Surgery

VOIDING DYSFUNCTION - PROSTATE CANCER

OBJECTIVES:

After studying the summary of prostate cancer the student should be able to:

A. Give a differential diagnosis for a firm prostate nodule detected by digital rectal exam.
B. State the normal age specific PSA values.
C. Give a differential diagnosis for an elevated PSA in a 60-year-old man.
D. State the TNM staging for prostate cancer.
E. State three types of "curative" therapy for clinically localized prostate cancer.
F. State two important complications of each therapy.
G. Describe a hormonal therapy for a patient with locally advanced or metastatic prostate cancer.

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INTRODUCTION:

1. Prostate Cancer (CaP) is the most frequently diagnosed malignancy in North American men (except for non-melanotic skin cancer).

- CaP is the second leading cause of cancer-related deaths in North American men (after lung cancer).
- The lifetime risk of being diagnosed with CaP is 1 in 8, which is approximately the same as breast cancer for women.
- The lifetime risk of being diagnosed for a 50 year old male increases to 50%.
- The lifetime risk of dying from CaP is 1 in 26.

2. Few risk factors are known for CaP.

- Men with a first-degree relation (father or brother) with CaP have a 2X greater risk of developing CaP themselves. A man with two first-degree relatives with CaP has a relative risk of 9X the normal population.
- African American men have a higher risk of developing CaP and a higher mortality rate.
- Diets high in saturated fats may increase the risk of CaP and diets high in soy may be protective (perhaps explaining the lower prevalence in Asian men compared to North American men).

3. Benign prostatic hyperplasia is not a precursor or risk factor for prostate cancer.

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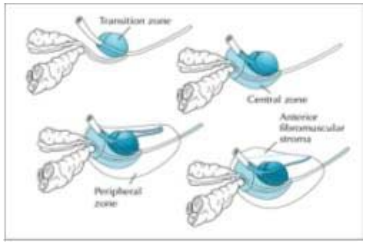
CLINICAL PRESENTATION:

1. The majority of patients are diagnosed because of abnormalities on a PSA test or digital rectal exam. Few symptoms occur unless the tumour is locally advanced or has metastasized to the bones (most common site for metastases).
2. The majority (60-70%) of nodules develop in the peripheral zone of the prostate and does not usually produce voiding symptoms (bladder outlet obstruction) unless it has progressed to a large size. 10-20% of tumours arise in the transition zone and 5-10% develop in the central zone.



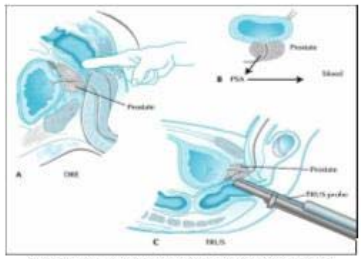
Zonal Anatomy of the Prostate

3. Differential Diagnosis of a firm prostate nodule detected by DRE:

A. Bening Prostatic Hyperplasia (BPH)
B. Prostatic calculi
C. Prostatic cysts
D. Prostatic tuberculosis
E. Chronic granulomatis prostatitis
F. Previous TURP or needle biopsy

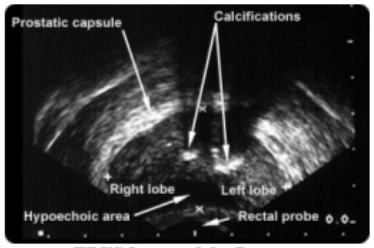
4. **The diagnosis is made by needle biopsy of the prostate guided by transrectal ultrasound (TRUS)** where 6 to 12 separate biopsies are taken from the apex, middle and base of the gland on both sides.

- Indications for TRUS with needle biopsy include a PSA > 4 ng/dl or palpable nodule in men who are candidates for treatment.
- When arranging a TRUS with biopsy, the patient should be told to stop any aspirin, NSAIDs or Coumadin well in advance of the procedure. They are given antibiotics to take around the time of the biopsy.
- TRUS with prostate biopsy is usually well tolerated although hematuria, hematospermia and blood per rectum may occur.
- **Transurethral resection of the prostate (i.e.: for BPH) is not used as a biopsy since most cancers arise from the peripheral zone of the gland and would not be detected. Similarly, transurethral resection of the prostate will not "cure" prostate cancer since the tissues from the peripheral zone of the gland are not completely removed.**



Work-up for prostate cancer involves the DRE, PSA and TRUS

Needle biopsy of prostate guided by TRUS



TRUS Image of the Prostate

5. Metastatic symptoms include:

A. Weight loss and loss of appetite
B. Bone pain with or without pathologic fracture (because prostate cancer, when metastatic, has a strong predilection for bone)
C. Lower extremity pain and edema from nodal metastases obstructing venous and lymphatic tributaries

6. Indications for bone scan (after biopsy shows prostate cancer) include:

- PSA > 10 ng/dl
- DRE suggesting stage T3 or T4
- Gleason score > 7

- Bone pain

Metastatic Prostate Ca seen on bone scan

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BACKGROUND ON PSA:

1. Before prostate-specific antigen (PSA) was available, the only methods to help detect this disease were the patient's symptoms, digital rectal examination (DRE) and the serum marker prostate acid phosphatase. With these diagnostic tools, nearly 75% of men with prostate cancer had locally advanced or metastatic disease at the time of diagnosis. Currently, the number of men with metastatic disease at diagnosis is less than 5%. Because of PSA testing, 30-35% of patients with clinically significant prostate cancer can be diagnosed before the disease can be palpated in the prostate; in more than 90% of patients, prostate cancer can be diagnosed before symptoms occur.

2. **For clinical purposes, PSA is considered prostate organ specific but not prostate cancer specific.** A major limitation of PSA as a prostate cancer marker is the overlap in values between BPH and prostate cancer. The PSA produced by cancer cells may vary according to the grade of the cancer. High-grade cancer cells tend to lose their ability to shed tumour markers. A Gleason grade 5 prostate cancer produces less PSA than a grade 3 cancer. Some patients with advanced prostate cancer may have low or undetectable PSA levels.

3. **Differential Diagnosis for elevated PSA:**

A. BPH Acute
B. Subclinical or chronic prostatitis infection
C. Prostatic infarction
D. Vigorous prostate massage (no change with normal DRE)
E. Prostate needle biopsy (increases PSA by a median of 7.9 ng/mL or 6.5 times baseline values within 5 minutes following the biopsy, and this level persists for 24 hours)

4. PSA levels can be altered by pharmacologic therapies:

- The 5-alpha reductase inhibitor finasteride (Proscar) tends to decrease PSA by 50% in most men with BPH after a 6-month course of therapy, and then the level remains stable.
- The alpha-1-adrenergic antagonists do not alter PSA levels.

5. A modest increase in PSA levels has been reported following ejaculation.

6. Cystoscopy, urethral catheterization, and transrectal prostate ultrasonography do not usually elevate PSA..

7. The half-life and metabolic clearance rate have been determined from studies of patients undergoing radical prostatectomy. Stamey et al (1987) found the half-life to be 2.2 days +/- 0.8, while Oesterling et al (1993) calculated it to be 3.2 days +/- 0.1. Because of its relatively long half-life, a minimum of 2-3 weeks is required for the serum PSA to reach its nadir following radical prostatectomy, when it should be undetectable.

8. **PSA should always be interpreted along with the findings on digital rectal exam.** The following table shows the risk of detecting prostate cancer on a transrectal biopsy of the prostate given the PSA and DRE findings.

	PSA < 4 ng/ml	PSA 4 – 10 ng/ml	PSA > 10 ng/ml
DRE "benign"	2 – 5 %	20 – 30 %	50 – 60 %

DRE "nodule"	10 – 20%	60 – 70 %	90 %

• The majority of men with a PSA > 4 ng/ml will have a benign prostate biopsy so efforts have been made to improve the specificity of PSA testing (and decrease the number of unnecessary biopsies). Specificity can be improved by using age-adjusted values, PSA velocity and determinations of free/total PSA ratios.
9. Strategies to increase specificity of PSA:
A. Age-adjusted reference range for PSA (based on the assumption that older men have bigger prostates due to BPH);

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9. Strategies to increase specificity of PSA:

A. Age-adjusted reference range for PSA (based on the assumption that older men have bigger prostates due to BPH);

Age (years)	Upper limit of normal PSA (ng/dl)
40 – 49	2.5
50 – 59	3.5
60 – 69	4.5
70 – 79	6.5

• Use of this reference range will increase the number of biopsies in younger men and decrease the number of biopsies in older men. These values have not been universally adopted and many clinicians still use a cut-off of 4.0 ng/dl as an indication for biopsy.

B. **PSA velocity** refers to the change in PSA values over time. It has been shown that PSA values are likely to rise more rapidly with CaP than with BPH. In general, three measurements are required separated by 6 months. An increase in PSA of greater than 0.75 ng/dl per year is suggestive of CaP. For men with a low PSA, an increase of greater than 20% per year is suggestive of CaP.
C. **Free versus total PSA** refers to the amount of PSA that is free within the serum versus the amount of PSA bound to serum proteins (alpha-1-antichymotrypsin and alpha-2-macroglobulin). **Elevations of PSA due to benign disease are more likely to raise the free PSA** ("It's good to be free").

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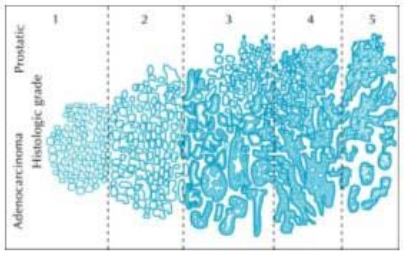
PSA SUMMARY:

Because of these statistics showing a relatively low mortality for untreated, organ-confined CaP, screening the healthy male population to detect such cases is a controversial topic. PSA screening is widely advocated by many American organizations but it received a class "C" recommendation from the Canadian Task Force on the Periodic Health Examination (insufficient evidence to recommend or refute). When a PSA of 4.0 ng/dl or greater in asymptomatic men aged 55 to 74 years is used for screening purposes, the sensitivity is 87% and the specificity is 83%. For comparison, screening mammography in women aged 50 – 59 years has a sensitivity of 90% and a specificity of 83%. The essential argument about the importance of PSA screening for CaP is that the population survival may not change with early diagnosis and treatment since many (or most) men will eventually die of causes other than prostate cancer. The other side of this argument is that CaP is already the second leading cause of cancer deaths in men and there is no curative treatment once the cancer is spread beyond the prostate. **In the absence of solid evidence, physicians and patients must make their own decision about PSA screening based on their own perceived life expectancy, risk of CaP, fear of cancer, acceptance of surgery or radiation and fear of treatment-related complications.**

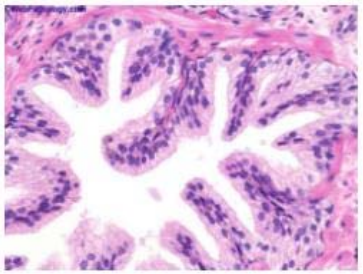
TNM - Staging
T1 - clinically unapparent (not palpable or visible by imaging)
T1a - incidental discovery in 5% or less of tissue resected (by TUPR)
T1b - incidental discovery in greater than 5% of tissue resected (by TUPR)
T1c - identified on needle biopsy (because of elevated PSA, for example)
T2 - palpable but confined to the prostate
T2a - involves one lobe
T2b - involves both lobes
T3 - extends beyond the prostatic capsule
T3a - extracapsular extension
T3b - involves seminal vesicle(s)
T4 - invades adjacent structures such as bladder neck, external sphincter, rectum, levator muscles

Grading
1. Histologic grading of CaP is done with the "**Gleason score**". The Gleason system is based on the histologic pattern of glandular differentiation as seen under low magnification. A "grade" is given to the predominant pattern seen as well as a second "grade" to the second most prevalent pattern. The two grades are added together to give a Gleason score. Gleason grades range from 1 (well-differentiated) to 5 (poorly-differentiated):

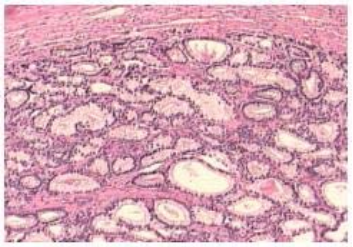
• Gleason scores of 2, 3 or 4 are considered low grade or well-differentiated.
• Scores of 5, 6 or 7 are considered moderate grade or moderately differentiated.
• Scores of 8, 9 or 10 are high grade or poorly differentiated.



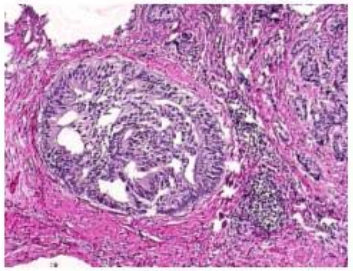
Gleasing Grading System



Normal Prostate Gland
In this benign gland, the luminal contour shows tufts and papillary infoldings.
The tall secretory epithelial cells have pale clear cytoplasm and uniform round or oval nuclei.
Prominent nucleoli are not seen. Many basal cells can be identified.

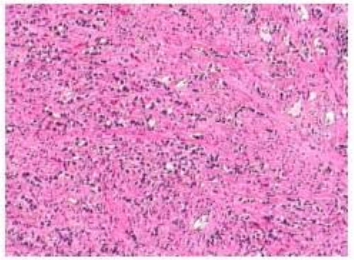


Gleason Grade 1
The focus of cancer is not circumscribed. The glands are round to oval and uniformly placed.
There are no sharply-angulated or distorted glands.



Gleason Grade 3

Gleason grade 3 is the most commonly seen pattern. Even at low magnification,
one can easily appreciate the variation in size, shape, and spacing of glands. Many small
glands have occluded or abortive lumens. There is no evidence of glandular fusion.



Gleason Grade 5
Tumor cells are arranged in solid sheets with no attempts at
gland formation in this example of Gleason grade 5.

2. The Gleason score and the clinical stage are the two most important factors influencing prognosis.

3. The natural history of clinically localized CaP is variable causing much debate about the importance of early detection. Some retrospective studies have attempted to describe the natural history of untreated, organ-confined CaP (see below). Of course, there may be considerable morbidity associated with the diagnosis of CaP that is not reflected in these mortality statistics.

10 year disease-specific survival with no treatment

Author	Well-Differentiated (2,3,4)	Moderately-differentiated (5,6,7)	Poor-differentiated (8,9,10)
Lu-Yao	93%	77%	45%
Albertson	91%	76%	54%
Chodak	87%	87%	34%

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MANAGEMENT:

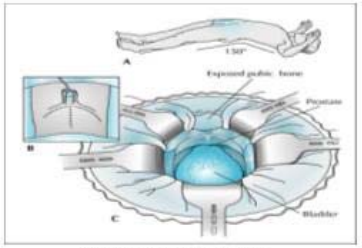
1. **"Watchful waiting"** is a term used to describe a program of ongoing, periodic rectal examinations and PSA measurements for men with organ-confined CaP who do not want or are not candidates for curative treatments. Given the natural history of CaP, **watchful waiting is a good choice for men with a life expectancy of 10 years or less and who have a low or intermediate Gleason score.**Local progression or the development of metastases during a program of watchful waiting is managed with radiotherapy or androgen ablation therapy.

2. **Curative treatments:**

A. Radical prostatectomy includes removal of the prostate and seminal vesicles with reconstruction of the bladder neck with the urethra. It may be performed through a perineal or retropubic (most common) approach. Outcomes after surgery depend on many variables including final pathologic stage, Gleason score, pre-operative PSA, positive surgical margins and lymph node involvement. Complications include:

a. Impotence
b. incontinence.

- Impotence rates vary widely and depend on whether the surgery attempts to spare the cavernosal nerves or not.
- Total incontinence is rare but some stress incontinence may occur in approximately 30% of patients.



Radical Prostatectomy

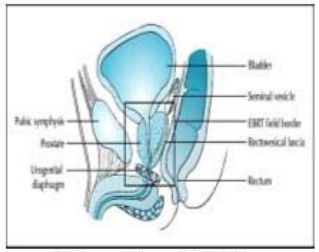
B. External beam radiotherapy delivers 45 to 50 Gy to the prostate delivered over multiple treatments. Bladder and rectal toxicity limit the amount of radiation that can be given using standard techniques. Using CT scanning to create a 3 dimensional template of the prostate has allowed for increased amounts of radiation (70 Gy or more) to be delivered to the prostate without causing excess bladder or rectal complications (called "conformal radiation therapy").

Acute complications (are common and typically do not require any specific treatment) include:

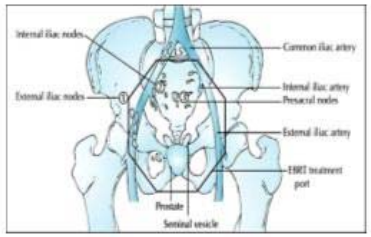
a. Fatigue
b. Urinary frequency
c. Diarrhea
d. Tenesmus

Later complications (may be more severe) include:

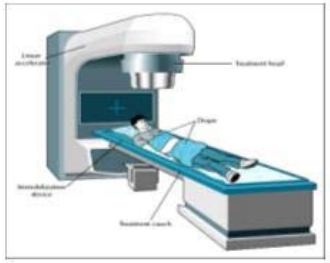
a. Recurrent hemorrhagic cystitis
b. Proctitis with persistent rectal bleeding
c. Impotence (in 50% of men)
d. Incontinence
e. Urethral strictures.



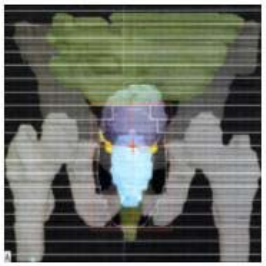
External Beam Radiation



External Beam Radiation



External Beam Radiation

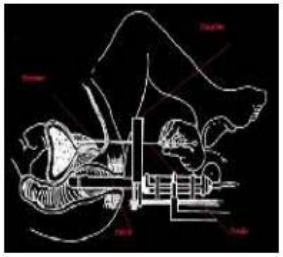


External Beam Radiaiton

"Conformal" radiaition therapy uses 3D reconstruction based on CT scanning.
This allows more precise delivery of a greater amount of radiation

C. Brachytherapy (implantable radioactive seeds) for CaP was originally studied in the 1970's but has become popular again with the development of newer radioactive isotopes. Currently, iodine, palladium and iridium isotopes are most commonly used. Under spinal or general anaesthesia, multiple "seeds" are placed into the prostate tissue via transperineal needles (guided by transrectal ultrasound). The seeds are left in the prostate permanently.
Complications:

a. Radiation cystitis, hematuria, urgency incontinence are very common (usually resolve after 1-2 months)
b. Urinary retention (10-20%)
c. Impotence
d. Radiaiton proctitis



Schematic of Inserting Brachytherapy
Radioactive seed implants contain iodine, iridum or palladium isotopes are placed by trans-perineal needle using TRUS to guide the needle

Inserting Brachytherapy

Brachytherapy Seeds seen on X-ray

Note: Curative treatment should probably not be offered to men with a life expectancy of less than 10 years as the risks of these treatments are significant and the natural history of the disease is often slowly progressive.

3. **Metastatic disease or locally advanced disease** is usually treated with hormonal therapy:

A. Surgical castration (bilateral orchiectomy) is simple and relatively risk-free but psychological barriers make medical therapies more acceptable.

B. LHRH analogues taken as 2 or 3 month depot injections is the most popular therapy for metastatic CaP.

- Pulsatile release of LHRH from the hypothalamus normally causes LH release from the pituitary gland but this is interrupted by the sustained, constant LHRH levels obtained via depot injection and pituitary secretion of LH is down-regulated.
- Side effects of LHRH injections are hot flashes, gynecomastia, loss of libido, impotence, lethargy and loss of bone/muscle mass.

C. Antiandrogens:

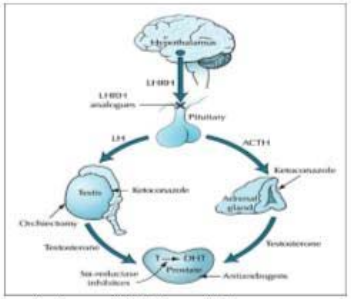
- Steroidal (cyproterone acetate) and non-steroidal (flutamide) both compete with dihydrotestoterone (DHT) for cytosolic receptors.
- Greater androgen blockade can be achieved by combining an antiandrogen with a LHRH agonist or orchiectomy.

D. Estrogens:

- Inhibits LH and induces apoptosis on tumour cells

Withdrawal of androgens induces apoptosis in normal and malignant prostatic epithelial cells however it will not completely eliminate the entire population of malignant cells. After complete, sustained androgen withdrawal, emergence of an androgen-independent cancer will occur in approximately 12 to 18 months and there are no

effective treatments that prolong survival. The median survival after the development of androgen independent CaP is 9 to 12 months. Although androgen withdrawal does not produce a durable response, no other treatment is superior. Metastatic bone lesions causing pain may be palliated with radiotherapy.



Androgen Withdrawal Therapy

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