CANCERS OF PROSTATE, PENIS, TESTES

Kenneth Alonso, MD, FACP

CANCER OF PENIS AND DISTAL URETHRA

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

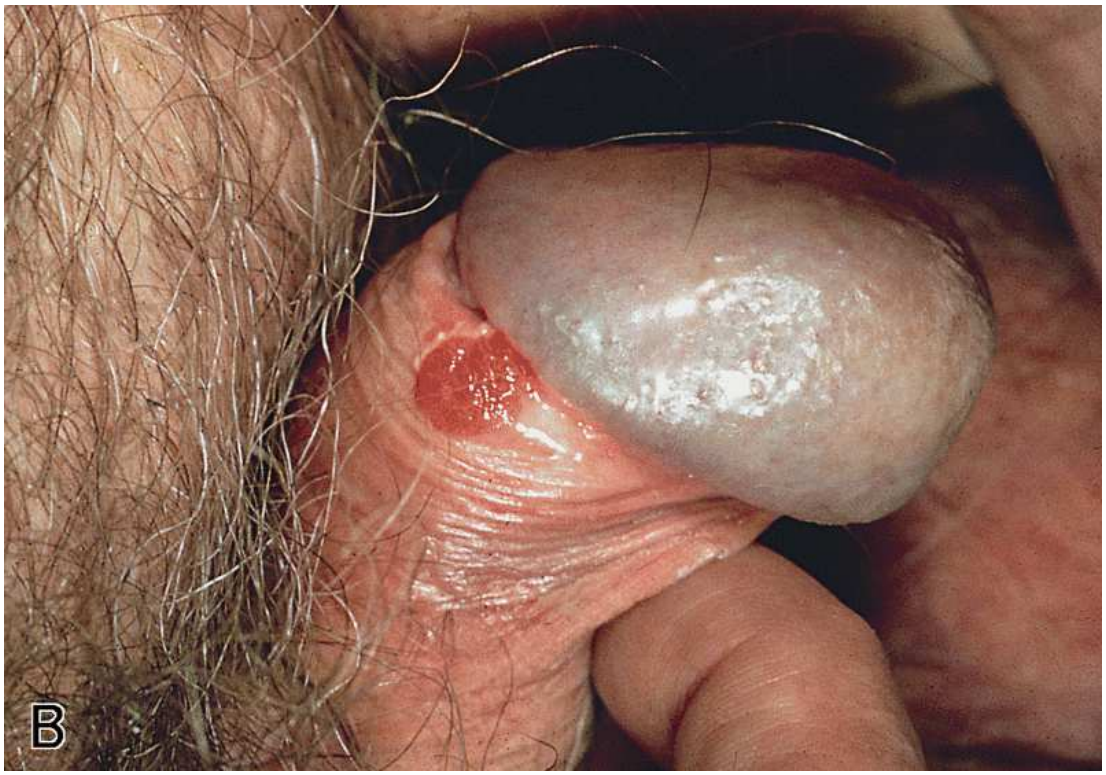


Fig. 10-15B

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.

Bowen’s disease of penis

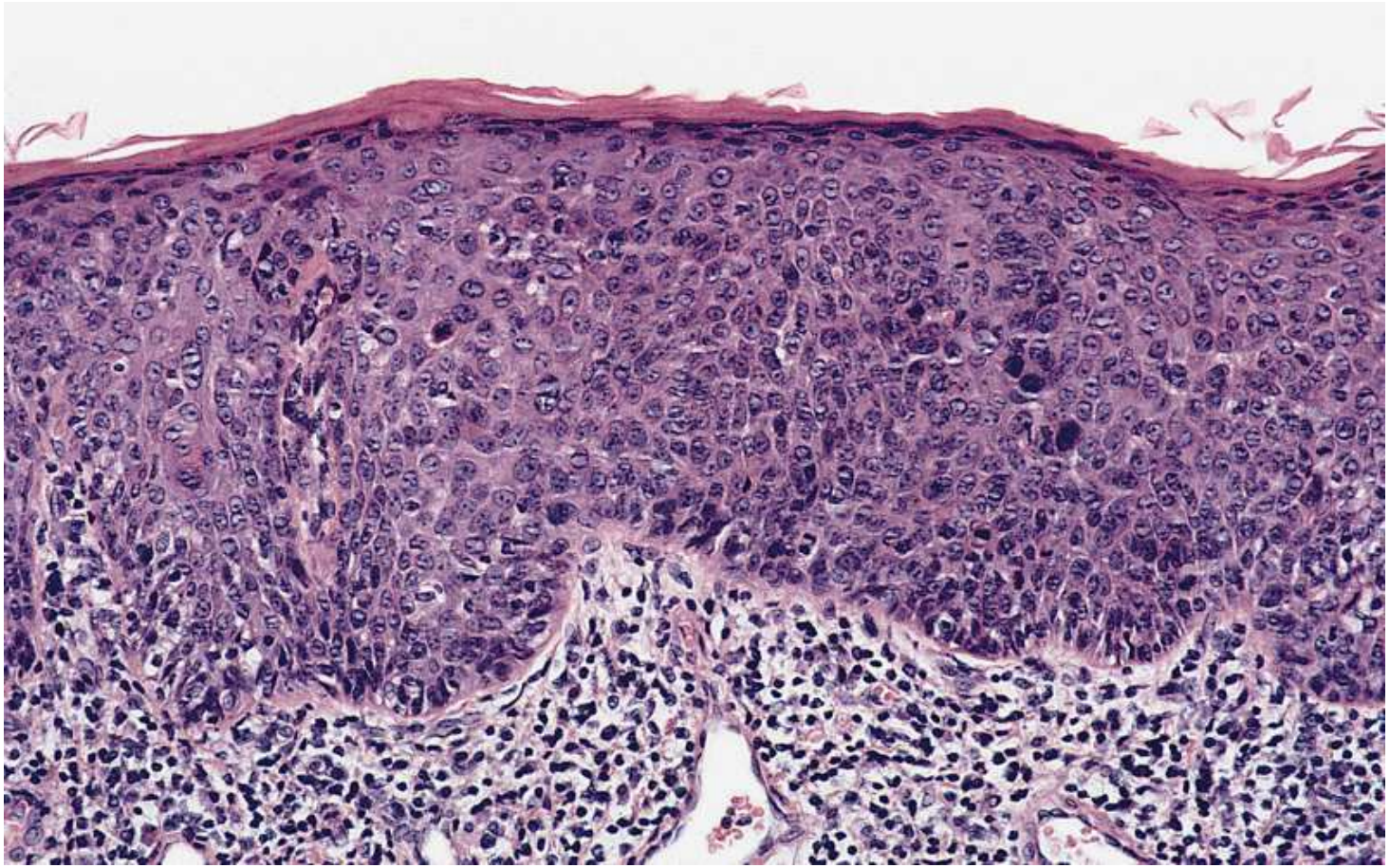


Fig. 10-17

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

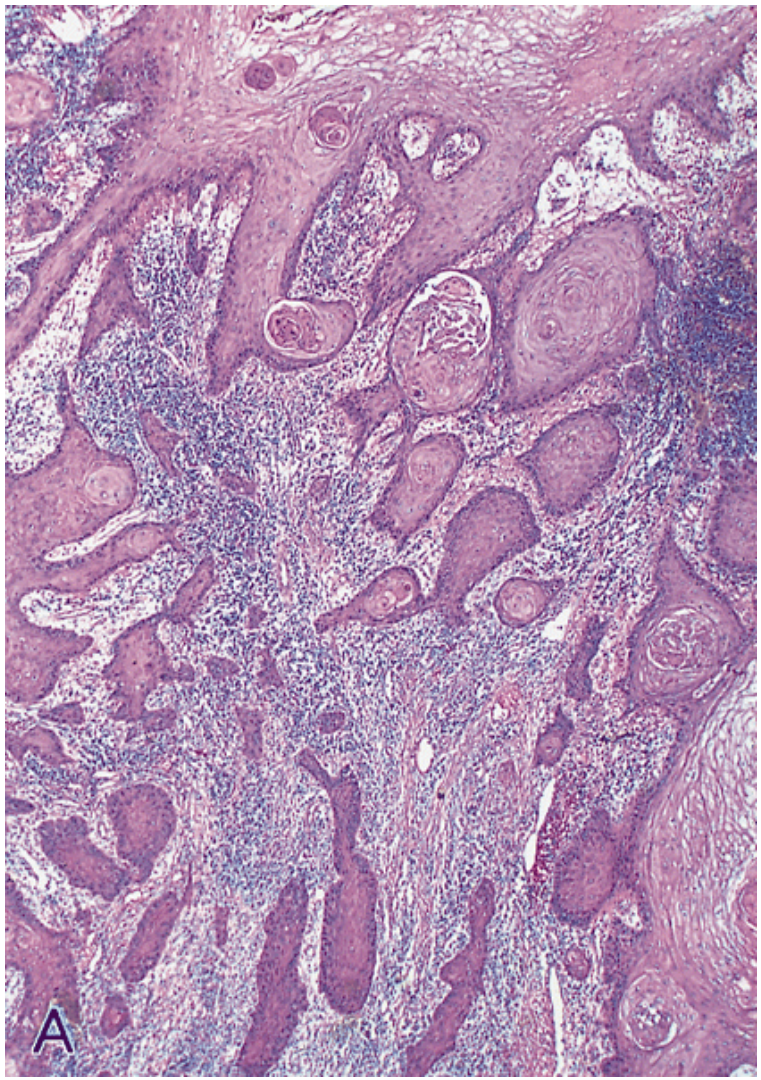


Fig. 10-34A

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

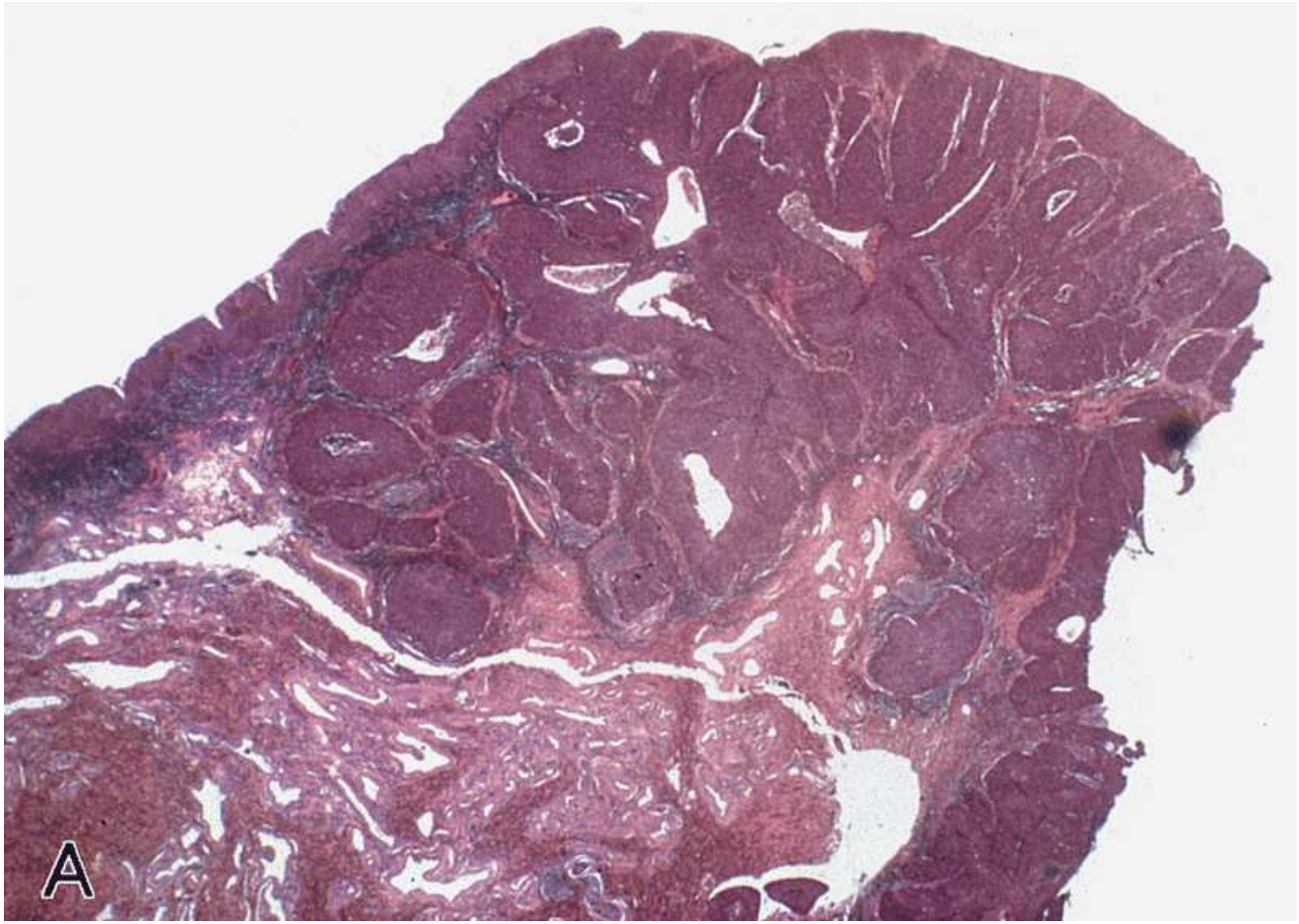


Fig. 10-37A

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.

Urethra

- Tumors arising within the proximal urethra tend to show urothelial differentiation and are analogous to those occurring within the bladder
- Tumors arising within the distal urethra are more often squamous cell carcinomas.

Squamous cell carcinoma of the urethra

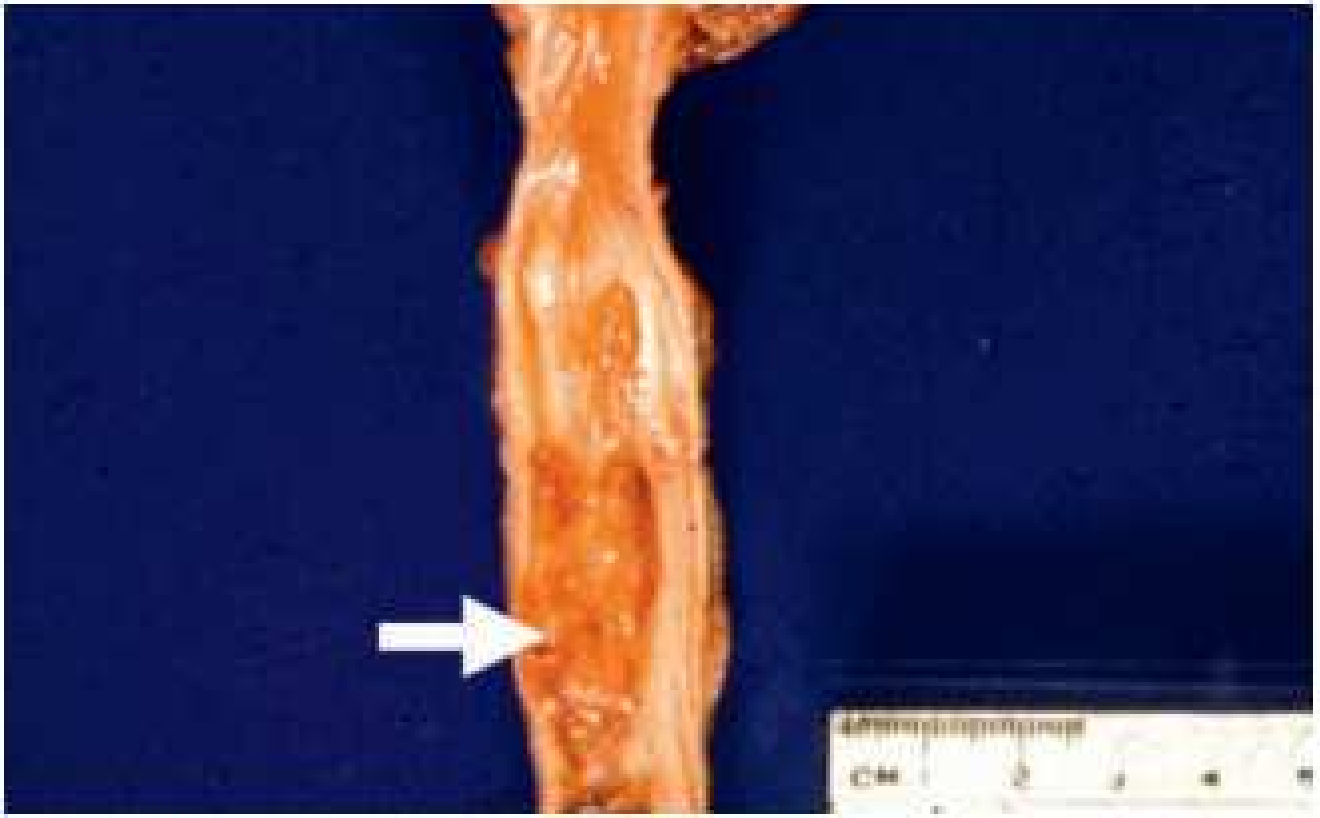


Figure 21-14 Carcinoma of urethra with typical fungating growth.

Squamous cell carcinoma of urethra

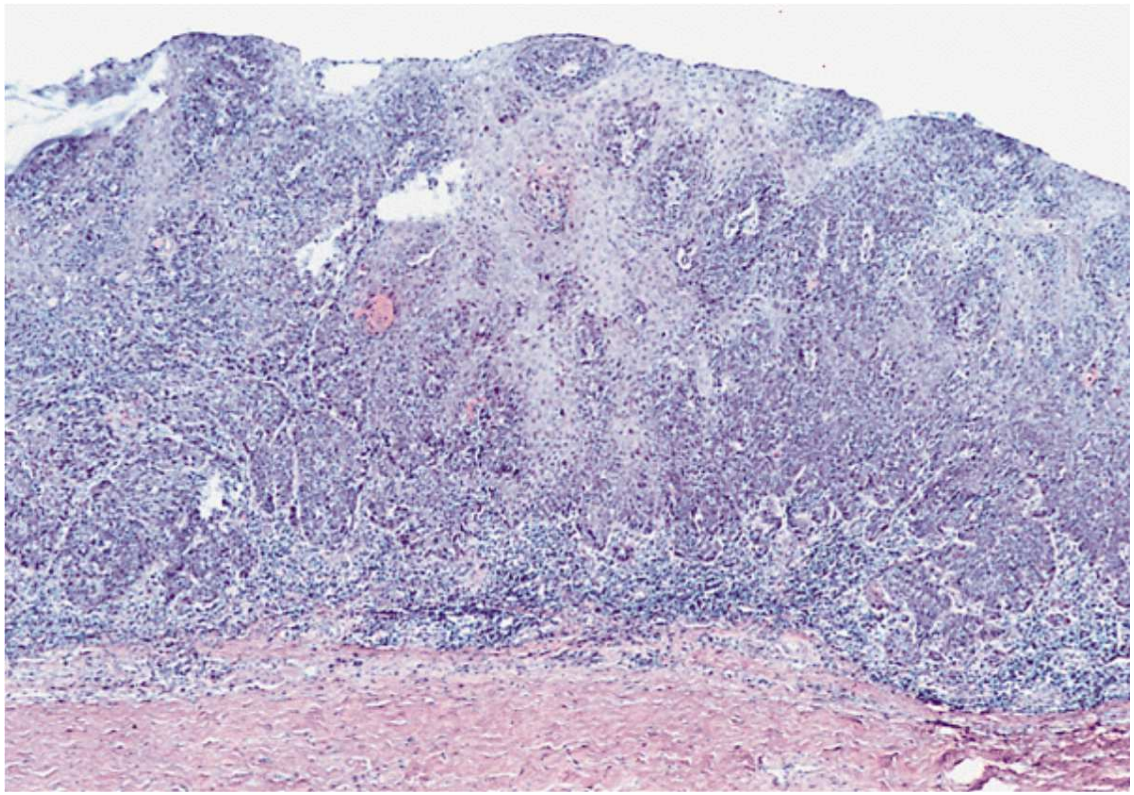


Fig. 9-14

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 CANCER

Screening for prostate cancer

- There are no data. suggesting survival improved through early screening
- Prevalence of prostate cancer is 0.01% prior to the fifth decade
- By the fifth decade it is 2.5%
- By the seventh decade, it is 7%
- By the eighth decade, it is 13%.

Screening for prostate cancer

- PSA at 50yo. If <3.0, repeat every 3 years; If 3.00-4.99, repeat every year.
- 25% of men with normal levels will have cancer
- Only 2% of these will be high grade.
- Begin screening at 40-years of age only if of sub-Saharan origin or if first degree relative with prostate cancer.
- 44% of men will be over- diagnosed with these parameters.
- If initial PSA <1.00 AND >65yo, repeat screening not necessary.

Screening for prostate cancer

- 85% cancers curable if found when PSA <5.0
- PSA velocity >0.5ng/yr is an indication for biopsy as it is associated with increased risk of cancer death over a follow-up period of 10-15 years.
- PSA velocity, however, is not a good screening tool.
- For those patients with negative biopsies but rising PSA, repeat biopsy is recommended at 1 year.
- Consider genetic testing. It is unlikely the patient will consent to a second round of biopsies.
- Median lobe must be examined in repeat biopsy.

Screening for prostate cancer

- Highest sensitivity to DHT associated with shortest CAG repeats in AR gene. Those of sub-Saharan ancestry have shortest CAG repeats; Asians, longest.
- Dutasteride reduces prostate cancer risk by >20% but raises risk of renal cancer.
- Early onset of male-pattern baldness associated with higher prostate cancer risk.
- PSA above age median associated with higher risk of prostate cancer deaths years later.

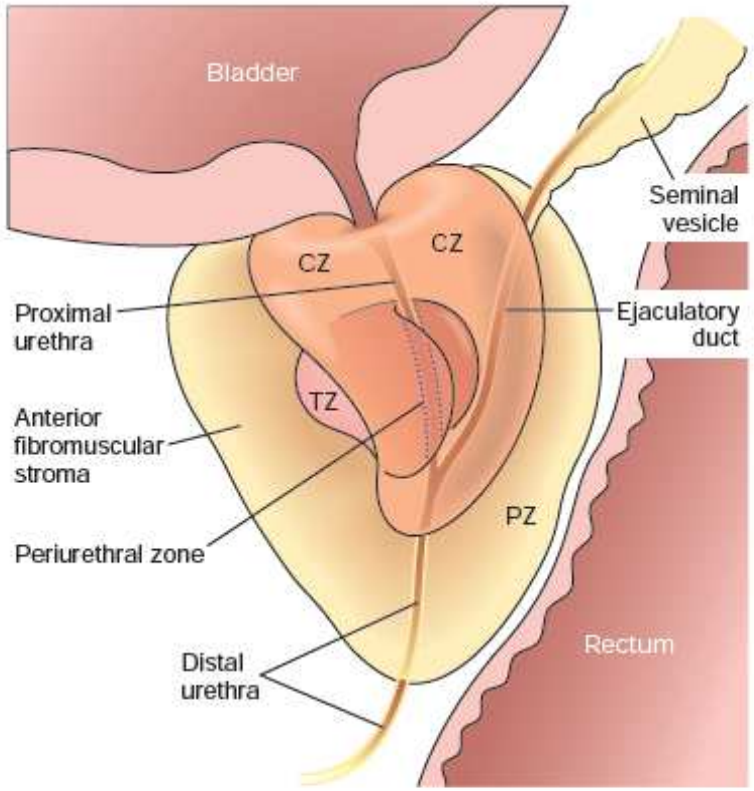


Figure 21-30 Adult prostate. The normal prostate contains several distinct regions, including a central zone (CZ), a peripheral zone (PZ), a transitional zone (TZ), and a periurethral zone. Most carcinomas arise from the peripheral zone and may be palpable during digital examination of the rectum. Nodular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

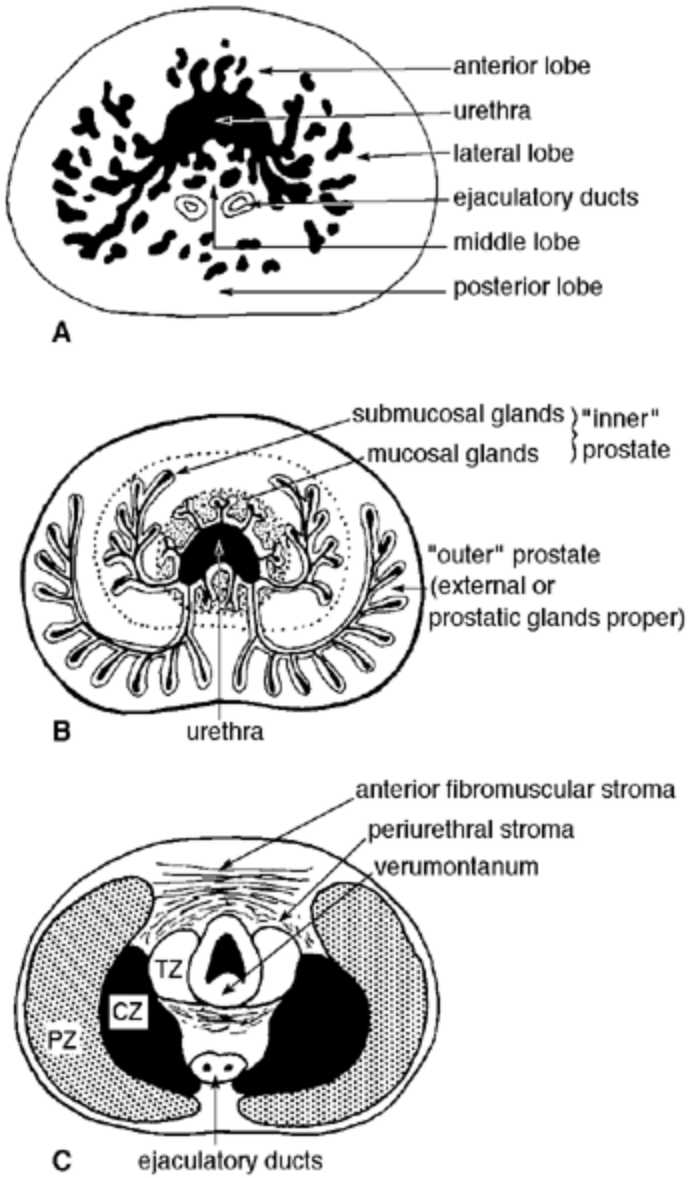
Four biologically and anatomically distinct zones:

- Peripheral,
- Central
- Transitional
- Periurethral

Most hyperplasias arise in the transitional zone.

Most carcinomas originate in the peripheral zone.

Prostate



A: Lowsley's lobar model. Note location of anterior, posterior, lateral, and middle lobes. B: Frank's concentric zone model showing mucosal and submucosal glands comprising the "inner" prostate and the peripheral glands comprising the "outer" prostate. C: McNeal's zonal model displaying the periurethral transition zone (TZ), the central zone (CZ) closely related to ejaculatory ducts, and the peripheral zone (PZ) wrapping around the CZ. In the anterior aspect, stroma predominates and is referred to as the anterior fibromuscular stroma.

Fig. 1-4

Young RH, Srigley JR, Amin MB, Ulbright, TM, Cubilla AL., “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, D.C.: 2004.

Adenocarcinoma of the prostate

- 90% of lesions are acinar type adenocarcinoma.
- Histologic findings:
- Haphazard infiltrating patterns
- Small glandular structures
- Cribriform patterns with poorly-formed glands or solid sheet/individual cells with no obvious glandular formation.
- Loss of basal cells, nuclear atypia and prominent nucleoli.

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

High grade intracellular neoplasia

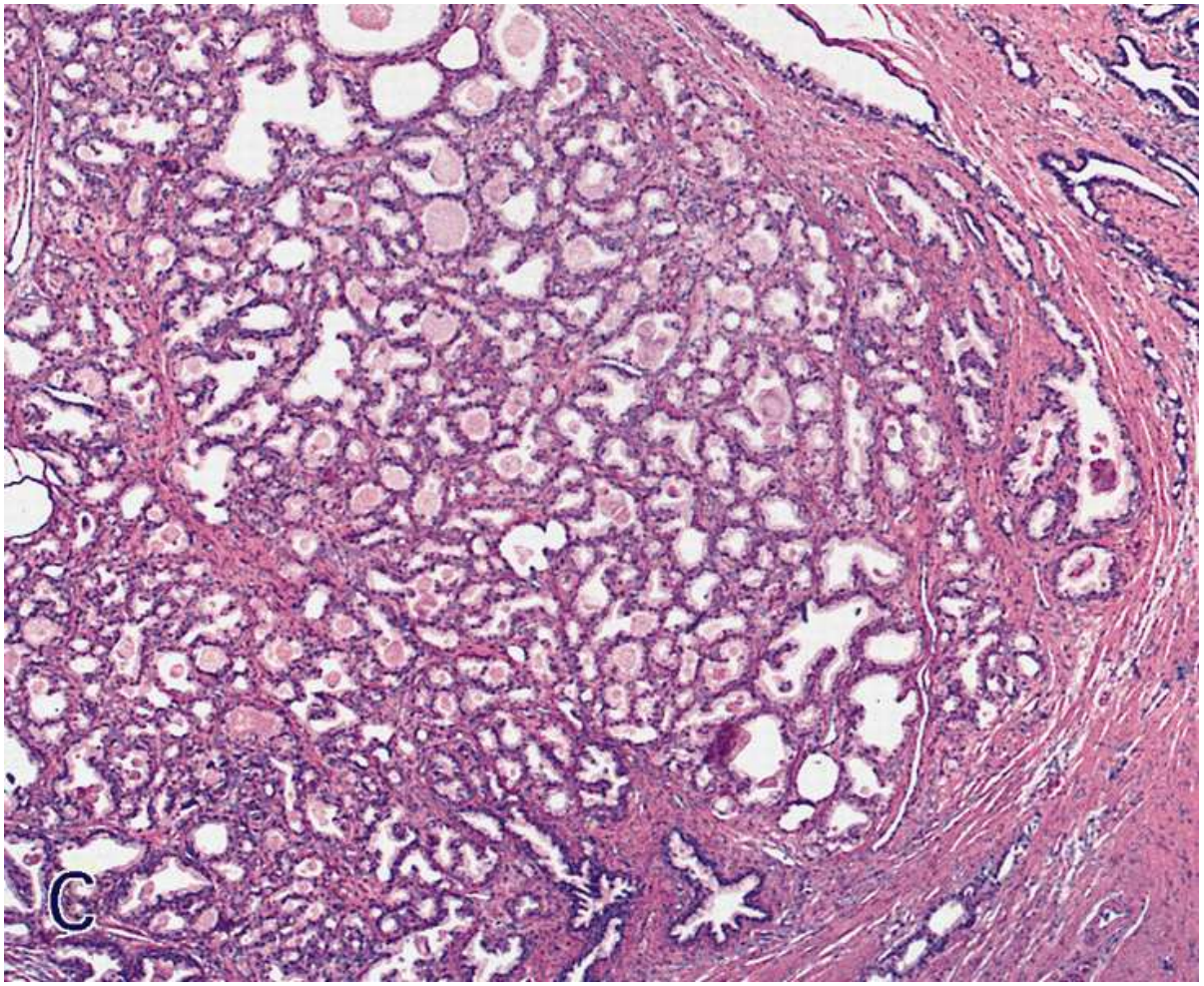
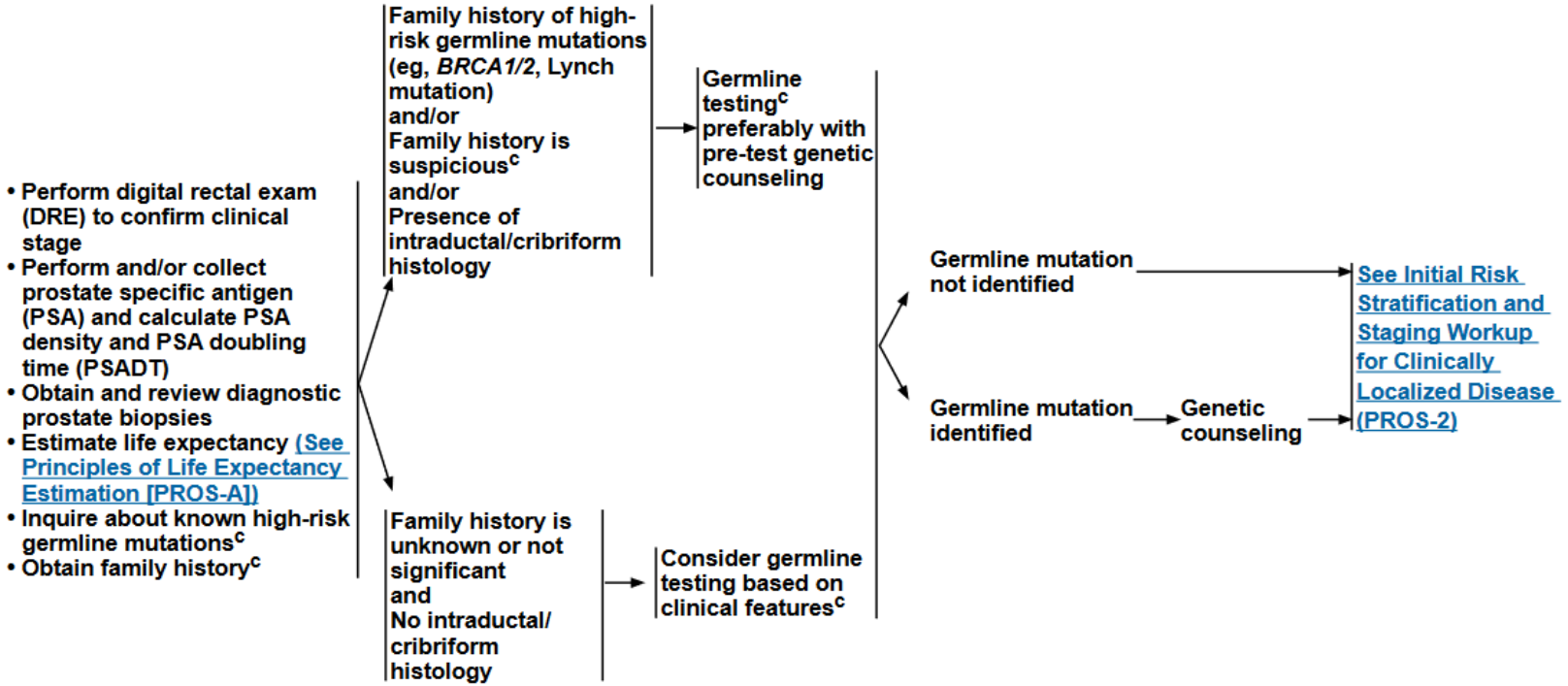


Fig. 3-29C

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.

INITIAL PROSTATE CANCER DIAGNOSIS[a,b,c]



[a] See NCCN Guidelines for Older Adult Oncology for tools to aid optimal assessment and management of older adults.

[b] See NCCN Guidelines for Prostate Cancer Early Detection.

[c] See Principles of Genetics (PROS-B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

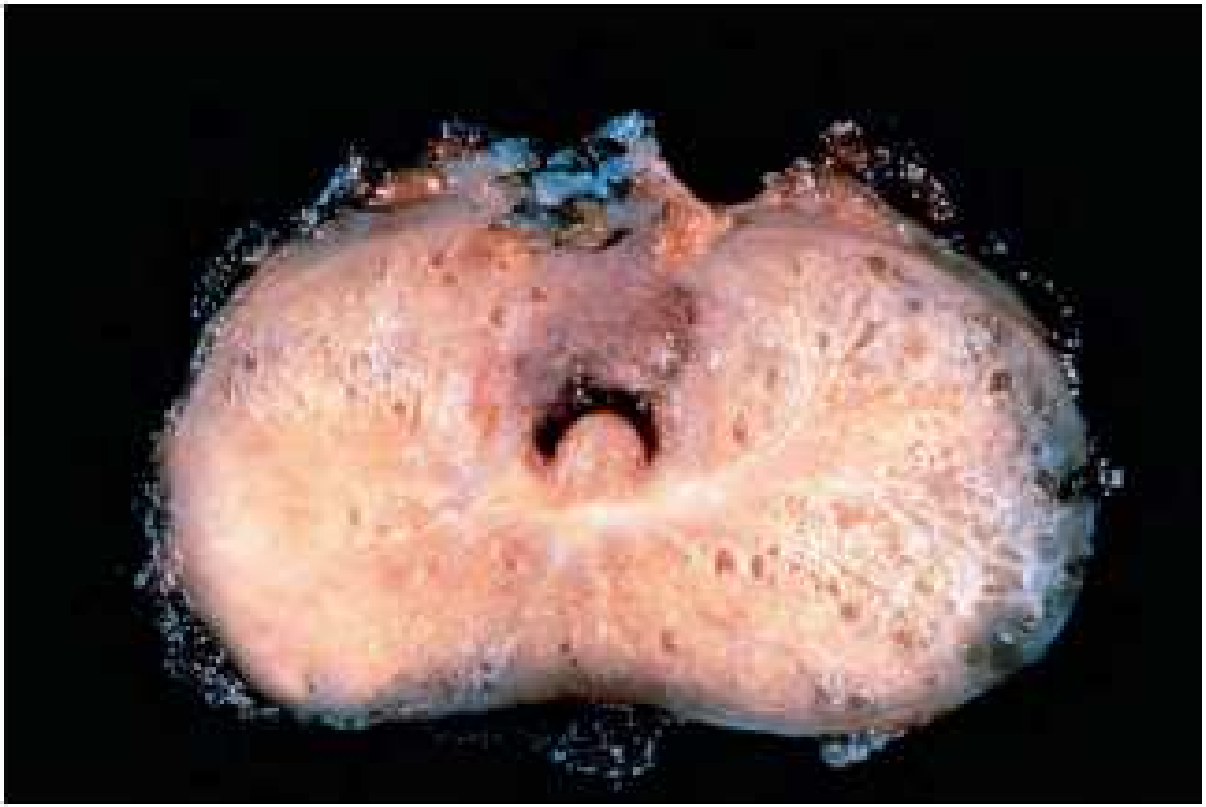


Figure 21-34 Adenocarcinoma of the prostate. Carcinomatous tissue is seen on the posterior aspect *(lower left)*. Note solid whiter tissue of cancer in contrast to spongy appearance of benign peripheral zone in the contralateral side.

Peripheral zone adenocarcinoma

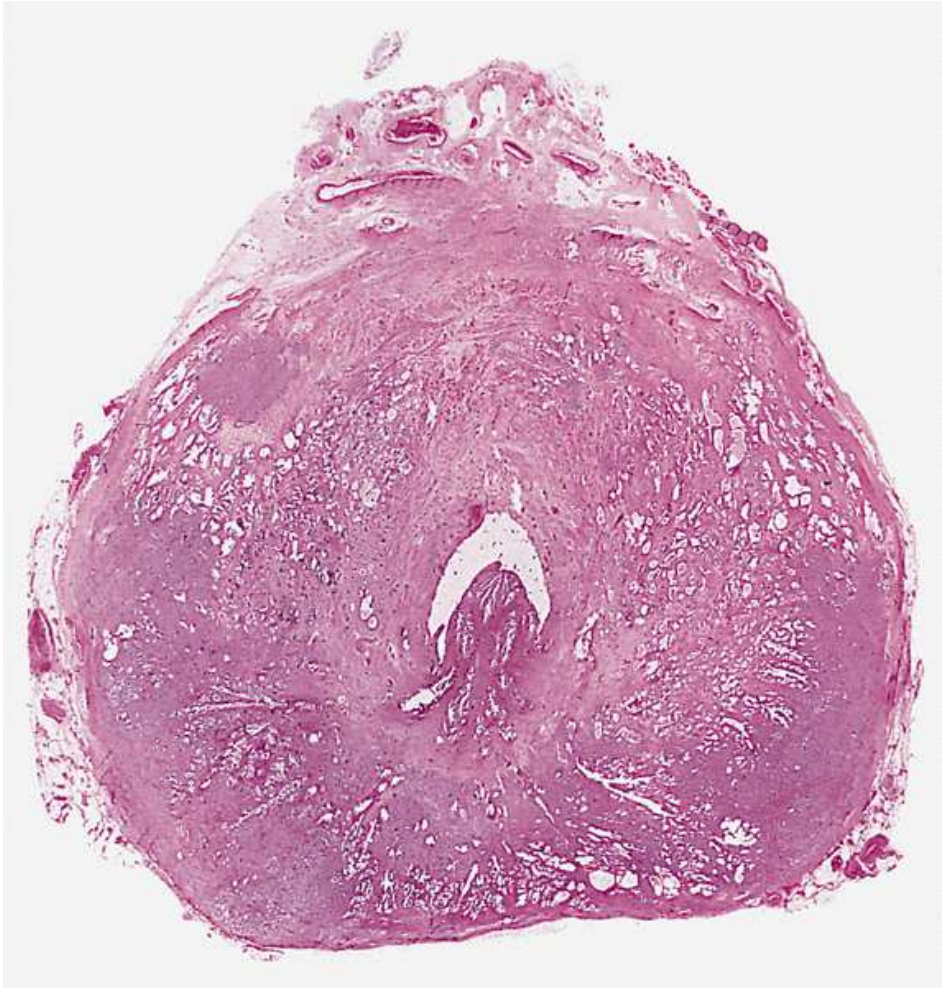


Fig. 4-10R

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.

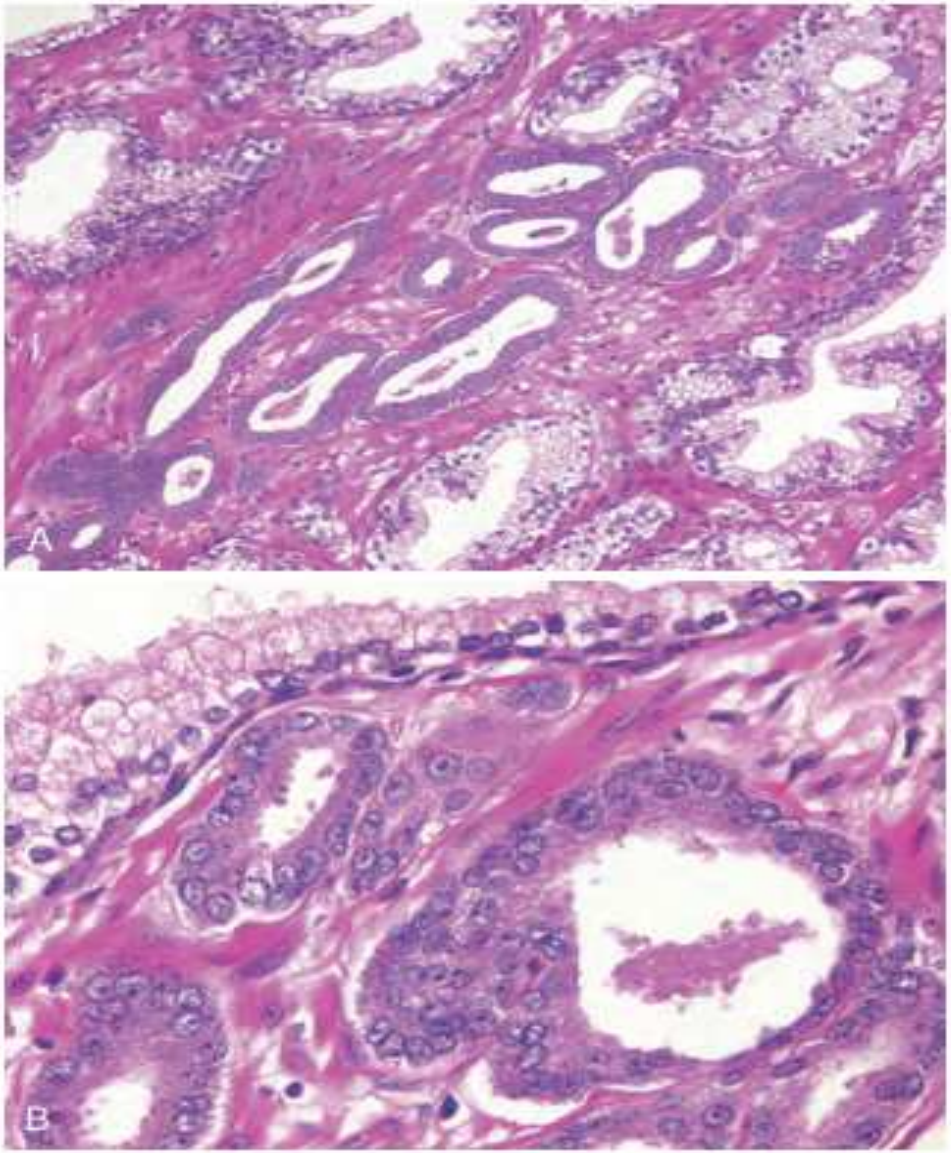


Figure 21-36 **A,** Photomicrograph of small focus of adenocarcinoma of the prostate demonstrating small glands crowded in between larger benign glands. **B,** Higher magnification shows several small malignant glands with enlarged nuclei, prominent nucleoli, and dark cytoplasm, compared with larger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

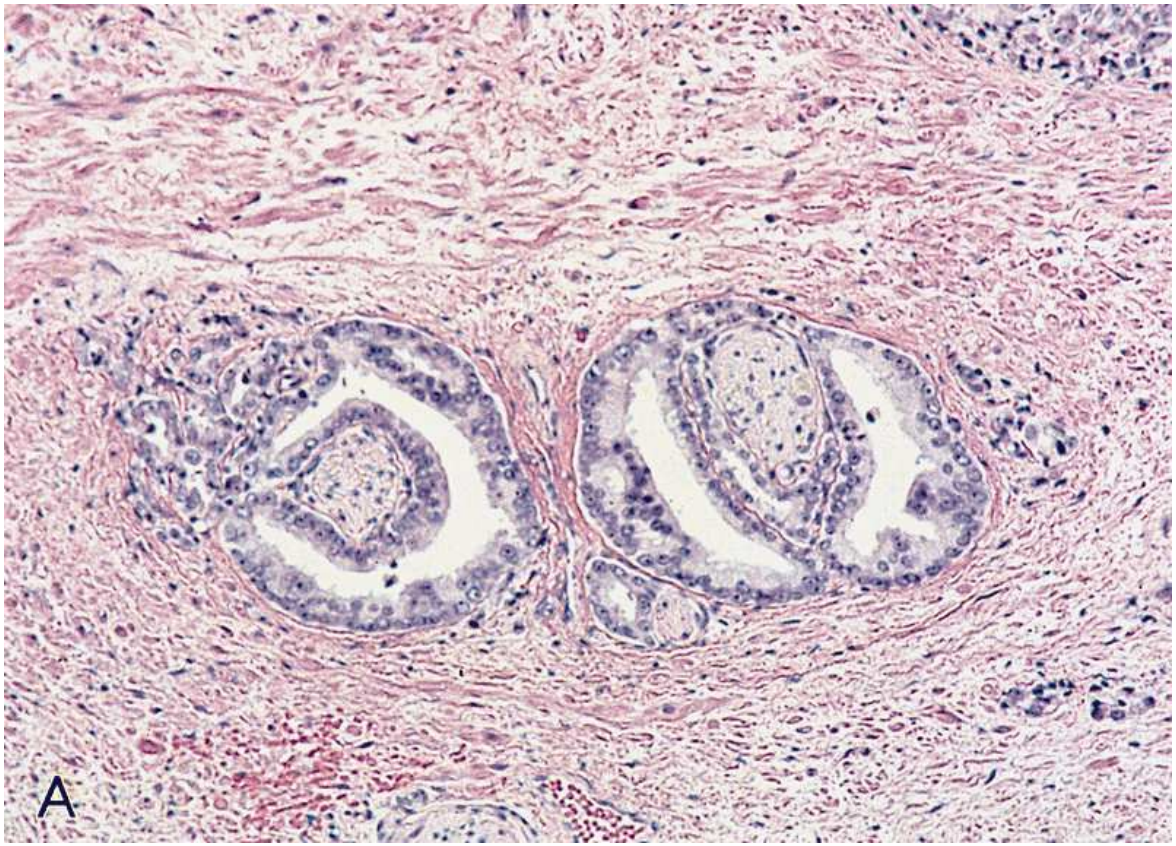


Fig. 4-13A

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.

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.

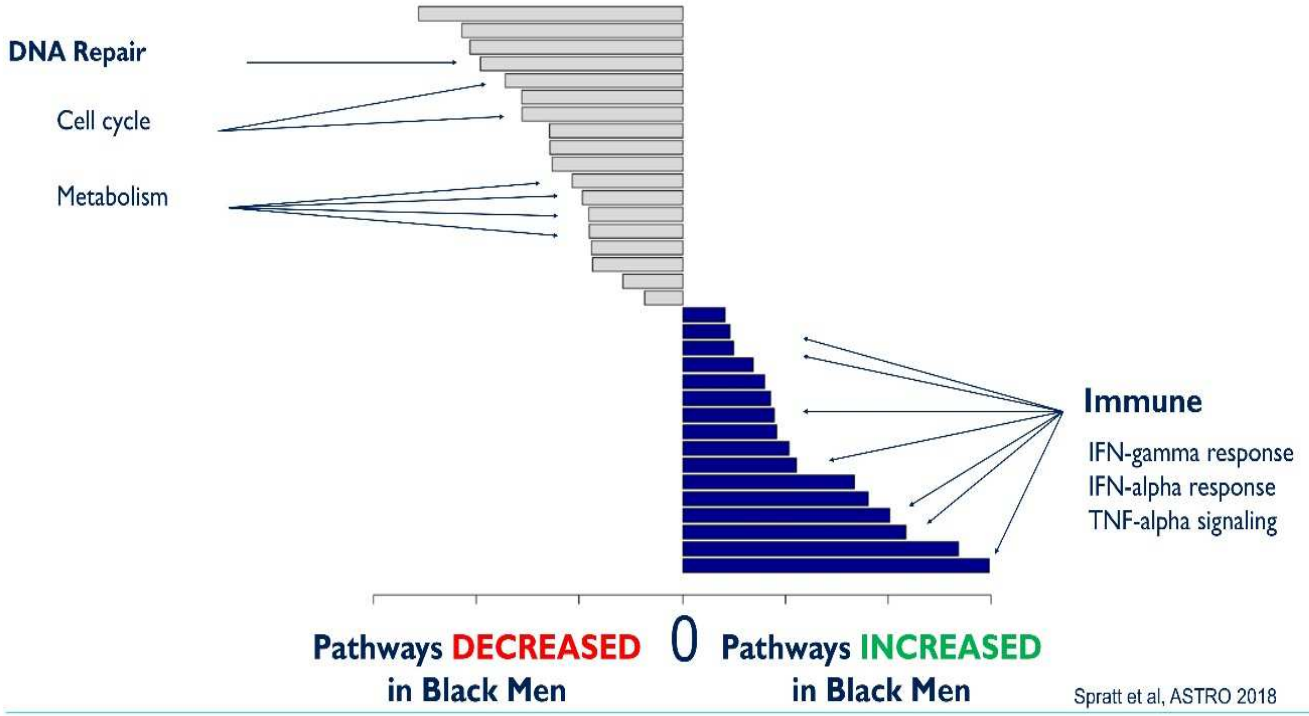
Other molecular changes

- 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



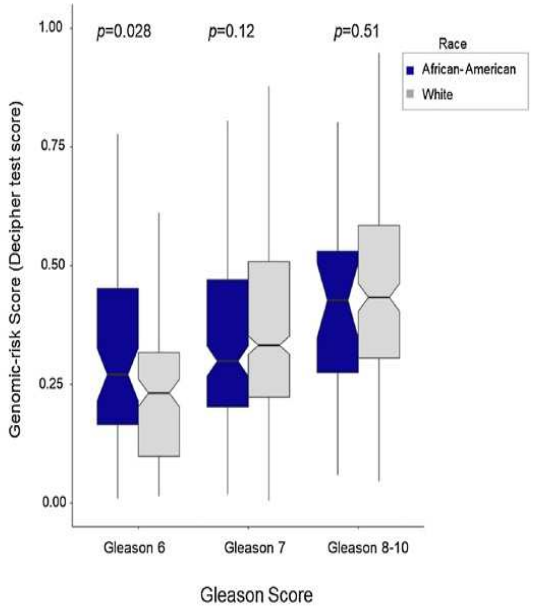
Spratt et al, ASTRO 2018

Genomic Risk Scores Across Race and Gleason Score

1240 men (286 Black men) who underwent surgery.

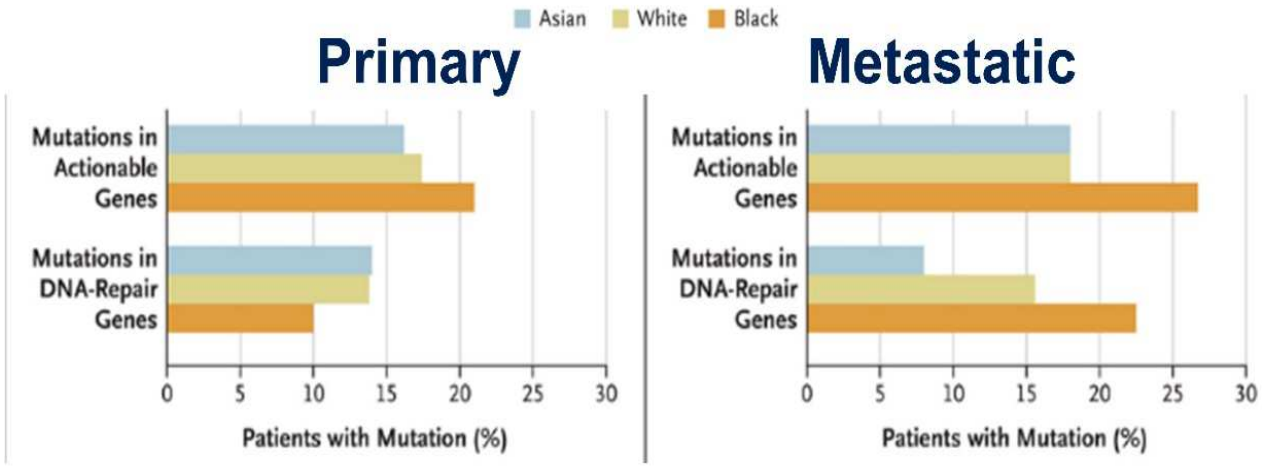
Examined genomic-risk scores that predict for risk of developing metastatic disease. Intermediate to high-risk scores have a 15% risk of metastatic disease at 10 years.

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

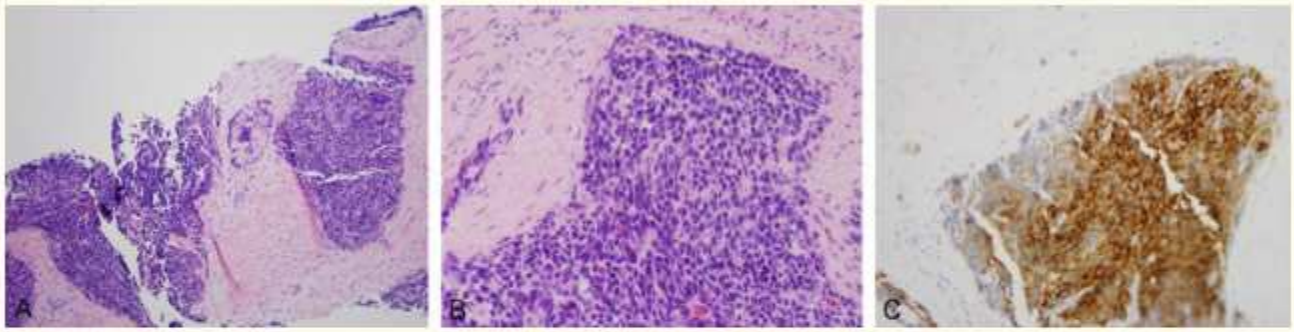


Figure 2

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

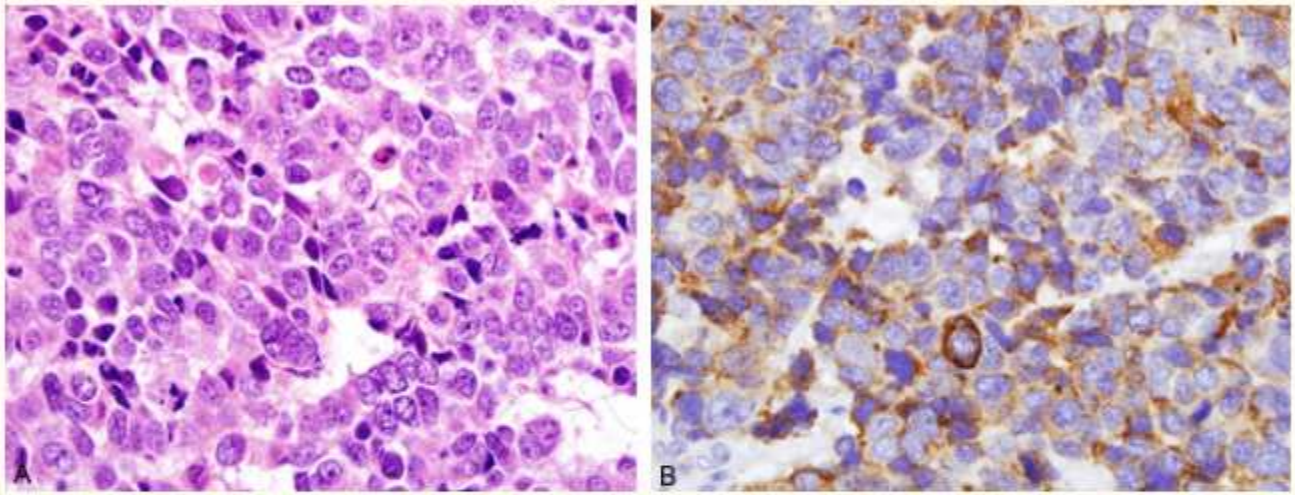


Figure 3

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

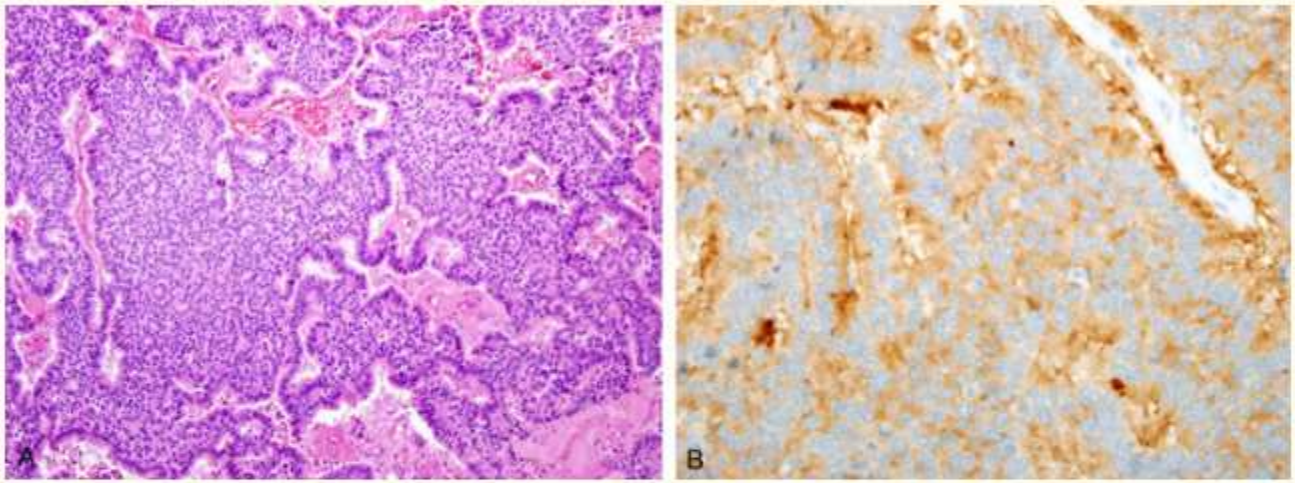


Figure 4

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

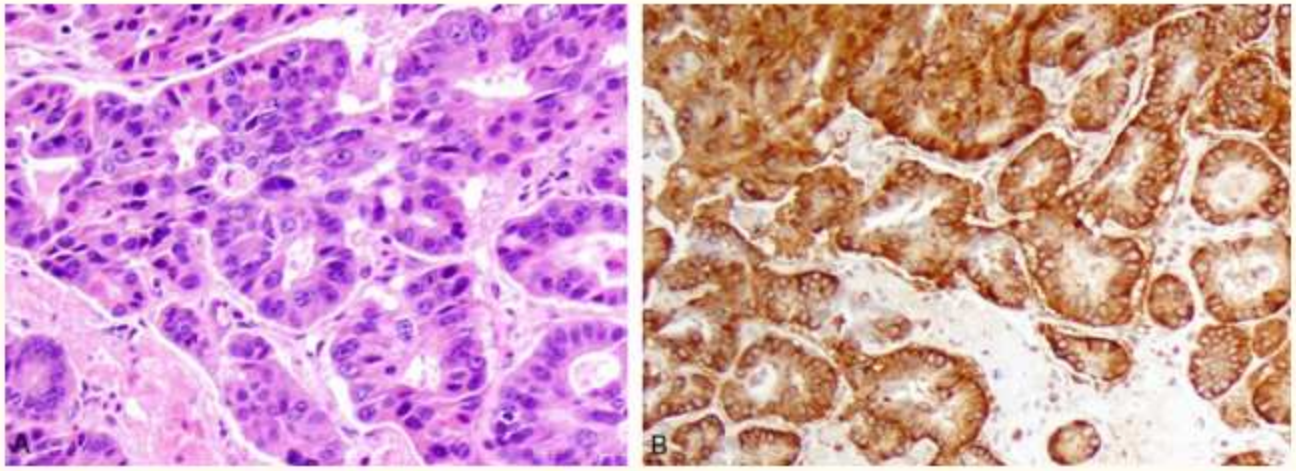


Figure 5

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

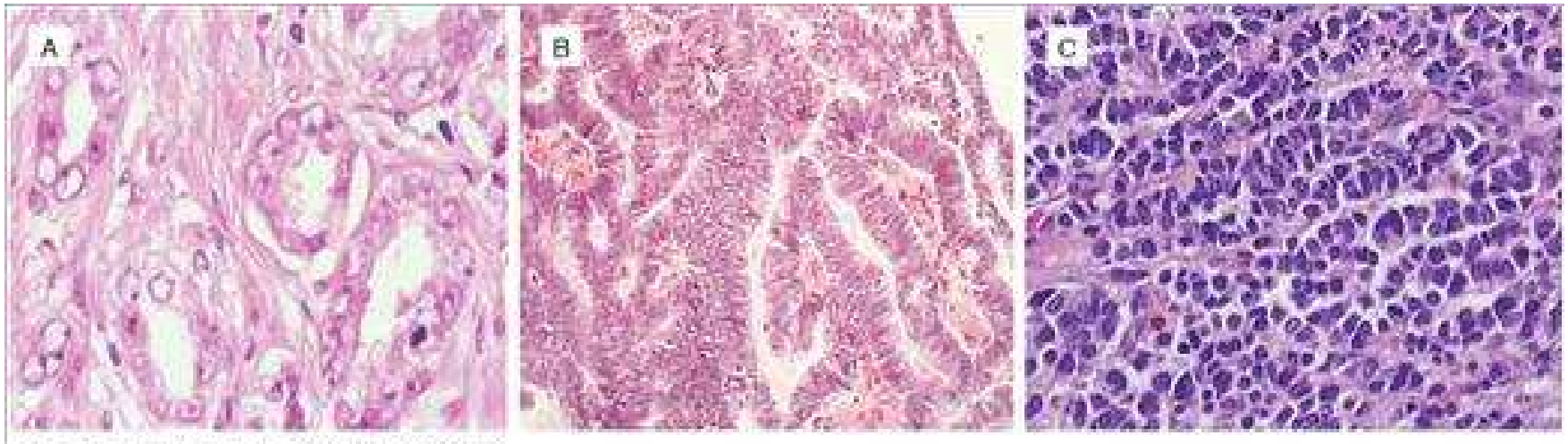
Grading

- 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.

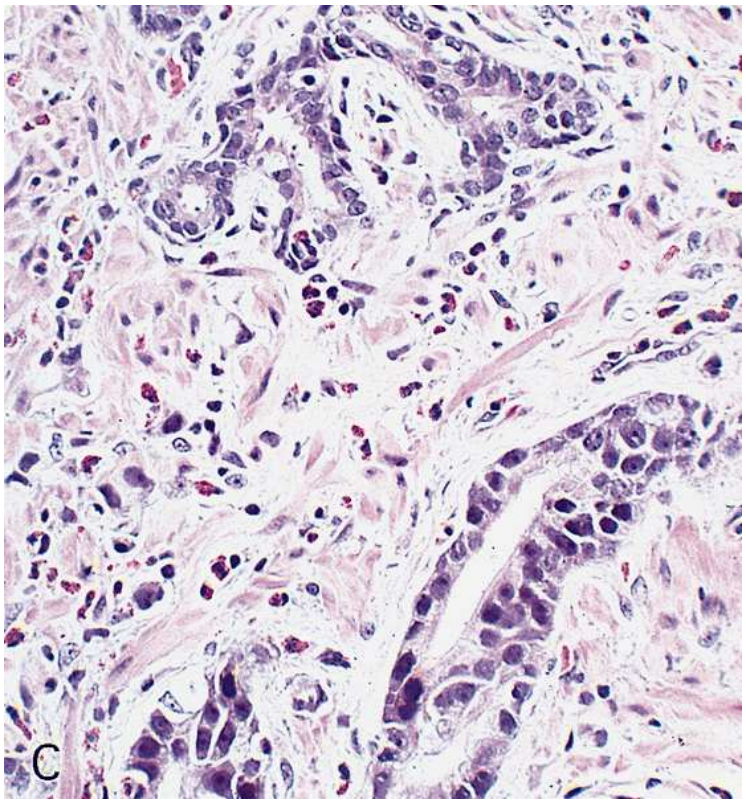
Architecture

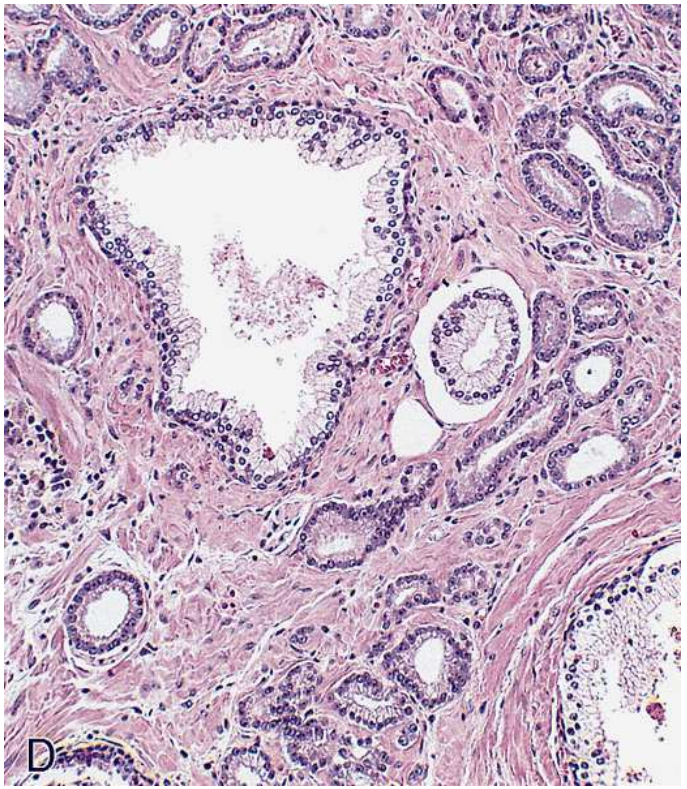


A. Prostate adenocarcinoma. B. Prostate ductal carcinoma. C. Prostate small cell carcinoma.

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.

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.

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

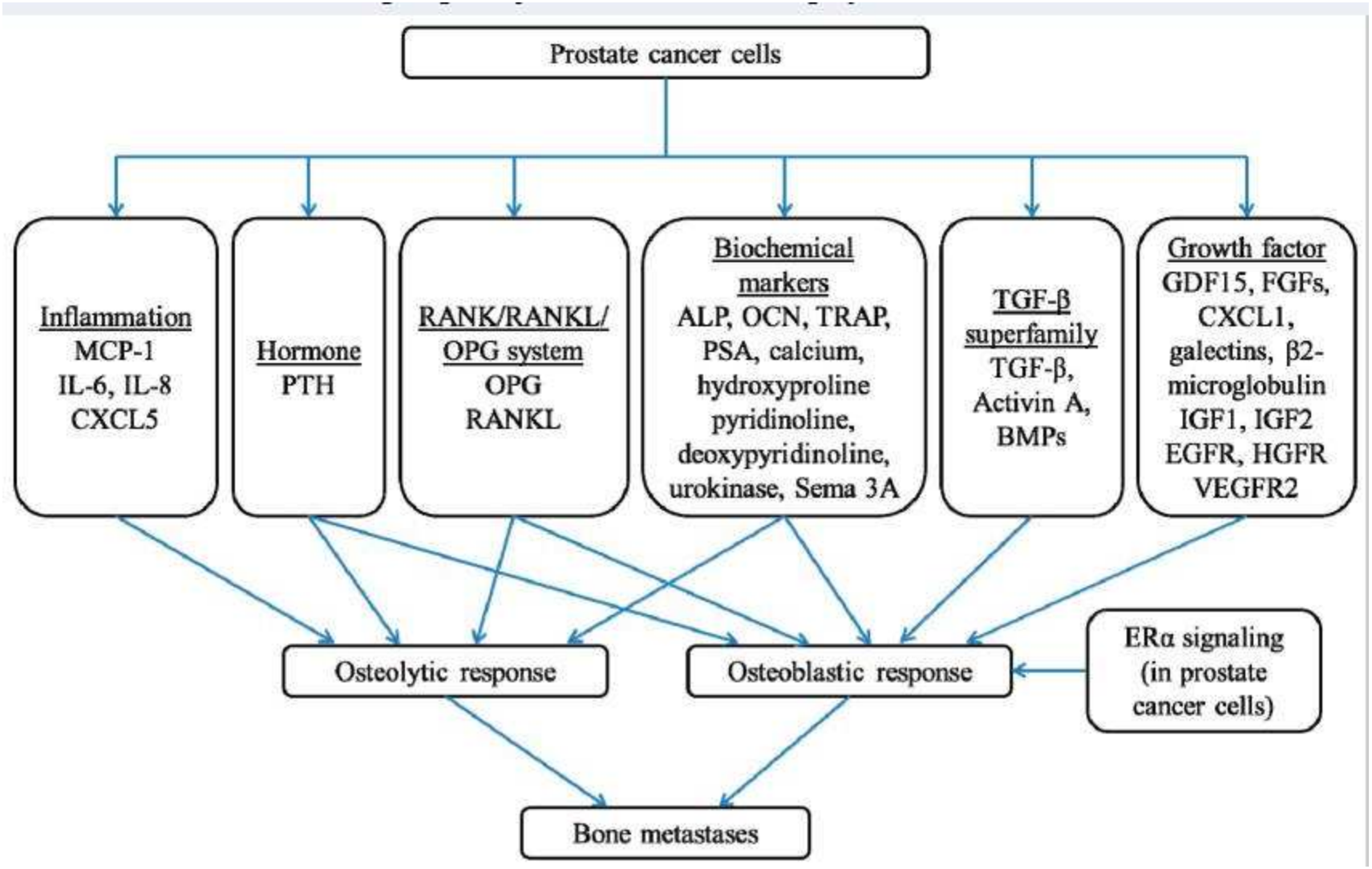
PSA, Prostate-specific antigen.

Metastasis

- Parathyroid hormone-related peptide (PTHrP) is produced by tumor cells.
- Up-regulates RANKL and down-regulates osteoprotegerin (OPG) by osteoblast to activate osteoclastogenesis and bone resorption.
- Accelerated bone resorption promotes the release of TGF-β and IGF)-1 from bone.
- The raised extracellular calcium concentration further supports the growth of cancer cells.

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.
- Poor risk are patients M1 de novo or within 3 months of presentation



10.3390/ijms20102587

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

- 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.

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.

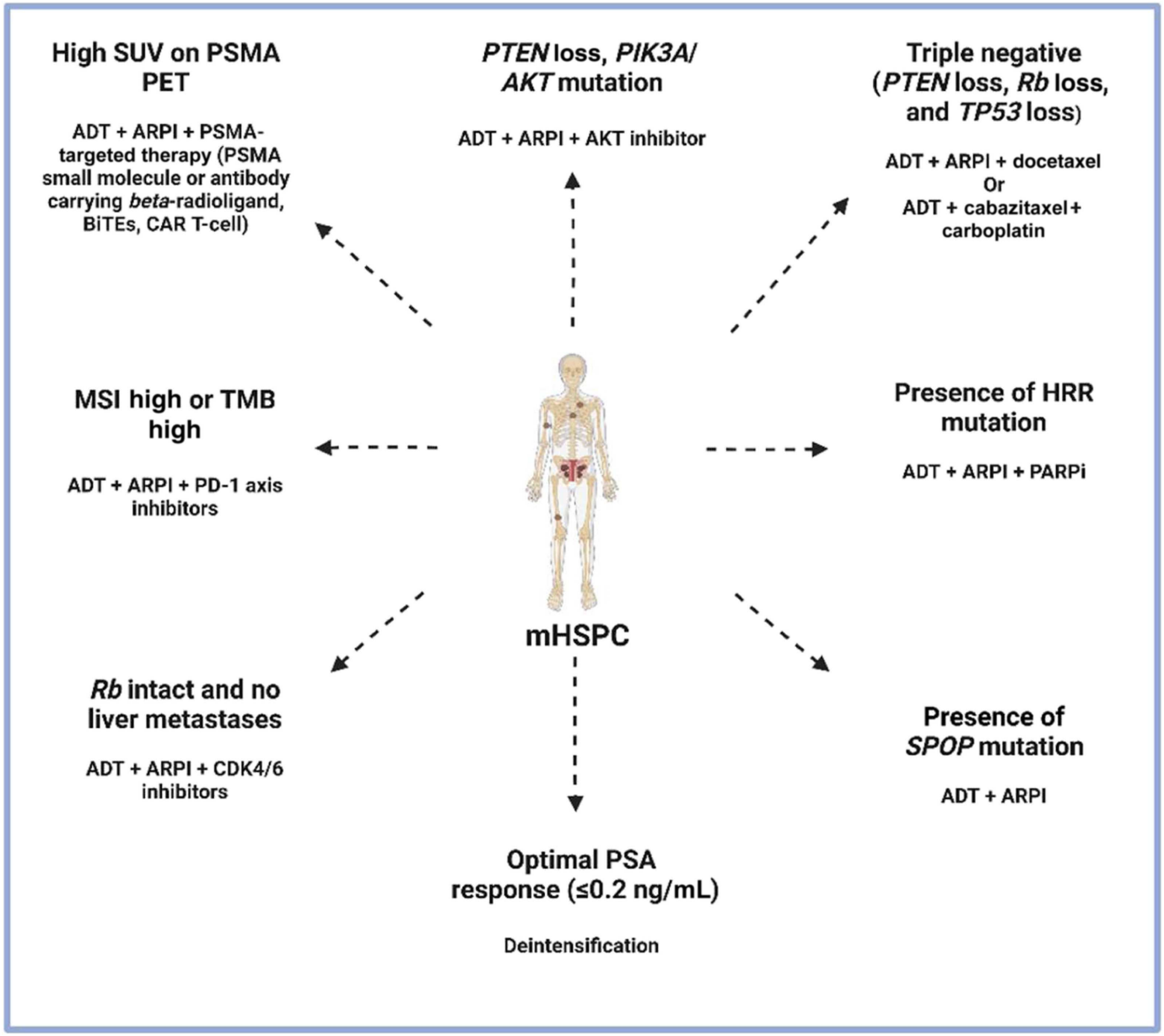
Therapy of prostate cancer

- 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.


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

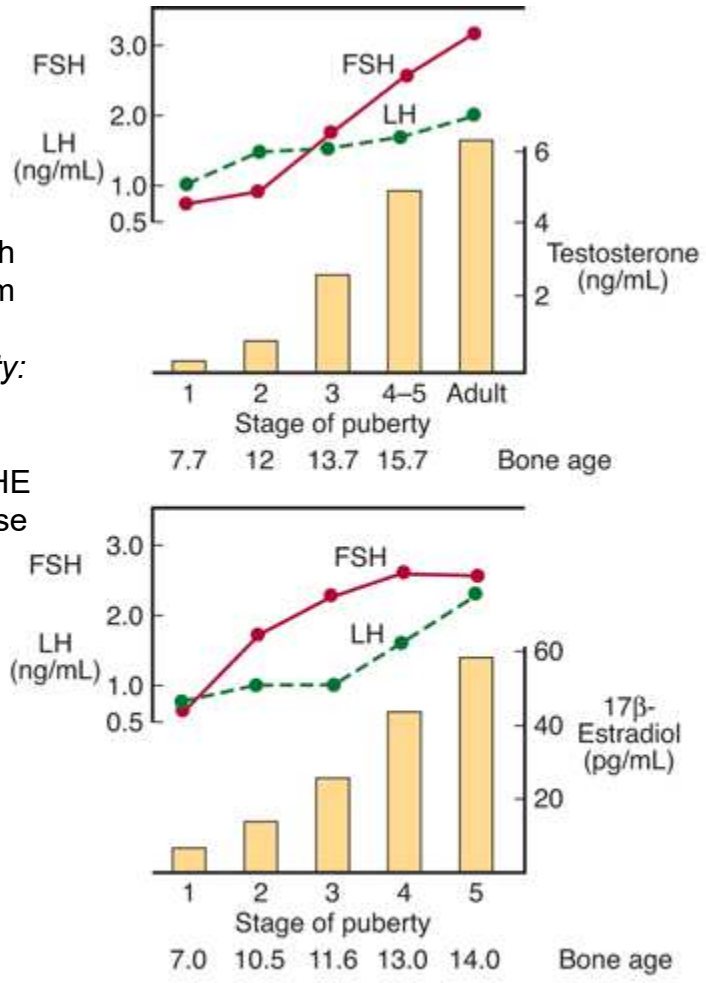
- Radiation to painful bone metastases offers effective palliation (two vertebral bodies above and below involved body).
- Spinal cord compression is an emergency.
- Begin dexamethasone, then radiotherapy. As spinal cord tolerates up to 50Gy radiation, initial treatment with 30 Gy permits retreatment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

Therapy of prostate cancer

- ^{89}Strontium (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

TESTICULAR CANCER

Puberty (boys)



(Modified and reproduced with permission from Berenberg SR (editor): *Puberty: Biologic and Psychosocial Components.* HE Stenfoert Kroese BV, 1975.)

Stage 1 of puberty is preadolescence.
Stage 2 is characterized by beginning enlargement of the testes.
Stage 3 is charactrized by penile enlargement.
Stage 4 is characterized by growth of the glans penis.
Stage 5 is characterized by adult genitalia.

Fig. 25-9
Accessed 02/01/2010

Precocious puberty

- Secondary sex characteristics develop before 9 years of age in boys.
- Short stature may be present because of epiphyseal closure.
- Testicular enlargement suggests increased LH, FSH secretion. Determine HCG as well.
- Consider tumor (pituitary, pineal, testes).
- No testicular enlargement suggests an exogenous or adrenal source.
- Hypothyroid state can lead to precocious puberty. Check TSH.

Testicular cancer

- 1% all malignancies in men
- Presents as testicular mass
- 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 contra-lateral testis a risk factor.
- HIV also risk factor.
- 95% are germ cell tumors.

Testicular cancer

- Klinefelter syndrome (XXY)
- Increased risk of mediastinal germ tumor, not testicular germ cell tumor

Testicular cancer

- 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.

Testicular tumors

- 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 are 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

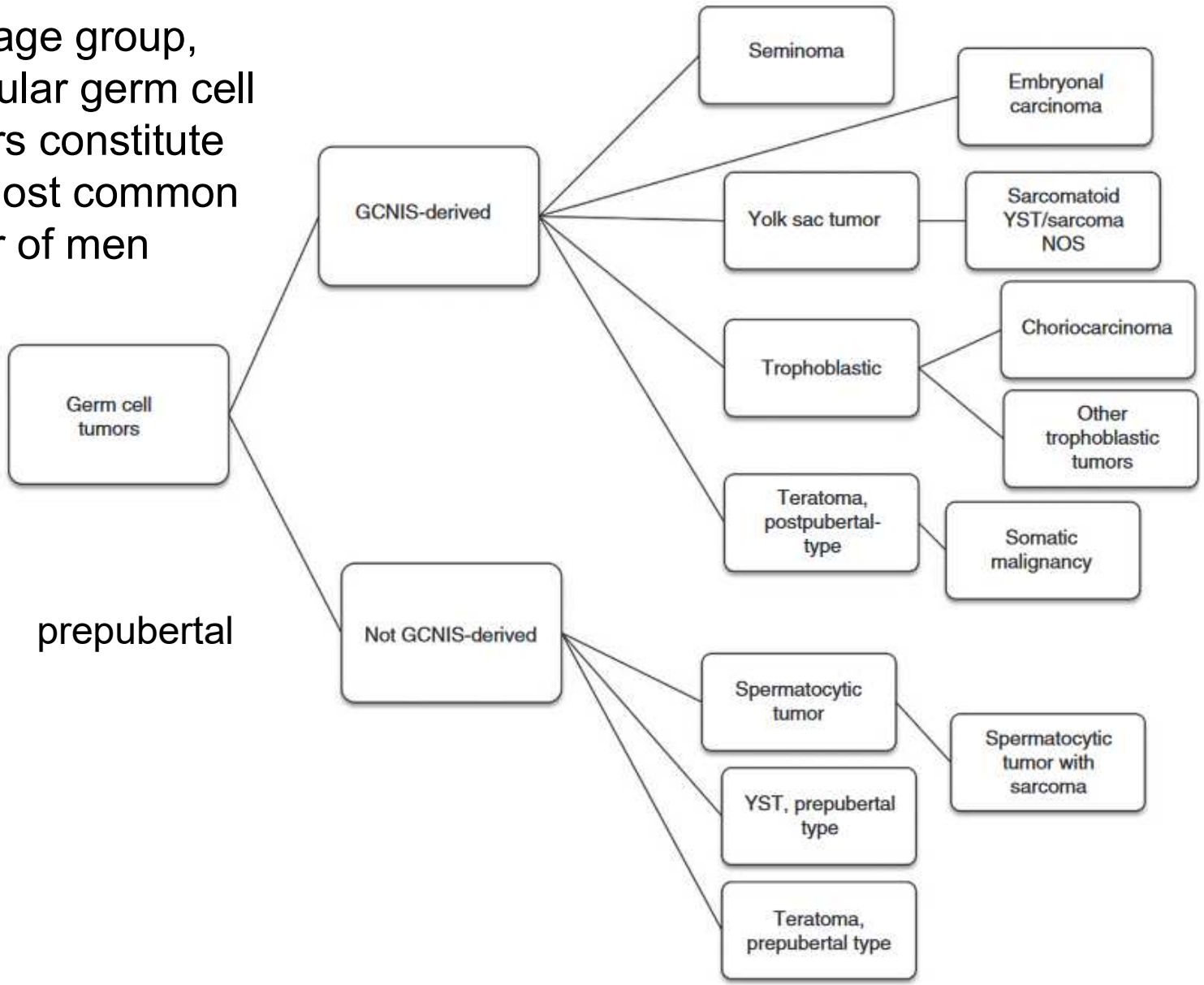


Figure 2. In the 2016 edition of the World Health Organization classification, germ cell tumour classification is restructured into tumours derived from germ cell neoplasia *in situ* (GCNIS) and those not derived from GCNIS. NOS, not otherwise specified; YST, yolk sac tumour.

Testicular cancer

- Screen with ultrasound.
- Chest x-ray to exclude pulmonary metastases.
- β-HCG. 24 hour half-life. Choriocarcinoma. Proliferation of syncytiotrophoblasts and cytotrophoblasts.
- AFP. 5-7 day half-life. Non-seminomatous elements; generally yolk-sac or embryonal cell cancers.
- CT of chest, abdomen, and pelvis to establish extent of disease dissemination.
- MRI when results equivocal or in presence of CNS symptoms.

Treatment of precocious puberty

- Gonadotropin analogs will suppress endogenous secretion in gonadotropin dependent disease.
- Gonadotropin independent disease in boys treated with antiandrogens (spironolactone), ketoconazole, aromatase inhibitors are used.
- Dysgerminoma of the pineal is radiosensitive.
- Hepatoblastoma has very poor prognosis.

Testicular cancers

- Germ cell tumors may have a single tissue component;
- However, up to 60% conatin mixtures of seminomatous and non-seminomatous elements.
- Arise as an intratubular germ cell neoplasm.
- OCT3/4 and NANOG over-expressed.
- i12p found

Testicular cancers

- Seminomatous tumors are characterized by cells that resemble primoridal germ cells or early gonocytes.
- Non-seminomatous tumors may contain undifferentiated cells that resemble embryonic stem cells.
- The malignant cells can differentiate into various lineages, however.
- Teratomas contain tissues of the three germ layers.

Seminoma

- 50% of testicular tumors are seminomas.
- It is a germ cell tumor.
- Peak incidence in third decade.
- Never seen in infants.
- Generally, the tunica albuginea is not penetrated.

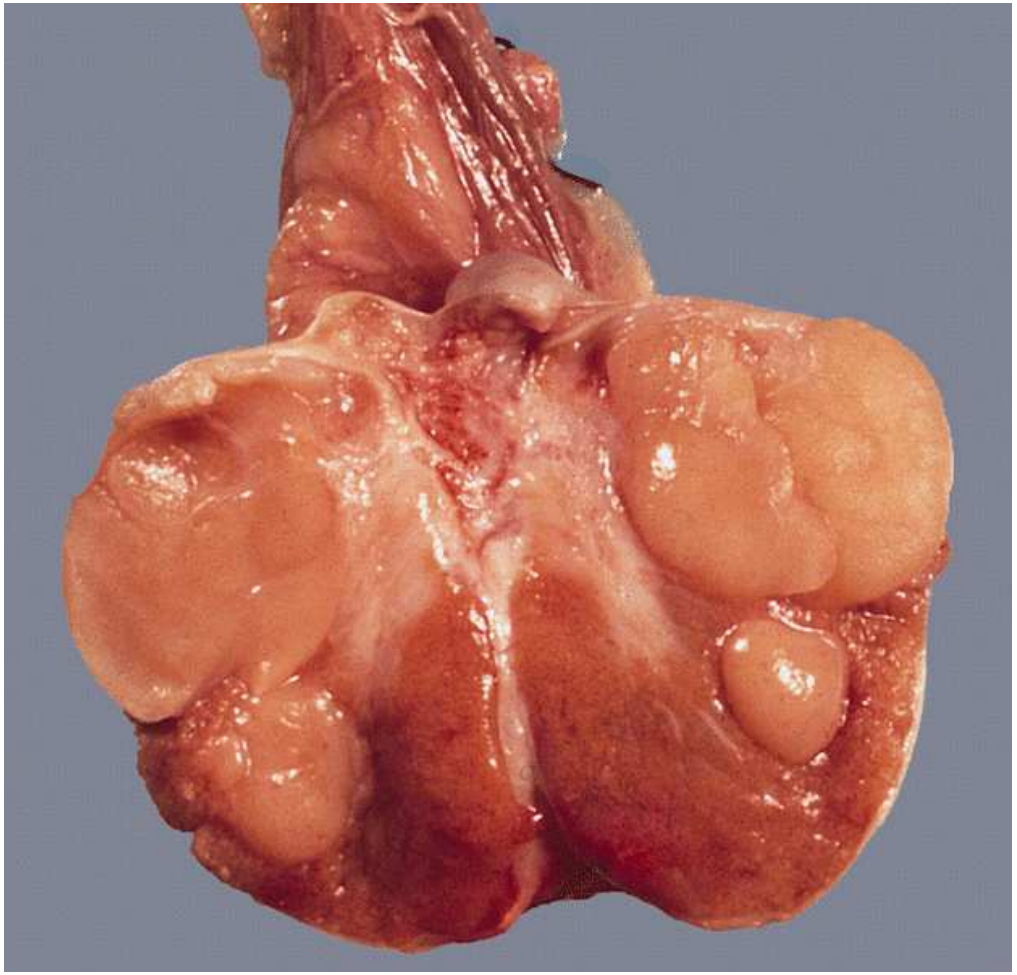
Seminoma

- The typical seminoma has a homogeneous, graywhite, lobulated cut surface, usually devoid of hemorrhage or necrosis
- Characterized by sheets of uniform cells divided into poorly loculated lobules by delicate fibrous tissue septa containing lymphocytes.
- Tumor cells are large and round with distinct cell membranes. The cytoplasm is clear.
- There is a large central nucleus with one or two prominent nucleoli ("fried egg" appearance).

Seminoma

- Mitoses vary in frequency.
- Anaplastic elements of no prognostic value
- 15% of seminomas may contain syncytiotrophoblasts (and elevated HCG).
- Granulomatous reaction may also be seen.
- Occasionally tumor giant cells are identified.
- Contain i(12p), OCT3/4, NANOG
- 25% have c-kit mutations

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

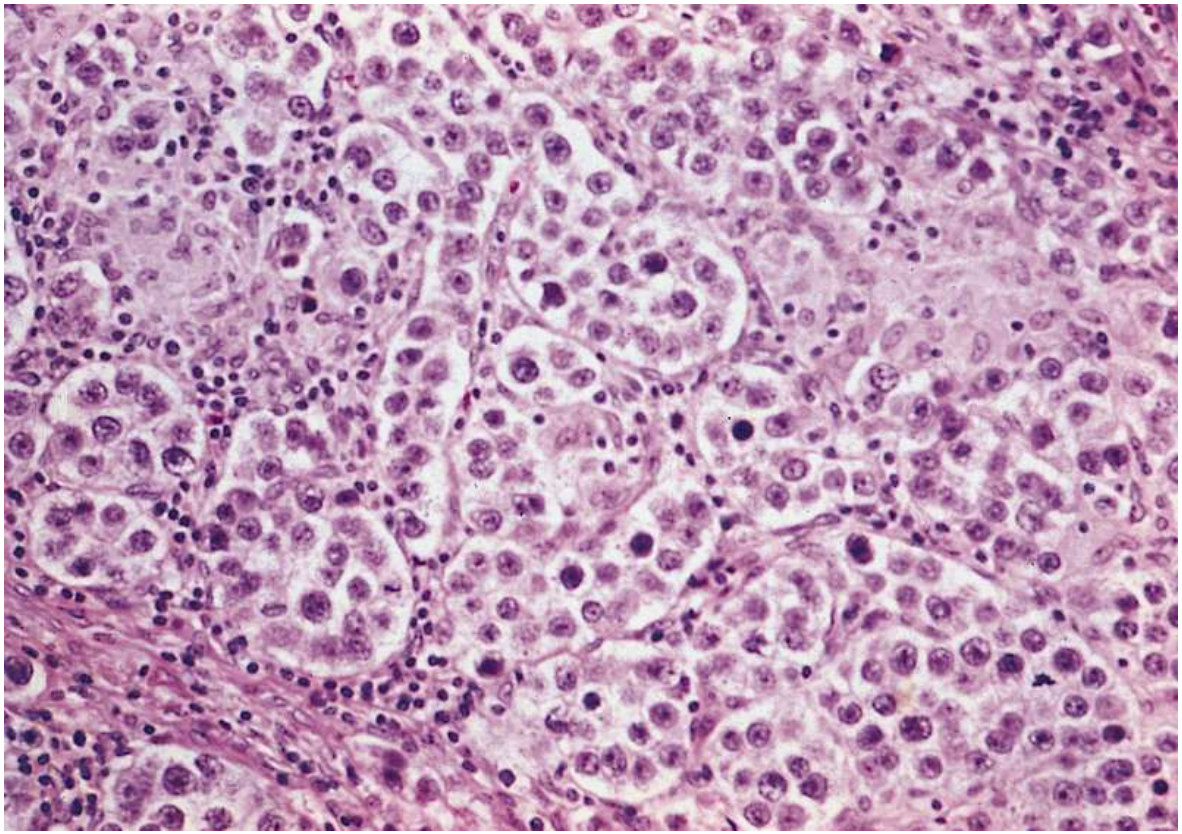


Fig. 3-07
T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

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.

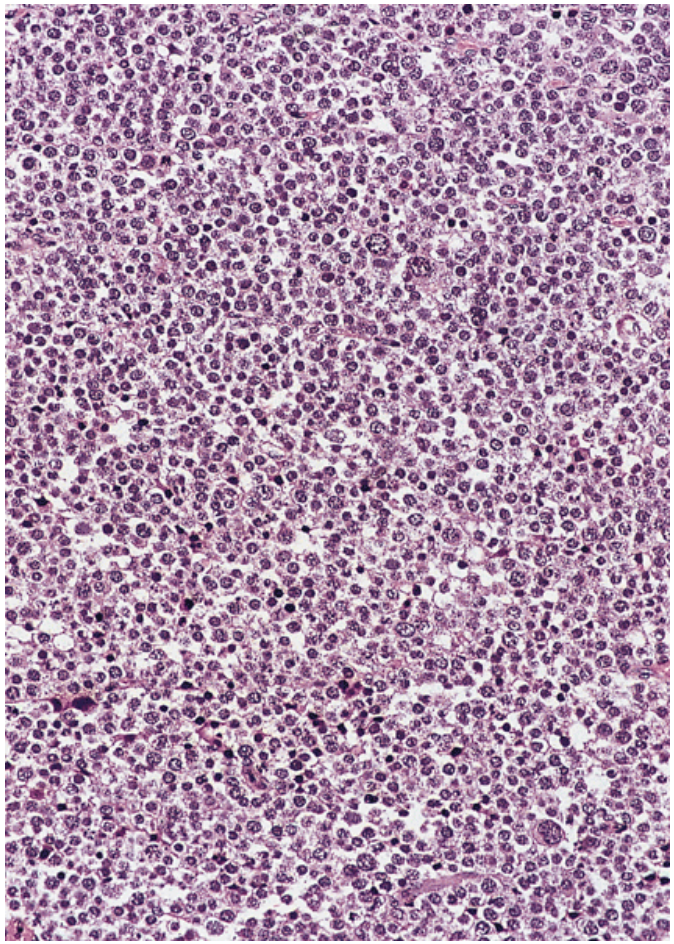
Spermatocytic tumor

- 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

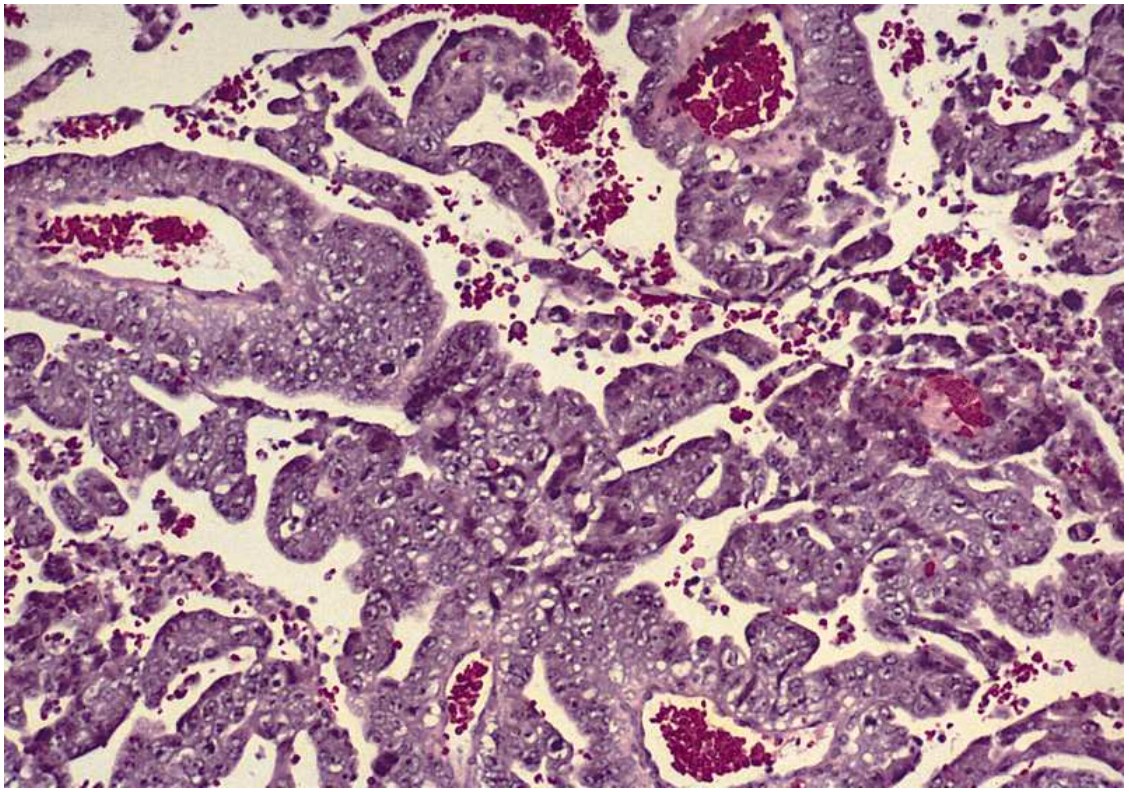


Fig. 13-32

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

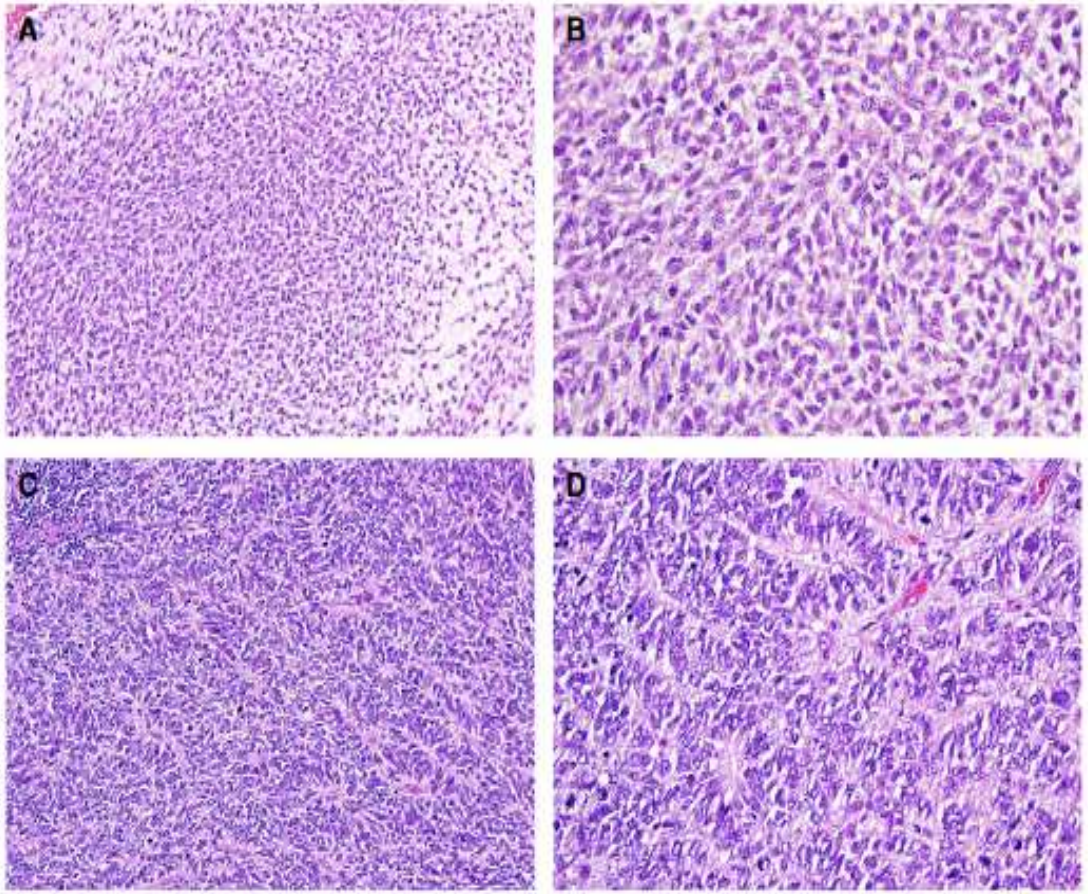


Figure 5. Secondary, somatic-type malignancy arising from germ cell tumour may assume various histologies. Sarcomas are common, including embryonal rhabdomyosarcoma (**A,B**), here forming a primitive small-cell neoplasm with spindle-shaped cells and brisk mitotic activity. Immunohistochemical staining 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

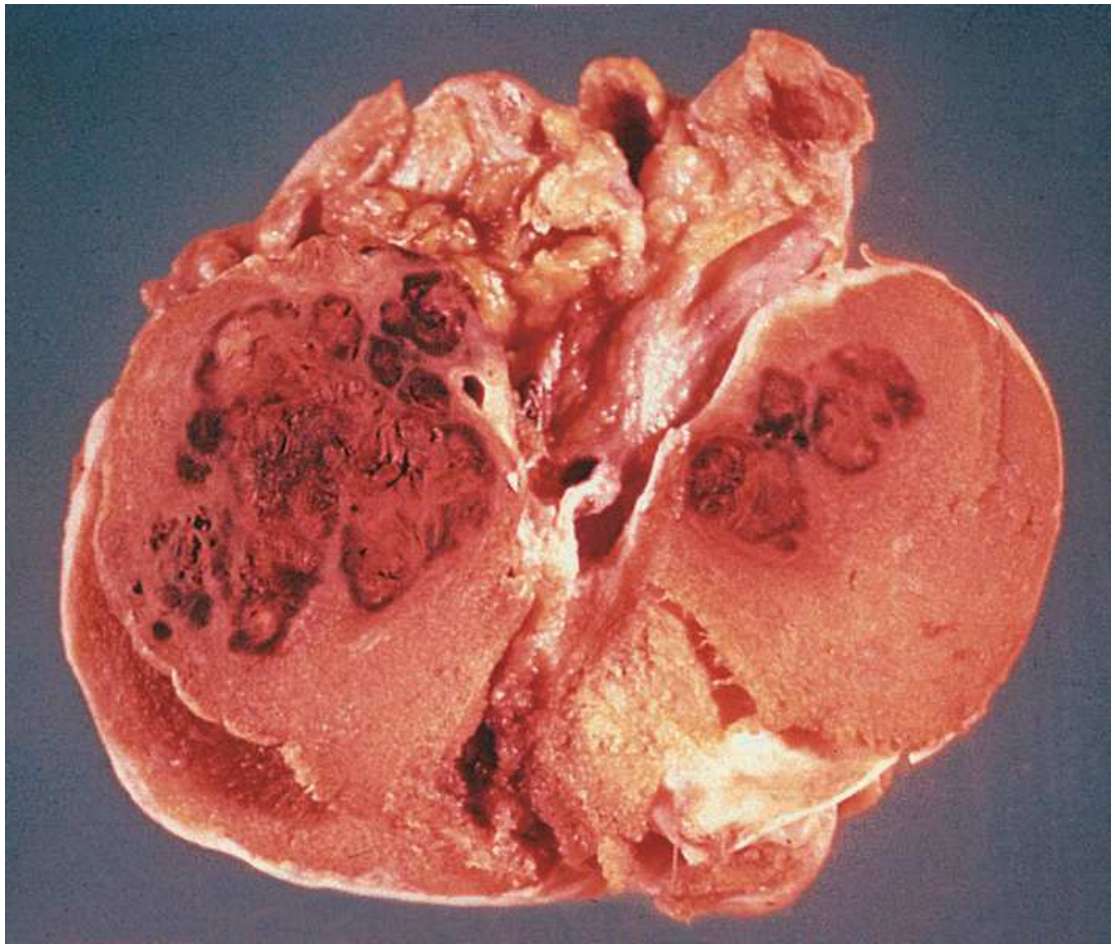
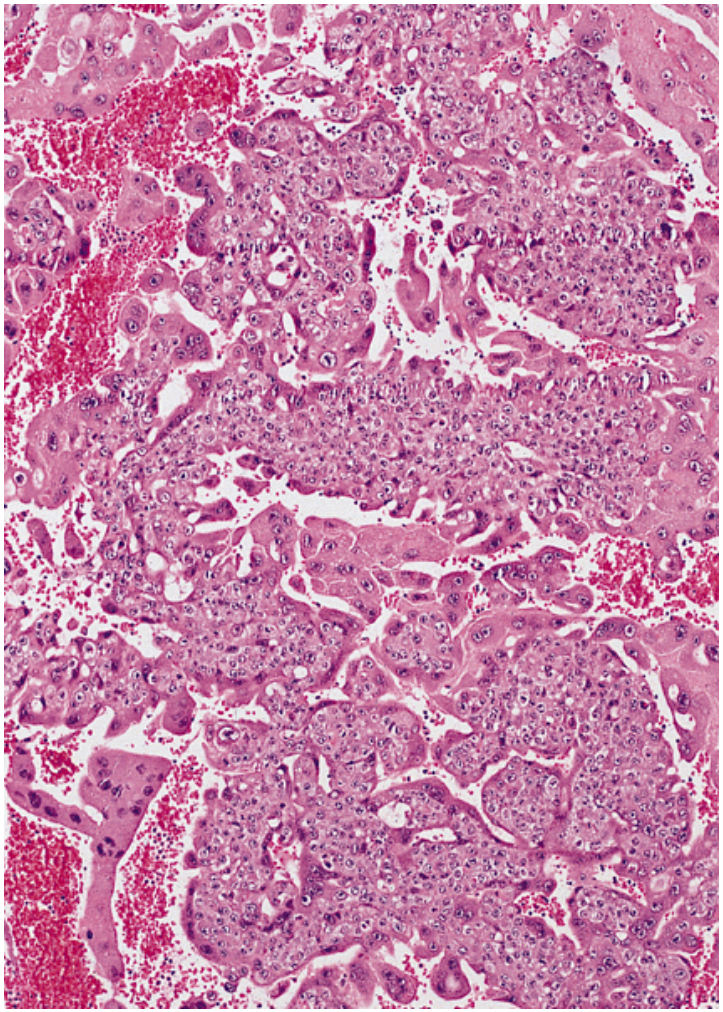


Fig. 4-59

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

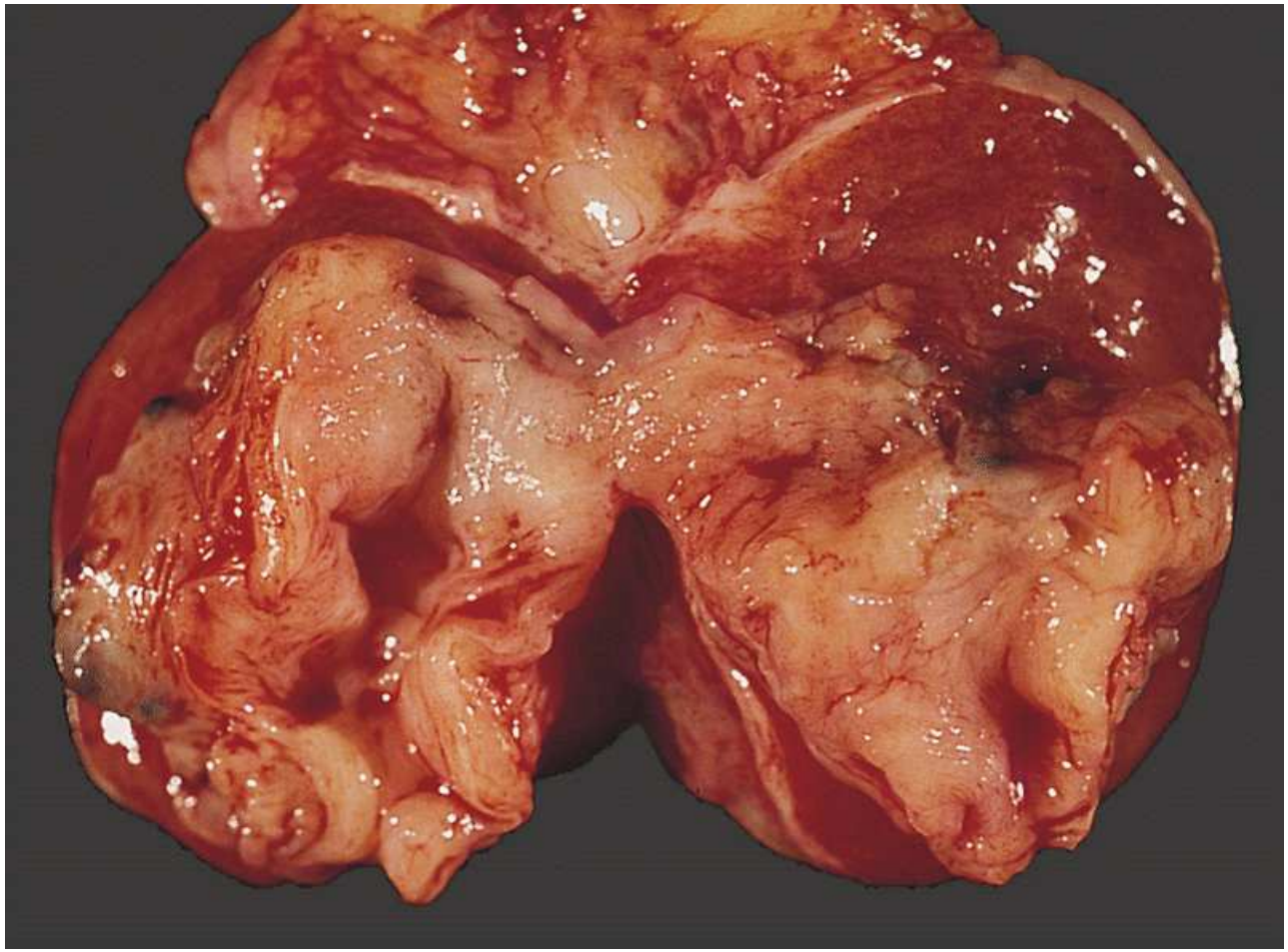
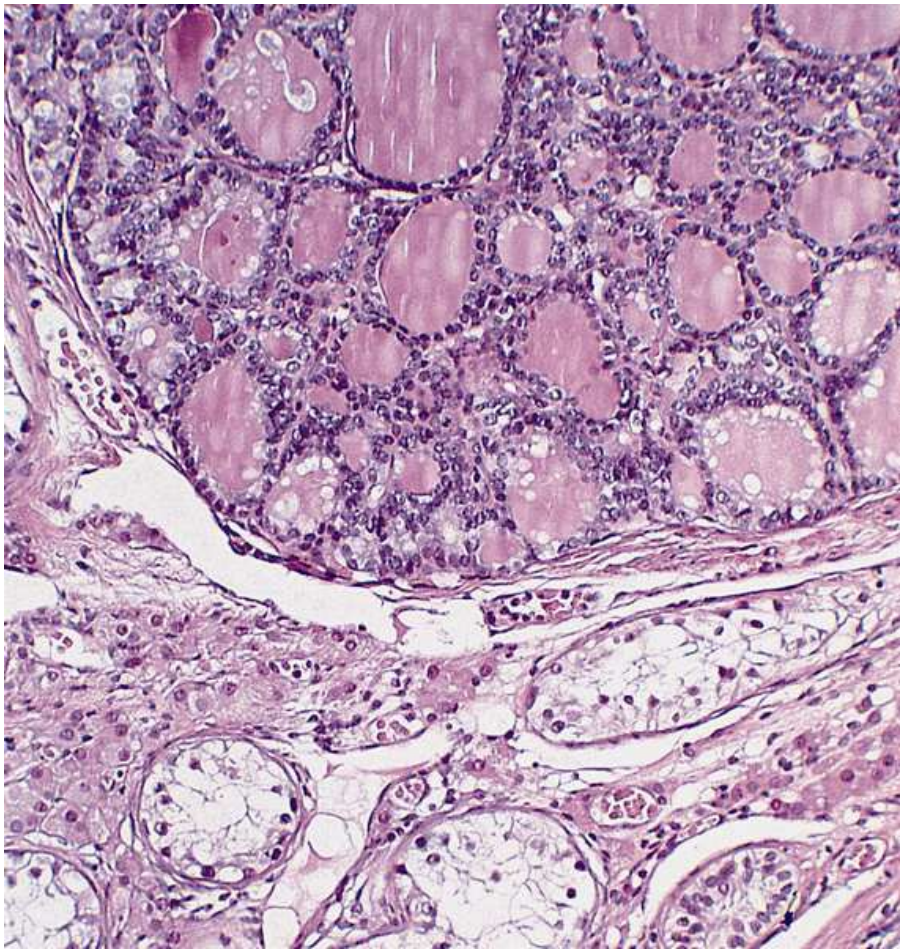


Fig. 4-77

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

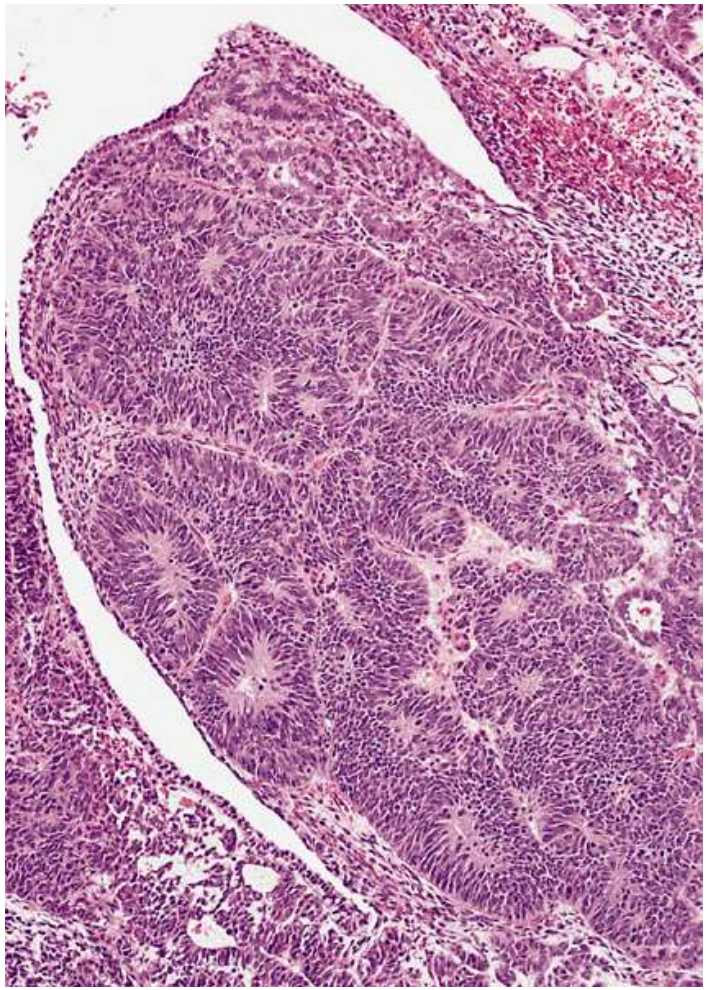


Comprised of endodermal, ectodermal, and mesenchymal elements.
If no neural tissues, nor other carcinomas, are benign.
Here, note thyroid tissue in testis.

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.

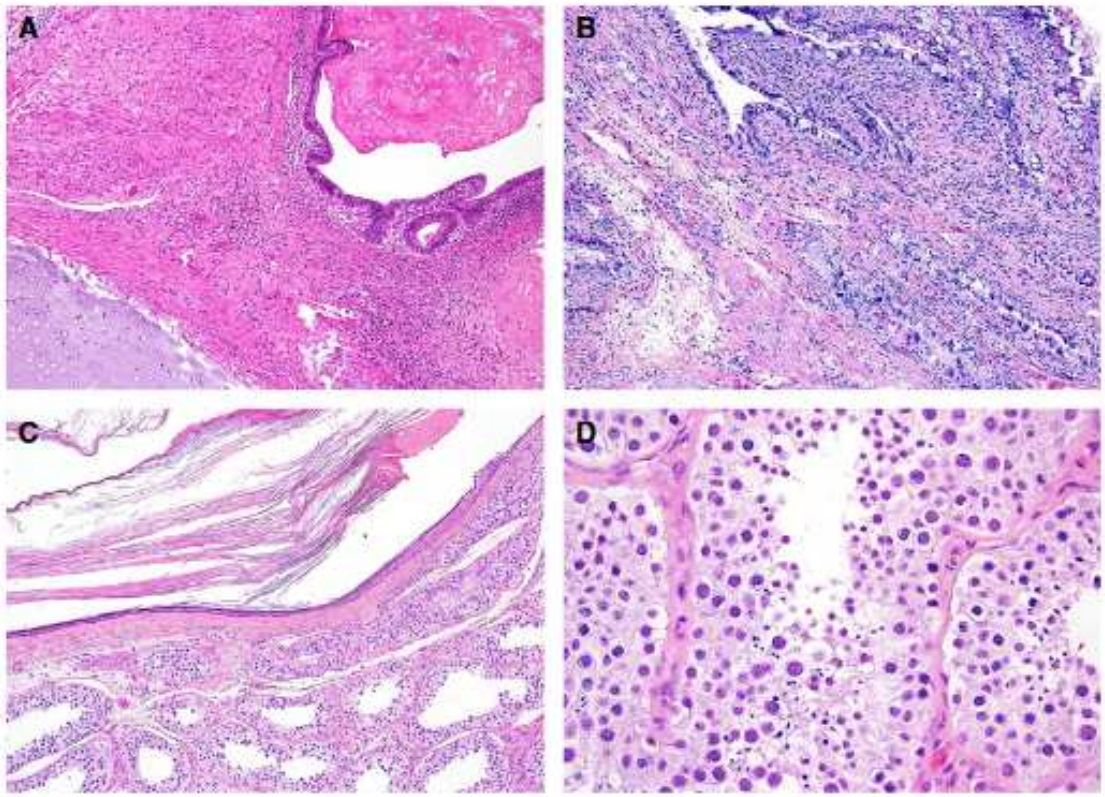


Figure 4. Postpubertal-type teratoma (A) is composed of a haphazard arrangement of varying amounts of ectodermal, mesodermal or endodermal elements, sometimes with substantial cytological atypia (B). In the absence of overgrowth or destructive invasion by a single element, cytological atypia alone does 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 pattern
- 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.

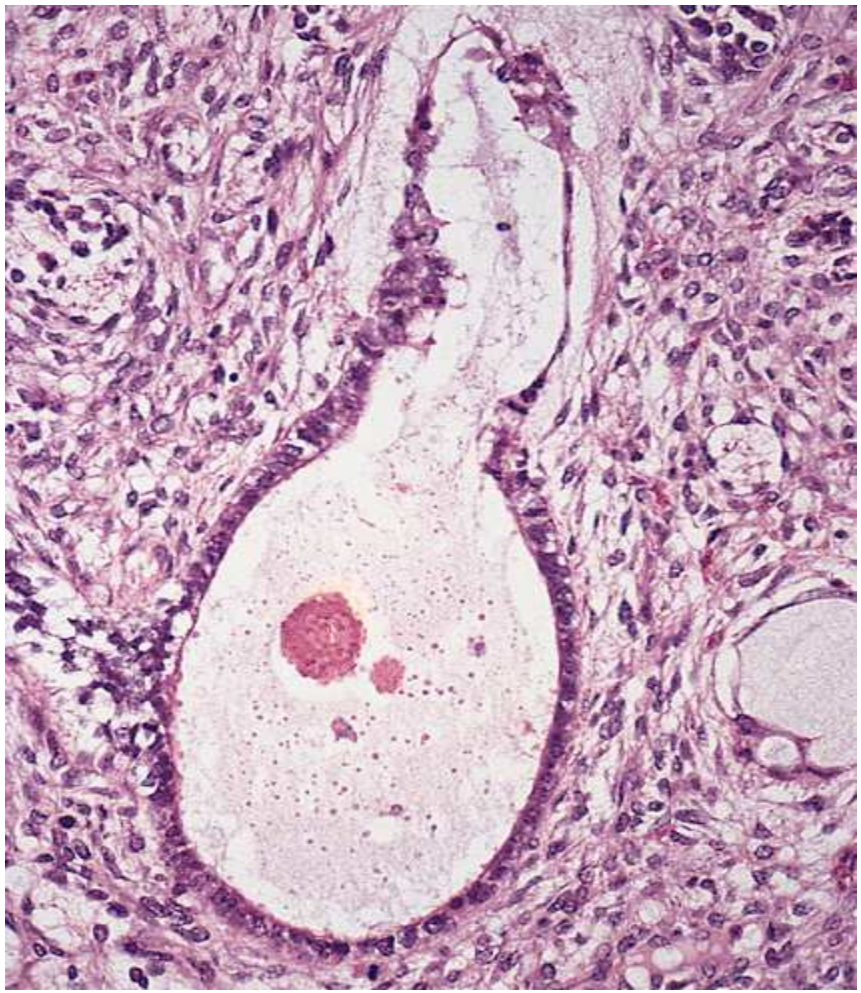
Yolk sac tumors

- 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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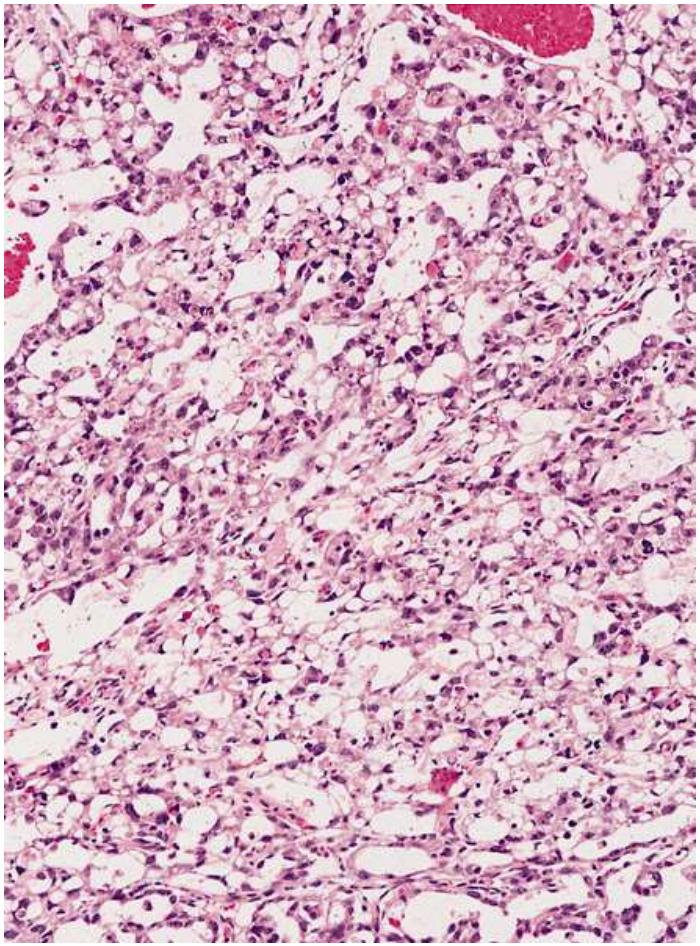
Yolk sac tumor of testis

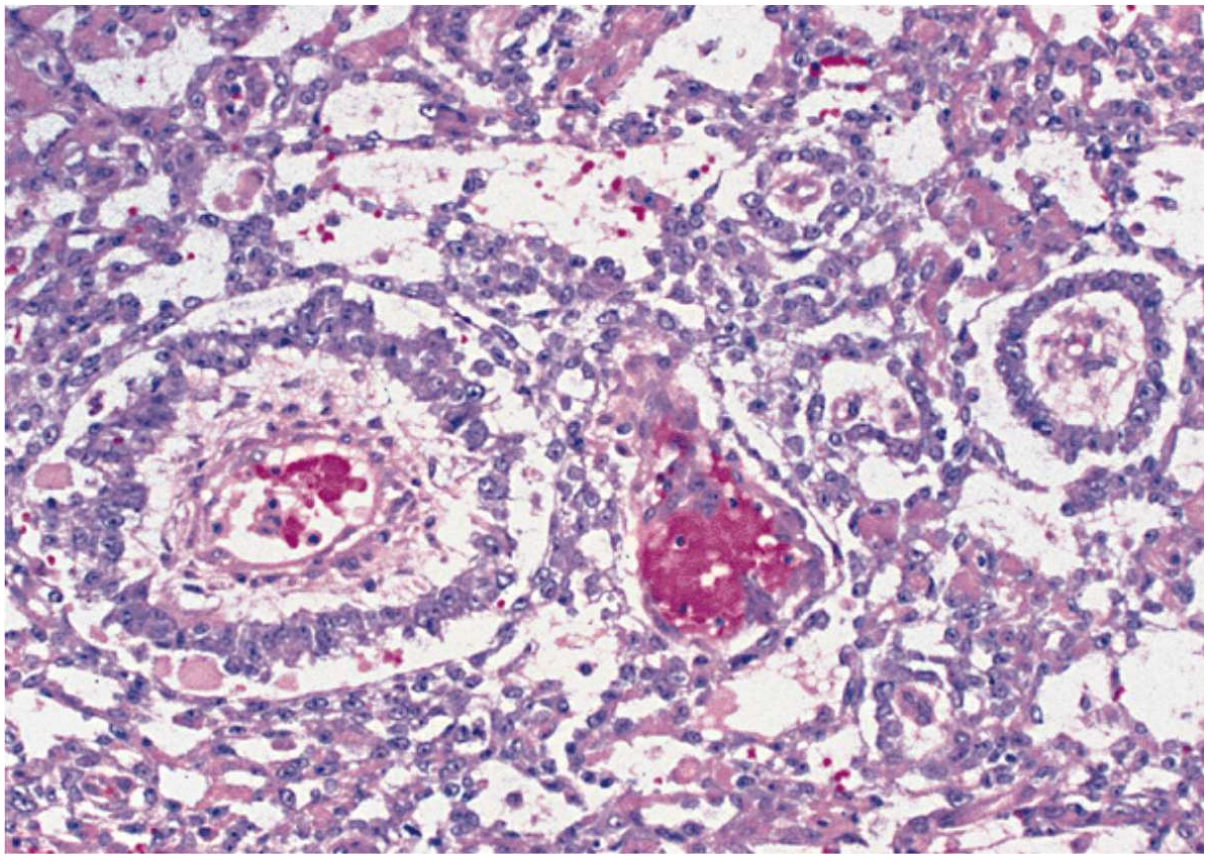


Reticulated pattern. The most common form.

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.

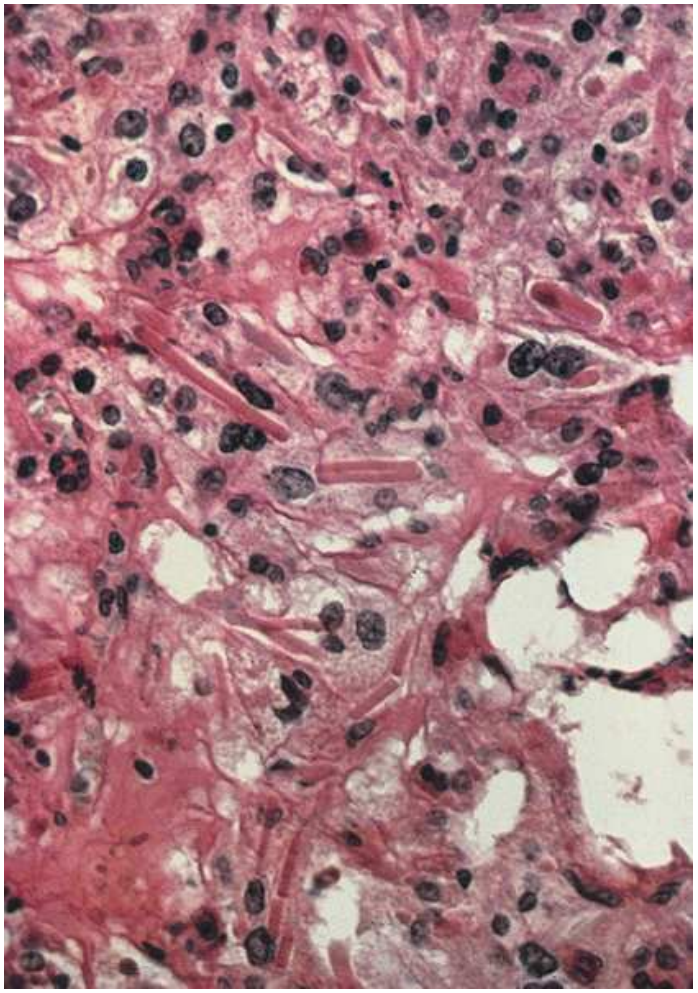
Other tumors

- 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.

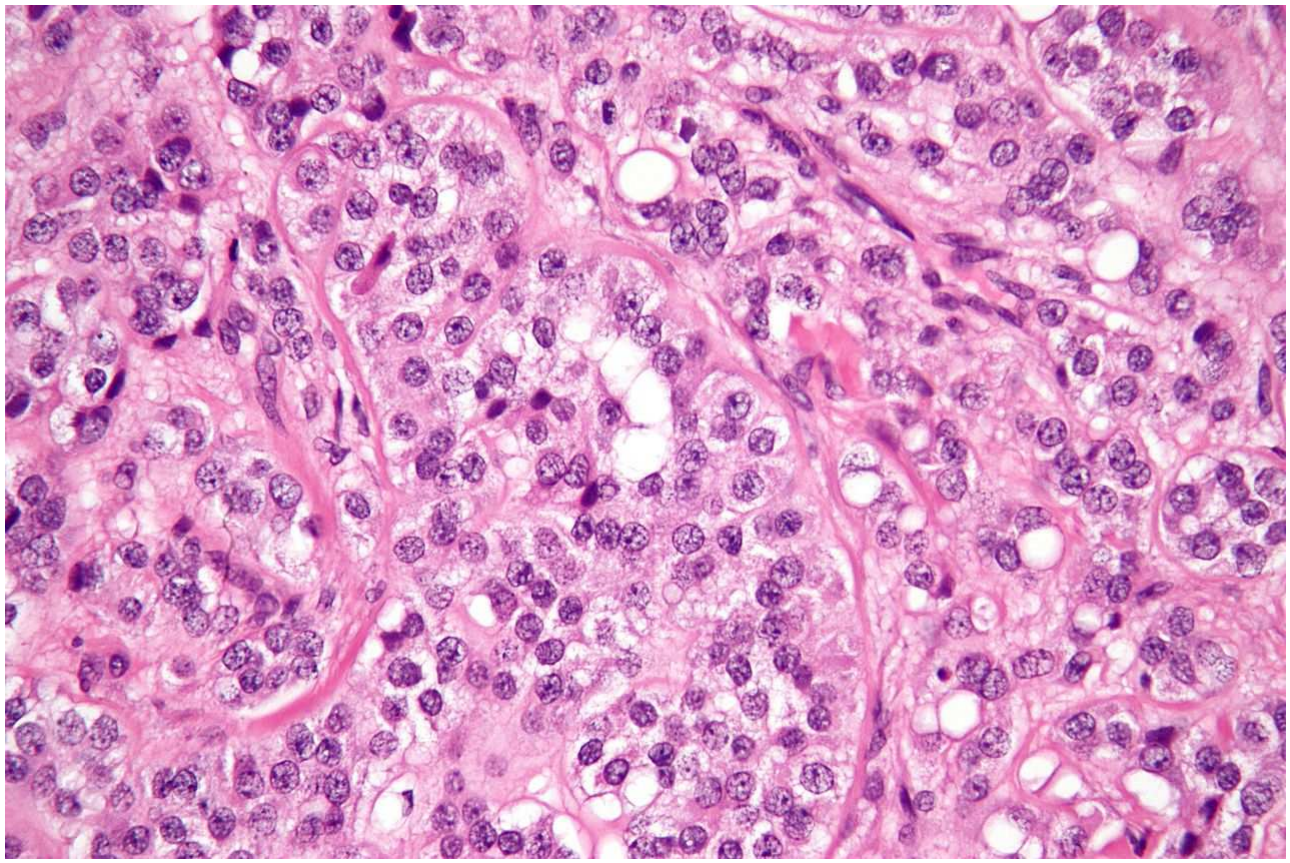
Fig. 12-11

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

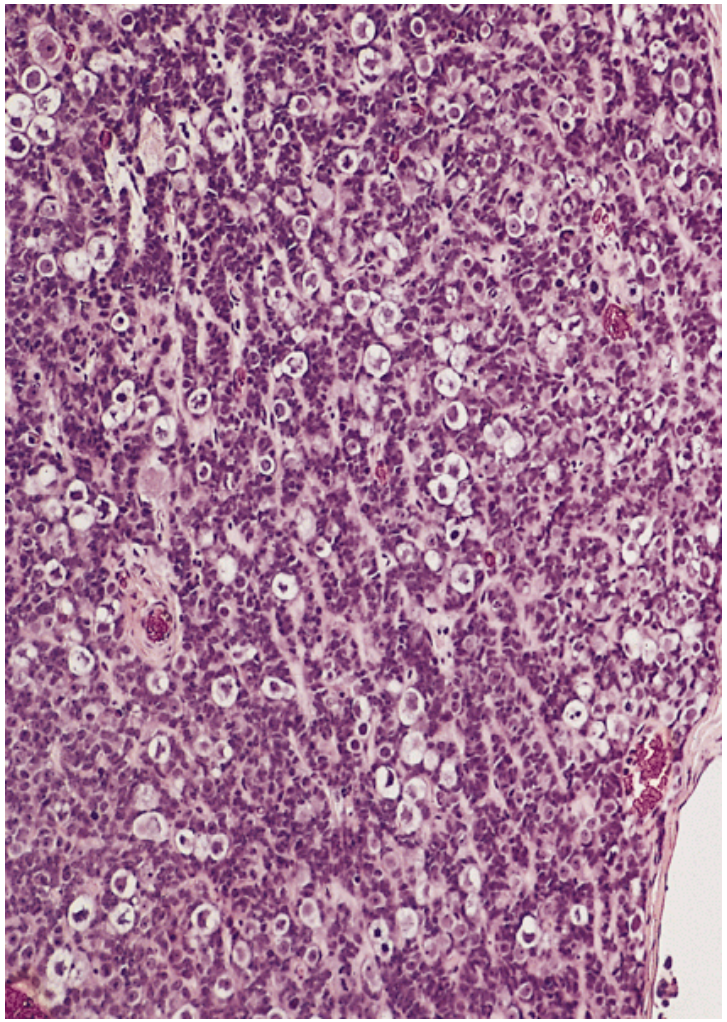


https://en.wikipedia.org/wiki/Sertoli_cell_tumour#/media/File:Sertoli_cell_tumour_high_mag.jpg
Accessed 05/10/2020

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

Gonadoblastoma

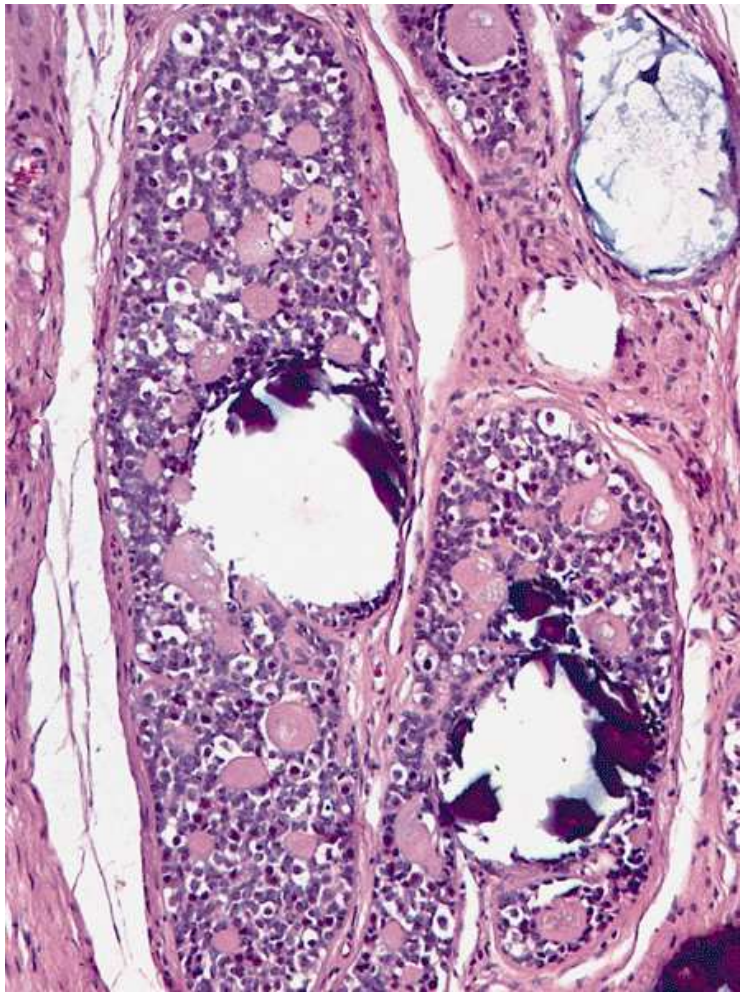


Fig. 5-16

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

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)

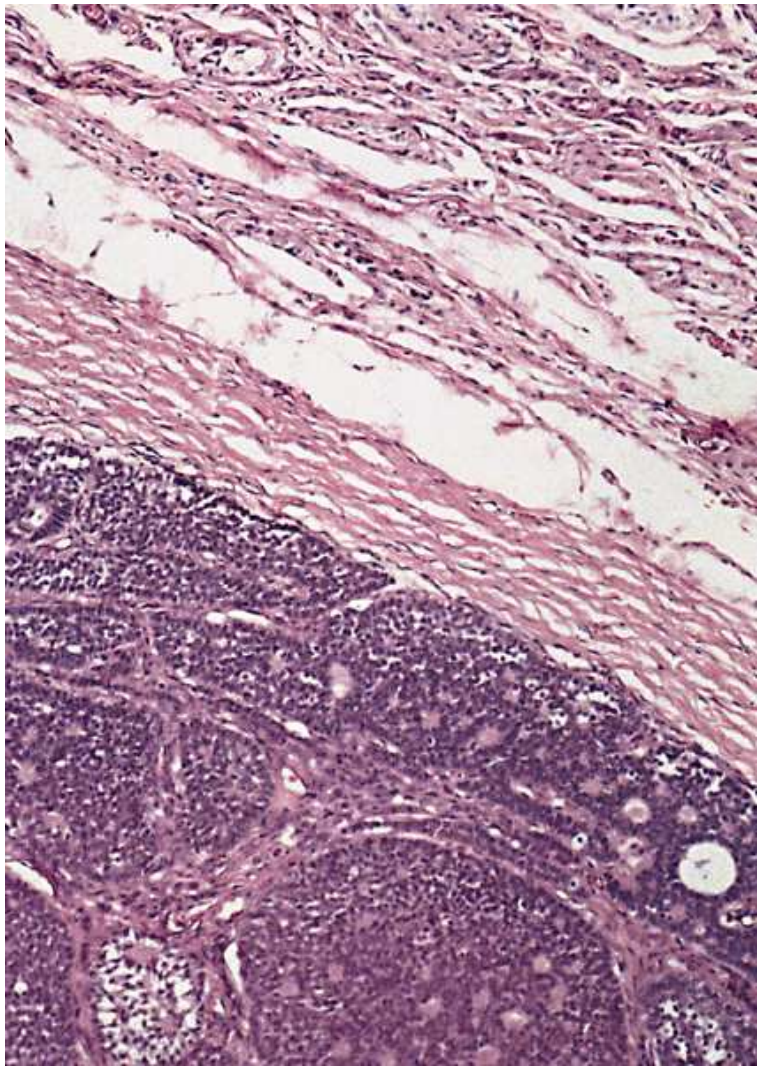
Granulosa cell tumor of testis

- 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

Granulosa cell tumor of testis



Call-Exner bodies are prominent.

Fig. 6-57

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.

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 %

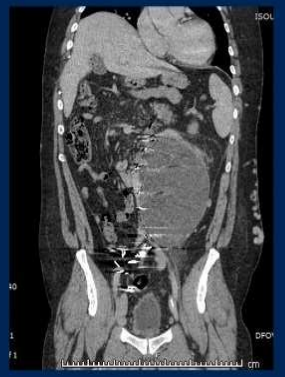
Sarcomas and adenocarcinoma in 3–23 %

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.