

PROSTATE CANCER: SCREENING AND MANAGEMENT

KEY WORDS: Prostate cancer, PSA, Screening, Radical Prostatectomy

LEARNING OBJECTIVES

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

- Identify and name the basic anatomic zones of the prostate gland, including the locations where prostate cancer develops
- Describe the physiologic role of the prostate – “what does the prostate do?”
- Describe the distinctive epidemiological features of prostate cancer
- List the signs & symptoms of prostate cancer
- Describe the natural history and the common patterns of progression of prostate cancer
- List the major components in the staging of prostate cancer
- Briefly describe the treatment options for localized and metastatic prostate cancer
- 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. [\[CLICK HERE TO VIEW FIGURE 90-2 FROM 9TH ED, CAMPBELL-WALSH\]](#). 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

There are no symptoms with early prostate cancer. Prostate cancer screening is currently recommended for all adult men and is comprised of yearly digital rectal exam and serum PSA. The serum PSA test is not a substitute for digital rectal exam since they are complimentary. Neither of these tests is diagnostic but rather an indication to proceed to a prostate biopsy. The optimum age to begin and end screening has not been established. The AUA has recently revised its guidelines for PSA screening (April 2009) and now recommends that baseline PSA screening be considered in men at age 40 years of age instead of age 50 years. If significant risk factors such as a strong family history or African American race are present, then screening should be considered on a regular basis after that. It is now felt that prostate cancer screening should end at age 74 years. The PSA threshold level that performs best is not known. In prior guidelines, the standard cut off for a normal, absolute PSA level was 4.0 ng/ml. Above this level, a prostate biopsy was routinely recommended. More recently, investigators have been debated whether an absolute level of 2.5 ng/mL should be used instead of 4ng/mL. To summarize this issue, the latest PSA screening guidelines now state that no single PSA threshold value should be used to prompt a prostate biopsy. Instead, the decision to biopsy should be fueled by DRE results, other PSA performance variables (velocity, density, free and total levels), and clinical information including patient age and ethnicity, comorbidities and prior biopsy history.

Given this, various strategies have been employed to improve the performance of PSA screening in clinical practice.

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 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. [[CLICK HERE TO VIEW TABLE 94-5 FROM 9TH ED, CAMPBELL-WALSH](#)] 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 or 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 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, and osteopenia. 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.

READING LIST

AUA Guidelines for prostate cancer screening: <http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/psa09.pdf>

AUA Guidelines for the management of clinically localized prostate cancer: 2007 update. <http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/proscan07/content.pdf>

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