gene mutation.

CCUS, clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential; ICUS, idiopathic cytopenia of undetermined significance; IDUS, idiopathic dysplasia of undetermined significance.

QUESTIONS

1. A 68-year-old man with hypertension, hyperlipidemia, and type 2 diabetes is referred to your clinic to discuss a test result. The patient was being evaluated as a potential donor for a stem cell transplant and elected to enroll in a clinical study. As part of the study, a 500 gene next-generation sequencing panel was performed on a sample of his peripheral blood. A mutation in *ASXL1* at a variant allele frequency of 4% was reported and he is referred to you to discuss the significance of this result. Laboratory testing reveals a white blood cell (WBC) count of 7,000, hemoglobin of 14.6, and platelet count of 250,000. The WBC differential is normal. He reports that he feels well and has not noticed any changes in his health recently. His physical exam reveals no masses or abnormalities.

In addition to an increased risk of developing MDS and/or acute myeloid leukemia (AML), what other medical conditions are associated with this patient's mutation?

A. Pancreatitis
B. Coronary artery disease
C. Glaucoma
D. Parkinson's Disease
E. Bleeding

2. A 77-year-old woman is referred to your clinic for a second opinion. She has been followed for several years by an outside physician for normocytic anemia. Her hemoglobin is usually around 12. Over the last 6 months, her hemoglobin has down trended to the 11s and she has developed a slight macrocytosis, with mean corpuscular volume (MCVs) in the low 100s. She has also developed mild thrombocytopenia (~110,000) but maintained a normal white blood cell (WBC) and neutrophil count. A workup including vitamin B12, folate, and copper levels was normal and a laboratory workup for hemolysis was negative. Hypothyroidism was excluded with laboratory studies and her liver enzymes were normal. The reticulocyte index was low. A bone marrow biopsy was performed that showed >10% dysplasia in the myeloid lineage with 1% blasts seen in her aspirate. Cytogenetics showed a normal female karyotype in all 20 analyzed cells. She has never had red blood cell or platelet transfusion. The patient denies any symptoms related to her blood counts.

What is the best treatment option for the patient?

A. Proceed with allogeneic stem cell transplant
B. Observation
C. Hypomethylating agent
D. Lenalidomide
E. Hypomethylating agent

3. A 62-year-old man with no other comorbidities and a good performance status was diagnosed with myelodysplastic syndrome (MDS) 2 years ago. He was on observation because he had mild cytopenias initially and he was asymptomatic. Over the last few months, his counts started to drop, and his most recent complete blood count (CBC) showed white blood cell (WBC) count 1, absolute neutrophil count (ANC) 0.5, hemoglobin 8.5, and platelets 40. A bone marrow biopsy was repeated and demonstrated a hypercellular marrow with dysplasia in all lineages, 12% blasts on the aspirate smear, and a complex karyotype.

Which of the following is the best treatment option for this patient?

A. Red blood cell transfusions only
B. Allogeneic stem cell transplant (ASCT)
C. Lenalidomide
D. Erythropoietin-stimulating agent in combination with thrombopoietin-stimulating agent
E. Hypomethylating agent

4. A 78-year-old man with a history of coronary artery disease, chronic obstructive pulmonary disease (COPD), and hypertension has high-risk myelodysplastic syndrome (MDS) with pancytopenia (white blood cell [WBC] count 0.8, absolute neutrophil count [ANC] 0.3, hemoglobin 8.5, platelets 35). Bone marrow showed 11% blasts and cytogenetics demonstrated a complex karyotype.

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Which of the following is the best treatment option for this patient?

A. Red blood cell transfusions only
B. Allogeneic stem cell transplant (ASCT)
C. Lenalidomide
D. Erythropoietin-stimulating agent in combination with thrombopoietin-stimulating agent
E. Hypomethylating agent

5. A 59-year-old woman has a diagnosis of chronic myelomonocytic leukemia (CMML) with a most recent complete blood count (CBC) showing a white blood cell (WBC) count 40,000 (absolute neutrophil count [ANC] 25, absolute monocyte count [AMC] 10), hemoglobin 7.5, and platelets of 200. Her spleen is palpated 6 cm below the left costal margin. A recent bone marrow aspiration and biopsy showed 7% blasts. She has fatigue and shortness of breath on moderate exertion. The patient has no other comorbidities.

Which of the following is the best treatment option for this patient?

A. Allogeneic stem cell transplant (ASCT)
B. Lenalidomide
C. Erythropoietin-stimulating agent in combination with thrombopoietin-stimulating agent
D. Hypomethylating agent

6. A 77-year-old man presents for ongoing management of his MDS-EB-2. He was originally diagnosed 3 months ago after presenting to his primary care with fatigue and a complete blood count (CBC) that demonstrated white blood cell (WBC) of 0.1, hemoglobin of 6.4, and platelets of 21. A bone marrow biopsy was performed and showed dysplasia in >10% of erythroid and megakaryocyte lineages as well as a complex karyotype. Twelve percent blasts were measured on the marrow aspirate. The patient presents after two cycles of decitabine to consider treatment with a third cycle. He continues to receive biweekly transfusions of packed red blood cells and platelets and remains neutropenic. He is not a candidate for allogeneic stem cell transplant (ASCT) and is tolerating treatment well.

What is the best treatment approach for this patient?

A. Switch to azacitidine
B. Continue treatment with decitabine
C. Treat with luspatercept
D. Stop treatment and recommend palliative transfusions

ANSWERS

1. **B. Coronary artery disease.** The patient's incidental finding of an *ASXL1* mutation at a relatively low VAF (4%) in the absence of any evidence of hematologic malignancy is most suggestive of clonal hematopoiesis of indeterminant potential (CHIP). The incidence of CHIP increases with age and is thought to follow the paradigm by which an acquired mutation in a population of hematopoietic cells confers a survival advantage. CHIP is associated with coronary artery disease and the development of diabetes. Strategies for primary prevention and risk factor control need to be discussed with this patient.

2. **B. Observation.** The patient in this question has myelodysplastic syndrome with single lineage dysplasia and a normal blast percentage. According to the International Prognostic Scoring System-revised (IPSS-R) score, this patient is very low risk, with a score of 1. The median survival for these patients is 8.8 years with a small risk of progression to acute myeloid leukemia (AML). The patient is asymptomatic from her disease and is not requiring transfusions. Therefore, it is reasonable to observe the patient at this time. The risks of allogeneic stem cell transplant would not be justified in her case nor would the risks associated with treatment with a hypomethylating agent. Lenalidomide can be used to treat anemia in low-risk patients with del(5q) which was not seen on this patient's karyotype.

3. **B. Allogeneic stem cell transplant (ASCT).** This is a patient with high-risk MDS. ASCT is the only curative modality. A retrospective analysis showed that patients with high-risk MDS have better overall survival if they undergo ASCT. Hypomethylating agents prior to ASCT are not routinely recommended and have not been shown to add value in patients planning to proceed with ASCT; therefore, hypomethylating agents should be considered in patients whose ASCT is expected to be delayed or who are not candidates for ASCT. This patient has a good performance status and does not have other comorbidities and would be a candidate for ASCT.

4. **E. Hypomethylating agent.** This is a patient with high-risk MDS. Though ASCT is the only curative modality, this patient is not a candidate for ASCT. Hypomethylating agents are the agents of choice. Studies have demonstrated that a hypomethylating agent (azacitidine) given to intermediate-2- or high-risk (International Prognostic Scoring System [IPSS]) MDS patients delayed progression to acute myeloid leukemia (AML) and improved overall survival compared to supportive care alone.

5. **A. Allogeneic stem cell transplant (ASCT).** The patient has CMML-1 with symptomatic anemia. The only curative option is ASCT. This patient requires therapy for CMML given the symptomatic anemia and should be directed toward ASCT. If ASCT has to be delayed, then a hypomethylating agent should be strongly considered as a bridge to curative intent therapy.

ALGRAWANY

6. **B. Continue treatment with decitabine.** This patient has received two cycles of decitabine and remains cytopenic and transfusion dependent. However, it can take 3 to 4 cycles of therapy to see a hematologic response and therefore this patient should receive more cycles prior to being deemed as having a treatment failure. There is no evidence to support switching between hypomethylating agents, and luspatercept is only considered to treat anemia refractory to erythropoietin-stimulating agents (ESAs) in very-low-, low-, or intermediate-risk MDS with ringed sideroblasts (MDS-RS).

5 Hodgkin Lymphoma

Darren King and Ryan A. Wilcox

EPIDEMIOLOGY

1. How common is Hodgkin lymphoma?

- Hodgkin lymphoma accounts for approximately 12% of all lymphomas in the United States (over 9,000 cases annually).

2. How is Hodgkin lymphoma classified?

- Classical Hodgkin lymphoma (cHL) makes up 95% of cases. Its subtypes are the following:
  - Nodular sclerosis (70%)
  - Mixed cellularity (25%)
  - Lymphocyte rich (5%)
  - Lymphocyte depleted (<1%)
- Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) makes up 5% of "Hodgkin lymphoma" cases.
  - Characterized by an indolent course, late relapses, and is clinically managed like an indolent non-Hodgkin lymphoma (NHL).

3. What are the demographics of Hodgkin lymphoma?

- Bimodal age distribution with the first peak around age 20 and the second near age 65
- In cHL there is a slight male predominance, whereas 75% of patients with NLPHL are male.

ETIOLOGY AND RISK FACTORS

1. What are risk factors for Hodgkin lymphoma?

- Socioeconomic status is directly associated with the nodular sclerosing subtype and inversely associated with the mixed cellularity variant.
- Immunosuppression (e.g., solid organ or hematopoietic transplants)
- Autoimmune diseases (e.g., rheumatoid arthritis)
- HIV/AIDS is associated with Epstein–Barr virus (EBV) positive, lymphocyte-depleted subtype.
- There is an increased incidence in patients with affected family members, but no known genetic predisposition.

ALGRAWANY

STAGING

1. Define the staging for Hodgkin lymphoma.

TABLE 5.1 ■ Ann Arbor Staging

Stage	Description
I	Involvement of single lymph node region or structure (e.g., spleen, thymus, Waldeyer's ring) or a single extranodal site
II	Involvement of two or more lymph nodes or lymphoid structures on the same side of the diaphragm
III	Involvement of lymph nodes or lymphoid structures on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extranodal organs beyond I_E* including any liver or bone marrow involvement, with or without associated lymph node involvement

*Contiguous extranodal extension indicated by "E."

Note: B symptoms (significant unexplained fever, night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis) indicated by "A" (absence) or "B" (presence); bulky disease (mediastinal mass >1/3 diameter of thorax or any mass >10 cm) indicated by "X."

SIGNS AND SYMPTOMS

1. What are the common signs and symptoms of Hodgkin lymphoma?

- Most patients present with asymptomatic lymphadenopathy or an incidentally discovered mediastinal mass.
  - B symptoms include the following:
    - Fevers (unexplained, persistent/recurring temperature >38°C)
    - Drenching night sweats
    - Weight loss (>10% over preceding 6 months), seen in 20% of early- and 50% of advanced-stage disease.

2. What is the pattern of disease involvement in Hodgkin lymphoma?

- Cervical nodes are most commonly affected followed by mediastinal nodes.
- Spread is generally to adjacent lymph nodes.
- Bone marrow involvement is observed in fewer than 5% of cases.

DIAGNOSTIC CRITERIA

1. What is the optimal approach to the diagnosis of Hodgkin lymphoma?

- Excisional lymph node biopsy. Tumor in Hodgkin lymphoma has a very small component of malignant cells, with a surrounding reactive milieu of lymphocytes, eosinophils, and fibrosis (sclerosis). Excisional lymph node biopsy is far better at documenting this architecture than core biopsy.
- Clinical staging done using CT and PET/CT scans.
- Bone marrow biopsy is no longer required for staging if PET/CT is consistent with marrow involvement. Bone marrow biopsy should be performed in the presence of cytopenias and a negative PET/CT.

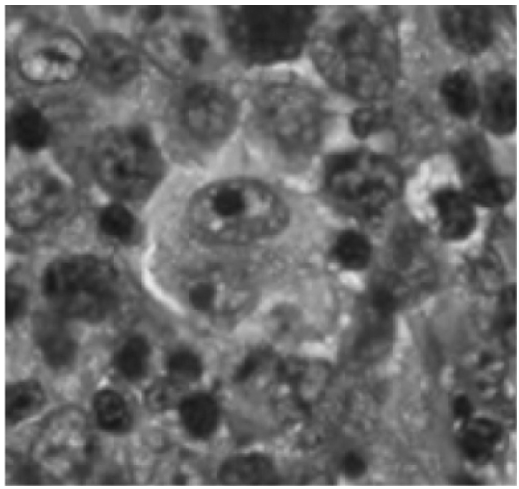

FIGURE 5.1 ■ Reed–Sternberg cell surrounded by inflammatory infiltrate.

2. How is the diagnosis of cHL made?

- Presence of multinucleate Reed–Sternberg (RS) cells in an appropriate inflammatory background (see Figure 5.1).
- Typical immunophenotype of cHL is CD15 and CD30 positive with absence of the usual B-cell markers CD20, CD79a, and the common leukocyte antigen CD45. PD-L1 is often highly expressed.

3. What are the characteristics of PD-L1/PD-L2 expression in Hodgkin lymphoma?

- RS cells typically show overexpression of PD-L1 and PD-L2 on the cell surface, which may contribute to the ineffective but exuberant inflammatory cell background that characterize the disease.
- Amplification of the *9p24.1* gene locus may lead to increased PD-L1 and PD-L2 expression, as well as increased JAK2 signaling
- This overexpression of PD-L1 in Hodgkin lymphoma is an attractive target in checkpoint inhibitor therapies noted in the section titled Novel Therapies.

4. How is NLPHL diagnosed?

- Presence of lymphocytic and histiocytic cells with "popcorn" appearance
- Typical immunophenotype CD15 and CD30 negative with positivity for the B-cell markers CD20, CD79a, and the common leukocyte antigen CD45

5. What is the cell of origin of Hodgkin lymphoma?

- Despite their unique immunophenotype, cHL cells have been shown to derive from germinal center B-cells.

INDICATIONS FOR TREATMENT

1. Who requires treatment for Hodgkin lymphoma?

- All patients with cHL should be considered for initial treatment with curative intent.
  - Likewise, all patients with NLPHL should be considered for therapy at the time of diagnosis:
    - Radiation with nonbulky stage IA/IIA disease

ALGRAWANY

- Immunochemotherapy—for example, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]—in bulky limited-stage or advanced-stage disease
- Observation alone may be considered for some patients—for example, excised stage I disease.

PROGNOSTIC FACTORS

1. What are unfavorable factors in early-stage (I–IIA) cHL?

- Large mediastinal mass (greater than one-third of mediastinal diameter)
- Extranodal disease
- Erythrocyte sedimentation rate (ESR) ≥50 mm/hr without or ≥30 mm/hr with B symptoms,
- Greater than or equal to three nodal sites
- Age ≥50
- Bulky disease

2. What are unfavorable prognostic factors in advanced-stage (IIB–IV) cHL? How does this International Prognostic Factor score impact outcome? ONE POINT FOR EACH.

- Age >45
- Male sex
- Stage IV disease
- Albumin <4 g/dL
- Hemoglobin <10.5 g/dL
- White blood cell count >15,000/mm^3
- Lymphopenia with absolute lymphocyte count <600 lymphocytes/μL

Score	5-Year FFP (%)	5-Year OS (%)
0	84	89
1	77	90
2	67	81
3	60	78
4	51	61
5–7	42	56

FFP, freedom from progression; OS, overall survival.

3. What are other poor prognostic factors on Hodgkin lymphoma?

- Positive PET scan after two cycles of Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) strongly associated with inferior 2-year progression-free survival (PFS)
- Increased density of lymphoma-associated macrophages (CD68-positive cells)

4. What is the prognosis for Hodgkin lymphoma?

- Cure is obtained in over 80% of all patients.
- Five-year survival is >90% in early and >75% in advanced-stage disease.

TREATMENT

1. What is the initial treatment for early-stage (I–IIA) cHL?

- In limited-stage favorable-risk disease, a standard approach is combined modality therapy with two cycles of ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) with restaging PET/CT followed by 20 Gy of involved site radiation therapy (ISRT).
- Limited-stage, unfavorable-risk disease may be treated with four cycles of ABVD followed by 30 Gy of ISRT. An alternative approach, sparing radiation therapy and its potential risks, is three to six cycles of ABVD alone, in a risk-adapted fashion (i.e., depending upon the quality of response observed on interim PET/CT).
- The Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone) is an alternative to ABVD.

2. How is advanced-stage (IIB–IV) cHL managed?

- Chemotherapy alone with ABVD for six cycles. Outcome appears to be optimized if treatment delays and dose reductions are avoided. Stanford V is an alternative regimen.
- In select patients with high-risk disease (international prognostic score [IPS] ≥4, age <60) an alternative, more intense initial treatment option is escalated BEACOPP—bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone. There is current debate regarding the overall and PFSs of ABVD versus escalated BEACOPP, with patients receiving BEACOPP showing greater therapy-related toxicities, including increased risks for myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML).
- Consolidative radiation therapy is an option for patients with bulky disease.

RESPONSE-ADAPTED THERAPY

1. What role does interim PET/CT play in prognosis?

- The sensitivity of PET/CT has greatly impacted treatment strategy in Hodgkin lymphoma, with early PET/CT after two cycles of chemotherapy a better predictor of PFS and overall survival (OS) compared to traditional clinical prognostic factors.

2. How are PET/CT findings interpreted?

- Fluorodeoxyglucose (FDG) uptake avidity in PET scans for lymphoma tumor masses are scored per the Deauville Criteria:
  - Score 1—No uptake above background
  - Score 2—Uptake ≤ mediastinum
  - Score 3—Uptake > mediastinum but ≤ liver
  - Score 4—Uptake moderately increased compared to the liver
  - Score 5—Uptake markedly increased compared to the liver
- A score of 1 or 2 is considered negative for disease, scores of 4 and 5 are considered positive. A score of 3 prompts further clinical consideration of response but may still portend a good prognosis in Hodgkin lymphoma patients.

ALGRAWANY

3. How do early PET/CT results impact treatment course?

- A negative PET/CT after two cycles of chemotherapy may allow for an abbreviated number of cycles in early stage disease and/or omission of bleomycin from ABVD in subsequent cycles, thus sparing potential pulmonary toxicity. Patients receiving ABVD with an interim PET/CT positive for disease may be switched to a more aggressive regimen, such as escalated BEACOPP.

RELAPSED/REFRACTORY DISEASE

1. How common is disease relapse in Hodgkin lymphoma?

- 10% to 30% of patients achieving an initial complete remission will subsequently relapse.

2. How is relapsed Hodgkin lymphoma treated?

- Patients with relapsed disease have traditionally been treated with salvage chemotherapy regimens similar to NHL patients:
- Ifosfamide, carboplatin, etoposide (ICE)
- Gemcitabine-based regimens
- Those patients showing chemosensitivity to a salvage regimen may then go on to receive high-dose chemotherapy (e.g., BEAM—BCNU, etoposide, cytarabine, melphalan) followed by autologous stem cell transplant (autoSCT).

3. What is the role of consolidation therapy following autoSCT in Hodgkin lymphoma?

- Brentuximab vedotin has been approved as a post-autoSCT therapy for patients at high risk of relapse. Current trials are also exploring use of checkpoint inhibitors as consolidation therapy following autoSCT.

4. How is relapse treated following autoSCT?

- Patients who relapse or progress following salvage chemotherapy or autoSCT can be considered for therapy with the following:
  - Brentuximab
  - Checkpoint inhibitor (Pembrolizumab or Nivolumab)
  - Further chemotherapy (e.g., bendamustine)
- Those achieving a response are candidates for allogeneic stem cell transplant.
- Relapse or progression following allogeneic stem cell transplant may be treated (depending on the patient's disease and performance status) with the following:
  - Observation alone
  - Clinical trials
  - Single-agent therapy: mechanistic target of rapamycin (mTOR) inhibitor or histone deacetylase (HDAC) inhibitor
  - Radiation therapy

5. What is primary progressive/refractory disease?

- Primary progressive or refractory Hodgkin lymphoma is defined as disease that progresses or does not respond during initial therapy, or that progresses within 90 days of completing this therapy.
- Outcomes in these patients have traditionally been very poor with standard chemotherapy approaches, including high-dose chemotherapy followed by autoSCT.

NOVEL THERAPIES

1. What is brentuximab vedotin? What are its usual toxicities?

- Brentuximab vedotin is an anti-CD30 monoclonal antibody conjugated to a mitotic spindle inhibitor. Its use has been approved as post-autoSCT consolidation therapy for patients at high risk for relapse, in patients who relapse following autoSCT, or who are not deemed candidates for transplant.
- Brentuximab is now approved for frontline use in stage III/IV Hodgkin lymphoma in combination with traditional chemotherapy (e.g., Adriamycin, vinblastine, dacarbazine [AVD]). Brentuximab should **not** be used concurrently with bleomycin due to increased risk for pulmonary toxicity.
- Its main toxicity as a single agent is peripheral neuropathy.

2. What is the role of checkpoint inhibitor therapy in Hodgkin lymphoma?

- Given overexpression of PD-L1/PD-L2 by RS cells, checkpoint inhibitor therapy has proven an attractive treatment option in Hodgkin lymphoma. Anti-PD-1 therapies (e.g., pembrolizumab, nivolumab) have shown efficacy in relapsed disease, and are currently being investigated in earlier therapy, including as frontline agents and in combination with brentuximab.

SPECIAL CONSIDERATIONS

1. What are the significant toxicities from treatment?

- Pulmonary toxicity from bleomycin. Bleomycin can be safely omitted from cycles three to six of ABVD in patients with advanced-stage disease.
- Myelosuppression with ABVD. Less than 10% of patients develop febrile neutropenia. It is important (and safe) to maintain dose intensity through cytopenias.
- Infertility (much more common with BEACOPP regimen than ABVD).
- Cardiac dysfunction from radiation (e.g., pericarditis, coronary artery disease, and valvular disease) or chemotherapy (e.g., heart failure due to anthracyclines).
- Secondary malignancies (e.g., breast cancer in females who have received thoracic radiation). Therapy-related MDS and AML are less common in patients receiving ABVD than in patients who received mechlorethamine, vincristine, procarbazine, prednisone (MOPP) or BEACOPP regimens.

2. How is disease managed in the elderly?

- Given significant risk of therapy-related toxicity from traditional chemotherapy regimens, treatment of elderly patients with Hodgkin lymphoma has begun to focus more heavily on use of brentuximab and checkpoint inhibitors, often in combination, and potentially without use of any cytotoxic chemotherapy in the frontline setting.

3. How is nodular NLPHL managed?

- Radiation therapy alone for stages IA and IIA
- Chemotherapy ± radiation for stages IB and IIB
- Observation may be appropriate for asymptomatic patients with advanced-stage disease that is nonbulky and slowly progressive.
- Immunochemotherapy (e.g., R-CHOP) for symptomatic advanced disease

ALGRAWANY

QUESTIONS

1. A 25-year-old female diagnosed with stage IIIA classical Hodgkin lymphoma (cHL) has completed two cycles of treatment with Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD). An interim PET/CT is performed, with Deauville response score 2.

What is the most appropriate next step in therapy?

A. No further treatment is recommended
B. Continue treatment with four additional cycles of ABVD
C. Continue treatment with four cycles of Adriamycin, vinblastine, decarbazine (AVD), omitting further bleomycin
D. Escalate subsequent treatment to bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone (BEACOPP)

2. An otherwise healthy 45-year-old male completed six cycles of Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) for stage IV classical Hodgkin lymphoma (cHL). Six months following completion of treatment, he noticed an enlarging cervical lymph node. Biopsy was performed, which confirmed relapse. PET/CT shows diffuse disease.

Which of the following is the most appropriate next step in management?

A. Initiate bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone (BEACOPP)
B. Initiate brentuximab
C. Initiate salvage chemotherapy with ifosfamide/carboplatin/etoposide (ICE) and plan for autologous stem cell transplant (autoSCT)
D. Proceed to nonmyeloablative allogeneic stem cell transplant

3. An 81-year-old male is diagnosed with stage IVA classical Hodgkin lymphoma (cHL). He has an Eastern Cooperative Oncology Group (ECOG) performance status of 2. He wishes to pursue therapy for his lymphoma if possible but is concerned with quality of life in the setting of his comorbidities and current frailty. He has a history of hypertension, type 2 diabetes mellitus, and coronary artery disease.

Which of the following would be the most reasonable treatment recommendation?

A. No lymphoma-directed therapy should be offered, and patient may be referred to hospice.
B. Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) for six cycles
C. Bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone (BEACOPP) for six cycles
D. Treatment with combination of brentuximab vedotin and nivolumab

4. A 24-year-old female was diagnosed with stage IIIB classical Hodgkin lymphoma (cHL) with a bulky mediastinal mass. Her treatment comprised six cycles of Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) and radiation to the mediastinum. She completed treatment 4 years ago.

Long-term surveillance does not include which of the following:

A. Breast MRI or early mammogram
B. Thyroid function testing
C. Yearly history and physical exam
D. Annual PET scan

5. A 20-year-old male diagnosed with stage IVB classical Hodgkin lymphoma (cHL) has completed six cycles of Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD). Six months following completion of treatment he experiences a biopsy-confirmed relapse of disease. He undergoes salvage chemotherapy with ifosfamide/carboplatin/-etoposide (ICE), followed by high-dose chemotherapy (BEAM) and autologous stem cell transplant. PET/CT prior to transplant showed a partial response, with Deauville score of 4. The patient receives posttransplant brentuximab vedotin for 1 year given his high risk for relapse. Four months after completing brentuximab, he is found to have had a second relapse.

All of the following treatment options are reasonable at this point, except:

A. Resumption of brentuximab vedotin
B. Work-up for allogeneic stem cell transplant
C. Initiation of pembrolizumab
D. Enrollment in a clinical trial

6. A 75-year-old male was diagnosed with stage IA nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) of the mediastinum. He underwent radiation therapy to the mediastinum and did well for 5 years. Now, at age 80, he has a biopsy-proven recurrence in the right cervical lymph node chain, outside his prior radiation field. He is asymptomatic. PET/CT staging is consistent with stage III disease. The patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 1 to 2, but desires further treatment.

Which of the following would not be a reasonable treatment strategy?

A. Observation
B. Single agent rituximab
C. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
D. Bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone (BEACOPP)

ALGRAWANY

ANSWERS

1. **C. Continue treatment with four additional cycles of AVD.** A Deauville score of 2 is considered negative, and a good prognostic indicator following initial two cycles of ABVD, however further therapy is required. As per the response-adapted therapy for advanced Hodgkin lymphoma (RATHL) trial, bleomycin may be omitted from further cycles of treatment.

2. **C. Initiate salvage chemotherapy with ifosfamide/carboplatin/etoposide (ICE) and plan for autologous stem cell transplant (autoSCT).** Standard initial treatment for relapsed cHL is salvage chemotherapy (such as ICE) followed by autoSCT. Retreating with a combination chemotherapy regimen without autoSCT would not be indicated with a relapse this early. Brentuximab and allogeneic stem cell transplant are indicated in patients relapsing following autoSCT.

3. **D. Treatment with combination of brentuximab vedotin and nivolumab.** Emerging data have shown the combination of brentuximab vedotin and nivolumab to have high response rates with acceptable toxicity profile in elderly/frail patients with advanced stage cHL.

4. **D. Annual PET scan.** Because of its high cure rates, long-term follow-up for cHL requires monitoring of a number of possible late complications. Women who received radiation therapy to the chest are at higher risk of developing (often bilateral) breast cancer, and require close monitoring with breast MRI or early mammogram. Thyroid function should be monitored, as the gland may be affected by mediastinal radiation. After completion of treatment, National Comprehensive Cancer Network (NCCN) guidelines recommend that a history and physical should be performed every 3 to 6 months for the first 1 to 2 years, then every 6 to 12 months until year 3, and then yearly. Surveillance with PET scan is **not** indicated in the absence of clinical concern for relapse.

5. **A. Resumption of brentuximab vedotin.** Brentuximab vedotin has been approved for use following autologous stem cell transplant in patients with cHL at high risk for relapse. In this patient's case, his short duration of response to initial therapy (relapsing 6 months after completion of ABVD) and positive PET/CT at time of transplant are high-risk features justifying the use of posttransplant brentuximab vedotin for one year. Having relapsed within 4 months of completing brentuximab, there is no indication for resuming the drug and other treatment options should be pursued.

6. **D. Bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone (BEACOPP).** NLPHL typically follows an indolent course, but often with late relapses. Given its distinct clinical course and immunophenotype, the decision to treat should be approached in a way similar to the indolent non-Hodgkin lymphomas. Observation in an asymptomatic patient, single agent rituximab, and combination therapy with R-CHOP are reasonable options in a patient with advanced age and borderline performance status. BEACOPP would not be appropriate.

6 Non-Hodgkin Lymphoma

Richard A. King and Tycel J. Phillips

EPIDEMIOLOGY

1. Classify lymphomas into indolent or aggressive categories.

TABLE 6.1 ■ Lymphomas as Indolent or Aggressive

Indolent	Aggressive
Follicular lymphoma	Diffuse large B-cell lymphoma
Marginal zone lymphoma	Burkitt lymphoma
Small lymphocytic lymphoma/Chronic lymphocytic leukemia	Lymphoblastic lymphoma
	Mantle cell lymphoma*
Lymphoplasmacytic lymphoma/ Waldenström macroglobulinemia	Primary mediastinal large B-cell lymphoma
	Anaplastic large cell lymphoma
Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)	Angioimmunoblastic T-cell lymphoma
	Extranodal NK/T-cell lymphoma
Mantle cell lymphoma*	Peripheral T-cell lymphoma not otherwise specified

*Can have indolent and aggressive presentations and is discussed in Chapter 7.

NK cell, natural killer cell.

ETIOLOGY AND RISK FACTORS

1. What risk factors are associated with the development of non-Hodgkin lymphoma (NHL)?

- Farming (exposure to herbicides and pesticides, such as organochlorine, organophosphate, and phenoxyacid compounds)
- Infections (see Question 2)
- Immunosuppressive drug use
- Autoimmune diseases
- Post solid organ transplantation

2. What infections are associated with lymphoma, and what is the associated subtype of lymphoma?

- HIV: AIDS-associated lymphoma
- *Epstein–Barr virus* (EBV): Burkitt lymphoma in Africa, posttransplant lymphoproliferative disorders, natural killer (NK)/T-cell lymphoma, diffuse large B-cell lymphoma (DLBCL) of the elderly

ALGRAWANY

- Human T-cell leukemia virus , type 1 (HTLV-I): adult T-cell leukemia/lymphoma
- *Helicobacter pylori:* mucosa-associated lymphoid tissue (MALT) lymphoma
- Human herpesvirus-8: body cavity lymphoma
- Hepatitis C: splenic marginal zone lymphoma
- *Chlamydia psittaci:* orbital adnexal lymphoma
- *Campylobacter jejuni:* intestinal lymphoma
- *Borrelia burgdorferi:* cutaneous MALT lymphoma

STAGING

1. How is NHL staged?

- Ann Arbor staging system: refer to Chapter 5

SIGNS AND SYMPTOMS

1. What are the common presenting signs and symptoms of NHLs?

- Lymphadenopathy
- B symptoms
  - Fever (T >100.5°F)
  - Drenching night sweats
  - Unintentional weight loss (>10% loss within a 6-month period of time)
  - Anorexia
  - Fatigue
- Splenomegaly

DIAGNOSTIC FEATURES

1. What are the immunophenotypic markers of the indolent NHLs?

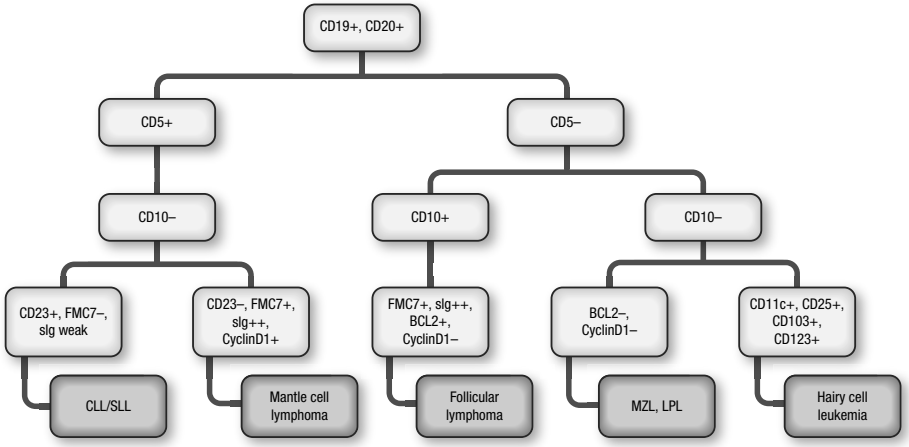

FIGURE 6.1 ■ Immunophenotypic markers for indolent non-Hodgkin B-cell lymphomas.
CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; MZL, marginal zone lymphoma; LPL, lymphoplasmacytic lymphoma.

2. What are the chromosomal translocations and their oncogene (and function) associated with indolent NHLs?

TABLE 6.2 ■ Chromosomal Translocations Associated with Indolent NHLs

NHL Subtype	Cytogenetics	Oncogene	Function
Follicular lymphoma	t(14;18)(q32;q21)	*BCL2*	Anti-apoptosis
Mantle cell lymphoma	t(11:14)(q13;q32)	Cyclin D1	Cell cycle regulator
Marginal zone lymphoma/extranodal marginal zone lymphoma	t(11;18)(q21;q21) Others: t(14;18) t(1;14) t(3;14)	*API2*-MALT	Resistance to *Helicobacter pylori* treatment
Lymphoplasmacytic lymphoma	t(9;14)(p13;q32) Rare, non-specific	*PAX-5*	Deregulation of *PAX-5* gene

NHL, non-Hodgkin lymphoma.

Follicular Lymphoma

GRADE AND PROGNOSTIC FACTORS

1. How do we determine the grade of follicular lymphoma (FL)?

- Grade 1 to 2 is defined by ≤15 centroblasts per high-power field
- Grade 3 is defined by >15 centroblasts per high-power field
  - Grade 3b is defined by sheets of centroblasts

2. What are the components of the Follicular Lymphoma International Prognostic Index (FLIPI)?

TABLE 6.3 ■ Follicular Lymphoma International Prognostic Index

Criteria (One Point for Each)	Risk Group
Age >60	Low (0–1 points)
Number of nodal sites >4	Intermediate (2 points)
Elevated LDH	High (3–5 points)
Hemoglobin level <12 g/dL	
Ann Arbor Stage III or IV	

LDH, lactate dehydrogenase.

3. What are the poor prognostic factors associated with FL?

- According to the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, the poor prognostic factors are the following:
  - Involvement of three or more nodal sites, each with a diameter of at least 3 cm
  - Any nodal/extranodal mass with a diameter of at least 7 cm

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- Presence of B symptoms
- Splenomegaly
- Pleural effusion or ascites
- Cytopenia(s)
- Circulating tumor cells (>5,000 malignant cells/mm^3)

TREATMENT

1. What are the treatment options for limited-stage (I–II) grade 1 to 2 FL <7 cm?

- Involved-site radiotherapy (ISRT) for stage I or contiguous stage II
  - Some may add anti-CD20 monoclonal antibody ± chemotherapy
- Anti-CD20 monoclonal antibody ± chemotherapy for noncontiguous stage II or stage I/II FL >7 cm
  - Some may add palliative ISRT
- Observation if toxicity outweighs benefit

2. What are the indications for treatment of FL?

- Symptomatic (B symptoms present)
- Threatened end-organ function
- Cytopenia secondary to lymphoma marrow involvement
- Bulky disease
- Steady progression

3. When treatment for FL is indicated, what are the first-line treatment regimens for stage III–IV, grade 1 to 2 FL?

- Bendamustine + rituximab or obinutuzumab
- Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) + rituximab or obinutuzumab
- Cyclophosphamide, vincristine, prednisone (CVP) + rituximab or obinutuzumab
- Lenalidomide + rituximab
- Rituximab monotherapy (low tumor burden)
- For elderly or for those who are expected to poorly tolerate the above regimens
  - Rituximab
  - Chlorambucil + rituximab
  - Cyclophosphamide + rituximab

4. How do you treat grade 3 FL or an aggressive presentation of FL?

- Grade 3a FL management is controversial and should be individualized.
- Grade 3b FL is treated like DLBCL.

5. What is the role of maintenance rituximab?

- Maintenance therapy is optional.
- After single-agent rituximab, retreatment with rituximab at recurrence provides comparable disease control to maintenance rituximab.
- In the PRIMA trial, rituximab (every 8 weeks for up to 2 years) after rituximab, cyclophosphamide, vincristine, prednisone (R-CVP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) improved progression-free survival (PFS), but not overall survival (OS).
- In the GALLIUM trial, obinutuzumab maintenance after obinutuzumab-based chemoimmunotherapy resulted in improved PFS, but no difference in OS, compared to rituximab maintenance after rituximab-based chemoimmunotherapy.

- In the FIT trial, ibritumomab tiuxetan (Y-90) after response to rituximab-containing regimens improved PFS, but not OS.

6. What are subsequent treatment regimens for relapsed/refractory grade 1 to 2 FL?

- Chemoimmunotherapy
  - First-line regimen that has not been previously used (see above)
  - Lenalidomide alone or with obinutuzumab
  - Obinutuzumab monotherapy
- Radioactive monoclonal antibody (radioimmunotherapy)
  - Ibritumomab tiuxetan (Y-90)
    - Requires bone marrow cellularity >15%, bone marrow lymphoma involvement <25%, and platelet count >100,000
- PI3K inhibitors (after two prior therapies)

TABLE 6.4 ■ Summary of PI3K Inhibitors Approved for Follicular Lymphoma

Drug	PI3K selectivity	Route	Adverse Effects
Copanlisib	Alpha	IV	1. Hepatoxicity
Duvelisib	Delta/gamma	Oral	2. Neutropenia
Idelalisib	Delta	Oral	3. Diarrhea (loperamide for low-grade) or colitis*
			4. Pneumonitis*
			5. Cutaneous reactions*
			6. Pneumocystis pneumonia: use prophylaxis
			7. CMV reactivation
			8. Hypertension, hyperglycemia (copanlisib)
			9. Intestinal perforation (idelalisib)
			Withhold drug for infection, pneumonitis, and severe cases of diarrhea or rash.

* Steroids used for severe cases.

CMV, cytomegalovirus.

7. How should we treat histological transformation of FL to aggressive lymphoma (such as DLBCL)?

- Transformed FL should be treated the same way as a DLBCL (see details in Chapter 7)

Marginal Zone Lymphoma

SIGNS AND SYMPTOMS

1. What is the clinical presentation of extranodal marginal zone (MALT) lymphoma?

- Signs and symptoms from involvement of the gastrointestinal (GI) tract, respiratory tract, salivary gland, kidney, prostate, lung, eye (conjunctiva), and other organs

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- Associated with autoimmune disease, such as Sjögren syndrome or Hashimoto thyroiditis

2. What is the clinical presentation of splenic marginal zone lymphoma?

- Splenomegaly, circulating lymphocytosis, cytopenias
- Peripheral circulating malignant lymphocytes may display villous cytoplasmic projections

TREATMENT

1. What is the initial treatment for stage I or II, gastric MALT lymphoma with positive *H. pylori*?

- Treatment of *H. pylori* with antibiotics
- If t(11;18) is present, then ISRT is also added (or rituximab if radiation is contraindicated)

2. What are the initial treatment options for stage I or II, gastric MALT lymphoma without *H. pylori* infection?

- ISRT
- Single-agent rituximab (if radiation is contraindicated)

3. What is the follow-up and subsequent management of stage I/II gastric MALT lymphoma?

- Repeat endoscopy and biopsy
  - After 3 months if antibiotic treatment alone
    - If *H. pylori* remains positive, then treat with second-line antibiotics
    - If lymphoma remains and the patient has symptoms, then ISRT
  - After 3 to 6 months, when ISRT or rituximab given
    - If *H. pylori* remains positive, consider additional antibiotic treatment
    - If lymphoma remains, then use first-line chemoimmunotherapy (see Question 3)
- After remission achieved, then endoscopy is repeated every 3 to 6 months for 5 years, then annually
  - Recurrences can be treated with ISRT if not previously given or with observation until indications for chemoimmunotherapy arise (symptoms, GI bleeding, bulky disease, rapid progression, or threatened end-organ function)
  - Chemoimmunotherapy options are similar to those used in FL

4. What is the treatment of stage III/IV MALT lymphoma that involves the stomach?

- Observation until an indication for treatment arises
- First-line chemoimmunotherapy or palliative radiation
- Endoscopy follow-up is the same as localized disease

5. What is the treatment for nongastric, noncutaneous MALT lymphoma?

- Localized disease (stage I/II) is managed with ISRT, surgery in select locations, rituximab, or observation.
- Advanced disease is treated with palliative ISRT or observation until an indication for chemoimmunotherapy arises.

6. What is the treatment for nodal marginal zone lymphoma?

- Nodal marginal zone lymphoma is managed similar to grade 1 to 2 FL

7. What is the initial treatment for symptomatic, splenic marginal zone lymphoma without hepatitis C infection?
- Splenectomy or single-agent rituximab

8. What is the treatment for symptomatic, splenic marginal zone lymphoma with hepatitis C infection?
- Treat hepatitis C infection first.
- If resolution of the lymphoma does not occur, then treat similar to splenic marginal zone without hepatitis C.

9. What is the treatment for asymptomatic, splenic marginal zone lymphoma?
- Observation
- Treat hepatitis C

Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

DIAGNOSIS

1. What are some additional tests needed during workup for lymphoplasmacytic lymphoma (LPL)?
- Bone marrow biopsy: diagnosis typically requires demonstration of infiltration by a lymphoplasmacytic cell population
- Quantitative immunoglobulins, serum protein electrophoresis with immunofixation, serum-free light chains to detect monoclonal gammopathy
- Labs and imaging to rule out multiple myeloma
- *MYD88* mutation testing (present in ~90% of cases) on bone marrow
- *CXCR4* gene mutation testing if considering ibrutinib

SIGNS AND SYMPTOMS

1. What is the clinical presentation of LPLs?
- Monoclonal gammopathy, hyperviscosity syndrome (30%), neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin disease
- Associated with hepatitis C infection

TREATMENT

1. What are the indications for treatment of LPL?
- Hyperviscosity syndrome
- Organomegaly
- Cryoglobulinemia
- Cold agglutinin disease
- Cytopenia
- Other disease-related symptoms

2. What are some treatment regimens for LPL?
- Chemoimmunotherapy
  - Bendamustine + rituximab
  - Rituximab + cyclophosphamide + dexamethasone/prednisone

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- Others (R-CHOP; fludarabine ± rituximab; fludarabine, cyclophosphamide, and rituximab (FCR); cladribine ± rituximab)
- Ibrutinib ± rituximab
- Proteasome inhibitor-based regimens
  - Bortezomib/rituximab
  - Bortezomib/dexamethasone (VD)
  - Bortezomib/dexamethasone/rituximab (RVD)
  - Carfilzomib/rituximab/dexamethasone (CRD)
- Avoid single-agent rituximab in patients with a markedly elevated serum immunoglobulin M (IgM)/serum viscosity without prior plasmapheresis due to concern for IgM flare, which can temporarily cause marked elevation in IgM and subsequent hyperviscosity.

3. What is the treatment for hyperviscosity syndrome as related to Waldenström macroglobulinemia?

- Plasmapheresis in emergent situations, then proceed with definitive therapy

SMALL LYMPHOCYTIC LYMPHOMA

For details about small lymphocytic lymphoma, see Chapter 2.

QUESTIONS

1. A 53-year-old male presents with several months of abdominal bloating, early satiety, fatigue, and 15-lb weight loss. Complete blood count is notable for a white blood cell (WBC) 13.2 (75% lymphocytes), hemoglobin 8.9, and platelet count of 95,000. Peripheral blood smear shows frequent atypical small lymphoid-appearing cells with surface villous projections. CT imaging of the abdomen shows a spleen 24 cm in maximum dimension. He undergoes a bone marrow biopsy, which shows intrasinusoidal lymphocytic infiltrates staining positive for CD20; negative for CD3, CD5, CD10, cyclinD1, BCL2, CD25, and CD103; and showing Ig light chain restriction. Peripheral blood flow cytometry shows the same phenotype.

Which of the following infections is most likely to be detected in this patient?

A. Epstein–Barr virus
B. Human T-cell leukemia virus, type 1 (HTLV-1)
C. *Chlamydia psittaci*
D. Hepatitis C virus
E. Human herpesvirus-8

2. A 57-year-old male presents with a 1 year of slowly enlarging lymph nodes in the neck and inguinal regions. He denies pain in the lymph nodes, fevers, drenching sweats, weight loss, or fatigue. Complete blood count is normal. He undergoes an excisional lymph node biopsy. Immunohistochemical staining on neoplastic cells show they are CD20+, CD5-, CD10+, BCL2+, BCL6+, cyclinD1-, and sIg bright. Centroblasts are observed at <15 per high-powered field. Ki-67 is <20%.

Which of the following is the most likely to be detected on fluorescence in situ hybridization (FISH)?

A. t(9;14)(p13;q32)
B. t(11;18)(q21;q21)
C. t(11;14)(q13;q32)
D. t(14;18)(q32;q21)

3. A 45-year-old female presents with enlarged lymph nodes in her axillary and inguinal regions. An excisional lymph node biopsy is performed and consistent with follicular lymphoma, grade 2. She has no symptoms, continues to work full time, and has an Eastern Cooperative Oncology Group (ECOG) performance score of 0. A complete blood count is normal. A PET scan reveals uptake in her cervical, axillary, and inguinal lymph nodes, and all nodes are less than 3 cm. She does not demonstrate any splenomegaly. Her bone marrow biopsy is negative for involvement of her follicular lymphoma.

What is the appropriate initial step in management?

A. Treatment with rituximab and bendamustine
B. Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
C. Observation
D. Treatment with rituximab monotherapy × four doses

4. The same patient described above returns to clinic in 3 months. She has developed nightly drenching sweats and 15-lb weight loss. A repeat PET/CT shows interval slight enlargement in several of her lymph nodes, which all have similar levels of fluorodeoxyglucose (FDG) avidity as her initial PET/CT. She undergoes treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for symptomatic follicular lymphoma. Her posttreatment PET scan reveals a complete remission. She has come to your clinic today and asks about the role of maintenance rituximab after chemotherapy.

Which of the following best describes the role of maintenance rituximab when compared to surveillance?

A. Rituximab can prolong her time to progression and prolong her overall survival.
B. Rituximab can prolong her time to progression but overall survival is not changed.
C. Rituximab does not change her time to progression but can improve overall survival.
D. Rituximab decreases her risk of lymphoma transformation.

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5. A 68-year-old female returns to clinic for biopsy-confirmed relapsed low-grade follicular lymphoma. She was previously treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and obtained a complete remission for 1 year before relapsing with symptomatic disease, at which point she was treated with rituximab and lenalidomide. She obtained a partial response before developing symptomatic progression. She has an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 1 and is interested in more therapy, but prefers oral agents only at this time. Her medical history includes hypertension for which she takes two antihypertensive medications, poorly controlled insulin-dependent type 2 diabetes mellitus, and a history of small bowel obstruction with perforation in the past.

Which of the following treatments would be the most reasonable in her case?

A. Copanlisib
B. Duvelisib
C. Ibrutinib
D. Idelalisib
E. Venetoclax

6. A 56-year-old male presents with progressive abdominal pain and weight loss. He was first evaluated by a gastroenterologist and underwent an upper endoscopy, which revealed a gastric ulcer and mild mucosal erythema of the gastric wall. Biopsy of the ulcer is consistent with gastric mucosa-associated lymphoid tissue (MALT) lymphoma. *Helicobacter pylori* testing on the biopsy specimen is positive. Complete blood counts and comprehensive metabolic panel are within normal range. CT scan of the abdomen and pelvis does not identify any abnormalities. He is considered to have stage II disease. He begins antibiotic treatment for the *H. pylori*.

Identification of which of the following abnormalities is most predictive of lack of response to antibiotics?

A. t(3;14)
B. t(11;14)
C. t(11;18)
D. t(14;18)

7. The patient in Question 6 is identified to have the translocation predicting poor response to antibiotics alone. He is managed with antibiotic therapy and involved-site radiation therapy. He had significant side effects from the radiation therapy, but gradually recovered completely. Three months after completion of therapy, repeat endoscopy and biopsy do not detect any lymphoma, and *Helicobacter pylori* testing is negative. He continues to undergo surveillance endoscopy every 3 to 6 months. Three years later, surveillance endoscopy shows mucosal erythema; biopsy is consistent with recurrent gastric mucosa-associated lymphoid tissue (MALT) lymphoma; *H. pylori* testing is negative. He has no symptoms. He has not observed any melena or bright red blood in his stool. Complete blood count and

comprehensive metabolic panel tests are normal. Repeat CT scans do not identify any bulky disease. He enjoys his current job, which involves frequent, long trips overseas, and prefers to avoid interruptions in his work at this time.

Which of the following is the best management choice?

A. Observation and repeat endoscopy in several months
B. Treatment with antibiotics alone
C. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
D. Repeat involved-site radiation therapy
E. Surgical resection

8. A 70-year-old male presents for evaluation of an incidentally discovered elevated immunoglobulin M (IgM) level. Serum protein electrophoresis and immunofixation were previously obtained and detected a monoclonal protein (IgM) at 2.5 g/dL. Serum free light chains are normal. Complete blood count is normal. Serum creatinine is 1.1 and serum calcium is 9.8. Bone marrow biopsy is obtained and is significant for a 20% infiltrate consisting of small lymphocytes, plasmacytoid lymphocytes, and plasma cells. The infiltrate has expression of CD19, CD20, CD22, and IgM, whereas negative for CD5, CD10, and CD103. PET/CT did not identify bone lesions or splenomegaly, but was notable for mildly enlarged intraabdominal and inguinal lymph nodes. Vital signs are normal, and he is asymptomatic.

Which of the following tests would be most useful to support the likely diagnosis?

A. *BCL2* rearrangement
B. Fluorescence in situ hybridization (FISH) for deletion of 17p
C. *MYD88* mutation testing
D. *BRAF V600E* mutation testing
E. *IRF4/MUM1* rearrangement

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ANSWERS

1. **D. Hepatitis C virus.** His clinical picture, peripheral blood smear, immunophenotype on flow cytometry and bone marrow are suggestive of a marginal zone lymphoma (MZL). The massive splenomegaly and bone marrow pattern (intrasinusoidal lymphoid infiltrate) are most strongly suggestive of a splenic MZL. The negative CD25 and CD103 argue against hairy cell leukemia, which can also present with splenomegaly and cytopenias. Splenic MZLs have been shown to be associated with chronic hepatitis C infection and can regress after treatment of the hepatitis C. Epstein–Barr virus infections can be seen in Burkitt lymphoma in Africa, posttransplant lymphoproliferative disorders, natural killer (NK)/T-cell lymphoma, and diffuse large B-cell lymphoma (DLBCL) of the elderly. The morphology and immunophenotype of the neoplastic cells in this patient do not fit any of these disorders. HTLV infections are associated with T-cell lymphomas, but the immunophenotype here is consistent with a B-cell disorder. *Chlamydia psittaci* has been associated with orbital adnexal lymphoma, not splenic marginal zone lymphoma (MZL). Human herpesvirus-8 is associated with body cavity lymphoma (also known as primary effusion lymphoma), usually in immunocompromised patients.

2. **D. t(14;18)(q32;q21).** The pattern observed on immunohistochemical stains is most consistent with follicular lymphoma. The most common translocation observed in follicular lymphoma is the t(14;18)(q32;q21), which involves the *IGH* gene on chromosome 14q32 and the *BCL2* gene on chromosome 18q21.

3. **C. Observation.** She has asymptomatic grade 2 follicular lymphoma; observation is appropriate at this time.

4. **B. Rituximab can prolong her time to progression but overall survival is not changed.** The PRIMA trial was a phase III trial that randomized patients with follicular lymphoma to observation or maintenance rituximab given every 8 weeks for 2 years in those who responded to first-line chemoimmunotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP], rituximab, cyclophosphamide, vincristine, prednisone (R-CVP), or rituximab, cyclophosphamide, fludarabine, mitoxantrone [R-FCM]). At 10 years, the progression-free survival was 51% in the maintenance rituximab arm versus 35% in the observation arm, a finding that was statistically significant. The overall survival was 80% in both arms. There was no difference in the risk of transformation or quality of life measures. There was an increased risk of infection in the maintenance of rituximab arm.

5. **B. Duvelisib.** Three PI3K inhibitors (copanlisib, duvelisib, and idelalisib) are approved in relapsed/refractor follicular lymphoma after two prior lines of therapy. Class side effects include hepatotoxicity, cytopenias, infection (pneumocystis jiroveci pneumonia [PCP], cytomegalovirus [CMV] reactivation), and immune-related diarrhea (can also be non-immune), pneumonitis, and cutaneous reactions. Copanlisib is given intravenously rather than orally and can cause or worsen hypertension or hyperglycemia; since this

patient already has poorly managed hypertension and diabetes, and prefers an oral medication, copanlisib would not be the best choice. Idelalisib has a black box warning for intestinal perforation; given her prior history of intestinal perforation, duvelisib may be a better choice. Single-agent ibrutinib or venetoclax are not currently approved for treatment of follicular lymphoma.

6. **D. t(11;18).** This translocation is predictive of lack of response to antibiotics in *H. pylori*-positive gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Such cases often require the addition of involved-site radiation therapy or rituximab in localized MALT lymphoma. t(1;14), t(3;14), and t(14;18) can also be found in gastric MALT lymphomas, but are not known to predict response to antibiotics.

7. **A. Observation and repeat endoscopy.** This patient had a complete response to antibiotics and involved-site radiation therapy for localized gastric mucosa-associated lymphoid tissue (MALT) lymphoma, then developed recurrence while undergoing surveillance endoscopy several years later. Patients with advanced stage or recurrent gastric MALT lymphoma can be observed if there are no indications for treatment (gastrointestinal [GI] bleeding, bulky disease, threatened end-organ damage, rapid progression). In this case, the patient does not have any indications for treatment so observation and repeat endoscopy would be most appropriate. If treatment is indicated, then chemoimmunotherapy would be appropriate at that time.

8. **C. *MYD88* mutation testing**. The patient in this scenario most likely has lymphoplasmacytic lymphoma (LPL). The lack of CRAB features, presence of lymphadenopathy, and lymphoplasmacytic features in the bone marrow point toward LPL rather than multiple myeloma. *MYD88* mutations are found in approximately 90% of patients with LPL. *BCL2* rearrangements can be found in B-cell lymphomas, but would not add diagnostic value in this setting. Deletion of 17p can be helpful in making treatment decisions in some B-cell neoplasms, but not in diagnosis. *BRAF V600E* mutations can be seen in classic hairy cell leukemia (HCL); in this case, HCL appears unlikely based on the negative CD103 and lack of other suggestive features. *IRF4/MUM1* rearrangements can be seen in large B-cell lymphoma with IRF4 rearrangement or in some cases of grade 3b follicular lymphoma.

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High-Grade Non-Hodgkin Lymphoma

7

Jennifer E. Girard and Tycel J. Phillips

- Aggressive B-cell non-Hodgkin lymphomas (NHLs) comprise a group of mature B-cell neoplasms that are clinically aggressive neoplasms, presenting most often in the fifth and sixth decade of life with acute onset of B symptoms and are usually curable with combination chemotherapy.
- This heterogenous group of diseases includes the following:
  - Diffuse large B-cell lymphoma (DLBCL)
  - Burkitt lymphoma (BL)
  - Mantle cell lymphoma (MCL)
  - Primary mediastinal B-cell lymphoma (PMBL)
  - High-grade B-cell lymphoma (HGBL): World Health Organization (WHO) classification for B-cell non-Hodgkin lymphoma (Figure 7.1) was updated in 2017 that changed "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma" to "high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements."

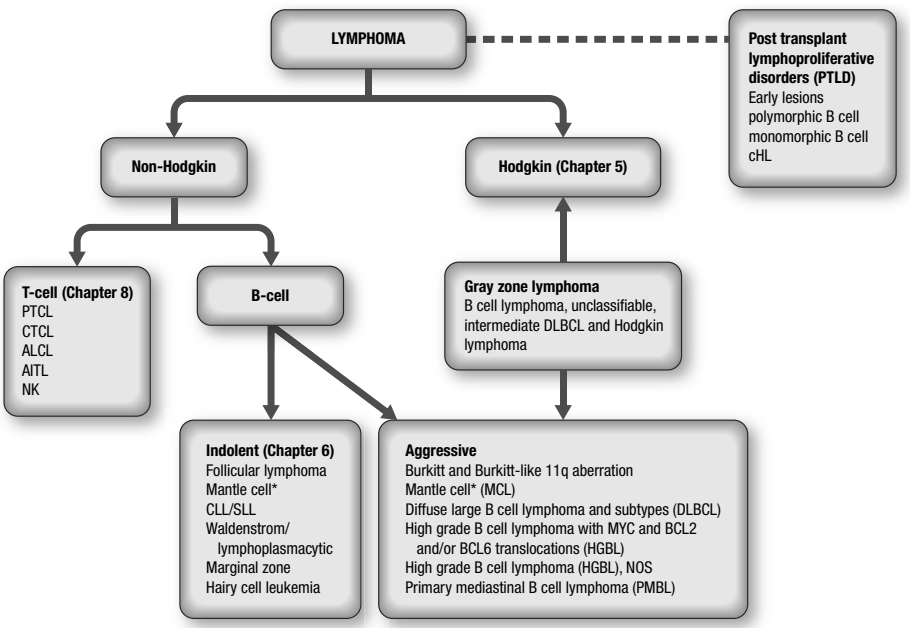

FIGURE 7.1 ■ World Health Organization (WHO) 2017 classification of mature B- and T-cell neoplasms.

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EPIDEMIOLOGY

1. How common are NHL and what is the most common subtype of aggressive B-cell NHL?

- There were 74,000 new cases of NHL (4% of all new cancer cases) in 2019 and B-cell lymphomas comprised 85% of all NHL in the United States with stable incidence since 1990.
- DLBCL is the most common subtype of NHL and comprises approximately 30% of all NHLs.

2. What are the risk factors associated with aggressive B-cell NHL?

- Infection, most commonly
  - HIV associated with DLBCL
  - Epstein–Barr virus (EBV) associated with BL in Africa and DLBCL in the elderly.
- Iatrogenic immunosuppression in organ transplantation leading to dysregulated B-cell proliferation and susceptibility to EBV infection.

DIAGNOSTIC WORKUP

1. How do you make a tissue diagnosis of an aggressive B-cell NHL?

- Excisional biopsy of fluorodeoxyglucose (FDG) avid lymph node as detected on PET/CT is preferred. Core needle biopsy is acceptable for inaccessible lymph nodes. Fine needle aspiration should be avoided since nodal architecture is difficult to fully assess.
  - **Hematoxylin and eosin (H&E) staining reveals diffuse infiltration by medium or large lymphoid monomorphic cells with high nuclear to cytoplasmic ratio and high mitotic rate.**
  - **Immunohistochemical (IHC) stains are usually positive for B-cell markers CD19, CD20, CD22, CD79a and variably positive for CD5, CD10, sIg, cyclin D1, BCL2, BCL6, MUM1 depending on type.**
  - **NOTE: TdT, a marker for lymphoid immunoblasts, is negative.**
  - **Ki67, a marker for cell proliferation, is usually >90%.**
- Aggressive B-cell NHLs arise from the germinal center of lymph node except for MCL (Figure 7.2).
  - **Diffuse large B-cell usually originates from germinal center B-cells (GCB) that express C10+, but can arise from activated B-cells that usually lose CD10+ and can express MUM1.**
  - BL and HGBL usually originate from GCBs.
  - **MCL originates from mantle zone and therefore is usually CD5+.**
- **HINTS:**
  - **If DLBCL and CD10+, it is germinal center type**
  - **If cyclin D1 positive by IHC and t(11;14) present by fluorescence in situ hybridization (FISH), it is MCL**
  - **BL expresses CD10, BCL6, and MYC, but rarely expresses BCL2.**

2. How is the cell of origin of DLBCL determined and how does cell of origin impact survival?

- Immunohistochemistry staining and use of the Hans (among others) as outlined in Figure 7.3.

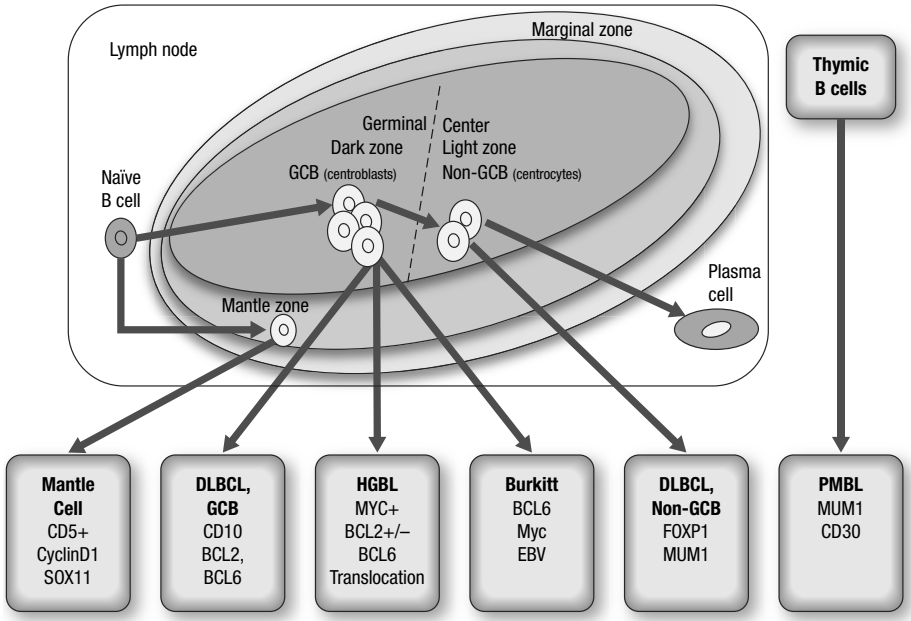

FIGURE 7.2 ■ Immunohistochemistry expression of aggressive B-cell non-Hodgkin lymphoma (NHL).

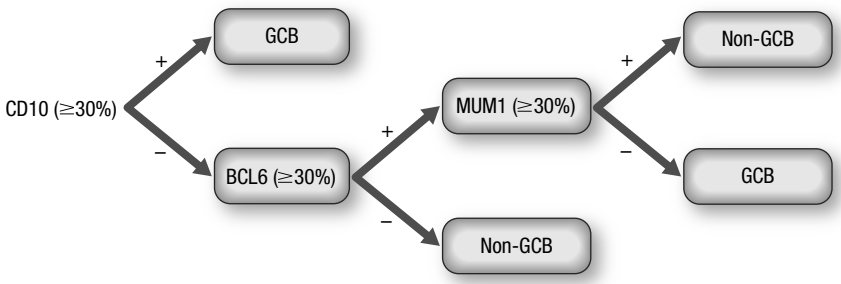

FIGURE 7.3 ■ Hans algorithm to determine diffuse large B-cell lymphoma (DLBCL) cell of origin.

- DLBCL, GCB type: better survival due to good response to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy (overall survival [OS] 5 year 70%)
- DLBCL, non-GCB type: usually activated B-cell, inferior survival due to poor response to R-CHOP therapy (OS 5 year 50%)

3. What does duel expresser mean in the context of DLBCL and how does it impact survival?

- Co-expression of c-MYC ≥40% and BCL2 ≥50% by IHC and predicts *inferior survival* when treated with R-CHOP therapy (3-year progression-free survival [PFS] 46% versus 65% and 3 year OS 46% versus 75%) for duel expressers but better prognosis when compared with HGBL with MYC and BCL2 and/or BCL6 translocation.

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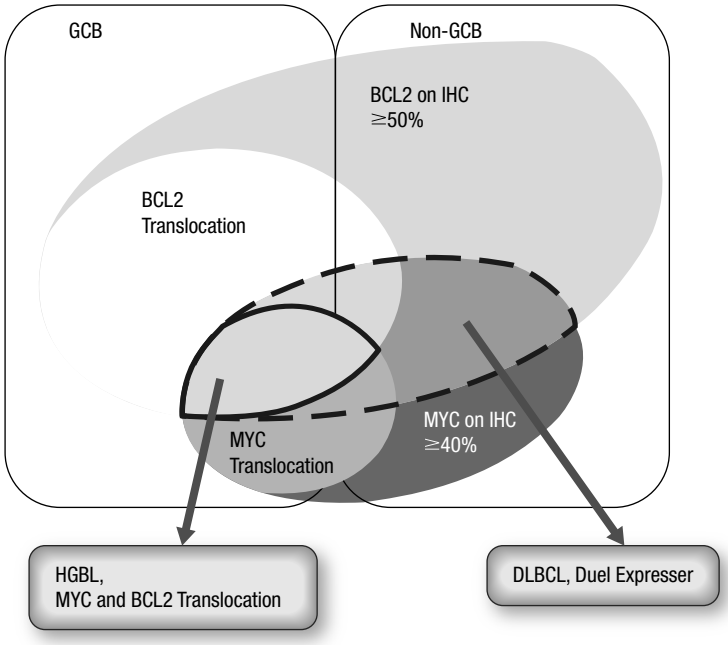

FIGURE 7.4 ■ Diffuse large B-cell lymphoma (DLBCL), duel expresser versus high-grade B-cell lymphoma (HGBL), MYC, and BCL2 translocation.

4. How is a HGBL with MYC and BCL2 and/or BCL6 rearrangements distinguished from a duel expresser DLBCL?

- If a large B-cell lymphoma expresses MYC ≥40% by IHC, send for FISH for MYC rearrangements and if positive send for FISH for BCL2 and BCL6 rearrangements.

5. What are the chromosomal translocations as detected by FISH and oncogenes (and function) associated with aggressive B-cell NHL?

TABLE 7.1 ■ Common Translocations in Aggressive B-Cell NHL

NHL B-Cell Subtype	Cytogenetics	Oncogene	Function
HGBL BCL 2	t(14:18)	BCL2	Anti-apoptosis
BCL6	t(3;14), t(3;v)	BCL6	Anti-apoptosis
MYC translocation	t(2;8), t(8;14), t(8;22)	cMyc	Transcription factor
Mantle cell lymphoma	t(11;14)(q13;q32)	Cyclin D1	Cell cycle regulator
Burkitt lymphoma	t(8;14) most common t(2;8), t(8;22)	cMYC	Transcription factor

NHL, non-Hodgkin lymphoma.

STAGING AND SPECIAL CONSIDERATIONS

1. What imaging and testing is required to complete staging prior to treatment of aggressive B-cell lymphomas?

- PET/CT is recommended, adequate to assess bone marrow involvement. (Exception: MCL requires bone marrow biopsy.) CT neck/chest/abdomen pelvis acceptable but requires bone marrow biopsy to assess bone marrow involvement.
- Staging: Ann Arbor staging system.
- Lumbar puncture (LP) for all patients HGBL, BL, and select patients with DLBCL (see Table 7.2) and MCL; check cell counts, protein, glucose, cytology, and flow cytometry on cerebrospinal fluid (CSF) examination.
- MRI brain recommended for those with extranodal disease and BL
- Labs: Complete blood count (CBC), lactate dehydrogenase (LDH), HIV testing, hepatitis B surface ag/ab, core IgG + IgM
- Fertility counseling recommended
- Multiple-gated acquisition (MUGA)/transthoracic echocardiography (TTE) if treating with anthracycline

TABLE 7.2 ■ NCCN-IPI for DLBCL Updated for the Rituximab Era

Risk Factors	Score	IPI Risk	5-Y OS (%)
■ Age: 1 pt > 40 to ≤ 60, 2pt > 60 to < 75, 3pt >75 ■ LDH: 1pt >1 to ≤ 3XULN, 1pt > 3XULN ■ Ann Arbor Stage III–IV 1pt ■ Extranodal disease 1pt ■ Performance status ≥ 2 1pt	0–1	Low	96
	2–3	Low intermediate	82
	4–5	High intermediate	64
	≥6	High	33

DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; NCCN IPI, National Comprehensive Cancer Network International Prognostic Index.

2. How are response to therapy and ongoing remission monitored (role of PET scan)?

- Repeat PET/CT after three to four cycles of chemotherapy to determine interval response to initial therapy, then after completion of chemotherapy but before planned RT.
  - Complete response (CR) is considered if FDG uptake on PET/CT is less than or equal to uptake in the liver (Lugano 1, 2, or 3) with no FDG uptake in the bone marrow.
  - Partial response (PR) is considered if FDG uptake on PET/CT is greater than that of liver (Lugano 4 or 5) but reduced compared to pretreatment PET/CT.
  - Obtain posttreatment PET/CT 6 to 8 weeks after completion of therapy.
- If PR to therapy, no response to therapy, or disease progression on interim or posttreatment PET/CT with biopsy proven persistent disease, proceed to second-line therapy.
- If CR, proceed to observation with H&P and labs every 3 to 6 months for 5 years posttherapy.

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NOTE: False-positive PET scans are frequent therefore, biopsy of PET-positive should be completed prior to change in treatment.

NOTE: Surveillance imaging has not been shown to have direct impact on patient outcomes in retrospective studies.

3. What are the hallmarks of tumor lysis syndrome (TLS), what are the risk factors and how should TLS be monitored and prevented?

- **BL presents the highest risk of spontaneous tumor lysis and TLS with initiation of cytotoxic chemotherapy.**
- Laboratory hallmarks of TLS include elevated K+, uric acid, phosphorous, and low calcium.
- Risk factors for TLS based on National Comprehensive Cancer Network (NCCN): bone marrow involvement, elevated white blood cell (WBC), evidence of spontaneous TLS, and decreased renal function at baseline.
- Prevent by starting high-risk patients on allopurinol and hydration
- Monitor uric acid, potassium, phosphorus, creatinine, calcium, and LDH.
- Treat TLS with allopurinol and hydration with normal saline in cases with evidence of TLS.
  - Consider febuxostat if renal failure, and
  - Rasburicase when uric acid is >12.

4. What is the role of hepatitis B prophylaxis in patients infected with hepatitis B who need treatment with rituximab?

- Treatment with Rituximab may cause hepatitis B reactivation.
  - If there is active hepatitis B virus (HBV) disease with positive polymerase chain reaction (PCR) viral load, treat for HBV.
- Prophylactic antiviral therapy is recommended for patients who are hepatitis B surface antigen (HBsAg), or HB core IgG, or IgM positive with negative HBV PCR viral load.
  - Prophylaxis with entecavir during and for 12 months after treatment with anti-CD20 antibody while monitoring HBV PCR viral loads during treatment.

NOTE: avoid lamivudine due to resistance.

5. In terms of anti-CD20 antibodies used to treat aggressive B-cell NHL, what is the role of obinutuzumab, subcutaneous injection of rituximab, and rituximab biosimilars?

- Rituximab is a murine type I antibody localizing CD20 into lipid rapids resulting in complement-dependent cytotoxicity (CDC) but minimal direct cell death (DCD).
  - Two Food and Drug Administration (FDA)-approved rituximab biosimilars (a) rituximab-abbs Truxima (b) rituximab-pvvr Ruxience can be substituted for rituximab in all subtypes B-cell NHL. However, are not interchangeable, that is, must use same antibody for the course of treatment.
- Subcutaneous rituximab Hycela hyaluronidase can be substituted for infusional rituximab after first infusional dose of rituximab in R-CHOP regimen to treat DLBCL but not for other types of aggressive B-cell NHL.
- Obinutuzumab is a fully humanized type II anti-CD20 antibody with homotypic adhesion resulting in DCD and more potent antibody-dependent cellular cytotoxicity (ADCC).

- G (obinutuzumab)-CHOP failed to show PFS, OS, or improved safety benefit compared to R-CHOP in phase III clinical trial GOYA and therefore is currently not used to treat DLBCL.
- Although FDA approved for the indication, use of obinutuzumab in treatment of aggressive B-cell lymphoma is not included in the NCCN guidelines and has not been widely adopted.

TREATMENT

The following section outlines treatment for aggressive B-cell NHL type that includes DLBCL, HGBL with translocations of MYC and BCL2 and/or BCL6 (HGBL DH/TH), BL, MCL, and PMBL summarized in Table 7.3.

DIFFUSE LARGE B CELL LYMPHOMA

DLBCL is the most common subtype of NHL and comprises approximately 30% of all NHLs.

1. What are the risk factors that determine prognosis in patients with DLBCL?

2. What are the risk factors for central nervous system (CNS) recurrence?

3. What is the first line treatment for DLBCL by stage?

- Treatment at all stages is with curative intent.
- *Stages I–II, nonbulky:* Three cycles R-CHOP followed by involved field radiation therapy (IFRT), or six cycles R-CHOP with or without IFRT
- *Stages II bulky–IV:* Six cycles R-CHOP consider IFRT to the "bulky" areas
  - R-CHOP is standard first-line therapy. R-CHOP should be given in 21-day cycles (R-CHOP-21). NOTE: Monitor for signs of congestive heart failure (CHF), neuropathy, myelosuppression, and liver or renal dysfunction.

    NOTE: Frontline treatment currently is not dependent on the DLBCL subtype (GCB versus non-GCB), however response rate to R-CHOP is inferior in the non-GCB subtype compared to GCB and also inferior in duel expressers (BCL2+ and MYC+ by IHC).

  - Add growth factor granulocyte colony-stimulating factor (G-CSF) if age >65 years or neutropenic fever
  - CNS prophylaxis: if there is high risk for CNS relapse based on CNS International Prognostic Index (IPI) prognostic model (Table 7.4), use intrathecal (IT) MTX up to four doses concurrent with R-CHOP therapy as CNS prophylaxis.
  - Parenchymal CNS disease: incorporate high-dose systemic methotrexate on day 15 of 21st day R-CHOP cycle with growth factor
  - Leptomeningeal disease: incorporate IT methotrexate or cytarabine twice weekly until CNS is negative for lymphoma concurrent with systemic R-CHOP. Consider high-dose systemic methotrexate on day 15 of 21 R-CHOP cycle or consolidation after R-CHOP plus IT therapy plus growth factor.

NOTE: If anthracycline contraindicated, consider rituximab, vincristine, etoposide, cyclophosphamide, prednisone(R-CEOP)

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TABLE 7.3 ■ Treatment for Aggressive B-Cell NHL

Subtype (% of NHL)	Staging	First-Line Therapy	CNS PPX	Anti-CD20 Maintenance	Second-Line Therapy	Third-Line Therapy
DLBCL (30%)	■ PET/CT ■ LP if CNS IPI High ■ EGD/colo if GI involved	■ I-II non-bulky: ■ II bulky-IV: ■ Cardiac issues: ■ No consolidation	Yes If CNS IPI High	No	■ Chemo ■ (R-ICE,R-GemOx, R-DHAP); ■ if CR HDT/ASCR or if PR CAR-T ■ Nontransplant: R-GemOx, R-GDP, non-GC: Ibrutinib, R2	■ Polatuzumab venotin + BR ■ Selinexor ■ Clinical Trial
HGBL DH/TH (2%–5%)	■ PET/CT ■ LP ■ EGD/colo if GI involved	■ R-DA-EPOCH ■ R-CODOX-M ■ R-Hyper-CVAD ■ No consolidation	Yes	No	■ (R-ICE,R-GemOx, R-DHAP); ■ if CR HDT/ASCR or if PR CAR-T	
BL (1%–2%)	■ PET/CT ■ LP	■ R-CODOX-M ■ R-Hyper-CVAD ■ DA-R-EPOCH ■ No consolidation	Yes	No	■ Transplant: DA-EPOCH, R-ICE, R-GDP and if CR HDT/ASCR ■ If localized add ISRT	■ Clinical Trial
MCL (5%)	■ PET/CT ■ BmBX ■ EGD/colo ■ LP blastoid, ki67≥30%	■ Age <65 transplant: NORDIC + HDT/ASCR ■ Age ≥65 nontransplant:	No	Yes after HDT/ASCR Every 2 months 3 y or R-CHOP Every 2 months for 2 y	■ BTK inhibitors ■ Nontransplant: ■ Ibrutinib plus venettoclax or palbociclib or R2	■ CAR T-cell therapy ■ Clinical Trial

TABLE 7.3 ■ Treatment for Aggressive B-Cell (NHL) (*continued*)

Subtype (% of NHL)	Staging	First-Line Therapy	CNS PPX	Anti-CD20 Maintenance	Second-Line Therapy	Third-Line Therapy
PMBL (2%–4%)	■ PET/CT	■ 6 × DA-EPOCH-R ■ 6 × R-CHOP + RT	No	No	■ Pembrolizumab ■ See DLBCL	
AIDS-related (1%–2%)	■ PET/CT ■ EBER-ISH ■ HHV8 ■ LP ■ CD4+/T cell subset	■ ART ■ HIV BL same as BL ■ HIV DLBCL: EPOCH-R ■ HIV PBL: CODOX-M, Hyper-CVAD	Yes	No	■ BV-R-ICE, R-ICE, ESHAP and if candidate, HDT/ASCT	
PTLD	■ PET/CT ■ EBER-ISH	■ Early: RI ■ Polymorphic: RI plus rituximab ■ Monomorphic B-cell: RI plus R-CHOP				

BL, Burkitt lymphoma; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; GI, gastrointestinal; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with methotrexate and cytarabine; HGBL, high-grade b-cell lymphoma; IPI, International Prognostic Index; ISRT, involved site radiation therapy; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphomas; NORDIC, rituximab, cyclophosphomide, doxorubcin, vincristine, prednisone alternative with high dose cytarabine; PMBL, primary mediastinal B-cell lymphoma; PTLD, posttransplant lymphoproliferative disorder; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RI, reduce immunosuppression.

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TABLE 7.4 ■ CNS IPI Prognostic Model to Assess the Risk of CNS Relapse in DLBC

Risk Factors	Score	IPI Risk	CNS PPX Recommended?
■ Age >60 1 pt ■ LDH: >normal 1pt ■ Ann Arbor Stage II–IV: 1pt ■ Extranodal >1 site 1pt ■ Kidney/adrenal gland involvement 1pt	0–1	Low	No
	2–3	Intermediate	No
	4–6	High	Yes
Special Cases: HIV lymphoma, testicular lymphoma, primary cutaneous lymphoma and stage IE DLBCL of the breast			Yes

CNS IPI, central nervous system International Prognostic Index; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase.

NOTE: There is no definitive role for high-dose chemotherapy/autologous stem cell rescue (HDT/ASCR) in the first-line setting

NOTE: There is ***no*** role for maintenance rituximab

4. What are second- and third-line treatments for relapsed or refractory DLBCL and what are the outcomes?

- **Prognosis is poor if short <6 months duration of response or no response to first-line therapy with OS 13% at 4 years.**
- **Prognosis is better if at least 12-month disease-free survival OS 40% at 4 years**
- **Relapse usually occurs within 2 years.**
- **Response to therapy predicted by IPI**
- If autologous stem cell transplant candidate:
  - R-(rituximab) plus ifosfamide, carboplatin, etoposide (ICE)
  - Gemcitabine-based regimen (gemcitabine, dexamethasone, cisplatin [GDP], or Gemcitabine, oxaliplatin [GemOx])
  - Dexamethasone, high dose cytarabine, cisplatin (DHAP)

TABLE 7.5 ■ sAAIPI Prognostic Model to Assess Response to Second-Line Therapy

Risk Factors	Score	sAAIPI Risk	OS at 4 Y
■ ECOG >1 1pt ■ LDH >ULN 1 pt ■ Ann Arbor Stage III–IV 1pt	0	Low	74%
	1	Intermediate	39%
	2, 3	High	16%

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OS, overall survival; sAAIPI, second-line age-adjusted International Prognostic Index; ULN, upper limit of normal.

- *Goal*: achieve a CR, then proceed to high-dose chemotherapy with typically R-BEAM (rituximab, carmustine, etoposide, cytarabine, melphalan) and autologous stem cell rescue (HDT ASCR).
- If not a transplant candidate: R-GemOx, R-GDP and if non-GCB consider Bruton's tyrosine kinase(BTK) inhibitor ibrutinib or R-lenalidomide.
- If there is a PR to second line or third line therapy, consider lymphodepleting chemotherapy (cytarabine ± fludarabine) followed by anti-CD19 CAR-T therapy with axicabtagene ciloleucel (Yescarta) or tisagenlecleucel (Kymriah).
- Third-line therapy with antibody-drug conjugate polatuzumab (anti CD79a) vedotin (microtubule inhibitor) + bendamustine + rituximab or selinexor (inhibitor of nuclear transport [SINE]).

5. Special case: What are the special features of transformation of follicular lymphoma to DLBCL?

- Transformation from follicular lymphoma to DLBCL occurs at a rate of approximately 3% per year and is associated with poor clinical outcomes. Prognosis is better in previously untreated patients with a localized area of transformation.
- Consider transformation if a patient with follicular lymphoma demonstrates disproportionately rapid growth of a lymph node group, elevated LDH, recurrent B-symptoms, or isolated area on a PET with disproportionately higher FDG uptake. Biopsy the more intensely PET avid lymph node.
- If previously untreated, treat initially with R-CHOP followed by radiation therapy if localized.
- If CR, consider 2 years rituximab maintenance if persistent FL.
- If PR to R-CHOP and persistent localized FDG avid biopsy-proven disease, consider ISRT or RIT (Yttrium 90-ibritumomab tiuxetan plus rituximab) to achieve CR prior to HDT/ASCR.
- If the patient has previously received R-CHOP, then treat with second-line salvage regimens such as R-ICE, R-DHAP, R-GemOX/R-GDP followed by HDT/ASCR.

BURKITT LYMPHOMA

BL is a rare type of aggressive lymphoma with three variants: sporadic (1%–2% of all lymphomas in American adults), immunodeficiency-associated (HIV, postorgan transplant, congenital immunodeficiency), and endemic (most common childhood malignancy in equatorial Africa, associated with EBV infection).

1. What are the risk factors that determine prognosis in patients with BL?

- Low risk: normal LDH, stage I with single nodal mass <10 cm or complete resected abdominal mass.
- Otherwise considered high risk.

2. What are the frequent clinical features of BL?

- Constitutional symptoms
- Spontaneous TLS
- Bone marrow involvement in up to 70% of patients at presentation
- Leptomeningeal involvement in up to 40% of patients at presentation
- Bulky abdominal (in adults) adenopathy.

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3. What is the preferred initial treatment for BL?

- **Treatment at all stages is with curative intent and requires intensive multiagent inpatient chemotherapy regimens that include IT chemotherapy for CNS treatment or prophylaxis as well as systemic Methotrexate to treat CNS disease. Patients require hospitalization with each cycle of therapy and often require outpatient platelet/blood transfusions and require G-CSF with each cycle of systemic therapy.**
- Treatment Regimens:
  - Cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M) alternating with ifosfamide, etoposide, high-dose cytarabine (IVAC), with IT methotrexate or Ara-C. Addition of rituximab may further improve outcomes in these patients.
  - Rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with methotrexate and cytarabine (R-Hyper-CVAD) (with IT methotrexate results in similar outcomes to CODOX-M).
  - Etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin + rituximab (DA-R-EPOCH) only if there is not parenchymal CNS and patients who cannot tolerate an intensive regimen.

NOTE: If patient presents with symptomatic CNS disease, start with arm of therapy that contains CNS penetrating agents.

NOTE: All patients with BL should receive CNS prophylaxis with systemic methotrexate and/or IT chemotherapy with methotrexate or cytarabine.

NOTE: Consolidation therapy only in special cases or in the context of clinical trial, but is not standard.

4. What is prognosis and second-line therapy for relapsed or refractory BL?

- Prognosis is very poor and there is no definitive second line therapy.
- If relapse occurs >6 to 18 months after initial therapy, consider DA-EPOCH, R-ICE, R-GDP followed by HDT/ASCT
- If localized, consider palliative ISRT

HIGH GRADE B-CELL LYMPHOMA

Translocations of MYC and BCL2 and/or BCL6 (Double/Triple-Hit Lymphoma, HGBL CH/TL) and NOS

HGBL double/triple hit, previously B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL, is a new subtype WHO 2017 classification based on a group of lymphomas that are aggressive large B-cell lymphomas, usually of GC type, that have translocation of MYC and BCL2 and rarely BCL6 by FISH resulting in poor prognosis and inferior response to R-CHOP therapy.

HGBL, NOS appear blastoid or intermediate between DLBCL and BL but lack MYC and BCL2 and/or BCL6 translocations. Histologic features are intermediate between DLBCL and BL: presence of "starry sky" pattern, some large cells, Ki-67 >90%.

1. What are the risk factors that determine prognosis in patients with Translocation MYC + BCL2 ± BCL?
Based on IPI (see Table 7.2)

2. What are the frequent clinical features of HGBL DH/TH or NOS?
- Presents with poor prognosis parameters including elevated LDH, bone marrow involvement, CNS involvement (10%–13%).

3. What is the first-line of therapy for treatment of HGBL, translocation MYC + BCL2 ± BCL or NOS?
- There is no standard of care
  - R-CHOP results in inferior outcomes and patients are not likely to achieve CR.
  - R-DA-EPOCH results in superior PFS (22 vs. 8 months) compared to R-CHOP but studies have failed to demonstrate improvement in OS.
  - In fit patients with disease with high IPI, consider intensive chemotherapy regimens with R-Hyper-CVAD or CODOX-M that demonstrate similar PFS as R-DA-EPOCH.
  - Consider consolidative RT for localized disease
  - CNS prophylaxis (PPX) for all patients, there no standard regimen but should include IT MTX or Cytarabine and systemic methotrexate.

NOTE: There is no PFS or OS benefit to consolidation therapy with HDT/ASCR following R-DA- EPOCH but can be considered in certain cases.

NOTE: If treated with R-CHOP and achieved CR, consider HDT/ASCR.

4. What is the second-line treatment for relapsed or refractory HGBL DH/TH or NOS?
Relapsed/refractory disease treated in the same manner as DLBCL.

MANTLE CELL LYMPHOMA

MCL is a subtype of B-cell lymphoma characterized by t(11;14) (q13;q32) translocation that results in overexpression of cyclin D1 and cell cycle dysregulation. Of cases, 85% to 90% are clinically aggressive and are considered conventional nodal MCL (cMCL). About 10% of cMCL present as a blastoid variant. Approximately 10% to 15% of cases are nonnodal disease that behave as indolent lymphomas and possess certain low-risk features that include circulating disease, immunoglobulin heavy chain (IGHV) hypermutation, SOX11 expression, low Ki67.

1. What are the risk factors that determine prognosis in patients with MCL?
- Mantle Cell Lymphoma International Prognostic Index (MIPI) is calculated using the following equation
- (0.03535 × age [years]) + 0.6978 (if Eastern Cooperative Oncology Group [ECOG]>1) + (1.367 × log10 [LDH/ULN]) + (0.9393 × log10 [WBC count per 10^{-6} L])
- Mutations in TP53 predict poor outcomes regardless of MIPI with median OS in TP53 mutated patients of 1.8 years versus 12.7 years in patients with nonmutated TP53.

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TABLE 7.6 ■ Mantle Cell Lymphoma International Prognostic Index

Risk Factors	Score	MIPI Risk	Median OS
■ Age ■ ECOG LDH >ULN 1 pt ■ LDH ■ WBC	<5.7	Low	5 y OS 60%
	5.7–6.2	Intermediate	51 months
	≥ 6.2	High	29 months

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OS, overall survival; WBC, white blood cell.

2. What is the typical first-line treatment for MCL by stage?

- **There is no standard of care for MCL**
- MCL is not a curable disease and will relapse, even after HDT/ASCR in complete remission (CR)
  - In indolent cases, a watch and wait approach does not decrease OS
  - Stages I–II, nonbulky: bendamustine, rituximab (BR), R-CHOP, R2 (lenalidomide, rituximab) followed by IFRT.
  - Stages II bulky–IV:
    - If patient is young (<65 years), fit and a stem cell transplant candidate, consider aggressive regimen that contains cytarabine. Addition of cytarabine improves PFS to 8 years and median OS of more than 10 years. NORDIC regimen (rituximab, maxi-CHOP alternating with HD MTX and cytarabine) or alternating R-CHOP/R-DHAP) followed by consolidation with HDT R-BEAM and ASCR with maintenance with Rituximab every 8 weeks for 3 years.
    - If patient is older (≥65 years) or not a transplant candidate, consider less aggressive therapy.
    - Six cycles BR (does not require maintenance)
    - Six cycles R-CHOP (requires maintenance with rituximab every 2 months for 2 years)
    - Six cycles VR-CAP (bortezomib, rituximab, cyclcophosphamide, doxorubicin, prednisone; no evidence for maintenance)
- *CNS:* Patients with blastoid histology or Ki67 ≥30% should undergo LP to assess for CSF involvement and treatment should include systemic high dose MTX. Role for CNS PPX is unknown. Ibrutinib cross the blood–brain barrier and treats CNS disease in patients with relapse of MCL.

3. What is second- and third-line therapy for relapsed or refractory MCL?

- **If refractory disease or shortened duration of response to initial chemoimmunotherapy (<expected PFS), consider second- and third-generation single-agent BTK inhibitors acalabrutinib, zanubrutinib, or combination first-generation BTK inhibitor ibrutinib plus rituximab. Second- and third-generation have higher specificity and lower off target effects, specifically lower incidence of atrial fibrillation.**
- If patient is a transplant candidate and there was a PR to first-line chemoimmunotherapy, consider treating with a first-line regimen not previously received.
- If patient is refractory to or relapses after first-line chemoimmunotherapy and second-line

- BTK inhibitor, consider lymphodepleting chemotherapy with cytarabine + fludarabine followed by CD19 directed CAR-T with brexucabtagene autoleucel (Tecartus)

NOTE: Avoid bendamustine in patients that are candidates for CAR-T cell therapy due to T-cell depletion that hinders collection of T cells for adoptive therapy.

PRIMARY MEDIASTINAL B-CELL LYMPHOMA

Arises from thymic B-cells in young (30–40s) females as mediastinal (stage I/II) disease and can present with superior vena cava (SVC) syndrome, pleural or pericardial effusion. Widespread extranodal involvement is uncommon on initial presentation.

1. What are the risk factors that determine prognosis in patients with primary mediastinal B-cell lymphoma (PMBL)?

- IPI is not helpful in predicting outcomes.
- Risk factors that predict poor prognosis are controversial and may include male sex, advanced stage disease at diagnosis, elevated LDH.

2. What is the typical first-line treatment for PMBL by stage?

- There is no standard of care and optimal first-line therapy is debated.
- Treatment at all stages with curative intent.
- Regimens that do not require radiation ARE ideal in first-line setting to decrease sequela of mediastinal radiation in young woman:
  - Six cycles DA-EPOCH-R
  - Six cycles R-CHOP followed by radiation therapy

NOTE: Residual masses on PET/CT are common after completion of therapy, biopsy prior to further therapy.

3. What is second- and third-line for relapsed or refractory PMBL?

- Treat as DLBCL
- Pembrolizumab

AIDS-RELATED B-CELL LYMPHOMAS

- DLBCL, BL, and primary central nervous system lymphoma (PCNSL) are the most common subtypes of NHL in patients with HIV.
- Primary effusion lymphoma (PEL) and multicentric Castelman's are associated with HHV8 infection and a less common cause of AIDS-related lymphoma.
- Plasmablastic lymphoma (PBL) is a rare AIDS-associated lymphoma and is an aggressive subtype involving jaw and oral cavity.
- EBER-ISH *is recommended* for all patients diagnosed with AIDS-associated lymphoma.

1. What are the risk factors and prognosis of patients with AIDS-related lymphoma?

- **Five-year OS in patients with HIV-associated DLBCL, BL, and PCNSL are 50%, 44%, and 23%, respectively.**
- **Risk factors that portend poor prognosis include older age, lymphoma occurrence while on ART, lower CD4+ less than 50/mcL at diagnosis, high HIV RNA viral load.**

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- **In HIV-infected patients with DLBCL treated with ART and R-CHOP, PFS did not differ from their HIV-negative counterparts.**

2. **What are the first-line therapies and special considerations for treating patients with AIDS-related lymphoma?**
   - **Treatment is with curative intent**
   - **Use G-CSF**
   - **Prophylaxis against viral reactivation with acyclovir and PJP prophylaxis with sulfamethoxazole (Bactrim®)**
   - **Hold rituximab therapy when CD4+ count is less than 50 to 100/mcL.**
   - **ART should be administered during chemotherapy. However, zidovudine, cobicistat, ritonavir should be avoided given their interaction with CYP3A4.**
   - CNS prophylaxis is recommended.
   - **For treatment of HIV-associated BL treat per section.**
   - **For treatment of HIV-associated DLBCL, HHV8-associated DLBCL or PEL, EPOCH-R is the preferred regimen.**
   - **For treatment of HIV-associated PBL, treat with CODOX-M, EPOCH or Hyper-CVAD ± rituximab with HDT/ASCR for patients with high-risk features (IPI>2, MYC translocation, TP53 deletion).**

3. **What is prognosis and second- and third-line therapy for relapsed or refractory AIDS-related lymphoma?**
   - **Prognosis is poor with OS at 1 year of 35%**
   - **BV-R-ICE (bortezomib, rituximab, ifosfamide carboplatin, etoposide), R-ICE or ESHAP (top eoside, methylprednisone, cytarabine, cisplatin) followed by HDT/ASCT.**

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

PTLDs are a heterogenous group of lymphomas that occur after solid organ transplant or allogeneic hematopoietic cell transplant resulting from immunosuppression and the EBV. PTLD after solid organ transplant involves the grafted organ and after allogenic HCT involves the donor organ.

1. **Which transplants are associated with a higher incidence of PTLD?**
   - PTLD after solid organ tumor transplants, particularly those that require higher degrees of immunosuppression: heart and lung (~10%) > liver (1%–6%) > pancreatic (<5%) > kidney (<3%) transplants.
   - PTLD after allotransplant depends on degree of HLA matching: highest haploidentical (>20%) > unrelated donors (4%–10%)> umbilical cord (4%–5%) > match related donor (1%–3%).
   - Late onset (~50%) >1 year from transplant, EBV negative, more likely germinal center type
   - Early onset, EBV positive, non-GCB type

2. **What are the WHO classifications and risk factors that determine prognosis in PTLD?**
   - **Early lesions (nondestructive) PTLD: plasmacytic, infectious mononucleosis, follicular hyperplasia; occur within 1 year and EBV positive.**

- Monomorphic PTLD (B-cell, T-cell, and natural killer (NK)-cell subtype), most common with most common subtype DLBCL
- **Polymorphic PTLD typically EBV positive**
- **Classical Hodgkin lymphoma PTLD typically EBV positive**

3. What is the first-line therapy for treatment of posttransplant lymphoproliferative disorder treated?

- Treatment depends on the subtype of lymphoma. Treatment with antiviral therapy is debated as 40% of EBV associated lymphoproliferative disorders in immunocompromised patients have replicating EBV therefore antivirals can be considered in patients with early or polymorphic PTLD.
- Early lesions (nondestructive) PTLD: reduce immunosuppression and if CR, monitor. If there is persistent/progressive disease despite reduction of immunosuppression, then treat with rituximab alone. Monitor EBV load by PCR.
- Polymorphic PTLD: reduce immunosuppressive therapy followed by rituximab alone. Local treatment such as radiation therapy or surgery along with rituximab can also be considered.
- Monomorphic B-cell lymphoma: reduce immunosuppressives and chemoimmunotherapy (for DLBCL, R-CHOP).
- If Hodgkin lymphoma, treat as Hodgkin lymphoma (see Chapter 5).

QUESTIONS

1. A 56-year-old female presents to the ED with 4 weeks of an enlarging left cervical lymph node, night sweats, and 20 pound weight loss over 1 month. On exam, there is a 5 × 6 cm left cervical lymph node, palpable right cervical lymph nodes. Serum lactate dehydrogenase 850 (normal range 100–240 U/L). Core needle biopsy of left cervical lymph node with effacement of nodal architecture with lymphoid proliferation. Immunohistochemistry with neoplastic cells expressing CD20, CD10, BCL2 60%, MYC >50%, BCL 6 but not expressing MUM1. Ki67 95%.

What additional testing is required to make a diagnosis and determine therapy?

A. Immunohistochemistry (IHC) for cyclin D1 only
B. Fluorescence in situ hybridization (FISH) for MYC and if positive, BCL2 and BCL6
C. Polymerase chain reaction (PCR) for MYD88
D. Next-generation sequencing for *TP53* mutation only
E. Next-generation sequencing for TET2

2. A 35-year-old female presents to her primary care physician with shortness of breath that persists despite treatment for pneumonia with antibiotics and an albuterol inhaler. Primary care physician orders a CT of the thorax that demonstrates a 6 × 10 cm mediastinal mass which is redemonstrated on PET/CT. Biopsy is positive for a primary mediastinal B cell lymphoma. She receives six cycles of DA-EPOCH-P. PET/CT completed 4 weeks after therapy demonstrates a residual mass.

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What is the appropriate next step?

A. Additional two cycles of DA-R-EPOCH
B. Radiation therapy to the residual mass
C. Second-line therapy with R-ICE, plan for consolidation with HDT/ASCR
D. Repeat biopsy of the residual mass to ensure persistent disease
E. Observe with plan for repeat PET in 3 months

3. A 46-year-old female with history of heart transplantation 5 years ago presents with inguinal lymphadenopathy. She undergoes an excisional lymph node biopsy, which reveals a monomorphic posttransplant lymphoproliferative disorder (PTLD). She denies any fevers, chills, or weight loss. Her labs reveal a white blood cell (WBC) count of 7.7/mcL, hemoglobin of 13 g/dL, and platelet count of 160/mcL. Her comprehensive metabolic panel is unremarkable. Her lactate dehydrogenase (LDH) is 165 U/L. She undergoes a PET scan, which shows low level uptake only in her right inguinal lymph nodes.

What is the appropriate initial step in treatment of her posttransplant lymphoproliferative disorder (PTLD)?

A. Reduce her immunosuppressives
B. Observation and repeat her PET scan in 3 months
C. Treat with rituximab alone
D. Treat with R-CHOP
E. Treat with radiation therapy only

4. A 52-year-old male presents to the ED with 1 week of double vision, large palpable masses in his groin and axilla. He has been experiencing night sweats, fevers, and weight loss. PET/CT demonstrates a large metabolically active abdominal mass as well as diffuse axillary, mesenteric, retroperitoneal, and inguinal metabolically active lymphadenopathy. His laboratory studies reveal a white blood cell (WBC) count of 15/mcL, hemoglobin of 8.5 g/dL, platelet count of 80/mcL, lactate dehydrogenase 1250 U/L (normal range 100–240 U/L), uric acid 13 mg/dL (normal range 2–6 mg/dL), creatinine 2.2 mg/dL (normal range 0.8–1.2 mg/dL). A CT-guided core biopsy of the large mass reveals medium sized monomorphic lymphocytes in a starry sky appearance. Ki67 staining is >95%. Fluorescence in situ hybridization (FISH) for MYC is positive and negative for BCL2.

What is the diagnosis and what are the next most important steps in management.

A. High-grade B-cell lymphoma, treat tumor lysis syndrome with allopurinol and hydration, start DA-R-EPOCH
B. Plasmablastic lymphoma, test for HIV status, treatment for tumor lysis syndrome with febuxostat and hydration, start etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin + rituximab (EPOCH).
C. Burkitt lymphoma, test for HIV, treat for tumor lysis syndrome with rasburicase and hydration, start rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with methotrexate and cytarabine (R-Hyper-CVAD) and perform lumbar puncture

D. Diffuse large B-cell lymphoma, treat for tumor lysis with allopurinol and hydration, start rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
E. Acute B-cell lymphoblastic leukemia, perform bone marrow biopsy and test for Philadelphia chromosome, treat for tumor lysis with rasburicase and hydration, start R-Hyper-CVAD

5. A 29-year-old male presents with night sweats and palpable lymphadenopathy. He is referred to your clinic because he was recently diagnosed with HIV last week and was found to have a CD4 count of 40. A PET scan reveals fluorodeoxyglucose (FDG) avid lymph nodes in his cervical, axillary, inguinal, and retroperitoneal lymph nodes. He undergoes an excisional lymph node biopsy, which reveals a CD20 positive diffuse large B-cell lymphoma.

Which of the following has been shown to improve HIV lymphoma treatment outcomes?

A. Use of antibiotic prophylaxis
B. Incorporation of antiretroviral therapy prior to and during chemotherapy
C. Delaying therapy until HIV viral load is undetectable
D. Avoidance of rituximab during entire treatment course because of his low CD4 count
E. Intrathecal prophylaxis to prevent central nervous system (CNS) involvement with his lymphoma

6. A 69-year-old male presents with night sweats and weight loss. He is found to have diffuse lymphadenopathy above and below the diaphragm. He underdoes an excisional lymph node biopsy of an axillary node, which is consistent with diffuse large B-cell lymphoma. Hepatitis serology negative for hepatitis B surface antigen but positive for hepatitis core antibody. Hepatitis B polymerase chain reaction (PCR) viral load is negative. Liver function testing is normal.

Which of the following is recommended while treating with rituximab therapy?

A. Lamivudine while receiving rituximab only
B. Lamivudine while receiving rituximab and for 12 months after completion of therapy
C. Entecavir while receiving rituximab only
D. Entecavir while receiving rituximab on and for 12 months after completion of rituximab therapy
E. Hepatitis B PCR viral load every 6 months while on rituximab therapy

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ANSWERS

1. **B. Fluorescence in situ hybridization (FISH) for MYC, BCL2, BCL6.** Patient has an aggressive B-cell germinal center neoplasm. FISH for MYC, BCL2, BCL6 will distinguish between a diffuse large B-cell lymphoma, GC type, high-grade B-cell lymphoma, double/triple hit, and Burkitt lymphoma. If FISH is positive for MYC and BCL2 and/or BCL6, diagnosis is a high-grade B-cell lymphoma treated with DA-EPOCH and CNS prophylaxis. If FISH is negative for MYC, diagnosis is diffuse large B-cell lymphoma treated with R-CHOP. If FISH is positive for only MYC, a diagnosis of Burkitt lymphoma should be considered with treatment of R-Hyper-CVAD plus CNS treatment if involved or CNS prophylaxis if uninvolved.

2. **D. Repeat biopsy of the residual mass to ensure persistent disease.** Residual masses in the mediastinum are common after treatment of primary mediastinal B-cell lymphoma (PMBL) therefore it is important to confirm the presence of disease with a biopsy prior to additional therapy.

3. **A. Reduce her immunosuppressives.** Reduction of immunosuppressives is the most appropriate first step in the management of her posttransplant lymphoproliferative disorder. Observation is not appropriate in this situation. Other treatment modalities could be considered if she continues to have persistent disease after reducing her immunosuppressives first.

4. **C. Burkitt lymphoma, test for HIV, treat for tumor lysis syndrome with rasburicase and hydration, start R-Hyper-CVAD and perform lumbar puncture**. Clinical presentation as well as morphologic appearance and fluorescence in situ hybridization (FISH) testing consistent with a diagnosis of Burkitt lymphoma. Patient is in renal failure with elevated uric acid suggestive of tumor lysis that requires treatment with uric acid lower agent and hydration in addition to multiagent cytotoxic chemotherapy. HIV is associated with Burkitt lymphoma and requires treatment if patient is HIV positive. Central nervous system (CNS) involvement is common in Burkitt and patient is presenting with CNS symptoms of double vision, lumbar puncture to assess CNS involvement is important to assess the need for CNS treatment.

5. **B. Incorporation of antiretroviral therapy prior to and during chemotherapy.** Antiretroviral therapy has been shown to improve lymphoma therapy outcomes in patients with HIV-associated lymphomas. The other answer options have not demonstrated improved outcomes in HIV lymphoma therapy.

6. **D. Entecavir while receiving rituximab on and for 12 months after completion of rituximab therapy.** Rituximab has a risk of reactivating hepatitis B and therefore patients with hepatitis B surface antigen or core IgG or core IgM positivity with negative hepatitis B PCR viral load, prophylaxis with Entecavir during and for 12 months after treatment is recommended to prevent reactivation. Lamivudine should be avoided due to resistance.

8 T-Cell Lymphoma

Jennifer E. Girard and Tycel J. Phillips

Mature T-cell leukemias/lymphomas are a heterogenous group of cutaneous and systemic diseases with the most common subtypes peripheral T-cell lymphomas (PTCL) and include breast implant–associated anaplastic large cell lymphoma (BIA-ALCL), T-cell large granular lymphocytic leukemia (TGLL), adult T-cell leukemia/lymphoma (ATLL), T-cell prolymphocytic leukemia (TPLL), hepatosplenic T-cell lymphoma (HSTCL), and extranodal NK/T-cell lymphoma, nasal type (ENKL).

Cutaneous T cell lymphomas (CTCL) include mycosis fungoides and Sezary syndrome as well as primary cutaneous CD30+ T-cell lymphoproliferative disorder.

RISK FACTORS

1. What are the risk factors and associations for various types of T-cell leukemias/lymphomas?

- Variable depending on the subtype
  - HSTCL: chronic immunosuppression
  - ATLL: human T-cell leukemia virus type 1 (HTLV-1) infection, most common in Caribbean islands and southern Japan
  - Enteropathy-associated T-cell lymphoma (EATL): celiac disease
  - ENKL: Epstein–Barr virus (EBV) infection, most common in Asia
  - BIA-ALCL: breast implants, lymphoma involving the fibrous capsule around the implant without invasion of underlying breast tissue

PERPHERIAL T-CELL LYMPHOMA

The following section outlines the diagnosis, pathology, prognosis, and treatment of the subtypes of PTCL.

1. What are the subtypes of PTCL and how common are they?

- PTCLs are a heterogeneous group of diseases that account for <15% of all non-Hodgkin lymphomas (NHLs) in Western countries, and 15% to 20% in Asia.
- There are many PTCL subtypes, and the most common subtypes of nodal PTCL are the following:
  - Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS; 26%)
  - Angioimmunoblastic T-cell lymphoma (AITL; 19%)
  - Anaplastic large cell lymphoma, ALK+/− (ALCL; 12%)
    - ALK(+) (6.6%): median age of onset 34 years
    - ALK(−) (5.5%): median age of onset 58 years
  - EATL (<5%)

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2. What are the signs and symptoms of patients with various subtypes of PTCL?

- Lymphadenopathy (LAD), cytopenias, elevated lactate dehydrogenase (LDH), and advanced-stage disease at presentation. Unique features are as follows:
  - PTCL-NOS: 50% with concurrent extranodal disease (liver, bone marrow, skin, and gastrointestinal [GI] tract)
  - AITL: Acute onset LAD, B symptoms, organomegaly, also associated with eosinophilia, pruritic rash, autoimmune events (rheumatoid arthritis, thyroid disease, vasculitis), polyarthritis, effusions/ascites, polyclonal hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), hypoalbuminemia, positive Coombs test

3. How is PTCL staged?

- Most subtypes of PTCL are staged according to the Ann Arbor lymphoma staging system (see Chapter 5).

PTCL PATHOLOGY

1. Are there common genetic mutations seen in nodal PTCL?

- ALK(–) ALCL: DUSP22 (prevalence 30%, favorable prognosis) and TP63 (prevalence 8%, unfavorable prognosis) rearrangements have been described
- ALK(+) ALCL (overall favorable prognosis): t(2;5), ALK rearranged with NPM

2. What are the lymph node histopathological features of nodal PTCL?

- PTCL-NOS
  - Effacement of lymph nodes with cells of variable size; sheets of atypical lymphocytes in a paracortical or diffuse pattern; mixture of plasma calls and eosinophils; high mitotic rate
- ALCL
  - Immunophenotypic markers: CD30+
  - Sinusoidal growth pattern (and may mimic metastatic carcinoma)
  - Classical variant: large blastic cells with prominent nucleoli and abundant cytoplasm
    - Hallmark cells: eccentric nuclei, eosinophilic paranuclear hof (Figure 8.1)

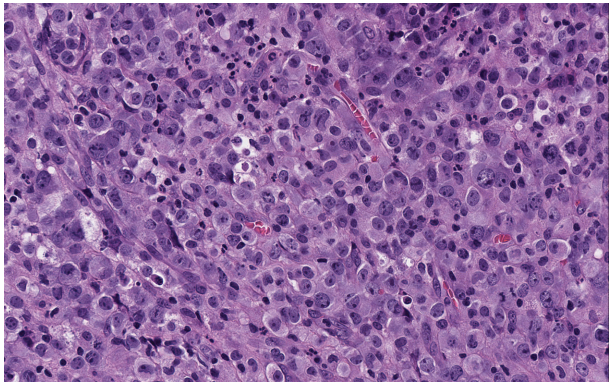

FIGURE 8.1 Hallmark cells with eccentric nuclei and eosinophilic paranuclear hof as seen in anaplastic large cell lymphoma.
Source: Reproduced with permission from Nathanael Bailey, MD, University of Pittsburgh, Department of Pathology.

- AITL
  - Partial or complete effacement of lymph nodes; neovascularization or arborizing endothelial venules. AITL are derived from follicular helper T-cells (explaining the B-cell and follicular dendritic cell expansion observed). Typified by a mixture of plasma cells, B-cell immunoblasts, small lymphocytes, eosinophils, follicular dendritic cells, and medium-sized malignant cells with abundant cytoplasm.
  - Usually requires excision lymph node biopsy to visualize the neovascularization in order to make the diagnosis.

PTCL PROGNOSTIC FACTORS

1. How are patients with PTCL risk stratified?

- In general, the International Prognostic Index (IPI) is applicable to PTCL.
- A similar Prognostic Index for T-cell lymphoma (PIT) can also be used.

IPI Prognostic Factors	PIT Prognostic Factors
Age >60 y	Age >60 y
LDH > ULN	LDH > ULN
ECOG PS ≥2	ECOG PS ≥2
Ann Arbor stage ≥3	Bone marrow involvement
Number of extranodal sites >2	

ECOG, Eastern Cooperative Oncology Group; PS, performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PIT, Prognostic Index for T-cell lymphoma; ULN, upper limit of normal.

Number of IPI factors determines the prognostic group: low = 0–1; low–intermediate = 2; high–intermediate = 3; high = 4–5.

2. How does the prognosis of PTCL compare with aggressive B-cell NHL?

- Stage-for-stage outcomes are inferior for patients with PTCL compared to those with aggressive B-cell NHL.

3. What is an additional important prognostic factor for ALCL?

- The presence or absence of an ALK fusion protein significantly affects ALCL prognosis.
- ALK(+) ALCL has a 5-year overall survival (OS) rate of 70%, whereas ALK(–) ALCL has a 5-year OS rate of 49%.

PTCL TREATMENT

Overall, the survival for patients with untreated PTCL is measured in months and treatment should be initiated once diagnosis is established. Goal is for cure but recognizing that 5-year OS for all comers with PTCL is 10% to 20% with Progression Free Survival (PFS) at 5 years of approximately 30% with only a small subset of patients maintaining a durable remission. Treatment for the most common subtypes of PTCL that include PTCL-NOS, AITL, ALCL ALK +/– are listed below.

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1. What is first line of therapy for PTCL subtypes?

- ALK(+) ALCL (Better prognosis)
  - Multiagent, anthracycline-based therapy ± etoposide × 6 cycles, ± radiation therapy (RT):
    - Age >60 years, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
    - Age <60 years, CHOEP (CHOP plus etoposide) or CHOP
  - Stage I–II disease: consider three to four cycles of chemotherapy followed by RT

2. PTCL-NOS, ALK(−), ALCL, AITL (worse prognosis)

- Consider clinical trial participation
- Multiagent chemotherapy (CHOP or CHOEP) × 6 cycles. Stage I–II disease: consider three to four cycles of chemotherapy followed by RT.

3. What is the role of consolidative autologous stem cell transplant (autoSCT) after complete response with first-line therapy?

- Patients with ALK(+) ALCL do not typically receive consolidative treatment in first remission due to favorable 5-year OS with chemotherapy.
- PTCL-NOS, ALK(−), ALCL, AITL Stage III/IV disease: In contrast to DLBCL, most transplant-eligible patients with stage III/IV PTCL-NOS, ALK(−) ALCL, and AITL achieving a complete remission with induction first-line therapy (CHOP or CHOEP) undergo consolidation with high-dose therapy (HDT) and autoSCT, as this approach appears to be associated with improved progression-free survival (PFS)/OS.
- PTCL-NOS, ALK(−), ALCL, AITL Stage I/II disease: autoSCT is considered for stage I–II (high–intermediate/high IPI) PTCL-NOS, ALK(−) ALCL, and AITL in first remission. Favorable outcomes have been reported in DUSP22 rearranged ALK(−) ALCL without autoSCT in first remission.

4. What is second-line therapy for PTCL subtypes?

- No standard second-line treatment and there clinical trials should be considered. Overall response rates in relapsed/refractory PTCL are ~20% to 50%; however, responses are not typically durable.
  - Single-agent regimens: brentuximab (ORR ~85% in ALCL), romidepsin, belinostat, pralatrexate (limited activity in AITL)
  - Multiagent chemotherapy is similar to aggressive B-cell lymphoma regimens without rituximab (e.g., ICE, DHAP, GemOx)
- Stem cell transplantation
  - HDT/autoSCT can be considered for patients who did not undergo transplant in first complete remission.
  - Allogeneic stem cell transplantation can lead to durable responses in up to 60% of relapsed/refractory cases, but is associated with up to a 30% rate of treatment-related mortality.
- Elderly AITL patients unable to tolerate chemotherapy: consider corticosteroids or immunosuppressive therapy with cyclosporine.

RARE T-CELL LEUKEMIAS/LYMPHOMAS

The following section describes the subtype, diagnosis, prognosis symptoms and treatment for the rare subtypes of T-cell leukemias/lymphomas plus primary cutaneous T-cell lymphoma.

TABLE 8.1 ■ T-Cell Leukemias/Lymphomas

Type/Prognosis	Diagnosis/Pathology	Symptoms	Treatment
T-PLL ■ Median age 65 y ■ Aggressive ■ Poor prognosis usually <1 y	Usually diagnosed from peripheral blood: ■ Small/medium prolymphocytes (mature post-thymic T cells): ■ CD52+, TdT— ■ TCR rearranged ■ 80% inv 14 ■ 75% trisomy 8q ■ 11q23 ATM	Generalized LAD, Hepatosplenomegaly, serous effusion, and skin involvement ■ Lymphocyte count usually >100 ■ Anemia/thrombocytopenia ■ HTLV-1 negative	■ Alemtuzumab IV (anti-CD52) ■ Alemtuzumab + pentostatin ■ FMC followed by Alemtuzumab ■ If CR, ASCT
T-LGLL ■ Age 45–75 y ■ Indolent ■ Median OS 10 y ■ STAT3 mutations with longer OS	Usually diagnosed from peripheral blood: ■ Mature cytotoxic T-cells ■ >6 months of LGL >2,000 ■ TCR oligo/monoclonal ■ TCRαβ/TIA/granzyme B+ ■ 30% STAT three mutations SH2 domain (longer OS)	Involves peripheral blood, bone marrow, and spleen ■ Concurrent with autoimmune/rheum syndrome (Crohn's, Sjogren's, psoriatic arthritis) ■ Indications to treat: ANC <0.5, Hgb <10, Plt <50, symptomatic splenomegaly/B symptoms	■ Low-dose MTX +/− Prednisone ■ Cyclophosphamide +/− Prednisone ■ Cyclosporine

(*continued*)

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TABLE 8.1 ■ T-Cell Leukemias/Lymphomas (*continued*)

Type/Prognosis	Diagnosis/Pathology	Symptoms	Treatment
ATLL ■ Median age 58 y ■ Endemic in Japan, Caribbean, Central Africa ■ Prognosis: smoldering/chronic years ■ Acute, lymphoma <2 y	Diagnosis requires HTLV-1 antibodies ■ HTLV-1 p40 transcriptional activating gene within infected lymphocytes ■ Acute: leukemic phase with flower cell ■ CD2/CD3/CD5+ but CD7− ■ CD25+, CD30+/− Alk- ■ TCR receptor rearranged	■ Acute: leukemic phase, elevated WBC with eosinophilia, HyperCa++, ■ Lymphoma: generalized LAD, B symptoms, elevated LDH ■ Chronic/Smoldering: exfoliating skin rash, normal WBC, no hyperCa++	■ Acute/Lymphoma: ■ Hyper-CVAD, DA-EPOCH, BV+CHP (CD30+ only) followed by ASCT, zidovudine + interferon (acute only) ■ Chronic/Smoldering: observe, skin-directed therapy or zidovudine + interferon

ASCT, allogeneic stem cell transplant; ATLL, adult T-cell leukemia/lymphoma; autoSCT, high-dose chemotherapy and autologous stem cell transplant; BV + CHP, brentuximab vedotin plus cyclophosphamide, doxorubicin, prednisone; DA-EPOCH, dose-adjusted etoposide, vincristine, cyclophosphamide, doxorubicin, prednisone; FMC, fludarabine, mitoxantrone, cyclophosphamide; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high dose cytarabine and systemic methotrexate; LAD, lymphadenopathy; LDH, lactate dehydrogenase; OS, overall survival; TCR, T-cell receptor; T-LGLL, T-cell large granular lymphocytic leukemia; T-PLL, T-cell prolymphocytic leukemia; WBC, white blood cell.

TABLE 8.2 ■ Rare Subtypes T-Cell Lymphomas

Type/Prognosis	Diagnosis/Pathology	Symptoms	Treatment
ENKL ■ Poor prognosis 5 y OS 42%	Biopsy of mass: ■ Angiodestructive, CD3ε + ■ Always EBER-ISH+ ■ 30% TCR rearranged	Mass of the paranasal sinus, nasopharynx, and GI involvement, skin ■ nasal obstruction/epistaxis	■ Stage I/II: Nasal disease only, unfit for chemo: RT ■ Stage I–IV fit: mSMILE + RT or 2 cycles P-GemOx + RT + 2-4 cycles P-GemOx ■ Consolidation autoSCT if extranasal/Stage IV
BIA-ALCL ■ Women <50 y ■ good prognosis 3y OS 94%	Diagnosed FNA of effusion or mass: ■ CD30+, Alk- ■ Somatic/Germline mutation JAK1/STAT3	■ History of breast implants with ultrasound with effusion or mass	■ Total capsulectomy and excision by surg onc plus radiation for incomplete resection and systemic therapy for stage III/IV (BV, BV+CHP, CHOP +/- ASCT)
HSTL ■ Aggressive median survival <2y ■ 20% chronic immunosuppression	■ medium lymphoid cells with sinusoidal infiltration ■ T cell receptor γδ type	Splenomegaly, hepatomegaly, bone marrow; lymph nodes NOT involved ■ Chronic immunosuppression: azathioprine or infliximab	■ ICE followed by ASCT ■ Other: Alemtuzumab + pentostatin, DA-EPOCH, Hyper-CVAD, BV-CHP (CD30+)

ASCT, allogeneic stem cell transplant; autoSCT, high-dose chemotherapy and autologous stem cell transplant; BIA-ALCL, breast implant-associated ALCL; BV + CHP, brentuximab vedotin plus cyclophosphamide, doxorubicin, prednisone; ENKL, **e**xtranodal NK/T-cell; HSTL, hepatosplenic T-cell lymphoma; P-GemOx, pegaspargase, gemcitabine, oxaliplatin; SMILE, etoposide, asparaginase, ifosfamide, methotrexate, dexamethasone.

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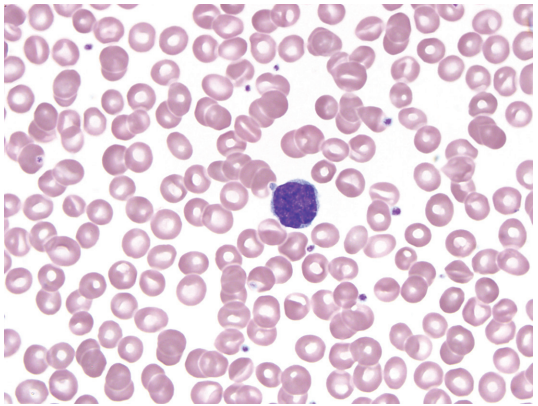
TABLE 8.3 ■ Primary Cutaneous T-Cell Lymphoma

Type/Prognosis	Diagnosis/Pathology	Treatment
MF ■ Malignant transformed effector T cells ■ Indolent course ■ Can progress/transform **Sezary syndrome** ■ Malignant transformed thymic T cells ■ Rare erythrodermic leukemic variant of MF	Pruritic patch/plaque with skin biopsy with cerebriform nuclei in upper dermis or Pautrier microabscesses  **FIGURE 8.2** ■ Peripheral blood smear with cerebriform (Sézary) cell.	■ Topical: corticosteroids, mechlorethamine, retinoids, imiquimod ■ Radiation: radiation to single lesion or total skin ■ Phototherapy UVB ■ ECP ■ Systemic: FDA approved Brentuximab (anti-CD30) Bexarotene (systemic retinoid) Vorinostat/ romidepsin (HDAC inhibitor) Mogamulizumab (anti-CD47). ■ Allotransplant after failing above therapies.
Primary Cutaneous CD30+ T Cell Lymphoproliferative Disorders	Punch biopsy of skin lesion with CD30+ T cells	■ Involved site radiation (ISRT) ■ Systemic: Brentuximab,± CHP, CHOP, CHOEP

ECP, extracorporeal photopheresis; MF, mycosis fungoides.

Cutaneous T-cell lymphomas (CTCL) primarily present and can progress to involve lymph nodes, blood and visceral organs. CTCLs are treatable but not curable. Staging based on percentage of Body Surface Area (BSA) with T1<10% and T4>80%.

Source: Figure 8.2 reproduced with permission from Nathanael Bailey, MD, University of Pittsburgh, Department of Pathology.

QUESTIONS

1. **Which of the following peripheral T-cell lymphoma (PTCL) subtypes has the best prognosis?**
   A. Angioimmunoblastic T-cell lymphoma (AITL)
   B. Anaplastic large cell lymphoma (ALCL), ALK(+)
   C. Extranodal NK/T-cell lymphoma
   D. ALCL, ALK(−)

2. **A 47-year-old Jamaican man presents with an elevated lymphocyte count and peripheral blood shows some cells with hyperlobated nuclei appearing like clovers. Which pathogen is typically associated with this peripheral T-cell lymphoma (PTCL) subtype?**
   A. *Helicobacter pylori*
   B. Epstein–Barr virus (EBV)
   C. Human T-cell leukemia virus type 1 (HTLV-1)
   D. Cytomegalovirus (CMV)

3. A 60-year-old man presents with years of pruritus with large scattered pink/erythematous patches on his chest, back, upper arms, and thighs. Biopsy shows mononuclear cells with cerebriform nuclei in upper dermis and epidermal keratinocytes with intraepidermal aggregates forming microabscess-like structures and he is diagnosed with mycosis fungoides. He is treated with topical therapy; however, his skin lesions progressed. He undergoes CT scan that demonstrates hepatosplenomegaly and lymphadenopathy.

   Which is NOT an appropriate next line of therapy?
   A. Systemic retinoids
   B. Histone deacetylase inhibitors
   C. Brentuximab vedotin
   D. Mogamulizumab
   E. Systemic chemotherapy with CHOP

4. A 45-year-old male with 2 months of night sweats developed large lymph nodes in his neck. He reports to his primary care physician (PCP) who notes cervical, axillary and inguinal lymphadenopathy on exam. CT scan demonstrates diffuse lymphadenopathy above and below the diaphragm. Pathology of an excised cervical lymph node demonstrates plasma cells, B cell immunoblasts, medium-sized malignant cells with abundant cytoplasm with neovascularization.

   What is the most likely diagnosis?
   A. Angioimmunoblastic T-cell lymphoma (AITL)
   B. Mycosis fungoides
   C. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
   D. Follicular lymphoma

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5. A 45-year-old woman presents with left breast pain. She reports breast implants 6 years prior. Mammogram reveals an effusion with a fibrous capsule surrounding the implant. She undergoes a capsulectomy and implant removal. Pathology demonstrates a lymphoma.

What type of lymphoma does she most likely have?

A. Angioimmunoblastic T-cell lymphoma (AITL)
B. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
C. Metastatic disease
D. Anaplastic large cell lymphoma (ALCL), ALK(–)

ANSWERS

1. **B. ALCL, ALK(+).** ALK(+) ALCL has the best overall prognosis of these PTCL subtypes with a 5-year overall survival rate of 70%. Note: The International Prognostic Index (IPI) risk group should also be taken into account and is still prognostic.

2. **C. HTLV-1.** This man most likely has adult T-cell leukemia/lymphoma (ATLL) given his heritage and peripheral blood features; this is associated with HTLV-1 infection.

3. **E. Systemic chemotherapy with CHOP.** There is not a role for multiagent systemic chemotherapy in the treatment mycosis fungoides/Sezary syndrome. FDA-approved treatment of systemic disease include Brentuximab vedotin, systemic retinoids Bexarotene, histone deacetylase (HDAC) inhibitors such as Romidepsin/Vorinostat and anti-CCR4 antibody Mogamulizumab.

4. **A. Angioimmunoblastic T-cell lymphoma (AITL).** AITL is the most likely diagnosis given the systemic symptoms of arthritis, effusions, B symptoms, and lymphadenopathy, as well as likely hemolytic anemia with an elevated bilirubin and lactate dehydrogenase (LDH).

5. **D. ALCL, ALK(–).** ALK(−) ALCL has been associated with breast implants. Implant removal and capsulectomy followed by observation is associated with favorable long-term disease-free survival for patients without an associated mass.

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9 Multiple Myeloma

Jason C. Chen and Erica Campagnaro

EPIDEMIOLOGY

1. What are the plasma cell dyscrasias?

- Multiple myeloma (MM; myeloma)
  - Active or symptomatic MM—myeloma-defining events present (see the following section Screening and Diagnostic Criteria)
  - Smoldering multiple myeloma (SMM)—no myeloma-defining events present
- Monoclonal gammopathy of undetermined significance (MGUS)
- Solitary plasmacytoma
- Light and heavy chain deposition diseases
- Primary (AL) amyloidosis
- POEMS (osteosclerotic myeloma)—polyneuropathy, organomegaly, endocrinopathy, M-spike, skin changes

2. How common is myeloma?

- Myeloma is the second most common hematologic malignancy, after non-Hodgkin lymphoma.

3. What is the significance of myeloma?

- Myeloma is still considered incurable, accounts for 20% of hematological malignancy deaths and 2% of all cancer deaths.

ETIOLOGY AND RISK FACTORS

1. What is the etiology of myeloma?

- Myeloma is a cancer of plasma cells, usually originating in bone marrow, caused by clonal somatic genetic mutations leading to abnormal proliferation and protein secretion (monoclonal protein, M-protein)

2. What are the risk factors of myeloma?

- Older age, male gender, African American race, obesity, family history of myeloma, personal history of MGUS, and certain environmental exposures, including radiation and benzene are associated with increased risk of myeloma.

SCREENING AND DIAGNOSTIC CRITERIA

1. Who should be evaluated for a potential plasma cell dyscrasia?

- Myeloma should be considered when a patient has otherwise unexplained hypercalcemia, renal failure, anemia, bone pain, or lytic bone lesions on imaging.

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- Other potential reasons to consider the diagnosis of myeloma include high or low serum total protein, signs of hyperviscosity, neuropathy, frequent infections, and generalized symptoms of advanced malignancy such as weight loss.
- In addition to what was mentioned previously, signs and symptoms of other plasma cell disorders include unexplained bleeding diathesis (amyloidosis), unexplained cardiac or liver failure (amyloidosis), autonomic neuropathy (amyloidosis), organomegaly (POEMS), hyperpigmentation (POEMS), or hypogonadism (POEMS).

2. What tests are important for assessing plasma cell dyscrasias, including myeloma?

- Complete blood count with differential and peripheral blood smear
- Comprehensive metabolic panel—to check electrolytes, calcium, renal function, total protein, and albumin
- Serum beta-2 microglobulin (B2M) and lactate dehydrogenase (LDH)
- Serum protein electrophoresis (SPEP) with immunofixation (IFIX)
- Twenty-four-hour urine protein electrophoresis (UPEP) with IFIX
- Serum quantitative immunoglobulins, IgG, IgA, and IgM (IgD and IgE only if suspected)
- Serum kappa and lambda free light chain (FLC) quantification
- Serum viscosity if: monoclonal immunoglobulin level is >5 g/dL or symptoms suggestive of hyperviscosity
- Imaging standards for screening for myeloma bone disease are evolving
  - Whole body low-dose CT is now preferred to X-ray skeletal survey (more sensitive and specific). When not available, skeletal survey may be reasonable.
  - In smoldering myeloma and solitary plasmacytoma, whole-body imaging that is more sensitive than bone survey is mandatory. Options include whole body low-dose CT, PET/CT, or MRI. If these options are not available, MRI spine and pelvis plus a skeletal survey is reasonable.
  - *Note:* Bone lesions in POEMS are typically sclerotic, not lytic
- Bone marrow biopsy with flow cytometry, conventional cytogenetics (karyotype), and fluorescence in situ hybridization (FISH) for commonly acquired genetic mutations
- If AL amyloidosis is suspected, confirm diagnosis with Congo red staining ("apple-green birefringence under polarized light") and amyloid protein identification by immunohistochemistry, immunofluorescence, and mass spectrometry (gold standard) on affected tissue.

3. What are the diagnostic criteria for active myeloma (requiring treatment)?

- Soft tissue or bone plasmacytoma *or* ≥10% clonal bone marrow plasma cells *and* at least *one* of the following (SLiM CRAB mnemonic):
  - S ("sixty"): Clonal plasma cells ≥*60% of bone marrow cellularity*
  - Li ("light chain ratio"): involved to uninvolved FLC ratio of ≥100 (*the involved FLC must be least ≥100 mg/L*
  - M: MRI with >*1 focal lesion in the bone or bone marrow* (size ≥5 mm)
  - Any plasma cell dyscrasia-related end-organ damage (CRAB criteria):
    - C: elevated serum calcium level (calcium >11 mg/dL)
    - R: renal insufficiency (creatinine >2 mg/dL or creatinine clearance <40 mL/min)
    - A: anemia (hemoglobin <10 g/dL or >2 g/dL below lower normal limit)
    - B: lytic bone lesions (one or more) on skeletal survey, CT, MRI, or PET/CT

4. What are the diagnostic criteria and characteristics of other plasma cell dyscrasias?

- MGUS
  - Serum M-protein <3 g/dL
  - Clonal plasma cells <10% of bone marrow
  - Absence of end-organ damage attributed to plasma cell dyscrasia
- SMM
  - Serum M-protein ≥3 g/dL
  - Clonal plasma cells 10% to 59% of bone marrow cellularity
  - No end-organ damage, other myeloma defining events or amyloidosis
- Solitary plasmacytoma
  - Solid clonal plasma cell tumor without bone marrow involvement or without evidence of end-organ damage attributable to monoclonal plasma cells
  - Patients with an apparently solitary plasmacytoma who have <10% clonal marrow plasma cells are considered to have solitary plasmacytoma with minimal marrow involvement. They are treated as solitary plasmacytoma, but the risk of recurrence or progression to myeloma is higher.
- POEMS
  - A rare paraneoplastic syndrome, typically associated with a small clone of plasma cells, that involves the following:
    - Polyneuropathy
    - Organomegaly
    - Endocrinopathy
    - Monoclonal gammopathy
    - Skin changes
  - Also known as osteosclerotic myeloma
  - Associated with increased serum vascular endothelial growth factor (VEGF)
- AL amyloidosis
  - AL amyloidosis ("amyloid light chain" or primary amyloidosis) is characterized by systemic deposition of amyloid protein that is composed of immunoglobulin light chains.
  - Amyloid protein deposition results in damage to the affected organ(s), resulting in problems such as congestive heart failure, pulmonary infiltrates, malabsorption, nephrotic syndrome, neuropathy, and others.

PATHOLOGY

1. What is the cell of origin for the malignant plasma cells of myeloma?

- Myeloma cells are postgerminal center plasma cells (a type of differentiated B-cell) identifiable by somatic mutations in the variable region of the immunoglobulin heavy chain gene.

SIGNS AND SYMPTOMS

1. What are the most common symptoms of active myeloma?

- Anemia (73%)
- Bone pain due to lytic lesions (58%)
- Increased creatinine (48%)
- Fatigue (32%)

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- Hypercalcemia (28%)
- Weight loss (24%)

2. What are uncommon but important signs and symptoms?

- Plasmacytoma (7%)
- Paresthesias (5%)
- Spinal cord compression (5%—due to plasmacytoma or vertebral body fracture)

RISK STRATIFICATION

1. How do we determine prognosis and risk stratification in Myeloma?

- Labs: B2M, LDH, albumin, peripheral plasma cell count
- Mutational testing (marrow): MM FISH panel, karyotype

2. Which features are associated with high-risk disease and worse prognosis?

- Revised International Staging System (R-ISS) stage III disease (see the following staging criteria)
  - FISH showing t(4;14), t(14;16), t(14;20), del(1p), gain(1q), del(17p), or hypodiploidy
  - LDH > upper limit of normal (ULN), B2M ≥5.5 mg/L
  - Primary plasma cell leukemia (≥20% circulating plasma cells on manual differential or ≥2,000 plasma cells/μL)
  - About 15% of people with myeloma have high-risk disease with median survival 2 to 3 years despite standard therapy and often relapse <12 months after prior therapy.

3. Which features are associated with standard-risk disease and better prognosis?

- R-ISS stage I disease (see the following staging criteria)
- Lack of high-risk cytogenetic abnormalities mentioned previously. Normal LDH and albumin, B2M <3.5 mg/L
- Trisomies, del(5q) and t(11;14) are considered standard risk mutations in myeloma.
- Median survival is 8 to 10 years.

4. Which features are associated with intermediate-risk disease?

- R-ISS stage II disease (not meeting criteria for stage I or III disease)

STAGING

1. Which staging system is preferred for active myeloma?

- The Revised International Staging System (R-ISS)

2. How is active myeloma staged according to the R-ISS?

- The R-ISS uses serum B2M, serum albumin, LDH, cytogenetics, and FISH for common mutations. Online calculators are widely available and useful in practice.
- Stage I: B2M <3.5 mg/L, albumin ≥3.5 g/dL, normal LDH, no del(17p), t(4;14), or t(14;16) (5-year progression-free survival [PFS] and overall survival [OS] of 55% and 82%, respectively)

- Stage II: neither stage I nor stage III (5-year PFS and OS of 36% and 62%, respectively)
- Stage III: B2M ≥5.5 mg/L, and LDH greater than ULN or del(17p), t(4;14), or t(14;16) by FISH (5-year PFS and OS of 24% and 40%, respectively)

TREATMENT

General Treatment Principles

1. Which plasma cell dyscrasias should be treated?

- There is no known benefit from treating MGUS or low-risk smoldering myeloma; observation is the standard of care.
- High-risk smoldering myeloma patients may benefit from treatment with lenalidomide and dexamethasone. The definition of high-risk smoldering myeloma varies, but the most commonly used model is the "2/20/20" criteria:
  - Monoclonal protein >2 g/dL
  - Bone marrow plasma cells >20%
  - With abnormal involved serum FLC ratio >20.
- Patients with active myeloma should be treated since, by definition, end-organ damage is present or imminent.
- Patients with other plasma cell disorders with systemic involvement such as AL amyloidosis also warrant treatment to prevent further organ damage.
- Patients with a solitary plasmacytoma without meeting criteria for MM can be treated with local radiation therapy with curative intent.

2. What are the main factors in determining best frontline therapy for patients with newly diagnosed active myeloma?

- Disease risk (R-ISS staging)
- Eligibility for high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (SCT)

3. How do we define criteria for disease response to therapy?

- The International Myeloma Working Group (IMWG) has established response criteria:
  - Stringent complete response (sCR)—no M-protein on IFIX, normal FLC ratio and no clonal plasma cells in marrow, no residual plasmacytoma
  - Complete response (CR)—no M-protein on IFIX, <5% plasma cells in marrow, no residual plasmacytoma
  - Very good partial response (VGPR)—≥90% reduction in M-protein though still detectable
  - Partial response (PR)—≥50% reduction in serum M-protein plus ≥90% reduction in urine light chains and total 24-hour urine light chains <1,200 mg. If no measurable serum or urine M-protein at baseline, then ≥50% reduction in serum FLC ratio (involved/uninvolved light chain), and, if present, ≥50% reduction in plasmacytoma size
  - Minimal response (MR)—≥25% to 49% reduction in the M-protein or plasmacytoma size
  - Stable disease (SD)—not meeting previously mentioned criteria
  - Progressive disease (PD)—≥25% increase in serum or urine M-protein, FLC ratio, bone marrow plasma cell %, new bone lesions or plasmacytomas, new hypercalcemia related to plasma cell disorder

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- Of note, minimal residual disease (MRD) testing is being more utilized, either by specialized flow cytometry or next-generation sequencing (NGS) testing, though not used for treatment decision-making.

4. How is newly diagnosed myeloma treated?

- In general, all patients should receive triplet (3-drug) combination therapy with a proteasome inhibitor (e.g., bortezomib), immunomodulatory agent (e.g., lenalidomide), and corticosteroid (most commonly dexamethasone).
- For patients who are frail or have contraindications to triplet therapy, can consider doublet (2-drug) combinations.

5. How do you decide what induction therapy to use?

- Disease risk stratification, patient factors (performance status, comorbidities, psychosocial support, patient goals), institutional resources (e.g., infusion and clinical trial availability), eligibility for autologous SCT

6. What happens after induction therapy?

- Consolidation: patients who achieve an optimal response to induction therapy can receive consolidation with high-dose chemotherapy (melphalan) followed by autologous SCT if eligible for transplant.
- Maintenance: after autologous SCT or after a longer course of induction therapy (if transplant-ineligible), patients are transitioned to maintenance therapy. Single-agent lenalidomide is the only approved agent at this time.

7. What are some key agents used in first-line active myeloma treatment and what are their common toxicities?

- Proteasome inhibitors
  - Bortezomib (Velcade®)
    - Administration: IV or SQ (preferred)
    - Side effects: peripheral (sensory) neuropathy, thrombocytopenia, gastrointestinal (GI; nausea, diarrhea), herpes zoster reactivation
    - *NOTE:* once-weekly infusion of bortezomib significantly reduces the incidence of peripheral neuropathy compared with the twice-weekly infusion and is not associated with any reduction in the efficacy.
    - Hepatic metabolism: liver dysfunction requires dose adjustment
    - No renal dose adjustment needed, useful in renal failure or chronic kidney disease (CKD) patients
    - Viral prophylaxis with acyclovir or valacyclovir is required to prevent zoster reactivation
- Immunomodulators
  - Lenalidomide (Revlimid®)
    - Administration: oral
    - Side effects: myelosuppression, venous thromboembolism, fatigue
    - Renal metabolism: significant *renal dysfunction requires dose adjustment*
    - Venous thromboembolism (VTE) prophylaxis REQUIRED: low-dose aspirin (e.g., 81 mg daily) or prophylactic low-molecular-weight heparin (LMWH; enoxaparin SQ 40 mg daily)
    - Teratogen: prescription and administration requires participation in a Risk Evaluation and Mitigation Strategy (REMS) program

- Corticosteroids
  - Dexamethasone (Decadron®)
    - Administration: oral or intravenous (IV)
    - Side effects: mental status changes, hyperglycemia, weight gain
    - No renal dose adjustments needed
    - VTE prophylaxis is considered when used as higher doses (>160 mg/cycle)
- Monoclonal antibodies
  - Daratumumab (Darzalex®)
    - Administration: IV or SC
    - Side effects: infusion reactions, increased infection risk
    - Interference with routine blood type and screen testing.
    - Mechanism: monoclonal antibody against CD38
    - Approved uses
      - Single agent for patients who have received three prior therapies
      - Combination with bortezomib, lenalidomide, and dexamethasone in patients who have received at least one line of prior therapy
      - Combination with bortezomib, melphalan, and prednisone in newly diagnosed patients NOT eligible for transplant

8. What is the role of bone-modifying agents (BMAs) in myeloma?

- BMAs decrease the risk of skeletal-related events (SREs), which are pathologic fracture, spinal cord compression, needing radiation or surgery for bone
- BMAs are recommended for patients with active myeloma, regardless of presence of lytic lesions
- Available BMA include the following:
  - Bisphosphonates: pamidronate and zoledronic acid
  - Receptor activator of nuclear factor-kB (RANKL) inhibitor: denosumab
- Optimal duration of treatment with BMAs is unknown, but current recommendation for bisphosphonates is every 1 to 3 months for 2 years, after which the decision to continue can be reassessed, depending on remission status.
- The current recommendation for denosumab is monthly, indefinitely. If denosumab is stopped, administration of a bisphosphonate should be considered to lower risk of rebound fracture.
- Important side effects of all BMAs include hypocalcemia, osteonecrosis of the jaw, and fragility fractures. Bisphosphonates may cause renal failure; renal function should be routinely monitored on treatment. Close monitoring and calcium supplementation is recommended with all BMAs, especially in severe renal failure (serum creatinine >3 mg/dL or CrCl <30 mL/min), as there is higher risk of severe, prolonged hypocalcemia

Principles of Autologous SCT in Myeloma

1. What is the role of autologous SCT in myeloma therapy?

- Autologous SCT results in higher response rates and prolonged progression-free survival (PFS) compared to standard therapies; data from phase 3 studies describing its impact on overall survival (OS) are mixed.
  - Autologous SCT should be considered in all MM patients who are eligible, particularly those with high-risk disease.

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2. Who is eligible for an autologous SCT?

- The eligibility criteria for autologous SCT are not standardized; the decision for hematopoietic cell transplantation (HCT) is often individualized rather than based on standard eligibility criteria.
- Age >75 years, Eastern Cooperative Oncology Group (ECOG) PS ≥3, or other significant comorbidities (e.g., heart failure, significant pulmonary disease) increase the risk of this treatment and are generally exclusions to autologous HCT.

3. When are autologous hematopoietic stem cells collected for myeloma patients?

- Usually after 2 to 4 months of therapy and/or after cytoreduction of myeloma by ≥50% (at least PR)

4. When is the best time to complete an autologous SCT?

- Autologous HCT can be completed to consolidate response "early" (preferred, after first treatment) or "late" (at the time of first relapse, after second treatment).

5. Can a patient undergo a second autologous SCT?

- Yes. Usually, enough hematopoietic stem cells are collected to perform two autologous HCTs.
- Because of increasing treatment options for relapsed myeloma, use of second autologous HCT is becoming more uncommon. It is generally reserved for consolidation of induction beyond first line of treatment if the response to the first autologous HCT was prolonged, beyond 3 years with maintenance therapy.

Principles of First-Line Therapy

1. What are the initial treatment options for myeloma patients who are autologous SCT candidates (transplant eligible)?

- Key point: avoid prolonged treatment with alkylating agents (cyclophosphamide or melphalan), or lenalidomide, which can interfere with stem cell collection.
- The most commonly used induction regimens for standard-risk myeloma are three-drug combinations such as bortezomib, lenalidomide, and dexamethasone (VRD), or cyclophosphamide, bortezomib, dexamethasone (CyBorD). Two-drug combinations, such as bortezomib or lenalidomide with dexamethasone (VD or RD). The three-drug combination of daratumumab with lenalidomide and dexamethasone (DaraRd), may be used in frail patients.
- After transplant, patients should be started on maintenance therapy to maintain or improve disease response
- *Standard-risk* MM
  - Induction therapy can be followed by upfront or delayed autologous SCT
  - Posttransplant maintenance therapy with lenalidomide
- *High-risk* MM
  - Use three-drug bortezomib-based regimens like VRD for induction or consideration of clinical trial
  - Induction therapy should be followed by early autologous SCT in most patients.
  - Posttransplant maintenance therapy with bortezomib. Additional agents are sometimes added depending on individual risk and physician discretion.

2. What are the initial treatment options for myeloma patients who are not autologous SCT candidates (transplant ineligible)?

- Induction therapy regimens similar to transplant-eligible patients
- Adjust treatment doses and schedules as needed for age, performance status, comorbidity (Guidelines published by the European Myeloma Network)

Relapsed or Refractory Disease

1. What is the definition of progressive disease after initial treatment?

- Progressive disease (PD)—≥25% increase in serum or urine M-protein, FLC ratio, bone marrow plasma cell %, new bone lesions or plasmacytomas, new hypercalcemia related to plasma cell disorder
- Relapse—development of CRAB criteria (new hypercalcemia, anemia, renal failure, bone lesions)

2. What treatment strategies are available for relapsed disease?

- If it has been ≥1 year since initial therapy without maintenance, repeating the initial therapy is reasonable.
- Combination therapy using agents from a different class than those used in prior treatment is preferred. Additional strategies include choosing different agents from already used drug classes, and using new combinations of previously used agents.
- Second autologous SCT can be considered in fit patients who had prolonged response after their first transplant.
- Allogeneic SCT is generally not recommended due to high treatment-related morbidity and mortality but can be considered in the context of a clinical trial.
- Generally, the duration and depth of response declines with lines of therapy.

3. What additional drugs are available for relapsed/refractory disease?

- Agents for relapsed/refractory disease are often given in two-, three- or four-drug combinations depending on the nature of relapse (indolent vs. aggressive), the patient's comorbidities, and the response to and tolerance of prior treatment.
- Immunomodulators
  - Pomalidomide (Pomalyst®): oral, similar side effect profile to lenalidomide including cytopenia and thrombosis risk
- Proteasome inhibitors:
  - Carfilzomib (Kyprolis®): IV only, less peripheral neuropathy than bortezomib, possible cardiac toxicity so requires baseline cardiac assessment
  - Ixazomib (Ninlaro®): oral drug, causes less peripheral neuropathy, but more GI toxicity (e.g., nausea and diarrhea) than bortezomib
- Monoclonal antibodies:
  - Daratumumab (Darzalex®): IV or SC, anti-CD38 antibody, see initial treatment section for more information
  - Isatuximab (Sarclisa®): IV anti-CD38 antibody, similar side effect profile to daratumumab
  - Elotuzumab (Empliciti®): IV anti-SLAMF7 antibody (glycoprotein expressed on natural killer and myeloma cells), side effects mainly infusion reactions and increased infection risk

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- Belantamab mafodotin (Blenrep®): antibody-drug conjugate targeting BCMA, major side effect is significant corneal toxicity requiring frequent ophthalmology exams before starting and during treatment

- Other agents
  - Panobinostat (Farydak®): oral histone deacetylase inhibitor, associated with significant GI toxicity and cytopenia
  - Selinexor (Xpovio®): oral selective inhibitor of nuclear export, associated with significant GI toxicity and cytopenia
- Combination chemotherapy (e.g., VTD-PACE, DCEP regimens): sometimes used for ultra-high-risk myeloma, such as plasma cell leukemia, and for myeloma refractory to several lines of therapy in patients who need urgent cytoreduction due to symptoms related to myeloma.

QUESTIONS

1. A 55-year-old woman was referred to you after workup of anemia revealed a monoclonal protein (M-protein) of 4.2 g/dL with several lytic lesions on skeletal survey. Immunofixation demonstrates IgG kappa M-protein. Bone marrow biopsy showed 25% clonal plasma cells, with normal karyotype and fluorescence in situ hybridization (FISH) testing. She is working full time as a registered nurse and runs about 15 miles per week. She wants aggressive therapy to improve her chances of survival if possible.

What is your treatment recommendation?

A. Bortezomib, lenalidomide, and dexamethasone (VRD), stem cell collection after four cycles, autologous stem cell transplant (SCT), lenalidomide maintenance
B. VRD for four cycles, lenalidomide maintenance
C. VRD, stem cell collection after four cycles, autologous SCT, no maintenance therapy
D. Lenalidomide and dexamethasone (RD), stem cell collection after four cycles, autologous hematopoietic cell transplantation (HCT), lenalidomide maintenance

2. A 78-year-old woman was recently diagnosed with multiple myeloma and planning to start treatment with weekly bortezomib, lenalidomide, and low-dose dexamethasone. She has no history of bleeding or prior thrombosis.

What is the best way to reduce her risk of venous thrombotic events (VTEs)?

A. Warfarin, 1 to 2 mg daily
B. Aspirin 81 mg daily
C. Enoxaparin 1 mg/kg daily
D. Compression stockings
E. None needed

3. Bisphosphonates in multiple myeloma patients do which of the following?

A. Reduce risk of skeletal-related events
B. Reduce bone pain
C. Reduce risk of myeloma-related renal dysfunction
D. Reduce risk of venous thromboembolism
E. A and B

4. A 67-year-old man presents with chronic right hip pain and was found to have a 2.4 cm pelvic bone mass on an MRI scan done during workup by primary care provider. PET/CT was done that showed fluorodeoxyglucose (FDG) uptake in the right pelvis mass, no other areas of suspicious uptake. Pelvic mass biopsy confirmed a lambda-restricted plasma cell population. Bone marrow biopsy showed 5% lambda-restricted plasma cells. Blood tests were negative for anemia, hypercalcemia, or renal dysfunction, though showed a monoclonal IgG lambda protein level of 1.2 g/dL.

How would you treat this patient?

A. ≥40 Gy radiation to the pelvic plasmacytoma followed by observation
B. ≥40 Gy radiation to the pelvic plasmacytoma followed by bortezomib, lenalidomide, and dexamethasone (VRD) and consideration for autologous stem cell transplant (SCT)
C. Surgical resection followed by observation
D. Surgical resection, followed by lenalidomide maintenance therapy

5. Which of the following characterize high-risk multiple myeloma (MM)?

A. del(5q)
B. t(11;14)
C. Trisomy 15
D. del(17p)

6. A 61-year-old woman was referred to you after her primary care physician found a monoclonal protein (M-protein) of 3.6 g/dL during a workup for elevated total protein levels. Immunofixation reveals an IgA kappa M-protein. She has normal hemoglobin, normal serum calcium, normal creatinine, and negative urine Bence Jones protein. Her serum kappa/lambda light chain ratio is 3.6. An X-ray skeletal survey was negative for lytic lesions. Bone marrow biopsy shows 35% monoclonal plasma cells.

What is your next step in management?

A. Obtain next-generation sequencing (NGS) from bone marrow aspirate to risk-stratify and determine therapy
B. Start bortezomib, lenalidomide, and dexamethasone (VRD) and refer to bone marrow transplant center in preparation for autologous stem cell transplant (SCT)
C. Observation and recheck appropriate labs in 6 to 8 weeks
D. Obtain an MRI of the spine and pelvis or PET/CT

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ANSWERS

1. **A. VRD, stem cell collection after four cycles, autologous SCT, lenalidomide maintenance.** This patient has standard-risk active myeloma and should receive triplet combination induction therapy with VRD. A doublet induction therapy (Rd) would be considered in a frail patient with comorbid conditions, not for this relatively healthy patient. This patient has a good performance status and should be considered for an autologous HCT after induction, and therefore her stem cells should be collected after approximately the fourth cycle of induction therapy. Not offering upfront autologous SCT would not be standard of care for this patient unless she was deemed transplant-ineligible. All patients who undergo SCT should receive post-transplant maintenance therapy. If the patient were to opt against SCT, then more than four cycles of induction should be used.

2. **B. Aspirin 81 mg daily.** Low-dose aspirin daily is effective in lowering thrombosis risk in people at standard-risk for VTE on lenalidomide therapy. Patients at higher risk for thrombosis (e.g., prior thrombosis, high-dose dexamethasone use) may require prophylactic or therapeutic anticoagulants. Low dose warfarin is inferior for VTE prophylaxis in elderly myeloma patients regardless of risk. Prophylactic dosing of enoxaparin (e.g., 40 mg daily) would be another option

3. **E. A and B.** Bisphosphonates have been shown in several studies to reduce risk of new skeletal events and reduce myeloma-related bone pain. Bisphosphonates may cause renal toxicity, so renal function must be monitored and doses adjusted as needed with treatment. Bisphosphonates are not known to increase VTE risk in myeloma patients.

4. **A. ≥40Gy radiation to the pelvic plasmacytoma followed by observation.** This patient has a solitary plasmacytoma of bone (SPB) with minimal (<10%) bone marrow involvement that does not meet the criteria for multiple myeloma (MM). Radiation with curative intent (total dose ≥40 Gy) is the standard of care for SPB, and after completing this, he would undergo surveillance for his underlying IgG lambda monoclonal gammopathy of undetermined significance (MGUS). PET/CT is important to rule out other bone lesions prior to a diagnosis of SPB with minimal marrow involvement. Surgical intervention for SPB can be considered in certain cases, such as impending fracture or cord compression, which is not the case for this patient.

5. **D. del(17p).** Mutations such as t(14;20), t(14;16), t(4;14), gain(1q), del(1p), and del(17p) are cytogenetic markers of high-risk myeloma, along with elevated lactate dehydrogenase (LDH) or evidence of plasma cell leukemia. Trisomies, del(5q), and t(11;14) are considered standard-risk mutations in myeloma.

6. **D. Obtain an MRI of the spine and pelvis or PET CT.** This patient likely has smoldering multiple myeloma based on her monoclonal serum protein of ≥3 g/dL and ≥10% clonal plasma cells in her bone marrow, without any evidence of end-organ damage. Prior to diagnosing her with smoldering myeloma, however, she needs to be assessed for bone lesions that may have been missed by skeletal survey. This can be completed with whole body MRI, MRI total spine and pelvis (if whole body MRI is not available), or PET/CT. Up to 50% of patients without lytic lesions on skeletal survey demonstrate tumor-related lesions using more sensitive imaging methods. NGS testing of bone marrow in myeloma patients is not standard of care, though is often used in the context of clinical trials or MRD monitoring.

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II

AERODIGESTIVE MALIGNANCIES

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10 Non–Small Cell Lung Cancer

Eric Schwartz and Gregory P. Kalemkerian

ETIOLOGY AND RISK FACTORS

1. What are the major risk factors for non–small cell lung cancer (NSCLC)?

- Smoking
- Passive (secondhand) smoke
- Radon
- Asbestos (synergistic with smoking)
- Chronic obstructive pulmonary disease (COPD; emphysema), pulmonary fibrosis
- Prior history of lung cancer

2. What are the two most common mutations in NSCLC?

- p53 (inactivating mutations) in 50% to 60%
- K-RAS (activating mutations) in 30% of adenocarcinomas

3. Does NSCLC have simple chromosomal and molecular abnormalities?

- No. NSCLC is characterized by complex chromosomal and molecular abnormalities, with the complexity being directly related to the extent of tobacco smoke exposure.

4. What is the major mechanism of smoking-induced carcinogenesis?

- Polycyclic aromatic hydrocarbons (benzopyrene), nitrosamines (nicotine-derived nitrosamine ketone [NNK]), and aromatic amines (4-aminobiphenyl) form DNA adducts by covalently binding to DNA, resulting in DNA misreplication and mutation.

SCREENING

1. Who should undergo lung cancer screening with annual low-dose CT scan?

- High-risk subjects
  - Current smokers or former smokers who quit within the last 15 years
  - Age 50 to 80
  - At least a 20 pack-year smoking history

2. What is the benefit of CT scan screening for lung cancer?

- Annual CT screening improves both lung-cancer-specific mortality and overall mortality in high-risk subjects.

PREVENTION

1. Are there any currently approved chemoprevention strategies for lung cancer?

- No, only smoking prevention/cessation and risk factor reduction

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PATHOLOGY

1. What are the major subtypes of NSCLC?

- Adenocarcinoma
- Squamous cell carcinoma
- Large cell undifferentiated carcinoma
- Mixed tumors (e.g., adenosquamous carcinoma)

SIGNS AND SYMPTOMS

1. What are the common paraneoplastic syndromes associated with NSCLC?

- Anorexia/cachexia
- Thromboembolic events (Trousseau syndrome)
- Humoral hypercalcemia (due to parathyroid hormone-related peptide [PTHrp])
- Hypertrophic pulmonary osteoarthropathy (HPOA) and digital clubbing

DIAGNOSTIC WORKUP

1. What is the initial workup of suspected lung malignancy?

- Fluorodeoxyglucose (FDG)-PET to evaluate for lymph node involvement and distant metastatic disease
- Biopsy should be directed at the site that will most effectively: (a) obtain a diagnosis, (b) help to define the stage of disease, and (c) provide adequate tumor sample for molecular diagnostic studies.
- A central mass could be biopsied by bronchoscopy with endobronchial ultrasound-guided biopsy (EBUS).
- Peripheral nodules can be biopsied by CT-guided percutaneous core needle biopsy or navigational bronchoscopic biopsy.
- Mediastinal lymph node sampling with EBUS or mediastinoscopy should be performed in any patient with suspicious lymph nodes detected by FDG-PET or CT.
- Brain MRI or CT with contrast should be done on all patients with stage III or IV NSCLC.

2. What immunohistochemical markers can be useful in the diagnosis or histologic subtyping of lung cancer?

- General
  - Cytokeratins: CK7+, CK20– (pattern in 80% of primary lung cancers)
- Adenocarcinoma
  - TTF-1+ (75% of primary lung adenocarcinoma and small cell lung cancer)
  - Napsin A+ (>80% of primary lung adenocarcinoma)
  - Negative for mesothelioma markers (calretinin, WT1, CK 5/6, D2-40)
- Squamous cell carcinoma
  - p63+, p40+
  - CK 5/6 (positive in squamous cell carcinoma and mesothelioma)

3. When should next-generation sequencing (NGS) for driver mutations be performed?

- Adenocarcinoma
- Never smokers with any histologic subtype
- Primarily stage IV or incurable disease. Testing for EGFR mutations can be considered for resected, stage II–III adenocarcinoma.

4. When should immunohistochemistry for PD-L1 expression be performed?

- Any histologic subtype of NSCLC
- Primarily stage IV or incurable disease; the utility of PD-L1 testing has not been clearly defined in stage I–III NSCLC, so routine testing is not cost-effective.

STAGING

1. What staging classification is used for NSCLC?

- The American Joint Committee on Cancer (AJCC) 8th edition staging is currently in use (Table 10.1)

TREATMENT

1. What is the appropriate treatment for patients with clinical stage IA, IB, IIA, and IIB?

- Surgical resection is recommended (lobectomy or pneumonectomy plus mediastinal lymph node sampling or dissection).
- All patients being considered for lung resection should undergo preoperative pulmonary function testing with spirometry plus diffusing capacity (diffusing capacity of the lungs for carbon monoxide [DLCO]).
- Lobectomy or pneumonectomy yields better survival than sublobar resections (segmentectomy or wedge resection).
- Sublobar resection can be considered in patients who cannot tolerate lobectomy
- In patients who are medically inoperable or who decline surgery, radiation therapy (RT) should be considered (e.g., stereotactic body RT [SBRT]).
- What should be done if resection margins are positive?
  - R1 (microscopic residual disease): reresect if possible; RT (if reresection is not possible or patient declines reoperation)
  - R2 (gross residual disease): concurrent chemotherapy plus RT

2. Is there a role for adjuvant therapy for patients with pathologic stage IA or IB NSCLC after complete resection?

- No proven benefit for adjuvant chemotherapy or radiotherapy for stage IA or IB (i.e., tumor <4 cm [T1-T2a], lymph nodes negative [N0])

3. Is there a role for adjuvant therapy for patients with pathologic stage II or III NSCLC after complete resection?

- Adjuvant chemotherapy recommended for patients with good performance status and uncomplicated surgical recovery.
- Cisplatin-based, two-drug regimens × 4 cycles can improve 5-year overall survival by 4% to 15% in patients with stage II and III NSCLC. Cisplatin plus vinorelbine was the most commonly used regimen in trials of adjuvant chemotherapy that demonstrated a survival benefit. Cisplatin plus etoposide, gemcitabine, or pemetrexed (nonsquamous only) are also reasonable treatment options.
- Carboplatin-based, two-drug regimens × 4 cycles are acceptable in patients with contraindications or intolerance to cisplatin.
- Adjuvant osimertinib × 3 years has been shown to improve disease-free survival for patients with resected, EGFR-mutant adenocarcinoma, but an overall survival benefit has not been demonstrated.

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TABLE 10.1 ■ AJCC Eighth Edition Staging

			N0	N1	N2	N3
			No lymph nodes	Ipsilateral hilar or peribronchial	Ipsilateral mediastinal or subcarinal	Ipsilateral or contralateral scalene or supraclavicular; or contralateral mediastinal or hilar
T1	≤3 cm and no invasion of main bronchus	mi (≤5 mm invasion)	IA	IIB	IIIA	IIIB
		a (≤1 cm)				
		b (>1 and ≤2 cm)	IA2			
		c (>2 and ≤3 cm)	1A3			
T2	>3 and ≤5 cm; or invades visceral pleural or involves main bronchus	a (>3 and ≤4 cm)	IB			
		b (>4 and ≤5 cm)	IIA			
T3	>5 and ≤7 cm; or invades parietal pleura, chest wall, phrenic nerve, parietal pericardium; or separate pericardium; or separate tumor nodules in same lobe		IIB			
T4	>7 cm; or invades mediastinum, heart, great vessels, esophagus, diaphragm, vertebral body, trachea, carina, recurrent laryngeal nerve; or separate tumor nodules in different ipsilateral lobe		IIIA		IIIB	IIC

(*continued*)

TABLE 10.1 ■ AJCC Eighth Edition Staging (*continued*)

			N0	N1	N2	N3
			No lymph nodes	**Ipsilateral hilar or peribronchial**	**Ipsilateral mediastinal or subcarinal**	**Ipsilateral or contralateral scalene or supraclavicular; or contralateral mediastinal or hilar**
M1	Metastatic disease	a (contralateral lung nodules; or pleural or pericardial nodules or effusion)	IVA			
		b (single extrathoracic metastasis)				
		c (multiple extrathoracic metastases)	IVB			

AJCC, American Joint Committee on Cancer.

Source: Data from American Joint Committee on Cancer (AJCC), Eighth edition.

4. How are superior sulcus (Pancoast) tumors managed?

- Neoadjuvant concurrent chemotherapy plus RT followed by resection is recommended.
- If unresectable or medically inoperable, then recommend concurrent chemotherapy plus definitive RT.

5. What is the appropriate treatment for patients with clinical stage III NSCLC?

- Combination of chemotherapy and RT is a standard of care for most patients.
  - Concurrent chemotherapy plus RT is preferred due to improved survival over sequential chemotherapy followed by definitive RT.
  - Sequential chemotherapy followed by definitive RT is reasonable for patients with marginal performance status or significant weight loss.
  - Chemotherapy regimens that can be used safely with concurrent RT are
    - Cisplatin or carboplatin + pemetrexed (for adenocarcinoma only)
    - Cisplatin or carboplatin + etoposide
    - Weekly carboplatin plus paclitaxel
  - Durvalumab consolidation for 1 year after completion of chemotherapy plus RT improves overall survival compared to chemotherapy plus RT alone.
- Neoadjuvant chemotherapy or concurrent chemotherapy plus RT followed by surgical resection can be considered for patients with "nonbulky" N2 disease, good performance status, and tumor that can be resected without a pneumonectomy.

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6. What are the principles of treatment for patients with stage IV NSCLC?

- Stage IV NSCLC is incurable; treatment is given with palliative intent with the primary goals of improving disease-related symptoms, maintaining quality of life, and prolonging survival.
- The addition of early palliative care to standard oncologic care improves quality of life and overall survival.
- Cytologically confirmed malignant pleural or pericardial effusions indicate stage IV disease.
- A solitary, FDG-PET-positive site that would preclude curative resection or define stage IV disease requires biopsy for pathological confirmation.
- All patients with stage IV lung adenocarcinoma should have tumor or ctDNA tested for potentially targetable genetic driver mutations.
- Testing for driver mutations can be considered in patients with squamous cell histology, particularly if they have no smoking history.
- All patients with stage IV NSCLC should have tumor tested for PD-L1 expression by immunohistochemistry.

7. What is the most appropriate first-line therapy for patients with stage IV NSCLC?

DRIVER MUTATION POSITIVE

- If a driver mutation is identified, first-line therapy should be directed at that mutation.
  - ***EGFR* sensitizing mutations (exon 19 deletions or exon 21 L858R mutations)**
    - More common in nonsmokers, adenocarcinoma, women, and East Asians
    - First-line epidermal growth factor receptor (EGFR) inhibitor options: erlotinib or gefitinib (first generation); afatinib or dacomitinib (second generation); osimertinib (third generation); response rates of 60% to 70%
    - First-line EGFR inhibitors improve response rate and progression-free survival (PFS) compared to chemotherapy in patients with EGFR-mutant NSCLC.
    - Osimertinib is preferred first-line therapy as it improves PFS and overall survival over erlotinib or gefitinib.
    - Afatinib is approved for treating uncommon sensitizing *EGFR* mutations.
    - Erlotinib + ramucirumab (anti-vascular endothelial growth factor [VEGFR] monoclonal antibody) improved survival over erlotinib alone.
    - After progression on first- or second-generation EGFR inhibitors, obtain repeat biopsy to test for T790M resistance mutation; if T790M+, then treat with osimertinib
    - After progression on osimertinib, treat with first-line chemotherapy
  - ***ALK* rearrangement/fusion**
    - First-line anaplastic lymphoma kinase (ALK) inhibitor options: crizotinib (first generation); alectinib, brigatinib, or ceritinib (second generation); response rates of 60% to 70%.
    - Crizotinib, ceritinib, alectinib, and brigatinib improve response rate and PFS compared to chemotherapy.
    - Alectinib, brigatinib, or ceritinib can be used after progression on crizotinib with response rates of 50% to 60%.

- Lorlatinib (third generation) can be used after progression on ceritinib, alectinib, or brigatinib with response rate of 50%.
  - *Crizotinib* has *poor central nervous system (CNS) penetration*. All second- and third-generation ALK inhibitors have better CNS activity than crizotinib
- ***ROS1* rearrangement/fusion**
  - First-line ROS1 inhibitor options: **crizotinib** or **entrectinib** with response rates of 60% to 80%
- ***BRAF* V600E mutation**
  - First-line treatment with dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor) with response rate of 60%
- ***MET* exon 14 skip mutation**
  - Occurs in up to 20% of sarcomatoid carcinomas
  - First-line treatment with capmatinib with response rate of 70%
- ***RET* rearrangement/fusion**
  - First-line treatment with selpercatinib or pralsetinib with response rates of 60% to 80%
- ***NTRK* rearrangement/fusion**
  - Tumor-type agnostic Food and Drug Administration (FDA)-approval of larotrectinib or entrectinib
- ***KRAS G12C* mutation**
  - Sotorasib has response rate of 37% and is approved for patients with *KRAS G12C* mutant NSCLC who have had at least one prior systemic therapy.

DRIVER MUTATION NEGATIVE, NO CONTRAINDICATION FOR IMMUNOTHERAPY

- If PD-L1 expression is found in ≥50% of tumor cells (tumor proportional score [TPS] ≥50%), then first-line immunotherapy with single-agent pembrolizumab or atezolizumab is superior to chemotherapy with improved response rate and survival.
- Regardless of PD-L1 expression, first-line chemotherapy plus immunotherapy is superior to chemotherapy alone:
  - Nonsquamous carcinoma (adenocarcinoma) options
    - Carboplatin + pemetrexed + pembrolizumab followed by pemetrexed + pembrolizumab maintenance
    - Carboplatin + paclitaxel + bevacizumab + atezolizumab followed by bevacizumab + atezolizumab maintenance
    - Carboplatin + *nab*-paclitaxel + atezolizumab followed by atezolizumab maintenance
  - Squamous cell carcinoma options
    - Carboplatin + paclitaxel + pembrolizumab followed by pembrolizumab maintenance
    - Carboplatin + *nab*-paclitaxel + pembrolizumab followed by pembrolizumab maintenance
- If PD-L1 TPS ≥1%, the combination nivolumab + ipilimumab is superior to chemotherapy alone for any histology, but unclear if any benefit over single-agent immunotherapy or combination chemotherapy and immunotherapy.

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DRIVER MUTATION NEGATIVE, IMMUNOTHERAPY CONTRAINDICATED

- Two-drug, platinum-based chemotherapy for four to six cycles is recommended as first-line treatment
- Cisplatin and carboplatin are equivalent in efficacy in stage IV NSCLC. Carboplatin is less toxic, so it is preferable in the palliative setting.
- Chemotherapy for nonsquamous histology (adenocarcinoma, large cell carcinoma, NSCLC—not otherwise specified)
  - Carboplatin + pemetrexed followed by pemetrexed maintenance therapy is preferred first-line therapy
  - Bevacizumab + carboplatin + paclitaxel is superior to carboplatin + paclitaxel alone.
- Chemotherapy for squamous cell carcinoma
  - Pemetrexed is *not indicated* due to lack of efficacy in squamous cell carcinoma.
  - Bevacizumab is *contraindicated* due to excessive risk of massive hemoptysis.
  - The addition of necitumumab (anti-EGFR monoclonal antibody) to cisplatin + gemcitabine led to a modest improvement in survival compared to chemotherapy alone.
  - Common chemotherapy options include carboplatin + gemcitabine; carboplatin + paclitaxel; carboplatin + *nab*-paclitaxel.
  - No clear benefit for maintenance chemotherapy in squamous cell carcinoma.

8. What is the most appropriate subsequent therapy for patients with relapsed NSCLC?

- Driver mutation positive after progression on available targeted inhibitors or driver mutation negative after progression on single-agent immunotherapy
  - First-line chemotherapy with or without bevacizumab (nonsquamous only).
  - Immunotherapy has low potential for benefit in patients with *EGFR-*, *ALK-*, or *ROS1*-mutated NSCLC.
- After progression on first-line chemotherapy or chemoimmunotherapy
  - Docetaxel is superior to best supportive care
  - Pemetrexed is equivalent to docetaxel in nonsquamous carcinoma
  - Docetaxel plus ramucirumab provides a modest improvement in survival compared to docetaxel alone (all histologic subtypes included)
  - Nivolumab and atezolizumab are approved regardless of PD-L1 status. Pembrolizumab is approved as *second-line therapy* for patients with PD-L1 ≥1% or TMB ≥10. Further immunotherapy *not* used if patient was on immunotherapy at time of progression.

QUESTIONS

1. A 60-year-old man with a past medical history for hypertension and coronary artery disease and a 45 pack-year smoking history presents to his primary care physician for his annual physical examination. He has no history of cancer, but continues to smoke. His father, a smoker, died of lung cancer at age 64. He underwent his first screening colonoscopy 10 years ago and was told the colonoscopy did not show any polyps.

In addition to referring him for his 10-year screening colonoscopy, what other age-appropriate cancer screening should be recommended?

A. No other cancer screening is recommended at this time
B. Ultrasound of the prostate
C. Urinary cytology
D. Low-dose CT scan of the chest

2. A 72-year-old woman presents to the thoracic oncology clinic with a new diagnosis of lung cancer. CT scan shows a 4 cm right lower lobe mass, multiple lung nodules up to 1.5 cm, right hilar and bilateral mediastinal lymphadenopathy, and three enhancing lesions in the liver up to 2.4 cm. Percutaneous core needle biopsy of one of the liver nodules reveals poorly differentiated carcinoma that is immunohistochemically positive for CK7, TTF-1, and napsin A and negative for CK20, p63, and CK 5/6.

What molecular diagnostic studies would be useful in determining appropriate first-line therapy for this patient?

A. Immunohistochemistry for epidermal growth factor receptor (EGFR) expression
B. Genetic sequencing for *PD-L1* mutation
C. Next-generation sequencing for genetic driver mutations
D. Serum vascular endothelial growth factor (VEGF) concentration

3. A 63-year-old woman with a 60 pack-year smoking history presents to the medical oncology clinic to discuss treatment for newly diagnosed squamous cell carcinoma of the lung. CT of the chest shows a 7 cm left upper lobe mass with enlarged left hilar and bilateral mediastinal lymph nodes. PET/CT shows fluorodeoxyglucose (FDG) avidity in the left upper lobe mass and in the left hilar and bilateral mediastinal lymph nodes, but no evidence of distant metastases. MRI of the brain shows no metastases. Percutaneous biopsy of the left upper lobe nodule shows squamous cell carcinoma.

What is the next appropriate step in the management of this patient?

A. Endobronchial ultrasound guided biopsy of mediastinal lymph nodes
B. Definitive chemoradiotherapy
C. Palliative chemotherapy
D. Next-generation sequencing for genetic driver mutations

4. A 55-year-old man with a past medical history of tobacco use presents to the thoracic oncology clinic with a new diagnosis of lung cancer. He developed a productive cough a few weeks ago, which prompted a CT of the chest that showed a 3 cm right lower lobe spiculated mass with no lymphadenopathy. Pulmonary function testing revealed a mild obstructive deficit with intact diffusing capacity. He underwent a right lower lobectomy with mediastinal lymph node sampling. Surgical pathology confirmed a 2.9 cm squamous cell carcinoma with negative margins and no involvement

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of hilar or mediastinal lymph nodes. He now presents to the thoracic oncology clinic to discuss further care.

What is the most appropriate next step in the treatment of this patient?

A. Adjuvant chemotherapy with cisplatin + gemcitabine × 4 cycles
B. Adjuvant chemotherapy with cisplatin + pemetrexed × 4 cycles
C. Adjuvant radiation to the right hilum and mediastinum
D. Active surveillance with thoracic CT scans

5. A 73-year-old man with a 100 pack-year smoking history presents with progressive cough, dyspnea on exertion, and fatigue. His Eastern Cooperative Oncology Group (ECOG) performance status is 1 and he has had minimal weight loss. CT of the chest shows a large left hilar mass invading into the subcarinal space with enlarged bilateral paratracheal and prevascular lymph nodes. Bronchoscopic transbronchial biopsy of a right paratracheal lymph node reveals squamous cell carcinoma with PD-L1 tumor proportional score of 70%. PET scan shows fluorodeoxyglucose (FDG) avidity in the left hilar mass, bilateral mediastinal lymph nodes, and a left supraclavicular lymph node, but no distant metastases. MRI of the brain is normal.

What is the most appropriate treatment for this patient?

A. Palliative thoracic radiotherapy followed by single-agent pembrolizumab × 2 years
B. Carboplatin + paclitaxel + bevacizumab + atezolizumab × 4 cycles followed by maintenance bevacizumab + atezolizumab
C. Definitive thoracic radiotherapy + concurrent weekly carboplatin + paclitaxel followed by consolidation durvalumab × 1 year
D. Neoadjuvant chemoradiotherapy followed by surgical resection

6. A 60-year-old man with an 80 pack-year smoking history presents to the ED with right upper quadrant abdominal pain. CT of the abdomen shows multiple masses within the liver suspicious for metastatic disease. CT of the chest is notable for a left lower lobe 5.5 cm mass, multiple small bilateral pulmonary nodules, and enlarged ipsilateral hilar and mediastinal lymph nodes. MRI of the brain does not show any intracranial metastases. Percutaneous biopsy of a liver lesion reveals adenocarcinoma of lung primary. Next-generation sequencing for driver mutations reveals mutations in *p53*, *ATM*, and *STK11*. PD-L1 expression is present in 5% of tumor cells. His pain is controlled with hydrocodone–acetaminophen 10 to 325 mg as needed and his Eastern Cooperative Oncology Group (ECOG) performance status is 1.

What is the most appropriate first-line therapy for this patient's disease?

A. Cisplatin + gemcitabine + bevacizumab × 4 cycles followed by maintenance bevacizumab
B. Carboplatin + pemetrexed + pembrolizumab × 4 cycles followed by maintenance pemetrexed + pembrolizumab
C. Pembrolizumab every 6 weeks
D. Dabrafenib + trametinib

7. A 43-year-old Chinese woman presents with a nagging cough that has not improved with multiple courses of antibiotics, antacids, antihistamines, and inhalers. She is a never-smoker and has an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Chest radiograph shows multiple pulmonary nodules. CT scan confirms at least 20 bilateral lung nodules measuring up to 2.4 cm in diameter and a moderate right pleural effusion. Thoracentesis improves her cough and cytology reveals adenocarcinoma that is immunohistochemically positive for CK7, TTF1, and napsin A, but negative for CK20 and p40. PET scan shows fluorodeoxyglucose (FDG)-avidity in many lung nodules, right pleura, and right hilar lymph nodes with no evidence of distant metastases. MRI of the brain is normal. Molecular diagnostic studies reveal an *EGFR* L858R mutation and PD-L1 tumor proportional score of 50%.

What is the most appropriate next step in treatment for this patient?

A. Osimertinib
B. Selpercatinib
C. Nivolumab + ipilimumab
D. Alectinib

8. A 62-year-old former smoker with a diagnosis of stage IV squamous cell carcinoma of the lung completed four cycles of carboplatin + paclitaxel + pembrolizumab 3 months ago with good partial response and has been on maintenance pembrolizumab. He has had minimal side effects of treatment and has an Eastern Cooperative Oncology Group (ECOG) performance status of 1. A repeat CT scan shows growth of a right lower lobe mass from 3.0 to 4.5 cm, enlarging mediastinal lymph nodes and left adrenal mass, and multiple new liver lesions.

What is the most appropriate next step in treatment for this patient?

A. Cisplatin + vinorelbine
B. Docetaxel
C. Nivolumab + ipilimumab
D. Prophylactic cranial irradiation

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ANSWERS

1. **D. Low-dose CT scan of the chest.** A low-dose CT scan should be recommended for lung cancer screening in current smokers or former smokers who quit within the last 15 years who are 50 to 80 years of age and have at least a 20 pack-year smoking history. Annual CT screening improves lung-cancer-specific and overall mortality. The screening process should include counselling on the risks and benefits of the procedure and assistance with smoking cessation.

2. **C. Next-generation sequencing for genetic driver mutations.** Pathologic analysis of the patient's liver biopsy is consistent with metastatic lung adenocarcinoma. All metastatic lung adenocarcinomas should be tested for *EGFR*, *BRAF*, and *MET* sensitizing mutations, as well as *ALK*, *ROS1*, *RET*, and *NTRK* rearrangements at the time of diagnosis to determine whether they are candidates for first-line targeted therapy. The most efficient and cost-effective way to obtain these analyses is usually through next-generation sequencing. Expression of the EGFR protein is not useful for determining the utility of EGFR TKI therapy. PD-L1 expression may correlate with response to anti-PD1 therapy, but PD-L1 mutations have no known predictive value for guiding treatment. There are no validated biomarkers to predict the clinical utility of antiangiogenic therapy, so evaluation of VEGF levels is not indicated.

3. **A. Endobronchial ultrasound guided biopsy of mediastinal lymph nodes.** Patients with clinical evidence of mediastinal lymph node involvement by CT or PET imaging should undergo pathologic confirmation of lymph node involvement prior to the initiation of therapy. The false-positive rate of PET in mediastinal lymph nodes is about 10%, so the decision to forego potentially curative surgical resection should not be based on imaging studies alone. If stage III (N2+) non–small cell lung cancer (NSCLC) is proven by biopsy of a mediastinal lymph node, then appropriate therapy would be definitive chemoradiotherapy followed by consolidation immunotherapy. Molecular analysis for driver mutations does not have a role in the management of stage III NSCLC.

4. **D. Active surveillance with thoracic CT scans.** This patient has pathologic stage T1N0M0 disease, which translates to stage IA. There is no role for adjuvant chemotherapy or radiotherapy for patients with pathologic stage IA (T1N0M0) or IB (T2aN0M0) non–small cell lung carcinoma (NSCLC). Adjuvant chemotherapy improves overall survival in patients with completely resected, pathologic stage II or III NSCLC. The benefits of postoperative radiotherapy are controversial, with no randomized data supporting its use. Recommended follow-up for patients with pathologic stage IA NSCLC includes active surveillance with routine clinical evaluations and thoracic CT scans.

5. **C. Definitive thoracic radiotherapy + concurrent weekly carboplatin + paclitaxel followed by consolidation durvalumab × 1 year.** This patient has stage IIIC (T4N3M0) squamous cell lung cancer with good performance status and minimal weight loss. Standard treatment consists of definitive radiotherapy + concurrent chemotherapy followed by immunotherapy given with curative intent. The addition of consolidation durvalumab has demonstrated an improvement in overall survival over chemoradiotherapy alone. Surgery has no role in the treatment of patients with supraclavicular or contralateral mediastinal lymph node involvement (N3). A purely palliative approach with radiation, single-agent immunotherapy or combined chemoimmunotherapy is not appropriate in this relatively fit woman with potentially curative disease.

6. **B. Chemotherapy with carboplatin + pemetrexed + pembrolizumab × 4 cycles.** The patient has biopsy-proven metastatic lung adenocarcinoma without a targetable driver mutation and with a low PD-L1 tumor proportional score (TPS). Chemotherapy plus immunotherapy, such as carboplatin + pemetrexed + pembrolizumab, has been shown to improve response rates and survival when compared to chemotherapy alone in such patients. The addition of bevacizumab has not been shown to improve the efficacy of cisplatin + gemcitabine. Pembrolizumab single agent is preferred as first-line therapy in metastatic non–small cell lung cancer (NSCLC) if PD-L1 TPS is high (≥50%). The combination of dabrafenib (BRAF inhibitor) + trametinib (MEK inhibitor) is indicated only for patients with tumors harboring *BRAF* V600E mutations.

7. **A. Osimertinib.** This young, otherwise healthy, never-smoking, Asian woman has stage IV lung adenocarcinoma that harbors a sensitizing *EGFR* mutation. EGFR inhibitors yield high response rates and prolonged survival in patients with sensitizing *EGFR* mutations. Osimertinib is a third-generation, mutation-selective EGFR inhibitor that has been shown to improve survival when compared to first-generation EGFR inhibitors with lower rates of adverse events. *EGFR*-mutant tumors do not respond well to immunotherapy even if PD-L1 expression is high. Selpercatinib is a selective RET inhibitor that is approved for use in patients with *RET*-rearranged non–small cell lung cancer (NSCLC) and alectinib is an ALK inhibitor that is approved for use in patients with *ALK*-rearranged NSCLC.

8. **B. Docetaxel.** The patient has had progressive metastatic squamous cell carcinoma while on maintenance immunotherapy only 3 months after completion of first-line platinum-based therapy. Further platinum-based chemotherapy will not improve survival over single-agent therapy. He has progressed while on maintenance immunotherapy, so further immunotherapy is unlikely to provide further benefit. Furthermore, nivolumab + ipilimumab has not been approved in the relapsed setting. There is no role for prophylactic cranial irradiation in patients with any stage of non–small cell lung cancer (NSCLC).

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11 Small Cell Lung Cancer

Frank Weinberg and Angel Qin

BACKGROUND AND ETIOLOGY

- An aggressive neuroendocrine tumor distinct from non–small cell lung cancer (NSCLC)
- Approximately 15% of all diagnosed lung cancers
- Overall 5-year survival is around 5% (localized disease 27%, distant disease 3%)
- Smoking is the biggest risk factor for the development of small cell lung cancer (SCLC).

LUNG CANCER SCREENING

- Same population as those screened for NSCLC
  - High risk patients: that is, current or former smokers 50 to 80 years old with greater than or equal to 20 pack-year smoking history, who currently smoke or have quit within the past 15 years (United States Preventative Services Task Force recommendations).
  - There is no clear impact on mortality for patients with SCLC (as opposed to 20% reduction in mortality for those with NSCLC).

DIAGNOSIS

1. How is SCLC diagnosed?

- Histopathologic features include round small blue cells with high nuclear: cytoplasmic ratio.
- SCLC generally stains positive for thyroid transcription factor-1 (TTF-1), CK7, CD56 neural cell adhesion molecule (NCAM), synaptophysin, chromogranin A, and neuron-specific enolase (NSE).

STAGING

1. How is SCLC staged?

TABLE 11.1 ■ SCLC Staging

Limited stage	Median survival	14–20 months
Disease confined to ipsilateral hemithorax within a single radiation port	2-y survival	40%
Extensive stage	Median survival	8–12 months
Disease beyond ipsilateral hemithorax or obvious metastatic disease	2-y survival	5%

SCLC, small cell lung cancer.

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- Tumor, node, and metastasis (TNM) staging is useful in the selection of patients who should undergo surgical resection (i.e., T1–T2, N0) and follows the same TNM staging as NSCLC (American Joint Committee on Cancer [AJCC] eighth edition)

TREATMENT

1. Define treatment strategies for SCLC.

TABLE 11.2 ■ SCLC Treatment Strategies

Stage	Chemotherapy	Radiation	Surgery	Notes
LS-SCLC	Cisplatin/carboplatin and etoposide 4–6 cycles	Early, concurrent thoracic radiotherapy	T1–T2 disease†	PCI indicated for responders (complete or partial response)‡
ES-SCLC	Cisplatin/Carboplatin and Etoposide concurrent with immunotherapy (atezolizumab or durvalumab) 4–6 cycles followed by immunotherapy alone	Thoracic radiation if response (complete or partial) to initial systemic therapy*	Not indicated	Consider PCI for good responders with robust performance status.

*Thoracic radiation was not allowed in the chemo-immunotherapy trials involving patients with ES-SCLC. In practice many clinicians will still offer thoracic consolidative radiation if complete or partial response to initial chemo-immunotherapy.

†If surgical resection, adjuvant chemotherapy is recommended irrespective of pathologic stage.

‡The benefit of the use of PCI in patients who undergo surgical resection is unknown.

LS-SCLC, limited-stage small cell lung cancer; ES-SCLC, extensive-stage small cell lung cancer; PCI, prophylactic cranial irradiation.

TABLE 11.3 ■ SCLC Treatment Strategies for Recurrent/Relapsed Disease

Recurrent/ Relapsed Disease	Definitions of Disease Progression	Treatment
Sensitive relapse	Tumor progression occurs 90 days or more after the last day of initial treatment	Repeat initial platinum based regimen if the recurrence is >6 months later
Resistant relapse	Tumor progression occurs within 90 days after the last day of initial treatment	Proceed with second line treatment ■ Lurbinectedin ■ Topotecan ■ Other chemotherapy agents, including clinical trial

(*continued*)

TABLE 11.3 ■ SCLC Treatment Strategies for Recurrent/Relapsed Disease (*continued*)

Recurrent/ Relapsed Disease	Definitions of Disease Progression	Treatment
Refractory	Tumor progresses during the initial therapy or did not respond to initial therapy	Proceed with second-line treatment ■ Lurbinectedin ■ Topotecan ■ Other chemotherapy agents, including clinical trial

SCLC, small cell lung cancer.

LIMITED STAGE

- The goal is curative with concurrent chemotherapy and thoracic radiation. Concurrent chemoradiation has an increased risk of esophagitis, dysphagia, odynophagia, oropharyngeal/esophageal candidiasis, and pneumonitis.

EXTENSIVE STAGE

- The goal of therapy is palliative with chemo-immunotherapy.
- If brain metastases are present AND asymptomatic, can proceed with systemic treatment first followed by brain radiation after completion of induction systemic therapy. If brain metastases are symptomatic, then brain radiation should be administered prior to systemic therapy.
- Systemic chemo-immunotherapy is associated with increased risk for myelosuppression and immune-related side effects such as thyroid dysfunction, pneumonitis, colitis, and rash.
- Maintenance immunotherapy (e.g., durvalumab or atezolizumab) is continued if there is response to induction chemo-immunotherapy until progression or unacceptable toxicities.

SURVEILLANCE

1. How is surveillance performed?

TABLE 11.4 ■ Surveillance Methodologies

Modality	Limited Stage	Extensive Stage
Oncology visit	Every 3 months for year 1–2 then every 6 months for year 3, annually thereafter	Every 2 months for year 1 then every 3–4 months for year 2–3 then every 6 months for year 4–5, annually thereafter
CT chest, abdomen, pelvis	At every visit, as clinically indicated	
MRI brain	Every 3–4 months for year 1 then every 6 months for year 2 (regardless of PCI status)	

PCI, prophylactic cranial irradiation.

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OTHER CLINICAL PEARLS

- Up to 15% of SCLC patients will develop paraneoplastic syndromes due to ectopic production of polypeptides or antibodies irrespective of stage. SCLC is the most frequent cause of paraneoplastic syndromes.
- The most common paraneoplastic syndromes are the following:
  - Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
  - Ectopic adrenocorticotropic hormone (ACTH) production
  - Lambert–Eaton syndrome
- Effective treatment of the underlying tumor usually controls peptide-related endocrine syndromes
- Hypercalcemia due to parathyroid hormone-related peptide (PTHrP) is *rare* in SCLC; this paraneoplastic syndrome is more common in *squamous* histology.

TABLE 11.5 ■ Tumor Factor by Syndrome

Syndrome	Tumor Factor
Endocrine	
Cushing syndrome	ACTH
SIADH	Arginine vasopressin
Neurologic	
Central nervous system	
Subacute cerebellar degeneration	Anti-Hu Ab
Encephalomyelitis	Anti-Hu Ab
Myoclonus–opsoclonus	Unclear causative Ab
Cancer associated retinopathy	Antirecoverin Ab
Peripheral nervous system	
Subacute sensory neuropathy	Anti-Hu Ab
Subacute motor neuropathy	Anti-Hu antibody/anti-CV2 Ab
Autonomic neuropathy (Ogilvie syndrome)	Antibodies against myenteric plexuses
Neuromuscular junction	
Eaton–Lambert syndrome	Anti-P/Q calcium channel Ab

ACTH, adrenocorticotropic hormone; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

QUESTIONS

1. A 65-year-old male presented to his primary care physician (PCP) with a 20 lbs. weight loss and increasing cough. Chest X-ray (CXR) demonstrated a new left lung opacity. CT chest demonstrated a $6 \times 4 \times 2$ cm left hilar mass with mediastinal adenopathy. He was also noted to have elevated alanine transaminase (ALT) and aspartate transaminase (AST). CT abdomen/pelvis demonstrated multiple liver lesions. CT-guided biopsy of a

liver lesion demonstrated poorly differentiated neuroendocrine carcinoma, positive for synaptophysin and chromogranin. MRI brain was negative for intracranial metastasis.

Which of the following treatment plans is most appropriate?

A. Systemic chemotherapy (platinum/etoposide) for four to six cycles, followed by consolidation immunotherapy
B. Systemic chemotherapy with lurbinectedin for four to six cycles
C. Systemic chemotherapy (platinum/etoposide) with immunotherapy for four to six cycles, followed by maintenance immunotherapy
D. Immediate radiation to chest, liver, and brain

2. A 57-year-old female was recently diagnosed with extensive-stage small cell lung cancer (ES-SCLC). She underwent four cycles of carboplatin, etoposide, and atezolizumab with almost a complete response. She underwent consolidative thoracic radiation and was continued on maintenance atezolizumab for 6 months at which time repeat CT chest, abdomen, and pelvis demonstrated widespread progressive disease. Her MRI brain does not show any brain metastases. She continues to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1.

What is the most reasonable next step in treatment?

A. Start carboplatin and etoposide
B. Switch from atezolizumab maintenance to durvalumab maintenance
C. Refer to hospice
D. Send tumor for next generation sequencing

3. The patient in Question 2 receives two cycles of carboplatin and etoposide. Repeat imaging after two cycles demonstrates progression of her disease. She continues to have good performance status (Eastern Cooperative Oncology Group performance status [ECOG PS] 1).

What is the next best step in treatment?

A. Continue with carboplatin and etoposide
B. Refer to hospice
C. Start lurbinectedin
D. Start pembrolizumab

4. The patient in Questions 2 and 3 has a complete response with therapy after six cycles of lurbinectedin. Unfortunately, she developed neutropenia after cycle 4 with neutropenia persisting despite dose delay, dose reduction, and granulocyte colony-stimulating factor (G-CSF) interventions. It is decided to hold further treatment.

What is the next best step for this patient with complete response to lurbinectedin?

A. Start topotecan
B. CT chest, abdomen, pelvis in 2 months along with hematoxylin and eosin (H&P)
C. Observation
D. CT chest, abdomen, pelvis in 6 months along with H&P

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5. A 53-year-old female presents to clinic to discuss treatment options after 3 months of persistent cough and CT chest demonstrating a $6 \times 4 \times 2$ cm right upper lobe (RUL) lesion as well mediastinal lymph node enlargement. She had a bronchoscopy with biopsy of RUL mass and mediastinal lymph nodes that demonstrated small cell lung cancer (SCLC). PET/CT demonstrated only fluorodeoxyglucose (FDG) avidity of RUL lesion and mediastinal lymph nodes. MRI brain was negative.

What is the next best step in management?

A. Start platinum based chemotherapy plus etoposide
B. Refer to radiation oncology for radiation of RUL lesion and mediastinal lymph nodes
C. Start immunotherapy
D. Start platinum based chemotherapy plus etoposide and referral to radiation oncology for concurrent thoracic radiation

6. The patient in Question 5 completes induction therapy. She presents to clinic and reports she is feeling well, Eastern Cooperative Oncology Group performance status (ECOG PS) 0. Recent CT chest, abdomen, and pelvis demonstrated near complete response to treatment. MRI brain continues to show no intracranial metastasis.

What should you next consider in this 53-year-old female patient with limited-stage small cell lung cancer (LS-SCLC), good response to treatment, and robust performance status?

A. Start maintenance atezolizumab
B. Referral to Radiation Oncology for consideration of prophylactic cranial irradiation (PCI)
C. Observation
D. Radiation to the residual thoracic disease

7. A 67-year-old male presented to the ED with cough, shortness of breath, and a 20-lb weight loss over the past 2 months. He has a 100 pack-year history of smoking tobacco. Vitals are blood pressure 121/72, heart rate 67, and 97% oxygen saturation on room air. Labs are notable for a sodium of 128. He is admitted and is found to have extensive-stage small cell lung cancer (ES-SCLC) on biopsy of a liver lesion. Further work up of his hyponatremia demonstrates a serum osmolality of 250. Glucose and kidney function have been within normal limits during his admission.

What is the cause of his hyponatremia?

A. Dehydration
B. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
C. Cushing syndrome
D. Anti-sodium channel antibodies

ANSWERS

1. **C. Systemic chemotherapy (platinum/etoposide) with atezolizumab for four cycles. Followed by maintenance atezolizumab.** Standard care for extensive-stage small cell lung cancer (ES-SCLC) is four to six cycles of chemotherapy or as recently approved, chemo-immunotherapy followed by maintenance immunotherapy.

2. **A. Start carboplatin and etoposide.** The patient's disease would be classified as sensitive relapse as progression occurred after 90-day postinitial therapy. As such the most reasonable option, given her performance status, is to re-treat with the initial platinum based regimen (carboplatin and etoposide).

3. **C. Start lurbinectedin.** Lurbinectedin is a DNA alkylator that binds to DNA and inhibits cell cycle progression. It was approved by the Food and Drug Administration (FDA) in June 2020 for use in patients with metastatic small cell lung cancer (SCLC) after disease progression on or after platinum-based chemotherapy. This was based on improved overall survival (Study B-005). Major side effects include myelosuppression, fatigue, liver and kidney abnormalities, hyperglycemia, and gastrointestinal (GI) symptoms. It should be administered intravenously (IV), 3.2 mg/m^2 every 21 days until disease progression or unacceptable toxicity.

4. **B. CT chest, abdomen, pelvis in 2 months along with H&P.** Patients with extensive-stage small cell lung cancer (ES-SCLC) and complete or partial responses to treatment should be followed every 2 months with oncologic assessment and imaging. This continues for the first year after which imaging and oncologic assessment can be repeated every 3 to 4 months for year 2, every 6 months during year 3, followed by annual imaging and oncologic assessment indefinitely.

5. **D. Start platinum base chemotherapy plus etoposide with referral to radiation oncology for concurrent thoracic radiation**. This patient has limited-stage small cell lung cancer (LS-SCLC, a disease that is confined to one hemithorax or radiation field. The standard treatment for LS-SCLC is concurrent platinum based chemotherapy with etoposide and concurrent thoracic radiation.

6. **B. Referral to Radiation Oncology for consideration of prophylactic cranial irradiation (PCI).** For patients with LS-SCLC with good response (partial or complete) to initial therapy, it is strongly recommended that patients be considered for PCI after completing induction chemoradiation.

7. **B. SIADH.** Hyponatremia is seen in approximately 15% of patients with small cell lung cancer (SCLC) and 1% of patients with non–small cell lung cancer (NSCLC). The hyponatremia results from ectopic production of arginine vasopressin (AVP; also known as antidiuretic hormone [ADH]) from SCLC tumors. This will often resolve with treatment of the underlying malignancy.

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12 Mesothelioma

David E. Warner and Gregory P. Kalemkerian

EPIDEMIOLOGY

1. In what patient population does mesothelioma occur?

- Mesothelioma typically occurs in older men (median age at diagnosis is about 70 years) with a previous history of industrial asbestos exposure.

ETIOLOGY AND RISK FACTORS

1. What are the most common risk factors for the development of mesothelioma?

- Occupational asbestos exposure is documented in 75% of patients with pleural mesothelioma.
- Prior thoracic therapeutic irradiation
- Cigarette smoking is *not* associated with an increased risk of mesothelioma. However, cigarette smoking and asbestos exposure synergistically increase the risk of lung cancer.
- Familial mesothelioma is rare and is caused by heritable germline mutations in *BAP1* (BRCA1-associated protein)

2. What is the latency period between asbestos exposure and the development of mesothelioma?

- Three to four decades following exposure to asbestos

STAGING AND HISTOLOGICAL CLASSIFICATION

1. Define the staging for malignant pleural mesothelioma.

TABLE 12.1 ■ AJCC Eighth Edition Staging

Stage	Criteria
IA	Tumor involves ipsilateral parietal and/or visceral pleural surfaces only; without lymph node involvement or distant metastases (T1, N0, M0). Potentially resectable.
IB	Tumor involves ipsilateral parietal and/or visceral pleural surfaces with extension into at least one of the following: diaphragmatic muscle, underlying pulmonary parenchyma, endothoracic fascia, chest wall (solitary focus), mediastinal fat, or pericardium (nontransmural); without lymph node involvement or distant metastases (T2–3, N0, M0). Potentially resectable.

(*continued*)

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TABLE 12.1 ■ AJCC Eighth Edition Staging (*continued*)

Stage	Criteria
II	Tumor involves ipsilateral parietal and/or visceral pleural surfaces with or without extension into diaphragmatic muscle or underlying pulmonary parenchyma; with lymph node involvement limited to ipsilateral bronchopulmonary, hilar or mediastinal lymph nodes; without distant metastases (T1–2, N1, M0). Potentially resectable.
IIIA	Tumor involves ipsilateral parietal and/or visceral pleural surfaces with extension into at least one of the following: endothoracic fascia, chest wall (solitary focus), mediastinal fat, or pericardium (nontransmural); with lymph node involvement limited to ipsilateral bronchopulmonary, hilar or mediastinal lymph nodes; without distant metastases (T3, N1, M0). Borderline resectable.
IIIB	Tumor involves ipsilateral parietal and/or visceral pleural surfaces with or without extension into diaphragmatic muscle, underlying pulmonary parenchyma, endothoracic fascia, chest wall (solitary focus), mediastinal fat, or pericardium (nontransmural); with spread to supraclavicular (ipsilateral or contralateral) or contralateral mediastinal lymph nodes; without distant metastases (T1–3, N2, M0). Unresectable. or Tumor involves ipsilateral parietal and/or visceral pleural surfaces with extension into at least one of the following: chest wall (multifocal), peritoneum, contralateral pleura, mediastinal organs, spine, pericardium (transmural), or myocardium; with or without lymph node involvement; without distant metastases (T4, any N, M0). Unresectable.
IV	Any tumor; with or without lymph node involvement; with distant metastatic disease (any T, any N, M1)

Created by the authors based off of staging guidelines.

2. What are the histological subtypes of pleural mesothelioma?
- Epithelioid
- Mixed = epithelioid plus sarcomatoid
- Sarcomatoid (poorer prognosis)

SIGNS, SYMPTOMS, AND IMAGING FINDINGS

1. What are the common signs and symptoms of malignant pleural mesothelioma?
- Dyspnea
- Chest pain
- Cough
- Fatigue
- Weight loss
- Dullness to chest percussion or absent breath sounds
- Chest X-ray demonstrating a unilateral pleural effusion

2. What paraneoplastic syndromes are associated with mesothelioma?
- Thrombocytosis
- Anorexia/cachexia

- Hypercalcemia (secondary to production of parathyroid hormone-related peptide [PTHrp])
- Venous thrombosis
- Hypoglycemia (secondary to production of insulin-like growth factor II)

DIAGNOSIS

1. Initial workup of a pleural effusion with suspicion for mesothelioma should include which diagnostic tests?

- Thoracentesis with cytological assessment
- CT scan of chest with intravenous (IV) contrast
- Thoracoscopic pleural biopsy (if cytology is negative or nonspecific)

2. If mesothelioma is confirmed, what additional diagnostic testing is recommended?

- CT scan of abdomen with IV and oral contrast
- PET/CT scan (if being considered for surgical resection)
- Mediastinal lymph node biopsy (e.g., mediastinoscopy, endobronchial/endoscopic ultrasound-guided biopsy—if being considered for surgical resection)

PROGNOSTIC FACTORS

1. What histological features are associated with more favorable outcomes?

- The epithelioid histological subtype has a better prognosis relative to either the mixed or sarcomatoid subtypes

2. What are other favorable prognostic factors?

- Early-stage, localized disease
- Absence of lymph node involvement
- Absence of extensive chest wall involvement
- Good performance status
- Younger age
- Female gender

TREATMENT

1. What are the initial treatment decisions for management?

- Determine if the mesothelioma is resectable
- Determine the optimal intervention to control pleural effusion

2. For patients with potentially resectable mesothelioma, what additional testing is recommended to determine whether the patient is a candidate for surgery?

- Histologic subtyping—patients with sarcomatoid and mixed tumors have poor outcomes with aggressive surgical procedures, extensive resection is not recommended
- PET/CT to evaluate extent of disease, including mediastinal lymph node involvement and distant metastases
- Pulmonary function testing

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- Quantitative ventilation/perfusion (V/Q) scan, if pulmonary function tests are abnormal
- Cardiac stress testing

Early-Stage and Locally Advanced (Stage I–IIIA) Operable Disease

1. What are the treatment options for operable stage I–IIIA epithelioid mesothelioma?

- Induction chemotherapy (cisplatin/carboplatin plus pemetrexed) followed by surgery
- Primary surgery

2. What are the surgical options for operable malignant pleural mesothelioma?

- Partial pleurectomy/decortication (P/D)—removal of parietal and visceral pleura for diagnostic or palliative purposes leaving residual gross tumor.
- P/D—resection of parietal and visceral pleura with removal of all gross tumor without resection of diaphragm or pericardium.
- Extended P/D—resection of parietal and visceral pleura with removal of all gross tumor with resection of diaphragm and/or pericardium.
- Extrapleural pneumonectomy (EPP)—removal of affected lung, parietal and visceral pleura, hemidiaphragm, and ipsilateral pericardium, with mediastinal lymph node dissection.

3. What is the role of surgery in malignant pleural mesothelioma?

- The benefit of surgery remains controversial.
- Retrospective comparison of EPP versus P/D indicates a higher operative mortality with EPP than P/D (7% vs. 4%), with similar overall survival. Multivariate analysis favored P/D.
- A small, randomized trial comparing EPP to nonoperative management in patients with early-stage, resectable disease showed increased morbidity and mortality, and decreased quality of life in patients randomized to EPP.
- Trimodality approaches combining surgery, chemotherapy, and radiotherapy should be considered for younger patients with good performance status, epithelioid histology, and negative mediastinal nodes.
- Tumor debulking by thoracoscopic partial P/D does not improve survival, but is effective in controlling symptomatic pleural effusion.

4. When is adjuvant therapy employed?

- Following EPP, consider radiation to the affected hemithorax and mediastinum; and sequential adjuvant chemotherapy (cisplatin/carboplatin plus pemetrexed), if not given preoperatively.
- Following P/D, consider radiation to the mediastinum if lymph node involvement is found pathologically, and adjuvant chemotherapy (cisplatin/carboplatin plus pemetrexed), if not given preoperatively. Intensity-modulated radiotherapy (IMRT) is being explored in this setting, but remains investigational.

Inoperable (Stage I–IIIA) or Advanced (Stage IIIB–IV) Disease

1. What are the treatment options for inoperable or advanced-stage mesothelioma?

- Observation with short interval imaging to determine the pace of disease
- Systemic chemotherapy

- Immunotherapy
- Focal radiotherapy for control of localizable symptoms (e.g., chest wall pain)
- Tumor-treating fields (TTFs)
- Supportive care alone (if marginal or poor performance status)

Systemic Therapy

1. What are the first-line systemic therapy options for mesothelioma?

- The combination of nivolumab plus ipilimumab (Food and Drug Administration [FDA]-approved) improved overall survival compared to cisplatin/carboplatin plus pemetrexed (median, 18 months vs. 14 months) in a randomized phase III trial.
- Cisplatin plus pemetrexed (FDA-approved) improved overall survival compared to single-agent cisplatin (median, 12 months vs. 9 months) in a randomized phase III trial. Carboplatin is frequently substituted due to contraindications to cisplatin.
- Cisplatin (or carboplatin) plus pemetrexed plus bevacizumab improved overall survival compared to cisplatin plus pemetrexed (median, 19 months vs. 16 months) in a randomized phase III trial.
- Cisplatin/carboplatin plus gemcitabine
- Pemetrexed alone (for patients with marginal performance status)

2. What are subsequent-line systemic therapy options?

- If chemotherapy used first-line, nivolumab with or without ipilimumab, pembrolizumab
- If immunotherapy used first-line, cisplatin/carboplatin plus pemetrexed
- After combination chemotherapy and combination or single-agent immunotherapy, single-agent gemcitabine, vinorelbine, or doxorubicin/liposomal doxorubicin

Radiation Therapy

1. When should radiation therapy be considered?

- Hemithoracic radiotherapy is routinely recommended after EPP
- Palliative radiotherapy is useful for relief of localizable pain due to chest wall invasion
- Prophylactic radiotherapy to chest wall incisions or chest tube/thoracentesis sites does not decrease the incidence of chest wall metastases.
- IMRT is being explored in the neoadjuvant and post-P/D settings, but remains investigational.

Tumor-Treating Fields

1. What is TTF and what role does it have in mesothelioma?

- Electric fields created by an external chest wall pad are targeted to disrupt cell division
- FDA approved in combination with cisplatin/carboplatin plus pemetrexed for first-line treatment of unresectable, locally advanced, or metastatic mesothelioma based on a phase II, single-arm study that reported improved overall survival when compared to historical controls treated with chemotherapy alone.
- Side effects: dermatitis in up to 46% of patients
- Not routinely used due to lack of high quality studies and limited availability.

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SPECIAL CONSIDERATIONS

Pleural Effusions

1. What procedures are available for management of pleural effusions associated with mesothelioma?

- P/D
- Video-assisted thoracoscopic talc pleurodesis
- Placement of an indwelling, tunneled pleural catheter

QUESTIONS

1. A 72-year-old retired pipefitter presents with progressive exertional dyspnea, chest wall pain, and cough. He has smoked one pack per day for 54 years. His medical history is notable for Hodgkin lymphoma in his 30s treated with chemotherapy and mantle field radiation with no evidence of recurrence. He has a family history of mesothelioma in a paternal uncle and ocular melanoma in his father. CT scan shows a left-pleural-based mass with a moderate left pleural effusion. Percutaneous pleural biopsy confirms malignant sarcomatoid mesothelioma.

Which of the following is not a risk factor for the development of mesothelioma?

A. Tobacco use
B. Radiation exposure
C. Family history of mesothelioma
D. Occupational asbestos exposure

2. A 75-year-old retired foundry worker is found to have a right pleural effusion on chest radiography during an insurance examination. He has hypertension and a 60 pack-year smoking history. Exam reveals a good performance status, normal vital signs, and decreased breath sounds with dullness to percussion over the lower one-third of the right lung field. CT scan shows prominent right hilar soft tissue, moderate right pleural effusion with patchy nodular pleural thickening, and slightly enlarged right paratracheal and subcarinal lymph nodes. Right thoracentesis yields 800 mL of serosanguinous fluid and with negative cytology. Video-assisted thoracoscopy shows diffuse nodular pleural thickening and pleural biopsy reveals poorly differentiated malignant cells with intense desmoplastic reaction. Immunohistochemical staining of tumor cells is positive for CK 5/6, calretinin, and WT1 and negative for CEA, TTF1, napsin A, p40, and BAP1.

What is the most likely diagnosis?

A. Non–small cell lung cancer
B. Thymic carcinoma
C. Mesothelioma
D. Solitary fibrous tumor

3. A 67-year-old previously healthy man presents with progressive dyspnea, chest discomfort, fatigue, and peripheral edema. He has a blood pressure of 94/60, heart rate of 116, and respiratory rate of 28. His neck

veins are distended and heart sounds are distant with an audible rub. Echocardiogram shows a large pericardial effusion with early tamponade physiology. He undergoes pericardiocentesis with temporary catheter placement and cytologic evaluation of pericardial fluid reveals mesothelioma. CT shows diffuse left pleural thickening and a small pleural effusion with enlarged left hilar and mediastinal lymph nodes. After pericardial drainage, he is hemodynamically stable with a good performance status.

What is the best next step in management?
A. Bronchoscopy with biopsy of mediastinal lymph nodes
B. PET/CT
C. Pleurectomy/decortication with mediastinal lymph node sampling
D. Nivolumab plus ipilimumab

4. A 58-year-old woman with a history of cardiac transplantation and chronic renal insufficiency due to tacrolimus is evaluated for shortness of breath and diffuse left chest pain. A CT of the chest is notable for extensive nodular right pleural thickening that extends into the major fissure without frank chest wall invasion. There are multiple enlarged right hilar, paratracheal, and cardiophrenic lymph nodes. CT abdomen shows no evidence of metastatic disease. PET/CT shows intense fluorodeoxyglucose (FDG) avidity diffusely within the right pleura and in hilar and mediastinal lymph nodes. CT-guided pleural biopsy reveals malignant mesothelioma with sarcomatoid histology. She has a good performance status and is motivated for therapy.

What is the best next step in management?
A. Carboplatin plus pemetrexed
B. Nivolumab plus ipilimumab
C. Extrapleural pneumonectomy
D. Tumor-treating fields

5. An 84-year-old man with a history of coronary artery disease, type 2 diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, and moderate dementia is diagnosed with diffuse malignant pleural mesothelioma. His daily activities are significantly limited by generalized fatigue, chest pain, and shortness of breath from a rapidly recurrent large right pleural effusion. His comfort level and dyspnea improve after each thoracentesis, but then quickly worsen, and he continues to spend most of his day lying in bed or sitting in a recliner.

What is the most appropriate next recommendation for his care?
A. Palliative radiation to the affected hemithorax
B. Palliative chemotherapy with cisplatin, pemetrexed, and bevacizumab
C. Placement of an indwelling pleural catheter
D. Surgical consultation for pleurectomy/decortication

6. A 57-year-old retired construction worker presented with 3 months of shortness of breath and is found to have a large right pleural effusion. Thoracentesis with cytologic evaluation reveals malignant epithelioid mesothelioma. CT scan after pleural drainage reveals patchy, nodular

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pleural thickening with a pleural-based mass in the cardiophrenic recess, but no evidence of extensive chest wall invasion, lymph node enlargement or intra-abdominal disease. He receives induction therapy with cisplatin plus pemetrexed for four cycles, achieving a minor response. He then undergoes an extrapleural pneumonectomy and surgical margins are positive, but hilar and mediastinal lymph nodes are negative for malignancy.

What is the best next step in management?

A. Reoperation with resection of the positive margins
B. Postoperative hemithoracic radiotherapy
C. Adjuvant cisplatin plus gemcitabine for four cycles
D. Observation with serial CT scans

ANSWERS

1. **A. Tobacco use.** This elderly man was presumably exposed to asbestos while working as a pipefitter and occupational asbestos exposure is the primary cause of mesothelioma. Radiation exposure is also associated with an increased risk of mesothelioma. While extremely rare, germline mutations in *BAP1* have been associated with a familial risk of mesothelioma and melanocytic tumors. Smoking is not associated with the development of mesothelioma.

2. **C. Mesothelioma**. This elderly man likely has asbestos exposure from his prior work in a foundry. Occupational asbestos exposure increased the risk of both lung cancer and mesothelioma, and non–small cell lung cancer is actually the most common malignancy in people with prior asbestos exposure. This man's clinical and radiographic findings could be consistent with either diagnosis. However, the immunohistochemical studies clearly point to mesothelioma as the correct diagnosis. By standard microscopic histological assessment, it may be difficult to distinguish poorly differentiated adenocarcinoma from mesothelioma. Immunohistochemistry using a panel which includes several mesothelial markers (e.g., CK 5/6, calretinin, WT1, D2-40) and several adenocarcinoma markers (e.g., TTF1, napsin A, CEA, MOC-31) will usually differentiate between the two. In addition, loss of BAP1 expression is a common finding in mesothelioma, usually due to somatic aberrations, but rarely due to heritable germline mutations.

3. **D. Nivolumab plus ipilimumab.** This man has stage IV mesothelioma with pericardial involvement and cardiac tamponade. Given his good performance status, treatment with palliative systemic therapy to preserve quality of life and prolong survival is the most appropriate option. In a phase III, randomized trial, comparing nivolumab plus ipilimumab to cisplatin/carboplatin plus pemetrexed as first-line therapy for pleural mesothelioma, the combination immunotherapy regimen was shown to improve median overall survival by 4 months over chemotherapy. Surgical staging or resection is not indicated. PET/CT would not be useful since he already has pathologically proven advanced disease. If he should develop symptoms from worsening pleural effusion, then pleurectomy/decortication or talc pleurodesis would be appropriate options to maintain pulmonary function.

4. **A. Carboplatin plus pemetrexed.** This middle-aged woman has sarcomatoid histology and evidence of extensive lymph node involvement, which predict for a poor outcome with aggressive surgical procedures. In light of her symptoms and the aggressive histology of her tumor, systemic therapy would be the most appropriate treatment option. Immunotherapy is contraindicated by her prior cardiac transplantation and ongoing immunosuppression, and cisplatin is contraindicated by her renal insufficiency. Therefore, carboplatin plus pemetrexed is the most reasonable systemic treatment option. Tumor-treating fields have not been shown to be beneficial as single-modality therapy, but could be used along with chemotherapy. Palliative radiotherapy may be beneficial for symptom relief if she develops localizable pain associated with chest wall invasion.

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5. **C. Placement of an indwelling pleural catheter.** Insertion of a pleural catheter is the most reasonable supportive measure to maintain his comfort and functional status with minimal interventional morbidity. Given his advanced age, comorbidities, debility, and the palliative goals of care, surgical interventions and cisplatin-based chemotherapy would be contraindicated as the risks would outweigh the benefits. The diffuse nature of his disease and lack of localizable symptoms argue against palliative radiation. If his performance status significantly improves, he may become a candidate for single-agent systemic therapy.

6. **B. Postoperative hemithoracic radiotherapy.** The patient should be considered for radiation therapy in the setting of positive margins to improve local control. Further surgery will not be successful in obtaining negative resection margins. He has already had optimal chemotherapy with marginal response, so further chemotherapy is unlikely to provide significant benefit.

13 Thymoma

Kamya Sankar and Gregory P. Kalemkerian

OVERVIEW

- Thymic epithelial tumors originate in the thymus in the anterior mediastinum and include thymomas and thymic carcinoma.
- Thymic epithelial tumors are very rare (1.5 cases/million).
- Thymomas account for ~50% of all primary tumors in the anterior mediastinum.

ETIOLOGY, RISK FACTORS, AND CLINICAL FEATURES

1. What is the etiology of thymoma?

- The cause of thymic epithelial tumors is unknown.
- Thymic carcinoids are associated with multiple endocrine neoplasia syndrome, type 1 (MEN1).

2. What are the common risk factors associated with the development of thymoma?

- African Americans, Asians, and Pacific Islanders have an increased risk
- Older age
- Factors that are **not associated** with increased risk of thymoma include: alcohol, radiation exposure, tobacco use, immunosuppression

3. What clinical features are common to thymomas?

- 30% to 50% are asymptomatic; detected incidentally during chest imaging for unrelated reasons.
- Symptoms are primarily due to pressure on or invasion of mediastinal structures: anterior chest discomfort, cough, dysphagia, superior vena cava syndrome, hoarseness.
- Associated with autoimmune disease or paraneoplastic syndromes (myasthenia gravis in 30%–50%, hypogammaglobulinemia [Good syndrome] or pure red cell aplasia in 2%–5%)
- Paraneoplastic syndromes are much less common in thymic carcinoma.
- Patients with thymoma have an increased risk of developing second primary cancers, so suspected metastatic disease should be pathologically confirmed.

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4. What are the most common sites of metastatic disease for thymoma?

- The most common mode of spread is "drop metastases," via direct invasion into the pleural space, with development of pleural metastases and effusion.
- Hematogenous metastases are uncommon with thymoma, but may occur late in the course of the disease. Liver, lymph nodes, and bone are the most common extrathoracic sites of spread.
- Thymic carcinoma is much more commonly associated with hematogenous metastases.

DIAGNOSIS

1. What is the initial clinical evaluation of a mediastinal mass?

- CT scan of the chest with intravenous contrast
- Serum beta-human chorionic gonadotropin (β-HCG) and alpha-fetoprotein (AFP)
- Thyroid-stimulating hormone (TSH), T3, and T4
- Complete blood count
- Percutaneous biopsy is contraindicated in patients with an anterior mediastinal mass that is clinically and radiographically most consistent with primarily resectable thymoma. Biopsy may disrupt the capsule and foster tumor seeding.

2. What are the histologic subtypes of thymic epithelial tumors?

TABLE 13.1 ■ World Health Organization (WHO) Histological Classification of Thymic Epithelial Tumors

Type	Histologic Description
A	Bland, spindle/oval epithelial cells without atypia; paucity or absence of immature lymphocytes
AB	Mixed histology with regions resembling type A and type B
B1	Dispersed epithelial cells with architecture and cytology resembling normal thymus; abundant immature lymphocytes (lymphocyte-rich); areas of medullary differentiation
B2	Polygonal epithelial cells in small clusters at higher density than B1; abundant immature lymphocytes (lymphocyte-rich)
B3	Polygonal epithelial cells with mild-moderate atypia with a sheet-like, solid growth pattern (epithelium-predominant); paucity of immature lymphocytes
Thymic Carcinoma	Prominent cytologic atypia; nonthymic histologic features (squamous cell, undifferentiated, adenocarcinoma, neuroendocrine—large cell or small cell, lymphoepithelioma-like, sarcomatoid)

STAGING CLASSIFICATION

1. What is the Masaoka–Koga staging system for thymic tumors?

TABLE 13.2 ■ Masaoka-Koga Staging System for Thymic Tumors

Stage	Diagnostic Criteria
I	Microscopically and macroscopically completely encapsulated tumor
IIA	Microscopic transcapsular invasion
IIB	Macroscopic invasion into surrounding fatty tissue or grossly adherent to, but not through, mediastinal pleura, or pericardium.
III	Macroscopic invasion into adjacent organs (i.e., pericardium, great vessels, lung)
IVA	Pleural or pericardial dissemination
IVB	Hematogenous or lymphatic dissemination

2. What is the tumor, node, and metastasis (TNM) staging for thymic tumors (American Joint Committee on Cancer [AJCC] eighth edition)?

- See Table 13.3.

OUTCOMES

1. What is the overall survival of thymic epithelial tumors?

- The 5-year overall survival for thymoma is approximately 90%.
- Thymic carcinoma has a worse prognosis than thymoma, with an overall 5-year survival rate of approximately 50%.

2. What are the negative prognostic factors for thymoma?

- Advanced stage
- Thymic carcinoma histology
- Incomplete surgical resection
- Tumor size >10 cm
- Tracheal/vascular compromise
- Presence of paraneoplastic syndromes (except myasthenia gravis)

TREATMENT

1. What is the initial treatment decision for management of a mediastinal mass suspected to be a thymoma?

- The initial treatment decision is whether or not the tumor is primarily resectable. If an R0 resection (no residual tumor with clear margins) is feasible, then proceed with surgery.
- If tumor is not primarily resectable, then obtain tissue diagnosis with a core needle or open biopsy, taking care to avoid violating the pleural space.

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TABLE 13.3 ■ TNM Staging for Thymic Tumors

T category	T Description	N Category	N Description	M Category	M Description
T0	No evidence of primary tumor	**N0**	No regional lymph node metastasis	**M0**	No pleural, pericardial or distant metastasis
T1	Tumor limited to thymus with or without encapsulation or extending into the mediastinal fat (1a); with involvement of mediastinal pleura (1b)	**N1**	Anterior mediastinal (perithymic) lymph node metastasis	**M1a**	Separate pleural or pericardial metastasis
				M1b	Pulmonary intraparenchymal or distant organ metastasis
T2	Tumor directly invading pericardium	**N2**	Deep intrathoracic or cervical lymph node metastasis		
T3	Tumor directly invading lung, chest wall, phrenic nerve, superior vena cava, or pulmonary artery/vein				
T4	Tumor directly invading aorta, arch vessels, myocardium, trachea, or esophagus				

(*continued*)

TABLE 13.3 ■ TNM Staging for Thymic Tumors (*continued*)

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	any T	N1	M0
	any T	N0-N1	M1a
IVB	any T	N2	M0–M1a
	any T	any N	M1b

TNM, tumor, node, and metastasis.

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Resectable Disease (Stage I–II)

1. What further diagnostic evaluation is recommended prior to surgery for thymoma?

- Assessment for myasthenia gravis in order to prevent respiratory complications while under anesthesia. Perform a thorough neurologic examination and consider serum assay for anti-acetylcholine receptor antibody. Myasthenia gravis should be controlled prior to surgery.

2. Following surgery for resectable disease, what are the primary factors in determining recommendations for adjuvant therapy?

- Disease histology: thymoma versus thymic carcinoma
- Presence of microscopic or macroscopic capsular invasion (i.e., stage)
- Completeness of resection: no residual disease (R0); microscopic residual disease (R1); macroscopic residual disease (R2)

3. What is the postoperative management of primarily resectable disease?

- R0 resection (surgical margin negative)
  - Thymoma or thymic carcinoma with no capsular invasion: no further therapy
  - Thymoma or thymic carcinoma with capsular invasion: consider radiotherapy, less favored with thymoma types A and AB, more favored with thymic carcinoma
- R1 resection (surgical margin positive)
  - Thymoma: radiotherapy
  - Thymic carcinoma: radiotherapy ± chemotherapy
- R2 resection (gross residual disease)
  - Thymoma: definitive radiotherapy ± chemotherapy
  - Thymic carcinoma: definitive radiotherapy + chemotherapy

4. What is the appropriate surveillance after completion of therapy for resectable disease?

- Thymoma: surveillance CT scan of the chest every 6 to 12 months for 2 years, then annually for 10 years
- Thymic carcinoma: surveillance CT scan of the chest every 6 months for 2 years, then annually for 5 years

Locally Advanced, Potentially Resectable Disease

1. What is a "potentially resectable" thymic epithelial tumor?

- Potentially resectable thymic tumors are those for which an experienced thoracic surgeon deems that primary surgery would not yield an R0 resection, but that an R0 resection may be feasible if the tumor can be shrunk down with neoadjuvant therapy. These are mainly tumors that directly invade or encroach upon local structures included in the T3 designation (stage IIIA).

2. What is the appropriate treatment for locally advanced, potentially resectable disease?

- Neoadjuvant combination chemotherapy followed by radical resection followed by postoperative radiotherapy ± chemotherapy
- If tumor remains unresectable after neoadjuvant chemotherapy, then definitive radiotherapy ± chemotherapy

Unresectable or Metastatic Disease

1. What is an unresectable thymic epithelial tumor?

- Unresectable thymic tumors are those for which an experienced thoracic surgeon deems that surgery, with or without neoadjuvant therapy, would not yield an R0 resection. These are mainly tumors that directly invade or encroach upon local structures included in the T4 designation (stage IIIB) or those with metastatic spread (stage IV).

2. What is the appropriate treatment of locally advanced, unresectable disease?

- Definitive radiotherapy plus concurrent chemotherapy

3. What is the appropriate management of metastatic disease?

- For oligometastatic spread to the ipsilateral pleura, consider primary surgical resection, or neoadjuvant chemotherapy with subsequent reassessment for resection
- For more extensive pleural spread or extrathoracic metastases, palliative chemotherapy
- For palliation of focal symptoms (e.g., chest wall pain), palliative radiotherapy

Chemotherapy

1. What are appropriate first-line chemotherapy regimens for thymoma?

- First-line regimens are platinum-based
  - Cyclophosphamide, doxorubicin, and cisplatin (CAP)
  - cisplatin or carboplatin plus etoposide (PE; preferred for concurrent chemoradiotherapy)
  - Cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC)
  - Cisplatin, etoposide, and ifosfamide.
- Chemotherapy for thymic carcinoma should be tailored to histologic subtype (e.g., small cell carcinoma is treated with cisplatin or carboplatin plus etoposide). For undifferentiated thymic carcinoma, use same regimens as thymoma.

2. What is appropriate second-line chemotherapy for refractory or recurrent thymoma?

- Second-line therapy consists of single-agent chemotherapy or targeted therapy
  - Chemotherapy: pemetrexed, paclitaxel, gemcitabine ± capecitabine, 5-flouruoracil plus leucovorin, etoposide, or ifosfamide
  - Targeted therapy: sunitinib (for thymic carcinoma), everolimus, octreotide ± prednisone
- Approximately, 10% of thymic carcinomas harbor activating mutations of *c-KIT*. In such patients, imatinib has demonstrated clinical activity.

ALGRAWANY

QUESTIONS

1. A 54-year-old man presents with vague chest discomfort and progressive exertional dyspnea. Labs show hemoglobin of 4.6 g/dL, total leukocyte count of 8,400, and a platelet count of 169,000. Reticulocyte count is 0.1%. Chest radiography shows an anterior mediastinal mass. CT of the chest confirms a 5 cm, smoothly marginated, anterior mediastinal mass, which appears resectable. Serum anti-acetylcholine receptor antibody testing is negative.

   After administering a blood transfusion, which of the following is the most appropriate next step in management?
   A. Bone marrow biopsy with iron stains
   B. Thymectomy
   C. CT-guided biopsy of the anterior mediastinal mass
   D. Palliative radiation

2. A 67-year-old man underwent resection of a stage II thymoma (World Health Organization [WHO] type B2) followed by postoperative radiotherapy 3 years ago. He now presents with progressive dyspnea on exertion and mild left chest discomfort. CT scan shows diffuse left pleural thickening and multiple pleural-based nodules measuring up to 3.6 cm. Percutaneous biopsy of a pleural nodule confirms recurrent thymoma. He has a good performance status and is otherwise healthy.

   Which of the following would be the most appropriate next choice for therapy?
   A. 5-FU plus leucovorin
   B. Sunitinib
   C. Pemetrexed
   D. Cyclophosphamide, doxorubicin, and cisplatin (CAP)

3. A 45-year-old woman presents with chest pain, fatigue, and shortness of breath. Six months ago, she completed treatment for stage IVB thymic carcinoma with four cycles of cyclophosphamide, doxorubicin, and cisplatin (CAP). CT scans demonstrate progression of disease in left paratracheal and hilar lymph nodes, left pleura, and liver. Her Eastern Cooperative Oncology Group (ECOG) performance status is 1 and routine laboratory studies are normal. Molecular testing reveals a *c-KIT* exon 11 activating mutation.

   Which of the following is NOT an appropriate treatment option for this patient?
   A. Octreotide
   B. Sunitinib
   C. Imatinib
   D. Everolimus

4. A 53-year-old man is evaluated for chest pain and dyspnea. He is found to have an 8 cm anterior mediastinal mass. After appropriate preoperative evaluation, he undergoes resection. Pathology demonstrates undifferentiated thymic carcinoma with invasion into the superior vena cava and pericardium; margins and eight mediastinal lymph nodes are negative for carcinoma (R0 resection).

What is the most appropriate next step in patient management?

A. Observation with surveillance CT scans
B. Definitive radiation with concurrent chemotherapy
C. Postoperative adjuvant radiation therapy
D. Adjuvant chemotherapy only

5. A 65-year-old man presents with intermittent chest discomfort. CT scan of his chest shows a 3.5 cm sharply demarcated anterior mediastinal mass, suspicious for thymoma. Surgical consultation deems the mass to be resectable. Neurologic exam reveals left eyelid ptosis that is exacerbated by sustained upward gaze. Laboratory evaluation is positive for high-titer anti-acetylcholine receptor antibodies.

Which of the following is the most appropriate next step in management?

A. Refer to neurology for management of myasthenia gravis
B. Surgical resection of the anterior mediastinal mass
C. Radiation therapy to the anterior mediastinal mass
D. Consult interventional radiology for biopsy of the anterior mediastinal mass

6. A 64-year-old woman is diagnosed with locally advanced, primarily unresectable thymoma (World Health Organization [WHO] type B1), confirmed by CT-guided biopsy. She completes four cycles of cisplatin, doxorubicin, and cyclophosphamide, and a restaging CT shows an excellent tumor response. There is no evidence of pleural or extrathoracic metastatic disease.

Which of the following is the most appropriate next step in management?

A. Consolidative radiation therapy to the primary tumor
B. Maintenance chemotherapy with pemetrexed
C. CT surveillance every 6 months for 2 years
D. Surgical consultation to reconsider resection

ALGRAWANY

ANSWERS

1. **B. Thymectomy.** This middle-aged man has a clinical presentation consistent with thymoma and paraneoplastic pure red cell aplasia. The low reticulocyte count suggests that the anemia is due to reduced red cell production. If the clinical and radiographic suspicion of resectable thymoma is high, then a biopsy should be avoided to prevent capsular disruption and tumor seeding. The patient should undergo primary surgical resection.

2. **D. CAP.** Platinum-based combination chemotherapy, such as CAP, or cisplatin/carboplatin plus etoposide, would be an appropriate first-line chemotherapy option for stage IV thymoma in a patient with a good performance status. These regimens yield response rates of 40% to 50%. The other listed options could be considered for second-line therapy.

3. **A. Octreotide.** Phase II studies have demonstrated clinical activity for both sunitinib and everolimus in relapsed thymoma and thymic carcinoma. Sunitinib also has inhibitory activity against c-KIT, in addition to vascular endothelial growth factor (VEGFR) and platelet-derived growth factor receptor (PDGFR), making it a compelling option for this patient. Imatinib is a c-KIT inhibitor with a high level of clinical activity in c-*KIT* exon 11 mutant gastrointestinal stromal tumors (GIST). While prospective studies have not evaluated the role of imatinib in patients with c-*KIT*-mutated thymic carcinoma, clinical case reports have reported durable activity of imatinib in such patients. Octreotide has shown clinical activity against somatostatin receptor-positive thymoma, but not thymic carcinoma.

4. **C. Postoperative adjuvant radiation therapy.** The most appropriate treatment for patients with an R0 resection (surgical margins negative) for thymic carcinoma with transcapsular extension and invasion into adjacent structures (e.g., superior vena cava) is adjuvant radiation therapy. In this patient with stage III thymic carcinoma with R0 resection, postoperative radiation is indicated. Concurrent chemotherapy with radiotherapy would have been indicated if microscopic or gross residual disease were present (i.e., R1 or R2 resection).

5. **A. Refer to neurology for management of the myasthenia gravis.** Patients with suspected thymoma should have a thorough neurologic evaluation since 30% to 50% of patients will have myasthenia gravis. If diagnosed, myasthenia gravis must be brought under good symptomatic control prior to surgical resection of the thymoma in order to avoid intra-operative myasthenia crisis. Preoperative biopsy is not indicated for an anterior mediastinal tumor that is most consistent with thymoma.

6. **D. Surgical consultation to reconsider resection.** Patients with locally advanced, primarily unresectable thymic tumors who have had a good response to chemotherapy should be reassessed for surgical resection, since the completeness of resection is one of the strongest factors determining the prognosis of patients with thymic malignancies. If the tumor is resectable, then postoperative radiotherapy to the involved field should be considered. If the tumor is still deemed unresectable, then definitive radiation therapy should be initiated.

14 Head and Neck Cancers

Leigh K. Swartz and Paul L. Swiecicki

ETIOLOGY AND RISK FACTORS

1. What are the most common localizations of alcohol- and tobacco-related head and neck cancer?

- *Oral cavity* (floor of mouth, oral tongue, buccal mucosa, alveolar ridge, hard palate, retromolar trigone)
- *Pharynx* (nasopharynx, oropharynx—soft palate, uvula, base of tongue, tonsil, posterior pharyngeal wall)
- *Larynx* (supraglottic—false vocal cords, arytenoids, epiglottis; glottic—commissures; subglottic)
- *Nasal cavity and paranasal sinuses* (nasal cavity maxillary sinuses, ethmoid sinuses, frontal sinuses, sphenoid sinuses)

2. What are the most common localizations of human papillomavirus (HPV)-related squamous cell carcinoma of the head and neck (SCCHN)?

- Lingual and palatine tonsils, and base of the tongue
- Histologically identified by p16 staining

3. Which virus is associated with nasopharyngeal nonkeratinizing and undifferentiated cancers and where does this cancer typically present?

- Epstein–Barr virus (EBV); histologically identified by Epstein–Barr-encoded RNA (EBER) staining
- Fossa of Rosenmüller

STAGING

1. How is SCCHN staged?

- Staging of SCCHN is defined for the following specific regions:
  - Lip and oral cavity
  - Pharynx
    - Nasopharynx
    - Oropharynx
      - Separate staging based on HPV status as determined by p16 staining
    - Hypopharynx
  - Larynx
  - Nasal cavity and paranasal sinuses

ALGRAWANY

- Major salivary glands
- Mucosal melanoma of the head and neck

Note: Mucosal melanoma of the head and neck is a very aggressive cancer and is not reviewed in this chapter.

- Generic anatomic staging for HPV negative SCCHN is as follows:

	Anatomic Stage/Prognostic Groups			
Relatively small primary tumor with no or minimal nodal involvement	Stage 0	Tis	N0	M0
	Stage I	T1	N0	M0
	Stage II	*	*	M0
Larger primary tumor and/or nodal involvement	Stage III	*	*	M0
	Stage IVA	*	*	M0
	Stage IVB	*	*	M0
	Stage IVC	Any T	Any N	M1

*Specific for anatomic location.

- Anatomic staging for HPV-positive oropharyngeal SCCHN is as follows:

	Anatomic Stage/Prognostic Groups			
Tumors of any size with/without lymph node involvement <6 cm	Stage I	T0-2	N0-1	M0
	Stage II	T0-2	N2	M0
		T3	N0-2	M0
	Stage III	T0-4	N3	M0
		T4	Any N	M0
	Stage IV	Any T	Any N	M1

DIAGNOSTIC WORKUP

1. What is the "field cancerization" concept?

- Diffuse epithelial injury within the aerodigestive tract (head, neck, lungs, and esophagus) due to chronic exposure to carcinogens

2. Why is the field cancerization concept clinically important?

- Patients with squamous cell carcinoma of the head and neck (SCCHN) may present with second metachronous and synchronous cancers of the aerodigestive tract.
- It dictates thorough examination of head and neck with laryngoscopy, nasopharyngoscopy, bronchoscopy, and esophagoscopy as indicated.
- It mandates chest imaging (chest x-ray [CXR], CT, or PET/CT) for all patients because of the risk of a concurrent lung malignancy.

TREATMENT

General Approaches

1. What percentage of patients presents with early-stage cancer (stage I or II) and require single-modality therapy (surgery or radiation)?

- 30% to 40% of patients present with early-stage cancer (stage I or II).
- Survival is similar for both of these modalities.

2. What percentage of patients present with locally advanced disease (stages III, IVA, and IVB) and require combined-modality therapy?

- About 60% of patients present with locally advanced disease (stages III, IVA, and IVB).
- The exact sequence of treatment modality differs depending on cancer location and cancer center expertise (e.g., surgery followed by radiation ± chemotherapy or chemoradiotherapy followed by surgery as needed [full extirpation/neck dissection]).

Surgical Therapy

1. Which patients should receive surgery as a first-line therapy?

- Patients with limited disease (stage I or II); although lately, radiation is commonly used for these patients. Low bulk stage III—T1 to T2, N1 disease can also be surgically treated.
- Patients with locoregionally advanced disease (higher volume stage III/IV without distant metastases) as an *alternative* to chemoradiotherapy.

2. Involvement of which structures makes the SCCHN tumor unresectable?

- Extension of tumor to the skull base
- Direct extension to the superior nasopharynx or Eustachian tube
- Encasement of the common or internal carotid artery
- Direct extension to the mediastinum, prevertebral fascia, or cervical vertebra (there are exceptions)
- Direct extension of neck disease to the external skin (there are exceptions)
- Involvement of the pterygoid muscles (there are exceptions)

3. What is a "classical radical neck dissection?"

- It includes resection of all lymph nodes from levels I to V, as well as resection of internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle.
- It is rarely done nowadays due to severe morbidity.

4. What are the current classifications of surgical neck dissection?

- **Comprehensive** (removes all five lymph node levels that would be included in classical radical neck dissection, regardless of other structures resected or not)
- **Selective** (removes fewer than all five lymph node levels based on common pathways of spread of SCCHN)

5. In which situations can selective neck dissection be used?

- Selective neck dissection is mostly used for N0 (no palpable lymph nodes) disease.
- Selective neck dissection can be occasionally performed in certain patients with N1–N2 disease to prevent excessive morbidity.

ALGRAWANY

6. Is there a role for the surgery after radiation or chemoradiation therapy?
- Yes, if the patient has residual disease or suspected local progression; however, such surgery is complicated by poor wound healing, skin necrosis, or carotid exposure with risk for carotid blowout.

Radiation as a First-Line Therapy

1. When may radiation be used as a first-line therapy?
- In early-stage (stage I or II) patients
- When a patient's performance status is not suitable for upfront chemoradiotherapy or surgery

2. What is the major advantage of radiation therapy in SCCHN?
- Organ preservation

3. What is the major advantage of intensity-modulated radiation therapy (IMRT)?
- Decreased radiation-induced toxicity (especially xerostomia)
- It has a similar overall survival compared to conventional radiation therapy.

4. Is there any advantage to using accelerated fraction radiotherapy versus single fraction radiotherapy?
- Without chemotherapy: yes, accelerated fraction improves local control and survival.
- With chemotherapy: no, local control and survival are the same.

5. What is an important part of routine follow-up for patients who received radiation to the neck?
- Assessment of thyroid function (thyroid-stimulating hormone [TSH]) every 6 to 12 months (20%–25% of patients who received neck radiation have elevated TSH level)

6. Should nonsurgically treated patients be examined by a head and neck surgical oncologist regularly?
- Yes, to evaluate for early detection of local or regional recurrences of cancer and early salvage surgery.

Concomitant Chemoradiation as a First-Line Therapy

1. What is the role of concomitant chemoradiation as a first-line therapy?
- It may be used as a first-line therapy in locally advanced SCCHN (stage III/IVA/B) sparing some patients from surgical intervention; however, first-line therapy for oral cavity cancers is surgery given poor outcomes with radiation-based treatments.
- It is a therapy of choice for "very advanced SCCHN" patients (T4b, any N, and M0) who are usually not suitable candidates for surgery.
- Salvage surgery is reserved for patients with residual or locally recurrent disease.

2. Is sequential chemotherapy and radiation as effective as concomitant therapy?
- No. Concomitant chemoradiation is preferred for organ preservation; however, induction chemotherapy (cisplatin + 5-fluorouracil [5-FU] continuous infusion

for three cycles) followed by radiotherapy (70 Gy) is an alternative for those with stage III/IVAB larynx cancer (laryngectomy-free survival rate is the same with chemoradiation and induction chemotherapy).

3. What is the "standard" regimen for concomitant chemoradiation for SCCHN?

- Seventy Gy at daily 2.0 Gy fractions for 7 weeks with cisplatin given every 3 weeks at 100 mg/m^2

4. What is the role of cetuximab in SCCHN?

- Cetuximab can be used for patients who are not platinum candidates concurrently with radiation for locally advanced SCCHN; but has been found to be inferior to cisplatin in HPV-related oropharyngeal cancers.
- Metastatic disease: cetuximab in addition to platinum and 5-FU may be used as first-line treatment (improved survival rate over platinum and 5-FU).
- Metastatic disease: cetuximab as a single agent may be used as second-line therapy after platinum failure.

Adjuvant Therapy

1. What are the major and minor risk factors for local recurrence?

- **Major:**
  - Positive margins
  - Extracapsular nodal spread of tumor
- **Minor:**
  - Multiple positive nodes
  - Vascular/lymphatic/perineural invasion
  - pT3 or pT4 primary
  - Oral cavity or oropharynx primary with level 4 or 5 nodal involvement

2. Which patients should receive adjuvant radiation therapy alone?

- Patients with a single minor risk factor for local recurrence

3. Which patients should receive adjuvant chemoradiation therapy?

- Patients with one major risk factor for recurrence
- Patients with two or more minor risk factors for local recurrence can be considered for chemoradiotherapy

4. Is there a role for adjuvant systemic therapy alone?

- No. Neither chemotherapy nor immunotherapy alone is used in adjuvant settings for SCCHN.

5. What is the standard chemoradiation regimen in the adjuvant setting?

- Cisplatin (100 mg/m^2) once every 21 days with concurrent radiation (66 Gy)

Systemic Therapy

1. When is systemic therapy used alone in SCCHN?

- For palliation in unresectable recurrent, metastatic SCCHN patients, or in patients with locally advanced SCCHN that are no longer amenable to surgery or radiotherapy.

ALGRAWANY

2. What is the role for front-line immunotherapy in the recurrent/metastatic setting?

- A new biopsy of a metastatic site should be obtained and sent for PD-L1 combined positive score (CPS) using the 22C3 antibody upon diagnosis of recurrent/metastatic SCCHN.
- For PD-L1 CPS <1% in patients who are not immunotherapy candidates, first-line therapy remains platinum agent + 5-FU continuous infusion + cetuximab.
- For PD-L1 CPS <1%, first-line therapy options include platinum agent + 5-FU continuous infusion + cetuximab or platinum agent + 5-FU continuous infusion + pembrolizumab.
- For PD-L1 CPS ≥1%, treatment options include single-agent pembrolizumab or in combination with chemotherapy for front-line treatment.

3. What agents are used in patients who have failed platinum with radiation within 6 months of completing therapy or after platinum failures in the recurrent/metastatic setting?

- Nivolumab or pembrolizumab are standard second-line therapy, irrespective of PD-L1 testing.
- Single-agent cetuximab, weekly docetaxel, and weekly methotrexate are acceptable in patients who are not candidates for immunotherapy.

4. When is radiation used in the palliative setting for SCCHN?

- Reirradiation and concurrent chemotherapy with radiation are not considered the standard of care. Reirradiation may improve local control but does not improve overall survival.

LOCATION-SPECIFIC CONSIDERATIONS

Cancer of the Lip and Oral Cancer

- Sun is an additional risk factor for cancer of the lip.
- Lower lip cancers are associated with low incidence of metastases.
- Cancer of the upper lip and commissural areas has higher incidence of metastases at the time of diagnosis.
- Surgery is the preferred therapeutic option for bulky and locally advanced resectable disease.

Cancer of the Nasopharynx

- World Health Organization (WHO) classification of nasopharyngeal carcinoma is as follows:
  - Keratinizing squamous cell carcinoma (SCC; WHO type I)
  - Nonkeratinizing SCC (WHO type II)
  - Undifferentiated carcinoma (WHO type III)
- Neck mass is the most common presentation of nasopharyngeal carcinoma.
  - Nasopharyngeal carcinoma has a high metastatic potential (more in types II and III compared to type I).
- Type I has the worst prognosis, due to uncontrolled growth of primary tumor.

- Surgery is not recommended as a first-line therapy for nasopharyngeal cancer.
- Standard therapy includes the following:
  - For stages I and IIA—radiation alone
  - For stages IIB, III, and IV—chemoradiation with cisplatin 100 mg/m^2 every 21 days or weekly cisplatin 40 mg/m^2 followed by three courses of adjuvant cisplatin with 5-FU, OR induction chemotherapy with gemcitabine and cisplatin × three cycles, followed by chemoradiation with cisplatin 100 mg/m^2 intravenous (IV) every 21 days.
  - For stage IVC (metastatic disease)—cisplatin with gemcitabine or cisplatin with 5-FU or single agent docetaxel or paclitaxel

Cancer of the Oropharynx

- Eighth edition American Joint Committee on Cancer (AJCC) TNM staging (2017) distinguishes between HPV negative and positive cancers. Due to excellent prognosis, locoregionally advanced HPV-positive cancers have been downstaged as compared to prior staging systems. There is not yet evidence that treatment should differ between HPV-positive and HPV-negative cancers, and should still be based on AJCC 7th edition until further evidence becomes available.
- When surgery is used as an initial modality in stages 0–IVA oropharyngeal cancer, a transoral resection (TORS) is typically employed.
- In locoregionally advanced oropharyngeal cancer (stage IVB), surgery is reserved for the management of residual regional lymph node metastases following chemoradiotherapy and recurrent disease.

Cancer of the Hypopharynx

- May be treated with induction therapy (cisplatin + infusional 5-FU) × three cycles followed by radiotherapy or cisplatin (100 mg/m^2) every 21 days with radiation, if tumor is less than T4a (i.e., no thyroid cartilage invasion).
- T4a tumors are treated with *total laryngectomy* followed by radiation ± chemotherapy.

Cancer of the Larynx

- Divided into supraglottic, glottic, and subglottic laryngeal cancers; glottis tumors have the best prognosis and supraglottic tumors have the worst prognosis.
- Management options in locally advanced resectable cancers (T3–4 or T2N+) include resection followed by radiation versus organ preservation.
- Organ preservation approaches include the following:
  - Induction chemotherapy (cisplatin + infusional 5-FU × three cycles) followed by definitive radiation
  - Combined chemoradiation: radiation with concurrent cisplatin (100 mg/m^2 every 21 days × three doses)

NOTE: Though organ preservation is highest with concomitant chemoradiation, laryngectomy-free survival is similar for both regimens.

- Patients with bulky (T4a) disease of larynx should have *total laryngectomy* followed by adjuvant radiation (± chemotherapy) as it is unlikely to spare the function of the larynx in these patients.

ALGRAWANY

Cancer of the Nasal Cavity and Paranasal Sinuses

- Most of the tumors are symptomatic and present with advanced stage.
- Although surgical resection is generally preferred, it is difficult to perform due to advanced presentations, and patients are treated with chemoradiation (cisplatin and radiation).
- The most common histology is SCC; other histologies are adenocarcinoma, esthesioneuroblastoma (aka olfactory neuroblastoma), sarcoma, and undifferentiated carcinoma.
- Esthesioneuroblastomas require surgery and radiation with long-term follow-up because recurrence can occur even after 15 years. Chemotherapy is generally not indicated.

Cancer of the Major Salivary Glands

- Ionizing radiation, rubber, and automotive industries are risk factors.
- Seventy-five percent of parotid gland neoplasms are benign.
- Seventy-five percent of submandibular, sublingual, and minor salivary glands are malignant.
- Most common histologies are as follows:
  - Mucoepidermoid (metastatic high-grade tumors can be treated with chemotherapy regimens used to treat SCCHN)
  - Acinic
  - Adenocarcinoma
  - Adenoid cystic carcinoma (characterized by an indolent natural history, often followed with serial imaging; and has the best prognosis of all salivary gland tumors)
  - Malignant myoepithelial tumor
  - Squamous carcinoma (rare)
- SCCs of the surrounding skin frequently metastasize to the parotid glands (can be confused with primary parotid gland cancers).
- Complete surgical resection is a major therapeutic approach for all salivary gland tumors.
- The majority of cases require adjuvant radiation alone due to incomplete resection, close or positive margin, intermediate or high-grade histology, or neural/vascular/lymphatic invasion.
- Although chemoradiation could be considered, there is no role for adjuvant chemotherapy.

QUESTIONS

1. A healthy 67-year-old woman presents with the complaint of a slowly enlarging lump on the right side of her face. A CT is performed demonstrating a 2.2 × 3.1 cm mass within the parotid gland without evidence of other masses, lymphadenopathy, or bone/muscle infiltration. An ultrasound-guided core needle biopsy is performed and demonstrates moderately differentiated adenoid cystic carcinoma.

Which of the following is the most appropriate next step in this patient's management?

A. Stereotactic beam radiation therapy to the mass
B. Definitive chemoradiation utilizing cetuximab
C. Docetaxel, cisplatin, and infusional 5-fluorouracil (FU) for three cycles followed by definitive radiation therapy to the mass
D. Resection

2. A 37-year-old female with no past medical history is presented at multidisciplinary tumor board after being diagnosed with Epstein–Barr virus (EBV) + nasopharyngeal carcinoma, which was discovered in the workup of persistent epistaxis. The primary tumor was found to extend to the oropharynx without parapharyngeal involvement. Imaging of the neck revealed no involved lymph nodes. Fluorodeoxyglucose (FDG) PET/CT was obtained due to high EBV viral load and failed to demonstrate distant metastatic disease.

Which of the following is the most appropriate recommendation for the management of this patient?

A. Radiation
B. Platinum-based combination chemotherapy
C. Induction chemotherapy followed by concurrent chemoradiation
D. Concurrent chemoradiation
E. Surgical resection

3. A 45-year-old man with a history of chewing tobacco use presents for a 6-month history of a progressively enlarging mass on the roof of the mouth. A CT was obtained demonstrating a 2.1 × 1.7 cm mass located on the hard palate with erosion and right neck level I lymphadenopathy. A biopsy is obtained and demonstrates squamous cell carcinoma.

Which of the following is the most appropriate next step in this patient's management?

A. Surgical resection
B. Irradiation of the oral cavity mass and bilateral necks
C. Concurrent chemoradiation to the oral cavity mass and bilateral necks
D. Hospice referral

4. A 55-year-old female with a history of hypertension presents with an enlarging, non-tender, left-sided neck mass. Examination of the neck reveals multiple enlarged, left-sided cervical nodes. CT of the neck demonstrates a large, left-sided lymph node conglomeration measuring 6.2 cm in greatest dimension and a 2.5 cm soft palate mass. Fluorodeoxyglucose (FDG) PET/CT confirms the presence of the cervical neck mass and soft palate mass but does not show any additional sites of metastatic disease. Fine needle aspiration of the lymph node conglomeration is performed and demonstrates poorly differentiated squamous cell carcinoma, p16 positive.

ALGRAWANY

Which of the following is the most appropriate next step in this patient's management?

A. Radical neck dissection
B. Chemotherapy alone
C. Human papillomavirus (HPV) vaccination
D. Irradiation of soft palate mass and bilateral necks
E. Concurrent chemoradiation with cisplatin (100 mg/m^2) every 21 days

5. A 62-year-old man with a history of stage IVA oropharyngeal squamous cell carcinoma presents 3 months after completion of chemoradiation for disease monitoring. He has noted fullness in the right neck and supraclavicular region but thought it was due to a muscle spasm. A PET/CT is obtained and demonstrates multiple lymph nodes with intense fluorodeoxyglucose (FDG) avidity in the right neck.

Which of the following is the most appropriate next step in this patient's management?

A. Close surveillance with repeat PET/CT in 3 months
B. Six cycles of chemotherapy with cisplatin + 5-fluorouracil (FU) + cetuximab
C. Reirradiation of the mass utilizing hyperfractionation and a nonplatinum radiosensitizing agent
D. Modified radical neck dissection

6. A 73-year-old male with a history of hypertension, coronary artery disease, and a 50 pack-year smoking history is referred to you for evaluation of multiple lung nodules discovered on low-dose screening CT chest. Fluorodeoxyglucose (FDG) PET/CT reveals an FDG-avid mass at the right base of tongue and confirms innumerable, FDG-avid lung nodules measuring up to 2 cm in size. Biopsy of a peripheral lung nodule reveals squamous cell carcinoma that is p16 positive. PD-L1 combined positive score (CPS) is 25%. He lives alone and walks 2 miles every day.

Which of the following would be the most appropriate recommendation for first-line therapy for this patient's metastatic disease?

A. Sorafenib
B. Pembrolizumab
C. Cisplatin + 5- fluorouracil (FU) continuous infusion + cetuximab
D. Cisplatin + 5-FU continuous infusion
E. Carboplatin + paclitaxel

ANSWERS

1. **D. Resection.** Complete surgical resection is the first-line therapy for tumors of the major salivary glands. The remainder of the options listed here would not be appropriate therapeutic options.

2. **A. Radiation.** Definitive radiation to the nasopharynx with elective radiation to the neck is the preferred treatment modality in this patient with stage I (T1N0M0) nasopharyngeal carcinoma. Overall survival rates approach 90% in stage I patients treated with radiation alone. There is no role for chemotherapy or surgery as first-line therapy for stage I nasopharyngeal carcinoma.

3. **A. Surgical resection.** Surgical resection would be the most appropriate management treatment modality in this patient with oral cavity cancer. Surgical management has superior outcomes when utilized in the first-line setting compared to chemoradiation. Hence it is the treatment of choice.

4. **E. Concurrent chemoradiation with cisplatin (100 mg/m^2) every 21 days.** In this patient with stage III (T2N3M0), p16-positive oropharyngeal squamous cell carcinoma and in those patients with locally advanced oropharyngeal cancer, the preferred first-line therapy is concurrent chemoradiation. Alternatively, resection of the primary tumor and neck dissection could be considered, but this is not a listed answer choice. Radiation alone is insufficient to treat locally advanced oropharyngeal cancers. There is currently no role for HPV vaccination in the treatment of HPV-associated squamous cell carcinoma of the head and neck (SCCHN).

5. **D. Modified radical neck dissection.** Persistent disease after completion of chemoradiation is typically managed by surgical resection, specifically a modified radical neck dissection. Given the short time since his last radiation therapy, reirradiation is unlikely to be effective and is associated with a high risk for severe toxicities. Chemotherapy alone is reserved for patients with inoperable recurrent or metastatic disease.

6. **B. Pembrolizumab.** In patients who are candidates for immunotherapy with tumors that demonstrate PD-L1 CPS >1%, first-line treatment for unresectable recurrent or metastatic head and neck squamous cell carcinoma consists of pembrolizumab or a triplet containing a platinum agent, 5-fluorouracil (5-FU) continuous infusion, and pembrolizumab.

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III

ENDOCRINE MALIGNANCIES

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15 Thyroid Cancers

Debbie W. Chen and Megan R. Haymart

I. Thyroid Cancers

EPIDEMIOLOGY

- The three main types of thyroid cancer are differentiated (>90% of all thyroid cancers and includes papillary, follicular, and Hürthle cell), medullary (4%), and anaplastic (2%).
- According to Surveillance, Epidemiology, and End Results (SEER) data, about 67% of patients have localized, 28% have regional, and 4% have distant disease.
- The incidence of thyroid cancer has substantially increased over the last few decades while the mortality from thyroid cancer has remained relatively stable, with some studies suggesting that over diagnosis due to widespread use of thyroid ultrasound (US) is a contributing factor.
- Median age at diagnosis is 51 years.
- Three out of four cases of thyroid cancer occur in women.

RISK FACTORS

- Head and neck radiation exposure (the risk increases with larger doses of radiation and with younger age at treatment)
- Female sex (women are three times more likely to develop thyroid cancer)
- Hereditary conditions
  - The risk of medullary thyroid cancer (MTC) is increased in multiple endocrine neoplasia (MEN) type 2A and 2B.
  - The risk of papillary thyroid cancer is *increased* in Carney complex, PTEN hamartoma syndrome (Cowden's disease), and Familial adenomatous polyposis (FAP).

SIGNS AND SYMPTOMS

- Thyroid nodules may be palpated on physical exam or incidentally found on imaging studies.
- Patients may present with a large thyroid or goiter on physical exam or new-onset compressive symptoms (i.e., hoarseness, dysphagia, dyspnea).

DIAGNOSTIC WORKUP

- Evaluation of a thyroid nodule should include serum thyroid-stimulating hormone (TSH) and thyroid US.

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- If TSH is low, check serum free thyroxine (FT4) level. If there is biochemical evidence of hyperthyroidism (low TSH, high FT4), evaluate for the presence of hyperfunctioning nodule(s) with a radionuclide thyroid scan. A hyperfunctioning thyroid nodule is most likely benign and does not need to be biopsied.
- If the TSH is normal or high, or the thyroid nodule is not hyperfunctioning, perform a thyroid US to further characterize the thyroid nodule.

- While thyroid nodules are common in the adult population (prevalence of about 20%–70%), most are benign (about 10% are malignant).
- Bethesda system for reporting thyroid nodule fine needle aspiration (FNA) results.
  - Bethesda I: nondiagnostic or unsatisfactory
  - Bethesda II: benign
  - Bethesda III: atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) has a 5% to 15% risk of malignancy. Repeat FNA with molecular testing may be used to supplement malignancy risk assessment.
  - Bethesda IV: follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN) has a 15% to 30% risk of malignancy. Surgical excision may be considered for removal and definitive diagnosis.
  - Bethesda V: suspicious for malignancy
  - Bethesda VI: malignant

II. Differentiated Thyroid Cancer

- At least 80% of thyroid cancer is papillary thyroid cancer, which has an excellent prognosis in the majority of patients.

PREOPERATIVE EVALUATION

- Neck US with evaluation of the central and lateral neck lymph nodes
- Neck MRI or CT with intravenous (IV) contrast if there is a clinical suspicion for advanced disease. Additional imaging (i.e., chest CT) can be considered if suspicious for distant metastases.
- Routine preoperative measurement of serum thyroglobulin (Tg) or antithyroglobulin antibodies (TgAb) is not recommended.

SURGERY

- Near-total or total thyroidectomy is recommended for tumors >4 cm, or with gross extra-thyroidal extension (clinical T4), clinically apparent metastatic disease to lymph nodes (clinical N1), or distant sites (clinical M1).
  - Lymph node dissection should be performed if there is lymph node involvement.
- Total thyroidectomy or lobectomy for tumors >1 cm and <4 cm without extrathyroidal extension, and without clinical evidence of lymph node metastasis (cN0).
- Thyroid lobectomy or active surveillance for tumors <1 cm without extrathyroidal extension and without clinical evidence of lymph node metastasis in the absence of prior head and neck radiation or familial thyroid cancer.

POSTOPERATIVE STAGING

TABLE 15.1 ■ Staging for Differentiated Thyroid Cancer Based on the Eighth Edition of AJCC Staging System

AJCC STAGE	Age at Diagnosis	Description
STAGE I	≤55 y old	Tumor of any size without distant metastasis (any T, any N, M0)
	>55 y old	Tumors ≤4 cm that is confined to the thyroid without lymph node or distant metastasis (T1–T2, N0, M0)
STAGE II	≤55 y old	Tumor of any size with distant metastasis present (any T, any N, M1)
	>55 y old	Tumors >4 cm and confined to the thyroid (T3a, any N) or with gross extra-thyroidal extension into the strap muscles (T3b, any N), or tumors <4 cm with metastasis to regional lymph nodes (T1-T2, N1). No distant metastasis (M0)
STAGE III	>55 y old	Tumors of any size with gross extra-thyroidal extension into subcutaneous tissue, larynx, trachea, esophagus, recurrent laryngeal nerve without distant metastasis (T4a, any N, M0)
STAGE IV	>55 y old	Tumors of any size with gross extra-thyroidal extension into prevertebral fascia, encasing major vessels (T4b, any N, M0), or presence of distant metastasis (any T, any N, M1)

AJCC, American Joint Committee on Cancer.

Source: Adapted from AJCC Staging Manual, 8th Edition.

RADIOACTIVE IODINE THERAPY

1. What is the role of radioactive iodine (RAI) after thyroidectomy?

- RAI should only be given for iodine-avid disease. It is used to destroy normal residual thyroid tissue (remnant ablation) and presumed (adjuvant therapy) or known (targeted therapy) residual or metastatic disease.
- RAI remnant ablation is not routinely recommended for low-risk disease (defined as tumors ≤4 cm limited to the thyroid without lymph node or distant metastasis).
- RAI adjuvant therapy should be considered for intermediate-risk disease (i.e., aggressive papillary thyroid cancer histologies such as tall cell, diffuse sclerosing, and insular variants).
- RAI adjuvant therapy is routinely recommended for high-risk disease (defined as tumors with gross extra-thyroidal extension or distant metastasis).

2. What cumulative dose-related risks are associated with RAI therapy?

- Salivary gland damage, dental caries, nasolacrimal duct obstruction, secondary malignancies

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3. Special consideration for RAI therapy

- Women should avoid pregnancy for 6 to 12 months after RAI therapy to decrease the risk of miscarriage.
- RAI should not be given to nursing women.

TSH SUPPRESSION

TSH suppresion with a supraphysiologic dose of levothyroxine may prevent the growth and spread of differentiated thyroid cancer (DTC).

1. What is the appropriate degree of TSH suppression?

- Thyroid hormone suppressive therapy to maintain TSH <0.1 mU/L is recommended for high-risk patients (tumor with gross extra-thyroidal extension, incomplete tumor resection, or distant metastasis).
- TSH may be maintained between 0.1 and 0.5 mU/L for low-risk patients after total thyroidectomy and RAI remnant ablation with low serum Tg levels.
- TSH may be maintained at the lower end of the reference range (0.5–2.0 mU/L) for low-risk patients with undetectable serum Tg levels after total thyroidectomy, and for low-risk patients after lobectomy.

2. What are the adverse effects of TSH suppression?

- Increased risk of osteoporosis in postmenopausal women, atrial fibrillation among patients >60 years, and increased cardiovascular and all-cause mortality

LONG-TERM SURVEILLANCE

Long-term surveillance is performed to evaluate for evidence of biochemical and/or structural disease recurrence.

- Check serum Tg, TgAb, and TSH 4 to 6 weeks postoperatively, then trend every 6 to 12 months thereafter. Of note, it may take 6 to 12 months for the Tg level to reflect the full effect of RAI therapy.
  - Both Tg and TgAb assays may be affected by heterophilic antibodies.
  - The presence of TgAb, which occur in about 25% of thyroid cancer patients, can cause falsely low Tg measurements in immunometric assays. If TgAb is detected with immunometric assays, consider checking Tg and TgAb levels with liquid chromatography tandem-mass spectrometry (LC-MS/MS).
  - Tg <0.2 ng/mL is considered an excellent response, Tg >1.0 ng/mL suggest biochemical evidence of residual disease, and Tg between 0.2 and 1.0 ng/mL is considered an indeterminate response and warrants following.
  - A rising unstimulated or stimulated serum Tg suggests disease that is likely to become clinically apparent.
- To evaluate for evidence of structural disease recurrence, perform neck US 6 to 12 months postoperatively, then based on recurrence risk and Tg levels.
  - Papillary thyroid cancer tends to spread to lymph nodes in the neck.
  - Follicular thyroid cancer can also spread to lymph nodes in the neck, but is more likely to spread to distant organs, especially the lungs and bones.
- Consider 18F-fluorodeoxyglucose (FDG)-PET/CT scan in patients with elevated and/or rising Tg levels (generally >10 ng/mL) with negative RAI imaging to evaluate for non-iodine-avid disease.
- Consider cross-sectional imaging (CT or MRI) of the neck and upper chest for detection of metastatic disease.

TREATMENT FOR METASTATIC DIFFERENTIATED THYROID CANCER

- Surgical excision of locoregional disease
- RAI therapy for iodine-avid disease
- External beam radiation therapy, thermal ablation, ethanol ablation, or chemoembolization for patients with a single or few metastases
- Thyroid hormone suppressive therapy for patients with stable or slowly progressive asymptomatic disease. Patients with progressive disease are treated with thyroid hormone suppressive therapy in addition to other treatments.
- IV bisphosphonate or denosumab therapy for bone metastases
- Systemic therapy for progressive and/or symptomatic RAI-refractory DTC that is less likely to be treated adequately with regional disease management options such as surgery or radiation therapy.
  - Lenvatinib
    - An oral inhibitor of vascular endothelial growth factor receptors 1 to 3 (VEGFR1-3), fibroblast growth factor receptors 1 to 4, platelet-derived growth factor-alpha, and RET and KIT proto-oncogenes.
    - Common adverse events: hypertension, diarrhea, weight loss, and fatigue.
  - Sorafenib
    - An orally active inhibitor of VEGFR1-3 and Raf kinases.
    - Common adverse events: hand-foot skin reaction, diarrhea, alopecia, rash/desquamation, fatigue, weight loss, and hypertension.

1. What are the targeted specific therapies for RAI-refractory DTC?

- Selpercatinib
  - Highly selective small-molecule RET kinase inhibitor.
  - In DTC, only for *RET fusion-positive* thyroid cancer
  - Common adverse events: hypertension, increased alanine and aspartate aminotransferase levels, hyponatremia, and diarrhea
- Pralsetinib
  - Highly selective small-molecule RET kinase inhibitor
  - In DTC, only for *RET fusion-positive* thyroid cancer
  - Common adverse events: hypertension, constipation, fatigue, and musculoskeletal pain.
- Larotrectinib and entrectinib
  - Selective inhibitor of neurotrophic receptor kinase (NTRK) used in the therapy of NTRK-fusion solid tumors, including RAI-refractory DTC.
  - Common adverse effects: ocular changes, neurotoxicity, fatigue, cognitive impairment, peripheral neuropathy, nausea, vomiting, dizziness, joint pain.

III. Medullary Thyroid Cancer

- Neuroendocrine tumor of the parafollicular C-cells, which secrete calcitonin and carcinoembryonic antigen (CEA)
- The majority (75%) of MTC are sporadic. About 50% of these patients have somatic RET mutations.
- About 25% of MTC are inherited
  - MEN2A is characterized by MTC, pheochromocytoma, and hyperparathyroidism. Most common mutation is RET 634.

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- MEN2B is characterized by MTC, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromas, and marfanoid habitus. Most common mutation is *RET 918*.
- Familial MTC is defined by the presence of MTC and no evidence of pheochromocytoma or hyperparathyroidism in 4 to 10 or more family members.

PREOPERATIVE EVALUATION

- Measure serum levels of calcitonin and CEA.
- Perform genetic testing for presence of germline *RET* proto-oncogene mutation. If positive, measure urine or plasma free metanephrines, and serum calcium and parathyroid hormone levels to evaluate for pheochromocytoma and hyperparathyroidism, respectively.
- Neck US with evaluation of the central and lateral neck lymph nodes
- Cross-sectional imaging (i.e., neck/ chest/ abdominal CT, contrast-enhanced liver MRI, bone scintigraphy) in patients with extensive neck disease, signs and symptoms of regional or distant metastases, or serum calcitonin level >500 pg/mL.

SURGERY

- Prophylactic thyroidectomy is recommended in patients with a known *RET* mutation (i.e., *MEN2A* and *MEN2B*). The age at which surgery is recommended depends on the specific *RET* mutation.
- Total thyroidectomy with bilateral central neck dissection for all patients with MTC
- Consider prophylactic dissection of the ipsilateral (if calcitonin >20 pg/mL) and contralateral lateral neck (if calcitonin >200 pg/mL) based on calcitonin level.

POSTOPERATIVE STAGING

TABLE 15.2 ■ AJCC Staging for Medullary Thyroid Cancer

AJCC Stage	Description
Stage I	Tumor <2 cm limited to the thyroid with no lymph node or distant metastasis (T1, N0, M0)
Stage II	Tumor of any size limited to the thyroid or with minimal extrathyroidal extension with no lymph node or distant metastasis (T2–T3, N0, M0)
Stage III	Tumor of any size limited to the thyroid or with minimal extrathyroidal extension with involvement of level VI lymph nodes and no distant metastasis (T1-T3, N1a, M0)
Stage IVA	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a, any N); or involving level I-V lymph nodes (T1-T3, N1b). No distant metastasis (M0)

(*continued*)

TABLE 15.2 ■ AJCC Staging for Medullary Thyroid Cancer (Adapted) (*continued*)

AJCC Stage	Description
Stage IVB	Tumor of any size that invades prevertebral fascia or encases carotid artery or mediastinal vessels with or without lymph node involvement, and no distant metastasis (T4b, any N, M0)
Stage IVC	Tumor of any size with distant metastasis present (any T, any N, M1)

AJCC, American Joint Committee on Cancer.

Source: Adapted from AJCC Staging Manual, 8th Edition.

LONG-TERM SURVEILLANCE

- Measure serum TSH within 4 to 6 weeks postoperatively. May need to initiate levothyroxine to maintain serum TSH in the normal reference range.
- Measure serum calcitonin and CEA levels and follow doubling time, and perform neck US 3 months postoperatively.
  - If calcitonin undetectable or within the normal range and neck US normal, trend calcitonin and CEA levels every 6 months for 1 year, then annually thereafter.
  - If calcitonin elevated <150 pg/mL and neck US normal, trend calcitonin and CEA levels every 3 to 6 months, and repeat neck US every 6 months.
  - If calcitonin elevated >150 pg/mL, perform cross-sectional imaging to look for recurrent disease.

TREATMENT FOR METASTATIC MEDULLARY THROID CANCER

- Total thyroidectomy with bilateral central neck dissection w/wo lateral neck dissection
- Majority of MTC do not respond to external beam radiotherapy.
- Chemoembolization, percutaneous ethanol ablation, or radiofrequency ablation for liver metastases
- IV bisphosphonate or denosumab therapy for bone metastases

1. What are the non-RET-specific targeted therapies for metastatic MTC?

- Multitargeted tyrosine kinase inhibitors for unresectable disease that is symptomatic or progressing
  - Vandetanib
    - An oral agent that targets VEGFR, RET, and epidermal growth factor receptor signaling.
    - Common adverse events included diarrhea, nausea, skin rash, hypertension, and QTc interval prolongation.
  - Cabozantinib
    - An oral drug that inhibits VEGFR, cMET, and RET.
    - For patients with RET M918T-positive disease, median overall survival was 44.3 months for cabozantinib versus 18.9 months for placebo ($P = 0.03$).
    - Common adverse events included fistula development in the GI tract or skin, diarrhea, weight loss, nausea, anorexia, palmar-plantar erythrodysesthesia syndrome, and fatigue.

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2. What are the RET-specific targeted therapies for metastatic MTC?

- Tyrosine kinase inhibitors for unresectable disease that is symptomatic or progressing and test positive for RET expression within the tumor
  - Selpercatinib
    - Highly selective small-molecule RET kinase inhibitor.
    - Common adverse events included hypertension, increased alanine and aspartate aminotransferase levels, hyponatremia, and diarrhea.
  - Pralsetinib
    - Highly potent and selective RET kinase inhibitor.
    - Common adverse events included hypertension, constipation, fatigue, and musculoskeletal pain.
- Clinical trials

IV. Anaplastic Thyroid Cancer

- Aggressive cancer with poor prognosis and high mortality. Median survival is about 5 to 6 months and 1-year survival is about 20%.
- More common in older patients (> age 65)
- It is thought to develop from existing papillary or follicular thyroid cancer.
- Patients typically present with a rapidly enlarging neck mass.

PREOPERATIVE EVALUATION

- Laboratory studies: complete blood count and differential, electrolytes, blood urea nitrogen, creatinine, glucose, liver function test, calcium, phosphorus, TSH, FT4, and coagulation studies
- Neck US to evaluate primary tumor, central and lateral neck lymph nodes, and airway patency
- Fiber optic laryngoscopy to evaluate the vocal cords
- Cross-sectional imaging of the neck and chest with MRI and/or CT to assess for presence of regional disease and distant metastasis
- 18F-FDG-PET/CT to evaluate for metastasis

TREATMENT

- If tumor is resectable and no distant metastases are present: surgery and locoregional radiation therapy with/without chemotherapy
  - If intrathyroidal anaplastic thyroid cancer (ATC): total lobectomy or total or near-total thyroidectomy with central and lateral neck dissection
  - If extrathyroidal invasion: consider en bloc resection
- If locoregionally confined, but unresectable disease: radiation therapy with/without chemotherapy. Surgery can be considered after neoadjuvant therapy.
- If systemic disease: consider palliative resection to prevent eventual airway or esophageal obstruction
- Chemotherapy often involves some combination of taxane (paclitaxel or docetaxel), anthracyclines (doxorubicin), and/or platin (cisplatin or carboplatin)
- Dabrafenib/trametinib for ATC with *BRAF V600E* mutation
- Clinical trials
- Include discussions on end-of-life issues and comfort care

STAGING

- All ATCs are considered American Joint Committee on Cancer (AJCC) stage IV.

TABLE 15.3 ■ AJCC Staging for Anaplastic Thyroid Cancer

AJCC Stage	Description
Stage IVA	Tumor of any size confined to the thyroid with no lymph node or distant metastasis (T1–T3a, N0, M0)
Stage IVB	Tumor of any size with gross extra-thyroidal extension invading the strap muscles (T3b, any N) or extending into major neck structures (T4, any N), or tumors confined to the thyroid with lymph node involvement (T1-T3a, N1). No distant metastasis (M0)
Stage IVC	Tumor of any size with distant metastasis present (any T, any N, M1)

AJCC, American Joint Committee on Cancer.

Source: Adapted from AJCC Staging Manual, 8th Edition.

SURVEILLANCE

Surveillance in patients with no evidence of disease after initial therapy.

- Cross-sectional imaging (i.e., of the brain, neck, chest, abdomen, and pelvis) every 1 to 3 months for 6 to 12 months, then every 4 to 6 months for at least 1 year.
- Consider 18F-FDG PET about 3 to 6 months after initial therapy.

QUESTIONS

1. A 69-year-old man presented with a complaint of dysphagia and wheezing. CT scan demonstrated a heterogeneously enhancing 5.2 × 4.3 cm mass arising from the thyroid gland that is encasing the larynx and esophagus; there is no evidence of lymph nodal or distant metastases. Fine needle aspiration of the mass was performed and demonstrates poorly differentiated anaplastic thyroid carcinoma. There was no somatic *BRAF V600E* mutation noted on additional tissue sample. He was evaluated by an endocrine surgeon who felt that he had unresectable disease.

   What is the most appropriate next step in management?
   A. External beam radiation therapy to the mass with radiosensitizing doxorubicin
   B. Total thyroidectomy
   C. Vandetanib
   D. Sorafenib

2. A 45-year-old man was found to have a palpable neck mass on physical exam. Thyroid ultrasound showed a 2.0 × 1.4 cm right thyroid nodule.

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Fine needle aspiration of the right thyroid nodule was performed and was positive for medullary thyroid cancer. Genetic testing was performed and positive for germline *RET* proto-oncogene mutation. Serum calcium and parathyroid hormone levels are checked, and both are within normal range.

What is the most appropriate next step in management?
A. Measure thyroid-stimulating hormone level
B. Radiation
C. Total thyroidectomy
D. Measure urine or plasma free metanephrine levels
E. Measure thyroglobulin level

3. A 54-year-woman was recently diagnosed with poorly differentiated anaplastic thyroid cancer. She underwent a total thyroidectomy with central and lateral neck dissection. Pathology showed that the tumor measured 1.8 cm and was confined to the thyroid gland with no lymph node involvement, extrathyroidal extension, or angioinvasion. Cross-section imaging with PET/CT scan did not show any evidence of distant metastases.

What is the American Joint Committee on Cancer (AJCC) stage for the patient's anaplastic thyroid cancer?
A. Stage I
B. Stage II
C. Stage III
D. Stage IV

4. A 38-year-old female presents for a second opinion on management of her papillary thyroid cancer for which she has already undergone a total thyroidectomy and is on thyroid-stimulating hormone (TSH) suppressive therapy with levothyroxine. The tissue was tested and positive for RET fusion. Six month postoperatively, her TSH is suppressed <0.1 mU/L, thyroglobulin level is elevated to 50 ng/mL, and thyroglobulin antibody is undetectable. Radioactive iodine (RAI) scan is performed and shows no evidence of iodine-avid disease. PET/CT scan is performed and shows fluorodeoxyglucose (FDG)-avid disease in the neck, lungs, and bone. Three months later, the CT scan is repeated, and it shows disease progression.

What is the most appropriate next step in management?
A. Radioactive iodine therapy
B. Vandetanib
C. External beam radiation therapy
D. Selpercatinib
E. Sorafenib

5. A 52-year-old woman was diagnosed with medullary thyroid cancer (MTC) and underwent a total thyroidectomy with central neck dissection about 10 years ago. Tissue was tested and negative for *RET* mutation. She was lost to follow-up until she was hospitalized for pneumonia and chest imaging demonstrated an obstructive lesion in the setting of an elevated serum calcitonin level of 105 ng/mL and carcinoembryonic antigen (CEA) level of 20 ng/mL. She was treated with external beam radiation. Three months later, calcitonin level was 36 ng/mL, and CEA level was 6 ng/mL. One year

later, she presents with severe diarrhea and unintentional weight loss of 30 lbs. Serum calcitonin level is 700 ng/mL and CEA level is 104 ng/mL, and CT demonstrates numerous pulmonary nodules concerning for metastases. Her tumor is RET-negative.

What is the most appropriate next step in management?

A. Supportive care and hospice referral
B. Doxorubicin
C. Radionuclide scan followed by radioactive iodine (RAI) therapy
D. Cabozantinib

6. A 64-year-old man was diagnosed with papillary thyroid cancer 6 years ago, and subsequently underwent total thyroidectomy. The tissue was tested and negative for RET fusion. Postoperatively, he was treated with 200 mCi of radioactive iodine (RAI) therapy. He has since been on thyroid hormone suppressive therapy with a supraphysiologic dose of levothyroxine. Over the ensuing years, he was found to have slowly progressive disease with innumerable pulmonary metastases. Seven months ago, RAI scan demonstrated innumerable metastases and he was treated with 353 mCi of RAI. In follow-up today, he complains of progressive chest fullness over the past 2 months. Thyroglobulin level was elevated to 152 ng/mL but repeat RAI scan demonstrated no evidence of disease. You order a PET/ CT scan, which demonstrates interval enlargement of the pulmonary metastases, which are enlarged compared to prior CT scan.

What would be the most appropriate treatment for this patient?

A. Repeat RAI therapy (200 millicuries)
B. Doxorubicin
C. Lenvatinib
D. Cabozantinib
E. Observation

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ANSWERS

1. **A. External beam radiation therapy to the mass with radiosensitizing doxorubicin.** External beam radiation therapy to the mass with radiosensitizing doxorubicin is the treatment of choice for this patient who has stage IVB (T4a N0 M0) locoregionally confined, but unresectable disease. Surgical excision may be considered after neoadjuvant chemoradiation. If testing of the anaplastic thyroid cancer was positive for *BRAF V600E* mutation, then treatment with dabrafenib/trametinib would be considered.

2. **D. Measure urine or plasma free metanephrine levels.** Since genetic testing is positive for a germline *RET* proto-oncogene mutation, the medullary thyroid cancer may be due to an underlying genetic syndrome, specifically multiple endocrine neoplasia type 2A (MEN2A). Therefore, it is important to measure urine or plasma free metanephrines, and serum calcium and parathyroid hormone levels to evaluate for pheochromocytoma and hyperparathyroidism, respectively. If a pheochromocytoma is present, diagnosis followed by preoperative alpha-blockade is essential to minimize intraoperative hemodynamic instability.

3. **D. Stage IV disease.** All anaplastic thyroid cancers are considered AJCC stage IV disease at the time of diagnosis. This patient has stage IVA disease since the tumor is confined to the thyroid and there is no lymph node or distant metastasis.

4. **D. Selpercatinib**. For patients with RET-fusion positive differentiated thyroid cancer that is RAI-refractory, selpercatinib or pralsetinib would be appropriate treatment. If the papillary thyroid cancer was not RET-fusion positive, then lenvatinib or sorafenib would be appropriate treatment.

5. **D. Cabozantinib.** Cabozantinib is the treatment of choice for metastatic medullary thyroid cancer. Doxorubicin is a Food and Drug Administration (FDA)-approved cytotoxic agent approved for the treatment of metastatic differentiated thyroid cancer and does not have a role in the management of medullary thyroid cancer. RAI therapy does not have a role in the management of medullary thyroid cancer as these tumors are not iodine-avid. For patients with metastatic *RET*-mutant MTC, treatment with selpercatinib or pralsetinib would be considered.

6. **C. Lenvatinib.** Lenvatinib would be the appropriate treatment for this patient with radioiodine-refractory metastatic papillary thyroid cancer. Lenvatinib and sorafenib are approved by the Food and Drug Administration (FDA) for treatment of radioiodine-refractory differentiated thyroid cancer. Cabozantinib is FDA-approved for the treatment of metastatic medullary thyroid cancer and can be considered as a second-line therapy for RAI-refractory differentiated thyroid cancers. For patients with RET fusion-positive thyroid cancer that is RAI-refractory, treatment with Selpercatinib or Pralsetinib would be considered.

16 Adrenal Cortical Carcinoma

Xin He and Tobias Else

EPIDEMIOLOGY, PATHOGENESIS, AND RISK FACTORS

1. What is the most common adrenocortical tumor?

- Unilateral, benign, adrenocortical adenomas, which are usually less than 4 cm in size

2. What is the peak age of incidence for adrenocortical carcinoma (ACC)?

- Two peaks: early childhood (relative) and the fifth decade of life

3. What hereditary cancer syndromes are associated with increased risk of ACC? Are patients with ACC recommended to undergo genetic testing?

- Li–Fraumeni syndrome (prevalence of Li–Fraumeni syndrome in pediatric ACC patients is ~80%, adult ACC patients ~3%)
- Lynch syndrome (adults ~4%)
- Multiple endocrine neoplasia type 1
- Beckwith–Wiedemann syndrome (children)
- Offer genetic counseling and TP53 germline testing to all patients with ACC (Chompret criteria) and consider screening of tumor tissue for absence of DNA mismatch repair proteins (Lynch syndrome)

4. Which signaling pathways are commonly altered in hereditary or spontaneous ACC?

- IGF2, TP53, and Wnt/beta-catenin

STAGING

1. Define the staging for adrenal gland tumors as proposed by the European Network for the Study of Adrenal Tumors (ENSAT).

TABLE 16.1 ■ European Network for the Study of Adrenal Tumors Staging

Stage	Definition
I	Primary tumor ≤5 cm in greatest dimension, limited to the adrenal gland, and no LN involvement
II	Primary tumor >5 cm in greatest dimension, limited to the adrenal gland, and no LN involvement
III	Tumor of any size with invasion of periadrenal fat or adjacent organs or involvement of regional LN
IV	Any local tumor extent when distal metastases are present

ENSAT, European Network for the Study of Adrenal Tumors; LN, lymph node.

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SIGNS AND SYMPTOMS

1. What are the common manifestations of ACC?

- 60% of patients with ACC present with symptoms of excess steroid hormone production.
  - Cortisol production can present with weight gain, hypertension, hyperglycemia, proximal muscle weakness, supraclavicular fat pads, dorsocervical fat pads, truncal obesity, hypokalemia, purple abdominal striae, and skin bruising. Presentation of cortisol excess in ACC can be atypical (mainly catabolic symptoms, e.g., muscle wasting) due to the rapid rise in cortisol.
  - Androgen excess in women can result in hirsutism, menstrual irregularity, and virilization.
  - Mineralocorticoid excess can manifest as hypertension and hypokalemia, though this is rare in ACC.
  - Estrogen production in men can cause gynecomastia and testicular atrophy.
  - All adrenal masses producing androgens OR a combination of two or more hormone pathways are suspicious for ACC.
- ACC that is not hormone-producing may present with pain or abdominal discomfort due to compression of nearby structures.

DIAGNOSIS

1. How should an adrenal mass be worked up?

- Biochemical evaluation should always precede imaging.
- Endocrine evaluation for hormone secretion is recommended as follows:
  - Cortisol production: 1 mg overnight dexamethasone suppression test is preferred; 24-hour urine cortisol is less sensitive. Late-night salivary cortisol is another option.
  - Androgen production: serum dehydroepiandrosterone sulfate (DHEAS) and total testosterone.
  - Mineralocorticoid production: plasma aldosterone and renin activity.
  - Other hormone measurements: 11-deoxycortisol is a good diagnostic and follow-up marker. Measurement of 17-OH-progesterone or estradiol can be helpful in some settings (e.g., men with feminizing features).
  - Metanephrine production: fractionated plasma-free metanephrines or 24-hour urine-fractionated metanephrines should be checked to rule out pheochromocytoma.
  - Abnormal serum electrolytes: basic metabolic panel should be checked, as cortisol and mineralocorticoid excess can be associated with hypokalemia.
- Adrenal protocol CT or MRI allows for evaluation of radiologic features of malignancy.
- If malignant tumor is suspected, CT chest, abdomen, and pelvis should be performed to evaluate extent of disease.
- Pathology should be obtained for tumors suspicious for malignancy. Diagnosis of ACC is made on pathology, which must confirm adrenal origin (e.g., SF1 staining), extent of disease, Weiss score, and proliferation rate (KI67>10% or mitotic rate > 20/50hpf are regarded high risk criteria).

2. Which radiographic features help distinguish between adrenal adenomas and ACC?

- For homogenous tumors, attenuation of <10 Hounsfield units (HU) on noncontrast CT is reassuring for a lipid-rich benign adenoma. Measurement of Hounsfield units is not applicable for heterogeneous tumors.
- For homogenous lesions, contrast washout >60% at 15 minutes on contrast CT is also indicative of a benign adenoma.
- MRI signal drop in-phase/out-of-phase can also be used for determination of benign homogeneous lesions with >10 HU.
- Irregular borders, internally heterogeneous tumors, and local invasion on cross-sectional imaging are features concerning for ACC.
- Increased activity on 18-fluorodeoxyglucose (FDG)-PET/CT is useful in ambiguous cases. However, ~10% of adenomas are FDG avid.

TREATMENT OF LOCALIZED DISEASE

1. What surgery is recommended for ACC?

- Following surgical oncology principles, complete removal of ACC in its entirety, by open adrenalectomy at a large volume medical center, is preferred. Avoidance of capsule rupture to prevent seeding is essential.

2. What is one key perioperative medical management step at the time of adrenalectomy for ACC?

- If preoperative hormone testing reveals cortisol production, glucocorticoid replacement should be started perioperatively to prevent adrenal crises, as long-term hypercortisolism suppresses the adrenal axis.

3. What is the role of adjuvant treatments for ACC?

- There is currently no consensus on the role of adjuvant medical or radiation therapy. Management options should be discussed on an individual basis.
- In patients with high risk of recurrence, adjuvant mitotane may prolong recurrence-free survival.
- Retrospective data indicate adjuvant radiation therapy can improve recurrence-free survival and overall survival.

SURVEILLANCE

1. What surveillance measures should be taken for resected adrenal cancer?

- History and physical exam every 3 months, with special attention to signs of hormone excess and insufficiency.
- Imaging with CT chest, abdomen, and pelvis every 3 months for 2 years, then every 6 months for another 3 years.
- For hormone-producing tumors, repeat tumor markers (e.g., 11-deoxycortisol, DHEAS, or others) every 3 months.

ALGRAWANY

TREATMENT OF ADVANCED DISEASE

1. What are the systemic treatment options for locally advanced or metastatic ACC?

- Observation is appropriate for indolent disease.
- Mitotane monotherapy yields partial response in 10% to 30% of cases. Mitotane must be given with glucocorticoid replacement, which may be required lifelong.
- Cisplatin (or carboplatin) + etoposide + doxorubicin ± mitotane demonstrated significant improvements in response and progression-free survival (but not overall survival) when compared to streptozocin ± mitotane in a large, single-arm phase 3 trial.
- Streptozocin ± mitotane is generally considered after failure of cisplatin or carboplatin + etoposide + doxorubicin ± mitotane.
- Consider clinical trials. Many targeted agents are in development.
- In cases of hormone excess, antihormonal therapy may be needed to treat debilitating symptoms, particularly due to glucocorticoid production:
  - Hormone receptor antagonists (e.g., spironolactone or mifepristone).
  - Hormone synthesis inhibitors (e.g., ketoconazole, metyrapone).
  - Adrenolytic agents (e.g., mitotane).
  - Therapy for other complications associated with hypercortisolism, such as diabetes mellitus, osteoporosis, and opportunistic infections, may also be required.
- Advanced ACC is rarely curable and early involvement of palliative care is strongly recommended.

2. What is the role of partial resection in advanced ACC?

- The decision for partial resection or metastasectomy depends on the speed of disease progression. In general, if tumors are slow growing over 6 to 12 months, respond to initial chemotherapy, or if metastasis occurs in a resectable oligometastatic fashion over >6 to 12 months, surgical or local therapy intervention (e.g., radiofrequency ablation, radiation therapy) can be entertained.

QUESTIONS

1. A 28-year-old man presents with abdominal pain. A CT is ordered, which shows appendicitis. The scan also demonstrates the presence of a 2 cm well-circumscribed, homogeneous right adrenal lesion with an attenuation of 8 Hounsfield units.

What is the best management?

A. Adrenal protocol CT abdomen now
B. 18F-fluorodeoxyglucose (FDG)-PET scan
C. Obtain metanephrines to exclude pheochromocytoma prior to surgery
D. No follow-up is necessary

2. A 56-year-old woman is diagnosed with an adrenocortical carcinoma (ACC). She has a sister with colon cancer at age 48 and her mother had endometrial cancer in her early 50s. Her paternal grandfather had prostate cancer.

What underlying genetic diagnosis is most likely?
A. Lynch syndrome
B. Beckwith–Wiedemann syndrome (BWS)
C. Li–Fraumeni syndrome
D. Multiple endocrine neoplasia type 1 (MEN1)

3. A 37-year-old otherwise healthy woman presents with left flank pain and hyperglycemia. She is found to have a 12 cm left adrenal mass with multiple liver metastasis. A 1 mg overnight dexamethasone suppression test yields a following 8 a.m. cortisol of 14 mcg/dL, which is abnormally elevated.

What is the most appropriate initial management?
A. Left open radical adrenalectomy
B. Left open radical adrenalectomy and initiation of immunotherapy
C. Cytotoxic chemotherapy with cisplatin (or carboplatin), etoposide, doxorubicin (EDP) plus mitotane
D. Medical therapy with mitotane only

4. A 32-year-old woman presents with right flank pain and is found to have a right 13 cm ACC without hormone secretion. Staging with CT chest, abdomen, and pelvis did not reveal any metastases.

What is the most appropriate management?
A. Complete staging with 18F-fluorodeoxyglucose (FDG) PET scan to identify metastases that may not be evident on cross-sectional imaging
B. Complete staging with Technetium-99 bone scan to identify bone metastases
C. Start therapy with mitotane and streptozocin
D. Right radical open adrenalectomy followed by discussion for adjuvant therapy

5. A 43-year-old man presents with left abdominal pain and hyperglycemia. He is found to have a 15 cm left adrenal mass. A 1 mg dexamethasone suppression test confirms excess cortisol production. Imaging does not reveal distant metastases. He proceeds to a radical adrenalectomy. A lymph node dissection is also performed and reveals three positive nodes.

What, if any, additional therapy would you recommend?
A. Observation
B. Adjuvant mitotane and/or radiation therapy
C. Wide surgical re-excision
D. Adjuvant cyclophosphamide, etoposide, doxorubicin, and mitotane

6. A 55-year-old man presents for follow-up after left adrenalectomy for a 12 cm ACC. Postoperatively, the patient was initiated on mitotane and physiologic hydrocortisone replacement with 10 mg in the morning and 5 mg in the early afternoon. He complains today of new onset progressive anorexia, fatigue, and nausea. Postoperative evaluation by the surgeon is unrevealing.

What is the next best step?
A. Prescribe ondansetron
B. Increase his glucocorticoid dose
C. Check serum 8 a.m. cortisol
D. Monitor symptoms

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ANSWERS

1. **D. No follow-up is necessary.** The adrenal lesion is most likely benign based on the small size and Hounsfield units <10. If the lesion were indeterminate on imaging, one should obtain metanephrines in order to evaluate for presence of pheochromocytomas. The anesthesiologist and surgeon should be made aware of any concern for pheochromocytoma to prevent surgical complications.

2. **A. Lynch syndrome.** About 10% of patients with ACC have an underlying germline predisposition, the most common condition being Lynch syndrome. The patient has a family history supportive of Lynch syndrome. Li–Fraumeni is less common in adults, but present in 50% to 80% of children. BWS occurs in children, and MEN1 would present with a different family history (pancreatic neuroendocrine tumors, hyperparathyroidism, pituitary tumors). At this patient's age, one would expect an individual with MEN1 to have developed hyperparathyroidism.

3. **C. Cytotoxic chemotherapy with EDP plus mitotane.** If feasible, curative surgery is preferred in adrenocortical carcinoma (ACC). However, this patient has multiple liver metastasis. While immunotherapy is a reasonable choice, the classical therapy is EDP + mitotane. In addition, the patient needs control of hormone levels, which might be achieved by the adrenolytic activity of mitotane. The patient might need additional antihormonal therapy with mifepristone or metyrapone for further control of hypercortisolism.

4. **D. Right radical open adrenalectomy followed by discussion for adjuvant therapy.** Open adrenalectomy should be completed with curative intent. Adjuvant surgery should be entertained according to European Network for the Study of Adrenal Tumors (ENSAT)/European Society of Endocrinology (ESE) guidelines risk stratification.

5. **B. Adjuvant radiation therapy and/or adjuvant mitotane.** Adjuvant mitotane improves recurrence-free survival and should be considered. Radiation can be considered in patients with stage 3 disease and lymph node involvement, particularly those with R1, R2, Rx resection.

6. **B. Increase his glucocorticoid dose.** In addition to its adrenolytic activity, mitotane also induces CYP3A4, which leads to inactivation of glucocorticoids through increased liver and gut metabolism. Therefore, supraphysiologic levels of glucocorticoid replacement are needed in patients on mitotane to avoid adrenal insufficiency. Serum morning cortisol is not helpful in this case, as mitotane increases cortisol binding globulin and raises the measured cortisol. Administering ondansetron or monitoring symptoms would be inadequate.

17 Pheochromocytoma

Katherine I. Wolf and Tobias Else

EPIDEMIOLOGY

1. What is the median age at diagnosis?

- During the fifth decade of life; however, earlier presentations are seen with germline syndromic presentations.

2. What percentage of pheochromocytomas (PCCs)/paragangliomas (PGLs) are associated with genetic syndromes?

- Approximately 30% to 40%

ETIOLOGY AND RISK FACTORS

1. What is the cellular origin of PCC/PGLs?

- PCCs: chromaffin cells of the adrenal medulla
- PGLs: extra-adrenal parasympathetic (predominately in the head and neck) and sympathetic (predominately in the abdomen and pelvis) ganglia

2. Which PCC/PGL patients should undergo a genetic evaluation?

- All patients with a PCC/PGL should meet with a genetic counselor to discuss genetic testing

3. What genetic syndromes are associated with PCC/PGL?

- Multiple endocrine neoplasia (MEN) type 2A and 2B (*RET*)
- Neurofibromatosis type 1 (*NF1*)
- von Hippel–Lindau (*VHL*)
- Hereditary PGL syndrome (succinate dehydrogenase subunits [*SDHx*] A, B, C, and D)
- Hereditary PCC syndrome (*TMEM127*, *MAX*)

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4. What are the clinical and biochemical distinguishing features of hereditary PCC/PGLs?

TABLE 17.1 ■ Features of Hereditary PCC/PGLs

	Biochemical Phenotype	Malignant	PCC/PGL Predominant
MEN (*RET*)	EPI	<5%	PCC
NF1 (*NF1*)	EPI, NE	<5%	PCC
VHL (*VHL*)	NE	<5%	PCC
PGL 1–5 (*SDHx*)	NE, DA	>20% (*SDHB*)	PGL

DA, dopamine; EPI, epinephrine; MEN, multiple endocrine neoplasia; NE, norepinephrine; NF1, neurofibromatosis type 1; PCC, pheochromocytoma; PGL, paraganglioma; SDHB, succinate dehydrogenase subunit B; VHL, von-Hippel–Lindau.

5. Which two classes do PCC/PGL driver mutations fall into?

- Hypoxia/Pseudohypoxia: *VHL*, *SDHx*, hypoxia-inducible factor 2 alpha (*HIF2A*)
- Kinase: *RET*, *NF1*

SIGNS AND SYMPTOMS

1. What are the common clinical manifestations of PCC/PGLs?

- Classic triad: paroxysmal hypertension leading to *headache*, *diaphoresis*, and *tachycardia*
- Nonspecific symptoms related to hemodynamic and autonomic instability include hypertension, pallor, nausea, orthostatic hypotension, and hyperglycemia
- While classically described as episodic, tachycardia and/or hypertension can also be sustained
- Psychologic symptoms include anxiety, nervousness, and panic attacks

2. What are common symptomatic triggers?

- Symptoms occur spontaneously, but may be provoked by anesthesia (particularly during induction), intraoperative tumor manipulation, various medications, changes in posture, or micturition (bladder PGL).

DIAGNOSIS

1. What is the biochemical algorithm for PCC/PGL diagnosis?

- Prior to biochemical evaluation, monoamine oxidase inhibitors (MAOI), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), adrenergic agonists, and amphetamines should be held, if possible, to prevent assay interference.
- Gold standard diagnosis is fractionated plasma free metanephrines two-folds the upper reference limit (URL) of normal
  - Twenty-four-hour urinary metanephrines is a comparable alternative
  - Chromogranin A can increase specificity
  - Clonidine suppression test can reduce false-positive rate (clonidine administration decreases physiologic sympathetic discharge)
- If markedly elevated, proceed with anatomic localization. If minimally elevated, repeat biochemical evaluation or consider clonidine suppression test

- Important to note that some PCC/PGLs, particularly head and neck PGLs, are nonfunctional.

2. When is anatomic imaging recommended for PCC/PGL?

- Only pursue anatomic imaging with CT or MRI after biochemical confirmation
  - Initial focus should include adrenal or abdominal CT or MRI
  - If cross-sectional abdominopelvic imaging is negative and biochemistry is convincing, CT/MRI neck and chest should be pursued to evaluate for chest or head and neck PGLs

3. Which functional imaging modalities are used in PCC/PGL?

- Functional imaging is recommended in patients with
  - Suspected metastatic PCC/PGL to determine disease extent and potential treatment options with 131-iodine-metaiodobenylguanadine (^{131}I-MIBG) or 177-Lutetium-DOTATATE (^{177}Lu-DOTATATE, Lutathera®)
  - Observed tumor in a classic location that is NOT clearly a PCC/PGL and confirmation of diagnosis is necessary
- 18-flourine-flurodeoxyglucose (^{18}F-FDG) PET and 68-gallium DOTA coupled somatostatin analogs (^{68}Ga-SSTas) are preferred for the detection of metastatic disease, particularly in *SDHx*-related PCC/PGLs
- While previously the standard modality, 123-I-MIBG (^{123}I-MIBG) scintigraphy should be reserved for patients who are undergoing evaluation for treatment with ^{131}I-MIBG

TREATMENT: LOCALIZED DISEASE

1. What is the recommended treatment for PCC/PGL?

- Complete, laparoscopic surgical resection is preferred, if feasible.
- Debulking procedures should be pursued in patients with metastatic disease for palliative symptom control or decrease in overall tumor burden even though complete resection is not a viable option.

2. What preoperative management is required for PCC/PGL patients?

- Preoperative alpha-adrenoceptor antagonists such as phenoxybenzamine or doxazosin should be started *at least* seven (to 14) days prior to surgery and appropriately titrated to achieve adequate hemodynamic stability.
- If the patient develops tachycardia, a beta-adrenoceptor antagonist may be started two to three days after an alpha-adrenoceptor antagonist (beta-adrenoceptor antagonist without adequate alpha-blockade poses risk for hypertensive crisis).
- Salt and volume supplementation should be encouraged to ameliorate orthostatic symptoms and prevent postoperative hypotension.
- Calcium antagonists can be used as adjunct medications or as an alternative agent for blood pressure control.

TREATMENT: METASTATIC DISEASE

1. Where are the most common locations of metastatic progression?

- Lymph nodes, bone, liver, and lungs

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2. What are the treatment options in metastatic, unresectable PCC/PGL?

- Slowly progressive metastatic disease may be treated with a "watch-and-wait" approach.
- Chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) should be pursued in patients with rapidly progressive disease (progression over 3–6 months).
  - Alternative chemotherapeutic agents include temozolomide (TMZ) and capecitabine
- Radionuclide therapy with ^{177}Lu-DOTATATE or ^{131}I-MIBG can be pursued if the patient has ^{68}Ga-DOTATATE or ^{123}I-MIBG avid disease, respectively.
- Tyrosine kinase inhibitor somatostatin analogues can be considered, or clinical trial participation
- Symptom control with alpha- and beta-adrenoceptor antagonists

PROGNOSIS AND SURVEILLANCE

1. What are adverse prognostic features of PCC/PGL?

- Presence of metastatic disease
- Extraadrenal PGLs > PCC have a higher likelihood for malignancy
- *SDHB*-related disease (up to 30% metastatic)
- Histologic criteria are of limited value in predicting metastatic disease; however, tumor size, increased proliferation (Ki-67 index, mitotic count), and lymphovascular invasion have all been associated with increased risk for malignancy

2. Recommended surveillance for PCC/PGL patients

- Following surgery, PCC/PGL patients should undergo a physical exam with biochemical tumor markers 3 to 6 months postoperatively, followed by every 6 months for 3 years, and then annually
- Lifelong surveillance for patients based on germline predisposition
  - All: annual plasma free metanephrines
  - *SDHx*: biannual whole-body MRI
  - *VHL*: annual review of abdominal imaging (done for surveillance for renal cell carcinoma and pancreatic neuroendocrine tumors)
  - MEN2: biochemistry only
  - Even slightly elevated levels should provoke concern; do not wait for a two-fold increase

QUESTIONS

1. A 25-year-old man is found to have a pheochromocytoma. Review of his past medical history includes multiple hemangioblastomas of the brain and spinal cord. He has no known family history of cancer.

   Genetic testing is most likely to reveal a mutation in which gene?

   A. *VHL*
   B. *RET*
   C. *SDHB*
   D. *NF1*

2. A 37-year-old otherwise healthy woman develops poorly controlled hypertension on hydrochlorothiazide and lisinopril. Laboratory testing reveals elevated plasma metanephrines and a pheochromocytoma is diagnosed.

Which antihypertensive should be added to her regimen?
A. Doxazosin
B. Spironolactone
C. Metoprolol
D. Losartan

3. A 52-year-old man presents with diaphoresis and episodic hypertension. He is found to have eight-fold elevated 24-hour urinary metanephrines. An adrenal protocol CT abdomen demonstrates a 4.0 cm well-circumscribed left adrenal mass. CT chest and CT pelvis are normal.

What additional imaging is most appropriate?
A. No additional imaging
B. MRI abdomen
C. 18-flourine-flurodeoxyglucose (^{18}F-FDG)-PET/CT
D. 123-iodine-metaiodobenylguanadine (^{123}I-MIBG) scan

4. A 33-year-old otherwise healthy woman presents with hypertension and palpitations. She is found to have elevated plasma metanephrines and a 7.0 cm somewhat ill-defined left adrenal mass on abdominal CT. A ^{68}Ga-DOTATATE scan redemonstrates the left adrenal mass and an additional 3.0 cm area of uptake in the left lobe of her liver.

In addition to initiation of an alpha-blocker, what is the most appropriate management?
A. Laparoscopic left adrenalectomy and liver wedge resection
B. Laparoscopic left adrenalectomy only
C. Cyclophosphamide, vincristine, and dacarbazine
D. Medical therapy with 131-iodine-metaiodobenylguanadine (^{131}I-MIBG)

5. A 42-year-old man with a history of a pheochromocytoma 4 years ago had been diagnosed with a T4 and T7 bony metastasis and a 1.5 cm lung nodule one year ago. He received radiation therapy to the symptomatic T4 lesion. He feels well, blood pressure is well controlled and he had a recent scan that shows stable T4 and T7 lesions and the lung nodule now measures 1.7 cm.

Which of the following is the best next step in management?
A. Repeat imaging in 6 months
B. Start octreotide long-acting release (LAR)
C. Start capecitabine/temozolomide
D. Evaluate for 131-iodine-metaiodobenylguanadine (^{131}I-MIBG)-therapy

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6. A 57-year-old man with known succinate dehydrogenase subunit B (SDHB)-related metastatic pheochromocytoma presents for follow-up after progression (multiple bone metastasis, several abdominal lymph node metastases, seven liver metastasis) on several cycles of multiple cytotoxic chemotherapy regimens (cyclophosphamide, vincristine, and dacarbazine [CVD], capecitabine, and temozolomide). He is interested in pursuing more treatment options.

What is the most appropriate plan of action?

A. Continue with CVD
B. Consult surgery for widespread resection of metastases
C. Obtain a 123-iodine-metaiodobenylguanadine (^{123}I-MIBG)
D. Consult palliative care for pain management

ANSWERS

1. **A. *VHL*.** Pheochromocytoma and multiple hemangioblastomas of the cerebellum, brain stem, spinal cord, and eye are typical of von Hippel–Lindau (VHL) syndrome, which is characterized by mutations in the *VHL* tumor suppressor gene. Other syndrome manifestations include clear cell renal cell carcinoma, pancreatic neuroendocrine tumors, and renal cysts.

2. **A. Doxazosin.** This patient's presentation is suspicious for a pheochromocytoma. Metanephrine levels are usually elevated more than two-fold at initial presentation. The catecholamines released by a pheochromocytoma are best inhibited with an alpha-blocker such as doxazosin or phenoxybenzamine. In addition, the patient should be worked up with cross-sectional imaging to localize the tumor.

3. **A. No additional imaging.** The patient has a biochemically proven pheochromocytoma in a typical location. No further imaging is necessary. Indeed, chest and pelvis CT might have been unnecessary as well. ^{123}I-MIBG scan can be considered to prove that the adrenal mass is the source of elevated catecholamines. However, in the setting of vastly elevated metanephrine levels (>four- to five-fold) this is not necessary. Due to the size of this pheochromocytoma, this patient is not at increased risk of metastases. Thus, a functional imaging modality is not necessary. Although ^{123}I-MIBG is more specific, ^{18}F-FDG-PET or ^{68}Ga-DOTATATE is more sensitive for the diagnosis of metastasis.

4. **A. Laparoscopic left adrenalectomy and liver wedge resection.** Patients presenting with metastatic pheochromocytoma should have resection of their primary tumor and cytoreduction of metastases, if feasible, to provide palliation of symptoms and ease of medical management.

5. **A. Repeat imaging in 6 months.** The patient had at best minimal progression and therefore further wait and watch is the best option. All other options should be entertained if there is clear disease progression, either with more metastasis or tumor growth (cytotoxic chemotherapy) or uncontrolled blood pressure (^{131}I-MIBG therapy). It is most important to understand the speed of disease and to initiate therapy, when there is progression. Even when metastatic, pheochromocytomas can show very slow growth over a long time. In addition, the patient should be treated with bisphosphonates. Somatostatin analogues are sometimes used in the treatment of pheochromocytoma, but there is little evidence supporting this therapy.

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6. **C. Obtain a ^{123}I-MIBG.** Patients presenting with metastatic pheochromocytoma should undergo primary tumor resection or debulking, particularly for symptom control. However, the widespread metastatic disease in this patient is unlikely to be amenable to cytoreductive surgery. Given his progression on multiple cytotoxic chemotherapies (reasonable choices include CVD or temozolomide and capecitabine [TMZ]), another cycle is not warranted. If the patient is positive on ^{123}I-MIBG, treatment with ^{131}I-MIBG might be an option. While calling palliative care for pain management may be crucial to his quality of life, it is not the best presented option as it does not directly address his underlying pathology and his interest in further therapy.

BREAST CANCER

IV

ALGRAWANY

18 Breast Cancer

Haritha G. Reddy, Nicole M. Grogan, and Erin F. Cobain

ETIOLOGY AND RISK FACTORS

1. What are the risk factors for developing breast cancer?

- Proliferative breast lesions without atypia (may be associated with small increased risk for developing breast cancer:
  - Ductal hyperplasia
  - Intraductal papilloma
  - Sclerosing adenosis
  - Radial scar
  - Fibroadenomas
  - Duct ectasia is NOT a risk factor for breast cancer
- Proliferative breast lesions with atypia (associated with significantly increased risk for future breast cancer):
  - Lobular carcinoma in situ (LCIS)
  - Atypical hyperplasia: Atypical ductal hyperplasia, atypical lobular hyperplasia
- Patient characteristics
  - Female gender
  - Older age
  - Race: Highest rates of breast cancer occur among non-Hispanic white females
  - High mammographic breast density (dense breast tissue comprising ≥75%)
  - Personal history of breast cancer (in situ or invasive)
  - Family history of breast cancer in a first-degree relative
    - Further increase in risk if: diagnosis < 50, bilateral breast cancer or male breast cancer
  - History of chest irradiation
  - Younger age at menarche (≤age 12)
  - Older age at menopause (≥age 55)
  - Nulliparity or pauciparity
  - Older age at first birth (≥age 30)
  - Postmenopausal hormonal replacement therapy
  - No history of breast feeding
- Lifestyle:
  - Obesity (body mass index [BMI] ≥30 kg/m^2)—in postmenopausal women
  - Alcohol use
  - Smoking
- Genetics:
  - Predisposing genetic mutations:
    - High-penetrance genes for breast cancer and associated syndromes (associated with high lifetime risk for developing breast cancer):
      - *BRCA1/2*—Breast cancer susceptibility gene 1/2

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- High prevalence of pathogenic germline mutations in **Ashkenazi Jewish ethnicity**
- Lifetime risk of breast cancer higher and earlier in onset in *BRCA1* than *BRCA2* mutations
- *BRCA1*—Increased risk of breast (most commonly triple negative histology), ovarian, fallopian tube, primary peritoneal, pancreas, prostate cancers
- *BRCA2*—Increased risk of breast, ovarian, melanoma, fallopian tube, primary peritoneal, pancreas, prostate, stomach, gallbladder/biliary

- *TP53*—Li–Fraumeni syndrome (LFS)
  - Increased risk of breast cancer, sarcoma, central nervous system (CNS) malignancies, adrenocortical carcinoma, gastrointestinal (GI) cancer, leukemia
- *PTEN*—*PTEN* Hamartoma Tumor Syndrome:
  - Also known as Cowden syndrome
  - Increased risk of breast, endometrial, and thyroid cancers (particularly follicular thyroid cancer)
- *PALB2*—Partner and Localizer of *BRCA2*
  - Increased risk of breast, pancreatic, prostate, and ovarian cancers
- *CDH1*—Hereditary diffuse gastric cancer syndrome
  - Increased risk for highly invasive, signet ring carcinoma of the stomach, lobular breast cancers
- *STK11* (also called LKB1)—Peutz–Jeghers syndrome (PJS)
  - Mucocutaneous pigmented lesions, hamartomatous polyps in GI tract, increased risk of GI, breast, and ovarian cancers (sex cord stromal tumors).

- Moderate penetrance genes for breast cancer (associated with moderate lifetime risk for developing breast cancer):
  - *CHEK2*—Checkpoint kinase 2
    - Increased risk of breast, colorectal, stomach, prostate, kidney, thyroid cancer, and sarcoma
  - ATM—Ataxia-telangiectasia mutated
    - These patients are sensitive to ionizing radiation and chemotherapeutic agents that cause double-stranded breaks in DNA
    - Increased risk of breast, pancreatic, and ovarian cancers

STAGING

1. How is breast cancer staged by the American Joint Committee on Cancer (AJCC)?

TABLE 18.1 ■ Anatomic Staging Groups for Breast Cancer—Pathological

Stage	Criteria
0	Carcinoma in situ
I	Tumor ≤20 mm in greatest dimension with negative or micrometastatic lymph node disease (i.e., lymph node metastasis >0.2 mm and/or >200 metastatic cells, but ≤2.0 mm) No distant metastatic disease

(*continued*)

TABLE 18.1 ■ Anatomic Staging Groups for Breast Cancer—Pathological (*continued*)

Stage	Criteria
II	Tumor >20 mm but ≤50 mm in greatest dimension without surface skin involvement and without nodal disease *or* Tumor ≤50 mm in greatest dimension with 1–3 three positive lymph node metastases No distant metastatic disease
III	Any size tumor with ≥4 axillary lymph node metastases or any clinically diagnosed internal mammary lymph node metastases *or* Tumor >50 mm in greatest dimension with ≥1 axillary nodal metastases *or* Any size tumor with direct extension to the chest wall or skin regardless of nodal status *or* Any inflammatory breast cancer regardless of nodal status No distant metastatic disease
IV	Any breast cancer with distant metastatic disease

Data from staging criteria of the American Joint Committee on Cancer (AJCC).

The AJCC 8th edition has also identified prognostic stage groups, which incorporate the anatomic stage group, tumor grade, estrogen receptor (ER), progesterone receptor (PR) and HER2 status.

Note that extent of disease evaluation with CT chest, abdomen, pelvis and bone scan or PET CT should be performed in all patients who present with clinical stage III disease or those who have symptoms concerning for the presence of distant metastatic disease.

2. Describe screening for breast cancer

Assessment of Risk Factors:

- Personal history breast, ovarian, tubal, or peritoneal cancer
- Family history of breast, ovarian, tubal, peritoneal, pancreatic, or prostate cancers
- Ancestry (e.g., Ashkenazi Jewish associated with *BRCA1* or 2 mutations)
- Known carrier of hereditary breast and ovarian cancer syndrome pathogenic germline mutation or relative with pathogenic germline mutation
- Previous breast biopsy indicating high-risk lesion
- History of radiotherapy to the chest between 10 to 30 years of age

Risk Models:

- Gail Model for breast cancer risk:
  - Uses age, age at menarche, first live birth, first-degree relatives with breast cancer, previous breast biopsies and race/ethnicity to report estimated 5-year risk and lifetime risk of developing breast cancer (until age 90)
  - Used to determine whether chemoprevention therapy will be offered
  - Is NOT intended for patients with prior diagnosis of breast cancer, ductal carcinoma in situ (DCIS), LCIS, or those who have a strong family history of breast cancer

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- International Breast Cancer Intervention Study (IBIS)—Tyrer–Cuzick Model Breast Cancer Risk Evaluation Tool
  - Estimates the likelihood of a woman developing breast cancer within 10 years of current age and over the course of her lifetime.
  - Uses age, weight, height, age of menarche, birth to more than one child, age of menopause, hormone replacement usage, *BRCA1*, *BRCA2*, history of ovarian cancer, history of biopsy/benign breast lesions, family history of breast cancer, Ashkenazi Jew ancestry.
  - Useful in patients with personal or family history of breast, ovarian, tubal, or peritoneal cancer or suspected *BRCA1* or *BRCA2* germline mutation
- Claus Model:
  - Estimates a lifetime risk for developing breast cancer
  - Uses age at diagnosis of first- and second-degree relatives with a history of breast and ovarian cancer

Average Risk:
- Less than 15% lifetime risk of being diagnosed with breast cancer
- Guidelines vary in when to start screening mammography and frequency of screening, but routine screening between 50 to 69 years of age is generally well accepted.
- Guidelines regarding frequency of screening also vary from every 1 to 2 years in United States (maybe up to three internationally).
- Patients over the age of 74 should only be screened if life-expectancy is greater than 10 years.

High Risk:
- Greater than 20% lifetime risk of being diagnosed with breast cancer based on personal or family cancer history
- Includes individuals with pathogenic germline mutations conferring increased breast cancer risk or radiation to chest between 10 to 30 years of age
- These individuals should have annual mammogram and breast MRI for screening
- Note that some individuals with very high lifetime risk for breast cancer (i.e., *BRCA1*, *BRCA2* mutation carriers) may opt to undergo prophylactic bilateral mastectomies to decrease breast cancer risk

3. Describe Treatments for Breast Cancer.

Surgical Management:
- Breast conserving surgery:
  - Lumpectomy with whole breast irradiation:
    - Allows women to preserve their breast while achieving same clinical efficacy as mastectomy
    - Contraindications for breast conserving therapy may include:
      - Inflammatory breast cancer
      - Multicentric disease with two or more tumors
      - Diffuse microcalcifications on mammography
      - Persistently positive margins despite multiple reexcision attempts
      - Large tumor size relative to breast size
      - Contraindications to adjuvant radiation therapy (RT)
- Mastectomy
  - Compete removal of breast tissue and is indicated when patients are not candidates for breast conservation or by patient preference

- Following mastectomy breast reconstruction can either be immediate or delayed.
  - Immediate: occurs at the same time as mastectomy
  - Delayed: occurs after completion of cancer treatment (i.e., chemotherapy, radiation if indicated)

- Management of Axilla:
  - Clinically node negative patients:
    - Sentinel lymph node biopsy (SLNB) should be completed.
    - SLNB is NOT indicated for:
      - Large tumors (T3/T4)
      - DCIS when breast conserving surgery is planned
      - Inflammatory breast cancer
      - Pregnant breast cancer patients
  - Z-0011-eligibile criteria: If patients meet all of the following criteria, no further axillary surgery required after SLNB.
    - Clinically negative nodes based on physical exam and imaging
    - T1 or T2 (≤ 5 cm) primary breast cancer
    - Fewer than three metastatic sentinel lymph nodes (SLNs)
    - Patients undergoing breast-conserving therapy who will receive whole breast irradiation
  - Completion axillary lymph node dissection (ALND) is generally recommended if:
    - Patients have clinically node positive disease at presentation
    - Three or more metastatic sentinel lymph nodes (SLNs) are identified
  - Clinically palpable or suspicious axillary nodes at presentation: Axillary ultrasound with fine needle aspiration or core biopsy should be performed to determine whether SLN mapping or ALND is necessary.

- Types of reconstruction:
  - Implant-based reconstruction: The use of a prosthetic/expander and can be performed in one or two stages
    - One stage: Permanent implant is placed at the time of mastectomy
    - Two stage: A tissue expander is placed during mastectomy and then gradually filled to desired volume and then replaced with permanent implant.
  - Flap-based reconstruction: The use of autologous tissue to reconstruct the breast. Tissue can be from different parts of the body including abdomen, posterior chest, medial thigh, or buttock.
    - These tissues can be moved to the breast as a free tissue and the blood supply is reattached at the mastectomy site or they can be moved with blood vessels supplying the tissue intact
    - The most common flaps for breast reconstruction are taken from abdomen:
      - Deep inferior epigastric artery perforator (DIEP) flap
      - Transverse rectus abdominis musculocutaneous (TRAM) flap

Principles of Radiation Therapy

- Indications for adjuvant radiation therapy:
  - Women who underwent breast-conserving surgery
  - Women who underwent mastectomy and had any of the following:
    - Positive margins
    - Primary tumors >5 cm
    - Involvement of four or more LNs

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- Note that regional nodal radiation is also generally recommended for women with one to three positive nodes after mastectomy who have higher risk primary tumors (i.e., triple negative histology)

- Contraindications to undergoing breast-conserving therapy requiring radiation therapy:
  - Absolute contraindications:
    - Pregnancy
  - Relative contraindications:
    - Prior radiation to the chest wall or breast
    - Active connective tissue disease involving the skin (especially scleroderma and lupus)
    - Presence of a pathogenic germline variant conferring increased cancer risk postradiation (i.e., *TP53* or ATM mutation)

4. How is DCIS managed?

Principles of Testing

- While estrogen and progesterone expression should be reported, the current consensus guidelines do not recommend testing of pure DCIS for HER2 overexpression

Principles of Surgical Management

- Criteria for breast-conserving therapy (i.e., lumpectomy):
  - Absence of multicentric disease (i.e., two or more foci of DCIS separated by significant distance and usually involving more than one quadrant)
  - Ability to achieve a cosmetically acceptable resection
  - Histologically negative margins can be achieved with lumpectomy
  - Positive margins are defined as having ink on the invasive cancer and require further surgery
- Patients whose disease does not fit the criteria for breast-conserving therapy should proceed with mastectomy.
- SLNB generally not required for patients undergoing breast conserving surgery, but should be considered in patients undergoing mastectomy.

Principles of Radiation Therapy

- Radiation therapy is generally indicated for patients who undergo breast-conserving therapy. However, can consider omitting radiation in select patients with advanced age (>70), extensive comorbidities, or small foci of low-grade disease resected with widely negative margins
- If a patient does NOT undergo RT, surgical margins should be wider than 2 mm.

Principles of Chemoprevention

- Consideration of tamoxifen as chemoprevention (to decrease risk of future breast cancer) is generally recommended in ER-positive DCIS, although no survival benefit has been demonstrated. Anastrozole is an alternative to tamoxifen in postmenopausal women with ER-positive DCIS
- Tamoxifen is not indicated in patients who have undergone bilateral mastectomy

Principles of Chemotherapy

- There is NO role for adjuvant chemotherapy or anti-HER-2 therapy (traztuzumab) in the treatment of DCIS

5. How is hormone receptor positive, HER-2-negative invasive breast cancer managed?

Principles of Histology:

- Determination of hormone receptor status:
  - Immunohistochemistry (IHC) is used to quantify estrogen and PR expression.
  - Guidelines have established a threshold of at least 1% of cancer cells staining positive for ER or PR as a positive result for hormone receptor expression.
  - Cancers with ER/PR expression between 1% and 10% are considered ER-low-positive.

Neoadjuvant Systemic Therapy:

- Neoadjuvant versus adjuvant systemic therapy:
  - Hormone receptor positive, HER2 negative cancers rarely achieve pathologic complete response (pCR) after neoadjuvant therapy (2%–10%)
  - There is no overall survival benefit of neoadjuvant chemotherapy (NACT) as compared to adjuvant chemotherapy (National Surgical Adjuvant Breast and Bowel Project [NSABP] 18), however, NACT may improve surgical outcomes in patients with locally advanced disease:
    - Breast conservation rates are improved
    - May downstage inoperable tumors allowing for resection
- Indications for NACT:
  - Inflammatory breast cancer
  - Disease that is not resectable at time of diagnosis, but might be rendered resectable after systemic therapy
  - Clinical N2 or N3 regional LN involvement
  - Patients with need for tumor size reduction to permit breast-conserving therapy
  - Patients awaiting consultation with plastic surgery regarding breast reconstruction, results of genetic testing or resolution of illness/pregnancy and physicians do not wish to delay treatment
- Neoadjuvant endocrine therapy (NET):
  - May be considered in patients with strongly hormone receptor positive tumors, particularly in postmenopausal patients
  - NACT or upfront surgery is generally preferred in premenopausal women
  - Postmenopausal women who have strongly hormone receptor positive (≥ 50% ER staining), low proliferative index (Ki67 <10%–15%) are more likely to respond to NET
    - Aromatase inhibitor is preferred, as studies suggest better outcomes as compared with Tamoxifen
  - Duration of NET:
    - Typically plan for 4 to 6 months NET
    - If disease progression, patient proceeds directly to surgery
    - If breast conserving surgery is possible following 4 to 6 months, then proceed to definitive surgery
    - If clinical response or stable disease (i.e., no clinical evidence of progression) but not amenable to breast conserving surgery, then discuss mastectomy versus extending NET to total duration of 6–12 months.

Principles of Systemic Adjuvant Therapy:

- All patients with hormone receptor-positive early stage breast cancer are recommended to receive adjuvant endocrine therapy

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- Additional factors to consider when determining adjuvant therapy:
  - LN status
  - Size of tumor
  - Grade of tumor
  - Age of patient
  - Comorbid conditions
  - Results of gene expression profiling assay (i.e., Oncotype DX Recurrence Score)
- Patients with low-grade, T1b tumors (up to 0.5 cm) should receive adjuvant endocrine monotherapy (no chemotherapy treatment is indicated)
- Patients with invasive ductal or lobular carcinoma >0.5 cm without LN involvement should have multigene expression profiling assay to help estimate likelihood of recurrence and benefit from adjuvant chemotherapy
  - Oncotype DX: A 21-gene assay that provides a numerical score to quantify the 10-year risk of distant disease recurrence for ER/PR-positive, HER2 negative, LN negative breast cancer
    - Prognostic and predictive of adjuvant chemotherapy benefit
    - Can also use in patients with postmenopausal hormone receptor-positive breast cancer with limited axillary LN involvement (i.e., micrometastases [≤ 2 mm] or 1–3 positive LNs) to identify a low-risk population that obtain minimal absolute benefit from chemotherapy
    - Premenopausal patients with axillary LN involvement benefit from adjuvant chemotherapy and should be offered chemotherapy treatment if otherwise medically appropriate (RxPONDER study)
  - Oncotype DX RS 0 to 25:
    - No incremental benefit from adjuvant chemotherapy versus endocrine therapy alone in postmenopausal patients
  - Oncotype DX RS 16 to 25:
    - In women ≤50 years, consider adjuvant chemotherapy, based on benefit in subset analysis of TAILORx study
  - Oncotype DX RS >25:
    - Clear benefit from adjuvant chemotherapy
  - Other multigene assays may also be used to estimate risk of recurrence and potential benefit from adjuvant chemotherapy including:
    - Amsterdam 70-gene prognostic profile (*MammaPrint*), Prediction Analysis of Microarray 50 (*PAM50*), 12-gene assay (*EndoPredict*), Breast Cancer Index (*BCI*)
  - Patients with four or more involved LNs should receive adjuvant systemic chemotherapy followed by endocrine therapy if deemed appropriate based on performance status, comorbidities, and patient preferences
- Adjuvant Systemic Chemotherapy:
  - Timing of Adjuvant Chemotherapy:
    - If indicated, adjuvant chemotherapy should be started within 4 to 6 weeks after surgery and before adjuvant RT.
    - Delay of chemotherapy initiation by more than 3 months has been shown to be detrimental based on observational data.
    - If patient has received NACT, no further chemotherapy should be administered in the adjuvant setting.

- Preferred Chemotherapy Regimens:
  - Dose-dense doxorubicin and cyclophosphamide with sequential paclitaxel (AC-T) is standard
    - No other regimen has been proven to be superior
  - Docetaxel plus cyclophosphamide (TC)
    - This nonanthracycline-based regimen used in certain groups—(ABC trial):
      - LN negative
      - Patients with history of cardiac disease
      - Advanced age and chest wall radiation—these patients are at increased risk for anthracycline-related cardiotoxicity
  - Cyclophosphamide, methotrexate, fluorouracil (CMF)
    - May be considered if taxane is not tolerable due to peripheral neuropathy or steroid intolerance

- Adjuvant Endocrine Therapy:
  - Premenopausal women:
    - Tamoxifen
      - Mechanism of action:
        - Selective ER modulator
        - Competes with estrogen to bind to ER to decrease ER signaling-dependent growth in breast tissue
  - Side effects:
    - Venous thromboembolic disease
    - Increased risk for endometrial cancer
    - Hot flashes
    - Vaginal discharge/dryness
    - Arthralgias
    - Depression/changes in mood
    - Possible increased risk of stroke
    - Possible increased risk of cataracts
    - Elevated liver enzymes (rare)
  - Contraindications:
    - History of deep vein thrombosis or pulmonary embolism
    - Pregnancy/breastfeeding
  - Timing of Tamoxifen: Start following adjuvant chemotherapy. Maybe taken with or after completion of radiation
- Tamoxifen with ovarian suppression/ablation
  - Ovarian suppression is accomplished by giving monthly luteinizing hormone-releasing hormone (LHRH) agonist injections—goserelin or leuprolide
  - Ovarian ablation may also be achieved by surgical oophorectomy or by ovarian irradiation
  - Consider for high-risk tumors: younger age, high-grade tumor, LN involvement
- Aromatase inhibitor with ovarian suppression:
  - See the following for discussion of mechanism of action, contraindications for use, and side effects
  - Improved disease-free survival compared to tamoxifen with ovarian suppression but, without overall survival difference based on TEXT trial
  - Consider in aromatase inhibitor/ovarian suppression over tamoxifen with or without ovarian suppression in patients with *higher risk* of disease

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recurrence—young age, high-grade tumor, LN involvement, indications for adjuvant chemotherapy
  - SOFT trial: Premenopausal women with hormone receptor positive breast cancer compared tamoxifen alone, tamoxifen with ovarian suppression or aromatase inhibitor with ovarian suppression for 5 years. Demonstrated superior of disease-free survival at 5 years in aromatase inhibitor—ovarian suppression group over tamoxifen with or without ovarian suppression among women who received prior chemotherapy. No improvement in disease-free survival observed in women who did not receive chemotherapy
- Postmenopausal women:
  - Aromatase inhibitors: Anastrozole, exemestane, letrozole
    - Mechanism of action:
      - Inhibits aromatase which is an enzyme that converts adrenal androgens such as androstenedione and testosterone to estrone and estradiol
      - Anastrozole and letrozole are nonsteroidal reversible aromatase inhibitors and exemestane is a steroidal irreversible aromatase inactivator
    - Side effects:
      - Bone loss/Osteoporosis/increased risk of fractures
      - Arthralgias
      - Vaginal dryness
      - Hot flashes
      - Increased blood pressure
      - Increased cholesterol
      - Fatigue
      - Depression/changes in mood (higher risk with advanced age)
    - Contraindications:
      - Premenopausal women in the absence of ovarian suppression
    - Selection of therapy:
      - ATAC trial showed anastrozole resulted in fewer recurrences when compared to tamoxifen, but no difference in overall survival
- PR +, ER – or low positive: Use endocrine therapy in the neoadjuvant setting and not in the adjuvant setting
- Duration of therapy:
  - Adjuvant endocrine therapy is recommended for a minimum of 5 years
  - ATLAS trial: 10 versus 5 years of tamoxifen in pre- and postmenopausal women. Extended therapy provided benefit in reducing risk of recurrence, mortality, decreased contralateral breast cancer. The aTTom trial also confirmed reduction in recurrence and death from breast cancer with extended endocrine therapy
  - National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) MA.17 trial showed overall survival benefit for extended therapy with letrozole in patients with positive axillary LNs. However, the benefit was not present in LN negative patients
  - A minimum of 2 years of Tamoxifen is required before a woman should consider becoming pregnant; Tamoxifen is a teratogen and must be stopped if a woman desires to conceive
- Posttreatment surveillance for early stage breast cancer patients:
  - History and physical examinations (including breast exam) every 4 to 6 months for the first 5 years after primary therapy and then annually thereafter.

- Annual mammograms in patients without mastectomy, beginning 6 to 12 months after completion of RT.
- In absence of clinical symptoms of recurrent disease, no body imaging or laboratory studies should be routinely performed.
- Patients with an intact uterus should receive annual gynecologic assessments and rapid evaluation of vaginal spotting while taking tamoxifen.
- Patients on aromatase inhibitors or who experience ovarian failure secondary to adjuvant therapy should have bone density monitoring with dual-energy X-ray absorptiometry (DEXA) scans at baseline and every 2 years.
- If patient regains or maintains premenopausal status following breast cancer therapy, hormonal birth control is not recommended—alternative methods are recommended—intrauterine devices, barrier methods or if no future pregnancies planned consider tubal ligation or vasectomy for the partner.

- **Locally Advanced Unresectable/Metastatic Hormone Receptor-Positive Breast Cancer**:
  - Staging evaluation:
    - History and physical exam
    - Laboratory studies: Complete blood count, comprehensive metabolic panel to include liver function tests
    - CT chest and abdomen, bone scan, radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan. PET scan is also acceptable alternative to CT and bone scan.
    - Biopsy to prove metastasis and reassessment of receptor status
      - If hormone receptor positivity is confirmed, tumor phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) status should be assessed.
    - Genetic testing—testing for *BRCA1/2* germline mutations should be pursued in metastatic breast cancer to identify candidates for polyadenosine diphosphate ribose polymerase (PARP)-inhibitor therapy.
  - Resection of primary tumor in de novo metastatic disease is not indicated unless patient has significant symptoms from their breast disease
    - E2108 study showed patients with de novo stage IV breast cancer did not have an overall survival benefit with locoregional treatment with surgery and radiation for their primary breast tumor despite some retrospective analyses suggesting benefit
  - Treatment of bone metastases:
    - Bone modifying agent should be used such as, zolendronic acid, denosumab or pamidronate in addition to endocrine therapy or chemotherapy
      - Dental exam should be completed prior to initiation of therapy, due to risk of osteonecrosis of the jaw.
      - Zoledronic acid may be dosed every 12 weeks with similar efficacy to every 4-week dosing.
  - Systemic therapy:
    - Endocrine therapy is generally less toxic than chemotherapy and therefore favored in the first-line setting for metastatic breast cancer, unless there is evidence of visceral crisis/evidence of end-organ damage from metastases. In the latter circumstance, chemotherapy should be used.
    - Combination of endocrine therapy with targeted agents have improved progression-free survival

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- Preferred first-line therapy:
  - In women who progress at least 1 year after the end of adjuvant aromatase inhibitor therapy or those with de novo metastatic cancer:
    - Aromatase inhibitor plus cyclin-dependent kinase (CDK) 4/6 pathway inhibitor is preferred.
    - CDK 4/6 inhibitors: palbociclib, abemaciclib, ribociclib
      - Mechanism of action: Blocks progression of the cell from G1 to S phase leading to increased cell senescence/apoptosis and reducing cellular proliferation
      - Common side effects: Neutropenia, fatigue, anemia, thrombocytopenia, diarrhea
        - QT prolongation
          - Seen with ribociclib—must monitor EKGs at baseline, day 14 and prior to second cycle.
      - Rare side effects: Abnormalities of liver function tests, interstitial lung disease
      - Abemaciclib is the only CDK 4/6 inhibitor that can be used as a SINGLE agent and penetrates the CNS in leptomeningeal disease
  - If patient progresses on or within 1 year of completing adjuvant aromatase inhibitor therapy and they do not have evidence of visceral crises, they are eligible for second-line endocrine therapy
    - Fulvestrant
      - Mechanism of action: ER antagonist, competitively binding to ER and downregulating the ER protein
      - Side effects: Injection site pain, nausea, musculoskeletal pain, fatigue, hot flashes, increased hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [AP])
    - Fulvestrant plus CDK4/6 inhibitor
      - Palbociclib, ribociclib, and abemaciclib in combination with Fulvestrant improve progression-free and overall survival compared to Fulvestrant monotherapy (PALOMA3, MONALEESA3, and MONARCH2)
        - Abemaciclib is the only CDK4/6 inhibitor that can be used as single agent
    - Fulvestrant plus PI3KCA inhibitor
      - PIK3CA inhibitor = Alpelisib
      - Mechanism of action: Phosphatidlyinositol-3-kinase (PI3K) inhibitor in patients who have a gain of function mutation in the gene encoding the catalytic alpha-subunit (PIK3CA).
      - Side effects: Increased glucose levels, increased creatinine, diarrhea, rash (can be severe), pneumonitis/interstitial lung disease
    - Endocrine therapy plus Everolimus
      - Exemestane plus everolimus demonstrated improvement in progression-free survival over exemestane monotherapy in BOLERO-2 trial
  - If disease progresses through available lines of endocrine therapy, then generally patients are recommended to receive single-agent chemotherapy

- Endocrine therapy for premenopausal women:
  - Preferred first line: Ovarian suppression or ablation in combination with endocrine therapy with a targeted agent (as earlier)
  - As with postmenopausal women, single-agent chemotherapy should be utilized following progressive disease on available lines of endocrine therapy
- Ovarian suppression:
  - Allows premenopausal women to utilize aromatase inhibitors
  - MONALEESA-7 enrolled pre- or perimenopausal women with advanced hormone receptor-positive and HER2-negative breast cancer and compared ribociclib or placebo with goserelin and either tamoxifen or nonsteroidal aromatase inhibitor
    - First trial to demonstrate an overall survival benefit with the addition of CDK4/6 inhibitor to endocrine therapy in the premenopausal population
  - PALOMA3 trial included premenopausal women with advanced endocrine-resistant disease and compared palbociclib to combination of fulvestrant and goserelin showing improved progression-free survival and objective response rate
  - MONARCH2, which investigated addition of abemaciclib to fulvestrant included a subset of pre-/perimenopausal women who also received gonadotropin-releasing hormone (GnRH) agonist for ovarian suppression. On preliminary analysis, these patients also showed improvement in progression-free survival and objective response rate compared to those receiving fulvestrant and a GnRH agonist alone.
- PARP inhibitors:
  - For patient with metastatic HER2 negative breast cancer with germline mutation in *BRCA*
  - Preferably patients who are hormone positive receive at least one line of endocrine therapy prior PARP inhibitor use
  - PARP inhibitors approved for this setting: Olaparib, Talazoparib
    - Single-agent PARP inhibitors demonstrated improvement in progression-free survival and response rate compared to single-agent chemotherapy, although overall survival was not significantly different

6. How is Her2 positive invasive breast cancer managed?

Principles of Histology:

- HER2 receptor testing is performed by IHC, if an equivocal result is obtained by IHC then the number of HER2 gene copies is measured using in situ hybridization (ISH)
- Positive HER2 receptor expression:
  - IHC 3+:
    - Uniform, intense, circumferential membrane staining for HER2 >10% of invasive tumor cells
  - ISH:
    - Dual-probe HER2/chromosome enumeration probe 17 (HER2/CEP17) ratio ≥2.0
    - HER2/CEP17 ratio <2.0 with an average HER2 copy number 6.0 signals/cell

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- Equivocal HER2 receptor expression:
  - IHC 2+:
    - Circumferential membrane staining that is incomplete and/or weak/moderate within >10% of the invasive tumor cells
    - Complete and circumferential membrane staining that is intense and within less than or equal to 10% of the invasive tumor cells.
  - ISH:
    - Single-probe average HER2 copy number ≥4.0 and <6.0 signals/cell
    - Dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number ≥4.0 and <6.0 signals/cell.
- Negative HER2 receptor expression:
  - IHC 1+ or 0:
    - No staining is observed
    - Weak, incomplete membrane staining in any portion of tumor cells
    - Weak, complete membrane staining in <10% of cells
  - ISH:
    - Single-probe average HER2 copy number <4.0 signals/cell
    - Dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number <4.0 signals/cell
    - NOTE: IHC 1+ high grade or elevated Ki67 should undergo ISH testing

Neoadjuvant Systemic Therapy:

- High percentage of HER2 positive breast cancer patients will achieve a pCR to neoadjuvant systemic chemotherapy plus HER2 directed therapy (~40%–60%)
  - In HER2 positive breast cancer, pCR is associated with significantly improved rates of disease-free and overall survival
- Patients who are candidates for preoperative systemic therapy typically have stage II or III disease (T >2 or + LNs). They should receive chemotherapy plus trastuzumab and pertuzumab
  - Trastuzumab (Herceptin):
    - Mechanism of action: Humanized monoclonal antibody with specificity for extracellular domain of HER2 to block homodimerization
    - Side Effects: Decreased left ventricular ejection fraction (4%–22%), skin rash, diarrhea (less common)
    - Adjuvant radiation can be given in combination with traztuzumab
  - Pertuzumab (Perjeta):
    - Mechanism of action: Monoclonal antibody that binds to a different epitope on HER2 than trastuzumab and blocks HER2:HER3 heterodimerization.
    - Side effects: Cardiac toxicity as detailed above with Trastuzumab, diarrhea, skin rash
  - Neoadjuvant regimens Including chemotherapy plus Trastuzumab and Pertuzumab:
    - TCHP (Taxotere, Carboplatin, Trastuzumab, Pertuzumab)—TRYPHAENA study
    - AC-THP (Adriamycin, Cytoxan followed by Paclitaxel, Trastuzumab, Pertuzumab)

Adjuvant Systemic Therapy:

- Patients who were treated with neoadjuvant therapy:
  - If residual disease is present, then should receive ado-trastuzumab emtansine (T-DM1) × 14 cycles in adjuvant setting (KATHERINE trial)

- TDM-1
  - Mechanism of action: Antibody-drug conjugate of trastuzumab and a microtubule inhibitor—emtansine
  - Side effects: Thrombocytopenia, fatigue, elevated liver enzymes, peripheral neuropathy, interstitial lung disease, or pneumonitis (rare)
- If no residual disease is present, then adjuvant trastuzumab plus pertuzumab is continued to complete 1 year of therapy (APHINITY trial)
- After completion of 1 year of therapy as detailed earlier, may consider use of neratinib for an additional year (ExteNET)
  - May be more beneficial in patients with hormone receptor positive, HER2-positive disease
    - Neratinib:
      - Mechanism of action: Intracellular tyrosine kinase inhibitor that irreversibly binds to HER2, HER4, and epidermal growth factor receptor
      - Side effects: Diarrhea, nausea, abdominal pain, fatigue, vomiting, elevated liver enzymes
      - Administration: Should be given with antidiarrheal prophylaxis (i.e., scheduled loperamide)

- Patients who did not receive neoadjuvant therapy:
  - These tend to be patients with small tumors (<2 cm) and node negative disease
    - Adjuvant therapy typically consists of Paclitaxel and Trastuzumab (TH) for 12 weeks, followed by continuation of Trastuzumab to complete a total of 1 year
  - For larger tumors (>2 cm) or node positive disease with no neoadjuvant therapy:
    - Recommend chemotherapy plus Trastuzumab and Pertuzumab to be followed by completion of 1 year of Trastuzumab plus Pertuzumab as a part of the following regimens as detailed earlier:
      - Nonanthracycline-based: TCHP
      - Anthracycline-based: AC-THP

Treatment of Metastatic Disease:

- Previously untreated patients—no adjuvant therapy:
  - Taxane (Docetaxel or Paclitaxel), Trastuzumab and Pertuzumab (THP) (CLEOPATRA trial)
    - Treat to achievement of best response and then discontinue cytotoxic chemotherapy and continue HER2-directed therapy as maintenance
    - If hormone receptor positive, add endocrine therapy to HER2-directed therapy once cytotoxic therapy is discontinued
  - May consider single-agent trastuzumab or trastuzumab plus pertuzumab if patient is unable to tolerate cytotoxic chemotherapy
- Patients who have received neoadjuvant or adjuvant HER2-directed therapy:
  - If recurrence is after 6 months, then use a Taxane (Docetaxel or Paclitaxel), Trastuzumab and Pertuzumab (THP as earlier)
  - If recurrence is within 6 months, then use TDM-1, if not already administered in adjuvant setting (TH3RESA, EMILIA)
  - If recurrence is within 6 months of adjuvant TDM-1, then consider one of the following treatment options:
    - Tucatinib, capecitabine, trastuzumab (HER2CLIMB trial):
      - May be particularly beneficial in patients with brain metastases

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- Mechanism of action: Tucatinib is a tyrosine kinase inhibitor specific to kinase domain of HER2
- Side effects: Palmar-plantar erythrodysesthesia syndrome, diarrhea, fatigue, elevated liver enzymes

- Fam-trastuzumab deruxtecan (Enhertu) (DESTINY trial):
  - Mechanism of action: Antibody-drug conjugate composed of anti-HER2 antibody linked to topoisomerase I inhibitor
  - Side effects: Neutropenia, anemia, must monitor for rare but severe interstitial lung disease and pneumonitis
- Margetuximab
  - Administered in combination with single-agent chemotherapy
  - Mechanism of action: Fc-engineered anti-HER2-receptor monoclonal antibody with stronger affinity for HER2 receptor than Trastuzumab
  - Side effects: Diarrhea, palmar-plantar erythrodysethesia, elevated liver function tests, fatigue, neuropathy, cough, dyspnea
- Trastuzumab in combination with other single-agent cytotoxic agents can also be considered.

- Later lines of therapy:
  - Other tyrosine kinase inhibitor combinations:
    - Lapatinib plus trastuzumab
    - Lapatinib plus capecitabine

7. What is the management of ER/PR-negative, HER2-negative (triple-negative) breast cancer?

Principles of Histology

- By definition, triple negative breast cancer lacks IHC expression of ER, PR, and HER2 (i.e., ER 0%, PR 0%, HER2 negative).

1. Principles of Neoadjuvant Systemic Therapy

- Benefits include prognostic information based on response to therapy and the ability modify or add adjuvant systemic therapy for those with residual disease who are at higher risk of recurrence
- Neoadjuvant systemic therapy preferred if primary tumor is greater than 2 cm or if there are metastases to axillary LNs
- Preferred regimen: AC-T (doxorubicin, cyclophosphamide followed by weekly paclitaxel)
- For patients with very high-risk disease at presentation (i.e., multiple axillary LNs involved) consideration can be given to the addition of carboplatin to AC-T chemotherapy (AC-TC), which has been demonstrated to improves rates of pCR

2. Principles of Adjuvant Systemic Therapy

- Patients who did not receive AC-T in the neoadjuvant setting can be treated with this regimen in the adjuvant setting
- Tumors <0.5 cm do NOT need adjuvant chemotherapy; tumors 0.6 cm to 1 cm, chemotherapy can be considered and >1 cm chemotherapy should be given
- In patients who received neoadjuvant systemic therapy with AC-T and have residual disease at surgical resection, recommend treatment with adjuvant capecitabine (based on CREATE-X trial) for 6 to 8 cycles

3. **Principles of Metastatic Disease**
   - Patients with metastatic disease should undergo confirmatory biopsy if possible, with reassessment of ER, PR, and HER2 status and testing for PD-L1 (using Ventana [SP142] assay and/or 22C3 assay)
   - First-line systemic therapy for patients with PD-L1 positive tumors:
     - Nab-paclitaxel plus atezolizumab (based on Impassion130 trial)—addition of atezolizumab to chemotherapy improved progression-free survival over chemotherapy alone for patients with PD-L1 positive tumors
     - Pembrolizumab in addition to chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) was studied in KEYNOTE-355 and found to improve progression-free survival over chemotherapy alone
   - Systemic therapy for patients with germline *BRCA* mutations:
     - In patients with previous exposure to chemotherapy, recommend treatment with an oral inhibitor of PARP. Food and Drug Administration (FDA)-approved PARP inhibitors include olaparib (OlympiAD trial) and talazoparib (EMBRACA trial)
   - Systemic therapy for patients without germline *BRCA* mutations, negative PD-L1, or who have progressed on earlier therapy:
     - Sacituzumab govitecan is an antibody-drug conjugate targeting Trop-2, which is expressed in the majority of triple negative breast cancer. It is approved for use in patients with metastatic triple negative breast cancer who have had disease progression at least two previous treatments for metastatic disease
     - Sequential single-agent chemotherapy including taxanes (paclitaxel should be given weekly vs every 3 weeks), anthracycline, capecitabine, platinum (i.e., carboplatin or cisplatin), eribulin, and gemcitabine

8. What are the "special considerations" of breast cancer and how are they managed?

Medullary Breast Cancer

- Characterized by high nuclear grade, lymphocytic infiltration, and pushing border
- Treat like invasive ductal carcinoma (IDC)

LCIS: No surgery required; if PLEOMORPHIC LCIS, then surgery is required and anti-estrogen therapy is needed; achieving negative surgical margins and radiation are NOT required.

Postmenopausal patients with high-risk disease: (i.e., inflammatory breast CA), add in clodrinate OR zolendric acid (not denosumab) to prevent the development of bone metastases.

Mucinous, Tubular, Papillary Breast Cancer

- More favorable subtypes
- Treat mastectomy and if margins are <3 cm consider anti-estrogen; if ≥3 cm or + LN, then give anti-estrogen therapy.

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Breast Cancer During Pregnancy

Principles of Systemic Therapy

- Chemotherapy may safely be instituted after the first trimester of pregnancy and before 35 weeks of pregnancy or 3 weeks of anticipated delivery date (so as to avoid a peripartum bleeding diathesis)
- Cyclophosphamide and doxorubicin are considered safe during pregnancy. Fewer safety data are available for taxanes. Trastuzumab and pertuzumab are contraindicated during pregnancy
- Endocrine therapy is contraindicated during pregnancy and with breastfeeding

1. **Principles of Radiation Therapy**
   - Radiation therapy is contraindicated during pregnancy.

2. **Principles of Surgery**
   - The second trimester is considered the favorable trimester for nonemergent surgery.
   - In the first and second trimester, mastectomy should be formed with axillary staging In the third trimester, lumpectomy could be considered with completion of radiation postpartum (for appropriate surgical candidates).
   - Blue dyes used for SLNB are contraindicated in pregnancy secondary to the risk of anaphylaxis and unknown teratogenicity.

Fertility Preservation

- **Fertility Preservations Approaches**
  - All premenopausal women who will receive chemotherapy should be counseled regarding the potential decline in fertility related to this therapy. These women should be offered referral for fertility preservation prior to initiating therapy.
  - Fertility preservation approaches include oocyte and/or embryo cryopreservation, GnRH agonist administration concurrent with chemotherapy, and ovarian tissue cryopreservation (remains an experimental technique).

Inflammatory Breast Cancer

1. Diagnosis
   - Clinical diagnosis, characterized by cancer cell infiltration of the dermal lymphatics, which makes skin of the breast appear red, swollen, often with peau d'orange appearance.

2. Principles of Systemic Therapy
   - NACT generally including an anthracycline and taxane with trastuzumab and pertuzumab if the tumor is HER2-positive, is recommended prior to surgical treatment

3. Principles of Radiation Therapy
   - Adjuvant RT should be administered to all patients with inflammatory breast cancer. For patients who respond to NACT, RT is generally given postoperatively. If there is no response to NACT, consideration should be given to the use of radiation to downstage the tumor.

4. Principles of Surgery

- Even in the presence of a strong response to neoadjuvant therapy, breast conservation therapy and SLNB are contraindicated
- For patients who have an operable tumor following neoadjuvant therapy, should proceed with mastectomy with axillary dissection (i.e., modified radical mastectomy). Immediate reconstruction following surgery should be avoided given the need for postoperative RT as earlier

Paget's Disease of the Breast

1. Diagnostic Evaluation and Management

- Suspect in a patient who presents with areolar eczema with associated scaling, flaking, ulceration, bleeding, and itching. Assess for an underlying breast lesion with clinical exam and imaging
- A full thickness biopsy of the affected nipple–areola complex to assess for Paget's disease is recommended. If this biopsy is negative, interval follow-up is recommended with consideration of rebiopsy if breast skin alterations do not resolve.
- Ultimately a mastectomy with axillary LN staging or resection of the nipple–areola complex with whole breast RT is recommended; this is followed by adjuvant treatment as indicated based on tumor receptor status.
- If DCIS is detected in the breast and Paget disease in the skin, the treatment is the same as for invasive breast cancer except that axillary LN staging is not mandatory.

Phyllodes Tumor

1. Classification of Phyllodes Tumors

- Benign tumors: Characterized by increased stromal cellularity with mild-to-moderate cellular atypia, circumscribed tumor margins, low mitotic rate (less than four mitoses/hpf), and lack of stromal overgrowth
- Borderline tumors: Have a greater degree of stromal cellularity and atypia, a mitotic rate of four to nine mitoses/high power field, microscopic infiltrative borders, and lack of stromal overgrowth
- Malignant tumors: Characterized by marked stromal cellularity and atypia, infiltrative margins, high mitotic rate (more than 10 mitoses/hpf), and the presence of stromal overgrowth

2. Management of Phyllodes Tumor

- Phyllodes tumors should be completely excised with margins >1 cm; axillary LN dissection is not necessary
- Adjuvant RT may benefit borderline or malignant, but not benign tumors
- Chemotherapy is reserved for highly selected patients with large, high-risk, or recurrent malignancy phyllodes tumors
- Hormonal therapy is generally not used to treat phyllodes tumors

Metaplastic Breast Cancer

- A rare malignancy (<1%) characterized by the histologic presence of two or more cellular types, commonly a mixture of epithelial, poorly differentiated ductal adenocarcinoma, and mesenchymal components

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- Due to its rarity and heterogeneity, there is no "standard" therapy for patients with metaplastic breast cancer. As such, all metaplastic breast cancers are treated similarly to other invasive breast cancers based on receptor status

Male Breast Cancer

- About 90% are invasive ductal carcinomas (lobular carcinomas are rare)
- Known risk factors
  - Radiation to the chest wall
  - Klinefelter's syndrome
  - Family history of breast cancer
  - *BRCA2* carriers
- More likely to be ER+ PR+ and Her-2 negative
- Mastectomy is preferred over lumpectomy due to limited breast tissue in men
- Chemotherapy and adjuvant radiation should be offered to men with similar criteria that is used when treating women patients.
- Rx with Tamoxifen is the standard of care (SOC) adjuvant therapy and NOT aromatase inhibitor

QUESTIONS

1. A 63-year-old white woman is diagnosed with a left breast estrogen receptor (ER)/progesterone receptor (PR)-positive, HER2-negative 3.5 cm invasive ductal carcinoma. Axillary lymph node dissection confirms 2 of 16 lymph nodes involved with invasive carcinoma. She is recovering well and is otherwise asymptomatic with normal labs.

What staging studies are indicated at this time?

A. PET/CT
B. Bone scan
C. CT scan of chest, abdomen, and pelvis
D. No further imaging

2. A 68-year-old woman with history of stage III estrogen receptor (ER)-positive, HER2-negative breast cancer develops metastatic disease involving the bones while on adjuvant exemestane therapy. Her only symptoms are mild low back pain and right hip pain, corresponding to sites of bony metastases. Her performance status is 0.

Which of the following would be optimal as first-line systemic therapy for metastatic disease?

A. Tamoxifen
B. Ovarian suppression
C. Palbociclib with fulvestrant
D. Palbociclib with letrozole
E. Combination cytotoxic chemotherapy

3. A 56-year-old woman is diagnosed with a 4-cm invasive ductal carcinoma of the right breast, which is triple negative. The tumor invades through the skin (causing ulceration) and she has palpable right axillary lymphadenopathy. Staging for metastatic disease is negative.

What is the optimal treatment course?

A. Neoadjuvant chemotherapy followed by mastectomy with axillary lymph node dissection and postmastectomy radiation, with adjuvant systemic therapy determined by response to neoadjuvant chemotherapy at surgery
B. Neoadjuvant chemotherapy followed by mastectomy with axillary lymph node dissection
C. Upfront mastectomy with axillary lymph node dissection followed by adjuvant chemotherapy and radiation
D. Palliative chemotherapy

4. A 42-year-old female presents with a palpable 3-cm right breast mass. Core biopsy reveals invasive carcinoma. Her 38-year-old brother is currently undergoing palliative chemotherapy for unresectable gastric cancer.

What is the most likely histological subtype of the patient's breast cancer and associated germline genetic abnormality?

A. Medullary carcinoma and *BRCA1* mutation
B. Lobular carcinoma and epithelial cadherin (*CDH1*) mutation
C. Metaplastic carcinoma and STK11
D. Invasive ductal and *BRCA2* mutation

5. A 44-year-old woman is evaluated for a left-sided breast mass that has doubled in size over the last month. Exam reveals an 8 cm smooth, multinodular mass without associated palpable axillary lymphadenopathy. Core biopsy reveals characteristic leaf-like architecture containing papillary projections of epithelial-lined stroma with low mitotic rate and lack of stromal overgrowth. She undergoes wide local excision with negative margins.

What is the next step in management?

A. Complete staging with sentinel lymph node biopsy
B. Adjuvant radiation therapy
C. Adjuvant endocrine therapy
D. Surveillance

6. A 68-year-old female is diagnosed with metastatic estrogen receptor (ER)/progesterone receptor (PR)-negative, HER2+ breast cancer involving the lungs. Her disease is well controlled on docetaxel, trastuzumab, and pertuzumab followed by trastuzumab plus pertuzumab maintenance for 1.5 years until she develops liver metastases. She then receives ado-trastuzumab for 1 year when she presents with altered mental status and is found to have multiple (>5) brain metastases. Restaging reveals progression in her liver. She undergoes whole-brain radiotherapy. Performance status is 1 and she has preserved organ function.

Which of the following options is most reasonable?

A. Combination chemotherapy that includes an anthracycline
B. Retrial of trastuzumab and pertuzumab
C. Tucatinib, capecitabine, trastuzumab
D. Lapatinib alone
E. Hospice care

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ANSWERS

1. **D. No further imaging.** Patient has T2N1 breast cancer (stage IIB). In the absence of symptoms or abnormal labs concerning for metastatic disease, evaluating for distant disease is not indicated for stages I to II breast cancers.

2. **C. Palbociclib with fulvestrant.** Palbociclib, an oral cyclin-dependent kinase (CDK)4/6 inhibitor, is well tolerated and improves progression-free survival when combined with fulvestrant compared to fulvestrant alone in postmenopausal patients who have progressed on endocrine therapy, including an aromatase inhibitor.

3. **A. Neoadjuvant chemotherapy followed by mastectomy with axillary lymph node dissection and postmastectomy radiation.** The patient has what appears to be a locally advanced T4 breast cancer with clinical adenopathy (stage IIIB disease). For stage IIIB disease, neoadjuvant multiagent chemotherapy followed by mastectomy with axillary lymph node dissection and postmastectomy radiation is associated with the highest chance of cure.

4. **B. Lobular carcinoma and epithelial cadherin (*CDH1*) mutation.** This patient's family history is strongly suspicious for hereditary diffuse gastric cancer, which is associated with a germline mutation in the *CDH1* gene. Lobular breast cancers are found in 25% to 50% of families with hereditary diffuse gastric cancer. In women with known *CDH1* germline mutations, guidelines suggest annual breast MRI starting at age 30. If this patient is found to harbor a germline *CDH1* mutation, she should be considered for prophylactic gastrectomy.

5. **D. Surveillance.** The pathologic description is the characteristic of a benign phyllodes tumor. In the absence of high mitotic rate, marked stomal cellularity and atypia, the tumors are treated like fibroadenomas with wide local excision to negative margins (at least 1 cm) without adjuvant therapy. Adjuvant radiation can be considered for borderline or malignant phyllodes and adjuvant chemotherapy is reserved for select high-risk, recurrent, or large tumors.

6. **C. Tucatinib, Capecitabine, Trastuzumab.** Central nervous system (CNS) progression is not uncommon (8%–12%) in HER2+ metastatic breast cancer and up to 50% of patients will develop brain metastases. Although this patient has progressed on three anti-HER2 therapies (trastuzumab, pertuzumab, and ado-trastuzumab), additional anti-HER2 therapy should be considered and includes combination therapy with tucatinib, capecitabine, and trastuzumab. Tucatinib is an oral, small molecule tyrosine kinase inhibitor of HER2. In a randomized trial of heavily pretreated HER-2 positive metastatic breast cancer patients, this regimen showed statistically significant improvements in overall survival, progression-free survival (PFS), and confirmed objective response rate. The combination of tucatinib, capecitabine, and trastuzumab is particularly active in CNS disease with reported 35% 1-year CNS PFS compared to 0% in the placebo, capecitabine, trastuzumab arm (HER2CLIMB).

V

GENITOURINARY MALIGNANCIES

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19 Bladder Cancer

Jason R. Brown and Phillip L. Palmbos

PATHOLOGY/CANCER GENETICS

1. What are the histologic types of bladder cancer?

- Urothelial (90%–95%)
- Squamous (5%)
- Adenocarcinoma (1%–2%)
- Small cell (<1%)

2. What germline mutations play a role in urothelial malignancy?

- The hereditary nonpolyposis colorectal cancer (HNPCC) gene *MSH2* is associated with an increased risk of upper urologic tract malignancies.

STAGING

1. What tests are used for staging of muscle-invasive bladder cancer (MIBC)?

- CT abdomen/pelvis with contrast or MRI with gadolinium:
  - Imaging is preferably done prior to transurethral resection of bladder tumor (TURBT) since the procedure can cause bladder wall thickening or perivesical stranding that can be interpreted as extravesical disease in the absence of a procedure.
- Chest x-ray (CXR) or CT chest
- Bone scan (if bone pain or high alkaline phosphatase/calcium)

2. When is restaging TURBT needed after initial diagnosis of nonmuscle invasive bladder cancer (NMIBC)?

- If no muscle present in the specimen
- All T1 disease due to risk of understaging
- Complete endoscopic resection improves disease outcomes

3. What are the T stages of bladder cancer?

TABLE 19.1 ■ T Stages of Bladder Cancer

Nonmuscle Invasive (Stage 0–1)—75% of all bladder tumors
■ T0: No tumor
■ Ta: Noninvasive papillary lesion
■ Tis: Carcinoma in situ
■ T1: Invasion into the subepithelial connective tissue (lamina propria, muscularis mucosa, submucosa)

(*continued*)

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TABLE 19.1 ■ T Stages of Bladder Cancer (*continued*)

Muscle Invasive (Stage 2–3)
■ T2: Invasion into muscularis propria
■ T3: Invasion into perivesicular tissue
■ T4a: Spread to prostate/seminal vesicles/uterus/vagina
■ T4b: Invasion into pelvic/abdominal wall

4. What are the N stages of bladder cancer?

TABLE 19.2 ■ N Stages of Bladder Cancer

– N0: No lymph nodes
– N1: Single regional lymph node (hypogastric, obturator, external iliac, or presacral node)
– N2: Multiple regional lymph nodes
– N3: Common iliac lymph nodes

5. What is the T/N/M staging system for bladder cancer

TABLE 19.3 ■ T/N/M Staging for Bladder Cancer

Stage 0	Ta or Tis/N0/M0
Stage I	T1/N0/M0
Stage II	T2/N0/M0
Stage III	T3 or T4a or nodal disease
Stage IV	IVA: T4b or distant metastasis to lymph nodes beyond common iliac IVB: Nonlymph node distant metastasis

NONMUSCLE INVASIVE BLADDER CANCER

1. How is NMIBC treated initially?

- Surgery with TURBT
- Single dose of intravesicular chemotherapy within 24 hours (gemcitabine or mitomycin)
  - For low-risk tumors (Ta, low grade)

2. When is adjuvant intravesicular treatment indicated?

- If low-grade Ta: Observation is sufficient
- If high-grade Ta, Tis, or T1: Bacillus Calmette–Guérin (BCG) is preferred
  - 6 weekly doses followed by maintenance BCG

3. What treatments are recommended for recurrent or persistent NMIBC?

- Repeat TURBT with single-dose intravesicular chemotherapy
- If no residual disease after TURBT, restart maintenance BCG
- If residual disease present post-TURBT, can treat with intravesicular chemotherapy, pembrolizumab (BCG-unresponsive disease), or cystectomy

MUSCLE-INVASIVE BLADDER CANCER

1. How is stage II-IIIA (non-nodal) MIBC treated surgically?

- Radical cystectomy if surgical candidate; if undergoing a continent diversion as part of surgery, watch for Vitamin B12 deficiency
- Neoadjuvant chemotherapy if cisplatin-eligible (ECOG < 2, Creatinine Clearance > 60 mL/min, no significant hearing loss, heart failure, or peripheral neuropathy)
  - Early treatment of micrometastases and possible tumor downstaging leads to a less complicated surgery
  - When given postoperatively, patients frequently need delays or treatment breaks due to complications from postop recovery
  - ddMVAC + growth factor (methotrexate, vinblastine, doxorubicin, cisplatin)
  - Gemcitabine/cisplatin
- Carboplatin not recommended in neoadjuvant setting; if cisplatin-ineligible proceed directly to cystectomy
- If no neoadjuvant treatment, can consider adjuvant RT or cisplatin-based chemotherapy

2. What bladder-sparing options are available for MIBC?

- Considerations for eligibility for bladder-sparing treatment
  - Treatment can completely eradicate the tumor in the bladder
  - Low tumor volume
  - No hydronephrosis
  - No carcinoma in situ
  - Maximal TURBT
  - Bladder function is not substantially compromised
- Chemoradiation
  - For patients who are not candidates for cystectomy (i.e., compromised performance status [PS] or comorbid conditions)
  - Doublet chemotherapy preferred (cisplatin + 5-FU, cisplatin + paclitaxel, 5-FU + mitomycin)
  - Reassess tumor 2 to 3 months after completion and treat based on restaging

LOCALLY ADVANCED (NODE-POSITIVE)/METASTATIC BLADDER CANCER

1. What is first-line treatment for locally advanced/metastatic bladder cancer?

- Chemoradiation can be considered for disease without distant metastasis
- Systemic therapy depends on cisplatin-eligibility
- Pembrolizumab or atezolizumab first-line only if programmed death-ligand 1 (PD-L1) positive or not eligible for platinum

TABLE 19.4 ■ Cisplatin-Eligibility

Cisplatin-Eligible	Cisplatin-Ineligible
Cisplatin + gemcitabine	Carboplatin + gemcitabine
ddMVAC + growth factor support	Pembrolizumab if (CPS >10)
	Atezolizumab if (PD-L1 >5%)

CPS, combined positive score; PD-L1, programmed death-ligand 1.

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2. What is switch-maintenance therapy?

- Avelumab maintenance after response to four to six cycles of cisplatin-based chemotherapy shown to improve overall survival

3. What are second-line treatments for locally advanced/metastatic bladder cancer?

- Pembrolizumab preferred if no prior immunotherapy
  - Alternative immunotherapy (atezolizumab, nivolumab, duvalumab, avelumab) may be used
- Paclitaxel or docetaxel
- Gemcitabine
- Erdafitinib if FGFR3 or FGFR2 alterations

4. What are preferred subsequent lines of treatment?

TABLE 19.5 ■ Lines of Treatment

Treatment	Target	Common Toxicity
Erdafitinib	FGFR1–4	Hypophosphatemia, retinopathy
Enfortumab Vedotin	Nectin4	Neuropathy

QUESTIONS

1. A 62-year-old man develops hematuria and is referred to a urologist. Staging cystoscopy reveals a sessile bladder tumor. Pathology from the transurethral resection shows high-grade urothelial carcinoma invading the lamina propria but no muscle is included in the sample and is staged as T1.

Which therapy would you recommend?

A. Repeat staging with transurethral resection of bladder tumor (TURBT)
B. Intravesical bacillus Calmette–Guérin (BCG)
C. Watchful waiting
D. Chemoradiation
E. Cystectomy

2. A 69-year-old man is treated for localized T1 bladder cancer with bacillus Calmette–Guérin (BCG). On repeat transurethral resection of bladder tumor (TURBT), he appears to have residual disease. Pathology is consistent with urothelial carcinoma without invasion of muscularis propria (muscularis propria is present on the specimen, however).

What treatment would not be considered for his BCG-refractory bladder cancer?

A. Cystectomy
B. Pembrolizumab
C. Cisplatin
D. Intravesicular gemcitabine

3. A 84-year-old man is diagnosed with metastatic bladder cancer. He is initially treated with gemcitabine and carboplatin due to a history of diabetic neuropathy. He has no other comorbidities and excellent functional status. After six cycles of treatment, imaging demonstrates a partial response to treatment.

What management would be recommended next?

A. Two additional cycles of gemcitabine and carboplatin followed by repeat imaging
B. Switch carboplatin to cisplatin
C. Avelumab maintenance
D. Next generation sequencing with programmed death-ligand 1 (PD-L1) testing to determine candidacy for immunotherapy or targeted therapies
E. Surveillance with imaging in 6 weeks followed by immunotherapy upon progression
F. Hospice

4. A 65-year-old woman is found to have microscopic hematuria on a urinalysis done for a work physical. A follow-up cystoscopy shows a low-grade Ta bladder tumor.

What is the appropriate treatment?

A. Observation with urine cytology every 6 months
B. Observation with yearly cystoscopy
C. Transurethral resection of bladder tumor (TURBT)
D. TURBT followed by intravesical mitomycin
E. TURBT followed by intravesical bacillus Calmette–Guérin (BCG) with maintenance BCG

5. A 54-year-old man presents with gross hematuria. He undergoes transurethral resection of bladder tumor (TURBT), which diagnoses muscle-invasive (T2) bladder cancer. He has no comorbidities; however, he strongly prefers to not have a urostomy.

What would be the optimal management of his bladder cancer?

A. Cystectomy with ileal conduit
B. Repeat TURBT and bacillus Calmette–Guérin (BCG)
C. Chemoradiation with cisplatin and 5-fluorouracil (5-FU)
D. Immune-checkpoint inhibitor therapy
E. Surveillance

6. A 65-year-old woman is diagnosed with metastatic bladder cancer. She has a history of hypertension and chronic kidney disease with baseline creatinine of 2. Programmed death-ligand 1 (PD-L1) score is <1% and she has a FGFR2 mutation on next-generation sequencing.

What is the appropriate first-line treatment?

A. Dose-dense methotrexate, vinblastine, adriamycin, cisplatin (ddMVAC) with growth factor support
B. Carboplatin + gemcitabine
C. Pembrolizumab
D. Erdafitinib
E. Enfortumab vedotin

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ANSWERS

1. **A. Repeat staging with TURBT.** There was no muscle included in the sample and treatment depends on whether invasion into the muscularis propria is present or not.

2. **C. Cisplatin**. Options for management of T1 bladder cancer refractory to BCG include intravesicular chemotherapy, pembrolizumab, or cystectomy. Systemic cisplatin-based chemotherapy regimens are not used in this setting.

3. **C. Avelumab maintenance**. Per the Javelin 100 study, maintenance immunotherapy with avelumab was shown to prolong overall survival following four to six cycles of platinum-based chemotherapy if disease has not progressed. Avelumab maintenance was shown to be superior to best supportive care in the overall and PD-L1 positive populations, so PD-L1 testing is not necessary prior to starting avelumab.

4. **D. TURBT followed by intravesical mitomycin**. Although it is a low-grade tumor, it still requires resection. However, a single dose of intravesical chemotherapy should be sufficient to reduce recurrence.

5. **C. Chemoradiation with cisplatin and 5-FU.** Recommended options for muscle-invasive bladder cancer include cystectomy and chemoradiation. Because this patient prefers to avoid cystectomy, bladder-sparing options should be considered. Chemoradiation with doublet chemotherapy is preferred over single-agent chemotherapy in patients without contraindications.

6. **B. Carboplatin + gemcitabine.** Due to her chronic kidney disease (CKD), she would be considered cisplatin-ineligible. Platinum-based treatment would be still be preferable, and therefore carboplatin plus gemcitabine is the preferred regimen. PD-L1 score is too low for upfront checkpoint inhibitor therapy. Given the FGFR2 mutation, erdafitinib could be considered second-line but would not be used for front-line therapy.

20 Prostate Cancer

Eric Schwartz and Zachery R. Reichert

SCREENING

1. Who should be screened for prostate cancer?

- Screening for prostate cancer remains controversial.
- The U.S. Preventive Service Task Force (USPSTF) recommends discussing risks and benefits of screening in patients 55 to 70 (grade C) and against routine screening in patients over 70 (grade D).

PATHOLOGY

1. What are the common histologic subtypes in prostate cancer at diagnosis?

- Ninety-five percent of prostate cancers are adenocarcinomas.
- Other potential histologic variants include sarcoma, lymphoma, small cell or neuroendocrine cancer.

2. How is prostate cancer graded?

- Gleason grade is a grading system ranging from 1 to 5 that describes a cancer cell's morphologic differentiation from normal prostatic glands (grade 1) to tissue that has lost all glandular features (grade 5)
  - Primary Gleason grade denotes the dominant histologic pattern, while the secondary grade denotes the next most common histologic pattern.
  - The Gleason score is the sum of the primary and secondary Gleason grades.
  - Gleason score is the strongest predictor of clinical outcome.
  - New Gleason system has been proposed, which uses a grouping system for grading ranging from 1 (prior Gleason score 6) to 5 (prior Gleason score 9–10).

SIGNS AND SYMPTOMS

1. What are the symptoms of localized prostate cancer?

- Obstructive urinary symptoms (urinary frequency, nocturia, hesitancy) from an enlarged prostate can be the presenting symptoms from locally advanced disease.
- Hematuria or hematospermia may be present if there is local invasion.

DIAGNOSIS

1. How is localized prostate cancer diagnosed?

- Localized prostate cancer is diagnosed with prostate biopsy
  - Standard biopsy involves at least 12 core samples.

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GENETIC TESTING

1. Who should receive germline genetic testing with prostate cancer:

- Patients with high, very high risk or metastatic prostate cancer
- Patients with strong family history (brother or father with prostate cancer before 60, more than three cancers on one side of family)
- Patients with Ashkenazi Jewish ancestry
- Patients with known family history of inherited cancer syndrome (i.e., breast cancer susceptibility gene [*BRCA*] mutation)

STAGING

1. Define the staging system of prostate cancer:

- The current (eighth edition) American Joint Committee on Cancer (AJCC) staging system for prostate cancer includes Gleason score, prostate-specific antigen (PSA) level, and the extent of disease based on tumor, node, and metastasis (TNM) criteria.
  - T0: no evidence of primary tumor
  - T1: clinically inapparent tumor that is not palpable.
    - T1a: incidental finding in 5% or less of resected prostate tissue
    - T1b: incidental finding in >5% of resected prostate tissue
    - T1c: detected by needle biopsy found in one or both sides but not palpable
  - T2: tumor is palpable and confined to the prostate
    - T2a: involves half of one side or less
    - T2b: involves more than one half of one side but not both
    - T2c: involves both sides
  - T3: Extraprostatic tumor that is not fixed or does not invade adjacent structures
    - T3a: extraprostatic extension (unilateral or bilateral)
    - T3b: tumor invades a seminal vesicle
  - T4: tumor is fixed or invades adjacent structures other than the seminal vesicle
  - N0: no lymph nodes involved
  - N1: regional lymph nodes involved
  - M0: no evidence of metastatic disease
  - M1: distant metastatic disease
    - M1a: nonregional lymph nodes
    - M1b: bone involvement
    - M1c: other site

TABLE 20.1 ■ Staging System for Prostate Cancer

Stage	PSA (ng/mL)	Gleason Score	T	N	M
I	<10	6 or less	T1, T2a, pT2	N0	M0
IIA	<10	6 or less	T2b	N0	M0
	≥10 but <20	6 or less	T1, T2a, pT2	N0	M0
	<20	7	T1, T2a, T2b	N0	M0

(*continued*)

TABLE 20.1 ■ Staging System for Prostate Cancer (*continued*)

Stage	PSA (ng/mL)	Gleason Score	T	N	M
IIB	≤20	Any	T1, T2	N0	M0
	Any	8 or greater	T1, T2	N0	M0
	Any	Any	T2c	N0	M0
III	Any	Any	T3	N0	M0
IV	Any	Any	T4	N0 or N1	M0 or M1

PSA, prostate-specific antigen.

- Note that invasion of any surrounding structures other than the seminal vesicles and any dissemination to the nodes or other organs all fall under the umbrella of stage IV disease.

INDICATIONS FOR TREATMENT

1. Do all prostate cancers need to be treated?

- No. Patients with very low-risk or low-risk prostate cancer with life expectancies under 10 years should be observed
  - Very low or low-risk patients with life expectancy greater than 10 years can consider active surveillance, surgery, or radiation
    - Defined as having all of the following:
      - PSA <10
      - T1–T2a disease
      - Gleason score of 6
  - Men with intermediate- to very high-risk prostate cancer localized to the prostate, and who can tolerate therapy should consider definitive treatment (radiation or surgery)
  - Men with metastatic disease should be considered for systemic treatment
- **What is active surveillance?**
  - Active surveillance can also be considered delayed intervention for low-stage/low-grade prostate cancer.
    - Active surveillance involves monitoring the patient's PSA, digital rectal examination (DRE), and periodically rebiopsying the prostate gland as appropriate.
    - The role for MRI in active surveillance is unclear.
  - This differs from pure observation (coined watchful waiting), in which testing is only performed based on changes in symptoms

PROGNOSTIC FACTORS

1. What factors affect prognosis in prostate cancer?

- High Gleason grade/Gleason score
- High percentage and volume of cores involved with cancer on biopsy
- High PSA level or rapidly rising PSA
- Short interval between definitive local therapy and PSA relapse
- Advanced stage
- Inherited prostate cancer syndromes (most commonly *BRCA2*)

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TREATMENT

Treating Localized Disease

1. What is the preferred treatment for localized disease?

- Both surgery and radiation therapy are considered appropriate local treatment options for patients who elect treatment

2. Should lymph node dissection be done during radical prostatectomy surgery?

- Pelvic lymph node dissection should be done in patients with regional lymph node involvement
- Pelvic lymph node dissection is controversial in patients without known lymph node involvement

3. What kind of radiation can be used?

- External beam radiation therapy targets the whole prostate and sometimes a margin of extraprostatic tissue, seminal vesicles, and pelvic lymph nodes.
- Brachytherapy alone can be considered in patients with low-risk tumors, but it is not recommended for patients with intermediate- to high-risk tumors.
- Patients with unfavorable intermediate, high-risk or very high-risk disease should receive adjuvant androgen deprivation therapy (ADT) before, during, and/or after radiation.

4. Is adjuvant chemotherapy warranted and in which circumstances?

- Adjuvant chemotherapy is not recommended after radical prostatectomy
- Docetaxel is approved after definitive radiation for patients with very high-risk disease only
  - Very high risk defined with *all* of the following:
    - T3b-T4 disease
    - Primary Gleason pattern of 9 or 10
    - >4 cores with Gleason 8 to 10 pattern

5. Is adjuvant radiation warranted after surgery?

- Adjuvant radiation to the prostatic bed after radical prostatectomy should be considered in patients with extracapsular extension of their prostate cancer or those with positive surgical margins.
- This approach has been shown to *decrease the risk for local recurrence*, but there are conflicting reports about whether it affects overall or metastasis-free survival.
- Early salvage radiation, as soon as PSA is detectible, for biochemical recurrence appears equivalent to adjuvant radiation

6. What should be done if a patient has a rising PSA (biochemical recurrence) after definitive therapy?

- Biochemical recurrence is defined differently after surgery and radiation
  - Surgery: failure for PSA to become undetectable with surgery or PSA becomes detectible (PSA ≥0.2) on two consecutive samples
  - Radiation: failure is an increase of >2 ng/mL above the PSA nadir after radiation
- In the setting of biochemical recurrence, evaluation for metastatic disease can be considered based on risk stratification.
  - Imaging should involve CT chest/abdomen/pelvis and bone scan

- If conventional imaging is negative, molecular imaging (e.g., choline-PET, fluciclovine-PET) can be considered to evaluate for small volume relapsed disease but their impact on ultimate overall survival is unknown,
- Salvage radiation to the prostatic bed should be considered in patients who have a PSA recurrence (with or without local disease noted on imaging) after radical prostatectomy and be implemented when the PSA is measurable and confirmed. NOTE: *Salvage radiation at higher PSA levels upon relapse has inferior outcomes.*

7. If PSA continues to rise without evidence of metastatic disease, should anything else be done:

- Observation can be considered for slow rise in PSA (>6 months doubling time)
- For more rapid rise in PSA, androgen depravation therapy can be considered
- If PSA continues to rise on ADT (with confirmed testosterone level under 50 ng/dL) and there is no evidence of metastatic disease on imaging, this is known as *nonmetastatic* castration resistant disease
  - Secondary hormonal therapy (see the following) with apalutamide, darolutamide, or enzalutamide should be considered due to improved survival
  - Abiraterone not approved in this setting

Primary Treatment for Metastatic Prostate Cancer

1. What is the best initial therapy for newly diagnosed metastatic prostate cancer?

- Most patients who present with metastatic prostate cancer benefit from initial therapy with ADT.

2. What is ADT?

- ADT is therapy that deprives the body of natural androgens made by the testes. Androgens are normally produced by the testes and adrenal glands.
- The majority of prostate cancers are driven by testosterone and dihydrotestosterone. Therefore, reducing a patient's natural ability to produce testosterone or blocking the androgen receptor from binding testosterone deprives the cancer cells of their fuel source.
- Currently, gonadotropin-releasing hormone (GnRH) agonists are used for androgen suppression.
  - Goserelin, leuprolide, triptorelin, and buserelin are different GnRH agonists that can be given as depot injections. There are different doses of depots available to last varying lengths of time.
  - The continuous exposure of the pituitary to GnRH causes a transient surge of luteinizing hormone and hence a transient rise in systemic testosterone (testosterone flare) before the pituitary downregulates its GnRH receptors resulting in an ultimate decline in testosterone production. The decreased testosterone level start about 20 days after drug start. Oral antiandrogens (e.g., bicalutamide) are often used to block the transient testosterone rise but can be discontinued after testosterone is suppressed.
- GnRH antagonist:
  - GNRH antagonist (e.g., degarelix) may be used if a more urgent treatment response is required as it has no risk of testosterone surge and testosterone levels are decreased within 1 day.

ALGRAWANY

3. What is secondary hormonal therapy?

- The goal of further hormonal manipulation is to decrease/block androgen-mediated signaling. This is achieved by blocking other sources of testosterone production in the body (testosterone produced from the adrenal glands and the tumor itself) or inhibiting androgen receptor signaling.
- Abiraterone
  - Decreases testosterone biosynthesis reduction by inhibiting CYP17
  - Patients should have their blood pressure, liver function tests, and potassium levels monitored
  - Prednisone must be given with abiraterone. Abiraterone should be used with caution in patients with *hypertension, heart failure, liver disease,* or *arrhythmias*.
- Androgen receptor signaling inhibition
  - Enzalutamide, darolutamide, and apalutamide are second-generation antiandrogens that inhibit the binding of testosterone to the androgen receptor. Fatigue is a class wide side effect.
  - Enzalutamide should not be used in patients with a seizure disorder.

4. What other treatments can be given in conjunction with ADT in metastatic hormone sensitive prostate cancer (mHSPC)?

- Docetaxel for six cycles is approved in men who present with high-volume metastatic disease
  - High-volume disease is defined as either presence of *visceral metastases* or at least *four bone metastases* with one beyond the vertebral body/pelvis
- Abiraterone, apalutamide, and enzalutamide are used regardless of disease volume
- Either secondary hormonal therapy or docetaxel should be considered as all improve survival
  - Patients with low-volume metastatic disease and an untreated prostate should receive prostate-directed radiation

5. Is there a role for intermittent ADT in metastatic prostate cancer?

- Intermittent ADT (which is initiated or stopped based on PSA level) should not be recommended for men with metastatic disease.

6. What should be done when a patient has a rising PSA on ADT and bicalutamide?

- First, check a serum testosterone in this setting to be sure the patient is truly castrate
- Patients on first-generation antiandrogen agent (bicalutamide) should have that agent stopped
  - About 30% of patients will have decline in PSA due to androgen receptor mutations in tumor (antiandrogen withdrawal effect)

Treatment of Castration-Resistant Prostate Cancer

1. What is castration-resistant prostate cancer?

- Castration-resistant prostate cancer is cancer that is progressing despite effective androgen deprivation (testosterone must be under 50 ng/dL).
- Traditional duration of response to ADT monotherapy is around 18 months, but when combined with other agents, it can be over 3 years.

2. Should a patient's ADT be discontinued if they are castration-resistant?

- ADT should be continued despite castration resistance as the cancer remains driven by androgens and intrapatient tumoral heterogeneity.

3. What are treatment options for patients with castration-resistant prostate cancer?

- Secondary hormonal therapies (abiraterone, enzalutamide)
- Chemotherapy (docetaxel, cabazitaxel)
- Immunologic therapies (sipuleucel-T)
- Radiopharmaceutical (radium-223)
- Targeted therapies: Polyadenosine diphosphate-ribose polymerase (PARP) inhibitors
- Checkpoint inhibitors: Pembrolizumab
- Clinical trials
- The optimal sequencing of these treatments is unknown.

} **Nonhormonal therapies**

4. When are bone-strengthening agents used in metastatic prostate cancer?

- Bone-targeting agents (RANK-ligand-inhibitors OR bisphosphonate therapy) can be considered for patients who have bone metastases to prevent skeletal-related complications.
- Patients must be castrate resistant.
- *NOTE*: Pamidronate is NOT approved for use in prostate cancer.

5. What nonhormonal *first-line* options are possible in castration-resistant prostate cancer?

- Docetaxel has a demonstrated survival advantage as first-line treatment for men with castrate-resistant disease.
- Sipuleucel-T is a T-cell-based treatment approved for castration-resistant prostate cancer in asymptomatic patients typically with lower-volume disease.
  - Does not decrease PSA level but has shown a survival advantage
- Radium-223 is a radioactive element that mimics calcium and tracks to bone
  - Can only be used for patients with bone exclusive disease
  - Shown to have survival benefit and decrease time to symptomatic bone disease
  - Toxic to bone marrow so patients require adequate blood counts

6. What are appropriate *second-line* options for castration-resistant prostate cancer?

- Changing to a different agent from the approved first-line therapy options is commonly done.
  - Response rates are lower going from one hormonal treatment to another at progression
  - Converting to cabazitaxel (as opposed to a second-line hormonal agent) was found to be superior in the late disease setting
- Genetic testing of the tumor should be considered to find targetable events
  - Patients with mismatch repair deficiencies (microsatellite instability [MSI]–high) can receive pembrolizumab
  - Patients with somatic or germline homologous recombination defects (mainly *BRCA2*, but also *BRCA1* or ataxia–telangiectasia mutated [ATM] loss) are candidates for PARP inhibitors (Olaparib or Rucaparib).

ALGRAWANY

- Cabazitaxel is a taxane, approved ONLY after progression on docetaxel and has a survival advantage
- Mitoxantrone + prednisone have been shown to improve quality of life but not disease-free/overall survival or PSA reduction.
  - Rarely used given other available agents in current therapeutic landscape.

7. Treatment of Bone Metastases

- Patients with castration-resistant prostate cancer metastatic to the bone should be considered for treatment with a bone-targeting agent
- Denosumab or zoledronic acid are approved to prevent skeletal-related events
  - Denosumab may have slightly improved efficacy but higher cost and more frequent administration.
- Both denosumab and zoledronic acid can cause osteonecrosis of the jaw. Denosumab has higher rates of hypocalcemia
- Palliative radiation is given in circumstances of refractory pain and for treatment of spinal cord compression from infiltrating lesions from the vertebral spine

Complications of ADT

1. What are the adverse effects of ADT?

- Hot flashes
- Fatigue
- Loss of libido, decline in sexual function
- Increased risk for diabetes mellitus
- Decreased muscle mass and increased truncal obesity
- Increased cardiovascular risk
- Gynecomastia is seen more often when antiandrogen inhibitors (i.e., bicalutamide) are used as monotherapy, which is not standard
- Osteoporosis; decreased bone mineral density
- ADT has also been associated with a small but increased risk of cognitive effects

2. What should be done for bone health in men on chronic ADT?

- A baseline bone density test should be done in men prior to initiating or early on during therapy with ADT. Bone density should be repeated every 2 years while on ADT to monitor if bone supportive therapy is necessary.
- Unless medically contraindicated, men on ADT should take 1,200 mg of calcium daily and 800 IU of vitamin D daily.
- Lifestyle modifications such as weight-bearing exercises and smoking cessation can reduce the risk of fracture.

QUESTIONS

1. A 62-year-old patient returns to your office for continued management of his previously painful bone-only, castration-resistant metastatic prostate cancer. He is asymptomatic and has been maintained on continuous leuprolide while zoledronic acid and abiraterone + prednisone were added 6 months ago when he became castration-resistant. The addition of abiraterone + prednisone decreased his prostate-specific antigen (PSA) from 87 ng/mL to 65 ng/mL after 3 months and his pain improved. The PSA has risen today to 130 ng/mL. A CT of the chest/abdomen/pelvis was obtained, which shows two new suspicious liver lesions. His bone

scan described more intense uptake in three different lesions that were previously seen but no new lesions. Biopsy of a liver lesion confirms metastatic prostate cancer and next-generation sequencing reveals no homologous repair deficiencies.

Which of the following would be an appropriate next therapy for his progressive disease?

A. Docetaxel
B. Continue abiraterone but change zoledronic acid to denosumab
C. Olaparib
D. Radium-223

2. A healthy 68-year-old man comes to your medical oncology office 6 months after completing an 8-week course of external beam radiotherapy for his T1c Gleason score 3 + 4 = 7 prostate cancer. No androgen deprivation therapy was used. His pretreatment prostate-specific antigen (PSA) was 6 ng/mL and today it is 1.2 ng/mL. He has no rectal bleeding or dysuria. He is concerned about residual cancer with his PSA still being measurable and inquires what further therapy is needed.

Which of the following is the most appropriate next step in his treatment?

A. Salvage radical prostatectomy
B. Continued surveillance with a repeat PSA in 6 months
C. Androgen deprivation therapy
D. Sipuleucel-T

3. A 64-year-old man with diabetes and a myocardial infarction 7 years ago is diagnosed with T1c Gleason grade 4 + 3 prostate cancer after a screening prostate-specific antigen (PSA) was 14.5 ng/mL. He walks 2 miles a day and can do a flight of stairs without problem. He is on baby aspirin, lisinopril, metformin, and metoprolol.

Which of the following is the most appropriate next step in his treatment?

A. Radical prostatectomy with adjuvant androgen deprivation therapy (ADT)
B. External beam radiation
C. Active surveillance
D. Brachytherapy radiation

4. A 57-year-old man presents to his local ED with bone pains and constipation. On imaging he is found to have multiple lytic lesions involving two ribs, three vertebrae, and his left humerus. He has no spinal cord compression on MRI but CT of the abdomen and pelvis shows an enlarged prostate with external compression of the rectum causing complete obstruction. Prostate-specific antigen (PSA) is 180 ng/mL. He is otherwise healthy.

Which of these options is the preferred next step for him?

A. Biopsy of a malignant bone lesion
B. Radium-223
C. Leuprolide
D. Abiraterone + prednisone
E. Degarelix

ALGRAWANY

5. A 78-year-old man without comorbid conditions, but with metastatic prostate cancer to the bone, is coming to your office for regular follow-up. His primary disease was treated with external beam radiation therapy (EBRT) 10 years ago. He developed recurrence with bone metastases 3 years ago and was started on androgen deprivation therapy (ADT) and abiraterone + prednisone with a good response. After 18 months of treatment, he became castration-resistant based on rising PSA and several new bone lesions on bone scan involving his spine and appendicular skeleton. CT scans show no visceral disease. He remains asymptomatic and regularly goes for long walks.

Which of the following would be an appropriate next step for his treatment?

A. Radium-223
B. Best supportive care
C. Increase the abiraterone dose to 1,500 mg a day
D. Cabazitaxel
E. Docetaxel and Pamidronate

6. A 64-year-old man is diagnosed with metastatic prostate cancer when an x-ray for persistent lumbar back pain showed a sclerotic lesion in L4. Subsequent workup revealed a prostate-specific antigen (PSA) of 107 ng/mL. A CT with enlarged pelvic lymph nodes and prostate, and bone scan showed innumerous sclerotic lesions, including in L4, T4, left 12 rib, and right scapula. He is otherwise healthy. He has been on bicalutamide for 2 weeks that was prescribed by his urologist.

What is the best treatment plan?

A. Add leuprolide
B. Add high-dose finasteride
C. Add leuprolide and radium-223
D. Add leuprolide and six cycles of docetaxel
E. Add leuprolide and definitive radiation to the prostate

ANSWERS

1. **A. Docetaxel.** The patient has castration-resistant metastatic prostate cancer that initially responded to secondary hormonal therapy but has now progressed with new visceral metastatic disease and rapidly rising PSA. He appropriately underwent genetic testing; however, had no homologous repair deficiency so olaparib is inappropriate (choice C). Radium-223 is approved only for bone-only metastatic disease so confirmed liver lesions prohibit this option (choice D). Continuing abiraterone and switching to denosumab is inappropriate as he is having visceral progression has not any skeletal events on zoledronic acid (choice B). Switching to first-line chemotherapy with docetaxel is the most appropriate option in this patient.

2. **B. Continued surveillance with a repeat PSA in 6 months.** This patient has had a normal response to radiation. The PSA nadir may not occur for a year and may not be undetectable after radiation. Concurrent/adjuvant androgen deprivation therapy (ADT) could have been considered up front for his intermediate risk (based on Gleason score of 7) but plays no role this late after his treatment.

3. **B. External beam radiation.** This patient has intermediate risk prostate cancer based on his PSA and Gleason score. Therefore, either prostatectomy or external beam radiation. However, adjuvant ADT is not indicated after prostatectomy so A is incorrect. Observation is only recommended for low-risk prostate cancer. Likewise, brachytherapy is not recommended for patients with intermediate or high-risk disease so C and D are incorrect.

4. **E. Degarelix.** He likely has hormone naïve metastatic prostate cancer. A biopsy is desired but should not delay therapy in setting of markedly elevated PSA and consistent imaging findings. The flare from leuprolide may worsen his obstruction so this should not be initial treatment. Abiraterone may be considered for this patient but will not provide immediate benefit. Radium-223 is not appropriate for treatment of prostate primary. As a gonadotropin-releasing hormone (GnRH) antagonist, degarelix is immediate acting and does not carry the risk of flare. Hence it is preferred in this setting.

5. **A. Radium-223** This patient has progressive disease, which has newly become castration resistant. He currently has evidence of bone-only disease with no visceral lesions. As he appears to have good functional status and has not received any treatment for metastatic castration-resistant disease so supportive care alone is likely not appropriate. Increasing abiraterone dose is not recommended for progression. Cabazitaxel is approved after progression on Docetaxel but would be inappropriate for this patient. While all patients with castrate-resistant disease and bone mets should receive a bisphosphonate, only zoledronic acid, not pamidronate is approved for prostate cancer. Docetaxel would be an appropriate option but with zoledronic acid or denosumab, not pamidronate. Radium-223 is an approved treatment for men with bone-only castrate-resistant disease and the most appropriate of the listed options.

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6. **D. Add leuprolide and six cycles of docetaxel.** He has high-volume (defined as visceral disease or at least four bone metastases with one beyond vertebral body/pelvis) de novo metastatic prostate cancer. This chemohormonal strategy of adding six cycles of docetaxel to traditional androgen deprivation therapy improves overall survival. The addition of abiraterone, enzalutamide, or apalutamide would also have been appropriate. Choice E, the addition of radiation to the prostate is not appropriate since the patient does not have a low volume of disease.

21 Testicular Cancer

Jason R. Brown and Zachery R. Reichert

PATHOLOGY

1. What are the histological types of testis cancer?

- Germ-cell histologies account for 95% of all testis cancer
  - One-third of germ-cell tumors contain multiple histologies in the same mass.
  - If any nonseminoma component is present, that is used for treatment decisions.
- Germ cell; seminoma histologies:
  - Classical seminoma ("fried-egg" appearance, pure histology, 40%–50% of all testicular germ-cell tumors)
  - Spermatocytic tumor (elderly with indolent course—rare)
- Germ cell; nonseminoma histologies (more aggressive; 50%–60% of all tumors):
  - Embryonal cell (most undifferentiated subtype, worse prognosis)
  - Choriocarcinoma (most aggressive subtype, increased beta-human chorionic gonadotropin [beta-HCG])
  - Yolk sac (increased alpha-fetoprotein [AFP])
  - Teratoma (mature or immature)
  - Stroma tumors (Sertoli cell, Leydig cell, primitive gonadal structures; 1%–2% of tumors)

2. What are the associated serum tumor markers used in testicular cancer?

- Lactate dehydrogenase (LDH): not cancer type specific
- AFP: yolk sac, embryonal (never in seminoma); liver and gastrointestinal (GI) tract carcinomas; elimination half-life ($t_{½}$) 5 to 7 days
- Beta-HCG: nonseminoma (choriocarcinoma) or seminoma; $t_{½}$ 1 to 2 days

3. What are common tumor genomic events within testis cancer?

- Seminoma, nonseminoma: gain of 12p sequences or creation of an isochromosome 12p (i12p).
- Seminoma: *KIT* mutations
- Spermatocytic seminoma: chromosome 9 gain
- Most infantile yolk sac tumors and teratomas: no chromosomal changes

DIAGNOSTIC WORKUP

1. What are the main diagnostic and staging tests used in testis cancer?

- History, physical exam, comprehensive metabolic panel, and complete blood count
- Testicular ultrasound
- Serum markers (LDH, AFP, beta-HCG)
  - Care must be taken to consider other reasons for marker elevation (hepatobiliary disease, marijuana use, and hypogonadism).

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- CT abdomen/pelvis and chest x-ray (CXR)
- CT chest if CXR abnormal or retroperitoneal adenopathy on CT abdomen/pelvis
- Radical inguinal orchiectomy; consider open inguinal biopsy of the contralateral testis if cryptorchid, marked atrophy, hypoechoic mass, or macrocalcifications
- Discuss fertility consultation and sperm banking prior to chemotherapy, retroperitoneal lymph node dissection (RPLND), or radiation therapy (RT)

STAGING

1. How is testis cancer staged?

- Testicular cancer uses the American Joint Committee on Cancer (AJCC) staging system (tumor, node, and metastasis [TNM] and serum markers after orchiectomy)

TABLE 21.1 ■ AJCC 8th Edition Staging System

Stage	T (Pathologic)	N	M	S
IA	T1	N0	M0	S0
IB	T2–4	N0	M0	S0
IS	Any T	N0	M0	S1–3
IIA	Any T	N1	M0	S0–1
IIB	Any T	N2	M0	S0–1
IIC	Any T	N3	M0	S0–1
IIIA	Any T	Any N	M1a	S0–1
IIIB	Any T	N1–3	M0	S2
	Any T	Any N	M1a	S2
IIIC	Any T	N1–3	M0	S3
	Any T	Any N	M1a	S3
	Any T	Any N	M1b	Any S
pT0	No evidence of primary tumor (e.g., histologic scar in testis)			
pTis	Germ-cell neoplasia *in situ*			
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into tunica albuginea, but not the tunica vaginalis			
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, *or* tumor extending through tunica albuginea involving the tunica vaginalis			
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion			
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion			
N0	No regional LN metastasis			
N1, pN1	≤5 LN involved *and* all LNs ≤2 cm in greatest dimension on imaging *and* measured on pathology			

(*continued*)

TABLE 21.1 ■ AJCC 8th Edition Staging System (*continued*)

N2, pN2	>5 LN involved *or* any LN between 2 and 5 cm in greatest dimension on imaging or measured on pathology
N3, pN3	LN >5 cm in greatest dimension on imaging or pathology
M0	No distant metastasis
M1a	Nonregional nodal *or* lung metastasis
M1b	Distant metastasis other than nonregional nodal/lung
S0	LDH beta-HCG, AFP within normal limits
S1	LDH <1.5 × normal, *and* beta-HCG <5,000 mIU/mL *and* AFP <1,000 ng/mL
S2	LDH 1.5–10 × normal, *or* beta-HCG 5,000–50,000 mIU/mL *or* AFP 1,000–10,000 ng/mL
S3	LDH >10 × normal, *or* beta-HCG >50,000 mIU/mL, *or* AFP >10,000 ng/mL

AFP, alpha-fetoprotein; beta-HCG, beta-human chorionic gonadotropin; LDH, lactate dehydrogenase; LN, lymph node.

PROGNOSTIC FACTORS

TABLE 21.2 ■ Seminoma and Nonseminoma Risk Factors

	Seminoma	Nonseminoma
Good Risk	Primary site: Any Visceral metastasis: Lung Markers ■ Normal AFP ■ Any beta-HCG ■ Any LDH	Primary site: Testis or retroperitoneal Visceral metastasis: Lung only Markers (S0–S1) ■ AFP <1,000 ng/mL ■ beta-HCG <5,000 mIU/mL ■ LDH <1.5 × upper limit of normal
Intermediate Risk	Extrapulmonary visceral metastasis	Markers (S2) ■ AFP 1,000–10,000 ng/mL ■ beta-HCG <5,000–50,000 mIU/mL ■ LDH <1.5–10 × upper limit of normal
Poor risk	N/A	Primary site: Mediastinum Visceral metastasis: Outside lung Markers (S3) ■ AFP >10,000 ng/mL ■ beta-HCG >50,000 mIU/mL ■ LDH >10 × upper limit of normal

AFP, alpha-fetoprotein; beta-HCG, beta-human chorionic gonadotropin; LDH, lactate dehydrogenase.

Note: Markers are postorchiectomy only. Pay attention to elimination half-lives to determine rate of decline.

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TREATMENT

1. What are the parameters that affect management decisions in testis cancer?

- Histologic type, serum markers, stage, and patient clinical factors (pulmonary and renal status)

2. What is the goal of treatment?

- Treatment with curative intent (even in metastatic cases) should be pursued if the patient can tolerate therapy.

3. What chemotherapy regimens are used in testis cancer (all are 21-day cycles)?

- EP: etoposide/cisplatin
- BEP: bleomycin/etoposide/cisplatin (Note: Avoid bleomycin if any preexisting pulmonary pathology, e.g., chronic obstructive pulmonary disease (COPD), reduced GFR, or age >50 years)
- VIP: etoposide/ifosfamide/cisplatin
- TIP: paclitaxel/ifosfamide/cisplatin
- VeIP: vinblastine/ifosfamide/cisplatin

4. How is seminoma treated?

- Stage IA/B: Inguinal orchiectomy, followed by one of the following:
  - Surveillance (pT1/pT2/pT3) is preferred if the patient is compliant (15%–20% relapse rate, median time of relapse 1 year, late relapses are rare).
  - Single-agent carboplatin (AUC 7) for one or two cycles.
  - RT: infradiaphragmatic (20 Gy) including para-aortic lymph node (LN) (inclusion of ipsilateral iliac LN could be considered on special occasions). Avoid RT if prior RT in the intended field, horseshoe/pelvic kidney, inflammatory bowel disease.
- Stage IS: Inguinal orchiectomy and further therapy dictated by extent of disease on imaging.
  - Persistent elevation is rare and other causes of LDH, AFP, beta-HCG elevation must be ruled out.
- Stage IIA/B: Inguinal orchiectomy and one of the following:
  - RT: infradiaphragmatic (30–36 Gy) including para-aortic LN and ipsilateral iliac LN
  - Chemotherapy (BEP × three cycles or EP × four cycles)
- Stage IIC or III: inguinal orchiectomy and chemotherapy
  - Good risk: chemotherapy (BEP × three cycles or EP × four cycles)
  - Intermediate risk: chemotherapy (BEP × four cycles)
- For stage II and III, treatment response should be confirmed by tumor markers and CT postchemotherapy:
  - If markers are normal and mass is ≤3 cm, standard surveillance per national guidelines.
  - If markers are normal but residual tumor >3 cm, PET scan should be done at least 6 weeks after therapy completion.
  - If PET negative, then begin surveillance.
  - If PET positive, then resection of residual mass followed by either:
    a. If viable disease and complete resection: two additional cycles of adjuvant chemotherapy

b. If viable disease and incomplete resection: second-line therapy
c. No viable disease: begin surveillance

- If markers are persistently elevated, a residual mass is growing, or attempted residual mass resection is incomplete, then second-line chemotherapy.

5. How is early stage (stage IA/B, IIA/B (S0)) nonseminoma treated?

- Stage I: Treatment depends on risk factors, including lymphovascular invasion, spermatic cord invasion, and sometimes embryonal predominance
  - 50% relapse rate if lymphovascular invasion, high embryonal component
  - Absence of yolk sac, high tumor size, and high Ki-67 increase relapse risk

TABLE 21.3 Treatment for Early Stage Nonseminoma

Stage I A/B without risk factors	Stage I A/B with risk factors
Inguinal orchiectomy plus: ■ Surveillance **preferred** if the patient is compliant ■ Open nerve-sparing RPLND or chemotherapy (BEP × 1 cycle) may be considered if surveillance not feasible	Inguinal orchiectomy plus: ■ Surveillance (pT1–2 only) **or** ■ Chemotherapy (BEP × 1 cycle) **or** ■ Open nerve-sparing RPLND

BEP, bleomycin/etoposide/cisplatin; RPLND, retroperitoneal lymph node dissection.

- Stage II A/B: Inguinal orchiectomy and one of the following:
  - Modified bilateral (nerve-sparing if possible) RPLND.
    - For stage IIB, only may be considered if lymphatic drainage within expected drainage sites (chemotherapy remains an option). If aberrant drainage, RPLND is not an option.
  - Chemotherapy (BEP × 3 cycles or EP × 4 cycles)
- Adjuvant chemotherapy after RPLND depends on pathologic nodal status:
  - pN0: None
  - pN1: None (preferred) or EP × two cycles or BEP × two cycles
  - pN2: EP × two cycles or BEP × two cycles
  - pN3: BEP × three cycles or EP × four cycles pN3

6. How is advanced stage (stage IS, IIA/B (S1), IIC, III) nonseminoma treated after inguinal orchiectomy?

- Good risk
  - Chemotherapy (BEP × three cycles or EP × four cycles) (90% cure)
- Intermediate risk or stage IIIB
  - Chemotherapy (BEP × four cycles or VIP × four cycles) (70% cure)
- Poor risk or stage IIIC
  - Chemotherapy (BEP × four cycles or VIP × four cycles) (50% cure)
- Brain metastases: primary chemotherapy ± RT ± surgery

7. What is the management for advanced nonseminoma postchemotherapy (based on response)?

- Complete response
  - Surveillance if original stage IS
  - Surveillance preferred, can consider nerve-sparing bilateral RPLND in select cases

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- Partial response—Resection of residual masses plus:
  - Surveillance for teratoma (40% of patients) or necrosis (45% of patients)
  - Chemotherapy (EP or TIP or VIP or VeIP × two cycles) if residual disease is other cancer histology (15% of patients)
- Incomplete response or persistently elevated markers: clinical trial, second-line chemotherapy (resection of solitary mass would rarely be considered <5%).

8. How is refractory/recurrent disease treated (20%–30% of all patients)?

- Refractory or early relapse (<2 years from completion of therapy)
- Favorable (low markers, low volume, complete response on first-line therapy, testis primary):
  - Clinical trial, chemotherapy (TIP or VeIP) or high-dose chemotherapy with autologous stem cell rescue
- Unfavorable (high markers, high volume, incomplete response, extratesticular primary): one of the following:
  - Clinical trial (preferable)
  - Chemotherapy with TIP or VeIP
  - High-dose chemotherapy with autologous stem cell rescue
  - Surgical salvage (solitary site)
  - Late relapse (>2 years)
- Surgical salvage (preferred), clinical trial, chemotherapy, or high-dose chemotherapy with autologous stem cell rescue.

9. What is the surveillance after the initial treatment of seminoma and nonseminoma?

- History, physical exam, serum markers, CXR or CT chest, and CT abdomen/pelvis
- Interval between visits and tests depends on stage and treatment per guidelines (e.g., National Comprehensive Cancer Network [NCCN])
- Routine surveillance imaging not recommended beyond 5 years

SPECIAL CONSIDERATIONS

1. Are there any cancers associated with testis cancer?

- Teratoma can transform to several malignant histologic types.
- The exact frequency of treatment (radiation and chemotherapy)-related secondary malignancies is unclear but has typically been higher in testicular cancer survivors than age-matched controls (especially hematologic malignancies, nonmelanoma skin cancer). With the current trend of deescalating therapy, it is unclear how much a role this will play in the future but long-term clinical exam and awareness must be maintained.

2. What are noncancer medical complications from the management of testis cancer?

- Cardiovascular, neurologic, pulmonary, renal, infertility, hypothyroidism

3. Should doses be adjusted or cycle extended for neutropenia during chemotherapy?

- Chemotherapy doses should not be reduced or delayed. Growth factor support can be carefully utilized as per NCCN guidelines.

4. **What are some complications from RPLND (up to 20% of patients have complications with salvage RPLND after radiation)?**
   - Sexual dysfunction, infertility, retrograde ejaculation, bowel perforation, ascites, lymphocele, vascular injury, and pancreatitis

QUESTIONS

1. A 36-year-old man underwent a right inguinal orchiectomy 7 days ago for a pT1 pure embryonal histology germ-cell tumor with original markers of a normal lactate dehydrogenase/beta-human chorionic gonadotropin (LDH/beta-HCG) and alpha-fetoprotein (AFP) of 4,139 ng/mL. Markers were drawn today and show a persistently elevated AFP of 2,276 ng/mL while the others remain normal.

   What is the best next step?
   A. PET scan
   B. Brain MRI
   C. Four cycles of (etoposide/cisplatin) EP
   D. Repeat markers in 2 weeks

2. A 28-year-old man arrives in your office 4 weeks after undergoing a left orchiectomy with pathology showing dysmorphic cells with a "fried-egg" appearance. On further imaging, he is found to have enlarged pelvic lymph nodes and a 2 cm right upper lobe lung metastasis. No other organ metastases are found. You are discussing his prognosis and plan to obtain baseline alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), and beta-human chorionic gonadotropin (beta-HCG) prior to treatment.

   How would you characterize his risk of recurrence after definitive treatment?
   A. Good risk
   B. Intermediate risk
   C. Poor risk
   D. Need to know tumor markers prior to discussing risk

3. A 21-year-old man presents to his primary care physician (PCP) with a left testicular mass. Ultrasound reveals a 2.3 × 3.7 cm hypoechoic mass and he subsequently undergoes left orchiectomy. Pathology reveals a 4 cm mixed germ-cell tumor, which is 60% embryonal, 30% teratoma, and 10% yolk sac. Ki-67 staining is reported at 80%. There is lymphovascular invasion but no invasion of the spermatic cord. Further imaging reveals no lymph node or visceral organ metastases. Tumor markers prior to orchiectomy were alpha-fetoprotein (AFP) 300 ng/mL, beta-human chorionic gonadotropin (beta-HCG) 6,000 mIU/mL, and lactate dehydrogenase (LDH) 500 IU/L, all of which normalized after orchiectomy. Scar tissue but no masses are noted on testicular examination.

   Which of the following would not be a reasonable next step in his care?
   A. Surveillance with repeat imaging and tumor markers
   B. Radiation to the retroperitoneal lymph nodes
   C. BEP (bleomycin/etoposide/cisplatin) × one cycle
   D. Open nerve-sparing retroperitoneal lymph node dissection

ALGRAWANY

4. A 56-year-old man is seen 4 weeks after completing four cycles of BEP (bleomycin/etoposide/cisplatin) for a mixed germ-cell tumor involving both seminoma and choriocarcinoma on original orchiectomy. Disease originally involved the retroperitoneum and two solitary lung metastases. A new CT of his chest, abdomen, and pelvis reveals a residual conglomerate of lymph nodes in the retroperitoneal space measuring 5 × 3.5 cm (original size of 8 × 6.0 cm). Tumor markers are normal. He underwent retroperitoneal lymph node dissection (RPLND) and pathology showed necrosis and a 3.3 × 2.6 cm teratoma.

What is the next step?

A. Begin surveillance
B. Radiation to the surgical bed of resected tissue
C. Two cycles of TIP (etoposide/ifosfamide/cisplatin)
D. Prophylactic whole-brain radiotherapy

5. A 56 year-old man who is an active smoker with a history of chronic obstructive pulmonary disease (COPD) initially presented with new cough and progressively increasing shortness of breath over 2 months. Chest CT reveals a 7 × 5.5 cm anterior mediastinal mass. Biopsy of mass is performed and is consistent with pure yolk sac tumor. Tumor markers reveal alpha-fetoprotein (AFP) elevation to 8,941 ng/mL, lactate dehydrogenase (LDH) 273, and undetectable beta-human chorionic gonadotropin (beta-HCG). Testicular ultrasound was negative.

What is the most appropriate initial treatment for this patient?

A. Resection of the mediastinal mass
B. Four cycles of BEP (bleomycin/etoposide/cisplatin) chemotherapy
C. Four cycles of VIP (etoposide/ifosfamide/cisplatin) chemotherapy
D. Four cycles of EP (etoposide/cisplatin) chemotherapy

6. A 28-year-old man presents with a left testicular mass that is 2.8 × 1.4 cm on ultrasound. CT abdomen/pelvis shows enlarged para-aortic lymph nodes (long axis is 2.5 cm, short axis is 1.5 cm) around the left renal hilum. Tumor markers, including alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (beta-HCG), and lactate dehydrogenase (LDH) are obtained and all are normal. He undergoes radical inguinal orchiectomy and is found to have a mixed seminoma (95%) and embryonal carcinoma (5%). He is noted to have lymphovascular invasion and spermatic cord involvement. One month after orchiectomy, tumor markers remain negative.

What is the diagnosis and next step in treatment?

A. Seminoma; Surveillance
B. Seminoma; Radiation to ipsilateral iliac and paraaortic lymph node
C. Nonseminoma; 1 to 2 cycles of BEP (bleomycin/etoposide/cisplatin) chemotherapy
D. Nonseminoma; Bilateral nerve-sparing retroperitoneal lymph node dissection

ANSWERS

1. **D. Repeat markers in 2 weeks.** The tumor markers should be repeated in 2 weeks to confirm this normal decline. The elimination half-life ($t_{½}$) of AFP is between 5 and 7 days, so postorchiectomy changes need to be assessed within that context.

2. **A. Good risk.** This is a metastatic (stage III) seminoma, with no visceral metastases beyond the lungs. Therefore, he will be classified as good risk and would likely receive chemotherapy with BEP, provided no contraindications. Tumor markers, including AFP, LDH, and beta-HCG are used to stratify risk in nonseminoma but not in seminoma.

3. **B. Radiation to the retroperitoneal lymph nodes.** This is a pT2N0M0 (stage IB) nonseminoma. He has adverse risk factors on pathology, including embryonal pathology, and lymphovascular invasion. Therefore, potential options for treatment would be surveillance, chemotherapy, or a retroperitoneal lymph node dissection.

4. **A. Begin surveillance.** Teratoma is often chemotherapy resistant and requires surgical resection. As no seminoma, embryonal, yolk sac, or choriocarcinoma tissue was found, it is presumed all nonteratoma cancer was eradicated.

5. **C. Four cycles of VIP (Etoposide/Ifosfamide/Cisplatin) chemotherapy.** This patient has a primary mediastinal nonseminoma, which places him in the poor risk group. Therefore, treatments to be considered are BEP (bleomycin/etoposide/cisplatin) and VIP (etoposide/ifosfamide/cisplatin) for four cycles. Because he is over the age of 50 and is at higher risk of pulmonary toxicity due to his smoking and COPD history, bleomycin is contraindicated. If he had residual tumor after chemotherapy, then he would undergo resection of anterior mediastinal mass, but chemotherapy is the initial treatment.

6. **D. Nonsemioma; Bilateral nerve-sparing retroperitoneal lymph node dissection.** This is classified as a mixed germ-cell tumor and therefore nonseminoma despite the majority seminoma component. This is staged as IIB due to lymph node involvement >2 cm but <5 cm on longest axis. Left testicular lymphatic drainage occurs to the preaortic and para-aortic left renal hilum whereas right testicular lymphatic drainage initially occurs near the inferior vena cava (IVC). Because lymph nodes on imaging follow expected lymphatic drainage, appropriate treatment would be bilateral retroperitoneal lymph node dissection (three cycles of BEP or four cycles of EP would also be appropriate).

ALGRAWANY

22 Renal Cell Carcinoma

Vincent T. Ma and Sarah Yentz

GENETICS

1. What are the hereditary cancer syndromes associated with renal cell carcinoma (RCC)?

- *von Hippel–Lindau (VHL) disease*
  - VHL predisposes to clear cell carcinoma.
  - The RCCs are often bilateral, multicentric, and only clear cell type.
  - VHL is associated with pheochromocytomas, central nervous system (CNS) hemangioblastomas, retinal hemangioblastomas, endolymphatic sac tumors of the middle ear, papillary cystadenomas of the epididymis and broad ligament, and neuroendocrine tumors of the pancreas.
  - Autosomal dominant syndrome associated with a mutation in the *VHL* gene.
- *Hereditary papillary renal carcinoma (HPRC)*
  - HPRC predisposes to type 1 papillary RCC.
  - Bilateral, multifocal tumors
  - HPRC is a highly penetrant autosomal dominant condition
  - Associated with an activating mutation in the *MET* protooncogene.
- *Birt–Hogg–Dubé (BHD) syndrome*
  - Associated with chromophobe, hybrid chromophobe–oncocytomas, oncocytomas, dermatologic lesions (fibrofolliculomas), pulmonary cysts, and spontaneous pneumothoraces.
  - Associated with a mutation in the folliculin (*FLCN*) gene.
- *Hereditary leiomyomatosis and RCC (HLRCC)*
  - HLRCC predisposes to papillary type 2 RCC and multiple cutaneous and uterine leiomyomas.
  - Syndrome associated with a defect in (autosomal dominant inheritance) Krebs cycle enzyme gene, fumarate hydratase (*FH*).
- *Hereditary paraganglioma and pheochromocytoma (HPP)*
  - Predisposes to clear cell and chromophobe RCC.
  - Autosomal dominant condition caused by mutation in genes encoding succindate dehydrogenase (SDH; involved in the Krebs cycle).
  - Characterized by paragangliomas
- *Tuberous sclerosis complex*
  - Associated with an increased risk for renal angiomyolipomas, multifocal renal lesions, and only infrequently (<5%) with RCC.

ALGRAWANY

STAGING

1. How do we stage RCC?

TABLE 22.1 ■ AJCC 8th Edition Staging System for RCC

Stage	Description
I	Tumor ≤7 cm in greatest dimension, limited to the kidney
II	Tumor >7 cm in greatest dimension, limited to the kidney
III	Tumor limited to kidney with regional lymph node involvement or Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia with or without regional lymph node involvement
IV	Tumor involves ipsilateral adrenal gland and/or extends beyond Gerota's fascia or Presence of distant metastasis

AJCC, American Joint Committee on Cancer; RCC, renal cell carcinoma.

Source: Adapted from American Joint Committee on Cancer. Kidney. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer-Verlag; 2017. 747–756.

SIGNS AND SYMPTOMS

1. What is the most common presentation of RCC?

- Majority diagnosed via incidental tumor detection.
- Presenting with the Triad: hematuria, flank mass, and flank pain occurs in <10% of cases. Other presentations include fever, weight loss, anemia, or a varicocele.
- Few present with hypercalcemia from parathyroid-related protein (PTHrp), polycythemia from increased erythropoietin, and/or Stauffer syndrome (non-metastatic hepatic dysfunction that improves with removal of primary tumor).

DIAGNOSTIC WORKUP

1. What diagnostic imaging should be performed for a kidney mass that is suspicious for RCC?

- CT scan of the abdomen and pelvis with contrast. MRI abdomen may be helpful if CT is inconclusive or if needed for surgical planning.
- Chest X-ray (CXR) is routinely done, but if abnormal or if large primary tumor, chest CT is recommended.
- MRI brain or CT head with contrast is recommended for ALL patients with metastatic disease

PROGNOSTIC FACTORS

1. What are the predictors for poor prognosis in metastatic RCC treated with systemic therapy in the context of the International Metastatic RCC Database Consortium (IMDC) risk model?

- The following risk factors confer a poor prognosis:
  - Hemoglobin level lower than the lower limit of normal (<12 g/dL)
  - Neutrophil count greater than the upper limit of normal (>7.0 × 10^9/L)
  - Platelet count greater than the upper limit of normal (>400,000 cells/μL)
  - Corrected serum calcium level greater than the upper limit of normal (>8.5 mg/dL)
  - Karnofsky performance status <80%
  - Time from diagnosis to systemic treatment in less than 1 year

TABLE 22.2 ■ International Metastatic RCC Database Consortium (IMDC) Risk Classification

Number of Risk Factors	Risk Category	Median Overall Survival (months)
0	Favorable	43.2
1–2	Intermediate	22.5
3–6	Unfavorable	7.8

TREATMENT

1. When should we pursue surgical resection for RCC?

- Surgical resection is the only effective therapy for clinically localized RCC, with options being radical or partial nephrectomy.
- Radical nephrectomy is the preferred treatment for larger tumors (>7 cm) and/or if the tumor extends into the IVC.
- Stage IV patients with a solitary resectable metastasis can be considered for nephrectomy and metastasectomy.
- Palliative nephrectomy for metastatic disease can be considered for symptom relief in patients with significant pain, hematuria, or hypercalcemia if they are good surgical candidates.

2. Is there a role for any adjuvant treatment in completely resected stage I–III tumors?

- There is no role for adjuvant treatment after complete surgical resection outside of a clinical trial.
- Adjuvant sunitinib may be considered for select patients with high-risk disease given the possible disease-free survival benefits, though has not been shown to have an overall survival benefit.
- Observation is standard of care.

3. What are the medical treatment options for advanced/stage IV, previously untreated renal clear cell carcinoma?

- Active surveillance may be offered to asymptomatic patients with favorable risk disease and limited disease burden as these patients may have stable disease for many months without any therapy.
- If medical therapy is indicated, options of treatment include immunotherapy, molecularly targeted therapy, or combined immunotherapy and molecularly targeted therapy.

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4. What are the approved immunotherapy agents in advanced stage IV RCC?

- **Single-agent nivolumab**, an anti-programmed death-1 (PD-1) antibody inhibitor, has demonstrated prolonged overall survival compared to everolimus as a second-line therapy after progression on an initial vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).
- **Nivolumab and ipilimumab** used in combination has shown survival superiority compared to sunitinib in treatment-naïve (first-line therapy) advanced-stage RCC, particularly in intermediate and poor-risk patients.
- **High-dose interleukin-2 (IL-2)** activates the immune response against RCC cells, particularly with clear cell histology.
  - Due to severe toxicities, it is only appropriate for candidates with excellent performance status, normal organ function, and minimal disease burden.
  - In the era of immune checkpoint inhibitors and molecularly targeted therapy, the role of IL-2 has limited use in the current treatment paradigm.

5. What is the role of molecularly targeted therapy in advanced stage IV renal cell carcinoma?

- Multiple molecularly targeted therapies are approved for advanced or metastatic renal cell carcinoma including VEGF-TKIs and mTOR pathway inhibitors.
- For patients who are ineligible or choose to forego initial treatment with immunotherapy, feasible first-line VEGF-TKI options include the following:
  - **Pazopanib** (if favorable or intermediate risk)
  - **Sunitinib** (if favorable or intermediate risk)
  - **Cabozantinib** (if intermediate or high risk)
- Inhibitors of the mechanistic target of rapamycin (mTOR) pathway, temsirolimus and everolimus, have shown inferior survival outcomes compared to antiangiogenic targeted therapies, but they may be used as subsequent therapy.
- Other options of VEGF inhibition-based therapy that may be used in the second-line setting include axitinib, sorafenib, lenvatinib with everolimus, and bevacizumab with interferon (IFN)-alpha

6. What is the role of combined immunotherapy and antiangiogenic targeted therapy in advanced stage IV renal cell carcinoma?

- **Pembrolizumab plus axitinib** has demonstrated a progression-free survival and overall survival benefit compared to sunitinib in treatment-naïve patients, regardless of risk stratification.
- **Avelumab plus axitinib** has demonstrated a progression-free survival benefit compared to sunitinib in treatment-naïve patients, regardless of risk stratification.
- To date, there are no head to head trials directly comparing combination therapies between pembrolizumab/axitinib, avelumab/axitinib, and ipilimumab/nivolumab.

7. What are the treatment options for stage IV RCC of nonclear cell histology?

- The majority (80%–85%) of all RCC are *clear cell* tumors. The other histologic subtypes include papillary, chromophobe, collecting duct, translocation, and unclassified RCCs. Sarcomatoid features can be seen in any histologic subtype of RCC.

- Due to the rarity of non-clear cell histology and limited high-quality data to help inform management, participation in clinical trial for eligible patients is recommended.
- Metastatic *papillary RCC* is generally treated in a similar fashion to clear cell RCC with immunotherapy or VEGF-TKI with the exception that response rates may be lower.
- Patients with *sarcomatoid* features are often preferentially offered immunotherapy or combined immunotherapy with VEGF-TKI over VEGF-TKI monotherapy due to improved response rates seen in immunotherapy-based treatments.
- *Collecting duct* RCC and *renal medullary* carcinomas are typically treated with chemotherapy as initial therapy rather than VEGF inhibition-based therapies given that their biologic features are more similar to *urothelial carcinoma* than RCC.

8. Is there any role for chemotherapy in treatment of metastatic disease?

- A modest response rate in the realm of 5.5% to 6% has been reported with use of chemotherapy for clear cell RCC and is therefore **not** recommended.
- Chemotherapy is used in the rare subtypes of collecting duct RCC or renal medullary carcinoma. Platinum-based regimens are typically used.

QUESTIONS

1. A 51-year-old man, former smoker, presented to the ED complaining of acute onset left flank pain. Past medical history is significant for spontaneous pneumothoraces requiring bilateral thoracotomies and pleurodesis, and right upper lobectomy at 22 years old. Family history is significant for emphysema in mother, aunt, sister, and a son with history of pneumothorax. CT imaging on admission revealed a 0.5 cm kidney stone in the left mid-ureter and an indeterminate 3 cm lesion on the right kidney. He was eventually discharged with outpatient follow-up. During active surveillance, his right kidney mass increases in size. He is referred to urology for further evaluation. The patient undergoes a right radical nephrectomy with pathology revealing a diagnosis of chromophobe renal cell carcinoma.

Which of the following gene mutations is associated with this patient's condition?

A. *MET*
B. *FH*
C. Succinate dehydrogenase
D. *FLCN*
E. *HBB* (hemoglobin subunit beta)

2. A 65-year-old woman underwent a radical nephrectomy for a right kidney mass 2 years ago, initially identified by CT scan during a workup by her primary care physician for painless hematuria. Pathology revealed a 9 cm renal cell carcinoma (RCC), clear cell histology, with 4 of 10 lymph nodes involved by neoplasm. She was observed clinically after the operation.

ALGRAWANY

She is referred to you now after a CT obtained for right-sided abdominal pain showed five liver lesions measuring 2 cm each, and scattered noncalcified pulmonary nodules in both lungs. CT-guided core biopsy of one of the liver lesions showed clear cell carcinoma consistent with the histopathology of the primary kidney tumor removed 2 years ago.

She has a history of coronary artery disease and well-controlled hypertension and takes a thiazide diuretic as well as aspirin.

Her abdominal pain is well controlled with oral analgesics and she is otherwise asymptomatic. Her Eastern Cooperative Oncology Group (ECOG) performance status is 0.

What would you recommend next?

A. Nivolumab
B. Staged resections of liver metastases and lung metastases
C. Pembrolizumab/Pazopanib
D. Ipilimumab/nivolumab
E. High-dose interleukin-2 (IL-2)
F. Cisplatin and gemcitabine

3. Which of the following is true regarding renal cell carcinoma (RCC)?

A. There is no role for nephrectomy in stage IV RCC
B. Chemotherapy is a preferred first-line treatment due to high response rates across all histologies
C. Sarcomatoid differentiation is a poor risk feature in RCC
D. Adjuvant pembrolizumab improves survival compared to surveillance following resection of a primary RCC

4. An 82-year-old man is diagnosed with stage IV clear-cell renal cell carcinoma (RCC) with lung metastases. His comorbidities include mild dementia, coronary artery disease, history of transient ischemic attacks (TIAs), diabetes, and osteoarthritis. He was recently hospitalized after suffering from a fall leading to a right hip fracture, but is recovering well in rehab. Staging of his RCC reveals three metastatic lung lesions and a 3 cm left kidney mass. Review of prior imaging demonstrates that the lung lesions are unchanged over the past 9 months. He has no bone or central nervous system (CNS) metastases. He is asymptomatic from his disease. His blood counts, renal function, and liver function are all within normal limits. Based on his International Metastatic RCC Database Consortium (IMDC) risk model, he has favorable risk disease.

What would you recommend at this time?

A. Ipilimumab/nivolumab
B. Pembrolizumab/axitinib
C. Pazopanib
D. Sunitinib
E. Observation

ANSWERS

1. **D. *FLCN*.** This patient has **Birt–Hogg–Dubé (BHD) syndrome**, which is a hereditary condition characterized by a mutation in the folliculin (*FLCN*) gene. The disease can be manifested by pulmonary cysts leading to pneumothoraces, benign skin tumors, and renal cell carcinoma that is predominantly chromophobe and/or oncocytoma type. Genetic mutations in *MET* and *FH* are commonly associated with papillary-type renal cell carcinoma. The mutation associated with succinate dehydrogenase is associated with hereditary paraganglioma and pheochromocytoma (HPP) and predisposes to clear cell and chromophobe RCC. Sickle cell trait/disease, characterized by a point mutation in the *HBB* gene, predisposes to renal medullary carcinoma, a highly aggressive malignancy.

2. **D. Ipilimumab/nivolumab.** This patient has metastatic RCC, clear cell type. Combination ipilimumab/nivolumab is an effective frontline therapy for metastatic RCC of clear cell type, particularly in intermediate and poor-risk patients. It has superior overall survival and progression-free survival compared to sunitinib, a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI). Nivolumab, an anti-programmed death-1 antibody, has demonstrated prolonged overall survival compared to everolimus as a second-line therapy after progression on an initial VEGF-TKI. Combination immunotherapy with VEGF-TKI, such as pembrolizumab/axitinib or avelumab/axitinib, is an alternative frontline therapy option for metastatic RCC. Pembrolizumab/pazopanib is not a Food and Drug Administration (FDA)-approved combination therapy. High-dose IL-2 can induce durable remissions in a minority of patients with metastatic RCC; however, the patient's age, medical history, and volume of metastases make her a poor IL-2 candidate. Her volume and distribution of disease make metastasectomy a poor option. Cytotoxic chemotherapy is considered ineffective in metastatic kidney cancer.

3. **C. Sarcomatoid differentiation is a poor risk feature in RCC.** Palliative nephrectomy can be considered for symptom relief in patients with significant pain, hematuria, or hypercalcemia if they are good surgical candidates. Chemotherapy has a poor response rate (<10%) in RCC, so its use is not recommended. To date, there is no role for adjuvant immune checkpoint inhibitor for resected RCC.

4. **E. Observation.** Patients with metastatic RCC who are treatment-naïve with favorable risk may be candidates for systemic treatment with pazopanib, sunitinib, or pembrolizumab/axitinib. However, there are a subset of patients with metastatic RCC that have indolent disease growth. Due to the toxicities and palliative nature of systemic therapy, these patients may benefit from initial active surveillance. In an elderly patient who is still recovering from his fall and is asymptomatic from his disease, observation would be the best option in this case.

ALGRAWANY

GASTROINTESTINAL MALIGNANCIES

VI

ALGRAWANY

23 Esophageal Cancer

Jason C. Chen and Angel Qin

ETIOLOGY AND RISK FACTORS

1. What are the risk factors?

- Squamous cell carcinoma (SCC)
  - Smoking and alcohol
  - Diets high in nitrates (e.g., smoked/preserved foods), and low in fruits and vegetables
  - Previous ionizing radiation exposure
  - Anatomic abnormalities (esophageal webs, achalasia, and Zenker's diverticulum)
- Adenocarcinoma
  - Obesity
  - Gastroesophageal reflux disease (GERD)
  - Barrett's esophagus (intestinal metaplasia); rate of transformation is 0.5% per year
  - High-grade dysplasia (stage 0); rate of transformation is 10% to 15% per year

STAGING

1. What are the tumor, node, and metastasis (TNM) staging definitions?

TABLE 23.1 ■ Staging Definitions

	TNM	Description
Primary tumor (T)	Tx	Primary tumor cannot be assessed
	Tis	High-grade dysplasia
	T1a	Tumor invades lamina propria or muscularis mucosae
	T1b	Tumor invades submucosa
	T2	Tumor invades muscularis propria
	T3	Tumor invades adventitia
	T4a	Tumor invades adjacent structures (pleura, pericardium, or diaphragm), resectable
	T4b	Tumor invades adjacent structures (aorta, vertebral body, trachea, etc.), unresectable

(*continued*)

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TABLE 23.1 ■ Staging Definitions (*continued*)

	TNM	Description
Regional lymph nodes (N)	Nx	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1–2 regional lymph nodes
	N2	Metastasis in 3–6 regional lymph nodes
	N3	Metastasis in 7 or more regional lymph nodes
Distant metastases (M)	M0	No distant metastases
	M1	Distant metastases

TNM, tumor, node, and metastasis.

2. How is esophageal cancer staged?

- The staging system was updated in 2017, with separate stage groups for adenocarcinoma and SCC that use TNM, histologic grade, and, for SCC, location in the esophagus.
- Tumor confined to muscularis propria and no lymph node involvement is stage I disease.
- Presence of tumor in one to three lymph nodes increases the stage to at least stage IIB for both adenocarcinoma and SCC.
- Presence of distant metastasis increases the stage to stage IV.
- Siewert classification (I, II, III) is often discussed for tumors near the gastroesophageal (GE) junction; it is predominantly used for surgical planning.

3. What percentage are resectable at the time of diagnosis?

- Around 50% are resectable.

SIGNS AND SYMPTOMS

- Symptoms include
  - Dysphagia (75%, solids > liquids), weight loss (50%), GE reflux (25%).
  - Dyspepsia, odynophagia, epigastric or retrosternal pain, anorexia, malaise, hematemesis, cough, or hoarseness.
- Late signs on physical exam include
  - Horner syndrome, supraclavicular lymphadenopathy (Virchow's node)

WORKUP AND DIAGNOSIS

1. What tests should be ordered?

- History and physical, routine lab work (complete blood count [CBC], comprehensive metabolic profile [CMP]).
- Endoscopy with biopsy is diagnostic.
- Endoscopic ultrasound (EUS) adds T and N staging information and is recommended if no evidence of M1 unresectable disease
- CT or PET/CT scan of the chest, abdomen, and pelvis to assess for distant metastases; esophageal cancer frequently spreads to the liver and lung.

2. What is the pathology?

- Adenocarcinoma—more common in Western countries
- SCC—more common in Eastern European and Asian countries ("esophageal cancer belt")

3. Where are the tumors located?

- Fifty percent of tumors arise from the lower third of the esophagus, 25% from the mid-esophagus, and 25% from the upper third of the esophagus.
  - *Upper esophagus:* thoracic inlet to level of tracheal bifurcation, 18 to 23 cm from incisors.
  - *Middle esophagus:* tracheal bifurcation midway to GE junction, 24 to 32 cm from incisors.
  - *Lower esophagus:* midway between tracheal bifurcation and GE junction, to GE junction, 32 to 40 cm from incisors.
- Adenocarcinomas: the lower third of the esophagus or at the GE junction.
- SCCs: the upper half of the esophagus.

TREATMENT—FIRST LINE

1. What is the treatment of patients with high-grade dysplasia (stage 0)?

- Endoscopic mucosal resection (EMR), mucosal ablation, or esophagectomy
- The transformation rate of high-grade dysplasia to invasive cancer is 10% to 15% per year.

2. What is the treatment of patients with early-stage, node-negative disease (stage I)?

- Esophagectomy alone
  - Either the transhiatal or transthoracic approach is acceptable.

3. What are the treatment options for patients with locally advanced, *resectable* disease?

- Definitive chemoradiation
  - Preferred approach for cervical tumors (NOTE: tumors above the aortic arch are generally not resectable).
  - Preferred in patients with SCCs of the esophagus
  - Weekly carboplatin and paclitaxel with daily radiation (50–50.4 Gy lasting 5–5.5 weeks) is the standard of care.
  - Other concurrent chemotherapy options: 5-FU + oxaliplatin OR 5-FU + cisplatin.
- Preoperative chemoradiation followed by esophagectomy (trimodality therapy)
  - Weekly carboplatin and paclitaxel with daily radiation for 5 to 5.5 weeks is standard. (Another concurrent chemotherapy option is fluorouracil with oxaliplatin.)
  - If preoperative nutritional support is needed, nasogastric feeding tube or J-tube is preferred over percutaneous endoscopic gastrostomy (PEG) due to the need to use the stomach to create a conduit following removal of the esophagus.
- For patients who received neoadjuvant chemoradiation, there is *no role* for adjuvant chemotherapy or radiation even with residual disease
- Perioperative chemotherapy alone, without radiation, can also be considered

ALGRAWANY

4. What is the treatment for patients with locally advanced, *unresectable* disease?

- T4b esophageal cancer is unresectable.
- Chemoradiation is preferred; however, radiation alone is also an option for patients who are not candidates for treatment with chemotherapy.
  - If not a radiation candidate, then palliative systemic chemotherapy can also be considered (e.g. single-agent 5-FU)

5. What are the treatment options for patients with poor performance status?

- For stage 0 and stage I patients (not surgical candidates): EMR, mucosal ablation, or photodynamic therapy (PDT).
- For patients with locally advanced tumors (not chemotherapy candidates): radiation therapy alone.
- Best supportive care.

6. How should patients who have received therapy for locoregional disease be monitored?

- History and physical examination with routine blood work every 3 to 6 months for 1 to 2 years, then every 6 to 12 months for 3 to 5 years, then annually.
- Imaging (CT chest/abdomen with contrast) may be considered every 6 to 12 months for the first 3 years, and then as clinically indicated.
- Use of esophagogastroduodenoscopy (EGD) surveillance depends on what treatment was done initially
  - Endoscopic resection/ablation: EGD every 3 months for first year, then every 6 months for second year, then annually indefinitely afterward.
  - Chemoradiation: EGD every 3 to 6 months for first and second year, then every 6 months for third year, then as needed based on clinical assessment
  - Esophagectomy: EGD as needed based on clinical assessment (used to assess the surgical anastomosis to evaluate for stricture, recurrence, etc.)

TREATMENT—RECURRENT DISEASE

1. How is locally recurrent disease treated?

- Patients with localized recurrences who have not previously received radiation therapy in the region of the recurrence could be treated with concurrent chemoradiation.
  - Patients who have received only definitive chemoradiation and are surgical candidates may be considered for salvage esophagectomy.
  - Patients who are not candidates for chemoradiation or salvage esophagectomy should be treated like they have metastatic disease (see the following section, Treatment—Metastatic Disease).

TREATMENT—METASTATIC DISEASE

- First-line therapy: palliative platinum-based combination chemotherapy with 5-fluorouracil (FU)/capecitabine, a taxane, or irinotecan
  - If platinum agent is used, oxaliplatin is *preferred* over cisplatin given improved tolerance.
  - Doublet preferred over triplet combinations to improve tolerance, with the exception of adding trastuzumab for HER2/neu-positive adenocarcinomas.
- Second-line therapy: Ramucirumab with or without paclitaxel for adenocarcinomas.

- Checkpoint inhibitors have also shown to be beneficial in certain situations (and if patient has not previously progressed through immunotherapy). Checkpoint inhibitors are approved in the following scenarios:
  - Second-line: if microsatellite instability (MSI) high (histology agnostic): pembrolizumab
  - Second-line: if programmed death cell ligand (PD-L1) combined positive score (CPS) ≥10 and SCC: pembrolizumab
  - Second-line: if SCC and without need for MSI or PD-L1 testing: nivolumab
  - Third-line: if PD-L1 CPS ≥1 and adenocarcinoma: pembrolizumab
- Third-line: for GE junction adenocarcinomas: trifluridine/tipiracil
- Neurotrophic tropomyosin-related kinase (NTRK) mutation positive: entrectinib or larotrectinib
- Palliative radiation for dysphagia or pain
  - Brachytherapy or external beam
- PDT
- Best supportive care
  - Including esophageal stenting

SPECIAL CONSIDERATIONS

1. Who should be screened?

- Screening for the general population is not indicated in the United States.
- Patients with Barrett's esophagus are at higher risk of esophageal cancer.
  - Rate of transformation to esophageal cancer is 0.5% per year.
  - Consider screening EGD every 3 to 5 years

2. What are some life-threatening complications?

- Esophageal-airway fistula
  - Presents with cough, aspiration, and fever, frequently leading to pneumonia
  - Treated with a coated, expandable metal stent to seal the fistula

QUESTIONS

1. A 45-year-old man with history of gastroesophageal reflux disease presented with worsening dysphagia. Upper endoscopy reveals a 3 cm mass distal esophageal mass. Biopsy shows esophageal adenocarcinoma with HER2 overexpression invading the adventitia. PET/CT demonstrates distal esophageal uptake with several suspicious local lymph nodes. Patient is agreeable to aggressive treatment plan including surgery if needed.

What is the best initial treatment for this patient?

A. Neoadjuvant chemoradiation with carboplatin and paclitaxel
B. Neoadjuvant chemoradiation with carboplatin, paclitaxel, and trastuzumab
C. Perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil
D. Proceed to esophagectomy

2. Which of the following is a risk factor for esophageal adenocarcinoma?

A. Smoking
B. Obesity

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C. Ionizing radiation
D. *Helicobacter pylori* infection

3. Which of the following would be an appropriate first-line treatment option for a 75-year-old female with poorly controlled hypertension and stage IV esophageal adenocarcinoma with immunohistochemistry for HER2 showing 3+?
A. Ramucirumab plus paclitaxel
B. 5-fluorouracil (FU) and cisplatin
C. FOLFOX plus trastuzumab
D. Pembrolizumab

4. Which of the following is true about esophageal cancer?
A. First-line treatment of stage I esophageal squamous cell carcinoma of the cervical esophagus includes transhiatal resection followed by adjuvant capecitabine and radiation
B. Percutaneous endoscopic gastrostomy (PEG) tubes should be empirically placed for preoperative nutritional support in patients being treated with trimodality therapy
C. Invasion of the trachea is a contraindication to esophagectomy
D. Brachytherapy is a first-line treatment option in patients with locally advanced, unresectable esophageal cancer

5. Which of the following is true about the management of esophageal cancer in patients with poor performance status?
A. Endoscopic mucosal resection (EMR) is an option for patients with early-stage esophageal cancer
B. For patients with locally advanced tumors who are not chemotherapy candidates, radiation alone is not recommended
C. Empiric esophageal stenting should be considered to help the patients get through therapy
D. In elderly patients with localized disease, single-agent chemotherapy with capecitabine is an option

6. Which of the following would be appropriate surveillance for a 67-year-old female with locally advanced esophageal adenocarcinoma after successful completion of definitive chemoradiation with 5-fluorouracil (5-FU) and oxaliplatin, without evidence of residual disease?
A. Repeat esophagogastroduodenoscopy (EGD) in 1 month
B. Repeat EGD in 6 months
C. Repeat CT scans in 1 month
D. Repeat CT scans in 3 months

7. Which of the following is the best treatment option for a 60-year-old man with esophageal squamous cell carcinoma after prior definitive chemoradiation treatment and 5-fluorouracil (5-FU)/oxaliplatin for recurrent disease, who now presents with disease progression and tumor programmed death cell ligand (PD-L1) combined positive score (CPS) of 1?
A. Nivolumab
B. Trifluridine/tipiracil
C. Pembrolizumab
D. Ramucirumab

ANSWERS

1. **A. Neoadjuvant chemoradiation with carboplatin and paclitaxel.** The current standard of care for locally advanced, resectable esophageal cancer is 5 weeks of neoadjuvant carboplatin and paclitaxel and concurrent radiation followed by transhiatal resection based on the CROSS trial. Trastuzumab is not given concurrently with radiation. Rather, it is approved for HER2-positive esophageal and gastroesophageal junction (GEJ) cancer in the metastatic setting only. Perioperative epirubicin, cisplatin, and fluorouracil (ECF) is not recommended as first-line treatment for esophageal cancer. Surgery without attempting neoadjuvant treatment for his locally advanced disease is not recommended.

2. **B. Obesity.** Significant risk factors for the development of esophageal adenocarcinoma are obesity, gastroesophageal reflux disease (GERD), and Barrett's esophagus. Smoking, alcohol, and ionizing radiation are risk factors of the development of esophageal squamous cell carcinoma. Unlike gastric cancer, *H. pylori* is associated with a lower incidence of esophageal adenocarcinoma.

3. **C. FOLFOX plus trastuzumab.** The ToGA trial showed a survival advantage with the addition of trastuzumab to chemotherapy (platinum and fluoropyrimidine) in HER2-overexpressing esophageal adenocarcinoma. Ramucirumab (with or without paclitaxel) is approved in the second-line treatment of stage IV gastroesophageal junction (GEJ) adenocarcinoma. Uncontrolled hypertension is a relative contraindication to ramucirumab. Cisplatin should be avoided in metastatic patients due to toxicity, compared with oxaliplatin. Pembrolizumab alone is not approved as front-line treatment for metastatic esophageal cancer, though is approved in the second- and third-line setting.

4. **C. Invasion of the trachea is a contraindication to esophagectomy.** Invasion into local structures including the trachea defines T4b disease, which is considered to be unresectable. In the absence of metastatic disease, these patients are treated with radiation (+/− concomitant chemotherapy). Esophageal cancer of the cervical esophagus is less amenable to surgery given the need to perform an extensive surgery (pharyngo-laryngo-esophagectomy). Hence these are generally treated with definitive chemoradiation. Preoperative nutritional support is an important consideration in the treatment in patients with resectable esophageal cancer. However, PEG tubes are avoided given the need to use the stomach to create a conduit. Brachytherapy is a treatment option reserved for the palliative setting to relieve dysphagia or pain.

5. **A. EMR is an option for patients with early-stage esophageal cancer.** In patients with early-stage esophageal cancer and poor performance status, several nonsurgical options can be considered for local control including EMR. In patients with locally advanced tumors who are not chemotherapy candidates, definitive radiation is an option. There is no role for empiric esophageal stenting; this should be reserved for supportive care

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in the setting of symptomatic esophageal lesions. Similarly, there is no role for single-modality therapy using chemotherapy in localized disease. Chemotherapy should be reserved for use in combination with radiation or for the metastatic setting.

6. **B. Repeat EGD in 6 months.** Patients who have undergone chemoradiation only should be monitored with clinical exams every 3 to 6 months and repeat EGD every 3 to 6 months for the first 2 years. CT scans can be considered every 6 to 12 years for the first 3 years.

7. **A. Nivolumab**. This patient should be considered for second-line treatment options for his recurrent esophageal squamous cell carcinoma (SCC). Nivolumab is approved as second-line treatment for patients with SCC regardless of microsatellite instability (MSI) or PD-L1 testing, so this patient would be a candidate. Pembrolizumab is approved as second-line treatment but only if tumor PD-L1 CPS ≥10. Trifluridine/tipiracil is approved in the third-line setting for gastroesophageal (GE) junction adenocarcinoma only. Ramucirumab also is indicated for adenocarcinoma only.

24 Gastric Cancer

Jennifer E. Girard and Mark M. Zalupski

EPIDEMIOLOGY

1. What is the median age at diagnosis?

- Seventy years

2. What is the incidence of gastric cancer?

- There is a wide global variation in incidence of gastric cancer.
- The incidence of gastric cancer has steadily decreased in the United States and Western European countries during the last three decades likely related to changes in diet, food preparation and storage, and treatment of *Helicobacter pylori* infection. Over the past 80 years, gastric cancer incidence and mortality have decreased by almost 90%.
- At the same time, the incidence of tumors of the gastroesophageal junction (GEJ) among young white individuals has increased in Western countries secondary to the increase in the rates of obesity and reflux disease.

ETIOLOGY AND RISK FACTORS

1. What are the risk factors for gastric cancer?

- Risk factors
  - *H. pylori* infection
  - Dietary: high-salt diet, nitrosamine food content from fermenting/smoking process
  - Tobacco and alcohol exposure
  - Gastroesophageal reflux, obesity
  - Chronic gastritis
- Protective factors: diet rich in fruit and vegetables, refrigeration of food, exposure to vitamin C and other carotenoids
- Genetic predisposition (most gastric cancers are sporadic, 3%–5% associated with inherited cancer syndrome):
  - Hereditary diffuse gastric cancer (HDGC), germline truncating mutations in *CDH1*, which encodes for the protein E-cadherin (autosomal dominant).
    - Average age onset 37 with risk of developing gastric cancer by age 80: 67% for men and 83% for women
    - Prophylactic gastrectomy recommended for patients aged 18 to 40.
  - Lynch syndrome, deficiencies of mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2* autosomal dominant)
    - Third most common cancer associated with Lynch syndrome after colorectal and endometrial with 1% to 13% risk of developing gastric cancer

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- Juvenile polyposis syndrome (JPS) (*SMAD4*, *BMPR1A*; autosomal dominant)
- Peutz–Jeghers syndrome (*STK11*; autosomal dominant)
- Familial adenomatous polyposis (*APC*; autosomal dominant)

SIGNS AND SYMPTOMS

1. At what stages do gastric cancers present at diagnosis?

Stage at Diagnosis		Five-Year Survival
Localized	23%	62%
Locally advanced	32%	27%
Distant metastatic	34%	3%

STAGING

1. What is required in the staging workup for gastric cancer?

- CT scans of the abdomen and pelvis provide staging, which determines treatment and prognosis but results in understaging.
- PET/CT has lower sensitivity missing mucinous lesions with low fluorodeoxyglucose (FDG) uptake but greater specificity and accuracy rate in preoperative staging (useful in conjunction with CT scan).
- Esophagogastroduodenoscopy (EGD) is critical to visualize the tumor, evaluate its location and extent, and obtain tissue biopsy.
- Endoscopic ultrasound (EUS) is indicated to determine depth of tumor invasion (T stage) and regional nodal status, especially in early stage disease.

2. What determines tumor, node, and metastasis (TNM) staging for gastric cancer staged?

TABLE 24.1 ■ TNM Staging Classification for Gastric Cancer

Primary Tumor (T)	
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	T1a invades lamina propria, muscularis mucosae, T1b submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	T4a tumor invades serosa (visceral peritoneum), T4b invades adjacent structures
Regional Lymph Nodes (N)	
N1	One to two regional lymph nodes
N2	Three to six regional lymph nodes
N3	N3a seven to 15 regional lymph nodes, N3b 16 or more regional lymph nodes

(*continued*)

TABLE 24.1 ■ TNM Staging Classification for Gastric Cancer (*continued*)

Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Source: Adapted from Edge S, Byrd DR, Compton CC, et al. eds. *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer-Verlag; 2017.

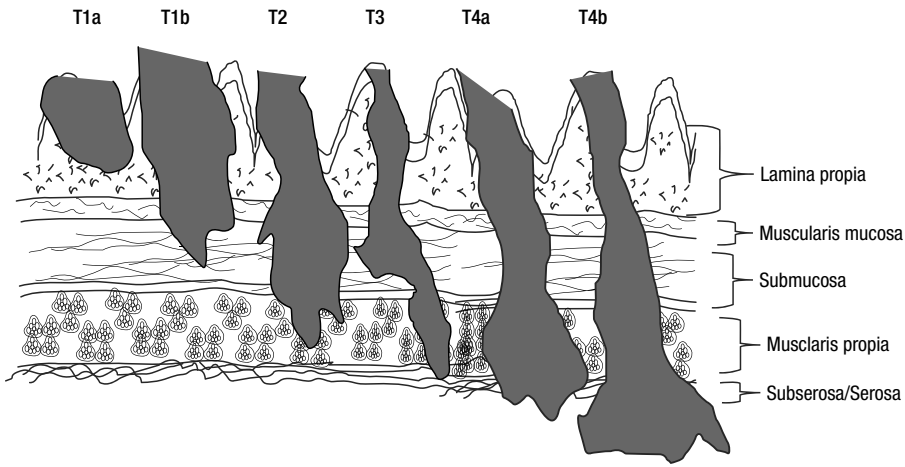

FIGURE 24.1 ■ Primary tumor staging.

3. What are the clinical and pathologic staging criteria for gastric cancer?

TABLE 24.2 ■ TNM Staging Classification for Gastric Cancer

	cTNM	**pTNM**
Stage 0 (M 0)	Tis N0	Tis N0 M0
Stage I (M 0)	T1–2 N0	A T1 N 0 B T1 N1 or T0 N1
Stage IIA(M 0)	T1–2 N 1–3	T1 N2, T2N1, T3 N0
Stage IIB (M 0)	T3–4a N0	T1 N3a, T2 N2, T3 N1, T4a N0
Stage III (M 0)	T3–4a N1–3	A: T2 N3a, T3 N2, T4a N2 T4b N0 B: T1–2 N3b, T3–4a N3a, T4b N1–2 C: T3–4a N3b, T4b N3a-b
Stage IVA	T4b M0	
Stage IVB	Any TN M1	Any TN M1

TNM, tumor, node, and metastasis.

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4. What is the definition of locally advances versus metastatic gastric cancer and how does it affect treatment?

In clinical settings, the classification most used is based on the potential for resection and evidence for extent of disease, thus dividing patients into resectable, locally advanced unresectable, and metastatic gastric cancer (Figure 24.2).

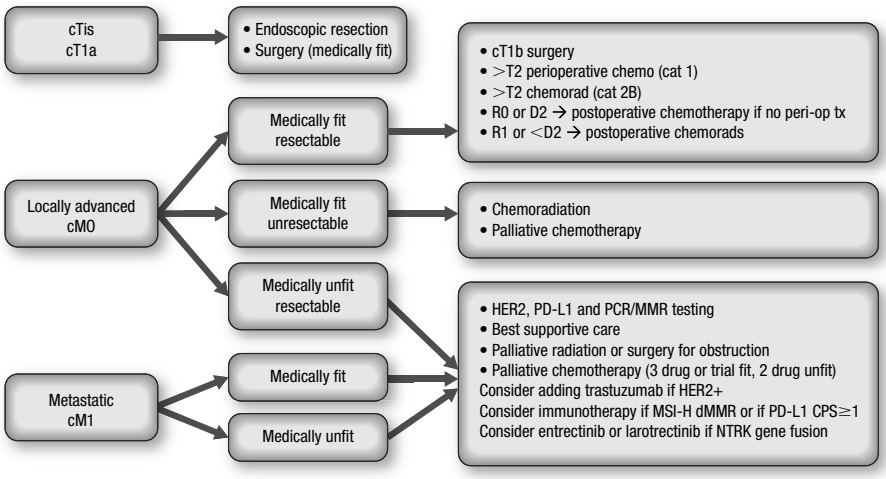

FIGURE 24.2 ■ Schematic algorithm for the treatment of gastric cancer.

DIAGNOSIS

1. What biomarkers are predictive and prognostic in gastric cancer and when do you test for them?

- The following testing should be done for all patients with metastatic gastric cancer:
  - HER2 status
  - Microsatellite instability (MSI) status by polymerase chain reaction (PCR) or mismatch repair (MMR) protein status by immunohistochemistry (IHC)
  - Programmed death cell ligand (PD-L1) expression
  - Tumor mutational burden (TMB ≥10)
  - Neurotrophic tropomyosin-related kinase (NTRK) gene fusions
- HER2 status (determined by IHC or HercepTest and fluorescence in situ hybridization [FISH])
  - HER2+ Positive status requires a score of 3+ by IHC or 2+ by IHC and HER2:CEP17 ration ≥2 or average HER2 copy number ≥6 by FISH.
  - Not prognostic, but predicative. Patients with HER2+ metastatic gastric cancer should be considered for the addition of trastuzumab to chemotherapy regimen in the first line setting.
- MSI-H (BAT25, BAT26, MONO27, NR21, NR24) by PCR or dMMR (MLH1, MSH2, MSH6, PMS2) by IHC
  - MSI-H status requires ≥30% markers exhibiting instability or more than two of five MSI-H instability
  - dMMR status requires loss of one or more of the MMR proteins by IHC

- Patients with MSI-H or dMMR metastatic gastric cancer who progressed through first-line therapy are candidates for pembrolizumab in the second-line setting.

- PD-L1 by number of PD-L1 staining cells in formalin fixed paraffin embedded (FFPE) tumor tissues
  - Combined positive score (CPS) ≥1 considered positive
  - Patients with CPS ≥1 metastatic gastric cancer who progressed through two prior lines of therapy are candidates for pembrolizumab in the third-line setting
- NTRK1, NTRK2, and NTRK3 gene fusions by next-generation sequencing (NGS)
  - Patients with NTRK fusions within metastatic gastric cancer are candidates for entrectinib or larotrectinib in the third-line or greater setting.
- Tumor mutational burden
  - TMB ≥10 candidates for pembrolizumab in the third-line setting

2. What are the clinical and pathologic subtypes of gastric cancer?

- Classification of the types of gastric cancer (see Table 24.3)
  - Anatomic location in the stomach and Lauren classification of the histological pattern
    - Cardia: involves the GEJ versus noncardia: located in the corporal or the antral area.
  - Intestinal forms rudimentary glands arising intestinal metaplasia due to chronic gastritis versus diffuse cells fail to form any recognizable structures, contain signet ring cells sometimes with interstitial mucin.

TABLE 24.3 ■ Classification of Gastric Cancer

	Cardiac GEJ	Noncardiac Intestinal	Noncardiac Diffuse
Epidemiology	Incidence increasing in Western countries	Incidence decreasing worldwide	Incidence stable
Biology	Possible link with HER2 biology	Lynch syndrome related	*CDH1* mutations, loss of E-cadherin
Risk factors	■ GERD ■ Obesity	■ *Helicobacter pylori* infection ■ Tobacco/alcohol ■ Salt intake ■ Poor fruit/vegetable diet	No clear relation to classical risk factors
Pathology		Stepwise progression: ■ Chronic gastritis ■ Intestinal metaplasia ■ Dysplasia	No precursor lesion ■ Signet ring cells ■ Interstitial mucin
HER2 status	32% GEJ	18% gastric cancer 32% intestinal	6% diffuse

GEJ, gastroesophageal junction; GERD, gastroesophageal reflux disease.

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TREATMENT

As noted in Figure 24.2, it is clinically useful to describe gastric cancers as locally advanced and resectable, locally advanced and unresectable, and metastatic. The following section describes the treatment for resectable, locally advanced unresectable, and metastatic gastric cancer.

1. What are the principles of surgical treatment for resectable gastric cancer?

- Medically fit patients with resectable T1b or higher and any N should receive surgery with lymph node dissection
  - Surgical treatment is aimed at curative resection although complete resection is sometimes not possible.
  - R0: no cancer at resection margins, R1: microscopic residual cancer R2: macroscopic residual cancer
- Extent of gastric luminal resection depends on location of the tumor and histologic subtype
  - Proximal: proximal subtotal gastrectomy for well- or moderately differentiated tumors that arise within the GEJ
  - Distal: total gastrectomy or a distal subtotal gastrectomy
  - Poorly differentiated tumors, those associated with Barrett's esophagus, and those extending into the esophagus: total gastrectomy with partial esophagectomy and a Roux-en-Y reconstruction
- Extent of the lymph node dissection
  - Continues to be debated, Western countries: standard is a modified D2 dissection, achieving the goal of removing at least 16 lymph nodes (see Figure 24.3)
  - D1: lymph nodes along greater and lesser omentum
  - D2: D1 dissection plus left gastric, common hepatic, splenic artery lymph nodes
  - D2 dissections offer a survival advantage over D1 dissections

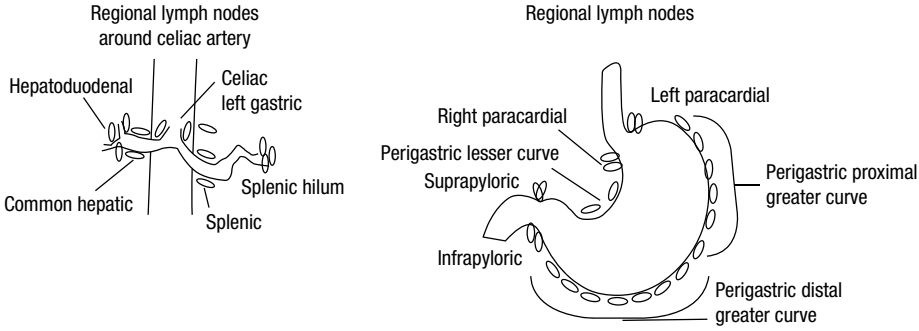

FIGURE 24.3 ■ Regional lymph nodes.

2. What is the role of combined modality therapy in resectable gastric cancer in a medically fit patient?

- Patients with T1b may receive surgery alone.
- Perioperative chemotherapy is a category 1 recommendation for medically fit patients with resectable T2 or higher, any N gastric cancer.

- 5-Fluorouracil (5-FU), leucovorin, oxaliplatin, docetaxel (FLOT) for four cycles pre- and four cycles postoperatively: Phase II/III FLOT4 trial compared FLOT to epirubicin, cisplatin, 5-fluorouracil (ECF) with superior overall survival (OS) in patients with good functional status
- 5-FU and oxaliplatin (FOLFOX) for patients that cannot tolerate FLOT
- ECF for three cycles pre- and three cycles postoperatively: MAGIC phase 3 trial compared demonstrated OS with ECF versus surgery alone. No longer a National Comprehensive Cancer Network (NCCN) recommendation.

- Preoperative chemoradiation is not recommended
- Postoperative chemoradiation with infusional 5-FU or oral capecitabine for the following patients based on Intergroup 0116 clinical trial that demonstrated improved 5-year OS
  - R0 resection that include T3–T4 Any N
  - Lymph node positive patients receiving less than a D2 resection without prior chemoradiation
  - For all patients after a R1 or R2 with residual disease at the margins
- Postoperative chemotherapy (for patients who did not receive preoperative therapy)
  - Capecitabine and oxaliplatin: CLASSIC phase III clinical trial in Japan in patients with stage II or IIB gastric cancer after curative gastrectomy with D2 lymph node dissection with 5-year OS 78% versus 69%.
  - FOLFOX

3. How do you treat patients with locally advanced unresectable gastric cancer who are medically fit?

- Chemoradiation
  - FOLFOX or 5-FU plus cisplatin and radiation: data extrapolated from esophageal carcinoma based on phase III clinical trial with FOLFOX or 5-FU plus cisplatin with radiation demonstrating similar survival in patients with or without surgery.
  - Restaging after treatment to determine if the patient is a surgical candidate based on response to therapy.

4. What is the first-line therapy in unfit patients with resectable or unresectable localized disease or patients with recurrent/metastatic gastric cancer?

- Patients should have their tumor tested for MSI, MMR, TMB PD-L1, HER2, and NTRK gene fusions
- Chemotherapy
  - Systemic therapy results better OS than best supportive care and combination chemotherapy results in superior OS compared to single agent.
  - Two-drug regimens can be considered in those patients who are unfit or low performance status.
    - Fluoropyrimidine (5-FU or capecitabine) plus oxaliplatin or cisplatin: phase III clinical trial FOLFOX versus 5-FU and cisplatin with similar OS but lower toxicity in FOLFOX arm
    - Low dose capecitabine and oxaliplatin (40% dose reduction): better OS, lower toxicity in elderly, frail patients
    - 5-FU and irinotecan (FOLFIRI): phase III trial of FOLFIRI versus ECF resulted in lower toxicity for FOLFIRI with similar OS ~9.5 months

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- Three-drug regimens in patients with metastatic disease and high performance status.
  - Nivolumab plus FOLFOX or nivolumab plus capecitabine and oxaliplatin (CapeOX) in patients with PD-L1 CPS ≥5 and HER2 negative: checkmate 649 demonstrated OS benefit with the addition of nivolumab to chemotherapy.
  - Dose-modified docetaxel, 5-FU, and cisplatin: addition of docetaxel to 5-FU and cisplatin with OS benefit 19 versus 12 months
  - Docetaxel, 5-FU, and oxaliplatin: phase II trial with improved OS compared to docetaxel and oxaliplatin
- HER2-positive patients should receive trastuzumab added to fluoropyrimidine and platinum containing regimen based on phase 3 ToGA trial but not recommended in combination with an anthracycline containing regimen due to cardiotoxicity.

5. What are the palliative treatment options for gastrointestinal (GI) bleeding, obstruction, and pain in patients in advanced gastric cancer?

- Acute and chronic GI bleeding
  - Endoscopic therapy with injection, mechanical clipping, ablative can initially be effective be rebleeding is likely
  - Interventional radiology for embolization usually in some situations
  - External beam radiation therapy (EBRT) effective at managing acute and chronic bleeding
  - Proton pump inhibitors
- Obstruction
  - Goal to reduce nausea, vomiting, and resumption of oral diet
  - Surgery with bypass with high morality 25% to 50% but overall improved survival in select patients
  - Endoscopic luminal stent placement: systemic review demonstrated patients with a stent were more likely to tolerate oral intake with shorter hospital stays vs. gastrojejunostomy
  - Venting gastrostomy tube (G-tube) when no other option for alleviation of obstruction

6. What is the standard second- and third-line treatment of metastatic gastric cancer?

- There is no standard second-line therapy for advanced gastric cancer, and choice depends on prior therapy and performance status of the patient.
  - Ramucirumab (anti VEGFR2 antibody) + paclitaxel: RAINBOW, phase 3 trial
  - Ramucirumab alone: REGARD, phase 3 trial
  - Taxanes alone (paclitaxel, docetaxel)
- Third-line and subsequent therapy for advanced gastric cancer
  - Trifluridine (thymidine phosphorylase inhibitor) and tipiracil (thymidine phosphorylase inhibitor): phase III TAGS trial versus best supportive care with improved median OS by 2.1 months; side effects of neutropenia, anemia.
  - Entrectinib, larotrectinib (neurotrophic tropomyosin-related kinase tyrosine kinase inhibitor [NTRK–TKI] inhibitors): approved for use in patients with solid tumors harboring an NTRK fusion. Entrectinib major side effects of liver enzyme elevation and constipation. Larotrectinib major central nervous system (CNS) events.
  - Pembrolizumab in patients with PD-L1 CPS ≥1, MSI-H, dMMR, or TMB ≥10

QUESTIONS

1. A 30-year-old man with no significant past medical history undergoes multigene panel testing based on his family history and is found to have a germline truncating mutation in *CDH1*.

In addition to routine age-appropriate screening, which of the following would you also recommend to the patient?

A. CT abdomen/pelvis yearly
B. Check carcinoembryonic tumor marker and then follow every 3 months
C. Diagnostic laparoscopy
D. Prophylactic gastrectomy
E. Surveillance esophagogastroduodenoscopy (EGD) at age 35 and then every 5 years

2. A 58-year-old otherwise healthy man has a 6-month progressive course of episodic upper abdominal pain, weight loss, and early satiety prompting an esophagogastroduodenoscopy (EGD), which identifies a gastric cardiac mass that is biopsied and confirms adenocarcinoma. She has no medical comorbidities and is otherwise fit. Staging endoscopic ultrasound (EUS) reveals a T3 lesion, and PET scan shows no other evidence for systemic disease. Diagnostic laparoscopy is negative for disease.

What is the treatment of choice for this patient's malignancy?

A. Gastrectomy followed by adjuvant chemotherapy ± radiation
B. Perioperative chemotherapy + gastrectomy with lymph node dissection
C. Best supportive care
D. Radiation alone to the mass
E. Endoscopic resection of the mass

3. A 62-year-old woman presents with a large gastric body mass and evidence of peritoneal metastases and ascites on CT imaging. An esophagogastroduodenoscopy (EGD) with biopsy of the gastric mass was performed and confirmed adenocarcinoma. She has had a 10-lb weight loss over the past month from early satiety, but she can eat and drink, she cleans her house daily and cooks two meals a day, she walks up and down the stairs in her house several times a day. She presents to you to discuss further management and treatment.

Which of the following would you recommend?

A. No further testing/procedures are recommended and proceed with palliative chemotherapy
B. HER2/neu testing only on the biopsied tissue
C. Diagnostic paracentesis
D. Duodenal stent placement
E. HER2/neu, mismatch repair/microsatellite instability (MMR/MSI), tumor mutational burden, PD-L1 and NTRK fusion protein testing on the biopsied tissue

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4. A 52-year-old man presents with 15-lb unintentional weight loss, dark stools. Esophagogastroduodenoscopy (EGD) reveals a 2 cm mass in the gastric body with endoscopic ultrasound (EUS) demonstrating at T3 lesion. CT chest/abdomen/pelvis with suspicious lymph nodes along greater curvature and PET/CT negative for systemic disease. Diagnostic laparoscopy negative for disease. He undergoes a D2 total gastrectomy collecting 18 lymph nodes, four positive for gastric adenocarcinoma. Postoperative CT chest/abdomen/pelvis without metastatic disease.

What is the best next step in therapy?

A. Adjuvant chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF)
B. Postoperative chemoradiation with 5-fluorouracil (5-FU)-based regimen
C. Observation
D. Test for HER2/neu and add trastuzumab
E. Immunotherapy

5. A 68-year-old fit female was found to have metastatic HER2/neu-positive gastric cancer involving a mass in the antrum of the stomach, PET-avid gastric lymph nodules with several PET-avid bilateral lung and liver nodules. Liver, kidney function is normal. Echocardiogram with left ventricular ejection fraction (LVEF) 60%.

Which of the following treatment regimens would be appropriate for this patient?

A. Epirubicin, cisplatin, 5-fluorouracil (5-FU) (ECF) + trastuzumab
B. ECF
C. Cisplatin, 5-FU, trastuzumab
D. Infusional 5-FU alone
E. Cisplatin, 5-FU + trastuzumab and pertuzumab

6. A 55-year-old man with metastatic gastric cancer (HER2/neu-negative) was treated with 4 months of 5-FU and oxaliplatin (FOLFOX). Imaging reevaluation shows evidence of disease progression. He has otherwise tolerated therapy well.

Which of the following are options for second-line management of this patient?

A. Ramucirumab + paclitaxel
B. Ramucirumab alone
C. Paclitaxel alone
D. Irinotecan-based therapy
E. All of the above

ANSWERS

1. **D. Prophylactic gastrectomy**. This patient's family history along with germline truncating mutation in *CDH1* is consistent with hereditary diffuse gastric cancer (HDGC) syndrome. Prophylactic gastrectomy is recommended given the patient's high risk for developing diffuse gastric cancer (lifetime risk by age 80 for males, 67%, and for females, 83%), which often involves the stomach lining rather than presenting with visible ulcer/tumor. Baseline EGD with multiple random biopsies is recommended prior to prophylactic gastrectomy and also every 6 to 12 months in those patients who decide not to undergo prophylactic gastrectomy. The other choices are not indicated.

2. **B. Gastrectomy with multimodality therapy given perioperatively**. If the patient was unfit for surgery, definitive chemoradiation could be considered, but radiation alone to the mass would be insufficient. Endoscopic resection is not an option for this stage of malignancy.

3. **E. HER2/neu, MMR/MSI, tumor mutational burden, PD-L1 and NTRK fusion protein testing on the biopsied tissue.** For patients with advanced gastric cancer, targeted therapies are available.
   - Addition of trastuzumab to chemotherapy in HER2/neu-positive patients
   - Addition of nivolumab to chemotherapy in patients with PD-L1 ≥5 in the first-line setting.
   - In patients with MSI-H, TMB ≥10, dMMR, or PD-L1 CPS ≥1 pembrolizumab can be considered in the third-line setting.
   - In patients with NTRK fusion entrectinib or larotrectinib can be offered as therapy in the third-line or greater setting.

4. **B. Postoperative chemoradiation with 5-FU-based regimen.** Postoperative chemoradiation with infusional 5-FU or oral capecitabine based on Intergroup 0116 clinical trial that demonstrated improved 5-year OS.
   - Recommended for patients with
     - R0 resection that include T3–T4 any N
     - Lymph node–positive patients receiving less than a D2 resection without prior chemoradiation
     - For all patients after a R1 or R2 with residual disease at the margins.

5. **C. Cisplatin, 5-FU, trastuzumab.**
   - Based on phase 3 data, trastuzumab would be recommended in this patient given the HER2/neu-positive status.
   - Unlike breast cancer, there is no evidence for use of combination HER2-directed therapies in metastatic gastric cancer.

6. **E. All of the above.** All of the choices are appropriate second-line treatment options. Therapy choice ultimately depends on the anticipated toxicities and patient preferences.

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25 Colon Cancer

Stephanie J. Hoffman and John C. Krauss

EPIDEMIOLOGY

1. Among all cancers, where does colorectal cancer (CRC) rank in terms of incidence and death?

- CRC is the second most common cause of cancer-related deaths, accounting for 8.4% of all cancer deaths. Lifetime incidence of CRC is about 5%.

2. What is the median overall survival of CRC?

- Overall, approximately one-third of patients diagnosed with colon cancer will die from the disease. Median survival: 48 months. Five-year survival for all CRC patients (all stages and sites) is 61%.

ETIOLOGY AND RISK FACTORS

1. What are the major molecular pathways of CRC development, and what molecular alterations do they involve?

TABLE 25.1 ■ Major Molecular Pathways of CRC Development

Pathways	Incidence	Relevant Mutations	Associated Inherited Disorders
Chromosomal instability	75%–80% sporadic colon cancers	*APC*, *KRAS*, *SMAD*, *p53* among others	FAP
CIMP	15% sporadic colon cancers	*CDKN2A*, *THBS1* (methylation of promotor regions)	
MSI high	3% of CRC	*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* (DNA repair enzymes)	Lynch syndrome or HNPCC

CIMP, CpG island methylator phenotype; CRC, colorectal cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; MSI, microsatellite instability.

2. What are the major risk factors associated with CRC?

TABLE 25.2 ■ Major Risk Factors Associated with CRC

Risk factors that impact CRC screening recommendations	Risk factors that *do not* impact CRC screening
■ Personal history of colon cancer, advanced adenomas (>1 cm, villous or tubulovillous histology and high-grade dysplasia)	■ Excessive alcohol use ■ Cigarette smoking

(*continued*)

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TABLE 25.2 ■ Major Risk Factors Associated with CRC (*continued*)

Risk factors that impact CRC screening recommendations	Risk factors that *do not* impact CRC screening
■ Inflammatory bowel disease (not including isolated proctitis or proctosigmoiditis) ■ First-degree relative(s) with colon cancer or advanced adenoma ■ Hereditary CRC syndromes: ■ HNPCC, FAP, MUTYH-associated polyposis (MAP), Cowden/Bannayan-Riley-Ruvalcaba syndrome (PTEN hamartoma syndrome) ■ Abdominal and pelvic radiation (higher risk of CRC 10 years posttreatment with at least 30 Gy to abdomen) ■ Age (>90% CRC occurs in individuals older than 50)	■ Obesity ■ Race (higher incidence and mortality in African-Americans) ■ Sex (CRC more common in men than women)

CRC, colorectal cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; MAP, MUTYH-associated polyposis; PTEN, phosphatase and tensin homolog.

SCREENING

1. Screening for CRC is recommended to begin at what age?

- For the average-risk patient, start screening at age 50 years.
- Family history of CRC or advanced adenoma: colonoscopy 10 years prior to the age of earliest occurrence, or beginning at age 40 years (whichever comes first), if an affected first-degree relative is <60 years old at diagnosis or if CRC or advanced adenomas are present in more than two first-degree relatives.

2. What clinical workup is recommended for patients who develop CRC before age 50?

- The tumor should be assessed for expression of mismatch repair proteins and or microsatellite status (MSI status). If the tumor is MSI high, or mismatch repair protein deficient, referral to a genetic counselor with germline mutational assessment of DNA or mismatch repair genes (*MLH1, MSH2, MSH6*, and *PMS2*).
- Additional germline mutational assessment, for example, of the *APC* or *MYH* genes if the family history or patient's clinical presentation is suggestive for these mutations.

3. Until what age is screening recommended?

- Screening is recommended to be continued up to 10 years prior to a patient's life expectancy.

4. What are the acceptable tests for screening and at what intervals should they be performed?

TABLE 25.3 ■ Screening Tests and Recommended Testing Intervals for CRC

Screening Test	Interval
Colonoscopy	10 y
Flexible sigmoidoscopy	5 y

(*continued*)

TABLE 25.3 ■ Screening Tests and Recommended Testing Intervals for CRC (*continued*)

Screening Test	Interval
FOBT	Yearly
FIT	Yearly
Fecal DNA testing	1–2 y

CRC, colorectal cancer; FIT, fecal immunochemical testing; FOBT, fecal occult blood testing.

PREVENTION

1. What lifestyle modifications and interventions reduce the risk of CRC?

TABLE 25.4 ■ Lifestyle Modifications/Interventions that Reduce CRC Risk

Lifestyle Modifications/Interventions that Reduce CRC Risk	
■ Daily aspirin	■ Reduced intake of red meat and fatty foods.
■ Postmenopausal estrogen and progesterone hormone replacement therapy	■ Diets rich in folate, fiber, calcium, vitamin D, magnesium, garlic and omega-3 fatty acids
■ Increased physical activity	
■ Polypectomy with adenoma removal	

CRC, colorectal cancer.

PATHOLOGY

1. What are the major subtypes of CRC?

TABLE 25.5 ■ Major Subtypes of CRC

Adenocarcinoma CK20, CDX2 (+), (90% of CRC)	Carcinoma	Other
Mucinous (produces extracellular mucin ≥50% tumor mass, dissects through tumor wall, increased risk of local spread, associated with ≥1 MMR gene deficiencies	Adenosquamous Squamous cell Spindle cell Undifferentiated	Non-Hodgkin Lymphoma (especially mantle cell) NETs
Nongland forming: ■ **Signet-ring cell:** ≥50% of tumor composed of cells with intracellular mucin displacing nucleus. Aggressive with high risk of intramural spread and peritoneal carcinomatosis ■ **Medullary:** large eosinophilic, polygonal cells growing in solid sheets with heavy infiltration of small lymphocytes. Characterized by high degree of MSI		

CRC, colorectal cancer; MSI, microsatellite instability; NET, neuroendocrine tumor.

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2. How is CRC graded?

- Based on degree of well-formed glands. Tumors are low grade (grade 1 or 2) if >50% of the tumor has well-formed glands and high grade (grade 3) if less.

3. How are appendiceal tumors classified?

- About 50% of appendiceal tumors will be low-grade neuroendocrine tumors (NETs).
- "Goblet cell carcinoids" are adenocarcinomas with some neuroendocrine differentiation. Considerable disagreement exists about this histologic type, but in general they should be treated like adenocarcinomas.
- Adenocarcinoma
- Signet ring carcinomas
- Appendiceal mucinous neoplasms are rare, and do not have an agreed upon classification, and have a variable malignant potential.

SIGNS AND SYMPTOMS

1. What are some of the most common clinical presentations of CRC?

- Gross or occult blood in stool
- Alterations in bowel habits, including constipation, cramping, or diarrhea
- Abdominal pain or discomfort
- Obstruction
- Decreased appetite, early satiety, weight loss, and fatigue
- Iron-deficiency anemia secondary to blood loss

DIAGNOSTIC WORKUP

1. What is the most accurate mode of diagnosis of CRC?

- Colonoscopy is the most accurate mode of diagnosis since it permits direct visualization and biopsy of a suspected lesion.

PROGNOSTIC AND RISK FACTORS

1. What are the poor prognostic factors related to CRC?

TABLE 25.6 ■ Poor Prognostic Factors for Stage II and III CRC

Poor Prognostic Factors Associated With CRC		
■ Elevated CEA	■ Increased depth of tumor invasion through intestinal wall (pT4)	■ <12 lymph nodes resected with surgical removal of CRC
■ Absence of microsatellite instability	■ Irregular tumor border	■ Positive surgical margins (circumferential, radial)
■ Presence of *KRAS*, *NRAS* or *BRAF* mutations	■ Poorly differentiated histology	■ Clinical bowel perforation or obstruction
	■ Lymphovascular and/or perineural invasion	
	■ Minimal tumor regression after preoperative treatment for rectal carcinomas	

CEA, carcinoembryonic antigen; CRC, colorectal cancer.

STAGING

TABLE 25.7 ■ Staging for Colon Cancer

Stage	Description
0	Carcinoma in situ; disease restricted to the intraepithelial glandular basement membrane or the intramucosal lamina propria without nodal or distal metastases
I	Tumor restricted to the submucosa or muscularis propria without nodal or distal metastases
II	Tumor penetrates beyond the muscularis propria to the pericolorectal tissue, to the surface of the visceral peritoneum or directly to other organs or structures without nodal or distal metastases
III	Any tumor with nodal metastases, or extranodal tumor deposits in fat, but without distant metastases
IV	Any tumor associated with distant metastases

GENERAL TREATMENT PRINCIPLES COLON CANCER

1. What are the general principles of treatment of locoregional colon cancer?

- Locoregional disease is managed surgically with curative intent (stages I–III).
- Chemotherapy with FOLFOX or CAPOX is recommended for all stage III patients (regional nodal disease) and selected high-risk stage II patients.

2. What are the general treatment principles of locoregional rectal cancer?

- The upper limit of the rectum is generally recognized as 15 cm from the anal verge by endoscopy, by the peritoneal reflection by MRI and intraoperatively. The radial and craniocaudal expansion and contraction of the rectum depending on stool loading and distension make it difficult to determine the precise distal extent of tumors in the upper third of the rectum, the rectosigmoid junction, and the lower sigmoid colon.
- All patients with polyps greater than 10 mm, and rectal cancer, and rectosigmoid cancers by a center that has a multidisciplinary team of surgery, medical oncology, radiation oncology, pathology, and radiology.
- T1 rectal cancers can be usually managed by transanal excision.
- Definitive management of T2 rectal cancers in abdominal perineal resection, while select low-risk T2 cancers can be managed by transanal excision.
- T3/T4 and node positive rectal cancers are managed with chemotherapy, radiation therapy, and surgery. The authors have adopted the total neoadjuvant approach in all medically fit patients, with systemic chemotherapy (FOLFOX or CAPOX) followed by capecitabine or infusional 5-fluorouracil (5-FU) + radiation being delivered before definitive surgery.

3. What are the general principles of the treatment of metastatic CRC?

- In selected stage IV patients with oligo metastatic disease (generally less than 3–5 metastatic sites in the lung and/or liver), long-term survival can be achieved with metastasectomy, in combination with preoperative or postoperative chemotherapy.

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- For patients with inoperable metastatic CRC, chemotherapy is palliative with treatment objectives limited to improving overall survival and quality of life. (a) Patients with perforation of their tumor or colonic obstruction need a palliative fecal diversion or tumor resection. (b) Patients with bleeding primary tumors, without bowel obstruction or perforation, should be treated with systemic chemotherapy without resection of the primary tumor. Combination chemotherapy is recommended for fit patients as first-line therapy in metastatic CRC as it helps obtain sufficient primary tumor control to permit a prolonged treatment course.

4. What are the frequently employed chemotherapy agents and regimens for the treatment of CRC?

TABLE 25.8 ■ Chemotherapy Agents and Regimens Used for CRC Treatment

Single Agents	Combination Regimens
5-FU (5-FU)/leucovorin Capecitabine Oxaliplatin (not active as a single agent) Irinotecan Trifluridine-tipiracil	FOLFOX (5-FU/leucovorin/oxaliplatin) FOLFIRI (5-FU/leucovorin/irinotecan) FOLFOXIRI (5-FU/leucovorin/oxaliplatin/irinotecan) CAPOX (capecitabine/oxaliplatin)

5-FU, 5-fluorouracil.

5. What are the targeted agents that are currently employed in the treatment of CRC?

TABLE 25.9 ■ Targeted Agents Used for CRC Treatment

Drug Name	Drug Type	Mechanism of Action
Bevacizumab	Humanized monoclonal antibody	Targets VEGF-A (ligand for VEGFR-1 and 2)
Ramucirumab	Human monoclonal antibody	Directed against VEGFR-2
Cetuximab	Chimeric mouse/human antibody	Targets EGFR. KRAS/NRAS wild type patients.
Panitumumab	Human monoclonal antibody	Targets EGFR. KRAS/NRAS wild type patients.
Aflibercept	Fusion protein with VEGF-1 and 2 receptors linked to Fc portion of human IgG1	Prevents VEGF-A,B and PGF from binding their respective receptors
Trastuzumab	Humanized monoclonal antibody	Targets extracellular domain of human epidermal growth factor receptor 2 protein, HER2. HER2 amplified, RAS/BRAF wild type patients.

(*continued*)

TABLE 25.9 ■ Targeted Agents Used for CRC Treatment (*continued*)

Drug Name	Drug Type	Mechanism of Action
Pertuzumab	Humanized monoclonal antibody	Targets extracellular dimerization domain of HER2. HER2 amplified, RAS/BRAF wild type patients.
Lapatinib	Tyrosine kinase inhibitor	Oral inhibitor of intracellular tyrosine kinase domains of EGFR and HER2. HER2 amplified, RAS/BRAF wild type patients.
Encorafenib	Kinase inhibitor	Oral kinase inhibitor targeting *BRAF* activating mutations. *BRAF* activating mutation positive patients.
Regorafenib	Kinase inhibitor	Oral inhibitor of angiogenic tyrosine kinases

VEGFR, vascular endothelial growth factor.

6. Prior to the use of cetuximab or panitumumab in any regimen, what testing must be performed?

- The tumor must be tested for mutations in exons 2 (codon 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146) in *KRAS* and *NRAS*, as mutations confer resistance to anti- epidermal growth factor receptor (EGFR) therapy.

7. How are appendiceal tumors managed?

- If a low-grade NET of the appendix is less than or equal to 2 cm, and completely resected with negative margins, the cure rate is 100%. If the tumor is greater than 2 cm, or positive margins, then a right hemicolectomy to obtain a negative margin and assesses local lymph node status.
- Goblet cell adenocarcinoma and signet ring histologies should be treated as colonic adenocarcinoma.
- Low-grade appendiceal mucinous neoplasms can be resected and observed. Low-grade appendiceal mucinous neoplasms with peritoneal metastases are treated with either primary resection or peritoneal resection with heated peritoneal chemotherapy (HiPEC) or FOLFOX followed by HiPEC

Principles of Colorectal Polyp Management

1. Which polyp has the greatest malignant potential?

- Adenomatous sessile polyps

2. What is the recommended therapy for a pedunculated or sessile polyp with pathological evidence of invasive cancer?

- Colonoscopy with complete assessment of colon and rectum with marking of the cancerous polyp site.
- For a pedunculated polyp or sessile polyp that is low grade, has a clear margin by greater than 1 mm, and is without lymphovascular or venous invasion, colonoscopic resection and surveillance can be performed. Surgical bowel resection should be performed for polyps that contain high grade carcinoma, for polyps with carcinoma involving or within 1 mm of the surgical margin, or have lymphovascular or venous invasion.

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Principles of Resectable CRC Management

Preoperative Workup for Resectable Disease

1. What is the recommended preoperative workup for a resectable CRC?

- Colonoscopy with complete assessment of the colon, a complete blood count, a comprehensive metabolic panel, a carcinoembryonic antigen (CEA), and a CT scan of the chest, abdomen, and pelvis.
- For a rectal cancer, a surgeon performed endoscopy, and a pelvic MRI (rectal cancer specific protocol), or if MRI not available, an endorectal ultrasound.

General Surgical Principles

1. What is the general surgical approach for a patient with resectable colon cancer?

TABLE 25.10 ■ Surgical Approaches for Resectable Colorectal Cancer by Tumor Location

Tumor Location	Surgery
Colon proximal to rectum	Partial colectomy with resection of primary tumor, adjoining mesentery, and regional lymph nodes, including those lymph nodes at the origin of the feeding blood vessel
Proximal two-thirds of rectum	Low anterior resection (spares anal sphincter)
Distal one-third of rectum with invasion of anal sphincter	APR with total mesorectal excision (permanent colostomy)
Distal small rectal tumors (T0, T1 or select T2 <3 cm)	Local transanal excision without resection of mesentery or lymph nodes

APR, abdominoperineal resection.

General Principles of Neoadjuvant and Adjuvant Therapies for resectable CRC

1. With regard to neoadjuvant and adjuvant therapies, which are considered for the management of CRC?

- Both neoadjuvant and adjuvant therapies may be employed in the management of locally advanced colon and rectal cancer.

2. What regimen is the standard of care for the neoadjuvant and adjuvant treatment of CRC?

- FOLFOX
- CAPOX
- Single-agent capecitabine or 5-FU/leucovorin for patients unable to receive oxaliplatin.

3. Are targeted agents employed in adjuvant regimens?

- No. Targeted agents are reserved for treatment of advanced-stage metastatic disease and are ***not*** used in adjuvant and neoadjuvant regimens.

4. Is irinotecan employed as part of an adjuvant or neoadjuvant regimen?

- No. Irinotecan is reserved for treatment of advanced-stage metastatic disease and is ***not*** used in adjuvant or neoadjuvant regimens.

TABLE 25.11 ■ Treatment of Colon Cancer by Stage

Stage	Treatment
0-I or II with MSI-H/dMMR	Surgical resection followed by surveillance.
II (early stage/T3, no high risk features, MSS/pMMR)	Surgical resection followed by surveillance versus adjuvant capecitabine or 5-FU/leucovorin
II (T3 with high risk features or late stage/T4, MSS/pMMR)	Surgical resection followed by adjuvant capecitabine or 5-FU/leucovorin vs. adjuvant FOLFOX or CAPOX vs. surveillance
III (T1–3, N1, low risk)	Surgical resection followed by [preferred] adjuvant CAPOX (3 months) or FOLFOX (6 months) vs. 6 months of capecitabine or 5-FU
III (T4, N1–2; T any, N2, high risk)	Surgical resection followed by [preferred] adjuvant CAPOX (6 months) or FOLFOX (6 months) vs. 6 months of capecitabine or 5-FU

5-FU, 5-fluorouracil; dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; pMMR, proficient mismatch repair.

TREATMENT BY STAGE

TABLE 25.12 ■ Treatment of Rectal Cancer by Stage

Stage	Treatment
0-I (Tis-T2; N0, M0)	Surgical resection (transanal excision if feasible otherwise APR or tumor-specific LAR if high-risk features or T2) followed by surveillance.
Locally advanced:	
II (T3-T4b; N0; M0) III (any; N1-2b; M0)	Three phases of treatment include concurrent chemotherapy and radiation, surgery, and chemotherapy. Traditionally, the order of treatment has been chemoradiation followed by surgical resection (total mesorectal excision) followed by adjuvant chemotherapy with eight doses of FOLFOX or six doses of CAPOX. The authors and others are using total neoadjuvant therapy (systemic chemotherapy followed by chemoradiation then surgical resection).

LAR, long-acting release.

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Principles of Stage IV CRC Management

Therapeutic Options for Advanced-Stage Disease

1. What are the chemotherapeutic options for the treatment of advanced-stage CRC disease?

TABLE 25.13 ■ Chemotherapeutic Options for Advanced-Stage CRC

LINE OF THERAPY	CHEMOTHERAPY
Initial, patient appropriate for intensive therapy	■ FOLFOX ± bevacizumab ■ CAPOX ± bevacizumab ■ FOLFOX + (cetuximab or panitumumab) (KRAS/NRAS/BRAF WT and left sided tumors only) ■ FOLFIRI ± bevacizumab ■ FOLFIRI + (cetuximab or panitumumab) (KRAS/NRAS/BRAF WT and left sided tumors only) ■ FOLFOXIRI ± bevacizumab ■ Pembrolizumab or nivolumab (dMMR/MSI-H only) ■ Nivolumab + ipilimumab (dMMR/MSI-H only)
Initial, patient not appropriate for intensive therapy	■ Infusional 5-FU + leucovorin ± bevacizumab ■ Capecitabine ± bevacizumab ■ (Cetuximab or panitumumab) (KRAS/NRAS/BRAF WT and left sided tumors only) ■ Cetuximab/encorafenib (BRAF activating mutations only) ■ Nivolumab or pembrolizumab (dMMR/MSI-H only) ■ Trastuzumab + (pertuzumab or lapatinib) (HER2-amplified and RAS/BRAF WT)
Subsequent therapy for fit patients	■ If FOLFOX backbone used first, use FOLFIRI ■ If FOLFIRI backbone used first, use FOLFOX ■ Once progression on Oxaliplatin, Irinotecan, and 5-FU, add EGFR inhibitor (cetuximab or panitumumab) for KRAS/NRAS/BRAF wild type tumors ■ Once progression on either FOLFOX or FOLFIRI, use cetuximab/encorafenib for BRAF activating mutation positive tumors (typically V600E positive) ■ Regorafenib or trifluorouradine/tipiracil once progression on oxaliplatin, irinotecan, 5-FU, angiogenesis inhibitor, EGFR inhibitor (if appropriate), HER2neu inhibitor (if appropriate)

5-FU, 5-fluorouracil; dMMR, deficient mismatch repair; MSI-H, microsatellite instability high.

Approaches to the Assessment of Synchronous Metastatic CRC

1. What does the workup for synchronous metastatic CRC entail?

- CT scan of chest, abdomen, and pelvis
- Colonoscopy in the case of potentially resectable disease
- Complete blood count (CBC), and chemistries, and CEA
- *KRAS*, *NRAS*, and *BRAF* mutational assessment, HER2neu expression by immunochemistry or predicted overexpression by next generation sequencing
- Mismatch repair protein deficiency assessment

- PET/CT in the case of potentially resectable metastatic disease
- MRI of the liver, in the setting of potentially resectable metastatic disease

Principles of Management of Synchronous Metastatic Colon Cancer

1. If a patient has resectable either hepatic or pulmonary only synchronous metastatic colon cancer, what is the appropriate management?

- Colectomy with simultaneous or later metastasectomy followed by 6 months of FOLFOX or CAPOX adjuvant therapy. Capecitabine or 5-FU/leucovorin can be considered in patients who cannot tolerate combination treatment
- Neoadjuvant FOLFOX, FOLFOXIRI, or CAPOX with or without a targeted agent followed by resection of primary and metastatic disease. A total of 6 months of perioperative chemotherapy is recommended
- Colectomy followed by FOLFOX, or CAPOX with or without a targeted agent followed by metastatectomy. A total of 6 months of chemotherapy is recommended.

2. If a patient has unresectable either hepatic or pulmonary only synchronous metastatic colon cancer, what is the appropriate management?

- Neoadjuvant FOLFOX, FOLFIRI, FOLFOXIRI, or CAPOX with or without a targeted agent followed by reassessment of resectability.
- If the metastatic disease remains unresectable, chemotherapy for advanced or metastatic disease is appropriate.
- If the metastatic disease becomes resectable, then colectomy and metastatectomy followed by chemotherapy for advanced or metastatic disease is appropriate.

3. If a patient has synchronous abdominal or peritoneal colon cancer metastases, what is the appropriate management?

- If the metastases are not causing bowel obstruction, systemic therapy for advanced or metastatic disease is appropriate.
- If the metastases are causing bowel obstruction, then relief of obstruction with surgery or stenting is recommended to alleviate the obstruction, followed by systemic therapy for metastatic disease.

Principles of Management of Synchronous Metastatic Rectal Cancer

1. What is the appropriate management of advanced-stage IV rectal cancer with resectable synchronous metastatic disease?

- FOLFOX, or CAPOX ± targeted agent, followed by radiation therapy plus 5-FU *or* radiation therapy plus capecitabine, after which simultaneous or sequential primary tumor resection and metastasectomy is performed
- Radiation therapy plus 5-FU *or* radiation therapy plus capecitabine followed by simultaneous *or* sequential primary tumor resection and metastatectomy with adjuvant FOLFOX, CAPOX, capecitabine ± targeted agent
- For a T1 or T2 primary tumor with metastatic disease, simultaneous or sequential tumor resection and metastasectomy followed by adjuvant therapy with FOLFOX, or CAPOX.

2. What is the appropriate management of advanced-stage IV rectal cancer with unresectable synchronous metastatic disease?

- If the primary tumor causes bowel obstruction, then relieve obstruction with colostomy, stent placement, or palliative resection.
- Systemic FOLFOX, FOLFIRI, or CAPOX with or without a targeted agent followed by reassessment of resectability.

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- If the metastatic disease remains unresectable, chemotherapy for advanced or metastatic disease is appropriate.
- If the metastatic disease becomes resectable, then primary tumor resection with simultaneous or later metastasectomy. If the patient is rendered free of cancer, chemotherapy can be stopped once a total of 6 months of FOLFOX or CAPOX has been administered.

Principles of Recurrent CRC Management

Approaches to the Assessment of Recurrent Disease

1. Following treatment for CRC, what is the recommended surveillance regimen?

- Clinical assessment every 3 to 6 months for the initial 24 months following treatment, and every 6 months thereafter for an additional 36 months
- For patients with tumor invading beyond the muscularis propria (i.e., T2), CEA measurements at each interval of clinical assessment
- For patients with a high risk of recurrence, CT scans of chest, abdomen, and pelvis each year for the first 36 to 60 months posttreatment.
- Colonoscopy at 1 year; or at 3 to 6 months' posttreatment if no preoperative colonoscopy was performed. Thereafter, colonoscopy should be repeated in 3 years followed by interval colonoscopies every 5 years. If an advanced adenoma at the time of follow-up colonoscopy, then, repeat colonoscopy is recommended at a 1-year interval.

2. If CEA levels suggest disease recurrence during surveillance, what is the indicated workup?

- Clinical assessment including physical exam, colonoscopy, and imaging studies with CT scan of chest, abdomen, and pelvis, MRI of the liver is useful in patients with hepatic steatosis, and PET/CT can be useful if other testing does not reveal cancer.

3. If workup following elevation of CEA does not confirm disease recurrence, what further assessment is indicated?

- Continue to follow the CEA level, and if it remains elevated, repeat imaging studies in 3 months' time.

Principles of Management of Recurrent Rectal Cancer at an Anastomotic Site

1. What is the appropriate management of resectable recurrent rectal cancer at an anastomotic site?

- Concurrent radiation therapy with 5-FU or capecitabine followed by surgical resection if feasible *and* if no prior radiation therapy was administered

2. What is the appropriate management of unresectable recurrent rectal cancer at an anastomotic site?

- Concurrent radiation therapy with 5-FU or capecitabine, or systemic chemotherapy.

Principles of Management of Metachronous Metastatic CRC

1. If a patient develops metachronous resectable metastatic CRC, what is the appropriate management?

- Resection is preferred over other local therapies. If previous oxaliplatin chemotherapy, then observation, if no previous oxaliplatin chemotherapy, then FOLFOX or CAPOX.

2. What is the appropriate management of unresectable, metachronous metastatic CRC?

- If the patient *has* received FOLFOX within the previous 12 months, FOLFIRI ± a targeted agent is recommended followed by periodic reevaluation for resectability.
- If the patient *has not* received FOLFOX within the previous 12 months, chemotherapy for advanced or metastatic colon cancer is appropriate followed by periodic reevaluation for resectability.
- If the disease becomes resectable, resection is performed, and if less than 6 months of systemic therapy prior to resection, additional systemic therapy for metastatic CRC can be administered.

QUESTIONS

1. A 35-year-old man admitted with melena was found to have a single tumor in the right colon with remainder of the colonoscopy unremarkable. Staging CT scans of chest/abdomen/pelvis were negative for metastatic disease and he underwent complete surgical resection of the tumor and regional lymph nodes with pathologic stage T3N0 (0/15 lymph nodes negative). The tumor was found to be mismatch repair (MMR) intact and microsatellite instability (MSI) stable.

Based on these findings, how would you counsel the patient regarding follow-up testing?

A. Counsel the patient that he has Lynch syndrome since his tumor is MMR intact and his family members should seek genetic testing
B. Instruct him to have his next colonoscopy in 5 years
C. Recommend that the patient's family members start colon cancer screening when they reach his current age (35 years old)
D. Recommend that the patient be referred to genetic counselling for extended testing for heritable causes of colon cancer

2. A 65-year-old woman presents with a newly diagnosed adenocarcinoma of the anterior wall of her distal rectum after undergoing flexible sigmoidoscopy for a several week history of hematochezia. MRI of the pelvis showed the tumor invades the bladder wall and is without evidence of lymphadenopathy. CT chest, abdomen, and pelvis are unremarkable for metastatic disease. She lives alone, and meets with friends during a 2-mile walk done three times a week.

How should her disease be treated?

A. Capecitabine chemoradiation, followed by FOLFOX followed by surgery
B. Capecitabine and oxaliplatin chemoradiation, followed by FOLFOX, followed by surgery
C. Capecitabine chemoradiation followed by surgery
D. Capecitabine and oxaliplatin chemoradiation followed by surgery

3. A 60-year-old man with newly diagnosed metastatic adenocarcinoma of the sigmoid colon to his lungs and liver presents to discuss starting therapy. His tumor is expresses mismatch repair proteins, and is wild type for KRAS, NRAS, and BRAF on next-generation sequencing. He has a history

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of myocardial infarction (MI) about 2 months ago and an ischemic stroke approximately 2 years ago without residual neurologic deficits. He continues to exercise about three times a week and works full time as a professor at a local college.

What regimen is most appropriate as first-line therapy?

A. FOLFOX + bevacizumab
B. FOLFOX + cetuximab
C. FOLFIRI
D. Regorafenib

4. A 55-year-old man who recently underwent resection of a stage III colon cancer presents to discuss the next step in his care. His tumor expresses mismatch repair proteins.

What adjuvant therapy would you recommend for him?

A. FOLFIRI
B. FOLFOX
C. FOLFOX + bevacizumab
D. FOLFOX + cetuximab

5. A 70-year-old man recently underwent colectomy of his stage I adenocarcinoma of the descending colon. He is doing well, with no complaints and his carcinoembryonic antigen (CEA) has become undetectable. His last colonoscopy was just prior to his diagnosis.

What follow-up should he expect in the next year?

A. History and physical every 3 to 6 months along with a CEA, and CT chest, abdomen, and pelvis every 6 months
B. Colonoscopy in 1 year
C. History and physical every 6 months along with CT chest, abdomen, and pelvis
D. History and physical every 3 to 6 months along with a CEA, and PET/CT every 6 months

6. A 63-year-old woman presents with iron-deficiency anemia, and is found to have an adenocarcinoma in the ascending colon and a single metastatic lesion in the periphery of the right hepatic lobe measuring 3 cm in diameter. By CT criteria, primary tumor and regional lymph nodes are surgically resectable. The tumor expresses mismatch repair proteins and is *KRAS G12d* mutant on next-generation sequencing.

What is the next step in management?

A. Synchronous resection of primary colon tumor and en bloc resection of regional lymph nodes, along with metastasectomy of liver lesion followed by 6 months of adjuvant FOLFOX
B. FOLFOX + bevacizumab until disease progression or intolerance
C. Neoadjuvant FOLFOX + cetuximab, followed by resection of the liver lesion and primary colon tumor with en bloc resection of regional lymph nodes
D. FOLFOX + cetuximab until disease progression or intolerance

ANSWERS

1. **D. Recommend that the patient be referred to genetic counseling for extended testing for heritable causes of colon cancer.** As tumor testing did not reveal mismatch repair protein deficiency or microsatellite instability, the patient does not have Lynch syndrome. However, due to his young age, cancer genetics referral for extended testing of heritable causes of colon cancer is indicated.

2. **A. Capecitabine chemoradiation, followed by FOLFOX, followed by surgery.** Locally advanced rectal cancer is treated with trimodal therapy: chemoradiation, chemotherapy, and surgery. Administering chemotherapy prior to chemoradiation, followed by surgery or chemoradiation, followed by surgery and then chemotherapy are both acceptable treatment options in the National Comprehensive Cancer Network (NCCN) guidelines. However, given the location of the patient's tumor, total neoadjuvant therapy (chemoradiation using capecitabine followed by chemotherapy prior to surgery) is preferable in order to allow for the greatest possibility of organ-preserving surgical resection. Delivering the chemotherapy prior to surgery increases the likelihood of completing the entire course of chemotherapy. Less than half of patients who undergo chemotherapy after surgery receive full dose and/or course due to morbidity of the prior therapy and surgery. Capecitabine used in combination with oxaliplatin for chemosensitization during radiation therapy has been shown to increase toxicity and lead to worse surgical outcomes without improving disease response.

3. **B. FOLFOX + cetuximab**. The patient's recent MI is a contraindication to the use of bevacizumab, given the increased risk of arterial thrombi with its use. Regorafenib is not recommended as first-line chemotherapy for metastatic colon cancer, and is approved for patients who have progressed after therapy with oxaliplatin, irinotecan, 5-fluorouracil (5-FU), bevacizumab, and cetuximab (if KRAS and NRAS wild type on next-generation sequencing).

4. **B. FOLFOX.** FOLFOX is the only approved adjuvant chemotherapy for stage III disease of the options provided. Targeted agents (i.e., bevacizumab and cetuximab) and irinotecan have no role in adjuvant therapy for stage III disease.

5. **B. Colonoscopy in 1 year.** As per National Comprehensive Cancer Network (NCCN) guidelines for surveillance after diagnosis and resection of stage I colon cancer, follow-up should entail a colonoscopy 1 year after preoperative colonoscopy. If this is negative, then a colonoscopy is repeated in 3 years.

6. **A. Synchronous resection of primary colon tumor and en bloc resection of regional lymph nodes, along with metastatectomy of liver lesion followed by 6 months of adjuvant FOLFOX.** This patient has a single metastatic lesion in her liver that is easily resectable as it is small, on the periphery, and localized to a single hepatic lobe. Therefore, the best management would be resection of both the metastatic liver lesion and

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her primary tumor, followed by adjuvant FOLFOX to target micrometastatic disease. Options B and D do not offer the possibility of resection of either the primary tumor or metastatic deposit, which would be inappropriate given the long-term survival benefit of metastasectomy. Furthermore, the patient is *KRAS* mutant and therefore would not benefit from therapy with cetuximab.

26 Anal Cancer

Stephanie J. Hoffman and John C. Krauss

EPIDEMIOLOGY

1. How common is anal cancer?

- About 8,000 cases are diagnosed annually in the United States, making up around 2.5% of all gastrointestinal cancers.

ETIOLOGY AND RISK FACTORS

1. What are the common risk factors for anal cancer?

- Seventy percent to 80% are associated with human papillomavirus (HPV), most commonly with HPV-16 and HPV-18.
- Risk factors include history of receptive anal intercourse; history of sexually transmitted diseases; lifetime sexual partners; immunosuppression (such as immunosuppressive medication use after solid organ transplantation or for autoimmune disorders, HIV infection); history of cervical, vulvar, or vaginal cancer; and smoking.

SCREENING AND PREVENTION

1. Who should be screened for anal cancer?

- There are no national guidelines, but some recommend screening men who have sex with men, HIV-positive women with history of cervical or vulvar dysplasia, and anyone with history of anal or genital condyloma.
- Screening is performed by rectal exam and a cytological smear of the anus (anal Pap smear). Optimal frequency of screening has not been defined. Abnormal cytology is followed up by high-resolution anoscopy with acetic acid application and biopsy if needed.

PATHOLOGY

1. What is intraepithelial neoplasia (AIN)?

- Anal AIN is a premalignant lesion for anal cancer.
- It is more commonly found in high-risk patients (e.g., human papillomavirus [HPV]/HIV infections, postorgan transplantation patients, and men who have sex with men) and development is driven by HPV infection

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2. What are the common tumor histologies of anal cancer?

TABLE 26.1 ■ Common Tumor Histologies of Anal Cancer

Tumor Type	Treatment Strategy
Transitional/anal squamous cell carcinoma (most common)	Treated as primary anal squamous cell carcinoma
Primary rectal squamous cell carcinoma	
Perianal skin cancer	Treated as primary skin squamous cell carcinoma if distinctly separate from the anal verge
Anal adenocarcinoma	Treated as rectal adenocarcinoma

SIGNS AND SYMPTOMS

1. What is the most common presentation of anal cancer?

- Bleeding (45%)
- Rectal pain or sensation of a foreign body (30%)
- Asymptomatic (20%)
- Anorectal condyloma history is present in 50% of homosexual men and <30% in heterosexual men and women who develop squamous cell cancer (SCC) of the anus.

DIAGNOSTIC WORKUP

1. What staging modalities/studies are indicated?

- Physical exam (including digital rectal examination [DRE], inguinal lymph node [LN] evaluation with consideration for biopsy if suspicious for involvement)
- CT chest/ abdomen/pelvis
- MRI pelvis if tumor not well visualized on CT scan
- Anoscopy with biopsy of the mass
- PET/CT may be considered, but does not replace diagnostic CT
- HIV testing (if status unknown)
- Females: pelvic exam and cervical cancer screening

STAGING

1. What are the anatomic boundaries of the anal canal?

- The histologically defined anal canal (lined by squamous mucosa) is limited by dentate line proximally and anal verge distally.

2. Define the staging for anal cancer.

TABLE 26.2 ■ Staging for Anal Cancer

AJCC UICC 2017 Stage	Definition
I	Primary tumor no more than 2 cm in greatest dimension and no LN involvement
IIA	Primary tumor >2 cm but ≤5 cm, without adjacent organ invasion (such as vagina, bladder, or urethra) and without LN involvement
IIB	Primary tumor >5 cm without adjacent organ invasion (such as vagina, bladder, or urethra) and without lymph node involvement
IIIA	Primary tumor ≤5 cm without adjacent organ invasion (such as vagina, bladder, or urethra) and with inguinal, mesorectal or iliac LN involvement
IIIB	Primary tumor with adjacent organ invasion (such as vagina, bladder, or urethra) and without inguinal, mesorectal and iliac LN involvement
IIIC	Tumor >5 cm or invading adjacent organs with inguinal, mesorectal, external iliac, or internal iliac LN involvement
IV	Presence of distant metastatic disease

AJCC, American Joint Committee on Cancer; LN, lymph node; UICC, International Union Against Cancer.

GENERAL PRINCIPLES OF TREATMENT

1. What treatment modalities are employed for all squamous cell carcinomas of the anus?

- Concurrent chemotherapy and radiation. Advanced-stage tumors (T3 or T4 and node positive disease) or residual T2 disease after 45 Gy, receive an additional boost of 10 to 14 Gy.

2. When is the response to first-line chemoradiotherapy assessed?

- In the United States, disease response is assessed at 8 to 12 weeks posttreatment, with decision to proceed with surgery for persistent disease at reassessment at 26 weeks.

3. When is the role of surgery for treatment of anal carcinomas?

- Squamous cell carcinomas: surgery is only utilized in the setting of persistent disease at 26 weeks after first-line radiotherapy + concurrent 5-fluorouracil (5-FU) and mitomycin C.

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TREATMENT BY STAGE

TABLE 26.3 ■ Anal Cancer Treatment by Stage

Stage	Treatment
Precursor lesions	
LG-AIN	Surveillance every 6 months vs. consider treatment with topical trichloroacetic or bichloroacetic acid, topical 5-FU, intraanal imiquimod, or anoscopy-guided electrocautery ablation
HG-AIN	Treatment as above vs. anoscopic surveillance every 3–4 months
I-IIIB	CRT with concurrent mitomycin C in combination with either 5-FU or capecitabine

5-FU, 5-fluorouracil; CRT, chemoradiation.

1. What clinical scenarios may constitute reasons to deviate from the above?

- Stage I tumors can be treated with attenuated therapy, such as 5-FU with concurrent radiotherapy (RT). This should be considered especially in older patients since morbidity of standard treatment may be very significant,
- Salvage surgical resection can be performed in cases of chemoradiation (CRT) failure.
- Anal margin cancers at most 2 cm in size with negative LNs (i.e., stage I) may be treated with wide local excision.

2. How should surveillance be conducted following primary treatment?

- DRE at 8 to 12 weeks following CRT.
- If complete response, follow up every 3 to 6 months, including DRE, anoscopy, LN exam, for 5 years, and annual CT chest, abdomen, and pelvis for the first 3 years if primary tumor was over 5 cm or LNs were positive.
- If partial response or stable primary tumor after CRT, repeat exam in 1 month. If decreasing, follow-up every 3 to 6 months, with DRE, anoscopy, LN exam for 5 years, and annual CT chest, abdomen, and pelvis for the first 3 years.
- Suspected progression on DRE should be confirmed by anoscopy with biopsies and restaging CT.

3. How should locoregional failure after primary therapy be managed?

- Locoregional failure rates after CRT are up to 30%.
- Abdominoperineal resection (APR) with very select cases being eligible for anal sphincter-sparing surgery.
- Recurrent or persistent disease in the LNs is managed primarily with inguinal lymphadenectomy if not candidates for additional radiation.
- Follow-up with clinical exam, including LN exam, every 3 to 6 months for 5 years, and annual CT chest, abdomen, and pelvis for the first 3 years.

4. What are the most common sites of distant metastatic disease?

- Liver, lungs, and extra pelvic LNs

5. **What are the first-line treatment options for metastatic (stage IV) anal cancer?**
   - Carboplatin and paclitaxel ± RT (preferred)
   - Cisplatin and 5-FU-based chemotherapy ± RT
   - FOLFOX ± RT

6. **What treatments can be considered for subsequent therapy of metastatic anal cancer?**
   - Nivolumab or pembrolizumab

7. **What is the treatment for oligo metastatic disease to the liver or paraaortic LN?**
   - Surgical resection of isolated liver metastases can be considered.
   - Chemoradiotherapy can be used to treat recurrent disease limited to the paraaortic LNs.

QUESTIONS

1. A 56-year-old man with a history of anal condyloma presents with intermittent bright red blood per rectum for the past 3 months. He reports no other symptoms such as weight loss, fever, chills, change in bowel habits, and night sweats.

   What workup would you recommend?
   A. Anoscopy with biopsy if a mass is seen
   B. A rectal exam with referral to gastrointestinal (GI) for hemorrhoid banding versus hemorrhoidectomy
   C. Colonoscopy to rule out a colonic lesion
   D. Digital rectal examination (DRE) and anoscopy with biopsy of any suspicious lesions in addition to inguinal lymph node exam

2. A 45-year-old HIV-positive man presents with newly diagnosed stage II squamous cell carcinoma of the anus. He is not compliant with his antiretroviral medications, and his last CD4 count a month ago was less than 200. He is asymptomatic, with the anal cancer having been found incidentally on digital rectal examination (DRE) when he decided to reestablish care with his infectious disease physician. He has no history of opportunistic infections.

   What treatment would you recommend for him?
   A. Concurrent 5-fluorouracil (5-FU), mitomycin, and radiation therapy without dose reduction, but with weekly monitoring of blood counts and close monitoring for treatment-related toxicity
   B. Concurrent 5-FU and radiation, omitting mitomycin due to concern for cytopenias
   C. Concurrent 5-FU, mitomycin, and radiation therapy with 25% dose reduction of mitomycin
   D. Radiation alone as he is too high risk for chemotherapy toxicity with his CD4 count <200

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3. A 65-year-old man presents with stage IIIB squamous cell carcinoma of the anus.

What factors are most predictive of his prognosis?

A. Nodal involvement and presence of angiolymphatic invasion
B. Tumor size, nodal involvement, and angiolymphatic invasion
C. Tumor size, nodal involvement, perineural and angiolymphatic invasion
D. Tumor size and nodal involvement

4. A 65-year-old man completed chemoradiation (CRT) for stage IIIB squamous cell carcinoma of the anus 12 months ago. He has since recovered and states his life has returned to normal. CT of his abdomen and pelvis today reveals a 2 cm tumor in his right hepatic lobe on the periphery. This was biopsied and pathology confirmed metastatic squamous cell carcinoma. He lives on his own, is able to shop for groceries, complete all of his household chores, and manage his finances. He continues to work full time as an office manager.

How would you treat him?

A. Refer to a surgeon for consideration of resection of a single small lesion within his liver once locoregional recurrence and chest metastases have been ruled out
B. Start systemic chemotherapy with 5-fluorouracil (5-FU) and mitomycin
C. Observe as he is asymptomatic and all therapy would be palliative in intent
D. Start systemic chemotherapy with 5-FU and cisplatin

5. A 58-year-old man presents for follow-up 12 weeks after completing chemoradiotherapy (CRT) with 5-fluorouracil (5-FU) and mitomycin for stage III primary anal squamous cell carcinoma. His tumor is unchanged in size compared to evaluation immediately after CRT completion. He is very anxious, and asks whether this means he will have to undergo surgery.

You tell him the following:

A. The need for surgery cannot be determined at this time as tumor regression after CRT has been shown to continue for up to 26 weeks post treatment completion
B. The stable tumor size is concerning for persistent disease, and you will refer him to a surgeon for an abdominoperineal resection
C. That you would like to biopsy the tumor to confirm that it is persistent disease
D. You'll refer him to a surgeon for local resection

6. A 55-year-old man presented with a 3-week history of foreign object sensation in his anus. Anoscopy revealed an anal tumor and biopsy of the lesion confirmed squamous cell carcinoma. PET/CT revealed fluorodeoxyglucose (FDG) avid left-sided perirectal adenopathy within the mesorectal fascia and external inguinal lymph adenopathy, the largest measuring 1.5 cm. There was no evidence of distant metastases.

How would you complete his staging workup?

A. Core needle biopsy a left external inguinal lymph node to confirm metastatic disease
B. No further workup is necessary
C. Complete surgical staging with abdominoperineal resection with total mesorectal excision (TME)
D. Biopsy perirectal lymph node

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ANSWERS

1. **D. DRE and anoscopy with biopsy of any suspicious lesions in addition to inguinal lymph node exam.** Patients with a history of anal condyloma are at high risk for human papillomavirus (HPV) + squamous cell carcinoma of the anus. In a patient with this history presenting with rectal bleeding, which is the most common symptom of anal carcinoma, workup for a possible anal carcinoma should be initiated. This includes DRE, anoscopy with biopsy of any suspicious lesions, and inguinal lymph node exam. If cancer is confirmed, further diagnostic imaging should be done to complete staging.

2. **A. Concurrent 5-FU, mitomycin, and radiation therapy without dose reduction, but with weekly monitoring of blood counts and close monitoring for treatment-related toxicity.** Although this man has uncontrolled HIV, he is young, otherwise healthy, and has never had complications from his disease. A CD4 count <200 alone is not an indication for modification of standard of care of his disease with chemoradiotherapy with 5-FU and mitomycin.

3. **D. Tumor size and nodal involvement.** Tumor size and nodal involvement are the most important prognostic factors for anal carcinoma. Five-year overall survival ranges from 70% for stage I disease, to 59% for stage II, 41% for stage III, and 19% for stage IV disease. Perineural and angiolymphatic invasions are markers of high-risk histology, which is not part of the main prognostic factors for anal carcinoma.

4. **A. Refer to a surgeon for consideration of resection of a single small lesion within his liver once locoregional recurrence and chest metastases have been ruled out.** This patient has metastatic disease limited to a small lesion within his right liver periphery, along with a preserved performance status, making him a good surgical candidate. While there are no prospective data to determine the optimal management of a patient with single lesion or oligo metastatic disease within the liver, a retrospective multicenter analysis suggests a subset of these patients may benefit from resection of isolated liver metastases.

5. **A. The need for surgery cannot be determined at this time as tumor regression after CRT has been shown to continue for up to 26 weeks post treatment completion.** The ACT II trial, in which 940 patients were randomized first to 5-FU with mitomycin or cisplatin and concurrent radiation, then randomized again to maintenance chemotherapy, assessed local disease responses at 11, 18, and 26 weeks. Analysis showed that 29% of those who were not in complete clinical response at 11 weeks did demonstrate complete clinical response at 26 weeks, supporting the view that anal squamous cell carcinoma continues to regress up to 26 weeks post completion of chemoradiotherapy.

6. **A. Core needle biopsy a left external inguinal lymph node to confirm metastatic disease.** Confirmation of metastatic disease within his lymph nodes should always be considered when it could result in upstaging a patient as it could impact prognosis and treatment. Since an inguinal lymph node is easily accessible for a needle biopsy, that would be the best next step in workup of his disease to complete his staging. Surgical staging has no role in anal squamous cell carcinoma.

27 Pancreatic and Biliary Cancers

Monica A. Patel and Mark M. Zalupski

EPIDEMIOLOGY

1. What are the typical features of pancreatic cancer at presentation?

- The majority of patients have unresectable or metastatic disease at diagnosis.
- Approximately two-thirds of exocrine pancreatic cancers are located in the head of the pancreas.

2. How are biliary cancers classified?

- Extrahepatic cholangiocarcinoma
  - Perihilar (Klatskin) tumors
  - Distal extrahepatic tumors
- Intrahepatic cholangiocarcinoma
- Gallbladder cancer

RISK FACTORS

1. What are the known risk factors for pancreatic cancer?

- Cigarette smoking
- Diabetes
- Obesity and lack of physical activity
- Hereditary risk factors include Li-Fraumeni (*TP53*), hereditary pancreatitis, Peutz–Jeghers syndrome (*STK11*), Lynch syndrome, familial atypical multiple-mole melanoma (FAMMM) syndrome (*CKDN2A*), *BRCA* mutations (*BRCA2*>*BRCA1*), *PALB2* mutations, and ataxia–telangiectasia-mutated (*ATM*) gene mutations

2. What are the known risk factors for biliary tract cancers?

- Gallstones
- Primary sclerosing cholangitis
- Chronic liver disease, including viral hepatitis and cirrhosis
- Genetic disorders, including Lynch syndrome, BRCA-associated protein 1 (BAP1) tumor predisposition syndrome, multiple biliary papillomatosis, and cystic fibrosis
- Infections, including parasitic infection with liver flukes

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STAGING

1. Define tumor, node, and metastasis (TNM) staging for pancreatic cancer.

Primary Tumor (T)	
T0	No evidence of primary tumor
Tis	Carcinoma in situ (includes PanIN with severe dysplasia)
T1	Tumor ≤2 cm
T2	Tumor >2 cm, ≤4 cm
T3	Tumor >4 cm
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
Regional Lymph Nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Stage	Description		
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1–3	N1	M0
III	T1–3	N2	M0
	T4	Any N	
IV	Any T	Any N	M1

Source: Adapted from the AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer-Verlag; 2017.

2. What are the important features for the staging of biliary malignancies?

- There are separate American Joint Committee on Cancer (AJCC) TNM staging systems for gallbladder cancer, intrahepatic bile duct tumors, perihilar bile duct tumors, and distal bile duct tumors.

DIAGNOSTIC CRITERIA

1. What are the histological subtypes of pancreatic cancer?

- Most cases arise from the ductal system of the exocrine pancreas and are classified as adenocarcinomas.

- Pancreatic neuroendocrine tumors (i.e., islet cell tumors) are much less common and may be associated with a variety of hormonal syndromes due to the secretion of insulin, glucagon, gastrin, and other neurohormonal substances.

2. What is the role of cancer antigen (CA) 19-9 in pancreatic and biliary cancers?

- CA 19-9 is elevated in a large majority of patients and the level relates to the extent of disease.
- Other malignancies and nonmalignant causes including cholangitis, cholelithiasis, and cirrhosis may also cause an elevated CA 19-9.

3. What imaging studies are used to diagnose pancreatic cancer?

- Triphasic CT is useful for identifying the presence of metastatic disease and for determining eligibility for resection.
- Endoscopic ultrasound (EUS) provides additional T and N staging, information on vascular invasion, and can be used to obtain a fine needle aspiration (FNA) for diagnosis.
- MRI may be helpful in cases where CT is nondiagnostic (e.g., isodense lesions)

4. What are the diagnostic considerations for biliary cancers?

- Diagnosis is often based on clinical presentation, serology (i.e., elevated CA 19-9), and radiographic findings (MRI is often useful).
- Endoscopic retrograde cholangiopancreatography (ERCP) can provide both anatomical information and cytologic/histologic diagnosis.

PROGNOSTIC FACTORS

1. What are unfavorable prognostic features?

- Poor prognostic factors include unresectable disease, advanced stage, poor performance status, and peritoneal disease.
- Poor prognostic factors for resected pancreatic and biliary tract cancers include ≥T2 stage, lymph node positive status, and R1 resection.

TREATMENT

1. How is surgically resectable pancreatic cancer best managed?

- Only 10% to 20% of patients have potentially resectable disease at diagnosis.
- A pancreaticoduodenectomy (Whipple procedure) involves removal of the pancreatic head along with the distal stomach, gallbladder, cystic and common bile ducts, duodenum, and proximal jejunum.
- For all patients who undergo resection without neoadjuvant therapy, 6 months of adjuvant therapy is recommended. This consists of either modified
  - FOLFIRINOX (5-fluorouracil [5-FU], irinotecan, oxaliplatin): preferred regimen (based on the PRODIGE-24 trial).
  - Gemcitabine and capecitabine
  - Gemcitabine alone with or without radiation
- Neoadjuvant chemotherapy ± radiation can be used for patients with potentially resectable or borderline resectable disease.
- *No* standard neoadjuvant chemotherapy regimen but FOLFIRINOX is preferred.

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2. How are patients with unresectable pancreatic cancer treated?

- Palliative chemotherapy is used for locally advanced or metastatic disease.
- For patients with *BRCA* or *PALB2* mutations: platinum-based chemotherapy regimen is preferred.
  - Good performance status: FOLFIRINOX is preferred.
  - FOLFOX (5-FU, oxaliplatin, leucovorin) can be considered.
  - *No* disease progression after at least 16 weeks of platinum-based chemotherapy: switch to maintenance therapy with PARP (poly ADP-ribose polymerase) inhibitor: Olaparib (based on the POLO trial)
- For all other untreated patients with a good performance status, preferred combination regimens are the following:
  - FOLFIRINOX
  - Gemcitabine + nab-paclitaxel.
- While gemcitabine + erlotinib is considered a treatment option, the absolute benefit of this regimen on survival is small.
- Other appropriate treatments include gemcitabine or fluoropyrimidines alone or in combination with other agents.
- Radiation concurrent with a fluoropyrimidine initially or following chemotherapy can be considered for locally advanced disease or for palliation in patients with metastatic disease with the benefit on overall survival unclear (LAP-07 trial)
- Supportive care for patients with poor performance status.

3. What is the optimal approach for localized biliary cancers?

- Complete surgical resection is the only curative option.
- Most patients found to have incidental cancer after cholecystectomy for presumed benign gallbladder disease should undergo additional surgery as many of these patients have residual disease in the liver and/or locoregional lymph nodes.
- Based on the Phase II SWOG S0809 trial, adjuvant therapy consisting of chemotherapy with gemcitabine + capecitabine followed by concurrent chemoradiation with capecitabine can be considered for resected extrahepatic cholangiocarcinoma or gallbladder carcinoma, especially for patients with high-risk disease features (≥T2, lymph node positive, R1 resection).
- Liver transplantation may be appropriate for highly selected patients with small central tumors.

4. What are the treatment options for advanced biliary malignancies?

- Gemcitabine and cisplatin was shown to be superior to single-agent gemcitabine in a phase 3 study of patients with advanced biliary cancers (ABC-02 trial).
- Gemcitabine or fluoropyrimidines combined or with another agent are also acceptable based on the performance status of the patient and anticipated toxicities.
- Regional therapies such as transarterial chemoembolization or radioembolization (using yttrium-90 or Y90) are options for some patients with intrahepatic cholangiocarcinoma.
- Chemotherapy with external beam radiation for locally advanced disease improves symptoms and may prolong survival.

SPECIAL CONSIDERATIONS

1. What are the common complications of pancreatic and biliary cancers?

- Venous thromboembolic disease is seen in 20% to 40% of patients with pancreatic cancer.
- Biliary obstruction with episodic cholangitis is often seen with pancreatic head or extrahepatic biliary tract tumors and is managed with biliary stent placement or palliative surgical intervention.
- Malabsorption due to pancreatic exocrine insufficiency can be managed with pancreatic enzyme replacement.
- Pain can be managed with opioid analgesics and celiac plexus neurolysis.

QUESTIONS

1. A 60-year-old male with no comorbidities underwent a pancreaticoduodenectomy for stage IIB pancreatic adenocarcinoma without complication 8 weeks ago. He is recovering well and is doing all his usual activities. He returns in follow-up for further management.

Which of the following would you recommend?

A. Observation alone
B. Adjuvant gemcitabine ± subsequent radiation
C. Obtain CA19-9 level to aid in deciding need for further therapy
D. FOLFIRINOX
E. Radiation therapy alone

2. A 69-year-old male with stage III chronic kidney disease and long-standing type 2 diabetes mellitus complicated by peripheral neuropathy is referred to your clinic with newly diagnosed stage IV pancreatic adenocarcinoma with a large pancreatic head mass and numerous liver and lung lesions. He has had a 40-lb weight loss over the past couple of months, becomes dyspneic with just walking a few feet, and is spending more than half of the day in bed. He now requires much assistance from his family for his activities of daily living (ADLs). He comes in a wheelchair accompanied by multiple family members regarding treatment options. He has not had any abdominal pain.

Which of the following would you recommend?

A. Gemcitabine alone
B. Gemcitabine + nab-paclitaxel
C. 5-fluorouracil (5-FU) alone
D. Radiation alone to the pancreatic mass
E. Hospice referral

3. A 61-year-old female with a germline *BRCA2* mutation is diagnosed with metastatic pancreas cancer involving the liver. She is treated with 6 months of systemic therapy with FOLFIRINOX, and interval imaging reveals a decrease in the size of her disease involving the pancreas and liver. She has grade 1 neuropathy related to oxaliplatin.

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Which of the following would you recommend for maintenance therapy?

A. Gemcitabine
B. Pembrolizumab
C. Durvalumab
D. Olaparib
E. None of the above

4. A 59-year-old male is found to have a 2 cm pancreatic tail mass, biopsy confirms adenocarcinoma. CT chest, abdomen, and pelvis are unremarkable are notable only for the pancreas mass but otherwise negative for distant/metastatic disease. Based on tumor board discussion, his disease is considered borderline resectable. He is referred to medical oncology to discuss his treatment options.

He meets with medical oncology and is determined to have an excellent performance status and no underlying neuropathy. He is very interested in aggressive treatment for his cancer.

Which of the following would you recommend prior to consideration of surgery?

A. Gemcitabine
B. Gemcitabine followed by radiation therapy
C. Concurrent chemoradiation with capecitabine
D. FOLFIRI (5-fluorouracil [5-FU], irinotecan, folinic acid) with or without radiation therapy
E. FOLFIRINOX (5-FU, irinotecan, oxaliplatin, folinic acid) with or without radiation therapy

5. A 65-year-old female presents with obstructive jaundice (total bilirubin 5.0) and is found to have a mass within the right lobe of the liver. CT of the chest, abdomen, and pelvis is obtained and reveals several other satellite lesions in the liver and concerning pulmonary nodules. Endoscopic retrograde cholangiopancreatography (ERCP) reveals compression of the right biliary system by the mass, and a metallic biliary stent is placed successfully, which appropriately relieves her obstruction. A biopsy of the mass is also obtained at the time of ERCP and shows adenocarcinoma, consistent with a biliary primary. The patient has no comorbidities and has an excellent performance status (Eastern Cooperative Oncology Group [ECOG] 0).

Which of the following would you recommend as initial treatment?

A. Gemcitabine + cisplatin
B. 5-Fluorouracil (5-FU) alone
C. Transarterial radioembolization (TARE) to the right lobe mass
D. Transarterial chemoembolization (TACE) to the right lobe mass
E. Stereotactic body radiation therapy (SBRT) to the right lobe mass

6. A 48-year-old male is diagnosed with metastatic pancreatic cancer. He has no comorbidities and has otherwise been healthy. His father was diagnosed with colon cancer at age 60, and his sister was diagnosed with uterine cancer at age 49. You are concerned for a familial cancer syndrome.

Which of the following genes is the most likely found to be altered in this patient?

A. *BRCA1*
B. *BRCA2*
C. *TP53*
D. *MSH2*
E. *STK11*

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ANSWERS

1. **D. FOLFIRINOX.** Adjuvant therapy is recommended in all patients who recover from operation and have an adequate performance status due to high risk of relapse with any stage of resected, invasive pancreatic cancer. For patients with a good performance status, FOLFIRINOX is the preferred regimen (based on the PRODIGE-24 trial). Observation could be considered if the patient declines adjuvant therapy. Radiation therapy alone would not reduce risk for systemic relapse, which is common in patients with pancreatic cancer.

2. **E. Hospice referral.** Best supportive care with hospice would be most appropriate in this patient with a poor performance status (Eastern Cooperative Oncology Group [ECOG] 3) whose anticipated benefits from systemic therapy are low and risks of toxicity from treatment are high. Radiation therapy for palliation could be considered if patient was symptomatic from his pancreatic lesion.

3. **D. Olaparib.** Given that she has a germline *BRCA2* mutation and has had a response to 6 months of FOLFIRINOX, maintenance therapy with olaparib, a poly ADP-ribose polymerase (PARP) inhibitor, should be considered. Based on the POLO trial, maintenance therapy with olaparib can be considered after at least 16 weeks of platinum-based chemotherapy as long as there is no disease progression. Since the patient has a response to FOLFIRINOX, gemcitabine would not be the best maintenance strategy at this time. In addition, immunotherapy (pembrolizumab, durvalumab) is not indicated as maintenance following FOLFIRINOX.

4. **E. FOLFIRINOX with or without radiation therapy.** This patient has borderline resectable pancreas cancer with an excellent performance status and no underlying neuropathy. As a result, neoadjuvant chemotherapy ± radiation should be recommended prior to consideration of surgery. Although there is no standard neoadjuvant chemotherapy regimen, FOLFIRINOX is favored for fit patients.

5. **A. Gemcitabine** + **cisplatin.** Systemic chemotherapy is the preferred therapy in this fit patient with metastatic cholangiocarcinoma. Gemcitabine + cisplatin is an option based on the phase 3 advanced biliary cancers (ABC-02) trial. Combination therapies are more effective than single agents alone and so preferred in those with good performance status. The last three choices allude to liver-directed therapies and could be options if the predominant disease was in the liver. In the patient's case with multiorgan involvement, systemic chemotherapy would be recommended initially.

6. **D. *MSH2*.** Lynch syndrome is raised based on the patient's diagnosis of pancreatic cancer, and the patient's family history of colon and uterine cancer. The other genes are implicated in other hereditary familial syndromes (*BRCA 1* and *2*—hereditary breast and ovarian cancer syndrome; *TP53*—Li–Fraumeni syndrome; *STK11*—Peutz–Jeghers syndrome), and are considerations but less likely based on the available family history.

28 Hepatocellular Carcinoma

Dempsey L. Hughes and Neehar D. Parikh

EPIDEMIOLOGY

Etiology and Risk Factors

1. What is the etiology of hepatocellular carcinoma (HCC)?

- HCC prevalence is most associated with hepatitis C virus (HCV) in the United States; primarily seen in Southeast Asia and sub-Saharan Africa, although rates are increasing in the United States and Europe due to increases in fatty liver disease-associated HCC.
- Primarily epithelial in origin, and typically (but not exclusively) occurs in the setting of chronic hepatocyte injury and fibrosis

2. What are the common risk factors for HCC?

- Toxins
  - Aflatoxin: mostly in patients with hepatitis B virus (HBV)
- Chronic liver disease
  - Chronic hepatitis infection: HBV, HCV. In the United States, HCV remains the driving force for increase in incidence, although HCC due to fatty liver disease and alcohol-related liver disease are increasing in incidence
  - Alcohol
  - Hereditary hemochromatosis
  - Alpha-1 antitrypsin deficiency
  - Primary biliary cirrhosis
  - Nonalcoholic fatty liver disease, including noncirrhotic fatty liver with HCC

3. What variant of HCC is more common in women, occurs at younger age, and is associated with a better prognosis?

- Fibrolamellar variant

STAGING

1. What is the staging for HCC?

- The tumor, node, and metastasis (TNM) staging system is not routinely utilized as it does not accurately reflect prognosis because of the significant competing risk of underlying liver disease.
- Factors that determine prognosis: performance status, hepatic function, and tumor burden, and these are best incorporated within the Barcelona Clinic Liver Cancer (BCLC) staging classification (see BCLC algorithm [Figure 28.2] listed under the section Prognostic Factors).

ALGRAWANY

SIGNS AND SYMPTOMS

1. What are the most common symptoms of HCC?

- Mostly asymptomatic in the early stage. However, for advanced stages, symptoms include
  - Upper abdominal pain, weight loss, generalized weakness, anorexia, and early satiety; emesis

2. What are the most common signs of HCC?

- For early and intermediate stage, there are no signs noted. For advanced stage
  - Hepatic bruit, hepatomegaly, ascites, jaundice, splenomegaly

3. What are the paraneoplastic syndromes associated with HCC?

- Extremely rare, but include
  - Hypercalcemia
  - Hypoglycemia
  - Erythrocytosis
  - Hypercholesterolemia
  - Dysfibrinogenemia
  - Carcinoid syndrome/diarrhea
  - Sexual changes (gynecomastia, testicular atrophy, precocious puberty)
  - Porphyria cutanea tarda

DIAGNOSTIC CRITERIA

1. What is the recommended algorithm for evaluating a liver nodule in a patient with risk factors for HCC?

- See Figure 28.1.

2. What serum markers are useful in the diagnosis of HCC?

- Alpha-fetoprotein (AFP) can be helpful in diagnosis, as well as surveillance and assessing response to treatment. However, AFP in isolation is not an adequate screening modality, as HCV itself can cause elevations in AFP.

3. What imaging studies are useful for diagnosing HCC?

- Ultrasound for surveillance in patients at risk (cirrhosis and certain populations with chronic hepatitis B)
- Contrast-enhanced multidetector CT or MRI—Liver Reporting and Data System (LIRADS) criteria used to objectively grade liver lesions in patients with liver nodules. HCC lesions are primarily fed by the hepatic artery, and therefore typically show the following enhancement pattern:
  - Arterial phase: HCC enhances more than surrounding normal liver tissue
  - Venous phase: HCC enhances less than surrounding liver, "washout period"
  - Delayed phase: persistent washout noted
- Approximately 15% of cases have atypical imaging appearance.
- Staging CT chest should be conducted once HCC is diagnosed.

4. When should the diagnosis be confirmed with liver nodule biopsy?

- When cross-sectional imaging does not meet the classic criteria of arterial enhancement and washout.

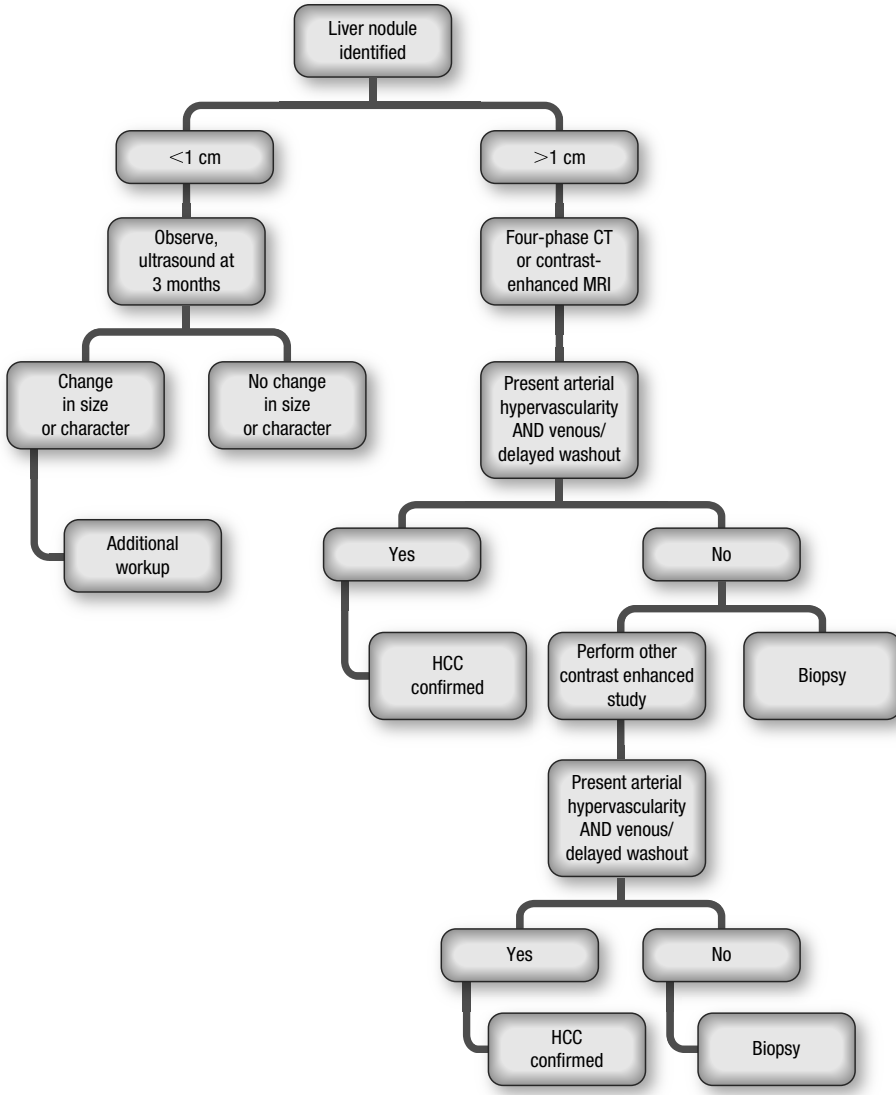

FIGURE 28.1 ■ Algorithm for evaluating a liver nodule in a patient with risk factors for hepatocellular carcinoma (HCC).

- Core biopsy preferred over fine needle aspiration (FNA).
- Risks of biopsy include bleeding (1%) and concern for needle tract seeding (<1%). False negative rate can be as high as 30%.
- Staining for CD34, CK7, glypican 3, HSP-70, and glutamine synthetase can help differentiate HCC from dysplastic lesions when HCC is not clear based on microscopy.

INDICATIONS FOR TREATMENT

1. What are the indications for therapy?

- A treatment modality is indicated in all cases that are not BCLC stage D

ALGRAWANY

PROGNOSTIC FACTORS

1. What are prognostic factors for HCC?

- Tumor extent (number/size of lesions), underlying liver function as classified by Child–Pugh, and performance status (Eastern Cooperative Oncology Group [ECOG] score)
- While multiple staging systems exist, including TNM, CLIP score, Hong Kong Liver Cancer Criteria, ITA.LI.CA staging system, and the MESIAH score, the BCLC staging system is the most widely accepted.

2. What is the Child–Pugh classification of severity of liver disease?

- An assessment of hepatic function, which is critical for stratification of patients with HCC

TABLE 28.1 ■ Child–Pugh Classification

	Number of Points Assigned		
Parameter	**1**	**2**	**3**
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (sec)	<4	4–6	>6
INR	<1.7	1.7–2.3	>2.3
Encephalopathy	None	Grades 1–2	Grades 3–4
Grade A: 5–6 points (early stage cirrhosis)			
Grade B: 7–9 points (intermediate-stage cirrhosis)			
Grade C: 10–15 points (advanced-stage cirrhosis)			

INR, international normalized ratio

3. What is the BCLC algorithm?

See Figure 28.2.

4. What is the survival rate based on BCLC classification?

- Stage 0 and stage A: 5-year survival 50% to 70%
- Stage B and stage C: 3-year survival 20% to 40% although this may be changing with the adoption of several new systemic therapies for HCC in recent years
- Stage D: 1-year survival 0% to 15%

TREATMENT

1. What surgical therapies are available for treatment of HCC?

- *Surgical resection*
  - Potentially curative, optimal treatment for HCC
  - Assessment of hepatic reserve is paramount for appropriate patient selection.
  - Ideal patient has solitary HCC confined to liver, no evidence of invasion into hepatic vasculature, no portal hypertension (platelet >100), and well-preserved hepatic function (bilirubin <1).

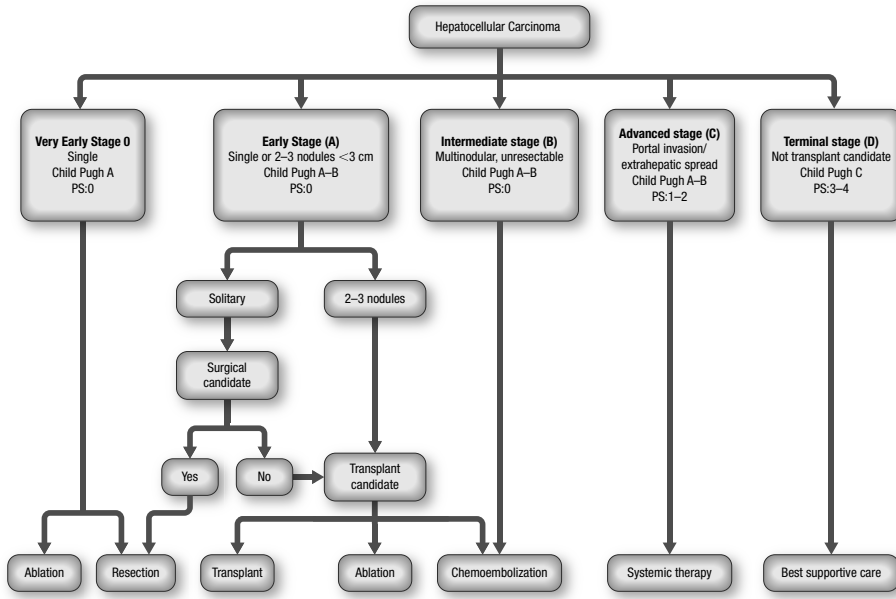

FIGURE 28.2 ■ The Barcelona clinic liver cancer algorithm.

- *Liver transplantation*
  - Primarily for patients with unresectable though early stage disease that is within Milan criteria (one tumor 2–5 cm in size or up to three tumors all less than 3 cm without vascular invasion or extrahepatic spread).
  - Limited by organ availability. Patients must otherwise be candidates for liver transplantation.

2. What liver-directed nonsurgical therapies are available for treatment of HCC (locoregional)?

- *Radiofrequency or microwave ablation*
  - For patients with disease confined to the liver who do not meet resectability criteria but are candidates for a liver-directed procedure, best outcomes are seen with tumors <3 to 4 cm in size.
  - Needle electrode delivers high-frequency alternating current that leads to frictional heating and subsequent tissue necrosis.
- Transarterial chemoembolization (TACE)
  - Injection of chemotherapeutic agent or drug-eluting microspheres into hepatic artery.
  - Commonly used as a bridging therapy prior to liver transplant, or as primary therapy for intermediate-stage HCC based on BCLC (about 60% of patients are at this stage).
- *External beam radiation*
  - No defined role and there are only case series to date. Although an emerging technology, there are no randomized-controlled trials (RCTs) comparing to other locoregional therapies.
- *Radioembolization*
  - Focal radiation by delivering radioactive isotopes (iodine-131, Lipiodol, or yttrium-90-tagged glass microspheres or resin) to tumor via hepatic artery.
  - Limited by lack of robust RCT data to support its use.

ALGRAWANY

3. What systemic therapies are available for treatment of HCC?

- *Immunotherapy*: First-line therapy for eligible patients is atezolizumab and bevacizumab every 3 weeks. This combination of an anti-programmed death cell ligand (PD-L1) monoclonal antibody plus an anti-vascular endothelial growth factor (VEGF) monoclonal antibody was shown to be superior to sorafenib in the IMBRAVE 150 phase III trial. In subsequent lines of therapy, nivolumab + ipilimumab, nivolumab, and pembrolizumab are approved for treatment of unresectable HCC, however, their use is not supported by phase III data.
- *Chemotherapy*: There are no data to support its use.
- *Molecular targeted therapy*
  - Several studies have shown a role for targeting EGFR/EGF (HER1), VEGF, and MEK/ERK pathways.
  - Sorafenib, a tyrosine kinase inhibitor (targets RAF kinase and VEGFR), was the standard of care monotherapy for patients with unresectable HCC, based

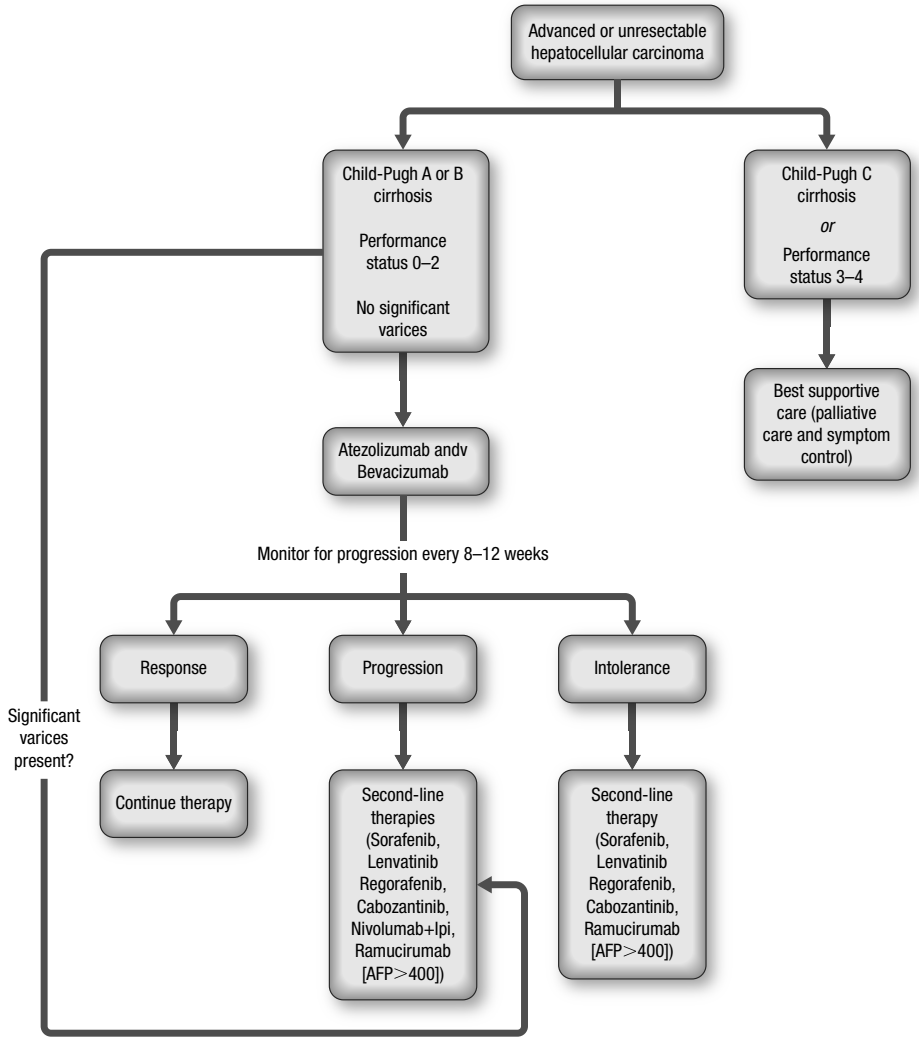

FIGURE 28.3 ■ Systemic therapies for hepatocellular carcinoma (HCC).

on SHARP trial (demonstrated overall survival benefit for sorafenib over supportive care alone).

- Lenvatinib was shown noninferior to sorafenib and is approved as a subsequent line of therapy based on data from the phase III REFLECT study.
- Regorafenib was superior to placebo in patients who progressed on sorafenib therapy in the phase III RESORCE trial and is approved in subsequent lines of therapy.
- Cabozantinib was superior to placebo in patients who progressed on first- or second-line therapy in the phase III COSMIC trial and is approved in subsequent lines of therapy.
- Ramucirumab, a monoclonal antibody to VEGFR2, was superior to placebo in the REACH-2 trial in patients with an alpha-fetoprotein >400 ng/dL and is approved in subsequent lines of therapy.

QUESTIONS

1. Which of the following patients would benefit from hepatocellular carcinoma (HCC) screening?

A. Nonalcoholic fatty liver disease without cirrhosis
B. History of chronic hepatitis C with Child–Pugh class A cirrhosis
C. Chronic hepatitis B with Child–Pugh class C cirrhosis not a candidate for liver transplantation
D. B and C
E. All of the above

2. A patient with three liver lesions concerning for hepatocellular carcinoma (HCC), size <3 cm, with platelets >100 and a bilirubin <1 and an Eastern Cooperative Oncology Group (ECOG) score of 0 would be considered what stage based on the Barcelona Clinic Liver Cancer (BCLC) criteria?

A. Stage 0
B. Stage A
C. Stage B
D. Stage C
E. Stage D

3. What is the classic enhancement pattern of hepatocellular carcinoma (HCC) on cross-sectional imaging with a venous, arterial, and delayed phase?

A. Arterial: decreased, venous: decreased, delayed: persistent washout
B. Arterial: decreased, venous: increased, delayed: no change
C. Arterial: increased, venous: decreased, delayed: persistent washout
D. Arterial: increased, venous: increased, delayed: persistent washout
E. Arterial: increased, venous: increased, delayed: no change

4. A 48-year-old male presents for discussion of treatment options for his hepatocellular carcinoma (HCC). A 6.0 cm tumor in segment 4b, consistent with HCC was seen on triple-phase CT. His platelet count is 88 and bilirubin is 1.1. He is otherwise in good health and has an Eastern Cooperative Oncology Group (ECOG) score of 0.

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What is the most appropriate treatment recommendation?

A. Liver transplantation
B. Local–regional therapy (transarterial chemoembolization [TACE] or transarterial radioembolization (TARE))
C. Systemic therapy
D. Surgical resection
E. Supportive care

5. A 68-year-old female with alcohol-related cirrhosis presents with a new diagnosis of hepatocellular carcinoma (HCC) based on imaging. Her albumin is 3.7, bilirubin 1.1, and international normalized ratio (INR) 1.1. Her Eastern Cooperative Oncology Group (ECOG) score is 0. She has no ascites, but does have hepatic encephalopathy controlled with lactulose. Imaging is consistent with 3.3 cm HCC in segment 8 with satellite lesions and main portal vein invasion.

What is the most appropriate treatment recommendation?

A. Liver transplantation
B. Local–regional therapy
C. Systemic therapy
D. Surgical resection
E. Supportive care

6. A 60-year-old female presents for discussion of treatment options for her hepatocellular carcinoma (HCC). Her albumin is 2.7, bilirubin 1.2, and international normalized ratio (INR) 1.5 with an Eastern Cooperative Oncology Group (ECOG) score of 1. She has minimal ascites, which is controlled with a low sodium diet, but does have hepatic encephalopathy. The patient is actively drinking alcohol and smoking cigarettes and has poor social support. Multiphasic MRI reveals one 2.8 cm consistent with HCC in segment 2.

What is the most appropriate initial treatment recommendation?

A. Liver transplantation
B. Local–regional therapy
C. Thermal ablation
D. Surgical resection
E. Supportive care

ANSWERS

1. **B. History of chronic hepatitis C with Child–Pugh class A cirrhosis—** Cirrhosis is the most important risk factor for developing HCC. Currently, there are no recommendations for screening for patients with nonalcoholic fatty liver disease without cirrhosis. In patients who are not transplant candidates with Child–Pugh C cirrhosis, there is no benefit to HCC screening due to the significant competing risk of liver-related mortality. The American Association for the Study of Liver Diseases (AASLD) practice guidelines recommend surveillance for HCC with abdominal ultrasound with or without serum alpha-fetoprotein every 6 months in all patients with cirrhosis.

2. **B. Stage A.** This patient has nonadvanced early stage disease given his three lesions <3 cm without the evidence of portal hypertension or significant underlying liver disease using platelets and bilirubin as proxy measures.

3. **C. Arterial: increased, venous: decreased, delayed: persistent washout.** HCC classically has increased enhancement on arterial phase with decreased enhancement on venous phase (washout period). On delayed phase, persistent washout is seen. Fifteen percent of cases will have atypical imaging findings. Diagnostic biopsy is not routinely needed for tumors, which have typical features.

4. **B. Locoregional therapy.** This patient has a large unifocal tumor that should be treated with an arterial-based therapy such as TACE or TARE. The tumor is too large for liver transplantation, as the patient is outside of Milan criteria, although the patient could be downstaged to within transplant criteria depending on response to therapy. The patient has signs of portal hypertension with a platelet count of 88, so surgical resection may not be well tolerated.

5. **C. Systemic therapy.** This patient has Child–Pugh grade A cirrhosis, with imaging consistent with portal invasion. She would, therefore, not be a candidate for primary surgical resection or local–regional therapy. Atezolizumab and bevacizumab infusion every 3 weeks after completion of an upper endoscopy to rule out the presence of varices or a clinic trial would be most appropriate based on the IMBRAVE 150 trial. The SARAH and SIRveNIB trials failed to show a survival benefit of radioembolization compared to sorafenib therapy in patients with locally advanced HCC.

6. **C. Thermal ablation.** This patient has Child–Pugh grade A cirrhosis. She has nonadvanced HCC given one tumor that is <3 cm in size. She is actively drinking and has poor social support. Currently, she would not be a liver transplant candidate and is not an ideal surgical candidate given active alcohol use. The best option is therefore thermal ablative therapy, such as microwave ablation.

ALGRAWANY

29 Neuroendocrine Tumors

Amy E. Chang and Vaibhav Sahai

Neuroendocrine neoplasms (NENs) are composed of a heterogeneous group of rare tumors arising from neuroendocrine cells throughout the body (including thorax, gastrointestinal [GI] tract, thyroid, adrenal glands, and others). These tumors have varying degrees of aggressiveness and are characterized by their ability to store and secrete different peptides and neuroamines. This review will focus on gastroenteropancreatic (GEP) NENs.

EPIDEMIOLOGY

1. What are the most common organs in which neuroendocrine tumors (NETs) arise?

- GI tract 47% (small intestine 18%, large intestine 13%, rectum 12%, stomach 5%)
- Lung 25%
- Pancreas 4%

PATHOLOGY

1. What pathologic characteristics are used to grade NENs?

- See Table 29.1.

TABLE 29.1 ■ WHO 2017 Staging System of GEP Neuroendocrine Neoplasms

		Morphology		Mitotic Rate (count/10 hpf)		Ki-67 Index (%)
NETs	**Grade 1**	Well differentiated	AND	<2	AND	<3%
	Grade 2		AND	2–20	OR	3%–20%
	Grade 3		AND	>20	OR	>20%
NEC	**Grade 3**	Poorly differentiated	OR	>20	OR	>20%

GEP, gastroenteropancreatic; NETs, neuroendocrine tumors; NEC, neuroendocrine carcinoma; WHO, World Health Organization.

Neuroendocrine carcinomas (NECs) are a heterogeneous group of highly aggressive malignancies with a high propensity for distant metastases and a dismal prognosis despite systemic therapy. They are usually poorly differentiated but sometimes categorized as small or large cell subtypes. NECs are genomically distinct from NETs. NEC has frequent *Tp53* alteration and Rb1 loss, whereas common mutations found in NETs are in *MEN1, DAXX, ATRX, BRCA2, VHL*.

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SIGNS AND SYMPTOMS

1. What is the difference between a "functional" NET and a "nonfunctional" NET?

- NETs store and secrete different peptides and neuroamines some of which may cause specific clinical syndromes and are termed "functional," whereas others may have elevated plasma or urine markers, but are without associated symptoms, and therefore "nonfunctional."

2. What are the symptomatic manifestations of the functional GEP NET syndromes?

- See Table 29.2.

TABLE 29.2 ■ Clinical Presentations and Syndromes of GEP NETs

Hormonal Syndrome	Hormone	Signs and Symptoms
Serotoninoma or carcinoid syndrome	Serotonin	Flushing (usually without diaphoresis), secretory diarrhea, wheezing, and carcinoid heart disease (tricuspid valve and/or pulmonic valve regurgitation)
Insulinoma	Insulin	Hypoglycemia (with neuroglycopenic symptoms, including confusion, altered consciousness) and sweating (from sympathetic overdrive)
Gastrinoma or Zollinger–Ellison syndrome	Gastrin	Abdominal pain due to peptic ulcer disease, diarrhea, and reflux esophagitis
Glucagonoma or 4D syndrome, or Sweet syndrome	Glucagon	4Ds include diarrhea, depression, deep venous thrombosis, and dermatitis (necrolytic migratory erythema). Also, glucose intolerance and weight loss can be seen
VIPoma or Verner–Morrison syndrome	VIP	Watery diarrhea, hypokalemia, and achlorhydria
Somatostatinoma or inhibitory syndrome	Somatostatin	Malabsorptive diarrhea/steatorrhea, diabetes mellitus, hypochlorhydria, and cholelithiasis

GEP NETs, gastroenteropancreatic neuroendocrine tumors; VIP, vasoactive intestinal peptide.

3. What is the underlying etiology of the typical symptoms of a functional midgut NET, or carcinoid syndrome?

- Flushing: prostaglandins, kallikrein, and serotonin 5-hydroxytryptamine (5-HT)
- Diarrhea: tachykinins release (persists with fasting in contrast to malabsorptive diarrhea)
- Wheezing: substance P, histamine, or 5-HT
- Carcinoid heart disease: 5-HT leading to fibrosis

4. Which heart valves are involved in carcinoid heart disease?

- Tricuspid and/or pulmonic valve regurgitation

5. What are the possible locations of primary NET in a patient with symptoms of carcinoid syndrome?

- Midgut or lung is most common.
- Patients with pancreatic NET have also been uncommonly described in literature.
- Majority of patients have liver metastases, which allow serotonin to bypass liver metabolism.

6. What are the more common familial syndromes associated with GEP NENs?

- See Table 29.3.

TABLE 29.3 ■ Common Familial Syndromes in Patients With GEP NENs

Familial Syndrome	Gene	Incidence	Signs and Symptoms
MEN1	*MEN1*	1:20,000 to 1:40,000	Pancreatic NETs, hyperparathyroidism (high parathyroid hormone and hypercalcemia), pituitary tumor
VHL	*VHL*	1:36,000	Pancreatic NETs, renal cell cancer, pheochromocytoma, hemangioblastomas of central nervous system

GEP NENs, gastroenteropancreatic neuroendocrine neoplasms; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; VHL, von Hippel–Lindau.

DIAGNOSTIC WORKUP

1. A 32-year-old woman has been diagnosed with metastatic grade 1 GEP NET. What staging diagnostic workup should be completed before considering treatment?

- **Which imaging study or studies should be considered?**
  - Functional imaging
    - Somatostatin receptor scintigraphy (also known as octreotide scan). Recommended (usually in grade 1 and 2 NETs) to evaluate extent of disease and presence of somatostatin receptors. Sensitivity is between 80% and 90%. This test is only useful at the time of diagnosis and not follow-up during treatment evaluation.
    - ^{68}Ga-DOTATATE PET/CT. **High sensitivity and specificity with much improved spatial resolution than octreotide scan**.
    - Metaiodobenzylguanidine (MIBG) scan. Low sensitivity but a positive scan may have implication for patient management with MIBG treatment.
  - **Anatomic imaging**
    - CT or MRI. Recommended as the octreotide scan does not provide anatomical detail, unless the ^{68}Ga-DOTATATE PET with a diagnostic CT scan is performed. Scans should be a multiphasic contrast-enhanced study, specifically of the liver.
    - Transthoracic echocardiogram (TTE). A TTE should be considered as part of staging diagnostic workup if the patient is diagnosed with a functional midgut NET.

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- **Which laboratory tests should be considered?**
  - See Table 29.4.

TABLE 29.4 ■ Laboratory Investigations for GEP NETs

Test	NET	Specifics
Insulin	Pancreas	Fasting; also check fasting glucose, proinsulin, and C-peptide
Gastrin		Fasting (>1,000 ng/L), consider gastric pH (<2.5), secretin provocation test
Glucagon		Levels between 500 and 1,000 pg/mL
Pancreatic polypeptide		Nonspecific marker for functional/nonfunctional NETs
Vasoactive intestinal polypeptide		Additionally, consider evaluation of electrolytes
Chromogranin A	GEP	Nonspecific marker for functional/nonfunctional NETs Correlates with treatment response, prognosis False-positive results may occur due to use of proton pump inhibitors, concurrent chronic atrophic gastritis, or impaired renal function
Somatostatin		Plasma SLI level
Neuron-specific enolase		Higher levels (>3× upper limit of normal) may correlate with worse overall survival
24-hour urine 5-HIAA	Midgut	Not known to correlate with treatment response False-positive results may occur with ingestion of certain foods, including bananas, kiwis, avocado, tomatoes, eggplants, walnuts, and pineapple

There are additional tests that can be considered, including serum serotonin, pancreastatin, and neurokinin A.

5-HIAA, 5-hydroxyindole acetic acid; GEP, gastroenteropancreatic; NETs, neuroendocrine tumors; SLI, somatostatin-like immunoreactivity.

TREATMENT

1. What is the role of surgery in the management of NETs?

- Surgery is recommended for resectable NET.
- For unresectable grade 1 (and low grade 2) NET, cytoreductive surgery can be considered if near complete resection can be achieved. Additionally, liver metastasectomy for oligometastatic disease can also be considered in this patient population. However, the supporting data for cytoreductive surgery are retrospective and sparse.

2. What are treatment options for grade 3 NECs?

- Grade 3 NECs are treated similar to small and large cell cancers of the lung.
  - Surgical metastasectomy is not recommended in the management of NEC.
  - Locoregional unresectable tumors are treated with systemic chemotherapy and radiation.

- Metastatic tumors are treated with systemic chemotherapy such as platinum-based chemotherapy with etoposide or irinotecan, and temozolomide with or without capecitabine.

3. A 52-year-old male was recently diagnosed with a nonfunctional, grade 1 GEP NET. An octreotide scan revealed bilobar metastatic disease to the liver. What treatment options should be considered at this time?

- **Observation:** Close monitoring with no active treatment is a reasonable option to consider in an asymptomatic patient with low burden of disease.
- **Somatostatin analogs such as octreotide long-acting release (LAR) or lanreotide:** These agents are associated with a significant improvement in progression-free survival (PFS) compared to placebo.
  - ***Octreotide LAR***—PROMID study (Phase 3B): Prospectively randomized 85 patients with well-differentiated locally unresectable or metastatic midgut NET to either octreotide LAR 30 mg intramuscularly once every 4 weeks, or placebo. After 6 months of treatment, stable disease was observed in 67% of patients in the octreotide group versus 37% in the placebo group.
  - ***Lanreotide***—CLARINET trial (Phase 3): Prospectively randomized 204 patients with well-differentiated or moderately differentiated, nonfunctioning, somatostatin-receptor-positive GEP NETs (grade 1 or 2) to either Lanreotide 120 mg subcutaneously once every 4 weeks, or placebo. The median PFS in the Lanreotide arm was not reached versus 18 months in the placebo arm (hazard ratio [HR], 0.47; 95% confidence intervals [CIs] [0.30, 0.73]; p <.001).

TABLE 29.5 ■ Biological Therapeutics in NETs

Study	Type of NET	Therapy	Progression-free survival (months)	HR; 95% CIs; p value
RADIANT-3 Study	Pancreatic	Everolimus	11.0	0.35; [0.27, 0.45]; p < .001
		Placebo	4.6	
Sunitinib Study	Pancreatic only	Sunitinib	11.4	0.42; [0.26, 0.66]; p <.001
		Placebo	5.5	
RADIANT-4 Study	Lung or gastrointestinal	Everolimus	11.0	0.48; [0.35, 0.67]; p < .001
		Placebo	3.9	

HR, hazard ratio; NET, neuroendocrine tumor.

4. The patient discussed earlier was noted to have disease progression after being on observation for 18 months. He subsequently started octreotide LAR 20 mg every 4 weeks with close monitoring with chromogranin A. The biomarker started increasing after 2 years, and on repeat CT scan he was noted to have worsening liver metastasis. What treatment options should be considered?

- Biological or targeted therapeutics such as sunitinib and everolimus (see Table 29.5)
  - **Everolimus** is Food and Drug Administration (FDA) approved for both GI and pancreatic NETs
  - **Sunitinib** is FDA approved *only* for pancreatic NETs.

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- Cytotoxic chemotherapy such as **temozolomide ± capecitabine (CAPTEM)**
  - Randomized phase II trial comparing CAPTEM to temozolomide only control group in patients with pancreatic NETs. Interim median PFS was 22.7 months in CAPTEM group versus 14.4 months in control group (HR 0.58; $p = .023$).
- **^{177}Lu-Dotatate (Peptide Receptor Radionuclide Therapy [PRRT]).**
  - NETTER-1 trial (phase 3): Randomized 229 patients with well-differentiated metastatic or locally advanced somatostatin-receptor-positive midgut NETs to either ^{177}Lu-Dotatate plus octreotide LAR or octreotide LAR alone. Patients on the ^{177}Lu-Dotatate arm had a significantly prolonged PFS at 20 months compared to octreotide LAR alone (65.2% vs. 10.8%; $p < .001$). In addition, patients on the ^{177}Lu-Dotatate group had better overall survival (OS) compared to control. OS was not reached in ^{177}Lu-Dotatate group versus 27.4 months in control group (HR 0.21; $p < .0001$).
- Liver-directed therapy including arterial-based (transarterial chemoembolization [TACE], transarterial or bland embolization [TAE], selective internal radiotherapy [SIRT, also known as transarterial radioembolization or TARE]) or nonarterial-based (radiofrequency, microwave, or cryoablation) therapy.
- Symptom management
  - **Telotristat** is a tryptophan hydroxylase inhibitor. In phase III randomized trial (9), it was found to be well tolerated and significantly decreases urine 5-HIAA level and number of bowel movements from carcinoid syndrome. It is now FDA approved for carcinoid syndrome diarrhea.

QUESTIONS

1. A 47-year-old female is found to have incidental hyperintense 1.5 cm pancreatic tail mass and 1 cm isolated liver lesion found on a routine CT scan. A liver biopsy reveals well-differentiated, small round cells with a mitotic count of 2 mitoses/10 high-power fields, and Ki-67 2%. She does not have any symptoms and is otherwise healthy without any chronic medical problem.

What treatment option would you consider?

A. Surgery
B. 5-fluorouracil, irinotecan, oxaliplatin, folinic acid (FOLFIRINOX)
C. Peptide Receptor Radionuclide Therapy (PRRT)
D. Cisplatin and etoposide

2. Which of the following additional imaging modalities would you consider for the diagnosis of gastroenteropancreatic (GEP) neuroendocrine tumor for the patient in Q1?

A. Metaiodobenzylguanidine (MIBG) scan
B. ^{68}Ga-DOTATATE PET/CT
C. MRI
D. ^{18}F-fluorodeoxyglucose (FDG) PET/CT

3. Patient in Q1 undergoes distal pancreatectomy and liver metastasectomy. Three years later, she returns with new abdominal pain. CT scan reveals 4.6 cm intra-abdominal lymph node, as well as diffuse hyperintense multiple liver lesions concerning for malignancy. Repeat biopsy of liver shows recurrent NET. You elected to start the patient on octreotide long-acting release (LAR) 20 mg intramuscularly (IM) every 4 weeks.

Which of the following symptoms is NOT a side effect of octreotide LAR?

A. Diarrhea
B. Cholelithiais
C. Hyperglycemia
D. Hyperkalemia

4. A 64-year-old male presents with flushing, watery diarrhea, and occasional wheezing. His 24-hr urine 5-hydroxyindole acetic acid (5-HIAA) level is 135 mg. His CT scan shows ileal mass as well as multiple liver mass. Biopsy confirms his diagnosis and you start him on lanreotide 120 mg SQ every 4 weeks. His symptoms improve but he continues to have four to six watery bowel movements each day despite dietary modifications and loperamide.

What additional Food and Drug Administration (FDA) approved treatment might improve his symptom?

A. Ruxolitinib
B. Metronidazole
C. Sunitinib
D. Telotristat

5. A 68-year-old male presents to ED with malaise, weight loss, fatigue, and jaundice. CT scan shows hyperintense pancreas mass and innumerable metastases to the liver and lymph nodes. He is admitted to the hospital for an expedited work up. Liver biopsy reveals poorly differentiated small round cells with Ki-67 of 70% and mitotic rate of 20 mitoses/10 high-power fields. He is diagnosed with metastatic grade 3 neuroendocrine carcinoma.

Which of the following treatment options would be most appropriate?

A. Somatostatin-analogue
B. 5-fluorouracil (5-FU) and oxaliplatin
C. Capecitabine and temozolomide
D. Cisplatin and etoposide

6. A 32-year-old female presents with newly diagnosed pancreatic neuroendocrine tumor (pNET).

Which of the following familial syndromes has been associated with pNET?

A. Multiple endocrine neoplasia type 2 (MEN2A)
B. von Hippel–Lindau (VHL)
C. Lynch
D. Li–Fraumeni

7. A 40-year-old gentleman with grade 1 metastatic pancreatic neuroendocrine tumor (pNET) has progression on octreotide long-acting release (LAR) 30 mg intramuscularly (IM) every 4 weeks. He has diabetes mellitus type 2 and his A1C is 9.5.

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Which Food and Drug Administration (FDA) approved medication would you consider for further management?

A. Lanreotide
B. Temozolomide
C. Peptide Receptor Radionuclide Therapy
D. Everolimus

ANSWERS

1. **A. Surgery.** This patient has grade 1 neuroendocrine tumor. Liver metastasectomy for oligometastatic disease can be considered in this clinical setting. FOLFIRINOX is for pancreatic adenocarcinoma which is not the diagnosis for this patient. PRRT can be considered for treatment of neuroendocrine tumor (NET) but usually not considered as first-line therapy for asymptomatic disease. Cisplatin and etoposide can be considered for high-grade neuroendocrine carcinoma, which is also not the diagnosis for this patient.

2. **B. ^{68}Ga-DOTATATE PET/CT.** ^{68}Ga-DOTATATE PET/CT has high sensitivity and specificity, and has treatment implications. If ^{68}Ga-DOTATATE PET/CT is not available, somatostatin receptor scintigraphy, or octreotide scan may be completed but has lower sensitivity. MIBG scan has lower sensitivity for GEP NETs. MRI is not required since the patient has had CT scan for anatomic assessment. ^{18}F-FDG PET scan also has low sensitivity for low- and intermediate-grade neuroendocrine tumors (NETs).

3. **C. Hyperkalemia.** Somatostatin analogs can cause malabsorptive diarrhea/steatorrhea due to inhibition of pancreatic enzymes. They can also cause cholelithiasis over months to years of therapy due to decreased gallbladder contraction due to impaired postprandial cholecystokinin release. Somatostatin analogs can also cause hypoglycemia or hyperglycemia due to decreased secretion of glucagon and insulin. Octreotide LAR does not cause hyperkalemia.

4. **D. Telotristat.** This patient has carcinoid syndrome from intestinal neuroendocrine tumor. Telotristat is a tryptophan hydroxylase that has shown to significantly decrease urine 5-HIAA level and number of bowel movements from carcinoid syndrome. It is now FDA approved for carcinoid syndrome diarrhea. Treatment of neuroendocrine tumor (NET) should certainly be considered. Sunitinib is only FDA approved for pancreatic NET at this time. There is no role of metronidazole in this patient.

5. **D. Cisplatin and etoposide.** Front-line treatment for high-grade neuroendocrine carcinoma is systemic chemotherapy usually with cisplatin (or carboplatin) and etoposide. Capecitabine and temozolomide are used for the treatment of low-grade neuroendocrine tumor (NET) with most data for pancreatic NETs. 5-fluorouracil and oxaliplatin (FOLFOX) is not considered front-line treatment for neuroendocrine neoplasms.

6. **B. VHL.** VHL is associated with pNETs, renal cell cancer, pheochromocytoma, and hemangioblastomas of the central nervous system. MEN2A is characterized by medullary thyroid cancer, pheochromocytoma, and primary parathyroid hyperplasia. MEN1 is the familial syndrome characterized by pNETs, parathyroidism, and pituitary tumors.

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7. **C. Peptide Receptor Radionuclide Therapy (PRRT).** Both PRRT and everolimus prolong progression-free survival (PFS) compared to placebo in patients with NETs. However, everolimus can be associated with hyperglycemia (in 13% of patients) and, therefore, PRRT would be a better choice in this patient with poorly controlled diabetes. The patient is already receiving a somatostatin analog, so addition of lanreotide is incorrect. Moreover, lanreotide binds to the same somatostatin receptors (SSTR2 and SSTR5) as octreotide LAR, so a change of therapy is also not recommended. Temozolomide has been used alone and in combination with other agents such as capecitabine; however, it is not FDA-approved.

SARCOMA

VII

ALGRAWANY

30

Sarcoma

Arathi Mohan and Rashmi Chugh

Sarcomas are rare cancers arising from connective tissue of mesenchymal origin. Sarcomas can typically be divided into two broad categories: soft tissue sarcomas (STSs) and bone sarcomas. There are over 50 subtypes of STS, which are broadly divided into gastrointestinal stromal tumor (GIST) and non-GIST.

TABLE 30.1 ■ Sarcoma Categories by Bone and Soft Tissue

Sarcoma categories	Bone (20%)	Osteosarcoma	
		Chondrosarcoma	
		Ewing Sarcoma	
	Soft tissue (80%)	Non-GIST	Leiomyosarcoma
			Liposarcoma
			Pleomorphic sarcoma
			MPNST
			Angiosarcoma
			Synovial sarcoma
			Alveolar soft part sarcoma
			Solitary fibrous tumor
			Well-differentiated liposarcoma
			Extraskeletal myxoid chondrosarcoma
		GIST	TK mutant
			SDH deficient

GIST, gastrointestinal stromal tumor; MPNST, malignant peripheral nerve sheath tumor; SDH, succinate dehydrogenase; TK, tyrosine kinase.

CLOSELY RELATED TO SARCOMA

There are a group of locally aggressive benign connective tissue tumors that are closely related to sarcoma and include desmoid tumor, giant cell tumor of bone, tenosynovial giant cell tumor, and chordoma.

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GENETICS AND RISK FACTORS

1. What genetic syndromes are associated with a greater risk for sarcoma?

- Li–Fraumeni syndrome (germline mutation in TP53)
  - Increased risk of STS and osteosarcoma
  - Other associated malignancies include breast cancer, adrenocortical cancer, brain cancer, leukemia, and lymphoma
- Neurofibromatosis type I (NF1 mutation)
  - NF1 patients have a 5% to 10% risk of developing an STS, most commonly malignant peripheral nerve sheath tumors (MPNSTs).
- Familial retinoblastoma (RB) syndrome (germline mutation in the RB tumor suppressor)
  - Increased risk for STS, particularly leiomyosarcoma.
- Carney–Stratakis syndrome (autosomal dominant)
  - Increased risk for GIST, specifically a rare variant with loss-of-function mutations within the succinate dehydrogenase (*SDH*) gene.
- Gardner syndrome (adenomatous polyposis coli [APC] mutation)
  - Predisposed to desmoid tumors.

2. What are some other risk factors for sarcoma?

- Chronic lymphedema is a risk factor for the development of lymphangiosarcoma (Stewart–Treves syndrome).
- Human herpes virus-8 (HHV-8) is associated with Kaposi sarcoma (KS).
- Prior radiation therapy with latency period of 5 to 10 years.

3. What cytogenetic molecular abnormalities are associated with the development of sarcoma?

- 80% of GISTs have a KIT mutation (exon 11 most common); 5% to 10% have a platelet-derived growth factor (PDGF) receptor alpha (PDGFRA) mutation.
- Nonmutant GISTs can have SDH deficiency as with Carney–Stratakis syndrome
- 30% of non-GIST STSs are also associated with specific genetic alterations. Many aberrancies have diagnostic value; changes with potential therapeutic implications are bolded in the following.

TABLE 30.2 ■ Cytogenic Molecular Abnormalities and Associate With Sarcoma Subtype

Sarcoma Subtype	Molecular Abnormality
GIST	**KIT** (CD117) mutation, exon 9 or 11 **PDGF receptor** alpha (PDGFRA) mutations
Well-differentiated/dedifferentiated liposarcoma	Giant or ring chromosomes (**CDK4**, MDM2 amplification) concurrently have aneuploidy
Synovial sarcoma	t(X;18)(p11:q11) SS18-SSX1 or SS18-SSX2
Alveolar soft part sarcoma	t(X;17)(p11.2;q25) ASPL-TFE3
Myxoid/round cell liposarcoma	t(12;16)(q13;p11) FUS-CHOP(DDIT3) t(12;22) EWSR1-CHOP(DDIT3)
Ewing sarcoma	t(11;22)(q24;q12) EWSR1-FLI1 t(21;22) EWSR1-ERG

(*continued*)

TABLE 30.2 ■ Cytogenic Molecular Abnormalities and Associate With Sarcoma Subtype (*continued*)

Sarcoma Subtype	Molecular Abnormality
Desmoplastic small round cell tumor	t(11;22)(p13;q12) EWSR1-WT1
Alveolar rhabdomyosarcoma	t(2:13)(q35;q14) PAX3-FOXO1A t(1;13)(p36;q14) PAX7-FOXO1A t(X;2)(q13;q35) PAX3-AFX

GIST, gastrointestinal stromal tumor; PDGFRA, PDGF receptor alpha.

FOXO1A, Forkhead box 01A receptor, also denoted in some texts as FKHR.

EVALUATION OF SUSPECTED SARCOMA

1. How do you evaluate a concerning mass?

- MRI is superior in imaging extremity and trunk sarcomas.
- CT is generally preferred for abdominal and pulmonary tumors.
- By x-ray, osteosarcomas present with lytic and blastic features in admixed bone. If osteosarcomas extend to the soft tissue, they can cause a periosteal reaction (Codman triangle) and ossification in a pattern perpendicular to the surface of the bone (sunburst pattern).
- By x-ray, chondrosarcomas appear as a radiolucent area with bony destruction and discrete calcified areas, usually involving the medullary cavity. They may cause what appears to be a multinodular growth pattern with scalloped edges.
- Ewing sarcoma usually affects the bone shaft in an infiltrative pattern called "onion skinning," which can be seen on CT but is harder to see on plain films.
- Core biopsy; fine needle aspiration (FNA) is not adequate
- CT chest for staging

STS STAGING

- The components for staging are:
  - Histologic Grade: Three-tier grading system is recommended in the most recent American Joint Committee on Cancer (AJCC) staging system and is scored based on tumor differentiation, mitotic count, and tumor necrosis. The scores are added to determine the grade.
    - Grade X, grade cannot be assessed
    - Grade 1, total differentiation, mitotic count, and necrosis score of 2 or 3
    - Grade 2, total differentiation, mitotic count, and necrosis score of 4 or 5
    - Grade 3, total differentiation, mitotic count, and necrosis score of 6, 7, or 8
  - Tumor staging definitions are dependent on location (i.e., extremity/trunk, retroperitoneum, and viscera of abdomen or thorax)
  - Nodal disease: observed in fewer than 10% of patients with STS
    - Epithelioid sarcoma, synovial sarcoma, rhabdomyosarcoma, and angiosarcoma have a propensity to spread to lymph nodes
    - N0 denotes no lymph node metastases
    - N1 denotes the presence of lymph node metastasis
  - Metastatic disease
    - M0 denotes no evidence of metastatic disease
    - M1 denotes the presence of metastatic disease

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TABLE 30.3 ■ 2017 8th Edition of the AJCC Staging System for Soft Tissue Sarcoma of the Trunk and Extremities

Stage	T	Grade Using a Three-Tier System	N	M
IA	T1	G1, GX	N0	M0
IB	T2–T4			
II	T1	G2, G3		
IIIA	T2			
IIIB	T3–T4			
IV	Any T	Any G	N1	M0
			Any N	M1

AJCC, American Joint Committee on Cancer.

Source: Adapted from *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer-Verlag; 2017.

GIST STAGING

- The components for staging are:
  - Mitotic Rate Grade
    - <5 mitoses per 50 high-powered fields (hpf) is low grade
    - >5 mitoses per 50 hpf is high grade
  - Tumor staging definitions are dependent on location (i.e., gastric vs. small intestine)
  - Nodal disease
    - N0 denotes no regional lymph node metastases
    - N1 denotes the presence of lymph node metastasis
  - Metastatic disease
    - M0 denotes no distant metastasis
    - M1 denotes distant metastasis

TABLE 30.4 ■ 2017 8th Edition of the AJCC Staging System for Gastric GIST

Stage	T	Mitotic Rate	N	M
IA	T1–T2	Low	N0	M0
IB	T3			
II	T1–T2	High		
	T4	Low		
IIIA	T3	High		
IIIB	T4			
IV	Any T	Any rate	N1	M0
			Any N	M1

AJCC, American Joint Committee on Cancer; GIST, gastrointestinal stromal tumor.

Source: Adapted from *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer-Verlag; 2017.

TABLE 30.5 ■ 2017 8th Edition of the AJCC Staging System for Small Intestinal GIST

Stage	T	Mitotic Rate	N	M
I	T1–T2	Low	N0	M0
II	T3			
IIIA	T1	High		
T4	Low			
IIIB	T2–T4	High		
IV	Any T	Any rate	N1	M0
			Any N	M1

AJCC, American Joint Committee on Cancer; GIST, gastrointestinal stromal tumor.

Source: Adapted from *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer-Verlag; 2017.

OSTEOSARCOMA STAGING

- The components for staging are:
  - Histologic Grade: based on differentiation
    - Grade X, grade cannot be assessed
    - Grade 1, well differentiated—low grade
    - Grade 2, moderately differentiated—high grade
    - Grade 3, poorly differentiated—high grade
  - Tumor staging definitions are dependent on location (i.e., appendicular skeleton/trunk/skull/facial bones vs spine)
  - Nodal disease
    - N0 denotes no regional lymph node metastases
    - N1 denotes the presence of lymph node metastasis
  - Metastatic disease
    - M0 denotes no evidence of metastatic disease
    - M1 denotes the presence of metastatic disease
      - M1a lung
      - M1b bone or other distant sites

TABLE 30.6 ■ 2017 8th Edition of the AJCC Staging System for Bone

Stage	T	Grade Using a Three-Tier System	N	M
IA	T1	G1, GX	N0	M0
IB	T2–T3			
IIA	T1	G2, G3		
IIB	T2			
III	T3			

(*continued*)

ALGRAWANY

TABLE 30.6 ■ 2017 8th Edition of the AJCC Staging System for Bone (*continued*)

Stage	T	Grade Using a Three-Tier System	N	M
IVA	Any T	Any G	N0	M1a
IVB			N1	Any M
			Any N	M1b

AJCC, American Joint Committee on Cancer.

Source: Adapted from *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer-Verlag; 2017.

TREATMENT FOR NON-GIST SOFT TISSUE SARCOMA

- Localized low-grade STS (majority of patients cured)
  - Surgery ± radiation
  - Majority of patient are cured with low-grade STS
- Localized high-grade STS (~50% of patients cured but also varies based on other factors such as size, histology)
  - Surgery → radiation OR radiation → surgery
  - Consider neoadjuvant or adjuvant chemotherapy if there is high risk of metastases—this remains controversial
- Metastatic/recurrent STS
  - Single-agent chemotherapy
    - Doxorubicin remains standard of care for most chemotherapy-sensitive subtypes of STS. Response rates in 10% to 15% range.
    - Ifosfamide
    - Dacarbazine
    - Gemcitabine
  - Combination Chemotherapy
    - Combinations are in adjuvant setting or in certain situations in metastatic setting. Typically, with more toxicity but higher response rates
      - Doxorubicin/ifosfamide—most common regimen in the adjuvant setting. In metastatic setting, no overall survival benefit.
      - Gemcitabine/docetaxel
      - Dacarbazine/gemcitabine
  - Other Food and Drug Administration (FDA) approved agents for non-GIST STS
    - Pazopanib: non-liposarcoma (LPS) after prior chemotherapy
    - Trabectedin: leiomyosarcoma and LPS after prior anthracycline
    - Eribulin: liposarcoma previously received an anthracycline
    - Tazemetostat: epithelioid sarcoma
  - Other FDA-approved agents for locally aggressive benign connective tissue tumors
    - Pexidartinib (pigmented villonodular synovitis [PVNS]), Denosumab (giant cell tumor)
  - Certain histologies, including ones that are not chemosensitive, may have more specific-targeted treatment.
  - Surgery or radiation for oligometastatic disease or palliation
    - Subset of patients can have long-term survival with complete resection of metastases particularly lung metastases

TABLE 30.7 ■ Subtype-Specific Treatment for Metastatic Non-GIST STS

STS Subtype	Target	Treatment
DFSP	t(17;22)—PDGFR activation	Imatinib
ASPS	ASPSCR1-TFE3	VEGFR-targeted tyrosine kinase inhibitors, checkpoint inhibitors
TGCT	t(1;2)—CSF1-COL6A3	Pexidartinib
PEComas	Tuberous sclerosis complex mutations	mTOR inhibitors
SFT	NAB2-STAT6IG2 secretion	Temozolomide/bevacizumab, VEGFR-targeted tyrosine kinase inhibitors

ASPS, alveolar soft part sarcoma; DFSP, dermatofibrosarcoma protuberans; GIST, gastrointestinal stromal tumor; PEComas, perivascular epithelioid tumors; SFT, solitary fibrous tumor; STS, soft tissue sarcoma; TGCT, tenosynovial giant cell tumor.

TREATMENT FOR BONE SARCOMAS

Osteosarcoma

- Cure rates increased with chemotherapy; 20% with surgery alone and 60% to 70% with surgery and chemotherapy
- Standard chemotherapy is methotrexate, Adriamycin, and cisplatin (MAP)
- Metastasis-directed therapy with surgery or radiation can help improve relapse free survival
- There is no improvement with bone modifying agents (bisphosphonates or denosumab)

Chondrosarcoma

- Often isocitrate dehydrogenase (IDH) mutated
- Principal treatment is surgery

Ewing Sarcoma

- Small blue round cell tumor
- Radiation and chemotherapy sensitive
- Cure rates increased with addition of chemotherapy
- Preoperative and adjuvant chemotherapy with vincristine, doxorubicin, and cyclophosphamide (VAC) alternating with ifosfamide and etoposide (IE) was shown to have a better progression-free and overall survival compared with VAC alone (category 1).
- Five-drug regimen is continued for 12 to 14 cycles total, divided before and after resection with optimal interval of every 2 weeks.
- Actinomycin-D should be substituted for doxorubicin after a cumulative dose of more than 450 mg/m^2 of doxorubicin has been given.

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TREATMENT FOR GISTs

- Cytotoxic chemotherapy and intraperitoneal chemotherapy have been attempted and studied but are largely ineffective.
- Tyrosine kinase inhibitors (TKIs) against c-KIT or PDGFRA are the standard of care for GIST and are associated with good response rates.
- Imatinib is used first line with daily dose of 400 mg and achieves disease control in 80% of patients with a c-KIT mutation in exon 11.
  - Side effects of imatinib include diuretic-resistant peripheral edema, liver function test (LFT) abnormalities, muscle cramps, and fatigue
- Sunitinib is second-line therapy for imatinib-refractory or imatinib-intolerant disease
  - Exon 9 c-KIT or Wild type (WT) GIST have best response rates to sunitinib
- Regorafenib can be used as third-line therapy for patients who are refractory or intolerant to both imatinib and sunitinib.
- Ripretinib is FDA approved for GIST when patients have received prior treatment with three or more kinase inhibitors
- Avapritinib is approved for PDGFR mutant GIST, which are typically imatinib resistant.
- If limited number of disease sites, debulking surgery or local ablative strategies should be considered. Patients should remain on tyrosine kinase inhibitor (TKI) prior to and following surgery since they usually experience rapid recurrence once treatment is discontinued.

KAPOSI SARCOMA

- Indolent, soft tissue vascular tumor involving skin, mucosa, and viscera
- Associated with herpes virus (Kaposi's sarcoma-associated herpesvirus [KSHV]/HHV-8) infection
- Screening for visceral involvement with stool guaiac and chest x-ray is recommended.
- Highly active antiretroviral therapy (HAART) can be used for AIDS-related disease if confined to the skin, oral cavity, and asymptomatic visceral disease.
- If progressive disease, or if extensive cutaneous or symptomatic visceral involvement or non-AIDS-related disease, additional therapies may be indicated.
  - Liposomal doxorubicin or paclitaxel is usually used in the first- or second-line setting.
  - Vinorelbine, etoposide, or interferon (IFN) alpha are possible options for progressive disease.
  - Pomalidomide was approved to treat AIDS-related Kaposi after failure of HAART and in HIV-negative patients.
  - Symptomatic-localized disease can be effectively treated with low dose radiation and intralesional chemotherapy.

QUESTIONS

1. **Which of the following is not a common side effect of imatinib?**
   A. Periorbital edema
   B. Fatigue
   C. Liver function test abnormalities
   D. Neuropathy
   E. Muscle cramps

2. **Which of following is a feature of a low-risk gastrointestinal stromal tumor (GIST)?**
   A. Ileal location
   B. Mitotic index <5/50 high-powered fields
   C. Size >10 cm
   D. Tumor rupture

3. **All of the following treatments could be considered for a patient with metastatic liposarcoma *except:***
   A. Doxorubicin
   B. Ifosfamide
   C. Eribulin
   D. Pazopanib

4. A 55-year-old man presents with a firm, painless mass that has been enlarging on his left thigh. Ultrasound-guided biopsy reveals an undifferentiated pleomorphic sarcoma.

   Which of the following is the next step in management?
   A. Doxorubicin and ifosfamide
   B. Surgical resection
   C. MRI of the left lower extremity and CT chest
   D. Bone scan

5. A 22-year-old woman develops pain in her right thigh. CT lower extremity demonstrates a 7.1 × 6.5 × 5.5 cm mass arising from the right femur. CT-guided biopsy reveals high-grade osteosarcoma. Bone scan reveals uptake in the right femur but no other sites of metastatic disease and CT chest is negative.

   What is the best treatment plan for this patient?
   A. Methotrexate, doxorubicin, and cisplatin followed by surgery
   B. Chemotherapy alone
   C. Surgery alone
   D. Radiation followed by surgery
   E. Best supportive care

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ANSWERS

1. **D. Neuropathy.** All other answers are common side effects of imatinib.

2. **B. Mitotic index <5/50 high-powered fields.** All others are features of high-risk GIST.

3. **D. Pazopanib.** Food and Drug Administration (FDA) approval for pazopanib is for nonadipocytic soft tissue sarcoma (STS). All other agents are FDA approved.

4. **C. MRI of the left lower extremity and CT chest.** Preoperative imaging to determine the extent of disease allows for accurate staging of sarcoma and formulating a treatment plan. A bone scan generally has no role in the staging of soft tissue sarcoma (STS).

5. **A. Methotrexate, doxorubicin, and cisplatin followed by surgery.** The optimal treatment of localized osteosarcoma includes combination treatment with chemotherapy and surgical resection. Chemotherapy increases the chance of cure and should be added to surgery. Radiation has no role in the curative setting. Best supportive care is not appropriate for this potentially curable patient.

MELANOMA

VIII

ALGRAWANY

31 Melanoma

Vincent T. Ma and Christopher D. Lao

PATHOLOGY

1. What are the various subtypes of melanoma? Describe the characteristics of each.

- *Cutaneous:* The majority of all melanomas arise from the skin. Various subtypes include superficial spreading (the most common subtype, often appears as classic irregular pigmented macule), lentigo maligna (associated with chronically solar-damaged skin), acral lentiginous (arise from plantar/palmer/subungual surfaces, more common in people of Asian and African descent), and desmoplastic (rare and can be deeply invasive).
- *Mucosal:* Arises from the mucosal surface of the sinonasal cavity, oral cavity, genitourinary tract, rectum, and anus
- *Uveal:* Arises in the uvea (choroid, ciliary body, and iris) and conjunctiva of the eye. This subtype can be and most often is diagnosed without a biopsy. Metastasis is hematogenous with liver as a common site.

RISK FACTORS

1. What inherited genetic mutations/polymorphisms have been associated with increased risk of melanoma?

- *CDKN2A* mutation (associated with pancreatic cancer)
- *BRCA2* > *BRCA1* mutation
- *BAP1* mutation (associated with uveal melanoma and mesothelioma)

2. What sporadic (somatic) gene mutations are seen in melanoma?

- *BRAF* is the most common somatic mutation seen in melanoma (40%–60% of cases). The *V600E* mutation makes up approximately 80% of cases, whereas most of the remainder are *V600K*.
- *NRAS* is mutated and activated in 15% to 20% of melanomas. This protein occurs upstream of *BRAF*. Mutations in both *NRAS* and *BRAF* are extremely rare.
- *KIT* mutations are seen in up to 10% of cases of melanoma, primarily in those occurring in areas not exposed to sun (acral, mucosal) or in lentigo maligna.
- *GNAQ/GNA11* and *BAP* mutations are seen in uveal melanomas.

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STAGING

1. Define the staging for cutaneous melanoma (AJCC 8th Edition)

TABLE 31.1 ■ Primary Tumor Stage

T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	≤1.0 mm in thickness
	T1a <0.8 mm without ulceration
	T1b <0.8 mm with ulceration or 0.8–1.0 mm with or without ulceration
T2	1.01–2.0 mm in thickness
	T2a without ulceration
	T2b with ulceration
T3	2.01–4.0 mm in thickness
	T3a without ulceration
	T3b with ulceration
T4	>4.0 mm in thickness
	T4a without ulceration
	T4b with ulceration

AJCC, American Joint Committee on Cancer.

TABLE 31.2 ■ Nodal Disease Staging

N0	No regional metastases detected
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases

TABLE 31.3 ■ Staging of Metastasis

M0	No detectable evidence of distant metastases
M1a*	Metastases to skin, soft tissue including muscle, and/or nonregional lymph node
M1b*	Lung metastases
M1c*	Distant metastases to non-CNS visceral sites (kidney, adrenal glands, etc.) with or without M1a or M1b sites of disease
M1d*	Metastases to CNS

CNS, central nervous system; LDH, lactate dehydrogenase

*Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.

TABLE 31.4 ■ Melanoma AJCC 8th edition TNM Stage Group (clinical)

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b, T2a	N0	M0
Stage IIA	T2b, T3a	N0	M0
Stage IIB	T3b, T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T, Tis	N1, N2, or N3	M0
Stage IV	Any T	Any N	M1

AJCC, American Joint Committee on Cancer; TNM, tumor, node, and metastasis.

DIAGNOSIS

1. What genetic mutations should be tested in patients with stage III or IV disease?

- *BRAF V600E* and *V600K* mutation (except in uveal melanomas, which do not harbor *BRAF* mutations)
- *KIT* (about 10%–15% of acral lentiginous and mucosal melanomas). *KIT*-targeted therapy can be considered if *KIT* mutation is identified.

PROGNOSTIC FACTORS

1. What are the various prognostic variables in melanoma?

- Primary lesion:
  - Breslow depth (tumor thickness): this is the most important prognostic factor
- Lymph node involvement
  - Ulceration
- Lactate dehydrogenase (LDH)
- Additional poor prognostic variables: poor performance status, older age, male gender, tumor location in the head and neck area

TREATMENT OF PRIMARY/LOCALIZED MELANOMA

1. What is the surgical management of a primary melanoma?

- Recommended surgical margins for wide excision of primary melanoma

Tumor Thickness	Clinical Margins
In situ	0.5–1 cm
<1 mm	1 cm
>1–2 mm	1–2 cm
>2–4 mm	2 cm
>4 mm	2 cm

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2. When should sentinel lymph node mapping be considered?

- In patients with clinically negative nodes *and* primary melanoma >1 mm thick *or* <0.8 mm thick but associated with ulceration, >1 mitosis/mm^2, positive deep margins, or lymphovascular invasion. There is an improvement in progression-free survival (PFS) with sentinel lymph node mapping, but no improvement in overall survival (OS).

3. What are the management options for a positive sentinel lymph node?

- If there is evidence of lymph node involvement on the sentinel lymph node biopsy, options of management are ultrasound surveillance of involved lymph node basin or immediate completion lymph node dissection depending on the extent of disease and patient choice. Disease-free survival is improved with immediate complete lymph node dissection, but there is no difference in melanoma-specific survival or OS with either approach.

4. What are the indications for adjuvant therapy?

- Adjuvant therapy is only recommended for resected stage III cutaneous melanoma

5. What adjuvant therapy options are approved for stage III melanoma?

- Active surveillance
- Dabrafenib and trametinib (if *BRAF V600* positive)
- Single-agent anti-programmed cell death protein 1 (PD-1) inhibitor (nivolumab or pembrolizumab)
- Alternative, but less preferred options include: ipilimumab (an anti-CTLA-4 inhibitor) and high-dose interferon (IFN) alfa.

TREATMENT OF METASTATIC DISEASE

1. What are the treatment options for metastatic melanoma?

- Categories of treatment for metastatic melanoma include targeted therapy, immunotherapy, surgical resection, chemotherapy, and radiation.

2. What is the role of targeted therapy in metastatic melanoma?

- The Food and Drug Administration (FDA) has approved three BRAF/MEK inhibitor combinations for treatment of unresectable or metastatic disease harboring the *BRAF V600* mutation:
  - Vemurafenib/cobimetinib ± atezolizumab (anti-programmed death ligand 1 [PD-L1] inhibitor)
  - Dabrafenib/trametinib
  - Encorafenib/binimetinib
- Combined therapy has shown higher response rates, longer duration of response, and longer survival compared to BRAF inhibition alone.
- Common side effects with combination therapy include rash, photosensitivity (mainly with vemurafenib/cobimetinib), fever (mainly with dabrafenib/trametinib and can be managed by dose interruption and dose reduction), nausea/vomiting, diarrhea, nonmelanoma skin cancers (lower rate compared to BRAF inhibition alone), ocular toxicity (mainly with encorafenib/binimetinib), cardiomyopathy, QT prolongation, and hepatitis.
- Patients with *KIT* mutations who have progressed on immunotherapy can sometimes be treated off-label with tyrosine kinase inhibitors such as imatinib.

3. What is the role of immunotherapy in treatment of metastatic melanoma?

- First-line immunotherapy options for metastatic melanoma (regardless of *BRAF V600* mutation status) include:
  - Single-agent anti-PD-1 inhibitor
  - Combination ipilimumab/nivolumab
  - Ipilimumab (less preferred)
  - High-dose interleukin-2 (less preferred)
- Single-agent anti-PD-1 inhibitors: Nivolumab and pembrolizumab are FDA-approved monoclonal antibodies for treatment of metastatic melanoma. The superior response rate and lower rates of autoimmune/inflammatory toxicities with single-agent anti-PD-1 inhibitors, favor its use over single-agent anti-CTLA-4 inhibitor (ipilimumab).
- Dual-agent therapy with anti-CTLA-4 and anti-PD-1 inhibitors: Combination ipilimumab/nivolumab is FDA approved for metastatic melanoma. Data from a randomized clinical trial shows a better response rate and PFS than single-agent nivolumab and improved OS compared to ipilimumab. However, rates of immune-related adverse events are significantly higher with combination therapy than single-agent immune checkpoint inhibitors.
- Single-agent anti-CTLA-4 inhibitor: Ipilimumab was the first agent shown to improve OS in metastatic melanoma compared to chemotherapy, but has now fallen out of favor in the frontline treatment setting.
- High-dose interleukin-2: IL-2 is seldom used nowadays given the introduction of immune checkpoint inhibitors. The infusion is commonly administered inpatient due to need for close monitoring of hypotension, acute renal failure, fever, nausea/vomiting/diarrhea, and respiratory failure.
- Talimogene laherparepvec (T-VEC): An oncolytic virus therapy used to treat unresectable, injectable cutaneous, subcutaneous, and nodal melanoma with limited visceral disease.

4. What are the some potential outcomes associated with immunotherapy treatment?

- A relative contraindication to use of immunotherapy is the presence of pre-existing autoimmune conditions, as these may be exacerbated by therapy. Immunotherapy with immune checkpoint inhibitors can cause unpredictable and potentially severe autoimmune inflammatory states involving multiple organ systems, termed immune-related adverse events (irAEs). Several examples of irAEs include dermatitis, arthritis, hypophysitis, thyroiditis, enterocolitis, hepatitis, pancreatitis, pneumonitis, myocarditis, and nephritis. Management of irAEs includes the use of immunosuppressive agents such as glucocorticoids, infliximab, and mycophenolate.
- Due to the (beneficial) recruitment of antitumor T cells to the sites of metastatic disease by the checkpoint inhibitors, increased inflammation can occur at tumor sites. This may lead to CT scans showing transient increases in size of lesions—this is referred to as "pseudoprogression," and in the absence of new lesions or clinical worsening, should not be taken as a sign of treatment failure, but rather monitored with close surveillance scans. Given the rapid growth in use of checkpoint-inhibitor-based therapy, Response Evaluation Criteria in Solid Tumors (RECIST) criteria for radiographic progression have now been replaced by immune-related response criteria (irRC) for patients receiving treatment with these drugs.

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5. How should targeted therapy and immunotherapy be sequenced in *BRAF V600* mutant patients with metastatic disease?

- BRAF/MEK inhibitors have been shown to provide rapid, though short duration of responses (typically between 9 and 12 months). Immunotherapy, conversely, can take longer to produce an objective response, but this response is much more durable.
- As a result, one approach to sequencing therapy is to use BRAF/MEK inhibition as frontline therapy in patients with rapidly progressive/symptomatic disease to achieve faster control, whereas patients with more indolent disease may be started on immune checkpoint inhibitor therapy as frontline treatment.

6. What is the role of chemotherapy in treatment of metastatic melanoma?

- Chemotherapy has traditionally been proven ineffective in metastatic melanoma with response rates typically between 5% and 15% and no improvement in OS.
- The only FDA-approved chemotherapy agent for melanoma is dacarbazine.

QUESTIONS

1. A 60-year-old male with melanoma with lung metastasis has begun frontline treatment with nivolumab. The patient's disease is BRAF wild type. He has been tolerating therapy without signs or symptoms of toxicity. He is feeling well. He undergoes his first set of follow-up CT scans for restaging after three cycles. These show interval growth in several lung nodules compared to pretreatment CT—one nodule has grown from 2 to 3 cm, and another from 1 to 2 cm. Multiple other pulmonary nodules are stable in size.

What should be the next step in treatment?

A. Continue nivolumab
B. Change from nivolumab to pembrolizumab
C. Add ipilimumab to nivolumab
D. Discontinue nivolumab and start standard chemotherapy with dacarbazine

2. A 55-year-old male undergoes complete resection of a 5 mm superficial spreading melanoma of the left thigh. Due to palpable inguinal lymph nodes, he undergoes a complete left inguinal lymph node dissection. This reveals macrometastatic nodal disease, and he is staged as stage IIIC. Mutational testing is negative for *BRAF* and *KIT* mutations. Staging PET/CT shows no additional sites of disease. The patient's oncologist informs him that his risk of relapse is high, and the patient asks what can be done to reduce this risk.

Which of the following statements is the most accurate regarding adjuvant treatment options in stage III melanoma?

A. Adjuvant use of ipilimumab has shown improvement in relapse-free survival (RFS) and overall survival (OS) in stage III melanoma
B. Adjuvant use of ipilimumab has shown improvement in RFS but not OS in stage III melanoma
C. Adjuvant use of nivolumab has shown improvement in OS but not RFS in stage III melanoma
D. Adjuvant use of pembrolizumab has shown improvement in OS but not RFS in stage III melanoma

3. A 60-year-old female is undergoing combination treatment with ipilimumab/nivolumab for metastatic melanoma with lung and liver involvement. She presents to the clinic for her fourth dose of treatment complaining of fatigue. Her blood pressure is noted to be low, at 80/45, and she is tachycardic to the 120s. She is afebrile, and appears fatigued but comfortable. Basic labs show a normal basic metabolic panel (BMP), liver function tests (LFTs), and thyroid-stimulating hormone (TSH). Complete blood count (CBC) is unremarkable. The patient is started on intravenous fluids (IVFs) while in clinic.

What should be the next step in management?
A. Initiate broad-spectrum intravenous antibiotics
B. Perform echocardiogram
C. Obtain AM cortisol and adrenocorticotropic hormone (ACTH)
D. Proceed with treatment as planned following IVF administration

4. A 50-year-old male has been receiving ipilimumab/nivolumab as treatment for metastatic melanoma. After three doses of treatment, he develops profuse watery diarrhea with abdominal cramping and anorexia. CT abdomen/pelvis is consistent with colitis. He is admitted to the hospital and started on high-dose steroids for immune-related colitis. After 1 week on steroids, his stool volume has not significantly decreased, and he continues to have abdominal discomfort. Testing for *Clostridium difficile* is negative and colonoscopy with mucosal biopsy confirms immune-mediated colitis.

In anticipation of the next therapeutic step in management, what diagnostic test should be performed?
A. Repeat CT abdomen/pelvis
B. HIV-1/2 antigen/antibody combination immunoassay testing
C. Antinuclear antibody (ANA) screening
D. Purified protein derivative (PPD) testing for tuberculosis (TB)

5. A 35-year-old female with multiple sclerosis is diagnosed with melanoma with metastases to the lungs. She is found to carry a *BRAF V600E* mutation. Clinically she is well-appearing.

What would be the most appropriate first line of therapy to use?
A. Dabrafenib/trametinib
B. Trametinib monotherapy
C. Ipilimumab/nivolumab
D. Nivolumab monotherapy
E. Dacarbazine

6. A 75-year-old male is diagnosed with melanoma of the rectal mucosa following workup for hematochezia.

Which of the following genetic mutations should you screen for?
A. *KIT*
B. *NRAS*
C. *CDKN2A*
D. *BRAF*
E. A and D

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ANSWERS

1. **A. Continue nivolumab.** The finding of initial tumor growth at some sites of disease early in a treatment course with an immune checkpoint inhibitor may be a sign of pseudoprogression, rather than true disease progression. Because of this unique effect of immunotherapy, a new set of response criteria have been developed, the immune-related response criteria (irRC) to substitute for RECIST. Nivolumab should be continued as the patient is clinically doing well and is tolerating treatment. There is no evidence for efficacy in changing from one anti-PD-1 inhibitor to another, or for adding ipilimumab once nivolumab has already been started. Standard chemotherapy with dacarbazine has shown inferior results compared to immune checkpoint inhibitor therapy.

2. **A. Adjuvant use of ipilimumab has shown improvement in RFS and OS in stage III melanoma.** As of 2020, ipilimumab is the only Food and Drug Administration (FDA)-approved agent to demonstrate improvement in RFS and OS in the adjuvant setting. Nivolumab and pembrolizumab have demonstrated improvement in RFS in stage III melanoma. To date, ongoing trial results are pending regarding the overall survival benefit of nivolumab and pembrolizumab. Due to higher toxicities associated with ipilimumab therapy, nivolumab or pembrolizumab are the preferred adjuvant immunotherapy agents for stage III melanoma without a *BRAF* mutation.

3. **C. Obtain AM cortisol and ACTH.** Common side effects associated with combination ipilimumab/nivolumab are immune-related adverse events, which can lead to endocrinopathies. Incidence seems to increase after the third or fourth doses of treatment. This includes hypophysitis, leading to a secondary adrenal insufficiency. Because symptoms may be nonspecific, there should be a low threshold for testing the pituitary-adrenal axis with serum cortisol, ACTH, ACTH stimulation, or consideration of brain MRI (if headaches due to enlarged pituitary gland). Cardiac and infectious toxicities are not commonly associated with immune checkpoint inhibitor therapy. In the presence of hypophysitis, treatment must be held and steroids may be initiated.

4. **D. PPD testing for TB.** In patients on immune checkpoint inhibitor therapy with immune-mediated colitis that is not improving with steroids, the next step in therapeutic management is initiation of infliximab. Infliximab is a monoclonal antibody targeting tumor necrosis factor alpha (TNF-α). Due to risk for reactivation, patients should undergo testing for TB prior to receiving infliximab.

5. **A. Dabrafenib/trametinib.** Although immune checkpoint inhibitors are approved as monotherapy (nivolumab or pembrolizumab) and in combination (ipilimumab/nivolumab) in patients regardless of *BRAF* mutation status, the patient is at high risk for exacerbation of her multiple sclerosis due to immune activation with these drugs. Thus, targeted therapy would likely

have a safer toxicity profile with the combination of dabrafenib/trametinib. Combination BRAF/MEK inhibitor is more efficacious than trametinib alone. Efficacy of dacarbazine in the frontline setting is low.

6. **E. A and D.** Melanomas arising from mucosal surfaces can harbor *BRAF* as well as *KIT* mutations. Testing for both can provide therapeutic options for these patients.

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CENTRAL NERVOUS SYSTEM MALIGNANCIES

IX

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32 Central Nervous System Tumors

Lisa Chu and Yoshie Umemura

GENERAL

1. What are the common presenting features of central nervous system (CNS) tumors?

- Headache
- Seizures
- Focal neurologic symptoms (focal weakness, gait disturbance, visual symptoms, language deficit)
- Cognitive deficits and behavior changes

2. What are the most important clinical factors in determining prognosis for primary CNS tumors?

- Age (in adults, young age is favorable)
- Performance status (PS)

3. What is the best imaging modality for primary CNS tumors?

- MRI brain. Gadolinium enhancement is a hallmark of high-grade tumors.

4. What primary CNS tumor types may require additional diagnostic evaluation beyond MRI brain?

- Medulloblastoma, CNS germ cell tumors, ependymoma require MRI of total spine. These types and primary CNS lymphoma require cerebrospinal fluid (CSF) examination.

INFILTRATING GLIOMAS

Diagnoses

- World Health Organization (WHO) grade II: Diffuse astrocytoma, oligodendroglioma
- WHO grade III: Anaplastic astrocytoma, anaplastic oligodendroglioma
- WHO grade IV: Glioblastoma (the most common primary malignant brain tumor in adult. Secondary glioblastoma arises in a tumor previously diagnosed as grade II or III glioma), Diffuse midline glioma with *H3K27M* mutation.

1. What are the key molecular diagnostic tests for gliomas?

- Methylguanine methyltransferase (MGMT) promoter methylation (specifically for glioblastoma, anaplastic gliomas, and isocitrate dehydrogenase [IDH] wildtype gliomas). Predictive of alkylator chemotherapy benefit and prognostically favorable regardless of treatment

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- *IDH1/IDH2* mutation. *IDH* mutation required for diagnosis of oligodendroglioma. IDH wildtype gliomas typically behaves similar to glioblastoma regardless of WHO grades. This mutation is actionable.
- Codeletion of 1p and 19q chromosomes (codeletion required for oligodendroglioma)
- *ATRX* mutation (typically seen in diffuse astrocytoma WHO grade II and III)
- *EGFR* and *TERT* mutation, often seen in glioblastoma.
- *H3K27M* mutation. Typically in young adults, midline tumor location.
- Next-generation sequencing of tumor is recommended to identify above and potentially actionable mutations in genes such as *BRAF*.

2. For diffuse gliomas, grades II to III, what are the three molecular classes?

- Most favorable: 1p19q codeletion *and IDH* mutation (molecular oligodendroglioma). Also predictive for treatment efficacy to PCV (procarbazine, CCNU, vincristine) and temozolomide chemotherapy.
- Intermediate: *IDH* mutation but no codeletion (molecularly astrocytoma)
- Most unfavorable: *IDH* wildtype, MGMT promotor unmethylated (majority of glioblastoma)

3. What are high-risk features in low-grade gliomas (LGGs)?

- Pignatti criteria (≥3 criteria of five associated with high risk):
  - Age older than 40
  - Astrocytoma histology
  - Maximum dimension >6 cm
  - Tumor crossing midline
  - Preoperative neurologic deficit

4. What is the standard treatment for newly diagnosed glioblastoma?

- For most adults up to age 70, maximum safe surgical removal, followed by radiation with concomitant daily temozolomide, followed by adjuvant temozolomide
- For most adults over 70, maximum safe surgical removal, followed by standard or hypofractionated radiation with concomitant daily temozolomide, followed by adjuvant temozolomide.
- For the elderly, specifically those with poor functional status, other options after surgery include standard or hypofractionated radiation with or without chemotherapy. May take MGMT promotor methylation status into consideration for chemotherapy decisions. Occasionally cyclic temozolomide monotherapy can be considered.
- For those with severe disability at any age, radiation without temozolomide. Another option is supportive care.
- The addition of bevacizumab to chemoradiation with temozolomide provides no overall survival benefit.
- Other treatments include tumor-treating fields (aka Optune, option to add is considered standard of care) and carmustine wafers (not generally recommended due to concern for infection rate and subsequent exclusion from most clinical trials).
- Patients may exhibit radiation-related changes or pseudoprogression on imaging, most commonly within 3 months after completion of treatment. It is difficult to distinguish from tumor progression. However, it is reasonable to continue

temozolomide with or without corticosteroid therapy and repeat imaging in 1 to 2 months before switching therapy. There are modified versions of response assessment in neuro-oncology (mRANO) and immunotherapy RANO (iRANO) that take pseudoprogression and treatment effect into consideration.

5. What are the most common treatments for recurrent glioblastoma?

- Resection, if the tumor is not in an eloquent area, especially if functional status is good and if time since previous resection approaches or exceeds 1 year.
- Systemic treatments include bevacizumab, temozolomide, lomustine or carmustine, PCV, or regorafenib

6. What is the standard treatment for newly diagnosed anaplastic glioma (grade III)?

- Maximal surgical resection followed by radiation (consider hypofractionated radiation in Karnofsky performance status [KPS] <70)
- For anaplastic or high-risk low-grade gliomas with 1p19q codeletion (oligodendroglioma per 2016 WHO criteria), two large studies have shown that PCV chemotherapy after radiation provides substantial benefit. Temozolomide is also known to have fairly high activity for these tumors. Comparison of temozolomide with PCV as initial treatment, together with radiation, is under assessment (CODEL trial, NCT00887146).
- For astrocytomas, no conclusive studies have been done to assess the benefit of PCV chemotherapy, but cyclic temozolomide after radiation has been shown to be of benefit in anaplastic gliomas without codeletion (CATNON trial, NCT00626990). The benefit of temozolomide concomitant with radiation for these tumors is under assessment.
- In general, at this time, anaplastic or high-risk low-grade astrocytomas are typically treated with upfront radiation with concurrent temozolomide followed by adjuvant temozolomide, and anaplastic or high-risk low-grade oligodendrogliomas are typically treated with one of the CODEL approaches.

7. What agent is approved for the treatment of recurrent anaplastic astrocytoma?

- Temozolomide

8. What is the standard treatment for newly diagnosed diffuse glioma (grade II astrocytoma, oligoastrocytoma, oligodendroglioma)?

- For most patients, optimal surgical resection
- If a patient is asymptomatic other than well-controlled seizures, and tumor is small or moderate in size and lacks enhancement, it may be reasonable to delay resection (i.e., watch-and-wait approach), however, establishing molecular diagnosis is favored as not all high-grade tumors enhance.
- Radiation alone is now outdated, as the addition of chemotherapy (PCV or temozolomide) has shown to provide survival benefit.
- Chemotherapy with PCV following radiation improves overall survival in patients with LGGs when compared to radiation treatment alone.
- Small studies report the use of cyclic temozolomide monotherapy after resection, mainly in patients with codeleted tumors having no neurologic symptoms other than well-controlled seizures, with some indications of benefit.

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9. What are the most common types of very low-grade (grade I) glioma?
- Pilocytic astrocytoma
- Ganglioglioma
- Subependymal giant cell astrocytoma (seen almost exclusively in patients with tuberous sclerosis)
- These tumors are most commonly seen in children and young adults

10. What is the standard treatment for grade I astrocytomas?
- Surgical resection is usually curative

MEDULLOBLASTOMA

Medulloblastoma usually occurs in children, but can also occur in adults—specifically young adults. They are most commonly found in the posterior fossa (cerebellar vermis in young children or hemispheres in older children and adults). Some cases can present with acute hydrocephalus with symptoms of headache, vomiting, somnolence, and gait disturbance.

1. What are the four molecular subtypes of medulloblastoma?
- WNT: best prognosis
- Sonic hedgehog (SHH): intermediate prognosis
- Group 3: characterized by overexpression of MYC, worst prognosis
- Group 4: intermediate prognosis

TREATMENT

1. How is medulloblastoma typically treated?
- Surgical resection of as much of the mass lesion as possible
- Adjuvant therapy depends on risk of recurrence:
  - Standard risk (no evidence of metastasis, small-volume residual disease, classic or desmoplastic histology): standard-dose craniospinal radiation or reduced-dose craniospinal radiation with chemotherapy followed by postradiation chemotherapy
  - High risk: craniospinal radiation with chemotherapy followed by postradiation chemotherapy
- Platinum-containing chemotherapy regimen: cisplatin, cyclophosphamide, lomustine vincristine

2. What staging characteristics identify medulloblastoma tumors to be at high risk for recurrence?
- Postoperative residual tumor >1.5 cm
- Dissemination within nervous system demonstrated by MRI or CSF analysis
- Large cell or anaplastic medulloblastoma

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (NON-AIDS)

Primary central nervous system lymphoma (PCNSL) is an aggressive, uncommon variant of extranodal non-Hodgkin lymphoma (NHL) involving brain, leptomeninges, eyes, or spinal cord without evidence of systemic disease. Pathology is usually diffuse

large B-cell lymphoma (DLBCL). About 20% have leptomeningeal dissemination and 15% have ocular disease at presentation; thus, lumbar puncture (if safe) and slit-lamp examination are important.

DIAGNOSIS

1. What is the best neuroimaging modality in PCNSL?

- MRI with and without gadolinium.

2. What is the MRI characteristic of PCNSL?

- Solitary or multiple homogeneously enhancing lesions, usually with minimal vasogenic edema (less than expected with similarly sized metastatic lesion or glioma)
- Supported by relative darkness on T2 images and evidence for restricted diffusion
- Disappearance (partial or complete) on MRI after initiation of steroid therapy strongly suggests PCNSL.

3. What are the typical locations of PCNSL?

- Periventricular white matter, subcortical/cortical locations, leptomeninges, and vitreous
- About 50% are single and 50% are multiple at diagnosis

4. What is the diagnostic procedure of choice for PCNSL?

- When imaging findings suggest PCNSL, cytologic and flow cytometry examination of the CSF can sometimes establish the diagnosis.
- In most case, stereotactic biopsy is needed for diagnosis.
- Resection is not generally recommended when PCNSL is suspected.

STAGING

1. What is the staging workup of PCNSL?

- Once diagnosis of PCNSL is confirmed, the International PCNSL Collaborative Group recommends:
  - CNS staging with:
    - Brain and total spine MRI (avoid obtaining MRI brain within 24 hours after lumbar puncture which can cause contrast artifact)
    - CSF exam (if lumbar puncture is safe). CSF should be evaluated for cell count with differential, protein, glucose, hematopathology review, flow cytometry at a minimum. Can consider adding IGH rearrangement for B-cell clonality.
    - Ophthalmology evaluation including slit-lamp exam.
  - Systemic staging with:
    - CT of the chest, abdomen, and pelvis, or body PET
    - HIV test
    - Lactate dehydrogenase (LDH)
    - Testicular exam in males versus testicular ultrasound (US) in men >60 years old
    - Bone marrow biopsy (often deferred if other systemic work up is negative)

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PROGNOSTIC FACTORS

1. What are the prognostic factors of PCNSL?

- From the International Extranodal Lymphoma Study Group, the following are negative prognostic predictors:
  - Age older than 60
  - Eastern Cooperative Oncology Group (ECOG) PS >1
  - Elevated serum LDH
  - Elevated CSF protein
  - Involvement of deep brain regions
  - Immunocompromised state also confers a worse prognosis
- From MSKCC in 2006, a simpler system was proposed that only consists of patient age and KPS.

TREATMENT

1. What is the role of steroids in PCNSL?

- When PCNSL is suspected, steroid therapy should be avoided prior to diagnosis (if safe to do so) to avoid:
  - "Vanishing tumor" syndrome with regression of tumor mass
  - Interference with histopathologic diagnosis
- Once diagnosis is established, steroid therapy is generally appropriate. It is important to have a taper plan to avoid complications related to long-term steroid use.

2. What is the current standard induction therapy of PCNSL?

- Selection of primary therapy depends on the general health and age
  - For healthy patients, a high-dose methotrexate-based multidrug chemotherapy regimen is recommended. Evidence supports inclusion of rituximab and cytarabine.
  - For patients who are not a candidate for systemic chemotherapy, whole-brain radiation therapy (WBRT) may be considered

3. What are commonly used induction chemotherapy regimens in PCNSL?

- High-dose methotrexate with rituximab, procarbazine, and vincristine (R-MPV, aka MSKCC regimen), followed by cytarabine consolidation ± low-dose WBRT
- High-dose methotrexate with rituximab and temozolomide (MTR, aka CALGB regimen), followed by consolidation with etoposide and cytarabine

4. What is the role of intrathecal chemotherapy in PCNSL?

- Leptomeningeal lymphoma. Preferred administration via intraventricular reservoir to avoid complications from multiple lumbar punctures and reduce toxicity to cauda equina.
- Prophylactic intrathecal chemotherapy has no evidence for clinical benefit.

5. What is the treatment of recurrent PCNSL following systemic therapy?

- If recurrence occurs later than 1 year, retreating with the same or different high-dose methotrexate-based regimen is an option.
- If recurrence occurs earlier than 1 year, WBRT with or without systemic therapy is recommended.
- Best supportive care is also an option, particularly for those with poor PS.

MENINGIOMA

Meningioma is an extra-axial CNS tumor arising from the arachnoid cap cells in the meninges. They are the most common primary brain tumors and while most are benign, they can cause problems depending on their location.

DIAGNOSIS

1. What is the best imaging modality for diagnosis of meningioma?

- MRI with gadolinium

2. What are the MRI characteristics of meningioma?

- Dome-shaped mass with broad dural attachment
- Smooth well-defined contours
- Isointense with gray matter
- Homogeneous enhancement
- Enhancing dural tail

GRADING, PROGNOSTIC FACTORS

1. What factors impact rate of recurrence in meningioma?

- Tumor grade
- Extent of resection

2. What is the grading system of meningioma? What is the risk of recurrence after gross total resection based on grade of meningioma?

TABLE 32.1 ■ Grading System of Meningioma

Grade	Incidence (%)	Risk of Recurrence (%)
I—typically benign	92	1–16
II—atypical	6	20–41
III—anaplastic	2	56–53

TREATMENT

1. What are the treatment options for meningioma?

- Observation: if small (≤3 cm) and asymptomatic (or symptomatic with well-controlled seizure)
- Surgery: if accessible and if treatment is needed (large, growing, or symptomatic)
- Radiation: if treatment is needed and not a surgical candidate

2. What are the indications for radiation in meningioma following resection?

- All grade III meningioma (even after gross total resection)
- Incompletely resected grade II
- Completely resected grade II (radiation optional)
- Large (>3 cm) unresectable grade I or large residual after resection of grade I
- Symptomatic unresectable grade I (including symptoms other than seizures)

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3. Which type of radiation modality is used in meningioma?
- Fractionated conformal radiotherapy
- Stereotactic radiosurgery (SRS) (generally only if maximum dimension is <3 cm)

4. What systemic therapies are used in meningioma?
- Sunitinib, bevacizumab monotherapy or with everolimus are all in use. However, there is no high-quality evidence supporting any of these.

BRAIN METASTASES

Brain metastases are more common than primary brain tumors. About 10% of cancer patients develop symptomatic brain metastases, presenting with headache, focal neurologic impairment, mental status changes, or seizures. The most common part of the brain affected by metastases is the cerebral hemisphere.

1. What are the most common cancers of origins of brain metastasis?
- Lung cancer
- Breast cancer
- Melanoma

TREATMENT

1. When multiple metastatic lesions are present, what is the role of resection?
- To obtain biopsy sample when diagnosis cannot be obtained systemically
- To relieve mass effect, uncommonly one large metastasis is resected in a patient who otherwise has a reasonable prognosis.

2. What is the role of radiotherapy for metastases?
- To decrease local recurrence (WBRT or SRS)
- To decrease recurrence at new sites in the brain (WBRT only)
- To decrease likelihood of neurologic disability and death

3. What is the best modality of treatment for limited (1–3) metastatic lesions?
- Depends on number of metastases and size of tumor
- For single metastasis, surgical resection if safe, followed by SRS if tumor bed <30 mm
- For single unresectable metastasis or for two to three metastases, if all are <30 mm in size, SRS alone
- Compared to treatment with SRS, WBRT is associated with identical survival, worse quality of life, worse cognitive function, but lower rate of recurrence elsewhere in brain
- For most patients with one to three metastases <3 cm in size, SRS is preferred over WBRT

4. In what situation is WBRT recommended?
- Any unresectable tumor >3 cm, or tumor bed >3 cm after resection
- Four or more metastases

QUESTIONS

1. A 56-year-old man presents to the neurology clinic due to concerns of intermittent right arm numbness. Imaging reveals the presence of a large left parietal mass. He undergoes surgery and has a subtotal resection of the tumor. Final pathology returns as anaplastic astrocytoma, isocitrate dehydrogenase (*IDH*) mutated.

   Which of the following statements is true regarding this patient's prognosis?
   A. *IDH* mutated tumors have an inferior prognosis
   B. *IDH* mutated tumors have a superior prognosis
   C. Prognosis is not impacted by *IDH* mutation status in anaplastic astrocytoma

2. A 59-year-old woman presented to her primary care physician due to increasing difficulty with word finding. MRI brain was ordered and the patient was found to have a ring-enhancing mass in the right frontal lobe. She underwent subtotal resection of the tumor and recovered well following the surgery. Pathology demonstrated glioblastoma with O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation.

   How would you treat this patient after surgery?
   A. Adjuvant radiation concurrent with temozolomide
   B. Adjuvant radiation concurrent with temozolomide followed by six cycles of postradiation temozolomide
   C. Adjuvant radiation concurrent with temozolomide followed by six cycles of postradiation temozolomide and bevacizumab
   D. Radiation only

3. A 53-year-old woman was diagnosed with a left parietal lobe glioblastoma approximately 3 months ago. She underwent maximum surgical resection and postoperative imaging did reveal minimal residual tumor. She subsequently underwent radiation therapy concurrent with temozolomide. She now returns to the clinic 4 weeks after radiation completion to begin postradiation temozolomide; however, MRI has revealed increased contrast enhancement in the area of the residual tumor. The patient feels well and has not developed any new symptoms since initiating therapy.

   What should you advise the patient?
   A. Stop temozolomide and initiate bevacizumab for treatment of recurrent disease
   B. Biopsy the area of concern to confirm disease recurrence
   C. Continue with adjuvant postradiation temozolomide as previously planned
   D. Continue with adjuvant postradiation temozolomide as previously planned, but add bevacizumab

4. A very active 60-year-old man presents to his primary care physician with his wife, who is concerned that the patient has "not been acting like himself" recently. She believes his behavior has been more impulsive. MRI of the brain reveals a solitary enhancing lesion approximately 3 cm

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in size with minimal vasogenic edema. The scan is read as suspicious for primary central nervous system (CNS) lymphoma. Cerebrospinal fluid (CSF) exam confirms a diagnosis of large B-cell lymphoma. There is no evidence of disease outside of the CNS on staging imaging. He is treated with a high-dose methotrexate-based multidrug chemotherapy and goes into remission. Unfortunately, 2 years later he is found to have recurrent CNS lymphoma. His performance status remains excellent.

The most appropriate initial therapy for this patient is as follows:

A. Radiation therapy concurrent with temozolomide
B. High-dose methotrexate-based multi-drug chemotherapy
C. Whole-brain radiation therapy (WBRT)
D. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
E. Best supportive care

5. A 45-year-old man with a history of stage II non–small cell lung cancer (NSCLC) diagnosed 4 years ago previously is brought to the ED after a seizure witnessed by his family members. MRI reveals the presence of at least 10 right temporal lobe masses, one of which is 3.2 cm with surrounding vasogenic edema, concerning for a neoplastic process. CT of chest/abdomen/pelvis to complete his staging shows several liver metastases. Biopsy of a liver lesion confirms the diagnosis of recurrent NSCLC.

In addition to urgent administration of steroids, what is the most appropriate initial treatment for his brain metastases?

A. Surgical resection
B. Whole-brain radiation therapy (WBRT)
C. EGFR inhibitor
D. Intrathecal chemotherapy

ANSWERS

1. **B. IDH mutated tumors have a superior prognosis.** *IDH* mutated anaplastic astrocytomas have superior outcomes compared to those without mutations. Additional molecular markers that have been associated with improved prognosis include methylation of the methylguanine methyltransferase (MGMT) promoter as well as codeletion of 1p/19q.

2. **B. Adjuvant radiation concurrent with temozolomide followed by six cycles of postradiation temozolomide.** MGMT promoter hypermethylation in patients with glioblastoma predicts benefit from temozolomide therapy. Additionally, MGMT promoter hypermethylation also portends a better prognosis regardless of treatment received. The addition of bevacizumab to standard chemoradiotherapy following optimal surgical debulking of glioblastoma has not been shown to improve overall survival and, therefore, is not recommended in this setting. Finally, temozolomide plus radiation therapy has been demonstrated to be superior to radiation therapy alone following maximum surgical debulking in glioblastoma.

3. **C. Continue with adjuvant postradiation temozolomide as previously planned.** The scenario described in this question may represent pseudoprogression, which is a common imaging finding in patients who have just received radiation plus temozolomide for treatment of glioblastoma.

4. **B. High-dose methotrexate-based multidrug chemotherapy.** High-dose methotrexate-based multidrug chemotherapy is the recommended treatment for recurrent primary CNS lymphoma for recurrence that occurs later than 1 year. This can be the same or different high-dose methotrexate-based regimen. If reoccurrence occurs earlier than 1 year, WBRT with or without systemic therapy is recommended. While R-CHOP is most commonly used for the treatment of systemic diffuse large B-cell lymphoma (DLBCL), it does not penetrate the CNS well and is not recommended as treatment for lymphoma arising in the CNS. Radiation plus temozolomide is the appropriate treatment for glioblastoma following maximum surgical debulking. Best supportive care is an option, particularly those with poor performance status.

5. **B. WBRT.** In the case of multiple brain metastasis or those >3 cm, WBRT is the preferred approach. Treatment depends on the number of metastases and size of the tumor. If he had three or less metastases (<3 cm), he could undergo surgical resection with stereotactic radiosurgery (SRS). In that situation, SRS as the initial approach could also be appropriate. While some EGFR inhibitors may have some penetration into the central nervous system (CNS), use of systemic therapy alone is not appropriate in this scenario.

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GYNECOLOGIC MALIGNANCIES

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Cervical, Vulvar, and Vaginal Cancers

33

Kevin W. McCool and Karen McLean

ETIOLOGY, RISK FACTORS, AND HISTOLOGIC SUBTYPES

1. What are risk factors for cervical cancer?

- Human papillomavirus (HPV) is associated with 99% of cases. The most common HPV viral subtypes associated with cervical cancer are 16 and 18, and the two viral types most frequently associated with genital warts are 6 and 11.
- Smoking, increased number of lifetime sexual partners, HIV infection, immunosuppression, and oral contraceptive use increase the risk.

2. What are the risk factors for vulvar or vaginal cancer?

- The majority (80%) of vulvar lesions are associated with HPV 16.
- Other risk factors include chronic inflammation (such as lichen sclerosis), prior history of cervical cancer, immunodeficiency or immunosuppression, and tobacco use.
- Bimodal distribution of vulvar cancer: Disease is HPV-associated in young women, while it is associated with lichen sclerosis in older women.

3. What are the histologic subtypes of cervical, vulvar, and vaginal cancers?

TABLE 33.1 ■ Histological Subtypes by Site

Site	Histology
Cervical	Squamous: 70%–80% Adenocarcinoma or adenosquamous: 20%–30%
Vulvar	Squamous: 90% Melanoma: 2%–10% Adenocarcinoma: <10% Extramammary Paget's: 1%–5% (rare intraepithelial lesion accounting for 1%–5% of lesions and can be associated with underlying adenocarcinoma of another primary site including rectum, bladder, or breast [15%–35%]).
Vaginal	Squamous: 80%–90% Adenocarcinoma: rare Clear cell: rare, associated with in utero diethylstilbestrol (DES) exposure Melanoma: rare Sarcoma: very rare

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STAGING

1. How is cervical cancer staged using International Federation of Gynecology and Obstetrics (FIGO) staging?

- Cervical cancer has historically utilized a strict clinical staging system (advanced imaging such as PET or MRI not allowed) due to the high incidence of cervical cancer in low-resource countries. The rationale was to establish parity in outcomes that was unaffected by country of diagnosis. However, a major staging update in 2018 now utilizes advanced imaging in the staging.

TABLE 33.2 ■ 2018 FIGO Cervical Cancer Staging

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
IA	Confined to the cervix, microscopic disease with maximum depth of invasion <5 mm
IA1	Measured stromal invasion <3 mm in depth
IA2	Measure stromal invasion ≥3 mm and <5 mm in depth
IB	Confined to the cervix, macroscopic disease
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The cervical carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	Invasion beyond cervix, with parametrial involvement
III	Extension to pelvic wall, and/or lower third of vagina, and/or causing hydronephrosis, and/or involving pelvic/para-aortic lymph nodes
IIIA	Carcinoma involves the lower third of the vagina, does not extend to pelvic sidewall
IIIB	Extension of carcinoma to pelvic sidewall, and/or hydronephrosis or nonfunctioning kidney
IIIC	Involvement of pelvic or para-aortic lymph nodes (notation of r or p is added to stage if diagnoses radiographically or pathologically, respectively)

(*continued*)

TABLE 33.2 ■ 2018 FIGO Cervical Cancer Staging (*continued*)

Stage	Description
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum
IVA	Extension beyond the true pelvis or involving mucosa of bladder or rectum (biopsy-proven)
IVB	Distant metastasis

FIGO, International Federation of Gynecology and Obstetrics.

2. How is vulvar cancer staged (FIGO staging, nonmelanoma)?

TABLE 33.3 ■ 2018 FIGO Vulvar Cancer Staging

Stage	Description
0	Carcinoma in situ
I	Tumor confined to the vulva and/or perineum
IA	Tumor confined to vulva or perineum, tumor size <2 cm, stromal invasion <1 mm
IB	Tumor confined to vulva or perineum, tumor size >2 cm, or any tumor size with stromal invasion >1 mm
II	Tumor of any size extends to adjacent perineal structures (anus, lower one-third of urethra or vagina), inguinal nodes negative
III	Tumor of any size with regional (i.e., inguinal) lymph node metastasis
IIIA	One or two lymph node metastases each less than 5 mm, or one lymph node metastasis greater than or equal to 5 mm
IIIB	Three or more lymph node metastases each less than 5 mm, or two or more lymph node metastases greater than or equal to 5 mm
IIIC	Lymph node(s) with extranodal extension
IV	Tumor of any size with regional visceral or bony extension, fixed or ulcerated lymph nodes or distant metastatic spread
IVA	Tumor invades upper two-thirds of urethra or vagina, bladder or rectal mucosa, or fixed to pelvic bone, or fixed or ulcerated inguinofemoral lymph nodes
IVB	Distant metastatic disease (including pelvic lymph nodes)

Vulvar melanoma staging—Starting in 2017, staged according to separate vulvar melanoma staging guidelines.

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TREATMENT

1. How is cervical cancer treated?

TABLE 33.4 ■ Cervical Cancer Treatment Methods by Stage

Stage	Treatment: Fertility-sparing option	Treatment: Nonfertility sparing option
Preinvasive dysplasia	Excisional procedure (e.g., loop electrosurgical excision or cold knife cone excision). In select circumstances, an ablative procedure can be performed.	
IA1 with no LVSI	Cervical conization (if negative margins)	Surgery with "simple" (nonradical) hysterectomy with removal of uterus and cervix
IA1 with LVSI, or IA2	Radical trachelectomy (removal of the cervix) + lymph node dissection	Modified radical hysterectomy* with pelvic lymph node dissection (see additional details in the Footnote)
IB1, IB2, or IIA1	Only in select cases of IB1 or IB2: Radical trachelectomy (removal of the cervix) + lymph node dissection	Radical hysterectomy* with parametrectomy, upper vaginectomy, and pelvic lymph node dissection (see additional details in the Footnote)
IB3 or IIA2	None	Preferred option: Definitive radiation (external beam + brachytherapy) with concurrent cisplatin chemosensitization OR Radical hysterectomy with parametrectomy, upper vaginectomy, and pelvic lymph node dissection
IIB, III, IVA	None	Definitive radiation (external beam + brachytherapy) with concurrent chemosensitization
IVB	None	Palliative systemic chemotherapy tumor-directed radiation therapy

*Additional details:

- Results from a randomized clinical trial indicate that radical hysterectomy should be performed via open abdominal route (i.e., avoid laparoscopic or robotic minimally invasive approach) due to increased risk of recurrence in minimally invasive surgery group.
- Adjuvant radiation is added following radical hysterectomy if pathology reveals a combination of poor pathologic prognostic factors known as "Sedlis Criteria" (+lymphovascular space invasion [LVSI], deep stromal invasion, large tumor size).

2. How is vulvar cancer treated?

TABLE 33.5 ■ Vulvar Cancer Treatment Methods by Stage

Stage	Treatment
Preinvasive dysplasia	Local therapy by one of the following methods: wide local excision, carbon dioxide laser photoablation, or topical therapy*
IA	Surgery: wide local excision
IB	Surgery: radical vulvar resection plus lymph node evaluation (increasingly via sentinel lymph node dissection) ■ For lymph node evaluation: if lesion is ≥2 cm from midline, an ipsilateral nodal evaluation is performed. If lesion is <2 cm from midline, bilateral nodal evaluation is performed
II, III, IVA	Neoadjuvant radiation with cisplatin (usually) or 5-flurouracil chemosensitization followed by surgical resection if persistent disease OR Radical surgical vulvar resection plus lymph node dissection
IVB	Palliative systemic chemotherapy ± tumor-directed radiation therapy

*5-Fluorouracil and imiquimod can be used off-label for treatment of high-grade vulvar dysplasia.

3. What is the role of palliative chemotherapy in advanced or recurrent cervical cancer?

- Recommended first-line treatment for metastatic or recurrent cervical cancer is cisplatin/paclitaxel/bevacizumab or topotecan/paclitaxel/bevacizumab (Level 1 evidence, overall survival benefit with addition of bevacizumab).
- Carboplatin can be substituted for cisplatin for recurrent disease if prior exposure to cisplatin during initial primary chemoradiation.
- Pembrolizumab is approved for programmed death cell ligand (PD-L1) positive tumors as second-line systemic therapy.
- Additional active agents include ifosfamide.
- Platinum doublets modestly improve response rates over single-agent therapy.
- Therapy has modest response rates of short duration (20%–30% response rates, median overall survival 10–12 months).

4. What is the role of palliative chemotherapy in advanced or recurrent vulvar cancer?

- Limited high-quality data due to low incidence.
- Most regimens are extrapolated from experience in cervical cancer (e.g., cisplatin/paclitaxel/bevacizumab).
- Overall response rates are low with short durations of response.

5. What treatment modalities are used to treat vaginal cancers?

- There are no RCTs to guide optimal treatment in vaginal cancer, so broad strategies are extrapolated from vulvar cancer treatment.

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- Radiation (external beam radiotherapy and/or brachytherapy). Consider chemosensitization with cisplatin or 5-fluorouracil.
- Surgery is used in select stage I cases.
- No clear role for systemic chemotherapy alone in up-front treatment.

SPECIAL CONSIDERATIONS

1. Prevention: What strategies are available to decrease cervical cancer risk?

- Smoking cessation: Tobacco exposure is unequivocally linked to persistent dysplasia and risk of progression to invasive cancer. Available epidemiologic data links smoking cessation with reduced incidence and size of cervical precancerous lesions.
- Vaccination. There have been three Food and Drug Administration (FDA)-approved HPV vaccines developed: Gardasil, Cervarix, and Gardasil 9 (only vaccine available in the United States as of 2020). Routine HPV vaccination of both males and females is recommended at 11 to 12 years and continuing up to 26 years of age. Vaccination can be offered to both males and females between age 27 and 45.

2. What are the components of cervical cancer screening and who sets the guidelines?

- Historically, Papanicolaou (Pap) testing consisted only of assessing cytology of cells obtained from a cervical smear/brush. Increasingly, molecular testing for HPV high-risk subtypes is being added to the algorithms for testing.
- Screening guidelines are set by the following national organizations:
  - American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ASCCP/ASCP)
  - American Cancer Society
  - U.S. Preventive Services Task Force (USPSTF)
- Although the FDA has approved an HPV-alone screening test, the ASCCP has not yet recommended this approach for cervical cancer screening.
- After age 65 years or hysterectomy for benign disease, continued screening is not indicated unless there is a history of moderate dysplasia (CIN2) or more severe cervical pathology diagnosis.

QUESTIONS

1. It is recommended that a human papillomavirus (HPV) vaccine series be administered to which of the following patient populations:

A. Only males 9 to 21 years old
B. Only females 9 to 26 years old
C. All sexually active women
D. Males and females 9 to 26 years old
E. It is not recommended as routine vaccination for any patients

2. A 31-year-old woman with abnormal Pap testing is referred to your clinic following a recent biopsy of the cervix during colposcopy that showed squamous cell carcinoma. There is no visible lesion on your exam in the office.

The next best step in her treatment is:
A. Excisional procedure such as cervical cold knife conization
B. Simple extra-fascial hysterectomy (uterus and cervix only)
C. Abdominal radical hysterectomy with parametrectomy, upper vaginectomy, and pelvic lymph node dissection
D. Radiation with cisplatin sensitization

3. A 78-year-old woman with a long-standing history of lichen sclerosus presents to your clinic with a 1.5 cm left vulvar carcinoma (3 mm depth of invasion) that is located approximately 3 cm from the midline. She has no palpable inguinal adenopathy on exam.

Recommended treatment is:
A. Systemic chemotherapy with cisplatin, paclitaxel, and bevacizumab
B. Radiation therapy to the vulva with cisplatin sensitization
C. Surgery with radical vulvectomy and bilateral lymph node dissection
D. Surgery with radical vulvectomy and left inguinal lymph node dissection

4. A 56-year-old patient with a history of stage IB2 squamous cell cancer of the cervix previously treated with definitive surgical management (radical hysterectomy with parametrectomy and upper vaginectomy, plus pelvic lymph node dissection) is found to have multiple new lung lesions. Biopsy confirms recurrent squamous cell carcinoma. The biopsy specimen shows a programmed death cell ligand (PD-L1) combined positive score (CPS) of 3 (positive).

The next best step in her treatment is:
A. Radiation with chemosensitization
B. Systemic chemotherapy with cisplatin, paclitaxel, and bevacizumab
C. Systemic therapy with pembrolizumab
D. Systemic chemotherapy with carboplatin and paclitaxel

5. A 37-year-old patient with limited prior medical care presents with 2 years of postcoital bleeding. Biopsy confirms invasive squamous cell carcinoma of the cervix, and clinical staging is consistent with Stage IB1.

What is the recommended treatment?
A. Definitive chemoradiation (external beam plus brachytherapy, with cisplatin sensitization)
B. Robotic radical hysterectomy with parametrectomy, upper vaginectomy, and pelvic lymph node dissection
C. Abdominal radical hysterectomy with parametrectomy, upper vaginectomy, and pelvic lymph node dissection
D. Systemic chemotherapy with cisplatin/paclitaxel/bevacizumab

6. Vulvar dysplasia may be treated with:
A. Surgical resection
B. Laser ablation
C. Topical treatment with imiquimod
D. All of the above

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ANSWERS

1. **D. Males and females 9 to 26 years old.** The Centers for Disease Control and Prevention recommends that an HPV vaccine series be administered to males and females aged 9 to 26 years. The preferred age for vaccination is 11 or 12 years old. Males and females up to age 26 should be offered "catch-up" vaccination if not previously immunized.

2. **A. Excisional procedure.** The key feature of this case is that the carcinoma was diagnosed by biopsy and there is no visible lesion. In the setting of microscopic disease, additional pathologic features that are not routinely available on cervical biopsies are essential to determine appropriate treatment. As a result, an excisional procedure (usually cold knife conization) is required to clarify stage and to assist in counseling a patient on fertility-sparing options for treatment. The other options potentially place the patient at risk of both over- or undertreatment, and thus additional pathologic data is needed first.

3. **D. Surgery with radical vulvectomy and left inguinal lymph node dissection.** Patients with squamous cell carcinoma of the vulva confined to the vulva/perineum should undergo surgical resection with radical vulvectomy. Inguinal lymph node dissection by either sentinel lymph node dissection or full lymphadenectomy is recommended if the depth of invasion of the primary lesion is greater than 1 mm. For lesions that are "lateralized" greater than 2 cm from the midline, a unilateral lymphadenectomy may be performed. Bilateral lymph node dissection is performed only for lesions close to the midline. If the tumor extends to adjacent structures such as the urethra or anus (not present in this case), primary radiation therapy with chemosensitization can be considered rather than resection for up-front therapy. Systemic chemotherapy is reserved for patients with recurrent or metastatic disease.

4. **B. Systemic chemotherapy with cisplatin, paclitaxel, and bevacizumab.** The question stem describes a first recurrence after prior definitive surgical management. The recommended frontline therapy for recurrent disease is systemic chemotherapy. Inclusion of bevacizumab is associated with a modest but measurable overall survival benefit. Radiation with chemosensitization can be a definitive primary therapy, but has limited role in setting of systemic recurrence. While this patient's tumor is PD-L1 positive, pembrolizumab is reserved for second-line therapy in the recurrent setting. Carboplatin and paclitaxel is a possible alternative, but the preferred frontline therapy is cisplatin/paclitaxel/bevacizumab.

5. **C. Abdominal radical hysterectomy with parametrectomy, upper vaginectomy, and pelvic lymph node dissection**. Based on the results of the Laparoscopic Approach to Cervical Cancer (LACC) trial, all patients undergoing radical hysterectomy for cervical cancer should be counseled on the increased risk of recurrence if surgery is performed via a minimally invasive route. As a result, the abdominal route is preferred. Appropriate surgical management of early stage cervical cancer is associated with high cure rates and lower long-term morbidity than definitive chemoradiation.

6. **D. All of the above.** All of these treatments are valid options for patients with preinvasive vulvar lesions. Topical treatments are currently not Food and Drug Administration (FDA)-approved but a systematic review showed that clinical response rates are as high as 50%.

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34 Ovarian Cancer

Nicole M. Grogan and Karen McLean

PATHOLOGY

- Ovarian cancers are a heterogenous set of diseases of different histologic subtypes, treatments, and outcomes. Table 34.1 summarizes the most common subtypes of ovarian cancer:

TABLE 34.1 ■ Summary of Most Common Subtypes of Ovarian Cancer

Tumor Type	Histologic Subtype	Disease Markers	Frequency
Epithelial	Papillary Serous	CA-125	80%–90% of ovarian cancers (papillary serous most common [50%], followed by endometrioid and mucinous [10%–15%])
	Endometrioid	CA-125	
	Mucinous	CA 19-9, CEA	
	Carcinosarcoma	CA-125	
	Clear cell	CA-125	
Sex cord-stromal	Granulosa cell	Inhibin A and B, Estradiol	3% of ovarian cancers
	Sertoli-Leydig	Testosterone	<1% of ovarian cancers
Germ cell	Dysgerminoma	LDH, placental alkaline phosphatase	3%–5% of ovarian cancers (dysgerminoma most common [50%])
	Teratoma	None	
	Endodermal Sinus (yolk sac tumor)	AFP	
	Embryonal Carcinoma	AFP, hCG	
Metastatic	Typically primary from gynecologic (endometrial, cervical), breast, lymphoma, or GI (Krukenberg tumors)	Dependent on primary tumor	5%–6% of ovarian cancers

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- High-grade serous carcinomas of ovarian, Fallopian tube, and primary peritoneal origins are considered to be similar diseases and are clinically treated as the same entity. The fimbriated end of the Fallopian tube is now believed to be the cell of origin for the majority of high-grade serous carcinomas, which remain collectively termed "ovarian cancer."
- Low-grade serous ovarian carcinoma is considered a separate entity from high-grade serous ovarian carcinoma, comprising less than 10% of the serous carcinomas of the ovary.
- Borderline or low malignant potential (LMP) tumors comprise a subset (approximately 15%–20%) of epithelial tumors. These are noninvasive tumors with malignant cytological features.

ETIOLOGY AND RISK FACTORS

1. The following are risk factors for and protective factors against the development of epithelial ovarian cancer:

TABLE 34.2 ■ Risk Factors and Protective Factors

Risk Factors	Protective Factors
Older age	History of salpingo-oophorectomy
Personal or family history of breast or ovarian cancer	Lactation
Early menarche or late menopause	Use of oral contraceptives for 5 y
Nulliparity, infertility, or age over 35 at first birth	Multiparity

2. The role of hereditary factors in epithelial ovarian cancer:

- Up to 15% to 20% of ovarian cancers have been associated with germline mutations, mainly in genes related to DNA damage repair, including *BRCA1* and *BRCA2*. Guideline recommendations are for genetic counseling and consideration of testing for all women with a personal history of ovarian cancer, independent of family history.
- Genes associated with hereditary breast and ovarian cancer syndromes

TABLE 34.3 ■ Summary of Genes Associated With Hereditary Breast and Ovarian Cancer Syndromes

Mechanism of Damage	Implicated Genes	Ovarian Cancer Risk Lifetime Risk	Additional Cancer Risk
Loss of DNA damage repair	*BRCA1*	16%–44%	Breast cancer
	BRCA2	20%	
	RAD51C	1%	Potential increase in breast cancer (triple-negative)
	RAD51D	2.3%	

(*continued*)

TABLE 34.3 ■ Summary of Genes Associated With Hereditary Breast and Ovarian Cancer Syndromes (*continued*)

Mechanism of Damage	Implicated Genes	Ovarian Cancer Risk Lifetime Risk	Additional Cancer Risk
Loss of DNA mismatch repair	*MSH2*	10%–38%	HNPCC: colon cancer, breast cancer (lobular), and endometrial cancer
	MLH1	5%–20%	
	MSH6	1%–11%	
	PMS2	Not well established	

HNPCC, hereditary nonpolyposis colorectal cancer.

STAGING

1. Simplified staging (substages not shown) for ovarian cancer based on the International Federation of Gynecology and Obstetrics (FIGO) stages for ovary, fallopian tube, and primary peritoneal cancer:

TABLE 34.4 ■ FIGO Stages for Ovary, Fallopian Tube, and Primary Peritoneal Cancer

Stage	Location of Disease
I	Tumor confined to ovaries
II	Tumor involves one or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer
III	Tumor involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IVA	Distant metastasis—pleural effusion with positive cytology
IVB	Distant metastasis—hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

FIGO, International Federation of Gynecology and Obstetrics.

- Seventy percent of patients have stage III or IV disease at the time of diagnosis.

MANAGEMENT

1. Principles of surgery:

- Comprehensive surgical staging includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, lymph node assessment, and resection of any visible disease.
- Fertility sparing surgery, including retention of the uterus/cervix and contralateral ovary, may be acceptable in a subset of patients, depending on histologic type and stage.
- Surgery should be performed by a gynecologic oncologist, as studies have demonstrated that patients have improved survival outcomes with surgery by these

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subspecialists as compared to when surgery is done by a surgical oncologist or general gynecologist.

- Goal of surgery is to resect all visible diseases such that only microscopic residual disease remains (i.e., to obtain an optimal debulking to zero measurable residual or "R0").
- In patients with suspected unresectable disease, consideration should be given to neoadjuvant chemotherapy prior to surgical debulking. Laparoscopic assessment of resectability may be employed.

2. Principles of first-line therapy:

- Treatment of patients with early-stage epithelial ovarian cancer
  - Surgery alone is the treatment for patients with stage IA or IB, grade 1 tumors. No chemotherapy is indicated.
  - For high-risk early stage disease (stage IA or B grade 2–3, or stage IC), surgery and three to six cycles of intravenous (IV) carboplatin with taxane are indicated.

TABLE 34.5 ■ Systemic Therapy for Patients with Stage II–IV Ovarian Cancer

Tumor Type	Histologic Subtype	Preferred First-Line Therapy Options	Maintenance Therapy
Epithelial	High-grade Serous Endometrioid Carcinosarcoma	1. Carboplatin + paclitaxel 2. Carboplatin + paclitaxel + bevacizumab 3. IV/IP: taxane + cisplatin	1. If *BRCA* mutation or HRD*: PARP inhibitor† 2. If given carboplatin + paclitaxel + bevacizumab as first line: bevacizumab maintenance
	Mucinous	1. FOLFOX: 5-FU + leucovorin + oxaliplatin 2. CAPOX: capecitabine + oxaliplatin	None
	Low-grade Serous	1. Carboplatin + paclitaxel 2. Carboplatin + paclitaxel + bevacizumab	1. If given carboplatin + paclitaxel + bevacizumab as first line: bevacizumab maintenance 2. Consider maintenance hormonal therapy (e.g., aromatase inhibitors)

(*continued*)

TABLE 34.5 ■ Systemic Therapy for Patients with Stage II–IV Ovarian Cancer (*continued*)

Tumor Type	Histologic Subtype	Preferred First-Line Therapy Options	Maintenance Therapy
Germ cell tumor		BEP: bleomycin + etoposide + cisplatin	None
Sex cord stromal tumor		1. Paclitaxel + carboplatin 2. EP: etoposide + cisplatin	None
Borderline or LMP tumor		None—surgery alone	None—surgery alone

*HRD, homologous recombination deficient, requires tumor testing that can be obtained through a number of commercial vendors.

†PARP inhibitor, poly ADP ribose polymerase inhibitors (niraparib, olaparib, rucaparib).

LMP, low malignant potential.

3. Principles of therapy for refractory and recurrent disease:

- Definitions
  - Platinum-refractory = progression or persistent disease while receiving primary platinum-based therapy
  - Platinum-resistant = achievement of a complete remission followed by relapse (6 months after completion of primary platinum-based therapy)
  - Platinum-sensitive = achievement of a complete clinical remission with relapse >6 months after primary platinum-based therapy

TABLE 34.6 ■ Therapy for Recurrent Disease

Disease Status	Surgery	Preferred Treatment Options	Maintenance Therapy
Recurrent High-Grade Epithelial Ovarian Cancer			
Platinum-refractory or Platinum-resistant	Not indicated	1. Liposomal doxorubicin 2. Gemcitabine 3. Topotecan 4. Etoposide	None
Platinum-sensitive	Potentially indicated in patients with limited site(s) of recurrence in whom R0 secondary cytoreduction may be achieved	1. Platinum-based regimen 2. If *BRCA* mutation consideration of: PARP inhibitor	PARP inhibitor (regardless of *BRCA* mutation status)

(*continued*)

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TABLE 34.6 ■ Therapy for Recurrent Disease (*continued*)

Disease Status	Surgery	Preferred Treatment Options	Maintenance Therapy
Recurrent Low-Grade Epithelial Ovarian Cancer			
	Repeat surgical resection preferred if feasible	1. Targeted therapy: trametinib (MEK inhibitor) 2. Hormone therapy	None

PARP, poly ADP-ribose polymerase.

QUESTIONS

1. A 24-year-old woman is diagnosed with a right ovarian yolk sac (endodermal sinus) tumor with ovarian capsule rupture. Postoperative alpha-fetoprotein is 500. CT imaging of the chest, abdomen, and pelvis is without evidence of disease.

What is the best next step in treatment?

A. Completion staging with a total abdominal hysterectomy, bilateral salpingectomy, left oophorectomy, and lymphadenectomy
B. Intravenous carboplatin and paclitaxel every 3 weeks for six cycles
C. Intravenous cisplatin and etoposide every 3 weeks with weekly bleomycin for first three to four cycles
D. Observation
E. Intravenous paclitaxel on day 1, intraperitoneal cisplatin on day 2, and intraperitoneal paclitaxel on day 8 of a 21-day cycle for six cycles

2. A 42-year-old woman presents with a pelvic mass. Surgical staging demonstrates a 5 cm ovarian mass with capsular rupture and multiple peritoneal implants without evidence of invasion. She is optimally debulked with less than 1 cm of residual disease. Pathology demonstrates an epithelial serous ovarian tumor of low malignant potential. The patient recovers well from surgery and presents to discuss adjuvant treatment options.

Which of the following is the best next step?

A. Adjuvant intravenous carboplatin and paclitaxel for three to six cycles
B. Intravenous paclitaxel on day 1, intraperitoneal cisplatin on day 2, and intraperitoneal paclitaxel on day 8 of a 21-day cycle for six cycles
C. Observation
D. Intravenous carboplatin and paclitaxel with bevacizumab every 3 weeks for six cycles followed by 6 months of bevacizumab maintenance therapy
E. Initiate Olaparib at 400 mg daily

3. A 52-year-old woman with recurrent high-grade serous ovarian cancer presents with abdominal pain and bloating with a rising CA-125 two months after completion of six cycles of intravenous carboplatin and

paclitaxel. CT scan confirms recurrent disease. She has a good performance status and wants to pursue additional therapy.

What is an appropriate next step in therapy?

A. Intravenous liposomal doxorubicin every 4 weeks
B. Restart intravenous carboplatin and paclitaxel every 3 weeks
C. Restart intravenous carboplatin and paclitaxel every 3 weeks with the addition of Bevacizumab
D. Secondary surgical debulking
E. Intravenous carboplatin and docetaxel every 3 weeks

4. A 49-year-old woman presents for follow-up. She was recently diagnosed with high-grade serous adenocarcinoma of the ovary and is planning to start treatment with intravenous carboplatin and paclitaxel. Her grandmother was diagnosed with breast cancer at age 72 and she has an uncle with a history of lung cancer.

Which of the following is correct?

A. A family history of lung cancer is an indication for further genetic testing.
B. Genetic testing is not indicated for patients with ovarian cancer, as it has no implication on treatment.
C. All women with a diagnosis of ovarian cancer should have a genetic risk evaluation, regardless of family history.
D. Genetic testing is not indicated in patients with ovarian cancer unless the patient progresses on first-line therapy.

5. A 49-year-old woman with a history of high-grade serious adenocarcinoma of the ovary and a deleterious *BRCA1* mutation has just completed carboplatin and paclitaxel for her first platinum-sensitive recurrence.

What is the recommended maintenance therapy for this patient?

A. Poly ADP-ribose polymerase (PARP) inhibitor therapy
B. Weekly paclitaxel
C. Bevacizumab
D. None, maintenance therapy is not indicated

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ANSWERS

1. **C. Intravenous cisplatin and etoposide every 3 weeks with weekly bleomycin for first three to four cycles.** Germ cell tumors of the ovary are treated similarly to germ cell tumors of the testes. In yolk sac tumors, which are a high-risk germ cell tumor, adjuvant chemotherapy with bleomycin, cisplatin, and etoposide is indicated for even early-stage, resected disease.

2. **C. Observation.** Ovarian epithelial tumors of low malignant potential, also known as borderline tumors, are noninvasive tumors and treatment is with surgical resection. Chemotherapy is not indicated even with advanced-stage disease.

3. **A. Intravenous liposomal doxorubicin every 4 weeks.** Ovarian cancer that recurs within 6 months of previous platinum therapy is considered platinum-resistant. Therefore, further platinum-based chemotherapy is not warranted. Liposomal doxorubicin is an active therapeutic option in women with platinum-resistant ovarian cancer.

4. **C. All women with a diagnosis of ovarian cancer should have a genetic risk evaluation, regardless of family history.** National Comprehensive Cancer Network (NCCN) guidelines recommend genetic testing for all women diagnosed with ovarian cancer at time of diagnosis, regardless of family history. A family history of lung cancer does not influence whether or not a patient qualifies for genetic testing for ovarian cancer. The results of genetic testing may have an implication on treatment options, as poly adenosine diphosphate-ribose polymerase (PARP) inhibitor therapy has been approved by the Food and Drug Administration (FDA) for cancer treatment or maintenance therapy in specific clinical situations women with germline *BRCA1/2* mutations.

5. **A. PARP inhibitor therapy.** Maintenance therapy with PARP inhibitor is now indicated for all patients following completion of a platinum-based regimen for their first platinum-sensitive recurrence. Improvement in clinical outcomes is greatest for women with *BRCA* mutations or homologous recombination deficient (HRD). Weekly paclitaxel maintenance therapy has been tested in the clinical trial setting and not shown to improve outcomes. Maintenance bevacizumab should only be continued in select patients who received bevacizumab with their primary therapy.

35 Endometrial Cancer

Aimee Rolston and Karen McLean

EPIDEMIOLOGY

- Most common gynecologic cancer in high-income countries
  - Second most common in middle-/low-income countries (cervical cancer more common)
- Incidence peaks between 60 and 70 years of age
- Incidence is higher in White women, but mortality is 2× higher in African Americans than in Whites
  - Likely multifactorial including issues that are both biological (such as higher incidence of more aggressive histologies) and societal (such as later stage at diagnosis, access to care)

ETIOLOGY AND RISK FACTORS

1. What are the most common risk factors for developing endometrial cancer?

- Increasing age
- Hypertension
- Diabetes
- Estrogen excess
  - Endogenous estrogen excess
    - Obesity
    - Polycystic ovary disease and chronic anovulation
    - Estrogen-secreting tumors of the ovary (such as granulosa cell tumors)
    - Liver disease
  - Endogenous prolonged estrogen exposure
    - Early menarche
    - Late menopause
    - Nulliparity
    - Irregular menses and infertility
  - Exogenous unopposed estrogen:
    - Hormone replacement therapy (HRT)
    - Selective estrogen receptor modulators (SERMs), such as tamoxifen
- Hereditary cancer syndromes
  - Hereditary nonpolyposis colorectal cancer (HNPCC), also termed Lynch syndrome
    - Found at a similar rate in patient diagnosed with endometrial cancer as colon cancer (~5%).

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- Women with Lynch syndrome have a 40% to 60% lifetime risk of developing endometrial cancer. Lifetime risk of ovarian cancer is 1% to 38%.
- Testing for genetic mutations associated with Lynch syndrome (mismatch repair [MMR] proteins, MLH1, MSH2, MSH6, PMS2, and microsatellite instability [MSI]) should be considered in all patients with endometrial cancer, especially in those under 50 or with a significant family history of colon, endometrial, or ovarian cancer. Most commonly this is done by immunohistochemistry for MMR proteins on endometrial cancer tissue.

2. What are protective factors against developing endometrial cancer?

- Oral contraceptives
  - Fifty percent decrease in relative risk if used for 12 months
  - Protective effect persists for at least 15 years after the cessation of use
- Postmenopausal progestin therapy
  - Progestin suppresses endometrial proliferation
- Physical activity
- Smoking (due to the anti-estrogen effects)
- Multiparity

3. When do you worry about endometrial hyperplasia?

- Endometrial hyperplasia is often a precursor to endometrial cancer.
- Endometrial hyperplasia is typically classified in four categories, each with their own risk of progression to cancer if left untreated—mnemonic to remember is "penny, nickel, dime, quarter" for 1%, 5%, 10%, and 25% based on simple/complex hyperplasia ± atypia (see Table 35.1).
- There is also risk of concomitant carcinoma at the time of hysterectomy for women with endometrial hyperplasia, which increases with severity of hyperplasia. Among women with a diagnosis of complex atypical hyperplasia, there is a 35% to 50% risk of concurrent carcinoma. Due to this high risk, preferred nomenclature for complex atypical hyperplasia (CAH) is now endometrial intraepithelial neoplasia (EIN).
- Simple endometrial hyperplasia can typically be treated with progestins.
- Unless fertility preservation is desired, patients with EIN/CAH should have a hysterectomy with considerations for staging.

TABLE 35.1 ■ Categories of Endometrial Hyperplasia

Type of Hyperplasia	Appearance	Risk of Progression (%)	Mnemonic
Simple	Dilated glands with some outpouching, abundant endometrial stroma	1	"Penny"
Complex	Crowded glands, little endometrial stroma, complex gland pattern, and outpouching formations	5	"Nickel"

(*continued*)

TABLE 35.1 ■ Categories of Endometrial Hyperplasia (*continued*)

Type of Hyperplasia	Appearance	Risk of Progression (%)	Mnemonic
Simple with atypia	Presence of cytologic atypia (hyperchromatic, enlarged epithelial cells with an increased N:C ratio)	10	"Dime"
Complex with atypia (CAH/EIN)	Presence of cytologic atypia (hyperchromatic, enlarged epithelial cells with an increased N:C ratio)	25	"Quarter"

CAH/EIN, complex atypical hyperplasia/endometrial intraepithelial neoplasia.

SCREENING AND PREVENTION

- Routine screening is not indicated in asymptomatic women.
- Endometrial biopsy is indicated for any patient with postmenopausal bleeding or spotting.
- Women with HNPCC
  - Consider screening every 1 to 2 years with endometrial biopsy (highly sensitive and specific)
  - Screening with pelvic ultrasound to assess endometrial thickness is not sensitive or specific and is not recommended in premenopausal women. Can be considered in postmenopausal women.
  - Consider risk-reducing surgery with total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) after completion of childbearing to reduce risk of endometrial and ovarian cancers, respectively.
- Women with hereditary *BRCA1* mutation
  - Consider risk-reducing hysterectomy (at the time of risk-reducing BSO) given current limited data to suggest a slightly increased risk of serous uterine cancer in this population.
- Women taking tamoxifen should have routine annual gynecologic exams.

SIGNS AND SYMPTOMS

1. What are the most common signs and symptoms of endometrial cancer?

- Abnormal bleeding—seen in 90%
  - Premenopausal women with abnormal uterine bleeding and risk factors, particularly obesity or a history of anovulation, should undergo endometrial biopsy.
  - Perimenopausal women with intermenstrual bleeding or menorrhagia should undergo endometrial biopsy.
  - All postmenopausal women with vaginal bleeding should be evaluated.
- Abnormal glandular tissue on Pap test in an asymptomatic woman—this requires further workup including endometrial biopsy
- Pelvic pain
- Palpable tumor or fullness palpated on bimanual exam
- Signs of advanced disease—pain, ascites, bloating, early satiety

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STAGING

1. What are the important steps in pretreatment evaluation?

- Physical exam with pelvic exam
- Complete blood count (CBC), comprehensive metabolic panel
- Tumor markers
  - CA-125 elevation may indicate extrauterine spread
- Radiographic studies
  - Pelvic/abdominal imaging unnecessary if surgical staging planned (low grade disease).
    - If necessary, MRI is most sensitive for assessing possible myometrial invasion and/or cervical involvement.
  - Chest radiograph is standard part of initial assessment.
  - Consider CT chest/abdomen/pelvis in high-grade/high-risk disease to assess for metastases.
- Assessment for hereditary cancer syndromes, such as Lynch syndrome

2. What is the typical approach to surgical staging for endometrial cancer?

- Total (uterus and cervix) hysterectomy with BSO and lymph node assessment (pelvic ± paraaortic lymph nodes).
  - Sentinel lymph node mapping is now standard
  - Paraaortic nodal evaluation should be considered for high-risk tumors
- Biopsy areas suspicious for metastases
- Cytoreduction often done when metastases are evident.
- Omental biopsy for high-grade histologies including papillary serous, carcinosarcoma, or clear cell.
- Surgical route may be abdominal, conventional laparoscopic, or robot-assisted laparoscopic. Minimally invasive approaches preferred when possible due to equivalent cancer outcomes and improved recovery.

3. How is endometrial cancer staged?

- Endometrial cancer is staged according to the joint 2010 International Federation of Gynecology and Obstetrics (FIGO)/tumor, node, and metastasis (TNM) classification system:

TABLE 35.2 ■ FIGO and TNM Classifications for Endometrial Cancer

TNM Categories	FIGO Stages	Definition
Primary Tumor (T) (Surgical–Pathologic Findings)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to corpus uteri, including endocervical glandular involvement
T1a	IA	Tumor limited to endometrium or invades less than one half of the myometrium
T1b	IB	Tumor invades one-half or more of the myometrium

(*continued*)

TABLE 35.2 ■ FIGO and TNM Classifications for Endometrial Cancer (*continued*)

TNM Categories	FIGO Stages	Definition
T2	II	Tumor invades stromal connective tissue of the cervix, but does not extend beyond uterus. Does not include endocervical glandular involvement.
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T any, N1	IIIC1	Metastasis to pelvic lymph nodes
T any, N2	IIIC2	Metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)
T any, N any, M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes and intraperitoneal disease)

FIGO, International Federation of Gynecology and Obstetrics; TNM, tumor, node, and metastasis.

PATHOLOGY

1. What are the most common types of endometrial cancer?

- Two major classes of endometrial cancer exist
  - Type I (endometrioid tumors)—80% of cases, estrogen-related.
  - Type II (papillary serous, clear cell, or carcinosarcoma tumors)—20% of cases, unrelated to estrogen stimulation, but carry much higher risk of metastatic disease.
- Carcinosarcoma of the uterus is a poorly differentiated carcinoma with areas of sarcomatoid differentiation and is treated as a carcinoma rather than a sarcoma.

DIAGNOSTIC CRITERIA

1. How is endometrial cancer diagnosed?

- Endometrial biopsy—in-office procedure as initial diagnostic test
- Hysteroscopy with dilation and curettage less common as initial step
  - Performed if initial biopsy negative for malignancy, but high suspicion of cancer still exists (e.g., hyperplasia with atypia, persistent bleeding).
- Transvaginal ultrasonography—helpful to distinguish bleeding due to atrophy versus anatomic lesion in postmenopausal women
  - Endometrial thickness <4 mm has <1% risk of malignancy.

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PROGNOSTIC FACTORS

1. What are the major prognostic factors in endometrial cancer?

- Older patient age
- Stage of disease
- Grade of tumor
- Histologic type (serous, clear cell, and carcinosarcoma have worse prognosis)
- Depth of myometrial invasion
- Tumor extension behind the uterine fundus
- Lower uterine segment (cervical) involvement
- Larger tumors of ≥2 cm have worse prognosis
- Lymphovascular space involvement (LVSI)
- Tumor hormone receptor status—estrogen receptor/progesterone receptor (ER/PR) positivity associated with longer progression-free survival (PFS)

TREATMENT

Primary treatment is surgical.

- Hysterectomy, BSO, and lymph node assessment (see earlier).
- Surgery completes staging of disease in addition to therapeutic resection of the cancer.
- Primary radiation therapy (RT) can be used for patients who are poor surgical candidates.

1. How do we decide who needs adjuvant treatment?

- Stage I disease (confined to the uterus):
  - Consider adjuvant RT in patients with high-intermediate risk disease. High intermediate risk as defined by the Gynecologic Oncology Group (GOG) includes age plus a number of the following additional risk factors: grade 2 to 3, presence of LVSI, or outer one-third myometrial invasion.
    - Age >70 years: plus one risk factor
    - Age 50 to 69 years: plus two risk factors
    - Age <50 year: all three risk factors
- Stage II disease (tumor involves cervix)
  - Adjuvant RT
- Stage III disease (tumor extends beyond the uterus)
  - Adjuvant chemotherapy ± RT
- Serous, clear cell, or carcinosarcoma histology is considered high risk, even in stage I disease. Therefore, adjuvant chemotherapy ± radiation therapy is warranted regardless of stage (though there is debate on the best approach in stage IA disease).
- The use of chemoradiation versus chemotherapy alone for stage III/IV and high-risk disease is an area of debate, due to conflicting studies on the impact of multimodal therapy on recurrence-free survival and no demonstrated improvement in overall survival (OS).

2. What type of RT is used?

- External beam pelvic RT (45–50 Gy)
- Vaginal brachytherapy
- *Adjuvant RT improves local control, but is not proven to improve survival.*

3. What type of adjuvant chemotherapy is used?

- Commonly used combination regimens include the following:
  - Intravenous carboplatin + paclitaxel for six cycles
  - Add trastuzumab to paclitaxel and carboplatin for stage III/IV (or recurrent) HER2-positive uterine serous carcinoma
- Important considerations
  - Chemotherapy has shown survival advantage over whole abdominal irradiation.
  - Paclitaxel-containing regimens may improve response, particularly in serous histology.
- Single-agent therapy options include platinum, doxorubicin, docetaxel, and topotecan.

4. How do you treat locally recurrent disease?

- Local recurrence occurs in 7% to 11% of patients.
- RT for patients with local recurrence and no prior radiation therapy
  - Combination of external beam RT and brachytherapy
  - Local control can be achieved in 40% to 75% of patients
  - Survival rate is highest in patients with isolated vaginal recurrence
- Surgical resection for patients with prior radiation
  - Pelvic exenteration considered for isolated central pelvic recurrence without extension to the pelvic sidewall and/or retroperitoneal involvement. Requires permanent urinary diversion and colostomy formation.
  - Exenterative procedures are undertaken with curative intent
  - Must be able to tolerate surgery; pelvic exenteration has high morbidity

5. What is the role of chemotherapy in recurrent disease at distant or multiple sites?

- In patients with excellent performance status or high-grade histology (grade 3, serous, clear cell, or carcinosarcoma), chemotherapy is offered.
  - Best regimen for salvage chemotherapy has not been established.
  - If chemonaïve, consider a platinum-doublet therapy such as carboplatin/paclitaxel.
- Pembrolizumab (anti-programmed cell death protein 1 [PD-1] antibody)
  - Use in microsatellite instability high (MSI-H)/deficient mismatch repair (MSI-H/dMMR) tumors that have progressed on prior treatment.
  - Combine with lenvatinib (multiple kinase inhibitor against the vascular endothelial growth factor 1 [VEGFR1], VEGFR2, and VEGFR3) for microsatellite stable tumors in those that are not candidates for surgery/radiation and have progressed on prior treatment.
- Trastuzumab (anti-HER2/neu receptor antibody)
  - Use in combination with carboplatin/paclitaxel for HER2 expression positive advanced stage or recurrent papillary serous histology endometrial cancers.
- Single-agent doxorubicin, gemcitabine, and topotecan have modest activity.

6. How do you treat distant recurrent or metastatic disease? What is the role of hormonal therapy in this setting?

- Hormonal therapy can be an effective treatment approach in recurrent or metastatic disease with low-symptom burden, indolent pace of disease, and/or low grade due to improved toxicity profile.

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- Produces response in 15% to 30% of patients, average length of response is 1 year.
- Treatment options include the following:
  - Megestrol
  - Medroxyprogesterone
  - Tamoxifen
  - Aromatase inhibitors

SPECIAL CONSIDERATIONS

1. What are the recommendations for post-treatment surveillance?

- Physical examination including pelvic exam every 3 to 6 months for 2 years, then every 6 months for up to year 5, then annually.
- Vaginal cytology does not have proven benefit and is not recommended by the National Comprehensive Cancer Network (NCCN) or Society of Gynecologic Oncology (SGO).
- Measurement of serum CA-125 if initially elevated and considered a marker for the patient
- CT/MRI only as clinically indicated based on symptoms and/or clinical concern for recurrent disease.

QUESTIONS

1. A 71-year-old otherwise healthy female presents with postmenopausal bleeding and endometrial biopsy demonstrates adenocarcinoma. Surgical staging including total hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy is performed. Pathology demonstrates a 2.3 cm grade 1 endometrioid adenocarcinoma invading 1.2 cm into a 2 cm myometrium with positive lymphovascular space invasion. Disease is confined to the uterus without cervical involvement.

What is the next step in treatment?

A. Observation
B. Adjuvant radiation therapy
C. Adjuvant platinum-based chemotherapy followed by radiation therapy
D. Adjuvant concurrent chemoradiation

2. A 64-year-old woman with a history of stage IIIC1 endometrioid endometrial cancer and known Lynch syndrome with *MSH2* gene mutation presents with multifocal recurrent disease. Four months ago she completed primary therapy consisting of surgical staging, followed by carboplatin and paclitaxel chemotherapy with radiation. She has no other medical problems and her performance status is excellent.

What next step in treatment has the highest response rate?

A. Single-agent bevacizumab
B. Carboplatin and paclitaxel chemotherapy
C. Pembrolizumab
D. Herceptin plus letrozole

3. A 68-year-old female presents with biopsy-proven recurrent grade 1 endometrioid endometrial adenocarcinoma metastatic to the lungs and pelvis. Tumor tissue immunohistochemical stains are positive for expression of

estrogen receptor (ER). She is asymptomatic from her current disease. She has residual peripheral neuropathy from her previous adjuvant carboplatin and paclitaxel chemotherapy completed 1 year ago.

What is the most appropriate next step in management?

A. Hormonal therapy with an aromatase inhibitor
B. Doublet chemotherapy with a platinum and taxane
C. Surgical resection of dominant lung nodule
D. Doublet chemotherapy with a platinum and anthracycline

4. A 59-year-old woman undergoes a total hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy for endometrial cancer. Pathology is consistent with a high-grade papillary serous adenocarcinoma invading 1.5 cm into a 2 cm myometrium with positive lymphovascular space invasion and positive pelvic lymph nodes (stage IIIC1). Immunohistochemical staining demonstrates HER2 positivity.

What is the preferred next step in treatment?

A. Observation
B. Adjuvant external beam radiation treatment
C. Adjuvant carboplatin and paclitaxel chemotherapy with consideration of radiation therapy
D. Adjuvant carboplatin, paclitaxel and trastuzumab chemotherapy with consideration of radiation therapy

5. A 59-year-old woman presents with postmenopausal bleeding and endometrial biopsy reveals grade 2 endometrioid endometrial cancer. She has a history of severe cardiopulmonary disease and a body mass index of 76 kg/m^2; she has not been cleared for hysterectomy. CT and MRI demonstrate disease confined to the uterus.

What is the best long-term treatment approach for her cancer?

A. Progesterone-secreting intrauterine device (IUD)
B. Primary radiation
C. Oral progesterone therapy
D. Carboplatin and paclitaxel chemotherapy without surgery

6. A 72-year-old woman with a history of stage IA endometrial cancer who underwent total hysterectomy and bilateral salpingo-oophorectomy 1 year ago and did not receive adjuvant therapy now presents with vaginal bleeding. Physical exam demonstrates a nodule at the vaginal cuff. Biopsy demonstrates recurrent grade 1 endometrioid endometrial cancer. CT chest/abdomen/pelvis and pelvic MRI demonstrate a 3 cm mass at the top of the vagina without further evidence of disease. The patient is otherwise fit and wishes to pursue therapy.

What is the next best step in treatment?

A. Surgical intervention with pelvic exenteration
B. Radiation therapy
C. Observation
D. Carboplatin and paclitaxel chemotherapy

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ANSWERS

1. **B. Adjuvant radiation therapy**. This is a 71-year-old patient with stage IB disease and 1 risk factor (lymphovascular space involvement [LVSI]) and therefore warrants radiation therapy, given the increased risk for local recurrence.

2. **C. Pembrolizumab.** Pembrolizumab is approved for the treatment of microsatellite instability high (MSI-H)/deficient mismatch repair (dMMR) tumors that have progressed on prior treatment. Given this patient's *MSH2* gene mutation and her prior carboplatin/paclitaxel chemotherapy, she is an excellent candidate for pembrolizumab as the next treatment approach. In a patient with recurrent disease that is not MSI-H/dMMR, pembrolizumab plus lenvatinib is a treatment option, generally after carboplatin and paclitaxel chemotherapy.

3. **A. Hormonal therapy with an aromatase inhibitor.** Hormonal therapy (including aromatase inhibitors, megestrol, or tamoxifen) is a well-tolerated treatment in women with low-grade metastatic endometrial cancer, especially with ER expression. Hormonal therapy is most appropriate in women without large symptom burden or rapidly growing disease.

4. **D. Adjuvant carboplatin, paclitaxel and trastuzumab chemotherapy with consideration of radiation therapy.** Trastuzumab should be added to carboplatin and paclitaxel in stage III/IV or recurrent papillary serous uterine cancer with HER2 positivity. The clinical benefit of radiation therapy in addition to chemotherapy is actively debated at this time, but radiation is often administered.

5. **B. Primary radiation.** For uterus-confined disease, radiation therapy can be as effective as surgery for treatment of endometrial cancer. Given this patient's comorbidities, including her obesity, radiation is much safer than surgery. Although progesterone therapy (via intrauterine device or orally) can lead to regression of disease, response rates are lower with grade 2 disease and it is only a temporizing approach rather than definitive therapy. Finally, systemic chemotherapy has much greater toxicity and would not be recommended for local disease.

6. **B. Radiation therapy**. Radiation therapy is appropriate for locally recurrent disease. Surgical resection could be considered but would require total pelvic exenteration with urinary and fecal diversion. Given the high morbidity of such a surgical approach, pelvic exenteration is generally reserved for patients with local recurrence who have already been treated with radiation therapy.

CANCER OF UNKNOWN PRIMARY

XI

ALGRAWANY

36 Cancer of Unknown Primary

Phoebe A. Tsao and Francis P. Worden

EPIDEMIOLOGY

1. How is the cancer of unknown primary (CUP) typically classified?

- Adenocarcinoma (70%), squamous cell carcinoma (~5%), neuroendocrine carcinoma (~1%), poorly differentiated carcinoma (20%–25%)

2. What are the five most common primary sites in CUP eventually diagnosed during life or at autopsy?

- Lung (23.7%), pancreas (21.1%), ovary (6.4%), kidney (5.5%), and colorectal (5.3%)

DIAGNOSIS

1. What is important in the workup of a patient with CUP?[1]

- History and physical: performance status, nutritional status, comorbidities, pain/symptoms
- Histologic tissue evaluation with immunohistochemistry
- CT of the chest, abdomen, and pelvis
- Symptom- and histology-driven assessment: endoscopy, digital rectal exam, breast exam/mammography, pelvic exam, laryngoscopic exam
- Breast MRI in women with axillary adenopathy and a normal mammogram
- PET/CT may be helpful (can detect primary tumor in approximately 30% of patients)
- Tumor markers (see the following)
- Emphasis should be on identifying treatable/curable subsets of patients and tumor types

2. What tumor markers may be useful in diagnosis?

- Beta-human chorionic gonadotropin (beta-HCG) and alpha-fetoprotein (AFP), especially in poorly/undifferentiated carcinomas, which may suggest germ-cell tumor primary site.
- Prostate-specific antigen (PSA) is specific for prostate cancer: consider in men with adenocarcinoma and bone-only metastases.
- Carcinoembryonic antigen (CEA), CA19-9, CA-125, and CA15-3 are nonspecific.

3. Should you obtain molecular profiling/tumor of origin testing?

- There are no prospective data supporting its clinical use. It may have diagnostic utility. The Food and Drug Administration (FDA) approved the Pathwork Tissue of Origin test in 2008.

ALGRAWANY

4. The following are some commonly used immunoperoxidase stains that are useful in the diagnosis of CUP:

TABLE 36.1 ■ Commonly Used Immunoperoxidase Stains in Diagnosis of CUP

Markers	Most Likely Cell Lineage*
Pan-keratin	Carcinoma
Chromogranin, synaptophysin	Neuroendocrine carcinoma
CK5/6, p63	Squamous cell carcinoma
S100, SOX10	Melanoma
OCT3/4, SALL4	Germ cell tumor
Desmin, vimentin	Sarcoma
LCA + CD 20 + CD 3+	Lymphoma

*These markers are not uniformly specific or sensitive

CUP, cancer of unknown primary.

Source: Reproduced with permission from Connor JR, Hornick JL. Metastatic carcinoma of unknown primary: diagnostic approach using immunohistochemistry. *Adv Anat Pathol* 2015;22(3):149–167.

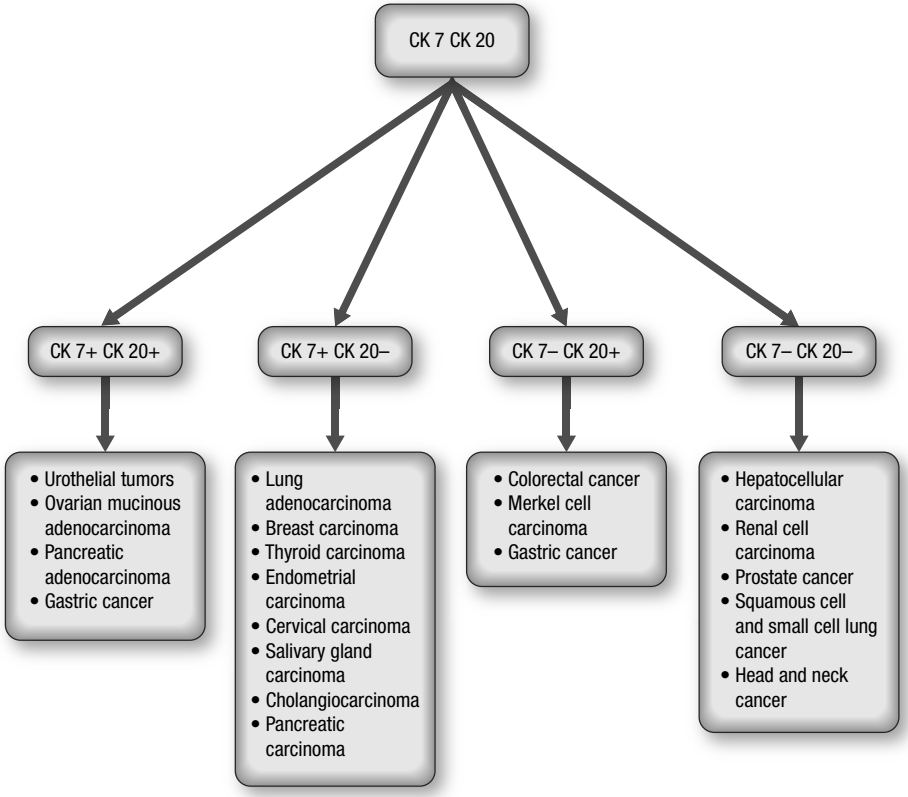

FIGURE 36.1 ■ Approach to immunohistochemical markers in cancer of unknown primary. *Source*: Varadhachary GR, Abbruzzese JL, Lenzi R. Diagnostic strategies for unknown primary. *Cancer*. 2004;100(9):1776–1785.

5. What additional markers should be considered after a preliminary workup with CK 7 and CK 20?

TABLE 36.2 ■ Additional Markers by Cancer Type

Cancer	Marker
Urothelial carcinoma	Uroplakin III, thrombomodulin, high–molecular-weight cytokeratin
Breast carcinoma	Gross cystic disease fluid protein, ER, PR
Lung (mainly adenocarcinoma)	TTF-1, surfactant A and B
Medullary thyroid cancer	TTF-1, calcitonin
Merkel cell carcinoma	CD117
Hepatocellular carcinoma	Hep par-1
Prostate cancer	PSA, PAP
Cholangiocarcinoma	CK 19
Mesothelioma	Calretinin

ER, estrogen receptor; PAP, prostate acid phosphatase; PR, progesterone receptor; PSA, prostate-specific antigen; TTF-1, thyroid transcription factor-1.

Source: Varadhachary GR, Abbruzzese JL, Lenzi R. Diagnostic strategies for unknown primary. *Cancer.* 2004;100(9):1776–1785.

PROGNOSIS

1. What are poor prognostic features in CUP?

- Male gender
- Adenocarcinoma histology
- Poorly differentiated neuroendocrine histology
- Multiple involved organ sites
- Supraclavicular lymphadenopathy
- Hepatic or adrenal involvement

TREATMENT

1. What additional testing may be useful in management?

- Next-generation sequencing
  - May identify a targetable mutation although no prospective studies investigating the efficacy of targeted therapies
- Mismatch repair (MMR) immunohistochemical staining and/or microsatellite instability (MSI) analysis
  - Pembrolizumab is FDA-approved for unresectable or metastatic MMR-deficient or MSI-high cancers regardless of tumor type[2]
- Tumor mutational burden
  - Pembrolizumab is FDA-approved for unresectable or metastatic cancers with a high tumor mutational burden (≥10 mutations/megabase) regardless of tumor type[3]

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2. Is chemotherapy helpful?

- Chemotherapy increases overall survival by 3 to 6 months compared to best supportive care. There is less than a 30% response rate.

3. How are unknown primary carcinomas treated and what are the preferred treatment regimens?

Poorly Differentiated Carcinomas

- Carboplatin and paclitaxel
- Docetaxel and carboplatin

Adenocarcinomas

- Combination chemotherapy, usually containing a platinum; that is
  - Paclitaxel, carboplatin, (±) etoposide
  - Docetaxel and carboplatin
  - Gemcitabine and cisplatin
  - Gemcitabine and docetaxel
  - mFOLFOX6
  - FOLFIRI

Squamous Cell Carcinomas

- Carboplatin and paclitaxel
- mFOLFOX6

4. How are women with adenocarcinoma of unknown primary with peritoneal carcinomatosis treated?

- As ovarian primary: consider surgical cytoreduction in the appropriate candidate, followed by platinum-based combination chemotherapy.

5. How are women with adenocarcinoma of unknown primary and axillary lymph node metastasis treated?

- As stage II or III breast cancer (occult breast primary found in 55%–75%)

6. How are squamous cell CUPs with high cervical nodes evaluated and treated?

- As head and neck primaries
  - Check p16 staining (human papillomavirus [HPV]) for level I to IV nodes; if positive, treated as an oropharyngeal primary
  - Check Epstein–Barr encoding region (EBER) in situ hybridization (ISH) for levels I to V; if positive, treated as nasopharyngeal carcinoma
- Panendoscopy should be performed with biopsies of the following:
  - Pyriform sinus, nasopharynx
  - Base of tongue, tonsils (bilateral simple tonsillectomies)

7. How are squamous cell CUPs with inguinal lymph nodes treated?

- As genital or anorectal primary
- Consider inguinal lymph node dissection, followed by inguinal radiotherapy ± chemotherapy

8. **How are high-grade neuroendocrine CUPs treated?**
   - Treat as small cell lung cancer (i.e., platinum combined with etoposide)

9. **How do you treat CUP with the extragonadal germ-cell syndrome?**
   - Consider in middle-aged men, midline adenopathy, elevated AFP/beta-HCG
   - Treat as poor risk germ cell tumor: responsive to platinum, response often durable

10. **How do you treat CUP with isolated bone metastases?**
    - In a man, check PSA and evaluate for prostate primary. If a woman, consider breast primary.
    - If solitary metastasis, consider radiotherapy followed by observation

11. **How do you treat CUP with isolated brain metastasis/metastases?**
    - Single site: resect ± adjuvant radiotherapy
    - Multiple lesions: whole-brain radiotherapy

QUESTIONS

1. A 58-year-old woman has multiple liver lesions identified in a CT scan of the chest, abdomen, and pelvis obtained during a routine workup for abdominal pain. There was no evidence of a primary tumor. A core biopsy of one of the liver lesions is performed, revealing a moderately differentiated adenocarcinoma with the following immunohistochemistry profile: CK 7 negative, CK 20 positive, CDX2 positive.

   Which of the following is the most likely primary site?
   A. Lung
   B. Colorectal
   C. Ovarian
   D. Gastric

2. A 49-year-old woman presents with a palpable and painless 3 cm left axillary mass. CT scan of the chest, abdomen, and pelvis is obtained, which reveals several enlarged axillary lymph nodes but no primary site identified. Bilateral mammograms show no abnormalities in the breasts. A core biopsy is obtained, which reveals adenocarcinoma.

   What would you recommend next?
   A. Bilateral mastectomy and bilateral axillary lymph node dissection
   B. Gemcitabine and docetaxel
   C. MRI of the breasts
   D. Left axillary lymph node dissection

3. A 61-year-old woman presents with a painless lump in her right groin that has been growing slowly over the past 3 months. She is otherwise asymptomatic. A basic physical exam and laboratory assessment is unremarkable, aside from the palpable fixed mass, measuring about 4 cm, in the left inguinal region. Biopsy is performed showing poorly differentiated

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squamous cell carcinoma. CT of the chest, abdomen, and pelvis shows no primary tumor.

What would you recommend next?

A. Gynecologic exam with colposcopy and anoscopy
B. PET/CT
C. Radiotherapy
D. Chemotherapy

4. A 71-year-old man, previously healthy, presents with a growing 2.5 cm left-sided chest mass over the past 6 months. A biopsy demonstrates adenocarcinoma, and a PET/CT scan shows no avid lesions aside from the chest wall mass. He has no comorbidities and has an Eastern Cooperative Oncology Group (ECOG) performance status of zero.

What would you recommend next?

A. Observation
B. Surgery followed by radiation
C. Chemotherapy
D. Radiation therapy alone

5. A 68-year-old woman is found to have two intraabdominal masses on a CT abdomen and pelvis obtained for abdominal discomfort. Biopsy of one of the masses reveals a poorly differentiated carcinoma. Immunohistochemical staining for mismatch repair proteins demonstrates loss of PMS2 and MLH1 and retained staining for MSH2 and MSH6.

Which of the following systemic therapy options would have the highest response rate?

A. Carboplatin and paclitaxel
B. Gemcitabine and cisplatin
C. Docetaxel and carboplatin
D. Pembrolizumab

ANSWERS

1. **B. Colorectal.** Immunohistochemical stains can often guide diagnosis of a primary site. Cytokeratin stains are a helpful first triage point. CK 7-negative/CK 20-positive tumors are often colorectal, Merkel cell, or gastric primaries. CDX2 is very specific for colorectal tumors.

2. **C. MRI of the breasts.** Women with isolated adenocarcinoma with axillary lymph node metastases require a thorough workup for a breast primary site. An MRI is useful in women with a normal mammogram and breast ultrasound. If no further sites are identified, following a stage II breast adenocarcinoma treatment paradigm should be considered.

3. **A. Gynecologic exam with colposcopy and anoscopy.** Squamous cell carcinoma isolated to inguinal lymph nodes represents a potentially curable subset of cancer of unknown primary (CUP). Attention to identifying a primary site via thorough gynecologic and anorectal examinations is indicated.

4. **B. Surgery followed by radiation.** Isolated metastases should be treated aggressively for cure in the appropriate candidates. Observation is not appropriate in treatment candidates. Resection followed by radiotherapy, with or without chemotherapy should be considered, in accordance with National Comprehensive Cancer Network (NCCN) guidelines.

5. **D. Pembrolizumab.** Traditional platinum-based chemotherapy regimens have a <30% response rate in CUPs. This patient has a mismatch repair deficient tumor for which pembrolizumab has a 34.3% objective response rate in advanced, noncolorectal mismatch repair-deficient/microsatellite instability-high tumors.

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GENETICS AND TUMOR BIOLOGY

XII

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37 Cancer Genetics

Christopher T. Su and Elena M. Stoffel

Introduction

- Inherited cancer syndromes comprise approximately 5% to 10% of all cancers.
- Majority of cancer syndromes are inherited in autosomal dominant manner.
- Genes affected may be proto-oncogenes, tumor suppressor genes, or mismatch repair genes.
- Patients with genetic predisposition should begin screening for certain cancers at younger ages.
- Genes, clinical features, and surveillance of inherited cancer syndromes are detailed in Tables 37.1 to 37.4.

HEREDITARY BREAST CANCER SYNDROMES

1. What are the most common hereditary cancer syndromes associated with increased risks for breast cancer?

- Hereditary breast and ovarian cancer syndrome (*BRCA1*, *BRCA2*)
- *PTEN* hamartoma tumor syndrome (*PTEN*, Cowden syndrome)
- Li–Fraumeni syndrome (*TP53*)

HEREDITARY COLORECTAL CANCER SYNDROMES

1. What are the most common hereditary cancer syndromes associated with increased risk for colorectal cancer?

- Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, TACSTD1/EPCAM*).
- Familial adenomatous polyposis (*APC*).
- Peutz–Jeghers (*STK11*).
- Juvenile polyposis (*SMAD4, BMPR1A*).

MULTIPLE ENDOCRINE NEOPLASIA

1. How are multiple endocrine neoplasias (MENs) classified?

- MEN1 (gene also *MEN1*), MEN2 (*RET* gene).
- MEN2 is classified into MEN2a and MEN2b.

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TABLE 37.1 ■ Clinical Manifestations and Major Screening Recommendations for Hereditary Breast Cancer Syndromes

Cancer Syndrome	Gene Involved	Incidence	Clinical Manifestations	Major Screening Recommendations
Hereditary breast-ovarian cancer (HBOC) syndrome	*BRCA1* and *BRCA2*	1 in 300 (**1 in 40** in people of Ashkenazi Jewish descent)	■ Early onset **breast and ovarian cancers,** *BRCA1* > *BRCA2* risk ■ Increased risk of other cancers such as **pancreatic, stomach, fallopian tube, and primary peritoneal cancers**	■ **Annual breast screening starting at age 25** ■ (annual breast MRI starting age ~25, adding mammogram at age 30) ■ Consider **prophylactic mastectomy** or chemoprevention with tamoxifen ■ Discuss ovarian cancer risk reduction with **BSO** after completion of childbearing or age >35 (80% risk reduction for ovarian cancer and 50% for breast cancer) ■ If no BSO, consider screening **transvaginal ultrasound and CA-125** twice yearly starting age ~35
PTEN hamartoma tumor syndrome (Cowden syndrome)	*PTEN*	1 in 200,000	■ **Mucocutaneous lesions/GI polyps** ■ **Thyroid** abnormalities ■ Increased risk of **breast, thyroid, endometrial, and kidney cancers**	■ **Annual mammogram and breast MRI** starting age ~30 or consider risk-reducing **mastectomy** ■ Annual **thyroid ultrasound** ■ Consider **endometrial cancer screening** age ~35 and/or discuss prophylactic hysterectomy ■ Consider **colonoscopy** age ~35
Li–Fraumeni syndrome	*TP53*	Very rare	■ Increased risk of **many malignancies**: sarcoma, breast cancer, brain tumor, leukemia, lung cancer, adrenocortical carcinoma ■ Risk of cancer is 90% by 60 years	■ **Breast MRI** starting age ~20–25 ■ **Colonoscopy** starting age ~20–25 ■ Consider surveillance with **whole body/brain MRI**

BSO, bilateral salpingo-oophorectomy; GI, gastrointestinal.

TABLE 37.2 ■ Clinical Manifestations and Major Screening Recommendations for Hereditary Colon Cancer Syndromes

Cancer Syndrome	Gene Involved	Incidence	Clinical Manifestations	Major Screening Recommendations
Lynch syndrome (HNPCC)	*MLH1, MSH2, MSH6, PMS2, TACSTD1/ EPCAM*	1 in 300	■ Increased risk of **colorectal, endometrial, ovarian, pancreas, small intestine, urothelial cancers, and sebaceous neoplasms of the skin**	■ **Annual colonoscopy** starting age ~20–25 ■ **Transvaginal ultrasound and endometrial biopsy** starting age ~30–35 ■ Consider **prophylactic hysterectomy and bilateral salpingo-oophorectomy**
Familial adenomatous polyposis (FAP)	*APC*	1 in 5,000–10,000	■ **100s–1,000s of adenomas** throughout gastrointestinal tract ■ Additional risk of **duodenal/ ampullary cancers, thyroid cancer, central nervous system tumors, hepatoblastoma**	■ **Colonoscopy yearly** for mutation carriers starting age ~10–12 ■ **Surgical colectomy strongly recommended** when polyps become too numerous to be removed endoscopically ■ **EGD** every 1–3 years once colonic polyps develop
Peutz–Jeghers syndrome	*LKB1/STK11*	1 in 200,000	■ **Hamartomatous gastrointestinal polyps**, often presenting as small bowel **intussusception** ■ Mucocutaneous hyperpigmentation ■ Increased risk of **breast, colon, stomach, small intestine, pancreatic, lung, genitourinary cancers**	■ **EGD and colonoscopy** at age ~15 ■ Small bowel imaging beginning age ~8 ■ Annual **breast MRIs** beginning age ~25 ■ Pancreatic cancer screening starting age ~30–35

(*continued*)

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TABLE 37.2 ■ Clinical Manifestations and Major Screening Recommendations for Hereditary Colon Cancer Syndromes (*continued*)

Cancer Syndrome	Gene Involved	Incidence	Clinical Manifestations	Major Screening Recommendations
Juvenile polyposis syndrome (JPS)	*SMAD4* and *BMPR1A*	1 in 100,000	■ **Hamartomatous juvenile polyps** predominantly in stomach and colon ■ Increased risk **of gastrointestinal and pancreas malignancies**	■ **EGD and colonoscopy** starting age ~15 (repeat 1–3 years based on polyp burden)

EGD, esophagogastroduodenoscopy; HNPCC, hereditary nonpolyposis colorectal cancer.

TABLE 37.3 ■ Clinical Manifestations and Major Screening Recommendations for Multiple Endocrine Neoplasias

Cancer Syndrome	Gene Involved	Incidence	Clinical Manifestations	Major Screening Recommendations
Multiple endocrine neoplasia, type 1 (MEN1)	*MEN1*	1–2 in 100,000	■ **"3 Ps:"** ● **Parathyroid** adenomas ● **Pancreatic** endocrine tumors ● **Pituitary** tumors	■ **Yearly parathyroid, pancreatic, pituitary enzyme testing**, starting age ~10 ■ **MRI of brain, pancreas, and adrenal gland** starting age ~10 ■ **CT or MRI of chest** starting age ~10
Multiple endocrine neoplasia, type 2 (MEN2)	*RET*	Unknown	■ **Medullary thyroid** cancer ■ **Pheochromocytoma** ■ **Hyperparathyroidism**	■ **Prophylactic thyroidectomy**, timing based on *RET* mutation type (**MEN2b** with younger onset)

TABLE 37.4 ■ Clinical Manifestations and Major Screening Recommendations for Other Inherited Cancer Syndromes

Cancer Syndrome	Gene Involved	Incidence	Clinical Manifestations	Major Screening Recommendations
Hereditary diffuse gastric cancer syndrome	E-cadherin (*CDH1*)	Unknown	■ **Gastric cancer** (70% lifetime risk) ■ **Lobular breast cancer** (40% lifetime risk)	■ **Total prophylactic gastrectomy** after age ~20 ■ Early **breast screening** in women (MRI beginning age 25)
Familial atypical multiple mole melanoma (FAMMM)	*CDKN2A, CDK4*	Unknown	■ **Multiple malignant melanomas** and atypical nevi, often diagnosed at a young age ■ **Pancreatic cancer** (16%–20% lifetime risk)	■ **Skin exam** starting ~10 years ■ Consider annual pancreatic cancer screening with EUS alternating with **MRCP**
Von Hippel–Lindau disease (VHL)	*VHL*	1 in 36,000	■ **Central nervous system hemangioblastomas** ■ **Retinal hemangiomas** ■ Renal cell carcinoma, **pheochromocytoma,** pancreatic tumors	■ **Retinal exam** ■ **Plasma metanephrines and normetanephrines** ■ **MRI brain, abdomen, pelvis**
Hereditary paraganglioma and pheochromocytoma	*SDHA, SDHAF2, SDHB, SDHC, SDHD*	Unknown	■ Head and neck **paraganglioma** ■ **Pheochromocytoma**	■ **Plasma metanephrines and normetanephrines** ■ **MRI head/neck, abdomen**

EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography.

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OTHER HEREDITARY CANCER SYNDROMES

1. What are some other highly penetrant hereditary cancer syndromes (associated with >5 fold increase in cancer risks)?

- Hereditary diffuse gastric cancer (HDGC) syndrome (*CDH1*).
- Familial atypical multiple melanoma syndrome (*CDKN2A, CDK4*).
- Von Hippel–Lindau *(VHL*).
- Hereditary paraganglioma and pheochromocytoma (*SDHB, SDHC, SDHD*).

TUMOR BIOLOGY AND TARGETED CANCER THERAPIES

TABLE 37.5 ■ Selected Targeted Cancer Therapies

Gene	Malignancy	Targeted Therapy
ABL	CML	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib
ALK	Lung, neuroblastoma, anaplastic large cell lymphoma	Crizotinib, alectinib, ceritinib, lorlatinib, entrectinib
BRAF	Melanoma, colon, thyroid	Vemurafenib, dabrafenib, encorafenib
BTK	CLL, lymphoma	Ibrutinib, acalabrutinib
CDK4/6	Breast	Palbociclib, abemaciclib
EGFR	Lung, glioblastoma	Erlotinib, gefitinib, afatinib, osimertinib (T790M mutation)
FLT3	AML	Midostaurin, gilteritinib
HER2/ERBB2	Breast	Lapatinib
JAK2	CML, myeloproliferative neoplasms	Ruxolitinib, fedratinib
c-KIT	GIST	Imatinib, sunitinib, pazopanib
MEK	Melanoma	Trametinib, cobimetinib, binimetinib
c-MET	Lung, gastric	Crizotinib, cabozantinib
MTOR	Renal cell	Temsirolimus, everolimus
NTRK	Pan-cancer	Larotrectinib
PARP	Ovarian, breast	Olaparib, rucaparib, niraparib, talazoparib
PDGFRA	GIST, glioblastoma	Sunitinib, sorafenib, imatinib
PI3K	CLL, breast cancer	Idelalisib, alpelisib
ROS1	Lung	Crizotinib, entrectinib
VEGF	RCC, HCC, others	Sunitinib, sorafenib, pazopanib, axitinib, cabozantinib

AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

TABLE 37.6 ■ Selected Monoclonal Antibody Therapies

Target	Malignancy	Monoclonal Antibody
CD19	Acute lymphoblastic leukemia	Blinatumomab
CD20	B-cell non-Hodgkin lymphoma	Rituximab, ofatumumab, obinutuzumab
CD30	Refractory/relapsed Hodgkin lymphoma, anaplastic large cell	Brentuximab
CD33	Acute myelogenous leukemia	Gemtuzumab ozogamicin
CD38	Multiple myeloma	Daratumumab
CD52	B-cell CLL	Alemtuzumab
CTLA-4	Melanoma	Ipilimumab
EGFR	Head and neck cancer	Cetuximab
HER2	Breast	Trastuzumab, pertuzumab
Nectin-4	Urothelial cancer	Enfortumab vedotin
PD-1	Multiple cancers	Nivolumab, pembrolizumab
PD-L1	Multiple cancers	Atezolizumab, durvalumab
SLAMF7	Multiple myeloma	Elotuzumab
VEGF	Multiple cancers	Bevacizumab, ramucirumab

CLL, chronic lymphocytic leukemia; PD-L1, programmed death cell ligand; VEGF, vascular endothelial growth factor

TABLE 37.7 ■ Miscellaneous Therapies

Drug	Malignancy	Mechanism of Action
Tamoxifen	Breast	SERMs
Fulvestrant	Breast	Destroys estrogen receptor
Anastrozole	Breast	Aromatase inhibitors
Exemestane	Breast	Aromatase inhibitors
Letrozole	Breast	Aromatase inhibitors
Leuprolide	Prostate	GnRH agonist
Goserelin	Prostate	GnRH agonist
Degarelix	Prostate	GnRH antagonist
Bicalutamide	Prostate	Anti-androgen
Abiraterone	Prostate	Anti-androgen
Enzalutamide	Prostate	Anti-androgen
Bortezomib	Multiple myeloma	Proteasome inhibitors
Carfilzomib	Multiple myeloma	Proteasome inhibitors
Ixazomib	Multiple myeloma	Proteasome inhibitors

GnRH, gonadotropin-releasing hormone; SERM, selective estrogen receptor modulator

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QUESTIONS

1. A 55-year-old woman with stage 2 breast cancer, treated with lumpectomy followed by adjuvant chemotherapy and radiation, is seen in your clinic. Her resected tumor was sent for genetic sequencing and was noted to have a "variant of uncertain significance" in *BRCA2*. She has no known family history of breast and ovarian cancer and her four adult daughters do not have a cancer history.

Which of the following statements are true?

A. Her daughters are strongly recommended to undergo *BRCA2* testing.
B. There is no evidence that the *BRCA2* variant is pathogenic, and this was an incidental finding that can be disregarded.
C. The *BRCA2* variant may be pathogenic and contributed to her cancer, but since it is of uncertain significance this finding can be disregarded.
D. None of the above.

2. A 35-year-old woman with a strong family history of breast cancer is referred to the cancer genetics clinic and is found to have a germline pathogenic variant in the *BRCA2* gene.

Compared to patients with germline *BRCA1* pathogenic variants, this patient is at a decreased risk of developing what type of tumor?

A. Thyroid cancer
B. Pancreatic cancer
C. Colorectal cancer
D. Ovarian cancer

3. A 54-year-old man is evaluated because of anorexia, vague abdominal discomfort, and 30 lb weight loss during the past 3 months. His father and his brother died of stomach cancer. Upper endoscopy shows diffuse gastric mucosal abnormalities and no discrete mass. Random biopsies confirm HER2-negative adenocarcinoma with signet-ring cells. Germline testing of his blood reveals a *CDH1* pathogenic variant. The patient's 24-year-old son is subsequently tested and carries the same pathogenic variant.

Which of the following should you recommend for this patient's son?

A. History and physical examination every 6 months
B. Surveillance endoscopy every year
C. Diet low in nitrites, nitrates, spicy and smoked foods, and alcohol
D. Total gastrectomy

4. You are in sarcoma clinic and receive a new referral for a 19-year-old patient who was newly diagnosed with osteosarcoma. You look back at his chart and notice that there is also a family history of astrocytoma and adrenocortical carcinoma. You decide to refer him to genetics clinic.

What gene is most likely to be implicated here?

A. *APC*
B. *KIT*
C. *PTPN11*
D. *TP53*
E. *WRN*

5. At a recent neighborhood block party, you run into a young 35-year-old Asian woman who, upon finding that you are an oncologist, excitedly tells you that she had recently completed a direct-to-consumer saliva DNA genetic testing that she bought online during a Black Friday sale. She mentioned that the genetic test report included some information about *BRCA1* and *BRCA2* and "I don't have the bad breast cancer gene and this is great!"

What do you tell her?

A. "Congratulations, this is a negative test and the likelihood that you have genetic predisposition to hereditary breast and ovarian cancer is very low."
B. "You should take the test results with a grain of salt, because it is possible the test only assessed for certain pathogenic variants of the *BRCA1* and *BRCA2* gene."
C. "You should read the report carefully to make sure you are interpreting the results correctly."
D. B and C.

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ANSWERS

1. **D. None of the above.** Variants of uncertain significance (VUS) are detected genetic changes for which there is currently insufficient information to determine their effect on gene function and/or association with disease. According to the American College of Medical Genetics, healthcare providers should not use a VUS genetic test result to guide management; rather, the patient's clinical and family history should be used to guide medical decision-making. In this case, there is no strong indication to test the patient's daughters for *BRCA2* as their mother's VUS result is not clinically informative, and there is no additional family history of breast and ovarian cancer on their father's side of the family. Over time, there may be additional information learned regarding this patient's *BRCA2* variant, which may cause it to be reclassified from VUS to (likely) pathogenic or (likely) benign. In the case a variant is reclassified to pathogenic, this would then be clinically actionable and be an indication for testing other family members. Thus, although a VUS genetic test result is not clinically informative at this time, it should not be disregarded and the patient should be counseled that this result may be reclassified in the future.

2. **D. Ovarian cancer**. Although the lifetime risk for ovarian cancer is higher for patients with *BRCA2* germline variants compared to the average population, when comparing to patients with germline *BRCA1* variants, patients with *BRCA2* pathogenic variants have a lower risk of developing ovarian cancer (40% vs. 15% at age 70 years for *BRCA1* and *BRCA2* carriers, respectively). Patients with *BRCA2* pathogenic variants are at an increased risk of pancreatic, prostate, and male breast cancers when compared to the general population and patients with germline *BRCA1* pathogenic variants. Thyroid and colorectal cancer are not associated with inherited breast and ovarian cancer syndromes.

3. **D. Total gastrectomy.** Hereditary diffuse gastric cancer (HDGC) is a relatively rare disorder, associated with pathogenic germline variants in the *CDH1* gene. Carriers of a germline mutation in *CDH1* have a lifetime risk of >80% of developing diffuse gastric cancer. Unfortunately, most diffuse gastric cancers cannot be detected through endoscopic surveillance. Since most patients with HDGC present with advanced stage disease (with high mortality), prophylactic total gastrectomy is advised for this patient group. Clinical surveillance and lifestyle modifications do not offer sufficient protection; and total prophylactic gastrectomy is the most effective intervention to reduce mortality from gastric cancer for patients with *CDH1* germline pathogenic/likely pathogenic variants.

4. **D. *TP53*.** *APC* is the tumor suppressor gene involved in familial adenomatous polyposis (FAP), an autosomal dominant syndrome of large bowel adenomas, which is also associated with desmoid tumors. *KIT* is the oncogene responsible for both sporadic and familial gastrointestinal stromal tumors (GISTs). *PTPN11* is implicated in Noonan Syndrome, an autosomal dominant disorder classically associated with dysmorphic facial features, short height, and congenital heart disease. Patients with Noonan syndrome

have an increased risk of malignancy, especially brain tumors, leukemia, and rhabdomyosarcoma. *TP53* is the tumor suppressor gene implicated in the autosomal dominant Li–Fraumeni syndrome (LFS), which is the correct answer to this question. Patients with LFS may develop multiple cancers early in life, including premenopausal breast cancers, sarcomas, brain tumors, adrenocortical carcinomas, and leukemias. Finally, *WRN* is the gene responsible for Werner's syndrome, an autosomal recessive disorder characterized by early aging, which is associated with melanoma and rarely with soft tissue sarcomas.

5. **D. B and C.** In March 2018, the Food and Drug Administration (FDA) authorized that direct-to-consumer genetic testing could include testing for *BRCA1* and *BRCA2* (as well as certain additional genes) without requiring an order from a healthcare provider. However, some companies whose reports include results for *BRCA1* and *BRCA2* actually test for only a few specific *BRCA1* and *BRCA2* variants (most often the 3 that are most common in individuals of Ashkenazi Jewish descent). There are actually more than 1,000 other known pathogenic *BRCA1* and *BRCA2* variants, so it is important to know whether the test included analysis for additional variants. Since this individual is not of Ashkenazi Jewish descent and if she was tested for only the 3 Ashkenazi Jewish founder mutations, then her result could actually be a false negative. Further, her personal and family history of cancers would be very important to assess in considering her overall risk. If she has a family history of cancer that is concerning for possible genetic susceptibility to cancer, this negative *BRCA1* and *BRCA2* mutation analysis from a direct-to-consumer test should not necessarily be trusted and the patient might be advised to undergo a more comprehensive clinical genetics evaluation.

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SUPPORTIVE AND PALLIATIVE CARE

XIII

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38 Supportive Care

Victoria D. Powell and Maria J. Silveira

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

1. What are the types of chemotherapy-induced nausea and vomiting (CINV)?

- **Acute:** Up to 24 hours after chemotherapy, mediated by 5-HT3 release from enterochromaffin cells
- **Delayed:** More than 24 hours after chemotherapy, mediated by NK_1 receptors
- **Anticipatory:** Occurs on the day of or some hours before the anticipated chemotherapy; typically triggered by taste, odor, sight, distressing thoughts, or anxiety

2. What is the emetogenicity of various chemotherapeutic agents?

- See Tables 38.1 and 38.2 for details.

3. What antiemetic agents are available?

- Serotonin ($5\text{-}HT_3$) receptor antagonists
  - First generation: Dolasetron, granisetron (transdermal patch option), ondansetron (oral dissolving tablet option), tropisetron
  - Second generation: Palonosetron (higher affinity for receptor and longer half-life)
  - Oral and intravenous (IV) forms are similarly effective
  - Side effects: Headache, diarrhea, transient transaminitis and EKG changes; prolonged QT interval seen primarily with dolasetron. Constipation can be severe.
- NK_1 receptor antagonists
  - Aprepitant, fosaprepitant, netupitant, fosnetupitant, rolapitant
  - Potential drug interactions: moderate inhibitor of CYP3A4
- Corticosteroids
  - Dexamethasone preferred; oral or parenteral equally effective
  - Side effects: insomnia, mood changes, irritability, and hyperglycemia
- Dopamine (D_2) receptor antagonists
  - Prochlorperazine, promethazine, chlorpromazine, haloperidol, metoclopramide, and olanzapine
  - Side effects: sedation, extrapyramidal reactions, anticholinergic effects, QT prolongation, hypotension with rapid IV administration (prochlorperazine, promethazine, chlorpromazine), tardive dyskinesia (long-term administration)
- Benzodiazepines
  - Lorazepam and alprazolam
  - Useful for anticipatory nausea

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TABLE 38.1 ■ Risk of Emesis (w/o Antiemetics)

	High >90%	Moderate 31%–90%	Low 10%–30%	Minimal <10%
IV agents	Carmustine >250 mg/m^2 Cisplatin Cyclophosphamide ≥1,500 mg/m^2 Dacarbazine Doxorubicin ≥60 mg/m^2 Epirubicin >90 mg/m^2 Ifosfamide ≥2g/m^2 Mechlorethamine Streptozotocin Any anthracycline plus cyclophosphamide (AC combination)	Aldesleukin >12 million IU/m^2 Amifostine >300 mg/m^2 Azacitidine Bendamustine Busulfan Cabazitaxel Carboplatin Carmustine ≤250 mg/m^2 Clofarabine Cyclophosphamide ≤1,500 mg/m^2 Cytarabine >200 mg/m^2 Dactinomycin Daunorubicin* Doxorubicin <60 mg/m^2 Epirubicin*≤90 mg/m^2 Idarubicin* Ifosfamide <2g/m^2 Irinotecan Melphalan Methotrexate (>250 mg/m^2)	Ado-trastuzumab emtansine Aldesleukin <12 million IU Amifostine ≤300 mg/ m^2 Arsenic trioxide Axicabtagene ciloleucel Belinostat Brentuximab vedotin Cabazitaxel Copanlisib Carfilzomib Cytarabine 100–200 mg/m^2 Docetaxel Doxorubicin (liposomal) Eribulin Etoposide 5-Fluorouracil Floxuridine Gemcitabine Gemtuzumab ozogamicin Inotuzumab ozogamicin Ixabepilone Methotrexate 50–250 mg/m^2	Alemtuzumab Atezolizumab Avelumab Asparaginase Bevacizumab Bleomycin Blinatumomab Bortezomib Cemiplimab Cladribine Cetuximab Cytarabine <100 mg/m^2 Daratumumab Decitabine Denileukin diftitox Dexrazoxane Durvalumab Elotuzumab Fludarabine Ipilimumab Methotrexate <50 mg/m^2 Nelarabine

(*continued*)

TABLE 38.1 ■ Risk of Emesis (w/o Antiemetics) (*continued*)

High >90%	Moderate 31%–90%	Low 10%–30%	Minimal <10%
	Oxaliplatin	Mitomycin	Nivolumab
	Temozolomide	Mitoxantrone	Obinutuzumab
	Trabectedin	Mogamulizumab	Ofatumumab
		Moxetumomab	Panitumumab
		Necitumumab	Pegaspargase
		Olaratumab	Peginterferon
		Omacetaxine	Pembrolizumab
		Paclitaxel	Pertuzumab
		Pemetrexed	Ramucirumab
		Pentostatin	Rituximab
		Polatuzumab vedotin	Siltuximab
		Pralatrexate	Temsirolimus
		Romidepsin	Trastuzumab
		Tagraxofusp	Valrubicin
		Talimogene laherparepvec	Vinblastine
		Thiotepa	Vincristine
		Tisagenlecleucel	Vinorelbine
		Topotecan	
		Ziv-aflibercept	

(*continued*)

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TABLE 38.1 ■ Risk of Emesis (w/o Antiemetics) (*continued*)

	High >90%	Moderate 31%–90%	Low 10%–30%	Minimal <10%
PO agents	Hexamethyl-melamine Procarbazine		Axitinib Bexarotene Capecitabine Cetuximab Dasatinib Estramustine Etoposide Everolimus Fludarabine Lapatinib Lenalidomide Nilotinib Panitumumab Pazopanib Sunitinib Tegafur uracil Thalidomide Topotecan Vemurafenib Vorinostata	6-Thioguanine Chlorambucil Erlotinib Gefitinib Hydroxyurea Melphalan Methotrexate Regorafenib Sorafenib Vorinostat

AC, anthracycline plus cyclophosphamide.

TABLE 38.2 ■ Risk of Emesis (w/o Antiemetics)

Moderate to High >30%	Min to Low
Altretamine	
Avapritinib	
Binimetinib	
Busulfan (≥4 mg/day)	
Ceritinib	
Crizotinib	
Cyclophosphamide (≥100 mg/m$^{2/}$day	
Dabrafenib	
Enasidenib	
Encorafenib	
Estramustine	
Etoposide	
Lenvatinib	
Lomustine	
Midostaurin	
Mitotane	
Niraparib	
Olaparib	
Procarbazine	
Rucaparib	
Selinexor	
Temozolomide (>75 mg m$^{2/}$day)	

- Side effects: dose-related sedation and delirium (especially in older patients), use with caution in patients receiving concomitant opioids due to potentiation of sedating effects.

■ Cannabinoids
- Dronabinol and nabilone (synthetic), medical marijuana (evidence unclear, not available in all states)
- Not first-line agents
- Side effects: sedation, confusion, dizziness, short-term memory loss, euphoria/dysphoria, ataxia, dry mouth, and orthostatic hypotension

■ Antihistamines
- Diphenhydramine, meclizine, scopolamine (patch) and hydroxyzine
- Are not useful for CINV, but helpful for motion sickness and vertigo
- Side effects: sedation, delirium (especially in older patients), dry mouth, visual changes, mydriasis, decreased gastrointestinal (GI) motility, urinary changes, and increased heart rate

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4. How do you prevent nausea and vomiting?

TABLE 38.3 ■ Prophylaxis Recommended

Risk	High		Moderate		Low	
	Day 1	Days 2–4	Day 1	Days 2–3	Day 1	Days2+
	Start prior to chemo: 5-HT3RA + dex 12 mg + NK1 RA + olanzapine	Olanzapine + NKR1 +dex 8 mg	5HT3RA + dex 12 mg	Dex 8 mg OR 5-HT3 RA	Start day prior to chemo, repeat day(s) of chemo Dex OR metoclopramide OR prochlorperazine OR 5-HT3 RA Dosed once daily	None or prn only

dex, dexamethasone; 5-HT3RA, serotonin receptor antagonist; NK1 RA, NK receptor antagonist; RA, receptor antagonist.

For minimal emetogenicity agents (<10%), no prophylaxis is needed.

Lorazepam may be added to any regimen for those with anticipatory nausea/vomiting.

5. How do you treat breakthrough and refractory CINV?

- Avoid repeated dosing of agents that were given for prophylaxis and already failed
- Add an agent from a novel class (e.g., olanzapine)
- Consider parenteral forms (IV, PR)
- Dose around-the-clock until nausea controlled

6. What are nonpharmacologic measures for antiemetic prophylaxis?

- Ginger capsules or chews (prior to and during treatment cycle)
- Cognitive distraction (i.e., playing video games during treatment)
- Systematic desensitization (visualization and learned relaxation techniques)
- Hypnosis
- Acupuncture, acupressure (i.e., wrist bands)
- Transcutaneous electrical nerve stimulation
- Mindfulness through guided meditation

PAIN MANAGEMENT

1. What are the critical features of a comprehensive pain assessment?

- Interview the patient to localize the pain and describe provoking/palliating factors, quality, severity, and timing of the pain. Rule out radiating or referred pain. Patients can have multiple sources of pain; each should be characterized separately.
- Identify psychosocial factors that may interfere with treatment of pain:
  - Concurrent mood disorders or psychological distress (i.e., catastrophizing)
  - Fear of addiction or death

- Social, financial, and spiritual stressors
- Prior history of substance abuse, tobacco, or chronic opioid use
  - Use of a validated screening tool for risk of misuse is strongly recommended (e.g., Opioid Risk Tool)

- Inspect and palpate the site of pain, looking for associated physical signs. Rule out neurologic deficits
- Reassess the patient when there is any change in quality or severity of pain or increased consumption of analgesics

Special Considerations

- Severe, uncontrollable pain/pain crisis
  - A medical emergency that may require IV therapy and/or hospitalization
  - Consider whether pain related to an oncologic emergency (pathologic fracture or impending fracture related to bone mets; cord compression; infection; obstruction or perforated viscus) and treat according to patient's goals (e.g., corticosteroids, emergency surgery)
- Nonverbal patient (e.g., severe delirium, dementia, sedation): use validated scale for behavioral/observational pain assessment (e.g., Behavioral Pain Scale, Critical-Care Pain Observation Tool)
- Non-English-speaking patient: obtain services of trained interpreter. Do not rely on English-speaking companions to interpret or on behavioral observations only
- Risk factors for undertreated pain: African American and other minority race/ethnicity, dementia, female sex, other cultural factors

2. What is an appropriate approach to cancer pain management?

- Determine the likely mechanism of the pain. Many patients with cancer have pain that is not cancer-related; chronic musculoskeletal pain should NOT be treated with opioids even in the context of active cancer
- Determine whether the patient is a good candidate for opioids. Patients should be able to take the medication safely and responsibly. Patients with prior history of polysubstance abuse should be provided opioids in smaller quantities (1–2 weeks at a time) and given additional supervision by staff.

An opioid use agreement is recommended, especially for patients who are expected to use opioids long term. Many states require providers to review prescription tracking records prior to writing for Schedule II medications. Urine drug screens should be carried out at least twice a year for patients on long-term opioids who are not in hospice (Table 38.4).

3. What are opioid equivalences as compared with single-dose morphine?

- See Table 38.5

4. What opioid should you choose?

- Short-acting opioids are indicated for intermittent or break through pain; dosing is q3h to q4h prn
- Long-acting opioids are indicated when patients are taking short-acting opioids, round-the-clock (generally ≥4 doses/24 hours) and the pain generator (i.e., the cancer) is likely continue to cause pain for a prolonged period of time.
- Compounded opioids (e.g., hydrocodone with acetaminophen) should be avoided in patients whose pain condition is likely to worsen over time as there is a ceiling level to acetaminophen that prevents upward titration

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TABLE 38.4 ■ Treatment of Pain Generator by Prognosis

		Good	Poor
Severity of Cancer Pain	**Mild**	NSAID and/or Acetaminophen prn	Dose find with strong, short-acting opioid prn; rotate to long-acting once dose is known
	Moderate/Severe	Strong, short-acting opioid q3–4h prn only	Strong, short-acting prn + long-acting opioid if ≥4 doses of short-acting opioid
	Pain Crisis	Hospitalization for treatment with IV medications/ expedited work-up	Needed/24 hours Hospitalization OR inpatient hospice based on goals

IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug.

- Choice of opioid depends upon the severity of the pain, past trials of opioids, and renal function
- First line:
  - Mild pain: nonopioids
  - Moderate to severe pain: hydrocodone, oxycodone, hydromorphone or morphine
- Some situations merit specific opioids:
  - Poor compliance or mild cognitive impairment: transdermal fentanyl
  - Intractable constipation: transdermal fentanyl
  - Neurotoxicity (e.g., myoclonus): hydromorphone, oxycodone, or methadone
  - Renal impairment: fentanyl, oxycodone, and methadone
  - Liver impairment: oxycodone
  - Opioid tolerance: hydromorphone
  - Complex pain (with heavy neuropathic component), opioid-induced hyperalgesia: methadone
  - Unable to take PO: transdermal fentanyl, sublingual morphine concentrate

5. How do you initiate short-acting opioids?

- For patients who are opioid-naïve, begin opioids at the lowest recommended dose (see Table 38.5); consider even lower doses for older patients or patients with renal or liver disease.
- Effectiveness of a given dose can be gauged within 1 hour of taking an oral opioid and 15 minutes of taking an IV opioid
- Dosing intervals for short-acting opioids are q3h to q4h prn
- For ambulatory patients with pain but not in crisis, start opioids as recommended earlier, have them keep a diary and follow-up within a week. When pain control is not achieved, increase dose in increments by 30% to 50%.
- For ambulatory patients with severe pain, start opioids as recommended earlier, have them keep a diary, and reassess within 24 hours. When pain is not controlled, increase dose by 100% and reassess again within 24 hours.
- Patients in crisis whose pain cannot be controlled at home with oral opioids should be admitted to the hospital for IV treatment ± additional workup as clinically indicated. IV is preferred for patients who have malabsorption or intractable vomiting.

TABLE 38.5 ■ Opioid Equivalences Compared With Single-Dose Morphine

Drug	Parenteral Dose (mg)	Oral Dose (mg)	Factor (IV ≥ PO)	Peak	Duration of Action (hours)	Starting IV Dose (opioid naïve)	Starting PO Dose (opioid naïve)
Morphine	10	30	3	PO: 1.5–2 hr IV: 20 min	3–4	2–4 mg q2–4h	7.5 mg (1/2 tab) immediate release OR 5 mg elixir q3–4h
Hydromorphone	1.5	7.5	5	PO and IV: 1 hr	2–3	0.2–1 mg q2h	2 mg q3–4h
Fentanyl	100 mcg	–	–	IV: 1–5 min Transdermal: 24 hr	1–3	25–50 mcg q2h prn	Transdermal: not for opioid naïve patients
Oxycodone	–	15–20	–	1–2 hr	3–5	–	2.5–5 mg q3–4h
Hydrocodone	–	30–45	–	2 hr	3–5	–	5 q3–4h with 325 mg acetaminophen

*Methadone's conversion ratio to oral morphine equivalents is dose-dependent. Codeine and tramadol should be avoided as first-line agents due to considerable interindividual variability in metabolism. Meperidine, pentazocine, nalbuphine, and butorphanol are not recommended.

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6. How do you initiate long-acting opioids?

- Patients should not be started on a long-acting opioid without first "dose finding" with a short-acting opioid to determine the total daily dose (TDD)
- Once the TDD is known, divide the TDD by the number of times the patient will be taking the long-acting opioid per day. For example, for BID long-acting morphine, 50% of the TDD should be given in the morning and 50% of the TDD should be given in the evening.
- Try to use the short- and long-acting forms of the same opioid. Rarely is a combination of different opioids helpful.
- When converting from one opioid to another (e.g., morphine to oxycodone), calculate the TDD of the initial opioid and convert to the equivalent TDD of the replacement opioid using the equianalgesic doses (see table above). Reduce the TDD of new opioid by 25% to 50% to account for incomplete cross-tolerance. Then convert into long- and short-acting forms.

7. What is appropriate dosing for breakthrough pain medication?

- Once patients are on a long-acting opioid, the short-acting breakthrough opioid should be dosed at 10% to 20% of the TDD.
  - For example, if a patient is taking 40 mg long-acting oxycodone twice daily, then an appropriate dose of breakthrough medication would be 5 to 10 mg oxycodone every 4 hours as needed.
- Oral opioids may be safely dosed as often as every 1 to 2 hours during a pain crisis
  - Short-acting opioids given orally reach peak effect at 1 hour and last no more than 4 hours

8. What are common side effects of opioids?

- All patients on opioids get constipation
- Other common side effects include delirium, myoclonus, urinary retention, sedation, nausea and vomiting, pruritus, and respiratory depression. Tolerance develops over time for all these effects except constipation, delirium, myoclonus, and urinary retention; these side effects and hypersensitivity reactions require switching to a different opioid.
- Prevent constipation in patients on opioids by administering a motility agent (bisacodyl or senna) daily
  - Titrate the dose every 2 to 3 days for a bowel movement at least once every 48 hours
  - Avoid constipating agents (e.g., fiber, anticholinergics, haloperidol, calcium channel blockers, iron, anticonvulsants, and ondansetron)
  - Opioid-induced constipation refractory to stimulant laxatives: start peripheral acting opioid antagonist (e.g., naloxegol, methylnaltrexone)

9. What are risks of long-term opioid use?

- Opioid use disorder: malingering for opioids is rare in patients with active cancer, but can be seen among patients whose cancers are in remission, especially those with a preceding history of polysubstance abuse. Titration off opioids, especially in remission, is an appropriate goal.
- Dependence: manifests as withdrawal symptoms (anxiety, nausea, diarrhea, piloerection ["goose bumps"], diaphoresis) at cessation or dose reduction
- Tolerance: all patients taking opioids regularly develop tolerance; providers should expect that TDD will go up over time, even when disease is stable.

- Hyperalgesia: increased pain sensitivity that develops with regular, long-term opioid use; precise mechanism is poorly understood; escalating the opioid dose may paradoxically increase the level of pain. Consider reduction in dose, rotation to methadone, or ketamine infusion, and other adjuvant analgesics and nonpharmacologic treatments.

10. When does one consider opioid dose reduction and how does one implement dose reduction or discontinuation of opioid therapy?

- Consider dose reduction by 10% to 20% TDD when stable disease or remission, seldom/never need breakthrough opioids, initial acute pain event subsided, severe side effects
- Decrease TDD by 10% to 20% and follow closely for signs/symptoms of withdrawal. Consider slower tapers for those receiving opioids long-term (>90 days).

11. What are examples of adjuvant analgesics?

- Alpha 2 delta ligands/gabapentinoids
  - Gabapentin, pregabalin
  - Useful in neuropathic and central pain syndromes. May be helpful for refractory cough in patients with lung cancer/metastases or capsular stretch in patients with liver metastases.
  - Requires renal dosing adjustment for patients with renal impairment.
  - Starting dose: gabapentin 100 to 300 mg qhs, pregabalin 75 mg BID. increase 50% to 100% up to q3 days
- Antidepressants
  - Serotonin–norepinephrine reuptake inhibitors (SNRIs; e.g., duloxetine) and tricyclic antidepressants (TCAs) (amitriptyline, nortriptyline, desipramine)
  - Useful for mood disorders, neuropathic pain, and central pain
  - For patients with cancer, they should be added once opioids have been initiated. Patients should be monitored for anticholinergic side effects. Avoid TCA use in >65 years old.
- Bisphosphonates
  - Pamidronate, ibandronate, and zoledronate
  - Effective for treating bone pain related to metastases
- Local anesthetics (i.e., lidocaine patch)
  - Effective for treating well localized, superficial neuropathic, and somatic pain syndromes.
- Corticosteroids
  - Effective for pain related to central nervous system (CNS) or boney metastases, liver capsule stretch, and GI obstruction
- Antispasmotics (i.e., dicyclomine)
  - Effective for visceral pain related to distention of hollow viscera
  - Can cause constipation
- Interventional pain clinic
  - Referral for nerve/plexus blocks, infusion pumps, stimulation units, kyphoplasty/vertebroplasty for patients with distinct pain syndromes who have contraindications to opioids, or do not respond to maximal pharmacologic management and cancer treatment. Patients typically need to have a life expectancy of at least 3 months, be able to come off anticoagulation, and have no known sources of infection to qualify for such procedures.

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12. What are examples of nonpharmacologic pain therapy?

- Acupuncture
- Relaxation/biofeedback/mindfulness meditation
- Recreation/art/music therapy
- Transcutaneous electrical nerve stimulation
- Myofascial trigger release
- Massage, healing touch
- Behavioral counseling (especially for maladaptive pain cognitions, e.g., catastrophizing)

CONSTIPATION

1. What should an assessment of constipation entail?

- Assess cause and severity of constipation:
  - Goal: one bowel movement every 24 to 48 hours
- Rule out and treat other causes such as:
  - Fecal impaction
  - Obstruction
  - Malignant neurogenic involvement/chemotherapy-induced bowel neuropathy
  - Medication-induced (5-HT3 antagonists, opioids)
  - Electrolyte imbalances (hypercalcemia)

2. What are preventive measures for constipation?

- Ensure adequate fluid intake and encourage physical activity
- Patients taking opioids should be instructed to stop fiber supplementation
- Initiate a stimulant laxative at the same time as initiation of opioids. Instruct patients that "every day you take a pain pill is a day you take a laxative."

3. How do you manage constipation?

- Ask patients to keep a log of their bowel movements
- When an opioid is prescribed, prescribe a stimulant laxative (senna or bisacodyl [causes more GI irritation] daily)
  - Adjust the dose every 2 to 3 days according to results
- If the patient goes more than 3 days without a bowel movement, first prescribe either a bisacodyl or glycerin suppository. If ineffective, recommend a phosphate enema daily until a good bowel movement is achieved.
  - Note: Do NOT use rectal approaches if patient is neutropenic or coagulopathic.
- For refractory opioid-induced constipation, consider addition of peripherally acting opioid antagonist (methylnaltrexone, naloxegol). Avoid in patients with bowel obstruction, transmural bowel metastases, and recent GI surgery due to case reports of bowel perforation

CANCER CACHEXIA

1. What is cancer cachexia?

- Characterized by loss of appetite, chronic nausea, fatigue, and weight loss (≥6% decrease over 6 months). Thought to be secondary to:
  - Proinflammatory cytokines (tumor necrosis factor [TNF], interleukin [IL]-1, IL-6, interferon [IFN]), which lead to hypermetabolism and anorexia (from changes in ghrelin, leptin, and serotonin production)

- Tumor production of proteolysis-inducing factor and lipid-mobilizing factor causes fat and muscle loss
- Inefficient energy metabolism and insulin resistance leads to further lean body mass depletion

- Cancer cachexia is an independent predictor of early mortality
- Overfeeding may lead to further metabolic derangement without resultant weight gain

2. What are appropriate interventions for anorexia/cachexia?

- Treat reversible causes: for example, nausea and vomiting, xerostomia, mucositis, dental issues, dysgeusia, dysphagia, early satiety, bowel obstruction, constipation, pain, and depression
  - Rule out endocrine abnormalities (e.g., hypercalcemia)
- Review and eliminate medications that interfere with appetite (e.g., some stimulants, antidepressants)
- Rule out social and economic factors
- Nutrition consultation can help identify barriers to increased intake or recommend dietary modifications
- Caloric supplementation:
  - Increased intake does not result in improved survival or tumor response
  - Enteral feeding is preferred (less infection risk, decreased catabolic hormones, improved wound healing, shorter hospital stays, and maintenance of gut integrity)
  - Parenteral nutrition (rarely indicated unless patient is NPO)
- Pharmacological interventions:
  - Metoclopramide helps treat nausea as well as delayed gastric emptying in patients who complain of early satiety. Watch for extrapyramidal symptoms (EPS).
  - Glucocorticoids help to increase appetite, but should be used for short periods of time due to the long-term effects
  - Megestrol works like steroids and is rarely effective if the patient has not responded to steroids in the past. Do not give megestrol concurrently with steroids. Note: megestrol can increase risk for thromboembolic events and for this reason is typically avoided in patients with malignancies
  - Mirtazapine can be considered especially if patient has concomitant insomnia or depression
  - Medical marijuana can help with appetite; usually given in oral form
- Dronabinol is not effective for increasing appetite in cancer patients

DYSPNEA

1. What is an appropriate approach to the management of dyspnea?

- Assess and identify the causes of the dyspnea
- Treat reversible causes:
  - Infection: antibiotics as indicated
  - Anemia: transfuse as needed
  - Bronchospasm
  - Pneumothorax
  - Pulmonary embolus: anticoagulation if possible
  - Airway mechanical obstruction (e.g., mass)
  - Pulmonary edema: diuretics, discontinue IV fluid

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- Effusions (pleural and pericardial): thoracentesis and pleurodesis
- Airway obstruction (e.g., superior vena cava [SVC] syndrome): bronchoscopic interventions and/or palliative radiation

- Comorbid chronic obstructive pulmonary disease [COPD]: inhaled corticosteroids and bronchodilators
- Relieve symptoms
  - Nonpharmacologic
    - Fans, cooler temperatures, stress management, and relaxation therapy
    - Supplemental oxygen for hypoxia (SaO_2 <90%) or subjective relief after trial
    - Emotional, psychosocial, and educational support
  - Pharmacologic
    - Low-dose opioids (i.e., 2.5–5 mg morphine elixir q2–4h) to reduce air hunger; doses are lower than for analgesia (typically <15 to 30 oral morphine equivalents [OME] daily are needed)
    - Anxiolytics should be used sparingly in patients taking opioids to avoid unintentional overdose, unless the patient is at the end of life. Generalized anxiety disorder should be treated with selective serotonin reuptake inhibitor (SSRI)
    - Expectorants (i.e., guaifenesin) to thin secretions
    - Antitussives (i.e., dextromethorphan, and low-dose hydrocodone) to reduce frequency of cough
    - Anticholinergics (i.e., atropine and hyoscine) to control secretions in patients at the end of life
  - Pulmonary rehab for patients with COPD and longer life expectancies

PSYCHIATRIC SYNDROMES

1. What are common psychiatric syndromes seen in cancer patients?

- Adjustment disorder
- Major depression
- Anxiety
- Delirium
- Demoralization and existential distress

2. What is adjustment disorder?

- Time-limited, maladaptive reaction to a specific stressor (e.g., cancer diagnosis and treatment)
- Onset within 3 months of stressor, duration <6 months
- Lack neurovegetative signs and suicidal ideation
- Treatment directed at crisis intervention, brief psychotherapy, and symptom management

3. What are the diagnostic criteria for major depressive disorder (MDD)?

- Persistently low mood or anhedonia plus five of the following for at least 2 weeks:
  - Sleep disturbance
  - Loss of interest
  - Feelings of hopelessness, helplessness, or guilt
  - Low energy (less helpful in advanced cancer)

- Poor concentration
- Appetite disturbance (less helpful in advanced cancer)
- Psychomotor retardation/agitation
- Suicidal ideation

- Screen using the Patient Health Questionnaire(PHQ)-2, and assess using the PHQ-9
- Rule out pseudodepression

4. What are some causes of pseudodepression?

- Uncontrolled pain
- Hypothyroidism
- Medications (steroids, certain chemotherapies such as IFN)
- Metabolic abnormalities (electrolytes, $B_{12,}$ or folate deficiency)
- Organic brain disease (metastatic brain involvement, endocrinopathies, etc.)
- Dementia
- Substance abuse
- Adjustment disorder
- Fatigue
- Personality disorders

5. What is the treatment of MDD?

- Psychotherapy
- Pharmacotherapy
  - SSRIs and SNRIs
  - 4 to 6 weeks to see full benefit
  - SNRIs especially useful in patients who also have neuropathic pain
  - TCAs should be avoided in patients >65
  - Mirtazapine is a good option for patients with cancer anorexia and/or insomnia
  - CNS stimulants (methylphenidate) have shorter onset of action and can be considered if life expectancy too limited for SNRI/SSRI; but they should be avoided in anyone who has insomnia, agitation, heart disease, or anxiety
  - Antidepressants should be continued for 12 months from the point of remission if first episode of MDD

6. What are commonly used antidepressants?

TABLE 38.6 ■ Commonly Used Antidepressants

Class	Name	Dose Range (mg)	Side Effects
SSRI	Fluoxetine	5–60	GI symptoms, weight changes, sleep disruption, sexual dysfunction, dry mouth, hyponatremia
	Sertraline	12.5–200	

(*continued*)

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TABLE 38.6 ■ Commonly Used Antidepressants (*continued*)

Class	Name	Dose Range (mg)	Side Effects
SNRI	Venlafaxine	37.5–300	GI symptoms, sexual dysfunction, anticholinergic effects, hypertension w/doses >225 mg, reduces hot flashes
SNRI	Duloxetine	20–120	GI symptoms, headache, dizziness; **preferred agent for neuropathic pain**
			Mixed agents
	Mirtazapine	7.5–45	Sedation, dry mouth, increased appetite and weight gain
Mixed agents	Trazodone	25–200	Sedation, orthostatic hypotension, priapism
	Bupropion	75–300	Anxiety, tremor (stimulant-like effects), lowered seizure threshold
Tricyclic antidepressants	Amitriptyline	25–150	Dry mouth, sedation, weight gain, GI symptoms, EKG changes, orthostatic hypotension, anticholinergic effects
	Nortriptyline	25–150	
	Desipramine	25–150	
	Doxepin	5–150	
CNS stimulants	Methylphenidate	2.5–60*	Hypertension, tachycardia, anxiety, insomnia
	Dextroamphetamine/ amphetamine salts	10–60	

CNS, central nervous system, GI, gastrointestinal; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

*For off-label use in depression, maximum dose is 20 mg and sustained release product is not recommended. For stimulant use, maximum daily dose is 60 mg.

7. What is the management of anxiety?

- Rule out reversible and organic causes
  - Poorly controlled symptoms (e.g., dyspnea)
  - Metabolic disturbances (e.g., hypercalcemia, hypoglycemia, and carcinoid syndrome)
  - Medications (e.g., levothyroxine, corticosteroids, psychostimulants)
- Nonpharmacologic treatment
  - Behavioral therapy, psychotherapy, mindfulness meditation, guided relaxation

- Pharmacologic treatment
  - Benzodiazepines (e.g., lorazepam, alprazolam, and clonazepam) work quickly but tolerance builds rapidly and dependence is possible with longer-term use.
  - Antidepressants (e.g., SSRIs, SNRIs) onset of action is several weeks. SSRIs are first line therapy for generalized anxiety disorder (GAD).
  - Neuroleptics (e.g., haloperidol and atypical antipsychotics) for severe and persistent anxiety
  - Second-line/alternate drugs: buspirone, propranolol (for autonomic symptoms), sedative hypnotics/Z drugs (e.g., zolpidem; for isolated insomnia), antihistamines (hydroxyzine)

8. What is the definition and management of demoralization and existential distress?

- Demoralization and existential distress
  - Spectrum of loss of meaning and purpose resulting in diminished ability to respond to the stresses of life-threatening illness such as cancer, hopelessness, and feelings of being a burden
  - More common than depression and linked with desire for hastened death
  - Meaning-centered psychotherapy, life review/legacy work, and dignity therapy have been shown to be helpful
  - Palliative care and /or spiritual care referral

9. What is delirium?

- Acute confusional state characterized by fluctuating course of cognitive impairment, perceptual disturbances, delusions, mood changes, and disruption of sleep–wake cycle
- May be hyperactive (agitated) or hypoactive (quiet)

10. What is the management of delirium?

- Identify and treat precipitating factors
  - Direct CNS causes
    - Brain tumor/metastases
    - Seizures (especially nonepileptic/nonconvulsive)
  - Indirect causes
    - Unrelieved pain
    - Metabolic encephalopathy/electrolyte derangement (e.g., hypercalcemia, hyperglycemia, hypernatremia, hypothyroidism, dehydration)
    - Medications (steroids, opioids, anticholinergics, antiemetics)
    - Infection
    - Nutritional deficiencies (e.g., thiamine deficiency in Wernicke's encephalopathy)
    - Paraneoplastic syndromes
    - Sleep disruption
    - Urinary retention, bowel obstruction
- Prevention
  - Environmental modification
  - Keep the environment calm and quiet with adequate, but soft, indirect light and limit noise levels

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- Provide glasses and hearing aids to maximize sensory perception
- Consider the use of night lights to combat nighttime confusion
- Use music which has an individual significance to the confused and agitated client to prevent the increase in or decrease agitated behaviors
- If possible, encourage family members to be present to redirect patient

- Pharmacologic treatment
  - No medication has been demonstrated to reduce delirium once it is present
  - Medications are directed at reduction of agitated behaviors to prevent harm to self and others
  - Dopamine antagonists/neuroleptics (e.g., chlorpromazine, haloperidol, olanzapine, quetiapine, risperidone)
    - Side effects: sedation, EPS, hypotension, QT prolongation.
    - Associated with increased mortality, metabolic syndrome, weight gain
  - Benzodiazepines (e.g., lorazepam, midazolam):
    - Should only be used in patients with refractory agitated delirium and avoided in hypoactive delirium
- Palliative sedation with benzodiazepines is reserved for terminal delirium/refractory suffering, with patient and/or surrogate consent)
  - IV Propofol 5 to 15 mcg/kg/minute
  - IV Midazolam 1 mg/hour, titrated until calm

QUESTIONS

1. A 28-year-old woman with synovial sarcoma metastatic to lungs undergoing treatment with an anthracycline-based regimen experiences chemotherapy-induced nausea and vomiting. She develops severe constipation as a result of antiemetics.

Which of the following medications is the most likely culprit?

A. Dexamethasone
B. Ondansetron
C. Metoclopramide
D. Aprepitant

2. You are seeing a 56-year-old woman with a history of metastatic breast cancer to bones currently on palliative chemotherapy with palbociclib and fulvestrant. She reports acute onset, severe 10/10 mid-back pain. She does not have chronic pain and is taking no analgesics. After ordering an urgent spine CT, a pathologic fracture of T10 suspicious for metastatic disease is discovered. She is admitted for pain control and a fentanyl patient-controlled analgesia infusion (PCA) is started. She receives a total of 1,000 mcg over the next 6 hours and radiation therapy is planned. She then develops sudden onset nausea, vomiting, and abdominal pain. On examination, her abdomen is distended and tympanic. There are hyperactive bowel sounds. She reports no bowel movement or flatus in the past few hours.

What is the most likely diagnosis?
A. Opioid-induced gastrointestinal hyperalgesia
B. Ileus
C. Malignant bowel obstruction
D. Opioid-induced constipation

3. You are seeing a 28-year-old male in outpatient oncology clinic. He was diagnosed with good risk advanced testicular germ cell tumor about 6 weeks ago. He is currently receiving bleomycin/etoposide/cisplatin (BEP) chemotherapy and is tolerating it well. On your interview today, he appears to be more withdrawn than usual. He admits to occasionally feeling down and depressed when thinking about his cancer diagnosis. He also thinks that he has become more irritable with his family and friends. He continues to work full time and finds pleasure in golfing, which has been his favorite recreational activity. He denies any thoughts of harming himself.

What is the most likely diagnosis?
A. Adjustment disorder
B. Major depressive disorder
C. Anxiety
D. Delirium

4. A 67-year-old male with past medical history of coronary artery disease (CAD) and chronic kidney disease (CKD) who was recently diagnosed with limited stage small cell lung cancer (SCLC), not yet started on chemotherapy, was brought to the ED for a 3-day history of somnolence and confusion at home. His wife also noticed that he's become progressively weaker. Vital signs are stable. Physical exam reveals a mildly distended abdomen with diffuse tenderness to deep palpation. Bloodwork reveals a serum calcium of 10 mg/dl, creatinine of 3.5 mg/dl (at baseline), and albumin of 2.5g/dl.

In addition to starting intravenous (IV) fluids, what other medications do you want to consider prescribing?
A. Pamidronate 30 mg IV
B. Denosumab 120 mg subq
C. Zoledronic acid 4 mg IV
D. Furosemide 40 mg IV

5. A 59-year-old male with a 100 pack smoking history presents to the ED with acute onset of shortness of breath. He states that this occurred suddenly 1 week ago and has become progressively worse. He does have a nonproductive cough, worse than his baseline. He states that he has tried over the counter (OTC) remedies without any improvement in his symptoms. He notices that laying down makes his coughing worse. On physical exam, he is noted to be markedly dyspneic with respiratory rate in the 30s. He is also tachycardic. There is facial fullness. You order a CT of the chest with intravenous (IV) contrast which preliminarily reveals a large mass in the

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right upper lobe but no evidence of any obvious thromboembolism; this has not been verified by radiology. As the patient is returning from CT, you notice that he has developed stridor and developing worsening mentation.

What is the next best step in management?

A. Start empiric IV heparin therapy as you are still highly suspicious for pulmonary embolism (PE)
B. Page radiation oncology for an emergent evaluation
C. Page thoracic surgery to obtain a stat tissue biopsy of the mass
D. Start glucocorticoid therapy

6. A 70-year-old man with past medical history significant for coronary artery disease status post pacemaker placement and degenerative joint disease status post left hip replacement was recently diagnosed with Stage IV non–small cell lung cancer (NSCLC) to the bones. He is scheduled to undergo palliative chemotherapy with carboplatin and pemetrexed and presents to your office for a prechemotherapy visit. On your interview, he states that he has been experiencing reduced appetite, weight loss, and trouble sleeping. His mood is depressed and he has been having crying spells and excessive feelings of guilt over his smoking history. You note a flat affect, slow speech, and poor eye contact on exam.

Which of the medications is most appropriate to start?

A. Bupropion
B. Escitalopram
C. Amitriptyline
D. Mirtazapine

ANSWERS

1. **B. Ondansetron.** Constipation is a very common side effect of ondansetron and other 5-HT3-receptor antagonists, caused by blockade of gut serotonin receptors. Dexamethasone and metoclopramide do not cause constipation; metoclopramide may be helpful to stimulate bowel motility. Aprepitant may exacerbate constipation in some patients, but is not likely to be the primary culprit.

2. **B. Ileus**. This patient has developed an ileus from receiving high-potency, high-dose parenteral opioids to control her severe back pain due to a pathologic fracture. While an uncommon complication of opioid therapy, it is important to recognize so opioids can be rotated and/or dose-reduced. It is managed similarly to other causes of ileus. Opioid-induced gastrointestinal hyperalgesia occurs in the setting of chronic opioid use and is characterized by worsening, generalized abdominal pain with increased doses of opioids. A malignant bowel obstruction may present with sudden onset of symptoms with the exam of the patient, but this would be an unusual manifestation metastatic breast cancer, and is less likely given the signs/symptoms presenting in relation to receiving high-dose opioids. Opioid-induced constipation would present with hypoactive or normal bowel sounds and flatus should still be present, if reduced from normal.

3. **A. Adjustment disorder.** While the diagnosis of adjustment disorder and depression can be difficult to differentiate, the lack of neurovegetative signs and suicidal ideation suggest the diagnosis of adjustment disorder in this patient. He will need continued assessment as by definition, the duration of adjustment disorder is less than 6 months.

4. **B. Denosumab 120 mg subq.** The patient has hypercalcemia (remember to correct for albumin; can also check an ionized calcium to confirm) likely from paraneoplastic secretion of parathyroid hormone-related peptide (PTHrP), which is commonly seen in SCLC. His poor renal function precludes him from receiving bisphosphonates and loop diuretics and therefore he should receive denosumab.

5. **B. Page radiation oncology for an emergent evaluation**. The patient is presenting with signs and symptoms concerning for superior vena cava (SVC) syndrome. While it is preferable to obtain a histologic diagnosis prior to therapy, the patient is developing stridor and is at high risk for respiratory failure and death. This is the only situation where emergent radiation therapy (RT) and stent placement should be done prior to confirming a histologic diagnosis.

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6. **D. Mirtazapine.** The patient meets criteria for major depressive disorder. Mirtazapine is one of the most effective antidepressants, is sedating, and has an appetite stimulant effect for many patients. These side effects may be beneficial for this patient with poor appetite and insomnia. Bupropion is a modestly effective antidepressant but can be stimulating and suppress appetite, which would not be ideal for this patient. Escitalopram is an effective antidepressant, but given his prominent insomnia and reduced appetite it is less preferred than mirtazapine. Amitriptyline is an effective tricyclic antidepressant and is sedating, but its prominent anticholinergic effects are not well-tolerated by older patients. Its use should be reserved for refractory cases. As it is effective for certain pain syndromes, it may be considered for patients with depression and chronic pain.

BONE MARROW TRANSPLANTATION

XIV

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Stem Cell Transplantation and Cellular Therapy

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Jason C. Chen and Mary Mansour Riwes

EPIDEMIOLOGY

1. How many allogeneic stem cell transplants are performed in the United States each year?

- More than 9,000 per year

2. How many autologous stem cell transplants are performed in the United States each year?

- More than 13,000 per year

CLASSIFICATION

1. How can stem cell transplants be classified?

- Modality
  - Autologous: patient's own stem cells transplanted
  - Allogeneic: stem cells from a human leukocyte antigen (HLA) matched donor transplanted
  - Syngeneic: stem cells from an HLA identical donor transplanted
- Donor source: for allogeneic transplants
  - Matched related: a related donor who is at least an 8/8 HLA match with the recipient (HLA-A, HLA-B, HLA-C, and HLA-DRB1 identical)
  - Matched unrelated: an unrelated donor who is at least an 8/8 HLA match with the recipient
  - Mismatched: a donor who is less than an 8/8 HLA match with the recipient
  - Haploidentical: a related donor who is mismatched at 3/6 HLA loci (HLA-A, HLA-B, and HLA-DR)
  - Umbilical cord blood: requires at least 4/6 HLA match at HLA-A, HLA-B, and HLA-DRB1
- Stem cell source
  - Peripheral blood stem cell (PBSC): stem cells are collected from donor with a peripheral blood pheresis procedure. Uses either chemotherapy-based or chemokine-based regimen to mobilize stem cells prior to collection.
  - Bone marrow: stem cells are collected directly from the bone marrow. Typically does not require any preprocedure mobilization medications.
  - Umbilical cord blood: stem cells are collected from umbilical cord and placenta after a baby is born. Relative immaturity of the immune system of donors allows for level of HLA mismatch that would otherwise be prohibitive in other sources. Adult recipients typically require two separate products due to relatively low stem cell dose per product.

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- Preparative regimen
  - Myeloablative: conditioning regimen that is expected to destroy hematopoietic stem cells with resulting long-lasting, usually irreversible, and often fatal pancytopenia unless patient is rescued with stem cell transplant. For example, total body irradiation (TBI) in doses ≥5 Gy in a single dose or busulfan >8 mg/kg.
  - Nonmyeloablative: conditioning regimen that causes less cytopenias but significant lymphopenia and would not require stem cell rescue. For example, fludarabine and cyclophosphamide, TBI ≤2 Gy.
  - Reduced intensity: intermediate between myeloablative and nonmyeloablative. For example, busulfan ≤8 mg/kg or melphalan at ≤140 mg/m^2.

2. Why would you not prefer a syngeneic transplant for a malignant condition?

- Patients with an identical twin donor, while they are not at risk for developing graft-versus-host disease (GVHD), have a higher risk of relapse of any underlying malignant condition. This is due to lack of a graft-versus-tumor reaction.

3. What donor source is preferred for allogeneic stem cell transplants?

- When available, a matched related transplant is preferred due to both clinical (less GVHD) and logistical (speed and ease of finding donor) factors.
- If a matched related donor is not available, it remains unknown which of several alternative donors is best—matched unrelated, haploidentical, or umbilical cord. Factors that are important in making a selection include the urgency of transplant and time needed to obtain a donor, the underlying disease process, recipient comorbidities, and the familiarity of the transplant center with the transplant modality.

4. What is the likelihood of finding a matched unrelated donor in the donor registry?

- The likelihood of finding an unrelated donor through the National Marrow Donor Program varies depending on race and ethnicity.
  - For white patients, the likelihood of a match is around 77%.
  - For American Indian and Alaskan Native patients, the likelihood is around 57%.
  - For Asian or Pacific Islanders, the likelihood is around 41%.
  - For Hispanic or Latino patients, the likelihood is around 46%.
  - For African American patients, the likelihood is around 23%.

5. When would you favor bone marrow harvest over peripheral blood stem cell (PBSC) collection in the setting of an allogeneic stem cell transplant?

- Studies have generally confirmed slightly faster engraftment with infusion of PBSCs versus bone marrow. However, most studies have documented less chronic GVHD with bone marrow transplant over PBSC.
- Therefore, marrow is preferred in situations where the concern for chronic GVHD is higher (i.e., matched unrelated transplants) or in nonmalignant conditions where there is no potential benefit of a graft-versus-tumor phenomenon.

6. What are the risks to a stem cell donor?

- The risks vary slightly depending on the source of the stem cells.
- For marrow donors, collection is typically done under regional or general anesthesia, with those inherent risks. Following the collection, some degree of

back or hip pain, bruising at the incision sites, and fatigue are common. The donor's marrow is naturally repleted within 4 to 6 weeks.

- For peripheral blood stem cell donors, filgrastim is administered to the donor to mobilize stem cells. These shots are administered for several days prior to the pheresis procedure where the stem cells are collected. Side effects from filgrastim include headaches, muscle, and bone pain. Serious side effects occur in <1% of donors but can include splenic rupture. The pheresis procedure may require placement of a central line, with those inherent risks, as well as bruising at the needle site, lowering of the platelet count, and mild muscle cramping or tingling around the mouth (due to calcium depletion from the citrate used during pheresis).

ELIGIBILITY

1. What testing must be performed prior to transplant (autologous and allogeneic) in order to consider a patient eligible?

- Many centers utilize the hematopoietic cell transplantation (HCT) Comorbidity Index (HCT-CI, www.hctci.org/) score to assess transplant eligibility. Factors include cardiac disease, rheumatologic disease, diabetes, stroke, psychiatric issues, hepatic, renal, or pulmonary impairment.
- While specific guidelines vary among institutions, there are some basic tests that must be done for all patients due to the known and expected toxicities of the transplant process. Testing typically includes
  - Pulmonary function testing
  - EKG and transthoracic echocardiography (TTE) or multigated acquisition scan (MUGA)
  - Liver function tests
  - Serum creatinine
  - Infectious disease screening
  - Assessment of performance status

INDICATIONS

1. What are the common indications for autologous stem cell transplant?

- Multiple myeloma or amyloidosis: considered as part of initial therapy for most transplant-eligible patients with myeloma or amyloidosis.
- Non-Hodgkin lymphomas: considered as the standard of care for relapsed diffuse large B-cell lymphoma (DLBCL), considered as up-front therapy for select groups of other high-grade lymphomas such as mantle cell lymphoma, and for select patients with refractory low-grade lymphomas (see Chapter 7, High-Grade Non-Hodgkin Lymphoma).
- Acute promyelocytic leukemia: considered for either relapsed disease or molecular persistence.
- Germ-cell tumors: considered for refractory or relapsed cases.

2. What are the common indications for allogeneic stem cell transplant?

- Acute myeloid leukemia: considered the standard of care for intermediate- or high-risk patients in first complete remission (CR1) as well as for all patients with relapsed disease in subsequent complete remission.
- Acute lymphoid leukemia, Philadelphia chromosome positive: recommended in CR1.

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- Acute lymphoid leukemia, Philadelphia chromosome negative: recommended in CR1 if other high-risk features.
- Chronic myeloid leukemia: recommended for patients presenting in accelerated or blast phase or in patients initially diagnosed as chronic phase but for whom tyrosine kinase inhibitors are failing.
- Myelodysplastic syndrome: considered for certain transplant-eligible patients depending on the status of their disease.
- Myelofibrosis: considered for certain transplant-eligible patients depending on the status of their disease.
- Chronic lymphocytic leukemia: considered for transplant-eligible patients with poor risk disease.
- Other nonmalignant conditions: aplastic anemia, sickle cell disease, and so on.

TOXICITY OF CONDITIONING REGIMENS

1. What are common toxicities of all myeloablative preparative regimens?

- Mucositis, nausea, vomiting, alopecia, diarrhea, rash, peripheral neuropathies

2. What are some busulfan-specific toxicities?

- Busulfan can cause interstitial lung disease, hepatic sinusoidal obstructive syndrome, and lowered seizure threshold. Prophylactic anticonvulsant therapy should be administered. Some institutions recommend monitoring busulfan pharmacokinetics to help reduce risk of these complications.

3. What are some TBI specific complications?

- Asymptomatic alteration in pulmonary function, cataracts, sicca syndrome, hypothyroidism, and thyroiditis.

4. What is hepatic sinusoidal obstruction syndrome (SOS)/hepatic veno-occlusive disease (VOD)?

- Hepatic SOS/hepatic VOD describes a nonthrombotic obliteration of the small intrahepatic veins. It is thought to be secondary to the conditioning regimen of stem cell transplant, though VOD has been reported after exposure to a wide variety of agents. Clinically, it is recognized by jaundice, tender hepatomegaly, weight gain, ascites, and platelet refractoriness.

COMPLICATIONS OF TRANSPLANT

1. What is GVHD? How common is it?

- GVHD is an immunological phenomenon where donor lymphocytes respond to polymorphic HLAs present in host tissues, and mount an attack against these tissues. The resulting clinical syndrome is best described as an inflammatory response predominantly involving the skin, intestine, and liver. The interactions between donor lymphocytes and polymorphic HLAs on host tissue are amplified by the significant tissue injury that occurs during the conditioning regimen.
- The risk of GVHD depends on many factors, including degree of HLA compatibility, stem cell source, and conditioning regimen. Acute GVHD can be estimated to occur in around 30% of patients undergoing an HLA-matched related stem cell transplant and 50% to 70% of patients undergoing an unrelated donor stem cell transplant. Chronic GVHD occurs in around 40% of all patients who undergo an allogeneic stem cell transplant and the majority of patients who develop acute GVHD.

2. What are the organs affected in acute GVHD?

- Acute GVHD classically affects the skin, gastrointestinal (GI) tract, and the liver.
  - Skin involvement is typically a maculopapular rash that may be painful or pruritic upon first development. In severe cases, rash may cover the whole body and be associated with bullae, vesicles, and desquamation.
  - Gut involvement can be either upper or lower GI involvement with symptoms most typically being diarrhea, but can also include abdominal pain, nausea, vomiting, or ileus.
  - Liver involvement is typically recognized by hyperbilirubinemia.

3. How is acute GVHD quantified?

Stage	Skin	Liver (Bilirubin)	Gut (Stool Output/ Day)
0	No GVHD rash	<2 mg/dL	<500 mL/day
1	Maculopapular rash <25% BSA	2–3 mg/dL	500–999 mL/day *or* Persistent nausea, vomiting, anorexia with a positive upper GI biopsy
2	Maculopapular rash 25%–50%	3.1–6 mg/dL	1,000–1,500 mL/day
3	Maculopapular rash >50%	6.1–15 mg/dL	>1,500 mL/day
4	Generalized erythroderma (>50% BSA) *plus* bullous formation and desquamation >5% BSA	>15 mg/dL	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume)

Overall clinical grade:

- Grade 0: no stage 1 to 4 of any organ involvement
- Grade I: stage 1 to 2 rash and no liver or gut involvement
- Grade II: stage 1 to 3 rash, or stage 1 liver or stage 1 gut involvement
- Grade III: stage 2 to 3 skin, liver, or gut involvement
- Grade IV: stage 1 to 4 skin, stage 2 to 4 liver involvement

4. What is graft failure? How common is it?

- Graft failure is the term used when donor stem cells are not engrafted within the host marrow and are failing to produce the necessary hematopoietic elements. This may be demonstrated by either failure of the donor stem cells to ever engraft (primary graft rejection), or loss of donor cells after initial engraftment (secondary graft rejection).
- The causes of graft failure may be rejection, an immunologic phenomenon, or other causes including infection and drugs.
- The risk of graft rejection is related to degree of HLA incompatibility, stem cell source, and intensity of conditioning—with higher risk of rejection with increased HLA incompatibility, cord blood, and reduced intensity conditioning. Graft failure remains relatively rare, occurring in <5% of transplants.

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5. What organs are typically affected in chronic GVHD?

- A multitude of organs can be affected by chronic GVHD. Typically, the following organs are considered:
  - Skin: variety of skin changes can be seen including atrophic changes, lichen sclerosis-like changes, sclerotic changes, hypo- or hyperpigmentation. Changes can include hair and nails
  - Eyes/mouth: lichenoid changes of oropharynx, leukoplakia, xerostomia, dry eye, photophobia
  - Liver: elevated bilirubin, alkaline phosphatase, or aminotransferases
    - Lungs: may present with dyspnea or wheezing. Pulmonary function tests (PFTs) demonstrate obstructive or restrictive changes. Lung biopsy can confirm bronchiolitis obliterans
  - Musculoskeletal: fasciitis, joint stiffness, or contractures

6. How is chronic GVHD graded?

- Mild disease involves two or fewer organs or sites without significant functional impairment.
- Moderate disease involves three or more organs or sites without significant functional impairment, or at least one site with significant impairment.
- Severe disease requires major disability related to chronic GVHD.

7. What measures are used to prevent GVHD?

- Nonpharmacologic preventive measures include use of properly matched donors, T-cell depletion, and minimizing pretransplant organ damage.
- Medications used to prevent GVHD vary by transplant center, preparative regimen, and donor source but common agents include cyclophosphamide, methotrexate, tacrolimus, mycophenolate, cyclosporine, and sirolimus.

8. What medications are used to treat acute GVHD?

- First-line therapy for acute GVHD depends on the initial GVHD grade.
  - For grade 1 (skin stage 1), topical steroids are recommended.
  - For grades II to IV, topical therapy in addition to high-dose intravenous (IV) steroids (methylprednisolone 2 mg/kg/day) is recommended.
- If GVHD is progressing after 3 days of therapy, or if there is no response to treatment after 5 days of therapy, second-line therapies should be considered. There is no standard second-line therapy and decisions should be tailored to the patient and clinical scenario. Options include extracorporeal photopheresis (ECP), ruxolitinib, infliximab, etanercept, mycophenolate, antithymocyte globulin, sirolimus, alemtuzumab, and octreotide.

9. What medications are used to treat chronic GVHD?

- First-line therapy for chronic GVHD typically consists of prednisone at a dose of 1 mg/kg/day for moderate or severe disease.
- Second-line treatment should be considered if there is progression of chronic GVHD despite optimal first-line treatment for 2 weeks or if there is no improvement after 4 to 8 weeks of sustained therapy or if there is an inability to taper prednisone. Second-line therapies include ECP, ruxolitinib, ibrutinib, tacrolimus, cyclosporine, mycophenolate, sirolimus, and rituximab.

10. What are the infectious risks associated with stem cell transplant?

- Infectious risks are distinct depending on the phase of transplant.
- *In the preengraftment period (approximately day 0 through day 30 posttransplant):* the major risk is related to neutropenia, altered barriers (mucositis and diarrhea), and vascular devices. Thus, bacterial organisms including skin, oral, and GI flora are the most common sources of infection. Invasive fungal infections and *herpes simplex virus* (HSV), typically reactivation, can be seen in this time period as well.
  - *In the postengraftment period (approximately day 30 through day 100 posttransplant):* severe neutropenia is resolved and barrier defenses are healing. However, patients remain immunosuppressed due to impaired cell-mediated immunity, humoral immunity, and decreased phagocyte function. If acute GVHD has occurred, this can impair immune function and damage immune barriers, in addition to the immunosuppressive effects of the GVHD-directed therapies, thereby multiplying the immunocompromised state of patients. Overall, bacterial infections become less common during this period. Instead, viral infections are the most common infections encountered in this period of time. Specific pathogens of note include cytomegalovirus (CMV), adenovirus, community-acquired respiratory viruses, enterovirus, human herpesvirus-6 (HHV-6), and BK virus. Invasive fungal infections can continue to occur, especially in those patients with GVHD. In addition, parasitic infections with *Pneumocystis jirovecii* can occur in this time period, necessitating prophylaxis to prevent this infection.
  - *In the late posttransplantation period (>100 days posttransplant):* cell-mediated immunity and humoral immunity recover. Immunosuppressive therapy is slowly withdrawn. Without GVHD, infection is unusual in this period. However, with chronic GVHD, there remain defects in both cellular and humoral immunity, as well as deficits in the barrier function of the skin, oropharynx, and GI tract. Infections during this period tend to be localized to the skin and upper and lower respiratory tracts. Pathogens tend to be viral, especially varicella zoster virus (VZV), followed by bacterial. Patients with chronic GVHD tend to have functional asplenia and therefore have increased susceptibility to encapsulated bacteria.

OTHER CELLULAR THERAPY (CAR-T)

1. What is CAR-T therapy?

- CAR-T stands for chimeric antigen receptor T-cell therapy. This is a novel approach using the patient's own (autologous) stem cells and engineering the surface T-cell receptors to recognize specific cell surface markers. This has demonstrated efficacy and has been approved for use in certain refractory hematologic malignancies.

2. How is a CAR-T product created and administered?

- Patients undergo pheresis procedure similar to autologous stem cell collection for stem cell transplant.
- The cells are frozen and shipped to a manufacturing facility where the T-cell population is enriched, then transduced with a viral vector containing the CAR transgene.

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- The newly engineered CAR-T cells are purified and expanded to target dose, then frozen for shipment back to patient's hospital.
- The frozen CAR-T product is thawed and transfused peripherally into the patient, after the patient has received a preparative lymphodepleting conditioning regimen (e.g., fludarabine, cyclophosphamide).

3. What are the different Food and Drug Administration (FDA)-approved CAR-T products and their indications?

- All currently approved CAR-T products target CD19 and are indicated for the treatment of relapsed/refractory B-cell lymphomas in adults.
- Tisagenlecleucel (Kymriah®)
  - **i.** Approved for adults with relapsed or refractory DLBCL.
  - **ii.** Also approved for young adults up to 25 years old for relapsed or refractory acute lymphoblastic leukemia.
- Axicabtagene ciloleucel (Yescarta®)
  - **i.** Approved for adults with relapsed or refractory B-cell lymphoma after two or more lines of prior therapy. This includes DLBCL and other high-grade B-cell lymphomas.
- Brexucabtagene autoleucel (Tecartus®)
  - **i.** Approved for adults with relapsed or refractory mantle cell lymphoma.

4. What is the efficacy of the various CAR-T products for B-cell lymphomas?

- Tisagenlecleucel—JULIET trial demonstrated CR rate of 40%, 12-month overall survival rate of 40%.
- Axicabtagene ciloleucel—ZUMA-1 trial demonstrated ORR of 82%, CR rate of 54%, 12-month overall survival rate of 59%.
- Brexucabtagene autoleucel—ZUMA-2 trial demonstrated ORR of 93%, CR rate of 67%, 12-month overall survival rate of 83%.

5. What are the adverse effects related to CAR-T therapy?

- Neutropenia, anemia, thrombocytopenia—related to preparative chemotherapy and depletion of B-cells from anti-CD19 targeting. This can happen both around time of infusion, after 21 days and can sometimes be prolonged.
- Increased risk of infections related to cytopenia and hypogammaglobulinemia requiring antimicrobial prophylaxis and IV immune globulin infusions.
- Cytokine release syndrome (CRS)—related to immune activation from CAR-T product. Patients can have systemic inflammatory symptoms ranging from mild (fevers, malaise, rash, arthralgias, diarrhea) to severe (cerebral edema, seizures, aphasia, respiratory and cardiac failure).
  - **i.** Early recognition is important with frequent clinical exams, vitals monitoring, and lab tests.
  - **ii.** Treatment includes supportive care with IV fluids, antipyretics, and antihistamines for mild cases. For severe cases, ICU admission often needed with administration of high-dose steroids +/− tocilizumab (anti-IL6 monoclonal antibody).

- Neurologic toxicity—also called immune effector cell-associated neurotoxicity syndrome (ICANS). Mechanisms are similar to CRS though this is considered a separate entity. Patients can present with delirium, stroke, seizures, intracranial hemorrhage, or other focal neurologic deficits.
  - **i.** Early recognition is important with frequent motor and cognition testing.
  - **ii.** Prompt use of high-dose steroids for moderate to severe ICANS.
  - **iii.** Tocilizumab is not indicated unless concurrent CRS, since it does not cross the blood–brain barrier.

QUESTIONS

1. A 52-year-old female was recently diagnosed with acute myeloid leukemia (AML), noted to have del(5q) on cytogenetic testing. She underwent induction treatment with fludarabine, cytarabine, and growth factor (FLAG) with postinduction marrow after count recovery showing no evidence of leukemia. She now presents to the transplant clinic to discuss proceeding with allogeneic stem cell transplant. She lives independently, walks 3 miles daily, and has no other medical comorbidities. Her blood type is O negative.

Which of the following would be an optimal donor?

A. Her daughter, who is a 5/10 human leukocyte antigen (HLA) match
B. Umbilical cord transplant
C. Her HLA identical 50-year-old brother who is otherwise healthy and is blood type O+
D. An HLA identical matched unrelated donor who is blood type O−

2. A 57-year-old woman is 145 days from a matched unrelated stem cell transplant for high-risk myelodysplastic syndrome. Her early transplant course was complicated by a severe viral pneumonia and gastrointestinal (GI) acute graft-versus-host disease (GVHD), which was treated with steroids with good improvement. She presents to clinic today complaining of progressive dry eyes and dry mouth as well as muscle and joint tightness. Her exam is notable for a mild weight loss of 2 kg, irritation of bilateral sclera, and an oropharynx that appears dry with lichenoid changes. She has limited range of motion of both her arms but no muscle tenderness on exam. She remains on tacrolimus for GVHD prophylaxis but this has been tapered. In addition, she continues to take acyclovir, fluconazole, and trimethoprim/sulfamethoxazole for infectious disease prophylaxis.

What is the most likely diagnosis?

A. Side effects from tacrolimus
B. Chronic GVHD
C. Infection with adenovirus
D. Sjögren syndrome

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3. A 61-year-old woman underwent a matched related stem cell transplant for therapy-related acute myeloid leukemia (AML) in first complete remission. She was started on tacrolimus and mycophenolate mofetil for graft-versus-host disease (GVHD) prophylaxis with therapeutic levels. She remains hospitalized posttransplant while her counts recover with an otherwise uneventful transplant course. However, over the past 4 days she has had worsening a painful red rash over her body, now affecting her entire chest, abdomen, and back. Skin biopsies confirm a diagnosis of acute GVHD.

What is the most important first step in management?

A. Increase tacrolimus dose
B. Start mycophenolate mofetil
C. Start photopheresis
D. Start high-dose steroids

4. A 51-year-old man with Philadelphia chromosome positive acute lymphoblastic leukemia (ALL) underwent a myeloablative transplantation 21 days ago. He received a conditioning regimen containing busulfan and fludarabine, followed by allogeneic stem cell infusion and initiation of tacrolimus and methotrexate for graft-versus-host disease (GVHD) prophylaxis. He now has abdominal pain, swelling, and unexpected weight gain. Laboratory testing is notable for a rising total bilirubin now at 8.2 mg/dL and mildly elevated transaminases. Liver biopsy notable for fibrous vascular occlusion, collagen deposition, and congestion by erythrocytes.

Which is the most likely explanation for his current condition?

A. Hepatic veno-occlusive disease
B. Engraftment syndrome
C. Methotrexate toxicity
D. Acute viral hepatitis

5. A 27-year-old healthy man who is volunteering as a peripheral stem cell donor for his sister develops sudden onset of severe left upper quadrant pain on his third day of taking high-dose filgrastim for mobilization. He denies any fevers, nausea, or vomiting; no hematuria or dysuria; no dyspnea or pleuritic pain.

What is the most likely cause of his abdominal pain?

A. Nephrolithiasis from a uric acid stone induced by mobilization
B. Rib pain from marrow expansion
C. Splenic rupture
D. Pulmonary embolism

6. A 60-year-old woman with Philadelphia chromosome negative acute lymphoblastic leukemia (ALL) underwent a matched unrelated transplant in CR2. Posttransplant course has been complicated by mild skin graft-versus-host disease (GVHD) and an admission for *Clostridium difficile*-associated diarrhea but has otherwise been unremarkable. At 3 months after transplant, she develops urinary urgency, suprapubic pain, and gross hematuria. Her laboratory work demonstrates only mild anemia to 11.1 g/dL and no abnormalities in kidney or liver function.

What is the most appropriate testing for further evaluation of the patient's symptoms?

A. CT of the abdomen and pelvis
B. Urine polymerase chain reaction (PCR) for viral DNA
C. Urine cytology and cystoscopy
D. Coombs test and measurement of haptoglobin

7. A 40-year-old man with diffuse large B-cell lymphoma (DLBCL) presents for further management after his refractory disease after he noted worsening night sweats, cervical adenopathy, and early satiety related to worsening splenomegaly. His disease has progressed through high-dose chemotherapy with autologous stem cell transplant, and three additional prior lines of therapy including brentuximab and polatuzumab. His most recent regimen was started 3 months ago. There are no clinical trials available to him at his current treatment center, though chimeric antigen receptor T-cell (CAR-T) therapy and allogeneic stem cell transplant are available. Other than his lymphoma, he has only mild fatigue and neuropathy without signs of organ failure or significantly impaired function. He wants to pursue aggressive therapy if feasible and safe with reasonable efficacy.

What is his next best option for treatment?

A. Referral for tisagenlecleucel therapy
B. Consideration for second autologous stem cell transplant
C. Trial of prior combination chemotherapy regimen
D. Referral for allogeneic stem cell transplant

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ANSWERS

1. **C. Her HLA identical 50-year-old brother who is otherwise healthy and is blood type O+.** While ABO compatibility is important to consider in deciding an optimal donor, this is only a minor ABO mismatch and related donor transplants remain preferred to unrelated donor transplants given lower rates of graft-versus-host disease (GVHD) with related transplants. There is no role for an umbilical cord transplant in a setting with available related donors. Use of an alternative donor such as a haploidentical child is not necessary if fully-matched related donor source available.

2. **B. Chronic GVHD.** Her symptoms of dry eyes, dry mouth, and joint tightness are classic for symptoms of chronic GVHD, as is her exam demonstrating irritated sclera and lichenoid changes in her oropharynx. This is an appropriate time frame for chronic GVHD to begin and her history of prior acute GVHD as well as her unrelated donor transplant are both risk factors for development of chronic GVHD. While the symptoms of dry eyes and dry mouth in a patient who had not previously undergone allogeneic stem cell transplant may be suggestive of Sjögren syndrome, GVHD is a better explanation in this case. Viral etiologies can certainly have a protean presentation of symptoms, but viral ulcerations in the oral cavity tend to be painful and not lichenoid. Tacrolimus does not cause dry eyes, dry mouth, or arthralgias. More commonly, it results in renal wasting of magnesium and rarely microangiopathic hemolytic anemia, neurologic changes, or renal dysfunction. More importantly, the patient's tacrolimus is being tapered suggesting her symptoms are related to the withdrawal of this immunosuppressant (i.e., GVHD) and are not a symptom of the medication itself.

3. **D. Start high-dose steroids.** This patient has at least grade 2 skin GVHD (25%–50% involvement) requiring treatment. Optimal first line therapy is high-dose steroids, with consideration of IV over PO formulations if concern for potential gut malabsorption. It is critical to recognize and initiate therapy promptly. There is no role for increasing tacrolimus when levels are already therapeutic as there is significant risk for toxicity with limited increasing therapeutic effect. Photopheresis and mycophenolate can both be effective therapies for GVHD but are typically reserved for patients who are not responding to steroids.

4. **A. Hepatic veno-occlusive disease (VOD).** This is also called hepatic sinusoidal obstruction syndrome (SOS). The patient's signs and symptoms, along with pathological findings on biopsy, are most suggestive of hepatic SOS/VOD as demonstrated by the rapid weight gain often associated with ascites and/or peripheral edema, tender hepatomegaly, and rapid rise in liver function tests (LFTs). The pathophysiology of this condition includes occlusion of the terminal hepatic venules and sinusoids, likely due to injury of the endothelium of hepatic venules. Most commonly, this condition is seen from 3 to 30 days after transplant. Severe cases are almost universally fatal, but most patients with mild to moderate disease will recover

with only supportive care. Engraftment syndrome more typically presents with fevers and a cytokine release syndrome. It would be unlikely to result in such significant LFT abnormalities. While methotrexate can cause LFT abnormalities, typically this is not associated with tender hepatomegaly. Viral hepatitis is uncommon in this population since patients are routinely screened for viral infections and hepatitis risk prior to transplant. In addition, acute viral hepatitis would usually present with markedly elevated transaminases on labs and prominent inflammatory cell infiltrates on biopsy pathology, which this patient does not have.

5. **C. Splenic rupture.** Splenic rupture is a potentially life-threatening complication of stem cell mobilization with the use of granulocyte colony-stimulating factors (G-CSFs), such as filgrastim. Luckily, it is an exceedingly rare complication but one that both providers and donors must be aware of. The patient's sudden onset of severe pain without any other significant symptoms is most suggestive of this diagnosis. Filgrastim is not known to cause uric acid stones and the lack of dysuria or hematuria argues against nephrolithiasis. While filgrastim can cause bony pain, this is more typically dull diffuse aches and not severe, sudden-onset focal pain. G-CSF is not known to induce pulmonary embolisms and a lack of pleuritic pain or dyspnea argues against this diagnosis.

6. **B. Urine PCR for viral DNA.** BK virus is a polyoma virus that can cause dysuria, hematuria, and suprapubic pain in posttransplant patients. It is best tested for with use of urine PCR test. With normal renal function and electrolytes, there is no indication for abdominal imaging at this time. While patients with previous chemotherapy exposure, such as this patient, may be at risk for a genitourinary malignancy, her current symptomatology is more consistent with BK infection and one would not consider screening for malignancy until infection is screened for and treated. While hemolytic anemia can result in dark-colored urine with mild dysuria, it would be unlikely to cause this degree of suprapubic pain, especially in light of a relatively stable hemoglobin.

7. **A. Referral for tisagenlecleucel therapy**. Tisagenlecleucel is an approved CAR-T therapy for relapsed/refractory DLBCL. While there are significant toxicities associated with CAR-T therapy (organ failure, CRS, neurotoxicity), the patient has good performance status without major organ dysfunction. He progressed relatively quickly after his prior chemotherapy regimens including novel agents, so consideration of additional chemotherapy options and repeat autologous stem cell transplant is not reasonable given the patient's overall goals. Allogeneic transplant would be an option if CAR-T therapy not available, though an allotransplant has associated long-term transplant-related toxicities including graft-versus-host disease and infections.

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BIOSTATISTICS

XV

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40 Biostatistics

Christopher T. Su and Emily Bellile

TABLE 40.1 ■ Basic Concepts and Definitions

Term	Definition
p value	Assumes a null hypothesis (often that two measurements are equal) and describes probability that the observed difference is due to chance or random variation alone. *p* value <.05 (5%) is usually sufficient to reject the null hypothesis (i.e., difference between two datasets are NOT due to chance alone).
Prevalence	Number of total cases in a population at a given point in time.
Incidence	Number of new cases that occur over a specific period of time.
Incidence proportion	Number of new cases (during a period of time) divided by total at risk (at the beginning of this period). Also known as cumulative incidence.
Relative risk/Risk ratio	Probability (incidence proportion) of an event in an exposed group (e.g., treatment) divided by probability (incidence proportion) of the same event in those not exposed. Used in randomized controlled studies and cohort studies.
Odds ratio	Odds (*probability*/[1 − *probability*]) of an event occurring in one group divided by the odds of the same event occurring in a different group. Summary measure in logistic regressions to measure the strength of association between an outcome and predictors. Used in multivariable analysis and case-controlled studies.
Absolute risk reduction (ARR)/Risk difference	Change in incidence due to an exposure. This is the proportion of patients who are spared the adverse outcome as a result of having received the experimental rather than the control therapy. Calculated by subtracting the incidence proportion of exposed group from the incidence proportion of the control group over a period of time.
Number needed to treat	Number of patients needed to be treated to prevent one event. Inverse of the absolute risk reduction (1/ARR).

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EXAMPLE 40.1

There were 10 new cases in 100 subjects over 1-year observation period. At the end of the observation period, there were 20 total cases (some had disease before the study).

Incidence proportion of disease is 10/100 = 10% in this population over 1 year.

Prevalence of the disease at the end of the study is 20/100 = 20% at the end of the study.

EXAMPLE 40.2

Consider the following table:

	Disease	No disease	Total
Treated	5 (A)	45 (B)	50 (A + B)
Not treated	20 (C)	80 (D)	100 (C + D)
Total	25 (A + C)	125 (B + D)	150 (A + B + C + D)

Risk ratio = risk of disease in those treated/risk of disease in those not treated

$$\text{RR} = \frac{\frac{A}{A+B}}{\frac{C}{C+D}} = \frac{\frac{5}{50}}{\frac{20}{100}} = \frac{0.1}{0.2} = 0.5$$

Odds ratio = odds of disease in those treated/odds of disease in those not treated

$$\text{OR} = \frac{\frac{0.1}{1-.1}}{\frac{0.2}{1-0.2}} = \frac{\frac{1}{9}}{\frac{2}{8}} = \frac{4}{9} = 0.45$$

An easier way is (A × D)/(B × C) (odds ratio is also called the cross-product ratio) with the same result: (5 × 80) divided by (45 × 20) = 4/9 = 0.45.

EXAMPLE 40.3

A new preventative treatment is introduced. Prior to the treatment, 10 people in 100 developed disease over a 1-year period. Now, only 5 people in 100 developed disease over the same period.

Absolute risk reduction is calculated: 5/100 = 5% in the treated group subtracted from 10/100 = 10% in the untreated group, so ARR is 5%.

Number needed to treat is 1 divided by ARR (0.05), which is 20 people.

DIAGNOSTIC TESTS

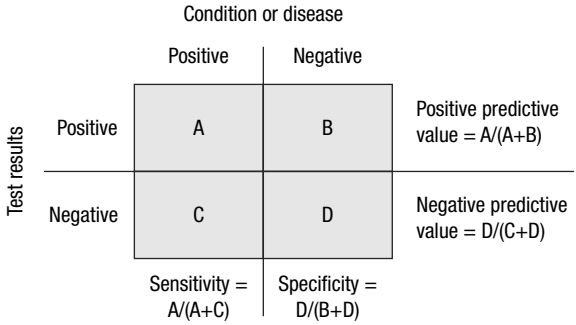

FIGURE 40.1 ■ Sensitivity, specificity, positive predictive value, and negative predictive value.

TABLE 40.2 ■ Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value

Term	Definition
Specificity	Number of positive tests divided by number with disease. How well the test detects disease in the population with disease—screening tests aim for high sensitivity (few false negatives).
Specificity	Number of negative tests divided by number without disease. How well the test confirms no disease in a population with no disease—diagnostic tests aim for high specificity (few false positives).
Positive likelihood ratio (for positive tests)	Probability of an individual with disease testing positive divided by probability of an individual with NO disease testing positive. ***sensitivity*/(1 − *specificity*)** ("how likely does an individual have the disease if they have a positive test?") The more the likelihood ratio for a positive test (LR+) is greater than 1, the more likely the disease or outcome.
Negative likelihood ratio (for negative tests)	Probability of an individual with disease testing negative divided by probability of an individual with NO disease testing negative. **(1 − *sensitivity*)/*specificity*** ("how likely does an individual have the disease if they have a negative test?") The more a likelihood ratio for a negative test <1, the less likely the disease or outcome.
Positive predictive value (PPV)	Number of positive tests in those that actually have disease divided by number of total positive tests. High PPV is desirable for a screening test—although this is dependent on the prevalence of disease in the population (i.e., a screening test can have high sensitivity and specificity, but have a low PPV if prevalence of disease is low in the studied population).
Negative predictive value (NPV)	Number of negative tests in those that do NOT have the disease divided by number of total negative tests. High NPV is also desirable for a screening test—similarly dependent on the overall population (see PPV abovementioned).

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CLINICAL STUDY DESIGN BIASES

TABLE 40.3 ■ Selected Biases in Clinical Study Design

Term	Definition
Selection bias	Study population does not reflect the target population.
Referral/volunteer (response) bias	A type of selection bias where those who volunteer for medical studies may be more aware of their health, thereby biasing the study outcomes with a sample that is healthier than the population at large. A related bias is centripetal bias where patients may seek out certain medical centers or providers due to prestige (e.g., traveling from out-of-state), artificially inflating the number of observed cases at the institution/location.
Attrition bias	A type of selection bias where losses and withdrawals in the exposure and control groups are unequal. Can be mitigated via intention-to-treat analysis in clinical trials.
Classification (measurement) bias	Improper, inadequate, or ambiguous recording of exposure or outcome variables.
Recall bias	A type of classification bias where participants of different study subgroups may remember exposures differently (e.g., patients may recall exposures better than control).
Detection bias	A type of classification bias where the observations in one (often the treatment) group are followed-up more rigorously than those in the other (control) group. Can be mitigated via study blinding.
Observer (confirmation) bias	A type of classification bias where study personnel make subjective determinations of outcome, sometimes fitting observations to an existing belief/hypothesis. Can be mitigated by study blinding and making outcomes objective rather than subjective.
Confounding bias	Variable of interest is not directly associated with the outcome, but associated with a range of other variables that are also associated with the outcome. Can be controlled for in analysis stage by statistically adjusting for confounders as long as they are properly identified.
Lead time bias	Artificial extension of perceived survival time by shifting forward the time of diagnosis due to better detection/screening while the biological onset of disease remains unchanged. The earlier we diagnose a disease, the longer a patient appears to survive.
Length time bias	Artificial inflation of the value of screening and survival time in slowly progressive disease over rapidly progressive disease, as screening is more likely to pick up slowly progressing disease (i.e., the individuals with early-onset or rapidly progressive disease might be detected from symptoms prior to screening).

(*continued*)

TABLE 40.3 ■ Selected Biases in Clinical Study Design (*continued*)

Term	Definition
Reporting bias	Statistically significant results (and studies) are more likely to be reported over those which are insignificant.
Hawthorne effect	Study subjects who are aware that they are being observed behave differently from those who are not. Can be controlled for by having a control group so all groups are under observation.

CLINICAL STUDY BASICS

TABLE 40.4 ■ Selected Terms Used in Clinical Trial Design

Term	Definition
Confidence interval	Range of values most likely to incorporate the true value in a population following repeated sampling. Dependent on number of observation and variance in dataset—confidence interval narrows with increasing observations and decreasing variance. Often reported at 95% confidence interval (true value will fall within reported range 95% of the time).
Null hypothesis	Claim that the study investigators want to disprove (e.g., there is no difference between treated and untreated patients).
Type I error (alpha)	Probability of rejecting the null hypothesis when it shouldn't be rejected (false positive). This related to the *p* value—if *p* value < alpha, we reject the null hypothesis. If *p* value > alpha, we fail to reject the null hypothesis.
Type II error (beta)	Probability of failing to reject the null hypothesis when it should be rejected (false negative). Power of study is related to type II error (beta).
Power	Probability of rejecting the null hypothesis when it should be rejected (true positive). Defined as 1-beta, related to sample size, variance, defined significance level (alpha), and effect size.
Cohort study	Type of observational study that compares two groups with different exposures and following for outcome. Can be prospective or retrospective. Helpful to determine how common an outcome is, and what exposures are associated with the outcome of interest. Measure of association between exposure and outcome can be relative risk or odds ratio.
Case-control study	Type of observational study that compares two groups with different outcomes and examines prior exposures. Retrospective. Helpful to investigate exposures that lead to an outcome. Measure of association between exposure and outcome is odds ratio.
Randomized control trial (RTC)	"Gold standard" for clinical investigation—randomly allocates subjects to control and treatment groups and follows for response. Randomization helps control for confounders.

(*continued*)

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TABLE 40.4 ■ Selected Terms Used in Clinical Trial Design (*continued*)

Term	Definition
Intention-to-treat analysis	Analyze study groups in an RTC according to randomization, rather than adherence to treatment or the actual treatment received. This helps to reduce attrition bias.
Primary endpoint	Goal of the study—should ideally be clinically relevant, sensitive to intervention, practical and affordable to measure, ideally unbiased (e.g., objective measure like death), and interpretable within the context of study.
Composite endpoint	Combination of several measures as a single endpoint (e.g., death, stroke, and cardiac arrest as one endpoint in studying cardiovascular disease). Advantages include increasing the number of outcome events (thereby decreasing sample size needed to achieve sufficient power). Disadvantages include subjective determination of measures that form the composite endpoint and potentially unequal contribution of identified measures that form the composite endpoint.
Surrogate endpoint	Selected measure that "stands-in" for a true clinical endpoint, used usually when the true clinical endpoint takes a long time to achieve or is difficult to measure (e.g., the true clinical endpoint is rare or is the patient's death). Progression-free survival and time to progression are commonly assessed surrogate endpoints.
Phase 0	First studies in humans—very small sample sizes, focused on pharmacokinetics and pharmacodynamics. Not always done or required.
Phase I	Safety and dose finding trials—doses escalate in study groups until adverse events and desired treatment effects are seen. Often performed with patients of different cancer types.
Phase II	Disease-specific/safety trials—done in larger groups than Phase I on patients with the same type of cancer with tolerable doses found in Phase I studies. Target drugs may be combined with other existing drugs and treatment efficacy assessed.
Phase III	"Which drug works better" trials—large RTCs with treatment and control arms (often the standard-of-care drug or a placebo). Positive results for a study drug in Phase III trials usually lead to Food and Drug Administration (FDA) application for approval.
Phase IV	Postmarketing trials—conducted to collect information on marketing data (cost effectiveness), long-lasting side effects, or other special considerations (drug-to-drug side effects, safety in special populations such as pregnant women).

QUESTIONS

1. **Which of the following quantities is not used when a power calculation is performed?**
   A. The magnitude of the expected difference between groups
   B. The number of subjects or events to be included in the study
   C. Statistical alpha
   D. The cost of the study
   E. The amount of statistical variance expected in the data

2. **The Kaplan–Meier statistic requires which of the following quantities to calculate median cancer specific survival?**
   A. Length of participating individuals' time in the study
   B. Number of participating individuals' deaths occurring during the study
   C. Participating individuals' date of cancer diagnosis
   D. A + B
   E. B + C

3. A new screening test for Cancer Z had just received Food and Drug Administration (FDA) approval. Patients with Cancer Z may be symptomatic or asymptomatic at the time of diagnosis. Although it is almost always diagnosed in a widely metastatic state, Cancer Z is heterogeneous in terms of known survival after diagnosis—some patients die quickly, while others go on to receive one to two lines of therapy for metastatic disease. The screening technology relies on a circulating tumor biomarker and detects the cancer in the localized disease phase when regional treatments may be an option.

   Researchers studying the clinical course of this cancer following the introduction of this novel screening method should be aware of what biases that are introduced by this test on overall survival?
   A. Lead time bias
   B. Length time bias
   C. Both
   D. Neither

4. **Which of the following statements regarding 95% confidence intervals is correct?**
   A. The width of the confidence interval is dependent only on data variability
   B. The confidence interval does not necessarily contain the true value
   C. It is narrower than the 90% confidence interval holding other parameters equal
   D. If this experiment was repeated on 20 samples, 19 of these intervals would contain the true value

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5. You come across the results of a clinical trial in a group of 50 multiple myeloma patients. The stated goal of the study was to assess the safety and efficacy of an investigational therapeutic, drug X, on multiple myeloma, given in conjunction with two other types of accepted treatment for multiple myeloma (drug X+lenalidomide and drug X+pomalidomide).

Given this information, this is most likely which type of clinical trial?

A. Phase I
B. Phase II
C. Phase III
D. Phase IV

ANSWERS

1. **D. The cost of the study.** While the number of events and number of individuals in a study are important, the cost of the study is not required for a power calculation. In a power calculation, four of the following are held constant and the fifth is calculated for statistical alpha, statistical beta, amount of variance, magnitude of expected variance, and number of subjects/events.

2. **D. A + B.** The Kaplan–Meier method can calculate the median survival for a clinical study that enrolls participants beginning at different time points, but will only require each participant's time on the study and their event class (e.g., withdrawal from study, death).

3. **C. Both.** Lead-time and length-time biases are often discussed in the context of screening tests. Lead-time bias refers to the apparent improved overall survival of a disease following the introduction of an efficacious screening test, where the time of diagnosis is simply shifted forward while the clinical course and therapeutic options remain unchanged. Lead-time bias is inherent in every efficacious screening test. Length-time bias refers to the fact that screening tests are more likely to pick up indolent, asymptomatic cases, rather than rapidly progressing cases who develop symptoms. Thus, screening tests may artificially inflate survival via disproportional detection of indolent disease (length-time bias). In this example, because Cancer Z presents in a heterogeneous manner, the screening test is more likely to pick up the subset with a more indolent course and can then go on to receive therapy, while still missing the subset with an aggressive disease course and die soon after diagnosis. Thus, researchers should be aware of both lead-time and length-time biases in this case.

4. **B. The confidence interval does not necessarily contain the true value.** Confidence intervals are a mechanism for calculating the amount of variability around a point estimate of a parameter. The calculation is based on the quantity and variability of data used in calculation. Confidence intervals with higher degrees of confidence (such as 95% vs. 90%) must be wider to accommodate more variability. A confidence interval does not necessarily contain the true value being estimated, and when repeating the study there is no guarantee for the number of successful estimations.

5. **B. Phase II.** This describes a classic Phase II trial, where an investigational drug that had been shown to be safe-in-human during Phase I trials is subsequently tested on a specific subset of patients with the same malignancy. Phase II trials often combine investigational agents with other disease-specific Food and Drug Administration (FDA)-approved agents to assess for possible synergistic effects in combination therapy. This is not true for Phase I trials, where only the study agent is being investigated for safety. Further, this vignette does not describe a Phase III trial because there is no comparison between an investigational therapy and standard-of-care or placebo. If an investigational regimen demonstrates disease-specific efficacy in Phase II studies, then that regimen can be advanced to a Phase III trial and tested against approved therapeutic options.

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