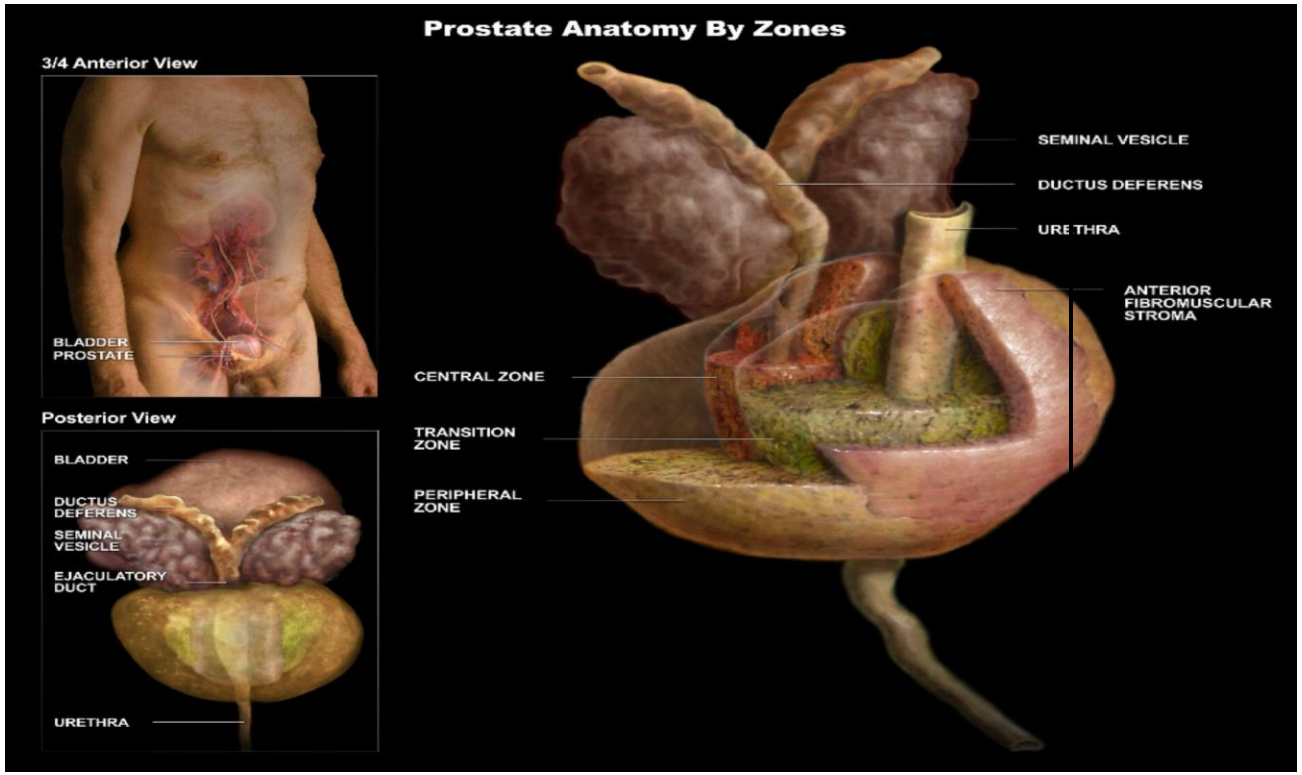
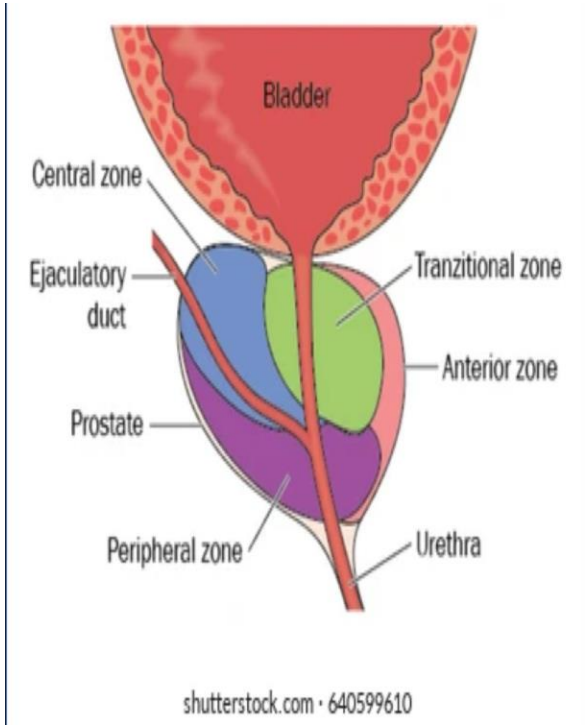

Prostate Anatomy By Zones
3/4 Anterior View
BLADDER
PROSTATE
Posterior View
BLADDER
DUCTUS DEFERENS
SEMINAL VESICLE
EJACULATORY DUCT
URETHRA
SEMINAL VESICLE
DUCTUS DEFERENS
URETHRA
ANTERIOR FIBROMUSCULAR STROMA
CENTRAL ZONE
TRANSITION ZONE
PERIPHERAL ZONE


Bladder
Central zone
Ejaculatory duct
Tranzitional zone
Anterior zone
Prostate
Peripheral zone
Urethra
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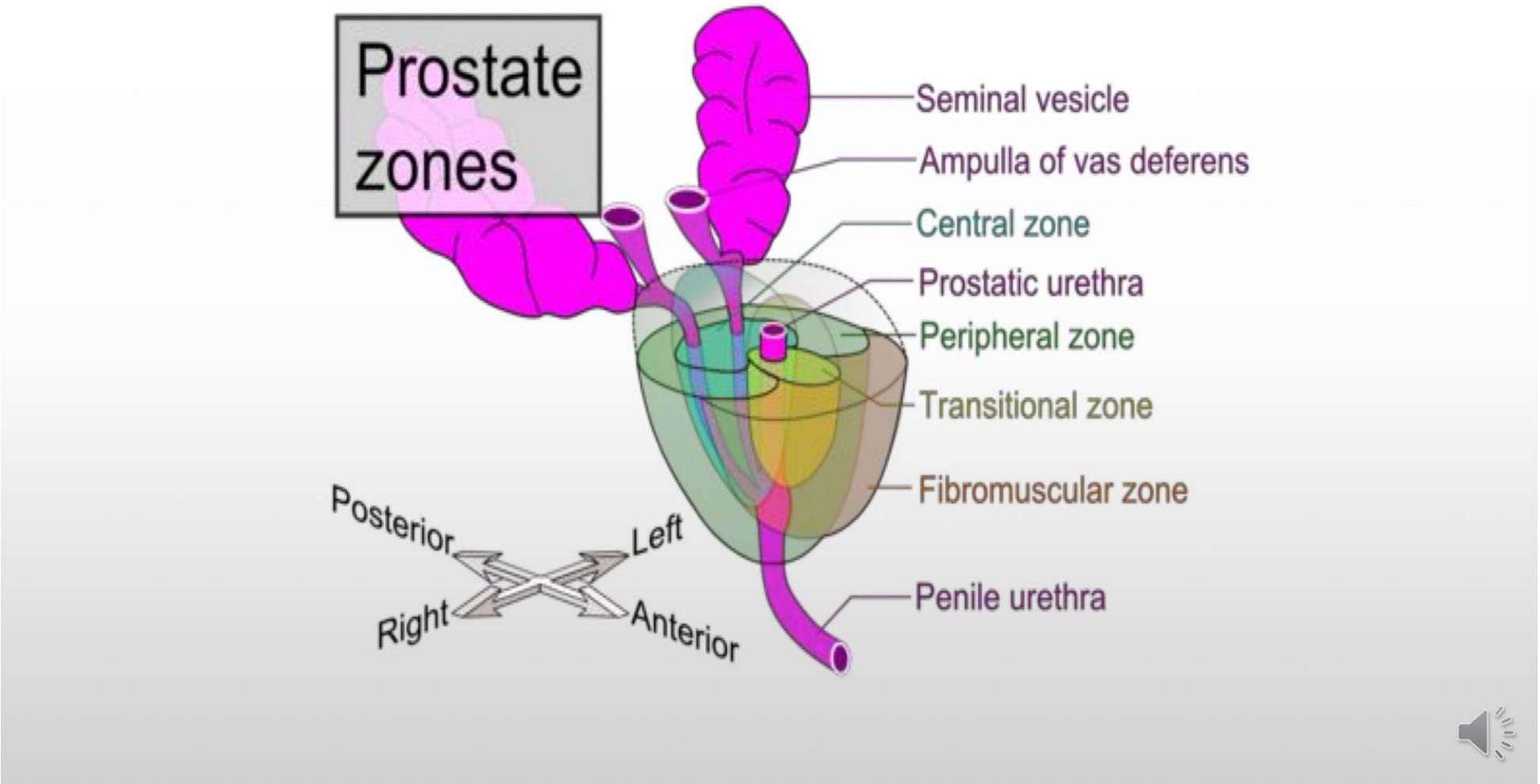
PROSTATE


Prostate zones
Seminal vesicle
Ampulla of vas deferens
Central zone
Prostatic urethra
Peripheral zone
Transitional zone
Fibromuscular zone
Penile urethra
Posterior
Left
Right
Anterior

PROST A TE

- **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 fromthe urethra or bladder or, by vascular channels from more distant sites.
- **Chronic prostatitis**.
- (1)may follow clinical episodes of acute prostatitis,
- (2) may develop insidiously, without previous episodes of acute infection.
- In some cases it is (1) chronic bacterial prostatitis, in which there is an increasenumber ofWBCs in prostatic secretions together with bacteria (similar to thoseresponsible for acute bacterial prostatitis) which can be isolated, however…
- (2) most cases are chronic abacterial prostatitis, with only an increase number ofWBCs in prostatic secretions; but bacteriologic findings are negative.

MORPHOLOGY OF CHRONIC PROSTATITIS.

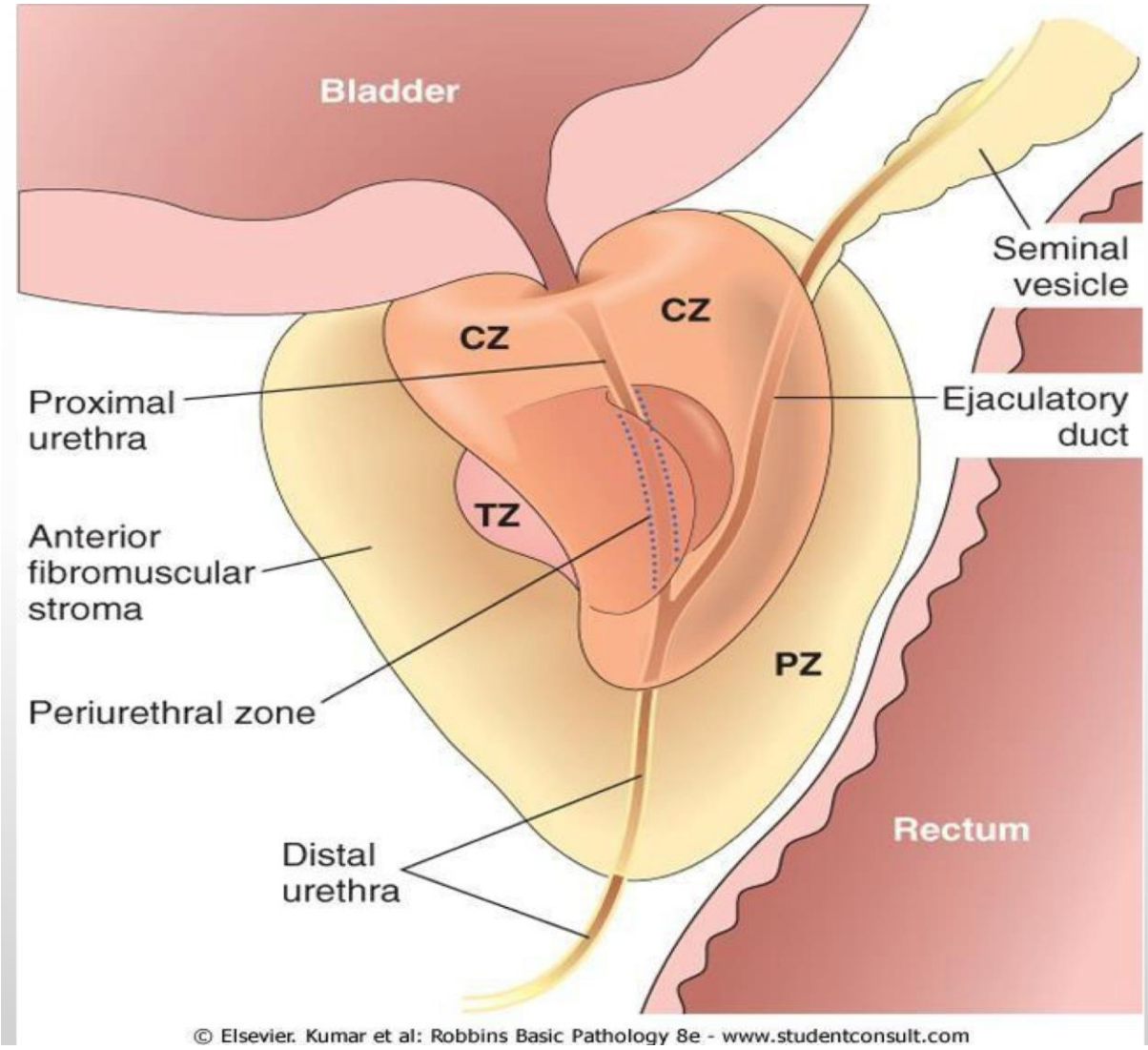
- **Histopathology :Acute prostatitis** characterized by congestion, edema &acute neutrophilic inflammatory infiltrate; initially most conspicuous within the prostatic glands, but, as the infection progresses, the inflammatory infiltrate destroys glandular epithelium & extends into the surrounding stroma, resulting in the formation of **microabscesses**.
- Grossly visible abscesses are uncommon but can develop with extensive tissue destruction, e.g. in DM.
- **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 transurethralresection (TUR) of prostatic tissue.

CLINICAL FEATURES OF CHRONIC PROSRATITIS

- •The clinical manifestations of prostatitis 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 is characterized by proliferation of both stromal & epithelial elements, with resultant enlargement of the P gland which in some Cases UT obstruction



Adult prostate

Z = zone.

CZ: central: NH,

TZ: transitional,

PZ: peripheral from which most carcinomas arise.

PATHOGENESIS OF NODULAR HYPERPLASIA (NH) OF THE PROSTATE (P)

- ▪ 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 5α-reductase, & its metabolite, 3α-androstanediol, 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 5α-reductase inhibitors in the treatment of symptomatic NH

MORPHOLOGY OF NH

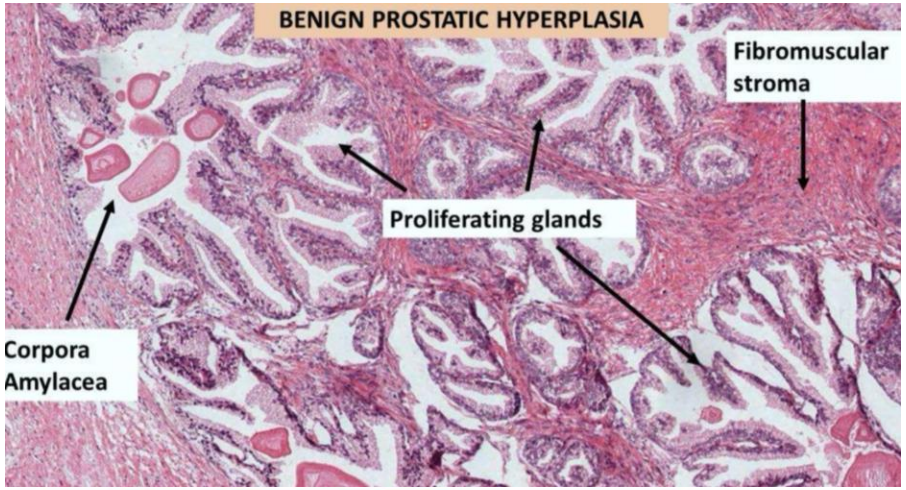
- GROSSLY , NH arises most commonly in the inner, periurethral glands of the P, particularly from those that lie above the verumontanum.
- The P is enlarged from its normal 20 gm to 300 gm or more in severe cases.
- Prostate C/S shows many well-circumscribed nodules that bulge from the cut surface , 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 slitlike orifice.

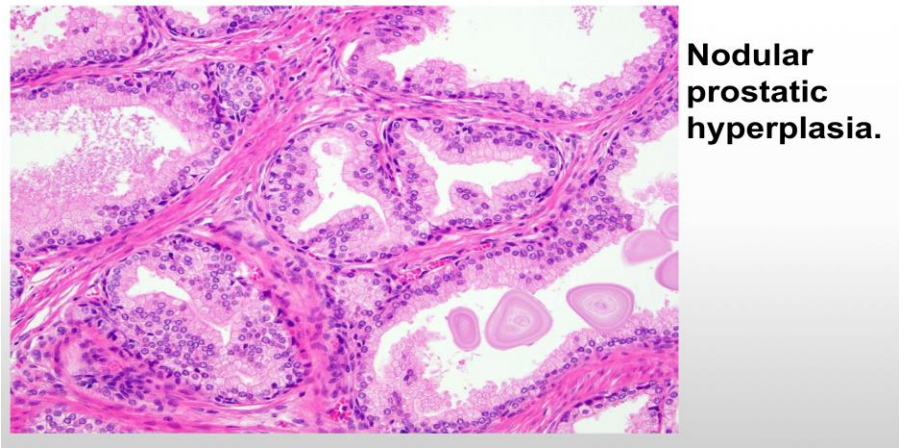
Nodular hyperplasia (NH) of the prostate

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

MICROSCOPICALLY

- the **hyperplastic nodules composed of**:
- (1) 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 amylacea.
- The hyperplastic glands are surrounded by proliferating stromal elements.
- Some nodules composed predominantly of spindle-shaped stromal cells &connective tissue.

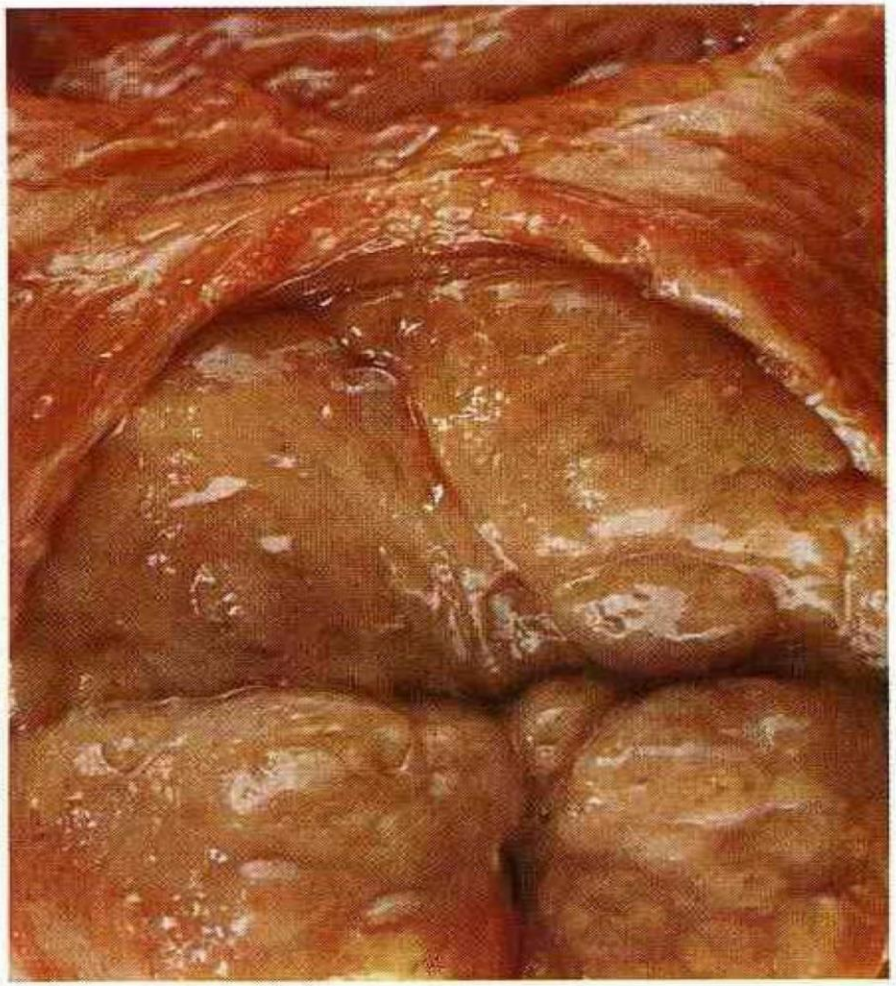




Nodular prostatic hyperplasia.

CLINICAL MANIFESTATIONS OF NH

- Clinical manifestations of NH occur 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.
- 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.



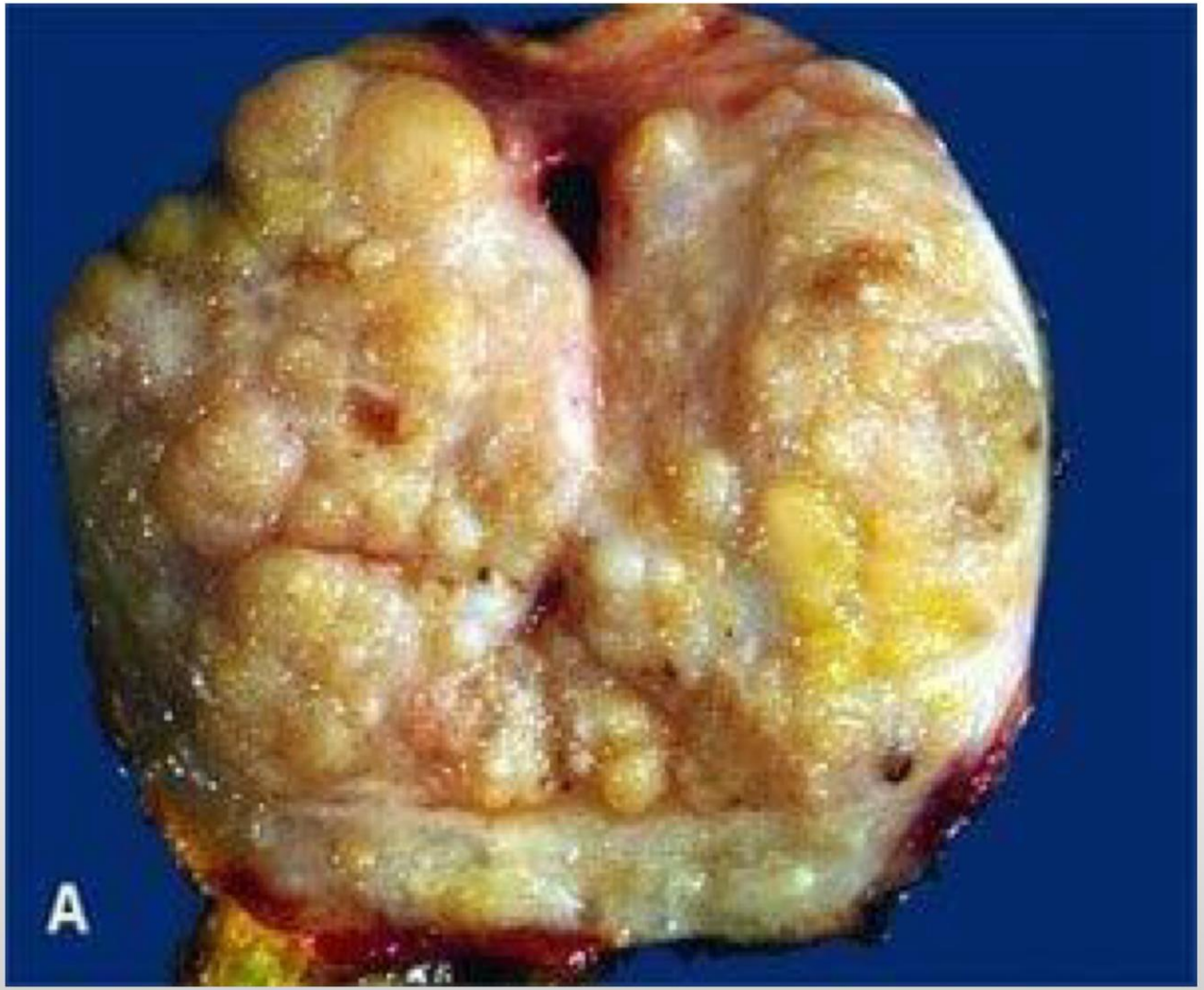
11.6 Adenomatous hyperplasia: prostate

Adenomatous hyperplasia: 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).

Benign prostatic hyperplasia



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 incidencebetween 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.

PROSTATIC CARCINOMA(PCA)

- 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.

RISKS OF PROSTATIC CARCINOMA(PCA)

- 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.
- 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.
- 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.

RISKS OF PROSTATIC CARCINOMA(PCA)

- .**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**.

MORPHOLOGY OF PROSTATIC CANCER

- 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 .

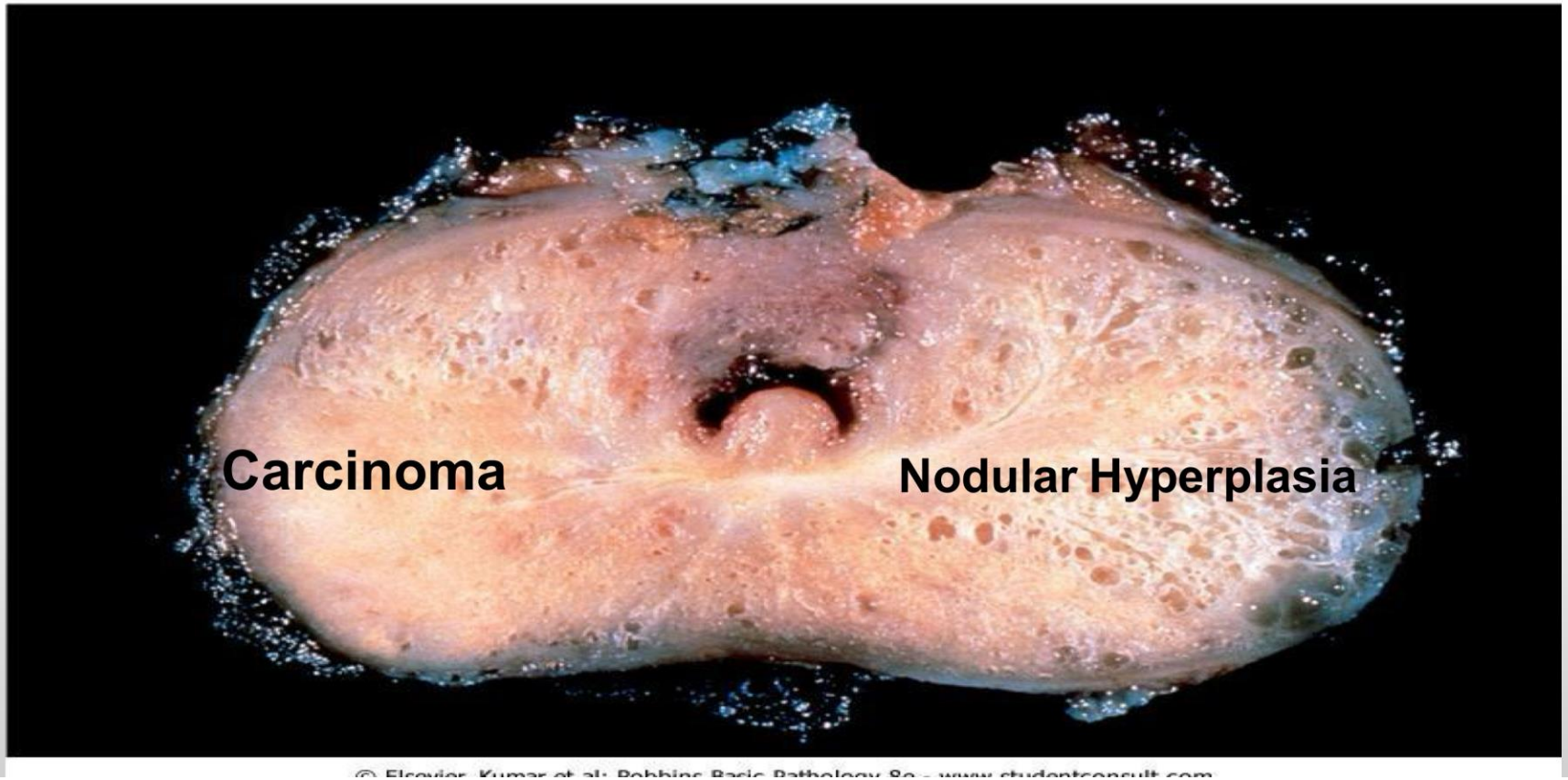
MORPHOLOGY (CONT.)

- 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.

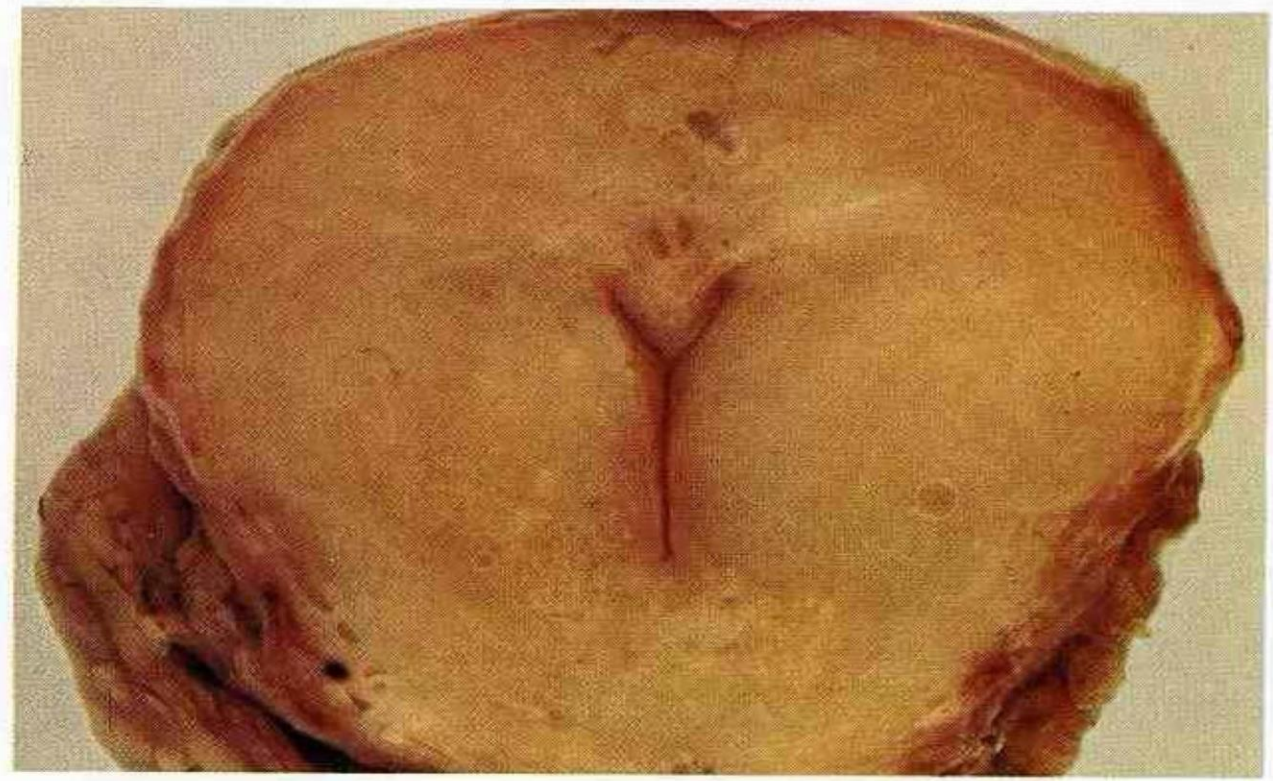
MORPHOLOGY (CONT.)

- **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 though 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 increase degrees of anaplasia, irregular, ragged glandular structures, papillary or cribriform epithelium & in extreme cases, sheets of poorly differentiated cells are present.

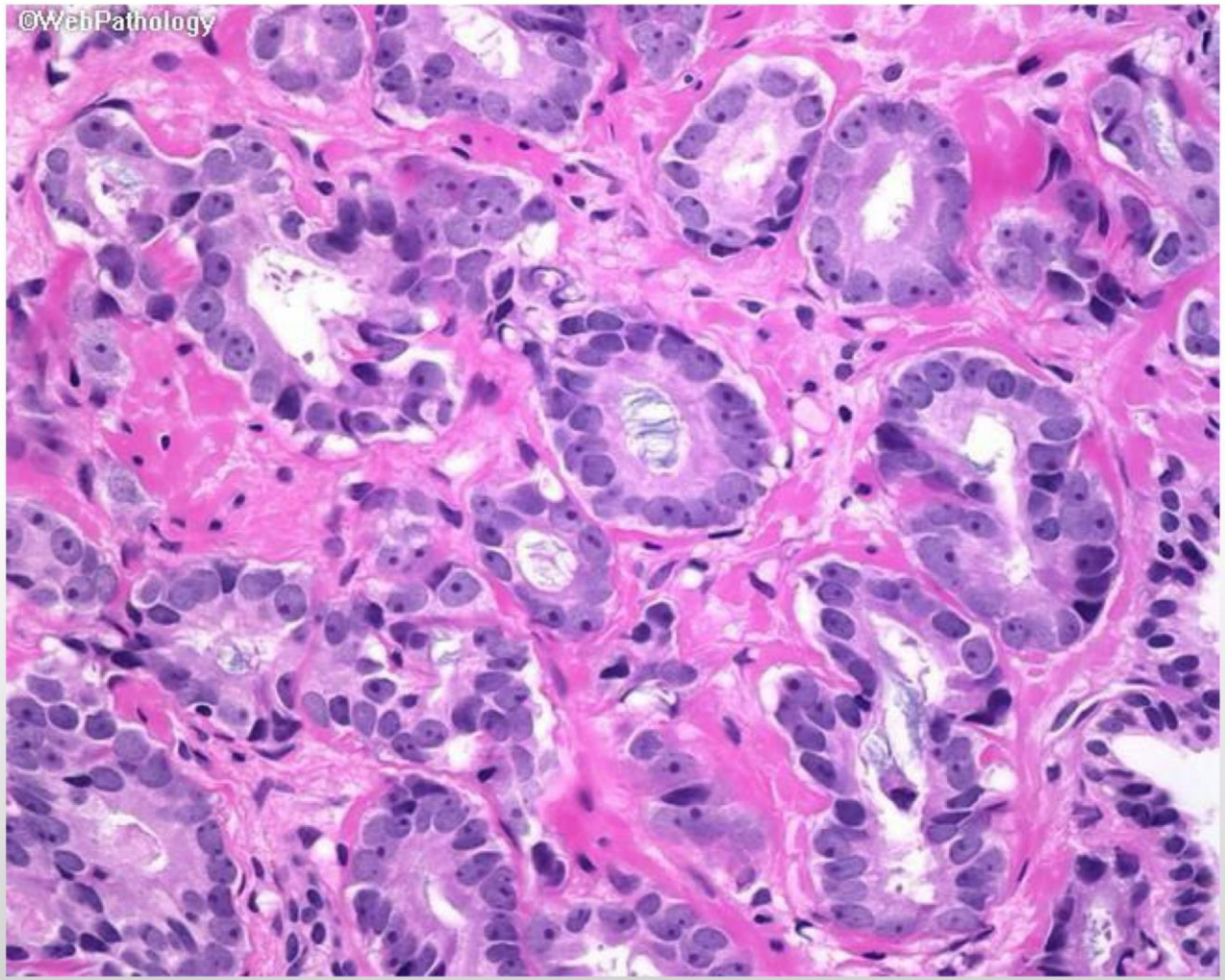
Prostatic adenocarcinoma. Carcinomatous tissue is seen in the lower left as...Subscapular solid whiter cancer in contrast to the Spongy benign peripheral zone on the other side



Adenocarcinoma: prostate. 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



- This focus of prostate cancer has all the essential histologic features - small crowded glands lined by a single layer of cells, nuclear enlargement and hyperchromasia, prominent nucleoli, and intraluminal blue mucin. A benign gland is partially visible at the lower right side of the image. Contrast its nuclear size to those of adjacent malignant glands.

PROSTATIC INTRAEPITHELIAL NEOPLASIA

- Because of its frequent coexistence with infiltrating Pca, **PIN** has been suggested as a probable precursor to P ca.
- **PIN (prostatic intraepithelial neoplasia)** 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.

CLINICAL FEATURES OF PROSTATIC CANCER

- Clinically, Prost ca is often clinically:
- **(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.**

CLINICAL FEATURES OF PROSTATIC CANCER

- 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, GATA3 and High molecular weight cytokeratin** 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.

DIAGNOSIS OF PROSTATIC CANCER

- 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.
- 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

-TNM- STAGING OF PROSTATIC CANCER

- Table 18-3 TNM Staging of Prostatic Adenocarcinoma
- T1-Clinically Inapparent Lesion By Palpation/Imaging Studies:
- T1a -Involvement of ≤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 ≤50% of one lobe
- T2b –Involvement of >50% of one lobe, but unilateral
- T2c –Involvement of both lobes

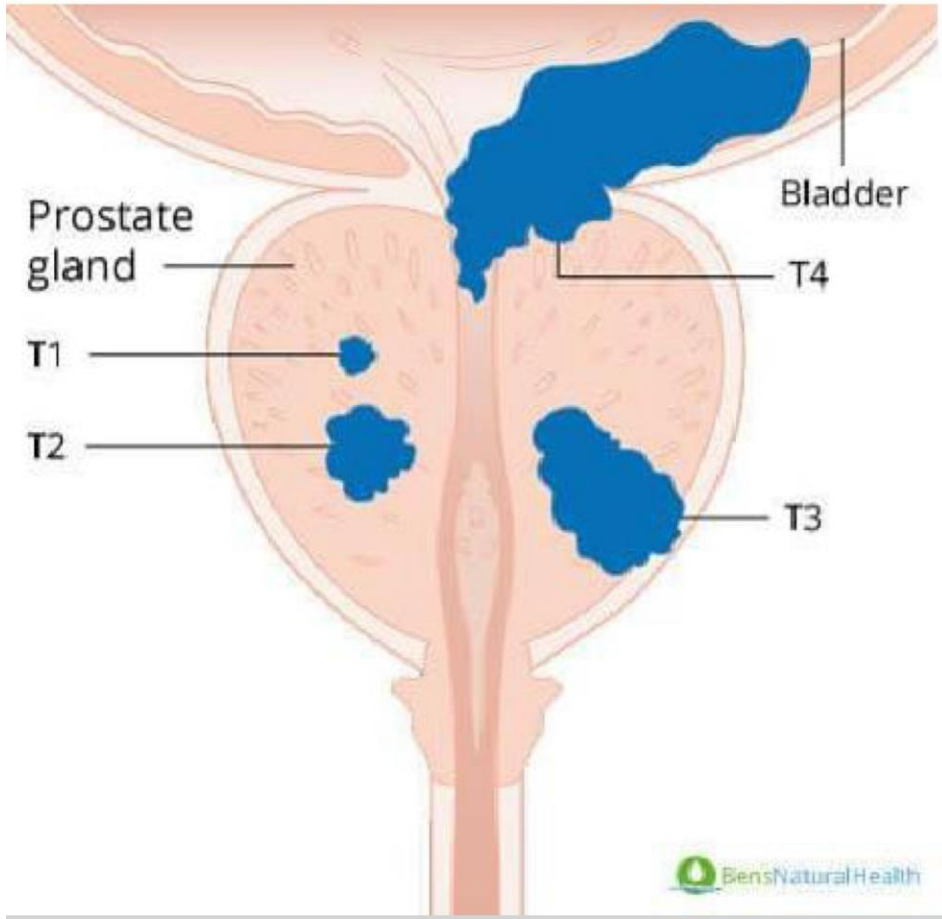
- T3-Local Extraprostatic Extension
- T3a-Extracapsular extension
- T3b-Seminal vesical invasion

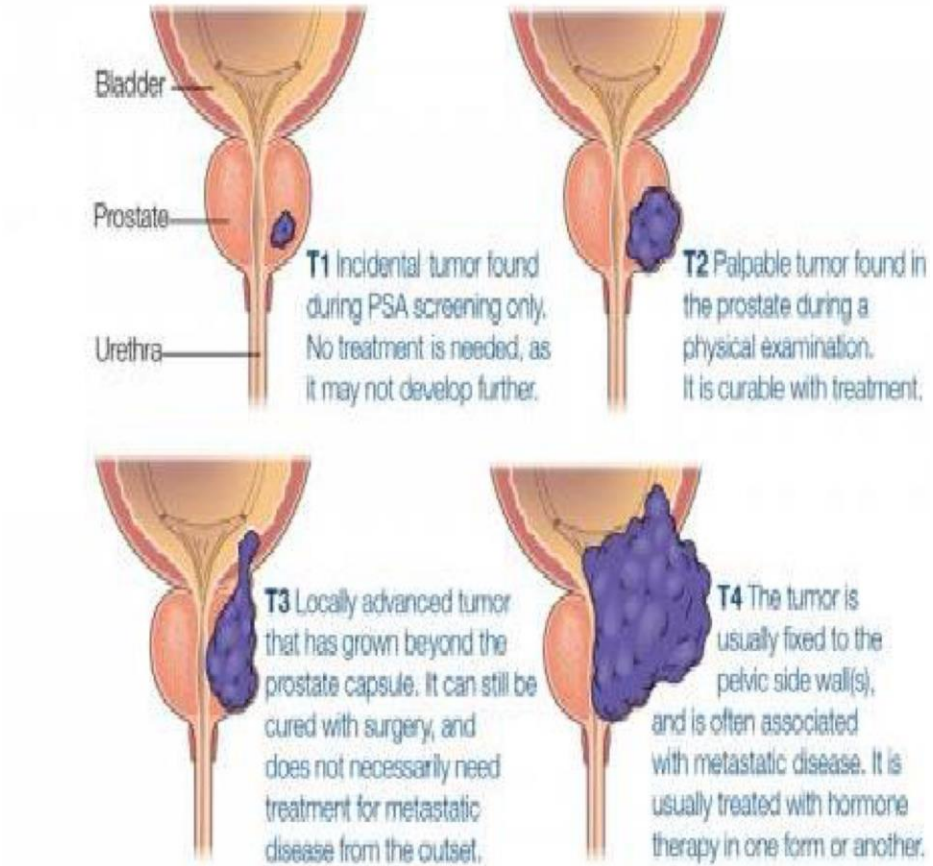
- T4-Invasion of Contiguous Organs And/Or Supporting Structures Including Bladder
- Neck, Rectum, External Sphincter, Levator Muscles, Or Pelvic Floor

-TNM- STAGING OF PROSTATIC CANCER

- **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 cancer stages





TREATMENT OF PROSTATIC CANCER

- 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.