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Chapter 154: Prostate Cancer

Daniel J. Crona; Amber B. Cipriani

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 65, Prostate Cancer.

KEY CONCEPTS

KEY CONCEPTS

1. Prostate cancer is the most frequent cancer in men in the United States. The risk of prostate cancer is higher in those with increased age, Black individuals, and those with a family history of prostate cancer.
2. Screening is not universally recommended and individuals should discuss with their provider about risks versus benefits of screening. Digital rectal examination (DRE) and prostate-specific antigen (PSA) may be incorporated into individualized screening plans.
3. The prognosis for patients with prostate cancer depends on the histologic grade, the tumor size, and the disease stage. More than 85% of patients with localized disease, but less than 1% of those with metastatic disease can be cured.
4. Androgen deprivation therapy (ADT) with a luteinizing hormone-releasing hormone (LHRH) agonist plus an antiandrogen should be used in addition to radiation therapy for patients with locally advanced prostate cancer to improve outcomes over radiation therapy alone.
5. Systemic therapy for nonmetastatic castration-naïve disease that has not been treated with ADT may include either orchiectomy, LHRH agonist with or without an antiandrogen, gonadotropin-releasing hormone (GnRH) antagonist, or observation.
6. In metastatic castration-naïve disease, the addition of the following therapies to ADT improves survival: docetaxel, abiraterone, enzalutamide, or apalutamide.
7. Prostate cancer that has progressed despite androgen deprivation is called castration-resistant prostate cancer. First-line treatment options for nonmetastatic castration-resistant prostate cancer include apalutamide, darolutamide, and enzalutamide.
8. In metastatic castration-resistant prostate cancer, first-line treatment options include docetaxel with prednisone, abiraterone with prednisone, and enzalutamide. ADT is continued in all cases.
9. Germline genetic testing is recommended in patients with high-risk prostate cancer and/or a relevant family history. Somatic tumor genetic testing is recommended in metastatic disease to identify genetic variants that can be targeted with drug therapy.
10. Pembrolizumab may be considered in men whose tumors show deficiencies in deoxyribonucleic acid (DNA) mismatch repair (dMMR), test high for microsatellite instability (MSI-H), or have a tumor mutation burden greater than or equal to 10 mutations per megabase (TMB ≥10 mut/Mb).
11. Poly (ADP ribose) polymerase (PARP) inhibitors, including olaparib and rucaparib, can be considered in men with metastatic castration-resistant prostate cancer who have specific somatic or germline alterations in genes involved in homologous recombination (HR), such as *BRCA1* and *BRCA2*.

PATIENT CARE PROCESS

Patient Care Process for Prostate Cancer

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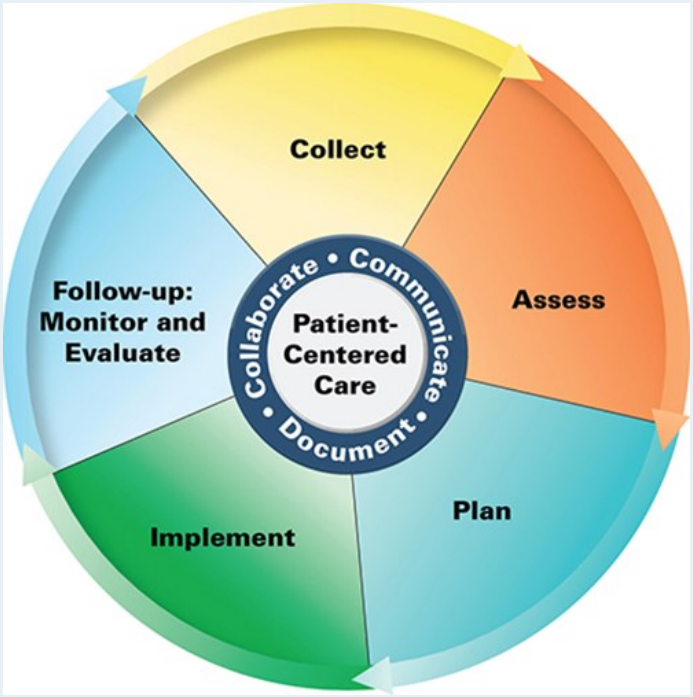

Collect

- Patient characteristics (eg, age, race/ethnicity)
- Patient history (past medical, family, social, dietary habits)
- Family cancer history (to determine eligibility for and to interpret germline genetic testing)
- Current signs and symptoms (eg, frequency of urination, dribbling, hesitancy, pain, fatigue, weight loss, shortness of breath)
- Thorough medication history (including prescription, nonprescription medications, and other substances), drug allergies, and intolerances
- Objective data (see Table 154-3)
  - BP, heart rate, height, and weight
  - Labs (PSA level, complete blood count, serum electrolytes, renal function, liver function tests)
  - Physical examination (DRE, edema, breath sounds, ascites)
  - Imaging (see Table 154-3)
  - Pathology (Gleason score, determine number of positive biopsy cores)
  - Genetic testing (germline and/or somatic [tumor] based on risk factors)

Assess

- Determine the stage and risk category of disease based on, laboratory testing, imaging, and biopsy information (Table 154-4)
- Estimate life expectancy of the patient (can use Social Security Administration Life Insurance calculator)
- Evaluate current medication regimen and past medical history for potential drug-drug interactions or treatment contraindications
- Consider comorbidities that may impact therapy choice (cardiovascular risk, diabetes, seizure disorders)
- Address symptoms that require palliative management (ie, pain, impotence, fatigue, nausea)

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- Identify concerns for medication access and medication adherence that could influence treatment choice
- Discuss short-term and long-term goals of care with the patient

Plan*

- Drug therapy regimen including drug(s), dose(s), route, frequency, and duration (see Table 154-7)
- Supportive care plan (antiemetics, premedication for chemotherapy, pain control, hot flash management)
- Monitoring parameters for adverse drug reactions (eg, complete blood count, liver function tests, subjective symptom assessments) and efficacy (eg, PSA levels, repeat imaging, symptom assessments)
- Patient education (self-monitoring for adverse drug reactions, expected timeframe for benefit and onset of adverse drug reactions, action needed for adverse drug reactions, monitoring schedule)
- Referrals to other providers when appropriate (eg, dietician, palliative care, urology)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Mitigate financial toxicity of drug therapy to ensure adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Presence of adverse drug reactions
- Monitoring response to treatment (eg, PSA, imaging studies depending on location of disease)
- Patient adherence to the treatment plan using multiple sources of information
- Patient satisfaction with the treatment plan
- New comorbidities or medications that may impact the treatment plan and patient treatment goals

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

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BEYOND THE BOOK

Review the following case and answer the questions based on the information provided in the chapter:

A 60-year-old male presents to the ED with worsening back pain over the past 2 months. His lab reports were notable for a decreased hemoglobin of 10.1 g/dL (101 g/L; 6.27 mmol/L), a blood glucose of 280 mg/dL (15.5 mmol/L), and an alkaline phosphatase of 324 IU/L (5.4 μkat/L). A CT scan of the chest, abdomen, and pelvis revealed diffuse spine masses and bilateral rib masses suspicious for malignancy. A biopsy of a pelvic bone mass was consistent with prostate adenocarcinoma. Other relevant information is as follows:

- Past medical history: HTN, Afib, T2DM
- Family history: Father died of a myocardial infarction at the age of 57 years, mother died of breast cancer at the age of 47 years
- Medications: apixaban 5 mg BID, metoprolol 50 mg BID, nifedipine ER 60 mg daily, simvastatin 40 mg qHS, metformin 1,000 mg PO BID, empagliflozin 10 mg daily
- Vitals: BP 130/80, HR 81, Ht 176 cm, Wt 103.2 kg
- Lab reports:
  - PSA 132 ng/mL (mcg/L)
  - Testosterone 350 ng/dL (12.1 nmol/L)

Questions for self-assessment:

1. How would you classify this patient's prostate cancer? Describe if the cancer is metastatic or nonmetastatic and the castration status of the patient.
2. What treatment options are available to this patient to treat his cancer (based on your classification above)?
3. Perform a drug interaction screen for the available agents being considered to treat this patient's prostate cancer. Are there any contraindications? What changes to the patient's current medication regimen would you recommend if any of the agents were to be initiated? (Hint: It might be helpful to make a table of the available options to treat prostate cancer and then consider these options with each of the drugs on the patient's current medication list.)
4. Would this patient be eligible for genetic testing? (You can review the detailed recommendations for genetic testing in prostate cancer by accessing the current NCCN® Guidelines at: http://nccn.org)
5. Bonus question: Using resources outside of the chapter, suggest a possible cause of the patient's elevated alkaline phosphatase.

INTRODUCTION

In this chapter, the term "male" is used only to reflect the biological sex of individuals at birth and not the gender identified by the patient. Moreover, we recognize that not all patients with prostate cancer identify as "men" at the time of diagnosis and treatment of this condition. Prostate cancer is the most commonly diagnosed cancer in biological males in the United States.[1] For most, prostate cancer has an indolent course, and treatment options for early disease include expectant management, surgery, or radiation. With expectant management, patients are monitored for disease progression or development of symptoms. Localized prostate cancer can be cured by surgery or radiation therapy, but advanced and metastatic prostate cancers are not yet curable. Treatments for advanced and metastatic prostate cancers can provide significant disease palliation for many patients for several years after diagnosis. The endocrine dependence of this tumor is well documented, and hormonal manipulation aimed at decreasing circulating androgens remains the basis for the treatment of advanced and metastatic disease.

EPIDEMIOLOGY

1 Prostate cancer is the most frequent cancer among biologically male individuals in the United States and represents the second leading cause of cancer-related deaths in biological males.[1] In the United States alone, it is estimated that 268,490 new cases of prostate cancer were diagnosed and more than 34,500 individuals died from this disease in 2022.[1] Although the incidence of prostate cancer increased during the late 1980s and early 1990s related to widespread PSA screening, the incidence declined rapidly from 2007 to 2014 because of recommendations against routine PSA screening. Deaths from prostate cancer have declined since 1993.[1] The slowing decline in prostate cancer mortality between 2013 and 2019 is probably related to the decrease in PSA screening and an increase in advanced-stage

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diagnoses.[1]

ETIOLOGY

Table 154-1 summarizes the possible risk factors associated with prostate cancer.[2-4] The widely accepted risk factors for prostate cancer are age, race/ethnicity, and family history of prostate cancer. The disease is rare in those younger than 40 years, but the incidence sharply increases with each subsequent decade of life. The increased risk can likely be attributed to cumulative lifetime exposure to testosterone, which is a known growth signal for the prostate.

TABLE 154-1

Risk Factors Associated with Prostate Cancer

Factor	Possible Relationship
Probable Risk Factors	
Age	Greater than 70% of cases are diagnosed in men older than 65 years
Race/Ethnicity	Black individuals in the United States have a higher incidence and death rate
Genetic	Familial prostate cancer is inherited in an autosomal dominant manner
	Germline mutations in *ATM, ATR, BRCA1, BRCA2, BRIP1, CHEK2, FAM175A, FH, GEN1, HOXB13, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C,* or *RAD51D* are more common in metastatic/high-risk prostate cancer compared to localized/low-risk
	Inherited polymorphisms (eg, CAG repeat length) that lead to increased androgen receptor (AR) activation
Possible Risk Factors	
Environmental	Incidence varies worldwide
	Nationalized individuals adopt intermediate incidence rates between those of the United States and their native country
Occupational	Increased risk associated with cadmium exposure
Diet	Mediterranean diet associated with reduced risk
	Increased risk associated with high-red meat and high-fat diets
	Decreased intake of 25-dihydroxyvitamin D, lycopene, and β-carotene increases risk

Race and Ethnicity

The incidence of clinical prostate cancer varies across geographic regions. Scandinavian countries and the United States report the highest incidence of prostate cancer, while the disease is relatively rare in Japan and other Asian countries.[5] Black individuals from the United States have the highest rate of prostate cancer in the world, and prostate cancer mortality among them is more than twice that seen in White populations in the United States.[1] Hormonal, dietary, and genetic differences, and differences in access to healthcare may contribute to the altered susceptibility to prostate cancer in these populations.[2,3]

In addition, genetic variations in the androgen receptor gene *(AR)* exist. *AR* activation is inversely associated with CAG trinucleotide repeat length. Under normal circumstances, a CAG trinucleotide, consisting of the DNA building blocks cytosine, adenine and guanine, is repeated 10 to 35 times within a given gene. However, shorter CAG repeat sequences in *AR* have been found in Black individuals, and a meta-analysis demonstrated that carriers of a short CAG repeat had a 20% increased risk of prostate cancer when compared to individuals with long CAG repeats.[2]

Genetics and Family History

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Approximately 5% to 10% of prostate cancers are believed to be inherited, but individuals with a brother or father with prostate cancer have twice the risk for developing prostate than the rest of the population.[6] Familial clustering of prostate cancer syndrome has been reported, and genome-wide scans have identified potential prostate cancer susceptibility candidate genes. Carriers of germline polymorphisms in one of 16 DNA damage repair genes (eg, *BRCA1*, *BRCA2*, and *CHEK2*) have been associated with an increased risk of developing aggressive prostate cancer.[4,5] Germline genetic testing to evaluate for inherited cancer susceptibility genes is now recommended in patients who are diagnosed with prostate cancer and have a relevant family history, or those who are diagnosed with advanced/high-risk disease.[7] Other genes implicated in hereditary prostate cancer are *MSH2* and *HOXB13*.[6] In addition to inherited genetics, common exposure to environmental and other risk factors may contribute to increased risk among patients with first-degree relatives with prostate cancer.[5]

Diet

The overall dietary factor associated with the lowest risk of developing prostate cancer appears to be adherence to a Mediterranean diet.[8] The typical Mediterranean diet is high in fruits, vegetables, legumes, fish, olive oil, and red wine, with low-to-moderate amounts of red meat, poultry, and dairy. In a meta-analysis that included approximately 1.5 million subjects, adherence to a Mediterranean diet was associated with a small, but significantly reduced risk of prostate cancer.[8]

Many individual dietary factors have been assessed to ascertain their role in the development or prevention of prostate cancer.[9] Green tea and lycopene are considered the most useful, and at least not harmful. Green tea consumption was associated with a reduced risk of prostate cancer in a small casecontrol study. Lycopene, obtained primarily from tomatoes, has been associated with a decreased risk of prostate cancer in small cohort studies, although a meta-analysis failed to show benefit for high tomato consumption.[9]

Consistent with the beneficial effects of the Mediterranean diet, red meat, and high milk intake have been clearly and consistently associated with an increased risk of prostate cancer in epidemiological studies.[9]

Other Factors

Benign prostatic hyperplasia (BPH) is a common problem among geriatric patients, affecting greater than 40% of men older than 70 years (see Chapter 104, "Benign Prostatic Hyperplasia"). BPH results in the urinary symptoms of increased hesitancy and frequency. Because prostate cancer affects a similar age group, and often has similar presenting signs and symptoms, the presence of BPH often complicates prostate cancer diagnoses. But importantly, a BPH diagnosis does not appear to increase the risk of developing prostate cancer.[3]

Interestingly, smoking has not been validated as a risk factor for developing prostate cancer. However, smokers with prostate cancer have almost a two-times greater risk of prostate cancer-related mortality when compared with nonsmokers with prostate cancer.[3] In addition, both clinical and translational study results did not detect an association between alcohol consumption and prostate cancer development.[10,11]

CHEMOPREVENTION

The use of 5-α-reductase inhibitors, finasteride and dutasteride, to prevent prostate cancer has been debated for more than a decade.[12-15] These drugs inhibit 5-α-reductase, an enzyme that converts testosterone to its more active form, dihydrotestosterone (DHT), which is involved in prostate epithelial proliferation. Both finasteride and dutasteride can falsely lower PSA by about 50% in patients, and this must be considered when one interprets PSA in patients on these medications.[16] Although a number of large chemoprevention trials demonstrated a decreased risk of prostate cancer in patients who received 5-α-reductase inhibitors, this was coupled with an increased risk of developing more aggressive tumors. A survival benefit from chemoprevention with 5-α-reductase inhibitors has not been confirmed, although more contemporary analyses have called into question the association of 5-α-reductase inhibitors with the development of higher grade tumors.[17] Patients treated with 5-α-reductase inhibitors can experience adverse drug reactions, including gynecomastia, decreased libido, and erectile dysfunction.[13] Based on the concern for the development of more aggressive tumors, lack of survival benefit, and increased risk of adverse drug reactions, neither finasteride nor dutasteride is approved or recommended for preventing prostate cancer.[14,18]

Selenium and vitamin E, either alone or in combination, were evaluated as possible chemopreventive agents in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a clinical trial of healthy individuals. The results of this trial showed that selenium or vitamin E taken alone or together did not prevent prostate cancer. Furthermore, with a longer follow-up of that trial, dietary supplementation with vitamin E was found to significantly increase the risk of prostate cancer by 17%.[19] Other agents, including lycopene, green tea, nonsteroidal anti-inflammatory agents, isoflavones, and statins, have been evaluated for prostate cancer prevention, but none are recommended for routine use outside of a clinical trial.[20]

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SCREENING

2 Screening is not routinely recommended for all individuals at risk for prostate cancer. Rather, it is recommended that the individual discusses with their provider about risks versus benefits of screening. If prostate cancer screening is performed, the PSA test is the method of choice. PSA is a kallikrein-like serine protease, which liquefies seminal secretions and is produced by the prostate epithelial cells. Although PSA is specific for the prostate, it is not specific for cancer, and low specificity is a major limitation of the test. PSA may be elevated in patients with acute urinary retention, acute prostatitis, and prostatic ischemia or infarction, as well as BPH.[18,21] PSA elevations between 4.1 and 10 ng/mL (μg/L) cannot distinguish between BPH and prostate cancer, which limits the utility of the PSA test alone for the early detection of prostate cancer. Additionally, many patients with clinically significant prostate cancer do not have a serum PSA outside the reference range.[22]

Early detection of potentially curable prostate cancers is the goal of prostate cancer screening. For cancer screening to be beneficial, it must reliably detect cancer at an early stage, when intervention would decrease mortality. Whether prostate cancer screening fits these criteria is debatable.[23-26] The European Randomized Study of Screening for Prostate Cancer study demonstrated that compared to no PSA testing, PSA testing every 4 years decreased prostate cancer deaths in the screened group by about 1 per 1,000 men. However, the false-positive rate was 76% in the group that underwent PSA screening, which resulted in more than 13,000 unnecessary biopsies.[27] In the United States, the Prostate, Lung, Colon, and Ovarian Screening study showed no reduction in prostate cancer death between the annual screening group (PSA and DRE) and the usual care group, which is not surprising given the small reduction in death expected, and that about one-half of the patients in the usual care groups had PSA and/or DRE screening performed.[28] An updated systematic review found similar results in that PSA screening for prostate cancer may reduce the risk of prostate cancer mortality, but is associated with harms including false-positive results, biopsy complications, and over diagnosis in 20% to 50% of screen-detected prostate cancers. Early, active treatment for screen-detected prostate cancer may reduce the risk of metastatic disease, although the long-term impact of early, active treatment on prostate cancer mortality remains unclear. Active treatments for prostate cancer are frequently associated with sexual and urinary difficulties and thus can decrease quality of life for many patients.[29]

The US Preventive Services Task Force recommended that biologically male individuals aged 55 to 69 years make an individual decision about prostate cancer screening with their clinician (recommendation grade C) and recommended against routine screening for those aged 70 and older (recommendation grade D).[29] The American Urological Association does not recommend routine screening in biologic males between the ages of 40 and 54 years of average risk, but they recommend that the risks and benefits of prostate cancer screening are discussed with individuals aged 55 to 69 years.[23] For biologic males who elect to be screened, the frequency should be no more than 2 years, and screening every 5 years may be adequate. The American Society of Clinical Oncology recommends that asymptomatic biologically male individuals who have at least a 10-year life expectancy have an opportunity to make an informed decision about prostate cancer screening, including discussion of the uncertainties, risks, and potential benefits associated with screening.[26]

PATHOPHYSIOLOGY

The prostate gland is a solid, rounded, heart-shaped organ positioned between the neck of the bladder and the urogenital diaphragm (Fig. 154-1). The normal prostate is composed of acinar secretory cells arranged in a radial shape and surrounded by a foundation of supporting tissue. The size, shape, or presence of acini is almost always altered in the gland that has been invaded by prostatic carcinoma. Adenocarcinoma, the major pathologic cell type, accounts for more than 95% of prostate cancer cases.[30,31] Much rarer tumor types include small cell neuroendocrine cancers, sarcomas, and transitional cell carcinomas.

FIGURE 154-1

The prostate gland within the male genitourinary system.

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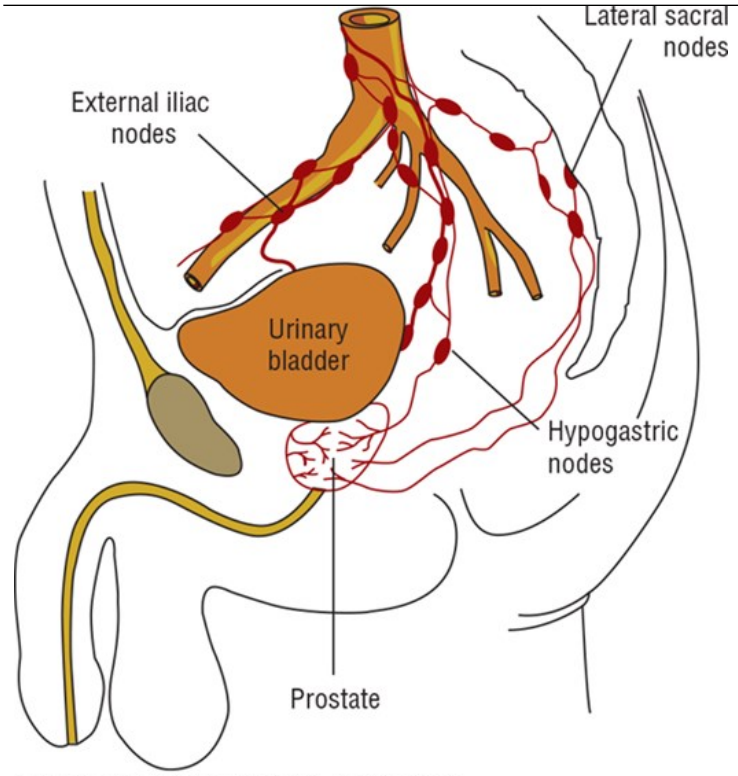

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Prostate cancer can be graded systematically according to the histologic appearance of the malignant cell and then grouped into well, moderately, or poorly differentiated grades.[31,32] Approximately 8 to 15 core biopsies are used to examine gland architecture and assess for malignancy. If malignancy is found then it is rated on a scale of 1 (well differentiated) to 5 (poorly differentiated). The two most common scores are added to give the Gleason pattern, with the most prevalent pattern represented as the first number (ie, 3+4 or 4+3). The biopsies are further classified into five Gleason groups, which are used to aid in prognosis, with Gleason Group 1 representing a Gleason score of ≤6 and Gleason Group 5 representing poorly differentiated disease with a Gleason score of 9 to 10. Poorly differentiated tumors grow rapidly (poor prognosis), while well-differentiated tumors grow slowly (better prognosis).

Metastatic spread can occur by local extension, lymphatic drainage, or hematogenous dissemination.[32,33] Lymph node metastases are more common in patients with large, undifferentiated tumors that invade the seminal vesicles. The pelvic and abdominal lymph node groups are the most common sites of lymph node involvement (see Fig. 154-1). Skeletal metastases from hematogenous spread are the most common sites of distant spread. Typically, the bone lesions are osteoblastic or a combination of osteoblastic and osteolytic. The most common site of bone involvement is the lumbar spine. Other sites of bone involvement include the proximal femur, pelvis, thoracic spine, ribs, sternum, skull, and humerus. The lung, liver, brain, and adrenal glands are the most common sites of visceral involvement, although these organs are not usually initially involved. About 25% to 35% of patients will have evidence of lymphangitic or nodular pulmonary infiltrates at autopsy. The prostate is rarely a site for metastatic involvement from other solid tumors.

Normal growth and differentiation of the prostate depend on the presence of androgens, specifically DHT.[33,34] The testes and the adrenal glands are the major sources of circulating androgens. Hormonal regulation of androgen synthesis is mediated through a series of biochemical interactions between the hypothalamus, pituitary, adrenal glands, and testes (Fig. 154-2). LHRH released from the hypothalamus stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. LH complexes with receptors on the Leydig cell testicular membrane, and stimulates the production of testosterone and small amounts of estrogen. FSH acts on the Sertoli cells within the testes to promote the maturation of LH receptors and to produce an androgen-binding protein. Circulating testosterone and estradiol influence the synthesis of LHRH, LH, and FSH by a negative feedback loop operating at the hypothalamic and pituitary level.[35] Prolactin, growth hormone, and estradiol areimportant accessory regulators for prostatic tissue permeability, receptor binding, and testosterone synthesis.

FIGURE 154-2

Hormonal regulation of the prostate gland. ACTH, adrenocorticotropic hormone; DNA, deoxyribonucleic acid; GH, growth hormone; mRNA, messenger ribonucleic acid; PROL, prolactin.

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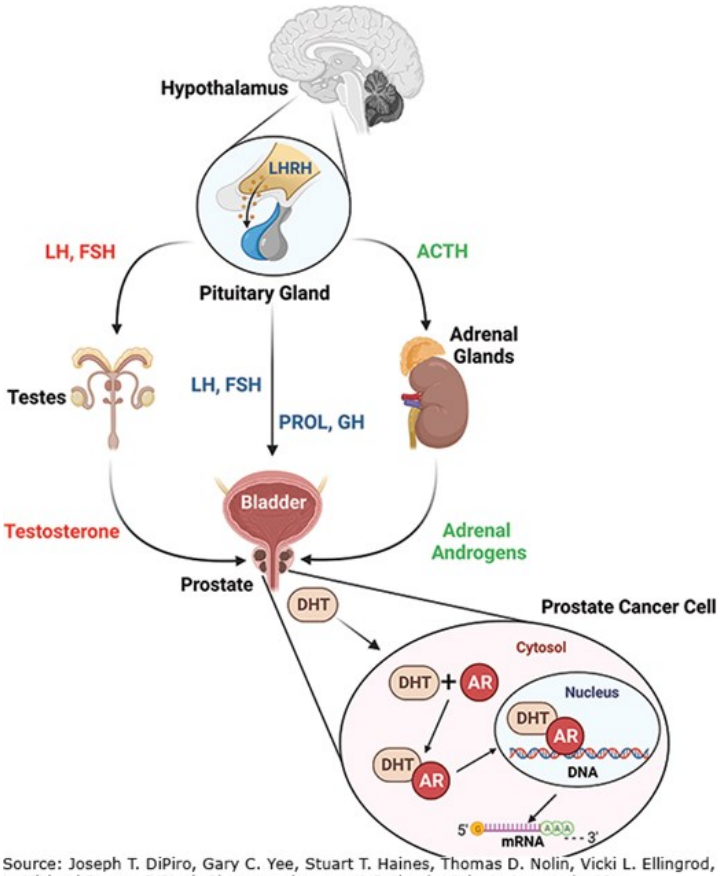

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Testosterone, the major androgenic hormone, accounts for 95% of the androgen concentration. The primary source of testosterone is the testes, but 3% to 5% of the testosterone concentration is derived from direct adrenal cortical secretion of testosterone or C19 steroids such as androstenedione.[32-34] 5α-reductase converts testosterone to DHT. When DHT is not bound to the AR, the AR remains inactive within the cytoplasm where it is bound to chaperone proteins (eg, heat shock protein 90 or HSP90).[36] However, when the AR is activated by DHT, the AR disassociates from heat shock protein 90, dimerizes, and then translocates into the nucleus where it binds to androgen response elements. AR binding to the androgen response elements regulates transcription of genes that regulate prostate cancer proliferation and cell survival (Fig. 154-2).[36,37]

In early-stage prostate cancers, aberrant tumor cell proliferation is promoted by the presence of androgens. For these tumors, the blockade of androgens induces tumor regression in most patients. Hormonal manipulations to ablate or reduce circulating androgens can occur through several mechanisms (Table 154-2).[33,34] The organs responsible for androgen production can be removed surgically (ie, orchiectomy, hypophysectomy, or adrenalectomy). Hormonal pathways that modulate prostatic growth can be interrupted at several steps (Fig. 154-2). Interference with LHRH or LH can reduce testosterone secretion by the testes.

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TABLE 154-2

Hormonal Manipulations in Prostate Cancer

Androgen source ablation	**Androgen synthesis inhibitors**
Adrenalectomy	Abiraterone acetate
Orchiectomy	Ketoconazole
Hypophysectomy	
	First-generation antiandrogens
LHRH agonists	Bicalutamide
Goserelin	Flutamide
Leuprolide	Nilutamide
Triptorelin	
	Second-generation antiandrogens
LHRH/GnRH antagonists	Apalutamide
Degarelix	Darolutamide
Relugolix	Enzalutamide

Isolation of the naturally occurring hypothalamic decapeptide hormone, LHRH (also known as gonadotropin-releasing hormone or GnRH) has provided another group of effective agents for advanced prostate cancer treatment. The physiologic response to LHRH depends on both the dose and the mode of administration. Intermittent pulsed LHRH administration, which mimics the endogenous release pattern, causes sustained release of both LH and FSH, whereas high-dose or continuous intravenous administration of LHRH inhibits gonadotropin release due to receptor downregulation.[27] Structural modification of the naturally occurring LHRH and innovative delivery have produced a series of LHRH agonists that cause a similar downregulation of pituitary receptors and a decrease in testosterone production.[35]

Androgen synthesis can also be inhibited in the testes or in the adrenal gland. Antiandrogens inhibit the formation of the DHT-receptor complex and therefore interfere with androgen activity at the cellular level.[35] In advanced stages of disease, prostate cancer cells may survive and proliferate without the signals normally provided by circulating androgens.[35] When this occurs, the tumor is no longer sensitive to therapies that depend on androgen blockade. These tumors are often referred to as hormone refractory, androgen independent, or castration-resistant. Re-exposure to androgens can still cause these castration-resistant tumors to proliferate, but they have developed resistance mechanisms to androgen suppression alone. Thus, ADT must be continued in patients with castration-resistant disease (in addition to therapies with other mechanisms of action), despite evidence that the prostate cancer is no longer sensitive to ADT when used alone.

CLINICAL PRESENTATION

Before the implementation of routine screening, prostate cancers were frequently diagnosed after the onset of symptoms, including urinary hesitancy, retention, painful urination, hematuria, and erectile dysfunction. With the introduction of screening, most prostate cancers are now identified before the development of symptoms, although this may change as routine screening is no longer the norm.

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CLINICAL PRESENTATION: Prostate Cancer

Localized Disease

- Usually asymptomatic

Locally Invasive Disease

- Ureteral dysfunction, frequency, hesitancy, and dribbling
- Impotence

Advanced Disease

- Back pain
- Spinal cord compression
- Lower extremity edema
- Pathologic fractures
- Anemia
- Weight loss

DIAGNOSIS AND STAGING

The information obtained from the diagnostic tests is used to stage the patient (Table 154-3). The eighth edition of the formal international classification system is the American Joint Committee on Cancer (AJCC) system (tumor, node, metastases [TNM]) (Table 154-4).

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TABLE 154-3

Diagnostic and Staging Workup for Prostate Cancer

Initial tests	DRE
	PSA level
	Biopsy
Staging tests	Gleason score on biopsy specimen
	Bone imaging
	Pelvic/abdominal imaging (mpMRI)
	Complete blood count
	Liver function tests
	Serum phosphatases (acid/alkaline)
Additional staging tests (depends on tumor classification, PSA, and Gleason score)	Obtain family cancer history/assess risk of germline genetic mutations Estimate life expectancy Somatic tumor mutation testing Lymph node evaluation Pelvic computed tomography PMSA-targeted PET-CT imaging (eg, Ga 68 PSMA-11 and piflufolastat F 18)

CT, computed tomography; mpMRI, multi-parametric magnetic resonance imaging; PET, positron emission tomography; PMSA, prostate-specific membrane antigen.

TABLE 154-4

Staging and Classification System for Prostate Cancer

AJCC 8th edition Classification
$T_xN_xM_x$ (cannot be assessed)
$T_0N_0M_0$ (nonpalpable)
T: Tumor
T_0: No evidence of primary tumor
T_1: Clinically inapparent tumor not palpable
T_{1a}: Tumor incidental histologic finding in 5% or less of tissue resected
T_{1b}: Tumor incidental histologic finding in 5% or more of tissue resected
T_{1c}: Tumor identified by needle biopsy found in one or both sides, but not palpable

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T_2: Tumor is palpable confined within the prostate
T_{2a}: Tumor involves one-half of one side or less
T_{2b}: Tumor involves more than one-half of one side, but not both sides
T_{2c}: Tumor involves both sides
T_3: Extraprostatic tumor that is not fixed or does not invade adjacent structures
T_{3a}: Extraprostatic extension (unilateral or bilateral)
T_{3b}: Tumor invades seminal vesicle(s)
T_4: Tumor is fixed or invades adjacent structures other than the seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
N: Regional Lymph Nodes
N_0: No positive regional lymph nodes
N_1: Metastasis in regional lymph nodes
M: Distant Metastasis
M_0: No distant metastasis
M_{1a}: Nonregional lymph node(s)
M_{1b}: Bone(s)
M_{1c}: Other site(s) with or without bone disease

3 The prognosis for patients with prostate cancer depends on the histologic grade (ie, Gleason score), the tumor size, and the local extent of the primary tumor.[31] The most important prognostic factor is the histologic grade because the degree of differentiation ultimately determines the stage of disease. Poorly differentiated tumors are highly associated with both regional lymph node involvement and distant metastases.[28]

Data from 2011 to 2017 showed that among all patients with prostate cancer, 5-year overall survival was estimated to be >99% when the disease is localized at diagnosis, and the 5-year survival rate for all stages combined is 98%. However, for individuals who are diagnosed initially with metastatic prostate cancer, 5-year survival drops to 30%. These same 2011 to 2017 data also showed that 5-year overall survival rates were estimated at 98% in White individuals and 96% in Black individuals.[1] For almost the same period, the survival rates for localized or regional disease and distant disease were also approximately the same in White and Black individuals in the United States.[1]

TREATMENT

Desired Outcomes

The desired outcome in early-stage prostate cancer is to minimize morbidity and mortality caused by prostate cancer.[7,38] The most appropriate therapy of early-stage prostate cancer is controversial. Early-stage disease may be treated with surgery, radiation, or expectant management. While surgery and radiation are curative, they are associated with significant morbidity and even mortality. Because the overall goal is to minimize morbidity and mortality associated with the

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disease, watchful waiting is appropriate in selected individuals. Advanced prostate cancer is not curable, and treatment should provide symptom relief and maintain quality of life. The mainstay of treatment for advanced prostate cancer is ADT, with a goal of reducing testosterone to castrate levels, with either surgical (eg, orchiectomy) or pharmacologic modalities (eg, LHRH agonist or LHRH/GnRH antagonist).

General Approach to Treatment

The initial treatment for prostate cancer depends primarily on the disease stage, the Gleason score, the presence of symptoms, and the life expectancy of the patient.[7] Prostate cancer is usually initially diagnosed by PSA and DRE, and then confirmed by a biopsy where the Gleason score is assigned. Asymptomatic patients with a low risk of recurrence may be managed by observation, radiation, or radical prostatectomy (Table 154-5). As patients with asymptomatic early-stage disease generally have an excellent 10-year survival, immediate morbidities of treatment must be balanced with the lower likelihood of dying from prostate cancer. More aggressive treatment of early-stage prostate cancer is generally reserved for younger individuals, although patient preference is a major consideration in all treatment decisions. In a patient with a normal life expectancy of less than 10 years, observation or radiation therapy may be offered. In those with a normal life expectancy of equal to or greater than 10 years, either active surveillance, radiation (external beam or brachytherapy), or radical prostatectomy with a pelvic lymph node dissection may be offered. Radiation therapy and radical prostatectomy are generally considered therapeutically equivalent for localized prostate cancer, although neither has been proven to be better than observation alone in those with low risks of recurrence.[39]

TABLE 154-5

Initial Management of Prostate Cancer Based on Expected Survival and Recurrence Risk

Recurrence Risk	Expected Survival (Years)	Initial Therapy
Very Low		
Has all of the following: ○ T_{1c} ○ Gleason group 1 ○ PSA less than 10 ng/mL (mcg/L) ○ Fewer than 3 prostate biopsies positive, ≤50% cancer in each core ○ PSA density <0.15 ng/mL/g (mcg/L/g)	<10	Observation
	10-20	Active surveillance
	20 or more	Active surveillance or radical prostatectomy or radiation therapy
Low		
Has all of the following but does not qualify for very low risk: ○ T_1-T_{2a} ○ Gleason Group 1 ○ PSA less than 10 ng/mL (mcg/L)	10 or more	Active surveillance or radical prostatectomy or radiation therapy
	<10	Observation
Intermediate		
• Has no high-risk group features • Intermediate risk factors (IRFs): ○ T_{2b}-T_{2c} ○ Gleason Group 2-3 ○ PSA10-20 ng/mL (mcg/L)		

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Favorable Intermediate risk	Has all of following: ○ Only 1 intermediate risk factor ○ Gleason Grade Group 1-2 ○ <50% biopsy cores positive	10 or more	Active surveillance or radical prostatectomy +/− pelvic lymph node dissection or radiation therapy
		<10	Observation or Radiation therapy or Brachytherapy
Unfavorable intermediate risk	Has one or more of the following: ○ 2 or 3 intermediate risk factors ○ Gleason Grade Group 3 ○ ≥50% biopsy cores positive	10 or more	Radical prostatectomy +/− pelvic lymph node dissection or radiation therapy + ADT[a,b] or radiation therapy + brachytherapy +/− ADT
		<10	Observation or radiation therapy + ADT[a,b] or radiation therapy + brachytherapy +/− ADT
High			
Has no very-high risk features and has exactly ONE high-risk feature: ○ T_{3a} or ○ Gleason Grade Group 4-5 or 8 ○ PSA >20 ng/mL (mcg/L)		5 or more	Radiation therapy + ADT +/− docetaxel or radiation therapy + ADT + brachytherapy or radical prostatectomy and pelvic lymph node dissection
Very High			
Has at least one of the following: ○ T_{3b}-T_4 ○ Primary Gleason pattern 5 ○ 2 or 3 high-risk features ○ 4 cores with Gleason Grade Group 4 or 5		5 or more	Radiation therapy + ADT +/− docetaxel or radiation therapy + ADT +brachytherapy or radical prostatectomy and pelvic lymph node dissection
Locally Advanced/Metastatic disease			
Any T, N_1		5 or more	ADT +/− abiraterone and prednisone or radiation therapy + ADT +/− with or without abiraterone and prednisone)
Any T, Any N, M_1			ADT alone or in addition to: Apalutamide Abiraterone with prednisone

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		Docetaxel Enzalutamide

[a]ADT therapy to achieve serum testosterone levels <50 ng/dL (1.7 nmol/L).

[b]LHRH agonists, LHRH/GnRH antagonists, or surgical castration are equivalent.

A systematic review of 18 randomized trials and 473 observational studies compared the effectiveness and potential complications across prostate cancer treatment modalities. However, the analysis revealed that a paucity of high-quality available evidence limited comparisons of effectiveness between radiation, radical prostatectomy, and ADT. While the adverse drug reaction profiles were similar, the severity varied among the treatments.[40] Because radiation and prostatectomy have significant and immediate mortality when compared with expectant management alone, many patients may elect to postpone therapy until symptoms develop.

Individuals with T_{2b} and T_{2c} disease, a Gleason Group 2-3, or a PSA ranging from 10 to 20 ng/mL (µg/L) are considered at intermediate risk for prostate cancer recurrence. The intermediate-risk category is further divided into favorable and unfavorable intermediate risk, with more aggressive treatment recommended for those with more intermediate risk factors present at diagnosis.[7] Individuals with less than a 10-year expected survival may be offered observation or radiation therapy. Individuals with favorable risk may also be offered brachytherapy alone. In some cases, individuals with unfavorable risk and less than a 10-year expected survival may be also offered either radiation therapy with or without 4 to 6 months of neoadjuvant ADT, or radiation therapy plus brachytherapy with or without 4 to 6 months of neoadjuvant ADT. Individuals with favorable risk and a greater than or equal to 10-year life expectancy may be offered active surveillance, radical prostatectomy, with or without a pelvic lymph node dissection, or radiation therapy. Individuals with unfavorable risk and a greater than or equal to 10-year life expectancy may be offered radical prostatectomy, with or without a pelvic lymph node dissection, radiation therapy with or without 4 to 6 months of neoadjuvant ADT, or radiation therapy plus brachytherapy with or without 4 to 6 months of neoadjuvant ADT (Table 154-5).[7]

The treatment of patients at high or very-high risk of recurrence (stage T_3, a Gleason score ranging from 8 to 9, or a PSA value greater than 20 ng/mL [µg/L]) may be treated with ADT for 1.5 to 3 years combined with radiation therapy with or without brachytherapy (Table 154-5). Selected individuals with a low tumor volume may receive a radical prostatectomy with a pelvic lymph node dissection and additional therapy based on pathological evaluation. Docetaxel, in addition to radiation and ADT, can also be considered for patients in this risk recurrence group.[7]

4 Patients with T_{3b} and T_4 disease have a very-high risk of recurrence and are usually not candidates for radical prostatectomy because of extensive local spread of disease.[7] ADT with an LHRH agonist plus an antiandrogen should be used either prior to, concurrent with, or following radiation therapy for patients with locally advanced prostate cancer to improve outcomes over radiation therapy alone in patients with localized prostate cancer. Androgen ablation should be instituted at diagnosis rather than waiting for symptomatic disease or progression to occur. In a randomized clinical trial of 500 patients with locally advanced prostate cancer who were randomized to either immediate initiation of ADT (either surgical or pharmacologic) or deferred hormonal therapy, patients who received immediate therapy had a median actuarial cause-specific survival of 7.5 years for immediate treatment as compared with 5.8 years for deferred treatment.[41]

5 Systemic therapy for nonmetastatic, castration-naïve disease, where the disease has not yet become resistant to ADT therapy, may include either orchiectomy, LHRH agonist with or without a first-generation antiandrogen (ie, combined androgen blockade [CAB]), GnRH antagonist, or observation. In patients with lymph node involvement (N_1) disease, abiraterone with a corticosteroid (eg, prednisone) can be used in addition to ADT (Table 154-6).[7]

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TABLE 154-6

First-Line Systemic Treatment Options for Advanced and Metastatic Prostate Cancer in Treatment-Naïve Patients

	Locally Advanced/Non-metastatic	Metastatic
Castration-naïve (ADT initiated to achieve testosterone <50 ng/mL [mcg/L] in all cases)	• ADT • ADT + abiraterone + corticosteroid[a]	• ADT • ADT + abiraterone + corticosteroid[a] • ADT + apalutamide • ADT + docetaxel • ADT + enzalutamide
Castration-resistant (ADT continued to maintain testosterone <50 ng/mL [mcg/L] in all cases)	• Apalutamide • Darolutamide • Enzalutamide	• Abiraterone + corticosteroid[b] • Enzalutamide • Docetaxel + prednisone • Radium-223 (if symptomatic bone metastases) • Sipuleucel-T

[a]Treatment-naïve refers to those who have not received novel hormone therapy or docetaxel.

[b]Choice of corticosteroid is dependent on multiple factors, including abiraterone formulation.

Data from Reference 7.

6 ADT in addition to one of the following: docetaxel (six cycles), abiraterone with a corticosteroid (eg, prednisone), enzalutamide, or apalutamide are recommended options for patients with metastatic castration-naïve disease (Table 154-6).[7]

When patients progress despite adequate androgen suppression, their disease is considered castration-resistant. Importantly, patients may progress on initial therapy without evidence of disease on scans. An increase in PSA or a rapid PSA doubling time (generally less than 10 months), could be indicative of progression and a biochemical recurrence. The development of new symptoms should also prompt a workup for disease progression. Importantly, further therapy is determined by the presence of symptomatic disease, or whether the metastatic progression is manifested as only a rising PSA (Table 154-6).[7]

7 For patients with nonmetastatic (M_0) castration-resistant disease, observation plus continued ADT is preferred if PSA doubling time is greater than 10 months. However, for patients with nonmetastatic castration-resistant prostate cancer who have a PSA doubling time less than or equal to 10 months, systemic therapy is recommended. Preferred systemic therapies for these patients include continuing ADT to maintain serum levels of testosterone less than 50 ng/dL (1.7 nmol/L) and a second-generation antiandrogen (eg, apalutamide, darolutamide, or enzalutamide) (Table 154-6).[7]

Patients with metastatic (M_1) castration-resistant prostate cancer should receive best supportive care in addition to other treatments (Fig. 154-3). ADT should continue, and initiating denosumab or an intravenous bisphosphonate should be considered in patients with bone metastases (see the discussion of LHRH agonists in the "Pharmacotherapy" section for more information). Palliative radiation therapy to bony metastases is also an option that may be utilized in these patients to provide relief of symptoms. When it comes to treatment selection for patients with metastatic castration-resistant prostate cancer, consideration should be given to previous lines of treatment, and providers should strive to choose an agent with a mechanism of action different from any therapies that the patient has failed (Fig. 154-3). Preferred first-line treatments (in conjunction with continuing ADT) include docetaxel plus prednisone, enzalutamide, or abiraterone. Sipuleucel-T, an immunotherapeutic, is also an option for patients without visceral metastases and who are clinically asymptomatic. Radium-223, an alpha emitter, is recommended for patients with bony metastases (and without evidence of visceral disease) (Table 154-6).[7]

8 In castration-resistant prostate cancer, genetic testing on tumor tissue (along with germline genetic testing if not already completed) is recommended to detect MSI-H, dMMR, or HR gene mutations (eg, *BRCA1/2*). Those whose tumors test positive for MSI-H, dMMR, or TMB greater than or equal to 10 mut/Mb are eligible for treatment with the programmed cell death receptor 1, or PD1, inhibitor pembrolizumab. Evidence of pathogenic gene mutations in genes involved in HR indicates eligibility for olaparib, while the presence of pathogenic *BRCA1/2* mutations specifically indicates eligibility for rucaparib. Other agents include cabazitaxel, which

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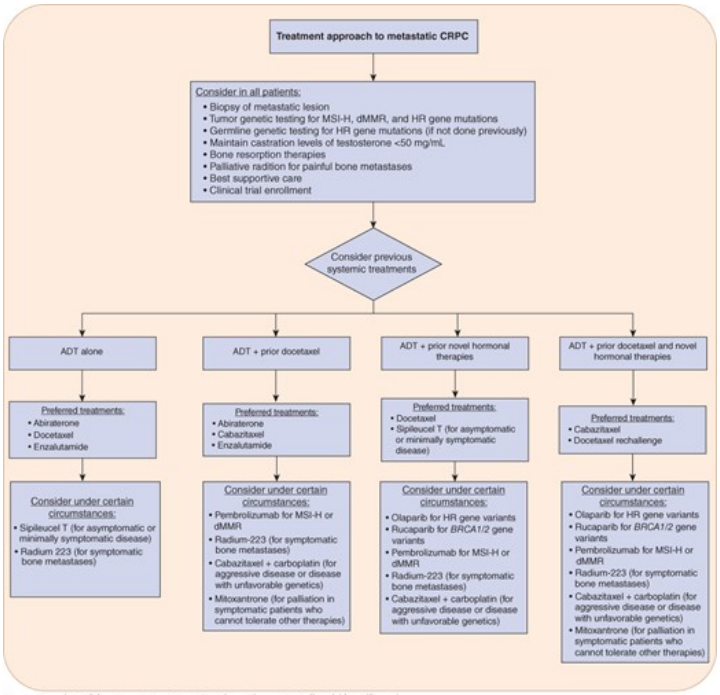
can be used if the patient has failed docetaxel, or mitoxantrone, which can be considered when patients present with visceral metastases and cannot tolerate other therapies (Fig. 154-3).[7]

FIGURE 154-3

Treatment of metastatic castration-resistant prostate cancer. (*Data from Reference 7.*)



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Nonpharmacologic Therapy

Observation/Active Surveillance

Observation is a treatment approach utilized in men with a shorter life expectancy and lower risk of disease. Observation involves monitoring the course of disease with laboratory testing and imaging, and starting palliative treatment if the cancer progresses. The advantages of observation are avoiding the adverse drug reactions associated with definitive therapies, such as radiation and radical prostatectomy, and minimizing the risk of unnecessary therapies. The major disadvantage of observation is the risk that cancer progresses and requires more intensive therapy. Active surveillance is similar to observation, although it may involve more invasive surveillance prostate biopsies. Those receiving active surveillance would generally be eligible for more aggressive treatment approaches upon progression.[7]

Orchiectomy

Bilateral orchiectomy, or surgical removal of the testes, is a form of ADT that rapidly reduces circulating androgens to castrate levels (less than 50 ng/dL [1.7 nmol/L]).[25] However, many patients are not surgical candidates because of advanced age, and other patients find this procedure psychologically unacceptable.[30] Orchiectomy is the preferred initial treatment in patients with impending spinal cord compression or ureteral obstruction, given their rapid onset.

Radiation

The two commonly used methods for radiation therapy are external beam radiotherapy and brachytherapy.[7] In external beam radiotherapy, doses of 70 to 75 Gy (7,000-7,500 rad) are delivered in 35 to 41 fractions in patients with low-grade prostate cancer and 75 to 80 Gy (7,500-8,000 rad) for those with intermediate- or high-grade prostate cancer. Brachytherapy involves the permanent implantation of radioactive beads of 145 Gy (14,500 rad) ^{125}iodine or 124 Gy (12,400 rad) ^{103}palladium and is generally reserved for individuals with low-risk cancers. Radiation therapy may also be given after surgery in patients with localized disease. Acute complications from radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence (30% incidence).[21,31] Chronic

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complications include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.[30,31] Because radiation therapy and radical prostatectomy have significant and immediate adverse effects compared with observation alone, many patients elect to postpone therapy until prostate cancer symptoms develop.

Radical Prostatectomy

Radical prostatectomy involves surgical removal of the prostate. Complications from radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve-sparing radical prostatectomy can be performed in many patients; 50% to 80% regain sexual potency within the first year. However, even in patients with good preoperative sexual health, many do not return to baseline after surgery even with the assistance of erectile dysfunction treatments.[42] Nerve-sparing radical prostatectomy can be performed in many patients; 50% to 80% regain sexual potency within the first year. The surgery can be accompanied by a pelvic lymph node dissection to determine if the disease has spread to any regional nodes.

Pharmacotherapy

LHRH Agonists

LHRH agonists are a reversible method of androgen ablation and are as effective as orchiectomy in treating prostate cancer.[7,43] Currently available LHRH agonists include leuprolide, leuprolide depot, leuprolide implant, triptorelin depot, triptorelin implant, and goserelin acetate implant (Table 154-7). The leuprolide depot formulation contains leuprolide acetate in coated pellets. The dose is administered intramuscularly, and the coating dissolves at different rates to allow sustained leuprolide levels throughout the dosing interval. Goserelin acetate implant contains goserelin acetate dispersed in a plastic matrix of D,L-lactic, and glycolic acid copolymer and is administered subcutaneously. Hydrolysis of the copolymer material provides continuous release of goserelin over the dosing period.

TABLE 154-7

Hormonal Therapies for Prostate Cancer

Drug	Usual Dose	Adverse Drug Reactions	Hepatic/Renal Adjustments	Monitoring Parameters	Drug Interactions	Administration
First-Generation Antiandrogens						
Bicalutamide	50 mg/day PO (up to 150 mg/day unlabeled use)	Gynecomastia Hot flashes Gastrointestinal disturbances (diarrhea) Decrease libido LFT abnormalities Breast tenderness	Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	Serum transaminases should be monitored prior to start of therapy and monthly for the first 4 months, then periodically thereafter Periodic monitoring of CBC, EKG, echocardiograms, serum testosterone, luteinizing hormone, and PSA	Inhibits CYP3A4 May increase the concentration of vitamin K antagonists	May be taken with or without food
Flutamide	750 mg/day PO	Gynecomastia Hot flashes Gastrointestinal disturbances (diarrhea) Loss of libido LFT abnormalities Breast tenderness Methemoglobinemia	Contraindicated in patients with hepatic impairment No dosage adjustment necessary in chronic renal impairment	Serum transaminases should be monitored prior to start of therapy and monthly for the first 4 months, then periodically thereafter Monitor for tumor reduction, PSA,	Substrate of CYP1A2 and CYP3A4	Administered orally in three divided doses; capsule may be opened into applesauce, pudding, or

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				testosterone/estrogen, and phosphatase serum levels		other soft foods
Nilutamide	300 mg/day PO for first month then 150 mg/day	Gynecomastia Hot flashes Gastrointestinal Disturbances (constipation) LFT abnormalities Breast tenderness Visual disturbances (impaired dark adaptation) Alcohol intolerance Interstitial pneumonitis	Contraindicated in patients with hepatic impairment Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	Serum transaminases should be monitored prior to start of therapy and monthly for the first 4 months, then periodically thereafter Chest x-ray at baseline and consideration of pulmonary function testing (at baseline), PSA periodically	Substrate of CYP2C19 and weak inhibitor of CYP2C19	May be taken with or without food
Second-Generation Antiandrogens						
Apalutamide	240 mg/day PO	Gastrointestinal disturbances (diarrhea, nausea) Hot flashes Fatigue Hyperthyroidism Hypertension Rash Decreased weight Falls and fractures Peripheral edema Seizures	No adjustment necessary for renal or hepatic impairment	Complete blood counts baseline and periodically LFTs baseline and periodically TSH at baseline and every 4 months, PSA periodically	Strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9	May be taken with or without food
Darolutamide	1,200 mg/day PO	Fatigue Gastrointestinal disturbances (diarrhea, constipation, nausea) Rash Musculoskeletal disorders (back pain, arthralgias, pain in an extremity) Falls, including accidents/bone fractures Hypertension Seizures	For moderate hepatic impairment or severe renal impairment (not on dialysis): dose should be reduced to 600 mg/day	Complete blood counts baseline and periodically LFTs baseline and periodically, PSA periodically	BCRP transporter Inhibitor Darolutamide inhibits OATP1B1 and OATP1B3	Take with food
Enzalutamide	160 mg/day PO	Gastrointestinal disturbances (diarrhea)	No adjustment necessary for renal or hepatic	Complete blood counts baseline and periodically	Strong CYP3A4 and moderate	May be taken with or without food

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		Musculoskeletal disorders (back pain, arthralgias, muscle pain, weakness) Asthenia Peripheral edema CNS (headache, dizziness) Seizures LFT abnormalities	impairment	LFTs baseline and periodically, PSA periodically	CYP2C9 and CYP2C19 inducer; avoid CYP3A4, CYP2C9, and CYP2C19 sensitive substrates. CYP2C8 substrate, avoid strong inducers and inhibitors of CYP2C8 If vitamin K antagonists are necessary, conduct additional INR monitoring	
Androgen Synthesis Inhibitor						
Abiraterone acetate	Abiraterone acetate: 1,000 mg/day PO + prednisone 5 mg daily PO (castration-naïve) or BID PO (CRPC). Micronized abiraterone: 500 mg daily PO + methylprednisolone 4 mg BID PO (CRPC)	Gastrointestinal disturbances (diarrhea) Edema Hypokalemia Hypophosphatemia LFT abnormalities Hypertriglyceridemia	250 mg daily for Child Pugh Class B; avoid use in Child Pugh Class C Withhold treatment if LFTs >5 times the ULN or bilirubin >3 ULN	Serum transaminases should be monitored prior to start of therapy, every 2 weeks for 3 months, then monthly thereafter Monitor for signs and symptoms of adrenocorticoid insufficiency; monthly for hypertension, hypokalemia, and fluid retention, PSA periodically	Substrate of CYP3A4 Use with caution with CYP3A4 inhibitors and inducers Inhibits CYP1A2, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4, and P-glycoprotein Use sensitive substrates with caution	For standard abiraterone, administer on an empty stomach, at least 1 hour before and 2 hours after food (micronized abiraterone can be given regardless of food)
Luteinizing-Hormone Releasing Hormone Agonists						
Goserelin	3.6 mg SQ implant every month 10.8 mg SQ implant every 3 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Monitor bone mineral density, serum calcium, and cholesterol/lipids, PSA periodically	May diminish the effects of antidiabetic agents	Vary injection site

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Leuprolide	7.5 mg IM every month 22.5 mg IM every 3 months 30 mg IM every 4 months 45 mg IM every 6 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Serum testosterone ~4 weeks after initiation, PSA, blood glucose, and $HgbA_{1c}$ prior to initiation and periodically thereafter, PSA periodically	May diminish the effects of antidiabetic agents	Vary injection site
Triptorelin	3.75 mg IM every month 11.25 mg IM every 3 months 22.5 mg IM every 6 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Monitor serum testosterone levels and PSA periodically	May diminish the effects of antidiabetic agents	Vary injection site
Luteinizing-Hormone Releasing Hormone/Gonadotropin-Releasing Hormone Receptor Antagonists						
Degarelix	240 mg SQ loading dose 80 mg SQ every 28 days (following 28 days after loading dose)	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	Use with caution with CL_{cr} <50 mL/min (0.83 mL/s) Do not use in patients with severe hepatic impairment	PSA periodically, serum testosterone monthly until castration achieved then every other month, LFTs at baseline in addition to serum electrolytes and bone mineral density	Use with caution with agents that may increase QTc interval	Vary injection site
Relugolix	360 mg PO followed by 120 mg PO daily	Hot flashes, Hypergylcemia, Hypertrigylceridemia, Musculoskeletal pain, Fatigue	No adjustment necessary for renal or hepatic impairment	PSA periodically, LFTs and serum electrolytes at baseline and periodically; bone mineral density periodically	Use with caution with agents that may increase QTc interval. Use with caution with CYP3A4 inhibitors and P-glycoprotein inhibitors	May be taken with or without food

ALT, alanine aminotransferase; BID, twice daily; BRCP, breast cancer resistance protein; CBC, complete blood count; CL_{cr}, creatinine clearance; CNS, central nervous system; CRPC, castrate-resistant prostate cancer; CYP, cytochrome P450; EKG, electrocardiogram; $HgbA_{1c}$, hemoglobin $A1_C$; IM, intramuscular injection; INR, international normalized ratio; LFT, liver function test; PO, oral administration; PSA, prostate surface antigen; QTc, corrected QT interval; SQ, subcutaneous injection; TSH, thyroid stimulating hormone; ULN, upper limit of normal.

Data from References 55-65 and 71.

Several randomized trials have demonstrated that leuprolide, goserelin, and triptorelin are effective agents when used alone in patients with advanced prostate cancer. Response rates of around 80% have been reported.[34] The currently available LHRH agonists or the dosage formulations have not been directly compared in

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clinical trials, but a meta-analysis showed no significant differences in efficacy or toxicity between leuprolide, goserelin, and orchiectomy.[44] Triptorelin is a more recent approval that is generally considered equally effective. Therefore, the choice between the three agents is usually made based on cost and patient and physician preference for a dosing schedule.

The most common adverse drug reactions reported with LHRH agonist therapy include a disease flare during the first week of therapy for patients with metastatic disease, hot flashes, erectile impotence, decreased libido, and injection-site reactions.[34] The disease flare is caused by an initial induction of LH and FSH by the LHRH agonist leading to an initial phase of increased testosterone production, and manifests clinically as either increased bone pain or increased urinary symptoms.[35] This flare reaction usually resolves after 2 weeks and has a similar onset and duration pattern for the depot LHRH products.[44,45] Tumor flare can be minimized by initiating an antiandrogen before the administration of the LHRH agonist and continuing for 2 to 4 weeks.[35] LHRH agonist monotherapy can be used as initial therapy, with response rates similar to those for orchiectomy. Caution should be exercised if initiating LHRH agonist therapy in patients with widely metastatic disease involving the spinal cord or having the potential for ureteral obstruction because irreversible complications may occur.

Another potentially serious complication of ADT is a decrease in bone mineral density leading to an increased risk for osteoporosis, osteopenia, and skeletal fractures. During initial therapy, bone mineral density of the hip and spine decreases by 2% to 3%.[46] Additionally, ADT has been associated with a 21% to 45% relative increase in fracture risk.[47-49] Therefore, most clinicians recommend that patients with increased risk for fracture based on the Fracture Assessment Tool, or FRAX, who are starting long-term ADT should have a baseline bone mineral density assessment performed, and all patients should have a bone mineral density assessment performed 1 year after initiating ADT. These individuals should also be initiated on a calcium and vitamin D supplement, based on the same guidance for the general population from the National Osteoporosis Foundation guidelines (see Chapter 112, "Osteoporosis," for more information).[7,35]

In addition, an antiresorptive agent, either zoledronic acid, alendronate, or denosumab should be initiated in men with osteoporosis at the same schedule and doses used in the treatment of the general population with osteoporosis (see Chapter 112, "Osteoporosis," for more information).[7] In men with metastatic castration-resistant prostate cancer and bone metastases, zoledronic acid or denosumab should be considered to reduce skeletal-related events (SREs). A meta-analysis combined data from three identically designed double-blind randomized controlled trials that compared the efficacy and safety of denosumab at a dose of 120 mg every 4 weeks with that of zoledronic acid at a dose of 4 mg administered IV every 4 weeks.[50] Almost 6,000 patients with breast and prostate cancer and multiple myeloma were included in the meta-analysis. Denosumab is superior to zoledronic acid in reducing the risk of first skeletal-related event (SRE) by 17% and prolonging the median time-to-first SRE was 8 months. The benefits were consistent across tumor types evaluated, and the incidence of adverse drug reactions was not significantly different between the denosumab and zoledronic acid groups.[50]

ADT has also been associated with a higher incidence of metabolic effects. In a landmark population-based trial, patients treated with an ADT using an LHRH agonist had a greater risk of new-onset diabetes, coronary artery disease, and myocardial infarctions.[51] However, it is not clear whether ADT increases the risk of cardiovascular death. A published meta-analysis of eight trials with 4,141 patients treated with ADT evaluated prostate cancer-specific mortality and all-cause mortality.[52] The trials included patients with nonmetastatic disease who were treated with immediate predominantly LHRH agonist–based ADT versus no immediate ADT (control group). The risk of cardiovascular death for ADT versus control was not significantly different, and these results suggest that ADT does not increase cardiovascular mortality. Patients receiving ADT should be screened for cardiovascular disease and diabetes and appropriate interventions to prevent and treat these complications should be initiated.[7]

LHRH/GnRH Antagonists

An alternative to LHRH agonists are the approved GnRH antagonists, degarelix, and relugolix. Degarelix and relugolix work by binding reversibly to GnRH receptors in the pituitary gland, which reduces the production of testosterone to castrate levels. The major advantage of the GnRH antagonists over LHRH agonists is the rapidity at which they reduce testosterone levels. Castration levels are achieved in 7 days or less with both degarelix and relugolix, as compared with 28 days with leuprolide. Tumor flare does not occur with either GnRH antagonist, and antiandrogens are not required.

Degarelix is equivalent to leuprolide in lowering testosterone levels for up to 1 year. Degarelix is available as 40 and 20 mg/mL vials for subcutaneous injection, and the starting dose is 240 mg followed by 80 mg every 28 days. The starting dose should be divided into two 120 mg injections.[53] Degarelix has not been studied in combination with antiandrogens, and routine use of the combination is not recommended. The most frequently reported adverse reactions are mild to moderate in nature and include transient injection site reactions, including pain, and erythema, and hot flashes. Other adverse drug reactions include elevations in liver function tests, which occur in about 10% of patients. These individuals should also be initiated on a calcium and vitamin D supplement, based on the same guidance for the general population from the National Osteoporosis Foundation guidelines (see Chapter 112, "Osteoporosis," for more information).[7,35,53]

Relugolix is an oral LHRH antagonist. In a phase 3 trial, patients administered relugolix (120 mg once daily after a single 360 mg oral loading dose) was evaluated against leuprolide. Relugolix demonstrated similar testosterone suppression to leuprolide, but in contrast to leuprolide, testosterone suppression was quickly reversible for those receiving relugolix, underscoring the need for adherence. But most importantly, in contrast to the other FDA-approved LHRH agonists and GnRH

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antagonists, there does not seem to be an increased cardiovascular risk with relugolix. In patients with pre-existing cardiovascular disease the incidence of major cardiovascular events was lower in patients treated with relugolix than patients treated with leuprolide (3.6% vs 17.8%).[54] Hot flashes, hypergylcemia, hypertrigylceridemia, musculoskeletal pain, fatigue were common toxicities, and providers should use with caution with medications that increase QTc interval, or are inhibitors of cytochrome P450 (CYP) 3A4 or the p-glycoprotein (P-gp) efflux transporter (Table 154-7).[55-59]

Antiandrogens

The first-generation antiandrogens include flutamide, bicalutamide, and nilutamide. Three second-generation antiandrogens, apalutamide, enzalutamide, and darolutamide, are currently available (Table 154-7).[55-65] Antiandrogens have been used as monotherapy in previously untreated patients, but a meta-analysis showed that monotherapy with antiandrogens is less effective than LHRH agonists.[44] Therefore, for advanced prostate cancer, flutamide, bicalutamide, and nilutamide are indicated only in combination with ADT. Flutamide and bicalutamide are indicated in combination with an LHRH agonist, and nilutamide is indicated in combination with orchiectomy.[66] Antiandrogens can reduce the symptoms from the flare phenomenon associated with LHRH agonist therapy in patients with metastatic disease.[7,35,66]

As with first-generation antiandrogens, second-generation antiandrogens do not lower androgen levels, but inhibit androgen receptor signaling by competitively inhibiting androgen binding without stimulation of the androgen receptor. Second-generation antiandrogens may have an advantage over the currently available first-generation antiandrogen agents because they inhibit AR nuclear translocation and AR binding to DNA and coactivator recruitment, which leads to a reduction of AR-mediated transcription of genes known to promote prostate cancer proliferation (Fig. 154-2). Enzalutamide also has a greater affinity for the AR, and has shown activity in patients resistant to first-generation antiandrogens. Initially approved only after docetaxel failure, enzalutamide may be used in the first-line setting to delay the initiation of chemotherapy in nonmetastatic castration-resistant prostate cancer, as well as metastatic castration-naïve and metastatic castration-resistant disease.[7,67] Apalutamide and darolutamide are also second-generation antiandrogens. Apalutamide is approved for the treatment of nonmetastatic castration-resistant prostate cancer and metastatic castration-naïve prostate cancer.[68] The most common adverse drug reactions associated with apalutamide are fatigue and rash, and apalutamide requires thyroid-stimulating hormone monitoring. The adverse drug reactions of apalutamide and enzalutamide are similar to those of the other antiandrogens, but they both have an increased risk of seizures. Darolutamide is a structurally distinct second-generation antiandrogen, consisting of two pharmacologically active diastereomers,[69,70] which lowers penetration past the blood–brain barrier and results in low binding affinity for γ-aminobutyric acid type A receptors. As a result, darolutamide may cause fewer and less severe adverse drug reactions (eg, less fatigue, and also potentially lower risk for seizures) than enzalutamide and apalutamide despite similar metastasis-free survival rates. Darolutamide is approved for nonmetastatic castration-resistant prostate cancer. The most common antiandrogen-related adverse drug reactions are listed in Table 154-7.

Combined Androgen Blockade

Although up to 80% of patients with advanced prostate cancer will respond to initial hormonal manipulation, almost all patients will progress within 2 to 4 years after initiating therapy.[30] Two mechanisms have been proposed to explain this tumor resistance. The tumor could be heterogeneously composed of cells that are hormone-dependent and hormone-independent, or the tumor could be stimulated by extratesticular androgens that are converted intracellularly to DHT. The rationale for CAB is to interfere with multiple hormonal pathways to completely eliminate androgen action. Antiandrogen therapy should precede, or be co-administered with LHRH agonists, and should be continued for at least 7 days for patients with overt metastases who are at high risk of developing symptoms associated with a testosterone flare that can occur with LHRH agonist therapy alone.[7] Studies of short term (4-6 months) and long term (2-3 years) of CAB in those patients with locally advanced disease with intermediate-, high-, and very-high-risk features have all assessed in the neoadjuvant and adjuvant settings, or even concurrently with radiation therapy.[7] Whether the addition of an antiandrogen to ADT is necessary requires further study, but any survival advantage for patients treated with CAB, if present, is small.[72,73] While controversy remains around the appropriate clinical use of CAB, clinicians should recognize that the consequences of financial toxicity and increased side effects must be weighed against modest survival benefit.[72]

Alternative Drug Treatments

Secondary or salvage therapies for patients who progress after their initial therapy depend on what was used for initial management.[7] For patients initially diagnosed with localized prostate cancer, radiotherapy can be used in the case of failed radical prostatectomy. Alternatively, ADT can be used in patients who progress after either radiation therapy or radical prostatectomy.

Abiraterone

Abiraterone is an androgen synthesis inhibitor that targets CYP17A1, which results in a decrease in circulating levels of testosterone.[71] Abiraterone is indicated in patients with metastatic castration-naïve prostate cancer or metastatic castration-resistant prostate cancer.[35] In both metastatic castration-naïve prostate cancer

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and castration-resistant prostate cancer, abiraterone improves overall survival.[7,74] Hypertension, hypokalemia, and edema may occur due to abiraterone-induced hypoadrenalism that is secondary to CYP17A1 inhibition. Corticosteroids (eg, prednisone) are prescribed concurrently with abiraterone to mitigate these potential adverse drug reactions. Abiraterone is available as the prodrug, abiraterone acetate, and should be taken on an empty stomach as food increases bioavailability by up to 10-fold.[71] A micronized formulation with improved bioavailability is available and can be taken with or without food and at a lower daily dose.[7] Monitoring of liver function tests is recommended at baseline, every 2 weeks for the first 3 months, and then monthly thereafter. Since abiraterone is an inhibitor of CYP2D6, medication profiles should be reviewed for potential drug interactions before initiation of abiraterone therapy.[71]

Chemotherapy

8 Chemotherapy with docetaxel improves survival in patients with metastatic castration-naïve and metastatic castration-resistant prostate cancer and is considered a first-line therapy option (see Table 154-8).[7,75-81] Docetaxel 75 mg/m^2 every 3 weeks combined with prednisone 5 mg twice a day was first studied in castration-resistant prostate cancer and shown to improve survival in this setting.[82] Subsequently, docetaxel 75 mg/m^2 every 3 weeks, without prednisone, was studied in the castration-sensitive setting and again shown to improve survival.[83] The most common adverse drug reactions with this regimen are nausea, alopecia, and bone marrow suppression. Other adverse drug reactions of docetaxel include fluid retention (premedication with corticosteroids can minimize) and peripheral neuropathy. Docetaxel is metabolized in the liver; patients with hepatic impairment may not be eligible for treatment with docetaxel because of an increased risk for toxicity (see Table 154-8).[81]

TABLE 154-8

Chemotherapy, Immunotherapy, and Targeted Therapy for Prostate Cancer

Drug	Usual Dose	Toxicities	Hepatic/Renal Adjustments	Monitoring Parameters	Drug Interactions	Administration
Antimicrotubule Agents						
Cabazitaxel	25 mg/m^2 IV every 3 weeks	Fluid retention, constipation, mucositis, myelosuppression, hypersensitivity	Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	CBC weekly during the first cycle, then prior to each treatment, PSA periodically, Monitor for hypersensitivity	Avoid concomitant use of CYP3A4 inducers and inhibitors	Administer IV infusion over 1 hour
Docetaxel	75 mg/m^2 IV every 3 weeks	Fluid retention, alopecia, mucositis, myelosuppression, hypersensitivity	AST/ALT >1.5 times the upper limit of normal and alkaline phosphatase >2.5 times the upper limit of normal do not administer	CBC with differential, LFTs, bilirubin, alkaline phosphatase, renal function, PSA periodically Monitor for hypersensitivity reactions	Avoid concomitant use of CYP3A4 inhibitors	Administer IV infusion over 1 hour Premedication with corticosteroids for 3 days beginning the day before
Immunotherapy						
Pembrolizumab	200 mg IV every 3 weeks or 400 mg IV	Fatigue and immune-mediated (eg, diarrhea,	No adjustment needed for	CBC, LFTs, renal function, thyroid	Immunosuppressants may decrease therapeutic effect	Administer over 30 minutes

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	every 6 weeks	pneumonitis, hepatitis, thyroiditis)	baseline renal/hepatic impairment; treat as immune-mediated toxicity if occurs during treatment	function, glucose at baseline and during therapy, PSA periodically		
Sipuleucel-T	Each injection contains >50 million autologous CD54+ cells (obtained through leukapheresis) activated with PAP-GM-CSF Dose is given every 2 weeks for 3 total doses	Hypersensitivity, chills, fatigue, fever, headache, myalgias	No dosage adjustment necessary for renal or hepatic dysfunction	No specific laboratory monitoring recommended, PSA periodically	Immunosuppressants may decrease the therapeutic effects of sipuleucel-T	Administer IV infusion over 1 hour Observe the patient for 30 minutes after the completion of the infusion Premedicate with acetaminophen and an antihistamine 30 minutes prior to administration
Targeted Therapy						
Olaparib	300 mg PO BID	Anemia, nausea, fatigue, decreased appetite, venous thromboembolism	Reduce dose for moderate renal impairment	CBC at baseline and monthly, renal function periodically, PSA periodically	Avoid CYP3A4 inhibitors and inducers; reduce olaparib dose if using CYP3A4 inhibitor	Administer with or without food
Rucaparib	600 mg PO BID	Fatigue, nausea, anemia, hepatotoxicity, decreased appetite	None	CBC at baseline and monthly, PSA periodically	Inhibits CYP1A2, CYP2C19, CYP2C9, and CYP3A4	Administer with or without food
Nuclear Medicine						
Radium-223	50 kBq/kg (1.35 µCi) administered every 4 weeks for 6 injections	Nausea, vomiting, diarrhea, peripheral edema, anemia, lymphocytopenia, thrombocytopenia, and neutropenia	None	CBC should be monitored prior to every injection, PSA periodically	None	Administer radium-223 by slow IV injection over 1 minute

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ALT, alanine aminotransferase; AST, asparate aminotransferase; BID, twice daily; CBC, complete blood count; CYP, cytochrome P450; IV, intravenous administration; LFT, liver function test; PAP-GM-CSF, prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor; PO, oral administration; PSA, prostate surface antigen.

Data from References 75-81.

Cabazitaxel is a taxane with demonstrated activity in docetaxel-resistant cell lines and animal models.[80] Cabazitaxel has a lower affinity for the P-gp efflux transporter than docetaxel, which may explain why cabazitaxel is active in the setting of docetaxel resistance. In patients previously treated with docetaxel and prednisone, cabazitaxel 25 mg/m^2 every 3 weeks with prednisone 10 mg daily significantly improved progression-free and overall survival over mitoxantrone and prednisone, but a reduced cabazitaxel dose of 20 mg/m^2 every 3 weeks (with prednisone) has been FDA-approved based on evidence of similar efficacy but better tolerability.[84,85] The addition of carboplatin (AUC 4 mg/mL per min) to cabazitaxel 25 mg/m^2 demonstrated improved progression-free survival versus cabazitaxel alone.[86] As result, guidelines suggest the use of this combination in high-risk metastatic castration-resistant prostate cancer patients who have been pretreated with docetaxel.[7] Neutropenia, febrile neutropenia, neuropathy, and diarrhea are the most significant toxicities. Hypersensitivity reactions may occur and premedication with an antihistamine, a corticosteroid, and an H_2 antagonist is recommended. Cabazitaxel is extensively metabolized in the liver and should be avoided in patients with hepatic dysfunction (Table 154-8).[80] Mitoxantrone plus prednisone has not demonstrated a survival improvement after failure of docetaxel, but remains a palliative therapeutic option, specifically in patients with evidence of visceral metastases and who are not candidates for cabazitaxel or radium-223 therapy.[7]

Immunotherapy

Sipuleucel-T is a novel autologous cellular immunotherapy FDA-approved for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.[79] Alternative treatment options for this patient population are secondary hormonal therapy, including antiandrogen therapy, withdrawal of antiandrogen therapy, ketoconazole, abiraterone acetate, enzalutamide, corticosteroids, estrogen, or enrollment on a clinical trial, although none of these options has been shown to improve overall survival. No clinical trials have compared sipuleucel-T to secondary hormonal therapies. Patients treated with sipuleucel-T undergo leukapheresis on day 1 to collect peripheral blood mononuclear cells, the cellular fraction that includes immune effector cells. These cells are incubated with the prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor, or PAP-GM-CSF, fusion protein. Prostatic acid phosphatase, or PAP, is the specific tumor antigen, and granulocyte-macrophage colony-stimulating factor, or GM-CSF, is the immune cell activator. The cellular product is then infused intravenously into the patient on day 3 or 4, providing an autologous infusion of activated cells. Each course of sipuleucel-T consists of three infusions of activated cells, given every 2 weeks. Sipuleucel-T prolongs overall survival by approximately 4 months.[79,87] Adverse drug reactions related to sipuleucel-T are generally mild.

9 Somatic and germline HR mutations are common in men with metastatic castration-resistant prostate cancer.[88] Germline genetic testing is recommended in patients with high-risk prostate cancer and/or a relevant family history. Somatic tumor genetic testing is recommended in metastatic disease to identify genetic variants that can be targeted with drug therapy. Pembrolizumab is a monoclonal antibody that inhibits the programmed cell death receptor–1 that is broadly FDA-approved for patients with metastatic solid tumors who have documented MSI-H, dMMR by molecular testing or TMB greater than or equal to 10 mut/Mb, who have progressed on prior treatment, and who have no alternative treatment options (Fig. 154-3).[78] Like other immune checkpoint inhibitors, pembrolizumab works by inhibiting signals that lead to T-cell senescence, and thereby increases the immune response to cancer (Table 154-8). MSI-H and dMMR are estimated to occur in approximately 5% to 12% metastatic castration-resistant prostate cancer patients, which makes pembrolizumab a viable treatment option.[88]

Targeted Therapy

9 11 PARP enzymes are involved in normal repair of both single-stand and double-strand DNA breaks. The combination of PARP enzyme inhibition by pharmacotherapy and inactivating HR gene mutations results in synthetic lethality that increases genetic instability and induces prostate cancer cell death. Olaparib has been proven effective in metastatic castration-resistant prostate cancer patients harboring pathogenic germline or somatic HR mutations (eg, *ATM*, *BRCA1/2*, *BRCA2*, *BARD*, *BRIP1*, *CDK12*, *CHEK1/2*, *FANCL*, *PALB2*, and *RAD51*) who had progressed on enzalutamide or abiraterone, by improving radiologic progression-free survival.[77] However, pre-specified subgroup analyses suggest that improvement is primarily observed in patients with *BRCA2* mutations.[89] A second PARP inhibitor, rucaparib, obtained FDA-accelerated approval in patients with metastatic castration-resistant prostate cancer. Rucaparib has been proven effective in metastatic castration-resistant prostate cancer patients who harbor germline or somatic mutations in *BRCA1/2*, and who have progressed after both second-generation antiandrogens or abiraterone- and taxane-based chemotherapy.[76] In this population, the overall response rate is approximately 44%, a majority of patients (56%) have a response duration >6 months, and progression-free survival is approximately 9 months.[90] Fatigue (including asthenia), nausea, vomiting, diarrhea, anemia, thrombocytopenia, and decreased appetite are the most common toxicities for these two PARP inhibitors. Both olaparib and rucaparib are CYP3A4 substrates. While olaparib doses should be adjusted when concomitantly with CYP3A4 inhibitors, doses of rucaparib do not require adjustments. However, rucaparib inhibits

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several CYP enzymes (including CYP3A4), and caution should be used with substrates of those enzymes concomitantly with rucaparib (Table 154-8).[76,77]

Nuclear Medicine

Radium-223, an alpha emitter, can be administered to target specific bone metastases with alpha particles in patients with metastatic castration-resistant prostate cancer. Radium-223 administered every 4 weeks improved overall survival by 2.8 months in patients who had already received, were not eligible for, or had declined docetaxel therapy. Improvements in skeletal pain, pain-related outcomes, and quality of life were also significant. Opioid needs were decreased in patients who received radium-223 (36% vs 50%). The most common adverse drug reactions of radium-223 include nausea, diarrhea, vomiting, peripheral edema, and bone marrow suppression.[75,91] Radium-223 may be used in first-, second-, or third-line therapy in patients with metastatic castration-resistant prostate cancer with symptomatic primary bone metastases. Radium-223 has not been approved for use with concomitant abiraterone, second-generation antiandrogens, chemotherapy, immunotherapy, or targeted therapy.

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring of prostate cancer depends on the grade and the stage of the cancer.[35] When definitive, and curative therapy is attempted, objective parameters should be assessed to evaluate tumor response. These include assessment of the primary tumor size and evaluation of involved lymph nodes through imaging studies, as well as the response of tumor markers, such as PSA, for recurrence or progression. For patients on active surveillance, PSA levels should be checked every 6 months and combined with annual DRE. Following definitive therapy with intent to cure, PSA levels should be checked every 6 to 12 months for the first 5 years and then annually thereafter. For patients at high risk of recurrence, every 3-month PSA testing can be considered.[7] Local recurrence in the absence of a rising PSA may occur, so annual DRE and radiologic studies based on patient-reported symptoms are also performed. In the castration-naïve setting, the response to ADT, radiation, or both dictates monitoring frequency; however, PSA measurement and physical examination every 3 to 6 months can be considered. In the metastatic setting, treatments that directly target the AR signaling axis, traditional cytotoxic chemotherapies, immunotherapies and targeted therapies have demonstrated that they increase survival.

Clinical efficacy is measured with imaging studies (typically CT scans of abdomen/pelvis and bone scans), performance status, symptom scores, weight changes, quality of life, analgesic requirements, and PSA response. However, because PSA is such a robust and reliable biomarker of clinical efficacy in most prostate cancer patients, imaging studies are routine but not performed as often as they are for other solid tumors. When using PSA as a surrogate for disease progression, it is important to consider not only the degree of elevation, but also the velocity at which the marker changes. A rapid PSA velocity has been associated with an increased risk of all-cause mortality, and should warrant consideration of therapeutic intervention.

Monitoring for adverse drug reactions is different for each treatment modality but is similarly important. Monitoring parameters and a review of common adverse drug reactions are provided for hormonal therapies (Table 154-7), as well as chemotherapies, immunotherapies and target therapies (Table 154-8). For pembrolizumab, clinicians and patients should monitor for signs and symptoms of immune-mediated adverse drug reactions (eg, colitis, endocrinopathies, hepatitis, nephritis, or pneumonitis). For sipuleucel-T, clinicians should recognize that traditional markers of benefit (eg, PSA decline or evidence of improvement by imaging studies) may not be present.[7] For orally administered treatments (eg, abiraterone, second-generation antiandrogens, PARP inhibitors, and relugolix), medication adherence is also an important monitoring parameter to evaluate at each clinic visit.

CONCLUSION

Prostate cancer is the most commonly diagnosed cancer in biologic males in the United States (greater than 20% of the new cases), but the death rate from prostate cancer has declined over the past three decades and only approximately 10% of the cancer-related deaths are attributed to prostate cancer among biologic males in the United States. This shows that for most prostate cancer patients, the disease has an indolent course, and treatment options for localized disease are often effective. While localized prostate cancer can be cured by surgery or radiation therapy, advanced and metastatic prostate cancer are not yet curable. Advanced and metastatic prostate cancer have a consistent pattern of progression, and are fatal. Advances over the past two decades, focusing on improved treatments directly targeting the AR signaling axis, chemotherapies, immunotherapies, and targeted therapies have extended survival for many patients with advanced and metastatic prostate cancer. An understanding of when to initiate early treatment before progression to advanced or metastatic disease continues to evolve (eg, the emergence of novel PMSA-based imaging modalities). Moreover, future research will help clinicians to understand how to combine or sequence treatments for castration-resistant prostate cancer, and continued development of novel therapeutics will prolong survival in patients with the most deadly forms of metastatic prostate cancer (eg, treatment-resistant castration-resistant prostate cancer and neuroendocrine prostate cancer).

ABBREVIATIONS

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ADT	androgen deprivation therapy
AJCC	American Joint Committee on Cancer
AR	androgen receptor
BPH	benign prostatic hyperplasia
CAB	combined androgen blockade
CAG	cytosine, adenine and guanine trinucleotide repeat
CYP	cytochrome P450
DHT	dihydrotestosterone
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DRE	digital rectal examination
FDA	United States Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HR	homologous recombination
LH	luteinizing hormone
LHRH	luteinizing hormone–releasing hormone
MSI-H	microsatellite instability high
PARP	poly-ADP ribose polymerase
PMSA	prostate-membrane specific antigen
PSA	prostate-specific antigen
SRE	skeletal-related event
TMB	tumor mutation burden
TNM	tumor, node, metastasis
US	United States

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SELF-ASSESSMENT QUESTIONS

1. MN is a 72-year-old individual who was diagnosed with prostate cancer and is initiated on a hormone agent for the first time for androgen deprivation. Which of the following agents will result in castration levels of testosterone within 7 days?

   A. Leuprolide

   B. Goserelin

   C. Triptorelin

   D. Degarelix

2. BB is a 61-year-old individual with nonmetastatic castration-resistant prostate cancer. He has failed treatment with ADT (leuprolide). He also has several other comorbid diseases including congestive heart failure and diabetes. Which of the following systemic agents is the most appropriate for this patient?

   A. Abiraterone + prednisone + leuprolide

   B. Bicalutamide

   C. Nilutamide

   D. Apalutamide + leuprolide

3. TW is a 68-year-old individual with a history of seizures and prostate cancer who was diagnosed with metastatic disease. He received ADT plus six cycles of docetaxel. His imaging demonstrates progression of disease with bone metastases, and he is complaining of significant back pain. His molecular testing is negative for alterations in homologous recombination genes (eg, *BRCA1/2*) or for MSI-H/dMMR status. Which of the following would you recommend?

   A. Sipuleucel-T

   B. Radium-223

   C. Pembrolizumab

   D. Enzalutamide

4. Which of the following characteristics increases the risk of developing prostate cancer?

   A. Asian ancestry

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B. Smoking

C. Advanced age (>65 years old)

D. Obesity

5. LJ is a 71-year-old individual with metastatic castration-resistant prostate cancer who has progressed following treatment with ADT + abiraterone and docetaxel. His somatic tumor genetic testing revealed a pathologic ATM mutation, but negative for MSI-H/dMMR status. Which of the following agents could be used to treat LJ based off of his molecular testing results?

A. Rucaparib

B. Olaparib

C. Pembrolizumab

D. Cabazitaxel

6. Denosumab is recommended in patients with prostate cancer for the prevention of SREs while on ADT. Which of the following adverse drug reactions may occur with denosumab?

A. Hypertriglyceridemia

B. Hypertension

C. Hypocalcemia

D. Infusion reactions

7. Which of the following medications should be taken on an empty stomach due to an increase in bioavailability when taken with food?

A. Bicalutamide

B. Abiraterone

C. Enzalutamide

D. Apalutamide

8. GS is a newly diagnosed patient with prostate cancer who will begin ADT with an LHRH agonist. Which of the following are appropriate counseling points for a new patient starting on an LHRH agonist, such as leuprolide?

A. Patients may experience adverse drug reactions, such as a loss in libido, hot flashes, and impotence

B. Patients may experience adverse drug reactions, such as changes in blood pressure

C. Patients may experience adverse drug reactions such as nausea/vomiting, alopecia, and weight loss

D. Patients may experience adverse drug reactions, such as arthralgias, peripheral edema, and seizures

9. SS is a 52-year-old biological male with a history of BPH. His father died of prostate cancer at the age of 74 years. He would like to discuss recommendations for prostate cancer screening, as he is concerned about his risk. Which of the following would you recommend for SS?

A. He should discuss the risks and benefits with his physician, as there are no age-based recommendations for prostate cancer screening

B. Based on his age and family history, he should receive PSA screening annually

C. Based on his age and family history, he should receive DRE screening annually

D. Based on his age and family history, he should undergo genetic testing to characterize his risk of developing prostate cancer

10. A 45-year-old biological male is being seen for the treatment of metastatic castration-resistant prostate cancer. He reports that his father and paternal uncle died

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of prostate cancer. His paternal grandmother died of breast cancer. He would like to know if he should obtain any genetic testing. What is the most appropriate recommendation for genetic testing for this patient?

A. He is not eligible for any genetic testing

B. He should receive germline genetic testing only to determine if he has a heritable cancer risk gene (ie, *BRCA1/2*)

C. He should receive somatic tumor mutation genetic testing only to determine if he is eligible for therapy with a PARP inhibitor

D. He should receive both germline and somatic tumor genetic testing to assess heritable cancer risk and determine appropriate therapy

11. JR is a 71-year-old individual who is diagnosed with metastatic castration-naïve prostate cancer and will be initiated on leuprolide. JR has significant disease involvement in his bones, and has bone pain at baseline. What is the most appropriate strategy to prevent bone pain from tumor flare when JR is initiated on an LHRH agonist?

A. Add bicalutamide

B. Add abiraterone

C. Switch leuprolide to goserelin

D. Discontinue leuprolide and use nilutamide monotherapy

12. Which of the following treatments would be appropriate to treat a patient with locally advanced, nonmetastatic, castration-naïve prostate cancer?

A. Orchiectomy + leuprolide

B. Bicalutamide alone

C. Enzalutamide + degarelix

D. Degarelix alone

13. Which of the following is the most common site of metastases for prostate cancer?

A. Brain

B. Bone marrow

C. Bone

D. Heart

14. Which of the following Gleason scores is considered the most aggressive?

A. 3+3

B. 4+5

C. 3+4

D. 4+4

15. Which of the following regimens is indicated for minimally symptomatic metastatic castration-resistant prostate cancer?

A. Mitoxantrone

B. Apalutamide

C. Radium-223

D. Sipuleucel-T

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SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Castration levels are achieved in 7 days or less with degarelix (an LHRH/GnRH antagonist), as compared with 28 days with leuprolide, goserelin, and triptorelin (LHRH agonists) (see the "LHRH/GnRH Antagonists" section).

2. **D.** Apalutamide is indicated for nonmetastatic castration-resistant prostate cancer in combination with androgen deprivation therapy to maintain testosterone levels less than50 ng/dL (1.7 nmol/L). Bicalutamide and nilutamide are first-generation antiandrogens that should not be used alone (without ADT). Abiraterone is not indicated in this setting and would also have the risk of worsening the patient's CHF and diabetes (see Table 154-7).

3. **B.** Radium-223 can be administered to target-specific bone metastases with alpha particles in patients with metastatic castration-resistant prostate cancer. Sipileucel-T is not appropriate given that the patient is symptomatic. He has no biomarkers to predict response to pembrolizumab. Enzalutamide would not be preferred in the setting of seizures (see Fig. 154-3 and Table 154-7).

4. **C.** The majority of prostate cancer cases occur in biological men over the age of 65 years. Geographically, the rate of prostate cancer is lower in Asia, and no increased risk of prostate cancer has been noted in those of Asian ancestry. While obesity and smoking increase the risk of other cancer types, they are not associated with an increased risk of prostate cancer (see Table 154-1).

5. **B.** Olaparib, a PARP inhibitor is approved in patients with a variety of mutations in the DNA repair genes, including *ATM*. Rucaparib is also a PARP inhibitor, but it is only approved in patients with *BRCA1/2* mutations. Pembrolizumab is not indicated in this patient, as they were negative for MSI-H or dMMR. Cabazitaxel is not a targeted therapy, but a cytotoxic chemotherapy (see Fig. 154-3).

6. **D.** Hypocalcemia can occur with denosumab. Patients with normal or low calcium levels should receive oral supplementation with vitamin D and calcium. Since denosumab is administered subcutaneously (versus the bisphosphonates that are given intravenously), infusion reactions are not a concern (see the "Pharmacotherapy: LHRH Aagonists" section).

7. **B.** Abiraterone should be taken on an empty stomach as food increases the bioavailability by 10-fold. Micronized abiraterone avoids this issue and may be administered without respect to meals (see Table 154-7).

8. **A.** LHRH agonists cause adverse drug reactions such as a loss in libido, hot flashes, and impotence. Docetaxel is associated with nausea/vomiting, weight loss, and alopecia. Enzalutamide is associated with arthralgias, edema, and seizures. Abiraterone is associated with changes in blood pressure (see Tables 154-7 and 154-8).

9. **A.** All available guidelines suggest that individuals should have a balanced discussion with their provider about the risks and benefits of prostate cancer screening. There are no age-based recommendations that apply outside of this discussion. If screening is pursued, PSA testing is preferred over DRE. While germline genetic testing is recommended in men with a family history after prostate diagnosis, it is not recommended in this individual who does not yet have prostate cancer and who has a single relative who succumbed to the disease at an advanced age (see the "Screening" section).

10. **D.** The patient should receive BOTH germline and somatic genetic testing based on his family history (multiple first-degree relatives with *BRCA*-related cancers) and the fact that he has metastatic disease that could be treated with targeted therapies, such as PARP inhibitors (see Key Conceptt #10, Genetics and Family History and Fig. 154-3).

11. **A.** LHRH agonists (eg, leuprolide or goserelin) can lead to tumor flare in the initial weeks of therapy before the negative feedback loop is activated to lead to androgen deprivation. Treatment with a first-generation antiandrogen, such as bicaluatmide, for the first 7 days can mitigate that risk (see the "Pharmacotherapy: LHRH Agonists" section).

12. **D.** Locally advanced, non-metastatic castration-naïve prostate cancer can be treated with ADT, orchiectomy, OR ADT + abiraterone. Degarelix, an LHRH/GnRH antagonist, would be appropriate as monotherapy as ADT. A patient who underwent orchiectomy as a means of testosterone suppression would not need the addition of an LHRH agonist, as either alone would be appropriate. Bicalutamide, a first generation anti-androgen, is not recommended as monotherapy for ADT. Enzalutamide is recommended in metastatic castration-naïve prostate cancer but not in the nonmetastatic setting (see Table 154-6).

13. **B.** The bone is the most common site of metastases for prostate cancer (see the "Pathophysiology" section).

14. **B.** A Gleason score of 4+5 for a total score of 9 is considered poorly differentiated and is considered aggressive (see the "Pathophysiology" section).

15. **D.** Sipuleucel-T, an autologous cellular immunotherapy, is indicated for minimally symptomatic metastatic castration-resistant prostate cancer. Mitoxantrone is indicated for those with symptomatic metastatic disease who cannot tolerate other treatments. Apalutamide is indicated for non-metastatic castration-resistant prostate cancer (not metastatic disease). Radium-223 is indicated specifically for bone metastases from prostate cancer (see Table 154-6 and Fig. 154-3).

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