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. 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 contribution of the prostate to the ejaculate includes; 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 behind lung cancer.

Autopsy 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. The incidence of clinically diagnosed prostate cancer and mortality is highest in Blacks, intermediate in
Caucasians and least in Asians. There currently is no effective systemic therapy for prostate cancer. 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 a palliative effect of hormonal therapy, there are no cures for metastatic prostate cancer.

**Prostate Cancer Screening**

Unfortunately, there are no symptoms with early prostate cancer. As such, the AUA currently recommends that interval prostate cancer screening be offered to all men beginning at 40 years of age in the form of baseline PSA measurement and digital rectal exam. The serum PSA test should not be considered a substitute for the digital rectal exam. Rather, the tests are complimentary and, 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, prostatitis, and urogenital tract instrumentation (ie catheter placement). 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 overdiagnosis: 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.

The AUA strongly disagrees with the USPSTF’s recommendation and has taken steps to better educate both the public and the health profession at large regarding the role of serum PSA and digital rectal exam in prostate cancer screening. Since the introduction of PSA as a screening tool in 1986, the number of total prostate cancer deaths has decreased by approximately 30%. Also, the number of patients suffering from the dire consequences of advanced prostate cancer (to include severe bone pain and bulky tumors that obstruct the urinary tract) has decreased, an important victory that the USPSTF’s recommendation fails to take into account. The American Cancer Society and the American Society of Clinical Oncologists agree with the AUA’s stance. Consequently, the AUA has worked with other patient and physician advocacy groups to introduce legislature that will allow for specialist input into the USPSTF’s recommendations and prevent the issuing of sweeping mandates that could potentially confuse patients and compromise care.

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.

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 main arterial blood supply to the prostate is the inferior vesical artery. 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. The clinical stage is based upon how it was detected and the digital rectal exam.
T1 disease is based upon whether it was discovered inadvertently in the tissue obtained during surgery for benign disease (T1a involving < 5% and T1b is >5%) or whether the cause of the biopsy was 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 treatment of localized prostate cancer includes radiation therapy, surgery, and expectant management (watchful waiting). 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. Expectant management 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.

Radiation therapy may be administered by external beam, brachytherapy or a combination of the two. 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. Moreover, brachytherapy cannot be performed in patients with large prostate glands.

Surgical removal of the prostate can be performed either by open surgery, radical retropubic or perineal, or by laparoscopic surgery with out without robotic assistance. 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. 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.”
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 and goserelin) that reduce pituitary drive to the testis to make testosterone; antiandrogens (flutamide, bicalutamide, and nilutamide) that block the action of testosterone on end organs; simple orchietomy 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 orchietomy 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, and osteopenia. Bone densitometry should be used periodically to assess bone strength. Antiandrogens can cause nausea, diarrhea, or breast growth or tenderness, skin rashes and rarely, liver problems

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 or expectant management is generally recommended for the patient over 70 years of age with localized cancer. The prognosis for most patients with early stage disease is quite good but some patients have metastases at the time of diagnosis. The management of metastatic disease today is palliative with hormonal manipulation in the absence of a cure.
INTERACTIVE CASES IN UROLOGY

Prostate Cancer 1 - The Case of Mr. Powers' Prostatic Nodule

Prostate Cancer 2 - The Case of Mr. Powers' Prostate Cancer Recurrence
<http://www.auanet.org/eforms/casestudies/index.cfm?slm=Prostate%20Cancer%20Recurrence>

PSA Screening 1 - Mr. Herman’s Prostate - Coming Soon

PSA Screening 2 - A Troop of Small Cases - Coming Soon

READING LIST

AUA Guidelines for prostate cancer screening:


AUA Speaks Out Against USPSTF Recommendations
http://www.auanet.org/content/health-policy/government-relations-and-advocacy/in-the-news/uspstf-psa-recommendations.cfm?WT.mc_id=EML6621MKT

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

*updated October, 2012*