OB/GYN

DISORDERS OF FEMALE SEX ORGANS AND URINARY SYSTEM

Kenneth Alonso, MD, FACP

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 10^{th} week it drains urine from the mesonephros.

Embryology

- The paramesonephric duct forms lateral to the mesonephric duct (invagination of celomic epithelium on cranial aspect of mesonephros).
- This Müllerian duct grows caudally and crosses over the mesonephric duct.
- At the midline it fuses with the contralateral duct and will become the uterus.
- The gonadal ridge contains mesenchymal cells (medulla: ovarian support stroma); mesothelial cells (primary sex cord: ovarian follicles).

Embryology

- 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 clitoris.
- The gubernaculum forms between the indifferent gonads and the labioscrotal swellings.
- This ligament will form the round ligaments of the uterus and ovaries.

Embryology

- In the absence of the SRY gene, primary sex cords degenerate and secondary sex cords form (primordial follicles in which a single germ cell is surrounded by a single layer of mesothelial follicle cells).
- Primordial germ cells undergo a series of mitotic divisions and differentiate into oögonia by week 12.
- Before birth, the oögonia enter the first prophase of meiosis. They remain dormant.
- The mesenchyme becomes ovarian stroma.
- Ovaries separate from the mesonephros and are suspended in pelvic mesentery (peritoneal covering is lost).

Embryology

- In the absence of Müllerian inhibiting substance (derived from the Sertoli cell), the Wolffian ducts regress and the Müllerian ducts differentiate into oviducts, uterus, and the upper four-fifths of the vagina.
- Myometrium develops from the surrounding mesenchyme.
- Parametrial tissue is lined by peritoneum.

Embryology

- The lower fifth of the vagina arises from the sinovaginal bulbs (urogenital sinus).
- It ascends and fuses with the paramesonephric system and later canalizes with only the thin cover of hymen remaining.
- Vestibular glands (Bartholin's, greater) are endodermal outgrowths of the urogenital sinus.

Embryology

- The gubernaculum initially separates into an upper and lower portion.
- The Müllerian ducts fuse in the midline; the lower portion of the gubernaculum separates.
- The suspensory ovarian ligament, ovarian round ligament, and uterine round ligament result.
- The broad ligament which covers the entire uterus develops when the paramesonephric ducts descend through the pelvis, pulling a fold of celomic epithelium and mesenchyme with it.

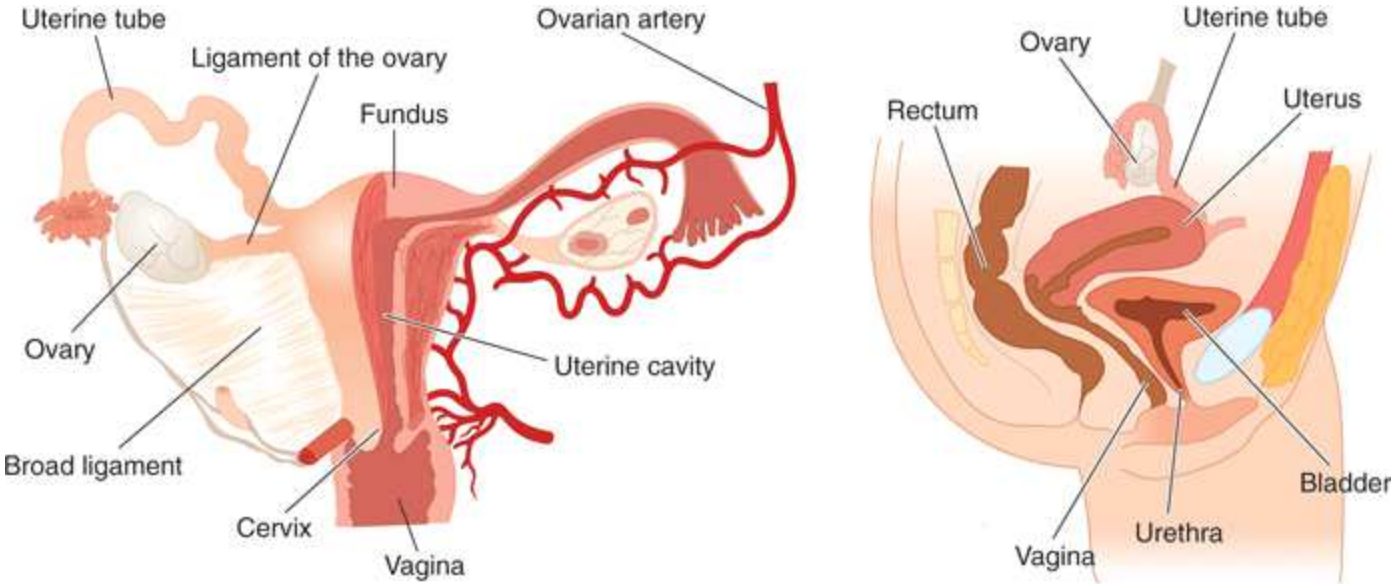
Anatomy

- The usual uterine position is anteverted and anteflexed with a 90° angle between the uterus and vagina and 15° between the uterine body and the cervix.
- The uterus is supported by the pubococcygeus, the urogenital diaphragm, bladder and areolar tissue, cardinal and utero-sacral ligaments.
- Uterine blood vessels course in the cardinal ligaments. The uterine artery is superior to the ureter.
- The uterus drains to the iliac, sacral, superficial inguinal, and lumbar lymph nodes.

Vessels

- The anterior division of the internal iliac artery provides the uterine and vaginal artery.
- The ovarian artery arises directly from the aorta (at L2).
- The right ovary drains to the inferior vena cava; the left ovary, to the renal vein.
- Ovarian drainage is to the lumbar lymph nodes.
- The ovarian vessels course along the suspensory ligament.

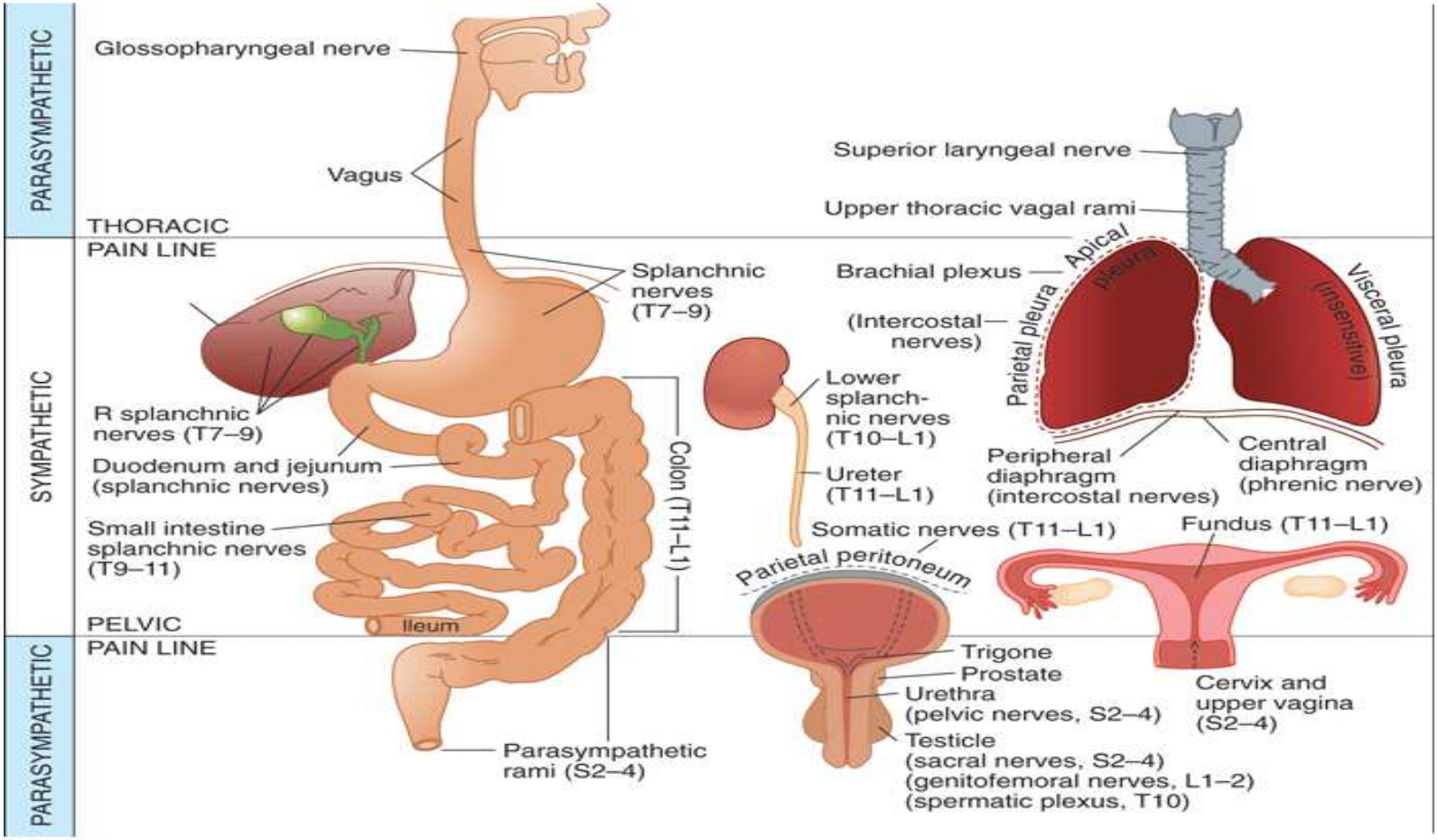
Anatomy



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fig. 25-1 Accessec 07/01/2010

Pain innervation of the viscera



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(After White JC. Reproduced with permission from Ruch TC: In *Physiology and Biophysics,* 19th ed. Ruch TC, Patton HD (editors). Saunders, 1965.)

Fig. 10-2 Accessed 07/01/2010

Congenital anomalies

- Labial fusion is associated with excess androgens (endogenous or exogenous).
- May have ambiguous genitalia.
- Congenital adrenal hyperplasia is the most common cause.
- Reconstructive surgery possible after primary disorder treated.

Congenital anomalies

- Müllerian dysgenesis (Mayer-Rokitansky-Küster-Hauser syndrome) may present with a vagina as a rudimentary pouch.
- Patient has ovaries and a 46,XX karyotype.
- Serial dilatation to keep open
- If no vagina, one can be constructed.

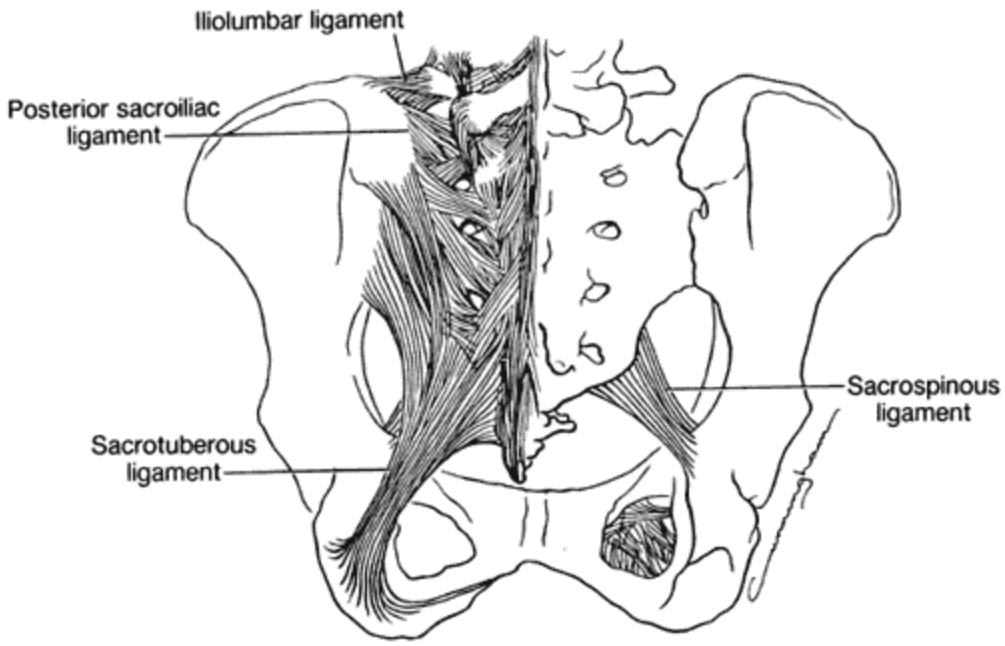
Congenital anomalies

- The hymen is located between the sinovaginal bulbs and the urogenital sinus and should have an opening.
- Imperforate hymen
- Presents as amenorrhea in the setting of menstrual cramps resulting from outflow obstruction.
- May also experience abdominal pain and an increase in lower abdominal girth as fluid accumulates.
- Blood can be visualized behind the hymen.
- Hymen may be opened surgically.

Congenital anomalies

- The vagina forms as the Müllerian system joins the sinovaginal bulb at the Müllerian tubercle, which is then canalized to form a vagina.
- Failure to canalize results in a transverse vaginal septum between the lower two-thirds and the upper third of the vagina.
- The canal may be opened surgically.
- Testicular feminization or lack of androgen receptors may present with a rudimentary vagina.
- No ovaries and a 46, XY karyotype.
- Undescended testicles may be palpable

Pelvis



Source: Tintinalli JE, Kelen GD, Stapczynski JS: *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th Edition: http://www.accessemergencymedicine.com

The major posterior stabilizing structures of the pelvic ring that are the posterior tension band of the pelvis include the iliolumbar ligament, the posterior sacroiliac ligaments, the sacrospinous ligaments, and the sacrotuberous ligaments.

(Reproduced with permission from Tile M, Kellam J, Helfet DL (eds): Anatomy, in *Fractures of the Pelvis and Acetabulum.* Baltimore: Williams & Wilkins, 1984, p 11.)

Fig. 273-1 Accessed 05/05/2010

Pelvis

- Consists of the two innominate bones (ilium, ischium, and pubis); the sacrum; and the coccyx.
- The two innominate bones and sacrum form a ring structure, which is the basis of pelvic stability.
- This stability is dependent on the strong posterior sacroiliac, sacro-tuberous, and sacro-spinous ligaments.
- The iliopectineal, or arcuate line, divides the pelvis into the upper, or false, pelvis, which is part of the abdomen, and the lower, true pelvis.
- This line constitutes the major portion of the femoro-sacral arch.

Pelvis

- The anterior superior iliac spine and pubic tubercle lie in the same vertical plane.
- The femoro-sacral arch with the subsidiary tie arch (bodies of pubic bones and superior rami), supports the body in the erect position.
- In the sitting position, the weight-bearing forces are transmitted by the ischio-sacral arch augmented by its tie arch, the pubic bones, inferior pubic rami, and ischial rami.

Pelvis

- Incorporated in the pelvic structure are five joints that allow some movement in the bony ring.
- The lumbosacral, sacro-iliac, and sacro-coccygeal joints, and the symphysis pubis allow little movement.
- The acetabulum is a ball-and-socket joint that is divided into three portions:
- The iliac portion, or superior dome, is the chief weight-bearing surface
- The thin inner wall consists of the pubis
- The posterior acetabulum is derived from the thick ischium.

Muscles of the pelvis

- The obturator internis lies on the pelvic surface of the ilium and ischium (and runs to the sacro-tuberous ligament below and the posterior border of the body of the ischium) and passes through the lesser sciatic foramen to insert on the greater trochanter of the femur.
- The pyfiromis lies on the pelvic surface of S2 to S4, attaches to the superior margin of the greater sciatic notch and sacro-tuberous ligament, and passes through the greater sciatic foramen to insert on the greater trochanter of the femur.

Muscles of the pelvis

- The coccygeus runs from the ischial spine and overlies the sacro-spinal ligament.
- It inserts on the inferior end of the sacrum.
- With the levator ani it forms the pelvic diaphragm that separates the pelvis from the perineum.
- The pubococcygeus arises from the pubis.
- It is the major part of the levator ani and supports the pelvic organs.
- The iliococcygeus also forms part of the levator ani.

Sacral plexus

- The sacral plexus supplies the lower limbs.
- Ventral rami of L4-S3 roots.
- The anterior division supplies the tibial nerve (L4-S3), and the nerves to the obturator internus (L4) and quadratus femoris (L5) muscles.
- The posterior division supplies the common fibular (S1-S2), superior (L4-S1) and inferior gluteal nerves (L5-S2).

Sacral plexus

- The nerves lie medial to pyriformis in the pelvis.
- The superior gluteal nerve passes superior to the pyriformis as it leaves the pelvis.
- The other nerves pass inferior to the pyriformis.

Pelvis

- The oburator artery and vein pass over the Psoas fascia and exit through the obturator foramen.
- The pudendal artery and nerve exit the greater foramen, re-enter the lesser foramen, and proceed to the urogenital diaphragm.
- The inferior rectal nerve, perineal nerve, and dorsal nerve of the clitoris branch from the pudendal nerve.
- The pudendal nerve innervates all muscles of the perineum.

Pelvis

- The urogenital diaphragm is pierced by the urethra.
- The urogenital diaphragm is composed of a superior layer of fascia, the deep transverse perineus and sphincter urethrae muscles, and the perineal membrane.
- It contains Bartholin’s glands.

Sphincters

- The external anal sphincter constricts the anal canal during peristalsis (resisting defecation).
- It supports and fixes the perineal body and the pelvic floor.
- The bulbospongiosus muscle supports and fixes the perineal body and pelvic floor.
- It may function as a vaginal sphincter (dentate vagina).
- It assists in erection of the clitoris and compresses the greater vestibular gland (and possibly the bulb of the vestibule).

Sphincters

- The ischiocavernosus muscles maintain erection of the clitoris by compressing outflow veins and by pushing blood from the root of the clitoris into the body of the clitoris.
- The superficial and deep transverse perineal muscles support and fix the perineal body and pelvic floor to support abdominalpelvic viscera and resist increased intra-abdominal pressure.
- The external urethra sphincter surrounds the urethra superior to the perineal membrane.
- It compresses the urethra to maintain urinary continence.
- It may also enclose and compress the vagina (urethrovaginal sphincter).

Superficial perineal space

- The crus of the clitoris and vestibular bulb as well as Bartholin's glands are found in the space.
- The perineal body is the central point of the perineum.
- Attached are the bulbospongiosus, superficial transverse perineus, deep transverse perineus, external anal sphincter, and pubovaginalis muscle.
- Colles' perineal membrane, the superior fascia of the urogenital diaphragm, the inferior fascia of the pelvic diaphragm, and the perimuscular fascia (Gallaudet's) are also attached.

URETERS, BLADDER, AND URETHRA

Ureters

- Run in retroperitoneum from kidneys to bladder
- Narrowed at:
- Utero-pelvic junction (UPJ)
- Where they cross the iliac arteries, an
- Where they enter the bladder
- Enter the bladder obliquely (slit like orifice).
- Permits the surrounding bladder musculature to function as valve.
- UPJ obstruction may be congenital
- Most common cause of hydronephrosis in the young
- 20% bilateral

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Ureters

- Lined by transitional epithelium (urothelium)
- 5-6 layers of cells with oval nuclei, often with nuclear grooves,
- Surface layer covered with large flattened cells with abundant cytoplasm (“umbrella cells”)
- Rest on basement membrane
- Lamina propria contains smooth muscle that forms a discontinuous muscularis mucosae

Congenital anomalies of ureter

- Double and bifid ureters.
- Double ureters are almost invariably associated with totally distinct double renal pelves or with the anomalous development of a large kidney having a partially bifid pelvis terminating in separate ureters.
- Double ureters may pursue separate courses to the bladder but commonly are joined within the bladder wall and drain through a single ureteral orifice.
- Most are unilateral and of no clinical significance.

Congenital anomalies of ureter

- Ureteropelvic junction (UPJ) obstruction
- The most common cause of hydronephrosis in infants and children.
- Bilateral in 20% of cases
- Males generally
- Often associated with other congenital anomalies
- There is agenesis of the contralateral kidney in a minority of cases.

Congenital anomalies of ureter

- Causes:
- Abnormal organization of smooth muscle bundles at the UPJ
- Excess stromal deposition of collagen between smooth muscle bundles
- Congenitally extrinsic compression of the UPJ by renal vessels.
- In adults, generally seen in women
- Unilateral

Congenital anomalies of ureter

- Diverticula
- Uncommon
- Most are asymptomatic, but urinary stasis within diverticula sometimes leads to recurrent infections.
- Dilation (hydroureter), elongation, and tortuosity of the ureters may occur as congenital anomalies or as acquired defects.

Unilateral obstruction typically results from proximal causes such as a stone.

Bilateral obstruction arises from distal causes such as retroperitoneal fibrosis, cystocele, or prostatic hypertrophy.

Table 21-1 Major Causes of Ureteral Obstruction

Type of Obstruction	Cause
Intrinsic	
Calculi	Of renal origin, rarely more than 5 mm in diameter Larger renal stones cannot enter ureters Impact at loci of ureteral narrowing—ureteropelvic junction, where ureters cross iliac vessels, and where they enter bladder—and cause excruciating "renal colic"
Strictures	Congenital or acquired (inflammations)
Tumors	Transitional cell carcinomas arising in ureters Rarely, benign tumors or fibroepithelial polyps
Blood clots	Massive hematuria from renal calculi, tumors, or papillary necrosis
Neurogenic	Interruption of the neural pathways to the bladder
Extrinsic	
Pregnancy	Physiologic relaxation of smooth muscle or pressure on ureters at pelvic brim from enlarging fundus
Periureteral inflammation	Salpingitis, diverticulitis, peritonitis, sclerosing retroperitoneal fibrosis
Endometriosis	With pelvic lesions, followed by scarring
Tumors	Cancers of the rectum, bladder, prostate, ovaries, uterus, cervix; lymphomas, sarcomas

Ureteritis

- Not associated with infection.
- Of little clinical importance.
- The accumulation or aggregation of lymphocytes forming germinal centers in the subepithelial region may cause slight elevations of the mucosa and produce a fine granular mucosal surface (ureteritis follicularis).
- At other times the mucosa may become sprinkled with fine cysts varying in diameter from 1 to 5 mm lined by flattened urothelium (ureteritis cystica)

Sclerosing retroperitoneal fibrosis.

- Uncommon cause of bilateral ureteral obstruction.
- Characterized by a fibrotic proliferative inflammatory process encasing the retroperitoneal structures and causing hydronephrosis.
- The disorder occurs in middle to late age
- More common in men.
- Involves other tissues as well, particularly exocrine organs such as the pancreas and salivary glands.
- Ergot derivatives, beta blockers as some causes.

Sclerosing retroperitoneal fibrosis.

- A subset of these cases is related to IgG4-related disease.
- Microscopic examination typically reveals fibrous tissue containing a prominent infiltrate of lymphocytes, often with germinal centers, plasma cells (frequently IgG4-positive), and eosinophils.

Benign ureteral tumor

- Fibroepithelial polyp is a tumor-like lesion that presents as a small mass projecting into the lumen, often in children.
- This lesion occurs more commonly in the ureters but may also involve the bladder, renal pelves, and urethra.
- The polyp is composed of loose, vascularized connective tissue overlaid by urothelium.

Bladder anatomy

- The trigone is the smooth triangular area at the base of the bladder.
- The uvula is the upward bulge of the trigone caused by the prostate.
- The detrusor muscle functions as a sphincter.
- It constricts about ureteral openings during micturition.
- The sphincter about the internal urethral orifice relaxes in micturition.
- The micturition reflex is mediated by the parasympathetics (S2-S4).

Bladder anatomy

- The pubovesical ligaments extend from bladder neck to pubis bones and stabilize the bladder.
- The median umbilical ligament (obliterated urachus) attaches the apex of the bladder to the abdominal wall.
- The superior and inferior vesical arteries supply the bladder.

Congenital anomalies of bladder

- Vesicoureteral reflux is the most common and serious congenital anomaly.
- A major contributor to renal infection and scarring.
- Abnormal connections between the bladder and the vagina, rectum, or uterus may create congenital vesico-uterine fistulae.
- Congenital diverticula may be due to a focal failure of development of the normal musculature or to some urinary tract obstruction during fetal development.
- Acquired diverticula are most often seen with prostatic enlargement.
- Urinary stasis a problem.

Congenital anomalies of bladder

- Exstrophy of the bladder is a failure in development of the anterior wall of the abdomen and the bladder.
- The bladder either communicates directly through a large defect with the surface of the body or lies as an opened sac.
- Undergoes colonic metaplasia
- Increased risk for infection as well as for devlopment of adenocarcinoma.

Congenital anomalies of bladder

- The urachus is the canal that connects the fetal bladder with the allantois; it is normally obliterated after birth.
- When totally patent, a fistulous urinary tract connects the bladder with the umbilicus.
- In other instances, only the central region of the urachus persists, giving rise to urachal cysts, lined by either urothelium or metaplastic glandular epithelium.
- 20-40% of all adenocarcinomas of the bladder.

Cystitis

- In acute cystitis there is hyperemia of the mucosa and neutrophilic infiltrate, sometimes associated with exudate.
- Burning on urination, frequency, and lower abdominal pain as presenting signs
- Escherichia coli, Proteus, Klebsiella, and other Enterobacter species are the common causes of cystitis.
- Schistosoma is common in Puerto Rico and in the Mideast.
- Mycobacterium tuberculosis follows infection of the renal pelvis.

Cystitis

- Chlamydia and Mycoplasma may also be causes
- Candida albicans or Cryptoccous in the immunosuppressed.
- Adenovirus causes hemorrhagic cystitis
- High dose cyclophosphamide causes hemorrhagic cystitis.
- Chronic inflammation may lead to cystic and metaplastic changes in the bladder.

Cystitis

- Interstitial cystitis is a persistent form of chronic cystitis occurring principally in women and associated with inflammation and fibrosis of all layers of the bladder wall.
- May have superficial fissures and punctate hemorrhages
- In the late phase (Hunner) ulcers are found.
- Transmural fibrosis in the late phase as well.
- The cause is not known.
- Mast cells abound.

Cystitis

- Follicular cystitis is characterized by the presence of lymphoid follicles within the bladder mucosa and underlying wall.
- Eosinophilic cystitis, manifested by infiltration with submucosal eosinophils, typically is a non-specific subacute inflammation but may also be a manifestation of a systemic allergic disorder.
- Polypoid cystitis is an inflammatory lesion resulting from irritation of the bladder mucosa.
- Indwelling catheters are the most common causes.
- The urothelium is thrown into broad bulbous polypoid projections as a result of marked submucosal edema.

Malakoplakia

- Defect in phagocytosis
- Associated with Escherichia coli infection.
- Immunosuppressed patients
- Vesical inflammatory reaction characterized macroscopically by soft, yellow, slightly raised mucosal plaques 3 to 4 cm in diameter

Malakoplakia

- Microscopically:
- Infiltration with large, foamy macrophages with occasional multinucleate giant cells and interspersed lymphocytes.
- Macrophages have an abundant granular PAS positive cytoplasm due to phagosomes stuffed with particulate and membranous debris of bacterial origin.
- Calcium concretions deposited within lysosomes are called Michaelis-Gutman bodies.

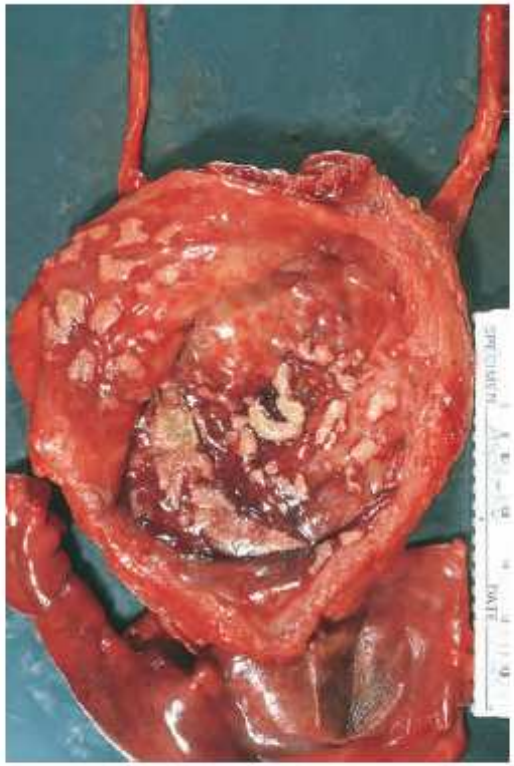


Figure 21-4 Cystitis with malakoplakia showing inflammatory exudate and broad, flat plaques.

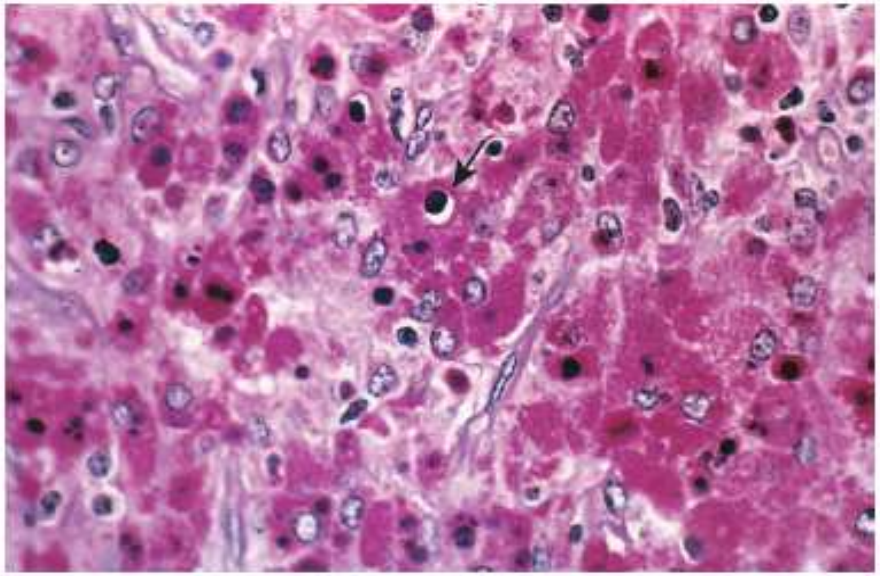


Figure 21-5 Malacoplakia, periodic acid–Schiff (PAS) stain. Note the large macrophages with granular PAS-positive cytoplasm and several dense, round Michaelis-Gutmann bodies surrounded by artifactual cleared holes in the upper middle field *(arrow)*.

Cystitis glandularis
Cystitis cystica

- Associated with downward growth of urothelial nests (Brunn nests) into the lamina propria and the subsequent metaplastic transformation of the nests of urothelium.
- Microscopically:
- Cuboidal or columnar epithelial cells may be found as lining epithelium.
- Cystic spaces may be filled with clear fluid but with a urothelial lining.
- A third variant may demonstrate intestinal epithelium.

Metaplasia

- Squamous metaplasia is frequently a response to chronic inflammation.
- Occasionally shed renal cells implant in injured urothelium (nephrogenic adenoma)

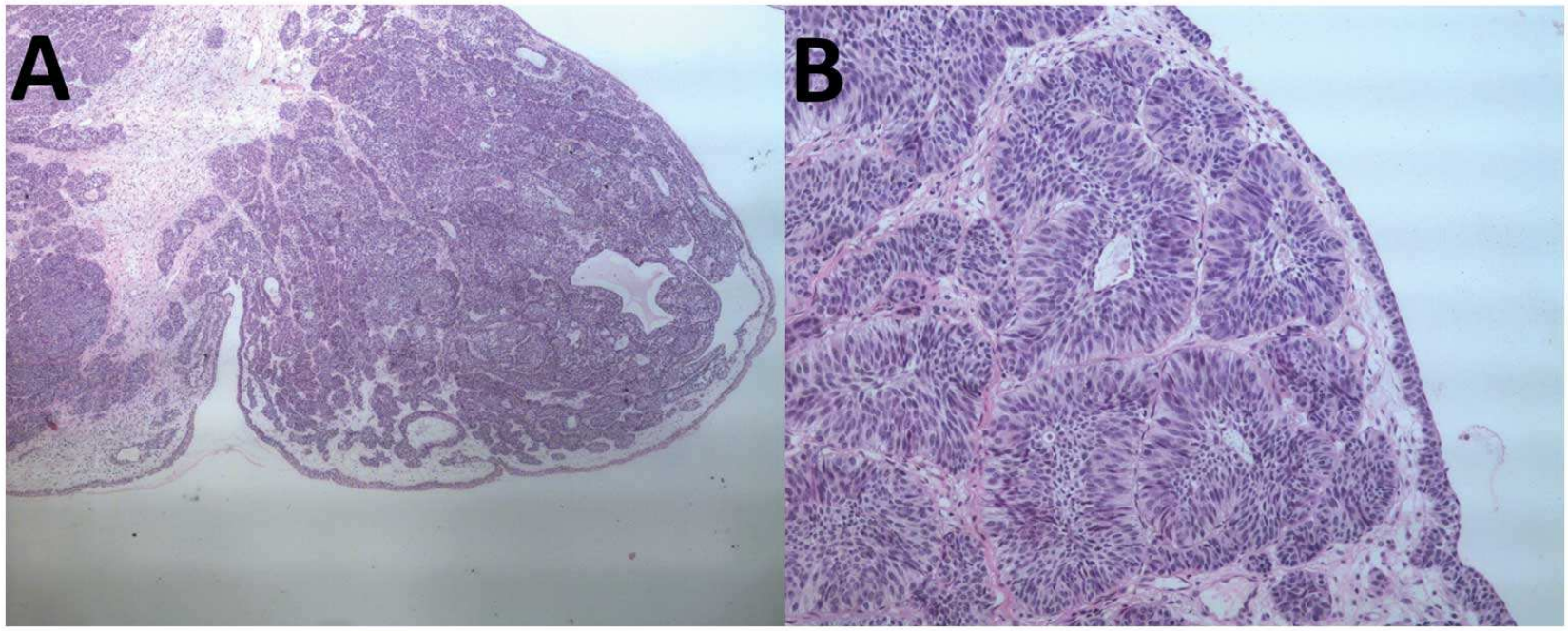
Inverted bladder papilloma

- <1% bladder neoplasms
- Generally benign
- Men, 6th and 7th decades
- Painless hematuria
- May have irritative bladder symptoms (urgency)
- Solitary with minimal exophytic component
- May have squamous differentiation

Inverted bladder papilloma

- Trabecular subtype is classic.
- Urothelial buds at various points underlying urothelial surface
- Irregular downward growing cords from overlying epithelium
- Spindle cells with central streaming and in palisade
- Glandular subtype
- Nests of urothelium with pseudoglandular urothelial lined spaces or true glands containing mucous secreting goblet cells

Inverted bladder papilloma



A. The polypoid growth of the lesion is demonstrated. B. Thin cords are present in the lamina propria. Urothelium with central streaming and peripheral palisading.

https://www.spandidos-publications.com/article_images/ol/4/1/OL-04-01-0071-g00.jpg Accessed 01/20/2020

Bladder cancer

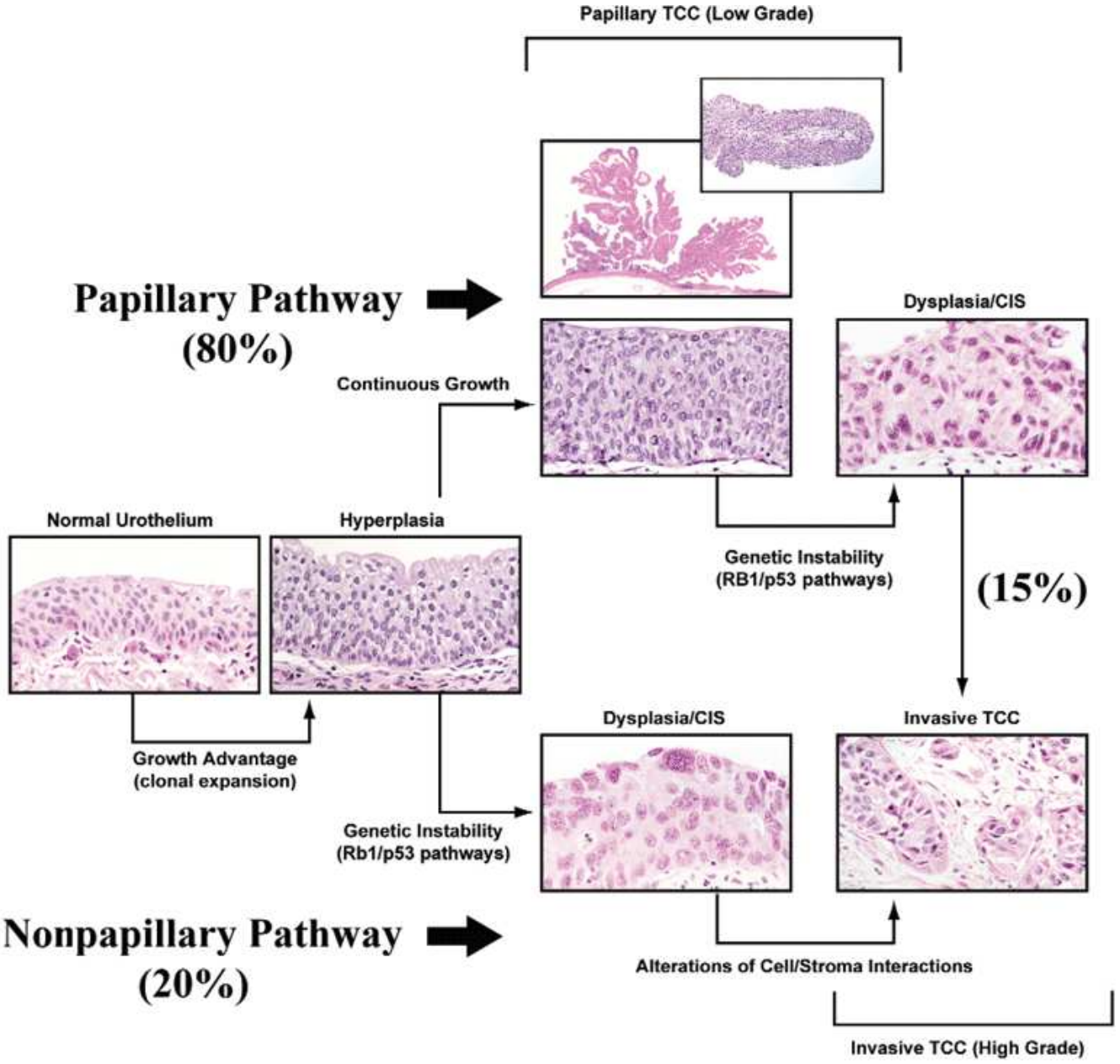
- 3:1 men
- 80% are 50-80 years of age
- Not familial
- 50-80% associated with cigarette use
- Painless hematuria
- Cystoscopy with hexaminolevulinate imaging and urine cytology critical for detection and surveillance of bladder cancer.

Bladder cancer

- Risks:
- Exposure to 2-naphthylamine
- Cancers occur 15-40 years after exposure
- Schistosoma hematobium infection
- Chronic inflammatory changes from encystation in bladder wall
- 70% are adenocarcinomas
- Radiation exposure
- Cyclophosphamide use
- Long term analgesic use

Bladder cancer

- Two distinct precursors to invasive bladder cancer:
- Papillary tumors
- Arising from previous transitional cell hyperplasia, 9q- (usually CDKN2A; PTCH and TSC1 loss also possible with loss of mTOR signaling)
- FGFR3 gain of function mutation
- Flat urothelial carcinoma in situ
- FGFR3/cyclin D, HRAS, 11p-
- p53 mutation needed for high grade dysplasia.
- Rb inactivation, 8p- needed for invasion.



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 28-1
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Infiltrating Urothelial Carcinoma
Urothelial carcinoma with divergent differentiation
Squamous differentiation
Glandular differentiation
Trophoblastic differentiation
Nested, including large nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Plasmacytoid
Sarcomatoid
Giant cell
Poorly differentiated
Lipid-rich
Clear cell (glycogen-rich)

Data based on and derived from [1]Moch H, Humphrey PA, Ulbright TM, et al., eds. *WHO Classification of Tumours of the Urinary System and Male Genital Organs*. 4th ed. Lyon, France: IARC Press; 2016. *World Health Organization Classification of Tumours*; vol 8.

Bladder cancer

- Presents with painless hematuria
- Irritative signs common
- 95% are urothelial cancers.
- 3-5% are squamous carcinomas
- Embryonal rhabdomyosarcoma occurs in children <5 years of age
- "Field change" disease as the entire urothelium is at risk for tumor formation.
- Tobacco, exposure to aniline dyes, Schistosoma infection are major environmental risk elements.
- Lifelong surveillance needed.
- Men three times more likely to have bladder cancer

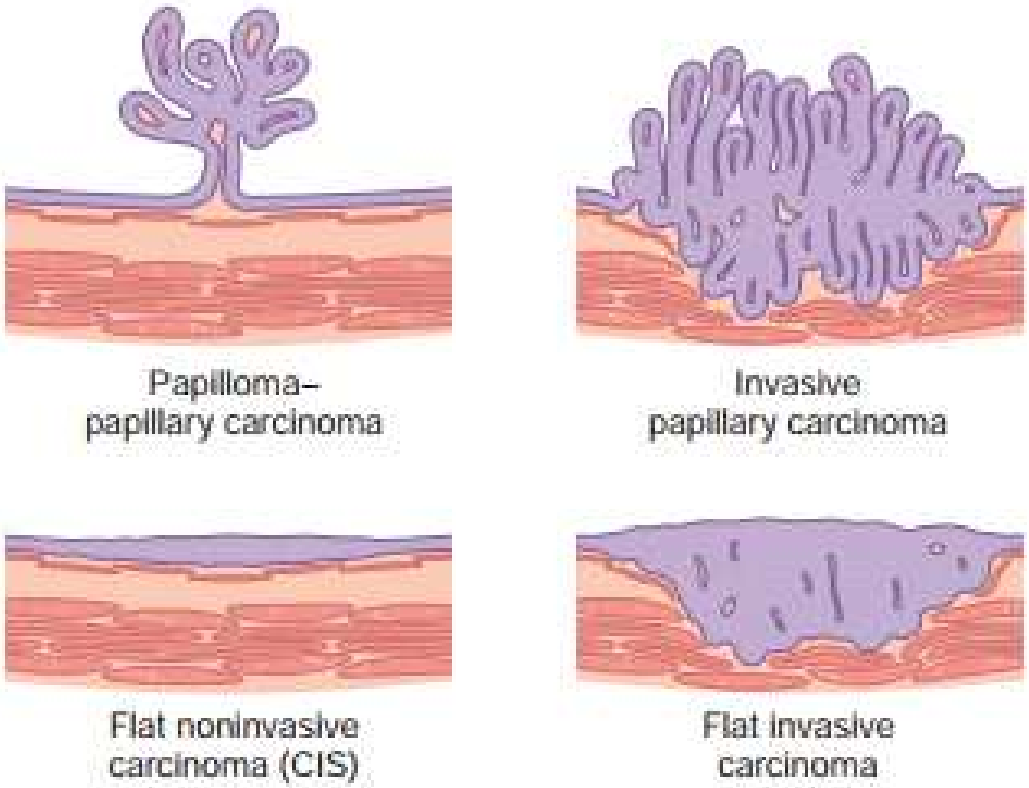


Figure 21-6 Four morphologic patterns of bladder tumors. CIS, Carcinoma in situ.

Papillary lesions

- Papillary lesions are red, elevated excrescences ranging in size from less than 1 cm in diameter to large masses up to 5 cm in diameter
- Most arise from the lateral or posterior walls at the bladder base.
- Multiple discrete tumors are often present
- Exophytic papillary lesions are attached to the mucosa by a stalk
- Individual finger-like papillae have a central core of loose fibrovascular tissue covered by bland epithelium
- Recurrences and progression are rare

Papillary lesions

- Papillary urothelial neoplasms of low malignant potential have a thicker epithelium
- Low-grade papillary urothelial carcinomas
- Have an orderly architectural and cytologic appearance. The cells are evenly spaced (maintain polarity) and cohesive.
- There is a mild degree of nuclear atypia consisting of scattered hyperchromatic nuclei, infrequent mitotic figures predominantly toward the base, and slight variation in nuclear size and shape
- <10% of low-grade cancers invade muscle

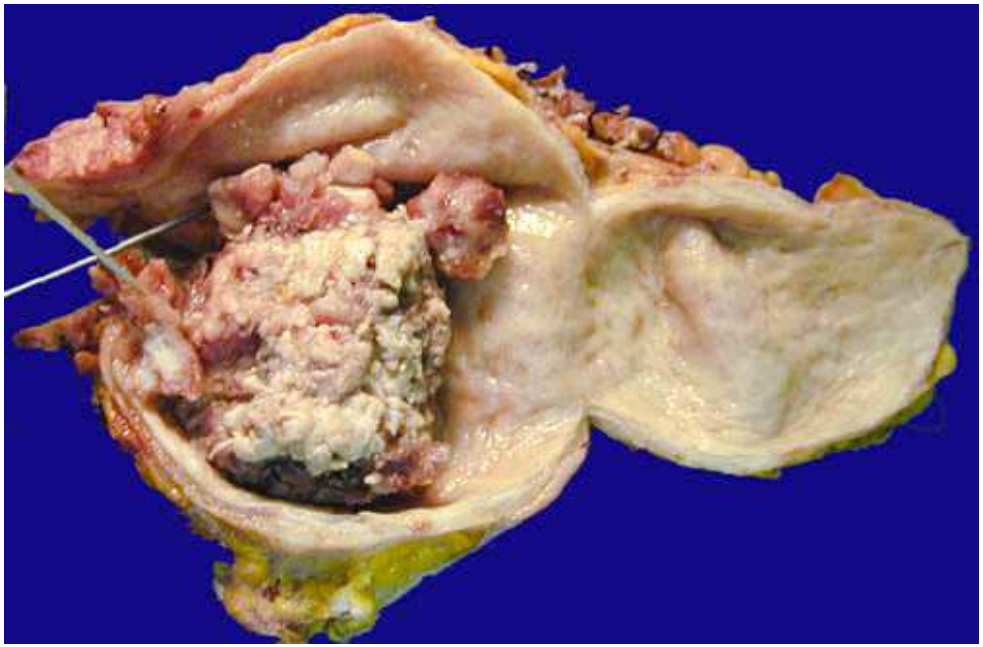
Papillary lesions

- High-grade papillary urothelial cancers contain poorly cohesive cells with large hyperchromatic nuclei.
- Mitotic figures are frequent.
- Architecturally, there is disarray and loss of polarity.
- 80% are invasive.
- May extend into the bladder wall and adjacent structures.
- About 40% of these deeply invasive tumors metastasize to regional lymph nodes.
- Hematogenous dissemination, principally to the liver, lungs, and bone marrow, may result.

Bladder cancer

- Carcinoma in situ (CIS) may range from full-thickness cytologic atypia to scattered malignant cells in an otherwise normal urothelium (pagetoid spread)
- A common feature shared with high-grade papillary urothelial carcinoma is a lack of cohesiveness, which leads to the shedding of malignant cells into the urine
- Invasive bladder cancer.
- The extent of the invasion into the muscularis mucosae is of prognostic significance

Bladder cancer



https://webpath.med.utah.edu/RENAHTML/BLAD069.html
Accessed 01/20/2020

The opened bladder removed surgically reveals a mass of a neoplasm that histologically proved to be urothelial carcinoma (previously known as a transitional cell carcinoma).

Urothelial carcinoma can arise anywhere in the urothelium lining the urinary tract from the urethra to the calyces, but is most common in bladder.

Urothelial carcinoma is often multifocal and has a tendency to recur.

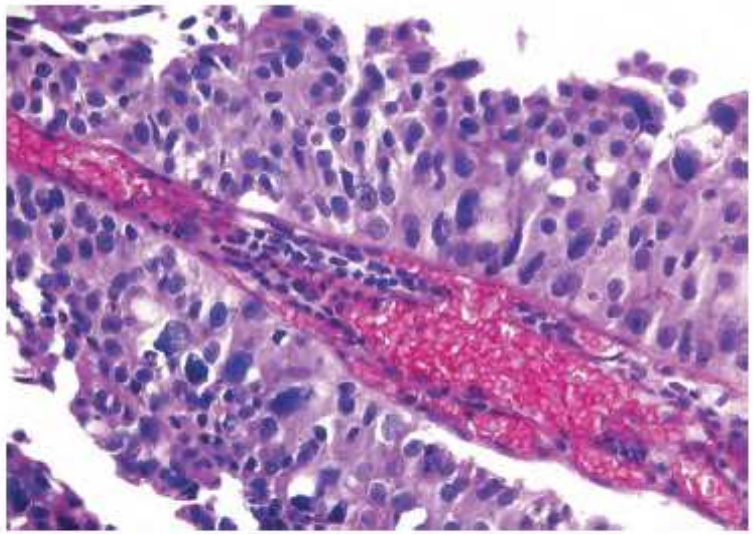


Figure 21-10 High-grade papillary urothelial carcinoma with marked cytologic atypia.

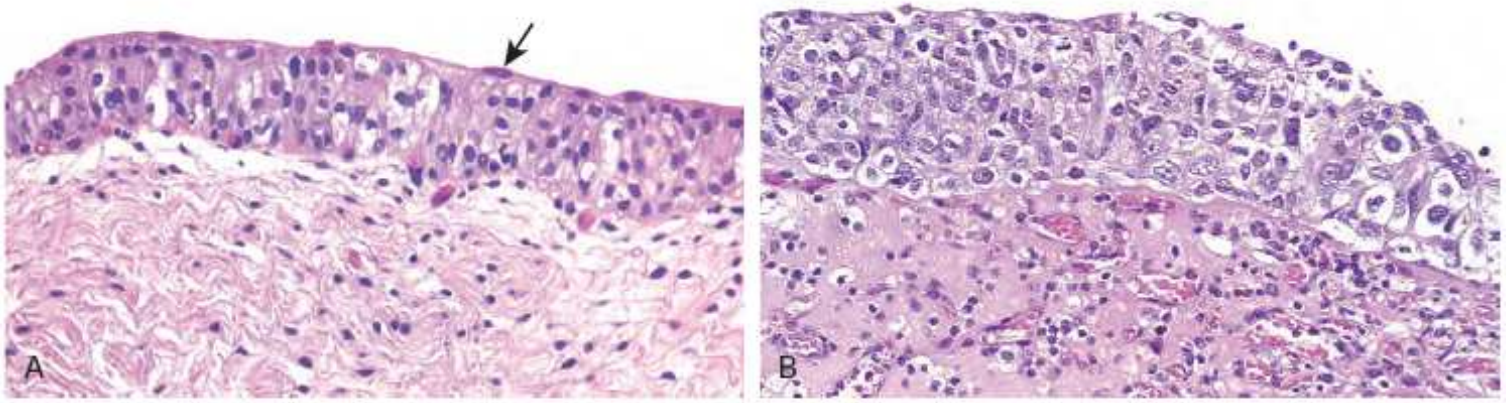


Figure 21-11 **A,** Normal urothelium with uniform nuclei and well-developed umbrella cell layer *(arrow)*. **B,** Flat carcinoma in situ with numerous cells having enlarged and pleomorphic nuclei.

Urothelial carcinoma variants

- Micropapillary urothelial carcinoma
- HER2 amplifications or mutations
- Plasmacytoid urothelial carcinoma
- Loss of E-cadherin and CDH1 gene loss of function mutations or methylation
- Worse prognosis associated with micropapillary and plasmacytoid urothelial carcinoma variants
- Uniformly poor prognosis for sarcomatoid, poorly differentiated and giant cell urothelial carcinoma

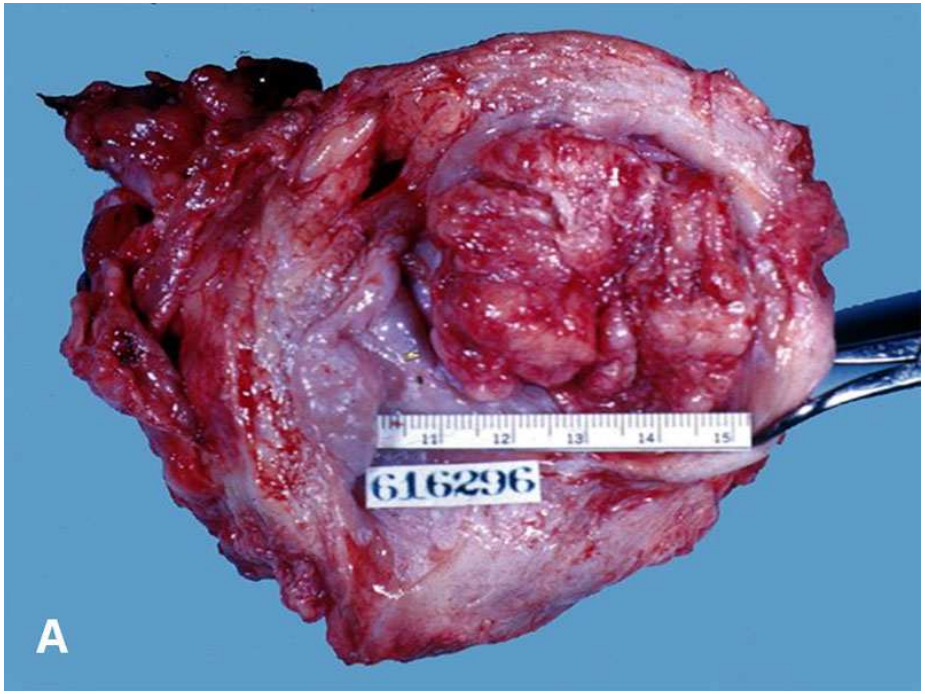
Urothelial carcinoma variants

- No significant association with Epstein-Barr virus (EBV) or human papillomavirus (HPV) infection and urothelial carcinoma development
- Nested variant, lipid rich and urothelial carcinoma with divergent differentiation (squamous, glandular, or trophoblastic) are more likely to present with advanced disease but when adjusted by stage had no survival differences with respect to conventional urothelial carcinoma.

Squamous carcinoma

- Pure squamous carcinomas associated with chronic inflammation.
- Mixed urothelial carcinomas with areas of squamous carcinoma are more frequent than pure squamous cell carcinomas.
- Most are invasive, fungating tumors or are infiltrative and ulcerative.
- 7% of bladder cancers
- Other cancers include adenocarinoma and small cell carcinoma

Squamous carcinoma



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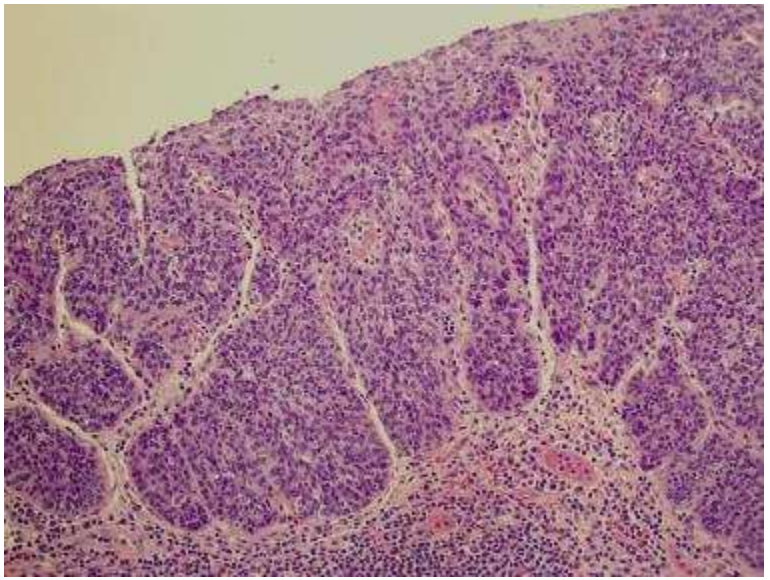

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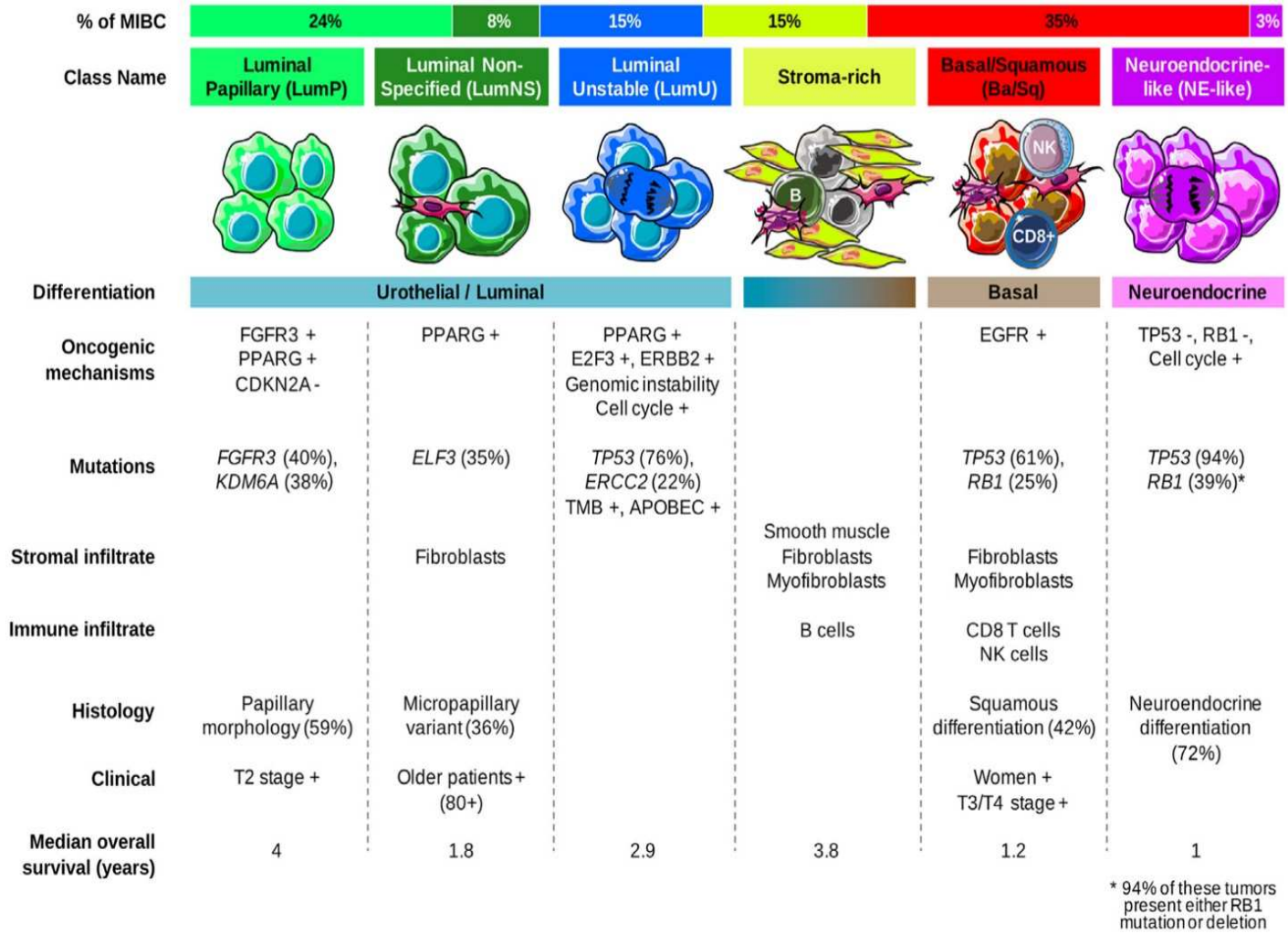

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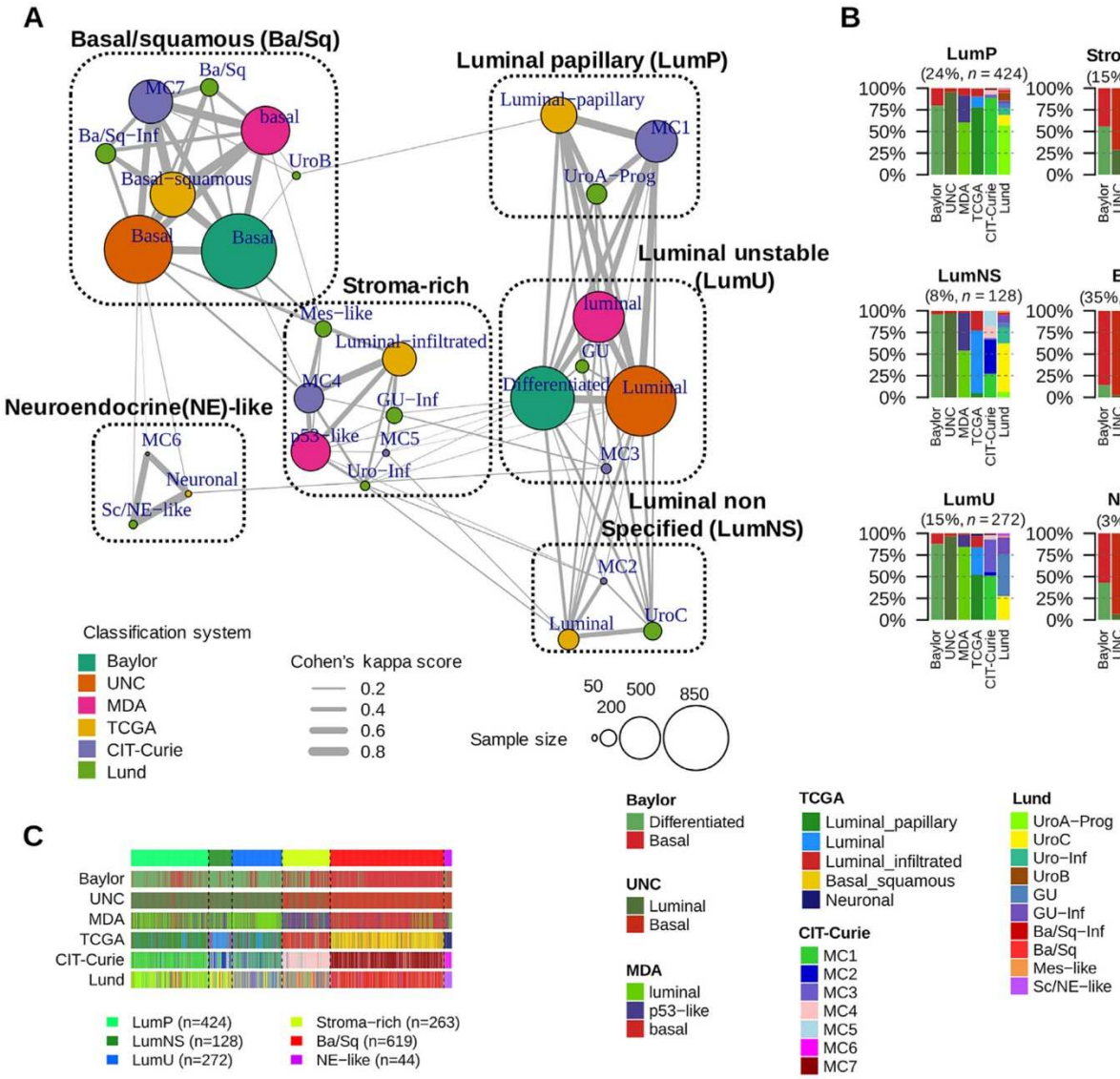


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7690647/

Molecular characterization of subtypes

- Luminal Papillary tumors were mainly enriched in FGFR3 (55%)
- Homozygous/deep deletions of CDKN2A in 33%.
- Younger age at presentation
- The Luminal Non-specified subtype was mainly characterized by enrichment of mutations in ELF3 (35%), which is an early regulator of urothelial differentiation and is activated by PPARG
- PPARG was significantly altered as well (76%)
- Older age at presentation

Molecular characterization of subtypes

- Luminal Unstable tumors harbored frequent PPARG alterations (89%)
- High-level amplifications of a 6p22.3 region that contains E2F3 and SOX4 (76%),
- ERBB2 amplifications were noted in 39%
- No significant association was found between ERBB2 mutations and any of the consensus classes
- Frequent mutations in TP53 (76%) and in ERCC2, which codes for a core nucleotide-excision repair component (22%)
- Generally the most genomically altered subtype

Molecular characterization of subtypes

- For Basal/Squamous tumors, the most frequently mutated genes based are TP53 (63% of cases) and RB1.
- Found principally in women
- For Neuroendocrine-like tumors, TP53 was almost always mutated (94%)and co-occurred with RB1 alteration by either mutations or deletions (94%)
- The Stroma enriched subtype is characterized by the presence of smooth muscle, fibroblasts and myofibroblasts, as well as B cell infiltrates
- No characteristic mutations

Genetics and chemotherapy response

- FGFR mutations found in up to 20%
- Defective DNA repair (DDR) germline mutations found in 13-19%
- Somatic mutations of ATM/RB1/FANCC/ERCC2 were found to correlate with better response and survival in patients treated with cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy

Genetics and chemotherapy response

- DDR genomic alterations (excluding ATM) are associated with overall survival benefit in general but not with response to platinum-based chemo-therapy.
- ATM mutations associated with shorter survival

Genetics and chemotherapy response

- ATM gene at 11q22–23, encodes a PI3K-related serine/threonine protein kinase
- Maintains genomic integrity by its central role in activation of DDR pathways, including those involved in cell-cycle checkpoint arrest (CHK2), DNA repair(BRCA1 and RAD51), and apoptosis (p53)
- ATM acts as a binary switch that dictates the effect of p53 activation on tumor response to chemotherapy in lung and breast cancer

Genetics and chemotherapy response

- ATM function loss has been implicated in accelerated epithelial mesenchymal transformation (and metastasis)
- FAS inhibitors sensitize cancer cells to cisplatin through apoptosis

Bladder cancer treatment

- Transurethral resection of the bladder tumor is the first step in the initial management of bladder cancer.
- Resection of the prostatic urethra considered if tumor is at the bladder neck or within the prostatic urethra.
- Following transurethral resection, intravesical therapy is instituted within 6 hours.
- Mitomycin C (with heat) and gemcitabine are the agents of choice for non-muscle invasive bladder cancer.
- BCG is also an option

Bladder cancer treatment

- Patients who fail an initial course of intravesical chemotherapy will respond to BCG.
- Patients who fail an initial course of intravesical BCG therapy will likely not respond to chemotherapy.
- A second course of BCG (with interferon-α) may be effective in up to half these failures.
- Refractory patients should be considered for cystectomy.

Bladder cancer treatment

- 20% low risk develop invasive disease, 10% metastasize
- High grade, high risk (45% invade and 50% metastasize)
- Non-urothelial carcinomas, those urothelial carcinomas with lymphovascular invasion, as well as those with deep prostatic involvement should be considered for cystectomy even though no muscle invasion is detected.

Bladder cancer treatment

- Invasion into the detrusor muscle is associated with high mortality rates.
- Radical cystectomy is the treatment of choice.
- Considered for cystectomy even though no muscle invasion is detected:
- Non-urothelial carcinomas
- Urothelial carcinomas with lymphovascular invasion
- Urothelial carcinomas with deep prostatic invasion

Bladder cancer treatment

- Radiation therapy may be given following trans-urethral resection of the bladder
- Patients with large or extensive bladder lesions
- Are treated with radiation therapy as well in combination with chemotherapy with cisplatin (with or without 5-FU) or mitomycin C with 5FU.
- Those with metastatic disease are treated with gemcitabine and cisplatin chemotherapy or dose-dense methotrexate, vinblastine, doxorubicin, cisplatin chemotherapy.
- No optimal chemotherapy regimen has been identified.

Bladder cancer treatment

- A PD1/PDL1 inhibitor such as avelomab post platinum based chemotherapy has shown to be active in refractory disease
- Bladder cancer cells usually have the Nectin-4 protein on their surface.
- Enfortumab vedotin-ejfv is an anti-Nectin-4 antibody attached to the drug, monomethyl auristatin E (MMAE).
- Useful in post-chemotherapy, post-PD1/PDL1 failures

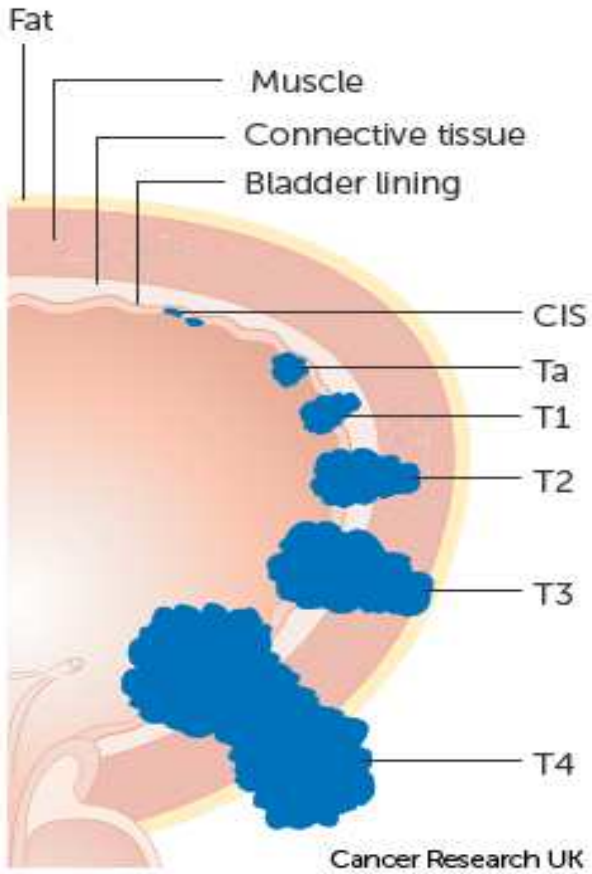


Table 21-4 Pathologic T (Primary Tumor) Staging of Bladder Carcinoma

Depth of Invasion	AJCC/UICC
Ta	Noninvasive, papillary
Tis	Carcinoma in situ (noninvasive, flat)
T1	Lamina propria invasion
T2	Muscularis propria invasion
T3a	Microscopic extravesicle invasion
T3b	Grossly apparent extravesicle invasion
T4	Invades adjacent structures

AJCC/UICC, American Joint Commission on Cancer/Union Internationale Contre le Cancer.

Prognosis depends on the histologic grade and the stage at diagnosis

Urethra

- Urethritis is either gonococcal or non-gonococcal in origin
- Chlamydia trachomatis or Mycoplasma urealyticum each as causes of >25% of cases
- May be accompanied by cystitis (woman) or prostatitis (man)
- Reactive arthritis (Reiter's syndrome) is manifest by urethritis, uveitis, and reactive polyarthritis
- HLA-B27 common
- Salmonella, Shigella, or Campylobacter as triggers
- May resolve spontaneously in 12 months
- Primary carcinomas are uncommon

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

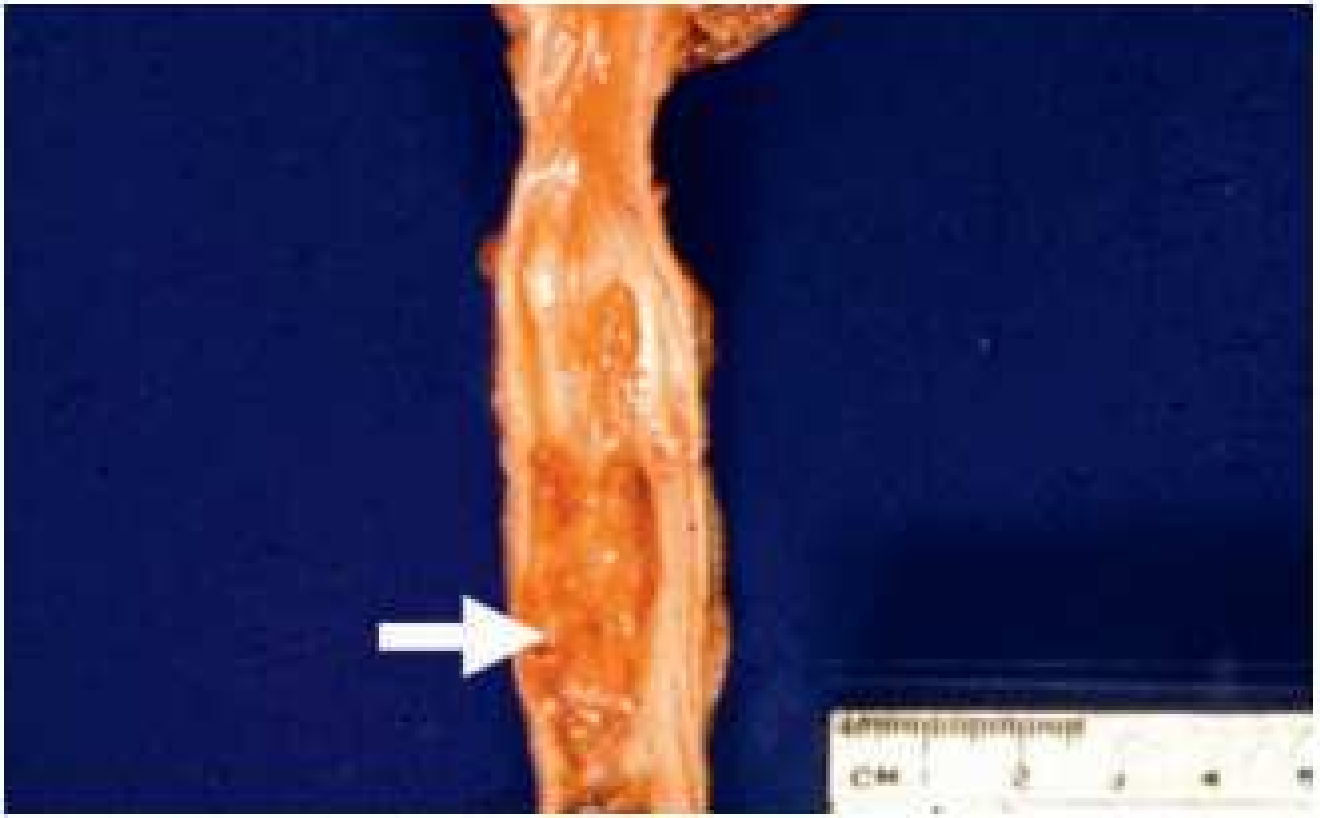


Figure 21-14 Carcinoma of urethra with typical fungating growth.

Squamous cell carcinoma of urethra

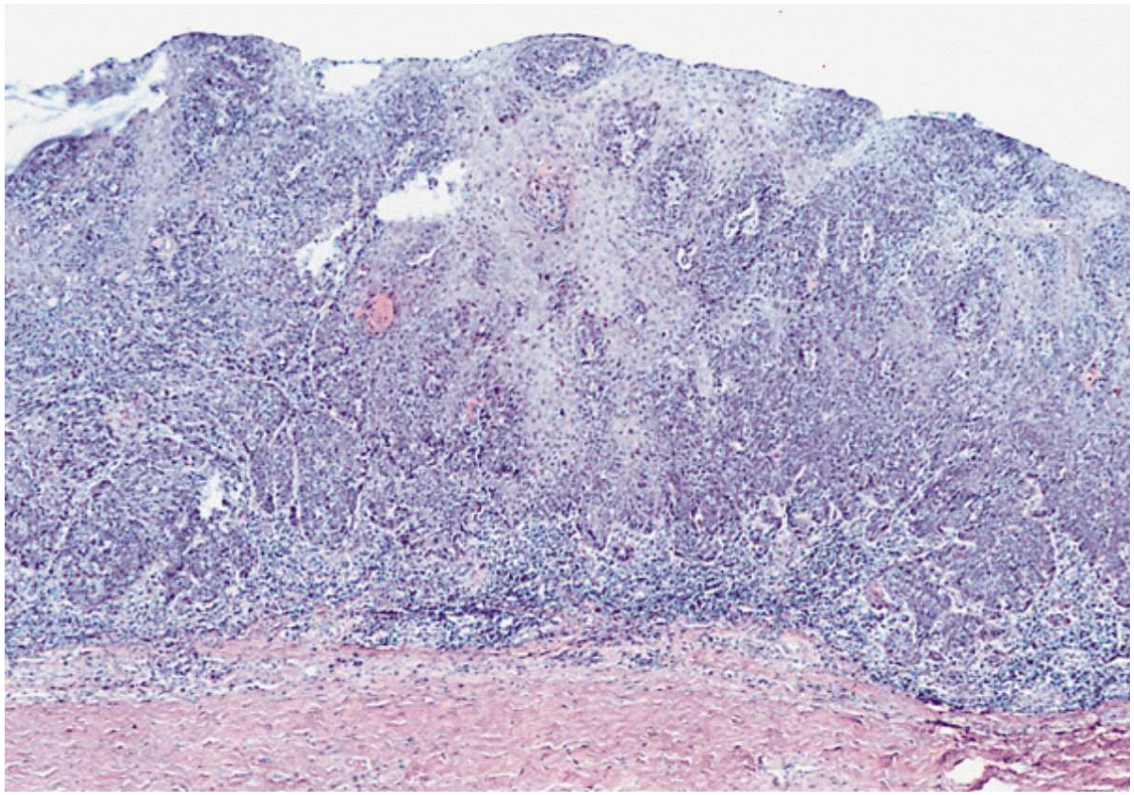


Fig. 9-14

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.

VULVA

Infections

- HPV infections involve the vulva (warty projections), vagina and cervix.
- Condyloma accuminatum
- Usually HPV6 and HPV11
- Mollluscum contagiosum (poxvirus) infections present as pearly, dome-shaped papules with dimpled centers.
- Usually MSC1 and MSC2
- Cytoplasmic inclusions noted in central waxy core

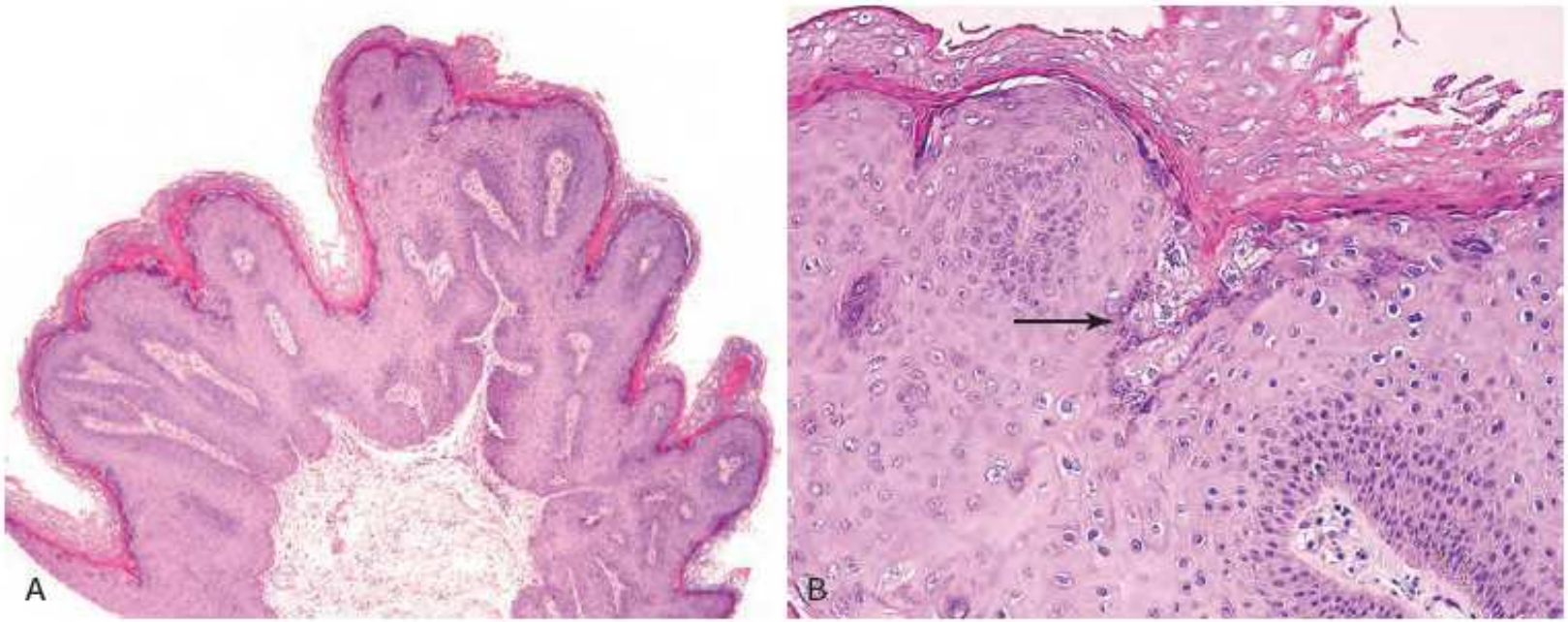


Figure 22-6 Condyloma acuminatum. **A,** Low-power view showing exophytic, papillary architecture. **B,** High-power view reveals HPV cytopathic effect (koilocytic atypia) characterized by atypical, enlarged, hyperchromatic nuclei with perinuclear halos *(arrow)*.

Molluscum contagiosum

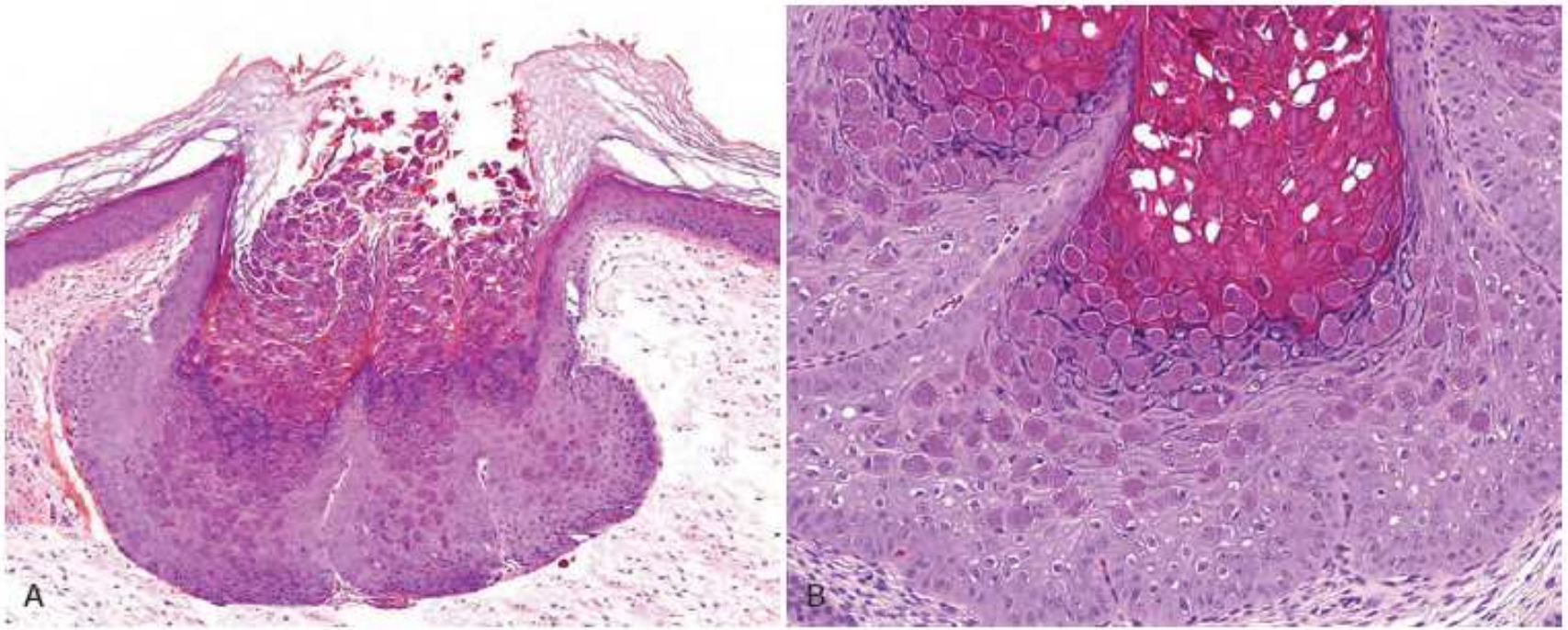


Figure 22-3 Molluscum contagiosum infection. **A,** Low power appearance of a dome-shaped papule with dimpled center. **B,** High power magnification reveals intracytoplasmic viral inclusions.

Vulva

- Squamous cell carcinoma is the most common histologic type of vulvar cancer.
- Basaloid and warty carcinomas related to infection with high risk HPVs (30% of cases), most commonly HPV-16.
- Arise from classic vulvar intraepithelial neoplasia
- Classic VIN presents either as a discrete white (hyperkeratotic) or a slightly raised, pigmented lesion.
- Epidermal thickening, nuclear atypia, increased mitoses, and lack of cellular maturation
- Occur at younger ages.

Vulva

- Keratinizing squamous cell carcinomas unrelated to HPV infection (70% of cases).
- These are more common in older women.
- Leukoplakia as precursor lesion
- Arise from differentiated vulvar intraepithelial neoplasia
- Marked atypia of the basal layer of the squamous epithelium and normal-appearing differentiation of the more superficial layers

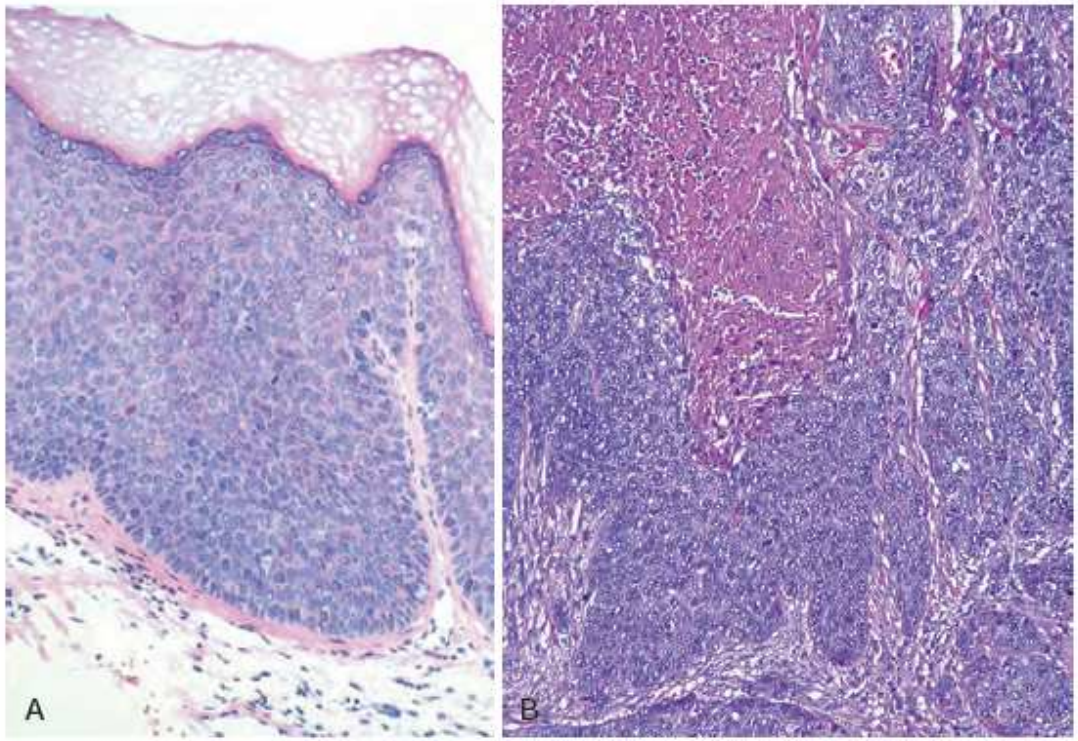


Figure 22-7 Variants of vulvar intraepithelial neoplasia. **A,** Classic vulvar intraepithelial neoplasia (HPV positive), showing nuclear enlargement, hyperchromasia, and small immature basaloid cells extending up to the epithelial surface. **B,** Basaloid vulvar carcinoma (HPV positive), composed of small, immature (basaloid) cells. This invasive tumor has an area of central necrosis.

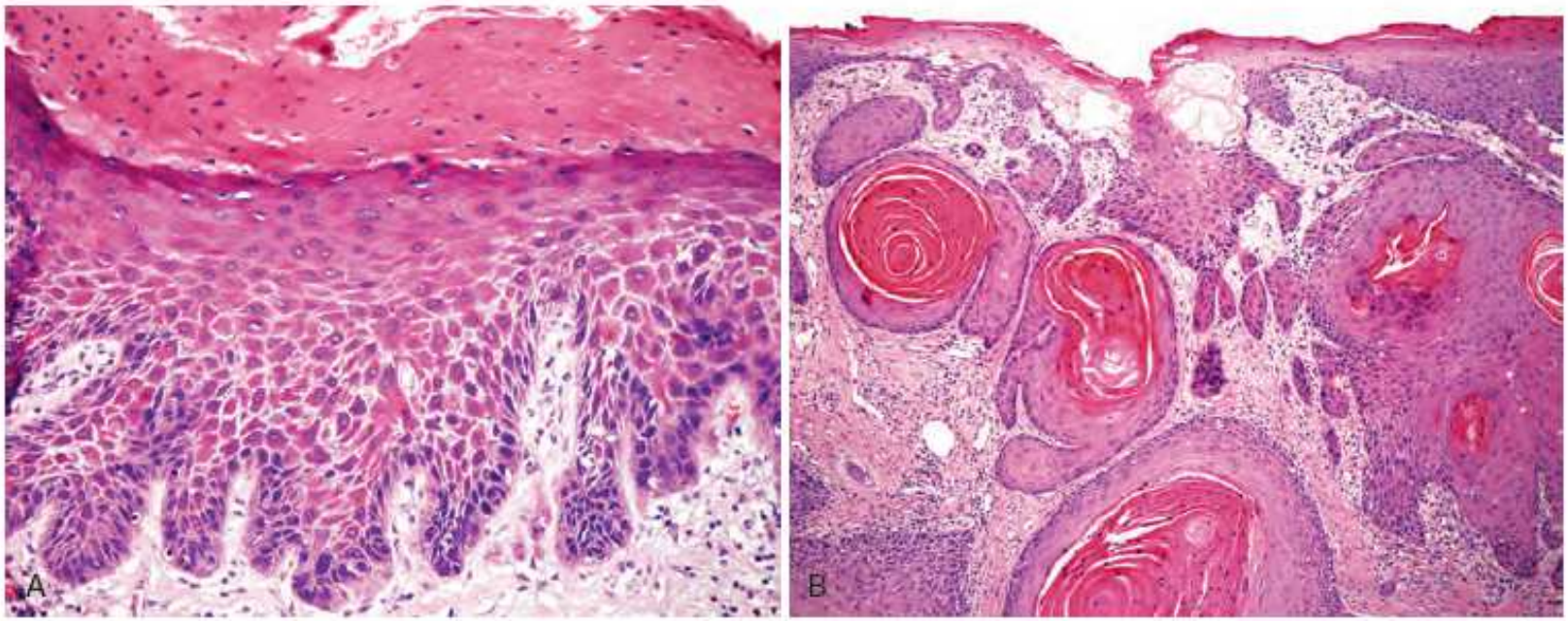


Figure 22-8 **A,** Differentiated vulvar intraepithelial neoplasia (HPV negative), showing maturation of the superficial layers, hyperkeratosis, and basal cell atypia. This is in-situ lesion; no invasion is present. **B,** Well-differentiated, keratinizing squamous cell carcinoma of the vulva (HPV negative).

Papillary hidradenoma

- Presents as a sharply circumscribed nodule, most commonly on the labia majora or interlabial folds
- May ulcerate.
- Consists of papillary projections covered with two layers of cells:
- An upper layer of columnar secretory cells covering a deeper layer of flattened myoepithelial cells.

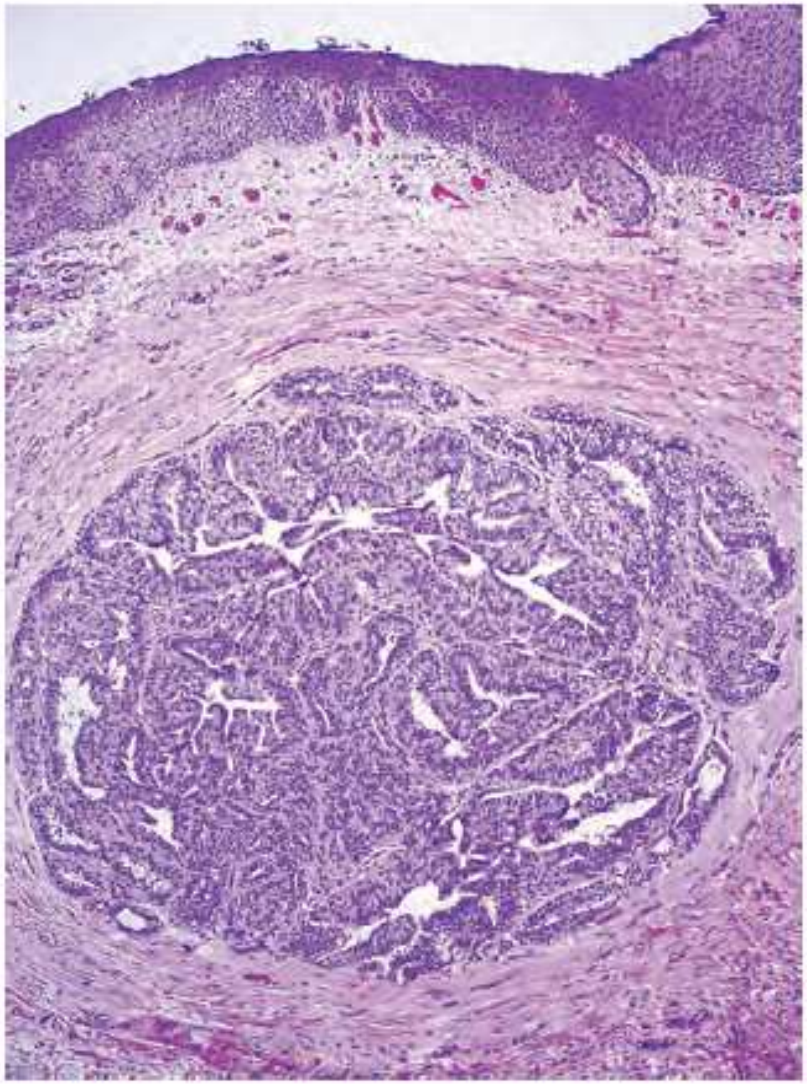


Figure 22-9 Papillary hidradenoma of the vulva, a well-circumscribed tumor composed of benign papillary projections covered with columnar secretory epithelium and underlying myoepithelial cells.

Extramammary Paget's disease

- Vulvar Paget's disease is typically not associated with underlying cancer and is confined to the epidermis of vulvar skin.
- Pruritic, crusted, usually on labia majora
- Paget's disease is a distinctive intraepithelial proliferation of malignant cells.
- Paget cells are larger than surrounding keratinocytes and are seen singly or in small clusters within the epidermis
- The cells have pale cytoplasm containing mucopolysaccharide (stain with Alcian blue or mucin)

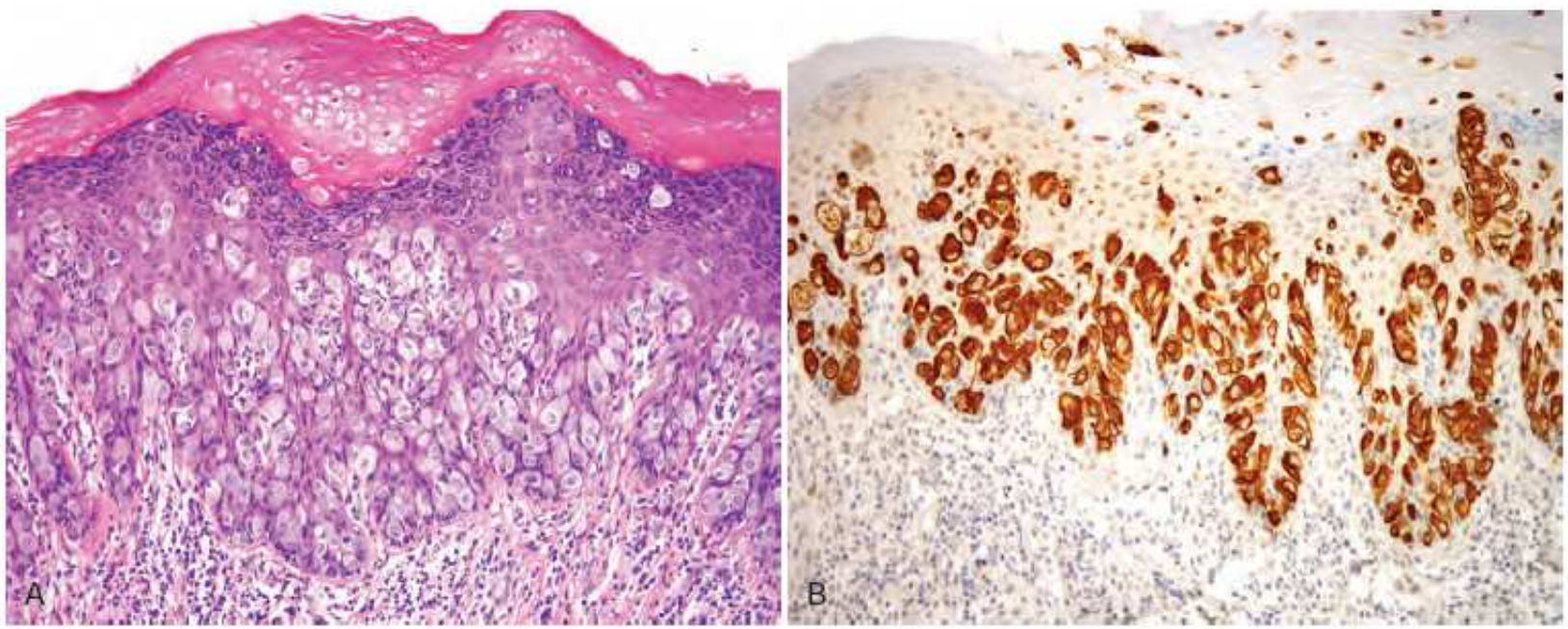


Figure 22-10 Paget disease of the vulva. **A,** The epidermis is infiltrated by large cells with pale-pink cytoplasm that are spreading along the basal portion of the squamous epithelium. There is inflammation in the underlying dermis. **B,** Immunostaining for cytokeratin 7 highlights the intraepidermal Paget cells.

VAGINA

Infections

- Candida albicans infections are largely vulvo-vaginal.
- White thick discharge.
- Defective neutrophil or T_H17 T-cell function
- Non-septate hyphae with pseudospores
- Trichomonal vaginalis presents with a vaginitis and cervicitis
- Inflammatory change in the cervix with dilated vessels is referred to as "strawberry cervix"
- Frothy watery discharge.
- Flagellated protozoan

Infections

- Gardnerella presents with a cervicitis
- The discharge has an ammoniacal or fish odor.
- Bacterial vaginosis
- Gram negative coccobacillus
- Associated with onset of premature labor

Congenital abnormalities

- Septate, or double, vagina
- Arises from a failure of Müllerian duct fusion and is accompanied by a double uterus (uterus didelphys).
- Vaginal adenosis
- Small patches of residual glandular epithelium may persist into adult life
- Gartner duct cysts
- Arise from Wolffian (mesonephric) duct rests

Squamous carcinoma

- Squamous carcinoma of the vagina is usually from extension from the cervix (upper posterior vagina)
- Virtually all primary carcinomas of the vagina are squamous cell carcinomas associated with high risk HPVs
- Arise from vaginal intraepithelial neoplasia
- Lesions in the upper-third spreas to iliac nodes while those in the lower two-thirds spread to inguinal nodes

Embryonal rhabdomyosarcoma

- Sarcoma botyroides
- <5 years of age
- Polypoid, rounded, bulky masses that have the appearance and consistency of grapelike clusters
- The tumor cells are small and have oval nuclei, with small protrusions of cytoplasm from one end, resembling a tennis racket.
- Beneath the vaginal epithelium, the tumor cells are crowded in a cambium layer, but in the deep regions they lie within a loose fibromyxomatous stroma that is edematous and may contain many inflammatory cells

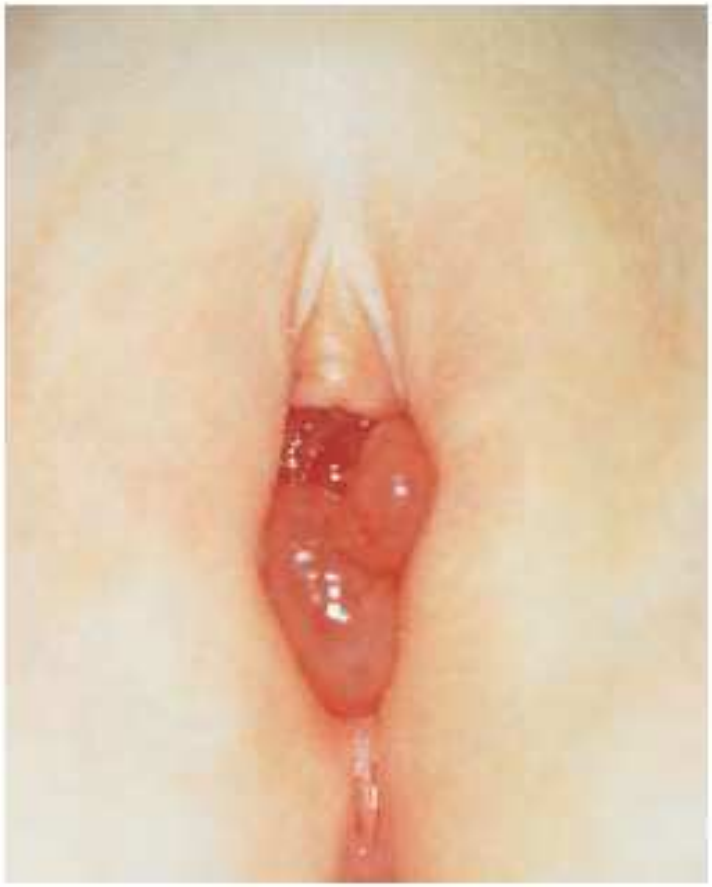


Figure 22-11 Sarcoma botryoides (embryonal rhabdomyosarcoma) of the vagina appearing as a polypoid mass protruding from the vagina. (Courtesy Dr. Michael Donovan, Children's Hospital, Boston, Mass.)

CERVIX

Urethra and cervix

- Urethritis is generally gonococcal in origin
- Presents as cervicitis and may be accompanied by cystitis
- Ureaplasma urealyticum or Mycoplasma hominis as cause of >25% of cases
- Associated with chorioamnionitis in pregnancy
- Chlamydia trachomatis as cause of 25% of cases
- May ascend to involve the fallopian tube, leading to salpingitis and fibrosis
- Painful if acute. Fever present.
- Soft, tender mass palpable in adnexa on bimanual examination. No rebound tenderness.

Urethra and cervix

- The initial gonococcal infection most commonly involves the endocervical mucosa
- It may also begin in the Bartholin gland and other vestibular, or periurethral, glands.
- From these sites the organisms may spread upward to involve the fallopian tubes and tubo-ovarian region.
- Gram negative intracellular diplococci

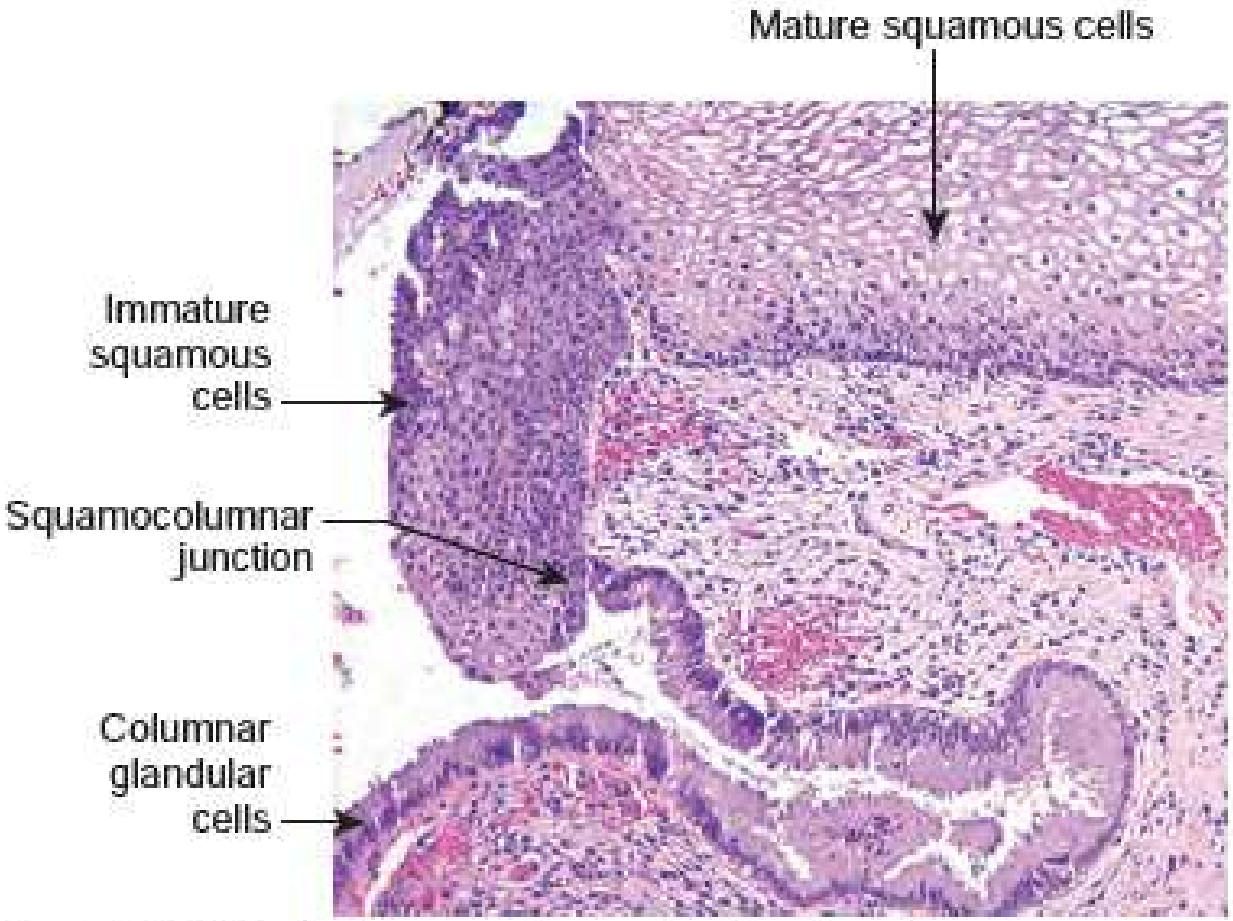


Figure 22-12 Cervical squamocolumnar junction showing mature, glycogenized squamous epithelium, immature squamous metaplastic cells, and columnar endocervical glandular epithelium.

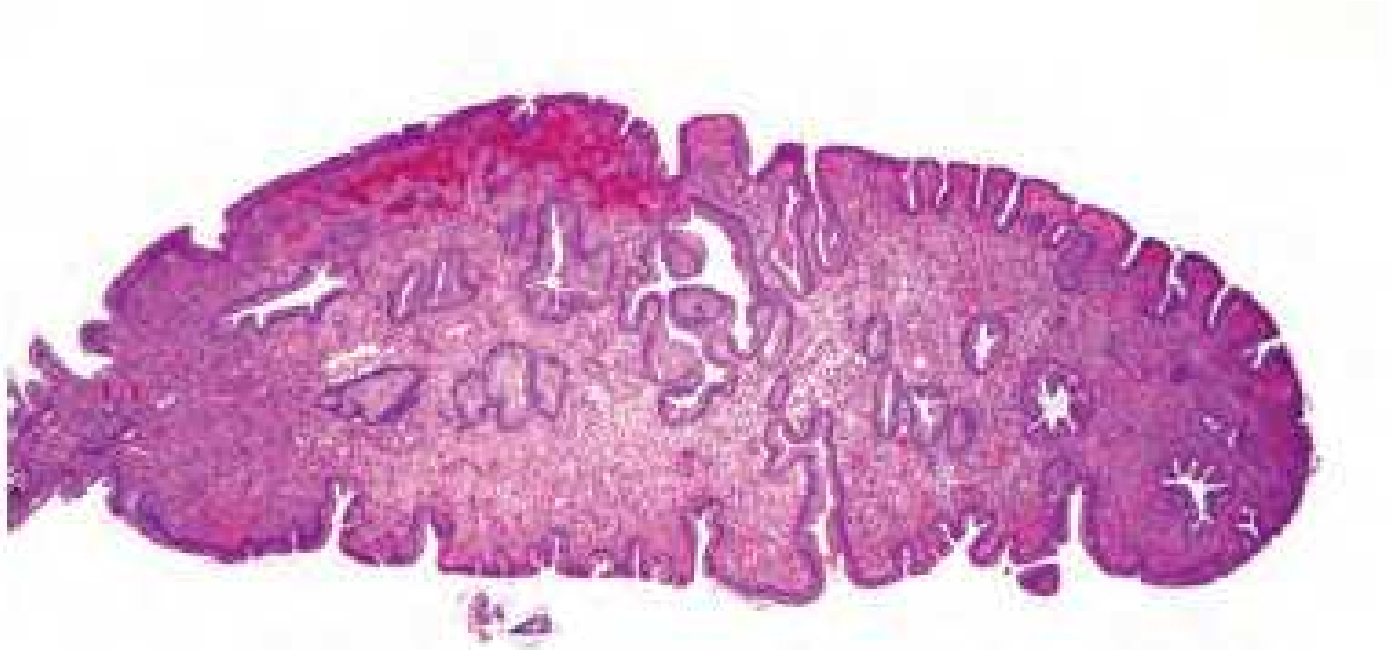


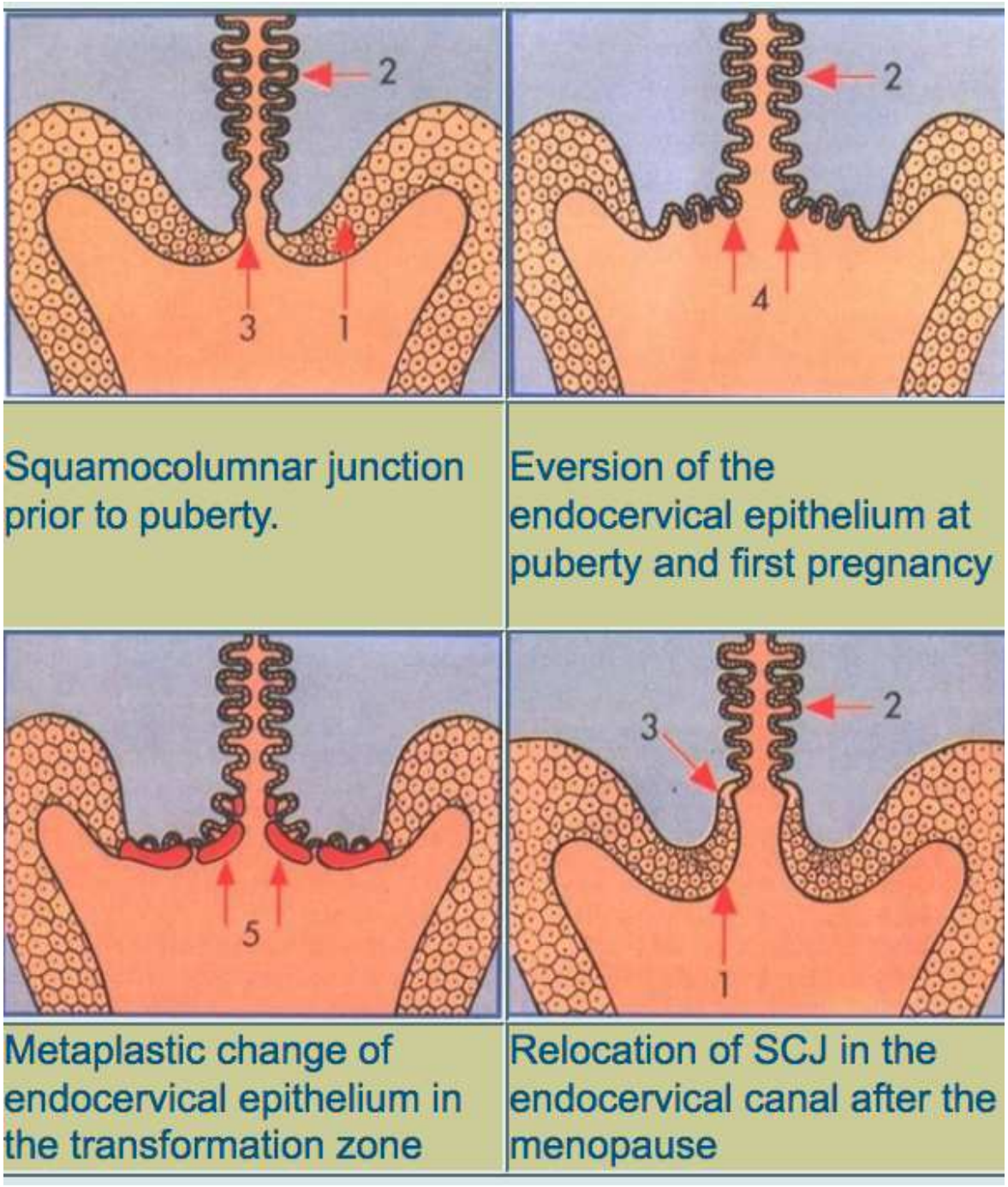
Figure 22-13 Endocervical polyp composed of a dense fibrous stroma covered with endocervical columnar epithelium.

Carcinoma of the cervix

- The major risk is infection by HPV.
- HPV16, 60% of cases
- HPV18,10% of cases
- The cervix, with its relatively large areas of immature squamous metaplastic epithelium, is particularly vulnerable to HPV infection
- Viral proteins E6 and E7 interfere with the activity of tumor suppressor proteins that regulate cell growth and, thus, impair DNA repair as well
- Viral DNA integrated into chromosome

Carcinoma of the cervix

- E7 binds to the activated form of RB and promotes its degradation by proteasomes
- E7 interferes with p21 and p27 (cyclin dependent kinase inhibitors)
- E6 binds to p53 and promotes its degradation by proteasomes
- E6 of low risk HPV (e.g., 6 and 11) does not bind p53
- Interferes with Notch signaling
- Low risk HPV DNA remains epichromosomal



Carcinoma of the cervix begins at the endocervical junction.

The routine Pap smear

- Screen throughout active sexual life
- False negative rate is up to 20% and largely represents error sampling of cervix.
- Risk factors for cervical cancer include:
- First intercourse earlier than 18 years of age
- More than six sexual partners
- Oral contraceptive use for more than 10 years
- Screen no more frequently than every 2-3 years if significant dysplasia is not found.

The routine Pap smear

- A negative liquid based Pap smear every 2 years until the age of 30 may then yield to less frequent screening (every 3 years) with concomitant HPV testing in patients at risk for HPV infection, not simply with condylomata.
- Terminate screening at age 70 or following hysterectomy if not performed for cancer.

The routine Pap smear

- History of genital warts is not an indication for HPV testing as the HPV strains are not associated with cervical cancer.
- Screen only if dysplasia found.
- Partner with penile cancer or whose previous partner has had cervical cancer
- Cis-gender sexual activity transmits HPV
- Chlamydia screens are only for those less than 24 years of age or pregnant and at high risk

Pap smear

- Atypical squamous cells of uncertain significance [ASUS] may represent HPV infection if no other abnormality present. HPV determination is indicated.
- Absence of cells from transformation zone may reflect inadequate scraping of endocervical canal.
- Presence of endometrial cells in the Pap smear of a woman older than 40 not on hormone therapy requires further investigation.

Bethesda grading system

Mild dysplasia CIN-I	Moderate dysplasia CIN-II	Severe dysplasia or carcinoma in situ CIN-III	Invasive
Atypical squamous cells of undetermined significance (ASC-US)	Low-grade squamous intraepithelial lesion (LGSIL or LSIL)	Atypical squamous cells – cannot exclude HSIL (ASC-H) High grade squamous intraepithelial lesion (HGSIL or HSIL)	Squamous cell carcinoma
Occupies lower third of mucosal thickness	Occupies at least 50% of mucosal thickness	Occupies entire mucosal thickness; basement membrane intact	Invades basement membrane

Pap smear

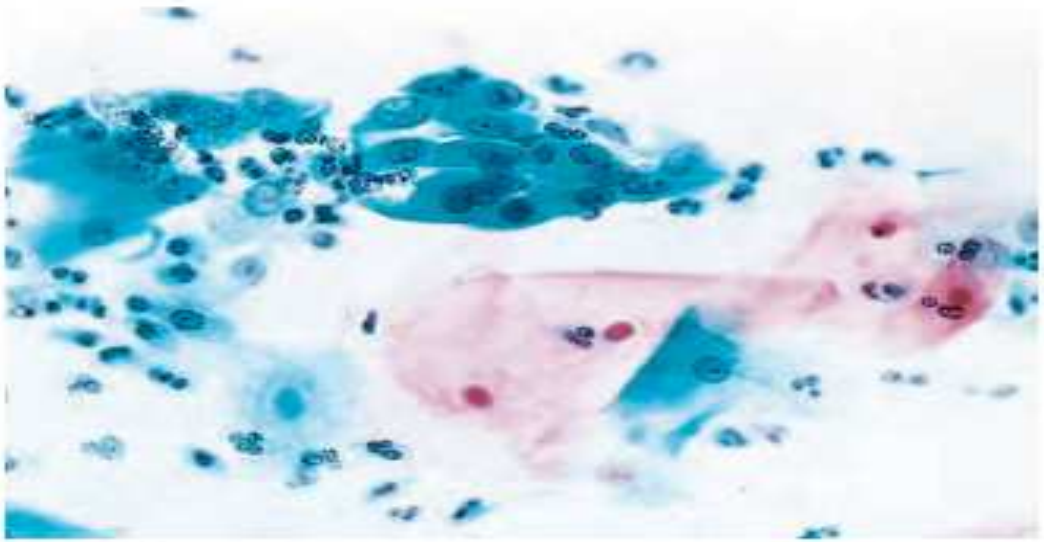
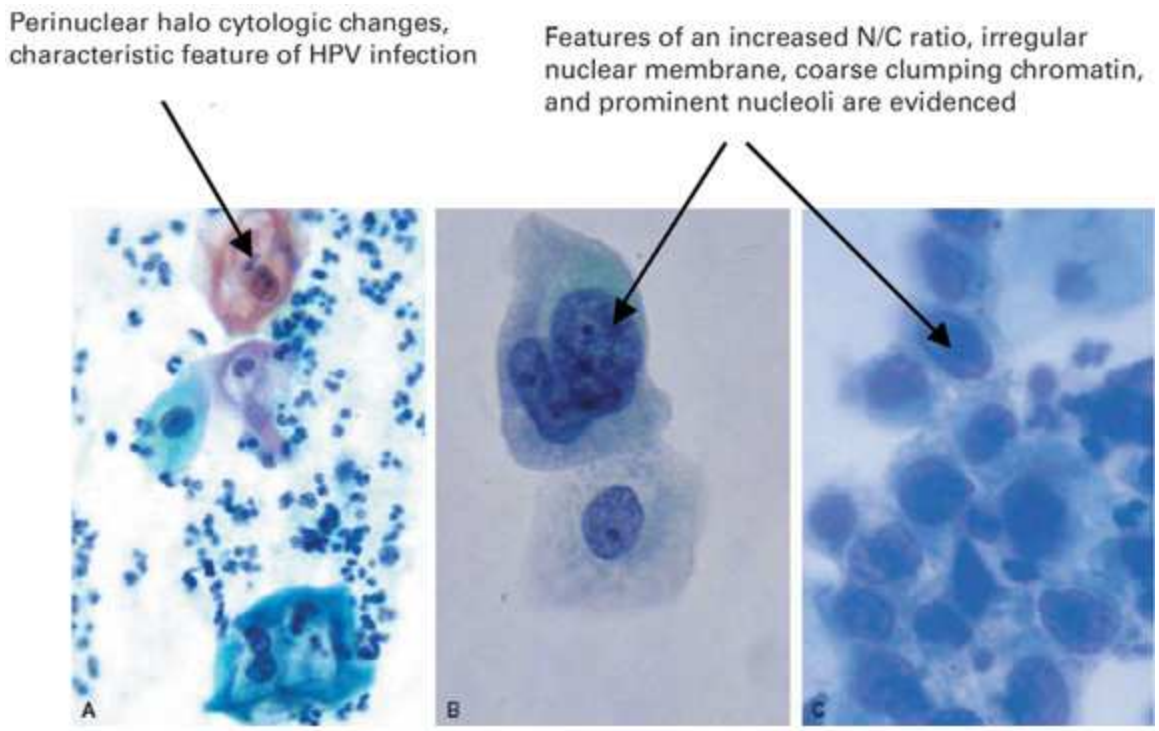


Figure 7-47 A normal cervicovaginal smear shows large, flattened squamous cells and groups of metaplastic cells; interspersed are neutrophils. There are no malignant cells. (Courtesy Dr. P. K. Gupta, University of Pennsylvania, Philadelphia, Pa.)

Pap smear



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Cytologic changes associated with cervical intraepithelial neoplasia (CIN), including CIN1 with koilocytotic feature of HPV infection A. x600 magnification, CIN2 B. x1000 magnification, and CIN3 C. x1000 magnification.

Fig. 24-10 Accessed 08/01/2010

Pap smear

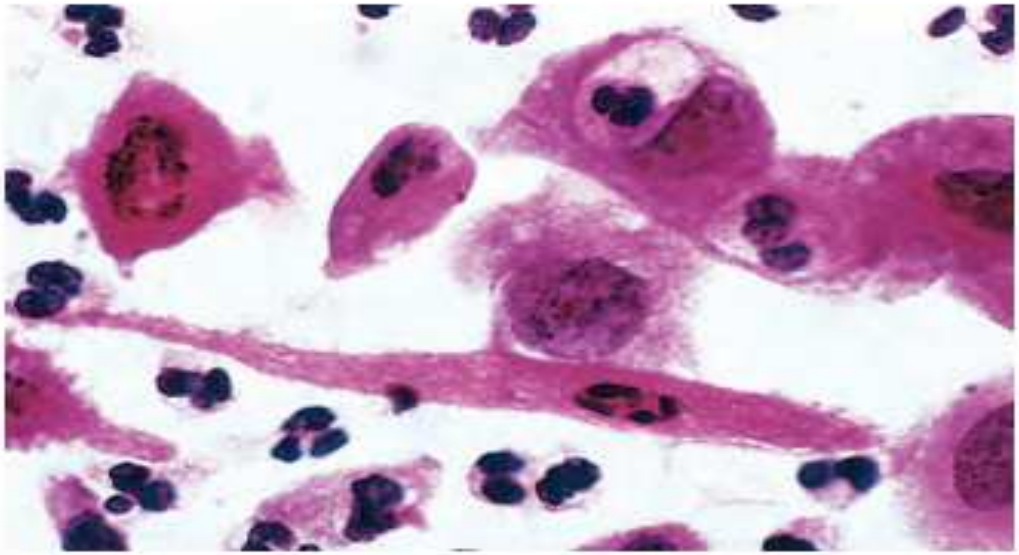
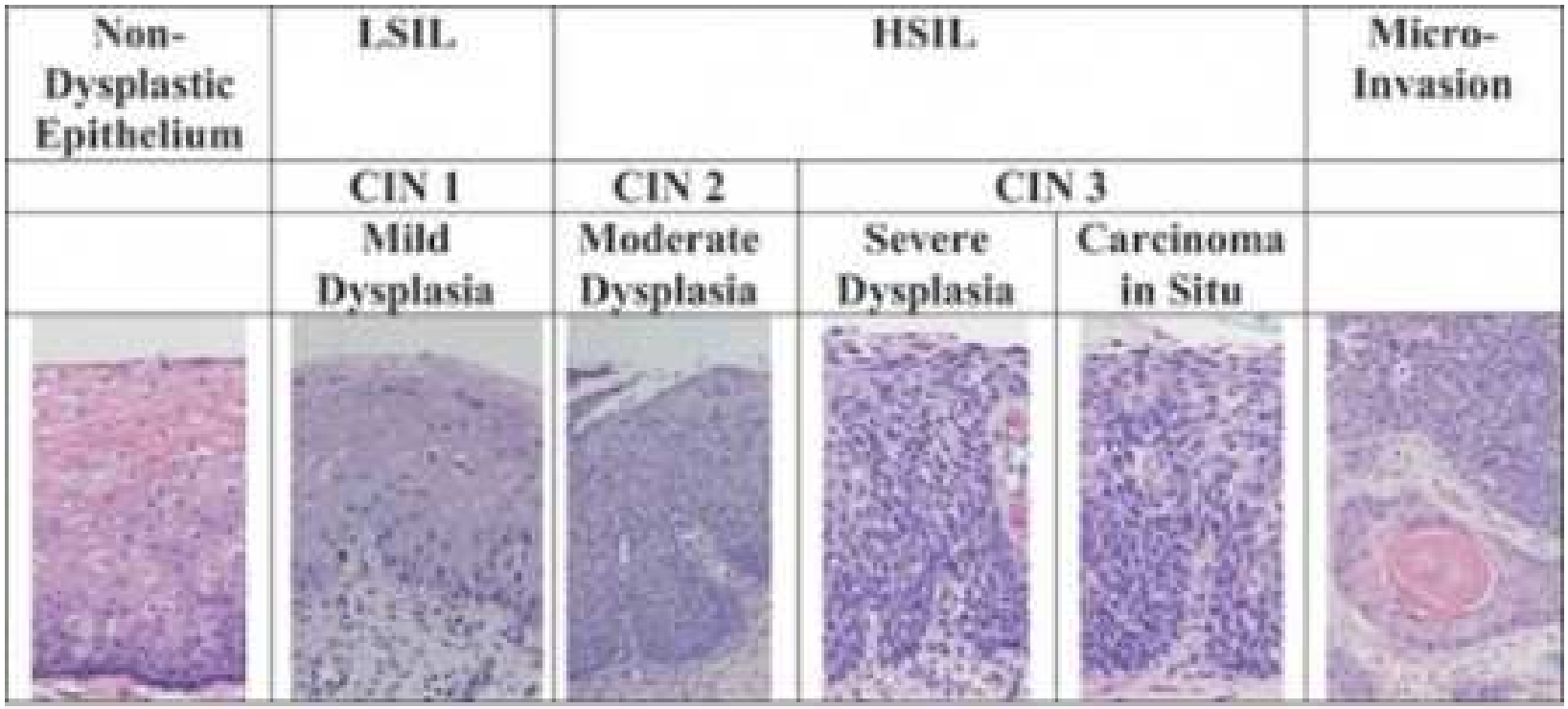


Figure 7-48 An abnormal cervicovaginal smear shows numerous malignant cells that have pleomorphic, hyperchromatic nuclei; interspersed are normal polymorphonuclear leukocytes. (Courtesy Dr. P. K. Gupta, University of Pennsylvania, Philadelphia, Pa.)

Carcinoma of the cervix

- The rate of progression from mild to moderate dysplasia is 1%/year, and can be followed on Pap smear.
- However, progression from moderate to severe dysplasia, the risk is 16% within 2 years and 25% within 5 years.
- Severe dysplasia if untreated leads to cancer in 12% of patients over a period of 20 years.
- Presents with abnormal vaginal bleeding (often postcoital). May complain of dyspareunia.



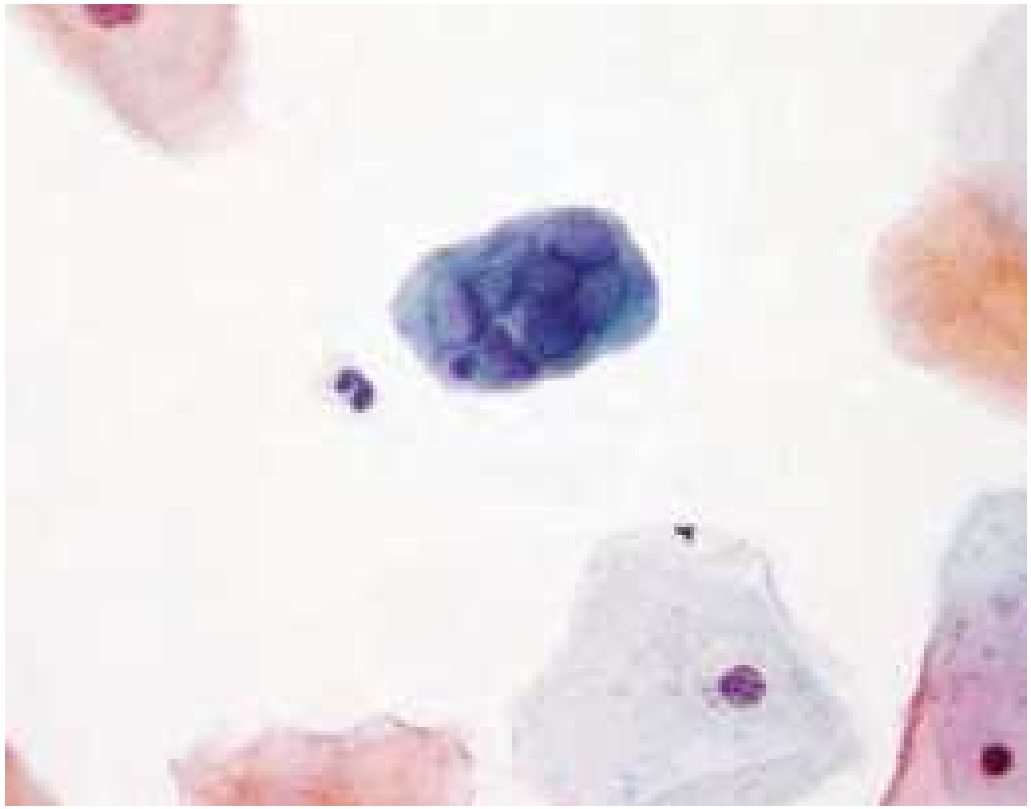
Images courtesy of Chisa Aoyama, MD, David Geffen School of Medicine at UCLA.

https://hackteria.org/wiki/images/thumb/0/0e/CIN-4.jpg/447px-CIN-4.jpg
Accessed 05/05/2020

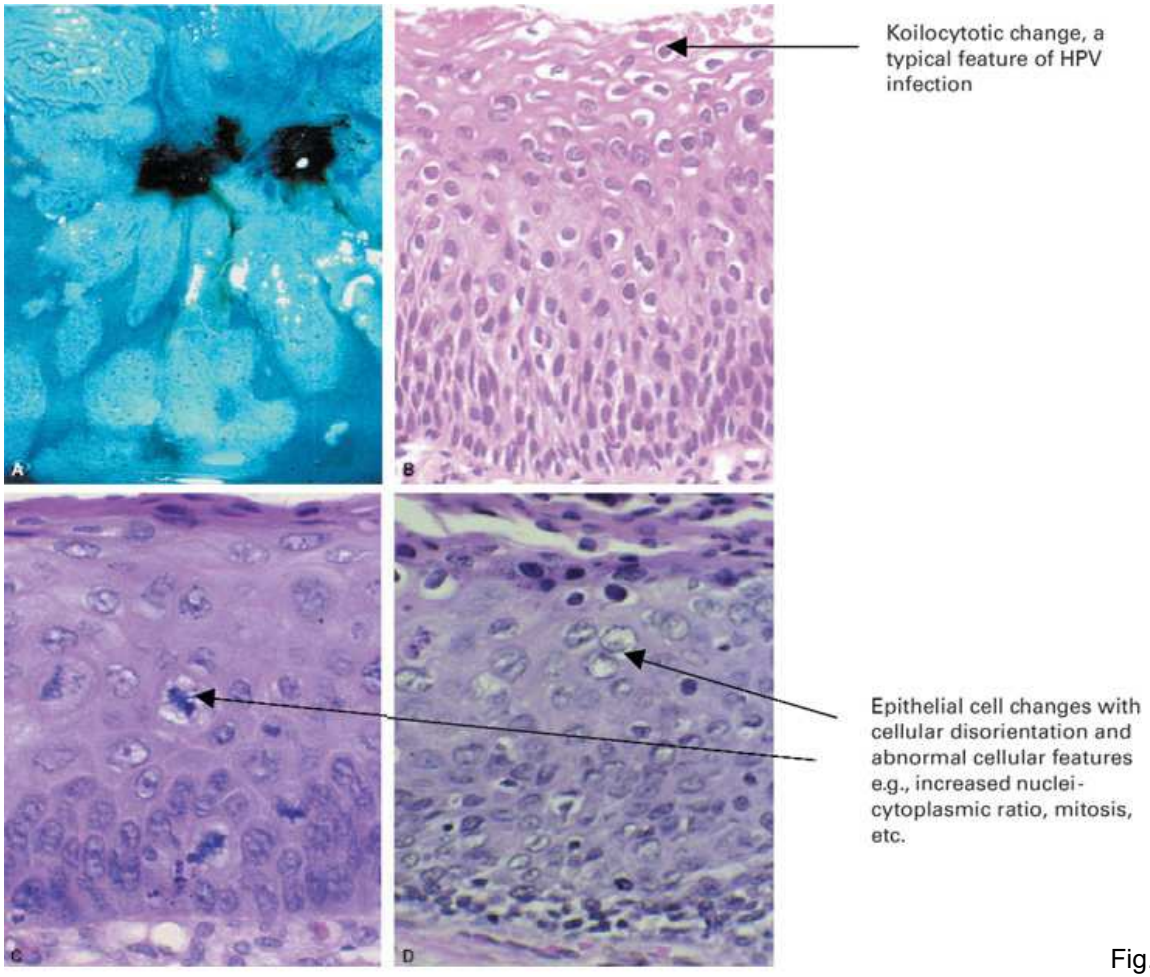
Infections

- Herpes virus infections (HSV1, HSV2) cause painful cervical ulcers. May also be present on vulva.
- Onset 3-7 days post infection.
- Virus migrates to lumbosacral nerve ganglia and establishes latent infection.
- May reactivate by stress, trauma, change in hormone levels.
- HSV1 infection may preclude later HSV2 infection
- HSV2 infection enhances later HSV1 infection
- Risk to neonate if vaginal delivery.
- Infected cells become multinucleated and contain intra-nuclear viral inclusions with a characteristic “ground-glass” appearance

HSV cytopathic effect



Grading



A. Colpophotograph illustrating a low-grade cervical intraepithelial neoplasia (CIN) in the transformation zone. B, C, and D. Histopathology of cervical intraepithelial neoplasia (CIN I, II, and III respectively) (H&E stain; x400 magnification).

Fig. 24-4 Accessed 08/01/2010

Grading

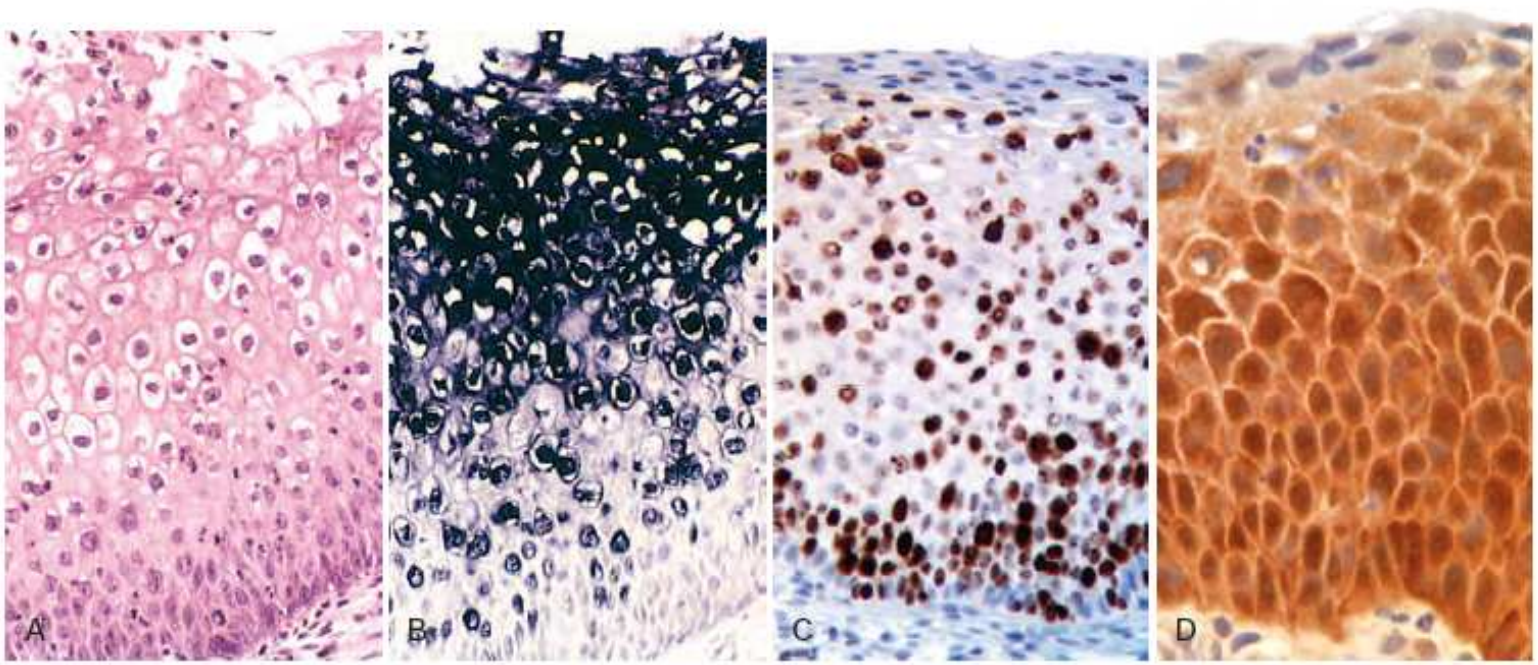


Figure 22-15 **A,** Low-grade squamous intraepithelial lesion (LSIL)—Routine hematoxylin and eosin staining shows marked koilocytic change, seen as perinuclear "halos" in suprabasilar cells. **B,** In situ hybridization test for HPV DNA. The dark granular staining denotes HPV DNA, which is typically most abundant in the koilocytes. **C,** Diffuse positivity for the proliferation marker Ki-67 (seen as brown nuclear staining), illustrates abnormal expansion of the proliferating cells from the normal basal location to the superficial layers of the epithelium. **D,** Upregulation of the cyclin-dependent kinase inhibitor p16 (seen here as brown staining) characterizes high-risk HPV infections.

Carcinoma of the cervix

- May be exophytic or invasive
- Spread by direct extension
- Squamous cell carcinoma (70%)
- Composed of nests and tongues of malignant squamous epithelium, either keratinizing or non-keratinizing, which invade the underlying cervical stroma
- Invasive carcinoma is usually non-keratinizing.
- Almost all are PD-L1 positive

Carcinoma of the cervix

- Adenocarcinoma (20-25%)
- Characterized by proliferation of glandular epithelium composed of malignant endocervical cells with large, hyperchromatic nuclei and relatively mucin-depleted cytoplasm
- HPV related
- HPV18 common
- Generally, ER+, PD-L1 negative

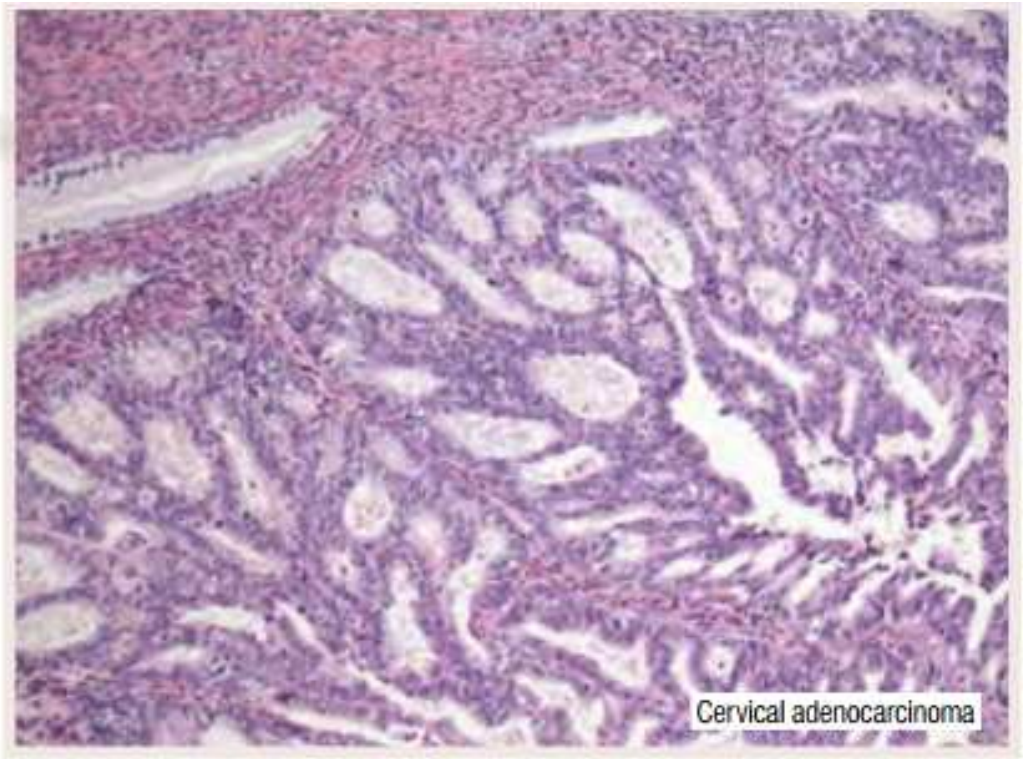
Carcinoma of the cervix

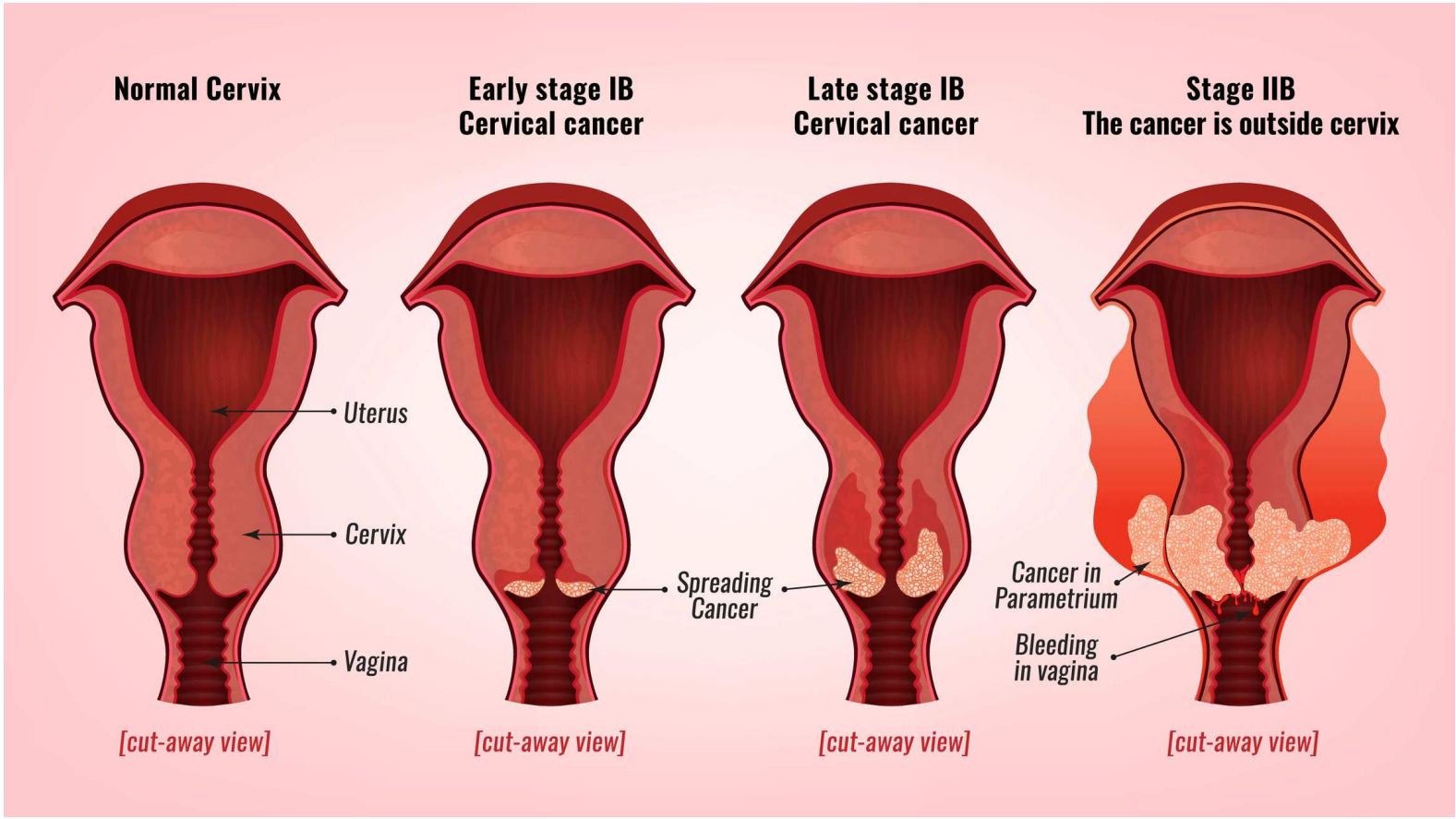
- Histological types include endocervical and mucinous; mixed adenosquamous carcinomas may occur.
- Gastric type mucinous and clear cell adenocarcinoma and adenocarcinoma arising from mesonephric remnants are not HPV related

- Neurodenocrine carcinoma (5%)
- 80%, small cell variant
- HPV related
- PIK3CA, KRAS, and TP53 usual mutations
- Highly aggressive

Carcinoma of the cervix

- Serious reactions have been reported with the general administration of HPV vaccine (infertility, loss of bladder function)
- Vaccination regimens in advanced and precancerous lesions are associated with >50% clinical response rates and evidence of induction of HPV-specific immunity.


Cervical adenocarcinoma



https://physicianreviews.org/wp-content/uploads/2018/12/Stages-of-Cervical-Cancer.gif

Stage	Extent of disease	5-year survival
0	Carcinoma in situ (CIN)	~100%
I	Limited to cervix	
Ia1	Microscopic disease: stromal invasion <3mm, lateral spread <7mm	>95%
Ia2	Microscopic disease: stromal invasion <3mm and >5mm, lateral spread <7mm	
Ib1	Macroscopic lesion <4cm in greatest dimension	~90%
Ib2	Macroscopic lesion >4cm in greatest dimension	80-85%
II	Extension to uterus/parametria/vagina	~75-78%
IIa1	Involvement of upper two thirds of vagina *without* parametrial invasion, <4cm greatest diameter	
IIa2	Involvement of upper two thirds of vagina *without* parametrial invasion, >4cm greatest diameter	
IIb1	Involvement of upper two thirds of vagina *with* parametrial invasion	
III	Extension to pelvic side wall and/or lower third of vagina	~47-50%
IIIa	Involvement of lower third of vagina	
IIIb	Extension to pelvic side wall and/or hydronephrosis	
IV	Extension to adjacent organs or beyond true pelvis	~20-30%
IVa	Extension to adjacent organs e.g. bladder, bowel	
IVb	Distant metastases	

https://www.bing.com/images/search?view=detailV2&ccid=kuUo8sHH&id=589F93720A53C9B67CAEDA66A518C6D744008DBE&thid=OIP.kuUo8sHHPPeF2EVCJe9chwHaGh&mediaurl=http%3A%2F%2Fgeekymedics.com%2Fwp-content%2Fuploads%2F2014%2F01%2Fcervical-cancer-staging-FIGO.jpg&exph=611&expw=693&q=staging+cervical+cancer&simid=608019725107987627&ck=73EB5120E100286

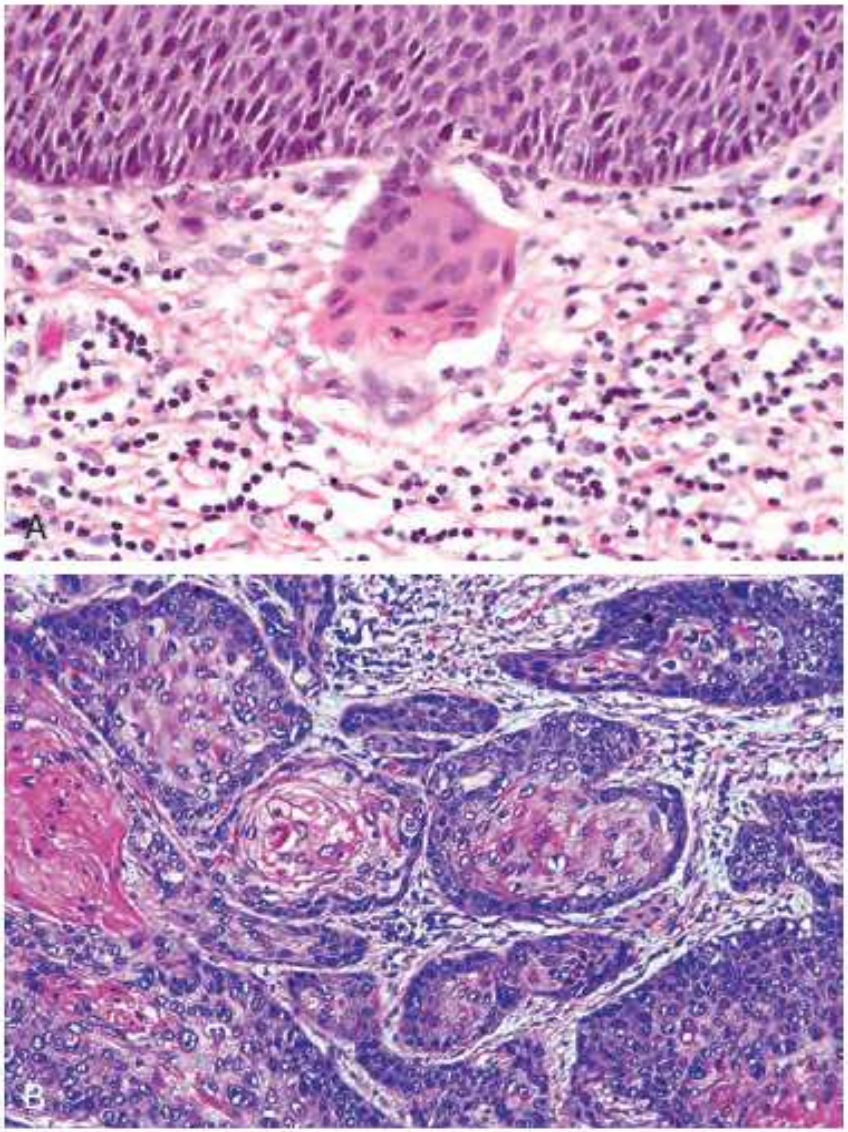


Figure 22-16 Squamous cell carcinoma of the cervix. **A,** Microinvasive squamous cell carcinoma with invasive nest breaking through the basement membrane of high-grade squamous intraepithelial lesion. **B,** Invasive squamous cell carcinoma.

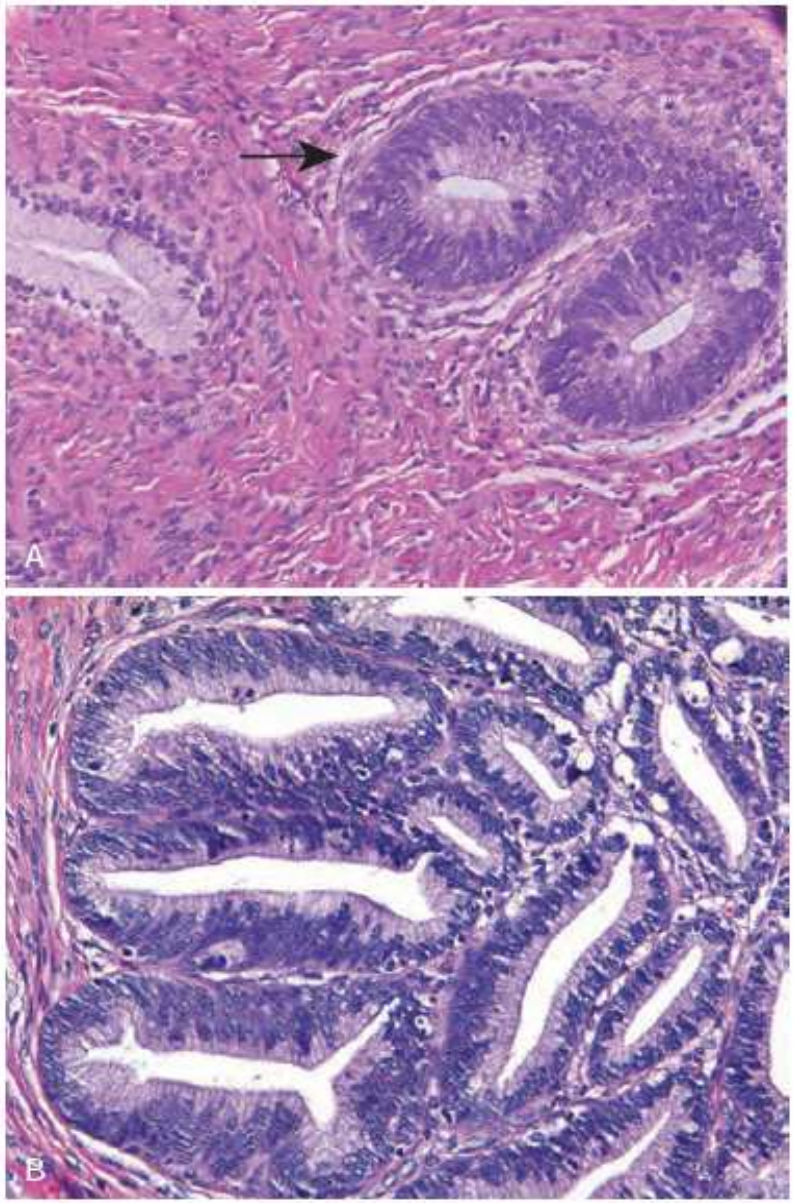


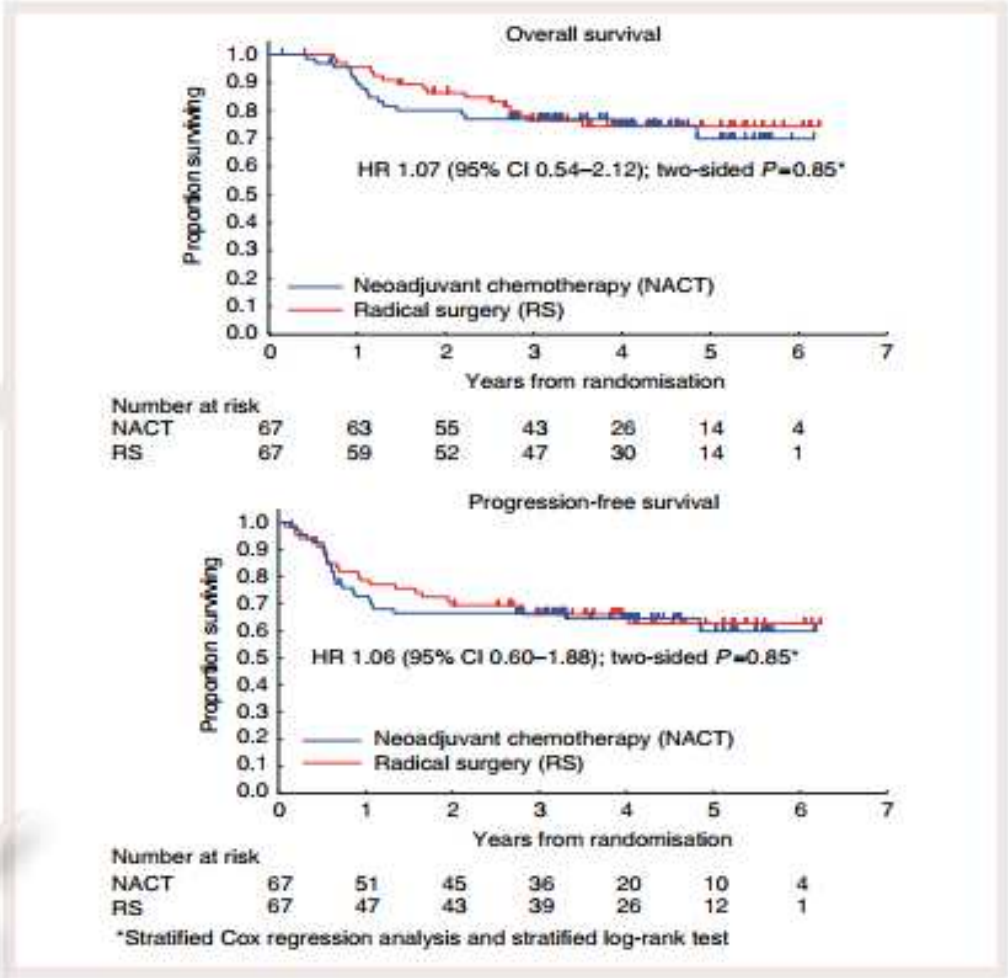
Figure 22-17 Adenocarcinoma of the cervix. **A,** Adenocarcinoma in situ *(arrow)* showing dark glands adjacent to normal pale endocervical glands. **B,** Invasive adenocarcinoma.

Therapy

- Simple hysterectomy or conization is considered a sufficient procedure for Stage IA cervical cancer, due to the very low risk of parametrial involvement and an excellent prognosis.
- No lymph node staging required
- LN staging is mostly recommended in Stage IA2, due to a higher risk of LN involvement. These cases are good candidates for SLN biopsy and ultrastaging (search for micrometastases).
- 15-30% with local disease have para-aortic disease

Therapy

- The principle of radical hysterectomy (RH) is removal of tissue surrounding the cervix (parametrium) and/or the upper part of the vagina in addition to the uterus with or without adnexa.
- If the aim is to preserve fertility, the distal part of the cervix, with the upper part of the vagina, is removed either with the parametrium (radical trachelectomy) or without it (simple trachelectomy).
- 2-3% recurrence
- Postoperative morbidity is caused mostly by the resection of the parametria and upper vagina.



CI, Confidence interval; HR, hazard ratio.

Therapy

- 10-50% have voiding dysfunction following surgery
- 10-30% have anorectal dysfunction following surgery
- 30% lymphedema or pelvic lymphocele as a consequence of pelvic lymphadenectomy
- Prognostic significance of para-aortic lymphadenectomy uncertain
- Micrometastases associated with worse prognosis
- Stage IB and IIA may be treated with radiation and chemotherapy (Cisplatin, 5FU) as alternative to radical hysterectomy and chemotherapy

Therapy

- Chemoradiation is the standard treatment option for ≥FIGO Stage IIB, III and IVA.
- Ovaries removed from field to preserve fertility.
- In pregnancy, chemotherapy in second or third trimester well tolerated (55% cisplatin to fetus)
- Cisplatin and paclitaxel chemotherapy with bevacizumab in Stage IVB, relapsed, and metastatic disease.
- If PD-L1 positive, addition of pembrolizumab (PD-L1)
- Radiotherapy is used to control bleeding from cervix
- Tisotumab vedotin-tftv (anti-Tissue Factor antibody conjugated with microtubule disruptor, MMAE) if PD-L1 negative. Blocks angiogenesis as well.
- Ocular toxicity

Therapy

- Pelvic exenteration (PE) is a treatment of choice in cases with central pelvic recurrence or tumor progression, with or without previous radiotherapy.
- PE can be performed as an anterior (preserving rectum), posterior (preserving urinary bladder and urethra) or total procedure, with consequent creation of a colostomy and/or urostomy (continent or incontinent).

Therapy

- PE is associated with high postoperative morbidity (50%–90%), mortality (up to 10%) and in some cases a long-term deterioration in quality of life, depending on the indication and stage of the disease.
- Overall survival 50%
- Para-aortic lymph nodes most important prognostic parameter

UTERUS

Menstrual cycle

- Average menstruation is 3-5 days with 30-50ml blood loss.
- Uterine cramps may result from liberation of prostaglandin $F_{2\alpha}$ from the endometrium (sloughed from progesterone withdrawal).
- First day of menstrual cycle is day 1.

Menstrual cycle

- Proliferative phase
- Marked by rapid growth of glands and stroma arising from the deeper portion of the endometrium (basalis).
- The glands are straight, tubular structures lined by regular, tall, pseudostratified columnar cells. Mitotic figures are numerous, and there is no evidence of mucus secretion or vacuolation.
- The endometrial stroma is composed of actively proliferating spindle cells with scant cytoplasm.

Menstrual cycle

- FSH is elevated
- Sitmulates estrogen secretion and maturation of ovarian follicles and the selection of a dominant follicle.
- Estrogen is produced principally in the ovarian follicle.
- cAMP is the second messenger for FSH
- FSH falls, LH rises as estradiol levels rise.

Menstrual cycle

- Progesterone is produced principally in the corpus luteum of the ovary.
- LH stimulates its production.
- cAMP is the second messenger.
- Ovulation occurs day 11-13.
- LH surge.
- Postovulation is initially marked by the appearance of secretory vacuoles beneath the nuclei in the glandular epithelium

Menstrual cycle

- Secretory activity is most prominent during the third week of the menstrual cycle, when the basal vacuoles progressively move to the apical surface.
- When secretion is maximal, between 18 and 24 days, the glands are dilated.
- By the fourth week the glands are tortuous, producing a serrated appearance.
- This serrated or “saw-toothed” appearance is accentuated by secretory exhaustion and shrinkage of the glands.

Menstrual cycle

- Prominent spiral arterioles appear by days 21 to 22 accompanied by an increase in ground substance and edema between the stromal cells.
- By days 23 to 24, stromal cell hypertrophy, increased cytoplasmic eosinophilia (predecidual change) and a resurgence of stromal mitoses appear
- Predecidual changes spread throughout the functionalis during days 24 to 28 and are accompanied by a sparse infiltrate of neutrophils and lymphocytes
- Endometrial biopsy for dating is usually taken days 23-25.

Menstrual cycle

- Corpus luteum maintained by progesterone.
- In the absence of fertilization, corpus lutum involutes.
- Estrogen induces endometrial stroma to produce IGFR1 and EGFR, stimulating glandular proliferation.
- Progesterone inhibits proliferation in both glands and stroma, decreasing estrogen receptor expression.

Endometrial cycle

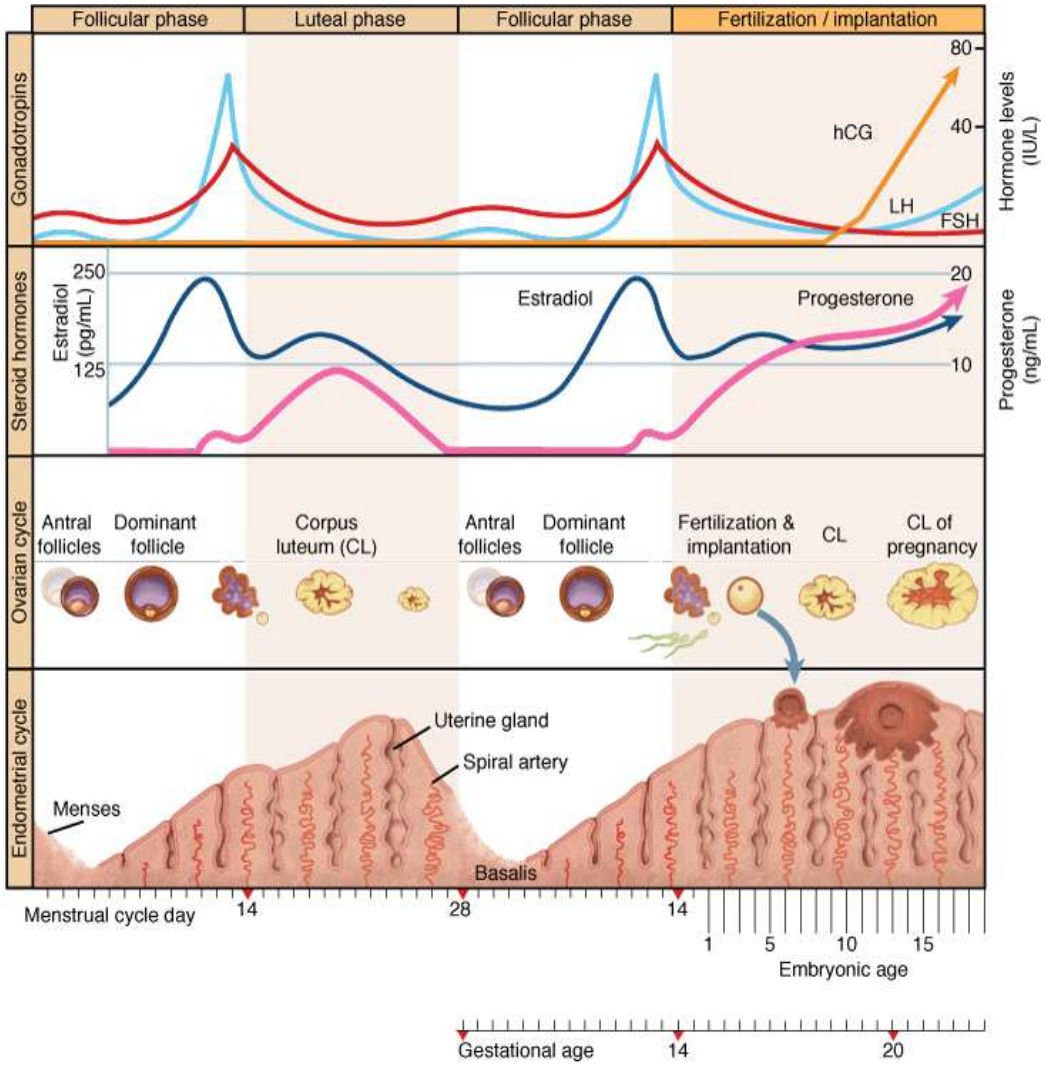


Fig. 3-1 Accessed 02/01/2010.

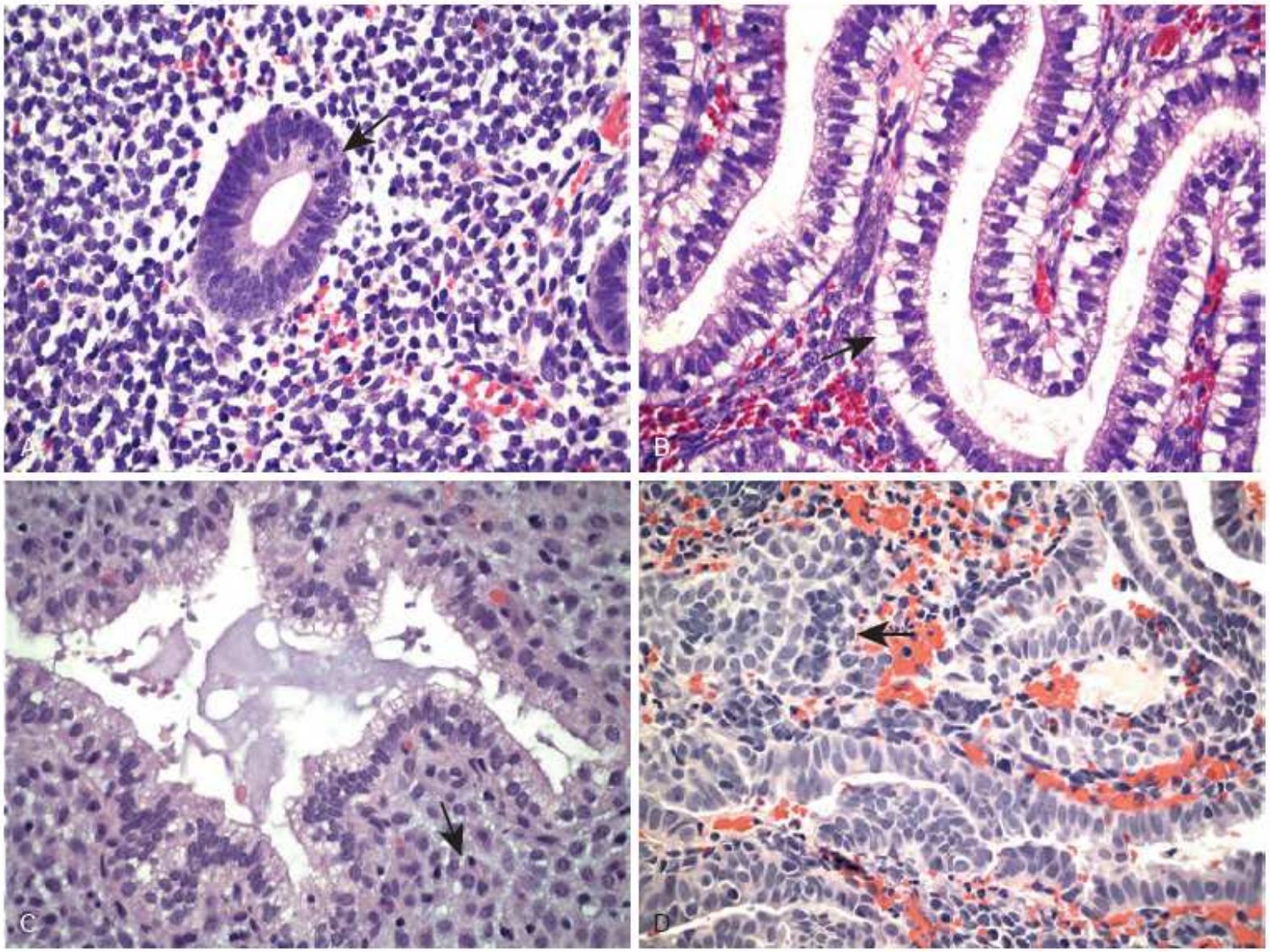
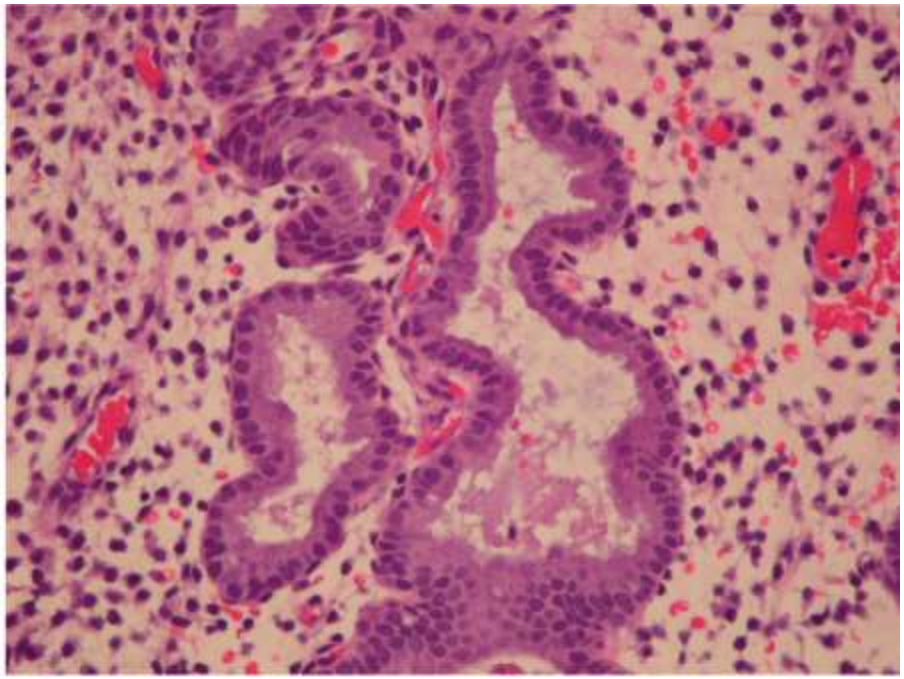


Figure 22-19 Histology of the menstrual cycle. **A,** Proliferative phase with mitoses *(arrow)*. **B,** Early secretory phase with subnuclear vacuoles *(arrow)*. **C,** Late

Enometrial dating

- Stroma is edematous. Spiral arterioles are prominent. Stromal cells are plump and cuff arterioles. Endometrial glands are dilated ("sawtooth"), lined by columnar cells, and contain secretory material centrally.



C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fig. 15-24
Accessed 02/01/2010

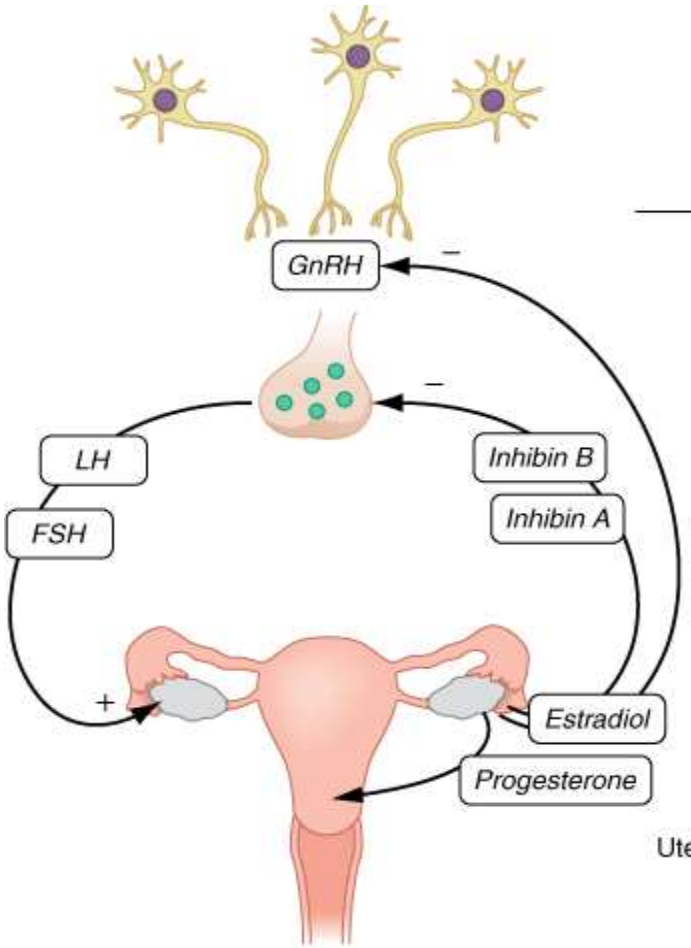
Primary amenorrhea

- Is there a uterus? (confirm with pelvic ultrasound)
- If there is a uterus, are there secondary sex characteristics?
- What was the age of onset of menses of the mother (and sisters)?
- This may distinguish normal maturation from gonadal or pituitary insufficiency.
- Turner's or Testicular Feminization changes?
- Pregnant? (always do a pregnancy test)

Secondary amenorrhea

- Determination of TSH, LH, FSH, and Prolactin are indicated.
- Some prefer to administer a progesterone bolus and wait to see whether menses ensue before determining pituitary hormone levels.
- Low levels of LH and FSH are associated with pituitary disease.
- An elevated prolactin is compatible with pituitary microadenoma.
- MRI of the sella turcica is indicated.
- Elevated LH and FSH are associated with ovarian failure.

Causes of amenorrhea



	Primary	Secondary
Hypothalamus	27%	36%
Pituitary	2%	15%
PCOS	7%	30%
Ovary	43%	12%
Uterus/outflow tract	19%	7%

Fig. 51-4
Accessed 02/01/2010

Diagnostic strategy

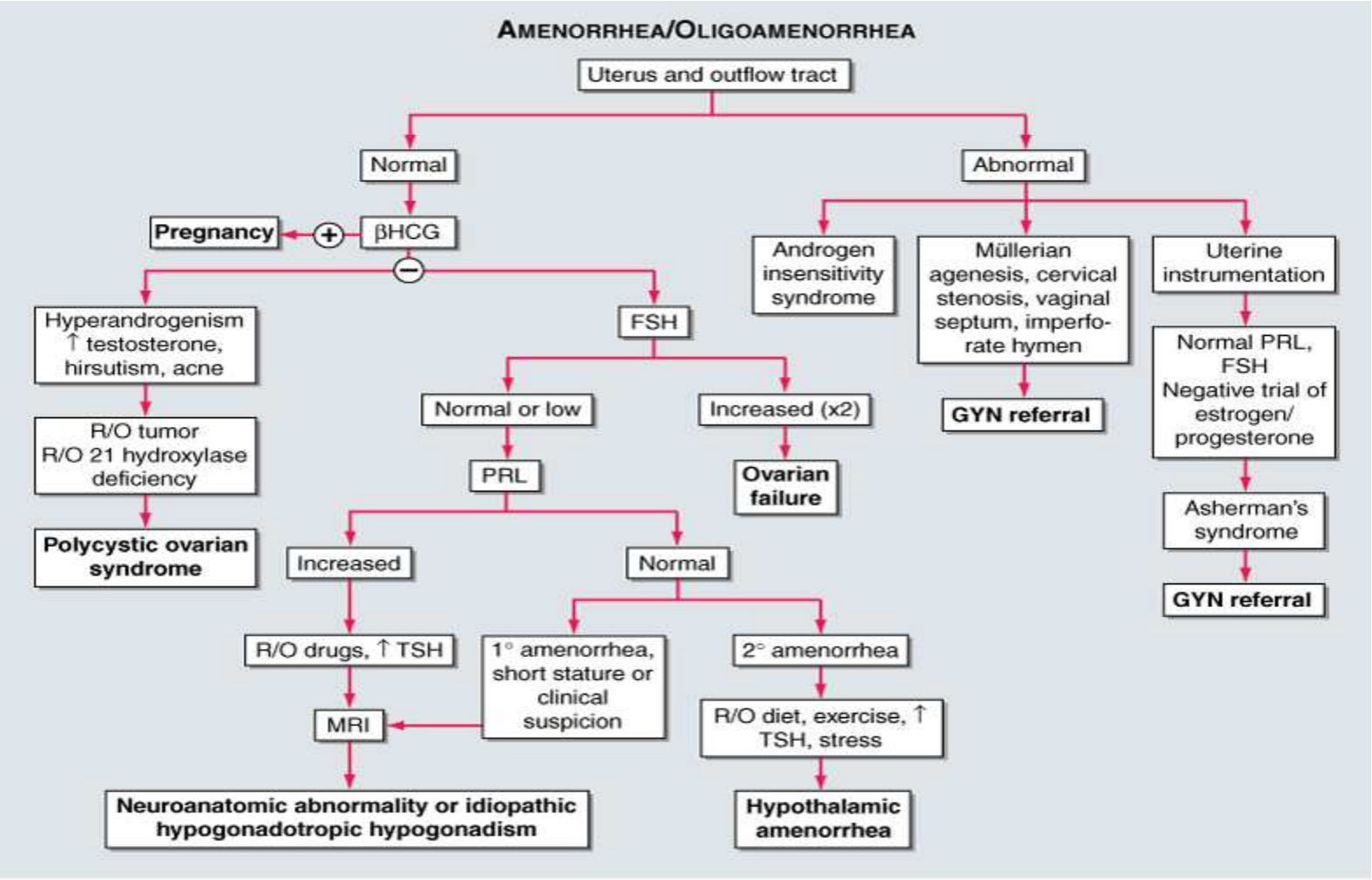


Fig. 51-2 Accessed 02/01/2010

Table 22-3 Causes of Abnormal Uterine Bleeding by Age Group

Age Group	Causes
Prepuberty	Precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence	Anovulatory cycle, coagulation disorders
Reproductive age	Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy) Anatomic lesions (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma) Dysfunctional uterine bleeding Anovulatory cycle Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)
Perimenopausal	Dysfunctional uterine bleeding Anovulatory cycle Anatomic lesions (carcinoma, hyperplasia, polyps)
Postmenopausal	Endometrial atrophy Anatomic lesions (carcinoma, hyperplasia, polyps)

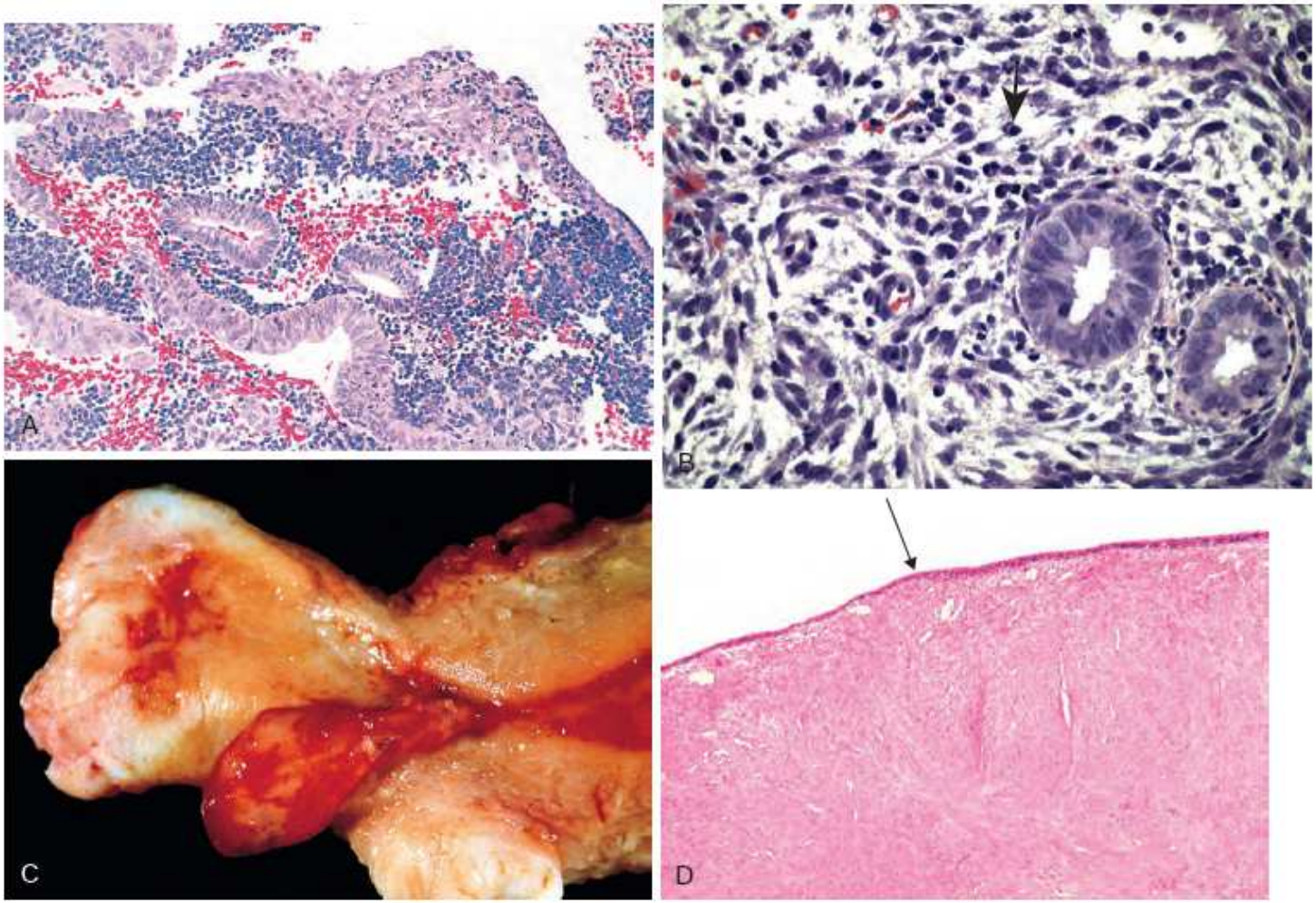


Figure 22-20 Common causes of abnormal uterine bleeding. **A,** The most common is dysfunctional uterine bleeding, seen here as anovulatory endometrium with stromal breakdown. Note breakdown associated with proliferative glands. **B,** Chronic endometritis with numerous plasma cells *(arrow)*. **C,** Endometrial polyp. **D,** Submucosal leiomyoma with attenuation of the endometrial lining *(arrow)*.

Anovulation

- The most frequent cause of dysfunctional bleeding is anovulation (failure to ovulate).
- Failure of ovulation results in excessive endometrial stimulation by estrogens that is unopposed by progesterone.
- Other causes include endocrine disorders, polycystic ovary disease, functioning ovarian tumors.

Uterine bleeding

- Is the patient on hormonal medications (or has thyroid disease)? Or using an IUD?
- Pregnant or elevated HCG?
- Threatened abortion, ectopic pregnancy, or trophoblastic disease must be considered.
- Dysuria, pelvic tenderness?
- Cervicitis or endometriosis must be considered.
- Cancer?
- Liver disease or coagulation disorders will likely manifest with bleeding at other sites.
- Else, dysfunctional uterine bleeding (disordered proliferative endometrium on biopsy).

Causes of abnormal uterine bleeding

Age	Cause
Prepuberty	Pecocious puberty
Adolescence	Anovulatory cycle; Coagulation disorder
Reproductive age	Complications of pregnancy Leiomyoma, adenomyosis, hyperplasia, carcinoma, polyps Anovulatory cycle Dysfunctional uterine bleeding (inadequate luteal phase)
Premenopausal	Anovulatory cycle Dysfunctional uterine bleeding (inadequate luteal phase) Leiomyoma, hyperplasia, polyps
Postmenopausal	Carcinoma, hyperplasia, polyps Atrophy

Dysfunctional uterine bleeding

- Failure of ovulation results in prolonged, excessive endometrial stimulation by estrogens.
- Disordered proliferative phase
- Stromal condensation and eosinophilic epithelial metaplasia similar to those seen in menstrual endometrium. Lacks glandular secretory changes.
- Stromal pre-decidualization of pseudostratified glands
- Contains scattered mitotic figures
- Manifests clinically as infertility, with either increased bleeding or as amenorrhea.

Menopause

- Characterized by irregular bleeding, insomnia, night sweats, emotional lability, and vaginal dryness.
- Cessation of menses for one year is consensus definition of menopause.
- May still conceive.

Endometriosis

- Frequently associated with genital outflow tract obstructions in adolescents.
- Usually diagnosed in the third decade of life, however.
- Usually regresses after menopause however, 5% of women are diagnosed after menopause.
- Commonly involves ovaries (60%) and pelvic lymph nodes (30%).
- Painful as the deposits swell with the menstrual cycle.
- 10% of general female population
- 40% of infertile females
- 80% of chronic pelvic pain patients
- Fusobacterium

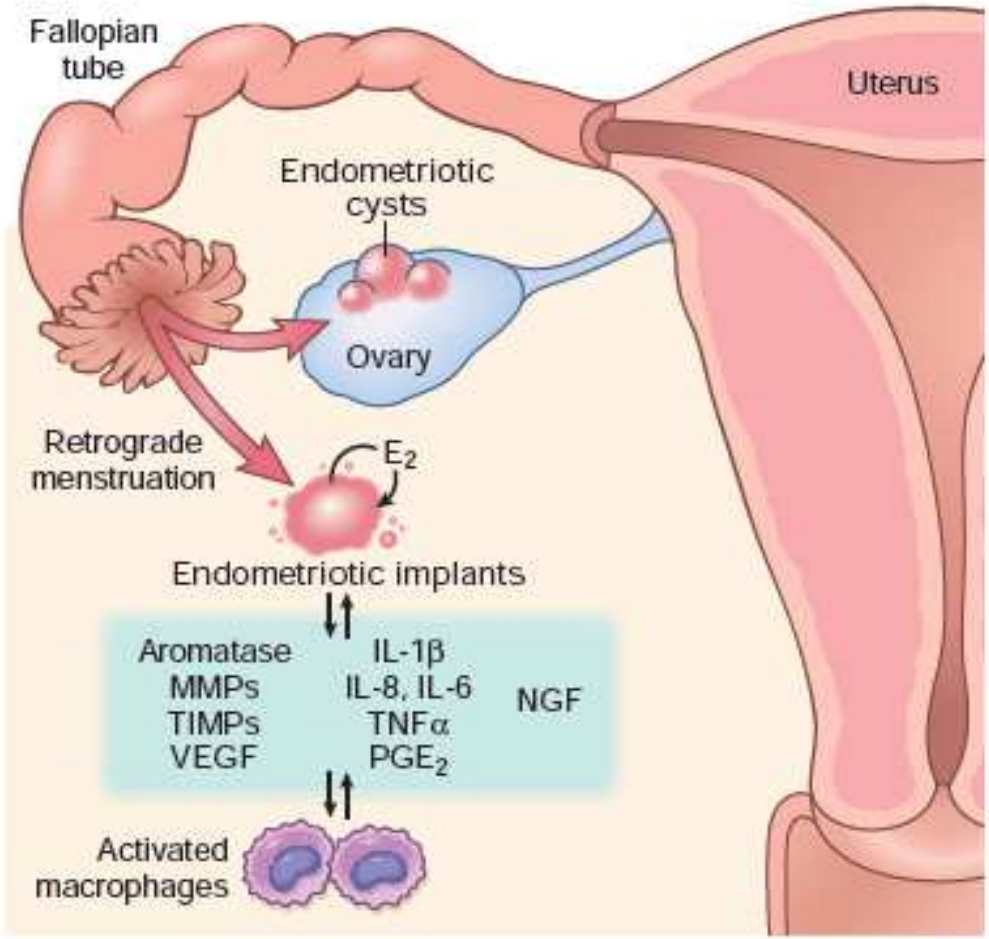


Figure 22-22 Pathogenesis of endometriosis. The factors expressed in endometriotic implants, eutopic endometrium and activated macrophages that play a role in the establishment and maintenance of endometriotic implants.

Etiology

- Five Theories of Development:
- Retrograde Menstruation.
- Retrograde menstruation occurs in up to 90% of women.
- There is increased risk of endometriosis in cervical stenosis or vaginal atresia/imperforate hymen.
- Müllerian (coelomic) Metaplasia
- Lymphatic and Vascular Transport

Etiology

- Immunologic Defect
- Antibodies to endometrial antigens detected
- Genetic Predisposition.
- Monozygotic twins have a marked concordance for endometriosis.
- There is a ten fold increase in first degree relatives of affected women.
- May lead to endometrioid carcinoma.
- ER-β and steroidogenic-1 nuclear receptors overexpressed.

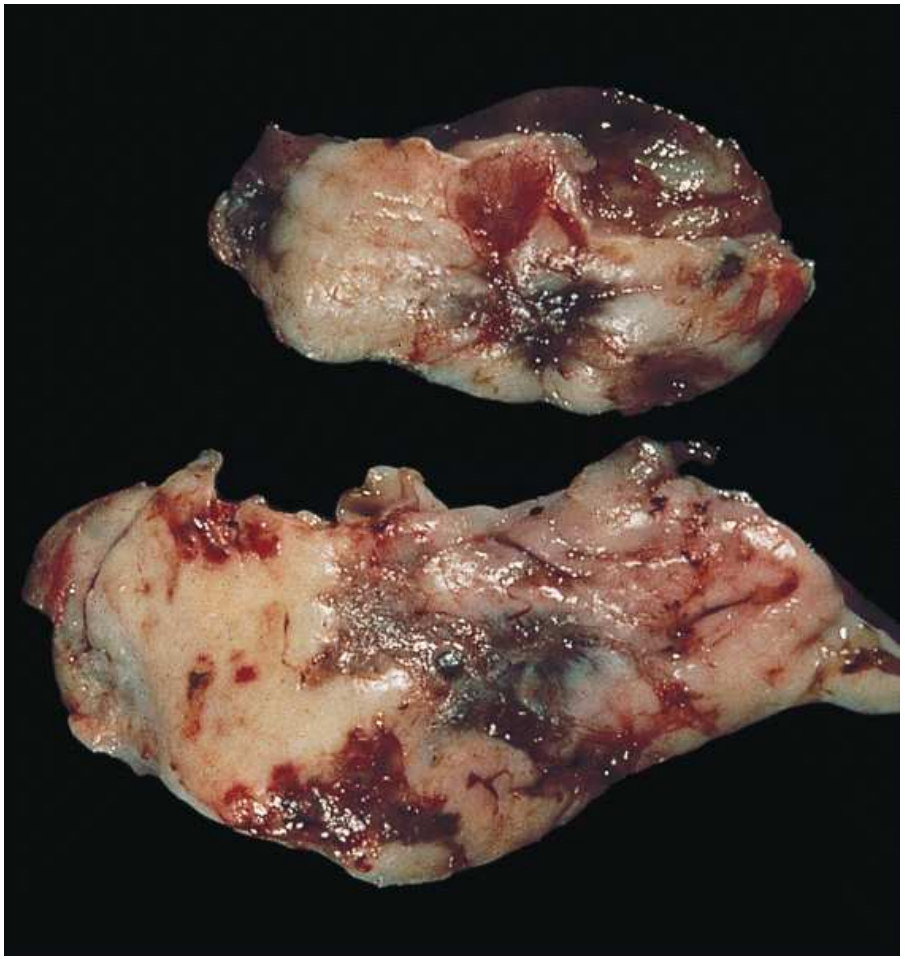
Tissue changes

- Elevated levels of prostaglandin E_2, IL-1β, TNF-α, and IL-6 identified.
- PGE_2 stimulates local synthesis of estrogen.
- Elevated levels of aromatase in stromal cells (absent in normal endometrial tissue).
- Resistant to progesterone suppression of estrogen.
- PTEN and ARID1A mutations seen as well in endometrial cysts and clear cell ovarian cancer.

Signs and symptoms

- Dyspareunia, dysmennorhea, dyschezia.
- May see infertility.
- Tender fixed adnexal mass on bimanual exam.
- Frequently find a retroverted uterus in these women.
- Sharp, firm, very tender nodule felt on utero-sacral ligaments.
- Grossly present as chocolate cyst (hemorrhage).
- Histologic changes of secretory phase endometrium with decidual stromal change

Endometriosis



The external surfaces of ovarian wedges show red, blue, and brown areas, several of which are associated with fibrotic puckering.

Fig. 22-48

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

Treatment

- NSAIDS.
- 30-50% recur after medical therapy (oral contraceptives, GRH antagonists)
- 5-20% per year recurrence after conservative surgery.
- If during radical surgery an uninvolved ovary is preserved, there is a 6-fold increased risk of recurrence as compared to removing both ovaries.
- Neither approach addresses infertility.

Adenomyosis

- The extension of endometrial glands and stroma into the uterine musculature.
- About 15% of patients with adenomyosis have associated endometriosis.
- Incidence peaks in women in their 40’s.
- Menorrhagia and dysmenorrhea.
- Gross appearance that of a diffusely enlarged myometrium with focal glandular abnormalities.
- Surgery only effective option.

Leiomyoma

- Uterine leiomyomas (fibroids) are perhaps the most common tumor in humans.
- Present in 75% of females of reproductive age.
- May be asymptomatic.
- Occur within the myometrium (intramural), just beneath the endometrium (submucosal) or beneath the serosa (subserosal)
- If submucosal or intramural, may compromise uterine cavity and interfere with pregnancy.
- Often multiple
- Malignant transformation rare.

Leiomyoma

- Whorled bundles of smooth muscle cells with rare mitotic figures characterizes leiomyoma.
- Each uterine leiomyoma is a unique clonal neoplasm.
- 40% have chromosomal abnormality:
- t(12;14)(q14-15;q23-24), del 7(q22-32), trisomy 12, and rearrangements of 6p, 3q, and 10q
- 12q14 and 6q involve HMGIC and HMGIY genes that encode closely related DNA-binding factors that regulate chromatin structure.

Leiomyoma

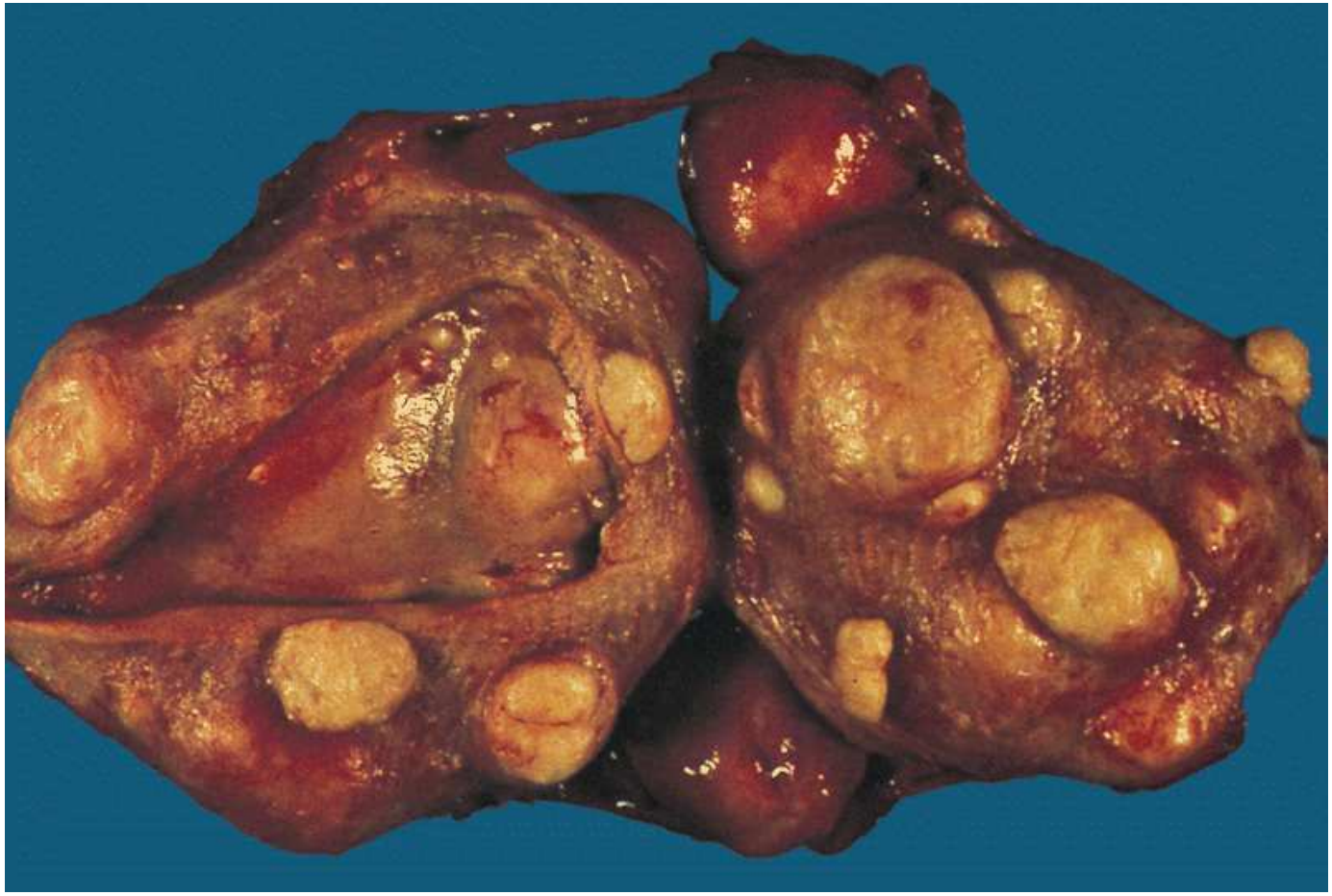


Plate 4A

Silverberg, Steven S, and Kurman, Robert J, “Tumors of the uterine corpus and gestational trophoblastic disease,” Atlas of Tumor Pathology. Third Series, Fascicle 3. Armed Forces Institute of Pathology. Washington, DC . 1991.

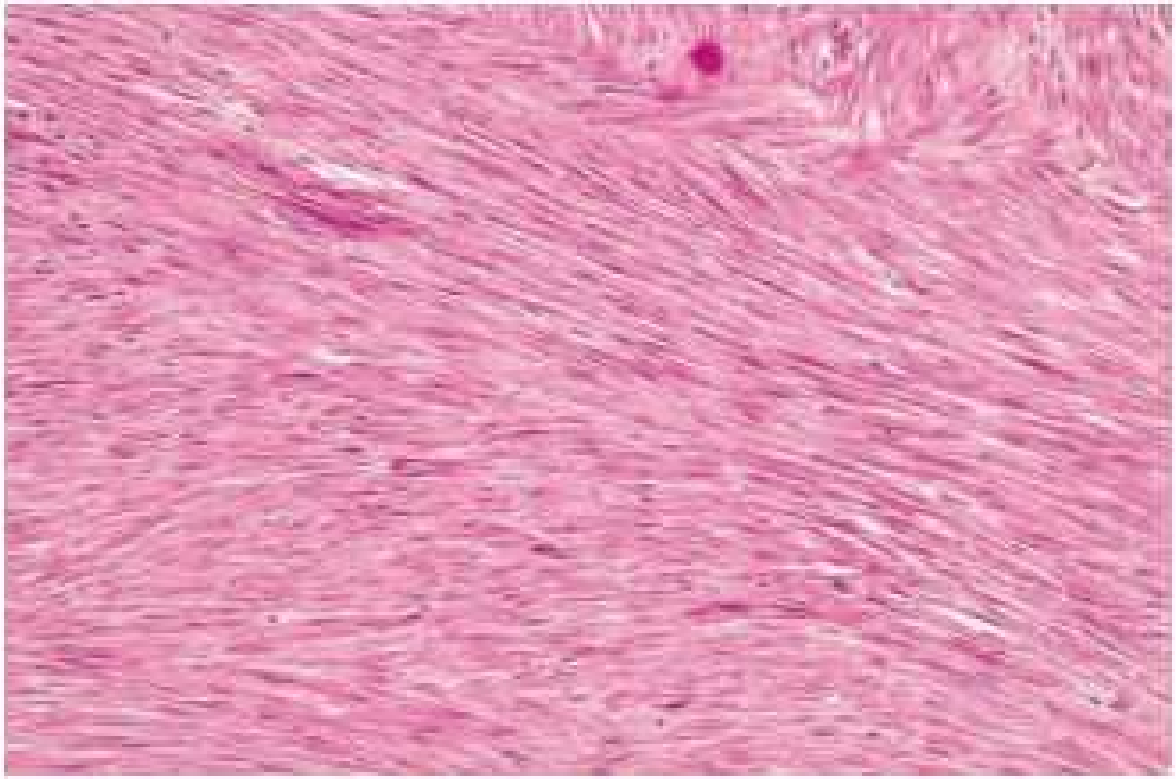
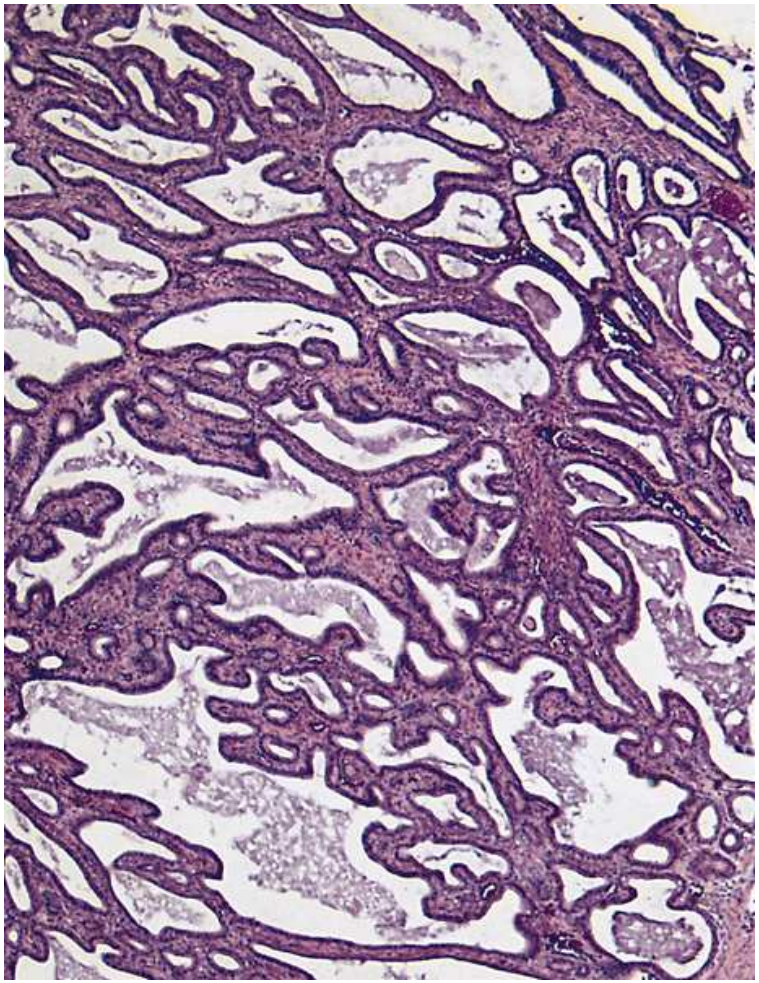


Figure 7-4 Leiomyoma of the uterus. This benign, well-differentiated tumor contains interlacing bundles of neoplastic smooth muscle cells that are virtually identical in appearance to normal smooth muscle cells in the myometrium.

Endometrial polyp

- Stroma is neoplastic
- Glands may be atrophic or hypeplastic
- Little response to progesterone

Endometrioid polyp



The glands are lined by benign epithelium and are separated by small amounts of fibrous stroma.

Fig. 5-11

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.

Endometrial hyperplasia

- Presents as a proliferation of glands and stroma, with crowding of glands, increase in mitotic figures, and prominent nucleoli in nucleus.
- Unopposed estrogen stimulation
- Pap smear rarely shows hyperplasia but it may be suggested by AGUS result (abnormal glandular cells of undetermined significance) on Pap smear.
- A pre-malignant lesion.

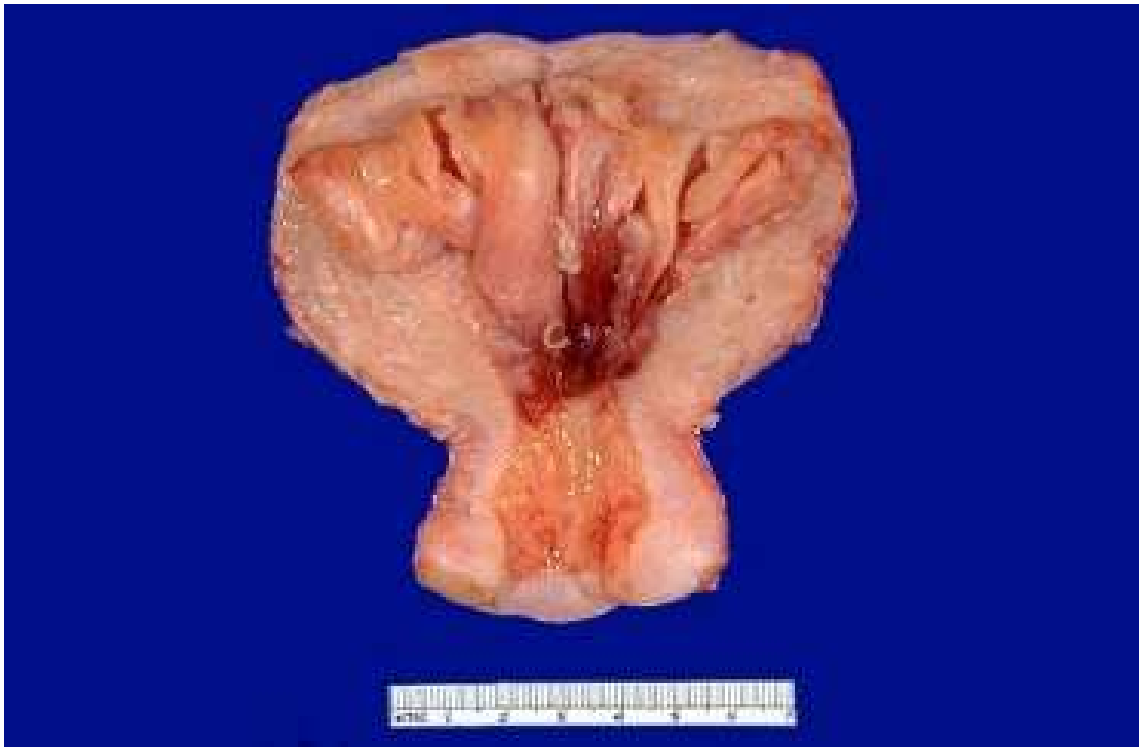
Endometrial hyperplasia

- Non-atypical endometrial hyperplasia
- Simple.
- Regular glandular pattern. No cytologic atypia.
- 1% will progress to cancer.
- Complex.
- Irregular glands crowded back to back. No atypia.
- 3% will progress to cancer.

Endometrial hyperplasia

- Atypical endometrial hyperplasia (endometrial intraepithelial carcinoma)
- Simple with atypia.
- 8% will progress to cancer.
- Complex with atypia.
- 29% will progress to cancer.
- PTEN lost (PI3K/AKT overactive)
- Enhances the ability of the estrogen receptor to turn on the expression of its target gene
- Up to 20% of hyperplasias and 80% of endometrial carcinomas

Endometrial hyperplasia



Endometrial hyperplasia usually results with conditions of prolonged estrogen excess and can lead to metrorrhagia (uterine bleeding at irregular intervals), menorrhagia (excessive bleeding with menstrual periods), or menometrorrhagia.
https://webpath.med.utah.edu/FEMHTML/FEM019.html Accessed 05/05/2020

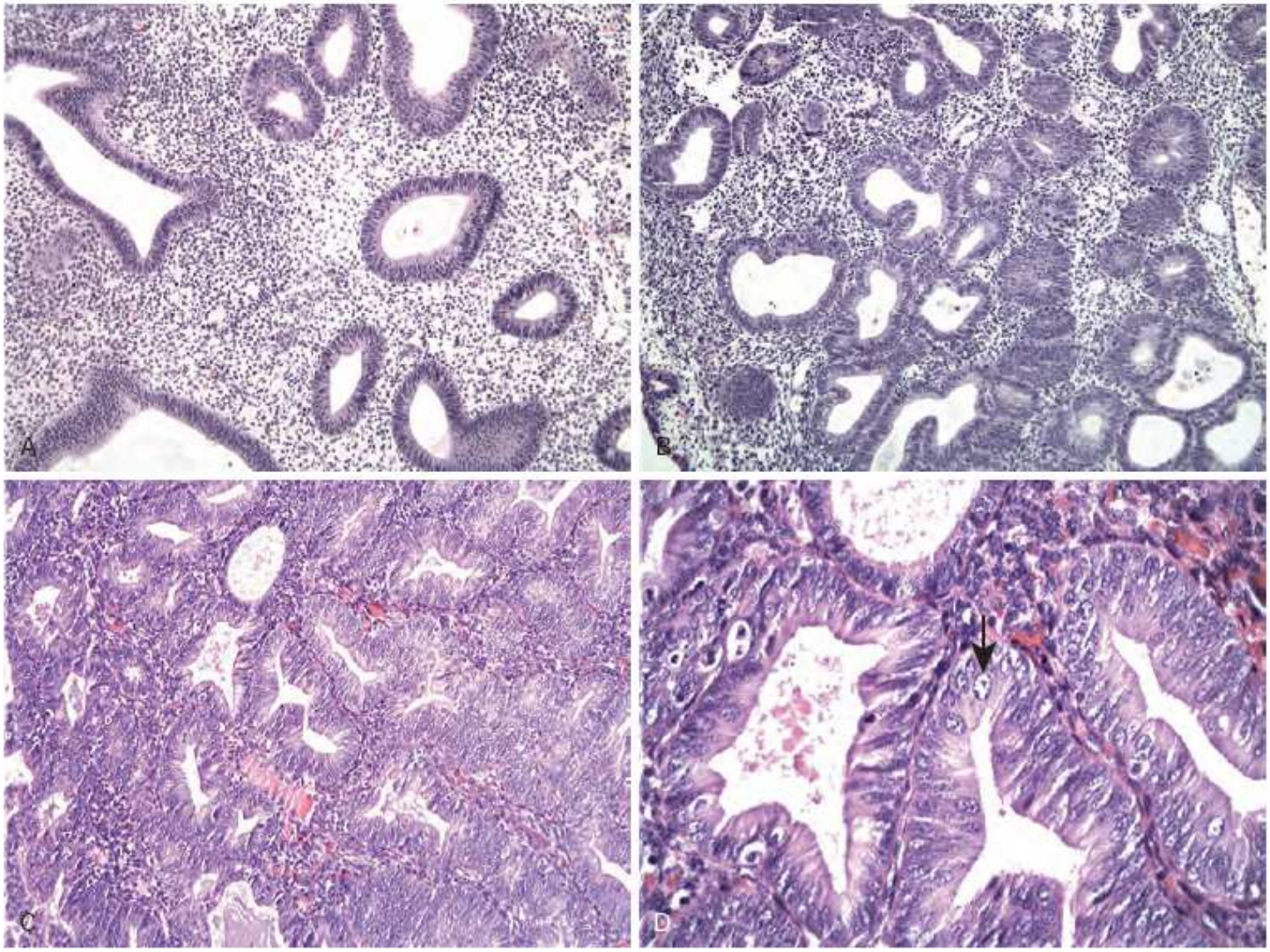


Figure 22-23 Endometrial hyperplasia. **A,** Hyperplasia without atypia. Note architectural abnormalities including mild glandular crowding and cystic glandular dilatation. **B,** Hyperplasia without atypia demonstrating increased glandular crowding with areas of back-to-back glands and cytologic features similar to proliferative endometrium. **C,** Atypical hyperplasia with further increase in glandular crowding and abnormal cytologic features. **D,** High magnification of atypical hyperplasia showing rounded, vesicular nuclei with prominent nucleoli *(arrow)*.

Endometrial carcinoma

- Most common invasive cancer of female genital tract
- 75% are Type I (endometrioid carcinoma)
- Related to hyper-estrogen state
- 81% of endometrial cancers associated with a BMI>30
- Diabetes mellitus, nulliparity, polycystic ovary syndrome and tamoxifen administration as other risk factors.
- Insulin resistance common

Endometrial carcinoma

- Lynch syndrome and hereditary non-polyposis colon cancer are other risk factors.
- Protective factors include the use of oral contraception, increasing age at menarche, number of delivered children and smoking.
- Twice as common in those of African descent
- Peak incidence 50-65 years of age
- Presents with abnormal vaginal bleeding

Endometrioid carcinoma

- Ultrasonography of uterus as screening test
- >3mm endometrial thickness as cutoff
- Tampon collections or uterine swabs may collect cells to identify GYPC mutation noted in endometrioid cancer.
- Can take the form of a localized polypoid tumor or a tumor that diffusely infiltrates the endometrial lining.
- Uterine risk factors included grade 2 or 3, presence of lymph vascular space invasion, and depth of invasion to the outer one-third of the myometrium.
- May be associated with extensive peritoneal disease

Endometrioid carcinoma

- Spread generally occurs by myometrial invasion followed by direct extension to adjacent structures.
- Invasion of the broad ligaments may create a palpable mass.
- Disseminates to regional lymph nodes
- Hematogenous spread

Endometrial carcinoma

- Usually PI3K/AKT and BCL-2 pathways involved together with K-RAS mutations and microsatellite instability.
- PTEN mutated in up to 80%
- PI3CKA mutated in 40%
- KRAS mutated in 25%
- ARID1A mutated in 33%
- MLH mutated in 20%
- TP53 mutated in 50% of poorly differentiated lesions

Endometrioid carcinoma

- Demonstrates glandular growth patterns resembling normal endometrial epithelium.
- If fewer than 50% of the tumor is composed of solid growth, it is moderately well differentiated.
- If >50%, poorly differentiated
- 20% have areas of squamous differentiation

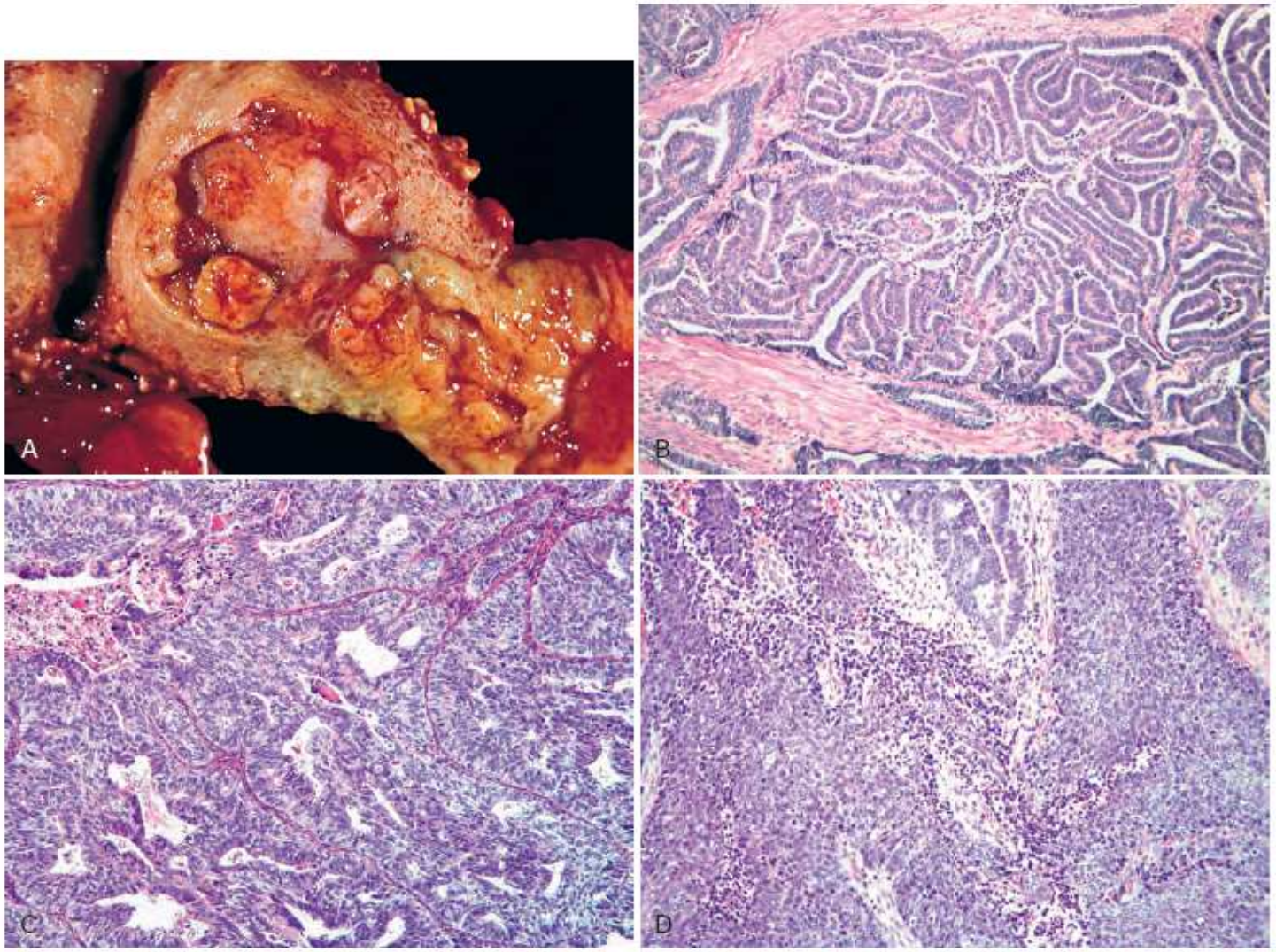


Figure 22-25 Type I endometrial carcinoma. **A,** Endometrial adenocarcinoma presenting as a fungating mass in the fundus of the uterus. **B,** Well-differentiated (grade 1) endometrioid adenocarcinoma with preserved glandular architecture but lack of intervening stroma. **C,** Moderately differentiated (grade 2) endometrioid adenocarcinoma with glandular architecture admixed with solid areas. **D,** Poorly differentiated (grade 3) endometrioid adenocarcinoma with a predominantly solid growth pattern.

Serous carcinoma

- Malignant cells identical to those of serous carcinoma of the ovary are confined to the epithelial surfaces
- The invasive lesions may have a papillary growth pattern composed of cells with marked cytologic atypia, atypical mitotic figures, hyperchromasia, and prominent nucleoli
- May also have a predominantly glandular growth pattern
- Distinguished from endometrioid carcinoma by the marked cytologic atypia.
- More frequent if of African ancestry, not obese

Serous carcinoma

- Surgical staging as with serous epithelial ovarian cancer
- Sentinel node detection still not standardized
- Low-risk patients do not benefit from pelvic and para-aortic lymph node dissection
- In intermediate- and high-risk patients with higher risk of lymph node involvement, pelvic (and para-aortic) lymph node dissection will help to guide the necessity for and tailor the type of adjuvant therapy
- Micrometastases associated with worse prognosis

Serous carcinoma

- Laparoscopic surgical staging for uterine cancer results in fewer complications in obese patients, shorter hospital stay, with equivalent oncological outcome
- However, robotic surgery, which utilizes a reverse Trendellenberg position, poses an increased risk for ischemic retinal atrophy

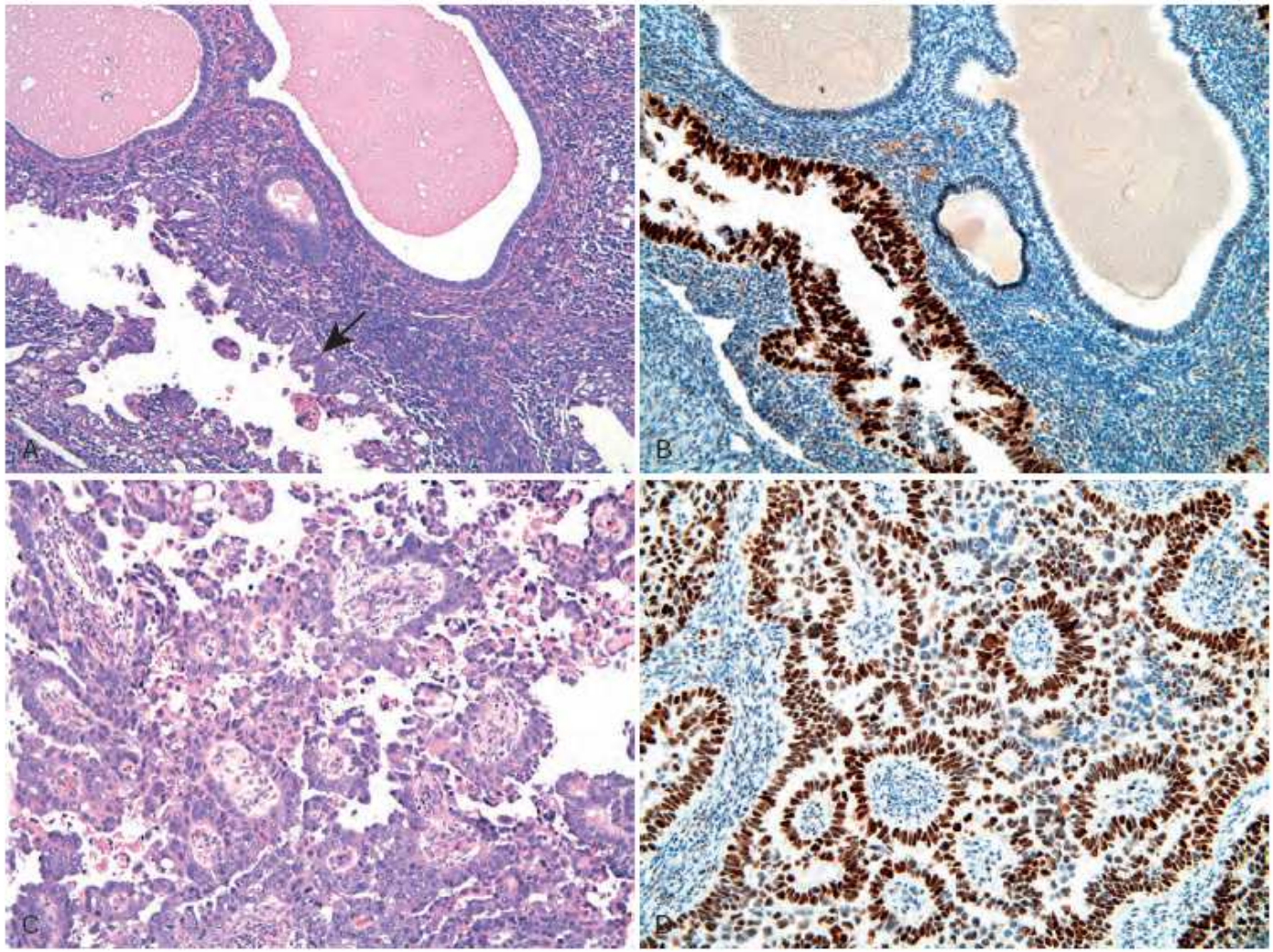
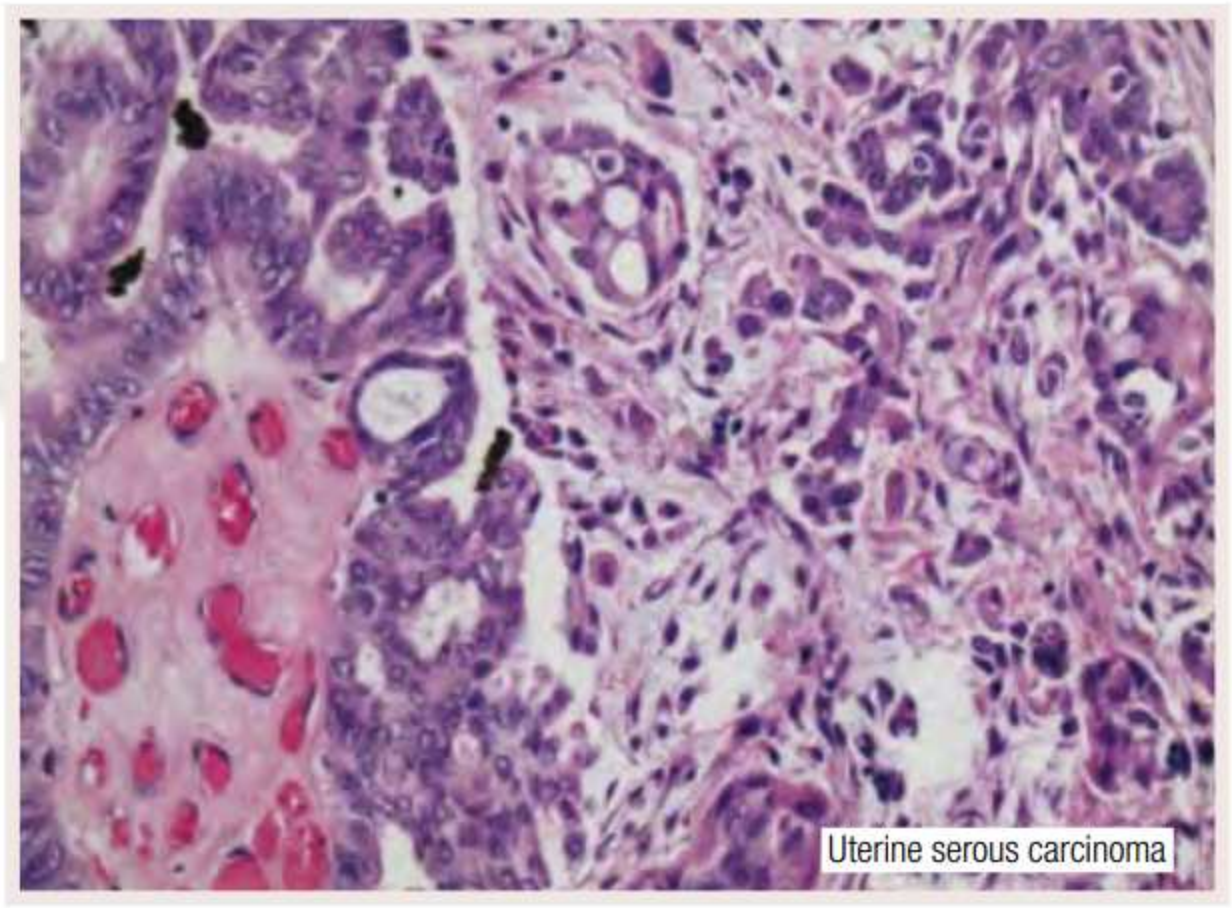


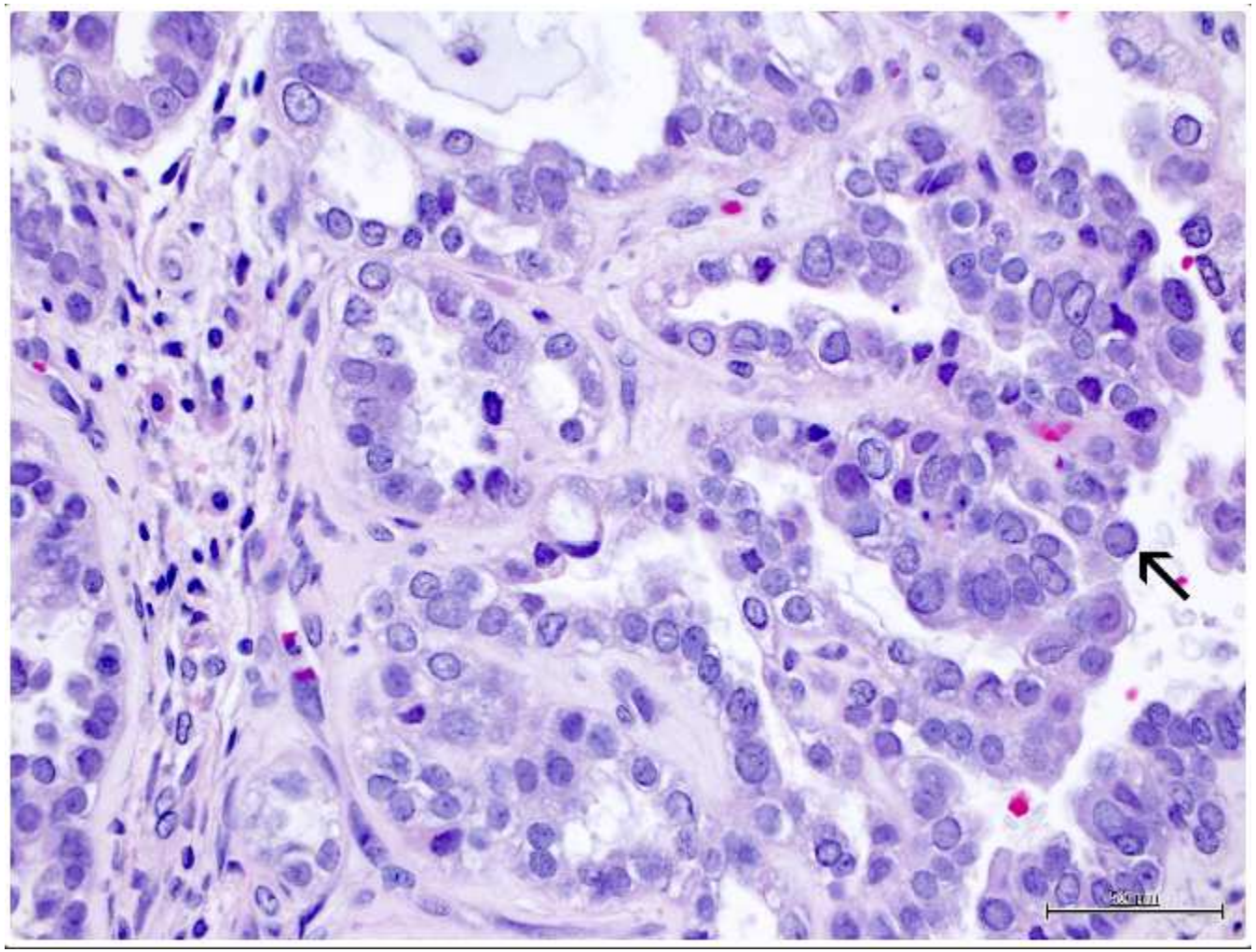
Figure 22-26 Type II endometrial carcinoma. **A,** Endometrial intraepithelial carcinoma, the precursor to serous carcinoma showing malignant cells *(arrow)* with morphologic features identical to serous carcinoma lining the surfaces of the endometrial glands without obvious stromal invasion. **B,** Strong, diffuse expression of p53 as detected by immunohistochemistry in endometrial intraepithelial carcinoma. **C,** Serous carcinoma of the endometrium with papillary growth pattern consisting of malignant cells with marked cytologic atypia including high nuclear-to-cytoplasmic ratio, atypical mitotic figures, and hyperchromasia. **D,** As with the previous lesion, there is an accumulation of p53 protein in the nucleus.


Uterine serous carcinoma

Endometrial carcinoma

- Clear cell subtype
- Oxyphil or hobnail cells
- Low mitotic activity
- Solid, glandular, or papillary pattern
- No specific molecular profile
- Mixed-Müllerian tumors (carcinosarcomas)
- Endometrial carcinoma with malignant mesenchymal component:
- Stromal sarcoma or leiomyosarcoma
- Rhabdomyosarcoma or chondrosarcoma
- Occur in post-menopausal women
- Present with abnormal vaginal bleeding

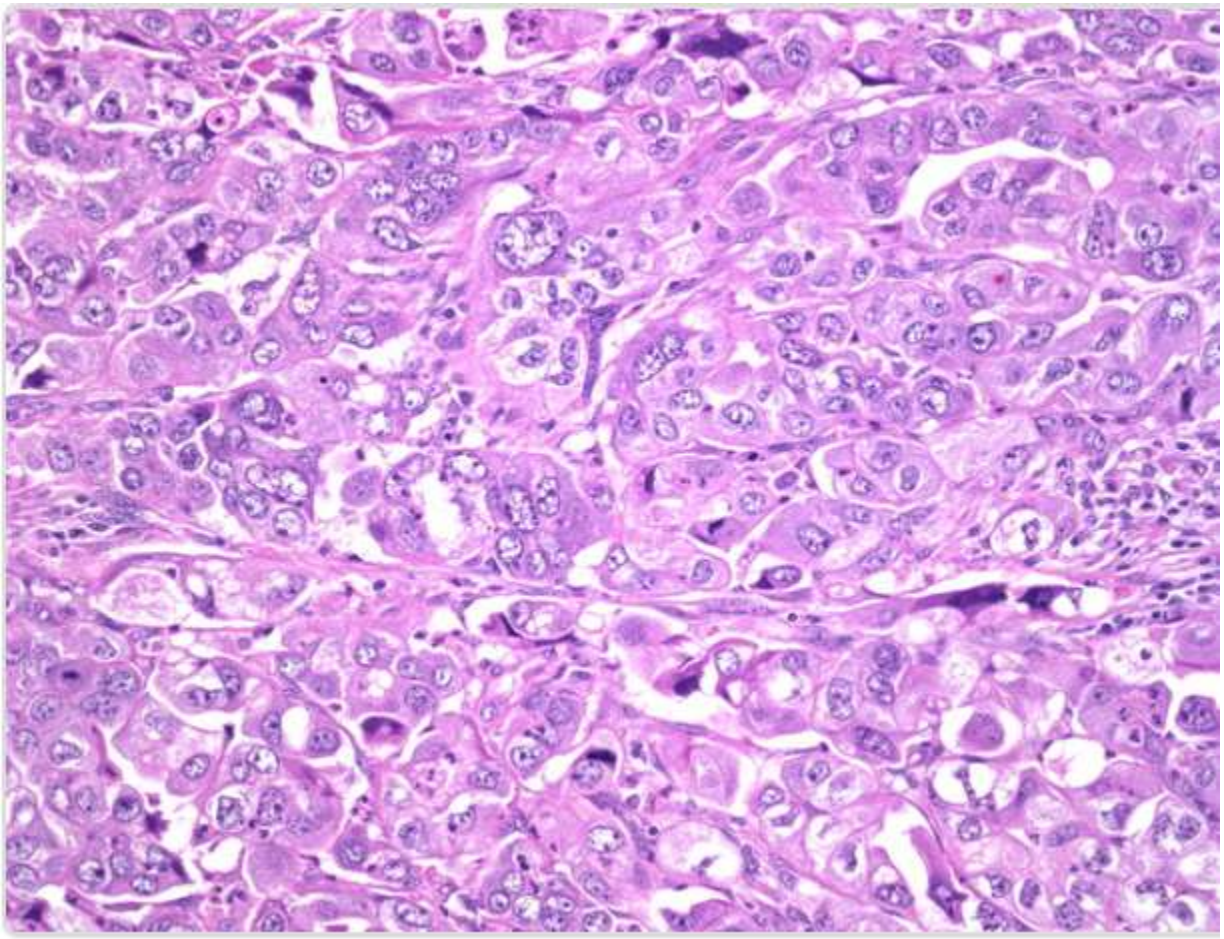
Clear cell carcinoma



Hobnail cell (arrow)

www.pathologyoutlines.com/uterus.htm
Contributed by Jutta Havila, MD

Clear cell carcinoma



http://webpathology.com/image.asp?case=569&n=28

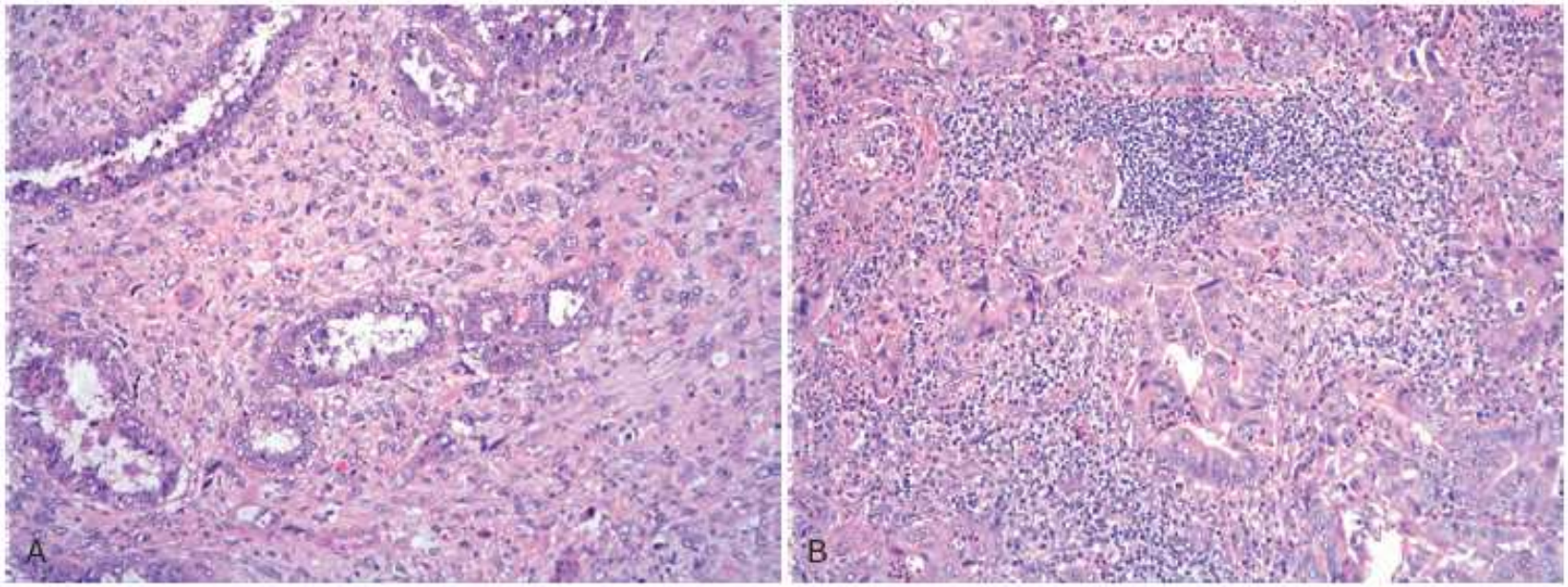


Figure 22-27 Malignant mixed müllerian tumor (MMMT). **A,** Micrograph showing both malignant epithelial and stromal components. **B,** Lymph node metastasis from a MMMT showing only the epithelial component, as is typically the case.

Endometrial carcinoma

- WHO 2020 classification adds:
- Mesonephric adenocarcinoma
- Mesonephric-like adenocarcinoma
- squamous cell carcinoma
- Mucinous carcinoma, gastrointestinal type
- In each of these it is important to rule out extension from the cervix as this is overwhelmingly the more common site of a primary carcinoma with this morphology.

Table 22-4 Characteristics of Type I and Type II Endometrial Carcinoma

Characteristics	Type I	Type II
Age	55-65 yr	65-75 yr
Clinical setting	Unopposed estrogen Obesity Hypertension Diabetes	Atrophy Thin physique
Morphology	Endometrioid	Serous Clear cell Mixed müllerian tumor
Precursor	Hyperplasia	Serous endometrial intraepithelial carcinoma
Mutated genes/ genetic abnormalities	*PTEN* *ARID1A* (regulator of chromatin) *PIK3CA* (PI3K) *KRAS* *FGF2* (growth factor) MSI* *CTNNB1* (Wnt signaling) *TP53*	*TP53* Aneuploidy *PIK3CA* (PI3K) *FBXW7* (regulator of MYC, cyclin E) *CHD4* (regulator of chromatin) *PPP2R1A* (PP2A)
Behavior	Indolent Spreads via lymphatics	Aggressive Intraperitoneal and lymphatic spread

*MSI, Microsatellite instability; CTNNB1, beta-catenin gene

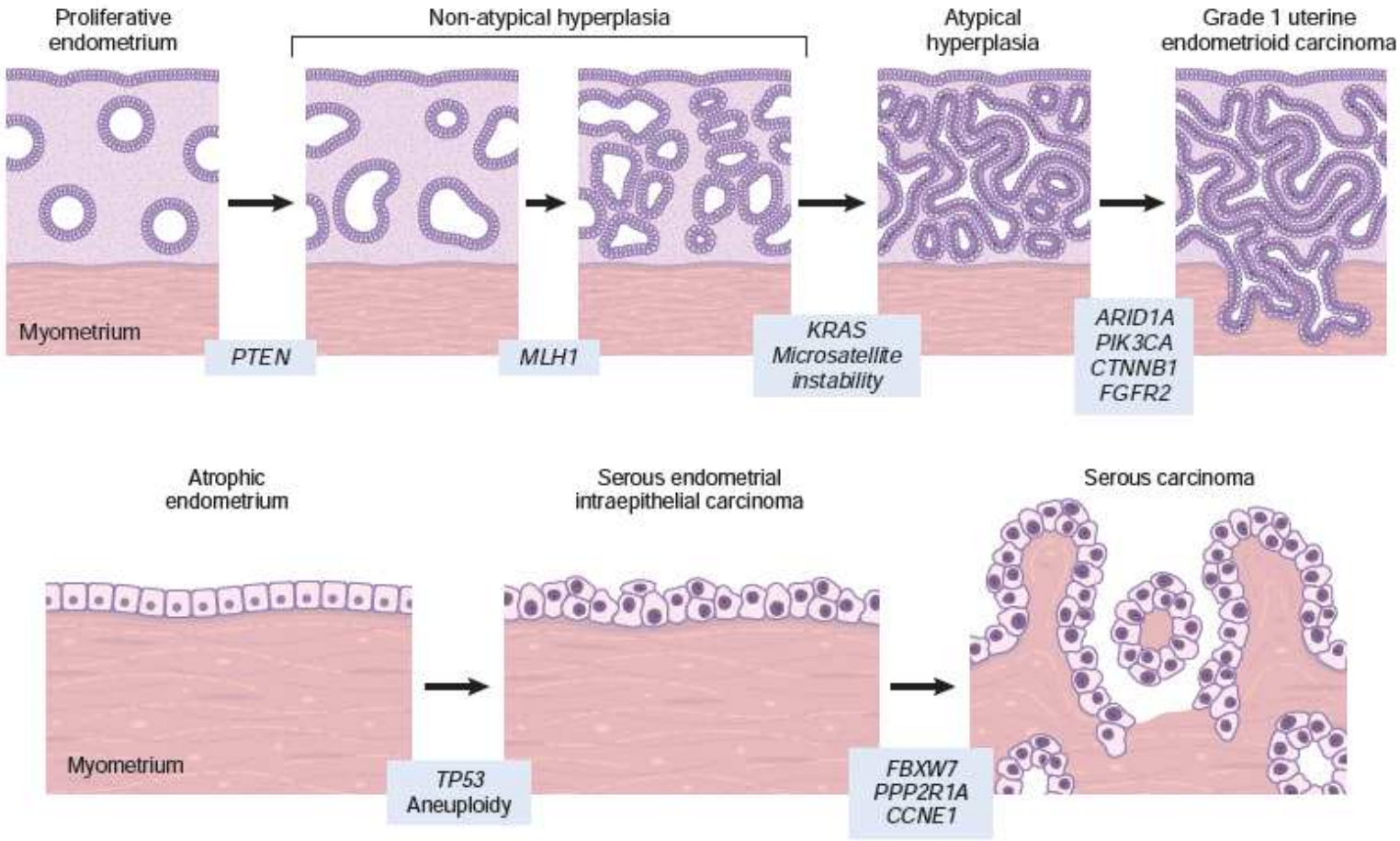
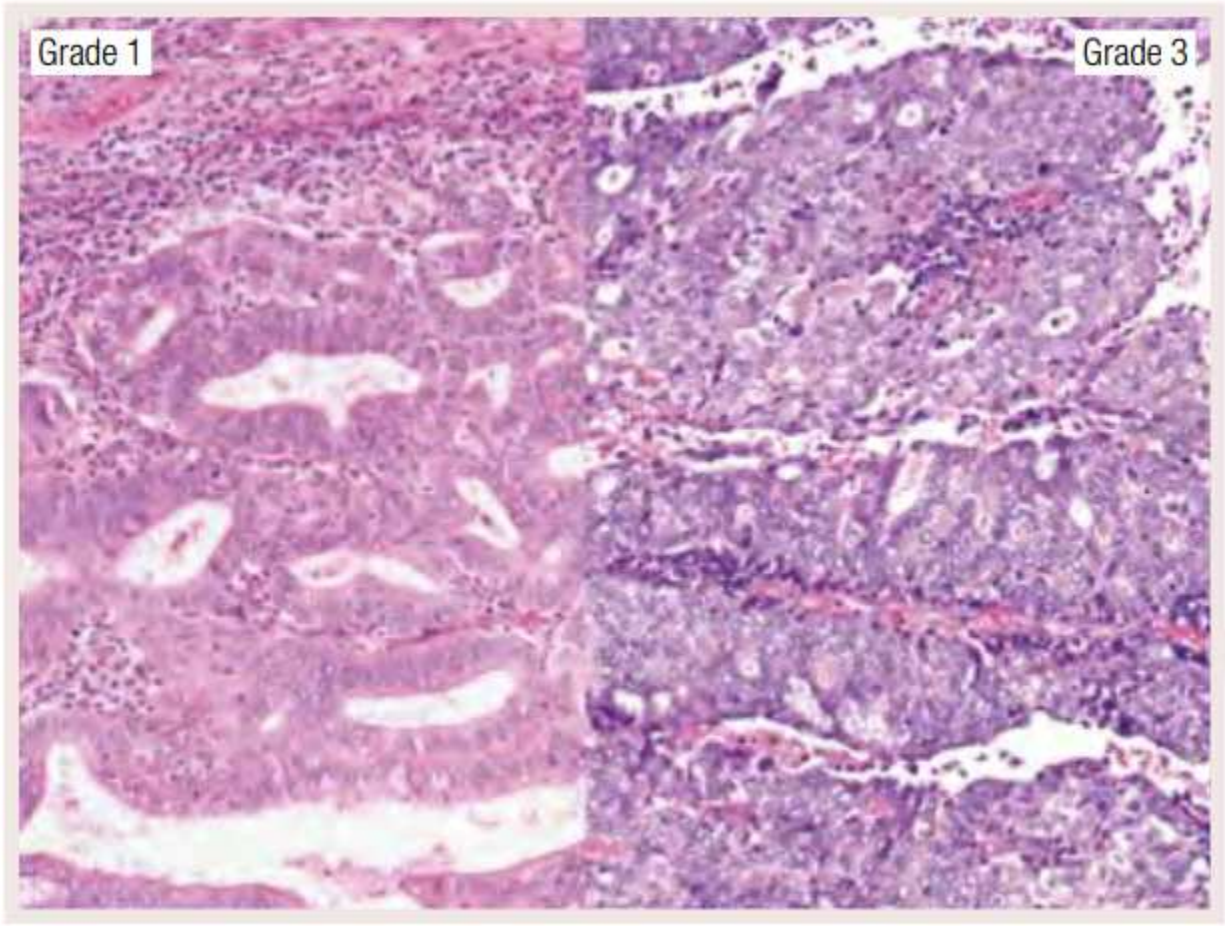


Figure 22-24 **A,** Schematic depicting the development of type I endometrial carcinoma arising in the setting of hyperplasia. **B,** Schematic diagram of the development of type II endometrial carcinoma. The most common molecular genetic alterations are shown at the time they are most likely to occur during the progression of the disease. *MI, Microsatellite instability. *CTNNB1*, beta-catenin gene; *PPP2R1A*, PP2A gene; *CCNE1*, cyclin E gene.


Grade 1
Grade 3

Stage I—Carcinoma is confined to the corpus uteri itself.

Stage II—Carcinoma involves the corpus and the cervix.

Stage III—Carcinoma extends outside the uterus but not outside the true pelvis.

Stage IV—Carcinoma extends outside the true pelvis or involves the mucosa of the bladder or the rectum.

Endometrial carcinoma

- Four molecular types identified
- Polymerase Epsilon exonuclease domain mutated (POLE EDM)
- Mismatch repair deficient (MMRd)
- p53 wild-type/copy-number-low (p53 wt)
- p53-mutated/copy-number-high (p53 abn)
- Benefit of external beam radiotherapy limited to this group
- Bevacizumab plus chemotherapy if p53 overexpressed
- In those with none of the above molecular types, vaginal brachytherapy beneficial

Endometrial Cancer: Molecular Subtypes

***POLE* ultramutated**	• Ultra-high somatic mutation frequency; MSS; frequent mutations in the exonuclease domain of *POLE*; high ASNS and CCNB1 expression • Represents ~4% of endometrioid tumors* • Best prognosis
MSI hypermutated	• High mutation rate and few copy number alterations; high rate of *MLH1* promoter methylation; high phospho-AKT; low PTEN expression; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations • Represents ~39% of endometrioid tumors*†
Copy-number low‡	• High frequency of mutations in *CTNNB1, KRAS, SOX17*; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations; elevated levels of progesterone receptor and RAD50 expression • Represents ~49% of endometrioid tumors*
Copy-number high‡	• Greatest transcriptional activity; frequent *TP53* mutations; decreased levels of phospho-AKT; mutually exclusive *PIK3CA, PIK3R1,* and *PTEN* mutations • Represents ~9% of endometrioid tumors* • Worst prognosis

G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

Therapy

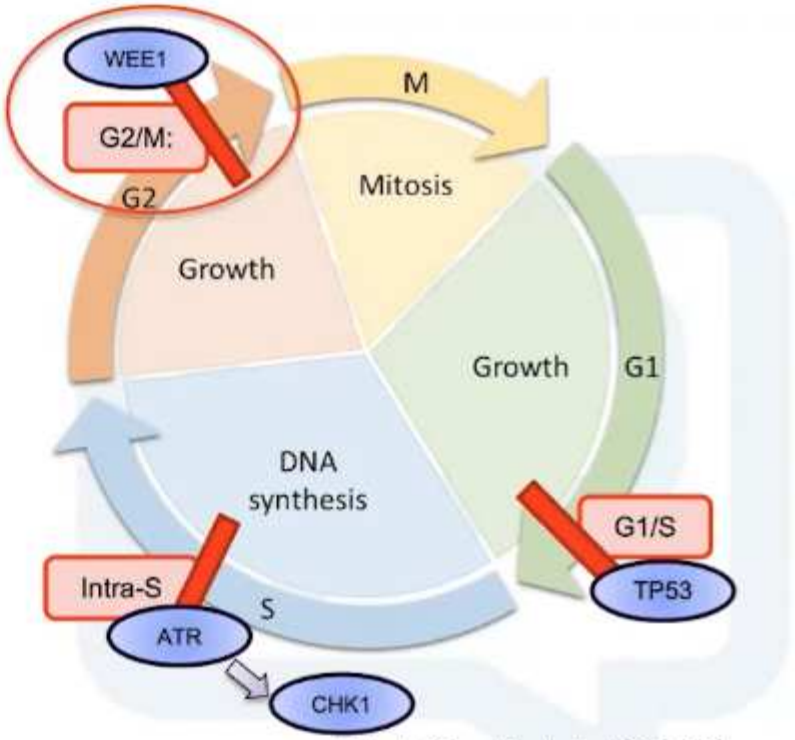
- Adjuvant radiotherapy confers better local control.
- BUT, significantly inferior survival in patients receiving adjuvant radiotherapy.
- Double the risk of a second cancer.
- Adjuvant chemotherapy may not be beneficial.
- Chemotherapy with carboplatin and paclitaxel as standard
- 88% of serous tumors are incurable
- Majority die within one year
- Endocrine therapy of no benefit
- In advanced or recurrent disease, 30% will benefit by progesterone administration (ER/PR positive)

Therapy

- Pembrolizumab and levatinib in recurrent disease in patients in microsatellite stable disease as well as those mismatch repair proficient.
- If HER+, add trastuzumab
- Benefit appears in chemotherapy naive
- If recurrence, measure TMB; immunotherapy
- Anti-angiogenic therapy may be useful if TP53 mutated
- Evorlimus with letrozole beneficial in endometrioid carcinoma
- Palcociclib (CDK 4/6 inhibitor) beneficial

WEE1 is a potential target in cells with high replication stress

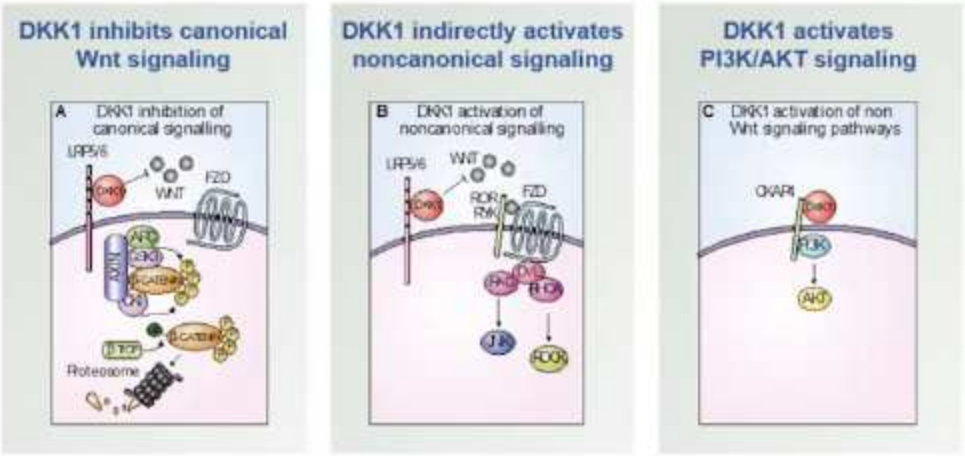
- Replication stress
  - Occurs when DNA replication is hindered
  - Multiple causes, including unrepaired DNA damage or oncogenic drivers
- High replication stress can increase dependency on cell cycle checkpoints
  - Slow down cell cycle
  - Prevent progression to mitosis with underreplicated DNA
- Inhibition of WEE1 abrogates the G2/M checkpoint and can also directly increase replication stress



Adapted from Liu et al., ASCO 2020

Targeting DKK1 in endometrial cancers

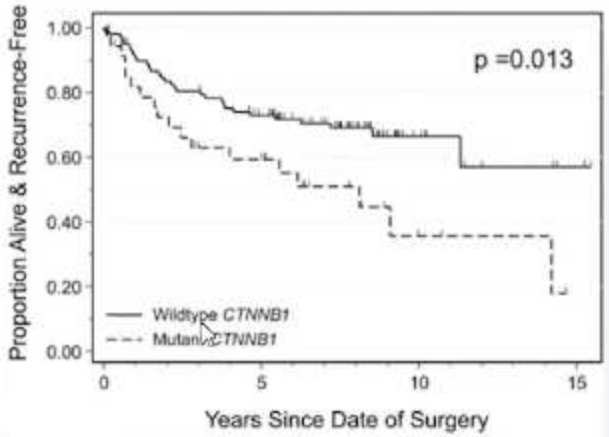
Model of DKK1 Regulation of Signaling Pathways



Mataldi et al., Cell, 2016; D'Amico et al., J Exp Med, 2016; Kimura et al., J Clin Invest, 2016; Krause et al., Cell Death Dis, 2014; Tao et al., Dig Liver Dis, 2013; Thudi et al., Prostate, 2011; Wang and Zhang, Clin Exp Metastasis, 2011

- DKN-01 is a humanized monoclonal antibody [IgG4] targeting DKK1

Arend et al., 2021 SGO Annual Meeting



Kurnit et al., Mod Pathol 2017

Stromal tumors

- Adenosarcoma
- Present as broad based endometrial polyp
- 30-40 years of age
- Low-grade
- Estrogen sensitive
- 25% recur
- Endometrial stromal tumor
- JAZF1 fusion genes silence placement of repressive histone marks into chromatin (Polycomb complex)
- Up to 80% recur
- 15% die from late distant metastases

Leiomyosarcoma

- Peak incidence 40-60 years of age
- High recurrence rate
- High metastatic rate
- Distinction from leiomyoma is based on mitotic index (>10 mitoses/high power field) or mitotic index (5-9 mitoses/high power field) with nuclear atypia and zonal necrosis

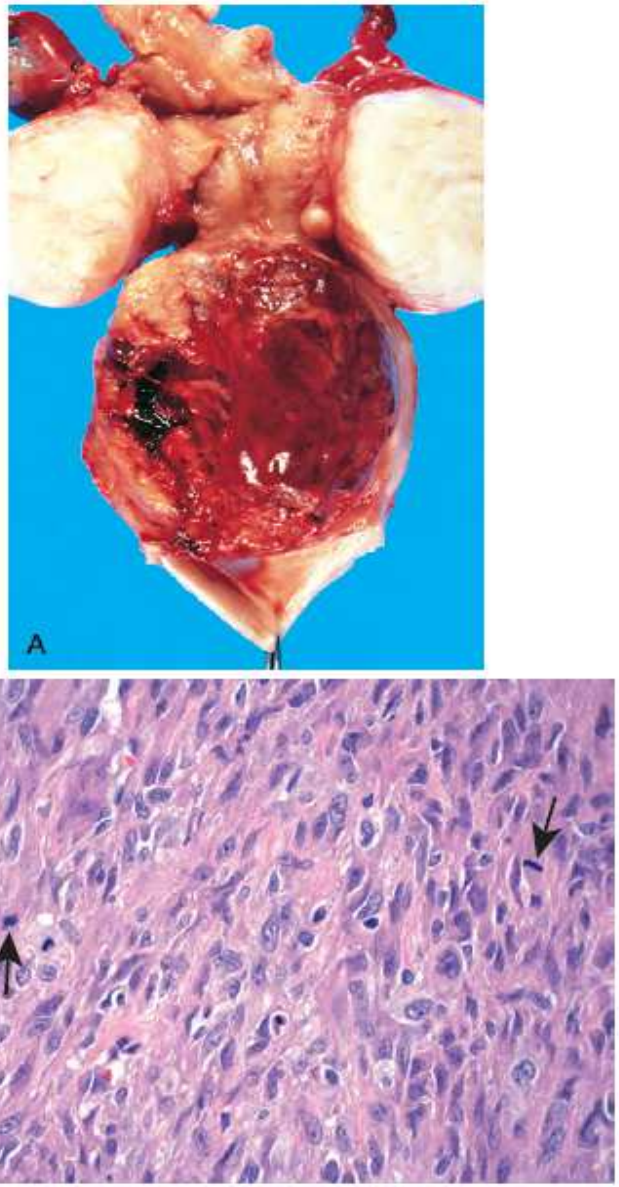
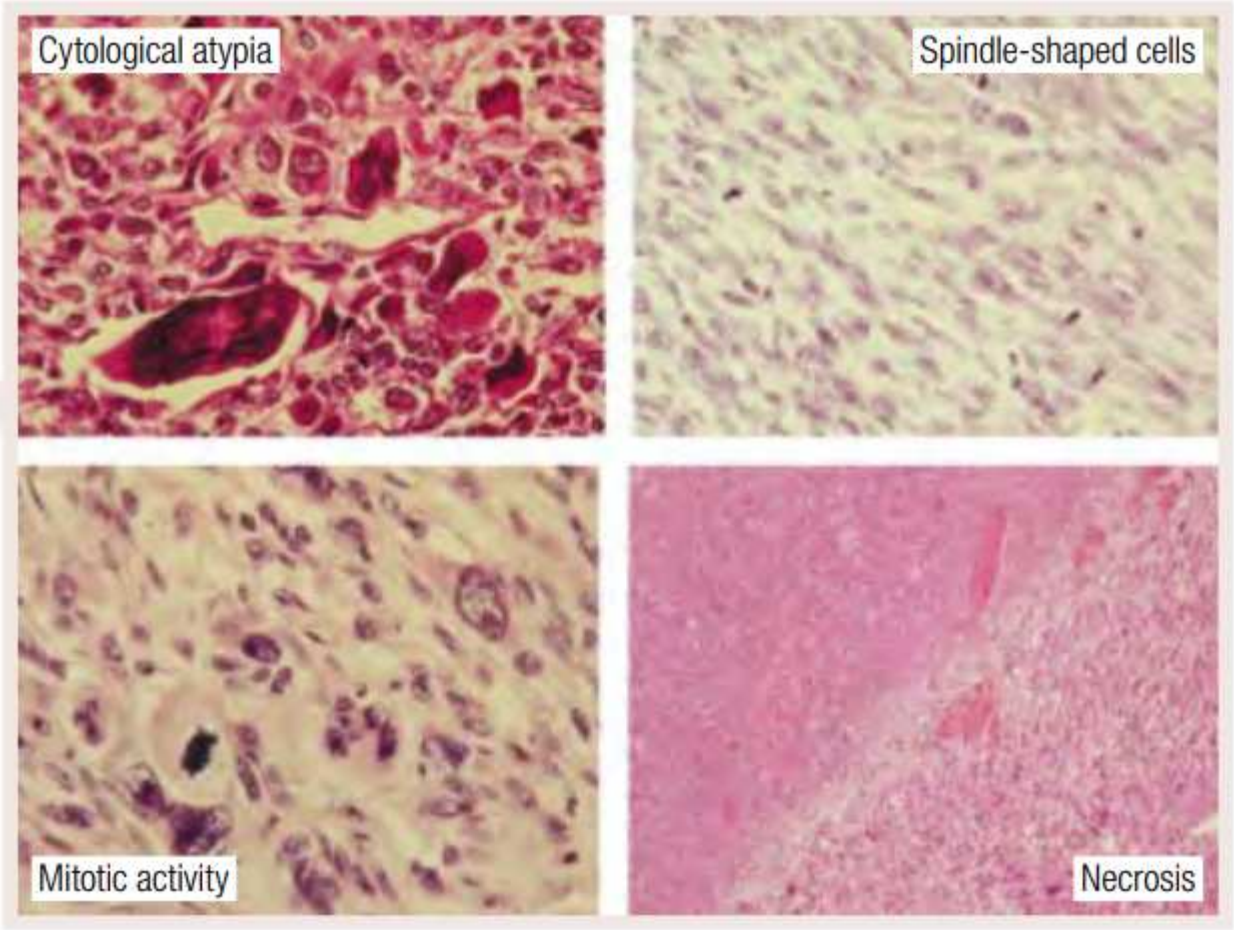


Figure 22-29 Leiomyosarcoma. **A,** A large hemorrhagic tumor mass distends the lower corpus and is flanked by two leiomyomas. **B,** The tumor cells are irregular in size and have hyperchromatic nuclei. Numerous mitotic figures are present *(arrows)*.


Cytological atypia
Spindle-shaped cells
Mitotic activity
Necrosis

Molar pregnancy

- Presents with irregular or heavy bleeding, often early in pregnancy.
- Uterine contractions noted.
- May see hyperemesis.
- Hydaditiform mole.
- Grape-like tissue clusters may be seen protruding from cervical canal.

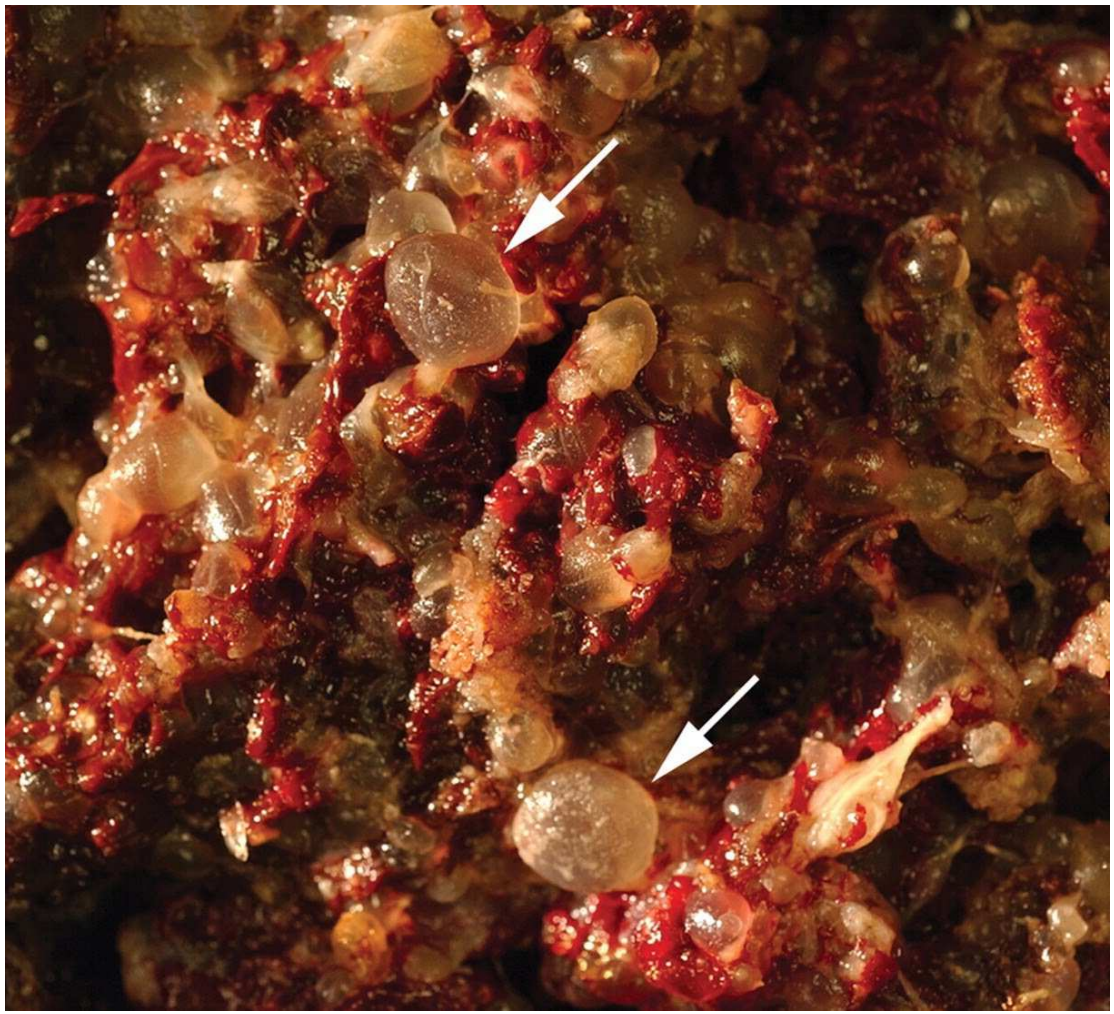
Molar pregnancy

- A complete mole
- Arises from syncytiotrophoblast cells.
- No embryoblast.
- Results from fertilization of an empty oöcyte.
- An incomplete mole
- Contains trophoblastic tissue with abnormal fetus.
- Always triploid.

Molar pregnancy

- HCG elevated.
- Ultrasound shows a “snowstorm” pattern in uterus with no fetus present.
- Bilateral, large theca-lutein cysts.
- Trophoblastic tissue embolism may lead to ARDS.
- If trophoblastic tissue functional, may see hyperthyroid state.
- Evacuate uterus.
- Follow with HCG levels for one year. No pregnancy permitted during that time.
- 5% will evolve to choriocarcinoma.

Hydaditiform mole



https://gyn101.files.wordpress.com/2011/10/37237511.jpg

Choriocarcinoma

- Gestational choriocarcinoma is a malignant neoplasm of trophoblastic cells derived from a previously normal or abnormal pregnancy, such as an extrauterine ectopic pregnancy.
- Choriocarcinoma is rapidly invasive and metastasizes widely, principally to lungs and vagina
- Choriocarcinoma is a soft, fleshy, yellow-white tumor that usually has large pale areas of necrosis and extensive hemorrhage.
- Histologically, it does not produce chorionic villi and consists entirely of proliferating syncytiotrophoblasts and cytotrophoblasts

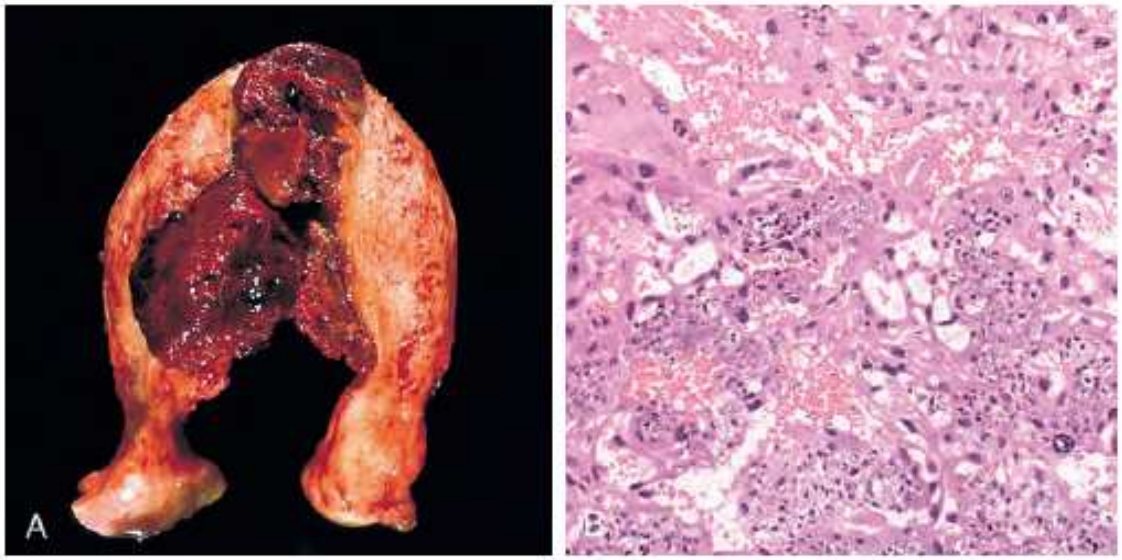


Figure 22-55 Choriocarcinoma. **A,** Choriocarcinoma presenting as a bulky hemorrhagic mass invading the uterine wall. **B,** Photomicrograph illustrating neoplastic cytotrophoblasts and syncytiotrophoblasts. (Courtesy Dr. David R. Genest, Brigham and Women's Hospital, Boston, Mass.)

Endometritis

- Acute endometritis usually follows abortion or delivery when products of conception are retained.
- Usually Strep. and Staph.
- Chronic endometritis may also follow pelvic inflammatory disease or tuberculous salpingitis.
- Plasma cells are prominent in the stroma

FALLOPIAN TUBE AND OVARY

Pelvic inflammatory disease

- The tubal mucosa becomes congested and diffusely infiltrated by neutrophils, plasma cells, and lymphocytes
- Results in epithelial injury and sloughing of the plicae.
- The tubal lumen fills with purulent exudate that may leak out of the fimbriated end.
- The infectionmay then spread to the ovary to create a salpingo-oophoritis.
- Collections of pus may accumulate within the ovary and tube (tubo-ovarian abscesses) or tubal lumen (pyosalpinx)

Pelvic inflammatory disease

- Over time the tubal plicae, denuded of epithelium, adhere to one another and slowly fuse
- May see glandlike spaces and blind pouches (chronic salpingitis)
- The scarring of the tubal lumen and fimbriae may prevent the uptake and passage of oocytes, leading to infertility or ectopic pregnancy.
- Hydrosalpinx may also develop as a consequence of the fusion of the fimbriae and the subsequent accumulation of the tubal secretions and tubal distention

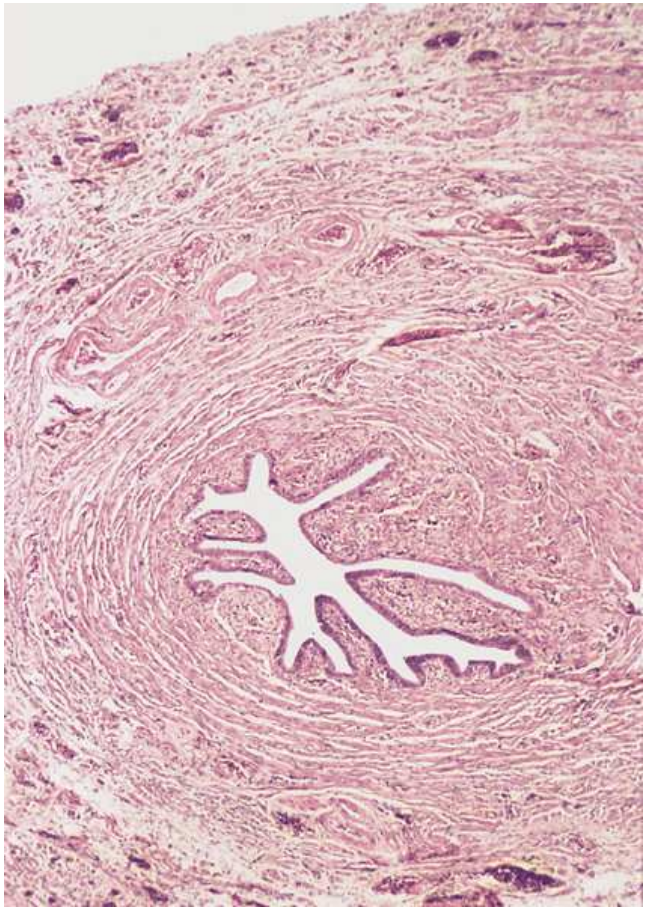
Pelvic inflammatory disease

- The non-gonococcal bacterial infections that follow induced abortion, dilation and curettage of the uterus, and other surgical procedures are thought to spread upwards from the uterus through the lymphatics or venous channels
- Are usually Staph., Strep., coliforms, or Clostrdium perfringens
- Show less involvement of the mucosa and the tube lumen, and more inflammation within the deeper tissue layers.

Pelvic inflammatory disease

- These infections often spread throughout the wall to involve the serosa and the broad ligaments, pelvic structures, and peritoneum.
- Bacteremia is more common than with gonococcal infection.
- May develop peritonitis, endocarditis, suppurative arthritis

Fallopian tube

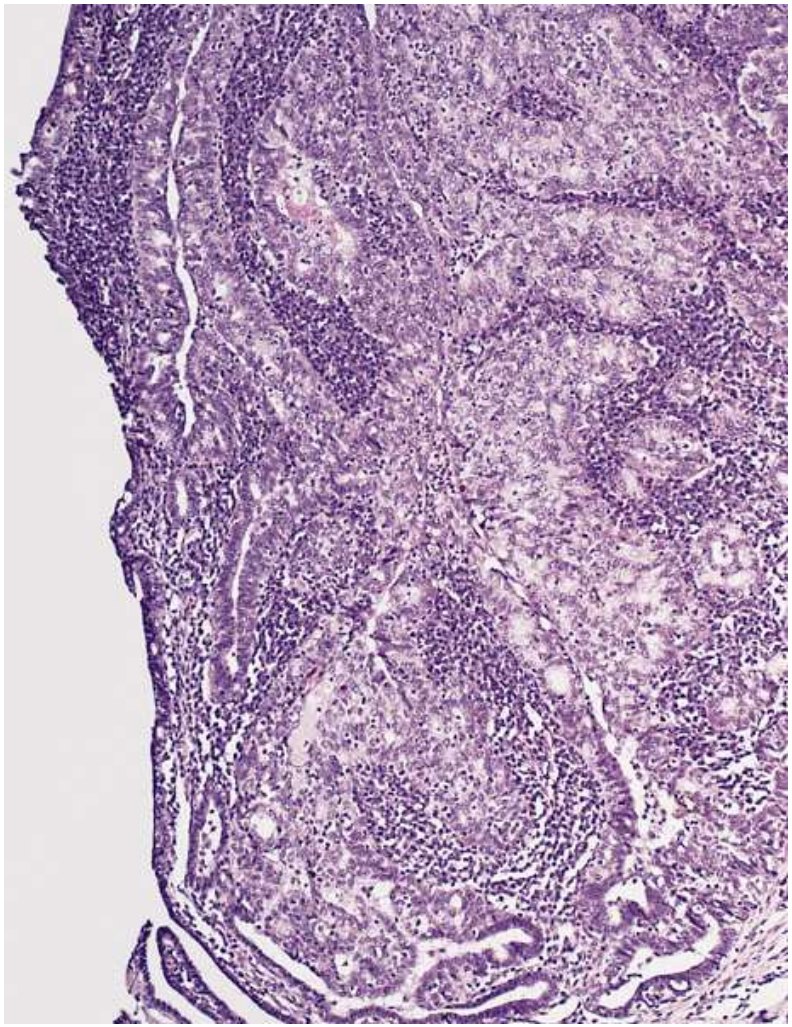


The lumen is surrounded by mucosa with plicae, muscularis, and serosa.

Fig. 24-1

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

Salpingitis



Groups of closely packed gland-like structures (center) are separated by a dense inflammatory infiltrate.

Fig. 26-23

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

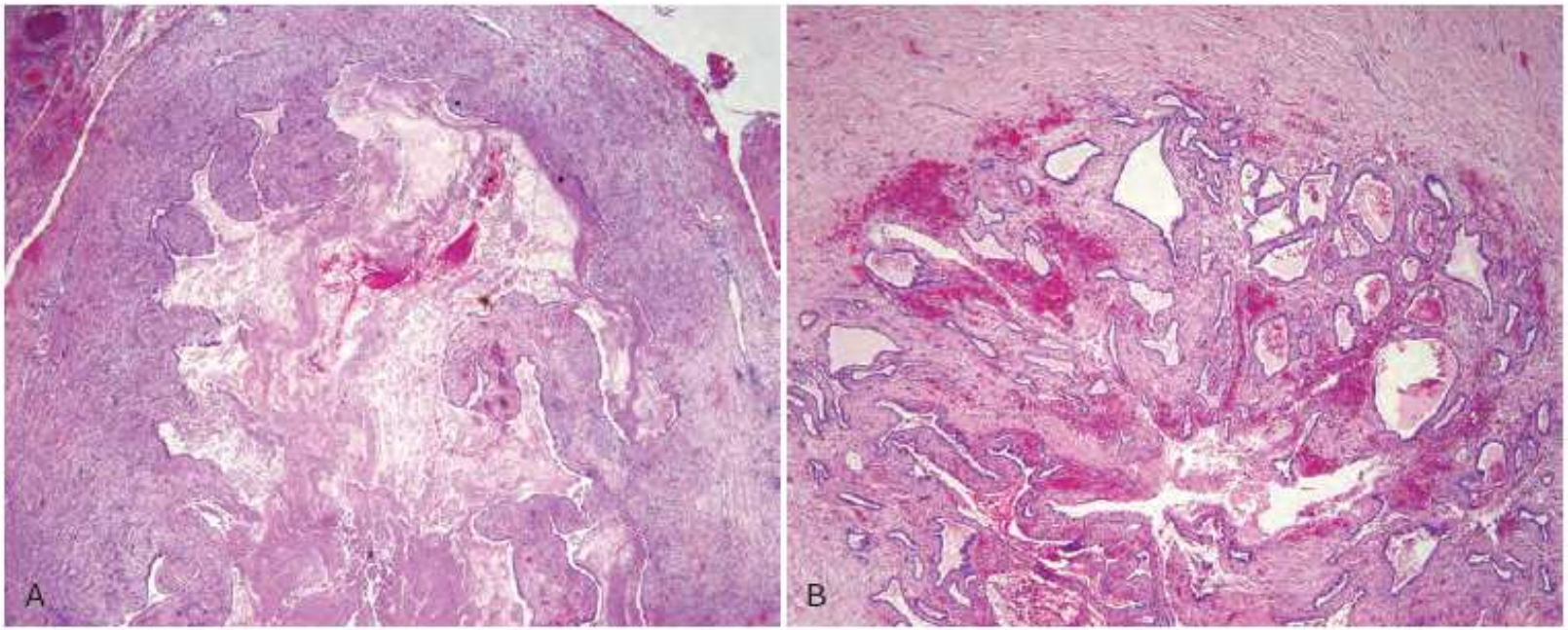
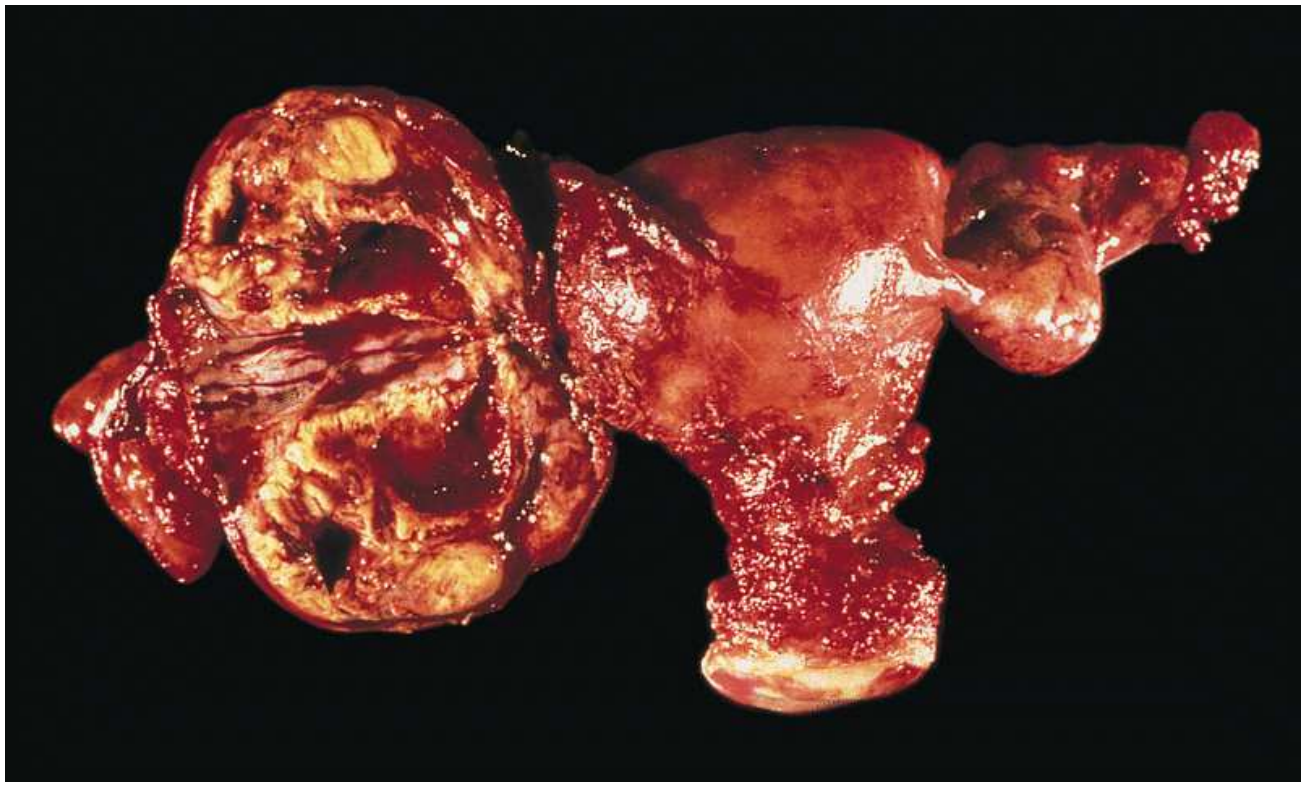


Figure 22-4 Acute salpingitis. **A,** Note the dilated tube lumen and edematous tubal plicae expanded by inflammatory cell infiltrates. Pus fills the center of the fallopian tube. **B,** Chronic salpingitis showing scarring and fusion of the plicae. Such scarring may cause infertility or ectopic tubal pregnancy.

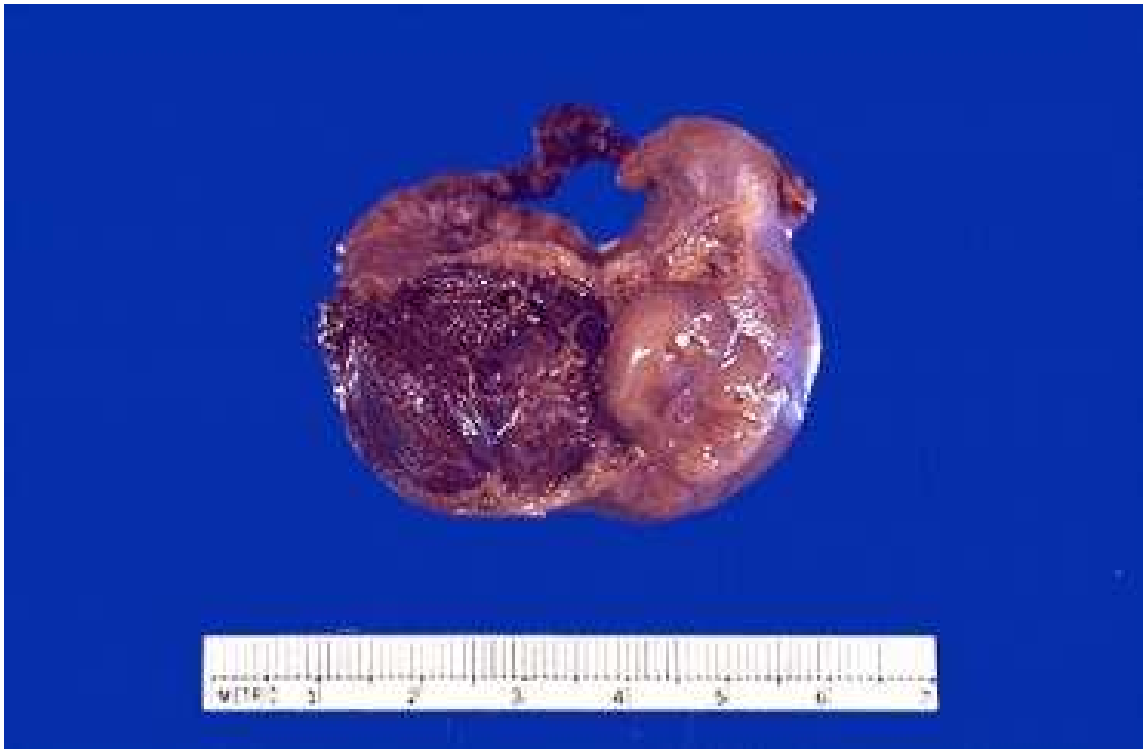
Tubo-ovarian abscess



The left ovary and tube have been transformed into a multicystic mass.

Fig. 22-61

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



This is a ruptured tubal ectopic pregnancy. Note the twin embryos at the lower right adjacent to the blood clot at the left. About half of ectopic pregnancies occur because of an identifiable lesion such as chronic salpingitis from pelvic inflammatory disease or adhesions from appendicitis, endometriosis, or previous laparotomy

https://webpath.med.utah.edu/FEMHTML/FEM038.html

Fallopian tube

- Serous cysts (Hydatids of Morgagni)
- Müllerian remnants
- Fimbriated ends of fallopian tube
- Adenomatoid tumors (mesotheliomas)
- Counterpart of adenomatoid tumor of testis
- Subserosal or in mesosalpinx
- Adenocarcinoma is rare

Ovarian follicle

- Cystic follicles
- Very common in the ovary.
- Originate from unruptured Graafian follicles or in follicles that have ruptured and immediately sealed
- Multiple
- Clear serous cysts
- Granulosa cell lining
- Outer layer of theca cells
- May be painful if enlarged or rupture

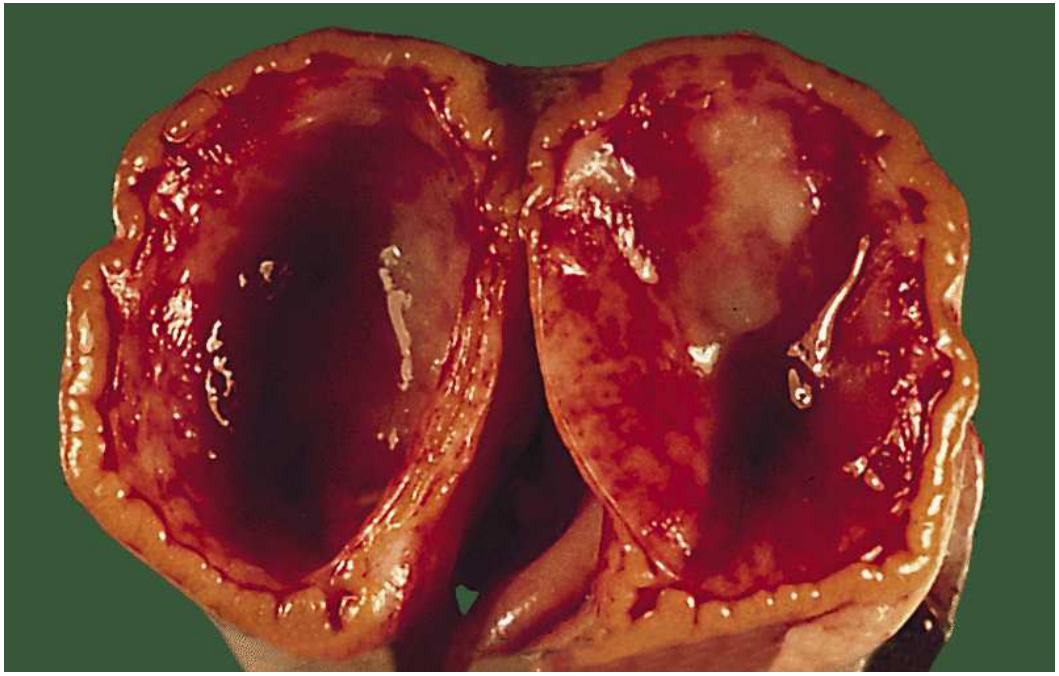
Ovarian follicle

- Luteal cysts (corpora lutea) are present in the normal ovaries of women of reproductive age.
- Lined by a rim of bright yellow tissue containing luteinized granulosa cells.

Corpus luteum cyst

- Cysts in prepubertal or postmenopausal women should be explored (laparoscopy).
- Cysts larger than 8cm or present for more than 60 days in a woman of reproductive age should be explored (laparoscopy).
- Oral contraceptives with low levels of progestins (e.g., Tri Cyclen) are used to suppress gonadotropin secretion.

Corpus luteum cyst



The wall is thick and yellow; the lining is smooth.

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

Ovarian follicle maturation

- By week 12 of development, a population of oögonia enter the first meiotic prophase and become dormant.
- The first meiotic division is completed just prior to ovulation forming a secondary oöcyte and the first polar body.
- As a result of changes in LH and FSH, the follicular cells of between 5-12 primordial follicles begin to thicken to cuboidal cells (primary follicles).

Ovarian follicle maturation

- The follicle cells and the oöcyte together secrete a glycoprotein coat called the zona pellucida.
- The follicle cells then differentiate to form a multilayered capsule around the oöcyte (still called a primary follicle).

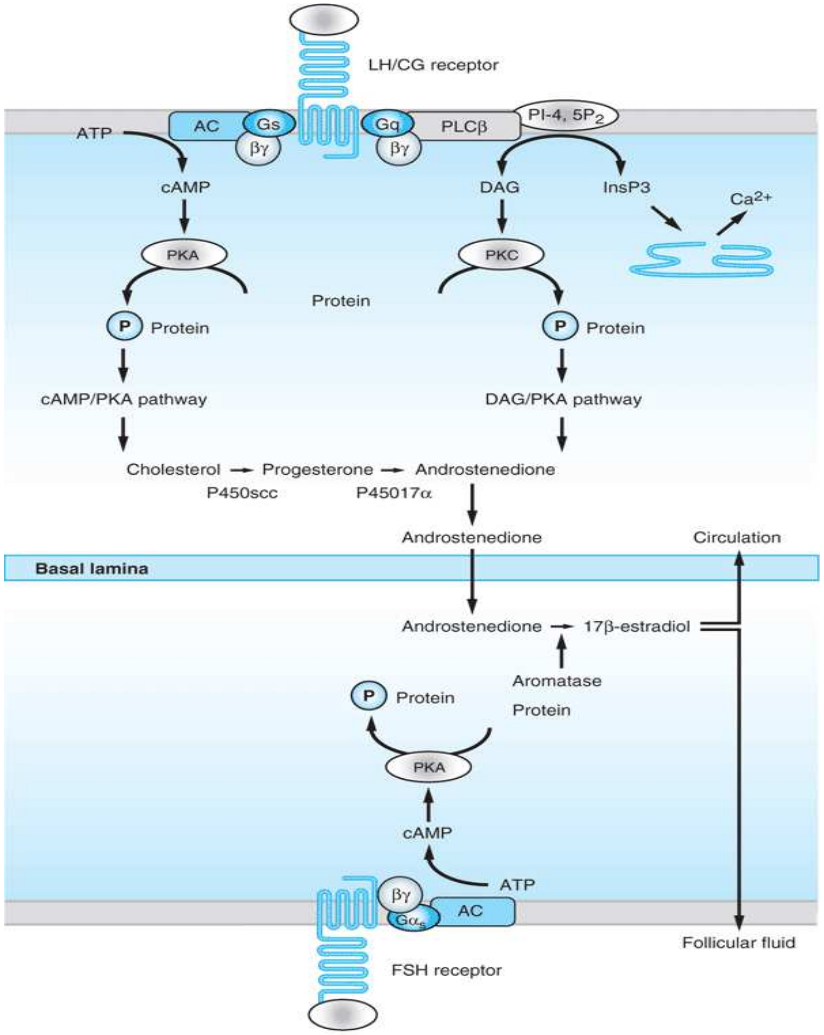
Ovarian follicle maturation

- Typically only one of the growing follcilces develops; the others degenerate.
- The second meiotic division begins immediately but does not finish unless fertilization takes place.
- The developing (Graafian) follicle takes up fluid, forming an antrum.
- The connective tissue surrounding the ovary differentiates into two layers.

Ovarian follicle maturation

- If there is no implantation, the corpus luteum degenerates.
- Progesterone maintains the corpus luteum.
- If there is implantation, the syncytiotrophoblast of the placenta produces HCG, maintaining the corpus luteum until the placenta is capable of producing progesterone (5^{th} month).

Ovarian follicle maturation



Source: Molina PE: *Endocrine Physiology*, 2nd Edition: http://www.accessmedicine.com

Fig. 9-2
Accessed
02/01/2010

Secretion of estradiol by the dominant follicle requires cooperation between theca cells, which synthesize androstenedione and testosterone, and granulosa cells of mature follicles, which convert androgens to estradiol and estrone.

In the corpus luteum, granulosa-lutein cells gain vascularity, LH receptors, and the enzymes necessary for progesterone synthesis. The theca-lutein cells remain the source of androstenedione for estradiol production in granulosa-lutein cells

Cellular sources of estrogen

- Granulosa cells and the corpus luteum produce the most estrogens.
- Estradiol is the primary estrogen produced by the ovary
- Estrone, in postmenopausal women.
- Peripheral aromatization of androgens produce significant amounts of estrogens.
- During pregnancy, 50% of estradiol is produced by aromatization of maternal adrenal derived androgens.
- Estriol, derived from fetal androgens, is the dominant estrogen in pregnancy.

Sex hormones

- Estrogens (C18 estranes) bind to sex-hormone binding globulin.
- More weakly bound than are androgens (C19 androstanes).
- Progestins (C21 pregnanes) bind to corticosteroid binding globulin.
- The sex steroid hormones bind to intracellular receptors that are members of the steroid-thyroid hormone receptor superfamily.

Sex hormones

- Hormone receptors are dimers that are stabilized in the cytosol by heat shock proteins, which dissociate after the hormone binds to the receptor
- The hormone-receptor complex binds to a hormone response element (HRE) upstream of a gene and acts as a transacting factor that modulates the transcription frequency of RNA Polymerase II, which is bound to the promotor element (PE).
- Affects ribonucleoprotein synthesis.
- Binding of cytosolic mRNA to ribonucleoprotein particles stabilizes mRNA, limits degradation.

Hormone receptors

- Peptide hormone receptors span the plasma membrane and bind ligand outside the cell.
- The hormone binding signal is transduced to the cell interior by binding to a series of G- proteins that lead to the production of the second messenger, principally cAMP.
- Steroid hormone receptors are ligand-activated proteins that regulate transcription of selected genes.
- Hormone receptors for glucocorticoids and aldosterone are found principally in the cytosol.
- When activated they translate to the nucleus.

Steroid-thyroid hormone receptor superfamily

- Steroid hormone receptors belong to the steroid and thyroid hormone receptor super-family of proteins, that includes receptors for steroid hormones, thyroid hormones, vitamin D and vitamin A (retinoic acid).
- Receptors may be up-regulated or down-regulated with exposure to hormone or deprivation of hormone.

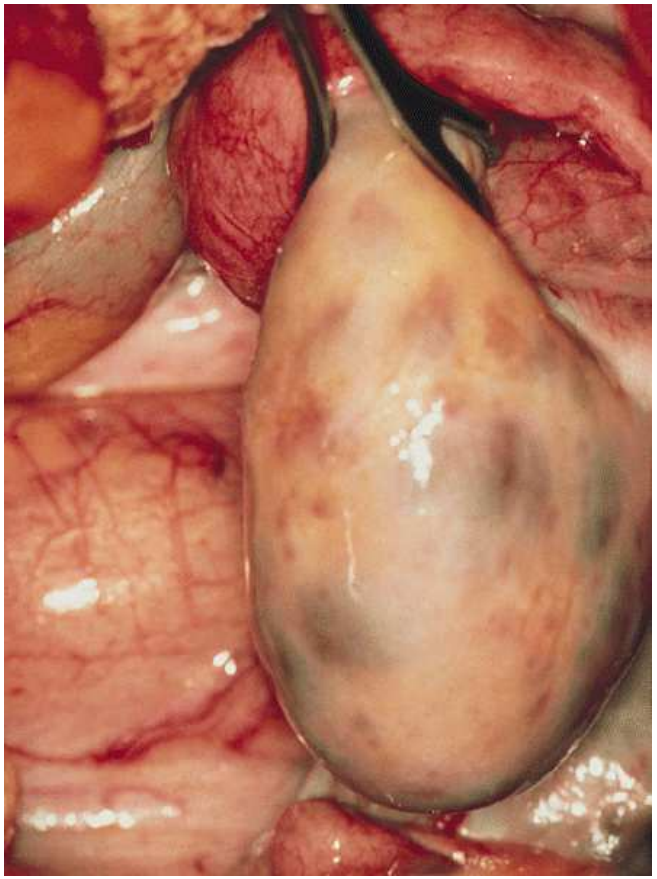
Polycystic ovary disease

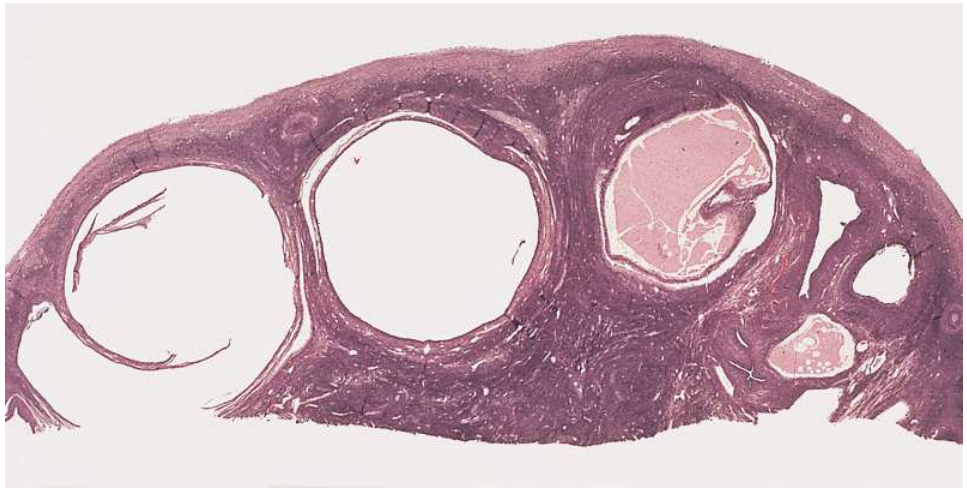
- Stein-Leventhal syndrome
- Complex endocrine disorder characterized by:
- Hyperandrogenism (but not virilization)
- Menstrual abnormalities
- Polycystic ovaries
- Chronic anovulation
- Decreased fertility.
- 6-10% of reproductive age women
- Also associated with obesity, type 2 diabetes, and premature atherosclerosis
- Dysregulation of enzymes that regulate androgen metabolism

Polycystic ovary disease

- Cysts lined by granulosa cells.
- Luteinization of outer thecal cell layer often prominent.
- Stromal thecosis is a distinct condition that shares many signs and symptoms with polycystic ovary.
- Virilization is prominent.
- Three-fold elevation of endometrial cancer risk as well as three-fold elevation of breast cancer risk at menopause.

Polycystic ovary disease





Figs. 22-6 and 22-7

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

Menopause

- Characterized by irregular bleeding, insomnia, night sweats, emotional lability, and vaginal dryness.
- Cessation of menses for one year is consensus definition of menopause.
- Vasomotor symptoms may be eased with venlexafine, clonidine, vitamin E, soy protein, or phytoestrogens.
- May still conceive.

Hormone replacement therapy

- Short term treatment [<1yr] may control vasomotor symptoms.
- Long term treatment benefits for those who begin therapy before age 50 are a
- 50% reduction in vertebral fracture and
- 30% reduction in hip fracture
- (15% volume loss or 4mm fall in height of vertebral body is regarded as fracture)

Hormone replacement therapy

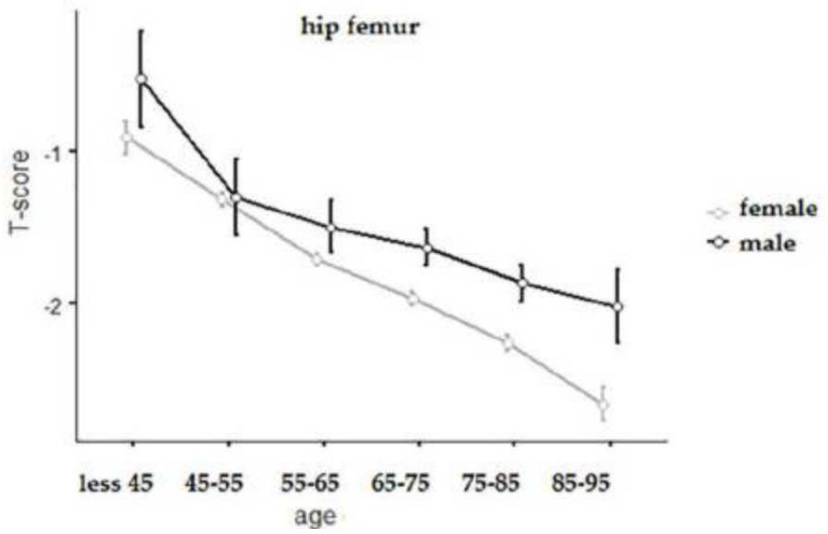
- Long term treatment risks are
- 24x increase in endometrial cancer
- 2x increase in venous thrombosis
- 29% increase in coronary artery disease
- 41% increase in stroke
- 25% increase in gall-gladder disease

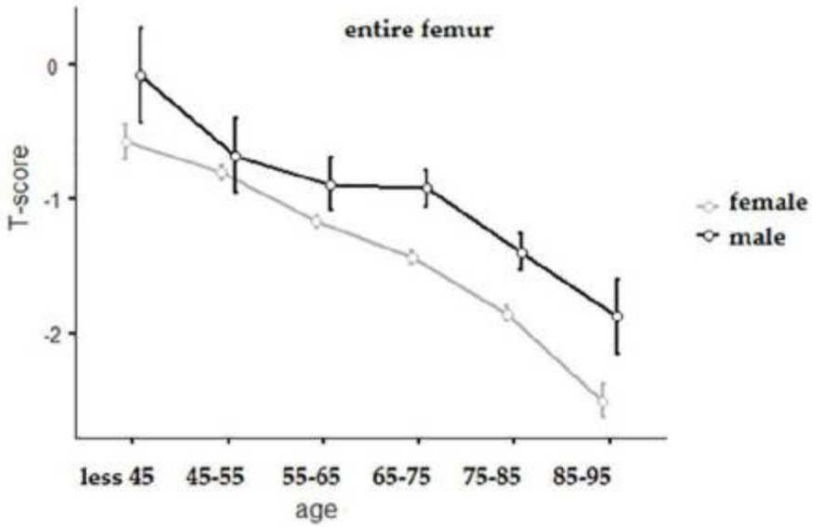
Osteoporosis

- At risk are women of European [BMP-2 gene] and of Asian origin.
- Also, men older than 70.
- Osteoporosis is not common in women of Sub-Saharan origin or in men.
- At risk are those on long-term steroid therapy (six weeks or more).

Osteoporosis

- Medicare pays for DXA screening.
- There is no evidence that early therapy limits later fracture.
- DXA scan does not change significantly with therapy nor over time
- No difference in lumbar or vertebral sites
- Over estimates bone loss compared to histology
- Ionizing radiation scan (not DXA) does not over estimate bone loss and accurately reflects bone strength (used in Europe)


hip femur
T-score
-1
-2
less 45
45-55
55-65
65-75
75-85
85-95
age
female
male


entire femur
T-score
0
-1
-2
less 45
45-55
55-65
65-75
75-85
85-95
age
female
male

Osteoporosis

- Therapy instituted if bone density (DXA) T-score is above 3.
- Fracture risk increases two to three times for each standard deviation from the mean.
- But, 5-6% difference in bone density depending on where the test was done.
- May change the T-score by 0.2-0.4 (which equates to a decade of bone loss)

Osteoporosis

- Daily intake of Calcium, vitamin D may retard osteoporosis.
- Boron cross-links fibrous matrix on which Calcium deposited
- Fracture risk decreases with daily intake.
- Back and leg strengthening exercises helpful.

Table 3 Significant fracture risk reductions* for osteoporotic therapies over time

	6 Month	1 Year	2 Years	3 Years	4 Years	5 Years	6-7 Years
Alendronate[†9-12]		□ ●	□ ●	■ □ ●	■		
Risedronate[‡13-18,28]	□ ●	■ □ ●	■ ●	■ ●		■ ●	■
Ibandronate[19]			■	■ □			
Raloxifene[20-22]		□	□	■ □	■		
Hormone therapy[§23,24]							□ ●
Calcitonin (200 IU/d)[26]				■		■	
Teriparatide[¶27]			■ ●				

■=morphometric vertebral fractures; □=clinical vertebral fractures; ●=nonvertebral fractures

FIT=Fracture Intervention Trial; FOSIT=Fosamax International Trial.

*Clinical comparisons performed between patients receiving therapeutic agent vs placebo at each specified time point. Both prospective and retrospective analyses from clinical studies are included.

†In the 1-year FOSIT study, nonvertebral fractures were captured through adverse event reporting. For the 2- and 3-y results from the FIT study, nonvertebral fractures were confirmed by radiologic procedure and defined as all nonvertebral fractures with the exception of those of the skull or face. Also excluded were pathologic fractures and those due to trauma that would fracture a bone in a young adult.

‡Nonvertebral fractures were confirmed radiographically and defined as fractures of the clavicle, humerus, wrist, pelvis, hip, or leg, regardless of trauma.

§Nonvertebral fractures were reported in a semiannual questionnaire and confirmed radiographically. Reports of nonvertebral fractures excluded those of the skull, face, ribs, chest/sternum, cervical vertebrae, toes, and fingers.

¶Nonvertebral fractures were confirmed radiographically and included all nonspine fractures.

Source: Created for Geriatrics by RG Miller, MD, MBA

Osteoporosis therapy

- Biphosphonates bind to matrix proteins.
- Inhibit osteoclast activity and promote apoptosis.
- Diminish risk of vertebral as well as non-vertebral fractures but not associated with new bone formation
- 0.1% will suffer osteonecrosis of jaw
- Doubles risk of developing atrial fibrillation
- Drugs of choice.
- Oral medications may precipitate bone pain.
- Zoledronic acid infusion once or twice yearly appears to be adequate.
- May diminish bone pain following compression fractures

Osteoporosis therapy

- Calcitonin (nasal administration) associated with 30% increase in bone density
- Many side effects
- Teriapatide (injection) associated with 60% increase in bone density particularly if used in conjunction with hormone replacement.
- Synthetic parathyroid hormone.

Ovarian cancer

- Three theories as to origins:
- Extra uterine Müllerian epithelium of the fallopian tube as well as from endometriosis
- Germ cells, which migrate to the ovary from the yolk sac, and are pluripotent
- Stromal cells, including the sex cords, which are forerunners of the endocrine apparatus of the postnatal ovary

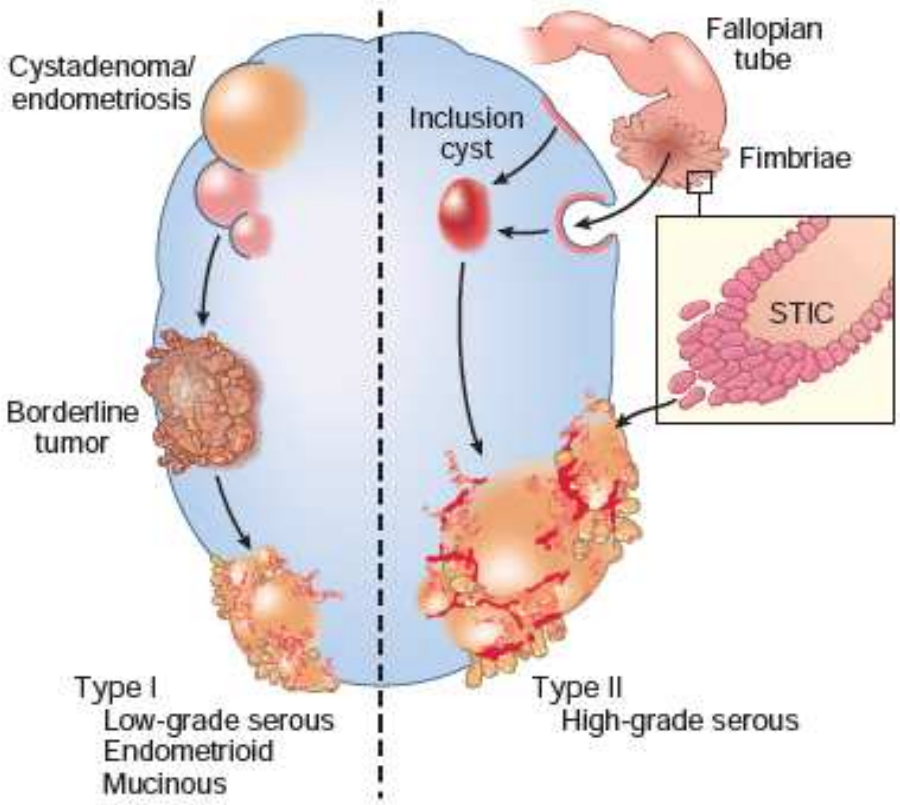


Figure 22-30 Schematic diagram of the pathogenesis of ovarian epithelial tumors. Type I tumors progress from benign tumors through borderline tumors that may give rise to a low-grade carcinoma. These include low-grade serous, endometrioid and mucinous carcinomas. Type II tumors arise from inclusions cysts/fallopian tube epithelium via intraepithelial precursors that are often not identified. They demonstrate high-grade features and are most commonly of serous histology. STIC, serous tubal intraepithelial carcinoma.

Ovarian cancer

- Risk increases with age and positive family history (first degree relatives).
- Hereditary breast (BRCA1mutation) and ovarian cancer syndromes (BRCA2 mutation) as well as hereditary nonpolyposis cancer (Lynch syndrome) (MLH mutation) pose high risk.
- Bilaterality common in malignant serous carcinomas, endometrioid carcinomas, and clear cell carcinomas.

Ovarian cancer

- CA125 is not a good screening tool.
- Produced in a number of tissues
- Predictive value is low
- Best used in conjunction with HE4 (human epidydimis protein) as HE4 not generally expressed by benign conditions
- Used for triage in women with pelvic mass
- Negative predictive value >99%
- May eliminate need for second surgery and debulking by separating high and low risk disease
- CA125 is surrogate marker for epithelial tumor response.

Classification of Tumours of the Ovary
Epithelial tumours (ET)
Sex cord–stromal tumours (SCST)
Germ cell tumours (GCT)
Monodermal teratoma and somatic type tumours arising from dermoid cyst
Germ cell–sex cord stromal tumours
Mesenchymal and mixed epithelial and mesenchymal tumours
Other rare tumours, tumour-like conditions
Lymphoid and myeloid tumours
Secondary tumours

WHO, 2014

Carcinomas, accounting for over 80% of cancers, peak at the 6th decade; SCSTs peak in the perimenopausal period; GCTs peak in the first three decades.

Table 22-5 WHO Classification of Ovarian Neoplasms

Surface Epithelial-Stromal Tumors
Serous tumors
Benign (cystadenoma, cystadenofibroma)
Borderline (serous borderline tumor)
Malignant (low- and high-grade serous adenocarcinoma)
Mucinous tumors, endocervical-like and intestinal type
Benign (cystadenoma, cystadenofibroma)
Borderline (mucinous borderline tumor)
Malignant (mucinous adenocarcinoma)
Endometrioid tumors
Benign (cystadenoma, cystadenofibroma)
Borderline (endometrioid borderline tumor)
Malignant (endometrioid adenocarcinoma)
Clear cell tumors
Benign
Borderline
Malignant (clear cell adenocarcinoma)
Transitional cell tumors
Benign Brenner tumor
Brenner tumor of borderline malignancy
Malignant Brenner tumor
Epithelial-stromal
Adenosarcoma
Malignant mixed müllerian tumor
Sex Cord-Stromal Tumors
Granulosa tumors
Fibromas
Fibrothecomas
Thecomas
Sertoli-Leydig cell tumors
Steroid (lipid) cell tumors
Germ Cell Tumors
Teratoma
Immature
Mature
Solid
Cystic (dermoid cyst)
Monodermal (e.g., struma ovarii, carcinoid)
Dysgerminoma
Yolk sac tumor
Mixed germ cell tumors
Metastatic Cancer From Non-ovarian Primary
Colonic, appendiceal
Gastric
Pancreaticobiliary
Breast

Table 22-6 Frequency of Major Ovarian Tumors

Type	Percentage of Malignant Ovarian Tumors	Percentage That Are Bilateral
Serous		
Benign (60%)		25
Borderline (15%)	47	30
Malignant (25%)		65
Mucinous		
Benign (80%)		5
Borderline (10%)	3	10
Malignant (10%)		<5
Endometrioid carcinoma	20	40
Undifferentiated carcinoma	10	—
Clear cell carcinoma	6	40
Granulosa cell tumor	5	5
Teratoma		15
Benign (96%)	1	Rare
Malignant (4%)		
Metastatic	5	>50
Others	3	—

Ovarian cancer

- Six distinct subtypes have been identified with molecular screening:
- Low malignant potential serous carcinoma (C3 subtype)
- Low expression of proliferation markers (MKI67, TOP2A, CCNB1, CDC2, KIF11)
- Overexpression of MAPK pathway genes (DUSP4, DUSP6, SERPIN5A, MAP3K5, SPRY2), likely associated with mutations in MAPK pathway members KRAS and BRAF
- Overexpression of axonemal dyneins (associated with enrichment of ciliated cells)

Ovarian cancer

- Low malignant potential endometrioid carcinoma (C6 subtype)
- Low expression of proliferation markers (MKI67, TOP2A, CCNB1, CDC2, KIF11)
- Overexpression of transcriptional targets of the β-catenin/LEF/TCF complex

Ovarian cancer

- High stroma (C1 subtype)
- Low numbers of intratumoral CD3+ T-cell numbers
- Early relapse
- An enhanced stromal response has a significant negative effect on tumor behavior and clinical outcome across many cancer types

Ovarian cancer

- Mesenchymal (C5 subtype)
- Characterized by overexpression of genes associated with WNT signaling, developmental transcription factors in combination with reduced membranous E-cadherin staining is strongly suggestive of epithelial-mesenchymal transition (EMT).
- Overexpress homeobox genes.
- Low expression of CA-125 and MUC1 cancer markers
- Low numbers of intratumoral CD3+ T-cells

Ovarian cancer

- Immune (C2 subtype)
- Increased numbers of CD3+ intratumoral T-cells
- Differentiated (C4 subtype)
- Little stromal reaction

Ovarian cancer

- High-grade endometrioid and serous tumors are molecularly similar
- The sine qua non of high-grade serous cancers is the dysregulation of p53 and associated effects on DNA repair, leading to genomic instability and the characteristic of high copy number variability. These tumors are also characterized by expression of WT-1, ERα, and PAX8.
- Invasive serous cancers are composed exclusively of the secretory cell, not ciliated cell, type

Ovarian cancer

- The most validated prognostic and predictive biomarker within high-grade serous cancers is germline deleterious mutation in either BRCA1 or BRCA2 (noted in 14%).
- Loss of function of these genes requires loss normal p53 regulation for cellular viability
- 33% have either germline or biallelic mutations
- Germline BRCA mutation is prognostic of generally good outcomes, and is predictive of platinum sensitivity and PARP inhibitor sensitivity

Ovarian cancer

- Disruption of the G1/S cell-cycle transition by CCNE1 amplification (20%), by overexpression or amplification of CCND1 or CCND2 (19%), or loss of regulation of the G1/S checkpoint by loss of function of pRB (10%) will account for nearly one-third to one-half of cases.
- Disruption of normal G1/S transitions also leads to poor DNA repair, also contributing to the classic genomic instability phenotype of ovarian cancers that overexpress Cyclin E.

Ovarian cancer

- More than 90% of ovarian tumors have an epithelial origin:
- High risk:
- Serous (high grade), 70% of ovarian tumors;
- Clear cell, 10% of ovarian tumors;
- Malignant Brenner tumor (transitional cell)
- Intermediate risk:
- Mucinous, 4% of ovarian tumors
- Low risk:
- Endometrioid, 10% of ovarian tumors
- Serous (low grade), 3% of ovarian tumors
- Transitional cell (low grade)

Site of origin (+ immunohistochemical markers) and histological type (+ *genetic association*) of ovarian carcinomas

Fallopian tube (PAX8, WT1)
High-grade serous (*p53, BRCA1, BRCA2*)

Endosalpingiosis, serous borderline tumours (PAX8, WT1)
Low-grade serous (*BRAF, Kras, PIK3CA, MSI*)

Endometriosis (PAX8, ER, PR)
Clear cell (*ARID1a*)
Endometrioid (*ARID1a, β-catenin, PTEN, MSI*)

Not known, tubal peritoneal-junction? (-)
Mucinous (*Kras, HER2*)
Brenner

Stage I: Tumour confined to ovaries or Fallopian tube(s)
IA: Tumour limited to 1 ovary (capsule intact) or Fallopian tube; no tumour on ovarian or Fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IB: Tumour limited to both ovaries (capsules intact) or Fallopian tubes; no tumour on ovarian or Fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IC: Tumour limited to 1 or both ovaries or Fallopian tubes, with any of the following: • **IC1:** Surgical spill • **IC2:** Capsule ruptured before surgery or tumour on ovarian or Fallopian tube surface • **IC3:** Malignant cells in the ascites or peritoneal washings
Stage II: Tumour involves 1 or both ovaries or Fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
IIA: Extension and/or implants on uterus and/or Fallopian tubes and/or ovaries
IIB: Extension to other pelvic intraperitoneal tissues

FIGO, 2013

Stage III: Tumour involves 1 or both ovaries or Fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

IIIA1: Positive retroperitoneal lymph nodes only
- IIIA1(i) Metastasis up to 10 mm
- IIIA1(ii) Metastasis more than 10 mm

IIIA2: Microscopic extrapelvic peritoneal involvement with or without positive lymph nodes

IIIB: Macroscopic extrapelvic peritoneal metastasis up to 2 cm, with or without metastasis to the retroperitoneal lymph nodes

IIIC: Extrapelvic peritoneal metastasis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes

Stage IV: Distant metastasis excluding peritoneal metastases

IVA: Pleural effusion with positive cytology

IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

FIGO, 2013

Serous carcinoma

- This distinction is made based on the degree of nuclear atypia:
- Low-grade (well-differentiated) carcinoma
- Low-grade carcinomas may arise in association with serous borderline tumors
- Can develop from inclusion cysts
- Low-grade tumors arising in serous borderline tumors have mutations in the KRAS, BRAF, or ERBB2 oncogenes
- Usually have wild type TP53 genes

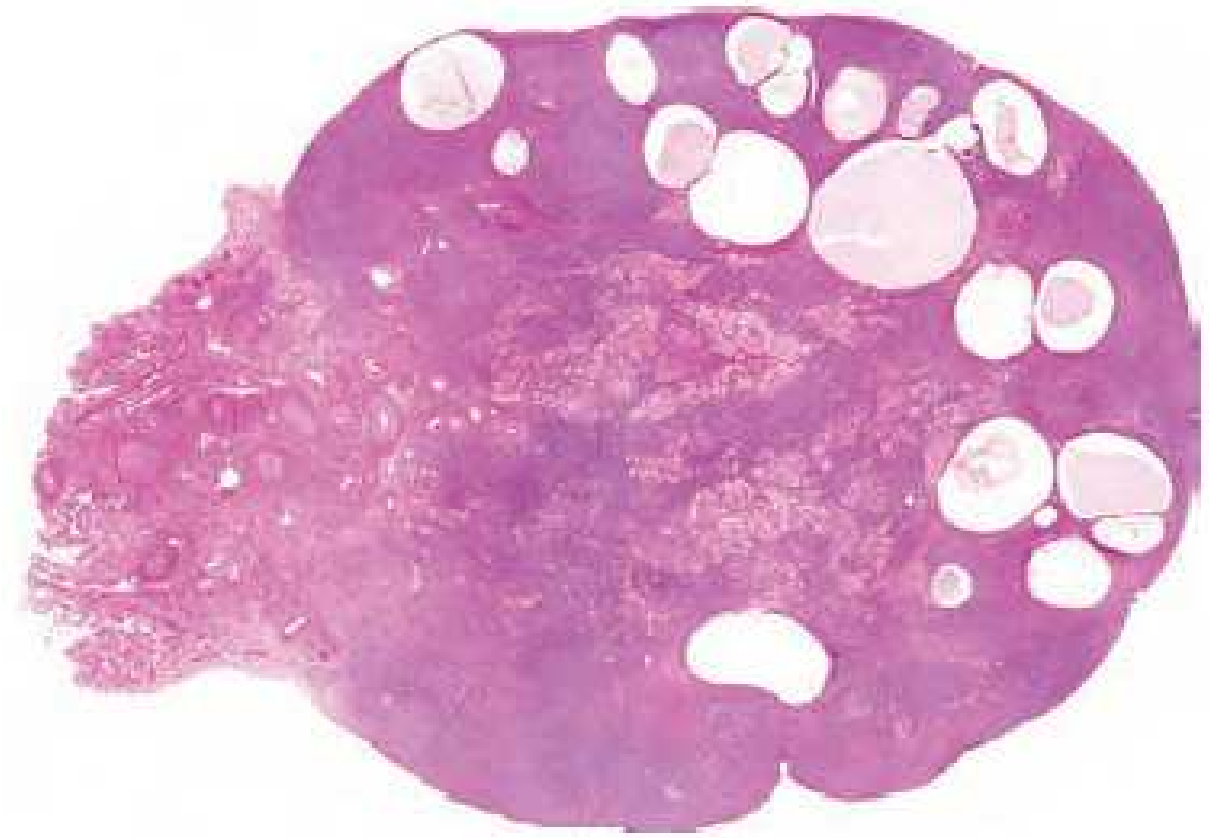
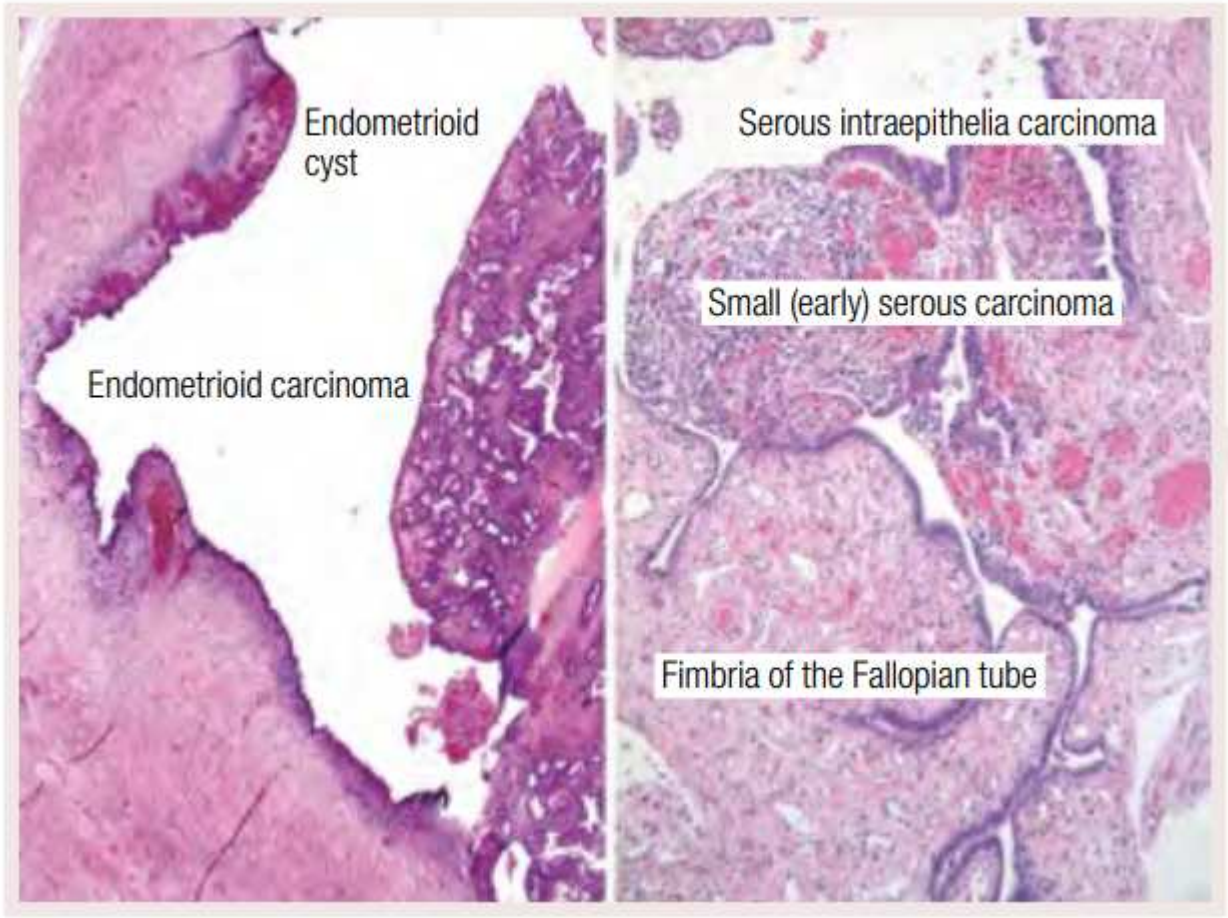


Figure 22-31 Cortical inclusion cysts of the ovary.


Endometrioid cyst
Endometrioid carcinoma
Serous intraepithelia carcinoma
Small (early) serous carcinoma
Fimbria of the Fallopian tube

Serous carcinoma

- Present as either a multicystic lesion in which papillary epithelium is contained within a few fibrous walled cysts (intracystic) or as a mass projecting from the ovarian surface.
- Benign tumors typically have a smooth glistening cyst wall with no epithelial thickening or with small papillary projections.
- Borderline tumors contain an increased number of papillary projections

Serous carcinoma

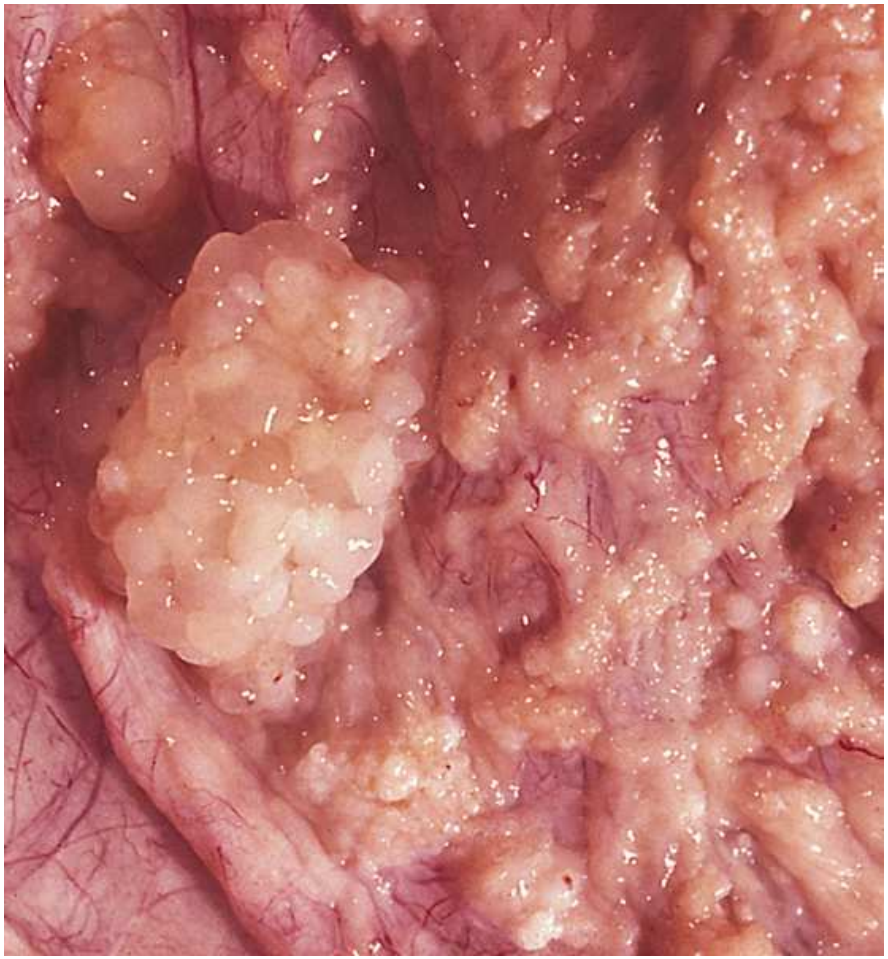
- High-grade (moderately to poorly differentiated) carcinoma.
- High-grade carcinomas arise from in situ lesions in the fallopian tube fimbriae (in BRCA patients) or from serous inclusion cysts within the ovary (serous tubal intraepithelial carcinoma, STIC)
- Cortical cysts arise from implantation of detached fallopian tube epithelium at sites where ovulation has disrupted the surface of the ovary
- High-grade tumors have a high frequency of TP53 mutations and lack mutations in either KRAS or BRAF.
- Familial BRCA1/2 mutations

Serous carcinoma

- Individual tumor cells display marked nuclear atypia, including pleomorphism, atypical mitotic figures, and multinucleation.
- The serous tubal intraepithelial carcinomas consist of cells morphologically identical to high-grade serous carcinomas but are distinguished by the lack of invasion.
- Psammoma bodies
- Spread to peritoneum

Ovarian Carcinomas			
Type	**%**	**Stage 1 %**	**Survival %**
Type 1			
Endometrioid	10	>60	78
Clear cell	10	>60	80
Mucinous	3	80	80
Low-grade serous	<5		>85
Type 2			
High-grade serous	70	<5	40

Serous cystadenoma

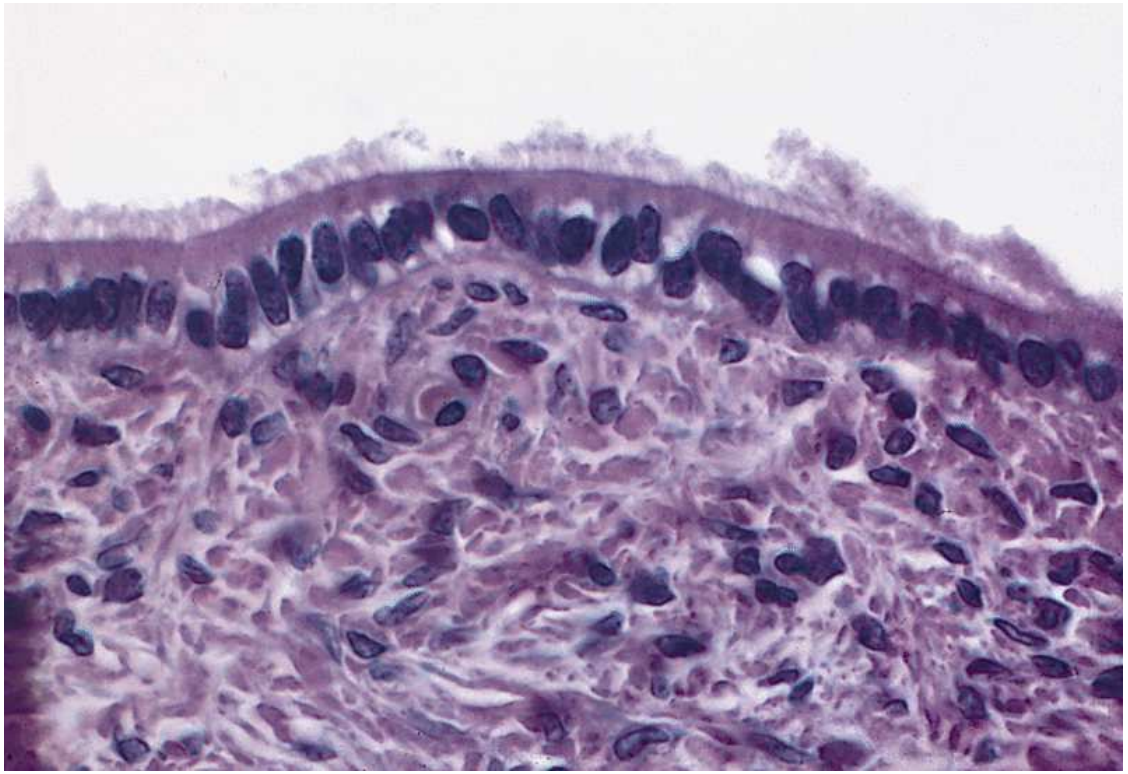


Serous cystadenoma is composed of one or more thin-walled cysts filled with watery fluid.The cyst lining may bear polypoid excrescences composed almost entirely of stroma and characterized by a firm consistency if the stroma is dense and fibrous, or a soft consistency if it is edematous.

Fig. 3-2R

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.

Serous cystadenoma

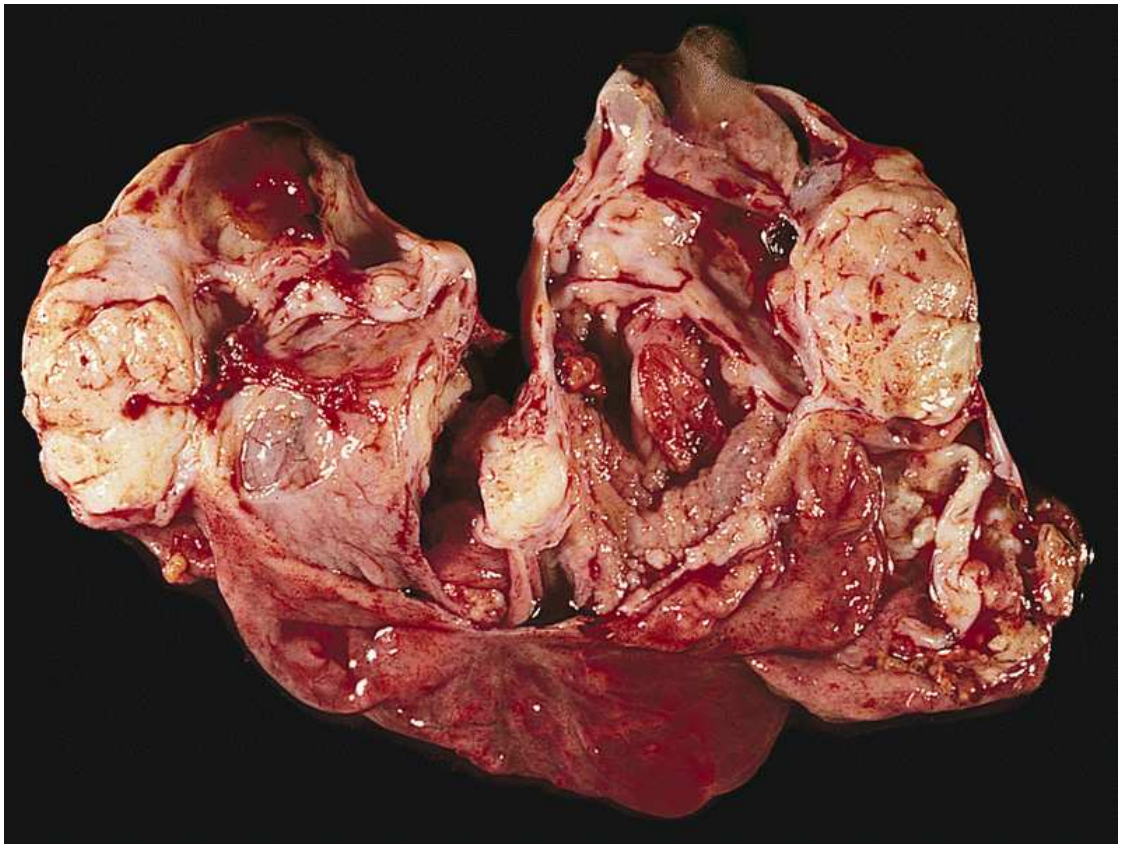


The cyst is lined by ciliated epithelium without significant nuclear atypia.

Fig. 3-9

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.

Serous adenocarcinoma



The tumors are partly solid and partly cystic. The rough- surfaced polypoid tumor has extended through the capsule.

Fig. 3-7

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.

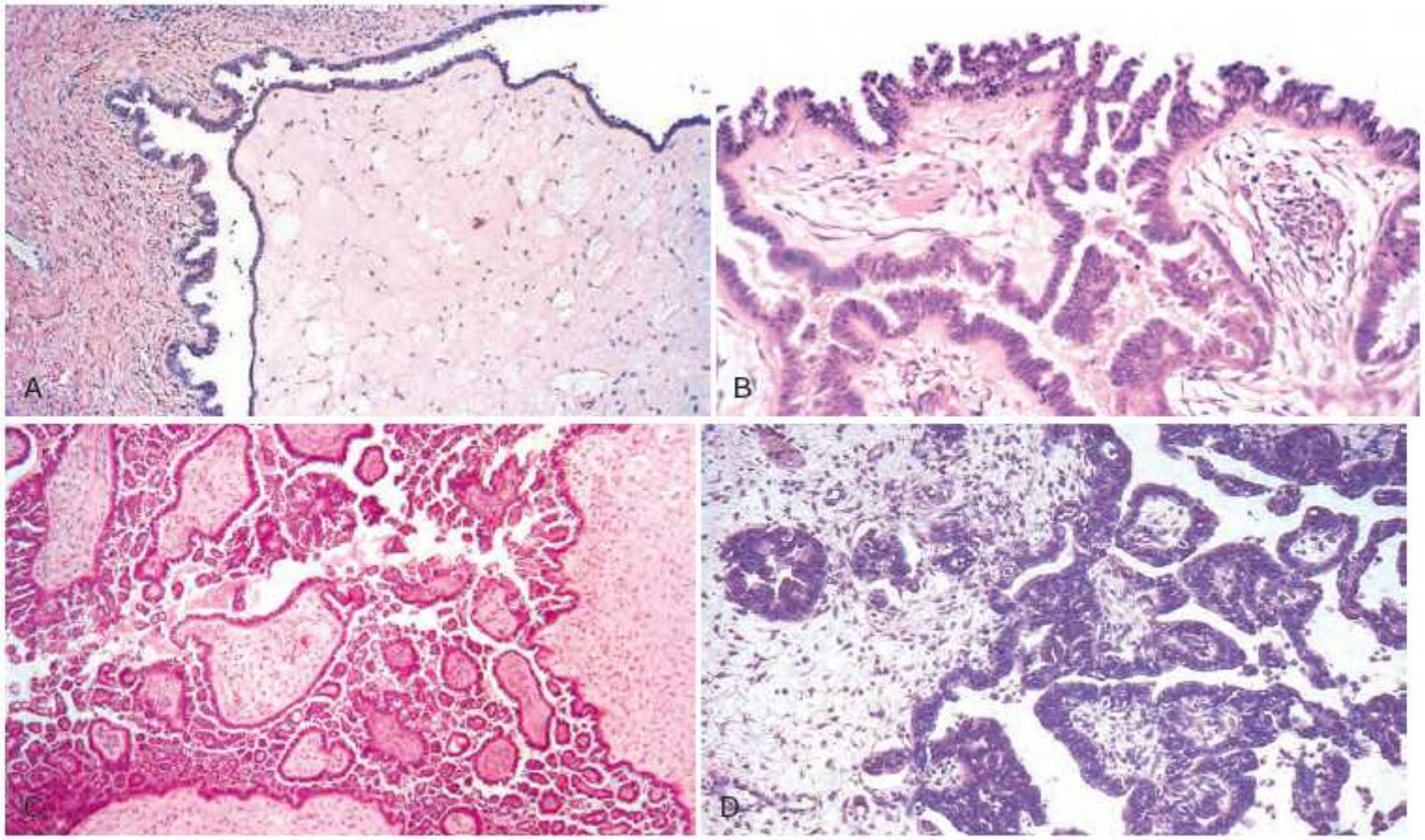
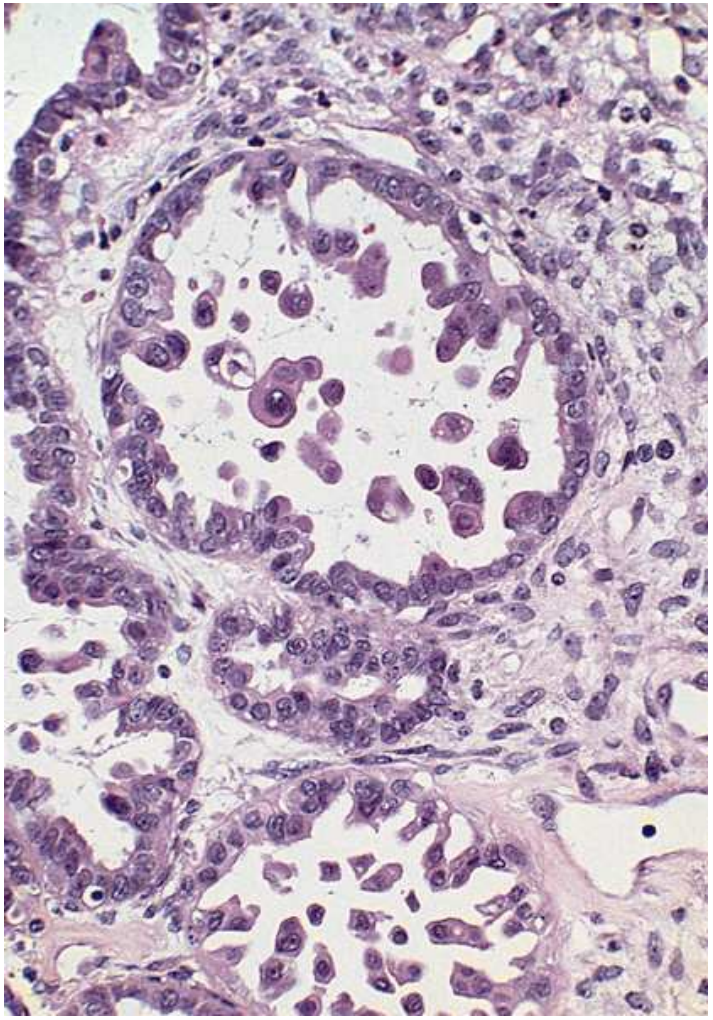


Figure 22-33 Microscopic appearances of serous tumors of the ovary. **A,** Serous cystadenoma revealing stromal papillae with a columnar epithelium. **B,** Borderline serous tumor showing increased architectural complexity and epithelial cell stratification. **C,** Complex micropapillary growth defines a low-grade "micropapillary" serous carcinoma. **D,** High-grade serous carcinoma of the ovary with invasion of underlying stroma.

Serous cystic tumor of borderline malignancy

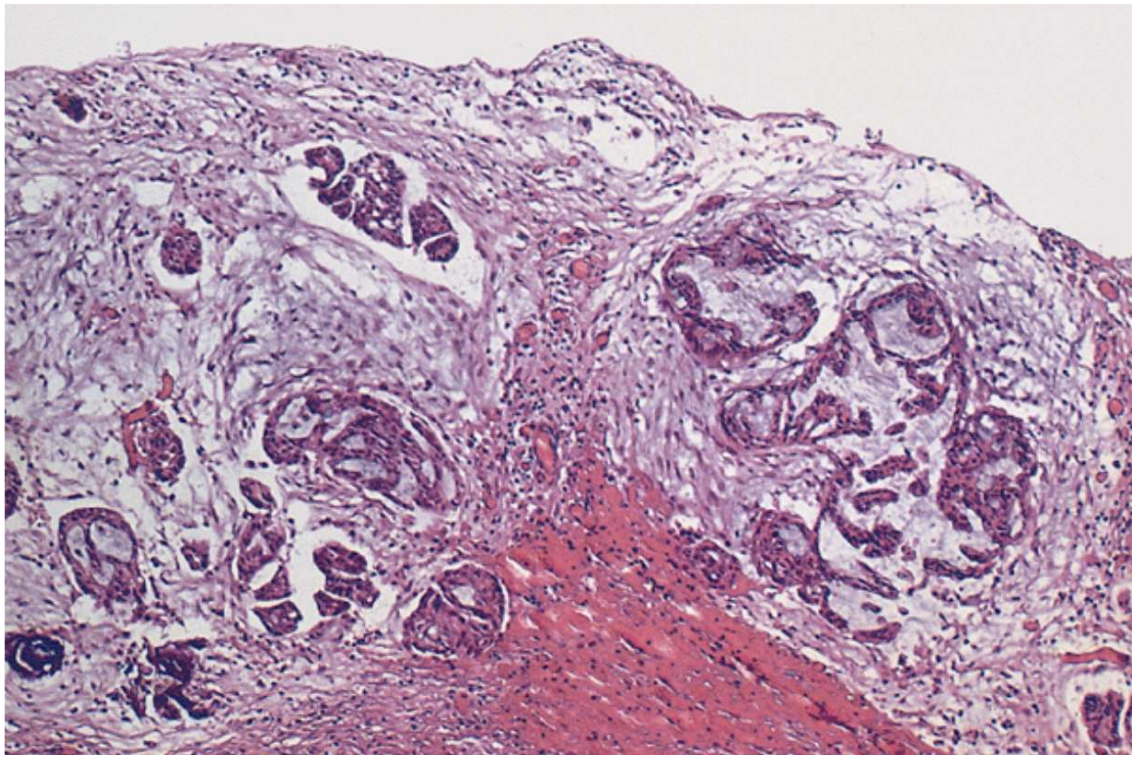


The lining cells are stratified with cellular budding. The nuclei are moderately atypical
and the cytoplasm is moderately abundant.

Fig. 3-14

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.

Serosal implant

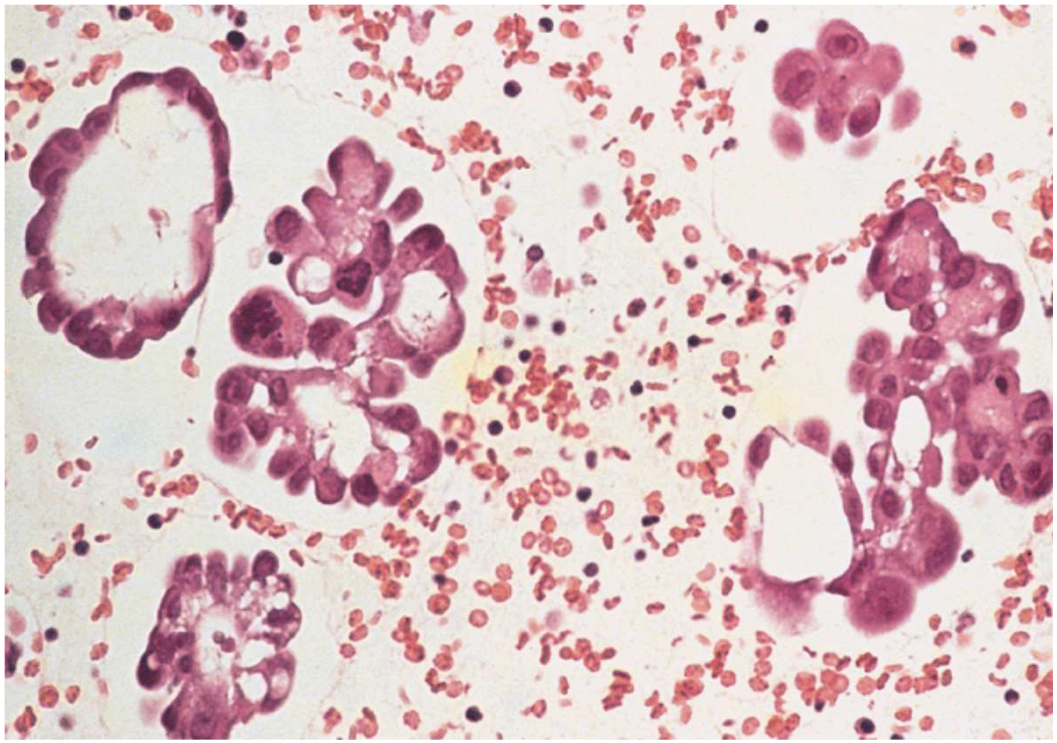


Large numbers of epithelial cell islands are present.

Fig. 3-31L

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.

Ovarian carcinoma

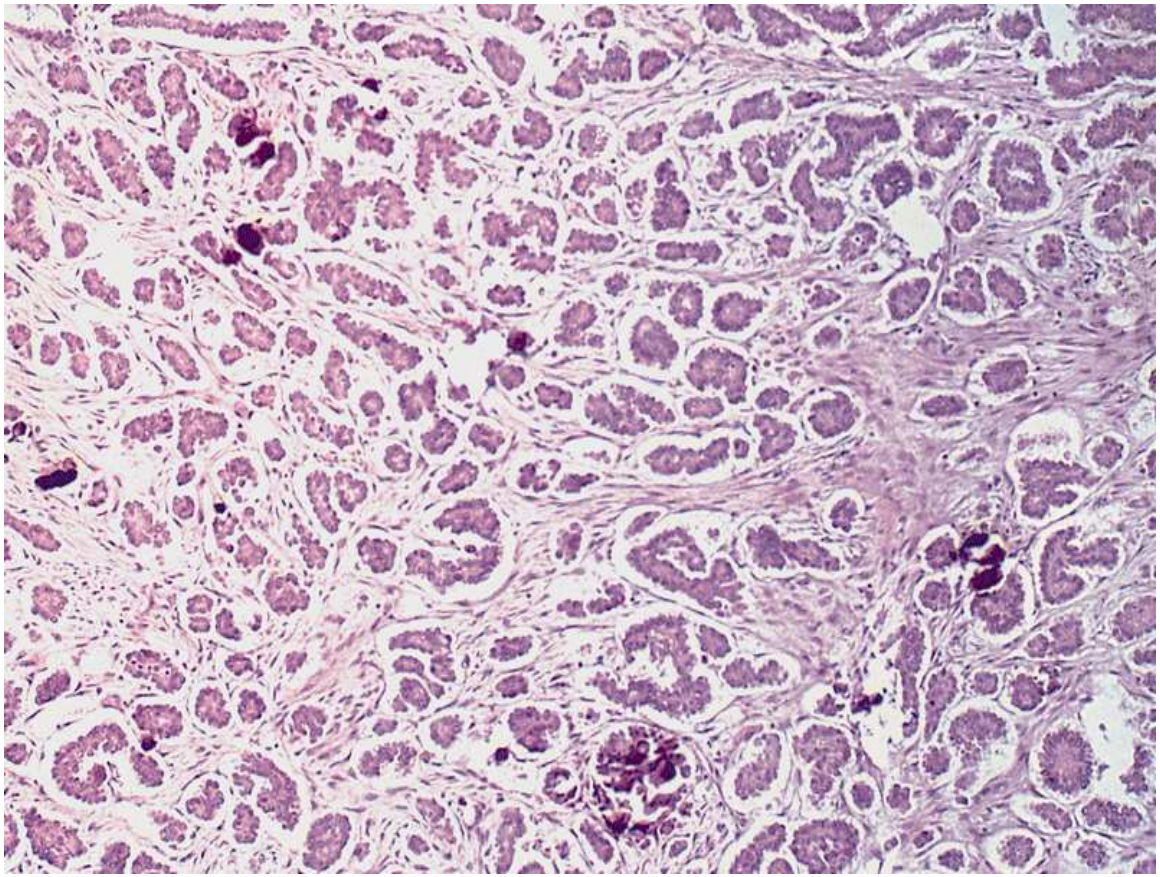


Papillary clusters of vacuolated carcinoma cells in cell block.

Fig. 2-17

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.

Serous adenocarcinoma



The tumor is composed of small nests of well-differentiated epithelial cells lying in a fibrous stroma, with occasional psammoma body formation.

Fig. 3-37

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.

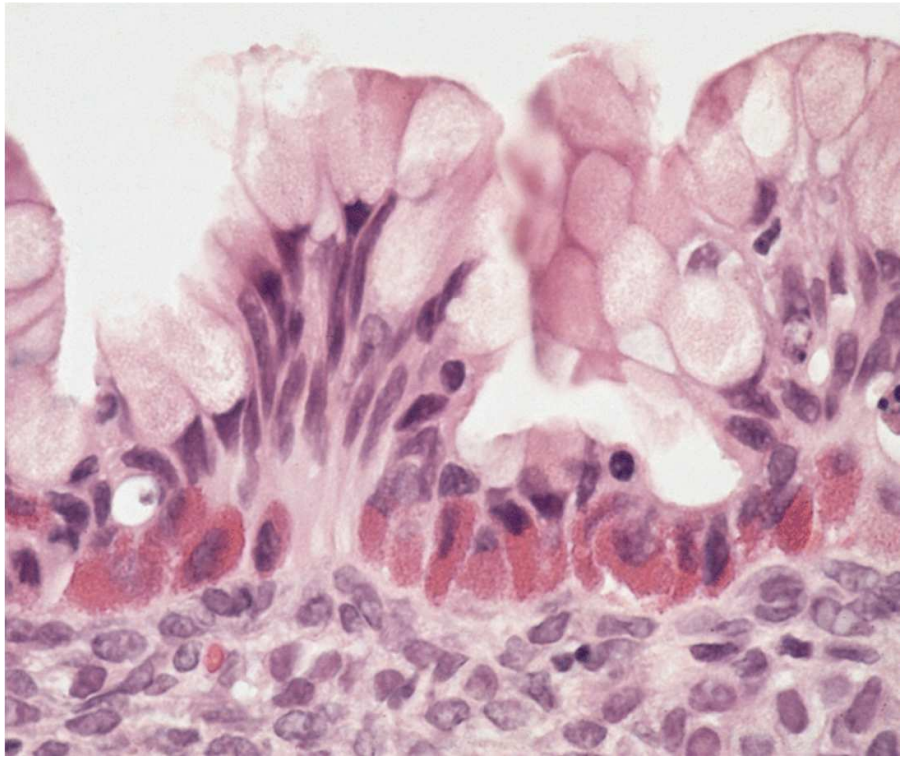
Mucinous cancer

- Ovarian surface rarely involved
- Multi-loculated, filled with gelatinous glycoprotein rich fluid
- The vast majority demonstrate gastric or intestinal type differentiation
- Uncommonly, tumors may show endocervical type mucinous differentiation

Mucinous cancer

- Mucinous borderline tumors are distinguished from cystadenomas by epithelial stratification, tufting, and/or papillary intraglandular growth
- Mucinous carcinomas characteristically demonstrate confluent glandular growth ("expansile" invasion).
- KRAS mutation common
- Bilateral presentation requires exclusion of non-ovarian origin
- Pseudomyomatous peritoneii usual from appendiceal carcinoma

Mucinous cystic tumor



The epithelial lining contains both goblet cells and argentaffin cells with coarse orange- red granules in their basal cytoplasm.

Fig. 4-4

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.

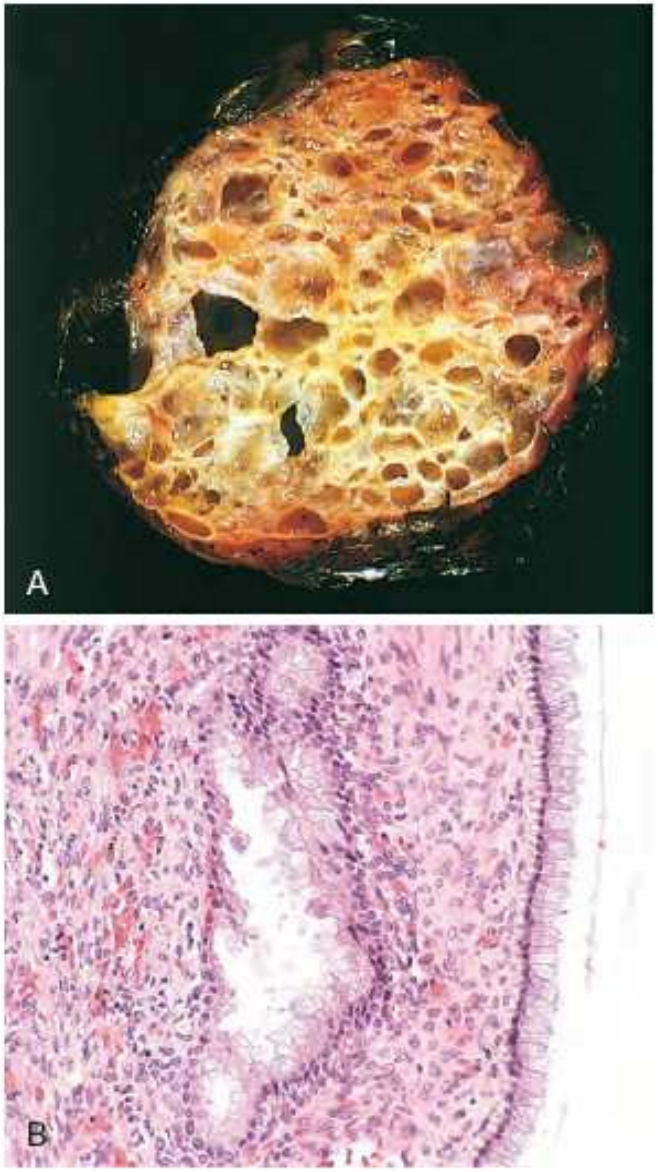
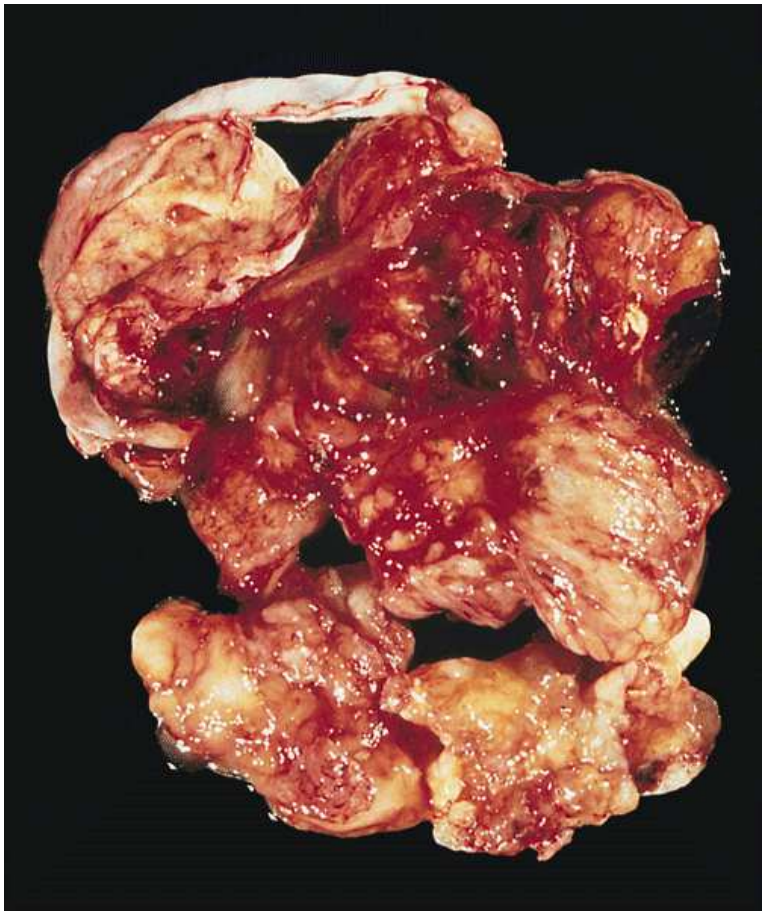


Figure 22-34 Mucinous cystadenoma **A,** Note the multicystic appearance, delicate septa, and the presence of glistening mucin within the cysts. **B,** Columnar cells lining the cysts.

Mucinous cystadenocarcinoma

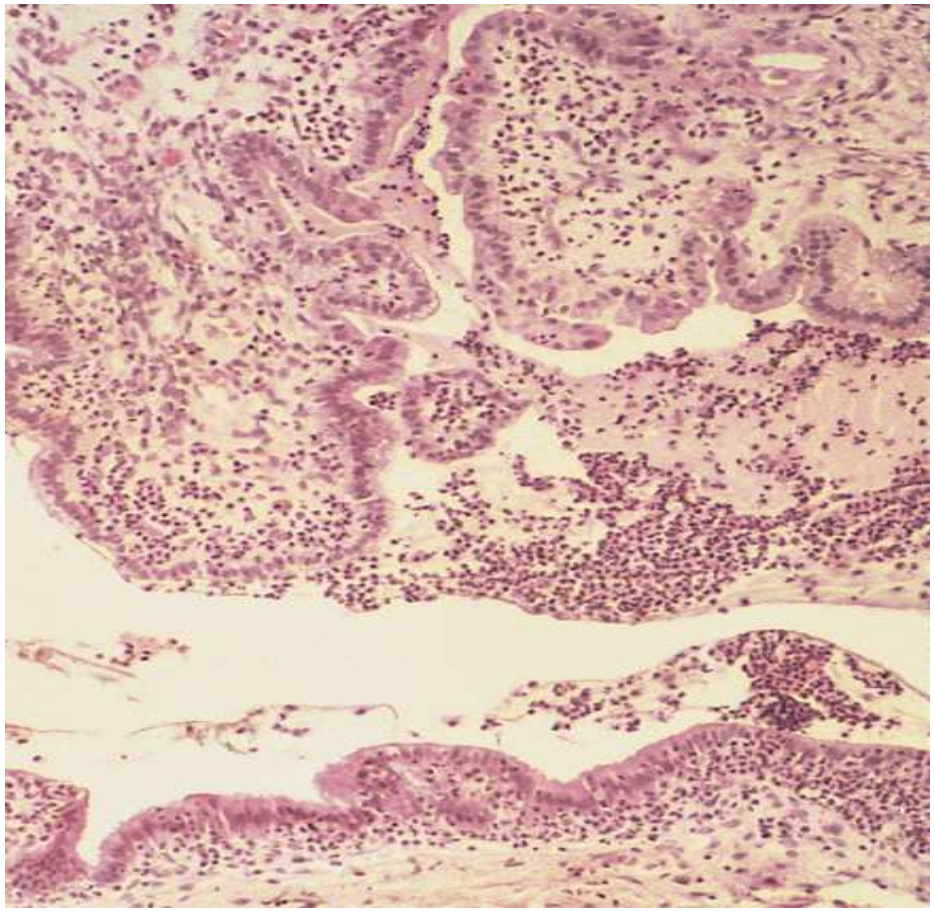


The sectioned surface appears gelatinous, with extensive hemorrhage and necrosis.

Fig. 4-8

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.

Mucinous cystadenocarcinoma

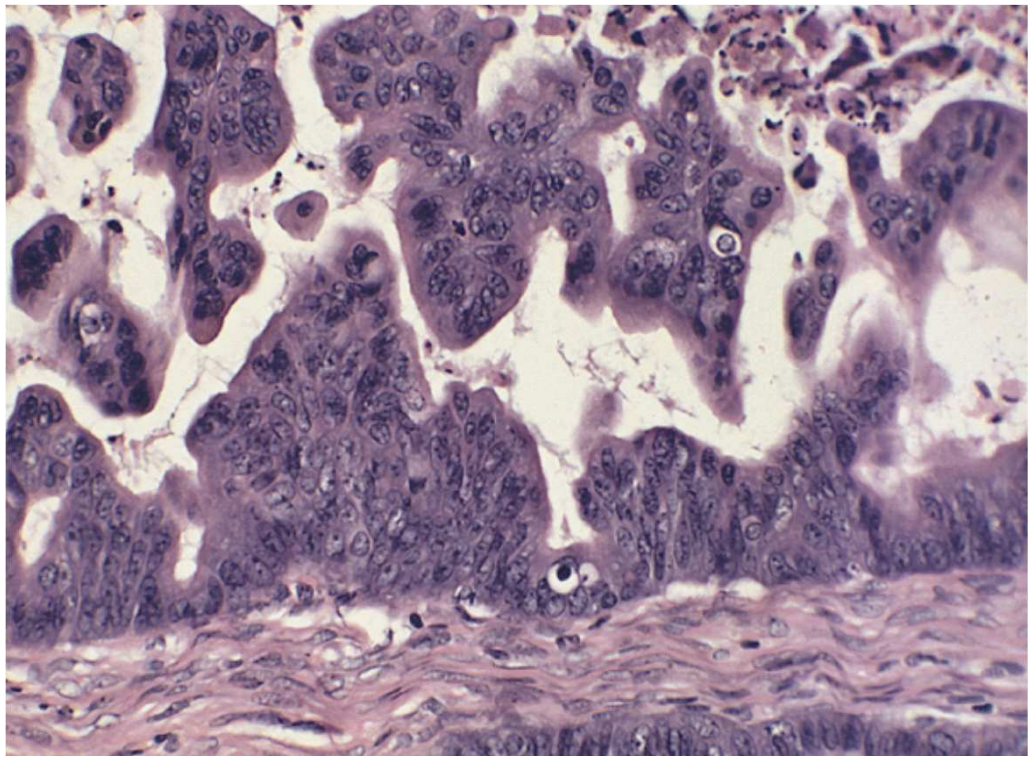


The tumor resembles endocervical tissue.

Fig. 4-18

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.

Mucinous cystadenocarcinoma



The tumor is well differentiated and characterized by stroma- free cellular papillae and marked nuclear atypia.

Fig. 4-20

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.

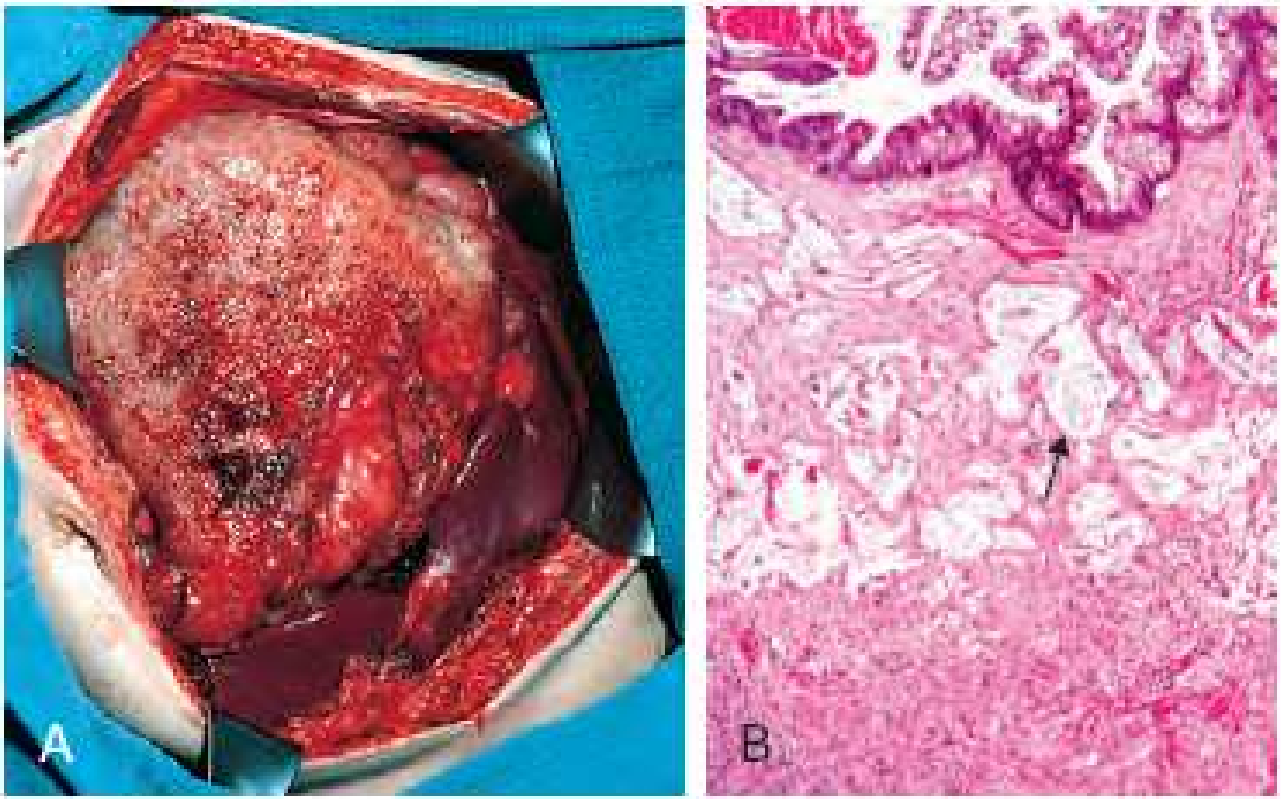
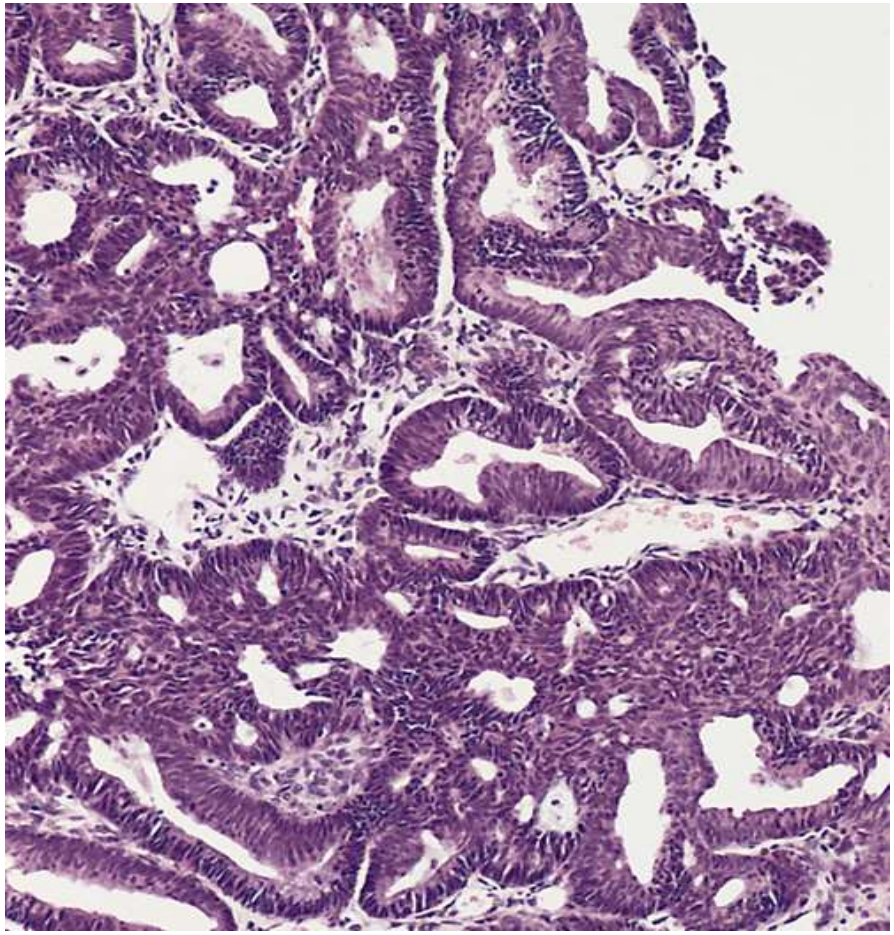


Figure 22-35 Pseudomyxoma peritonei. **A,** View at laparotomy revealing massive overgrowth of a gelatinous metastatic tumor. **B,** Histology of peritoneal implants from an appendiceal tumor, showing mucin-producing epithelium and free mucin *(arrow)*. (**A,** Courtesy Dr. Paul H. Sugarbaker, Washington Hospital Cancer Center, Washington, D.C.)

Endometrioid carcinoma

- 15-30% associated with endometrial carcinoma (independent origin)
- 15-20% co-exist with endometriosis
- Both solid and cystic growth
- PI3K/AKT pathway signaling mutations (in PTEN, PIK3CA, ARID1A, and KRAS) and mutations in mismatch DNA repair genes and CTNNB1 (β-catenin) and mutations in PTEN
- TP53 mutation in poorly differentiated cancers

Endometrioid carcinoma



Endometrioid adenocarcinoma is characterized by invasive round, oval, or tubular glands lined by stratified nonmucin-containing epithelium.

Fig. 5-15

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.

Clear cell carcinoma

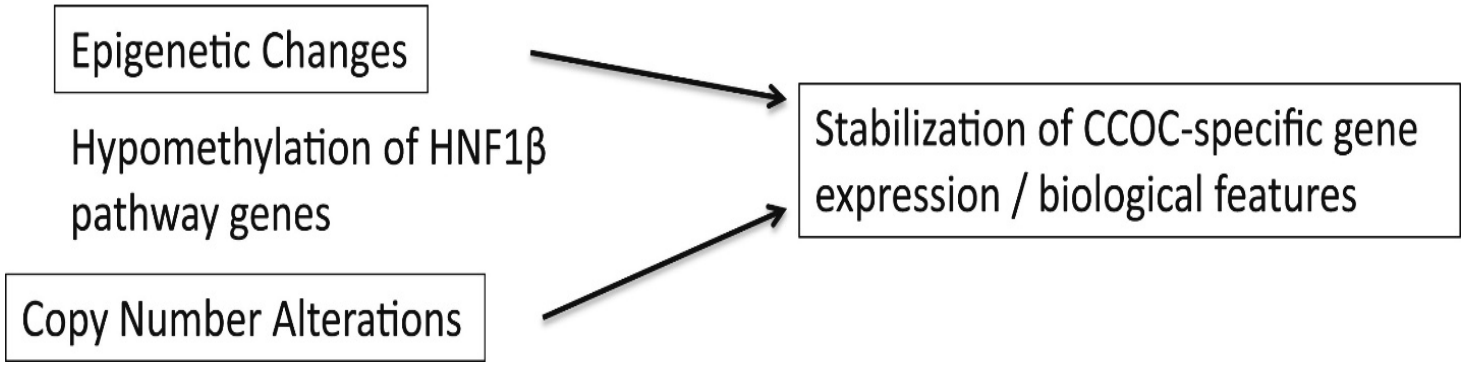
- Variant of endometrioid carcinoma
- Progresses from endometriosis
- HNF-1β mutation
- PIK3CA, ARID1A, KRAS, PTEN, TP53 mutations also identified
- Ki 67 (proliferation index) low
- High risk of extra-uterine metastases.
- Intermediate prognosis although poorly responsive to chemotherapy

Clear cell carcinoma

Progression from endometriosis:

Fe-induced oxidative stress → DNA damage
→ PIK3CA mutation and ARID1A mutation
→ Carcinogenesis of CCOC ; HNF1β↑ & IL6/STAT3↑

HNF1β ; Warburg effect / Resistance to Oxidative Stress
→ Progression in stressful condition of endometiotic cyst / Platinum resistance



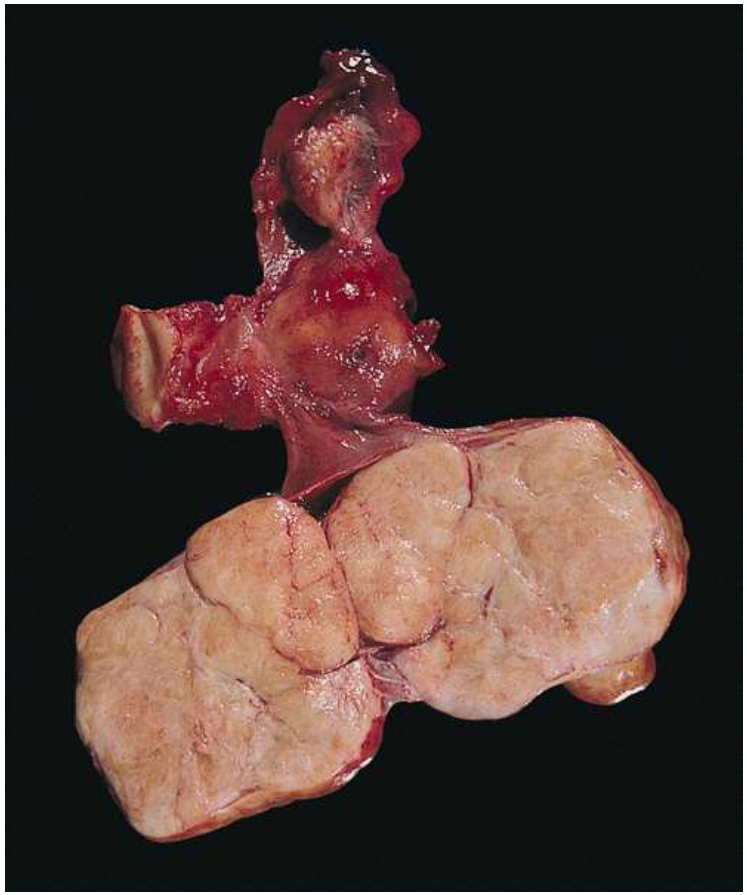
Clear cell carcinoma

- Composed of large epithelial cells with abundant clear cytoplasm, an appearance that resembles hypersecretory gestational endometrium.
- In the solid variety, the clear cells are arranged in sheets or tubules
- In the cystic variety, the neoplastic cells line the spaces.
- Copy number is distinct between histologic subtypes.

Brenner tumor

- Transitional cell
- 10% of epithelial tumors
- 90% unilateral
- The fibrous stroma resembles that of the normal ovary
- It is marked by sharply demarcated nests of of epithelial cells resembling urothelium
- Mucinous glands may be found in the nests.
- Infrequently, the stroma is composed of somewhat plump fibroblasts resembling theca cells
- Hormonally active
- Generally benign tumors

Brenner tumor



There is a solid fibrous tissue component as well as two cysts (lined by transitional epithelium).

Fig. 7-2

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

Ovarian fibroma

- Develop from mature fibroblasts.
- May present with ascites (and/or Meig's syndrome of fibroma, ascites, and right hydrothorax).
- Total hysterectomy with bilateral salpingo-oöphorectomy as primary therapy.

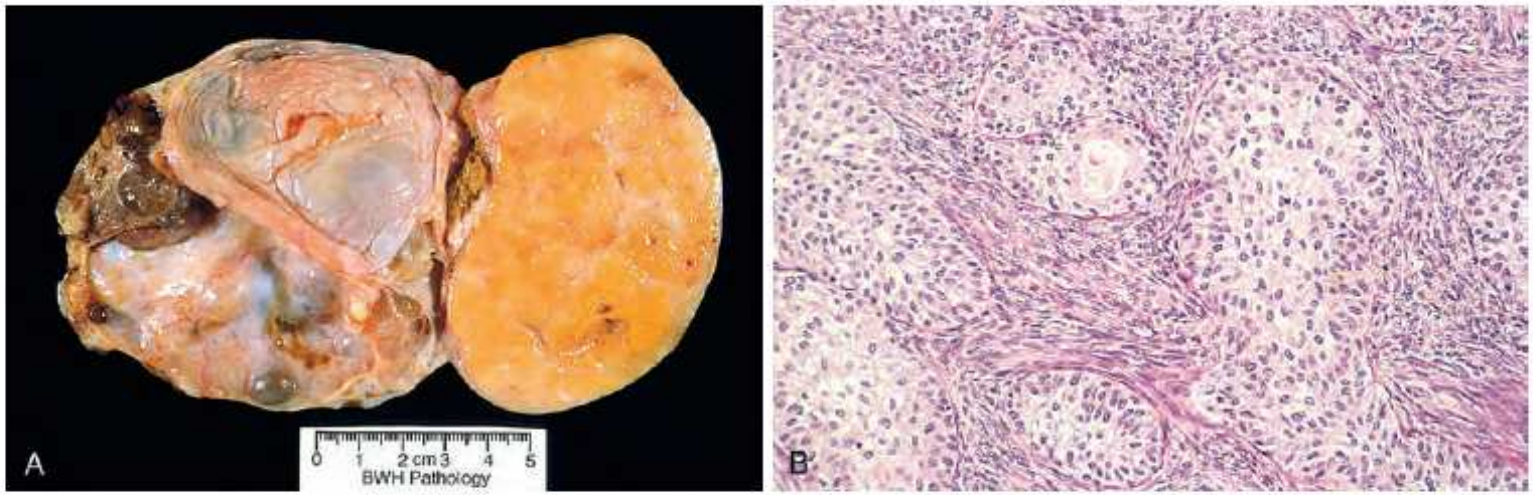


Figure 22-36 Brenner tumor **A,** Brenner tumor *(right)* associated with a benign cystic teratoma *(left)*. **B,** Histologic detail of characteristic epithelial nests within the ovarian stroma. (Courtesy Dr. M. Nucci, Brigham and Women's Hospital, Boston, Mass.)

Germ cell tumors

- 15-20% of ovarian tumors
- Arise from totipotent germ cells.
- Occurs in adolescents and young women. Rapidly enlarging adnexal mass with abdominal pain.
- 95% benign.
- AFP elevated in embryonal and endodermal sinus carcinomas
- HCG elevated in primary choriocarcinoma.

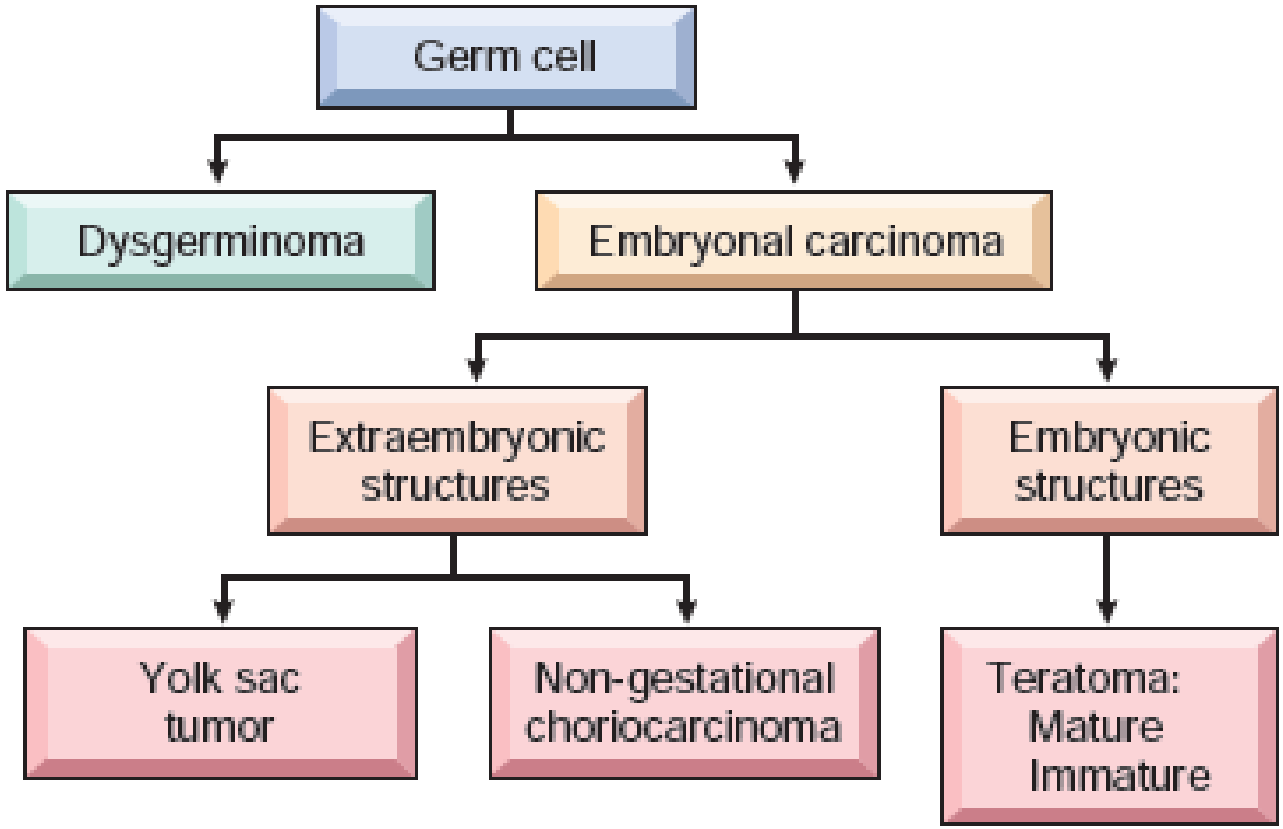
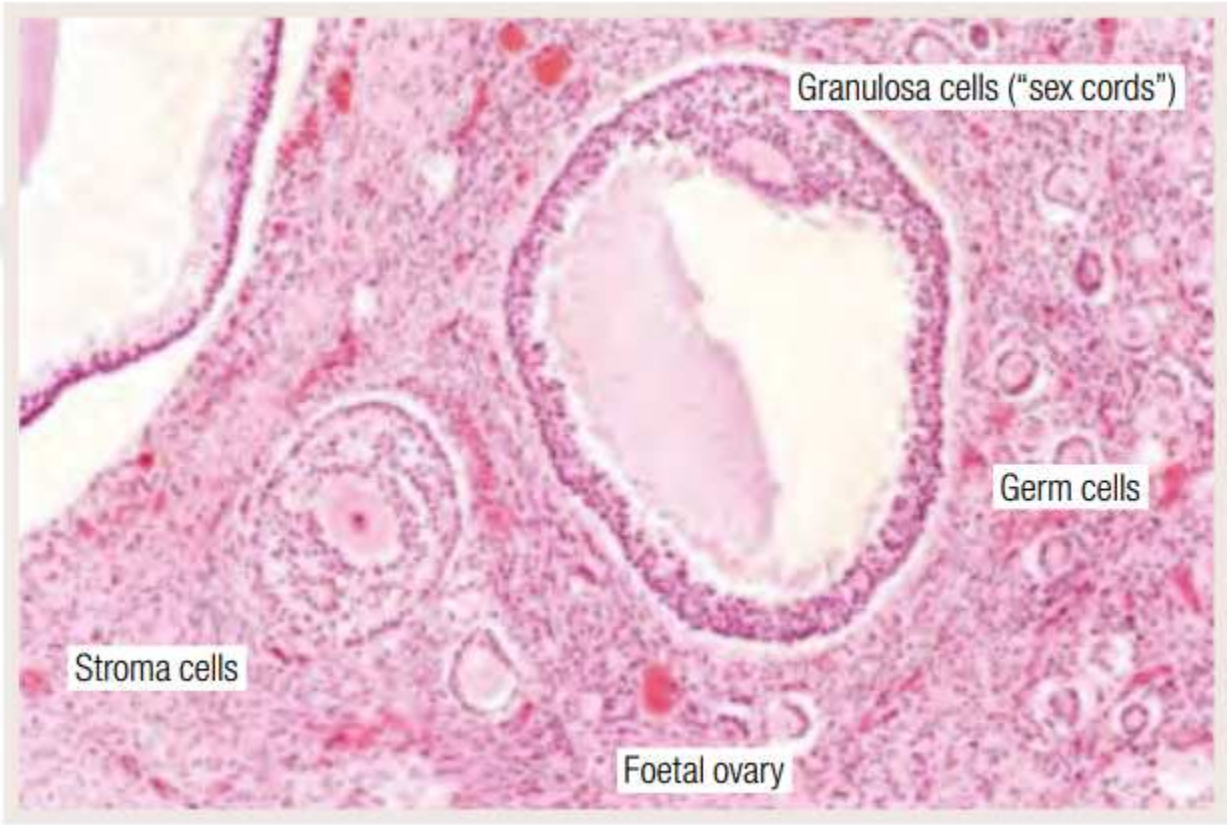


Figure 22-37 Histogenesis and interrelationships of tumors of germ cell origin.

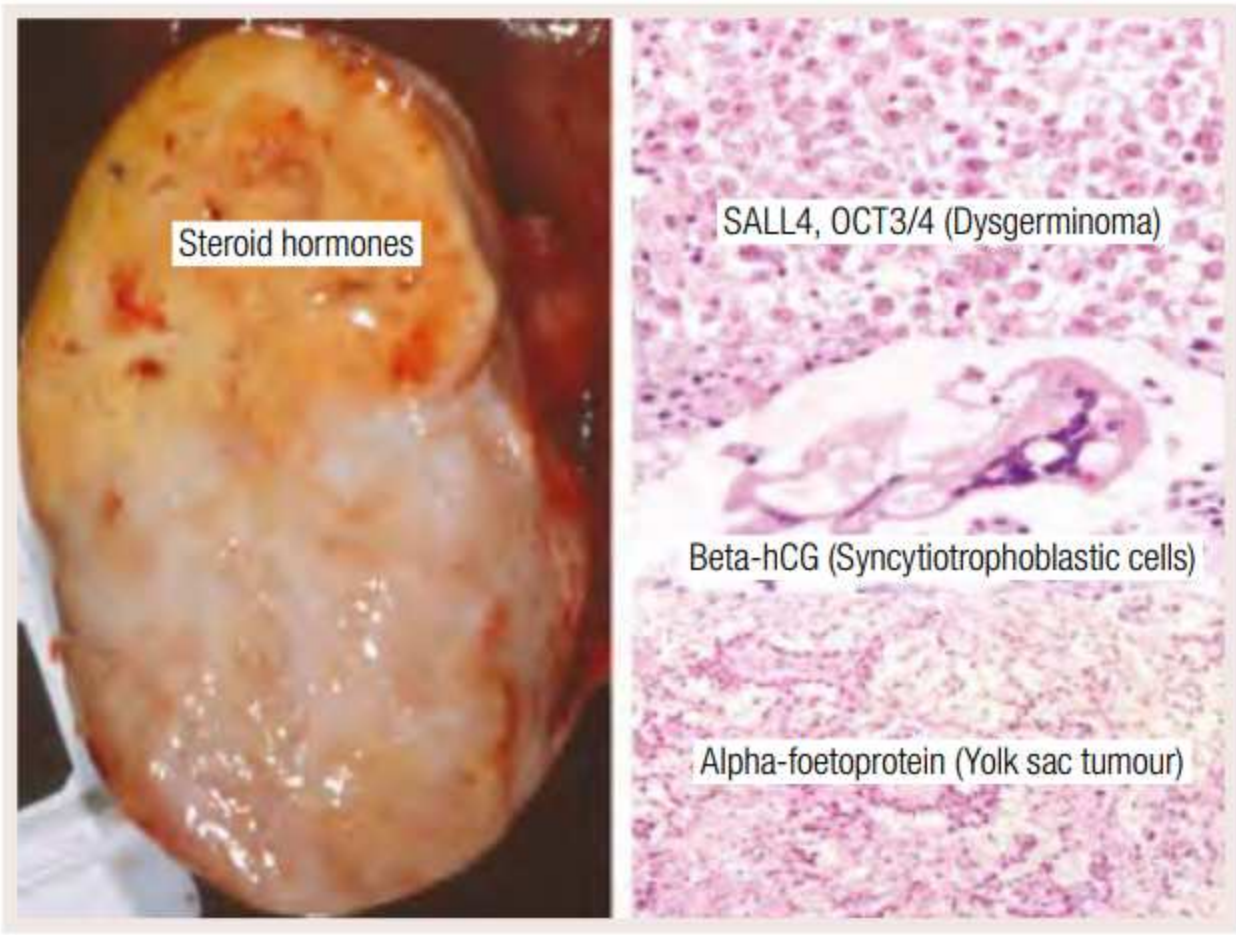

Granulosa cells ("sex cords")
Germ cells
Stroma cells
Foetal ovary

Germ cell tumors

- Most GCTs are benign mature teratomas (dermoid cysts)
- Only rarely may a malignant tumor arise from somatic-type teratomatous tissues.
- Primitive (malignant) GCTs are similar to those occurring in males;
- Include dysgerminoma, yolk sac tumor, embryonal carcinoma, and choriocarcinoma alone or in combination (10%).
- Immature (embryonal) teratomas also are in this group.

Germ cell tumors

- A few occur in subjects with disorders of sexual development (most phenotypically females with Y chromosome) from a mixed germ cell–sex cord stromal tumor (gonadoblastoma).
- Steroid cell tumors can be malignant.


Steroid hormones
SALL4, OCT3/4 (Dysgerminoma)
Beta-hCG (Syncytiotrophoblastic cells)
Alpha-foetoprotein (Yolk sac tumour)

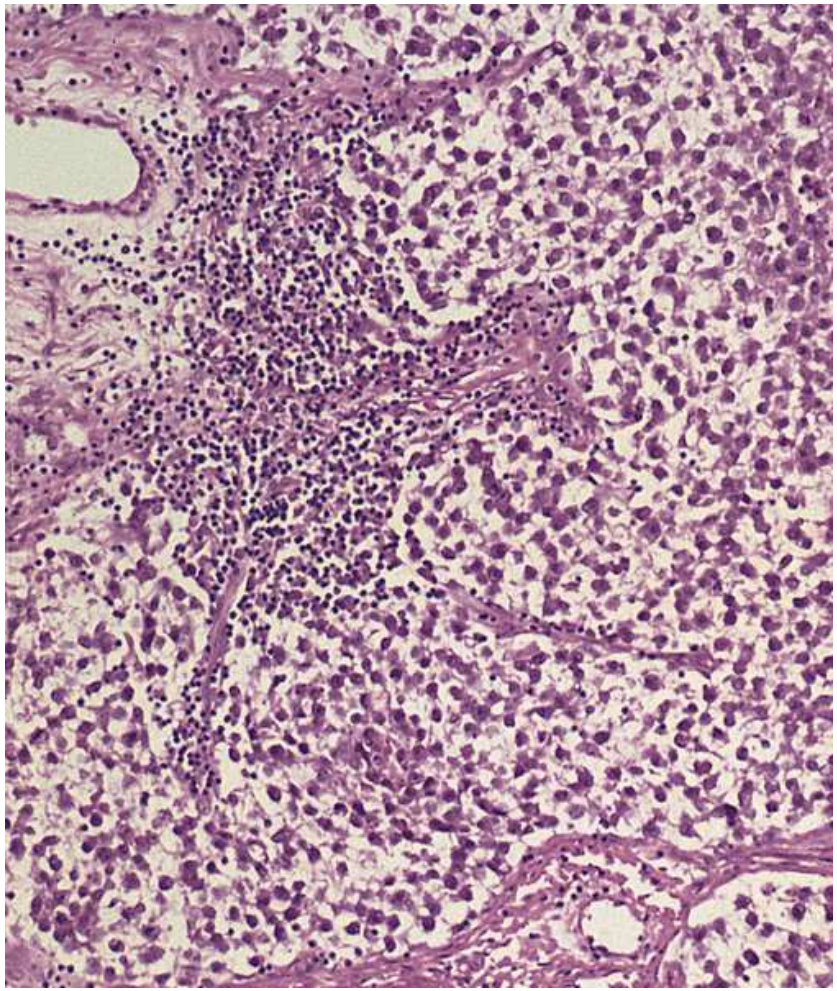
Dysgerminoma

- 50% of malignant ovarian tumors
- 75% occur in teens and twenties
- 90% unilateral
- Counterpart of seminoma in the male
- OCT3/4 and NANOG expressed (reflecting pluripotency)
- 33% have activating C-KIT mutation

Dysgerminoma

- Solid yellow-white to gray-pink appearance
- Composed of large vesicular cells having a clear cytoplasm, well-defined cell boundaries, and centrally placed regular nuclei.
- The tumor cells grow in sheets or cords separated by scant fibrous stroma, which is infiltrated by mature lymphocytes.
- May produce HCG if syncytiotrophoblasts present

Dysgerminoma

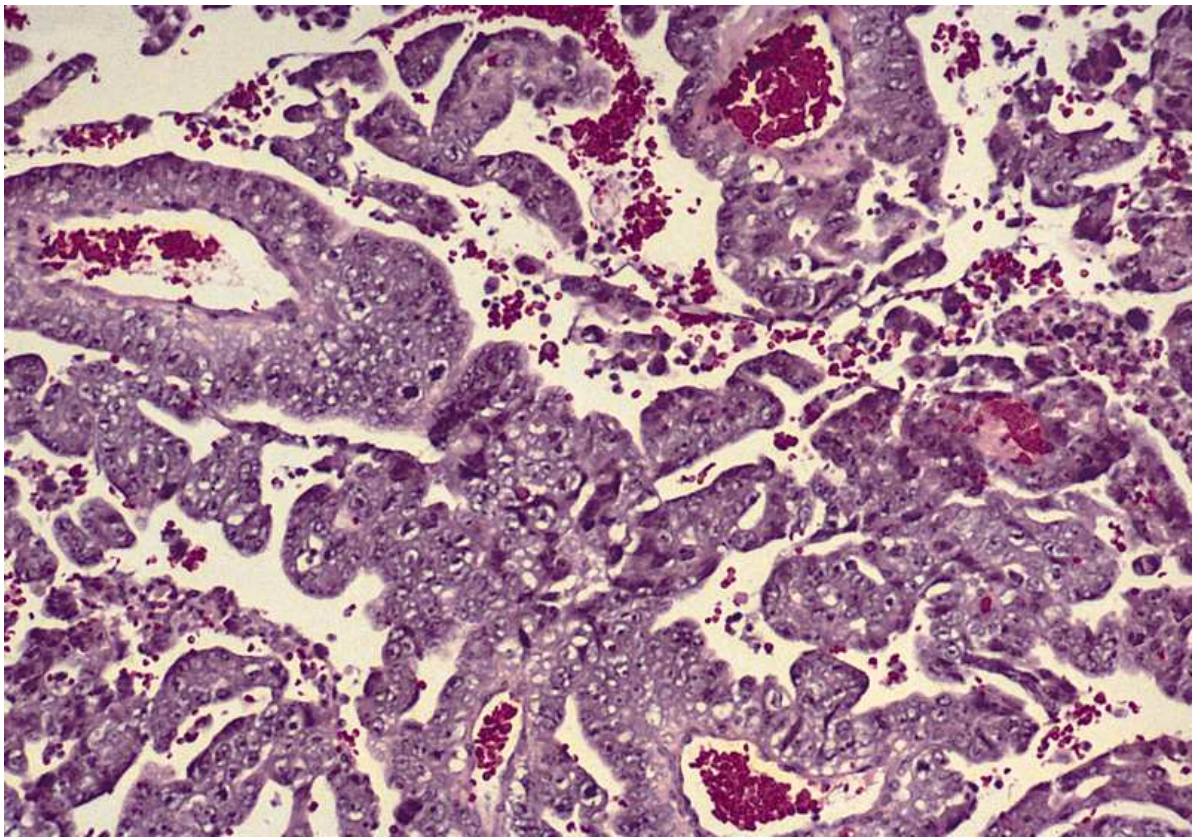


The tumor is composed of uniform cells resembling primordial germ cells in diffuse, insular, trabecular, and cord-like patterns. Rarely, the tumor cells line irregular or rounded gland-like spaces or form solid tubular structures.

Fig. 13-4

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

Embryonal carcinoma



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.

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

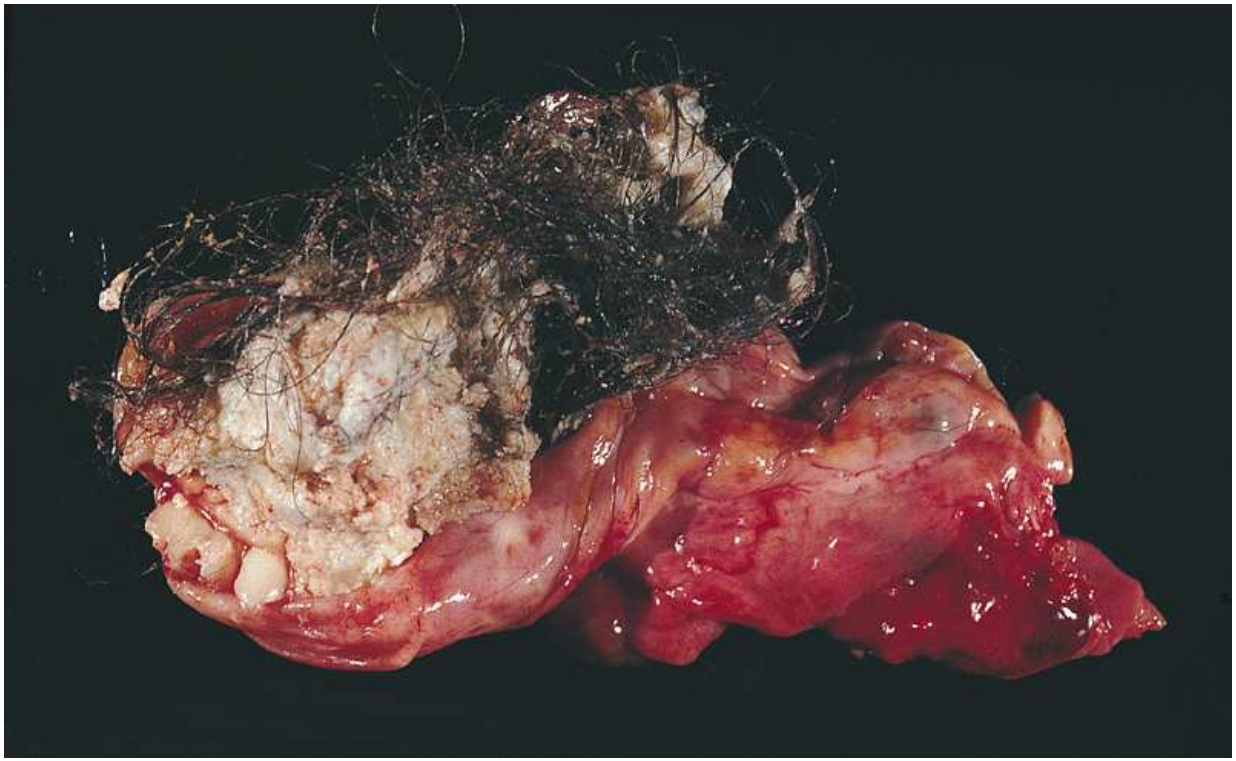
Mature teratoma

- Benign
- Bilateral in 10% to 15% of cases.
- Unilocular cysts containing hair and sebaceous material
- The cyst wall is thin and lined by an opaque, gray-white, wrinkled epidermis, frequently with protruding hair shafts.
- It is common to find grossly evident tooth structures and areas of calcification.

Mature teratoma

- Microscopically, the cyst wall is composed of stratified squamous epithelium with underlying sebaceous glands, hair shafts, and other skin adnexal structures
- Tissues from other germ layers can be identified
- The karyotype of almost all benign ovarian teratomas is 46,XX.
- The majority of teratomas arise from an ovum after the first meiotic division, while a minority arise before the first division.

Mature teratoma (dermoid cyst)



The cyst is filled with hair and sebaceous material. Several teeth are visible.

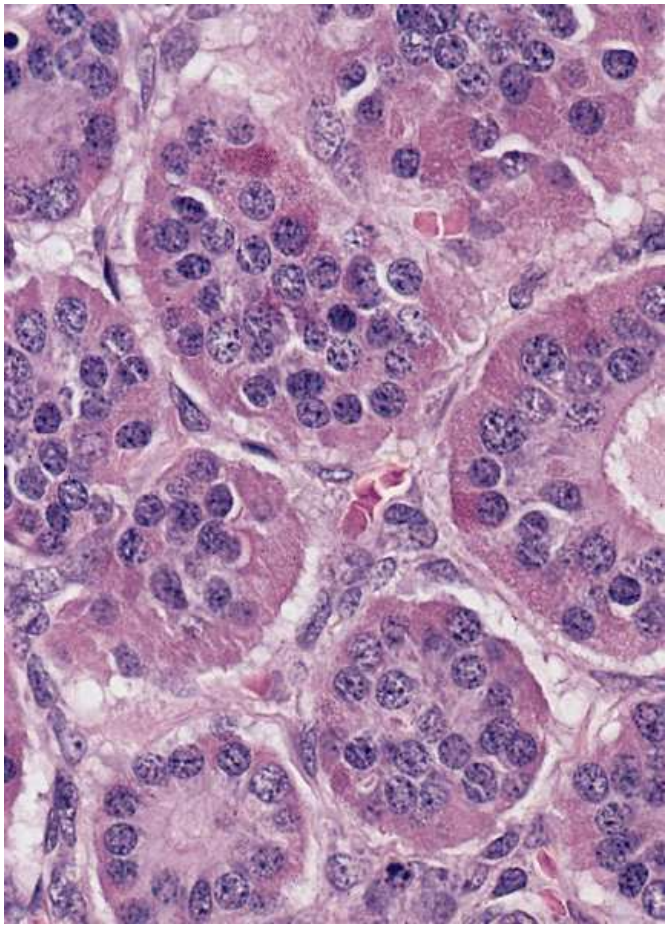
Fig. 14-14

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

Specialized teratoma

- Usually unilateral
- Struma ovarii
- Comprised of mature thyroid tissue
- Carcinoid
- May be functional
- Symptomatic as ovarian veins drain into vena cava
- If bilateral, probably metastasis
- Both struma ovarii and carcinoid may be found in rare tumors

Struma ovarii



The struma may resemble normal thyroid tissue; a thyroid adenoma, with patterns including macrofollicular, microfollicular, pseudotubular, trabecular, and solid (nests or sheets), alone or in combination as demonstrated here; or a thyroid carcinoma. The neoplastic cells typically have bland or minimally atypical. Mitotic activity may be low. Colloid within the follicles often contains birefringent calcium oxalate crystals.

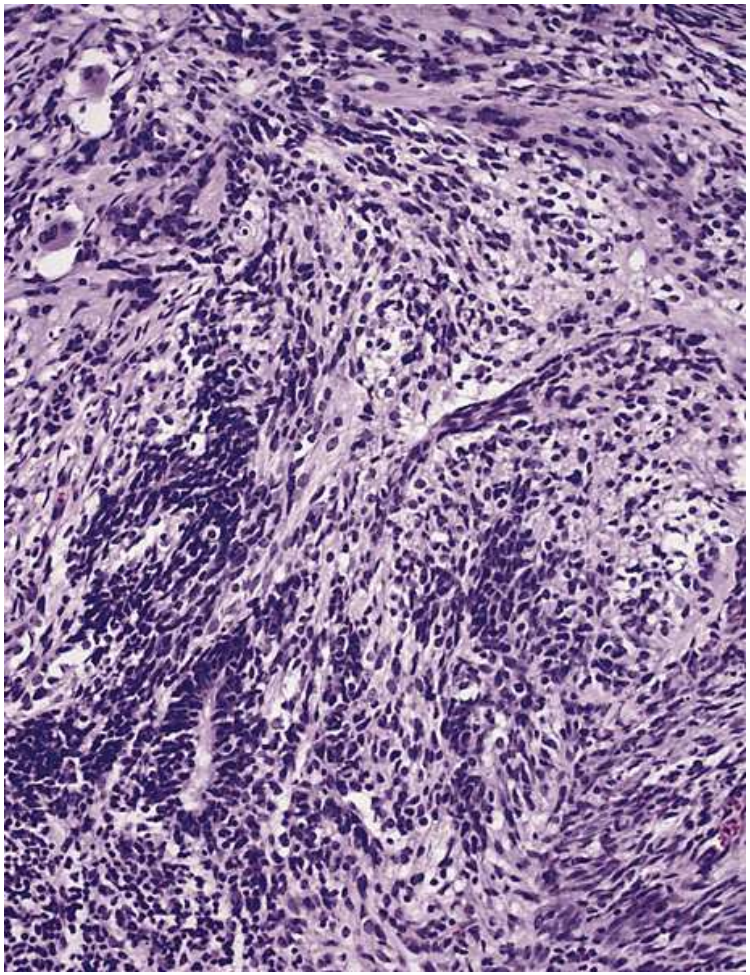
Fig. 15-5

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

Immature teratoma

- Prepubertal adolescents and young women
- Unilateral
- Differ from mature teratoma in that there are varying amounts of immature neuroepithelium, cartilage, bone, muscle, and other elements.
- The extent of immature neural tissue determines the grade (and risk)
- Frequently penetrate the capsule and spread locally (initially)

Immature teratoma



This peritoneal implant is composed exclusively of Immature neuroectodermal tissue.

May be associated with anti-NDMA receptor encephalitis.

Fig. 14-10

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

Yolk sac tumors

- Second most common malignant germ cell tumor
- Reticular pattern
- A loose meshwork of communicating spaces lined by primitive tumor cells with clear cytoplasm, containing glycogen
- Reticular areas frequently merge with microcystic or macrocystic areas.
- Eosinophilic AFP-positive and α_1-antitrypsin hyaline globules present within and outside cytoplasm.

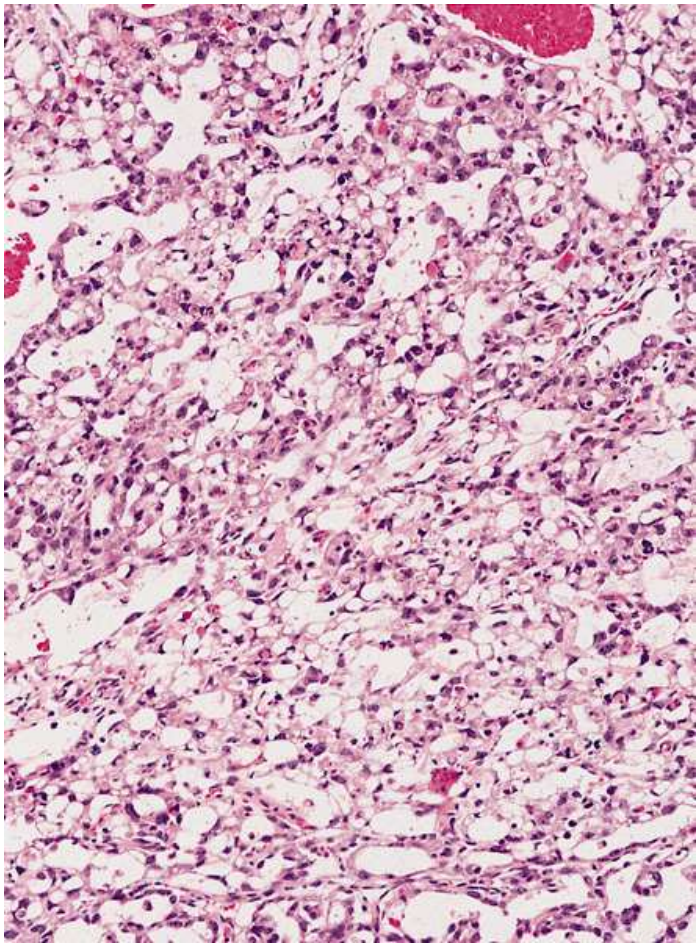
Yolk sac tumors

- Endodermal sinus pattern
- The presence of single papillae superficially resembling a glomerulus, are characteristic of yolk sac tumor
- They are lined by primitive epithelium, with fibrovascular cores containing single vessels and occupying spaces lined by hobnail cells (Schiller-Duval bodies)
-

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 tumor

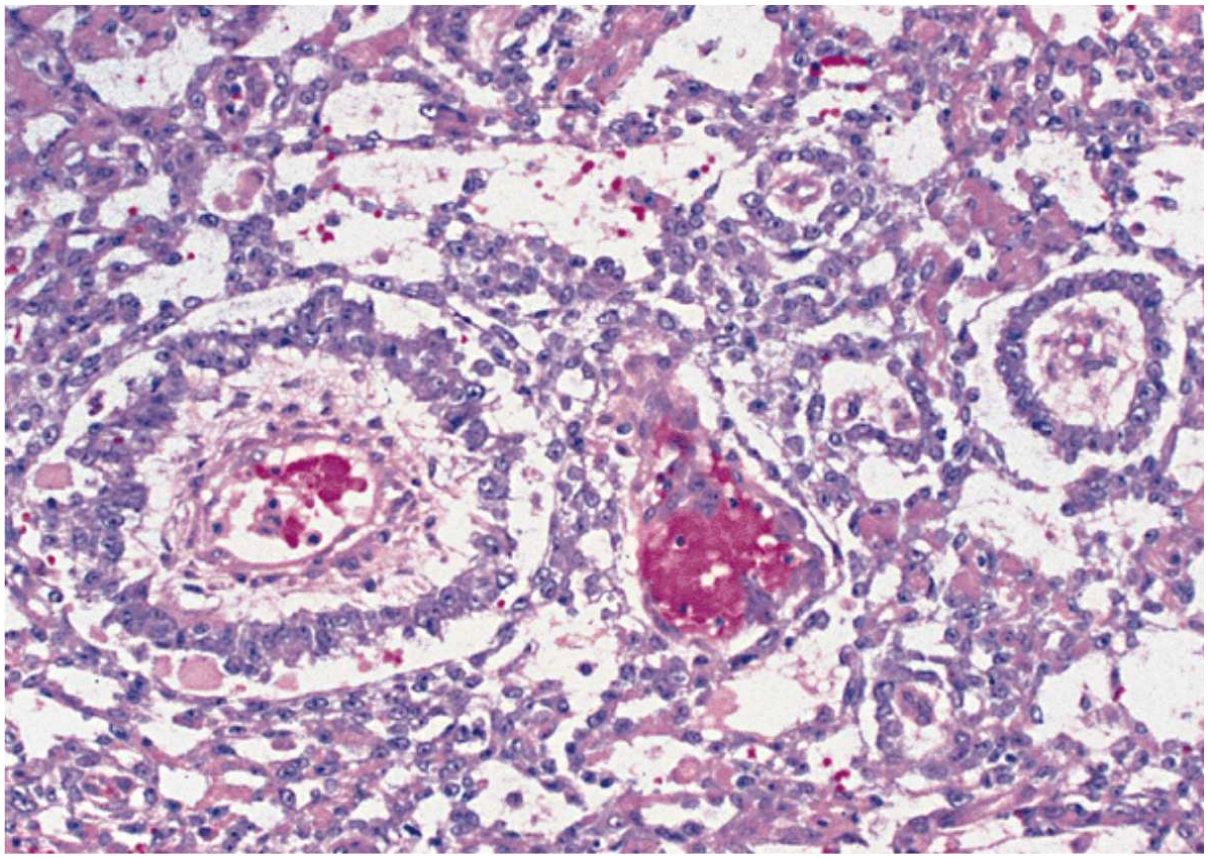


Reticulated pattern. The most common form.

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

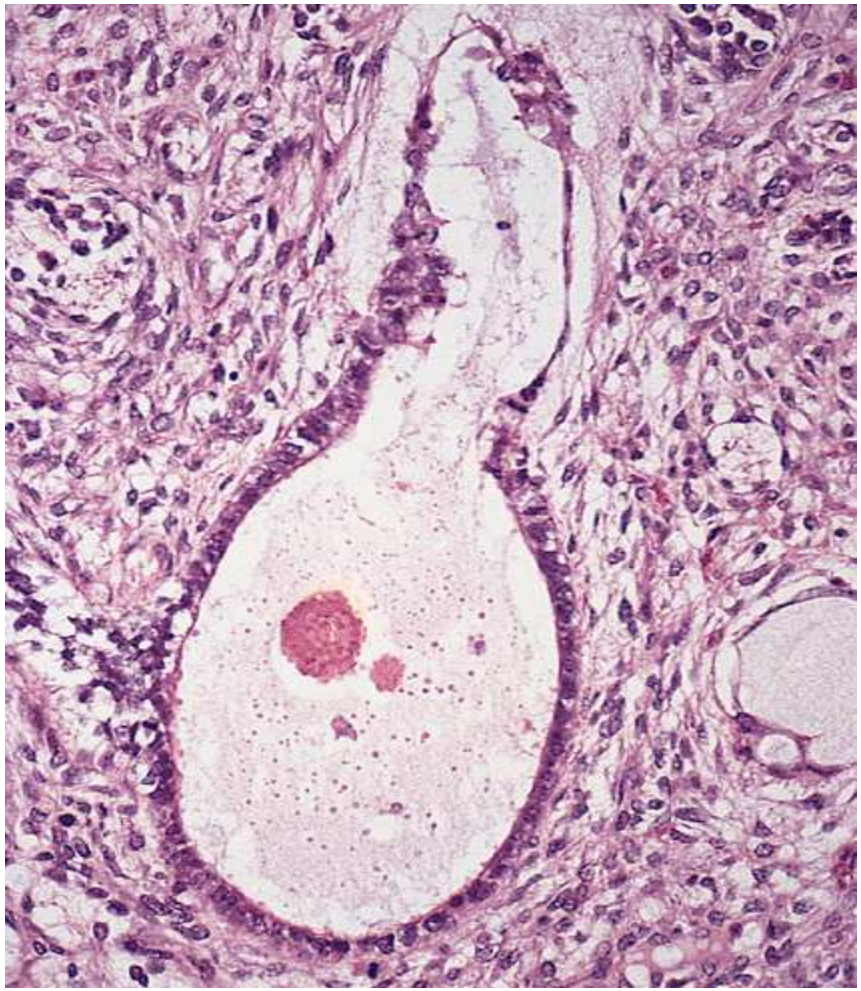


Endodermal sinus pattern.

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.

Yolk sac tumor



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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Choriocarcinoma

- More commonly of placental origin
- An example of extraembryonic differentiation of malignant germ cells.
- It is generally held that a germ cell origin can be confirmed only in prepubertal females, because after this age an origin from an ovarian ectopic pregnancy cannot be excluded.
- Most ovarian choriocarcinomas exist in combination with other germ cell tumors, and pure choriocarcinoma is extremely rare.
- Produce HCG abundantly

Sex cord stromal tumors

- Derived from the ovarian stroma, which in turn is derived from the sex cords of the embryonic gonad.
- The undifferentiated gonadal mesenchyme produces Sertoli and Leydig cells in the male and granulosa and theca cells in the female gonads
- Granulosa and theca cells normally secrete estrogens.
- Tumors are feminizing.
- Leydig cells normally secrete androgens.
- Tumors are masculinizing.

Fibrothecoma

- 4% of ovarian tumors
- 90% unilateral
- Solid, encapsulated, gray-white masses
- Composed of well-differentiated fibroblasts and a scant interspersed collagenous stroma. Focal areas of thecal differentiation may be identified.
- 40% associated with ascites and right hydrothorax (Meig's syndrome)
- Generally benign

Granulosa-theca cell tumors

- 5% of all ovarian tumors
- Commonly bilateral.
- 40-70 years of age.
- May metastasize
- If in pre-puberty, cause precocious feminization
- Rarely, masculinization.
- May see postmenopausal bleeding.
- Juvenile type of different origin

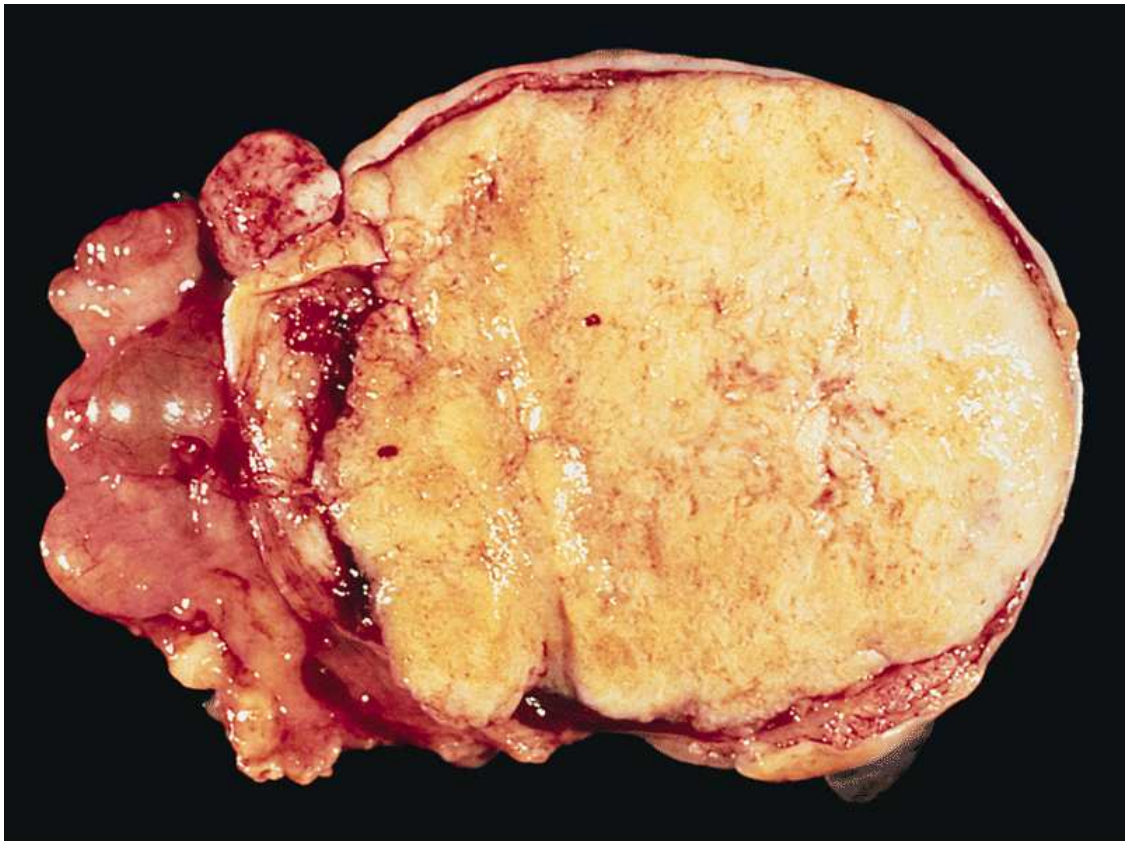
Granulosa-theca cell tumors

- Inhibin levels elevated
- 97% of adult type have FOXL2 mutation
- GATA4 mutations also common
- Controls granulosa cell development
- KRAS activation and PTEN loss are causal
- Loss of GATA4 associated with better prognosis

Granulosa-theca cell tumors

- Tumors that are hormonally active have a yellow coloration to their cut surfaces, due to intracellular lipids.
- Characterized by small, cuboidal to polygonal cells that grow in anastomosing cords, sheets, or strands.
- Small, distinctive, glandlike structures filled with an acidophilic material recall immature follicles (Call-Exner bodies).
- Occasionally, there is a predominant thecoma component that consists of clusters or sheets of cuboidal to polygonal cells.
- Luteinized change may occur.

Granulosa cell tumor

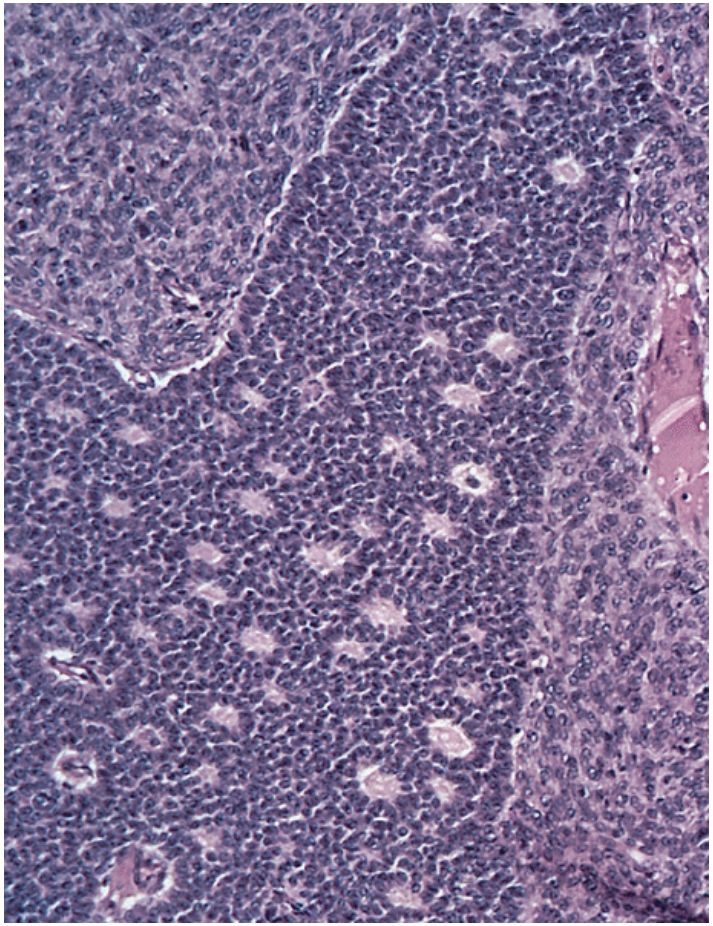


The sectioned surface is uniformly solid and yellow.

Fig. 9-2

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

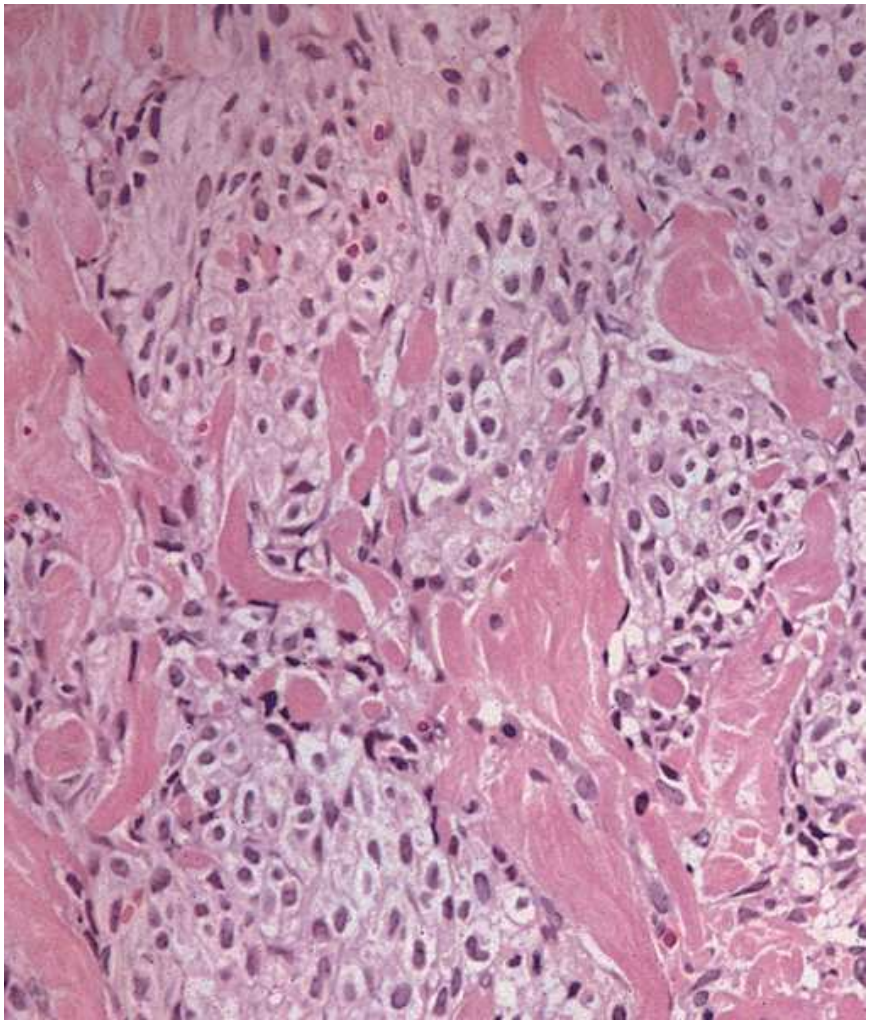


A large, discrete island of granulosa cells contains numerous Call- Exner bodies and is surrounded by a diffuse pattern of granulosa cells.

Fig. 9-7

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

Theca cell tumor



The cytoplasm is abundant and vacuolated or pale and dense; it usually contains moderate to large amounts of lipid. The nuclei vary from round to spindle shaped and typically exhibit little or no atypia; mitotic figures are absent or infrequent. Rarely, large bizarre nuclei with a degenerative appearance are seen. Hyaline plaques are often conspicuous.

Fig. 10-3

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

Sertoli-Leydig cell tumor

- Teens and twenties
- Unilatera;
- These tumors are often functional and commonly produce masculinization or defeminization, but a few have estrogenic effects.
- Produce testosterone as well as other androgens.
- Hirsutism, voice change (deepens), acne, and clitoromegaly.
- DICER1 mutations suggests the genesis of male-directed stromal cells may involve abnormalities of gene expression related to dysregulation of miRNAs.

Sertoli-Leydig cell tumor

- Solid, yellow
- Well-differentiated tumors show tubules composed of Sertoli cells or Leydig cells interspersed with stroma.
- The intermediate forms show only outlines of immature tubules and large eosinophilic Leydig cells.
- The poorly differentiated tumors have a sarcomatous pattern with a disorderly disposition of epithelial cell cords. Leydig cells may be absent.
- Rarely metastasize.

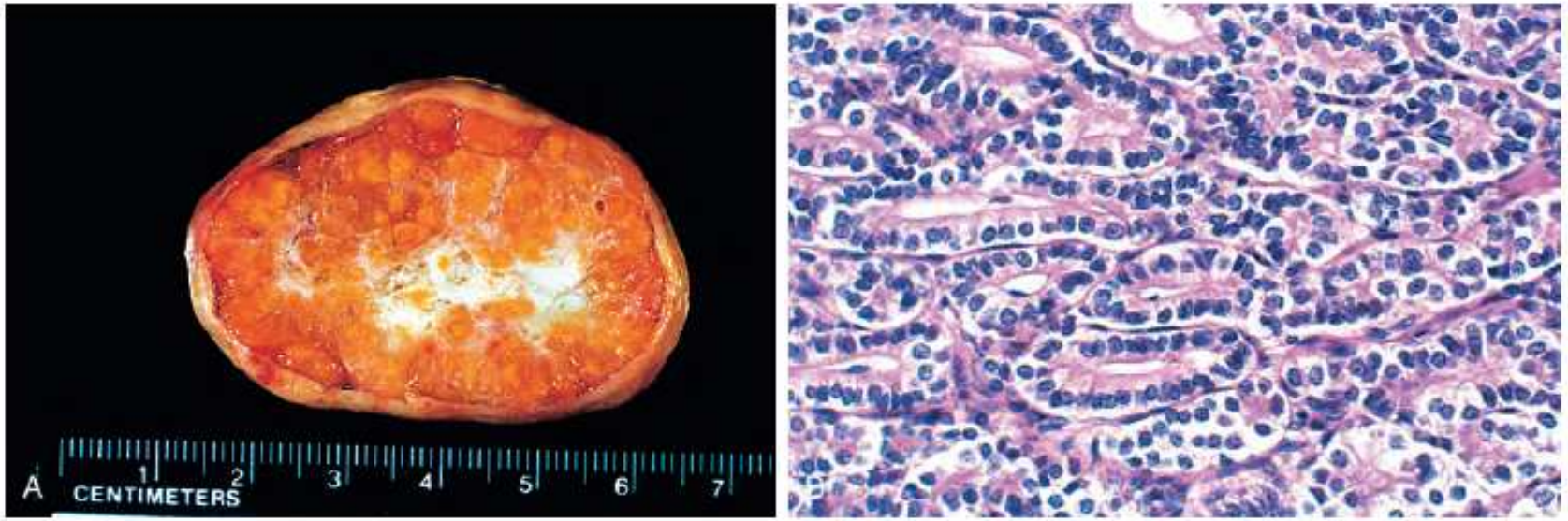
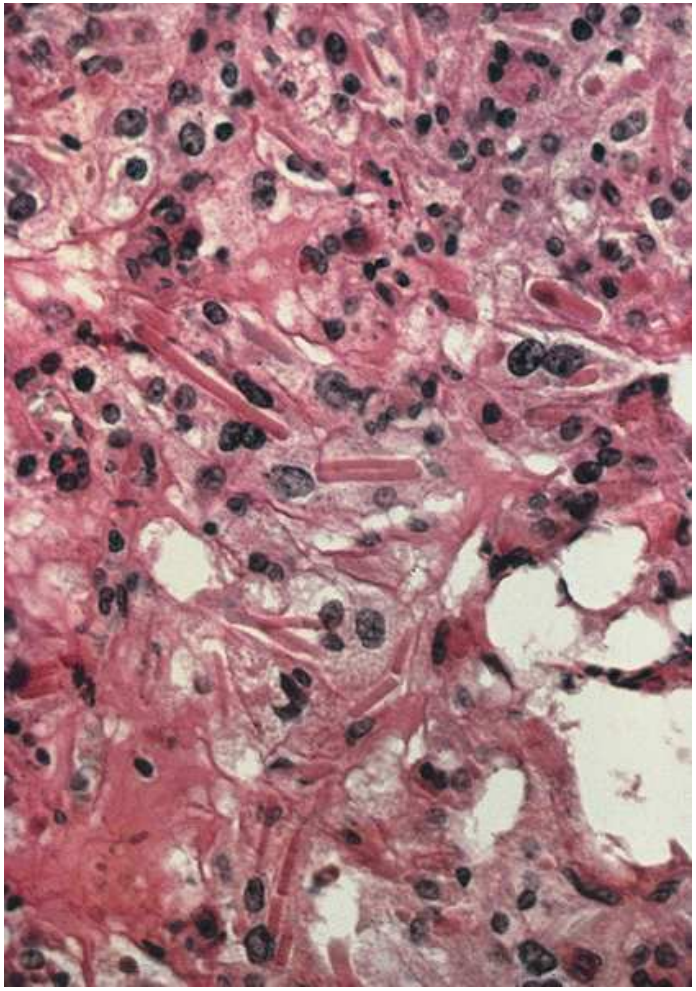


Figure 22-45 Sertoli cell tumor. **A,** Gross photograph illustrating characteristic golden-yellow appearance of the tumor. **B,** Photomicrograph showing well-differentiated Sertoli cell tubules. (Courtesy Dr. William Welch, Brigham and Women's Hospital, Boston, Mass.)

Other ovarian tumors

- Hilus cell tumors (pure Leydig cell tumors)
- Derived from clusters of polygonal cells arranged around hilar vessels.
- Unilateral
- Large lipid-laden Leydig cells with distinct borders and characteristic cytoplasmic structures (Reinke crystalloids).
- Masculinizing as produce testosterone
- Pregnancy luteoma
- Resembles corpus luteum
- May produce virilization in pregnant patients and their female infants.

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.

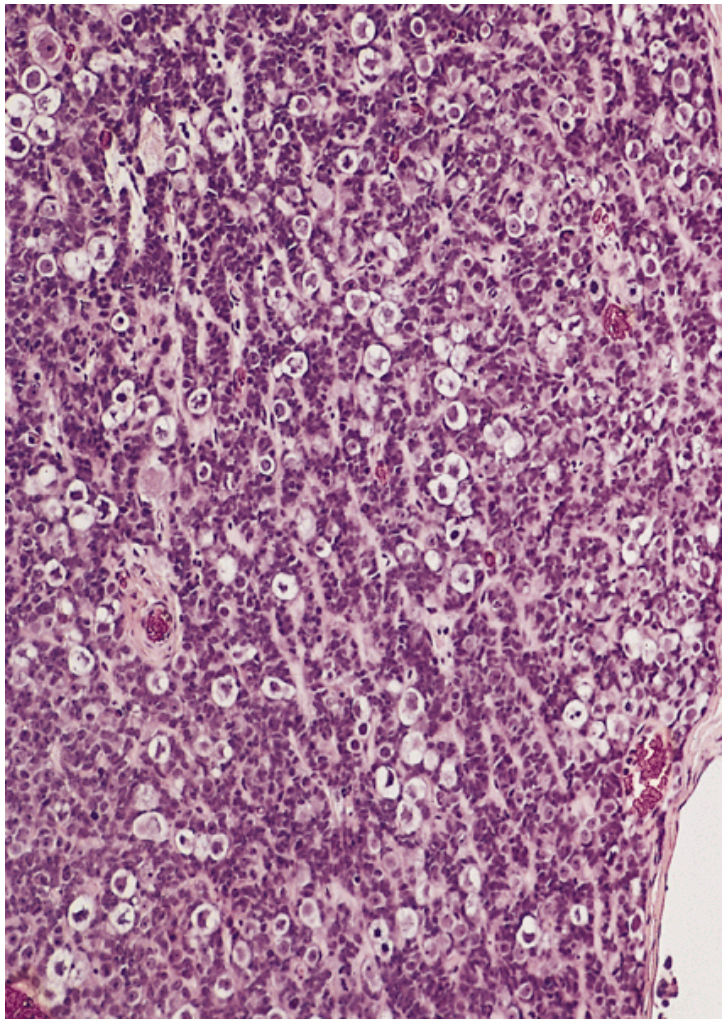
Fig. 12-11

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 ovarian tumors

- Gonadoblastoma
- Composed of germ cells and sex cord-stroma derivatives resembling immature Sertoli and granulosa cells.
- It occurs in individuals with abnormal sexual development and in gonads of indeterminate nature.
- 80%, phenotypic females
- 20%, phenotypic males with undescended testicles and female internal secondary organs.
- A coexistent dysgerminoma occurs in 50% of the cases.

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

Undifferentiated tumors

- Among undifferentiated cancers, some mimic undifferentiated carcinomas of other organs (lung)
- One aggressive type associated with hypercalcemia typically arises in the first decades.
- Metastatic tumors from the gastrointestinal tract may simulate primary mucinous carcinomas.

Therapy

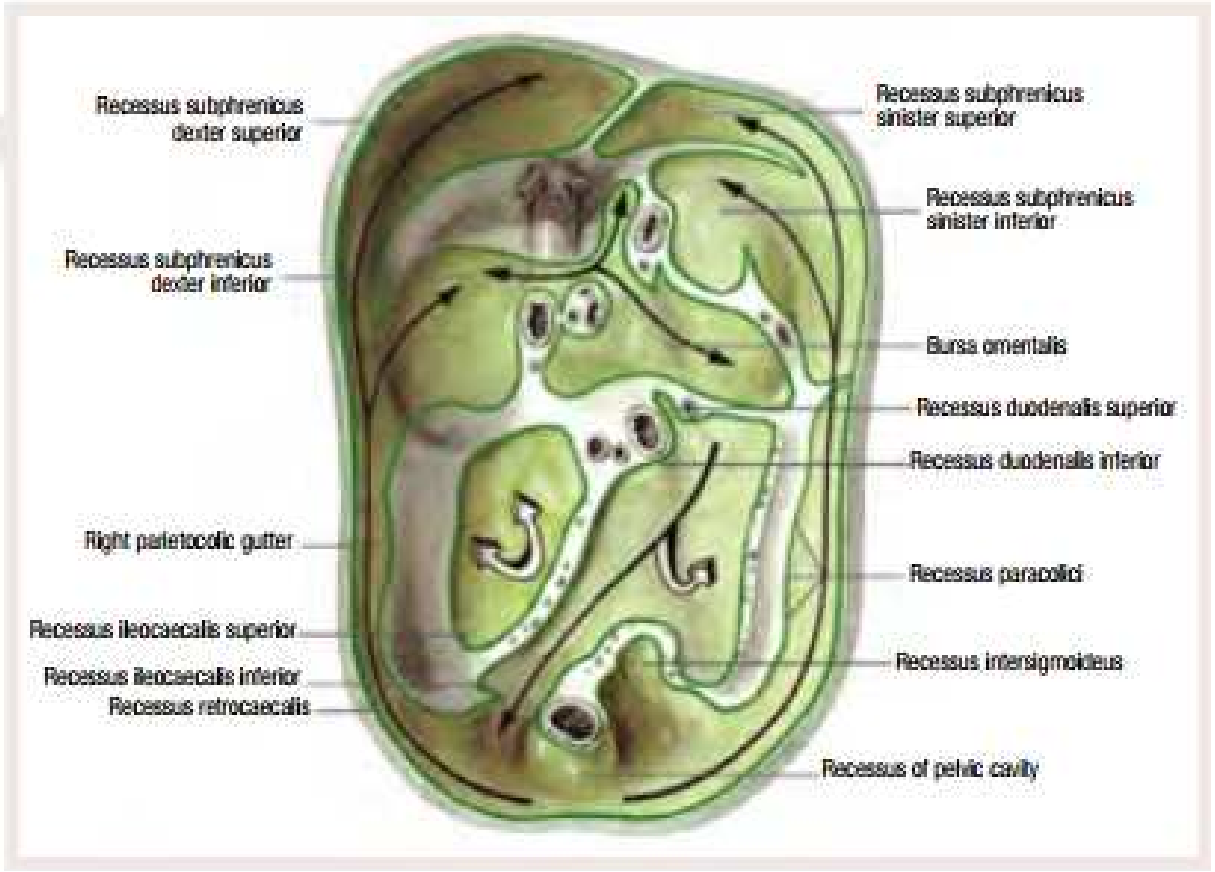
- Complete staging in assumed early-stage ovarian cancer consists of:
- Systematic assessment of the abdominal cavity
- Hysterectomy with bilateral salpingo-oophorectomy, omentectomy, appendectomy (in mucinous histology)
- Peritoneal mapping, peritoneal washing
- Systematic pelvic and para-aortic lymphadenectomy.
- Systematic lymphadenectomy results in detection of metastasis in 22% of patients, compared to 9% with lymph-node sampling only.

Therapy

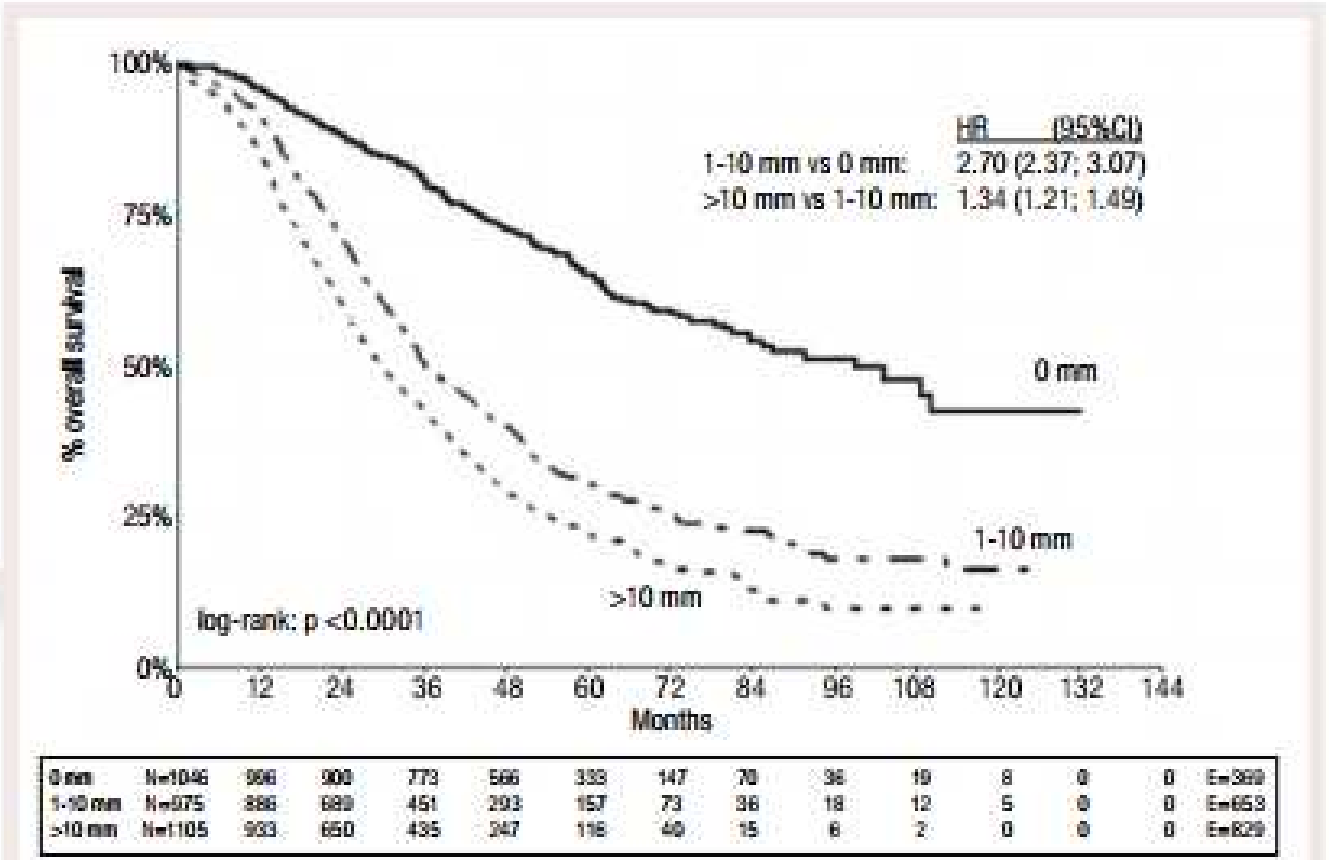
- In case of ovarian cancer confined to one of the ovaries, fertility-sparing surgery should be discussed with women with childbearing potential.
- The overall recurrence rate is higher in fertility-sparing surgery, however.
- Open incision surgery is the standard of care.
- Given the biology and tumor spread of ovarian cancer, complete tactile and visual exploration of the abdomen can only be performed through open surgery.
- Laparascopic and robotic surgery are not recommended

Therapy

- A major principal of surgery in advanced ovarian cancer is the extraperitoneal en-bloc resection of the peritoneum together with the tumor.
- Resection of the sigmoid colon is necessary in about 60%–70% of patients
- The pelvis can be cleared of tumor with this approach.
- Surgical debulking important.
- Residual disease >1mm is associated with poor outcomes.



Sites of tumor spread in the peritoneum (green)



CI, Confidence interval; HR, hazard ratio.

Therapy

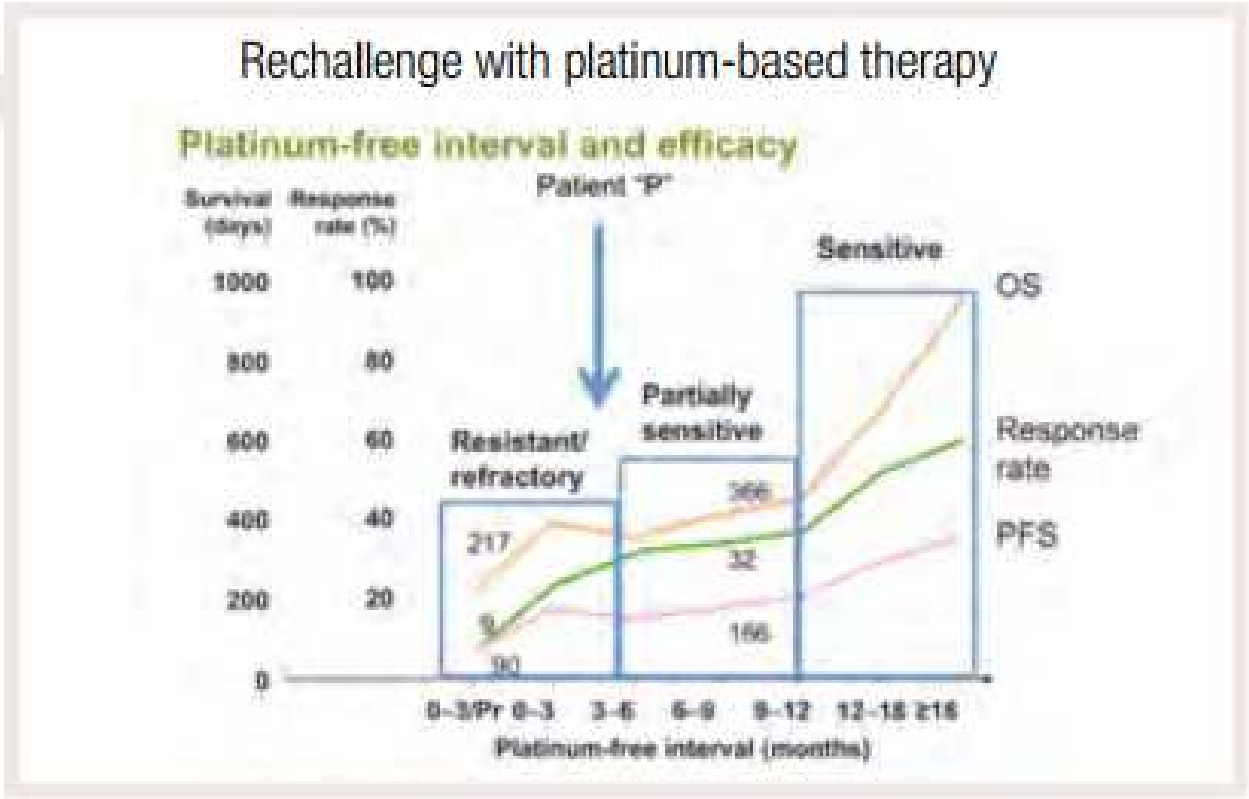
- Adjuvant platinum-based chemotherapy confers an overall survival benefit compared to observation for patients with FIGO Stage 1 ovarian cancer, especially in those with higher grade stage early cancers (G2/3 Stage 1b/c).
- Else, observation alone is acceptable if optimally staged,
- Chemotherapy with carboplatin and paclitaxel is now first line therapy for women with FIGO Stage II-IV ovarian cancer.

Therapy

- The addition of bevacizumab and increasing maintenance to 12 months improves overall survival in those with residual disease
- Intraperitoneal chemotherapy leads to better outcomes.
- 70% of Stage III/IV patients will relapse

Therapy

- A rising CA125 is not a reason to reinstitute chemotherapy (in the absence of the presence of demonstrable tumor)
- Maintenance with the PARP inhibitor, olaparib, improves progression free survival in patients with a germline BRCA mutation.
- There is no agreed upon therapy for platinum resistant tumors.



OS, Overall survival; PFS, progression-free survival.

Therapy

- 25% of chemotherapy treated germ cell tumor patients develop metabolic syndrome
- 2% germ cell tumors relapse after 2 years

Therapy

- Bevacizumab (Anti-VEGF) delays progression in recurrent ovarian cancer as well as in those women with residual tumors >1cm or who are Stage IV at diagnosis.
- Bevacimuzab and olaparpib (PARP inhibitor) enhance response in ovarian adenocarcinoma.