Kidney tumors histology

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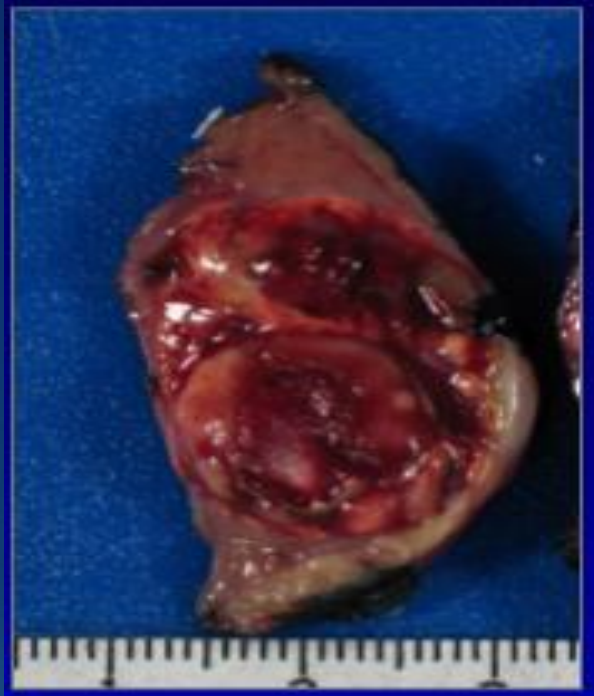
- The 2016 WHO classification of renal tumors is based on a combination of morphological, molecular and genetic features
- RCCs represent the most common renal tumor in adults and are divided into a number of different histological types.
- The most common is the clear cell type (70–90%), followed by papillary (10–15%) and chromophobe RCCs (3–5%).
- Many studies, including large multicentre studies, have shown that tumor type has prognostic significance
- Tumor type also has utility in selection of patients for adjuvant therapy

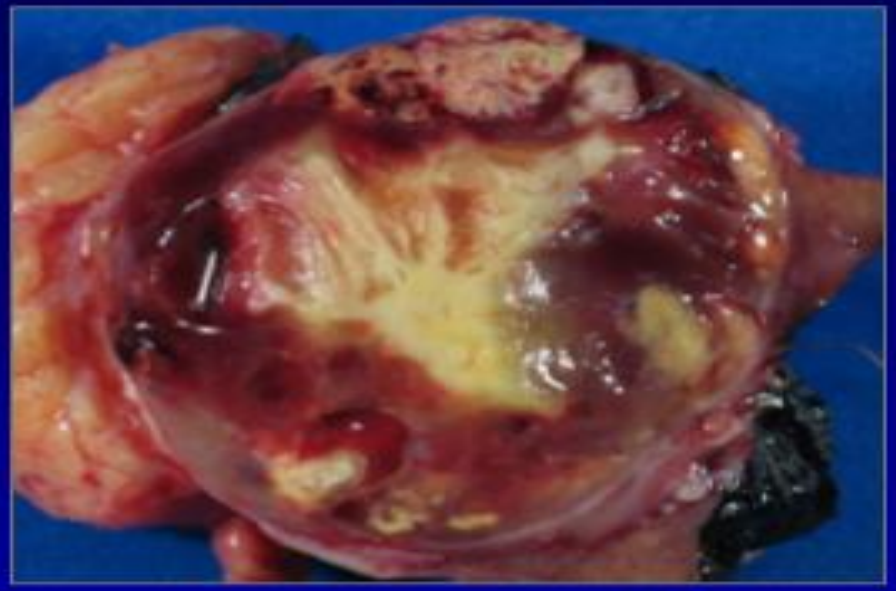
Clear cell RCC

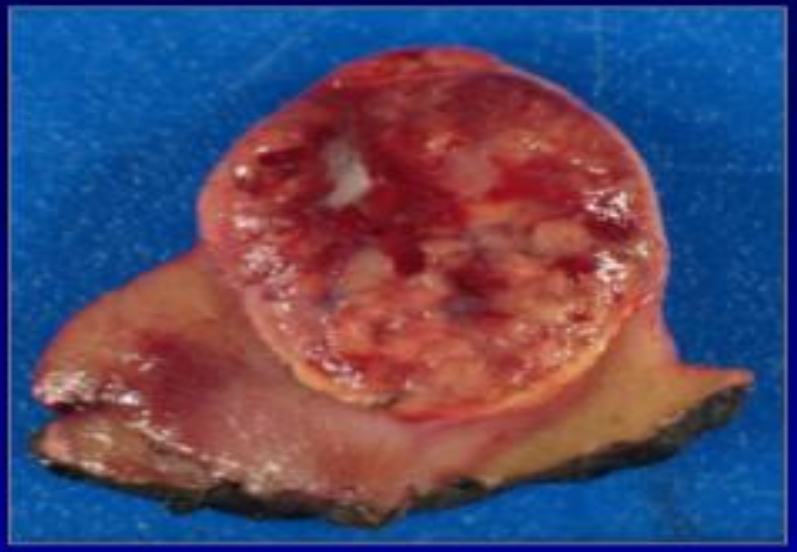
- worse prognosis than papillary or chromophobe RCCs, when matched for stage, and is more likely to present at an advanced stage or with existing metastases
- In 90% of cases, these tumors exhibit alterations in the von Hippel–Lindau tumor suppressor (VHL) gene on chromosome 3
- Most tumors are sporadic, but multiple bilateral tumors are seen in von Hippel–Lindau syndrome, a rare autosomal dominant condition also associated with a variety of other tumors that include haemangioblastomas of the retina and central nervous system

Clear cell RCC

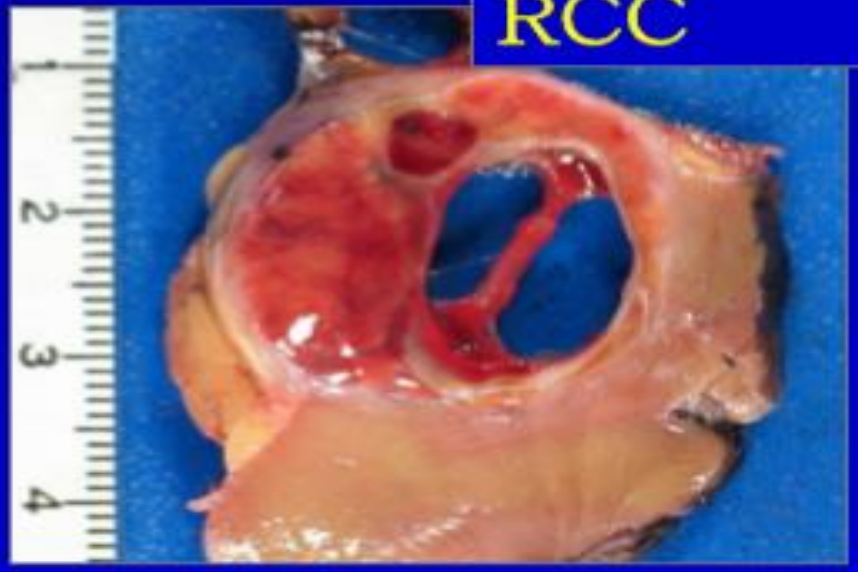
- Grossly, clear cell RCCs characteristically contain solid yellow areas with variable amounts of cystic change, hemorrhage and necrosis
- Although on microscopy they are classically composed of clear cells set within a fine intricate vascular network, they may consist entirely of cells with eosinophilic granular cytoplasm, particularly if high grade
- On immunohistochemistry they characteristically co-express pan-cytokeratin and vimentin and are carbonic anhydrase IX (CA-IX) positive, but are usually Cytokeratin 7 (CK7) negative

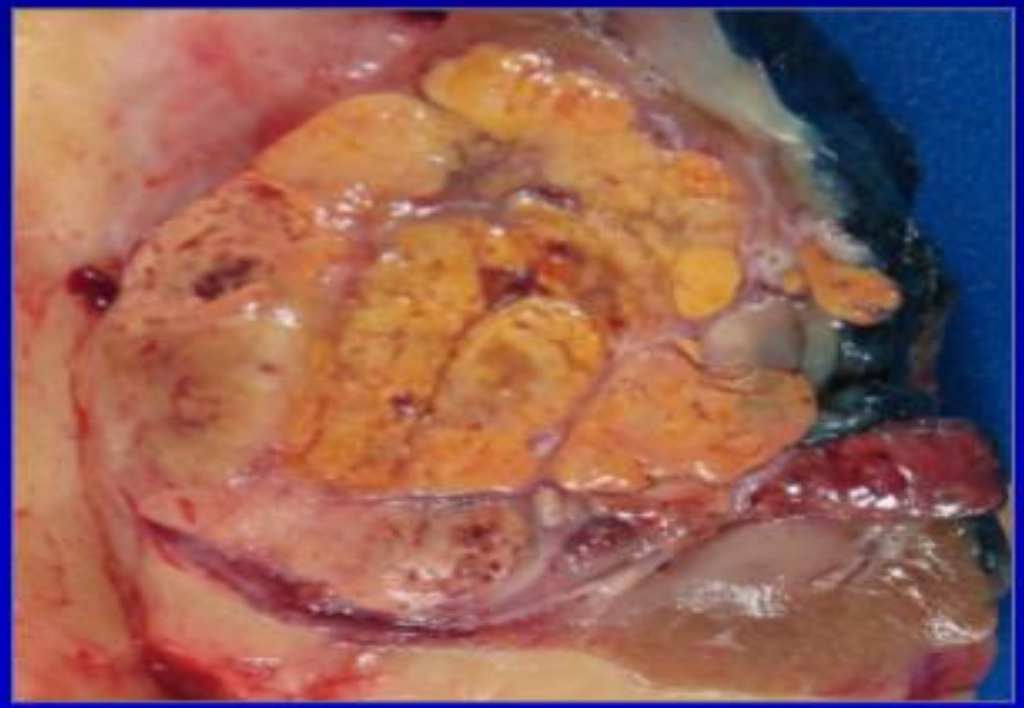




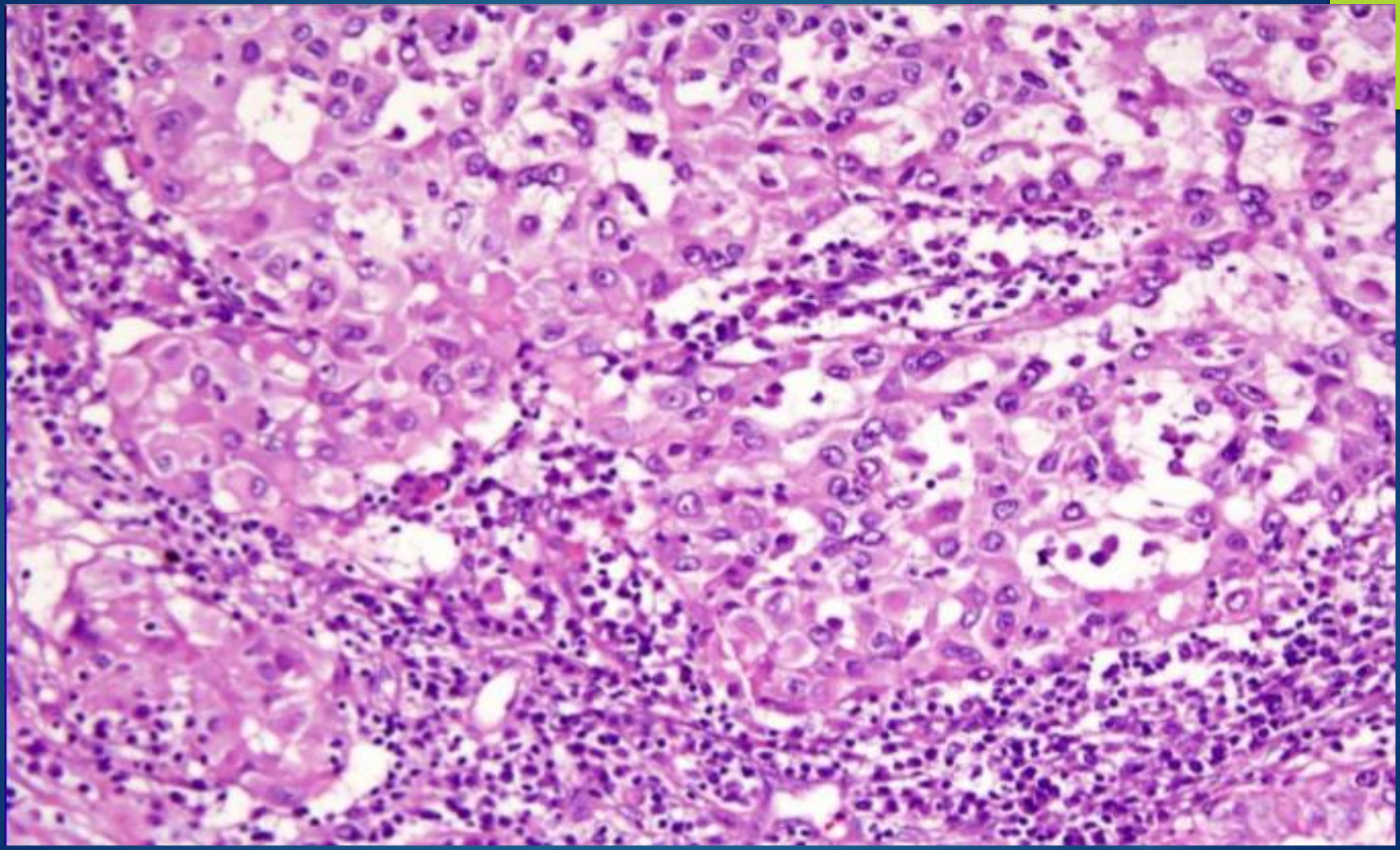


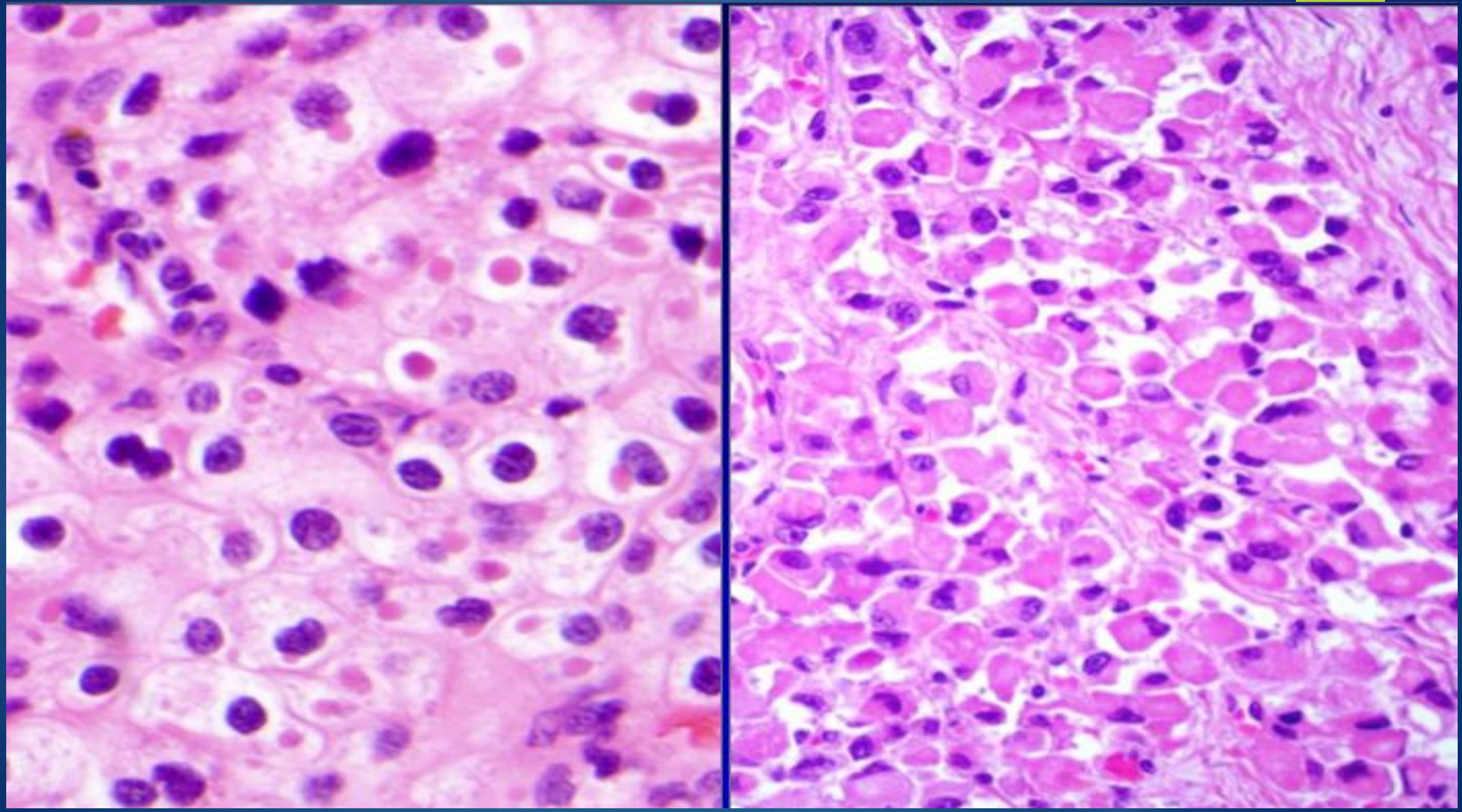
Clear Cell
RCC






Growth Patterns
Classic (solid/acinar)
Tubular
Cystic
Pseudopapillary
Hemorrhagic
Hyalinzed
Cytomorphology
Classic clear cell
Granular
Epithelioid
Rhabdoid
Spindle/sarcomatoid





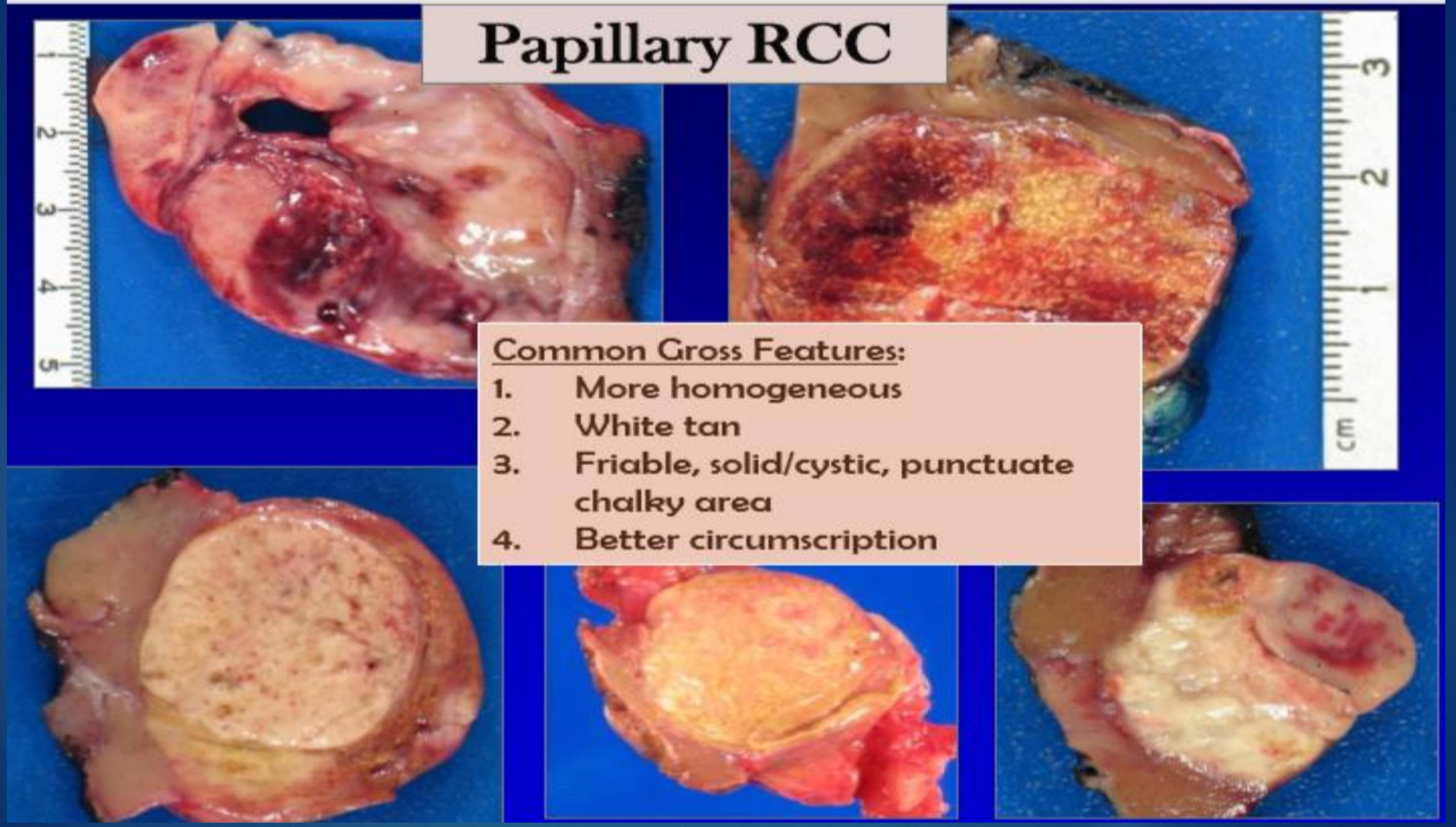
Clear Cell RCC Differential Diagnoses

- Chromophobe RCC
- Papillary RCC type 2
- Cellular or epithelioid angiomyolipoma
- Adrenal cortical carcinoma

Papillary RCCs

- Solid, with or without cystic change or encapsulation, and are often grey or brown in colour with a soft friable cut surface showing frequent necrosis and hemorrhage
- On microscopy, according to the current WHO classification, they are divided into type 1 or type 2 determined primarily by their differing cytological features, and mixed patterns occur
- An oncocytic variant (composed of cells with abundant eosinophilic/pink cytoplasm) has also been described morphologically, but is included under the general category of papillary RCC in this classification system

Papillary RCC



Common Gross Features:

1. More homogeneous
2. White tan
3. Friable, solid/cystic, punctuate chalky area
4. Better circumscription

Type 1 papillary RCCs

- Type 1 papillary RCCs usually consist of papillary structures lined by cuboidal cells with low-grade nuclei.
- Collections of foamy macrophages are often present within the papillary fibrovascular cores and calcifications (psammoma bodies) and intracellular hemosiderin are common.
- They may also show solid growth, with very compact papillary structures.
- The tumors have a typical profile on immunohistochemistry, including strong CK7 and alpha-methylacyl-CoA racemase (AMACR) expression and at most focal CA-IX expression

Papillary RCC

Growth Patterns

Papillary

Tubular

Tubulopapillary

Solid

Cytomorphology

Classic (basophilic)

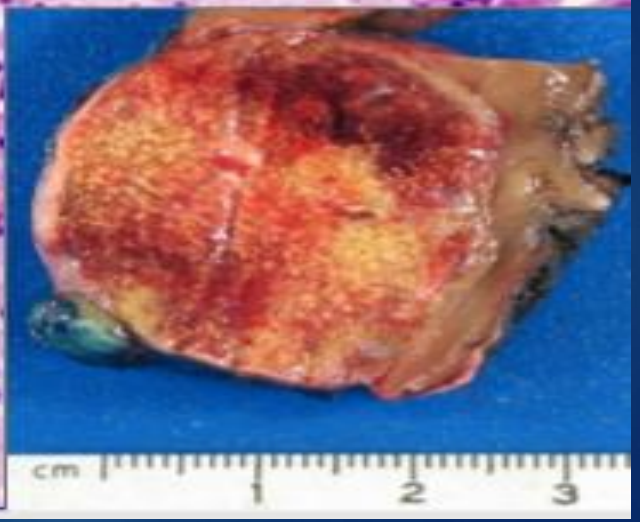
Eosinophilic

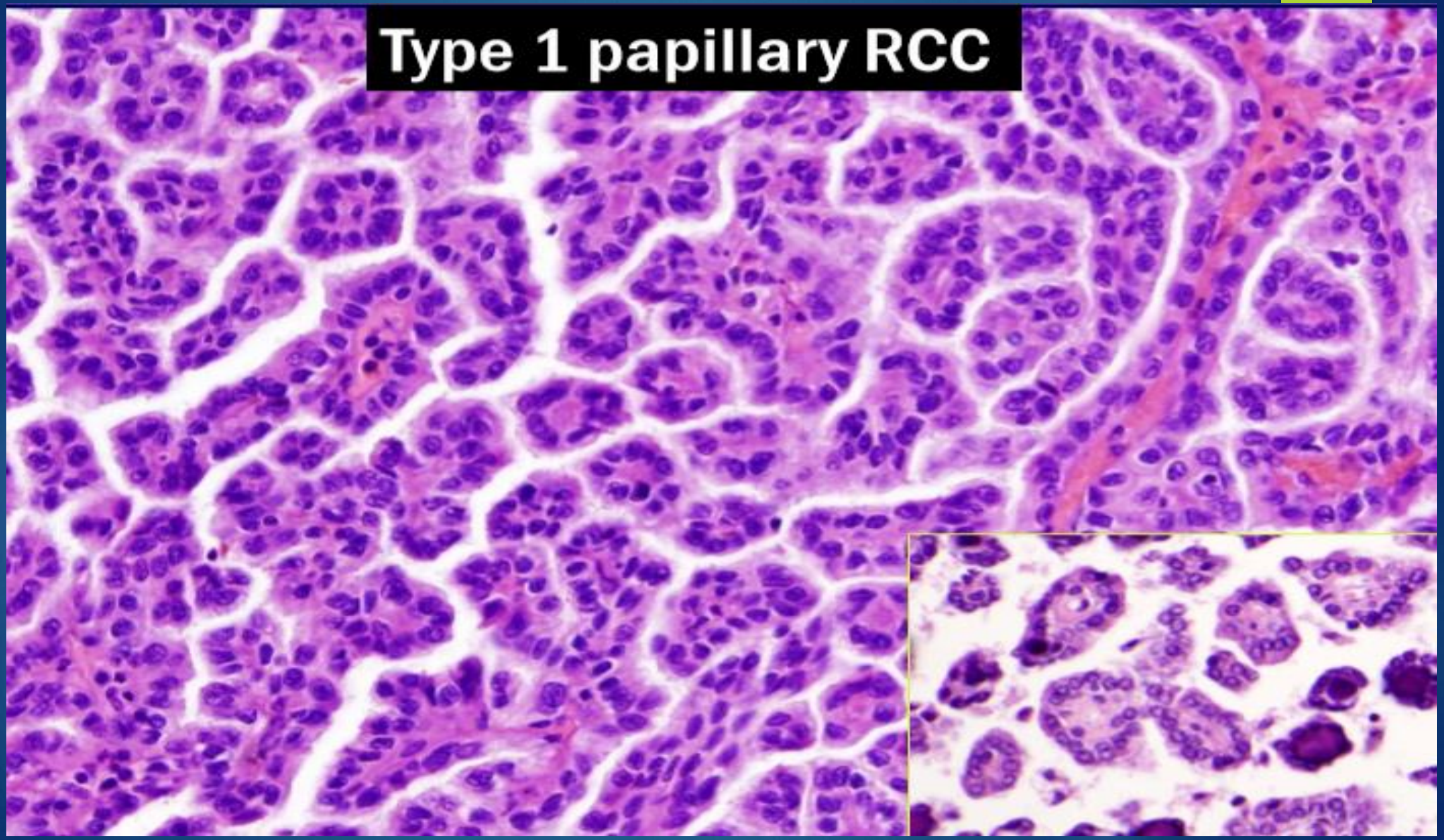
Clear cell

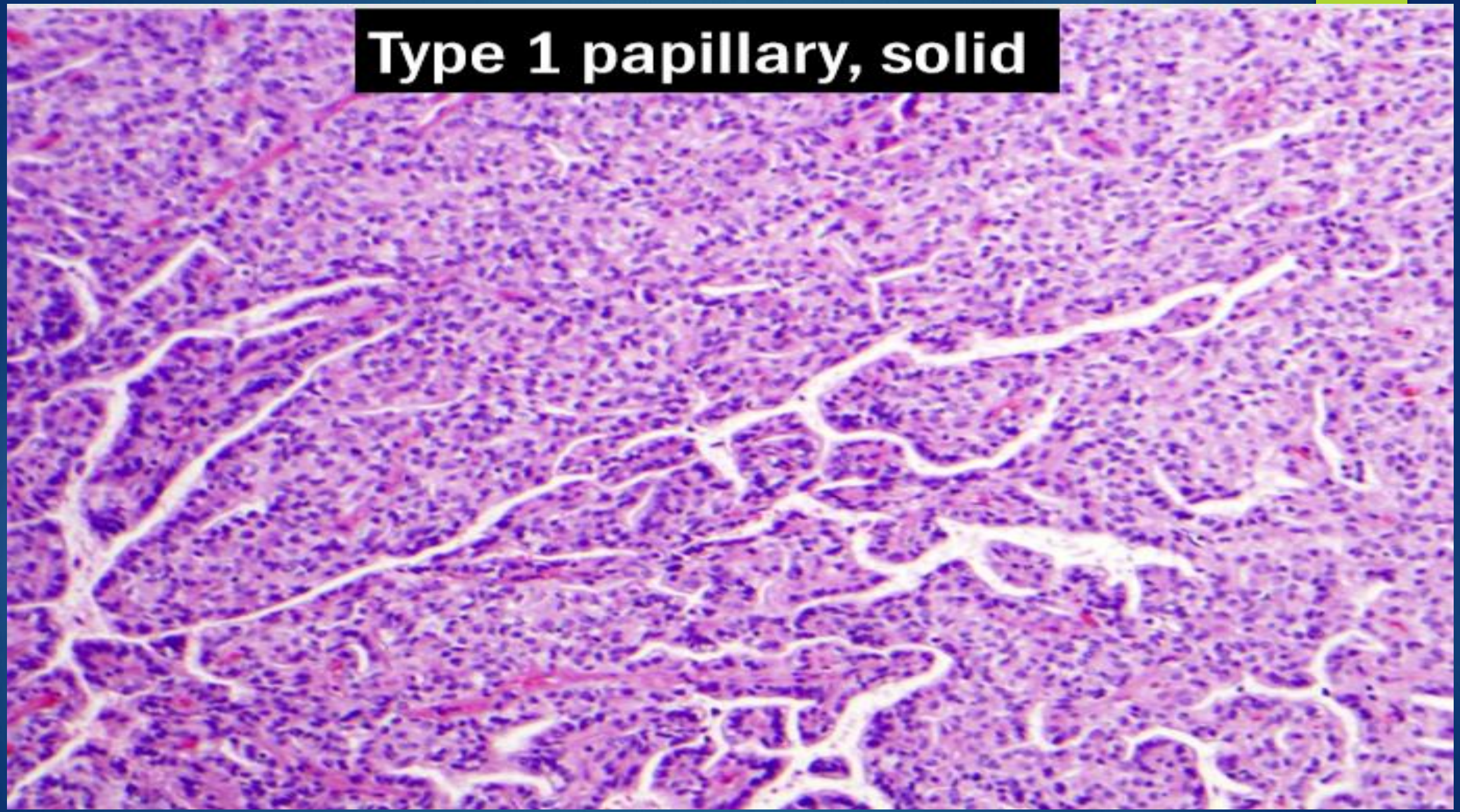
Mixed

Sarcomatoid

Foamy Macrophages




Type 1 papillary RCC

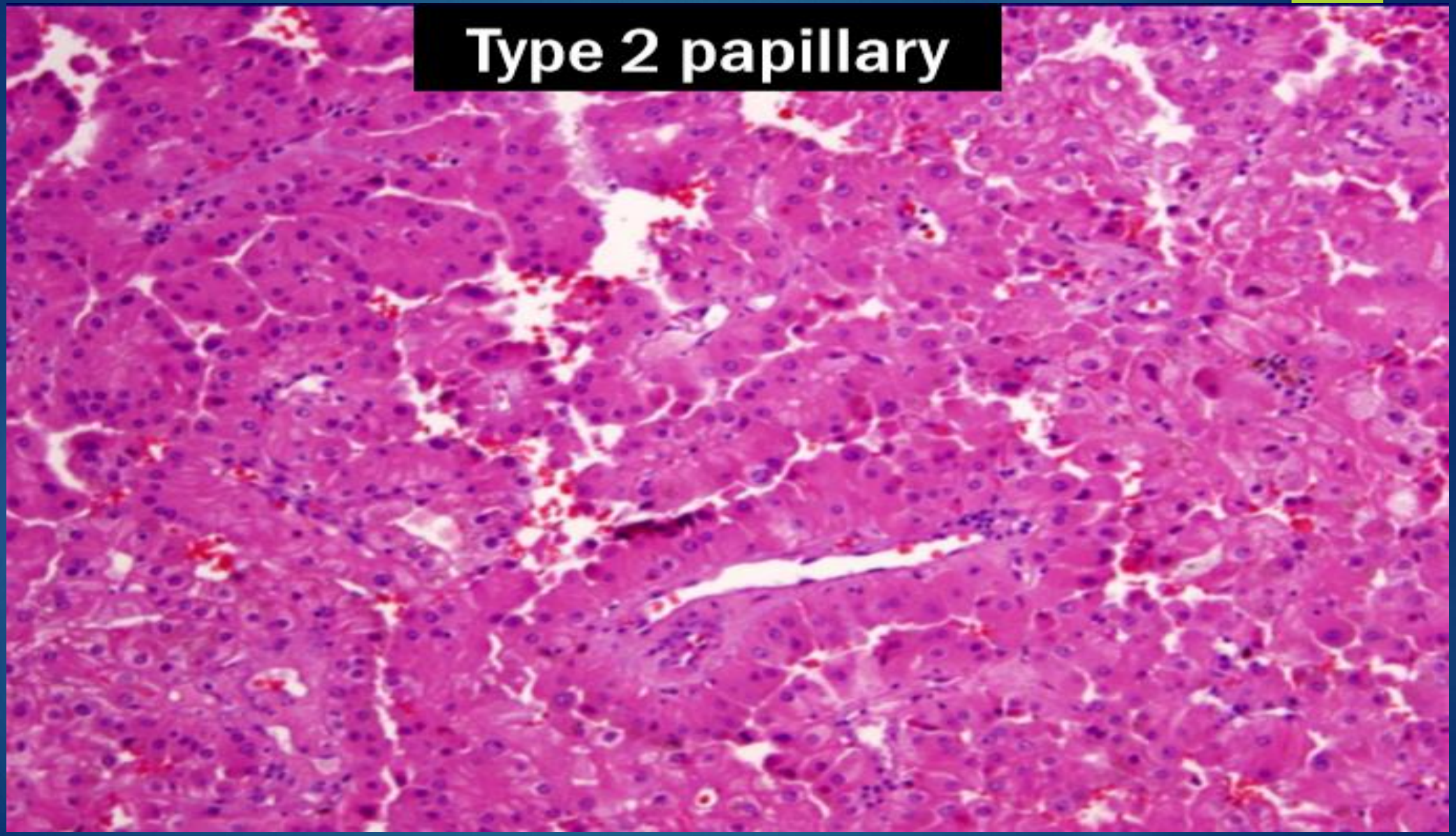

Type 1 papillary, solid

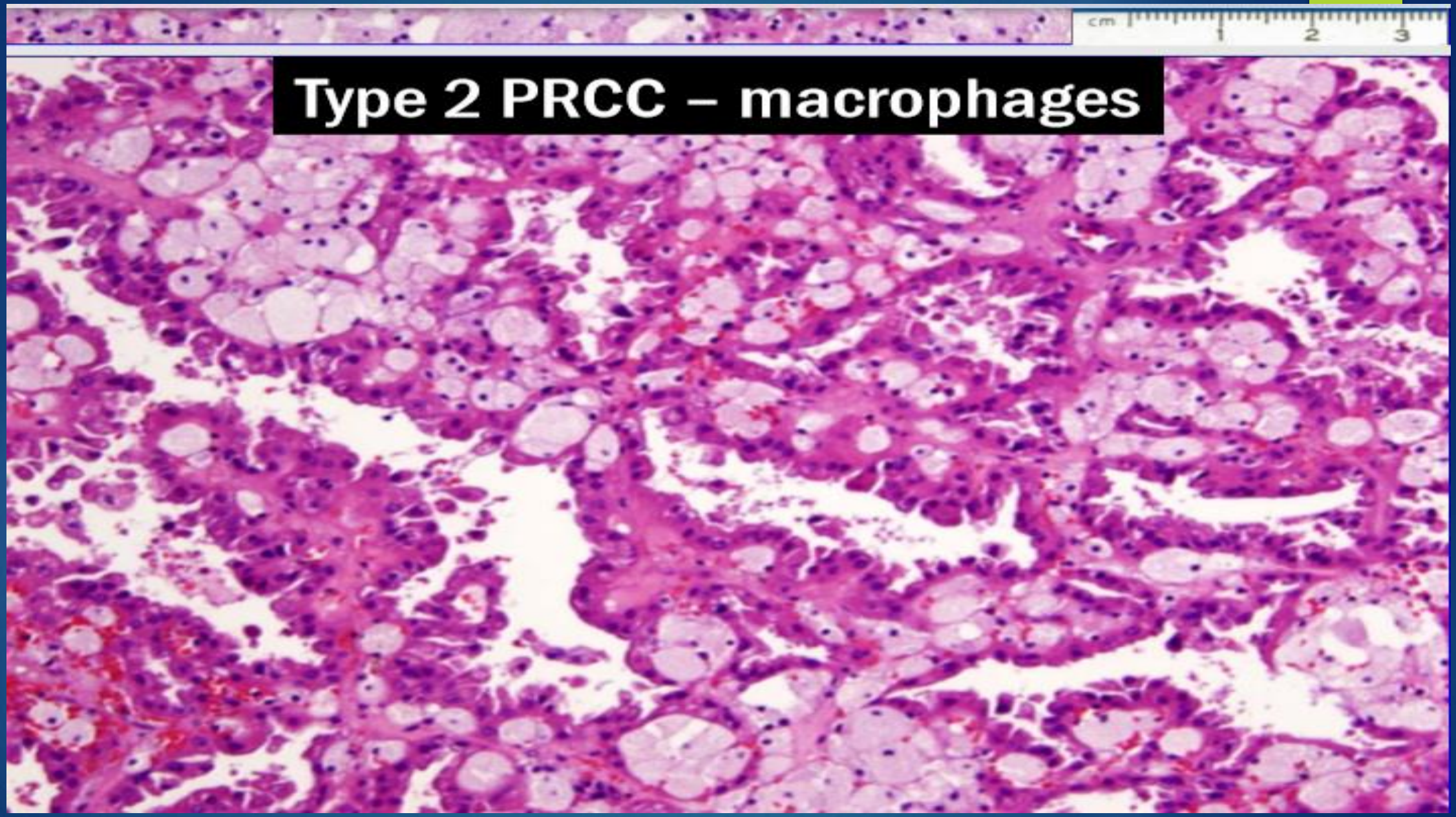
Type 1 papillary RCCs

- At the molecular level, type 1 tumors typically show gains in chromosomes 7 and 17, and Y chromosome loss.
- Most tumors are sporadic, but there are familial cases in the autosomal dominant hereditary papillary RCC syndrome, where germline MET proto-oncogene mutations on chromosome 7 result in multiple bilateral tumors
- Type 1 tumors generally present with a lower grade and stage at diagnosis and have a better outcome than type 2 tumors .
- Tumors with the histological appearance of a non-encapsulated type 1 tumor and up to 15 mm in size are classified as papillary adenomas, rather than carcinomas, because they show benign clinical behaviour

Type 2 papillary RCCs

- Morphologically, type 2 tumors have cells with more abundant eosinophilic cytoplasm that show nuclear pseudostratification and higher grade nuclei.
- They also show more variable protein expression on immunohistochemistry than type 1 tumors, often including loss of CK7.
- At the molecular level, these tumors are associated with NRF2–ARE pathway activation and can be divided into several distinct molecular subtypes that are associated with differing patient survival

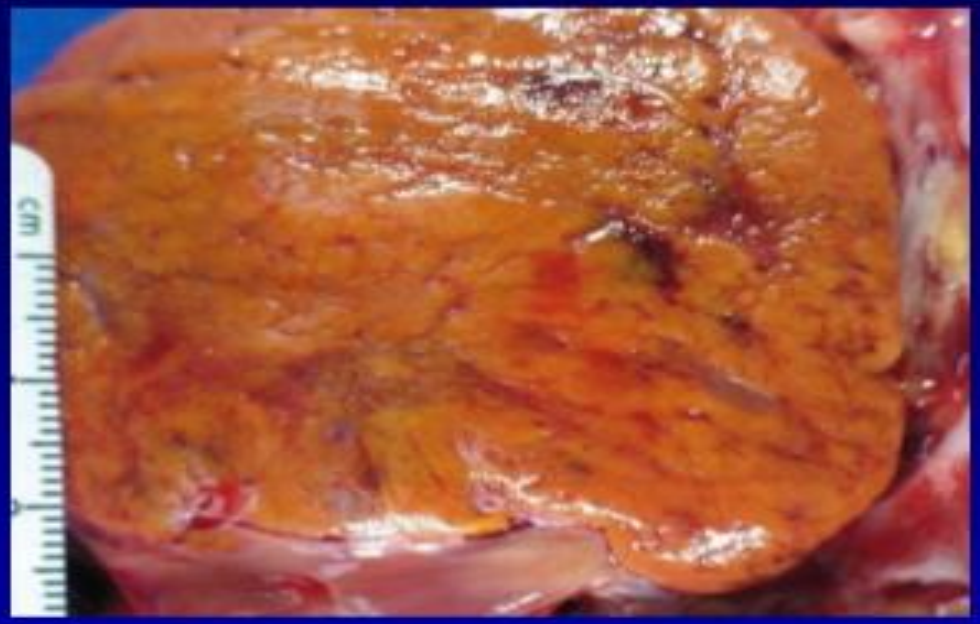

Type 2 papillary


Type 2 PRCC – macrophages

- Papillary RCC is more often multifocal and bilateral than the other common tumor types, as seen in approximately 10% of cases
- Papillary RCCs are also more frequent in acquired cystic kidney disease
- A less common tumor that may show overlapping morphology with type 1 papillary RCCs, particularly in limited biopsy samples, is the mucinous tubular and spindle cell carcinoma (MTSCC) :elongated tubules and spindle cells, both cytologically low grade, and abundant intercellular mucin. It has a similar immunohistochemical profile to papillary RCCs, adding to the difficulty in distinguishing these tumors in some cases

Chromophobe RCC

- usually sporadic and generally has a good prognosis. Most of these tumors are confined to the kidney at diagnosis, though they may be large at the time of presentation
- They are characteristically tan in color, similar to the benign renal oncocytoma that is the main differential diagnosis
- On microscopy, chromophobe RCCs characteristically consist of large cells with prominent cell membranes, pale cytoplasm and crinkled 'raisinoid' nuclei with perinuclear halos.
- An eosinophilic variant also occurs, where the cells have an oncocytic cytoplasmic appearance and the nuclear features described are often less apparent

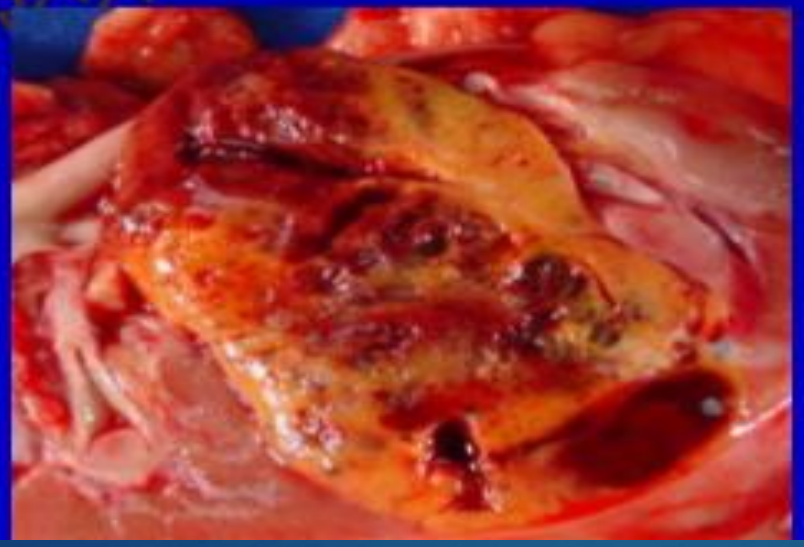


Common Gro$$ Feature$:

1. **Homogeneou$**
2. **Mahogany brown**
3. **$olid**
4. **Well circum$cription**

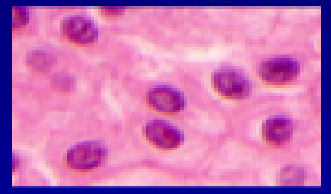
Chromophobe

RCC

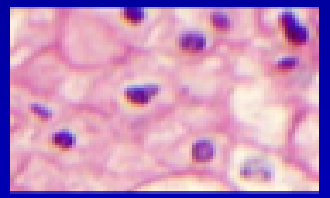


Chromophobe RCC

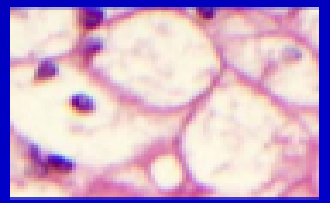
Three Types of Cells



Type 1: Eosinophilic cell with no perinuclear halo



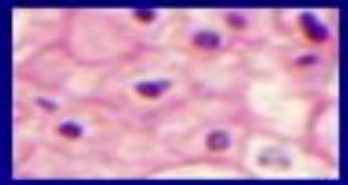
Type 2: Eosinophilic cell with perinuclear halo



Type 3: Largest polygonal cells with voluminous, reticulated cytoplasm

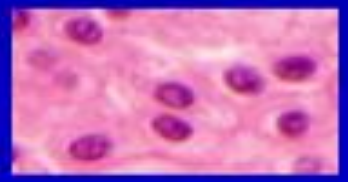
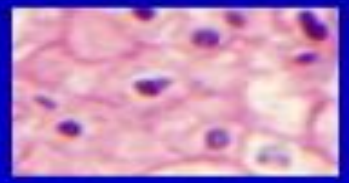
Chromophobe RCC

Morphologic Spectrum

- **Typical:**  + 

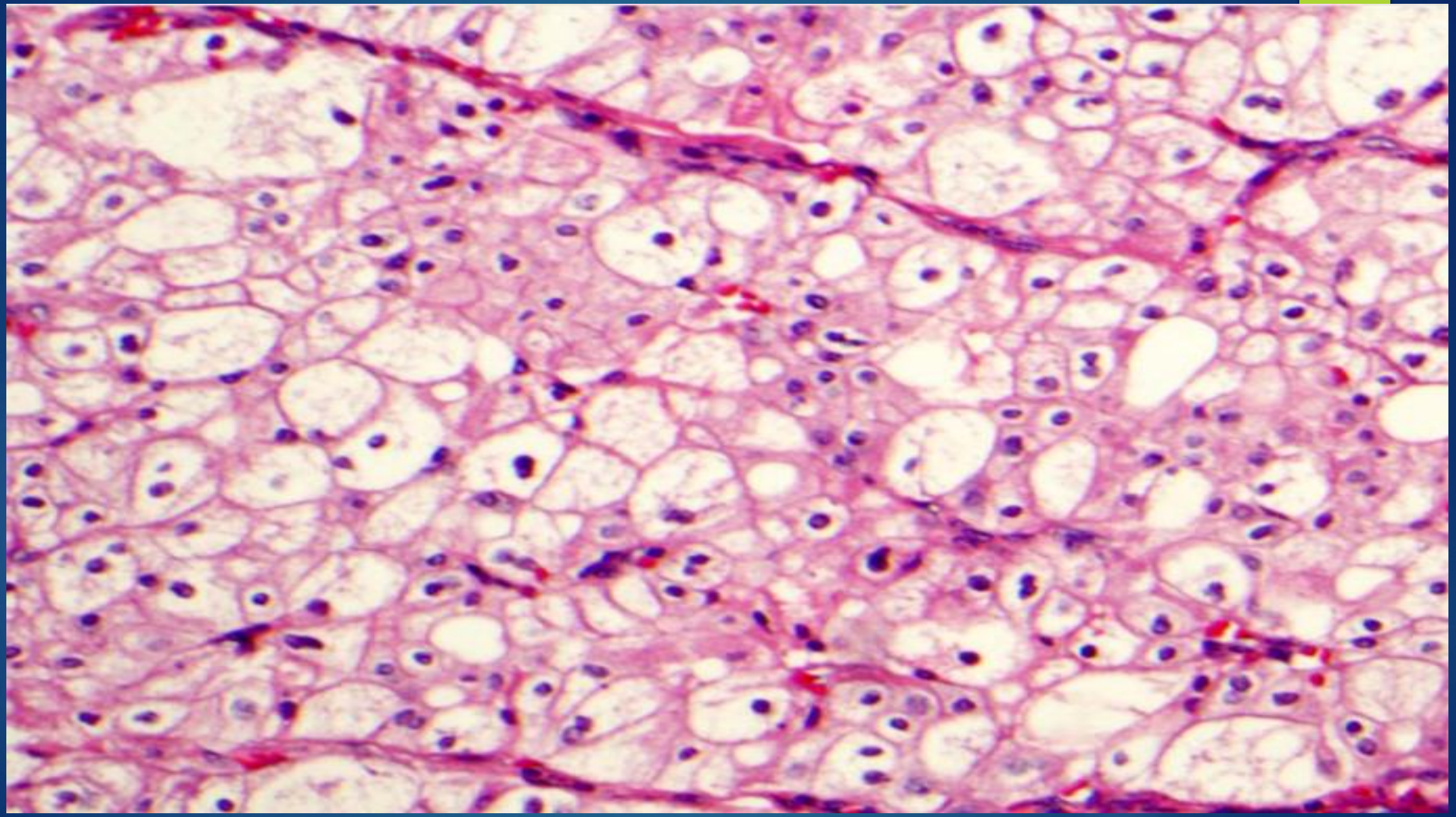
  Easy to diagnose

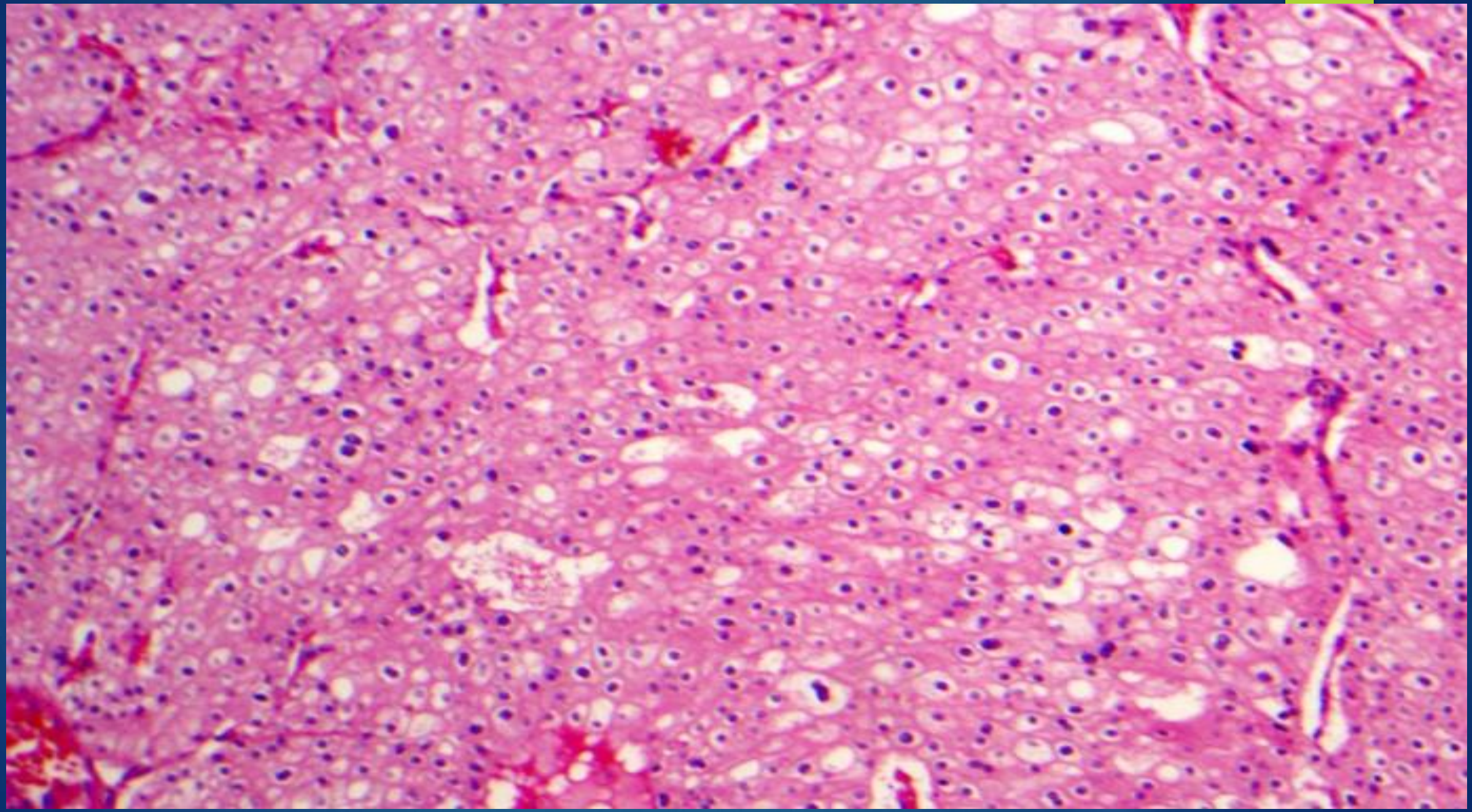
  May be confused with clear cell RCC

- **Eosinophilic:**  + 

  Predominant type 1 or type 2 cells;

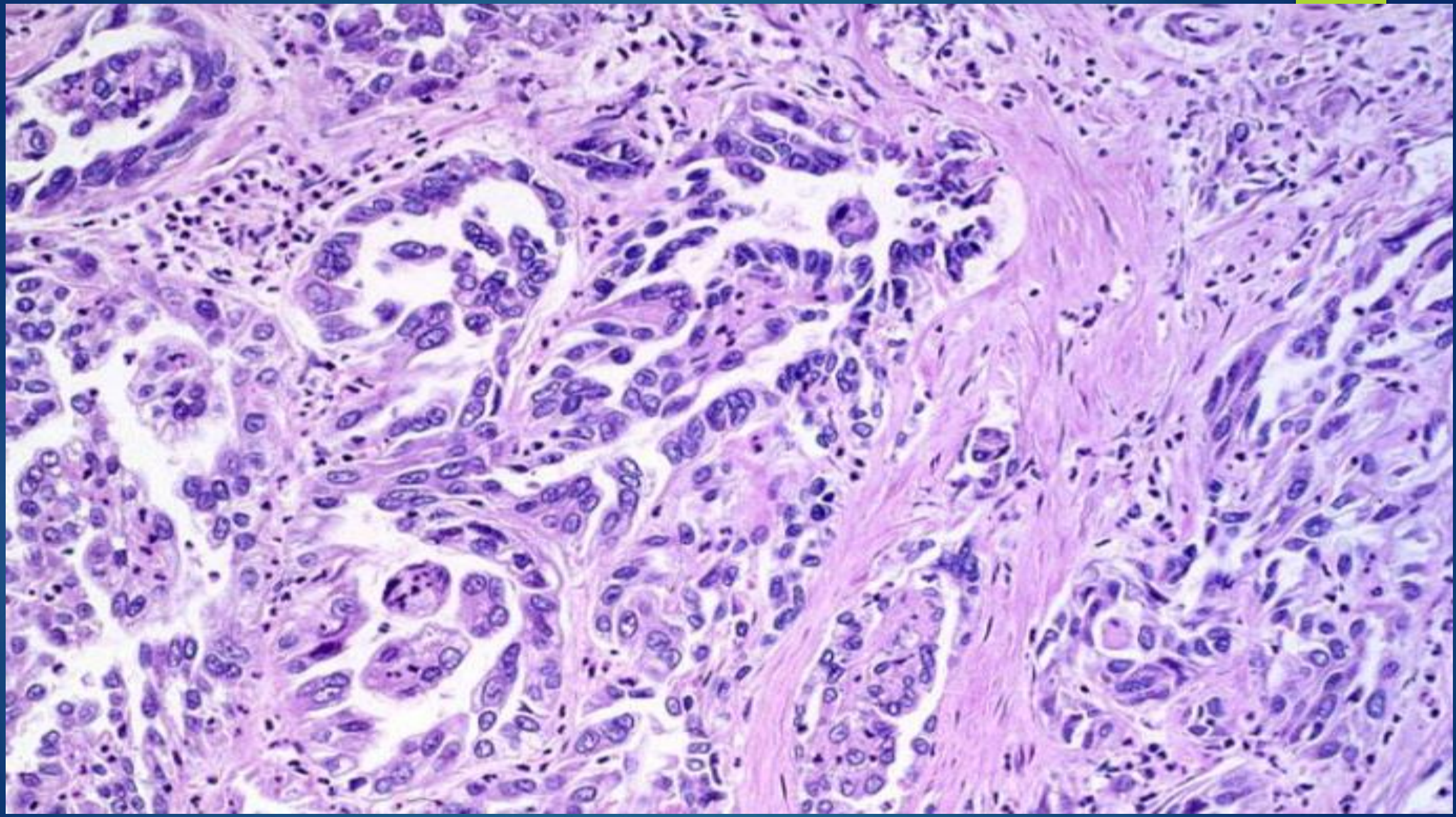
  May be confused with oncocytoma

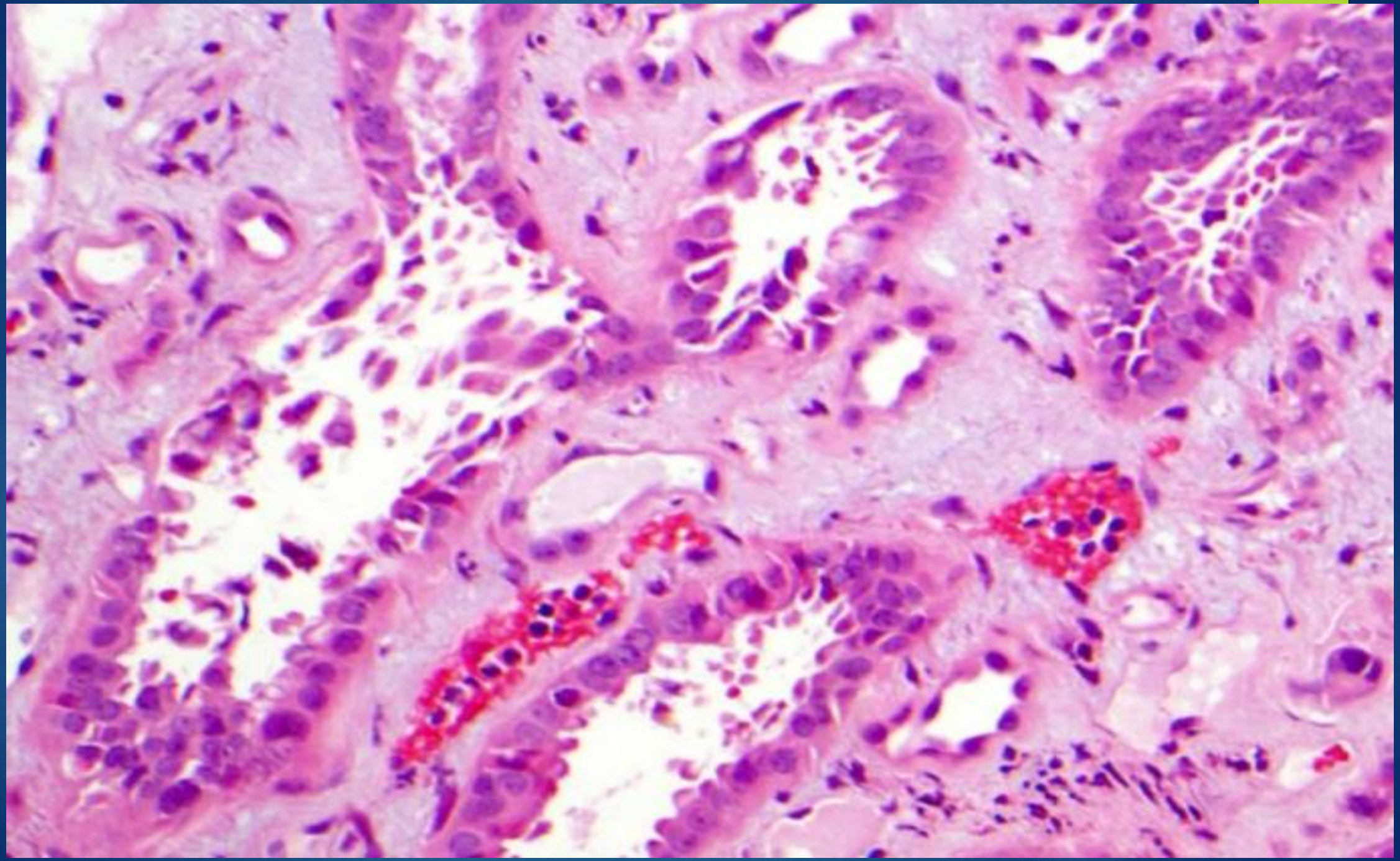




Collecting duct carcinoma

- rare (1–2%) and highly aggressive type of RCC arising in the renal medulla. It may be difficult to distinguish histologically from urothelial carcinoma of the renal pelvicalyceal system, due to similar infiltrative high-grade variable morphology and their overlapping immunohistochemistry profiles.
- Distinction from metastatic tumors may also be problematic, particularly adenocarcinomas, and diagnosis is by exclusion of other entities.
- Metastatic disease is common at the time of diagnosis and the majority of patients do not survive 2 years from diagnosis





Renal medullary carcinoma

- Renal medullary carcinoma has similar morphology (Like collecting duct carcinoma)and occurs in association with sickle cell trait or disease. This is rare, aggressive and occurs more often in younger adults.
- In contrast to collecting duct carcinomas, these tumors may express OCT3/4 on immunohistochemistry and show loss of expression of SMARCB1 (INI1)

MiT family translocation RCCs

- rare and should be considered particularly in children and young adults
- They result from gene fusions involving the MiT transcription factor genes TFE3 and TFEB, with differing fusion partners.
- The best morphologically described tumors of the group are those associated with Xp11 and t(6;11) translocations.
- The former may be recognised by their distinctive clear cell morphology with voluminous cells, and a papillary architecture, sometimes with frequent calcifications (psammoma bodies).
- The less common t(6;11) translocation tumors have a characteristic biphasic pattern with distinct groups of large and small epithelioid cells.
- The MiT family translocation RCCs commonly show weak expression of epithelial markers on immunohistochemistry and some express melanoma markers and cathepsin-K.
- Diagnosis requires fluorescence in situ hybridisation (FISH) to confirm the presence of the translocation

Tubulocystic RCC

- rare, usually indolent, good prognosis tumor type more frequently seen in men. It was thought to be related to papillary RCCs, but is now accepted as a separate entity
- It has a characteristic 'bubble wrap' appearance grossly, due to the presence of fibrotic stroma separating cystic spaces.
- Small tubules are present within the stroma microscopically and are lined by cells with eosinophilic cytoplasm and round nuclei with nucleoli of variable prominence.
- The tumor cells may also have a 'hobnail' appearance. These tumors express AMACR and CK7 on immunohistochemistry

	RCC, low grade papillary	RCC, tubulocystic	RCC, high grade papillary
H&E	A	B	C
AMACR	D	E	F
CK7	G	H	I

Succinate dehydrogenase-deficient RCC

- rare and results from inherited germline mutations in the succinate dehydrogenase (SDH) gene, most commonly SDHB but also in SDHA, SDHC and SDHD.
- Affected patients may also present with paragangliomas and gastrointestinal stromal tumors (GISTs).
- The associated RCCs may be multifocal and bilaterality occurs in around 25% of cases .
- On microscopy, the RCCs are usually solid and are composed of cells with eosinophilic cytoplasm with distinctive cytoplasmic vacuolation and inclusions, although focal limited presence of these changes may hamper pathological recognition .
- Intratumoral mast cells are also a common feature. Immunohistochemistry for demonstration SDHB is available, where a loss of staining is indicative of a mutation in the SDHB (most common), SDHC or SDHD genes. SDHA gene mutation can be demonstrated by additional absence of staining for SDHA. Most tumors are low grade and have a good prognosis

Unclassified RCC

- Approximately 5% of tumors remain difficult to categorise after thorough sampling and immunohistochemical assessment, because the tumor is purely sarcomatoid, the immunoprofile is not definitive or there are unusual or overlapping morphological features.

- Tumors composed of eosinophilic cells have been shown to cause particular difficulty in classification when they do not show distinctive features

RCC, Unclassified

Definition: tumor that does not fit into any known types by morphology or genetics

- RCC with mucin production ?
- Composites of recognizable types ?
- Unrecognizable cell types
- RCC with sarcomatoid change in which the epithelial elements cannot be assigned to one of the known categories

Renal Cell Carcinoma, Unclassified

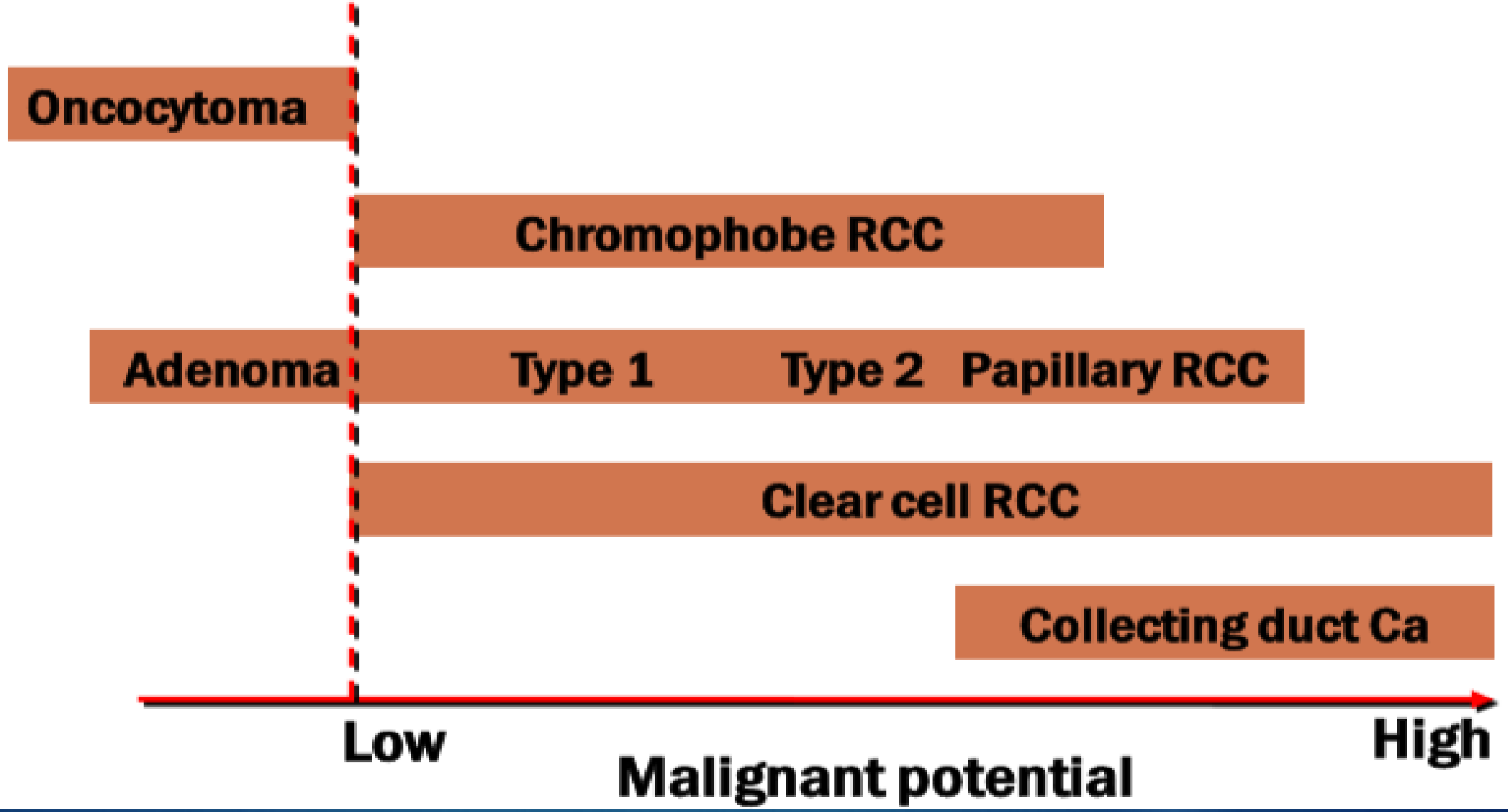
- Reserved for those truly unclassifiable based on adequate sampling of tumor
- Rule out metastatic tumor
- Consultation is advisable
- Immunohistochemical stains may be helpful
- Cytogenetic analysis?

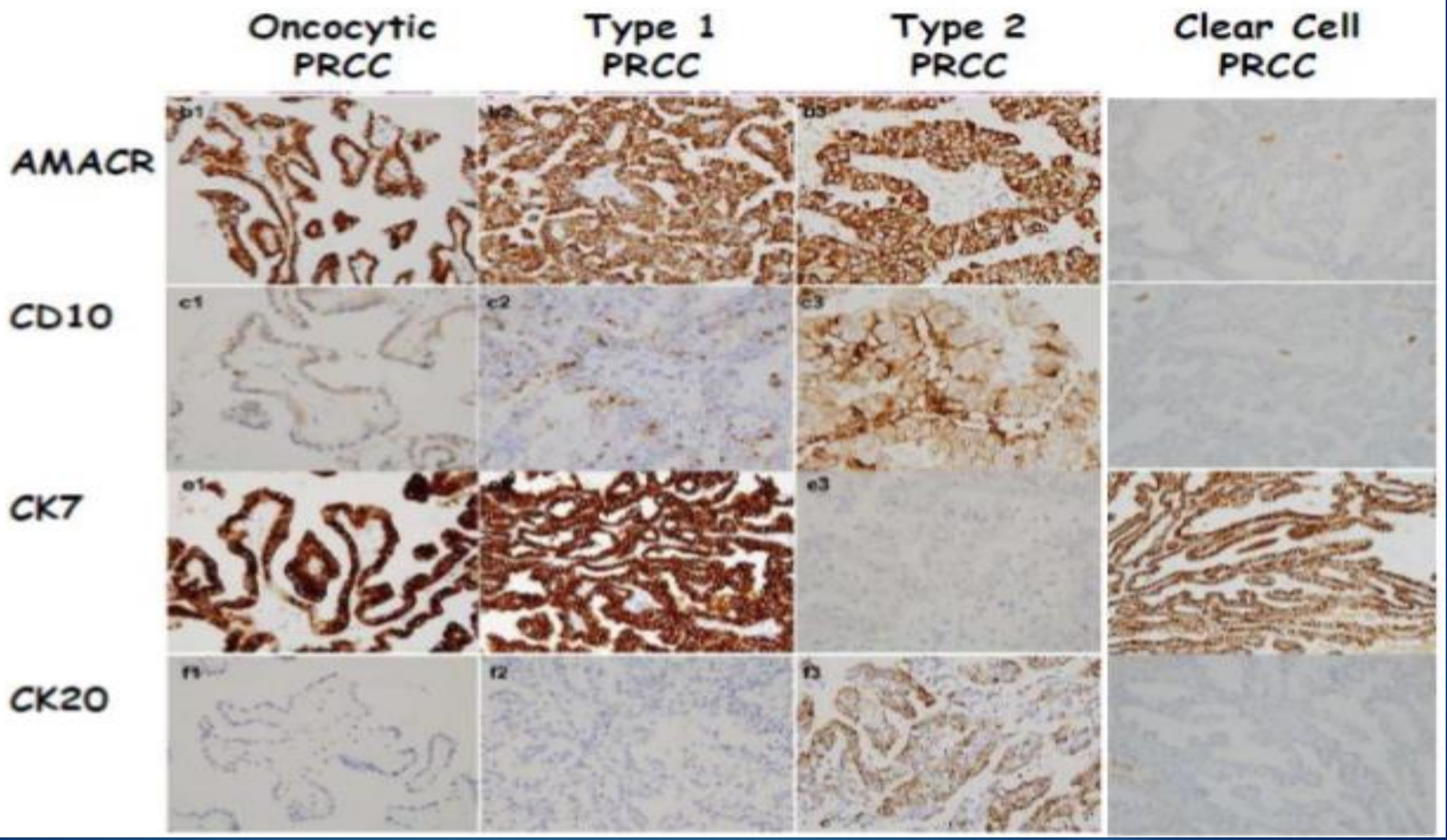
Challenges in tumor typing

- a papillary architecture seen in a variety of renal tumors. A particularly problematic area is the separation of oncocytic tumors, where benign and malignant entities may have overlapping morphology.
- It is well known that distinguishing a benign renal oncocytoma from a chromophobe RCC may be difficult, particularly as fat invasion or vascular involvement, features normally associated with malignancy, does not necessarily exclude the diagnosis of an oncocytoma
- CK7 immunohistochemistry may help, as oncocytomas should show only focal staining whereas there is strong and diffuse staining in most chromophobe
- Fluorescence in situ hybridisation (FISH) can also be utilised, as multiple chromosome abnormalities typically occur in chromophobe RCCs, but this investigation is not necessarily routinely available

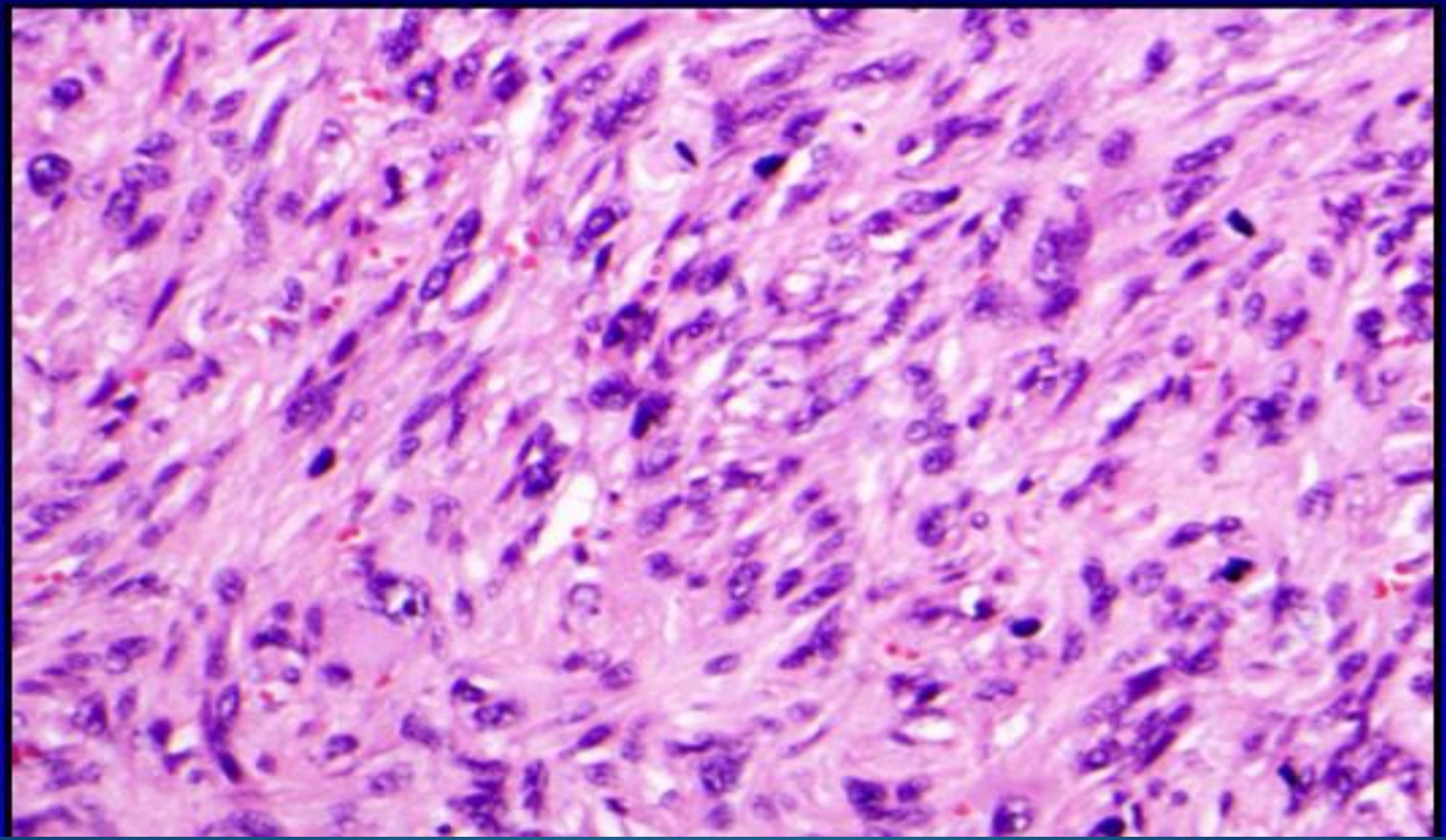
- Pax-8 is helpful for determining renal origin, but is also positive in tumours from other sites, such as the thyroid gland and gynaecological tract tumors of Müllerian origin. Additionally, the rarity of some tumors, which may show only subtle morphological changes from the more common RCC types, makes it difficult to ensure that pathologists are able to recognise these unusual tumor types.

(*Simplistic view*)



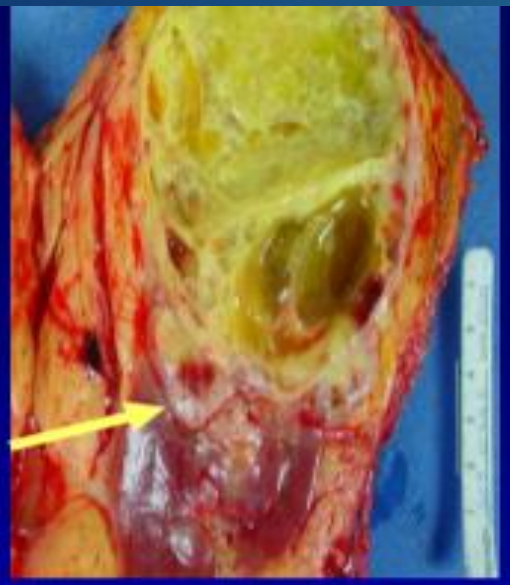

Oncocytic PRCC
Type 1 PRCC
Type 2 PRCC
Clear Cell PRCC
AMACR
CD10
CK7
CK20

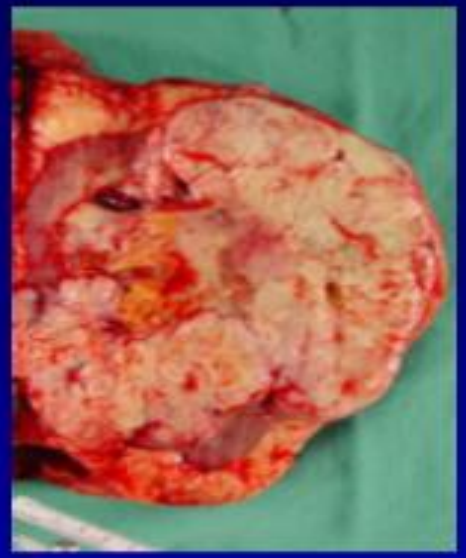
“Sarcomatoid” RCC

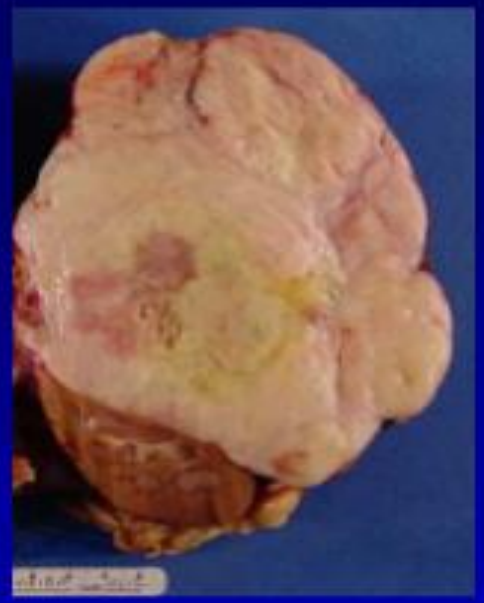


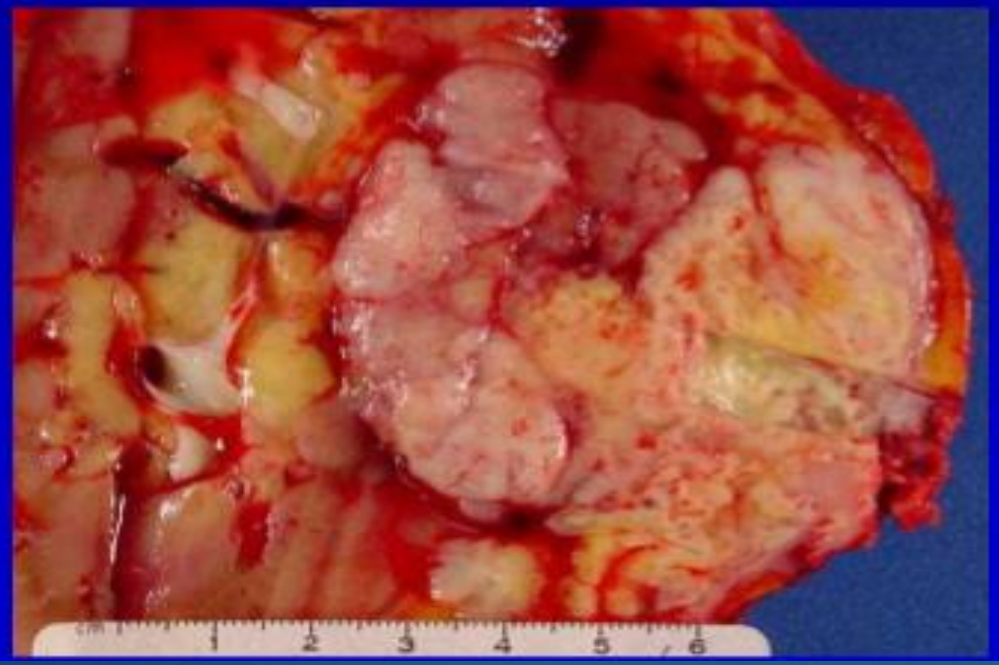
Sarcomatoid Changes Occur in All Types of RCC

	# Cases	# Sarcomatoid (%)
Clear cell	818	44 (5.4)
Papillary	149	7 (4.5)
Chromophobe	60	1 (1.7)
Collecting duct	6	4 (66.7)
Unclassified	15	6 (40)
Total	1048	62 (6)

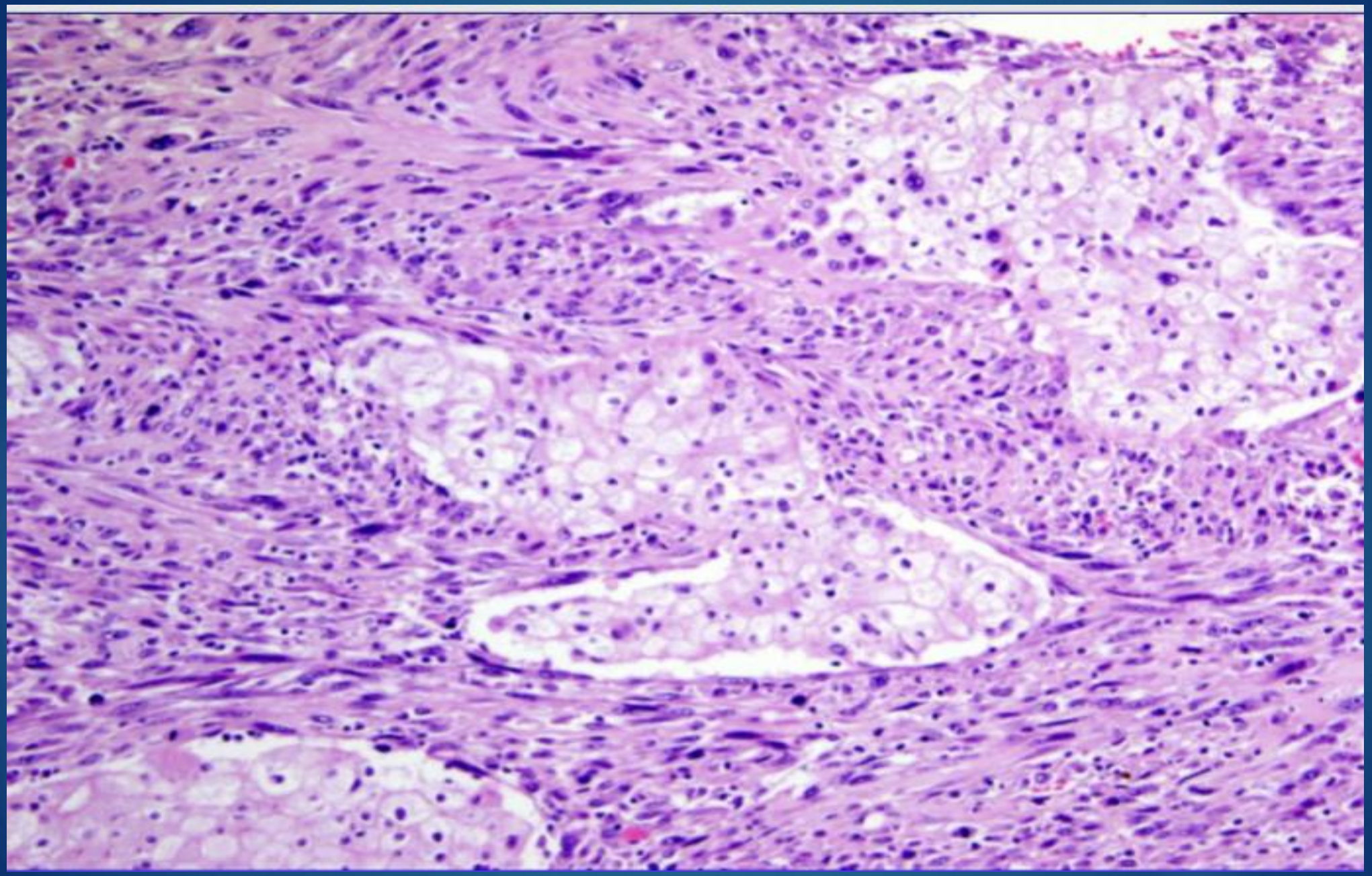




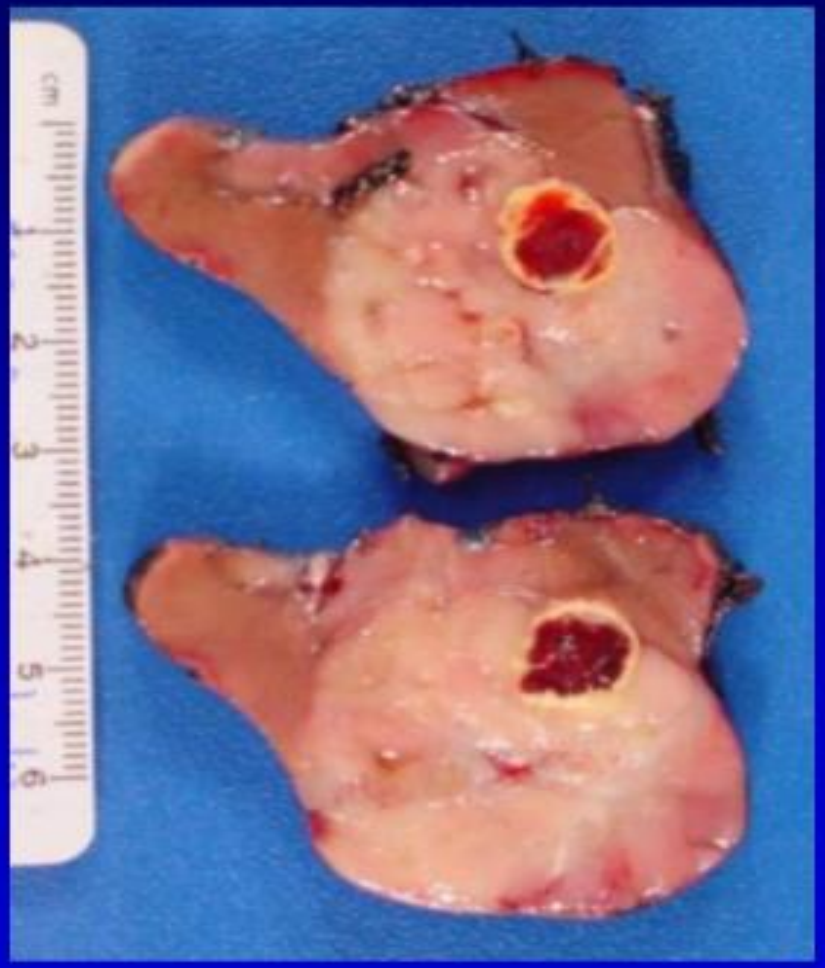


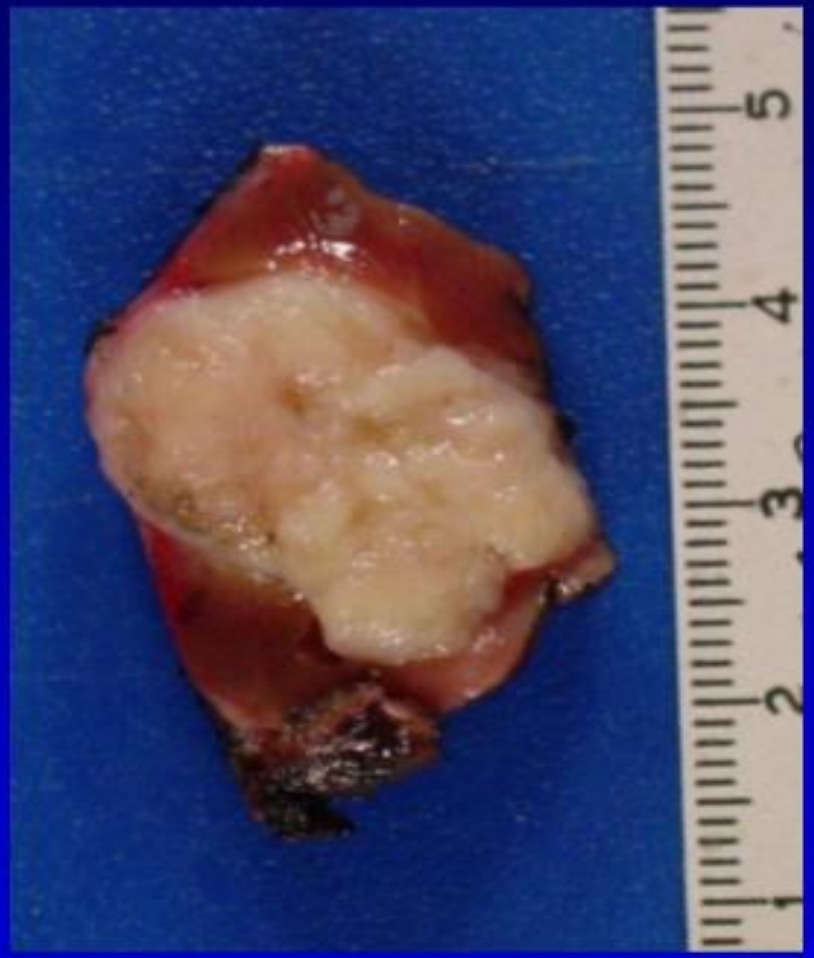


Sampling is important

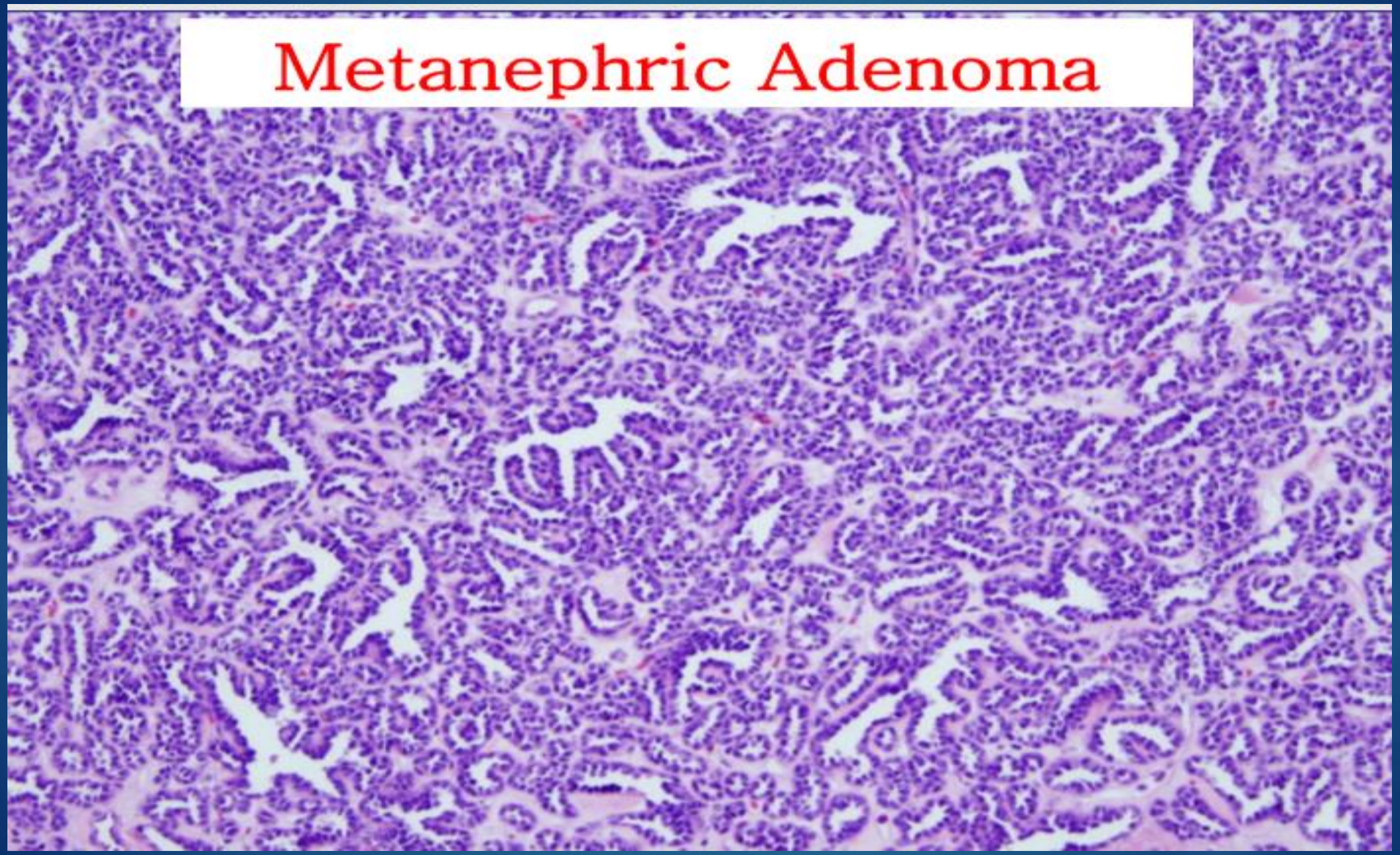


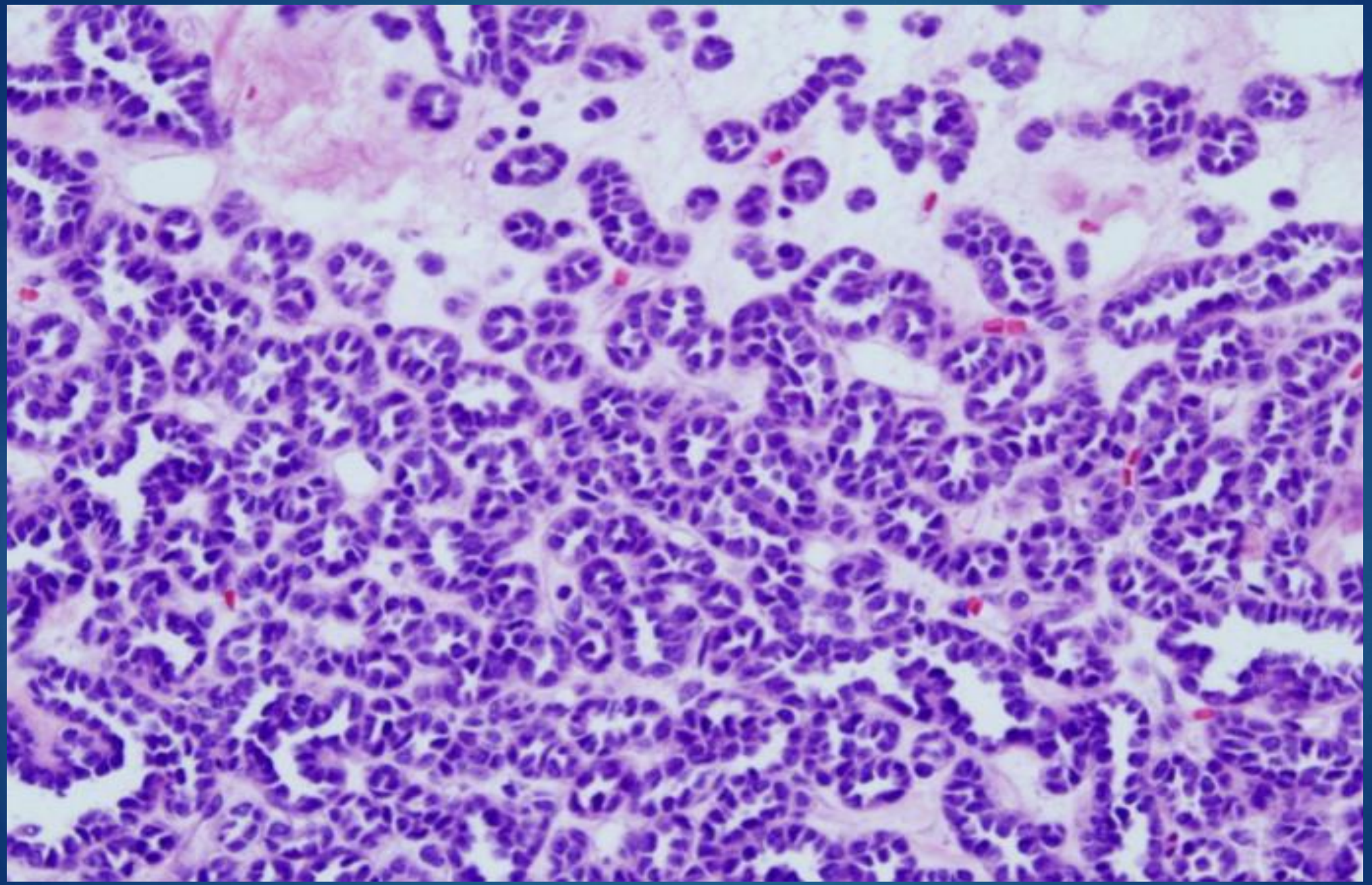
Metanephric Adenoma





Metanephric Adenoma



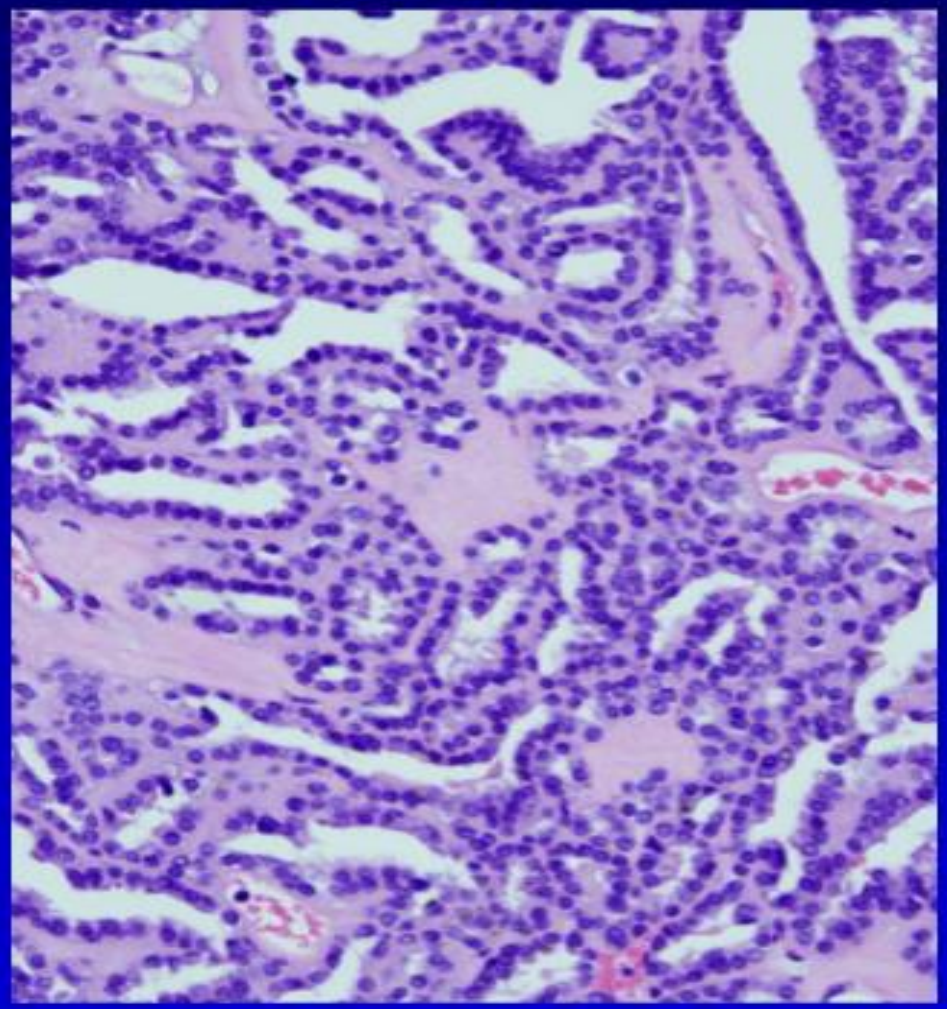


Morphologic Overlapping

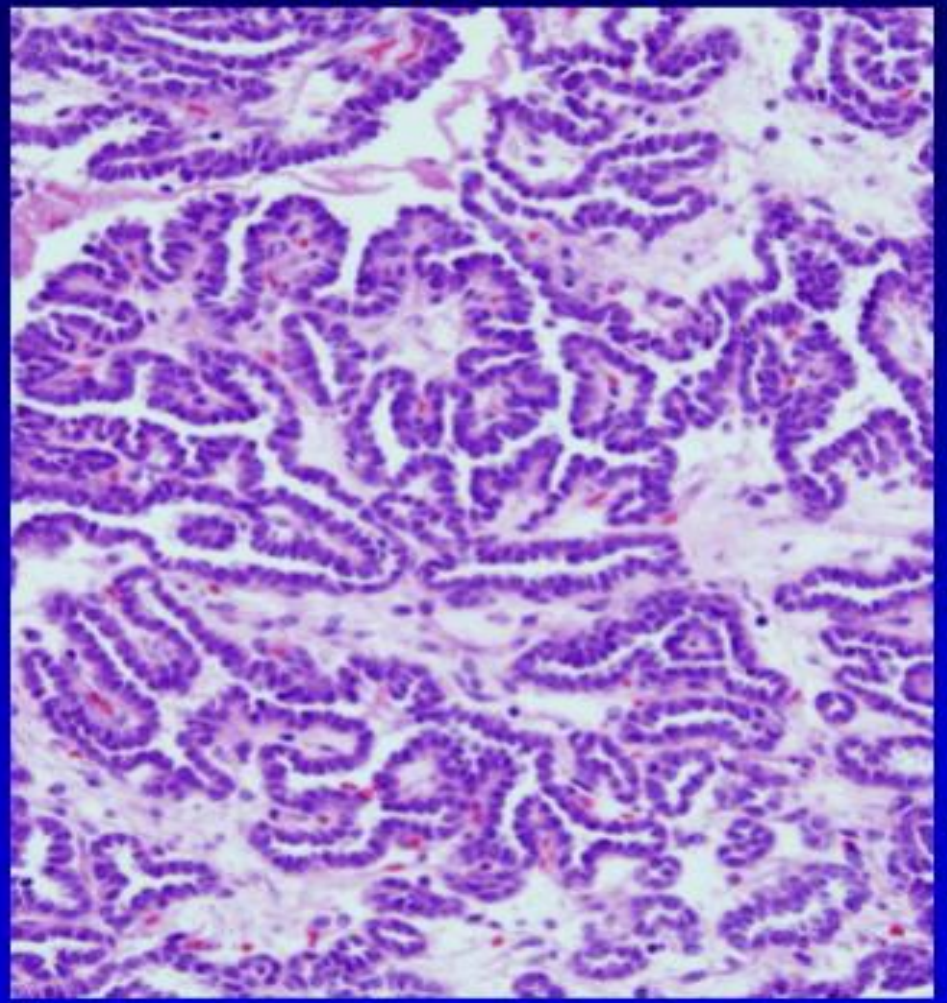
Metanephric Adenoma (MA) and Papillary RCC

	Papillary Pattern	Glomeruloid Pattern	Solid Pattern	Psammoma Bodies	Macrophages
MA	6/8 (75%)	4/8 (50%)	8/8 (100%)	6/8 (75%)	1/8 (13%)
PRCC	11/11 (100%)	4/11 (36%)	7/11 (64%)	1/11 (9%)	7/11 (64%)

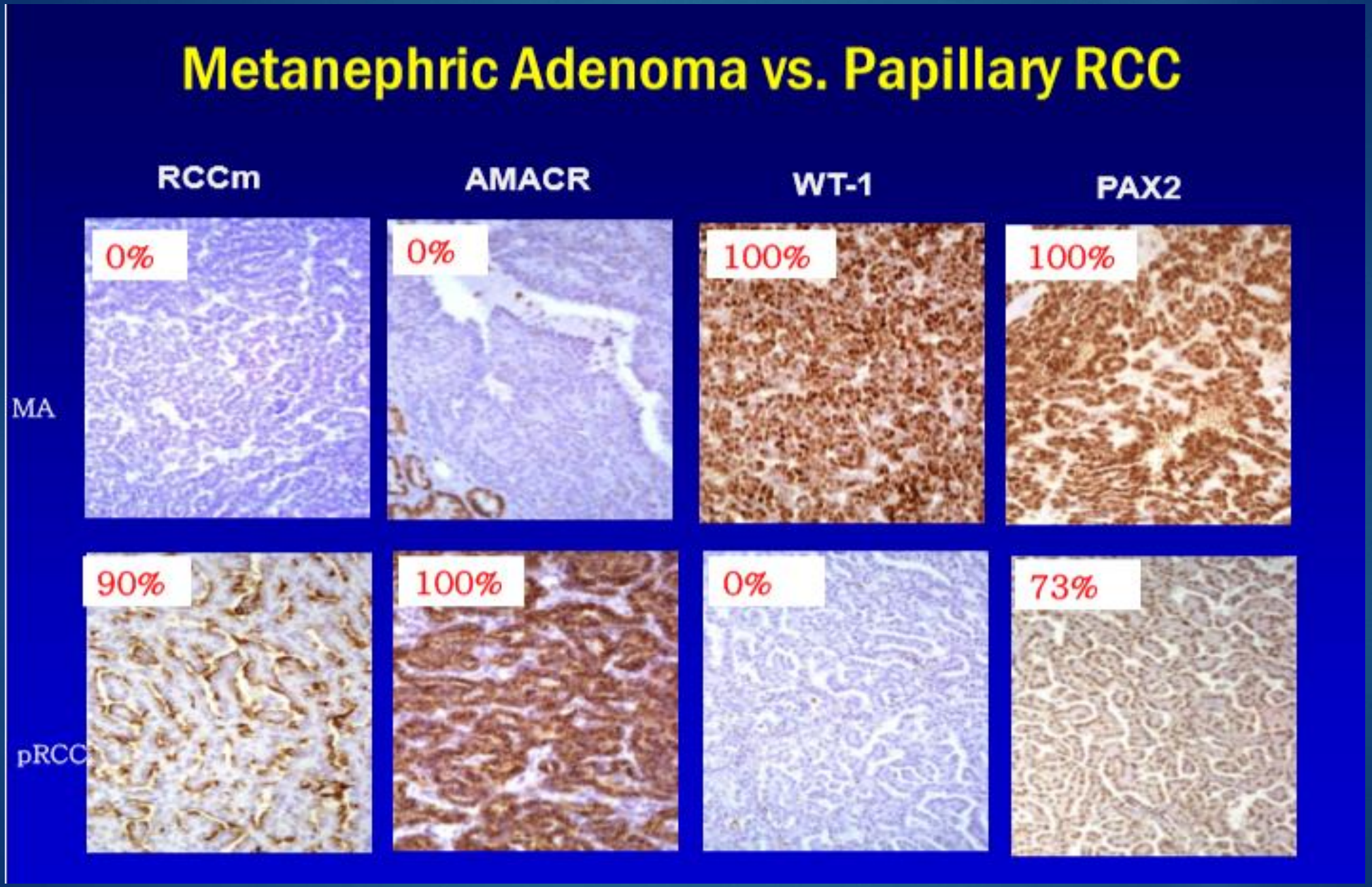
Papillary RCC



Metanephric Adenoma

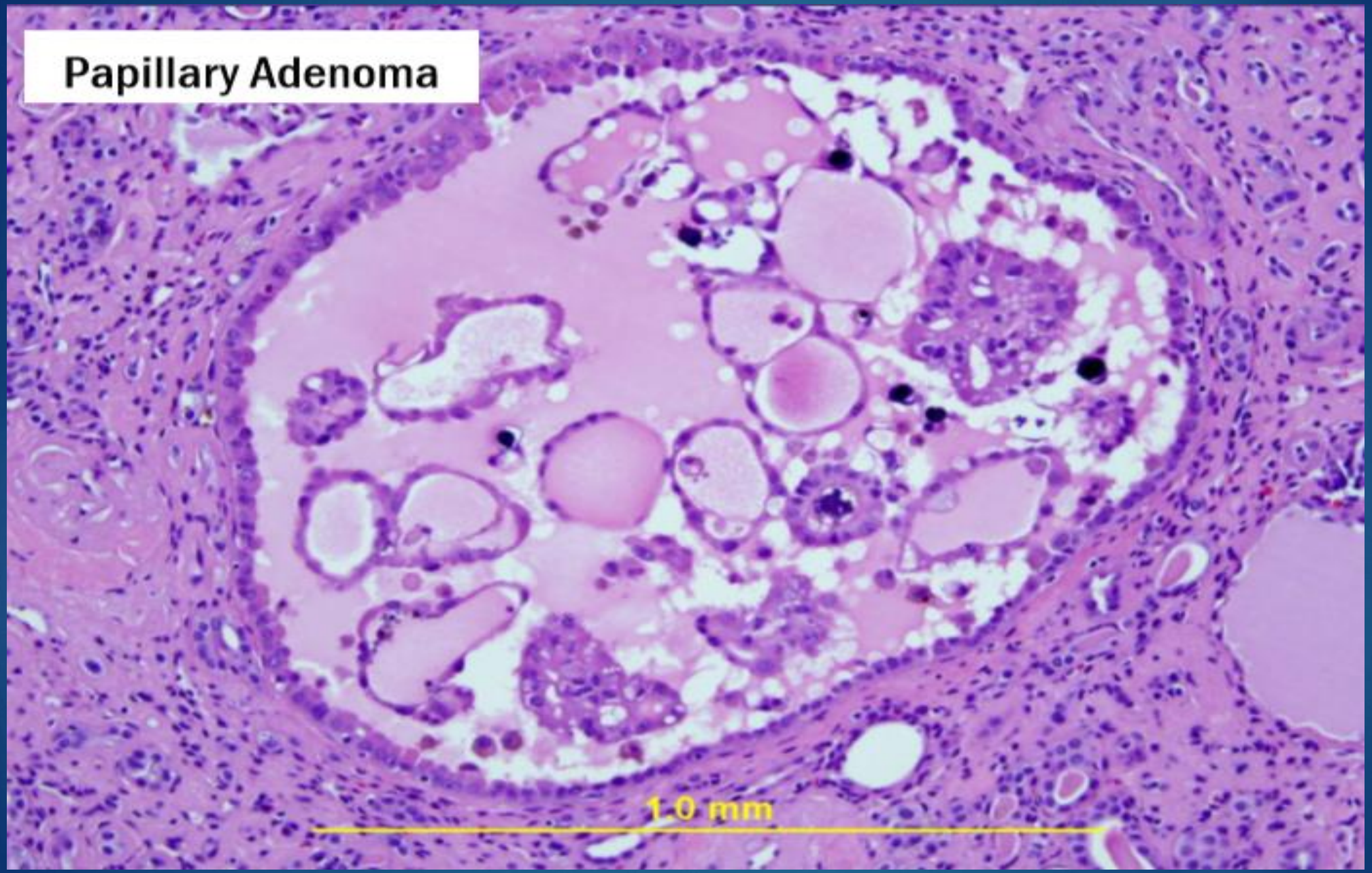


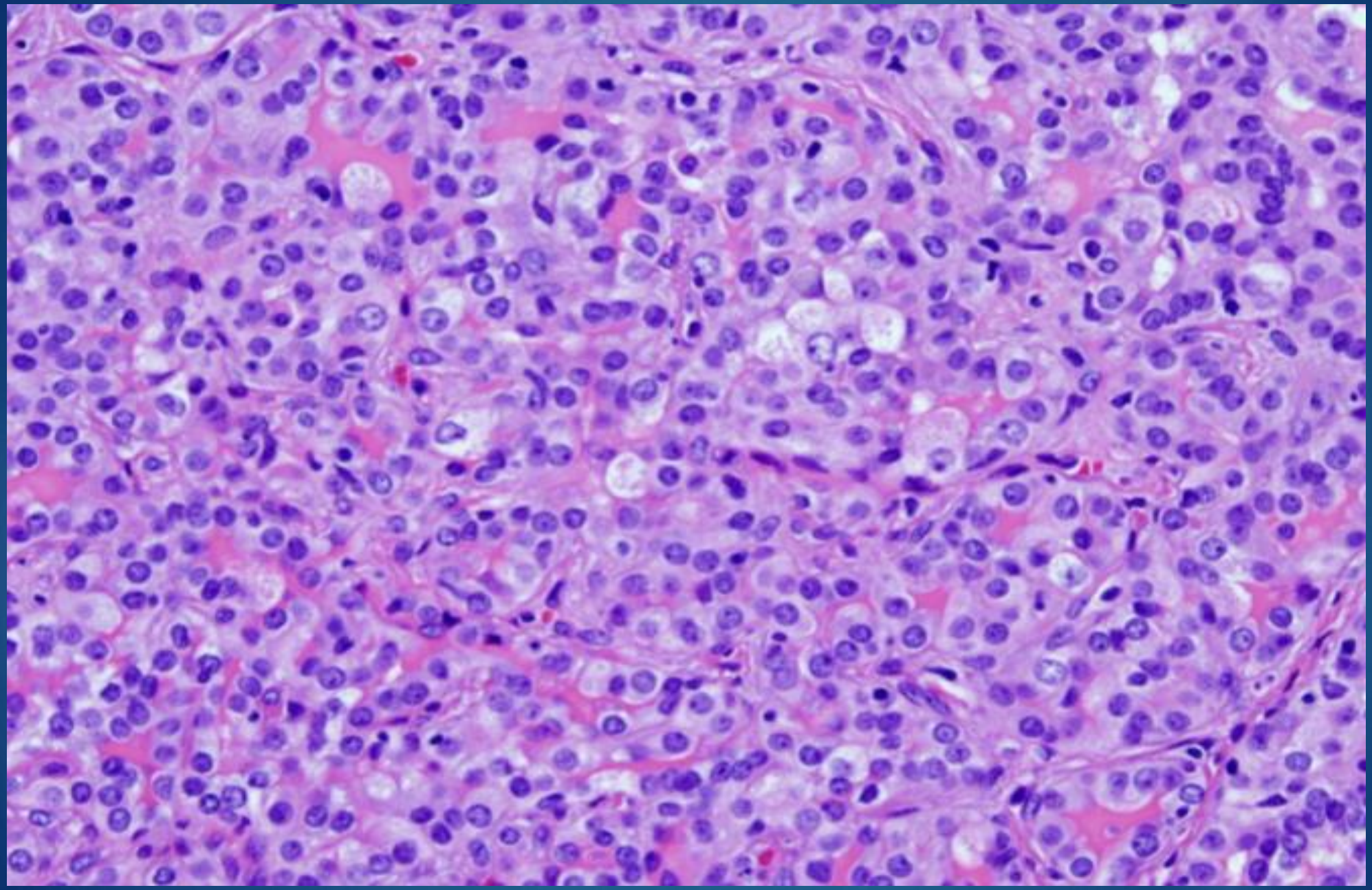
Metanephric Adenoma vs. Papillary RCC



Papillary Adenoma

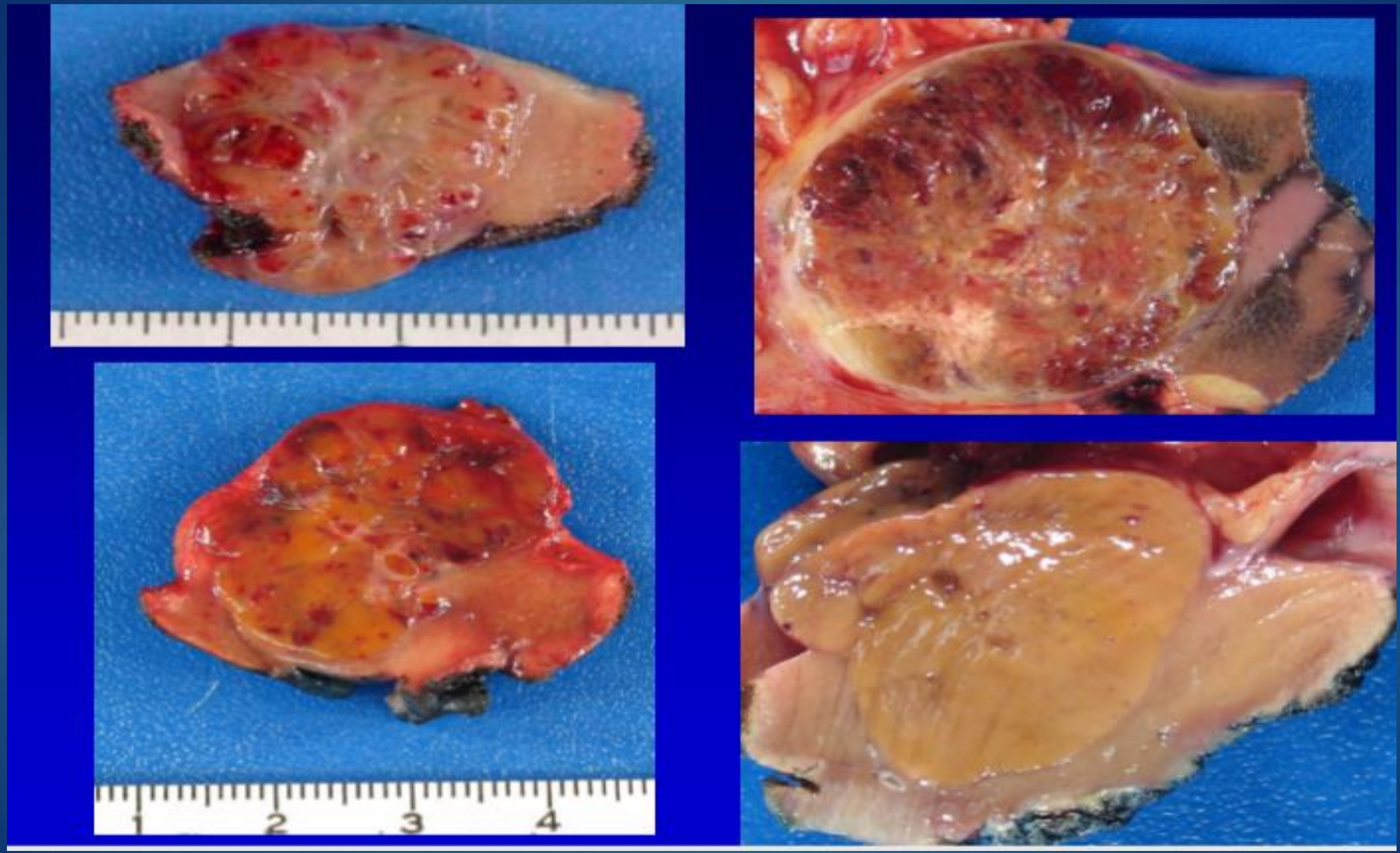
- "Baby" (≤0.5 cm) low grade papillary RCC
- Incidental findings
- Often associated with end stage renal D
- Associated with papillary RCC
- Frequently multiple

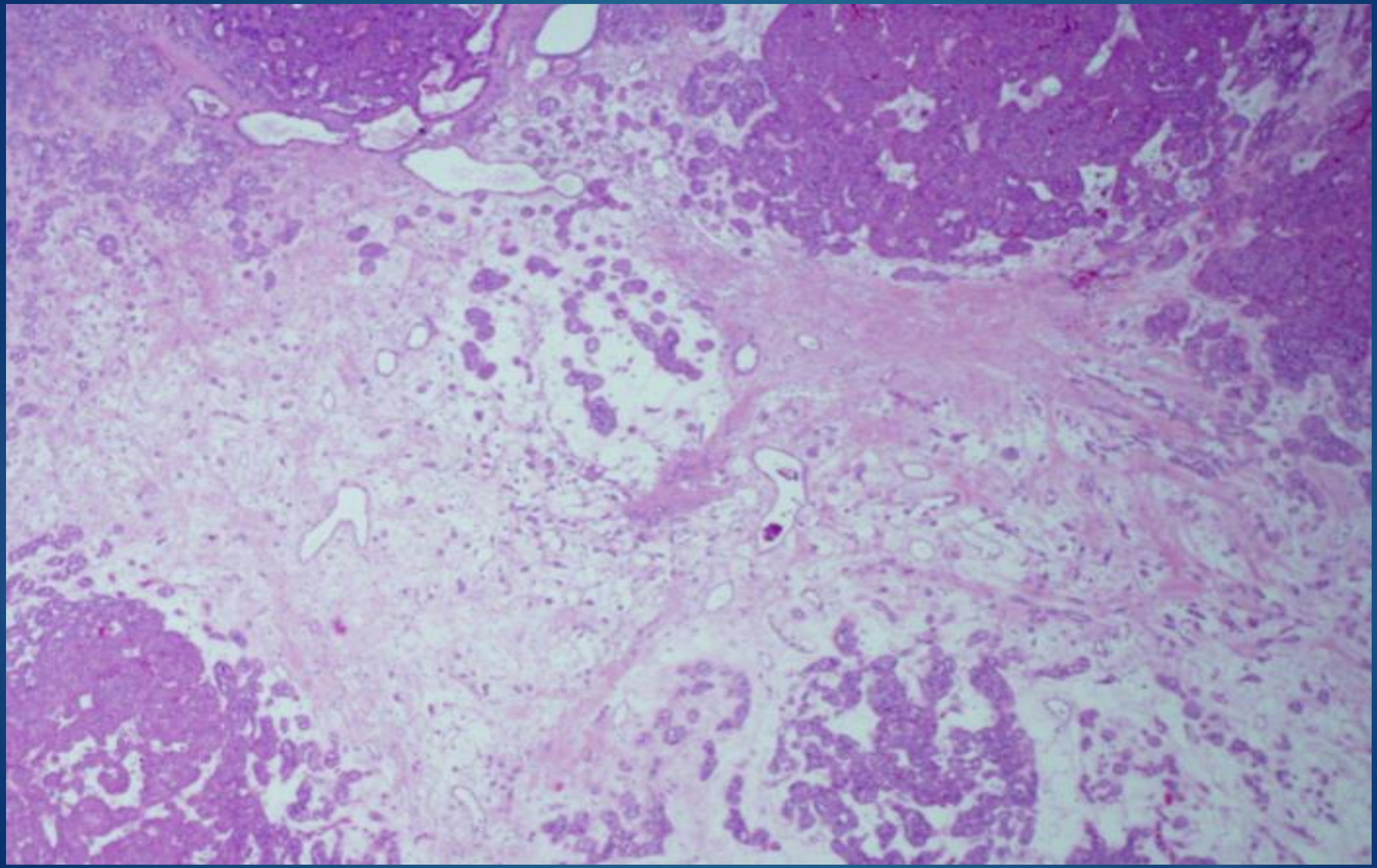

Papillary Adenoma
1.0 mm

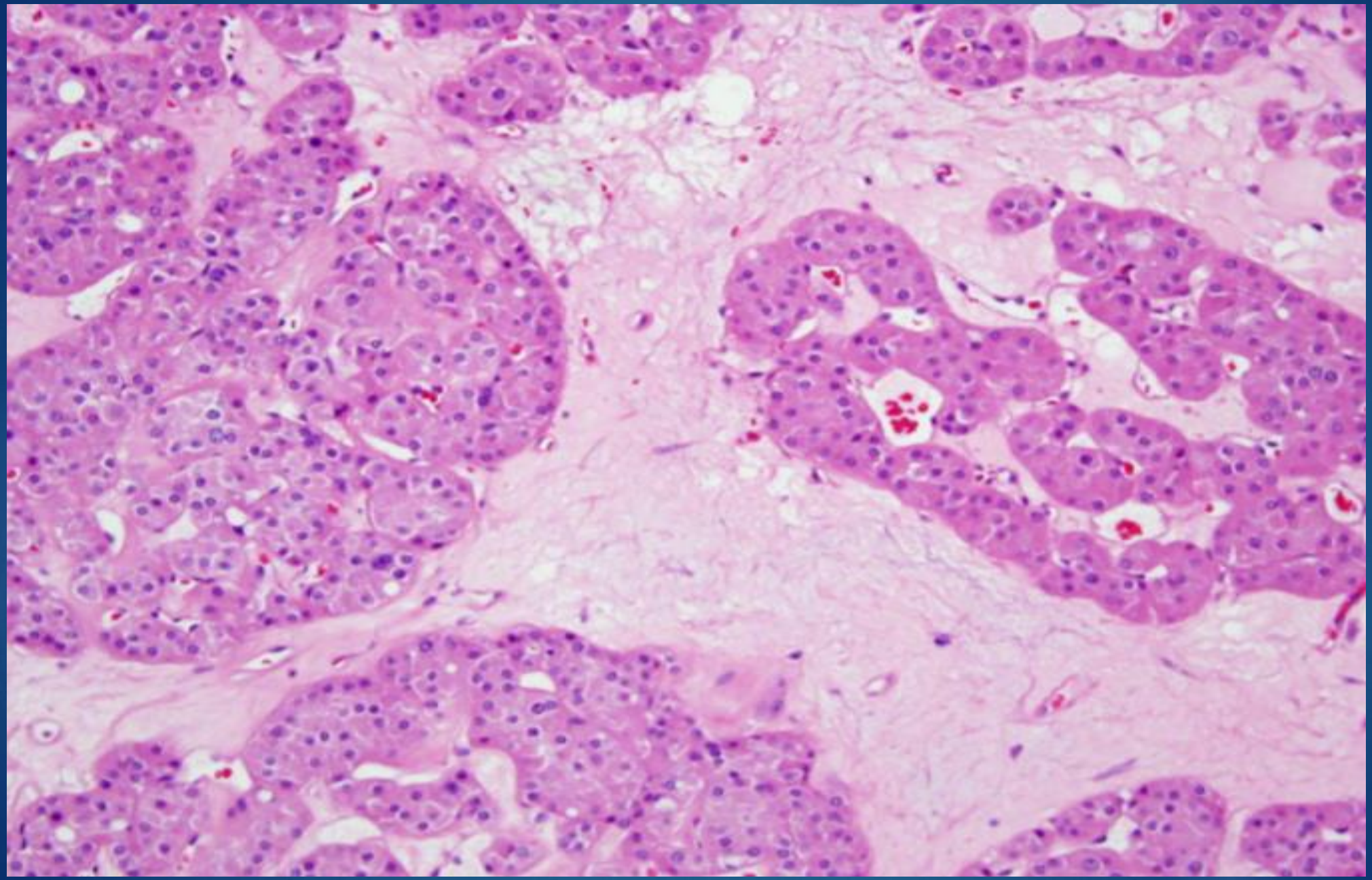


Oncocytoma

- Most frequent benign renal neoplasm
- Benign behavior
- Cytogenetic: normal or losses of -1, -Y
- Close relation with chromophobe RCC


1
2
3
4





Oncocytoma: Atypical Features

- Focal nuclear atypia (~10%)
- Hemorrhage
- Fat invasion (rare)
- Vascular invasion (rare)
- Large size