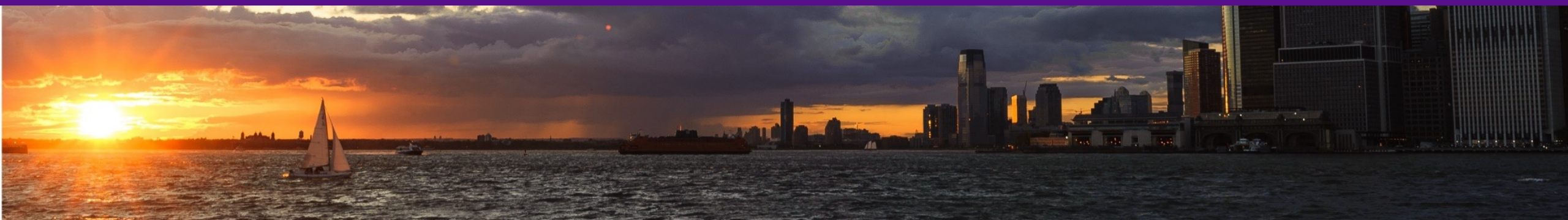


# Kidney Tumors to Consider in Daily Practice



### **Education:**

Residency: NYPH-Weill Cornell Medicine

Fellowship: NYPH-Weill Cornell Medicine



### **Current Position & Institution:**

- **Clinical Associate Professor**

### **Subspecialty area:**

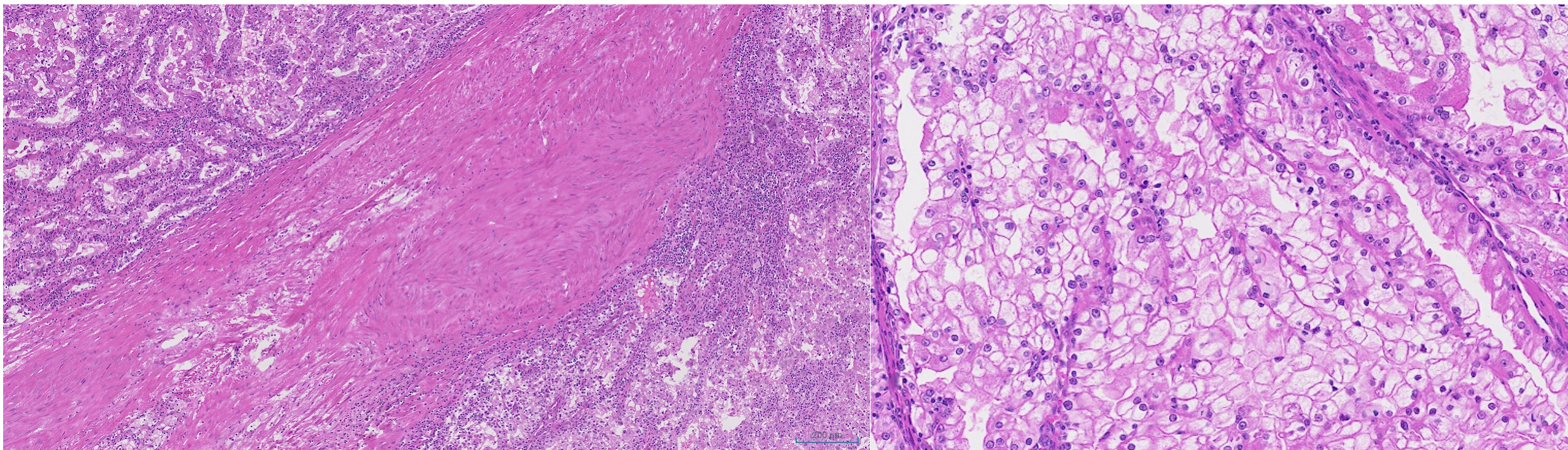
- **Molecular and GU Pathology**

# 2022 WHO (5<sup>th</sup> ed.) – Renal cell tumors

- Clear cell renal tumors
  - Clear cell RCC
  - Multilocular cystic renal neoplasm of low malignant potential
- Papillary renal tumors
  - Renal papillary adenoma
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- Molecularly defined renal carcinomas
  - *TFE3* rearranged RCC
  - *TFEB* altered RCC
  - *ELOC*-mutated RCC
  - FH-def RCC
  - SDH-def RCC
  - *ALK*-rearranged RCC
  - SMARCB1-def renal medullary carcinoma



## Case #1. 43 yo M





# Renal cell carcinoma with clear cell features and leiomyomatous stroma

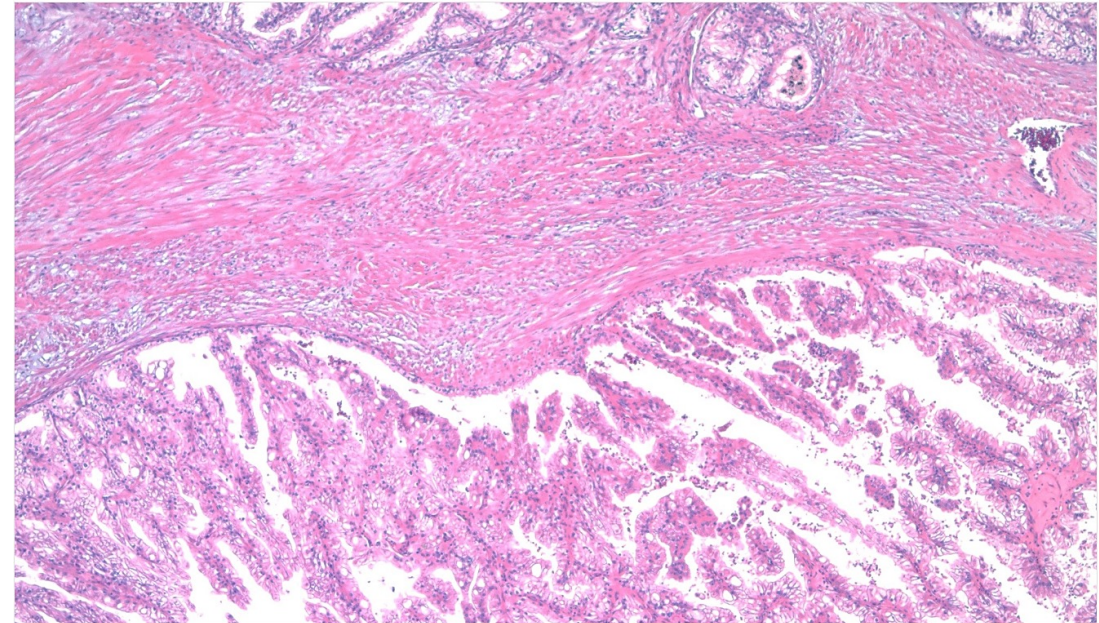
- DDx
  - Clear cell RCC with prominent stromal component
  - Clear cell papillary renal cell tumor
  - *ELOC* mutated RCC
  - *TSC* associated RCC
  - *TFE3* rearranged RCC

		ccRCC	CCPRCT	<i>ELOC</i> mRCC
M:F		1.94:1	No predilection	Male (>90%)
Age		≥ 60 yrs (median=62)	Mean of 58.2	Median of 60
Morphology		Clear cytoplasm with “chicken-wire” vessels	Linear luminal nuclear polarization, low nucleolar grade	Voluminous clear cytoplasm and prominent cell borders; nodular appearance with thick transecting fibromuscular bands
IHC	CAIX	+	+ (cup-like)	+ (diffuse membranous)
	CK7	-	+	+
	CD10	+	-	+
	HMWCK	-	+	-
Molecular features		3p LOH and <i>VHL</i> inactivation (mutation/methylation)	Diploid, metabolic profile with mtDNA depletion	<i>ELOC</i> mutations, 8q LOH/monosomy 8
Prognosis		5 year survival: 50 - 70% after nephrectomy, 10% in metastatic disease	Usually pT1; Indolent tumors	Mostly pT1a; Majority with indolent course



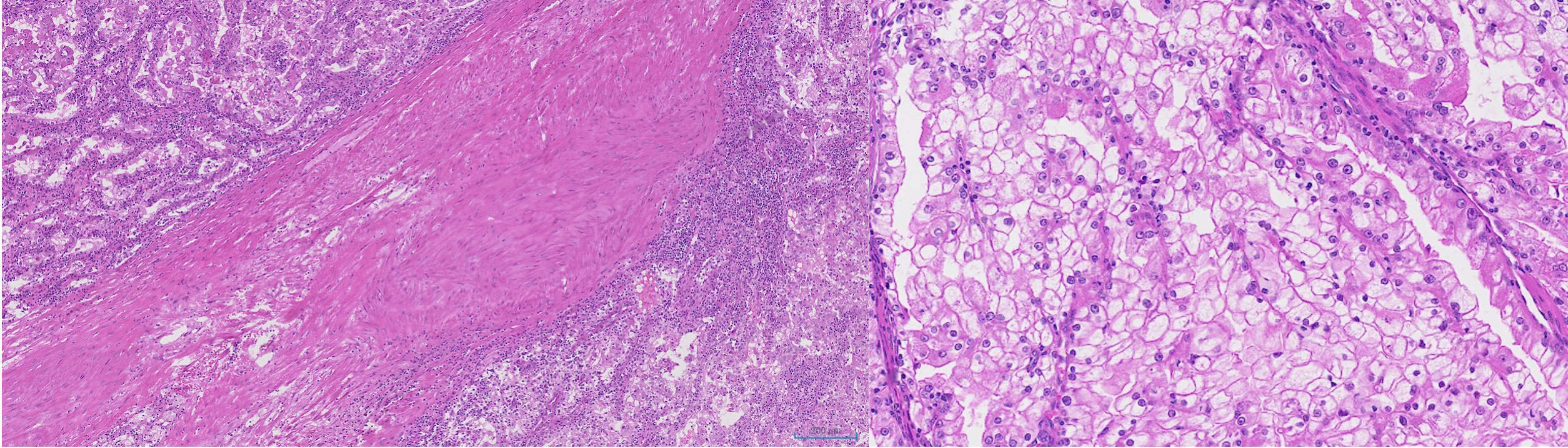
# *ELOC* (formerly *TCEB1*)-mutated RCC

- Involve VHL binding site residue Y79, resulting in non-binding with VHL complex and consequent HIF1 $\alpha$  accumulation and overexpression
- Essential diagnostic criteria: demonstration of *ELOC* mutation is required to definitively diagnose this neoplasm
- Without molecular corroboration, one can reasonably refer to neoplasms meeting morphological criteria as clear cell RCCs with prominent fibromuscular septations and CK7 positivity, and give a differential diagnosis.





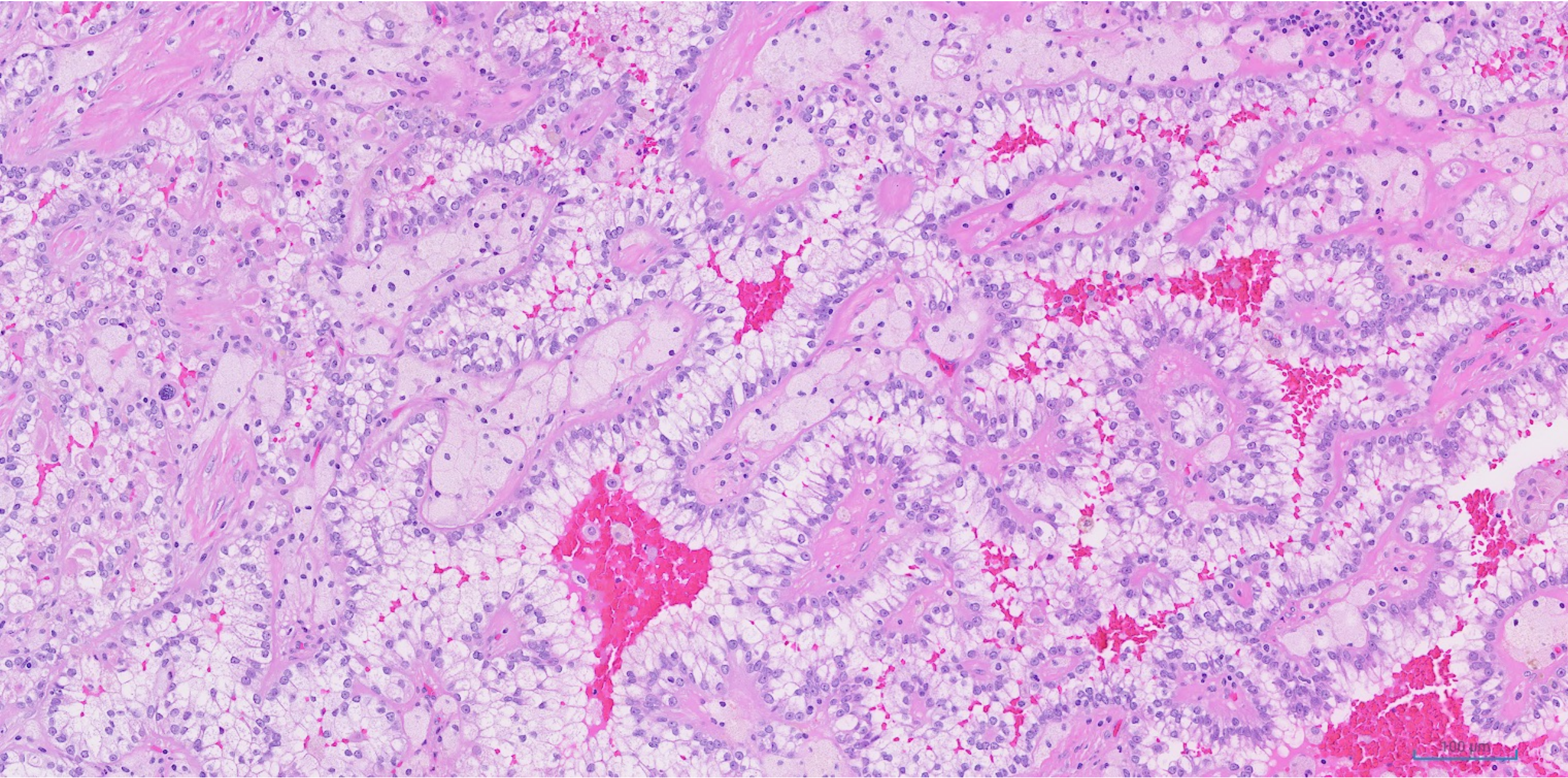
## Case #1. 43 yo M, 10.5 cm, WHO/ISUP grade 4, pT3a



- Positive for CAIX
- Focally positive for vimentin and CD10
- Negative for CK7, Melan A
- *TFE3/TFEB* FISH negative

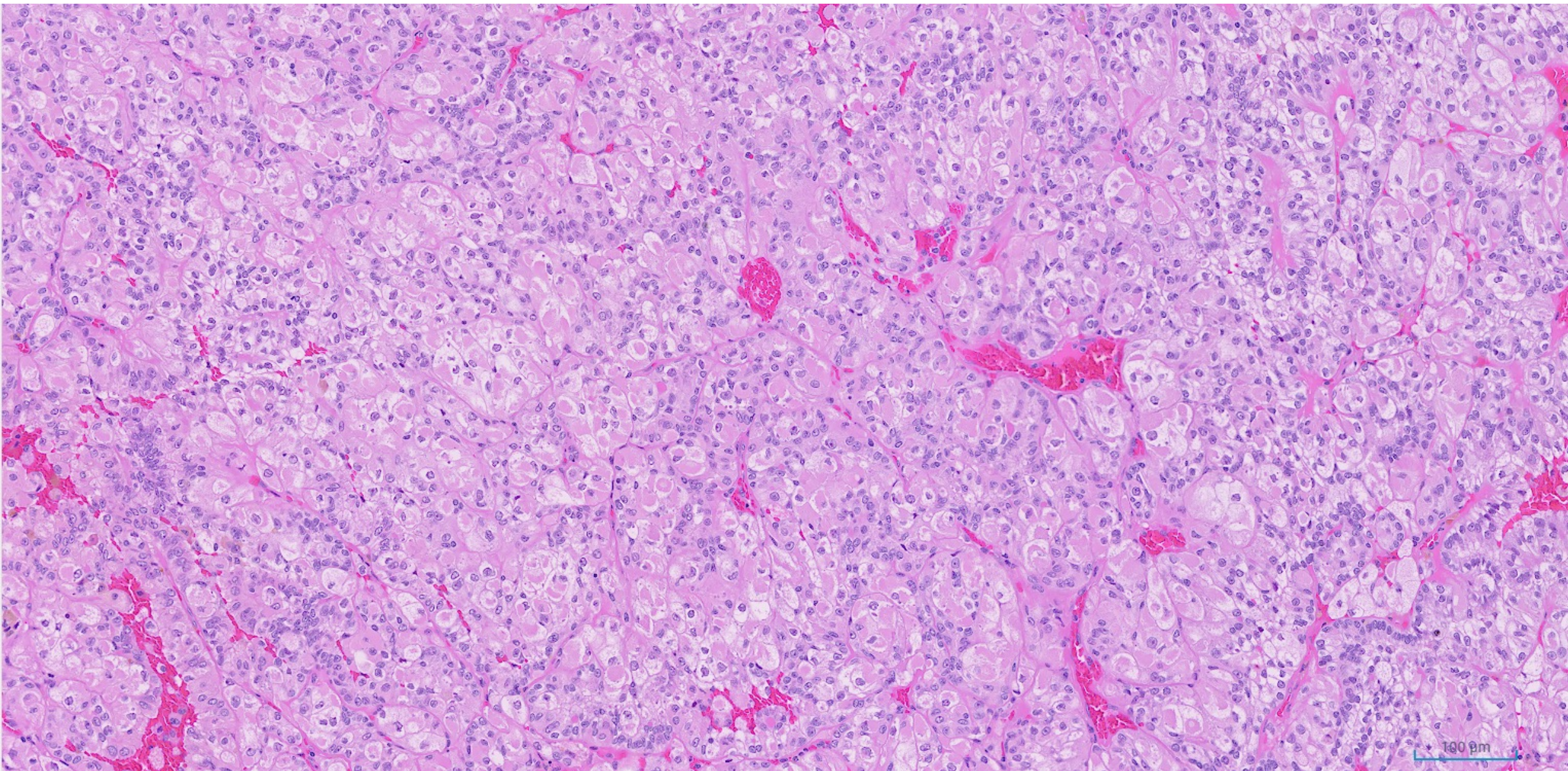


Case 2. 45 yo M, 1.8 cm right renal mass





Case 2. 45 yo M, 1.8 cm right renal mass

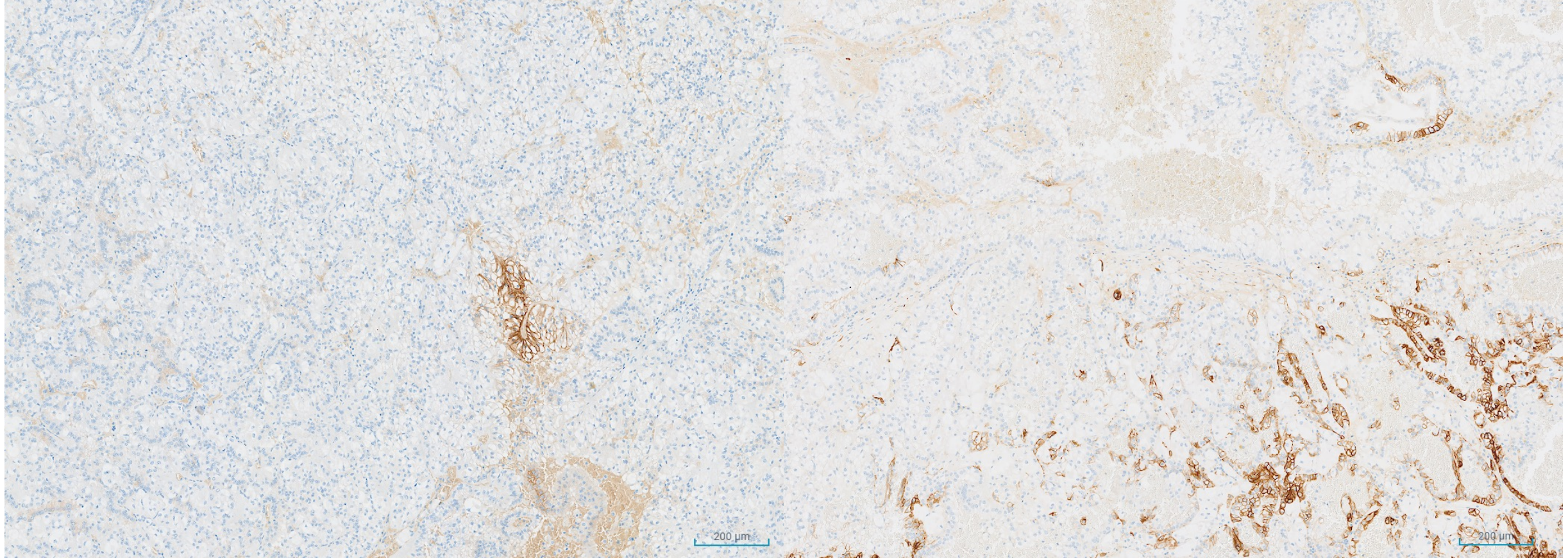




## Case 2. 45 yo M, 1.8 cm right renal mass

CAIX

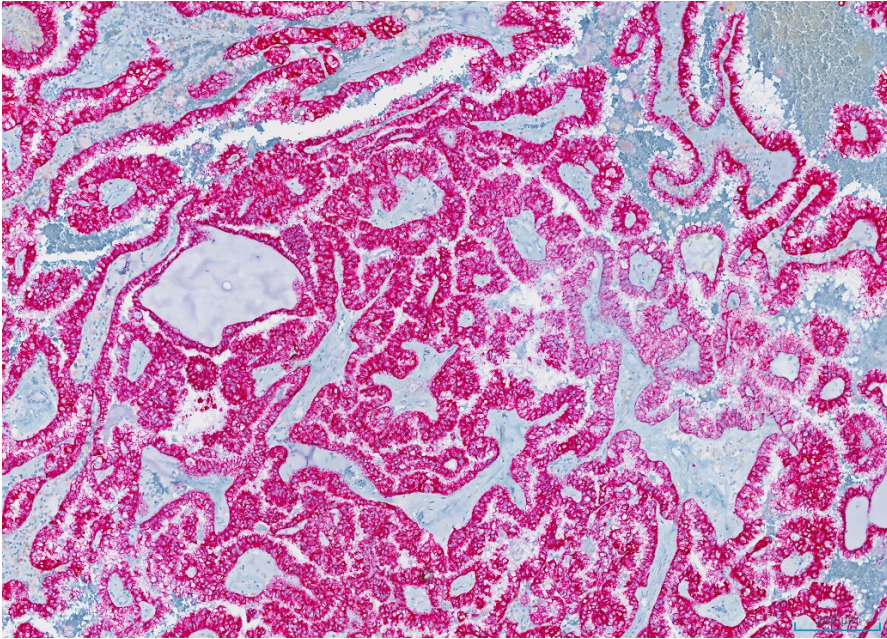
CK7





## Case 2. 45 yo M, 1.8 cm right renal mass, pT1a

### AMACR



- AMACR positive
- CK AE1/AE3, CK7, CAIX – focal positivity
- 34BE12 negative
- Melan-A and HMB45 – non-specific staining

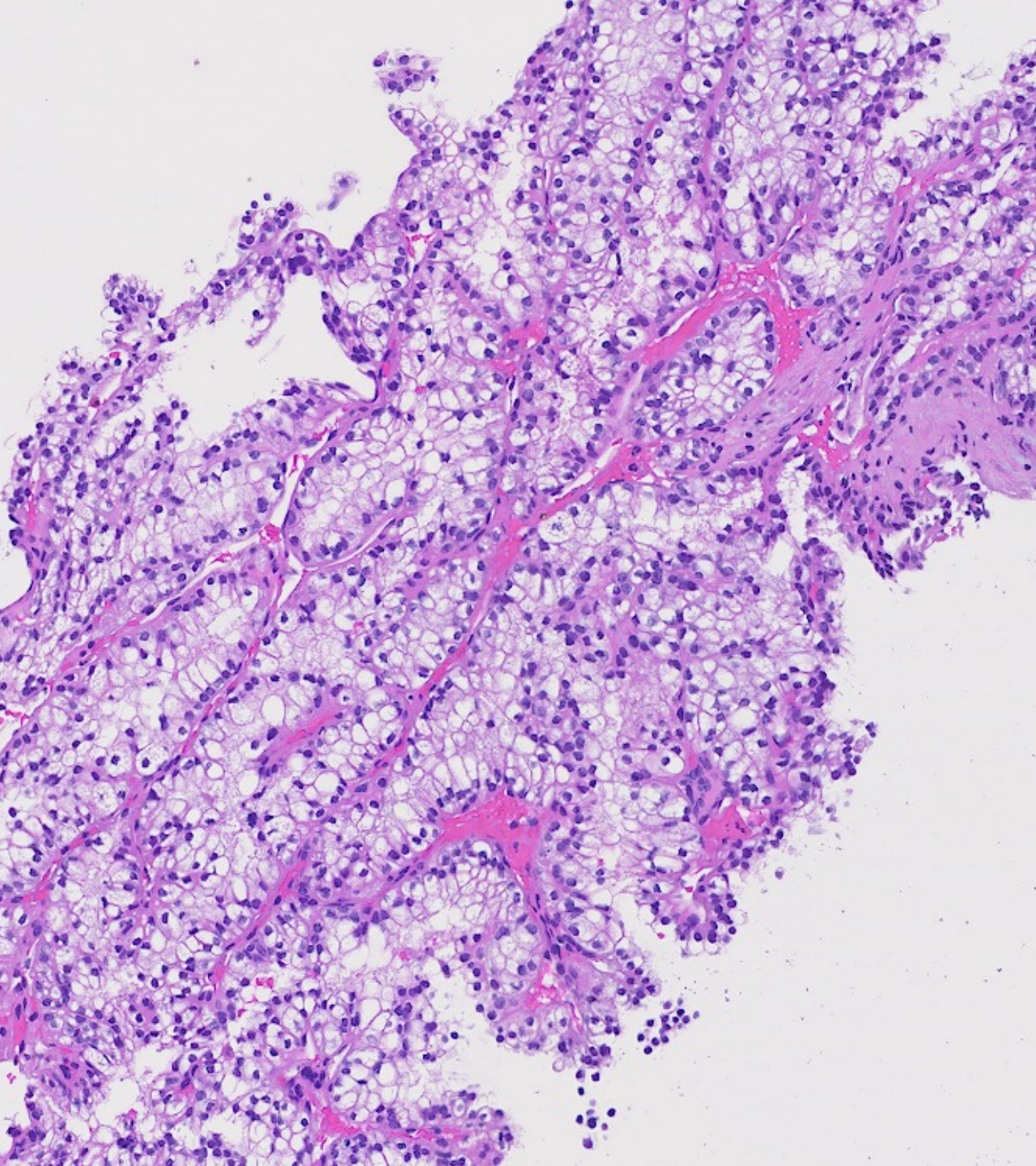
chr1:156738031,chrX:48895967





# TFE3-rearranged RCC

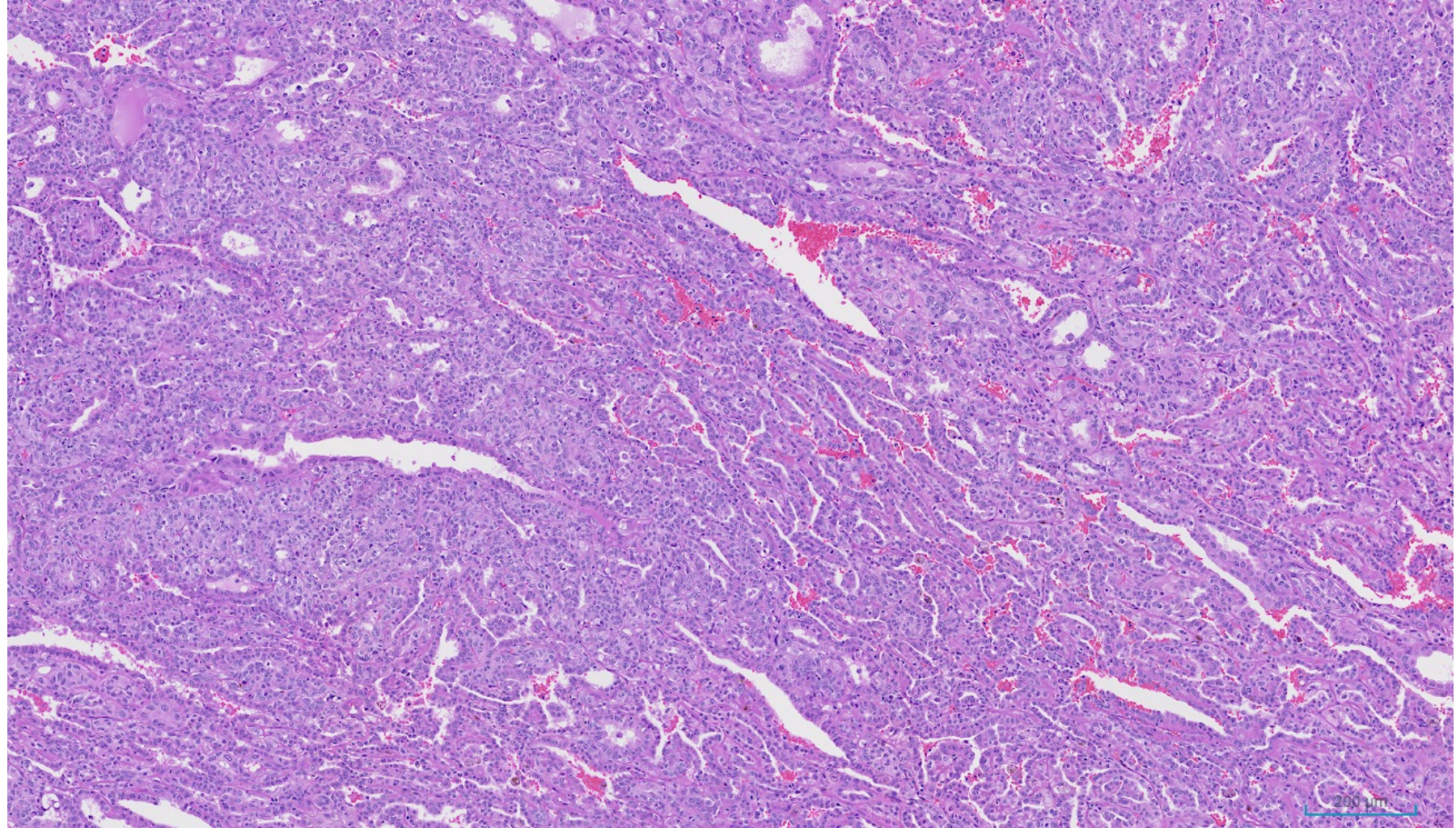
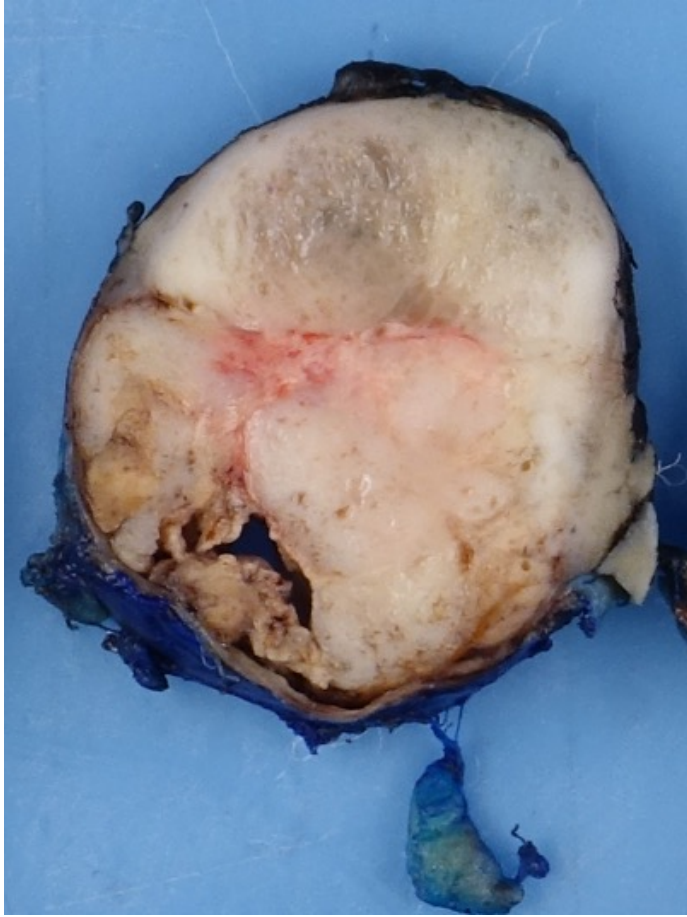
- ~40% of pediatric, ~15% of RCCs <45 yo, 1.6-4% of adult RCC cases
- F:M = 2:1
- Predominantly clear cells, papillary architecture and psammoma bodies
- *TFE3* on chrXp11.23 with >20 different partner genes  
(*ASPSCR1*, *EWSR1*, *CLTC*, *DVL2*, *FUBP1*, *KAT6A*, *MED15*, *NEAT1*, *NONO*, *PARP14*, *PRCC*, *RBM10*, *SFPQ*, etc)
  - *ASPSCR1::TFE3*
  - *PRCC::TFE3*
  - *SFPQ::TFE3*
- Overexpressed TFE3 fusion proteins act as aberrant TFs that activate the expression of melanocytic markers or cathepsin K
- TFE3 IHC highly sensitive and specific
- Survival similar to ccRCC and worse than pRCC



- 28 yo M
- MRI enterography for a history of Crohn's disease
- Incidental 2.8 cm right lower pole renal mass
- Positive for CAIX and CK AE1/AE3

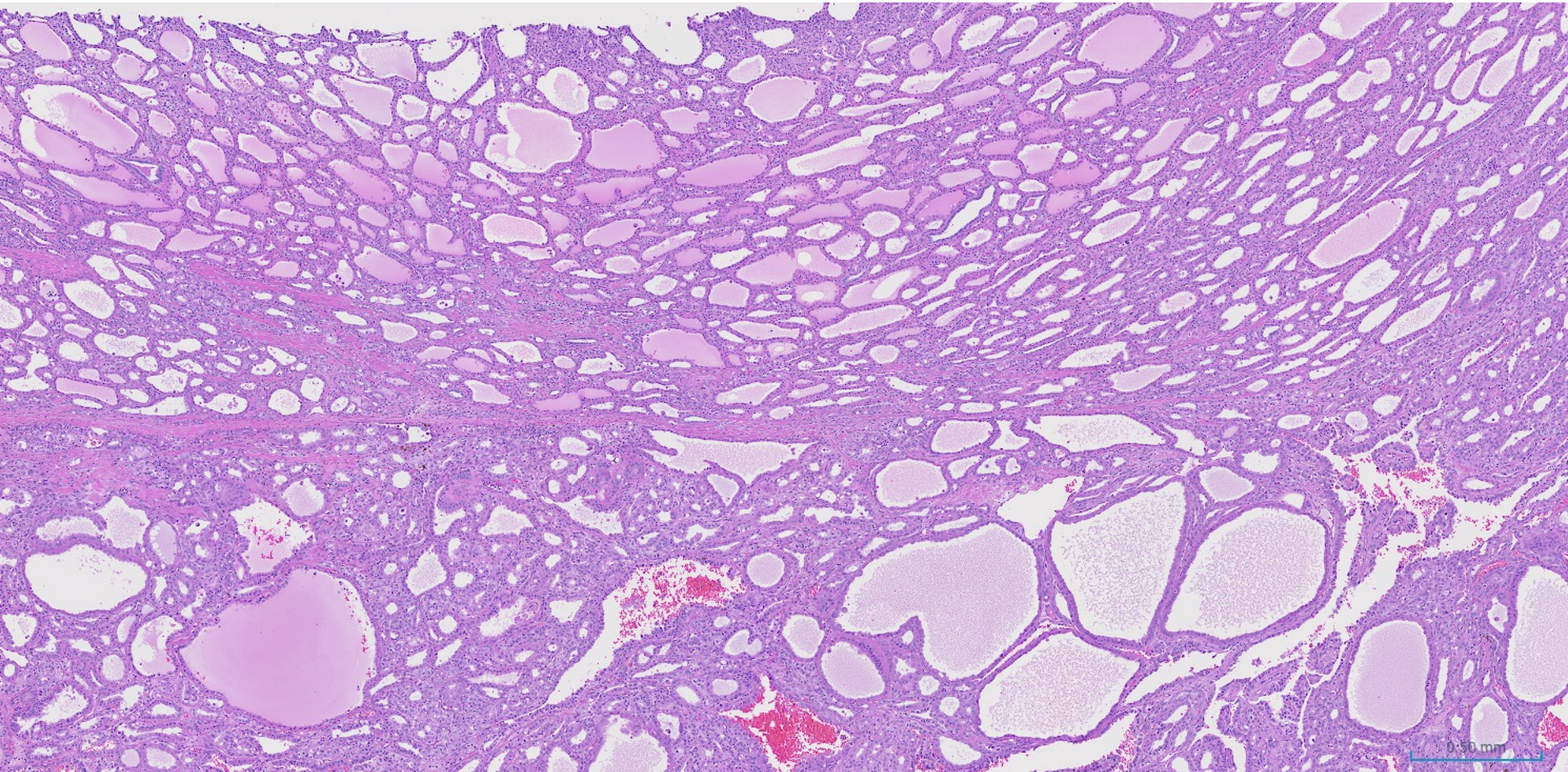


### Case 3. 72 yo M with 3.1 cm right renal mass



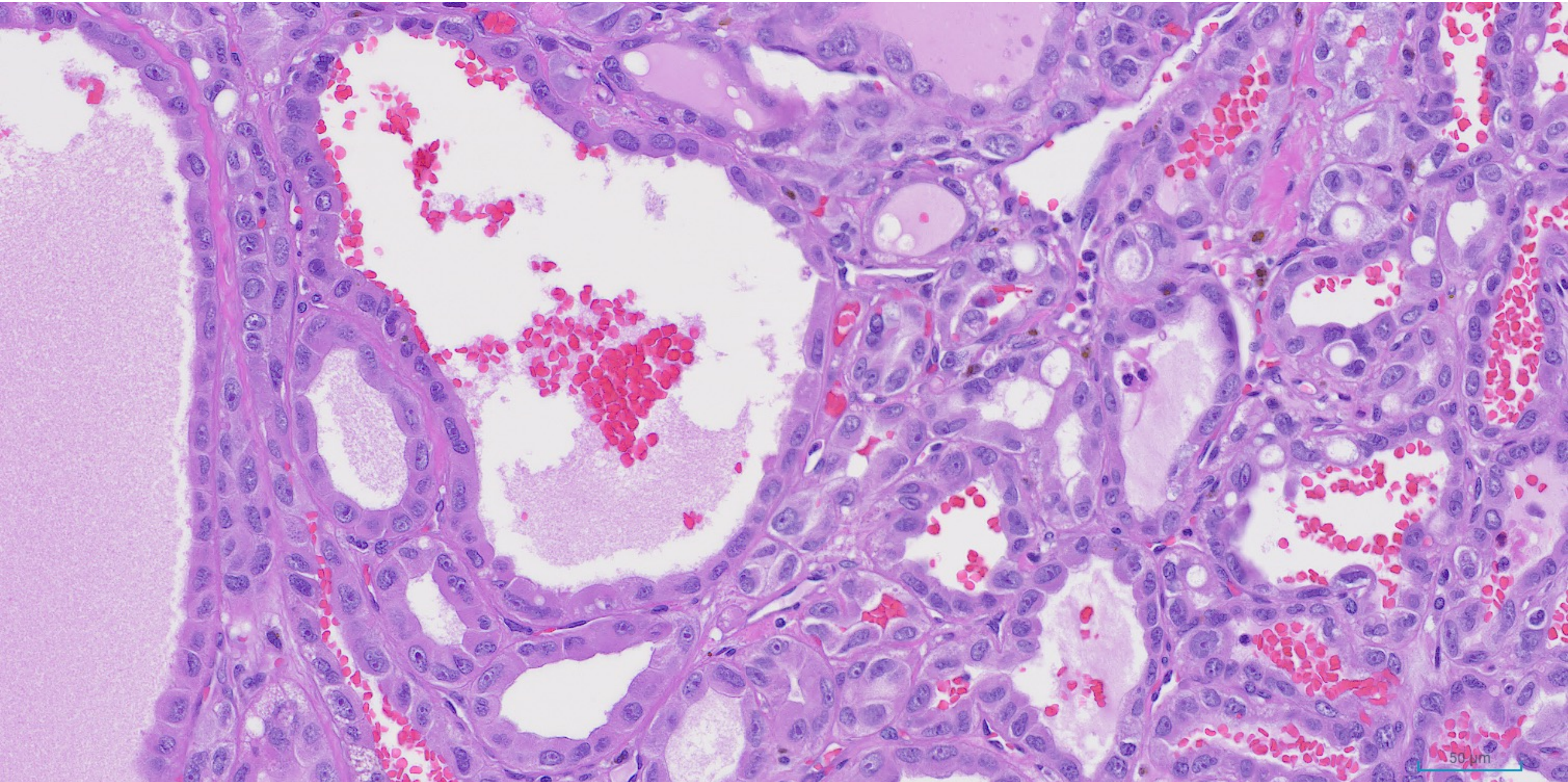


Case 3. 72 yo M with 3.1 cm right renal mass





Case 3. 72 yo M with 3.1 cm right renal mass

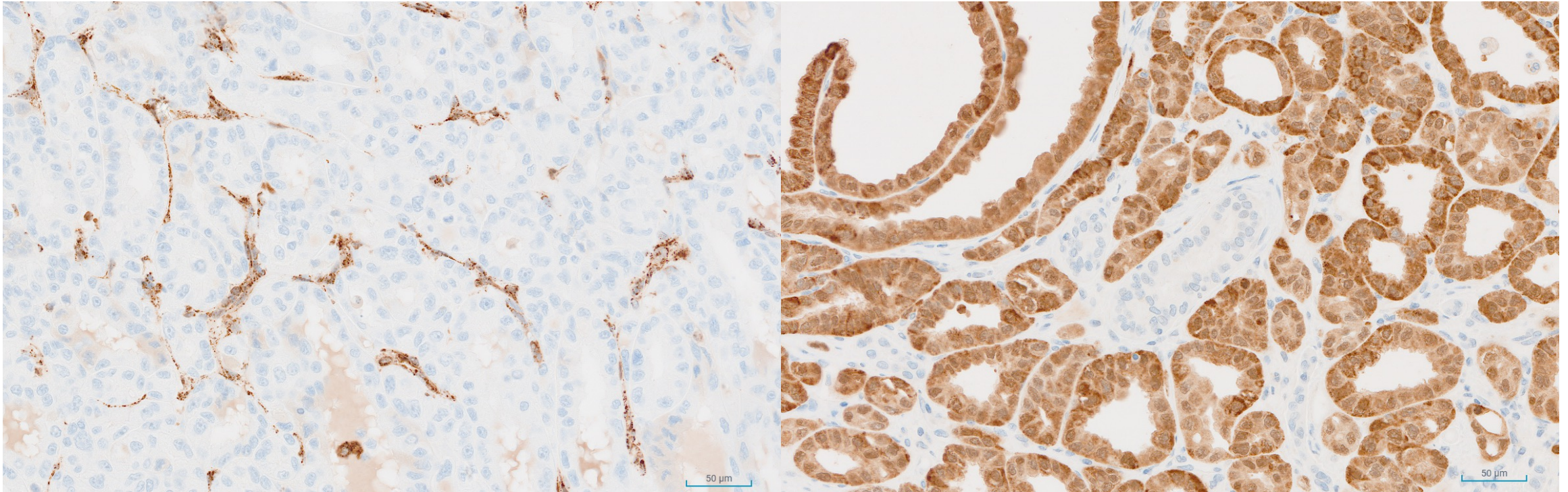




## Case 3. 72 yo M with 3.1 cm right renal mass, pT3a

FH

2-SC



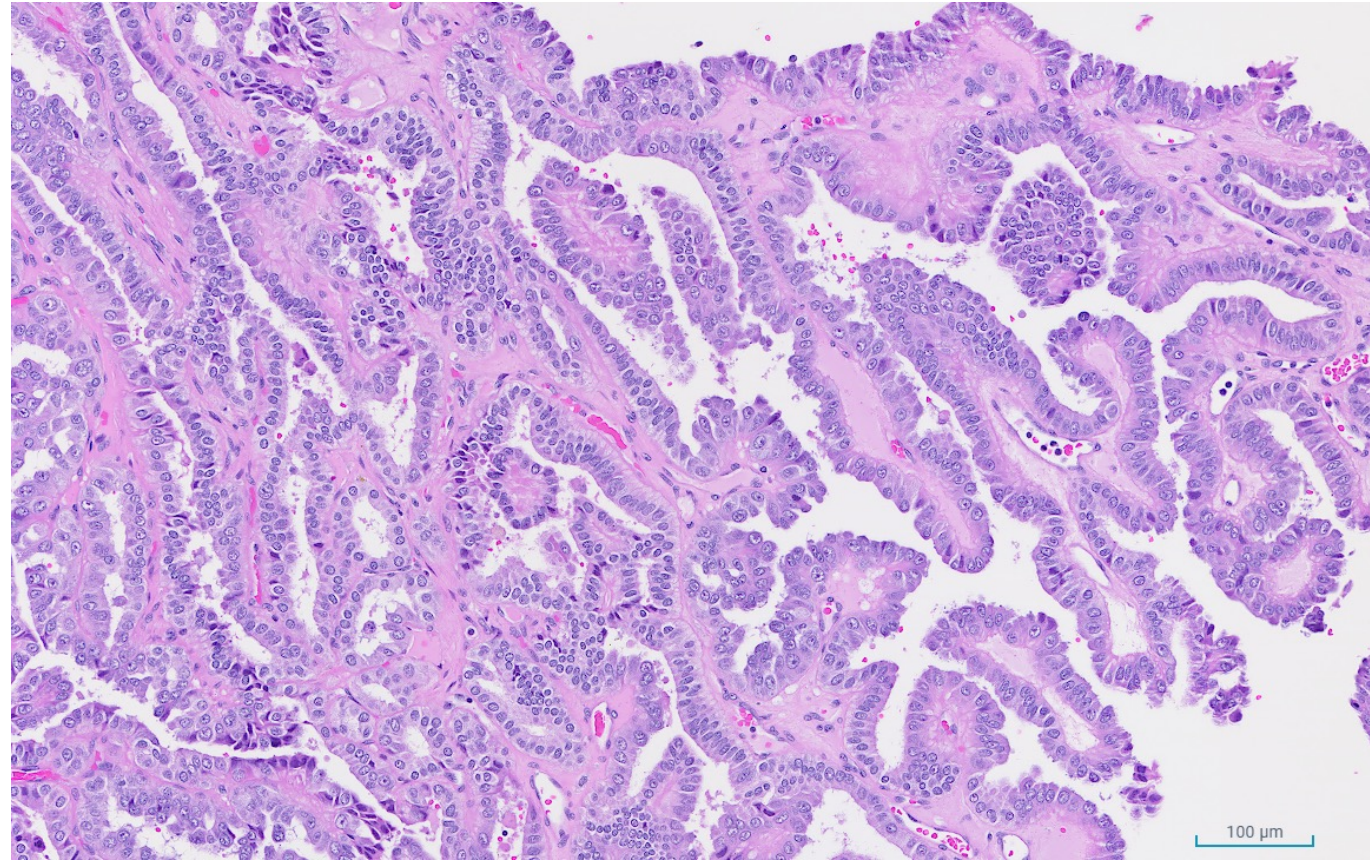
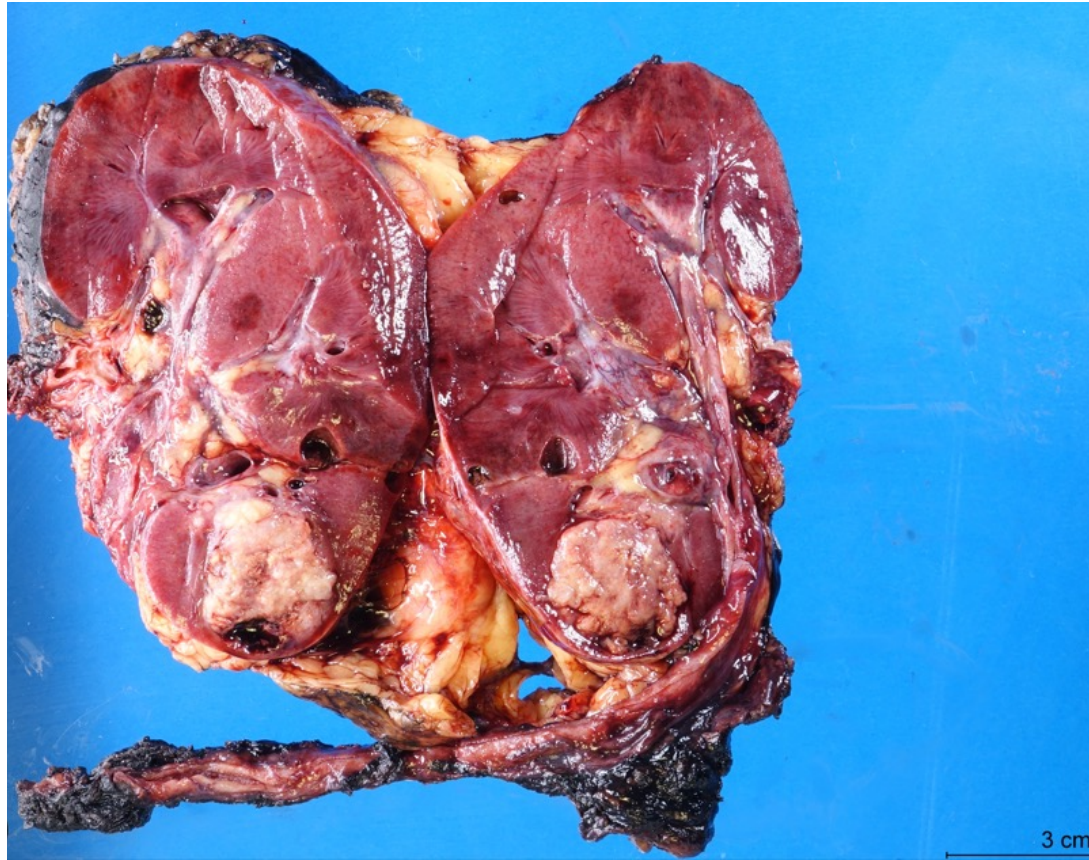
- Positive for CK AE1/AE3 and AMACR
- Negative for CK7, CK20, CD117
- SDHB expression - retained



# Fumarate hydratase-deficient RCC

- M:F = 1.9:1
- ~15% of pts with HLRCC syndrome develop renal carcinomas (median age = 44 yrs)
- FH-deficient RCCs have been documented in a sporadic setting – preferred terminology when the clinical and family history of skin/uterine leiomyomas is uncertain and the genetic status is unknown
- Genetic counseling for the patient's family should be initiated
- Multiple morphological patterns – papillary, solid, tubulocystic, cribriform, cystic
- High grade prominent eosinophilic macronucleoli with perinucleolar halo
- 2-succino-cysteine overexpression (nuclear and cytoplasmic staining)
- Negative FH, CAIX, AMACR, CK7, HMWCK, TFE3, CK20
- FH (1q43) mutations – fumarate impairs HIF prolyl hydroxylase leading to upregulation of HIF1 $\alpha$  and nonenzymatic modification of cysteine residues in multiple proteins
- Poor prognosis with early and widespread mets; 39% died of disease and 26% showed disease progression after a mean follow-up of 27 months

30 yo M with 4.5 cm mass



- Positive for CK AE1/AE3 and AMACR
- Negative for CK7, Melan A, CK20
- Loss of FH and positive 2-SC

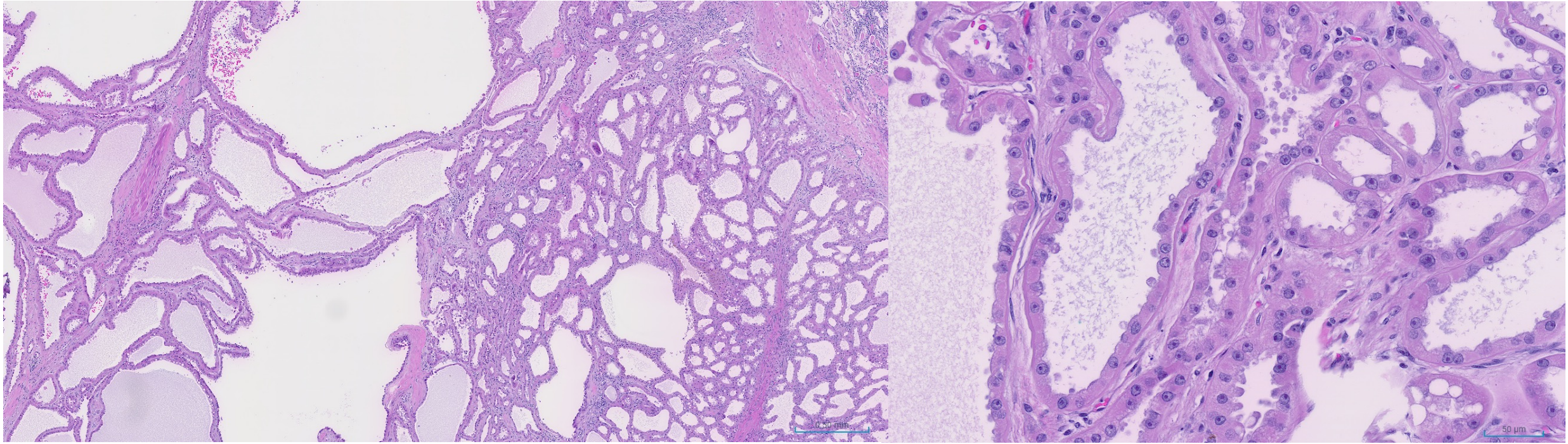


30 yo M with 4.5 cm mass

- Left nephroureterectomy (2022) – pT3aN0
- Bladder mass and lung nodule (2023) – FH-def RCC
- Carrier of *FH* mutation



## DDx – Tubulocystic RCC, 2.4 cm, pT1a

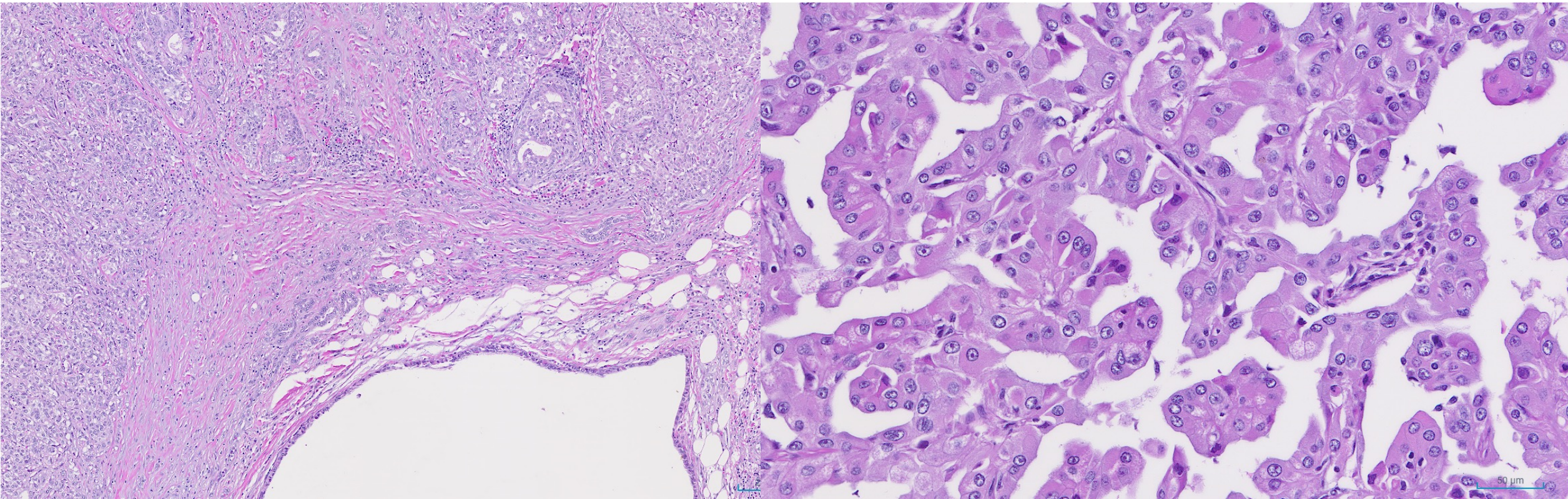


- Positive for AMACR, CD10
- Negative for GATA3, CD117, CK7, CK20, cathepsin K, Melan A, HMB45
- Intact SDHB/FH expression
- 2-SC with cytoplasmic expression

Low-grade FH-def RCC must be excluded by IHC



## DDx – Collecting duct carcinoma

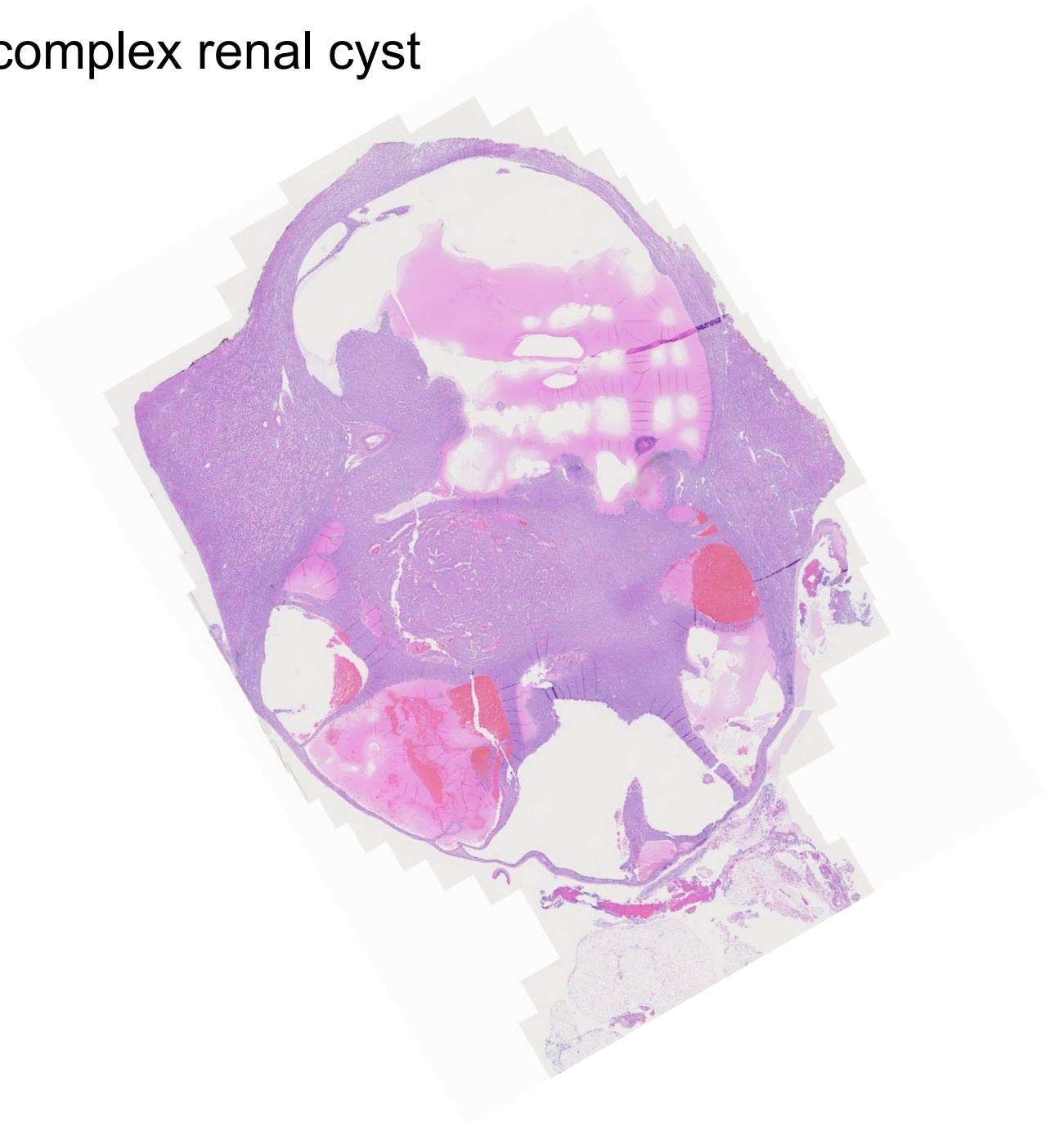
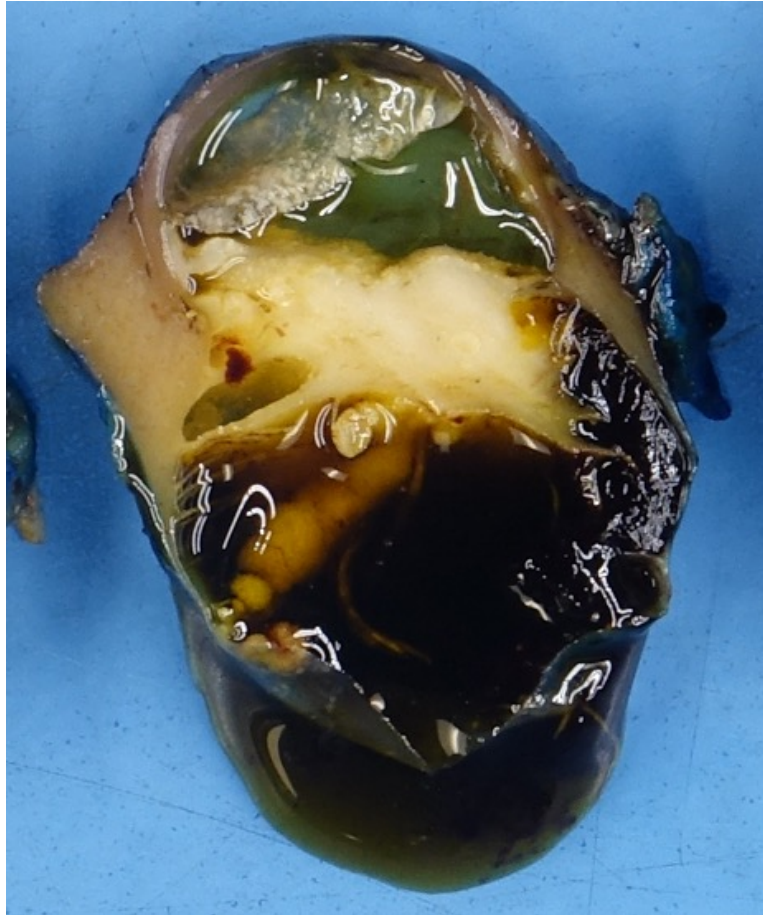


- Positive for PAX8, vimentin
- Negative for CK7, p63, CK5/6
- Intact INI-1/FH expression
- 2-SC with focal cytoplasmic expression

In one large cohort, 25% of cases dx'ed as CDC were reclassified as FH-def RCC.

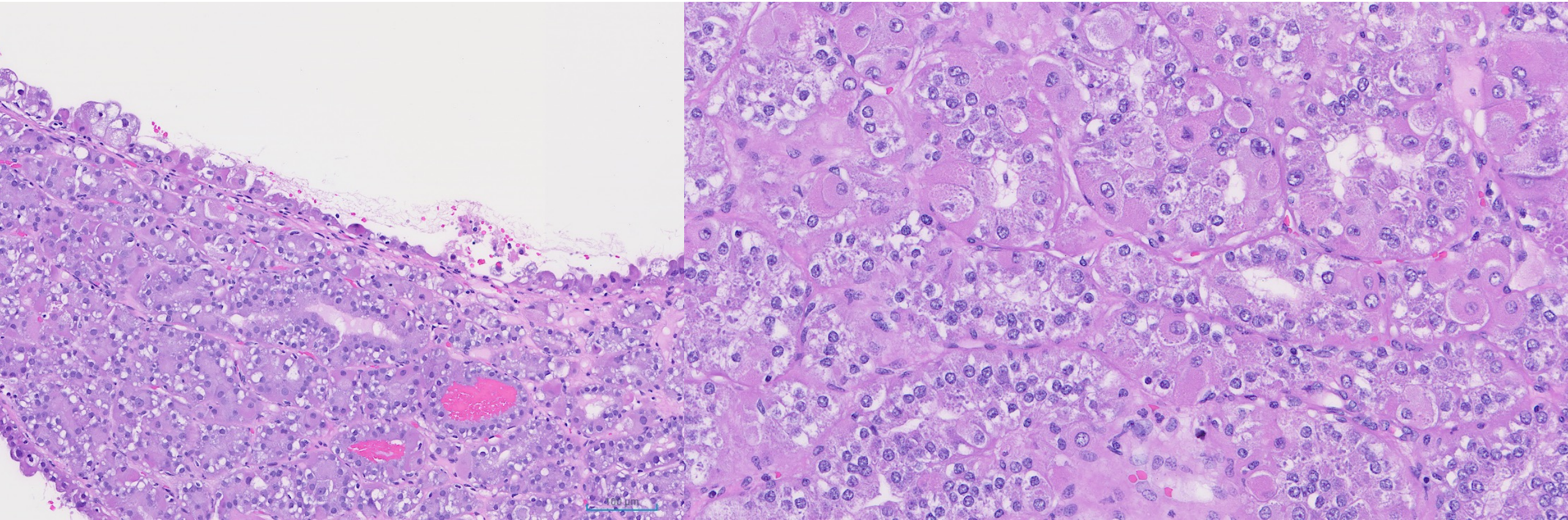


Case 4. 76 yo F with 2.5 cm right complex renal cyst





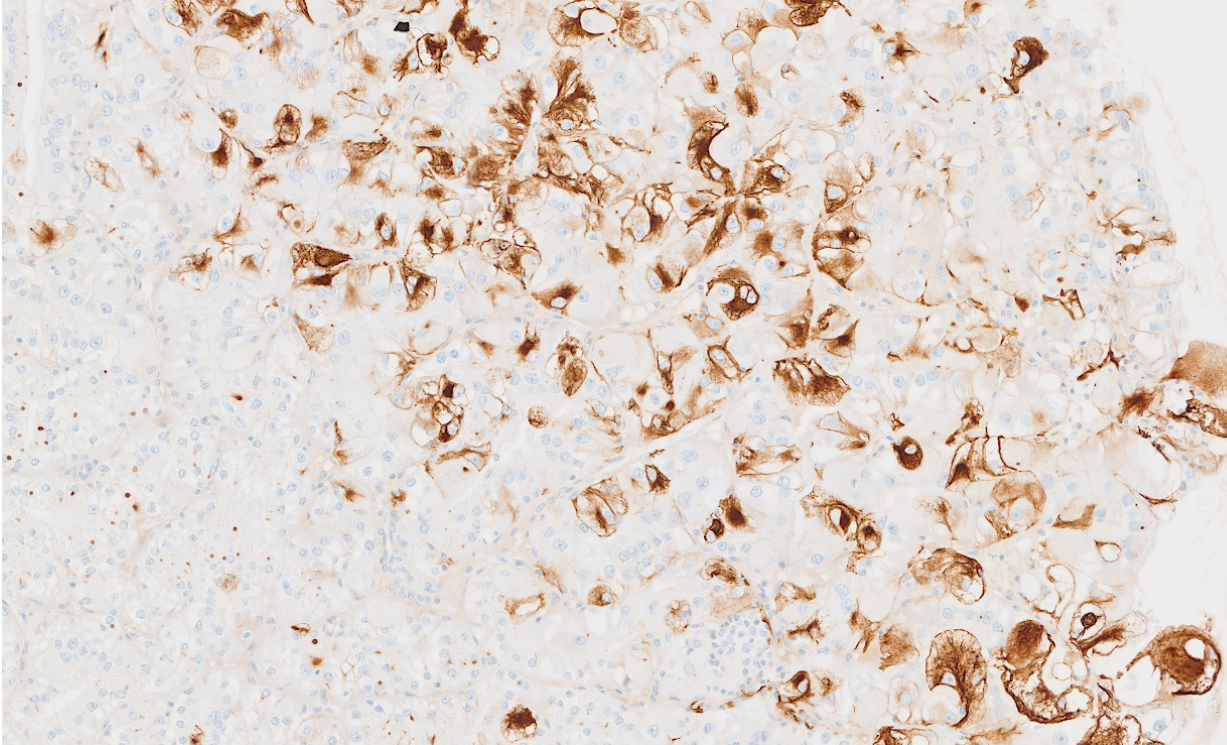
Case 4. 76 yo F with 2.5 cm right renal mass



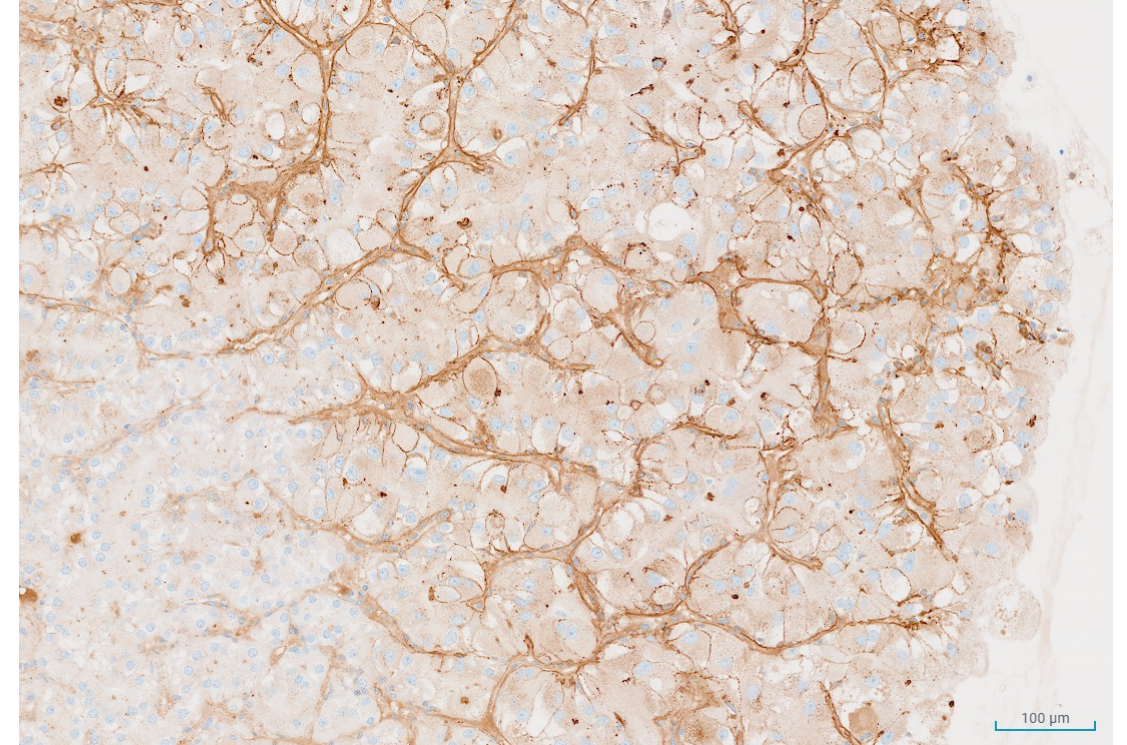


## Case 4. 76 yo F with 2.5 cm right renal mass, pT1a

CK20



Cathepsin K

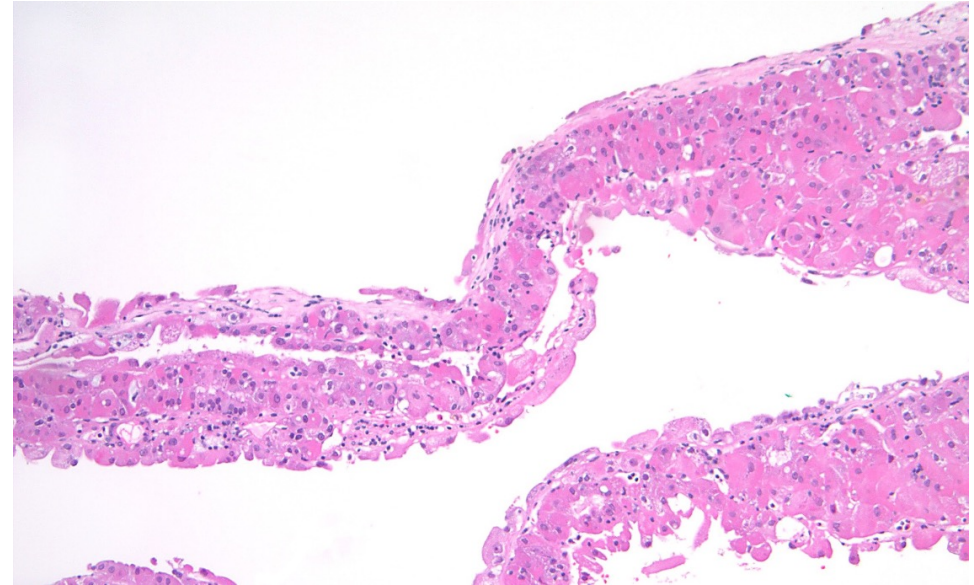


- Positive Cam5.2, CD10, CK20 and cathepsin K (focal)
- Negative for CK7, CD117, HMB45
- SDHB and FH with intact expression
- 2-SC with focal cytoplasmic expression



# Eosinophilic, solid and cystic RCC

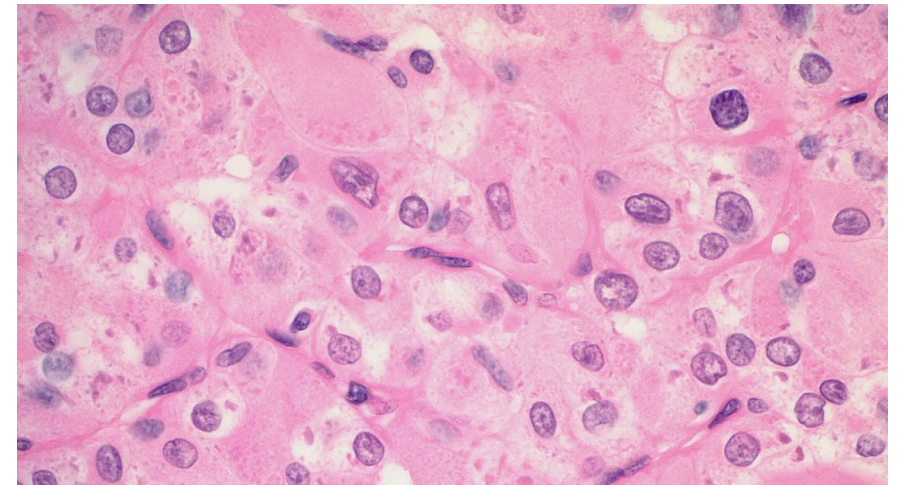
- F>M
- Broad age range (14-75 yo)
- Yellow-tan solid nodules interspersed with macrocystic spaces
- Unencapsulated
- Solid or compact nested growth of eosinophilic cells admixed with macroscopic cysts or microscopic tubules/cysts
- Round to oval nuclei with minimal pleomorphism and variably prominent nucleoli
- Coarsely granular basophilic cytoplasmic stippling





# Eosinophilic, solid and cystic RCC

- Patchy CK20 and cathepsin K positivity
- Negative CAIX, TFE3, CK7 (focal in 31%), CD117 (focal in 5%)
- Somatic loss of function mutations in *TSC1* (hamartin, 9q34.13)/ *TSC2* (tuberin, 16p13) - mTORC1 activation
- Mostly pT1





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# Thank You

NYU Langone Health

