Prostate Cancer

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Faculty

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Faculty Disclosure

Contributing faculty, John J. Whyte, MD, MPH, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all physicians, nurses, surgical professionals, and social work/counseling groups involved in the care of patients with prostate cancer.

Accreditations & Approvals

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Course Objective
Although prostate cancer is the most common cancer diagnosed in men, it has a relatively good prognosis when diagnosed and treated early. The purpose of this course is to educate healthcare professionals about the epidemiology, screening, diagnosis, and treatment of prostate cancer to ensure that the disease is diagnosed early and treated properly.

Learning Objectives
Upon completion of this course, you should be able to:

1. Review the epidemiology and demographics of prostate cancer.
2. Discuss what is known about the pathophysiology of prostate cancer.
3. Discuss the associated symptoms and diagnosis of prostate cancer.
4. State the current recommendations regarding prostate cancer screening.
5. Describe the potential role of diet in reducing prostate cancer risk.
6. Discuss the role of active surveillance, surgery and radiotherapy as treatment options for localized prostate cancer.
7. Describe the role of androgen deprivation therapy for the treatment of prostate cancer.
8. Discuss the role of chemotherapy as a treatment for prostate cancer.
9. Analyze the research and use of 5-alpha reductase inhibitors as a treatment for prostate cancer.
10. Recommend interventions for men who have experienced erectile dysfunction or depression as a result of prostate cancer, including considerations for non-English-proficient patients.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men, accounting for about 27% of cancer diagnoses [1]. Although prostate cancer is the second leading cause of cancer-related deaths in men, the survival rate is high if diagnosed and treated early. However, many cases are not diagnosed until a later stage and thus may be at a lower survival rate.

Because prostate cancer has a high prevalence and significant impact on society, much research has focused on diagnosis and treatment. Some of the developments have improved outcomes associated with treatment in early stages of disease and may potentially improve outcomes in advanced cases. Healthcare professionals may not be aware of the most recent advances related to prostate cancer.

This course will review the epidemiology, diagnosis, screening, and pathophysiology of prostate cancer. It will also review the risks and benefits associated with screening and the potential role of diet in reducing risk of prostate cancer. Treatment options, including active surveillance, surgery, and radiotherapy for localized disease, and chemotherapy, androgen deprivation therapy (ADT), and 5-alpha reductase inhibitors for advanced disease, are discussed.

EPIDEMIOLOGY

Despite the advances in early detection and a decline in the death rate over the last decade, prostate cancer continues to cause substantial mortality in the United States. It ranked second among the 10 leading cancer-related causes of death for men in 2022; lung and bronchus cancer remained the number one cause [1]. The clinical incidence of prostate cancer in the United States has changed during the past several decades, increasing from less than 100 cases per age-adjusted 100,000 population in 1975 to a peak of 240 cases per 100,000 men in 1992, then fluctuating but declining (-4.0%) (averaging 155 cases per 100,000 men) between 2003 and 2012 [1; 3]. The trend has continued to decline (-7.0% per year) with 109.5 cases per 100,000 men between 2012 and 2016 [1; 3].

One in every nine American men will be diagnosed with prostate cancer at some point during his lifetime [1]. In 2022, the estimated projected number of new prostate cancer diagnoses is 268,490, and the projected number of deaths related to prostate cancer is 34,500 [1]. Prostate cancer accounts for 27.3% of all new cancer diagnoses among men [1]. The majority of newly diagnosed prostate cancers have localized disease and a good prognosis. Ninety percent of men are diagnosed with local (77%) or regional (13%) disease, and the five-year survival rate for localized or regional prostate cancer is 100% [3]. However, metastatic prostate cancer at the time of diagnosis has shown a five-year survival rate as low as 30.5% [1; 3].

The incidence of prostate cancer increases with age. According to one report of prostate cancer cases in the United States between 2012 and 2016, approximately 58% of cases were diagnosed in men 65 years of age or older [3]. Nearly 8.7% of cases were diagnosed in men between the ages of 45 and 54 years, a drastic increase from almost no cases in younger age groups [3]. Men 65 to 74 years of age represented the largest percentage of diagnosed cases (39.2%). In addition, 14.9% of cases were diagnosed in men 75 to 84 years of age, and roughly 4% of cases were found in men 85 years of age or older [3].

A meta-analysis of autopsy studies by Bell and colleagues revealed an age-dependent increase in prostate cancer [7]. Among the study group, about 15% of men 40 to 50 years of age and 59% of men older than 79 years of age had prostate cancer [7]. The analysis included 29 studies conducted between 1948 and 2013. The United States will continue to see an increase in prostate cancer as the population ages and becomes more diverse [4; 5; 6].

In regard to race and ethnicity, Black men appear to be disproportionately affected [1; 3]. An analysis of data from Surveillance, Epidemiology, and End Results (SEER) and from the North American Association of Central Cancer Registries found an age-adjusted incidence rate of prostate cancer nearly 73% higher for African Americans compared to White men. The highest prostate cancer incidence rates worldwide occur in Black men and Jamaican men of African descent, suggesting a possible inherited genetic susceptibility [6]. The increased risk seen in the Black population is believed to be multifactorial, caused by alterations in an individual's environment (e.g., diet, exposure to toxins), participation in screening, genetic background, and physiologic status (e.g., sex steroid hormone levels) [5; 8]. The SEER study's age-adjusted data confirmed the differences in race/ethnic populations. In the United States, the incidence of prostate cancer is highest among Black men (172.6 cases per 100,000), lower among White and Hispanic/Latino men (99.9 and 85.3 per 100,000), and lowest among Asian American/Pacific Islander men (55.0 per 100,000) [1].

Death from prostate cancer is also highest among Black men, with a mortality rate (37.9 per 100,000) more than twice that of other races/ethnicities (17.8 among White men, 21.0 among American Indian and Alaska Native men, 15.6 among Hispanic/Latino men, and 8.6 among Asian American and Pacific Islander men) [1]. Overall, the mortality rate from prostate cancer decreased 4.1% per year between 2009 and 2019, in part because of improvements in early detection and treatment [1].

It is interesting to note that men diagnosed with prostate cancer have higher rates of non-cancer-related mortality than men in the general population [9]. Some of this excess mortality may be attributed to treatment, such as ADT, that is used for metastatic disease [10]. Because prostate cancer that is detected and treated early has a favorable prognosis, selection of treatments is particularly important. In fact, unwanted effects of treatments (e.g., adverse effects, complications) may have a greater negative impact on overall health and quality of life than the prostate cancer itself.

PATHOPHYSIOLOGY

Almost all cases of prostate cancer are adenocarcinoma [11; 12]. According to most studies, about 4% of prostate cancer cases exhibit transitional cell morphology and may originate in the urogenital lining of the prostatic urethra [13]. A few cases of prostate cancer have neuroendocrine morphology, originating either in neuroendocrine stem cells normally present in the prostate or as a result of aberrant cell transformation whereby benign prostatic hyperplasia (BPH) develops [13].

The prostate gland consists of the prostate capsule and four zones. The transition zone typically constitutes about 5% to 10% of the glandular volume of the prostate and surrounds the urethra at the point that the ejaculatory ducts enter the gland [11; 14]. The central zone surrounds the transition zone and accounts for approximately 20% to 25% of the mass of the normal glandular prostate [11; 14]. The ejaculatory ducts pass through the central zone before entering the urethra [11]. The peripheral zone makes up about 75% of the prostatic volume in healthy adult males. It is a double row of duct buds that laterally surround the central zone, and it occupies the region of the prostate closest to the rectum [11; 14]. The anterior zone is nonglandular (primarily made of fibromuscular tissue) and constitutes about one-third of the mass within the prostatic capsule. It is an intermingled region, with fibers descending from the bladder neck and urethral sphincter [11]. It is the portion of the prostate closest to the abdomen.

Most prostate cancer cases (about 70%) originate in the peripheral zone [11; 13; 14]. The rest develop in the transitional zone (10% to 15%) and in the central zone (15% to 20%) [13]. Most men have clinically localized disease at diagnosis. The majority of cases are multifocal (i.e., multiple separate malignant groups) [15]. These multicentric lesions are often present in different zones of the prostate and typically are of different grades.

Testosterone is the main circulating androgen in men and is a significant factor involved in the physiologic development of prostate cancer [16; 17]. In the prostate and other organs, testosterone functions as a prohormone. The prostatic stromal and basal cells convert testosterone to dihydrotestosterone (DHT) [19]. This process is caused by 5-alpha reductase (5AR), an intracellular enzyme present in the prostate, skin, and liver [19]. The ratio of testosterone to DHT in blood samples is approximately 10:1, but this ratio is reversed in the prostate [18].

SYMPTOMS AND DIAGNOSIS

Men with early prostate cancer are usually asymptomatic. More advanced disease may be associated with changes in urinary habits, such as a slowing of the urinary stream, sense of incomplete voiding, nocturia, and frequency, as well as dysuria, hematuria, or pain in the lower back or pelvis. Because many of these symptoms are similar to those linked to benign prostate conditions, prostate cancer cannot be diagnosed on the basis of symptoms alone. The initial diagnostic methods are the same as those used for screening: prostate-specific antigen (PSA), digital rectal examination (DRE), and transrectal ultrasonography. In performing the DRE, the clinician should focus on the size, consistency, and abnormalities within or beyond the gland. Characteristic signs indicative of prostate cancer on DRE are focal dense (hard) areas of irregular nodularity.

Prostate cancer has been detected in asymptomatic men who have focal abnormalities in the prostate on DRE [20; 21]. As a result, there has been movement in the past several decades to expand prostate cancer screening in asymptomatic populations [22; 37]. Despite the resulting increase in early detections/diagnoses, the benefits versus the harms of aggressive detection and treatment have been re-evaluated, and screening for prostate cancer, especially in average-risk groups, is generally no longer recommended or is explicitly discouraged. In patients with more advanced presentation, there can be urinary retention and neurologic symptoms resulting from epidural metastases and cord compression [23]. Screening and assessment is usually recommended for patients with signs of prostate disease.

PROSTATE-SPECIFIC ANTIGEN LEVELS

PSA is a serine protease that liquefies the seminal fluid. Although it is found in a much greater concentration in seminal fluid, it can also be measured in serum. It is considered a more readily available and less invasive test for both screening and management of prostate cancer [22]. Unfortunately, PSA levels can also be elevated in benign prostatic conditions, such as BPH and prostatitis, leading to false-positive readings [22; 24]. In fact, inflammation itself may play a role in the pathogenesis of prostate cancer, making it difficult to exclude any relationship between prostate cancer and a palpable abnormality in another neighboring area [25].

Newer definitions of an abnormal PSA level have also been debated. Lower PSA thresholds are used now to recommend biopsy, with a corresponding increase in the number of men undergoing biopsy and the number of cancers found in men with low PSA levels [26]. A PSA level greater than 4.0 ng/mL is considered abnormal. However, a value of greater than 2.6 ng/mL has been advocated for the detection of small, organ-confined tumors [27].

When PSA levels are found to be outside of normal limits, the free PSA (fPSA) test is recommended before biopsy [37; 147]. Biopsy is associated with significant burden and harm (e.g., pain, urinary tract infection, hospitalization). The test measures the percentage of free PSA relative to PSA and is expressed as %fPSA, with a lower number indicating increased cancer risk. A man with a %fPSA greater than 25 has an 8% chance of having prostate cancer, while the likelihood of prostate cancer rises to 56% with a %fPSA less than 10 [147]. The fPSA test is noninvasive and has a 95% specificity for detecting cancer in men with %fPSA less than 10.

AMERICAN JOINT COMMISSION ON CANCER TNM CLASSIFICATION FOR PROSTATE CANCER		
Grade	**Evidence**	
Tumor (T)		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	Clinically inapparent tumor not palpable nor visible by imaging	a: Tumor incidental histologic finding in 5% or less of tissue resected
		b: Tumor incidental histologic finding in more than 5% of tissue resected
		c: Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumor confined within prostate[a]	a: Tumor involves 50% or less of one lobe
		b: Tumor involves more than 50% of one lobe but not both lobes
		c: Tumor involves both lobes
T3	Tumor extends through the prostate capsule[b]	a: Extracapsular extension (unilateral or bilateral)
		b: Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles (e.g., bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall)	
Regional Lymph Nodes (N)		
NX	Regional lymph nodes were not assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in regional lymph node(s)	
Distant Metastases (M)		
MX	Distant metastasis cannot be assessed (not evaluated by any modality)	
M0	No distant metastasis	
M1	Distant metastasis	a: Nonregional lymph node(s)
		b: Bone(s)
		c: Other site(s) with or without bone disease
Histopathic Grade (G)		
GX	Grade cannot be assessed	
G1	Well differentiated (slight anaplasia) (Gleason score of 2–4)	
G2	Moderately differentiated (moderate anaplasia) (Gleason score of 5–6)	
G3-4	Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10)	

[a] Tumor that is found in one or both lobes by needle biopsy but is not palpable or reliably visible by imaging is classified as T1c.
[b] Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified as T2, not T3.

Source: [124] *Table 1*

GRADING AND STAGING

Tumor aggressiveness can be determined by a pathologist's examination of the microscopic pattern of the cancer cells. The most commonly used tumor grading system is the Gleason grading [28]. This system assigns a grade for each prostate cancer from 1 (least aggressive) to 5 (most aggressive) based on the degree of architectural differentiation of the tumor. The Gleason score is obtained by assigning a primary grade to the most predominant grade present and a secondary grade to the second most predominant grade [28].

The standard T (extent of local tumor), N (status of regional lymph nodes), and M (distant metastasis) system has been used to stage prostate cancer tumors (***Table 1***) [29; 124]. The TNM staging for prostate cancer also includes a category for histopathologic grade (G), which takes into consideration the Gleason grading score. After each of the four categories has been graded, the cancer may be assigned a stage [124].

PROGNOSIS

Patient risk stratification schemes have been developed by the American Urology Association (AUA) and the American Medical Association based on the PSA level, biopsy Gleason score, and American Journal of Cancer Care (AJCC) clinical T-category. The cancer is graded based on the risk of PSA failure and prostate-cancer-specific mortality following radical prostatectomy, external beam radiotherapy, or interstitial prostate brachytherapy [30]:

- Very low risk: PSA <10 ng/mL, Gleason score 6 or less, clinical stage T1c, presence of disease in fewer than three biopsy cores, ≤50% prostate cancer involvement in any core, and PSA density ≤0.15 ng/mL/cm^3
- Low risk: PSA <10 ng/mL, Gleason score of 6 or less, and clinical stage T1c to T2a
- Intermediate risk: PSA 10–20 ng/mL, or a Gleason score of 7, or clinical stage T2b to T2c (Note: Patients with multiple adverse factors may be shifted into the high-risk category.)
- High risk: PSA >20 ng/mL, or Gleason score of 8 to 10, or clinical localized stage T3a
- Very high risk: Clinical stage T3b to T4

Expectant management, historically termed watchful waiting, is generally reserved in older men with limited life expectancy (less than five years), offering hormonal therapy at the time of disease progression. However, the impact of age on the treatment effect of radical prostatectomy, independent of life expectancy, remains unclear. Thus, another management strategy concept, active surveillance, has been introduced. This strategy identifies prostate cancer progression signs and the patient is treated accordingly; it is an effective option for low-risk cancers. As opposed to watchful waiting, active surveillance allows for men with features of low-risk disease to defer (rather than reject) prostate cancer therapy and any related morbidity [31].

SCREENING

Before the discovery of PSA, DRE was the primary tool used to screen for prostate cancer [22; 25]. A positive DRE was followed by biopsy. Findings suggesting cancer or obstructive symptoms then led to transurethral resection of the prostate (TURP). However, a prostate tumor must reach a significant size to be palpable, and as with PSA, false-positive tests can also occur with DRE. Furthermore, prostate cancer is not always detected in the same area of the prostate with suspicious findings on DRE [32].

Thus, other tests were needed to assist in prostate cancer diagnosis, and the PSA appeared to fill that need. As early as the late 1980s, physicians in the United States began to analyze PSA levels in men who did not have prostate cancer but were considered at high risk of having the disease (i.e., most men older than 50 years of age) [26]. In 1986, the U.S. Food and Drug Administration (FDA) approved the PSA test to monitor the disease status in patients with prostate cancer [26]. In 1994, the FDA approved PSA for use as an aid in the early detection of prostate cancer. In the United States, the use of the PSA test in White men reached an annual rate of 38% in 1995 [33]. In 1996, a PSA test preceded 83% of the prostate cancer diagnoses in White patients and 77% in African American patients [33]. In 2005, nearly 50% of Black and White men 50 to 79 years of age had undergone a PSA test in the past two years [173]. The literature has shown that PSA and DRE are best used in a complementary fashion [21]. Evidence has shown that prostate cancers detected either by PSA or DRE alone have more favorable pathologic characteristics than those found due to abnormalities in both PSA and DRE [21].

In 2012, the FDA approved the Prostate Health Index (PHI) blood test for men older than 50 years of age with a PSA level 4–10 ng/mL and negative DRE findings. The PHI uses a mathematic formula that provides a probability of prostate cancer by combining results from three tests—PSA, free PSA, and p2PSA—into a single score, which is used to distinguish between prostate cancer and benign prostatic conditions, thereby guiding clinical decision making [42]. One study of 506 men who received the phi test concluded that there was a significant reduction in biopsy procedures based on the results of the PHI test when compared with a historical control group (36.4% versus 60.3%, respectively) [42; 52].

RECOMMENDATIONS

Available screening methods and enhanced awareness has led to an increased number of men in whom prostate cancer is diagnosed at an earlier stage. The primary benefit of screening is a lower stage and grade of cancer at the time of diagnosis, and the high rate of localized disease at the time of diagnosis (92% to 96%) reflects, in part, the increased number of cancers that are detected earlier through screening [38; 150; 151]. Despite this benefit, an effect of screening on mortality has not been clearly demonstrated. The National Cancer Institute's Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was a U.S.-based randomized trial with enrollment from 1993–2001, involving 76,693 men at 10 study centers. After 13 years of follow-up in the PLCO trial, there was no benefit of annual screening on mortality [49]. A meta-analysis (five randomized controlled trials) similarly demonstrated no effect of screening on prostate cancer-specific or overall mortality [152]. However, data from the European Randomized Study of Screening for Prostate Cancer demonstrated that screening reduced the risk for prostate cancer death by 7% to 9% per year [175].

In addition to a lack of effect on mortality, screening is associated with high rates of false-positive results, overdiagnosis and subsequent overtreatment, and complications. Among men who have had four PSA tests, the cumulative risk for at least one false-positive result is 12.9% [150]. Rates of overdiagnosis have been estimated at 17% to 50%, and 23% to 42% of all screen-detected prostate cancers are overtreated [150; 153]. Furthermore, treatment is associated with complication rates of 20% to 50% [39; 150]. These findings have led expert panels to update their screening recommendations (***Table 2***) [30; 35; 36; 37; 38; 39; 149].

PROSTATE CANCER SCREENING RECOMMENDATIONS FROM VARIOUS ORGANIZATIONS			
Organization	**Year of Publication**	**Recommendation**	**Notes**
U.S. Preventive Services Task Force	2018	Recommends against routine prostate cancer screening in men 70 years of age and older. For men 55 to 69 years of age, the decision should be an individual one made after discussion of benefits and risks.	Clinicians should not screen men who do not express a preference for screening.
National Comprehensive Cancer Network	2022	No consensus reached	Offer baseline PSA testing (with DRE) to average-risk men 45 to 75 years of age, or 40 to 75 years of age for Black/African American men and those with germline mutations that increase risk. If PSA values <1 ng/mL, repeat screening every 2 to 4 years. Consider PSA testing only in very healthy patients older than 75 years of age.
American Urological Association	2013 (Reviewed and validity confirmed 2018)	No routine screening	Decisions should be individualized for men younger than 55 years who are at high risk. Shared decision-making should take place for men 55 to 69 years of age, for whom screening is of greatest benefit.
American College of Physicians	2013	No routine screening with PSA for average-risk men younger than 50 years of age, men older than 69 years of age, or men with a life expectancy of less than 10 to 15 years	—
American Society of Clinical Oncology	2012	Discourages general screening for men with a life expectancy of ≤10 years, as the harms outweigh the benefits	Discuss the individual appropriateness of screening with men who have a life expectancy >10 years.
American Cancer Society	2010	No routine screening	Discuss potential benefits and limitations of prostate cancer early detection at specified ages. Men should choose to be screened only after they receive information about the uncertainties, risks, and potential benefits associated with prostate cancer screening.
American College of Preventive Medicine	2008	Insufficient evidence to recommend routine population screening with DRE and PSA.	Give men information about potential benefits and harms of screening, including limits of current evidence, and allow them to make their own decision. Discussion should be done annually. "Usual age" for screening is 50 to 70 years in average-risk men. Effectiveness is questionable in men with life expectancy <10 years. More information is needed regarding possible benefit of screening high-risk men at younger ages.

Source: [30; 35; 36; 37; 38; 39; 149; 178] *Table 2*

Overall, experts recommend against routine screening for most men and emphasize the need to consider life expectancy and the patient's age and risk factors for the disease. The age to start a discussion about screening varies slightly among the guidelines. For example, the American Urological Association (AUA) and the American Cancer Society (ACS) do not recommend routine screening for men of any age [2; 39]. Instead, the ACS advises that patients with greater than a 10-year life expectancy make an informed decision whether to be screened after discussing the uncertainties, risk, and potential benefits of screening with their healthcare provider. The ACS early detection guideline suggests the information with which to make a decision should be provided to men at various ages based on risk level [2]:

- Age 50: Men at average risk
- Age 45: Men at higher risk (e.g., Black race with a first-degree relative diagnosed with prostate cancer before 65 years of age)
- Age 40: High-risk populations (e.g., multiple family members diagnosed with prostate cancer before 65 years of age)

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force recommends against prostate-specific antigen (PSA)-based screening for prostate cancer in men 70 years of age and older.

(https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prostate-cancer-screening.
Last accessed October 24, 2022.)

Level of Evidence: D (There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Discourage the use of this service.)

The AUA panel recommends that the screening decision be based on individual risk and on the patient's personal values and preferences regarding early detection [39]. The AUA notes that the benefit of screening is greatest for men 55 to 69 years of age; routine PSA screening in men 70 years of age or older and men with a life expectancy less than 10 to 15 years is not recommended. In contrast, the U.S. Preventive Services Task Force (USPSTF) recommends screening be individualized based on patient preference [36; 148].

In spite of these conflicting guidelines, many physicians believe that healthy men should be offered the opportunity for prostate cancer screening [22]. As prostate cancer is rare for men younger than 40 years of age, screening is not typically initiated until at least the fifth decade [7]. However, baseline PSA measurements at a young age can be useful to predict the risk of ever developing prostate cancer; a measurement at 45 years of age may be useful to create a personalized risk profile and avoid missing signs of prostate cancer diagnosis [22; 30]. The National Comprehensive Cancer Network (NCCN) updated its screening guidelines in 2022, recommending baseline PSA (with DRE) be offered based on considerations of age (beginning at 45 years of age for all men, or 40 years for Black men), other risk factors, and life expectancy, with repeat testing every two to four years when initial screening results are normal [178].

Every medical intervention, whether it is therapeutic or diagnostic, does have risk. ***Table 3*** summarizes some of the risks associated with prostate cancer screening.

The European Randomized Study of Screening for Prostate Cancer followed 182,000 men from seven European countries, 50 to 74 years of age. The "core" age group used for analysis was 55 to 69 years, which accounted for 162,243 subjects. The average follow-up was 8.8 years. Participants were randomized to PSA screening (on average, once every four years) or no screening. In most centers, the cutoff was 3.0 ng/mL. Compliance in the screening group was 82% for at least one test. Overall, 16.2% of tests were positive, and compliance with biopsy recommendations was 85.8%. However, 75.9% of biopsies showed that the PSA was a false positive [50]. The cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in controls. In intention-to-screen analysis, death from prostate cancer was lower in the screening group. Absolute risk difference was 0.71 death/1,000 men. By intention-to-screen analysis,

RISKS ASSOCIATED WITH SCREENING
False-positive incidence
Discomfort of biopsy
False reassurance
Results may not be accurate
Unnecessary treatment of indolent disease
More harm than benefit with disease
Psychologic harm
Men with false-positive readings may worry more about prostate cancer
Risk of significant bleeding, infection
Source: [35; 36] *Table 3*

to prevent one death 1,410 men would need to be screened and 48 additional cases treated. Including only men who were actually screened, 1,068 men would need to be screened and 48 treated to prevent one death [50].

Researchers continue to investigate ways to make screening more effective. Using a higher PSA threshold for biopsy for older men and less frequent screening for men with low PSA levels are strategies that may reduce the risk of overdiagnosis as well as prostate cancer-related mortality [154].

Informed decision making is integral in selecting approaches to screening, with every guideline emphasizing the need to discuss the potential benefits, harms, and limitations associated with screening with their male patients. The ACS notes that men should receive information about screening directly from their healthcare provider or be referred to reliable and "culturally appropriate" sources [38]. Decision aids can be especially useful in helping men and their healthcare providers weigh the benefits and risks of screening, and studies of decision aids have led to improved knowledge and have increased men's desire for an active role in decision making [38; 39; 155]. The NCCN guideline offers talking points for discussion, and the American Society of Clinical Oncology provides a decision aid tool (https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/2012-psa-pco-decision-aid.pdf).

Despite the continued emphasis on informed decision making, the percentage of men who report having had a discussion with their healthcare providers about screening is about 63% to 66% of the general male population [156; 157]. This may reflect prostate cancer screening guidelines that stress that routine screening is no longer recommended. Black men were most likely to have had a discussion, and men without a usual source of care were the least likely [157]. Awareness in the African American community regarding increased risk of prostate cancer has led to more Black than White men 40 to 49 years of age being screened [173].

For men who choose to have screening for prostate cancer, the combination of PSA followed by DRE, if warranted, is the preferred method per the USPSTF guidelines, providing better predictive value than either method alone [150]. The sensitivity of PSA testing is higher than that of DRE, especially for tumors that are more aggressive [151]. However, the PSA level can vary as a result of several factors.

BIOPSY

Biopsy of the prostate provides the definitive diagnosis of cancer; histopathologic analysis enables assessment of tumor aggressiveness and clinical prognosis. Multiple factors should be taken into account before proceeding to biopsy, including PSA and DRE results, free/total PSA, PSA velocity, PSA density, family history, ethnicity, prior biopsy history, age, and comorbidities. The NCCN recommends pelvic imaging studies (e.g., computed tomography [CT], magnetic resonance imaging [MRI]) before proceeding to biopsy [30].

Before 1989, most non-TURP prostate biopsies were obtained by directed needle biopsy of palpably abnormal nodules in the gland [45]. Since then, spring-loaded biopsy devices using small-bore (18-gauge) needles, in combination with transrectal ultrasonography (TRUS), have led to random systematic sextant ultrasound-guided transrectal biopsies of the prostate [46]. This procedure was quickly adopted as the method of choice for obtaining tissue from patients with suspected prostate

cancer [47]. However, it became apparent that the widely adopted sextant protocol did not detect as many cancer cases as a more extensive biopsy procedure. In one study, the cancer detection rate was 30% for a 6-core biopsy and 49% for a 12-core biopsy in patients with a PSA level of 4.1–10 ng/mL [40; 48]. Today, urologists routinely take 10 to 14 cores per biopsy session. For patients with previously negative biopsy findings and a persistently elevated PSA level, saturation biopsies consisting of more than 30 biopsy cores have been advocated by some physicians, pushing to a new limit in the search for small foci of cancer [48].

Prostate cancer is found in about 25% of biopsy specimens, illustrating a problem regarding a well-defined threshold at which to obtain a biopsy specimen [44]. Although most cancer is detected with use of a PSA threshold of 4 ng/mL, some studies have shown that prostate cancer is subsequently found in 15% of men with levels <4.0 ng/mL [30]. These findings led the NCCN to suggest considering biopsy for men with a PSA level >3.0 ng/mL [30; 167]. A positive DRE, regardless of PSA results, should prompt an imaging study and/or biopsy (if indicated by CT or MRI) [30].

RISK CALCULATORS

There are more than 100 prostate cancer risk calculators developed to aid in screening decisions and treatment planning, most of which have undergone some form of validation [160]. Many are used clinically; however, their effectiveness continues to be debated. One reason uncertainty exists is that the same data set used to create the prediction models is typically used to validate them [159]. Thus, true validation may not exist for most of the available risk calculators, and even when independent data is used, flaws remain (e.g., poor calibration/discrimination) that have the potential to cause harm to a significant number of patients. Despite these facts, it is believed that prediction models are superior to conventional decision making based on PSA screening and DRE, particularly for the detection of patients at risk for aggressive, high-grade cancers [158; 161; 162].

The widely used Prostate Cancer Prevention Trial Prostate Cancer Risk Calculator (PCPTRC) uses race, age, PSA, family history, DRE, prior biopsy information, and finasteride status to assign a risk level [51]. The tool was developed using data derived from the 5,519 men in the placebo group of the PCPT, and its efficacy was validated in a separate study [158]. However, the PCTRC has been replaced by the Prostate Biopsy Collaborative Group (PBCG) risk calculator. The PBCG risk calculator was found to be a superior risk prediction tool compared to the PCTRC in a study of 15,611 men undergoing prostate biopsy. The PBCG may be accessed online at http://riskcalc.org:3838/PBCG [34].

The Prostate Cancer Research Foundation has a collection of eight risk calculators designed to determine risk of prostate cancer depending on level of known information. The Risk Calculator 1 is a general health calculator and reviews family history, age, and any medical issues with urination. The Risk Calculator 2 incorporates PSA levels to determine if further action is required. The first two calculators can be used without any medical knowledge, and the remaining six are used to help guide clinic decision making. Risk Calculator 3 and 4 (with TRUS or DRE) use prostate volume and MRI information to give a more accurate estimation of prostate cancer risk. The PHI result may also be combined with Risk Calculators 3 and 4, slightly increasing predictive capability. Risk Calculator 5 estimates the risk of indolent prostate cancer, which may not require immediate treatment, and Risk Calculator 6 assesses future risk over the next four years, taking into account age, prostate-specific antigen, DRE, family history, prostate volume, and previous biopsy status [176]. These calculators may be accessed online at https://www.prostatecancer-riskcalculator.com.

PROSTATE CANCER PREVENTION

DIET: IMPACT ON PROSTATE CANCER

There have been studies indicating that diet may impact both the development of prostate cancer and the aggressiveness of tumors [25; 54]. However, determining a causal relationship between individual foods and nutrients and prostate cancer is not simple. It is generally believed that dietary associations are modified by genetic sensitivity [55; 56]. Chan and colleagues concluded that consuming a diet of a wide variety of plant-based foods (cruciferous vegetables) and fish may prevent prostate cancer; more controlled evidence is still needed regarding specific dietary components [54].

Carmody and colleagues conducted a randomized trial of an intervention of men with recurrent prostate cancer changing to a primarily plant- and fish-based diet and assessed the effect of the change on their quality of life and rate of PSA increase [57]. The clinical trial faced multiple challenges, as only a minority of prostate cancer survivors adhered to the ACS recommended diet of five servings of fruit and vegetables daily [58]. This challenge in adherence was found to be a barrier to improved treatment outcomes.

Crawford and colleagues also noted some correlation between diet and rates of prostate cancer [4]. This relationship was seen previously in studies showing prostate cancer incidence increased considerably in Japanese men who immigrated to the United States [59]. However, subsequent studies showed inconclusive results. For example, the Cancer Prevention Study II Nutrition Cohort found an association between higher total red meat intake and an increased risk of prostate cancer in African American men but not in White men [60]. However, these results were not duplicated by the Multiethnic Cohort Study, which failed to identify an association between fat/meat intake and prostate cancer risk in any of the four racial/ethnic groups studied (African Americans, Japanese Americans, Hispanics, and White men) [61].

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is the largest-ever prostate cancer prevention trial. Its focus is to determine the validity of previous studies suggesting that selenium and vitamin E (alone or in combination) might reduce the risk of developing prostate cancer by 60% and 30%, respectively [53; 62]. However, study data from the SELECT trial (ongoing) are not promising; supplemental selenium (200 mcg/day) and vitamin E (400 IU/day), taken either alone or together for 7 to 12 years, did not decrease the risk of developing prostate cancer [63]. The data also show two concerning trends: a significant increase in the number of prostate cancer cases in men taking only vitamin E and slight increases in the number of cases in men taking only selenium and selenium/vitamin E combined [63]. The absolute increase in risk of prostate cancer per 1,000 person-years was 1.6 for vitamin E, 0.8 for selenium, and 0.4 for the combination.

Linking diet to the risk of prostate cancer, however, remains an intriguing topic for future research, and other studies have focused on nutritional links. Gao and colleagues found a relationship between increased calcium intake and a possible increased risk of prostate cancer [64]. According to their meta-analysis from prospective studies, the relative risk of prostate cancer was more likely in men with the highest intake of dairy products and calcium compared with men with the lowest intake; however, the apparent increase was small [64]. Building on research indicating that higher dairy milk intake may be associated with increased incidence of prostate cancer, a large cohort study of the Physicians' Health Study (n=21,660) found that whole milk intake, specifically, was associated with fatal disease and progression to fatal disease after diagnosis, whereas nonfat/lowfat milk was associated with a greater risk of nonaggressive disease but not death [163]. A separate 2010 animal study concluded that a Western diet (i.e., high in fat and cholesterol) increased prostate tumor incidence, grade, and burden [164]. A 2015 systematic review and meta-analysis of studies investigating dairy and calcium intakes on prostate cancer risk

concluded that another component of dairy products is the likely culprit rather than dietary calcium or fat [174].

Yan and colleagues, based on meta-analysis of cohort and case-control studies, found a possible protective effect from the ingestion of soy products [65]. The cause of this decreased risk is not clearly known, but it is theorized to be either caused by an estrogenic effect or the inhibition of 5AR [65]. Giovannucci and colleagues investigated the link between tomato products and lycopene and the risk of prostate cancer [66]. While there was a potential protective effect, there was not sufficient evidence to support a health claim [66; 67]. Other studies have investigated animal fats and vitamin D; some studies have shown a link between increases in both animal fat consumption and prostate cancer incidence, while other studies have not [68]. Meanwhile, some studies have investigated whether vitamin D analogs have a potential role in prostate cancer therapy [69].

ASPIRIN AND NSAIDs

There have been investigations into the role for aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) in the prevention of prostate cancer. The rationale of the role of aspirin and NSAIDs in prostate cancer prevention is most likely related to elevated prostaglandins and upregulation of cyclooxygenase-2 (COX-2) found in prostate cancer cell lines [70; 71]. Two significant studies have focused on epidemiologic evidence related to this potential approach [70; 71].

Jacobs and colleagues discovered that, in the ACS Cancer Prevention Study II Nutrition Cohort, ingesting 30 or more pills per month over 5 or more years (either adult-strength aspirin or NSAIDs) was associated with a lower risk of prostate cancer [70]. Meanwhile, a meta-analysis of observational epidemiologic studies by Mahmud and colleagues found the epidemiologic evidence for a protective effect of aspirin and NSAID use against prostate cancer to be suggestive but not conclusive [71]. While both of these studies were promising, more information is needed related to reduction in PSA levels and the effect on PSA sensitivity.

TREATMENTS FOR LOCAL AND ADVANCED PROSTATE CANCER

Prostate cancer often follows an indolent course. Approximately 60% of newly diagnosed cases occur in men older than 65 years of age, and the majority die "with" prostate cancer but "from" other causes. A published review of issues pertinent to prostate cancer screening cited autopsy studies suggesting that 30% of men older than 50 years of age and 70% of those older than 70 years of age have occult prostate cancer [177]. Further, an analysis of national surveillance registry and Medicare claims data has evaluated outcomes of almost 90,000 older men who received a diagnosis of early-stage prostate cancer between 1992 and 2002 and were provided ongoing medical care without attempted curative therapy. Results showed the 10-year risk of death from prostate cancer ranged from 8% among men with well-differentiated tumors to 26% among those with poorly differentiated tumors, while risk of death from other medical causes over the same period of time was 60%, regardless of tumor grade [177].

For these and other reasons, specialty guidelines recommend using a risk stratification classification when making management decisions for patients with localized prostate cancer. Stratification refers to classifying the likelihood of disease recurrence following specific treatment, based on initial tumor characteristics, Gleason score, and PSA level. The AUA/American Society of Radiation Oncology (ASTRO) Clinically Localized Prostate Cancer Guideline uses a framework stratified by risk to facilitate care decisions and assist clinicians in the selection of management options [179]. The AUA/ASTRO management guideline stratifies likelihood of recurrence into low, intermediate, and high-risk categories [179].

The three primary management options for localized/low-risk prostate cancer are active surveillance (also known as expectant management or watchful waiting), surgery (prostatectomy), and radiation therapy (external beam radiation or radioactive tumor seeding [brachytherapy]) [77]. Clinicians should inform patients that all prostate treatments carry risk. In discussing management choices, the risks of treatment to urinary, sexual, and bowel function should be incorporated with risks posed by the cancer, patient life expectancy, co-morbidities, and patient preferences to facilitate a shared decision-making approach to management [179].

ADT and chemotherapy are treatment options for advanced prostate cancer [10]. ADT is preferred for patients with hormone-sensitive prostate cancer, while chemotherapy is reserved primarily for the treatment of men with advanced or recurrent prostate cancer that does not respond to hormone therapy [10; 73; 74]. There are promising findings but, as with the early-stage type, no effective systemic therapies for the treatment of late-stage prostate cancer exist.

Other experimental modalities are being studied for use in the treatment of prostate cancer, including high-intensity focused ultrasound (HIFU). HIFU, which consists of ablating the tumor prostate with focused ultrasound waves via the endorectal probe, has shown some promise for patients with localized (early-stage) disease [143; 144]. However, some studies have reported significant adverse effects, and additional research is necessary before it can be incorporated into treatment recommendations [145].

ACTIVE SURVEILLANCE

In reference to management of prostate cancer, active surveillance is not always synonymous with watchful waiting. Active surveillance denotes an approach in which men with localized, very-low-risk prostate cancer are followed regularly for clinical signs that prompt definitive treatment with curative intent should intervention become necessary [179]. Watchful waiting is the strategy recommended for patients with asymptomatic prostate cancer and limited life expectancy. Some studies draw further distinction, defining watchful waiting as observation and provision of palliative care when prostate cancer becomes symptomatic, while active surveillance is defined as close follow-up (with DRE, PSA levels, and biopsies) and provision of treatment at signs of disease progression. Patients with a life expectancy of less than five years do not benefit from prostate cancer screening, diagnosis, or treatment, as prostate cancer treatment does not improve survival within five years of follow-up [179].

NCCN and AUA panels recommend active surveillance for all men with low-risk prostate cancer and a life expectancy of less than 20 years and suggest that surveillance be considered for those with very-low-risk prostate cancer and a life expectancy of more than 20 years [178; 179]. When active surveillance is the management strategy, monitoring the PSA level is recommended no more often than every 6 months, unless clinically indicated, and physical exam with DRE every 12 months [178]. An increase in PSA should prompt re-testing as transient PSA elevations are common. Serial PSA increases, new DRE abnormalities, or other concerns for clinical progression should prompt re-evaluation with prostate MRI and possible prostate biopsy [178; 179].

SURGERY

Before a radical prostatectomy is considered, physicians should ensure the disease is contained within the prostate gland. If so, there is a higher likelihood that surgery will be successful. A radical prostatectomy is a procedure whereby the prostate gland and the seminal vesicles are completely removed. Usually, this surgical procedure is performed in younger patients (40 to 60 years of age) with no metastases, as they have a greater chance of prostate-cancer-related death than older patients (70 to 90 years of age) [55]. Surgery has been widely documented to reduce mortality and rates of metastases in patients with prostate cancer [55; 75].

There are several surgical options when completing a prostatectomy [76]. The first option is either retropubic or perineal prostatectomy. With the retropubic procedure, the surgeon makes an incision in the abdomen to reach the prostate and may also remove nearby lymph nodes as a precautionary measure to prevent spread of disease [75]. The second option is a perineal prostatectomy, in which the surgeon makes an incision in the perineum; another abdominal incision is needed to remove lymph nodes [76]. In some hospitals, surgeons may do a laparoscopic prostatectomy, whereby instruments are passed through a few small incisions. While the laparoscopic procedure is generally associated with fewer complications and faster recovery, it is technically challenging and not always appropriate for removing all prostate tumors [76].

Cancer that has spread to lymph nodes signals the likelihood of more extensive disease that is less likely to be cured by surgery. This knowledge is vital when determining a treatment plan, so a pelvic lymphadenectomy is often completed prior to prostatectomy to check for prostate cancer spread [72]. The removed nodes are examined by a pathologist for evidence of cancer cells. If the nodes display evidence of cancer, radical prostatectomy would usually be excluded as a treatment option [72].

Cryosurgery

Some treatment centers also perform cryosurgery. This is a technique whereby prostate tissue is ablated by alternate freezing and thawing. It can be an outpatient procedure. The experience with this type of surgery for prostate cancer is limited, as there has been little published data documenting the effect of cryosurgery on metastasis-free, prostate-cancer-specific, or overall survival [79]. The five-year biochemical disease-free survival rates have ranged from 48% to 92%, depending on the risk of recurrence, but long-term data on prostate cancer-specific survival are not yet available and there are no clearly defined guidelines for patient selection for cryosurgery as a salvage procedure [78]. However, the AUA notes that primary cryosurgery is an option for men with organ-specific disease without metastases [78]. Poorer outcomes after cryosurgery were noted for patients with larger prostates, as it is more difficult to uniformly freeze larger areas. A 2013 review of literature from 1980 to 2013 noted that this form of treatment has greatly improved over time, with biochemical disease-free survival rates now comparable to other treatment modalities [168]. Treatment-related morbidities have also decreased. Adjuvant ADT should be considered for men with clinical stage T3 prostate cancer [169].

Cryotherapy is a good option for eligible patients who cannot undergo radical prostatectomy due to comorbidities, obesity, or history of pelvic surgery [78]. Salvage cryotherapy may be beneficial for men with locally recurrent disease, a PSA less than 4 ng/mL, and no metastases for whom radiotherapy was not effective [78]. It is important to note that serious toxic effects have been noted with cryosurgery, including bladder outlet injury, urinary incontinence, sexual impotence, and rectal injury [77].

RADIOTHERAPY

Radiotherapy is an option for cancer confined to the prostate and/or local tissues [10; 72; 77; 80]. A randomized trial of external-beam radiation for prostate cancer found that long-term adjuvant treatment with ADT (gonadotropin-releasing hormone [GnRH] agonist) was associated with greater noncancer mortality than short-term therapy [81]. Another observational study of primary brachytherapy in men with early-stage prostate cancer found that men who received brachytherapy and short-term hormonal therapy had worse overall survival rates than men who did not receive such therapy, but there were no differences in prostate cancer-specific survival [82].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Radiologists asserts that external beam irradiation may be used as definitive therapy in patients with early and locally advanced prostate cancer, and increasing dose has been associated with improved outcomes.

(https://acsearch.acr.org/docs/69350/Narrative. Last accessed October 24, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

In addition, published retrospective series have shown adjuvant radiotherapy to reduce the risk of biochemical failure while improving local and distant disease control [83; 84; 85]. Biochemical failure is defined as three consecutive measurements of an increase of PSA greater than 2 ng/mL compared to the lowest pretreatment level. Three randomized trials comparing treatment with adjuvant radiotherapy to observation (active surveillance) in men with pathologic stage T3 or margin-positive disease showed a significant improvement in biochemical-failure-free survival in the radiotherapy group [83; 84; 85]. In spite of these promising outcomes, no effect on overall survival has been reported [80].

There has been no accepted optimal dose of radiotherapy as an adjuvant treatment for prostate cancer in spite of its use in the postoperative period. Reported doses have varied between 45 Gray (Gy) to 81 Gy, although most investigators have advocated a cumulative dose greater than 60 Gy [83; 84; 85]. According to the National Cancer Institute, greater improvements have been shown with higher doses of radiation (78–81 Gy) compared to conventional doses [77]. A treatment guideline published by the NCCN recommends the following dose schedule [30]:

- 75.6–79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) in patients with clinically localized prostate cancer at low risk
- Up to 81 Gy in patients at intermediate or high risk

Despite the lack of an identified optimal dose, radiotherapy has shown a significant benefit for prostate cancer therapy. Anscher and colleagues reported an improved rate of localized disease control with the addition of radiotherapy after prostatectomy; the 10-year local control rate was 92% with the addition of radiotherapy compared to 60% with observation alone [83]. In addition, Leibovich and colleagues reported that subjects who received adjuvant radiotherapy experienced no local or distance recurrence in men compared to a 16% rate of recurrence with observation alone [86]. Studies completed prior to the regular assessment of PSA levels have indicated significantly improved local disease control with adjuvant radiotherapy [87; 88]. For example, a phase III study of adjuvant radiotherapy in men with stage T3 disease and a primary endpoint of metastasis-free survival found the 10-year rate favored adjuvant radiotherapy to observation alone; however, the difference was not significant [89]. Macdonald and colleagues noted their five-year rate of freedom from both local recurrence and distant metastasis with adjuvant radiotherapy treatment was significant, at respective rates of 95% and 97%, indicating that radiotherapy has a demonstrated benefit for many patients with prostate cancer [80].

Three large, randomized studies of radiotherapy compared with observation after surgery for pathologic stage T3 disease revealed a significant improvement in biochemical-failure-free survival after adjuvant therapy [89; 90; 91]. A European series trial by Bolla and colleagues reported improvements in biochemical survival and local control with radiotherapy [90]. Thompson and colleagues reported significant benefits in both PSA-free (>0.4 ng/mL) and relapse-free survival in men receiving adjuvant radiotherapy (60–64 Gy) [89]. Wiegel and colleagues reported an increase in the four-year rate of biochemical-failure-free survival of 81% for radiotherapy-treated men compared with 60% in the control group [91]. However, Macdonald and colleagues analyzed the results with caution, recognizing that none of the men in their series had disease as advanced as those included in the other randomized trials [80; 89; 90; 91].

The most common form of external beam radiation for prostate cancer is intensity-modulated radiation therapy (IMRT), which allows the greatest concentration of radiation to be more finely focused. In one large study comparing IMRT with conformal radiation therapy and proton therapy, IMRT was associated with a lower rate of gastrointestinal morbidity and fewer hip fractures [172]. Patients who underwent IMRT were also less likely to require additional cancer therapies than those who received conformal radiation therapy. Moderately hypofractionated image-guided IMRT regimens (2.4–4.0 Gy per fraction over four to six weeks) can be considered as an alternative to conventionally fractionated regimens, when indicated [30]. Randomized clinical trials report efficacy and toxicity similar to conventionally fractionated IMRT.

Other radiation techniques, including proton-beam therapy and cyber knife, are being studied for use in the treatment of prostate cancer. In particular, the National Cancer Institute has noted that incorporating proton therapy is an attractive option, but more research is necessary to determine efficacy and safety [77].

The radiopharmaceutical radium-223 has been shown to extend survival in men who have castration-resistant prostate cancer with symptomatic bone metastases, but no visceral metastases [30]. It is administered intravenously once a month for six months. Radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression.

ANDROGEN DEPRIVATION THERAPY

ADT is usually reserved for older men and for treatment of men with more advanced disease. The therapy is based on the premise that androgens can stimulate prostate cancer growth [10; 16; 92]. ADT can include either orchiectomies or medical castration with a GnRH agonist and has been shown to achieve significant responses in more than 80% of treated patients [93].

Most men are treated with a GnRH agonist rather than bilateral orchiectomies, as GnRH agonists are easily administered, reversible, and more acceptable to patients. GnRH agonist use has risen markedly over the last two decades across all ages, disease stages, and tumor grades [94]. More than one-third of the estimated 2 million prostate cancer survivors in the United States are treated with GnRH agonists [10]. GnRH agonists have been shown to improve disease-free and overall survival in combination with radiation for locally advanced or high-risk nonmetastatic disease [95]. Adjuvant therapy with a GnRH agonist also improves survival in men with node-positive disease after radical prostatectomy [96].

ADT is also used in situations where the potential benefit of primary therapeutic options is less clear. PSA monitoring after primary therapy often detects recurrences long before they are revealed by either symptoms or imaging [97]. A rising PSA after primary surgery or radiation therapy commonly leads to long-term ADT, although the effects of early ADT on elevated PSA recurrences have not been adequately characterized. Additionally, some men with localized disease opt for long-term ADT instead of radiation or surgery, which has not been shown to improve survival rates relative to observation [98].

EVIDENCE-BASED PRACTICE RECOMMENDATION

For patients with unfavorable intermediate- or high-risk prostate cancer and estimated life expectancy greater than 10 years, clinicians should offer a choice between radical prostatectomy or radiation therapy plus ADT.

(https://www.auajournals.org/doi/10.1097/JU.0000000000002757. Last accessed October 24, 2022.)

Strength of Recommendation/Level of Evidence: Strong, grade A (Net benefit is substantial, and applies to most patients in most circumstances and future research is unlikely to change confidence.)

It is important to note that ADT, and especially the use of GnRH agonists, leads to a significant reduction in serum testosterone and a number of physiologic changes in bone mineral density, body composition, lipid profiles, and insulin sensitivity [14]. Men receiving GnRH agonists are at an increased risk for bone fracture as well as diabetes and cardiovascular disease [14; 99]. Treatment options to increase bone density, a surrogate for fracture risk in men without metastases, include denosumab (60 mg SQ every 6 months), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly) [30]. The increased risk of diabetes and cardiovascular disease may explain in part the excess number of noncancer deaths associated with ADT. GnRH agonists significantly increase fat mass and fasting insulin levels and decrease insulin sensitivity [100; 101]. Treatment-related changes in serum lipoproteins and arterial stiffness, as well as possible QT interval prolongation, may also contribute to the association between GnRH agonists and adverse cardiovascular effects [14; 102]. Although ADT has improved outcomes in patients with metastatic prostatic cancer, research is needed to address the adverse effects often seen with this therapy.

Secondary hormone therapy options include second-generation antiandrogens (i.e., apalutamide, enzalutamide, or darolutamide) and the addition of the androgen metabolism inhibitor abiraterone [30; 166].

CHEMOTHERAPY

Cytotoxic chemotherapy has shown promise in treating prostate cancer after periods when previous treatment has fallen short. Results of the TAX 327 clinical trial indicated that treatment with docetaxel and prednisone (given every three weeks) led to superior survival and improved response in patients' pain, PSA levels, and quality of life [73]. Meanwhile, the SWOG 99-16 clinical trial noted an increase in median survival rate with docetaxel and estramustine treatment; however, greater toxicity is noted with this treatment [74]. These clinical trials established docetaxel as the standard chemotherapeutic treatment for prostate cancer. Other chemotherapy options are also being explored to improve patient outcomes. The combinations of mitoxantrone-prednisone and cabazitaxel-prednisone are often used to treat prostate cancer [166].

Other therapies are being developed for patients who are docetaxel-resistant. Many of the newer chemotherapies have monoclonal antibodies for targeting angiogenesis. This treatment strategy relies on suppressing several angiogenic proteins, including those in the VEGF family and endothelin (ET)-A, that are expressed in prostatic tissue and may cause prostate cancer [103; 104; 105]. Preliminary research using a combination of the monoclonal antibody bevacizumab, which acts against VEGF-A, and docetaxel have shown some positive results in patients experiencing docetaxel failure [106]. The Cancer and Leukemia Group B (CALGB) phase III trial in the United States (CALGB 90401) was conducted to determine if adding the monoclonal antibody bevacizumab to docetaxel and prednisone would increase overall survival rates [105]. Despite an improvement in progression-free survival and objective response, the addition of bevacizumab to docetaxel and prednisone did not improve overall survival in men with metastatic castration-resistant prostate cancer and was associated with greater toxicity [171]. Bevacizumab was approved in 2014 for platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer; use of bevacizumab for hormone-resistant prostate cancer is off-label [166].

Another novel angiogenic treatment pathway is the endothelin axis. Endothelin is a potent vasoconstrictor protein produced by the vascular endothelium. It has an important role in both vascular homeostasis and mediation of osteoblast growth and function [107]. In the normal prostate gland, endothelin-1 (ET-1) is produced by the prostate epithelial cells; its clearance is regulated

through binding with the ET-B receptor (ETBR) and neural endopeptidase, which is responsible for the metabolism of several bioactive peptides [108]. In prostate cancer, ET-1 overexpression causes dysregulation of ET-1 components, specifically reducing ETBR binding and neural endopeptidase activity. Increased ET-1/ET-A receptor expression is observed during advanced prostate cancer. This dysregulated pathway is relevant in the link to bone metastases, because osteoblasts express ETAR in high density. Tumor-derived ET-1 promotes osteoblast proliferation and new bone formation through that receptor [109; 110]. Thus, osteoblast proliferation generates other growth factors that appear to promote local metastatic bone formation [105]. Therapies that can effectively treat the spread of bone metastases are being investigated as future prostate cancer treatments.

Other studies are focusing on docetaxel combinations with other antiangiogenic agents and monoclonal antibodies in recurrent disease patients. These include both early efficacy trials with thalidomide and exploratory trials with sorafenib, a potent multityrosine kinase inhibitor that blocks encoding by the genes *BRAF*, *RAF1*, *KIT*, *KDR*, and *PDGFRB* [105; 111]. A systematic review of docetaxel plus thalidomide found a greater PSA decline, longer median progression-free survival, and higher 18-month survival rate than with docetaxel alone; however, these findings should be confirmed in large-scale clinical trials [112].

5-ALPHA REDUCTASE INHIBITORS

As noted previously, androgens influence the development of prostate cancer. Thus, decreasing androgen levels has been and remains a goal of prostate cancer treatment. This process has been discussed as part of ADT and the development of new pharmacotherapy approaches. The development of finasteride, an inhibitor of 5AR, the enzyme that converts testosterone to the more potent androgen dihydrotestosterone, has shown that lowering androgen levels in the prostate may reduce the overall risk of prostate cancer [113].

Three isoforms of 5AR have been identified; a separate gene encodes each isoform [114; 115]. The type 1 isoform is prevalent in extraprostatic tissue (i.e., nongenital skin, the liver, and certain brain regions) and is present throughout life [4]. Several studies have suggested that type 1 5AR is also present in the prostate and foreskin [116]. Its expression is low in BPH tissue but increases steadily in prostatic intraepithelial neoplasia as well as in primary, recurrent, and metastatic prostate cancer. The type 2 isoenzyme of 5AR is prevalent in the prostate and is also present in the seminal vesicles, epididymis, and fetal genital skin [116]. More recently, another 5AR isoenzyme, type 3, has been discovered in hormone-refractory prostate cancer cells with little or no expression in normal adults. This isoenzyme appears to play a role in hormone-refractory prostate cancer growth and progression, but its potential role in prostate cancer remains under investigation [115].

The activity of 5AR is different in various ethnic groups, and it has been found to be greater among groups with increased incidences of prostate cancer [117]. Studies indirectly estimating 5AR activity have shown elevated activity among White men compared with Chinese American men and with White and African American men compared with Japanese American men [118]. Wu and colleagues documented this development by calculating DHT-to-testosterone ratios to indirectly measure the activity of 5AR [119]. The ratio was significantly lower among Chinese Americans than among White and African American men, but the difference between African American and White men was not statistically significant. The DHT-to-testosterone ratio was found to be lower (but not significant) among Asian-born Asians than among North American-born Asians; this is notable as greater incidences of prostate cancer have been observed among Japanese-born men who immigrate to the United States [59]. A study of a community-based sample of 1,899 men in Boston (age range: 30 to 79 years) reported significantly greater DHT-to-testosterone ratios in

African American men compared to White and Hispanic men, suggesting African American men had greater 5AR activity [120].

Finasteride is a low-toxicity chemopreventive agent that inhibits the conversion of testosterone to the more potent androgen DHT within the prostate. It originally became available for the treatment of BPH, and since then, it has been approved for the treatment of male pattern baldness. However, little was known about its long-term effects on the prostate. Thompson and colleagues undertook a study to determine whether finasteride can reduce the prevalence of prostate cancer among initially healthy men during a seven-year period [113]. Data from the PCPT showed a 24.8% overall reduction in prostate cancer prevalence with the use of finasteride (18.4%) compared to the placebo group (24.4%). However, there was a greater incidence of high-grade cancers (Gleason scores: 7–10) found in the finasteride arm (37%) versus placebo (22.2%) [43]. An 18-year follow-up study of the PCPT published in 2013 found that despite the increased incidence of high-grade cancers in the finasteride group compared to the placebo group, there was no significant between-group difference in the rates of overall survival or survival after the diagnosis of prostate cancer [41].

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial was a four-year, multicenter, randomized, double-blind, and placebo-controlled study evaluating the efficacy and safety of oral dutasteride (0.5 mg/day) in reducing the incidence of prostate cancer among men identified as being at increased risk for the disease (PSA between 2.5 and 10 ng/mL) [122; 123]. Dutasteride differs from finasteride in that it inhibits both 5AR isoenzymes 1 and 2. The REDUCE trial also attempted to find the reason for an increased incidence of 5AR inhibitor-associated high-grade prostate cancer tumors [43]. Data from the REDUCE trials show a significant decrease in prostate cancer incidence in dutasteride-treated patients during the four years (relative risk reduction: 23%) [72]. In the dutasteride group, cancer was detected in 659 of the 3,305 men, compared with 858 of the 3,424 men in the placebo group. Whether dutasteride increases the incidence of high-grade tumors was somewhat unclear. In the dutasteride group, 29 men had tumors with a Gleason score of 8 to 10, compared with 19 in the placebo group. However, 141 men with tumors with a Gleason score of 5 to 7 were removed from the study during the first two years. It is speculated that the difference in number of high-grade tumors between groups would be statistically insignificant had these men not dropped out [146].

Starting in 2011, the FDA required new labeling on 5AR inhibitors to include a warning for an increased risk of high-grade prostate cancer with their use based on the results of the PCPT and the REDUCE trials [121; 165; 170]. The results of the two trials indicated that the cancers prevented by 5AR inhibitors were Gleason ≤6 tumors, which would be expected to cause little-to-no morbidity in an individual's lifetime. Conversely, the increased number of high-grade cancers (Gleason ≥8 tumors) in the treatment groups was cause for serious concern. The FDA is unlikely to approve 5AR inhibitors for prostate cancer prevention (as manufacturers were requesting in 2011), and despite the agents' continued use for benign prostatic hyperplasia (BPH) and male pattern baldness, they are not recommended for prostate cancer chemoprevention and should not be used as such [121; 165]. The FDA does recommend the continued use of finasteride/dutasteride for BPH, as the benefit outweighs the risk of prostate cancer, and is assessing the risk/benefit for male-pattern baldness [170]. Alpha-blockers have not been shown to reduce the risk of urinary retention or surgery related to BPH, and switching patients to one is not recommended. Men prescribed a 5AR inhibitor should be screened for prostate cancer using DRE in addition to PSA, and it should be remembered that PSA levels are 50% lower in men taking these drugs [170].

FOLLOW-UP

Primary care physicians, nurses, and other healthcare professionals who see patients on a regular basis play an important role in the follow-up evaluation for men who opt for watchful waiting/active surveillance, as well as for those who have been treated by an oncologist. After treatment for prostate cancer, men should be followed up with a history and physical examination and PSA testing every 6 months to 12 months for 5 years and annually thereafter; they should also receive a DRE annually (in coordination with their cancer specialist) [125]. Primary care clinicians can also aid in the management of the side effects of treatment and screening for secondary cancers.

CONSIDERATIONS FOR PATIENTS WITH PROSTATE CANCER

ERECTILE DYSFUNCTION

One key consideration for patients with prostate cancer is the potential sexual side effects related to the available treatment options. Radical prostatectomy, radiation therapy, cryotherapy, and hormone therapy are all associated with a potential for decreased libido and erectile dysfunction. In one study of 2,636 men being treated for prostate cancer, 85% indicated they experienced problems with sexual potency; approximately one-third disclosed having sexual dysfunction prior to treatment [130]. In fact, this potential complication of cancer treatment, which can have devastating effects on quality of life and satisfaction with the care received, may result in men delaying or avoiding treatment altogether.

In the past, erectile dysfunction was often a silent condition, with many men being too embarrassed or ashamed to discuss the issue with their physicians. Today, there are many treatment options available to manage erectile dysfunction, including oral drug therapy, injection medications, suppositories or pellets that are deposited in the urethra of the penis, and surgery to insert penile implants or prostheses [126]. The most common approach is oral medication therapy with a phosphodiesterase-5 inhibitor (sildenafil, vardenafil, or tadalafil), with one guideline recommending initiation of therapy early in the course of recovering [125]. However, it is unclear how many post-treatment patients will benefit from the use of these medications [126]. In one study, only 38% of patients who had received either definitive radiotherapy or prostatectomy for localized prostate cancer reported improvements in sexual functions as the result of medication interventions [131]. If pharmacotherapy in unsuccessful, referral to a urologist or sexual health specialist warranted [125].

The FDA has issued mandates to revise labeling of phosphodiesterase-5 inhibitors. In 2005, the agency required the labels for all three of the agents to reflect the possibility of sudden vision loss after taking the drugs for a period of time [127]. The alert was associated with several case reports that suggested a temporal association between use of one of the drugs and nonarteritic anterior ischemic optical neuropathy (NAION), a cause of irreversible vision loss [127]. However, subsequent studies showed that the risk of NAION was similar among men who were and were not taking a phosphodiesterase-5 inhibitor; the risk of "possible" NAION was increased [128; 129]. Still, some researchers have suggested that an examination of the ocular fundus be performed on men who may be at higher risk for NAION before a phosphodiesterase-5 inhibitor is prescribed [127]. Patients should be properly educated regarding the potential effects of both prostate cancer treatments and medications available to manage post-treatment sexual dysfunction.

DEPRESSION

A diagnosis of prostate cancer is often the cause of psychologic distress, and some men may become depressed as a result of the effect of the cancer or treatment. As discussed, the treatments available for patients with prostate cancer can have significant effects on men's quality of life, negatively

impacting self-esteem, relationships, and personal identity. Unfortunately, depression is underdiagnosed in men as the result of a divergence of factors, including clinicians' lack of appropriate training and discomfort with dealing with depression and issues related to male gender identity, such as:

- Reluctance of men to seek help
- Lack of men's recognition of the symptoms of depression
- Hesitancy of men to express emotions
- Inconsistency of men's symptoms with those in the *Diagnostic and Statistical Manual of Mental Disorders*
- Tendency for men to see depression as a weakness
- Men's misconceptions about mental illness and its treatment

Depression that is associated with chronic illness is often seen as an inevitable consequence of the disease, but the depression should be treated. Frequently, the treatment improves the overall outcome and can elevate quality of life [132]. The treatment approach will depend on the severity of symptoms and the patient's preference. In general, a combination of psychotherapy and pharmacologic management provides the best results for most men [132; 133]. Potential psychotherapy approaches include cognitive behavior therapy and interpersonal psychotherapy [133; 134; 135].

NON-ENGLISH-PROFICIENT PATIENTS

Language and cultural barriers have the potential for far-reaching effect, given the growing percentages of racial/ethnic populations. As noted, patient understanding of the risks and benefits of treatment options is an essential aspect of prostate cancer care, and it must be assured that all patients have a clear understanding of the concepts discussed. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

According to U.S. Census Bureau data from 2020, 21.5% of the American population speak a language other than English, and of those, 38% speak English less than "very well" [136]. Clinicians should ask their patients what language they prefer for their medical care information, as some individuals prefer their native language even though they have said they can understand and discuss symptoms in English [137]. Translation services should be provided for patients who do not understand the clinician's language. "Ad hoc" interpreters (family members, friends, bilingual staff members,) are often used instead of professional interpreters for a variety of reasons, including convenience and cost. However, clinicians should check with their state's health officials about the use of ad hoc interpreters, as several states have laws about who can interpret medical information for a patient [138]. Even when allowed by law, the use of a patient's family member or friend as an interpreter should be avoided, as the patient may not be as forthcoming with information and the family member or friend may not remain objective [138]. Children should especially be avoided as interpreters, as their understanding of medical language is limited and they may filter information to protect their parents or other adult family members [138]. Individuals with limited English language skills have actually indicated a preference for professional interpreters rather than family members [139].

Most important, perhaps, is the fact that clinical consequences are more likely with ad hoc interpreters than with professional interpreters [140]. A systematic review of the literature showed that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters, and many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care and that the use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [141; 142].

Clinicians should use plain language in their discussions with their patients who have low literacy or limited English proficiency. They should ask them to repeat pertinent information in their own words to confirm understanding, and reinforcement with the use of low-literacy or translated educational materials may be helpful.

CASE STUDY

Patient A is an active man, 59 years of age, who missed his last yearly DRE and PSA, tests that had been recommended by his primary care provider. The results of these tests had been within normal limits in all previously elected examinations. At his next examination, a firm prostate nodule, approximately 2 mm in diameter, is palpated, and the PSA level is 14 ng/mL. A needle biopsy of the prostate is performed within one week of the PSA measurement. The biopsy shows several sites containing cells indicative of adenocarcinoma of the prostate, with a Gleason score of between 8 and 9.

After carefully evaluating the treatment options for an aggressive tumor, Patient A chooses radical prostatectomy and seeks care at an institution where nerve-sparing surgery is performed with the assistance of a robotic, computer-controlled device, to help reduce the risk of adverse events. According to the pathology report, the tumor is an adenocarcinoma that has extended beyond the capsule of the gland but has not involved the seminal vesicles.

Staging studies, including magnetic resonance imaging of the pelvis and abdomen and a bone scan, confirm the extent of the tumor and demonstrate lack of lymph node involvement or distant metastasis (T3a, N0, M0). Because of the T3a finding, a course of external radiation therapy to the local site is prescribed.

At the three-month follow-up visit, the PSA level has increased to 20 ng/mL, and a bone scan demonstrates multiple skeletal lesions, primarily in the ribs, pelvis, and skull, none of which had been seen on the previous scan. Due to the rapid progression of disease and the metastatic lesions, the patient's survival is estimated to be less than three years.

After a discussion with his surgeon, oncologist, and urologist, the patient decides to forego ADT, choosing instead treatment consisting of chemotherapy with docetaxel in combination with the angiogenesis inhibitor bevacizumab over a course of several months. The treatment causes some nausea, malaise, and hair loss, but the patient tolerates the effects well. His primary complaint is of oral ulcers, which require topical treatment. The PSA level drops steadily during follow-up, reaching a level of 0.4 ng/mL after approximately six months of treatment.

Patient A continues to feel well after two years of follow-up, and the PSA level has remained at 0.2 ng/mL or less. Incontinence that was present after the surgery has ended, but erectile dysfunction remains, despite the use of medications.

CONCLUSION

Prostate cancer is a potentially debilitating illness that affects work, interpersonal relationships, and overall quality of life. Evidence has shown that if caught early, this cancer can be treated effectively. However, there are disagreements related to the risks and benefits of screening, which may interfere with early diagnosis. Healthcare professionals must be familiar with key concepts related to the diagnosis and screening of prostate cancer in order to best treat these patients. They must also be familiar with emerging trends, such as diet, that can be effective for prostate cancer and other diseases as well.

Standard prostate cancer therapies, such as surgery, radiation, chemotherapy, and ADT, can relieve symptoms in some patients and provide partial improvement in others. However, some patients may have prostate cancer that is refractory to treatment, and knowledge of more experimental therapies can be helpful to patient outcomes. Effectively treating prostate cancer, whether by standard therapy or emerging treatments, can be beneficial to both healthcare professionals and their patients.

RESOURCES

Prostate Cancer Foundation (PCF)
https://www.pcf.org
An organization that investigates new treatments and an eventual cure for prostate cancer. The PCF has funded more than 2,200 programs at nearly 220 research centers in 22 countries around the world.

Zero: The End of Prostate Cancer
https://zerocancer.org
An organization that provides comprehensive patient treatment information, educates high-risk populations, and conducts free prostate cancer testing throughout the United States. It obtains research funds from the federal government to find new treatments and to pursue a better test for the disease.

American Cancer Society
https://www.cancer.org
A nationwide, community-based, voluntary health organization dedicated to preventing cancer, saving lives, and diminishing suffering from cancer through research, education, advocacy, and service.

FACULTY BIOGRAPHY

John J. Whyte, MD, MPH, is currently the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research. Previously, Dr. Whyte served as the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications. In this role, Dr. Whyte developed, designed, and delivered educational programming that appeals to both a medical and lay audience.

Prior to this, Dr. Whyte was in the Immediate Office of the Director at the Agency for Healthcare Research Quality. He served as Medical Advisor/Director of the Council on Private Sector Initiatives to Improve the Safety, Security, and Quality of Healthcare. Prior to this assignment, Dr. Whyte was the Acting Director, Division of Medical Items and Devices in the Coverage and Analysis Group in the Centers for Medicare & Medicaid Services (CMS). CMS is the federal agency responsible for administering the Medicare and Medicaid programs. In his role at CMS, Dr.Whyte made recommendations as to whether or not the Medicare program should pay for certain procedures, equipment, or services. His division was responsible for durable medical equipment, orthotics/prosthetics, drugs/biologics/therapeutics, medical items, laboratory tests, and non-implantable devices. As Division Director as well as Medical Officer/Senior Advisor, Dr. Whyte was responsible for more national coverage decisions than any other CMS staff.

Dr. Whyte is a board-certified internist. He completed an internal medicine residency at Duke University Medical Center as well as earned a Master's of Public Health (MPH) in Health Policy and Management at Harvard University School of Public Health. Prior to arriving in Washington, Dr. Whyte was a health services research fellow at Stanford and attending physician in the Department of Medicine. He has written extensively in the medical and lay press on health policy issues.

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