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Prostate Cancer

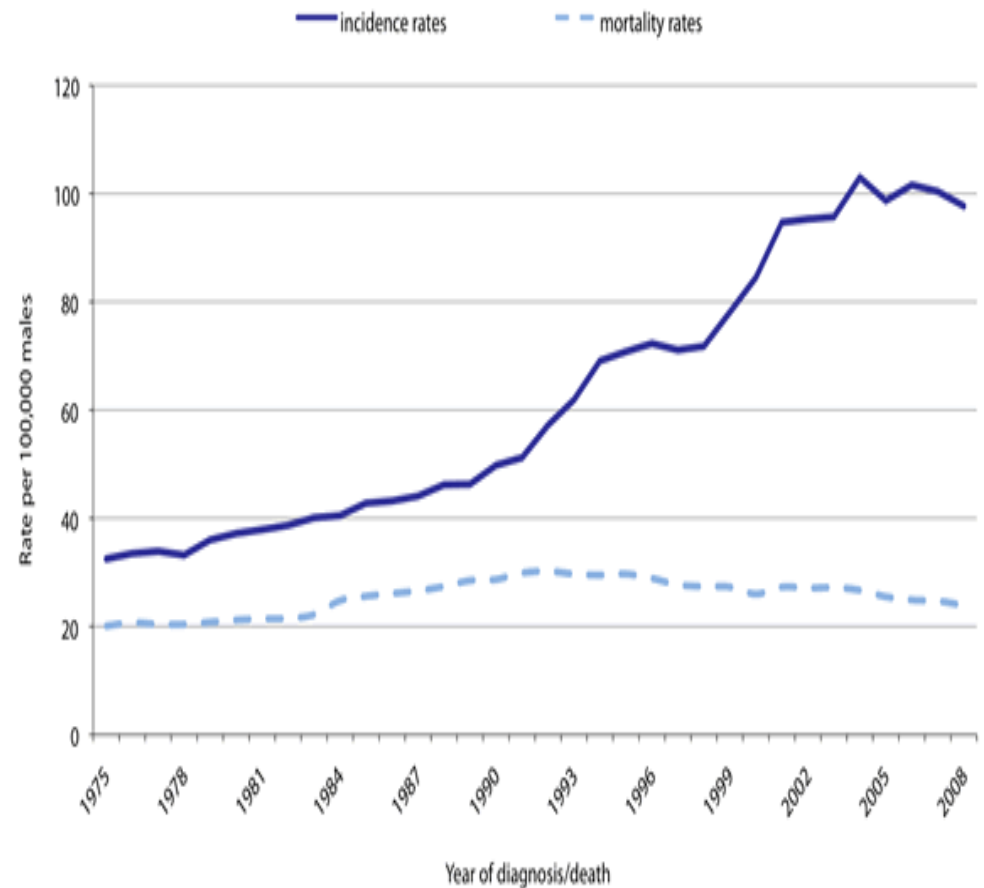
Epidemiology

IN the U.S :

- Prostate Cancer is **The most common non cutaneous Cancer**
- **200 000** new cases every year
- **30 000** Die annually
- Mortality dropped **40 % last 20 years** ?

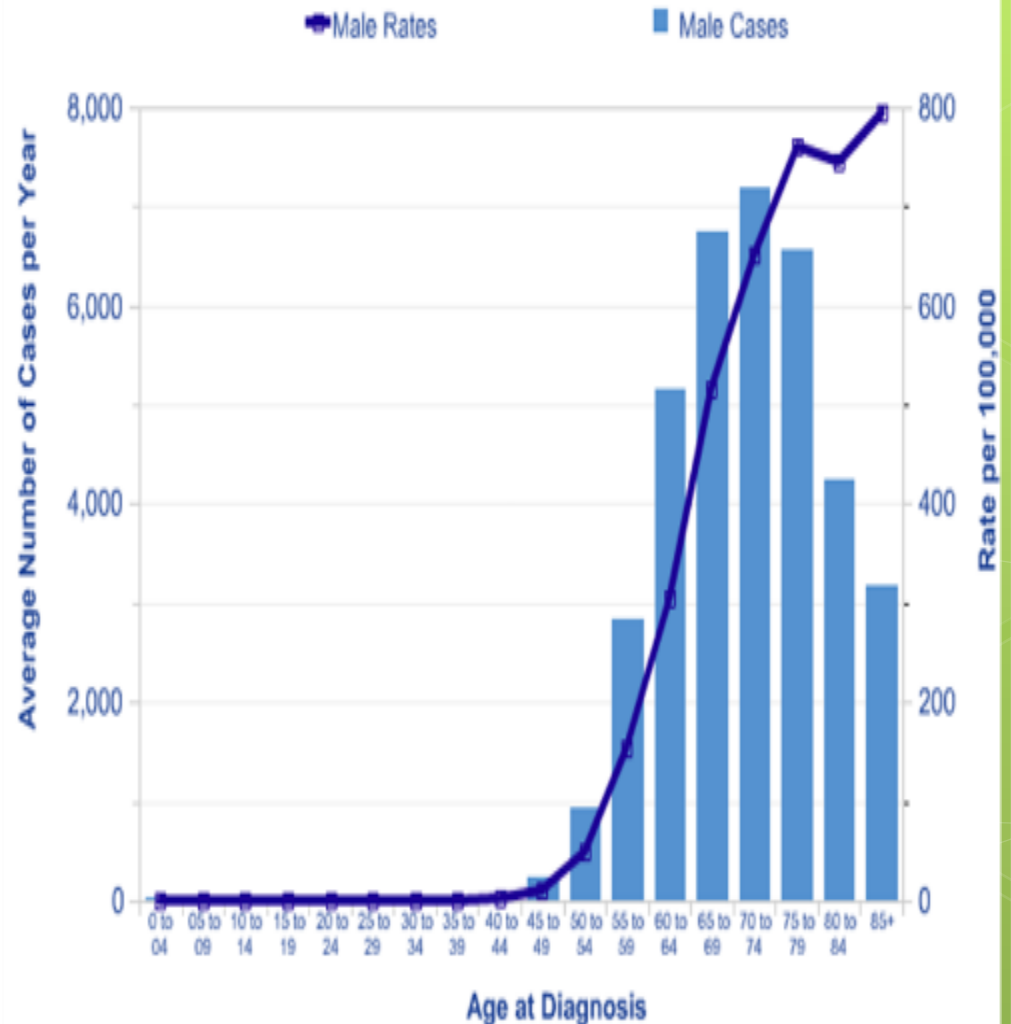
Better **screening** programs + improved **treatment**

- Number of prostate **CA deaths annually is far outweighed by the number of diagnoses**, and **most men** diagnosed ultimately die of other causes, most often **CVD**.
- Prevalence of prostate ca **increases with age**; However, unlike most cancers, which have a peak age of incidence, there is **no peak** for Prostate ca



Risk Factors

- Age : dramatic increase ;
probability in
men **< 40 Y/O :
1 in 10 000**
probability in
men **40 – 59 Y/O :
1 in 103**
probability in
men **60-79 Y/O :
1 in 8**



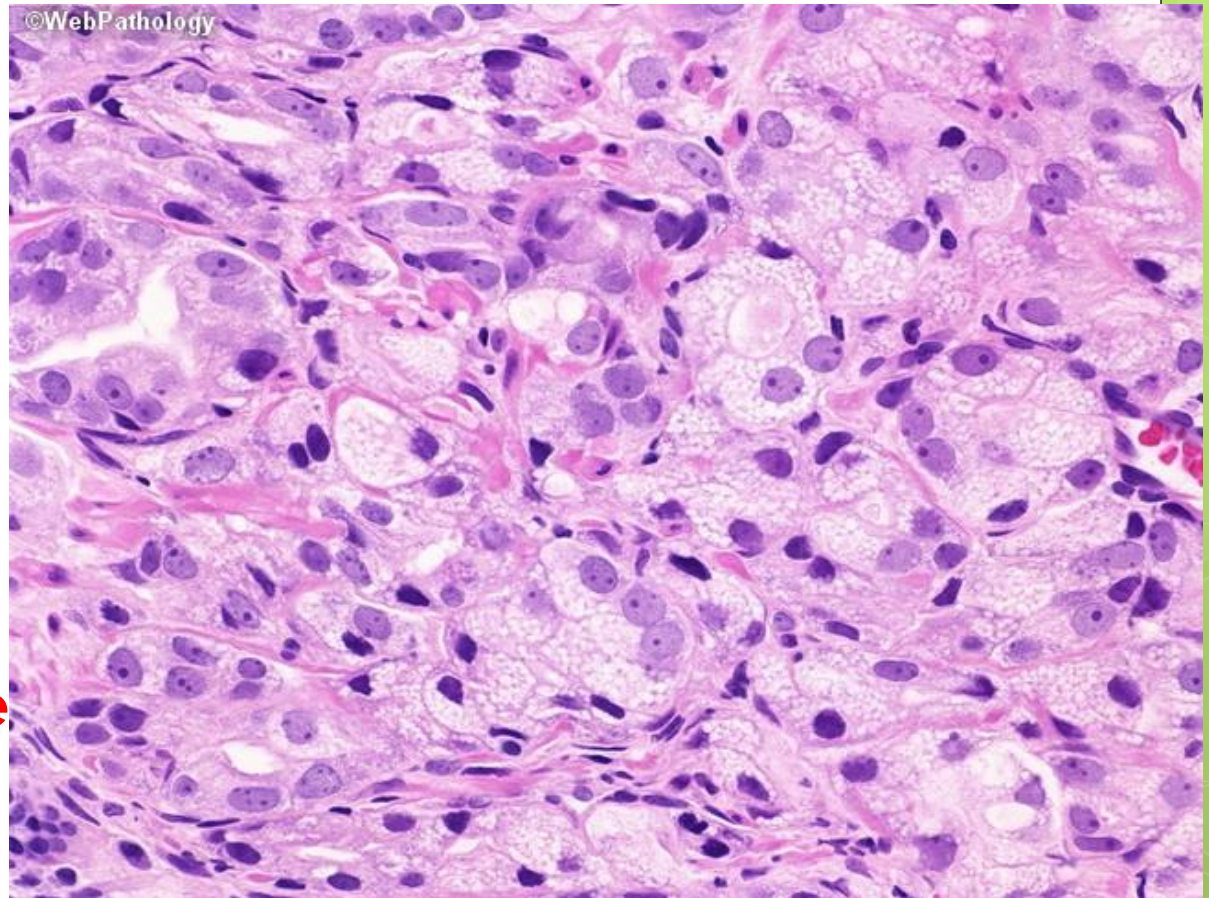
- **African Americans** have higher risk than other ethnicities
- **Family history** is a risk factor for itself + the **age of onset** in that person affects as well
- **70- fourfold**
- **60-fivefold**
- **50-sevenfold**

- Differences in diet, **Total fat intake, animal fat intake, and red meat intake** are associated with an increased risk of prostate cancer, whereas intake of **fish** is associated with a decreased risk.
- **Obesity ?** Higher grade+ recurrence
- In addition, lycopene, **selenium**, omega-3 fatty acids (fish), and **vitamin E** intake have been shown to be **protective**, whereas **vitamin D and calcium increase** risk

Pathology :

- More than **95 %** of the prosate cancers are **Adenocarcinomas**
- Nonadenocarcinomas ,:
- **Epithelial** : endometrioid, mucinous, signet-ring, adenoid cystic, adenosquamous, squamous cell, transitional cell, neuroendocrine, and comedocarcinoma
- **Nonepithelial** rhabdomyosarcoma, leiomyosarcoma, osteosarcoma, angiosarcoma, carcinosarcoma, malignant lymphoma, and metastatic neoplasms

- Cytologic features :
- **Hyperchromatic enlarged nuclei with prominent nucleoli**
- **Cytoplasm :**
- **Abundant , Blue tinged , basophilic**



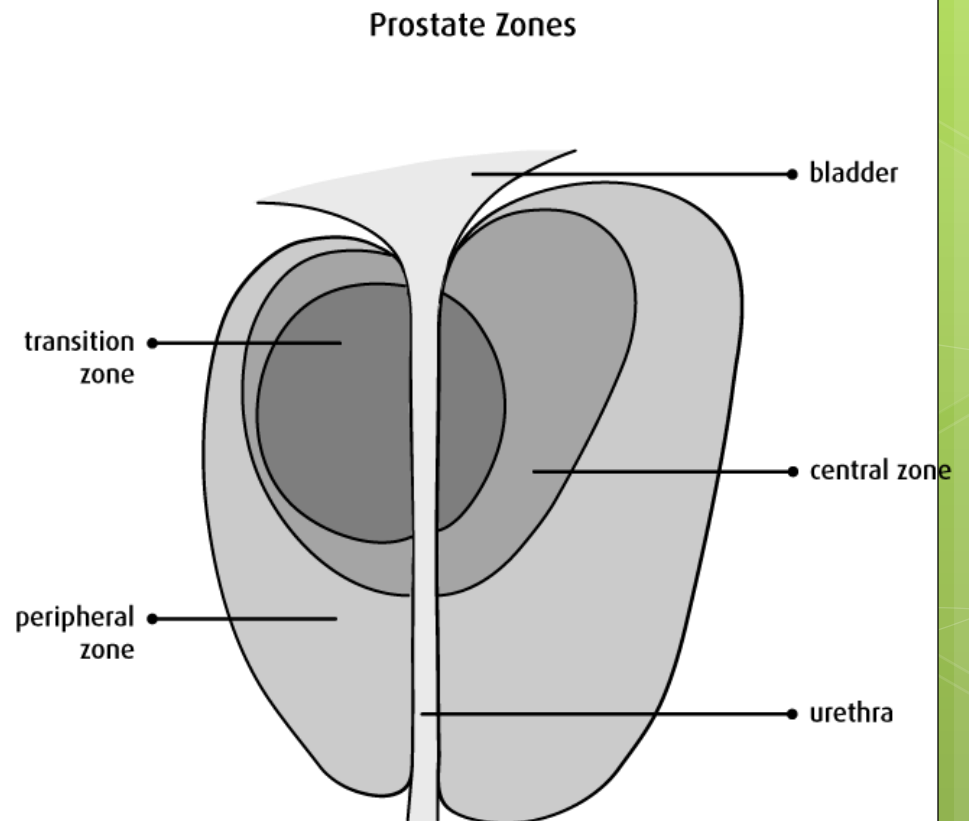
- The **basal cell layer is absent** in CaP, whereas it is present in normal glands, BPH glands, and the precursor lesions of CaP. If the diagnosis of CaP is in question, **high molecular- weight keratin immunohistochemical staining** is useful, as it preferentially stains basal cells.
- **Absence** of staining is thus consistent with CaP
- If still undetermined further stains **AMACR**
EPCA can help in diagnosis

Precursors

- Some lesions are thought to be **precursors** for Pca , **Prostatic intraepithelial neoplasia (PIN)** and **atypical small acinar proliferation (ASAP)**
- Risk is **higher** with (ASAP)
- **High** grade PIN is **almost similar** to Pca cytologically , except for the presence of a **basal cell layer**

Anatomical Distribution

- Approximately
- **60–70%** of cases of CaP originate in the **peripheral** zone,
- **10–20%** originate in the **transitional** zone,
- and **5–10%** in the **central** zone.



local invasion

- **Penetration of the prostatic capsule** by cancer is a common event and often occurs along perineural spaces:
- **Seminal vesicle** invasion
- Locally advanced CaP may invade the bladder trigone
- **Rectal involvement is rare** as Denonvilliers' fascia represents a strong barrier

Distant Mets


- **The axial skeleton is the most usual site of distant metastases**, with the **lumbar spine** being most frequently implicated.
- Involvement of **long bones can lead to pathologic fractures**
- **Vertebral body** involvement with significant tumor masses extending into the epidural space can result in **cord compression**.
- **Visceral metastases** most commonly involve the **lung, liver, and adrenal glands**

ANDROGENS ?

Meta-analysis: Testosterone Is Not a Risk for Prostate Cancer, But...

Nick Mulcahy

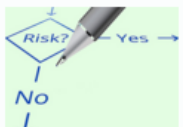
May 19, 2015

 16 comments



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EDITORS' RECOMMENDATIONS



**No Prostate Cancer Risk
With Testosterone for
Hypogonadism**

NEW ORLEANS — Testosterone, whether occurring naturally or taken as replacement therapy, does not cause prostate cancer or spur increases in prostate-specific antigen (PSA) levels in men, according to a new meta-analysis.

Clinical findings

Symptoms

- Most of them are **asymptomatic**
- Presence of symptoms suggests locally advanced or metastatic tumor
- **Obstructive or irritative voiding** complaints can result from local growth of the tumor into the urethra or bladder neck or from its direct **extension into the trigone** of the bladder, or much more commonly due to **coexisting BPH**.

- Metastatic disease may cause bone pain, symptoms of cord compression, including paresthesias and weakness of the lower extremities and urinary or fecal incontinence.

Signs

- **Direct rectal exam** may reveal **Induration or nodularity**, if detected, must alert the physician to the possibility of cancer and the need for further evaluation (ie, PSA, TRUS, and biopsy).
- Locally advanced disease with bulky **regional lymphadenopathy** may lead to **lymphedema** of the lower extremities
- Specific **signs of cord compression** relate to the level of the compression and may include weakness or spasticity of the lower extremities

Laboratory findings

- **Azotemia** can result from bilateral ureteral obstruction either from direct extension into the trigone or from retroperitoneal adenopathy.
- **Anemia** => metastatic disease.
- **Alkaline phosphatase elevation** => bone metastases.
- **Serum acid phosphatase elevation** => disease outside the confines of the prostate.



Prostate specific Antigen **PSA**

- PSA is a serine protease in the human kallikrein (hK) family produced by benign and malignant prostate tissues.
- **Liquefies the semen , dissolves the cervical mucus**
- It circulates in the serum as (free or **unbound**) or (**bound**) forms. PSA is used both as a **diagnostic** (screening) tool and as a means of **risk-stratifying** known prostate cancers.

- **Normal <4ng/ ml**
- Positive predictive value of raised PAS
 - 4-10 ng/ml : 20-30 %**
 - >10 ng/ ml : 42-71.**
- There is **no** level of PSA below which prostate cancer risk falls to zero.
- PSA is rather **indicative** of a continuum of risk; **the higher the level, the higher the risk**

False positive

- **BPH**
- **Trauma**
- **Iatrogenic**
- **Prostatitis**

- **It's prostate , not cancer specific**

False negative

Use of medications such as **5 α -reductase inhibitors** (like finasteride) must be ascertained, as these medications can **artificially lower** the PSA by approximately 50%. Interestingly, serum PSA levels have also been noted to be decreased in men with **high body mass indexes** compared with normal weight men, likely as a result of **hemodilution**

- Numerous strategies to *refine* PSA for cancer detection have been explored. Their common goal in general has been to **decrease the number of false-positive test results**, thus increasing the **specificity and positive predictive value** of the test and lead to fewer **unnecessary biopsies, lower costs, and reduced morbidity** of cancer detection.

- Attempts at refining PSA have included:
 - **PSA velocity** (change of PSA over time).
 - **PSA density** (standardizing levels in relation to the size of the prostate).
 - **PSA isoforms** (free vs. protein-bound molecular forms of PSA).

1. PSA kinetics-PSAV

- Refers to the **rate** of change of serum PSA; men with prostate cancer have amore rapidly rising serum PSA in the years before diagnosis than do men without prostate cancer. **Patients whose serum PSA increases by 0.75 ng/mL per year** appear to be at an increased risk of harboring cancer. However, an elevated PSAV should be considered significant only when several serum PSA assays are carried out by the same laboratory over a period of at least 18 months.
- Very rapid PSA increases may be indicative of prostatitis (symptomatic or otherwise) rather than cancer.
- the optimal use of PSA kinetics remains controversial

2- PSA Density

- PSA levels are elevated on average approximately 0.12 ng/mL per gram of BPH tissue. Thus, patients with enlarged glands due to BPH may have elevated PSA levels. **The ratio of PSA to gland volume is the psa density.**
- prostate biopsy taken only if the PSA density exceeds **0.1 or 0.15**
- Problems with this approach include the facts that (1) epithelial–stromal ratios vary from gland to gland and only the epithelium produces PSA, (2) errors in calculating prostatic volume based on TRUS may approach 25%, (3) it still requires TRUS, which, is still invasive and uncomfortable.
- **Instead of adjusting the PSA to total prostate volume, some have advocated adjusting it to transition zone volume (PSA transition zone density, PSAT.)**

3- Molecular forms of PSA

- Early studies suggest that prostate cancer patients demonstrate a **lower percentage of free PSA** than do patients with benign disease.

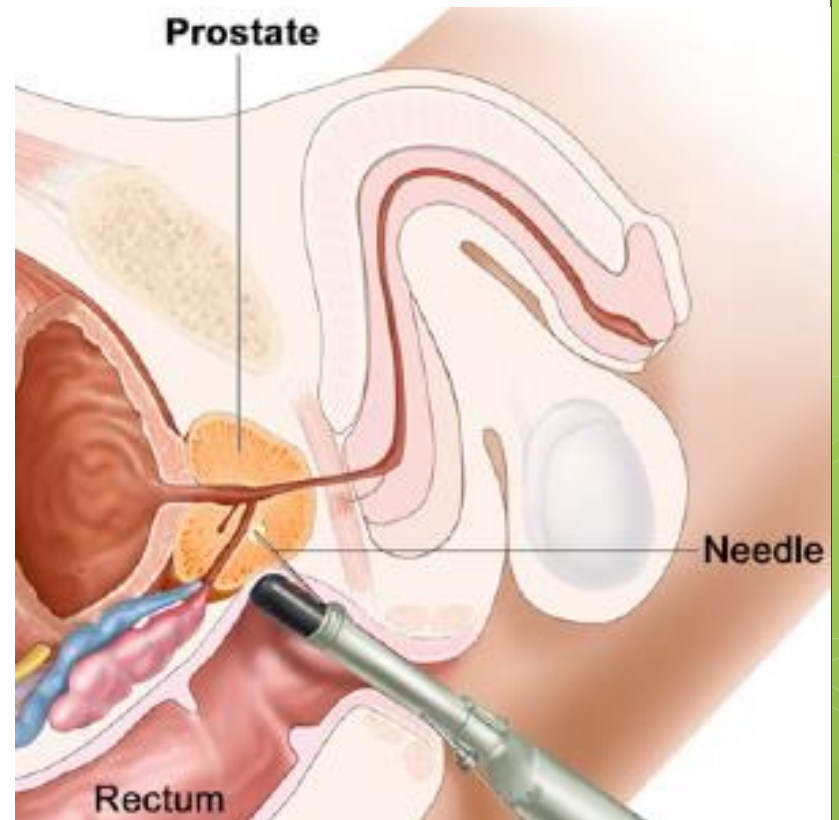
4- PCA3

- Prostate cancer antigen 3 (PCA3) is a noncoding, prostate-specific mRNA, which is overexpressed in the majority of prostate cancers
- PCA3 predicts the presence of cancer in a biopsy setting with an accuracy of 74.6%

Diagnosis and evaluation

Prostate biopsy

- Consider it when an abnormal rectal exam and/or elevated PSA levels
- Biopsy is done with the guidance of **TRUS**



How is it Done ?

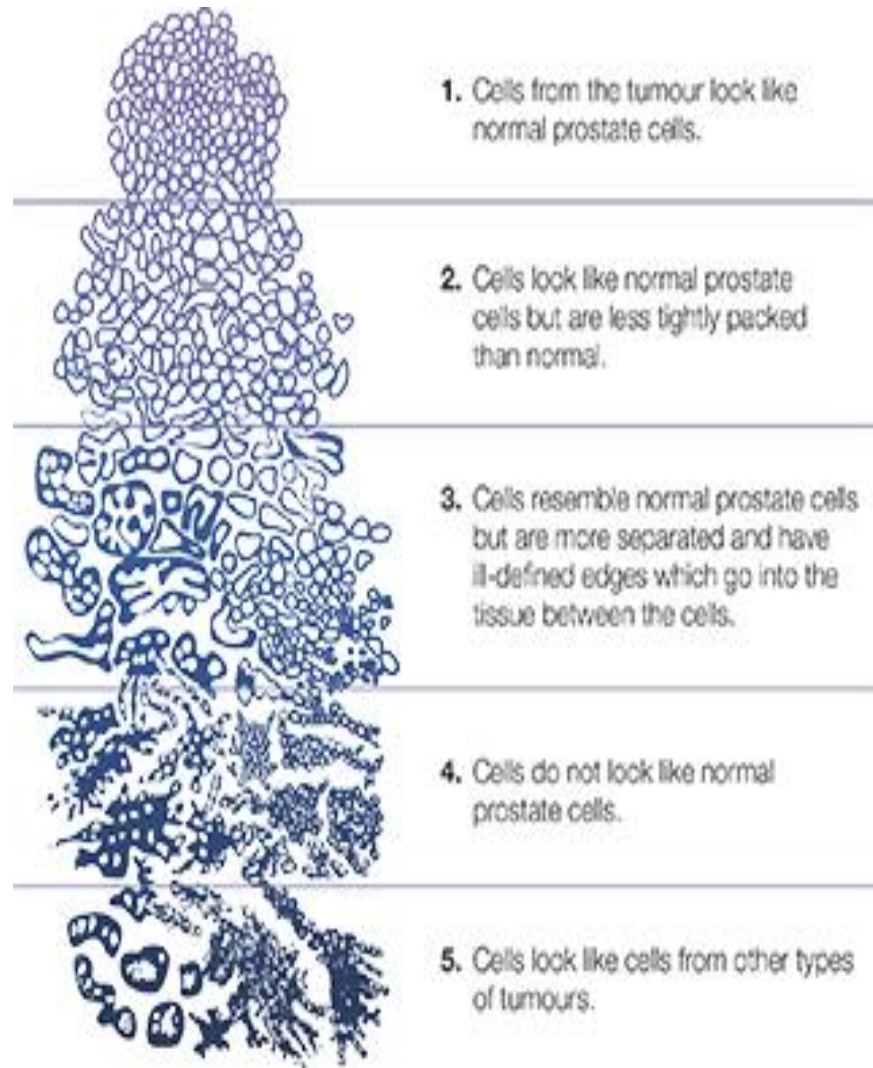
- Traditionally **6 biopsies** are taken from the peripheral zone
- New evidence showed that taking **10** or more biopsies , more **laterally** would increase the detection rate by **20 %**
- Procedure is done under **local anesthesia** , with the use of **prophylactic antibiotics**
- Complications include :**Hemospermia, hematochezia, and hematuria** occurring in 40-50 %

Grading and staging

Gleason system

- the most commonly employed grading system
- The system relies on the **low-power appearance of the glandular architecture under the microscope.**
- **primary grade** to the pattern of cancer that is most commonly observed
- a **secondary grade** to the second most commonly observed pattern in the specimen

- Grades range from **1 – 5**
- If the entire specimen has only one pattern present, then both the primary and secondary grades are reported as the same grade (eg, 3 + 3).
- The *Gleason score* or *Gleason sum* is obtained by **adding the primary and secondary grades together.**
- Traditionally, Gleason grades ranged from 1 to 5, and Gleason scores thus ranged from 2 to 10.
- Gleason scores of
- 2–4, mild differentiated**
- 5–7, moderate differentiated**
- 8–10, poorly differentiated**



- However, pathology grading practices have changed over time, and **this grouping** is largely **outdated**
- In contemporary pathology practice, **Gleason patterns 1 and 2 are rarely assigned.**
- so **Gleason pattern 3** corresponds with low grade disease, (normal stroma, normal glands)
- **Gleason pattern 4** corresponds with intermediate grade disease (incompletely formed glands)
- **Gleason pattern 5** corresponds with high grade disease. (no gland formation)

TNM

- Depends on TRUS and DRE Only
- No role for biopsy here

| Stage | Definition |
|-----------------------------|--|
| Primary tumor | |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Clinically, the tumor is neither palpable nor visible with imaging |
| T1a | Tumor is an incidental histologic finding in 5% or less of tissue resected |
| T1b | Tumor is an incidental histologic finding in more than 5% of tissue resected |
| T1c | Tumor identified with needle biopsy (eg, because of an elevated PSA level) |
| T2 | Tumor confined within the prostate |
| T2a | Tumor involves one-half of one lobe or less |
| T2b | Tumor involves more than one-half of one lobe but not both lobes |
| T2c | Tumor involves both lobes |
| T3 | Tumor extends through the prostate capsule |
| T3a | Extracapsular extension (unilateral or bilateral) |
| T3b | Tumor invades seminal vesicle(s) |
| T4 | Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall |
| Regional lymph nodes | |
| NX | Regional lymph nodes were not assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in regional lymph node(s) |
| Distant metastasis | |
| MX | Distant metastasis cannot be assessed (not evaluated with any modality) |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Nonregional lymph node(s) |
| M1b | Bone(s) |
| M1c | Other site(s) with or without bone disease |

Examples

- If a patient has a **palpable** abnormality **on one side** of the prostate, even though biopsies demonstrate bilateral disease, his clinical stage **remains T2a**.

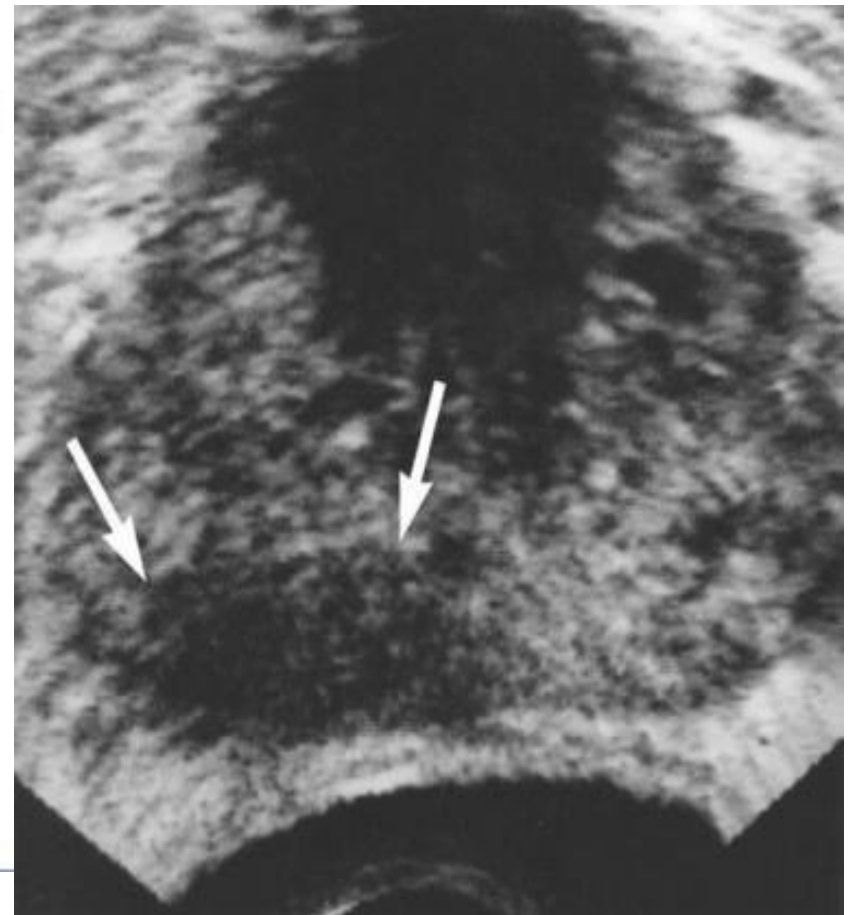
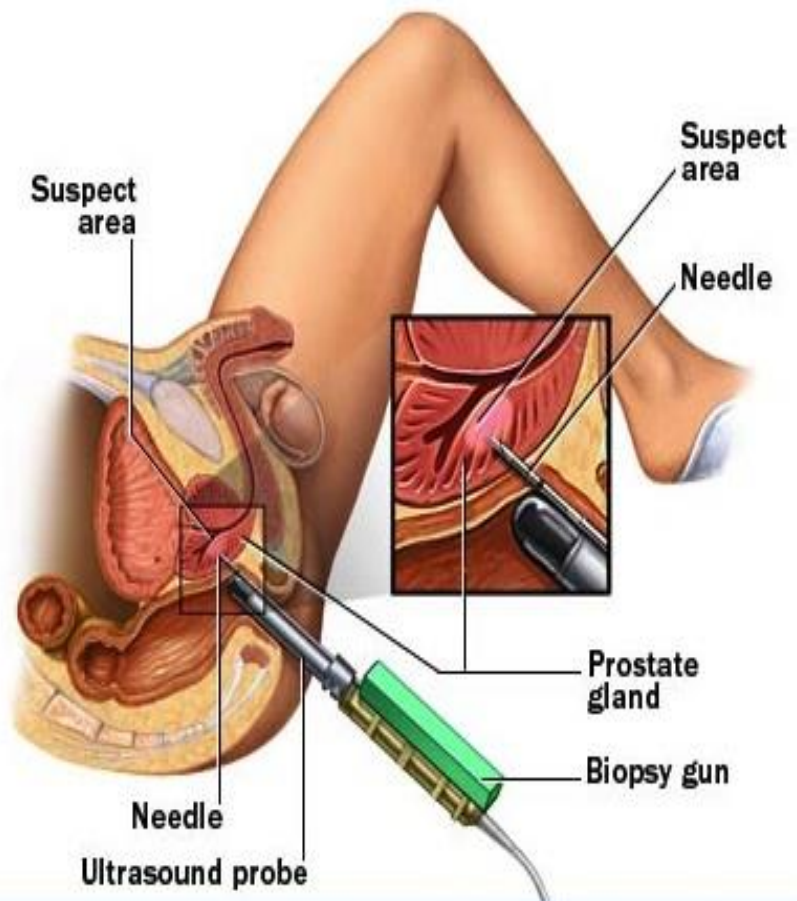
clinical T stage in prostate cancer is a relatively weak prognostic factor.

- due to the subjectivity of DRE and TRUS interpretation

Imaging

TRUS

- ◉ Trans-rectal ultrasound
- ◉ More helpful than DRE in staging
- ◉ Guidance for biopsies
- ◉ Appears as **Hypoechoic** region in periphery



Endorectal MRI

- The reported staging accuracy of endorectal MRI varies from 51% to 92%.



- **Axial imaging (CT, MRI)**
- **selectively performed to exclude lymph node metastases in high-risk patients**
- Patients identified as having lymphadenopathy on imaging may occasionally undergo CT-guided fine-needle aspiration if the diagnosis is equivocal.
- **criteria for axial imaging, including :-**
- negative bone scans and either T3 cancers or a PSA >20 ng/mL and primary Gleason grade 4 or 5 cancers.

- **Bone scan**— When prostate cancer metastasizes, it most commonly does so to the bone . Soft tissue metastases (eg, lung and liver) are rare at the time of initial presentation.

- **Antibody imaging**— ProstaScint is a murine monoclonal antibody to prostate-specific membrane antigen (PSMA)
- After infusion of the antibody, single photon emission computed tomography (SPECT) images are usually obtained.



Prostate cancer screening and prevention

Screening

- Ongoing controversy
- Against and for arguments



For

- ◉ Disease is **burdensome**
- ◉ PSA **detects clinically important** without detecting unimportant cancers
- ◉ Most detectable tumors are **curable**
- ◉ Prostate cancer **mortality is decreasing** in regions where there is screening programs

Against

- **Overdetection** : many of tumors detected would not benefit much if treatment , and outcome would be the same if left untreated

Screening program

- Most guidelines recommend screening **>50 years**
- Some argue for screening **> 40** : ?
less confounding of **BPH** at earlier ages on PSA

The fact that old age patients already have high risk factors .

- **Annual screening**
- **Every 2-3 years** for men with **PSA < 1ng/dl**

Treatment

. General considerations

- Treatment decisions are **based on the grade and stage** of the tumor, **the life expectancy of the patient**, the ability of each therapy to **ensure disease-free survival**, its associated **morbidity**, and **patient and physician preferences**.
- men who underwent RP were less likely to die of prostate cancer .
- The advantage to surgery was most apparent in younger patients (<65 years old at diagnosis).

- what is clear is that many men with low-risk disease are candidates for active surveillance; those with low- to intermediate-risk disease should receive local monotherapy (surgery or radiation),
- and those with higher-risk disease usually need multimodal therapy, either radiation with hormonal therapy or surgery followed selectively by radiation depending on the pathology and early PSA outcomes.

Watchful waiting and surveillance

- For low risk
- New “ active surveillance “
low- to intermediate grade cancer are followed very carefully with **serial DRE and PSA** assessments, and **follow-up TRUS-guided biopsies** to ensure stability of the tumor.
Cancers are usually **treated at the first sign of subclinical progression**

Radical Prostatectomy

- **Low to Moderate grade**
- Lymph node **dissection** in suspected mets
- **Laparoscopes** revolutionized the procedure
- Laparoscopy **reduces blood loss** substantially, **shortens the overall recovery time**, and in some **series reduces hospitalization time**.
- **PSA should fall to undetectable levels within 6 weeks of surgery in most cases.**

- **Cryosurgery**—

- treatment for **localized CaP** , less invasive.

- **Freezing of the prostate** is carried out by using a multiprobe cryosurgical device

- ***Radiotherapy***

- **Focal therapy**—
- Prostate cancer tends to be an infiltrative disease, with cancerous glands interspersed with normal ones, and is **frequently multifocal**.
- Multiple modalities are under investigation for this purpose including limited **cryotherapy, high-intensity focused ultrasound (HIFU), interstitial laser therapy**, and others..



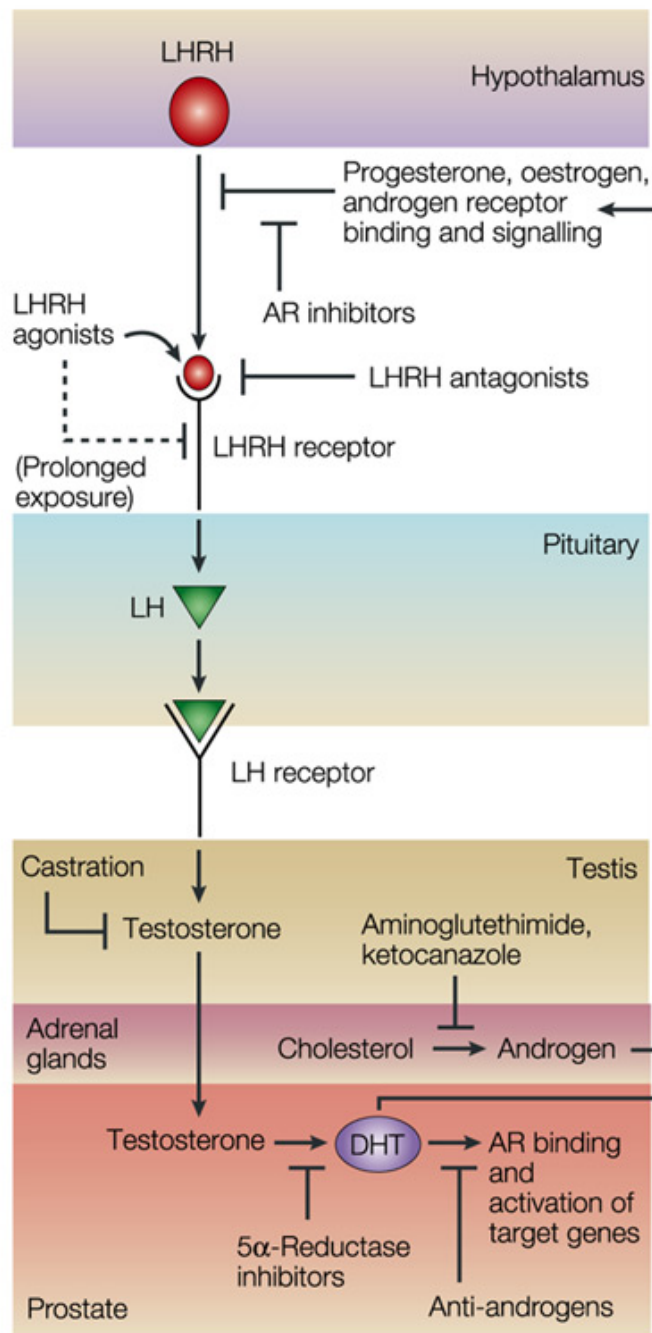
Hormone (androgen deprivation) therapy for prostate cancer

- Most prostate carcinomas are **androgen dependent**
- Prostate tumor cells express **androgen receptors (testosterone)**
- Converts it to **DHT** and leads to cell duplication thus **tumor growth**
- Treatment aims to **deprive** the prostate cells of androgens

- Most would agree that androgen deprivation should be instituted in all those with **metastatic disease**, whether symptomatic or not.
- Androgen deprivation is not without **side effects including**
 - hot flashes,
 - anemia
 - , loss of libido and sexual function,
 - loss of bone mineral density,
 - increased weight and body fat,
 - cognitive changes.

- Use of a class of **drugs (LHRH agonists)** has allowed induction of androgen deprivation without orchiectomy or administration of diethylstilbestrol.
- 4 FDA approved drugs :
- **goserelin acetate**
- **triptorelin pamoate**
- **histrelin acetate**
- **leuprolide acetate.**

- Other Class is LHRH antagonist **Degarelix**
- **LHRH antagonists avoid the “flare” phenomenon** associated with LHRH agonists, in which serum testosterone concentrations increase before falling
- **Estrogen** cause androgen inhibition by feedback inhibition on the pituitary hypothalamus axis



- **Ultimately, most prostate cancers will adapt to survive without androgens**, at which point they are denoted “hormone refractory” or “castrate resistant.”
- **Cessation of antiandrogen** therapy if the patient has been on combined androgen blockade.
- **Secondary hormonal therapy aimed at the androgen biosynthesis pathway** (ketoconazole, abiraterone).
- **Taxane-based chemotherapy** (docetaxel, cabazitaxel).



Thank you