

Prostate Cancer

Objectives

1. Importance
2. Natural history
3. Etiology
4. Pathology
5. Staging
6. Clinical presentation, evaluation, diagnosis
7. Management methods
8. Stage wise management
9. HRPC and its treatment
10. Prognosis

Prostate Cancer

- No.1 cancer in U.S. No.3 in Indian
- 1 out of 9 will get PCa; 1 out of 41 will die of PCa (US)
- Disease of age; rare below 40
- Avg. 70; range 45 – 90 years
- 65% are over 65 yrs age
- Heterogeneous behavior
- Many sub-clinical

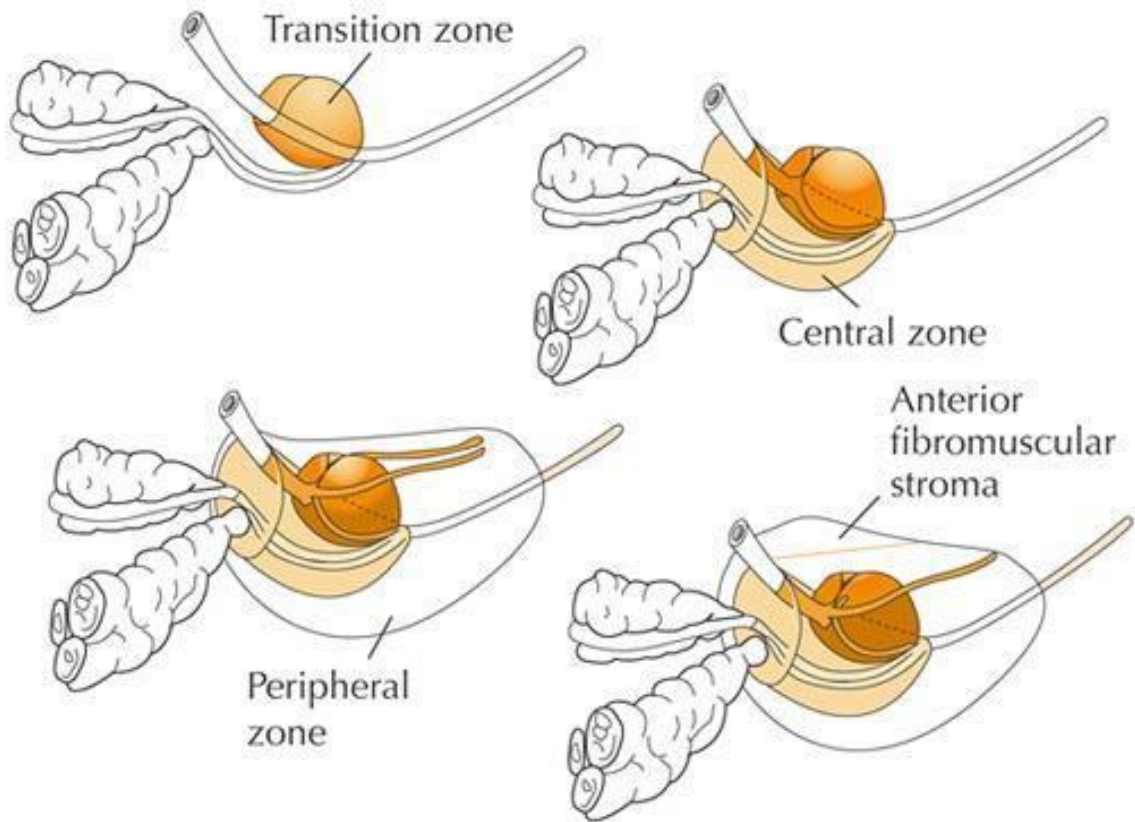
Natural History

- Autopsy incidence 30% - insignificant (0.5 ml or less).
- Intercurrent illnesses competes.
- Low stage, low grade, low vol., old age. -good prognosis any way.
- High grade, high vol, high stage – poor prognosis.
- In between group – treatment makes a difference.
- Treatment has significant side effects

Risk factors

- Familial: 10% overall BUT 45% of < 55yrs grp.
- 1st degree- Father or brother – 2X
- Race: Blacks more commonly affected and poorer prognosis (? Late detection?)
- Geography: China / Japan < USA / Scandinavia– Diet / Environment.
- Genetics – BRCA2 increase risk, but account for very small percentage of P Ca; Lynch syndrome have a higher risk.
- Androgen : Testosterone.
- Diet, Obesity, Diet, Exercise, prostatitis, STDs, Vasectomy – not much effect.

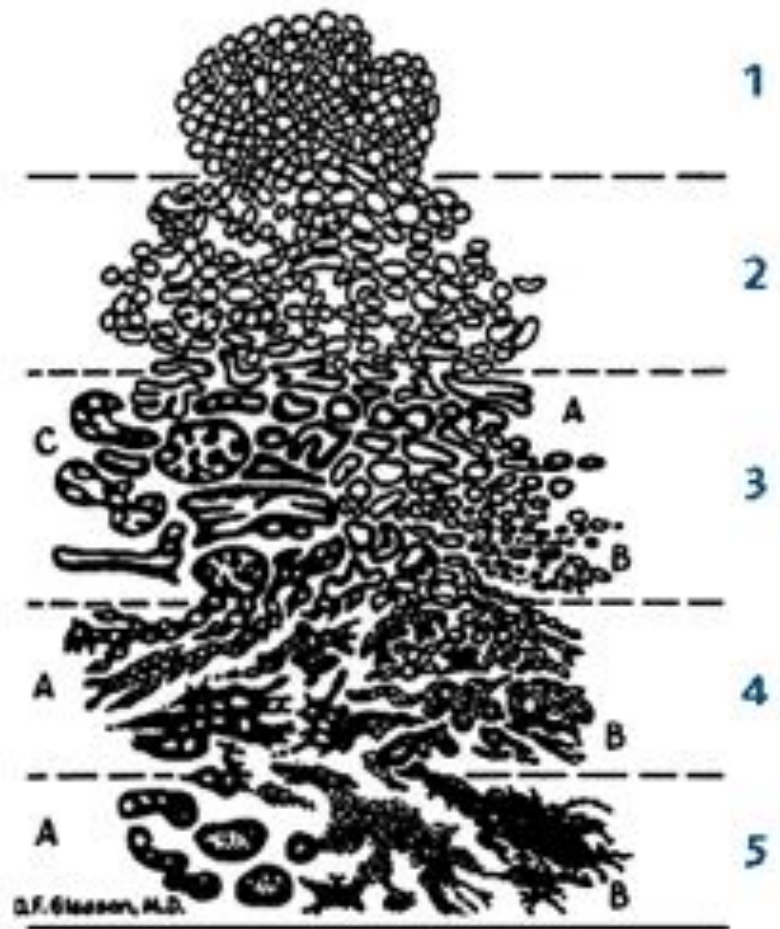
Zonal Anatomy of Prostate



Pathology

- 95% adenocarcinoma
 - Zone PZ CZ TZ
 - Size 70% 20% 10%
 - CA 85% 2% 13%
-
- Progress – nerves, local, LN, distant mets.
 - Bones – (Pre-vertebral plexus)
 - Rectum involvement rare.

Gleason's Grade
(Reported on low
power of
microscope)
Nuclear features – no
role
Grades I-V; 1 & 2 no
longer to be reported
Gleason's Sum
5-6 well diff
7 mod diff
8 – 10 poor diff.



Gleason's Grade Group

- Grade Group 1 - Gleason score ≤ 6
- Grade Group 2 - Gleason score $3+4=7$
- Grade Group 3 - Gleason score $4+3=7$
- Grade Group 4 - Gleason score 8
($4+4/3+5/5+3$)
- Grade Group 5 - Gleason scores 9-10

Stage

TNM	Disease Status
Tx, To	
T1a	Incidental focal <5% resected or excised tissue
T1b	Incidental diffuse >5% resected or excised tissue
T1c	Non palpable (PSA)
T2a	Palpable < 1/2 lobe one side only
T2b	Palpable > 1/2 lobe one side only
T2c	Palpable tumor on both sides
T3 a.	Extracapsular Extension
b.	Seminal vesicle Extension
T4	Bladder Neck, sphincter, rectum, Pelvic wall
<u>NODES :</u>	
No / Nx	
N1	Regional (Pelvic) lymphnode involvement
<u>METASTASES</u>	
M0 / M1a,b,c	Nonregional LN, Bone secondaries, Visceral secondaries

Symptoms

- LUTS (Prostatism) & retention
- Hematuria, Incontinence, UTI
- Bone pain / neuro symptoms, bowel /UB incontinence
- ST mass (Occult 1^o)
- Incidental
 1. Screening- Rectal or screening
 2. TURP / Open prostatectomy

Signs

General: Signs of uremia.

- Abdomen – kidney, bladder, iliac nodes, liver.
- Genitalia : Edema.
- Pedal lymphedema.
- Neurological deficit.
- **P/R (DRE):** Nodular, hard, consistency different; lateral grooves, fixity, mucosa high/index of suspicion.

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D/D – BPH, calculus, Ch. Prostatitis- TB, Non TB, hematoma, cyst

How to Diagnose?

- Dx : Needle Bx (Trucut)
 - TRUS guided transrectal biopsy
 - Digital – finger guided (Advanced disease).
- FNAC ?Role
- Metastasis → Sp. Staining
 1. PSA.
 2. PAP.
 3. HMW cytokeratin (34 β E12)

Investigation

- **LAB** :Hb, KFT, LFT, Urine R/M/C, Ca, P, [PSA](#), PAP
- **Imaging**: CXR, TRUS, CT, MRI, Bone scan

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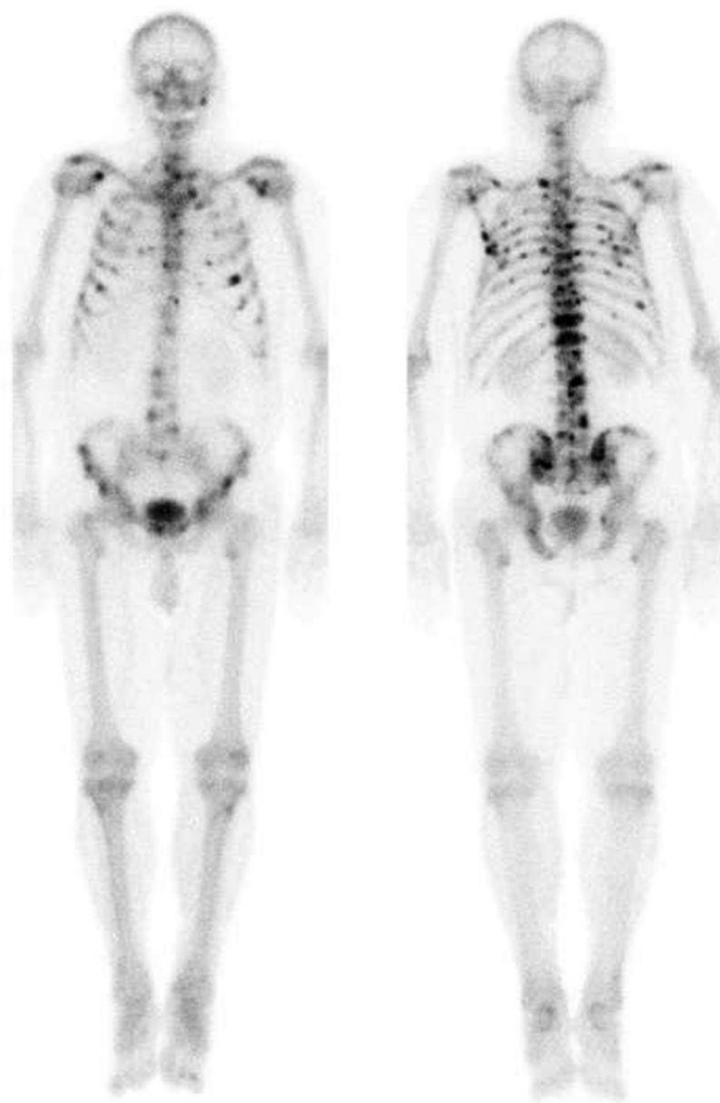


For LN Sensitivity 68 – 70%; Sp. 85 – 95%.

Serum Prostate Specific Antigen

- **PSA** an enzyme – Acinar cell cytoplasm – Liquefaction of semen.
- Tumor marker $\propto$ vol. of tumor
- $>10\text{ng/ml}$ 50% risk; >4 to 10ng/ml – 25% risk of cancer
- Normal= 0 – 4ng/ml .
- Even for PSA $<4\text{ng/ml}$ 15% have prostate cancer.

(PSA = 25.0)





PSA organ specific; not disease specific

- Increase
 - BPH
 - Age
 - Prostatitis
 - Ejaculation
- Decrease
 - Finasteride, dutasteride
 - Some herbal mixtures
 - Obesity

Role of PSA

- **Planning Rx** –
 - Lymphadenectomy for staging not reqd. if $<10\text{ng/ml}$.
 - Bone scan not reqd if $<10\text{ng/ml}$
- **Follow up:** $\uparrow$ PSA $\rightarrow$ Recurrence
- **Assess Rx:** $\uparrow$ PSA after rad. Prostatectomy
 $\rightarrow$ residual disease
- **Screening** – controversial; perhaps not to be recommended at least in India.
- PSA $>4\text{ng/ml}$ (2ng/ml)-> TRUS Prostate Biopsy

PSA >4ng/ml (2ng/ml)

Negative Biopsy?

- **PSA derivatives**
 - Free to total PSA >25%
 - PSAD <0.15ng/ml/g
 - PSAV >0.75ng/ml/yr
- PCA3 (<35)
- PHI (-2 ProPSA) < 27
- 4Kscore with human kallikrein 2 (<7.5% risk of Gleason 7)
- mpMRI guided biopsy (PIRAD 3 or more)

Treatment options

- Active surveillance
- Radical prostatectomy
- Radiotherapy EBRT & Brachytherapy
- Watchful waiting
- Androgen deprivation therapy
- Chemotherapy
- Palliative therapy

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Active surveillance

- A.K.A. expectant therapy or deferred therapy.
- Diagnosis of an early-stage (T1-T2), low-grade tumor, Grade Group 1, PSA<10ng/ml.
- No medical treatment is provided.
- Patient receives regular follow-up to monitor tumor with PSA testing and prostate biopsy if needed.
- Disadvantages : Anxiety & loss of opportunity to cure.

Treatment options

- Active surveillance (Watchful waiting)
- **Radical prostatectomy**
- Radiotherapy EBRT & Brachytherapy
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- Androgen deprivation therapy
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Radical retropubic prostatectomy

- Through an abdominal incision
- Prostate, seminal vesicles removed.
- Bladder neck directly sewed to urethra.
- Pelvic lymphadenectomy
- Open, Laparoscopic, Robotic assisted laparoscopy
- Can also be performed through perineal route
– i.e Radical perineal prostatectomy

The Da Vinci Robot for robotic Assisted Lap RP



RP Complications

- Severe or life-threatening complications possible but rare.
- Stress Incontinence / Complete incontinence
- Impotence (Erectile Dysfunction):
- If both neurovascular bundles were spared, potency rates range from 30-86%, depending on institution.
- Usually improves over time
- Other ED and incontinence treatments can work.

Treatment options

- Active surveillance (Watchful waiting)
- Radical prostatectomy
- **Radiotherapy EBRT & Brachytherapy**
- Watchful waiting
- Androgen deprivation therapy
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Radiotherapy

- High-Powered X-Rays that damage DNA and kill prostate cancer cells.
- External Beam Radiation Therapy (EBRT): X-rays aimed at prostate about 80Gy.
- 3D CRT, IMRT, IGRT
- Brachytherapy: Radioactive seed implants into prostate.

RT complications - EBRT

- Most symptoms occur during treatments and subside after completion.
- Diarrhea, rectal irritation, fatigue, frequent and painful urination, blood in the urine.
- Erectile dysfunction: less common than radical prostatectomy following treatment but slower recovery.

Treatment options

- Active surveillance (Watchful waiting)
- Radical prostatectomy
- Radiotherapy EBRT & Brachytherapy
- **Watchful waiting**
- Androgen deprivation therapy
- Chemotherapy
- Palliative therapy

Watchful waiting

- Indicated in patients with no metastatic prostate cancer with life expectancy < 5 years
- Patient periodically visits physician and development of any new symptom is monitored.
- ADT started when symptoms develop

Treatment options

- Active surveillance (Watchful waiting)
- Radical prostatectomy
- Radiotherapy EBRT & Brachytherapy
- Watchful waiting
- **Androgen deprivation therapy**
- Chemotherapy
- Palliative therapy

Androgen Deprivation Therapy (ADT)

- Orchiectomy (Surgical castration).
 - LHRH analogues (Medical castration) – goserelin, leuprolide, triptorelin, pamorelin
 - GnRH receptor blocker – Degarelix
 - Antiandrogens : flutamide, bicalutamide
 - Total androgen ablation-not useful
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- Complications of ADT-CVS, Gynecomastia, ↓Libido and ED., Impotence, Hot flashes, Weight gain, Fatigue, Reduced brain function, Loss of muscle and bone mass
 - Vit D and Calcium, Exercise

Stage-wise treatment

Stage	Gleason	PSA	LE	Management
T1a or c N0M0	6	<10 ng/ml	Any	Active surveillance; follow up with PSA. If progressive - treat.
T1b or T2a-T2b N0M0	7	<10 ng/ml	<10 yrs	-Radical prostatectomy - 2nd choice 3D-CRT 70 Gy to prostate. - Brachytherapy is an alternative.

Stage-wise treatment

Stage	Gleason	PSA	LE	Management
T1b – T2b N0M0	7	<10 ng/ml	>10 yrs & Good PS	• Radical prostatectomy • 3D-CRT 70-80 Gy to prostate & 45 Gy to pelvic LN. • Brachytherapy
T3,4 N0M0, or PSA>10ng/dl or Gleason >7			> 5 yrs	• Neo adjuvant Hormonal Rx + EBRT (3D-CRT/ IMRT/ IGRT). • Surgery + Adjuvant RT • ? Cryoablation

Stage-wise treatment

Stage	Gleason	PSA	LE	Management
T1 or T2 N0M0, and PSA<10ng/dl and Gleason <7			< 5 yrs Or Poor PS	Watchful waiting
T3,4 N0M0, or PSA>10ng/dl or Gleason >7			< 5 yrs Or Poor PS	Androgen Deprivation Therapy-ADT
Nodal or distant metastases (N+ M+)			Any	ADT Or ADT +/- Docetaxel, Abiraterone, Enzalutamide or Apalutamide

Hormone Refractory Prostate Cancer

- Response to chemotherapy & prognosis poor.
- Abiraterone+ Prednisolone, Enzalutamide, Apalutamide
- Docetaxel & prednisolone based chemotherapy.
- Cabazitaxel, and Sipelucel T
- Radium 223 IV q monthly
- Mitoxantrone, Estramustine.
- Bisphosphonate (Zolindronate), Denosumab.

Palliation

- RT to bones 20 Gy in 2 weeks
- Strontium 89 (β emitter); Samarium 153
- Pain therapy
- TURP
- PCN for B/L ureteral obstruction causing renal failure especially in early stages

Survival (Nonmetastatic)

Stage	5 yrs (DFS)	10 yrs (DFS)
T1	85%	70%
T2	70 %	55 %
T3	55 %	40 %

Survival (Metastatic)

Median 2yrs; 5 year survival may be up to 30%.

Thank you

RT complications - Brachytherapy

- High initial dose of radiation that slowly fades over 1 year.
- Prostate inflammation and swelling, sometimes with severe urinary symptoms.
- Other, more rare symptoms include persistent urinary and bowel frequency and urgency.
- Erectile dysfunction: similar to EBRT.

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11. Screening
12. Chemoprevention

Why screening controversial?

Pros

- Prostate cancer can be a significant source of morbidity.
- Prostate cancer can kill.
- Screening helps pick up cancers when curable.
- Effective treatment exists that can cure disease & prolong life.

Cons

- Tests imperfect; no clear normal /abnormal value.
- Many false neg/ positive.
- Biopsy technique imperfect.
- Detects many insignificant cancers- over-treatment.
- Treatment has serious harms
- Substantial costs.

Early detection and screening

- Digital rectal exam – Feel for nodules
 - PSA – How high? 2.5ng/ml or 4ng/ml?
 - Transrectal ultrasound- for Bx – not for screening
- First two tests are convenient and inexpensive, but consequences may not be
- The USPSTF – in 2008 – ‘the risks of screening for PCa outweigh the benefits for men ≥ 75 yrs & in 2012 –Any age!
 - The ACS and AUA recommend that health care professionals *offer the option of testing for early detection of prostate cancer to all men who are at least 50 years old (or younger if at higher risk).*

Finasteride chemoprevention

- Finasteride = 5-alpha reductase inhibitor, blocks intracellular conversion of testosterone to DHT
- Evidence that chemoprevention with finasteride reduces the incidence of prostate cancer (6% absolute; 25% relative risk reduction)
- But the evidence is inadequate to demonstrate reduced mortality.
- Harms: erectile dysfunction, loss of libido, gynecomastia, higher grade cancers.
- The Selenium and vitamin E Cancer prevention Trial was a large randomized placebo-controlled trial of Vitamin E and selenium, alone or in combination but showed no use.

