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Benign and Malignant

Diseases of the Prostate Benign and malignant changes in the prostate increase with age. Autopsies of men in the eighth decade of life show hyperplastic changes in >90% and malignant changes in >70% of individuals. The high prevalence of these diseases among the elderly, who often have competing causes of morbidity and mortality, mandates a risk-adapted approach to diagnosis and treatment. This can be achieved by consid ering these diseases as a series of states. Each state represents a distinct clinical milestone for which therapy(ies) may be recommended based on disease extent, current symptoms, risk of developing symptoms, and/or the risk of death from prostate cancer in relation to death from other causes. Given the complexities and, at times, the uncertainties of optimal decision-making, patient preferences are an important consid eration. For benign proliferative disorders, symptoms of bladder outlet obstruction and potential complications including urinary retention and urinary tract infection are weighed against the side effects and complications of medical or surgical intervention. For prostate malig nancies, the likelihood that a clinically significant cancer is present in the gland and the concomitant risk of symptoms or death from cancer are necessarily balanced against the risks and morbidities of the recom mended treatments. ANATOMY AND PATHOLOGY The prostate is in the pelvis and is adjacent to the rectum, the bladder, the periprostatic and dorsal vein complexes, the

neurovascular bundles that are responsible for erectile function, and the urinary sphincter that is responsible for passive urinary control. The prostate is composed of branching tubuloalveolar glands arranged in lobules surrounded by fibromuscular stroma. The acinar unit includes an epithelial compartment made up of epithelial, basal, and neuroendocrine cells separated by a basement membrane and a stromal compartment that includes fibroblasts and smooth-muscle cells. Prostate-specific antigen (PSA) is produced in the epithelial cells. Both prostate epithelial cells and stromal cells express androgen receptors (ARs) and depend on androgens for growth. Testosterone, the major circulating androgen, is converted by prostatic 5α-reductase to dihydrotestosterone, a more potent androgen. The periurethral portion of the gland increases in size during puberty and after the age of 55 years due to the growth of nonma lignant cells in the transition zone of the prostate that surrounds the urethra. Most cancers develop in the peripheral zone, and cancers in this location may or may not be palpated during a digital rectal exami nation (DRE).

PROSTATE CANCER The American Cancer Society’s estimates for prostate cancer in the United States for 2024 are 299,010 new prostate cancer cases and 35,250 deaths from prostate cancer. In the United States, prostate

cancer is the most common nonskin malignancy in men and the sec ond leading cause of cancer death. The absolute number of prostate cancer deaths has decreased in the past 30 years, attributed by some to the widespread use of PSA-based detection strategies. The incidence/ mortality ratio for prostate cancer is extremely high relative to most other malignancies, and most men diagnosed with prostate cancer will not die from their disease.

■ ■EPIDEMIOLOGY Epidemiologic studies show that the risk of being diagnosed with pros tate cancer increases 2.5-fold if one first-degree relative is affected and even more if two or more are affected. Risk is greatest for those whose relatives are diagnosed before the age of 65. Current estimates are that 40% of early-onset and 5–10% of all prostate cancers are hereditary. Prostate cancer affects ethnic groups differently. Matched for age, African-American patients have a higher incidence and present at a more advanced stage with higher-grade, more aggressive cancers. The causes for this disparity are debated, but genetic, environmental, and societal factors are implicated. Genome-wide association studies (GWAS) have identified >100 prostate cancer susceptibility loci that are estimated to explain up to 25% of prostate cancer risk. Each prostatic risk loci typically confers only a small incremental risk of cancer, but combinations are more impactful. Some mutated genes such as BRCA2, HOXB13, ATM, and PALB2 clearly confer an increased risk of prostate cancer; however, that risk can be substantially modulated by presence or absence of additional genomic prostatic risk loci. Polygenic risk scores to better ascertain prostate cancer risk are under development but not routinely available for clinical care today. CHAPTER 92 Benign and Malignant Diseases of the Prostate The prevalence of autopsy-detected cancers is relatively similar around the world, while the incidence of clinical disease varies. In part, this is due to the substantial variations in the use of PSA screening tests. Environ mental and dietary factors may play a role in prostate cancer growth and progression. High consumption of dietary fats, such as α-linoleic acid or polycyclic aromatic hydrocarbons that form when red meats are cooked, is believed to increase risk. Like breast cancer in Asians, the risk of prostate cancer in Asians increases when they move to Western environ ments. Reasons for this are poorly understood but in part likely reflect a greater probability of PSA screening tests in the Western world. Protec tive

factors may include consumption of lycopene found in tomatoes and inhibitors of cholesterol biosynthesis (e.g., statin drugs). Not smoking and avoiding obesity reduce the risk of disease progression. ■ ■DIAGNOSIS AND TREATMENT BY CLINICAL STATE The prostate cancer continuum—from the appearance of a preneo plastic and invasive lesion that is localized to the gland to a metastatic lesion causing symptoms and, ultimately, mortality—can span years to decades. To limit overdiagnosis of clinically insignificant cancers and for disease management in general, competing risks are considered in the context of a series of clinical states (Fig. 92-1). The states are defined operationally based on whether or not a cancer diagnosis has been established and, for those with a diagnosis, the state of the primary tumor (treated vs untreated), the presence of absence of metastases on imaging studies, and the measured level of testosterone in the blood. With this approach, an individual resides in only one state and remains in that state until progression. At each assessment, the decision to offer treatment and the specific form of treatment are based on the presence or absence of cancer-related symptoms and, if absent, the risk posed by the cancer relative to competing causes of morbidity and mortality that may be present in that individual. It follows that the more advanced the disease, the greater is the need for treatment. Individual decision-making and patient preferences are key for prostate cancer throughout the continuum. Considerable heterogeneity can be encountered in patients seeking treatment recommendations given widely varying perceptions of risks and benefits, especially for those with early-stage disease.

Rising PSA: no visible metastases: castrate Rising PSA: no visible metastases: non-castrate Clinically localized disease No cancer diagnosis Clinical metastases: non-castrate Death from cancer exceeds death from other causes PART 4 Oncology and Hematology FIGURE 92-1 Clinical states of prostate cancer. PSA, prostate-specific antigen. For those without a cancer diagnosis, the decision to undergo testing to detect a cancer is based on the individual’s estimated life expectancy and, separately, the probability that a clinically significant cancer may be present. For those with a prostate cancer diagnosis, the clinical states model considers the probability of developing symptoms or dying from the disease. Thus, a patient with a localized tumor that has been surgically removed remains in the state of localized disease if the PSA remains undetectable. The time within a state then becomes a measure of the efficacy of an intervention. Because many patients with active cancer are not at risk for developing metastases, symptoms, or death, the clinical states model allows a distinction between cure—the elimination of all cancer cells, the primary therapeutic objective of treatment for most cancers—and cancer control, by which the tempo of the illness is determined to be so slow or has been altered by treatment to the point where it is unlikely to cause symptoms, to metastasize, or to shorten a patient’s life expectancy. Importantly, from a patient standpoint, both outcomes can be considered equivalent therapeuti cally assuming the patient has not experienced symptoms of the dis ease or the treatment needed to control it. Even when a recurrence is documented, immediate therapy is not always necessary. Rather, as at the time of diagnosis, the need for intervention is based on the tempo of the illness as it unfolds in the individual, relative to the risk-tobenefit ratio of the intervention being considered. Assessment of the future risk and tempo of the cancer, balanced with an understanding of the patient’s morbidities and life expectancy, is key to management of prostate cancer. ■ ■NO CANCER DIAGNOSIS Prevention No agent is currently approved for the prevention of prostate cancer. The results from several large double-blind, random ized chemoprevention trials have established 5α-reductase inhibitors (5ARIs) as the predominant therapy to reduce the future risk of a pros tate cancer diagnosis; however, most of the prevented cancers were low risk, and those

cancers typically require no treatment as their natural history is indolent. No drug is approved for prostate cancer prevention. Various vitamins and supplements have been studied in large-scale prostate cancer prevention trials, but no intervention has been shown to be effective. Early Detection and Diagnosis The decision to pursue a diag nosis of prostate cancer must balance the benefit from detecting

Clinical metastases: castrate first line Clinical metastases: castrate second line Clinical metastases: castrate third line Detectable metastases and treating clinically significant cancers that, left untreated, would adversely affect a patient’s quality and duration of life, against the morbidity associated with the overtreatment of clinically insignifi cant cancers highly prevalent in the general population. The balance is best approached through shared decision-making between the patient and physician; however, the complexities of the subject and the limited time available for most primary care physicians often preclude truly informed decisions. Considerations regarding whether to pursue a diagnosis include symptoms, an abnormal DRE, or more typically, a change in or elevated serum PSA. Genetic risk and family history are also relevant in the decision-making process, and those with a family history of lethal cancer represent patients of particular concern. PHYSICAL EXAMINATION The digital rectal exam (DRE) focuses on prostate size, symmetry, consistency, and abnormalities within and/or beyond the gland. Most cancers occur in the peripheral zone and may be palpated on DRE. Carcinomas are characteristically hard, nodular, irregular, and often result in an asymmetric DRE finding. Induration may also be due to benign prostatic hyperplasia (BPH) or calculi. Over all, 20–25% of patients with an abnormal DRE have prostate cancer. The DRE is a not accepted as a validated prostate cancer screening test given the frequent false positives and false negatives associated with this exam. PROSTATE-SPECIFIC ANTIGEN PSA (kallikrein-related peptidase 3; KLK3) is a kallikrein-related serine protease that causes liquefaction of seminal coagulum. It is produced by both nonmalignant and malignant epithelial cells and, as such, is prostate specific, not prostate cancer specific. Serum levels of PSA may increase from prostatitis, BPH, or prostate cancer. PSA circulating in the blood is inactive and mainly occurs as a complex with the protease inhibitor α1-antichymotrypsin and as free (unbound) PSA forms. A lower free PSA is more likely to be associated with cancer at the time of biopsy. PSA levels should be undetectable after about 6 weeks if the prostate has been completely removed (radical prostatectomy). If there is no prostate, there should be no detectable PSA. Persistence of measurable serum PSA after pros tate removal is typical of recurrent cancer. PSA testing was approved by the U.S. Food and Drug Administra tion (FDA) in 1994 for early detection of prostate cancer, and the widespread use of the test has played a significant role in the propor tion of patients diagnosed with early-stage cancers: today, >70–80% of

newly diagnosed cancers are clinically organ confined. The level of PSA in blood is strongly associated with the risk and outcome of prostate

cancer. A single PSA measured at age 60 is associated (area under the curve [AUC] of 0.90) with lifetime risk of death from prostate cancer. Most (90%) prostate cancer deaths occur among patients with PSA lev els in the top quartile (>2 ng/mL), although only a minority of patients with PSA >2 ng/mL will develop lethal prostate cancer. Despite this and mortality rate reductions reported from large, randomized prostate cancer screening trials, routine use of the test remains controversial given both false positives and false negatives and the fact that PSA test ing may lead to the diagnosis and treatment of indolent cancers that pose little risk to the patient’s overall

health. The U.S. Preventive Services Task Force (USPSTF) current guideline states, “For men aged 55 to 69 years, the decision to undergo periodic PSA-based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an oppor tunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision.” The USPSTF recommends against screening men aged 70 or older. The USPSTF guideline can be accessed at https://www.uspreven tiveservicestaskforce.org/uspstf/draft-update-summary/prostate-cancerscreening-adults. The American Urologic Association (AUA) guidelines indicate that “clinicians should engage in shared decision-making with people for whom prostate cancer screening would be appropriate and proceed based on a person’s values and preferences.” In contrast to the USPSTF, the AUA guidelines state that “clinicians should offer prostate cancer screening beginning at age 40 to 45 years for people at increased risk of developing prostate cancer based on the following factors: Black ancestry, germline mutations, strong family history of prostate cancer.” Further, “clinicians should offer regular prostate cancer screening every 2 to 4 years to people aged 50 to 69 years.” The current AUA guide lines are available at https://www.auanet.org/guidelines-and-quality/ guidelines/early-detection-of-prostate-cancer-guidelines. There is no rationale for recommending PSA screening in asymp tomatic patients with a short life expectancy. Hence, patients over the age of 70 should only be tested in selected circumstances, such as a higher than median PSA measured before age 70 or excellent overall health. In addition, because a baseline PSA is a strong predictor of the future risk of lethal prostate cancer, patients with low PSAs, for example <1 ng/mL, can undergo testing less frequently, perhaps every 4 years, with screening possibly ending at age 60 if the PSA remains at ≤1 ng/mL Though early detection of prostate cancer can potentially reduce the risk of prostate cancer death, high proportions of patients with screendetected prostate cancer may not need immediate treatment and can be managed by active surveillance. The goal of prostate cancer screening should be to maximize the benefits of early cancer detection among patients who can benefit from treatment and minimize its harms. The PSA criteria used to recommend additional testing have evolved over time. However, based on the commonly used cut point (a total PSA ≥4 ng/mL), most patients with a PSA elevation do not have histologic evidence of prostate cancer at biopsy. In addition, many patients with PSA levels below this cut point harbor cancer cells in their prostate. Information from the large Prostate Cancer Prevention Trial demonstrates that there is no PSA below which the risk of prostate cancer is zero. Thus, the PSA level helps establish the likelihood that a person will harbor cancer if he undergoes a prostate biopsy. The goal is to increase the sensitivity of the test for younger patients harboring clinically significant cancers that may shorten survival and to reduce the frequency of detecting cancers of low malignant potential in patients more likely to die of other causes. Patients with symptomatic bacterial prostatitis should have a course of antibiotics before biopsy. However, the routine use of antibiotics in an asymptomatic person with an elevated PSA level is discouraged. SECOND-LINE SCREENING TESTS Several tests have been developed to better stratify patients with an elevated PSA test into those more or less likely to have clinically significant prostate cancer. The 4K Score Test

(OPKO Lab, Nashville, TN) measures four prostate-specific kallikreins (total PSA, free PSA, intact PSA, and human kallikrein 2). The results are combined with clinical information in an algorithm that estimates an individual’s percent risk of having an aggressive prostate cancer should that individual opt for a prostate biopsy.

The Prostate Health Index (PHI; Innovative Diagnostic Laboratory, Richmond, VA) is a blood test that estimates the risk of having prostate cancer. The PHI test is a combination of free PSA, total PSA, and the [–2]proPSA isoform of free PSA. These three tests are combined in a formula that calculates the PHI score. The PHI score is a better predic tor of prostate cancer than the total PSA test alone or the free PSA test alone. Urine-based testing measuring exosomes (ExoDx Prostate Test) or mRNA levels of prostate cancer–related genes (Select-MDx) are also available. The most important current test to stratify risk after detection of an elevated PSA is multiparametric prostate magnetic resonance imaging (mpMRI). The mpMRI varies from a traditional magnetic resonance imaging (MRI) by including not only the T1/T2-weighted images but also measurement of diffusion-weighted imaging with or without dynamic contrast enhancement. Using a structured reading system termed the Prostate Imaging Reporting and Data System (PI-RADS), patients can be risk stratified to determine the risk of clinically sig nificant cancer. Data indicate that men with a PI-RADS 1–2 lesion can safely avoid biopsy, whereas patients with a PI-RADS 3–5 lesion can have targeted biopsies that are more likely to yield a true sense of the findings within the gland. The addition of an mpMRI in the prebiopsy decision-making unequivocally reduces the number of patients under going biopsy and reduces the diagnosis of Gleason 6 (grade group 1) cancers, without compromising the diagnosis of clinically relevant can cers. Today, an mpMRI of the prostate should be obtained in most cases prior to performing a prostate biopsy. Doing so will reduce the number of patients who are recommended to have a biopsy and improve the accuracy of the biopsies that are performed. CHAPTER 92 Benign and Malignant Diseases of the Prostate PROSTATE BIOPSY A diagnosis of cancer is established by an imageguided needle biopsy. Direct visualization of the gland by transrectal ultrasound (TRUS), MRI, or fusion of the ultrasound and MRI images ensures that all areas of the gland, including suspicious areas, are sampled. Contemporary schemas advise an extended-pattern 12-core biopsy that includes sampling from the peripheral zone as well as a lesion-directed palpable nodule or suspicious image-guided sampling. MRI-guided biopsy is superior to that of ultrasound-guided biopsy in terms of ascertaining an accurate depiction of the prostate pathology. Patients with an elevated PSA and a negative biopsy should continue to be followed as a negative biopsy does not rule out a future diagnosis of cancer. PATHOLOGY Each core of the biopsy is examined for the presence of cancer, and the amount of cancer should be quantified based on the length of the cancer within the core and the percentage of the core involved. Of the cancers identified, >95% are adenocarcinomas; the rest are squamous or transitional cell tumors or, rarely, carcinosarco mas or small-cell histologies. Metastases to the prostate are rare, but colon cancers or transitional cell tumors of the bladder can invade the gland by direct extension. When prostate cancer is diagnosed, a measure of histologic aggres siveness is assigned using the Gleason grading system, in which the dominant and secondary glandular histologic patterns are scored from 1 (well differentiated) to 5 (undifferentiated) and summed to give a total score of 6–10 for each tumor. The most poorly differentiated area of tumor (i.e., the area with the highest histologic grade) often determines biologic behavior. The presence or absence of perineural invasion and extracapsular spread should also be recorded. Over the years, the Gleason grading system has undergone several changes. Currently, Gleason total scores of 2–5 are no longer assigned, and in practice, the lowest total score now assigned is 6. This leads to a logical yet incorrect assumption on the part of patients that a Gleason 6 cancer is in the middle of the scale, triggering the fear that their can cer is serious and the assumption that treatment is necessary despite

TABLE 92-1 TNM Classification TNM (tumor, node, metastasis) Staging System for Prostate Cancera Tx Primary tumor cannot be assessed T0 No evidence of primary tumor Localized Disease T1 Clinically inapparent tumor, neither palpable nor visible by imaging T1a Tumor incidental histologic finding in ≤5% of resected tissue; not palpable T1b Tumor incidental histologic finding in >5% of resected tissue T1c Tumor identified by needle biopsy (e.g., because of elevated PSA) T2 Tumor confined within prostateb T2a Tumor involves half of one lobe or less T2b Tumor involves more than one half of one lobe, not both lobes T2c Tumor involves both lobes Local Extension T3 Tumor extends through the prostate capsulec T3a Extracapsular extension (unilateral or bilateral) T3b Tumor invades seminal vesicles T4 Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall PART 4 Oncology and Hematology Metastatic Disease N1 Positive regional lymph nodes M1 Distant metastases aRevised from SB Edge et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010. bTumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c. cInvasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2. Abbreviation: PSA, prostate-specific antigen. Gleason score 6 being favorable risk. To address these issues, a new five-grade group system has been developed: Grade group 1 (Gleason score ≤6) Grade group 2 (Gleason score 3 + 4 = 7) Grade group 3 (Gleason score 4 + 3 = 7) Grade group 4 (Gleason score 4 + 4 = 8) Grade group 5 (Gleason scores 9 and 10) The new system simplifies the grading of prostate cancer, appropri ately classifying the lowest risk as grade group 1 (rather than Gleason score 6), and accurately predicts prognosis. PROSTATE CANCER STAGING The TNM (tumor, node, metastasis) staging system includes categories for cancers that are identified solely based on an abnormal PSA (T1c), those that are palpable but clinically confined to the gland (T2), and those that have extended outside the gland (T3 and T4) (Table 92-1 and Fig. 92-2). DRE alone is inaccurate A B C D FIGURE 92-2 T stages of prostate cancer. A. T1—Clinically inapparent tumor, neither palpable nor visible by imaging. B. T2—Tumor confined within prostate. C. T3—Tumor extends through prostate capsule and may invade the seminal vesicles. D. T4—Tumor is fixed or invades adjacent structures. Eighty percent of patients present with local disease (T1 and T2), which is associated with a 5-year survival rate of 100%. An additional 12% of patients present with regional disease (T3 and T4 without metastases), which is also associated with a 100% survival rate after 5 years. Four percent of patients present with distant disease (T4 with metastases), which is associated with a 30% 5-year survival rate. (Three percent of patients are ungraded.)

in determining the extent of disease within the gland, the presence or absence of capsular invasion, involvement of seminal vesicles, and extension of disease to lymph nodes. Unfortunately, no single test has been proven to perfectly indicate the stage or the presence of organconfined disease, seminal vesicle involvement, or lymph node spread in part due to fact that cancer cells can microscopically spread below the limits of sensitivity for any imaging test. That said, mpMRI imag ing can often reveal evidence of extracapsular spread or seminal vesicle invasion with a higher degree of accuracy than DRE, and taking MRI findings into account is typically done in staging today. Prognosis and classification for nonmetastatic prostate cancer are typically done in three broad categories (low, intermediate, and high risk). Low-risk tumors are confined to the prostate with a PSA of <10 ng/mL and grade group 1. Intermediate-risk tumors are confined to the prostate, have a PSA between 10 and 20 ng/mL, or are grade group 2 or 3 (Gleason 7). This category is typically divided into a “favor able” and “unfavorable” intermediate risk depending on

grade group 2 (favorable) or 3 (unfavorable) and number of positive biopsies (>50% of cores positive for cancer is unfavorable). High-risk tumors extend outside the prostate, have a PSA >20 ng/mL, or are grade group 4 or 5 (Gleason 8–10). There is also a subset of high-risk tumors termed “very high risk” in which the cancer extends into the seminal vesicles (T3b) or adjacent organs, i.e., rectum or bladder (T4), or there are multiple biopsy samples with high-grade cancer. Computed tomography (CT) lacks sensitivity and specificity to detect extraprostatic extension and is inferior to MRI in visualization of lymph nodes. In general, mpMRI is superior to CT to detect cancers in the prostate, to assess local disease extent, and fused with ultrasound imaging, to guide sites to biopsy within the gland. Thus, mpMRI can be quite useful for the planning of surgery and radiation therapy. The use of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scans has radically altered the assessment of prostate cancer spread beyond the prostate. This scan is now FDA approved for patients with intermediate- and high-risk prostate cancer and is substantially more sensitive and accurate in the detection of metastases as compared to conventional imaging (including MRI). Currently, state-of-the-art staging for Gleason grade group 3 and higher patients involves PSMA PET imaging before treatment. PSMA PET scans significantly improve specificity over conventional imaging while maintaining comparable sensitivity. PSMA PET scans are not capable of detecting low-volume microscopic disease. In studies where surgically removed lymph nodes were assessed for metastatic prostate cancer, sensitivity was consistently <50%. Simply stated, PET scans cannot detect microscopic disease (<2 mm focus), and a negative scan cannot rule out the possibility of cancer spread. We emphasize that no test is capable of microscopic cancer detection and note that a “nega tive” scan is not equated with the definitive absence of cancer. Radionuclide bone scans (bone scintigraphy) have been used in the past to evaluate spread to osseous sites. This test is insensitive relative to PSMA PET and nonspecific because it does not detect the cancer itself, only reaction of the bone in the presence of the cancer. Staging

early-stage cancers with a bone scan is much less effective than using PSMA PET, and most centers no longer routinely use bone scans for initial staging in patients with suspected localized cancer given its known insensitivity and propensity for false-positive findings. TREATMENT Prostate Cancer CLINICALLY LOCALIZED PROSTATE CANCER Patients with clinically localized disease are typically managed by radical prostatectomy, radiation therapy, or active surveillance. Choice of therapy requires the consideration of several factors: the presence of symptoms, the probability that the untreated tumor will adversely affect the quality or duration of survival, and the probability that the tumor can be cured by single-modality therapy directed to the prostate versus requiring combinations of both local and systemic therapy. There is no clear evidence for the superiority of any one form of local therapy relative to another. This is due to the lack of prospec tive randomized trials, referral bias and physician bias, variation in the experience of the treating teams, and differences in trial end points and the definitions of cancer control. Often, PSA relapsefree survival is used because an effect on metastatic progression or survival may not be apparent for years (if ever). A PSA recurrence does not necessarily mean that the disease will cause symptoms or shorten survival. The rate at which PSA doubles (PSA doubling time [PSADT]) is an important predictor of future clinical impact. Those with a PSADT of 14 months or greater are at low risk of clinical consequences, while those with a more rapid PSADT, espe cially those with a doubling time of 3 months or less, are at much higher risk for future clinically relevant events. Understanding the PSADT and the age/comorbidities of the patient is essential for decision-making. After radical surgery to remove all prostate tissue, PSA should become undetectable in the blood within 6

weeks. If PSA remains or becomes detectable after radical prostatectomy, the patient is considered to have persistent or recurrent disease. A patient with no prostate should have no detectable PSA. After radiation therapy, in contrast, PSA does not become undetectable because the remaining nonmalignant elements of the gland continue to produce PSA even if the cancer cells have been eliminated. Similarly, cancer control is not well defined by PSA for a patient managed by active surveillance. For patients with an intact prostate and a PSA of <10 ng/mL, the fluctuations in PSA are more reflec tive of the benign rather than malignant cells in the prostate. Other outcomes are time to objective progression (local or systemic), cancer-specific survival, and overall survival; however, these out comes may take years to ascertain; thus, studies of localized disease are necessarily large, long, and often quite expensive. The more extensive the local disease, the higher the probability of regional lymph node involvement (even when imaging studies are normal), the lower the probability of local control, and the higher the probability of relapse and the development of metastases. More important is that within the categories of clinical stage T1, T2, and T3 disease are cancers with a range of prognoses. Some T3 tumors are curable with therapy directed solely at the prostate, and some T1 lesions have a high probability of systemic relapse that requires the integration of local and systemic therapy to achieve cure. For T1c cancers, stage alone is inadequate to predict outcome and select treatment; other factors (especially Gleason score) must be considered. Genomic stratification of risk is increasingly viewed as important, and tools such as transcriptomic profiling may one day be routinely used in addition to traditional pathology. To better assess risk and guide treatment selection, many groups have developed prognostic models or nomograms that use a com bination of the initial clinical T stage, biopsy Gleason score, number of biopsy cores in which cancer is detected, and baseline PSA. Not all variables are equally important, and Gleason score is required

to make accurate prognostication. Some prognostic models use discrete cut points, as mentioned above (PSA <10 or ≥10 ng/mL; Gleason score of ≤6, 7, or ≥8), while others employ nomograms that use PSA and Gleason score as continuous variables. More than 100 nomograms have been reported to predict (1) the probability that a clinically significant cancer is present, (2) disease extent (organconfined vs non–organ-confined, node-negative or -positive), or (3) the relative probability of treatment success for specific local therapies using pretreatment variables.

Exactly what probability of success or failure would lead a physi cian to recommend and a patient to seek alternative approaches is controversial and highly dependent on the age and comorbidities of the patient. As an example, it may be appropriate to recommend radical surgery for a younger patient with intermediate-risk disease, while recommending surveillance for an older patient with a tumor having identical characteristics. Nomograms and various biomark ers are being refined continually to incorporate additional clinical parameters and biologic determinants that can affect outcomes, making treatment decisions a dynamic process. Patient prefer ences are also critically important in shared decision-making. Side effects of therapy are not the same for various treatment options, and patient preferences for one approach or another may require careful discussions that extend beyond the simple calculations of risk and benefit. CHAPTER 92 Radical Prostatectomy The goal of radical prostatectomy is to excise the cancer completely with a clear margin, to maintain conti nence by preserving the external sphincter, and to preserve potency by sparing the autonomic nerves in the neurovascular bundle. The procedure is advised for patients with a life expectancy of 10 years or more with a Gleason score 7 or higher disease. Radical prostatectomy can be performed via a retropubic or perineal approach or via a min imally invasive

robotic-assisted or handheld laparoscopic approach. Outcomes can be predicted using postoperative nomograms that consider pretreatment factors and the pathologic findings at surgery. PSA failure is usually defined as a value >0.1 or 0.2 ng/mL, but as stated above, the patient without a prostate should typically have no detectable PSA. Specific criteria to guide the choice of one surgical approach over another are lacking. Minimally invasive approaches offer the advantage of a shorter hospital stay and reduced blood loss. Rates of cancer control, recovery of continence, and recovery of erectile function are comparable for robotic and open surgery. The individual surgeon, rather than the surgical approach used, is most important in determining outcomes after surgery. Benign and Malignant Diseases of the Prostate Neoadjuvant hormonal treatment with gonadotropin-releasing hormone (GnRH) agonists/antagonists alone has also been explored to improve the outcomes of surgery for high-risk patients using a variety of definitions. The results of several large trials evaluating 3 or 8 months of androgen depletion before surgery have not been shown to improve clinically relevant outcomes. Currently, neoadju vant hormonal therapies are not considered to be standard of care for surgically treated patients. Factors associated with incontinence following radical prosta tectomy include older age and membranous urethral length, which impacts the ability to preserve the urethra beyond the apex and the distal sphincter. The skill and experience of the surgeon are also critical factors. The likelihood of recovery of erectile function is associated with younger age, quality of erections before surgery, and the absence of damage to the neurovascular bundles. In general, erectile func tion begins to return ~6 months after surgery if neurovascular tissue has been preserved. Potency is reduced by half if at least one neurovascular bundle is sacrificed. Overall, with the availability of drugs such as sildenafil, intraurethral inserts of alprostadil, and intracavernosal injections of vasodilators, many patients recover satisfactory sexual function. Radiation Therapy Radiation therapy is given by external beam, by radioactive sources implanted into the gland, or by a combina tion of the two techniques.

Contemporary external beam intensity-modulated radiation therapy (IMRT) permits shaping of the dose and allows the delivery of higher doses to the prostate and a dramatic reduction in normal tissue exposure compared to three-dimensional conformal treat ment alone. These advances have enabled the safe administration of doses >78 Gy and resulted in higher local control rates and fewer side effects. Proton beam radiation has not been demonstrated to have superior outcomes as compared to conventional radiation with IMRT. Lack of randomized studies prevents the use of routinely adopting proton beam as a standard of care.

Cancer control after radiation therapy has been defined by vari ous criteria, including a decline in PSA to <0.5 or 1 ng/mL, “non rising” PSA values, and (rarely) a negative biopsy of the prostate

2 years after completion of treatment. The standard definition of biochemical failure is a rise in PSA by ≥2 ng/mL higher than the lowest PSA achieved; however, newer data question whether the cut off should be lower, particularly in those with higher grade cancers. Radiation dose is critical to the eradication of prostate cancer. In a representative study, a PSA nadir of <1.0 ng/mL was achieved in 90% of patients receiving 81.0 Gy versus 76% and 56% of those receiving 70.2 and 64.8 Gy, respectively. Positive biopsy rates at 2.5 years were 4% for those treated with 81 Gy versus 27% and 36% for those receiving 75.6 and 70.2 Gy, respectively. Higher doses of radiation, however, may be associated with a higher risk of adverse events. PART 4 Oncology and Hematology Hypofractionation schedules, utilizing fewer treatments of higher radiation doses, have been

evaluated and shown to provide good cancer control rates based on posttreatment biopsies showing no evidence of cancer, with no apparent increase in treatmentrelated morbidity. Hypofractionated treatments can range from as few as 5 treatments to upward of 26 treatments, with both regimens representing substantial reductions in treatment length. Multiple clinical trials have evaluated the use of androgen depri vation therapy (ADT) in combination with radiation. In patients with unfavorable intermediate-risk prostate cancer, short-course ADT (6 months), when combined with external beam radiotherapy, has demonstrated significant improvements in overall survival. Higher doses of radiation cannot substitute for ADT. In patients with high-risk localized disease, longer courses of ADT (18–36 months) have proven superior to shorter courses and represent the current standard of care when combined with radiotherapy. Novel genomic and transcriptomic biomarkers are being explored to assess the responsiveness of tumors to ADT, but as of yet, there are no accepted biomarkers that determine who should or should not receive ADT. Artificial intelligence assessments are promising, and new assays suggest the possibility that prostate cancers treated with radiation can be stratified into those that do and do not benefit from androgen deprivation. For patients with nonmetastatic cancer by conventional imaging (bone scan, CT, or MRI) and two or more high risk factors (Gleason 8–10, stage T3/T4, or PSA ≥40 ng/mL) or positive pelvic lymph nodes, a large randomized trial demonstrated that the addition of abiraterone/prednisone to 2 years of ADT and radiotherapy is supe rior to 3 years of ADT and radiotherapy. This study defined a new standard of care for these particularly high-risk patients. The Prostate Testing for Cancer and Treatment (ProtecT) trial investigated the effects of active monitoring, radical prostatectomy, and radical radiotherapy with hormones on patient-reported out comes in patients diagnosed with predominantly low-risk prostate cancer (~75% with Gleason score 6 or grade group 1 cancer). Cancer outcomes were essentially the same for these three approaches. Patient-reported outcomes among 1643 patients who completed questionnaires before diagnosis, at 6 and 12 months, and annually thereafter were compared. Of the three treatments, prostatectomy had the greatest negative effect on sexual function and urinary continence, and although there was some recovery, these outcomes remained worse in the prostatectomy group than in the other groups throughout the trial. The negative effect of radiotherapy on sexual function was greatest at 6 months, but sexual function

then recovered somewhat and was stable thereafter; radiotherapy had little effect on urinary continence. Sexual and urinary function declined gradually in the active-monitoring group. Bowel function was worse in the radiotherapy group at 6 months than in the other groups but then recovered somewhat, except for the increasing fre quency of bloody stools; bowel function was unchanged in the other groups. Urinary voiding and nocturia were worse in the radio therapy group at 6 months but then mostly recovered and were like the other groups after 12 months. Effects on quality of life mirrored the reported changes in function. No significant differences were observed among the groups in measures of anxiety, depression, or general health-related or cancer-related quality of life. Taken together, both surgery and radiation had clear side effects, but these side effects were distinct. Brachytherapy Brachytherapy is the direct implantation of radio active sources into the prostate. It is based on the principle that the deposition of radiation energy in tissues decreases as a function of the square of the distance from the source (Chap. 78). The goal is to deliver intensive irradiation to the prostate, minimizing the exposure of the surrounding tissues. The current standard tech nique achieves a more homogeneous dose distribution by delivering radiation according to a customized template based on imaging assessment of the cancer and computer-optimized dosimetry. The implantation is typically performed transperineally

as an outpatient procedure with real-time imaging. Improvements in brachytherapy techniques have resulted in fewer complications and a marked reduction in local failure rates. In a series of 197 patients followed for a median of 3 years, 5-year actuarial PSA relapse–free survival for patients with pretherapy PSA levels of 0–4, 4–10, and >10 ng/mL were 98, 90, and 89%, respectively. In a separate report of 201 patients who underwent posttreatment biopsies, 80% were negative, 17% were indetermi nate, and 3% were positive. The results did not change with longer follow-up. Brachytherapy is well tolerated, although most patients experience urinary frequency and urgency that can persist for several months. Higher complication rates are observed in patients who have undergone a prior transurethral resection of the prostate (TURP), while those with obstructive symptoms at baseline are at a higher risk for retention and persistent voiding symptoms. Proctitis has been reported in <2% of patients. Like surgery, brachytherapy is best performed by those well-practiced in the technique. Active Surveillance With the advent of PSA testing, many patients are diagnosed with low-risk prostate cancers that may not pose a threat to either the quantity or quality of a person’s life. Active surveillance, described previously as watchful waiting or deferred therapy, initially evolved from (1) studies that evaluated predominantly elderly patients with well-differentiated tumors (Gleason 6 or grade group 1) who remained untreated and demon strated no clinically significant progression for protracted periods, (2) recognition of the contrast between incidence and disease-

specific mortality, (3) the high prevalence of autopsy cancers, and (4) an effort to reduce overtreatment and treatment-related side effects. In practice, active surveillance is the treatment recom mended to patients with cancers of low aggressiveness that can be safely monitored at fixed intervals with DREs, PSA measurements, imaging (best done with prostate mpMRI), and repeat prostate biopsies as indicated until histopathologic or serologic changes correlative of progression warrant treatment with curative intent. It is important to recognize that no treatment has proven superior to active surveillance for those with PSA-detected grade group 1 (Gleason score 6) disease. Surveillance remains underutilized today, and needless morbidity can result from overtreatment of those who have little chance to benefit from therapy given the indolent nature of the vast majority of patients with Gleason 6 localized disease. Case selection is critical, and determining the clinical parameters predictive of cancer aggressiveness that can be used to reliably select patients most likely to benefit from active surveillance is an area of intense study. One set of criteria includes patients with clinical T1c

tumors that are biopsy Gleason grade 6. Nomograms to help predict which patients can safely be managed by active surveillance con tinue to be refined, and as their predictive accuracy improves, it can be anticipated that more patients will be candidates. Older patients and those with substantial comorbidities can have more permissive criteria for surveillance including those with Gleason 3 + 4 = 7 (grade group 2) localized disease. Treatment decision-making for all localized prostate cancers depends on both the characteristics of the cancer and the age and comorbidities of the patient. Anxiety remains a problem for some patients with untreated cancers, and management of that anxiety can at times be problematic. RISING PSA AFTER DEFINITIVE LOCAL THERAPY Patients in this state include those in whom the sole manifestation of disease is a rising PSA after surgery and/or radiation therapy. For most of these patients in the initial phases, there is no evidence of disease on imaging studies. For these patients, the central issue is whether the rise in PSA results from persistent disease in the pri mary site, systemic disease, or both. Disease in the primary site may still be curable by additional local treatment. The decision to recommend

radiation therapy after prosta tectomy is guided by the age and comorbidities of the patient, pathologic findings at surgery, the timing of PSA failure, the PSA doubling time, and the PSA level at the time of failure. Traditional imaging (MRI, CT, and radionucleotide bone scans), especially at low levels of PSA, is typically uninformative, but newer imaging methods may or may not be useful. New PET tracers such as 18F-fluciclovine and 18F- or 68Ga-PSMA that directly image the cancer are more sensitive and can detect low-volume disease in the prostate bed or other sites to better inform the decisions regarding treatment. Detection rates, both in and outside the prostate bed, correlate with the absolute level of PSA and the rate of PSA rise. Factors that predict for response to salvage radiation therapy after radical prostatectomy are a positive surgical margin, lower Gleason score in the surgical specimen, a long interval from surgery to PSA failure, slower PSA doubling time, a low (<0.5 ng/mL) PSA value at the time of radiation treat ment, and the absence of distant disease when using a PSMA or fluciclovine PET scan. For patients with a rising PSA after radiation therapy, salvage local therapy can be considered if persistent disease has been docu mented by a biopsy of the prostate and if no disease is detectable outside of the prostate bed or regional lymph nodes by imaging. Unfortunately, case selection is poorly defined in most series. Local treatment options for patients with recurrence after radiation include salvage radical prostatectomy, salvage cryotherapy, salvage radiation therapy, and salvage high-intensity focused ultrasound. Unfortunately, morbidities can be significant in the postradiated patient. A rise in PSA after surgery or radiation therapy may indicate subclinical or micrometastatic disease with or without local recur rence. The need for treatment depends, in part, on the estimated probability that the patient will develop clinical symptoms and in what time frame. That immediate therapy is not always required was shown in a well-annotated series where patients who developed a rising PSA after radical prostatectomy received no systemic ther apy until metastatic disease was documented. Overall, the median time to metastatic progression was 8 years, and 63% of the patients with rising PSA values remained free of metastases at 5 years. Fac tors associated with progression included the Gleason score of the radical prostatectomy specimen, time to recurrence after surgery, and PSADT. For those with Gleason score ≥8, the probability of metastatic progression was 37, 51, and 71% at 3, 5, and 7 years, respectively. If the time to recurrence was <2 years and PSADT was long (>10 months), the proportions with metastatic disease at the same time intervals were 23, 32, and 53%, versus 47, 69, and 79% if the doubling time was short (<10 months). PSADTs are also prognostic for survival. Most physicians advise treatment when PSA doubling times are ≤10 months. A difficulty

with predicting the risk of metastatic spread, symptoms, or death from disease in the rising PSA state is that many patients receive some form of therapy before the development of metastases as detected by conventional imaging. Nevertheless, predictive models continue to be refined with a consensus that lower risk patients can be watched, whereas higher risk patients may require some inter vention. Given that new molecular imaging techniques are now FDA approved, the interplay between imaging and risk continues to be refined.

METASTATIC DISEASE: NONCASTRATE The state of noncastrate metastatic disease includes patients with metastases visible on an imaging study at the time of diagnosis or after local therapy(ies) who have noncastrate levels of testosterone (>50 ng/dL). The prognosis is distinct for those with metastases detected by conventional imaging versus those detected only with molecular imaging. Symptoms of metastatic disease may include pain from osseous spread, although many patients are asymptom atic despite extensive spread. Less common are symptoms

related to weight loss, fatigue, malaise, lymphedema, marrow infiltration by tumor (myelophthisis), coagulopathy, blood clots, or spinal cord compression. Standard treatment is to deplete or lower androgens via ADT by medical or surgical means, the latter being the least acceptable to patients. More than 90% of male hormones originate in the testes; <10% are synthesized in the adrenal gland (Fig. 92-3). CHAPTER 92 Testosterone-Lowering Agents Medical therapies that lower tes tosterone levels include the GnRH agonists/antagonists, pure GnRH antagonists, 17,20-lyase inhibitors, CYP17 inhibitors, and estrogens such as oral diethylstilbestrol (DES) (Fig. 92-3). DES is not utilized today due to the excessive risk of vascular complica tions that include fluid retention, phlebitis, emboli, and stroke. GnRH agonists, such as leuprolide acetate and goserelin acetate, ini tially produce a very brief rise in luteinizing hormone and folliclestimulating hormone followed by a downregulation of receptors in the pituitary gland, which causes a chemical castration. Regulatory approval was based on randomized trials showing reduced cardio vascular toxicities relative to DES, with equivalent potency. The ini tial rise in testosterone may occasionally result in a clinical flare of the disease, and as such, these agents are relatively contraindicated in patients with significant urinary obstructive symptoms, cancerrelated pain, or spinal cord compromise. AR antagonists that block testosterone binding to the receptor are commonly used to reduce the risk of flare. Increases in testosterone do not occur with GnRH antagonists such as degarelix, given by injection, or relugolix, given orally, and these agents as well as abiraterone acetate rapidly achieve castrate levels of testosterone. Benign and Malignant Diseases of the Prostate Agents that lower testosterone are associated with an androgendeprivation syndrome that includes hot flushes, weakness, fatigue, loss of muscle mass, risk of osteoporosis and fracture, anemia, changes in cognition and personality, and depression. Changes in lipids, obesity, and insulin resistance and an increased risk of diabetes and cardiovascular disease may also be seen, along with a decrease in bone density that worsens over time and may result in an increased risk of clinical fractures. This is a particular concern in patients with preexisting osteopenia that results from hypogonadism that may be worsened with steroid or alcohol use and significantly underappreciated. Baseline fracture risk can be assessed using the FRAX scale, and to minimize fracture risk, patients can be advised to take a bisphosphonate or RANK-ligand inhibitor (denosumab) in combination with calcium and vitamin D supplementation. Hot flushes may be ameliorated by oxybutynin or certain antidepressants such as venlafaxine. Antiandrogens Nonsteroidal first-generation antiandrogens such bicalutamide and nilutamide have largely been replaced by the more potent next-generation agents (enzalutamide, apalutamide, and darolutamide) that do not lower serum androgen levels and result in fewer hot flushes, less of an effect on libido, less muscle wasting, fewer personality changes, and less bone loss relative to

Hypothalamus GnRH CRH Pituitary GnRH agonists GnRH antagonists Degarelix Relugolix Estrogens Prednisone ACTH LH Testis Adrenal glands CYP17 inhibitors abiraterone PART 4 Oncology and Hematology Testosterone Androstenedione DHEA DHEA-S Dutasteride Prostate DHT Prostate cell Next generation anti-androgens AR Enzalutamide Apalutamide Darolutamide AR AR DHT AR Prostate cell nucleus AR DHT ARE DNA FIGURE 92-3 Sites of action of different hormone therapies. testosterone-lowering therapies. However, over time, testosterone levels increase and are converted to estrogen, which can result in mastalgia and gynecomastia that limits long-term use. The side effect of antiandrogens as monotherapy can be prevented in part by tamoxifen, aromatase inhibitors, or prophylactic breast irradiation. Most reported randomized trials in metastatic patients suggest that the cancer-specific outcomes are inferior when antiandrogens are used alone. Bicalutamide, even at a dose of 150 mg (three times the approved dose for use in

combination in GnRH agonists),

resulted in a shorter time to progression and inferior survival com pared to surgical castration for patients with established metastatic disease. Newer studies for those without metastatic disease suggest that enzalutamide is appropriate in selected patients with a PSADT of 10 months or less. Improving on the outcomes with ADT alone was a focus of the field for decades. Older antiandrogens such as bicalutamide or flu tamide did not convincingly achieve these goals. Practice standards changed when an improvement in time to progression and overall survival was shown when ADT was combined with docetaxel rela tive to ADT alone. The greatest benefit was seen for patients with “high-volume” disease defined as the presence of ≥4 lesions on radionuclide bone scan or visceral disease. Longer progressionfree and overall survival times have been noted in separate phase 3 trials comparing ADT with abiraterone, a CYP17 inhibitor that blocks androgen synthesis, and ADT with the AR antagonists such as enzalutamide and apalutamide versus the ADT standard, further changing the standard of care. Intermittent Androgen Deprivation Therapy One way to reduce the side effects of androgen depletion is to administer hormonal therapy on an intermittent basis; however, the use of this approach in metastatic disease has yet to be proven useful for those being treated with ADT plus a novel hormone such as abiraterone, apalu tamide, or enzalutamide. Additional studies in the metastatic set ting with intermittent therapy are under consideration. Chemotherapy Studies with ADT plus docetaxel indicate that patients with high-volume metastatic disease benefit from the addition of docetaxel. However, more recent studies indicate that ADT and docetaxel are not appropriate choices today given that the addition of abiraterone or darolutamide is superior to that of ADT plus docetaxel. Consultation with a clinician practiced in the art of advanced prostate cancer is appropriate given the rapidly changing standards of care. Outcomes of Androgen Deprivation The anti–prostate cancer effects of the various newer androgen depletion strategies (abi raterone, apalutamide, or enzalutamide in combination with medical or surgical castration) are similar, and the clinical course is predict able: an initial response, a period of stability in which tumor cells are dormant and nonproliferative, followed after a variable period of time by a rise in PSA and regrowth that is visible on a scan as a castration-resistant lesion. Androgen depletion is not curative because cells that survive castration are present when the disease is first diagnosed. Considered by disease manifestation, PSA levels return to normal in 60–70% of patients, and measurable disease regression occurs in >50%. Duration of survival is inversely pro portional to disease extent at the time androgen depletion is first started and the nadir level of PSA at 6–8 months. Patients with nadir PSA values >4 ng/mL have markedly inferior survival times and should be considered for alternative approaches. METASTATIC DISEASE: CASTRATE Castration-resistant prostate cancer (CRPC), disease that pro gresses while the measured levels of testosterone in the blood are

50 ng/mL or lower, can produce some of the most feared complica tions of the disease and is lethal for most patients. The most com mon manifestation is a rising PSA, frequently co-occurring with progression in bone. Nodal and/or visceral progression is less fre quent. Symptoms may or may not be present. Critical for manage ment is that therapeutic objectives be based on the manifestations of the disease in the individual at the time a change in therapy is being considered. As such, for the patient with symptomatic bone disease, relief of pain can be more clinically relevant than lowering the PSA. Naturally, for all patients, the central focus is delaying or preventing disease progression, symptoms, and death from disease. Through 2010, docetaxel was the only FDA-approved life-

prolonging therapy for CRPC. Since then, our understanding of the biology of the disease has increased significantly, which in turn has led to improved therapies. It is now recognized that the majority of

metastatic CRPCs continue to express the AR and remain AR sig naling dependent. For those with progression after ADT alone, the next-generation antiandrogen enzalutamide and the CYP17 inhibi tor abiraterone acetate (given in combination with prednisone) have been proven to prolong life and are FDA approved for use in CRPC in both the pre- and postchemotherapy setting. Large-scale molecular profiling efforts have led to a biologically based disease taxonomy that continues to evolve and showed a mark edly higher than expected frequency of germline (~6% of patients) and somatic BRCA (also ~6% of patients) alterations, along with other genes in the DNA damage repair pathway that have been targeted successfully with poly-ADP ribose polymerase (PARP) inhibitors of which two, olaparib and rucaparib, are FDA approved as monothera pies. Combinations of abiraterone and olaparib are FDA approved for BRCA1/BRCA2-mutated CRPC patients, and enzalutamide/talozapa rib combinations are approved for BRCA1/BRCA2-mutated patients and other DNA repair pathway mutations. Also approved are the checkpoint inhibitors pembrolizumab and dostarlimab for tumors with high microsatellite instability (MSI) scores, mismatch repair gene deficiency, or patients with a high tumor mutational burden. These alterations are found in ~3% of prostate cancers. Other classes of therapy approved for selected CRPC patients based on demonstrated survival benefits include the biologic agent sipuleucel-T, the second-generation taxane cabazitaxel, the α-emitting bone-targeting radiopharmaceutical radium-223, and the PSMA-directed radionuclide therapy 177-lutetium PSMA-617. The use of 177-lutetium PSMA-617 has garnered intense interest given that this targeted form of radiation was able to extend sur vival in patients who had exhausted most conventional forms of therapy. Overall, an intense focus of current CRPC research is to understand the optimal sequence in which to utilize these agents to maximize benefit for the individual patient. Most of these agents are also being tested earlier in the course of the disease when tumor burdens are lower and the disease less heterogeneous. The result has been an increase in the frequency of late-state tumors that have undergone a lineage transformation from epithelial to alternative phenotypes (neuroendocrine and more) and are highly resistant to available therapies. Pain Management Pain secondary to osseous metastases is one of the most feared complications of the disease and a major cause of morbidity, worsened by the narcotics needed to control symptoms. Management requires accurate diagnoses because noncancer eti ologies including degenerative disease, spinal stenosis, and vertebral TABLE 92-2 AUA Symptom Index QUESTIONS TO BE ANSWERED NOT AT ALL Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating? 0+

Over the past month, how often have you had to urinate again less than 2 h after you finished urinating?

Over the past month, how often have you found you stopped and started again several times when you urinated?

Over the past month, how often have you found it difficult to postpone urination?

Over the past month, how often have you had a weak urinary stream?

Over the past month, how often have you had to push or strain to begin urination?

Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning? (None) (1 time) (2 times) (3 times) (4 times) (5 times) Sum of 7 circled numbers (AUA Symptom Score): ____ Abbreviation: AUA, American Urological Association. Source: Modified with permission from MJ Barry et al: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 148:1549, 1992.

collapse secondary to bone loss are common. Neurologic symptoms, including those suggestive of base of skull disease or spinal cord compromise, require emergency evaluation because loss of function may be permanent if not addressed quickly. Neurologic symptoms and loss of function are best treated with external beam radiation, as are single sites of pain. Diffuse symptoms in the absence of neu rologic deficits can be treated with bone-seeking radioisotopes, such as radium-223 or the β emitter 153Sm–ethylene-diamine-tetrameth ylene-phosphonic acid (EDTMP); mitoxantrone; or other systemic therapies. Radium-223 is indicated for patients with symptoms and has been shown to prolong survival, whereas 153Sm-EDTMP and mitoxantrone are approved for the palliation of pain but have not been shown to prolong life. Abiraterone, enzalutamide, docetaxel, cabazitaxel, and Lu-177 PSMA-617 do not have a formal indication for pain but were shown to palliate pain in the registration trials that led to their approval by showing a survival benefit.

Other bone-targeting agents, including bisphosphonates such as zoledronic acid and the RANK-ligand inhibitor denosumab, have been shown to reduce the frequency and development of skeletal complications including pain requiring analgesia, neurologic com promise from epidural extension of tumor, and/or the need for surgery or radiation therapy to treat symptomatic osseous disease. It is important to note that, for all of these agents, the direct effects on the tumor are limited and benefits are seen without declines in PSA or improvements on imaging. CHAPTER 92 BENIGN DISEASE Benign and Malignant Diseases of the Prostate ■ ■BENIGN PROSTATIC HYPERPLASIA BPH is a pathologic process that contributes to the development of lower urinary tract symptoms (LUTS) in patients. LUTS, arising from lower urinary tract dysfunction, are further subdivided into obstruc tive symptoms (urinary hesitancy, straining, weak stream, terminal dribbling, prolonged voiding, incomplete emptying) and irritative symptoms (urinary frequency, urgency, urge incontinence, small voided volumes). LUTS and other sequelae of BPH are not just due to a mass effect but are also likely due to a combination of the prostatic enlargement and age-related detrusor dysfunction. Diagnostic Procedures and Treatment LUTS are generally measured using a validated, reproducible index that is designed to determine disease severity and response to therapy—the AUA’s Symp tom Index (AUASI), also adopted as the International Prostate Symp tom Score (IPSS) (Table 92-2). Serial AUASI is particularly useful in AUA SYMPTOM SCORE (CIRCLE 1 NUMBER ON EACH LINE) LESS THAN 1 TIME IN 5 LESS THAN HALF THE TIME ABOUT HALF THE TIME MORE THAN HALF THE TIME ALMOST ALWAYS

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