PATHOLOGY TEAM
439

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Tumors of Kidney and UT

Renal neoplasm-pathoma
Renal carcinoma - osmosis
UT tumors-pathoma

Objectives:

- Recognize the benign tumors of the kidney.
- Describe renal cell carcinoma and Wilm's tumor.
- Recognize transitional cell and squamous carcinoma of the urinary bladder.

Key outlines:

- Benign tumors of the kidney.
- Renal Cell Carcinoma.
- Wilm's tumor (nephroblastoma).
- Transitional Cell and Squamous Carcinoma of bladder.

Index:
Important
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Extra Information

TUMORS OF THE KIDNEY

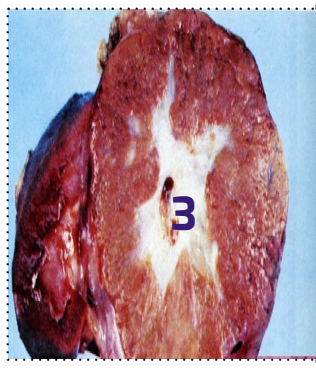
Benign tumors		Malignant tumors	
	Renal oncocytoma		Renal Cell Carcinoma (RCC)
	Angiomyolipoma		Wilms Tumor (nephroblastoma)

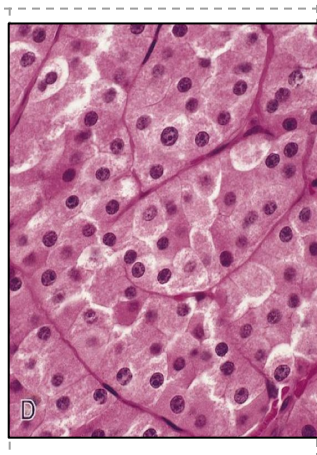
Benign Tumors

Renal Oncocytoma

Benign tumors that arises from the **intercalated cells** of the collecting ducts in the kidney.

Grossly	• **Well circumscribed** • Mahogany-brown colored tumor • With a central **stellate scar** (star-shaped) (Useful in diagnosis)
Microscopically	They are composed of uniform round polygonal cells with abundant, intensely **eosinophilic** (pink) **and granular cytoplasm** with uniform round and central nuclei. These cells are called as **oncocytes** or oncocytic cells.
Electron microscopy:	There are **numerous mitochondria** in the cytoplasm.
Radiologically	They mimic renal cell carcinoma.
Complications	Spontaneous hemorrhage (كل م كبر الورم يدخل ع ال Abdomen = rupture of the peritoneum causing bleeding).

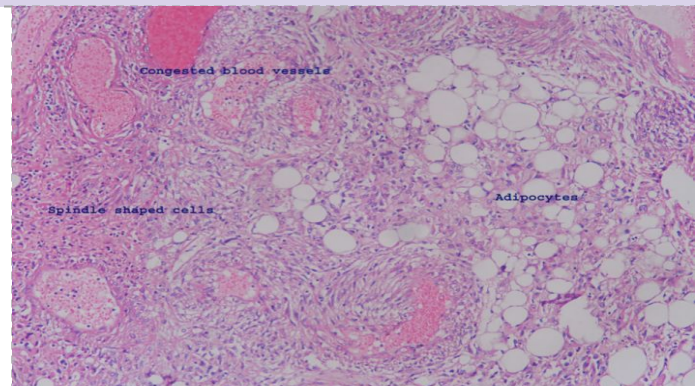




Angiomyolipoma

Angio=blood vessel, Myo=muscle, Lipoma= Fat + benign

- Angiomyolipomas benign neoplasm composed of **admixture of blood vessels, smooth muscle and adipose tissue**
- The amount of each component is variable
- They are usually associated with tuberous sclerosis syndrome.



Malignant Tumors

Renal cell carcinoma (RCC)

- Renal cell carcinoma is the **most common** primary cancer of the kidney,It accounts for 80% of all renal cancers. It arises from **renal tubular epithelial cells**.
- Seen in men ranging from 50-60 years of age.
- Men affected more than women.

Types	**A. Clear cell type 65%** B. Papillary type 10-15% C. Chromophobe type 5% D. Others 15%

Risk factors

1. Tobacco (smoked or chewed)
2. Chronic hypertension
3. Obesity
4. Occupational exposure to cadmium
5. **Acquired cystic kidney disease due to:**

End stage renal disease → Chronic dialysis → Complications in chronic dialysis → Acquired cystic kidney disease → predispose to papillary RCC

6. Genetic risk factors

about 5% are inherited, Hereditary RCCs tend to be multifocal & bilateral & appear at a younger age than sporadic RCC.

Hereditary clear cell RCC	**Hereditary papillary RCC**
Associated with Von Hippel-Lindau (VHL) Syndrome in which there is an autosomal dominant germline **mutation of VHL gene at chromosome 3** (VHL syndrome is characterized by cerebellar hemangioblastomas, retinal angiomas,clear cell RCC, pheochromocytoma and cysts in kidney).	Associated with mutations in the c-MET proto-oncogene **at chromosome 7**. There is no association with the VHL gene

RCC Clinical features:

• The incidence of RCC peaks in the sixth decade.	• RCC is twice as frequent in men as in women.	• **Hematuria** is the single most common presenting sign.
• The classic clinical triad : hematuria, flank pain and a palpable abdominal mass.	• Some patients develop polycythemia.	• These tumor have a high tendency to invade the renal vein and metastasize. • Sometimes RCC is a silent and discovered only after metastasis. • The tumor spreads most frequently to the lungs and bone

- Uncommonly, these tumors produce paraneoplastic syndromes e.g.:

1-Secretion of a parathormone-like substance leads to hyperparathyroidism and hypercalcemia.	2-Production of erythropoietin causes erythrocytosis and polycythemia.	3-Release of renin results in hypertension.	4-may present with Cushing syndrome, masculinization.

RCC Types

A. Clear cell type

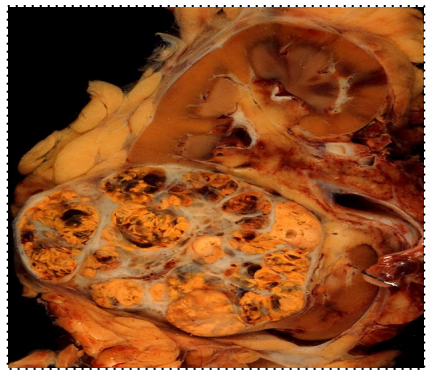
These are the **most common type** and **arises from proximal tubular epithelial cells**. The majority of them are **sporadic**. Uncommonly associated with VHL disease.

Grossly

- usually solitary and **large**.

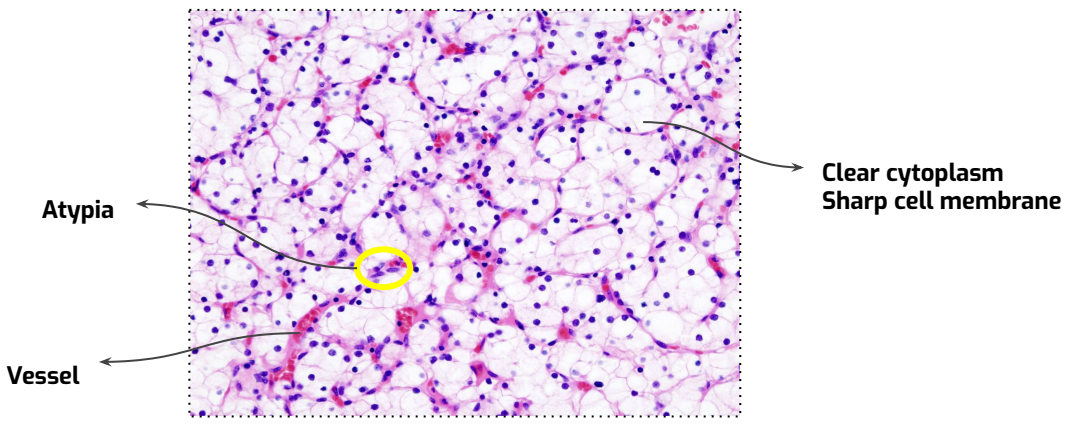
cut surface:

- well circumscribed, solid
- **heterogenous** partly yellow and partly hemorrhagic mass.
- May be cystic and necrotic.
- Tumor commonly **invades** the **renal vein**.
- direct invasion into the **perinephric fat** and **adrenal gland.**



Microscopically

- Tumor is made up of cells with
- **Clear cytoplasm** (=clear cell type) and **sharp cell membrane**.
- The cells are often arranged in sheets or nests.
- The **stroma is highly vascularized**.
- The nuclei can range from no atypia to marked atypia/pleomorphism.
- Some tumors exhibit marked degrees of anaplasia (undifferentiation)



B. papillary cell type

- The tumors have a papillary growth pattern.
- They can be sporadic or familial.
- The familial forms are uncommon and show mutation in the MET proto-oncogene.

C. Chromophobe cell type

- The tumors are made up of chromophobic cells (they are acidophilic (pink) granular cells).

NOTE; papillary and chromophobe RCCs have a better prognosis than the clear cell RCC.

Wilms tumor (nephroblastoma)

Definition	It is a malignant neoplasm arising from embryonic nephrogenic elements composed of mixtures of **blastemal**, **stromal** , and **epithelial tissue**.

- The Precursor lesions for the wilms tumor are Nephrogenic rests
- Can be associated with WAGR syndrome, Denys Drash syndrome and Beckwith weidmann syndrome.

Epidemiology	• It is the most common primary tumor of the kidney in **children** • Most cases of Wilms tumor are sporadic and unilateral. • Some cases of Wilms tumor are **familial with deletion of WT1 gene on chromosome 11p13.**m

Clinical features

1. Wilms tumor usually presents between **1 and 3 years of age and 98% occur before 10 years of age.**
2. **Abdominal mass** (commonest sign)
3. **Hematuria**
4. **Pain abdomen**
5. **Hypertension**

Chemotherapy and **radiation therapy** combined with **surgical resection**, have dramatically improved the outlook of patients with this tumor.

Treatment

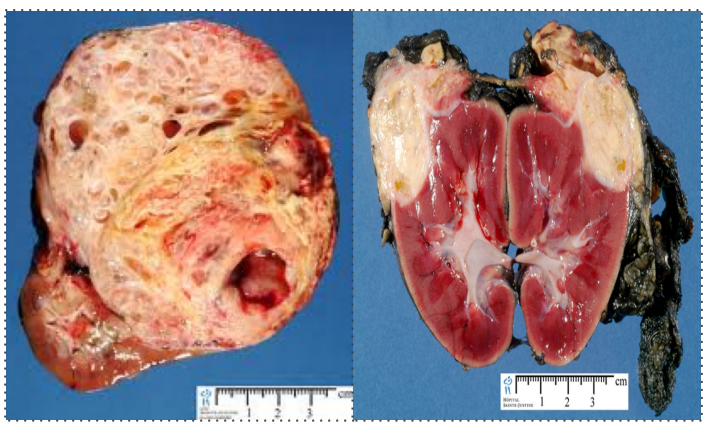
Prognosis

The prognosis for Wilms' tumor is generally **very good.**

Morphology

Grossly

- Huge Unilateral (10% bilateral), solitary, **well circumscribed lesion.**
- By the time Wilms tumor is detected it is **large.**
- Cut section: uniform, pale gray and soft in consistency (**Fish flesh like**).
- The tumor may show **foci of hemorrhage**, **cystic degeneration & necrosis**

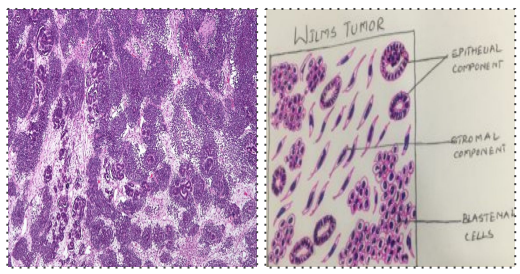


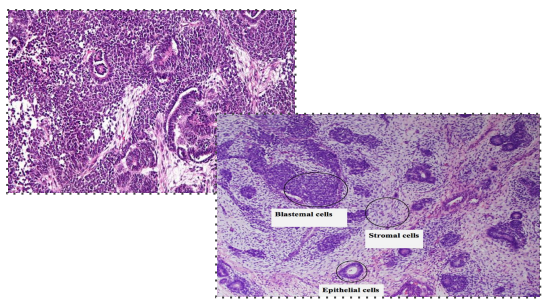
Microscopically

- It is composed of the classical triphasic combination of:

1-Blastemal component: composed of densely packed small round blue cells with scanty cytoplasm and brisk mitosis.	**2-Epithelial component**: composed of immature primitive tubular structures (rosettes) and immature glomeruli.	**3-Stromal component**: composed of loose immature stroma of undifferentiated mesenchymal cells (i.e.immature spindle cells and myxoid material).

- Biphasic and monophasic patterns can also occur.
- 5% of tumors contain foci of **anaplasia**. Anaplasia is an indication of **poor** prognosis.



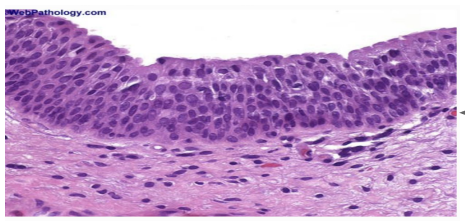


TUMORS OF THE LOWER URINARY TRACT
Urothelial Carcinoma

- Tumors in the collecting system above the bladder are relatively uncommon.
- A small lesion in the ureter may cause urinary outflow obstruction and have greater clinical significance than a much larger mass in the large capacious bladder.

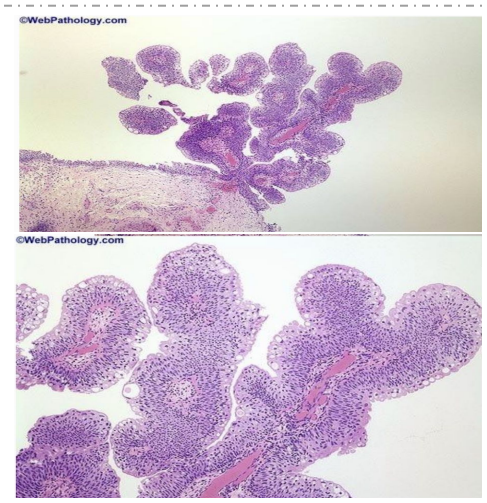
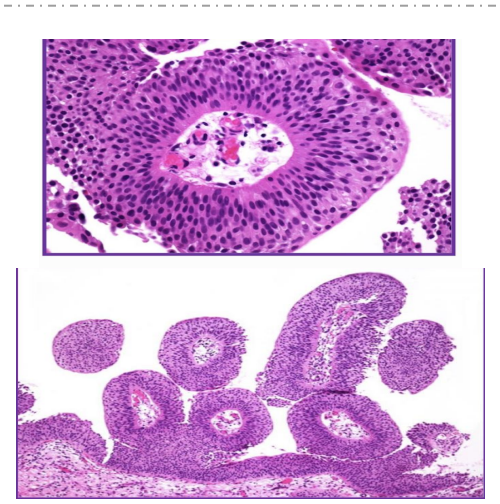
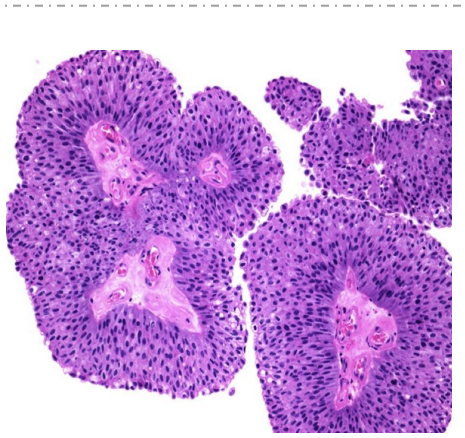
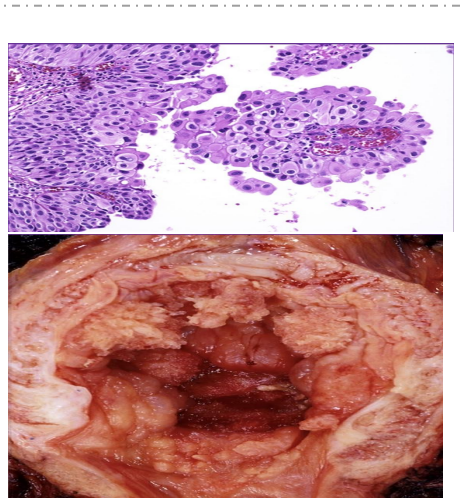
Types of urothelial

- A. Non invasive papillary lesions
  - **Papilloma** (benign)
  - **PUNLMP** (borderline)
  - **Noninvasive papillary urothelial carcinoma low grade** (malignant)
  - **Noninvasive papillary urothelial carcinoma high grade** (malignant)
- B. Non invasive flat lesions (**Flat urothelial carcinoma in situ)**
- C. Invasive urothelial carcinoma.



Normal urothelium

A.Non invasive papillary lesions

Papilloma (Benign)	**Papillary urothelial neoplasm of low malignant potential (PUNLMP)** (Borderline)	**Noninvasive papillary urothelial carcinoma LOW GRADE** (Malignant)	**Noninvasive papillary urothelial carcinoma HIGH GRADE** (Malignant)
-They are non-invasive papillary tumor lined by benign transitional epithelium. -Rare and benign -Usually solitary. -Do not recur once removed.	-Uncommon. -They are non-invasive papillary tumors with nuclear features intermediate between papilloma and low grade papillary urothelial carcinomas - may recur after removal.	- Non-invasive papillary tumors made up of papillary projections lined by malignant urothelial cells with mild atypia / pleomorphism and mild mitotic activity.	-Non-invasive papillary tumor made up of papillary projections lined by poorly differentiated malignant urothelial cells with marked atypia/ pleomorphism and significant (brisk) mitotic activity. -Majority of high grade papillary urothelial carcinomas progress → and they invade into the underlying lamina propria and the muscularis propria becoming → invasive urothelial carcinoma.
			

B.Non invasive flat lesions

Flat urothelial carcinoma in situ

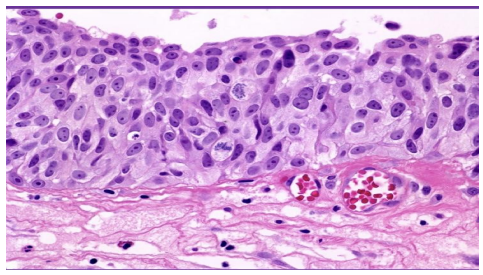
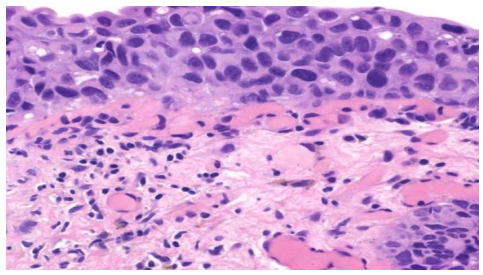
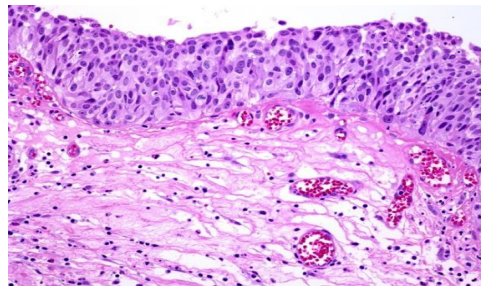
- Non-papillary, non-invasive flat lesions.

- Tend to be multifocal.

- There is the full-thickness dysplasia of the urothelium (hyperchromatic and pleomorphic cells with prominent nucleoli).

- There may be excessive **shedding of malignant cells in urine.(useful for diagnosis)**

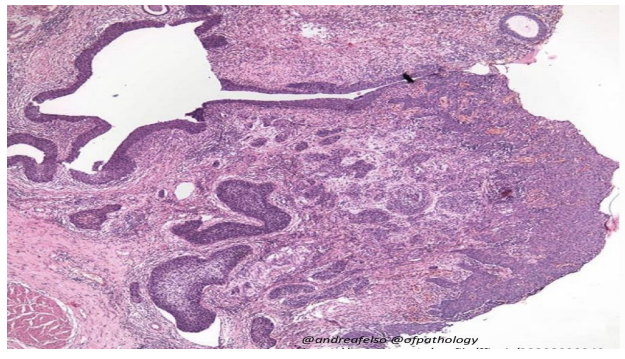
- In about 50% of cases it is associated with subsequent invasion into the underlying lamina propria and the muscularis propria becoming → invasive urothelial carcinoma.

C.Invasive urothelial carcinoma

- Invasive urothelial carcinoma usually progresses from:
  1. High grade papillary urothelial carcinoma
  2. flat urothelial carcinoma in situ.

- Microscopically, the tumor cells infiltrate beyond the basement membrane into the underlying tissue (lamina propria and muscularis propria i.e. the detrusor muscle) in the form of irregular nests, lobules and single cells.



Urothelial Carcinoma Clinical Features and Predisposing Factors

- ❖ More in men
- ❖ Age: 50 to 70 years.

Clinical features

Painless hematuria is the dominant clinical presentation of all these tumors and less frequently as dysuria. Cystoscopy reveals the tumor.

Bladder cancers vary from exophytic, flat, ulcerated to deeply invasive.

Bladder cancer metastasize to regional lymph nodes, liver, lung, and bone.

Predisposing Factors

1. **Bladder tumors**
in those exposed to chemicals called aromatic amines ((arylamines) such as benzidine and beta-naphthylamine). which are sometimes used in the dye industry(aniline and Azo dyes)

2. **Cigarette smoking and chronic cystitis**

3. **Chronic bladder irritation from stones or long term bladder catheters**

4. **Chemotherapy (long-term use of cyclophosphamide)**

5. **Radiotherapy**

Non-Urothelial neoplasms

NON-UROTHELIAL CARCINOMAS OF THE LOWER URINARY TRACT

- Squamous cell carcinoma
- Adenocarcinoma
- Small cell neuroendocrine carcinoma
- Sarcomas (leiomyosarcoma, rhabdomyosarcoma)
- Metastatic (from cervix, prostate etc)

They are rare and have very poor prognosis

Squamous cell carcinoma of the bladder

- Squamous cell carcinoma of the bladder develops in foci of squamous metaplasia.
- Long standing Schistosoma haematobium infections can predispose to squamous cell carcinoma of the urinary bladder

Quiz

1-A 58 y-o man is suffering from hypertension present with flank pain, hematuria, and weight loss. He admits smoking for the past 25 years of his life, and his BMI before is 32. Both his BP and temperature were elevated. Which of the following is the most likely diagnosis?			
a-Wilms tumor	b-Oncocytoma	c-Renal Cell Carcinoma	d-Angiomyolipoma
2-A toddler was brought to the hospital because of an abdominal mass and hematuria. Histology lab report shows epithelial, blastemal, and stromal elements. The doctor diagnosed him with Wilms tumor. What part of the DNA do you think is deleted in this toddler?			
a-WT1 gene on chromosome 11p13	b-WT2 gene on chromosome 12p13	c-WT1 gene on chromosome 13p11	d-WT2 gene on chromosome 13p12
3-The mother of a 12-month-old boy palpates a mass on the right side of the infant's abdomen. The surgical specimen is shown. Microscopically, the tumor is composed of multiple elements, including blastemal, stromal, and epithelial tissues. Which of the following is the most likely diagnosis?			
a-Papilloma	b-Renal Cell Carcinoma	c-Oncocytoma	d-Wilms tumor
4-A 50-year-old man is found to have blood in his urine during a routine checkup. He is otherwise in excellent health, except for a mild microcytic, hypochromic anemia. An enlarged right kidney is found on X-ray examination, and CT scan reveals a renal mass of irregular shape, measuring 6 cm in diameter. Which of the following is the most likely diagnosis?			
a-Wilms tumor	b-RCC	c-Nephroblastoma	d-Metastatic carcinoma
5-For the patient described in Question 4, a fine-needle aspiration of the renal mass shows glycogen-rich tumor cells. Molecular studies would most likely identify mutations in which of the following growth regulatory genes?			
a-VHL	b-WT1	c-ADPKD	d-IGF-2

1-C
2-A
3-D
4-B
5-A

Summary

This summary was taken from Robbins & Team 438

Benign Tumors of The Kidney

Oncocytoma	Angiomyolipoma
Arise from intercalated cells of collecting ducts	Composed of admixture of: ○ Blood vessels ○ Smooth muscle ○ Adipose tissue
They mimic renal cell carcinoma	Associated with Tuberous sclerosis syndrome

Malignant Tumors of The Kidney

Renal Cell Carcinoma Arise from renal tubular epithelial cells			WILMS Tumor (Nephroblastoma)
Clear Cell	**Papillary**	**Chromophobe**	Childhood tumor (<10yrs)
Proximal tubular epithelial cells	-	Intercalated cells of collecting ducts	Embryonic nephrogenic elements: ○ Blastemal ○ Stromal ○ Epithelial tissue
Mutation of the VHL gene on chromosome 3	Mutation in c-met proto-oncogene (MET) located on chromosome 7	less common	Deletion of WT1 gene on chromosome 11p13
Hematuria (most common), can spread to the lungs and bones			Abdominal mass (most common)
involves the renal vein	Better prognosis than Clear Cell RCC		Very good prognosis, if anaplasia is indicated → poor prognosis

Tumor of The Lower Urinary Tract

Papilloma	PUNLMP	Low grade papillary urothelial carcinoma	High grade papillary urothelial carcinoma	Urothelial carcinoma in situ
Benign	Intermediate	Malignant	Malignant and invasive	Malignant and invasive
Rarely recurs after removal	May recur after removal	Minimal pleomorphism and mitotic activity	Marked hyperchromasia, pleomorphism and rapid mitosis	Lacks cohesiveness → shedding of malignant cells in the urine

SUMMARY

Renal Cell Carcinoma

Renal cell carcinomas account for 2% to 3% of all cancers in adults and are classified into three types:

- *Clear cell carcinomas* are the most common and are associated with homozygous loss of the VHL tumor suppressor protein; tumors frequently invade the renal vein.
- *Papillary renal cell carcinomas* frequently are associated with increased expression and activating mutations of the *MET* oncogene; they tend to be bilateral and multiple and show variable papilla formation.
- *Chromophobe renal cell carcinomas* are less common; tumor cells are not as clear as in the other renal cell carcinomas.

SUMMARY

WILMS TUMOR

- Wilms tumor is the most common renal neoplasm of childhood.
- Patients with three syndromes are at increased risk for Wilms tumors: Denys-Drash, Beckwith-Wiedemann, and Wilms tumor, aniridia, genital abnormalities, and mental retardation (WGAR) syndrome.
- WAGR syndrome and DDS are associated with WT1 inactivation, whereas Beckwith-Wiedemann arises through imprinting abnormalities at the WT2 locus, principally involving the *IGF2* gene.
- The morphologic components of Wilms tumor include blastema (small, round blue cells) and epithelial and stromal elements.
- Nephrogenic rests are precursor lesions of Wilms tumors.

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