



This document was last amended in August 2020 to reflect literature that was released since the original publication of this content in May 2013. This document will continue to be periodically updated to reflect the growing body of literature related to this topic.

PROSTATE CANCER: SCREENING AND MANAGEMENT

KEYWORDS: Prostate cancer, PSA, Screening, Radical Prostatectomy

At the end of medical school, the medical student will be able to...

1. Identify the basics of prostate anatomy and physiology
2. Describe the epidemiological features of prostate cancer
3. Understand the controversy surrounding prostate cancer screening
4. Describe the general approaches to prostate cancer screening and diagnosis
5. List the major components of prostate cancer staging
6. Describe the basic treatment options for localized and advanced prostate cancer

Basic prostate anatomy and function

The prostate is a male sex accessory gland located within the pelvis below the bladder and above the urogenital diaphragm. The prostate encircles the urethra like a doughnut and is embryologically derived from the urogenital sinus (**Figure 1**). There are 4 basic anatomic zones of the prostate: the anterior zone, the peripheral zone, the central zone, and the transition zone. The vast majority of prostate cancers arise in the peripheral zone of the prostate, whereas benign prostatic hyperplasia (BPH) occurs in the transition zone. Since the majority of the peripheral zone is located posteriorly and the prostate is directly anterior to the rectum, prostate tumors that form nodules can often be palpated on a digital rectal exam (DRE; **Figure 2**). Additionally, since the peripheral zone is relatively distant from the urethra, men with prostate cancer most often have no urinary symptoms. With regards to BPH, the prostate continues to grow (hyperplasia) predominantly in the transition zone with age. These benign changes can cause voiding symptoms mainly due to obstruction.

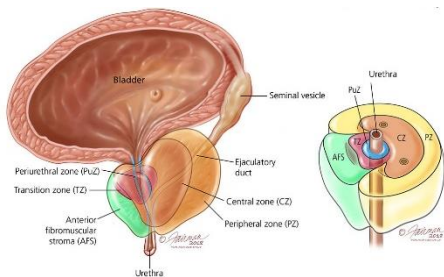


Figure 1. Prostate Anatomy.

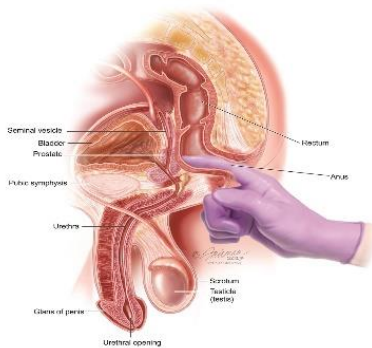


Figure 2. Digital rectal exam of the Prostate.

The role of the prostate is to secrete about 30% of the fluid that comprises the ejaculate. Prostatic secretions help prolong the lifespan of sperm in the vagina and contains high amount of zinc and a substance called prostate-specific antigen (PSA). PSA is an enzyme responsible for the liquefaction of semen and is normally only present in small amounts in serum.

Epidemiologically, prostate cancer is the most common solid organ cancer in men and is currently the second leading cause of cancer death in men after lung cancer in the United States. **About 1 in 9 men in the United States will be diagnosed with prostate cancer and over 3 million men have a prior diagnosis of prostate cancer.** The risks of a new prostate cancer and death due to prostate cancer are highest in Black men, older men (**mean age at diagnosis about 66 years**), and in those with a first degree relative (brother or father) with prostate cancer.

Prostate cancer screening: Background of controversies

As noted above, PSA is present in high quantities in the prostate and normally in very minimal amounts in the serum. In men with prostate cancer, serum PSA values may increase. This observation was first used clinically in the late 1980's to screen men for prostate cancer. Subsequently, many men in the 1990's were diagnosed with early stage prostate cancer. Prior to this point, men with prostate cancer would most often present symptomatic from incurable, metastatic disease.

Over the next several years, studies suggested **a large portion of prostate cancers did not require treatment and men were often being overtreated** – receiving surgery or radiation for a cancer that would have never caused health issues in their lifetime. These treatments are also commonly associated with various adverse effects including bowel, urinary, and sexual dysfunction. In response to these findings, the United States Preventive Services Task Force (USPSTF), a very influential panel of experts that gives recommendations on preventive and screening measures for American patients, recommended against routine prostate cancer screening for elderly men older than age 75 in 2008, since these men often die of non-prostate cancer causes as opposed to a screen-detected prostate cancer. **Then in 2012, the USPSTF recommended against routine screening for all men**, suggesting the harms of screening were not worth the benefits.

Importantly, these recommendations were largely based on the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial conducted in the United States. This trial showed no difference in mortality between men randomized to screening or no screening. However,

several issues emerged following the 2012 recommendation. **The amount of contamination (PSA screening) in the control arm of the PLCO trial was found to be substantial which minimized the measured effect of screening in the treatment arm.** Additionally, trials from Europe with less contamination did note a decrease in mortality in men screened for prostate cancer. Screening was also noted to result in decreases in the incidence of metastatic prostate cancer which can lead to significant morbidity in patients due the cancer itself and the additional treatments needed. Finally, the indolent course of some low-grade prostate cancers had been noted, and more urologists were managing these men with surveillance strategies to minimize overtreatment (see “**Localized prostate cancer management**” below)

Subsequently, the USPSTF changed their stance on prostate cancer screening in 2018. **For men age 55 to 69 years, they recommend the decision to initiate screening should be made after an informed conversation between men and their clinicians about the risk and benefits of screening.** For men age 70 years and older, a recommendation against screening was maintained.

Prostate cancer screening: Who?

Importantly most prostate cancer screening is not performed by a urologist or oncologist but by a primary care physician. Thus, it is important for primary care physicians to know who and how best to screen for prostate cancer and for the urologist to know, of those who screen positive, who to biopsy. The AUA has several specific statements on this matter. For **men age less than 40 years**, they recommend against routine screening due to the low prevalence in this age group. For **men age 40 to 54 years**, they recommend potentially initiating screening for men at a higher risk of prostate cancer including those of Black race and those with a family history of metastatic or lethal adenocarcinomas such as prostate, ovarian, breast, or pancreatic cancer. For the latter group, this is usually qualified by first-degree relatives or multiple generation of affected relatives, in particular at young ages. In the age range of **55 to 69 years**, the AUA acknowledges that these men are the most likely to benefit from routine screening. For that reason, they state these men should start screening after an **informed decision-making process** regarding the risk and benefits of screening (See “**Prostate cancer screening: The risk and benefits**” below). Finally, **men age 70 and older**, and most importantly, **men with a life expectancy of less than 10 to 15 years** should not be screened for prostate cancer as they most likely have other healthcare issues that should be prioritized over treatment of asymptomatic prostate cancer. Men older than 70 years who are in excellent health may still benefit from screening.

Prostate cancer screening: The risk and benefits

Discussing the risk and benefits of prostate cancer screening is key to a complete decision-making process for those considering initiating screening. In general, it is recommended the patient be supplied with decision aid tools specific to prostate cancer screening. Although many exist and are constantly being updated, the best options are those available from reputable clinical societies (e.g. the American Cancer Society, AUA, and others).

The benefits of screening include finding and treating a prostate cancer before it has metastasized outside of the prostate. This would prevent not only the comorbidities and

shortened expected life-span due to metastatic prostate cancer, but would also obviate the need for life-long androgen deprivation therapy and other systemic therapies used to treat metastatic prostate cancer. These treatments come with numerous potential adverse effects. **The risks of prostate cancer screening are many and should be discussed with all patients considering screening.** Bleeding and infectious complications following a prostate biopsy can lead to hospitalizations. Men who undergo surgery or radiotherapy can expect issues with erectile, bowel, and urinary dysfunction depending on the actual treatment. For those who undergo active surveillance, many will still eventually receive surgery or radiotherapy and some who stay on surveillance experience anxiety related to harboring an untreated cancer. Although many sources exist to estimate an individual patient’s risk of aggressive prostate cancer and adverse effects related to treatment, ultimately a complete discussion of the risk benefits includes **assessing the patient’s priorities when it comes to prostate cancer screening.**

Prostate cancer screening: How?

The AUA recommends men who have agreed to initiate screening following a shared decision-making process be **screened at an interval of every two or more years.** This interval is expected to reduce the risk of overdiagnosis compared to annual screening without compromising the benefits of screening.

The interpretation of a serum PSA value should be made in the context of the entire patient. Several factors outside of prostate cancer can lead to elevated PSA including inflammation/infection, prostate enlargement (BPH), and recent genitourinary tract manipulation (e.g. urethral catheter or cystoscopy). Generally, PSA-based screening should only be performed well after (greater than 4 weeks) a potential infection or prostate manipulation has occurred. **No strict PSA cutoff for referral or biopsy exists. Age specific PSA guidelines do exist and can help primary providers make appropriate referrals to urologists (Table 1).**

Table 1: General screening PSA cutoffs for referral to urologist

Patient age (years)	PSA (ng/mL)
<50	≥ 1.5
50-54	≥ 2.0
55-59	≥ 3.0
60-69	≥ 4.0
≤70	≥ 6.0

Several tools help incorporate multiple factors to help predict the risk a patient may harbor a high-grade cancer. For instance, the Prostate Cancer Prevention Trial Risk Calculator uses prospective data to generate an individual patient’s risk along with visual graphics to use in a patient encounter (<https://riskcalc.org/PCPTRC/>)

Once a referral to an urologist is made, the urologist may use an array of adjunct tests to form a recommendation and need for a prostate biopsy (Table 2). Aside from the DRE which is used almost universally in conjunction with PSA measurements for screening, the rest of the tests are used variably based on the urologist's experience and test availability.

Table 2: Adjunct prostate cancer screening tests

Adjunct pre-biopsy tests	Notes
PSA kinetics	Rapid and sustained PSA rises are more indicative of cancer
Free/total PSA ratio	Lower ratio of unbound (free) to total serum PSA suggests a higher risk of cancer
Prostate Health Index (PHI)	Determines risk of prostate cancer based on the different molecular forms of serum PSA
Magnetic resonance imaging	Scores lesions in the prostate based on risk of harboring aggressive prostate cancer. Can also be used to aid targeted biopsies and focal therapy
Digital rectal exam (DRE)	Palpation of a nodule or induration can be indicative of a prostate cancer
Urinary markers (e.g. PCA3)	Can help predict the risk of prostate cancer

As a final point, **prostate cancer screening should cease if a given patient's health status changes** and other health issues take priority over detecting asymptomatic prostate cancer.

Diagnosing prostate cancer

The diagnosis of prostate is made with histological evidence from a biopsy of the prostate except in some case of metastatic disease. In the United States this is most often performed via a transrectal approach (**Figure 3**). An ultrasound probe is passed in the rectum of the patient usually at least 12 cores are sampled in a systematic manner that assesses the peripheral zone. This is often performed in the office setting with a local anesthetic block and prophylactic oral antibiotic.

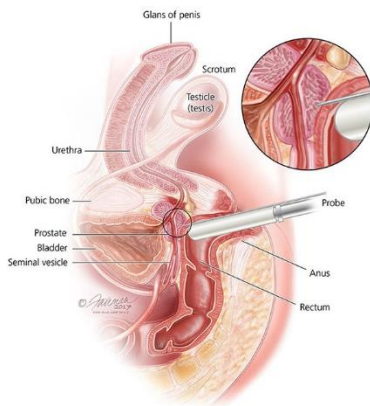


Figure 3. Prostate Biopsy: Transrectal Ultrasound

The most common complications of prostate biopsies include those related to bleeding, infection, and urinary retention. Bleeding occurs invariably in the urine and ejaculate and patients should be counseled to expect these for several weeks after the biopsy. All patients should also be advised that any unexplained fever in the 4 weeks following a biopsy, and especially those with urinary symptoms warrants an emergency department visit for potential acute prostatitis. The risk of a hospitalization following a prostate biopsy is less than 3% in the United States.

Recent advancements in magnetic resonance imaging (MRI) have led to the incorporation of the MRI into prostate cancer detection. MRI may be used to help locate tumors in men with a high suspicion of prostate cancer but a prior negative biopsy. They may also help urologists target tumors in the prostate to help increase the yield of high grade tumor detection and lower the detection of low grade, indolent tumors.

Finally, in the United States, interest in transperineal prostate biopsies has increased. Although a transrectal ultrasound is still used to target the prostate, the avoidance of a transrectal biopsy has the potential to substantially reduce the infection risk and need for broad antibiotics. This modality is still being compared to the transrectal approach and optimized in terms of the anesthetic block employed to make the office-based procedure tolerable to patients.

Prostate cancer staging, grading, and risk groups

The four relevant tools to risk stratifying patients include American Joint Committee on Cancer (AJCC) TNM staging (Figure 4) , grade group, and National Comprehensive Cancer Network (NCCN) risk groups for localized disease, and disease burden for metastatic disease. For urologist, familiarity with these tools helps guide further cancer evaluations and management options. TNM staging is based on the most recent edition of AJCC. The most relevant distinctions to make at the time of diagnosis include non-palpable on DRE (cT1) vs palpable (cT2) and the presence of pathologically enlarges lymph nodes or metastatic disease based on imaging which most often includes a CT and bone scan.

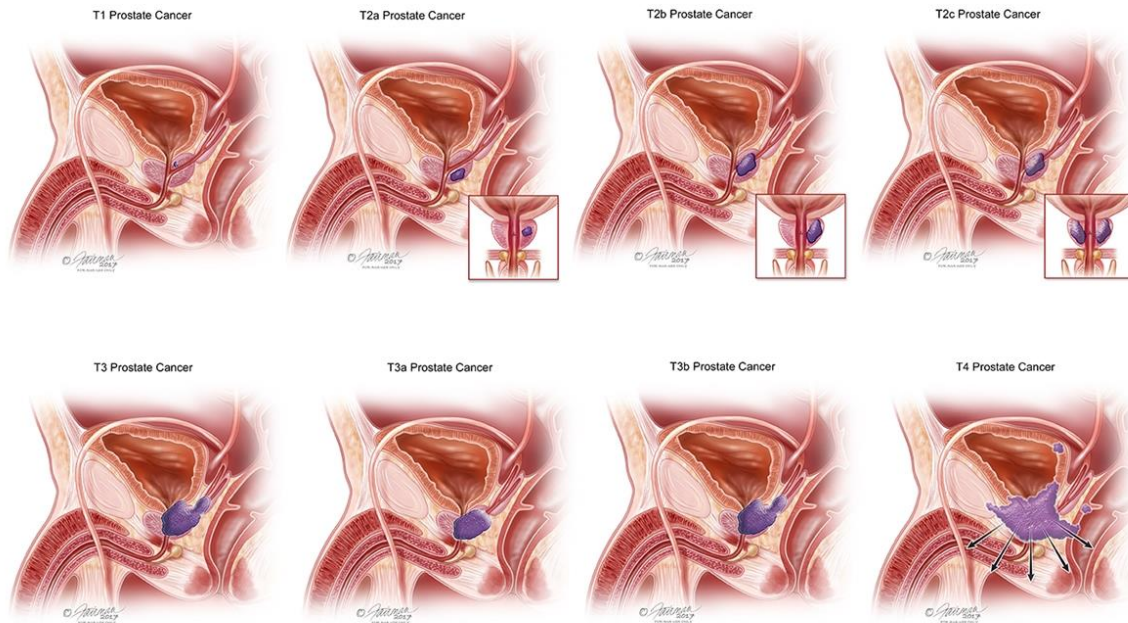


Figure 4. TNM staging

Prostate cancer is generally an adenocarcinoma. The degree of architectural abnormality on the biopsy is based on the Gleason Grade which is a scale of 1-5. One is close to a normal prostate gland (well differentiated) and 5 is poorly differentiated. The most predominant and the second most predominant pattern are then combined to formulate a Gleason Score and is commonly written as “primary+ secondary.” **These are further divided into Gleason Groups 1 to 5 based on the 2016 guidelines from the International Society of Urological Pathology (ISUP; Table 3).**

Table 3: Gleason grade groups

Gleason score	Grade group
3+3 = 6	1
3+4 = 7	2
4+3 = 7	3
8	4
9-10	5

For men with localized prostate cancer, NCCN groups ultimately refine precision care. As new data continues to be published, these groups are optimized to improve personalized management and should be revisited as the NCCN guidelines update. Components of the risk groups include grade group, PSA at time of diagnosis, TNM staging, and the amount of biopsy cores with cancer. The patients in the lower risk groups are not recommended to receive additional imaging as their risk of metastatic disease is low. Men with higher risk disease or

those with family history or certain histologic findings may also warrant germline DNA testing.

For men with metastatic prostate cancer at diagnosis, patients are often classified as having a low volume (oligometastatic) or high volume (widespread metastatic) disease. Although many definitions exist, the most common is derived from the CHAARTED randomized controlled trial which **defined high volume as four or more bone metastases with one or more outside the vertebral bodies or pelvis or any visceral metastases**. These groupings may help guide the best choice for treatment but are more often applied for prognostic value.

Localized prostate cancer management

Given the high prevalence of prostate cancer, a basic understanding of the management options is imperative for both specialist and primary care physicians.

Active surveillance and watchful waiting

Recent years have seen tremendous increases in the use of surveillance approaches for men with low-risk prostate cancer (~40% in the United States). **Active surveillance is defined as deferred treatment with disease monitoring with intention to treat for disease progression or patient preference**. This is the preferred management option for men with low- and, particularly, very low-risk prostate cancer to prevent unnecessary treatment-related adverse effects. Monitoring varies by practice but typically includes DRE's and PSA measurements about every 6 to 12 months and regular repeat biopsies. More recently MRI's have been tested as a form of disease monitoring. Importantly, about 50% of men who start on active surveillance will avoid definitive treatment after 10 to 15 years. **Watchful waiting is defined as deferred treatment except for symptomatic disease progression**. Men who elect watchful waiting typically have other comorbid health issues that render them less suitable candidates for definitive treatments.

Radical prostatectomy

Radical prostatectomy is a management option for men with localized prostate cancer. A standard radical prostatectomy can be performed with a lower midline abdominal incision or via a minimally invasive laparoscopic approach typically with robotic assistance. Men are often hospitalized for one to two nights. **In this surgery, the prostate, seminal vesicles, and pelvic lymph nodes are removed. The reconstructive portion involves reconnecting the bladder neck the urethra**. Men have varying degree of stress incontinence following surgery. This reliably improves in the months following surgery with Kegel exercising to strengthen the pelvic floor musculature as those muscles assume a larger role in urinary continence.

Because the **cavernous nerves which help with erections** run in paired bundles along the sides of the prostate, a prostatectomy invariably results in worse erectile function (**Figure 5**). Depending on the aggressiveness of the cancer and location of the tumor in the prostate, the surgeon may be able to "spare" transecting those nerves which helps with erectile function recovery. However, in men who cannot have either pair of nerve bundles spared, erectile

function will be severely compromised.

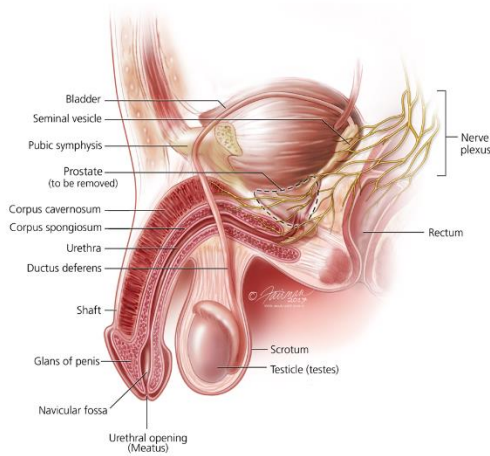


Figure 5. Male reproductive system

Men with adverse pathological features at surgery (seminal vesicle involvement, extraprostatic extension, or positive surgical margins) may benefit from radiotherapy.

Radiotherapy

Radiotherapy can be delivered either in the form of external beam radiotherapy (EBRT) or radioactive seed implants (brachytherapy). EBRT is delivered during short sessions several times a week (**Figure 6**). The number of sessions or fractions of radiation dosing is highest for the most conventional, low dose form of EBRT during which 1.8 to 2 Gy are delivered depending on the risk group over the course of about 37 to 45 sessions. Over more recent years, the use of fewer fractions, hypofractionation, but higher dosing of radiation, 2.5 to 3 Gy, has gained favor with most data suggesting similar outcomes. Brachytherapy consists of implanting radioactive seeds within the prostate transperineally under general anesthesia (**Figure 7**). **Brachytherapy or EBRT monotherapy are usually for men with favorable risk localized prostate cancer. For men with higher risk disease, EBRT is combined with androgen deprivation (ADT) and sometimes with brachytherapy.** For radiation therapy options, the combination of EBRT, brachytherapy and ADT has the best oncologic results for men with very high-risk prostate cancer. Side effects of radiation therapy include radiation related cystitis, proctitis, irritative voiding symptoms, as well as erectile dysfunction.



Figure 6. Patient Receiving External Radiation

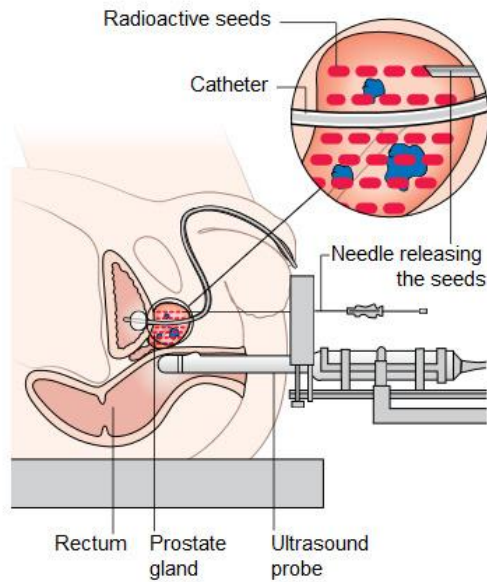


Figure 7. Brachytherapy

Comparing surgery and radiotherapy

In terms of oncologic outcomes, surgery and radiotherapy are considered comparable.

Younger healthier men are often recommended to undergo surgery as the most significant adverse effects of radiotherapy (radiation cystitis, chronic hematuria, etc.) tend to manifest 10 to 15 years following treatment. Additionally, following surgery, radiotherapy in the form of EBRT may be offered as adjuvant or salvage treatment. While surgery can be performed following primary radiotherapy, it is often not done due to the complexity of the surgery following radiation and the substantially increased risk of incontinence and erectile dysfunction.

Radiotherapy is often preferred for older men with shorter life expectancies and those who are not optimal surgical candidates. Additionally, if the patient's preference is to avoid the substantially greater short-term adverse effects of radical prostatectomy, radiotherapy is often the best initial treatment option. **Monitoring for cancer recurrence is similar following both surgery and radiotherapy with routine PSA measurements for the rest of the patient's life.**

Focal therapies and other options

Other treatments exist with the main purpose of providing some oncologic efficacy while minimizing treatment adverse effects. High-intensity focused ultrasound (HIFU) and cryotherapy represent the most sort of these treatments which can be used to treat the whole prostate (whole gland) or only the tumor within the prostate (focal therapy). However, most guidelines note **these treatments are currently still considered investigational as the primary treatment for prostate cancer.**

Advanced prostate cancer management

The AUA recently drafted guidelines for advanced prostate cancer management with key terminologies defined (see link below). The basic treatment options can be determined based on the clinical setting of the disease.

Biochemical recurrence without evidence of metastatic disease

In men with biochemical recurrence, PSA elevation, following definitive treatment with surgery or radiotherapy and no evidence of metastatic disease on imaging, **most guidelines advise against the routine use of androgen deprivation therapy (ADT) due to the minimal oncologic benefit of starting treatment at this stage.** However, ADT is still often given based on provider preference.

Metastatic hormone sensitive

For men with metastatic disease and no history of ADT use, hormone sensitive, permanent ADT in the form of regular dosing of luteinizing hormone releasing hormone (LHRH) agonists or antagonists or surgical castration (bilateral orchiectomy). **These treatments remove testosterone production from the testicles which can potentiate prostate cancer growth and progression.** For men receiving LHRH agonists, treatment is often preceded by several days of treatment with a non-steroidal antiandrogen (e.g. bicalutamide) to prevent a symptomatic flare of their disease due to the temporary elevation in testosterone before levels decrease to extremely low, castrate-levels. Treatment with ADT is accompanied with one of several agents, each of which has high level clinical trial evidence to support their use (**Table 4**).

Table 4: Treatments for men with metastatic prostate cancer in combination with androgen deprivation therapy

Treatment	Mechanism	Clinical setting
Abiraterone	Block production of androgens in the prostate and adrenal glands in addition to the testes	Metastatic hormone sensitive and metastatic castrate-resistant
Enzalutamide	Androgen receptor antagonist	Metastatic hormone sensitive, non-metastatic castrate-resistant, and metastatic castrate-resistant
Apalutamide	Androgen receptor antagonist	Metastatic hormone sensitive and non-metastatic castrate-resistant
Darolutamide	Androgen receptor antagonist	Non-metastatic castrate-resistant
Docetaxel	Taxane chemotherapy	Metastatic hormone sensitive and metastatic castrate-resistant
Cabazitaxel	Taxane chemotherapy	Metastatic castrate-resistant
Radiotherapy to the prostate	Radiotherapy	Metastatic hormone sensitive and low volume of metastatic disease

PARP inhibitors	Inhibit repair of single-strand DNA breaks leading to double-strand breaks	Metastatic castrate-resistant with homologous recombination gene mutations
Radium-223	Intravenous alpha radiation-emitting agent that targets osteoblastic metastatic lesions in bones	Metastatic castrate-resistant with symptomatic bone metastases and no visceral metastases.
Sipuleucel-T	Autologous leukocytes sensitized to prostate cancer antigens	Metastatic castrate-resistant and asymptomatic or minimally symptomatic disease

Non-metastatic castration resistant

In men who receive hormonal therapy for biochemical recurrence and no metastatic disease, their prostate cancer invariably become resistant to ADT and can grow and progress despite castration levels of testosterone as indicated by a rise in serum PSA. Historically, these men were treated with ADT alone until metastatic disease was detected on imaging. However, the use of androgen receptor antagonists (**Table 4**) can actually improve survival and prolong time to metastatic recurrence.

Metastatic castration resistant

Several options exist for men with metastatic disease and disease progression (growth or rising PSA) despite ADT (**Table 4**). **The choice of exact treatment is dependent on previous treatments given and various other clinical scenarios.** For instance, Radium-223 is only given to men with symptomatic bone metastases.

Treatment adverse effect and health monitoring

The adverse effect profiles of the many treatment options for men with advanced prostate cancer are broad and require monitoring outside of cancer monitoring. **ADT is often associated with increased risk of dysmetabolic syndrome, cardiovascular disease, reduced bone health and increased risk of fractures, and cognitive impairment with longer duration of treatment worsening risks of adverse effects.** Suppression of androgen production with and activity with ADT leads to declines in libido. Abiraterone can inhibit glucocorticoid synthesis and is dosed with prednisone to prevent related effects. Familiarity with the treatments received by or ongoing treatments for patients with prostate cancer can help guide providers towards minimizing adverse effects.

REFERENCES

Prostate Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology
https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

AUA Clinical Guidelines: Early Detection of Prostate Cancer (2018)

<https://www.auanet.org/guidelines/prostate-cancer-early-detection-guideline>

AUA Clinical Guidelines: Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline (2017)

<https://www.auanet.org/guidelines/prostate-cancer-clinically-localized-guideline>

AUA Clinical Guidelines: Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline

<https://www.auanet.org/guidelines/advanced-prostate-cancer>

AUTHORS

2020

Adam B. Weiner, MD

Chicago, IL

Disclosures: Nothing to disclose

Moben Mirza, MD

Kansas City, KS

Disclosures: Nothing to disclose

2018

Moben Mirza, MD

Kansas City, KS

Disclosures: Nothing to disclose

2016

Michael Hollis, MD

Brighton, MA

Disclosures: Nothing to disclose

Jessica Kreshover, MD

Brooklyn, NY

Disclosures: Nothing to disclose

2013

Gilad Amiel, MD

Houston, TX

Disclosures: Nothing to disclose

Martha Terris, MD

Augusta, GA

Disclosures: Nothing to disclose

Acknowledgements:

Alexander Tatem, 4th year medical student at the Medical College of Georgia contributed to this review.

