Prostate

- **The prostate can be divided into biologically distinct regions:**

1. The peripheral zone

2. The the central zone

3. The transition zone

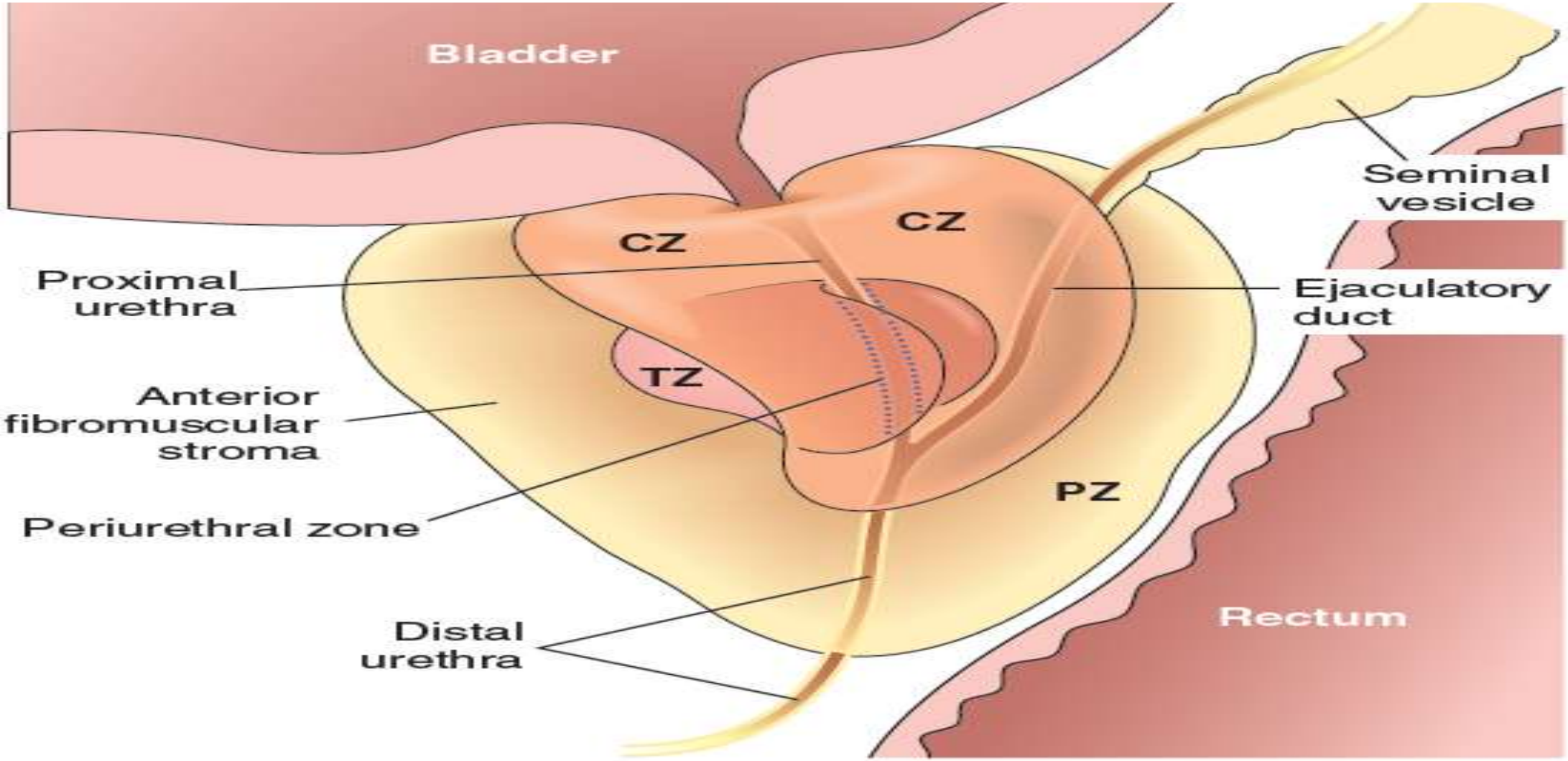


Fig. 18.10 Adult prostate. The normal prostate contains several distinct regions, including a central zone (CZ), a peripheral zone (PZ), a transitional zone (TZ), and a periurethral zone. Most carcinomas arise from the peripheral glands of the organ, whereas nodular hyperplasia arises from more centrally situated glands.

- **<u>The normal prostate contains glands with two cell layers:</u>**

1. **Flat basal cell layer**
2. **Overlying columnar secretory cell layer**

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

- **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.**

Benign Prostatic Hyperplasia

- **Benign prostatic hyperplasia (BPH) is an extremely common cause of prostatic enlargement resulting from proliferation of of stromal and glandular elements.**
- **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**
- **The 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**
- BPH does not occur in males who are castrated before the onset of puberty or in males with genetic diseases that block androgen activity.

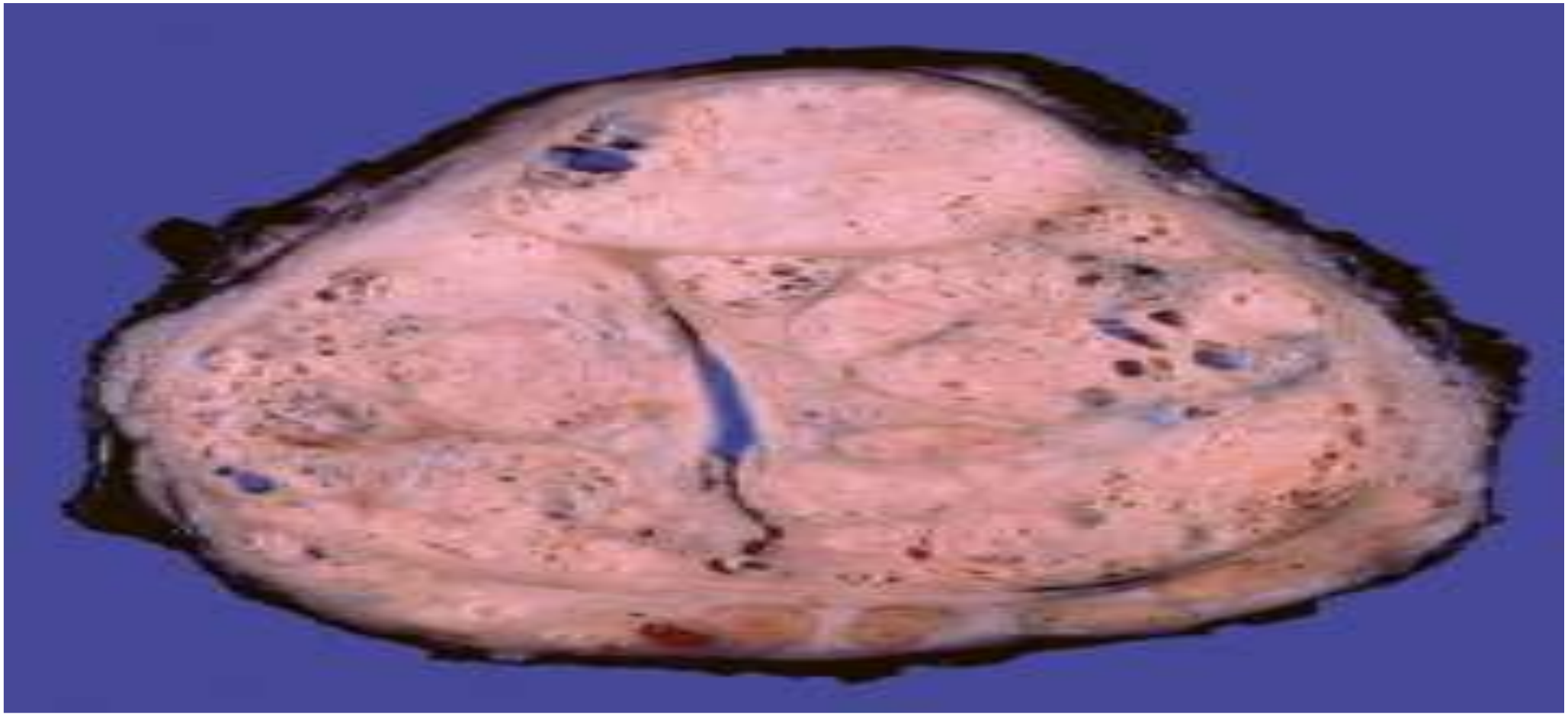
Morphology

- **BPH virtually always occurs in the inner transition zone of the prostate.**
- The affected prostate is enlarged, typically weighing between 60 and 100 g
- Contains many well circumscribed nodules that bulge from the cut surface

- **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.**
- **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.**

- **Microscopically**
- **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.**

Nodular hyperplasia
Well defind nodules compressing the urethra into slitlike lumen



Clinical features

- **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 in starting the stream of urine (hesitancy) and intermittent interruption of the urinary stream while voiding**
- **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 increases the risk for urinary tract infections**
- **Complete urinary obstruction, with resultant painful distention of the bladder**
- **Hydronephrosis**

Carcinoma of the Prostate

- **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**
- **Its 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 commonly is found incidentally at autopsy in men dying of other causes**

Pathogenesis

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

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**
- **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**

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 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 5-fold increase in risk compared to the general population.**

Environment

- **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 since the diet in this region becomes more westernized, t**
- **However, the relationship between specific dietary components and prostate cancer risk is unclear**

Acquired genetic aberrations

- The most common gene rearrangements in prostate cancer create fusion genes consisting of the androgenregulated 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 they 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 of these, 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 typically are 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**

Adenocarcinoma of the prostate. 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.

- **Some variation in nuclear size and shape is usual**
- **Mitotic figures are uncommon.**
- **With increasing grade, irregular or ragged glandular In approximately 80% of cases**
- **Prostatic tissue removed for carcinoma also harbors presumptive precursor lesions, referred to as high-grade prostatic intraepithelial neoplasia (HGPIN)**

Gleason system

- Prostate cancer is graded by the **Gleason system**
- According to this system prostate cancers are stratified into five grades on the basis of glandular patterns of differentiation
- **Grade 1** represents the most well differentiated tumors
- **Grade 5** tumors show no glandular differentiation
- **Grade 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 two numerical grades are then added to obtain a combined Gleason score.

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 *TPRSS2-ETS* fusion genes or act to enhance PI3K/AKT signaling which promotes 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.**

- **Some 70-80% of prostate cancers arise in the outer (peripheral) glands, and a subset of these 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 the 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**

- **The PSA assay is the most widely used test in the diagnosis and management of prostate cancer**
- **Limitations:**
- **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 requiring no treatment sometimes 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 all may increase serum

  PSA levels
- 20-40% of patients with organ confined prostate cancer have PSA values below the cutoffs that are used to identify patients who are likely to have prostate cancer.