DISORDERS OF PENIS, PROSTATE, AND TESTES

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Embryology

- Mesonephric duct is derived from mesoderm. It forms as a longitudinal solid cord of tissue dorsolateral to the mesonephric tubules in the thoracic region.
- The cords grow caudally and fuse with the ventrolateral wall of the cloaca, forming the urogenital sinus. Subsequently canalizes. At 10th week it drains urine from the mesonephros.
- The paramesonephric duct forms lateral to the mesonephric duct (invagination of celomic epithelium on cranial aspect of mesonephros).

Embryology

- The gonadal ridge contains mesenchymal cells (medulla: Leydig's cells); mesothelial cells (primary sex cord: seminiferous tubules).
- Primordial germ cells enter the primary sex cords as gametes.
- At the 4th week, five ectodermal covered mesenchymal swellings form around the cloacal membrane: the genital tubercle, two urogenital and two labioscrotal folds.
- The genital tubercle will become the glans penis.
- The gubernaculum forms between the indifferent gonads and the labioscrotal swellings. This ligament will guide testes into the scrotum.

Embryology

- Testis differentiation factor is the transcription product of the SRY gene. Indifferent gonads differentiate into coiled solid testis cords (the ends stay straight and join near the hilum to form the rete testes).
- The rete testes and mesonephric tubule remnants become efferent ductules.
- The mesenchyme thickens into the tunica albuginea.
- The testes enlarge and separate form the mesonephros, following the lower gubernaculum to reach the scrotum via the inguinal canal. The upper gubernacula then degenerate.

Embryology

- The process vaginalis (peritoneum) also descends with the layers of the abdominal wall (forming the scrotal wall) and remains as the tunica vaginalis.
- At the 8th week, Sertoli's cells secrete müllerian inhibiting substance which induces regression of the paramesonephric duct.
- Leydig's cells begin to secrete androgens; mesonephric (Wolffian) ducts differentiate into epididymis, ductus deferens, ejaculatory duct, and seminal vesicles.
- The prostate forms as an endodermal outgrowth from the urogenital sinus that forms the prostatic uretrhra. Mesoderm from mesonephric and paramesonephric duct remnants may be found in the median lobe.

PENIS

Penis

- Malformation of the urethral groove and urethral canal may create an abnormal urethral opening either on the ventral surface of the penis (hypospadias) or on the dorsal surface (epispadias).
- Either of these two anomalies may be associated with failure of normal descent of the testes and with malformations of the urinary tract.
- Hypospadias is more common.
- When the orifice of the prepuce is too small to permit its normal retraction, the condition is designated phimosis.
- Usually a result of infection.

Penis

- Infection of the glans and prepuce (balanoposthitis) usually due to Candida or Gardnerella.
- Poor hygiene in uncircumcised men permits accumulation of epithelial cells, sweat, and debris (or smegma) and leads to chronic inflammation.

Penis

- Peyronie's disease
- Fibrous bands involve the corpus cavernosum.
- The penis is curved
- Intercourse is painful.
- Collagenase clostridium histolyticum injection into plaques leads to lysis of collagen as this particular collagenase attacks the triple helical form of collagen.

Penis

- Condyloma accuminatum generally occurs around coronal sulcus and inner surface of the prepuce.
- May occur anywhere on perineum.
- Sessile or pedunculated red papillary excrescenes.
- Histologically, a branching, villous, papillary connective tissue stroma is covered by epithelium that may be hyperkeratotic. Underlying epidermis may be acanthotic. Vacuolated cells are present (koilocytic atypia)
- HPV 6 and 11

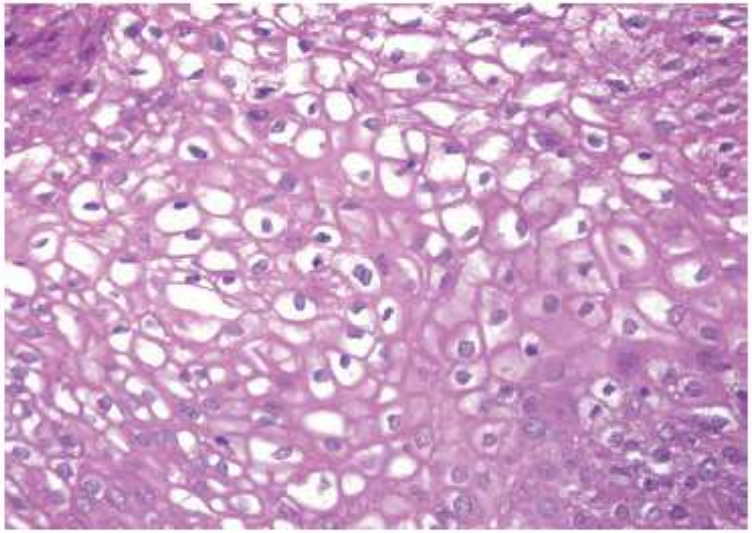


Figure 21-17 Condyloma acuminatum of the penis. The epithelium shows vacuolization (koilocytosis) characteristic of human papillomavirus infection.

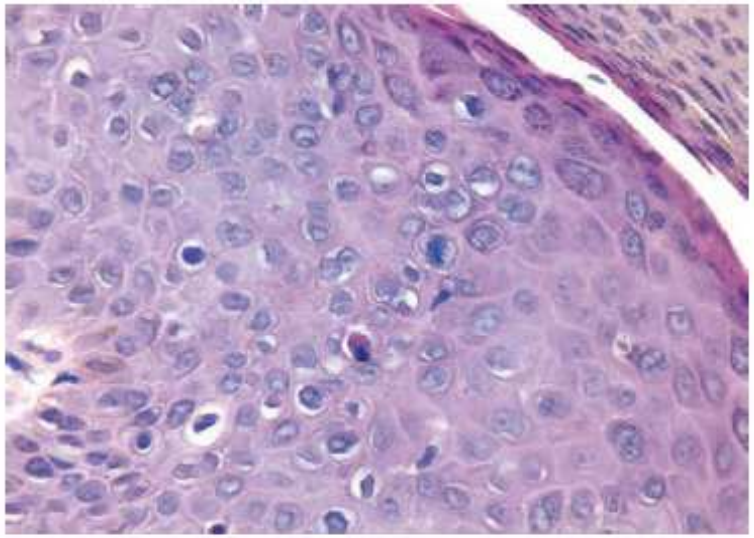


Figure 21-18 Bowen disease (carcinoma in situ) of the penis. Note the hyperchromatic, dysplastic dyskeratotic epithelial cells with scattered mitoses above the basal layer. The intact basement membrane is not readily seen in this picture.

Cancer-in-situ of the penis

- Bowen disease
- Occurs in the genital region of both men and women
- >35 years old
- Prone to involve the skin of the shaft of the penis and the scrotum.
- Gross:
- Solitary, thickened, gray-white, opaque plaque with shallow ulceration and crusting.
- It can also manifest on the glans and prepuce as single or multiple shiny red, sometimes velvety, plaques where it is clinically referred to as Erythroplasia of Queyrat.

Cancer-in-situ of the penis

- Histologically:
- Epidermal proliferation with numerous mitoses, some atypical.
- The cells are markedly dysplastic with large hyperchromatic nuclei and lack of orderly maturation.
- Intact basement membrane.
- Bowenoid papulosis is indistinguishable from Bowen disease other than by spontaneous regression.

Carcinoma-in-situ of the penis

- HPV 16
- 10% progress to invasive carcinoma
- No spontaneous regression
- Bowenoid papulosis noted in younger men; multiple lesions
- May regress spontaneously although HPV 16

Erythroplasia of Queyrat

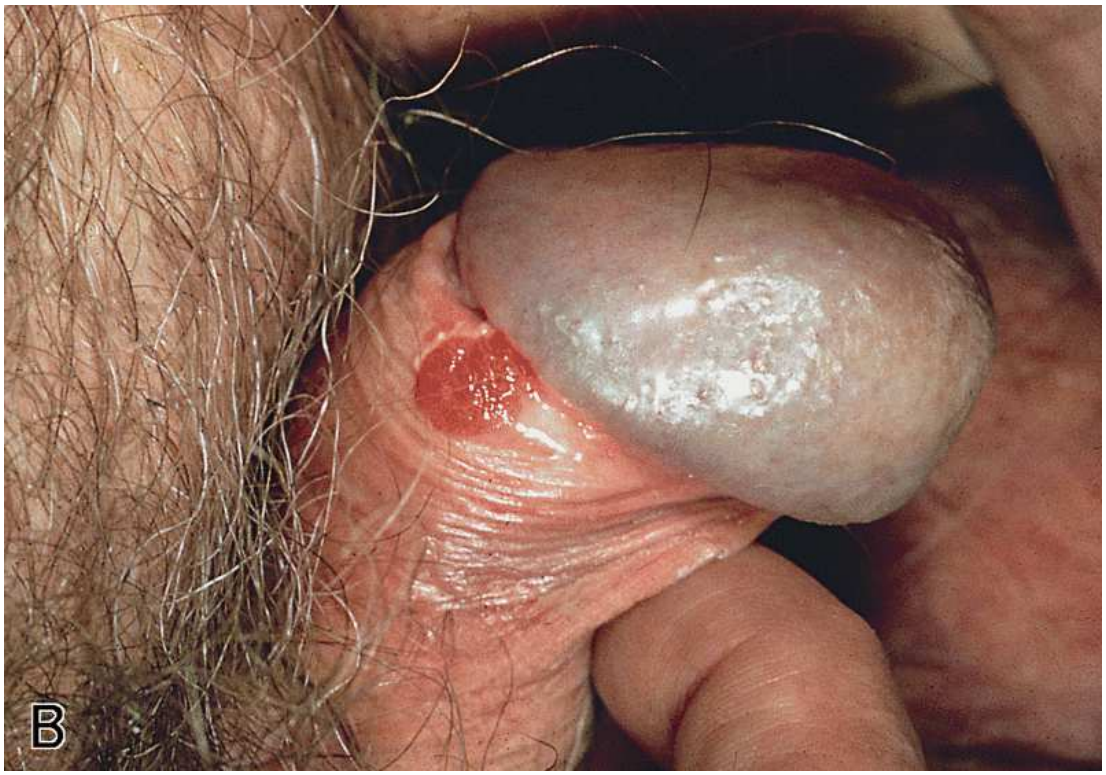


Fig. 10-15B

Young, Robert H., Srigley, John R., Amin, Mahul B., Ulbright, Thomas, M, Cubrilla, Antonio, L. , “Tumors of the prostate gland, seminal vesicles, male urethra, and penis.” Atlas of Tumor Pathology. Third series. Fascicle 28. Armed Forces Institute of Pathology. Washington, DC. 2000.

Carcinoma of the penis

- Squamous carcinoma
- 40-70 years of age
- Non-painful
- Slowly growing
- Drains to inguinal nodes (glans, to deep nodes)
- Smoking and poor hygiene are risk factors
- Circumcision is protective
- HPV 16 and 18 found in up to 50% of cases
- 5-year survival 66% if tumor localized; 27% if inguinal metastases

Cancer of the penis

- HPV infection (condyloma accuminatum) is associated with an elevated risk of cancer of the penis.
- HPV 16 is most common strain.
- Squamous cancer begins on the glans or near the prepuce.
- Locally invasive.
- Late metastases.
- Penile amputation and node dissection as primary therapy.

Squamous cell carcinoma of the penis

- Squamous cell carcinoma of the penis usually begins on the glans or inner surface of the prepuce near the coronal sulcus.
- Two macroscopic patterns are seen:
- Papillary lesions simulate condylomata acuminata
- There is a verrucoid variant
- Flat lesions appear as areas of epithelial thickening accompanied by graying and fissuring of the mucosal surface. With progression, an ulcerated papule develops.

Squamous carcinoma of penis

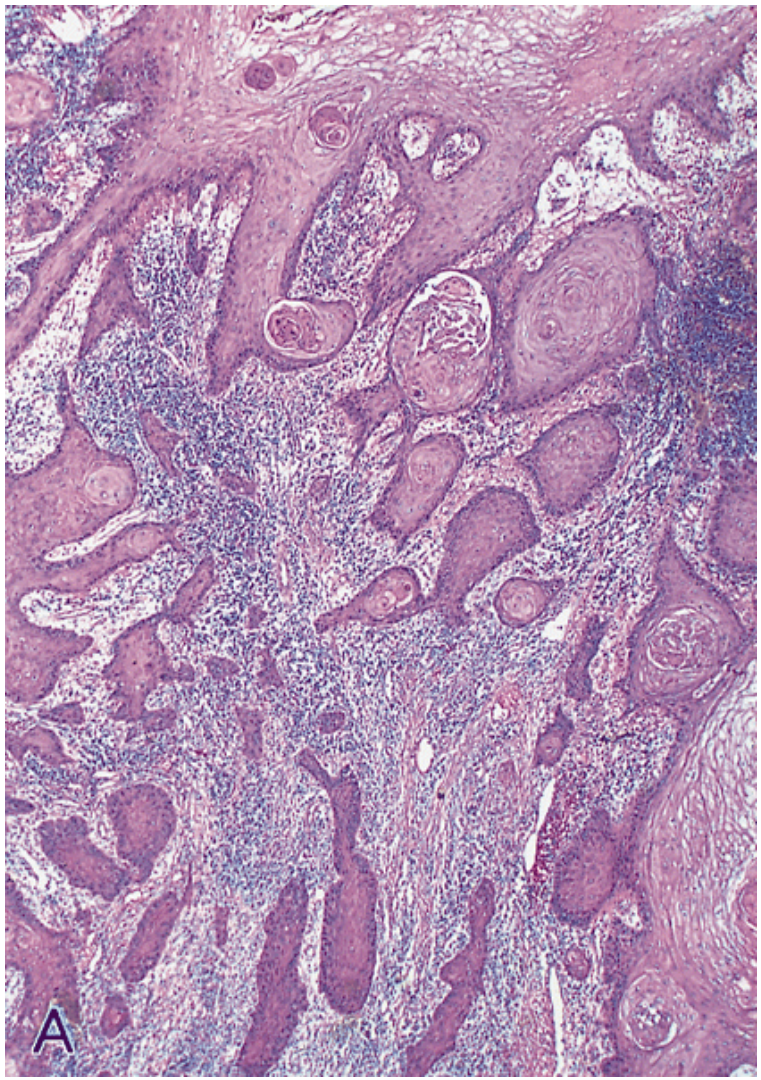


Fig. 10-34A

Young, Robert H., Srigley, John R., Amin, Mahul B., Ulbright, Thomas, M, Cubrilla, Antonio, L. , “Tumors of the prostate gland, seminal vesicles, male urethra, and penis.” Atlas of Tumor Pathology. Third series. Fascicle 28. Armed Forces Institute of Pathology. Washington, DC. 2000.

Basaloid carcinoma of penis

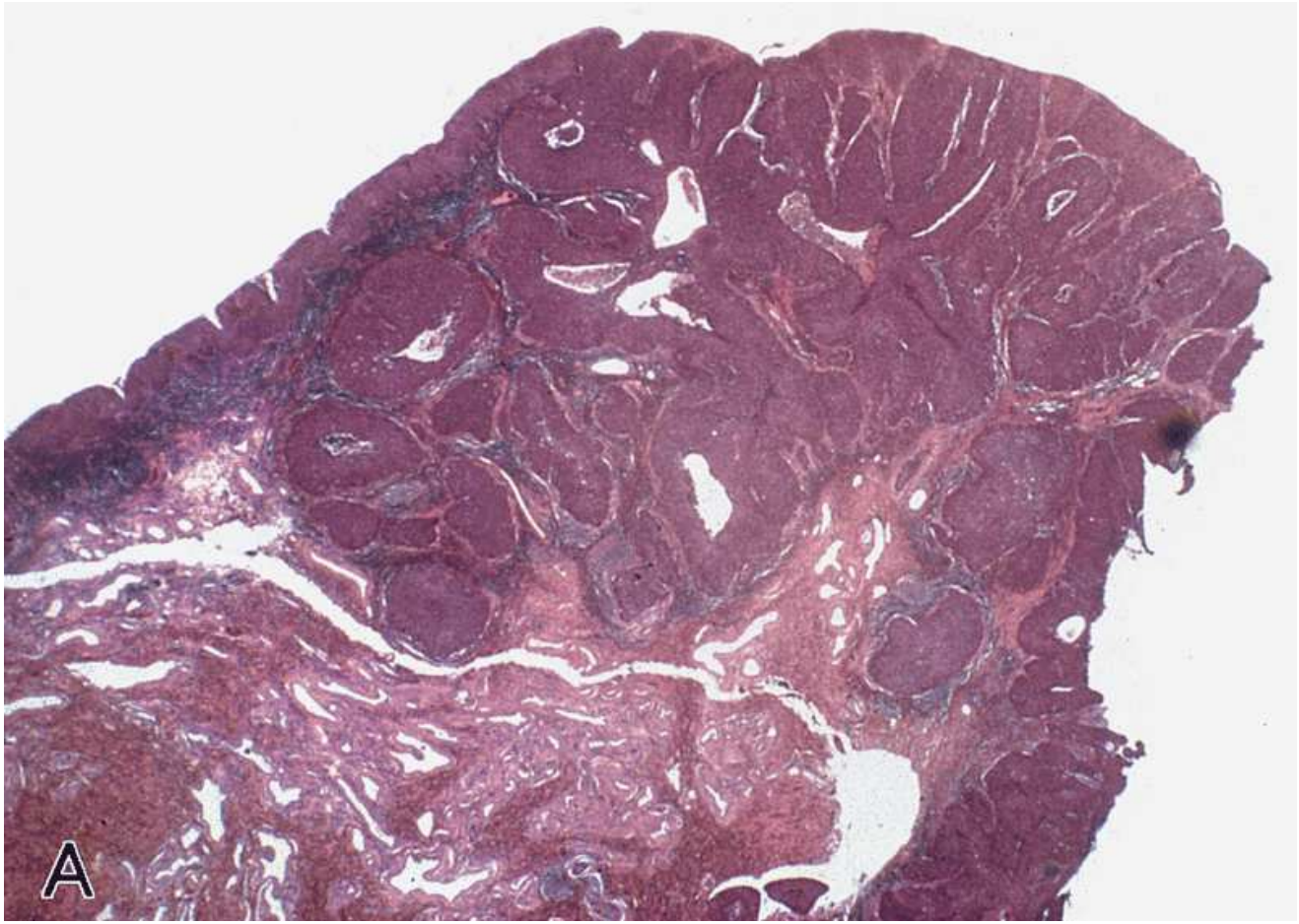


Fig. 10-37A

Young, Robert H., Srigley, John R., Amin, Mahul B., Ulbright, Thomas, M, Cubrilla, Antonio, L. , “Tumors of the prostate gland, seminal vesicles, male urethra, and penis.” Atlas of Tumor Pathology. Third series. Fascicle 28. Armed Forces Institute of Pathology. Washington, DC. 2000.

PROSTATE

Prostate

- Paired median and lateral lobes.
- Lies (with its apex) on the urogenital diaphragm. Base contacts the bladder.
- Separated from rectum by Denonvillier's fascia.
- Traversed by the urethra.
- Seminal vesicles lie lateral to the vas deferens. Ducts join in the prostate to form the ejaculatory duct.
- Prostatic ducts open into prostatic sinuses that lie lateral to the urethral crest.
- Inferior vesical, middle rectal, and internal pudendal arteries supply the prostate.

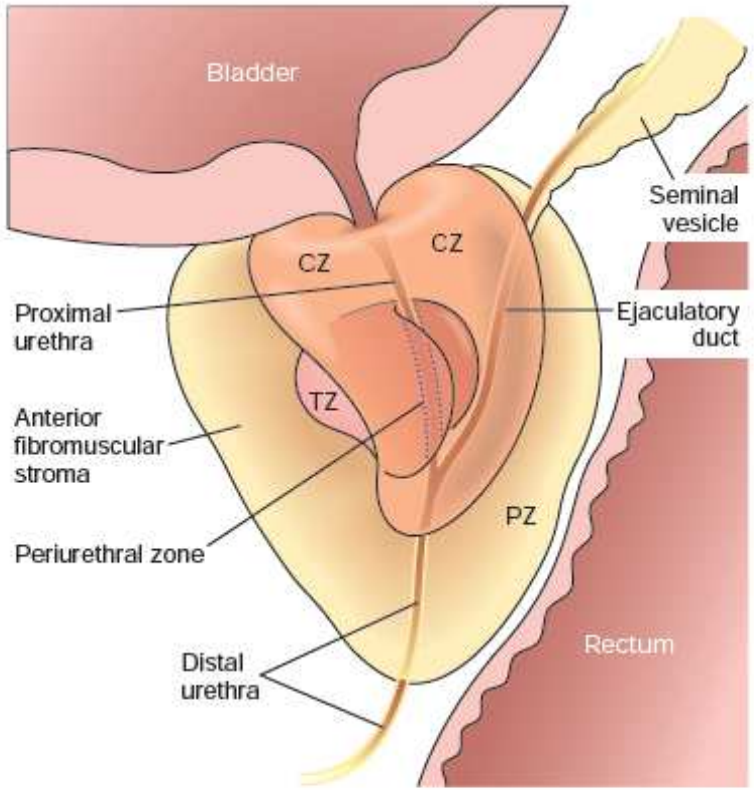


Figure 21-30 Adult prostate. The normal prostate contains several distinct regions, including a central zone (CZ), a peripheral zone (PZ), a transitional zone (TZ), and a periurethral zone. Most carcinomas arise from the peripheral zone and may be palpable during digital examination of the rectum. Nodular hyperplasia, in contrast, arises from the more centrally situated transitional zone and often produces urinary obstruction.

Four biologically and anatomically distinct zones:

- Peripheral,
- Central
- Transitional
- Periurethral

Most hyperplasias arise in the transitional zone.

Most carcinomas originate in the peripheral zone.

Prostate

- Histologically the prostate is composed of glands lined by two layers of cells:
- A basal layer of low cuboidal epithelium covered by a layer of columnar secretory cells.
- In many areas there are small papillary infoldings of the epithelium.
- These glands are separated by abundant fibromuscular stroma.

Acute prostatitis

- Infections generally follow intraprostatic reflux of the urine from the posterior urethra or bladder.
- Burning during or after urination
- Difficulty starting the urine stream
- Dribbling after urination has been completed
- A need to urinate frequently or urgently
- A sensation that the bladder cannot be emptied completely
- Pain felt above the penis, in or below the scrotum, or in the back or rectum
- Pain experienced during or after orgasm

Acute prostatitis

- May present with fever and chills
- Escherichia coli, Proteus and Enterobacter species, Enterococcus, Staphylococcus saprophyticus common organisms.
- Microabscesses in gland
- As antibiotics penetrate prostate poorly, may lead to chronic prostatitis
- Granulomatous change if BCG instillation into bladder
- Fungal causes only in immunosuppressed

Chronic non-bacterial prostatitis

- The most common prostatitis seen today.
- 25% of all visits to a urologist
- White cells found in abundance in seminal fluid.
- No organisms demonstrated.
- Chronic pelvic pain
- Young men

Prostate hyperplasia

- Present with obstruction of urethra.
- Hesitation
- Weak urinary stream
- Incomplete bladder emptying
- Common after age 50.
- 30% of men have condition by 30 years of age
- 50% of men with condition are asymptomatic
- Smooth muscle mediated contraction of the prostate mediated by α_1 adrenreceptor in prostatic stroma.

Prostate hyperplasia

- Hyperplasia stems from impaired cell death, resulting in the accumulation of senescent cells in the prostate.
- Androgens not only increase cellular proliferation, but also inhibit cell death.
- Stromal cells, site of 5α-dihydrotestosterone (DHT) reductase type 2, convert testosterone.
- Autocrine effect on stromal cells;
- Paracrine effect (diffusion of FGF-7) on epithelial cells.
- Type 1 5α-DHT reductase not found in testis but in liver and skin. May contribute to development.

Prostate hyperplasia

- DHT shows high affinity binding to the nuclear androgen receptor.
- Testosterone much lower binding affinity
- Highest sensitivity to DHT associated with shortest CAG repeats in AR (androgen receptor) gene at Xq12
- DHT mediates gene transcription and promotes production of FGF.
- FGF-1, FGF-2, and TGF-β promote fibroblast proliferation.

Prostate hyperplasia

- Nodular hyperplasia of the prostate originates almost exclusively in the inner aspect of the prostate gland (transition zone).
- May encroach on the lateral walls of the urethra to compress it to a slit-like orifice.
- If nodular enlargement projects up into the floor of the urethra as a hemispheric mass directly beneath the mucosa of the urethra, it is termed median lobe hypertrophy.

Prostate hyperplasia

- The early nodules are composed almost entirely of stromal fibromuscular tissue.
- Epithelial nodules arise later.
- Nodules do not have true capsules but are separated from surrounding prostatic tissue by a cleavage plane.
- Nodules that contain mostly glands are yellow-pink and soft, and exude a milky white prostatic fluid.
- Nodules composed primarily of fibromuscular troma are pale gray and tough; and do not exude fluid

Nodular hyperplasia of prostate

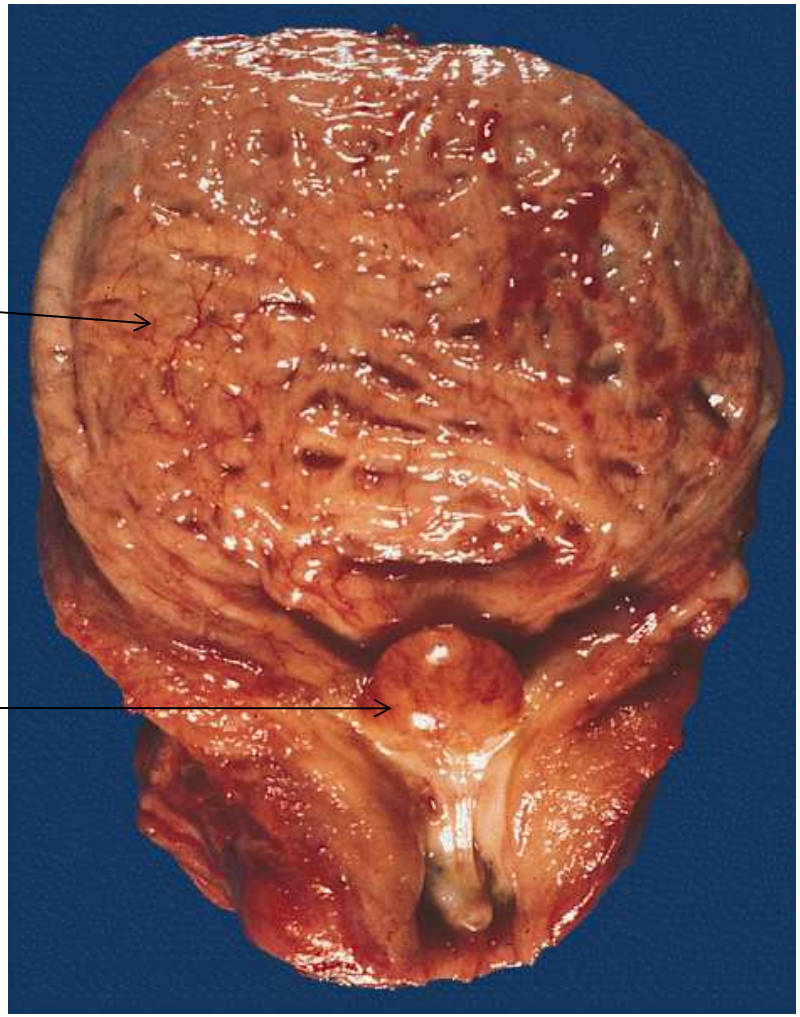


Fig. 2-1

Young, Robert H., Srigley, John R., Amin, Mahul B., Ulbright, Thomas, M, Cubrilla, Antonio, L. , “Tumors of the prostate gland, seminal vesicles, male urethra, and penis.” Atlas of Tumor Pathology. Third series. Fascicle 28. Armed Forces Institute of Pathology. Washington, DC. 2000.

Nodular hyperplasia of prostate

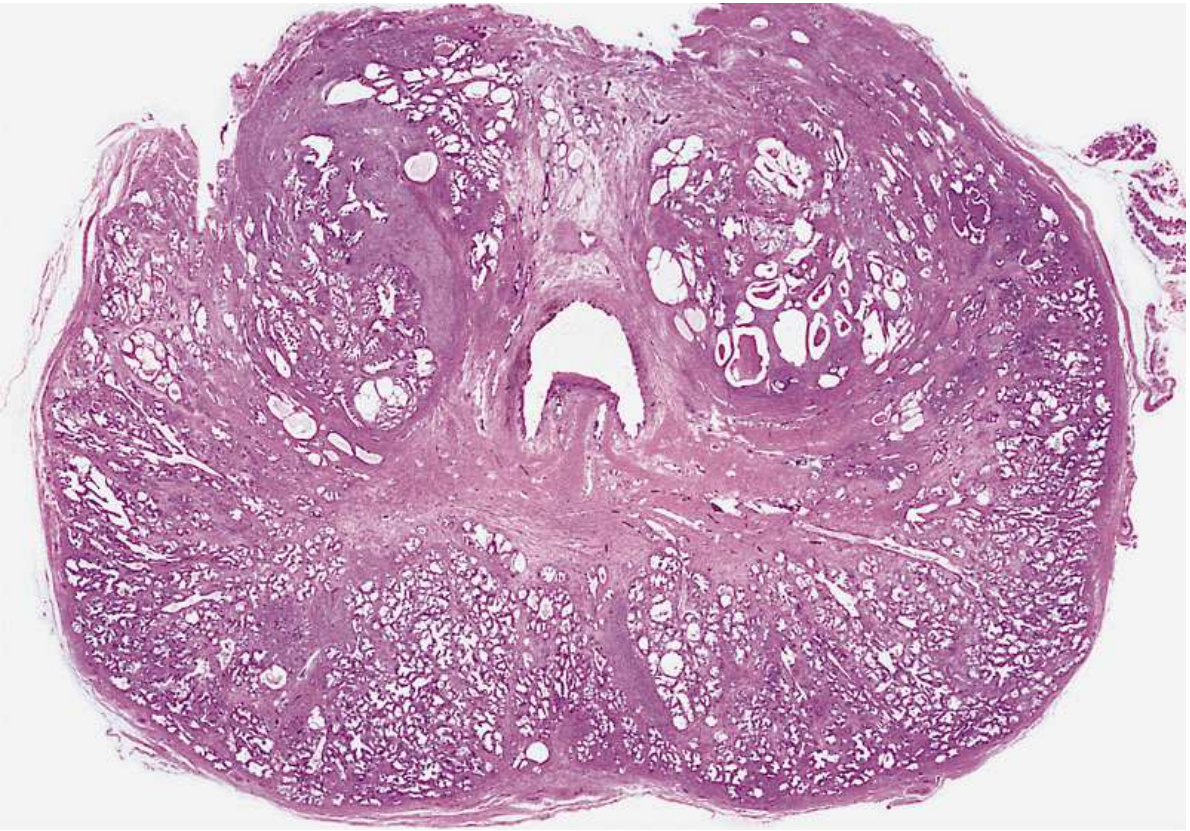


Fig. 2-06 T

Young, Robert H., Srigley, John R., Amin, Mahul B., Ulbright, Thomas, M, Cubrilla, Antonio, L. , “Tumors of the prostate gland, seminal vesicles, male urethra, and penis.” Atlas of Tumor Pathology. Third series. Fascicle 28. Armed Forces Institute of Pathology. Washington, DC. 2000.

Treatment of prostate hyperplasia

- Finasteride is a 5α-DHT reductase inhibitor
- Used to reduce prostate size.
- Major side effect is impotence.
- Though bone loss will occur over time, the addition of Calcium is not recommended as it promotes carcinogenesis in the prostate.
- Tamsulosin inhibits α-adrenergic tone
- The prostate size does not decrease.

Treatment of prostate hyperplasia

- Saw palmetto attenuates upregulation of α_1-adrenoreceptors and blocks 5α-DHT reductase
- The prostate size does not decrease
- Less sexual dysfunction
- When these measures fail, transurethral resection of prostatic material is used to open the urinary tract.

High grade intracellular neoplasia

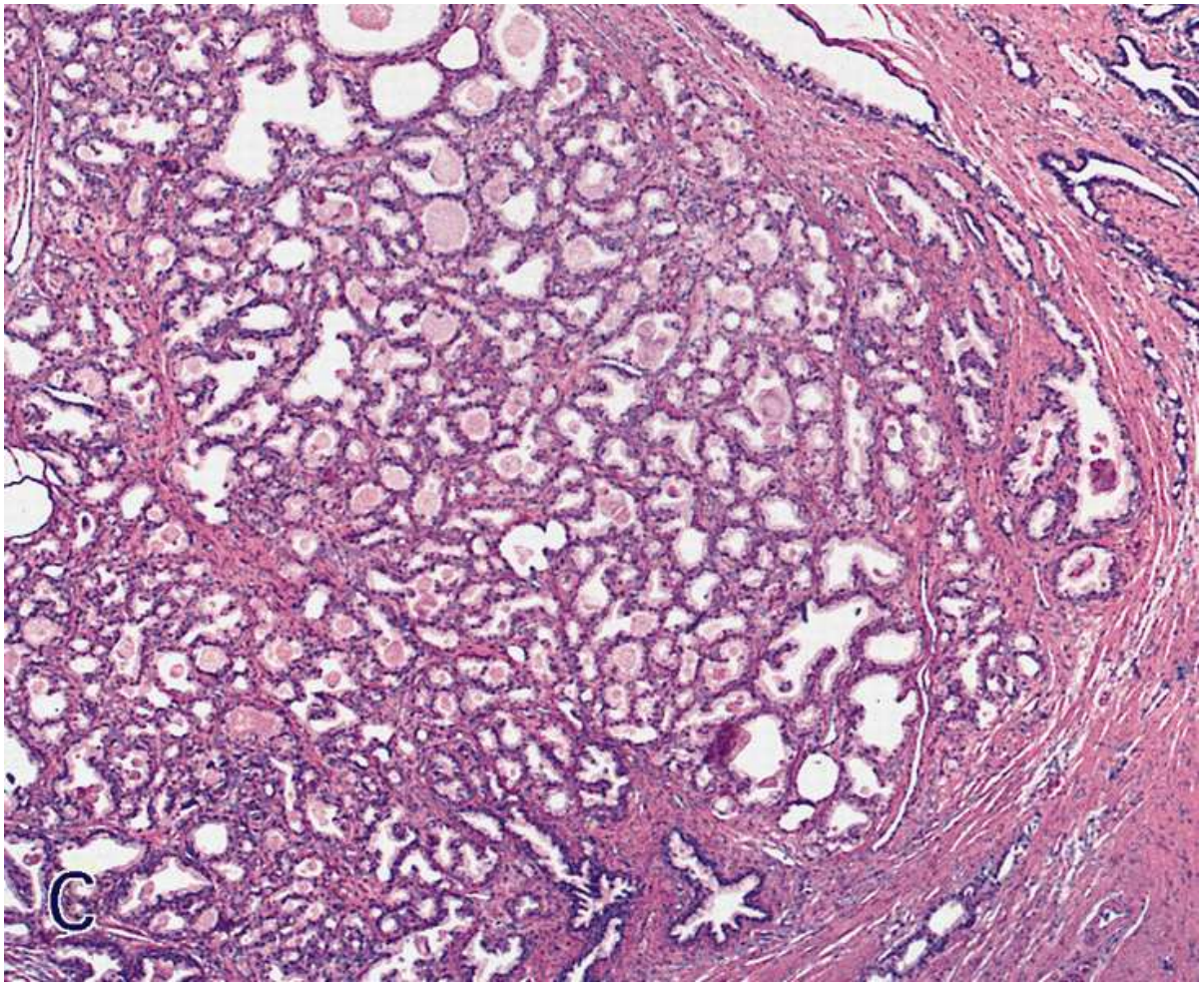


Fig. 3-29C

Young, Robert H., Srigley, John R., Amin, Mahul B., Ulbright, Thomas, M, Cubrilla, Antonio, L. , “Tumors of the prostate gland, seminal vesicles, male urethra, and penis.” Atlas of Tumor Pathology. Third series. Fascicle 28. Armed Forces Institute of Pathology. Washington, DC. 2000.

Adenocarcinoma of the prostate

- The most common form of cancer in men
- 1% of cancer deaths
- There is a one in six lifetime probability of being diagnosed with prostate cancer.
- Incidence increases from 20% in men in their 50s to approximately 70% in men between the ages of 70 and 80 years.
- Uncommon in Asians and occurs most frequently among those of sub-Saharan origin.
- Inversely related to length of repeats of codon CAG in the AR gene at Xq12 (codes for glutamine).

Adenocarcinoma of the prostate

- 70% occur in a peripheral zone and in a posterior location
- 90% of lesions are acinar type adenocarcinoma.
- Neoplastic tissue is gritty and firm.
- STAT5 at 17q11 thought to drive prostate cancer.
- Affects apoptosis

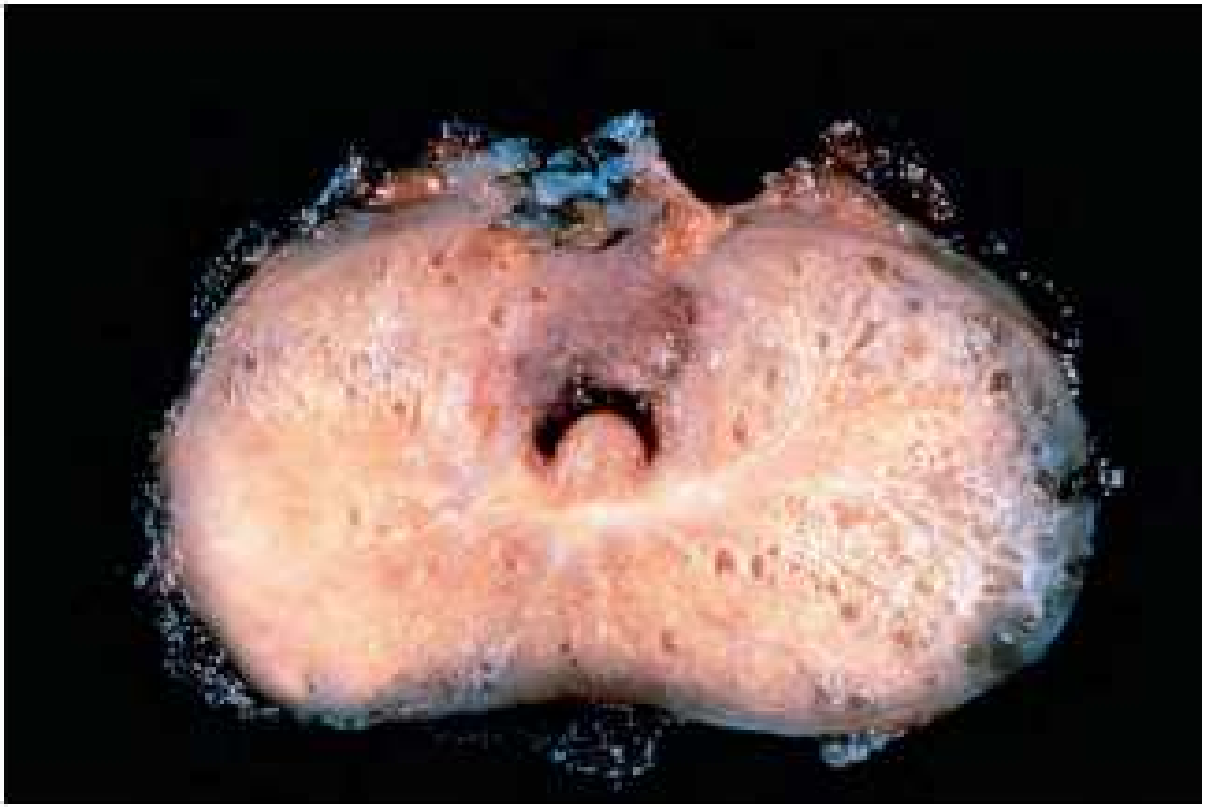


Figure 21-34 Adenocarcinoma of the prostate. Carcinomatous tissue is seen on the posterior aspect *(lower left)*. Note solid whiter tissue of cancer in contrast to spongy appearance of benign peripheral zone in the contralateral side.

Peripheral zone adenocarcinoma

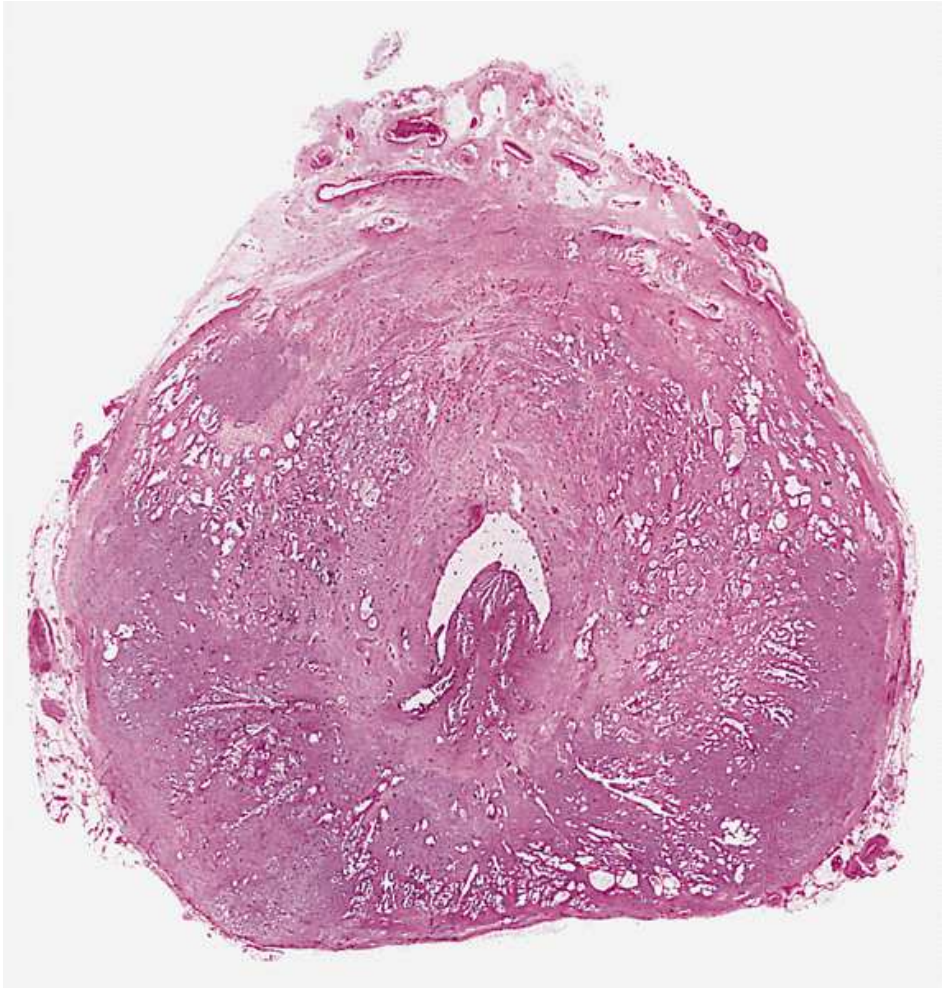


Fig. 4-10R

Young, Robert H., Srigley, John R., Amin, Mahul B., Ulbright, Thomas, M, Cubrilla, Antonio, L. , "Tumors of the prostate gland, seminal vesicles, male urethra, and penis." Atlas of Tumor Pathology. Third series. Fascicle 28. Armed Forces Institute of Pathology. Washington, DC. 2000.

Adenocarcinoma of the prostate

- Histologic findings:
- Small glands lined by a single uniform layer of cuboidal or low columnar epithelium.
- Glands are crowded, and characteristically lack branching and papillary infolding. The outer basal cell layer typical of benign glands is absent.
- The cytoplasm of the tumor cells ranges from pale-clear to a distinctive amphophilic appearance.
- Nuclei are large and often contain one or more large nucleoli.

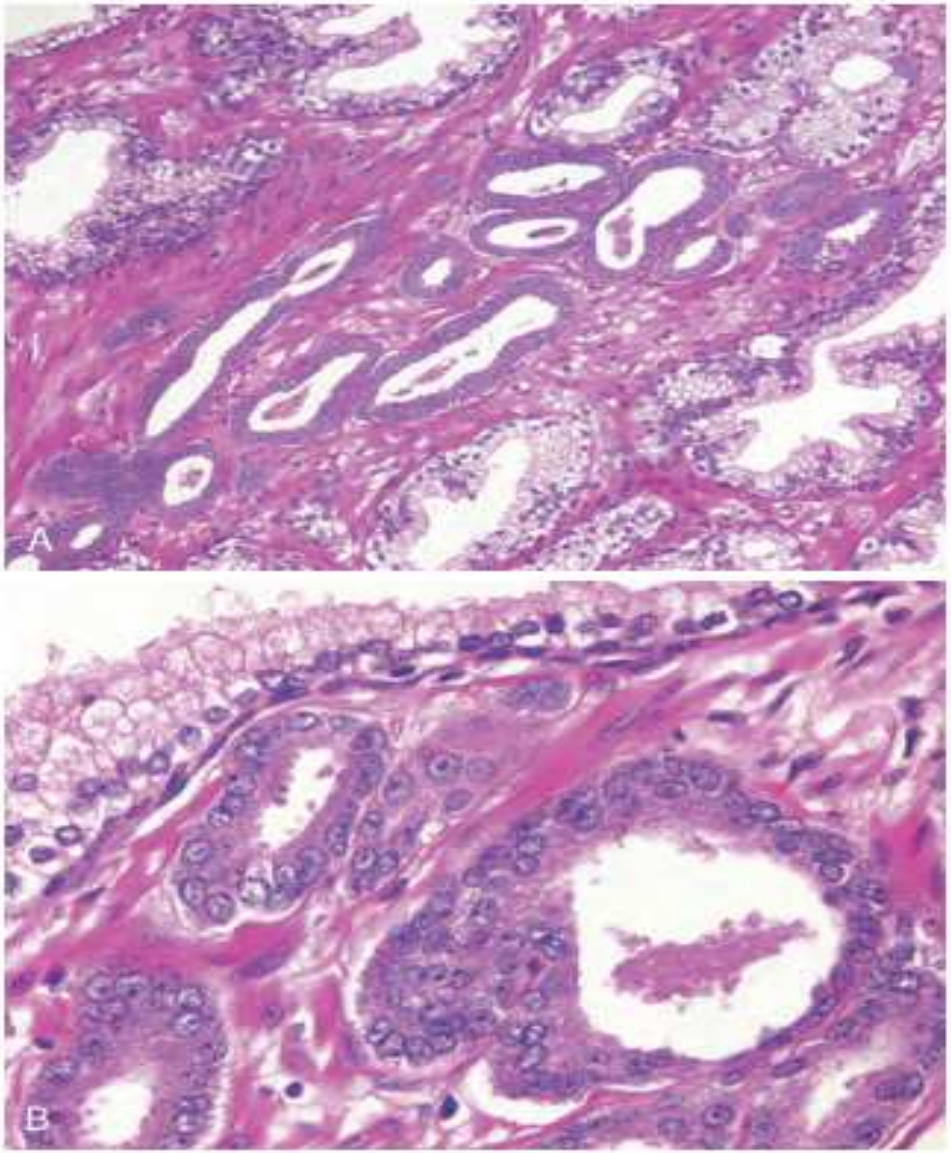


Figure 21-36 **A,** Photomicrograph of small focus of adenocarcinoma of the prostate demonstrating small glands crowded in between larger benign glands. **B,** Higher magnification shows several small malignant glands with enlarged nuclei, prominent nucleoli, and dark cytoplasm, compared with larger benign gland *(top)*.

Adenocarcinoma of the prostate

- Other diagnostic features:
- Perineural invasion
- Glomeruloid formation (protrusion of one gland into another lumen)
- Collagenous micronodules (mucinous fibroplasias)
- May see pale pink secretions, luminal crystalloids, blue luminal mucin and thin intra-luminal collagen fibers

Perineural invasion

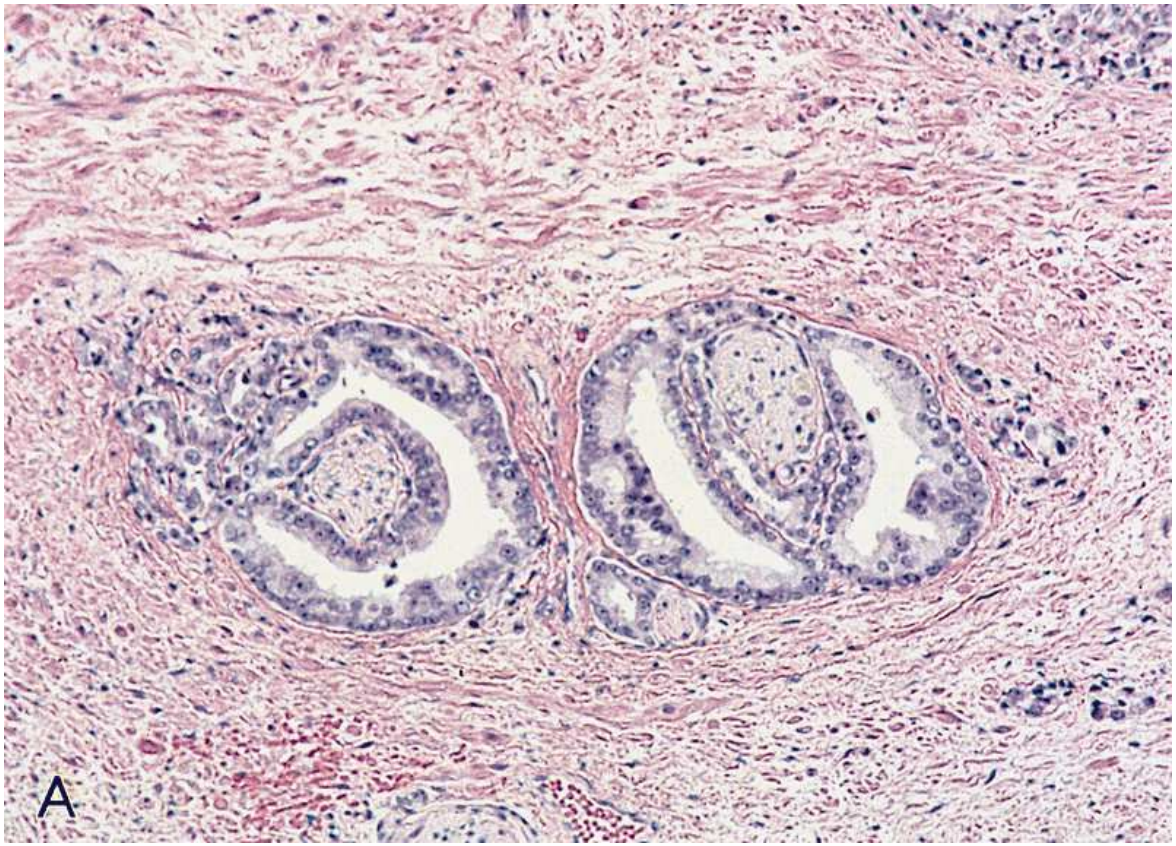


Fig. 4-13A

Young, Robert H., Srigley, John R., Amin, Mahul B., Ulbright, Thomas, M, Cubrilla, Antonio, L. , “Tumors of the prostate gland, seminal vesicles, male urethra, and penis.” Atlas of Tumor Pathology. Third series. Fascicle 28. Armed Forces Institute of Pathology. Washington, DC. 2000.

Regional spread

- Local extension most commonly involves periprostatic tissue, seminal vesicles, and the base of the urinary bladder.
- May produce ureteral obstruction
- Tartrate resistant (prostatic) acid phosphatase elevation compatible with extracapsular extension.
- Metastases spread via lymphatics to the obturator nodes and eventually to the para-aortic nodes.

Metastasis

- Hematogenous spread occurs chiefly to the bones, particularly the axial skeleton
- The bony metastases are typically osteoblastic
- The bones commonly involved, in descending order of frequency, are lumbar spine (via Batson's plexus), proximal femur, pelvis, thoracic spine, and ribs.
- Visceral dissemination is an exception.

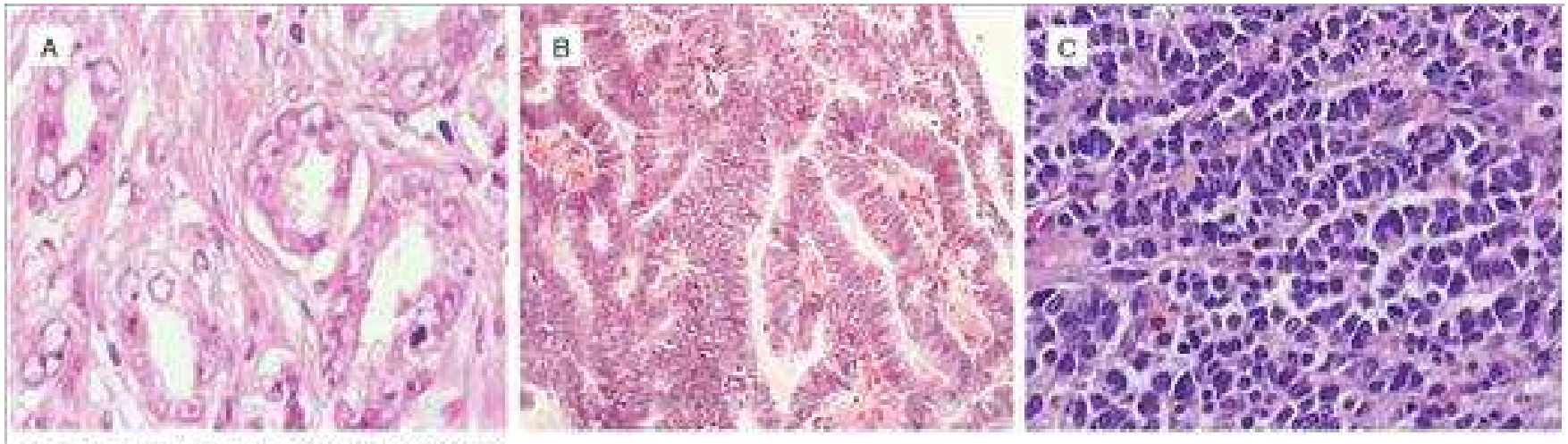
Grading

- The Gleason score is determined only for pure adenocarcinomas.
- The most poorly differentiated element (scale 1-5) is summed with the extent of involvement in tissue (1-5).
- Mucinous carcinoma is considered a Gleason 4 pattern.
- Extent of involvement cannot be determined on a single needle biopsy alone unless three patterns are present.
- A Gleason score >7 is high risk disease.

Grading

- Low-grade prostate cancer consists of back to back, uniformly sized malignant glands.
- Glands contain eosinophilic intraluminal prostatic crystalloids, a feature that is more commonly seen in cancer than in benign glands and more frequently seen in lower grade than in higher grade prostate cancer.
- Variably sized, more widely dispersed glands are noted in moderately differentiated adenocarcinoma.
- Poorly differentiated adenocarcinoma is characterized by sheets of malignant cells.

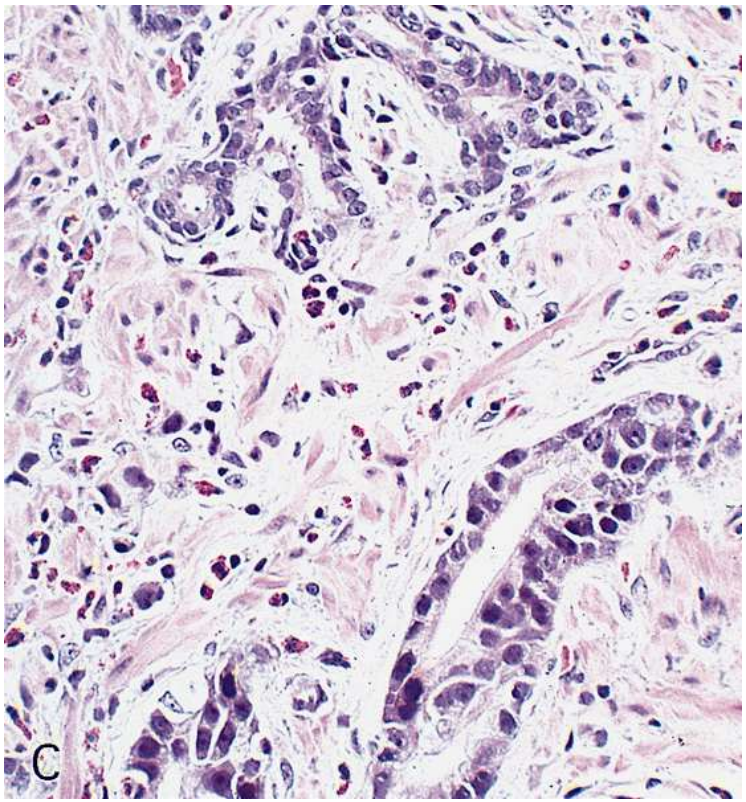
Architecture

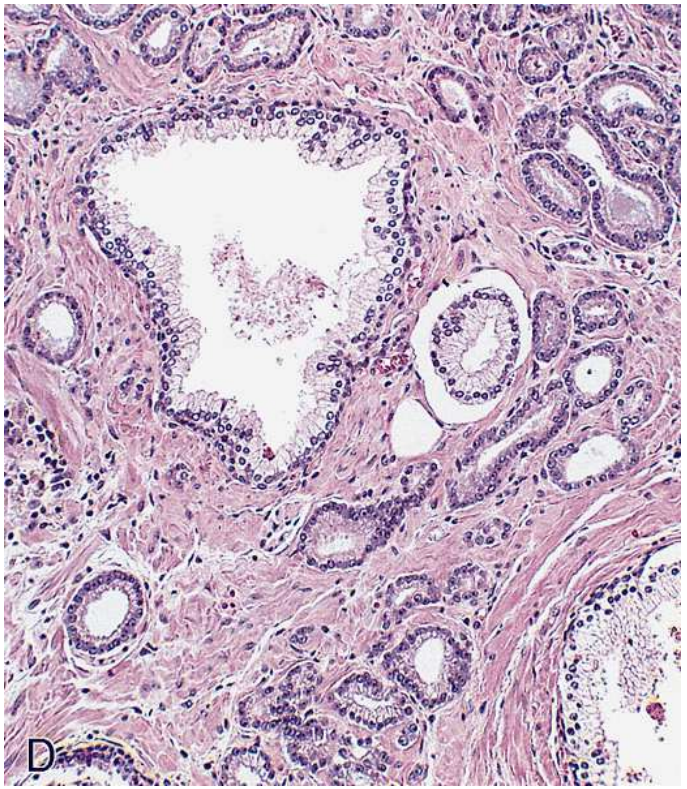


A. Prostate adenocarcinoma. B. Prostate ductal carcinoma. C. Prostate small cell carcinoma.

Fig. 34-2 Accessed 02/04/2016

Adenocarcinoma of prostate (Gleason 3)





Figs. 4-12C and 4-11D

Young, Robert H., Srigley, John R., Amin, Mahul B., Ulbright, Thomas, M, Cubrilla, Antonio, L. , “Tumors of the prostate gland, seminal vesicles, male urethra, and penis.” Atlas of Tumor Pathology. Third series. Fascicle 28. Armed Forces Institute of Pathology. Washington, DC. 2000.

Table 21-6 Staging of Prostatic Adenocarcinoma Using the TNM System

TNM Designation	Anatomic Findings
Extent of Primary Tumor (T)	
T1	Clinically inapparent lesion (by palpation/imaging studies)
T1a	Involvement of ≤ 5% of resected tissue
T1b	Involvement of > 5% of resected tissue
T1c	Carcinoma present on needle biopsy (following elevated PSA)
T2	Palpable or visible cancer confined to prostate
T2a	Involvement of ≤ 5% of one lobe
T2b	Involvement of > 5% 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 nodal metastases
N1	Metastasis in regional lymph nodes
Distant Metastases (M)	
M0	No distant metastases
M1	Distant metastases present
M1a	Metastases to distant lymph nodes
M1b	Bone metastases
M1c	Other distant sites

PSA, Prostate-specific antigen.

Adenocarcinoma of the prostate

- STAT5 at 17q11 thought to drive prostate cancer.
- Affects apoptosis
- Seven molecular subtypes based on distinct oncogenic drivers:
- (1) 46%, fusion of ETS family genes (usually ERG) at 21q22 with androgen-regulated TMPRSS2 promoter gene at 21q22, which lead to their expression in an androgen dependent fashion.
- Both are androgen regulated.
- TMPRSS2 is preferentially expressed in the prostate.

Adenocarcinoma of the prostate

- TMPRSS2 fusion mutations in 20% of Asians, 39.8% of whites, and 25.2% of blacks. The differences are significant.
- ERG mutations found in 29.5% of whites and 15.3% of blacks. The differences are significant.

Adenocarcinoma of the prostate

- (2) 8%, ETV1 (7q22) fusion
- Matrix metalloprotease production increases (invasion).
- (3) 4%, ETV4 (17q22.31) fusion
- Affects signaling in GCPR path, altering signal transduction
- (4) 1%, FTL1 fusion
- (5) 11%, SPOP mutation (ubiquitin ligase)
- Mutually exclusive with ETS fusions

Adenocarcinoma of the prostate

- (6) 3%, FOXA1 mutation
- FOXA1 mutations are found in 40% of Asians and 13.1% of whites. The differences are significant.
- Class 1 mutations enhance the velocity of transcription factor androgen receptor partnering and promote oncogenesis. This is an early driving mutation.
- Class 2 mutations truncate the transcription the factor, enhancing DNA binding. This is noted in hormone resistant cancers. Facilitate metastasis.
- Class 3 mutations drive overexpression of FOXA1 and ETV fusions.

Adenocarcinoma of the prostate

- Class 1 mutations are mutually exclusive with ETS fusions and SPOP mutations.
- Class 2 mutations are co-associated with RB1 alterations.
- (7) 1%, IDH1 mutation
- ETS fusion-negative and SPOP wildtype, have little SCNA burden, and possess elevated levels of genome-wide methylation.
- Younger age at presentation

Adenocarcinoma of the prostate

- Androgen receptor gene mutations are not significantly different between races.
- MYC mutations found in 32.5% of whites, 19% of blacks. The differences are significant.
- ZFHX3 mutations found in 14.3% of Asians, 6.3% of whites, and 3.4% of blacks. The differences of significant. Castration resistant.

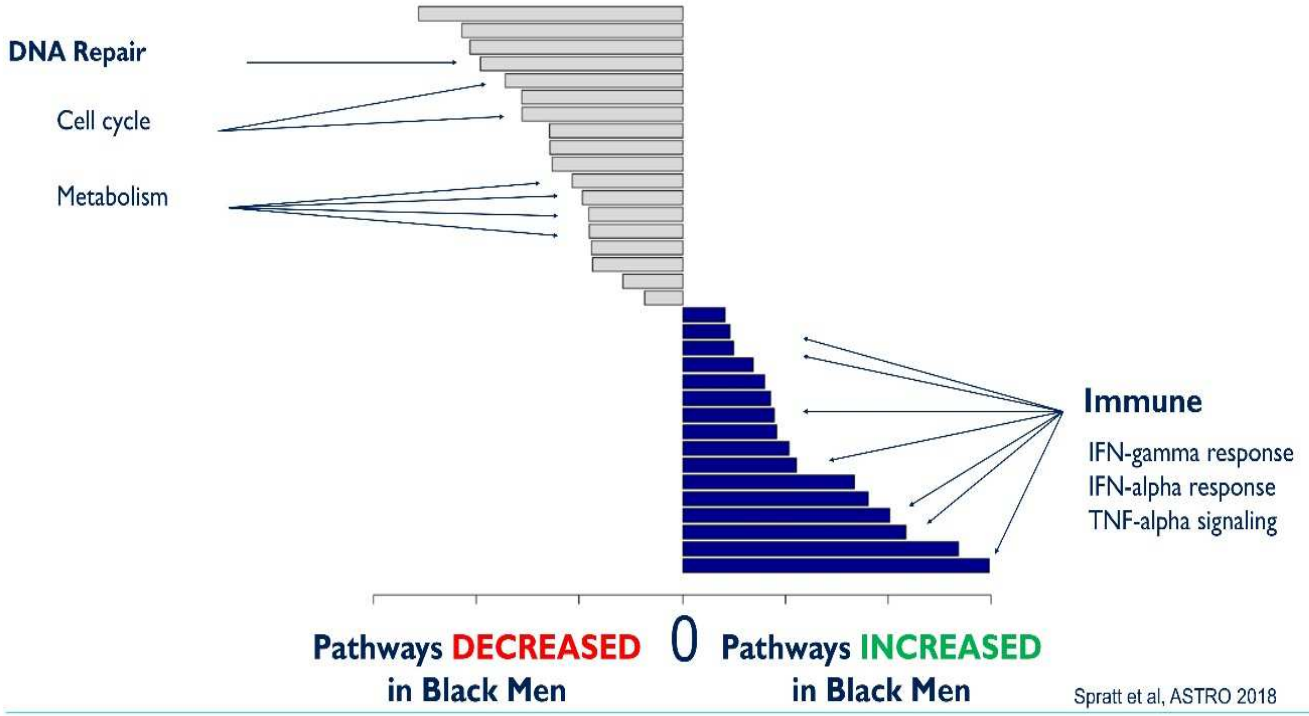
Other molecular changes

- Hypermethylation of glutathione S-transferase (GSTP1) gene (11q13) downregulates its expression.
- E-cadherin is also lost in prostate carcinoma as EZH-2 at 7q36.1 is overexpressed
- Histone methylransferase
- PCA3 at 9q21, encodes a regulatory RNA gene lost in prostate carcinoma.
- Good molecular marker.
- recurrent genomic gains of chromosome 7 and 8q and heterozygous losses of 8p, 13q, 16q and 18

Other molecular changes

- AMACR (5p13-q11), an enzyme involved in the β-oxidation of branched chain amino acids, is elevated in 80% of prostate carcinomas and precursor lesions.
- BRCA2 germline mutations are associated with aggressive prostate cancer.
- Occurs at age <50 years old
- HOXB13 gene at 17q21 mutation affects DNA transcription
- Associated with aggressive prostate cancer

Black Men have Distinct Cancer Hallmark Gene Expression Compared with White Men



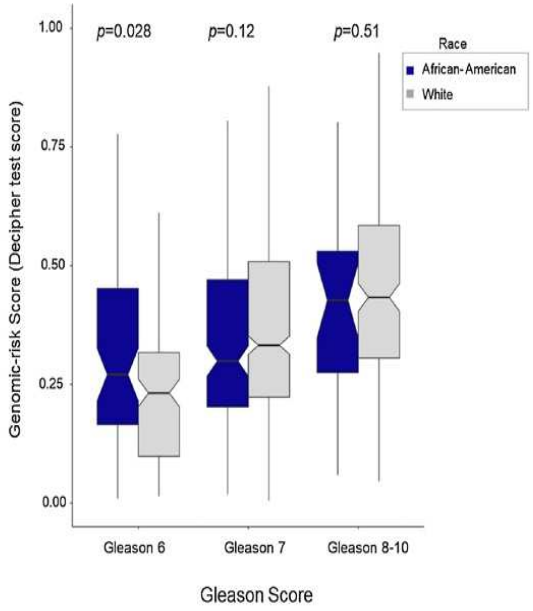
Spratt et al, ASTRO 2018

Genomic Risk Scores Across Race and Gleason Score

1240 men (286 Black men) who underwent surgery.

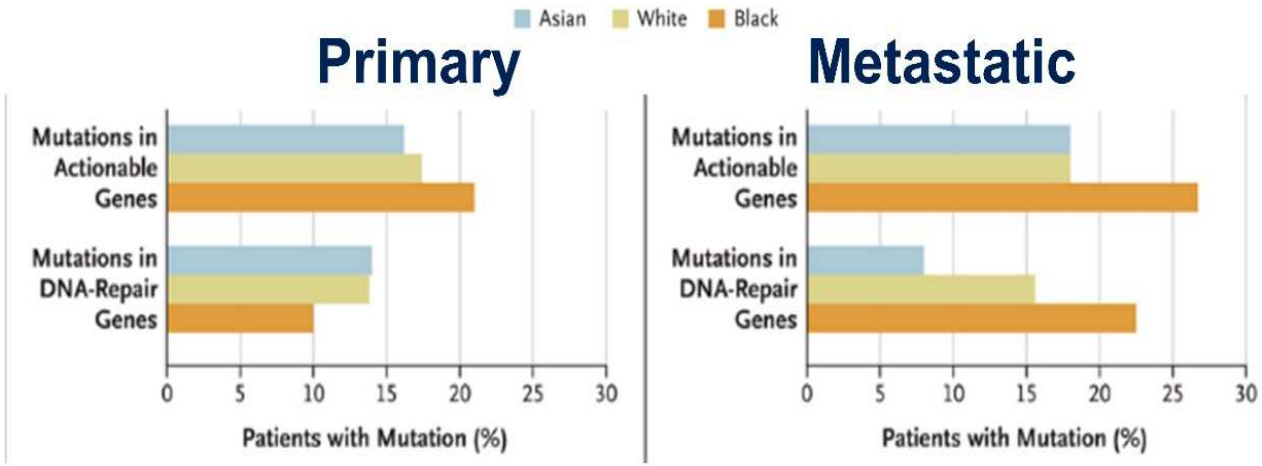
Examined genomic-risk scores that predict for risk of developing metastatic disease. Intermediate to high-risk scores have a 15% risk of metastatic disease at 10 years.

25% of Black men with Gleason 6 disease had intermediate to high-risk genomic risk scores versus 13% of white men.



Mahal et al, Eur Uro 2019

Actionable and DNA Repair Mutations by Race



-***DNA repair genes include:*** *ERCC5, MRE11, TP53BP1, POLE, RAD21, MSH2, MSH6, BRCA1/2, ATR, and ATM*
-***Actional mutations include:*** *ABL1, EGFR, ERBB2, BRAF, BRCA1/2, FGFR2/3, KIT, NTRK1/2/3, PDGFRA, RET, ROS1, ALK, PIK3CA*

Mahal et al, NEJM 2020

Adenocarcinoma of the prostate

- 2% are neuroendocrine carcinoma
- Chromogranin A is an independent activator of androgen receptor
- PSA not elevated.
- Worse prognosis.
- Subtypes are small cell carcinoma, large cell carcinoma, and carcinoid
- Neuroendocrine carcinoma follows androgen deprivation therapy

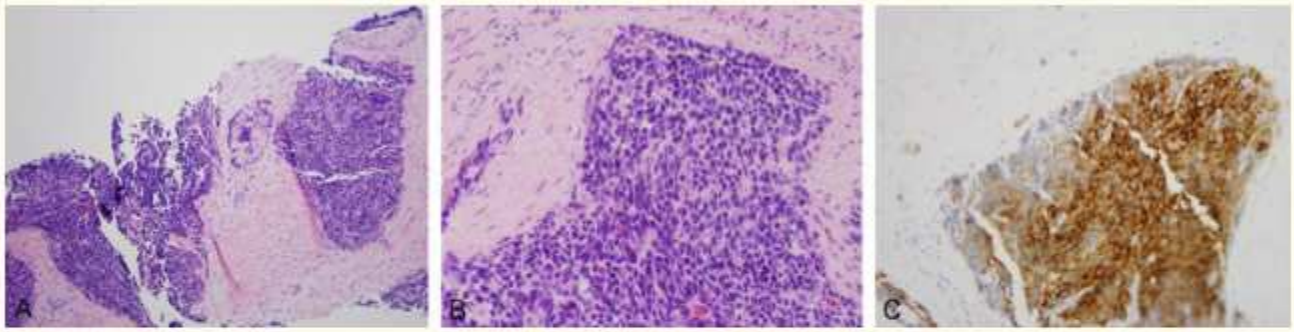


Figure 2

Small cell carcinoma of the prostate seen on a needle core biopsy (A). Similar to pulmonary counterpart, these tumor cells display characteristic "small blue cell" appearance (B), confirmed by neuroendocrine marker synaptophysin (C).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4297323/
Accessed 05/05/2020

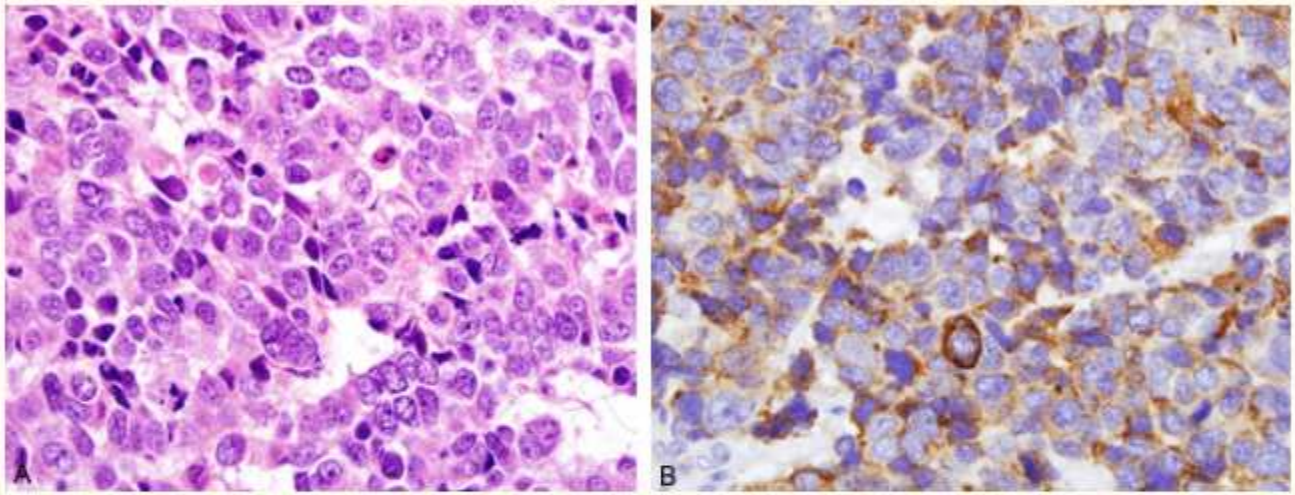


Figure 3

Large cell neuroendocrine carcinoma of the prostate shows typical "salt-and-pepper" chromatin patterns, but the tumor cells are much larger than the ones in small cell carcinoma (A). Neuroendocrine marker such as chromogranin (B) is necessary.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4297323/
Accessed 05/05/2020

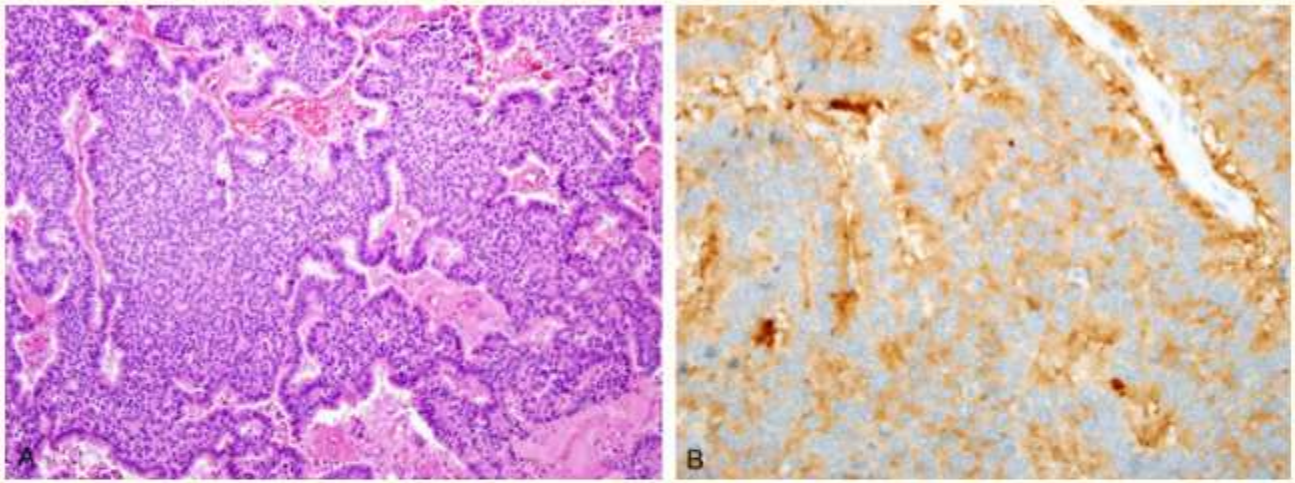


Figure 4

Carcinoid tumor of the prostate is rare, and can be either primary or secondary to a metastasis from the gastrointestinal tract. Carcinoid tumor (A) is characteristized by large islands of cells with low nuclear grade and salt and pepper chromatin. Neuroendocrine markers such as synaptophysin (B) are positive although these immunomarkers are not usually needed to confirm the diagnosis given its classic morphologic features.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4297323/
Accessed 05/05/2020

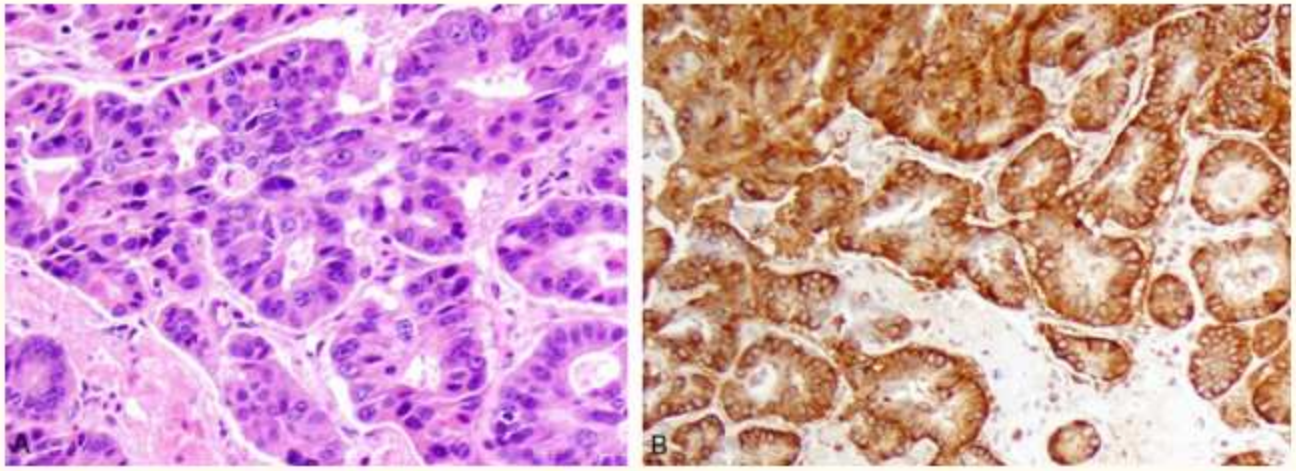


Figure 5

Prostatic adenocarcinoma with neuroendocrine differentiation on H&E (A) which is confirmed by strong positive staining for chromogranin (B).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4297323/
Accessed 05/05/2020

Therapy of prostate cancer

- Active surveillance is the only recommendation for men with low-risk cancer and life expectancy <10 years and with very-low-risk cancer and life expectancy < 20 years.
- Long-term results for radical prostatectomy, external beam radiation therapy, or brachytherapy are equivalent in T1-3 N0 MO low-risk disease.
- Incontinence and impotence common with prostatectomy and with radiation therapy.
- Fewer problems with brachytherapy.

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE[e]

Risk Group	Clinical/Pathologic Features See Staging (ST-1)			Additional Evaluation[h,i]	Initial Therapy
Very low[f]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] • PSA density <0.15 ng/mL/g			• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See PROS-3
Low[f]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL			• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See PROS-4
Intermediate[f]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[g]	• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[g]	Bone and soft tissue imaging[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-6
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			Bone and soft tissue imaging[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			Bone and soft tissue imaging[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7

Therapy of prostate cancer

- Radical prostatectomy in locally advanced disease.
- No significant improvement in biochemical event-free survival for patients receiving adjuvant radiotherapy compared with early salvage radiotherapy (PSA rising).
- Hormonal therapy with radiation therapy is a standard of care for patients with high-risk localized prostate cancer

Therapy of prostate cancer

- Androgen deprivation therapy for 24 months follows.
- Rising PSA following radiation may respond to intermittent androgen blockade.
- If surgical option chosen, usually not offered to those with T3/T4 disease.
- Lymph node dissection only in high risk disease.

Therapy of prostate cancer

- Neurovascular bundle sparing in a radical prostatectomy is lobe specific.
- It is not employed if there is perineural invasion or if a low grade tumor comprises more than 50% of the volume of the lobe (30% if high grade) as positive margins may remain.
- The use of a cautery is associated with nerve damage.

Therapy of prostate cancer

- Intrafascial dissection more likely to preserve sexual potency than is an extra-fascial or wider dissection (64% vs. 40% at 1 year).
- Reconstruction of the posterior musculofascial plate prior to the anastamosis of the bladder to the urethra maintains continence (56% vs. 17% at 6 weeks).

Therapy of prostate cancer

- Enzlutamide or apalutamide (androgen inhibitor at testosterone receptor) or darolutamide is employed with LHRH agonist in treatment of advanced cancer (castration sensitive).
- Serum testosterone maintained <50 ng/dL
- Apalutamide increases cardiovascular risk.
- CYP2C8 and CYP3A4 inhibitors
- PSA Doubling Time <10/months is high risk disease.
- If PSA increasing, is metastatic disease. May not be noted with conventional imaging, but with PMSA PET scan.

Therapy of prostate cancer

- Androgen pathway remains active in castration resistant prostate cancer.
- However, hormone manipulation not effective as PI3K/AKT pathway active.
- Castration resistant prostate cancer may be treated effectively with enzalutamide, or apalutamide, or darolutamide, and an androgen receptor blocker, or abiraterone acetate, a CYP17 blocker, if no evidence of visceral metastases, avoiding the need for chemotherapy until failure.
- Docetaxel is only chemotherapy agent effective.
- Pembromizulab if dMMR or MSI-H identified.

Therapy of prostate cancer

- Cabozantinib (tyrosine kinase inhibitor) inhibits MET, VEGFR2, RET, and KIT. Slows tumor growth and is associated with elimination of bone metastases Employed if docetaxel failure..
- Mutations in BRCA1/2 sensitize cells to PARP inhibition
- If docetaxel failure, Olaparib or Rucaparib, PARP inhibitors

- LHRH agonists or receptor blockers associated with accelerated bone loss, increased incidence of cardiovascular events; offer marginal benefit

Therapy of prostate cancer

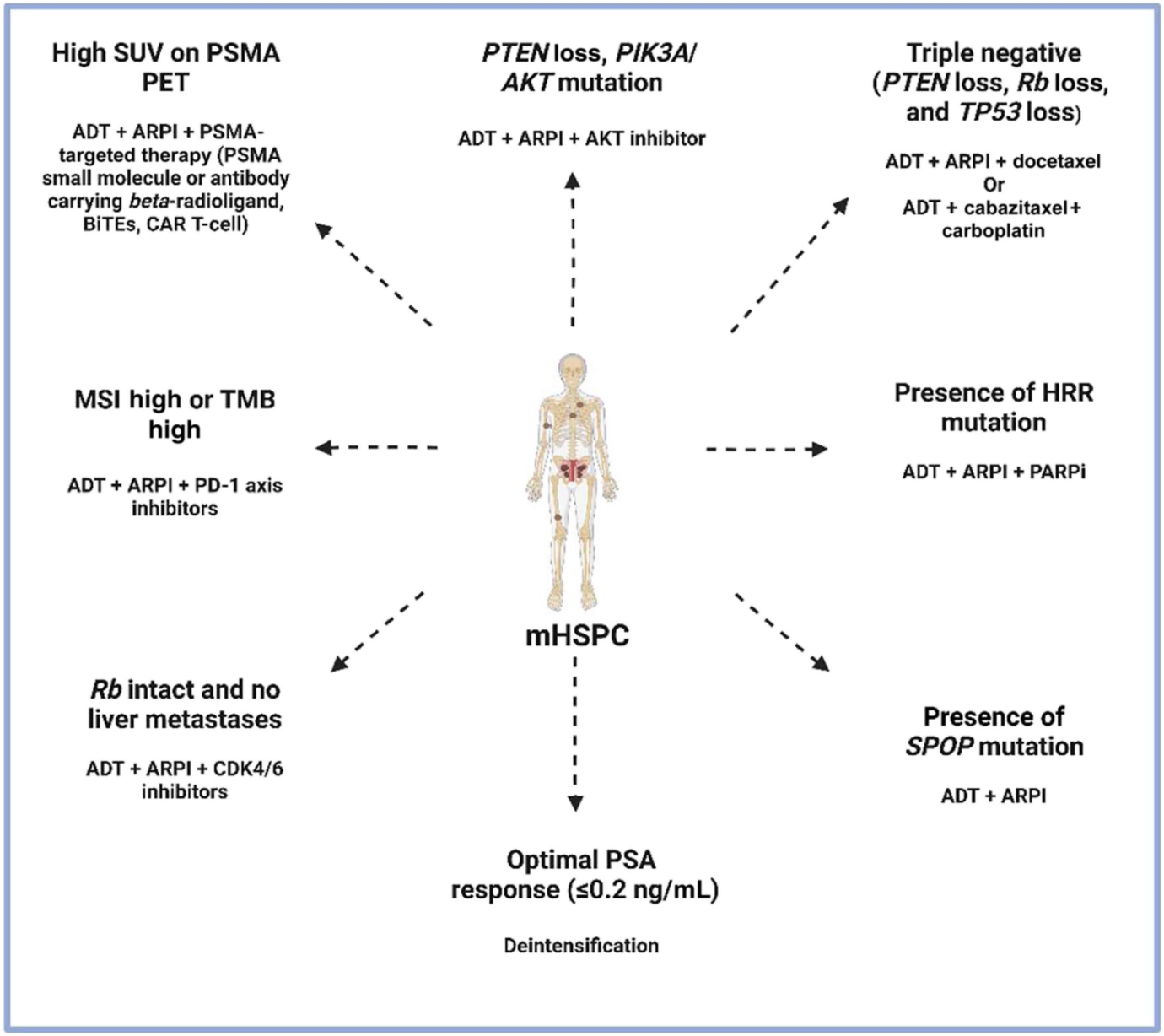
- Small-cell neuroendocrine prostate cancer (t-SCNC), which arises in the castration-resistant setting after the application of AR-targeted therapy is treated with a platinum/taxane or platinum/etoposide regimen.

Therapy of prostate cancer

- 20-25% of castration resistant disease have abnormalities in DNA repair genes
- Carboplatin
- 5-7% of those with metastatic disease have MSI-H/dMMR mutation
- 20% of those have Lynch syndrome
- Pembrolizumab (Checkpoint inhibitor)

Therapy of prostate cancer

- 10% have germline mutations
- 20% if metastatic disease
- 12% have hereditary breast and ovarian cancer
- BRA2 (44%), ATM (13.5%), CHEK2 (11%), BRCA1 (7%)
- Test patients if regional disease or metastases, family history, or cribiform or intraductal pattern


High SUV on PSMA PET
ADT + ARPI + PSMA-targeted therapy (PSMA small molecule or antibody carrying *beta*-radioligand, BiTEs, CAR T-cell)
PTEN loss, *PIK3A/AKT* mutation
ADT + ARPI + AKT inhibitor
Triple negative (*PTEN* loss, *Rb* loss, and *TP53* loss)
ADT + ARPI + docetaxel
Or
ADT + cabazitaxel + carboplatin
MSI high or TMB high
ADT + ARPI + PD-1 axis inhibitors
Presence of HRR mutation
ADT + ARPI + PARPi
mHSPC
Rb intact and no liver metastases
ADT + ARPI + CDK4/6 inhibitors
Presence of *SPOP* mutation
ADT + ARPI
Optimal PSA response (≤0.2 ng/mL)
Deintensification

Therapy of prostate cancer

- Biphosphonates slow metastasis to bone.
- 1-5% of those treated with bisphosphonates or denosumab may develop osteonecrosis of the jaw
- Presents with mouth ulcer, bleeding, and tooth mobility.
- Both docetaxel and zoledronic acid employed in castration resistant prostate cancer.

Therapy of prostate cancer

- Radiation to painful bone metastases offers effective palliation (two vertebral bodies above and below involved body).
- Spinal cord compression is an emergency.
- Begin dexamethasone, then radiotherapy. As spinal cord tolerates up to 50Gy radiation, initial treatment with 30 Gy permits retreatment if needed.

Therapy of prostate cancer

- 89-Strontium (a Calcium analog) can be administered systemically for palliation.
- 15% show pronounced tumor flare;
- 25%, thrombocytopenia.
- Strontium may be repeated.

Therapy of prostate cancer

- Radiation to painful bone metastases offers effective palliation (two vertebral bodies above and below involved body).
- Spinal cord compression is an emergency.
- Begin dexamethasone, then radiotherapy.
- As spinal cord tolerates up to 50Gy radiation, initial treatment with 30 Gy permits retreatment if needed.

Therapy of prostate cancer

- ^{89}Strontium (Sr, a Ca^{2+} analog) can be administered systemically for palliation.
- β-emitter with 50 day half-life
- 15% show pronounced tumor flare;
- 25%, thrombocytopenia.
- Sr may be repeated.
- Does not affect survival
- ^{223}Radium prolongs survival
- α particle emitter

TESTES

Cryptorchidism

- Complete or partial failure of intra-abdominal testis to descend into the scrotal sac
- 1% of 1-year-old boys
- Usually isolated anomaly
- May be associated with hypospadias
- May be associated with prune belly syndrome
- May be associated with omphalocele
- Usually indirect inguinal hernia is present
- Tunica vaginalis does not develop appropriately
- Increased risk of testicular cancer
- 60% of tumors are seminoma

Cryptorchidism

- Most common congenital disorder identified at birth
- 35% undescended
- 60% retractile (retract easily out of scrotum)
- 3% ectopic
- Spontaneous descent may occur later in premature infants
- Orchipexy by 1-year-of age to avoid defective maturation of testis
- Else, arrested germ cell development associated with marked hyalinization and thickening of the basement membrane of the spermatic tubules.
- Leydig cells are spared.

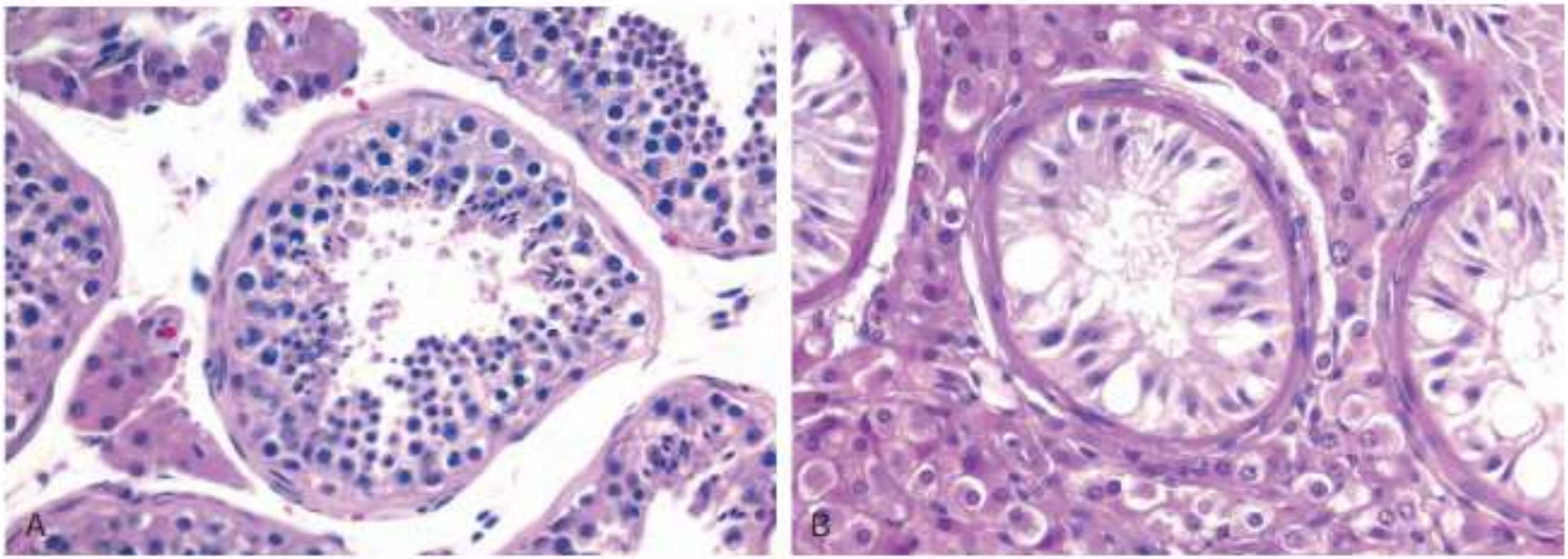


Figure 21-20 **A,** Normal testis shows tubules with active spermatogenesis. **B,** Testicular atrophy in cryptorchidism. The tubules show Sertoli cells but no spermatogenesis. There is thickening of basement membranes and an apparent increase in interstitial Leydig cells.

Table 43-1 Evaluation of Bilateral Nonpalpable Cryptorchidism

	Cryptorchidism	Anorchidism	Female Pseudohermaphroditism
Karyotype	46,XY	46,XY	46,XX
Serum testosterone			
Baseline	Normal	Low	Variable
hCG stimulation test	Positive	Negative	Negative
Gonadotropins	Normal	Increased	Normal
AMH/MIS	Positive	Negative	Negative
Adrenal steroid precursors	Normal	Normal	Increased
Ultrasonography			
Gonads	Testes or negative	Negative	Ovaries or negative
Internal ducts	Negative	Negative	Uterus/müllerian system
Genitogram	Male urethra	Male urethra	Urogenital sinus and/or müllerian structures
Laparoscopy			
Gonads	Testes	Blind-ending vessels	Ovaries
Internal ducts	Wolffian	Wolffian	Müllerian

AMH/MIS, anti-müllerian hormone/müllerian inhibiting substance; hCG, human chorionic gonadotropin.

Testicular descent

- Occurs in two morphologically and hormonally distinct phases.
- During the first phase (transabdominal), the testis comes to lie at the brim of the pelvis.
- This phase is dependent upon ISL3 (insulin like substance 3) secreted from fetal Leydig cells, and is controlled by MIS (Müllerian-inhibiting substance) which inhibits Wolffian duct development.
- MIS is secreted in an exocrine manner down the Wolffian duct and triggers its development into epididymis and vas deferens, as well as formation of a distal bud to become the seminal vesicle

Testicular descent

- In the second phase (inguinoscrotal), the testes descend through the inguinal canal into the scrotal sac.
- This phase is androgen-dependent and is possibly mediated by androgen-induced release of CRGP (calcitonin generated peptide), a potent vasodilator, from the genitofemoral nerve.
- CRGP involved in development of migraine, from trigeminal nerve

Testicular atrophy

- Causes:
- Progressive atherosclerotic narrowing of the blood supply in old age
- The end stage of an inflammatory orchitis
- Cryptorchidism
- Hypopituitarism
- Generalized malnutrition or cachexia
- Irradiation
- Prolonged administration of anti-androgens
- Exhaustion atrophy, which may follow persistent stimulation by high levels of follicle-stimulating pituitary hormone.

Tunica vaginalis

- Mesothelial lined surface exterior to testis
- Hydrocele is a collection of serous fluid between testis and scrotal sac.
- Transilluminates
- Hematocele contains blood.
- Usually follows torsion or trauma
- Chylocele contains lymph
- Elephantiasis
- Spermatocele refers to cystic collection of semen in dilated efferent ducts or rete testis
- Varicocele is dilated vein in the spermatic cord
- Implicated in male infertility

Epidydimitis

- Acute epidydimitis in those under 35 years of age is usually caused by Neisseria gonorrheae or Chlamydia trachomatis.
- Acute epidydimitis in those over 35 years of age is usually E. Coli or Pseudomonas.
- Initially limited to the interstitial connective tissue.
- Rapidly extends to involve the tubules and may progress to abscess formation and extend into testis.
- Fibrous scarring leads to sterility.
- The Leydig cells are not totally destroyed
- Mumps orchitis is generally post-pubertal.
- 20% of cases

Epidydimitis

- Chronic epidydimitis is usually M. tuberculosis. Infection.
- However, there is a granulomatous epidydimitis that is of autoimmune origin.
- The morphologic pattern of congenital as well as acquired syphilis the reaction takes two forms:
- (1) the production of gummas, or
- (2) a diffuse interstitial inflammation that produces an obliterative endarteritis associated with perivascular cuffs of lymphocytes and plasma cells (pathognomonic).

Torsion

- Increased risk due to anatomic abnormality between spermatic cord and vessels (shortened gubernaculum in those with undescended testes)
- Sudden onset of testicular pain
- Marked venous congestion leads to swelling of the testis and the scrotal sac.
- In contrast to neonatal torsion, adult torsion results from a bilateral anatomic defect that leads to increased mobility of the testes (bell-clapper abnormality).
- If the testis is manually untwisted within approximately 6 hours of the onset of torsion, there is a good chance that the testis will remain viable.

Testicular cancer

- Presents as testicular mass.
- 1% all malignancies in men
- 95% are germ cell tumors.
- Undescended (cryptorchid) testes are risk factor.
- Intra-abdominal testes at higher risk than are inguinal testes.
- Contralateral normally descended testis also at higher risk.
- Testicular cancer in contralateral testis a risk factor.
- HIV also risk factor
- Klinefelter syndrome (XXY)
- Develop mediastinal, not testicular germ cell tumor

Testicular tumors

- Testicular germ cell tumors are associated with a spectrum of disorders collectively known as testicular dysgenesis syndrome (TDS).
- Components of this syndrome include cryptorchidism, hypospadias, and poor sperm quality.
- It has been proposed that these conditions are increased by in utero exposures to pesticides and nonsteroidal estrogens.
- Germ cell tumors originate from a precursor lesion called intratubular germ cell neoplasia (now, GCNIS).
- The precursors of yolk sac tumor, teratoma, or spermatocytic seminoma is not known.

Testicular tumors

- ITGCN is believed to arise in utero and stay dormant until puberty, after which it may progress to seminoma or nonseminomatous tumors.
- The lesion consists of atypical primordial germ cells with large nuclei and clear cytoplasm
- These cells retain the expression of the transcription factors OCT3/4 and NANOG, which are important in maintenance of pluripotent stem cells.
- i(12p) and c-kit mutations
- 50% of individuals with ITGCN develop invasive germ cell tumors within five years after diagnosis

In the 15- to 34-year age group, testicular germ cell tumors constitute the most common tumor of men

prepubertal

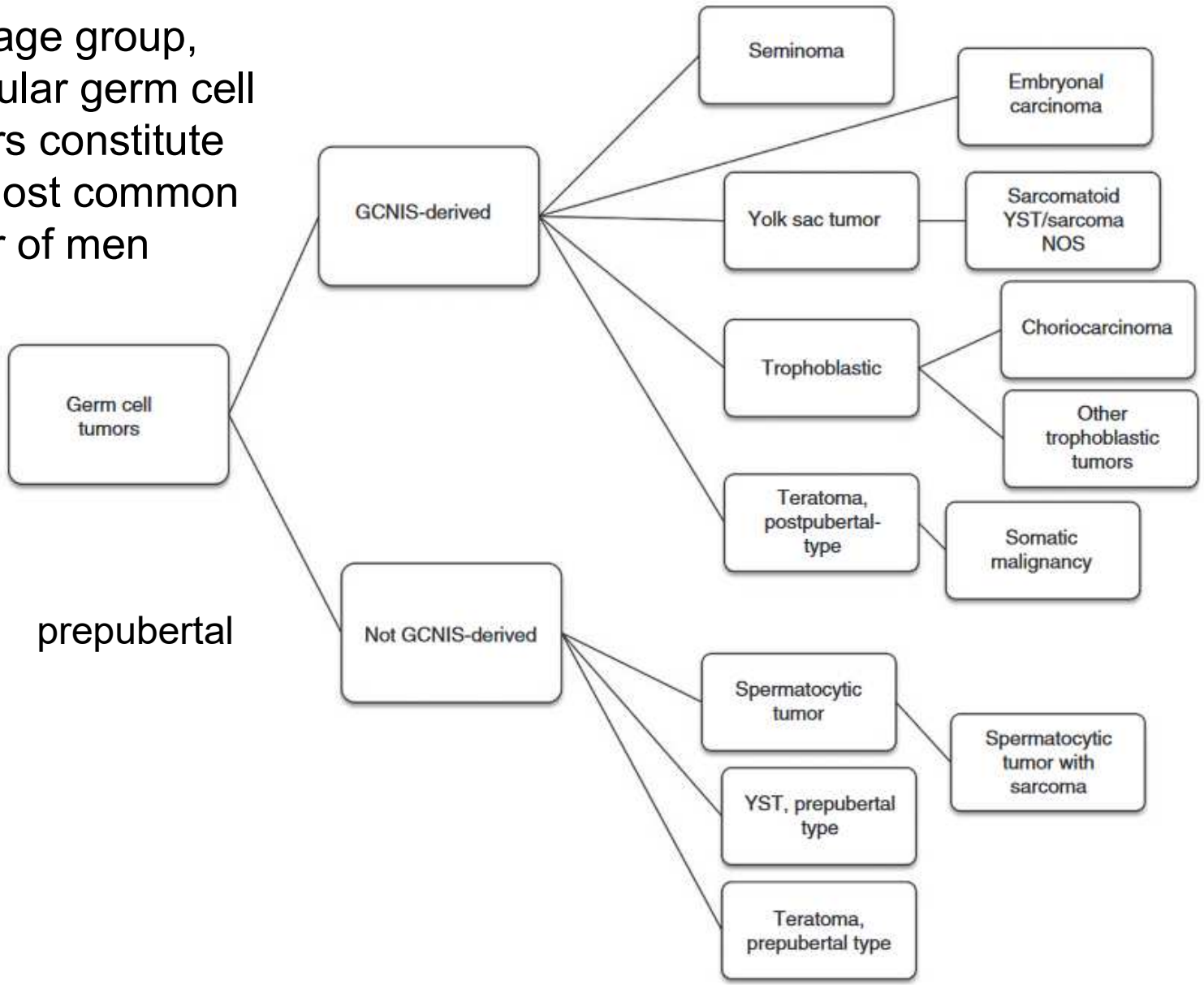


Figure 2. In the 2016 edition of the World Health Organization classification, germ cell tumour classification is restructured into tumours derived from germ cell neoplasia *in situ* (GCNIS) and those not derived from GCNIS. NOS, not otherwise specified; YST, yolk sac tumour.

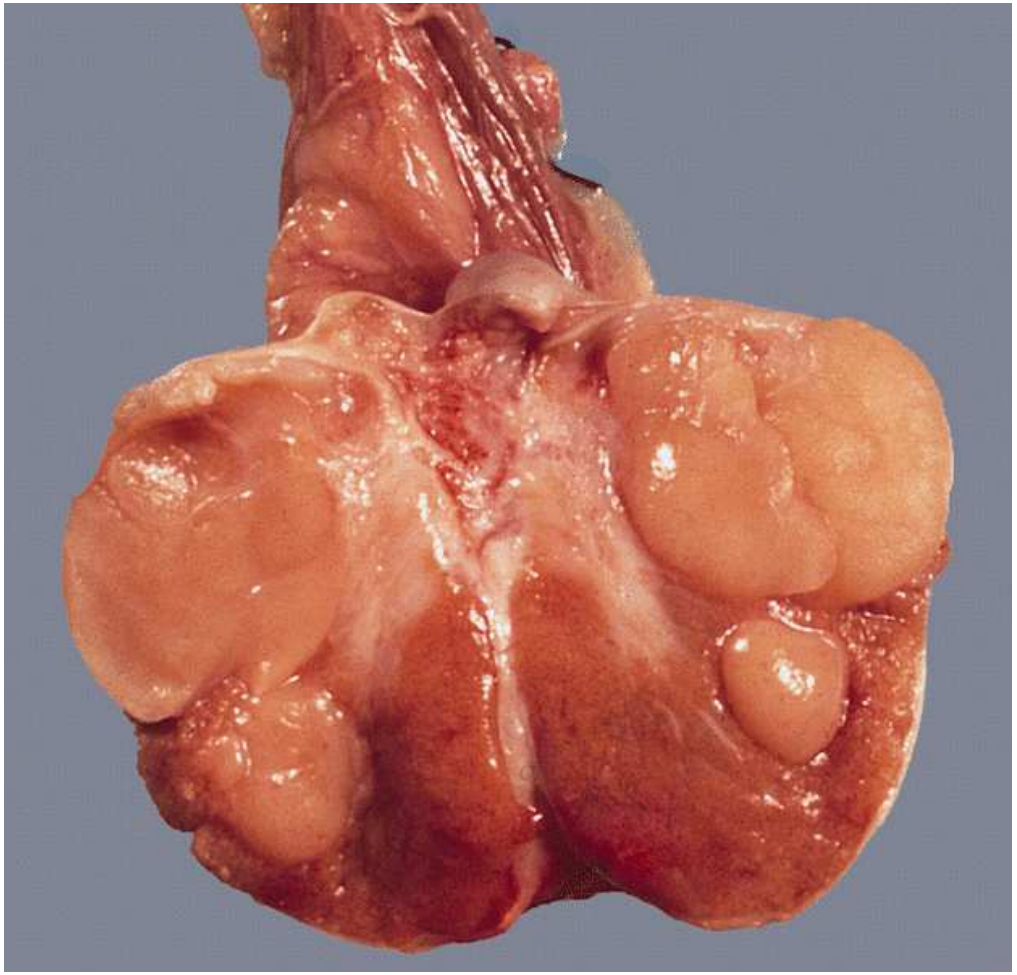
Seminoma

- 50% of germ cell tumors
- Peak in third decade
- Never seen in infants
- The typical seminoma has a homogeneous, graywhite, lobulated cut surface, usually devoid of hemorrhage or necrosis
- Generally the tunica albuginea is not penetrated
- Contain i(12p), OCT3/4, NANOG
- 25% have c-kit mutations

Seminoma

- Sheets of uniform cells divided into poorly demarcated lobules by delicate fibrous septa containing a lymphocytic infiltrate.
- The cell is large, round to polyhedral, and has a distinct cell membrane; clear or watery-appearing cytoplasm; and a large, central nucleus with one or two prominent nucleoli
- Mitoses vary in frequency.
- Anaplastic elements of no prognostic value
- 15% of seminomas contain syncytiotrophoblasts but lack the mononuclear trophoblastic component of choriocarcinoma.

Seminoma of testis



The typical seminoma has a homogeneous, graywhite, lobulated cut surface, usually devoid of hemorrhage or necrosis. Generally the tunica albuginea is not penetrated, but occasionally extension to the epididymis, spermatic cord, or scrotal sac occurs

Fig. 3-1

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Seminoma of testis

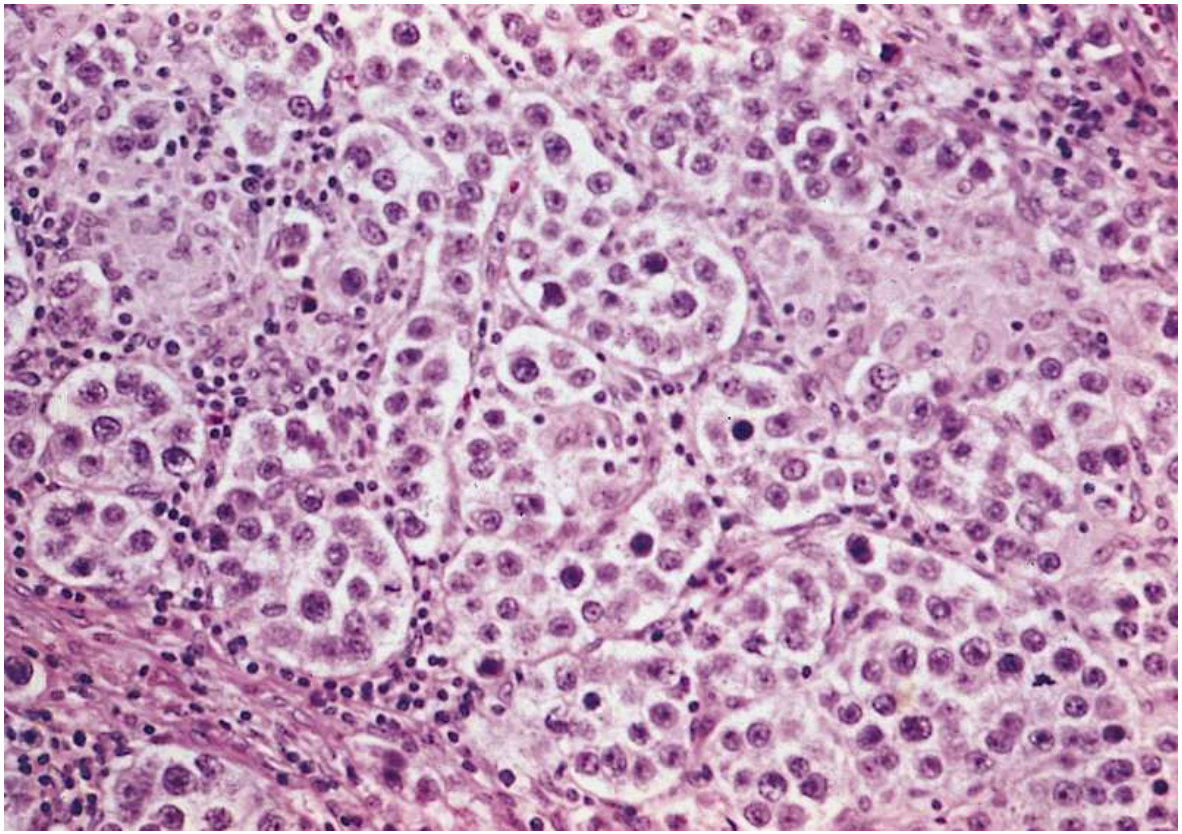


Fig. 3-07
T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Sheets
of uniform cells divided into poorly demarcated lobules by delicate fibrous septa containing a lymphocytic infiltrate The classic seminoma cell is large and round to
polyhedral and has a distinct cell membrane; clear or
watery-appearing cytoplasm; and a large, central nucleus with one or two prominent nucleoli (“fried egg” appearance)

Spermatocytic seminoma

- Spermatocytic seminoma
- 1-2% germ cell tumors
- Generally presents in those over 65 years of age.
- Do not have their origin as an intratubular germ cell neoplasm.
- Rarely metastasize.

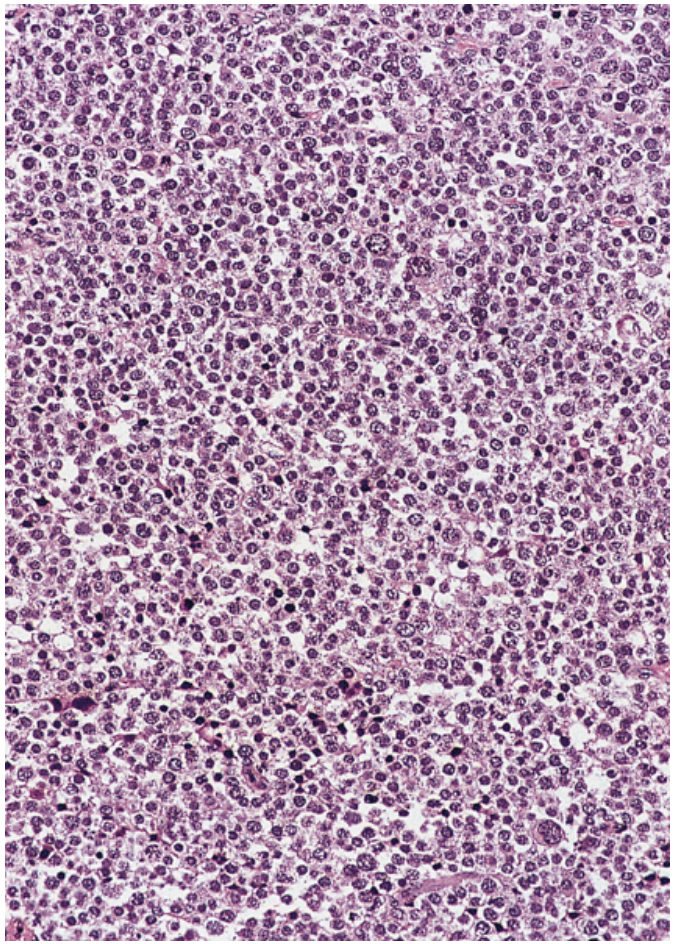
Spermatocytic tumor

- Contain three cell populations, all intermixed:
- (1) medium-sized cells containing a round nucleus and eosinophilic cytoplasm (resemble spermatocytes);
- (2) smaller cells with a narrow rim of eosinophilic cytoplasm resembling secondary spermatocytes;
- (3) scattered giant cells, either uninucleate or multinucleate.
- The chromatin in some intermediate-sized cells is similar to that seen in the meiotic phase of non-neoplastic spermatocytes (spireme chromatin).

Spermatocytic tumor

- There is a lack of lymphocytic infiltrate microscopically.
- Syncytiotrophoblasts or granulomas are not found.
- OCT 3/4 negative
- i(12p) negative
- May dedifferentiate into sarcoma

Spermatocytic tumor



Spermatocytic tumors contain three cell populations, all intermixed: (1) medium-sized cells, the most numerous, containing a round nucleus and eosinophilic cytoplasm; (2) smaller cells with a narrow rim of eosinophilic cytoplasm resembling secondary spermatocytes; and (3) scattered giant cells

Fig. 3-42

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Embryonal carcinoma

- Most common in third decade.
- Extension through the tunica occurs frequently.
- Tumor cells grow in alveolar or tubular patterns, at times with papillary convolutions.
- More undifferentiated lesions may display sheets of cells.
- Neoplastic cells are large, anaplastic, have hyperchromatic nuceli and prominent nucleoli. Cell borders are indistinct.
- Mitoses are common as are giant tumor cells.
- Show cytokeratin and CD30.
- Are negative for c-kit.

Embryonal carcinoma

- Cells grow in alveolar or tubular patterns, sometimes with papillary convolutions.
- Solid sheets and nests of cells, often with central necrosis, gland-like spaces, and papillae composed of or lined by large primitive cells or atypical forms, are usually numerous.
- Syncytiotrophoblast giant cells are generally found.
- OCT 3/4 and PLAP positive, but differs from seminoma by being positive for cytokeratin and CD30, and negative for KIT.

Embryonal carcinoma

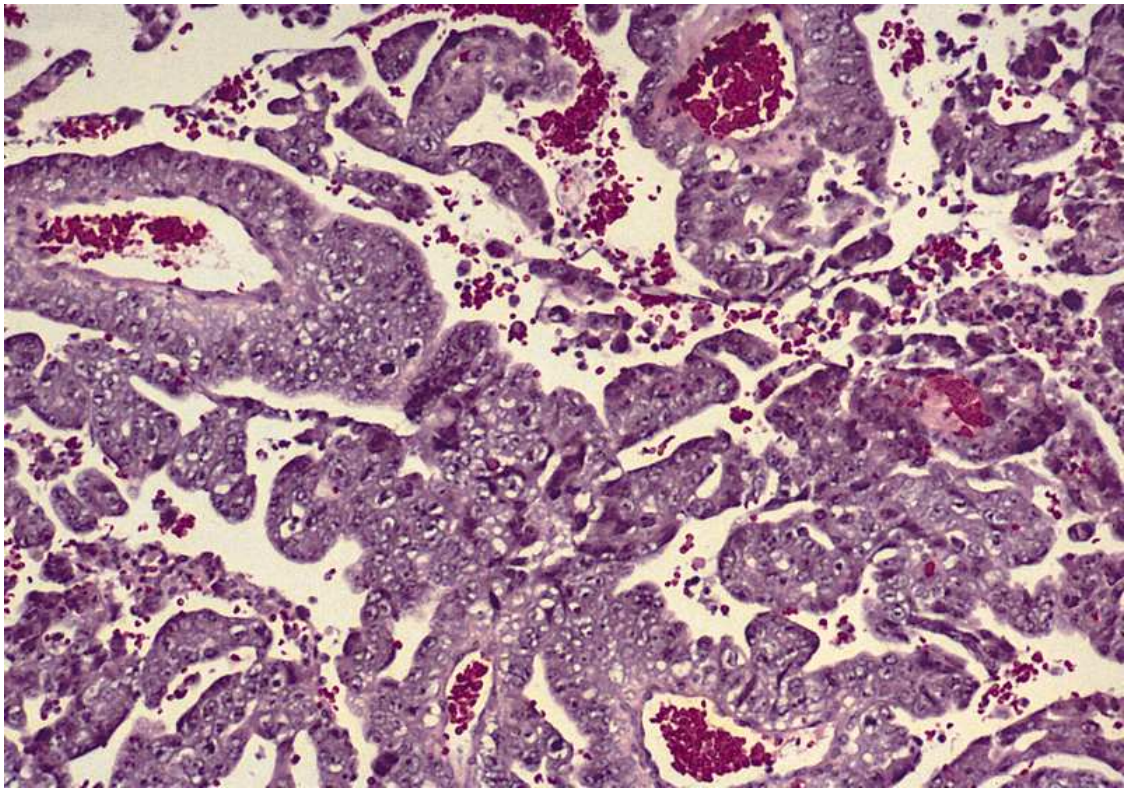


Fig. 13-32

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

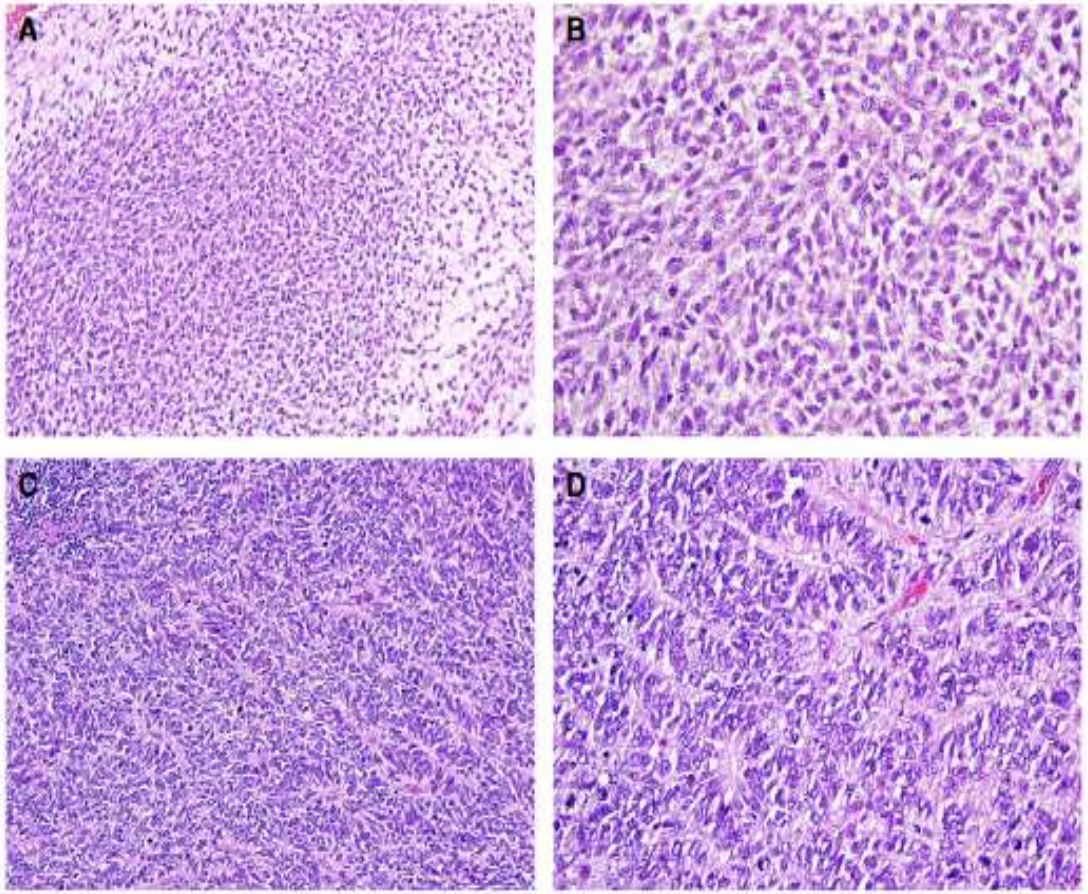


Figure 5. Secondary, somatic-type malignancy arising from germ cell tumour may assume various histologies. Sarcomas are common, including embryonal rhabdomyosarcoma (**A,B**), here forming a primitive small-cell neoplasm with spindle-shaped cells and brisk mitotic activity. Immunohistochemical staining in this case demonstrated patchy positivity for myogenin (not shown), supporting an embryonal rhabdomyosarcoma phenotype. Another common form of secondary somatic-type malignancy is primitive neuroectodermal tumour (**C,D**), here forming rosettes.

Other testicular tumors

- Pure choriocarcinoma is uncommon.
- Often small tumors.
- HCG production is marked.
- Teratomas are generally large.
- In the post-pubertal male, all teratomas are regarded as malignant.
- The presence of immature elements, principally neural tissue, is a sign of malignant potential.
- Testicular tumors may present with differing morphologic patterns at metastatic sites.
- Lymphatic spread is first to para-aortic nodes.
- Hematogenous spread is principally to lungs.

Choriocarcinoma

- 1% of all germ cell tumors
- Biphasic growth pattern of syncytiotrophopblasts (large cells with abundant eosinophilic cytoplasm containing HCG) and cytotrophoblasts (polygonal, with distinct borders and clear cytoplasm)
- Cytotrophoblasts grow in cords or masses and have a single, fairly uniform nucleus
- p63 positive; HPL negative staining
- Elements may be present in other tumors; poor prognosis

Choriocarcinoma of testis

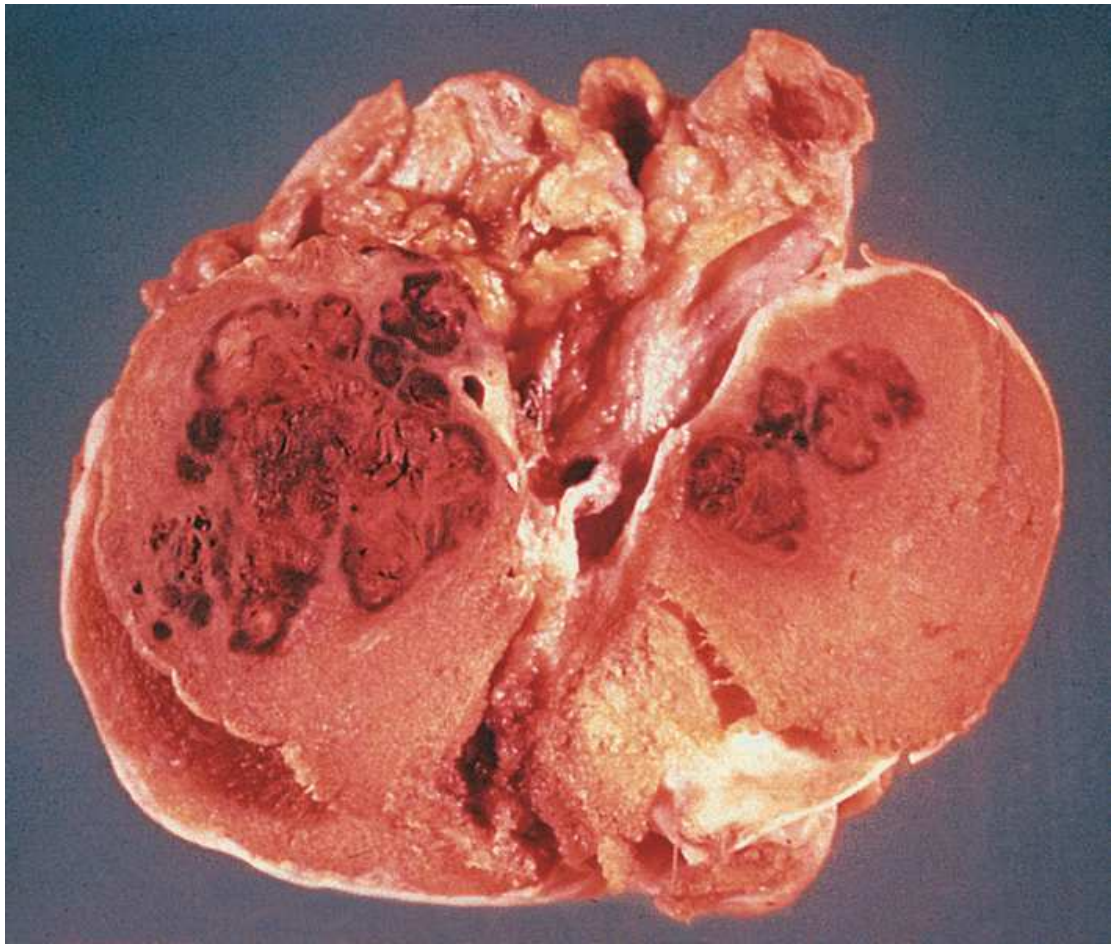
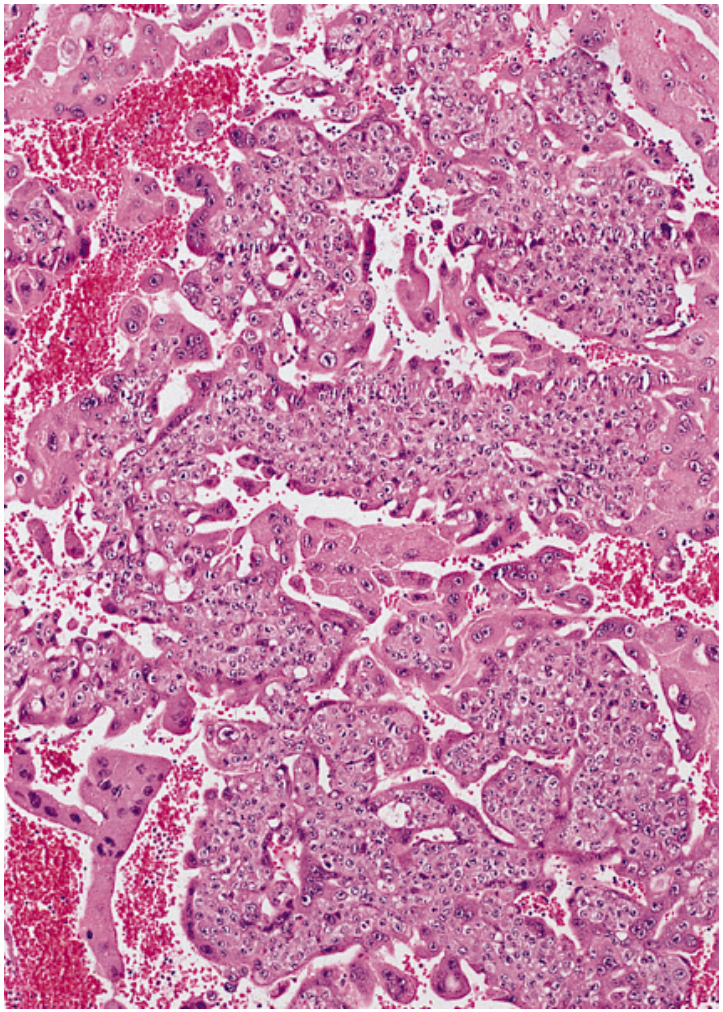


Fig. 4-59

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Choriocarcinoma



The tumors contain syncytiotrophoblasts and cytotrophoblasts.
Syncytiotrophoblasts are large multinucleated cells with abundant eosinophilic vacuolated cytoplasm containing HCG.
Cytotrophoblasts tend to be polygonal, with distinct borders and clear cytoplasm; they grow in cords or masses and have a single, fairly uniform nucleus.

Fig. 4-61

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Teratoma

- In adults, 2% to 3% of germ cell tumors.
- Teratomas mixed with other germ cell tumors in approximately 45%.
- In the postpubertal male all teratomas are regarded as malignant as they are derived from other germ cell types
- Overgrowth of primitive neuroectodermal elements is compatible with primitive neuroectodermal tumor.
- EWSR 1 rearrangements absent
- Pure forms of teratoma are fairly common in infants and children, second in frequency only to yolk sac tumors.

Teratoma of testis

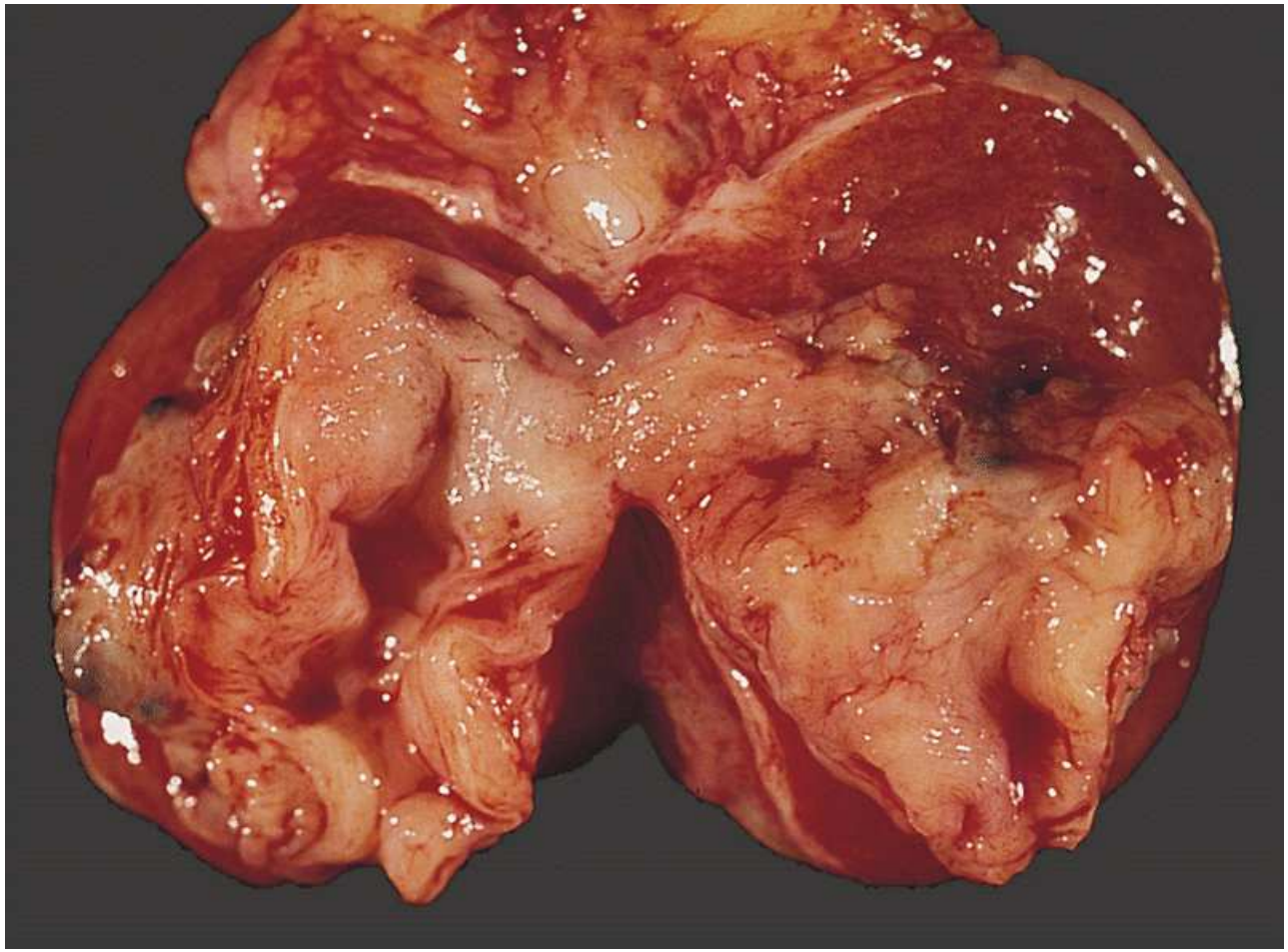
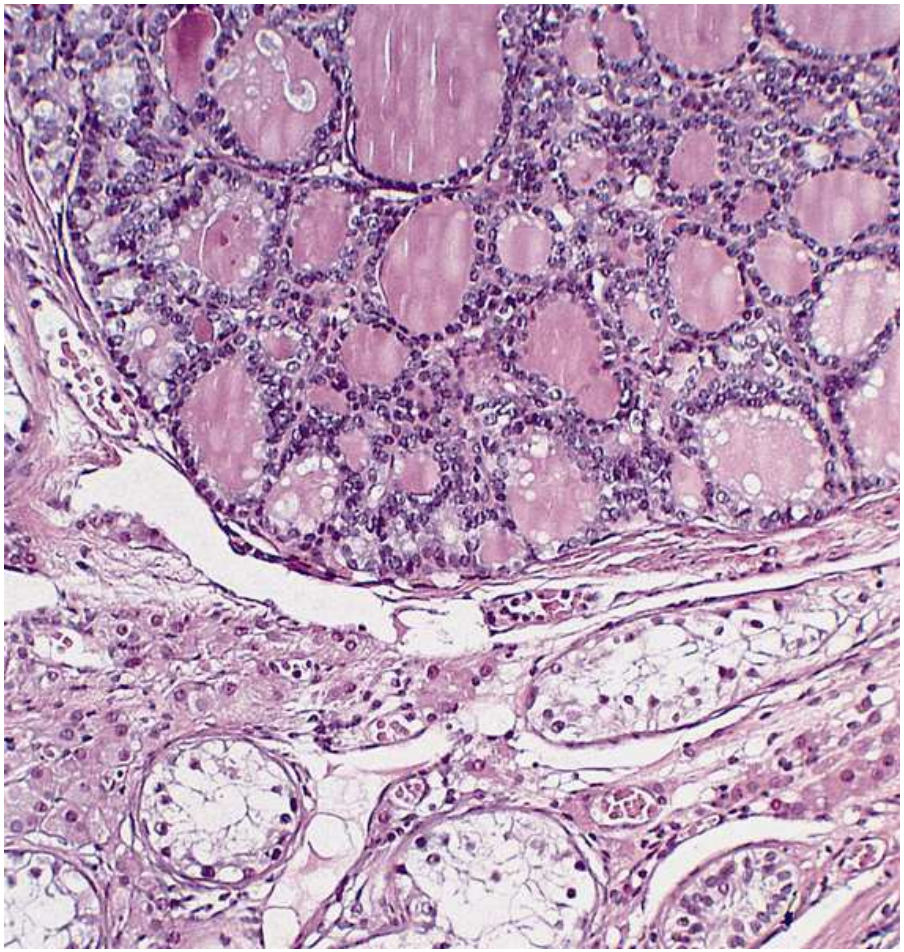


Fig. 4-77

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Teratoma

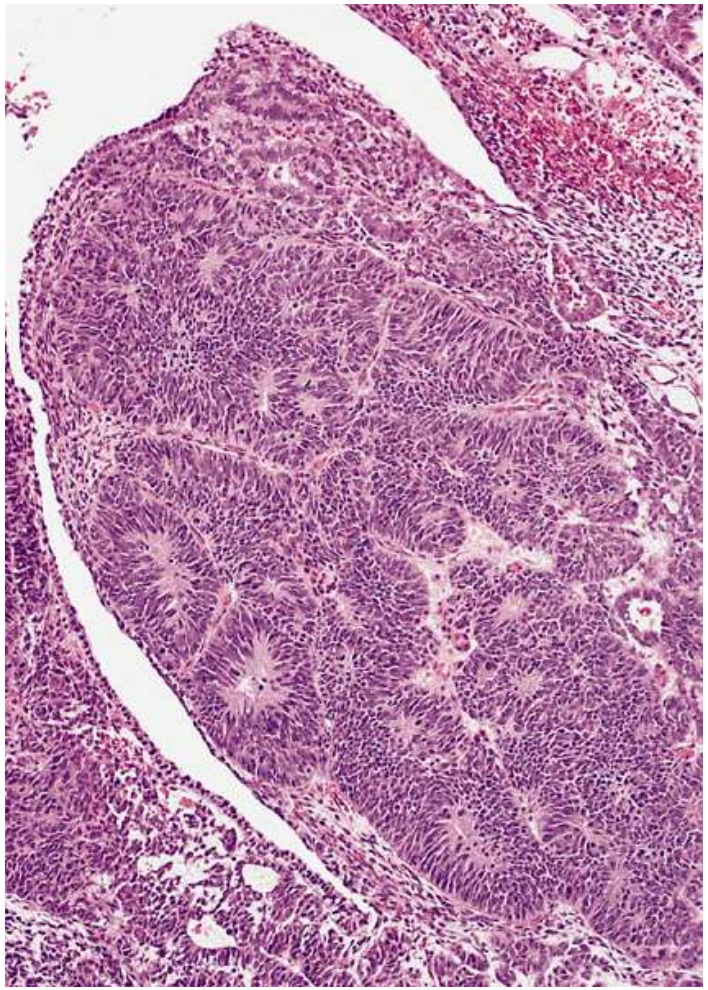


Comprised of endodermal, ectodermal, and mesenchymal elements.
If no neural tissues, nor other carcinomas, are benign.
Here, note thyroid tissue in testis.

Fig. 4-87

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Teratoma



Immature neural elements identified. High risk.

Fig. 4-92

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

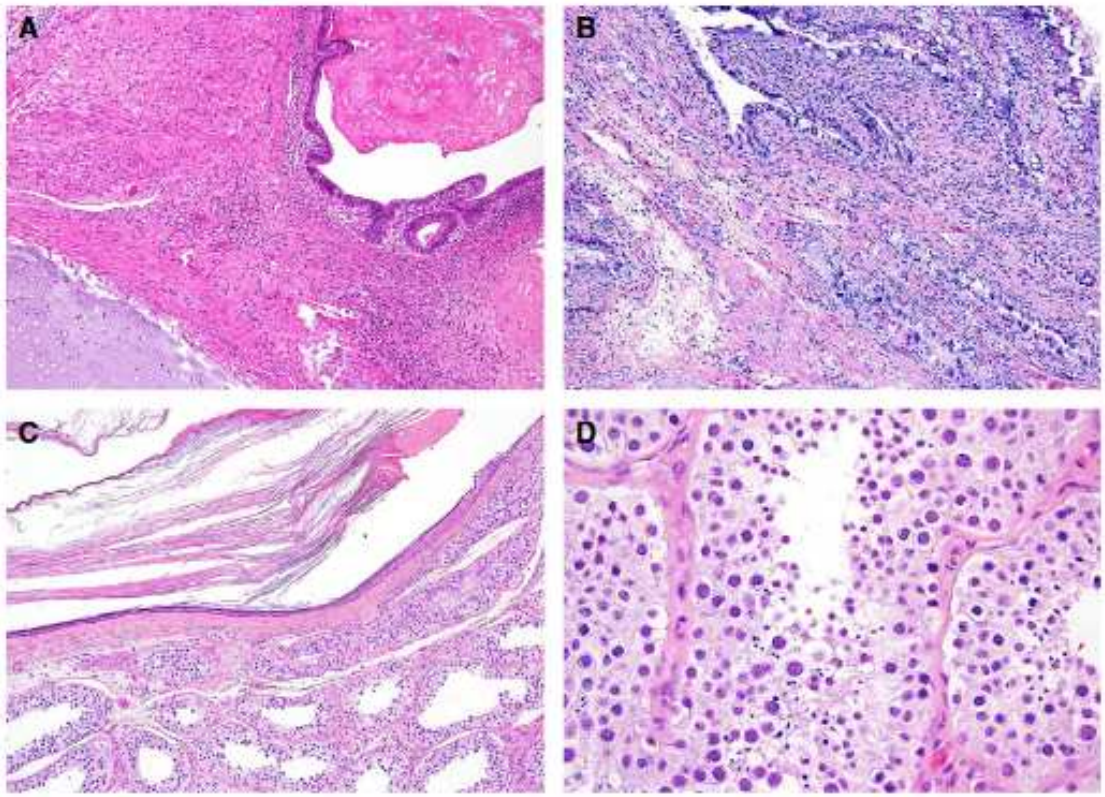


Figure 4. Postpubertal-type teratoma (A) is composed of a haphazard arrangement of varying amounts of ectodermal, mesodermal or endodermal elements, sometimes with substantial cytological atypia (B). In the absence of overgrowth or destructive invasion by a single element, cytological atypia alone does not warrant interpretation as secondary somatic-type malignancy. Epidermoid cyst (C) is one form of prepubertal-type teratoma. Prepubertal teratomas are not associated with germ cell neoplasia *in situ*, and should show normal spermatogenesis in adjacent tubules (D).

Yolk sac tumor

- Endodermal sinus tumor
- Most common testicular tumor in infants and children up to 3 years of age
- In this age group the prognosis is good.
- In children, yolk sac tumor occurs primarily in pure form rather than as a component of a mixed germ cell tumor
- The opposite occurs in post-pubertal patients
- In the uncommon mixed examples, yolk sac tumor is only associated with teratoma and not with other germ cell tumor types

Yolk sac tumor

- The tumor is non-encapsulated
- Most tumors have a reticular pattern characterized by a loose meshwork of communicating spaces lined by primitive tumor cells with cytoplasm that is typically clear, containing glycogen and occasionally, lipid.
- Single papillae, lined by primitive epithelium, with fibrovascular cores containing single vessels and occupying spaces lined by hobnail cells, representing endodermal sinuses (Schiller-Duval bodies)
- These resemble primitive glomeruli.
- Found in up to 50% of cases.

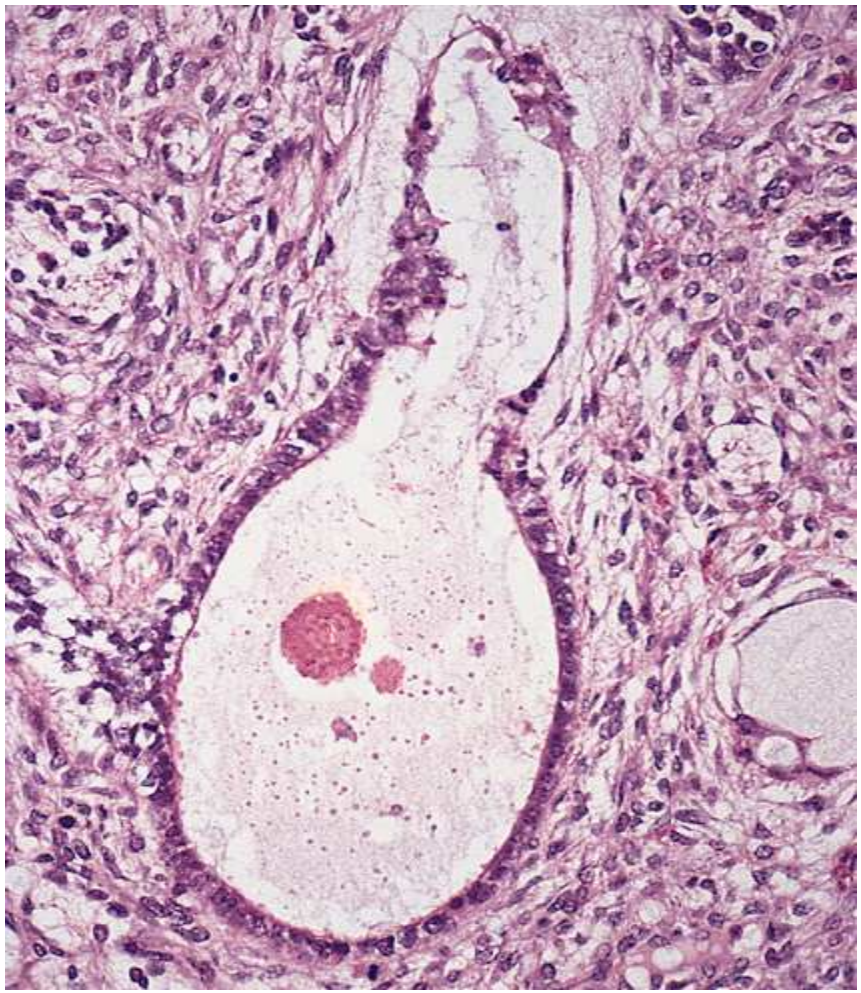
Yolk sac tumors

- Polyvesicular vitelline
- Prominent cysts lined by flattened to columnar cells within a variably cellular stroma, occasionally with eccentric constriction
- Resembles the division of the primary yolk sac vesicle
- Other patterns are possible
- A malignant primitive germ cell tumor that shows various patterns of endodermal differentiation (primitive gut, mesenchyme, secondary yolk sac), including their derivatives (intestine, liver, lung)

Yolk sac tumors

- Reticular areas frequently merge with microcystic or macrocystic areas.
- Disordered angiogenesis present
- Similar features are present in glioblastoma multiforme
- Eosinophilic AFP-positive and α_1-antitrypsin hyaline globules present within and outside cytoplasm.
- AFP elevated

Yolk sac tumor of testis



Polyvesicular vitelline pattern.

Fig. 4-47

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

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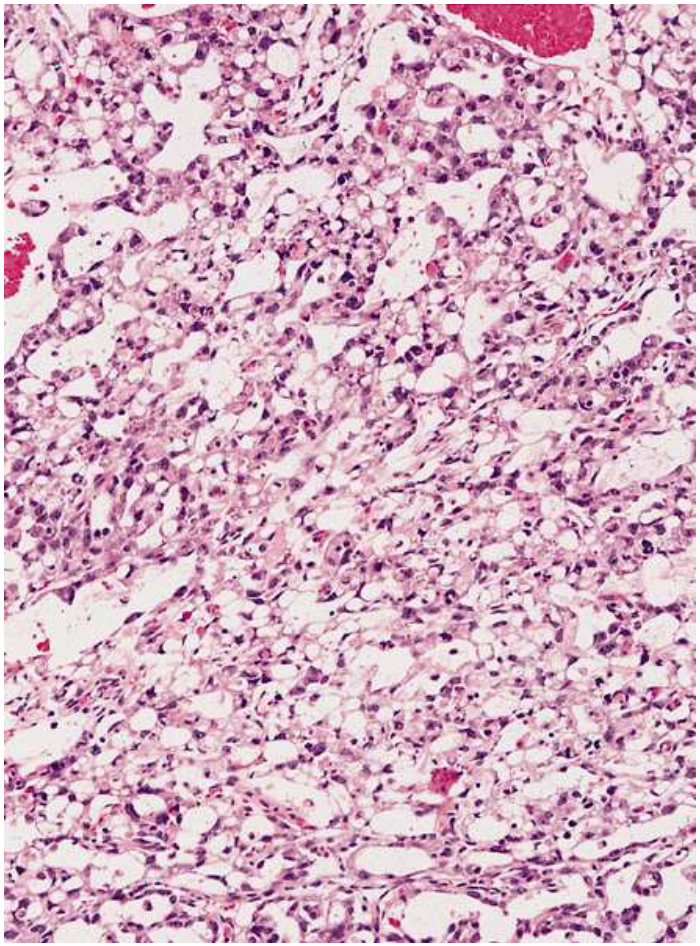
Yolk sac tumor of testis

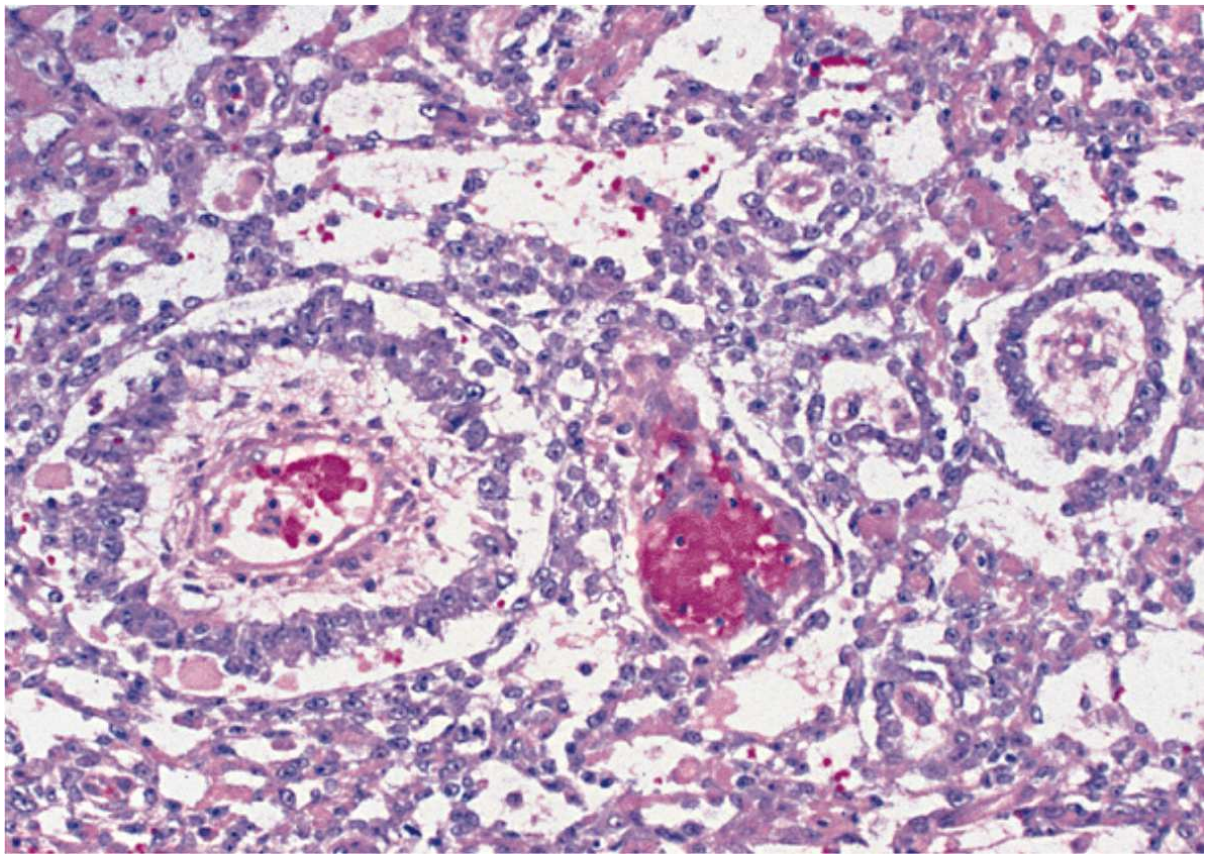


Reticulated pattern. The most common form.

Fig. 4-26

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Yolk sac tumor of testis



Endodermal sinus pattern.

Fig. 4-32

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Paratesticular tumors

- The most common benign paratesticular tumor is adenomatoid tumor (mesothelial).
- Adenomatoid tumors are usually small nodules, typically occurring near the upper pole of the epididymis.
- Although grossly well circumscribed, microscopically they may be minimally invasive into the adjacent testis.
- The most common malignant paratesticular tumors are rhabdomyosarcomas in children and liposarcomas in adults.

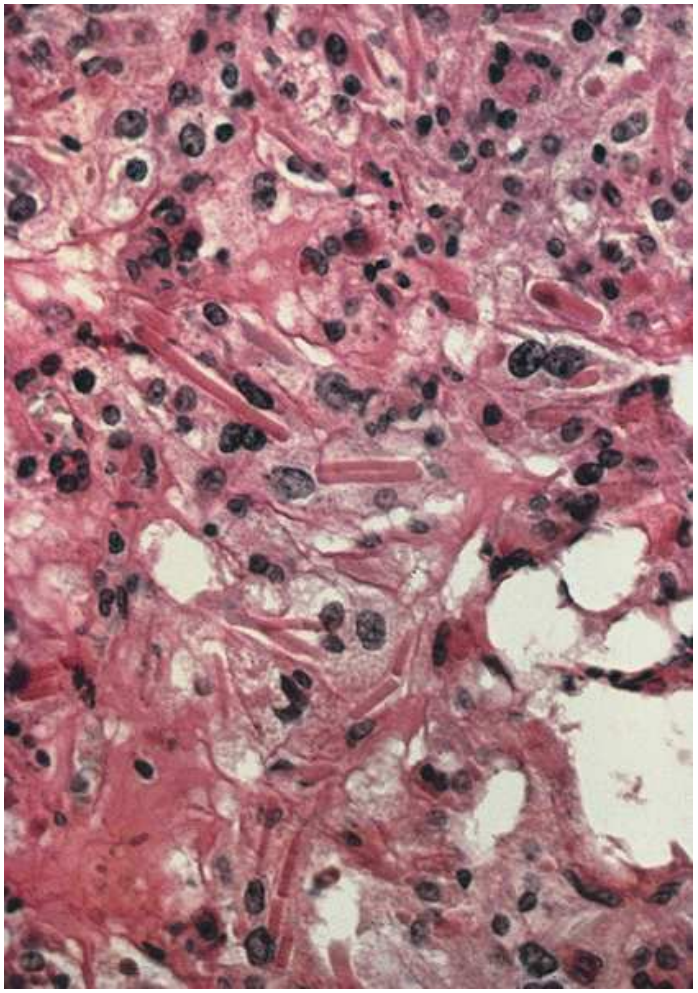
Other tumors

- As many as 60% of germ cell tumors are mixed and contain more than one component.
- Leydig cell (stromal) tumor
- Painless testicular mass.
- May see precocious puberty in children, gynecomastia in adults.
- 90% are benign tumors.

Other tumors

- They have a distinctive golden brown, homogeneous cut surface.
- Histologically, neoplastic Leydig cells are large in size and have round or polygonal cell outlines, abundant granular eosinophilic cytoplasm, and a round central nucleus.
- 25% contain lipid droplets, vacuoles, or lipofuscin pigment, and, most characteristically, rod-shaped crystalloids of Reinke

Leydig cell tumor



A prominent fibrous stroma subdivides the tumor into cellular lobules. Many of the nuclei have enlarged, hyperchromatic, bizarre nuclei. Elongated eosinophilic crystals of Reinke are conspicuous in the cytoplasm of several tumor cells.

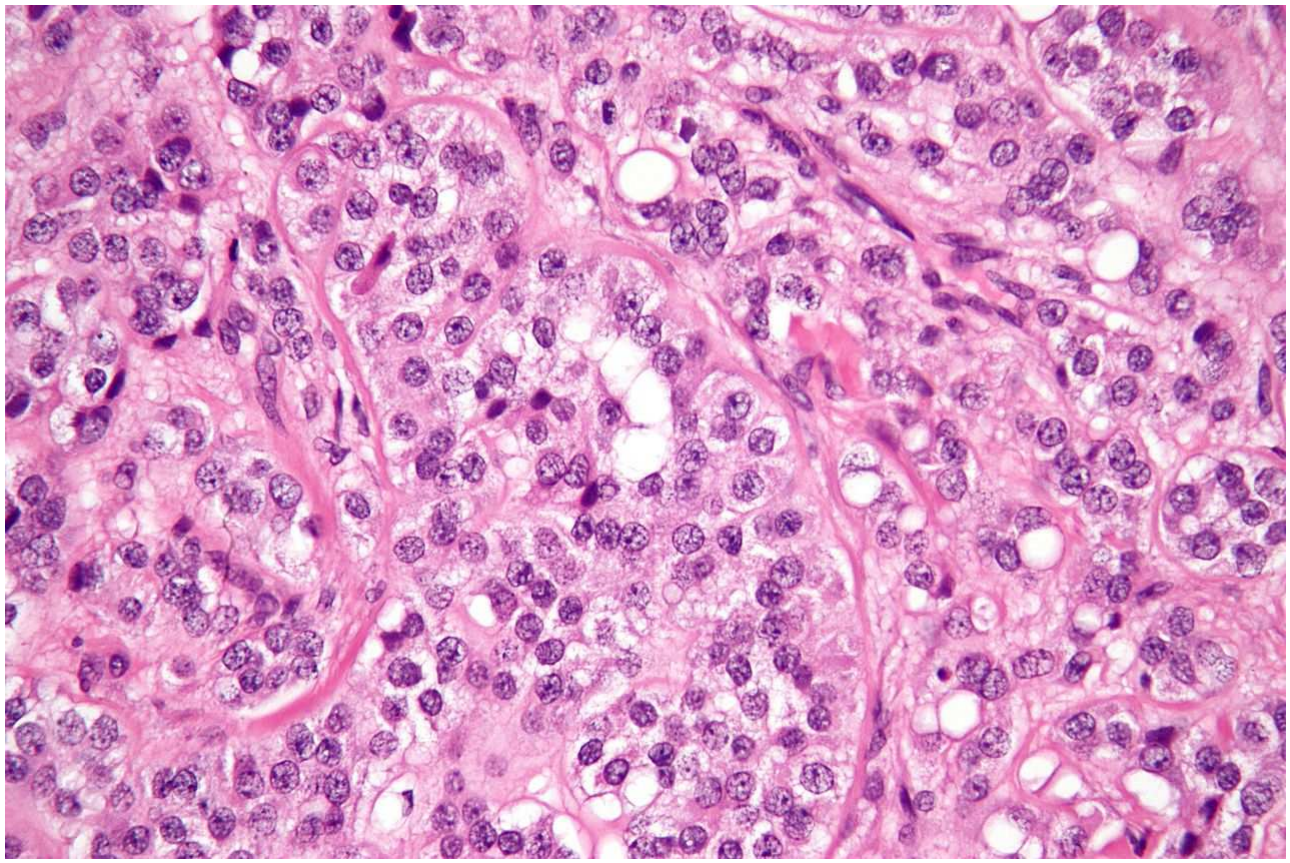
Fig. 12-11

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Other tumors

- Most Sertoli cell tumors are hormonally silent and present as a testicular mass.
- Firm, small nodules with a homogeneous gray-white to yellow cut surface.
- Histologically the tumor cells are arranged in distinctive trabeculae that tend to form cordlike structures and tubules.
- 10% may progress to

Sertoli cell tumor

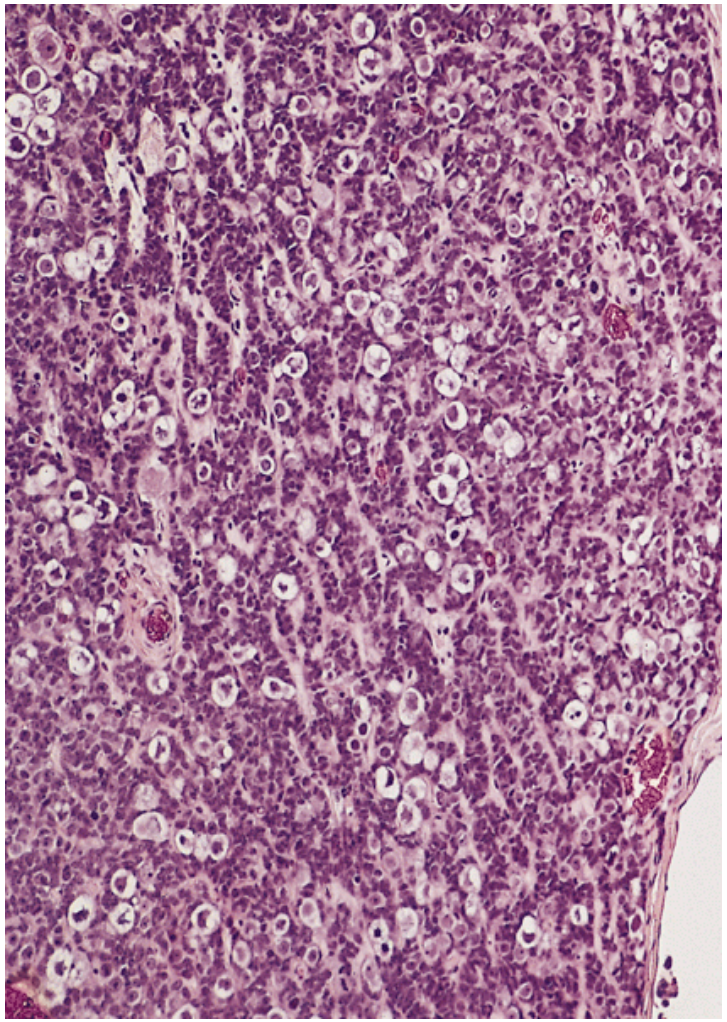


https://en.wikipedia.org/wiki/Sertoli_cell_tumour#/media/File:Sertoli_cell_tumour_high_mag.jpg
Accessed 05/10/2020

Other tumors

- Gonadoblastomas
- Comprised of a mixture of germ cells and gonadal stromal elements.
- Arise in gonads with some form of testicular dysgenesis.
- The germ cell component may give rise to seminoma.

Gonadoblastoma



An admixture of germ cells and smaller cells with abundant clear cytoplasm are scattered within long, anastomosing cords and trabeculae.

Fig. 16.6

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Granulosa cell tumor of testis

- Most frequent congenital testicular tumor
- 6% of all prepubertal testicular tumors
- Most tumors present in the perinatal period, occurrence after first year is rare
- Scrotal mass
- More common in left testis
- 30% abdominal testis, often associated with undescended contra-lateral testis

Granulosa cell tumor of testis

- 20% have ambiguous genitalia
- Most frequently mixed gonadal dysgenesis and hypospadias
- 45 / 46XY mosaicism, trisomy 12 or structural anomalies of Y chromosome
- Not associated with gynecomastia or endocrine abnormality
- Do not metastasize
- No recurrence following excision or orchiectomy (in child, not adult)

Granulosa cell tumor of testis

- Multi-cystic tumors with intervening solid areas
- Partly encapsulated
- Solid areas intermixed with follicle-like structures filled with mucoid material
- Macrofollicular pattern is common, with multilayered tumor cells surrounded by spindle cell stroma
- Cells are pale and can have abundant luteinized cytoplasm
- Nuclei are round, hyperchromatic and lack grooves, unlike adult type; nucleoli are prominent

Granulosa cell tumor of testis

- Mitoses are common and sometimes can be numerous, unlike the adult type
- Cellular atypia is typically less than that ovarian granulosa cell tumor
- Call-Exner bodies are uncommon
- KRAS activation and PTEN loss causal
- FOXL2 found as in normal ovarian granulosa cells
- SOX9 sequestered in cytoplasm
- Normally in the nucleus
- Loss of GATA4 may be favorable marker

Gonadoblastoma

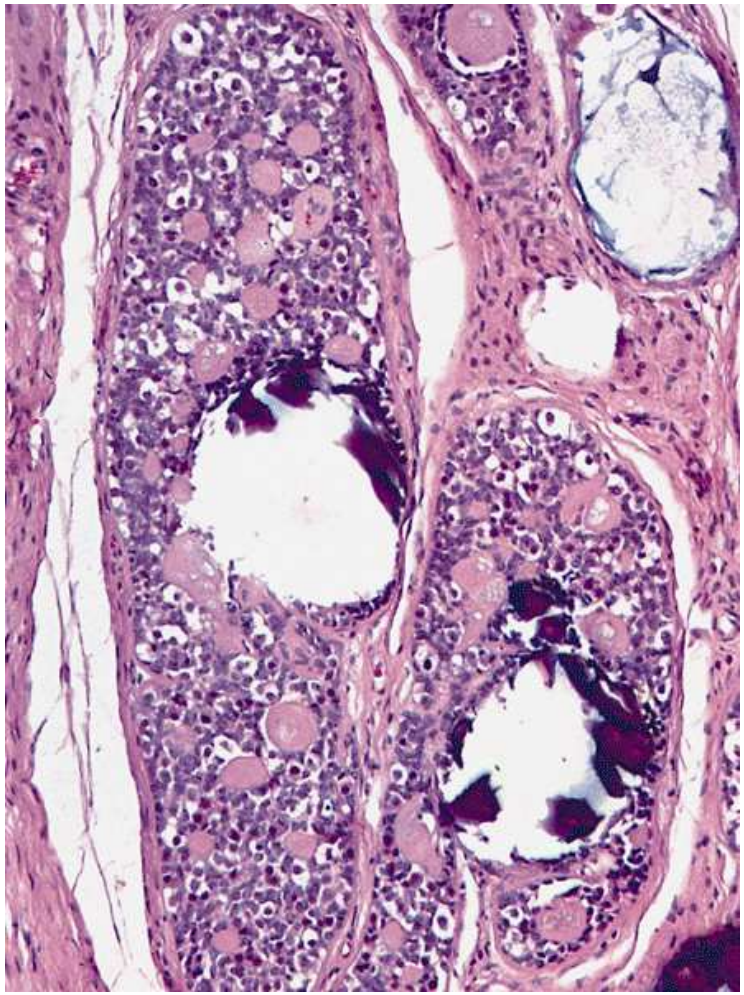


Fig. 5-16

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Other tumors

- Lymphoma is the most common testicular tumor in men over age 65.
- Diffuse large B-cell lymphoma, Burkitt's lymphoma, and EBV-positive extranodal NK/T-cell lymphoma are the most common forms
- May have CNS involvement

Tumor spread

- Lymphatic spread to retroperitoneal and para-aortic lymph nodes
- Seminomas slow-growing, often confined to lymph nodes
- Hematogenous spread to lungs
- Non-seminomatous tumors metastasize earlier
- Histology may differ from primary lesion (are totipotent cells)

Late relapse

Histology of relapse

Teratoma accompanied germ cell and non-germ cell histologies in 60 %

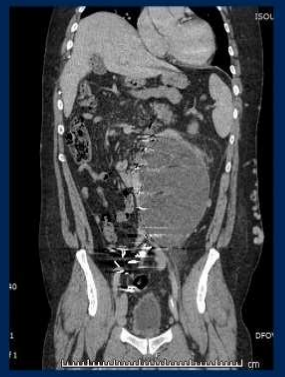
Sarcomas and adenocarcinoma in 3–23 %

AFP predominant marker 52-76%
β-HCG 10- 28%

Retroperitoneum most common site (52%)

Mediastinum (12%)

Most common symptoms:
-back and abdominal pain



Ehrlich, Rosenbaum & Baniel- Late Relapse of Testis Cancer. *Curr Urol Rep* (2013) 14:518–524

Testicular cancer evaluation

- Screen testis with ultrasound.
- β-HCG
- 24 hour half-life.
- Elevated in Choriocarcinoma
- AFP
- 5-7 day half-life.
- Elevated if non-seminomatous elements present
- Generally yolk-sac or embryonal cell cancers.
- CT of chest to exclude pulmonary metastases.
- CT of chest, abdomen, and pelvis to establish extent of disease dissemination.
- MRI when results equivocal or in presence of CNS symptoms.

Stage

- Stage I
- Tumor confined to the testis, epididymis, or spermatic cord
- Stage II
- Distant spread confined to retroperitoneal nodes below the diaphragm
- Stage III
- Metastases outside the retroperitoneal nodes or above the diaphragm
- Prognosis related to stage and tumor type

Testicular cancer treatment

- High inguinal orchiectomy with complete removal of the testis and spermatic cord through the inguinal ring preferred method for pathologic evaluation of tumor.
- Seminomas better cured by both radiation and chemotherapy.
- Cure rate >90% (all stages).
- Germ cell tumors are treated with four cycles of bleomycin, etoposide, cisplatin (BEP) chemotherapy

Testicular cancer treatment

- Stage IA, IB seminoma may be treated with single agent carboplatin or radiotherapy for
- IIA seminoma may be treated with radiotherapy to para-aortic and ipsilateral iliac nodes OR with [bleomycin], etoposide, cisplatin chemotherapy
- IIB seminoma treated with chemotherapy; radiotherapy if bulky lesions (>3cm)
- IIC, III seminoma treated with chemotherapy
- Bleomycin, etoposide, cisplatin administered for four cycles is preferred.
- Fewer instances of paresthesias and muscle cramps than with cisplatin, vinblastine, bleomycin; less hematologic toxicity than with etoposide, ifosfamide, cisplatin.

Testicular cancer treatment

- Stage I non-seminoma treated with one cycle of bleomycin, etoposide, cisplatin (BEP) chemotherapy OR nerve sparing retroperitoneal lymph node dissection [RPLND].
- RPLND is preferred therapy for transformed teratoma (somatic type malignancy).
- II, IIIA non-seminoma treated with three cycles of BEP chemotherapy
- IIIB, IIIC non-seminoma treated with four cycles of BEP chemotherapy.
- Etoposide, ifosfamide, MESNA, cisplatin chemotherapy as alternative

Testicular cancer treatment

- 25% oligospermic before therapy.
- Sperm banking may be recommended; many patients recover sperm production after completion of therapy. No increased risk of congential malformations.
- Bleomycin is toxic to lungs. Rarely fatal if total cumulative dose <400 units.
- Nephrotoxicity, ototoxicity with cisplatin.
- Secondary leukemias are generally myeloid in lineage.
- 11q23 abnormality, present several years after treatment, generally related to etoposide use.

Testicular cancer treatment

- Stage I miRNA371 negative
- Surveillance
- Stage I miRNA371 positive
- Retroperitoneal lymph node dissection
- Stage IIA miRNA371 negative
- Tumor is <3cm
- Retroperitoneal lymph node dissection

Testicular cancer treatment

- Stage IIA miRNA371 positive
- Retroperitoneal lymph node dissection
- 2 cycles BEP chemotherapy
- Stage >IIB/C
- 3-4 cycles of BEP or VIP chemotherapy with or without retroperitoneal lymph node dissection
- Late relapse (3%) chemoresistant

Adverse outcomes

- 25% of chemotherapy treated germ cell tumor patients develop metabolic syndrome
- 25% of those with germ cell tumors will have residual tumor mass post-chemotherapy, principally in the retroperitoneum. (45% will harbor teratoma; 10%, viable cancer).
- Retroperitoneal node dissection only for those with post-chemotherapy masses >1cm.
- 2 % germ cell tumors relapse after 2 years.