Updates in the WHO Classification of Adult Renal Neoplasia

(including differential diagnoses and diagnostic pitfalls)

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Disclosures

- I have no disclosures related to renal tumors.

WHY today's topic?

- Kidney tumors rock!
- Recent updates/changes in the WHO for GU Tumors, especially subtypes of Renal Cell Carcinoma (RCC)
- The differential diagnosis of renal oncocytic tumors is growing; important to be aware of new entities
- Morphologic overlap between various renal cell tumor subtypes; distinction may affect follow-up, prognosis and treatment options

Lecture Objectives

1. Be familiar with the new and emerging entities in the WHO Classification of adult renal epithelial tumors.

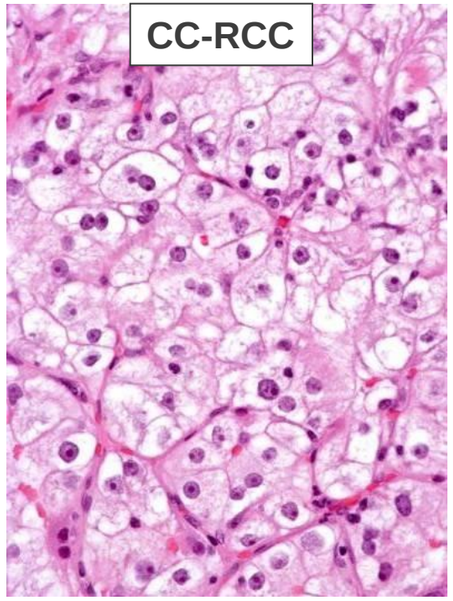
2. Use morphologic features to form a differential diagnosis for adult renal epithelial tumor subtypes.

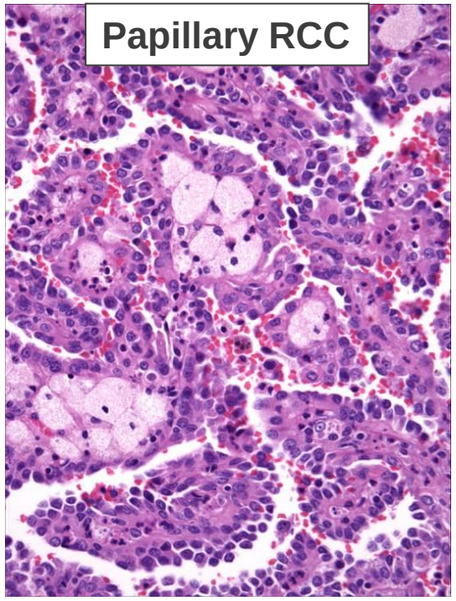
3. Use ancillary studies to more accurately diagnose adult renal epithelial tumor subtypes.

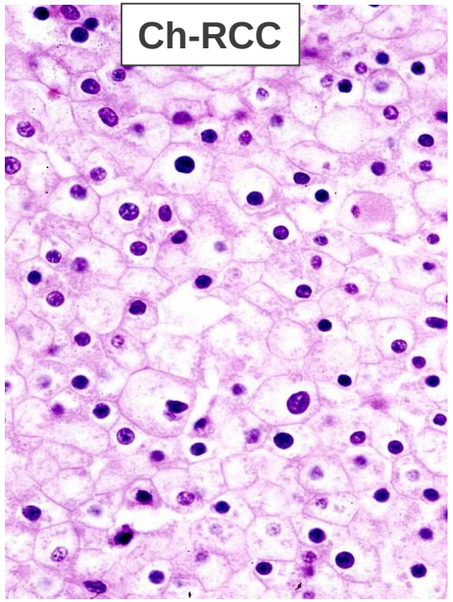
4. Be familiar with (a subset of) kidney tumors that are associated with familial syndromes.

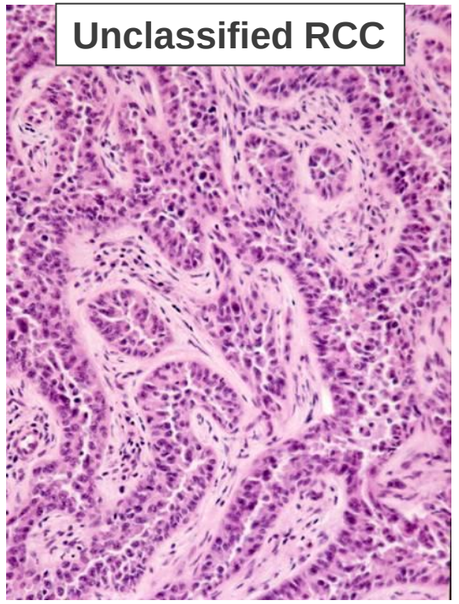
5. Address pitfalls/outliers in renal epithelial tumor diagnoses.

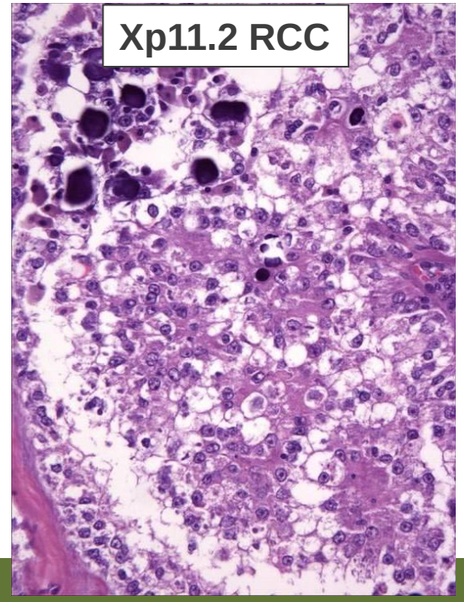
Renal Cell Carcinoma – A Heterogeneous Group of Carcinomas

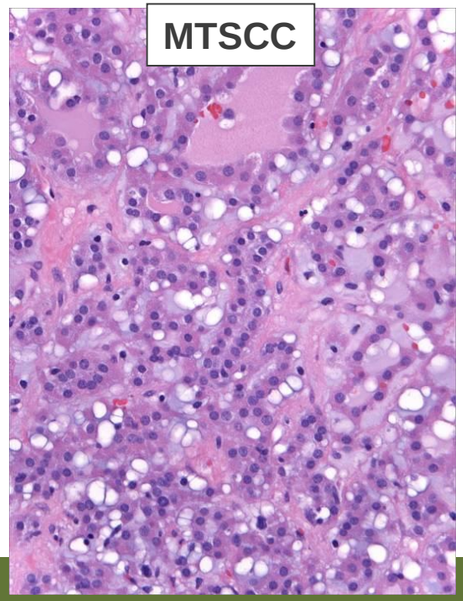


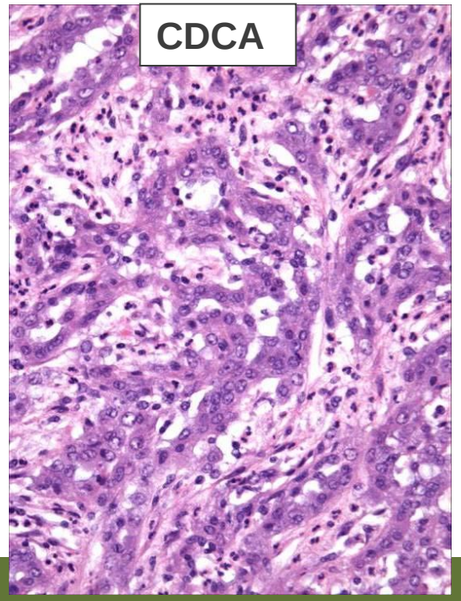


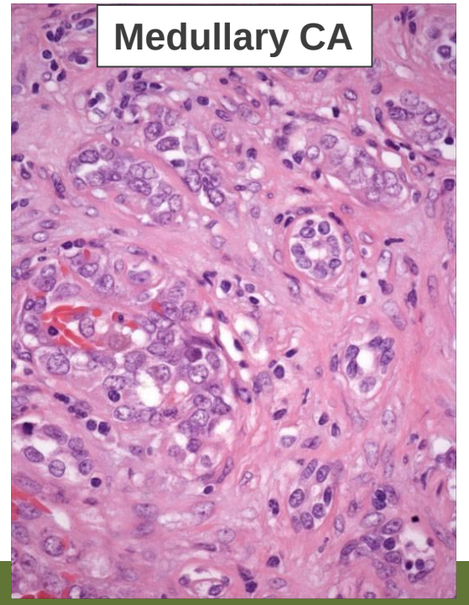


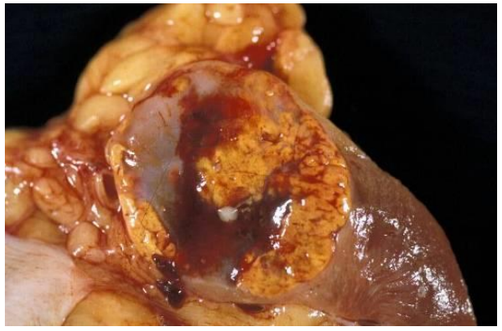


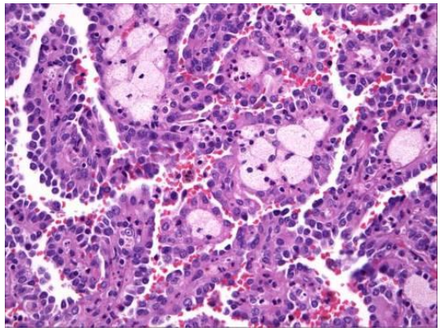


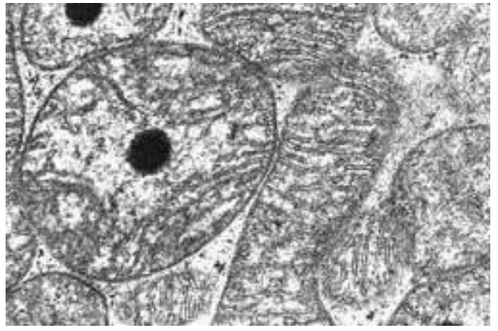


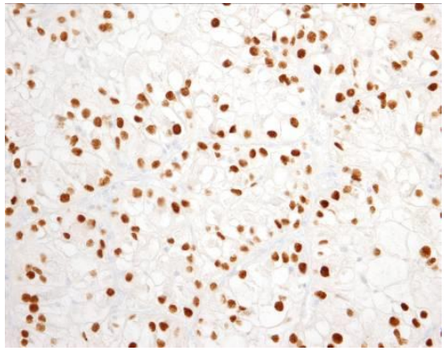


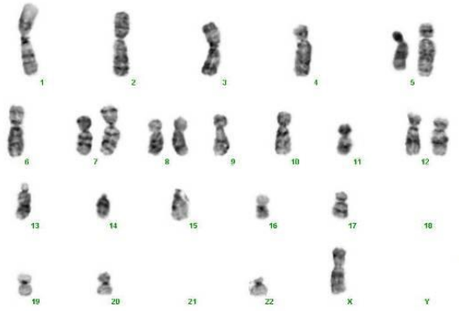


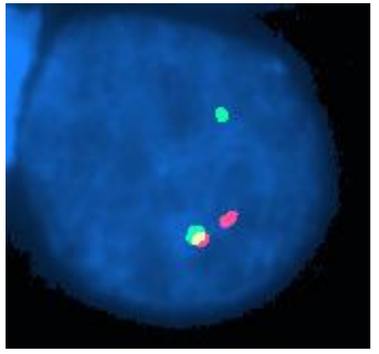


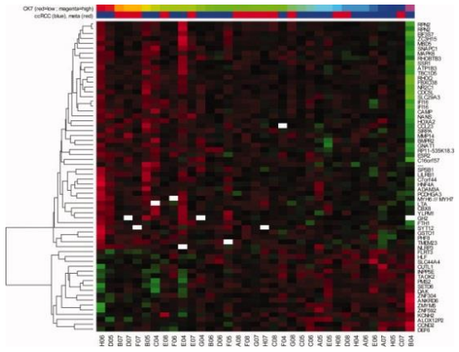


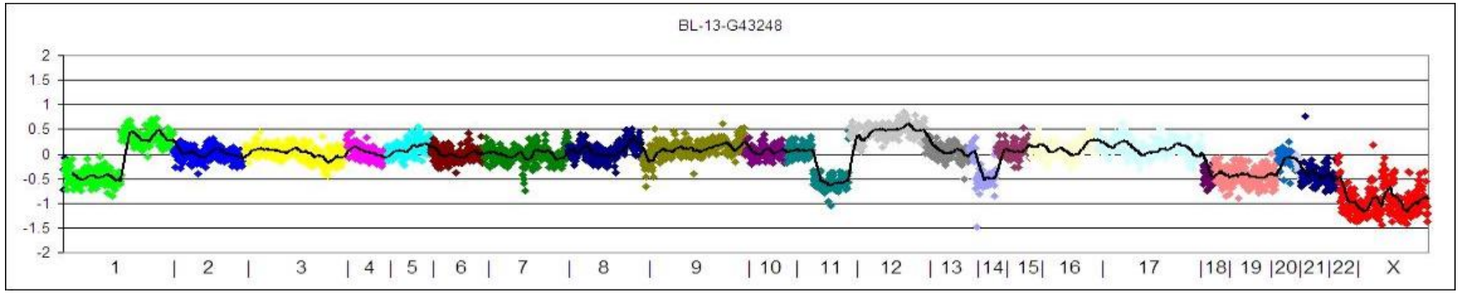












The Cancer Genome Atlas

Understanding genomics to improve cancer care

WHO Classification of Adult RCCs

1st / 2nd Edition

- Clear Cell/Conventional RCC
- Papillary RCC
- Chromophobe RCC
- Collecting Duct Carcinoma / Renal Medullary CA
- Unclassified RCC

3rd Edition (2004)

- Clear Cell/Conventional RCC
- Multilocular Clear Cell RCC
- Papillary RCC
- Chromophobe RCC
- Unclassified RCC
- Xp11.2 (TFE3) Translocation RCC
- Collecting Duct Carcinoma
- Renal Medullary Carcinoma
- Mucinous Tubular& Spindle Cell CA
- RCC associated with Neuroblastoma

4th Edition (2016)

- Clear Cell/Conventional RCC
- Multilocular cystic renal neoplasm, LMP
- Papillary RCC
- Chromophobe RCC
- Unclassified RCC
- MiTF (TFE3/TFEB) Translocation RCC
- Collecting Duct Carcinoma
- Renal Medullary Carcinoma
- Mucinous Tubular and Spindle Cell CA
- Tubulocystic Carcinoma
- Clear Cell Tubulopapillary RCC/RAT
- Succinate Dehydrogenase Deficient RCC
- Hereditary Leiomyomatosis and RCC
- Acquired cystic disease – associated RCC

Food for thought…..

SPLITTERS versus LUMPERS

Splitters - those who tend to break things into parts (deconstruction)
Lumpers - those who tend to put parts together into a whole (construction)

*https://blog.cabreraresearch.org/the-systems-rule

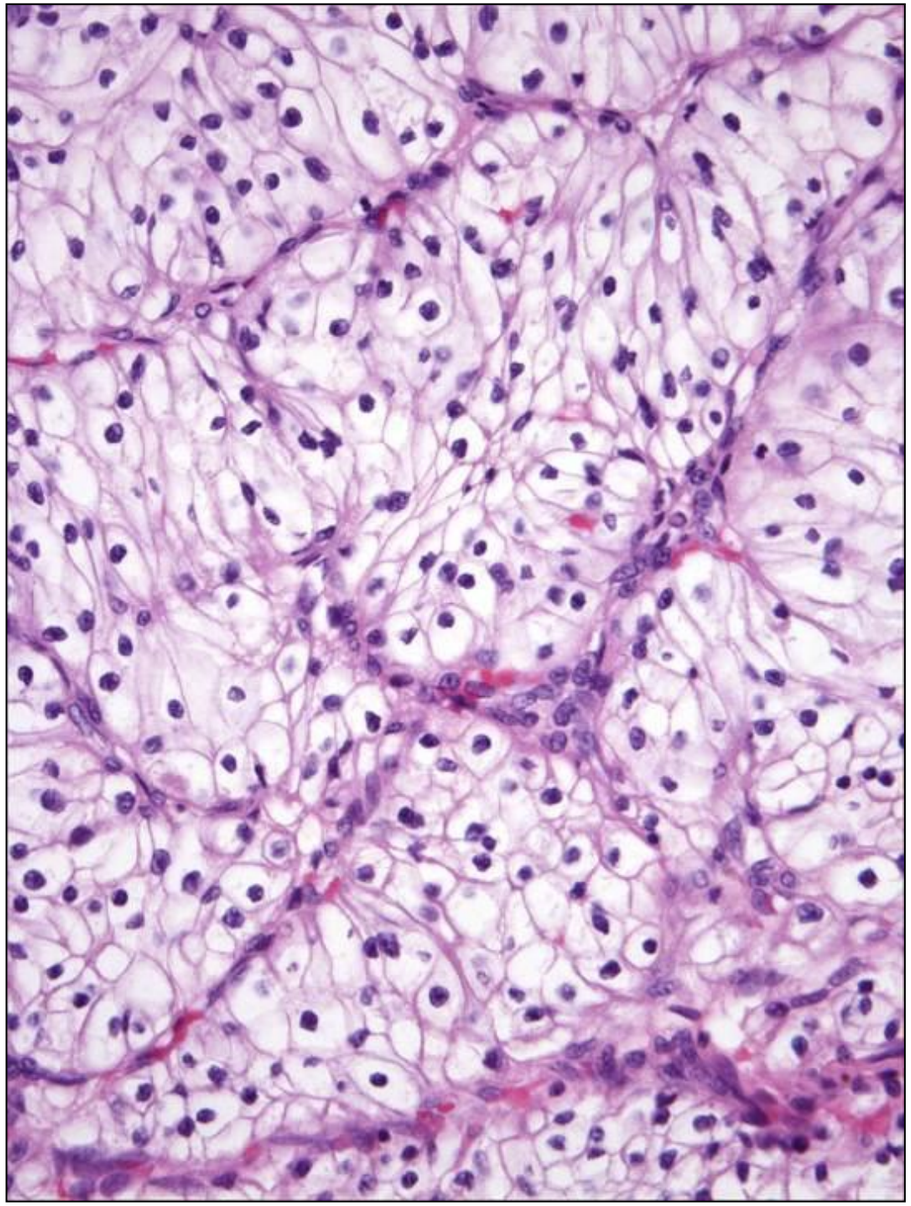
Excerpt from the book: Systems Thinking Made Simple, Chapter 3

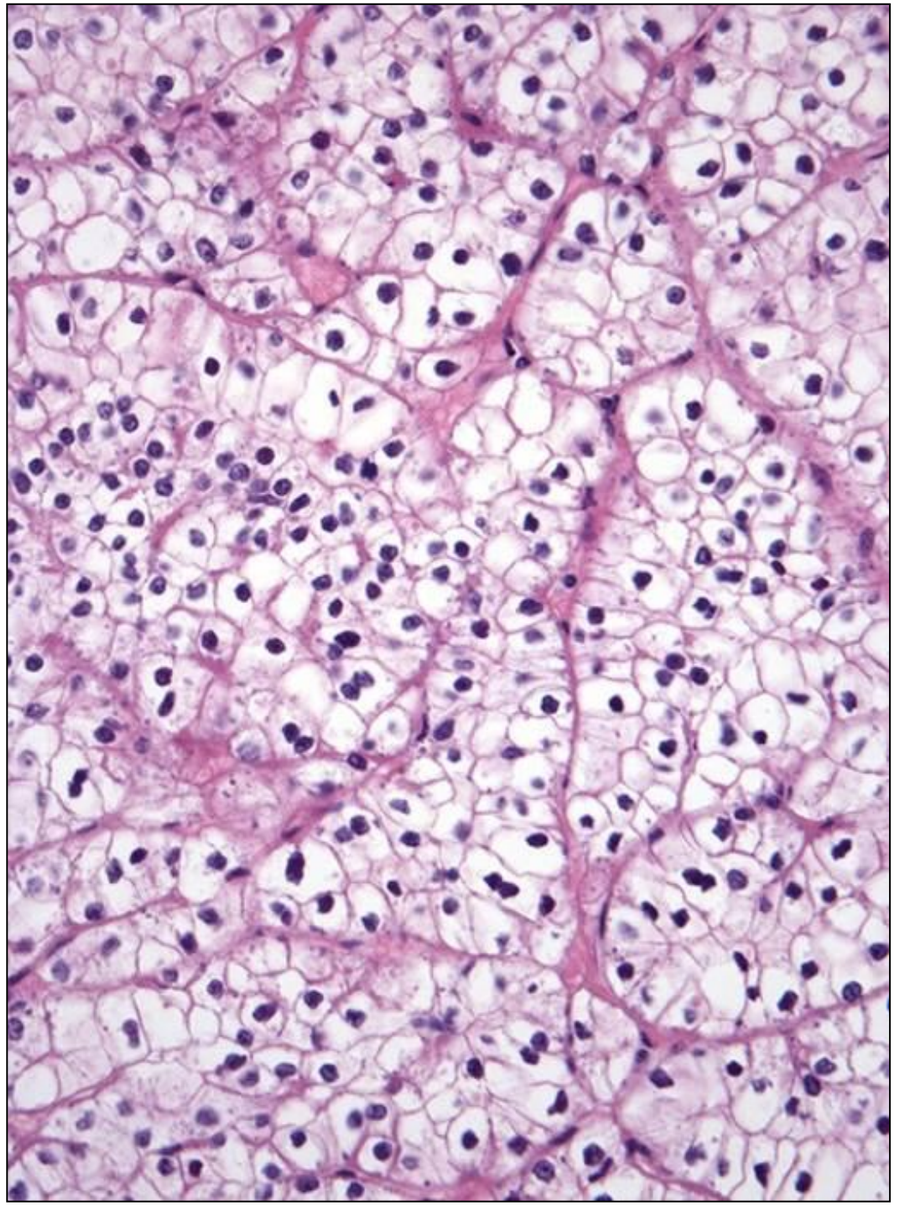
PROS AND CONS – LUMPER VS SPLITTER

- PROS FOR LUMPING
  - Easier to diagnose
  - Fewer ancillary studies required for diagnosis
  - May not significantly alter treatment options (i.e., CC vs non-CC vs medullary based tumors)

- PROS FOR SPLITTING
  - Demonstrate true pathologic differences
  - Better understanding of pathophysiology
  - Directed treatment options / clinical trial design; including tumor with familial association

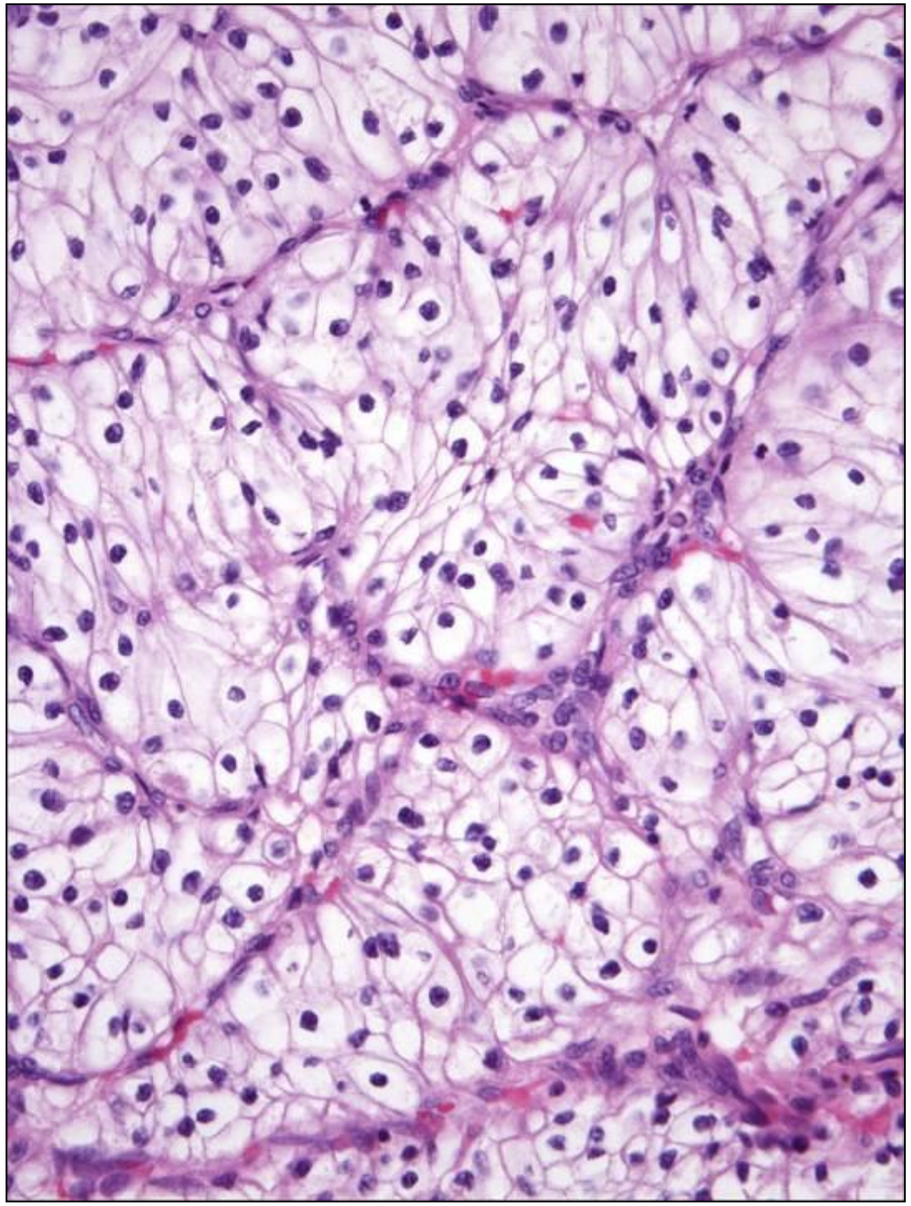
Clear Cell Renal Tumors*



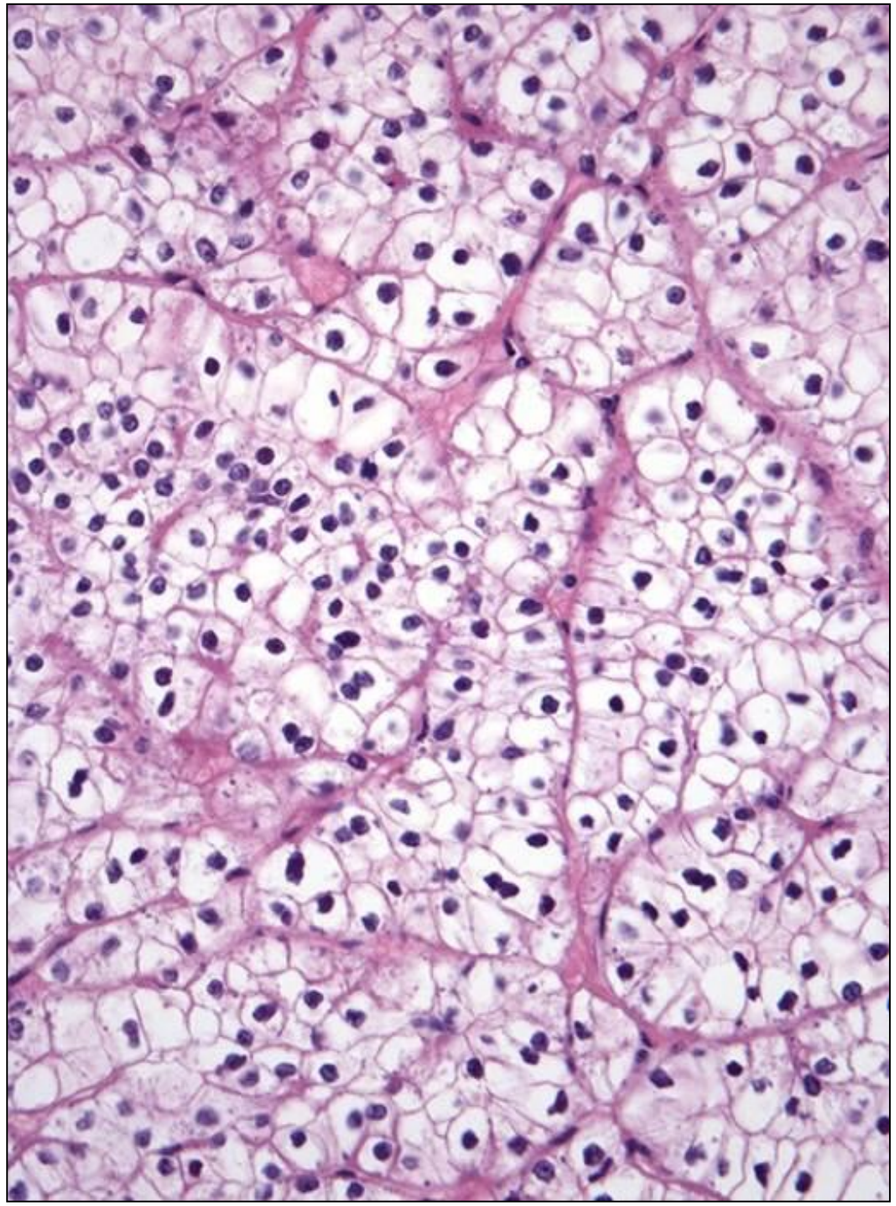


*Lumper

Clear Cell RCC*



Xp11.2 (TFE3) RCC*



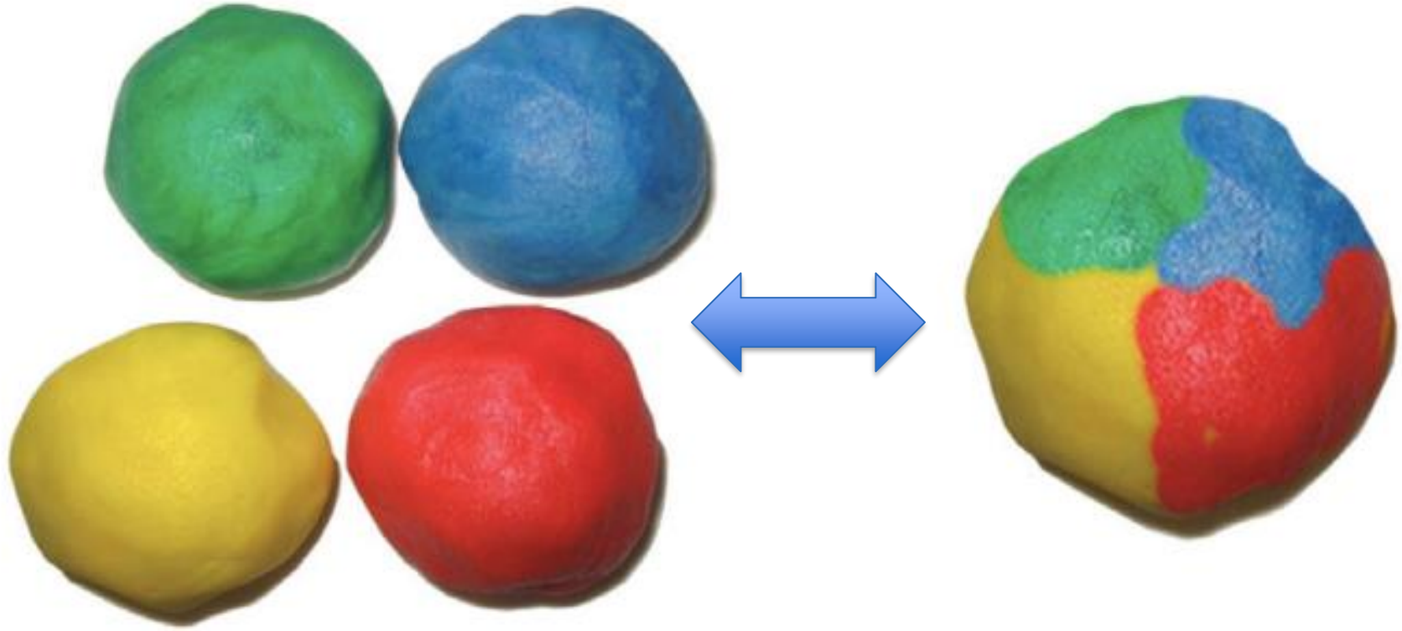
*Splitter

Kidney Cancer Classification - Examples

	Morphology/ Cytology	**Architecture**	**Immuno-staining**	**Tumor Location**	**Chromosomal Change**	**Molecular Alterations**
Qualifier Example	Clear cells	Papillary	CK7+	Renal medulla	Multiple chromosome loss	TSC/mTOR
Tumor Types	CCRCC, TFE3 RCC, CCTP-T, RCC-FMS, TCEB1 RCC	PRCC, TFE3 RCC, CCTP-T, FH-def RCC	PRCC, MTSCC CCTP-T, RCC-FMS, ChRCC, LOT	RMC, CDCA, ALK RCC, FH def-RCC, UNC RCC	MTSCC, CDCA, ChRCC	RCC-FMS, ESC, TCEB1 RCC, LOT, EVT
Select References	Trplov K & Hes O, Histopathol 2019; Robila V et al, Cancer Cytopathol 2019; Srigley JR et al, AJSP 2013; Goyal R et al, Arch Pathol Lab Med 2013	Caliò et al, Pathol 2020; Akhtar M et al, Adv Anat Pathol 2019; Taylor AS, Arch Pathol Lab Med 2019	Kim M, Cacners 2020; Reuter VE et al, AJSP 2014; Amin MB et al, AJSP 2014;	Baniak et al, Arch Pathol Lab med 2020; Singh JA et al, Pathol Int 2018	Liu YJ et al, Hum Pathol 2020; Yang C et al, Mod Pathol, 2020; Beaumont M, Hum Pathol 2019; Sadimin ET et al, Histopathol 2017; Zhao M et al, Diag Pathol 2015;	Williamson SE et al, AJSP 2020; Alaghehbandan R et al, Cancers 2020; Inamura K, Int J Mol Sci 2017; Manley BJ & Hakimi AA, Curr Opin Urol 2016; Chen F et al, Cell Rep 2016

Food for thought…..

~~SPLITTERS versus LUMPERS~~



SLUMPERS - people who have the ability to both construct or synthesize ideas, and also to deconstruct ideas to further our understanding (“systems thinker”)

*https://blog.cabreraresearch.org/the-systems-rule

Excerpt from the book: Systems Thinking Made Simple, Chapter 3

WHO Classification, 5th Ed

Clear cell renal tumours
Clear cell RCC
Multilocular cystic renal neoplasm of LMP

Papillary renal tumours
Renal papillary adenoma
Papillary RCC

Oncocytic and chromophobe renal tumours
Oncocytoma of the kidney
Chromophobe RCC
Other oncocytic tumours of the kidney

Collecting duct tumours
Collecting duct carcinoma

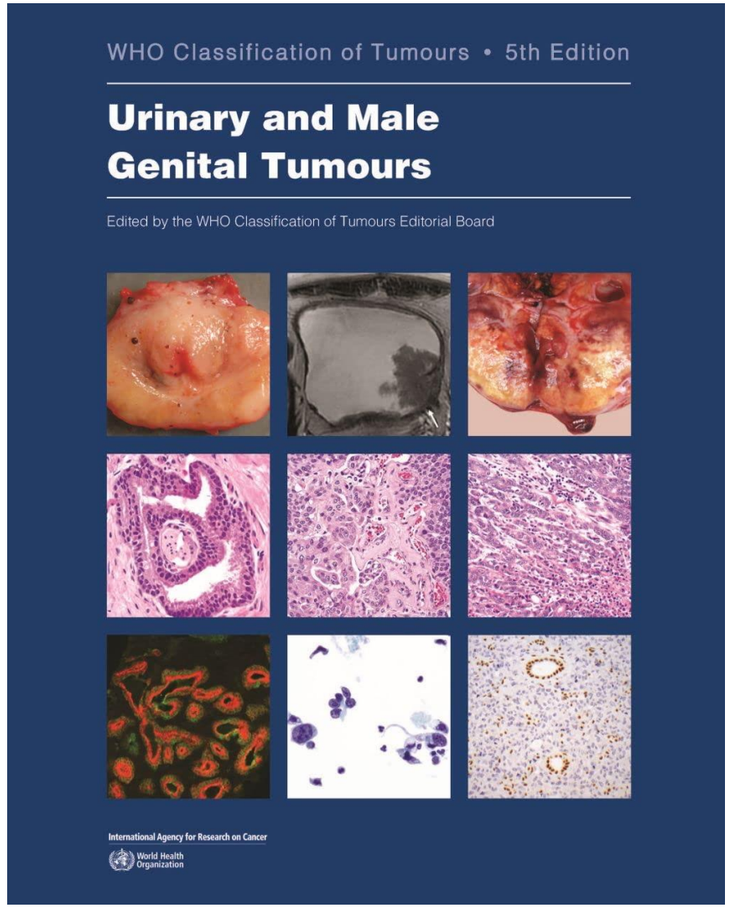
Other renal tumours
Clear cell (tubulo)papillary renal cell tumour
Mucinous tubular and spindle cell CA
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated RCC
Eosinophilic solid and cystic RCC
Renal cell carcinoma NOS

Molecularly defined renal CAs
TFE3-rearranged RCC
TFEB-rearranged RCC
ELOC (formerly TCEB1)-mutated RCC
FH (fumarate hydratase)-deficient RCC
SDH (succinate dehydrogenase)-deficient RCC
ALK-rearranged RCC
SMARCB1-deficient Renal Medullary CA

WHO Updates in Kidney Pathology*

Major Updates:

- **Reorganization of tumor types ➔**
  - “molecularly defined”
  - “other renal tumors”
- **‘Downgraded’ one RCC subtype to a benign neoplasm**
- **Included three new RCCs (from prior emerging group of tumors)**
- **Officially removed the Type I/II designation for PRCC**

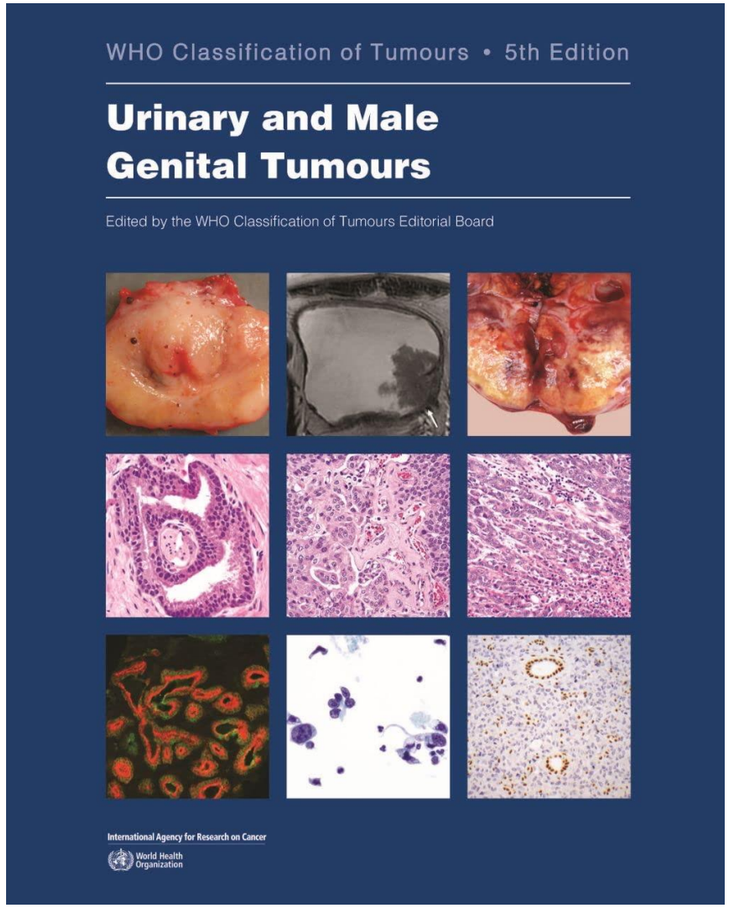


*published in 2022

WHO Updates in Kidney Pathology*

Minor Updates:

- **New set of emerging entities**
- **Included an “other oncocytic tumors of the kidney” category (includes emerging entities)**
- **Includes ‘subtypes’ of PRCC (some emerging entities)**
- **Changed “unclassified” to NOS**
- **Officially changed HLRCC-Associated RCC to “FH-deficient RCC” (to reflect that some may be secondary to a somatic mutation)**

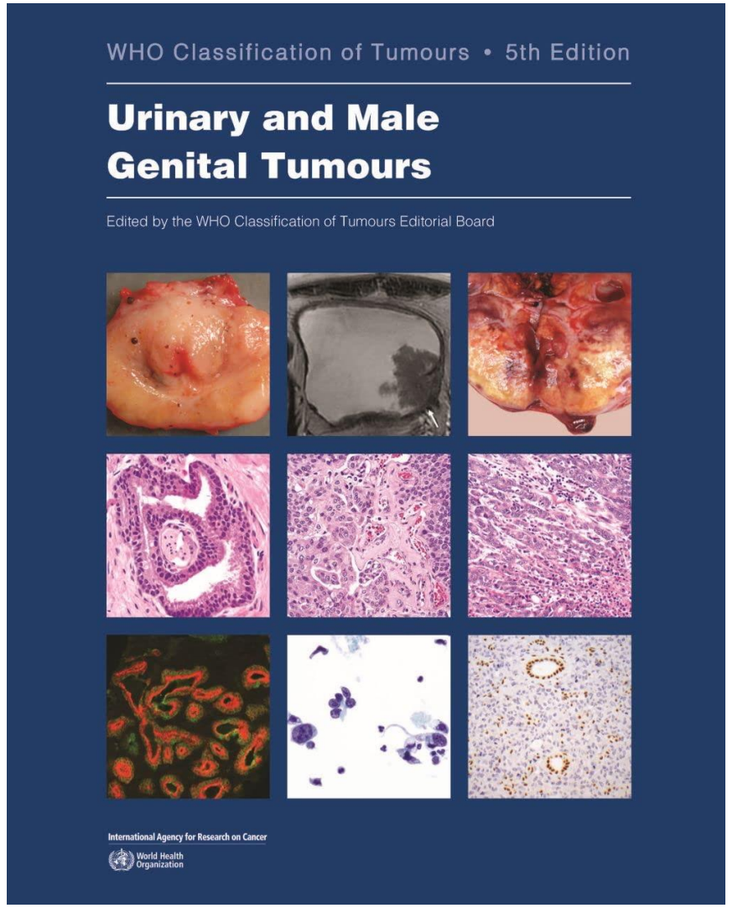


*published in 2022

WHO Updates in Kidney Pathology*

<u>Unresolved Issues</u>:

- **Grading of specific RCCs (ie, ChRCC)**
- **Multiple emerging entities**



*published in 2022

Emerging Entitles / Tumors that Require Additional Research

- CCRCC with giant cells and emperipolesis
- RCC with fibromyomatous stroma (FMS)
- Biphasic (alveolar/squamoid) PRCC
- Papillary renal cell neoplasm with reverse polarity
- Biphasic hyalinzing psammomatous RCC (with NF2 mutations)
- Warthin-like PRCC
- Solid PRCC
- Pigmented microcystic ChRCC
- Hybrid oncocytic tumor (HOT) / hybrid oncocytic chromophobe tumor (HOCT)
- Low grade oncocytic tumor (LOT)
- Eosinophilic vacuolated tumor (EVT)
- Renal Neoplasia Occurring Post-Chemotherapy / Radiation in Pediatric Patients
- Atrophic Kidney-Like Lesion

Existing and Emerging Subtypes of Renal Tumors

Modern Pathology
https://doi.org/10.1038/s41379-021-00779-w

ARTICLE

New developments in existing WHO entities and evolving molecular concepts: The Genitourinary Pathology Society (GUPS) update on renal neoplasia

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Modern Pathology
https://doi.org/10.1038/s41379-021-00737-6

ARTICLE

Novel, emerging and provisional renal entities: The Genitourinary Pathology Society (GUPS) update on renal neoplasia

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Update #1 ➔ CCTP ‘RCC’ is now Benign

Other renal tumours

Clear cell (tubulo)papillary renal cell tumour*

Mucinous tubular and spindle cell CA

Tubulocystic renal cell carcinoma

Acquired cystic disease-associated RCC

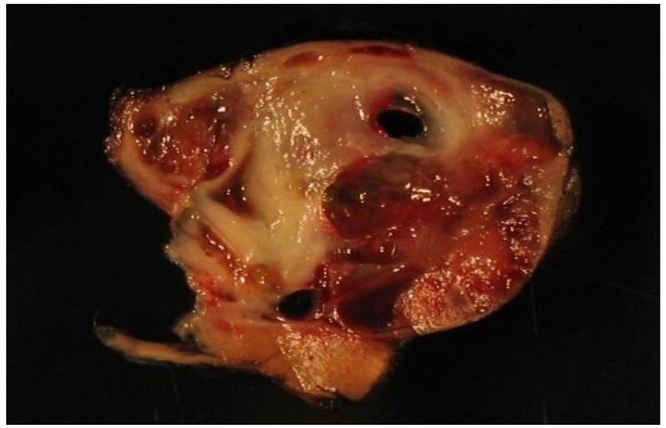
Eosinophilic solid and cystic RCC

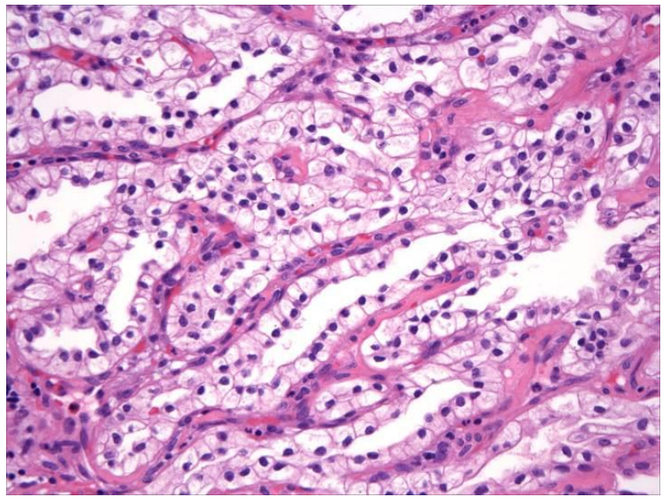
Renal cell carcinoma NOS

*Synonymous with ‘clear cell papillary renal cell tumor’

Clear Cell Tubulopapillary TUMOR

- WHO ➔ Other Renal Tumor Category
- Synonymous WHO name ➔ clear cell papillary tumor
- Previously/currently (mis)diagnosed as CCRCC (or PRCC)
- 4th most common renal tumor subtype
- Associated with ESKD, also sporadic
- Well circumscribed, encapsulated, small (range 0.5-6.0 cm)
- Solid and cystic, may be multifocal and/or bilateral
- Low nuclear grade
- Favorable outcome (hundreds reported in literature)

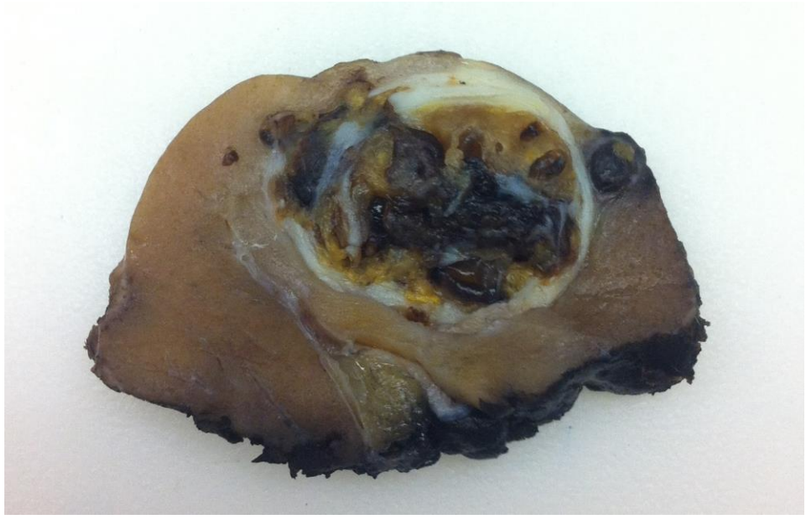


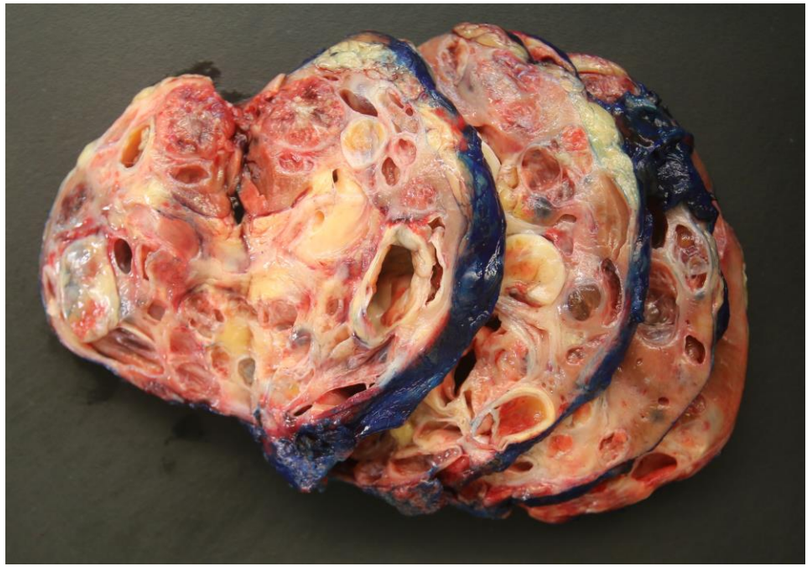


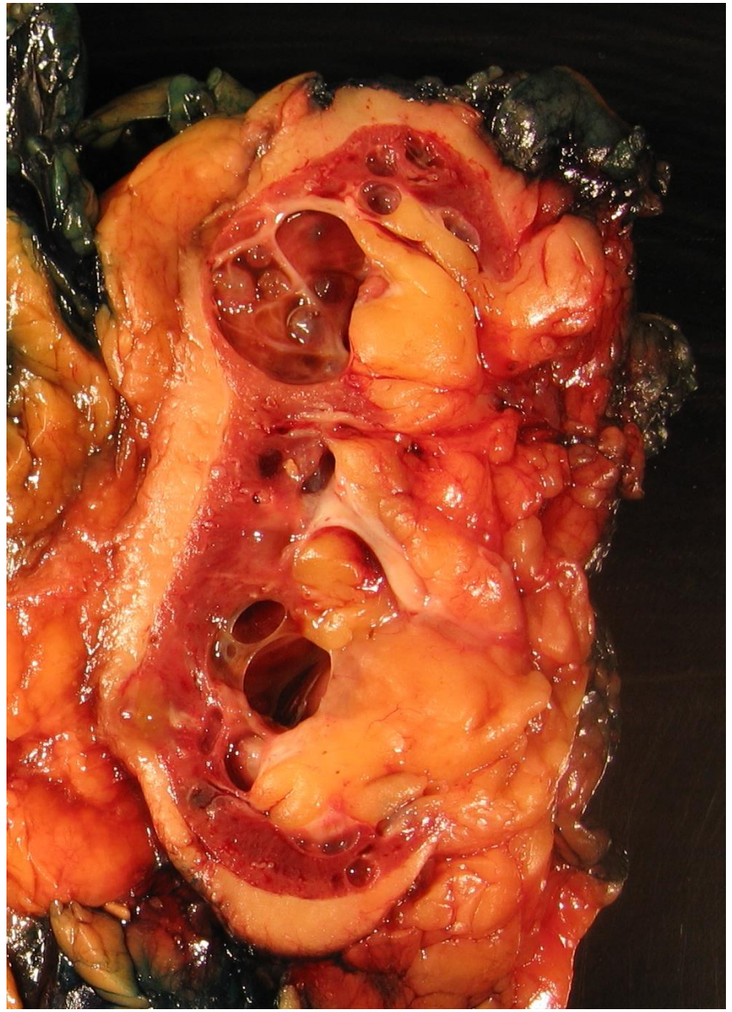
now considered a BENIGN entity!

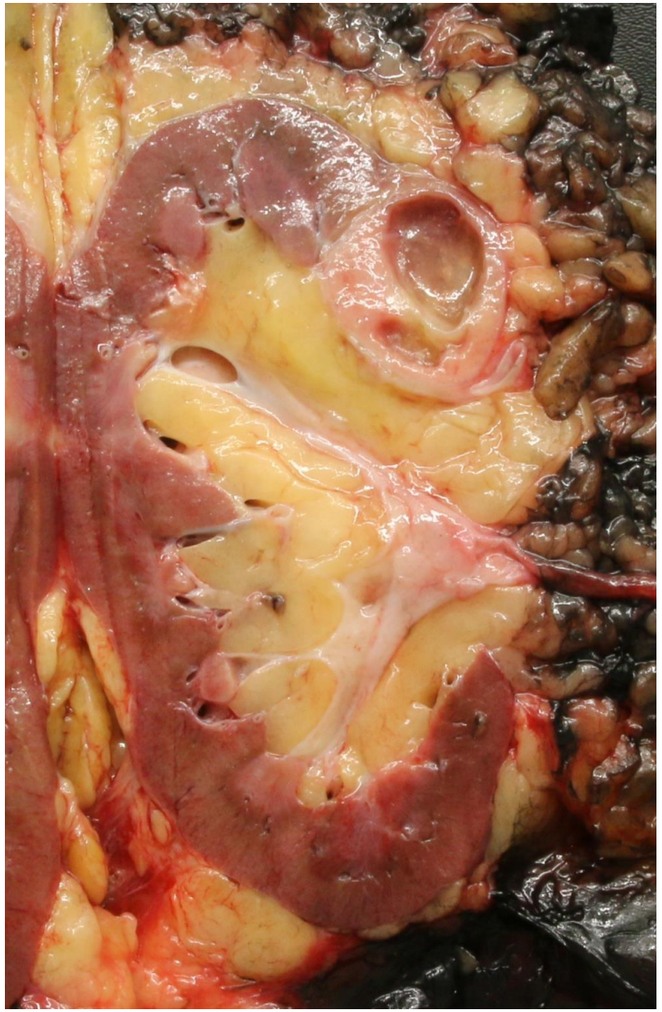
Clinical significance ➔ less fear for the patient, fewer CTs, AS vs ablation vs nephron-sparing surgery

Clear Cell Tubulopapillary TUMOR

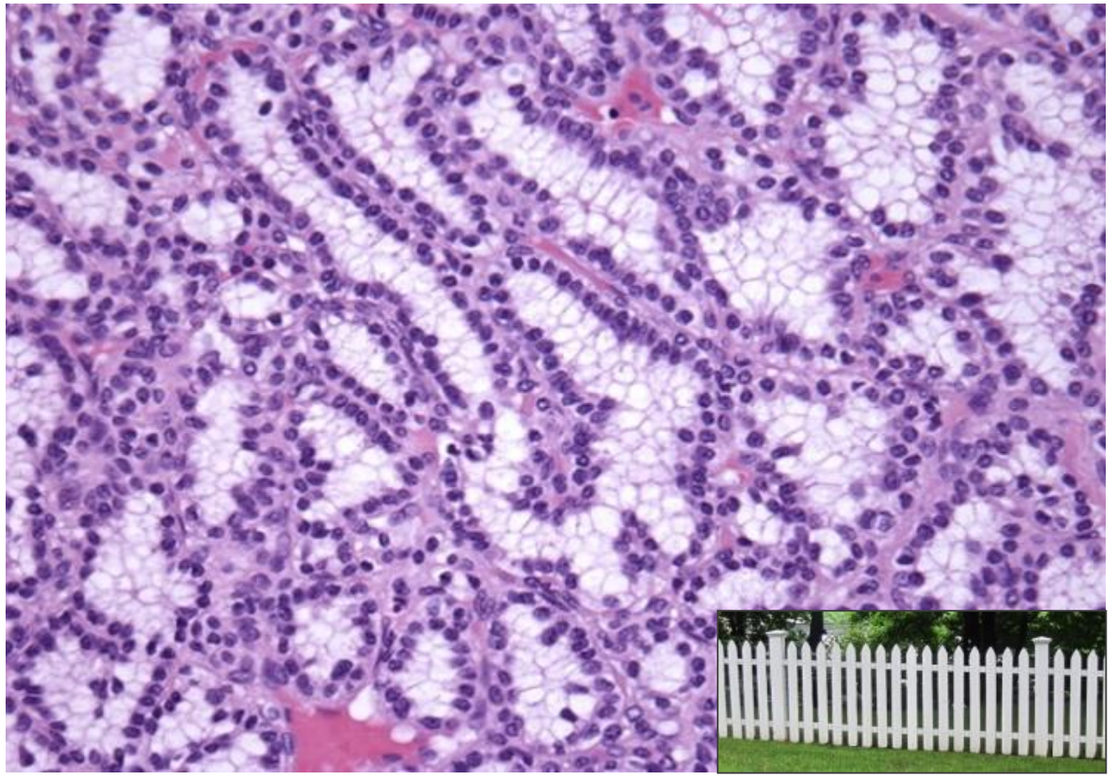


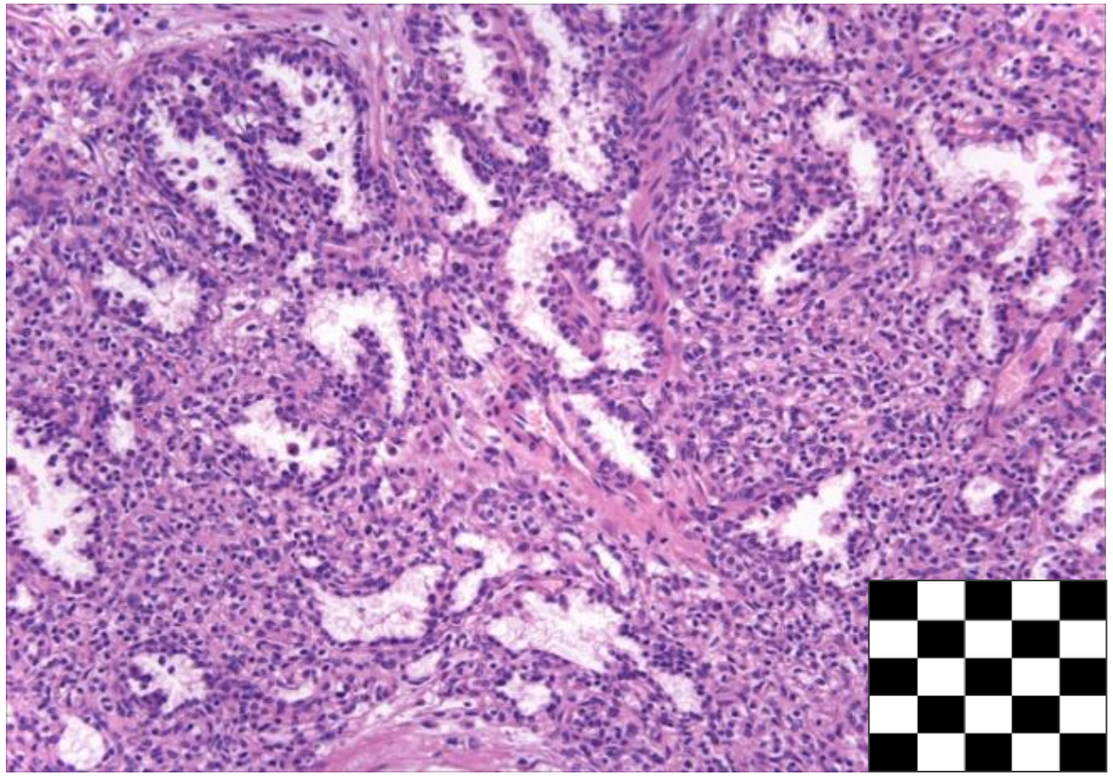






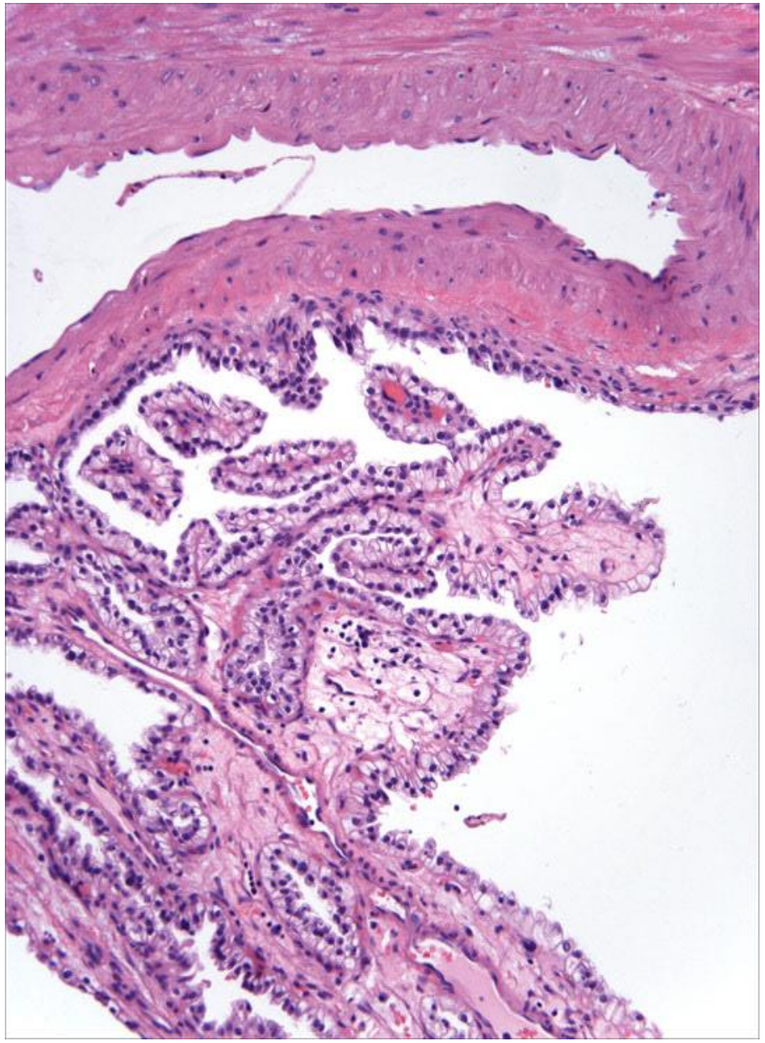
Clear Cell Tubulopapillary Tumor

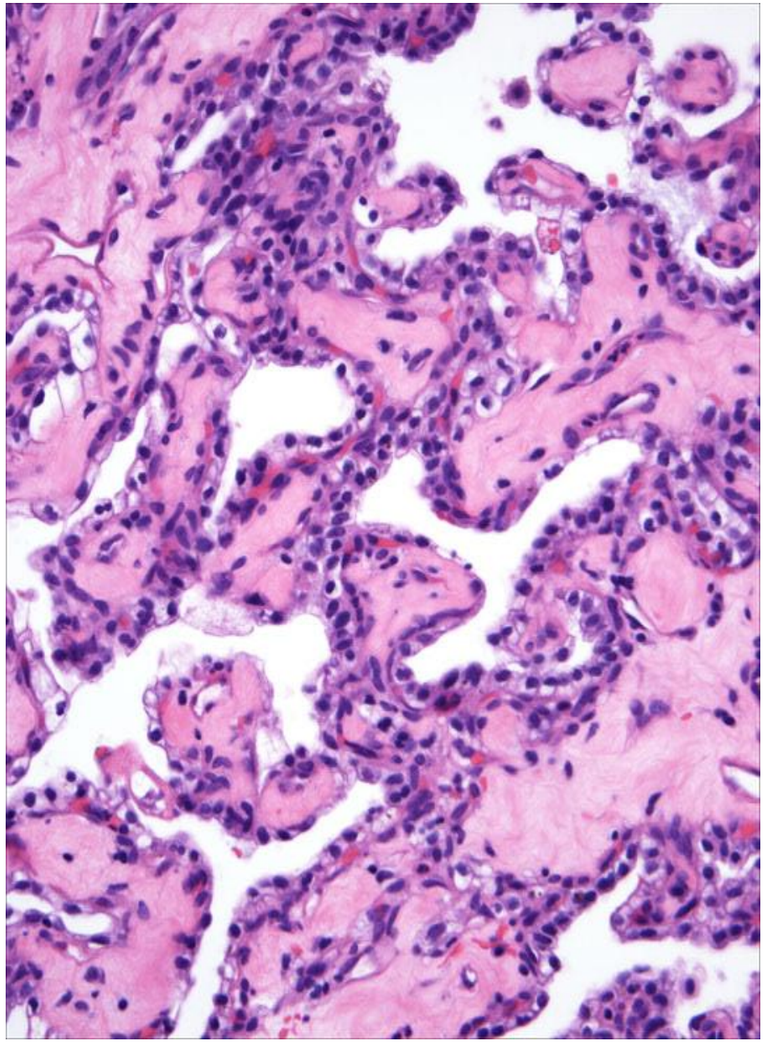


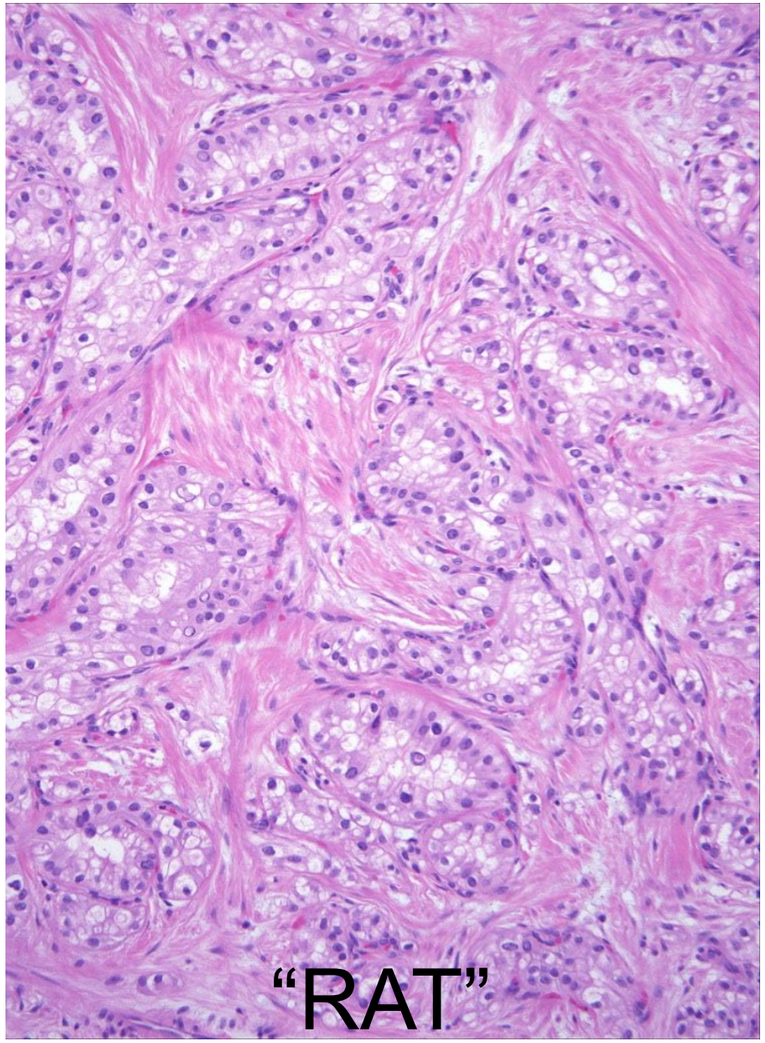


Morphology can vary ➔ tubular, tubulopapillary, solid, biphasic……

Clear Cell Tubulopapillary Tumor

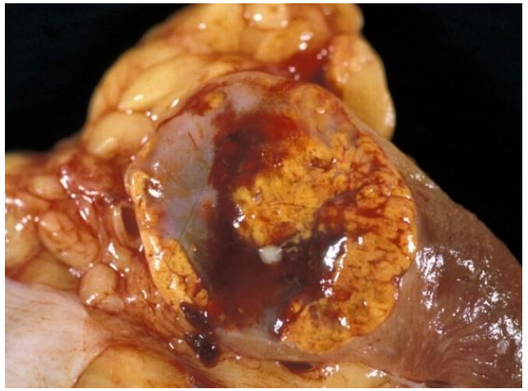


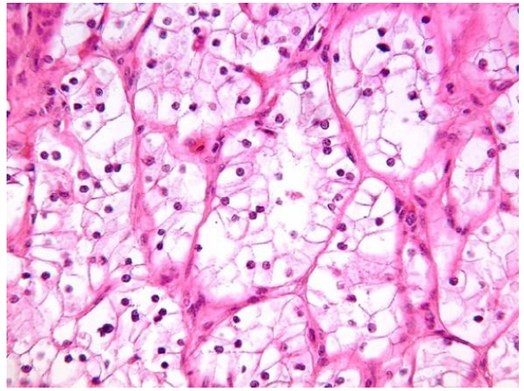


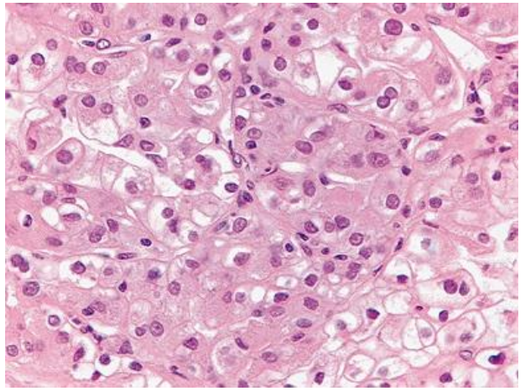


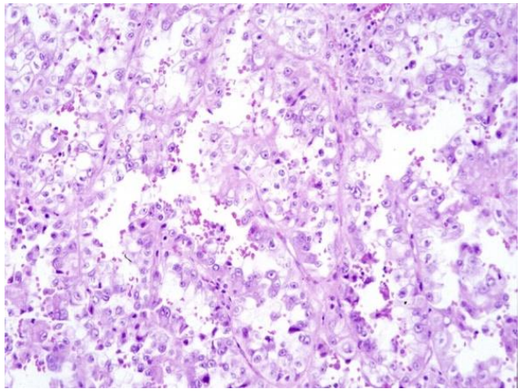
Morphology can vary ➔ Papillary, cystic, tubulocystic, solid, hyalinized, FMS…..

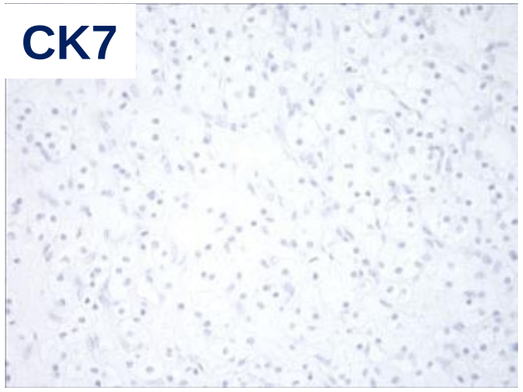
DDx ➔ Clear Cell RCC (~70% of RENs)

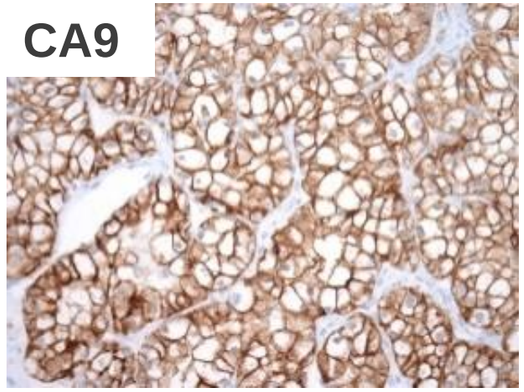


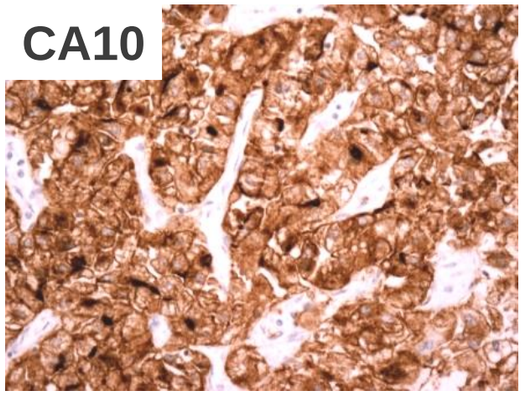


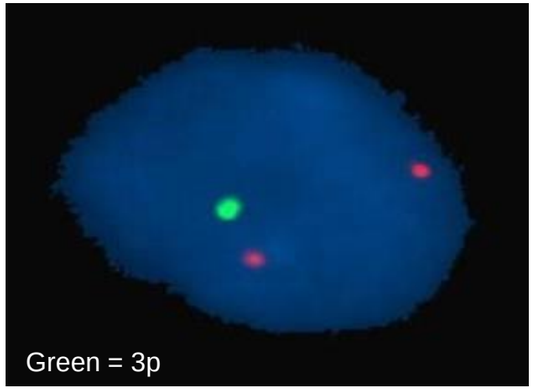










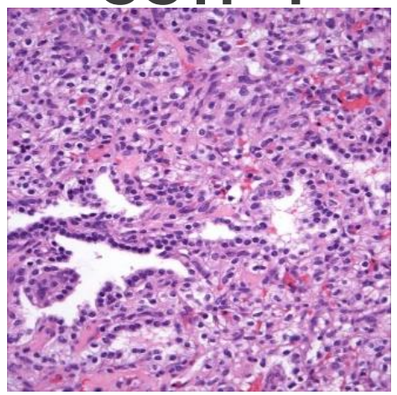


Common gene mutations* – *VHL, PBRM1, SETD2, BAP1, etc*

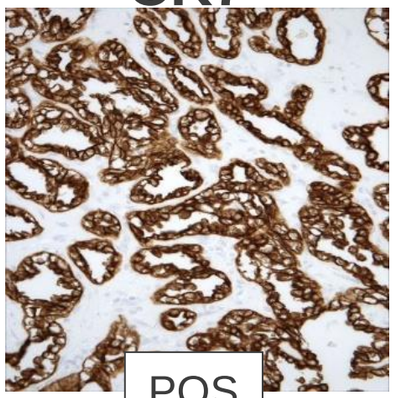
*Manley BJ, Hakimi AA. Molecular profiling of renal cell carcinoma: building a bridge toward clinical impact. *Curr Opin Urol*. 2016;26(5):383-387.

Clear Cell Tubulopapillary Tumor

CCTP-T

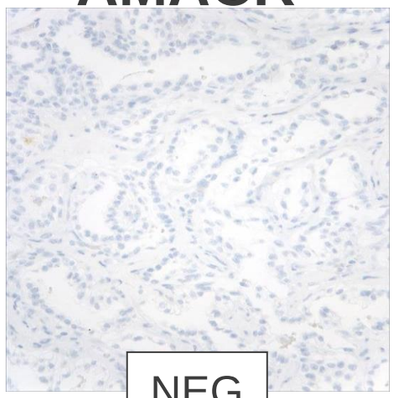


CK7



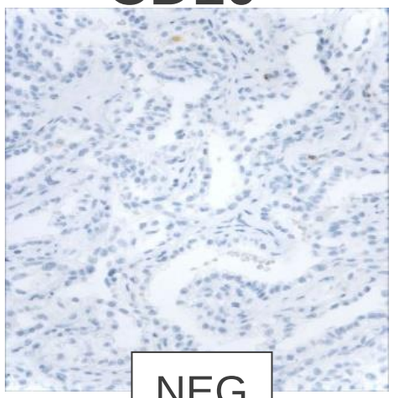
POS

AMACR



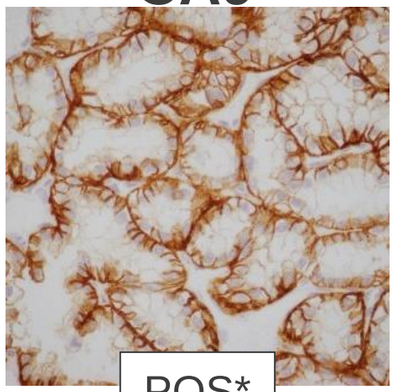
NEG

CD10



NEG

CA9*

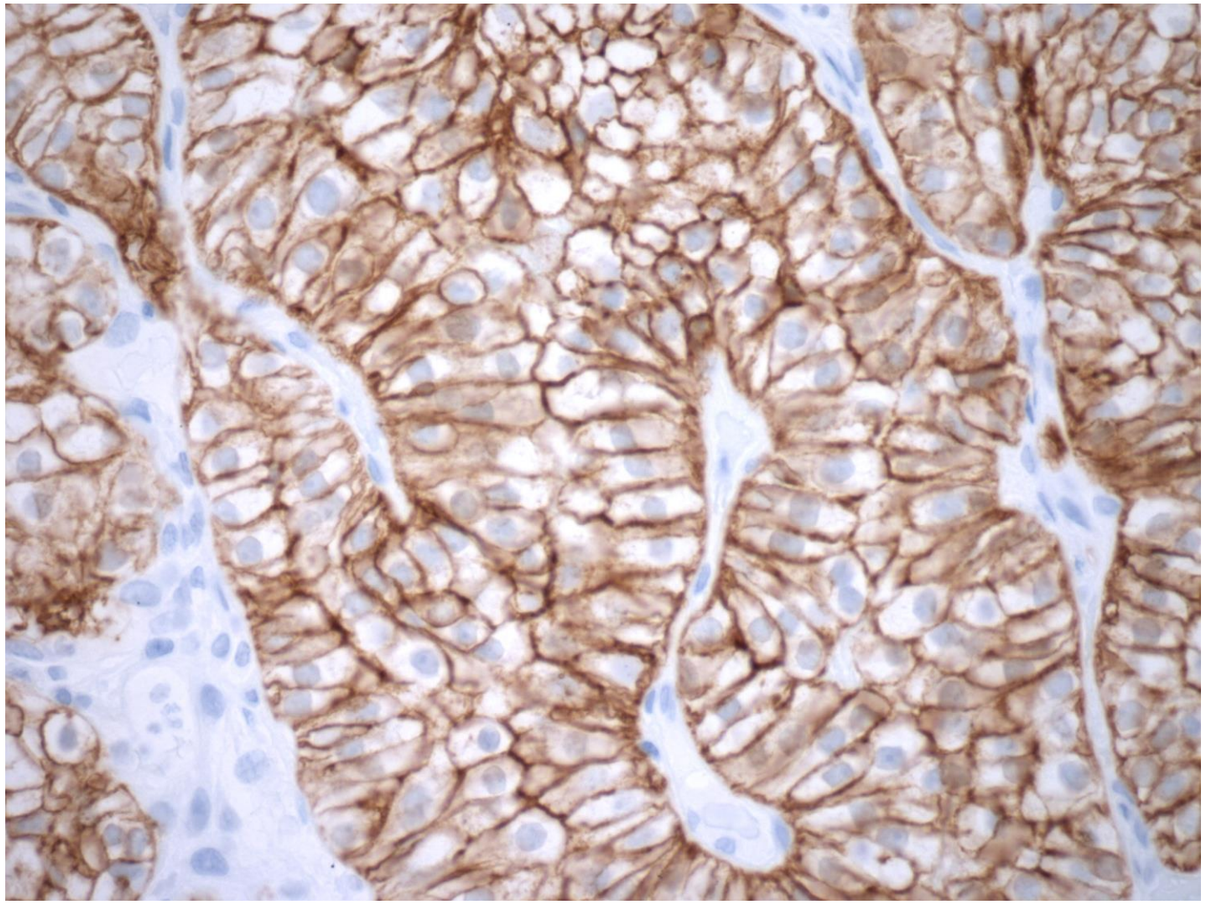


POS*

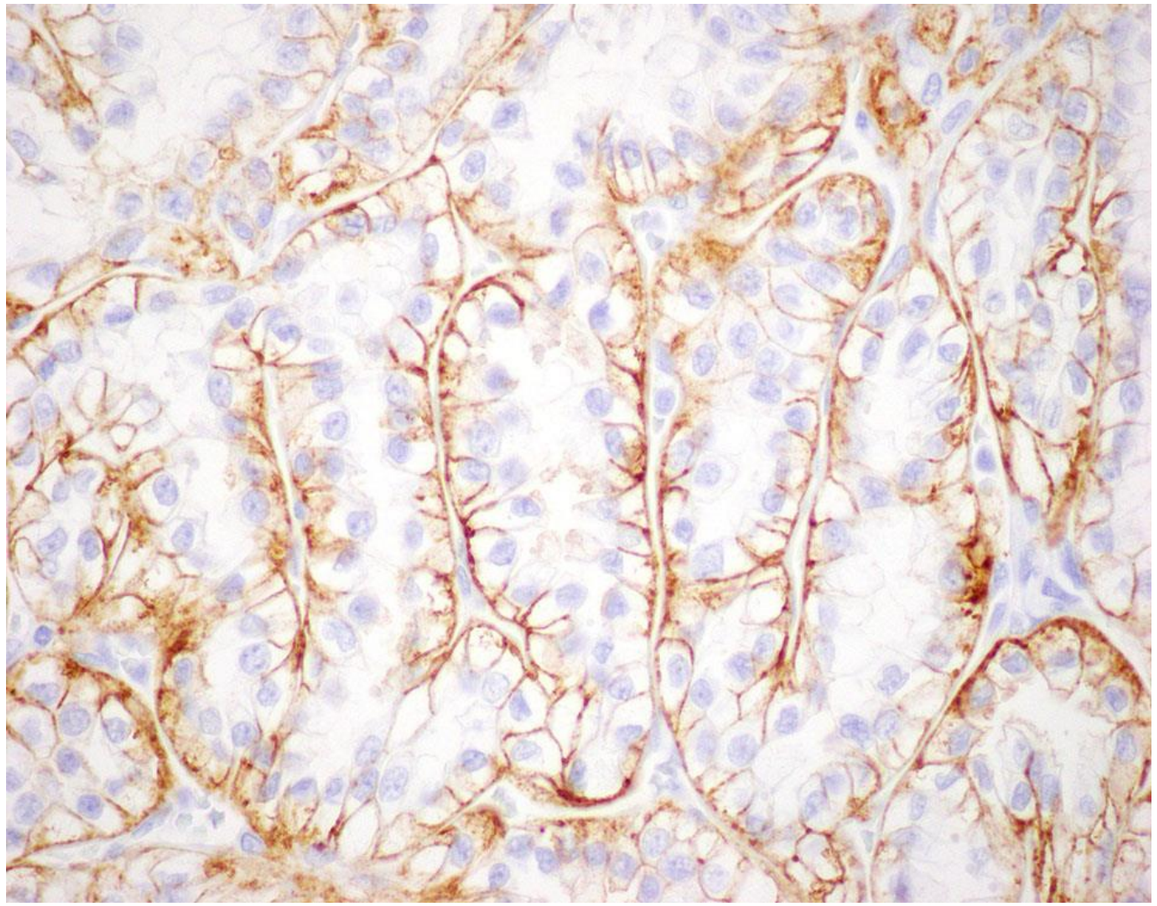
	CK7	AMACR	CD10	TFE3	CAIX	Cytogenetics
CCTP-T	POS	NEG	NEG	NEG	POS*	Diploid
CCRCC	NEG	POS	POS	NEG	POS	3p-

*CUP-LIKE EXPRESSION

CA9 Expression



CCRCC ➔ Box-Like



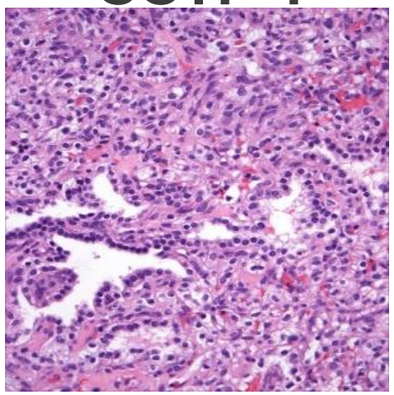
CCTP-T ➔ Cup-Like

Trpkov K, et al. Mod Pathol. 2021 Jul;34(7):1392-1424. PMID: 33664427; Baniak N, et al. Histopathol. 2020 Oct;77(4):659-666. PMID: 32639054; Aydin H et al. Am J Surg Pathol. 2010 Nov;34(11):1608-21. PMID: 20924276.

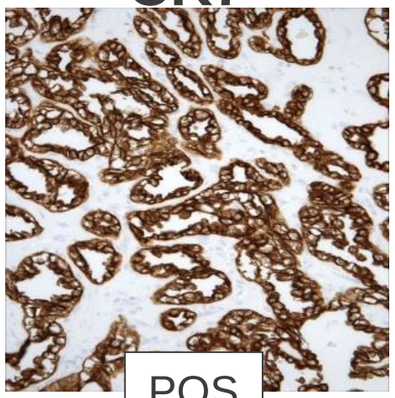
Clear Cell Tubulopapillary Tumor

DDx ➔ CCRCC, PRCC, Translocation RCC, ELOC/TCEB1-mutated RCC

CCTP-T

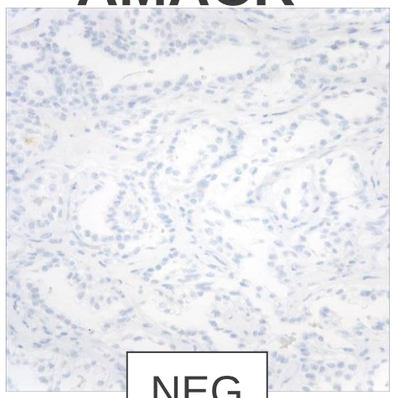


CK7



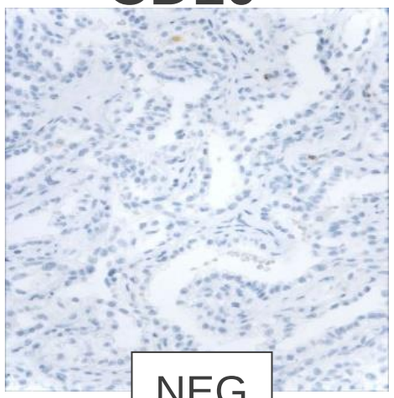
POS

AMACR



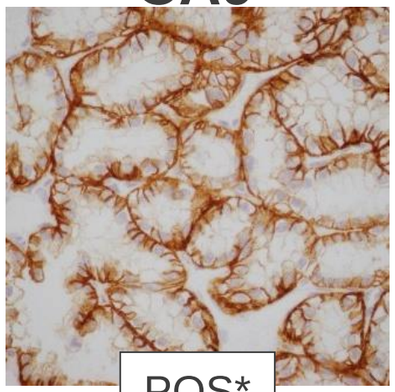
NEG

CD10



NEG

CA9*

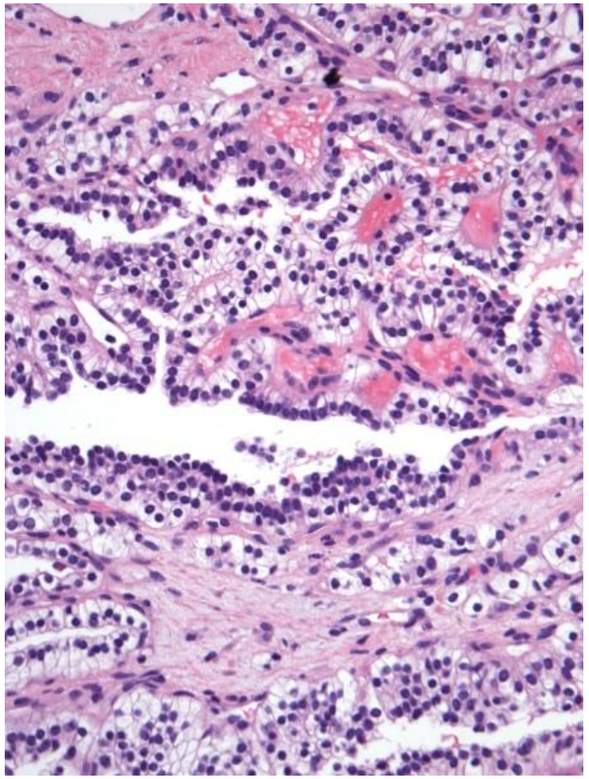


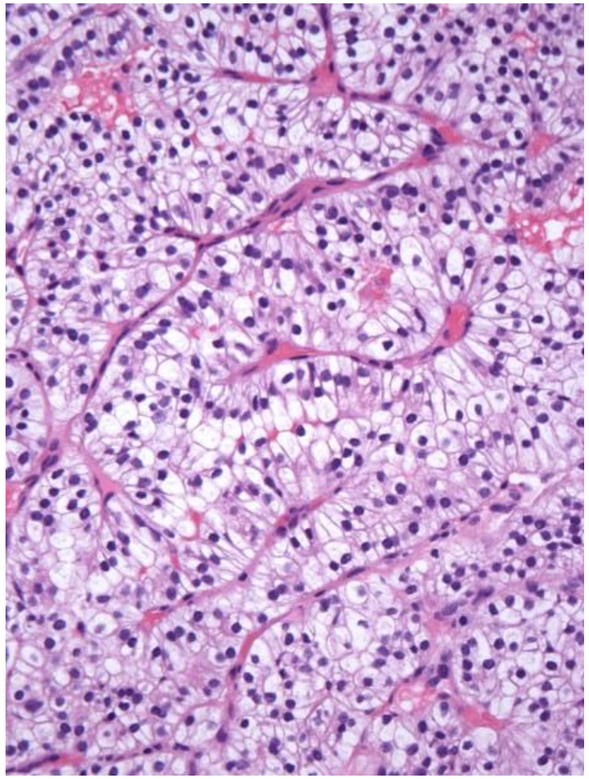
POS*

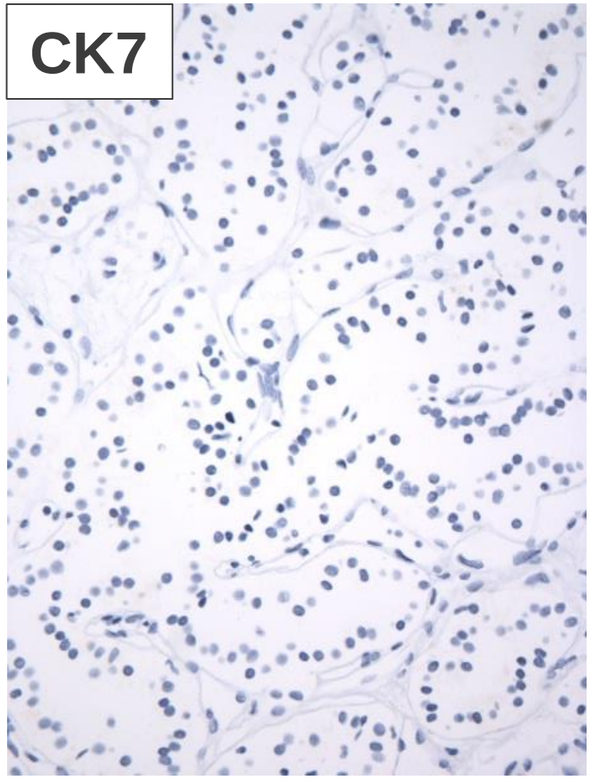
	CK7	AMACR	CD10	TFE3	CAIX	Cytogenetics
CCTP-T	POS	NEG	NEG	NEG	POS*	Diploid
CCRCC	NEG	POS	POS	NEG	POS	3p-
PRCC	POS	POS	POS	NEG	NEG	+7/+17
Tr-RCC	NEG	POS	NEG	POS	NEG	TFE3 translocation
ELOC-RCC	POS	NEG	POS	NEG	POS	Monosomy 8

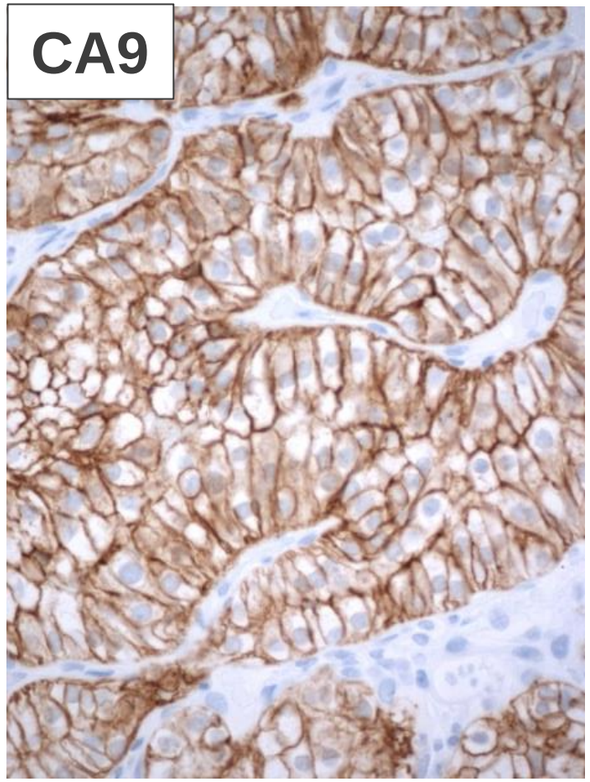
*CUP-LIKE EXPRESSION

Pitfall Alert!
Some CCRCCs have a tubular component





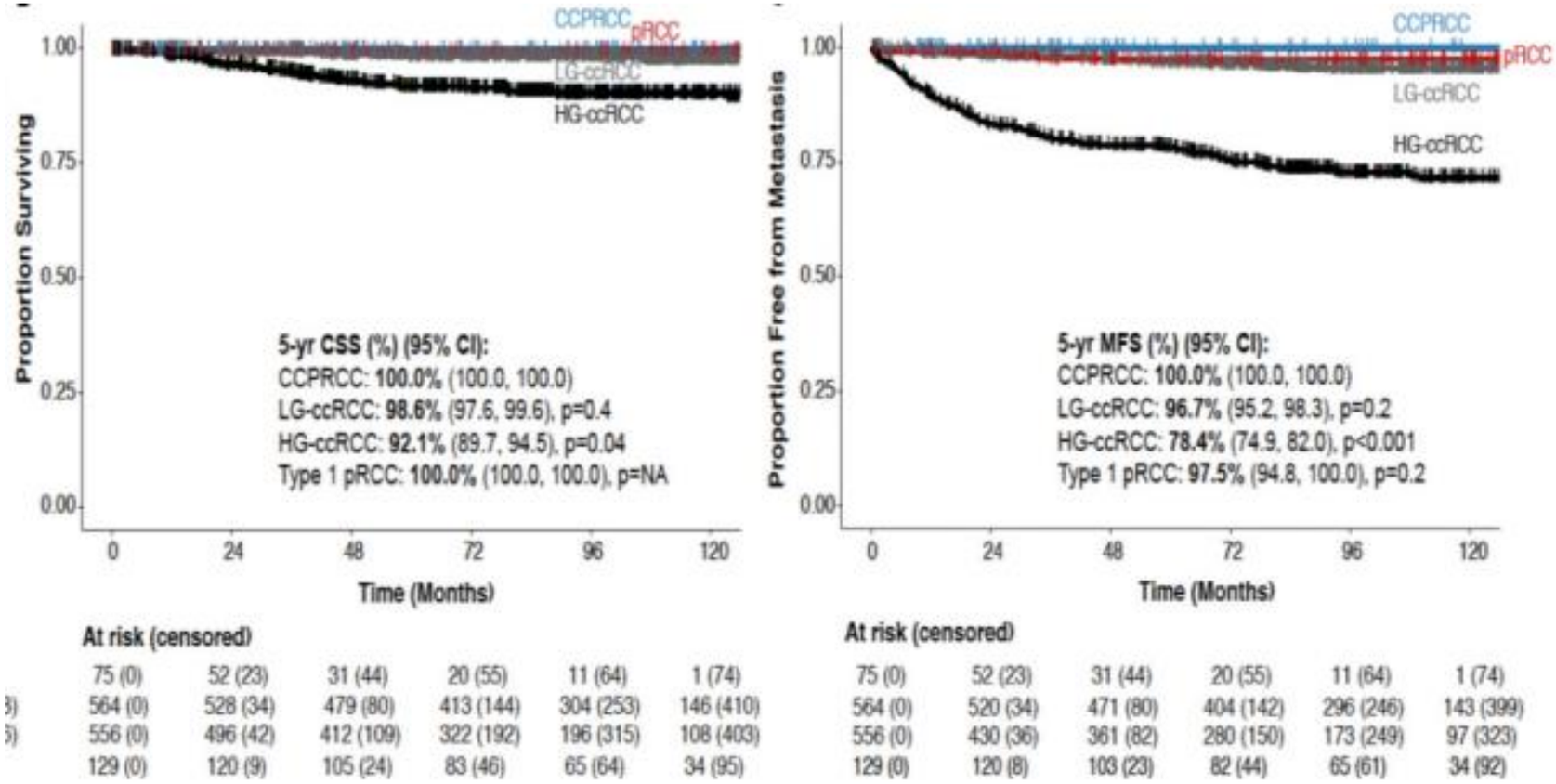




➔ Clear cell RCC

(look for more conventional areas of CCRCC)

CCTP-RT



➔ NOW A BENIGN ENTITY!

Weng S, et al. The Clinicopathologic and Molecular Landscape of Clear Cell Papillary Renal Cell Carcinoma: Implications in Diagnosis and Management. Eur Urol. 2021 Apr;79(4):468-477. PMCID: PMC8327325.

Update #2 ➔ Newly Added Entities

Molecularly defined renal CAs

TFE3-rearranged RCC
TFEB-rearranged RCC
ELOC (formerly TCEB1)-mutated RCC
FH (fumarate hydratase)-deficient RCC
SDH (succinate dehydrogenase)-deficient RCC
ALK-rearranged RCC
SMARCB1-deficient Renal Medullary CA

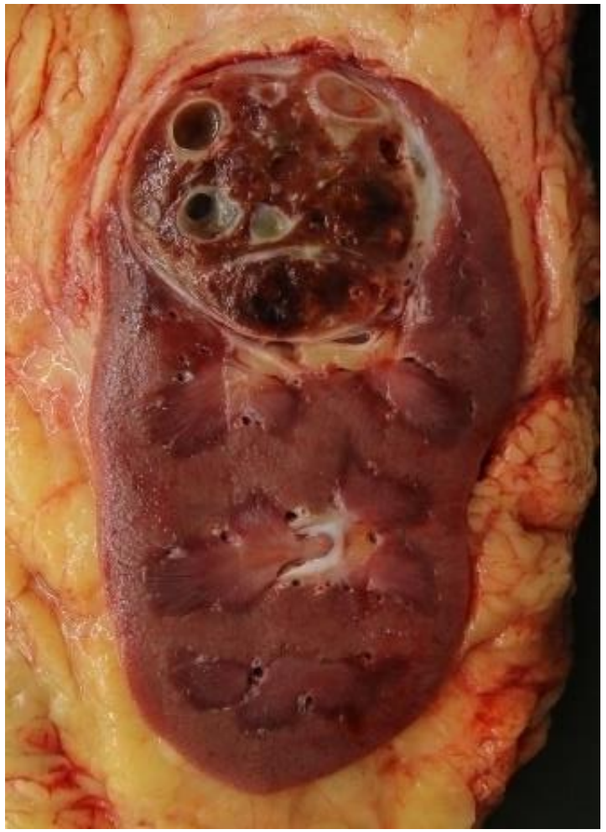
Other renal tumours

Clear cell (tubulo)papillary renal cell tumour
Mucinous tubular and spindle cell CA
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated RCC
Eosinophilic solid and cystic RCC
Renal cell carcinoma NOS

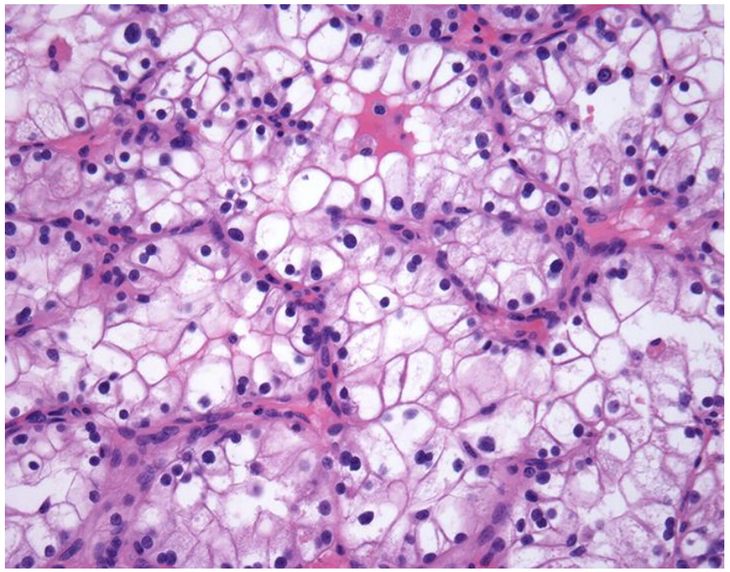
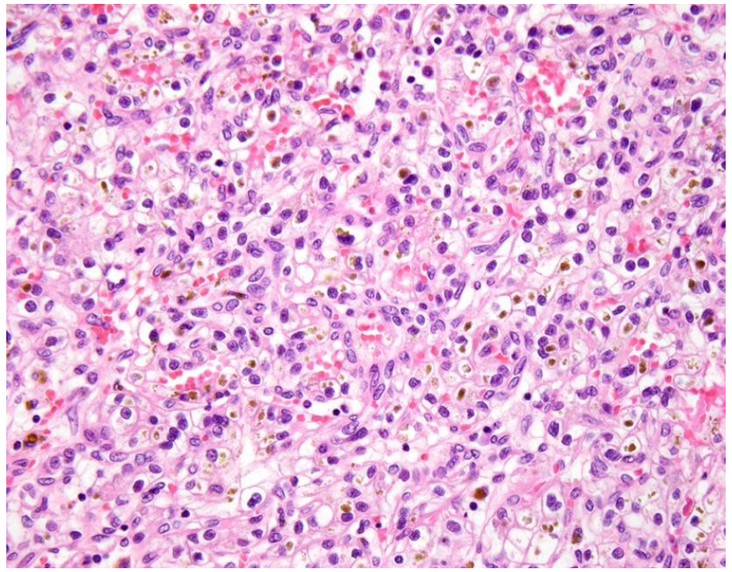
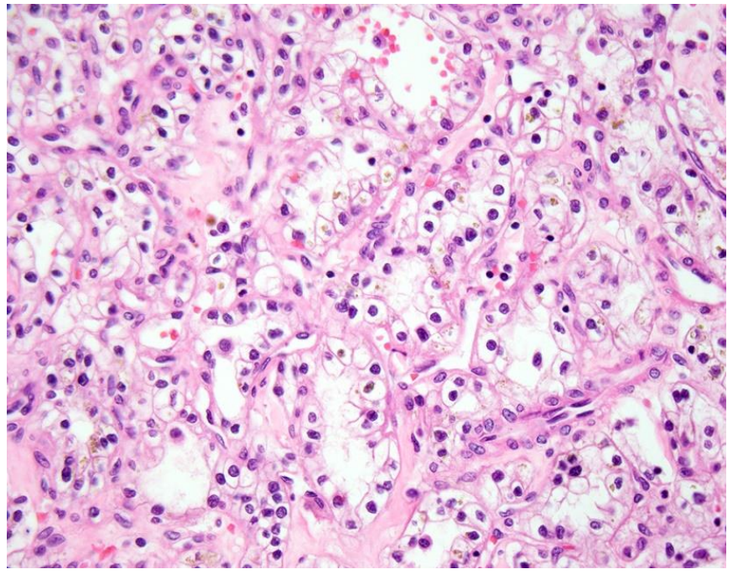
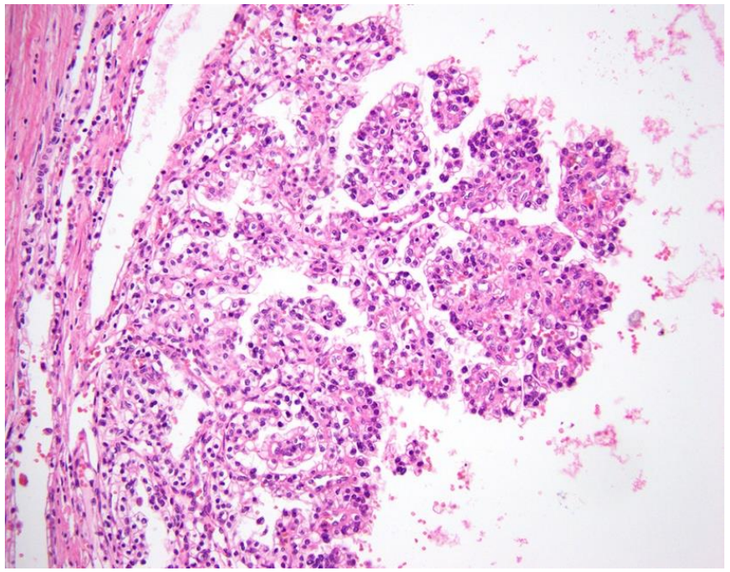
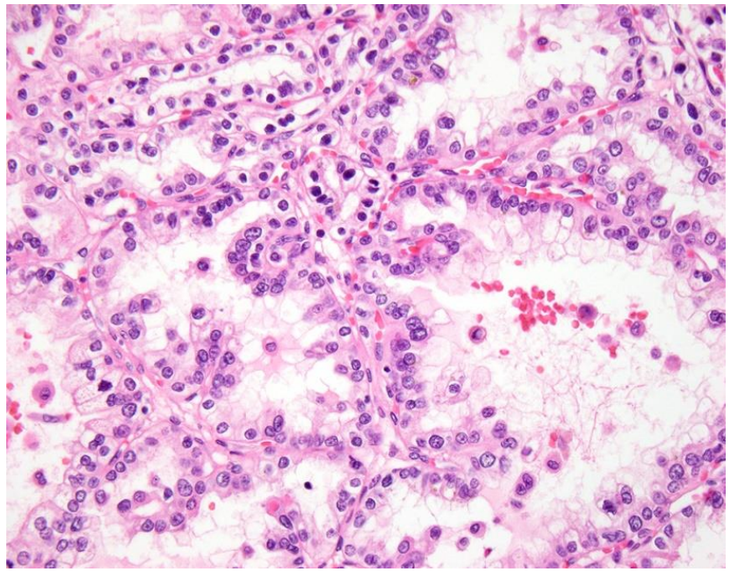
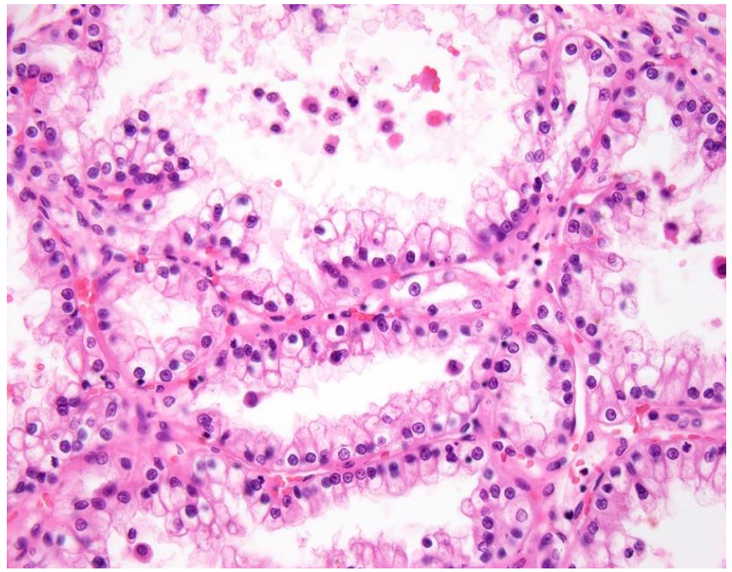
All 3 were previously recognized in the 4th ed as ‘emerging entities’

TCEB1 (ELOC)-mutated / Monosomy 8 RCC

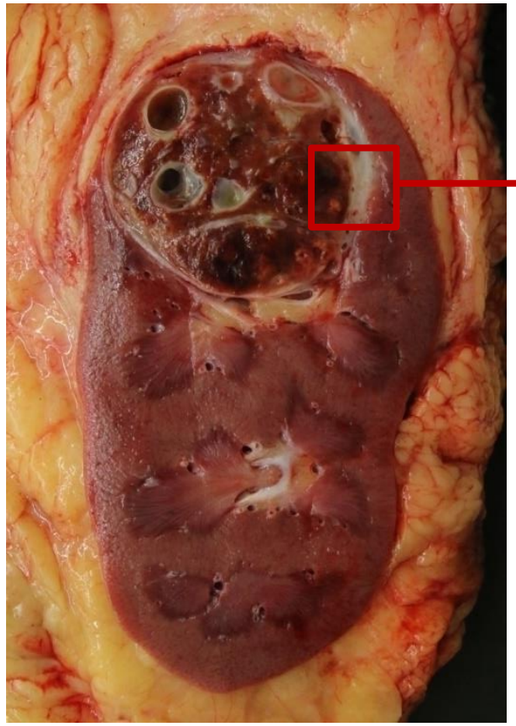
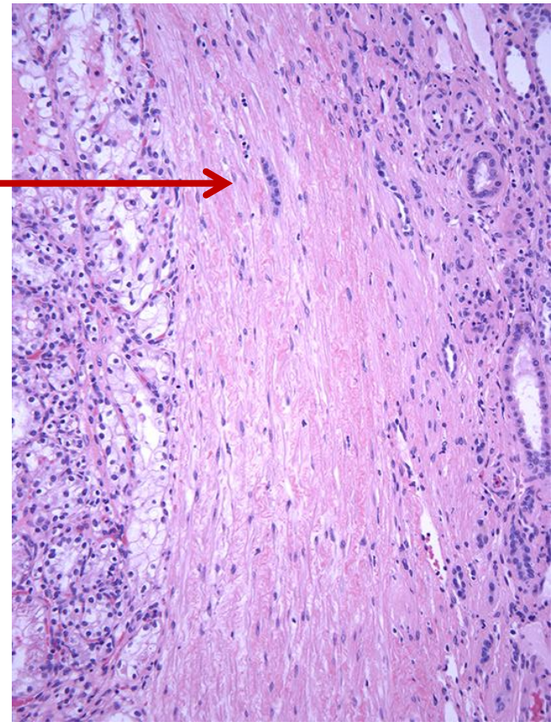
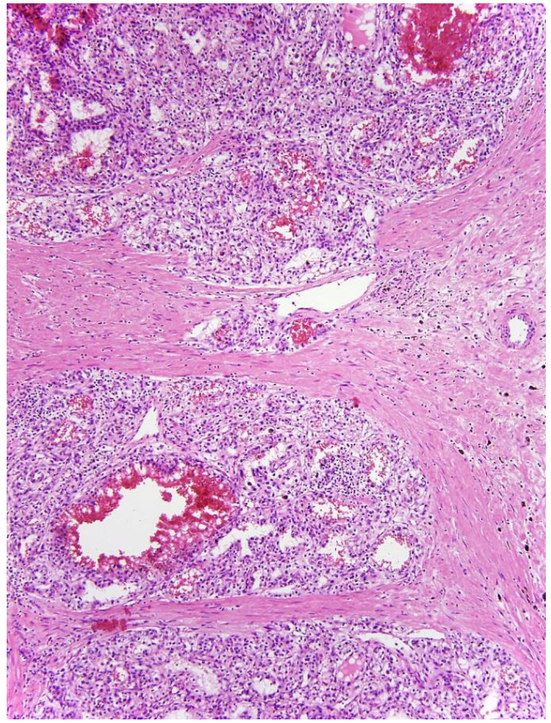
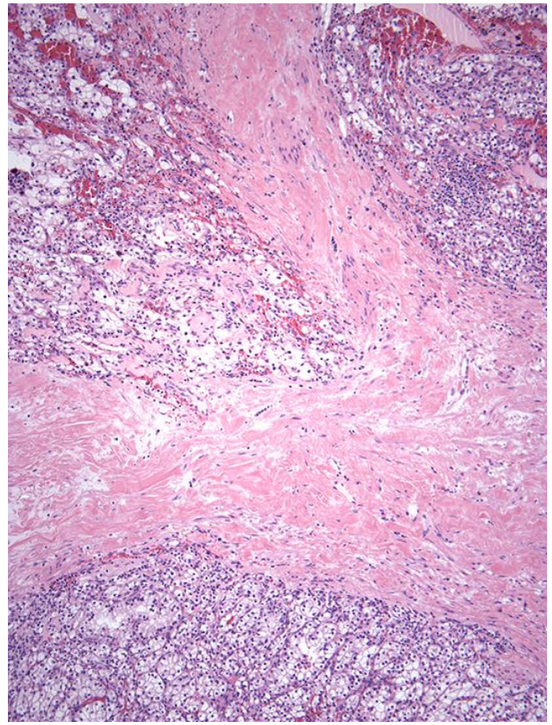
- WHO ➔ Molecularly Defined Group of RCCs
- First described at MSKCC (Hakimi et al) and BWH (Hirsch et al) in 2015
- Biallelic inactivation of *TCEB1* (mutation plus LOH) which encodes for the elongin C (ELOC) protein in the VHL complex on chromosome 8 (8q21.11); lacks VHL (3p) mutation
- Approximately 30 cases in the literature, most pT1
- Generally thought to be indolent; however, in recent cohort, 5 cases with stage pT3/4 and 2 with metastatic disease



Refs: Hakimi AA, et al. Mod Pathol. 2015 Jun;28(6):845-853; Hirsch et al, Mod Pathol, 28(S2):229A, 2015; Lan TT et al, Virchows Arch, 2016; Rueckert J, et al. J Assoc Genet Technol. 2018;44(1):5-9; DiNatale RG, et al. Eur Urol Focus. 2021 Mar;7(2):381-389; Wang Y, et al. Pathol Res Pract. 2022 Jul;235:153960.

TCEB1 (ELOC)-mutated / Monosomy 8 RCC

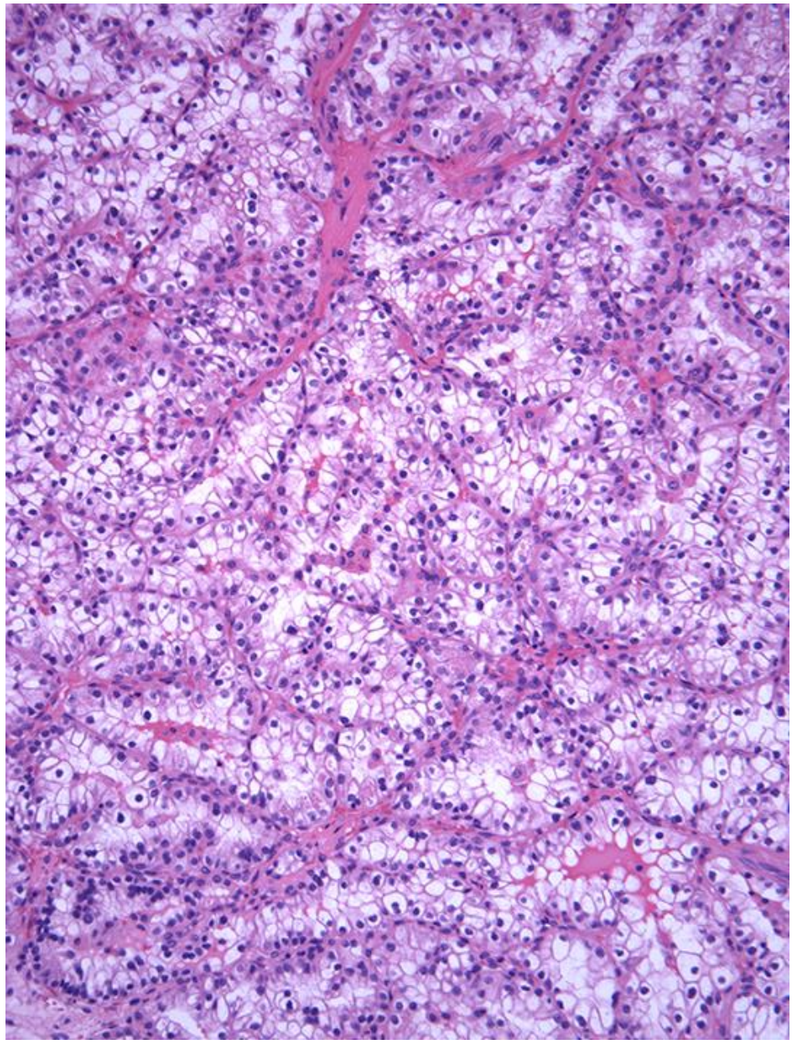





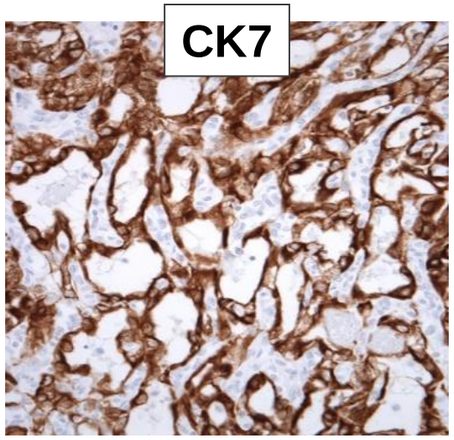
- Thick fibrous capsule
- Dissecting fibrous/fibromyomatous bands

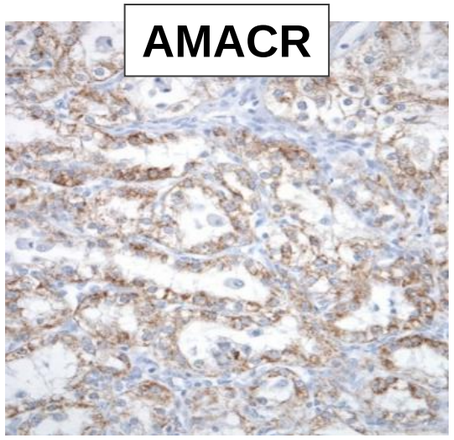
TCEB1 (ELOC)-mutated / Monosomy 8 RCC

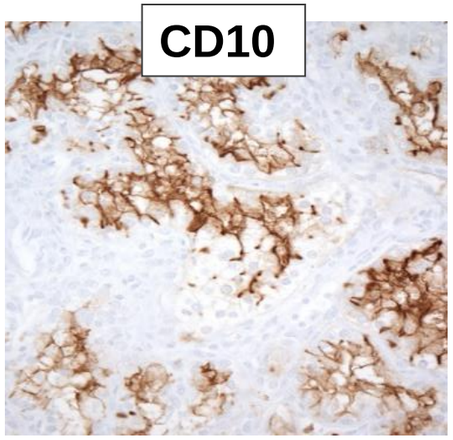
Differential Diagnosis incudes:

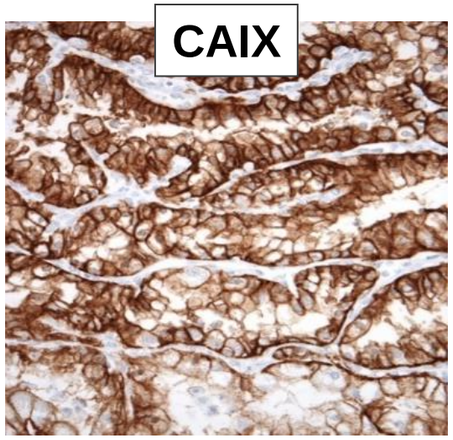
- CCRCC
- Translocation RCC
- Clear cell (tubulo)papillary tumor (& ‘RAT’)
- RCC with fibromyomatous stroma (FMS)





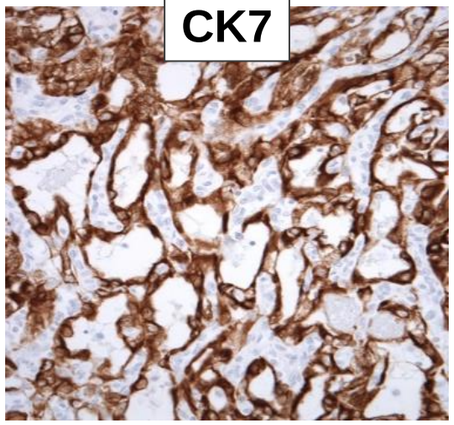


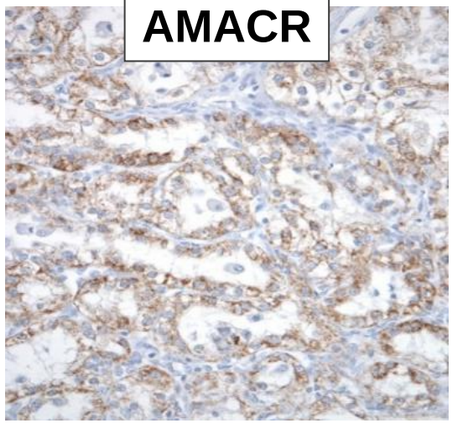


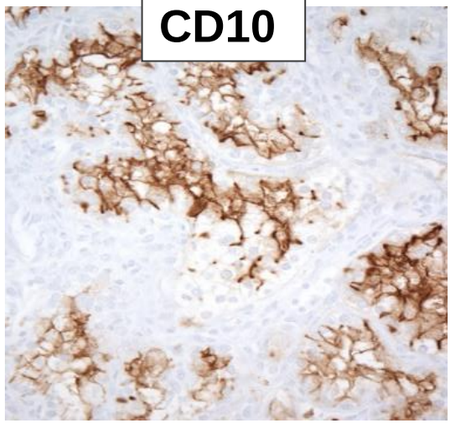


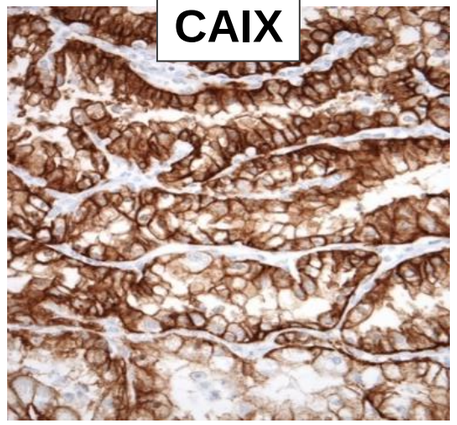
- CK7 positive (argues against CCRCC)
- AMACR and CD10 positive (argues against CCTPT)
- CA9 (box-like) positive (also seen in CCRCC)

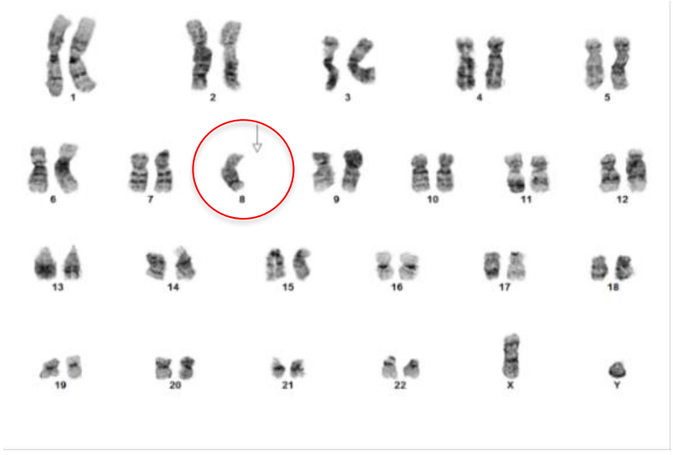
} IHC supportive but not specific

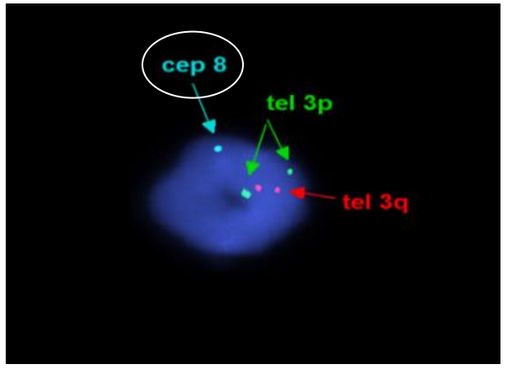


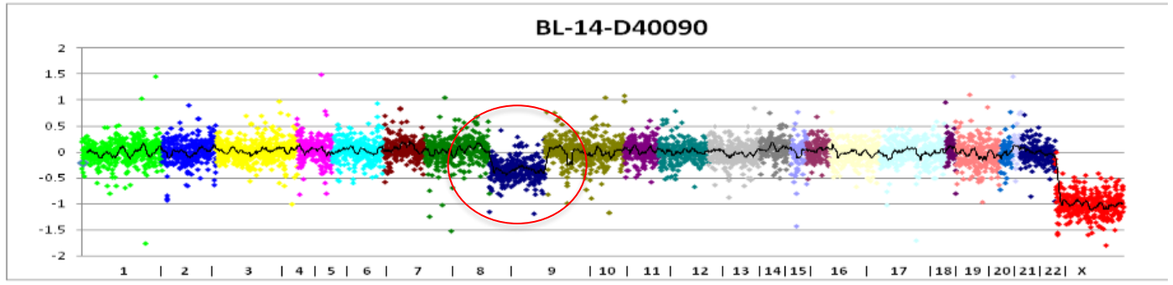












monosomy 8; 3p intact

- CK7 positive (argues against CCRCC)
- AMACR and CD10 positive (argues against CCTPT)
- CA9 (box-like) positive (also seen in CCRCC)
- **Molecular ➔ confirms the dx of ELOC (TCEB1)-mutated RCC (monosomy ch8)**

ALK-Translocated RCC

- WHO ➔ Molecularly Defined Group of RCCs
- Rare, ~50 cases in the literature
- Likely previously misdiagnosed as RMC or high grade PRCC
- Relatively distinct clinical (+/- SCT) and molecular (fusion partner) findings based on age:
  - Young children with SCT and *VCL-ALK*
  - Adults without SCT and alternative (non-*VCL*) fusion partner with *ALK*
    - *TPM3* most common, others include *HOOK1*, *STRN*, *PLEKHA7, EML4, CLIP1*, *KIF5B* and *KIAA1217*

Refs: Mariño-Enríquez A et al. Genes Chromosomes Cancer. 2011 Mar;50(3):146-53; Yu W, et al. Histopathology. 2017 Jul;71(1):53-62; Trpkov K and Hes O, Histopathol 2018; 74:31-59; Yang J et al., Diagn Pathol. 2019;14(1):112; Kuroda N, et al. Mod Pathol. 2020 Dec;33(12):2564-2579; Wangsiricharoen S, et al. Int J Surg Pathol. 2021 Oct;29(7):808-814.

ALK-Translocated RCC – Morphology

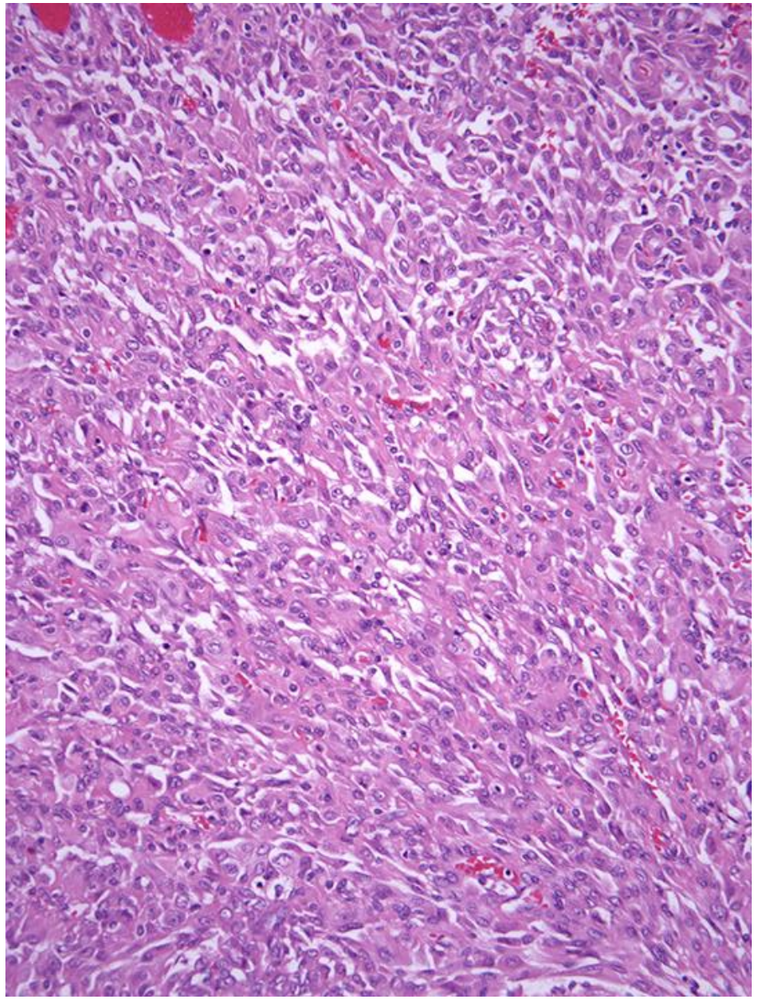
Consistent morphology with VCL-*ALK* cases and sickle cell trait:

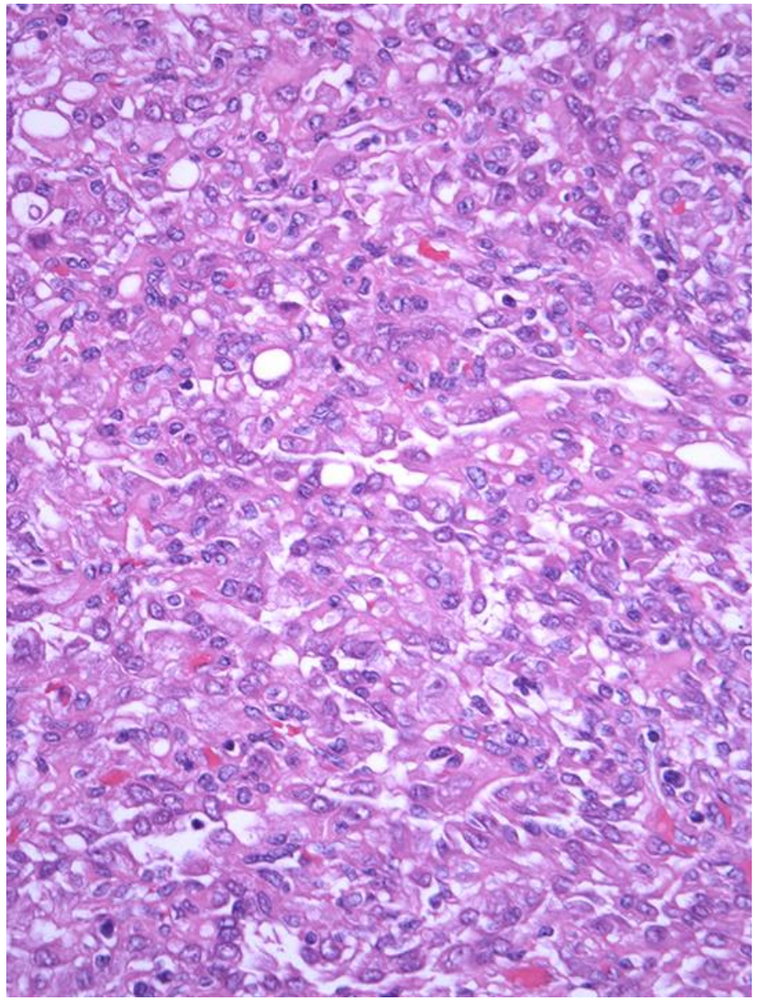
➔ solid growth pattern, polygonal to spindle-shaped cells, eosinophilic cytoplasm, intracytoplasmic vacuoles, large vesicular nuclei and abundant lymphoplasmacytic infiltrate

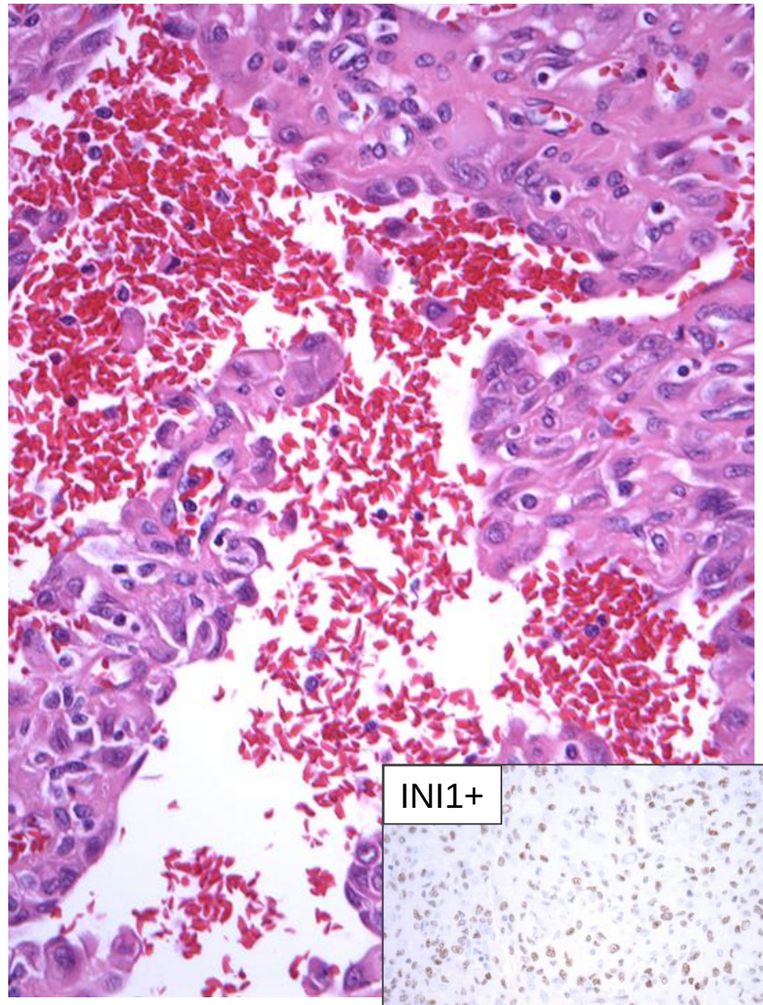
Variable morphology in adult /'non-*VCL-ALK'* cases:

➔ solid growth, nests, papillary, tubular and cribriform architectures, can also have eosinophilic cytoplasm, vacuoles

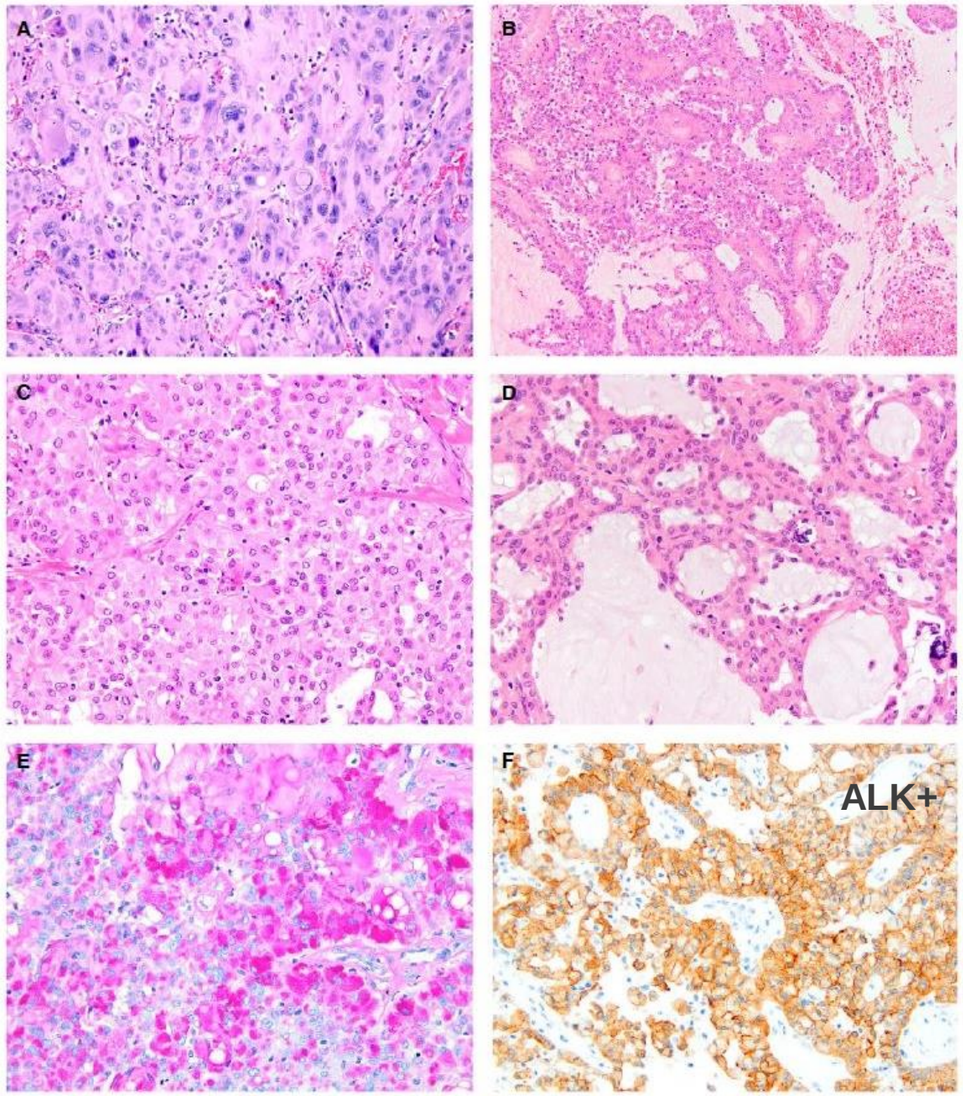
ALK-translocated RCC in a child with SCT (*VCL-ALK*)







ALK-Translocated RCC



Trpkov K and Hes O, Histopathol 2018; 74:31-59.

PAX8 +

ALK+

GATA3-

CK7+/CK20-

AMACR+

INI1 intact

FH intact / 2SC-

SDH intact

CathpsinK-

TFE3-/+ (FISH-)

DDx of ALK-Rearranged RCC

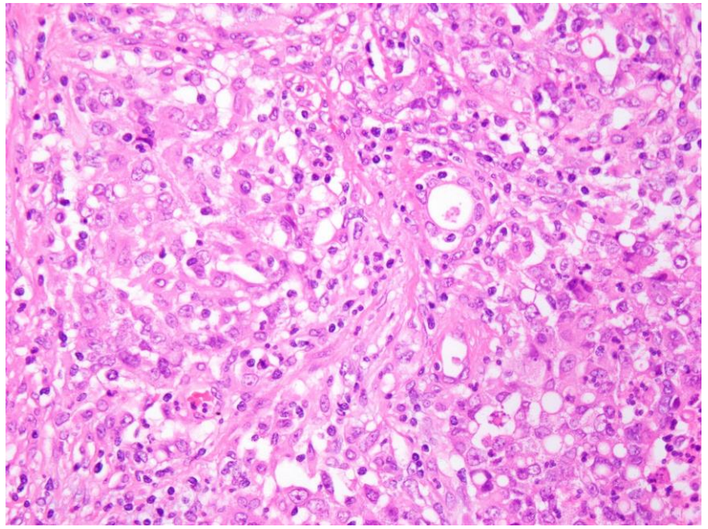
- Papillary RCC
- Collecting Duct Carcinoma
- FH-Deficient RCC
- RMC (sickle cell trait and SMARCB1 deficient)
- Unclassified RCC +/- medullary features
- Metastatic carcinoma

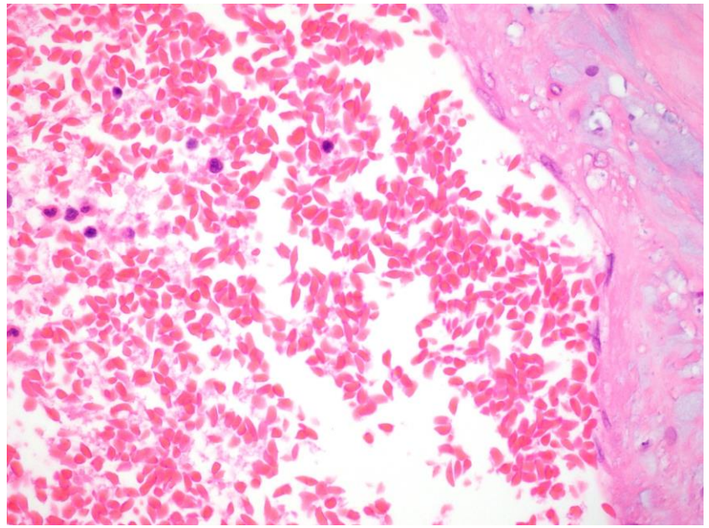
"…..if you don't think about it, you won't diagnose it!"

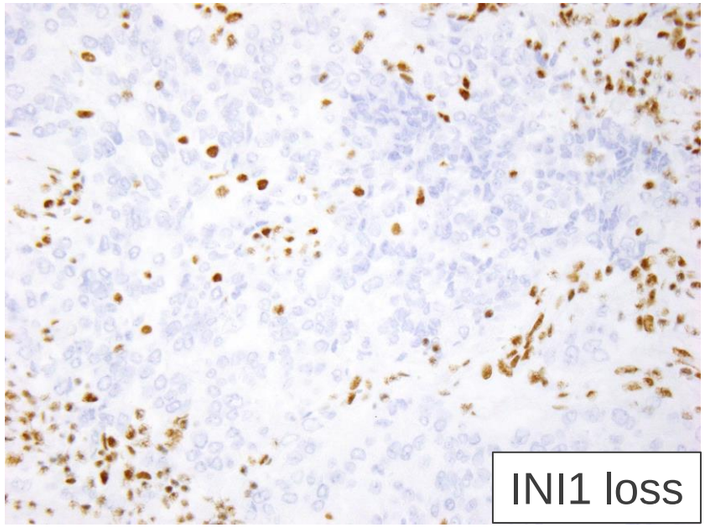
Refs: Baniak N, Tsai H, Hirsch MS. The Differential Diagnosis of Medullary-Based Renal Masses. Arch Pathol Lab Med. 2021 Sep 1;145(9):1148-1170. PMID: 33406251;
Sirohi D, et al. Renal cell carcinoma, unclassified with medullary phenotype: poorly differentiated adenocarcinomas overlapping with renal medullary carcinoma. Hum Pathol. 2017 Sep;67:134-145. PMID: 28716439.

SMARCB1-Deficient RCCs (Molecularly Defined Category of RCCs)

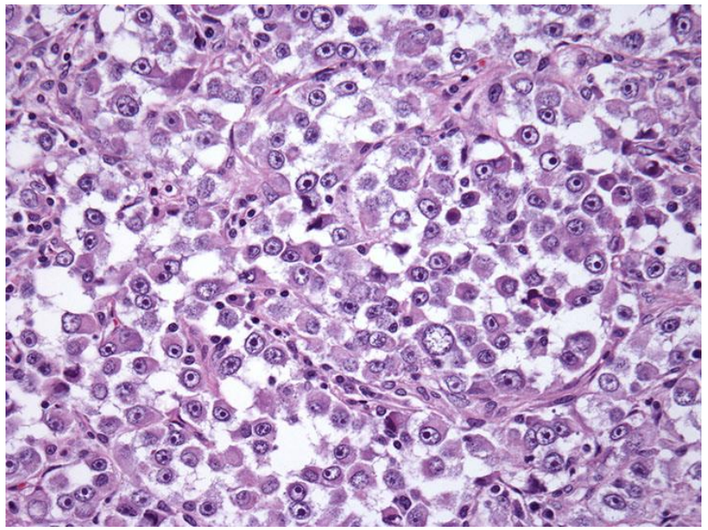
Renal Medullary Carcinoma (children/young adults)

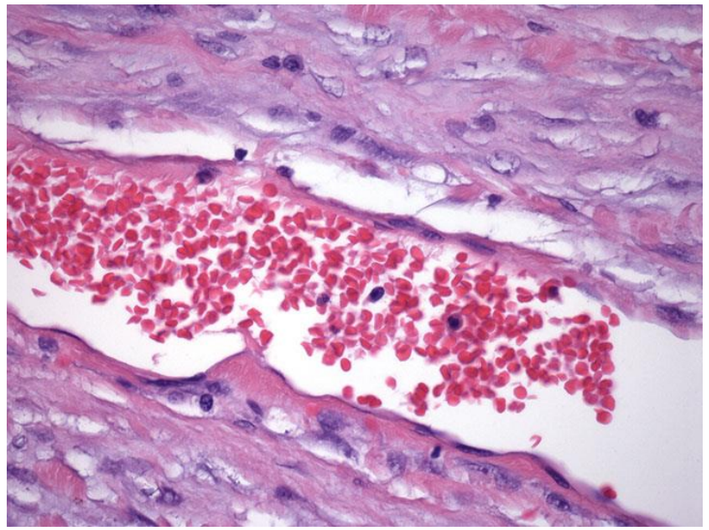


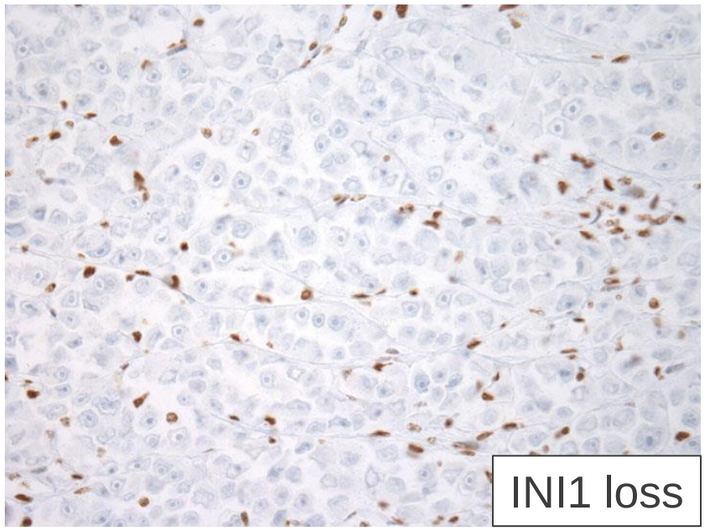




Unclassified RCC with Medullary Features (adults)

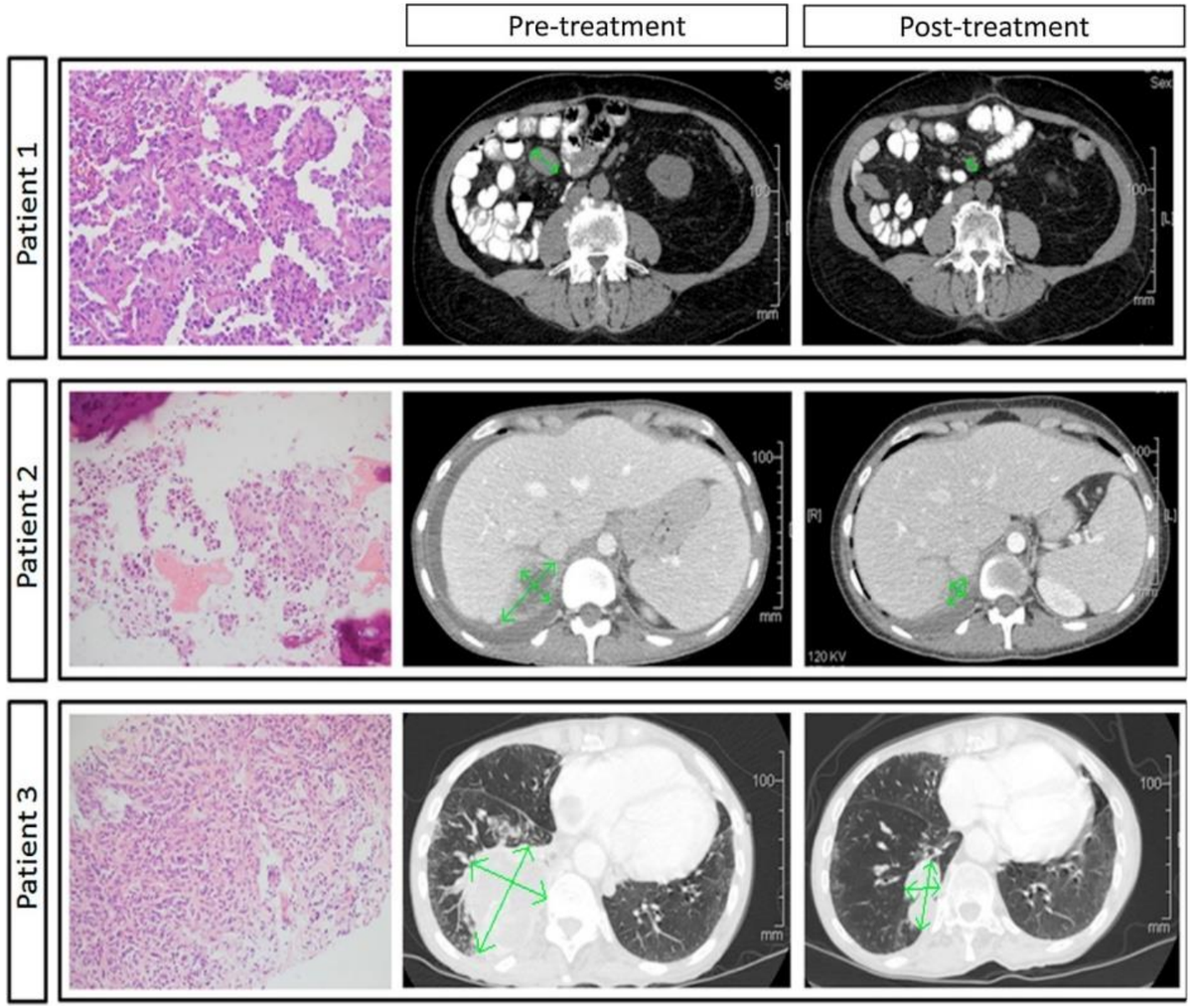






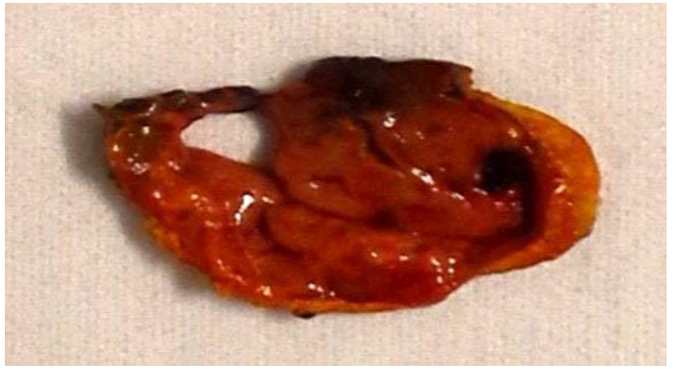
Response to *ALK* Inhibitors and Outcome

- Majority appear to be indolent
- ~25% with malignant behavior (including metastatic dz and death)
- May benefit from ALK inhibitors
- Therefore, important to distinguish from other RCC subtypes, including ('so-called' type 2) PRCC!

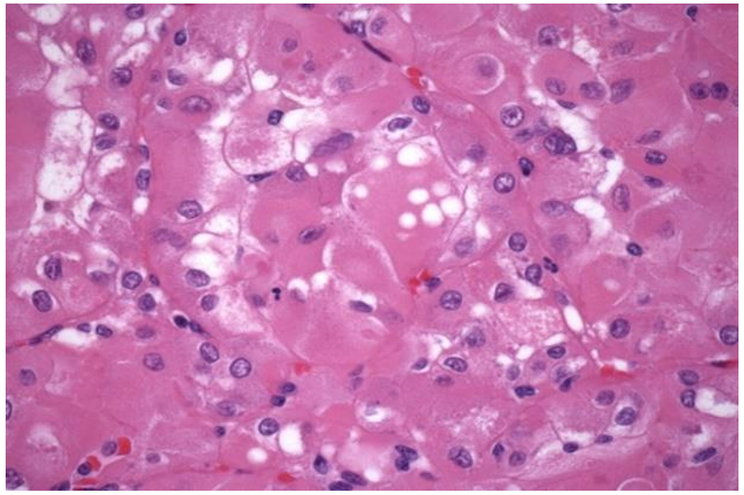


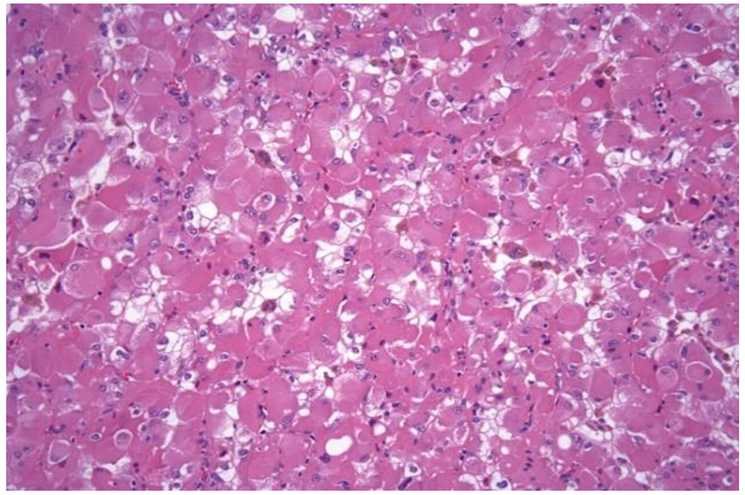
Pal SK et al, Responses to alectinib in *ALK*-rearranged papillary renal cell carcinoma. Eur Urol 2018;74:124-8.

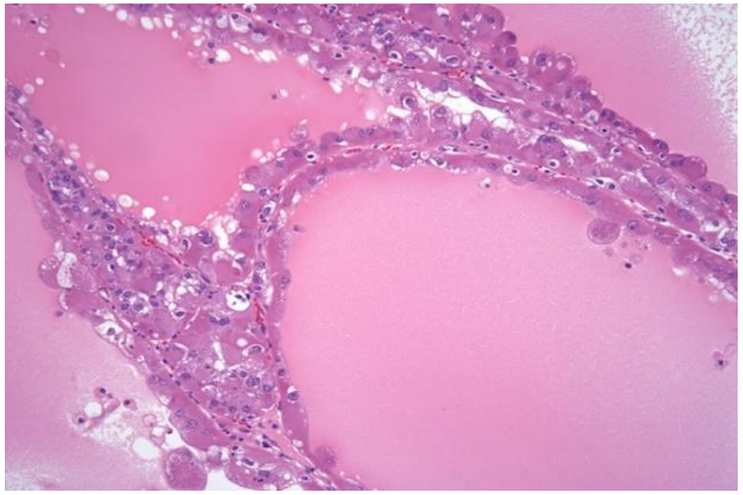
Eosinophilic Solid and Cystic RCC



- WHO ➔ Other Renal Tumor Category
- Fewer than 1% of RCC cases, 60+ in the literature
- Median size ~3.0 cm (range 1-13 cm)
- 13:1 F:M; median age 55 (range 14-79)

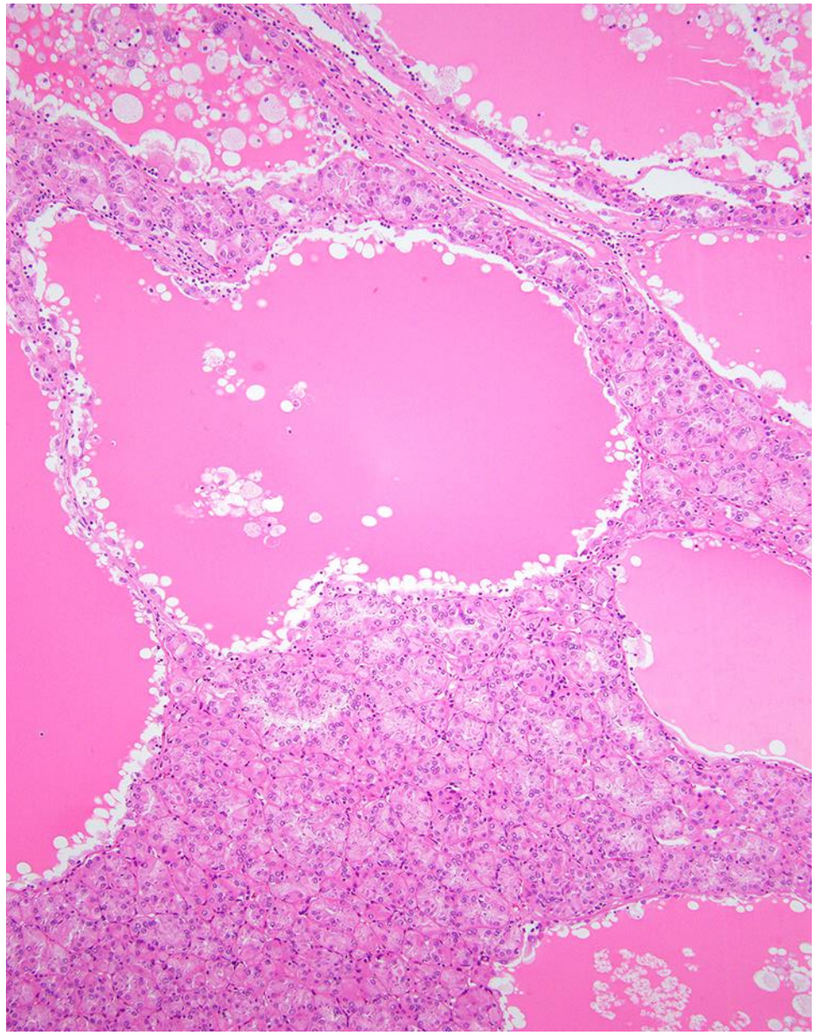




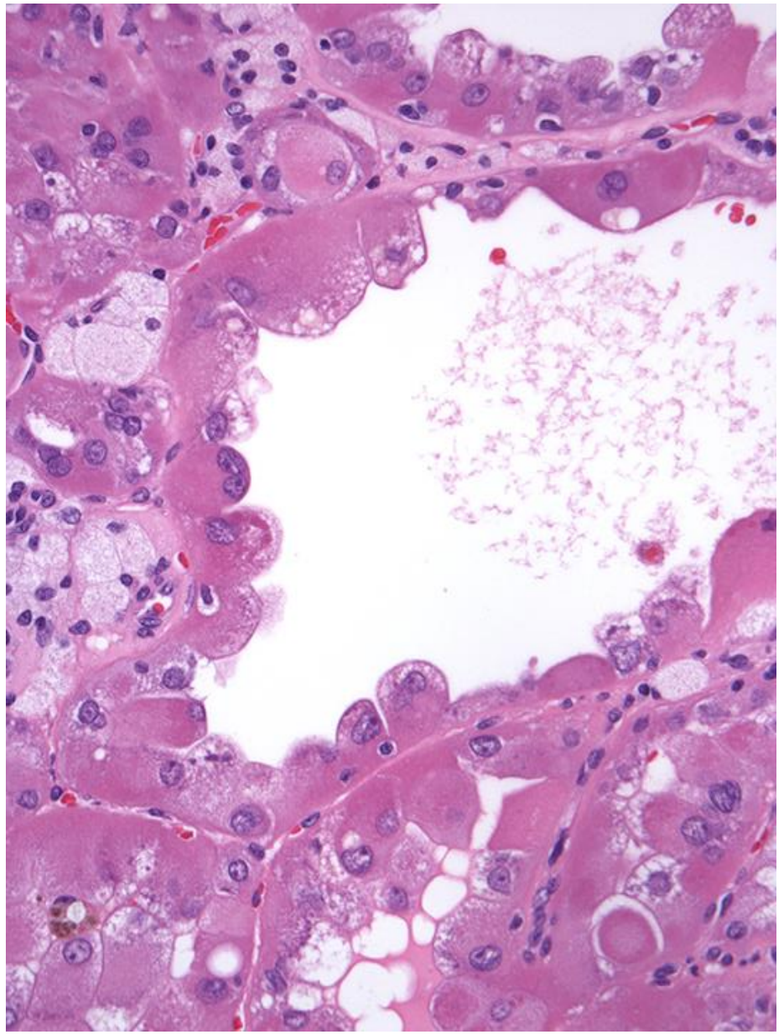


Trpkov K & Hes O. Histopathol, 2019, 74, 31–59; Siadat F and Trpkov K. Cancers, 2020;12:168-180; Baniak et al, Adv Anat Pathol, 2021

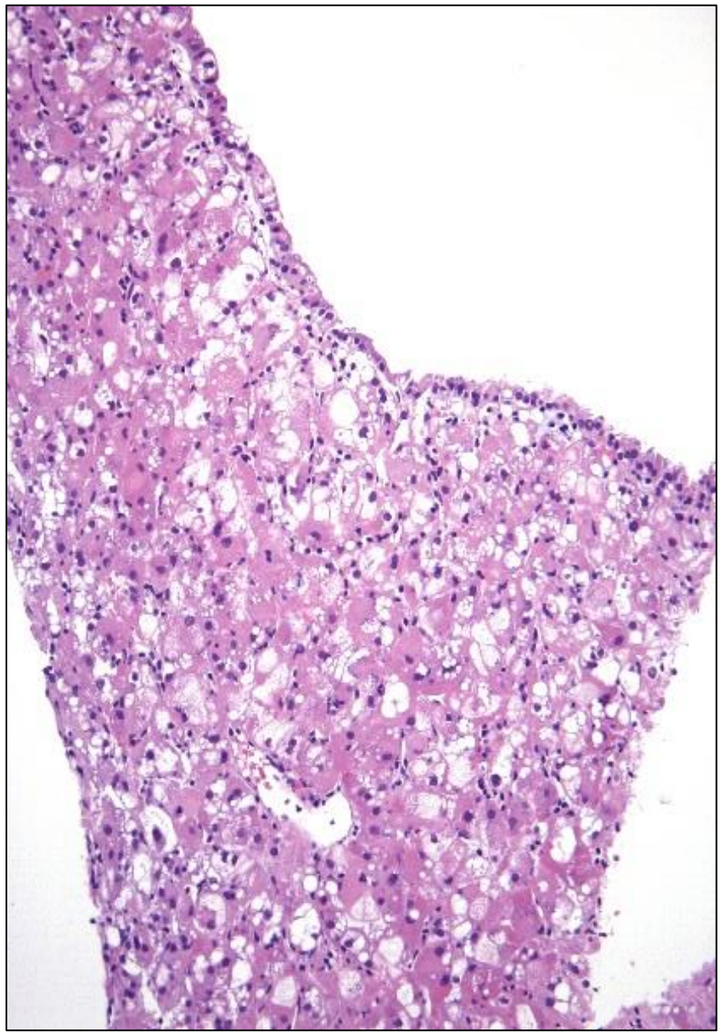
Eosinophilic Solid and Cystic RCC



Macrocystic

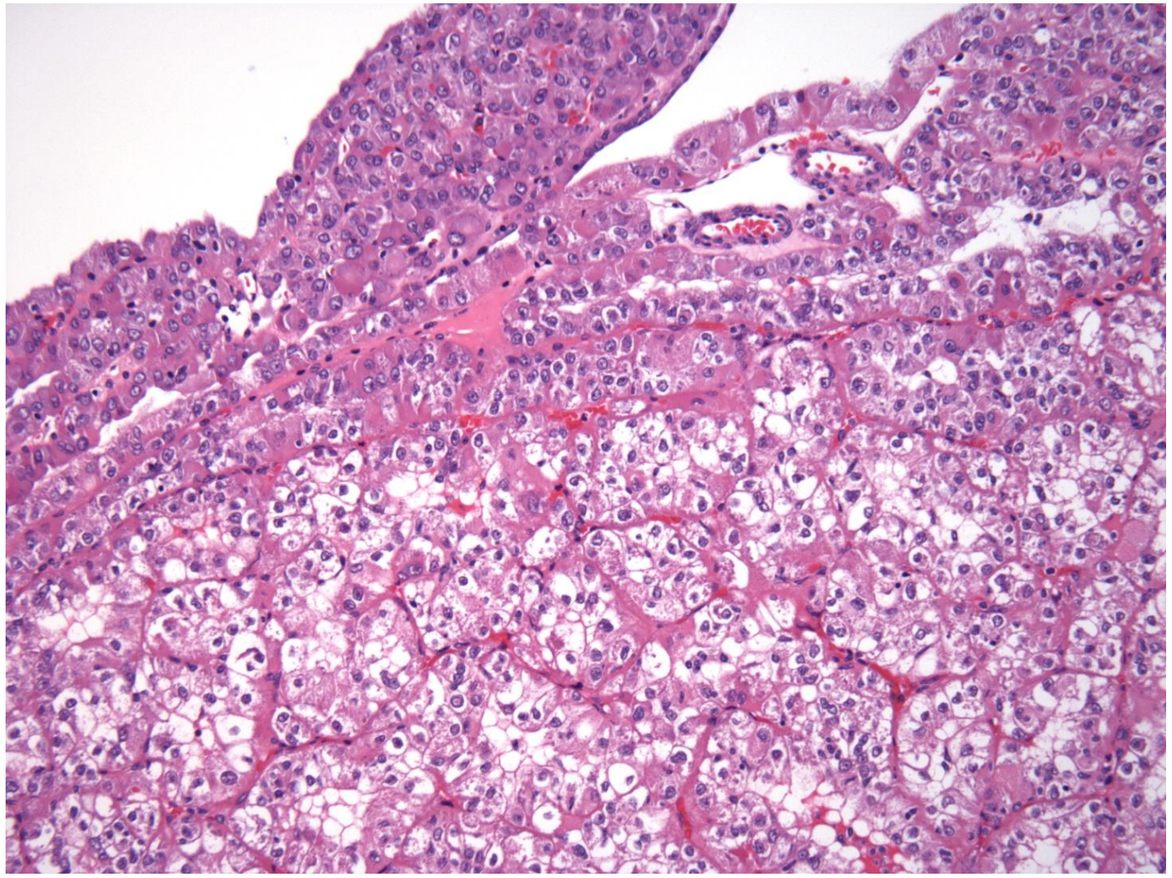


Microcystic

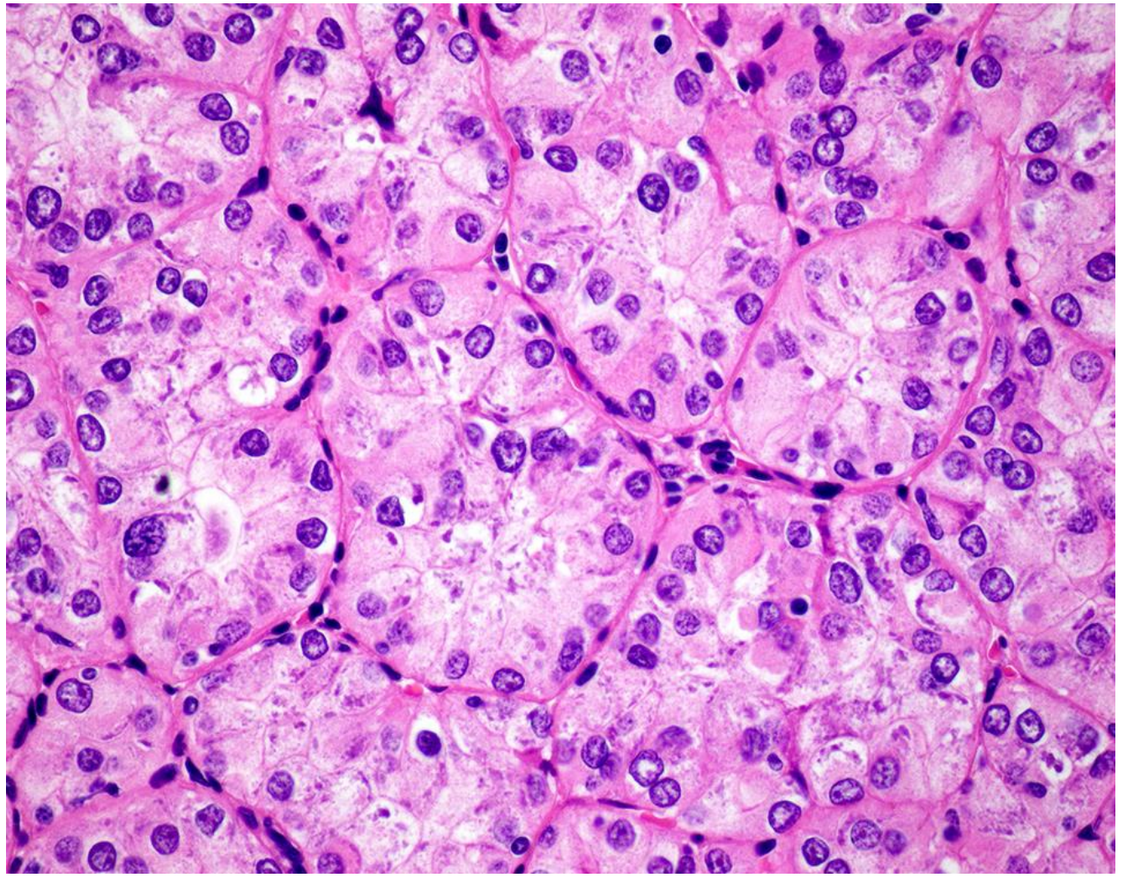


Cyst in Core Bx

Eosinophilic Solid and Cystic RCC



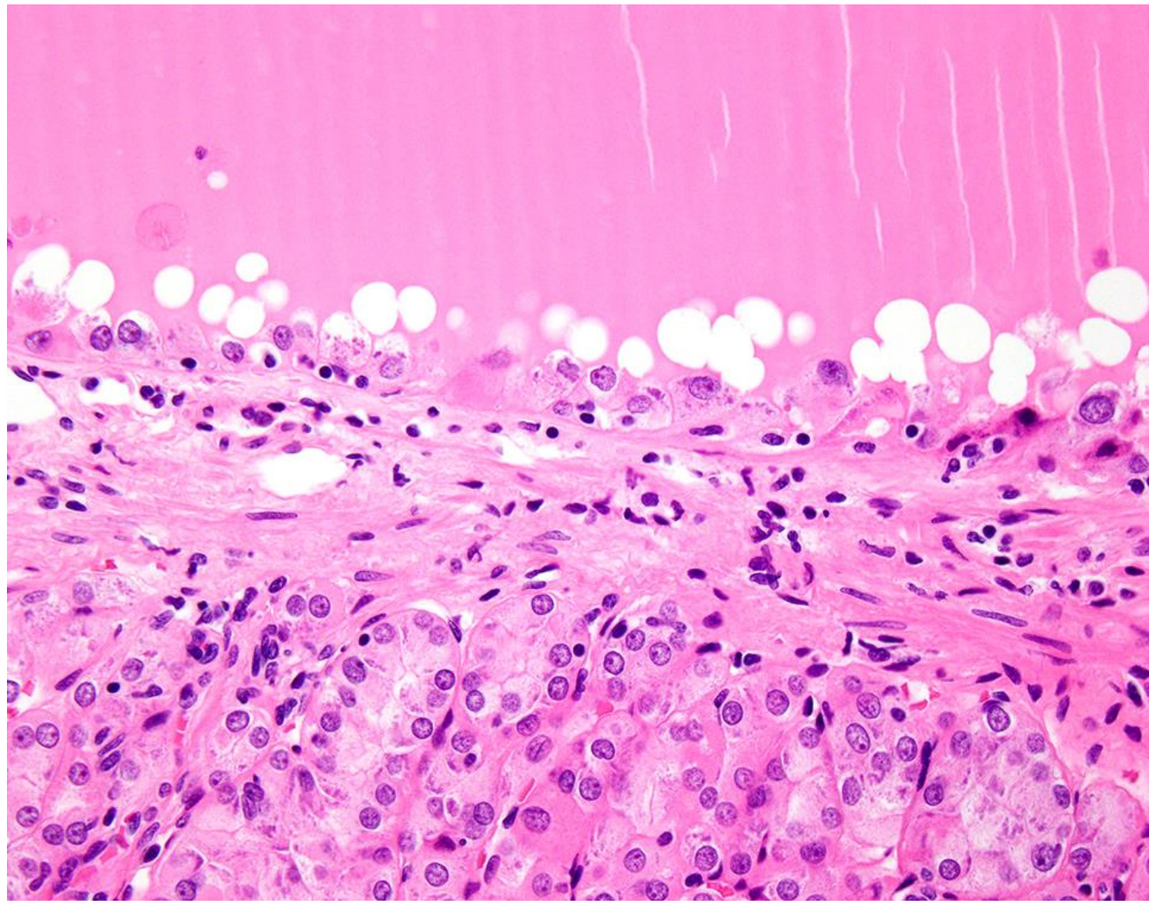
Clear cell features



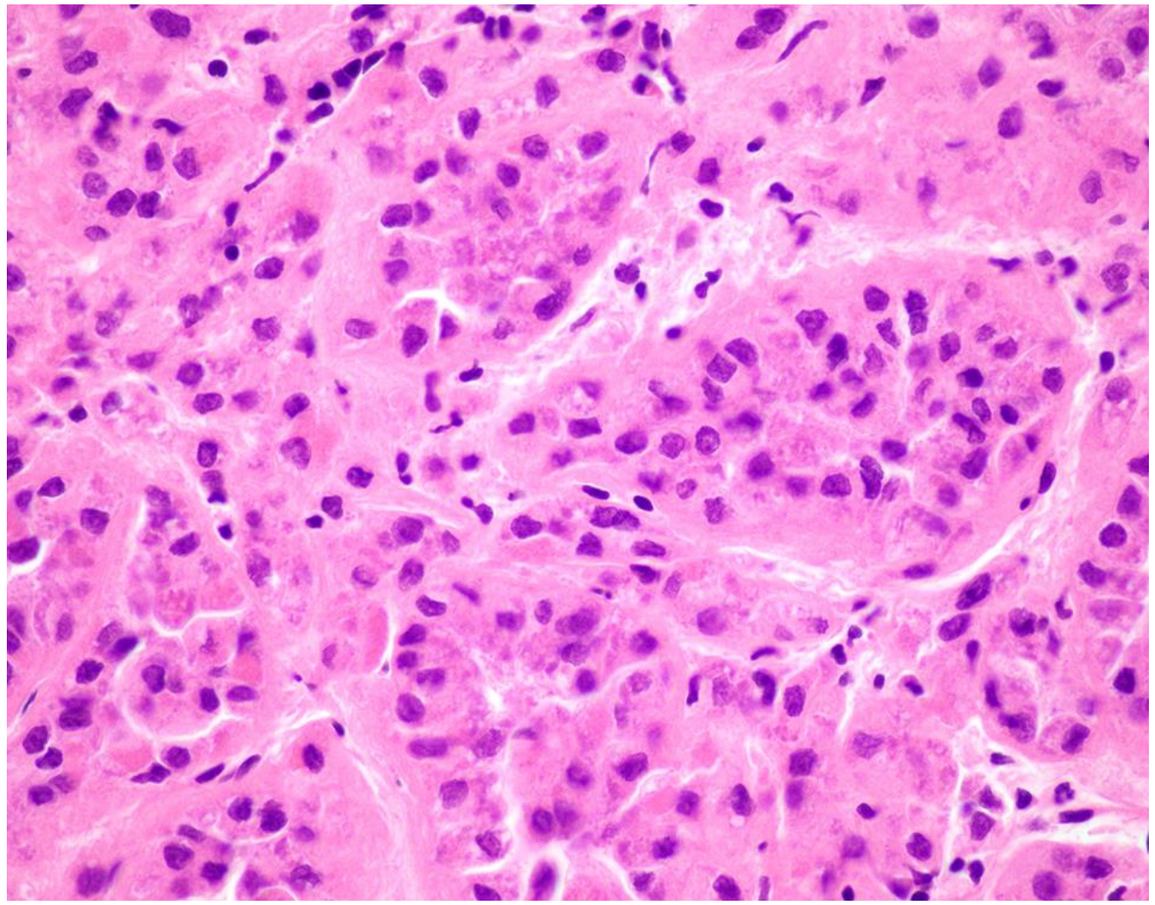
Basophilic Stippling

Eosinophilic Solid and Cystic RCC

Basophilic stippling



Cyst lining



Frozen tissue

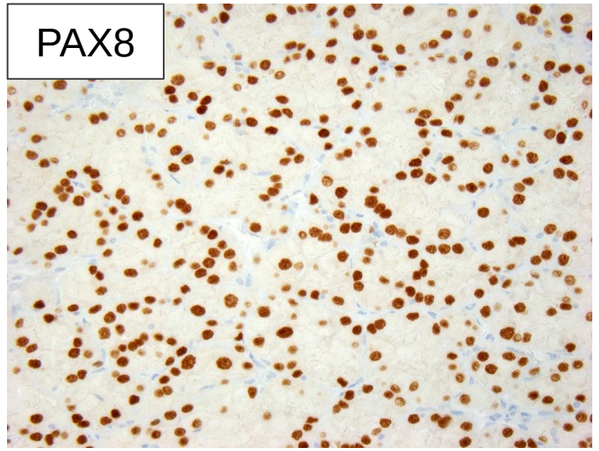
Eosinophilic Solid and Cystic RCC

- DDx
  - Translocation RCC (female predominance, subset eosinophilic)
  - SDH-deficient RCC (vacuoles, usually solid)
  - FH-deficient RCC (including the ‘low grade’ variant)
  - Eosinophilic vacuolated tumor (EVT)
  - PEComa

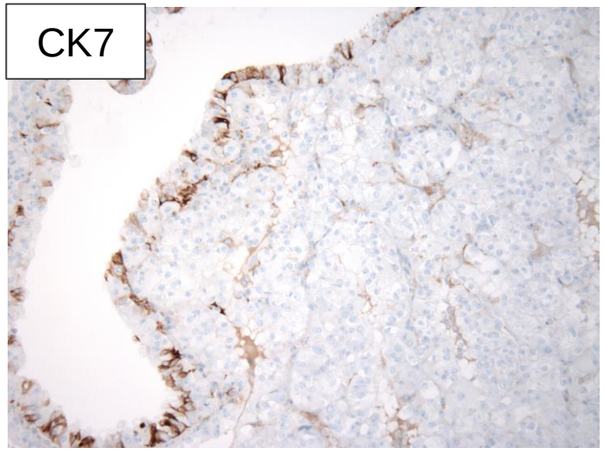
Trpkov K & Hes O. Histopathol, 2019; Siadat F and Trpkov K. Cancers, 2020; Trpkov et al, Mod Pathol, 2021; Baniac et al, Adv Anat Pathol, 2021

Immunoprofile* - Eosinophilic Solid and Cystic RCC

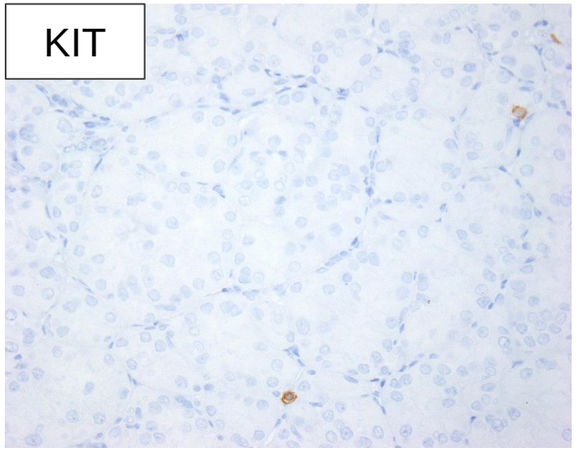
PAX8



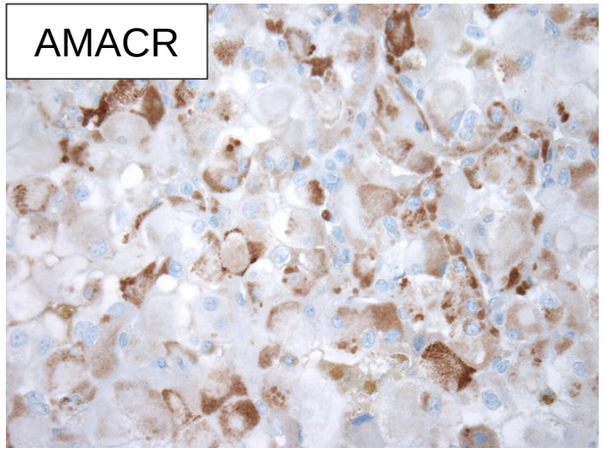
CK7



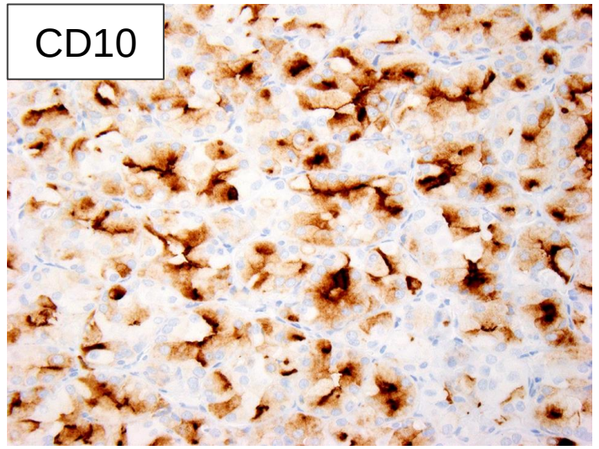
KIT



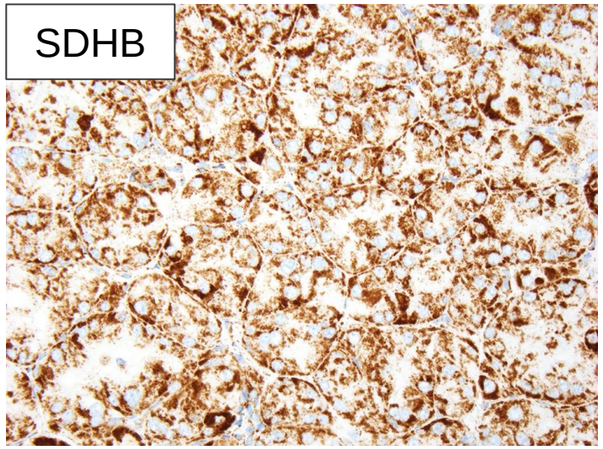
AMACR



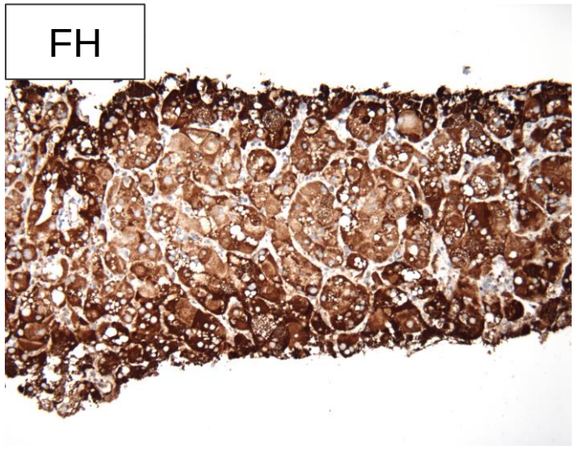
CD10



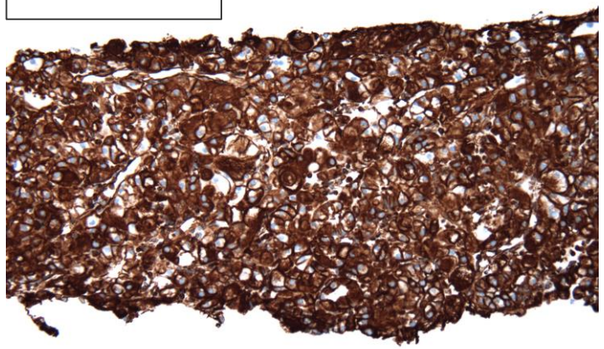
SDHB



FH



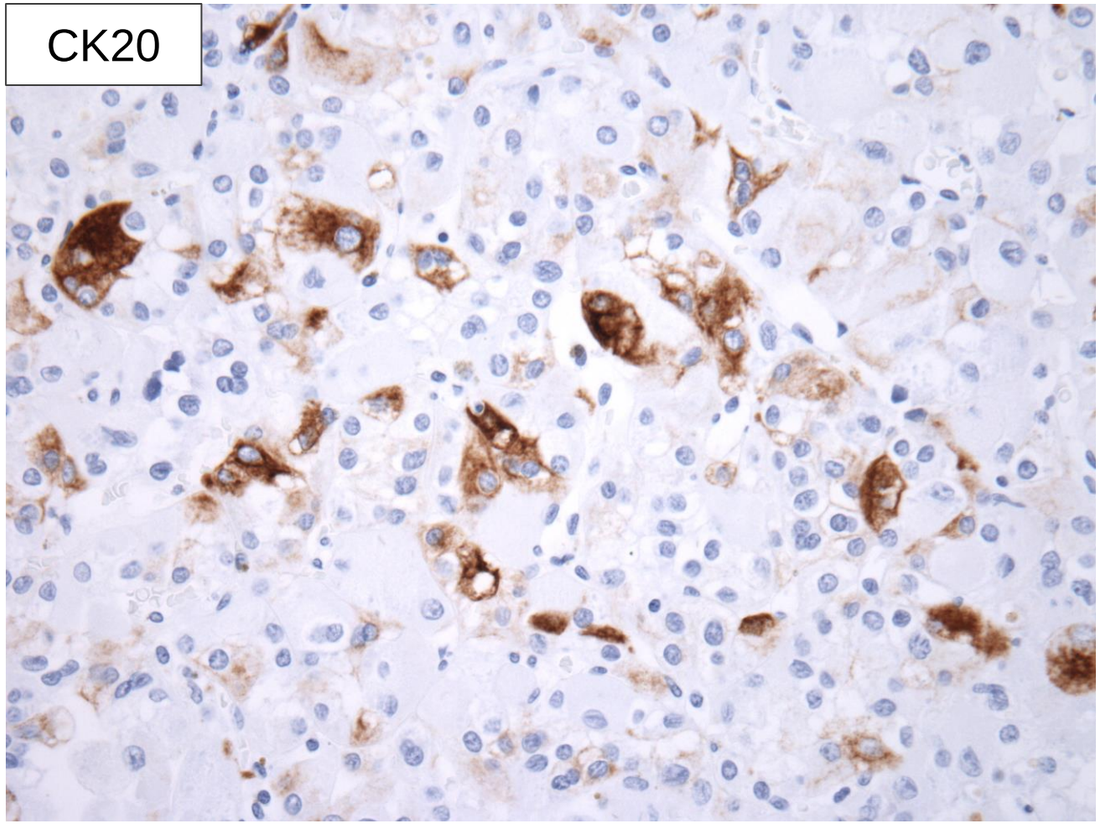
Vimentin



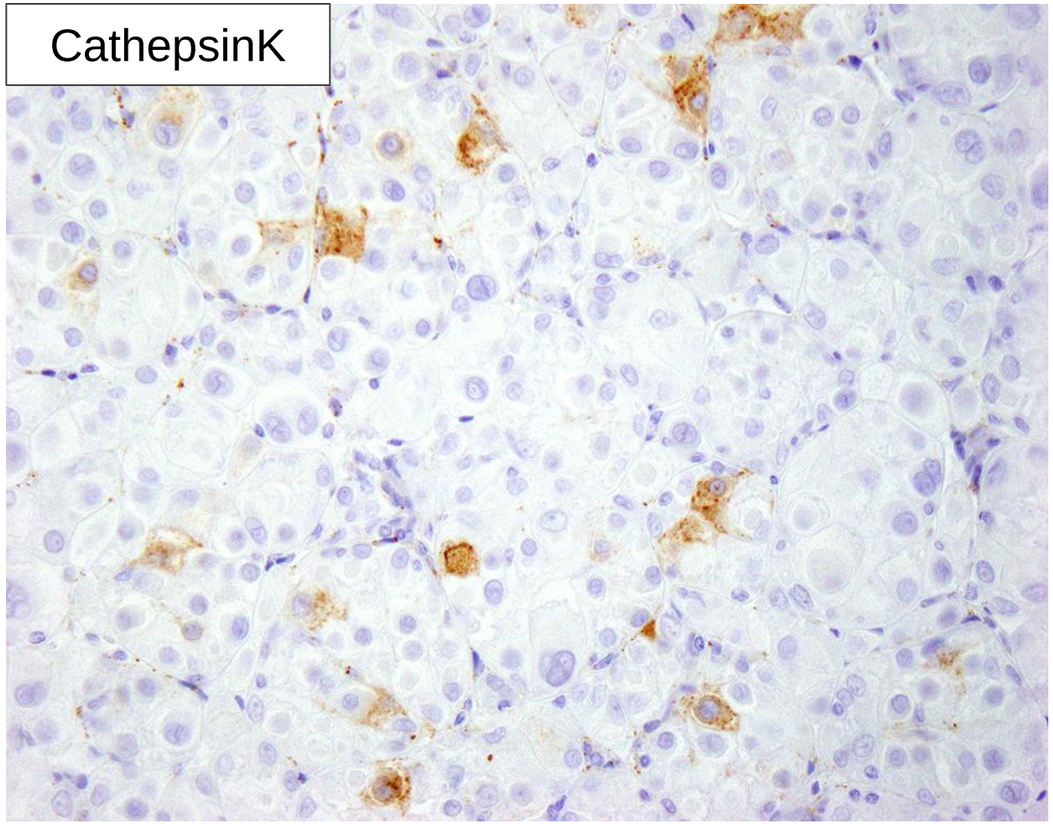
*Biomarker examples shown from multiple cases; also TFE3 negative

Immunoprofile - Eosinophilic Solid and Cystic RCC

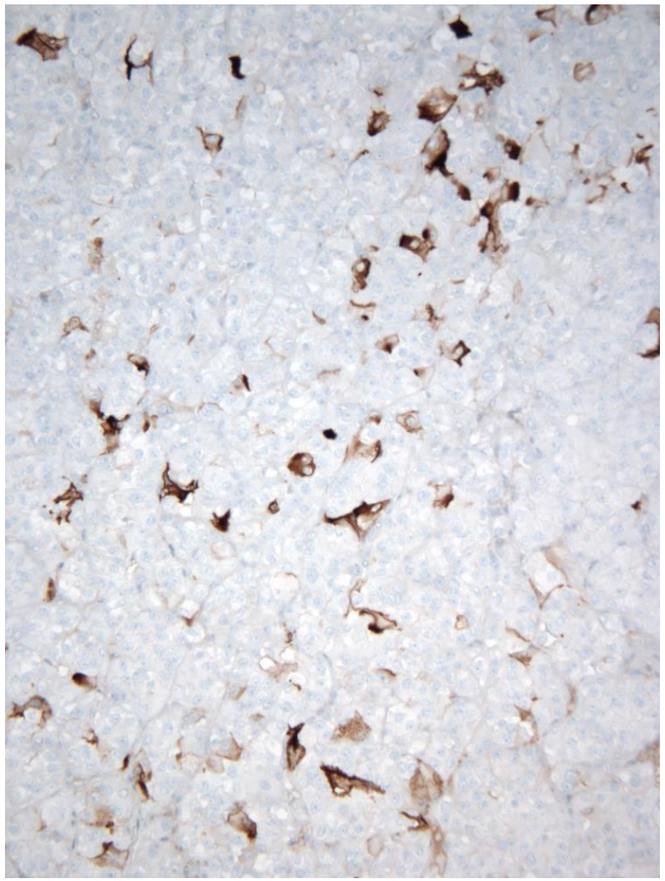
CK20

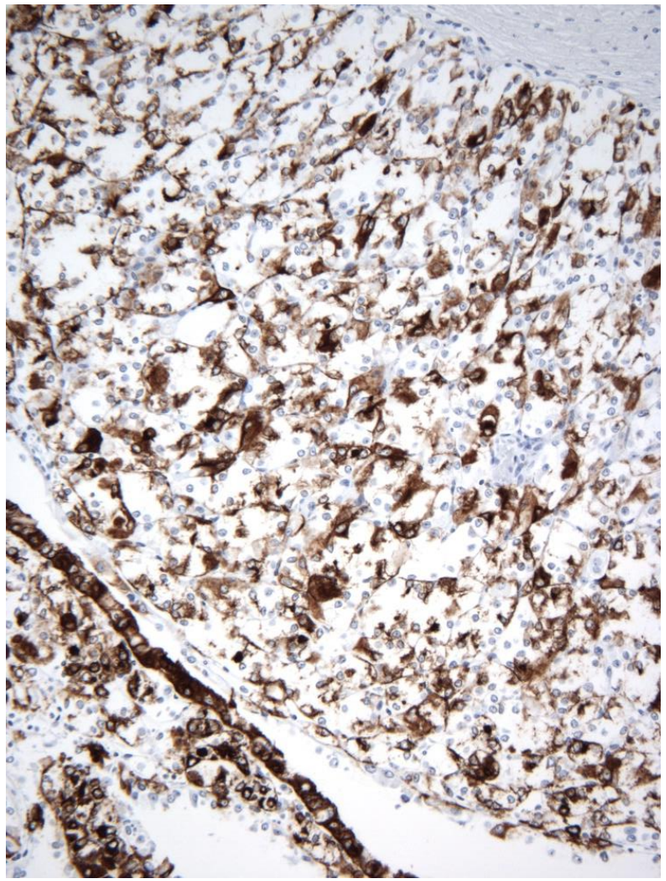


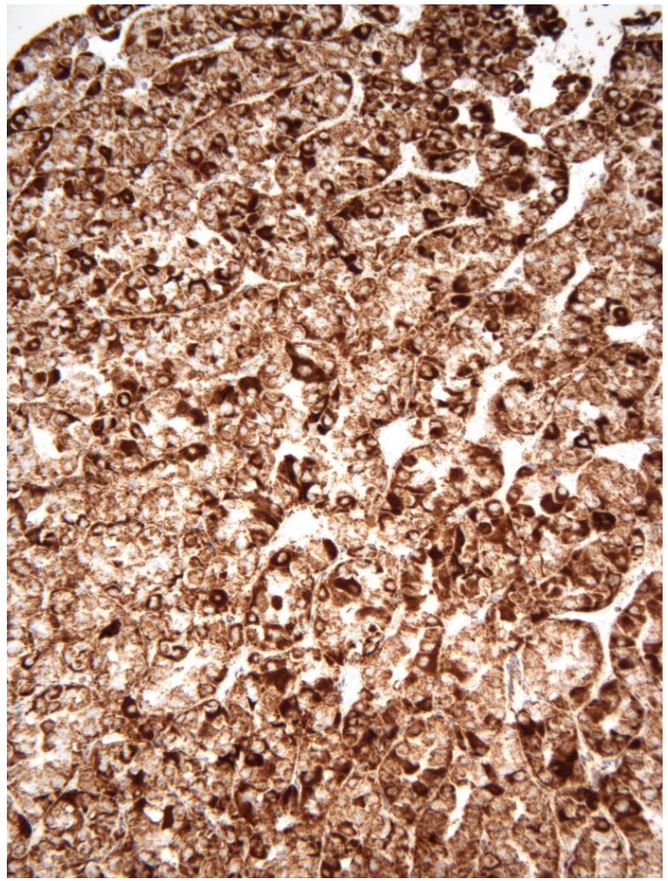
CathepsinK



Eosinophilic Solid and Cystic RCC



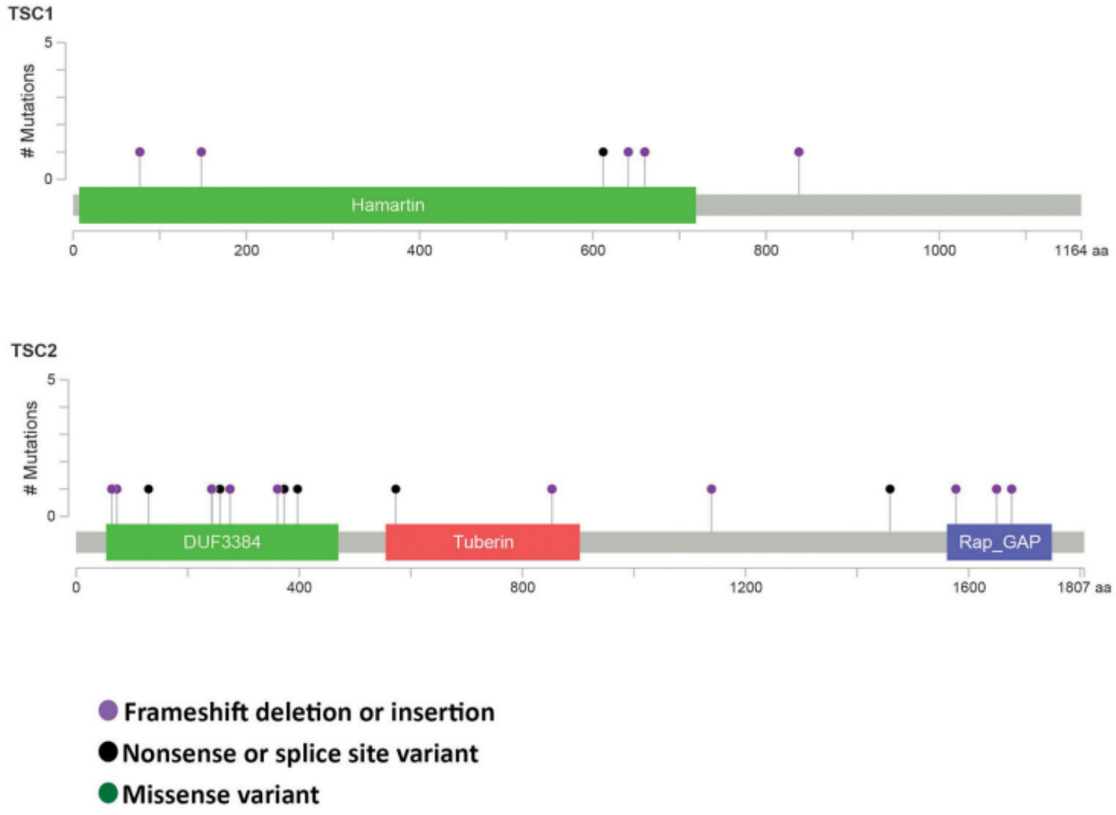




CK20 Expression (single case)

Eosinophilic Solid and Cystic RCC

- Molecular
  - Somatic biallelic TSC1/2 mutations, with activation of mTORC1
  - Distinct chromosomal copy number changes also reported
- Prognosis
  - Predominantly indolent
  - 5-10% with aggressive behavior



Palsgrove DN, et al. Am J Surg Pathol. 2018 Sep;42(9):1166-1181.

Trpkov K & Hes O. Histopathol, 2019; Siadat F and Trpkov K. Cancers, 2020; Trpkov et al, Mod Pathol, 2021; Baniac et al, Adv Anat Pathol, 2021

Update #3 ➔ So-called Type I / II PRCC has been officially omitted from the WHO Classification of Kidney Tumors

Papillary renal tumours

Renal papillary adenoma

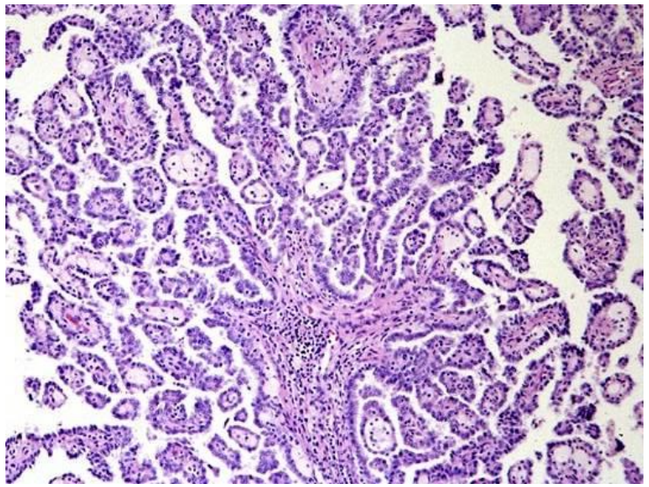
Papillary RCC

*Type I/II has NEVER been utilized at BWH

Type 1 vs Type 2 Papillary RCC*
(‘official’ in 2004 WHO)

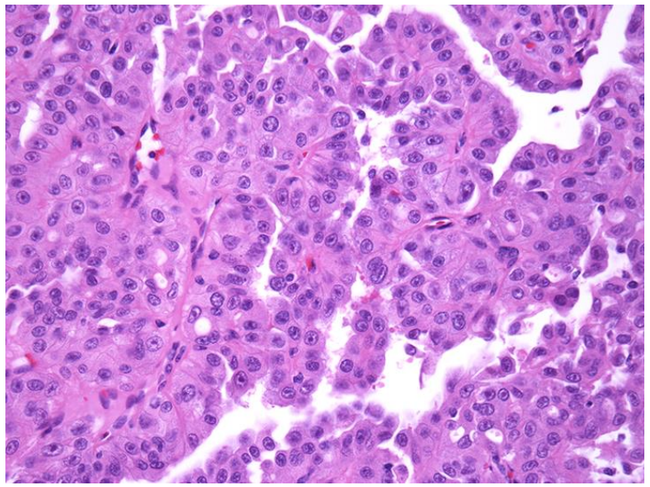
Type 1 PRCC:

- small basophilic cells
- single layer of cells on FVCs
- low grade
- CK7+, AMACR+
- Trisomy 7/17



Type 2 PRCC:

- larger eosinophilic cells
- pseudostratified cells on FVCs
- higher grade
- CK7-/+, AMACR+
- Subset with trisomy 7/17



*has never been subclassified at BWH

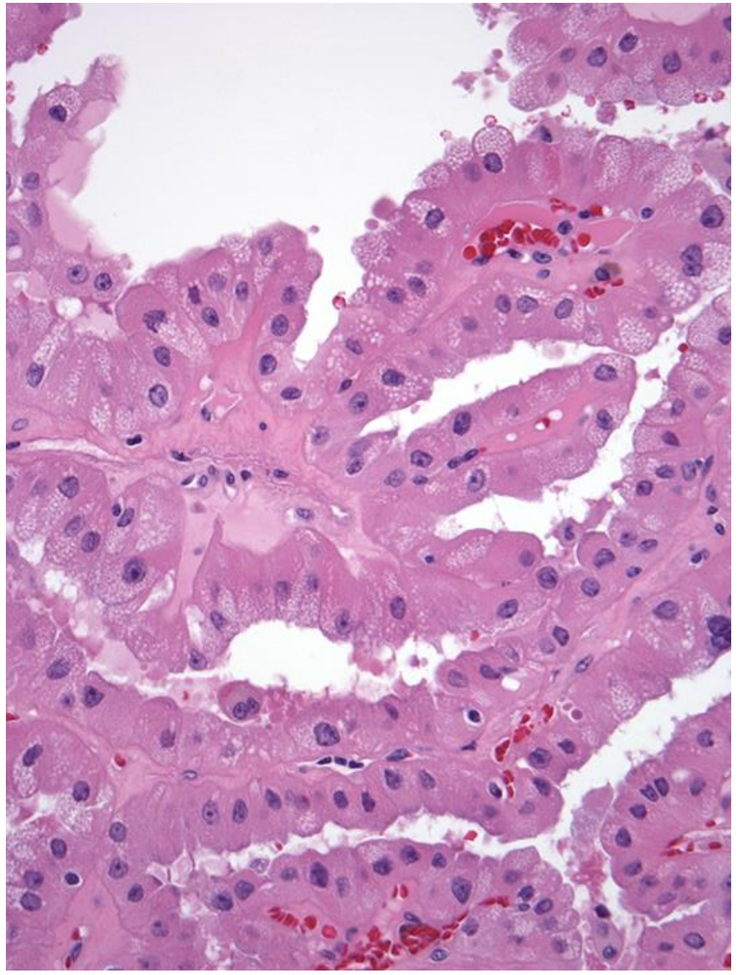
Type 1 vs Type 2 Papillary RCC*
(‘official’ in 2004 WHO)

Type 1 PRCC:

- ~~small basophilic cells~~
- single layer of cells on FVCs
- low grade
- ~~CK7+, AMACR+~~
- Trisomy 7/17

Type 2 PRCC:

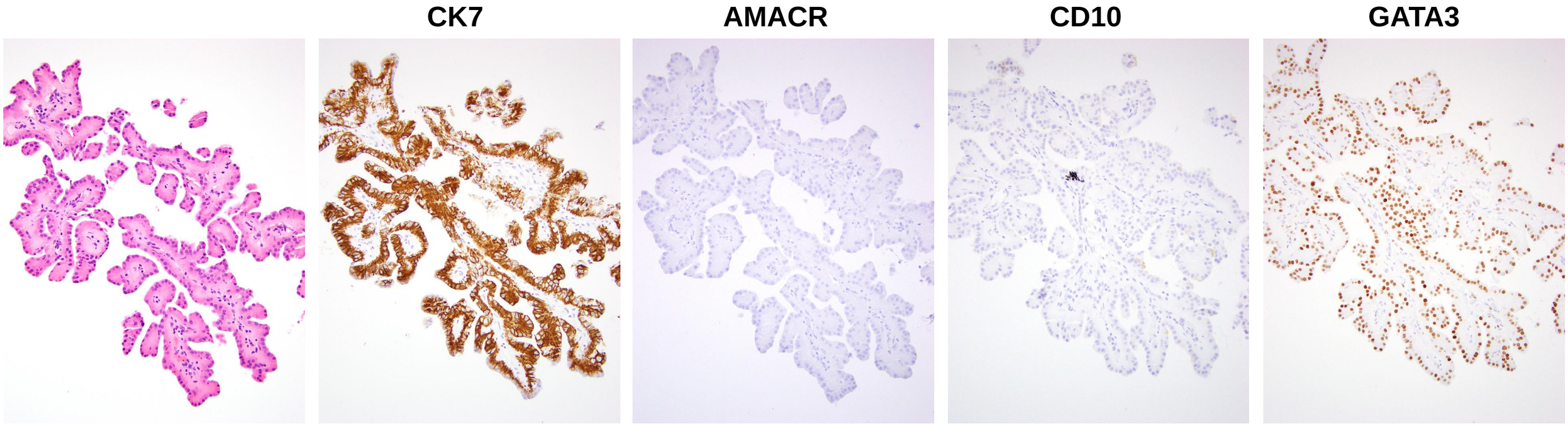
- ~~larger~~ eosinophilic ~~cells~~
- ~~pseudostratified cells on FVCs~~
- ~~higher grade~~
- CK7-/+, AMACR+
- ~~Subset with trisomy 7/17~~



*has never been subclassified at BWH

➢ Papillary Renal Neoplasm with Reverse Polarity

- M=F, median 66 yo, pT1a
- In one study (N=18):
  - CK7+/-, AMACR-/+, CD10-/+, GATA3+, CKIT-
  - +7 (33%), +17 (33%), +7/+17 (20%)
  - KRAS mutation



Al-Obaidy K et al, AJSP 2019

More evidence to NOT ‘type’ PRCC

ORIGINAL ARTICLE

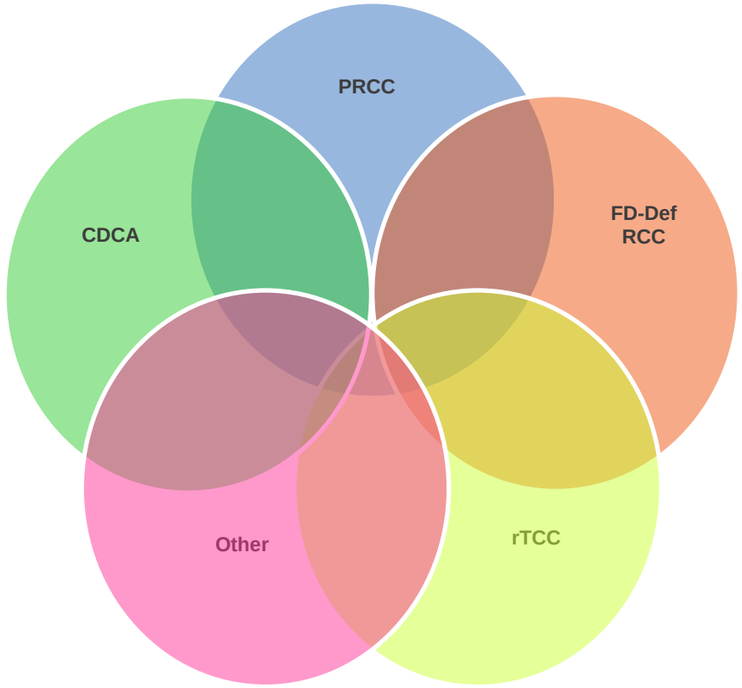
High WHO/ISUP Grade and Unfavorable Architecture, Rather Than Typing of Papillary Renal Cell Carcinoma, May Be Associated With Worse Prognosis

Chen Yang, MD, Brian Shuch, MD,† Harriet Kluger, MD, PhD,‡ Peter A. Humphrey, MD, PhD,* and Adebowale J. Adeniran, MD**

Am J Surg Pathol 2020;44:582–593

- 185 PRCC cases were evaluated:
  - 117 (63.2%) type 1, 45 (24.3%) type 2, and 11 (5.9%) mixed type 1 and type 2
- WHO/ISUP grade, pathologic stage, tumor size, and solid, micropapillary, or hobnail architecture associated with worse DFS and OS (univariate analysis, $P<0.05$)
- **No difference in DFS ($P=0.8237$) and OS ($P=0.8222$) for type 1 versus type 2 PRCC**

Differential Diagnosis of So-Called Type II PRCC



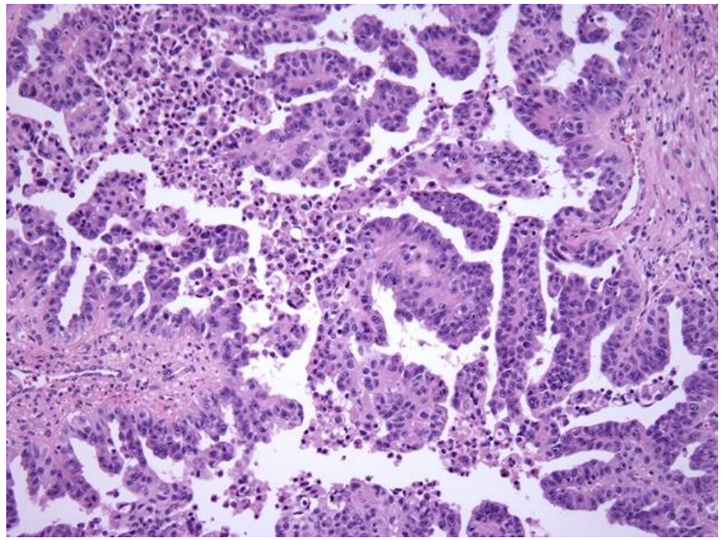
Heterogenous group of tumors with overlapping morphologic findings; many with distinct genetic/molecular alterations

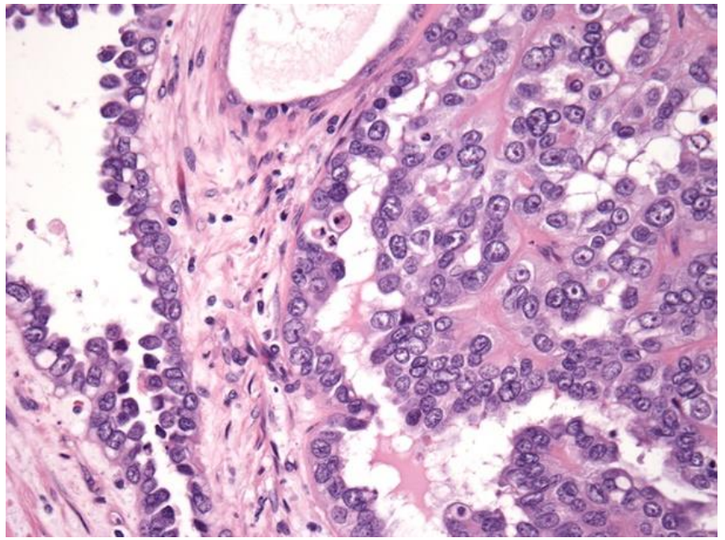
- Papillary RCC
- Collecting Duct Carcinoma
- Tubulocystic RCC
- FH-Deficient RCC
- ALK-Translocated RCC
- TFE3-Translocated RCC
- Biphasic Hyalinizing Psammo RCC
- Unclassified RCC

Papillary Architecture

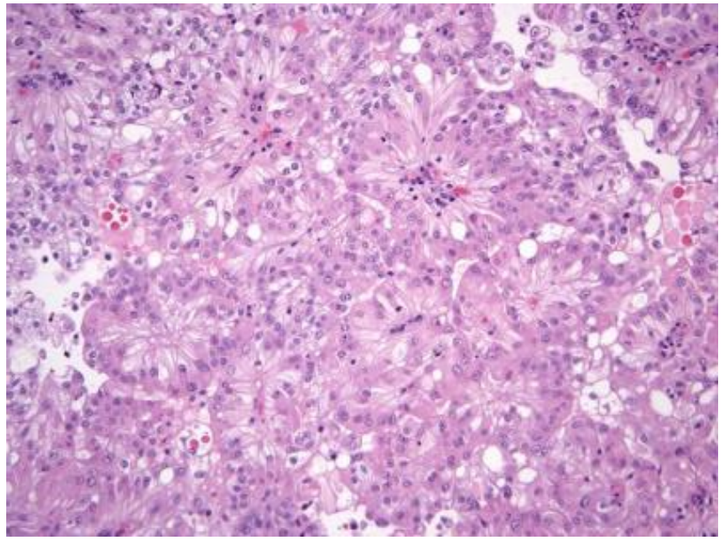
High grade cytology

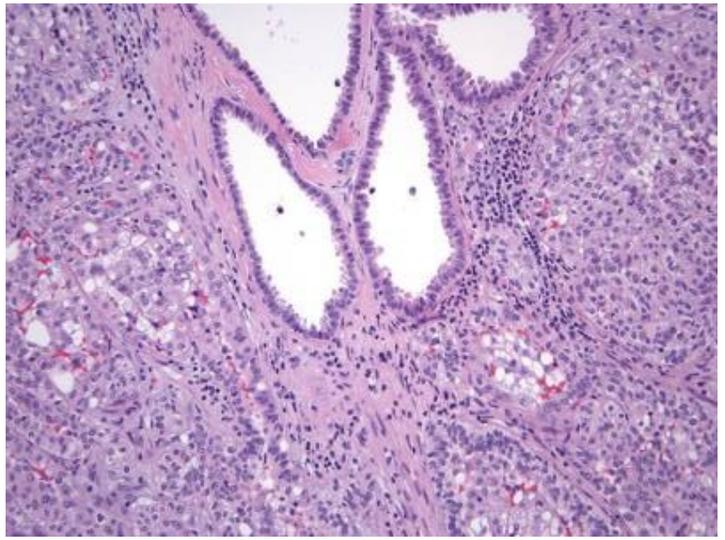
CASE #1





CASE #2



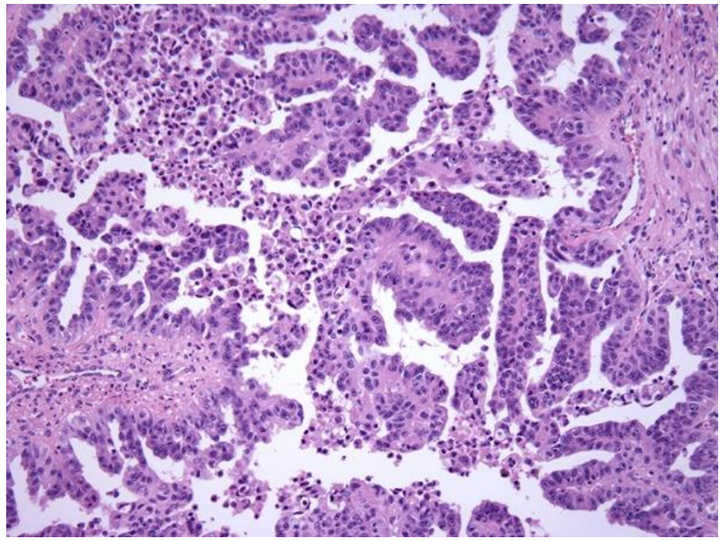


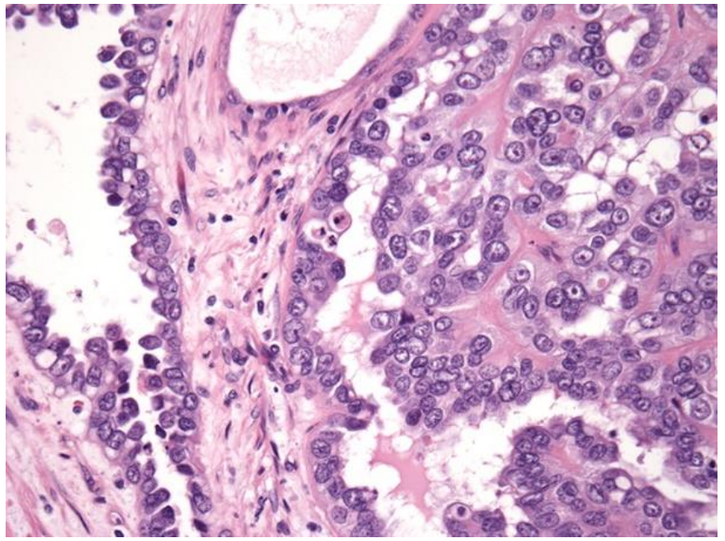
Papillary Architecture

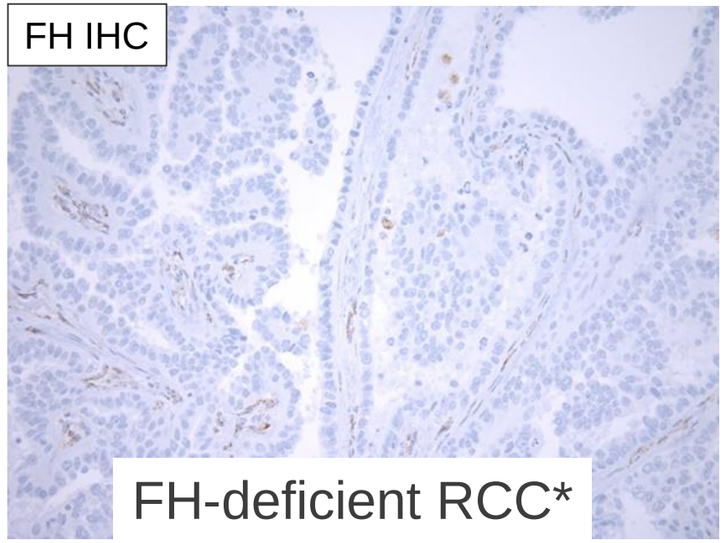
High grade cytology

Distinct IHC / Genetics

CASE #1







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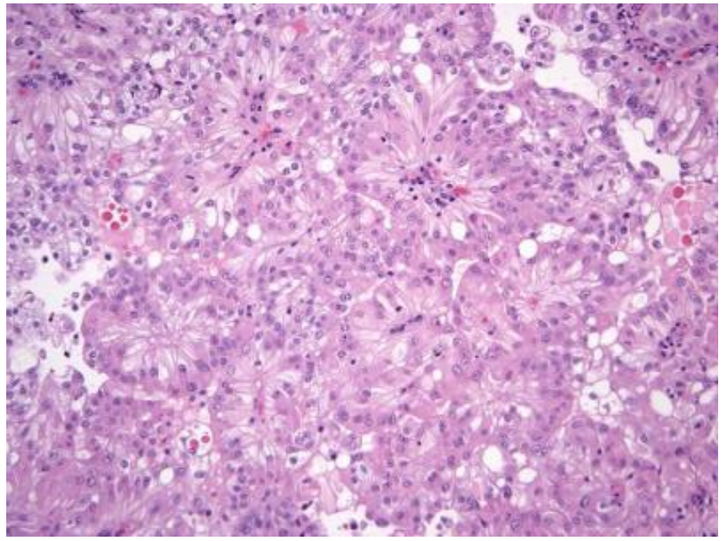
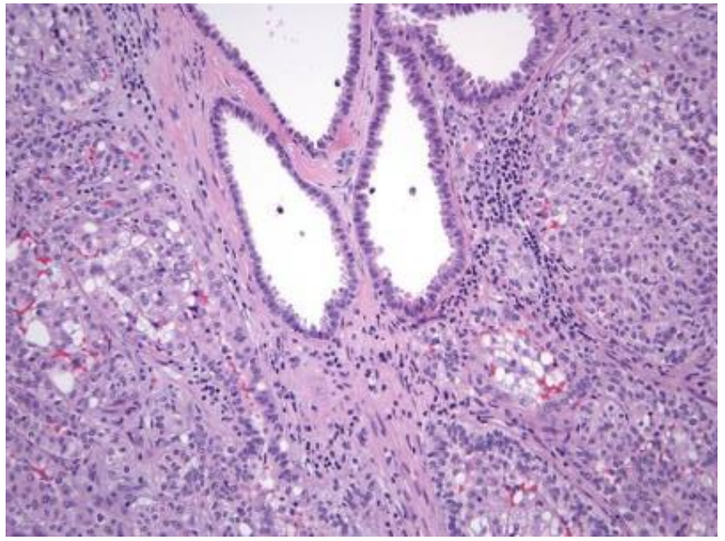
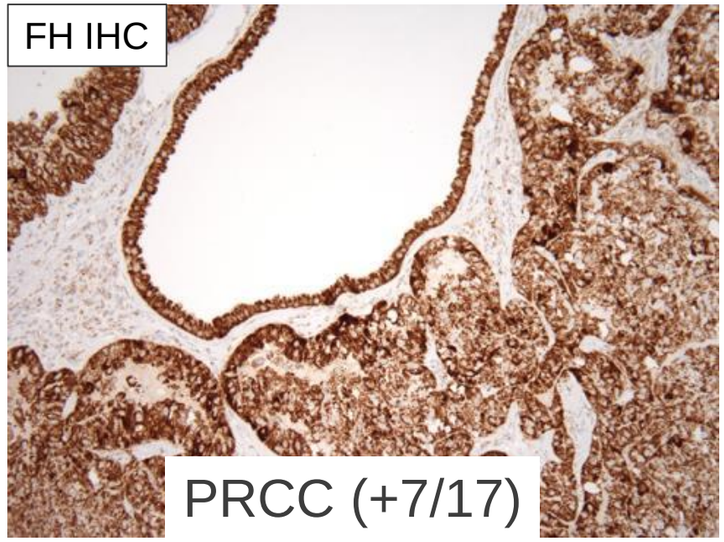






*Requires genetic work up for HLRCC

RCC associated with FH-Deficiency/HLRCC

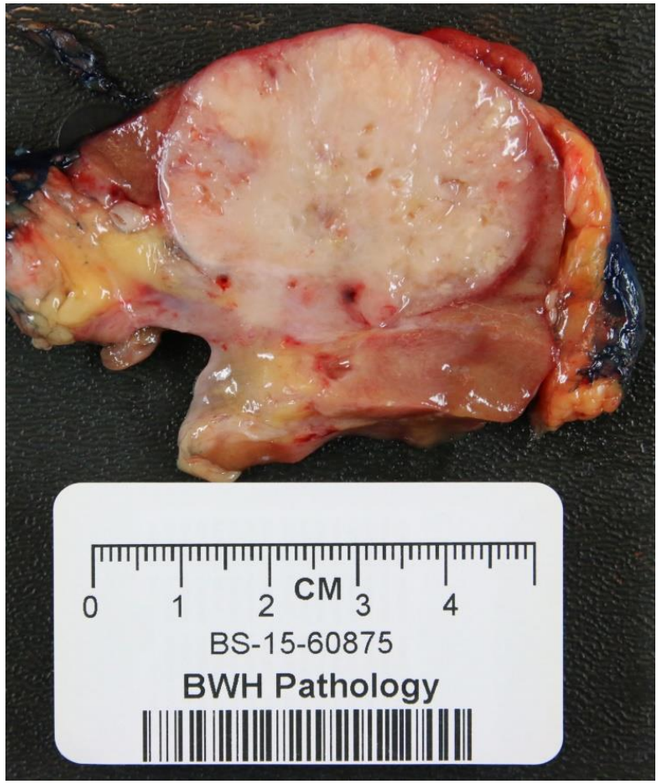
- Part of ‘hereditary leiomyomatosis and renal cell cancer syndrome’ (HLRCC)
- Genetics: Autosomal dominant, mutation in the fumarate hydratase (FH) gene
- Clinical presentation: SMTs (cutaneous and uterine leiomyomata, occasionally LMS) and RCCs (predominantly aggressive)

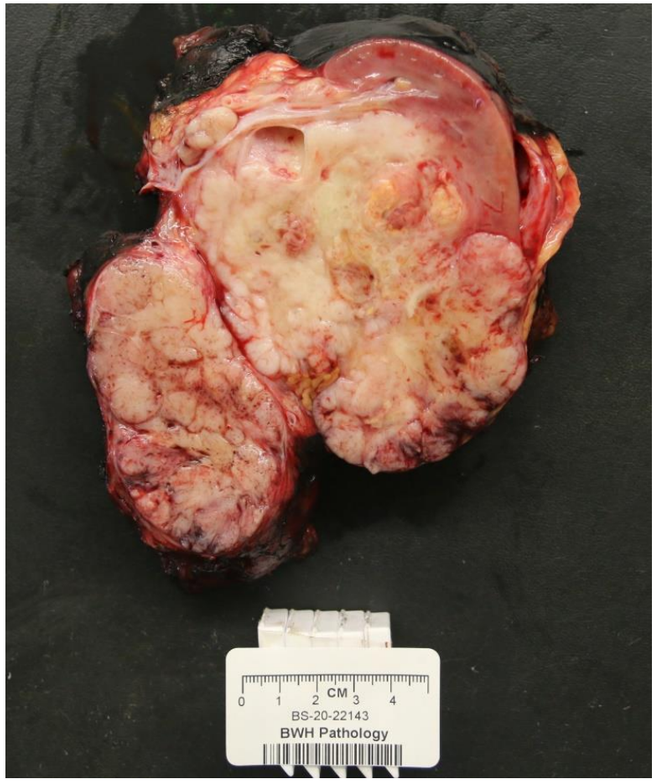
Renal Pathology – Important Update in Terminology

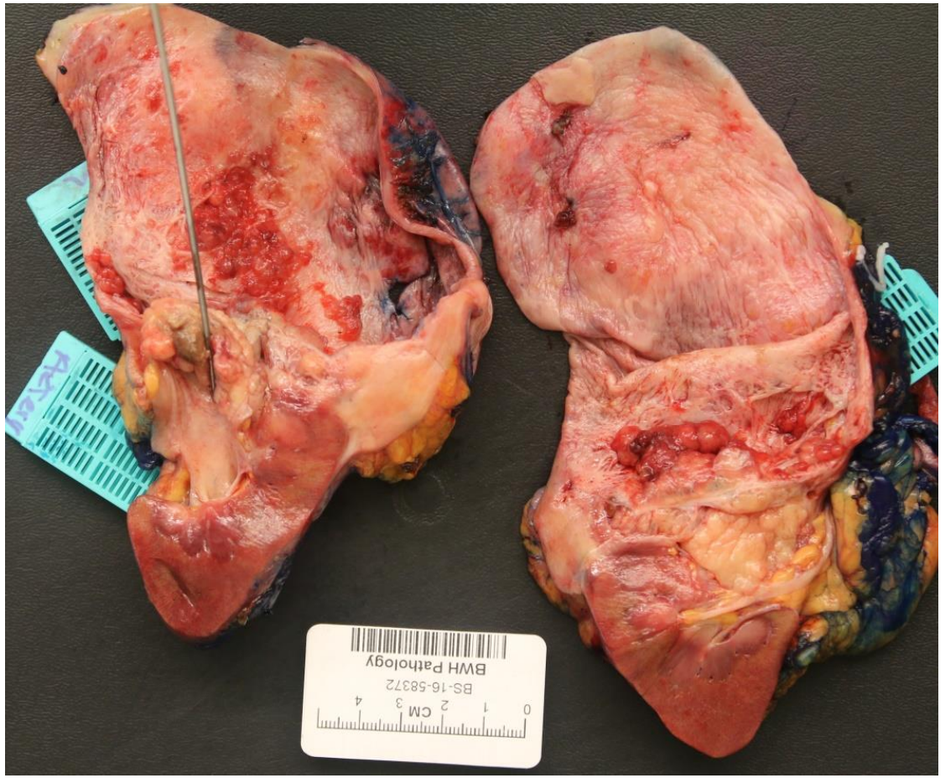
In 2016 WHO ➔ HLRCC Syndrome-Associated RCC
Only applicable if patient has HLRCC (germline)

In 2022 WHO ➔ Fumarate Hydratase (FH) -Deficient RCC
Uncertain regarding HLRCC (germline vs somatic)

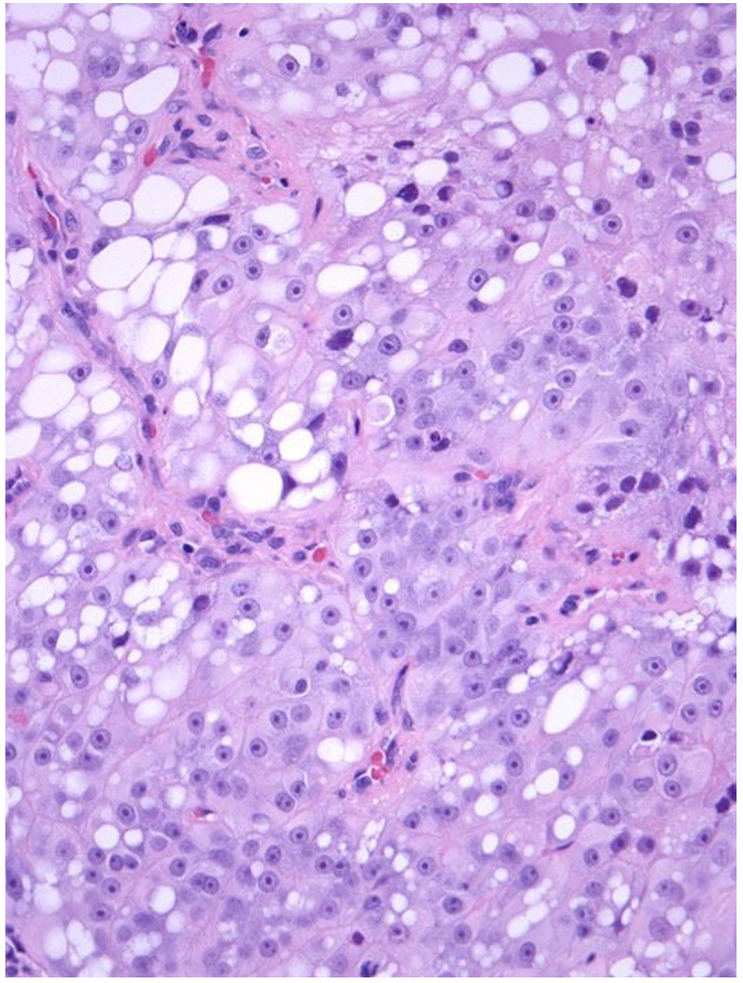
FH-Deficient RCC – Gross Findings

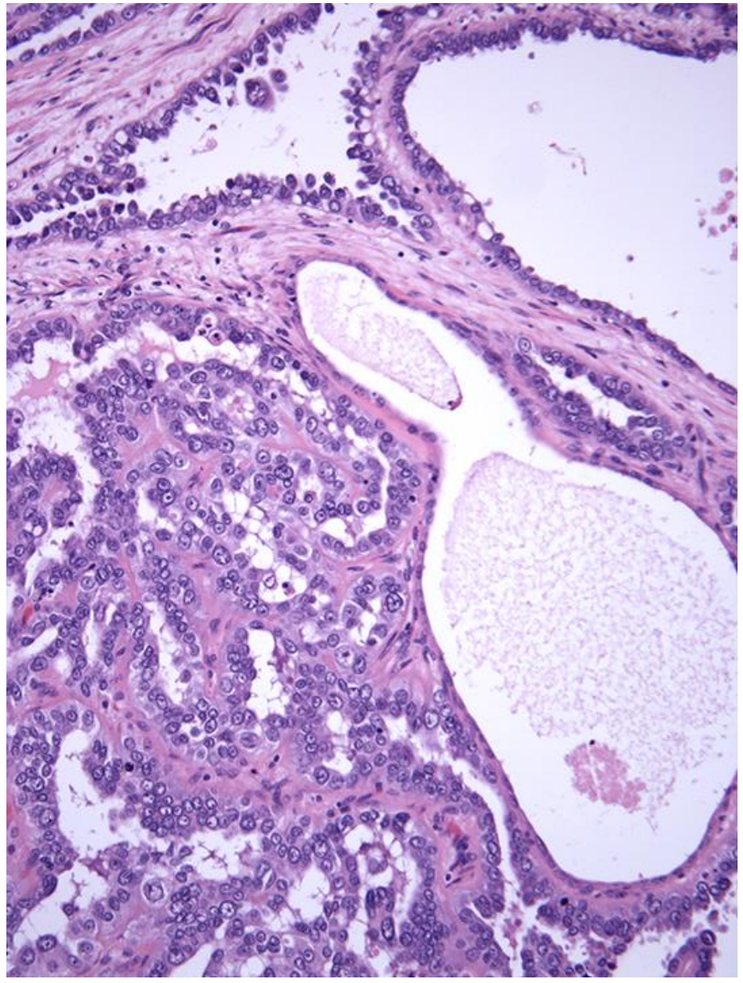


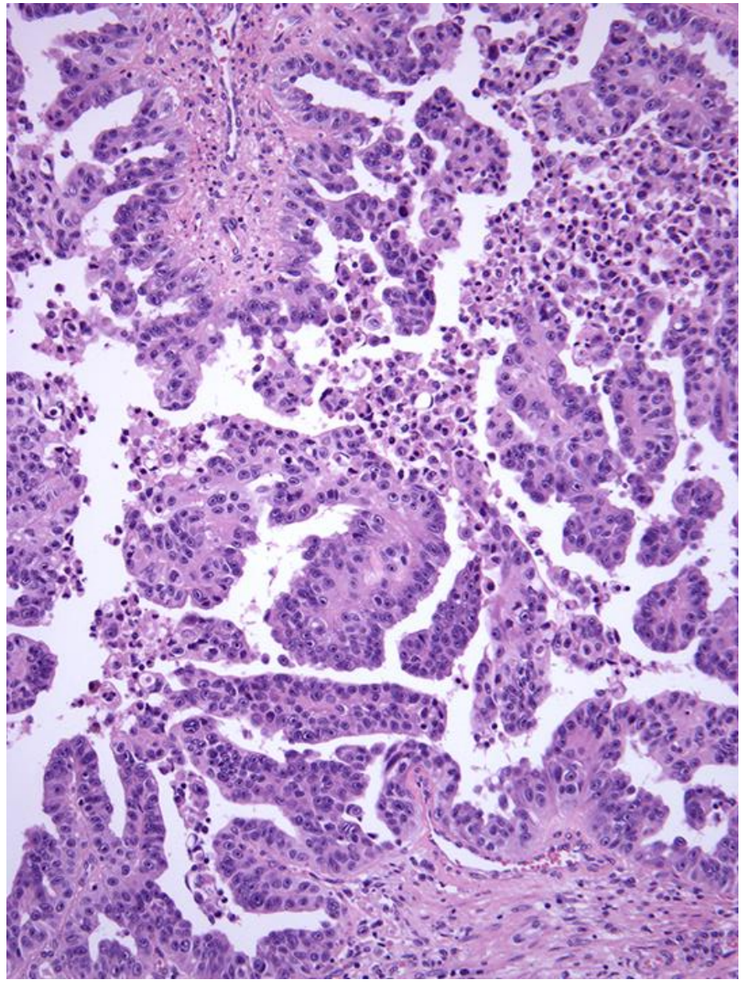




FH-Deficient RCC – Histologic Findings

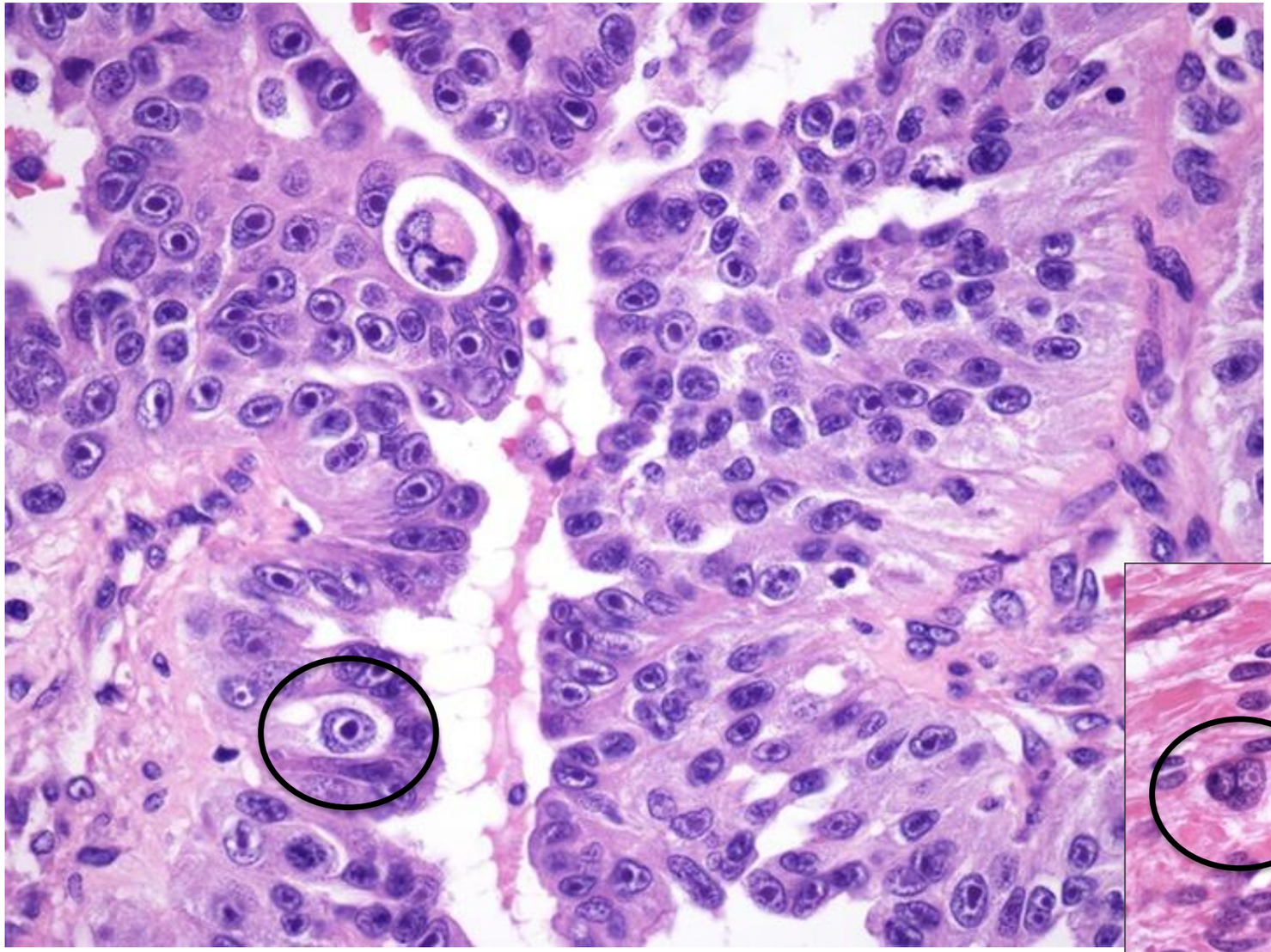




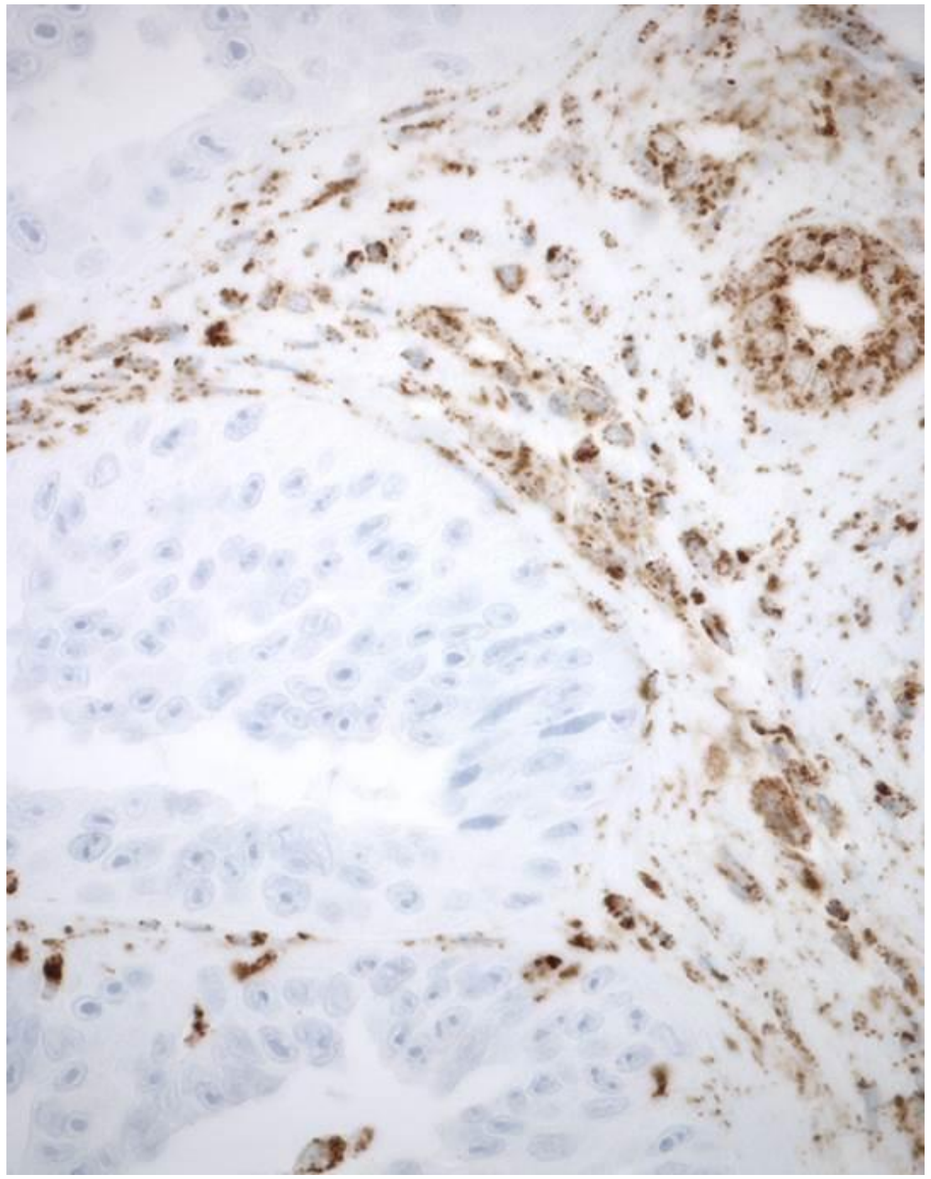


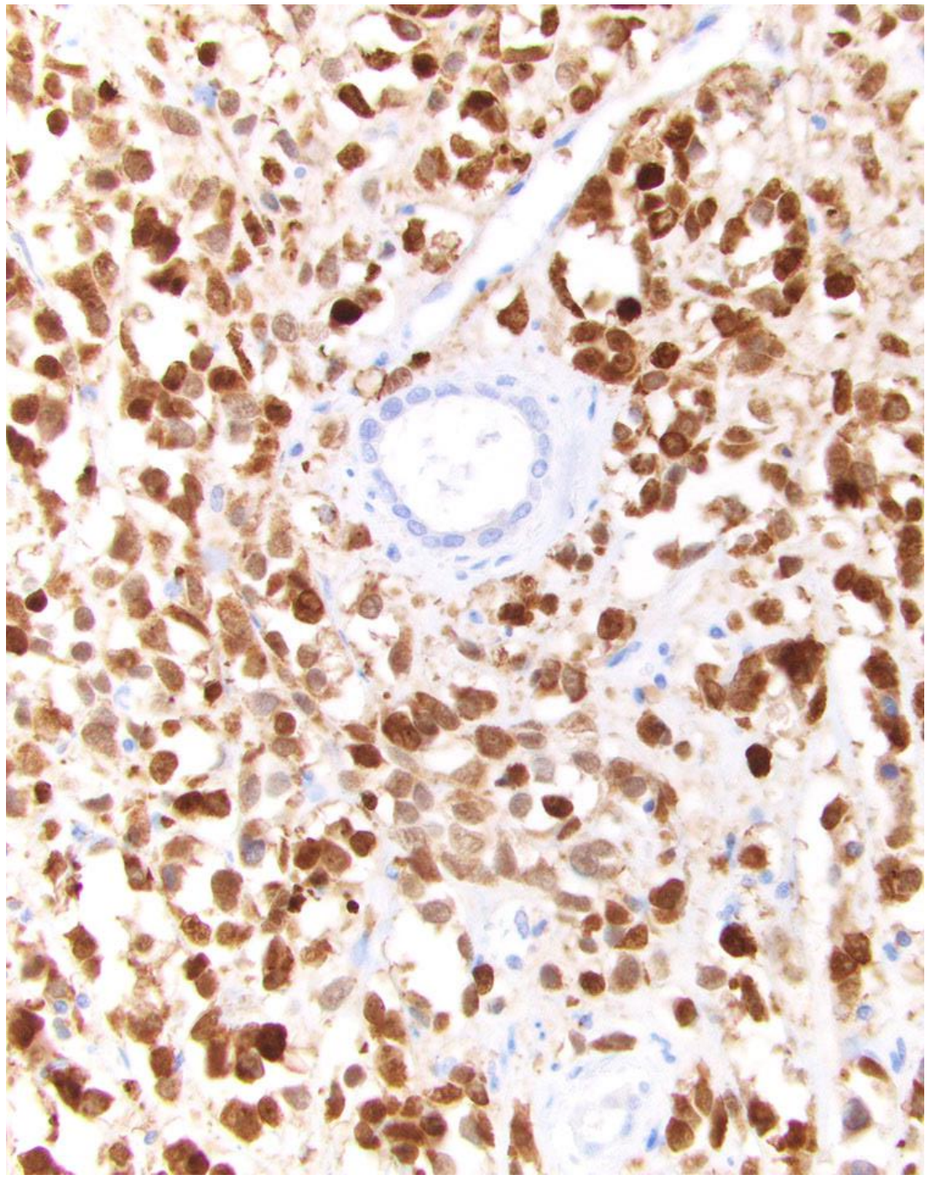
If you don’t think about it, and work it up, you won’t diagnose it!

FH-Deficient RCC – Cytologic Findings



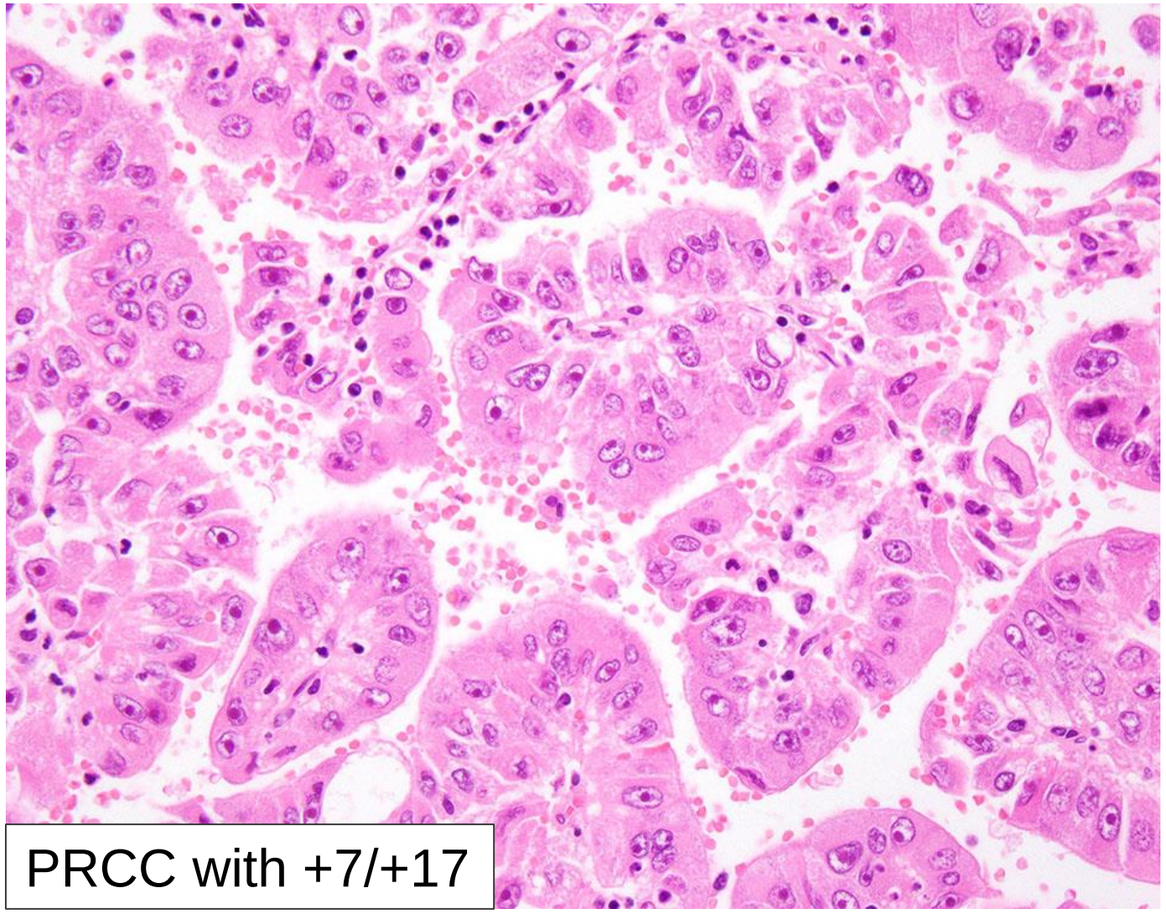
Confirmation of Diagnosis ➔ Loss of FH / 2SC Expression



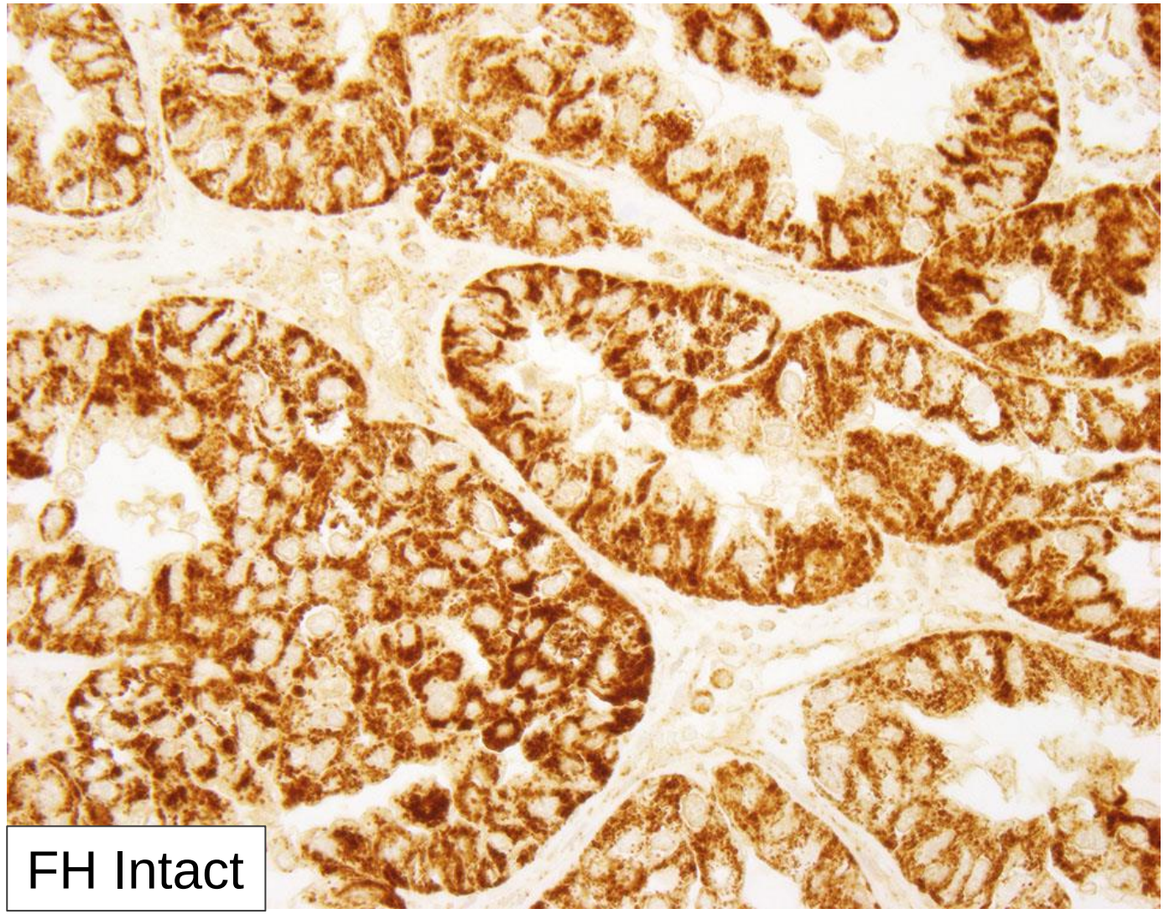


*FH loss ~80% sensitive; presence of 2-Succinocysteine (2SC) is confirmatory

Pitfall Alert
Cytologic/Nuclear Features are NOT Entirely Specific

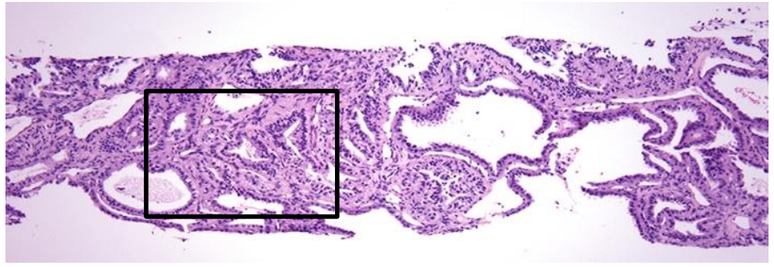


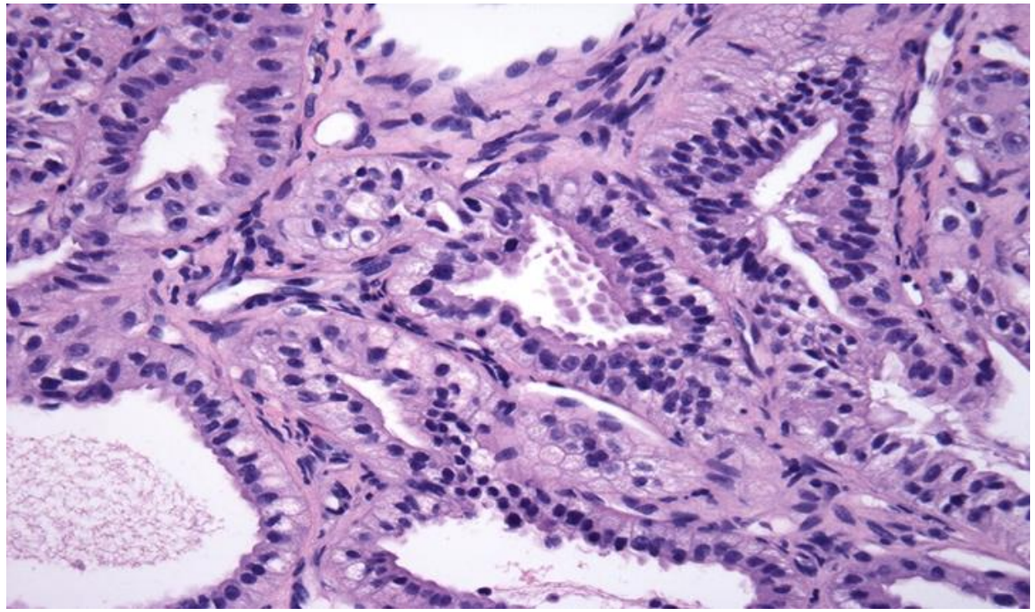
PRCC with +7/+17

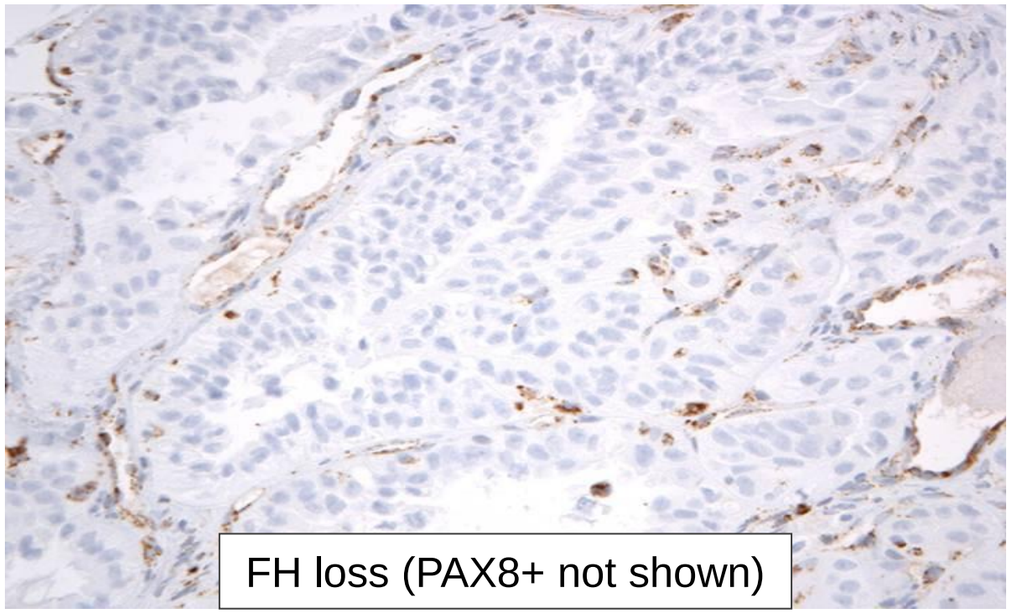


FH Intact

Pitfall Alert
Cytologic/Nuclear Features are NOT 100% Sensitive

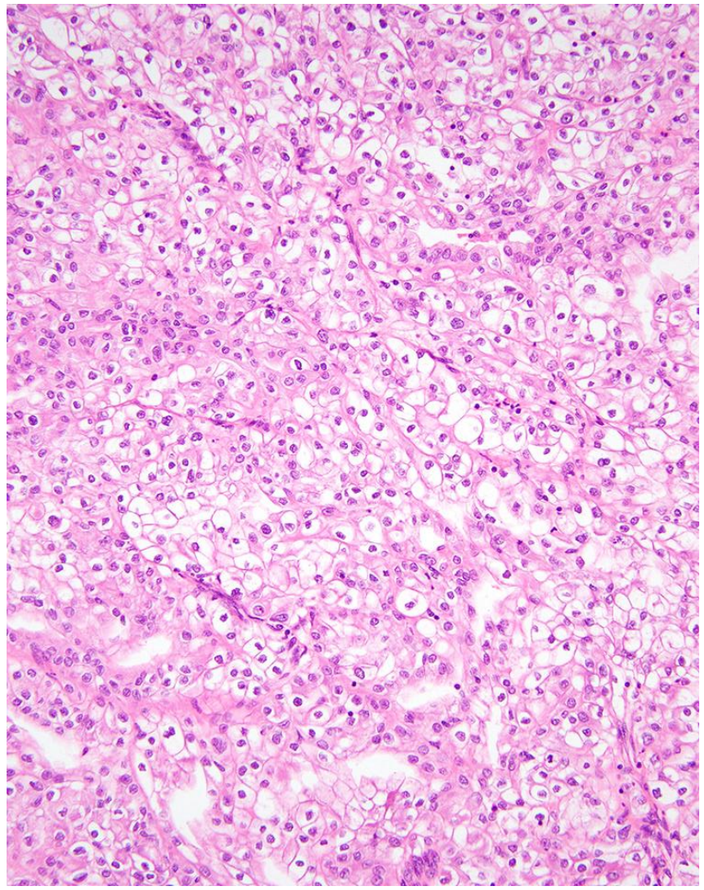
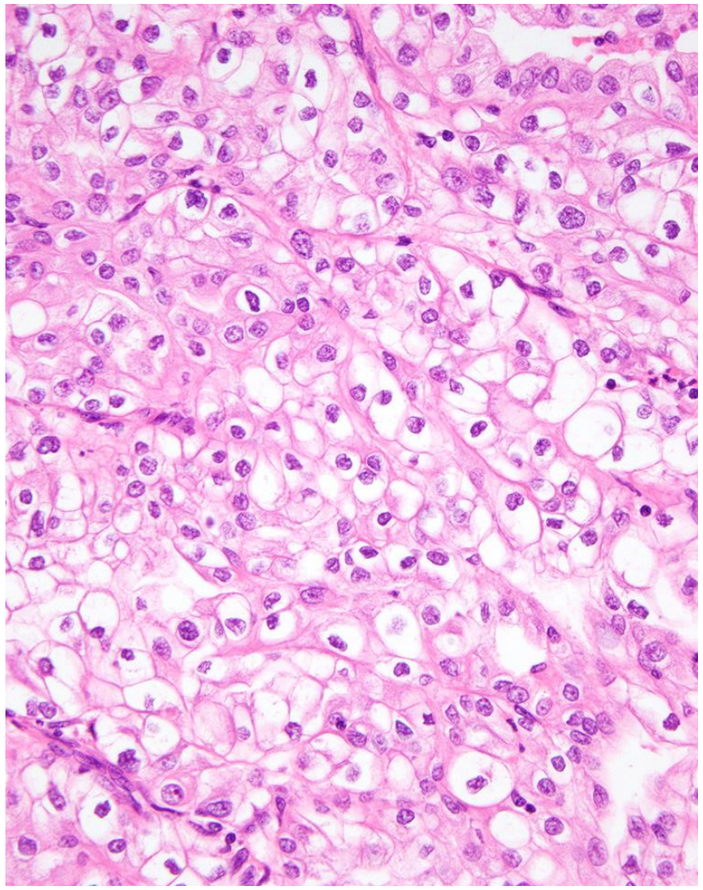
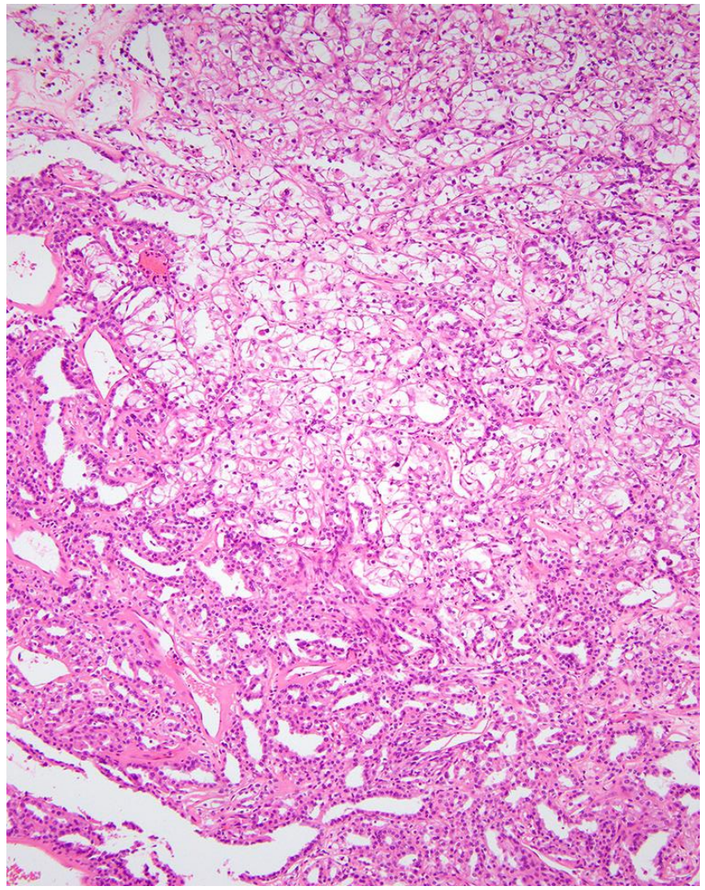






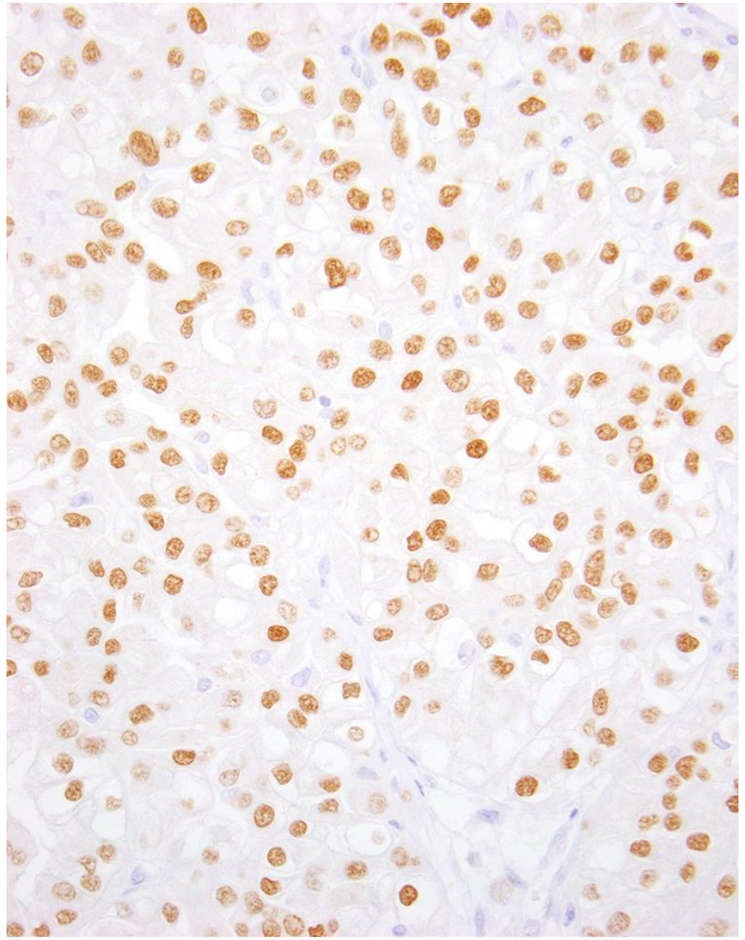
47yo male with small renal mass and bone lesions ➔ T7 Bone Biopsy

Pitfall Alert
Cytologic/Nuclear Features are NOT 100% Sensitive

83yo male with a renal mass

PAX8



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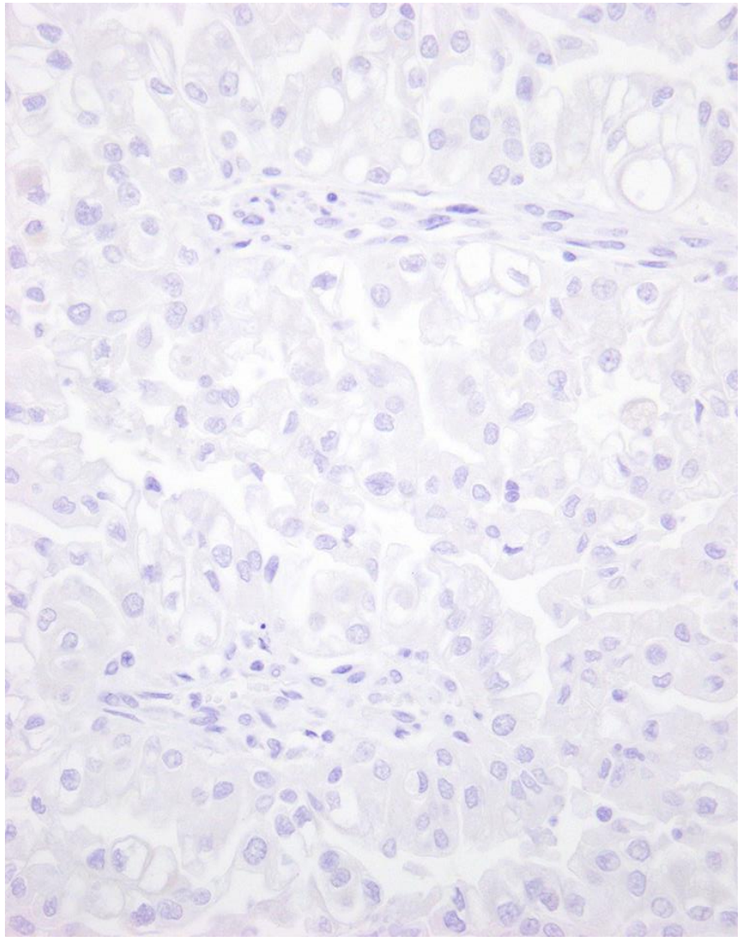
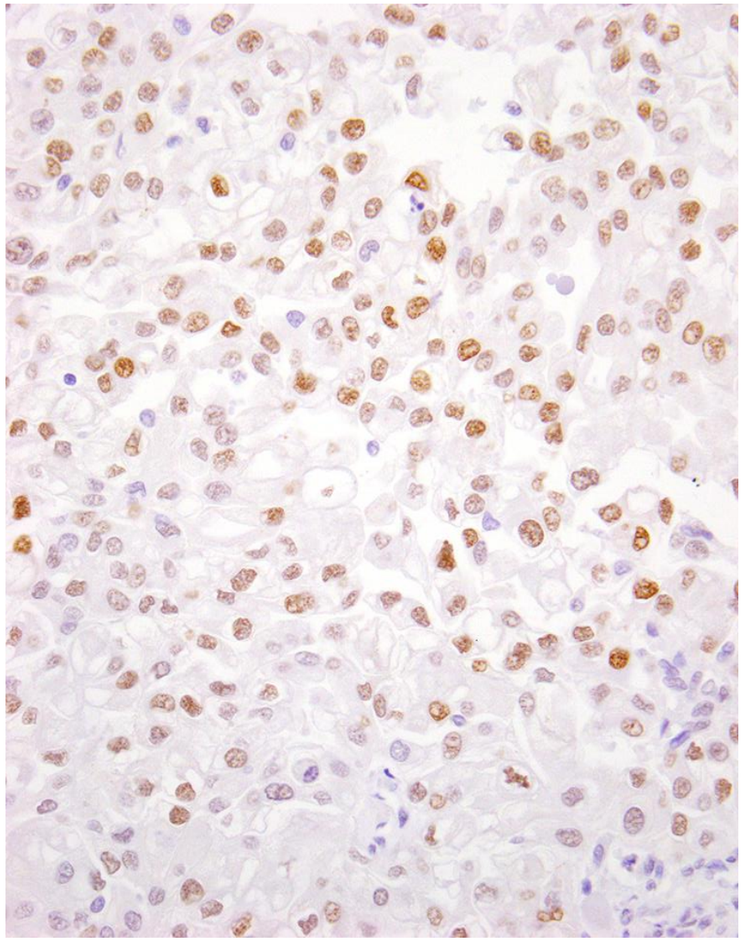
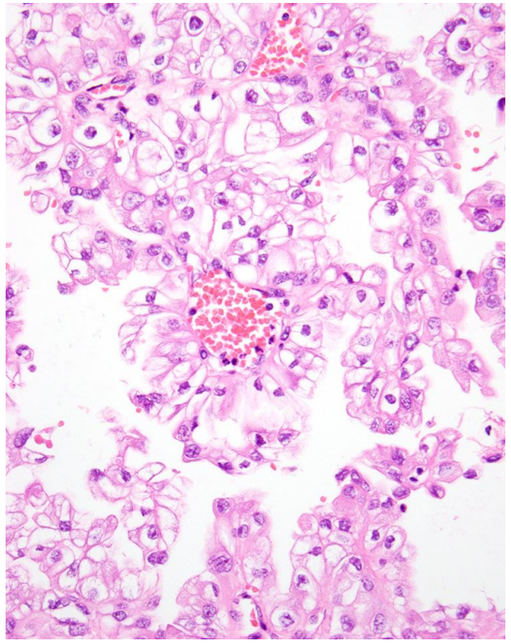
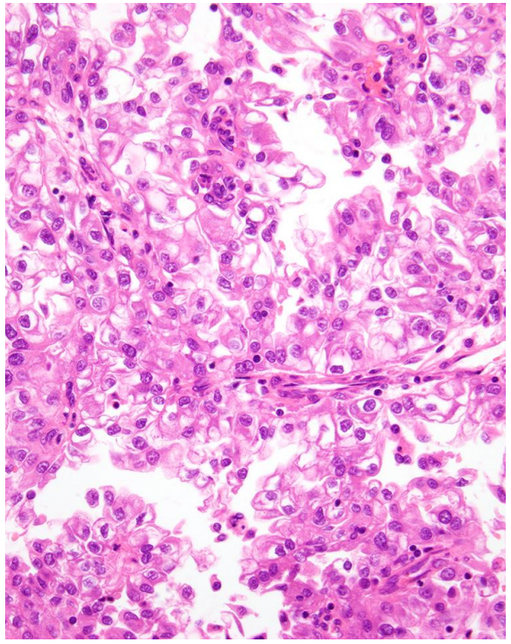
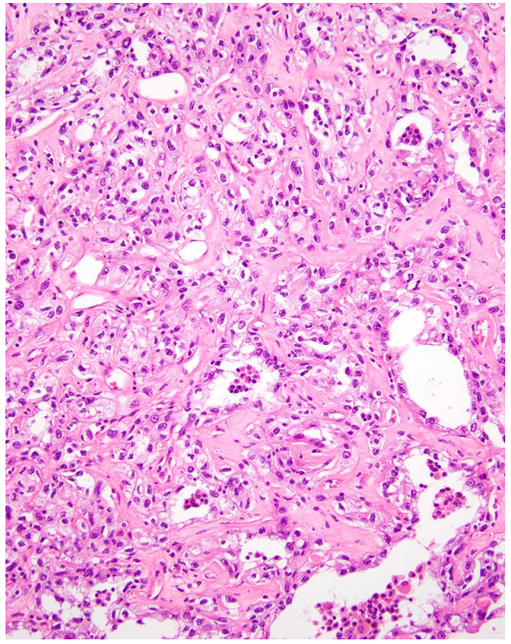
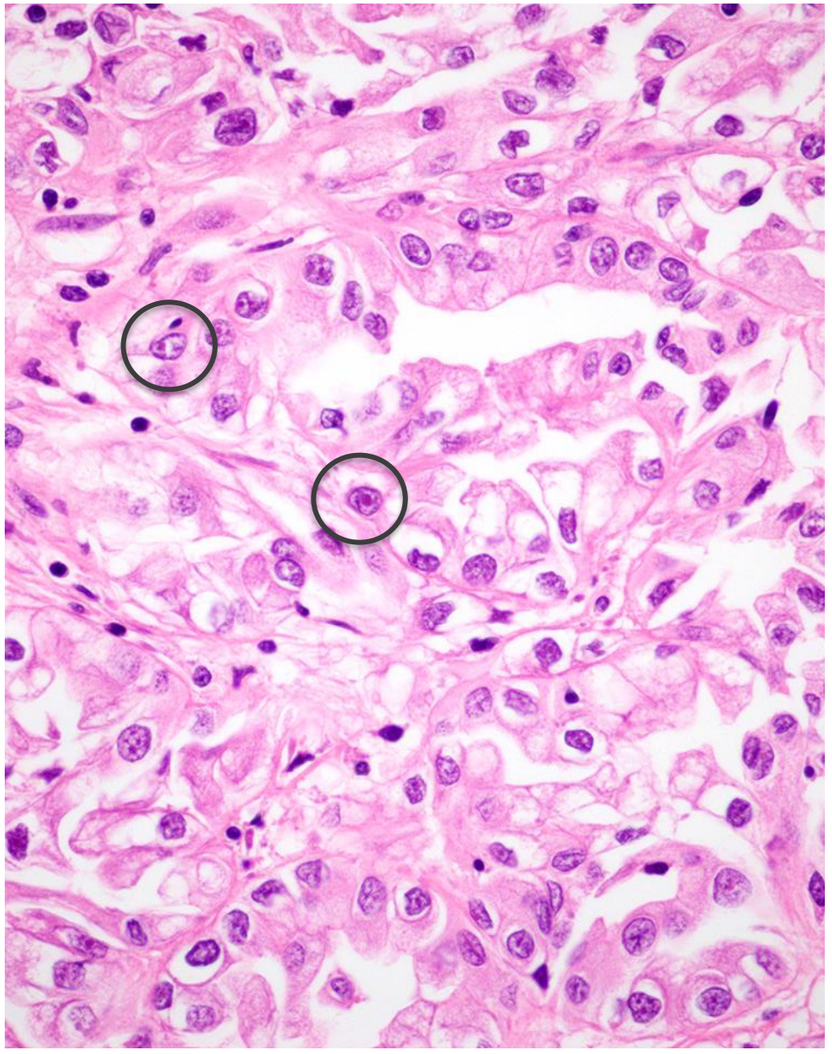
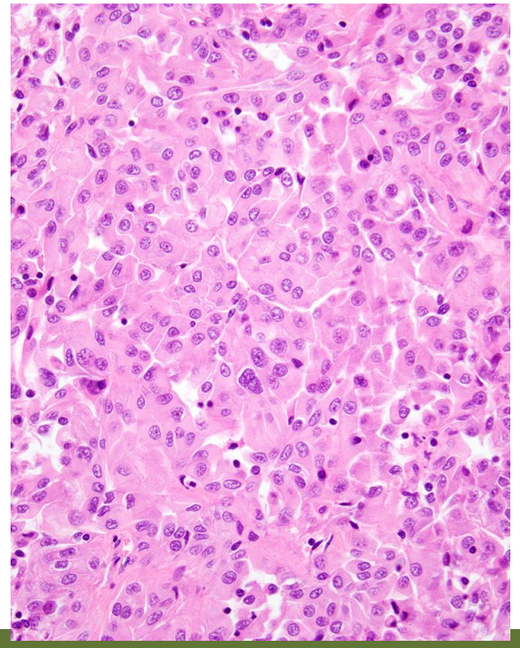
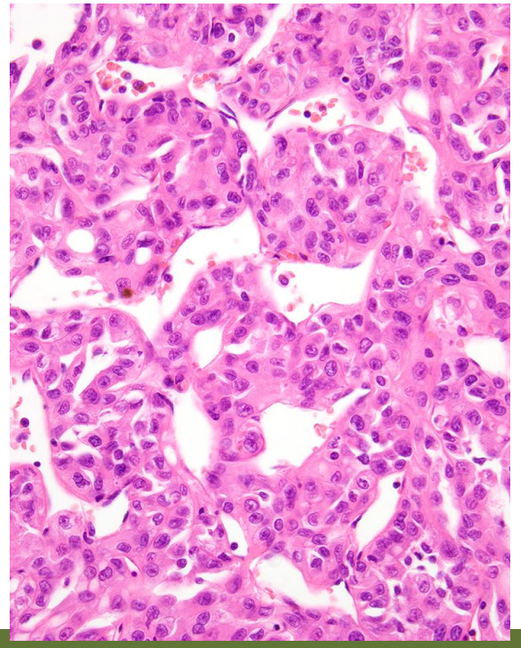
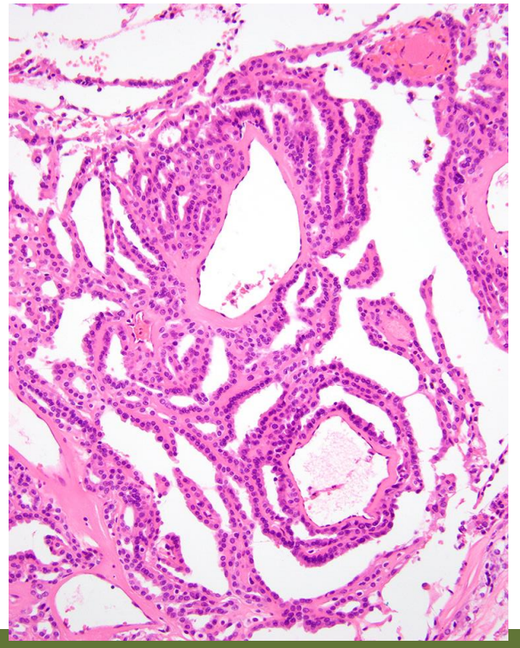


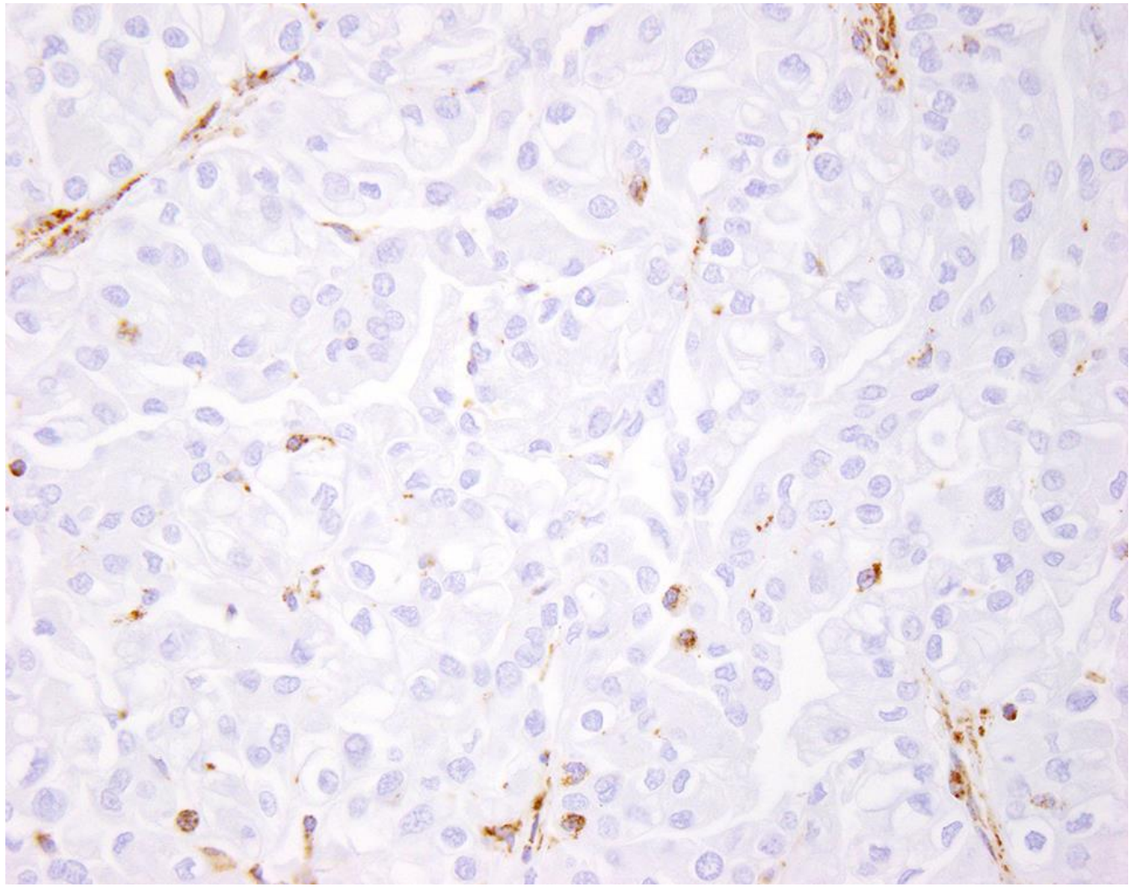
TFE3



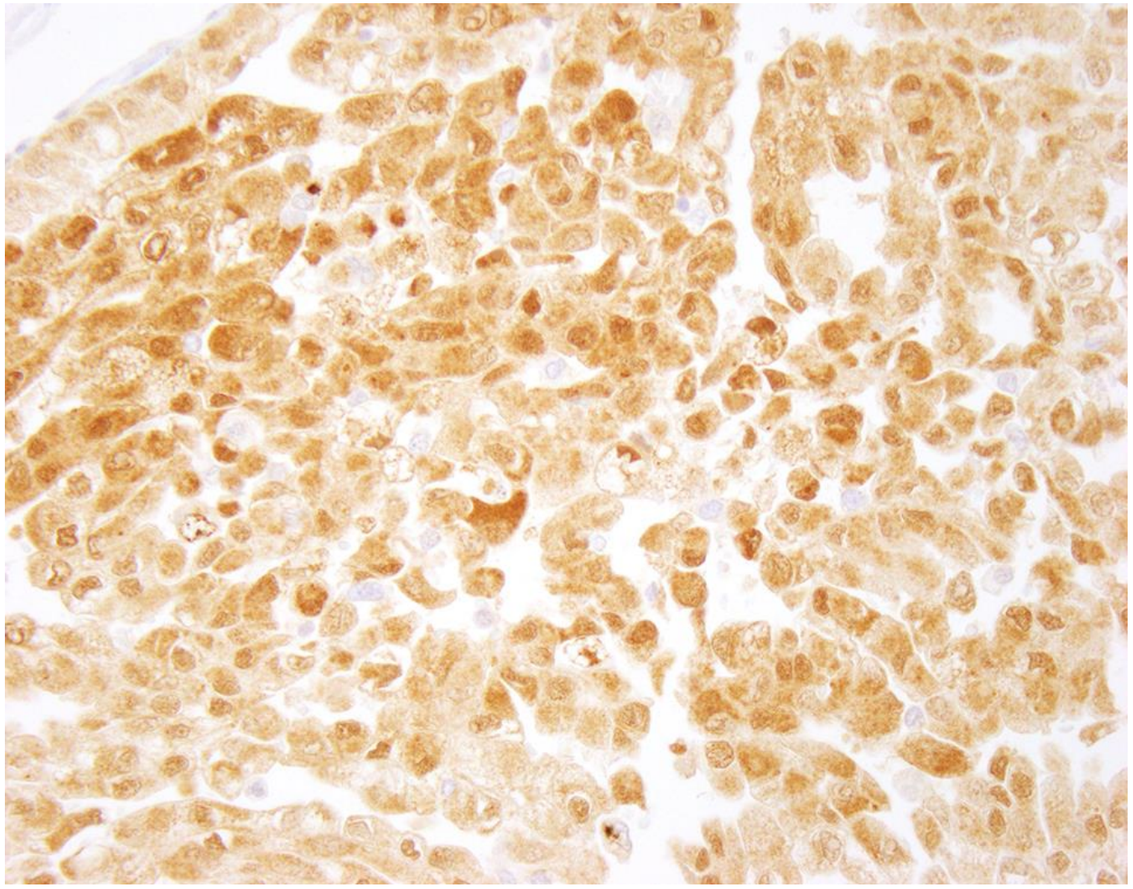
83yo male with a renal mass

FH

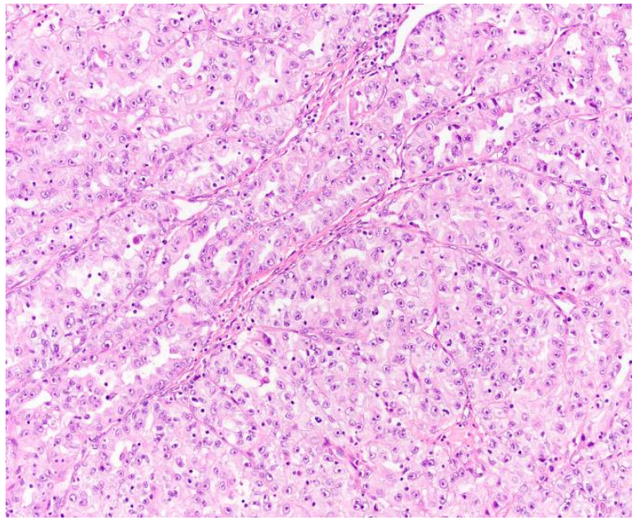


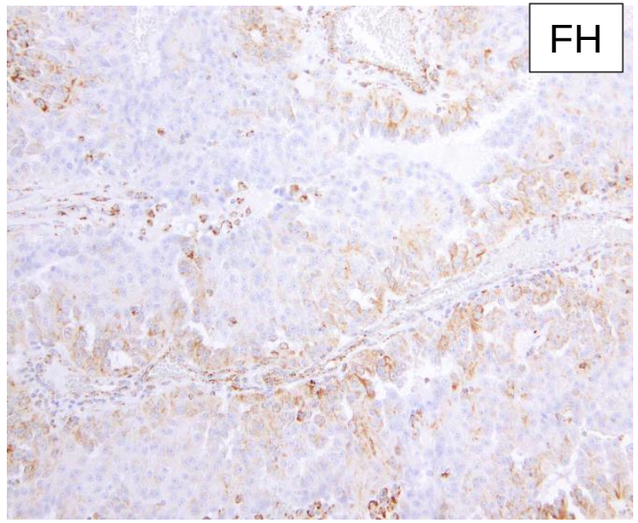
2SC

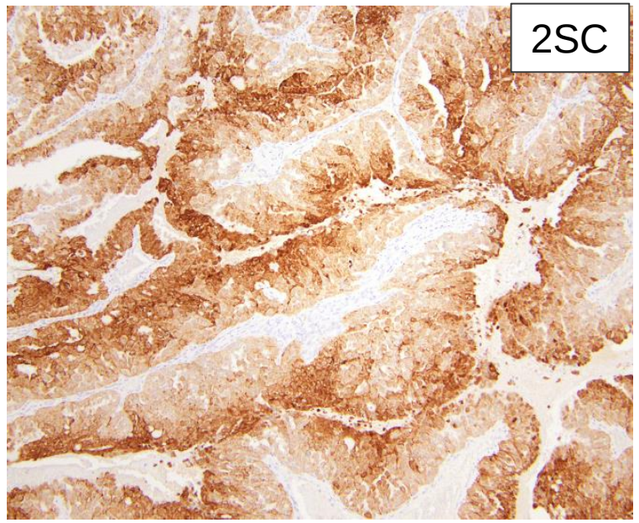


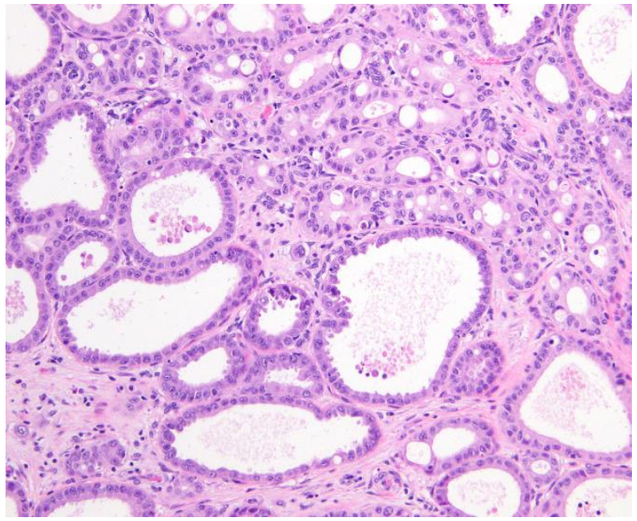
83yo male with a renal mass ➔ FH-Deficient RCC

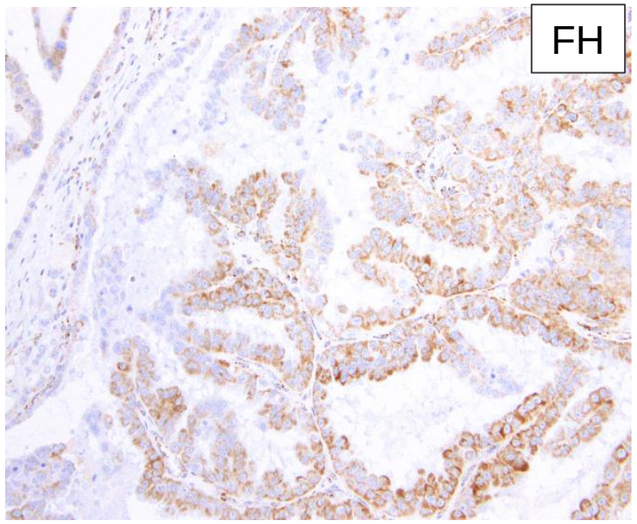
Pitfall Alert - Heterogeneous FH Expression
(20% of FH-deficient RCC are FH Intact & Sometimes Patchy +)

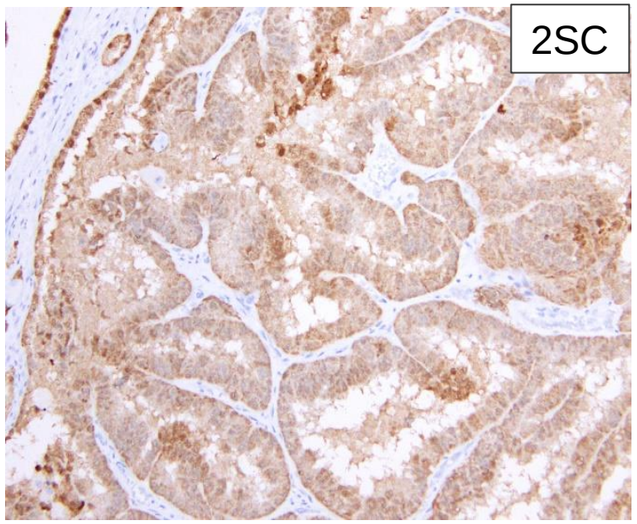




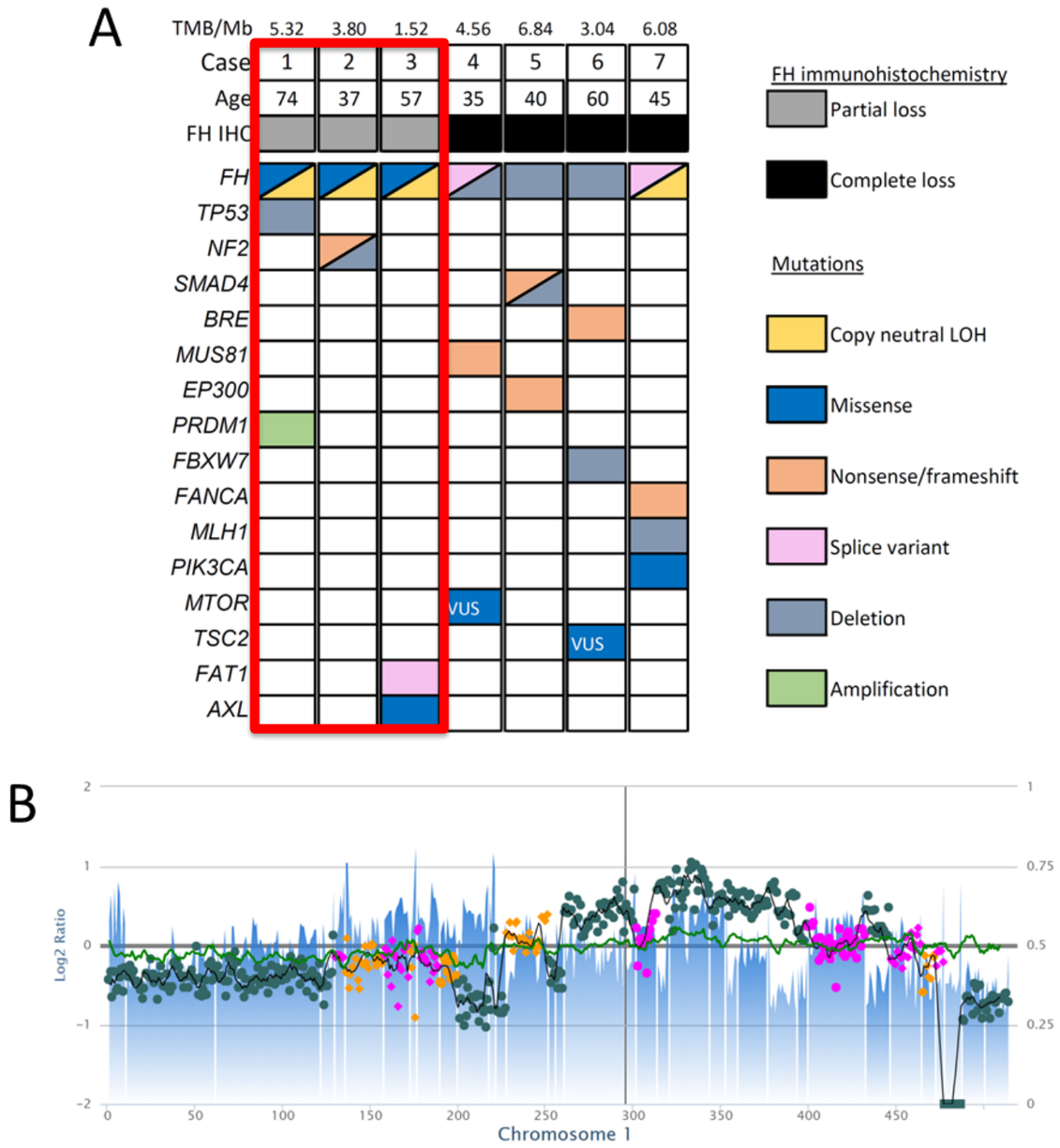






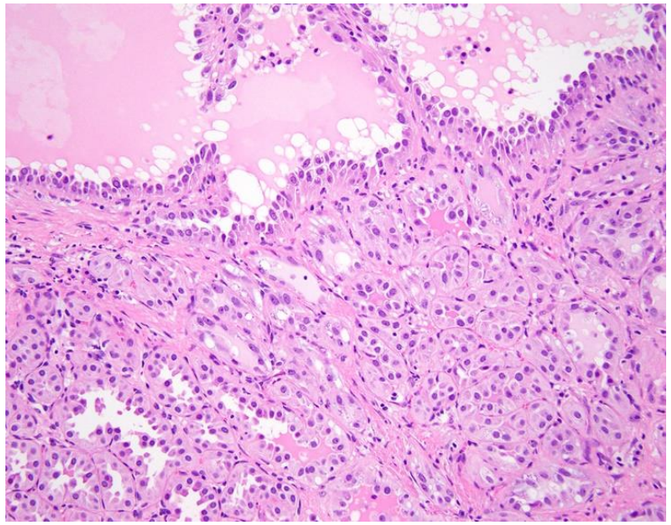


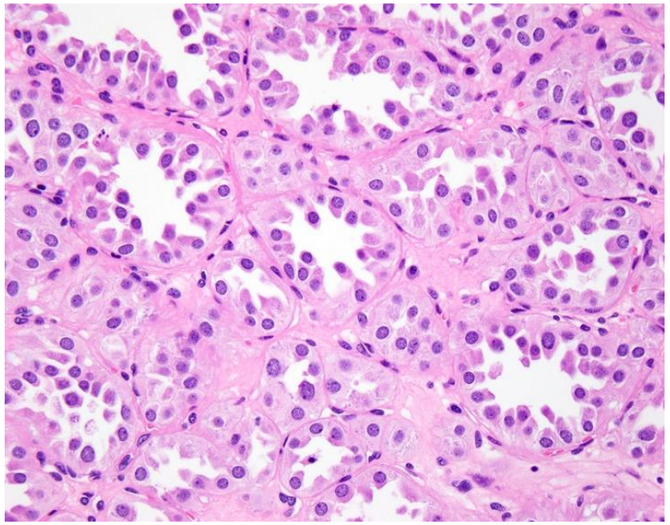
Anderson WJ, et al. *In J Surg Pathol,* 2022 Sep;30(6):606-615. PMID: 35048731

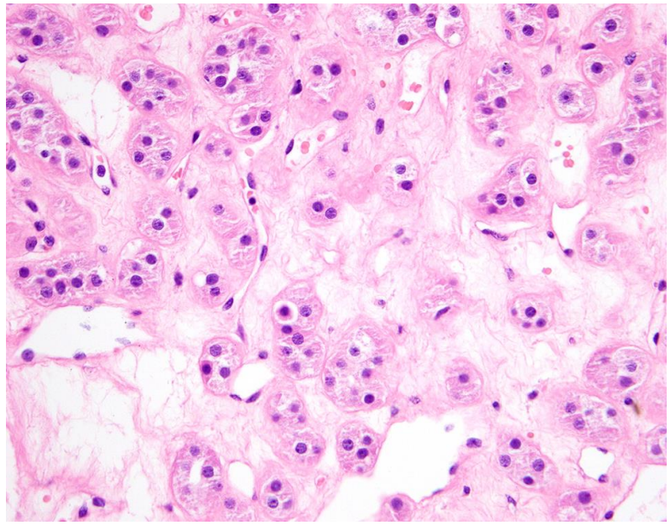


Anderson WJ, et al. *In J Surg Pathol,* 2022 Sep;30(6):606-615. PMID: 35048731

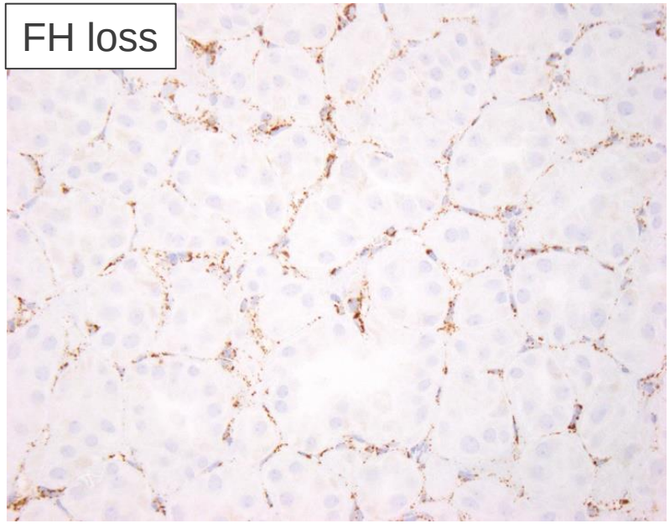
Pitfall Alert
Not All FH-Deficient RCCs are ‘High Grade’

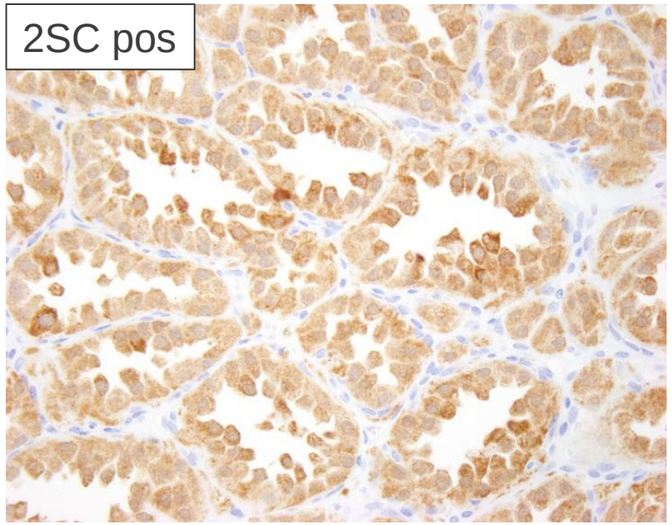




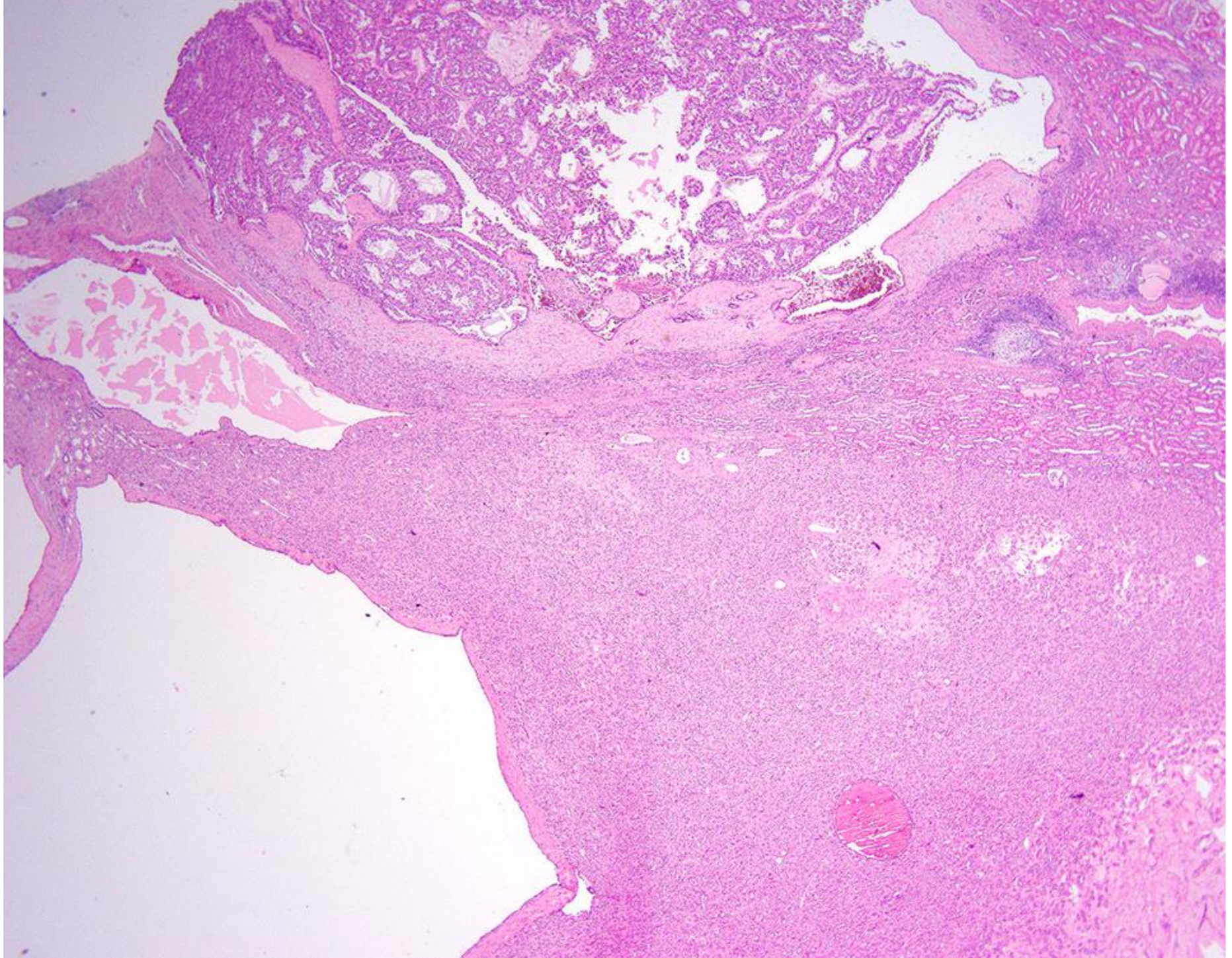


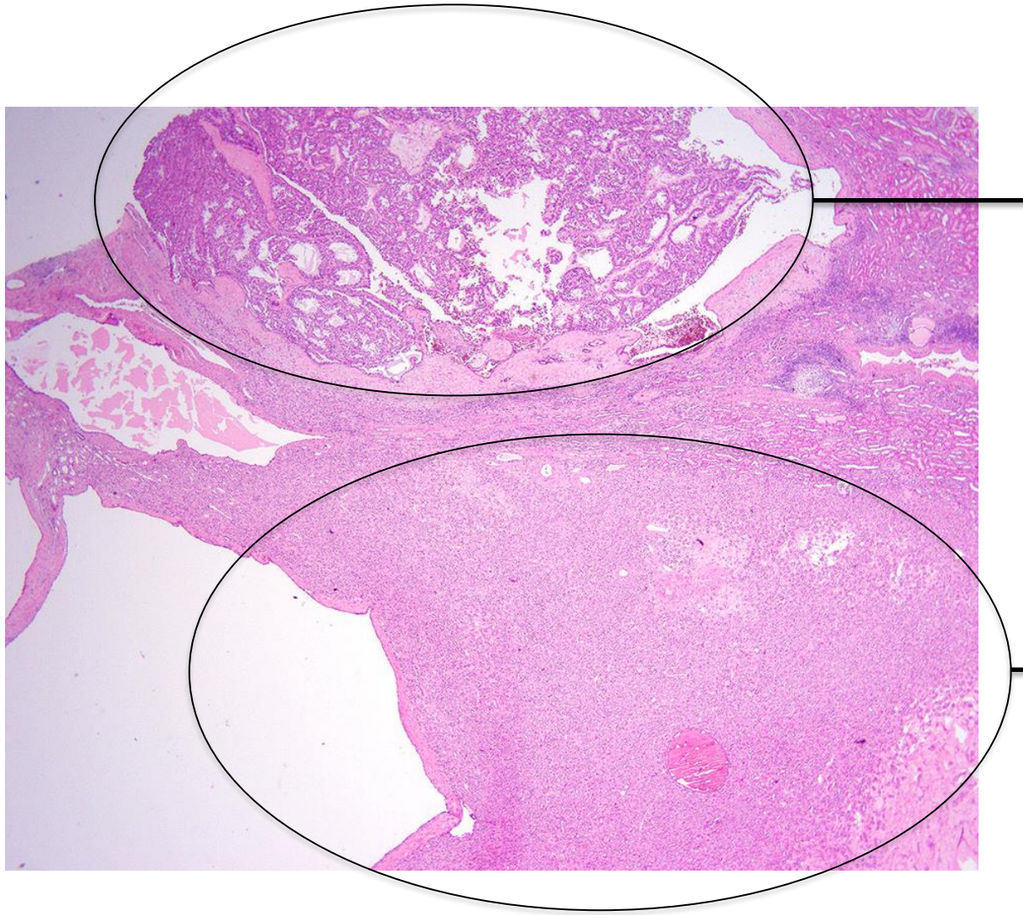
- Solid, cystic, eosinophilic, hobail, nested, lack ‘typical’ FH nuclear features
- DDX: Other RON (SDH, etc)
- IHC: FH-/2SC+
- Variable behavior; F/U required

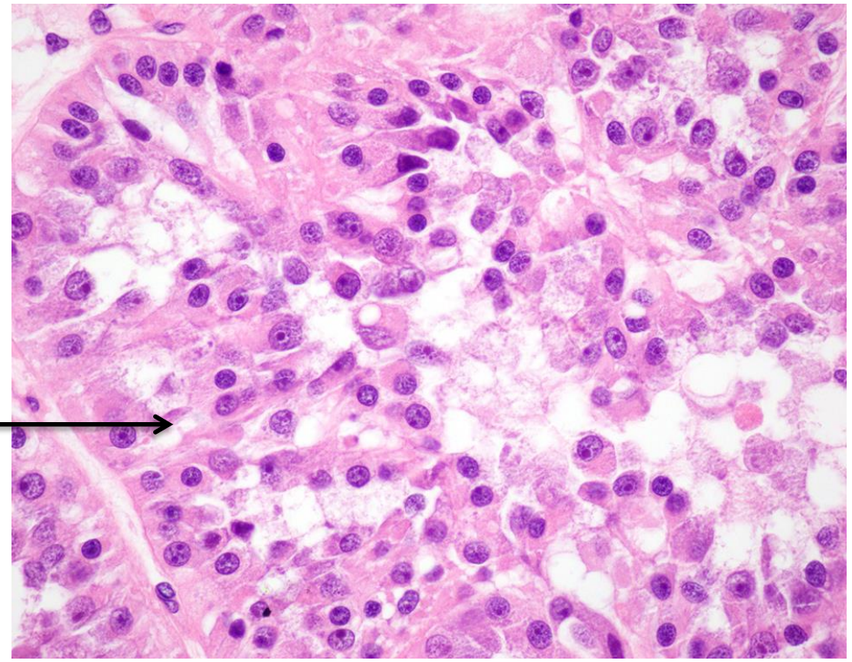


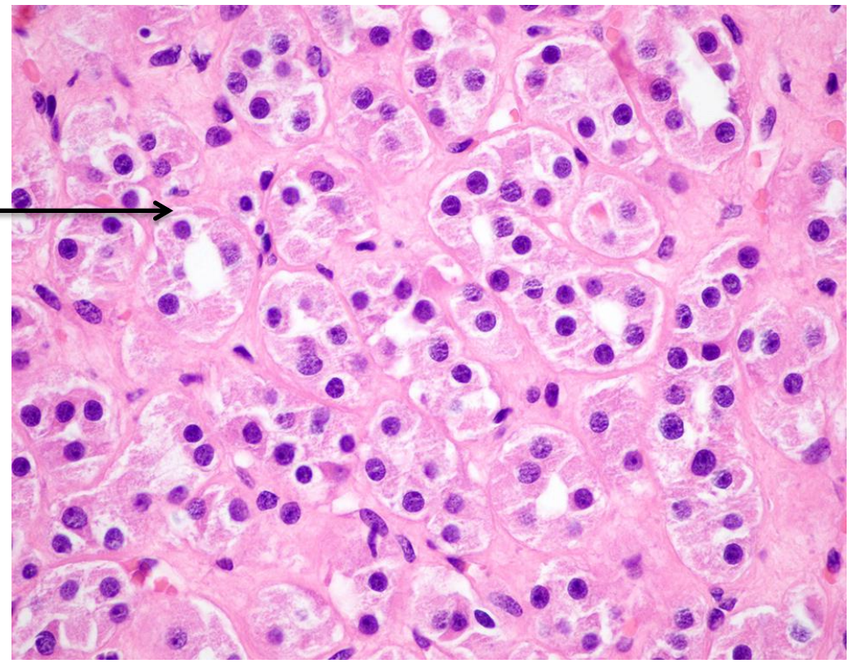


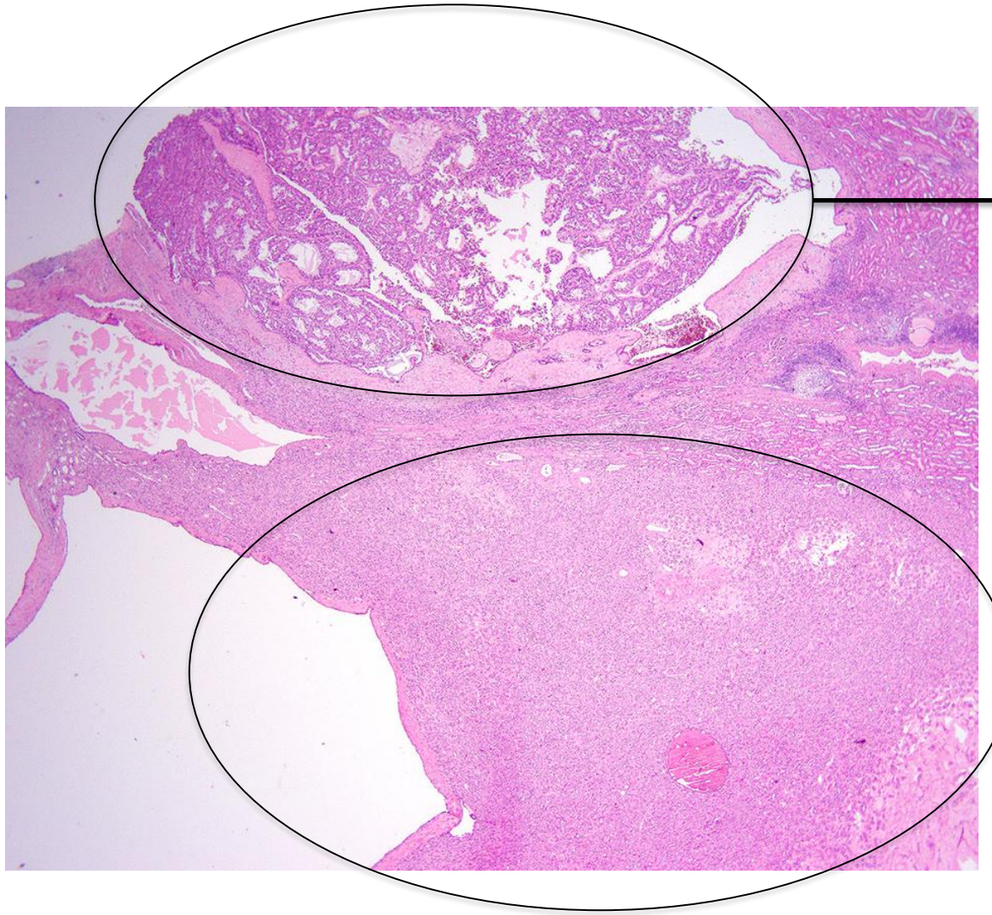
Wyvekens N, et al. *Int J Surg Pathol*, 2022 Apr;30(2):184-189; Hamza A et al, Adv Anat Pathol. 2021 Nov 1;28(6):396-407; Smith SC et al, Histopathology. 2017 Jul;71(1):42-52

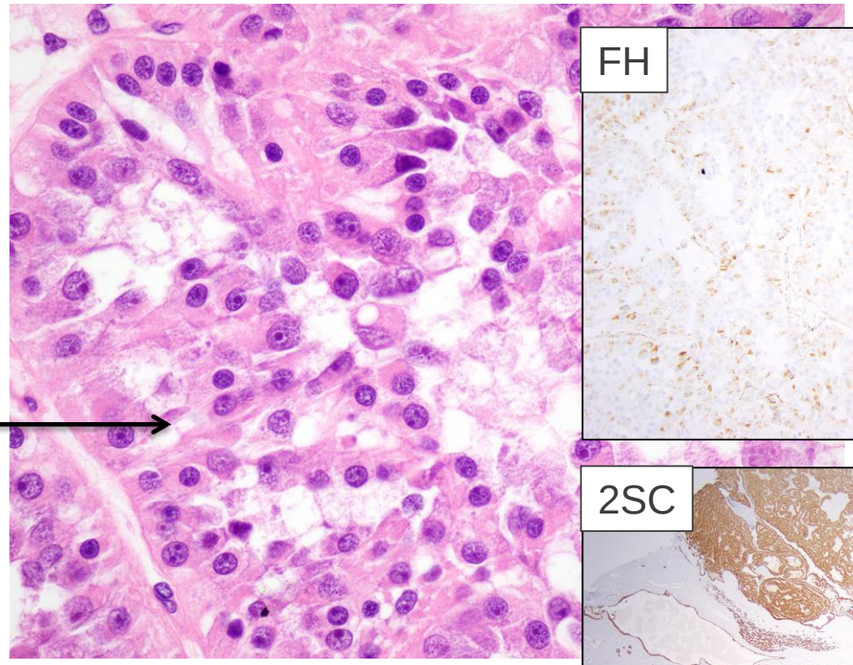


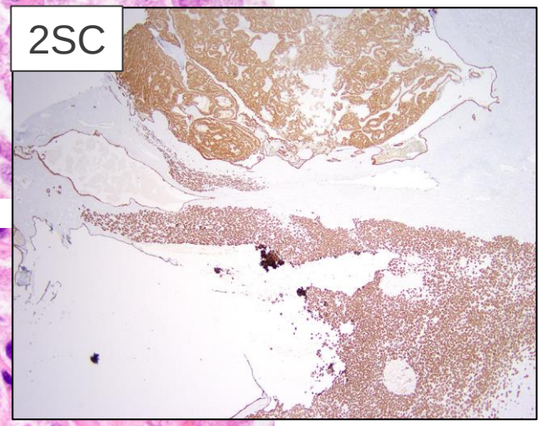


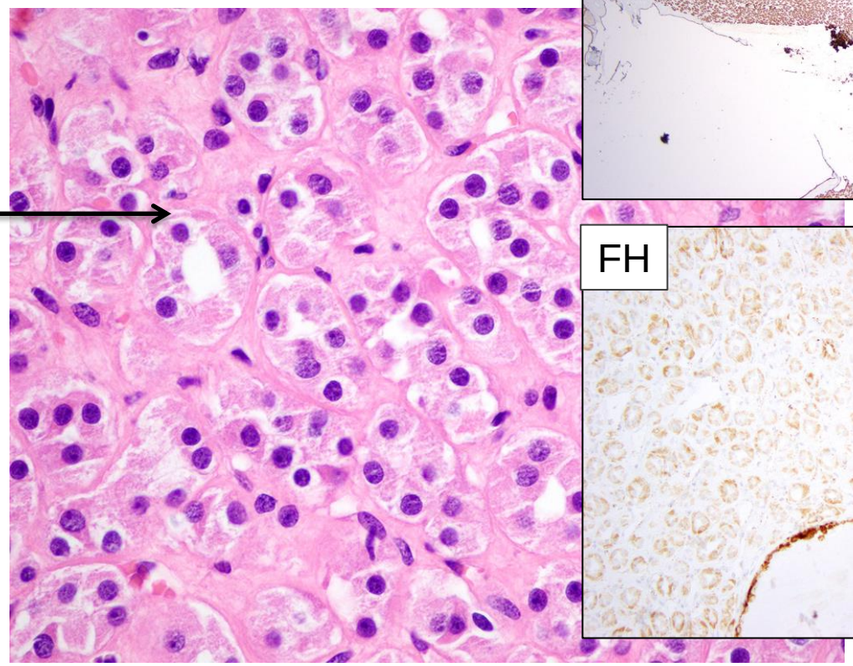












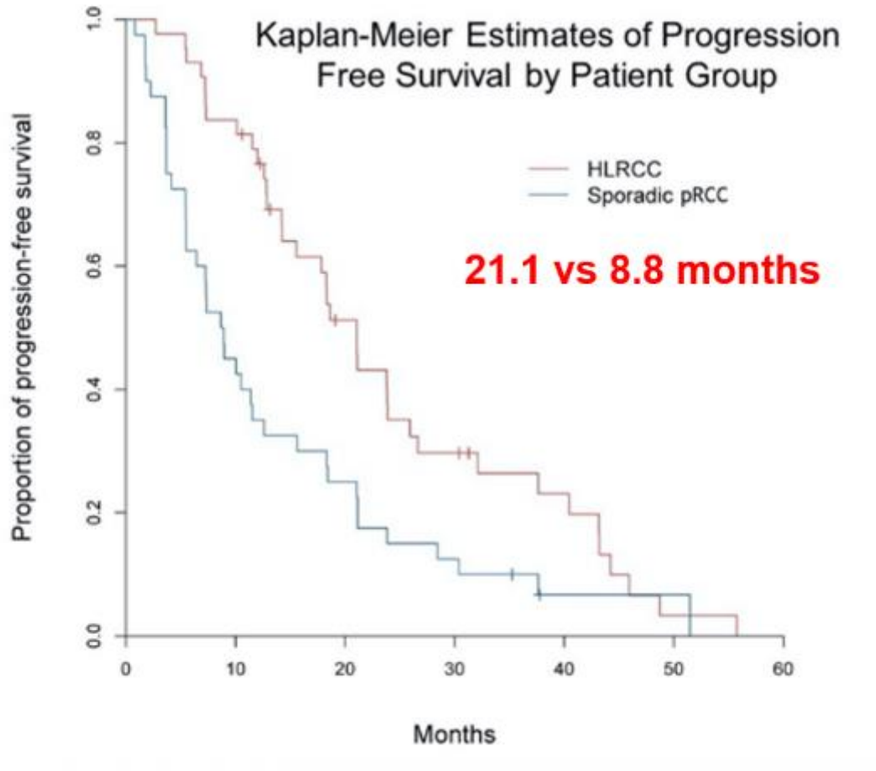
FH-Deficient RCC - Summary

- Prognosis is poor if not detected early ➔ tumors will metastasize and many pt DOD within months to years
  - Try to identify FH-deficient leiomyomas BEFORE develop RCC
- Evaluation of other family members for germline FH mutation is important
- Consider for HG and/or LG eosinophilic RCC with heterogeneous papillary/tubulopapillary architecture; clear cell cytology may be present
- Understand infrequent limitations of morphologic features and FH IHC
- Remember, papillary architecture does not always equal (so-called type 2) papillary RCC, and it is important to specifically distinguish other RCC subtypes, such as FH-deficient RCC, from papillary RCC
  - Why “split”……

FH-Deficient RCC vs Papillary RCC

Bevacizumab + Erlotinib Combination (NCI experience)

Confirmed Best Response	HLRCC, n (%) (N = 43)	Sporadic, n (%) (N = 40)
Complete Response	2 (4.7)	0 (0)
Partial Response	29 (67)	14 (35)
Stable Disease	12 (28)	21 (53)
Unconfirmed Partial Response	0 (0)	1 (2.5)
Progressive Disease	0 (0)	4 (10)
ORR	**72%**	**35%**

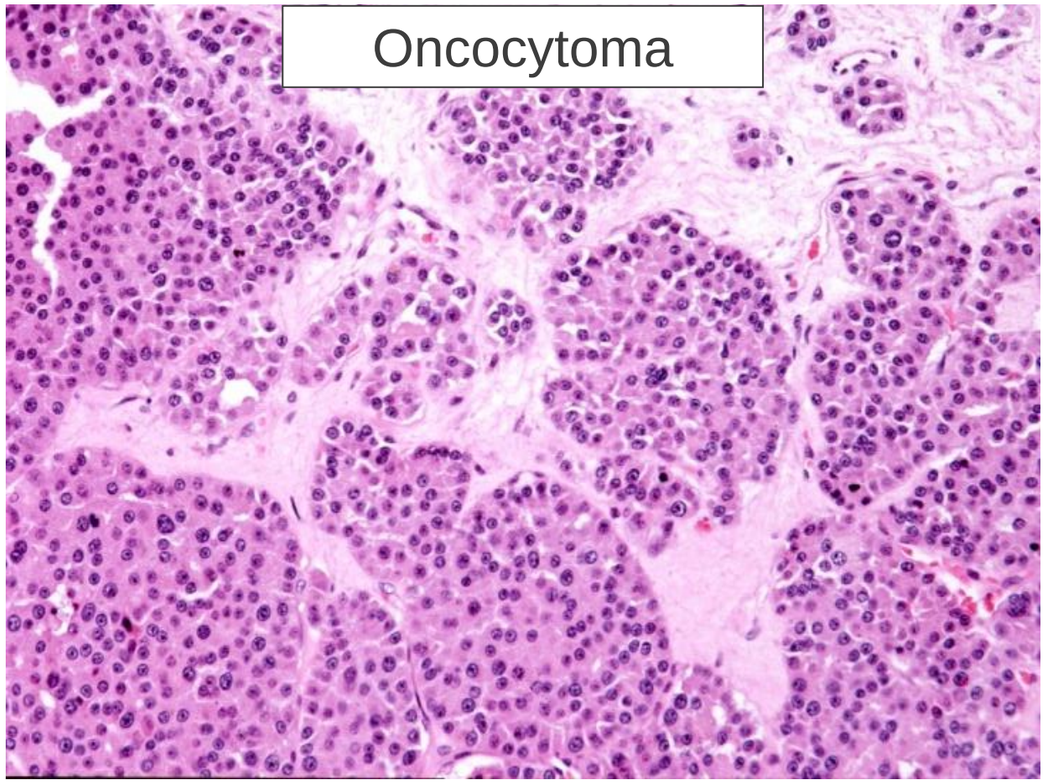


Slide courtesy of Dr. Brad McGregor (DFCI, GU Medical Oncology) (data from Srinivasan, ASCO 2020)

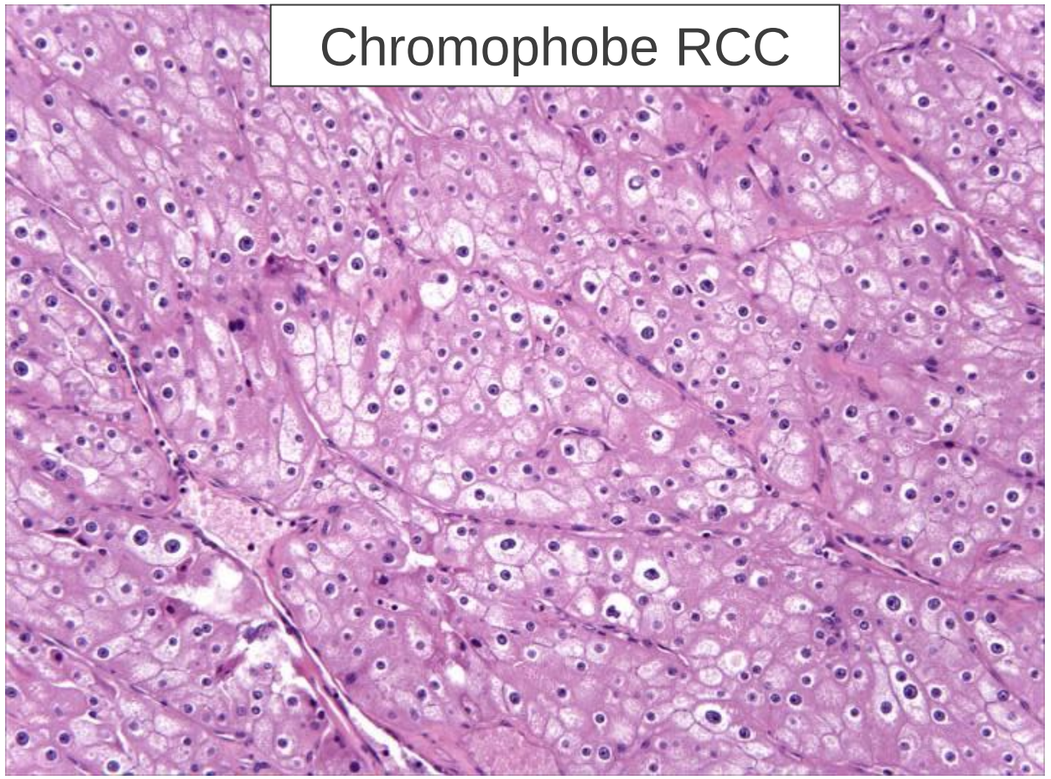
Update #4 ➔ Emerging Oncocytic Tumors

Oncocytic and chromophobe renal tumours
Oncocytoma of the kidney
Chromophobe RCC
Other oncocytic tumours of the kidney

Oncocytic Tumors – “The Classics”

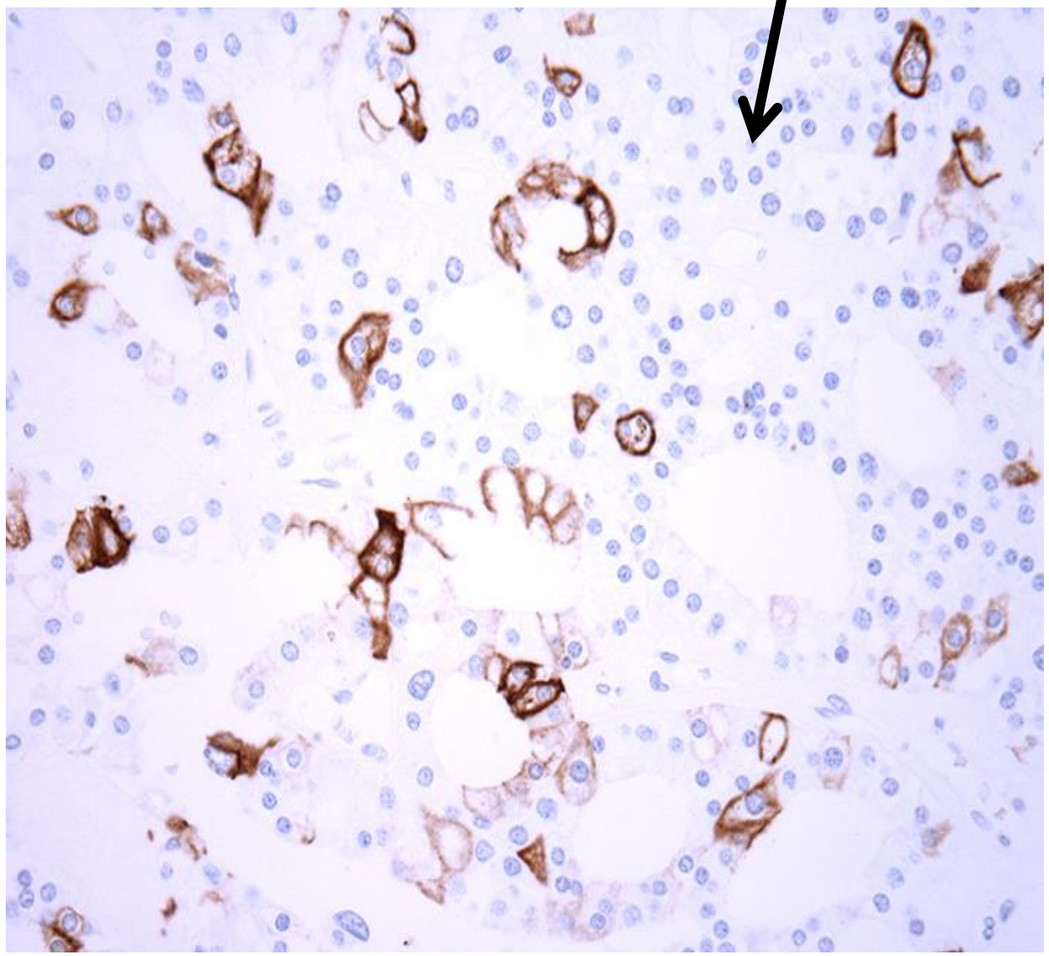


CK7-/rare, AMACR-, CD10-, S100A1+, KIT+
i.e., alterations involving Y, ch1, ch11

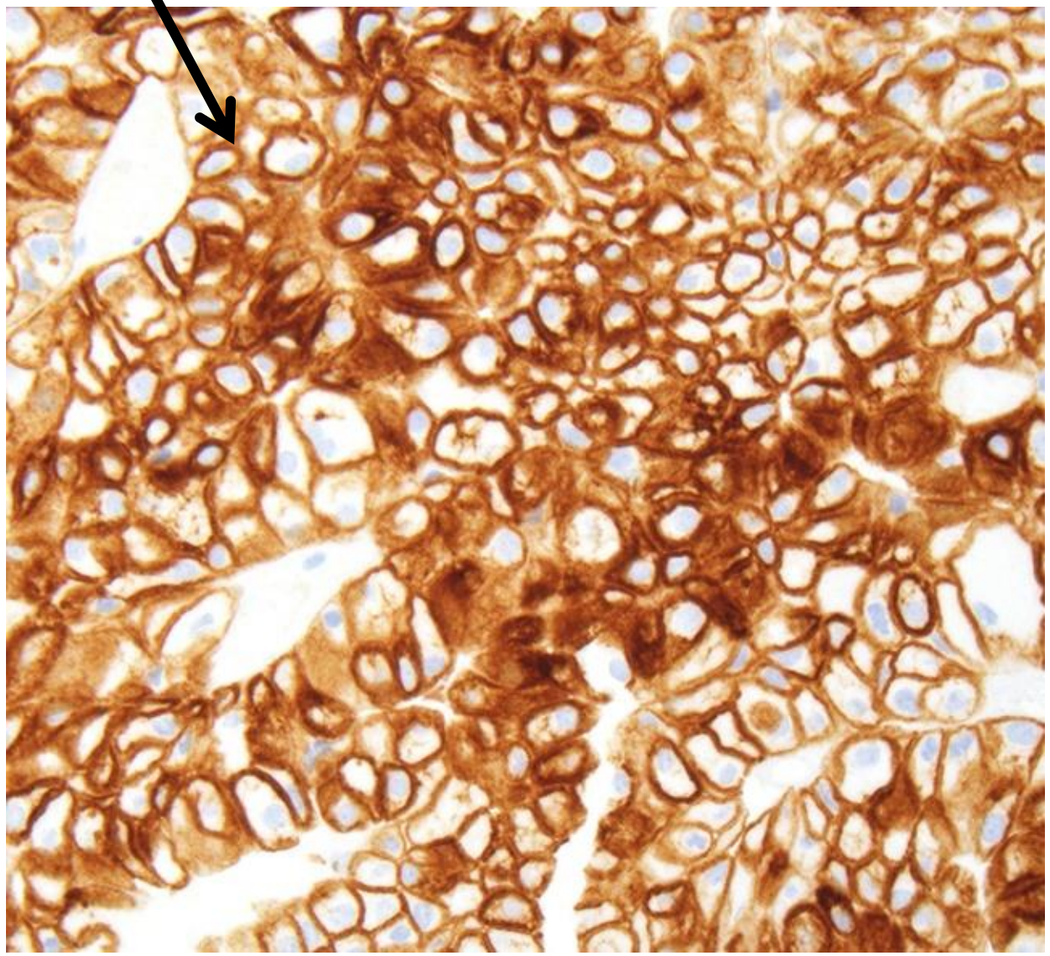


CK7+, AMACR-, CD10-, S100A1-, KIT+
i.e., 36,X,-Y,-1,-2,-6,-8,-10,-13,-15,-17,-22

CK7 Expression – RO vs ChRCC (both KIT positive)

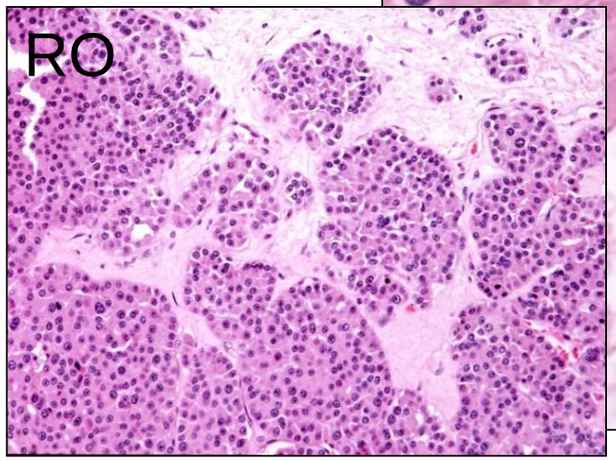


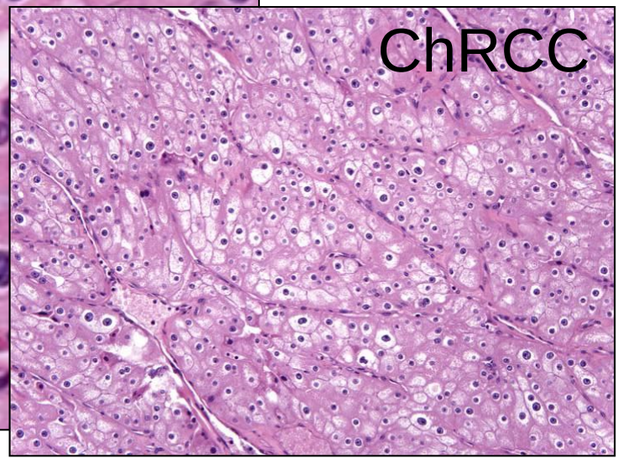
CK7



CK7

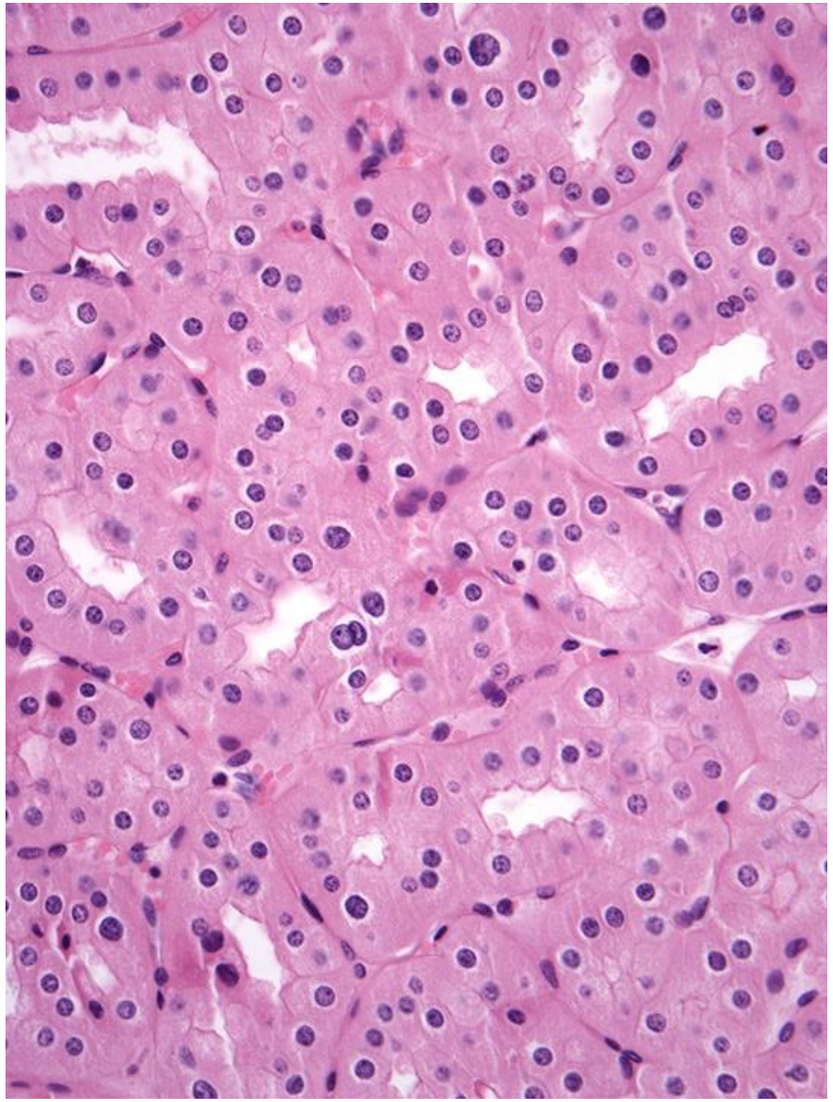
?? mixed features ??





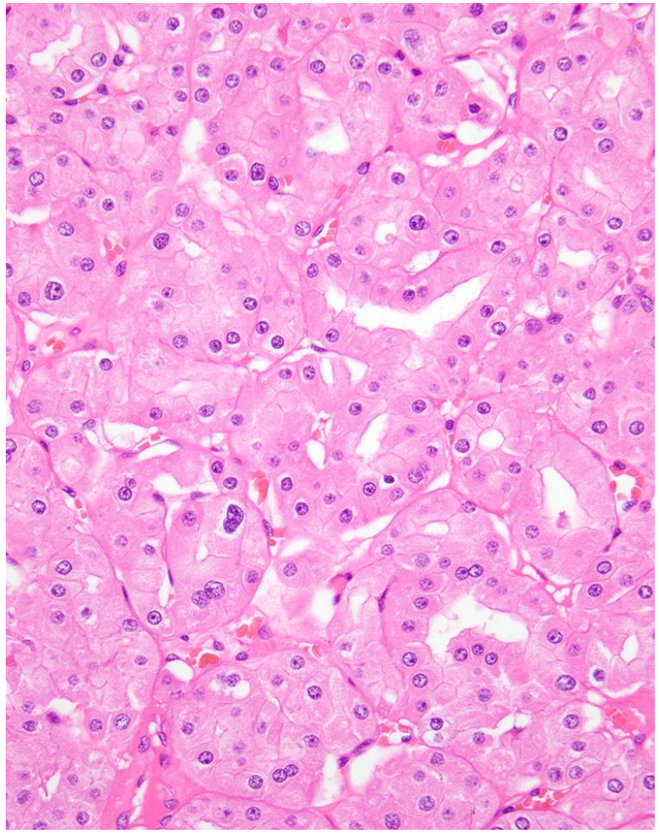
Low Grade Oncocytic Tumor (LOT)

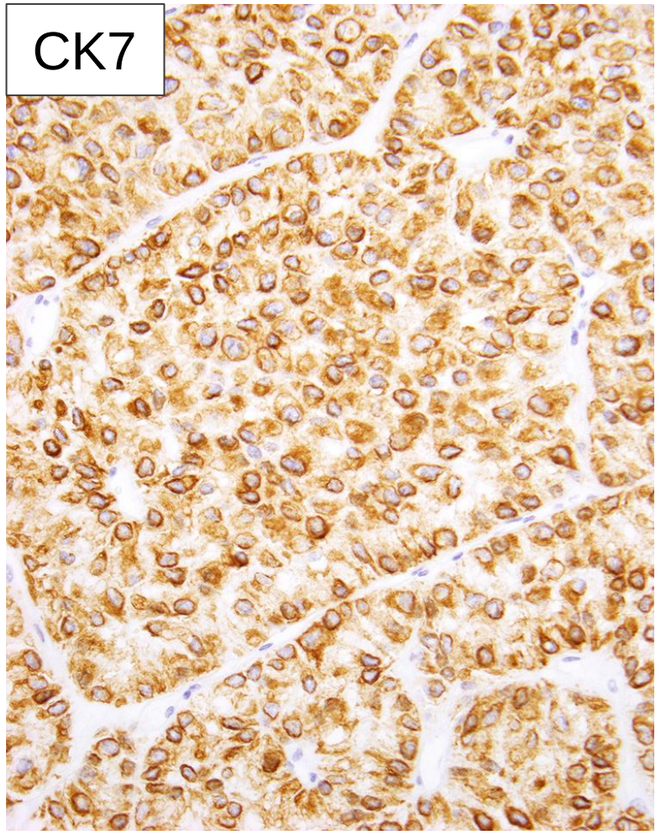
- Still considered an ‘emerging entity’ by the WHO
  - WHO ➔ Other Oncocytic Tumors
- Originally referred to as ‘CK7+ LG oncocytic tumor’
- Indolent behavior / considered benign
- Median age 66, variable F:M (?F>M)
- Morphologic features
  - Lack a peripheral capsule
  - Solid, compact nested or tubular growth patterns
  - Low grade cytology
  - Perinuclear halos may be present
  - Edematous stromal may be present
- Defined by diffuse CK7 expression, KIT negative (RO/ChRCC KIT+)

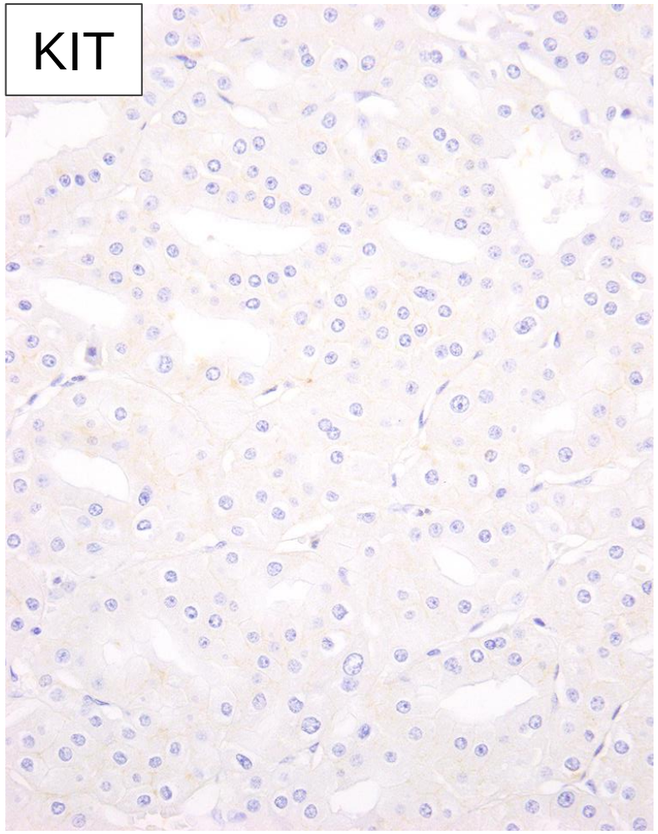


*Trpkov K et al, Histopathol 2019; Trpkov K & Hes O, Histopathol 2019; Siadat F & Trpkov K, Cancers 2020; Trpkov et al, Mod Pathol, 2021

Low Grade Oncocytic Tumor (LOT)

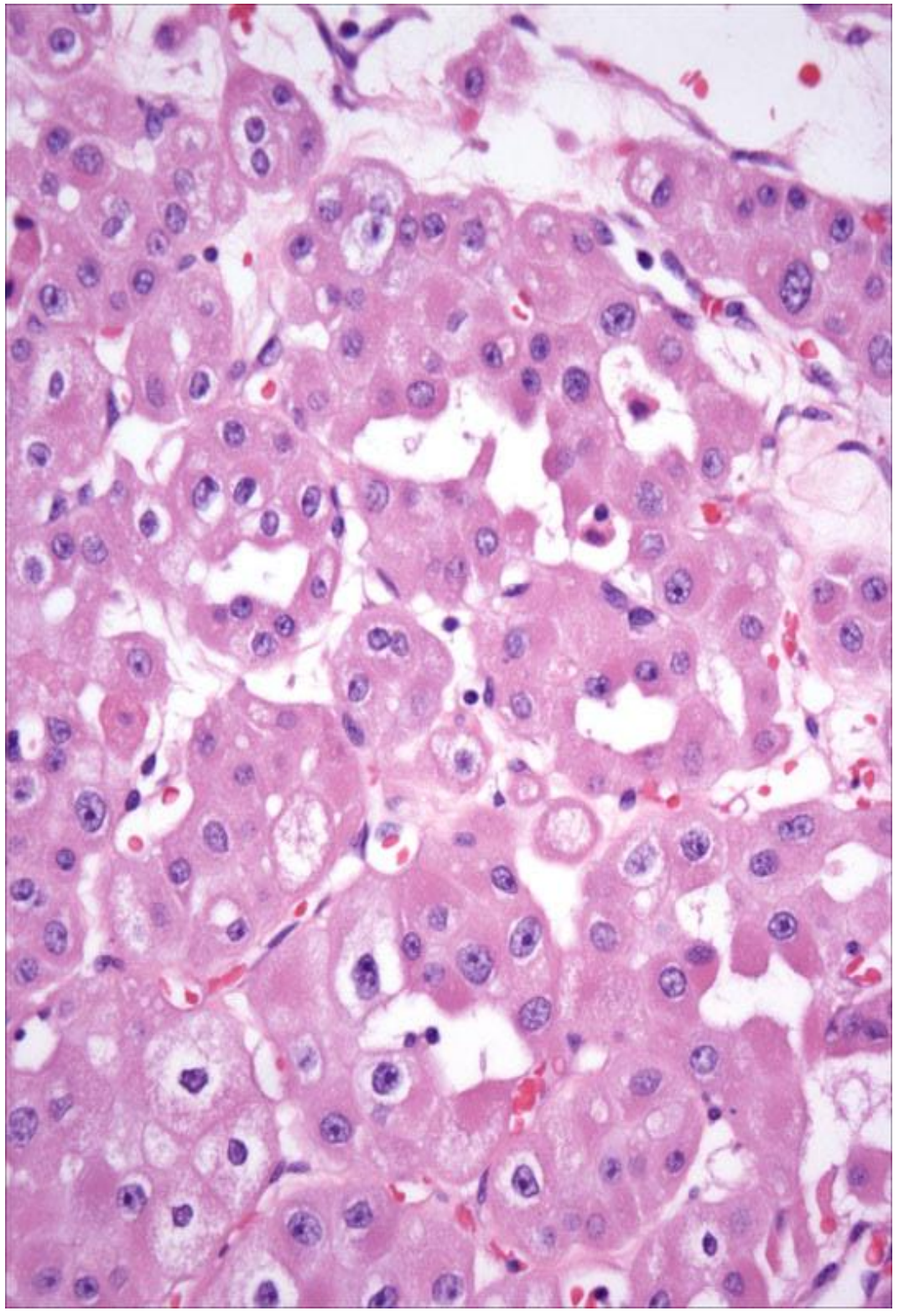


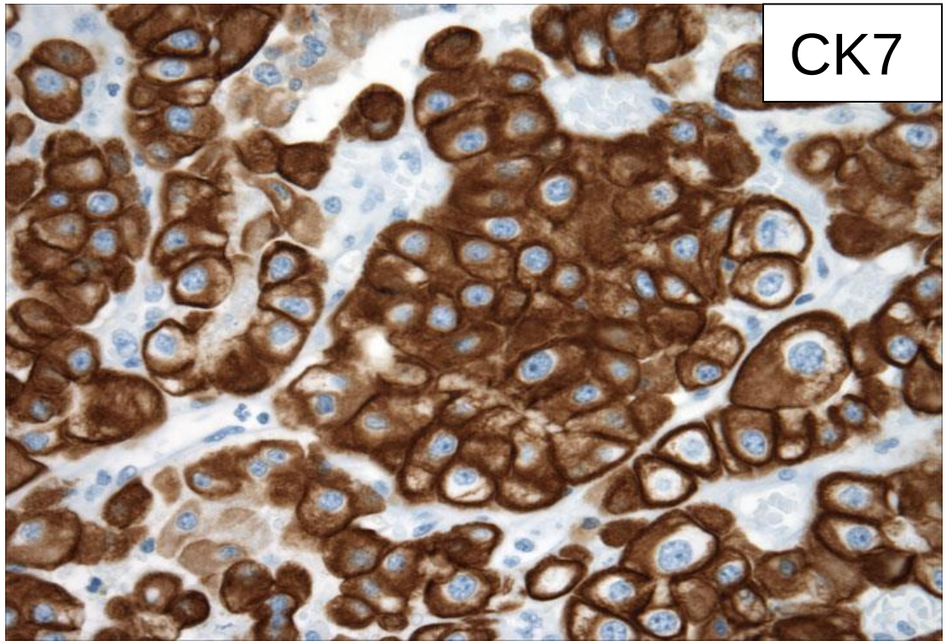


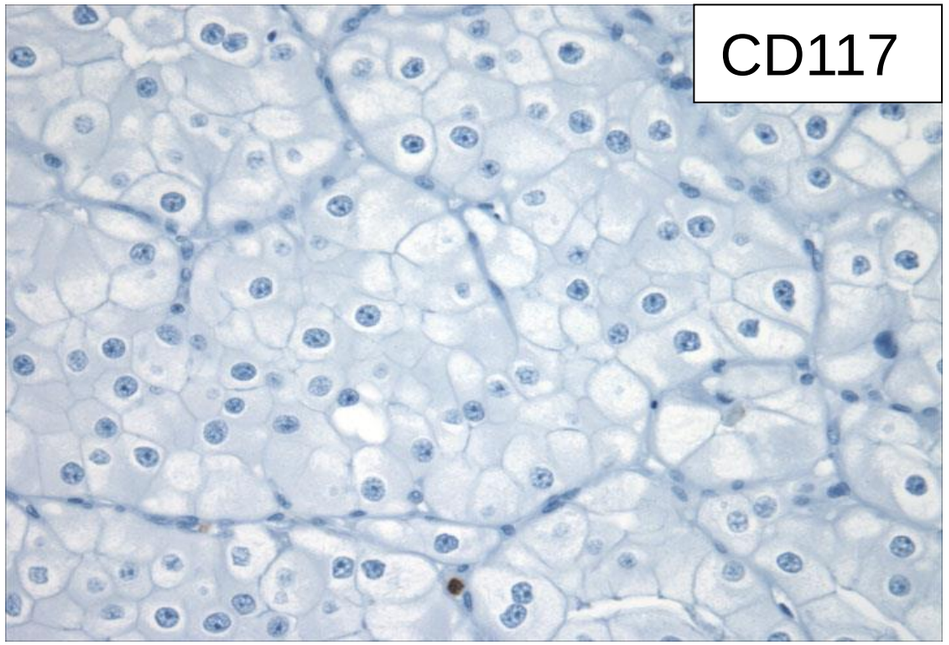


Immunohistochemistry:

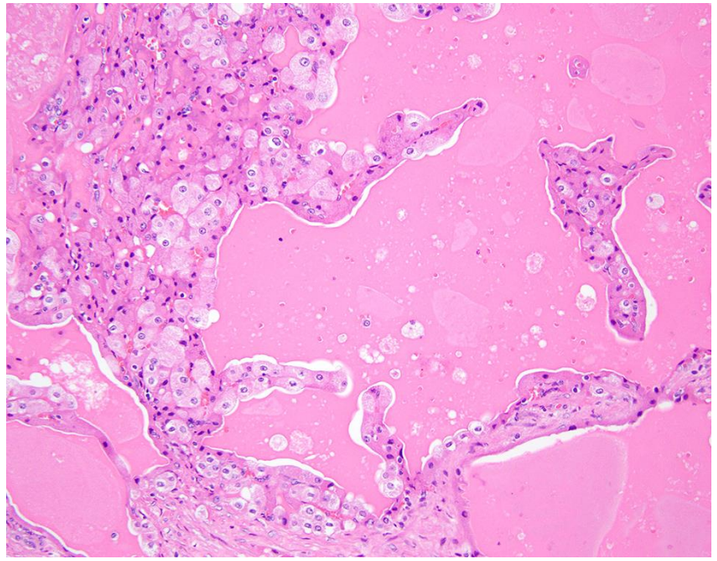
- Positive IHC ➔ PAX8, CK7 (diffuse), S100A1, SDHB intact, FH intact
- Focal to Negative IHC ➔ AMACR, CD10
- Negative IHC ➔ CD117, Vimentin, PEComa markers, CA9

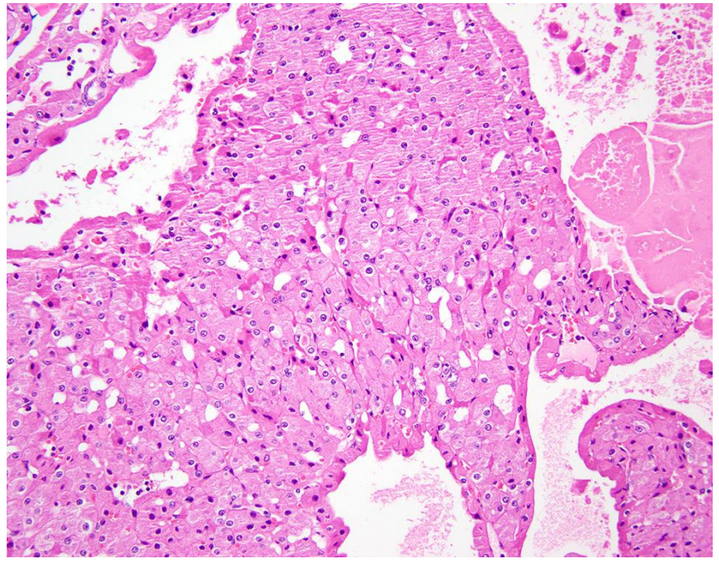


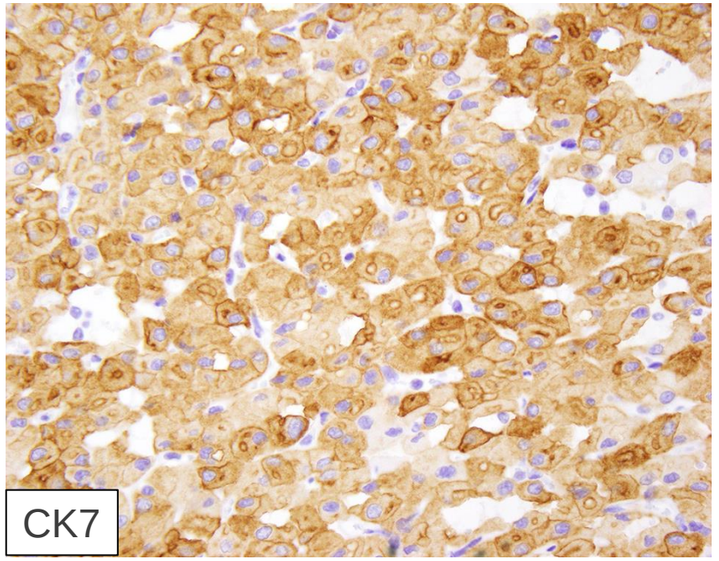


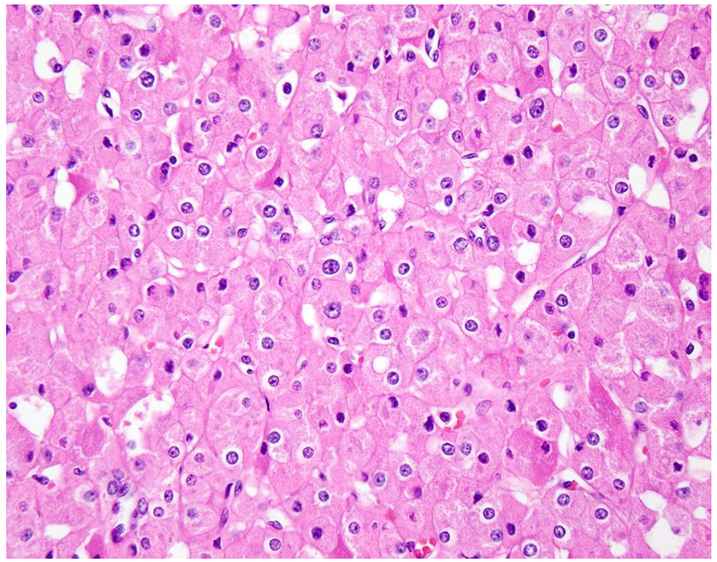


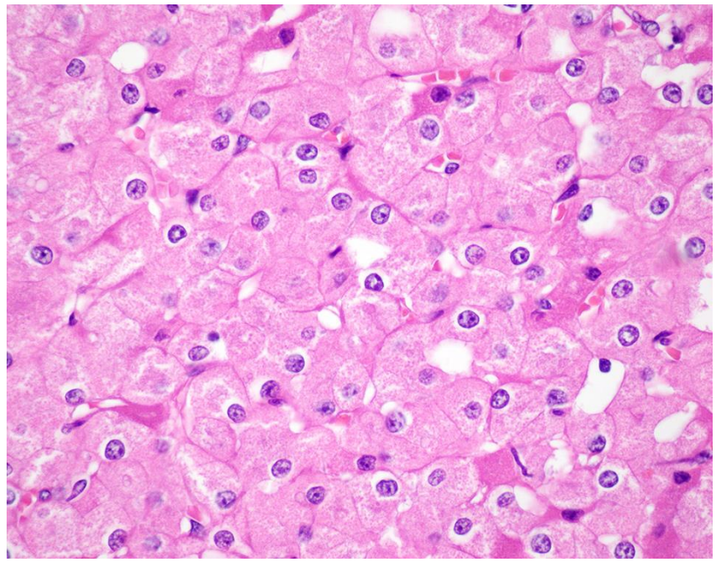
Pitfall ➔‘Cystic’ Low Grade Oncocytic Tumor (LOT)

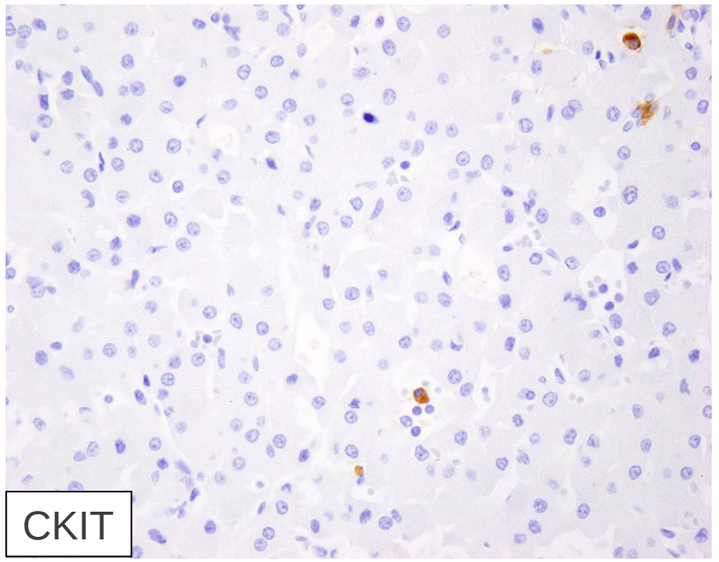






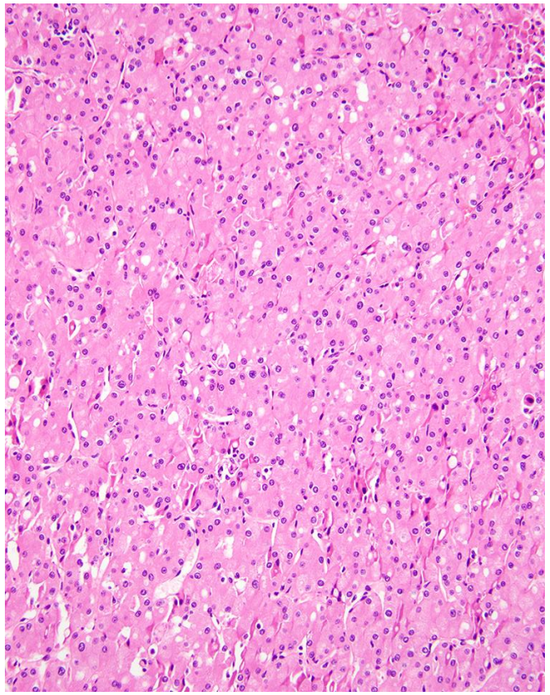


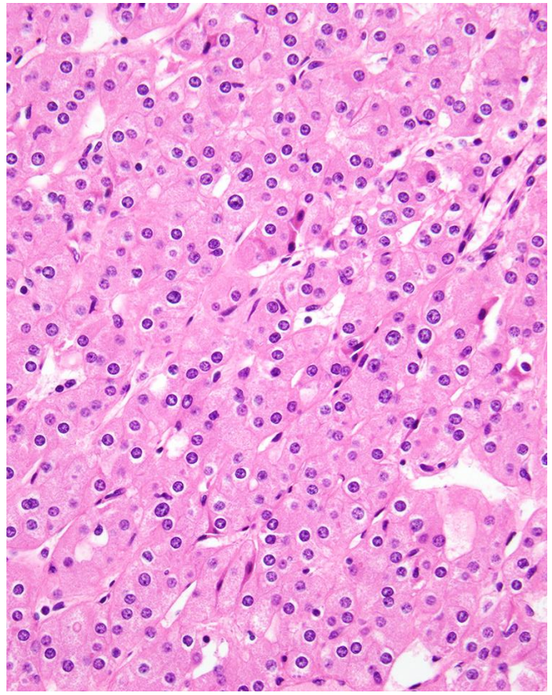


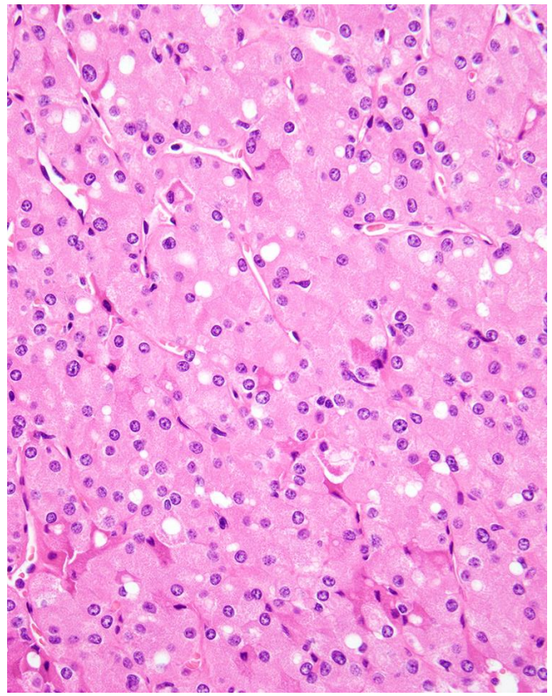


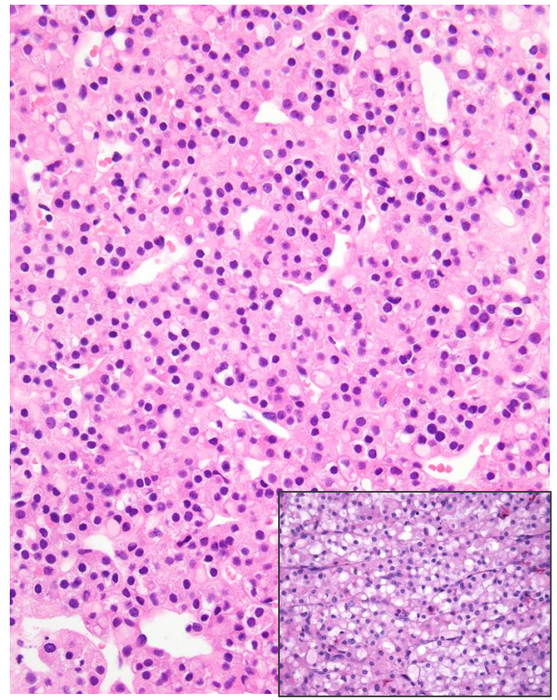
DDx ➔ ESC, LG FH-deficient RCC, Translocation RCC

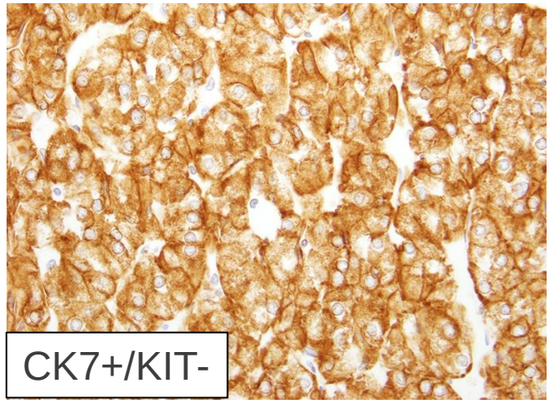
Pitfall ➔ LOT with Solid Growth and Vacuoles

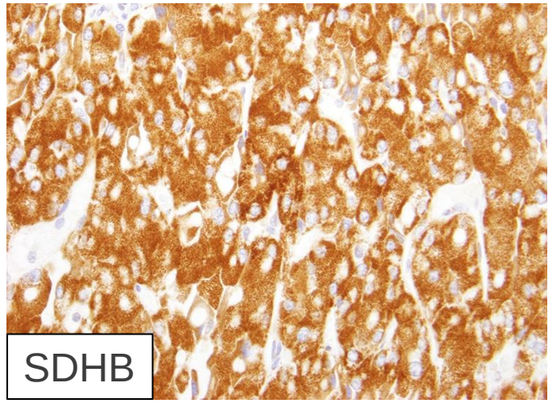


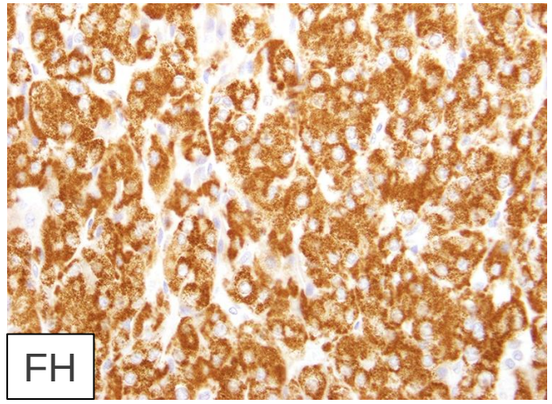


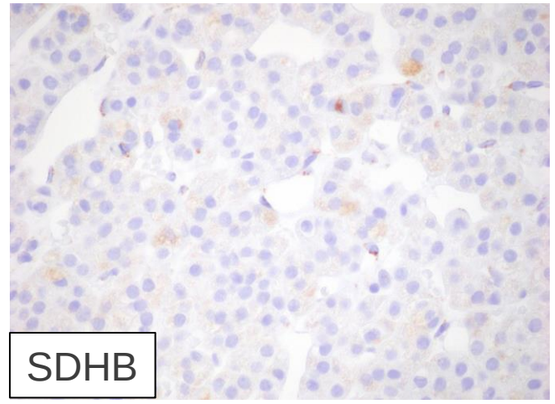






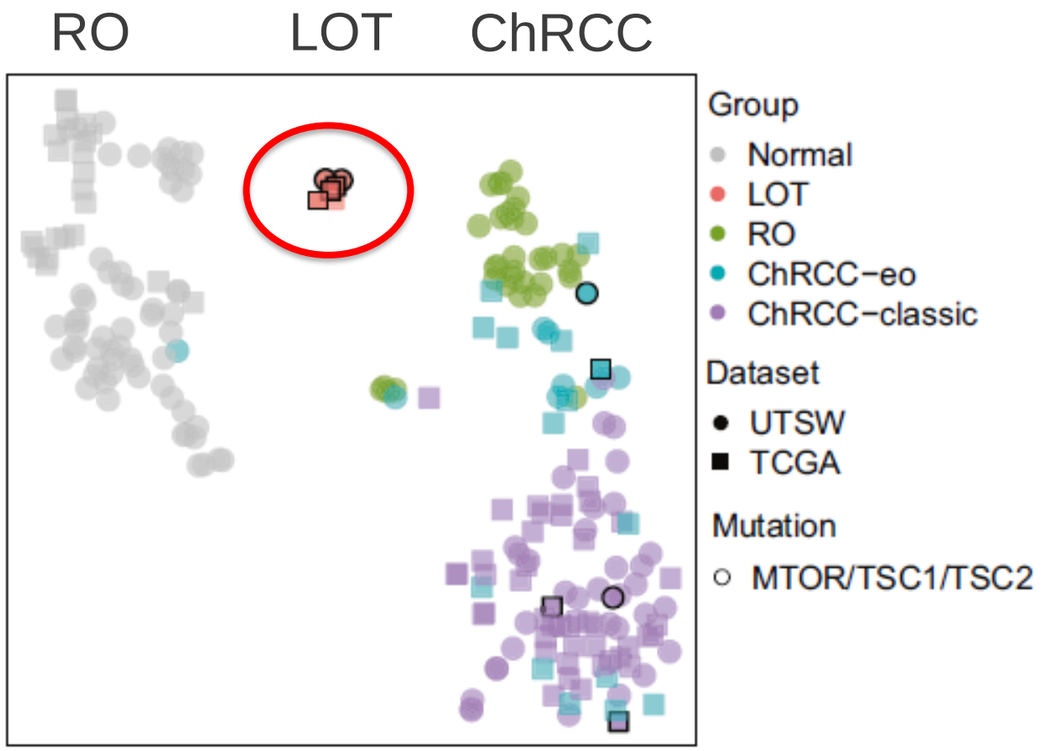


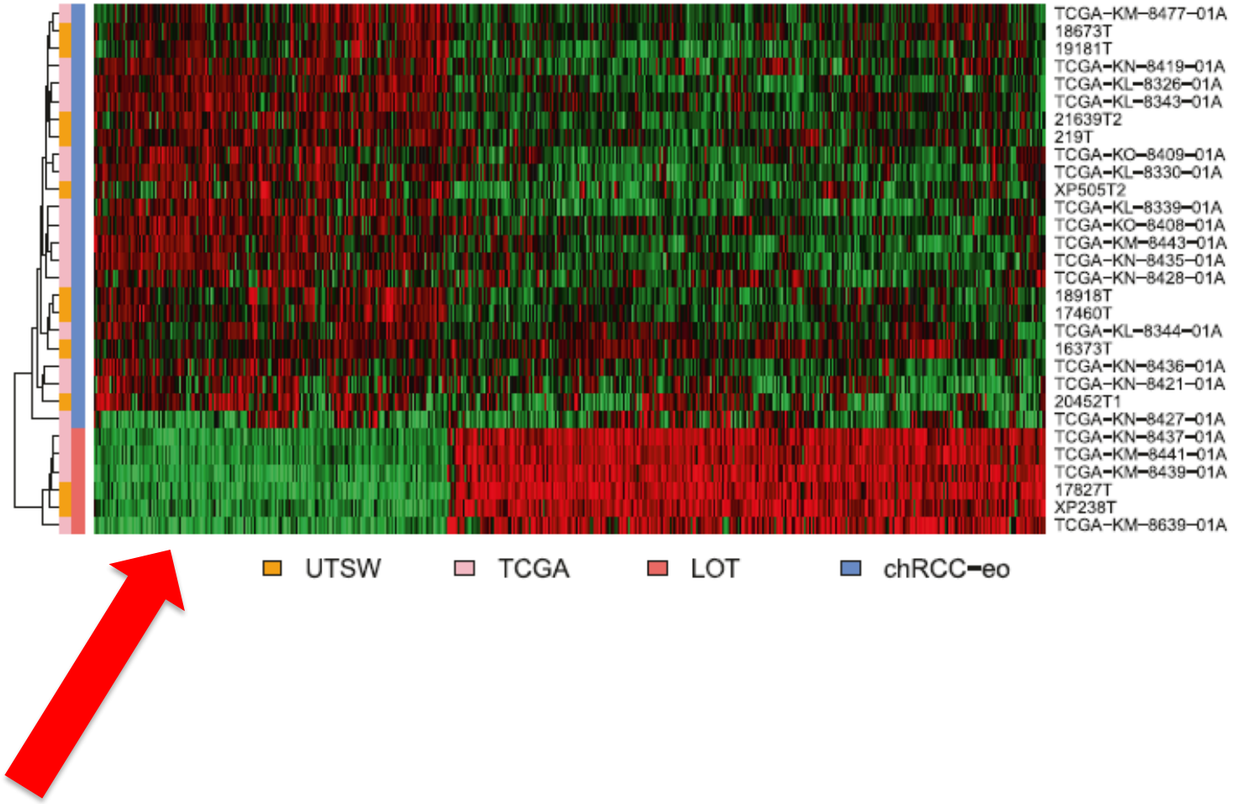




DDx ➔ SDH-deficient RCC, ESC, LG FH-deficient RCC, RO, ChRCC

Low Grade Oncocytic Tumor (LOT) - Molecular





Kapur P, et al. Mod Pathol, 2022. PMID: 34538873.

Low Grade Oncocytic Tumor (LOT) - Molecular

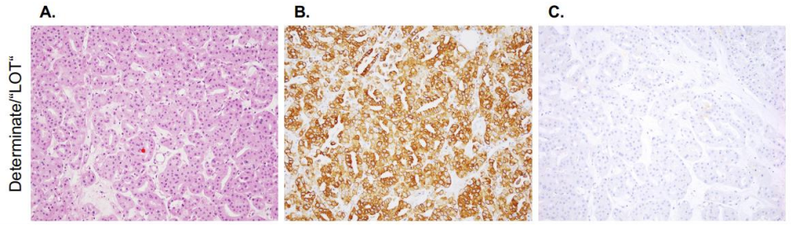
- Frequently demonstrate TSC/MTOR pathway mutations; however, not entirely sensitive (~80% of cases), nor specific

Study*	TSC1	TSC2	MTOR
Williamson et al (N=17)	41%	12%	29%
Zhang et al (N=7)	57%	71%	14%
Morini et al (N=10)	70%	0%	10%

*Retrospective reviews, cases based on H&E and CK7+/KIT- IHC

Williamson SR, et al. Histopathol, 2022. PMID: 36208048; Zhang HZ et al. Virchows Arch, 2022. PMID: 35099634; Morini A, et al, Mod Pathol. 2022. PMID: 34531523. Mohanty SK, et al, Mod Pathol, 2022. PMID: 34802045; Kapur P, et al. Mod Pathol, 2022. PMID: 34538873.

Low Grade Oncocytic Tumor (LOT) - Molecular



+Morph, CK7+, CKIT-
(all 3 criteria present)

?MTOR pathway mutation?

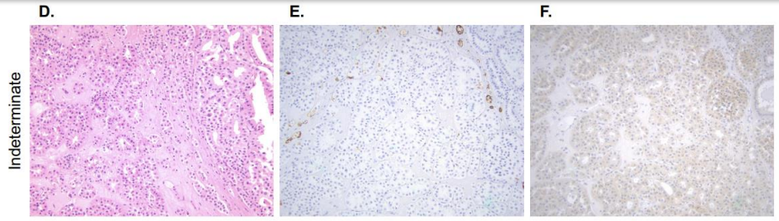
30 RONs*

Blinded

NGS

+/- Morph, +/-CK7, +/-CKIT
(<3 criteria present)

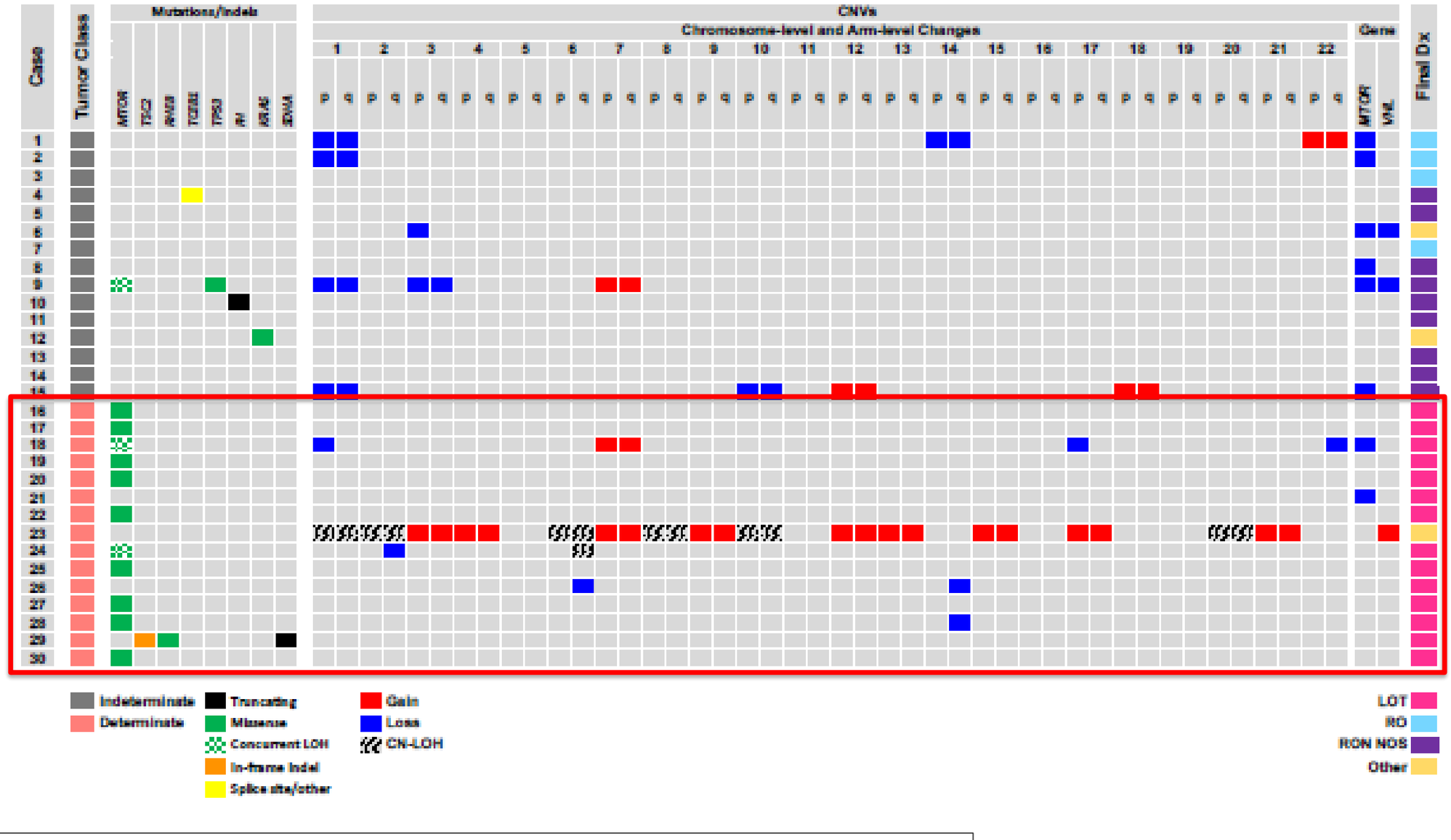
?MTOR pathway mutation?

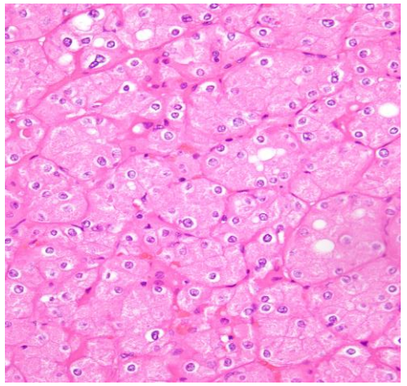


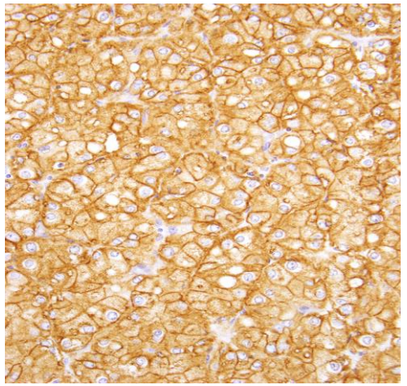
*Siegmund et al, 2022 USCAP poster; manuscript in preparation

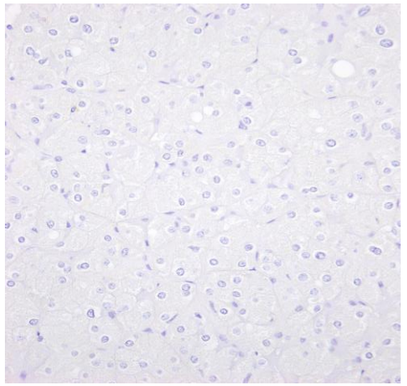
Determinate Group

Case 29







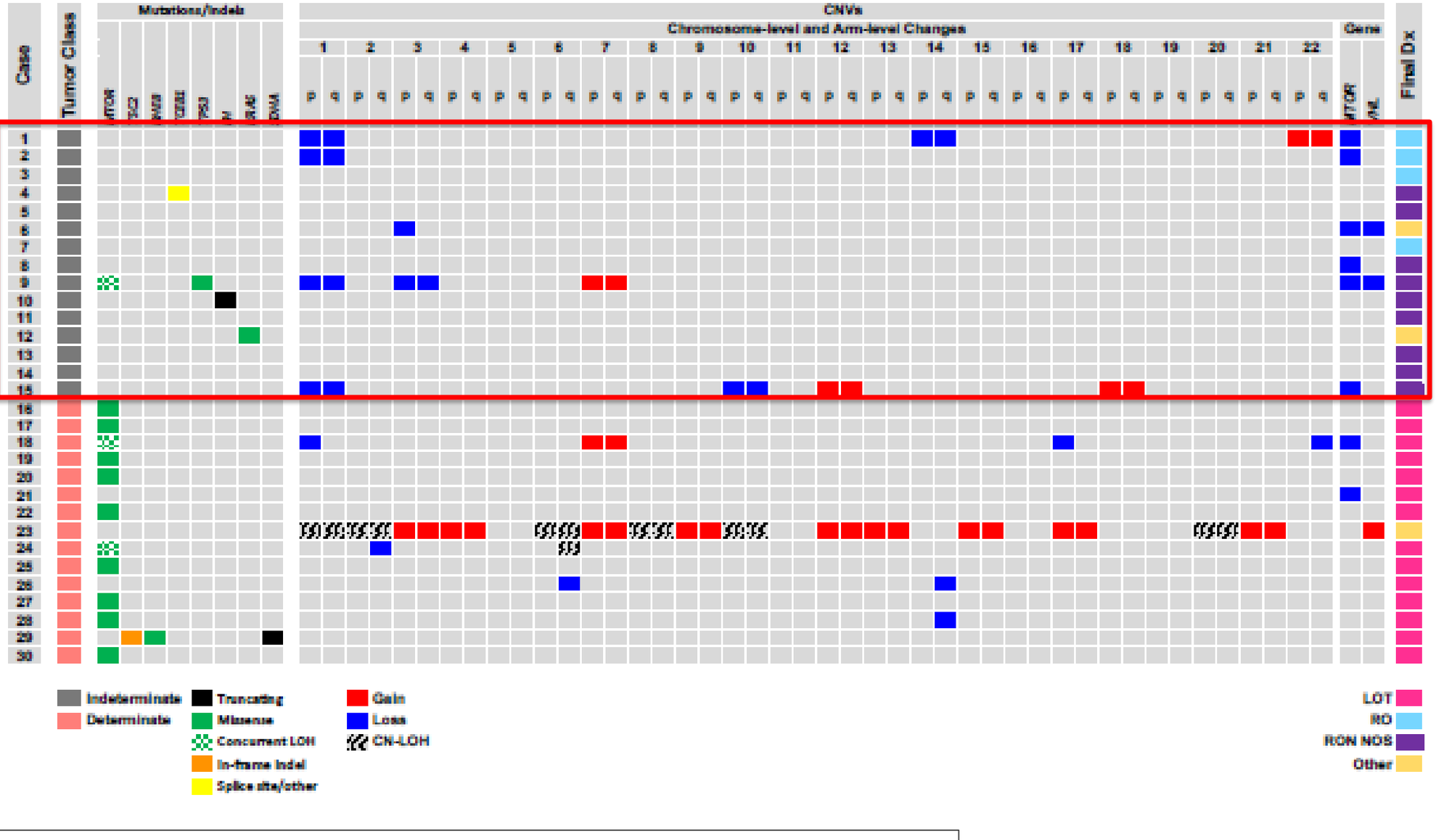


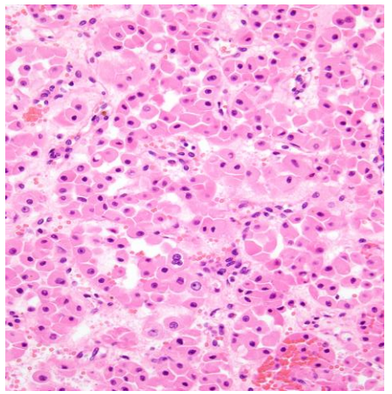
➔ 12/15 (80%) MTOR pathway mutation

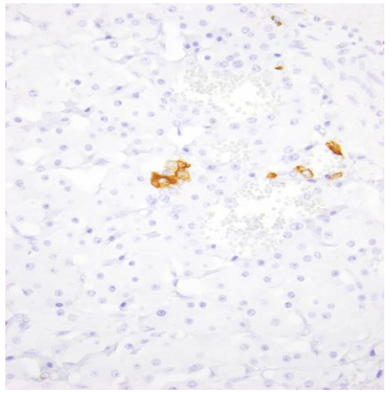
*Siegmund et al, 2022 USCAP poster; manuscript in preparation

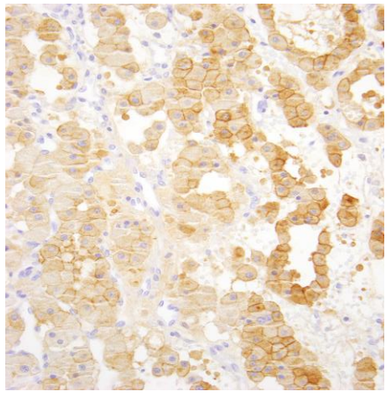
Indeterminate Group

Case 9









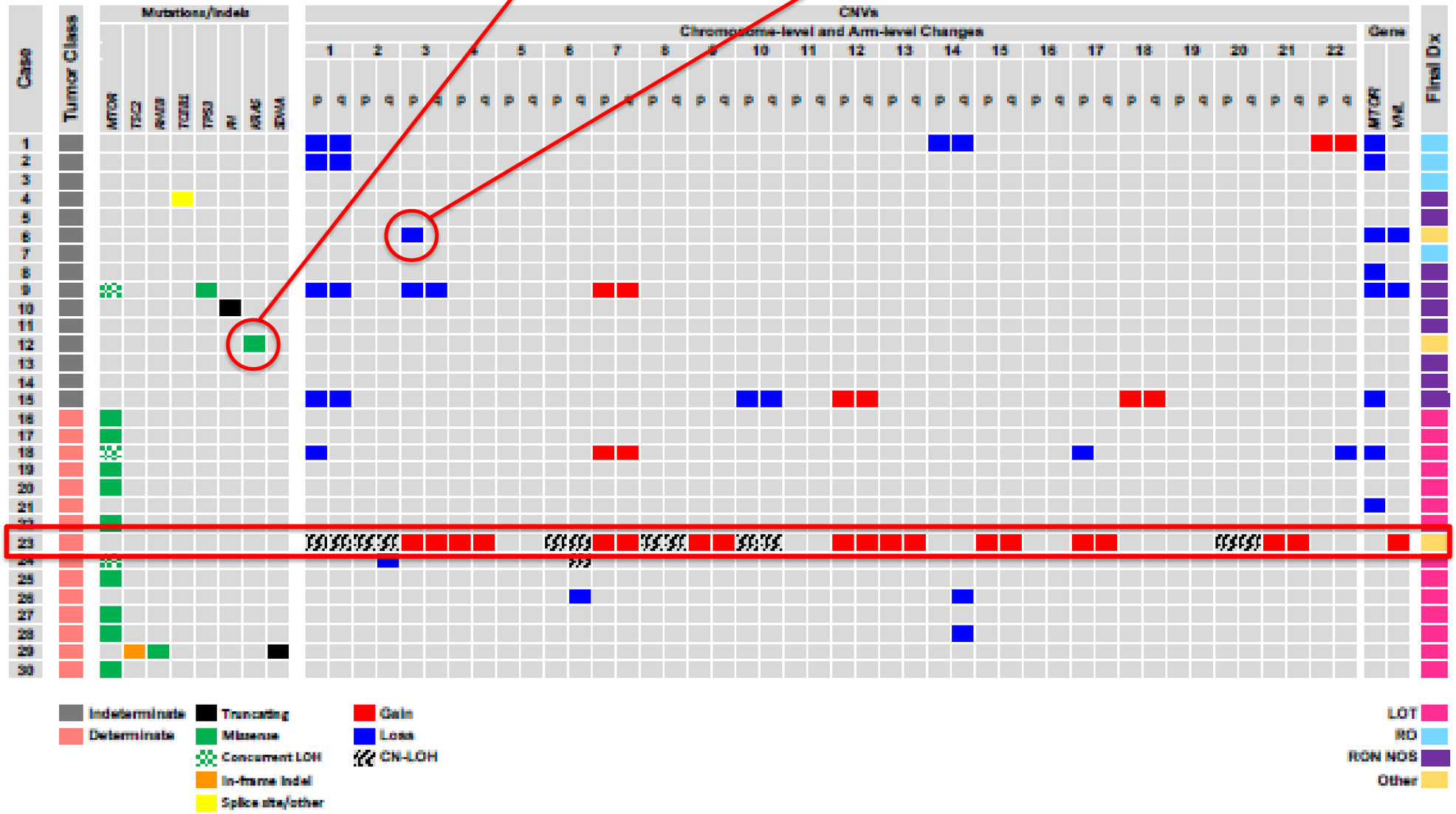
➔ 1/15 (7%) MTOR pathway mutation

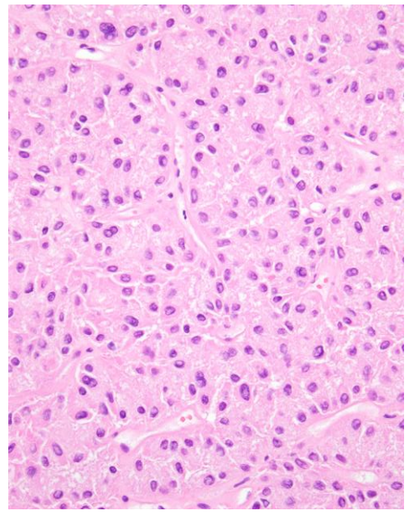
*Siegmund et al, 2022 USCAP poster; manuscript in preparation

Pitfalls……

PRCC-RP (GATA3)

CCRCC (CA9+)



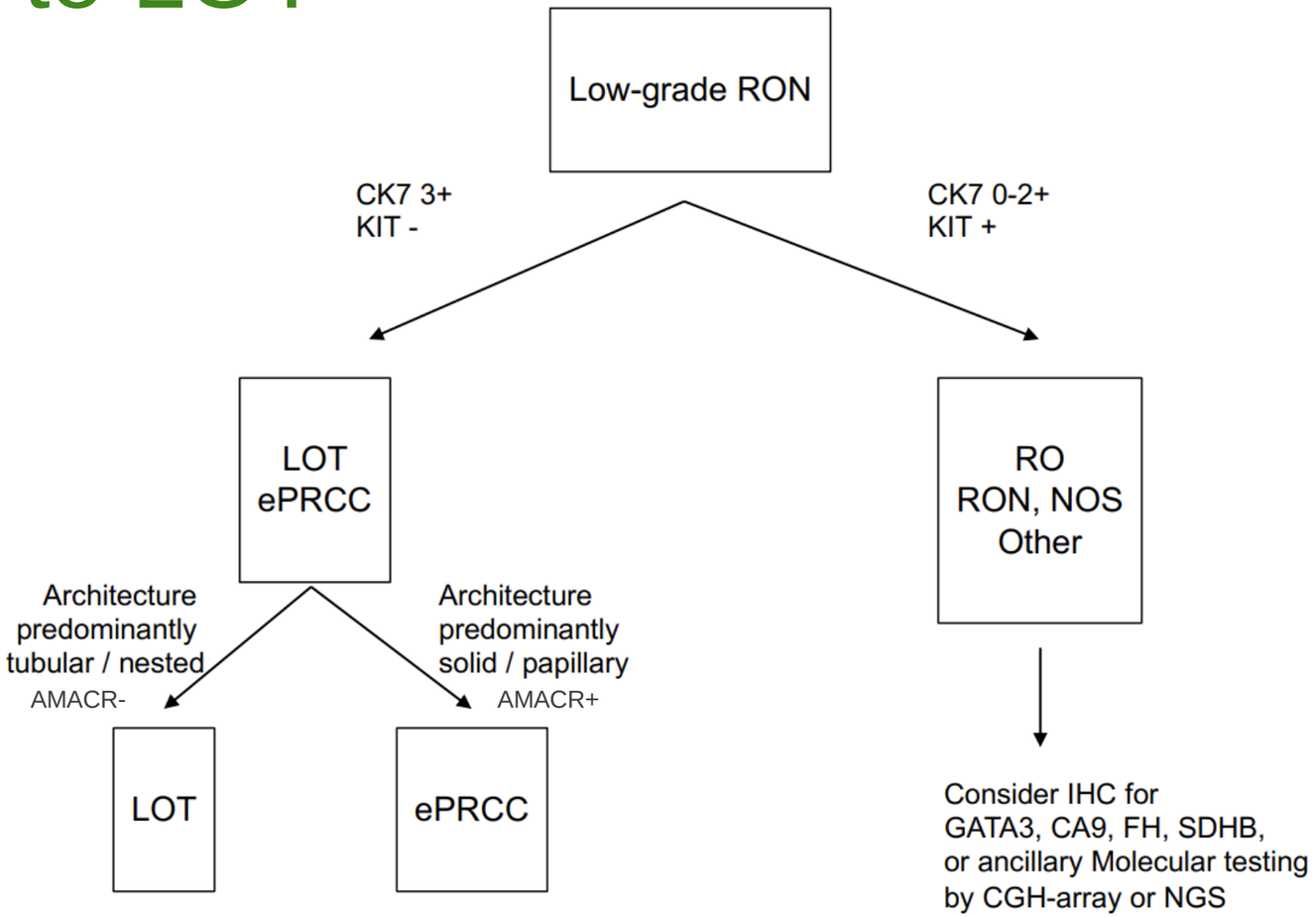


Papillary RCC

- Oncocytic
- Solid, focal papillary
- CK7+, KIT-, AMACR+
- +7/+17

*Siegmund et al, 2022 USCAP poster; manuscript in preparation

Approach to LOT



- ➔ Still and evolving/emerging entity
- ➔ Molecular not required for diagnosis
- ➔ Clinically significant distinction is benign vs malignant

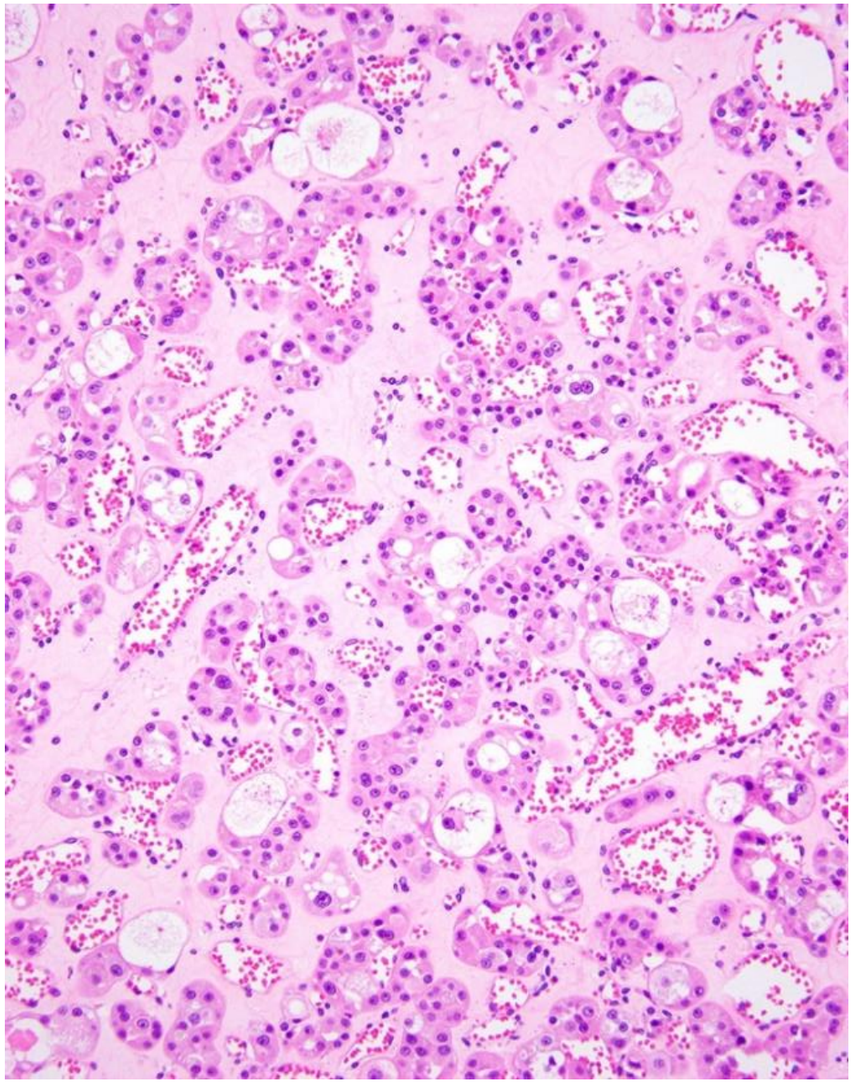
Eosinophilic Vacuolated Tumors (EVT)

- Acknowledged by WHO as an emerging entity
  - WHO ➔ Other Oncocytic Tumors
- EVT is proposed terminology in recent GUPS manuscript
- In prior publications, previously referred to as:
  - High Grade Oncocytic Tumor (HOT) (not to be confused with HOT/HOCT/BHD)
  - Sporadic RCC with eosinophilic and vacuolated cytoplasm
  - Vacuolated Oncocytic tumors (VOT)
- DDx: RO, ChRCC, BHD, ESC, SDH RCC, FH RCC, Translocation RCC, PEComa
- Associated with TSC mutations, majority sporadic
- F>M(4:1), mean 50 yo (ra 15-73)
- Solitary small renal masses, 4.3 cm mean (ra 1.5-11.5 cm)
- Indolent/benign

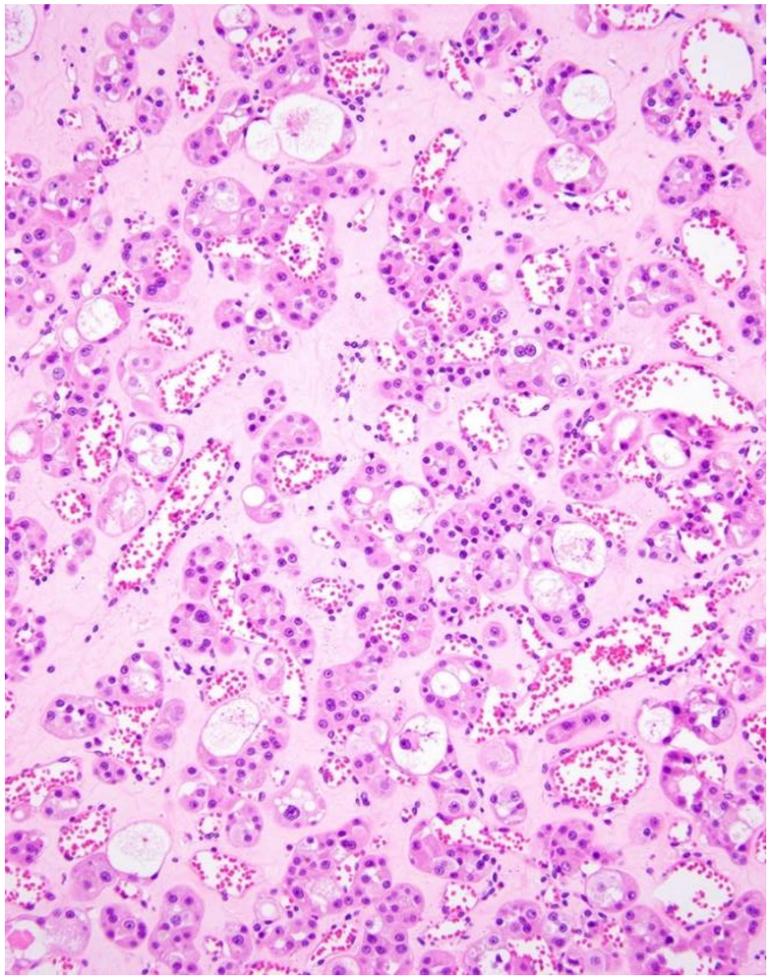
He H et al, Virchows Arch. 2018; Chen YB et al, AJSP, 2019; Siadat F and Trpkov K, Cancers 2020;
Baniak et al, Adv Anat Pathol 2021;Trpkov K et al, Mod Pathol, 2021; Farcaş M, et al. Mod Pathol 2022

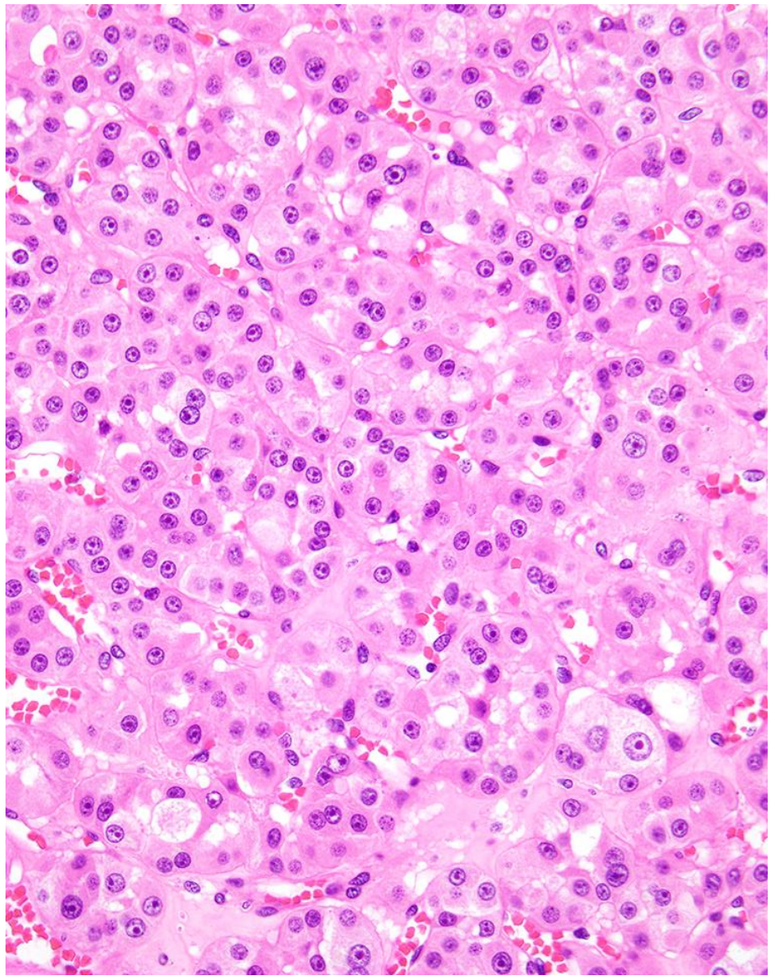
Eosinophilic Vacuolated Tumors (EVT)

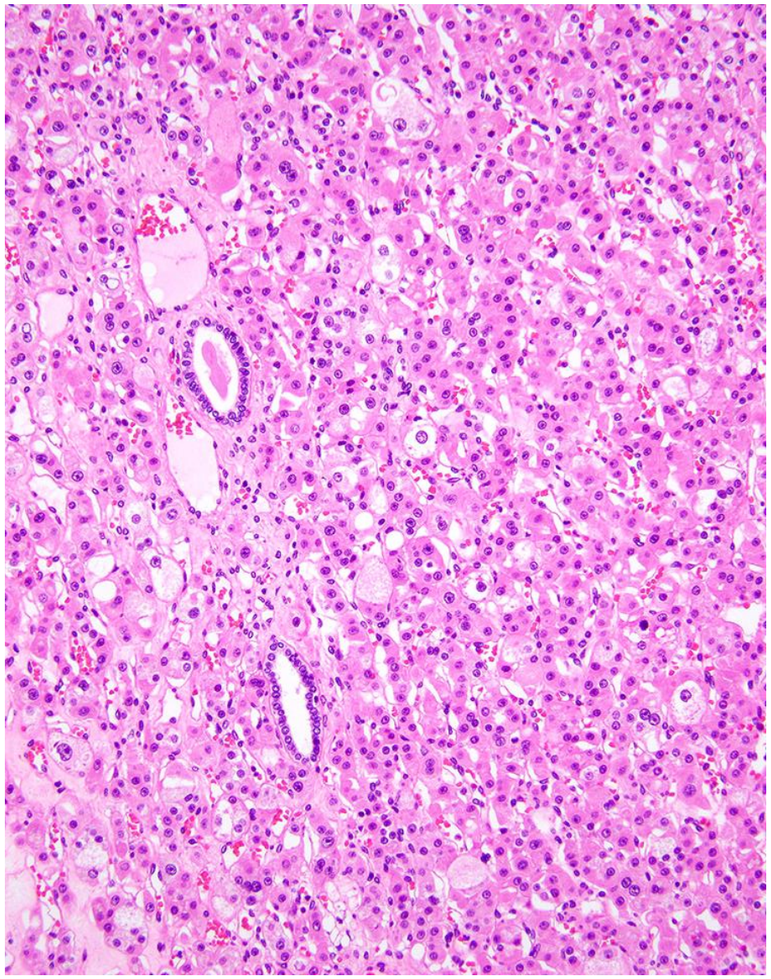
- DDx: RO, ChRCC, HOCT/BHD, ESC, SDH RCC, FH def-RCC, Translocation RCC, PEComa
- Resembles RO at low magnification
  - Solid growth, nested, unencapsulated
  - Hyalinized to edematous stroma
  - Entrapped non-neoplastic tubules
- But, also has distinct features
  - Voluminous eosinophilic cells with vacuolated cytoplasm
  - Large prominent nucleoli
  - Calcifications +/-



Eosinophilic Vacuolated Tumors (EVT) – Resembles RO…..

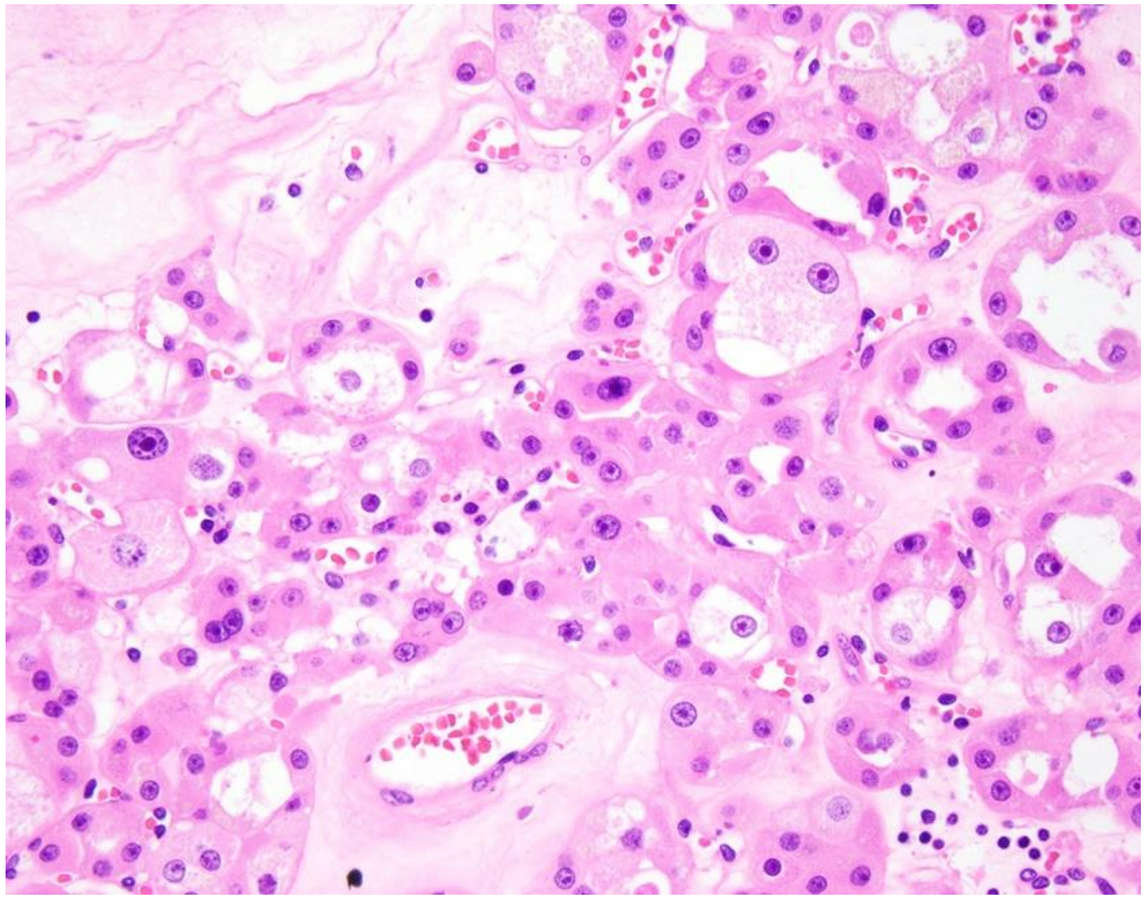


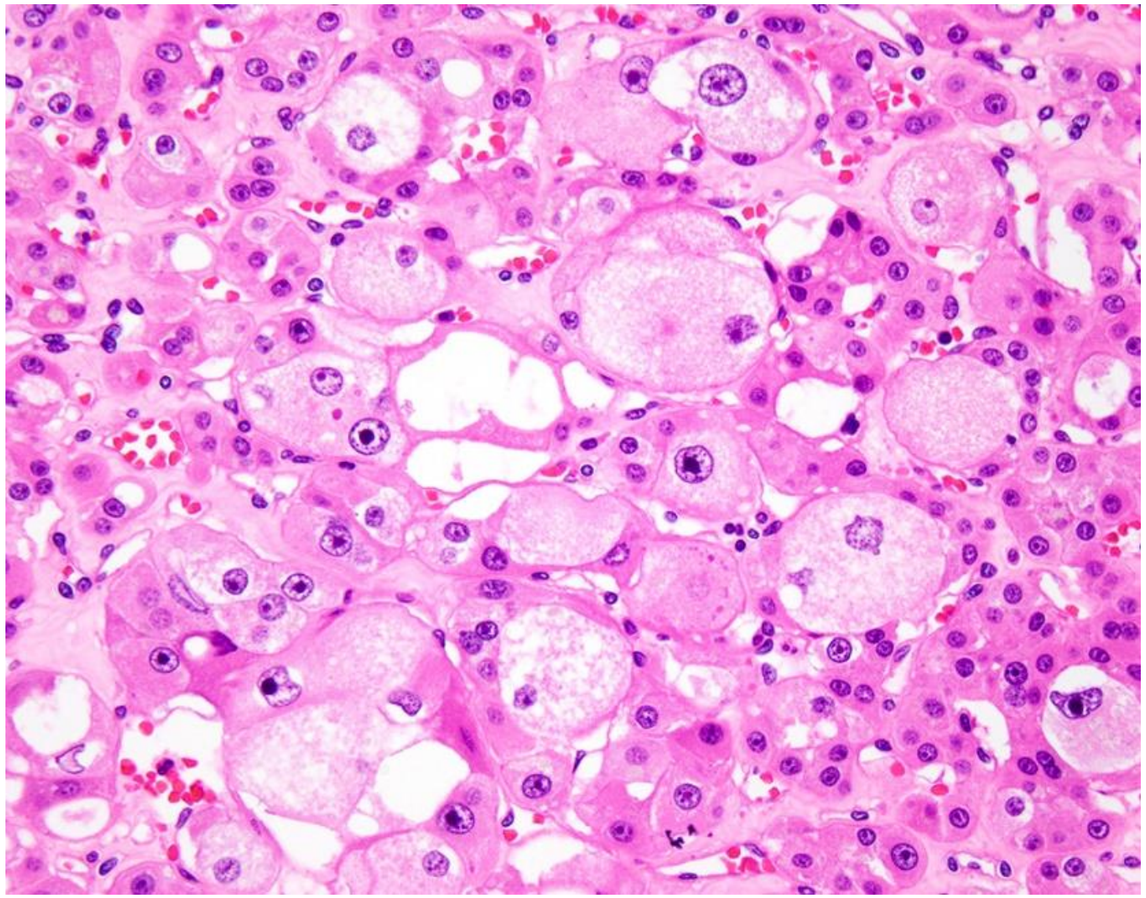




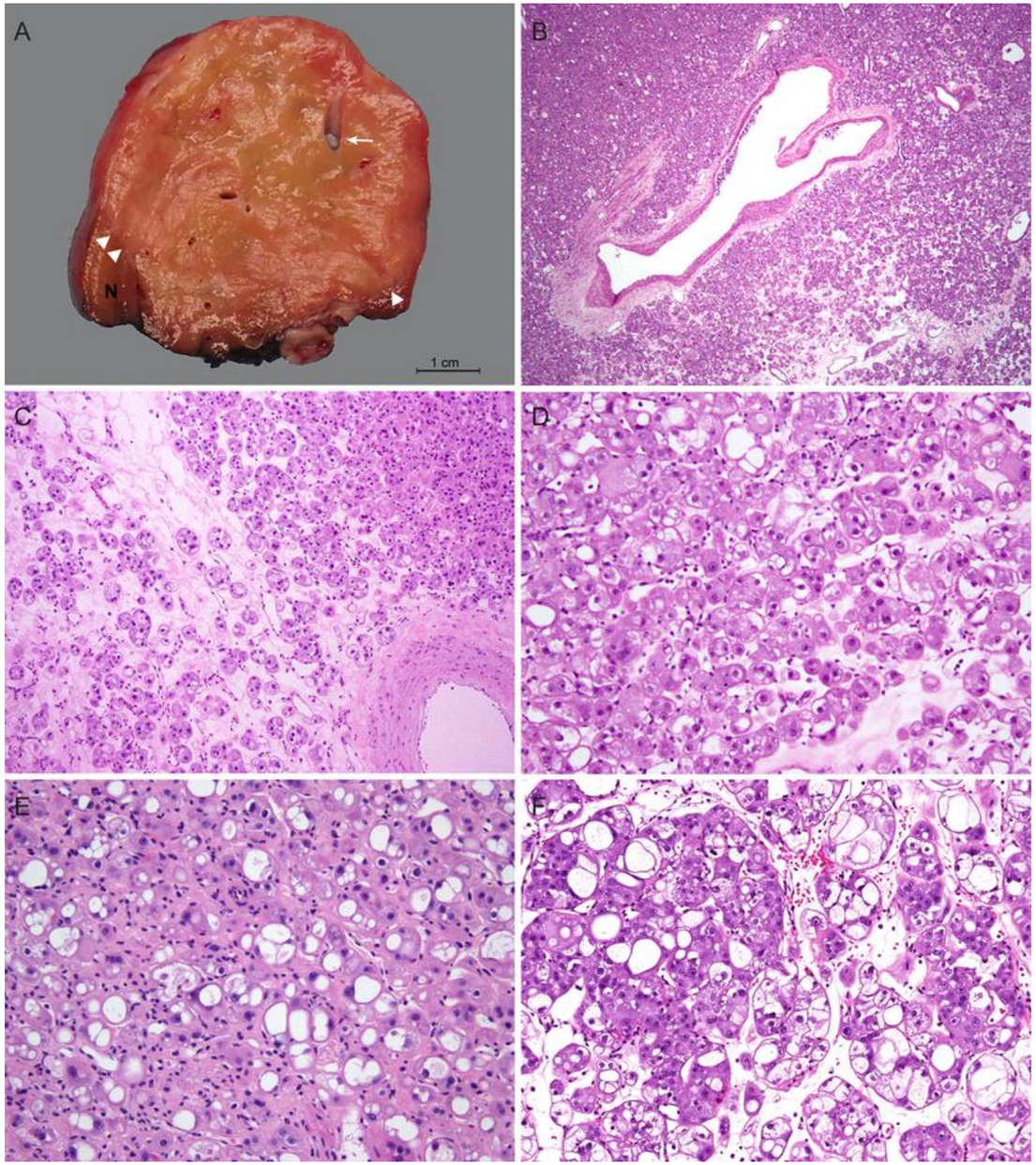
- Unencapsulated, solid, nested, hyalinized to edematous stroma, entrapped non-neoplastic tubules

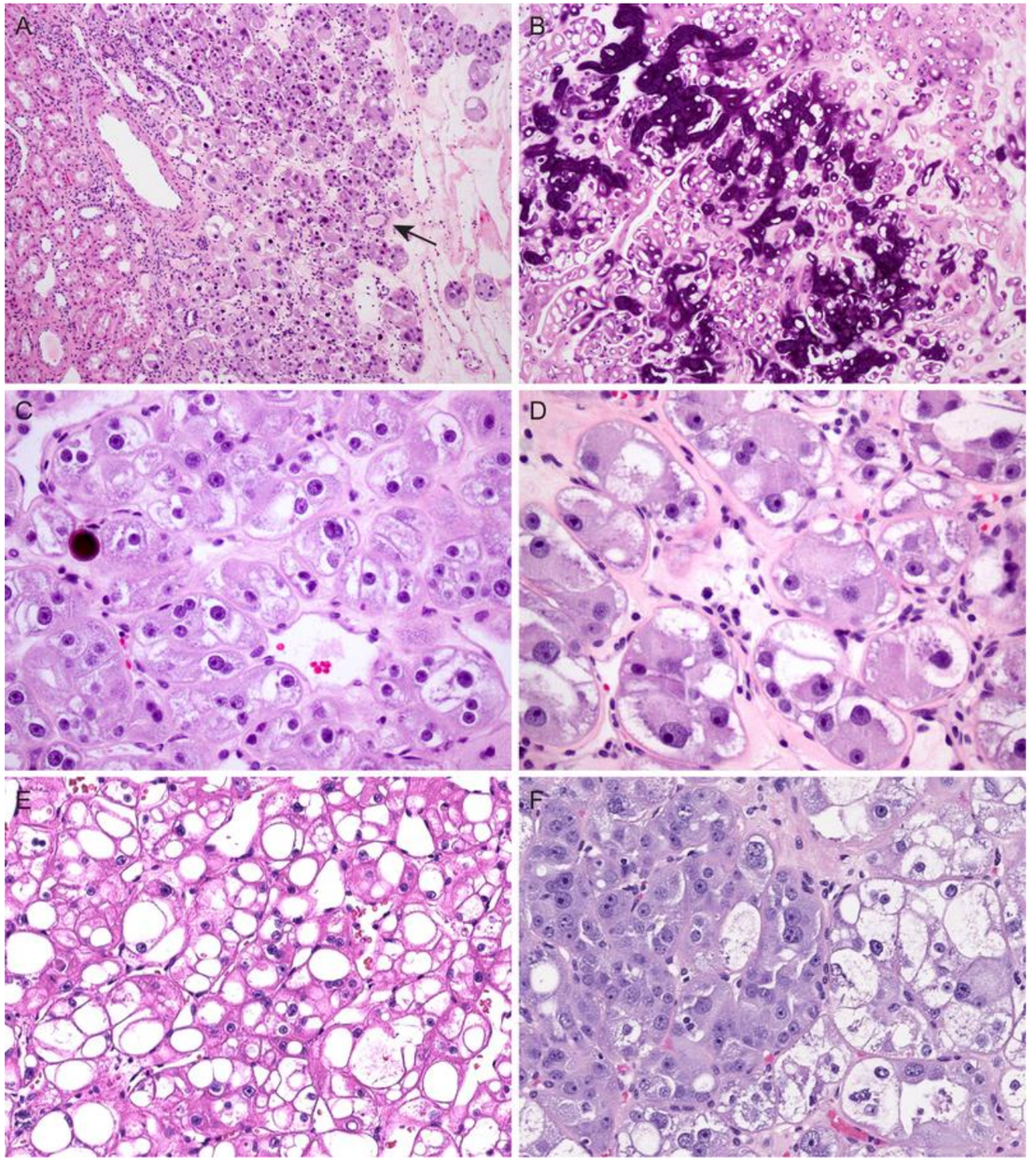
Eosinophilic Vacuolated Tumors (EVT) – Distinct Features





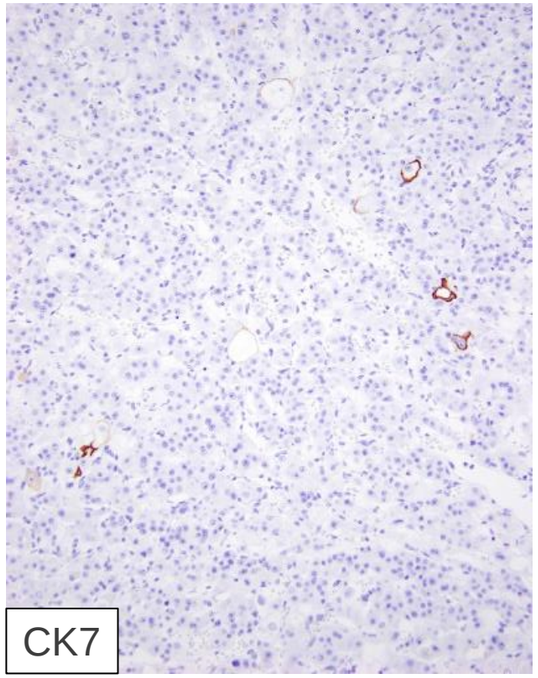
❖Voluminous eosinophilic cells with vacuolated cytoplasm, large prominent nucleoli, calcifications +/-

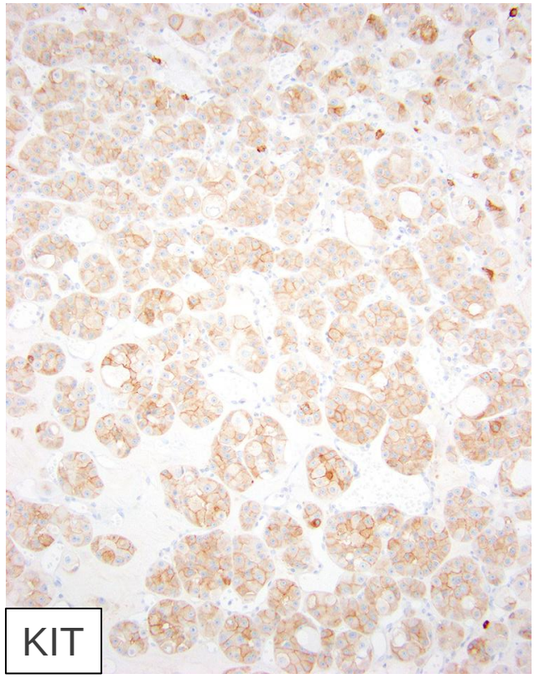


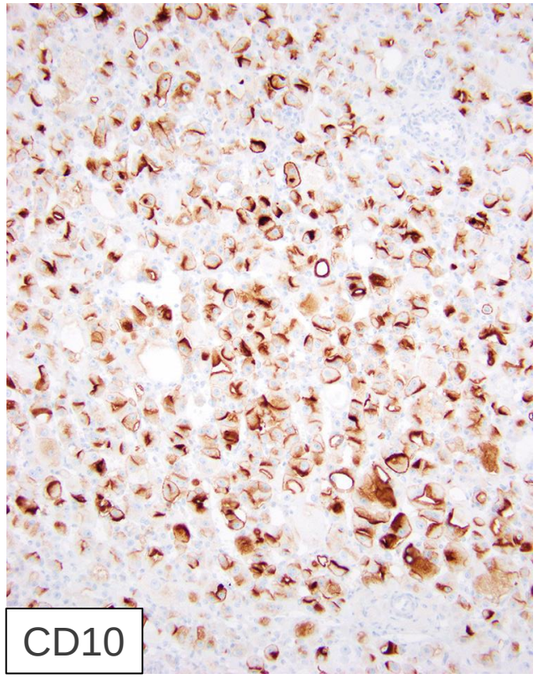


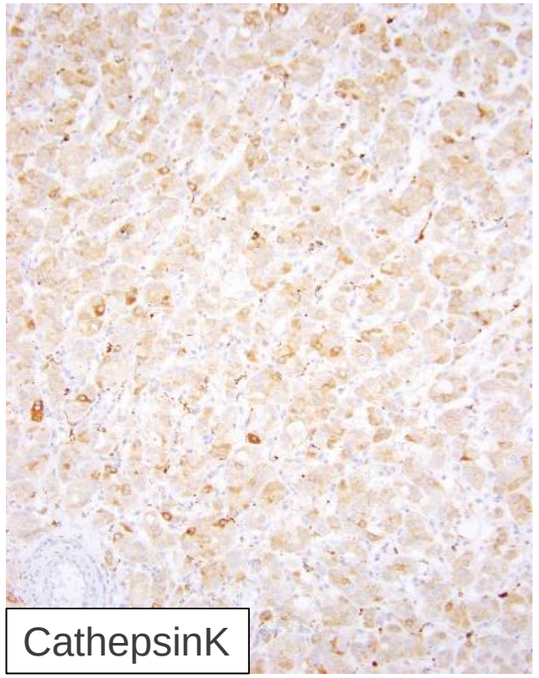
Chen YB et al, AJSP, 43(1):121-131 2019

CK7/KIT expression similar to RO, but other distinct findings….









- Genetics ➔Loss Ch1, loss Ch19, LOH 16p and 1q
- NGS ➔ Somatic inactivating mutations of *TSC2* or activating mutations of *MTOR*, consistent with hyperactive mTOR complex 1 (mTORC1)
- Prognosis ➔ Indolent, no reported metastases

*PAX8+/FH intact/SDH intact

Summary of Immunostains for Oncocytic Kidney Tumors

	PAX8	CK7	CK20	AMACR	CD10	S100A1	HNF1b	CD117	Vim	CA9	CathepK
RO	+	+ (sc)	-	-/+	-	+	+	+/-	-	-	-
ChRCC	+	+/-	-	-/+	-	-	-	+/-	-	-	-
ESC	+	-	+	-/+	?	?	?	-	+	-	-/+
LOT	+	+	-	-/+ (f)	-/+(f)	?	?	-	-/+	-	?
EVT	+	+ (sc)	-/+ (sc)	?	+	?	?	+	-	?	+
SDH RCC	+	-	-	-	-/+	+	+	-	-/+	-	-
FH RCC	+	-/+	-	-/+	?	?	?	-	?	-/+	-
CCRCC	+	-	-	+/-	+	+	+	-	+	+	-
PEComa	-	-	-	?	?	?	?	?	?	-	+

*sc, scattered cells; f, focal

“TextBook” Summary of Immunostains for Oncocytic Kidney Tumors*

RO ➔ Pos: CK7 (sc), KIT; Neg: CK20 CD10, CathepsinK

ChRCC ➔ Pos: CK7 (d), KIT; Neg: CK20 CD10, CathepsinK

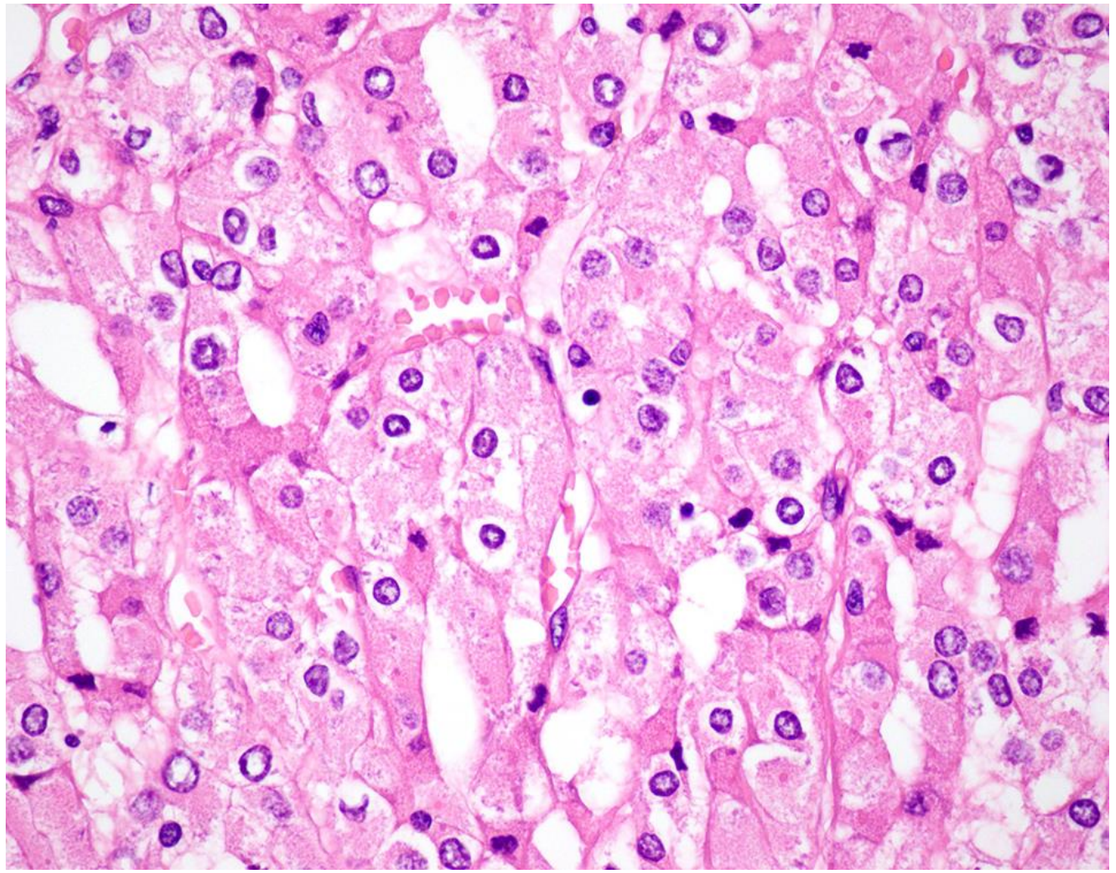
ESC ➔ Pos: CK20; Neg: CK7, KIT; Variable: CathepsinK

LOT ➔ Pos: CK7 (d); Neg: KIT, CK20 CathepsinK

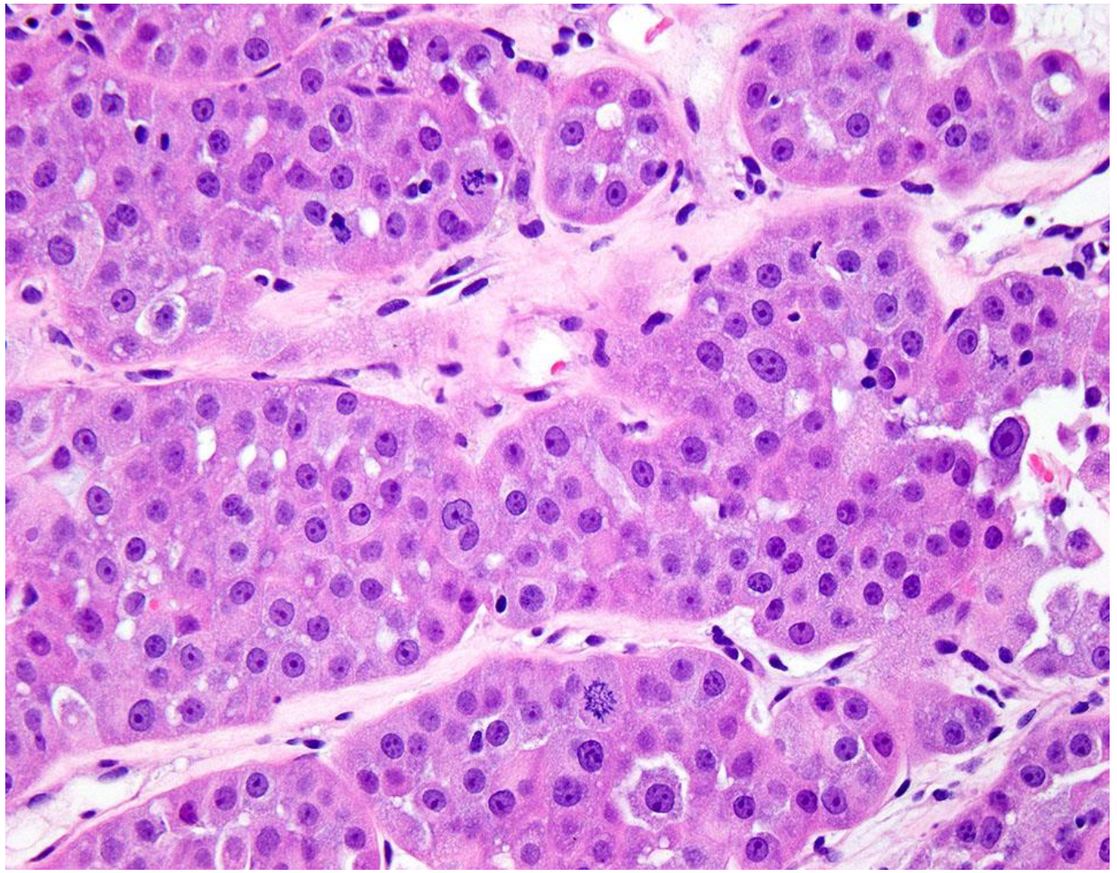
EVT ➔ Pos: KIT, CD10, CathepsinK; Neg: CK7, CK20

*sc = scattered cells, d = diffuse

Renal Oncocytic Neoplasm, NOS/UNC, LG/HG

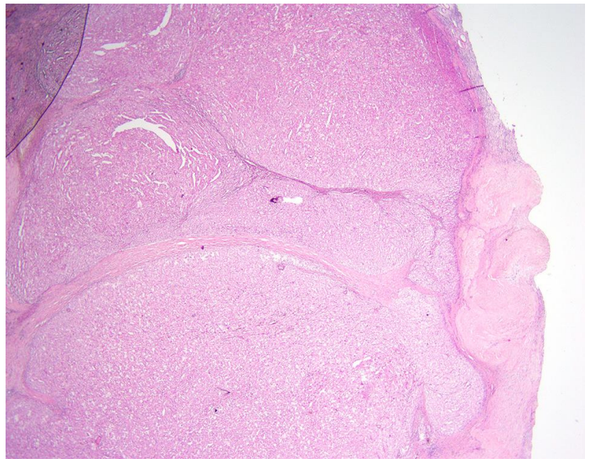
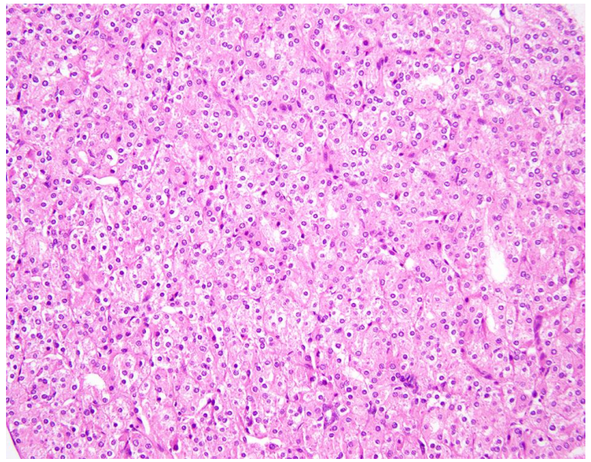
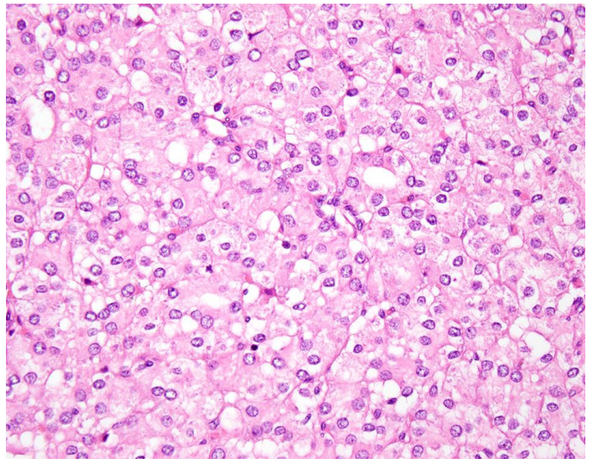
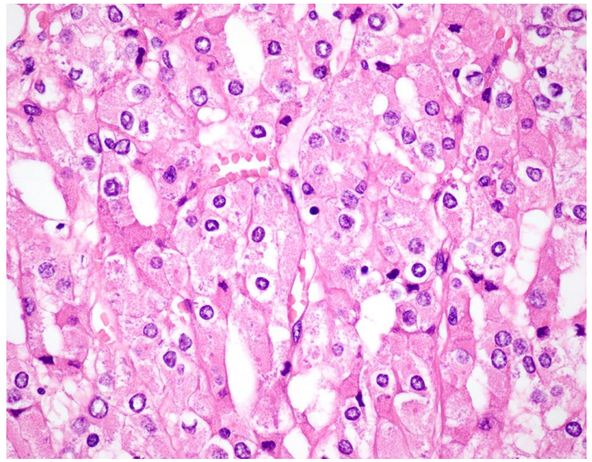


Case 1



Case 2

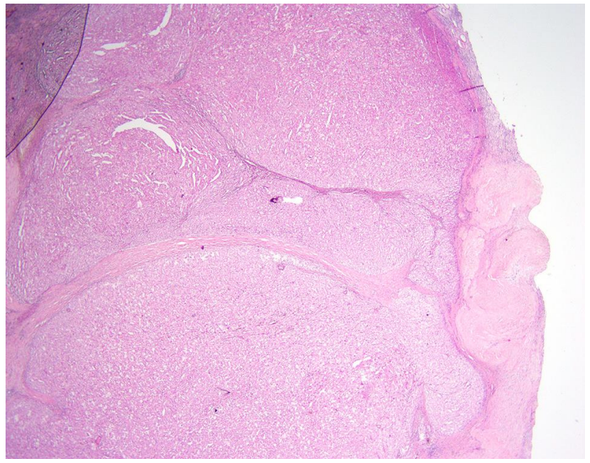
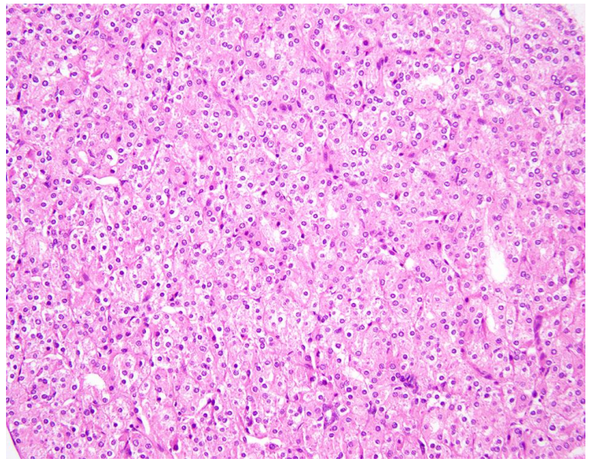
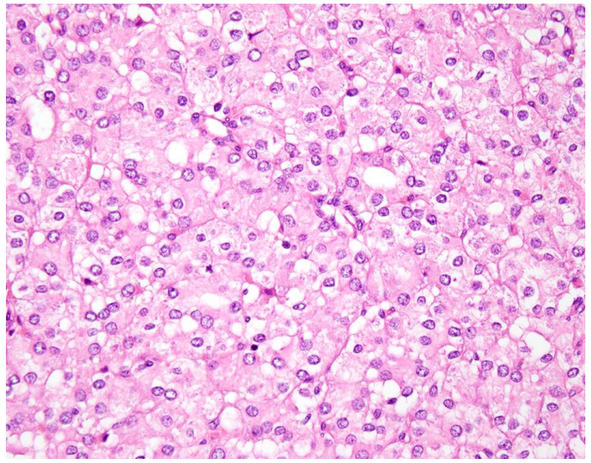
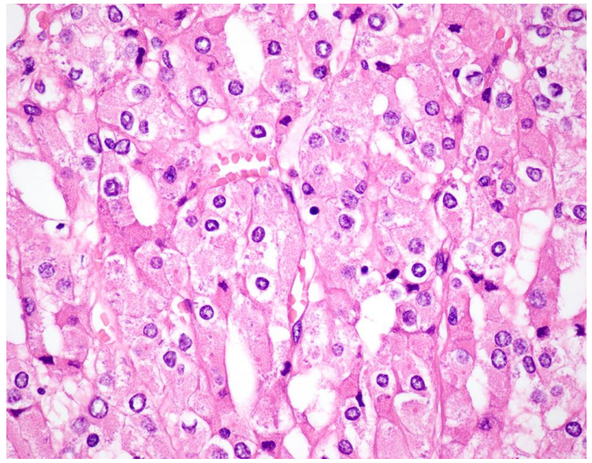
Case 1 - 54 yo male, 2.5 cm mass ➔ ? REN Subtype?

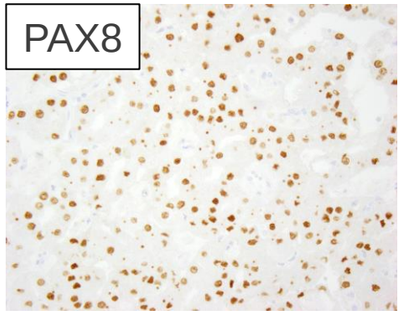
DDX:

- RO
- ChRCC
- ESC
- LOT
- EVT
- FH-Def RCC
- SDH-Def RCC
- Translocation RCC
- CCRCC
- PEComa

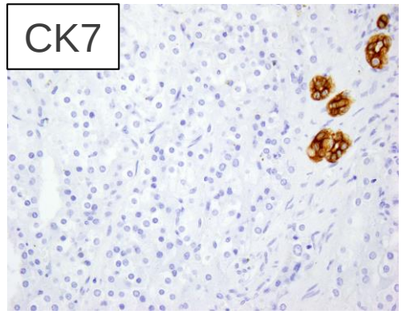
Case 1 - 54 yo male, 2.5 cm mass ➔ RON, NOS (UNC)

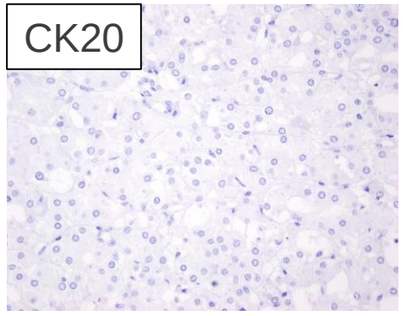
PAX8



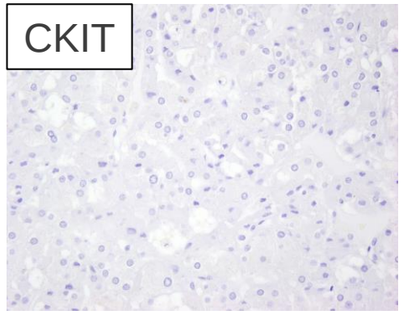
CK7



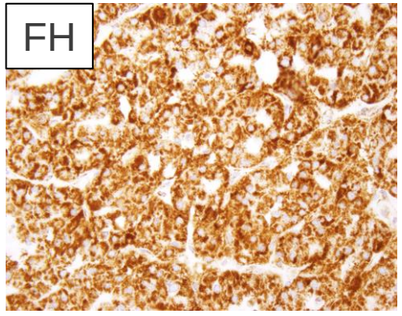
CK20



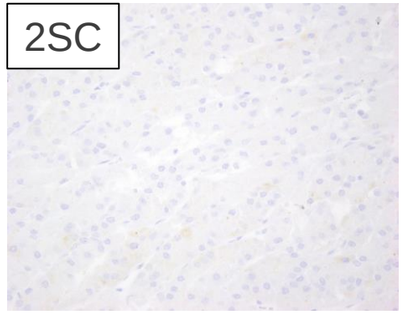
CKIT



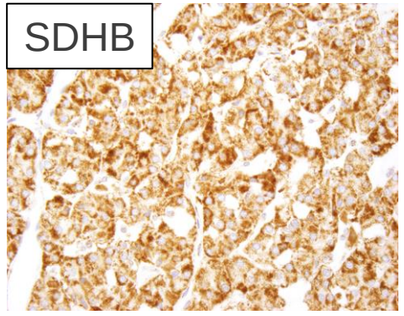
FH



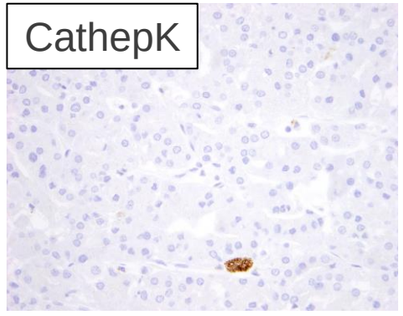
2SC



SDHB



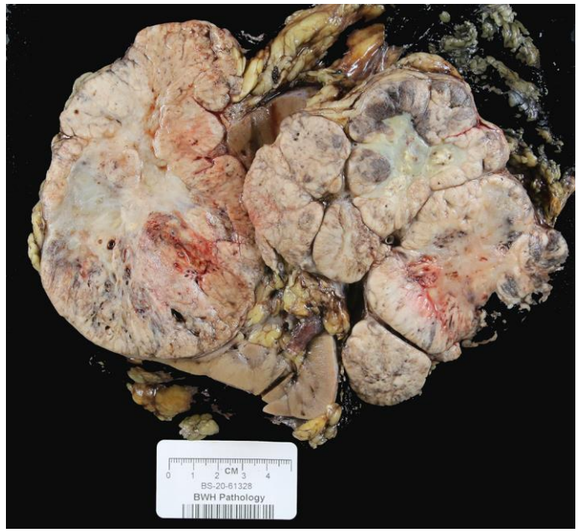
CathepK

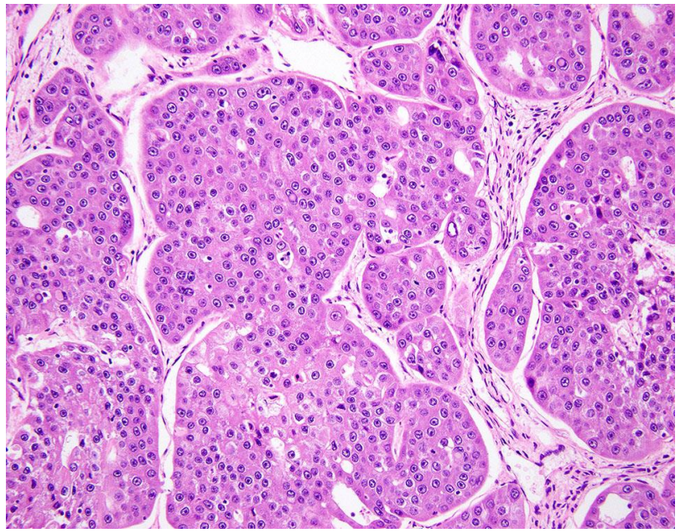


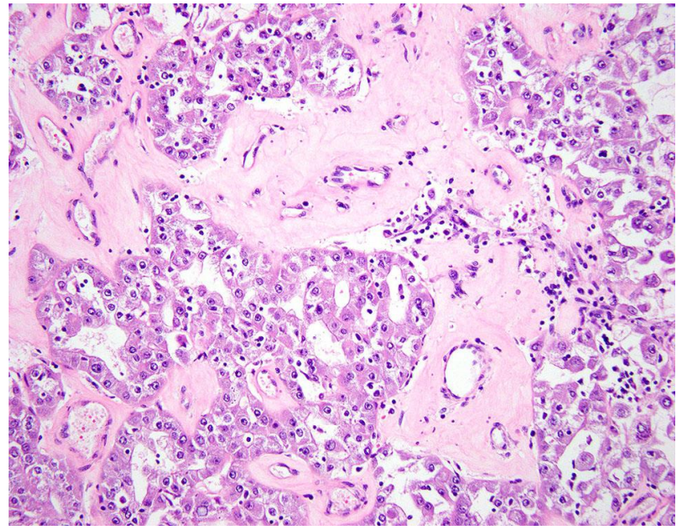
DDX:

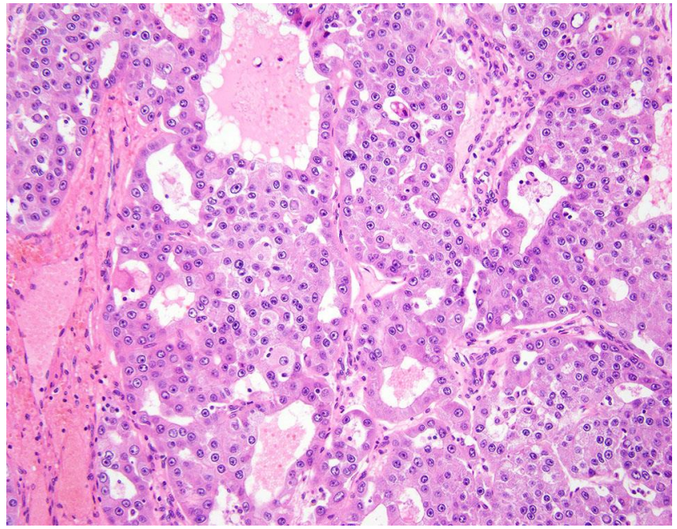
- ~~RO~~ (KIT-)
- ~~ChRCC~~ (CK7-, KIT-)
- ~~ESC~~ (CK20-)
- ~~LOT~~ (CK7-)
- ~~EVT~~ (KIT-, CathepK-)
- ~~FH-Def RCC~~ (FH intact, 2SC-)
- ~~SDH-Def RCC~~ (SDHB intact)
- ~~Translocation RCC~~ (male, TFE3-)
- ~~CCRCC~~ (CA9-)
- ~~PEComa~~ (PAX8+)

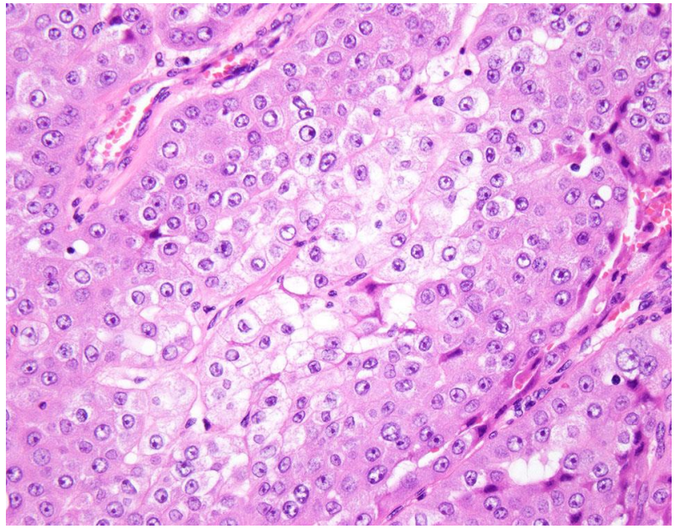
Case 2 - 48 yo female, renal, retroperitoneal, mediastinal masses

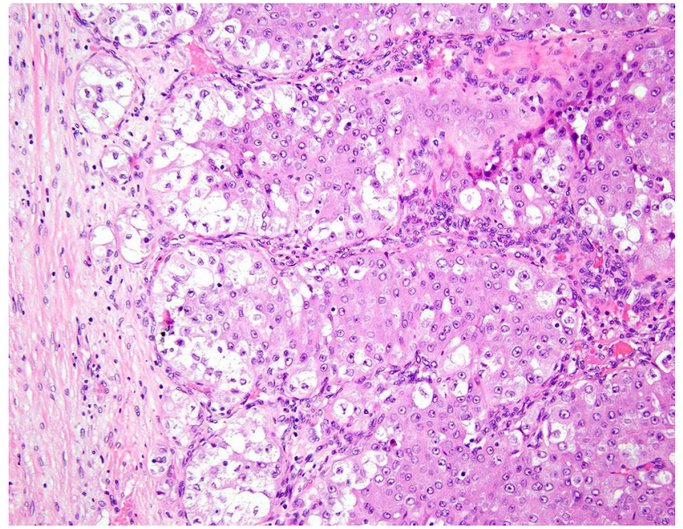




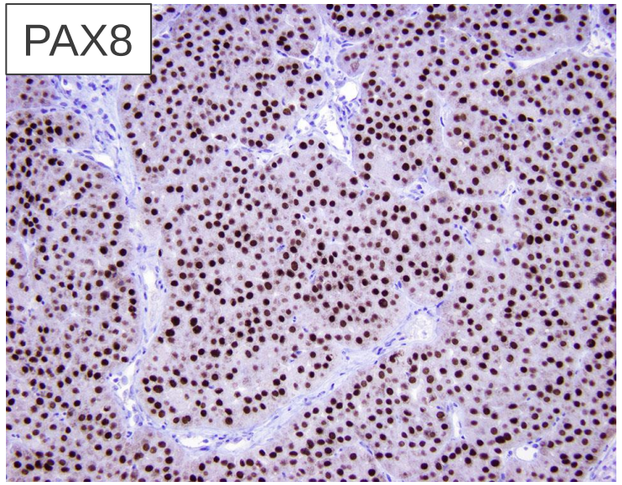


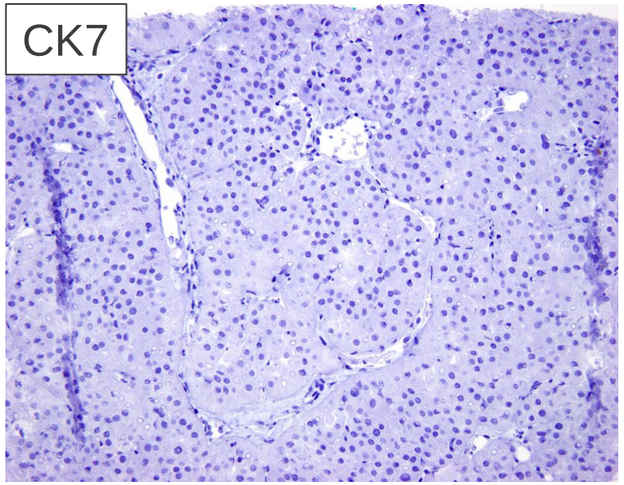


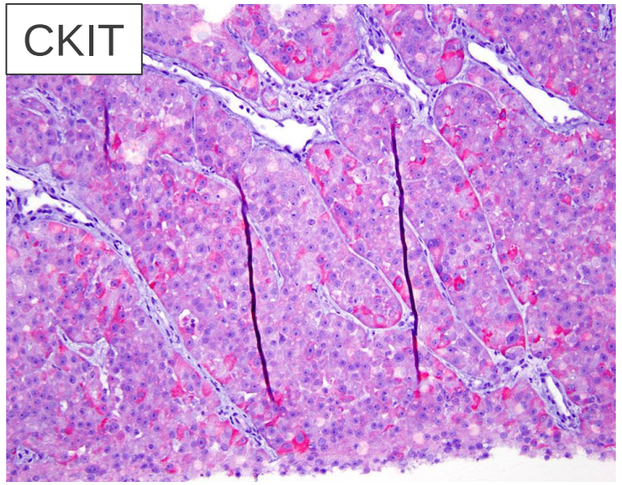


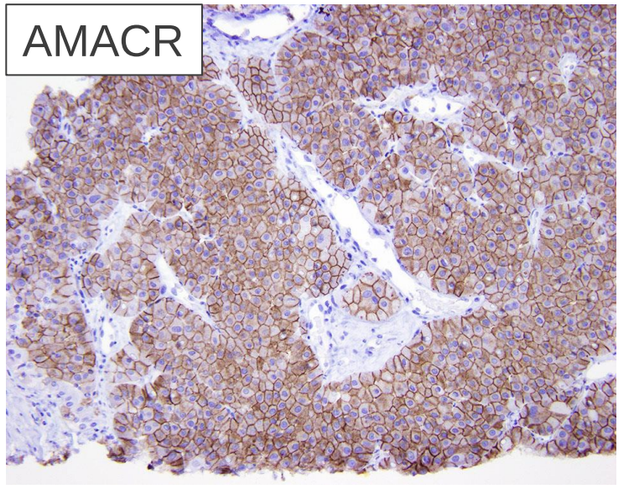


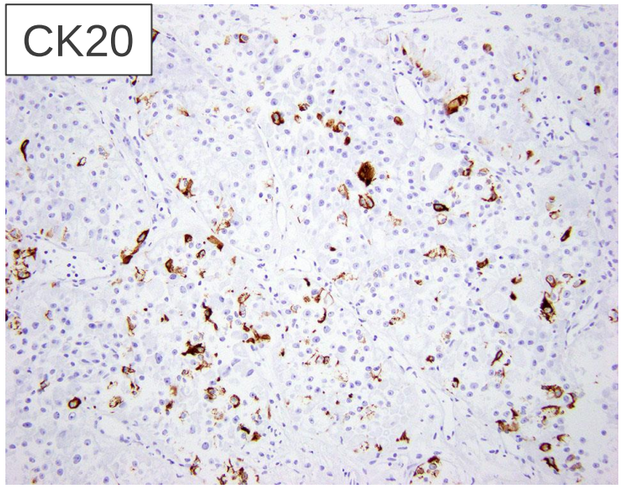
Ancillary Studies:

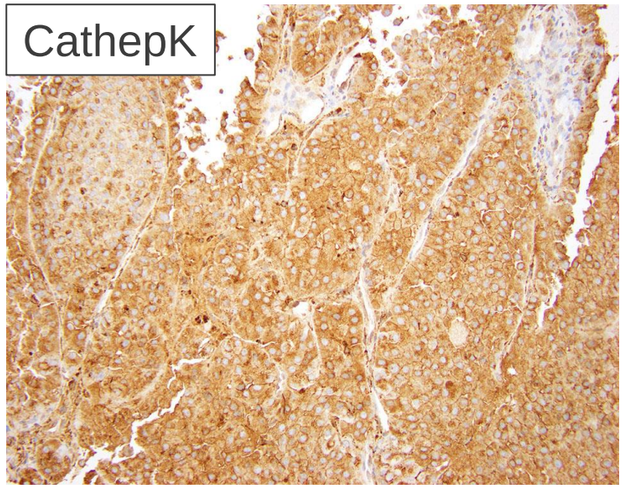










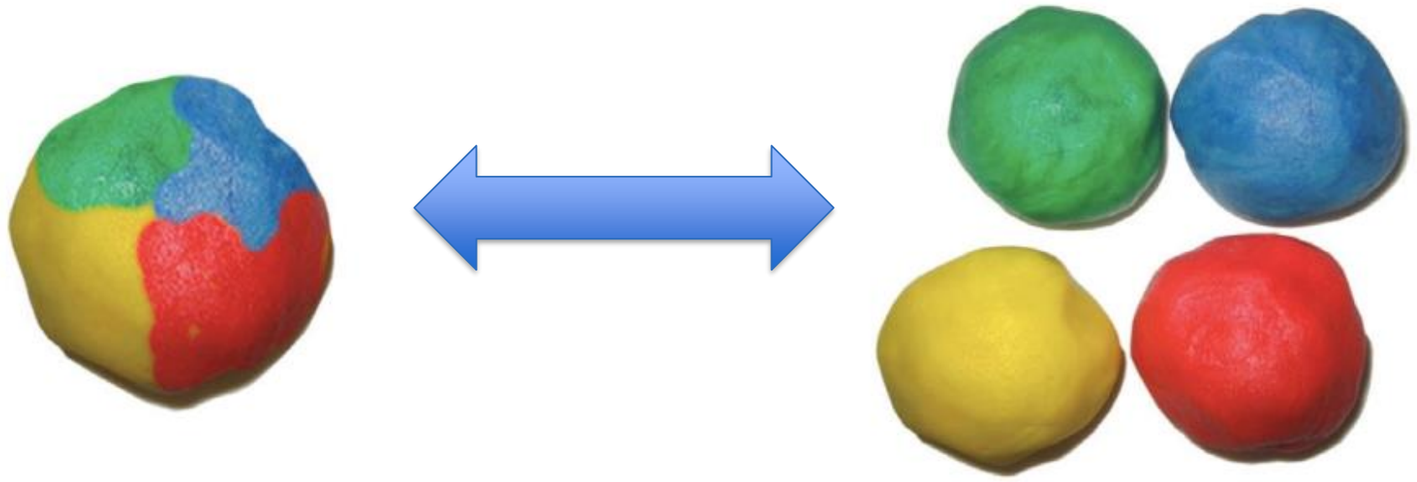


FH intact
2SC neg
SDHB intact
TFE3 neg*
TFEB neg*

➔ HG RCC UNCLASSIFIED (NGS ➔ TSC2)

*by FISH

Update #5 ➔ TSC/mTOR pathway mutations do NOT define a distinct subset of renal tumors



(*TSC/mTOR*-mutated tumors)

(ESC, LOT, EVT, PEComa)

Xia QY, et al. Am J Surg Pathol. 2022;46(11):1562-1576; Trpkov K et al, Mod Pathol. 2021 Jun;34(6):1167-1184; Trpkov K et al, Mod Pathol. 2021 Jul;34(7):1392-1424

TSC/mTOR Mutations in Renal Tumors

- Eosinophilic solid and cystic (ESC) renal cell carcinomas harbor TSC mutations: Molecular analysis supports an expanding clinicopathologic spectrum. Palsgrove DN, et al, Am J Surg Pathol. 2018 Sep;42(9):1166-1181.

- TSC/MTOR mutated eosinophilic renal tumors are a distinct entity that are CK7+/CK20-/vimentin-: a validation study. Tjota MY et al, Hum Pathol. 2020 Dec 19:S0046-8177(20)30259-8.

- Eosinophilic renal cell tumors with TSC and MTOR Gene Mutations are morphologically and immunohistochemically heterogeneous: Clinicopathologic and molecular study. Tjota M et al, Am J Surg Pathol. 2020 Jul;44(7):943-954.

- Renal cell carcinoma with leiomyomatous stroma harbor somatic mutations of TSC1, TSC2, MTOR, and/or ELOC (TCEB1): Clinicopathologic and Molecular Characterization of 18 Sporadic Tumors Supports a distinct entity. Shah RB et al, Am J Surg Pathol. 2020 May;44(5):571-581.

- Germline and sporadic mTOR pathway mutations in low-grade oncocytic tumor of the kidney. Kapur P et al, Mod Pathol. 2022.

- Low-grade oncocytic renal tumor (LOT): mutations in mTOR pathway genes and low expression of FOXI1. Morini A et al, Mod Pathol. 2022.

- TSC/MTOR-associated Eosinophilic Renal Tumors Exhibit a Heterogeneous Clinicopathologic Spectrum : A Targeted Next-generation Sequencing and Gene Expression Profiling. Study. Xia QY, et al. Am J Surg Pathol. 2022;46(11):1562-1576.

Renal Tumors with reported TSC/mTOR Pathway Mutations

Clear cell renal tumours
Clear cell RCC
Multilocular cystic renal neoplasm of LMP

Papillary renal tumours
Renal papillary adenoma
Papillary RCC

Oncocytic and chromophobe renal tumours
Oncocytoma of the kidney
Chromophobe RCC
Other oncocytic tumours of the kidney

Collecting duct tumours
Collecting duct carcinoma

Molecularly defined renal CAs
TFE3-rearranged RCC
TFEB-rearranged RCC
ELOC (formerly TCEB1)-mutated RCC
FH (fumarate hydratase)-deficient RCC
SDH (succinate dehydrogenase)-deficient RCC
ALK-rearranged RCC
SMARCB1-deficient Renal Medullary CA

Other renal tumours
Clear cell (tubulo)papillary renal cell tumour
Mucinous tubular and spindle cell CA
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated RCC
Eosinophilic solid and cystic RCC
Renal cell carcinoma NOS

'Emerging' renal CAs
CCRCC with giant cells and emperipolesis
RCC with fibromyomatous stroma (FMS)
Biphasic (alveolar/squamoid) PRCC
Biphasic hyalinzing psammomatous RCC (with NF2 mutations)
Warthin-like PRCC
Solid PRCC
Pigmented microcystic ChRCC
Hybrid oncocytic chromophobe tumor (HOCT)
Low grade oncocytic tumor (LOT)
Eosinophilic vacuolated tumor (EVT)
Renal Neoplasia Occurring Post-Chemotherapy / Radiation
Atrophic Kidney-Like Lesion

Non-epithelial renal tumours
AML/epithelioid AML/PEComa

IMO, do NOT diagnose 'TSC-mutated RCC/Tumor' as a distinct subtype

Summary

➢ Be familiar with the WHO classification of renal tumors

- CCTPRCC ➔ CCTP Tumor
- Discontinue “typing” of PRCC!
- New WHO Category ➔ Molecularly Defined Renal Carcinomas
  - ✓TFE3, TFEB, ELOC (TCEB1), FH, SDH, ALK, SMARCB1
- Some entities still in ‘research phase’ (emerging)

➢ Beware of overlapping morphology and diagnostic pitfalls

- Use biomarkers and molecular testing judiciously and as needed
- If you don’t think about it, you won’t diagnose it
- Tumors don’t read textbooks

➢ Be a ‘SLUMPER’ (aka a ‘systems thinker’)!

- Best understanding of composite pathophysiology

➢ Why do all this?

- Affects prognosis, genetic work-up, treatment options, clinical trials, etc
- (also, ‘JOB SECURITY!)

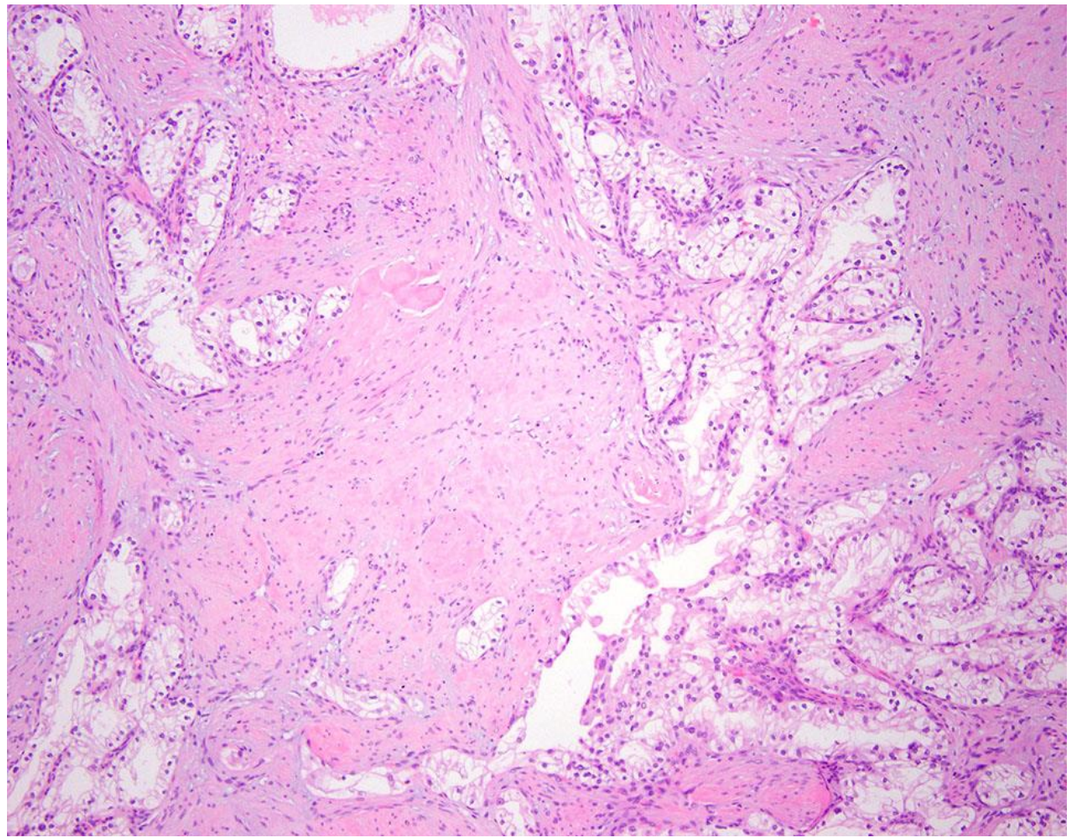
BWH

Thank you!

mhirsch1@bwh.harvard.edu

Emerging Entities/Concept ➔ Renal Tumors with CC Cytology and Fibromyomatous (Leiomyomatous*) Stroma

- “RCC-FMS” originally described as a tumor associated with TSC (familial)
- **Debate remains whether these emerging entities represents a distinct entity or a <u>heterogenous group of RCCs with overlapping morphology</u> (lump or split?)**
- Multiple small cohorts of RCC-FMS ➔ 1) some CCRCC, 2) some CCTPRT/RAT, 3) some TCEB1 mutated, 4) some with TSC/MTOR mutations (sporadic)
- IMO, Dx of exclusion, especially if unable to perform molecular studies



*NOTE: ‘Leiomyomatous stroma (LMS)’ recently changed to ‘Fibromyomatous stroma (FMS)’ so not to confuse with ‘Leiomyosarcoma (LMS)’

Trpkov K and Hes O, Histopathol 2018; Petersson F et al., Appl Immunohistochem Mol Morphol. 2018; Parilla M et al, AJSP; 2019; Shah R et al, Am J Surg Pathol 2020, Trpkov et al, Mod Pathol 2021