Renal Block

Lecture Six

Tumors of The Kidney

Objectives:

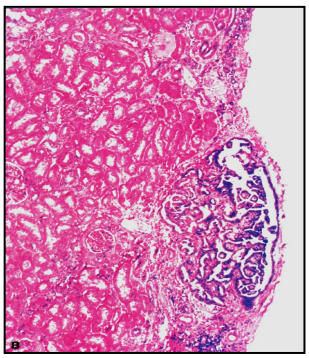
- Recognize the benign tumors of the kidney.
- Describe renal cell carcinoma and Wilms tumor.
- Recognize transitional cell and squamous
- Carcinoma of the urinary bladder

Benign tumors of the kidney:

1. Adenoma:

- This tumor is most often small and asymptomatic. It is derived from renal tubules.
- It may be a precursor lesion to renal carcinoma.

Kidney with ischemic atrophy also bears very small subcapsular **adenomas** near to each pole.



Histology of a subcapsular papillary **adenoma** shows tubules arranged in a papillary fashion.

2. Angiomyolipoma:

It is often associated with the tuberous sclerosis syndrome[1].

3. Oncocytoma:

It's a benign tumor that arises from the intercalated cells of collecting ducts. These tumors are associated with genetic changes— loss of chromosomes 1, 14, and Y.

Malignant Renal Neoplasms:

Neoplasms of the Renal Parenchyma:

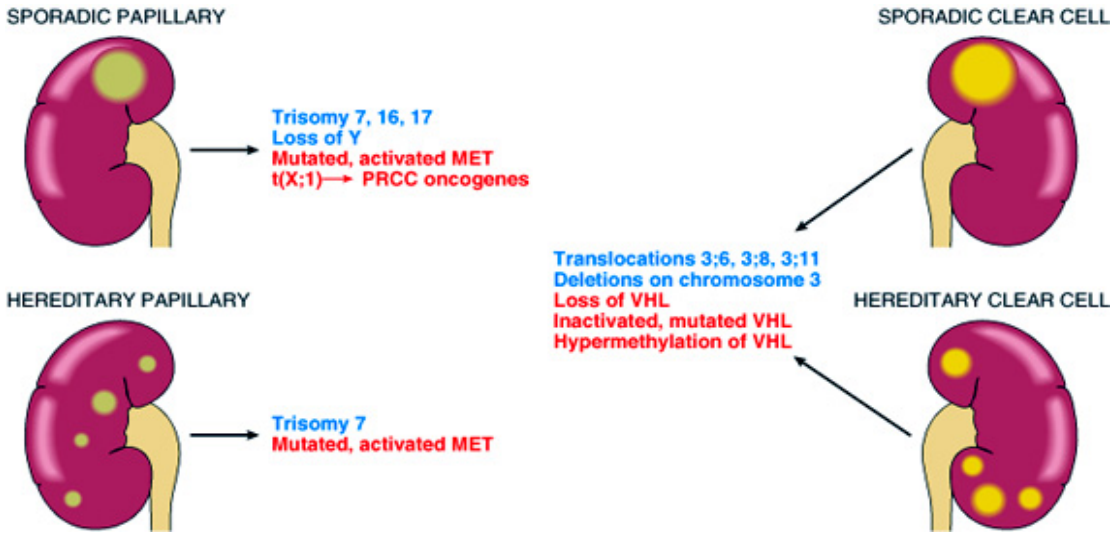
A. Renal cell carcinoma (renal adenocarcinoma; hypernephroma)
B. Nephroblastoma (Wilms tumor)
C. Urothelial tumors

Tumors of the lower urinary tract are about twice as common as renal cell carcinomas

The most common malignant tumor of the kidney is renal cell carcinoma, followed in frequency by nephroblastoma (Wilms tumor) and by primary tumors of the calyces and pelvis.

[1] A rare, multi-system genetic disease that causes benign tumors to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin. It usually affects the central nervous system and results in a combination of symptoms including seizures, developmental delay, behavioral problems, skin abnormalities, and kidney disease.

Renal cell carcinoma:

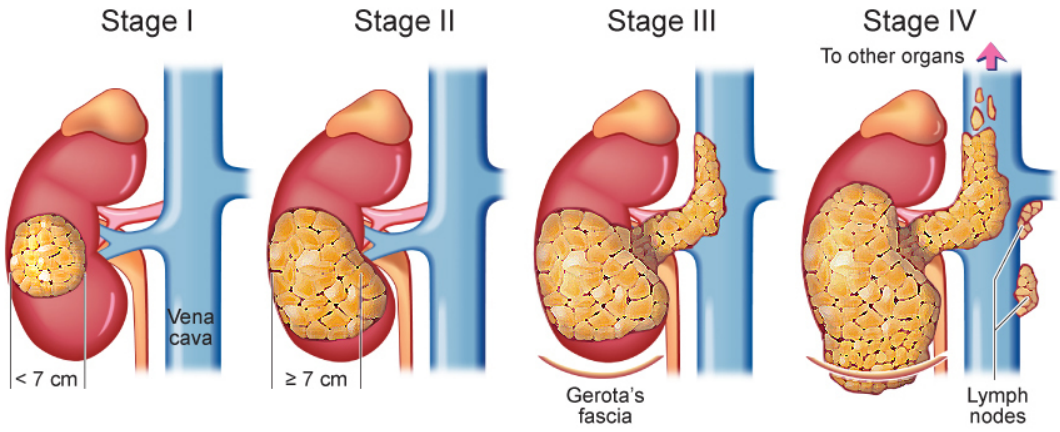


Etiology:

It is more common in men, occurs most often from 50-70 years of age and has higher incidence in **cigarette smokers**, hypertensive or obese patients, and those who have had occupational exposure to cadmium.

Pathogenesis:

- In some instances, it is associated with **gene deletions in chromosome 3;** it can also be associated with **von Hippel-Lindau disease**[2], which is caused by alterations in a gene localized in **chromosomes 3.**
- The carcinoma originates in renal tubules (because it's derived from the renal tubular epithelium and hence they are located predominantly in the cortex.) Most often, it arises in one of the renal poles, frequently the upper pole. (This is why it was called hypernephroma)
- Frequently the tumor invades renal veins or the vena cava and can extend up the vena cava. Early hematogenous dissemination may occur.

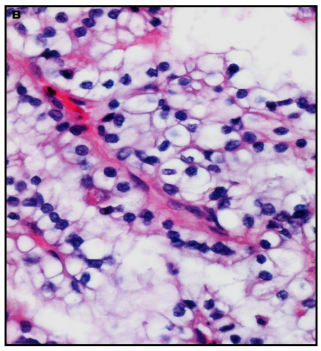


[2] An inherited disorder characterized by the formation of tumors and fluid-filled sacs (cysts) in many different parts of the body.

Morphology:

- Histologic characteristics include polygonal clear cells, sometimes with vestigial (primitive) tubule formation.
- The three most common forms are:
  - Clear cell carcinoma
  - Papillary renal cell carcinoma
  - Chromophobe renal carcinoma.

- **Clear cell cancers:**
  - Usually are solitary, large and spherical masses, which may arise anywhere in the cortex.
  - The cut is **yellow to orange to gray-white, with prominent areas of cystic softening or of hemorrhage**.
  - The margins of the tumor are well defined.
  - As the tumor enlarges, it may **fungate** through the walls of the collecting system.
  - Occasionally, direct invasion into the **perinephric fat and adrenal gland** may be seen.
  - Depending on the amounts of lipid and glycogen present, **the tumor cells may appear almost vacuolated or may be solid.**
    → The vacuolated (lipid-laden) are demarcated only by their cell membranes and the nuclei are usually small and round.
  - At the other extreme are granular cells, which have small, round, regular nuclei and granular pink cytoplasm



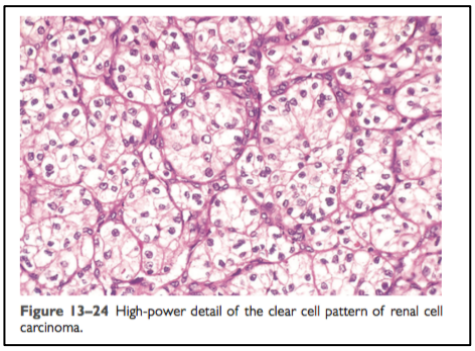
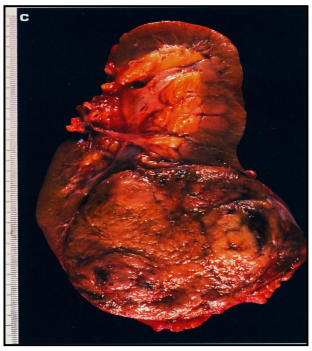
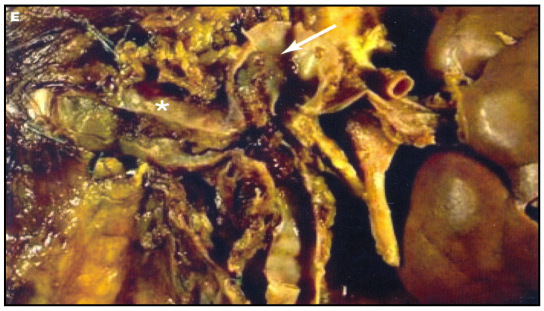


Figure 13–24 High-power detail of the clear cell pattern of renal cell carcinoma.



Typical lobulated, whorled, tan-colored cut surface of **renal cell carcinoma**.

Small clear cell **renal cell carcinoma** (hypernephroma, Grawitz tumor) is spreading into perirenal adipose tissue.



Invasion of the renal vein and inferior vena cava (arrow) by **renal cell carcinoma**.

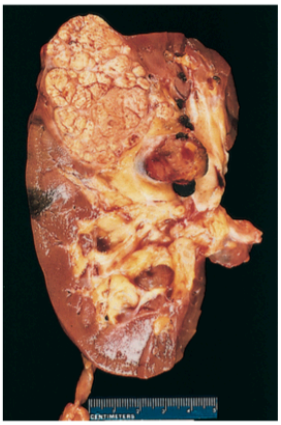


Figure 13–23 Renal cell carcinoma: Representative cross-section showing yellowish, spherical neoplasm in one pole of the kidney. Note the tumor in the dilated, thrombosed renal vein.

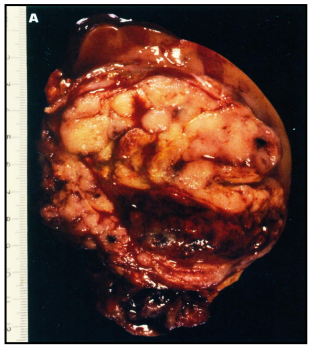
- **Papillary renal cell carcinomas:**
  - Exhibit papilla formation with **fibrovascular** cores.
  - They tend to be **bilateral and multiple.**
  - They also show **necrosis**, hemorrhage, and cystic degeneration.
  - The cells may have clear or, more commonly, **pink cytoplasm**
- **Chromophobe Renal Carcinomas:**
  - The least common, representing 5% of all renal cell carcinomas,
  - They arise from intercalated cells of collecting ducts.
  - Tumor cells stain more darkly, so they are less clear than cells in clear cell carcinomas.
  - Shows extreme **hypodiploidy**, by losing entire chromosomes, including chromosomes 1, 2, 6, 10, 13, 17, and 21.
  - **Grossly, they tend to be** tan-brown.
  - The cells usually have clear, flocculent cytoplasm with very prominent, distinct cell membranes,
  - In general, chromophobe renal cancers have a good prognosis

Presenting features:

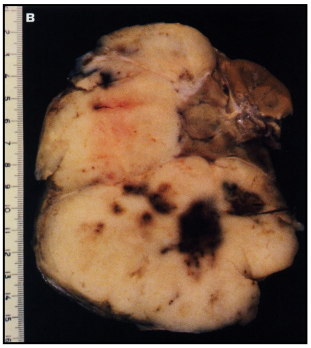
May include the triad of flank pain, palpable mass and hematuria. Hematuria is the most frequent presenting abnormality. Renal cell carcinoma may be manifest clinically by any if the following additional findings:

1. **Fever**
2. **Secondary polycythemia** (results from erythropoietin production by cancer cells) The risk of developing renal cell cancer is increased 30-fold in persons who acquire polycystic disease as a complication of chronic dialysis.
3. **Ectopic production** of various hormones or hormone like substances. (eg., ACTH, prolactin, gonadotropins, and renin) paraneoplastic parathyroid-like hormone can also cause hypercalcemia.
4. Other **paraneoplastic syndromes** include: hypertension, Cushing syndrome, feminization or masculinization
5. Nowadays, even smaller tumors are detected.
6. In many patients, the primary tumor remains silent and is discovered only after its metastases have produced symptoms. The prevalent locations for metastases are the lungs and the bones.

Wilms tumor (nephroblastoma):



Solid, bulging, fleshy tan-white, partially necrotic tumor has replaced much of the kidney and is encompassed by a thin rim of renal tissue..



This **Wilms' tumor** appears whiter due to formalin fixation and has extended beyond the confines of the kidney

Etiology:

- This cancer is the most common renal malignancy of early childhood.
- Incidence peaks in children 2-4 years of age. Inherited as an autosomal dominant trait

Pathogenesis:

- Originates from primitive metanephric tissue (derived from the mesoderm).
- Often associated with deletions of the **short arm of chromosome 11**. The **WT-1 and WT-2** genes localized to this chromosome are cancer suppressor genes.
- **The disease can be part of the AGR (or WAGR) complex:**
  - → Wilms tumor
  - → Aniridia (absence of the choroid layer in the eye)
  - → Genitourinary malformations
  - → Mental-motor retardation.

  This set of anomalies is associated with deletion of the **WT-1** tumor suppressor and other nearby genes.

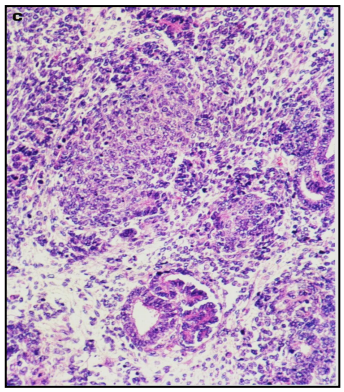
  (In WAGR syndrome whereas DDS involves negative inactivation mutation of gene – explained below-)
- **It can also be associated with Beckwith-Wiedemann syndrome:**
  - → Hemihypertrophy

    (Gross asymmetry due to unilateral muscular hypertrophy, enlargement of entire body segment).
  - → Marcoglossia
  - → Organomegaly: Enlargement of individual body organ (e.g., liver, kidney, or tongue)
  - → Neonatal hypoglycemia
  - → Various embryonal tumors.
  - → Adrenal cytomegaly: Enlargement of adrenal cortical cells
  - → Wilms tumor

  Associated with deletion of the **WT-2 gene.**

Morphology:

- Characteristics are varied with immature stoma, primitive tubules and glomeruli, and mesenchymal elements such as fibrous connective tissue and cartilage bone
- In most lesions, **triphasic combination** of blastemal, stromal and epithelial cell types is observed.
- The tumor is large, solitary, and well-circumscribed mass.
- On cut section, the tumor is soft, homogenous, and tan to gray, with occasional foci of hemorrhage, cystic degeneration, and necrosis.
- **Nephrogenic rests**[3] are precursor lesions of Wilms tumors.



Histology shows hypercellular areas comprising undifferentiated blastema, loose stroma with undifferentiated glomeruloid body.

Presenting Features:

- Most often, the presenting feature is **palpable flank mass**, which may extend across the midline and down to the pelvis (often huge).
- Less often, the patient will present with fever, abdominal pain, hematuria, or intestinal obstruction as a result of pressure from tumor.

Three congenital malformations increase the risk for development of Wilms tumor. Those include:

1- **WAGR syndrome.**

2- **Denys Drash syndrome (DDS):**

- This syndrome is characterized by gonadal dysgenesis and renal abnormalities.
- DDS has high risk for development of tumor "about 90%"

- **Both WAGR and DDS** are associated with abnormalities **of Wilms tumor 1 gene (WT1)** located on 11p13.
- The WT1 gene is critical to normal renal and gonadal development "that is why we have genital abnormality with both syndromes"

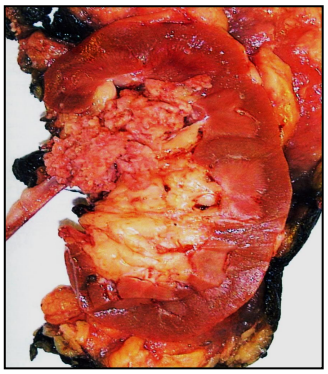
[3] A fragment of embryonic tissue in the kidney retained after the period of embryonic development

3- **Beckwith-Wiedemann syndrome**

- The gene involved in these patients are 11p15.5 "WT2"
- The prognosis is very good, and excellent results are obtained with a combination of **nephrectomy and chemotherapy**.
- The prognosis is also associated with anaplasia, if we have **focal anaplasia** which is restricted within the nephrectomy → prognosis is good
- **Diffused anaplasia** → have the least favorable outcome"

Transitional cell carcinoma

This cancer is the most common tumor of the urinary collecting system and can occur in renal calyces, pelvis, ureter, or bladder. It's often multifocal in origin.



Papillary urothelial (transitional cell) carcinoma of renal pelvis. Note the exophytic, multifronded nature of the tumor.

- In the renal pelvis, transitional cell carcinoma has been associated with **phenacetin abuse.**
- This carcinoma is likely to recur after removal.
- Most often, the presenting feature is **hematuria.**
- There is tendency to spend by local extension to surrounding tissues.
- Associated toxic exposures may sometimes be involved, including the following:
  - Industrial exposure to **benzidine** or **β-naphthylamine**, which is an **aniline dye.**
  - Cigarette **smoking.**
  - Long term treatment with **cyclophosphamide**

Squamous cell carcinoma constitutes a minority of urinary tract malignancies.

- This cancer may result from **chronic inflammatory processes**, such as chronic bacterial infection or Schistosoma haematobium infection.
- It can also be associated with renal calculi.

Malignant tumors of the bladder:

Recap of anatomy:

The renal pelves, ureters, bladder, and urethra are lined by urothelium. Beneath the mucosa are the lamina propria and, deeper yet, the muscularis propria (detrusor muscle), which makes up the bladder wall.

- By far the common malignant tumor of the bladder in adults is the urthelial-delieverd transitional cell carcinoma (TCC).
- However, in the pediatric age group a common malignant tumor of the bladder is the rhabdomyosarcoma.
- Carcinoma of the bladder is more common in men than in women
- Squamous cell carcinomas are much more common in countries where urinary schistosomiasis is endemic. They typically show extensive keratinization and are nearly always associated with chronic bladder irritation and infection.
- Adenocarcinomas of the bladder are rare and some arise from urachal remnants in the dome of the bladder or in association with extensive intestinal metaplasia.

Pathogenesis:

- Bladder cancer, with rare exceptions, is not familial.
- Cancers occurring in the setting of schistosoma infections arise in a background of chronic inflammation.
- The tumor is **initiated by deletions of tumor-suppressor** genes on 9p and 9q, leading to formation of superficial papillary tumors, a few of which may then acquire ***TP53*** mutations and progress to invasion.
  - The underlying genetic alterations in superficial tumors include fibroblast **growth factor receptor 3 (FGFR3) mutations** and **activation of the Ras pathway**.
- A second pathway, possibly **initiated by *TP53* mutations**, leads first to carcinoma in situ and then, with loss of chromosome 9, progresses to invasion.

Morphology:

Two distinct precursor lesions to invasive urothelial carcinoma are recognized:

1- **The most common is a noninvasive papillary tumor:**

Noninvasive papillary urothelial neoplasms demonstrate a range of atypia and are graded to reflect their biologic behavior. The most common grading system classifies tumors as follows:

1) Papilloma
2) Papillary urothelial neoplasm of low malignant potential (PUNLMP)
3) Low-grade papillary urothelial carcinoma
4) High-grade papillary urothelial carcinoma.

These exophytic papillary neoplasms are to be distinguished from **inverted urothelial papilloma**, which is entirely benign and not associated with an increased risk for subsequent carcinoma.

2- **The other precursor is carcinoma in situ (CIS):**

CIS is defined by the presence of cytologically malignant cells within a flat urothelium. Like high-grade papillary urothelial carcinoma, CIS tumor cells **lack cohesiveness**. This leads to the shedding of malignant cells into the urine, where they can be detected by cytology.

CIS commonly is **multifocal** and sometimes involves most of the bladder surface or extends into the ureters and urethra. Without treatment, some CIS cases progress to muscle-invasive cancer

3- In about half of the patients with invasive bladder cancer, no precursor lesion is found; it is presumed that the precursor lesion was overgrown by the high-grade invasive component.

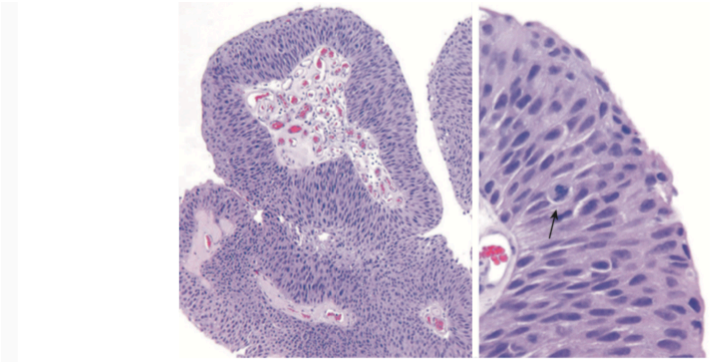


Figure 17–17 Noninvasive low-grade papillary urothelial carcinoma. Higher magnification (*right*) shows slightly irregular nuclei with scattered mitotic figures (*arrow*).

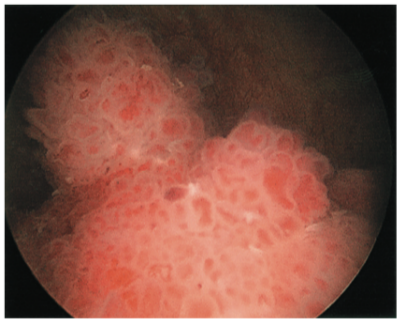


Figure 17–16 Cystoscopic appearance of a papillary urothelial tumor, resembling coral, within the bladder.

Invasive urothelial cancer associated with papillary urothelial cancer (usually of high grade) or CIS may superficially invade the lamina propria or extend more deeply into underlying muscle.

Underestimation of the extent of invasion in biopsy specimens is a significant problem. **The extent of invasion and spread (staging) at the time of initial diagnosis is the most important prognostic factor.** Almost all infiltrating urothelial carcinomas are of high grade.

Clinical Features

- Bladder tumors most commonly present with ***painless hematuria***.
- Patients with urothelial tumors, whatever their grade, have a tendency to develop new tumors after excision, and **recurrences** may exhibit a higher grade.
- Most recurrent tumors arise at sites *different* than that of the original lesion, yet share the same clonal abnormalities as those of the initial tumor.
- **High-grade papillary urothelial carcinomas** are frequently associated with either concurrent or subsequent invasive urothelial carcinoma.
- **Lower-grade papillary urothelial neoplasms** often recur but infrequently invade.

The treatment for bladder cancer depends on tumor grade and stage and on whether the lesion is flat or papillary.

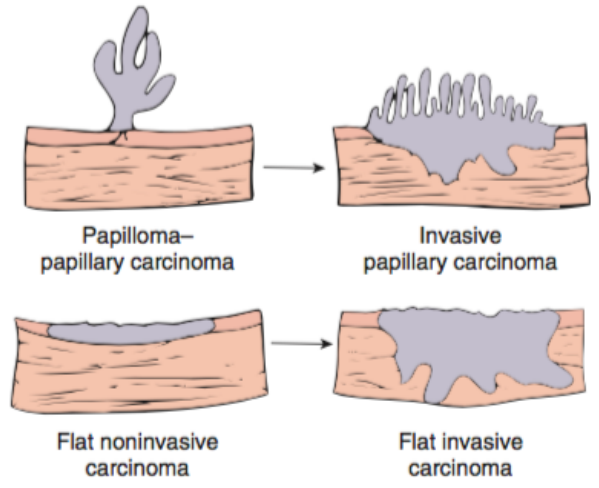


Figure 17–15 Precursor lesions of invasive urothelial carcinoma.

Transitional cell carcinoma-in-situ:

It's believed by many authorities to precede the development of TCC in some patients (as evidenced by the presence of TCC is in the majority cases of TCC).

Transitional Cell Carcinoma:

Characterized by:

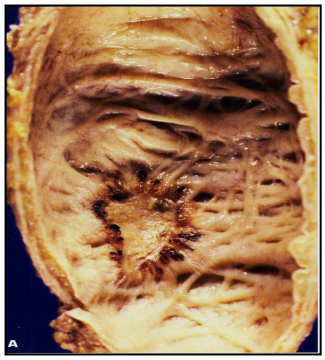
Flat and thickened or gently undulating full thickness dysplastic urothelium (nuclear pleomorphism, abnormal mitoses and apoptotic figures are seen). Often appearing as red patch, the disease may be multifocal within the bladder.

Etiology:

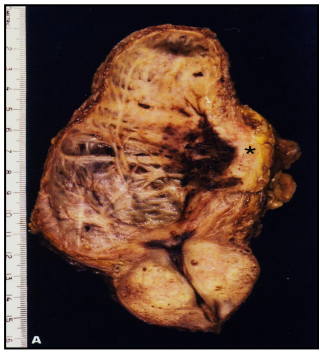
Most patients are over 50 years of age and there are definite risk factors for development of TCC. The most important of which are mentioned in box I. The tumor may present hematuria, frequency or urgency. TCC may be multifocal within the bladder or the urinary tract.

Clinical Features:

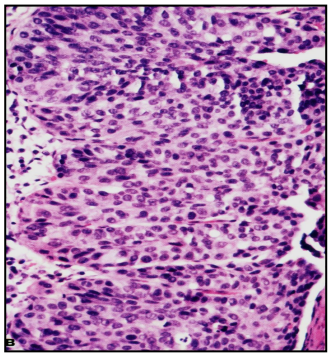
- As in other parts of the urothelium-lined urinary tract, the tumor can have a very varied appearance, both macroscopically **(fronded and seaweed-like to solid)** and **microscopically (well differentiated and papillary to poorly differentiated and widely muscle-invasive).**
- Numerous cytogenetic and molecular alterations have been found in TCC, including monosomy or deletions of the short (p) or long (q) arm of chromosome 9 and deletions of 17p (which involves the p53 gene).
- **Squamous metaplasia of the urothelium** can occur in a variety of circumstances, for example as a response to bladder stones, indwelling catheters and infection by schistosoma (schistosomiasis is endemic in countries such as Egypt).
- Under these circumstances, squamous cell carcinoma of the bladder can develop. Often this tumor has invaded the bladder wall at time of presentation.



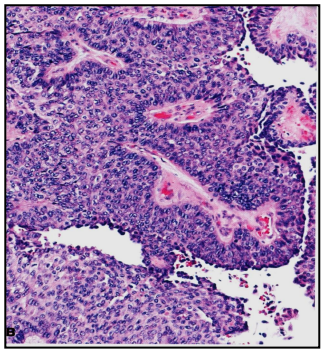
Urothelial (transitional cell) carcinoma in situ of the urinary bladder if untreated, up to 75% of cases go on to invasive cancer.



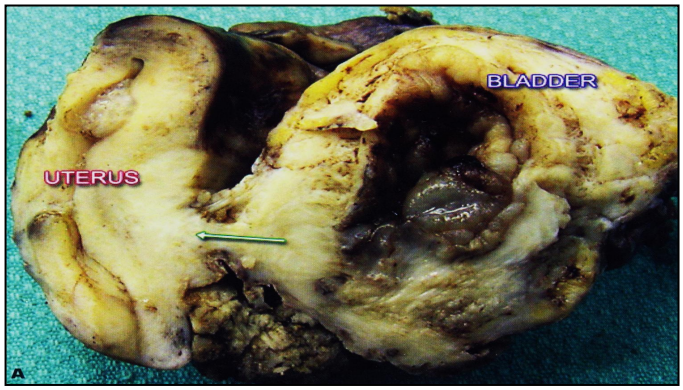
Invasive urothelial carcinoma of the bladder is invading the muscle coat on the right side of the picture.



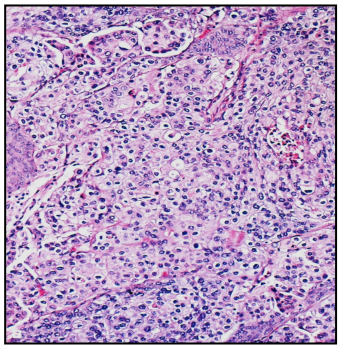
Histology of carcinoma in situ (surface is to the right).



Urothelial carcinoma of bladder.



Advanced urothelial cancer of the bladder has spread posteriorly (arrow)to invade the uterus.



Poorly differentiated urothelial carcinoma.

Box I. confirmed or suspected risk factors for transitional cell carcinoma

Smoking	Increases risk up to five times
Analgesics	Mainly associated with renal pelvis transitional cell carcinoma, but also bladder tumors
Occupation	Workers in aniline dye, rubber and chemical industries due to exposure to β-naphthylanine (which in the liver is converted to carcinogen that must be activated in the bladder). These workers need regular bladder checks.
Cyclophosphamide	Can cause bladder cancer in the long term (although used for cancer treatment)
Schistosomiasis	Causes chronic inflammation and metaplasia (squamous) of the bladder mucosa (leading to squamous cell carcinoma)
Chronic infections/inflammation	Some authorities believe that any chronic inflammatory may predispose to cancer

Box II. Grading and staging of bladder transitional cell carcinoma (TNM)

Grade	Definition
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated/undifferentiated
Stage	**Definition**
Tis	In situ carcinoma
Ta	Non-invasive, papillary tumor
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propia
T3	Tumor invades beyond muscularis propia
T4	Tumor invades prostate, uterus, vagina or pelvic wall/abdominal wall
N1	Single lymph node metastases (≤2cm)
N2	Single metastasis (>2cm) or multiple metastases (≤5cm)
N3	Multiple metastases (>5cm)

The prognosis of TCC of the bladder depends largely on the grade and the stage of tumor but most patients with metastases bladder TCC die within five years of diagnosis.

Contact us: Pathology435@gmail.com

Team Members

Nouf Altwaijri

Aljohara Almazroua

Amjad Alduhaish

Budoor Julaidan

Deema Alfaris

Kayan Kaaki

Khawla Alammari

Lamees Altamimi

Nojood Alhaidri

Noura AlBulushi

Noura AlKharraz

Nouf Alabdulkarim

Reem AlAqeel

Khalid Aburas

Ahmad Taha Alkhiary

Ammar Saleh Almansour

Anas Baleegh Mohammad Ali

Faris Ibrahim Alwarhi

Hamzah Abdullah Alfiar

NaiF MoHaMMeD AlHaDi

Qusai Abdulbaqi Ajlan

Rayan Abdulrahman Almuneef

Zeyad Abdulaziz Alsalem

قال صلى الله عليه وسلم: (من سلك طريقًا يلتمس فيه علمًا سهّل الله له به طريقًا إلى الجنة).

دعواتنا لكم بالتوفيق.