

CLEAR CELL RENAL CELL TUMORS

DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS

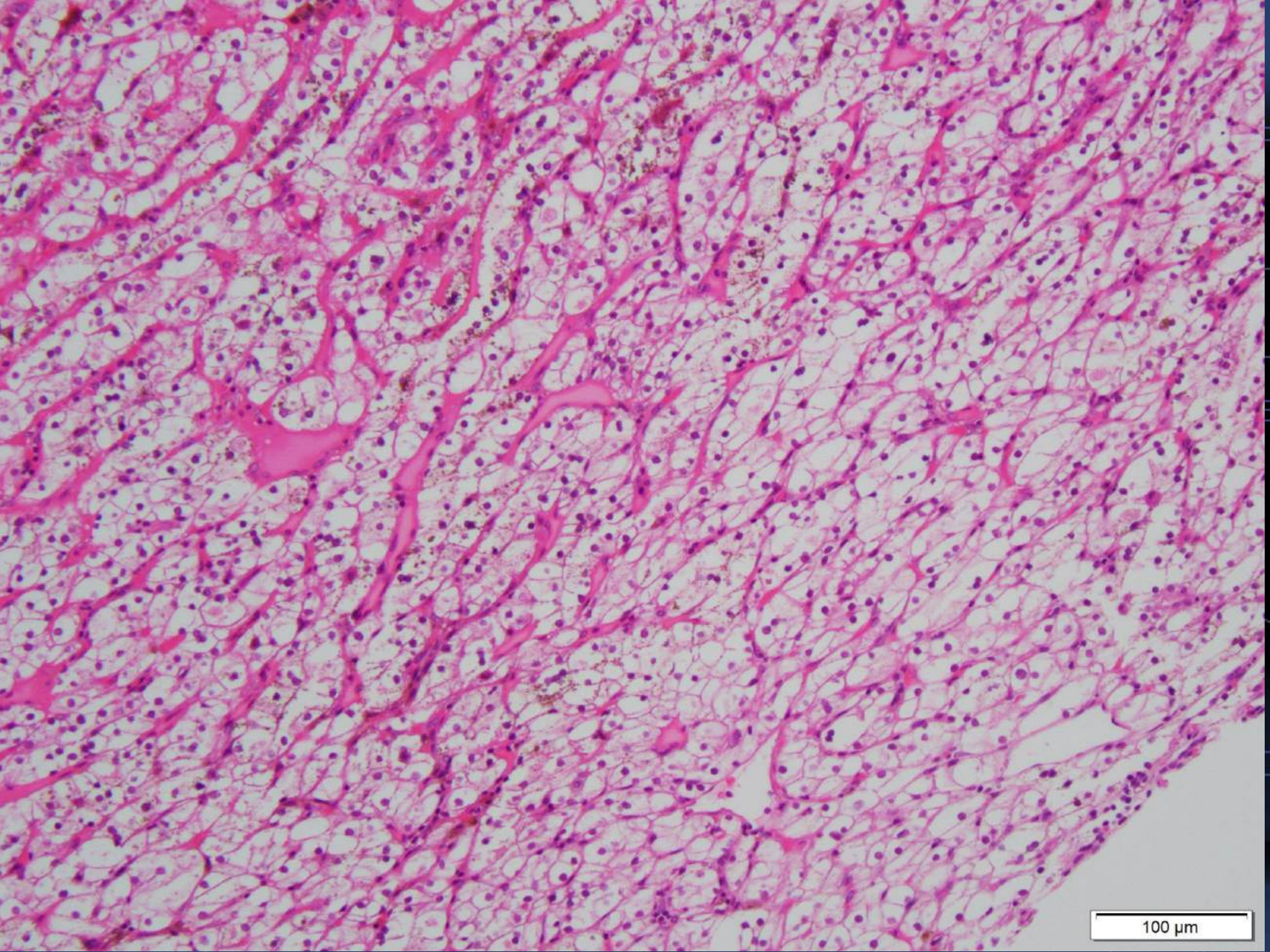


Memorial Sloan Kettering
Cancer Center™

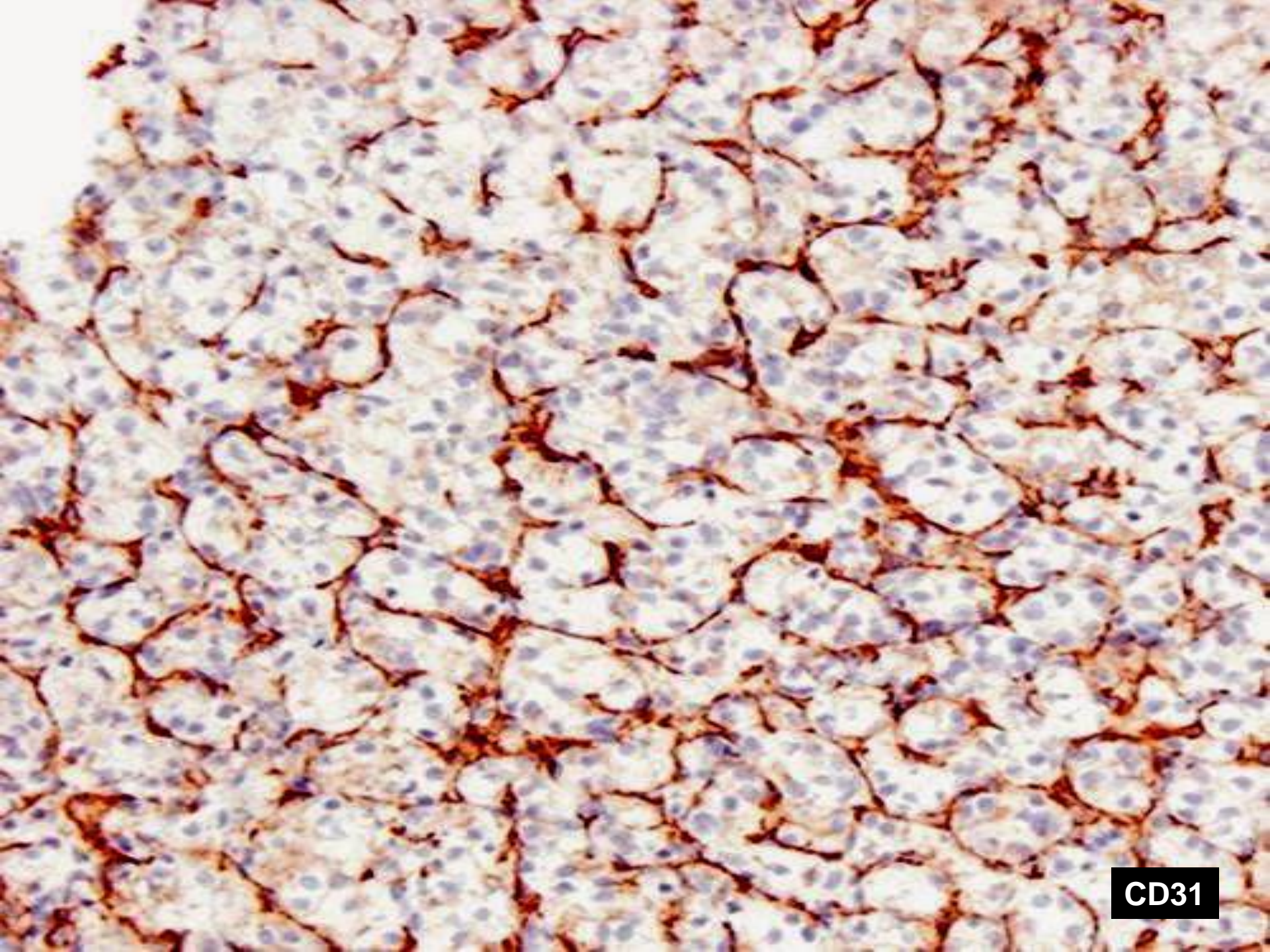
Satish K. Tickoo

RENAL CELL TUMORS WITH CLEAR CELL FEATURES

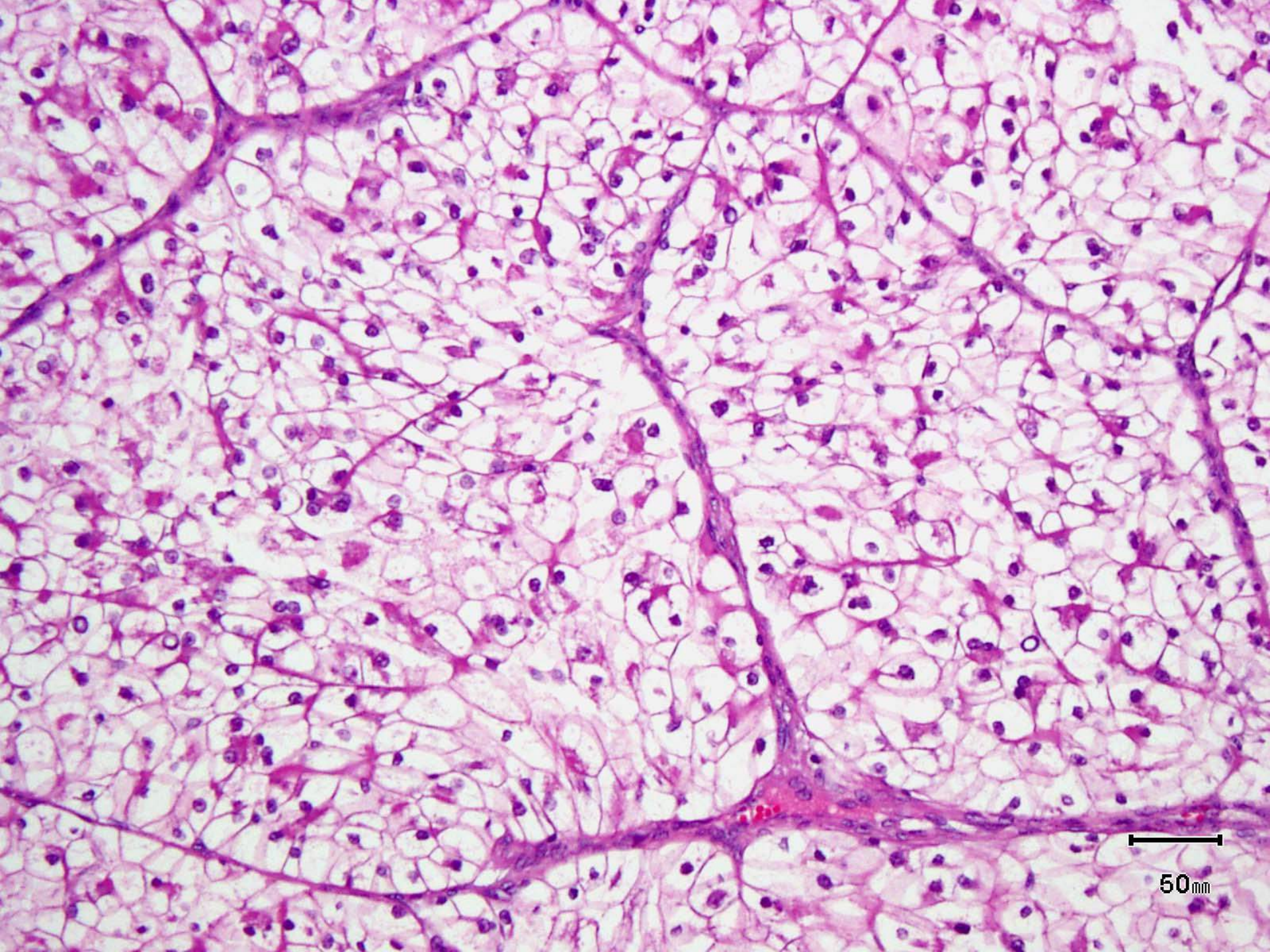
**Clear cell renal cell carcinomas
that
may not look like clear cell RCC**



100 μm



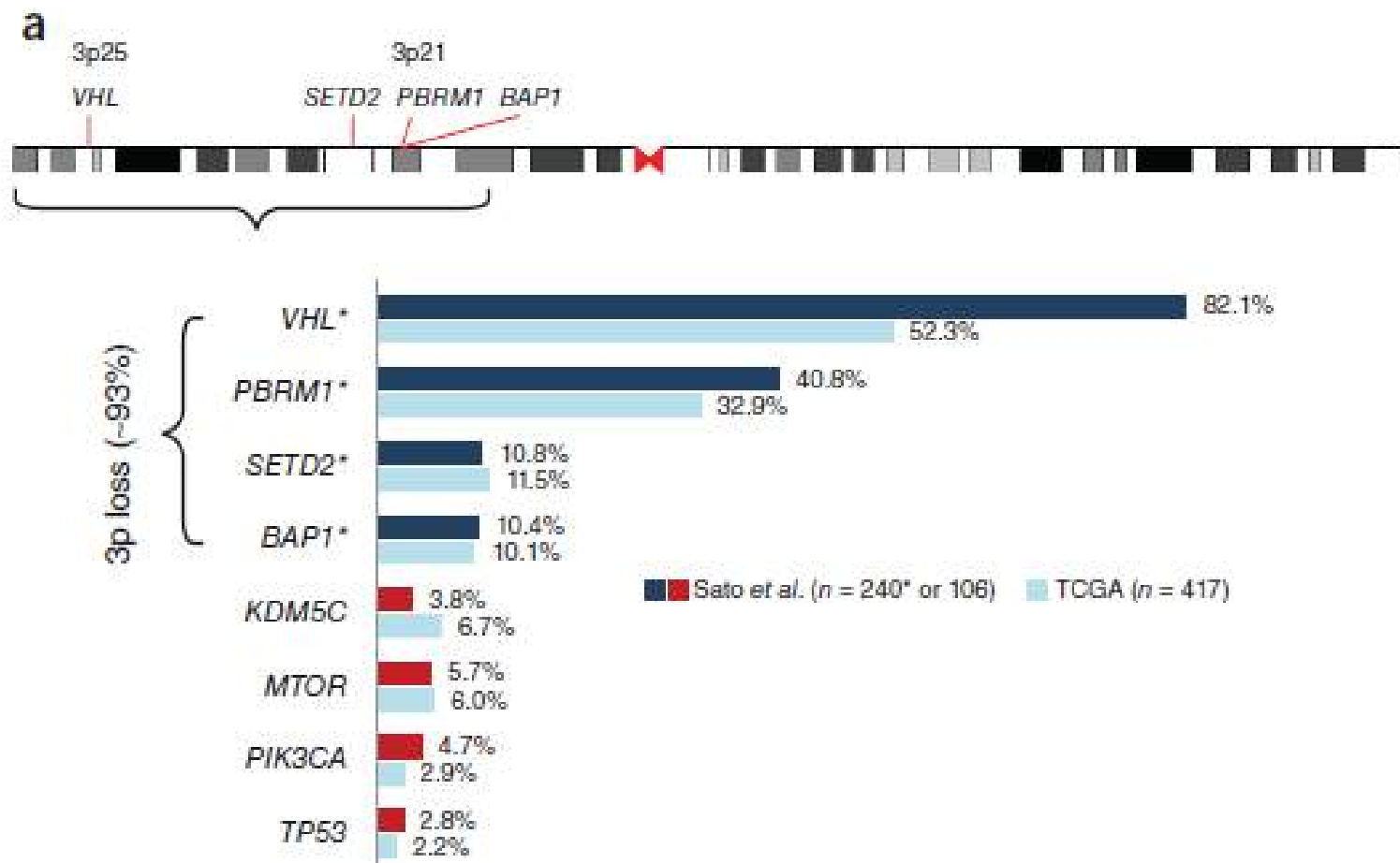
CD31



50mm

A clear picture of renal cell carcinoma

A Ari Hakimi, Can G Pham & James J Hsieh

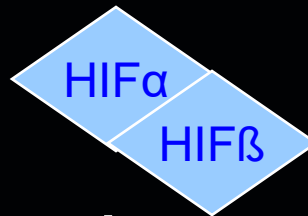
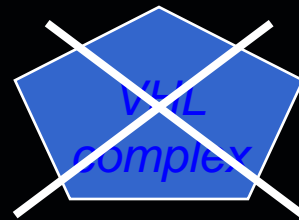
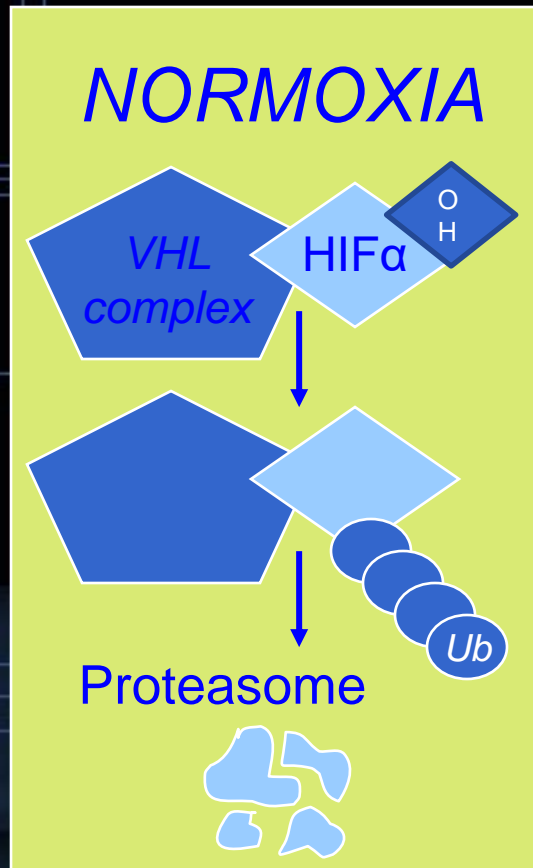


MOLECULAR PATHWAYS IN CLEAR CELL RENAL CELL CARCINOMA

Endothelial or Stromal cell

TKr

Hypoxia/silenced VHL



HIF Responsive Elements

VEGF
PDGF
EPO
GLUT1
CA9

TKr

PI3K

Ras

AKT

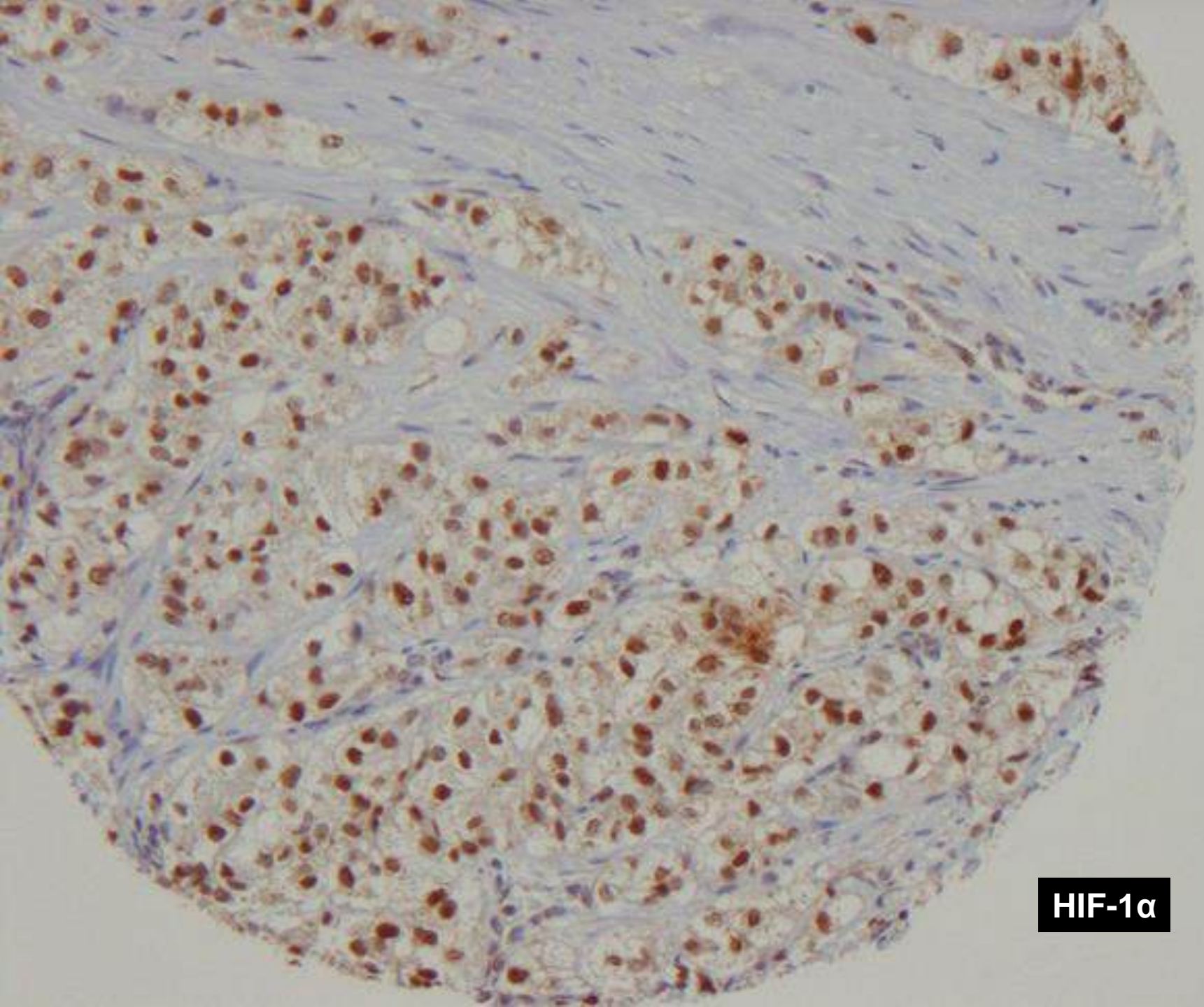
Raf

mTOR

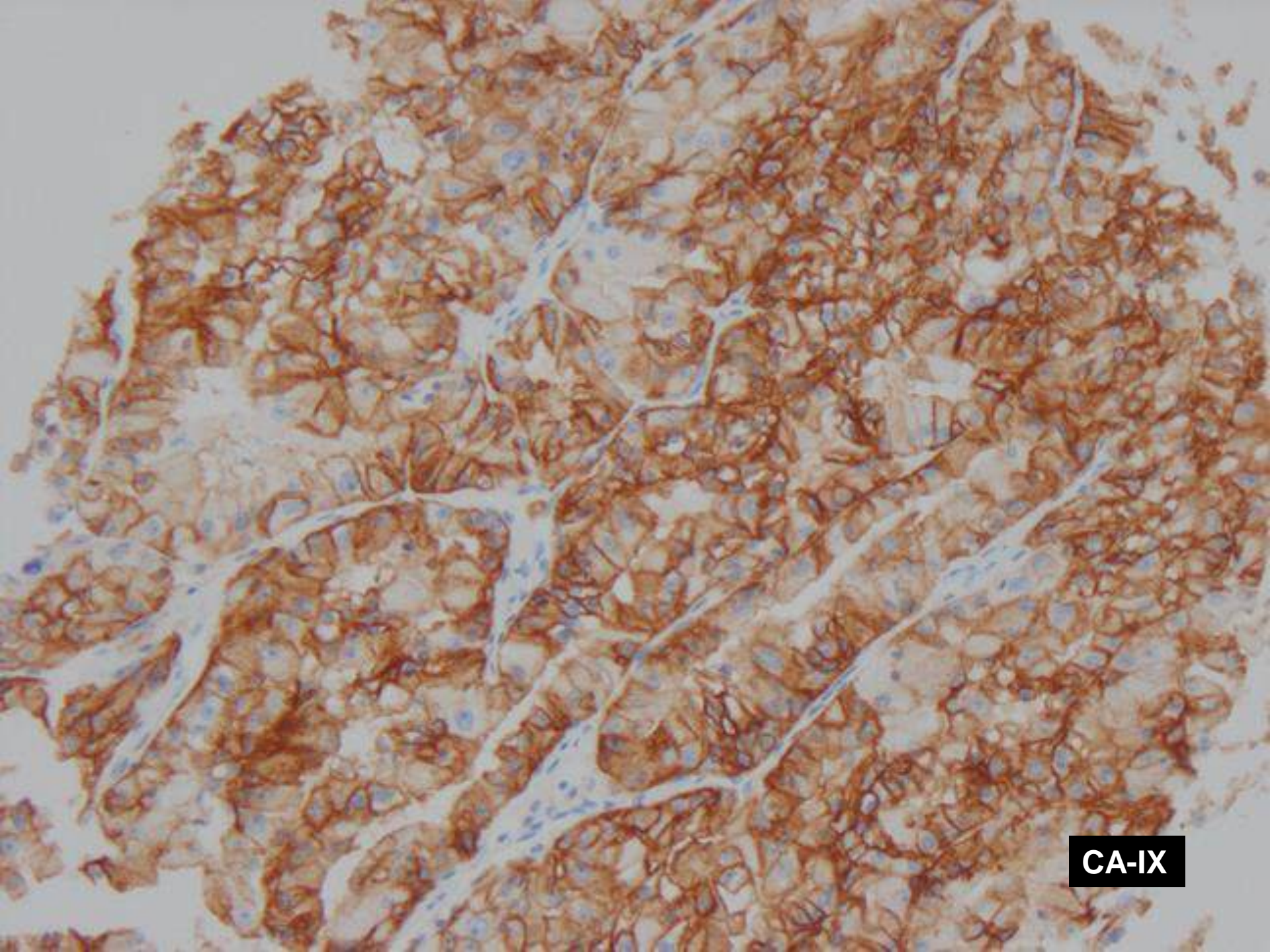
MEK 1,2

MAPK

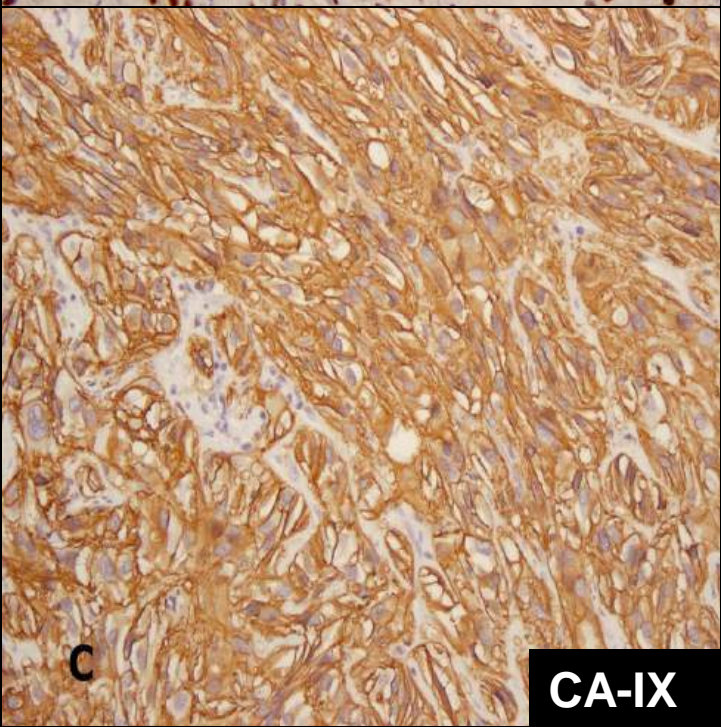
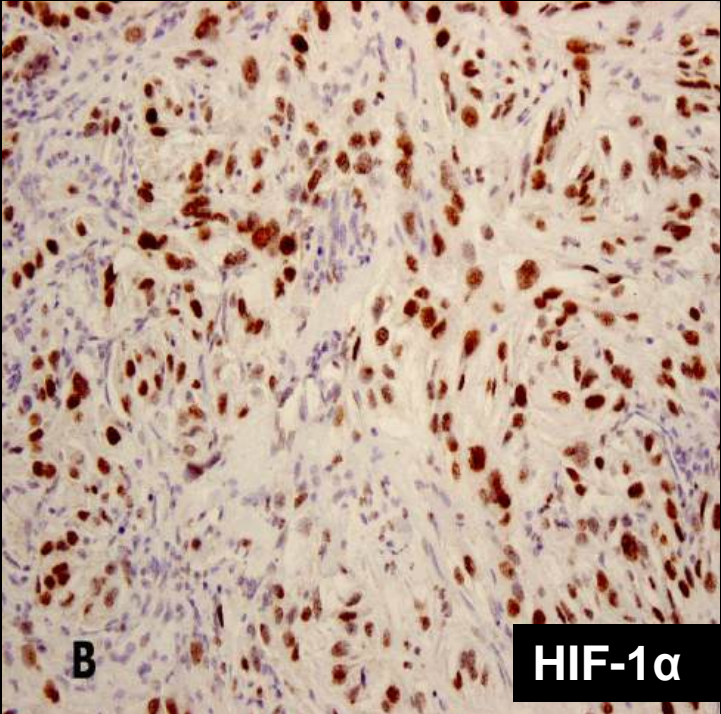
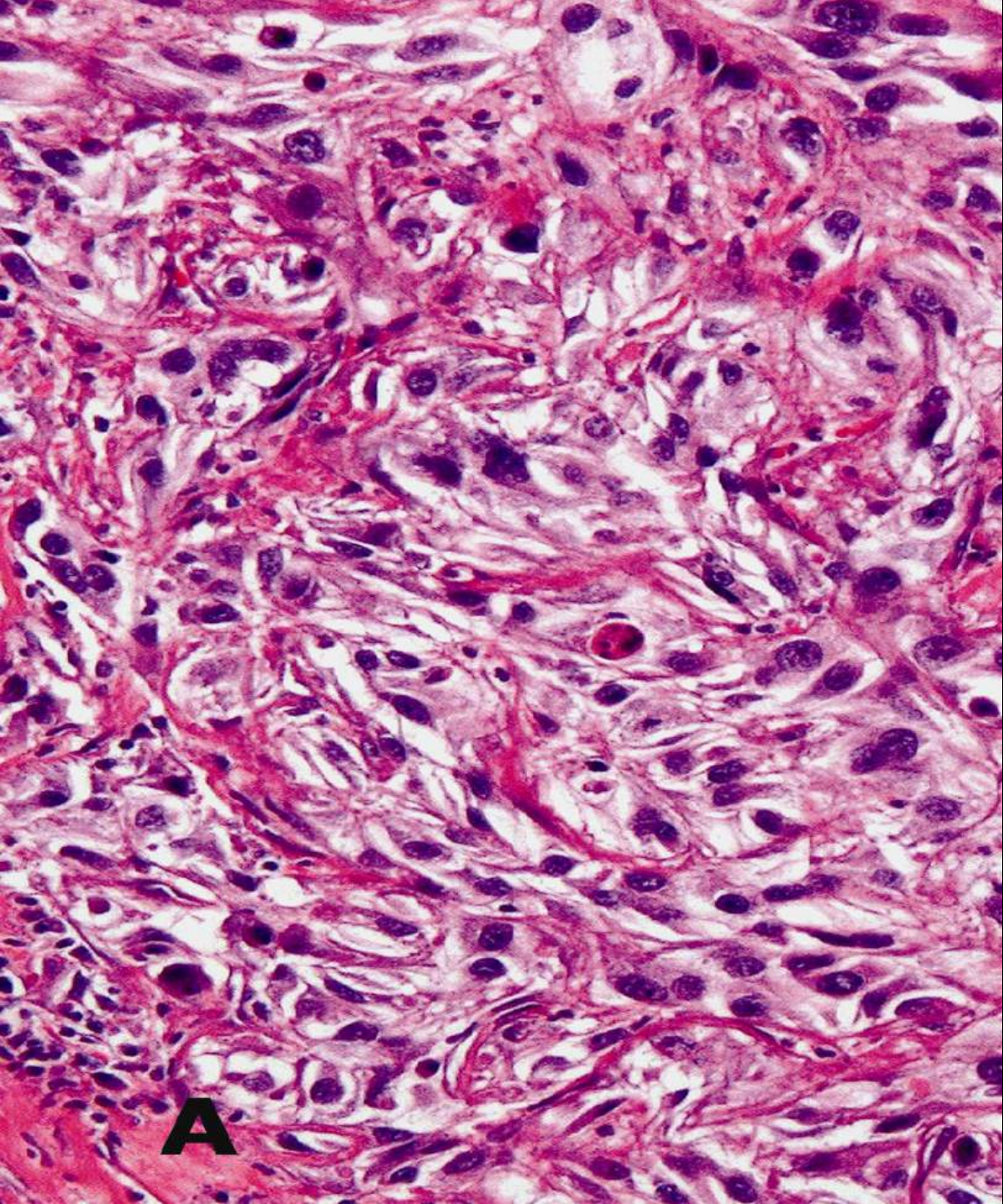
VEGF
PDGF



HIF-1 α

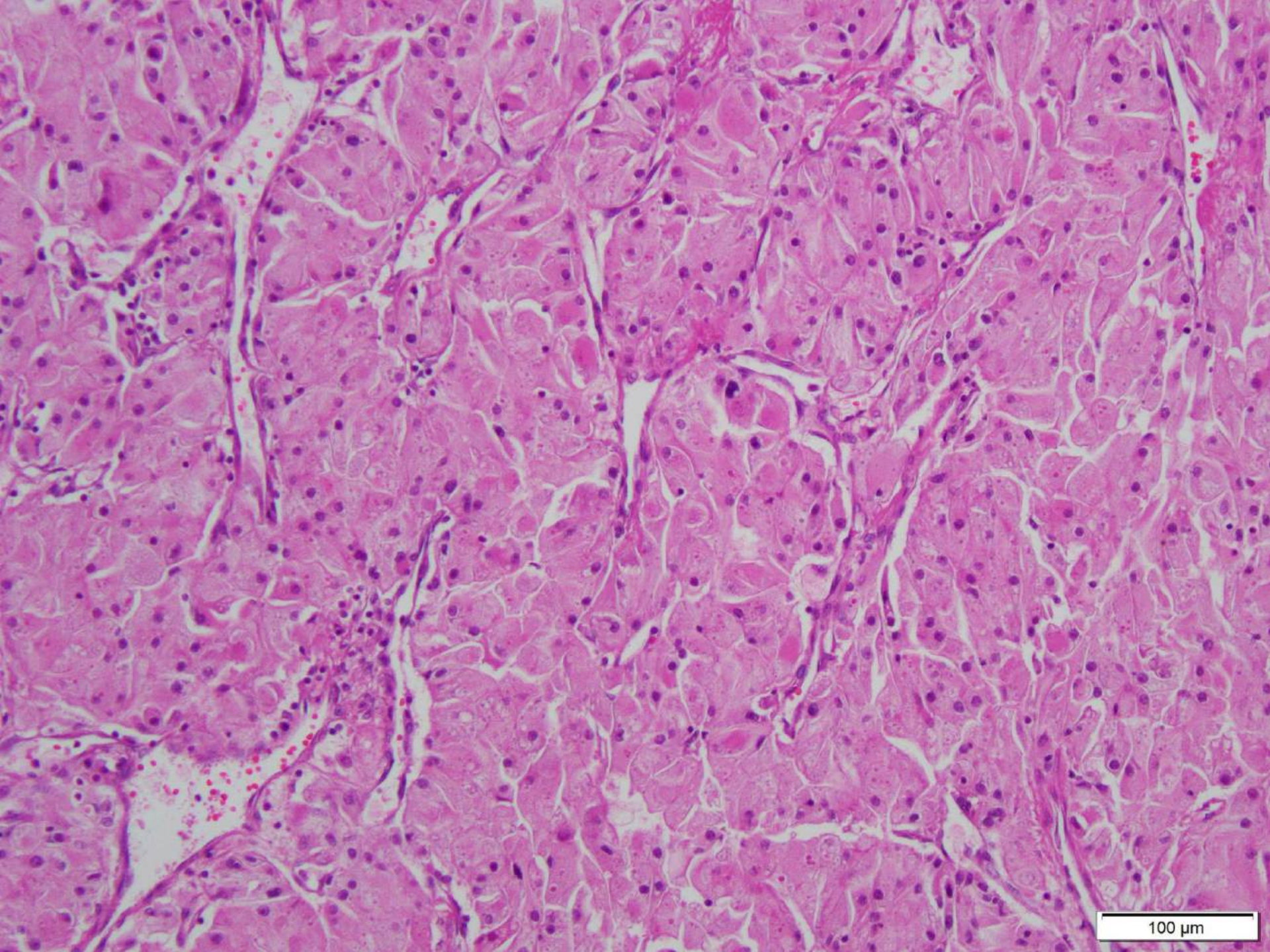


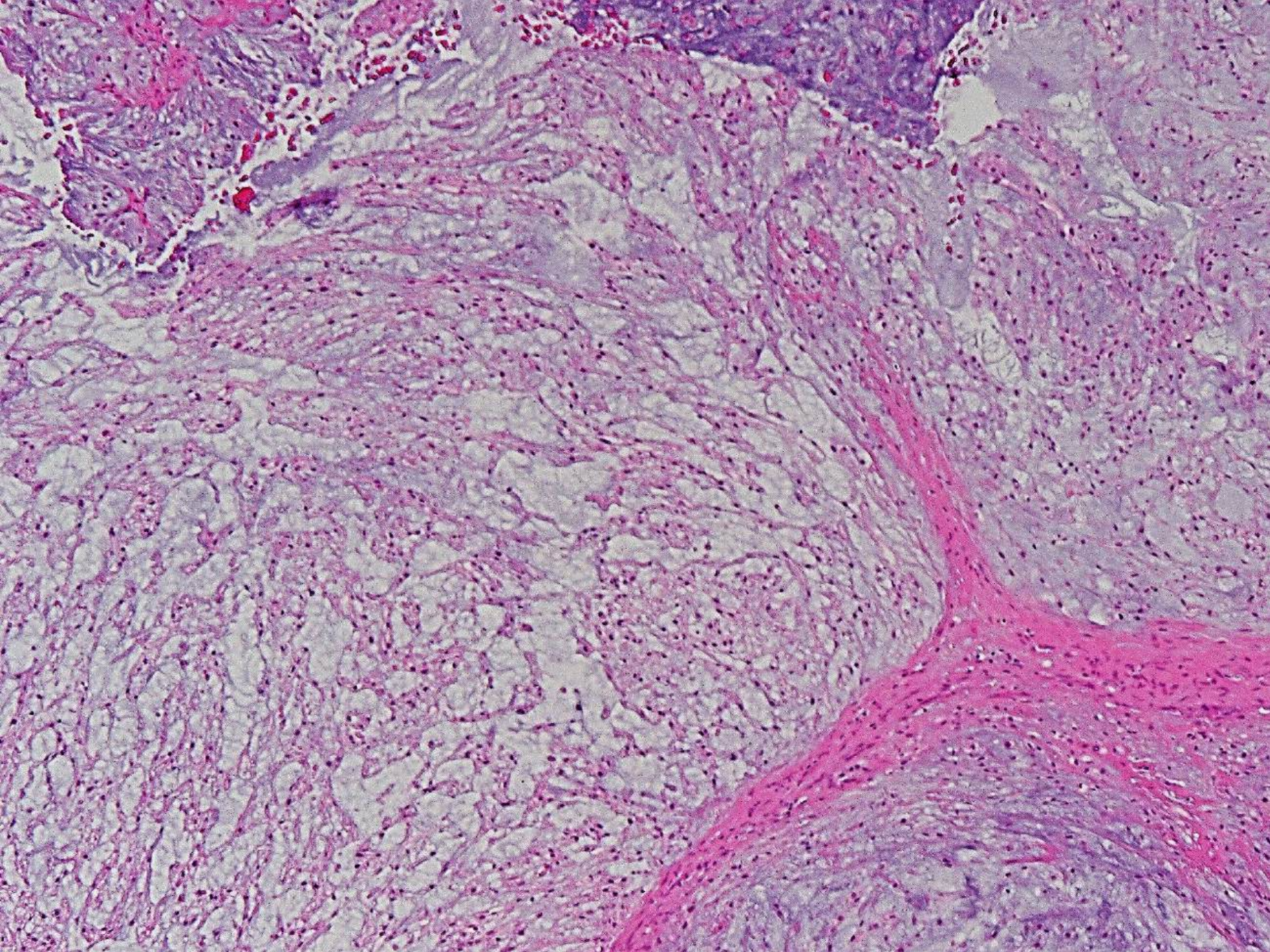
CA-IX

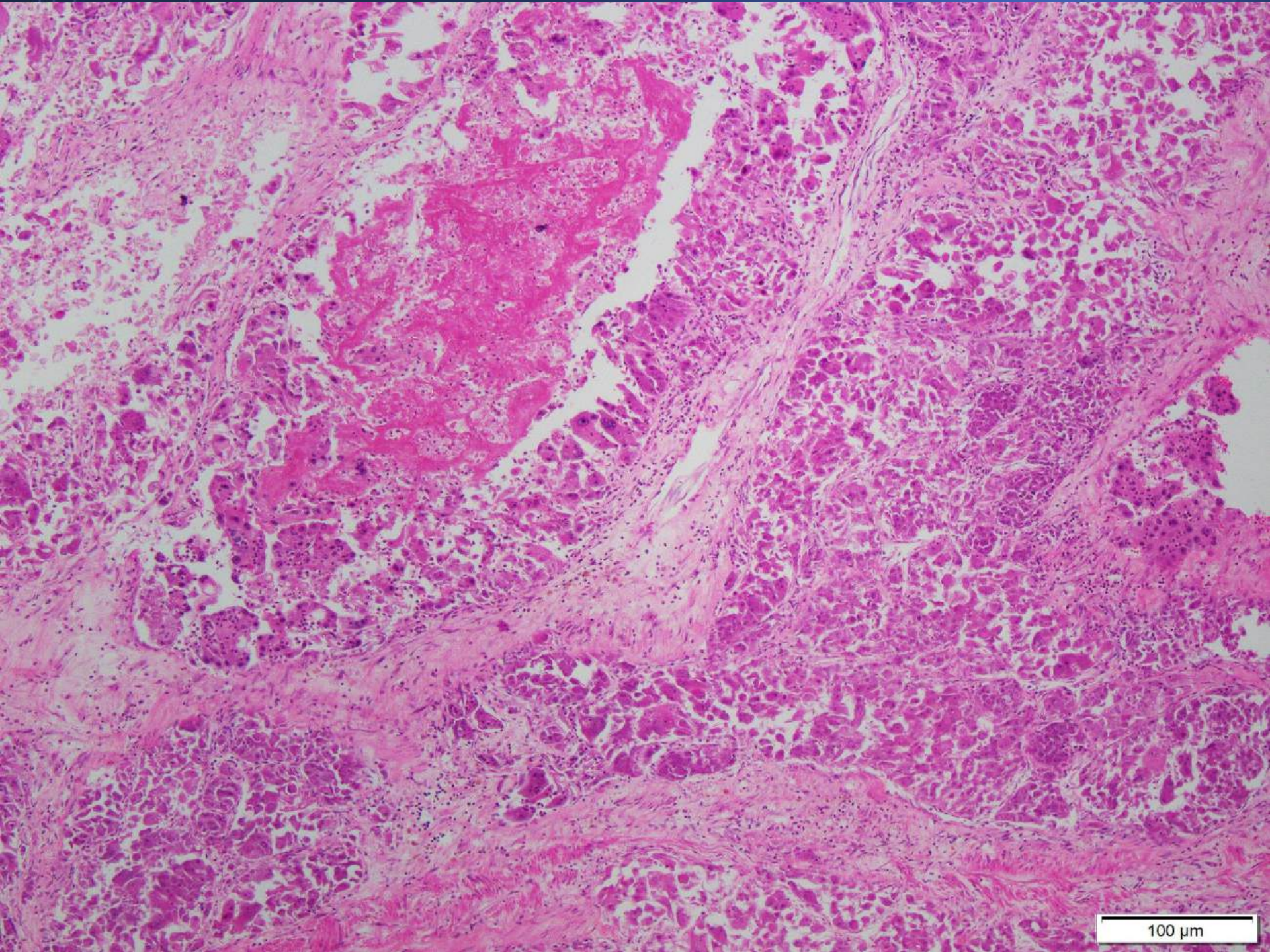


EXAMPLES

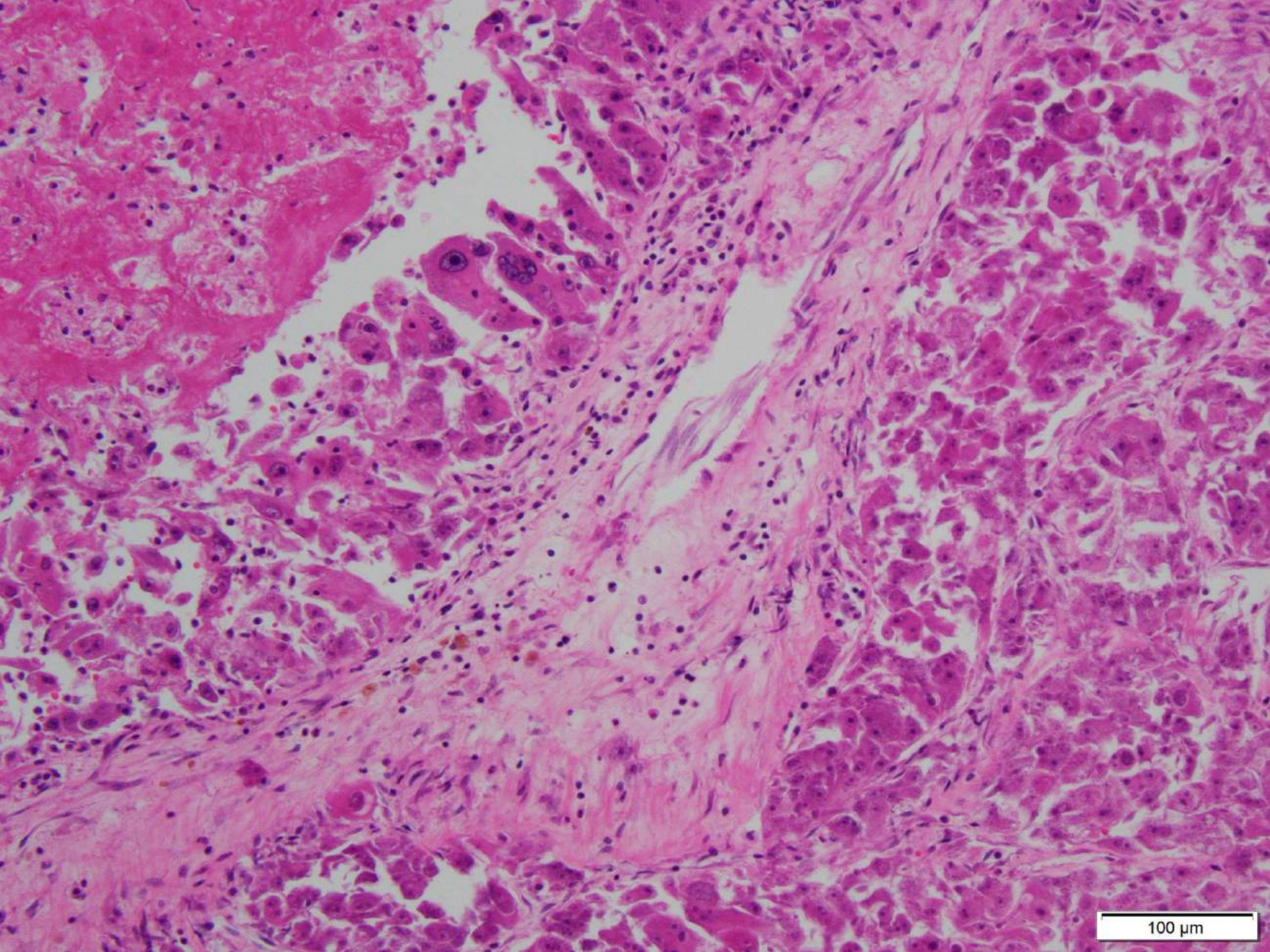
Clear cell vs. Not clear cell



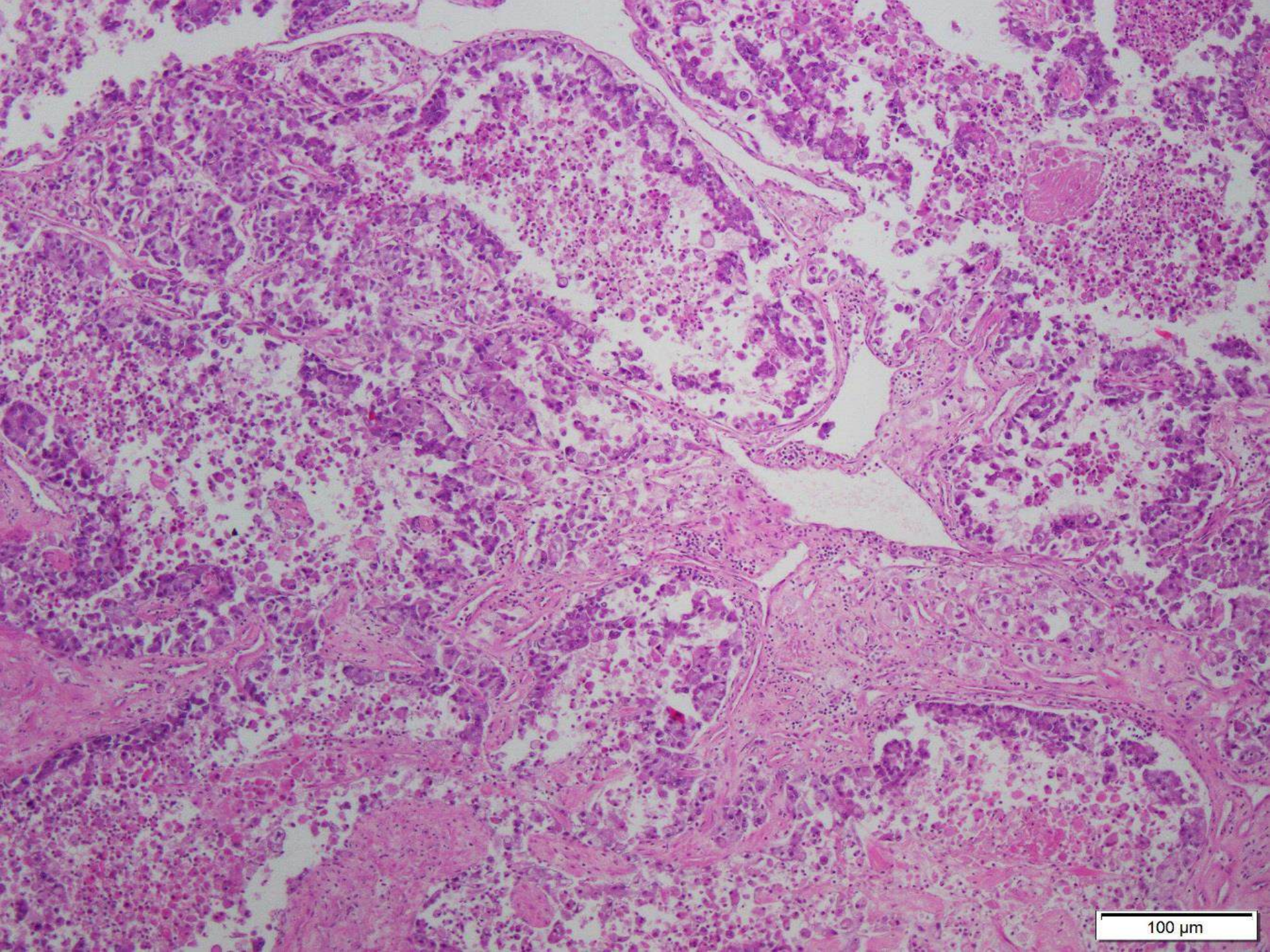




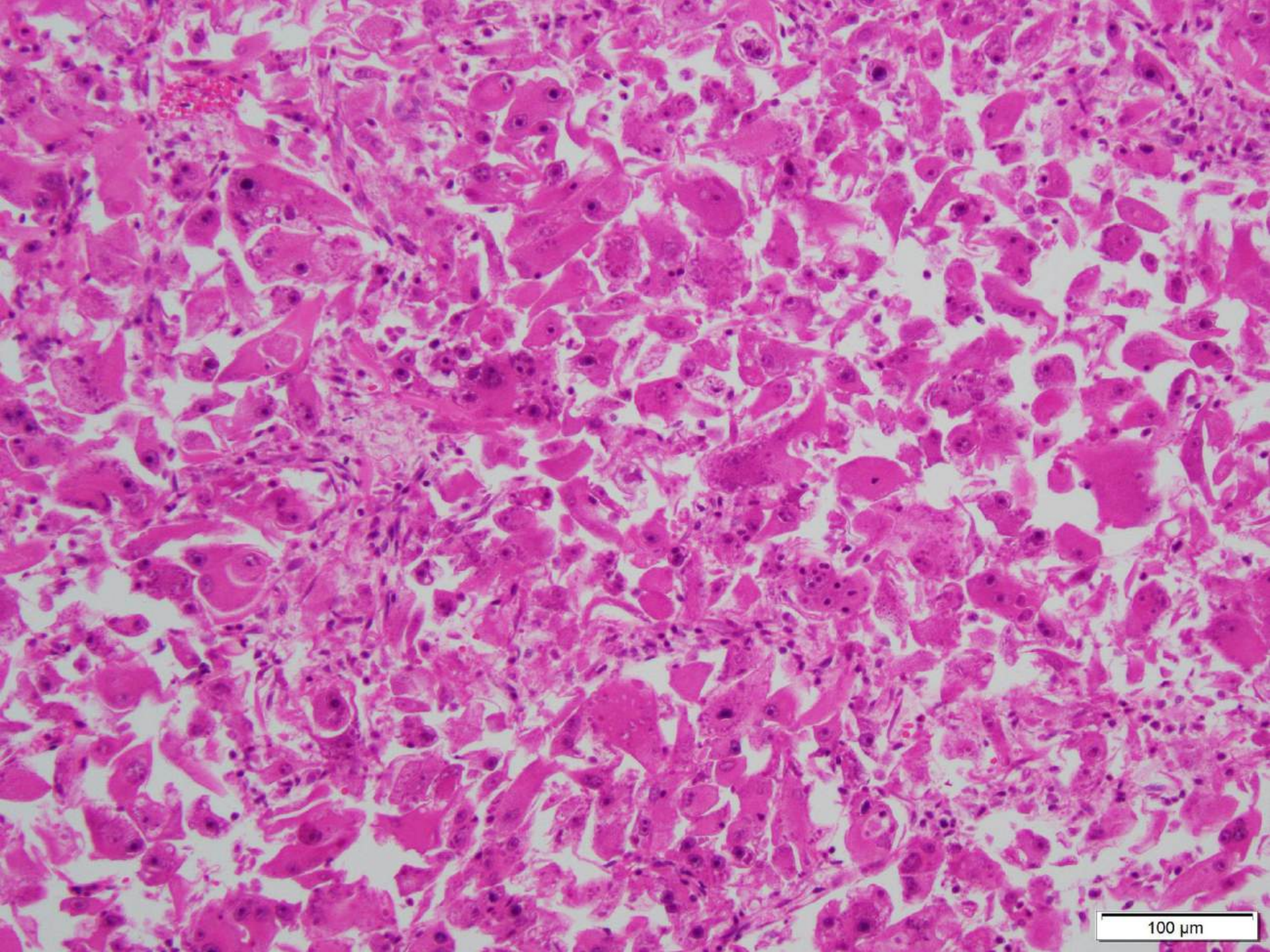
100 μ m

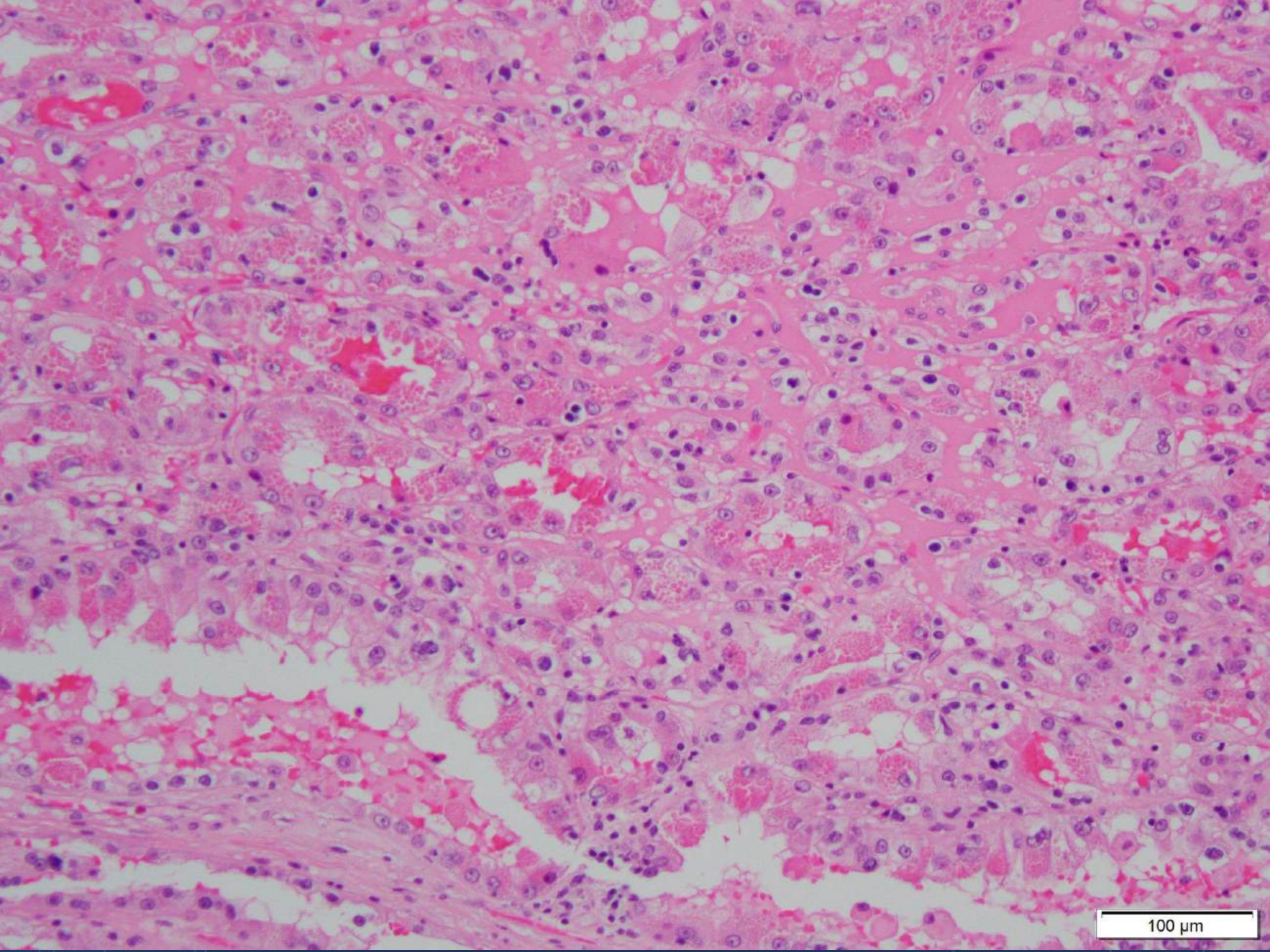


100 μ m

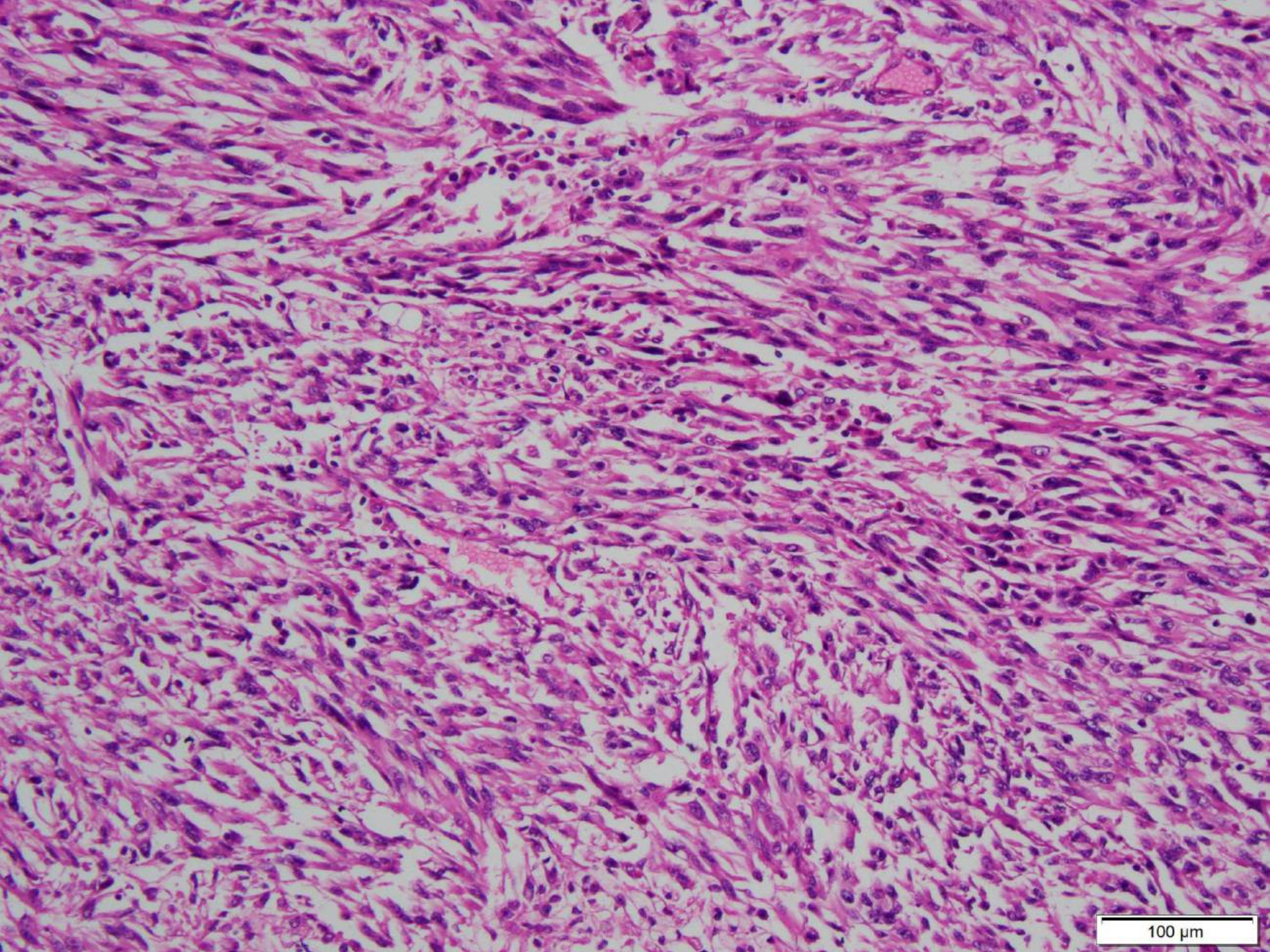


100 μm





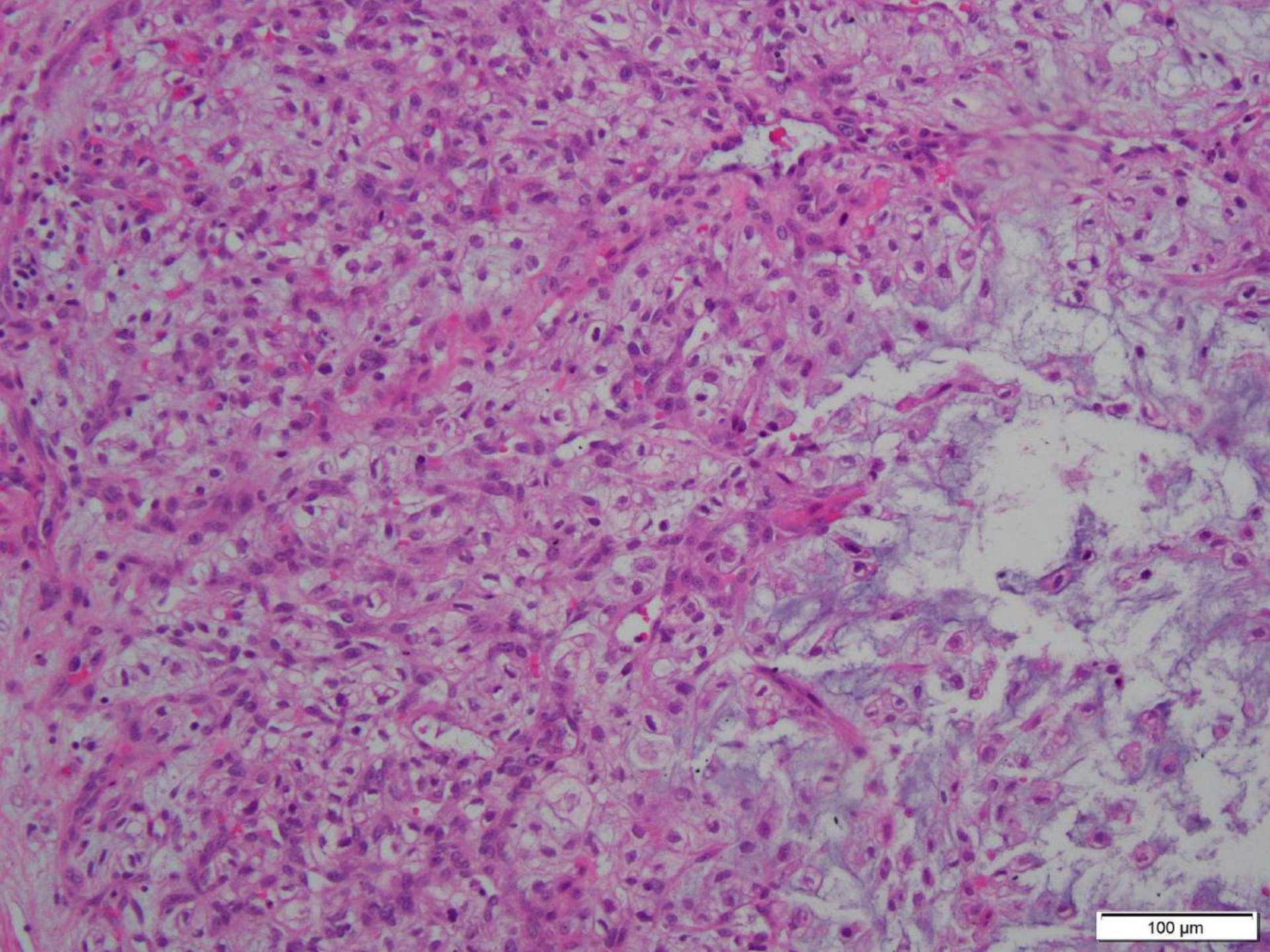
100 μm



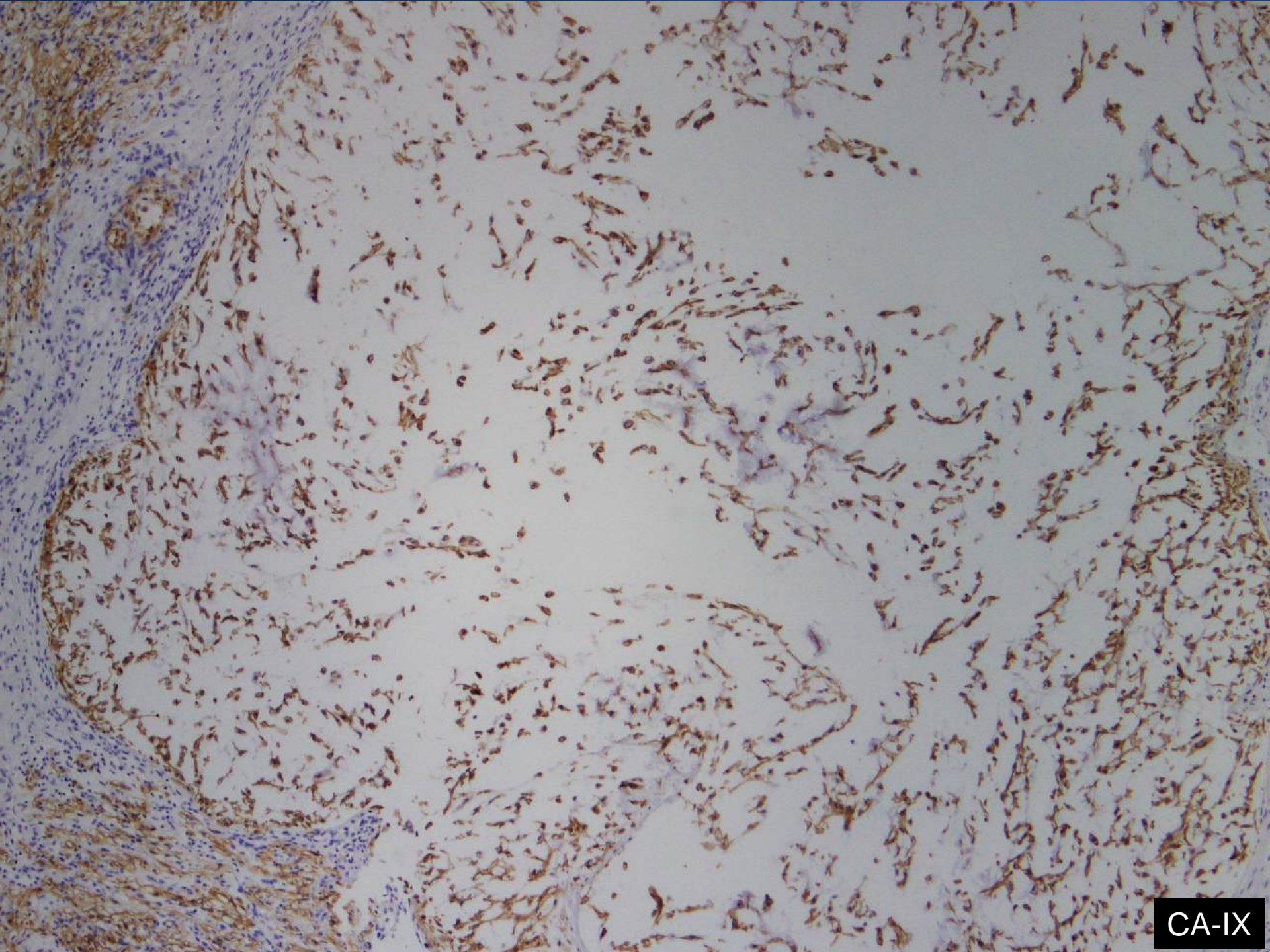
100 μm

High grade tumors

- 2/3 RCCs are still clear cell RCC
- Unless the tumor shows features specific to other tumor types, do not completely give up on clear cell RCC
- Careful examination for even very focal typical clear cell RCC areas is imperative
- In some cases, CA-IX may help



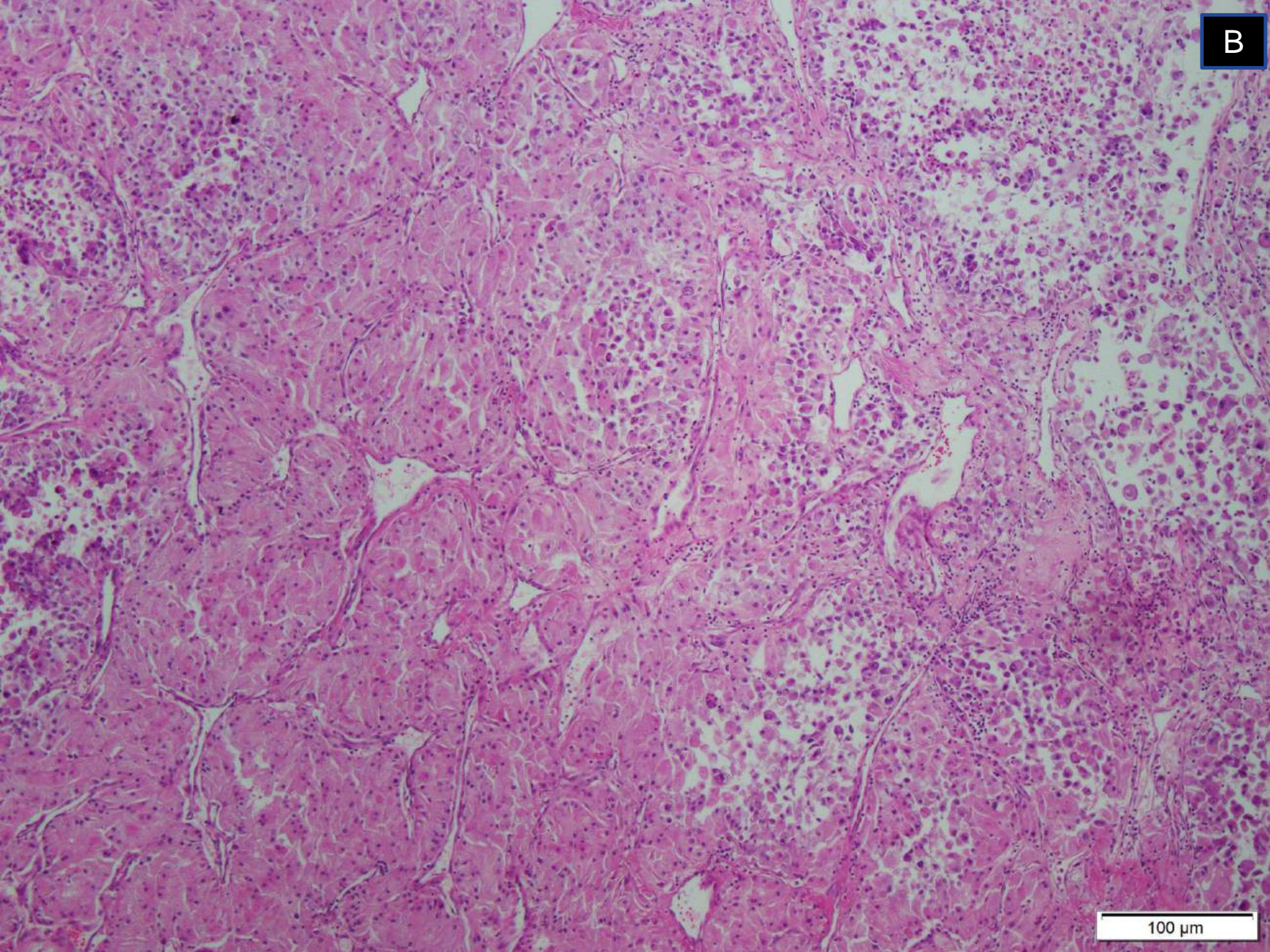
100 μm



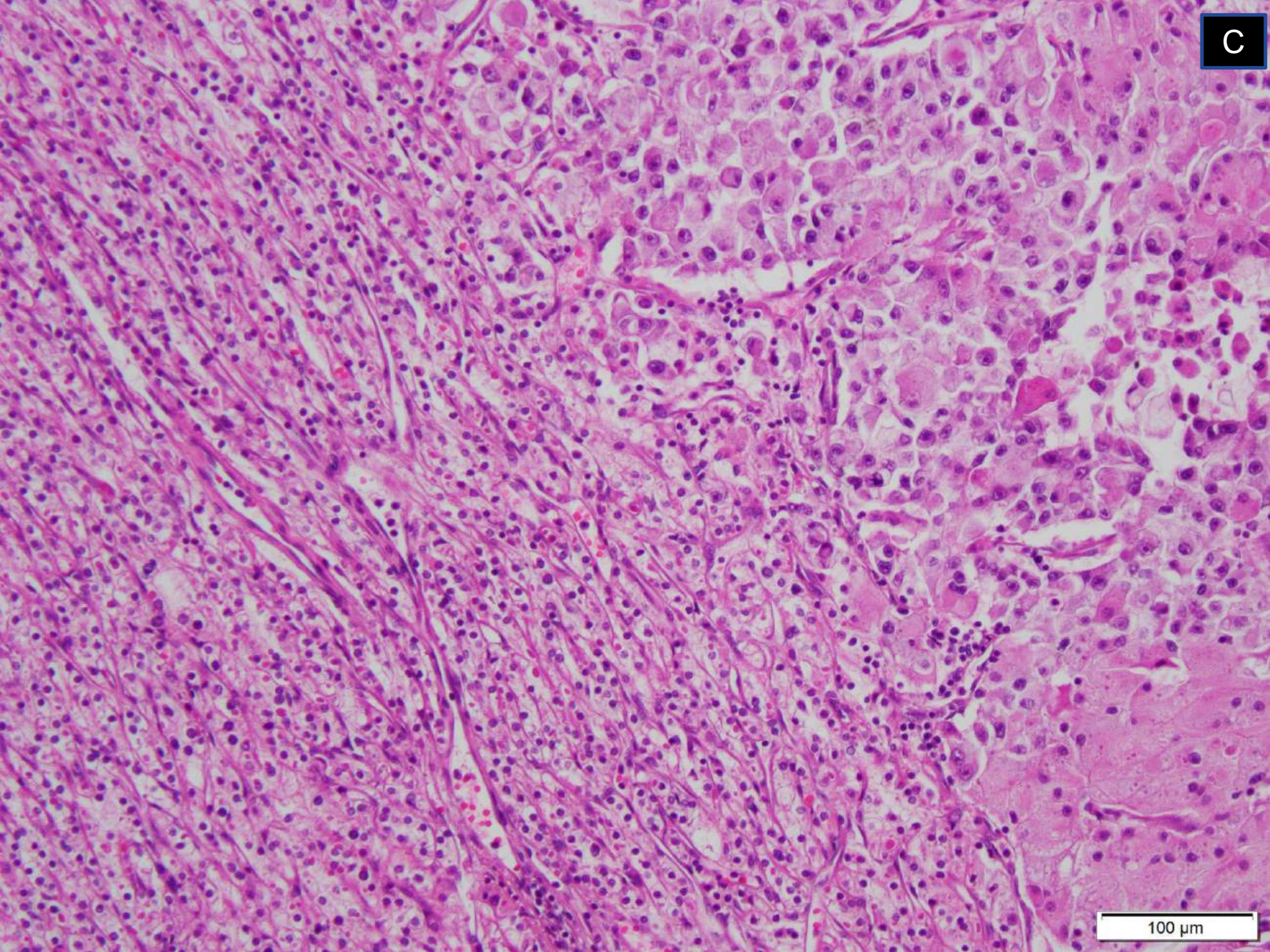
CA-IX

B

100 μ m

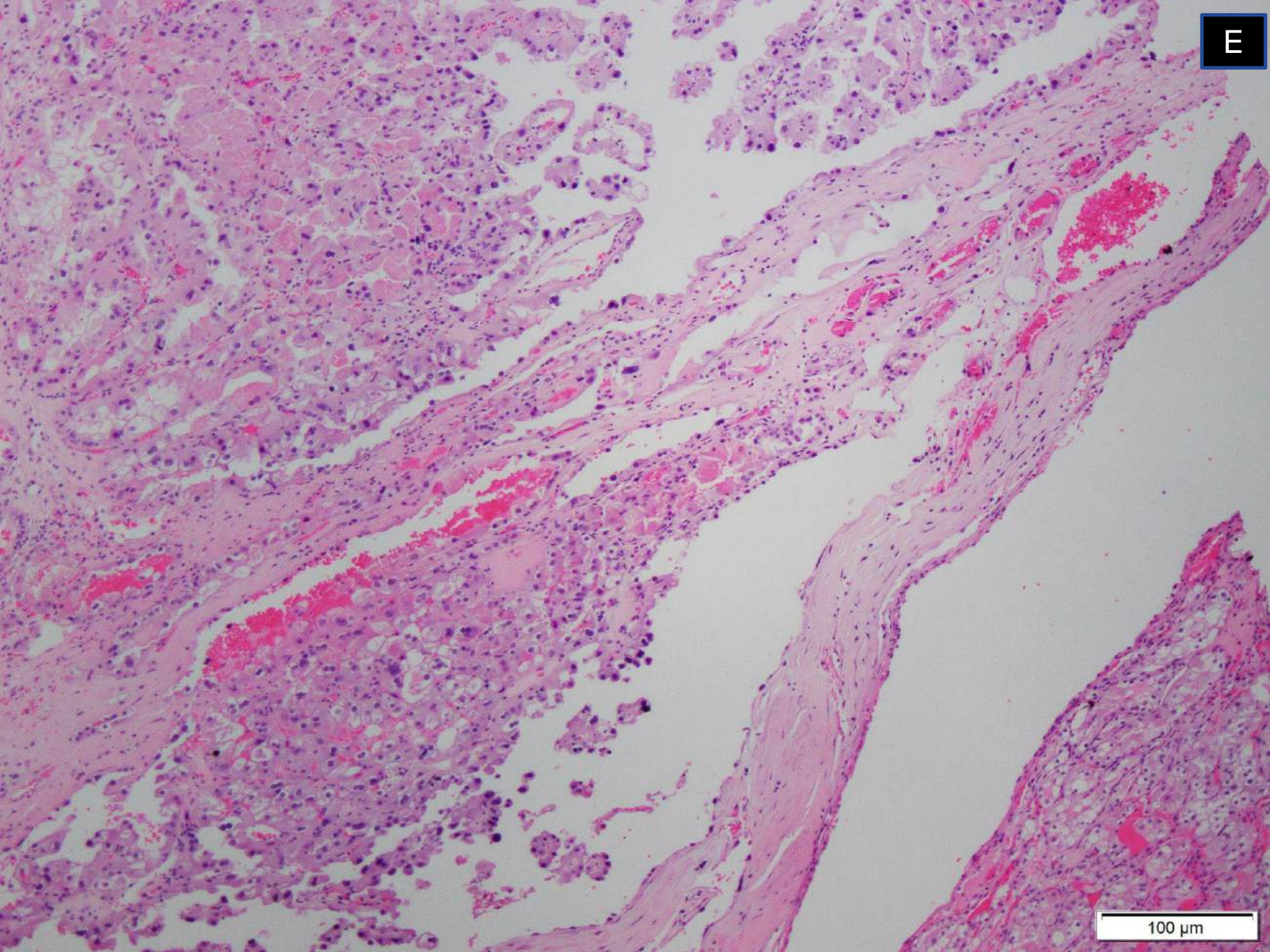


C

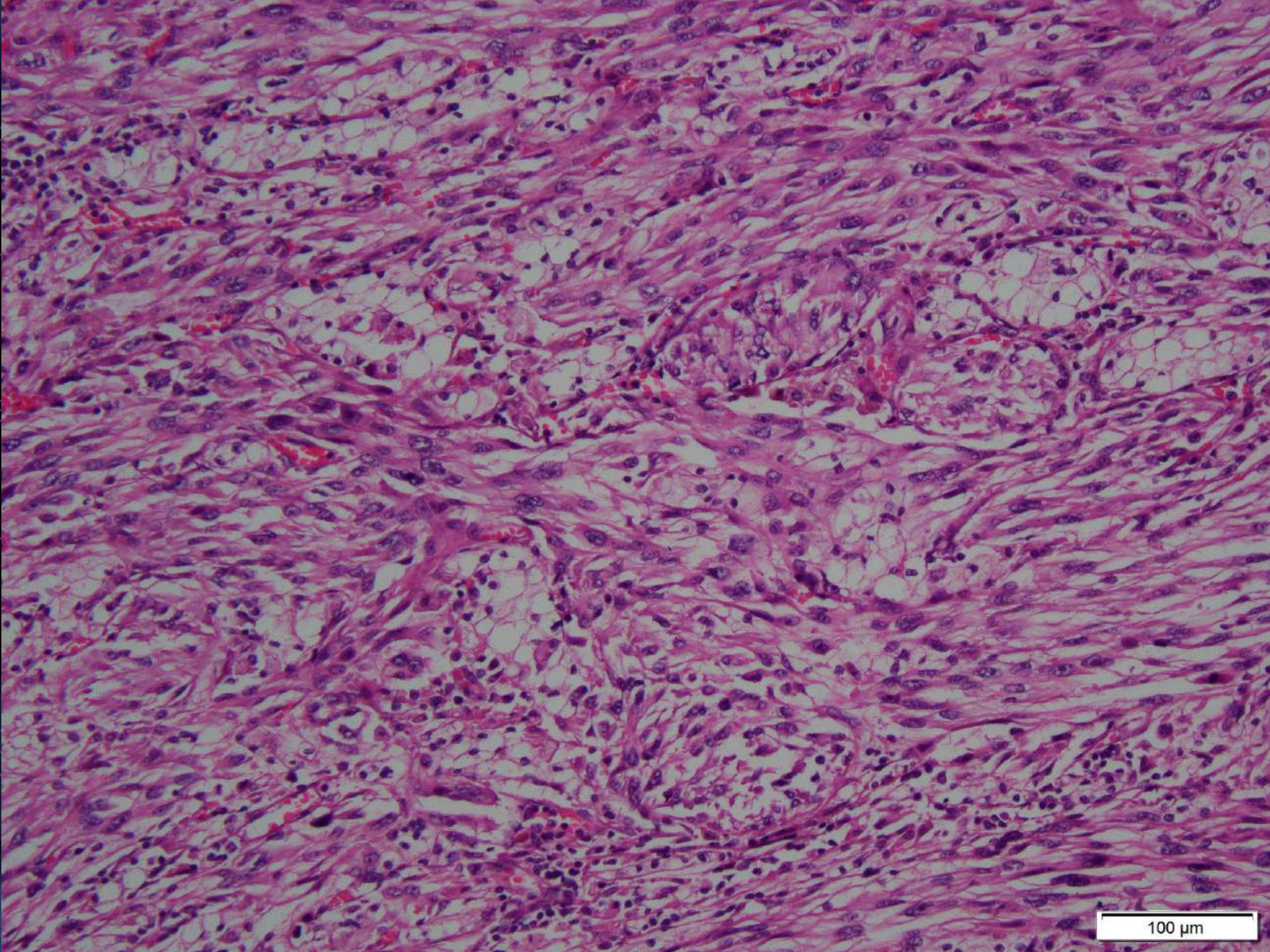


100 μ m

E

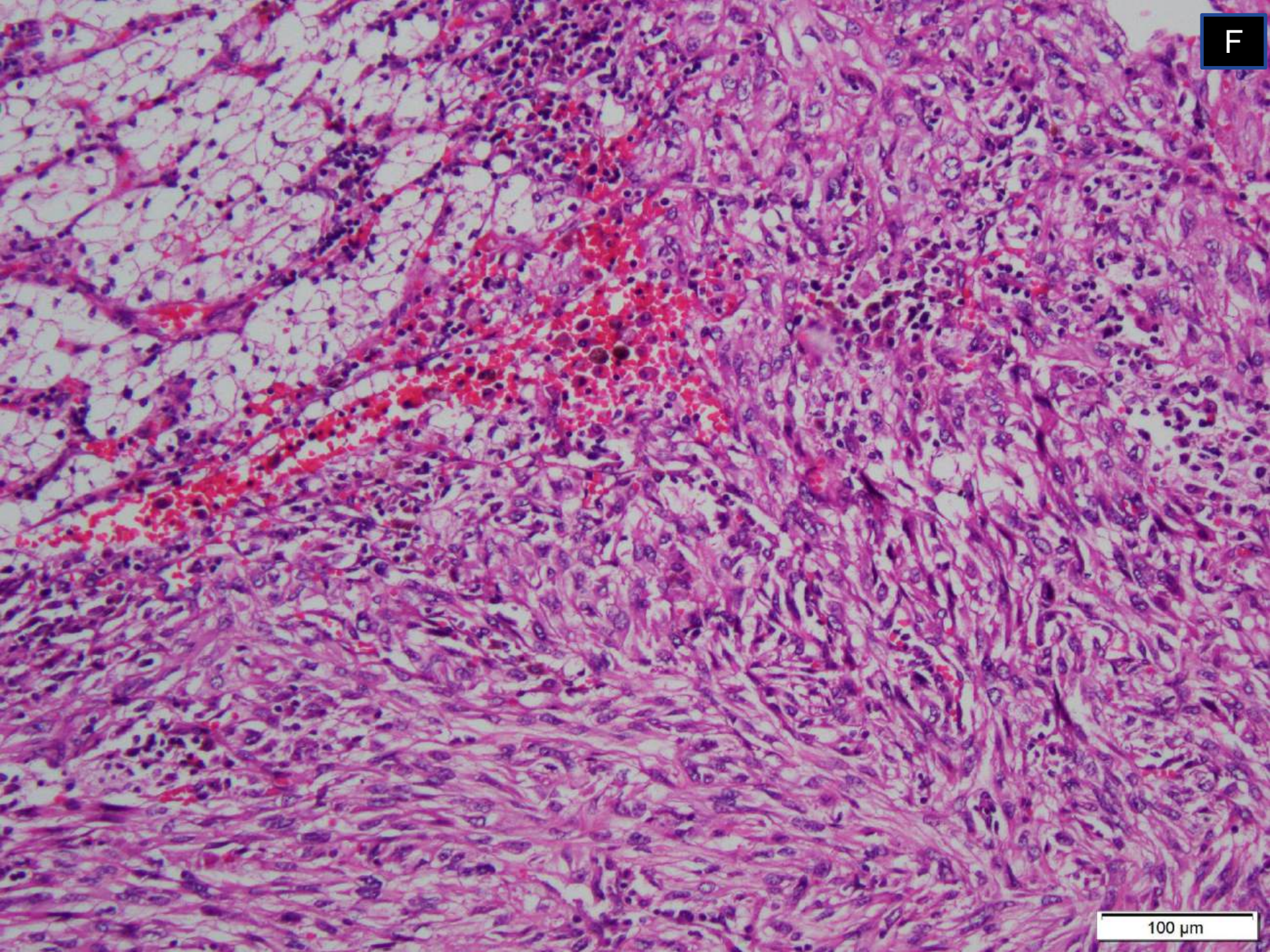


100 μm



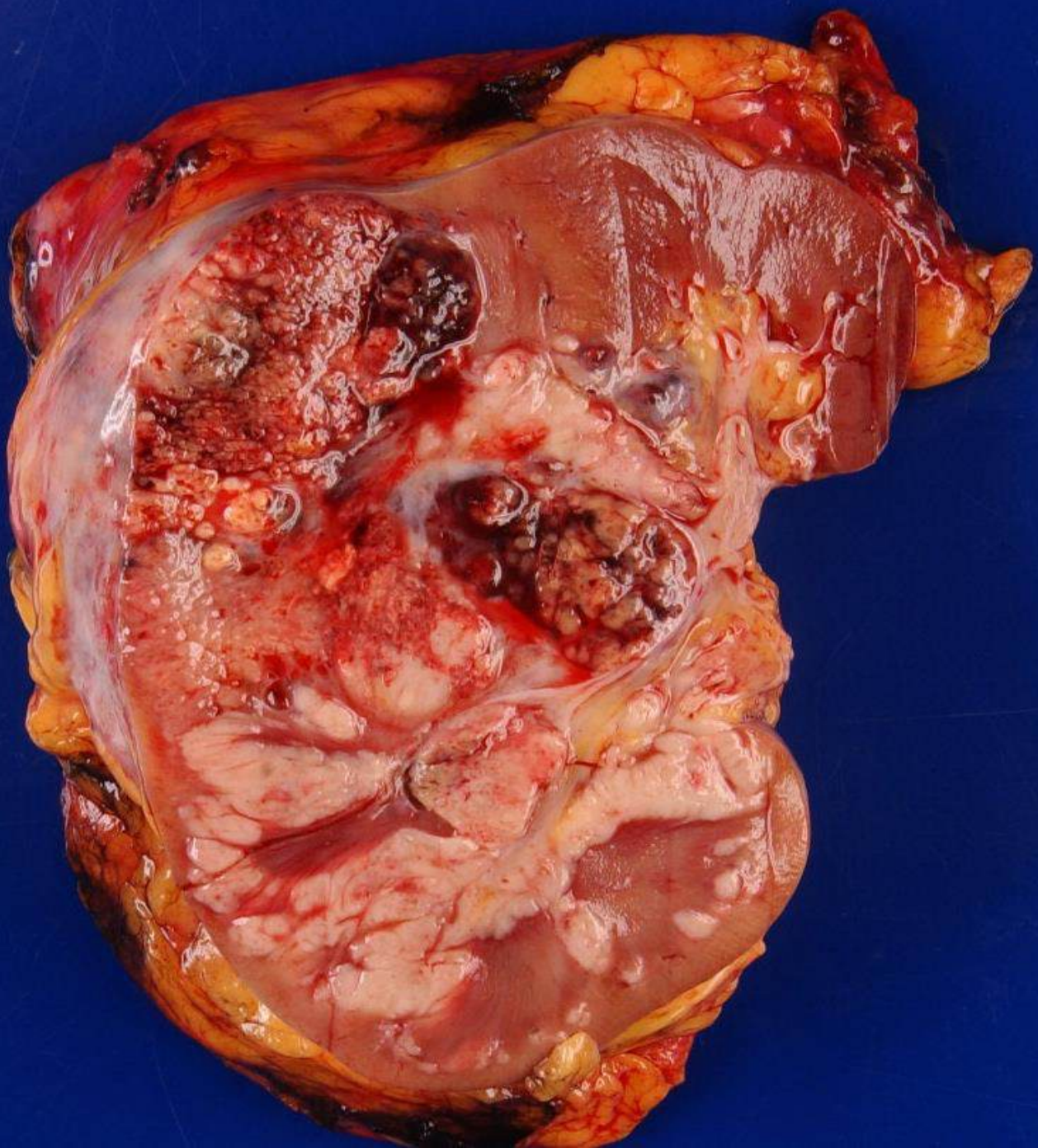
100 μm

F



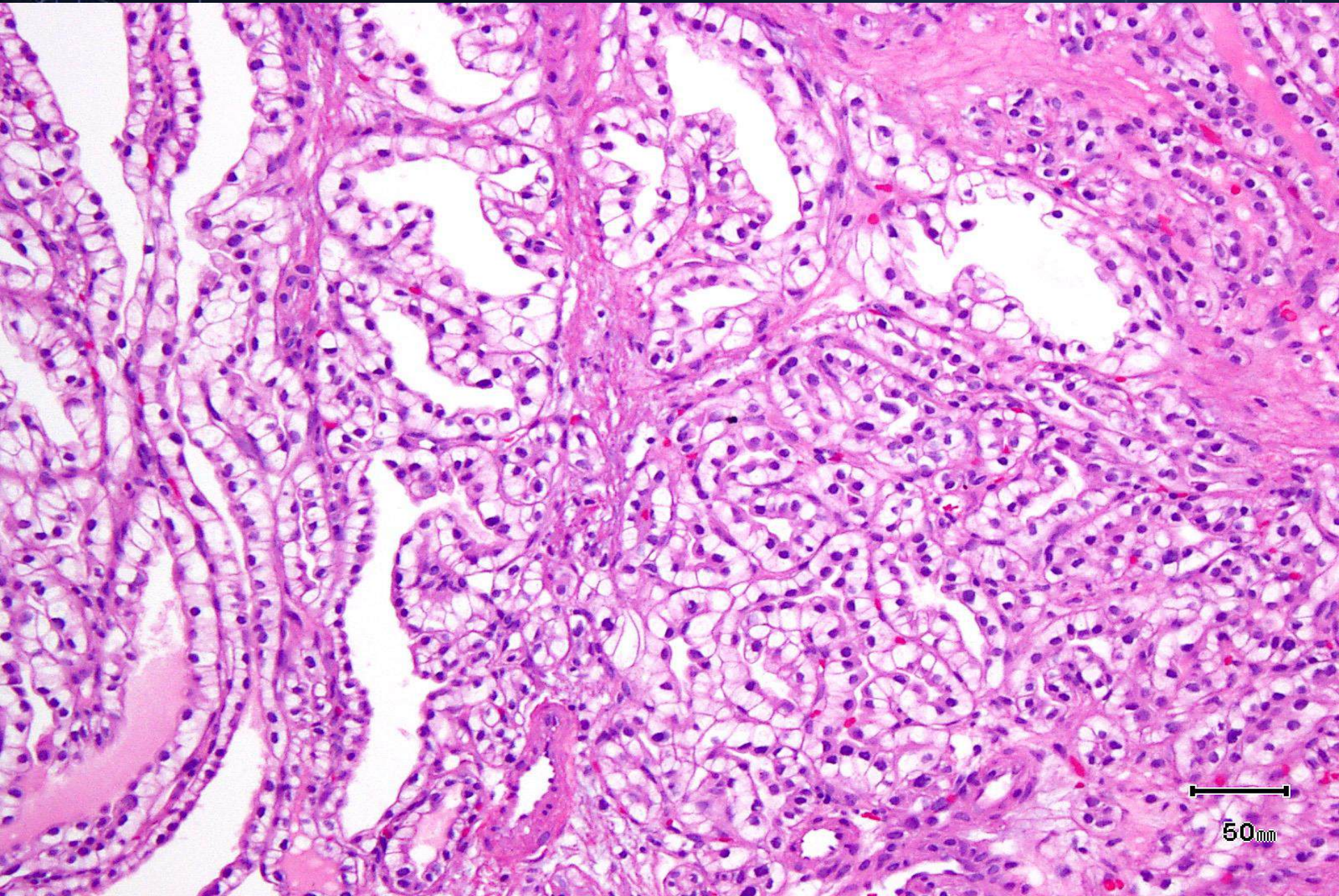
100 μ m

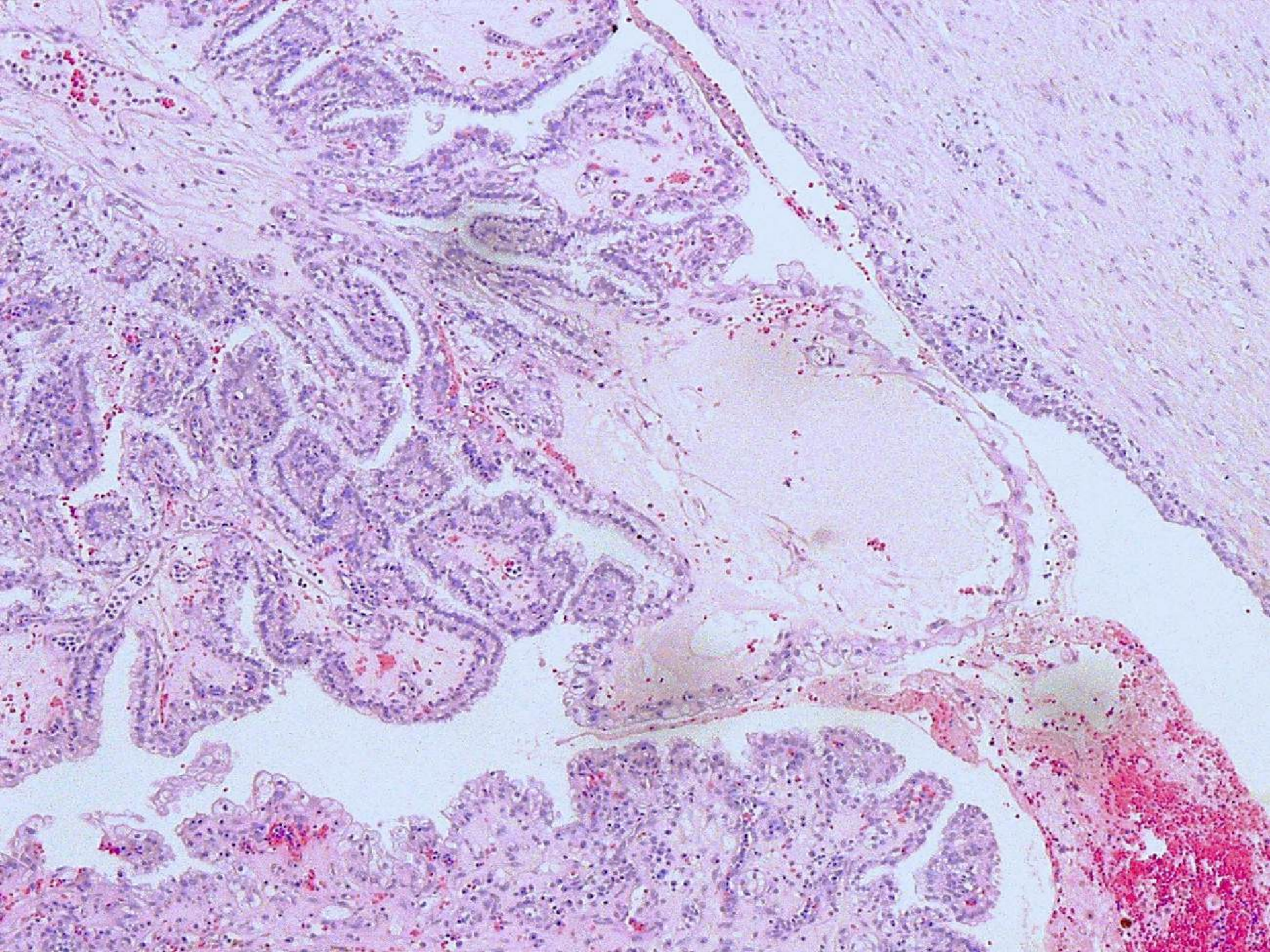
BACK TO THE GROSS SPECIMEN

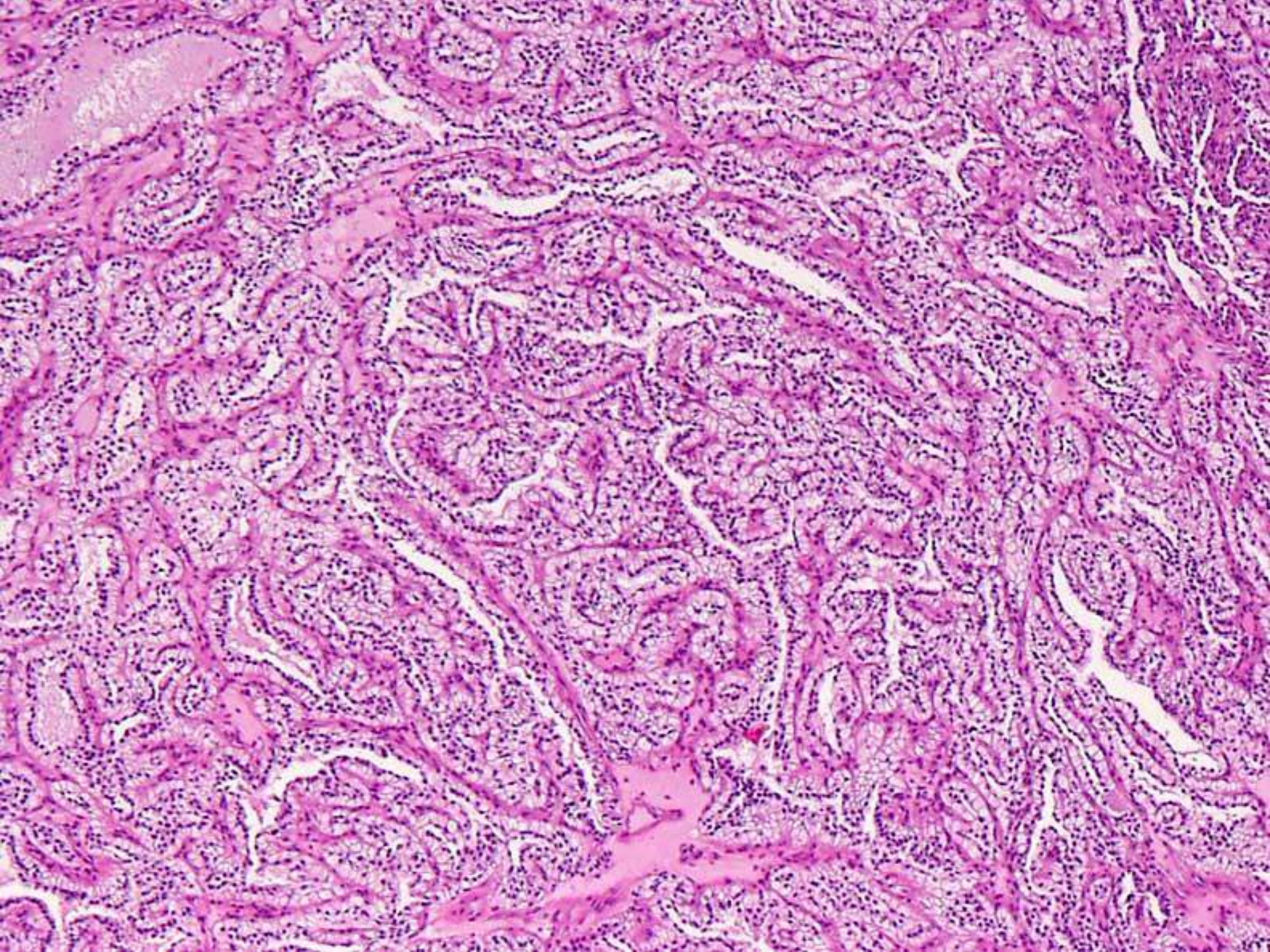


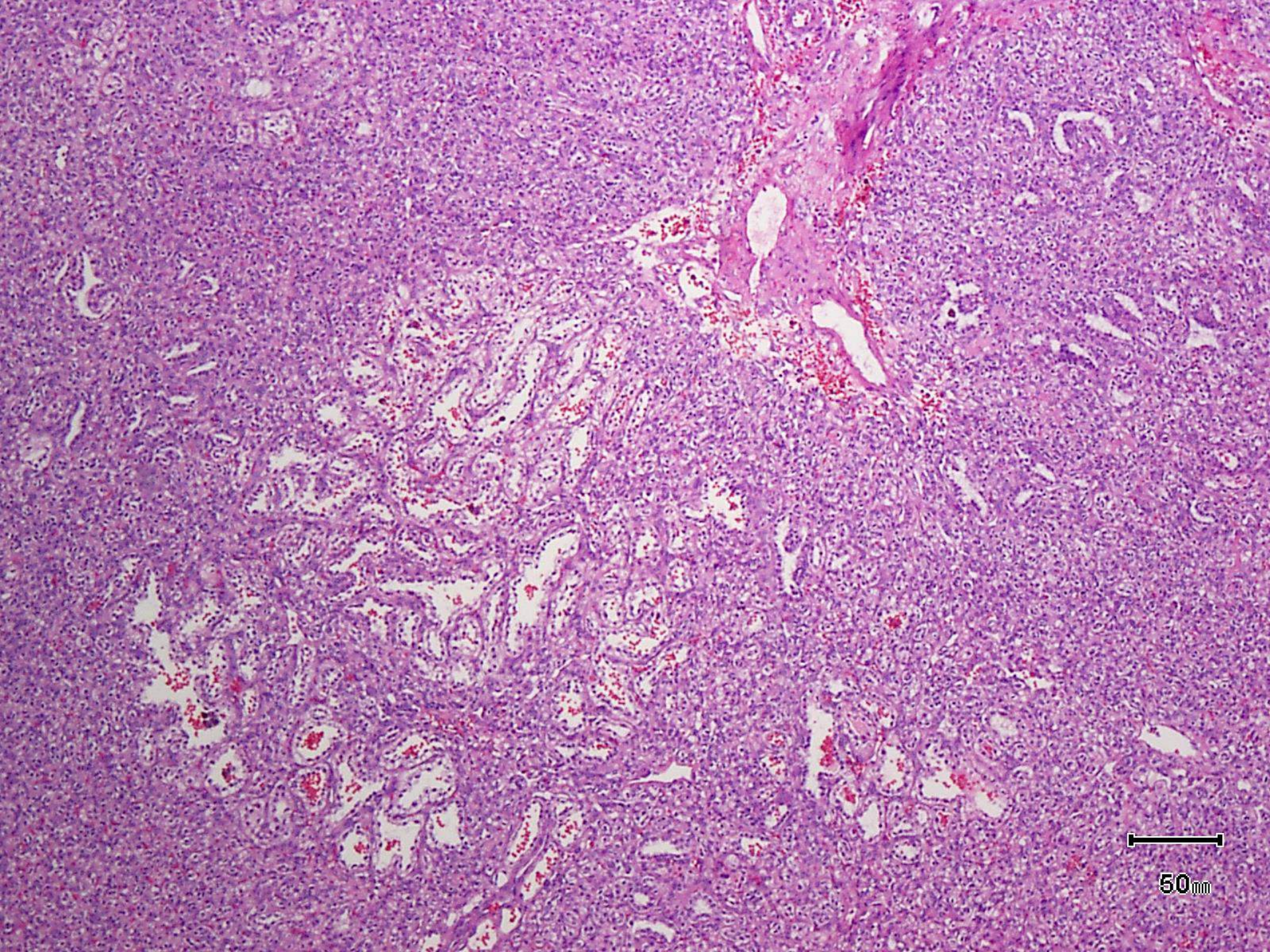
**May look like clear cell RCC
but
are not**

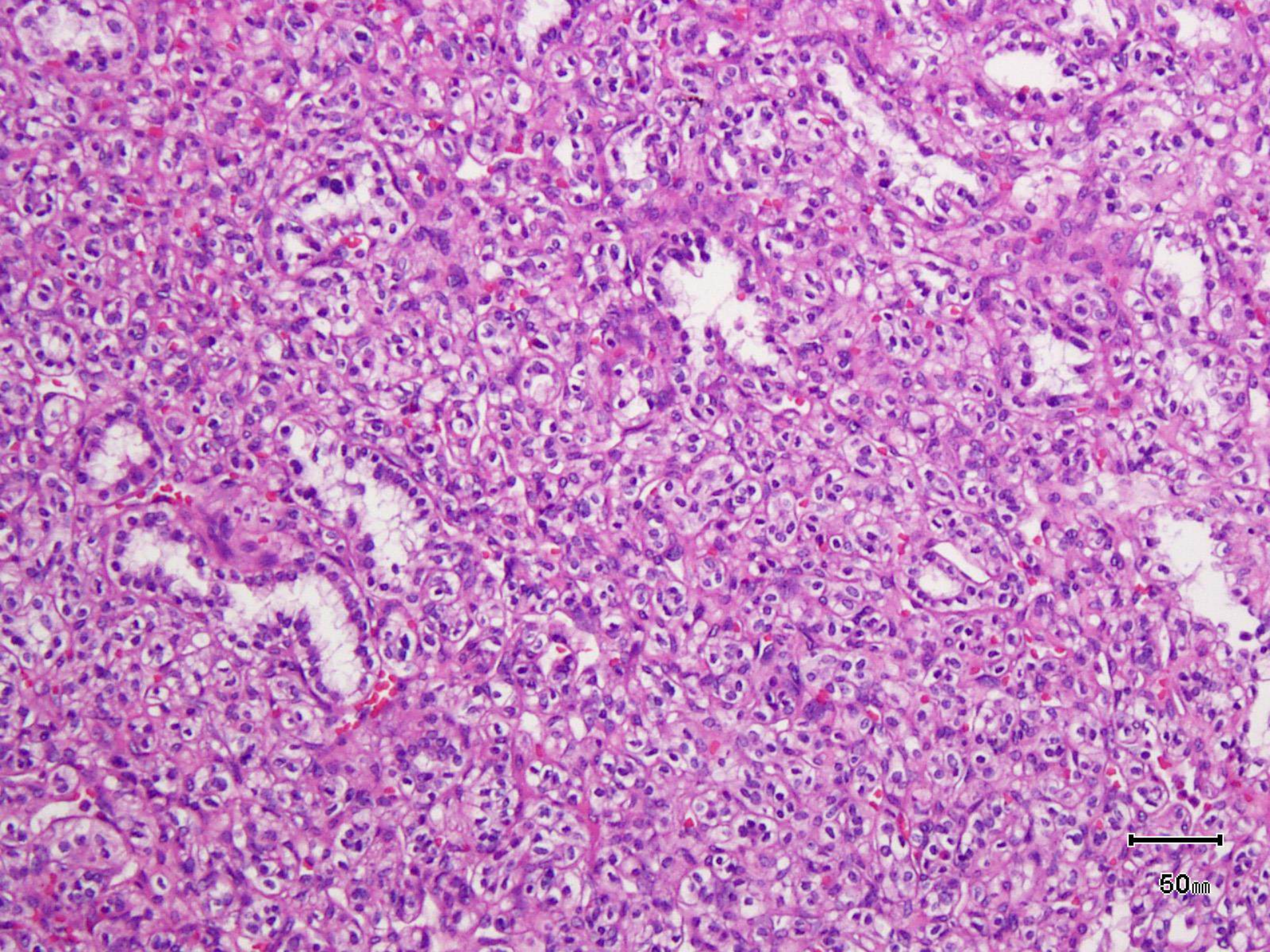
CLEAR CELL PAPILLARY RENAL CELL CARCINOMA



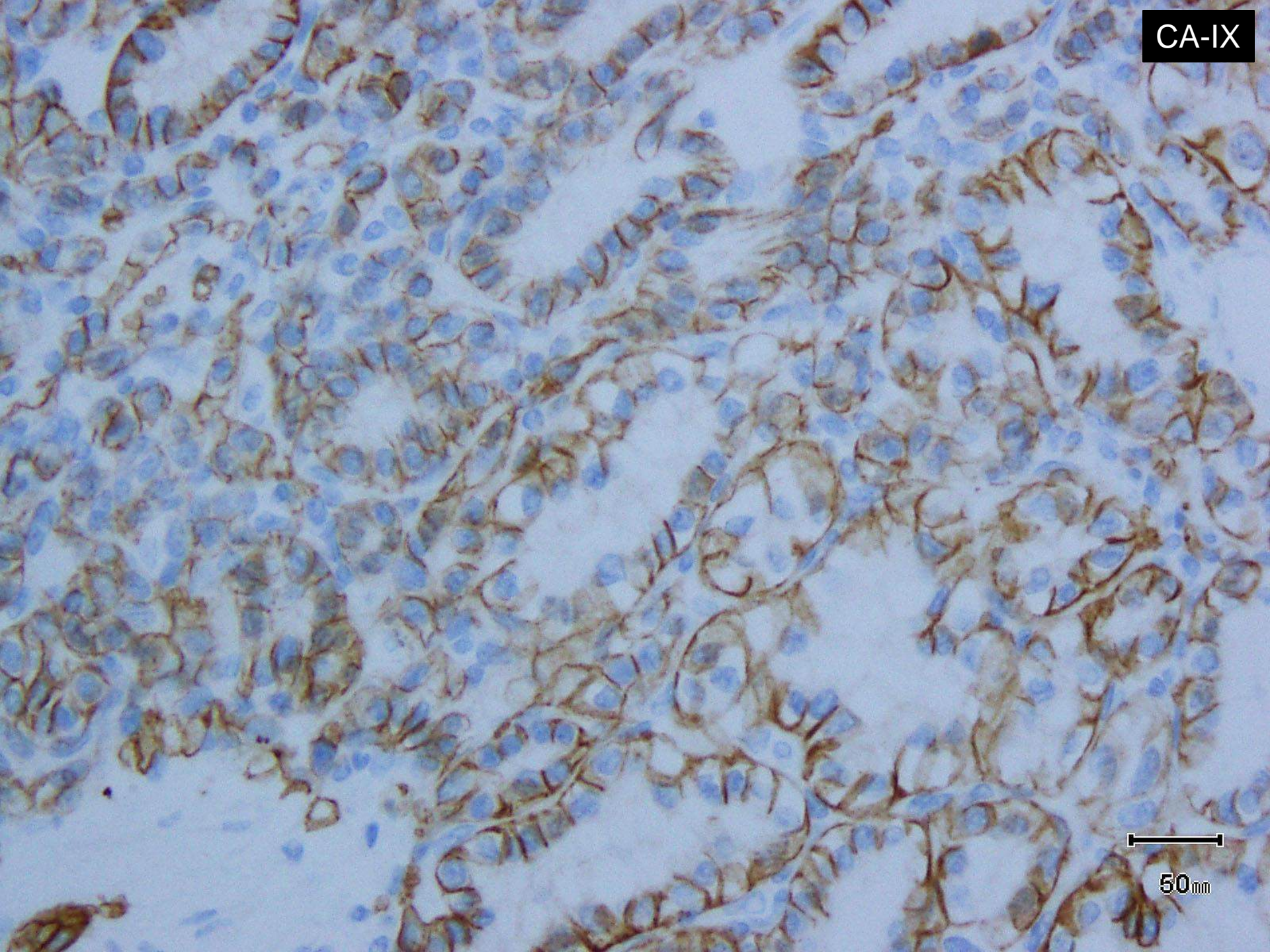






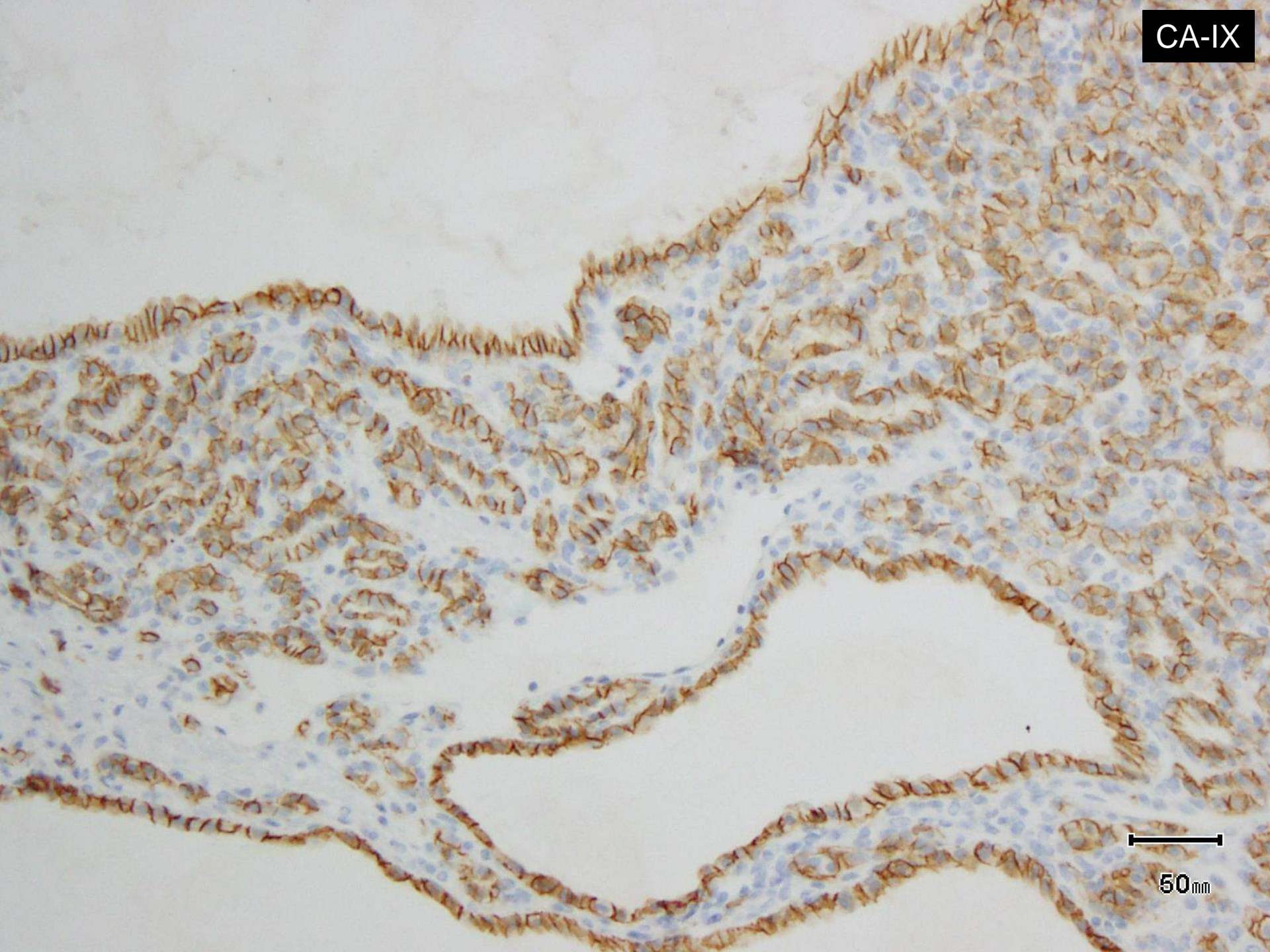


CA-IX



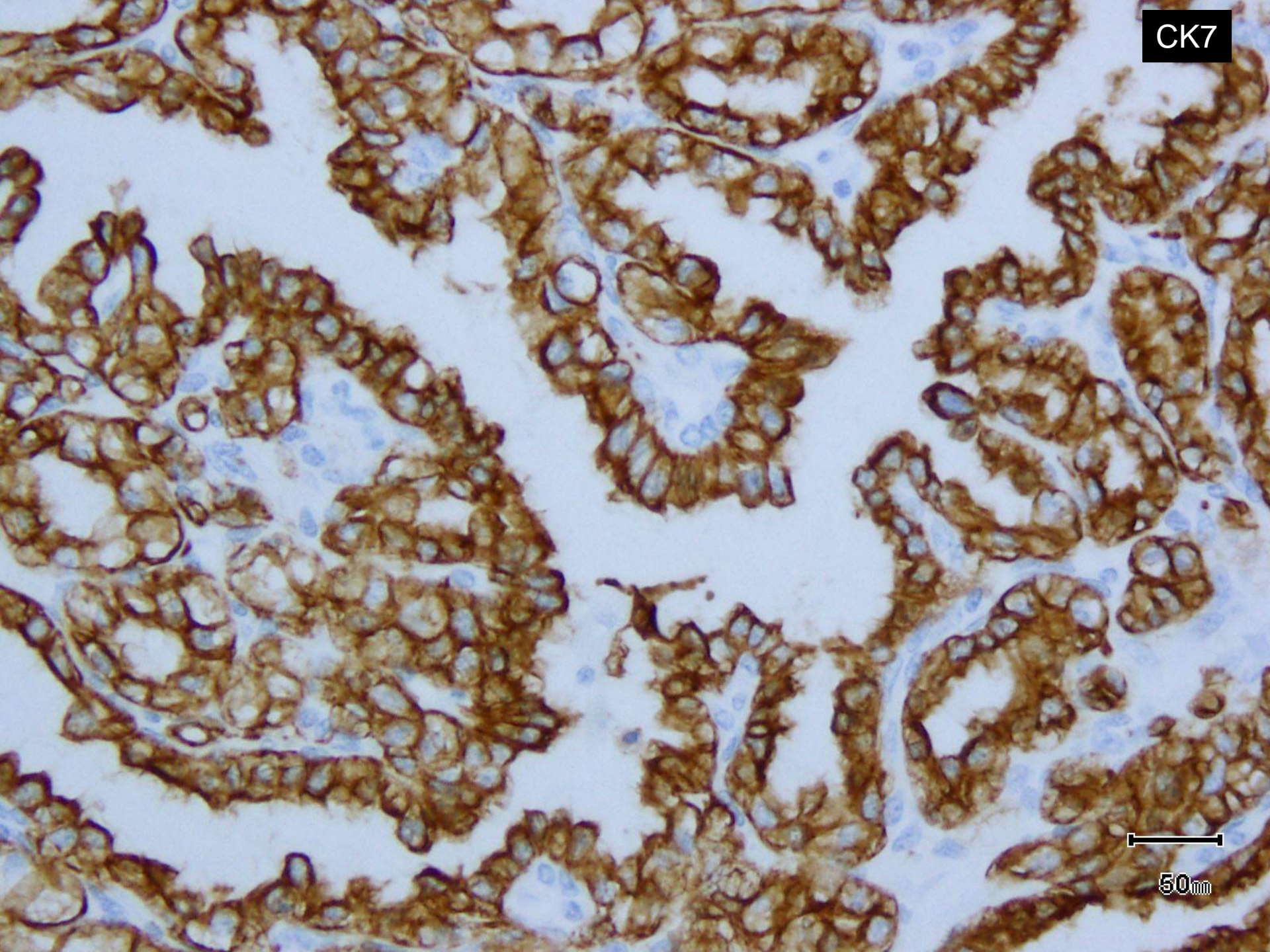
50mm

CA-IX



50mm

CK7

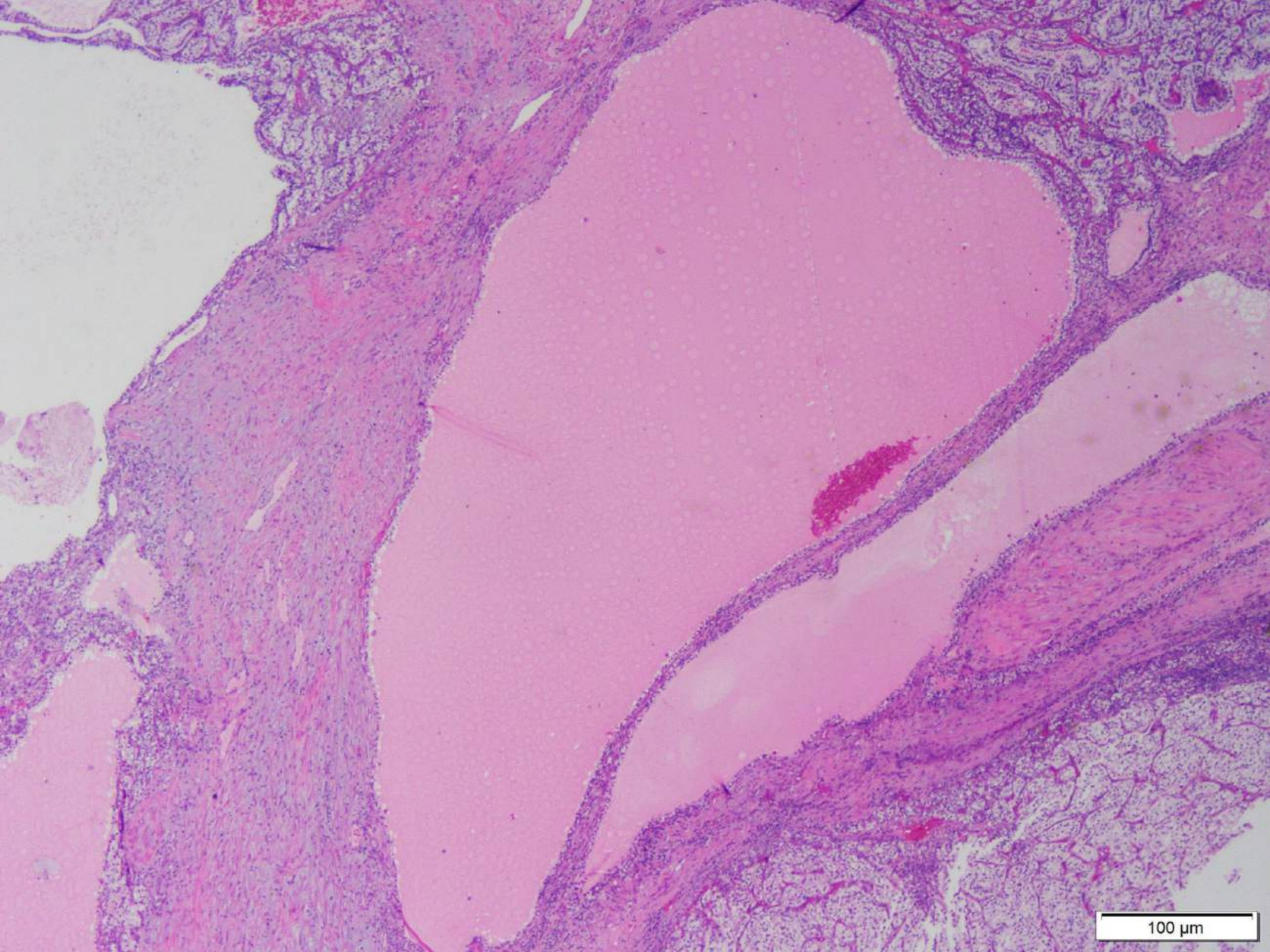


50µm

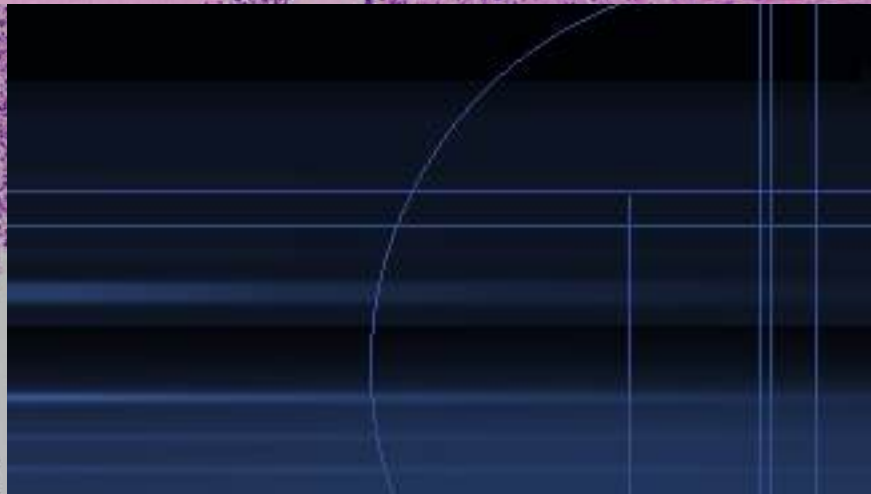
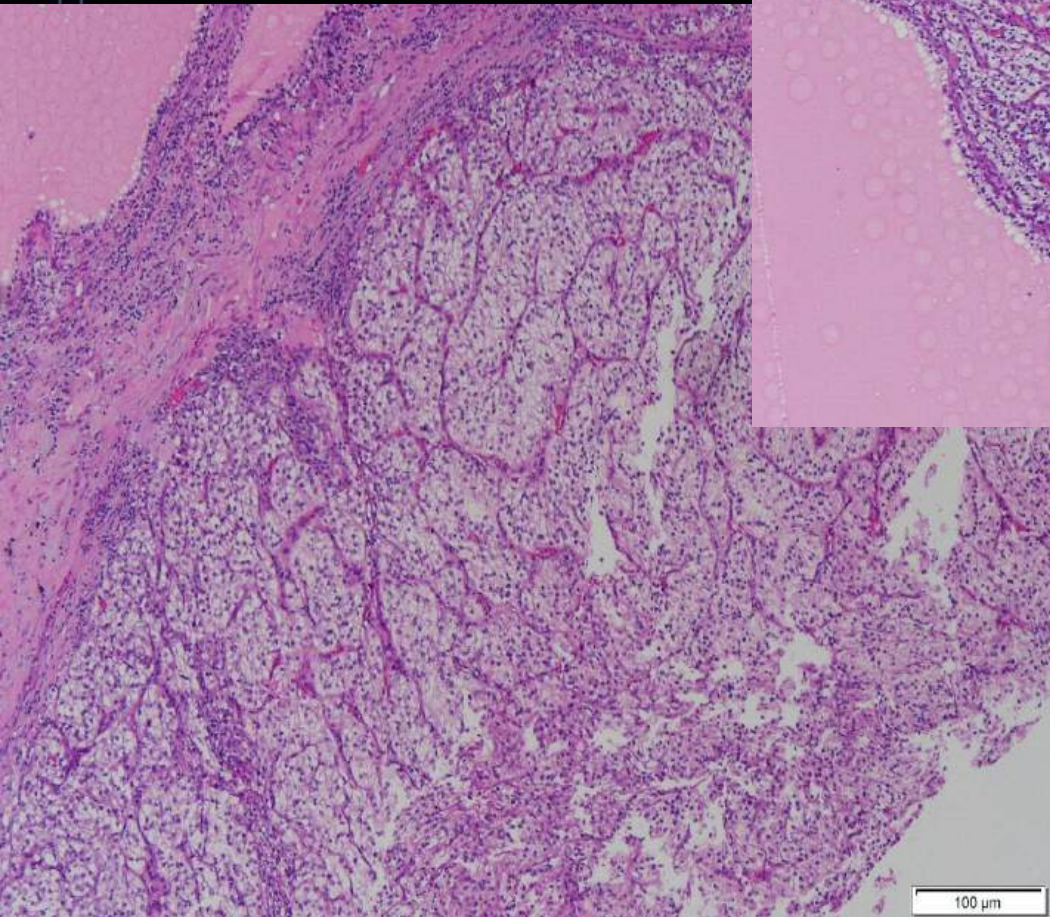
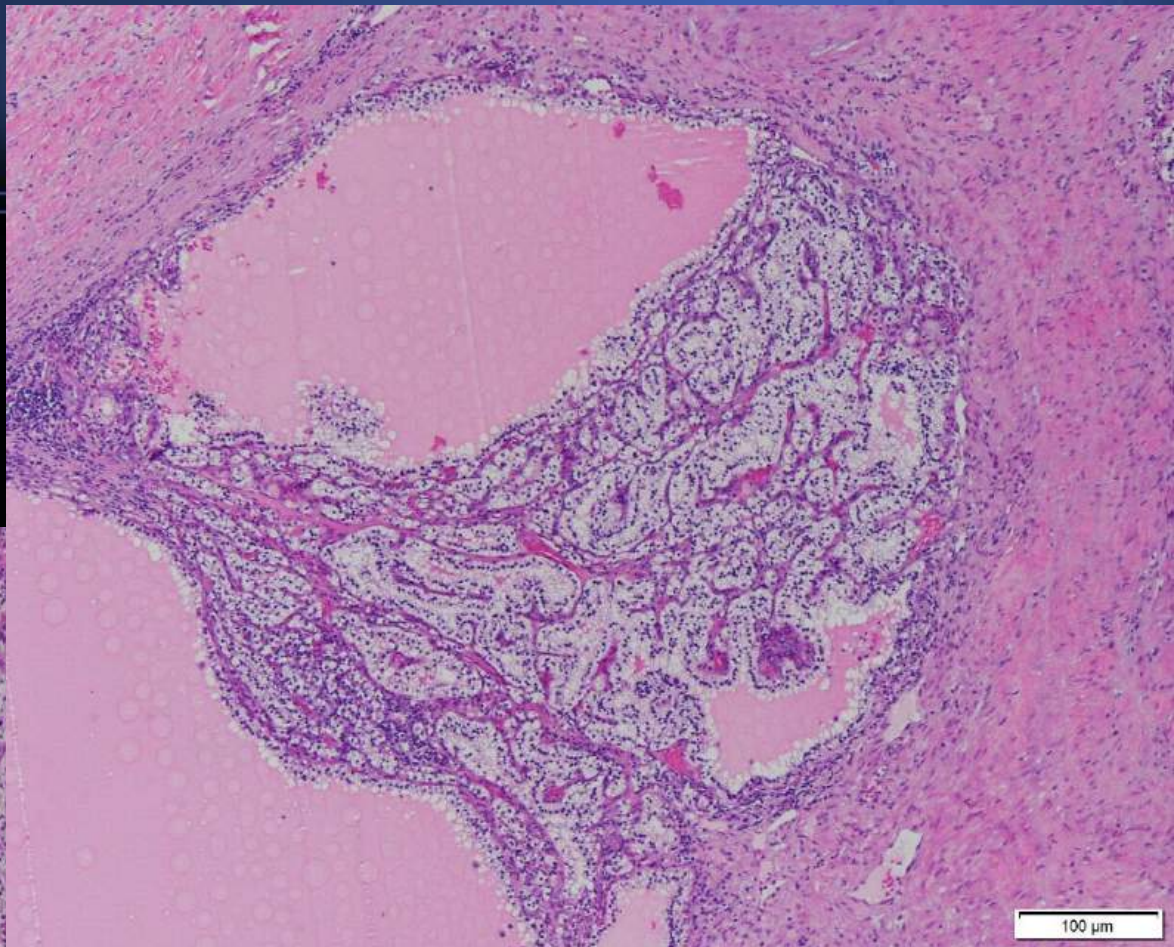
Abnormal oxidative metabolism in a quiet genomic background underlies clear cell papillary renal cell carcinoma

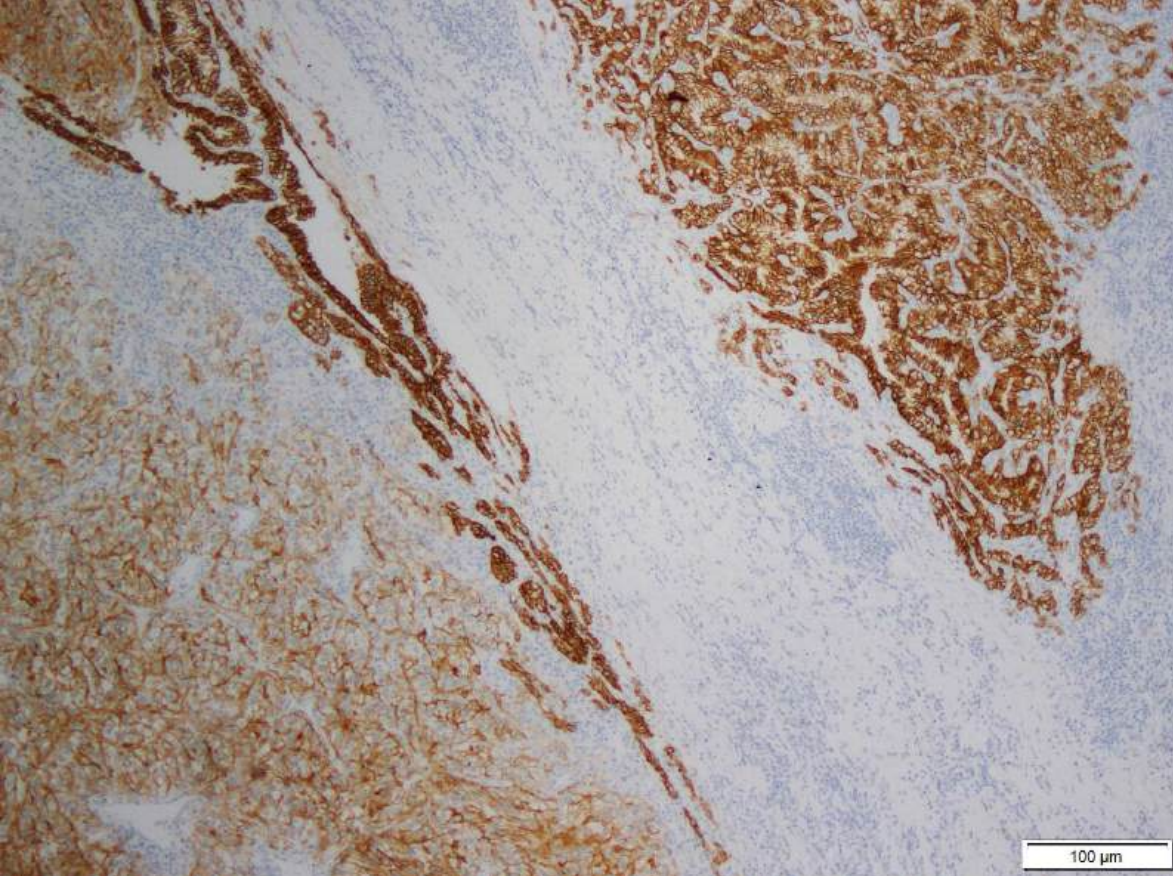
- Wild-type nuclear genome
- Severe depletion of mitochondrial DNA and RNA
- Exhibit high levels of oxidative stress
- Distinct metabolic phenotype characterized by accumulation of the sugar alcohol sorbitol.

Xu J et al. Elife. 2019 Apr 1;8. pii: e38986.

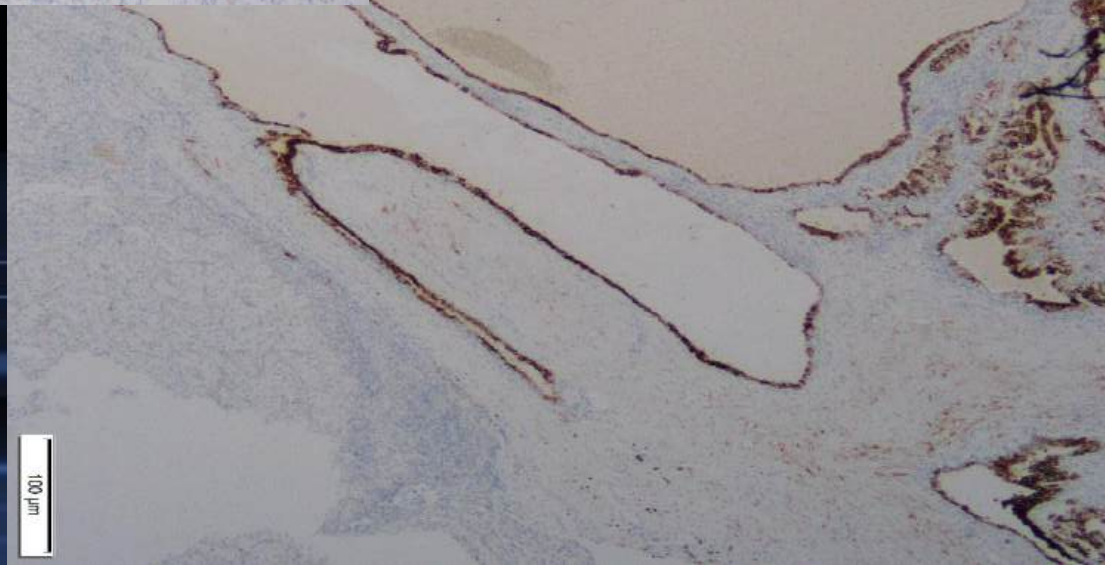


100 μm





100 μ m

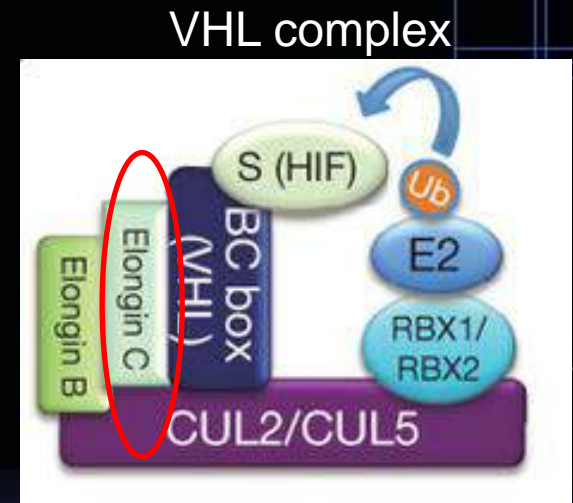


100 μ m

**Other tumors with clear
cytoplasm, prominent
fibromuscular stroma, and CK7
positivity**

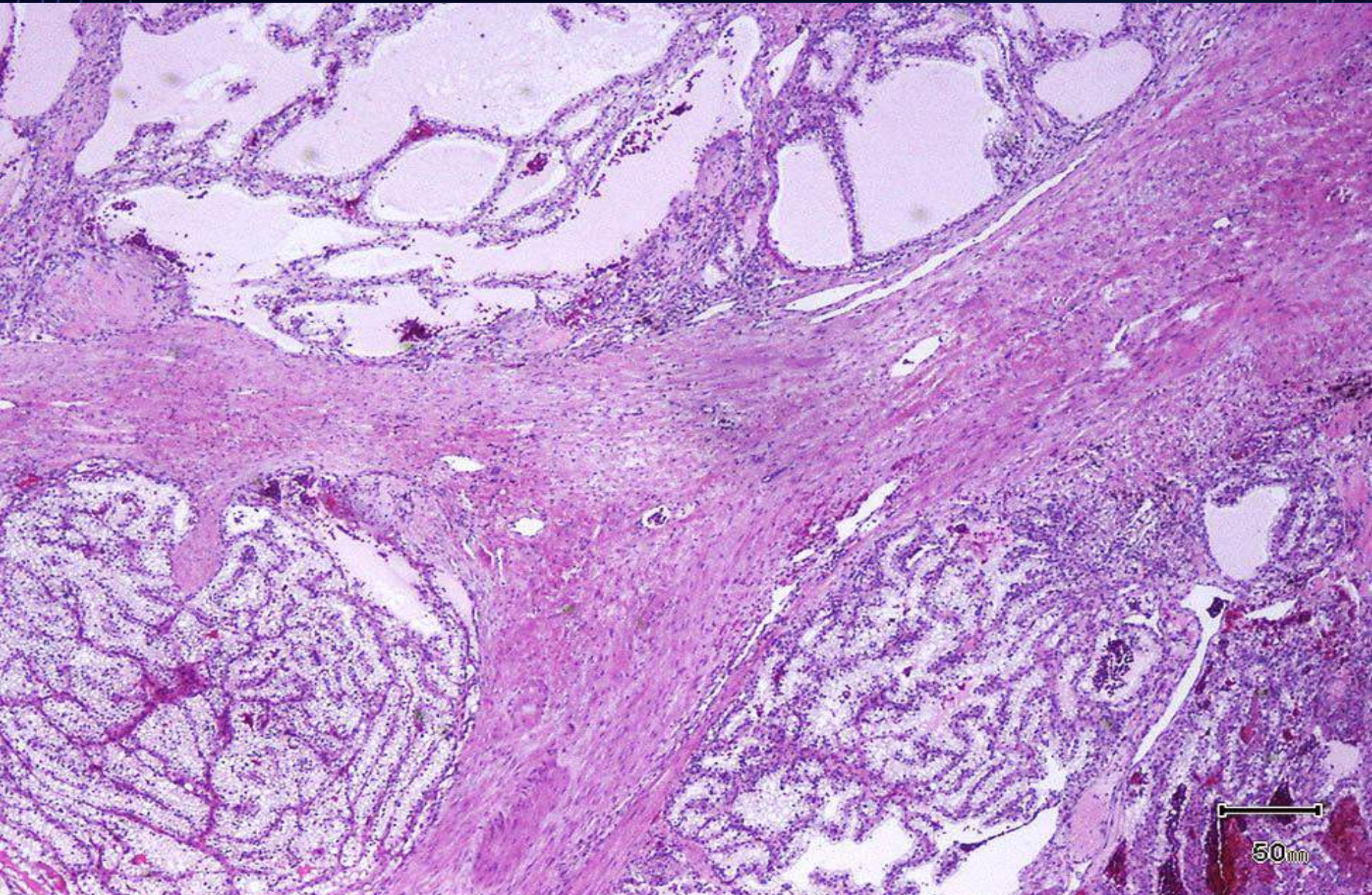
TCEB1-mutated RCC

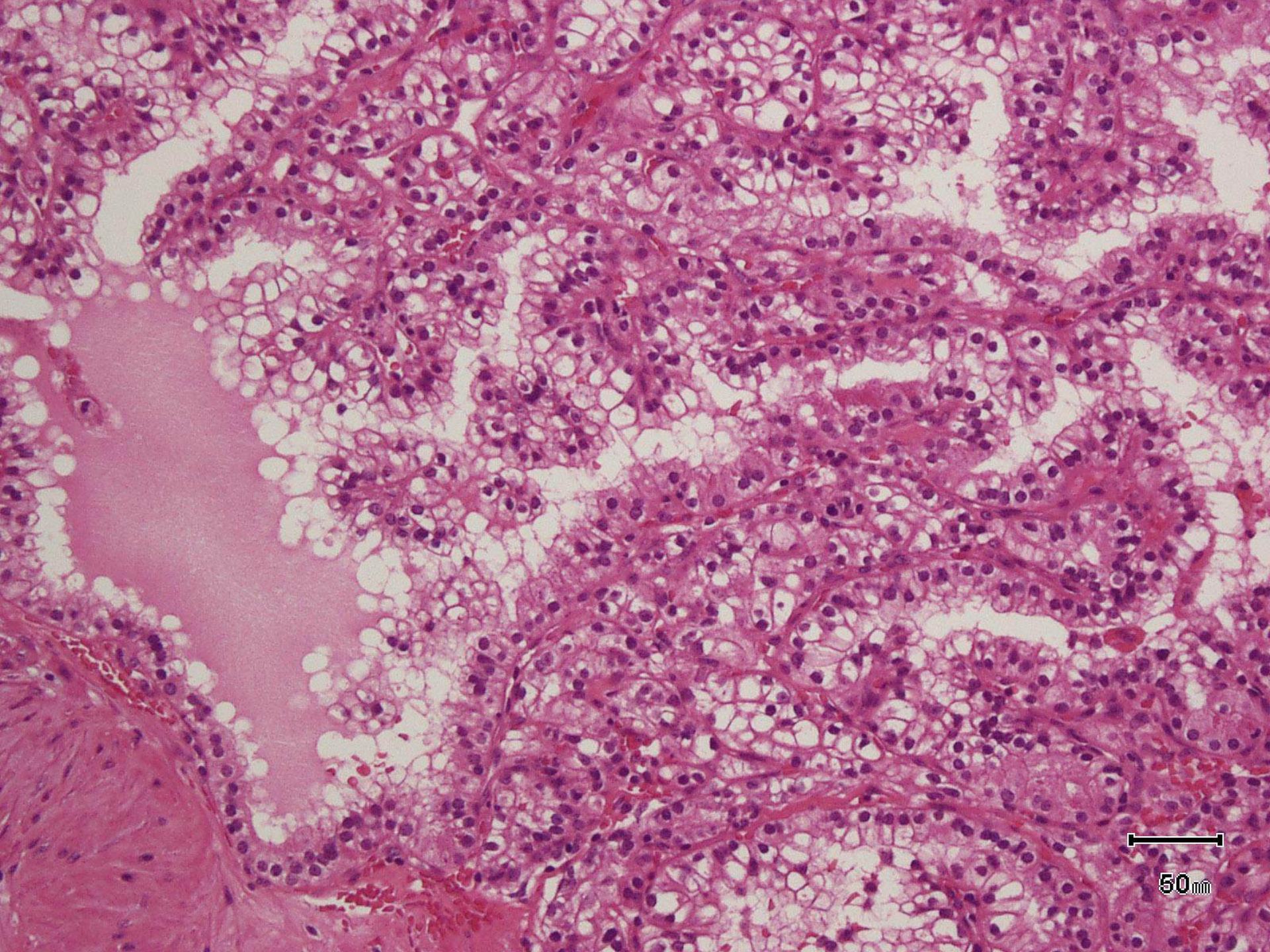
- Encodes Elongin C, a 112-residue protein identified as a subunit of the heterotrimeric RNA polymerase II elongation factor complex (Elongin)
- A vital component of the VHL complex
- Located on Chromosome 8

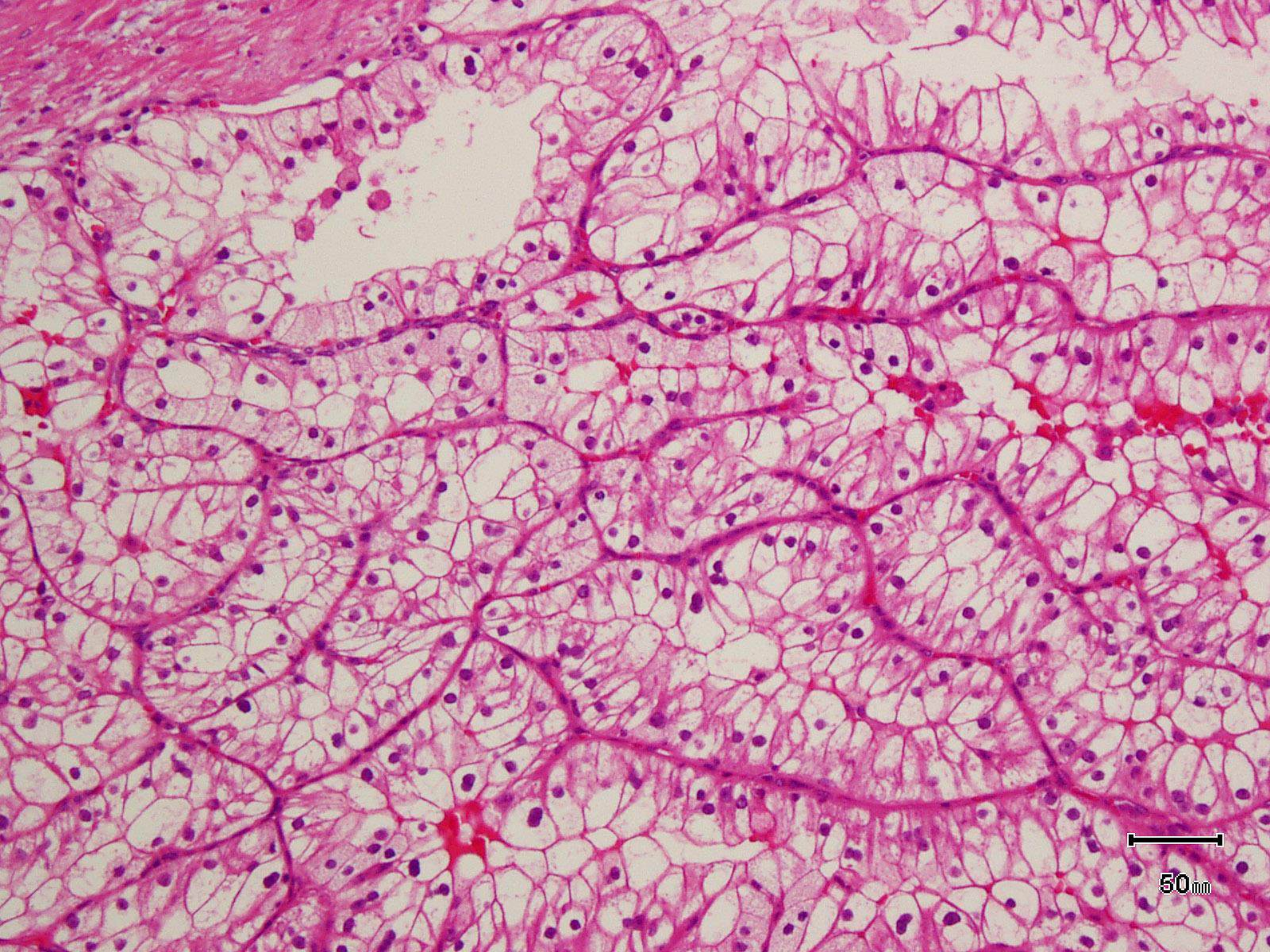


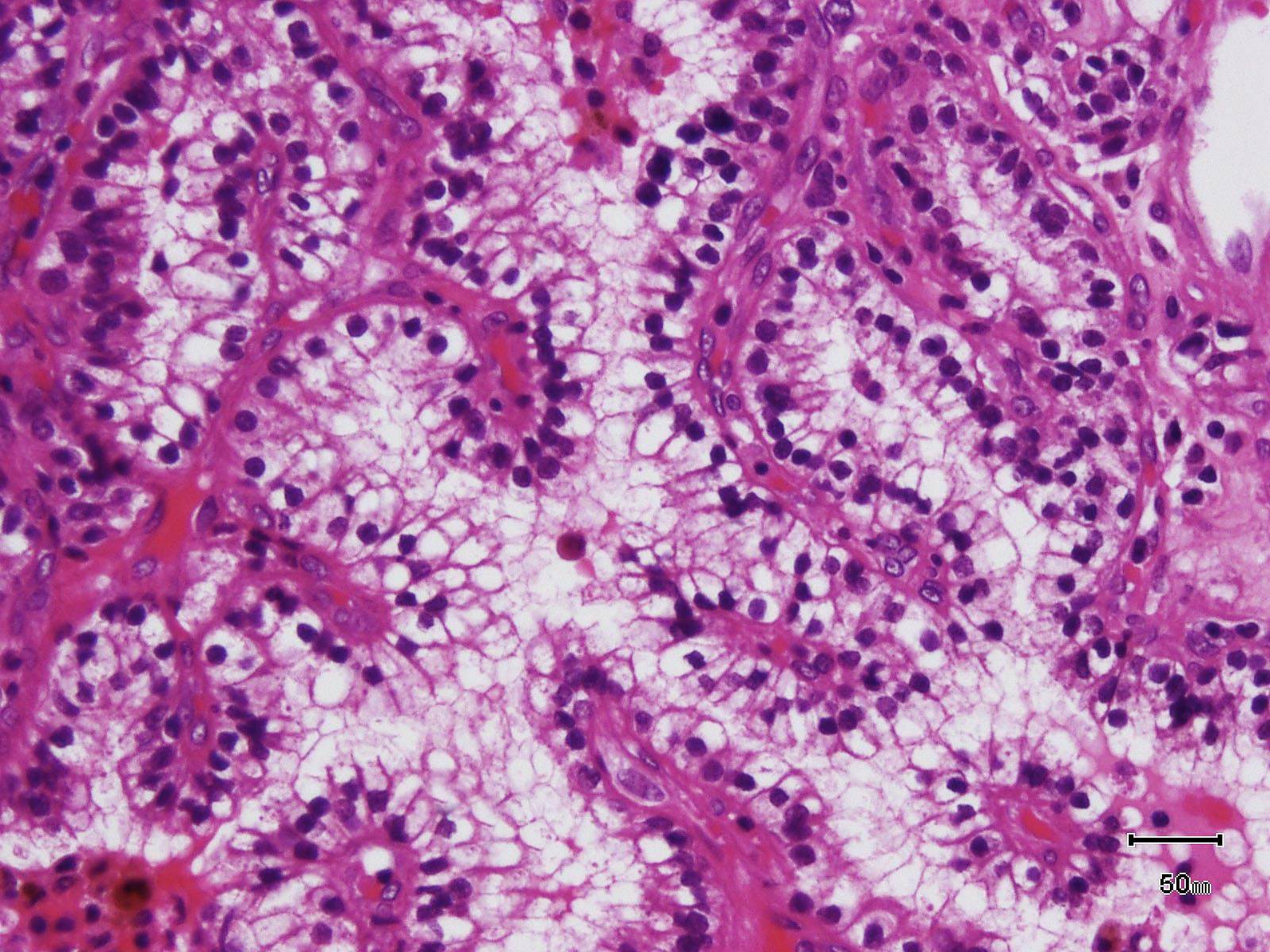
- Exclusively involves two conserved amino acids, Tyr79 and Ala100
- *TCEB1* mutations always accompanied by loss of chromosome 8

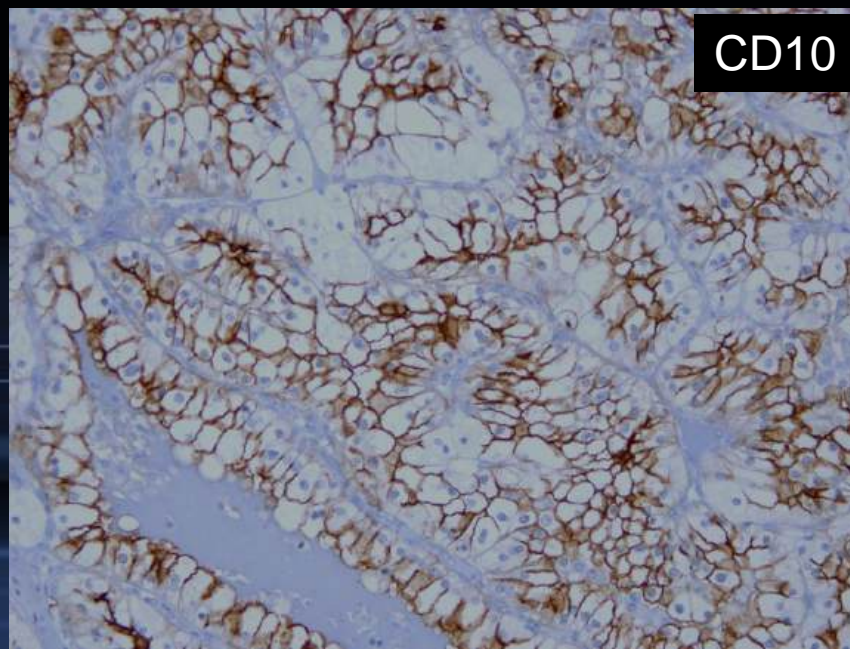
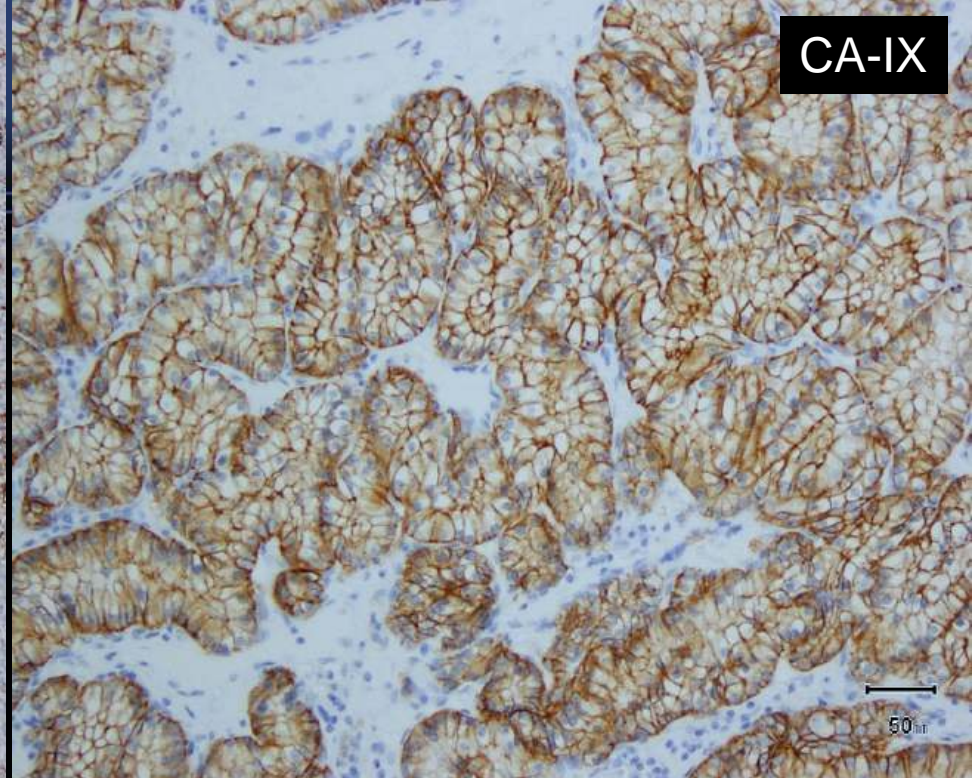
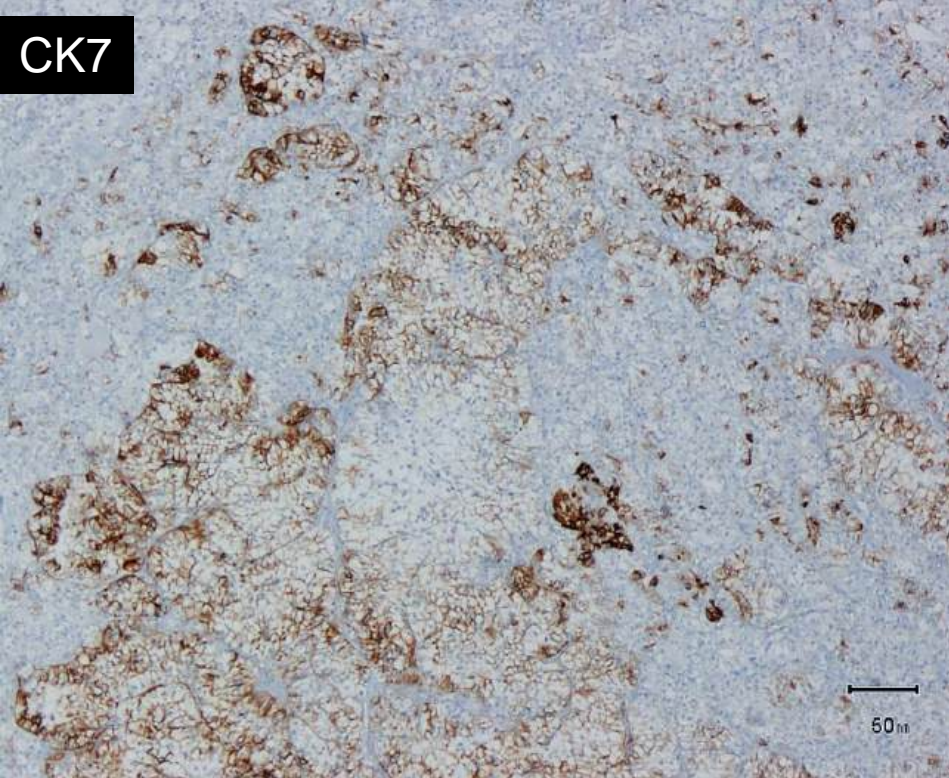
TCEB1-mutated RCC



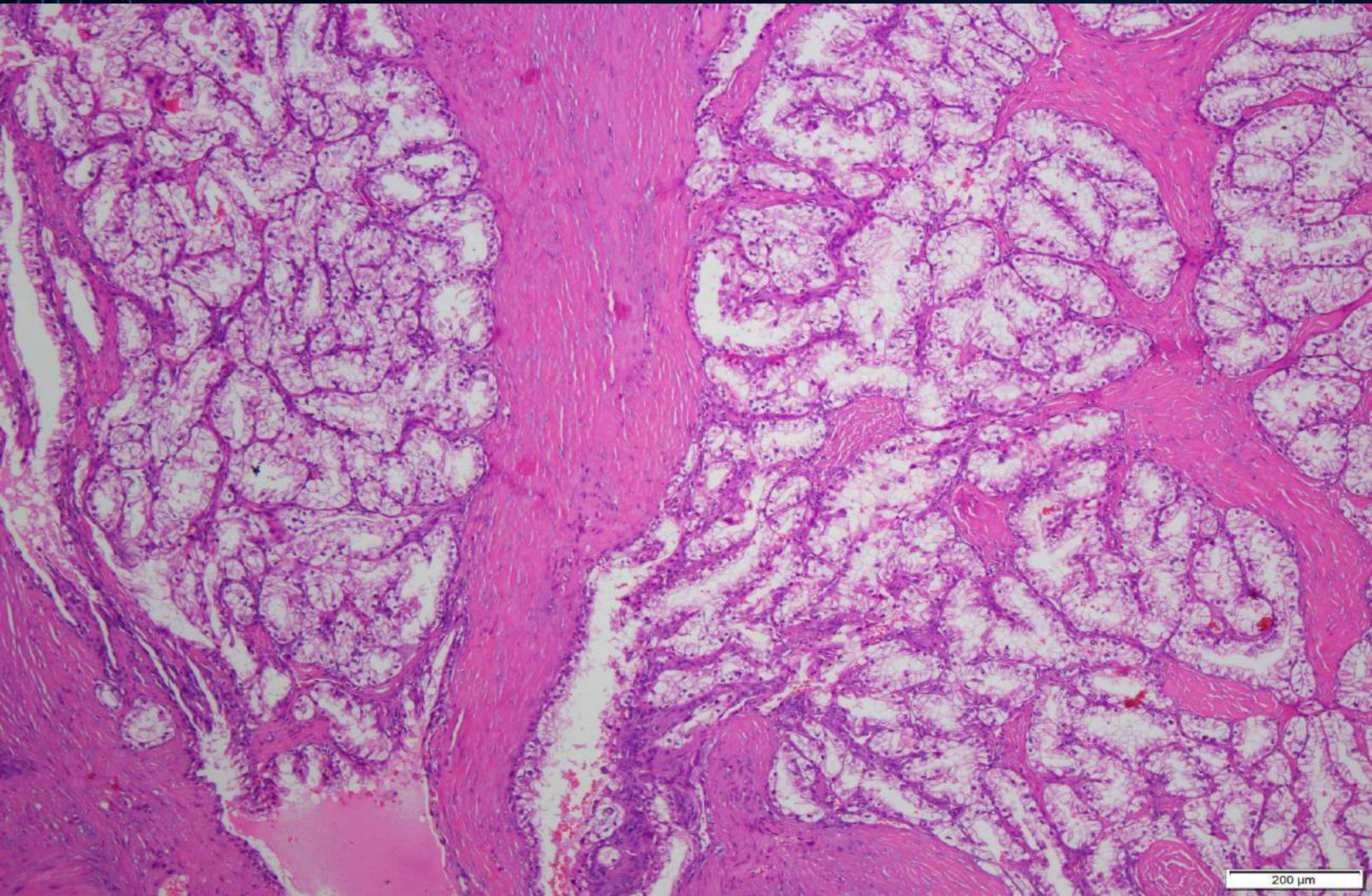




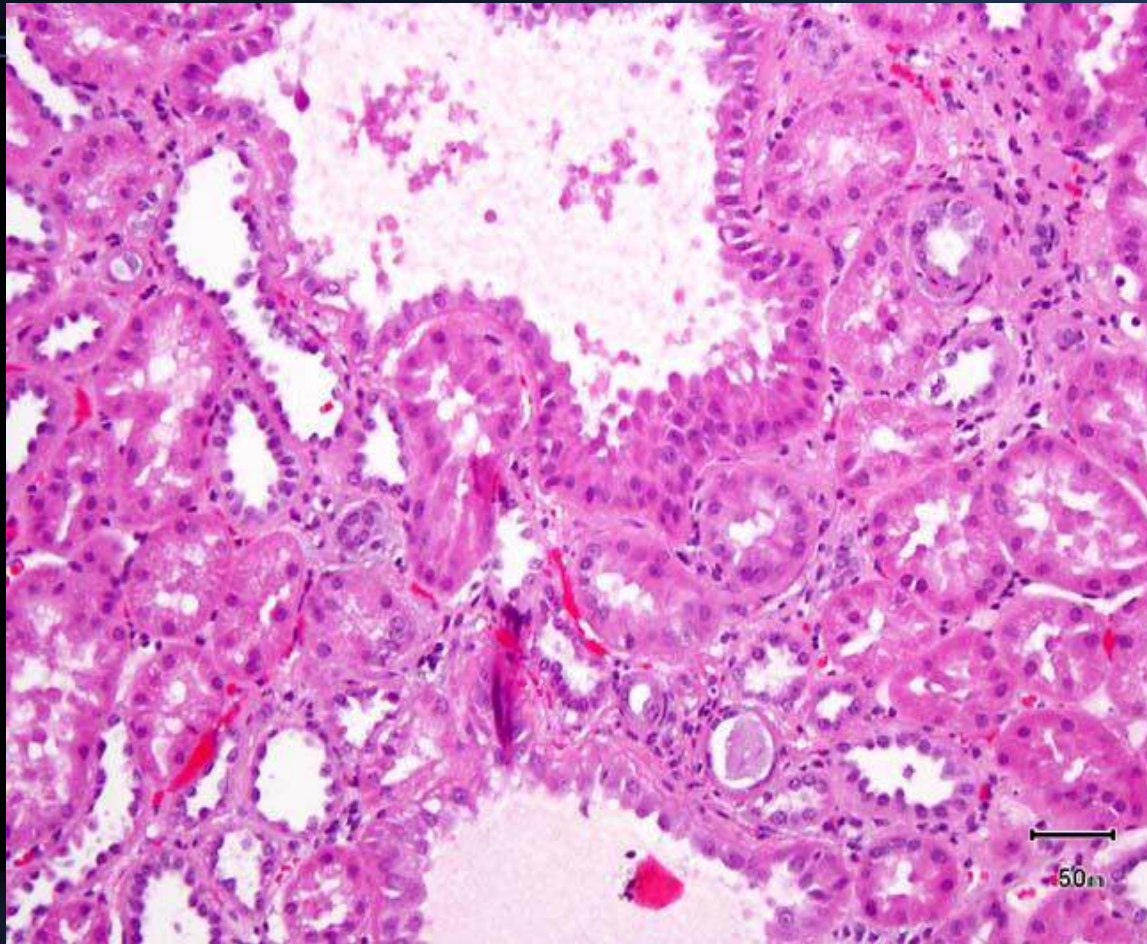




TSC-associated RCC

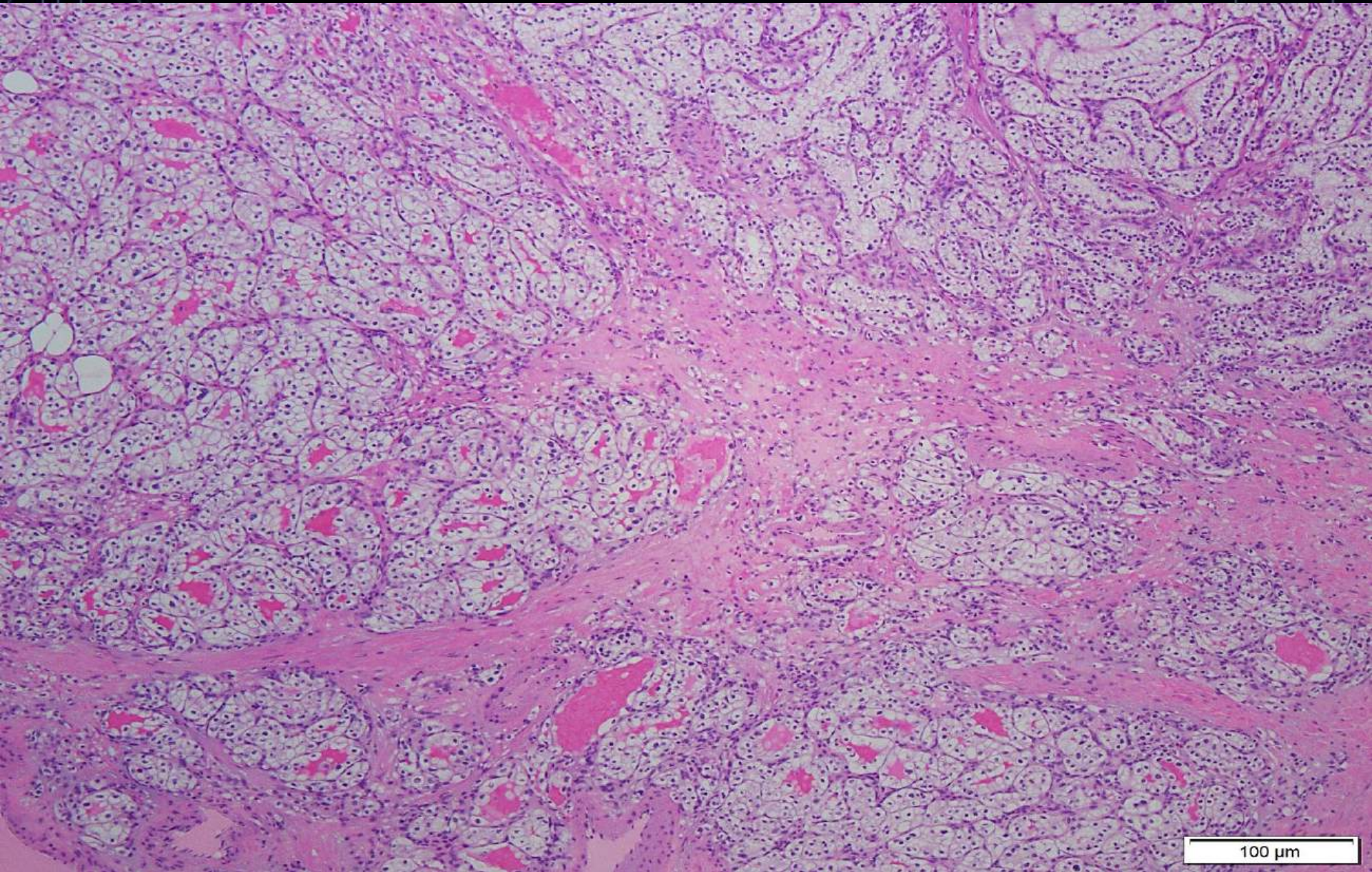


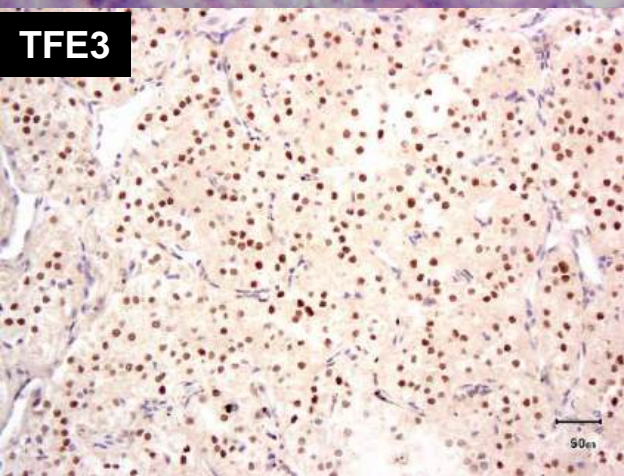
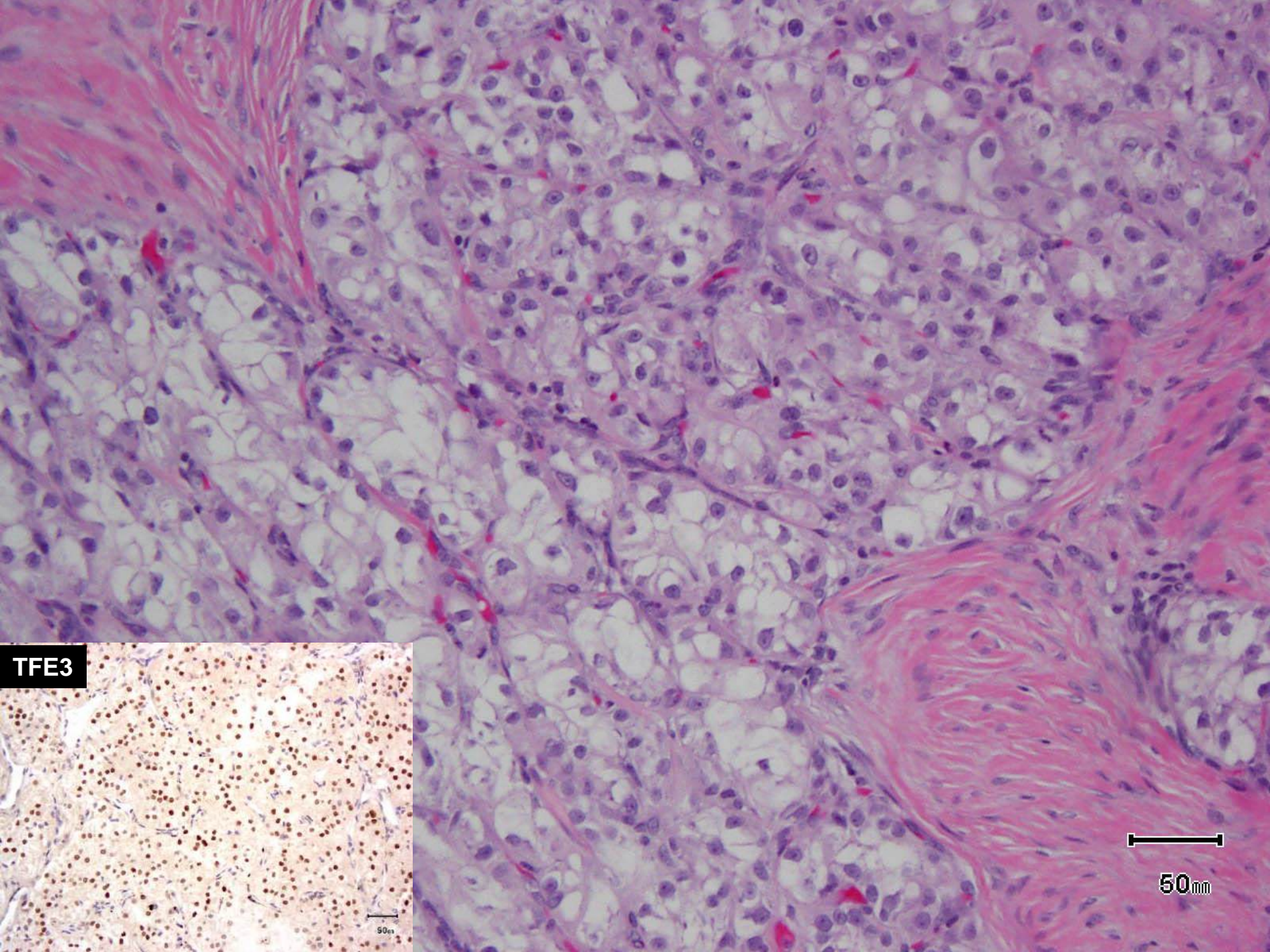
TSC-associated RCC



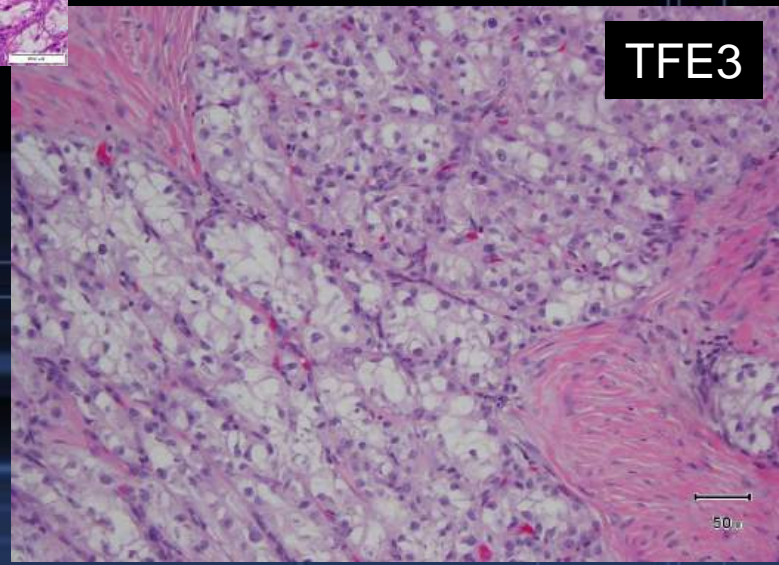
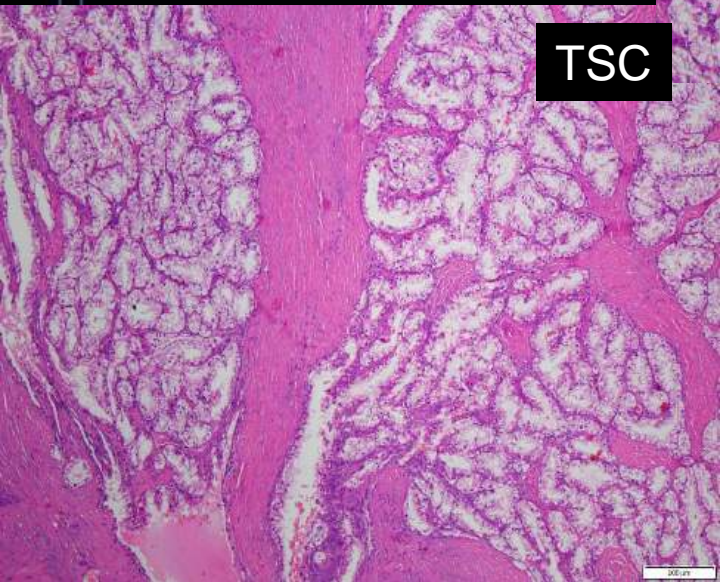
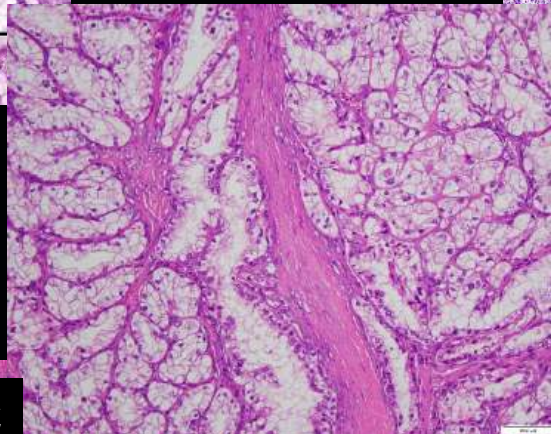
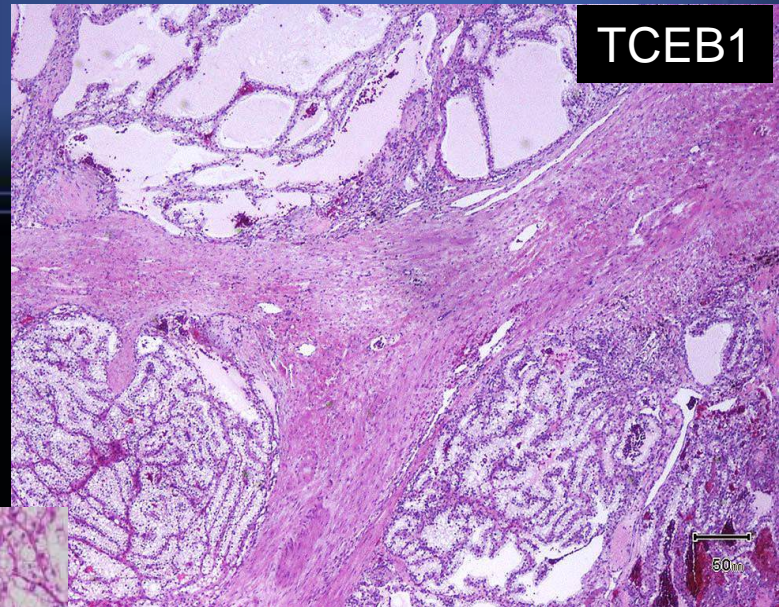
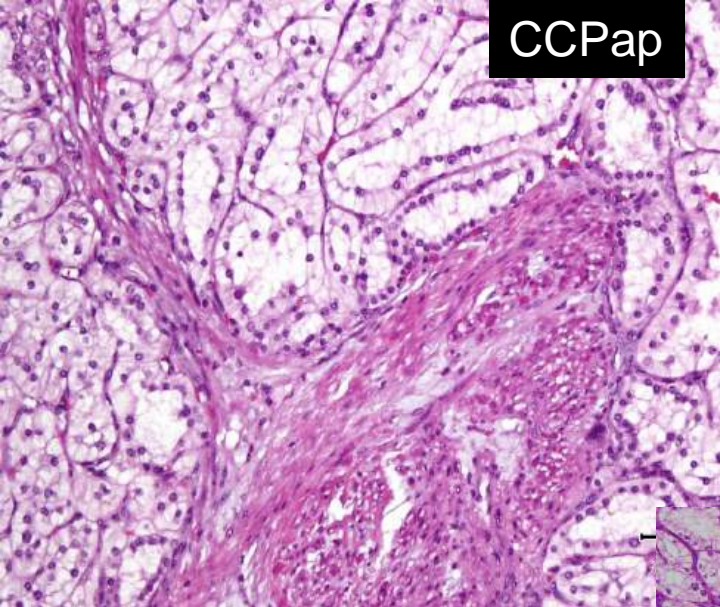
- Multifocality, variable tumor types
- Cysts
- Angiomyolipomas

MiTF/TFE family translocation-associated RCC



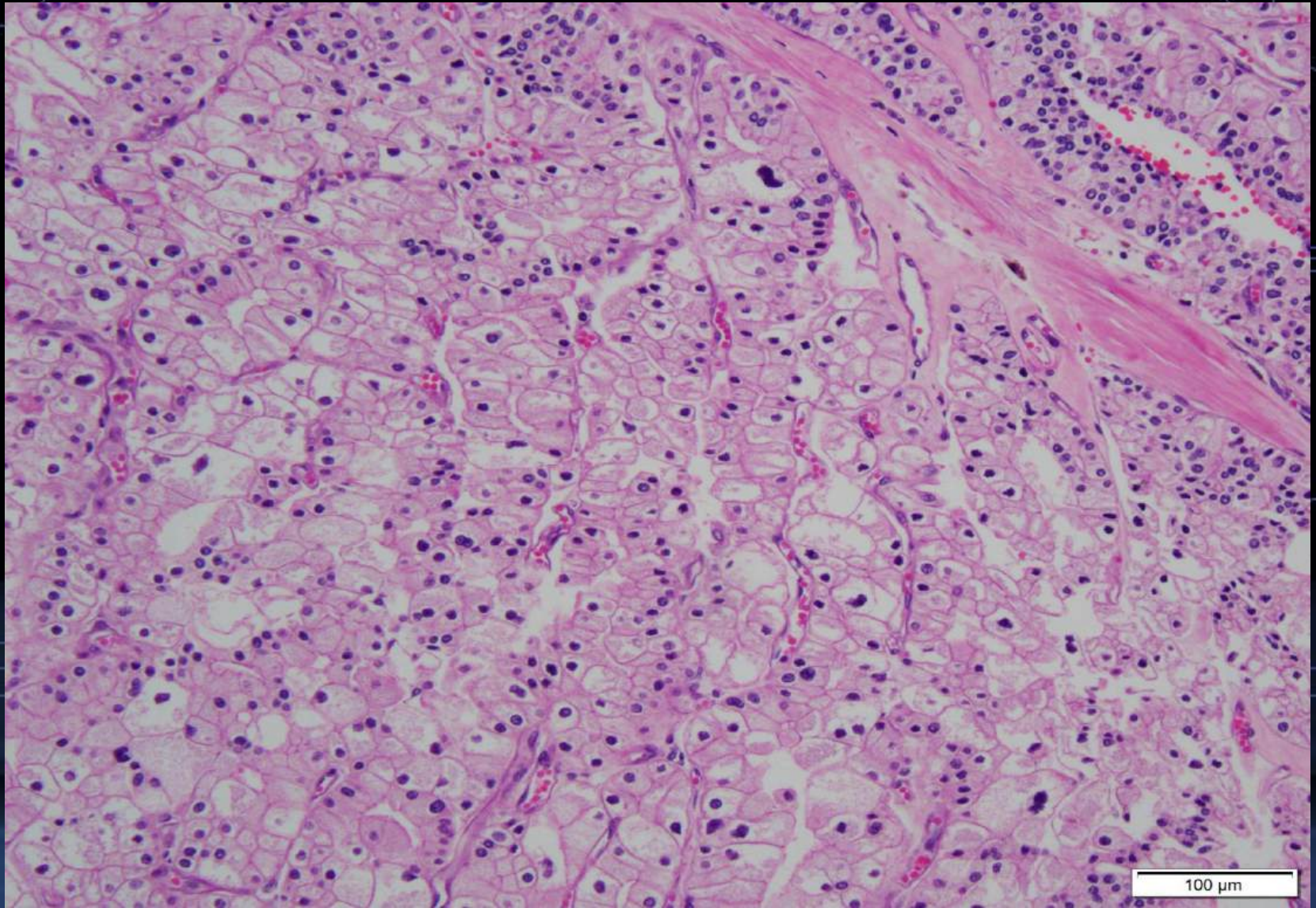


TFE3

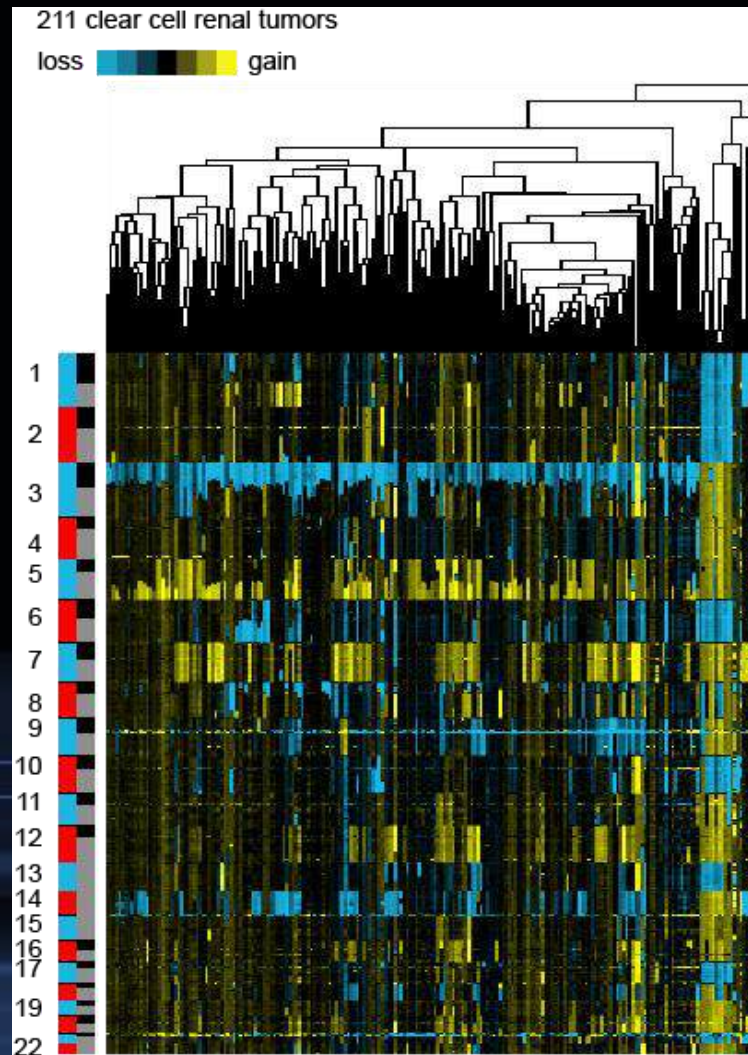


**Clear cell carcinoma with prominent fibromuscular/
leiomyomatous stroma and CK7 positivity**

Chromophobe RCC



Unsupervised clustering of DNA copy number profiles



Clear cell RCC - TCGA

Case Outliers*

Pathology review**

Category	Number
Clear cell/likely clear cell	18
Clear cell papillary	4
Chromophobe/likely chromophobe	15
Oncocytoma/likely oncocytoma	2
Not clear cell or chromophobe	6
Not reviewed	16
Total	61

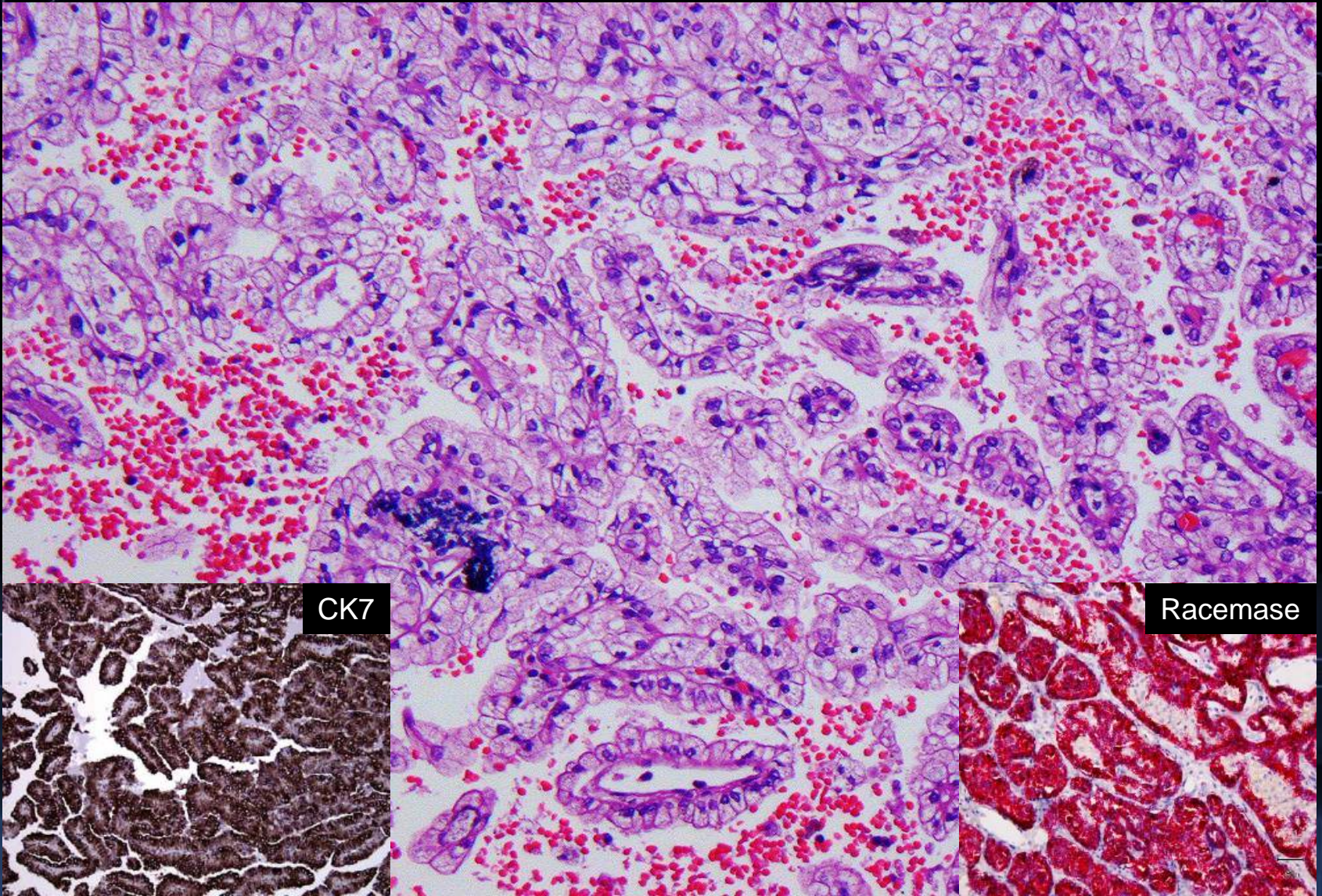
*Outliers:

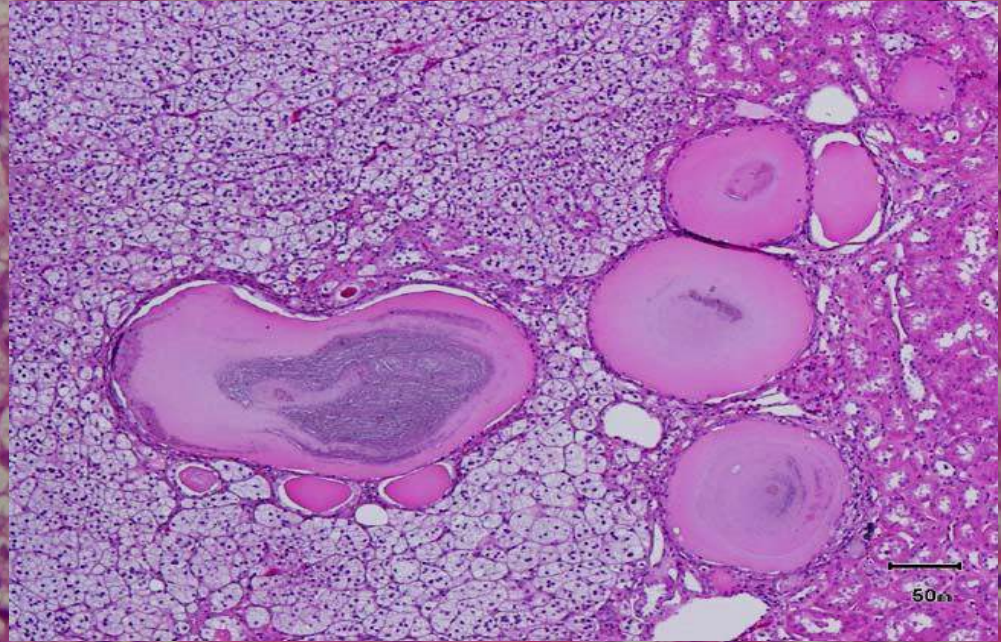
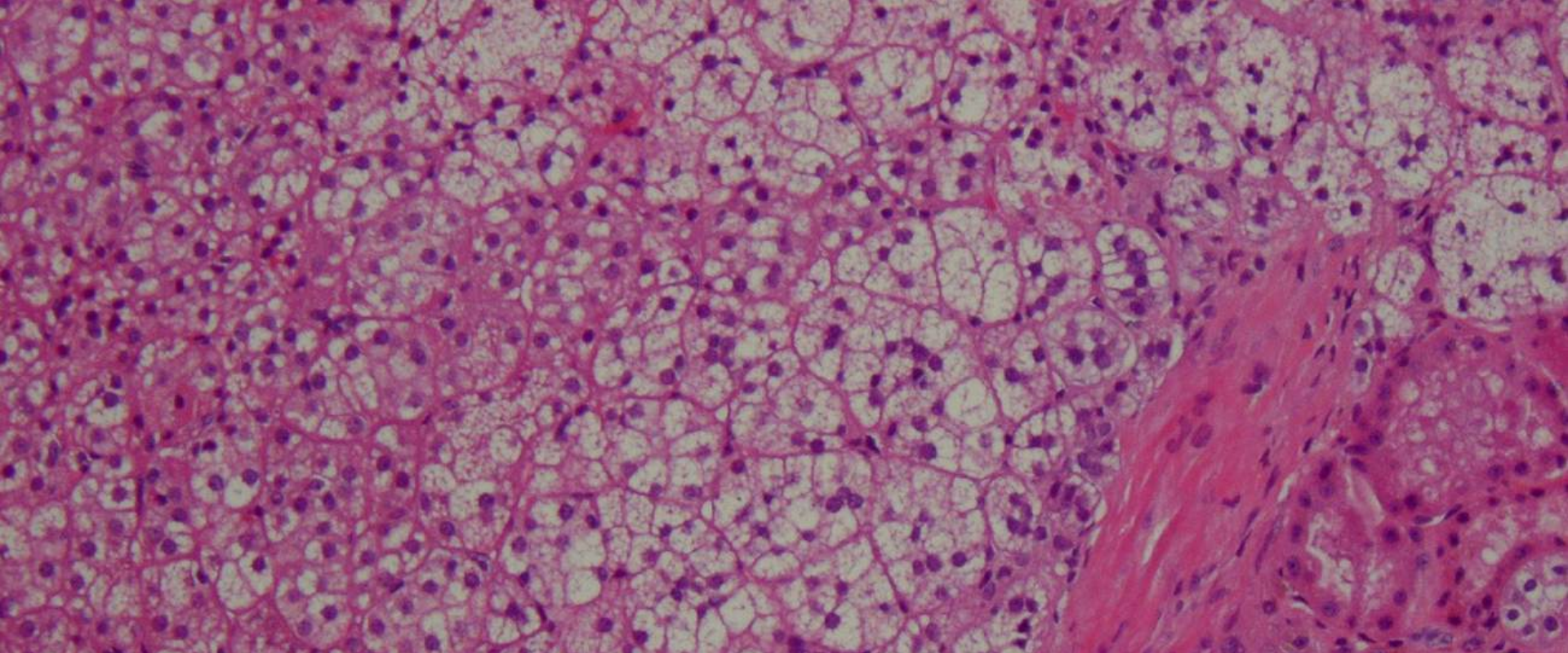
Chomo-like genotype
wtVHL
No 3p loss

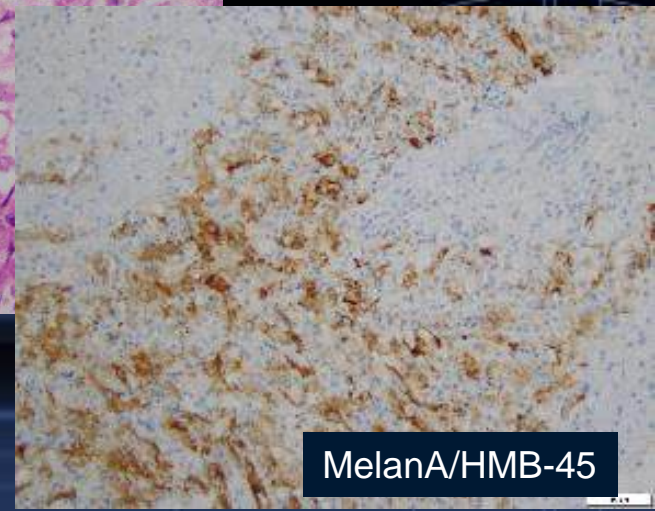
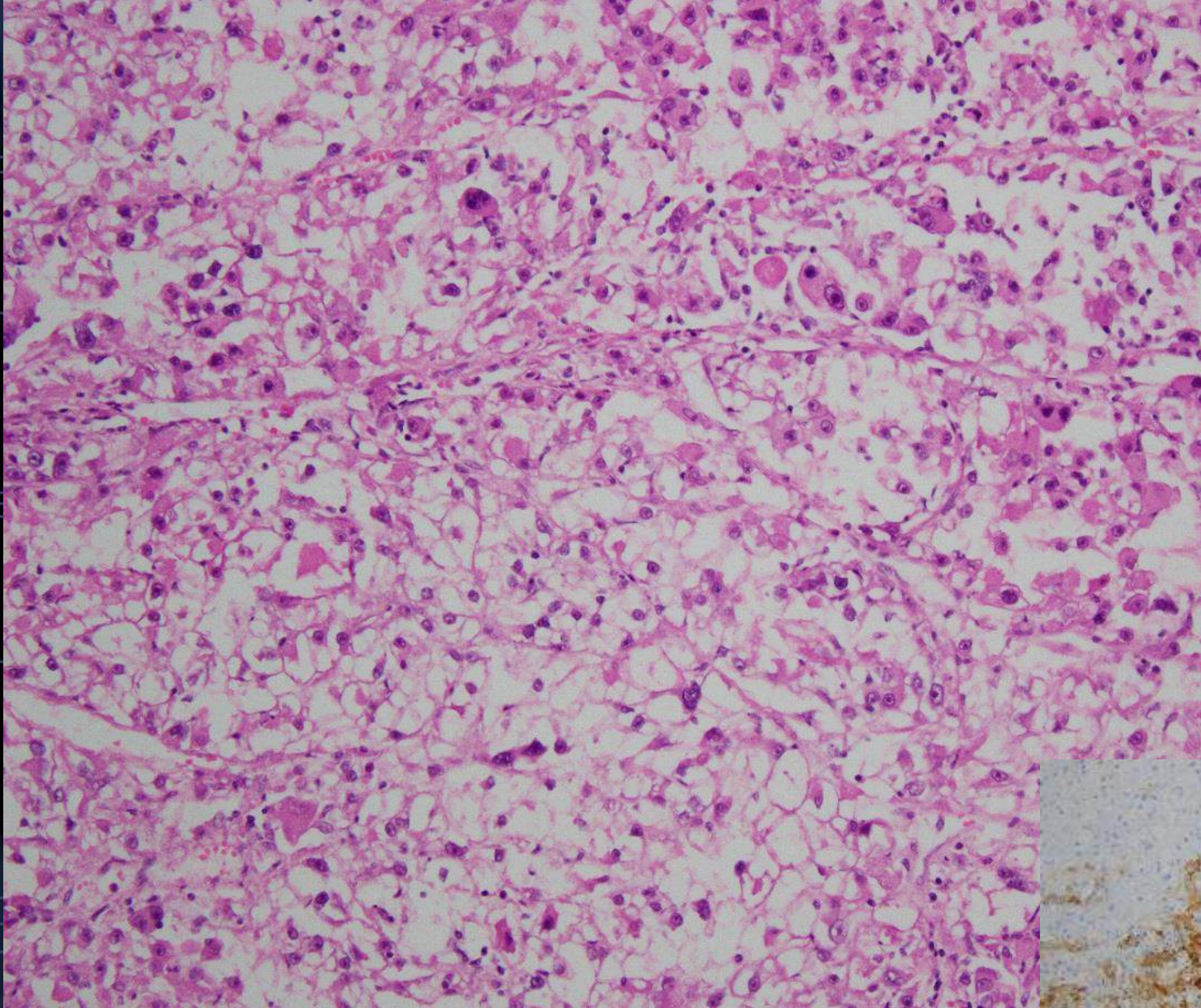
** Pathologists

Victor Reuter (MSKCC)
Satish Tickoo (MSKCC)
Pheroze Tamboli (MDACC)
Maria Merino (NCI)
Sabina Signoretti (DFCC)

Papillary RCC







MelanA/HMB-45

Thank you