Updates on Pathology of Kidney Neoplasms

Ximing J. Yang, M.D., Ph.D.

Marie A Flaming Professor of Pathology
Chief of Urologic Pathology

Northwestern University
Feinberg School of Medicine
Chicago, Illinois

Top Ten Most Common Cancers in US

	2018	2003	
1	**Prostate**	**Prostate**	
2	Breast	Breast	
3	Lung & Bronchus	Lung & Bronchus	
4	Colon & Rectum	Colon & Rectum	
5	Melanoma	Corpus& Uterus	
6	**Urinary bladder**	**Urinary Bladder**	
7	Non-Hodgkin lymphoma	Non-Hodgkin lymphoma	
8	**Kidney**	Melanoma	
9	Thyroid	**Kidney**	
10	Uterus/Leukemia	Ovary	

WHO classification of kidney tumor 2016

Renal cell tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1*
Papillary renal cell carcinoma	8260/3
▲ Hereditary leiomyomatosis and renal cell carcinoma–associated renal cell carcinoma	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3*
MiT family translocation renal cell carcinomas	8311/3*
▲ Succinate dehydrogenase–deficient renal carcinoma	8311/3
Mucinous tubular and spindle cell carcinoma	8480/3*
▲ Tubulocystic renal cell carcinoma	8316/3*
▲ Acquired cystic disease–associated renal cell carcinoma	8316/3
▲ Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0

Topics

- Common RCC subtypes
- Uncommon tumors
- Newly defined RCCs
- Mimickers of RCC

777 Renal Cell Neoplasms at NMH
Pathological Classification

Renal Tumor	Frequency	5 yr Survival
Clear Cell RCC	58.6%	70%
Papillary RCC	15.4%	88%
Oncocytoma	8.4%	100%
Chromophobe RCC	7.3%	94%
Sarcomatoid RCC	1.6%	27%
Others	8.7%	

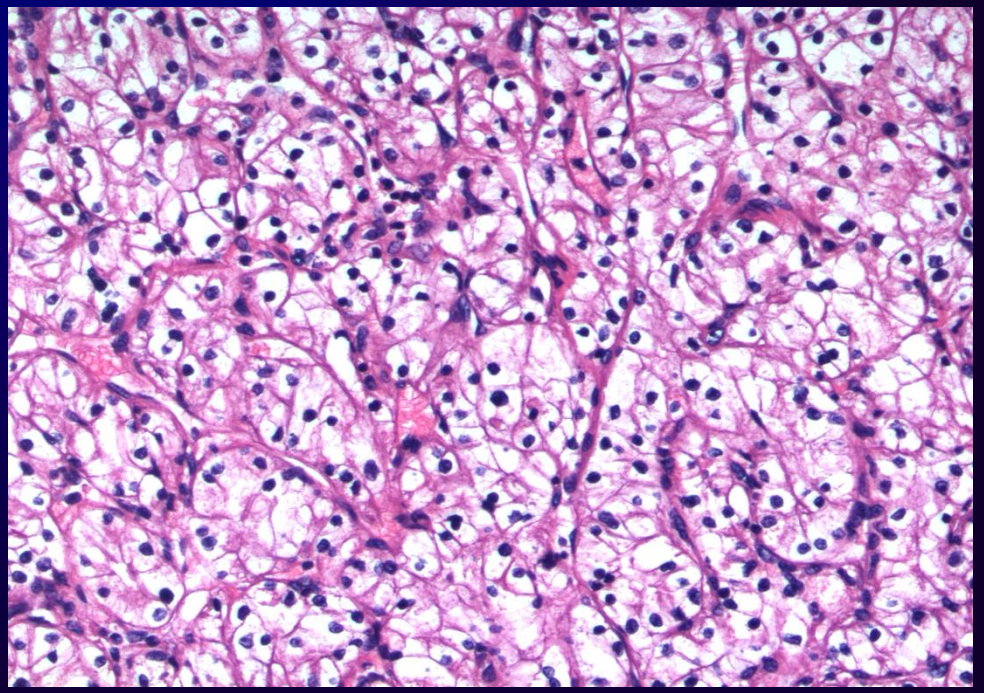
Histology Classification of Kidney Tumors

Common

- Clear cell RCC
- Papillary RCC
- Chromophobe RCC
- Papillary adenoma
- Multilocular cystic renal cell neoplasia of LMP
- Oncocytoma

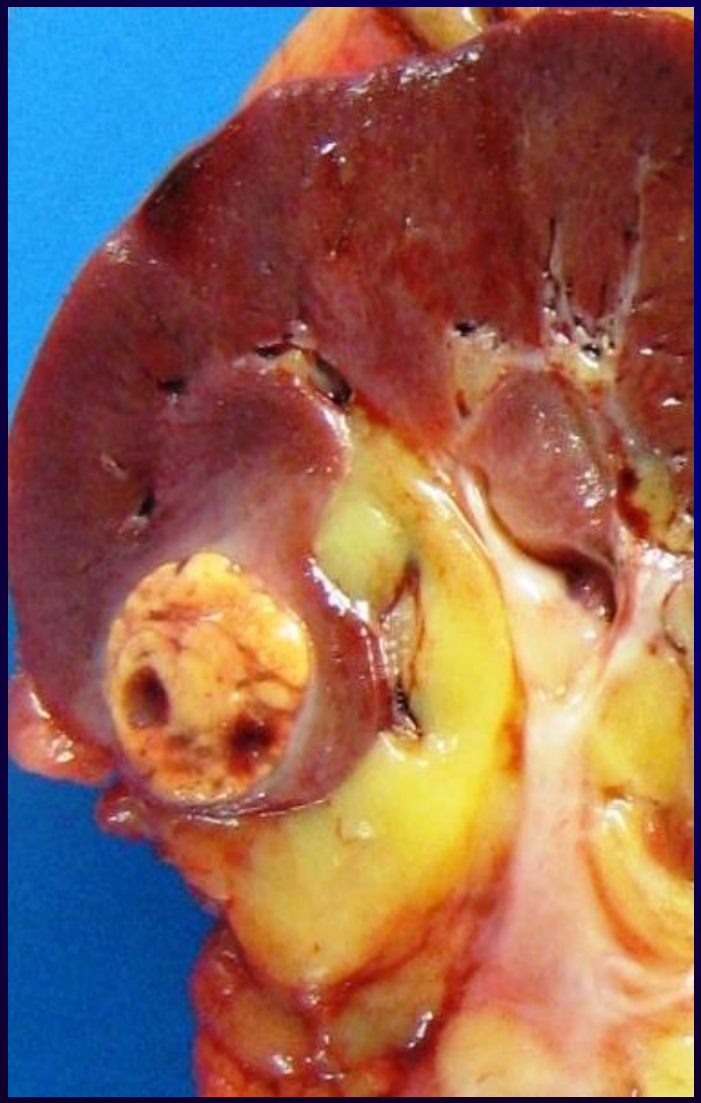
Clear cell RCC

- Cytoplasmic content:
- Glycogen and lipid
- Responsible for the 90% of RCC metastatic cases

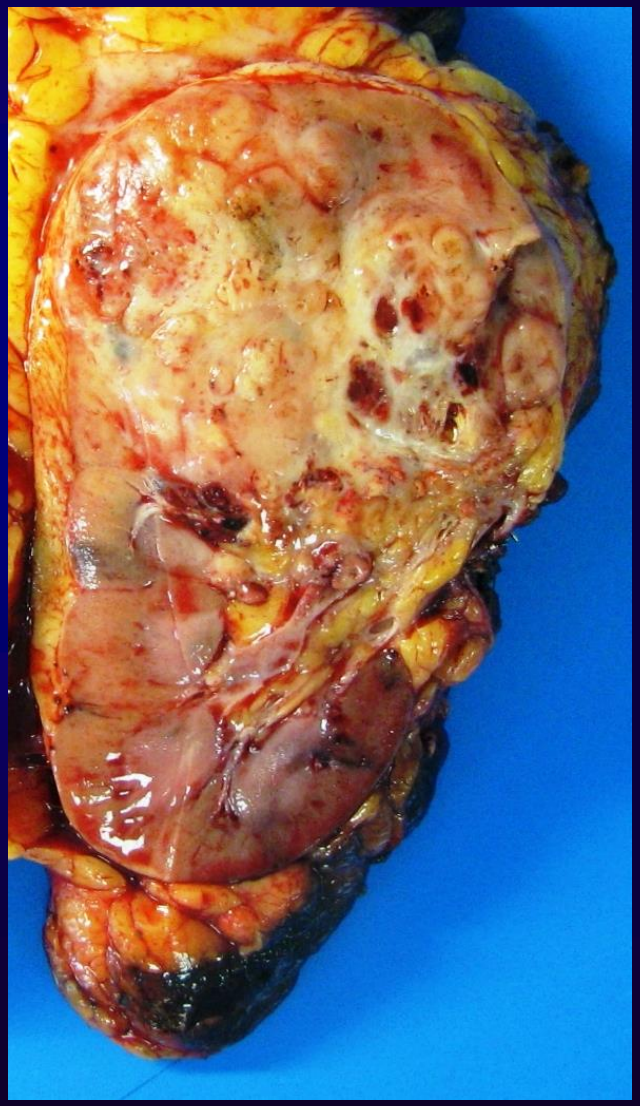


High grade Clear cell RCC

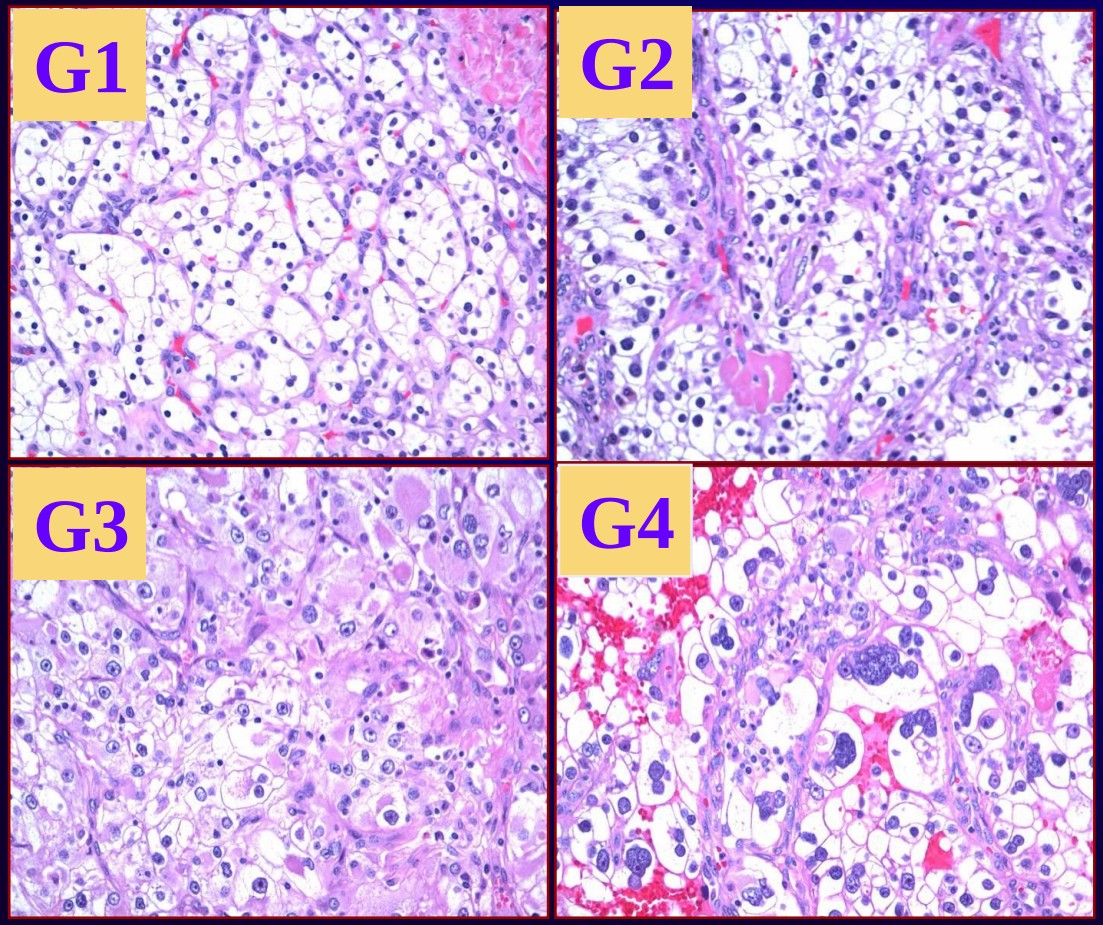
Low grade



High grade



Renal Cell Carcinoma
4 Fuhrman grades



G1	Nucleoli not seen
G2	Nucleoli High power
G3	Nucleoli Low power
G4	Bizarre nuclei

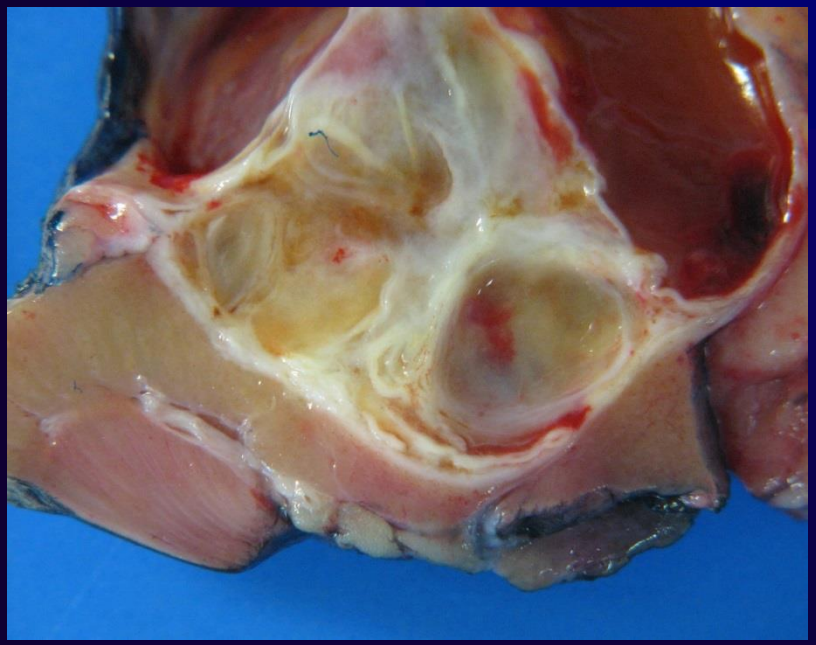
Multilocular Cystic Renal Neoplasm of Low Malignant Potential (multilocular cystic RCC)

(An older entity with new name)

- A well defined mass composed of multilocular cysts
- Lining by clear epithelial cells
- Cluster of clear cells in cystic wall

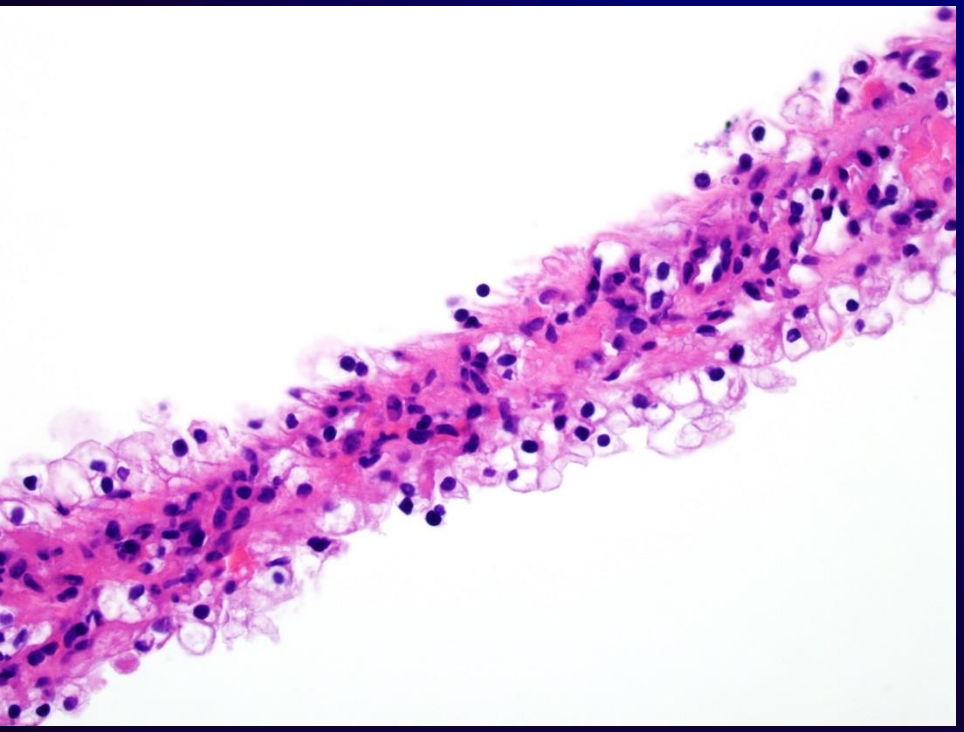
- Male : Female 3:1
- Nuclear Grade 1
- Good prognosis (no recurrence or metastasis)

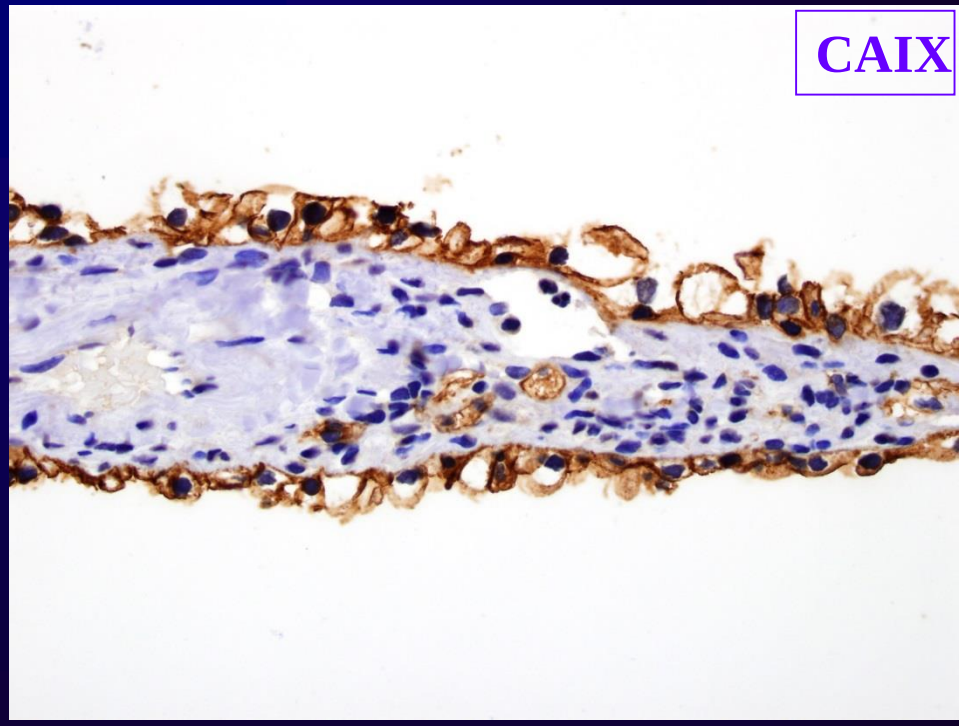
Multilocular cystic renal neoplasm of LMP (MCRCC)



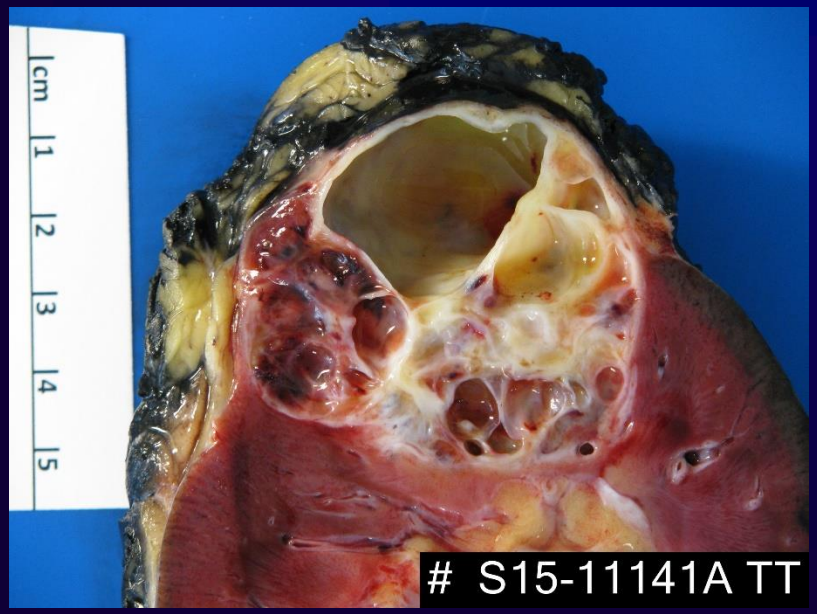
- Multilocular cyst
- Thin septa
- No solid areas
- Clear cell lining the cysts
- Low nuclear grade
- Almost no metastatic potential

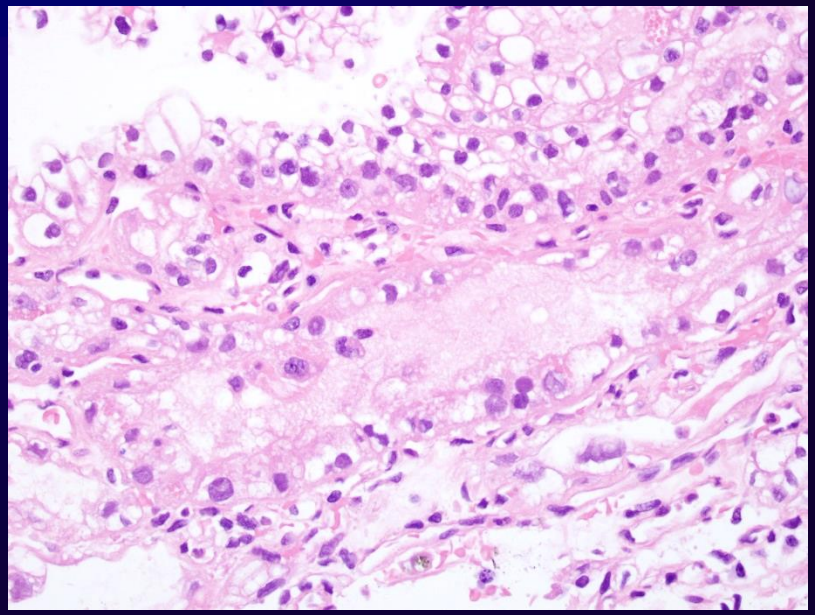
Multilocular Cystic Renal Neoplasia of Low Malignant Potential



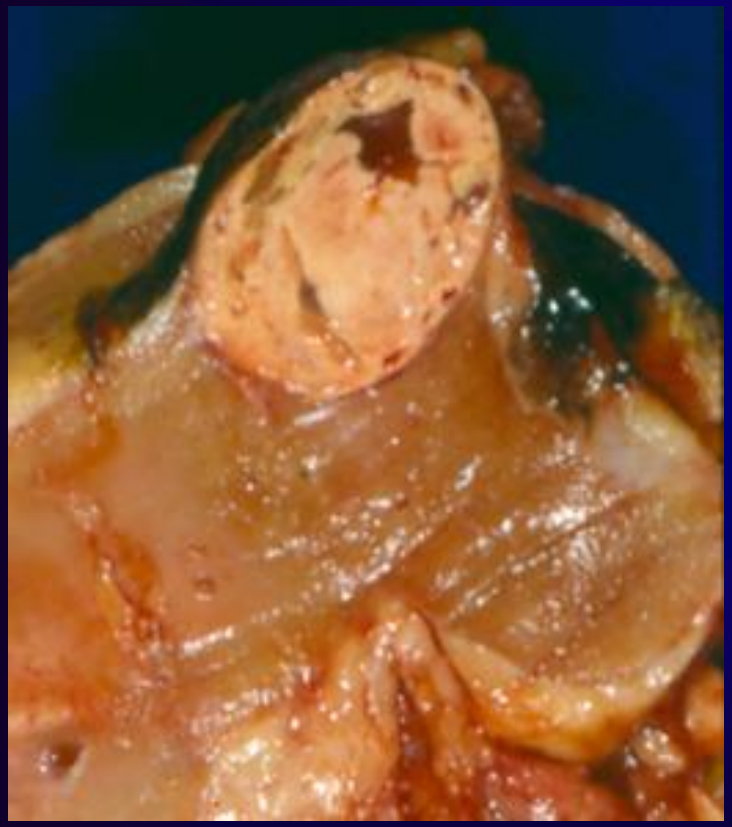


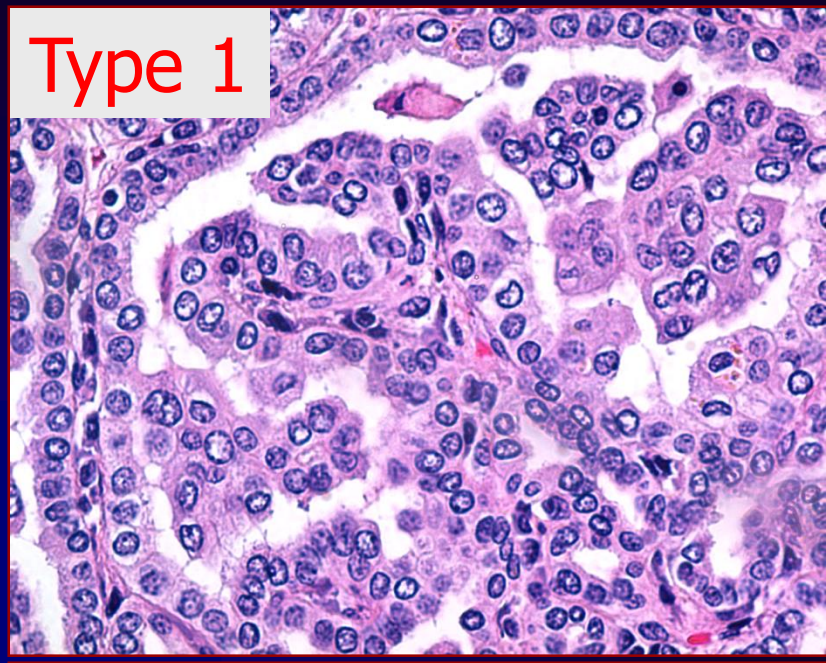
Cystic clear cell RCC

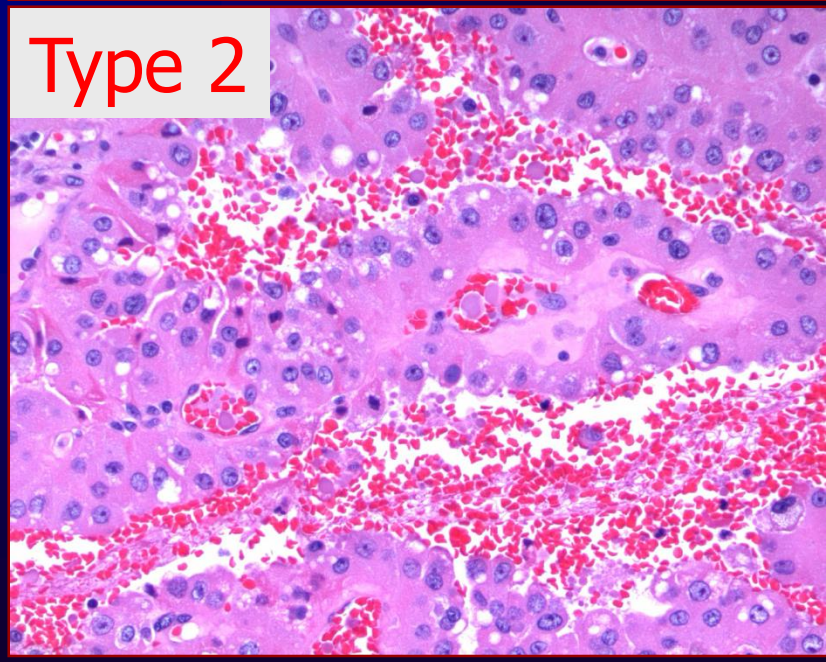




Papillary RCC

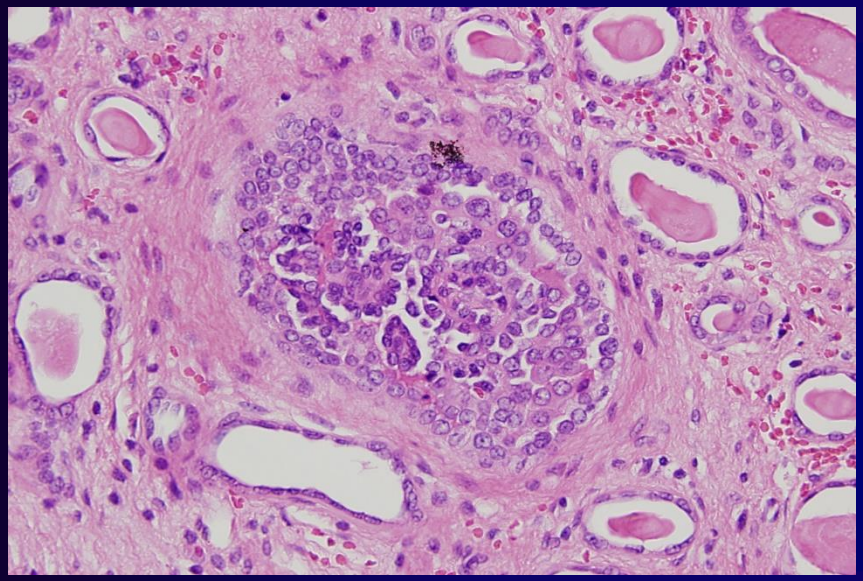




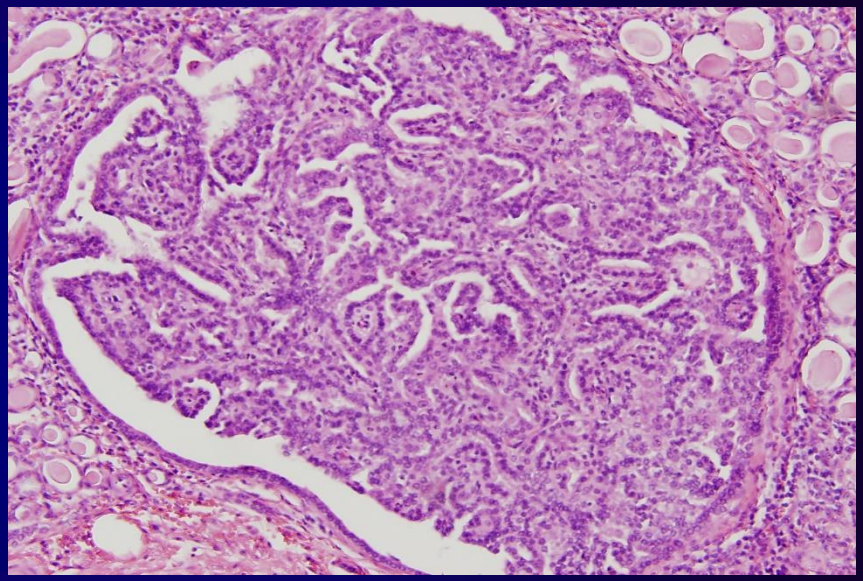


Size and nuclear grade

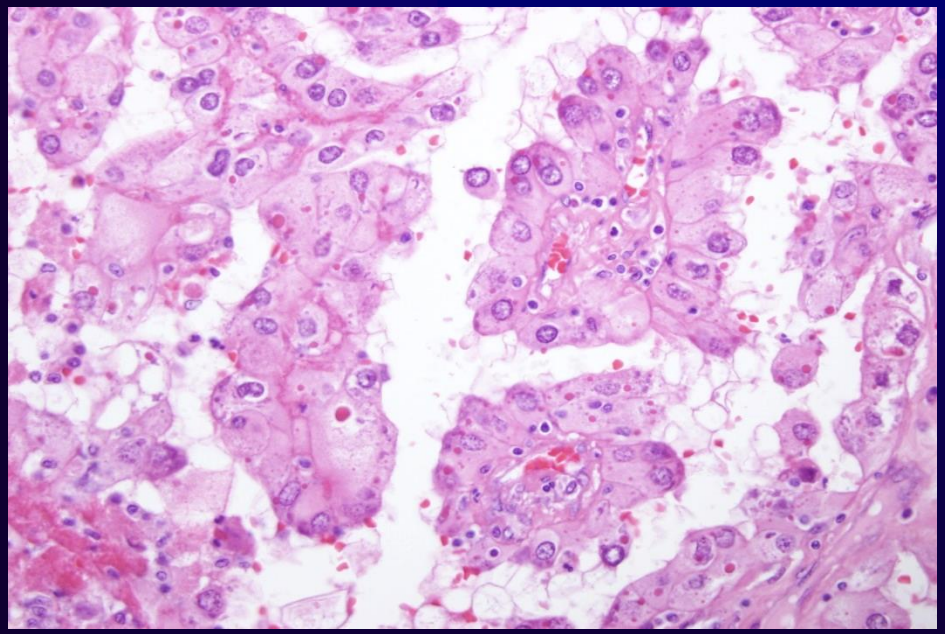
Papillary Adenoma (≤ 1.5 cm)

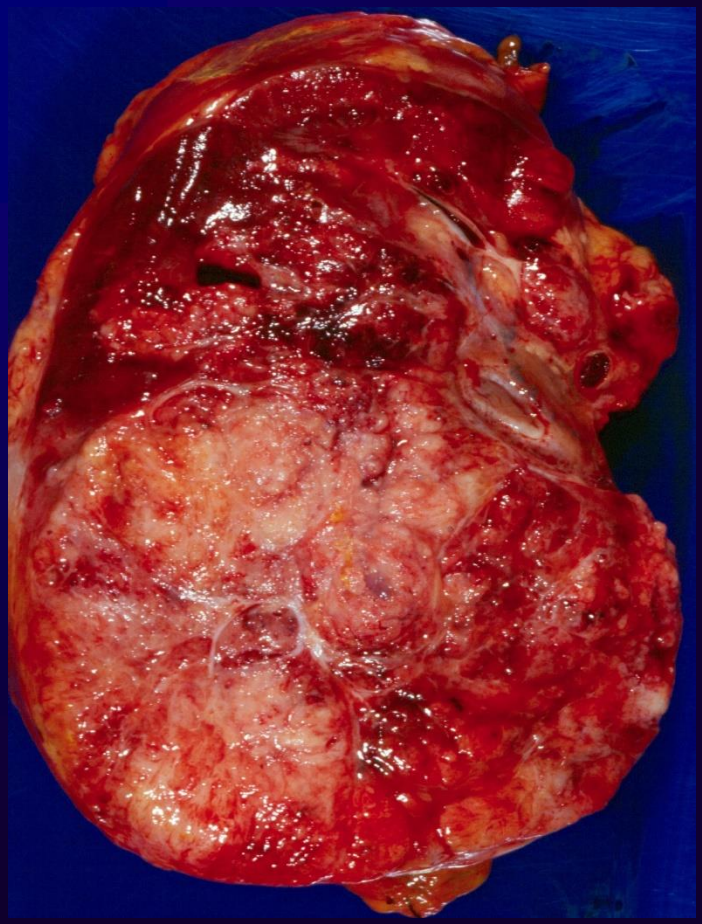


Papillary RCC (> 1.5 cm)

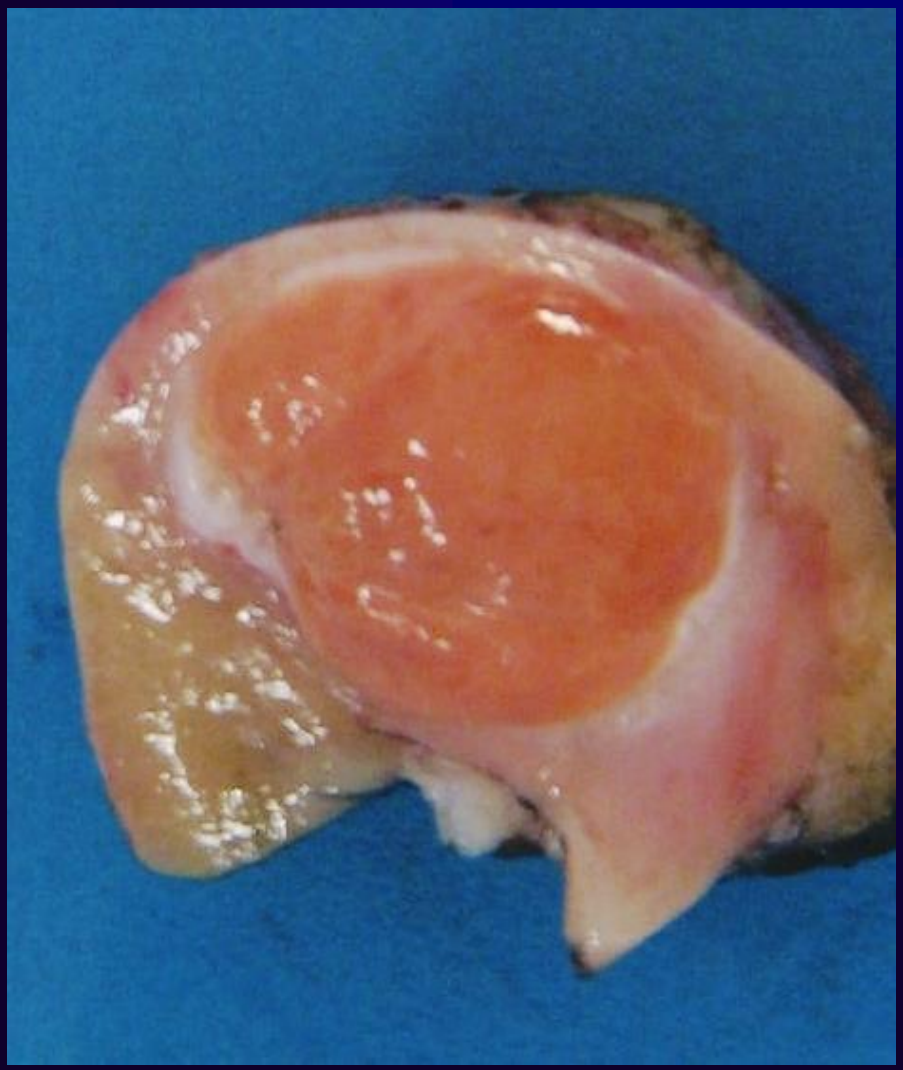


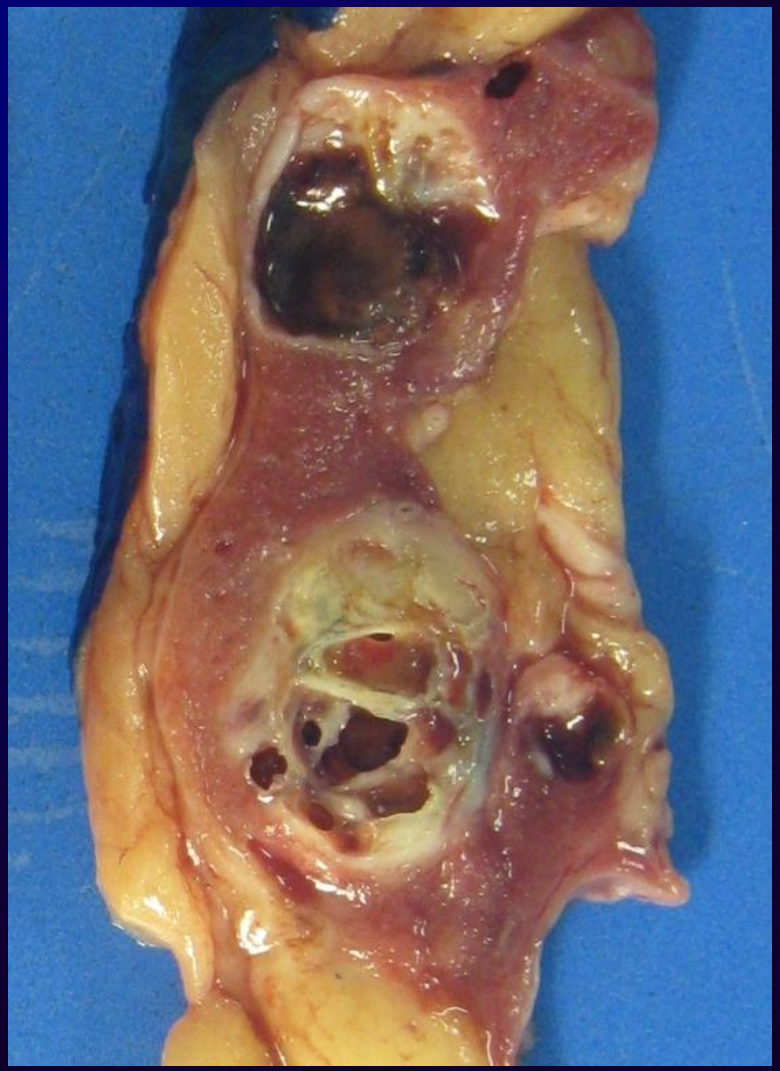
High Grade Pap RCC
(Fuhrman 3 and 4 grades)

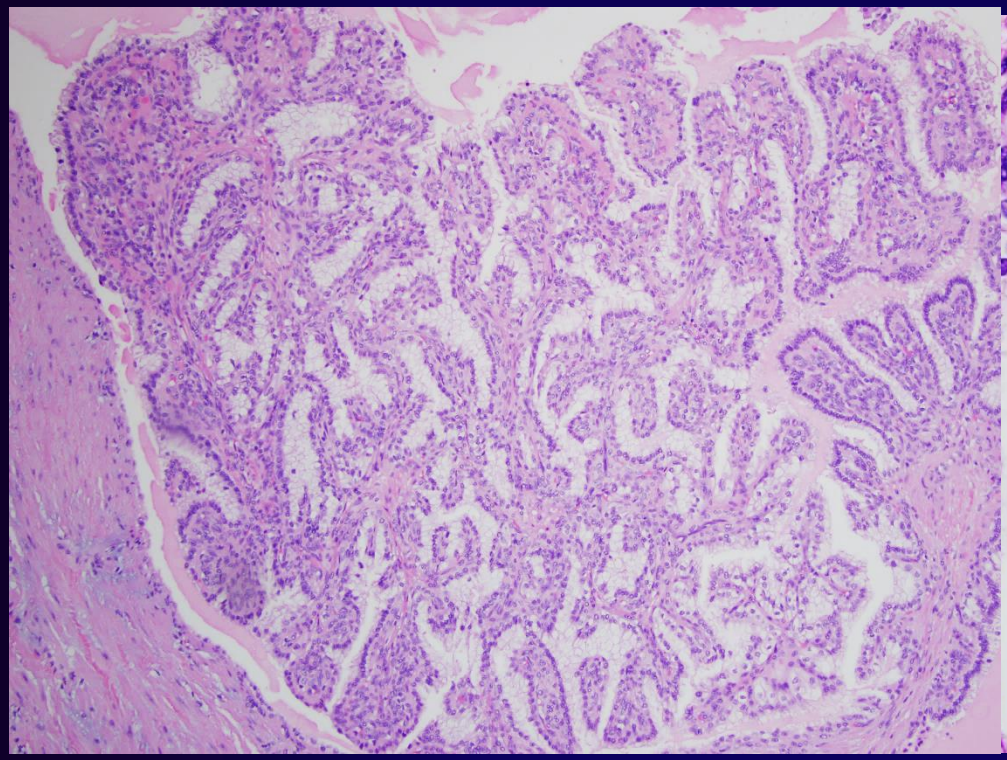


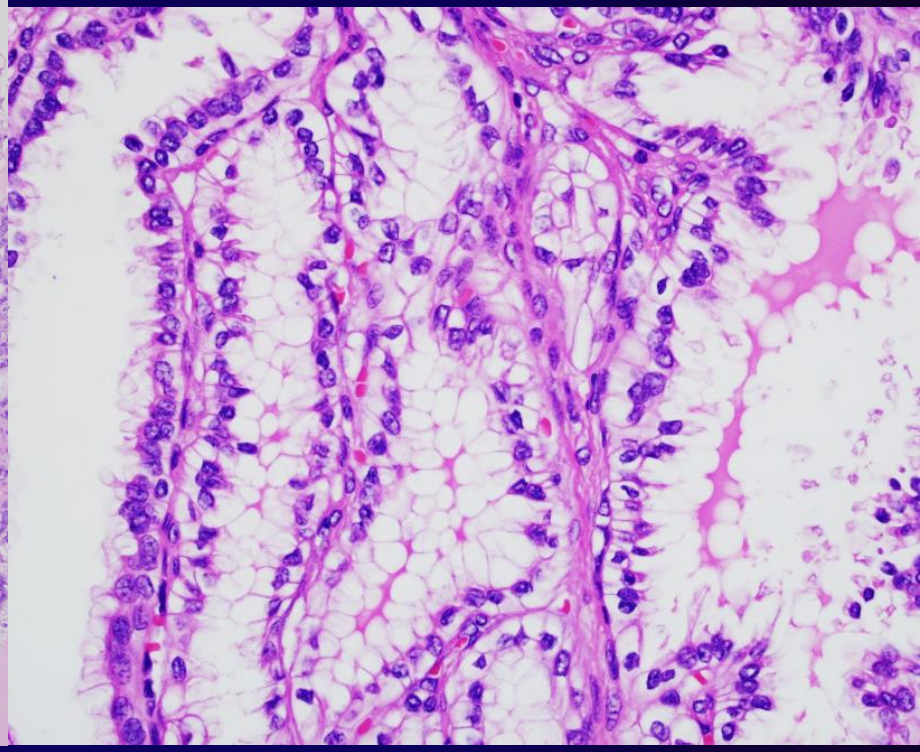


Clear cell papillary RCC







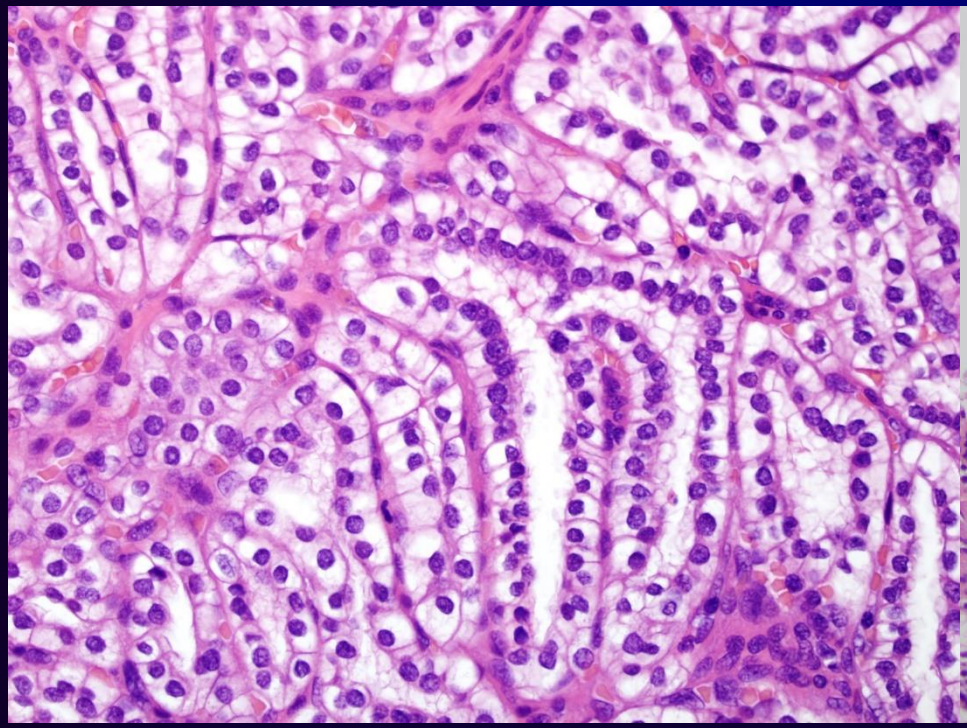


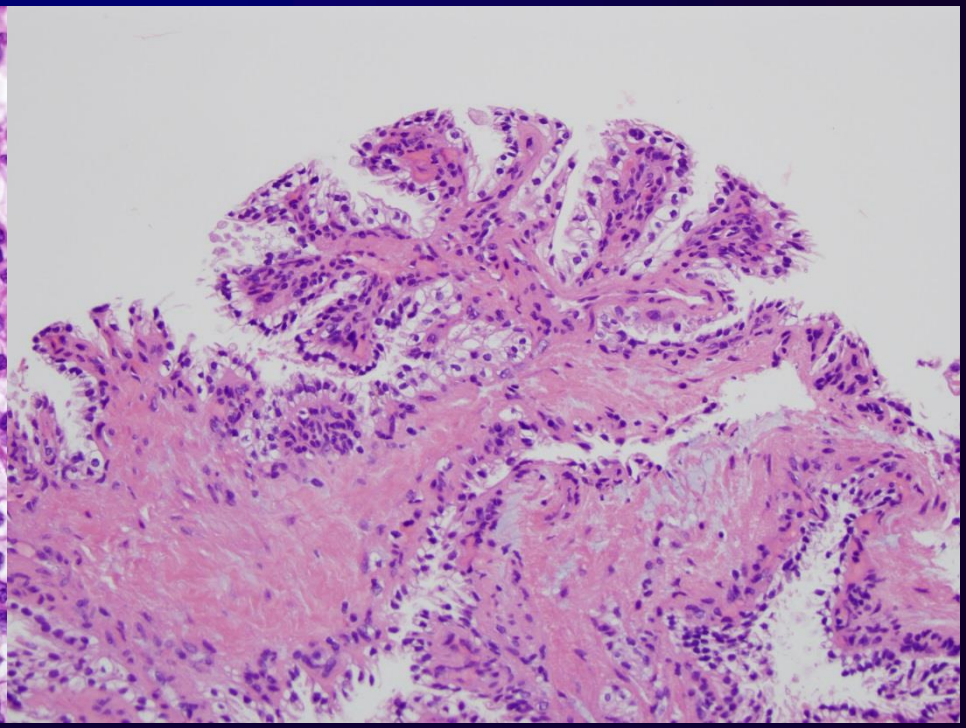
Clear cell papillary RCC

- Other terms
  - Clear cell tubulopapillary RCC
  - Clear cell papillary RCC of end stage kidneys
  - Renal angiomyomatous tumor (RAT)
- Develop in ACD or in normal kidney
- Incidence: 5-10%
- No metastasis has been reported

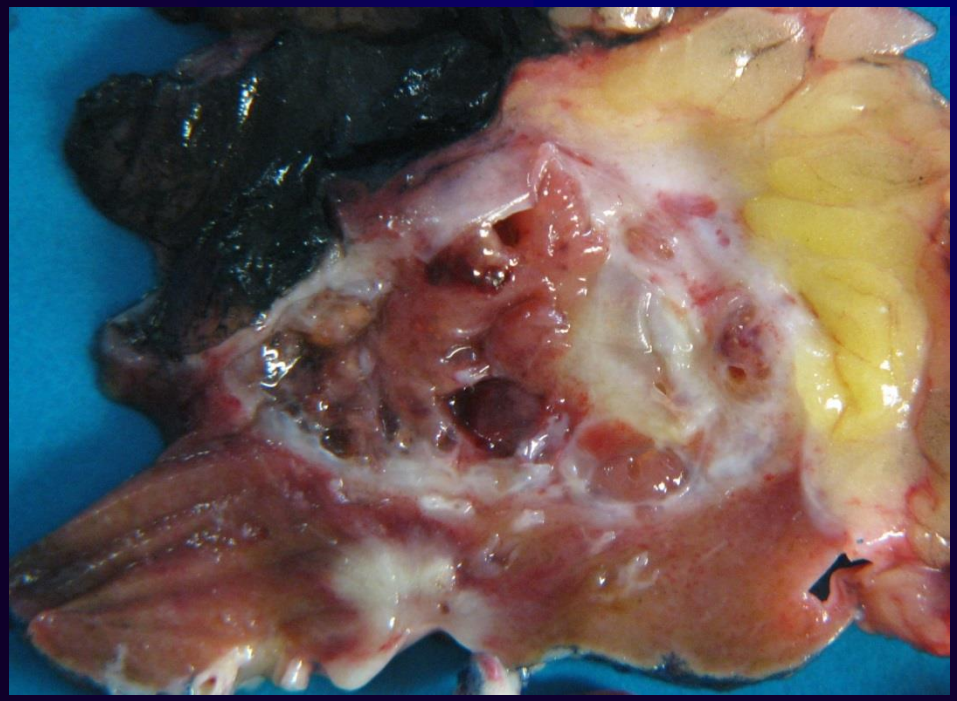
- Key diagnostic features
  - Grossly not bright yellow, often cystic
  - Nuclei pulling away from the basement membrane "piano-key"
  - Shark teeth or prostate gland like structures
  - Always low nuclear (Fuhrman 1-2) grade
  - CAIX "cup-shaped" membranous staining

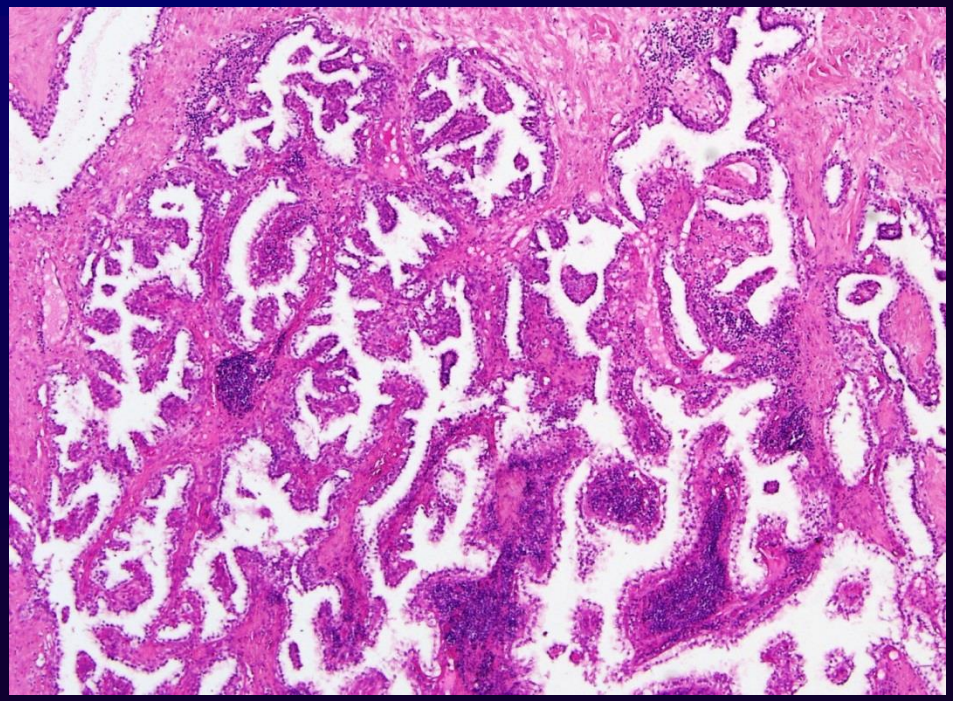
Tumor Cells "Piano-Key" Appearance in papillary or tubular patterns

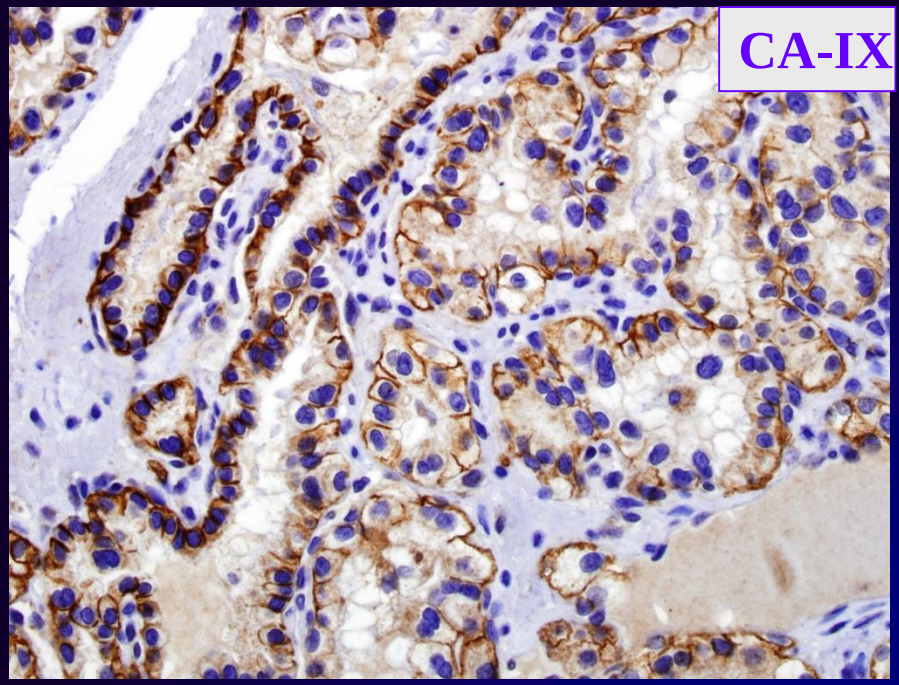


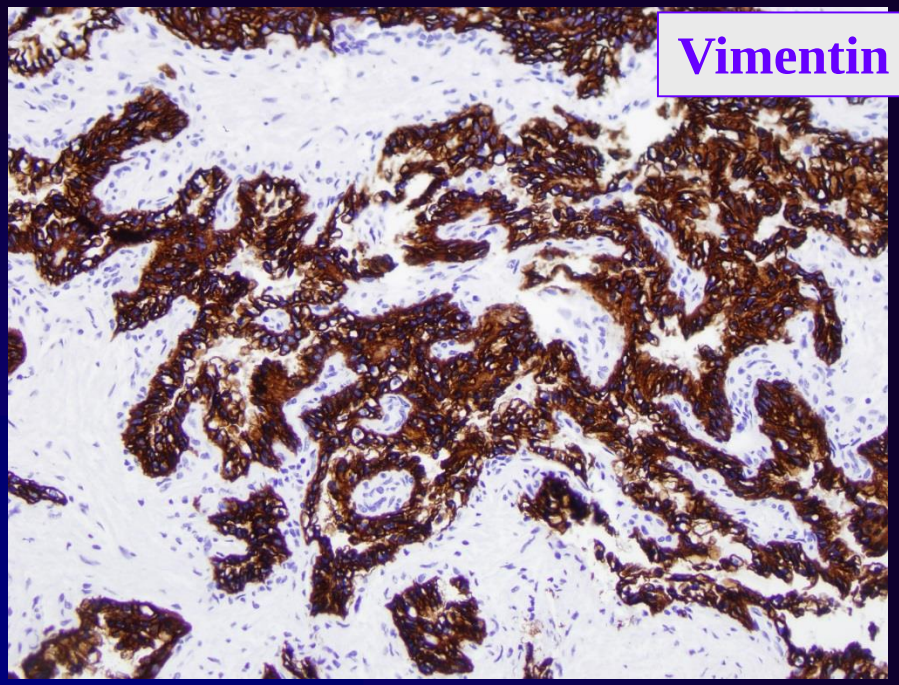


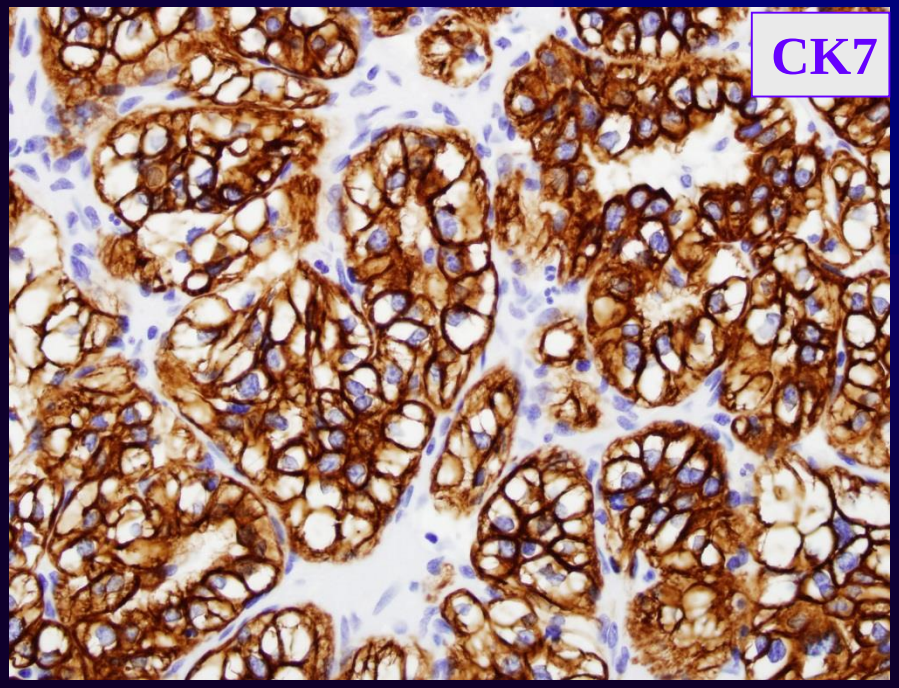
Renal angiomyomatous tumor (RAT)
- Likely a variant of cc pap RCC

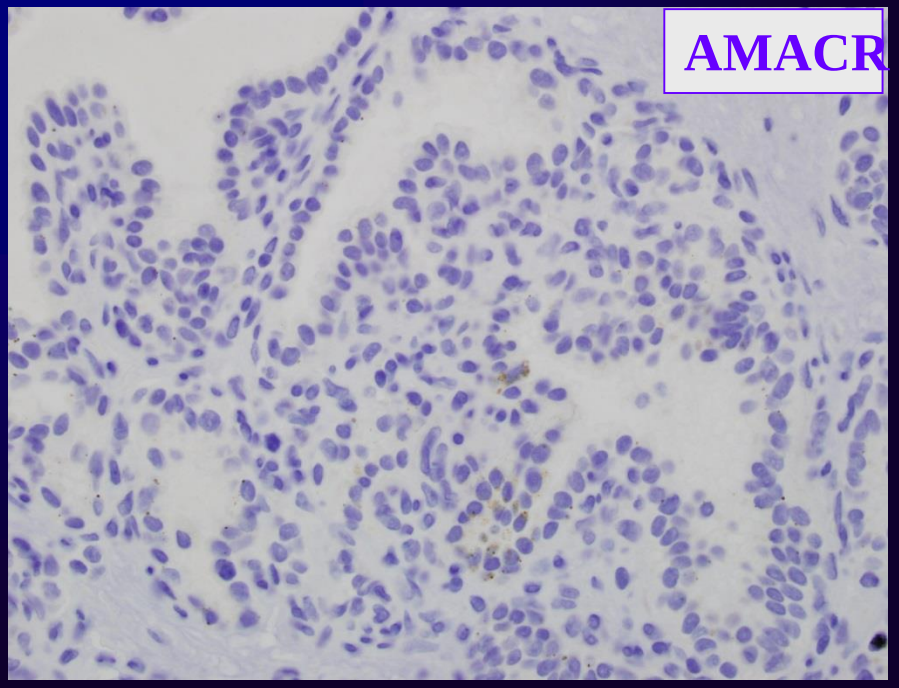





CA-IX

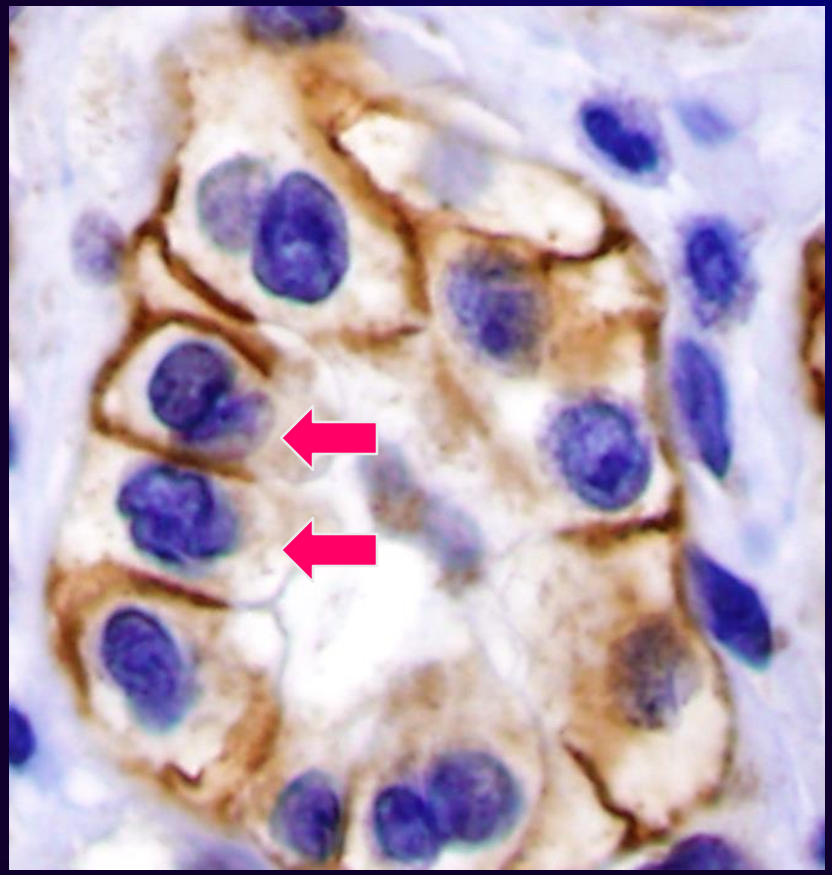

Vimentin


CK7

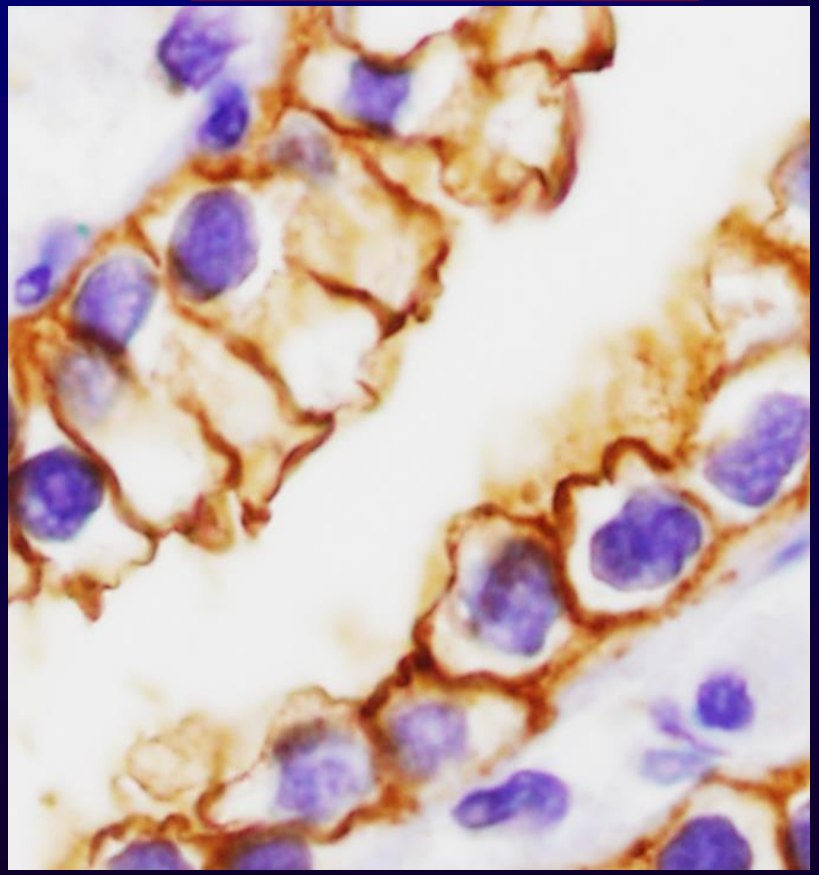

AMACR

Comparison by CAIX Immunostaining

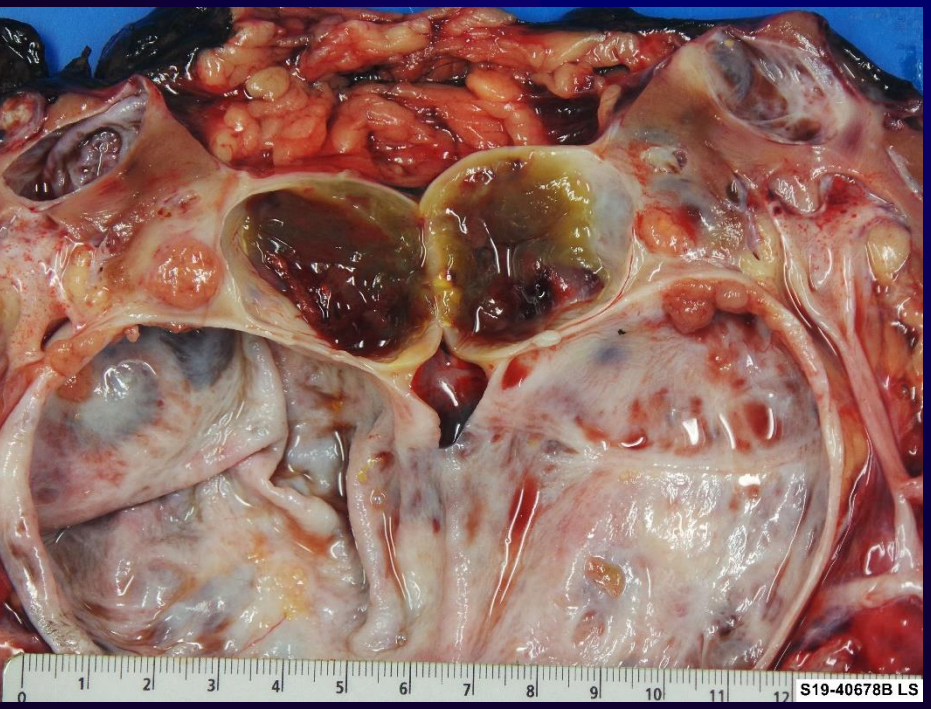
Clear cell pap RCC "Cup-Shaped"

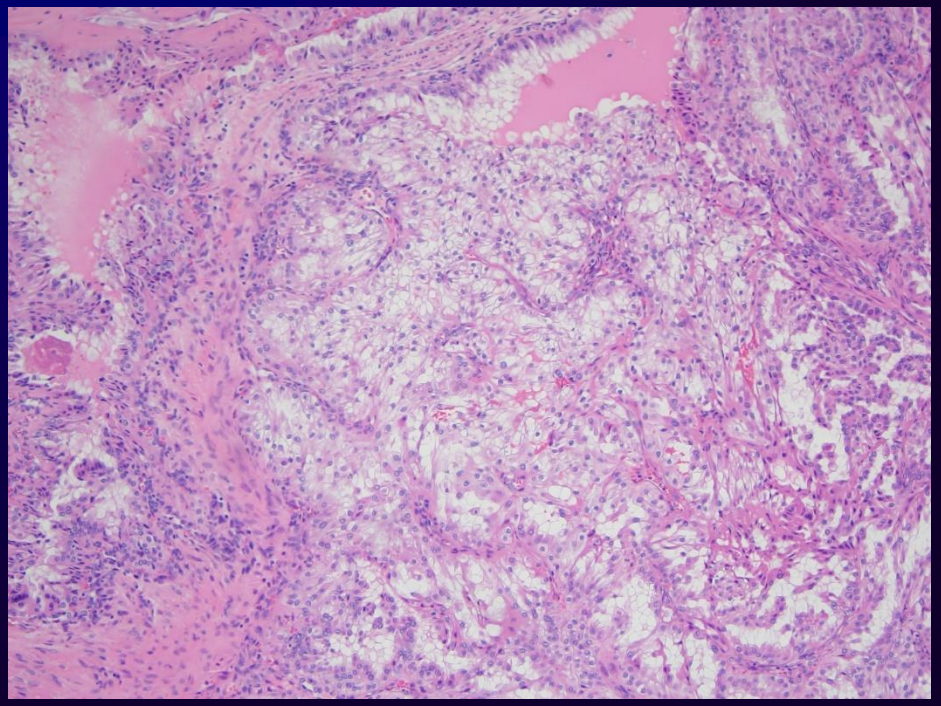


Clear cell RCC "Box-Shaped"

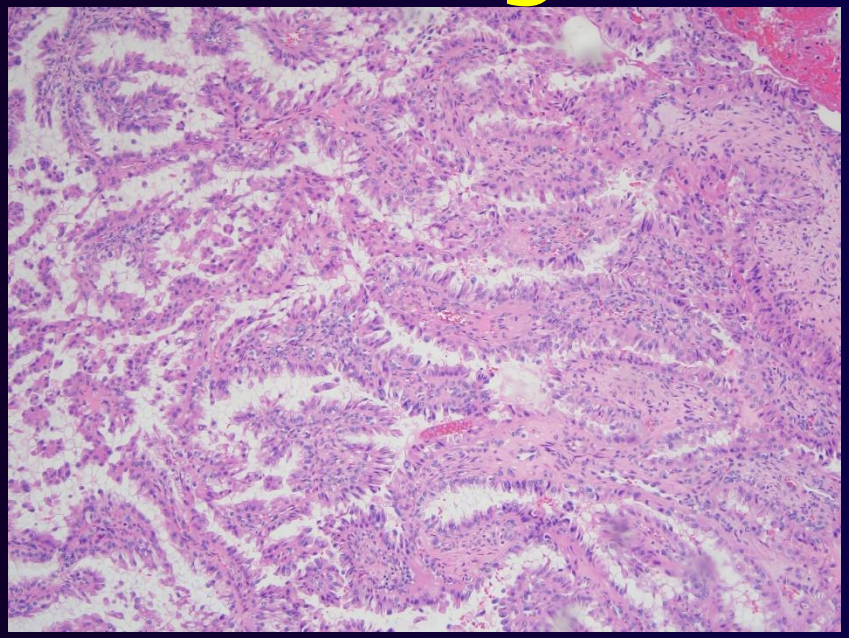


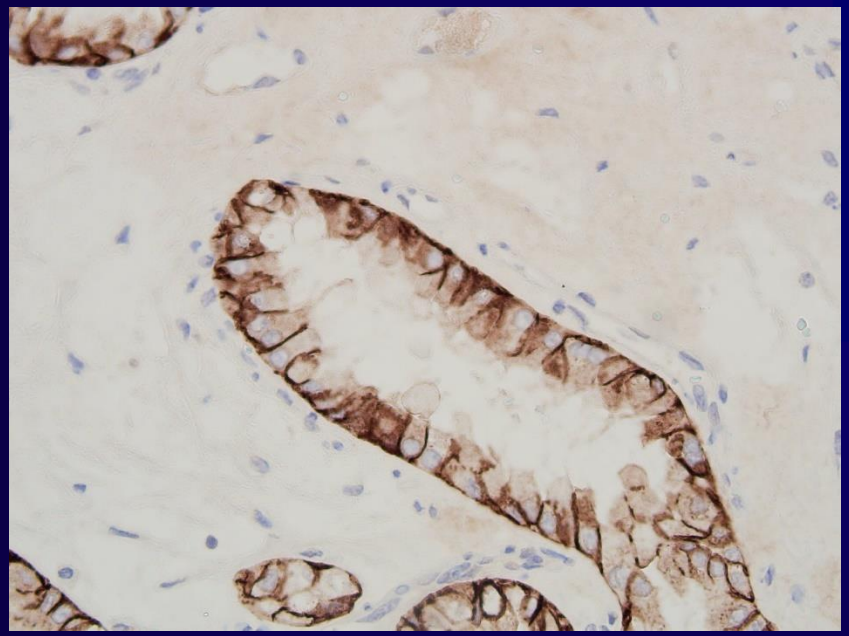
Recent case with features of CCPRCC

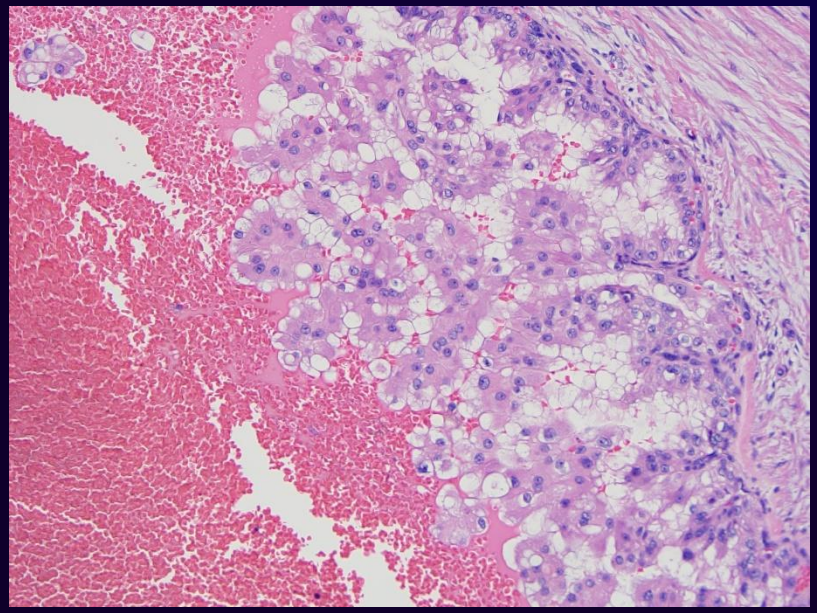


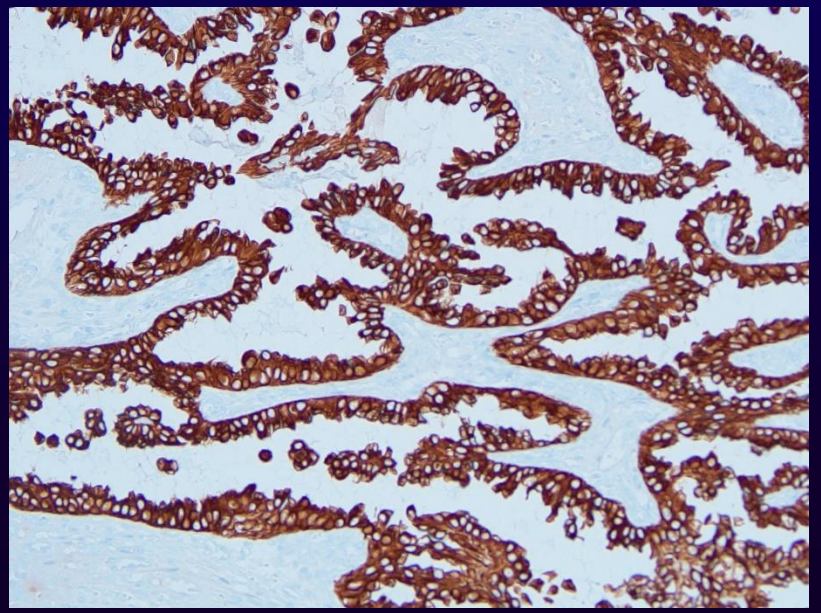


High nuclear grade

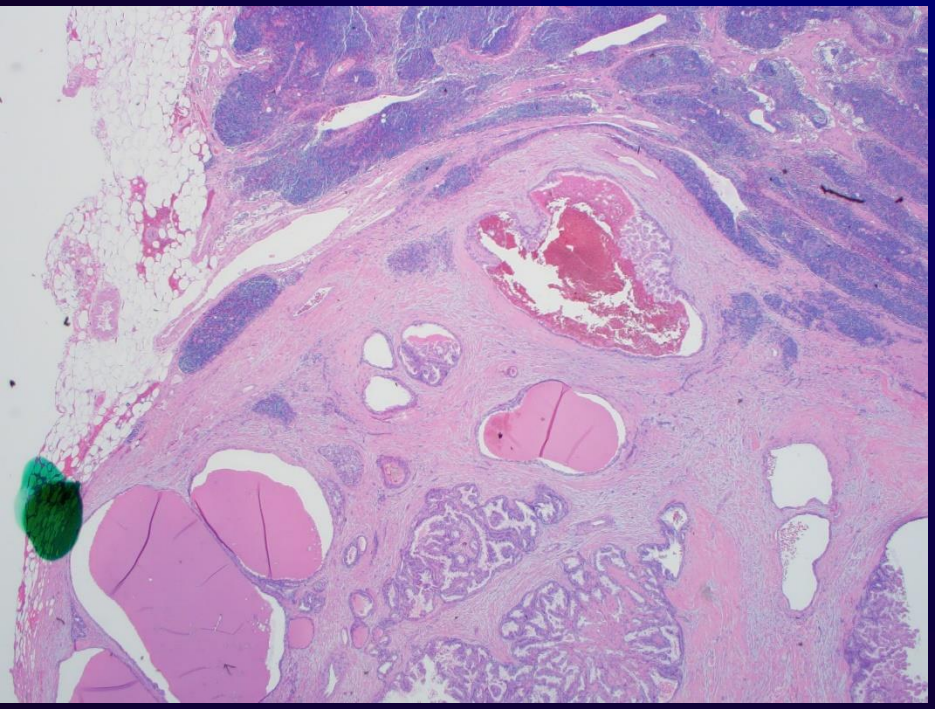


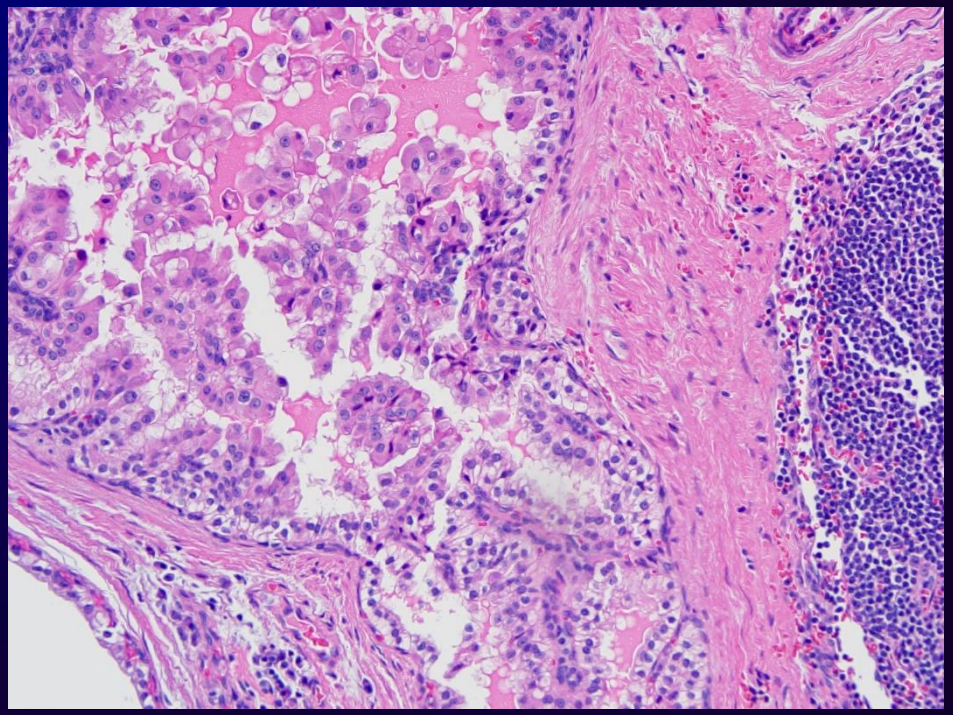






Lymph node metastasis
Is this a high grade CCPRCC?





Uncommon Tumors

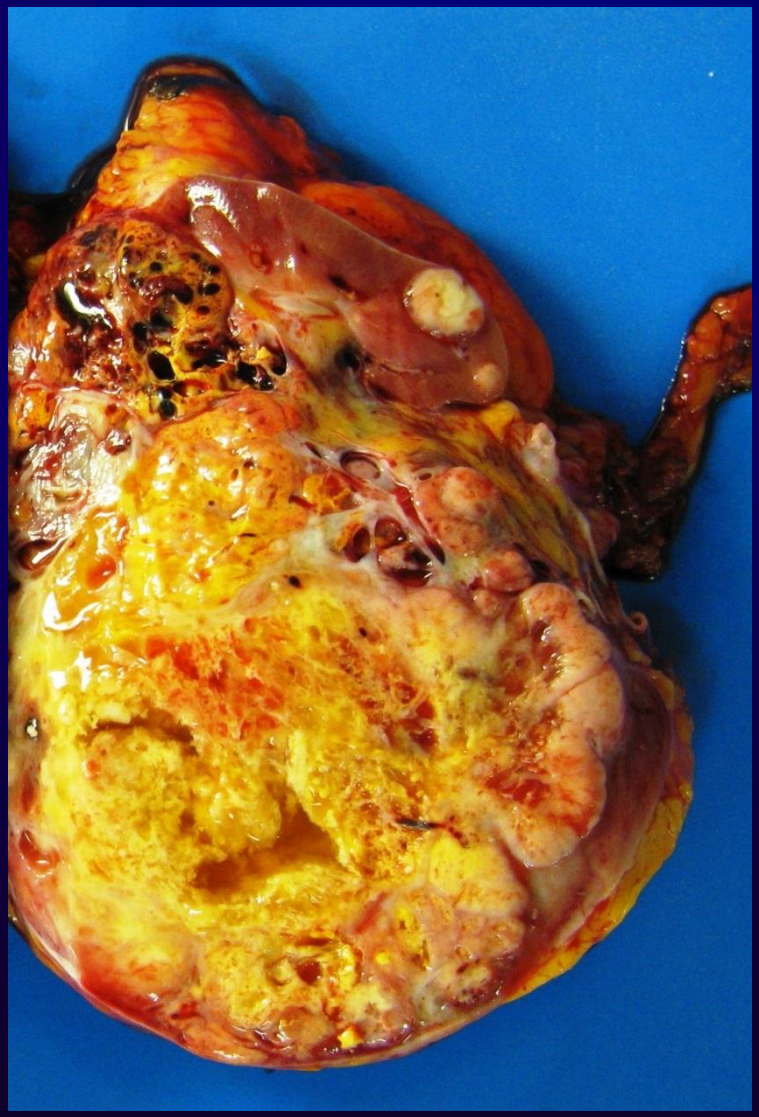
Uncommon Renal Tumors

- Sarcomatoid RCC
- Collecting Duct Ca
- Medullary Ca
- Mucinous tubular spindle cell Ca
- Xp Translocation Ca
- Angiomyolipoma

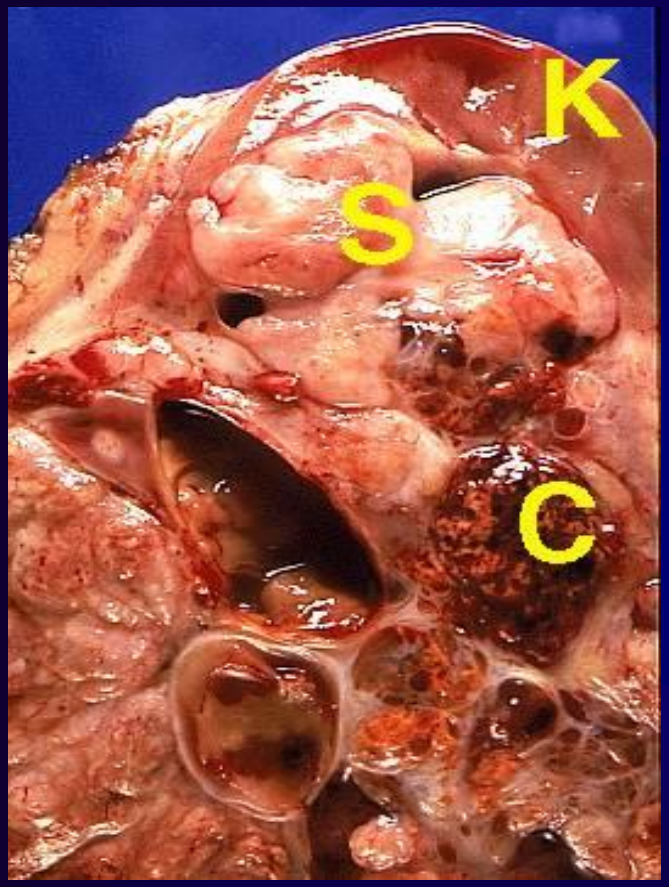
New

- *(Clear Cell Papillary Carcinoma)*
- Tubulocystic Carcinoma
- Acquired Cystic Disease Associated RCC
- Hereditary leiomyomatosis-RCC associated RCC (Fumarate hydratase mutation)

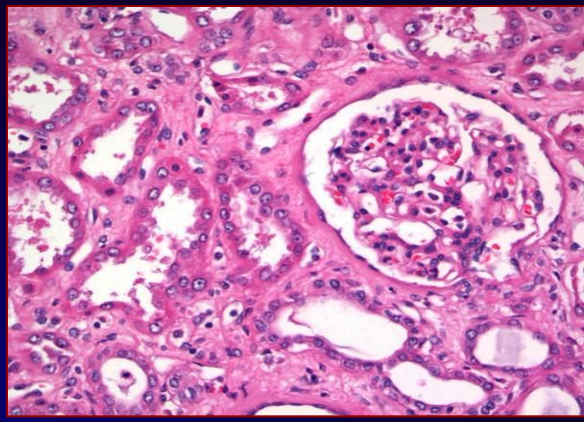
1. Sarcomatoid RCC



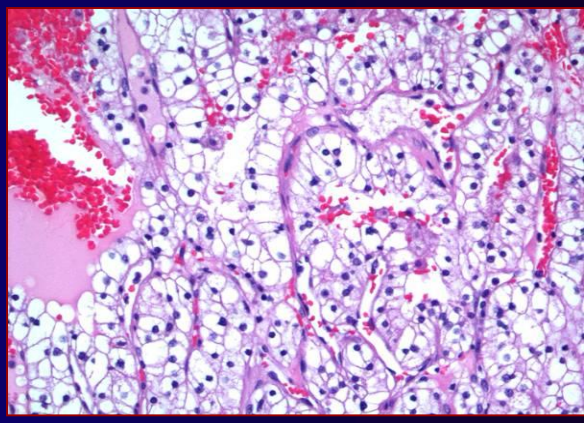
Sarcomatoid RCC



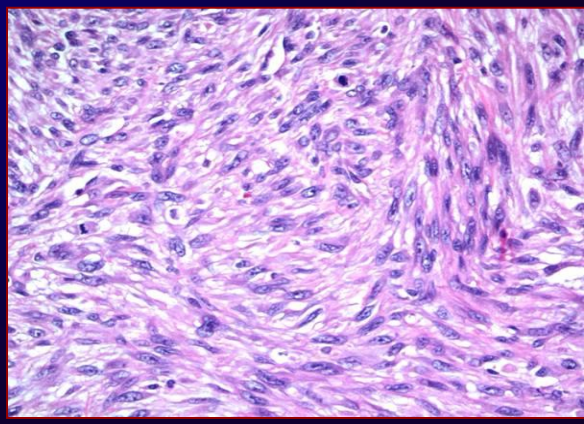
K: Normal cortex



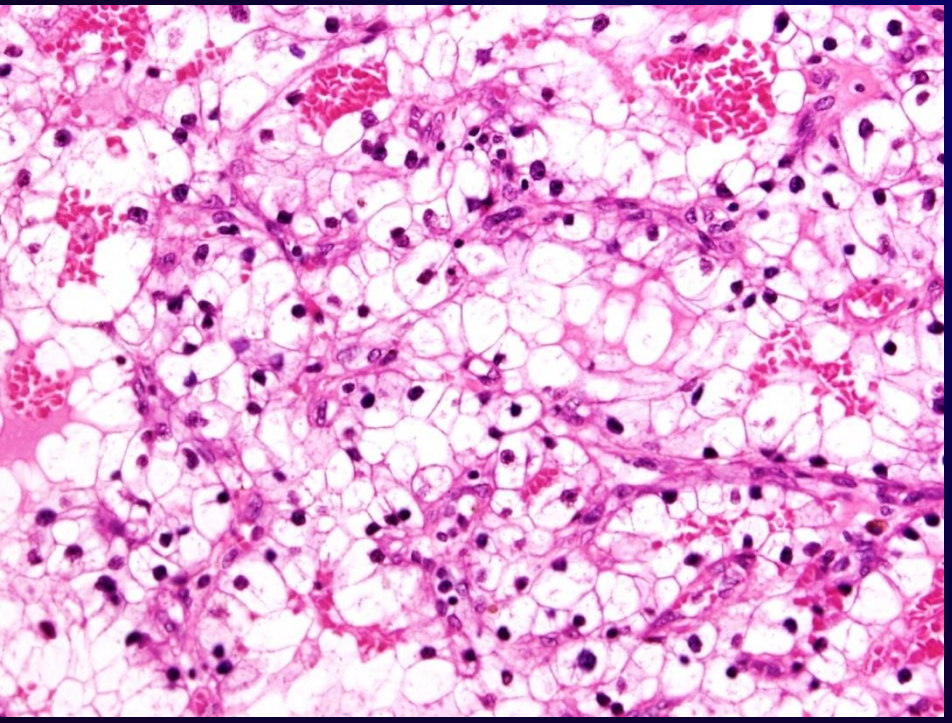
C: Clear cell component

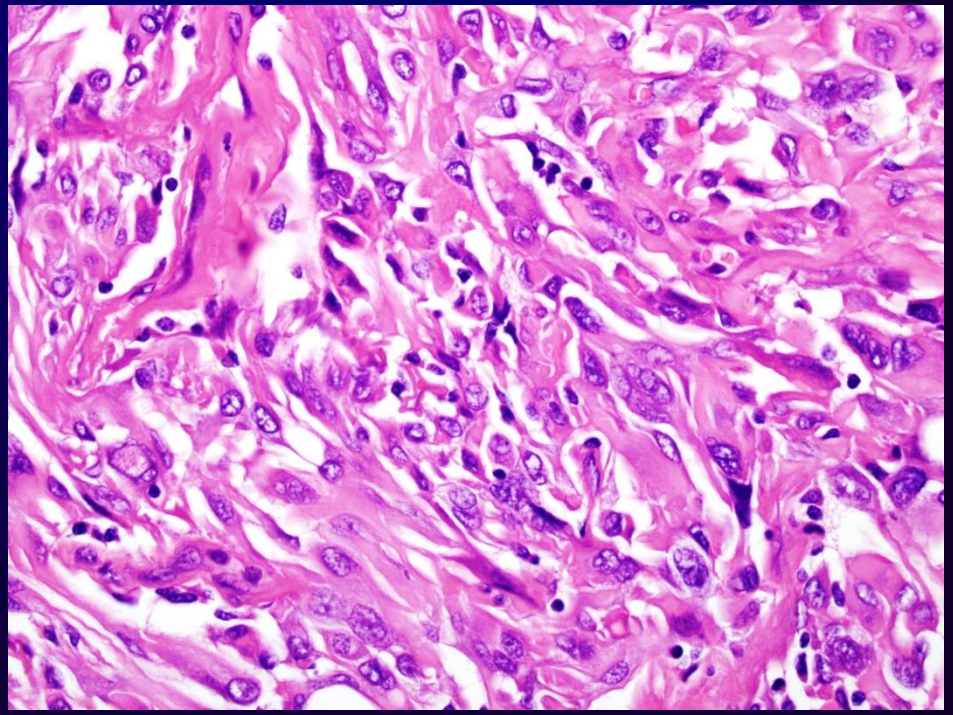


S: Sarcomatoid component

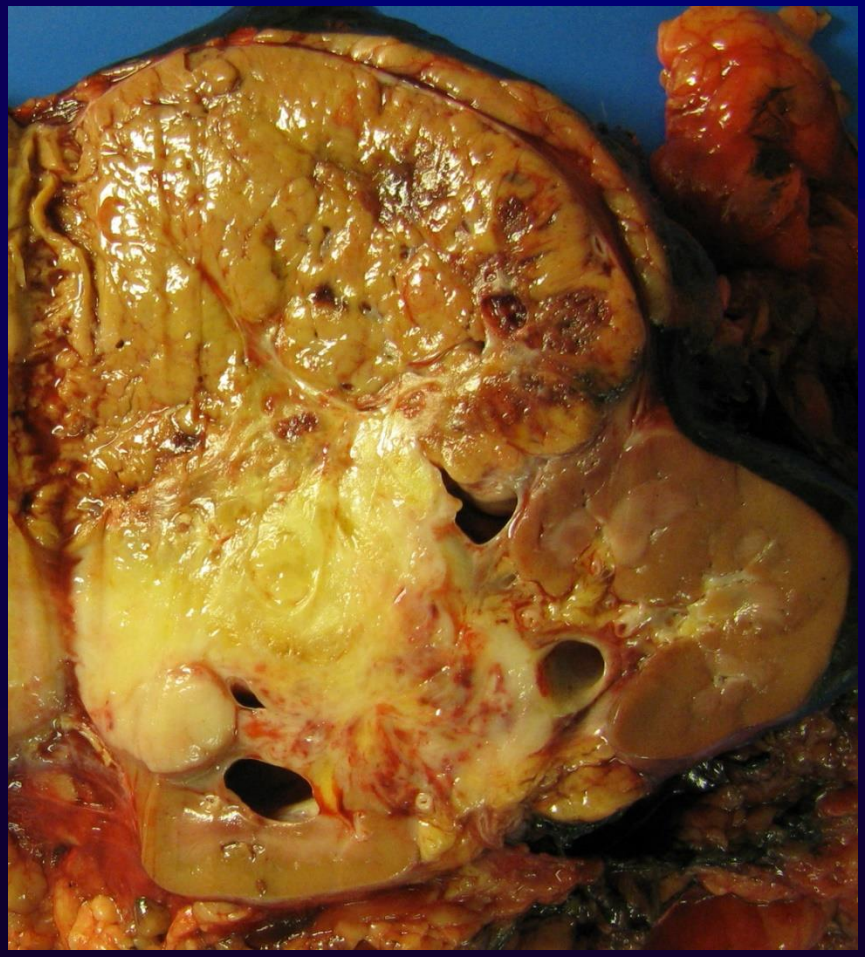


Low Grade clear cell RCC and Sarcomatoid RCC Components

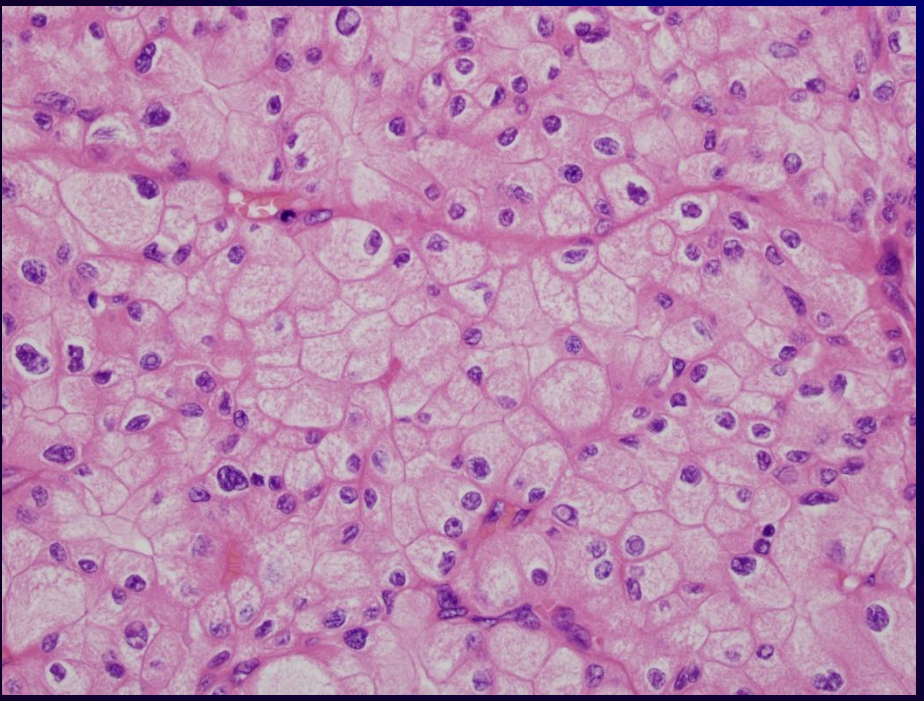


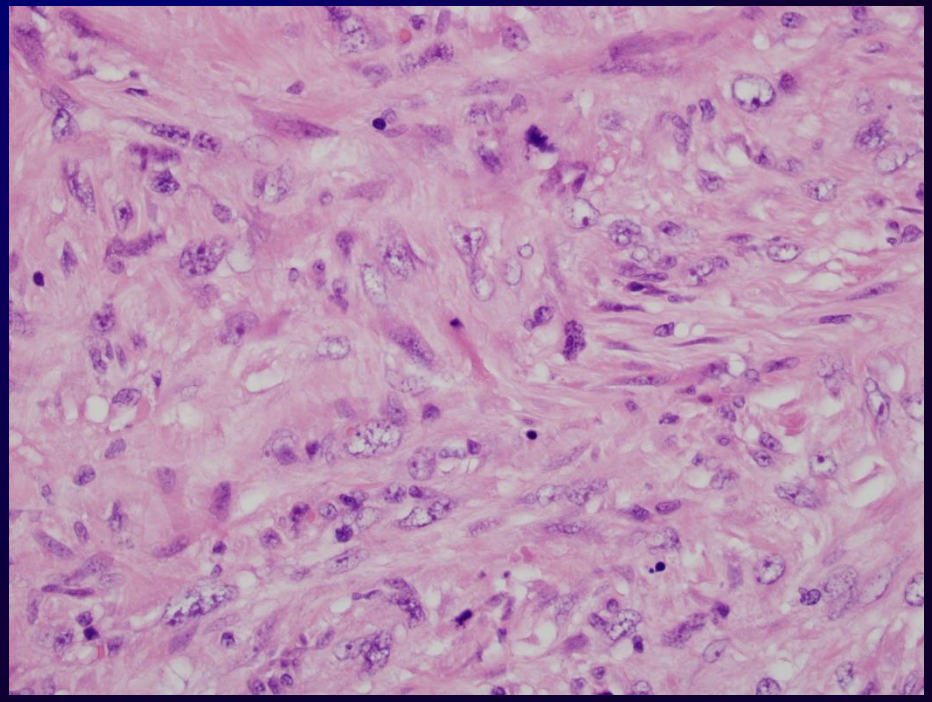


Sarcomatoid chromophobe RCC



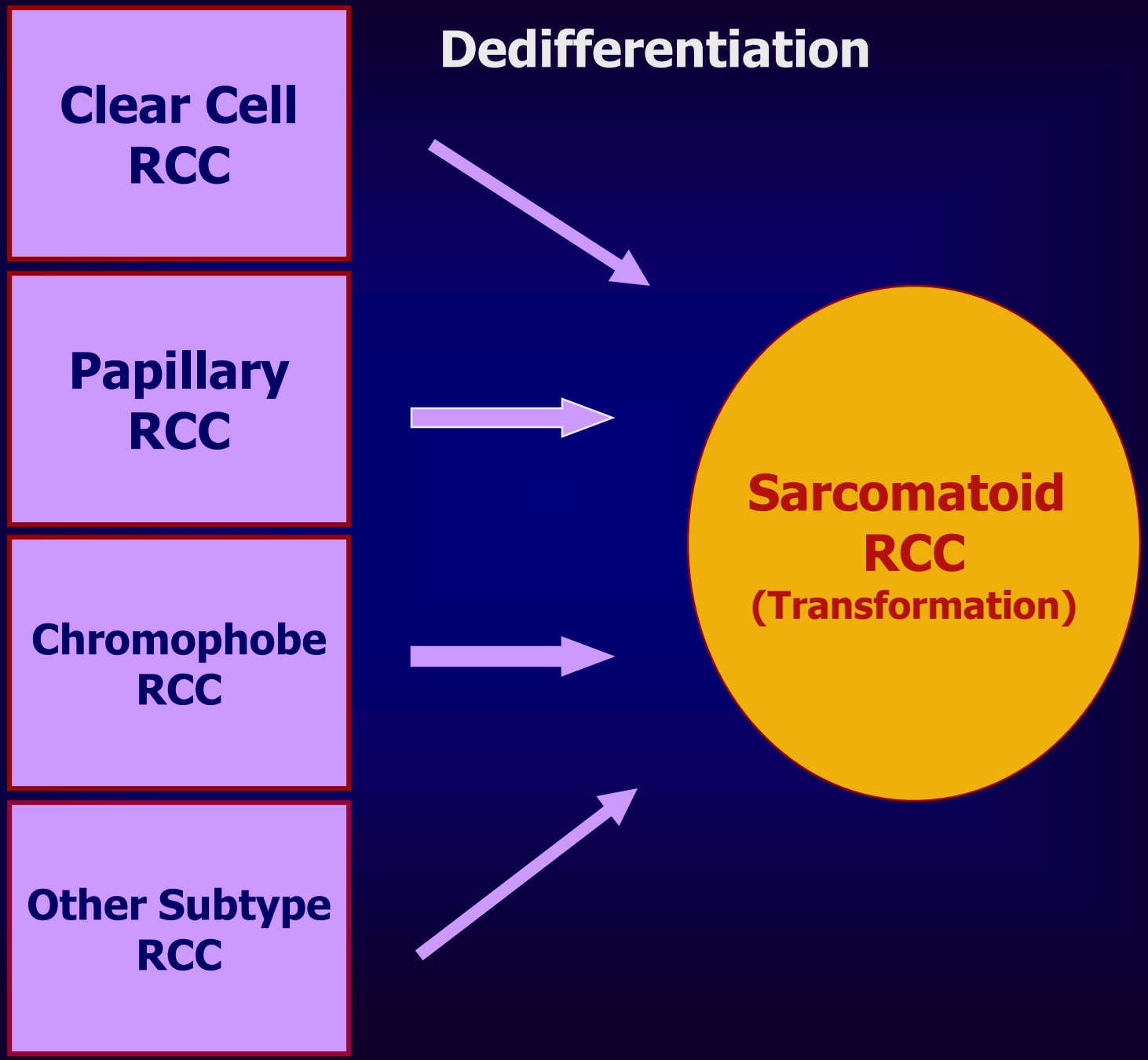
Chromophobe + Sarcomatoid





Sarcomatoid RCC

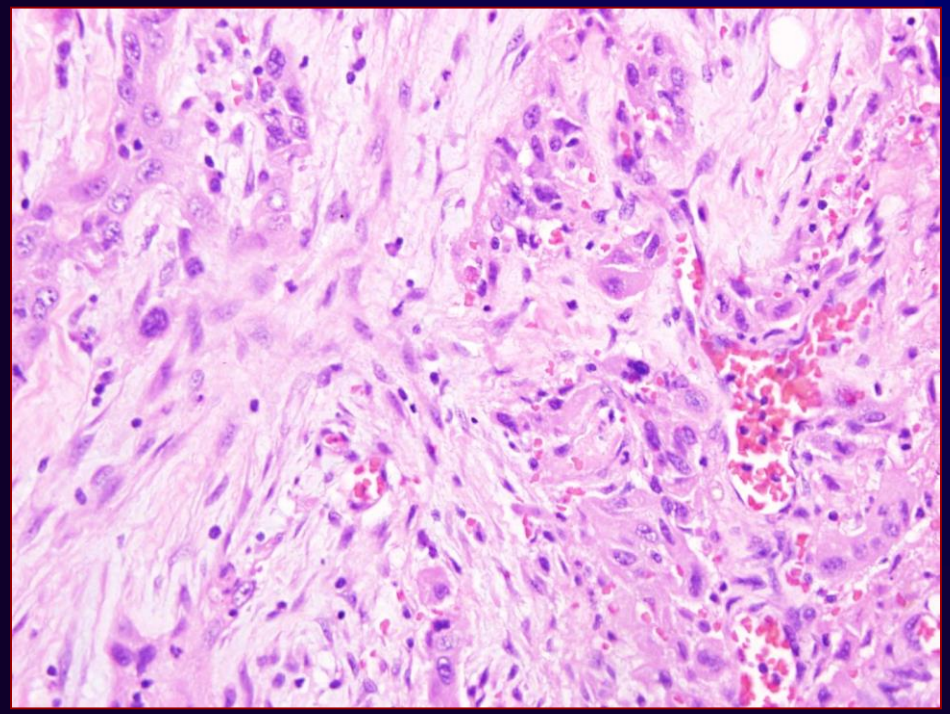
- High grade transformation of any low grade subtype of RCC
- Much more common than renal sarcoma
- Large tumor masses (typically >10 cm)
- Diagnosis depending on the presence of both low grade RCC and high grade sarcomatoid components
- Keratin markers positive

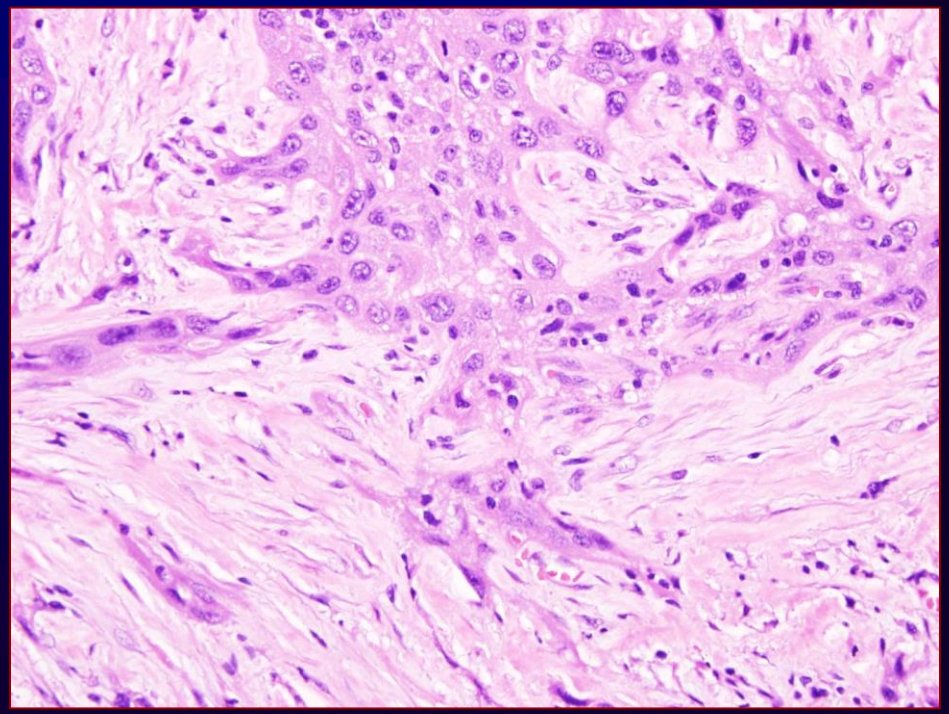

Dedifferentiation
Clear Cell RCC
Papillary RCC
Chromophobe RCC
Other Subtype RCC
Sarcomatoid RCC
(Transformation)

2. Collecting duct carcinoma

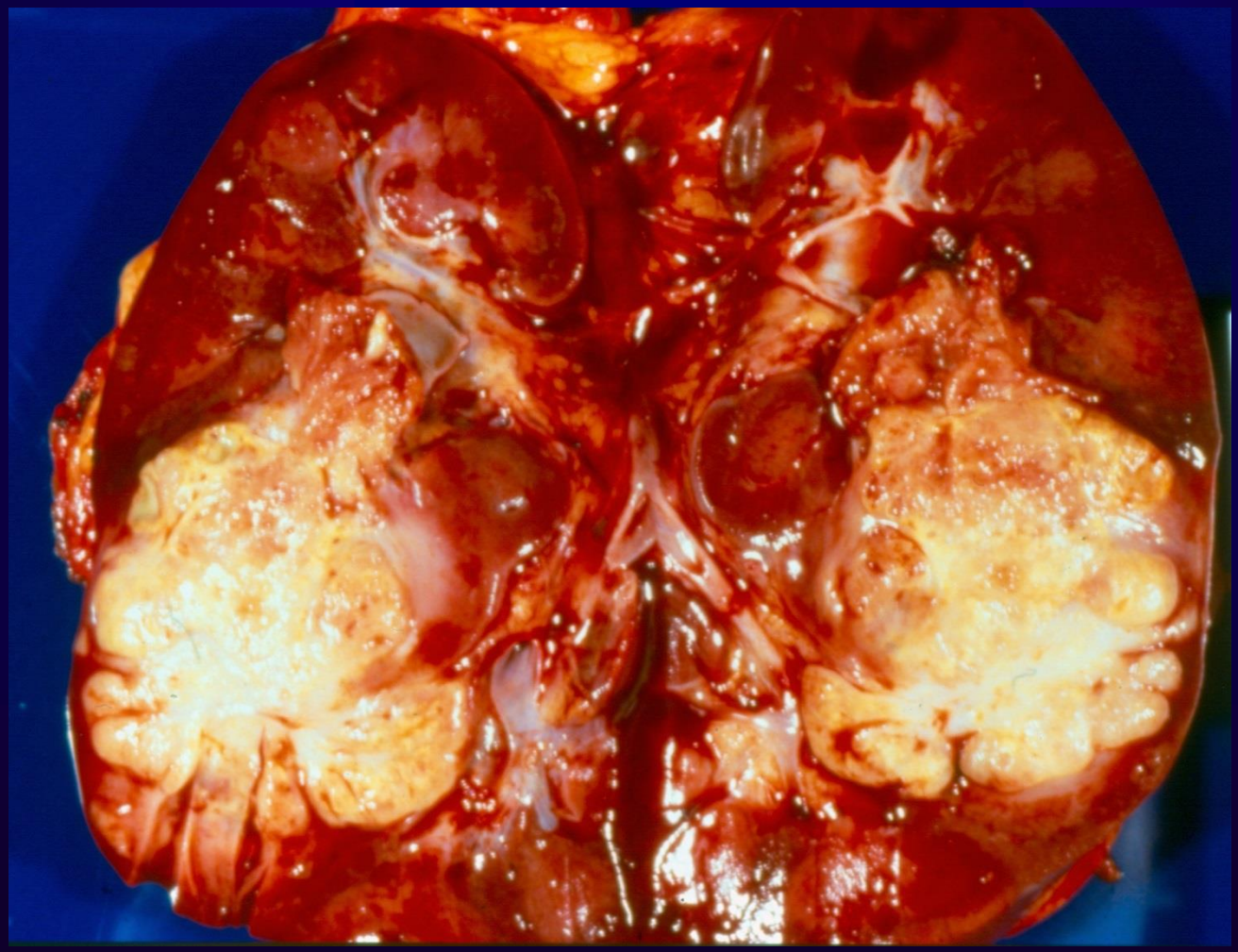
- Mass located in medulla with infiltrating border
- Histologically composed of small malignant tubules similar collecting ducts
- Aggressive high grade tumor

Collecting Duct Carcinoma





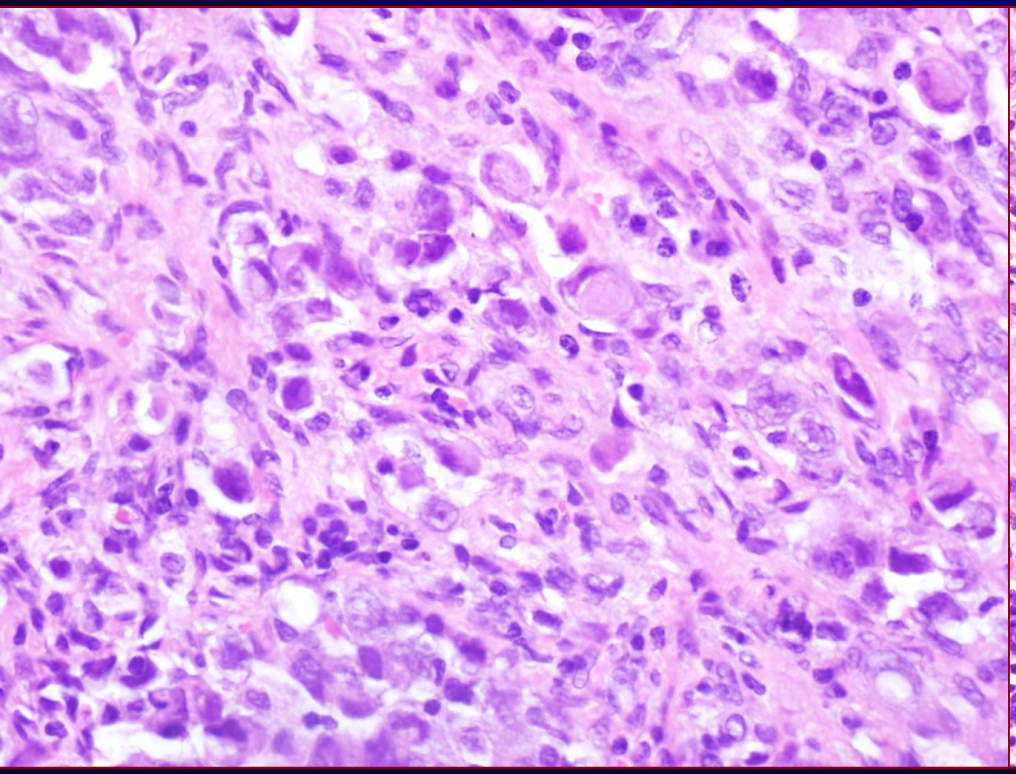
3. Medullary Carcinoma

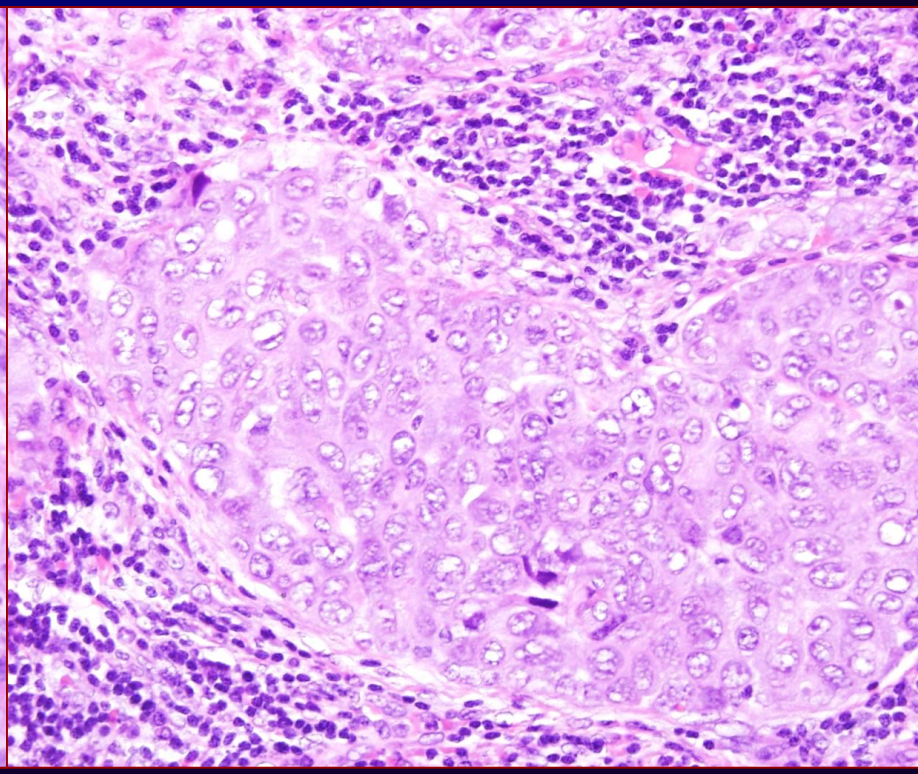


Renal Medullary Carcinoma

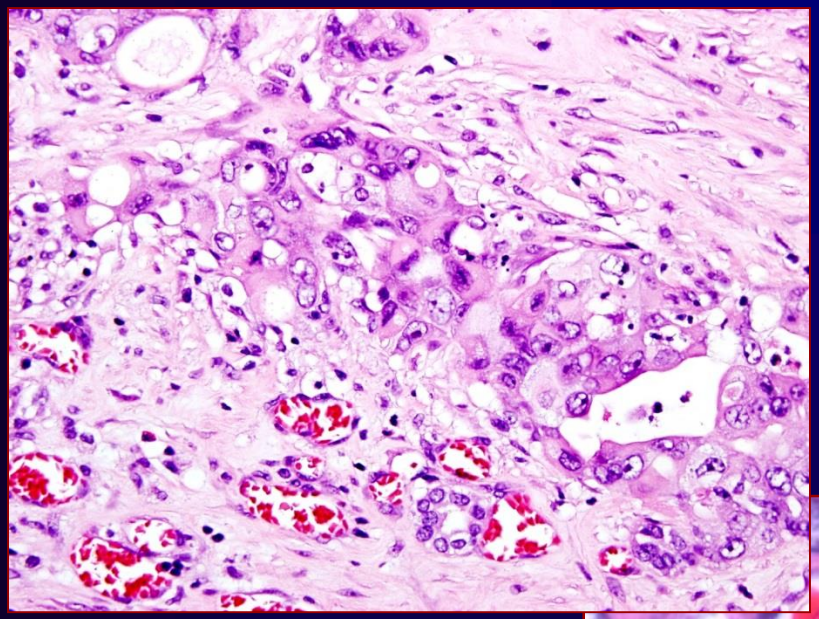
- Associated with sickle cell trait
- Very aggressive disease
- Young patients
- Histologic features: tubuloglandular
- Inflammatory and necrosis
- Molecular analysis shows its closer to urothelial carcinoma than RCC

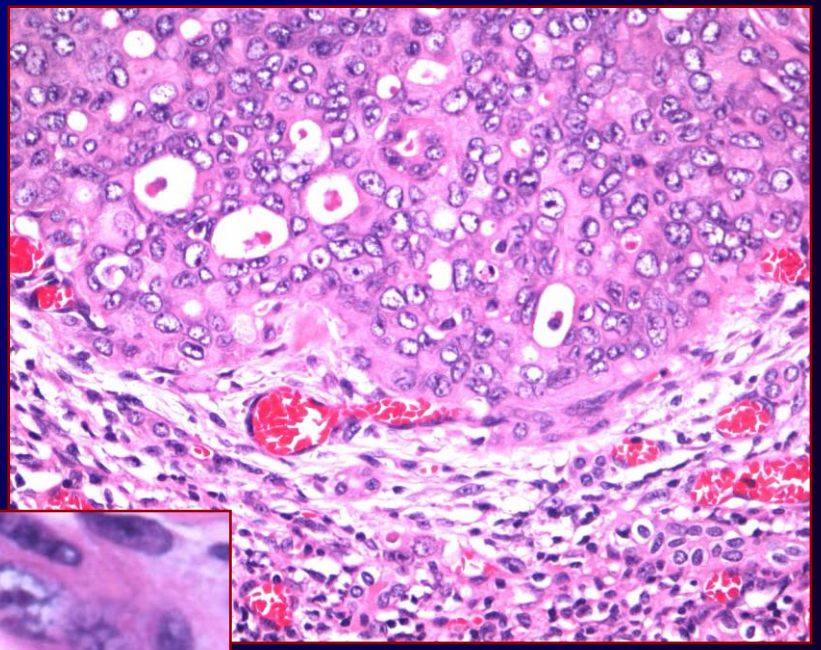
Renal Medullary Carcinoma

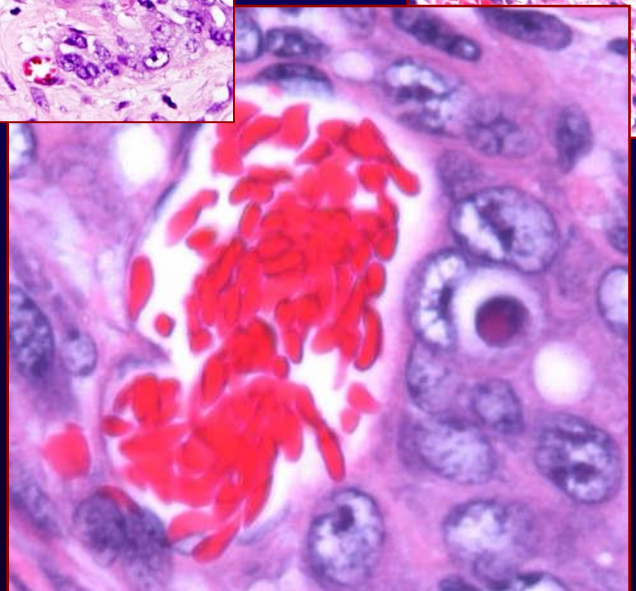




Renal Medullary Carcinoma

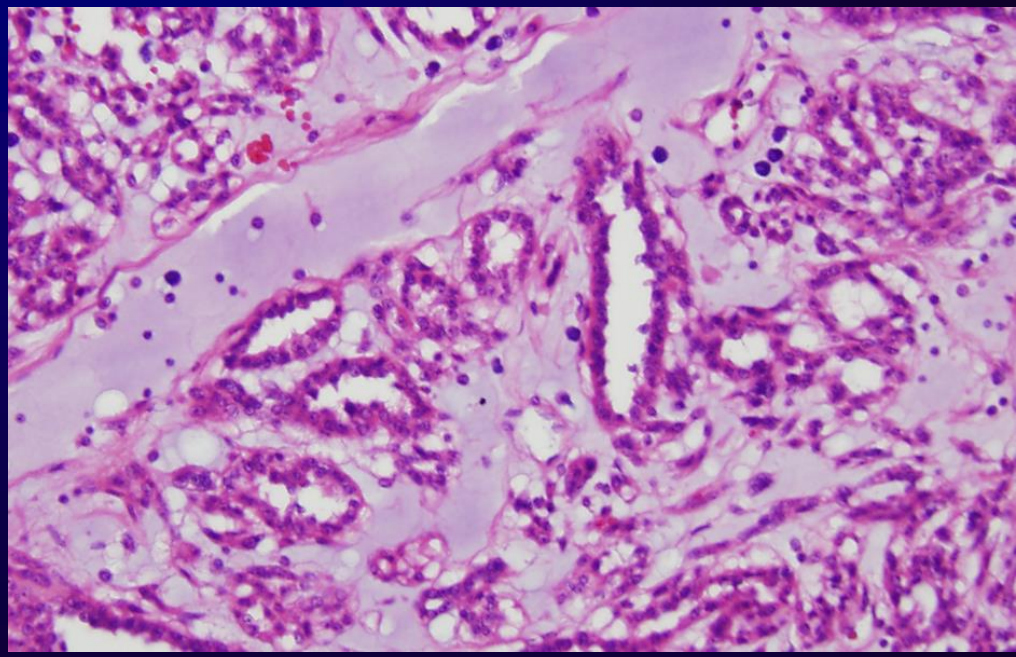






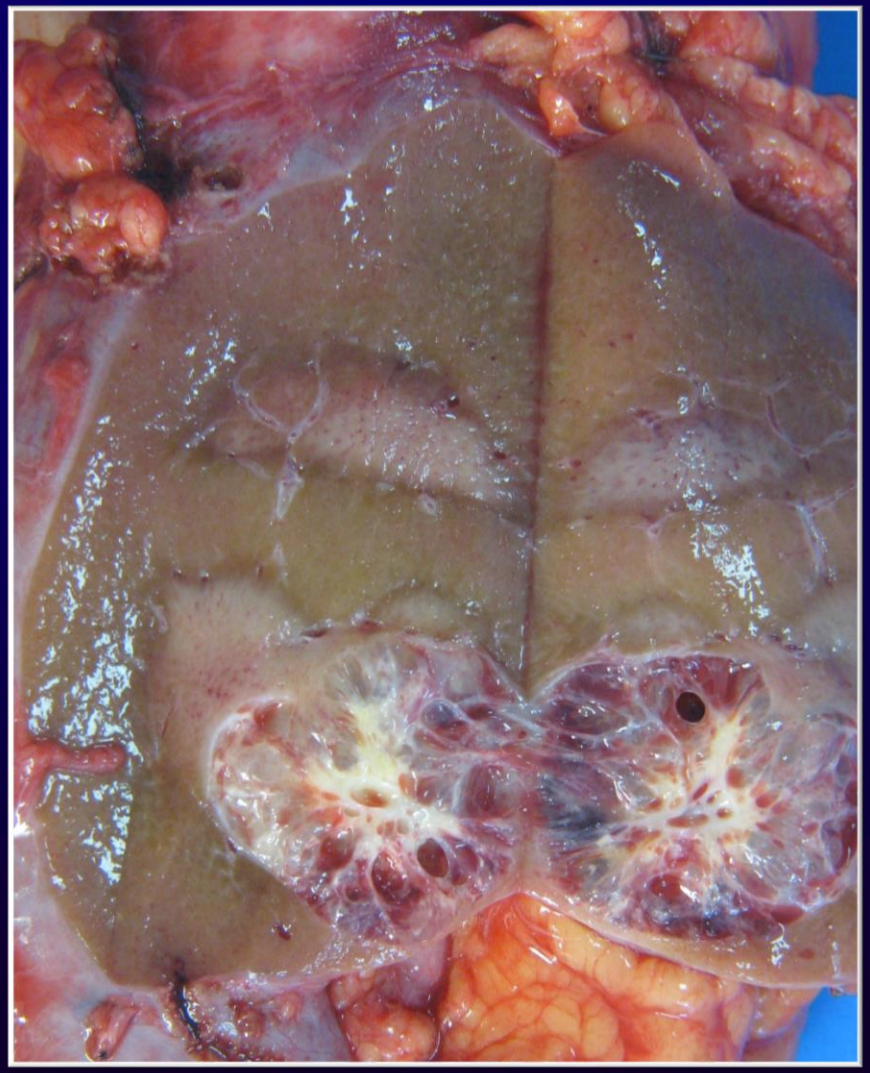
4. Mucinous tubular and spindle cell carcinoma (MTSCC)

- A new subtype of RCC
- Three components
  - Tubules
  - Spindle cells
  - Mucinous material
- Often low grade
- May be related to pap RCC

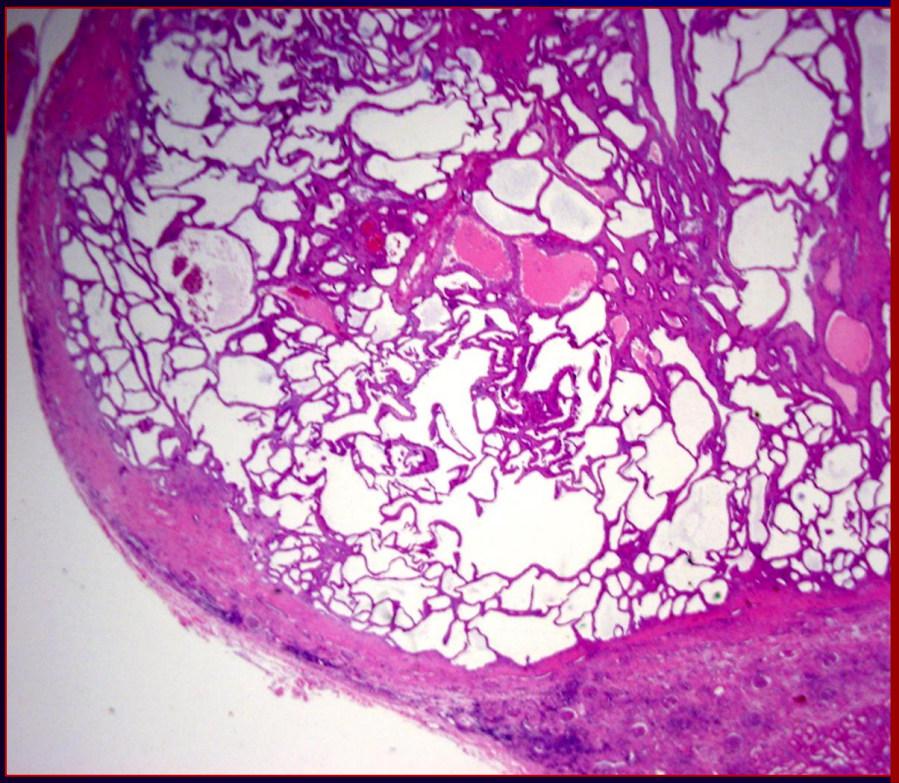


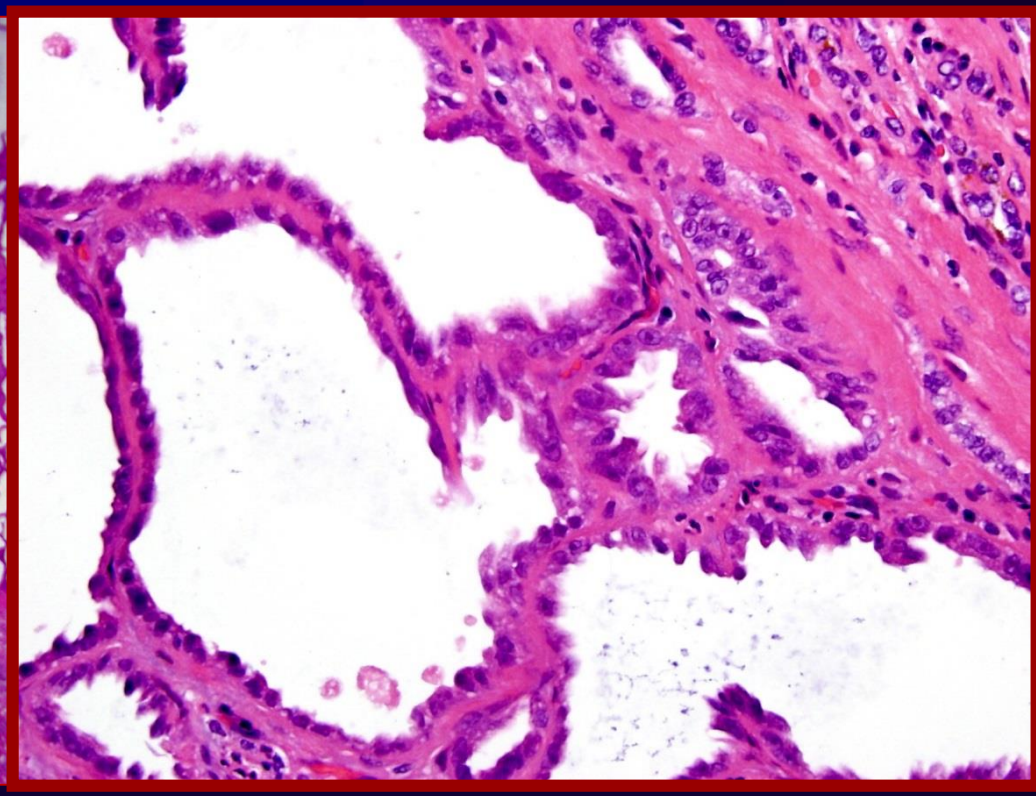
5. Tubulocystic Carcinoma

- 39-year man with a 3-cm renal mass
- Multilocular cystic lesion
- Background kidney unremarkable



Tubulocystic carcinoma



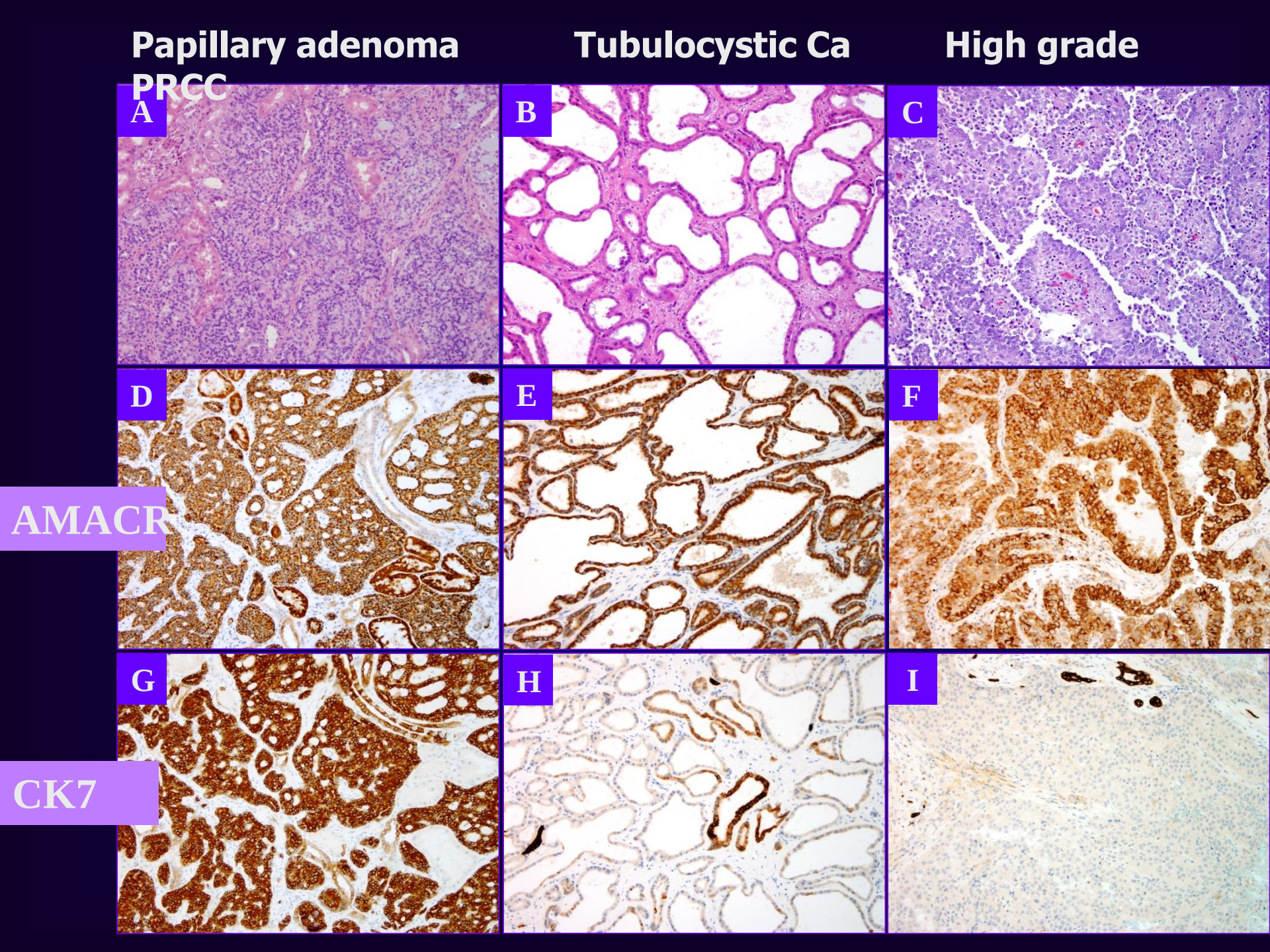


Tubulocystic Carcinoma of the Kidney

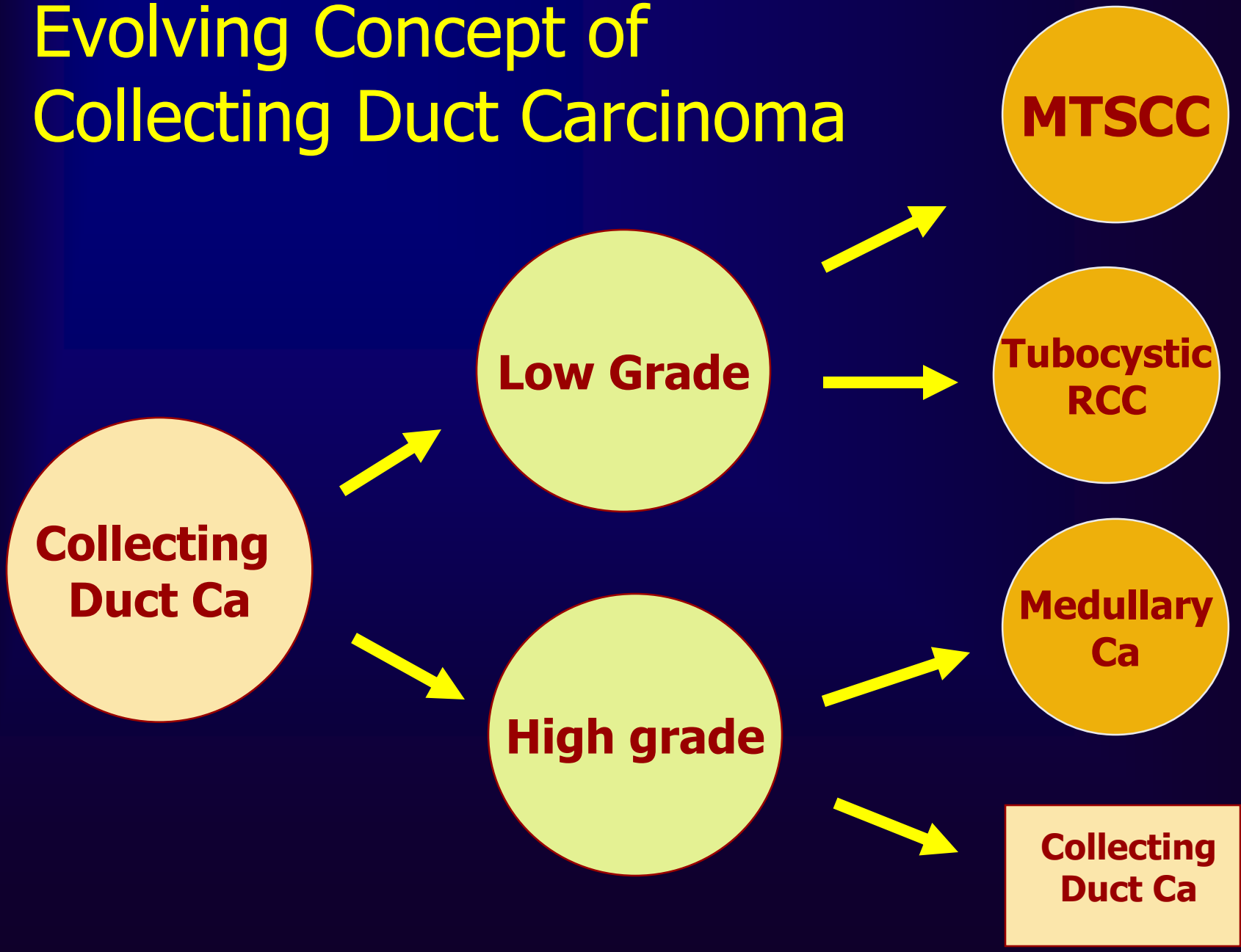
not related to collecting duct

-Yang et al AJSP 2008

- Location of the tumor either cortex or cortex/medulla
- Co-existing papillary cell neoplasm in 30% of cases
- Expression profiles closely related to papillary RCC rather than collecting duct carcinoma
- Chromosomal changes of trisomy 7 and trisomy 17 identified
- IHC profile similar to papillary RCC


Papillary adenoma PRCC
Tubulocystic Ca
High grade
A
B
C
D
E
F
AMACR
G
H
I
CK7

Evolving Concept of Collecting Duct Carcinoma

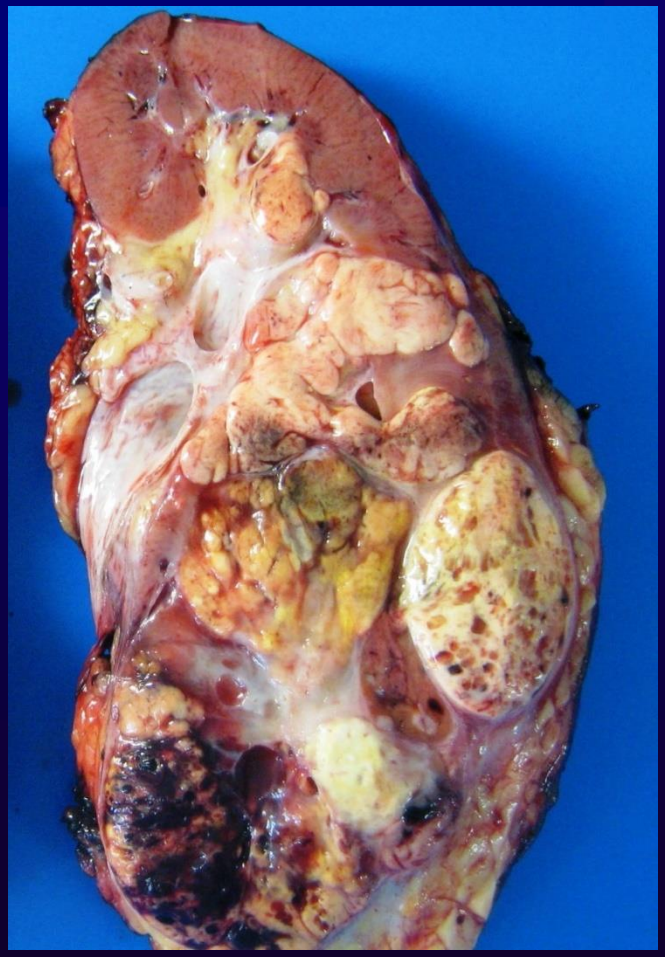


6. MiT Family Translocation Renal Cell Carcinoma

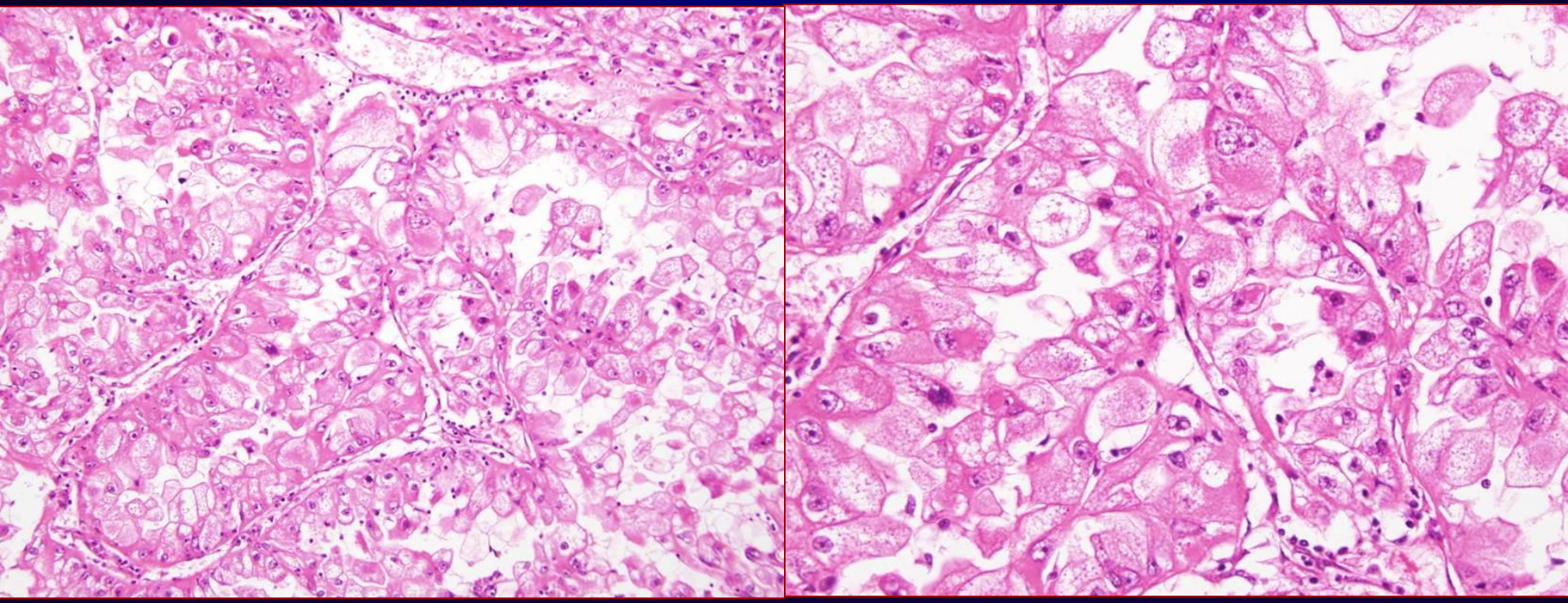
(TFE3/TFEB Translocation and amplification)

- Unique histologic features with papillary structures
- Clear, granular or eosinophilic cytoplasm
- Wide range of ages
- Aggressive in adults
- Several types of translocation
  - PRCC-TFE3 t(X;1) (p11.2; q21)
  - ASPL-TFE3 t(X;17) (p11.2; q25)
  - Alpha-TFEB t(6;11) (p21; q13)

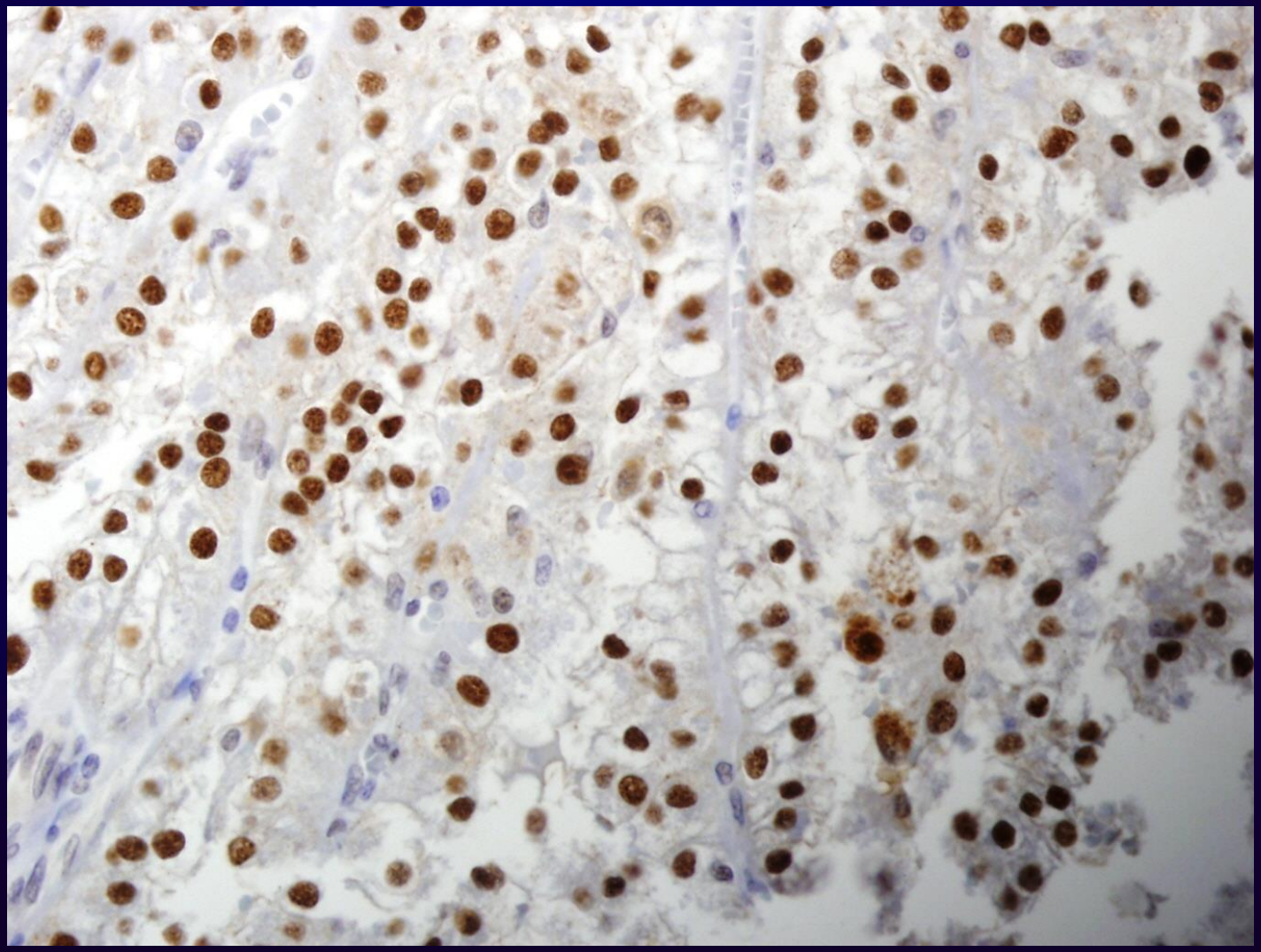
TFE-3 (Xp11)Translocation RCC

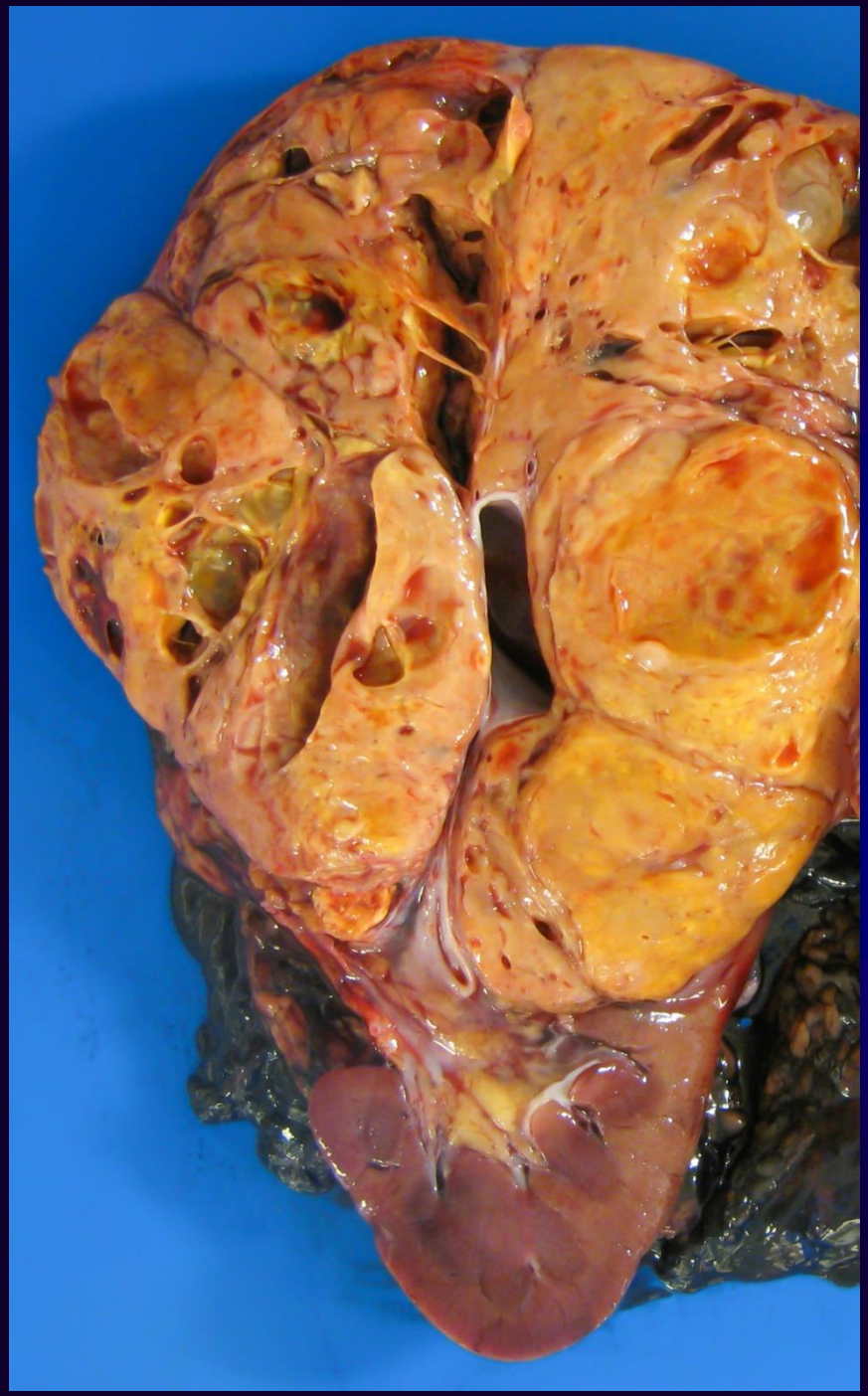


TFE3 Translocation Carcinoma

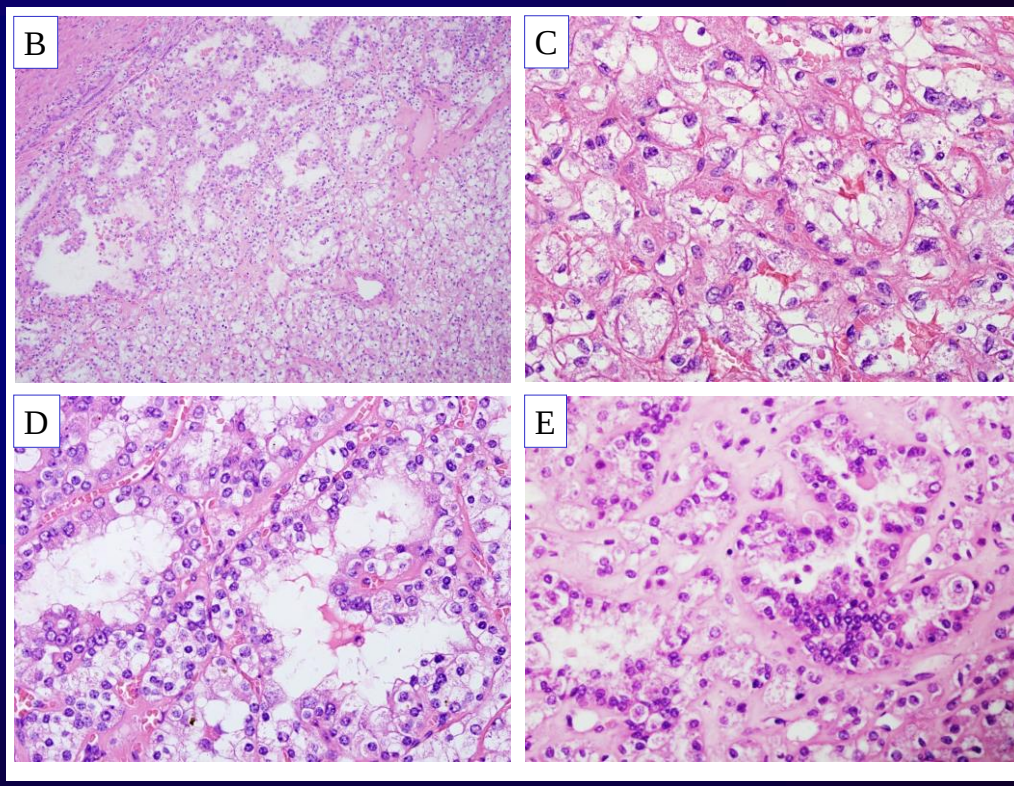


TFE3 immunostaining



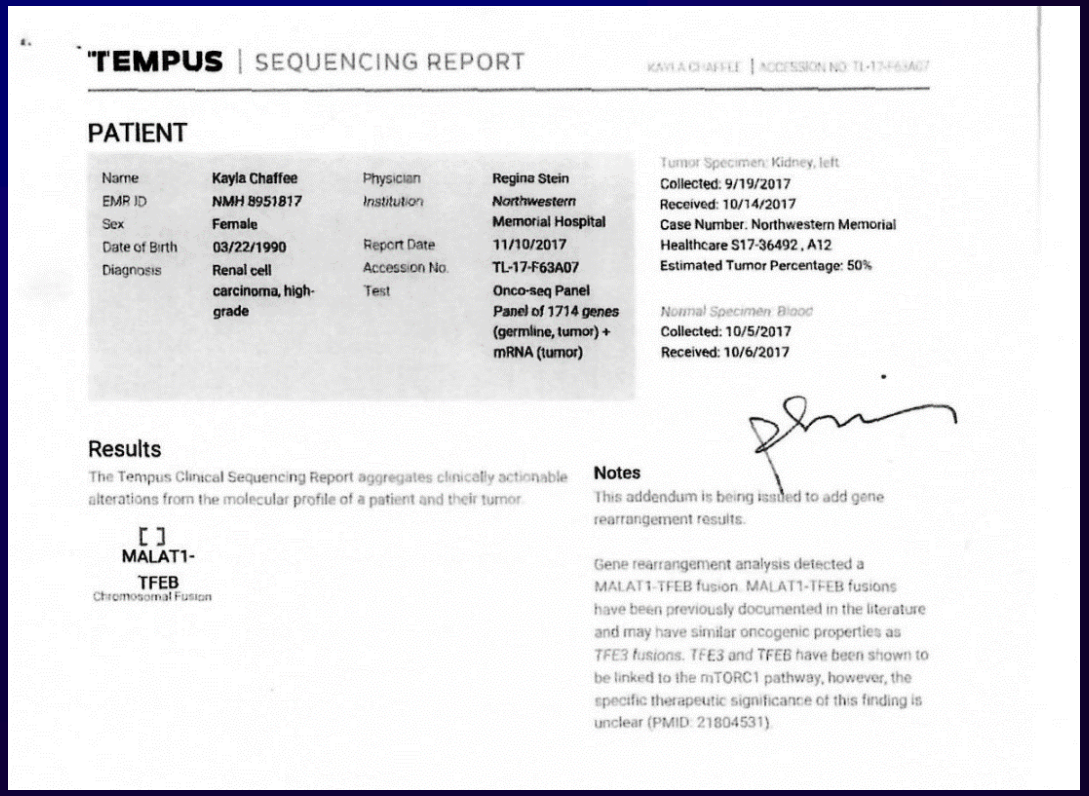


A Large renal mass in 35-y-o female



TFE-B translocation carcinoma

- Histology similar to TFE-3 RCC
- TFE3 staining negative
- Molecular or FISH analysis for confirmation the diagnosis



TEMPUS | SEQUENCING REPORT

KAYLA CHAFFEE | ACCESSION NO. TL-17-F63A07

PATIENT

Name	Kayla Chaffee	Physician	Regina Stein
EMR ID	NMH 8951817	*Institution*	*Northwestern Memorial Hospital*
Sex	Female		
Date of Birth	03/22/1990	Report Date	11/10/2017
Diagnosis	Renal cell carcinoma, high-grade	Accession No.	TL-17-F63A07
		Test	Onco-seq Panel Panel of 1714 genes (germline, tumor) + mRNA (tumor)

Tumor Specimen: Kidney, left
Collected: 9/19/2017
Received: 10/14/2017
Case Number: Northwestern Memorial Healthcare S17-36492 , A12
Estimated Tumor Percentage: 50%

Normal Specimen: Blood
Collected: 10/5/2017
Received: 10/6/2017

Results

The Tempus Clinical Sequencing Report aggregates clinically actionable alterations from the molecular profile of a patient and their tumor.

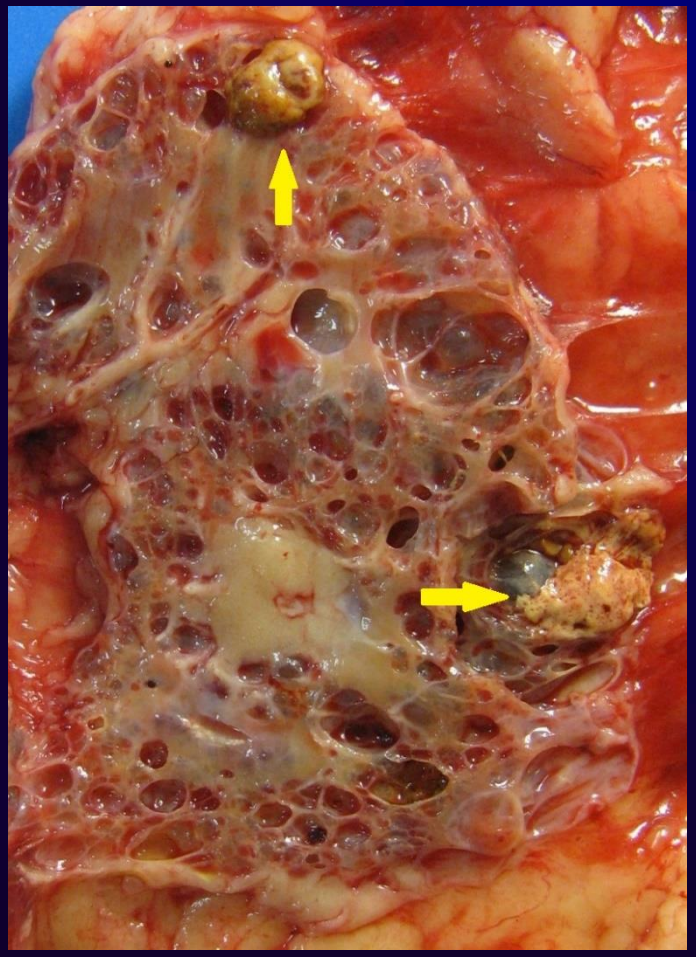
[ ]
MALAT1-
TFEB
Chromosomal Fusion

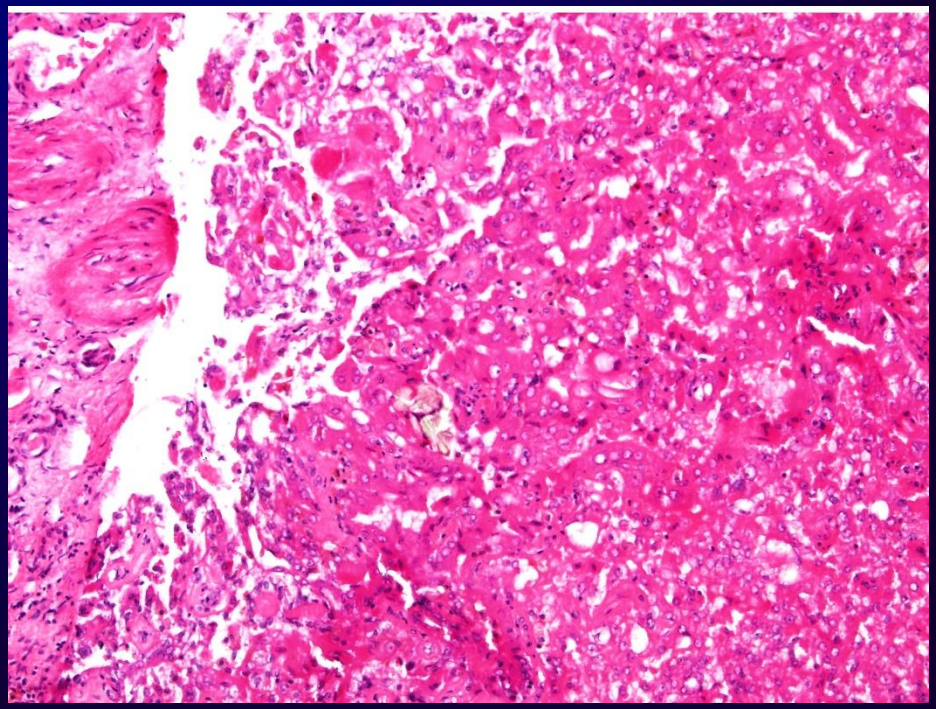
Notes

This addendum is being issued to add gene rearrangement results.

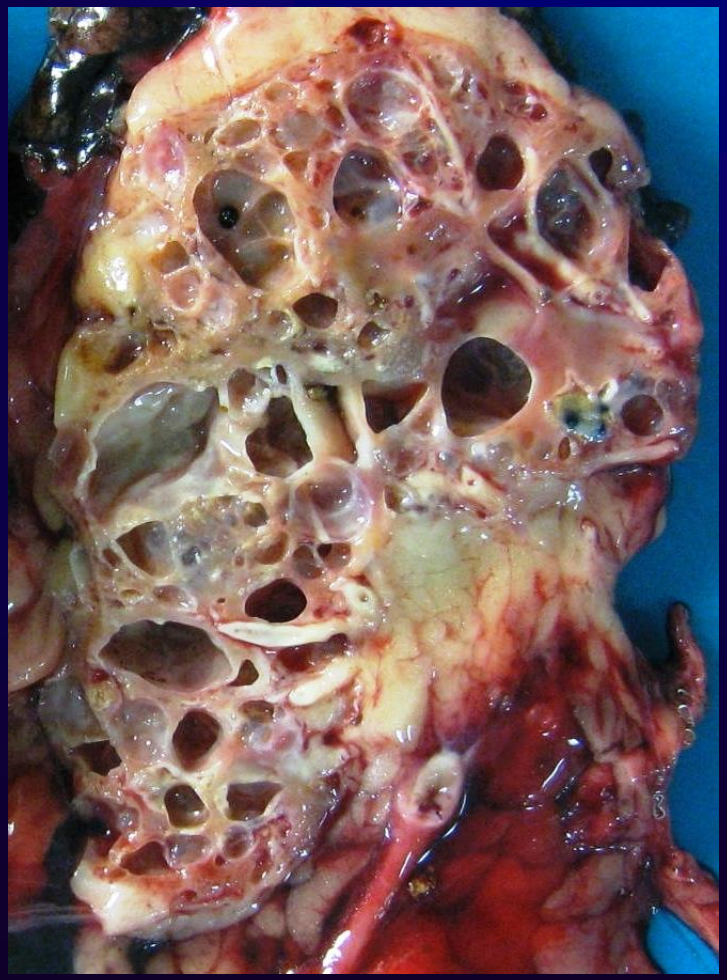
Gene rearrangement analysis detected a MALAT1-TFEB fusion. MALAT1-TFEB fusions have been previously documented in the literature and may have similar oncogenic properties as *TFE3* fusions. *TFE3* and *TFEB* have been shown to be linked to the mTORC1 pathway, however, the specific therapeutic significance of this finding is unclear (PMID: 21804531).

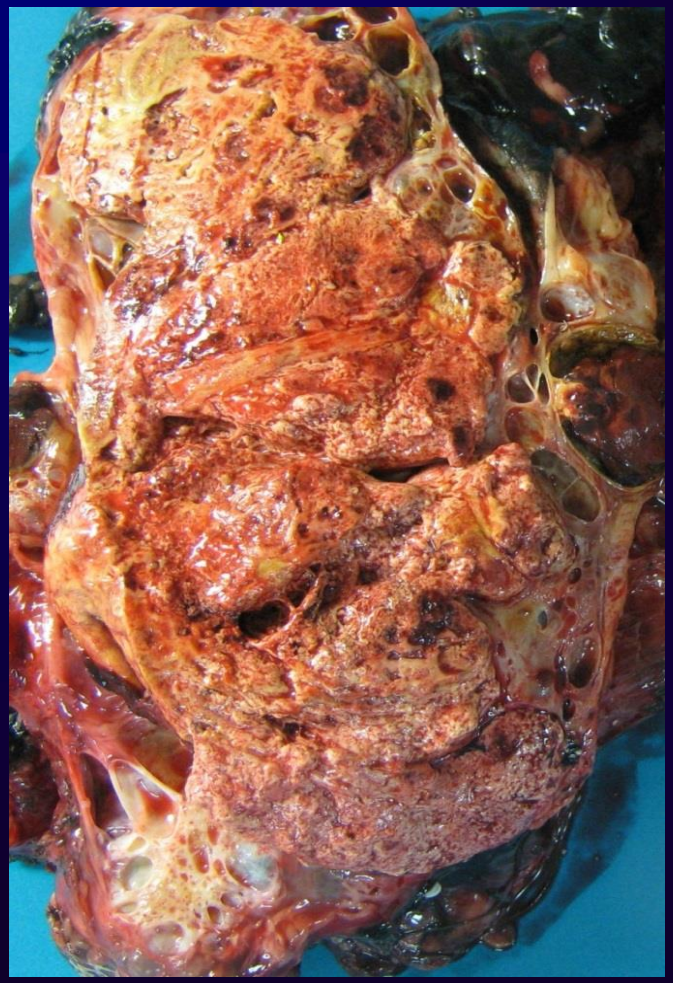
7. Acquired cystic disease (ACD) associated RCC





A Large RCC Associated with Acquired Cystic Disease

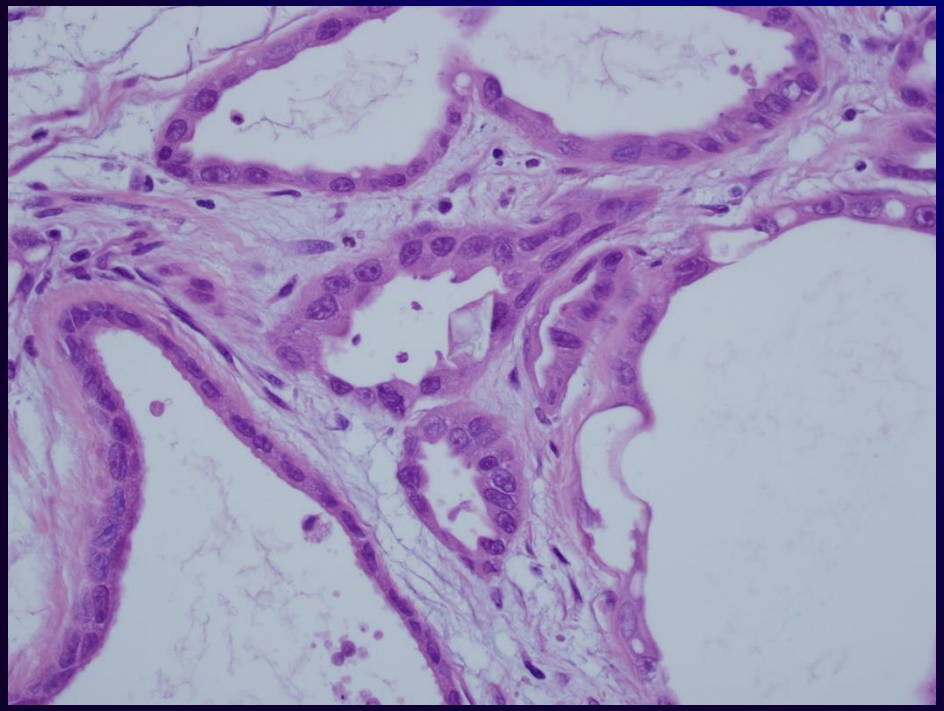


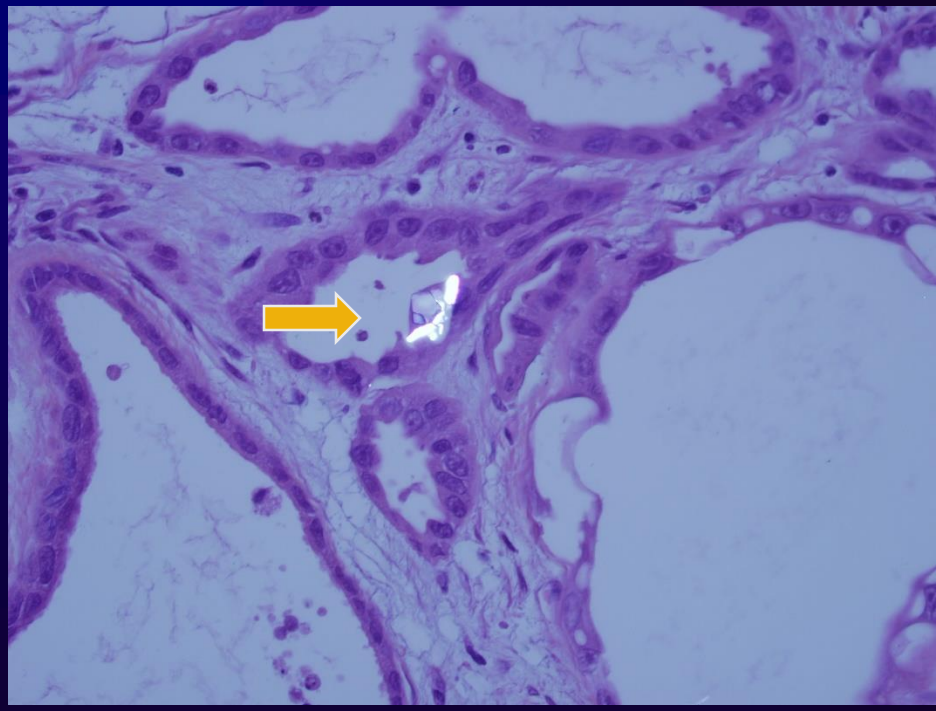


ACD Associated RCC

- ACD background
- Multiple histologic patterns
  - Cribriform
  - Tubulocystic
  - Solid or papillary
- Intracytoplasmic vacuoles
- Presence of calcium oxalate crystals inside the tumor

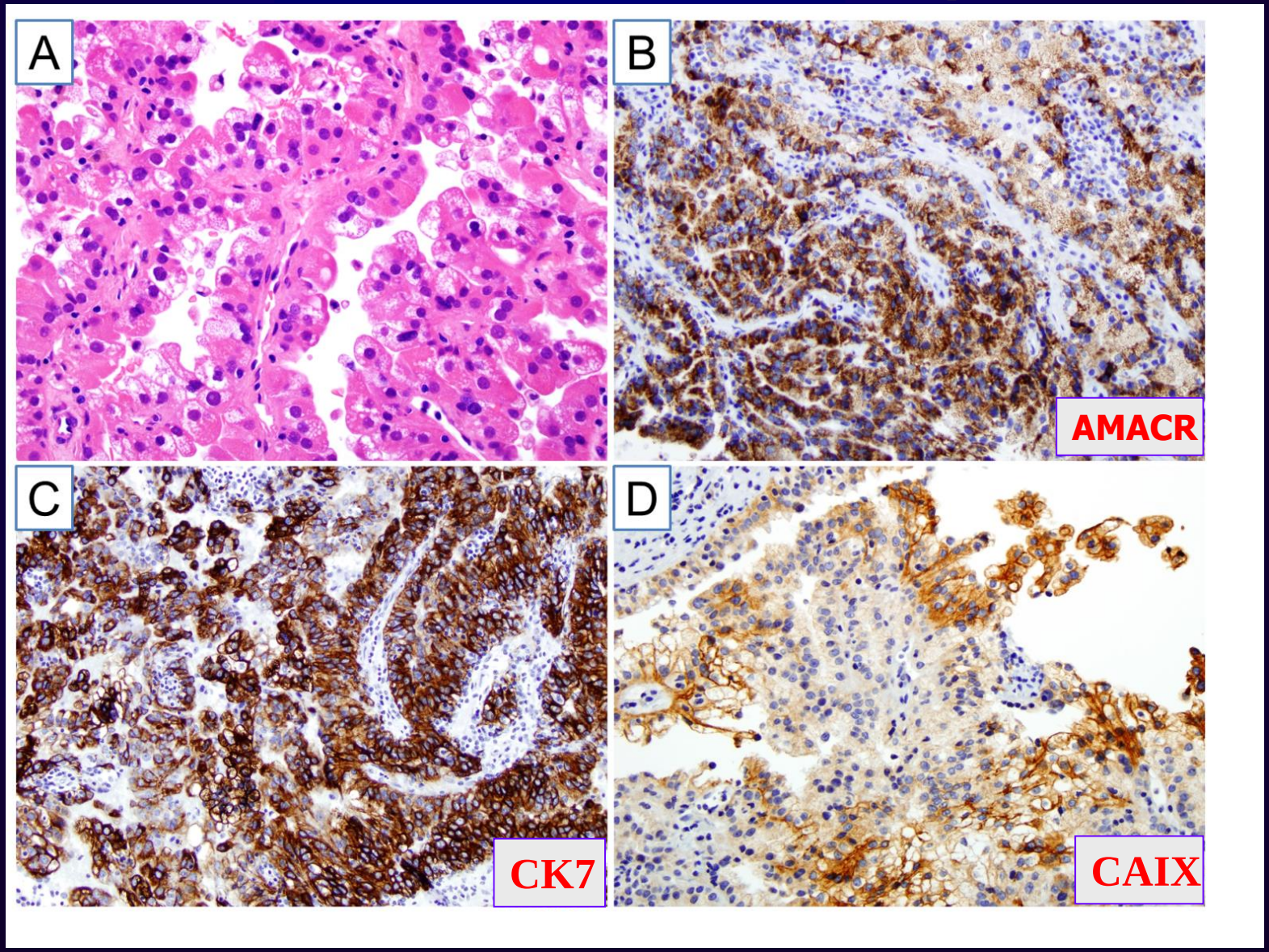
Presence of (calcium oxalate) crystals in the tumor





Polarized dark field

Immunohistochemical profile



Study of 279 Nonfunctional Kidneys

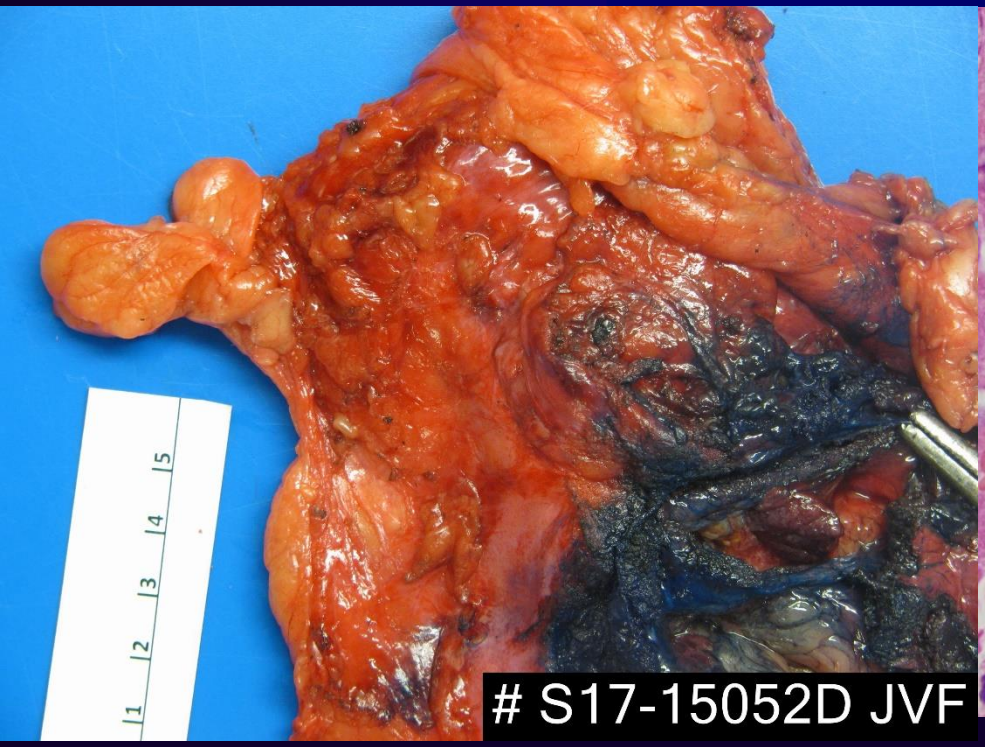
Goyal, Lin and Yang

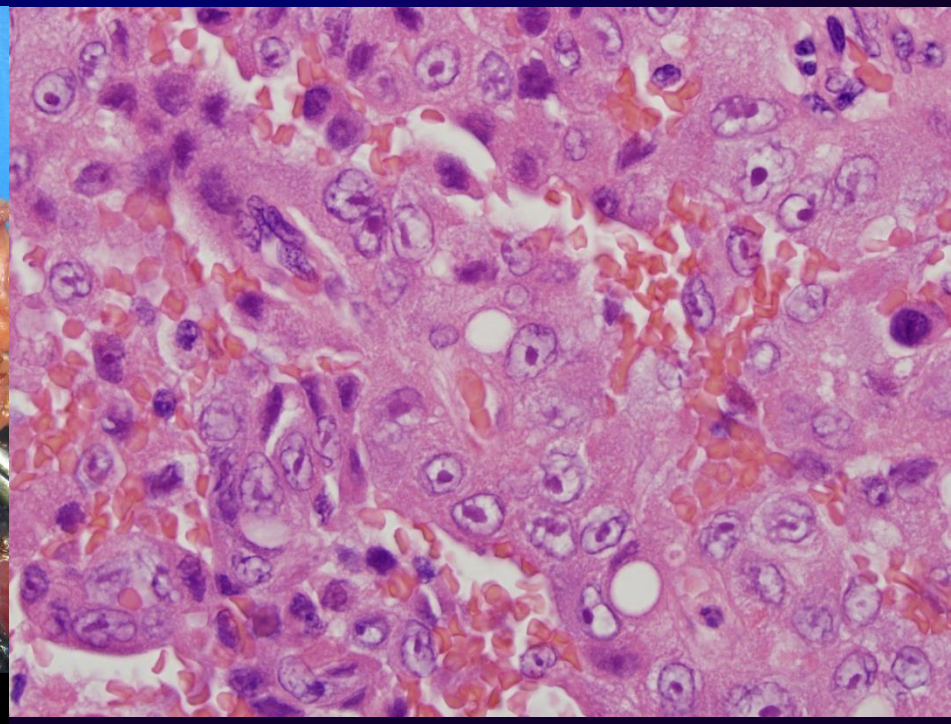
- Hum Pathology in press

Disease types	ESRD (55)	Acquired Cystic (49)	APKD (40)	Transplant (95)	Obstructive (40)
Cancer Incidence	44% (24)	76% (37)	3% (1)	0	5% (2)
Clear cell RCC	14	14	0	0	1
Papillary RCC	11	13	1	0	0
Clear cell papillary RCC	1	13	0	0	0
ACD-RCC	0	10	0	0	0
Other RCC	6	0	0	0	1
Dialysis History	44% (22)	65% (26)	36% (13)	Not significant	Not significant
Mean Dialysis Duration (Mo)	22.6	82.5	24.3	Not significant	Not significant

8. Hereditary leiomyomatosis-RCC syndrome associated RCC (Fumarate Hydratase-deficient)

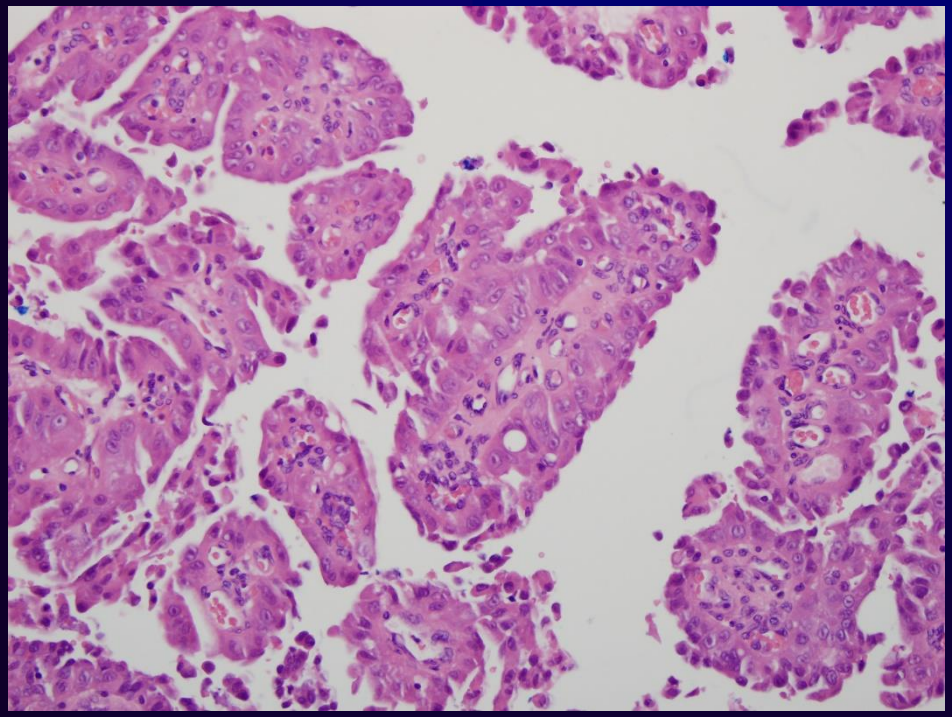
- Histologically similar to pap RCC
- CMV like nuclear inclusion

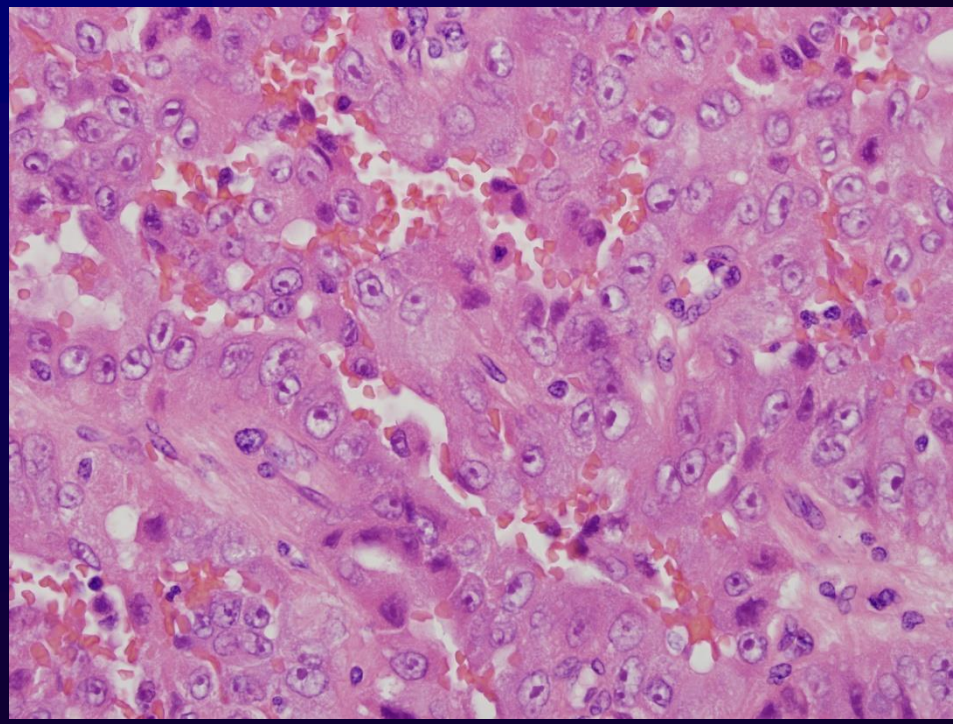




Recurrent tumor after 1 year

Papillary RCC (type 2 HG) with "CMV" inclusion like nucleoli

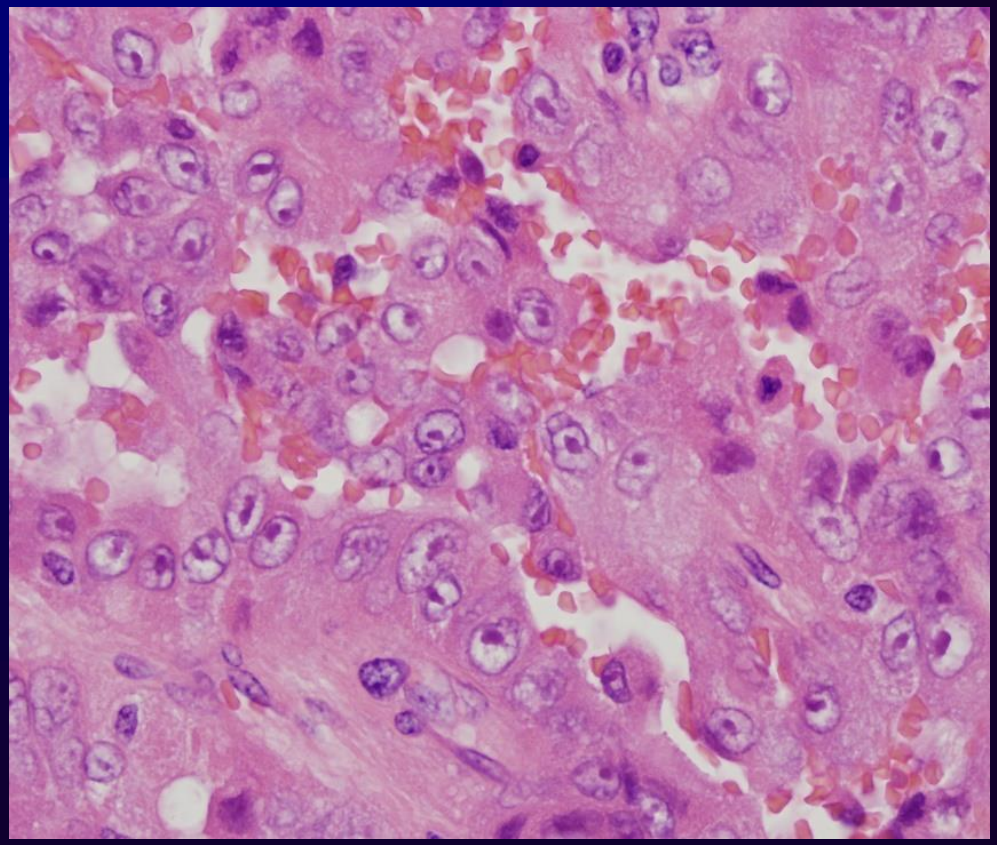




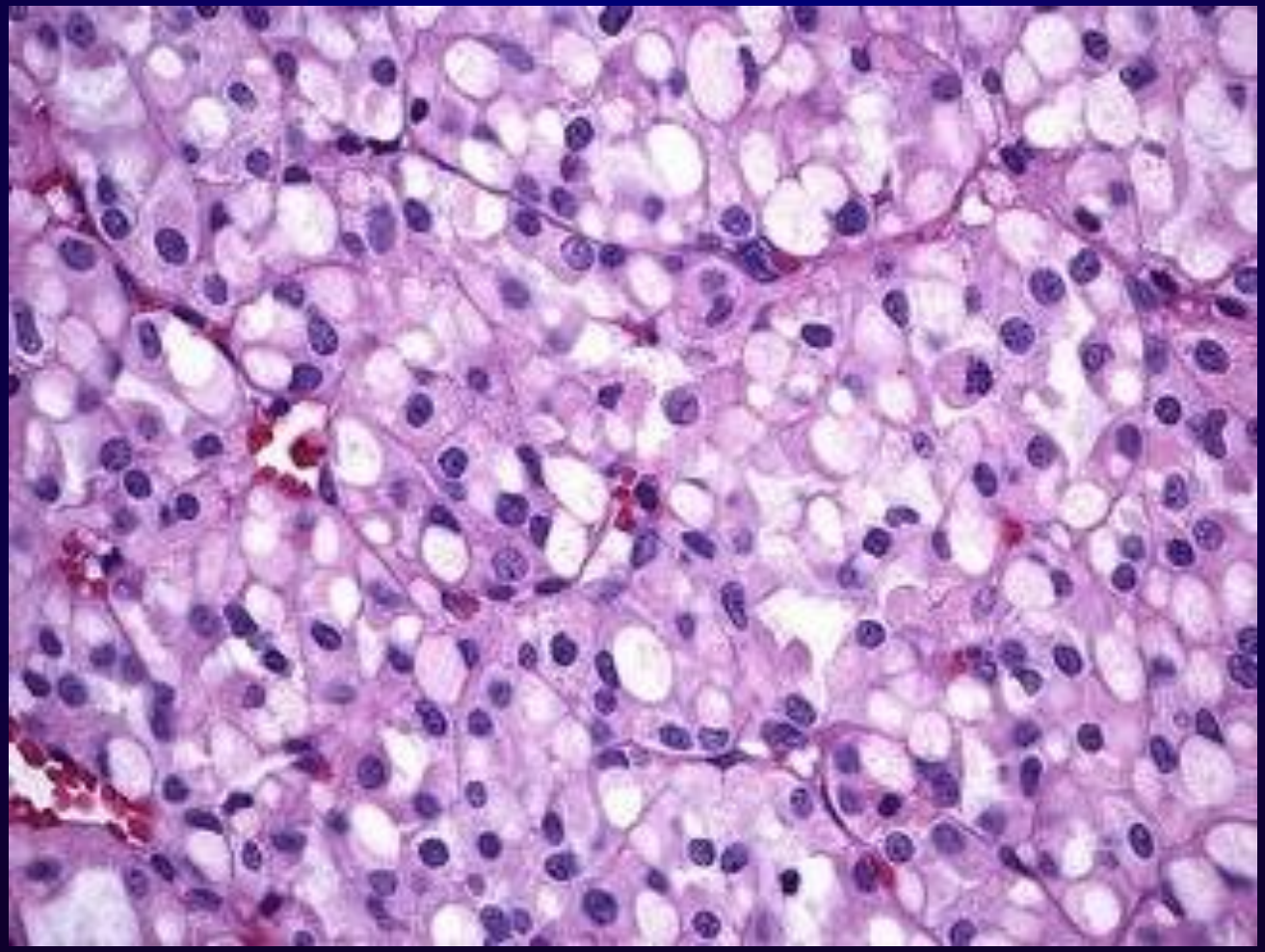
RCC in patients with Fumarate Hydratase Deficiency (FH gene mutation)

(Hereditary leiomyomatosis-RCC associated RCC)

- Variable patterns of papillary or tubular cystic
- CMV-like inclusion
- IHC
  - Loss of FH
  - Overexpression of S-(2-succino)cysteine
- Molecular test for FH mutation

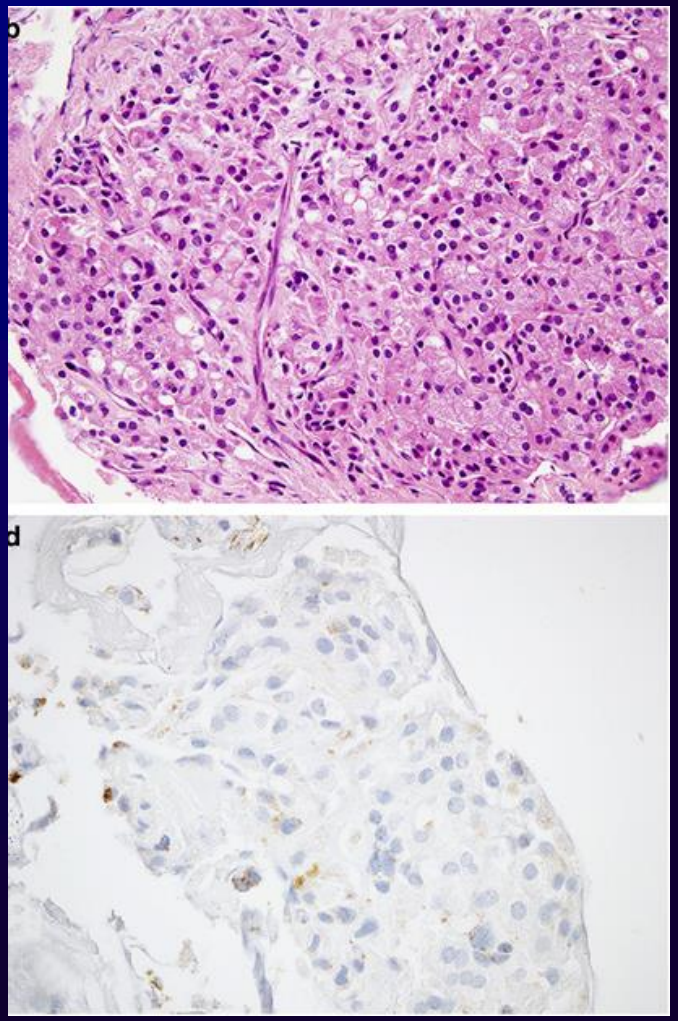


9. 35-year man with renal mass



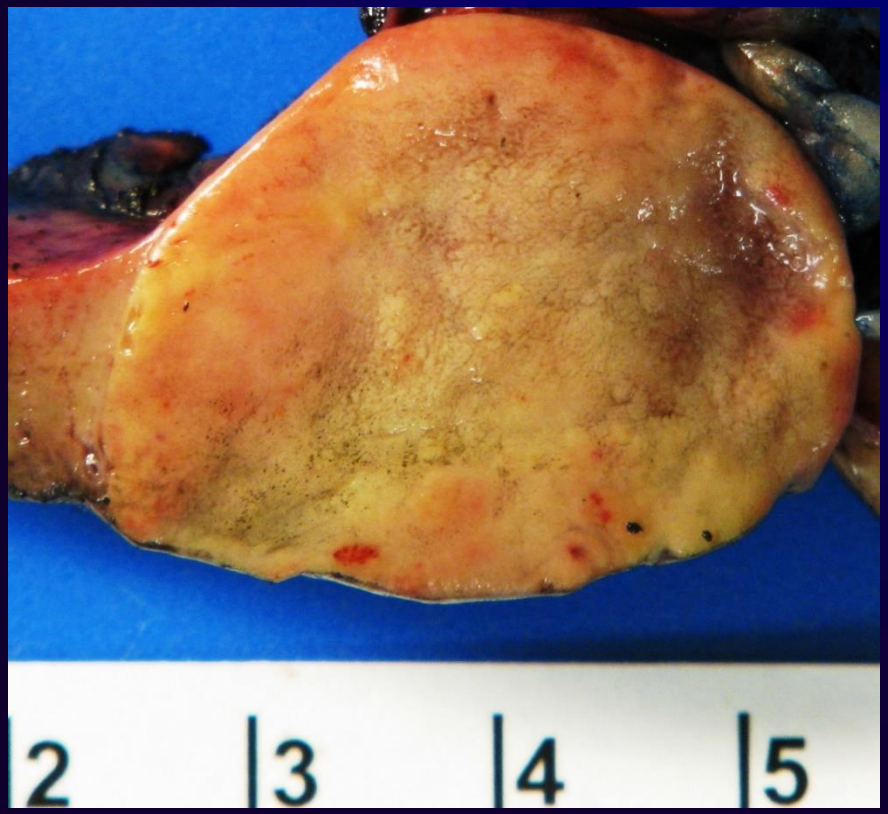
Diagnosis
Succinate dehydrogenase-Deficient RCC

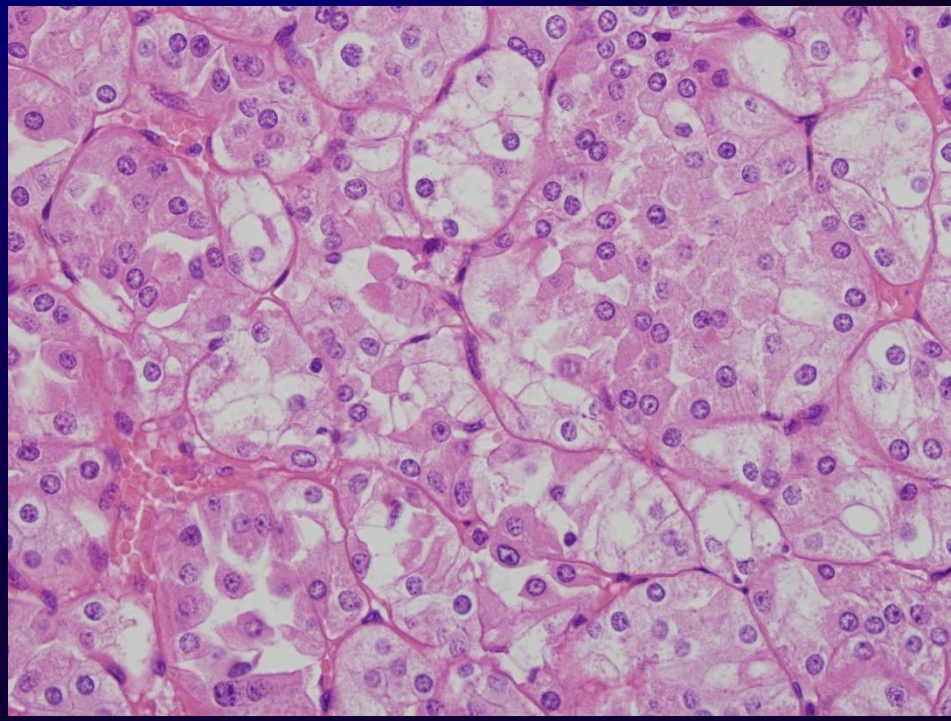
- SDH gene mutation
- Paraganglioma, GST and RCC (rare)
- Absence of SDHB immunostaining
- Eosinophilic cytoplasm cells containing vacuoles or inclusions
- 75% low grade, but some may be progressive



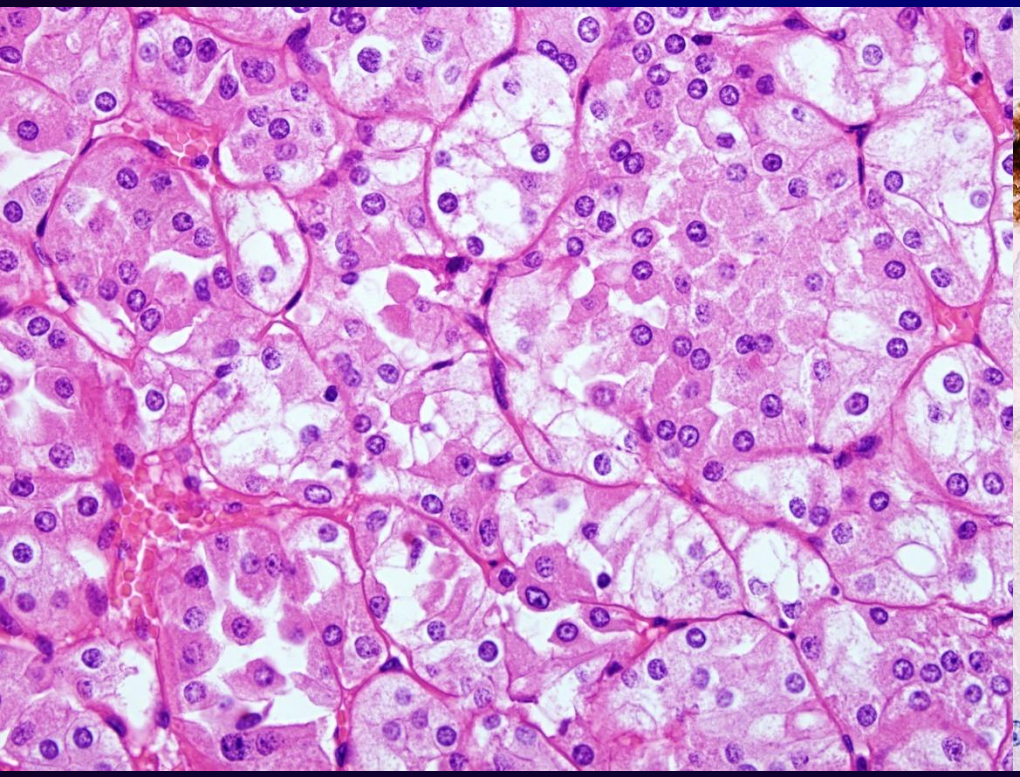
Williamson, SR et al Mod Path 2015

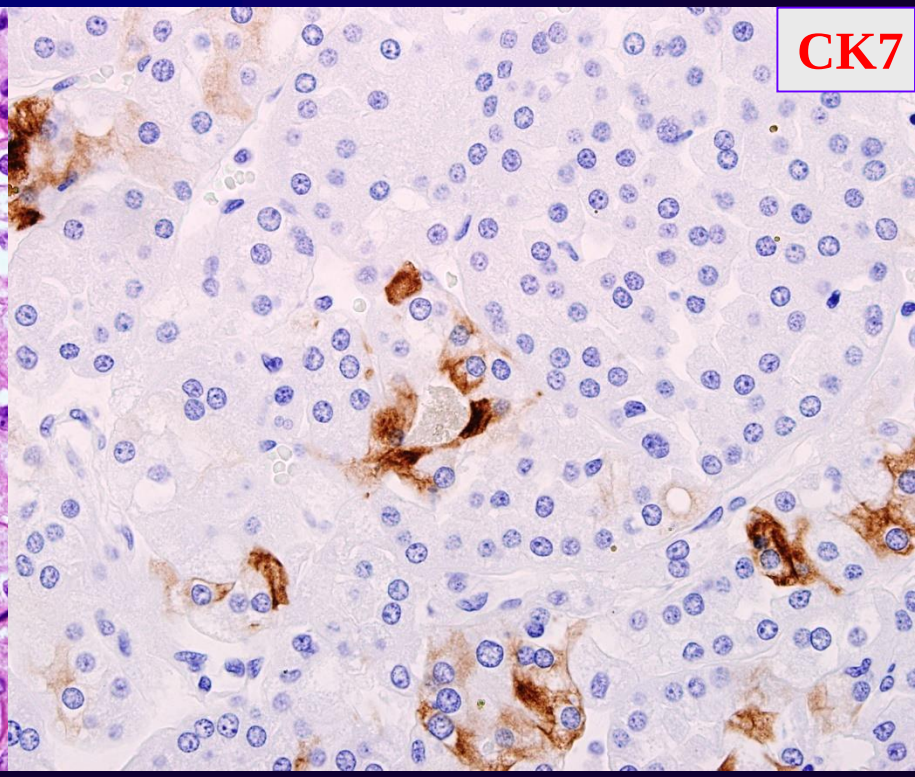
10. Hybrid Oncocytic Tumor





BHD associated hybrid tumor

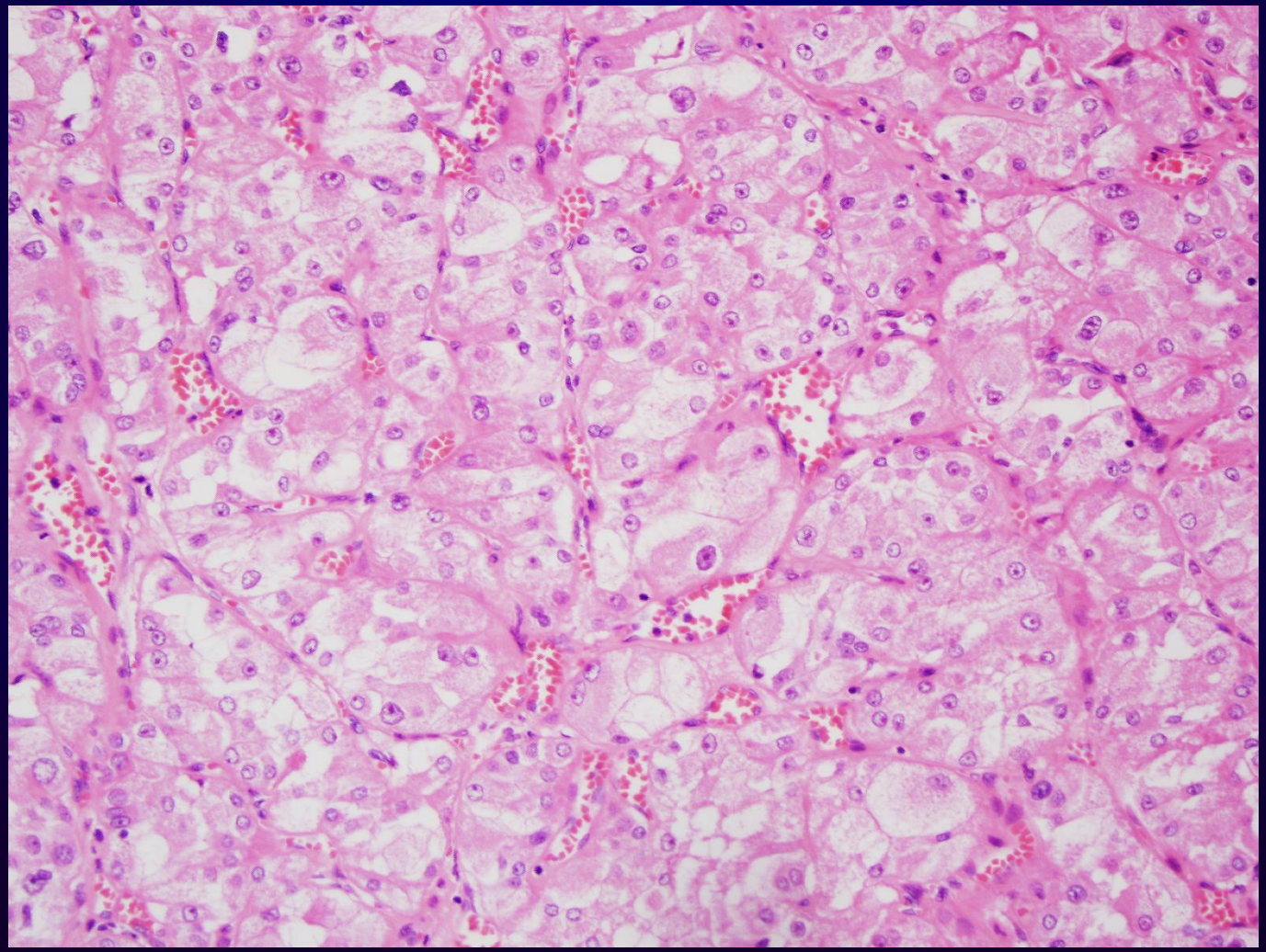




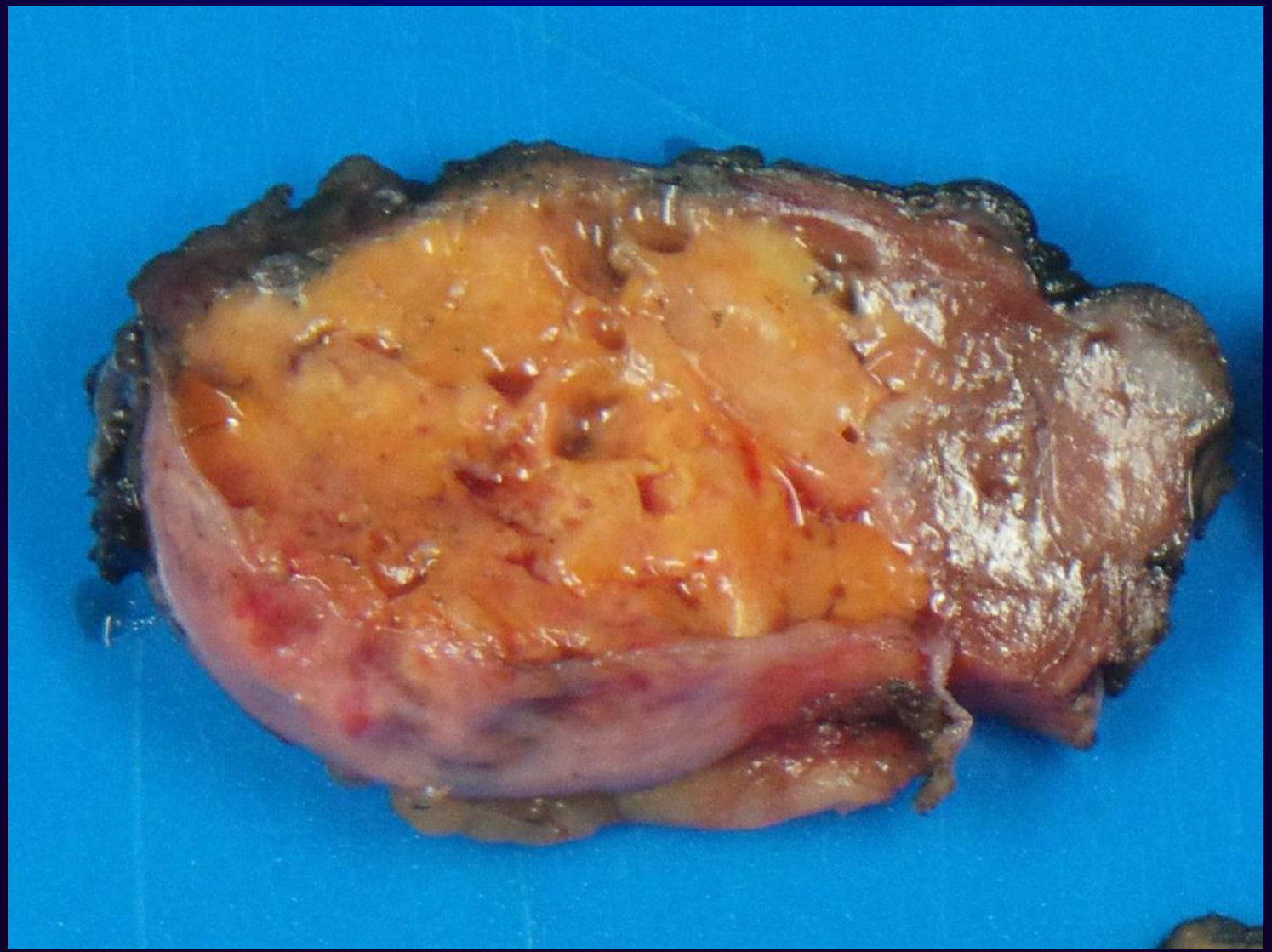
Hybrid oncocytic tumors in BHD patients

- Relative unique histology
- Recommended genetic testing
- BHD gene mutation confirmed
- Patient and family members need genetic consulting

Hybrid tumor NOT associated with BHD



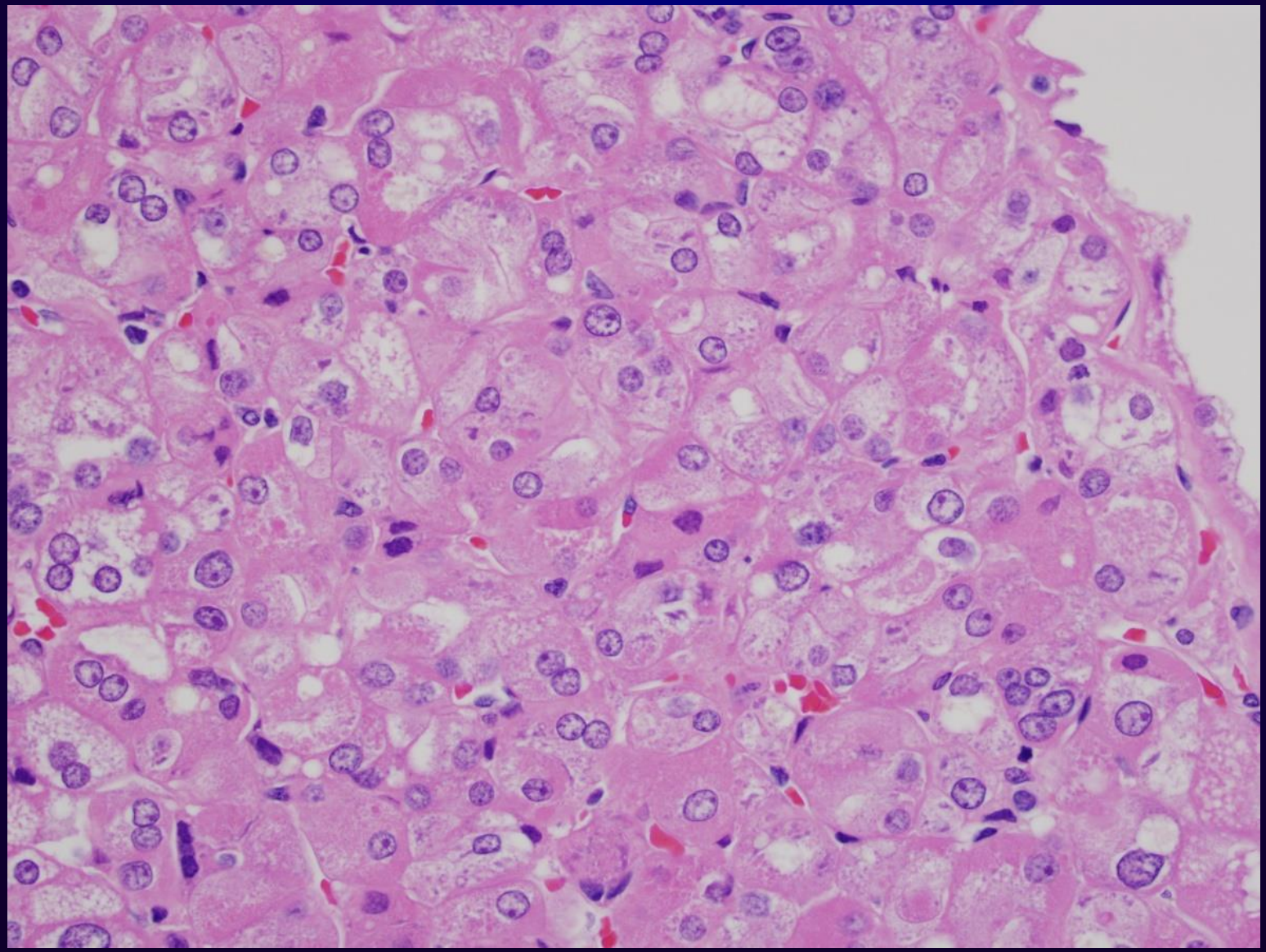
11. ESC RCC



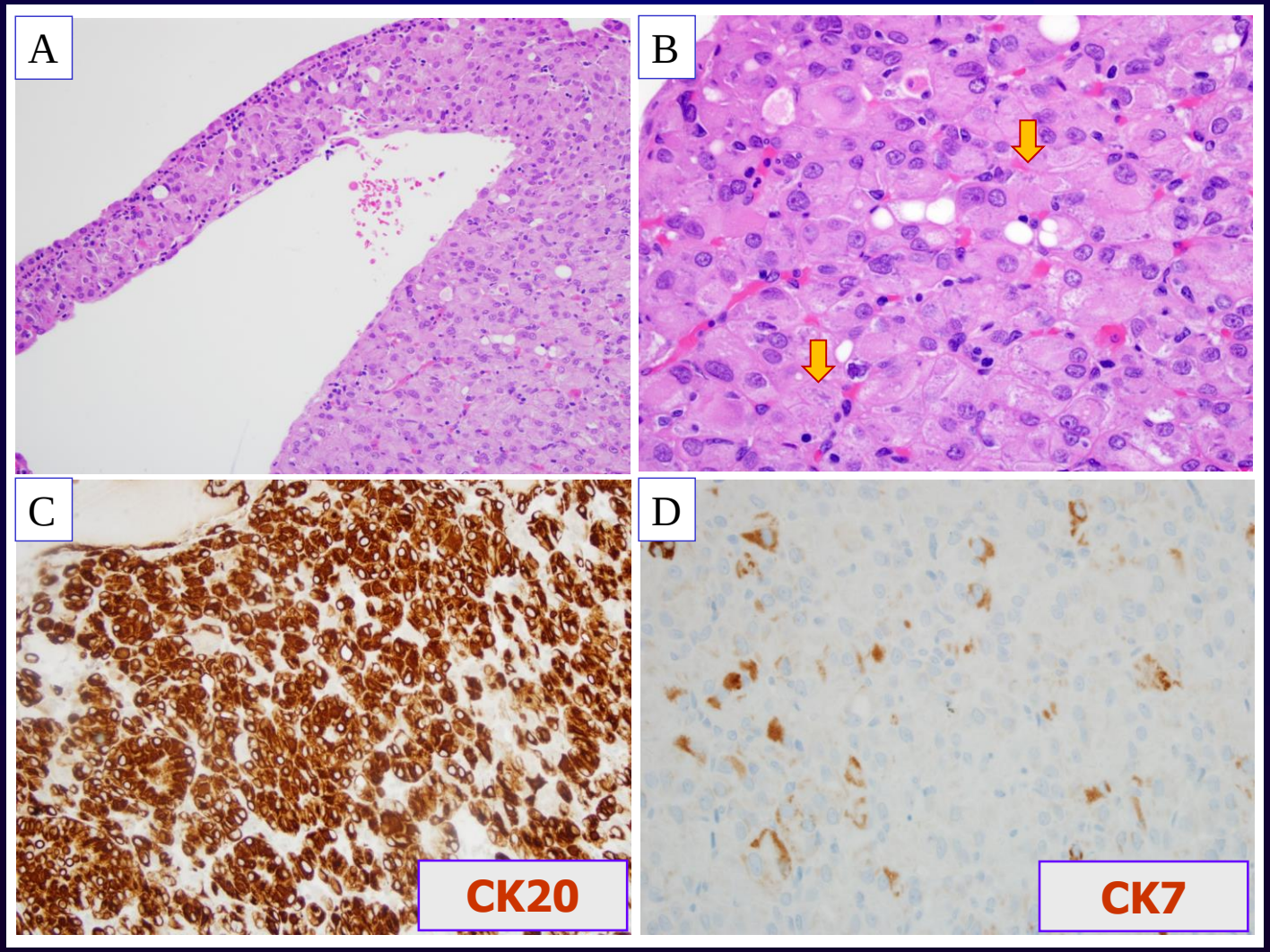
Eosinophilic solid cystic (ESC) RCC

- Solid and cystic patterns
- Eosinophilic cytoplasm
- Prominent granular cytoplasmic stippling.
- CK20 positive
- TSC1 or TSC2 mutations
- Usually low grade

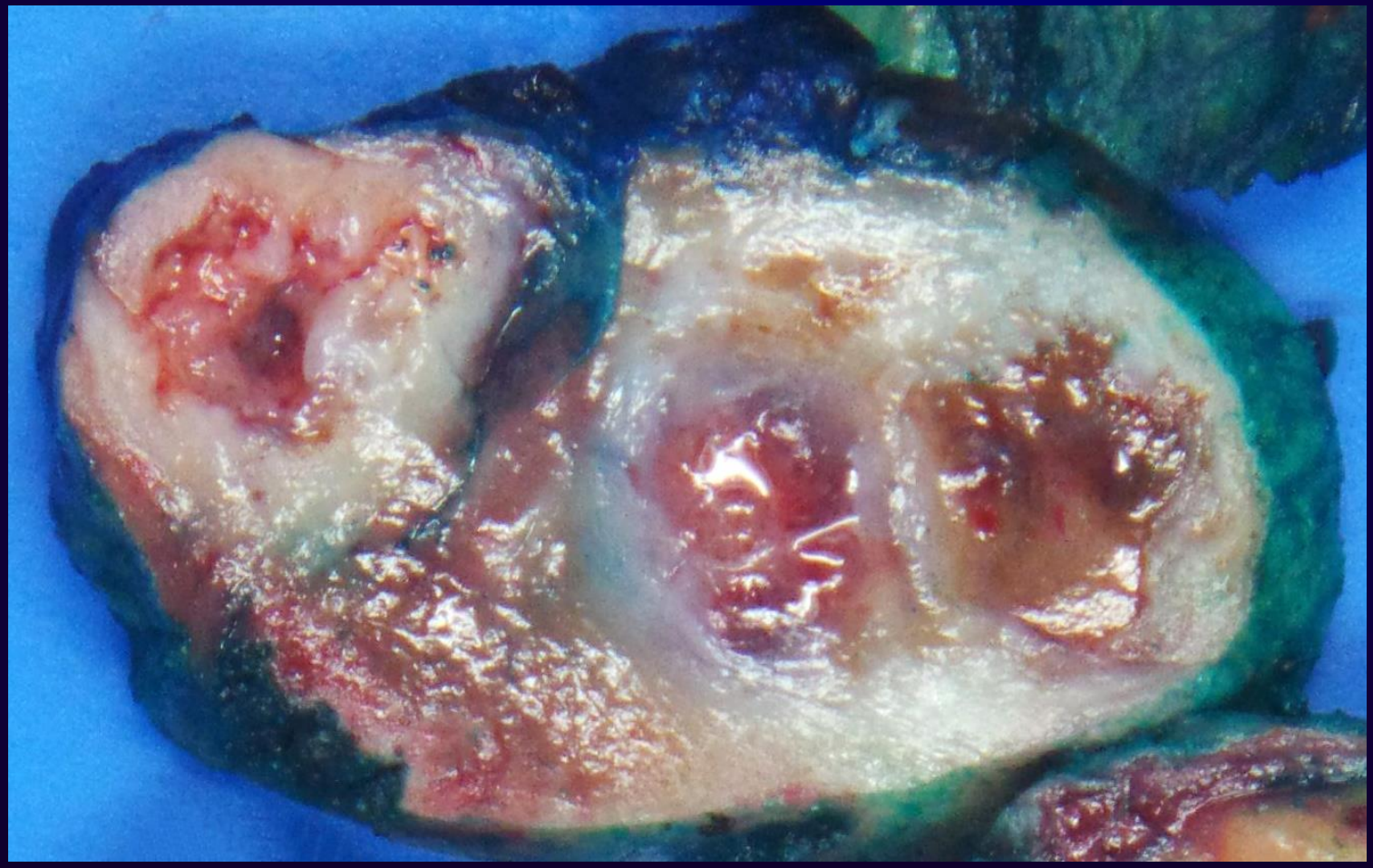
Cytoplasmic stippling



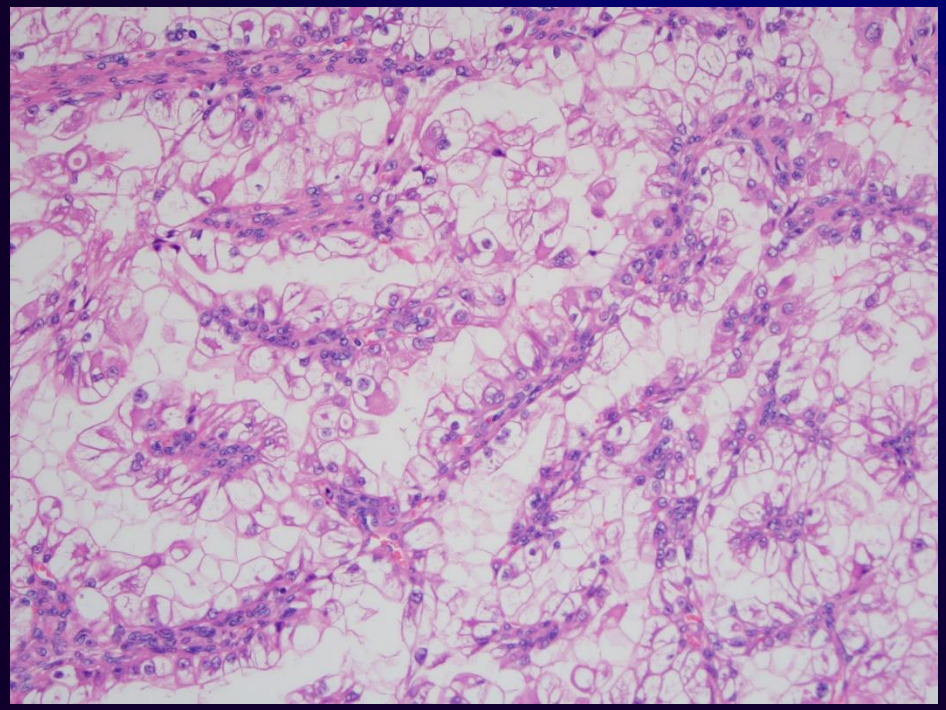
ESC (Eosinophilic solid cystic RCC)

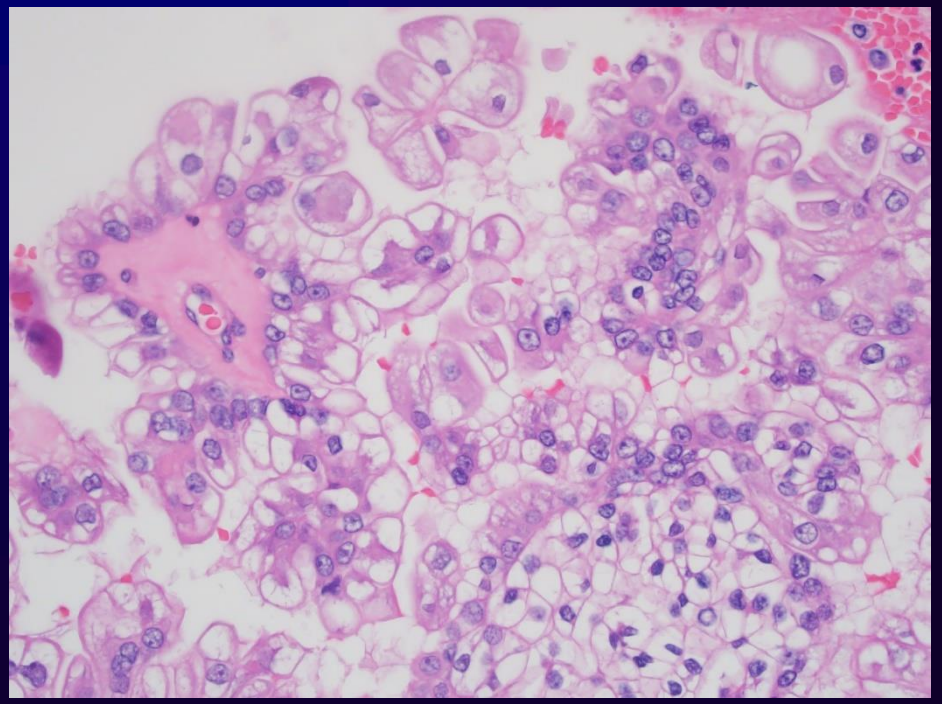


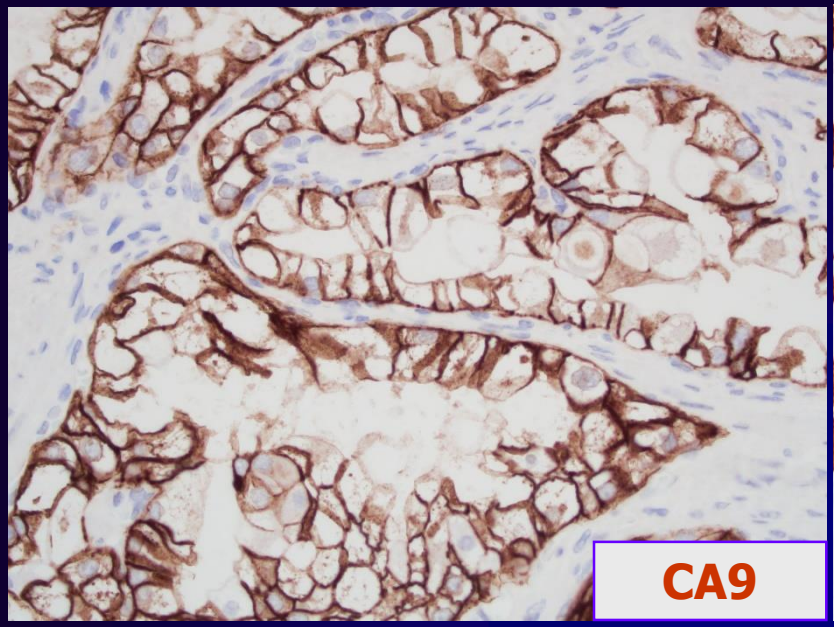
Case 12. 35 y-o patient with tuberous sclerosis complex (TSC)

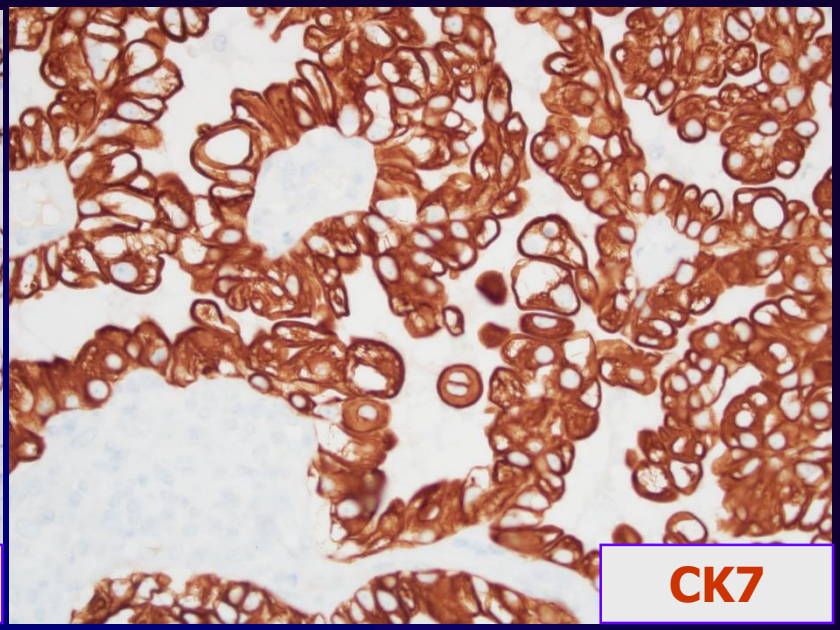


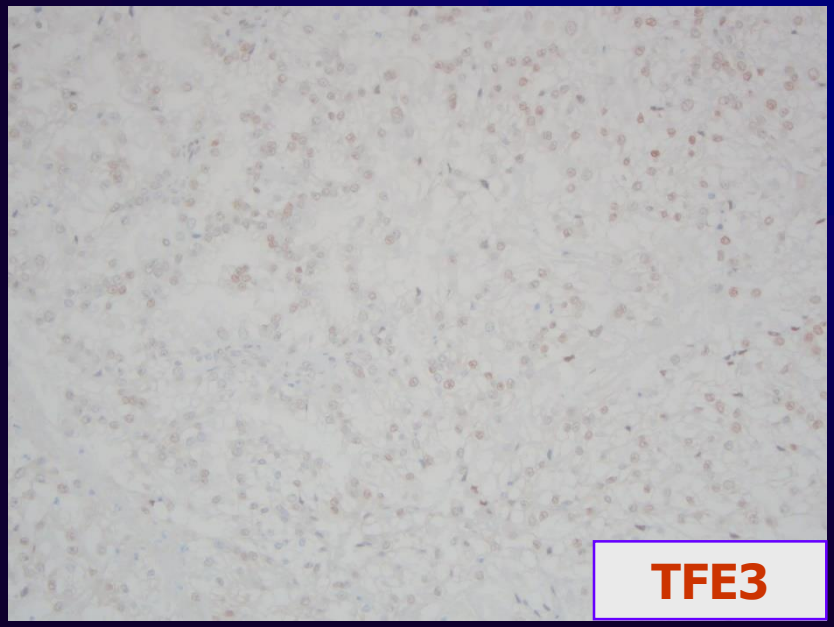
TSC associated RCC
Special subtype?

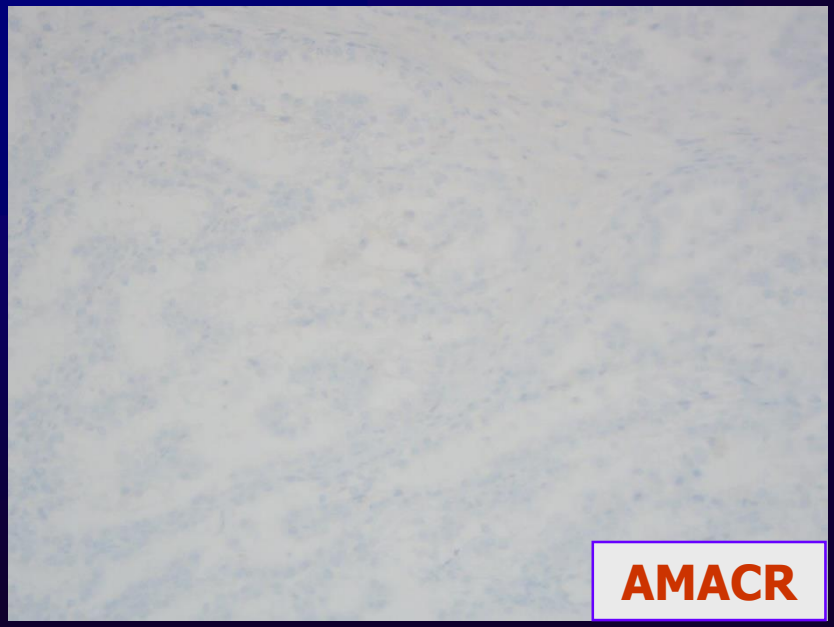





CA9


CK7


TFE3


AMACR

List of Terminology Changes in the Kidney

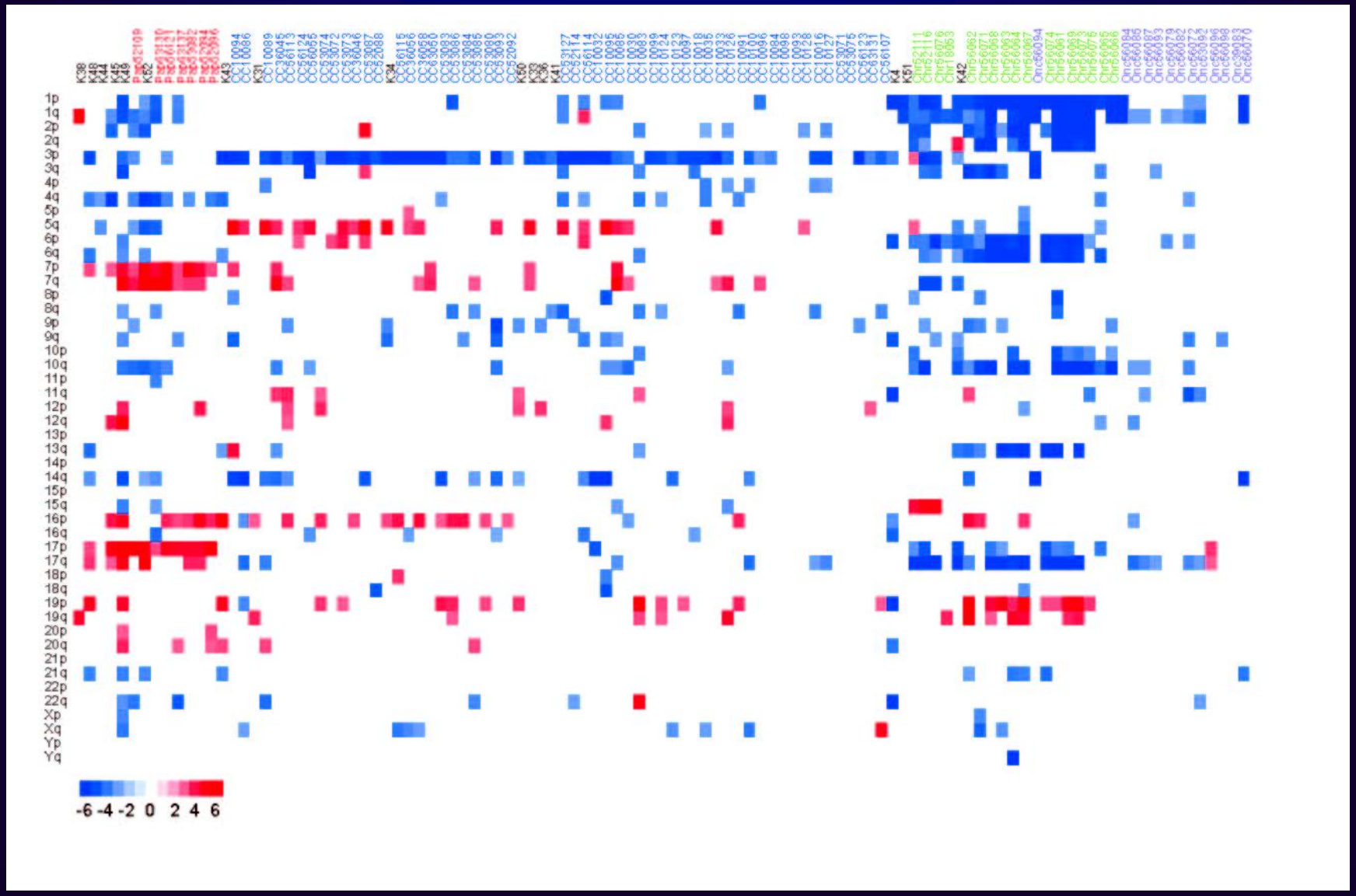
2004 WHO	2016 WHO
None	Tubulocystic RCC
None	Acquired cystic disease-associated RCC
None	Clear cell papillary RCC
None	Hereditary leiomyomatosis-RCC associated RCC (Fumarate hydratase mutation)
Multilocular cystic RCC	Multilocular cystic renal neoplasm of low malignant potential
Renal carcinomas associated with Xp11.2 translocation/TFE3 gene fusions	MiT family translocation RCC TFE3 (Xp11), TFEB t(6;11)
Papillary adenoma ($\leq$ 0.5 cm)	Papillary adenoma ($\leq$ 1.5 cm)
Cystic nephroma Mixed epithelial and stromal tumor	Mixed epithelial and stromal tumor family

The Questions and Challenges

- Is molecular classification of kidney tumors necessary?
- Do we need to classify kidney tumors to more than 100 different subtypes?
- Is the molecular classification lead to better clinical management of kidney tumors?

Genetic Diversity of Kidney Tumors

PapRCC **CCRCC** **ChrRCC** **Onc**



Take home message

- New entities of renal tumors
- New terminology of renal tumors
- Immunohistochemical markers may help differential diagnosis
- Mostly important thing is to know the clinical impact of our diagnosis

Northwestern Memorial Hospital