DOPAMINE
SCIENTIFIC TEAM

UGS PATHOLOGY

MID | LECTURE 7

PROSTATE DISEASES

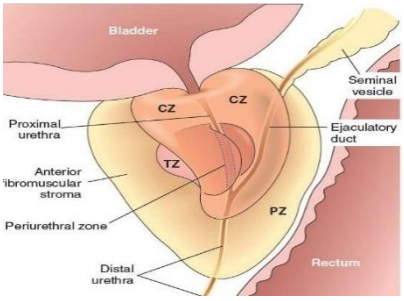
Done by:

Laith Alhuniti

Mahmoud Aljunaidi

❖ Prostate

- The prostate can be divided into biologically distinct regions:



1. The peripheral zone (PZ)
2. The central zone (CZ)
3. The transition zone (TZ)

- Understanding the anatomical zones of the prostate is important because they are arranged around the proximal urethra and have different clinical significance. The prostate is commonly divided into three main zones: the **central zone**, which lies close to and surrounds the urethra; the **peripheral zone**, located more superficially and posteriorly; and the **transitional zone**.
- These zones are clinically relevant because specific diseases tend to arise in particular regions. For example, most **prostate tumors** develop in the peripheral zone, whereas **benign prostatic hyperplasia (BPH)** usually originates in the central/transitional region around the urethra. As a result, the zone involved often influences the patient's symptoms and clinical presentation.

❖ Prostate Internal Structure

- The normal prostate is composed of two components: glandular and stromal components.
- The normal prostate contains glands with two cell layers:

1. A flat basal cell layer
2. An overlying columnar secretory cell layer

❖ The surrounding prostatic stroma contains a **mixture of smooth muscle** and **fibrous tissue.**

❖ Prostatic Tumors

- Most **hyperplastic lesions** arise in the inner transition zone.
- Most **carcinomas** (70–80%) arise in the peripheral zones.
- Carcinomas are often detected by **rectal examination**, whereas hyperplasias are more likely to cause urinary obstruction.
- When we say that hyperplasia originates in the central zone, this does not mean that benign prostatic hyperplasia remains limited to that area. In advanced cases, enlargement may involve most or all of the prostate gland.
- During a per rectal (digital rectal) examination, the prostate can be palpated to assess its size, consistency, and to detect any abnormal masses or nodules. Prostatic

carcinoma may coexist with hyperplasia, while benign prostatic hyperplasia usually causes a more diffuse and symmetrical enlargement.

- If a distinct enlarged nodule or suspicious hard mass is felt on examination, further evaluation with a biopsy is required to determine the exact nature of the lesion.

❖ Benign Prostatic Hyperplasia (BPH)

- Benign prostatic hyperplasia (BPH) is an extremely common cause of prostatic enlargement resulting from proliferation of stromal and glandular elements.
- In benign prostatic hyperplasia, the relative **contribution of tissue components can vary**. In some cases, the glandular element is more prominent, leading to increased proliferation of prostatic glands, while in other cases the enlargement is mainly due to stromal hyperplasia, involving proliferation of smooth muscle and fibrous connective tissue.
- It is present in a significant number of men by 40 years of age, and its frequency rises progressively thereafter, reaching 90% by the eighth decade of life.
- Enlargement of the prostate in men with BPH is an important cause of **urinary obstruction.**
- BPH is due to **excessive androgen-dependent growth** of stromal and glandular elements. This indicates that androgen stimulation is a mechanism in the development of the disease.
- BPH does **not** occur in males who are castrated before the onset of puberty or in males with genetic diseases that block androgen activity.
- A very important feature of this condition is that it can lead to significant clinical manifestations. Patients often need regular follow-up and treatment of complications that may arise over time. These complications are usually not caused by the hyperplasia itself, but by **urinary outflow obstruction** secondary to enlargement of the prostate.
- As mentioned, the enlargement typically occurs in the **periurethral/central transitional region of the prostate**, where it compresses the urethra. This causes narrowing of the urethral lumen and, in severe cases, may result in partial or complete obstruction. Consequently, patients may develop a range of lower urinary tract symptoms such as hesitancy, **weak urinary stream**, incomplete bladder emptying, **urinary frequency**, **urgency**, and **retention**.

❖ Morphology

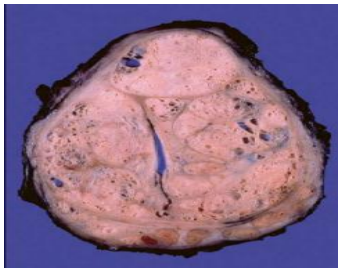
- BPH virtually always occurs in the inner transition zone of the prostate.
- The affected prostate is enlarged, typically weighing between 60 and 100 g. A normal, healthy adult prostate typically weighs between 15 and 30 grams.
- It contains many **well-circumscribed nodules** that bulge from the cut surface.
- These nodules often vary in size and shape. When the **glandular component** predominates, some glands may become dilated and enlarged, with accumulation of retained secretions within their lumens.

- Stasis of these secretions can predispose to **inflammation or infection**, which may increase the likelihood of recurrent episodes of prostatitis or lower urinary tract irritation in some patients.
- The nodules may appear solid or contain cystic spaces corresponding to dilated glands.
- The **urethra is usually compressed**, often to a narrow slit, by the hyperplastic nodules, leading to obstructive manifestations, mentioned earlier, esp. urinary retention.
- Hyperplastic glandular and stromal elements lying just under the epithelium of the proximal prostatic urethra project into the bladder lumen as a pedunculated mass, producing **a ball-valve type of urethral obstruction**. Enlarged prostate tissue near the urethra forms a small mass that protrudes into the bladder and acts like a valve, intermittently blocking urine flow.

❖ **Microscopy**

- The hyperplastic nodules are composed of variable proportions of proliferating glandular elements and fibromuscular stroma.
- The hyperplastic glands are lined by tall columnar epithelial cells and a peripheral layer of flattened basal cells.
- The glandular lumina often contain laminated proteinaceous secretory material known as **corpora amylacea**.

❖ **Benign Nodular Hyperplasia**



- Well-defined nodules compress the urethra into a slit-like lumen.
- The cut surface on the right appears **nodular** and is divided by bands of **fibrous stromal tissue**. Some areas demonstrate fibrosis, while the rounded or hole-like spaces represent the **glandular component**. Several of these glands may be **dilated**, often due to accumulated secretions.

❖ **Clinical Features of Benign Prostate Hyperplasia (BPH)**

- Because BPH preferentially involves the inner portions of the prostate, **the most common manifestations** are related to lower urinary tract obstruction, in the form of difficulty starting the stream of urine (**hesitancy**) and intermittent interruption of the urinary stream while voiding.
  - Because of the narrowing of the urethra due to fibrotic prostatic tissue, **urination becomes more difficult.**
- Urinary **urgency**, **frequency**, and **nocturia** - all indicative of bladder irritation.

- Clinical manifestations of prostatic hyperplasia occur in only about 10% of men with pathologic evidence of BPH.
- The presence of residual urine in the bladder due to chronic obstruction and incomplete emptying **increases the risk for urinary tract infections.**
- Complete urinary obstruction, with resultant **painful distention of the bladder**.
- In some cases, urethral obstruction may become complete, leading to **acute urinary retention** with accumulation of a large volume of urine. This is a medical emergency because bladder overdistension is painful and requires urgent decompression, usually with catheterization.
- Obstruction may also develop gradually as a **chronic process**, particularly when narrowing is severe and persistent. Chronic retention can cause incomplete bladder emptying, progressive bladder distension, and increased intravesical pressure.
- This elevated pressure may be transmitted backward to the **ureters** and then to the **kidneys**, resulting in **hydroureter** and **Hydronephrosis**. Over time, prolonged back pressure can damage the renal parenchyma and may impair kidney function, potentially leading to obstructive nephropathy.

❖ Carcinoma of the Prostate

- Originates from the gland and the lining epithelium.
- Adenocarcinoma of the prostate is the **most common form of cancer in men**, accounting for 27% of cancer cases in the United States in 2014.
- It is uncommon before the age of 50 years.
- Over the past several decades, mortality from prostate cancer has **decreased significantly**, and it currently causes only 10% of cancer deaths in the United States.
- The relatively low rate of mortality in men with prostate cancer is related in part to **increased detection of the disease through screening**.
- Prostate carcinoma is commonly found incidentally at autopsy in men dying of other causes.

❖ Pathogenesis and Predisposing Factors:

1. Androgens
2. Heredity
3. Environmental factors
4. Acquired somatic mutations

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1. Androgens

- Cancer of the prostate does not develop in males who are castrated before puberty.

- This dependence on androgens extends to established cancers, which often regress for a time in response to surgical or chemical castration.
- Prostate cancer cells depend on male hormones (androgens, like testosterone) to grow and survive. Even after the cancer has already developed, many tumor cells still rely on these hormones. So, when androgen levels are reduced—either by surgical removal of the testes or by medications that block hormone production—the cancer cells lose their growth stimulus and the tumor often shrinks or slows down. However, this response is usually temporary because some cancer cells eventually adapt and continue growing despite low androgen levels.
- Tumors that are resistant to anti-androgen therapy often acquire androgen receptor gene amplifications or mutations that permit androgen receptors to activate the expression of their target genes despite therapy.
  Some prostate tumors become resistant to anti-androgen therapy by changing their androgen receptors. They may increase the number of receptor genes (amplification) or develop mutations that make the receptors more sensitive or active. As a result, even very low levels of androgens—or sometimes no androgens at all—can still trigger these receptors, allowing cancer cells to keep activating growth-related genes and continue growing despite treatment.

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2. Heredity

- There is an **increased risk among first-degree relatives** of patients with prostate cancer.
- The incidence is highest among African Americans and in Scandinavian countries.
- It is **uncommon** in Asians and is **more aggressive.**
- Clinically significant disease is more common in African Americans than in Caucasians.
- Genome-wide association studies have identified a number of genetic variants that are associated with increased risk for developing prostate cancer.
- Men with multiple risk alleles may have up to a **fivefold increase in risk** compared to the general population.

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3. Environment

- Among Japanese immigrants to the United States, the incidence of the disease ***rises*** (**although not to the level seen in native-born Americans**).
- The incidence of clinically significant prostate cancer in Asia is increasing as the **diet in this region becomes more westernized.**

- However, the relationship between specific dietary components and prostate cancer risk is unclear.

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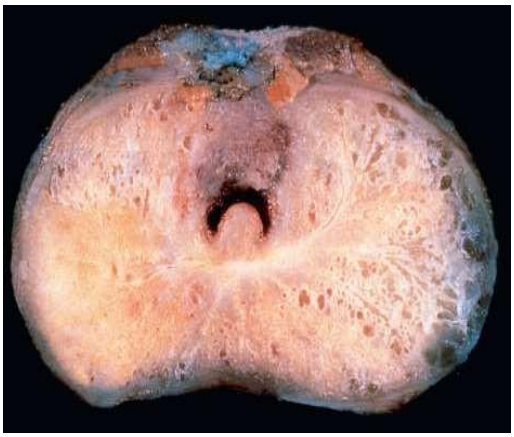
4. Acquired Genetic Aberrations

- Involves genes that regulate or control androgen secretion.
- The **most common** gene rearrangements in prostate cancer create **fusion genes** consisting of the **androgen-regulated promoter of the TMPRSS2 gene** and the **coding sequence of ETS family transcription factors**.
- ***TMPRSS2-ETS fusion genes*** are found in approximately 40–60% of prostate cancers in Caucasian populations and occur relatively **early** in tumorigenesis.
- The prevalence of these rearrangements is **lower** among African Americans and other ethnic groups.
- Other mutations commonly lead to activation of the **PI3K/AKT signaling pathway**; the most common are **loss-of-function mutations involving the tumor suppressor PTEN**, which acts as a brake on PI3K activity.

❖ Morphology

- Most prostate cancers are **moderately differentiated adenocarcinomas** that produce **well-defined glands**.
- The glands are typically **smaller** than benign glands and are lined by a single uniform layer of cuboidal or low columnar epithelium lacking the basal cell layer seen in benign glands.
- In further contrast with benign glands, malignant glands are crowded together and characteristically lack branching and papillary infolding.
- The cytoplasm of the tumor cells ranges from **pale-clear** (as in benign glands) to a distinctive **amphophilic** (dark purple) appearance.
- **Nuclei are enlarged** and often contain one or more prominent nucleoli.
- Some variation in nuclear size and shape is usual.
- Mitotic figures are **uncommon**.
- With increasing grade, irregular or ragged glandular patterns are seen in approximately 80% of cases.
- Prostatic tissue removed for carcinoma also harbors **presumptive precursor lesions** referred to as **high-grade prostatic intraepithelial neoplasia (HGPIN).**

❖ Adenocarcinoma of the prostate (Microscopy).



- Carcinomatous tissue is seen on the posterior aspect (lower left). Note the solid whiter tissue of cancer, in contrast with the spongy appearance of the benign peripheral zone on the contralateral side.
- This prostate is enlarged overall, but the nodules are not markedly prominent on gross examination.
- There are **variable-sized cystic spaces**, which are consistent with **benign prostatic hyperplasia** due to dilated hyperplastic glands. However, when comparing the two sides, one side shows a more **firm, solid area**. This appearance is suspicious for **prostatic carcinoma**.
- Malignant prostatic glands are typically **small, crowded, and infiltrative**, rather than dilated. They often lose the normal glandular architecture, including the usual branching and infolding pattern. As a result, the side containing the tumor appears more **solid and homogeneous** than the side showing benign hyperplastic changes.

❖ Gleason System

- An important part of diagnosing this condition is **tumor grading**, which helps assess how aggressive the cancer is. Therefore, prostate cancer is **graded by the Gleason system**.
- According to this system, prostate cancers are stratified into five grades **based on glandular patterns of differentiation:**
    - Grade 1 represents the most well-differentiated tumors.
    - Grade 5 tumors show no glandular differentiation.
    - In grades 3, 4, or 5, the majority of tumors contain more than one pattern; a primary grade is assigned to the dominant pattern and a secondary grade to the next most frequent pattern.
- The assessment begins with identifying the dominant histological pattern of the tumor. The lesion may be composed entirely of well-differentiated tissue or entirely of poorly differentiated tissue.
- First, the most prevalent area is evaluated and assigned a grade based on glandular differentiation, ranging from 1 to 5. Next, the second most common pattern is identified and graded in the same manner.
- The two numerical grades are then added to obtain a **combined Gleason score** (out of 10).
- Based on this total, tumors are classified as follows:
    - Low grade: ≤ 6
    - Intermediate grade: 7
    - High grade: 8–10

✓ This grading system is important because it correlates directly with tumor aggressiveness and overall patient prognosis.

❖ Clinical Features

- In the United States, most prostate cancers are small, nonpalpable, asymptomatic lesions discovered on needle biopsy performed to investigate an **elevated serum prostate-specific antigen (PSA) level.**
- Carcinoma of the prostate is a common cancer of older men between 65–75 years of age.
- Prostate carcinomas range from **indolent lesions** that will never cause harm to **aggressive fatal tumors**, which are more common in African Americans.
- The **most common acquired mutations** in prostatic carcinomas create TMPRSS2-ETS fusion genes **or** enhance PI3K/AKT signaling, promoting tumor cell growth and survival.
- Carcinomas of the prostate arise most commonly in the **outer peripheral zone** of the gland and may be palpable by rectal examination.
- Grading of prostate cancer by the Gleason system **correlates with pathologic stage and prognosis.**
- **Serum PSA** measurement is a controversial cancer screening test but has clear value in monitoring progressive or recurrent prostate cancer.
- About 70–80% of prostate cancers arise in the outer (peripheral) glands, and a subset may be palpable as **irregular hard nodules on digital rectal examination**.
- A **minority** of carcinomas is discovered unexpectedly during histologic examination of prostate tissue removed by transurethral resection for BPH.
- Because of the peripheral location, prostate cancer is **less likely than BPH to cause urethral obstruction in its initial stages.**
- **Locally** advanced cancers often infiltrate the seminal vesicles and periurethral zones of the prostate and may invade adjacent soft tissues, the wall of the urinary bladder, or (less commonly) the rectum.
- **Bone metastases**, particularly to the axial skeleton, are frequent late in the disease and typically cause osteoblastic (bone-producing) lesions that can be detected on radionuclide bone scans.
- **So Clinical features are:** Elevated PSA serum levels, Palpable nodules on per rectal examination, Incidental finding and bone metastasis.

❖ Diagnosis and Metastatic Patterns of Prostate Carcinoma

- Markedly elevated PSA levels can suggest an **increased risk of prostate carcinoma**, but PSA is not specific and may also rise in benign conditions such as prostatitis or other inflammatory processes.
- When prostate cancer is suspected clinically or biochemically, diagnosis is confirmed by a core needle biopsy. Multiple tissue samples are taken from different regions of the prostate to improve diagnostic yield. In some cases, the

carcinoma may be very small and discovered incidentally. For this reason, all prostate biopsy specimens must be thoroughly and carefully examined, as clinically silent malignancy may still be present.

- On imaging, metastatic prostate carcinoma particularly in the axial skeleton - classically produces **sclerotic** (osteoblastic) lesions, which appear **radiodense** or "white" on radiographs. This reflects abnormal bone formation stimulated by tumor spread. In contrast, many other malignancies tend to produce lytic lesions, which destroy bone and therefore appear darker or radiolucent on imaging studies.

❖ Prostate Specific Antigen (PSA)

- The PSA assay is the most widely used test in the diagnosis and management of prostate cancer.

❖ Limitations of PSA use:

1) **PSA is a product of prostatic epithelium and is normally secreted in the semen**.
   • PSA screening can detect prostate cancers early in their course that are clinically insignificant, sometimes requiring no treatment for decades.
   • Overtreatment of these indolent cancers can cause significant morbidity, particularly erectile dysfunction and incontinence.
2) **PSA as a biomarker is not cancer-specific**.
   • BPH, prostatitis, prostatic infarcts, instrumentation of the prostate, and ejaculation may all increase serum PSA levels.
   • 20–40% of patients with organ-confined prostate cancer have PSA values below the cutoffs used to identify patients likely to have prostate cancer.
   This means that not all prostate cancers cause a high PSA level. Even when the cancer is still limited to the prostate (organ-confined), about 20–40% of patients have PSA levels that fall below the usual cutoff used to suspect cancer. So, a "normal" PSA does not completely rule out prostate cancer, which is one limitation of relying on PSA screening alone.

Quiz on this lecture: [Link]

Anything wrong? [Feedback Form]