Pathology of urinary system

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URETERS

Congenital Anomalies

Congenital anomalies of the ureters are found in about 2% to 3% of all autopsies . Although most have little clinical significance, certain anomalies may lead to obstruction of the flow of urine and thus cause clinical disease. Ureteropelvic junction (UPJ) obstruction is the most common cause of hydronephrosis in infants and children.

- Vesiculoureteral reflux.
- Double and bifid ureters.
- Ureteropelvic junction obstruction.
- Diverticula.

Tumors and Tumor-Like Lesions

Primary tumors of the ureter are rare. Benign tumors are generally of mesenchymal origin.

Fibroepithelial polyp, a tumor-like lesion often occurring in children, is composed of loose, vascularized connective tissue overlaid by urothelium.

Primary malignant tumors of the ureter resemble those arising in the renal pelvis, calyces, and bladder. The majority are urothelial carcinomas . They occur most frequently during the sixth and seventh decades of life and cause obstruction of the ureteral lumen. They commonly occur concurrently with urothelial carcinomas of bladder or renal pelvis.

Obstructive Lesions:

Intrinsic and extrinsic lesions may obstruct the ureters and may give rise to hydroureter, hydronephrosis, and pyelonephritis . Unilateral obstruction typically results from proximal intrinsic or extrinsic causes (e.g., stones, neoplasms etc.), whereas bilateral obstruction arises from distal causes, such as nodular hyperplasia of the prostate

Cause of Obstruction	Characteristics/Mechanisms
Intrinsic	
Calculi	Typically of renal origin Usually small (5 mm in diameter or less) Impact at loci of ureteral narrowing—ureteropelvic junction, where ureters cross iliac vessels and where they enter bladder—and cause excruciating "renal colic"
Strictures	May be congenital or acquired
Tumors	Urothelial 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 associated with scarring
Tumors	Cancers of the rectum, bladder, prostate, ovaries, uterus, cervix; lymphomas, sarcomas

Sclerosing Retroperitoneal Fibrosis

This rare lesion is characterized by a fibrotic proliferative inflammatory process that encases retroperitoneal structures and causes hydronephrosis. The disorder occurs in middle to late age and is more common in males than females. At least a subset of these cases is related to IgG4-related disease, a recently described entity associated with elevated levels
of serum immunoglobulin G4 (IgG4) and fibroinflammatory lesions rich in IgG4-secreting plasma cells, that also affects other organs . Other etiologies for retroperitoneal fibrosis include drug exposures (ergot derivatives, β-adrenergic blockers), inflammatory conditions (vasculitis, diverticulitis, Crohn disease), or malignancies (lymphomas, urinary tract carcinomas). Most, however, have no obvious cause and are considered primary or idiopathic (Ormond disease).
Microscopic examination typically reveals fibrous tissue containing a prominent infiltrate of lymphocytes, often with germinal centers, plasma cells (frequently IgG4-positive), and eosinophils. Treatment initially involves corticosteroids, although many patients eventually become resistant and require ureteral stents or surgical extrication of the ureters from the surrounding fibrous tissue (ureterolysis).

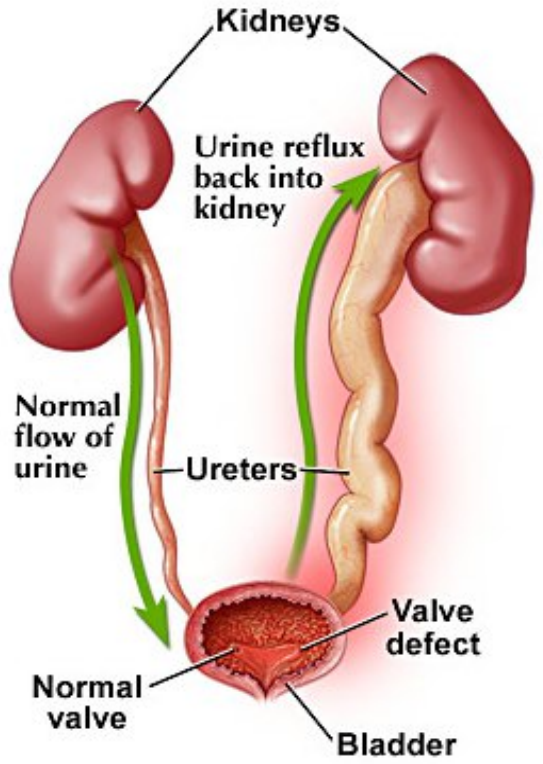
URINARY BLADDER

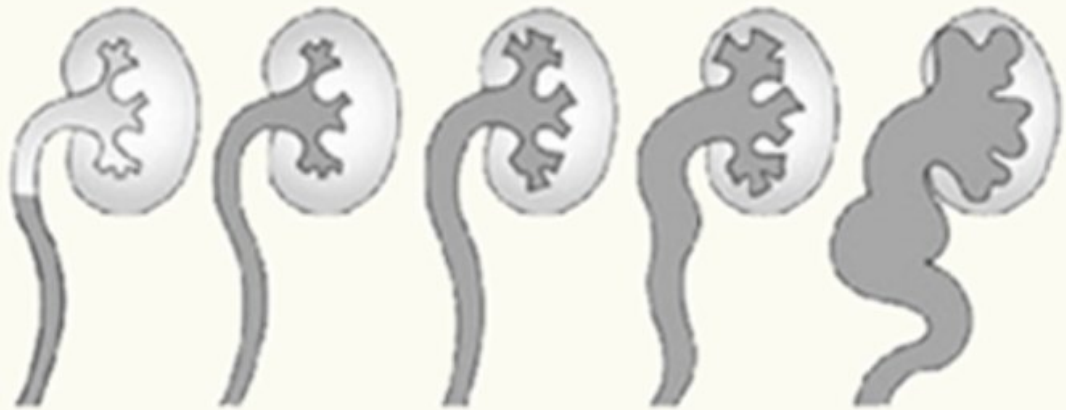
Congenital Anomalies

Several different types of congenital abnormalities of the bladder are recognized; these are variously associated with increased risk of infection or neoplasia.

• Vesicoureteral reflux is the most common and serious congenital anomaly. vesicoureteral reflux predispose ascending
pyelonephritis and loss of renal function.

Abnormal connections between the bladder and the vagina, rectum, or uterus may create congenital vesicouterine fistulae.

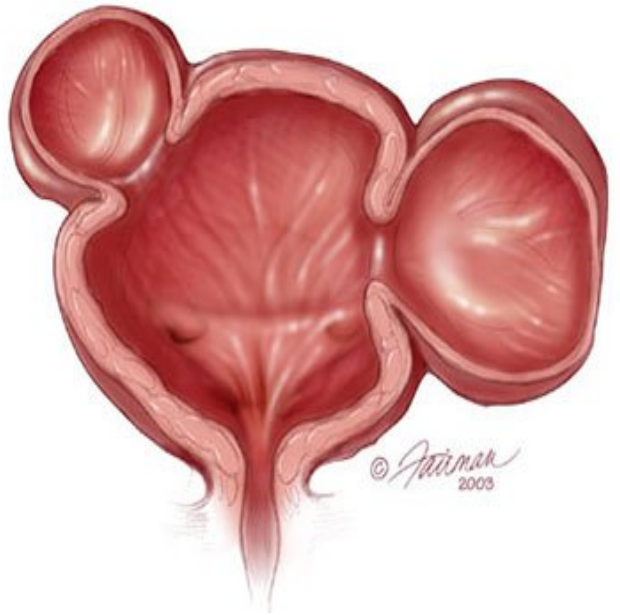




Grade	Description
I	Into a nondilated ureter
II	Into the pelvis and calyces without dilation
III	Mild to moderate dilation of the ureter, renal pelvis, and calyces with minimal blunting of the fornices
IV	Moderate ureteral tortuosity and dilation of the pelvis and calyces
V	Gross dilation of the ureter, pelvis, and calyces; loss of papillary impressions; and ureteral tortuosity

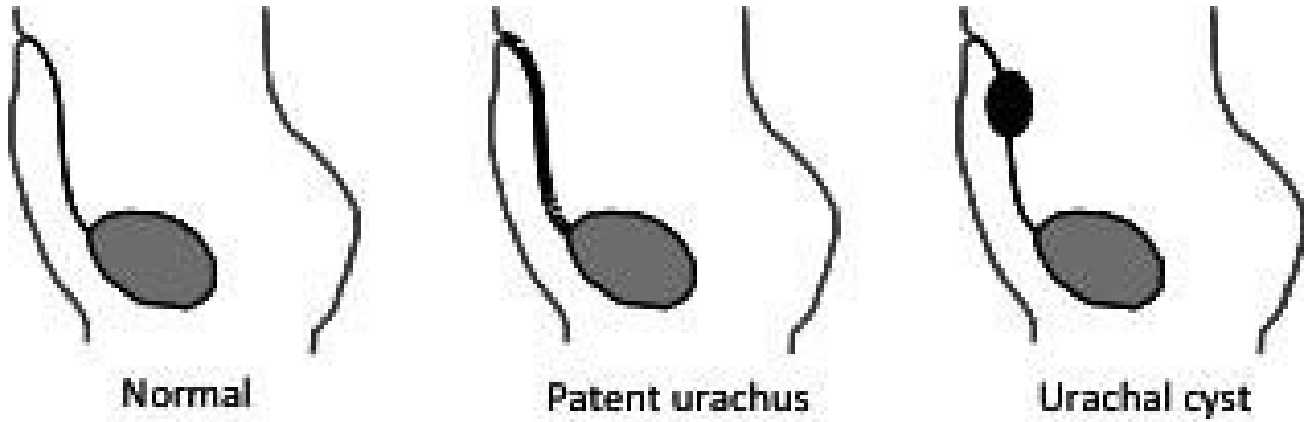
Diverticula are pouch-like invaginations of the bladder wall that vary from less than 1 cm to 10 cm in diameter and may be congenital or acquired. Congenital diverticula may be due to a focal failure of development of the normal musculature or to a urinary tract obstruction during fetal development. Acquired diverticula are most often associated with prostatic hyperplasia, producing urinary outflow obstruction. The resulting increase in intravesical pressure causes outpouching of the bladder wall and the formation of diverticula.

Exstrophy of the bladder is a developmental failu in the anterior wall of the abdomen and the bladd As a result, the bladder communicates directly with the abdominal surface



Urachal anomalies:

The urachal canal connects the fetal bladder with the allantois and normally is obliterated at birth. Rarely, it remains fully or partially patent. The former creates a fistulous urinary tract connection between the bladder and umbilicus.



Inflammation

Acute and Chronic Cystitis

Bacterial pyelonephritis is frequently preceded by infection of the urinary bladder, with retrograde spread of microorganisms into the kidneys and their collecting systems .Predisposing factors for cystitis include bladder calculi, urinary obstruction, diabetes mellitus, instrumentation, and immune deficiency. The most common etiologic agents of cystitis are the coliforms: Escherichia coli, followed by Proteus, Klebsiella, and Enterobacter. Women are more likely to develop cystitis as a result of their shorter urethras.

Tuberculous cystitis is almost always a sequel to renal tuberculosis. Candida albicans and, much less often, cryptococcal agents may cause cystitis, particularly in immunosuppressed patients or those receiving long-term antibiotics.

Schistosomiasis (Schistosoma haematobium) remains an important cause of cystitis in certain African and Middle Eastern countries. Viruses (e.g., adenovirus), Chlamydia, and Mycoplasma may also cause cystitis.

Adenovirus and BK virus (member of the polyomavirus family)infections may result in hemorrhagic cystitis. Gas-forming bacteria (such as Clostridium perfringens) result in emphysematous cystitis (gas-filled vesicles in the bladder wall).

Other types of non-infectious cystitis include **iatrogenic, follicular, and eosinophilic cystitis.** Patients receiving systemic chemotherapy or pelvic irradiation may develop iatrogenic cystitis. cytotoxic agents, such as cyclophosphamide, may cause hemorrhagic cystitis. Acute and chronic radiation cystitis may occur following the irradiation of the bladder region. Follicular cystitis is characterized by the presence of lymphoid follicles within the bladder mucosa and underlying wall. Eosinophilic cystitis, manifested by infiltration of the submucosa by eosinophils, typically is a nonspecific subacute inflammation but may also be a manifestation of a systemic allergic disorder.

Clinical Features

All forms of cystitis are characterized by a triad of symptoms:

(1) frequency, which in acute cases may necessitate urination every 15 to 20 minutes.

(2) lower abdominal pain localized over the bladder region or in the suprapubic region.

(3) dysuria (pain or burning on urination).

Special Forms of Cystitis

Several variants of cystitis have distinctive causes or morphologic appearances.

Interstitial Cystitis (Chronic Pelvic Pain Syndrome).
is a disorder of unknown etiology that occurs most frequently in women. The associated pain syndrome is defined by the American Urological Association as “an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes.” It is characterized by intermittent, often severe, suprapubic pain; urinary frequency; urgency; hematuria; and dysuria. Typical cystoscopic findings include mucosal fissures and punctate hemorrhages.
Microscopically, the pathologic findings are nonspecific; mast cells are often increased in the submucosa, but the pathogenic significance of this finding is uncertain. The main role of biopsy is to rule out carcinoma in situ (CIS), which clinically mimics interstitial cystitis. Treatment is largely empiric. Some cases are associated with chronic mucosal ulcers (Hunner ulcers); this is termed the late (classic, ulcerative) phase. Late in the

Polypoid Cystitis: Polypoid cystitis is an inflammatory lesion resulting from irritation of the bladder mucosa, most commonly as a result of instrumentation.

Metaplastic Lesions

Several lesions that stem from true metaplasia or conditions that mimic metaplasia affect the bladder.

Cystitis glandularis and cystitis cystica.

These are common lesions of the urinary bladder in which nests of urothelium (von Brunn nests) grow downward into the lamina propria. Here, epithelial cells in the center of the nest undergo metaplasia and take on a cuboidal or columnar appearance (cystitis glandularis) or retract to produce cystic spaces lined by flattened urothelium (cystitis cystica).

Squamous metaplasia: As a response to chronic injury, the urothelium is often replaced by nonkeratinizing or keratinizing squamous epithelium.

Malakoplakia:

Malakoplakia is a distinctive chronic inflammatory reaction that appears to stem from acquired defects in phagocyte function.

MORPHOLOGY Cystoscopically, malakoplakia takes the form of soft yellow, slightly raised mucosal plaques, 3 to 4 cm in diameter.

Histologically, the lesion is composed of aggregates of large foamy macrophages with occasional multinucleate giant cells and lymphocytes. The macrophages have abundant granular cytoplasm due to phagosomes stuffed with particulate and membranous debris of bacterial origin, which are believed to accumulate due to defective phagolysosome function. In addition, laminated mineralized concretions resulting from deposition of calcium in enlarged

Neoplasms

Bladder cancer is the ninth most common cancer type worldwide and is responsible for significant morbidity and mortality. It is the fourth most common cancer in American men (7% of all new cases). The overwhelming majority (>95%) of bladder tumors are of epithelial origin , with urothelial neoplasms being by far the most common type followed by squamous and glandular neoplasms.

Tumors of the Urinary Bladder

Urothelial (transitional) tumors.

- Noninvasive urothelial (transitional cell) tumors
- Infiltrating urothelial carcinoma
- Variants: nested, microcystic, micropapillary, plasmacytoid, sarcomatoid, giant cell, poorly differentiated, lipid-rich, and clear cell

Adenocarcinoma.

Squamous cell carcinoma.

Mixed carcinoma.

Small-cell carcinoma.

Sarcomas.

Urothelial Neoplasms

Urothelial neoplasms represent about 90% of all bladder tumors and run the gamut from small benign lesions that do not recur to aggressive cancers that are often fatal. Many of these tumors are multifocal at presentation. Though most common in the bladder, all of the urothelial lesions described here may be seen at any site where there is urothelium, from the renal pelvis to the distal urethra. There are two distinct precursor lesions to invasive urothelial carcinoma: noninvasive papillary tumors and flat noninvasive urothelial carcinoma in situ (CIS) . The most common precursor lesions are the noninvasive papillary tumors, which originate from papillary urothelial hyperplasia.

Table 21.4 Grading of Noninvasive Urothelial (Transitional Cell) Tumors

WHO/ISUP Grades (2016)
Flat Lesions
• Urothelial proliferation of uncertain malignant potential (flat hyperplasia) • Urothelial dysplasia • Urothelial carcinoma in situ
Exophytic Papillary Lesions
• Papilloma • Urothelial proliferation of uncertain malignant potential (papillary hyperplasia) • Papillary urothelial neoplasms of low malignant potential • Papillary urothelial carcinoma, low grade • Papillary urothelial carcinoma, high grade

Epidemiology.

The incidence of bladder cancer is higher in men (male-to-female ratio of 3: 1), in higher income nations, and in urban dwellers. About 80% of patients are between 50 and 80 years of age. Bladder cancer, with rare exceptions, is not familial.

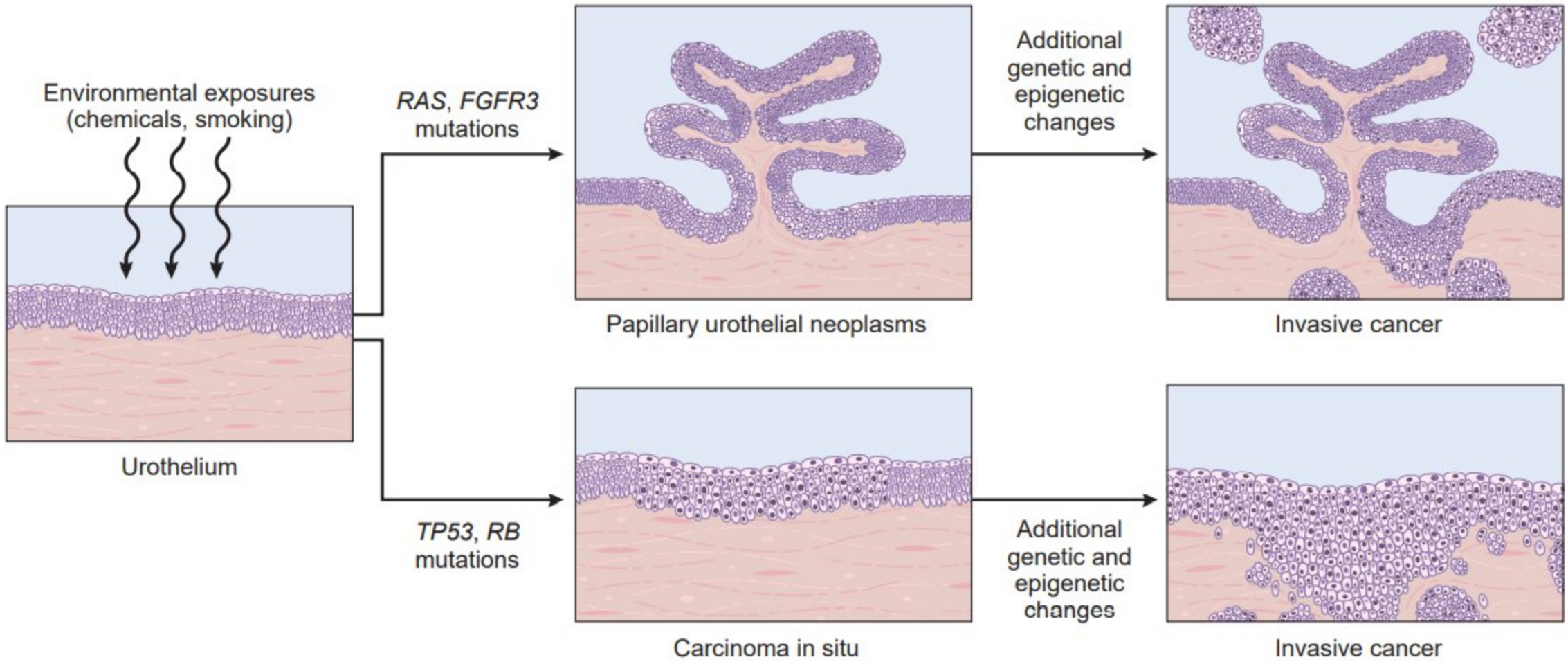
Several factors have been implicated in the causation of urothelial carcinoma, including the following:

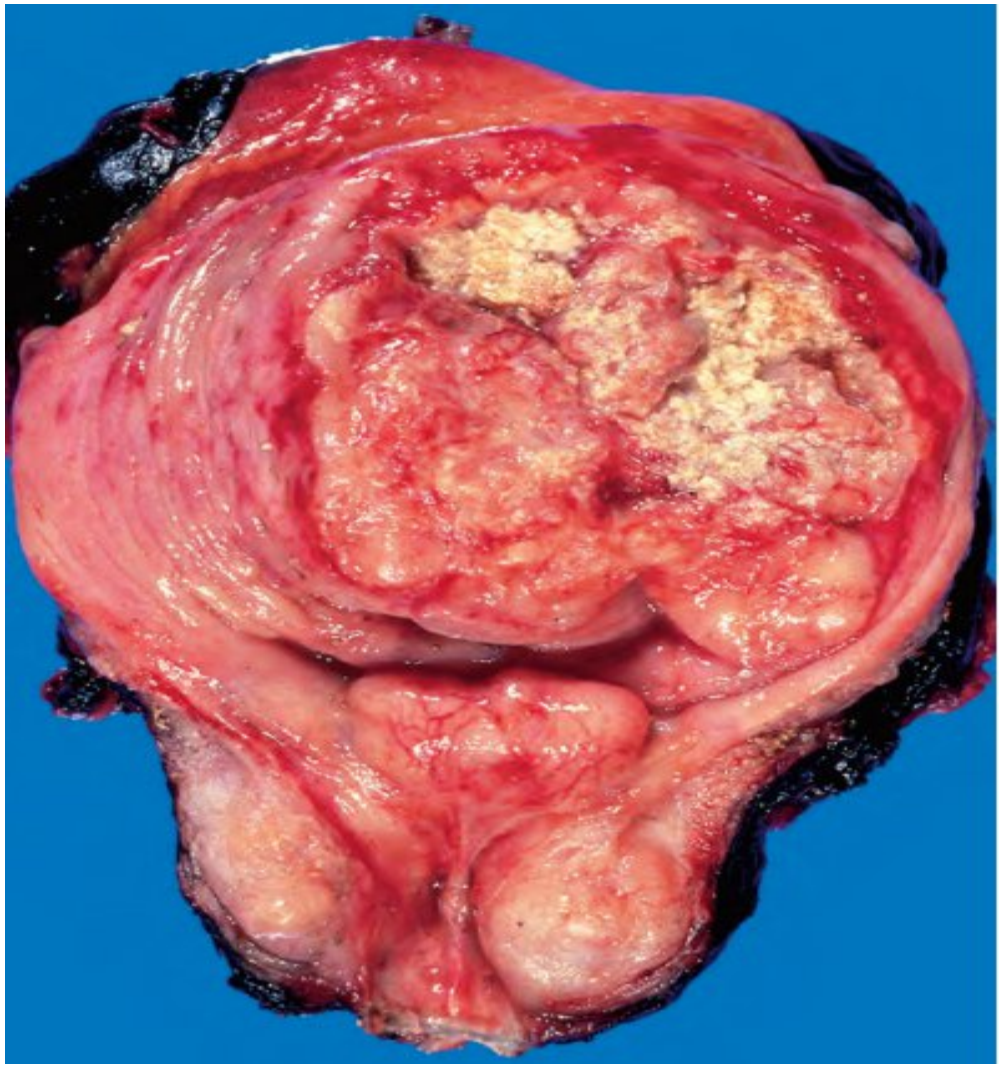
• Cigarette smoking is clearly the most important influence, increasing the risk threefold to sevenfold, depending on the duration and type of tobacco use. Between 50% and 80% of all bladder cancers among men are associated with the use of cigarettes.

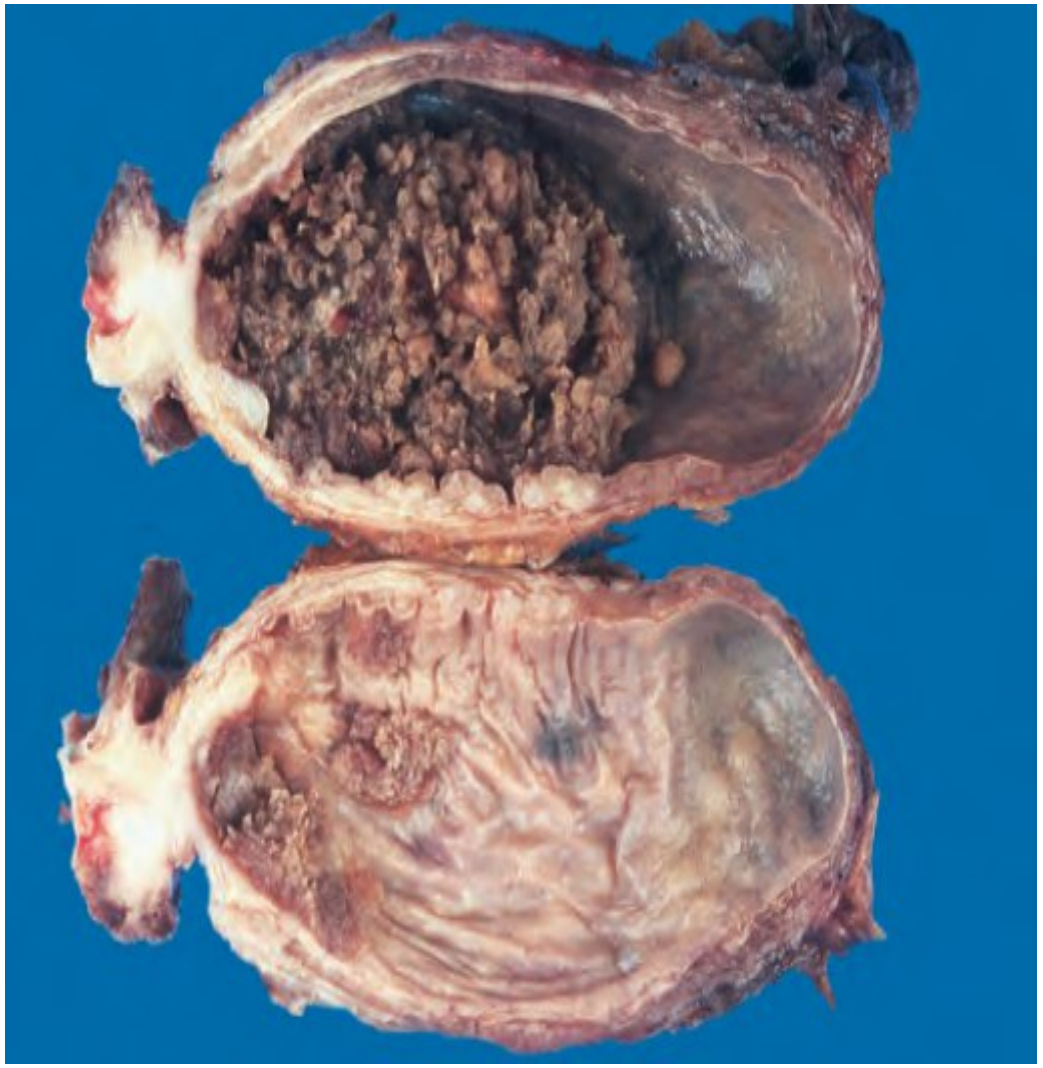
Industrial exposure to aryl amines.
Schistosoma haematobium infections in endemic areas.
Long-term use of analgesics.
Heavy long-term exposure to cyclophosphamide.
Irradiation.

Pathogenesis

Analysis of the genomes of precursor lesions and invasive bladder carcinomas has identified two relatively distinct molecular pathways of tumor progression


Environmental exposures
(chemicals, smoking)
Urothelium
RAS, FGFR3
mutations
Papillary urothelial neoplasms
Additional
genetic and
epigenetic
changes
Invasive cancer
TP53, RB
mutations
Carcinoma in situ
Additional
genetic and
epigenetic
changes
Invasive cancer





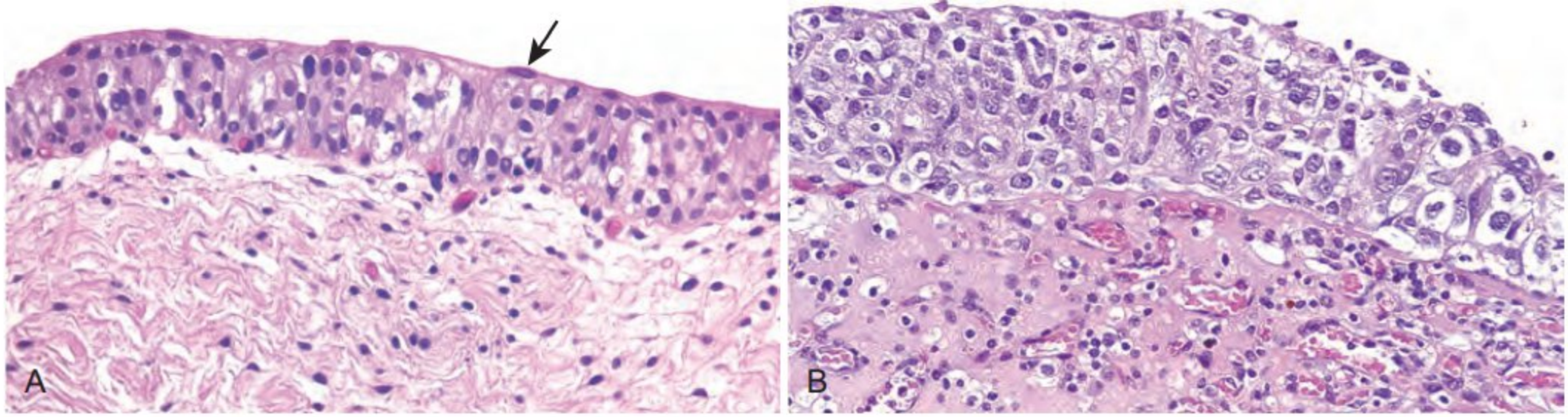
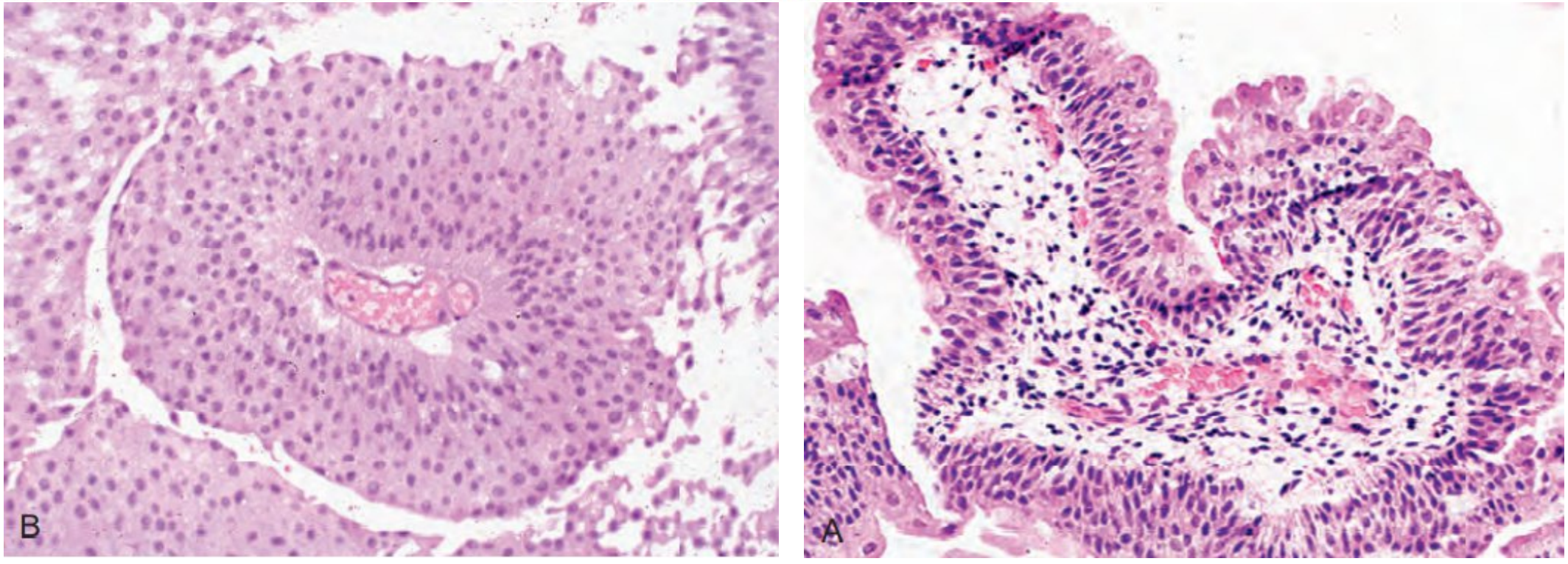
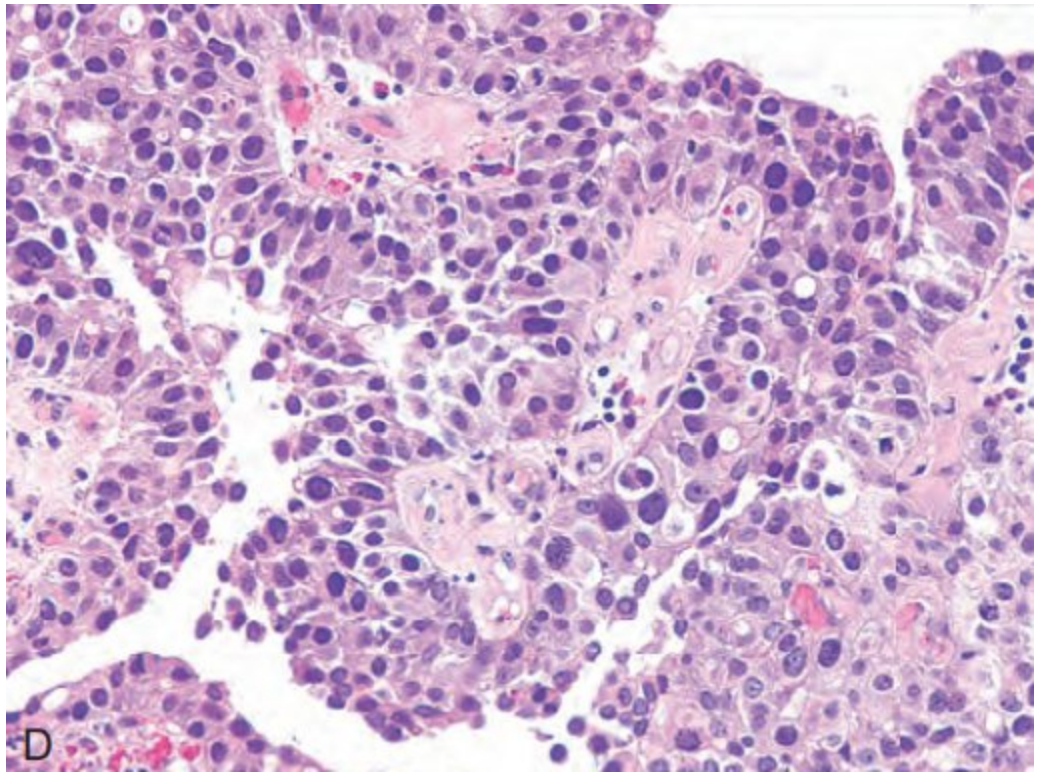


Figure 21.8 Bladder carcinoma in situ. (A) Normal urothelium with uniform nuclei and well-developed umbrella cell layer. (B) Carcinoma in situ showing a disorganized urothelium containing numerous cells having markedly enlarged and pleomorphic nuclei.

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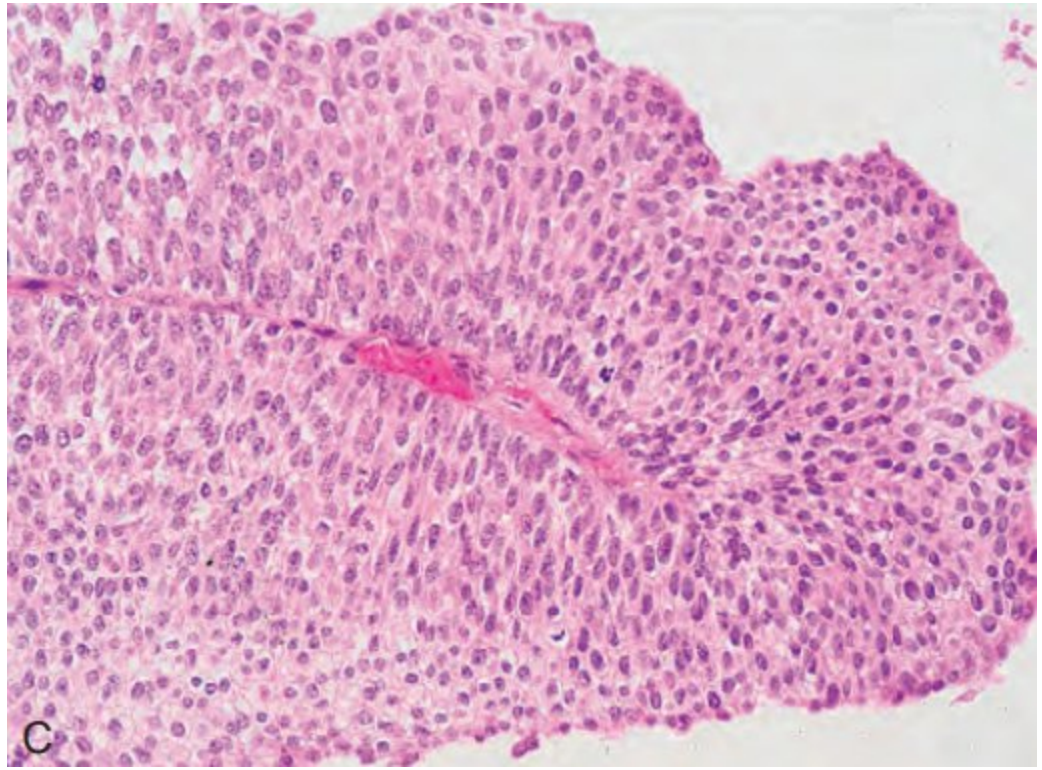
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pTNM, AJCC 8th Edition	
Tumor	
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Urothelial carcinoma in situ: "flat tumor"
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria
T2a	Tumor invades superficial muscularis propria (inner half)
T2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical soft tissue
T3a	Tumor invades perivesical soft tissue microscopically
T3b	Tumor invades perivesical soft tissue macroscopically (extravesical mass)
T4	Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades directly into prostatic stroma, seminal vesicles, uterus, or vagina
T4b	Extravesical tumor invades pelvic wall or abdominal wall

Clinical Features

Painless hematuria is the most common symptom of bladder cancer. Frequency, urgency, and dysuria may accompany hematuria. Occasionally, obstruction of the ureteral orifice may lead to pyelonephritis or hydronephrosis.

Other Epithelial Bladder Tumors

Squamous cell carcinomas resembling squamous cell cancers occurring at other sites make up 3% to 7% of bladder cancers in the United States but are much more frequent in countries where urinary schistosomiasis is endemic. Mixed urothelial carcinoma with areas of squamous carcinoma is more frequent than pure squamous cell carcinoma.

Adenocarcinoma of the bladder is rare and histologically identical to adenocarcinomas seen in the gastrointestinal tract. Some arise from urachal remnants or in association with extensive intestinal metaplasia

Small-cell carcinoma

Mesenchymal Tumors

Benign Tumors: A great variety of benign mesenchymal tumors may arise in the bladder, having the histologic features of their counterparts elsewhere. Even collectively, they are rare. The most common is leiomyoma.

Sarcomas. True sarcomas are distinctly uncommon in the bladder. Inflammatory myofibroblastic tumors and various carcinomas that assume sarcomatoid growth patterns are more common than true sarcomas

The most common bladder sarcoma in infancy or childhood is embryonal rhabdomyosarcoma.

The most common bladder sarcoma in adults is leiomyosarcoma

Secondary malignant involvement of the bladder is most often due to direct extension of cancers arising in adjacent organs, mainly the cervix, uterus, prostate, and rectum

Obstruction

Obstruction of the bladder outlet is of major clinical importance because of its eventual effect on the kidney. In males, the most common cause is enlargement of the prostate gland due to benign prostatic hyperplasia (BPH). Bladder obstruction is less common in females and is most often caused by cystocele of the bladder. Infrequent causes are

(1) congenital urethral strictures;
(2) inflammatory urethral strictures;
(3) inflammatory fibrosis and contraction of the bladder;
(4) bladder tumors, either benign or malignant;
(5) invasion of the bladder neck by tumors arising in contiguous organs;
(6) mechanical obstructions caused by foreign bodies and calculi; and

URETHRA

Inflammation

Urethritis is classically divided into gonococcal and nongonococcal causes. Gonococcal urethritis is one of the earliest manifestations of this venereal infection. Nongonococcal urethritis is common and can be caused by several different organisms. Various strains of Chlamydia (e.g.Chlamydia trachomatis) are the cause of 25% to 60% of nongonococcal urethritis in men and about 20% in women. Mycoplasma (Ureaplasma urealyticum) also accounts for symptoms of urethritis in many cases. Urethritis is often accompanied by cystitis in women and by prostatitis in men. In many instances of suspected bacterial urethritis, no organism can be isolated. Some urethritis is truly noninfectious in origin. An example of such an inflammatory urethritis is a disorder known as reactive arthritis (formerly Reiter syndrome), which is associated with the clinical triad of arthritis,

Tumors and Tumor-Like Lesions

Urethral caruncle is an inflammatory lesion that presents as a small, red, painful mass about the external urethral meatus, typically in older females. It consists of inflamed granulation tissue covered by an intact but friable mucosa, which may ulcerate and bleed with the slightest trauma. Surgical excision affords prompt relief and cure. Benign epithelial tumors of the urethra include squamous and urothelial papillomas, inverted urothelial papillomas, and condylomas. Primary carcinoma of the urethra is an uncommon lesion . Cancers arising within the proximal urethra tend to show urothelial differentiation and are analogous to those occurring within the bladder, whereas lesions originating within the distal urethra are more often squamous cell carcinomas and HPV-related. Adenocarcinomas are infrequent in the urethra and generally occur in women