

MODULE 8: PROSTATE CANCER: SCREENING & MANAGEMENT

KEYWORDS: Prostate cancer, PSA, Screening, Radical Prostatectomy

LEARNING OBJECTIVES

At the end of this clerkship, the medical student will be able to:

1. Identify and name the basic anatomic zones of the prostate gland, including the locations where prostate cancer develops
2. Describe the physiologic role of the prostate - "what does the prostate do?"
3. Describe the distinctive epidemiological features of prostate cancer
4. Understand the controversy surrounding the use of serum PSA as a screening tool for prostate cancer
5. List the signs & symptoms of prostate cancer
6. Describe the natural history and the common patterns of progression of prostate cancer
7. List the major components in the staging of prostate cancer
8. Briefly describe the treatment options for localized and metastatic prostate cancer
9. Describe when prostate cancer does NOT need to be treated

INTRODUCTION

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 derived from the urogenital sinus. 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 prostatic carcinomas arise in the peripheral zone of the prostate, whereas benign prostatic hyperplasia (BPH) occurs in the transition zone. The role of the prostate is to secrete fluid into the ejaculate that accompanies sperm and seminal vesicle fluid to make up the semen. The contributions of the prostate to the ejaculate include; acid, zinc and a serine protease known as PSA (prostate specific antigen) that is an enzyme responsible for the liquefaction of semen. The prostate continues to grow (hyperplasia) with age and may cause voiding dysfunction. 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. Studies suggest that this cancer is much more common than observed clinically and thus any screening strategy must take care not to diagnose cancer in patients that will not suffer clinically from the disease—e.g. autopsy studies have shown about 70% of men

deceased in their seventies have prostate cancer present. The incidence of clinically diagnosed prostate cancer and mortality is highest in Blacks, intermediate in Caucasians and least in Asians. Being derived from a sex accessory gland, most prostate cancers are hormone sensitive and respond favorably to androgen hormonal ablation but the effect is short-lived due to either the development of or selection for hormone insensitive clones within the malignancy. Thus, the treatment stratagem for prostate cancer today is early detection whilst the tumor is confined to the prostate or surrounding tissues and can be cured by either removal or treatments aimed at the primary. Although there are low response rates to currently available chemotherapies and immunotherapies and a palliative effect of hormonal therapy, there are no cures for metastatic prostate cancer.

PROSTATE CANCER SCREENING

While there are no symptoms with early stages of prostate cancer; early detection, including PSA screening, has played a part in decreasing prostate cancer mortality. The serum PSA test and the digital rectal exam are complimentary tests that, along with other key variables including patient ethnicity, age and family history, should serve as a strategic fund of knowledge to be used when deciding whether or not to proceed with biopsy.

A flawless and standardized interpretation of elevated PSA values has yet to be determined. Although it has been well demonstrated that patients with elevated serum PSA levels are more likely to be harboring aggressive disease, elevated PSA levels can also be seen in less biologically aggressive prostate cancers. Other potential causes of elevated PSA values include benign prostatic hypertrophy, infection, urogenital tract instrumentation (i.e. catheter placement) and anything that can cause inflammation within the prostate gland. As such, serum PSA screening interpreted outside the context of important patient-specific variables carries with it a significant risk of what has been called over diagnosis: the identification and treatment of patients who might otherwise have lived out the rest of their lives without experiencing any of the terrible symptoms associated with advanced prostate cancer. Since the treatment of prostate cancer is associated with a significant level of patient morbidity (including bowel dysfunction, urinary dysfunction, and impotence), the use of serum PSA as a screening tool has been a topic of significant controversy.

In May of 2012, the United States Preventative Services Task Force (USPSTF), a federally appointed group of 16 individuals commissioned to make recommendations concerning clinical preventative services, issued a Class D recommendation regarding the use of serum PSA in prostate cancer screening. This means they believe that they have found "fair evidence that [PSA screening] is ineffective or that harms outweigh the benefits." They argue that the use of PSA screening and digital rectal exam in asymptomatic patients will cause more harm in the form of treatment morbidity than

benefit. It should be noted that while the board includes members with both primary care and nursing backgrounds, none of them are board certified urologists.

Nevertheless, the AUA recognizes that the interpretation of an asymptomatic patient's PSA level is a nuanced exercise that must be tailored to the patient in question. Therefore, the AUA no longer recommends one single PSA threshold for biopsy. Although previous thresholds such as 2.5 and 4.0 ng/mL have been used in the past, the AUA now recommends that the decision to biopsy should take into account the patient's DRE results, age, ethnicity, comorbidities, and prior biopsy history in addition to their serum PSA level.

In order to increase the efficacy of serum PSA interpretation, a number of performance variables are used clinically. These include age-adjusted PSA, density, velocity, and the free-to-complexed PSA ratio:

- a) Age Adjusted PSA: Since PSA normally rises with age, age-adjusted thresholds have been described. Benign growth of the prostate that normally occurs with age is the most common cause of PSA elevation. Roughly 70% of patients with an elevated PSA level between 4 and 10 will have a negative prostate biopsy. Conversely, there is no level of PSA at which you can guarantee a patient that they do not have cancer. Moreover, the absolute PSA level does not predict whether or not prostate cancer is harmful. General age adjusted PSA (ng/dL) thresholds are as follows: age 40-49 = 2.5; age 50-59 = 3.5; 60-69 = 4.5; 70-79 = 6.5.
- b) PSA Density: Another strategy used to improve the results of PSA screening is the calculation of PSA density by measuring prostate volume and dividing the absolute PSA level by the prostate volume (in mL). Prostate volume measurements can be obtained by either transrectal ultrasound or MRI. By these criteria, a PSA density threshold of 0.15 or greater is an indication for prostate biopsy.
- c) PSA Velocity: Since prostate cancer presumably grows faster than normal prostate, PSA velocity (or change in PSA levels over time) is another strategy to detect prostate cancers in men with "normal" PSA levels. PSA values fluctuate significantly over time due to physiological variation, thus PSA velocity is best determined using at least 3 measurements obtained over a 2-year period. The threshold value for PSA velocity is dependent on the total PSA. The threshold is 0.35 ng/ml/year for PSA values < 4 ng/ml and 0.75 ng/ml/year for patients with total PSA values >4 ng/ml.
- d) Free-Complexed PSA: PSA exists in the serum in two forms, free and complexed to protease inhibitors. Patients with prostate cancer tend to have a higher percentage of PSA complexed to protease inhibitors and thus the percentage of free PSA within the serum is used to add information to the total PSA in patients with PSA levels between 4 and 10 and help determine the

degree of suspicion for biopsy. Although there again is no agreement on the best threshold value for free PSA, values above 25% reliably predict the absence of clinically significant prostate cancer.

PROSTATE CANCER STAGING AND TREATMENT

Prostatic anatomy is described in zones. The central and transition zone surround the urethra and are the site of benign prostatic hyperplasia. Prostate cancer most often occurs in the peripheral zone which is closest to the rectum. Prostate cancer is diagnosed by prostate biopsy, as described above, in patients with either an abnormal DRE and/or abnormal PSA. The vast majority of patients who are diagnosed today were identified by prostate cancer screening and have early potentially curable disease. The TNM staging is used for prostate cancer. Prostate cancer has both clinical staging and pathologic staging. The clinical stage is based upon how it was detected. T1 disease is based upon disease discovered by means other than palpable disease. Clinical T1a and T1b stages are when prostate cancer is incidentally found in tissue obtained during surgery for benign disease (T1a involving < 5% and T1b is >5% of tissue obtained), e.g. during transurethral resection of the prostate. Clinical T1c stage are for cancers discovered during biopsy performed on patients with an elevated PSA (T1c). T2 disease is based upon the palpation of cancer in the prostate on digital rectal exam (a: less than half of one side, b: more than half of one side, and c: both sides of the prostate). Patients have T3 disease when cancer is palpable outside the prostate either laterally or involving the seminal vesicles.

Besides clinical stage, the histology of the cancer has a significant impact upon prognosis. The Gleason score (or sum) is the standard measure of the differentiation of prostate cancer. There are five patterns (1 - 5) with 5 being the worst. The biopsy material is examined under low power magnification the most common and second most common patterns are identified. These two numbers are added up to obtain the final Gleason score. The individual numbers and order are just as important in predicting prognosis as the total score since a patient with a Gleason score of $3 + 5 = 8$ has a better prognosis as a patient with $5 + 3 = 8$.

The management options for localized prostate cancer include radiation therapy, surgery, and active surveillance. The decision on how to manage prostate cancer in a newly diagnosed patient is quite complex and filled with controversy. The age (life expectancy) and health of the patient in addition to the characteristics of the cancer are taken into account. A frequent concern today is whether or not the cancer that is diagnosed is clinically significant. Active surveillance is offered to patients who have very low grade (no Gleason pattern 4 or higher) and low volume disease (< 3 biopsy cores involved) or <10-year life expectancy due to medical illness or age and a reasonable expectation that they will be compliant to the observation protocol. Younger and healthier men or men with more aggressive cancers should undergo therapy with either radiation or surgery. Alternative therapies such as cryosurgery, high intensity focused ultrasound, and herbal therapy have not been fully assessed for

the management of clinically localized prostate cancer. There is no clear evidence to suggest that one approach is significantly better than another and the decision is often left to the treating physician and patient.

Radiation therapy may be administered by external beam, brachytherapy or a combination of the two. There are newer radiation modalities that fractionate the radiation differently (e.g. IMRT, cyberknife) that serve to decrease the number of treatments but these are all still different forms of external beam radiotherapy. The major side effects of radiation therapy are erectile dysfunction, in approximately 40%, and radiation proctitis. Stress urinary incontinence does not often occur after radiation therapy, but severe voiding symptoms due to bladder irritation occurs in approximately 15% of patients with significant voiding symptoms (AUA symptom score of > 15 out of 35) who undergo brachytherapy. Brachytherapy cannot be performed in patients with large prostate glands. Side effects from radiation may be minimal at first and tend to increase with time.

Surgical removal of the prostate can be performed either by open surgery or by laparoscopic surgery with or without robotic assistance and via a retropubic or perineal approach. The major risks of surgery are erectile dysfunction and stress urinary incontinence. The results vary based upon patient age, experience of the surgeon and whether or not the patient is a candidate for "nerve-sparing." In general, side effects are greatest immediately after surgery and tend to improve with time. For non-localized prostate cancer, hormonal therapy is also used. Prostate cancer was the first malignancy to be shown to be hormone dependent and for this discovery, a Nobel Prize was awarded in the mid twentieth century. Hormone therapy involves depriving the prostate cancer of male sex hormones (androgens) to control cancer activity. Hormonal manipulation to decrease androgens in the blood stream by either surgical castration or the use of long acting drugs to suppress pituitary function is used to suppress cancer activity. Forms of androgen deprivation include luteinizing hormone-releasing hormone (LH-RH) agonists (leuprolide acetate, goserelin, triptorelin, and histrelin) that reduce pituitary drive to the testes to make testosterone (after initial surge or "flare" in pituitary drive); LH-RH antagonists (degarelix) that reduce pituitary drive to the tests to make testosterone without an initial surge in production; antiandrogens (flutamide, bicalutamide, nilutamide, and enzalutamide) that block the action of testosterone on end organs; surgical castration with simple orchiectomy to remove the testicles and reduce natural testosterone levels; and adrenal gland testosterone blockers (ketoconazole and aminoglutethimide) that block the remaining 5% of testosterone that is made by the adrenal gland. When hormonal treatments are combined to bring testosterone levels as low as possible, this is known as total androgen blockade. Studies have not shown whether total androgen blockade is more effective than orchiectomy or an LH-RH agonist alone.

Hormone therapy is most commonly used to control cancer growth after it has metastasized. Since hormone therapy is only palliative and not curative, most prostate cancers will become hormone refractory and grow in the absence of testosterone. Side effects from hormonal therapy include impotence, hot flashes, loss

of sexual desire, breast growth or tenderness and osteoporosis. Antiandrogens can cause nausea, diarrhea, or breast growth or tenderness, skin rashes and rarely, liver problems but fewer sexual side effects.

There is no clear "right" answer for the typical patient diagnosed with prostate cancer today. Surgical therapy is generally preferred method of management for the younger patient with a 30-year life expectancy who has localized cancer. Radiation is generally recommended for the patient over 70 years of age with localized cancer. There is an increasing role for active surveillance given the increased diagnosis of prostate cancer in the post-PSA era. The prognosis for most patients with early stage disease is quite good but some patients have metastases at the time of diagnosis. For further information about the management of clinically localized prostate cancer, please refer to the AUA clinical practice guidelines (<http://www.auanet.org/education/guidelines/prostate-cancer.cfm>). The management of metastatic disease today is palliative with hormonal manipulation in the absence of a cure.

REFERENCES

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AUA Speaks Out Against USPSTF Recommendations http://www.auanet.org/press-media/press_releases/article.cfm?articleNo=323

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