# Prostate Cancer

## Epidemiology
- The most common cancer in western men while incidence is low in Far East
- Usually presents after the age of 50
- The incidence is increasing with advancing age
- By the age of 80 years, about 80% of men will have malignant foci which are clinically insignificant in the vast majority

## Risk factors

### Environmental
- Western diet is rich in animal fats and meats, poor in fruits and vegetables
- Vitamin D and sunlight may be protective

### Prostatic inflammation
- Chronic or recurrent inflammation has a role in development of liver, stomach, esophagus, and bladder cancer
- A precursor lesion, proliferative inflammatory atrophy (PIA) may be a link between prostatitis and cancer
- An increased risk of PCa is associated with STD

### Endocrine factors
- Persistent androgenic stimulation leads to growth of tumor cells
- Prostatic cancer is hormone dependent and responds to castration
- However, testosterone is not tumorogenic

### Family history
- The risk increased by 2 folds when the first degree relative (father or brother) has prostate cancer.
- Inherited susceptibility genes may have a role

## Precancerous lesion
- Prostatic inflammatory atrophy (PIA) & prostatic intraepithelial neoplasia (PIN)

## Morphology
- Solid nodule → yellow, orange, bulging, hard
- Peripheral zone predilection so prostatectomy for BPH (endoscopic or surgical adenectomy) confers no protection from subsequent prostate cancer
- Peripheral zone (70%) > central > transition
- Multifocal

## Microscopy
- Prostatic adenocarcinoma >95%; TCC and sarcoma 5%
- Architectures → malignant glands are irregular and variable in size, shape, distribution. Absent basal cell layer
- Cytology → hyperchromatism pleomorphism, irregular mitosis, prominent nucleoli

## Gleason grade
- Simple, standard, based on the glandular architectural features
- Strong prognostic indicator
- Add the 2 most prominent pattern (eg 3 +4 = 6)
- Low (2 – 4), intermediate (5 – 6 ), High (7 – 10)

## TNM Staging

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>T1</td>
<td>N0</td>
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<td>T2</td>
<td>N0</td>
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<td>T3</td>
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<tr>
<td>T4</td>
<td>N0</td>
<td>M1</td>
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1. Spread → direct, lymphatic, blood
   - Direct → Trigone, seminal vesicles, lower ureters, prostatic urethra. Extension into the rectum is limited by rectovesical fascia of Denovilliers
   - Lymphatic → pelvic nodes (obturator, internal iliac, external and common iliac) & late spread to para aortic nodes
   - Blood → bony metastasis are the most common, in the form of osteosclerotic deposits in pelvis, lumbar vertebrae, femoral and ribs. Pulmonary metastasis are common

2. Urologic hematuria, urine retention, obstructive anuria, renal failure

## Complication

## Natural history and biological activity
- The disease is often indolent, slowly growing and patients are elderly
- 1 – 3 men over the age of 50 have histologic prostate cancer
- 80% are clinically insignificant
- PSA is the most clinically useful tumor marker in PCa today
- Most men die with PCa rather than from it

## Prognostic factors
1. Stage
2. Grade
3. PSA
### Symptoms

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td>Asymptomatic</td>
<td>Prostate cancer may be incidental finding on screening by PSA measurement, DRE or histological examination of excised or resected prostate. Even advanced cases may be silent.</td>
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<tr>
<td>Manifest</td>
<td>Progressive lower urinary tract symptoms</td>
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<tr>
<td>Complicated</td>
<td>Hematuria, retention, anuria, renal failure, UTI</td>
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<tr>
<td>Metastatic</td>
<td>Bulky LN metastasis may present with unilateral or bilateral LL edema</td>
</tr>
<tr>
<td></td>
<td>Symptoms from 2ry in bone and lungs</td>
</tr>
<tr>
<td></td>
<td>Men with bony metastases often present with pain or pathologic fractures</td>
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<tr>
<td></td>
<td>Spinal cord compression may lead to paraplegia</td>
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### Signs

#### General examination:
- Abdominal examination: 
  - DRE is crucial in diagnosis of prostatic disorders.

#### Features of prostate by DRE in health and disease

<table>
<thead>
<tr>
<th>Feature</th>
<th>Normal</th>
<th>BPH</th>
<th>Cancer</th>
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<tbody>
<tr>
<td>Site</td>
<td>The prostate is a palpable pelvic organ in front of the lower rectum.</td>
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<tr>
<td>Shape</td>
<td>Inverted pyramid</td>
<td>Generalized enlargement</td>
<td>According to tumor stage</td>
</tr>
<tr>
<td>Size</td>
<td>Chestnut (4x3x2 cm)</td>
<td>Mild, moderate or marked</td>
<td>Variable</td>
</tr>
<tr>
<td>Suci</td>
<td>One median and two lateral</td>
<td>Exaggerated or deep</td>
<td>Obliterated</td>
</tr>
<tr>
<td>Rectal mucosa</td>
<td>Sliding</td>
<td>Sliding</td>
<td>Moving except late</td>
</tr>
<tr>
<td>Consistency</td>
<td>Rubbery, homogenous</td>
<td>Grim elastic, homogenous</td>
<td>Rocky hard, heterogeneous</td>
</tr>
<tr>
<td>Mobility</td>
<td>Little, variable</td>
<td>Little</td>
<td>T4 is fixed</td>
</tr>
</tbody>
</table>

### DDx

#### Differential diagnosis of prostatic nodule
1. Prostate cancer
2. Nodular BPH
3. Granulomatous prostatitis
4. Fibrosis
5. Infarct
6. Prostatic calculi

#### Causes of high serum PSA
1. Prostate cancer
2. BPH
3. Acute bacterial prostatitis and prostate abscess
4. Prostatic infarction
5. Manipulation of prostate (biopsy, cystoscopy)

### Investigations

#### PSA
- Protease glycoprotein secreted by prostatic epithelial cells
- Prostatic specific
- Not cancer specific
- Normal value up to 4 ng/ml

#### Importance of PSA in PCa
1. Useful in screening, diagnosis, prognostication, monitoring of treatment
2. Most sensitive method for early detection uses both DRE + PSA
3. PSA measurement misses 20–30% of PCa

#### TRUS
- Transrectal ultrasound guided biopsy is the standard for diagnosis in cases of suspicious DRE and and or elevated PSA
  - It determines size, site, and extend of spread through the capsule
  - It guides the biopsy needle
  - Cancer appears as hypo-echoic area
  - Diagnosis is confirmed by histopathologic examination

#### CXR
- Shows cannon ball metastases

#### KUB
- Multiple osteosclerotic metastases

#### CT scan
- Staging of prostate cancer
- Evaluate LN, liver, bone, kidney

#### Bone scan
- Bone metastases
### Treatment of prostate cancer

#### Observation
- The indication of watchful waiting are
  1. Short life expectancy, significant comorbidity
  2. Low probability of therapeutic benefit as high grade advanced tumor
- Treatment is directed to palliate symptom
- Active surveillance is indicated in cases of low probability of death from PCa
- Curative treatment is provided if the disease is progressive

#### Radical prostatectomy
- Is indicated when cancer is localized to the prostate and the patient is fit
- It entails removal of the whole prostate and both seminal vesicles. Bladder neck is reanastomosed to the urethra
- RP may be accomplished by open surgery, laparoscopic or robotic
- Complications → bleeding, rectal injury, incomplete tumor removal, urine incontinence, impotence.

#### Radiotherapy
- External beam radiotherapy or brachytherapy (radioactive seed implant)
- Efficacy is similar to radical prostatectomy

#### Hormonal therapy
- The most common indication of HT is symptomatic metastasis.
- Androgen deprivation effectively palliates symptoms and reduces the catastrophic sequelae → SC compression, pathological fracture, ureteral obstruction

<table>
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<tr>
<th>Surgical castration</th>
<th>Bilateral subcapular orchidectomy is the standard treatment</th>
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<td>Complication → psychological problem, impotence, hot flushes and osteoporosis</td>
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<tr>
<th>Medical castration</th>
<th>Oral estrogens are not used because of severe toxicity (fluid retention leading to HTN and HF, DVT/PE, gynaecomastia, depression, impotence)</th>
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<tbody>
<tr>
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<td>Parenteral estrogen have lower risk due to bypass of portal circulation</td>
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<td>Estrogen controls bone mineralization in women and men therefore they don't have osteoporosis</td>
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<th>LHRH analogues</th>
<th>Goserelin (Zoladex), Leuprolide (Lupron, Eligard)</th>
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<td>LHRH analogues initially stimulate LHRH followed by subsequent suppression of LH and testosterone level</td>
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<td>Complications → osteoporosis, edema, obesity, UTO, orgasm failure</td>
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<th>Antiandrogens</th>
<th>Steroidal → cyproterone acetate</th>
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<td>Non steroidal → flutamide &amp; bicalutamide</td>
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| Adrenal androgen synthesis inhibitors | 5%of androgens are produced by adrenal glands |

#### Metastatic castration resistant PCa
1. Secondary hormone treatment (ketonazole & abiterone)
2. Chemotherapy → docetaxel, prednisone
3. Bone target agent → bisphosphonates
4. Immunotherapy
5. Antiangiogenesis → Bevacizumab
6. Radiopharmaceuticals