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Objectives

Renal tumors

RCC

Types

Bladder Tumours

Prognosis

Staging



TUMORS

- ▶ The commonest malignant T of the kidney is the
 - ❖ (1) **Renal cell carcinoma =RCC (85%)**, followed by
 - ❖ (2) **Nephroblastoma = Wilm's tumor (10%)** & by
 - ❖ (3) **Carcinoma of the renal calyces & pelvis (5%)**.
- ▶ Benign renal T, such as small (<0.5 cm) **cortical papillary adenomas** or interstitial cell medullary **fibromas** have no clinical significance.
- ▶ Tumors of bladder are much more common than the RCC.



Renal Cell Carcinoma (RCC)

Renal cell carcinoma (RCC) is the third most common cancer of the genitourinary tract and the most lethal urologic cancer, accounting for approximately 2% of all cancer deaths

- ▶ **RCC** are derived from the **renal tubular epithelium**, & hence they are located predominantly in the renal cortex.
- ▶ **RCC** represent **85%** of all primary renal cancers.
- ▶ **RCC** are most common from the 6th to 7th decades, & men are affected about twice as commonly as women.



- ▶ Approximately one-third of the patients with RCC will present with metastases, and many patients will develop metastasis after surgical resection.
- ▶ Traditionally, RCC is known to be resistant to chemotherapy. However, there has been tremendous development in effective molecular targeted therapies in the past few years for specific types of RCC with well-defined histology and molecular abnormalities.
- ▶ Therefore, accurate histologic diagnosis and classification is increasingly important
- ▶ **The risk of developing RCC is higher in :**
- ▶ **smokers**, **hypertensive**, **obese** patients, & those who have had occupational exposure to **cadmium**;



- **30-fold in individuals who develop acquired polycystic disease as a complication of chronic dialysis.**

The role of genetic factors in the causation of RCC is discussed below.

Based on their molecular origins, RCC are classified in 3 forms:

- ▶ **(I) Clear Cell RCC (80%)**
- ▶ **(II) Papillary RCC (15%)**
- ▶ **(III) Chromophobe RCC (5%).**



(I) Clear cell RCC

- ▶ Commonest type, comprises **80%** of all RCC, Tumor cells show clear or granular cytoplasm. **Majority** are **sporadic**, also occur in **familial** forms or in association with...
- ▶ **An autosomal dominant von Hippel-Lindau (VHL) disease** characterized by predisposition to a variety of tumors, but particularly to **hemangioblastomas** of the cerebellum & retina.
Hundreds of **bilateral renal cysts & bilateral, multiple, clear cell RCC** develop in 40% to 60% of **VHL disease** patients.
- ▶ **Those with VHL syndrome inherit a germ-line mutation of the VHL gene on chromosome 3p25 & lose of the second allele by somatic mutation.**
- ▶ **Thus, the loss of both copies of this tumor suppressor gene gives rise to clear cell RCC.**



► The VHL gene is also involved in the majority of **sporadic** clear cell RCC. Thus, **homozygous loss of the VHL gene** seems to be the common underlying molecular abnormality in **both sporadic & familial forms of clear cell RCC**.

► The VHL protein is involved in limiting the angiogenic response to hypoxia; thus, its absence may lead to angiogenesis & tumor growth.



(II) Papillary RCC

- ▶ Comprises **15%** of RCC.
- ▶ Shows **papillary growth** pattern.
- ▶ Are frequently **multifocal & bilateral**;
- ▶ Occurs in **familial & sporadic** forms,
- ▶ The cause is the **MET proto-oncogene**, located on chromosome 7q31.
- ▶ **Trisomy of chromosome 7 is seen commonly in both familial & sporadic cases**, with the addition of an activating mutation of the MET gene in the familial cases only.



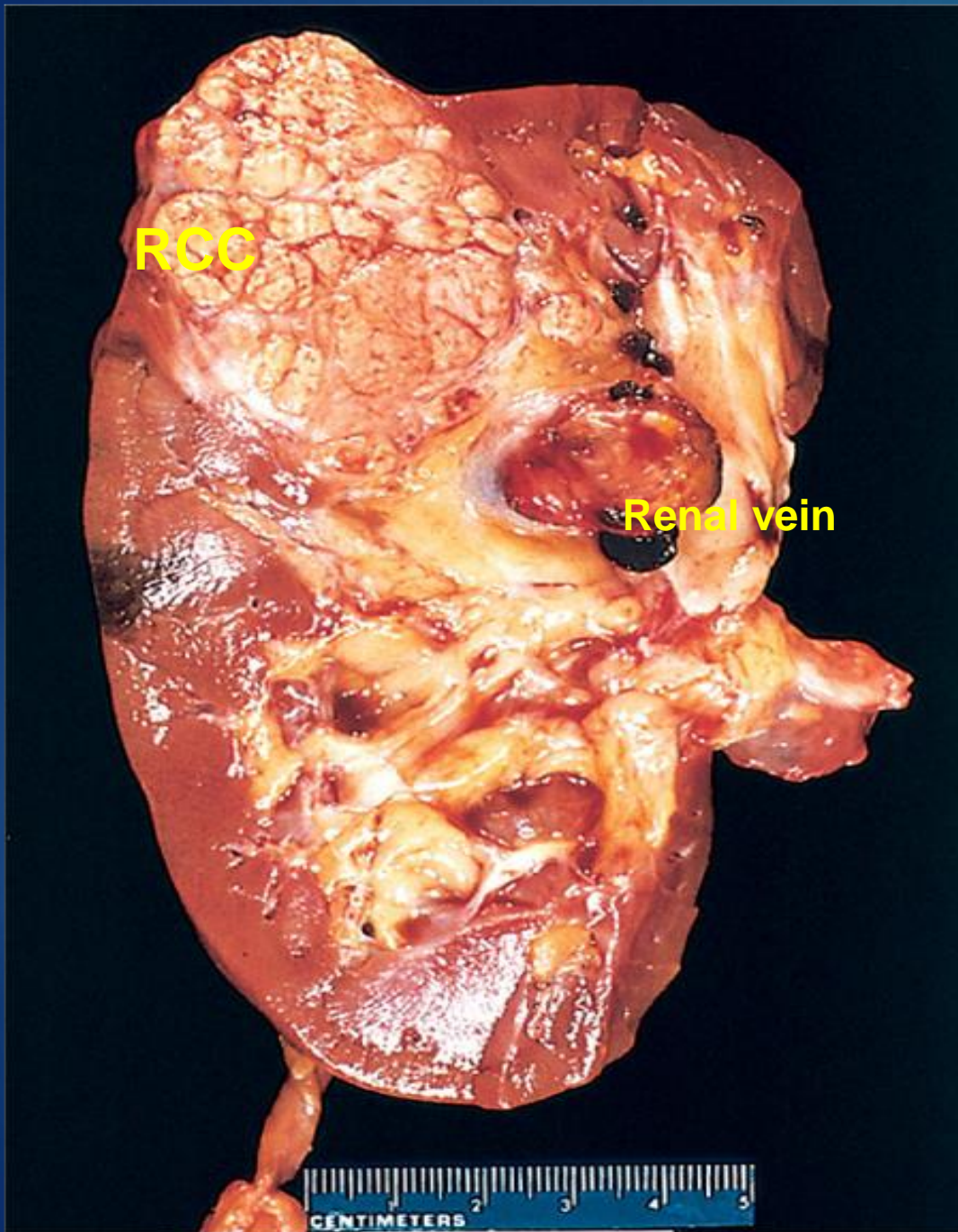
(III) Chromophobe RCC

- ▶ **Rarest (5%) type** of RCC.
- ▶ **Arise** from intercalated cells of collecting ducts.
- ▶ Tumor cells **stain more darkly** (hence the name, i.e., they are less clear than cells in clear cell RCC).
- ❑ **Unique** in having **multiple losses of entire chromosomes**, including chromosomes 1, 2, 6, 10, 13, 17, & 21.
- ❑ In general, chromophobe RCC have a good prognosis.

Morphology

- ▶ **Grossly, the clear cell RCC** is usually **solitary, spherical & large** mass, up to 15 cm in \emptyset , arising anywhere in the cortex, & its cut surface is **yellow orange** with areas of **cystic necrosis** & fresh or old **hemorrhages**.

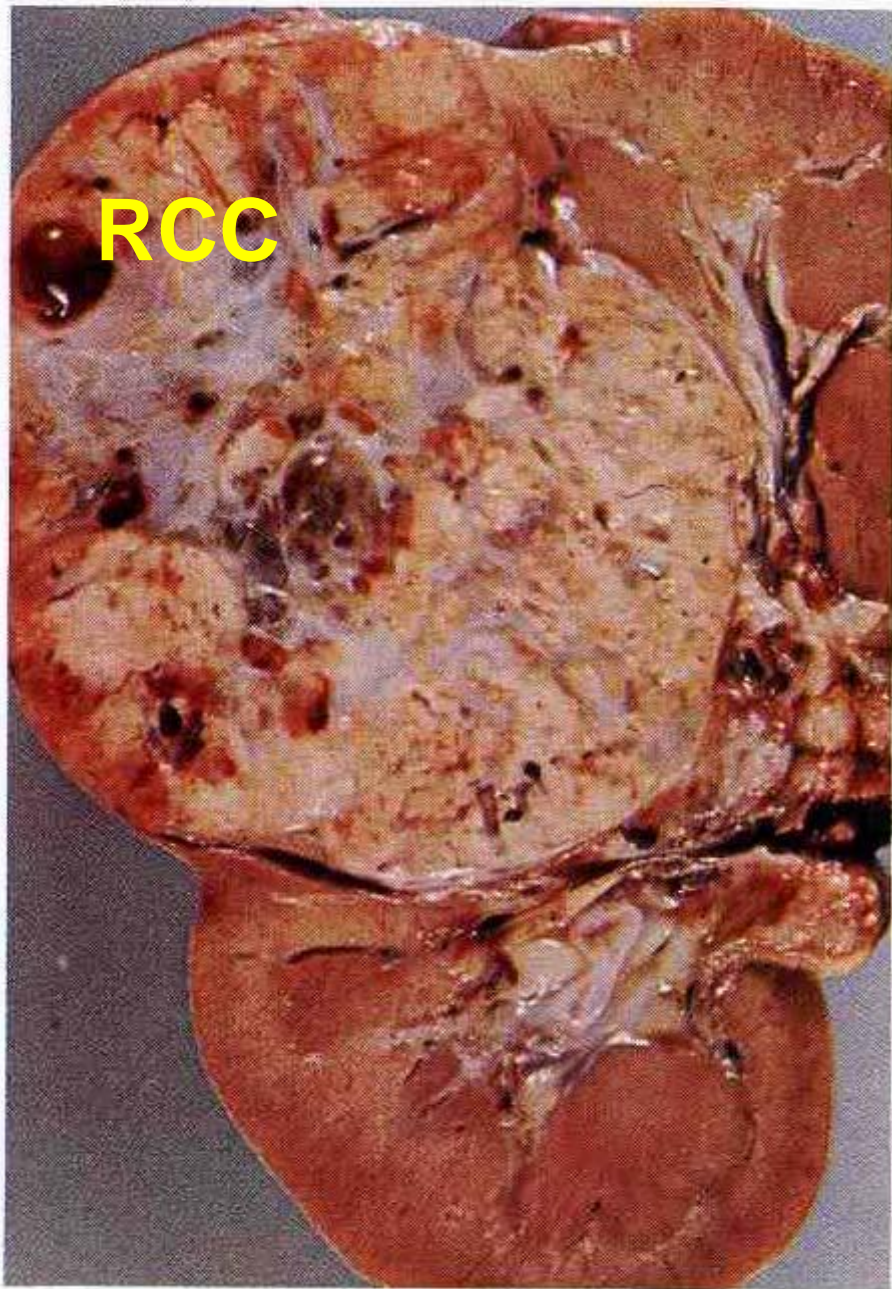




Renal cell carcinoma (RCC): typical cross-section of ★ yellowish, spherical tumor in the upper pole of the kidney.
★ Note the tumor invasion in the dilated thrombosed renal vein



Renal cell carcinoma



- Smooth rounded tumor mass in the upper pole of the kidney invading the renal vein.
- Yellow cut surface, with greyish fibrous septa, areas of hemorrhage & cystic necrosis

10.54 Adenocarcinoma: kidney



- ▶ As the tumor enlarges, it **frequently invades** the
 - ❖ (a) **renal vein** growing as a solid column within it, sometimes extending as far as the inferior vena cava & even into the right side of the heart.
 - ❖ Less frequently, it may **invade** through the
 - (b) Walls of the **calyces, pelvis & the ureter, & occasionally,**
 - (c) in to the **perinephric fat & adrenal gland.**

▶ **Histologicaly,**

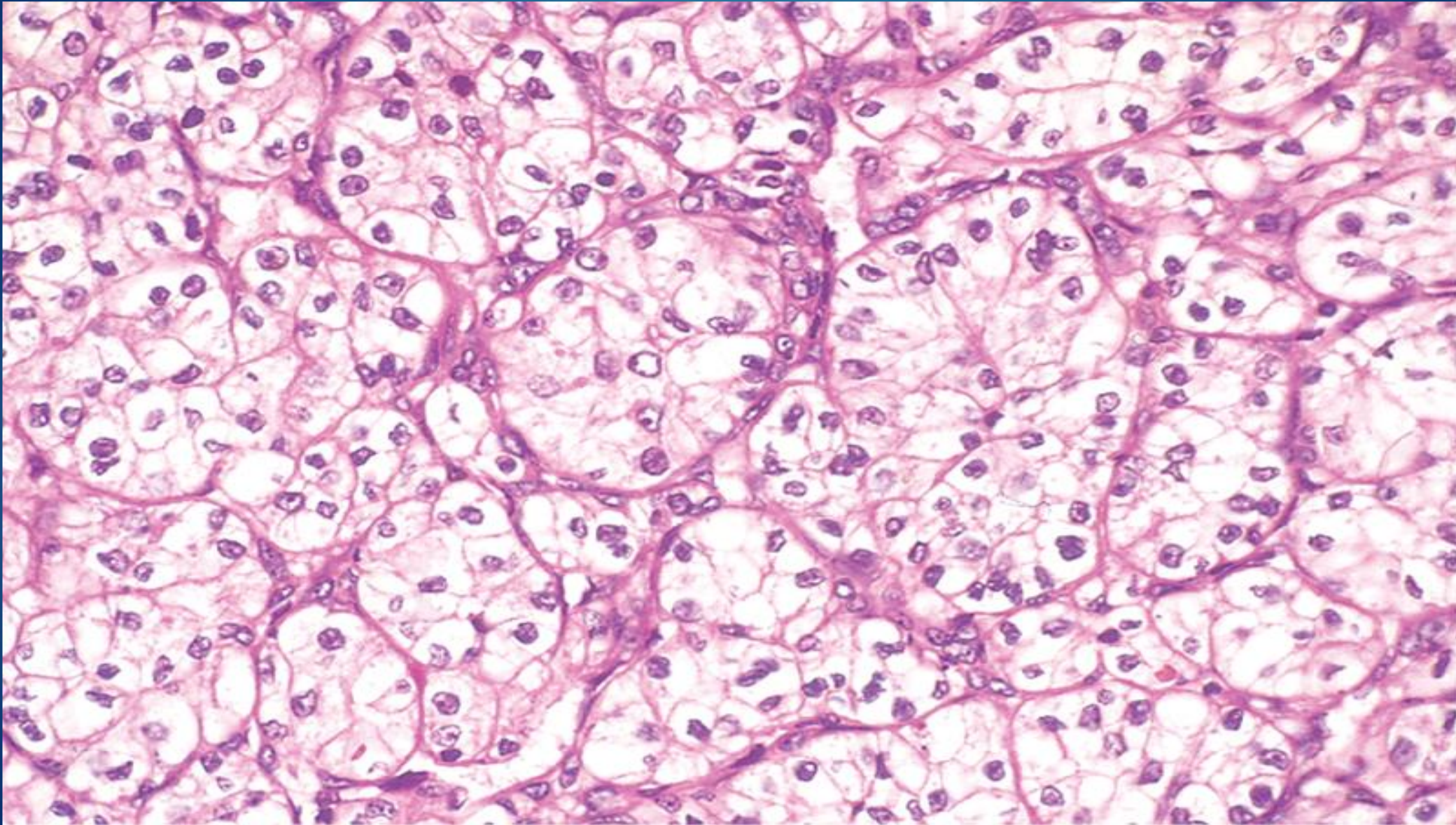
- ▶ Depending on the amounts of lipid & glycogen present, the tumor cells may appear:
- ▶ (a) Classically **vacuolated**, with lipid-laden **clear** cells, with small round nuclei, or



- ▶ **(b) Granular cells**, resembling the tubular epithelium, with granular pink cytoplasm.
- Some tumors exhibit marked degrees of **anaplasia**, with numerous mitotic figures & markedly enlarged, hyperchromatic, pleomorphic nuclei.
- The cellular arrangement, too, varies widely, with cells forming **tubules, cords** or **disorganized masses**. The stroma is usually scant, but highly vascularized



High power detail of the clear cell pattern of renal cell carcinoma



Grossly:

- the papillary RCC exhibit □ papillary formation with fibrovascular cores. They tend to be bilateral & □ multiple, & may show gross evidence of cystic degeneration, necrosis & hemorrhage; but because of their lower lipid content, they are less orange-yellow in color. □ The cells can have clear or pink cytoplasm.
- Chromophobe RCC tends to be □ tan-brown grossly. □ Their cells usually have clear, flocculent cytoplasm with very prominent, distinct cell membranes. The nuclei are surrounded by halos of cleared cytoplasm. By EM, large numbers of characteristic macrovesicles are seen.



Clinically,

- ▶ the most frequent & characteristic presenting manifestation of all RCCs is
- ▶ **(I) Hematuria, occurring in more than 50% of cases.**
Less commonly as;
- ▶ **(II) painful, palpable flank mass, or may**
- ▶ **(III) present with metastases, in which the primary T may remain silent & is discovered only after it metastasizes to other sites, the commonest are the lungs & bones.**
- ▶ Extra-renal nonspecific effects of RCC are **(1) fever, (2) polycythemia affecting 5% to 10% of persons with RCC resulting from elaboration of erythropoietin by tumor cells.**
- ▶ Uncommonly, RCC may cause **(3) paraneoplastic syndromes due to their production of a variety of hormone-like substances, resulting in hypercalcemia, hypertension, Cushing syndrome, feminization or masculinization.**



IMMUNOHISTOCHEMICAL TECHNIQUES IN RENAL NEOPLASMS

- ▶ Immunohistochemical techniques with a variety of markers have been applied more frequently in diagnostic pathology of renal neoplasm
- ▶ Some of the most important and useful markers for the diagnosis of renal neoplasm include **cytokeratins, vimentin, PAX2, PAX8, RCC marker, CD10, E-cadherin, kidney-specific cadherin**, parvalbumin, **α-methylacyl coenzyme A racemase, CD117, TFE3, thrombomodulin, uroplakin III, p63, CD57**.
- ▶ Each marker has its diagnostic role in a specific diagnostic setting.
- ▶ The common diagnostic situations that call for immunohistochemical staining are differential diagnoses of renal versus non renal neoplasms,



▶ TNM staging (7th edition)

▶ T

▶ T1

- ▶ **T1a:** tumor confined to kidney, <4 cm
- ▶ **T1b:** tumor confined to kidney, >4 cm but <7 cm

▶ T2: limited to kidney >7 cm

- ▶ **T2a:** tumor confined to kidney, >7 cm but not >10 cm
- ▶ **T2b:** tumor confined to kidney, >10 cm

▶ T3: tumor extension into major veins or perinephric tissues, but not into ipsilateral adrenal gland or beyond Gerota's fascia

- ▶ **T3a:** tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
- ▶ **T3b:** spread to infra diaphragmatic IVC
- ▶ **T3c:** spread to supra diaphragmatic IVC or invades the wall of the IVC

▶ T4: involves ipsilateral adrenal gland or invades beyond Gerota's fascia

▶ N

- ▶ **N0:** no nodal involvement
- ▶ **N1:** metastatic involvement of regional lymph node(s)

▶ M

- ▶ **M0:** no distant metastases
- ▶ **M1:** distant metastases



- ▶ **Stage groupings**
- ▶ **stage I:** T1 N0 M0
- ▶ **stage II:** T2 N0 M0
- ▶ **stage III:** T3 or N1 with M0
- ▶ **stage IV:** T4 or M1

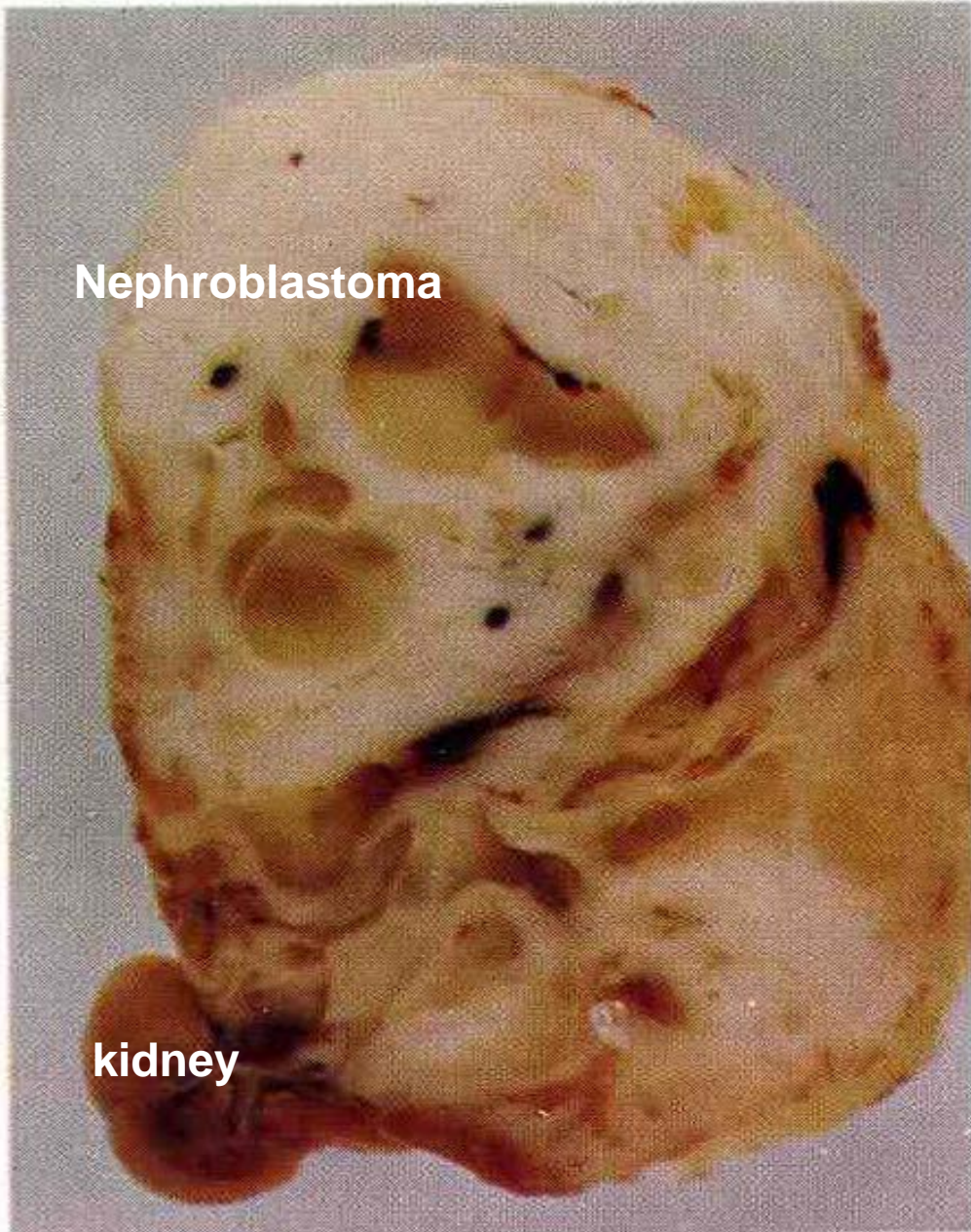


Nephroblastoma (Wilm's Tumor)

- Represent **10%** of all renal cancers.
- The **3rd most common solid cancer in children** younger than 10 years ;it occurs rarely in adults,
- A mixed tumor, contain a variety of cell & tissue components (epithelial & mesenchymal), **all derived from the mesoderm.**
- Like retinoblastoma, it may arise sporadically or be familial, **inherited as an autosomal dominant trait.**



Nephroblastoma (Wilms Tumor).



□ A creamy-white tumor has largely replaced the kidney, a small portion of which is visible at the lower left.

□ Numerous cysts & focal hemorrhages are present within the tumor.

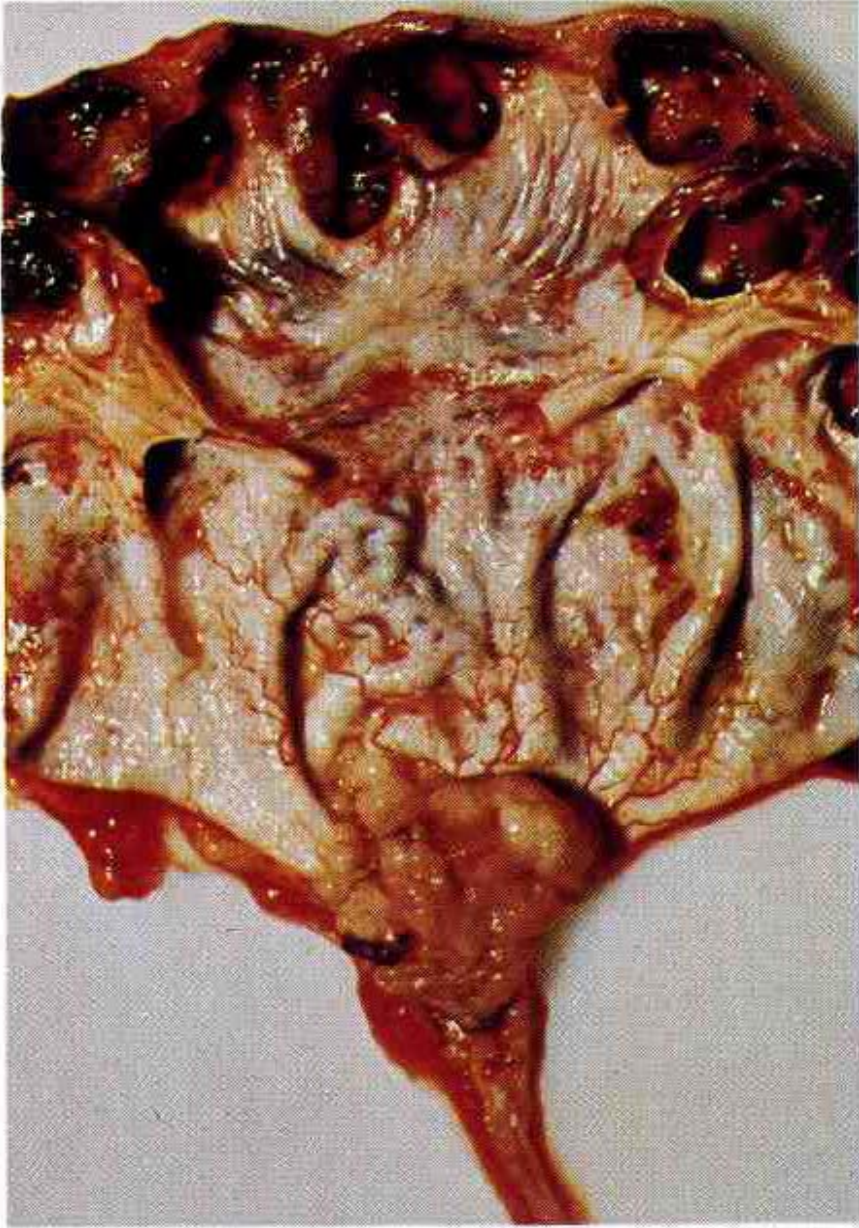
10.55 Wilms' tumour (nephroblastoma):
kidney



Tumors of the (Renal calyces, Pelvis, Ureter, Urinary Bladder & Urethra)

- ▶ The entire urinary collecting system, from renal calyces to urethra is lined by transitional epithelium, so its epithelial tumors assume transitional or “urothelial” patterns.
- ▶ Clinically, the most common presentation of all these tumors is **painless hematuria**
- ▶ A small tumor in the ureter may cause urinary outflow obstruction & hydro nephrosis, & have greater clinical significance than a much larger mass in the bladder.
- ▶ **Renal pelvis papillary TCC a carcinomas** (comprising 5% of all kidney ca), are much less frequent than bladder ca. Usually causes painless hematuria; but if they cause obstruction, it may result in hydronephrosis and pain in the costovertebral angle.
- ▶ **Infiltration of the walls of the pelvis, calyces, & renal vein worsens the prognosis**





10.59 Transitional cell carcinoma: renal pelvis

Transitional (urothelial) cell carcinoma: renal pelvis.

- A sessile papillary yellowish-grey TCCa at the pelvi-ureteric junction lead to obstructing the ureter and producing severe hydronephrosis, with...
- marked pelvic mucosal congestion & extensive calyceal hemorrhage



Bladder tumors classified into:

- ▶ (1) Very rare benign papillomas, usually solitary, 0.2-1.0 cm frond like structures having a delicate fibrovascular core covered by multilayered completely normal looking transitional epithelium. They are noninvasive & rarely recur once removed.
- ▶ (2) Papillary urothelial tumors of low malignant potential.
- ▶ (3) Transitional (Urothelial) carcinoma (TCCa) may be papillary or flat, noninvasive or invasive & low or high grade.
- ▶ **Low-grade (Grade I) ca**
 - are always papillary & rarely invasive, may recur after removal.



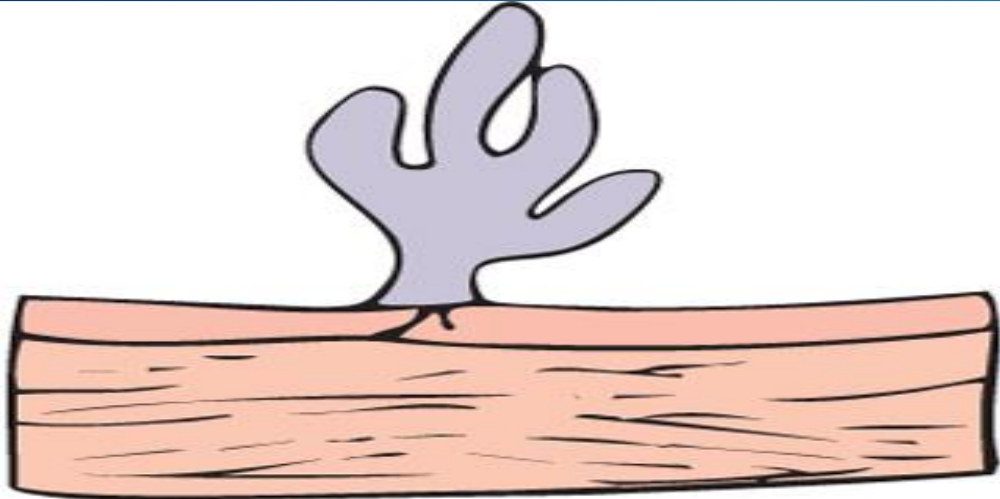
- Increasing degrees of cellular atypia & anaplasia are seen in papillary exophytic tumors accompanied by an increase in the size of the tumor & evidence of invasion of the submucosal.

▼ **High-grade (Grades II & III) ca** can be **papillary or flat** may cover **larger** areas of the mucosa, invade deeper in **the muscular layer**, may ulcerate, & may show foci of squamous differentiation.

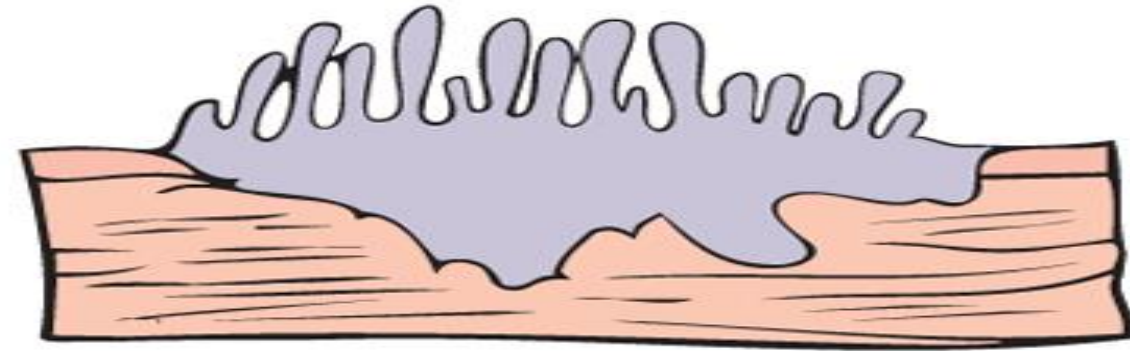
- **5% of bladder ca in US** (BUT up **50%** else where inworld) are usually associated with Schistosomal cystitis are **true squamous cell ca**



Four morphologic patterns of bladder tumor



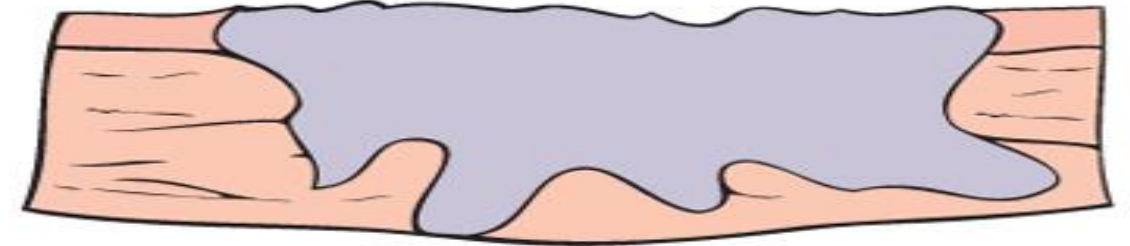
Papilloma–
papillary carcinoma



Invasive
papillary carcinoma



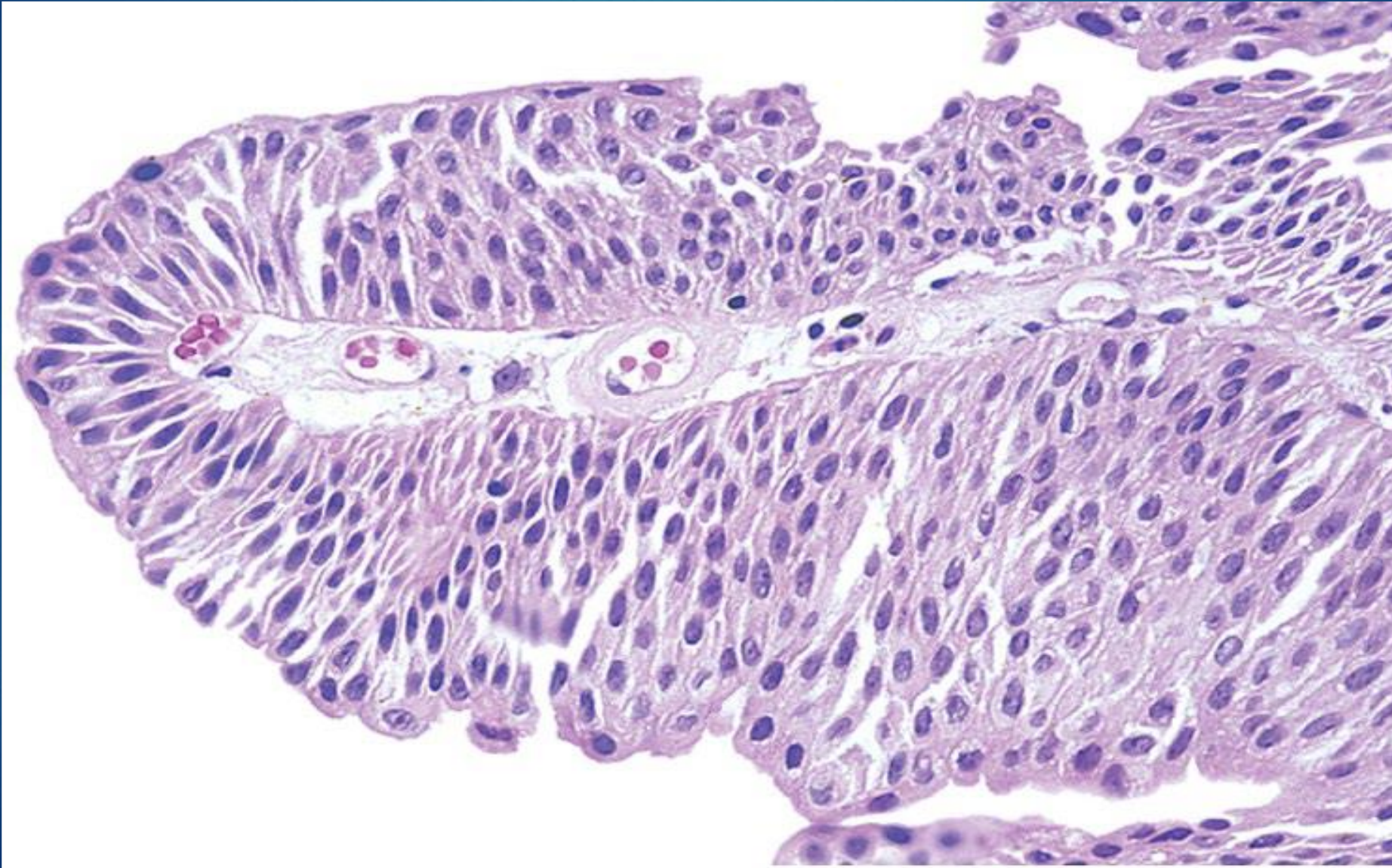
Flat noninvasive
carcinoma



Flat invasive
carcinoma



Low-grade papillary urothelial carcinoma of the bladder. The delicate papilla is covered by orderly transitional epithelium.





10.63 Papillomas: bladder

Low-grade papillary urothelial carcinoma: bladder.

- Multiple small sessile papillary tumors, covering large areas of the bladder.
- The patient worked for many years in the rubber industry.



Transitional cell carcinoma, Grade II X150. Papillae, covered by transitional epithelium, several times thicker than normal (thin arrow) & with a fibrovascular core (thick arrow).



- ▶ Grades II & III ca infiltrate surrounding structures, spread to regional LNs & occasionally metastasize.
- ▶ In addition to overt ca, an in situ (pre-invasive) stage of bladder carcinoma can be recognized, often in individuals with previous or simultaneous papillary or invasive tumors.
- ▶ Bladder ca affect men 3 times as frequently as women.
- ▶ It usually develop in the 50 to 70 years age group.



▶ **Bladder cancer are:**

- ▶ 50 times more common in aniline dye workers, due to carcinogenic effect of β -naphthylamine.
- ▶ It is more common in:
 - ▶ Schistosomiasis of the bladder &
 - ▶ Chronic cystitis,
 - ▶ Cigarette smoking,
 - ▶ Certain drugs (e.g., cyclophosphamide) are also believed to induce higher rates of bladder cancer



- ▶ **The most common genetic abnormalities seen in bladder cancers are mutations, involving several genes, on chromosome 9 (including p16), p53, & FGFR3.**
- ▶ **Bladder tumors prognosis depends** most importantly on the depth of the invasion of the ca (muscular invasion usually treated by total cystectomy) & on their histological grade.
- ▶ **Except for the clearly benign papillomas, all bladder tumors tend to recur after removal.**
- ▶ **Tumors invading ureteral or urethral orifices cause UT obstruction.**
- ▶ **Prognosis of low-grade shallow bladder tumors, after removal is generally good, but when...**
- ▶ **Deep penetration of the bladder wall muscles has occurred; the prognosis is poor with less than 20% 5-year survival rate**



Bladder cancer

- ▶ **Stage 0a:** This is an early cancer that is only found on the surface of the inner lining of the bladder. Cancer cells are grouped together and can often be easily removed. The cancer has not invaded the muscle or connective tissue of the bladder wall. This type of bladder cancer is also called noninvasive papillary urothelial carcinoma (Ta, N0, M0).
- ▶ **Stage 0is:** This stage of cancer, also known as a flat tumor or carcinoma in situ (CIS), is found only on the inner lining of the bladder. It has not grown in toward the hollow part of the bladder, and it has not spread to the thick layer of muscle or connective tissue of the bladder (Tis, N0, M0).



- ▶ This is always a high-grade cancer (see “Grades,” below) and is considered an aggressive disease because it can lead to muscle-invasive disease.
- ▶ **Stage I:** The cancer has grown through the inner lining of the bladder and into the lamina propria. It has not spread to the thick layer of muscle in the bladder wall or to lymph nodes or other organs (T1, N0, M0).
- ▶ **Stage II:** The cancer has spread into the thick muscle wall of the bladder. It is also called invasive cancer or muscle-invasive cancer. The tumor has not reached the fatty tissue surrounding the bladder and has not spread to the lymph nodes or other organs (T2, N0, M0).



- ▶ **Stage III:** The cancer has spread throughout the muscle wall to the fatty layer of tissue surrounding the bladder (perivesical tissue) or to the prostate in a man or the uterus and vagina in a woman. Or, the cancer has spread to the regional lymph nodes.
- ▶ **Stage IIIA:** The tumor has grown into the perivesical tissue or has spread to the prostate, uterus, or vagina, but has not spread to the lymph nodes or other organs (T3a, T3b, or T4a; N0; M0), or the cancer has spread to a single regional lymph node (T1 to T4a, N1, M0).
- ▶ **Stage IIIB:** The cancer has spread to 2 or more regional lymph nodes or to the common iliac lymph nodes (T1 to T4a, N2 or N3, M0).



- ▶ **Stage IV:** The tumor has spread into the pelvic wall or abdominal wall, or the cancer has spread to lymph nodes outside of the pelvis or to other parts of the body.
- ▶ **Stage IVA:** The tumor has spread to the pelvic wall or the abdominal wall but not to other parts of the body (T4b, any N, M0), or the cancer has spread to lymph nodes located outside of the pelvis (any T, any N, M1a).
- ▶ **Stage IVB:** The cancer has spread other parts of the body (any T, any N, M1b).



Thank You

&

Good luck

