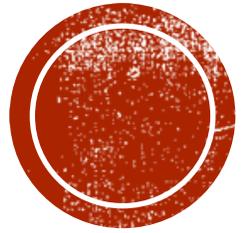




PATHOLOGY OF MALE REPRODUCTIVE SYSTEM

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PROSTATE



PROSTATITIS

- ❑ **Prostatitis** may be **acute or chronic**.
- ❑ **Acute** bacterial prostatitis is caused by the same organisms associated with other acute UTI, particularly **E. coli & other gram-negative rods**.
- ❑ Most patients with acute prostatitis have concomitant infection of the urethra & bladder; in which organisms may **reach** the prostate by **direct extension** from the urethra or bladder or, by **vascular channels** from more distant sites.
- ❑ **Chronic** prostatitis:
 - (1) May follow clinical episodes of acute prostatitis, or
 - (2) May develop insidiously, without previous episodes of acute infection.
- ❑ In **some cases**, it can be **chronic bacterial prostatitis**, in which there is an ↑number of WBCs in prostatic secretions together with bacteria (similar to those responsible for acute bacterial prostatitis) which can be isolated, however, **most cases** only have an ↑number of WBCs in prostatic secretions; but bacteriologic findings are negative.



□ Morphology:

- **Acute prostatitis** characterized by congestion, edema & acute **neutrophilic** inflammatory infiltrate; initially most conspicuous within the prostatic glands, but, as the infection progresses, the inflammatory infiltrate destroys glandular epithelium & extends into the surrounding stroma, resulting in the formation of **microabscesses**.
- **Chronic prostatitis** features are nonspecific & include lymphoid infiltrate, glandular injury, fibroblastic proliferation & frequently concomitant acute inflammatory changes.



- **Granulomatous prostatitis** is may be encountered with systemic inflammatory processes (e.g., TB, sarcoidosis, & fungal infections). It may also occur as a nonspecific reaction to inspissated prostatic secretions & after transurethral resection (TUR) of prostatic tissue.

□ **Clinical Features include:**

- Dysuria, urinary frequency, lower back pain, & poorly localized suprapubic or pelvic pain.
- On Per-Rectal (PR) examination, the prostate may be enlarged & tender, particularly in **acute** prostatitis, in which local symptoms are often accompanied by fever & leukocytosis.
- **Complications:** Chronic prostatitis, even if asymptomatic, may serve as a reservoir for organisms capable of causing UTI. Chronic bacterial prostatitis, therefore, is one of the most important causes of recurrent UTI in men.



Nodular Hyperplasia (NH) of the Prostate (P)

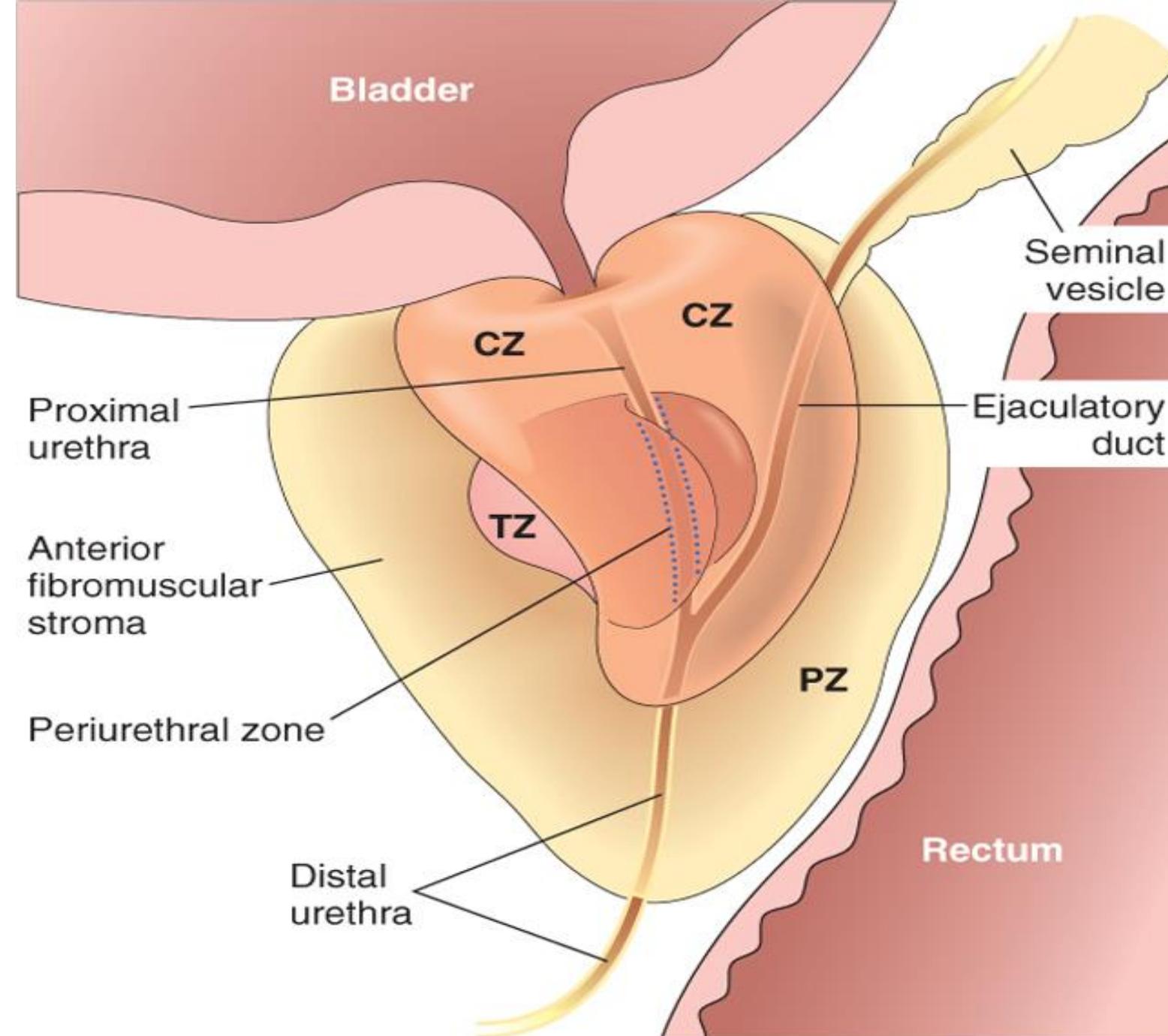
- ❖ Normal Prostate consists of glandular & stromal elements surrounding the urethra.
- ❖ It can be divided into periurethral, central, transitional, & peripheral, zones
- ❖ Most (70%-80%) **carcinomas** arise in the **peripheral** zones;
- ❖ Most **NH** lesions arise in the **central & inner transitional** zones of the Prostate.
- ❖ NH is an extremely common abnormality of the P, frequency rises progressively with age reaching 90% by the eighth decade.
- ❖ NH is characterized by proliferation of **both** stromal & epithelial elements, with resultant enlargement of the P gland which in some cases cause UT obstruction.



Adult prostate

★Z = zone.

CZ: central: NH,
TZ: transitional,
PZ: peripheral
from which most
carcinomas arise.



□ Pathogenesis:

Although the cause of NH remains incompletely understood, it is clear that **androgens** have a central role in its development, as:

(1) NH does not occur in males castrated before the onset of puberty or in men with genetic diseases that block androgen activity.

(2) **Dihydrotestosterone (DHT)**, an androgen derived from testosterone through the action of **5 α -reductase**, & its metabolite, 3 α -androstane-1,2-diol, seems to be major hormonal stimuli for stromal & glandular proliferation in men with NH. DHT binds to nuclear androgen receptors stimulating the synthesis of DNA, RNA, GFs, & other cytoplasmic proteins, leading to hyperplasia.

➤ This forms the basis for the current use of **5 α -reductase inhibitors** in the treatment of symptomatic NH.



❑ Morphology of NH:

- Grossly, NH arises most commonly in the inner, periurethral glands of the P, particularly from those that lie above the verumontanum.
- The P is enlarged from its normal 20 gm to 300 gm or more in severe cases.
- Prostate C/S shows many well-circumscribed nodules that bulge from the cut surface , most pronounced in the **inner (central & transitional)** region.
- Nodules may be solid or may contain cystic spaces (due to the dilated glandular elements seen histologically).



- The urethra is usually compressed by the hyperplastic nodules, often to a slit like orifice.
- In some cases, the NH elements lying just under the epithelium of the proximal prostatic urethra may project into the bladder lumen as a pedunculated mass, resulting in a ball-valve type of urethral obstruction.

□ **Microscopically:**

- The hyperplastic nodules composed of:
 - **hyperplastic glands** lined by characteristic dual (double) cell population, a central tall columnar epithelial cells; crowding of which results in the formation of papillary projections & a peripheral layer of flattened basal cells.
 - The glandular lumina often contain inspissated, proteinaceous secretory material, termed **corpora amylose**.
 - The hyperplastic glands are surrounded by proliferating **stromal** elements.
 - Some nodules composed predominantly of spindle-shaped stromal cells & connective tissue.

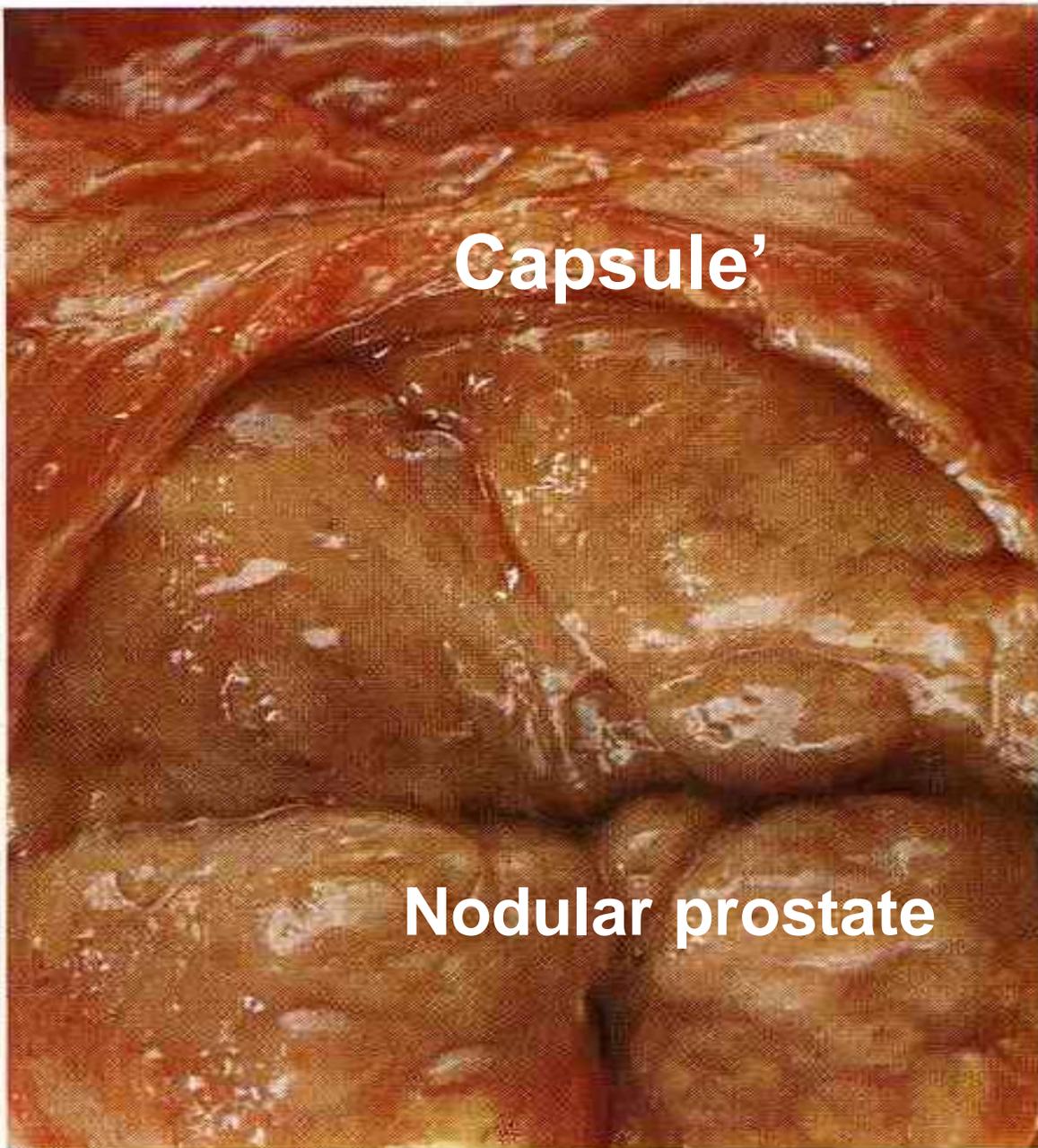




Nodular hyperplasia (NH) of the prostate.

★ Well-defined nodules, with cystic spaces, compress the urethra (arrowheads) into a slitlike lumen.





Adenomatous hyperplasia of the Prostate

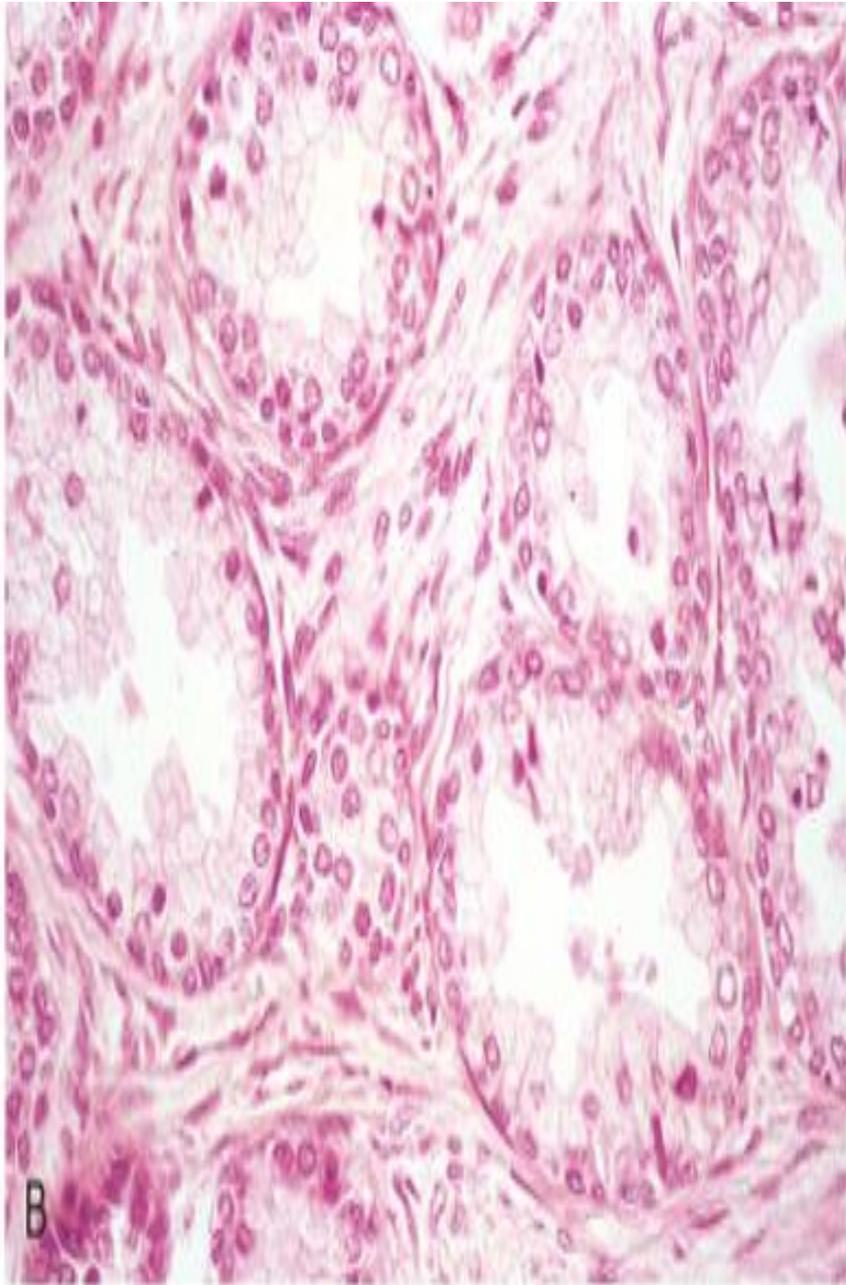
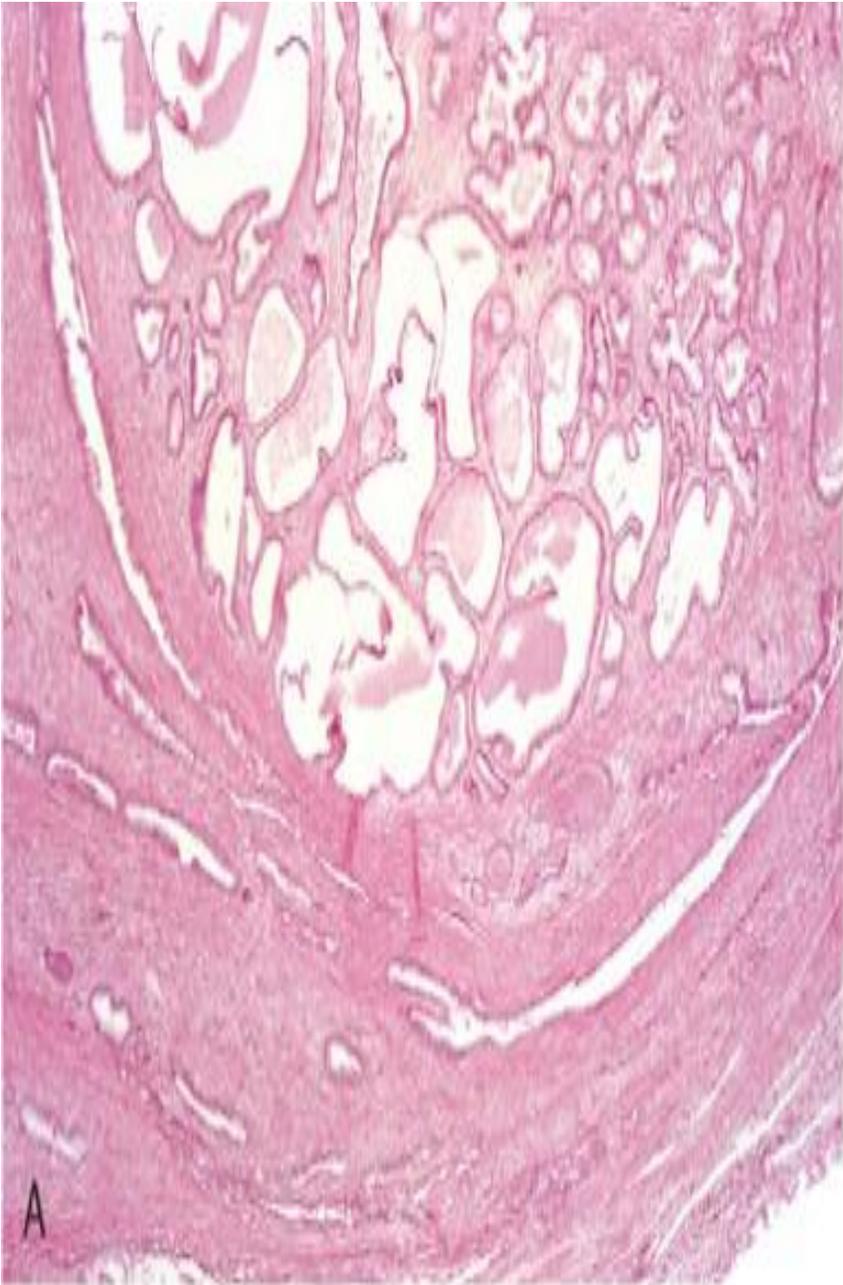
C/S of both lateral lobes of a very nodular prostate.

- ★ The creamy-white nodules vary in size & are separated by delicate greyish-white septa.
- ★ The spongy hyperplastic nodules have compressed the surrounding gland into a 'capsule' (top).



- Clinical manifestations of P NH occur in **only about 10%** of men with the disease.
- As NH preferentially involves the inner portions of the P, NH most common manifestations are those of **lower UT obstruction** including: difficulty in starting the stream of urine (hesitancy) & intermittent interruption of the urinary stream while voiding .
- Some men may develop complete urinary obstruction, with resultant painful distention of the bladder, if neglected, bilateral hydronephrosis & RF may develop.
- Urinary urgency, frequency, & nocturia, all indicative of bladder irritation.
- The combination of chronic obstruction and residual urine in the bladder increase the risk of UTI.



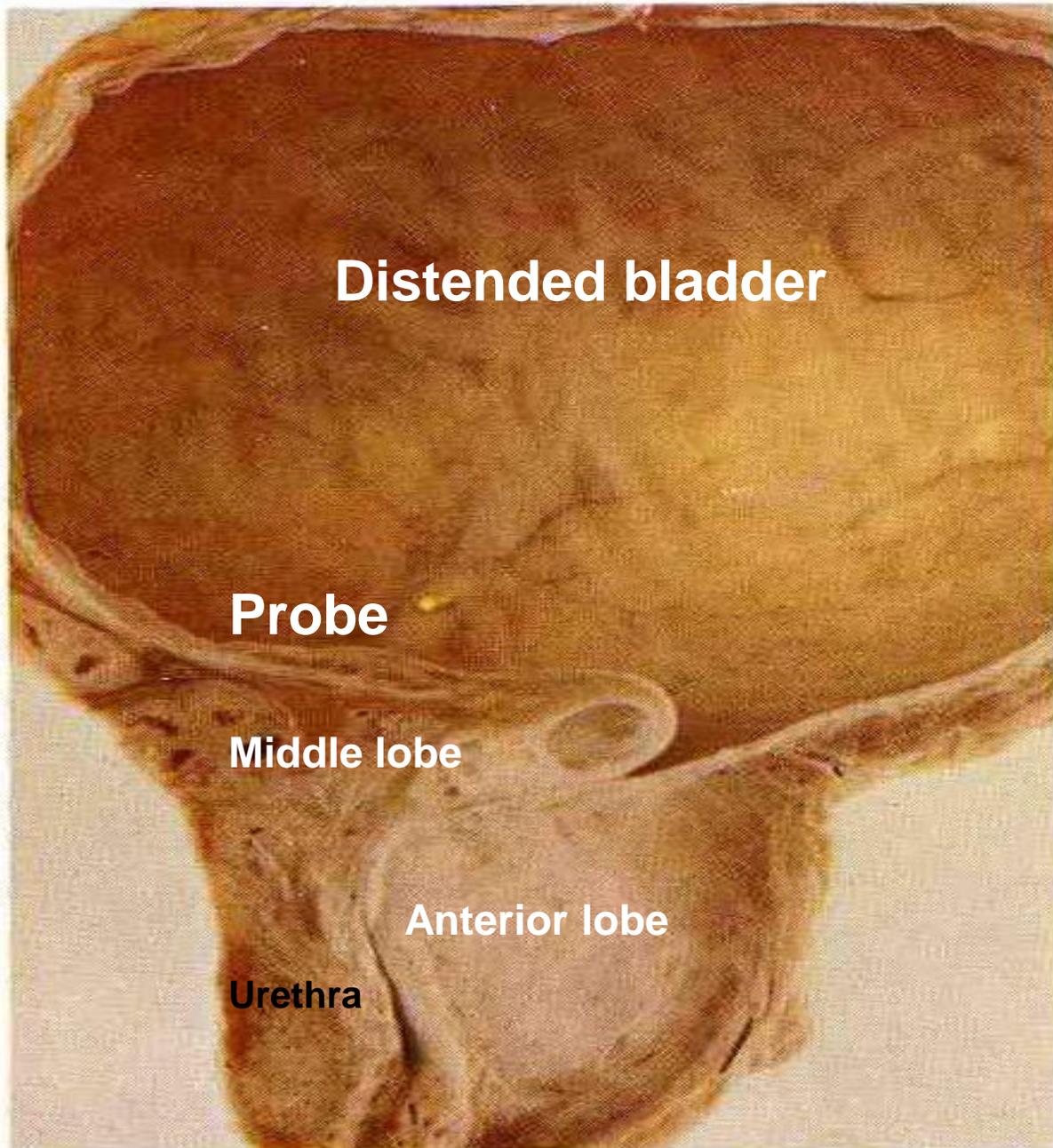


Nodular prostatic hyperplasia.

A: LP showing a well-demarcated nodule at top, populated by hyperplastic glands (in other nodules, stromal cell proliferation is more prominent than glandular one).

B: HP of the hyperplastic glands, with characteristic dual (**double**) cell population: inner columnar secretory & outer flattened basal cell layers.





Adenomatous hyperplasia of Prostate.

Sagittal section showing:

- ★ Uniform enlargement of the anterior lobe causes compression & elongation of the prostatic urethra.
- ★ Prostatic middle lobe enlargement result in elevation of the urinary outlet.
- ★ The bladder is distended, stretched causing incompetence of the uretric orifice.



Prostatic carcinoma (Pca)

- P ca is the **most common** visceral cancer in males (in the West), & ranks 2nd (after ca lung) as the most common cause of cancer-related deaths in men older than 50 y.
- P ca is a disease of older males, with a peak incidence between the ages of 65 & 75 years.
- Latent (**Hidden**) P ca are even more common than the clinically apparent P ca, with an overall frequency of more than 50% in men older than 80 years of age.



- Although the cause of Prost ca remains **unknown**, clinical & experimental observations suggest that hormones, genes, & environment all have a role in its pathogenesis.
- Hormones: the **androgens** contribution to the development of P ca is suggested by:
 - (1) Prost ca does not develop in males castrated before puberty.
 - (2) The fact that the growth of many Prost ca can be inhibited by orchiectomy or by the administration of estrogens such as diethylstilbestrol.



- ❑ **Hereditary:** there is ↑ risk of P ca among first-degree relatives of patients with P ca.
- ❑ **Racial:** Symptomatic Prost ca more common & occurs at an earlier age in American blacks than in whites, Asian and others.
- ❖ Whether such racial differences occur as a consequence of genetic influences, environmental factors, or some combination of the two remains unknown.
- ❑ **Genes:** Much effort is focused on finding Prost ca genes, but no definitive data are available. Overexpression of two ETS family transcription factors (which are also involved in Ewing sarcoma) were implicate in the pathogenesis of Prost ca.



- ❖ Interestingly, racial variations in the number of **CAG repeats** in the androgen receptor gene seem to be linked to the higher incidence of Pca in African Americans. Perhaps these polymorphisms influence the action of androgens on prostatic epithelium.

- Several inherited gene changes (mutations) seem to raise prostate cancer risk, but they probably account for only a small percentage of cases overall. For example:
 - Inherited mutations of the BRCA1 or BRCA2 genes, which are linked to an increased risk of breast and ovarian cancers in some families, can also increase prostate cancer risk in men (especially mutations in **BRCA2**).

 - Men with **Lynch syndrome** (also known as hereditary non-polyposis colorectal cancer, or HNPCC), a condition caused by inherited gene changes, have an increased risk for a number of cancers, including prostate cancer.



- ❑ **Environmental influences** is suggested by the
 - ❖ (1) ↑ frequency of Pca in certain industrial settings &
 - ❖ (2) significant geographic differences in the incidence of the Pca.
 - ❖ Males is immigrating from low-risk to high-risk areas maintain a lower risk of P ca; the risk is intermediate in subsequent generations, in keeping with an environmental influence on Pca development.

- ❖ Among environmental influences, a diet high in **animal fat** has been suggested as a risk factor.



- ❖ Many prostate cancers are detected on the basis of elevated plasmatic levels of prostate-specific antigen (**PSA** > 4 ng/mL), a glycoprotein normally expressed by prostate tissue.
- ❖ However, because men without cancer have also been found with elevated PSA, a **tissue biopsy** is the standard of care to confirm cancer's presence.

- ❑ GROSSLY, 70% to 80% P ca arise in the prostate **peripheral zone** & hence may be palpable as irregular hard nodules by PR examination, & because of this peripheral location, **early Pca is less likely** to cause urethral obstruction than is NH.
- ❑ Early Prost ca typically appears as hard, ill-defined subcapsular masses, C/S appear firm, gray-white to yellow lesions that infiltrate the adjacent gland .



- ❑ Locally advanced ca often infiltrate the (1) periurethral zones of the prostate, (2) seminal vesicles & (3) may invade bladder wall.
- ❑ **Denonvilliers fascia**, the connective tissue layer separating the lower genitourinary structures from the rectum, usually prevents growth of the P ca **posteriorly** resulting in the infrequent Prost ca invasion of the rectum.
- ❑ Metastases to regional pelvic LNs may occur early.
- ❖ **Microscopically**: most Prost ca are adenocarcinomas exhibiting variable degrees of differentiation.
- ❑ The well differentiated Prost ca composed of small glands that infiltrate the adjacent stroma in an irregular, haphazard fashion.

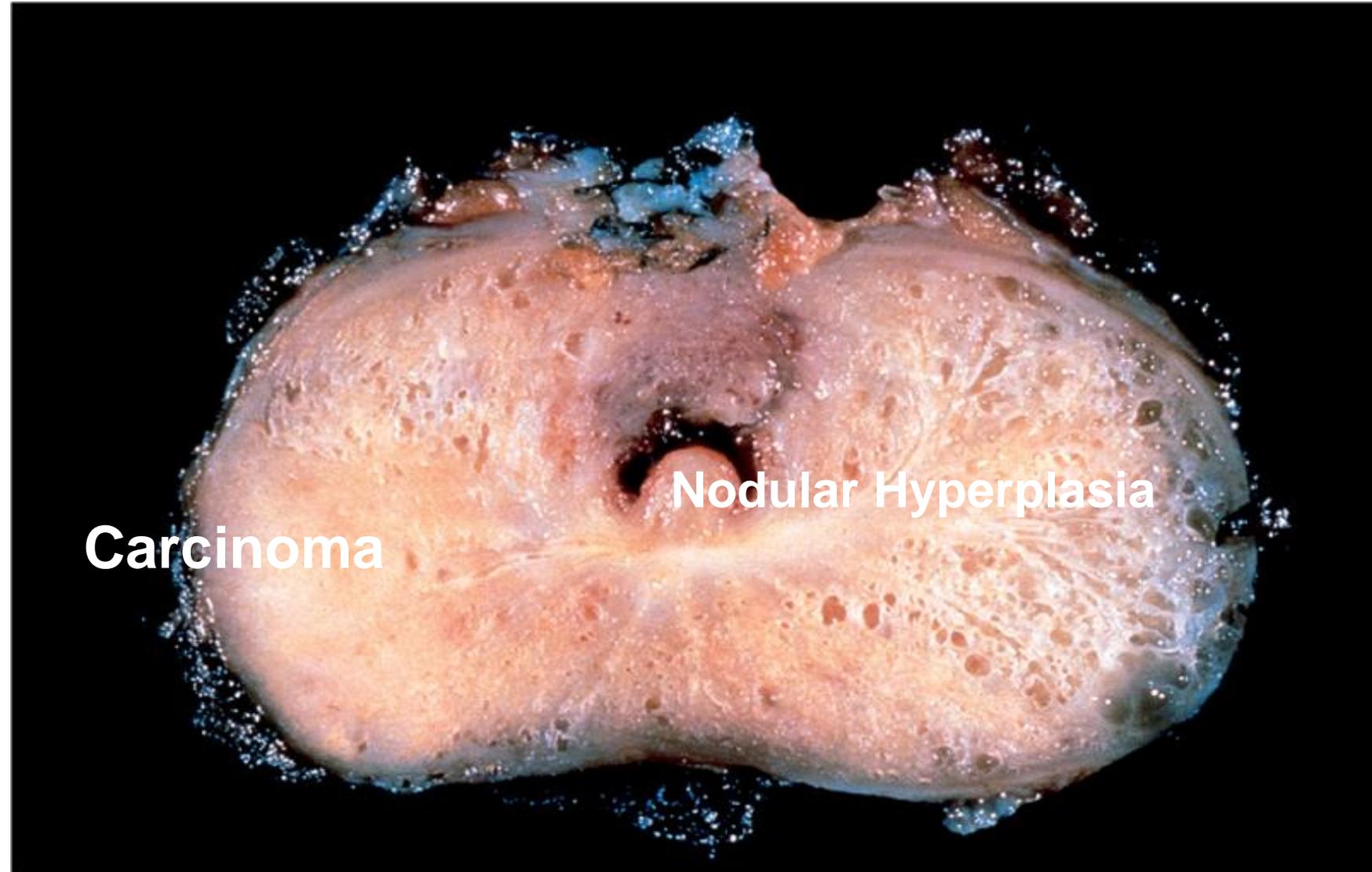


- ❖ In contrast to normal & hyperplastic prostate:
 - ❑ (1) Due to **scant stroma**, the glands in Prost ca lie back to back & appear to dissect sharply through the stroma,
 - ❑ (2) in Prost ca , the glands are lined by a single layer of cuboidal cells with **absence of the basal cell layer** seen in normal or NH glands
 - ❑ (3) cell nuclei show conspicuous **nucleoli**.
 - ❑ With ↑degrees of anaplasia, irregular, ragged glandular structures, papillary or cribriform epithelium & in extreme cases, sheets of poorly differentiated cells are present.



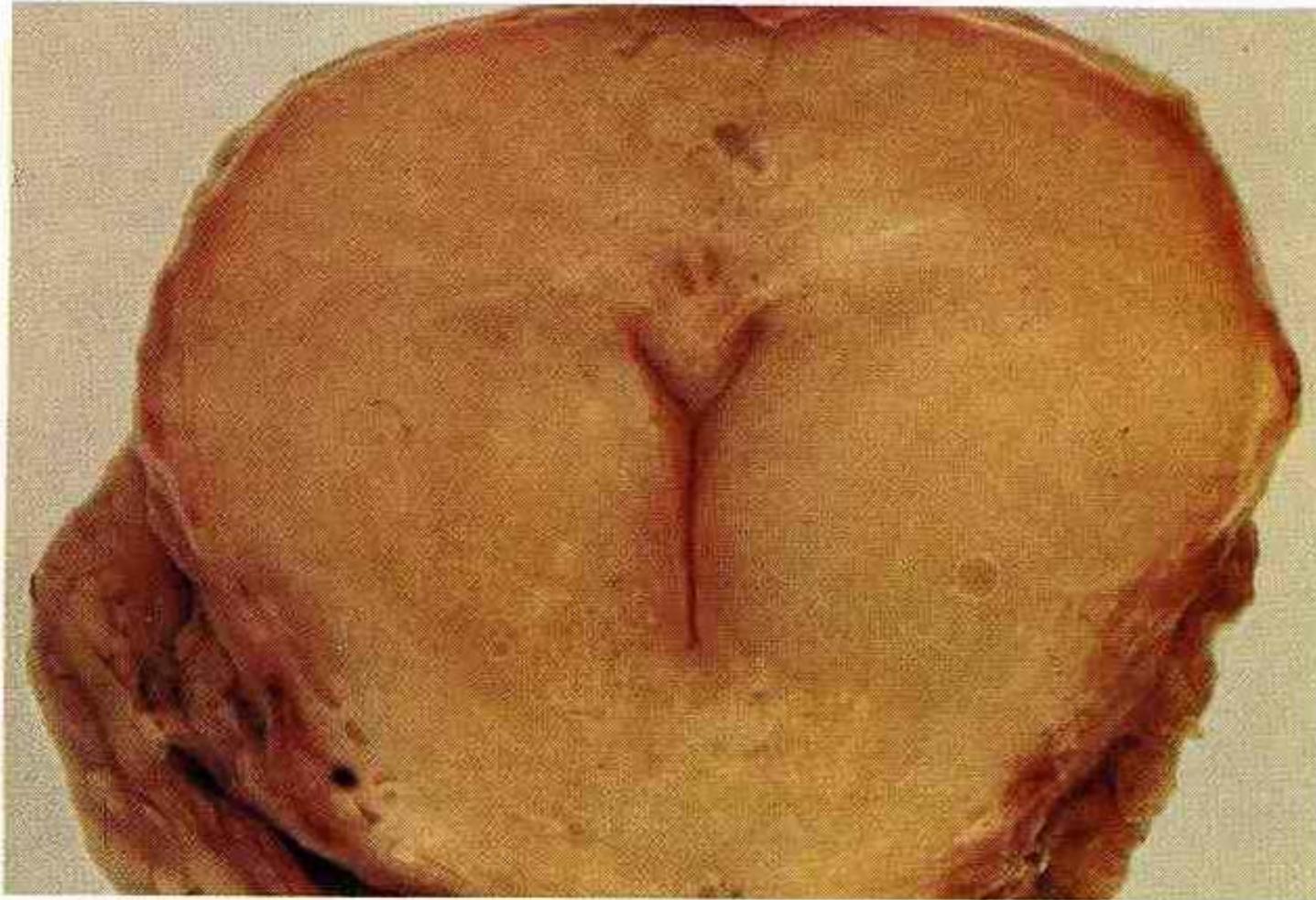
Prostatic adenocarcinoma.

The carcinomatous tissue is seen in the lower left as...Subcapsular solid whiter cancer in contrast to the Spongy benign peripheral zone on the other side



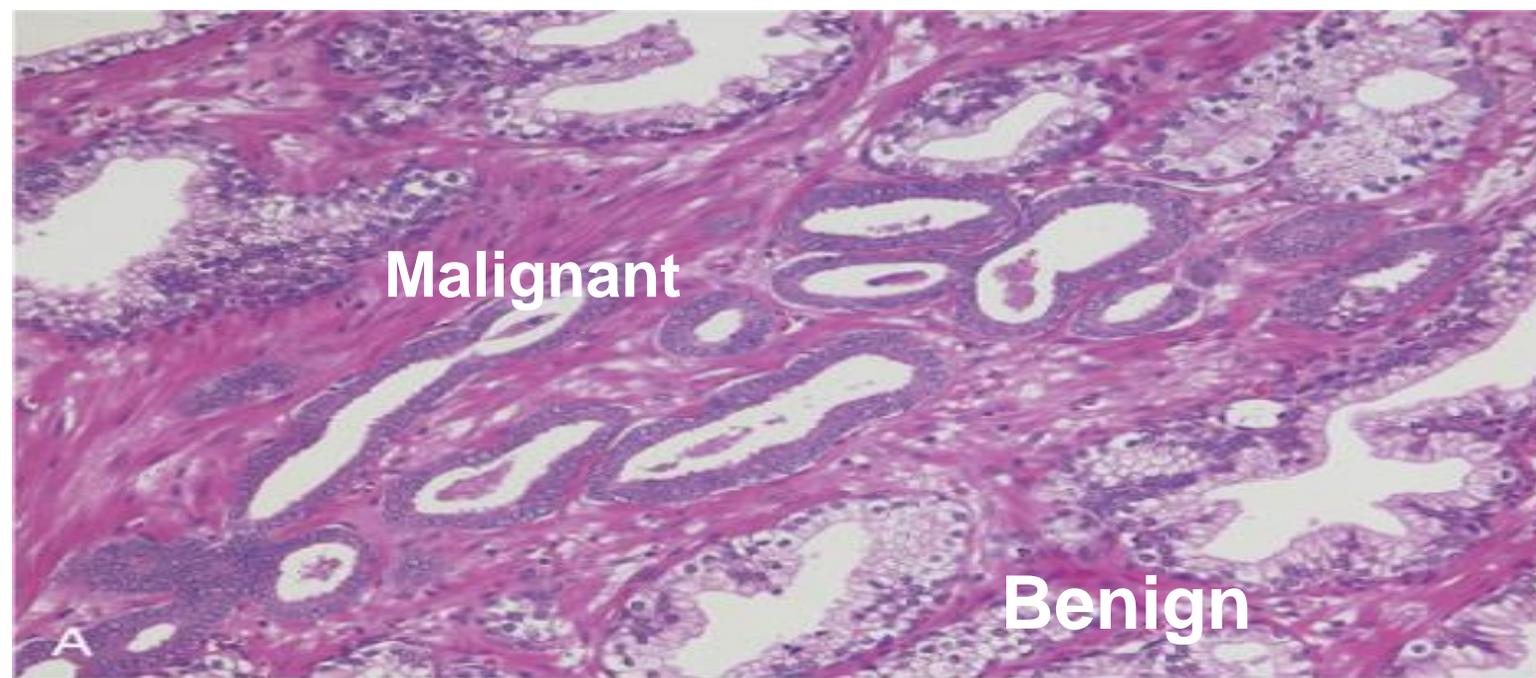
Adenocarcinoma: Diffusely enlarged malignant prostate.

Note: (1) absence of nodularity, & (2) yellow-orange color, with yellowish areas of necrosis. Remember: Prostatic carcinoma is hard in consistency on P/R exam.

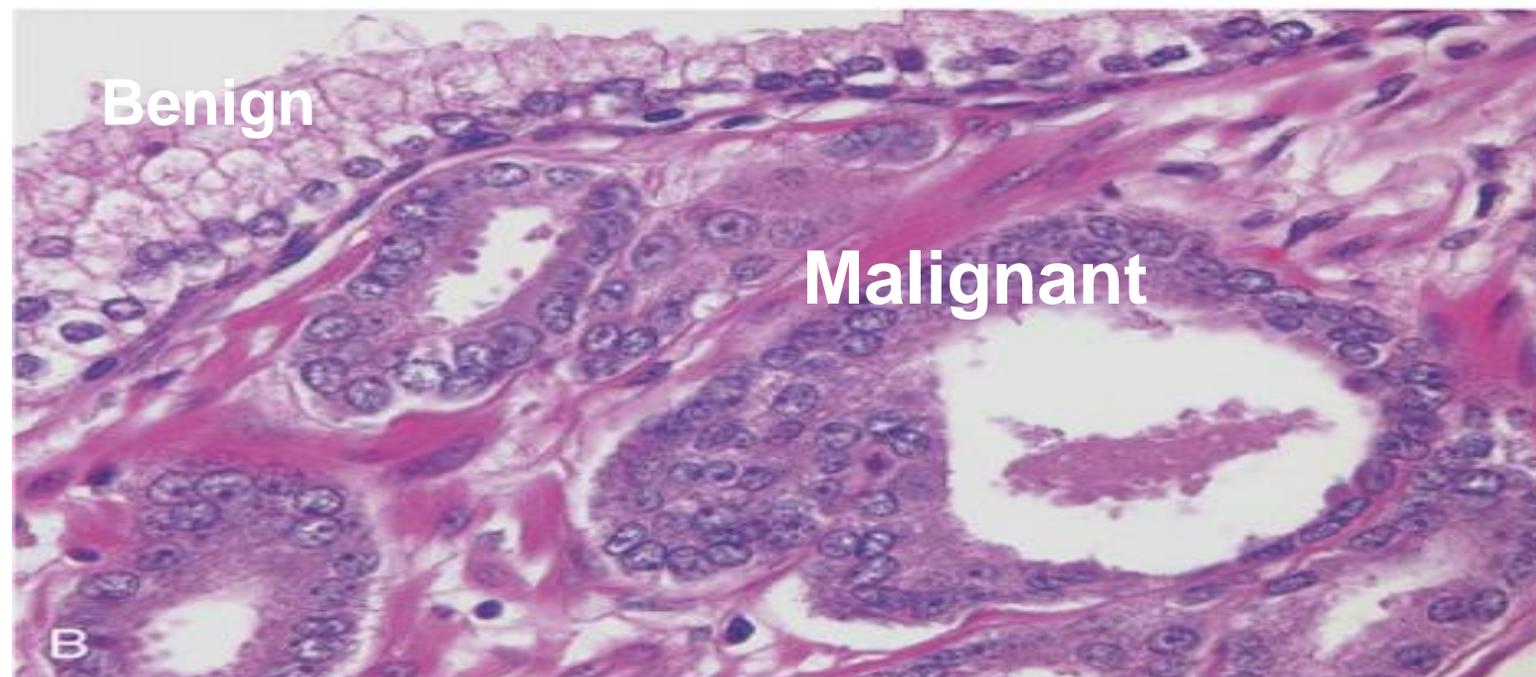


11.10 Adenocarcinoma: prostate





A: LP view of a small focus of prostatic adenocarcinoma, showing small glands crowded in between larger benign glands.



B: HP view shows several malignant glands with enlarged nuclei, prominent **nucleoli**, & dark cytoplasm, as compared with larger benign glands (top).



PIN (Prostatic Intraepithelial Neoplasia)

- ❑ Because of its frequent coexistence with infiltrating Pca, PIN has been suggested as a **probable precursor** to P ca.
- ❑ PIN has been subdivided into **high-& low-grade** patterns, depending on the degree of atypia.
- ❑ Importantly, high-grade PIN shares molecular changes with invasive Pca, supporting the argument that PIN is an intermediate between normal & frankly malignant P tissue.
- ❑ The commonly used method for P ca histologic grading is the **Gleason system** (1 to 5 degrees), based on the degree of glandular architecture & differentiation + nuclear anaplasia + mitotic activity.



❑ Despite the potential difficulties associated with incomplete sampling in biopsy material & the subjectivity inherent in histologic evaluation; the Gleason grade has proved to correlate reasonably well with both the anatomic stage of Prost ca & the prognosis.

❑ **Clinically:** Prost ca is often:

(1) silent ,particularly during their early stages.

- 10% of localized Prost ca are discovered unexpectedly, during histologic examination of P tissue removed for NH, while in autopsy studies, the incidence approaches 30% in men between 30 and 40y.



❑ As most Prost ca begin in the peripheral regions of the prostate, they may be discovered during routine PR exam.

(2) Extensive disease may produce "prostatism", i.e., local discomfort & evidence of **lower UT obstruction**, & with hard, fixed prostate on PR examination.

(3) Regrettably, an uncommon mode of presentation is evidence of **metastases**.

❑ Bone metastases, particularly to the axial skeleton, are common & may cause either osteolytic or, more commonly, **osteoblastic** (presence of which in an older male is strongly suggestive of advanced P ca) lesions.



- ❑ The pathologic distinction between high-grade prostate adenocarcinoma (PAC) involving the urinary bladder and high-grade urothelial carcinoma (UC) infiltrating the prostate can be difficult. However, making this distinction is clinically important because of the different treatment modalities for these two entities.
- ❑ Prostatic and urothelial markers, including PSA, NKX3.1, p63, thrombomodulin, and **GATA3** are very useful for differentiating PAC from **UC**.
- ❑ The optimal combination of prostatic and urothelial markers could improve the ability to differentiate PAC from UC pathologically.



- ❑ Prostate-specific antigen (**PSA**) and prostate acid phosphatase (**PAP**) have been known to assist in verifying the prostatic lineage in cases of **metastatic** carcinoma of unknown origin . However, in poorly differentiated carcinomas, the sensitivities of PSA and PAP decrease.
- ❑ PSA is a proteolytic enzyme produced by both normal & neoplastic prostatic epithelium. Assay of serum levels of prostate-specific antigen(PSA) has gained widespread use in the diagnosis of early P ca.
- ❑ Traditionally, a serum PSA level of **4.0** ng/L has been used as the upper normal limit.
- ❑ Cancer cells produce more PSA (but NH, & prostatitis may also cause an increase in serum levels of PSA).
- ❑ Moreover, in a **minority** of cases of Prost ca, especially those confined to the prostate, serum PSA is **not** elevated.



- ❑ Because of these problems with both specificity & sensitivity, PSA is of limited value when used as an isolated screening test for cancer of the prostate.
- ❑ PSA diagnostic value is enhanced considerably, however, when it is used in conjunction with other procedures, such as (1) PR examination, (2) transrectal sonography, & (3) needle biopsy.
- ❑ In contrast to its limitations as a diagnostic screening test, serum PSA concentration is of great value in monitoring patients after treatment for P ca, with rising levels after ablative therapy indicative of recurrence and/or the development of metastases



Table 18-3 TNM Staging of Prostatic Adenocarcinoma:

T1-Clinically Inapparent Lesion By Palpation/Imaging Studies.

T1a -Involvement of $\leq 5\%$ of resected tissue

T1b -Involvement of $>5\%$ of resected tissue

T1c -Ca present on needle biopsy(following elevated PSA)

T2-Palpable Or Visible Cancer Confined To Prostate

T2a -Involvement of $\leq 50\%$ of one lobe

T2b -Involvement of $>50\%$ of one lobe, but unilateral

T2c -Involvement of **both** lobes

T3-Local Extraprostatic Extension

T3a-Extracapsular extension

T3b-**Seminal vesical invasion**

T4-Invasion of Contiguous Organs And/Or Supporting Structures Including Bladder Neck, Rectum, External Sphincter, Levator Muscles, Or Pelvic Floor



Status of Regional Lymph Nodes (N)

N0 -No Regional LN Metastases

N1 -Metastasis In Regional LN

Distant Metastases (M)

M0 -No Distant Metastases

M1 -Distant metastases present

- ❑ Anatomic staging of **Pca** (by clinical examination, surgical exploration, radiographic imaging techniques) &, in some systems, & the histologic **grade** of the T & levels of T markers has an important role in the evaluation & treatment of Pca & correlate well with prognosis.



- ❖ Prostatic ca is treated with various combinations of **surgery, radiation therapy, & hormonal** manipulations.
 - ❖ Localized disease is usually treated with surgery, external-beam, or internal radioactive seeds radiation therapy.
 - ❖ Hormonal therapy has a central role in the treatment of **advanced** ca. Specifically, most Pca are androgen sensitive & are inhibited to some degree by androgen ablation, & therefore surgical or pharmacologic **castration, estrogens,** & androgen receptor-blocking agents have all been used to control the growth of disseminated Prost ca.
- Prognosis: 90% of patients with stage T1 or T2 lesions survive 10 years or longer. The outlook for patients with disseminated disease remains poor.



THANK YOU

