Tumor of the kidney and urinary tracts

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- Many types of benign and malignant neoplasms occur in the urinary tract. In general, benign neoplasms such as small cortical papillary adenomas (<0.5 cm in diameter), which are found in up to 40% of adults in autopsies, have limited clinical significance.
- The most common malignant neoplasm of the kidney is renal cell carcinoma, followed in frequency by nephroblastoma (Wilms tumor) and by primary neoplasms of the calyces and pelvis.
- Other types of renal cancer are rare.
- Neoplasms of the lower urinary tract are about twice as common as renal cell carcinomas.

Renal Cell Carcinoma

- Renal cell carcinomas are derived from the renal tubular epithelium, and hence they are located predominantly in the cortex. These neoplasms represent 80% to 85% of all primary malignant neoplasms of the kidney and 2% to 3% of all cancers in adults.
- Carcinomas of the kidney are most common from the sixth to seventh decades, and men are affected about twice as commonly as women. The risk for developing these neoplasms is higher in smokers, hypertensive or obese patients, and those who have had occupational exposure to cadmium. The risk for developing renal cell cancer is increased in individuals with acquired polycystic disease as a complication of chronic dialysis.

- Renal cell cancers are classified on the basis of morphology and growth patterns. However, recent advances in the understanding of the genetic basis of renal carcinomas have led to a new classification that takes into account the molecular origins of these tumors. The three most common forms, are clear cell carcinoma, papillary renal cell carcinoma, and chromophobe renal carcinoma.

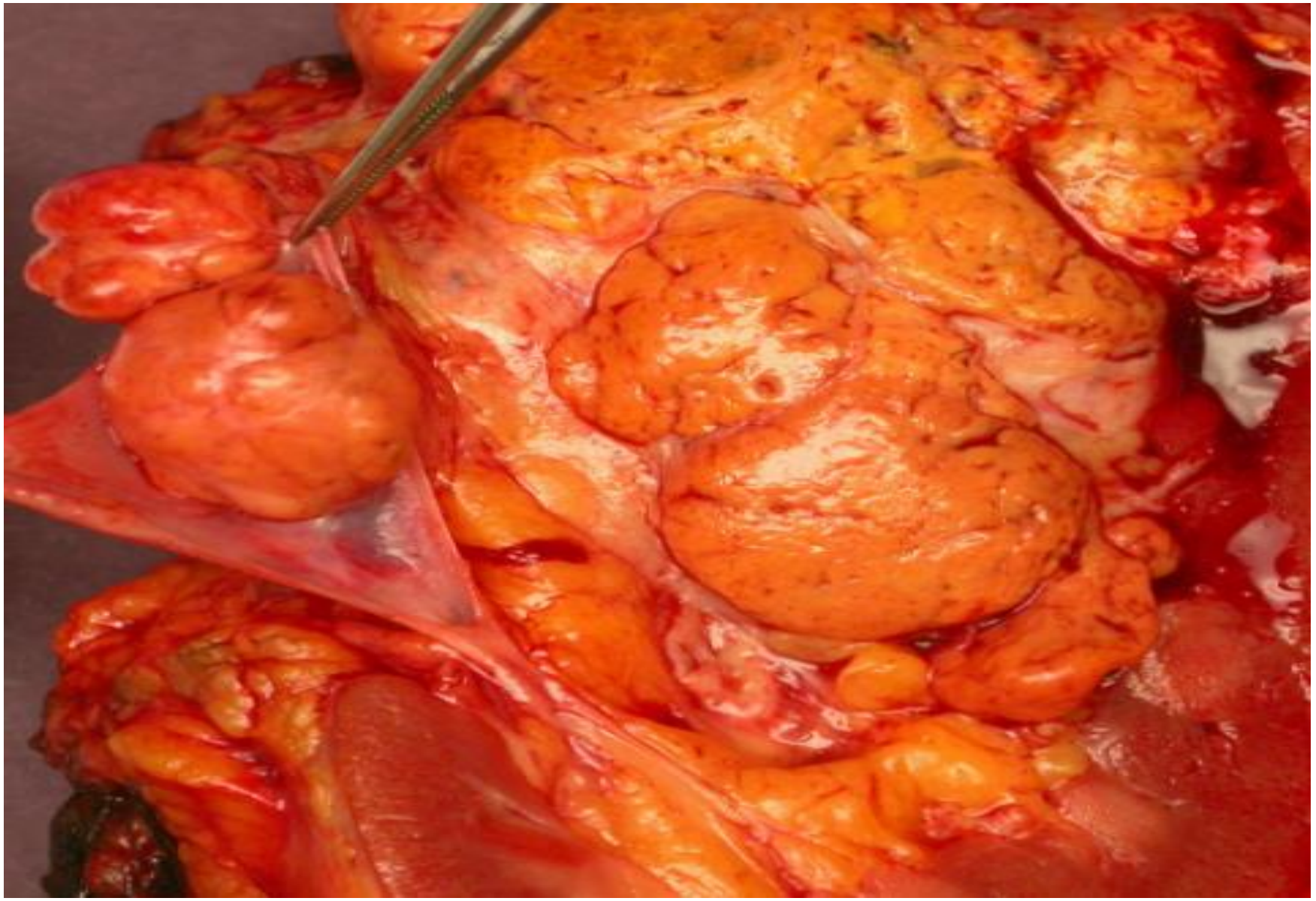
Clear Cell Carcinomas

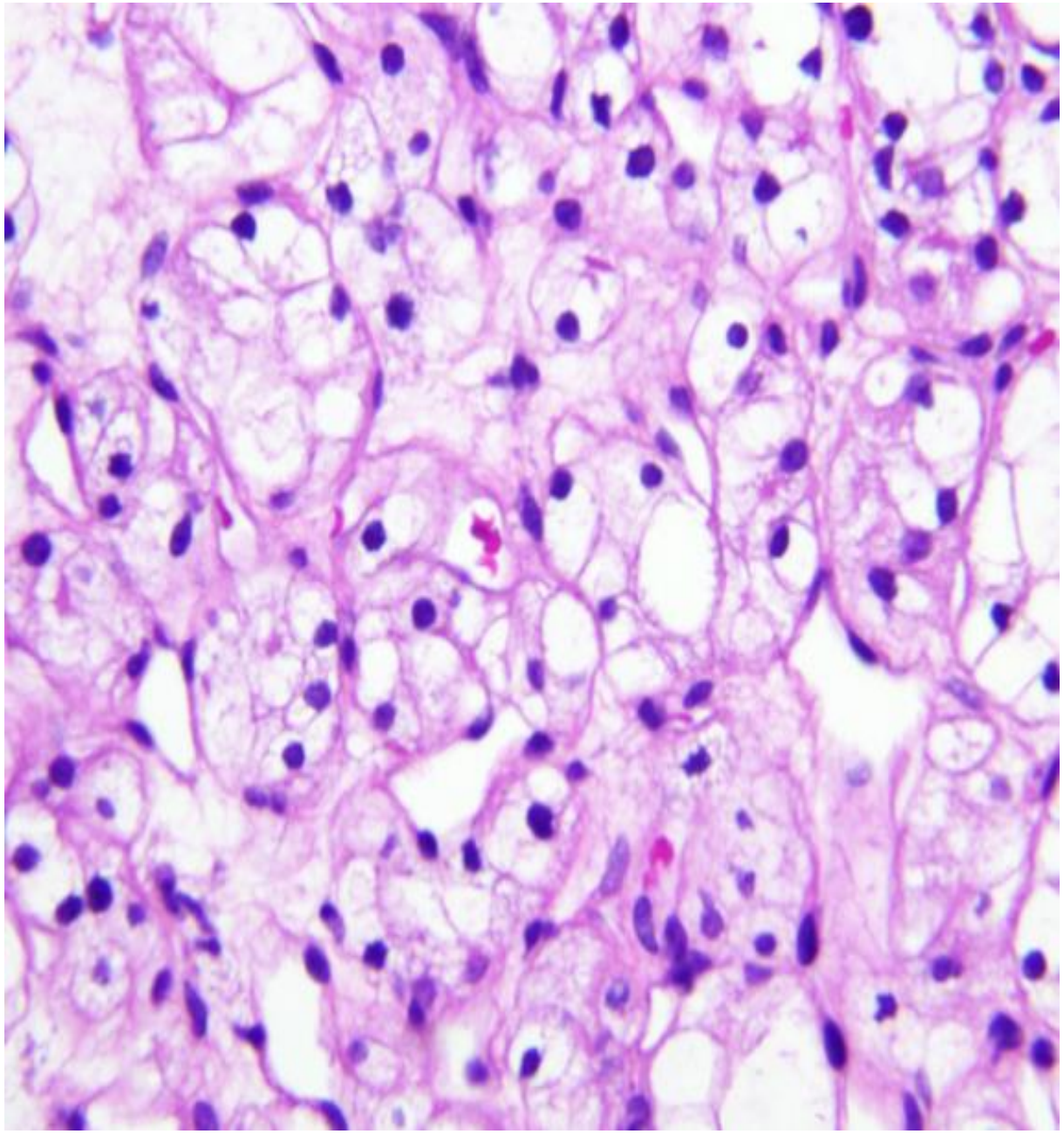
- Clear cell carcinomas are the most common type, accounting for 65% of renal cell cancers. Histologically, they are composed of cells with clear cytoplasm. Although most are sporadic, they also occur in familial forms or in association with von Hippel-Lindau (VHL) disease.
- VHL disease is inherited as an autosomal dominant trait and is characterized by predisposition to a variety of neoplasms, but particularly to hemangioblastomas of the cerebellum and retina. Hundreds of bilateral renal cysts and bilateral, often multiple, clear cell carcinomas develop in 40% to 60% of affected individuals.

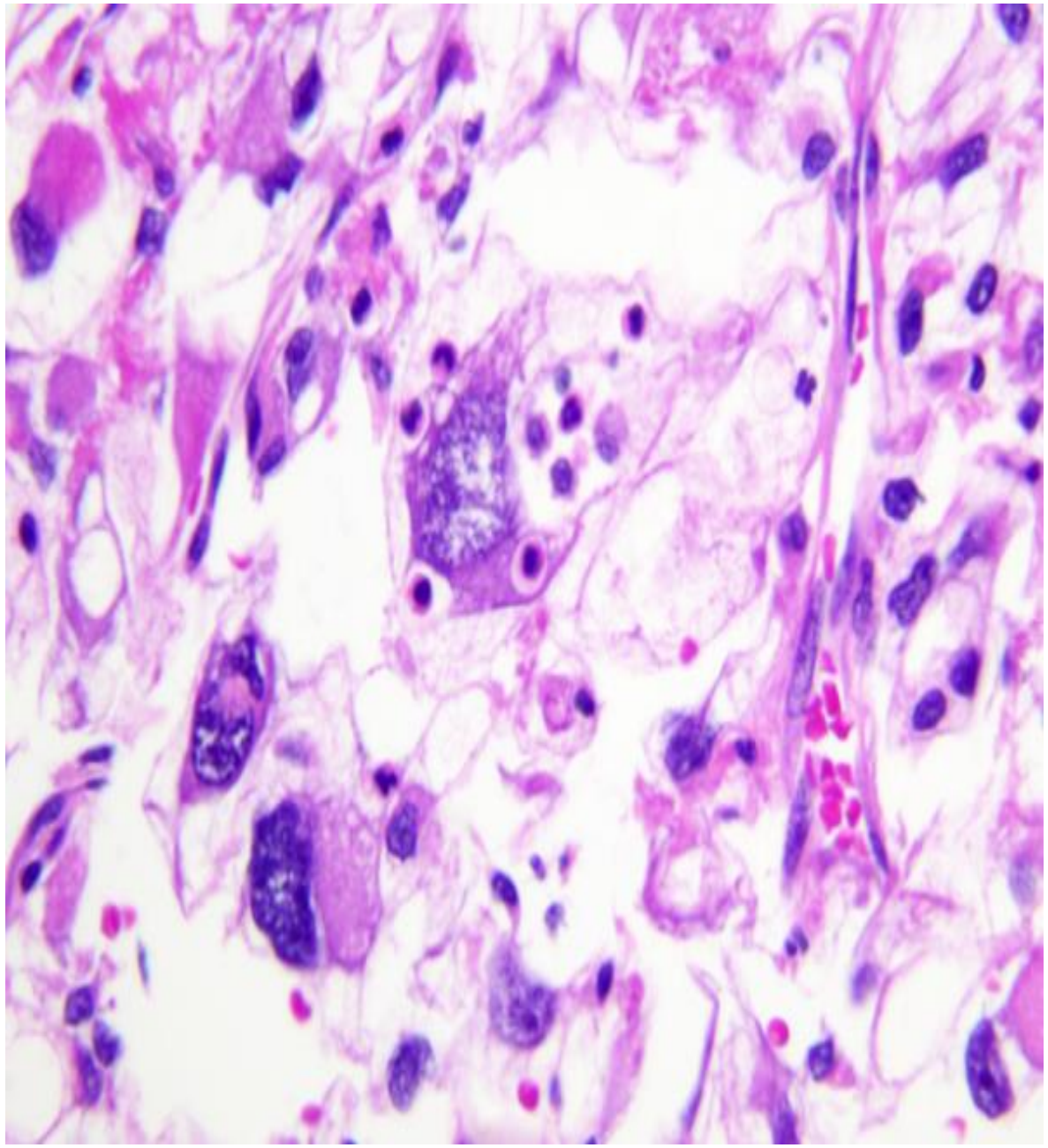
- loss or inactivation of both copies of the *VHL* gene seems to be the common underlying molecular abnormality in both sporadic and familial forms of clear cell carcinomas.
- The VHL protein causes the degradation of hypoxia-induced factors (HIFs), and in the absence of VHL, HIFs are stabilized.
- HIFs are transcription factors that contribute to carcinogenesis by stimulating the expression of vascular endothelial growth factor (VEGF), an important angiogenic factor, as well as a number of other genes that drive tumor cell growth.
- An uncommon familial form of clear cell carcinoma unrelated to VHL disease also is associated with cytogenetic abnormalities involving the short arm of chromosome 3 (3p).

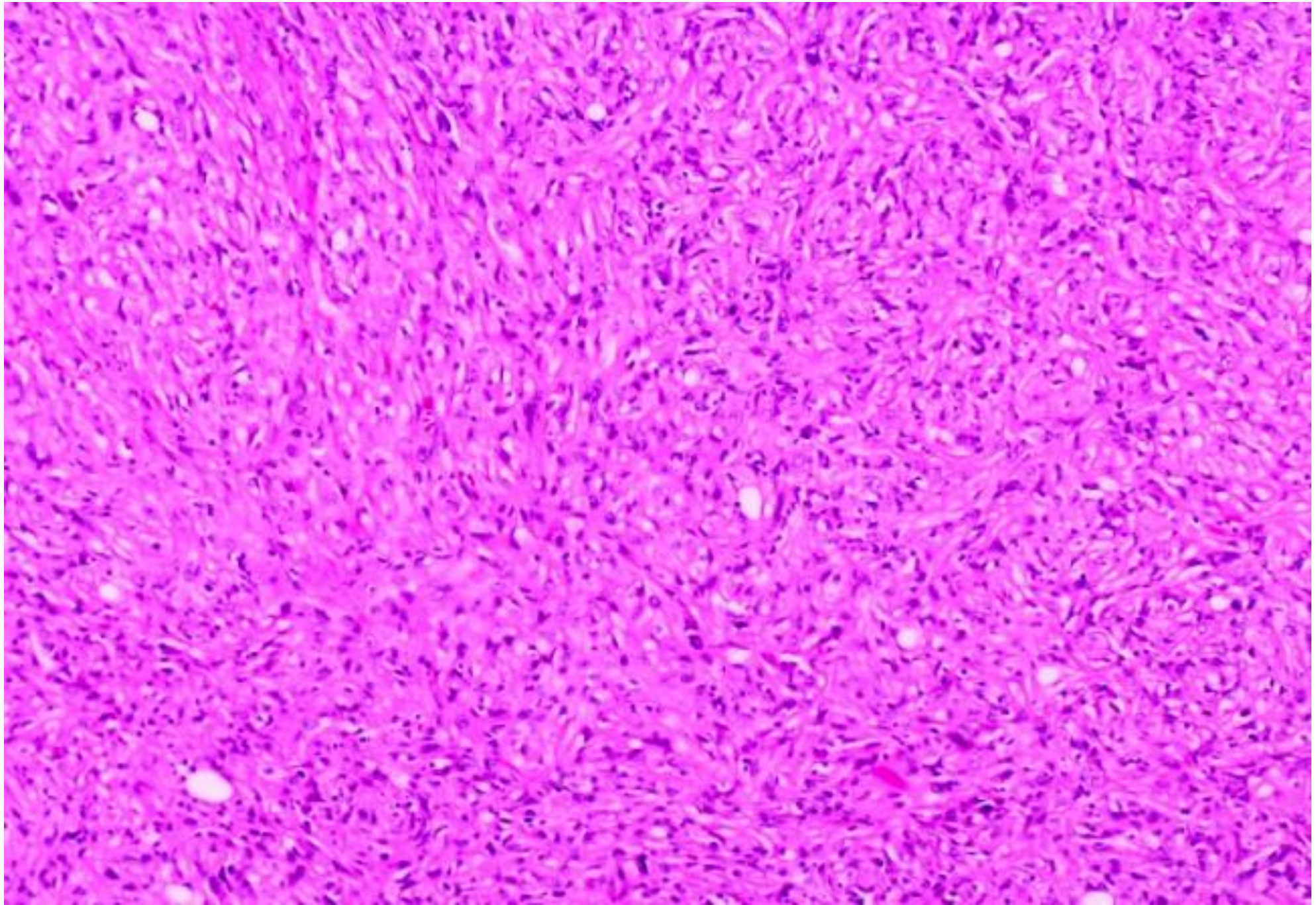
- Arises in epithelial cells lining the proximal convoluted tubule
- Cortical mass with golden yellow cut surface
- Clear or granular eosinophilic cytoplasm and prominent but delicate capillary network
- Metastases:
  - Hematogenous more common: lung (most common), bone, liver, pleura, CNS, head and neck
  - Lymphatic less common: hilar, aortic, caval and thoracic lymph nodes
  - Extension into the renal sinus the most common pathway of spread, usually involving extension within the renal vein

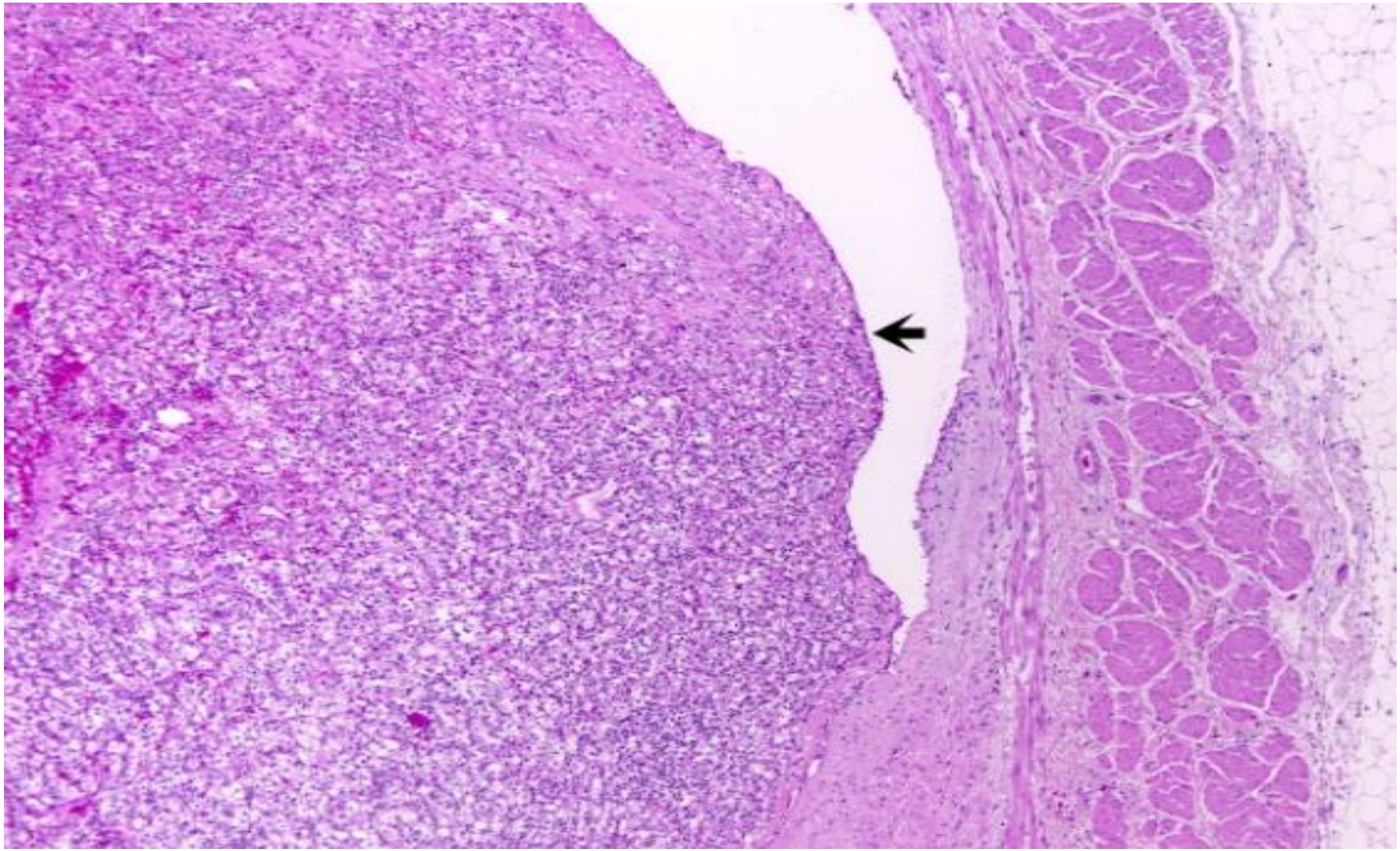
- Worse prognosis within the same stage: higher histologic grade, sarcomatoid and rhabdoid differentiation
- Clear cell RCC has worse prognosis than papillary and chromophobe RCC





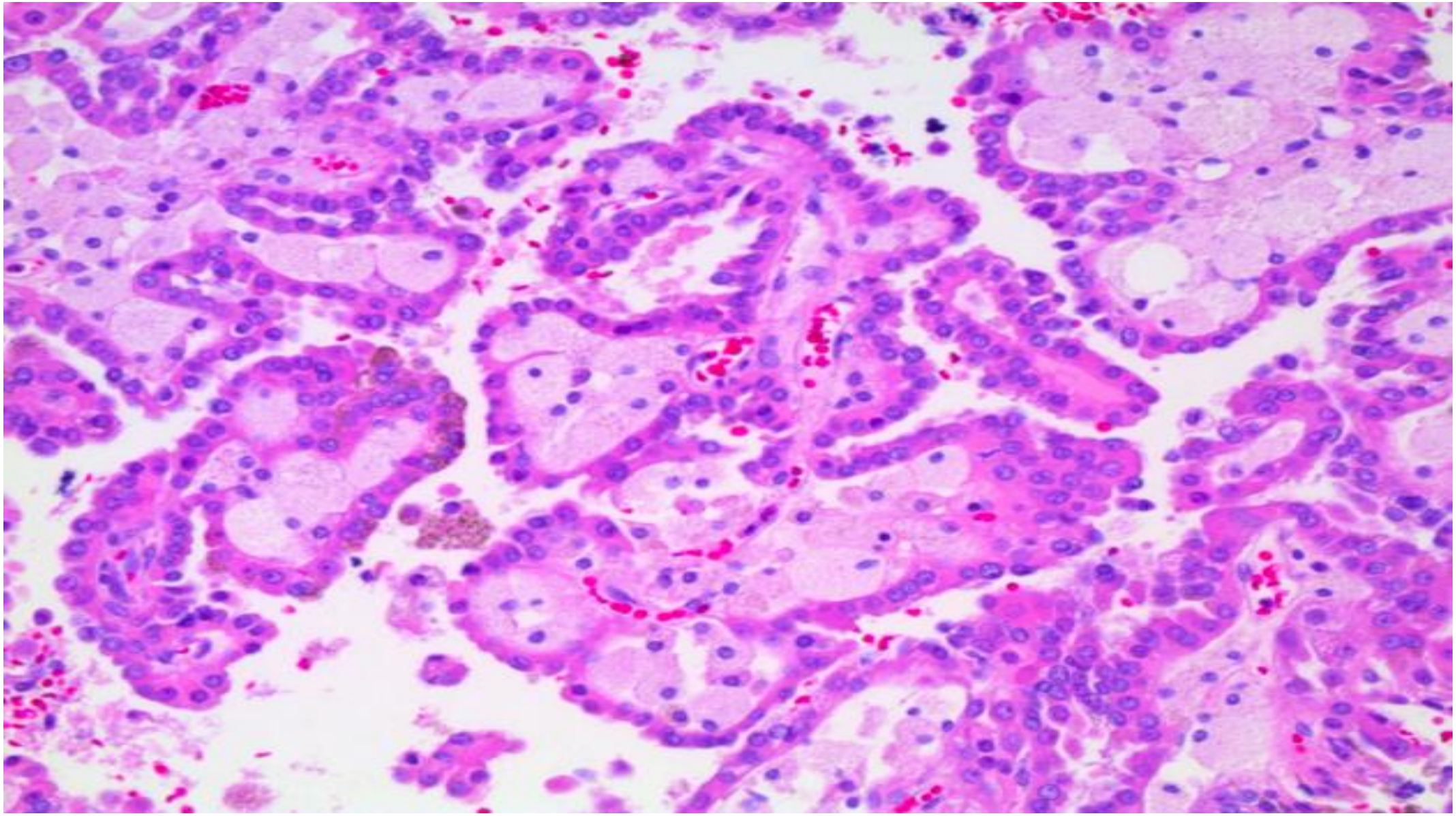


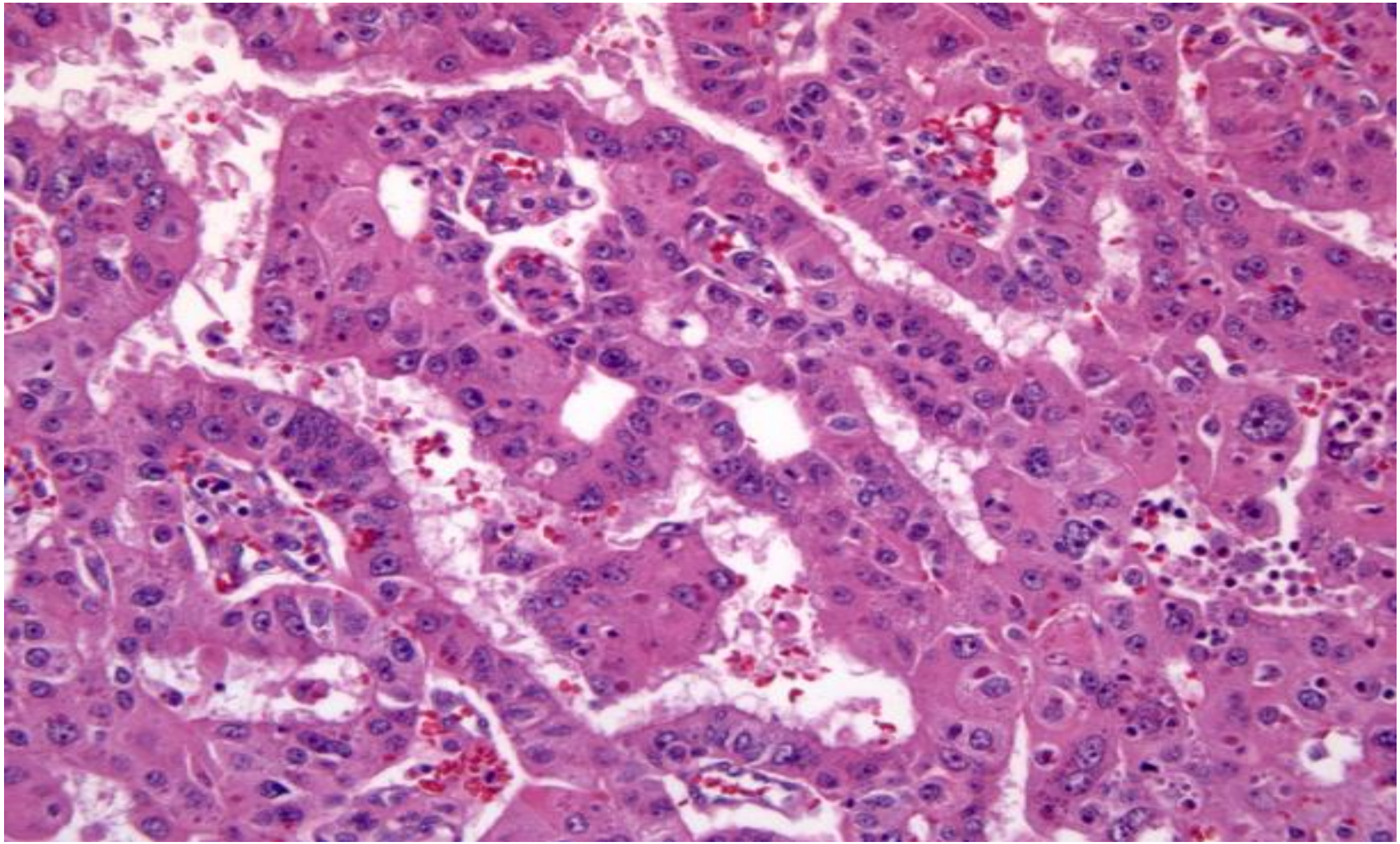




Papillary Renal Cell Carcinomas

- Papillary renal cell carcinomas account for 10% to 15% of all renal cancers and are defined in part by their papillary growth pattern. These neoplasms are frequently multifocal and bilateral and appear as early-stage tumors. Like clear cell carcinomas, they occur in familial and sporadic forms, but unlike these neoplasms, papillary renal cancers are not associated with abnormalities of chromosome 3.
- The culprit in most cases of hereditary papillary renal cell cancers is the *MET* proto-oncogene, located on chromosome 7q. The *MET* gene encodes a tyrosine kinase receptor for hepatocyte growth factor. The increased dosage of the *MET* gene due to duplications of chromosome 7 lead to abnormal growth in the proximal tubular epithelial cell precursors of papillary carcinomas.





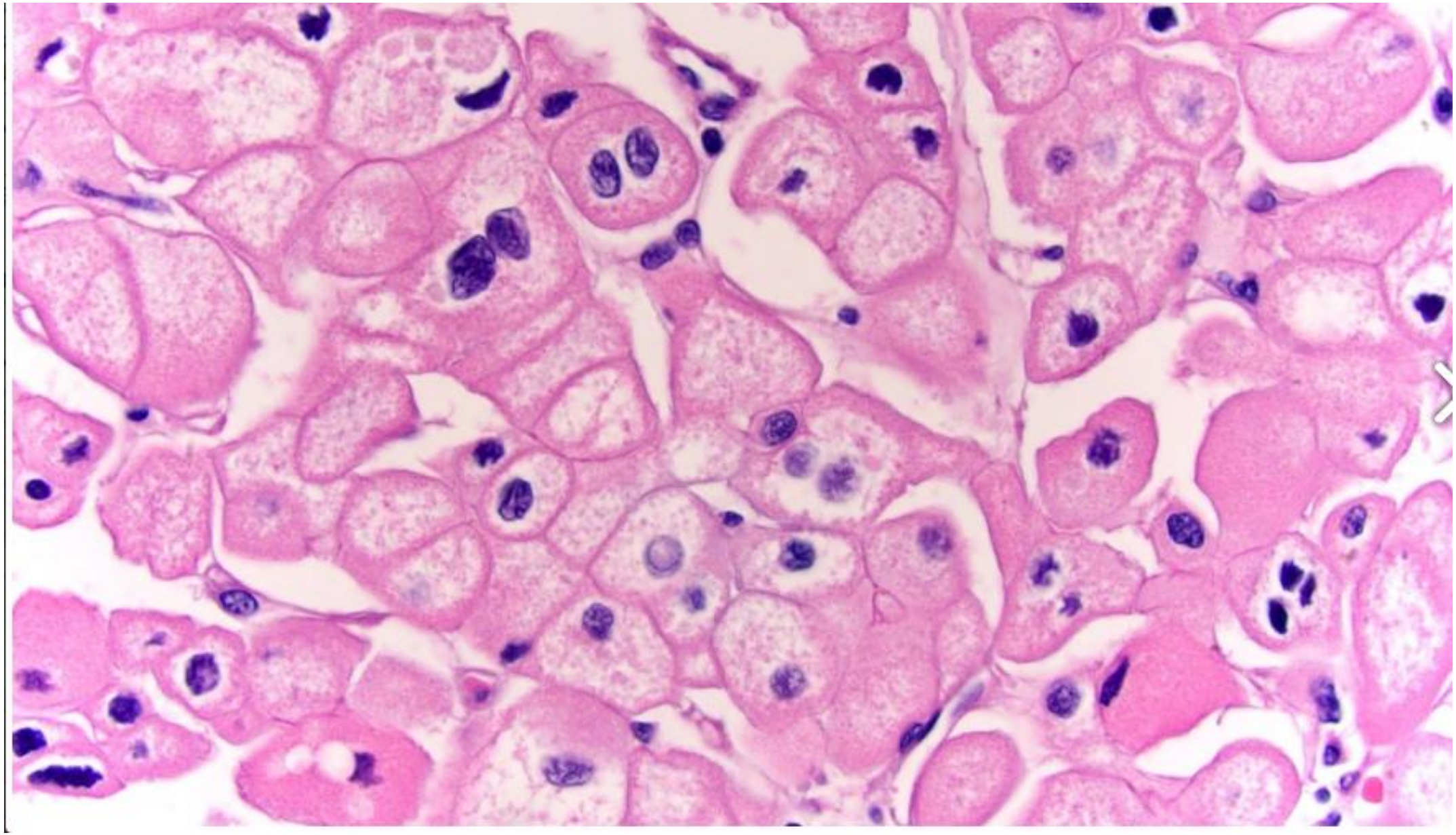
Chromophobe Renal Carcinomas

- Chromophobe renal carcinomas are the least common form, representing 5% of all renal cell carcinomas. Their name derives from the observation that the tumor cells stain more darkly (i.e., they are less clear) than cells in clear cell carcinomas. These neoplasms are unique in having multiple losses of entire chromosomes leading to extreme hypoploidy.
- In general, chromophobe renal cancers have a favorable prognosis.

- Solid tumor composed of granular pale cells with prominent cell borders, finely reticular cytoplasm, perinuclear halos and wrinkled hyperchromatic nuclei
- First described in 1985
- Cell of origin: intercalated cells of distal convoluted tubules
- Solitary kidney mass
- Most commonly in renal cortex

Birt-Hogg-Dubé syndrome

- Multiple tumors (mean 5.3); mean age 51 years at first renal tumor diagnosis
- Bilateral multifocal ChRCC, oncocytomas or hybrid oncocytic chromophobe tumor (HOCT), also may have oncocytosis
- Autosomal dominant syndrome: small dome shaped papular fibrofolliculomas of face, neck and upper trunk, renal tumors, lung cysts and spontaneous pneumothorax
- Mutations in the folliculin gene (*FLCN*) at 17p11.2.



Clinical Features

- The signs and symptoms vary, but the *most frequent presenting manifestation is hematuria, occurring in more than 50% of cases.* Macroscopic hematuria tends to be intermittent, superimposed on a steady microscopic hematuria. Less commonly, when it has grown large enough to produce flank pain and a *palpable mass*. Because of the widespread use of imaging studies for unrelated conditions, even smaller tumors are detected.
- Extrarenal effects are *fever* and *polycythemia.* Polycythemia affects 5% to 10% of affected individuals and results from production of erythropoietin by the cancer cells.

- Uncommonly, these tumors produce other hormone-like substances, resulting in hypercalcemia, hypertension, Cushing syndrome, or feminization or masculinization. These, as noted, are *paraneoplastic syndromes.* In some patients, the primary tumor remains silent and is discovered only after metastases produce symptoms. The common locations for metastases are the lungs and the bones. It must be apparent that renal cell carcinoma manifests in many ways, some quite devious, *but the triad of painless hematuria, a palpable abdominal mass, and dull flank pain is characteristic*

*Wilms Tumor (*nephroblastoma)

- Although Wilms tumor is rare in adults, it is the third most common solid (non-hematologic) cancer in children younger than 10 years of age.
- These neoplasms contain a variety of cell and tissue components, all derived from mesoderm. Wilms tumor, like retinoblastoma, may arise sporadically or be familial, with the susceptibility to tumorigenesis inherited as an autosomal dominant trait.
- *WT1* is critical to normal renal and gonadal development.

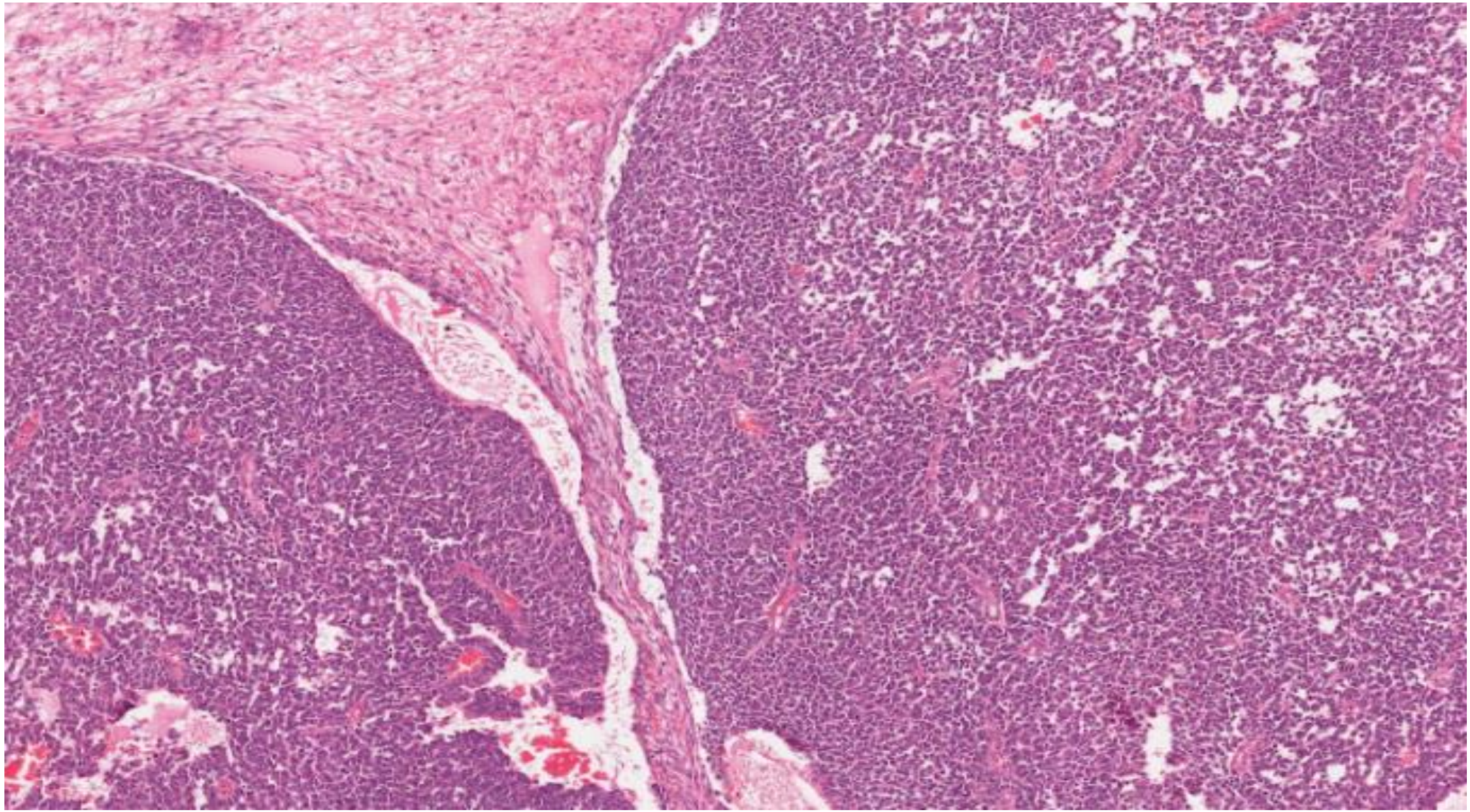
- Three groups of congenital malformations are associated with an increased risk for Wilms tumor. *These are WAGR syndrome (i.e., Wilms tumor, aniridia, genital abnormalities, and mental retardation); Denys-Drash syndrome (DDS), and Beckwith- Wiedemann syndrome (BWS).*
- Of patients with *WAGR syndrome* approximately one in three will go on to develop this tumor. Another group of patients, those with so-called *"Denys-Drash syndrome"* (DDS), have an even higher risk (approximately 90%) of Wilms tumor. DD syndrome is characterized by gonadal dysgenesis and early onset nephropathy leading to renal failure. Both of these conditions are associated with abnormalities of the Wilms tumor 1 *(WT1)* gene, located on 11p13. The nature of the genetic aberration differs, however: Patients with WAGR syndrome demonstrate loss of genetic material (i.e., deletions) of *WT1*, while persons with DDS harbor a negative inactivating mutation in WT1.

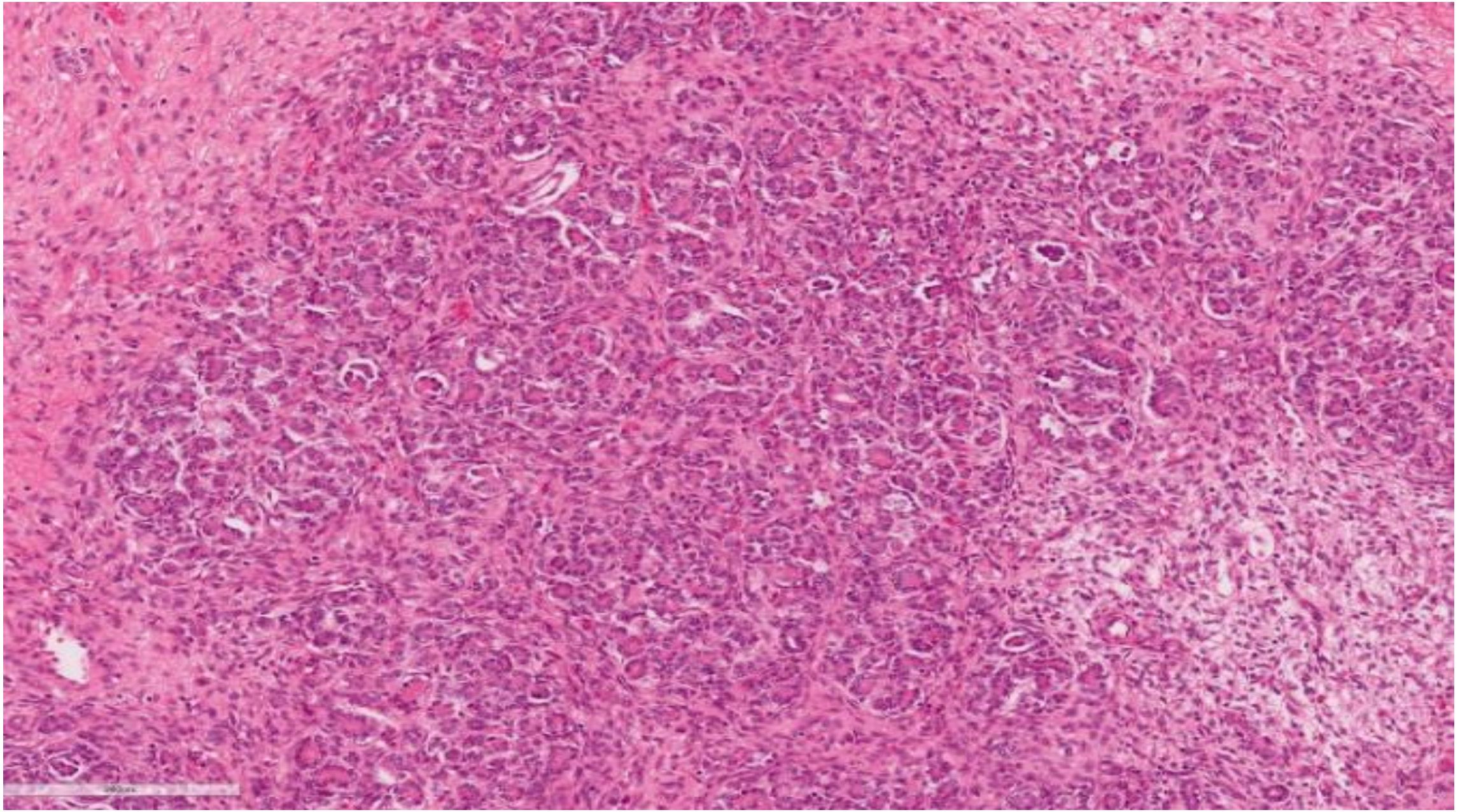
- A third group of patients, those with *Beckwith- Wiedemann syndrome* (BWS), also are at increased risk for the development of Wilms tumor. These patients exhibit enlargement of individual body organs (e.g., tongue, kidneys, or liver) or entire body segments (hemihypertrophy); enlargement of adrenal cortical cells (adrenal cytomegaly) is a characteristic microscopic feature. BWS is an example of a disorder of genomic imprinting. The genetic locus that is involved in these patients is in band p15.5 of chromosome 11 distal to the WT1 locus. Although this locus is called “WT2” for the second Wilms tumor locus.

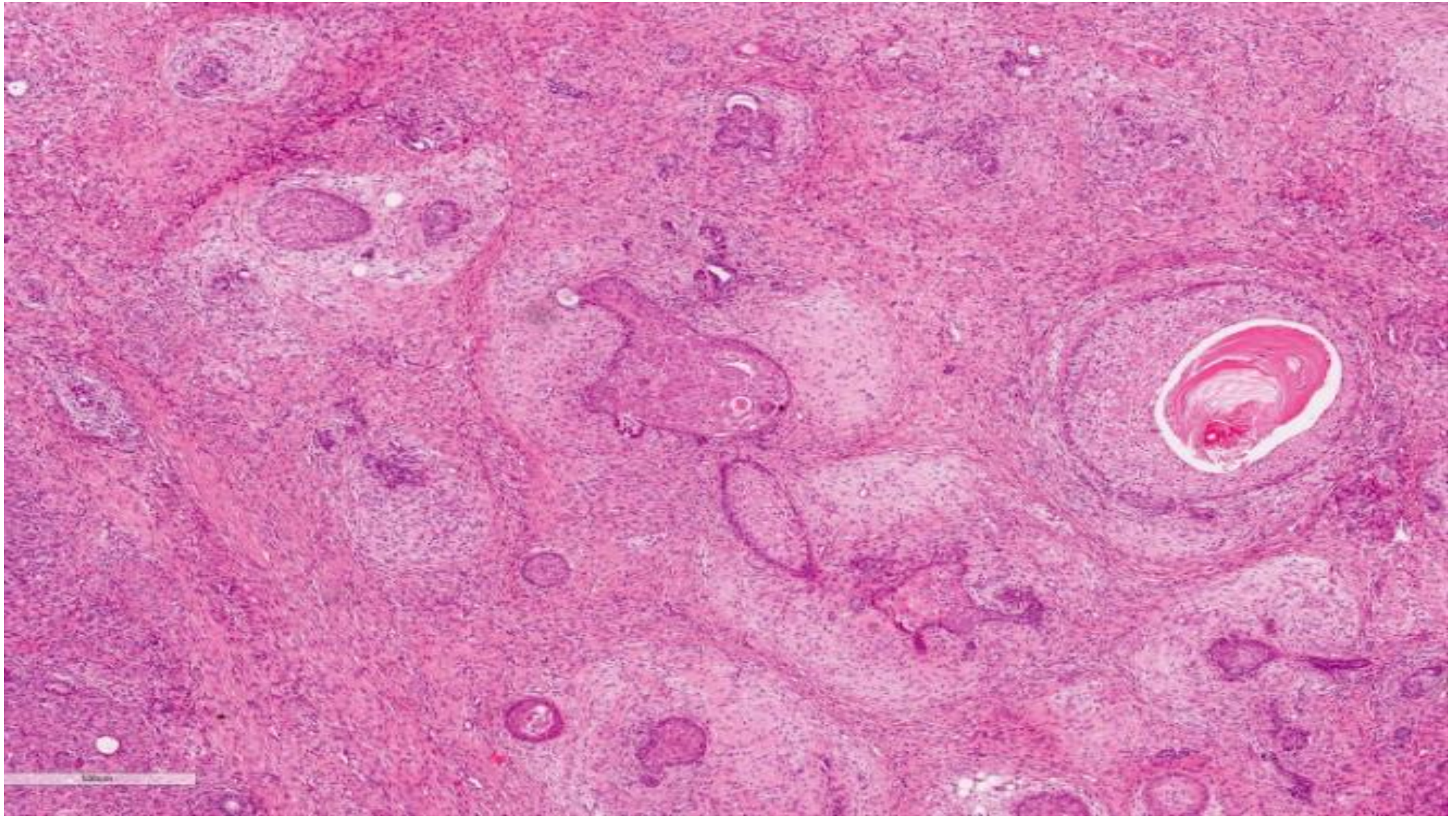
MORPHOLOGY

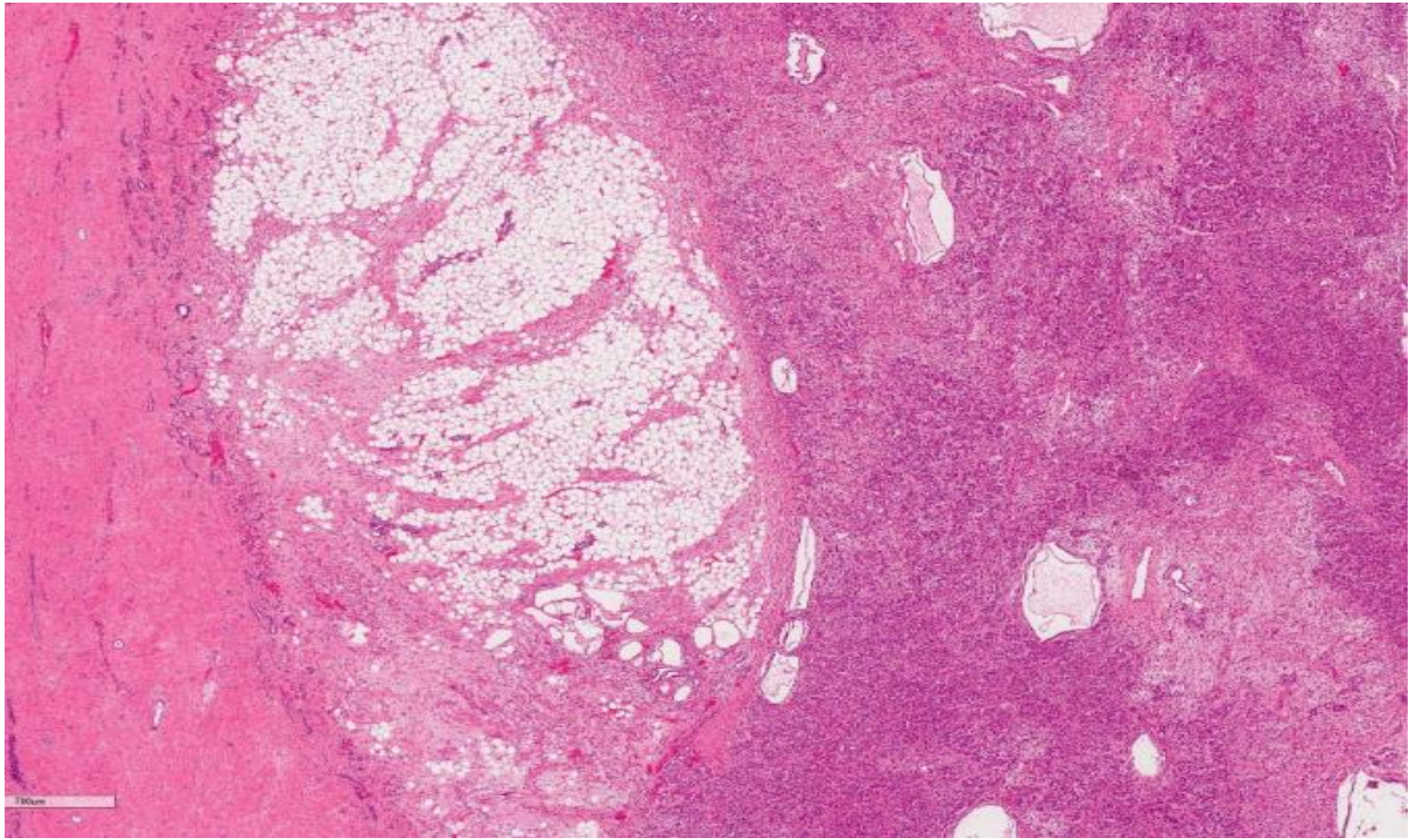
- Wilms tumor typically is a large, solitary, well-circumscribed mass, although 10% are either bilateral or multicentric at the time of diagnosis. On cut section, the tumor is soft, homogeneous, and tan to gray, with occasional foci of hemorrhage, cystic degeneration, and necrosis.
- The classic **triphasic combination** of blastemal, stromal, and epithelial cell types, although the percentage of each component is variable. Sheets of small blue cells, with few distinctive features, characterize the **blastemal component**. Epithelial "differentiation" usually takes the form of **abortive tubules or glomeruli**. Stromal cells are usually fibrocytic or myxoid in nature.
- Approximately 5% of tumors contain foci of **anaplasia** (cells with large, hyperchromatic, pleomorphic nuclei and abnormal mitoses). The presence of anaplasia correlates with the presence of acquired *TP53* mutations and the emergence of resistance to chemotherapy. The pattern of distribution of anaplastic cells within the primary tumor (focal versus diffuse) has important implications for prognosis.

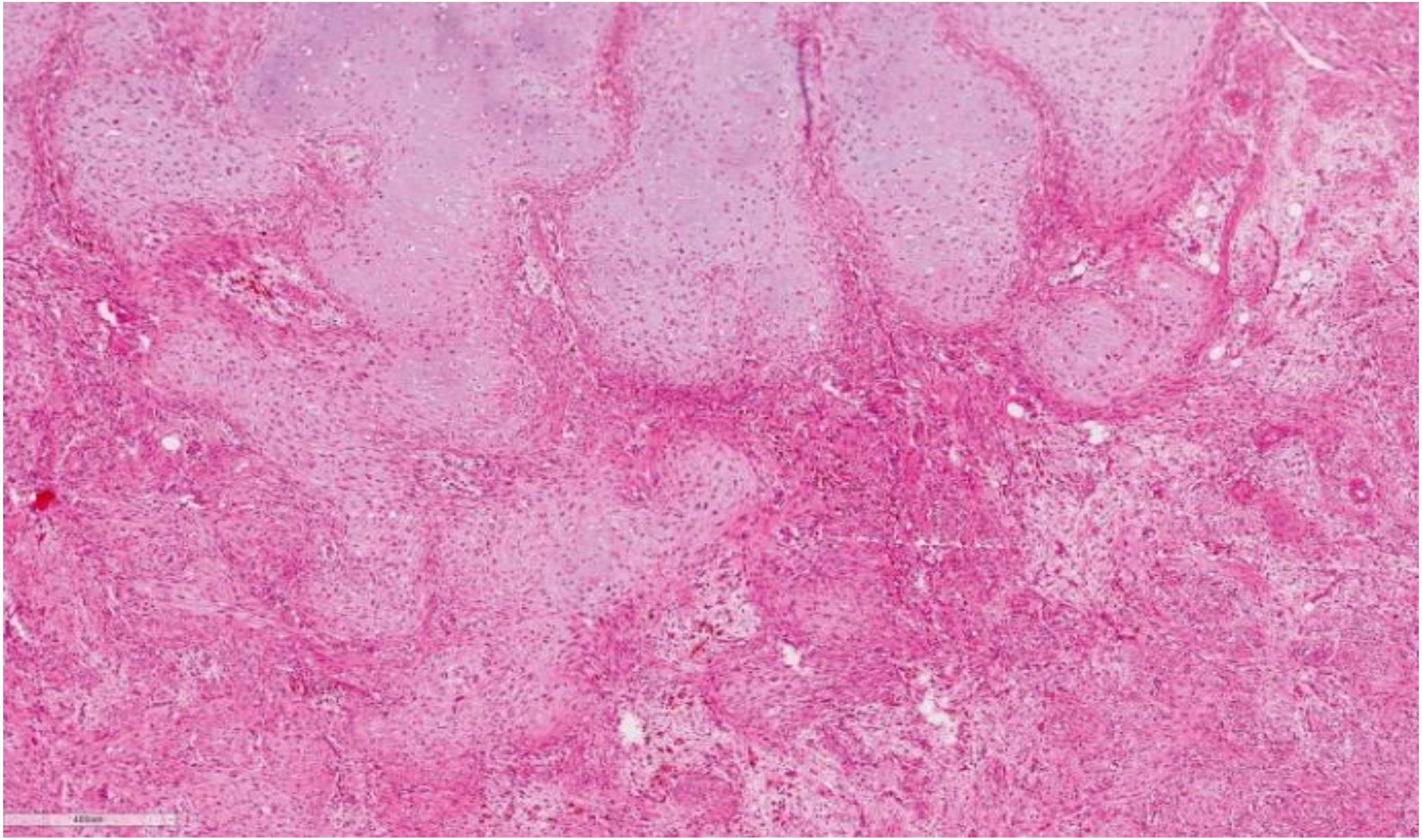
- **Nephrogenic rests** are precursor lesions of Wilms tumors and are sometimes present in the renal parenchyma adjacent to the tumor. Nephrogenic rests have a spectrum of histologic appearances, from expansile masses that resemble Wilms tumors (hyperplastic rests) to sclerotic rests consisting predominantly of fibrous tissue with occasional admixed immature tubules or glomeruli. It is important to document the presence of nephrogenic rests in the resected specimen, because these patients are at an increased risk for the development of Wilms tumors in the contralateral kidney.











Clinical Course

- Patients typically present with a palpable abdominal mass, which may extend across the midline and down into the pelvis. Less often, the presenting features are fever and abdominal pain, hematuria or, occasionally, intestinal obstruction as a result of pressure from the tumor.
- The prognosis for Wilms tumor generally is very good, and excellent results are obtained with a combination of nephrectomy and chemotherapy. Anaplasia is a harbinger of adverse prognosis, but only if it is diffuse. If the anaplasia is focal and confined within the resected nephrectomy the outcome is no different from that for tumors without evidence of anaplasia.

Urinary Bladder

- Bladder cancer accounts for approximately 5% of cancers. The vast majority of bladder cancers are urothelial carcinomas. Squamous cell carcinomas represent about 3% to 7% of bladder cancers in the United States but are much more common in countries such as Egypt, where urinary schistosomiasis is endemic. Adenocarcinomas of the bladder are rare.
- Carcinoma of the bladder is more common in men than in women, and in whites than in African- Americans. About 80% of patients are between 50 and 80 years of age.

Pathogenesis

- Environmental factors are important in the pathogenesis of urothelial carcinoma and include *cigarette smoking, various occupational carcinogens, and prior cyclophosphamide or radiation therapy.* A family history of bladder cancer is a known risk factor.
- Squamous cell carcinoma is related to *Schistosoma haematobium* infections in areas where it is endemic. Cancers occurring in the setting of schistosoma infections arise in a background of chronic inflammation.

- Based on these observations, a model for bladder carcinogenesis has been proposed in which the tumor is initiated by deletions of tumor-suppressor genes on 9p and 9q, leading to the formation of superficial papillary tumors, which may then acquire *TP53* mutations and progress to invasive disease. A second pathway, possibly initiated by *TP53* mutations, leads first to carcinoma in situ and then, with loss of genes from chromosome 9, progresses to invasion

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. The risk for recurrence is related to several factors, including tumor size, stage, grade, multifocality, mitotic index, and associated dysplasia and/or CIS in the surrounding mucosa.
- Many recurrent tumors arise at sites different than that of the original lesion, but may be share the same clonal abnormalities as those of the initial tumor; thus, these are true recurrences that stem from shedding and implantation of the original tumor cells at new sites. **Whereas high-grade papillary urothelial carcinomas frequently are associated with either concurrent or subsequent invasive urothelial carcinoma, lower-grade papillary urothelial neoplasms often recur but infrequently invade**

- Treatment of bladder cancer depends on tumor grade and stage and on whether the lesion is flat or papillary.
- For small, localized papillary tumors that are not high-grade, transurethral resection is both diagnostic and therapeutically sufficient. Patients with tumors that are at high risk for recurrence or progression typically receive topical immunotherapy consisting of intravesical instillation of an attenuated strain of the tuberculosis bacillus called *Bacillus Calmette-Guérin (BCG),* sometimes followed by intravesical chemotherapy.

- BCG elicits a granulomatous reaction that also triggers an effective local anti-tumor immune response. Patients are closely monitored for tumor recurrence with periodic cystoscopy and urine cytologic studies. Radical cystectomy is reserved for (1) tumor invading the muscularis propria; (2) CIS or high-grade papillary cancer refractory to BCG; and (3) CIS extending into the prostatic urethra and down the prostatic ducts, where BCG cannot come in contact the neoplastic cells.
- Advanced bladder cancer is treated using chemotherapy, which can palliate but is seldom curative.