

DISORDERS OF URETER, BLADDER, URETHRA (MALE)

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EMBRYOLOGY AND ANATOMY

Embryology

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

Embryology

- The gonadal ridge contains:
 - Mesenchymal cells (medulla: Leydig's cells)
 - Mesothelial cells (primary sex cord: seminiferous tubules).
- Primordial germ cells enter the primary sex cords as gametes.
- At the 4th week, five ectodermal covered mesenchymal swellings form around the cloacal membrane:
 - The genital tubercle,
 - Two urogenital,
 - Two labioscrotal folds.

Embryology

- The genital tubercle will become the glans penis.
- The gubernaculum forms between the indifferent gonads and the labioscrotal swellings.
- This ligament will guide testes into the scrotum.
- Testis differentiation factor is the transcription product of the SRY gene at Yp11.2.
- Indifferent gonads differentiate into coiled solid testis cords
- The ends stay straight and join near the hilum to form the rete testes.

Embryology

- The rete testes and mesonephric tubule remnants become efferent ductules.
- The mesenchyme thickens into the tunica albuginea.
- The testes enlarge and separate from the mesonephros, following the lower gubernaculum to reach the scrotum via the inguinal canal.
- The upper gubernacula then degenerate.
- The process vaginalis (peritoneum) also descends with the layers of the abdominal wall (forming the scrotal wall) and remains as the tunica vaginalis.

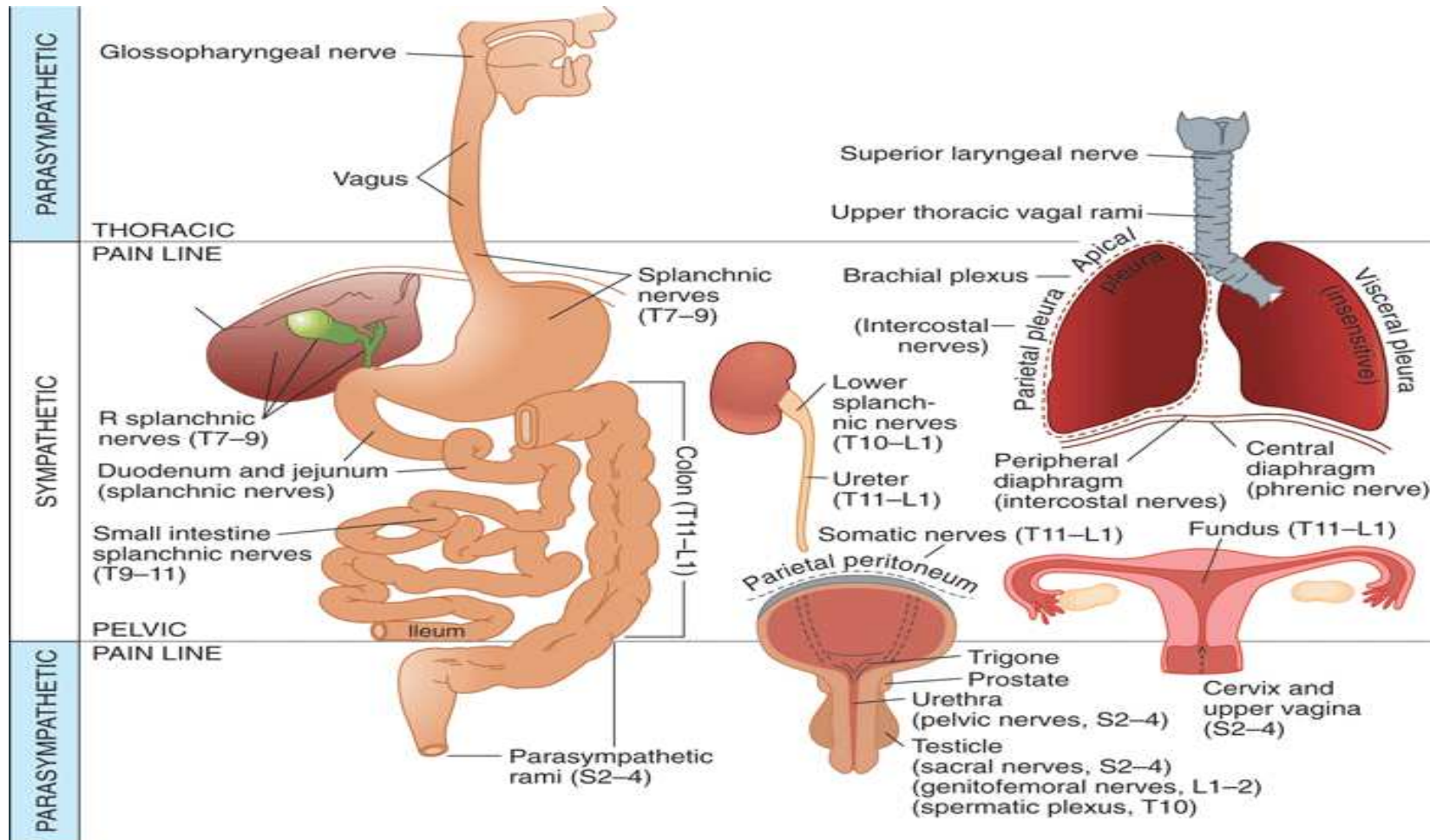
Embryology

- At the 8th week, Sertoli's cells secrete Müllerian inhibiting substance which induces regression of the paramesonephric duct.
- Leydig's cells begin to secrete androgens
- Mesonephric (Wolffian) ducts differentiate into epididymis, ductus deferens, ejaculatory duct, and seminal vesicles.
- The prostate forms as an endodermal outgrowth from the urogenital sinus that forms the prostatic urethra.
- Mesoderm from mesonephric and paramesonephric duct remnants may be found in the median lobe.

Anatomy

- Parasympathetic fibers of the cavernous nerves course independently from the pudendal nerve.
- They arise from the prostatic plexus (men) or vesical plexus (women) and terminate on the arteries of the erectile bodies.
- The glans drains to deep inguinal lymph nodes.
- The spongy and bulbar urethra drain to deep inguinal and internal iliac nodes.
- The skin of penis and scrotum drain to superficial inguinal nodes.

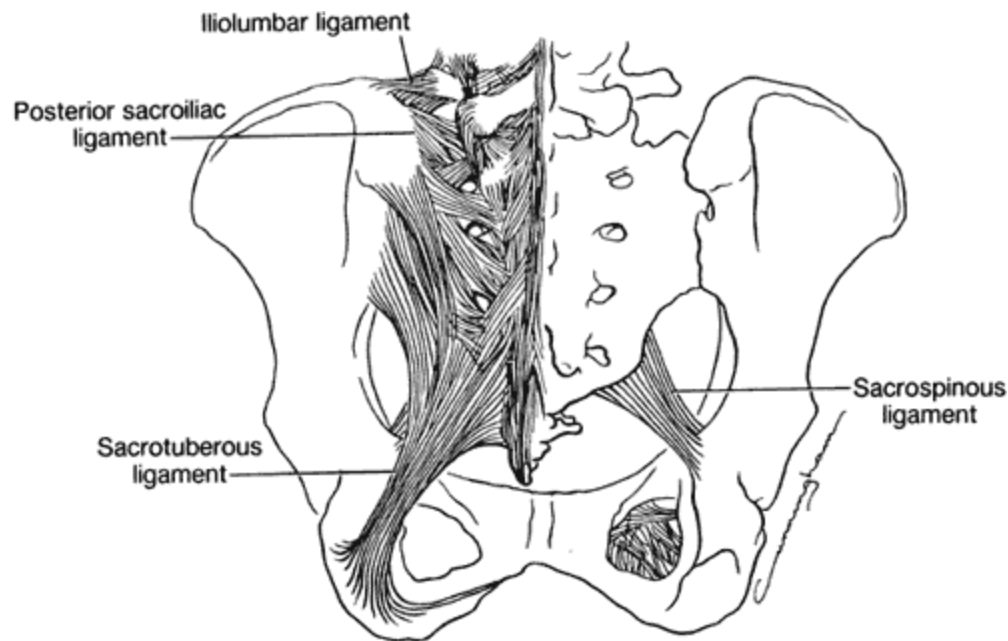
Pain innervation of the viscera



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

Pelvis



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.

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Source: Tintinalli JE, Kelen GD, Stapczynski JS: *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th Edition: <http://www.accessemergencymedicine.com>
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Fig. 273-1 Accessed 05/05/2010

Pelvis

- Consists of:
- The two innominate bones (ilium, ischium, and pubis)
- The sacrum
- 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.

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.

Pelvis

- 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

- 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.
- The anterior superior iliac spine and pubic tubercle lie in the same vertical plane.

Muscles of the pelvis

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

Pelvis

- The anterior division of the internal iliac artery provides the umbilical (and superior vesical), obturator, inferior vesical, middle rectal, internal pudendal and superficial gluteal arteries.
- In the female, the uterine and vaginal arteries also arise from the internal iliac.
- The posterior division provides the superior gluteal, lateral sacral, and iliolumbar arteries.

Pelvis

- The obturator 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 pudendal nerve innervates all muscles of the perineum.
- The inferior rectal nerve, perineal nerve, and dorsal nerve of the penis branch are from the pudendal nerve.

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 Cowper's glands.

Perineum

- Boundaries of the pelvic outlet are:
- The pubic symphysis
- Ischiopubic rami
- Ischial tuberosities,
- Sacro-tuberous ligaments
- The coccyx.
- A horizontal plane between the ischial tuberosities divides the urogenital triangle (anterior) from the anal triangle (posterior).

Perineum

- The ischioanal fossa is bounded by the anal canal and levator ani and the fascia overlying the obturator internus.
- The pudendal canal lies within the fascia of the obturator internus. The levator ani joins the fascia of the obturator internus and forms the apex of the fossa.
- Posteriorly, the coccyx bounds the fossa.

Sphincters

- The external anal sphincter constricts the anal canal during peristalsis (resisting defecation).
- Under volitional control
- Parasympathetic innervation
- It supports and fixes the perineal body and the pelvic floor.
- The bulbospongiosus muscle supports and fixes the perineal body and pelvic floor.
- It compresses the bulb of the penis to expel urine or semen.
- It assists erection by compressing outflow via the deep perineal vein and by pushing blood from the bulb into the body of the penis.

Sphincters

- The ischiocavernosus muscles maintain erection of the penis by compressing outflow veins and by pushing blood from the root of the clitoris into the body of the penis.
- The superficial and deep transverse perineal muscles support and fix the perineal body and pelvic floor to support abdominal-pelvic viscera and resist increased intra-abdominal pressure.
- The external urethra sphincter surrounds the urethra superior to the perineal membrane and ascends the anterior aspect of the prostate.
- It compresses the urethra to maintain urinary continence.
- Volitional control

Penis

- In the superficial perineal space are found the crura and bulb of the penis.
- The corpus cavernosa are paired.
- Each is continuous with the crus.
- Deep arteries lie within the corpus cavernosa to supply the erectile tissue.
- The corpus spongiosum is unpaired and contains the urethra.
- It is continuous with the bulb and the glans.
- Supplied by dorsal artery.

Penis

- Dorsal vein of the penis drains to the external pudendal (to the great saphenous).
- Deep veins drain to the prostatic plexus.
- Glans drains to deep inguinal lymph nodes.

URETERS, BLADDER, AND URETHRA

Ureters

- Run in retroperitoneum from kidneys to bladder
- Narrowed at:
 - Utero-pelvic junction (UPJ)
 - Where they cross the iliac arteries, and
 - 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)

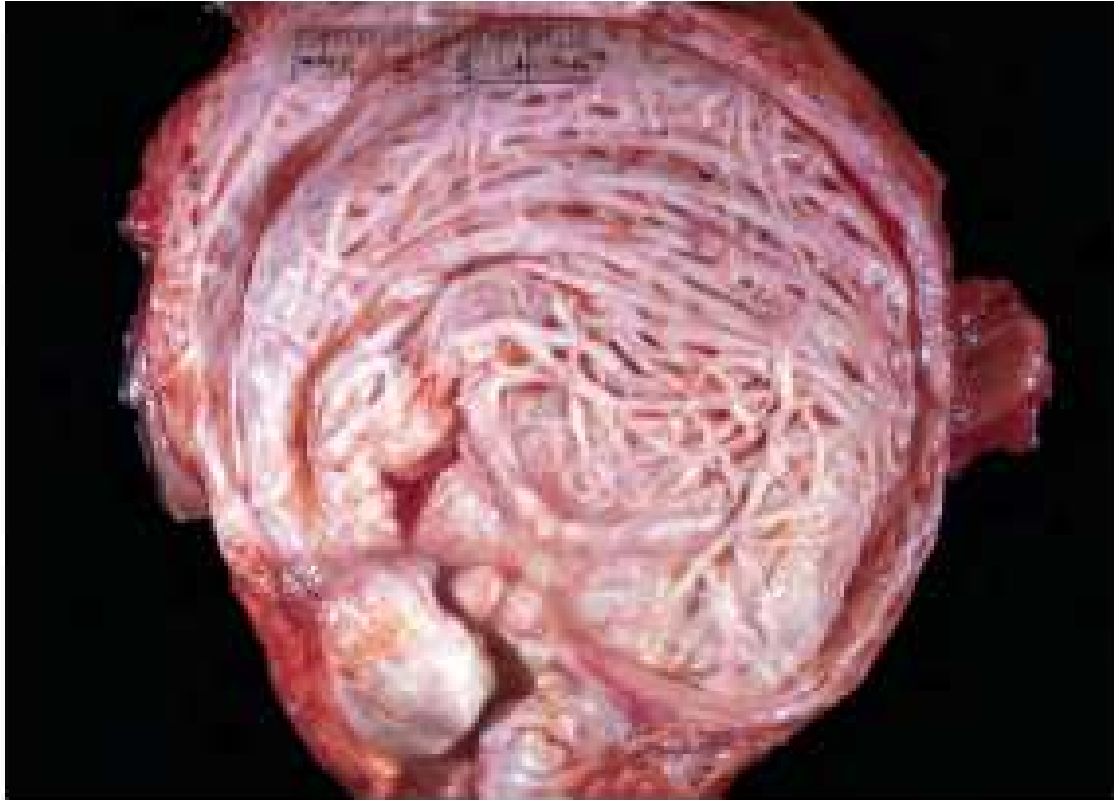


Figure 21-13 Hypertrophy and trabeculation of bladder wall secondary to polypoid hyperplasia of the prostate.

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.

Ureteral cancer

- Ureteral carcinoma may present with ureteral obstruction
- And retrograde hydronephrosis or shrunken kidney depending upon time course.
- Painless hematuria may also be seen.
- Papillary lesions
- 9p- or 9q- abnormalities found in up to 60% of urothelial lesions
- (9p21 involves p16/INK4 α as well as the related tumor suppressor gene p15).
- With loss of chromosome 9, frank invasion identified.

Ureteral cancer

- 17p- found in carcinomas (p53).
- Flat lesions
- FGFR3/ cyclin D mutation (11p-)
- Inverted papilloma cured by excision (not malignant).
- Excise and stent ureteral carcinomas.

Urothelial (transitional) cell carcinoma

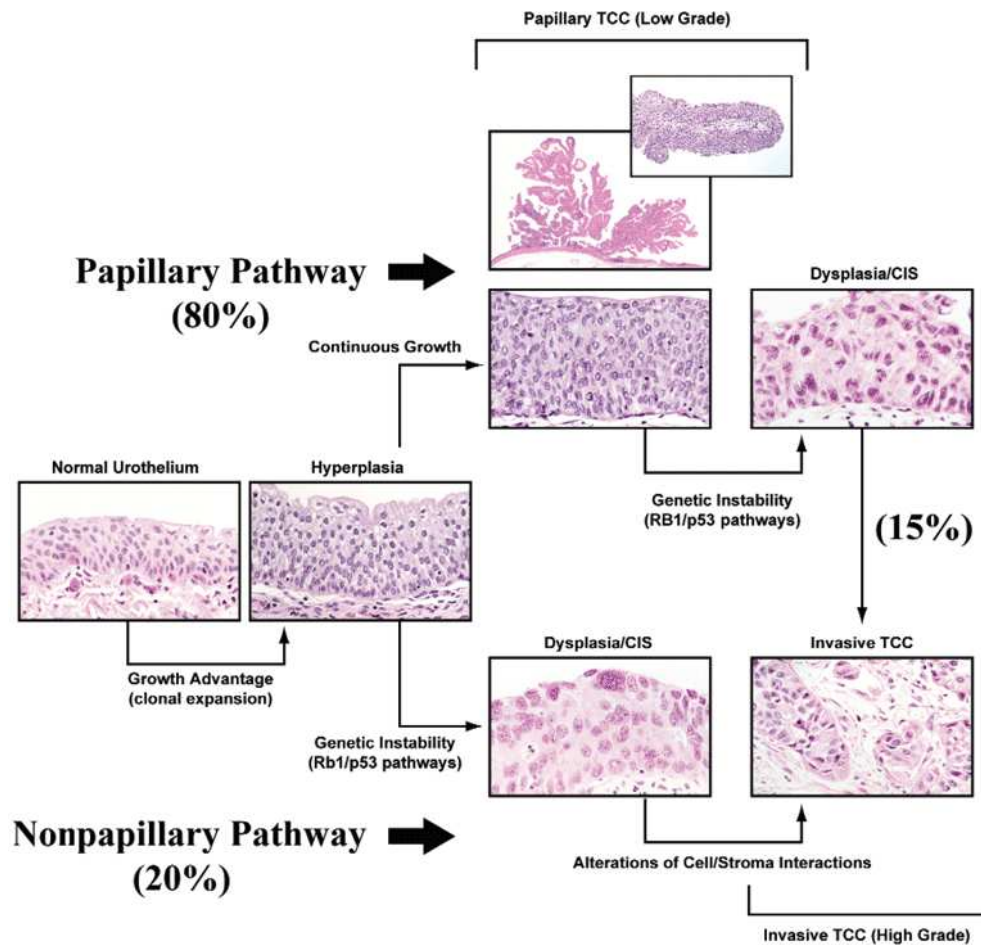
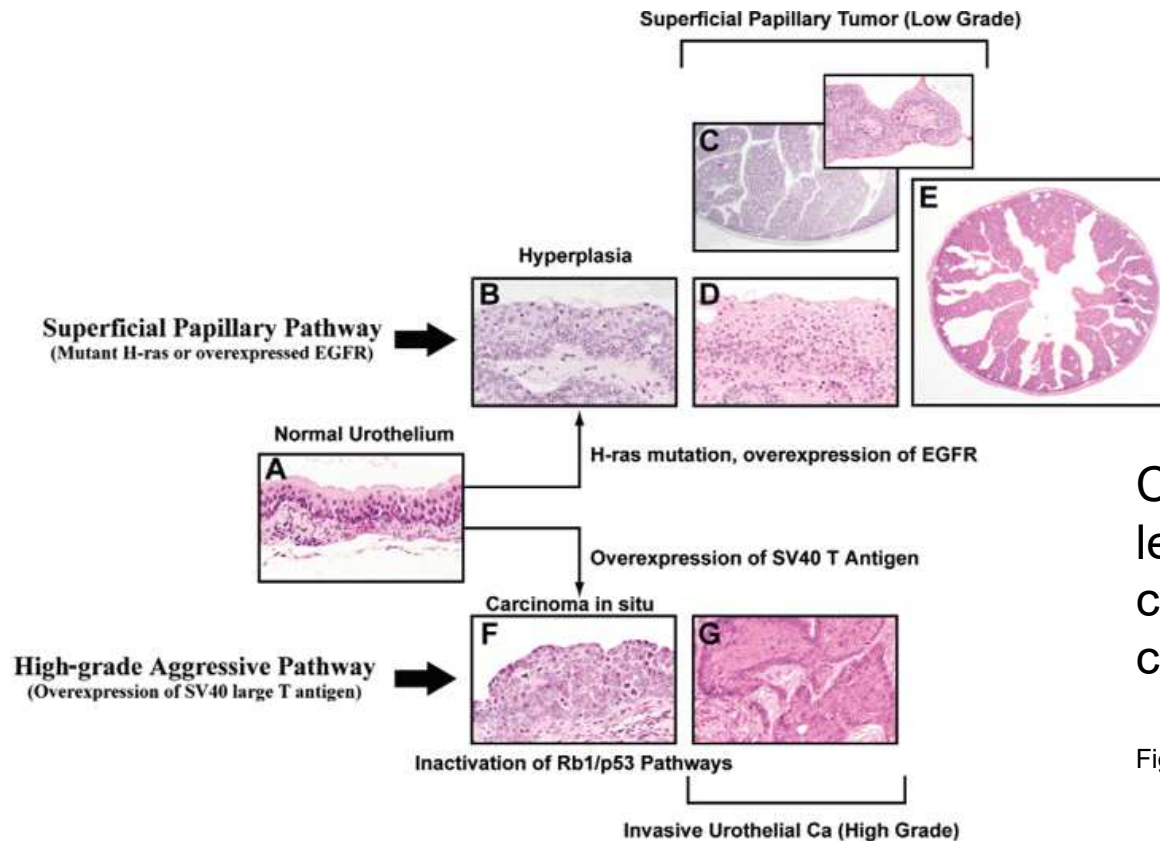


Fig. 28-1
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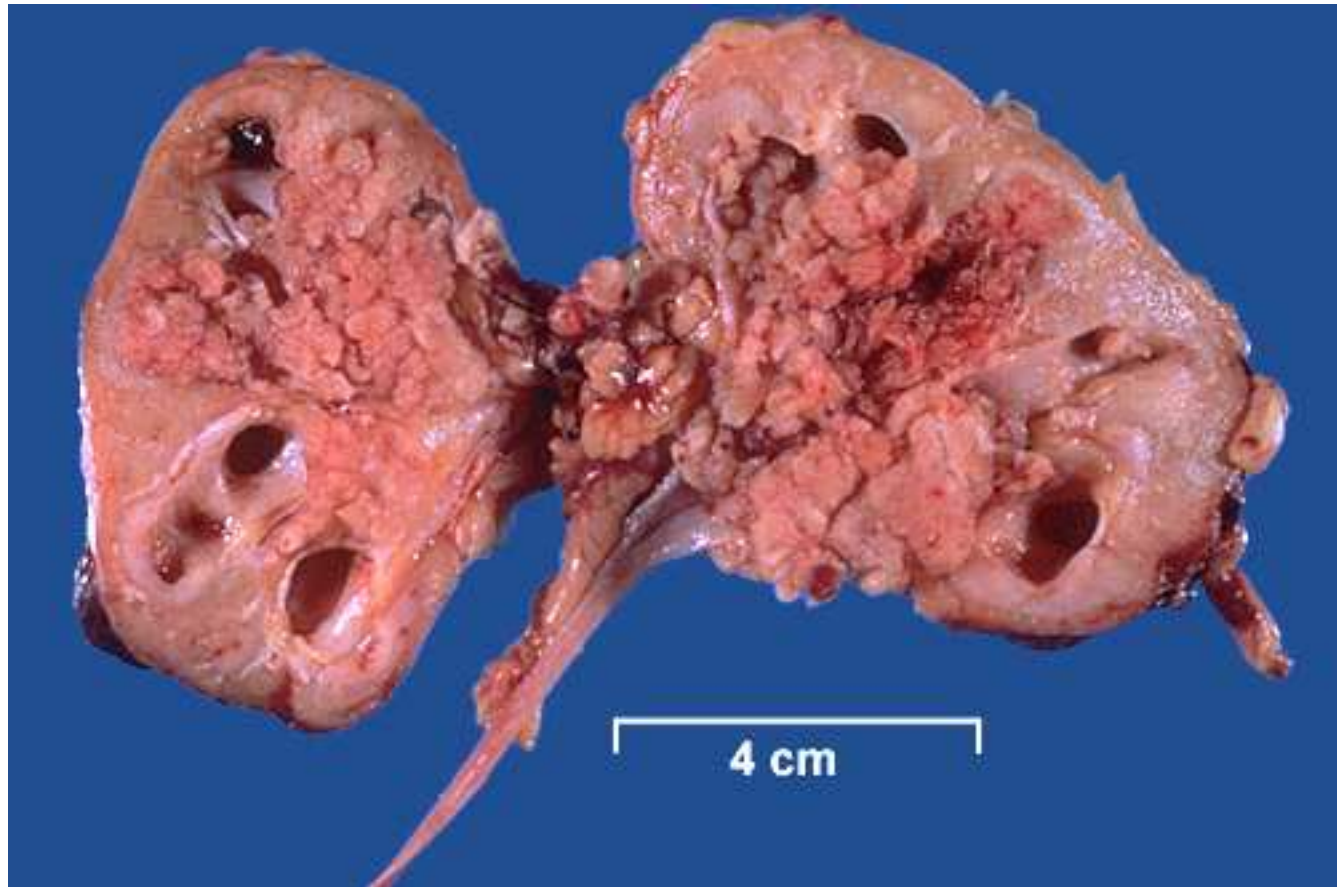
Urothelial (transitional) cell carcinoma



Characteristic genetic lesions in transitional cell carcinoma carcinogenesis.

Fig. 28-2 Accessed 08/01/2010

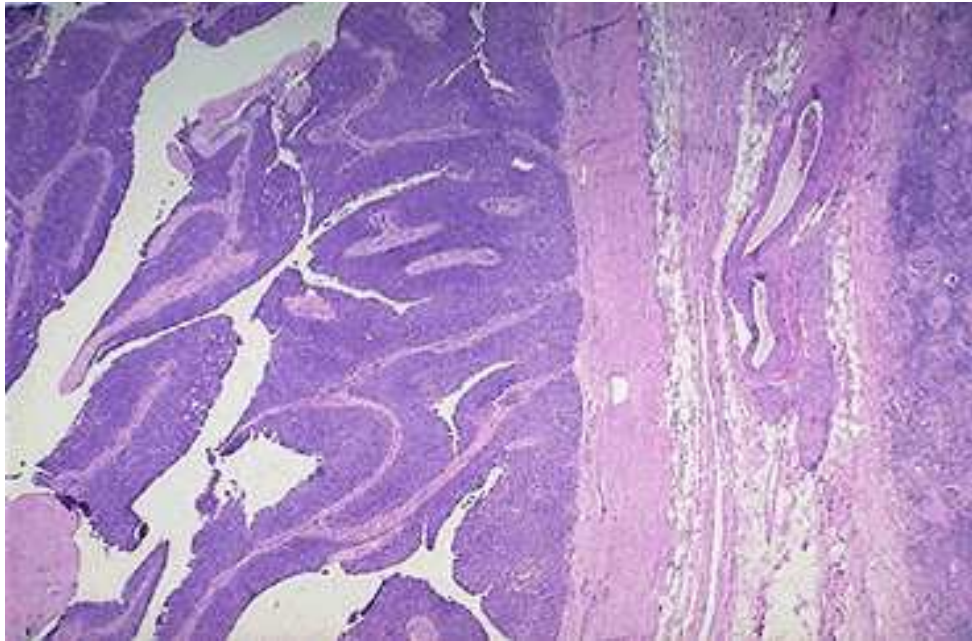
Urothelial cancer



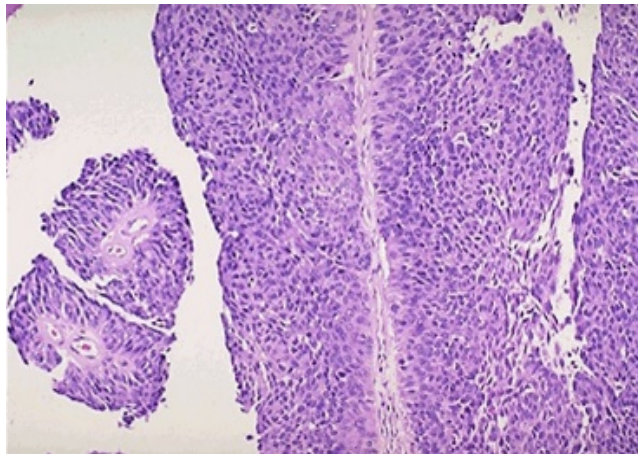
There is invasion of the renal parenchyma with obstruction and dilatation of the pelvis and the calyces to produce hydronephrosis.

<https://webpath.med.utah.edu/RENAHTML/RENAL056.html> Accessed 01/20/2020

Urothelial carcinoma



Note the frond-like papillary projections to the left. It is differentiated enough to resemble urothelium, but it is producing a mass effect. No invasion is seen to the right.



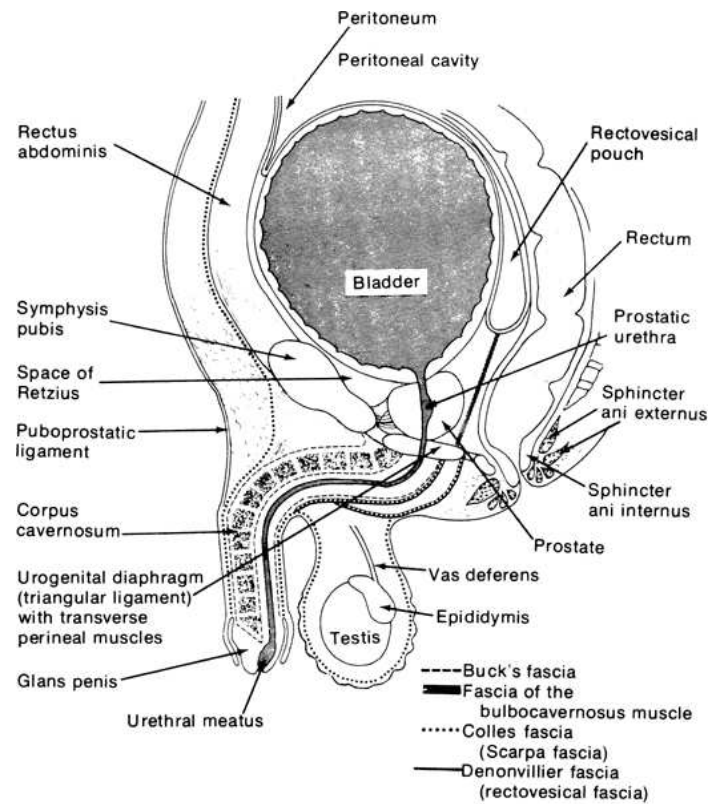
Below the thickness is much greater than normal urothelium, and the neoplastic cells show more pleomorphism.

<https://webpath.med.utah.edu/RENAHTML/BLAD063.html>

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Accessed 01/20/2020

Male pelvis



Source: Tintinalli JE, Kelen GD, Stapczynski JS: *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th Edition: <http://www.accessemergencymedicine.com>
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Fig. 273-2 Accessed 05/05/2010

Bladder

- 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 puboprostatic (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 development 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 Cryptococcus 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.

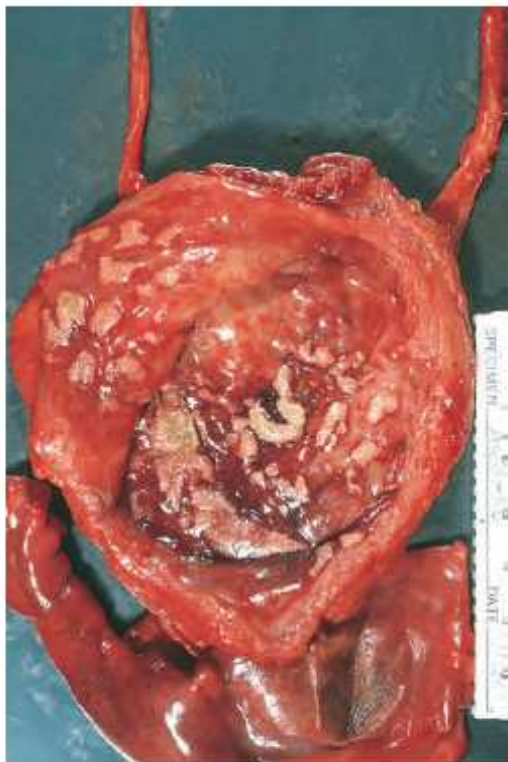


Figure 21-4 Cystitis with malakoplakia showing inflammatory exudate and broad, flat plaques.

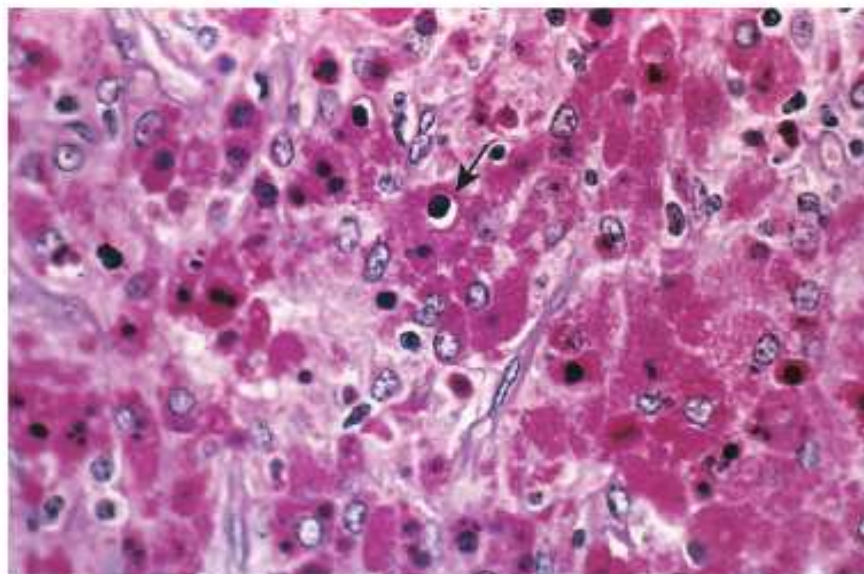


Figure 21-5 Malakoplakia, periodic acid-Schiff (PAS) stain. Note the large macrophages with granular PAS-positive cytoplasm and several dense, round Michaelis-Gutmann bodies surrounded by artifactual cleared holes in the upper middle field (*arrow*).

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)

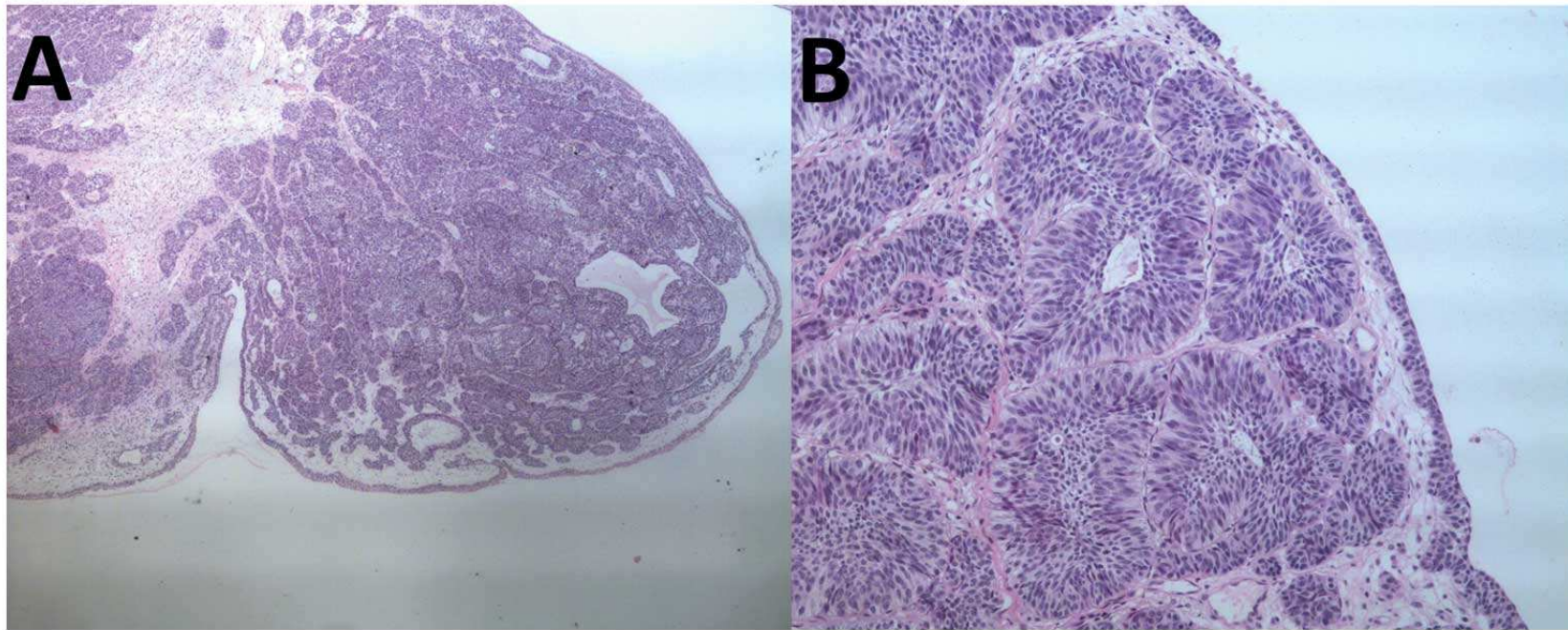
Inverted bladder papilloma

- <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.

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.

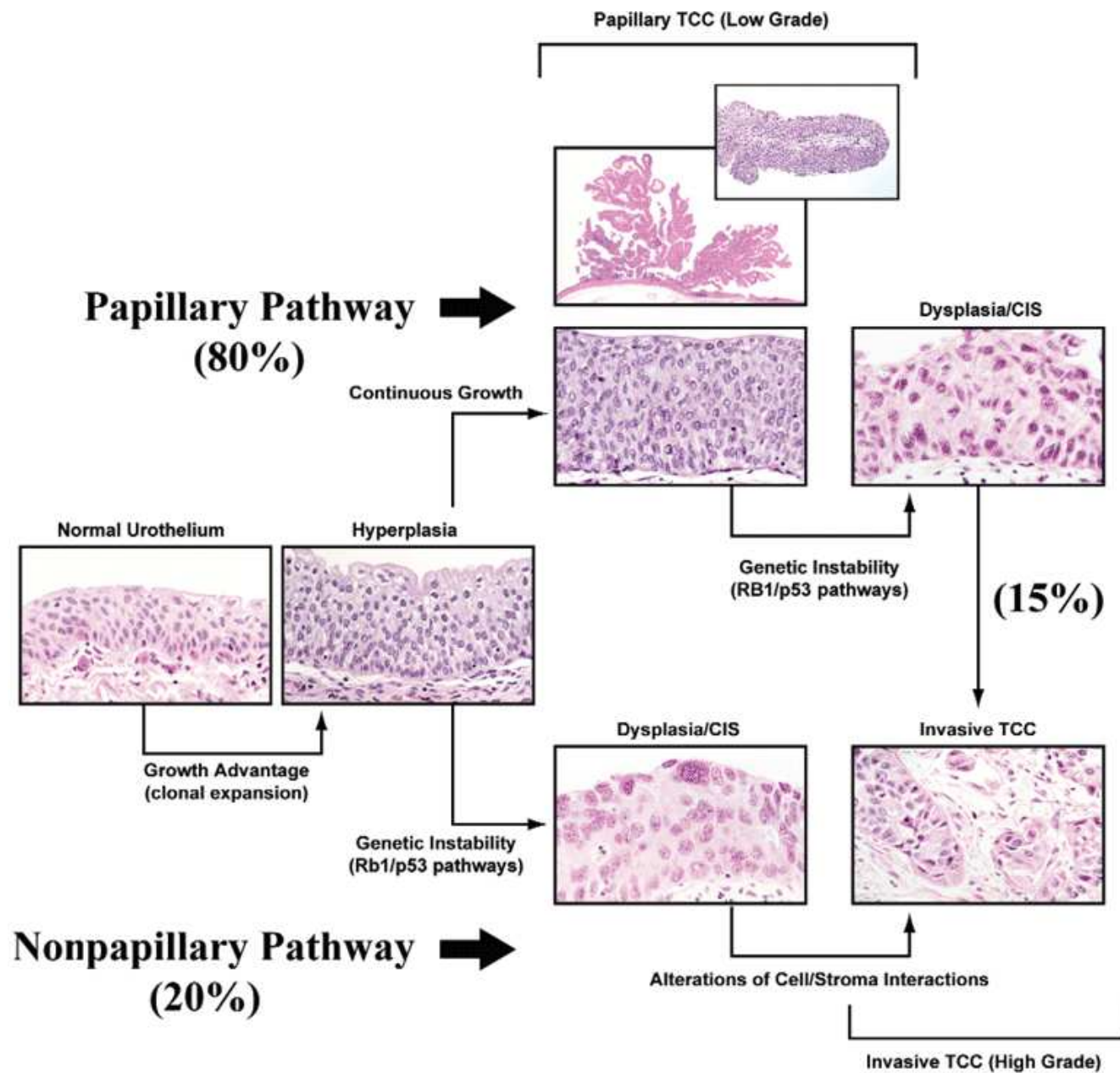


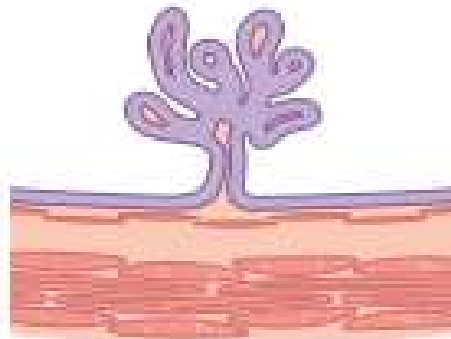
Fig. 28-1
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Infiltrating Urothelial Carcinoma
Urothelial carcinoma with divergent differentiation Squamous differentiation Glandular differentiation Trophoblastic differentiation Nested, including large nested Microcystic Micropapillary Lymphoepithelioma-like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

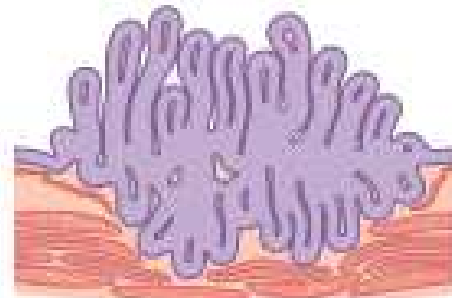
Data based on and derived from ¹Moch H, Humphrey PA, Ulbright TM, et al., eds. *WHO Classification of Tumours of the Urinary System and Male Genital Organs*. 4th ed. Lyon, France: IARC Press; 2016. *World Health Organization Classification of Tumours*; vol 8.

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



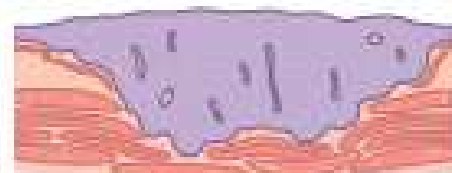
Papilloma-
papillary carcinoma



Invasive
papillary carcinoma



Flat noninvasive
carcinoma (CIS)



Flat invasive
carcinoma

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



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.

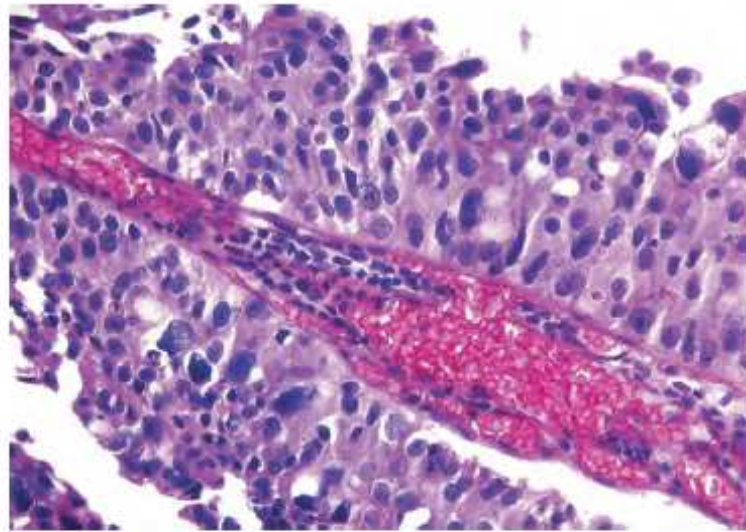


Figure 21-10 High-grade papillary urothelial carcinoma with marked cytologic atypia.

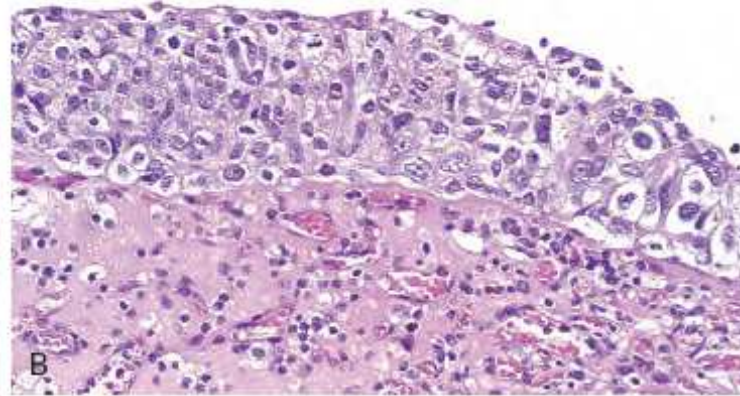
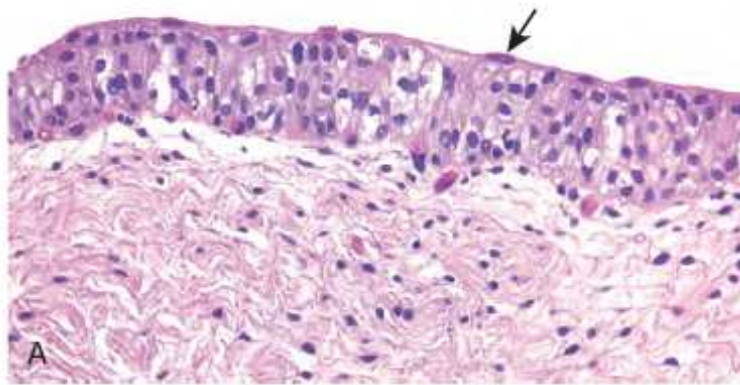


Figure 21-11 **A**, Normal urothelium with uniform nuclei and well-developed umbrella cell layer (*arrow*). **B**, Flat carcinoma in situ with numerous cells having enlarged and pleomorphic nuclei.

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

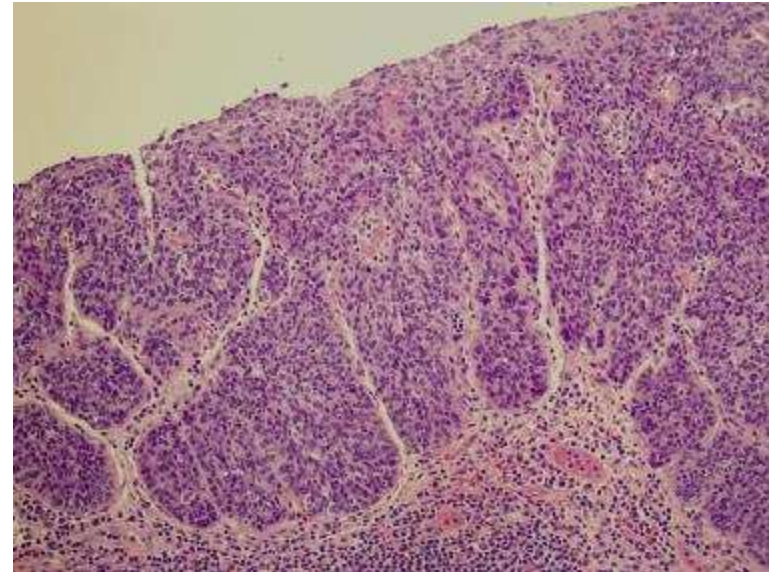
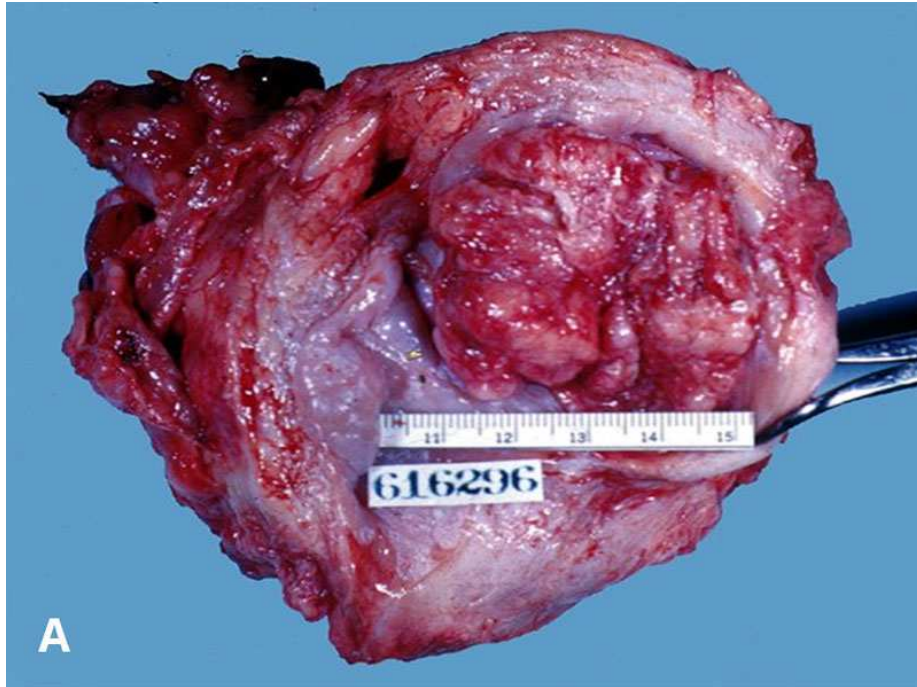
Urothelial carcinoma variants

- 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

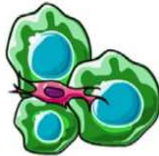
- Pure squamous carcinomas associated with chronic inflammation.
- Mixed urothelial carcinomas with areas of squamous carcinoma are more frequent than pure squamous cell carcinomas.
- Most are invasive, fungating tumors or are infiltrative and ulcerative.
- 7% of bladder cancers
- Other cancers include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

Squamous carcinoma



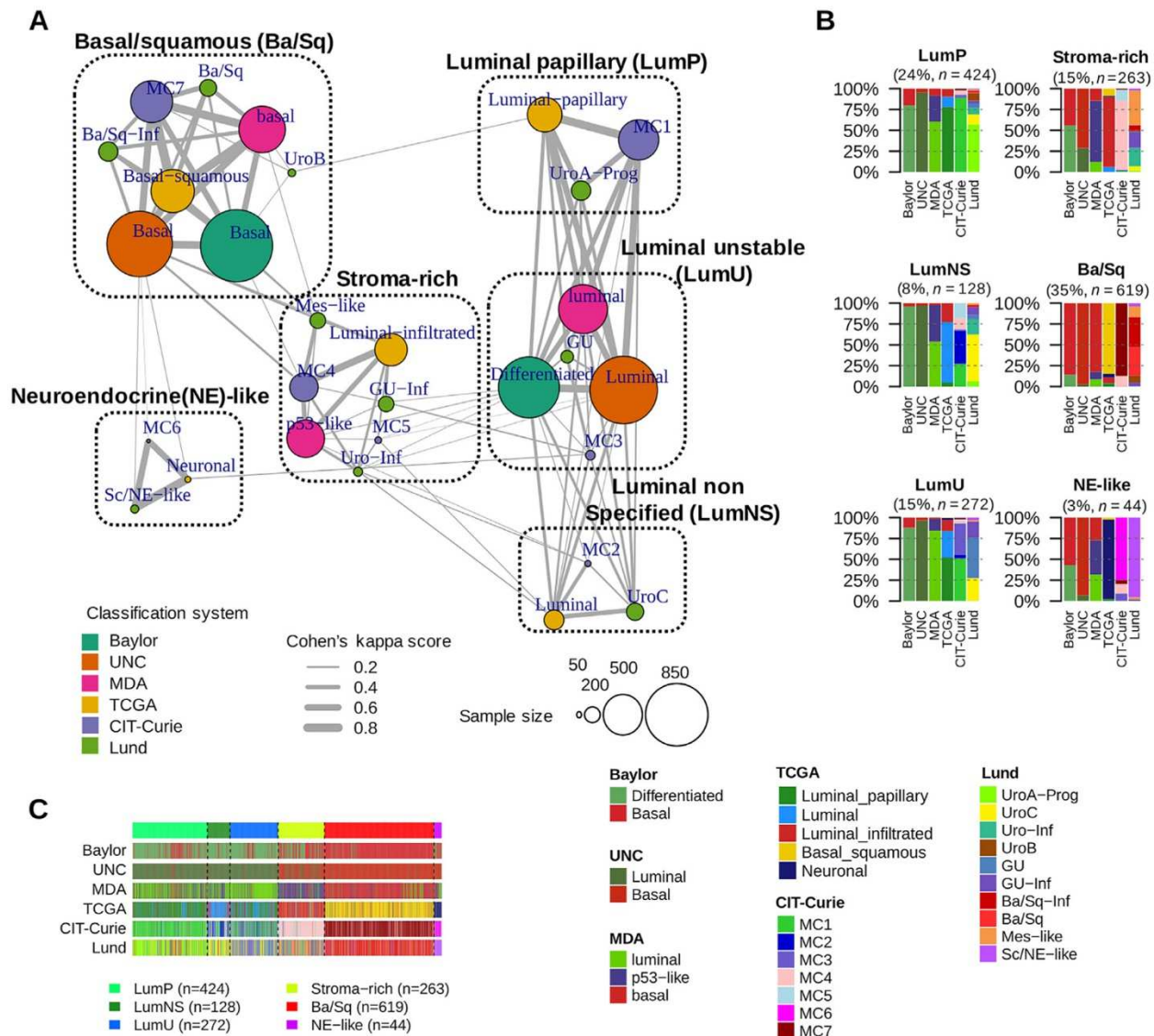
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% of MIBC	24%	8%	15%	15%	35%	3%
Class Name	Luminal Papillary (LumP)	Luminal Non-Specified (LumNS)	Luminal Unstable (LumU)	Stroma-rich	Basal/Squamous (Ba/Sq)	Neuroendocrine-like (NE-like)
						
Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 + PPARG + CDKN2A -	PPARG +	PPARG + E2F3 +, ERBB2 + Genomic instability Cell cycle +		EGFR +	TP53 -, RB1 -, Cell cycle +
Mutations	<i>FGFR3</i> (40%), <i>KDM6A</i> (38%)	<i>ELF3</i> (35%)	<i>TP53</i> (76%), <i>ERCC2</i> (22%) TMB +, APOBEC +		<i>TP53</i> (61%), <i>RB1</i> (25%)	<i>TP53</i> (94%) <i>RB1</i> (39%)*
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology (59%)	Micropapillary variant (36%)			Squamous differentiation (42%)	Neuroendocrine differentiation (72%)
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

* 94% of these tumors present either RB1 mutation or deletion

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



<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 chemotherapy.
- 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

Metastatic Urothelial Cancer

Cisplatin Eligible	Carboplatin Eligible	Platinum Unfit
Gemcitabine Cisplatin	Gemcitabine Carboplatin	ICI

Javelin 100
Keynote 360
IMvigor 130
DANUBE

Platinum Resistant

ICI

Keynote 045
BLC2001

ICI Resistant

Taxanes, Vinflunine

Novel Therapeutic Strategies

Enfortumab Vedotin
FGFR Inhibitors
Sacituzumab Govitecan

EV 301
BLC2001

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 transurethral 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

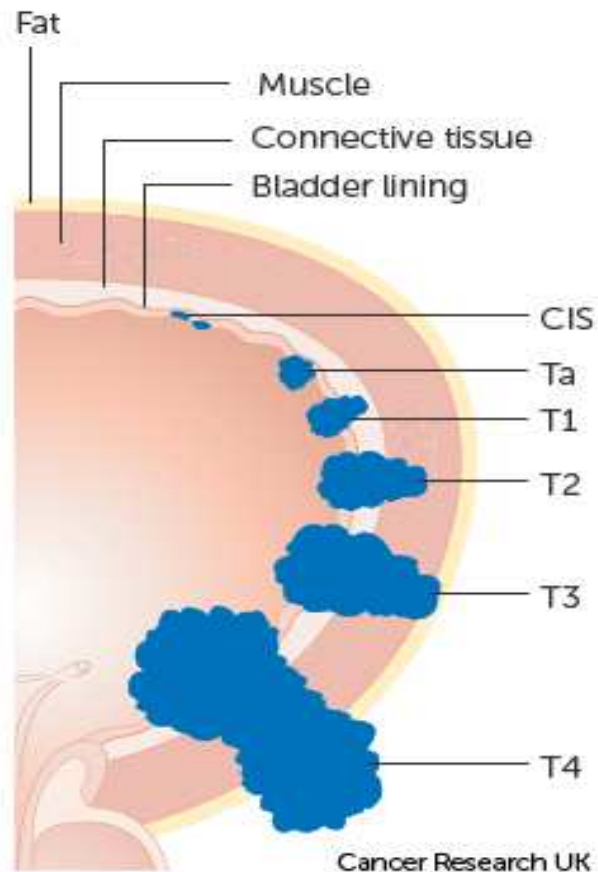


Table 21-4 Pathologic T (Primary Tumor) Staging of Bladder Carcinoma

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 polyarthrititis
- 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

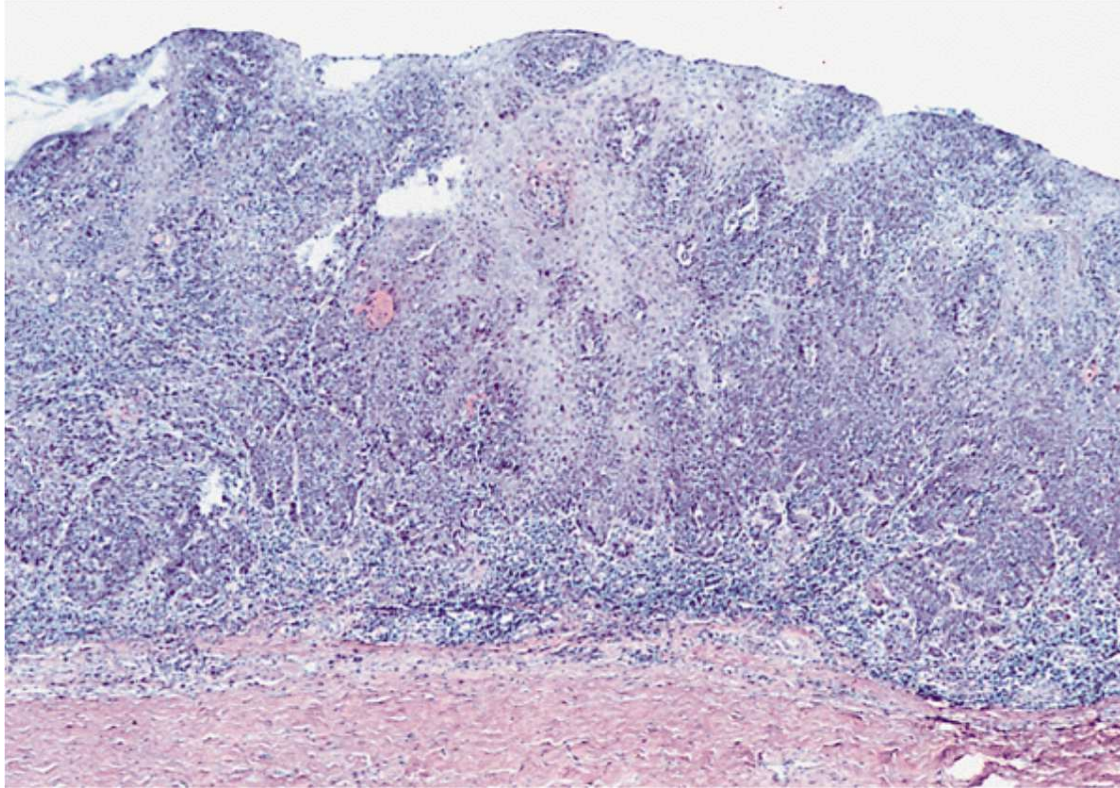


Fig. 9-14

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.