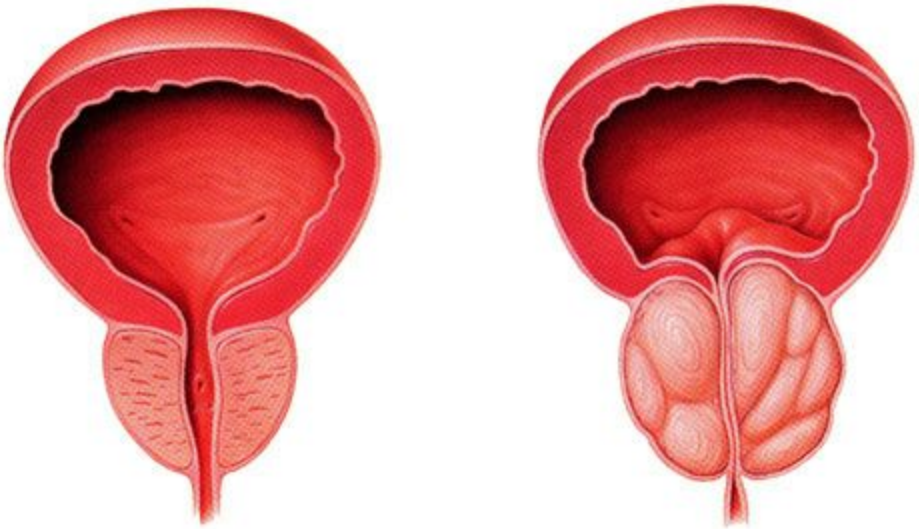
Prostatic Hyperplasia & Cancer



Objectives:

A. Understand the basic anatomical relations and zones of the prostatic gland.
B. Know the epidemiology, pathogenesis and histopathologic features of benign prostatic hyperplasia and carcinoma of the prostate.

Important note: Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all or our work: Pathology Edit.

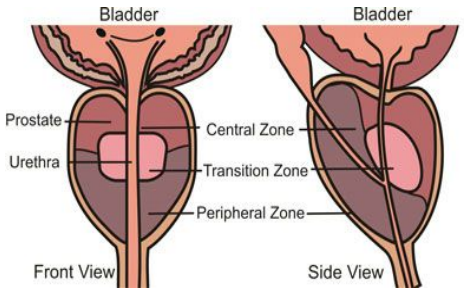
Grey = Extra
Red = Important

Introduction

- Prostate weighs 20 grams in normal adult.
- Retroperitoneal organ, encircling the neck of bladder and urethra.
- Devoid[1] of a distinct capsule.

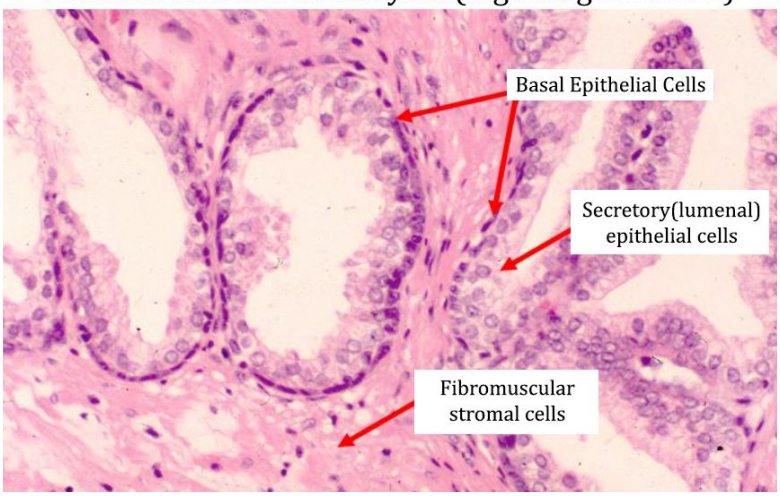
The prostate is divided into different zones:

1. **Central zone.**
2. **Transitional zone:** middle area that surrounds the urethra as it passes through the prostate. it's where **benign nodular hyperplasia** usually arise.
3. **Peripheral zone:** Where the majority of **prostate cancers** are found .



Microscopically:

Normal Prostate Parenchyma (high magnification)



- prostate is a *tubulo-alveolar*[2] *organ*.
- Lined by two layers of cells, *basal cells* & *columnar secretory cells* → important to differentiate benign cases from malignant ones.

Function: Secretes alkaline milky liquid that is added to sperms & seminal vesicle fluid.

Pathoma video of prostate gland:
https://drive.google.com/file/d/0B1EiB7WcXPNYUWs2SHZUa19qYTg/view?usp=sharing

[1] entirely lacking or free from
[2] gland having branching tubules which end in secretory alveoli

Benign Prostatic Hyperplasia (BPH)

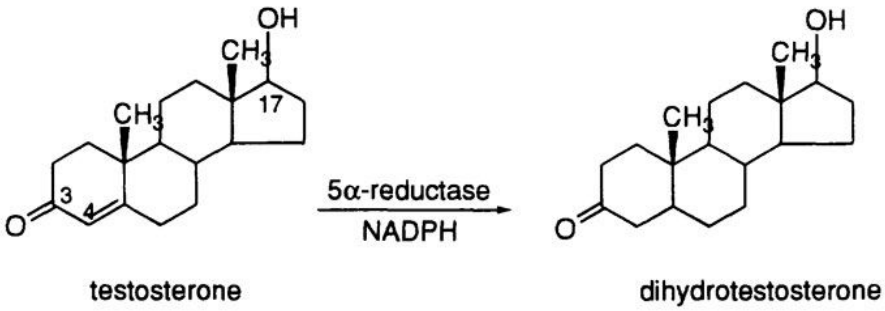
Also known as benign nodular hyperplasia. It is hyperplasia of *glands & stroma* of prostate results in large nodular enlargement.

- Occurs in the **periurethral region (transitional zone)** of the prostate.
- Nodular hyperplasia is not a premalignant lesion (no increase risk of cancer).

Incidence:

- Extremely common lesion in men over age 50.
- 20% in men over age 40, up to 70% by age 60, and 90% by age 80.

Pathogenesis:

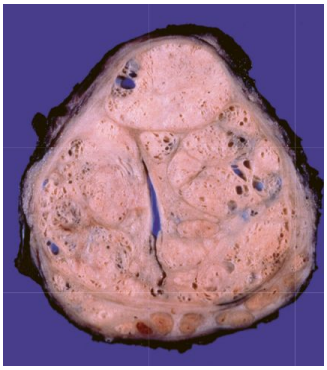
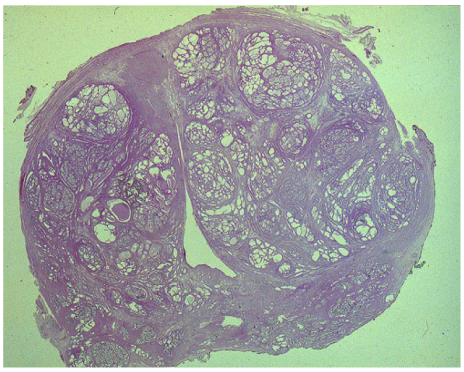
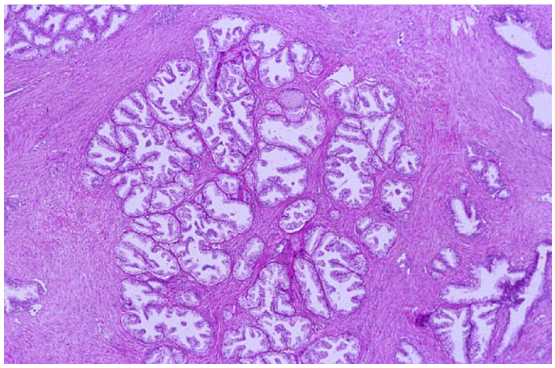


The essential cause of BPH is unknown. But there's some theory of it such as:

- Testosterone is converted to dihydrotestosterone (DHT) by **5-alpha reductase** enzymes.
- **Dihydrotestosterone (DHT) →** binds to androgen receptors in epithelial cells and stroma → increases the proliferation of stromal cells & inhibits epithelial cell death.
- So DTH play role in both prostatic hyperplasia (BPH) and adenocarcinoma.
- The pathogenesis is related to the action of *excessive androgen-dependent growth of stromal and glandular elements*.
- Although testosterone can bind to androgen receptors and stimulate growth, but DHT is 10 times more potent than testosterone → Drugs that act as inhibitors of 5-alpha reductase, therefore have an important role in the prevention and treatment of BPH and prostate cancer.
- Pre-pubertal castration[3] prevents BPH

[3] **Castration** (also known as gonadectomy) is any action, surgical, chemical, or otherwise, by which a biological male loses use of the testicles. Surgical **castration** is bilateral orchiectomy (excision of both testes), and chemical **castration** uses pharmaceutical drugs to inactivate the testes.

Morphology:

Nodular hyperplasia

Gross:

- Nodular hyperplasia occurs in inner and transitional zone of prostate.
- **The hallmark of BPH is nodularity due to glandular and fibro-muscular proliferation.**
- The affected prostate weighs between 60 and 100 grams contains many circumscribed nodules.
- The nodules may appear **solid** or contain **cystic spaces**.
- Cut-section shows nodules which vary in size, color and consistency depending on which element is proliferating more (glandular or fibro-muscular).
- It compress the wall of the urethra resulting in a slit-like orifice. → may cause cystitis.

Microscopic:

- Microscopically, the main feature of BPH is **nodularity.**

The nodules (hyperplastic nodules) can be:

1. Purely stromal nodules composed mainly of **fibromuscular element**.

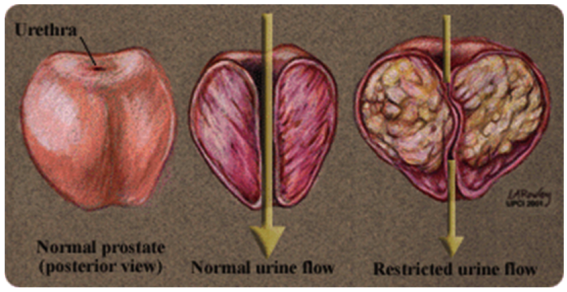
OR

2. **Fibroepithelial** which has both glandular and fibromuscular components. There is aggregation of small to large to cystically dilated glands, lined by two layers of epithelium surrounded by fibromuscular stroma.

- Needle biopsy **doesn't** sample the transitional zone where BPH begins and occurs, therefore the **diagnosis of BPH cannot be made on needle biopsy**. It may cause hemorrhage so we use per-rectal examination instead.

- The hyperplastic glands are lined by tall, columnar epithelial cells and peripheral layer of flattened basal cells→ is shown as two layers indicating benign prostate.

Clinical feature:



Urethra is located in the center of prostate, so since the hyperplasia occurs in the transitional zone around the urethra → once the nodules become large they compress the prostatic urethra → partial, or complete obstruction of the urethra leading to the following:

1. Retention of urine in the bladder (Impaired bladder emptying). Some patients present with acute urinary retention → sometimes it's severe to the point that the patient come to the ER to get a catheter.
2. Bladder wall smooth muscle hypertrophy → due to retention → may cause diverticula.
3. Infection → because of the inability to empty the bladder completely that leads to increase volume of residual urine and therefore infection.
4. Problems or difficulty in starting and stopping urine stream.
5. Dribbling[4].
6. Nocturia[5].
7. Increased urinary frequency.
8. Dysuria[6].
9. **PSA** is slightly elevated due extra gland in case of BPH. **Prostate-specific antigen (PSA)** is a protein produced by cells of the **prostate** gland. When there's hyperplasia of the gland → more cells → mora PSA.
10. Microscopic hematuria.

Complications of BPH (extra):

1. **Hydronephrosis** (dilatation of ureter & kidney). Due to BPH leading to obstruction of urinary bladder which may cause fluids back up to the kidney.
2. **UTI.**

Treatment:

- Mild cases of BPH may be treated with **α receptor blockers** and **5-α-reductase inhibitors.**
- Moderate to severe require **transurethral resection of the prostate** (TURP) → is a surgical procedure that involves ,trimming away excess prostate tissue that's blocking urine flow and increases the size of the channel that allows you to empty your bladder,

[4] dribbling is the phenomenon where urine remaining in the urethra after voiding the bladder slowly leaks out after urination.
[5] **Nocturia** is a condition in which you wake up during the night because you have to urinate.
[6] Painful or difficult urination.

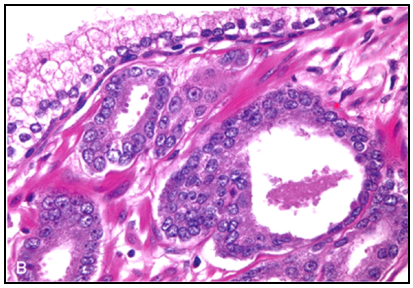
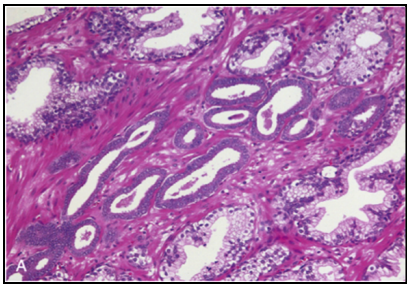
Prostatic Adenocarcinoma

It is the most common form of cancer in men. 2nd most common cause of cancer-related death. These tumors show a wide range of clinical behaviors. Androgen are believed to play a major role in the pathogenesis.

Incidence:

- Disease of men over age 50.
- More prevalent among African Americans. And less common in Asian
- **Etiology:** (Several risk factors) **Age**, **race**, **family history**, **hormone level (androgens)** & **environmental influences** such as high fat diet.

Morphology:


Gross:

- 70% arises in the peripheral zone of the posterior part of the gland.
- Tumor is firm and gritty and might be palpable on rectal exam. Because it's located peripheral zone.
- Spread by direct local invasion and through bloodstream and lymph.
- Local extension most commonly involves the periprostatic tissue, seminal vesicles and the base of the urinary bladder (leading to ureteral obstruction late in its course).

Microscopy:

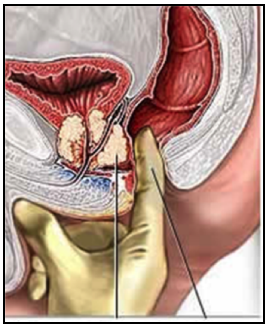
- Histologically, most lesions of adenocarcinomas produce well-defined gland patterns.
- The malignant glands are lined by a single layer (unlike BPH) of cuboidal or low columnar epithelium with large nuclei and one or more large , darks and prominent nucleoli.
- Nuclear pleomorphism is not marked.
- The outer basal cell layer (typical of benign glands) is absent.
- Commonly there is perineural invasion[7].

[7] Tumor invades the neurons

Metastasis:

- Metastases first spread via lymphatics: *initially* to the **obturator nodes** and *eventually* to the **para-aortic nodes**.
- Hematogenous extension occurs chiefly to the **bones**. The bony metastasis are typically **osteoblastic**. (means it will affect the osteoblast cells → increase of osteoblastic activity → raise of alkaline phosphatase levels in blood)

Clinical features:



Prostatic cancer is **asymptomatic** until the latest stages of it. It could be metastasized already when it's discovered **Why?**

- Microscopic cancers[8] are asymptomatic and are discovered incidentally[9].
- Most arise **in the peripheral zone**, away from urethra and therefore the urinary symptoms occur late.

- Sometimes patients present with back pain caused by vertebral metastases (most common place of metastasis)
- Careful digital rectal examination may detect some early cancers.
- **PSA** (Prostate Specific Antigen) levels are important in the diagnosis & management of prostate cancer. However, 20% - 40% of prostate confined cancers have low PSA.
- PSA is organ specific but not cancer specific because it could be increased in BPH and prostatitis.
- A transrectal needle biopsy is required to confirm the diagnosis.

Treatment:

- Surgery , radiotherapy and hormonal therapy.
- 90% of treated patients expected to live for 15 years (very good prognosis).
- Currently the most acceptable treatment for clinically localized cancer is radical surgery.

Locally advanced cancers	Advanced, metastatic carcinoma
Can be treated by: ● Radiotherapy ● hormonal therapy. Hormonal therapy (Anti-androgen therapy[10]) can induce remission.	Treated by androgen removal treatment, either by orchiectomy[11] or by hormonal anti-androgen therapy (estrogen).
The prognosis depends on the Gleason score and stage of tumor.	

[8] Very small cancers.

[9] يتم اكتشافه بالصدفة

[10] hormone suppression to reduce testosterone and DHT because prostate cancer is an androgen dependent

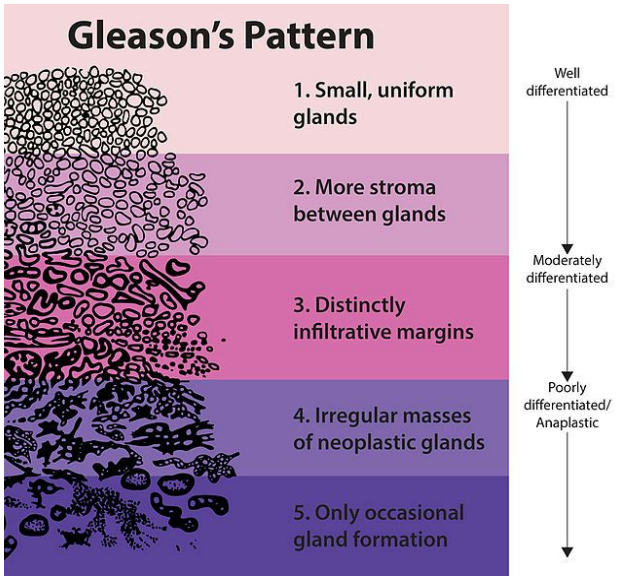
[11] Surgical removal of one or both testicles

Gleason Grading and Scoring

[Prostate Cancer 101: The Gleason Score Demystified]

Is a histological grading and scoring system for prostatic adenocarcinoma done on the microscopic level. "is based on architecture alone (and not nuclear atypia)"

- There are **five grades** (1 to 5) depending on the degree and pattern of differentiation as seen microscopically.
  - **grade 1= well-differentiated.**
  - **grade 5= very poorly differentiated.**
- A score (1- 5) is assigned for two distinct areas in the **biopsy** and then added to produce a final Gleason score (2-10).



Most common grade in the tumor **+** The second most common grade **=** score of the tumor

For example, if the Gleason score is written as 3+4=7, it means most of the tumor is grade 3 and less is grade 4 and they are added for a Gleason score of 7. The highest a Gleason score can be is 10.

- Very useful in predicting prognosis of a patient.
- Staging in prostate cancer depends on the TNM system. It is the most important indicator of prognosis.

TNM Classification of Malignant Tumours (**TNM**) is a cancer staging system that gives codes to describe the stage of a solid tumor.

- **T** describes the size of the original **tumor**.
- **N** describes nearby lymph **nodes** that are involved.
- **M** describes distant **metastasis**

Prostatic intraepithelial neoplasia (PIN).

- Defined by **neoplastic** growth of epithelial cells within preexisting benign **prostatic** acini or ducts.
- PIN is the precursor lesion for invasive carcinoma. It can be **low grade PIN** or **high grade PIN**. (*high grade PIN is like carcinoma in situ which is a precursor to prostate cancer*)
- PIN like carcinoma occurs in the **peripheral zone**.

Summary.

	Benign Prostatic Hyperplasia "BPH" (Benign nodular hyperplasia)	Prostatic Adenocarcinoma
Definition	Large nodular enlargement in the periurethral region of the prostate.(transitional zone)	70% arises in the peripheral zone of the posterior part of the gland(peripheral zone)
Epidemiology	- 20% in men over age 40. - Up to 70% by age 60. - 90% by age 80.	- Disease of men over age 50 - More prevalent among African Americans.
Pathogenesis	Related to the action of androgen, testosterone is converted to DHT by 5-α reductase enzymes. Dihydrotestesterone (DHT) is the ultimate mediator for prostatic growth. It increases the proliferation of stromal cells and inhibits epithelial cell death.	
Gross Morphology	- Nodular hyperplasia due to glandular and fibromuscular proliferation. - Slit-like orifice due to compression of the urethra.	Tumor is firm and gritty and is palpable on rectal exam.
Microscopy	**The nodules can be:** ➔ Purely stromal nodules composed mainly of fibromuscular element. ➔ Fibroepithelial with both glandular and fibromuscular component.	- Well-defined gland patterns. - The malignant glands are lined by a single layer of cuboidal or low columnar epithelium. - The outer basal cell layer typical of benign glands is absent. - Commonly there is perineural invasion.
Diagnosis	Cannot be made on needle biopsy	- Digital rectal examination - Prostate Specific Antigen (PSA) levels - Transrectal needle biopsy is required **Gleason Grading and Scoring is used**
Metastasis	-	- Lymphatics: initially to the obturator nodes and eventually to the para-aortic nodes - Hematogenous extension occurs chiefly to the bones (osteoblastic) .
Clinical Features	- Urine retention and bladder hypertrophy. - Infection - Increased urinary frequency - Nocturia and dysuria	Asymptomatic but Occasionally pts present with urinary symptoms or back pain caused by vertebral metastases.
Treatment	- Mild → α-blockers and 5-α-reductase inhibitors - Moderate to severe → transurethral resection of the prostate (TURP)	- Clinically localized cancer → radical surgery - Locally advanced cancers → radiotherapy and hormonal therapy. - Advanced, metastatic carcinoma → androgen removal treatment, either by orchiectomy or by hormonal anti-androgen therapy.

MCQ's.

1) Prostate problems are common in men in their 30s.

A. True
B. False

2) BPH may cause the bladder to...

A. Strengthen
B. Weaken

3) All men with BPH experience the same symptoms.

A. True
B. False

4) Prostate growth is stimulated by which of the following hormones?

A. Testosterone
B. Dihydrotestosterone
C. Thyroxine

5) Stimulation of which of the following receptors in the prostate results in a decrease in urethral lumen size?

A. Norepinephrine
B. Dopamine
C. Acetylcholine

6) A complication of benign prostatic hyperplasia includes

A. Urinary tract infection.
B. Deep venous thrombosis.
C. Disseminated intravascular coagulation.

7) a patient with an enlarged prostate, a peak urinary flow rate of 6 mL/s, and residual urine volume of 200 mL but no voiding complaints is described as having

A. Renal failure.
B. Prostate cancer.

8) A 62-year-old man presents with urinary urgency and frequency. Physical examination reveals a 1-cm, hard, right-sided prostate nodule. His serum prostate-specific antigen (PSA) level is 14 ng/mL. The best next step in managing this patient is to:

A. Repeat the PSA test in 3 months
B. Discuss potential treatment options with the patient
C. Obtain a transrectal ultrasound and, whether the results are abnormal or not, proceed with prostate needle biopsy
D. Begin hormone therapy with leuprolide
E. Begin treatment with terazosin and schedule a 3-month follow-up appointment

9. Which of the following has NOT been associated with prostate cancer risk?

A. Advanced age
B. African-American race
C. High-fat diet
D. An androgen-receptor germline polymorphism
E. Ionizing radiation

10. A 72-year-old man with a history of localized prostate cancer presents to his physician with pain in his ribs. He underwent a radical prostatectomy 4 years earlier but was subsequently lost to follow-up. A bone scan demonstrates diffuse skeletal metastases; the patient's serum PSA level is 97 ng/mL. The best next step in managing this patient is to:

A. Treat with strontium-89 to relieve the patient's pain
B. Perform a rib biopsy to rule out other malignancies
C. Perform an orchiectomy

11. Routine PSA testing in a 66-year-old otherwise healthy man reveals an increase from 3 to 7.7 ng/mL within 1 year. Biopsies demonstrate Gleason grade 3 + 3 adenocarcinoma in one of six needle cores. Treatment options for this patient include all of the following EXCEPT:

A. Radical retropubic prostatectomy
B. Radical perineal prostatectomy
C. Three-dimensional conformal radiotherapy
D. Brachytherapy
E. Laparoscopic pelvic lymphadenectomy

Answers: 1-B 2-A 3-B 4-B 5-A 6-A 7-A 8-C 9-E 10-C 11-E

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com
Twitter: @Pathology434
Ask us: www.ask.fm/Pathology434

GOOD LUCK !!

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