

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. List the signs & symptoms of prostate cancer
5. Describe the natural history and the common patterns of progression of prostate cancer
6. List the major components in the staging of prostate cancer
7. Briefly describe the treatment options for localized and metastatic prostate cancer
8. 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.

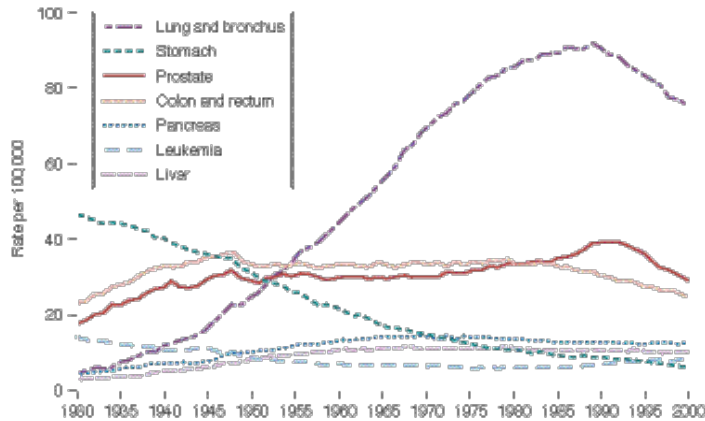


Figure 90-2 Cancer death rates for men, United States, 1930-2000, age adjusted to the 2000 U.S. standard population. (Source: Surveillance, Epidemiology, and End Results Program, 1975-2001, Division of Cancer Control and Population Sciences, National Cancer Institute, 2004.)

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

PSA Derivative	Definition	Limitations
PSA density	Serum PSA/prostate volume ≥ 0.15 associated with the presence of prostate cancer	Variations in prostate size, shape, ratio of stromal to epithelial tissue. Variations in ultrasound measurement.
PSA velocity	Rate of change of PSA $> 0.75\text{ng/mL}$ per year	Variations in assay, lack of previous results. Need for extended wait to make clinical recommendations.
Age-specific PSA	Age-specific normalized PSA values	Risk missing significant cancer in older men, over-detection in younger men.

PSA, prostate-specific antigen

Widespread prostate cancer screening initially led to a rise in the incidence of the disease that has subsequently fallen back to a lower incidence. The stage of most prostate cancers now is also earlier than it used to be. 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. Together, they are the most useful first-line test for diagnosis of prostate cancer. 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 but most guidelines recommend beginning by age 50 or earlier if you have significant risk factors such as a strong family history or African American race and ending screening at age 74 years. Men with a first-degree relative with prostate cancer have a twofold increased risk of developing prostate cancer. The PSA threshold level that performs best is not known. The standard cut off for a normal, absolute PSA level is 4.0 ng/ml. More recently, investigators have debated whether an absolute level of 2.5 ng/mL should be used instead of 4ng/mL. A strong correlation exists between serum PSA and prostate volume. Some medications affect PSA levels. Finasteride (Proscar) often times reduces serum levels in half. 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 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,

c. 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.

TNM				
1997	1992	Description	Whitmore-Jewett	Description
TX	TX	Primary tumor cannot be assessed	None*	None
T0	T0	No evidence of primary tumor	None	None
T1	T1	Nonpalpable tumor-not evident by imaging	A	Same as TNM
T1a	T1a	Tumor found in tissue removed at TUR; 5% or less is cancerous and histologic grade <7	A1	Same as TNM
T1b	T1b	Tumor found in tissue removed at TUR; >5% is cancerous or histologic grade >7	A2	Same as TNM
T1c	T1c	Tumor identified by prostate needle biopsy due to elevation in PSA	None	None
T2	T2	Palpable tumor confined to the prostate	B	Same as TNM
T2a		Tumor involves one lobe or less	B1	Same as TNM
	T2a	Tumor involves less than half of one lobe	B1N	Tumor involves half of lobe-surrounded by normal tissue on all sides
		Tumor involves more than one lobe	B2	Same as TNM
	T2b	Tumor involves more than half of a lobe but not both lobes	B1	Same as TNM
None	T2c	Tumor involves more than one lobe	B2	Same as TNM
T3	T3	Palpable tumor beyond prostate	C1	Tumor <6 cm in diameter
T3a	T3a	Unilateral extracapsular extension	C1	Same as TNM
T3b	T3b	Bilateral extracapsular extension	C1	Same as TNM
T3c	T3c	Tumor invades seminal vesicle(s)	C1	Same as TNM
T4	T4	Tumor is fixed or invades adjacent structures (not seminal vesicles)	C2	Same as TNM
T4a	T4a	Tumor invades bladder neck, external sphincter, and/or rectum	C2	Same as TNM
T4b	T4b	Tumor invades levator muscle and/or fixed to pelvic wall	C2	Same as TNM
N(+)	N(+)	Involvement of regional lymph nodes	D1	Same as TNM
None	None	None	D0	Elevated prostatic acid phosphatase
NX	NX	Regional lymph nodes cannot be assessed	None	None
N0	N0	No lymph node metastases	None	None
N1	N1	Metastases in single regional lymph node, ≤2 cm in dimension	D1	Same as TNM
N2	N2	Metastases in single (>2 but ≤5 cm) or multiple with none >5 cm	D1	Same as TNM
N3	N3	Metastases in regional lymph node >5 cm in dimension	D1	Same as TNM
M(+)	M(+)	Distant metastatic spread	D2	Same as TNM
MX	MX	Distant metastases cannot be assessed	None	None
M0	M0	No evidence of distant metastases	None	None
M1	M1	Distant metastases	D2	Same as TNM
M1a	M1a	Involvement of nonregional lymph nodes	D2	Same as TNM
M1b	M1b	Involvement of bones	D2	Same as TNM
M1c	M1c	Involvement of other distant sites	D2	Same as TNM
None	None	None	D3	Hormonal refractory disease

NM, tumor, node, metastasis; TUR, transurethral resection.

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. 4 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." Prior radiation to the prostate is a risk factor for developing incontinence after radical prostatectomy.

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. 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.

COMPUTER BASED LEARNING CASES

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

<http://mycourses.med.harvard.edu/vp_view.asp?frame=Y&case_id=%7b806E4FE8-0499-4128-B682-18832B91425B%7d>

Prostate Cancer 2 - The Case of Mr. Powers' Prostate Cancer Recurrence

<http://mycourses.med.harvard.edu/vp_view.asp?frame=Y&case_id=%7b7DA7A5D4-5A1D-49CD-AFEE-F1FFEA634EFB%7d>

PSA Screening 1 - The Case of Mr. Herman's Big Dilemma

<http://mycourses.med.harvard.edu/vp_view.asp?frame=Y&case_id=%7b807D8FD4-854D-4424-8C8A-ABAB6A55CEEA%7d>

PSA Screening 2 - A Troop of Small Cases

<http://mycourses.med.harvard.edu/vp_view.asp?frame=Y&case_id=%7b915080FA-D40A-4CEB-AA91-7B1E414420DB%7d>

READING LIST

AUA Guidelines for the management of clinically localized prostate cancer: 2007 update. <http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=pc>

Bostwick DG, Burke HB, Djakiew D et al: Human prostate cancer risk factors. *Cancer* 2004;101:2371-2490

Partin AW, Kattan MW, Subong EN et al: Combination of prostate specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. *JAMA* 1997;277:1445.

Allaf ME, Carter HB: Update on watchful waiting for prostate cancer. *Curr Opin Urol* 2004;14:171-175.

Sharifi N, Gulley JL, Dahut WL: Androgen deprivation therapy for prostate cancer. *JAMA* 2005;294:238-244.