# PROSTATE CANCER

# Epidomiology

In the U.S :

- Prostate Cancer (PCA) is The most common non cutaneous Cancer among american men.
- Around 200 000 new cases every year.
- 30 000 men die annually.
- Age adjusted mortality dropped 50 % over the last 30 years ?

Better screening programs and early detection+ improved treatment.

??Overdiagnosis and overtreatment.

# Epidomiology

- **Number of PCA deaths annually is far outweighed by the number of diagnoses, and most men diagnosed ultimately die of other causes, most often cardiovascular disease.**

- **Prevalence of PCA increases with age; However, unlike most cancers, which have a peak age of incidence, there is no peak for PCA.**

# Epidomiology

- The risk of latent prostate cancer (ie, detected as an incidental finding at autopsy, not related to the cause of death) by age 80 is 36% for Caucasian men and 51% for African-American men.
- The lifetime incidence of diagnosed prostate cancer is 15%, and the mortality rate 2.9%.
- Thus, many prostate cancers are indolent and inconsequential to the patient while others are more virulent, and if detected too late or left untreated, they result in considerable morbidity and ultimately in death.

# Risk Factors

- Age : dramatic increase ; probability of prostate cancer diagnosis in a men:
  - < 40 Y : 1 in 10 000
  - 40-59 Y : 1 in 103
  - 60-79 Y : 1 in 8

- African Americans have higher risk than other ethnicities .

- Family history: the age of onset in that person affects as well :
  - 70- four fold
  - 60-five old
  - 50-seven fold

# Risk Factors

- 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 ? More advanced disease at presentation and recurrence after treatment.
- In addition, lycopene, selenium, omega-3 fatty acids (fish), and vitamin E intake have been shown to be protective.
- whereas vitamin D and calcium may increase risk.
- More frequent ejaculation is associated with lower risk.
- Benign enlargement or growth (BPH) of the prostate is NOT a risk factor for prostate cancer.

# Pathology

- **Adenocarcinomas: More than 95 % of the PCA.**

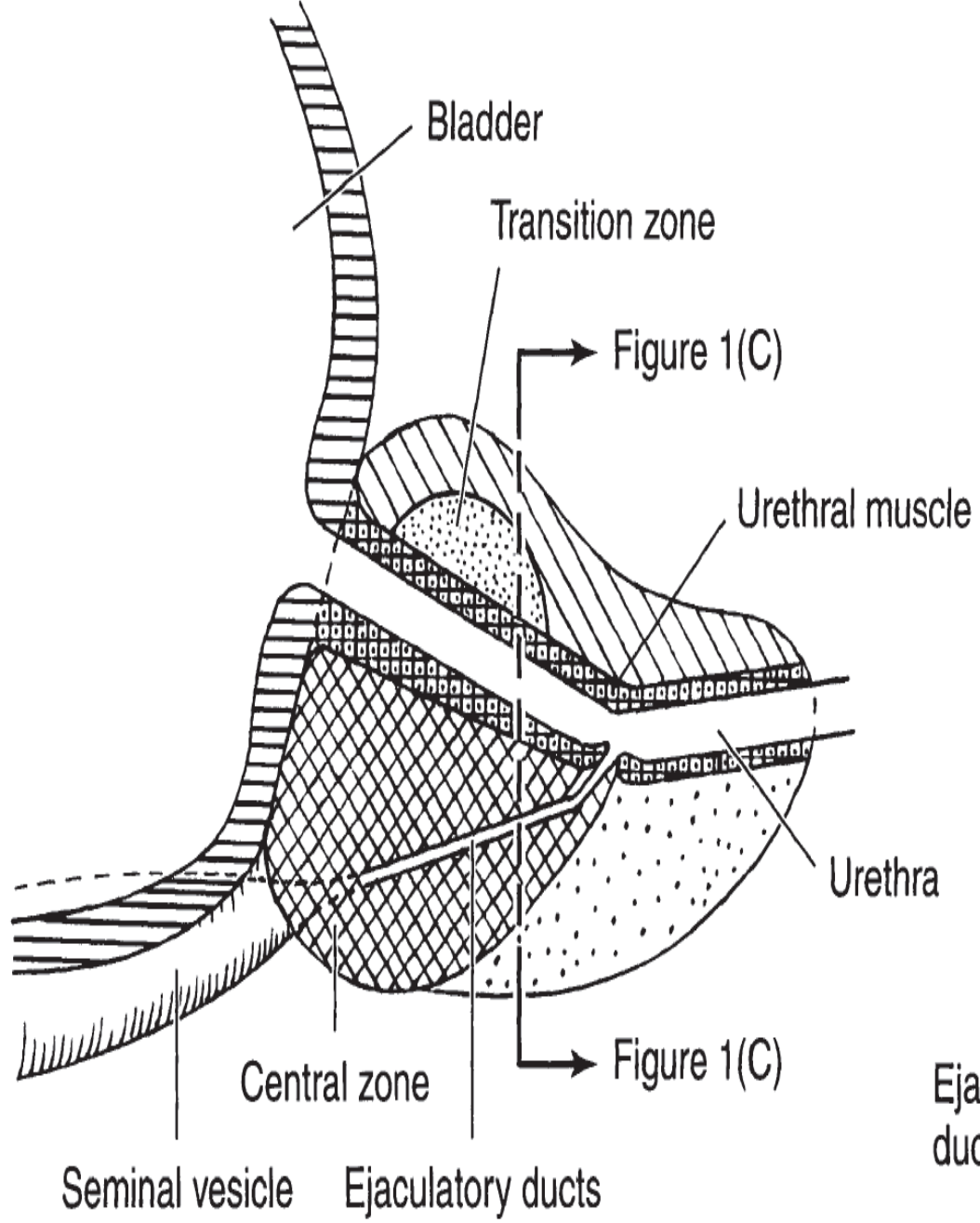
- **Nonadenocarcinomas:**

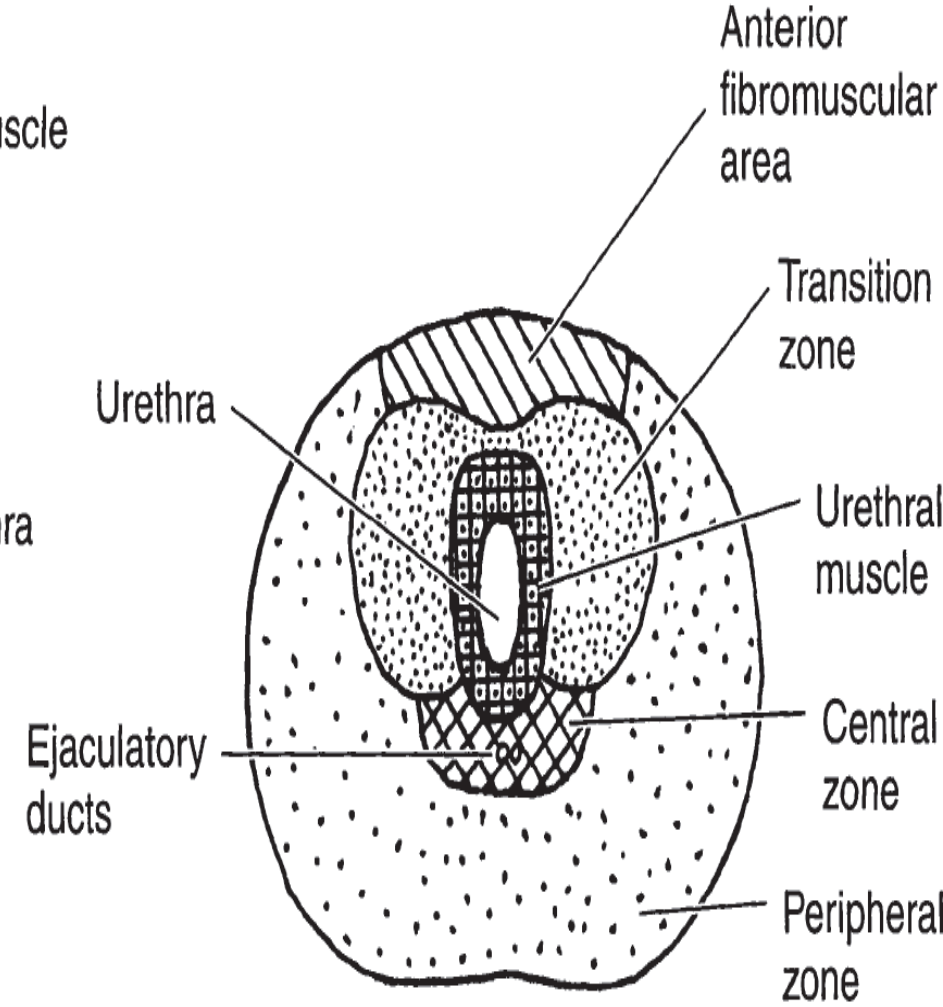
**Epithelial: endometrioid, mucinous, signet-ring, adenoid cystic, adenosquamous, squamous cell, transitional cell, neuroendocrine, and comedocarcinoma.**

**Nonepithelial: rhabdomyosarcoma, leiomyosarcoma, osteosarcoma, angiosarcoma, carcinosarcoma, malignant lymphoma, and metastatic neoplasms.**

# Anatomical Distribution

- 60–70% of cases of PCA originate in the peripheral zone.
- 10–20% originate in the transitional zone.
- 5–10% in the central zone.


Bladder
Transition zone
Figure 1(C)
Urethral muscle
Urethra
Figure 1(C)
Central zone
Seminal vesicle
Ejaculatory ducts


Anterior fibromuscular area
Transition zone
Urethra
Urethral muscle
Ejaculatory ducts
Central zone
Peripheral zone

# Invasion and metastases

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

- Metastases:
- 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.

# 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 co-existing 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 (hardness) or nodularity, if detected, must alert the physician to the possibility of cancer.
- 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 and 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, and for follow-up after treatment..

# Prostate specific Antigen (PSA)

- Normal <4ng/ ml (varies with age)
- Positive predictive value of raised PAS
  4-10 ng/ml : 20-30 %.
  >10 ng/ml : 42-71 %.
- About 15% of men with a PSA below 4 will have prostate cancer if a biopsy is done.
- There is no level of PSA below which PCA risk falls to zero.
- PSA is rather indicative of a continuum of risk; the higher the level, the higher the risk.
- Sensitivity of PSA has been estimated to be about 70-80%, while the specificity is estimated to be about 60-70%.

# Prostate specific Antigen (PSA)

**Other causes for PSA elevation:**

- **BPH.**
- **Prostatitis.**
- **Trauma… Including perineal insults such as prolonged bike riding.**
- **Iatrogenic and instrumentation.**
- **DRE and catheterization.**

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

**False negative**

**Use of medications such as 5α-reductase inhibitors (like finasteride) must be ascertained, as these medications can artificially lower the PSA by approximately 50%.**

**Serum PSA levels have also been noted to be decreased in men with high body mass index compared with normal weight men.**

# Prostate specific Antigen (PSA)

- 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).

# PSA velocity (PSAV)

# Refers to the rate of change of serum PSA; men with prostate cancer have a more rapidly rising serum PSA in the years before diagnosis than do men without prostate cancer. Patients whose serum PSA increases by more than 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 rather than cancer.

# The optimal use of PSAV remains controversial.

# PSA density

- The ratio of PSA to gland volume.
- 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.
- 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.

# Free/total PSA ratio

- Approximately 90% of the serum PSA is bound to α1-antichymotrypsin (ACT), and lesser amounts are free or are bound to α2- macroglobulins.
- Early studies suggest that prostate cancer patients demonstrate a lower percentage of free PSA than do patients with benign disease.
- In men with a normal DRE and a total PSA level between 4 and 10 ng/mL, a 25% free/total ratio (less than) PSA cutoff would detect 95% of cancers while avoiding 20% of unnecessary biopsies.

# PCA 3

- Prostate cancer antigen 3 (PCA3) is a noncoding, prostate-specific mRNA, which is overexpressed in the majority of prostate cancers.

- PCA3 is a urine based test that predicts the presence of cancer in a biopsy setting with an accuracy of 74.6%

# Imaging

**Trans-rectal ultrasound:**

- **More helpful than DRE in staging.**
- **Guidance for biopsies.**
- **Cancer appears as Hypoecheoic region in periphery.**

# Imaging

- **Multi-parametric MRI:**
- **A multi-parametric magnetic resonance imaging (mpMRI) scan is a special type of scan that creates more detailed pictures of the prostate than a standard MRI scan. It does this by combining four different types of image and used to detect and evaluate prostate cancer.**
- **mpMRI should include four sequences: T1-weighted images, T2-weighted images, diffusion-weighted images (DWI) and dynamic contrast-enhanced imaging (DCEI) and spectroscopic imaging.**
- **PI-RADS**

# Imaging

- **Axial imaging (CT, MRI)**
- selectively performed to exclude lymph node metastases in high-risk patients
- 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.

# Imaging

- PSMA scan (PET/CT scan).
- A prostate-specific membrane antigen
- More accurate for mets detection and disease recurrence.

# Biopsy

- When there is an abnormal DRE and/or elevated PSA levels.
- Biopsy is done with the guidance of TRUS.
- 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 %.
- Most biopsy templates today include medial and lateral sampling of the apex, midgland, and base on the right and left sides.(12 cores)
- Procedure is done under local anasthesia , with the use of prophylactic antibiotics.
- Complications include :Infection and sepsis, Hematospermia, hematochezia, and hematuria.
- Transperineal biopsy.
- saturation biopsy… 20 or more cores .

# PATHOLOGY

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

# PATHOLOGY

- 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.

# GRADING

- **GLEASON GRADING 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

# Grading

- However, pathology grading practices have changed over time.
- In contemporary pathology practice, Gleason patterns 1 and 2 are rarely assigned.
- so Gleason pattern 3 corresponds with low grade disease.
- Gleason pattern 4 corresponds with intermediate grade disease.
- Gleason pattern 5 corresponds with high grade disease.(no gland formation)

# STAGING

- **TNM staging system**

| 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 |

# Treatment

- Active surveillance.
- Radical Prostatectomy. (RP)
- Radiotherapy: External beam radiation, Brachytherapy.
- Focal therapy.
- Hormone (androgen deprivation) therapy.
- Chemotherapy.
- Watchful waiting.

# Treatment

- 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.

# Treatment

- Multivariable Risk Assessment.
- overtreatment of low-risk disease and undertreatment of high-risk disease.
- The critical variables for optimal risk stratification have been detailed earlier: the PSA level, the Gleason score, and some measure of tumor volume—clinical T stage and/or extent of biopsy core involvement (eg, percent of cores positive or percent of all biopsy tissue positive).
- Risk groups:
- Low risk—PSA ≤10, Gleason ≤6, and clinical stage T1 or T2a

  Intermediate risk—PSA 10–20, Gleason 7, or clinical stage T2b

  High risk—PSA >20, Gleason 8–10, or clinical stage T2c or T3a

| Risk group | D'Amico | NCCN | EAU | AUA |
|---|---|---|---|---|
| Very low | | PSA < 10, PSAD < 0.15, cT1c, GG1, ≤3 cores positive, ≤50% of any core positive | | PSA < 10, PSAD < 0.15, cT1c, GG1, ≤3 cores positive, ≤50% of any core positive |
| Low | PSA < 10, cT1/2a, GG1 | PSA < 10, cT1/2a, GG1 | PSA < 10, cT1/2a, GG1 | PSA < 10, cT1/2a, GG1 |
| Favorable intermediate | PSA 10–20, cT2b, GG2–3 | PSA 10–20, cT2b–c, GG2–3 | PSA 10–20, cT2b, GG2–3 | PSA 10–< 20 + GG1<br>or<br>PSA < 10 + GG2 |
| Unfavorable intermediate | | | | GG2 + PSA 10–<20 / cT2b–c<br>or<br>PSA < 20 + GG3 |
| High | PSA > 20, cT2c, GG4–5 | PSA > 20, cT3a, GG4–5 | PSA > 20, cT2c, GG4–5<br>or<br>any PSA, any GG, cT3–4, cN+ | PSA > 20, ≥cT3, GG4–5 |
| Very high | | cT3b-4, ≥4 cores with GG4–5 or primary Gleason pattern 5 | | |

# Active surveillance

- In active surveillance, men with very well-characterized, early-stage, and low- to intermediategrade 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.
- Although between 20% and 41% of men on such regimens may require treatment within 5 years of follow-up.

# Radical Prostatectomy

- Perineal Vs retropubic approach.
- Open Vs laparoscopic Vs robotic (daVinci).
- nerve-sparing techniques.
- Incontinance and erectile dysfunctions.
- Lymph node dissection.

# Radiotherapy

- External-beam therapy Vs Brachytherapy.

- Results of radiation therapy may be improved with the use of neoadjuvant, concurrent, and adjuvant androgen deprivation.

# Focal therapy

- Prostate cancer tends to be an infiltrative disease, with cancerous glands interspersed with normal ones, and is frequently multifocal.

- Multiple modalities:

Cryotherapy

High-intensity focused ultrasound (HIFU)

Interstitial laser therapy.

# Hormone (androgen deprivation) therapy.

- Most prostatic carcinomas are initially androgen-dependent, and the vast majority of men with metastatic prostate cancer respond initially to various forms of androgen deprivation.
- Androgen deprivation therapy (ADT)
- Orchiectomy.
- Luteinizing hormone-releasing hormone (LHRH) agonists.
- LHRH antagonists.
- Estrogens.
- Anti-androgens.
- Hormone refractory … castrate-resistant,,,,,,,,,,,,
- Second-generation antiandrogens (enzalutamide, apalutamide, darolutamide)

# CHEMOTHERAPY

- **Taxane-based chemotherapy (docetaxel, cabazitaxel).**

# Watchful waiting

- Implies no or minimal monitoring for prostate cancer.

# Screening

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

# Screening

- 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

# Chemoprevention

- The ideal agent should be nontoxic and of low cost, and the ideal patient would be one at high risk of acquiring the disease.
- 5α-reductase inhibitors.
- Selenium.
- Vitamin E.