Prostate Cancer

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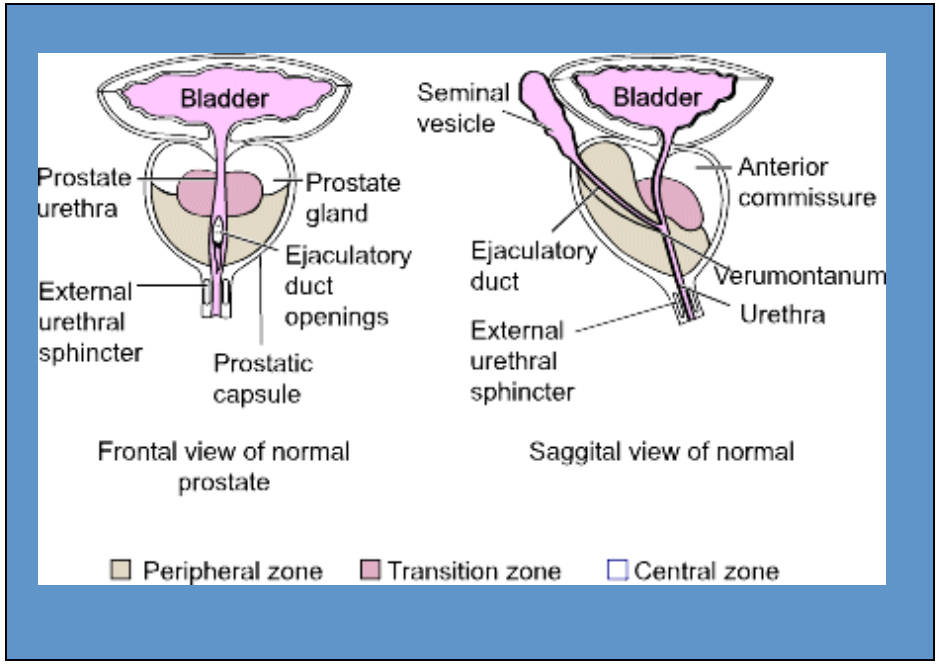
Objectives

- What Is Prostate Cancer?
- Causes, Risk Factors
- Early Detection, Diagnosis, and Staging
- Treating Prostate Cancer

Prostate Cancer

Anatomy

- Position
  - Prostate lies below the bladder
  - Encompasses the prostatic urethra
  - Surrounded by a capsule
- Separated from the rectum
  - Layer of fascia termed the Denonvilliers aponeurosis
- Blood supply
  - Inferior vesical artery
    - Derived from the internal iliac artery
    - Supplies blood to the base of the bladder and prostate
    - Capsular branches of the inferior vesical artery
      - Help identify the pelvic plexus
        - » Arising from the S2-4 and T10-12 nerve roots
- Nervous supply
  - Neurovascular bundle
    - Lies on either side of the prostate on the rectum
  - Derived from the pelvic plexus
  - Important for erectile function.



Theodorescu, D., *Prostate Cancer: Management of Localized Disease*, www.emedicine.com, 2004

Incidence

- prostate cancers is the 2nd most common cause of cancer deaths in USA.
- USA (blacks) 137/100,000 per year
- Germany 45/100,000 per year

Incidence

- Kuwait 6.5/100,000 per year (1998-2002)
- Kuwait 12.8/100,000 per year (2002-2005)

- China <1/100,000 per year

Etiology

Genetic predisposition, racial origin.
Autosomal dominant inheritance of
rarely yet highly penetrate gene.

Hormonal influences.

Dietary fatty foods implicated

Chronic exposure to cadmium and other environmental pollutants such as pesticides

Men working in rubber industries may have an increased risk

Infectious agents.

Sexual habits, multiple sexual partner.

Idiopathic

Pathogenesis

- Most prostate cancers are **adenocarcinomas** arising from prostatic acinar cells.
- 70% of prostate cancers arise in the peripheral zone of the prostate;
- 15-20% arise in the central zone;
- 10-15% arise in the transition zone.
- Most prostate cancers are **multicentric**.

Prostate Cancer

Pathophysiology

- Adenocarcinoma
  - –95% of prostate cancers
    - Developing in the acini of prostatic ducts

Prostate Cancer

Pathophysiology

- Rare histopathologic types of prostate carcinoma
  - Occur in approximately 5% of patients
  - Include
    - Small cell carcinoma
    - Mucinous carcinoma
    - Endometrioid cancer (prostatic ductal carcinoma)
    - Transitional cell cancer
    - Squamous cell carcinoma
    - Basal cell carcinoma
    - Adenoid cystic carcinoma (basaloid)
    - Signet-ring cell carcinoma
    - Neuroendocrine cancer

Prostate Cancer

Clinical Manifestations

- Early state (organ confined)
  - Asymptomatic
- Locally advanced
  - Obstructive voiding symptoms
    - Hesitancy
    - Intermittent urinary stream
    - Decreased force of stream
  - May have growth into the urethra or bladder neck
  - Hematuria
  - Hematospermia
- Advanced (spread to the regional pelvic lymph nodes)
  - Edema of the lower extremities
  - Pelvic and perineal discomfort

Prostate Cancer

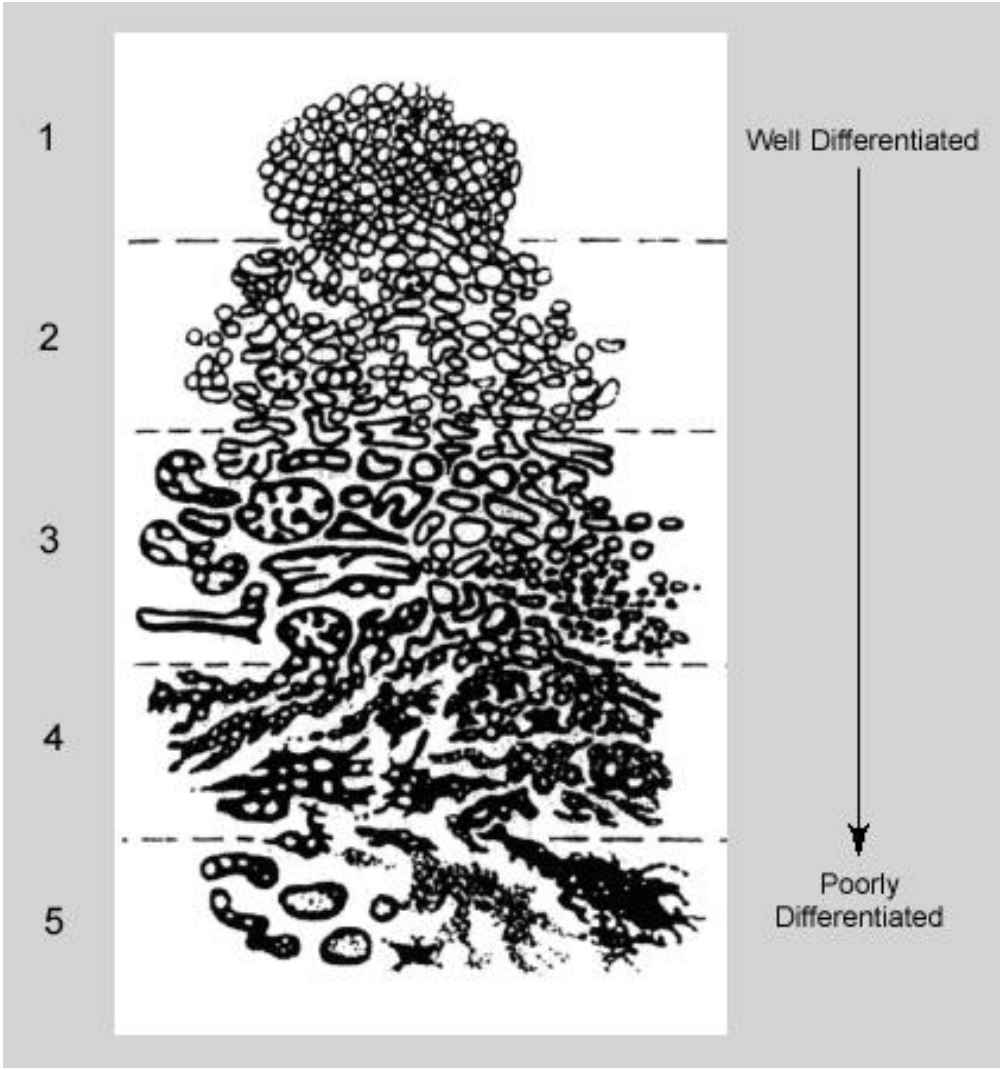
Clinical Manifestations

- Metastasis
  - Most commonly to bone (frequently asymptomatic)
    - Can cause severe and unremitting pain
  - Bone metastasis
    - Can result in pathologic fractures or
    - Spinal cord compression
  - Visceral metastases (rare)
  - Can develop pulmonary, hepatic, pleural, peritoneal, and central nervous system metastases late in the natural history or after hormonal therapies fail.

Histopathological Grading

- Gleason grading system
  - Grade 1-5
  - Score = primary + secondary grade
    - Well diffentiated (G1) 2-4
    - Mod diff (G2) 5-6
    - Poorly dif (G3-4) 8-10

Gleason Pathologic Scoring System for Prostate Cancer



Gleason Pathologic Scoring System for Prostate Cancer

Grade	Description[9]
1	Small nodules of uniform glands, tightly packed
2	Glands show various shapes and sizes, closely packed
3	Glands with marked variation in size and shape, infiltrating normal prostatic tissue
4	Large, irregular, fused glands
5	No obvious glands, solid sheets of tumor cells spreading through prostatic tissue

Adapted from Campbell's Urology[9]

Prostate Cancer

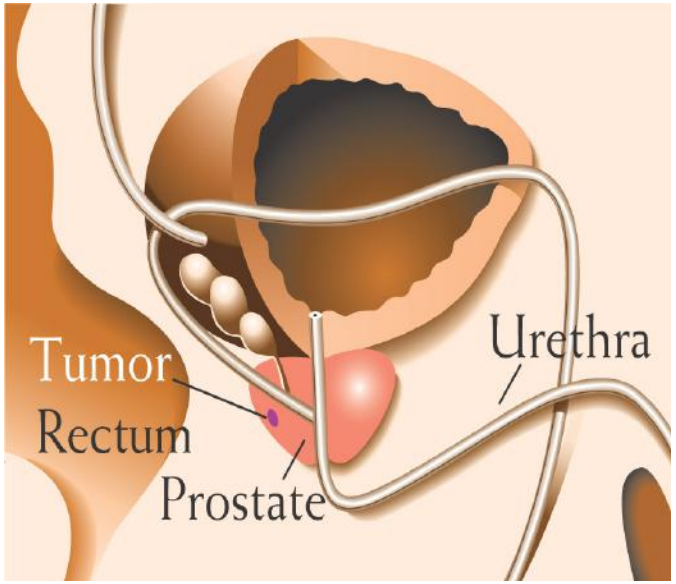
Prognosis

- Staging
  - Definition
    - Extent of disease determined by
      - Physical examination
      - Imaging studies
      - Pathology

Staging.

T1

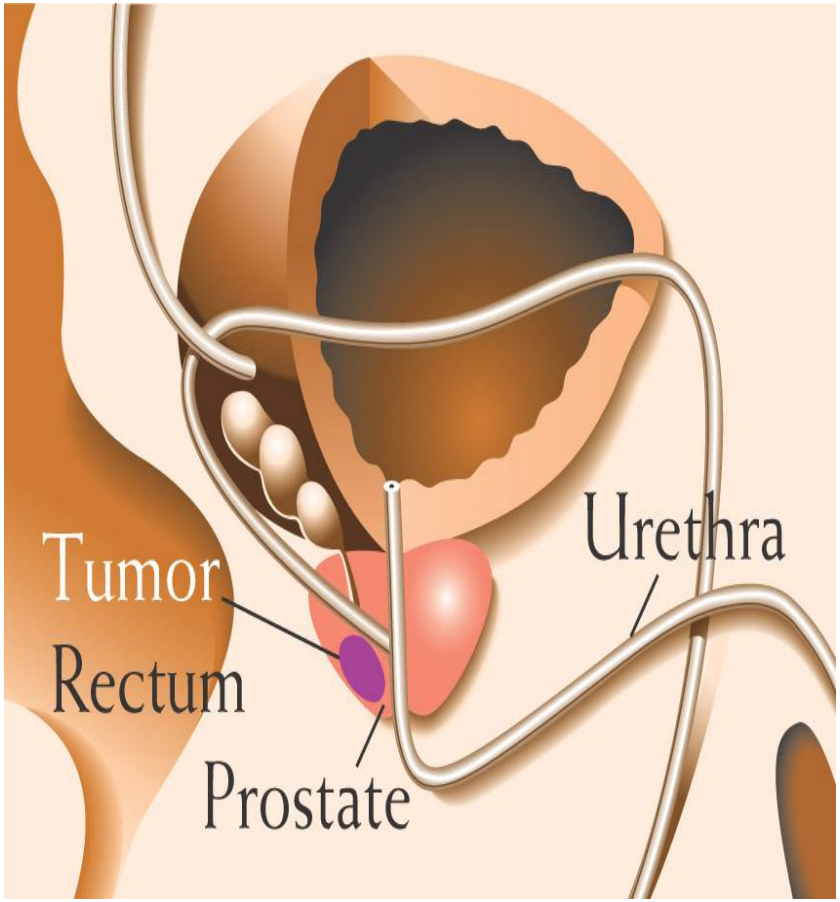
- Stage A is early cancer – the tumor is located within the prostate gland and can't be detected by a DRE[8]



Staging.

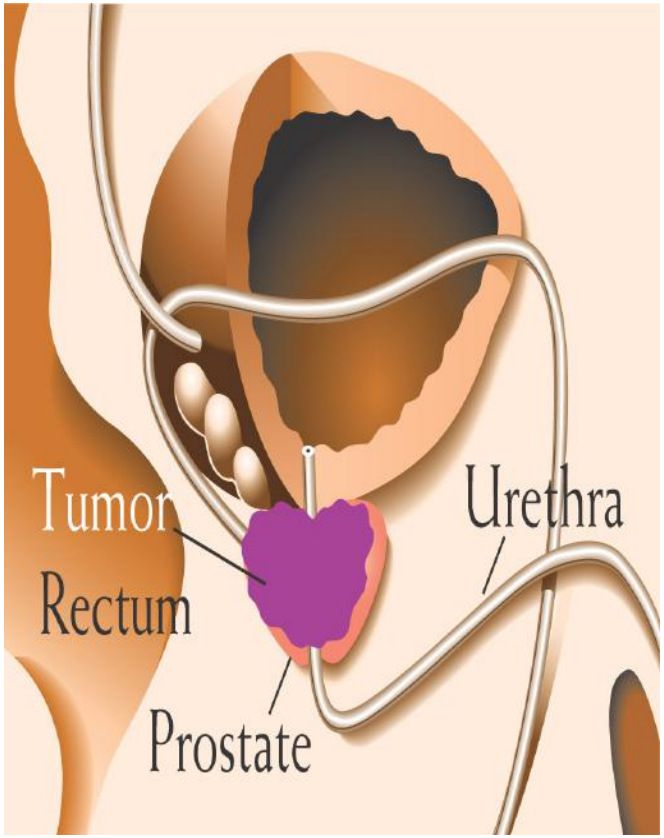
T2

- the tumor is confined to the prostate but large enough to be felt during a DRE



T3

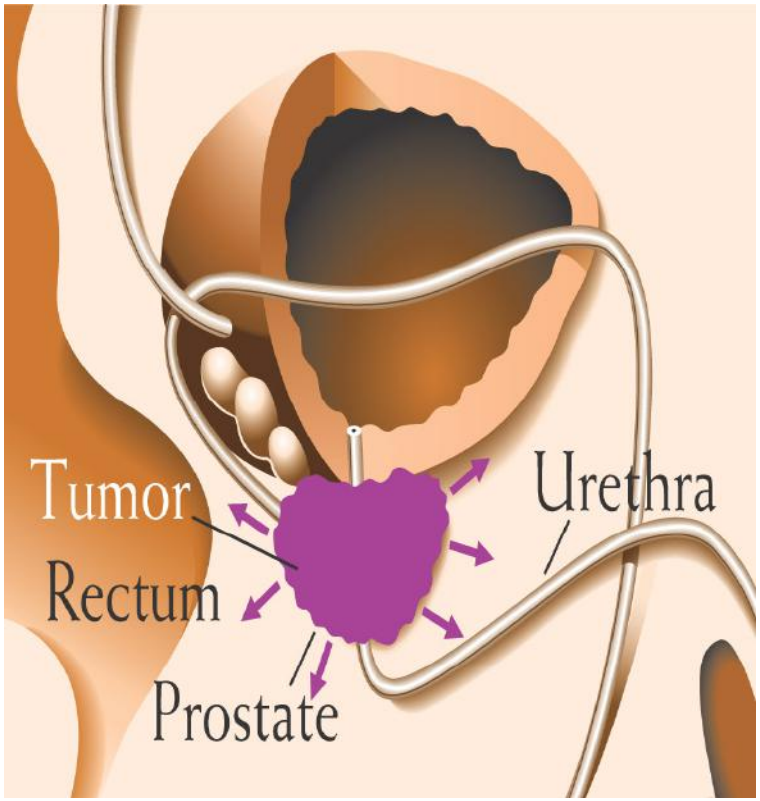
- the tumor has spread outside the prostate to some surrounding areas and can be felt during a DRE

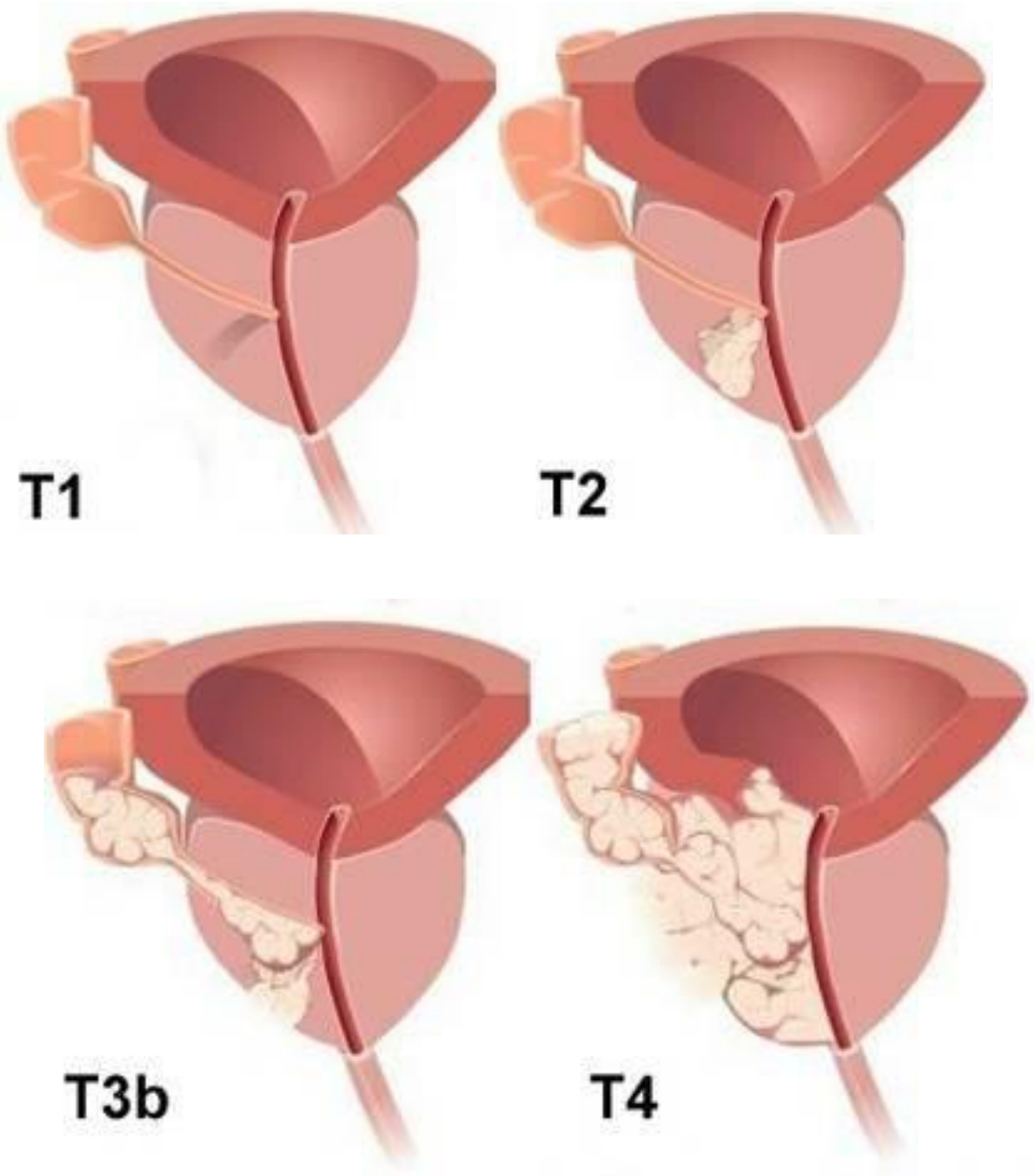


Grading

- T4

- the cancer has spread to the adjacent organ other than seminal vesicle




T1
T2
T3b
T4

Stages of Prostatic Cancer

T1

T1 Clinically inapparent; tumor not palpable or visible by imaging

T1a Incidental finding during transurethral resection of prostate; < 5% of tissue resected

T1b Incidental finding during transurethral resection of prostate; > 5% of tissue resected

T1c Tumor identified by needle biopsy (e.g. because of elevated PSA)

T2

T2 Tumor confined within prostate (palpable or visible on TRUS)

T2a Involves half of a lobe or less

T2b Involves more than half of a lobe one lobe but not both lobes

T2c Tumor involves both lobes

T3

T3 Tumor extends through prostatic capsule, bladder neck or seminal capsule

T3a Unilateral extracapsular extension

T3b Bilateral extracapsular extension

T3c Tumor invades seminal vesicle(s)

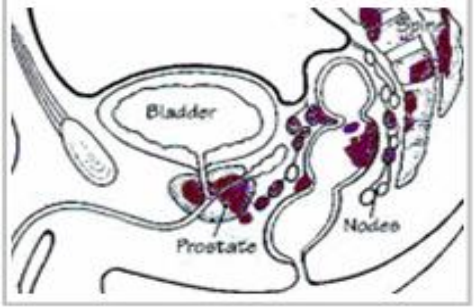
T4

T4 The tumor has spread or attached to tissues next to the prostate (other than the seminal vesicles).

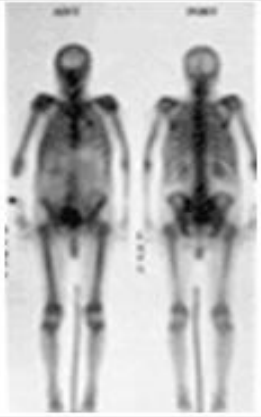
T4a The tumor has spread to the neck of the bladder, the external sphincter (muscles that help control urination), or the rectum.

T4b The tumor has spread to the floor and/or the wall of the pelvis.

N0-3



M0-1



N0 Cancer has not spread to any lymph nodes.
N1 Cancer has spread to a single regional lymph node (inside the pelvis) and is not larger than 2 centimeters
N2 Cancer has spread to one or more regional lymph nodes and is larger than 2 centimeters (¾ inch), but not larger than 5 centimeters
N3: Cancer has spread to a lymph node and is larger than 5 centimeters

M0: The cancer has not metastasized (spread) beyond the regional lymph nodes
M1: The cancer has metastasized to distant lymph nodes (outside of the pelvis), bones, or other distant organs such as lungs, liver, or brain

Pattern of Progression

Local Metastasis:

- Cancers arising in close proximity are prone to spread early to the urethra, periprostatic tissues, bladder and seminal vesicles.
- Spread to seminal vesicles indicates ominous prognosis with 50% of patients developing distant metastasis.
- Rectal invasion is rare, ? Due to the tough Denonvilliers' fascia in between.
- Ureteral invasion by direct extension can occur but late, usually lymph node and distant metastasis present at this time.

Pattern of Progression

Distant Metastasis

- Osseous metastases is most common form of hematogenous metastases and occur in 85% of patients dying from prostate cancer

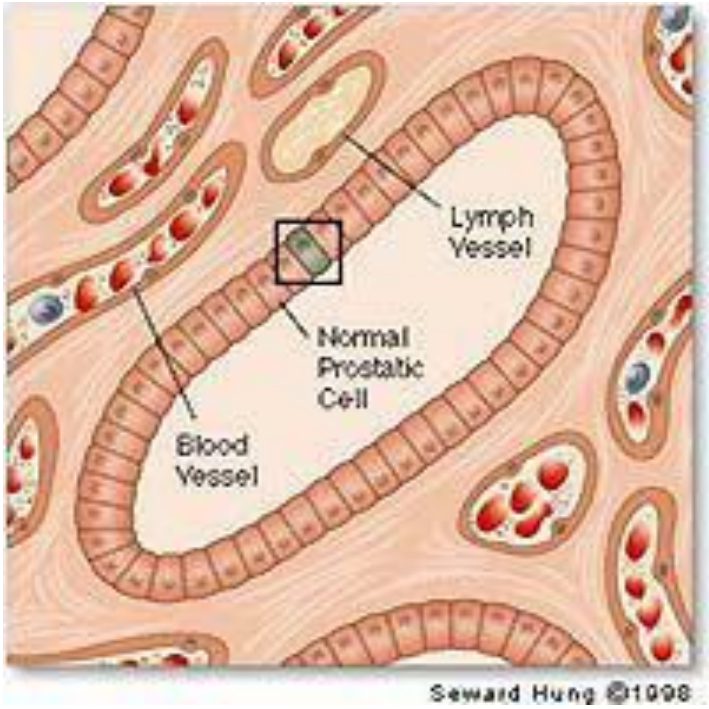
- Frequent sites: lumbar spines, pelvis, proximal femur, thoracic spines, ribs, sternum and skull.

- Extension to the axial skeleton vai the Batson's plexus of presacral veins which communicate with the pre & periprostatic venous complex.

Prostate Cancer

Detection and Diagnosis

- PSA level
  - Helpful in asymptomatic patients
    - > 60% of patients with prostate cancer are asymptomatic
    - Diagnosis is made solely because of an elevated screening PSA level
- A palpable nodule on digital rectal examination
  - Next most common clinical presentation
  - Prompts biopsy
- Much less commonly, patients are symptomatic
  - Advanced disease
    - Obstructive voiding symptoms
    - Pelvic or perineal discomfort
    - Lower extremity edema
    - Symptomatic bone lesions.




TEST YOUR BLOOD PRESSURE
CHECK YOUR PROSTATE
Roger's scan

Prostate Cancer

Detection and Diagnosis

- Digital rectal examination
  - Low sensitivity and specificity for diagnosis
  - Biopsy of a nodule or area of induration
    - Reveals cancer 50% of the time
    - Suggests
      - Prostate biopsy
        - » Should be undertaken in all men with palpable nodules.

Prostate Cancer

Treatment

- PSA screening
  - Early detection
    - Large number of nonpalpable tumors
      - Often clinical means of staging are inadequate
  - Careful risk assessment is required to identify patients who are appropriate candidates for definitive local treatment

Prostate Cancer

Detection and Diagnosis

- The PSA level
  - Better sensitivity but a low specificity
    - Benign prostatic hypertrophy and prostatitis
      - Cause false-positive PSA elevations
  - Threshold
    - Using a PSA threshold of 4ng/mL
      - 70 to 80% of tumors are detected

Prostate Cancer

Detection and Diagnosis

- PSA Velocity
  - Better measure of high risk patients
  - A rate > 0.75/year increase warrants biopsy

Prostate Cancer

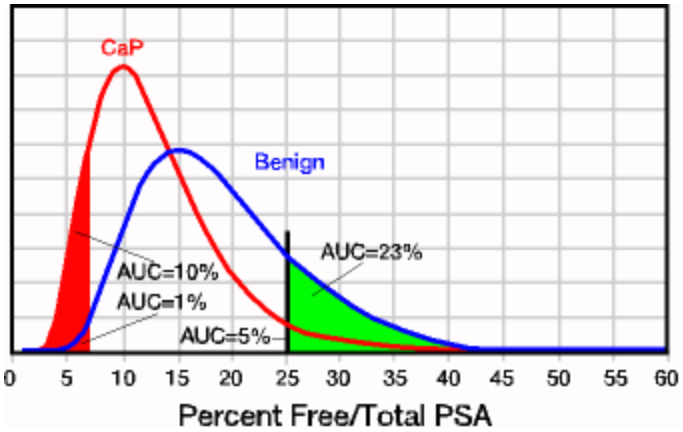
Recommendations

- PSA screening w/ DRE
  - Yearly after age 50 w/ 10 year life expectancy
  - May start at 45 w/ close relative w/ prostate cancer <65
  - May start at 40 for multiple close relatives w/ prostate cancer <65

Prostate Cancer

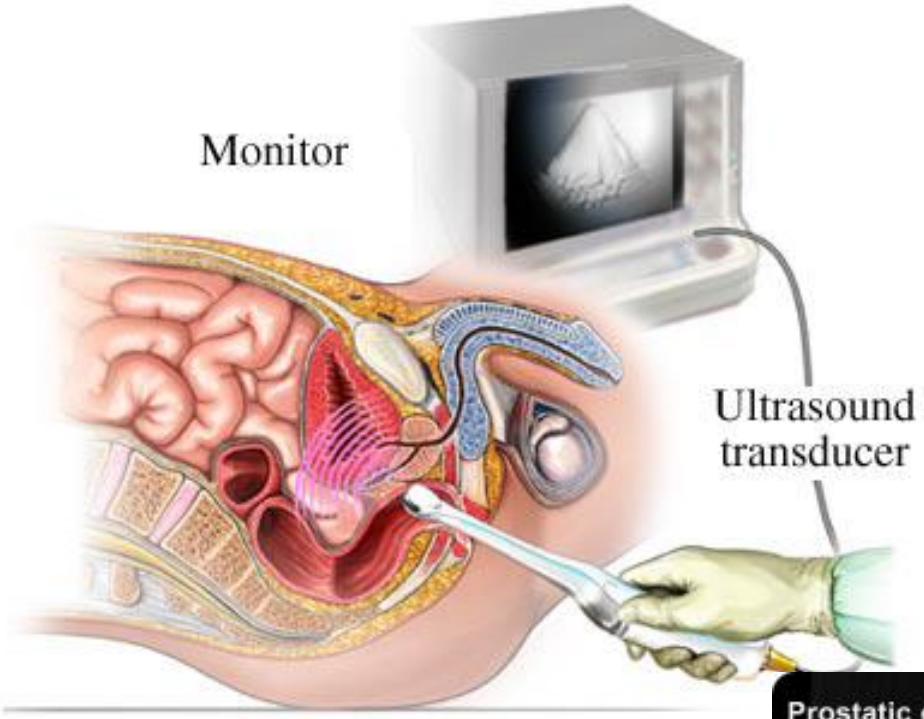
Detection and Diagnosis

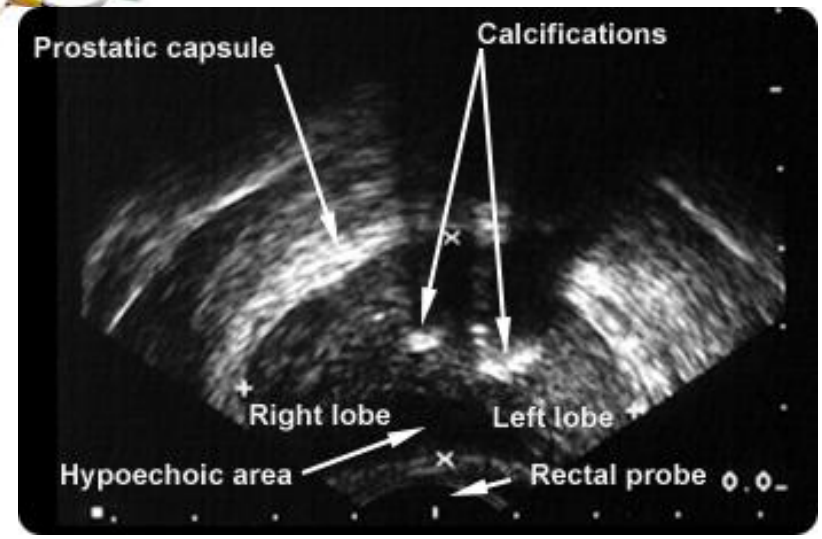
- Unbound PSA (free)
  - May distinguish prostate cancer from benign processes
  - A PSA level of 4 to 10ng/mL
    - The percentage of free PSA appears to be an independent predictor of prostate cancer
    - A cutoff value of a free PSA less than 25% can detect 95% of cancers while avoiding 20% of unnecessary biopsies.



Imaging

1) **Trans-rectal U/S**
   - Can identify 60% of cancers even if non-palpable.
   - By allowing precise placement of biopsy needle in various quadrants, adequate sampling achieved.
   - More accurate than DRE at detecting extra-capsular extension.
   - Allow biopsy of seminal vesicles which improve staging accuracy.
   - Disadvantage of TRUS include the inability to look at the pelvic lymph nodes.


Monitor
Ultrasound transducer


Prostatic capsule
Calcifications
Right lobe
Left lobe
Hypoechoic area
Rectal probe

Imaging

2) CT:

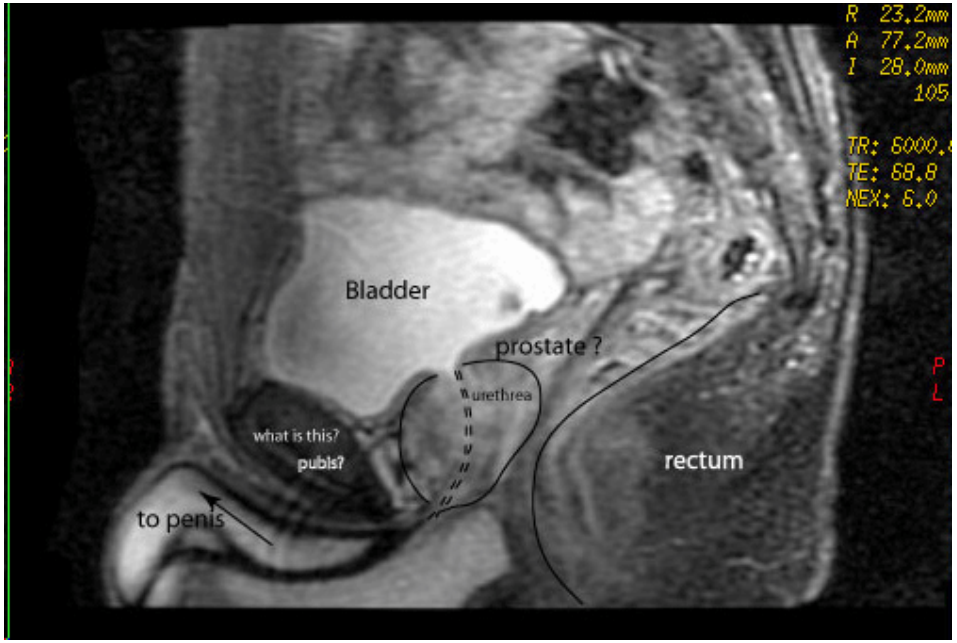
used only when extensive L.N. disease is suspected and it is based only on the size of the nodes thus false +ve and –ve are common.

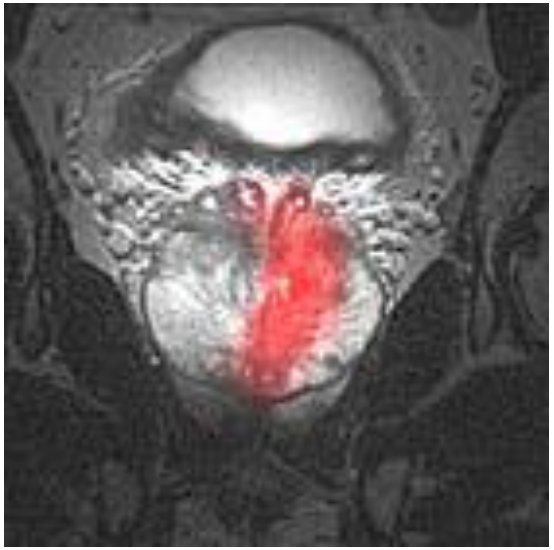
3) MRI:

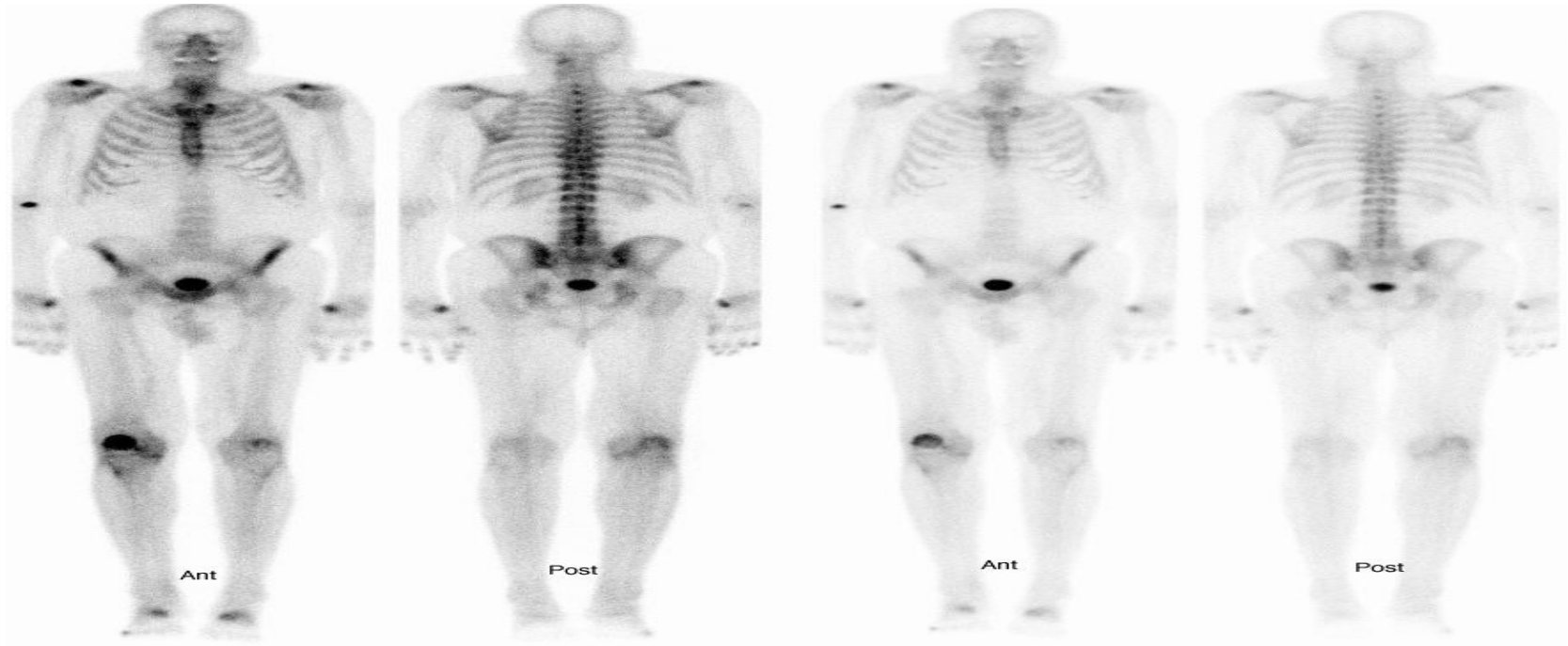
not useful because of the cost and the overlap in the appearance of benign & malignant processes, but its more accurate than TRUS for staging extracapsular extension and seminal vesicle involvement.

4) Bone scanning:

- most common way to assess systemic metastasis.
- False +ve rate is less than 2%.
- Diagnosis is confirmed by plain radiographs, thin section CT or MRI and bone biopsy


R 23.2mm
A 77.2mm
I 28.0mm
105
TR: 6000.
TE: 68.8
NEX: 6.0
Bladder
prostate ?
urethrea
what is this?
pubis?
rectum
to penis




Ant
Post
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Post

Prostate Cancer

Detection and Diagnosis

- A bone scan
  - Warranted only
    - PSA level greater than 10ng/mL
- Computed Tomography or magnetic resonance imaging
  - Abdominal and pelvic CT or MRI is usually unrevealing in patients with a PSA level less than 20ng/mL. .

Prostate Cancer

Prognosis

- Prognosis correlates with histologic grade and extent (stage) of disease
- Adenocarcinoma
  - > 95% of prostate cancers
  - Multifocality is common
- Grading
  - Ranges from 1 to 5
- Gleason score
  - Definition
    - Sum of the two most common histologic patterns seen on each tissue specimen
  - Ranges
    - From 2 (1 + 1)
    - To 10 (5 + 5)
  - Category
    - Well-differentiated (Gleason scores 2, 3, or 4)
    - Intermediate differentiation (Gleason scores 5, 6, or 7)
    - Poorly differentiated (Gleason scores 8, 9, or 10).

Prostate Cancer

Treatment

- **PRINCIPLES OF THERAPY**
  - May include
    - Watchful waiting
    - Androgen deprivation
    - External beam radiotherapy
    - Retropubic or perineal radical prostatectomy
      - with or without postoperative radiotherapy to the prostate margins and pelvis
    - Brachytherapy (either permanent or temporary radioactive seed implants)
      - with or without external beam radiotherapy to the prostate margins and pelvis.

Prostate Cancer

Treatment

- Require individualization
  - Must take into account
    - Patient's comorbidity
    - Life expectancy
    - Likelihood of cure
    - Personal preferences
      - Based on an understanding of potential morbidity associated with each treatment
    - A multidisciplinary approach (recommended)
      - Integrate
        - » Surgery
        - » Radiation therapy
        - » Androgen deprivation
        - » Behavioral therapy

Prostate Cancer

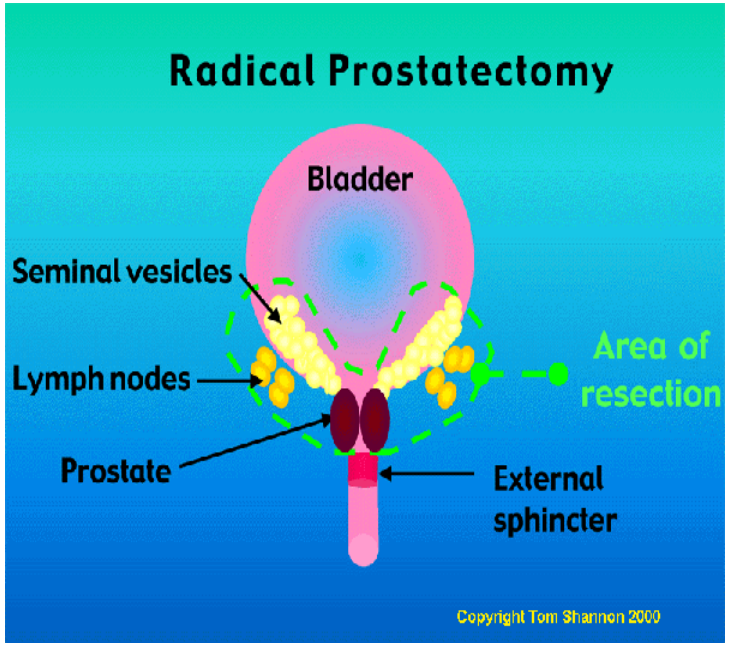
Treatment

- Surgery
  - Traditional
  - Robotic
- Radiation
  - Brachytherapy
  - External beam
- Cryotherapy
- Androgen Deprivation
- Watchful waiting

Radical Prostatectomy

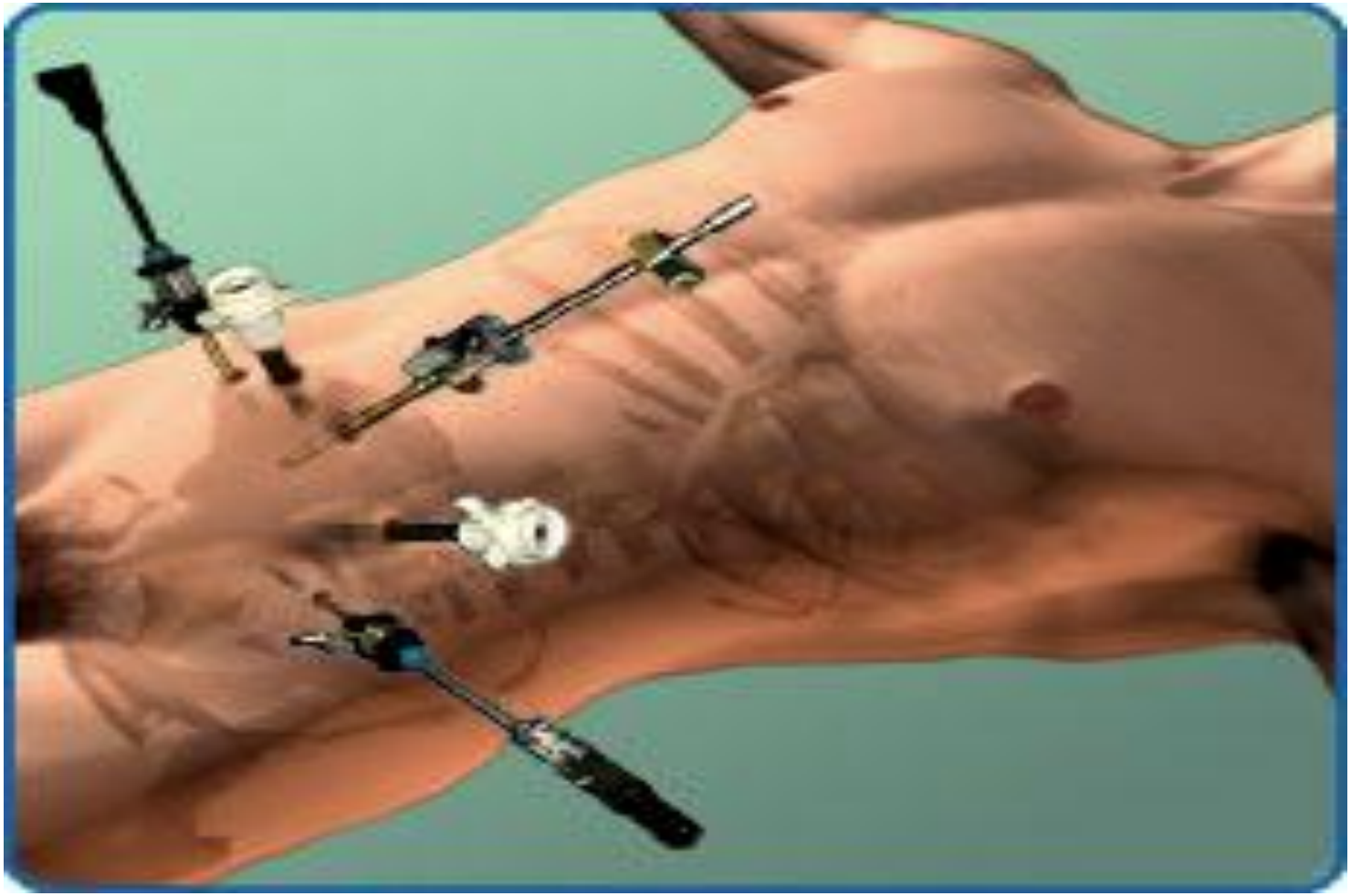
Advantages

- Can remove all the cancer



Disadvantages

- Major operation
- Erectile dysfunction
- Incontinence
- Scar tissue
- Rectal injury
- Wound infection, blood clots, heart attack, etc.
- Often doesn't remove all of the cancer



External Beam Radiation (EBRT)

Advantages

- Efficacy similar to prostatectomy
- Outpatient

A man getting radiation therapy from a linear accelerator for his prostate cancer

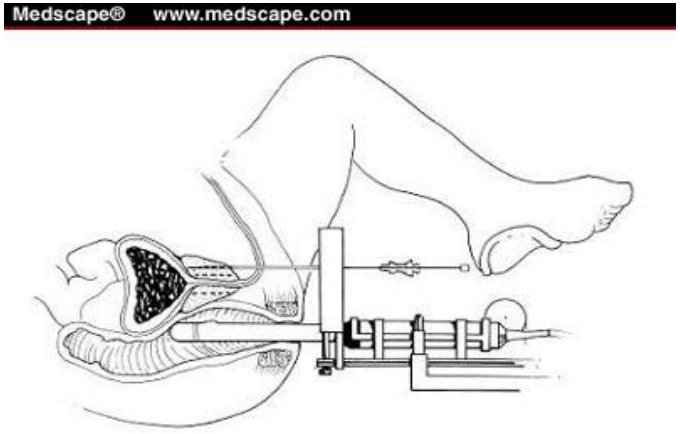
Disadvantages

- Erectile dysfunction
- Chronic bowel and bladder irritation (cystitis, proctitis)
- Requires roughly 7 weeks of daily treatment
- Increased risk of ***rectal & bladder cancer!***

Brachytherapy (radioactive seed implant)

Advantages

- Efficacy similar to EBRT or surgery
- Outpatient; one treatment

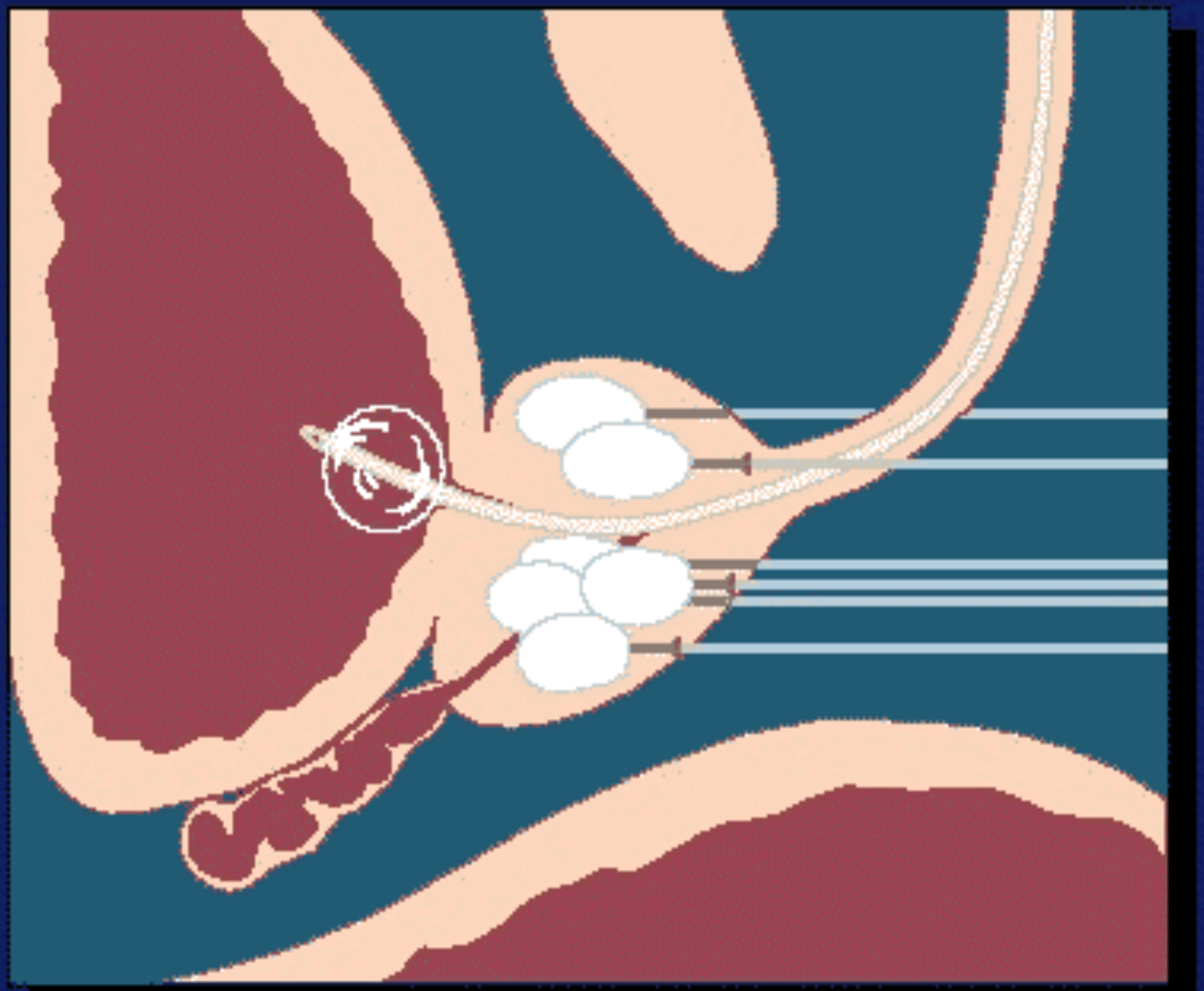


Disadvantages

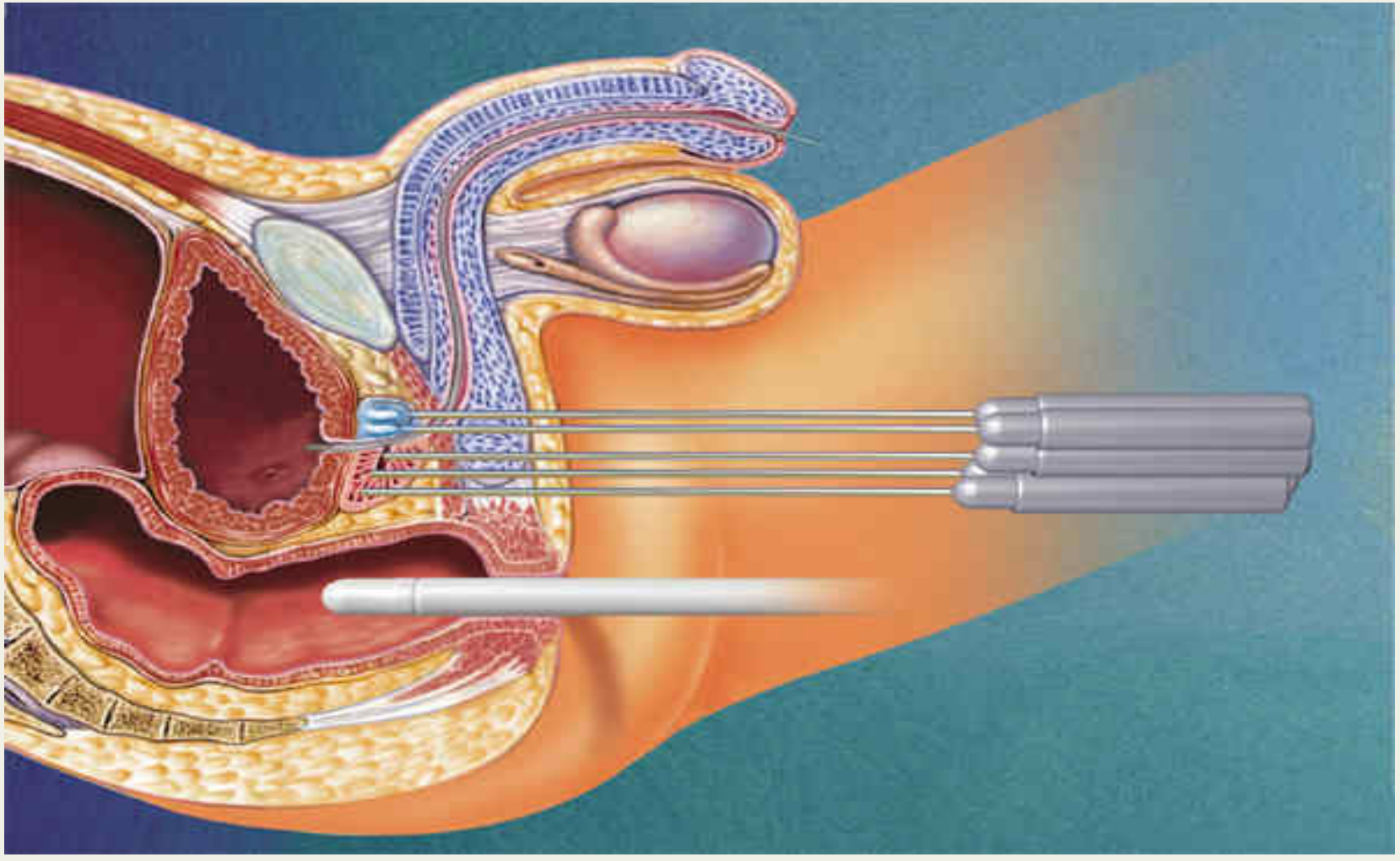
- Chronic bowel & bladder irritation
- Erectile dysfunction
- Seed migration 33%
- Can't treat large prostates
- Increased risk of ***rectal & bladder cancer!***

Brachytherapy (radioactive seed implant

Cryosurgery



Cryotherapy



Prostate Cancer

Treatment - LOW/INTERMEDIATE RISK DISEASE

- **LOW/INTERMEDIATE RISK DISEASE**
- Randomized trial
  - Under the age of 75
  - Clinical stage T1b, T1c, or T2 prostate cancer
  - Radical prostatectomy
    - Reduced the relative risk of death by 50% (a 2% absolute risk reduction)
    - Compared with watchful waiting
    - Despite a significant reduction in the risk of metastasis, overall mortality was unchanged
    - Adverse effects on quality of life
      - More dysfunction and urinary leakage after radical prostatectomy
      - More urinary obstruction with watchful waiting
      - Nerve-sparing radical prostatectomy was not routinely performed in this study
      - Less advanced disease with newer surgical techniques are not known

Prostate Cancer

Treatment - LOW/INTERMEDIATE RISK DISEASE

- Nonrandomized data
  - Suggest that watchful waiting may be judiciously used
    - Gleason score 2, 3, or 4 tumors with life expectancy of 10 years or less
    - Watchful waiting is probably not appropriate for young, otherwise healthy men with high-risk features as described earlier (PSA > 10, Gleason sum = 7, or clinical stage T3 or higher).

Prostate Cancer

Treatment - LOW/INTERMEDIATE RISK DISEASE

- Androgen deprivation has not been carefully studied as primary therapy for localized disease
  - More common approach in some men
  - To receive some therapy when not suited for or decline prostatectomy or radiation therapy.
- Surgery or radiation
  - Men with T1 or T2 prostate cancer
  - Life expectancy of more than 10 years
  - No significant comorbid illnesses
  - Long-term survival is excellent

Prostate Cancer

Treatment - LOW/INTERMEDIATE RISK DISEASE

- T1 or T2 tumors
  - Gleason scores of 7 or less
    - Have 8-year survival rates of 85 to 95%.
  - Gleason scores of 8 to 10
    - Have 8-year survival rates of about 70%.

Small, E., Cecil Textbook of Medicine, Prostate Cancer, 2004, WB Saunders, an Elsevier imprint

Prostate Cancer

Treatment - LOW/INTERMEDIATE RISK DISEASE

- Nerve-sparing procedures and careful dissection techniques
  - Decreased postoperative complications
    - Urinary incontinence (<10%)
    - Impotence (10-50%)
- Following a radical prostatectomy
  - PSA should become undetectable
  - Detectable PSA implies
    - Presence of cancer cells
    - Locally or at a metastatic site
  - Adjuvant postoperative radiotherapy is of unproven benefit unless the PSA remains or becomes detectable.

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Prostate Cancer

Treatment - LOW/INTERMEDIATE RISK DISEASE

- External beam radiation therapy (EBRT)
- Three-dimensional conformal radiation therapy (3D-CRT) (replacing EBRT)
  - Higher doses to the target tissue
  - Less toxicity
  - Randomized trials are required to assess any clinical benefits
- Complications of external radiotherapy
  - Cystitis
  - Proctitis
  - Enteritis
  - Impotence
  - Urinary retention
  - Incontinence (7-10%)

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Prostate Cancer

Treatment - LOW/INTERMEDIATE RISK DISEASE

- Brachytherapy
  - Placement of permanent or temporary radioactive seeds directly into the prostate
    - Adequate for
      - Intracapsular disease
      - No more than minimal transcapsular extension
      - It can be combined with external beam radiation therapy.

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Prostate Cancer

Treatment – High-risk disease

- **HIGH-RISK DISEASE.**
  - Patients with adverse risk features
  - (Gleason score 8 to 10, PSA > 10, stage T3)
- Treated with
  - Aggressive local therapy or
  - Androgen deprivation
    - Synergistic with radiation therapy
  - Trials
    - 4 months of androgen deprivation with radiation therapy
      - Improve local control and prolong progression-free survival in patients with intermediate risk features
      - Long-term androgen deprivation (up to 3 years)
        - » Prolongs local control
        - » Prolongs progression-free survival and overall survival in patients with high-risk features compared with radiation therapy.

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Prostate Cancer

Treatment – Recurrent disease

- **RECURRENT DISEASE**
  - ~50% of men treated with radiation therapy or prostatectomy develop evidence of recurrence
  - Defined by a climbing PSA level
- Local salvage therapy
  - Selected patients with clear local recurrences
    - Surgery for patients previously treated with radiation
    - Radiation for patients previously treated with surgery and androgen deprivation
- Early hormone therapy
  - Appears to be better than hormonal salvage therapy in terms of survival.

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Prostate Cancer

Treatment – Advanced disease

- **ADVANCED DISEASE**
- Microscopic involvement of lymph nodes
  - Revealed by radical prostatectomy
  - Immediate androgen deprivation prolongs survival
    - Should not wait until osseous metastases are detected
  - Patients at high risk of nodal invasion and who undergo external beam radiation
    - Benefit from concurrent short-term hormonal therapy.
- Newly diagnosed metastatic prostate cancer
  - Androgen deprivation is the mainstay of treatment
    - Results in symptomatic improvement and disease regression in approximately 80 to 90% of patients
    - Androgen deprivation can be achieved by orchiectomy or by medical castration
    - Luteinizing hormone-releasing hormone (LHRH) agonist (leuprolide acetate, goserelin acetate)
      - Safer and as effective as estrogen treatment.

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Prostate Cancer

Treatment – Advanced disease

- Side effects of LHRH agonist
  - LH and testosterone surge within 72 hours
    - Transient worsening of signs and symptoms during the first week of therapy
      - An antiandrogen (flutamide, bicalutamide, or nilutamide) should be given with the first LHRH injection to prevent a tumor flare
    - Medical castration occurs within 4 weeks
    - Hormone sensitivity
      - Duration
        - » 5 to 10 years for node-positive or high-risk localized (or recurrent) prostate cancer
        - » 18 to 24 months in patients with overt metastatic disease
  - Side effects androgen ablation
    - Loss of libido
    - Impotence
    - Hot flashes
    - Weight gain
    - Fatigue
    - Anemia
    - Osteoporosis
      - Bisphosphonates reduce bone mineral loss associated with androgen

Prostate Cancer

Treatment – Hormone resistant

- **HORMONE-RESISTANT PROSTATE CANCER**
- Climbing PSA
  - First manifestation of resistance to androgen deprivation
    - In the setting of anorchid levels of testosterone
- Therapy
  - Discontinuation of antiandrogen therapy (flutamide, bicalutamide, nilutamide) while continuing with LHRH agonists
    - Results in a PSA decline
    - Can be associated with symptomatic improvement
    - Can persist for 4 to 24 months or more
  - Secondary hormonal manipulations
    - Ketoconazole or
    - Estrogens
  - Chemotherapeutic regimens
    - Mitoxantrone plus corticosteroids or
    - Estramustine plus a taxane
- Monitoring
  - Serial PSA levels (best)
  - A decline of 50% or more is probably clinically significant

Prostate Cancer

Treatment – Hormone resistant

- **PALLIATIVE CARE**
  - Bone pain
    - Advanced prostate cancer
    - Analgesics
    - Glucocorticoids
      - Anti-inflammatory agents
      - Can alleviate bone pain
  - Widespread bony metastases not easily controlled with analgesics or local radiation
    - Strontium-89 and samarium-153
      - Selectively concentrated in bone metastases
      - Alleviate pain in 70% or more of treated patients.

Small, E., Cecil Textbook of Medicine, Prostate Cancer, 2004, WB Saunders, an Elsevier imprint

Prostate Cancer

Prognosis

- **PROGNOSIS**
- Gleason
  - 2-4
    - 10-year PSA progression-free survival is 70 to 80%
    - Treated with radiation therapy or surgery
  - 5-7
    - 50 to 70%
  - 8-10
    - 15 to 30%

- Climbing PSA after radical prostatectomy
  - Prognostic variables
    - Time to detectable PSA
    - Gleason score at the time of prostatectomy
    - PSA doubling time

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