Inflammation of Urinary Bladder (Cystitis):

1. Acute Cystitis:

- More common in female especially during pregnancy,
- In male is usually secondary to obstruction (mainly BPH, Urethral stricture).
- In non obstructive cases cystitis is due to E.coli, while in obstructed cases are due to mixed organisms, staphylococci, proteus).
- If cystitis is associated with Vesicoureteric reflux disease is usually extend to the upward toward the kidney.
- Mic:
- Inflamed, congested, edematous mucosa of urinary bladder.
- Clincal features:
- Dysuria, suprapubic pain.

2. Chronic Cystitis:

- □ It is result from repeated attacks of acute Cystitis.
- Common in male.
- \blacksquare Usually due to obstructive lesions (BPH).
- Usually due to mixed organisms (important one is Proteus).
- 3. Tuberculous Cystitis:

- Usually due to TB OF KIDNEY, or Iss common due to TB OF EPIDIDYMIIS.
- Usually situated at the base of bladder.
- May result in formation of small contracted bladder.

Bladder (Vesical) Stones:

Either

- 1. Stones descend from ureter, & greatly increased in the size in the bladder (enlargement is due to deposition of phosphate).
- 2. Stones are formed primarily in the bladder, usually associated with urethral obstruction & chronic cystitis.

- Fungal cystitis is usually due to Candida albican. It is particularly seen in immunosuppressed patients or those receiving long-term antibiotics.
- Schistosomal cystitis (Schistosoma haematobium) is common in certain Middle Eastern countries, notably Egypt. granulomatous cystitis with eosinophilic infiltrate & fibrosis. These granulomas are visible under endoscopy as minute granules referred to as "sand grain" cystitis. The eggs eventually die in the tissue with regressive calcification. The condition may be complicated by:
- a. Extensive fibrosis that may impinge on the ureteric orifices with eventual hydronephrosis.
- b. Carcinoma of bladder that is frequently squamous in type; as this form of cystitis can be associated with squamous metaplasia of the native transitional epithelium.
- Viruses (e.g., adenovirus), Chlamydia, and Mycoplasma may also be causes of cystitis.

Predisposing factors of cystitis include:

- 1. Urinary obstruction e.g. prostatic hyperplasia, bladder calculi,tumors.
- 2. cystocele or diverticula.
- 3. Diabetes mellitus.
- 4. Instrumentation.
- 5. Immune deficiency

Hypertrophy and trabeculation of bladder wall secondary to polypoid hyperplasia of the prostate.



Microscopic features

- In acute cystitis there are the expected features of acute inflammation.
- In chronic forms there is chronic inflammatory cells infiltration with fibrosis.

TUMORS OF THE URINARY BLADDER AND COLLECTING SYSTEM (Renal Calyces, Renal Pelvis, Ureter, and Urethra)

- The entire urinary collecting system from renal pelvis to urethra is lined with transitional epithelium, so its epithelial tumors assume similar morphologic patterns.
- Tumors in the collecting system above the bladder are relatively uncommon;
- those in the bladder, however, are a more frequent cause of death than are kidney tumors.

Urinary Bladder Neoplasms

 About 95% of them are of epithelial origin, the remainder being mesenchymal.

 Most epithelial tumors are composed of transitional type

Transitional Cell Tumors

- These represent about 90% of all bladder tumors and range from benign lesions to aggressive cancers.
- Many of these tumors are multifocal at presentation.
- Although most commonly seen in the bladder, they may be seen in the renal calyces, renal pelvis, ureters, and urethra.

Epidemiology and Pathogenesis

Male to female ratio of 3:1,

most at age 50-80,

urban>rural

Risk factors:

Associated w/ cigarette smoking,

B-naphthylamine & other aniline dyes,

long-term cyclophosphamide therapy, &

long-term analgesic use (phenacetin abuse ... TCC of renal pelvis)

Schistosoma hematobium infection. The ova are deposited in the bladder wall and incite chronic inflammatory response that induces progressive squamous metaplasia and dysplasia and, in some instances, neoplasia.

Prior exposure of the bladder to radiation. The cancer occurs many years after the radiation.

Clinical course

- Bladder tumors classically produce painless hematuria.
- Frequency, urgency and dysuria may be experienced as well.
- When ureteral orifice is involved lead to obstruction, pyelonephritis or hydronephrosis may follow.

Prognosis

Recurrence or new growth after excision is common

The risk of recurrence and progression is related to several factors; tumor size, stage, grade, multifocality, prior recurrence rate, and associated dysplasia and/or carcinoma in situ in the surrounding mucosa. (Tendency to spread by local invasion to adjacent structures, or may metastasize to liver, lungs, bone

Molecular genetic abnormality

- There are two different noninvasive precursor lesions to
- invasive urothelial carcinoma: papillary urothelial carcinoma
- (which may be low- or high-grade) and flat urothelial
- carcinoma in situ (uniformly high grade).
- <u>Noninvasive high-grade</u> urothelial carcinoma (either papillary or flat) is associated with loss of the TP53 and RB tumor suppressor genes and frequently progresses to muscle-invasive disease with the potential for systemic
- spread.
- Noninvasive low-grade papillary urothelial carcinoma is
- associated with gain of function FGFR3 and HRAS
- mutations. While these tumors are infrequently lifethreatening, they may locally recur and a subset may progress to high grade disease.

- There are two distinct precursor lesions to invasive
- urothelial carcinoma:
 - 1-noninvasive papillary tumors: papillary growth lined by transitional epithelium with mild nuclear atypia and pleomorphism
- 2- flat noninvasive urothelial carcinoma: (called carcinoma in situ CIS) cytologically atypical malignant cells within a flat urothelium
- The most common precursor lesions are the noninvasive papillary tumors, which originate from papillary urothelial hyperplasia.
- These tumors have a range of atypical changes, and are
- graded according to their biologic behavior.



Flat noninvasive carcinoma (CIS)

Flat invasive carcinoma

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

Grading of the tumors

- A most recent classification was adopted by the WHO in 2004,
 1. Urothelial papilloma.
 - 2. Urothelial neoplasm of low malignant potential.
 - 3. Papillary urothelial carcinoma, low grade
 - 5. Papillary urothelial carcinoma, high grade.

Morphology

The gross patterns vary from purely papillary to nodular or flat. The tumors may also be invasive or non. Papillary lesions range in size between 1-5cm. They may be multicentric.

Overall, the majority of papillary tumors are low grade and most arise from the lateral or posterior walls at the bladder base





Transitional cell Papillomas

- Represent 1% or fewer of all bladder tumors,
- Most commonly seen in younger patients.
- Usually solitary and exophytic, but, sometimes endophytic pattern is seen (inverted papilloma).
- The individual finger-like papillae have a central core of loose fibrovascular tissue covered by transitional epithelial cells that are Histologically identical to normal urothelium.
- Recurrences and progression are rare but may occur
- In contrast to exophytic papillomas, inverted papillomas are completely benign lesions consisting of inter-anastomosing cords of cytologically bland urothelium hat extend down into the lamina propria.

Papilloma consisting of small papillary fronds lined by normalappearing urothelium.



Papillary urothelial neoplasms of low malignant potential

- share many histologic features with papilloma, differing
- only in having thicker urothelium.
- At cystoscopy, these tumors tend to be larger than papillomas and may be indistinguishable
- from low- and high-grade papillary cancers.
- Recurrent tumors usually show the same morphology; progression to tumors of higher grade may occur but is rare.

Low-grade papillary urothelial carcinomas

- have an orderly architectural and cytologic appearance. The cells are
- evenly spaced (i.e., 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.
- These low-grade cancers may recur and, although infrequent, may also invade. Only rarely do these tumors pose a threat to the patient's life.

Low-grade papillary urothelial carcinoma with an overall orderly appearance, with a thicker lining than papilloma and scattered hyperchromatic nuclei and mitotic figures (arrows).



High-grade papillary urothelial cancers

- contain dyscohesive cells with large hyperchromatic nuclei.
 Some of the tumor cells are highly anaplastic .
- Mitotic figures, including atypical ones, are frequent. Architecturally, there is disarray and loss of polarity.
- As compared to low-grade lesions, these tumors have a much higher incidence of invasion into the **muscular layer**, a higher risk of progression, and, when associated with invasion, a significant metastatic potential.
- In most analyses, less than 10% of low grade cancers invade but as many as 80% of high grade cancers are invasive.



High-grade papillary urothelial carcinoma with marked cytologic atypia.



- Aggressive tumors extend to adjacent organs and in 40%, there are regional lymph nodes metastasis.
- Hematogenous dissemination, principally to the liver, lungs and bone marrow, generally occur late.

Carcinoma in situ (CIS, or flat urothelial carcinoma)

- Is defined by the presence of cytologically malignant cells within a flat urothelium. CIS may range from full-thickness cytologic atypia to scattered malignant cells in an otherwise normal urothelium, the latter termed pagetoid spread
- 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



Staging (extent of invasion at time of diagnosis) is most important factor in determining prognosis

- depth of invasion: lamina propria, muscularis propria, microscopic extra-vesicular, gross extra-vesicular, invasion of adjacent structures
- Once muscularis propria invasion occurs
 50% 5-year mortality rate

Pathologic Staging Of Bladder	Carcinoma
Noninvasive, papillary	Ta
Carcinoma in situ	Tis
Lamina propria invasion	T 1
Muscularis propria invasion	T2
Microscopic extravesicle invasion	T3a
Grossly apparent extravesicle invasion	T3b
Invades adjacent structures	T4

Other Types Of Carcinoma

Squamous Cell Carcinomas, represent about 3-7% of bladder cancers in general, but in endemic areas for urinary schistosomiasis, they occur much more frequently.

Most are invasive, fungating tumors or infiltrative and ulcerative.

Adenocarcinomas, are rare, some arise from bladder extrophy or urachal remnants or in association with extensive intestinal metaplasia.

Mesenchymal Tumors

- <u>Benign</u>, collectively are rare, the most common is leiomyoma.
- <u>Malignant</u>, sarcomas are extremely rare. The most common in infancy and childhood is embryonal
 <u>Rhabdomyosarcoma</u>. In adults, <u>Leiomyosarcoma</u> is the predominant one.

Secondary Tumors :

- Are most often as direct extension from adjacent organs (like prostate in male or cevix in female.
- Lymphoma may also involve the bladder as part of systemic disease.

ower Urinary Tract - Other

Hemorrhagic cystitis

- Due to radiation or cytotoxic drugs (cyclophosphamide)
- Chronic obstruction
 - Leads to bladder hyperplasia, diverticuli, and trabeculae
- Vesicoureteral reflux
 - Improper insertion angle of ureter into bladder

Cystitis cystica/glandularis

- Cell nests form cystic structures in bladder wall
- Glandularis: Colonic type metaplasia with goblet cells
 - May predispose to adenocarcinoma

Lower Urinary Tract -Other

Malakoplakia

- Associated w/ chronic bacterial infection (eg. immunosuppressed)
- Yellow plaques with foamy macrophages, multinucleated giant cells, <u>Michelis-Gutmann bodies</u> (dark blue staining mineralized concentrations)
- PAS-positive material

Interstitial cystitis

- Chronic autoimmune cystitis (women)
- Suprapubic pain, dysurea, urgency w/o infection
- <u>All layers of the bladder wall</u> demonstrate fibrosis, inflammatory infiltrate with mast cells
- <u>Hunner ulcers</u>