APRIL 2021 DIAGNOSIS LIST

21-0401: papillary renal neoplasm with reverse polarity (kidney; GU pathology)
21-0402: mucinous tubular and spindle cell carcinoma (kidney; GU pathology)
21-0403: biphasic squamoid alveolar renal cell carcinoma (kidney; GU pathology)
21-0404: renal papillary neoplasm (kidney; GU pathology)
21-0405: lymphoepithelioma-like carcinoma (ureter; GU pathology)
21-0406: renomedullary interstitial tumor (kidney; GU pathology)
21-0407: MiTF family translocation renal cell carcinoma (kidney; GU pathology)
21-0408: low grade oncocytic tumor (kidney; GU pathology)

Disclosures
April 5, 2021

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REVIEW ARTICLE

Current Management of Small Renal Masses, Including Patient Selection, Renal Tumor Biopsy, Active Surveillance, and Thermal Ablation

Alejandro Sanchez, Adam S. Feldman, and A. Ari Hakimi

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ABSTRACT

Renal cancer represents 2% to 3% of all cancers, and its incidence is rising. The increased use of ultrasonography and cross-sectional imaging has resulted in the clinical dilemma of incidentally detected small renal masses (SRMs). SRMs represent a heterogeneous group of tumors that span the full spectrum of metastatic potential, including benign, indolent, and more aggressive tumors. Currently, no composite model or biomarker exists that accurately predicts the diagnosis of kidney cancer before treatment selection, and the use of renal mass biopsy remains controversial. The management of SRMs has changed dramatically over the last two decades as our understanding of tumor biology and competing risks of mortality in this population has improved. In this review, we critically assess published consensus guidelines and recent literature on the diagnosis and management of SRMs, with a focus on patient treatment selection and use of renal mass biopsy, active surveillance, and thermal ablation. Finally, we highlight important opportunities for leveraging recent research discoveries to identify patients with SRMs at high risk for renal cell carcinoma–related mortality and minimize overtreatment and patient morbidity.

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Table 1. Review of Published Guideline Recommendations for the Use of RMB in Localized RCC

Guideline	Indications for RMB	Recommendation Against RMB
ASCO, 2017[3]	All SRMs should be considered for RMB when the results may alter management	Predominantly cystic renal masses
	Consider when a mass is suggestive of lymphoma, metastasis, infectious/inflammatory	Renal masses originating from the collecting system or suggestive of urothelial carcinoma
	Not necessary before entering AS protocols	
	Should be performed before TA (as separate procedure)	
AUA, 2017[22]	Consider when a mass is suggestive of hematologic, metastasis, or infectious/inflammatory	Young or healthy individuals unwilling to accept the uncertainties associated with RMB
	Counsel individuals about rationale, positive and negative predictive values, potential risks, and nondiagnostic rates	Frail or older patients who will be managed conservatively regardless of RMB findings
	Before TA for pathologic diagnosis and to guide surveillance	
	Consider after initial 3- to 6-month imaging with AS for further risk stratification	
NCCN, 2017[30]	Consider RMB to obtain or confirm a diagnosis of malignancy and guide AS and TA strategies	Not discussed
	Consider if urothelial carcinoma is suspected (eg, central) or lymphoma (eg, homogenous infiltration)	
EAU, 2015[23]	All patients who are considered for AS protocols	Cystic renal masses
	Before TA for pathologic diagnosis and to guide surveillance	Comorbid or frail patients who will be managed conservatively regardless of RMB findings
		Not required if surgery is planned

Abbreviations: AS, active surveillance; AUA, American Urological Association; EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network; RCC, renal cell carcinoma; RMB, renal mass biopsy; SRM, small renal mass; TA, thermal ablation.

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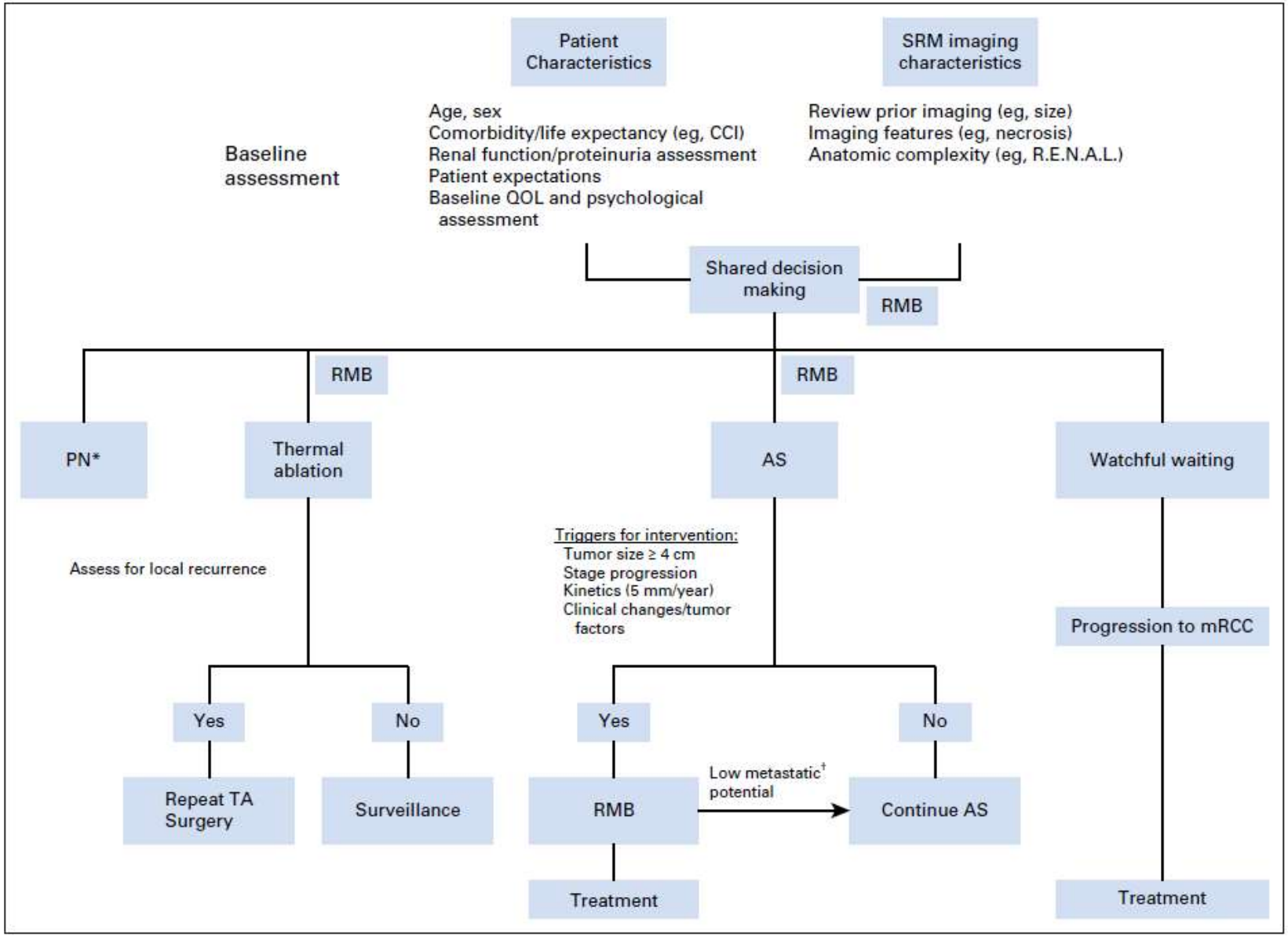


Fig 1. Suggested algorithm for the management of small renal masses (SRMs). Renal mass biopsy (RMB) depicts clinical scenarios in which RMB can be considered. (*) When technically feasible. (†) Benign pathology, chromophobe, papillary type 1, or Fuhrman grade 1 to 2 metastatic renal cell carcinoma (mRCC). AS, active surveillance; CCI, Charlson Comorbidity Index; PN, partial nephrectomy; QOL, quality of life; RCC, renal cell carcinoma; TA, thermal ablation.

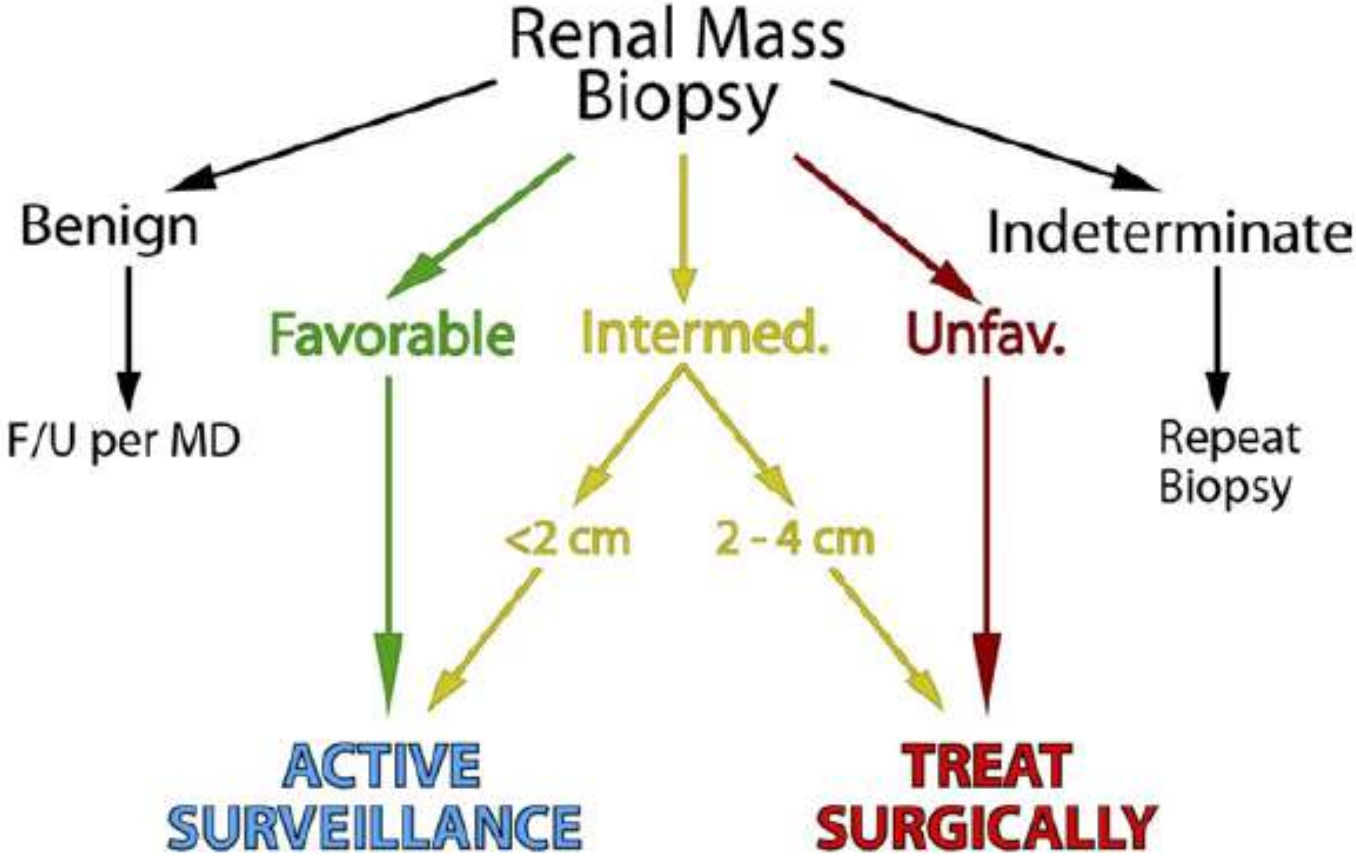
J Clin Oncol 36:3591-3600.

Renal mass biopsies

- **Generally good concordance with resection specimen**
  - Benign vs indeterminant vs malignant
- **Less aggressive management**
  - Generally obsolete risk of “tumor seeding”
  - Ablation Tx, surveillance
- **Offers molecular diagnostic & therapeutic opportunities**
  - Clinical trials, (neo)adjuvant therapy

Accuracy of Determining Small Renal Mass Management with Risk Stratified Biopsies: Confirmation by Final Pathology

Schuyler J. Halverson,* Lakshmi P. Kunju,* Ritu Bhalla,* Adam J. Gadzinski,* Megan Alderman,* David C. Miller,† Jeffrey S. Montgomery,* Alon Z. Weizer,* Angela Wu,* Khaled S. Hafez* and J. Stuart Wolf, Jr.*,‡

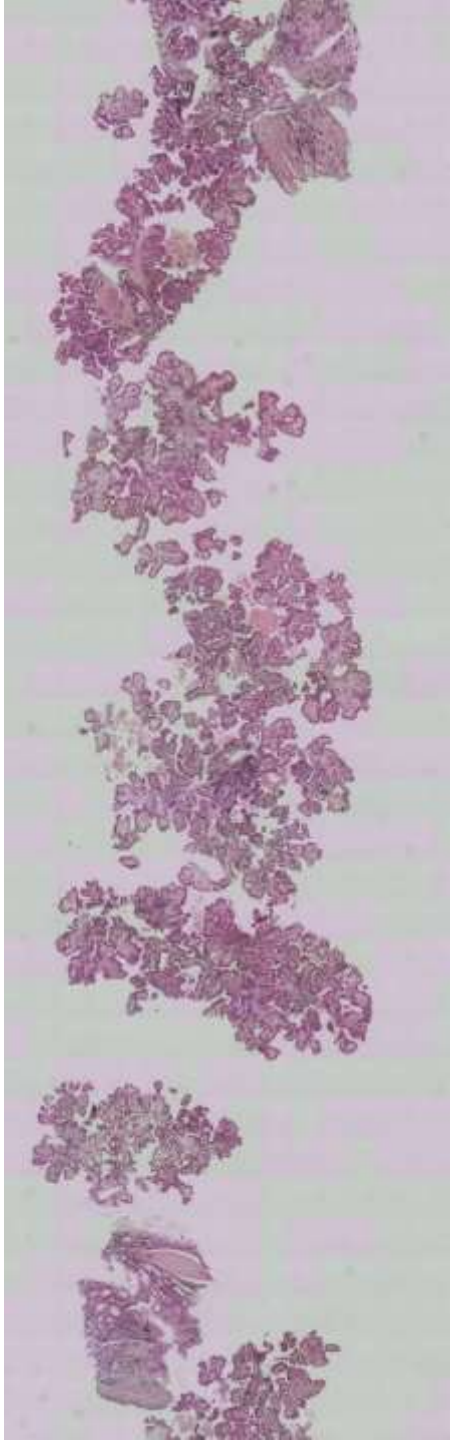


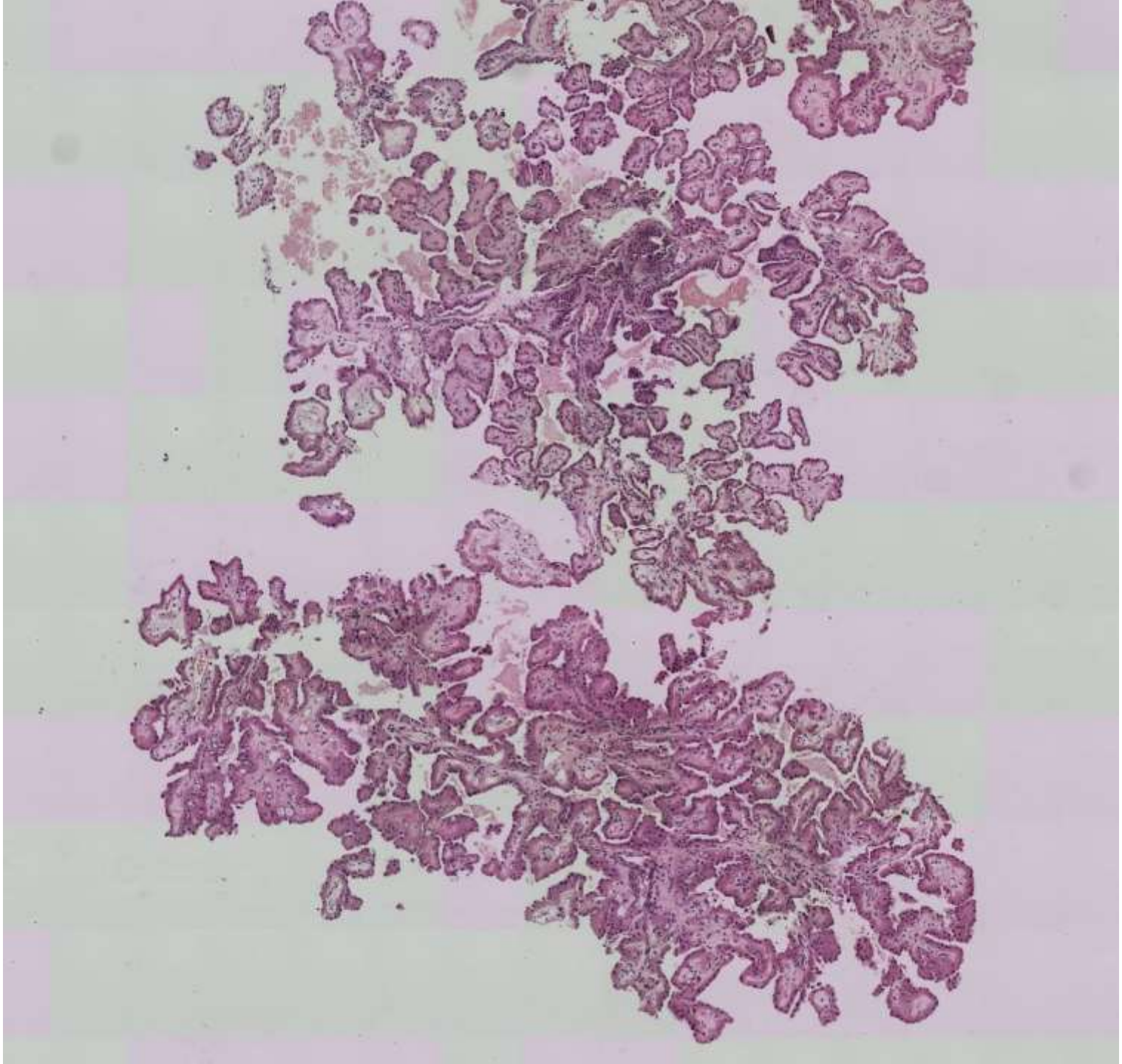
THE JOURNAL OF UROLOGY®
Vol. 189, 441-446, February 2013

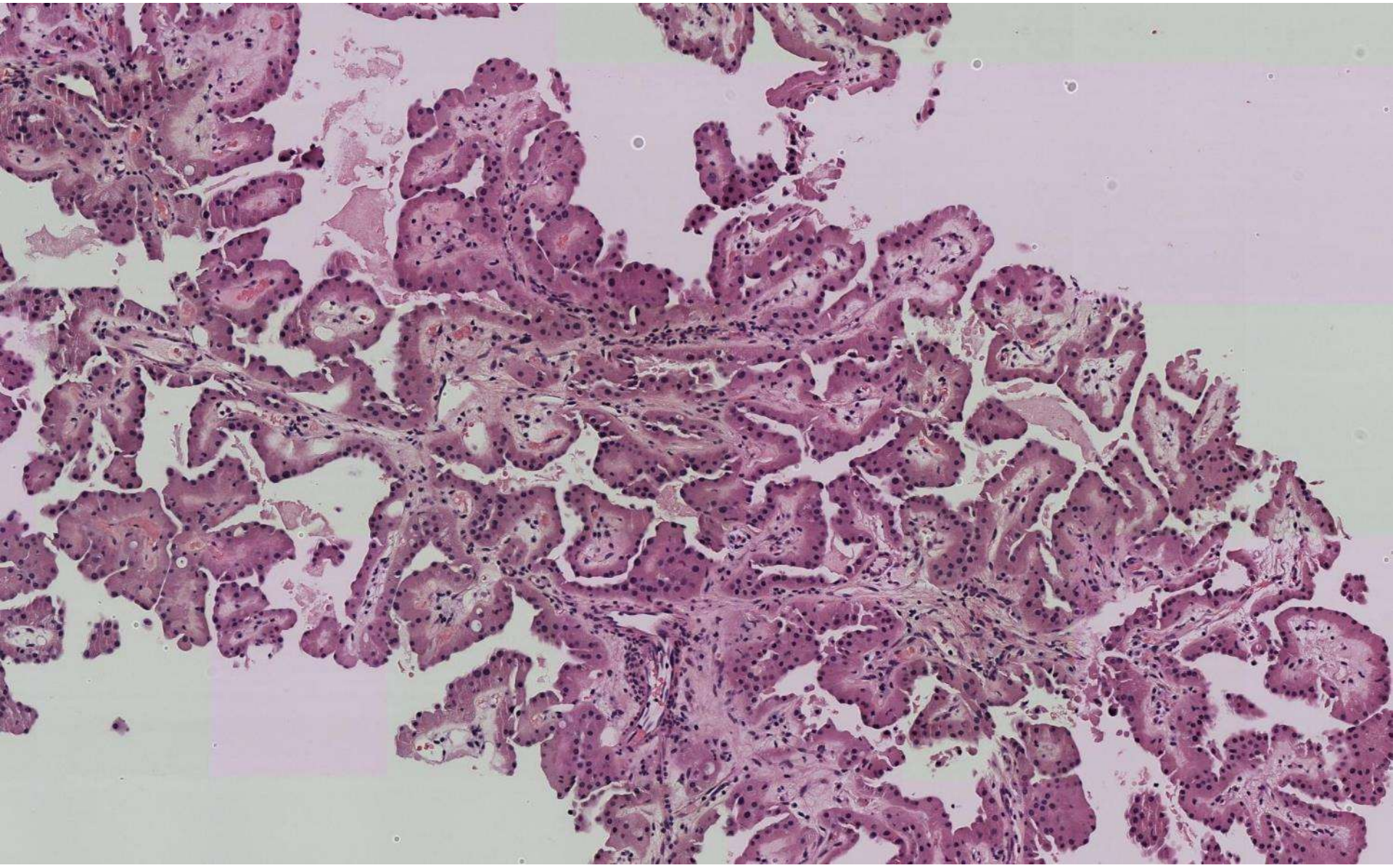
21-0401
scanned slide avail!

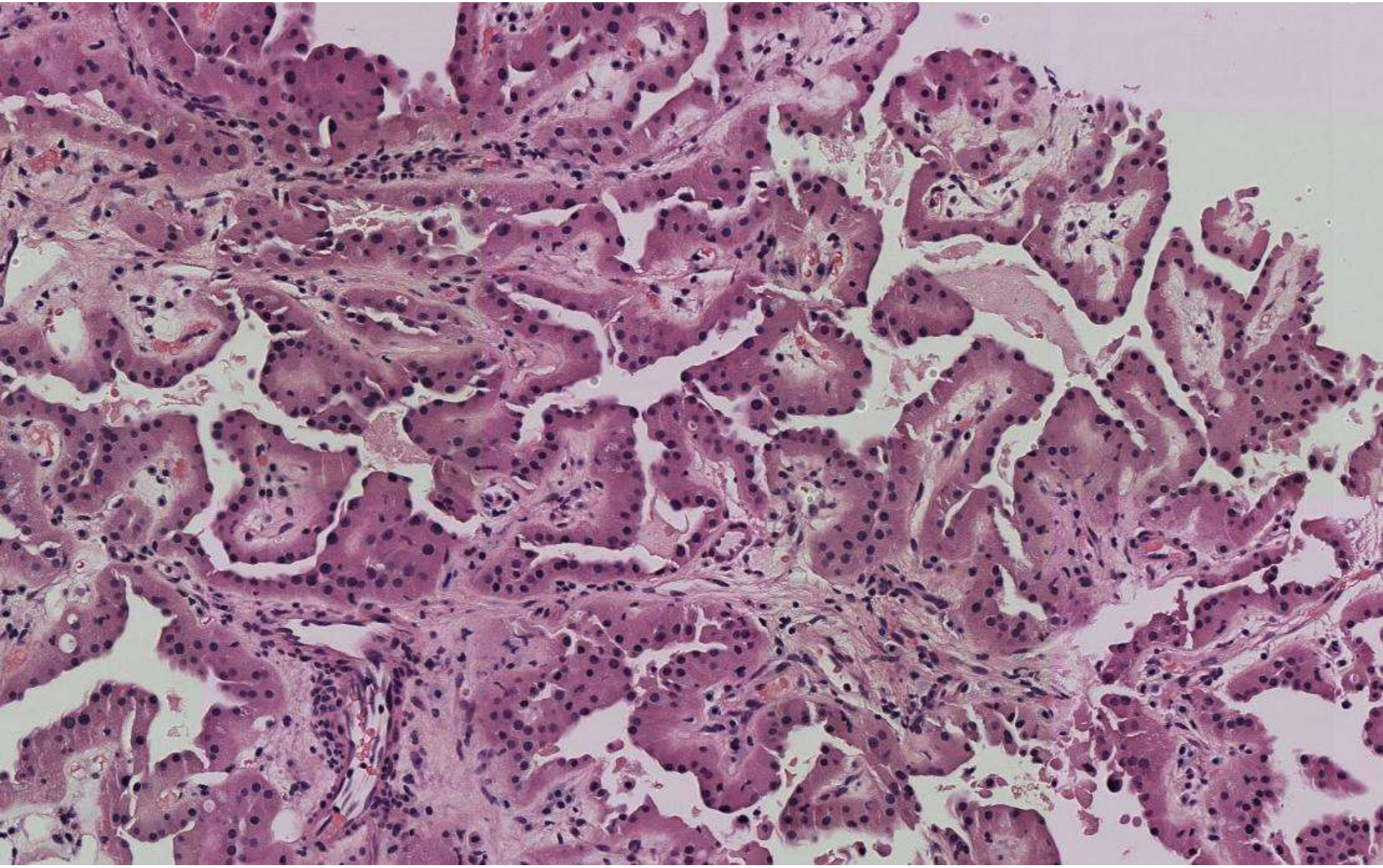
Ankur Sangoi; El Camino Hospital

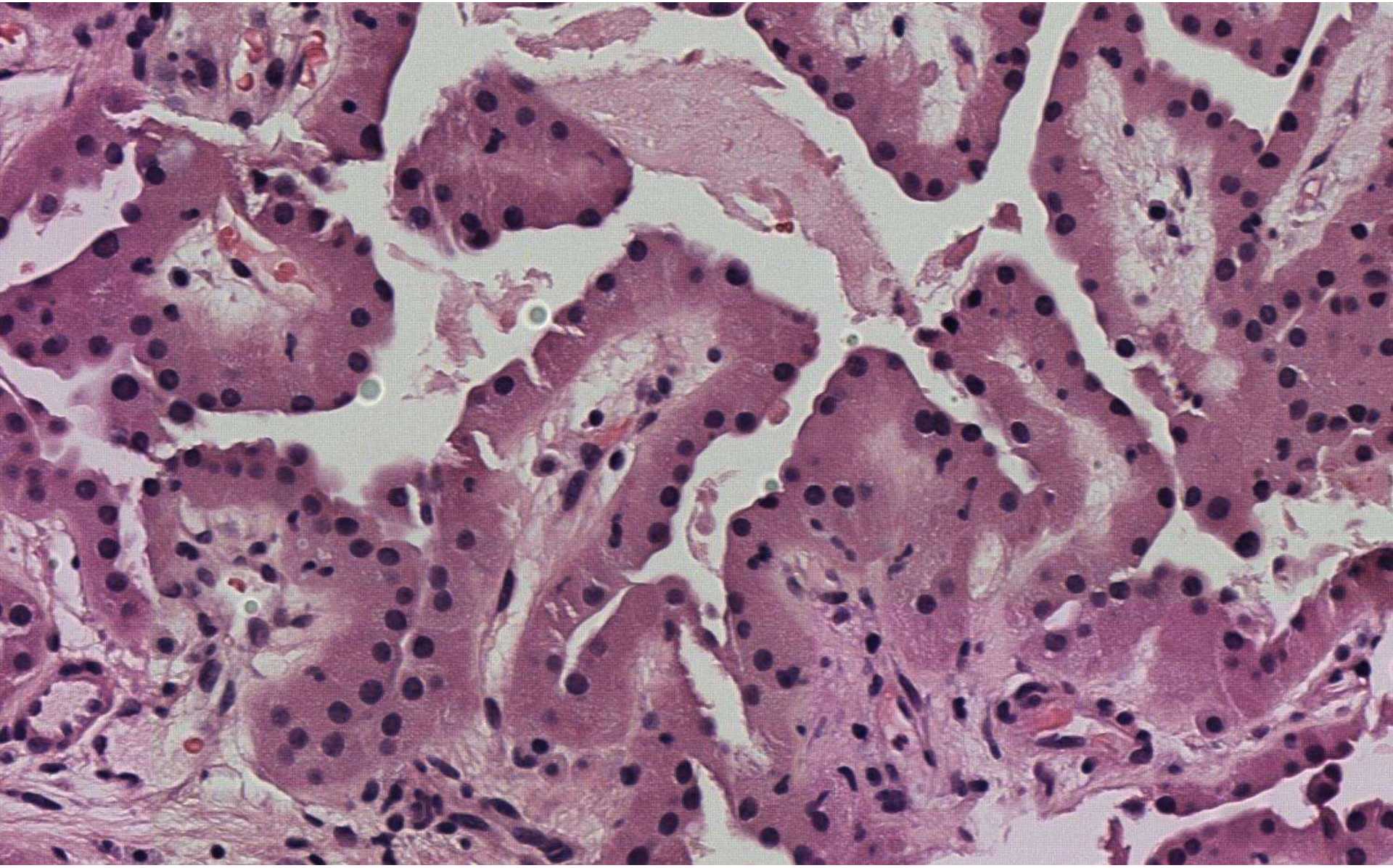
Adult F with kidney mass, core biopsy performed.





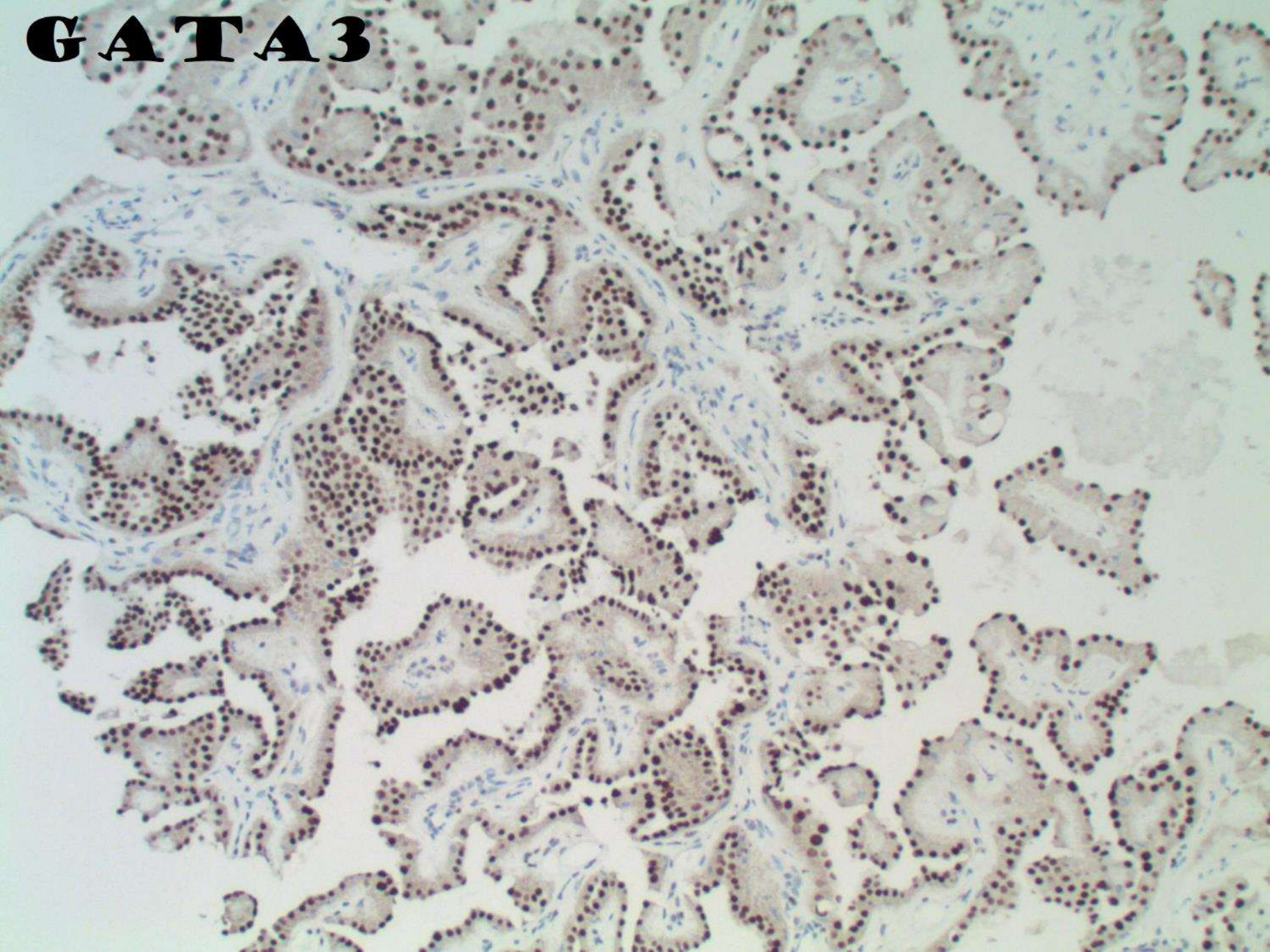


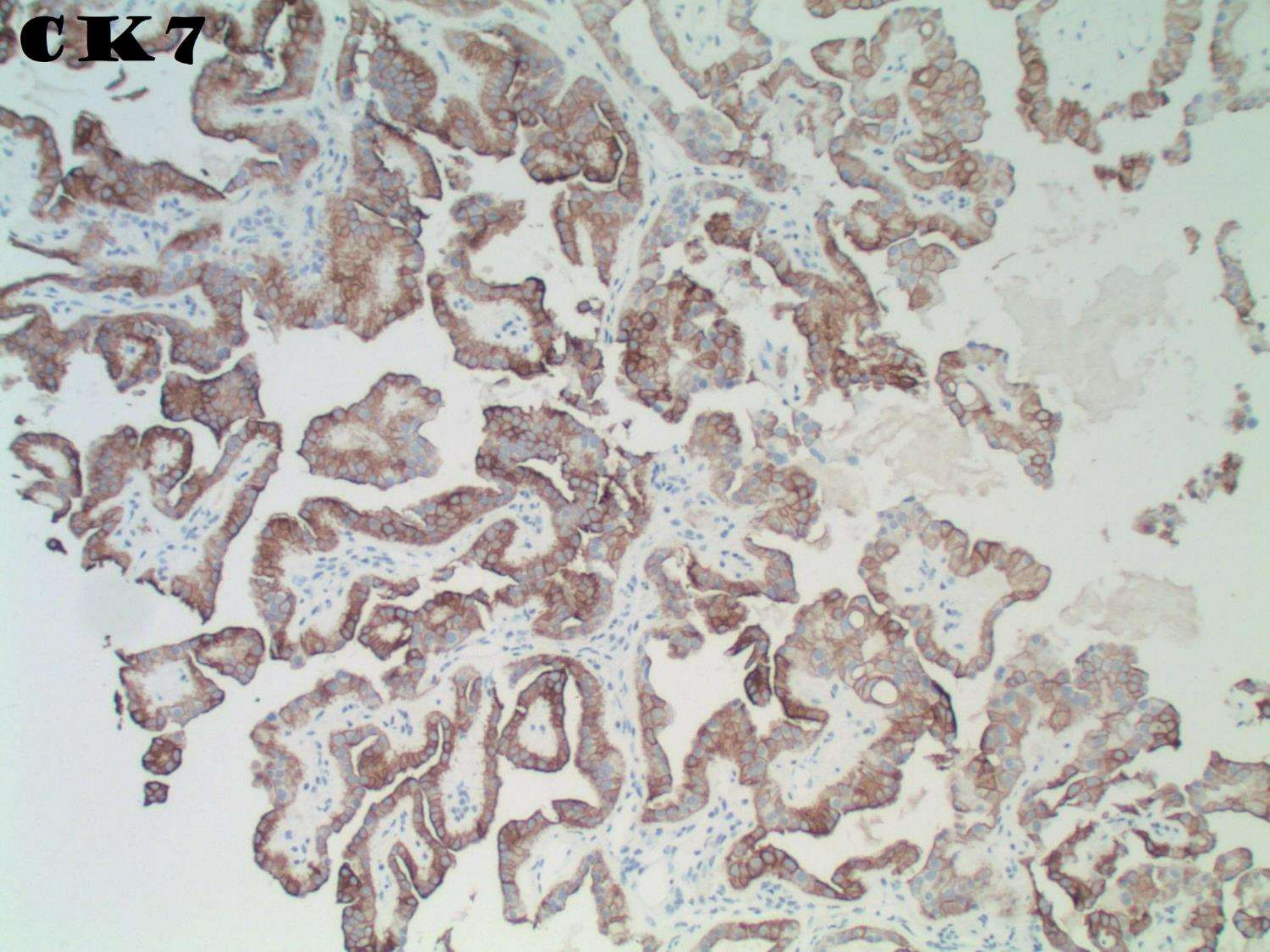


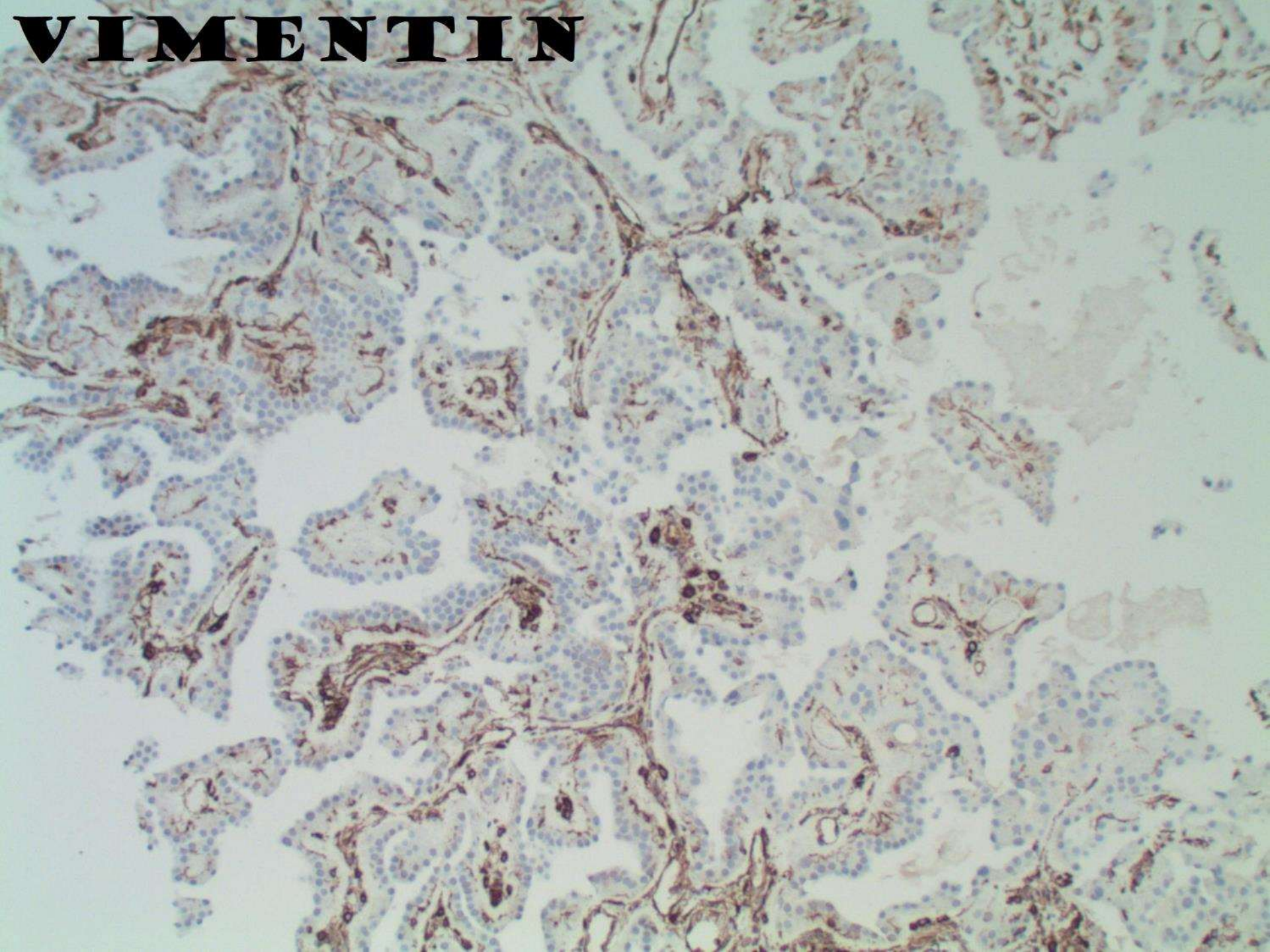


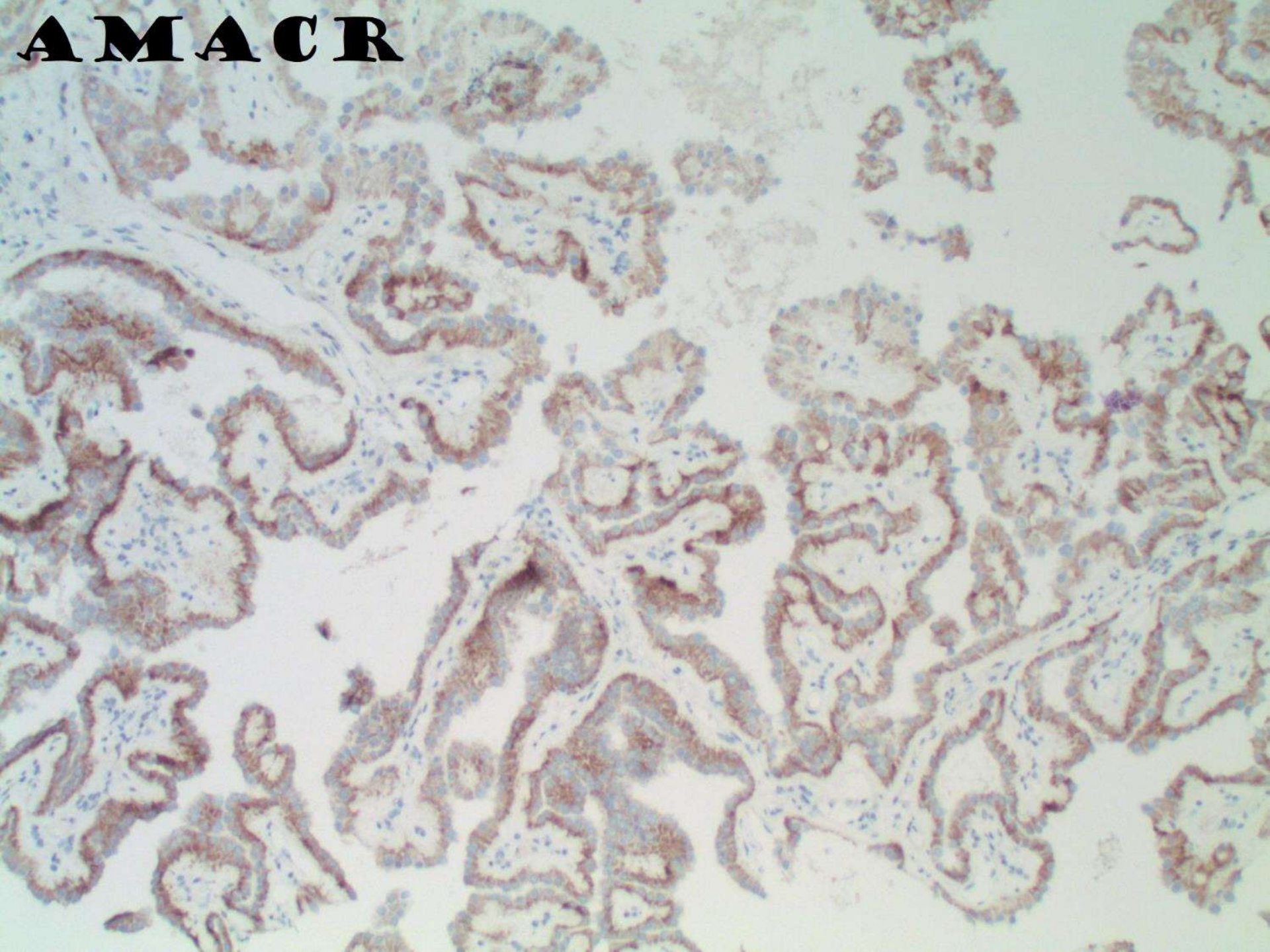
DDx

- **MALIGNANT**
  - papillary RCC
  - clear cell papillary (tubulopapillary) RCC
  - tubulocystic RCC
  - MiTF/Xp11 RCC
  - FH-deficient RCC
- **BENIGN**
  - papillary adenoma
  - atypical renal cyst
  - distal tubular hyperplasia


GATA3


CK7


VIMENTIN

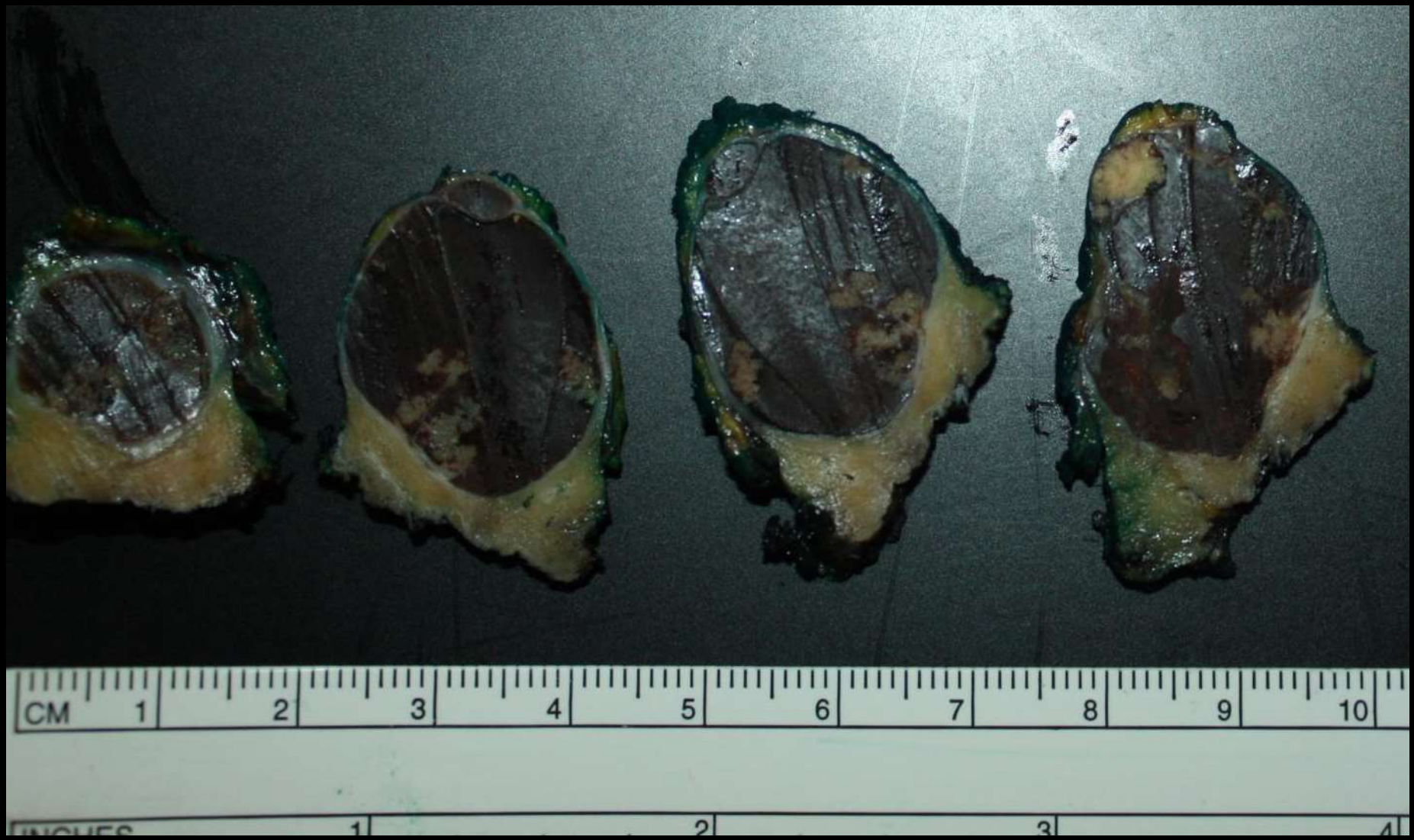

AMACR

Final Dx:

Papillary renal cell neoplasm with reverse polarity

- **Artists formerly known as:**

  - oncocytic low grade papillary renal cell carcinoma
  - type 4 papillary renal carcinoma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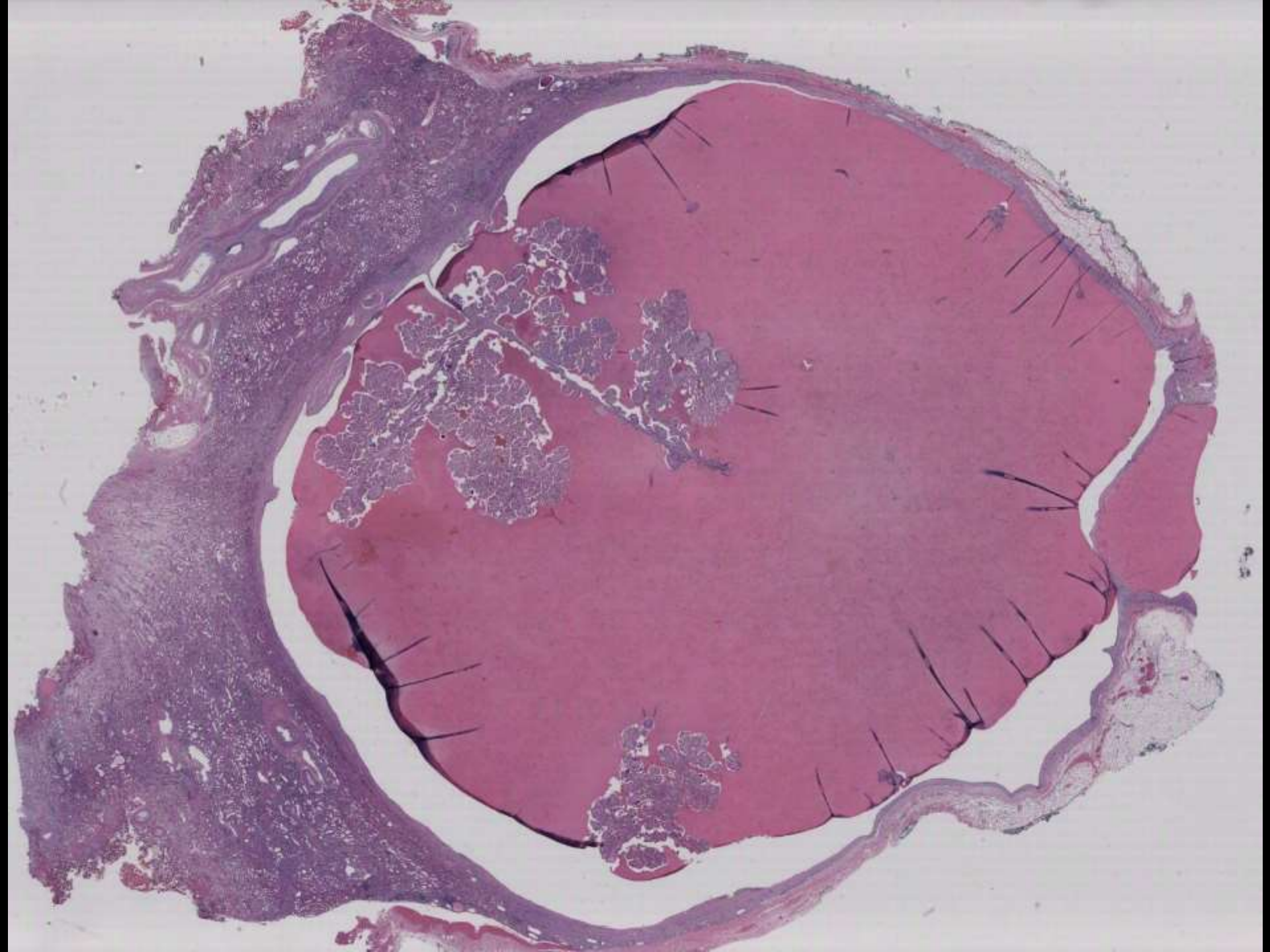
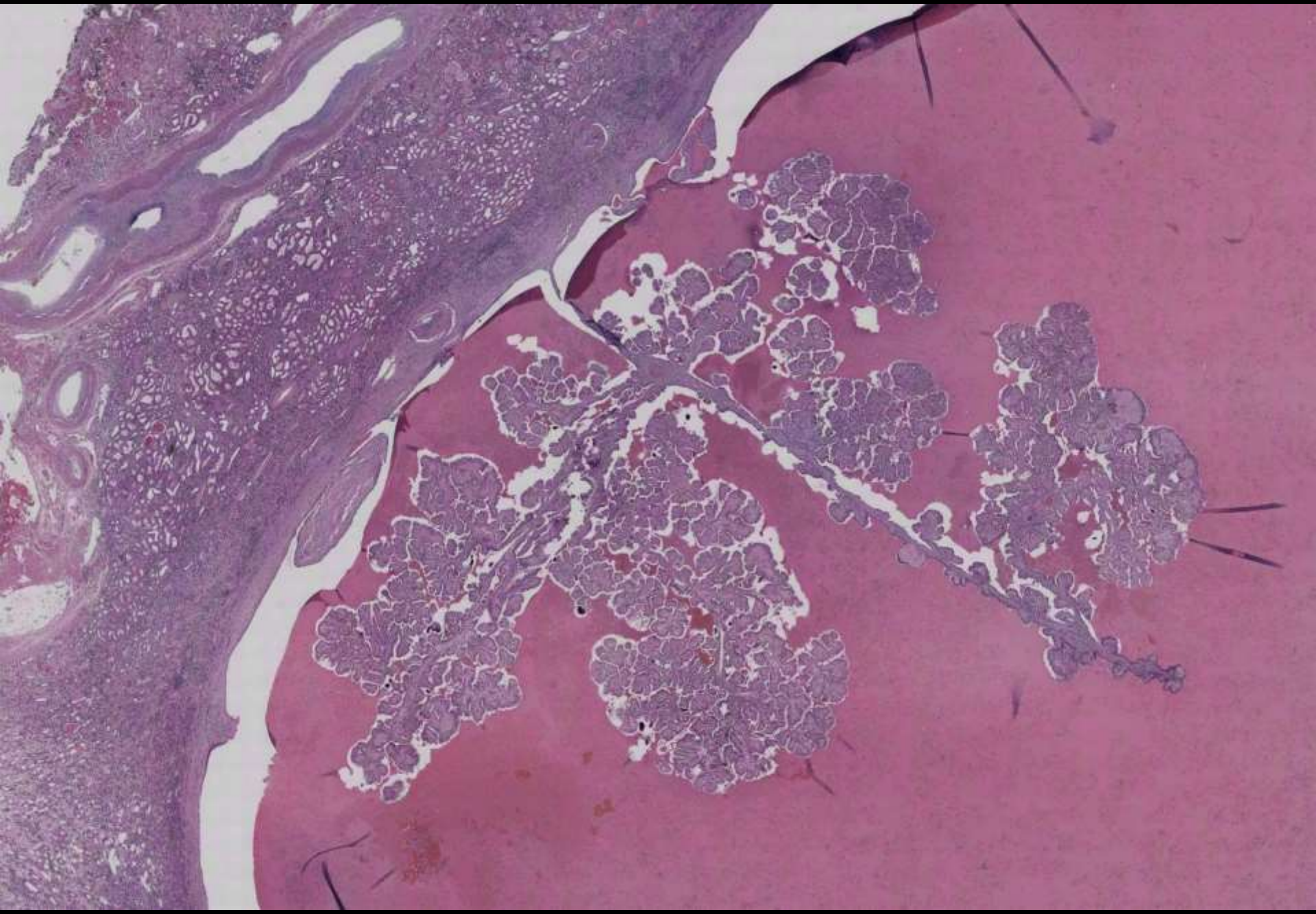




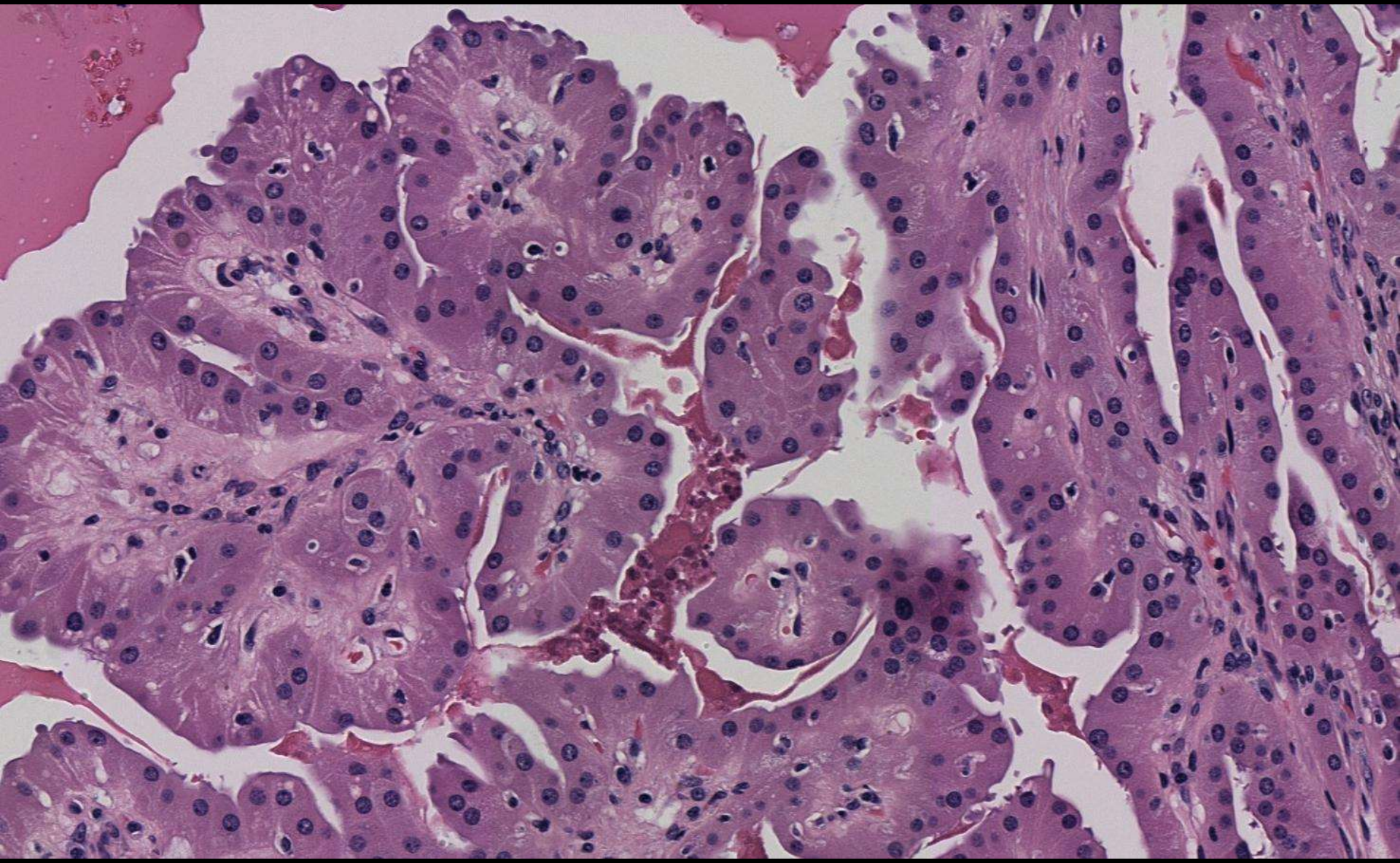
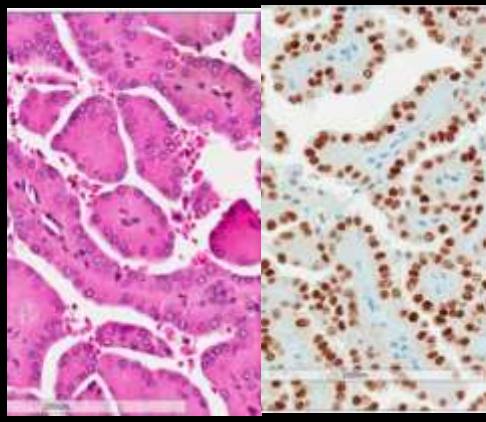


TABLE 1. Morphological Characteristics of the 4 PRCC Subtypes

Features	PRCC1	PRCC2	PRCC3	PRCC4/OLG
Cytoplasmic quantity	Scant, occasionally moderate	Abundant	Moderate	Abundant
Cytoplasmic color	Basophilic or eosinophilic or clearing	Eosinophilic or clearing	Eosinophilic, or clearing	Oncocytic eosinophilic
Cell size	Small to intermediate	Large	Intermediate	Large
Nucleolar prominence at ×10	Inconspicuous, rarely prominent	Very prominent	Often prominent	Inconspicuous, rarely prominent
% nucleolar prominence at ×10	If present <5	30-100	10-70	If present <5
Nuclear pseudostratification (presence or absence)	Absent	Mostly present, occasionally absent	Mostly absent, occasionally present	Absent. Linear. Nuclei arranged away from base of the cells
Nuclear size	Small	Large	Small to intermediate	Intermediate
Nuclear shape	Elongated oval (angulations and grooves) or round	Mostly round	Round or elongated	Round
Chromatin (open or closed)	Closed or open	Open vesicular nuclei, rarely focal areas with closed chromatin	Open, rarely closed	Open
ISUP nucleolar grade	1-2, very rarely focal 3	Mostly 3	Mostly 3	1-2
Foamy macrophages	Present or absent	Present or absent	Present or absent	Absent
ABCC2 IHC	Negative	Strong diffuse positive	Weaker patchy positive	Strong diffuse positive
CA9 IHC	Negative	Positive Golgi pattern (perinuclear dot)	Negative	Negative
GATA3 IHC	Negative	Negative	Negative	Positive



Am J Surg Pathol • Volume 41, Number 12, December 2017

Papillary Renal Neoplasm With Reverse Polarity

A Morphologic, Immunohistochemical, and Molecular Study

Khaleel I. Al-Obaidy, MD, John N. Eble, MD,* Liang Cheng, MD,* Sean R. Williamson, MD,† Wael A. Sakr, MD,‡ Nilesh Gupta, MD,† Muhammad T. Idrees, MBBS,* and David J. Grignon, MD**

Abstract: We evaluated the clinicopathologic and chromosomal characteristics of a distinct subset of papillary renal tumors and compared them to a control series of papillary renal cell carcinoma types 1 and 2. Of the 18 patients, 9 were women and 9 were men, ranging in age from 46 to 80 years (mean, 64 y; median, 66 y). The tumors ranged in diameter from 0.6 to 3 cm (mean, 1.63 cm; median, 1.4 cm). Fourteen tumors were WHO/ISUP grade 2 and 4 were grade 1. All were stage category pT1. The tumors had branching papillae with thin fibrovascular cores, covered by cuboidal to columnar cells with granular eosinophilic cytoplasm, smooth luminal borders, and mostly regular and apically located nuclei with occasional nuclear clearing and inconspicuous nucleoli. Tubule formation and clear cytoplasmic vacuoles were observed in 5 and 9 tumors, respectively. Ten tumors had pseudocapsules. Psammoma bodies, necrosis, mitotic figures and intracellular hemosiderin are absent from all tumors. In contrast, papillary renal cell carcinoma type 1 consisted of delicate papillae covered by a single layer of cells with scanty pale cytoplasm with nuclei generally located in a single layer on the basement membrane of the papillary cores, while type 2 tumors had broad papillae covered by pseudostratified cells with eosinophilic cytoplasm and more randomly located nuclei. Both had occasional psammoma bodies, foamy macrophages and intracellular hemosiderin. Immunohistochemically, all were positive for pancytokeratin AE1/AE3, epithelial membrane antigen, MUC1, CD10, GATA3, and L1CAM. Cytokeratin 7 was positive in 16 tumors (1 had <5% positivity). CD117 and vimentin were always negative. α-methylacyl-CoA-racemase (AMACR/p504s) showed variable staining (range, 10% to 80%) in 5 tumors. However, all tumors in the control group were negative for GATA3 and positive for AMACR/p504s and vimentin immunostains. Fluorescence in situ hybridization analysis of the study group demonstrated chromosome 7 trisomy in 5 tumors (33%), trisomy 17 in 5 tumors (33%), and trisomy 7 and 17 in 3 tumors (20%). Chromosome Y deletion was found in 1 of 7 male patients and chromosome 3p was present in all tumors. No tumor recurrence or metastasis occurred. In summary, we propose the term papillary renal neoplasm with reverse polarity for this entity.

Key Words: papillary renal cell carcinoma, oncocytic papillary renal cell carcinoma, renal cell neoplasm, renal cell carcinoma, reverse polarity

(*Am J Surg Pathol* 2019;43:1099–1111)

Since 1997, papillary renal cell carcinoma has been classified into types 1 and 2 based on morphologic features.[1] This categorization has been significant in term of patients' outcome. Patients with type 2 have a worse prognosis and tend to present at a higher stage than patients with type 1.[1,2] In the same year, the distinction between papillary adenoma and carcinoma based on size and architecture was proposed.[3] Subsequently, studies highlighting the genetic differences between papillary renal cell carcinoma types 1 and 2 have been published. These in part, explain some of the differences in morphology and clinical outcomes between the two, and the heterogeneity observed in papillary renal cell carcinoma type 2. This has been noted in the 2016 WHO classi-

Recurrent *KRAS* mutations in papillary renal neoplasm with reverse polarity

Khaleel I. Al-Obaidy[1] · John N. Eble[1] · Mehdi Nassiri[1] · Liang Cheng[1] · Mohammad K. Eldomery[1] · Sean R. Williamson[2] · Wael A. Sakr[3] · Nilesh Gupta[2] · Oudai Hassan[2] · Muhammad T. Idrees[1] · David J. Grignon[1]

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Abstract

We recently proposed that an epithelial renal tumor "papillary renal neoplasm with reverse polarity" represents a distinct entity. It constituted 4% of previously diagnosed papillary renal cell carcinoma at the participating institutions. Histologically, it is characterized by papillary or tubulopapillary architecture covered by a single layer of eosinophilic cells with finely granular cytoplasm and apically located nuclei. It is characteristically positive for GATA3 and L1CAM and lack vimentin and, to a lesser extent, α-methylacyl-CoA-racemase (AMACR/p504s) immunostaining. To investigate the molecular pathogenesis of these tumors, we performed targeted next-generation sequencing on ten previously reported papillary renal neoplasms with reverse polarity, followed by a targeted polymerase chain reaction analysis for *KRAS* mutations in a control series of 30 type 1 and 2 papillary renal cell carcinomas. *KRAS* missense mutations were identified in eight of ten papillary renal neoplasms with reverse polarity. These mutations were clustered in exon 2—codon 12: c.35 G > T ($n = 6$) or c.34 G > C ($n = 2$) resulting in p.Gly12Val and p.Gly12Arg alterations, respectively. One of the wild-type tumors had *BRAF* c.1798_1799delGTinsAG (p.Val600Arg) mutation. No *KRAS* mutations were identified in any of the 30 control tumors. In summary, this study supports our proposal that papillary renal neoplasm with reverse polarity is an entity distinct from papillary renal cell carcinoma and the only renal cell neoplasm to consistently harbor *KRAS* mutations.

Modern Pathology (2020) 33:1157–1164

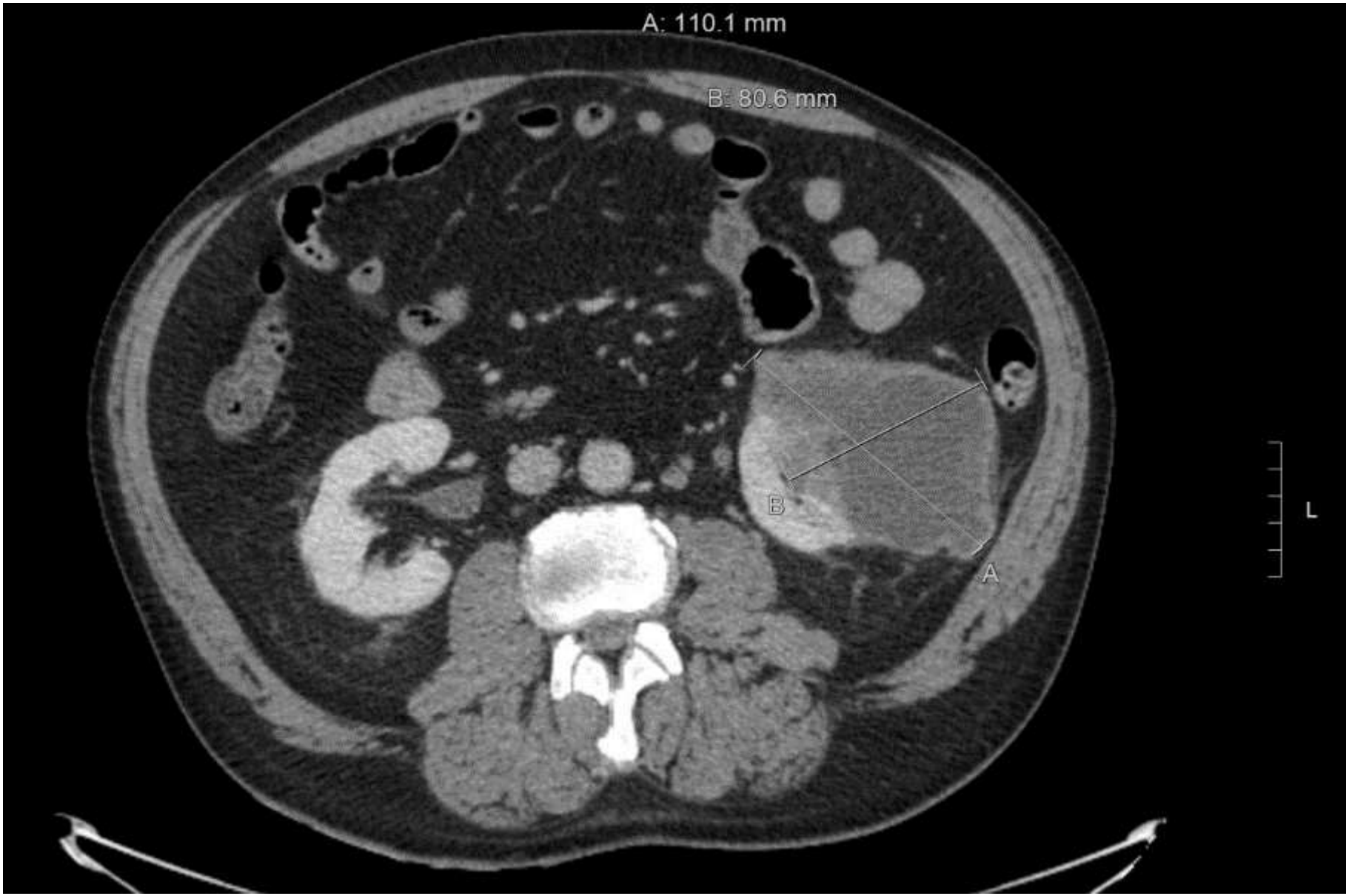
Take home points

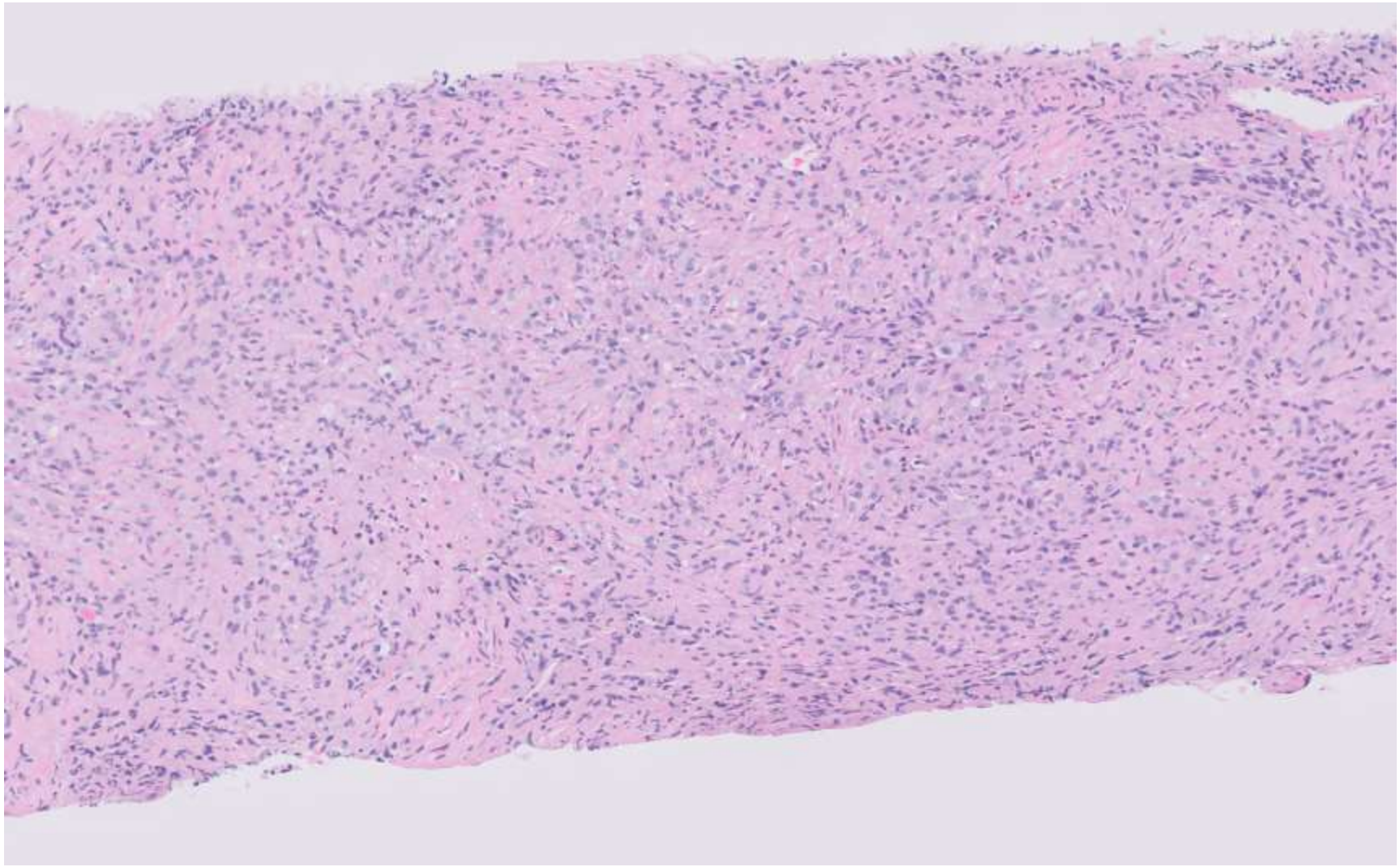
- **Typically small size, low stage, low WHO/FIGO grade**
- **Branching papillae, eosinophilic cytoplasm, "reverse-apical" nuclei**
  - Usually ABSENT: psammoma bodies, necrosis, mitoses, intracellular hemosiderin, tight clusters of foamy mac's
- **IHC: CK7+ GATA3+ vimentin- AMACR variable**
- **Good prognosis**

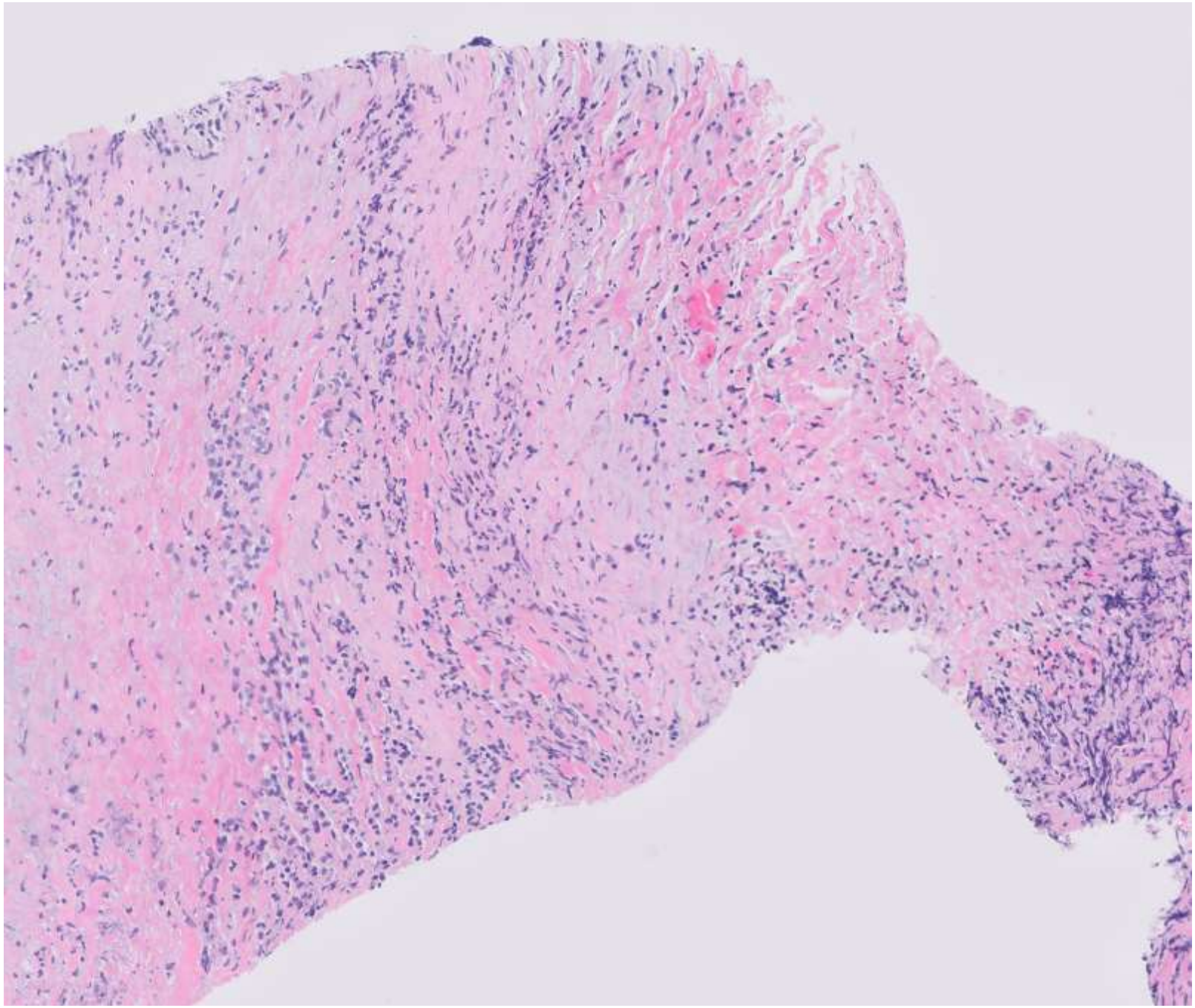
21-0402

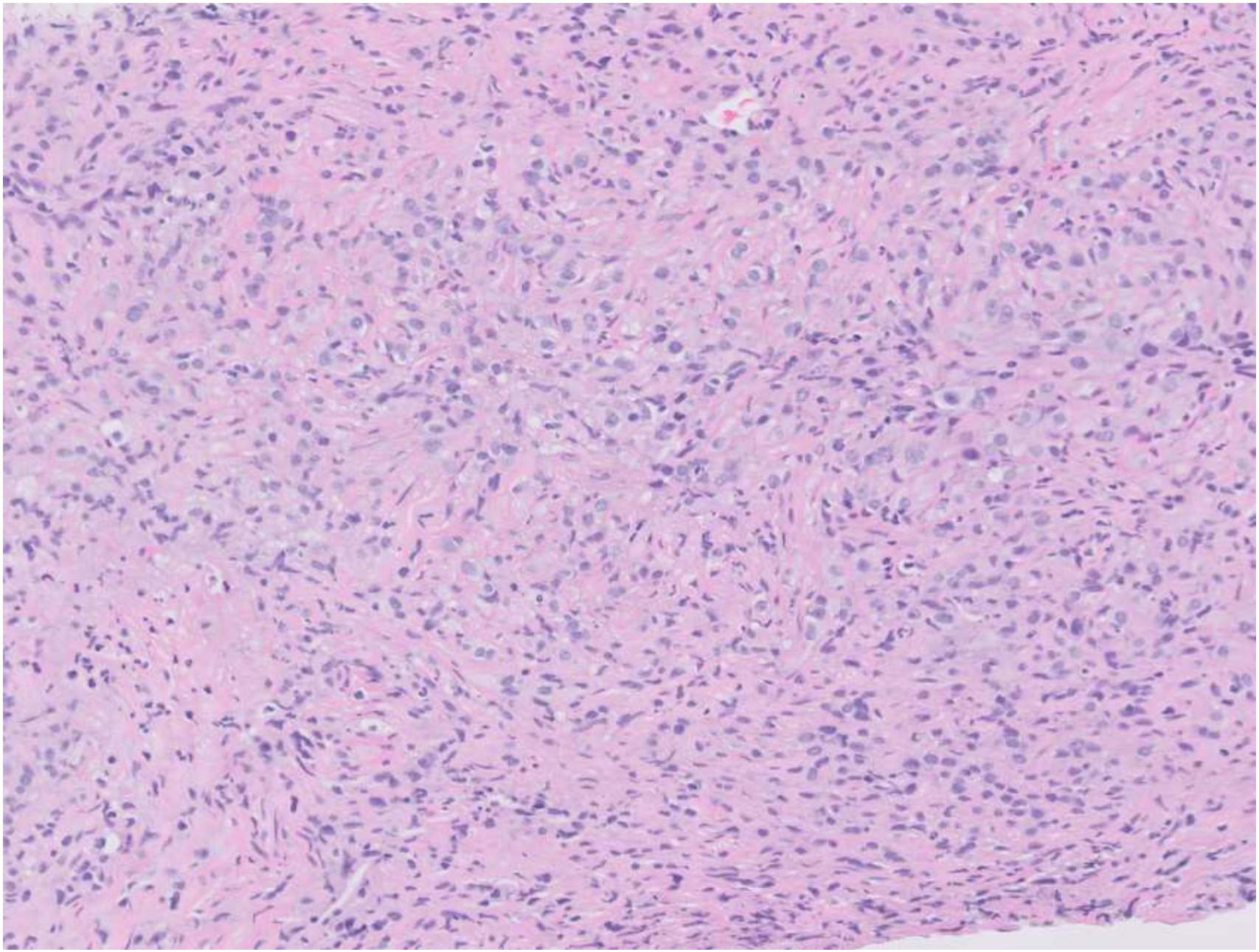
Emily Chan; UCSF

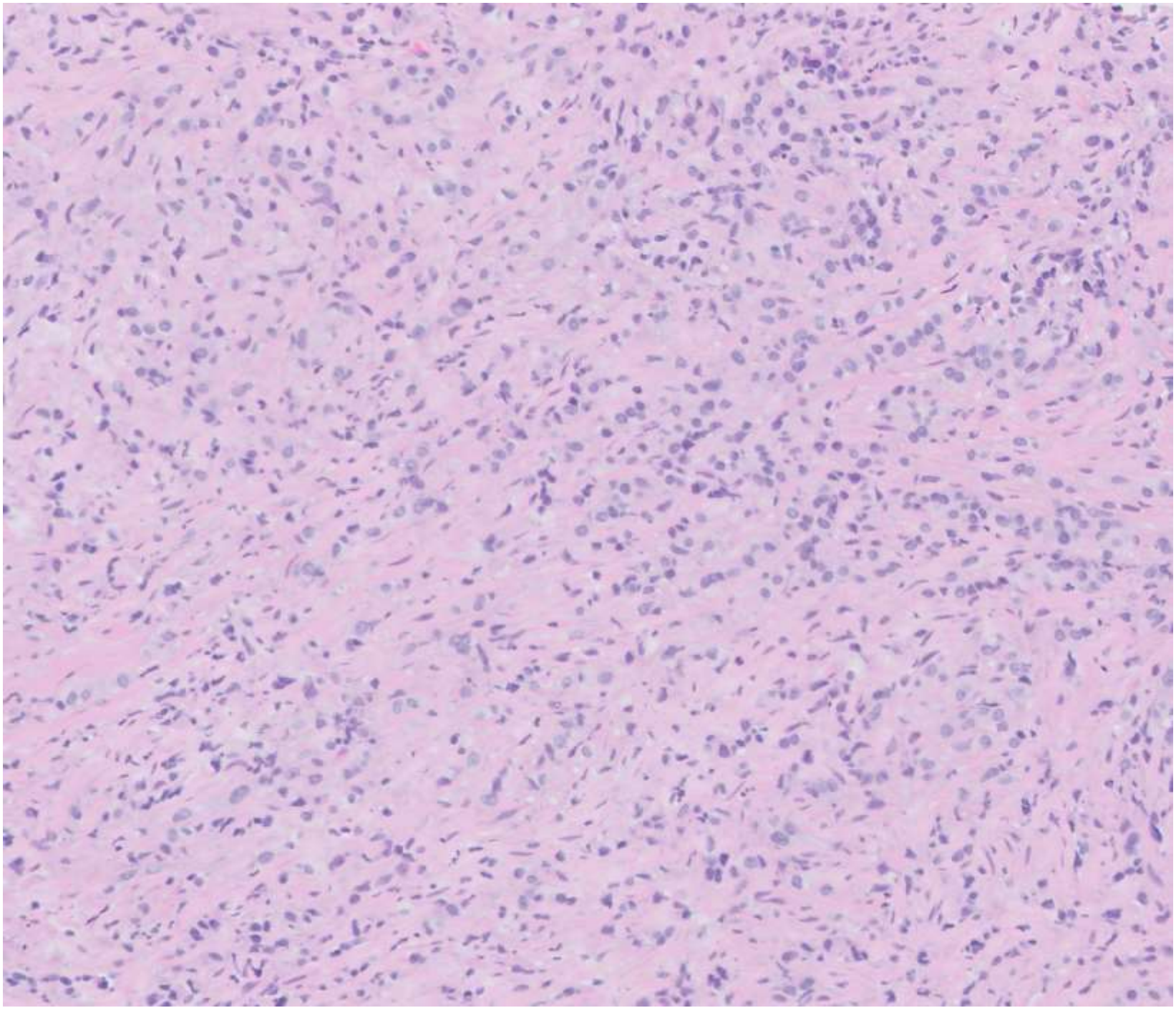
55-year-old M with hematuria and 11cm solid/cystic left lower renal pole mass. Core bx done.

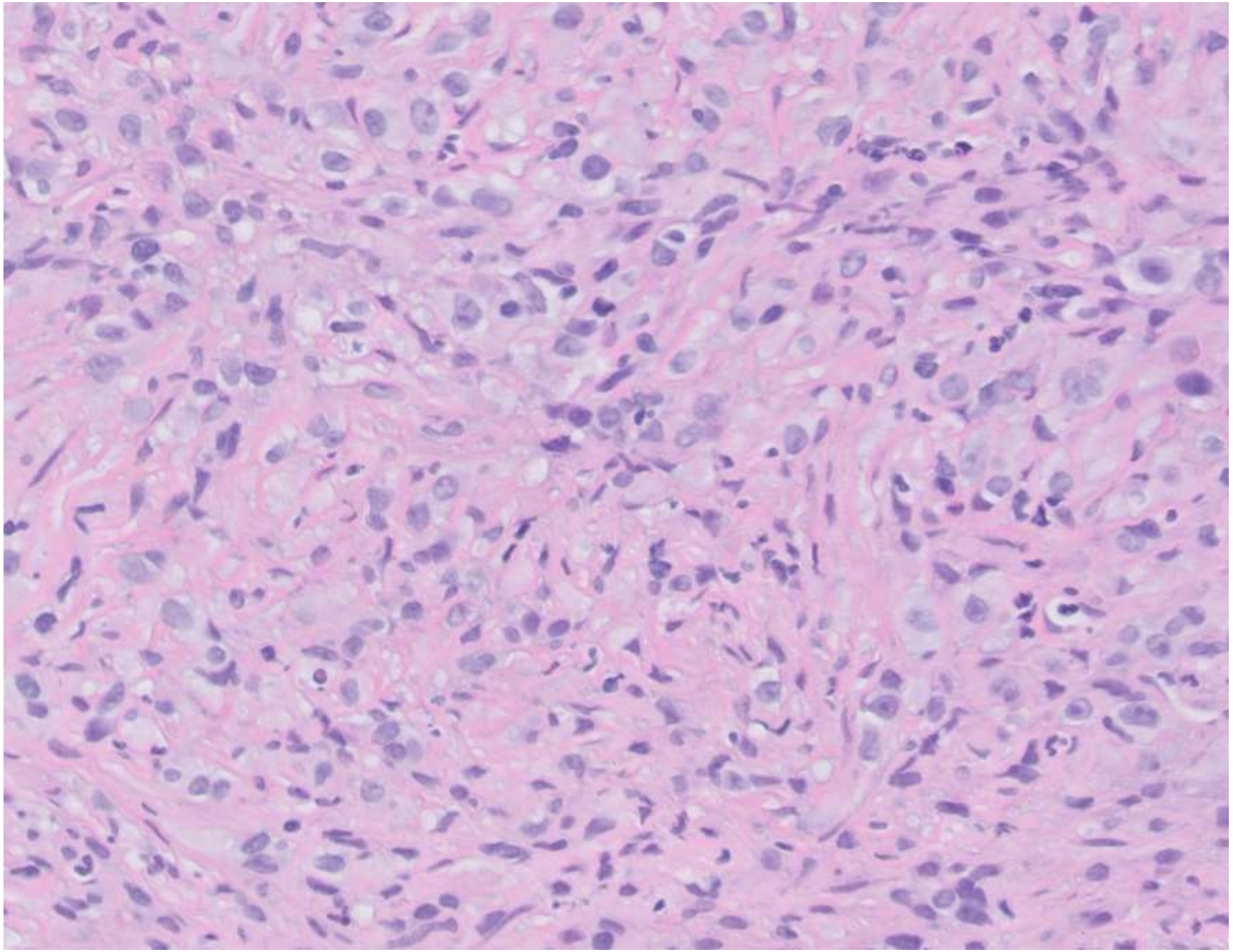

A: 110.1 mm
B: 80.6 mm
B
A
L

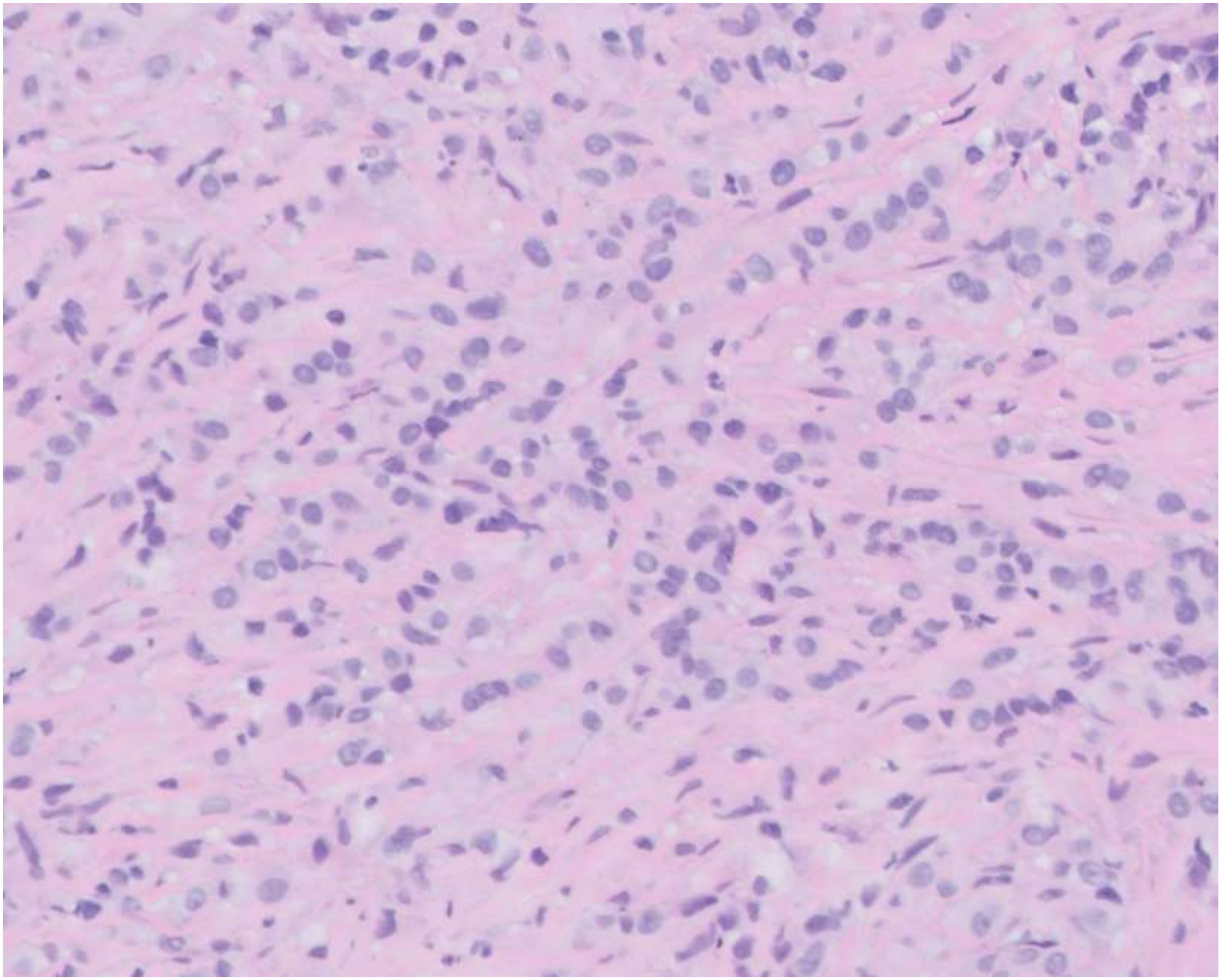


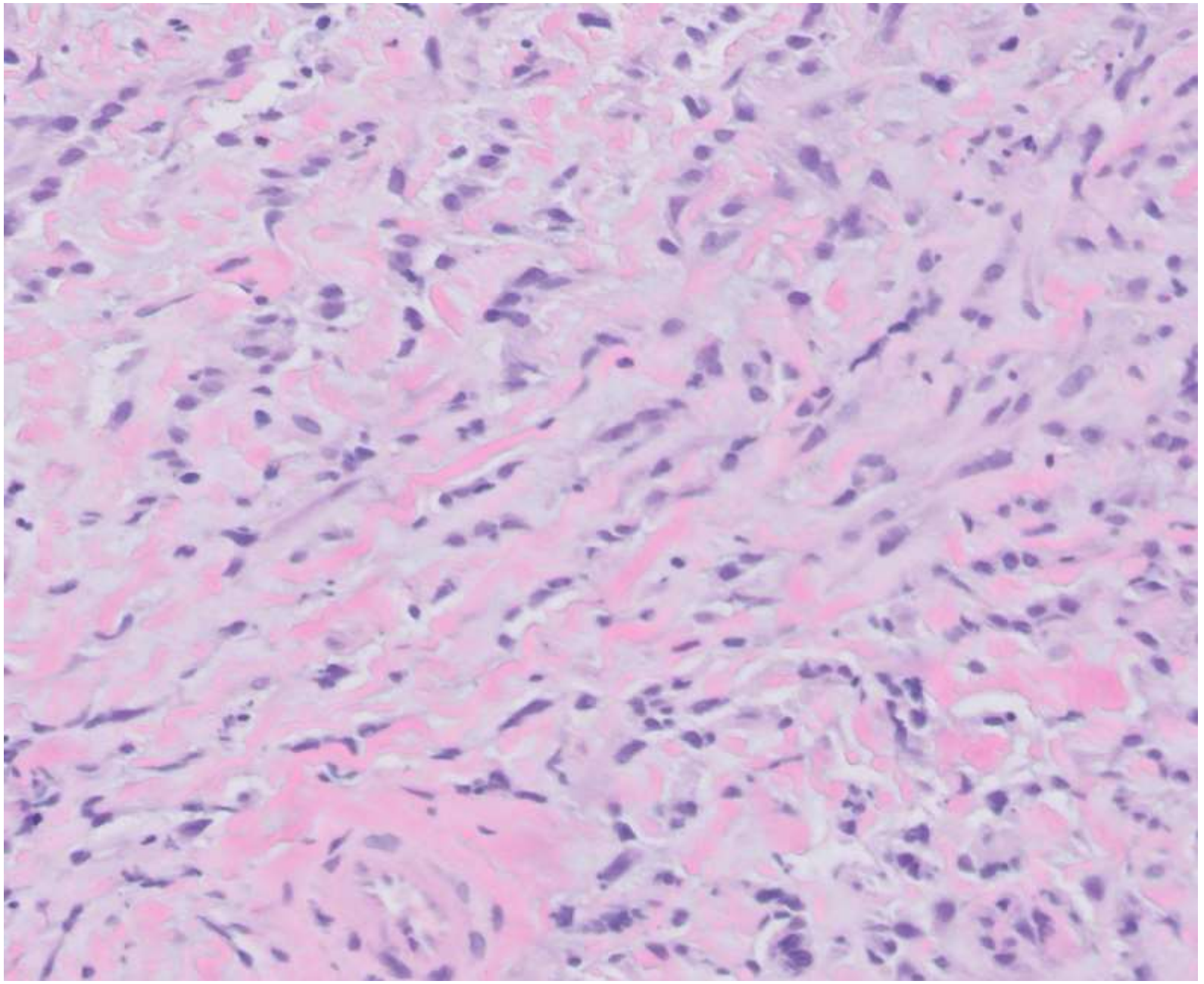


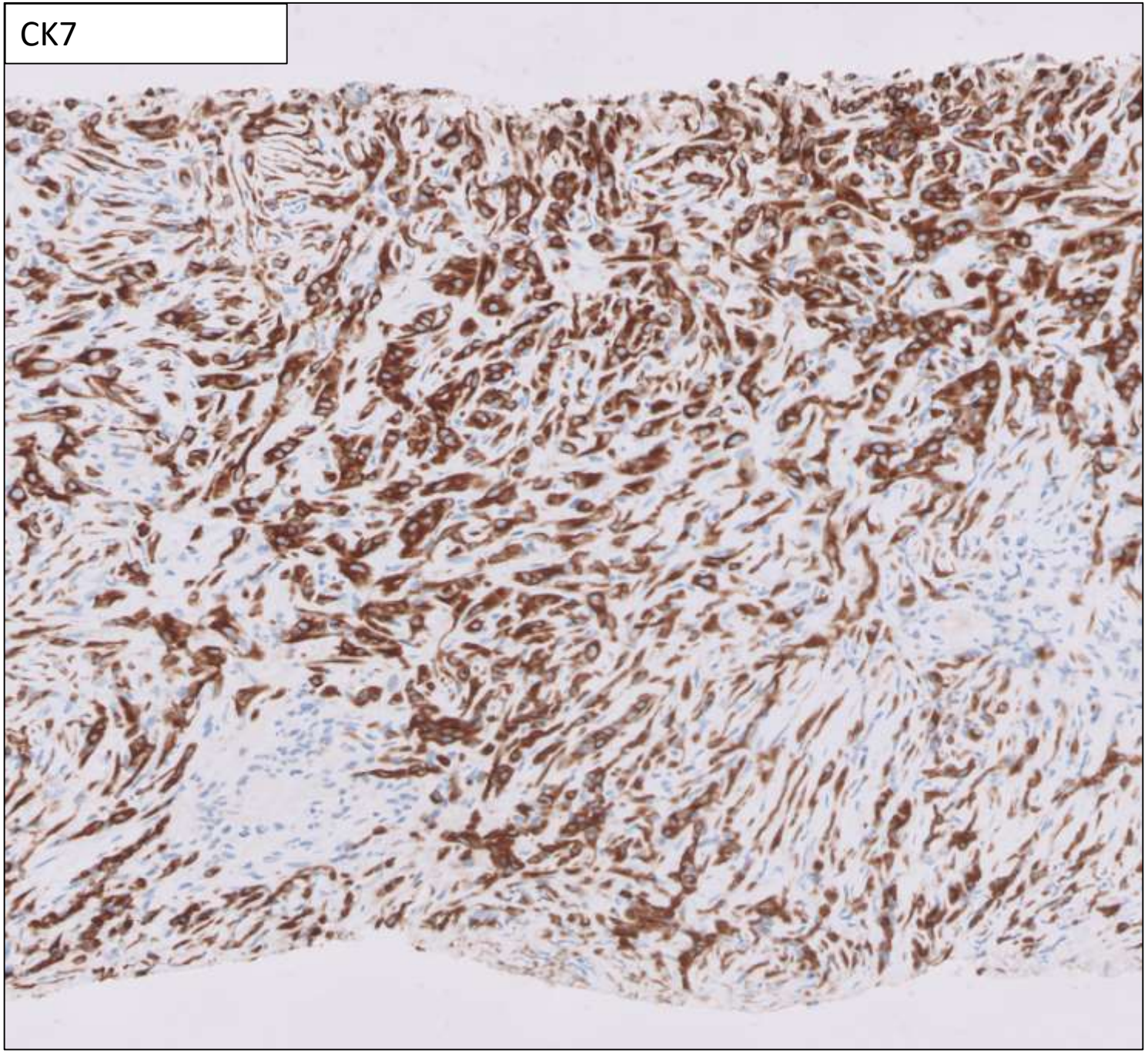


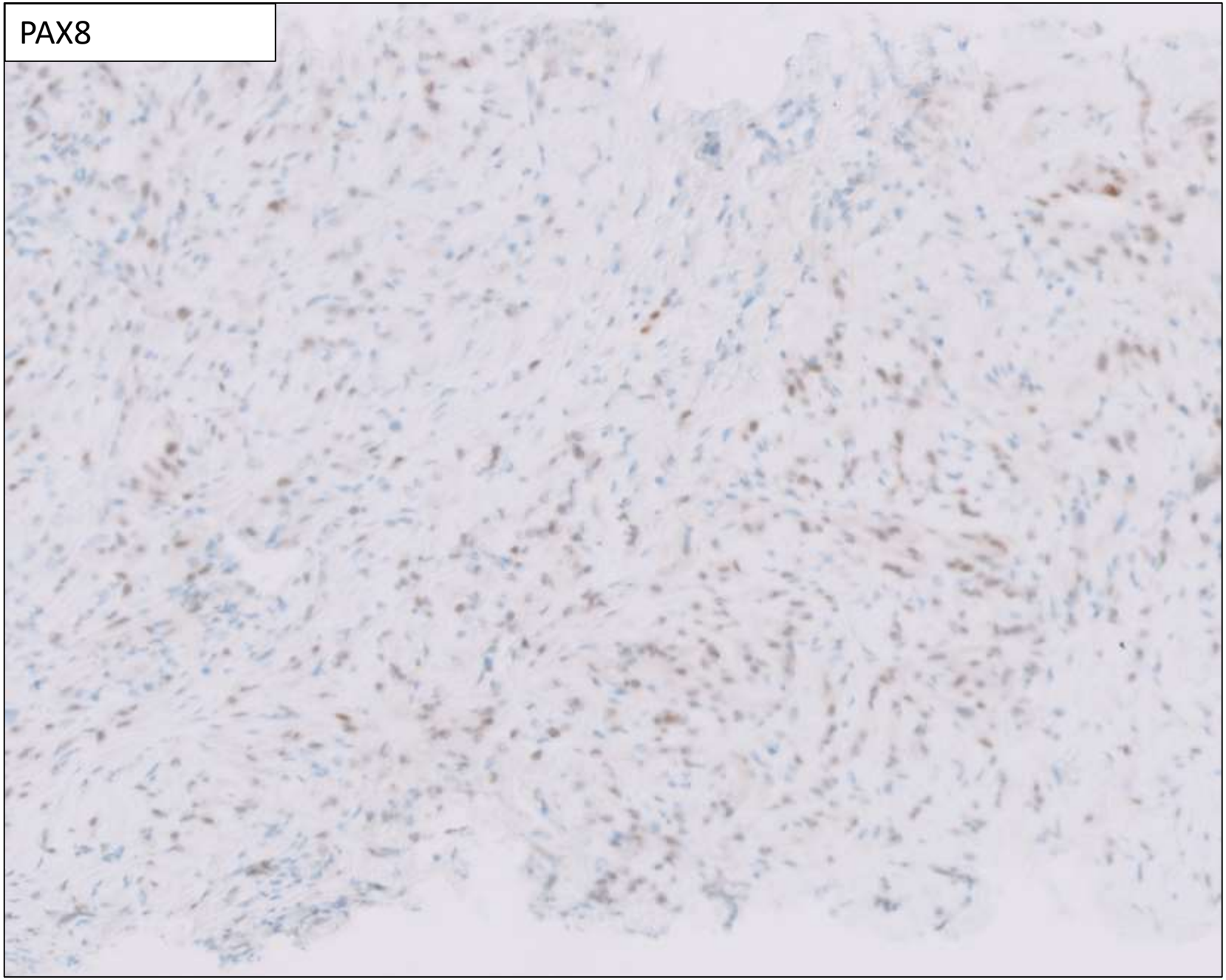




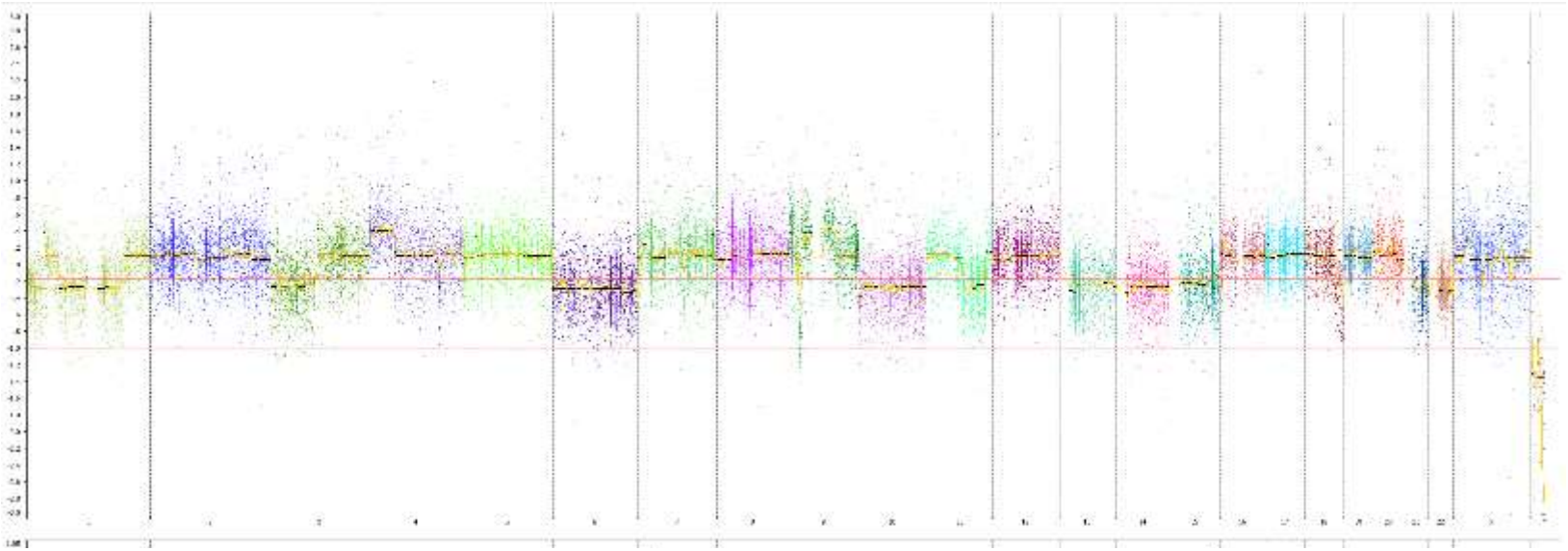





CK7


PAX8

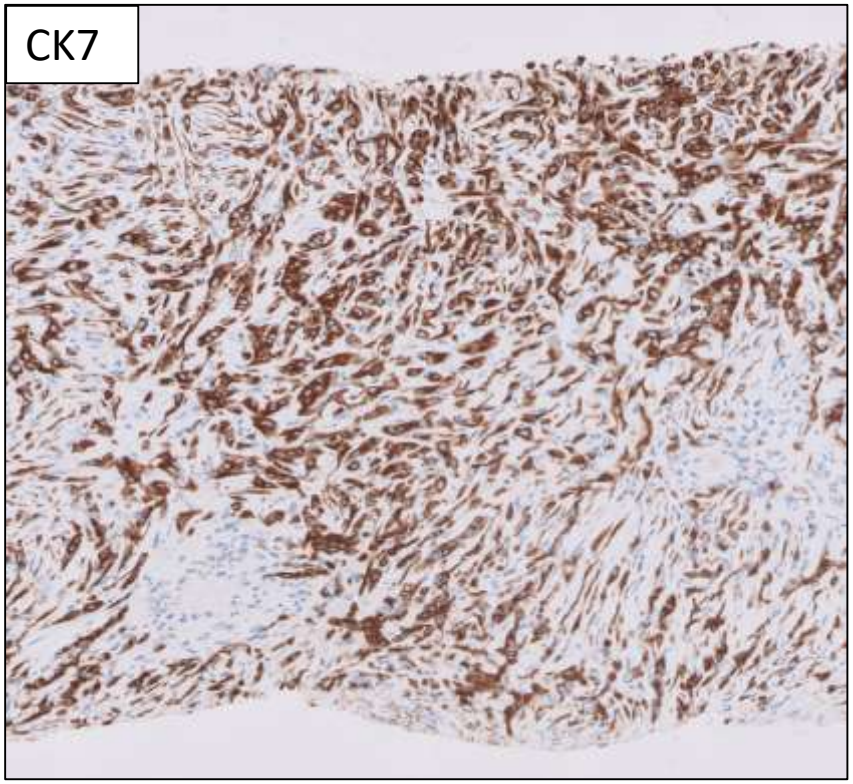
Mutation Analysis and Copy Number Profile from UCSF500 Next Generation Sequencing Assay

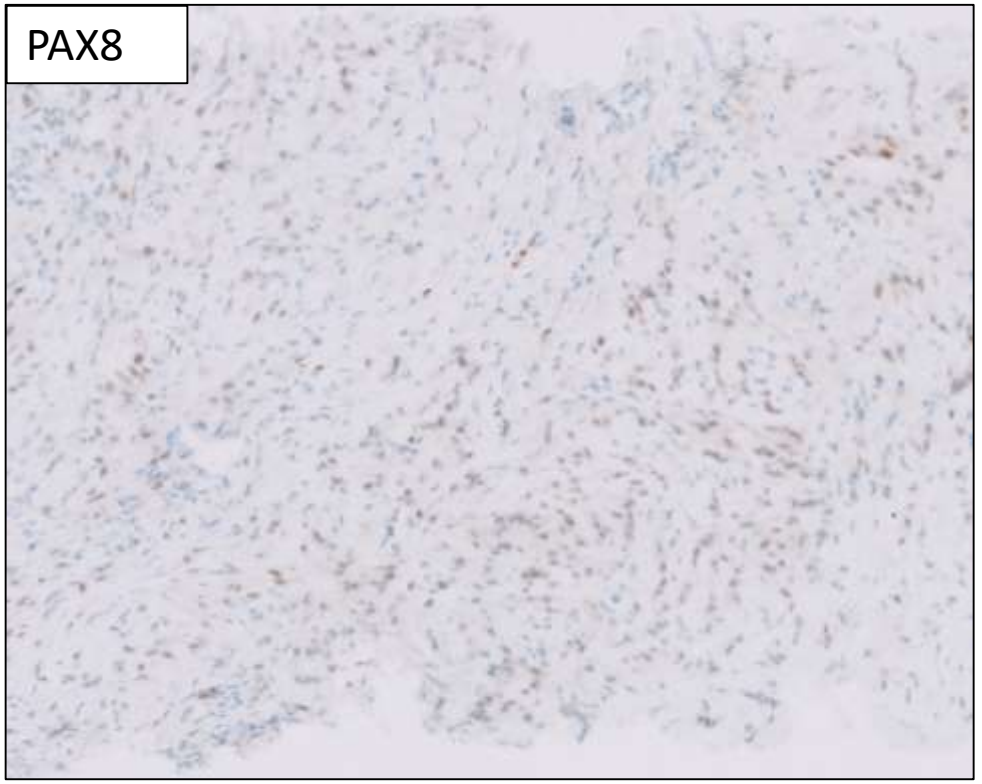


PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
CDKN2A,CDKN2B deep deletion	All	Pathogenic	N/A	N/A
LZTR1 p.R340*	NM_006767.3	Pathogenic	643	69%
NF2 p.V318fs	NM_000268.3	Pathogenic	490	30%
TET2 p.N338fs	NM_001127208.2	Likely Pathogenic	1171	47%

Differential diagnosis:

- Infiltrating urothelial carcinoma
- Renal cell carcinoma
  - Collecting duct
  - Unclassified
- Metastatic (lobular) breast carcinoma
- Mesothelioma
- Melanoma





Other IHC negative (minimal workup performed given needle biopsy):
CK20, P63, GATA3, HMWK, Uroplakin

Initial diagnosis:

Poorly differentiated carcinoma; PENDING UCSF500

Mutation and Copy Number Analysis from UCSF500 NGS Assay

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
CDKN2A,CDKN2B deep deletion	All	Pathogenic	N/A	N/A
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NF2 p.V318fs	NM_000268.3	Pathogenic	490	30%
TET2 p.N338fs	NM_001127208.2	Likely Pathogenic	1171	47%

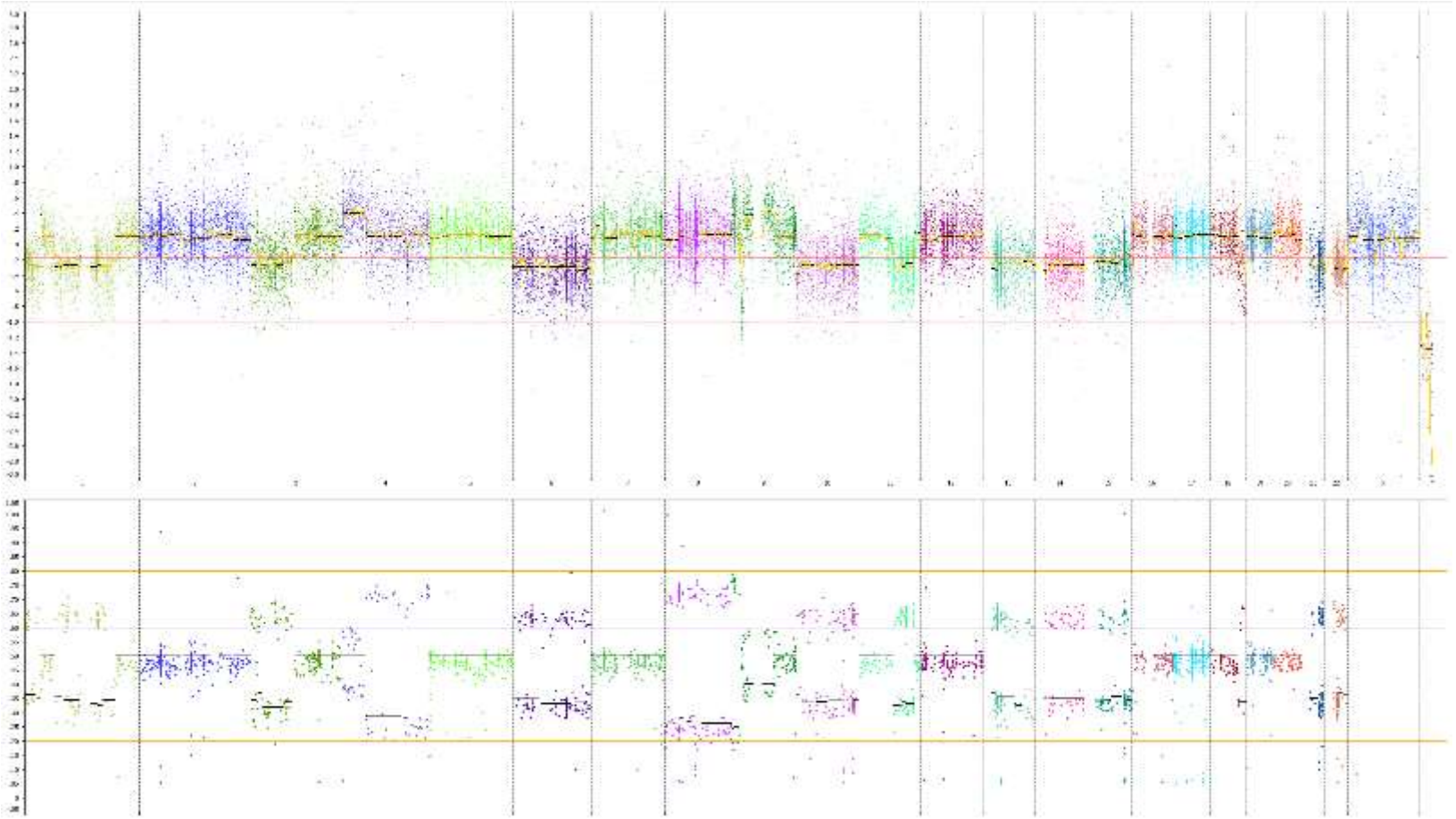
"Copy number analysis shows many large-scale gains and losses…significant for deep deletion of the CDKN2A and CDKN2B tumor suppressors"

"…Findings could be compatible with a malignant nerve sheath tumor…"

Additional IHC stains ordered and negative:

ER, TTF1, SOX10, BAF47, Calretinin, WT1

Lesson for kidney tumors: Look at Copy Number Profile in Detail



Copy number loss or copy neutral loss of heterozygosity of chromosomes 1, 3, 4, 6, 8, 9, 10, 11, 13, 14, 15, 21, 22

In consultation with Drs. Bradley Stohr and Jeffry Simko

Cancer Discov. 2016 Nov;6(11):1258-1266. doi: 10.1158/2159-8290.CD-16-0267. Epub 2016 Sep 7.

Biallelic Alteration and Dysregulation of the Hippo Pathway in Mucinous Tubular and Spindle Cell Carcinoma of the Kidney

Rohit Mehra [1 2 3], Pankaj Vats [1 3 4], Marcin Cieslik [3], Xuhong Cao [3 5], Fengyun Su [3], Sudhanshu Shukla [3], Aaron M Udager [1], Rui Wang [3], Jincheng Pan [6], Katayoon Kasaian [3], Robert Lonigro [3], Javed Siddiqui [3], Kumpati Premkumar [4], Ganesh Palapattu [7], Alon Weizer [2 7], Khaled S Hafez [7], J Stuart Wolf Jr [7], Ankur R Sangoi [8], Kiril Tr[illegible] Ming Zhou [11], Giovanna Giannico [12], Jesse K McKenney [13], S[illegible] Arul M Chinnaiyan [14 2 3 5 7]

Comparative Study > Am J Surg Pathol. 2018 Jun;42(6):767-777. doi: 10.1097/PAS.0000000000001038.

Distinct Genomic Copy Number Alterations Distinguish Mucinous Tubular and Spindle Cell Carcinoma of the Kidney From Papillary Renal Cell Carcinoma With Overlapping Histologic Features

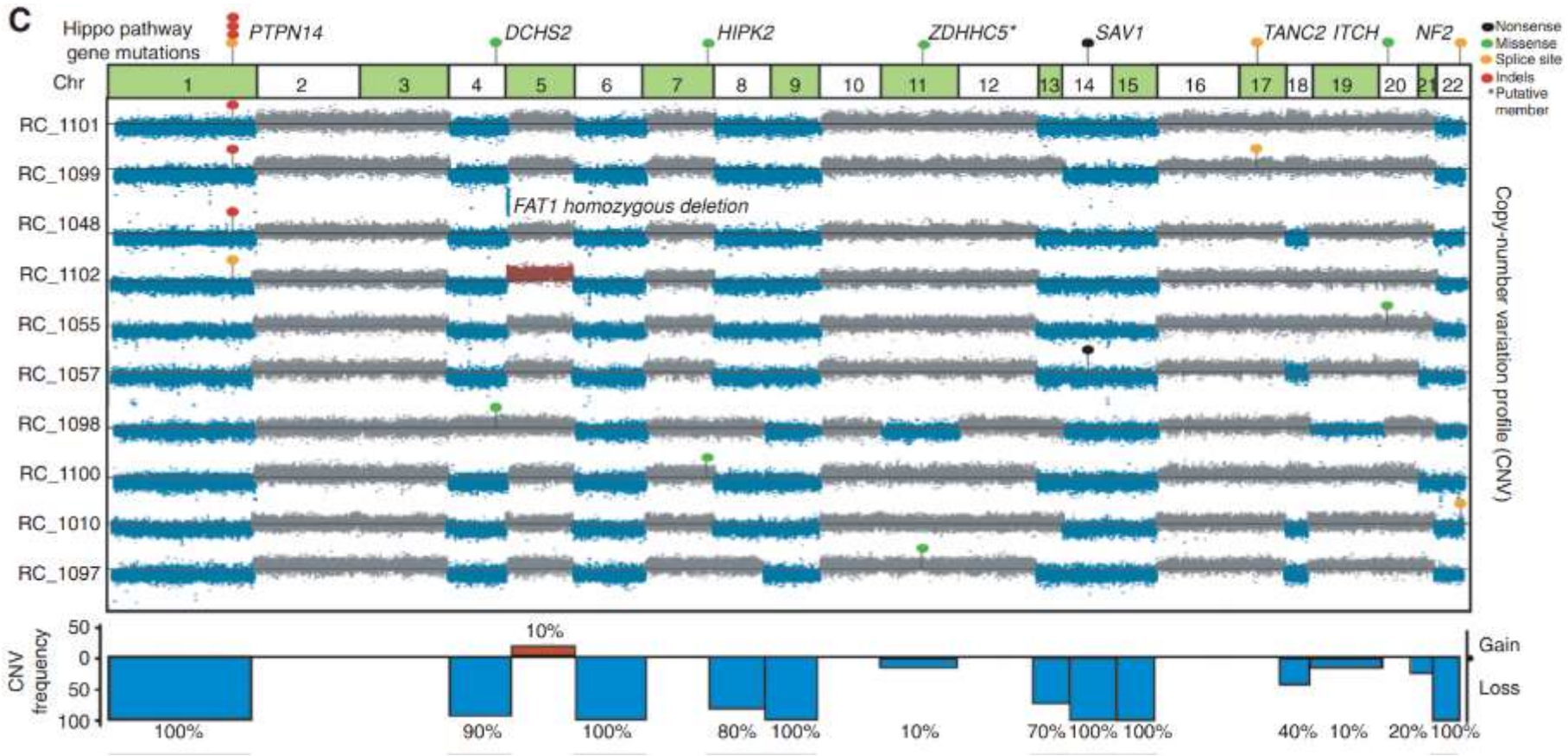
Qinghu Ren [1], Lu Wang, Hikmat A Al-Ahmadie, Samson W Fine, Anuradha Gopalan, [illegible]g-Bei Chen

Clin Genitourin Cancer. 2019 Aug;17(4):268-274.e1. doi: 10.1016/j.clgc.2019.04.006. Epub 2019 May 2.

Mucinous Tubular and Spindle-Cell Carcinoma of the Kidney: Clinical Features, Genomic Profiles, and Treatment Outcomes

Yasser Ged [1], Ying-Bei Chen [2], Andrea Knezevic [3], Mark T A Donoghue [4], Maria I Carlo [1], Chung-Han Lee [1], Darren R Feldman [1], Sujata Patil [3], A Ari Hakimi [5], Paul Russo [5], Martin H Voss [1], Robert J Motzer [6]

Copy number changes in MTSCC



- Monosomy 1, 6, 9, 14, 15, and 22 in 100% of cases
- 4, 8 and 13 in greater than 80% of cases

Mehra et al, Cancer Discovery, 2016

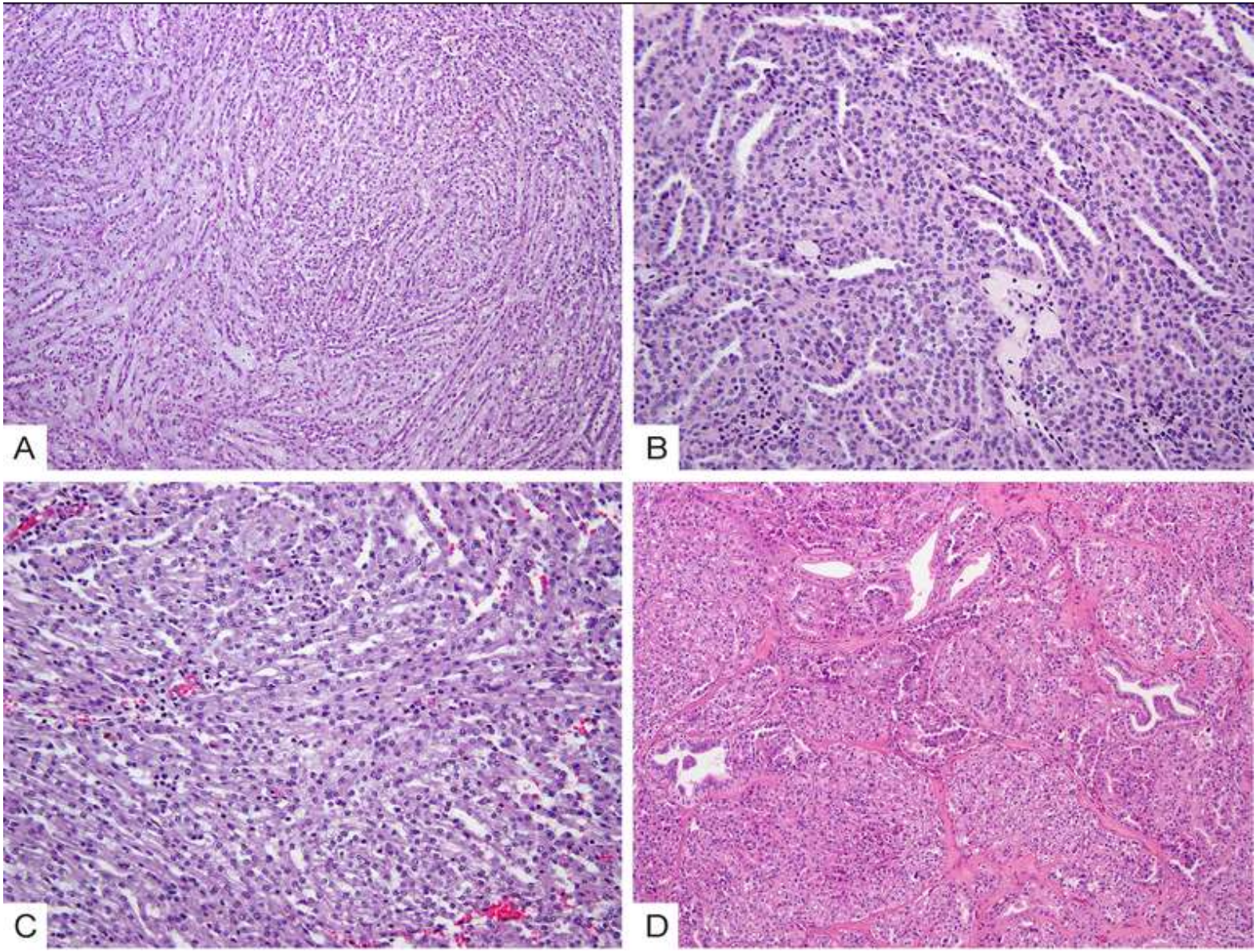
Updated diagnosis

- Poorly differentiated carcinoma, most compatible with mucinous tubular and spindle cell carcinoma (MTSCC)

Mucinous tubular and spindle cell carcinoma (MTSCC)

- Rare renal epithelial neoplasm, possibly arising from loop of Henle cells
- Low grade bland tubules and spindle cells set in a mucinous stroma
- Shows overlapping morphologic and IHC features with papillary RCC (CK7+/AMACR+), but has distinct copy number profile of multiple chromosomal losses as well as dysregulation of Hippo pathway
- YAP/TAZ IHC not helpful, but new markers VSTM2A and IRX5 recently shown to distinguish MTSCC from other RCC
- Most have indolent course though metastatic cases have been reported, typically with high-grade features

MTSCC morphologic spectrum

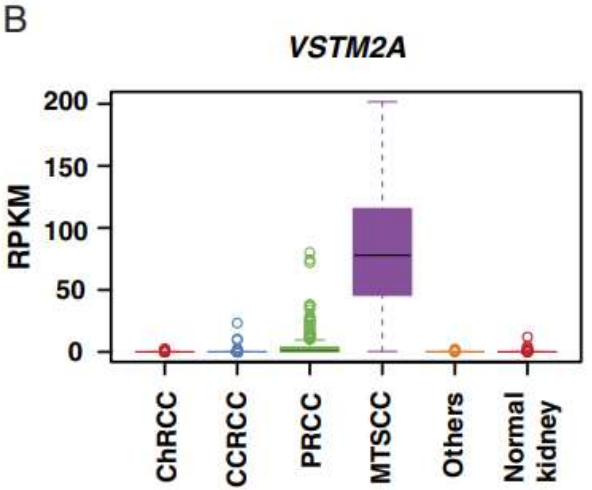


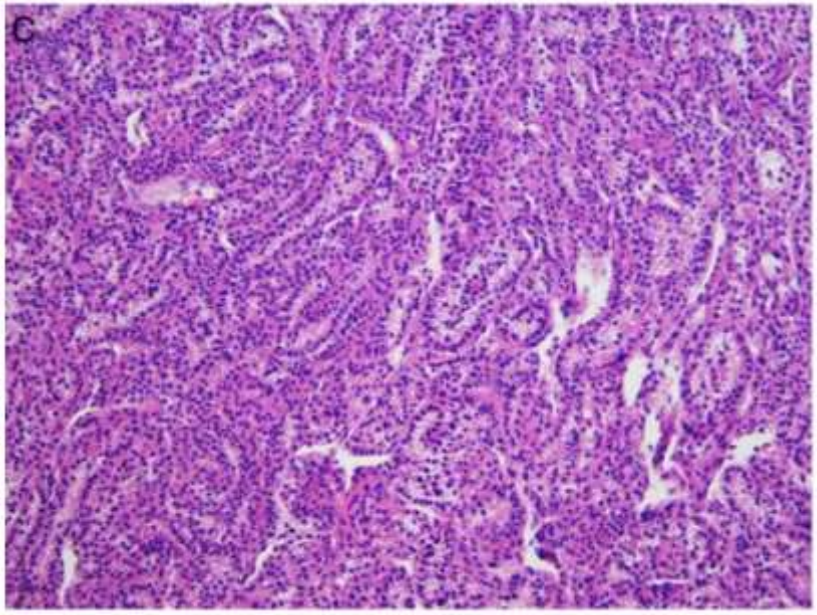
Ren et al AJSP 2018

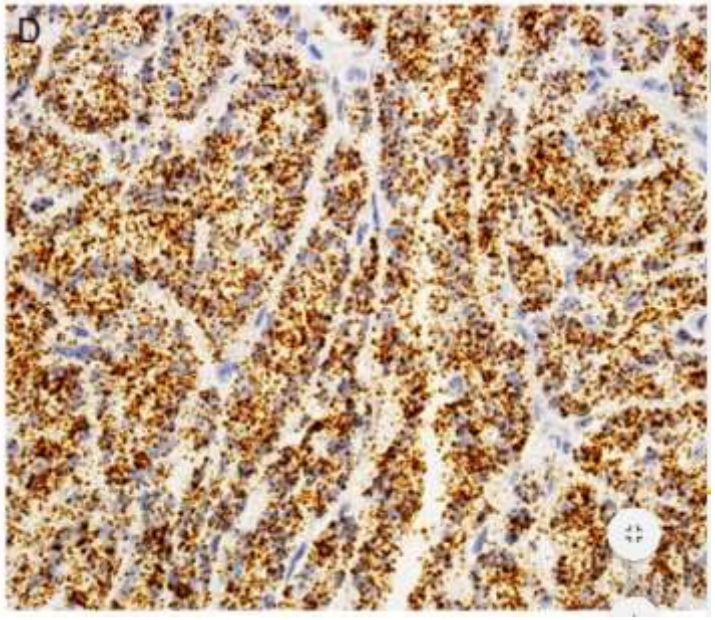
Multicenter Study > Am J Surg Pathol. 2018 Dec;42(12):1571-1584.
doi: 10.1097/PAS.0000000000001150.

VSTM2A Overexpression Is a Sensitive and Specific Biomarker for Mucinous Tubular and Spindle Cell Carcinoma (MTSCC) of the Kidney

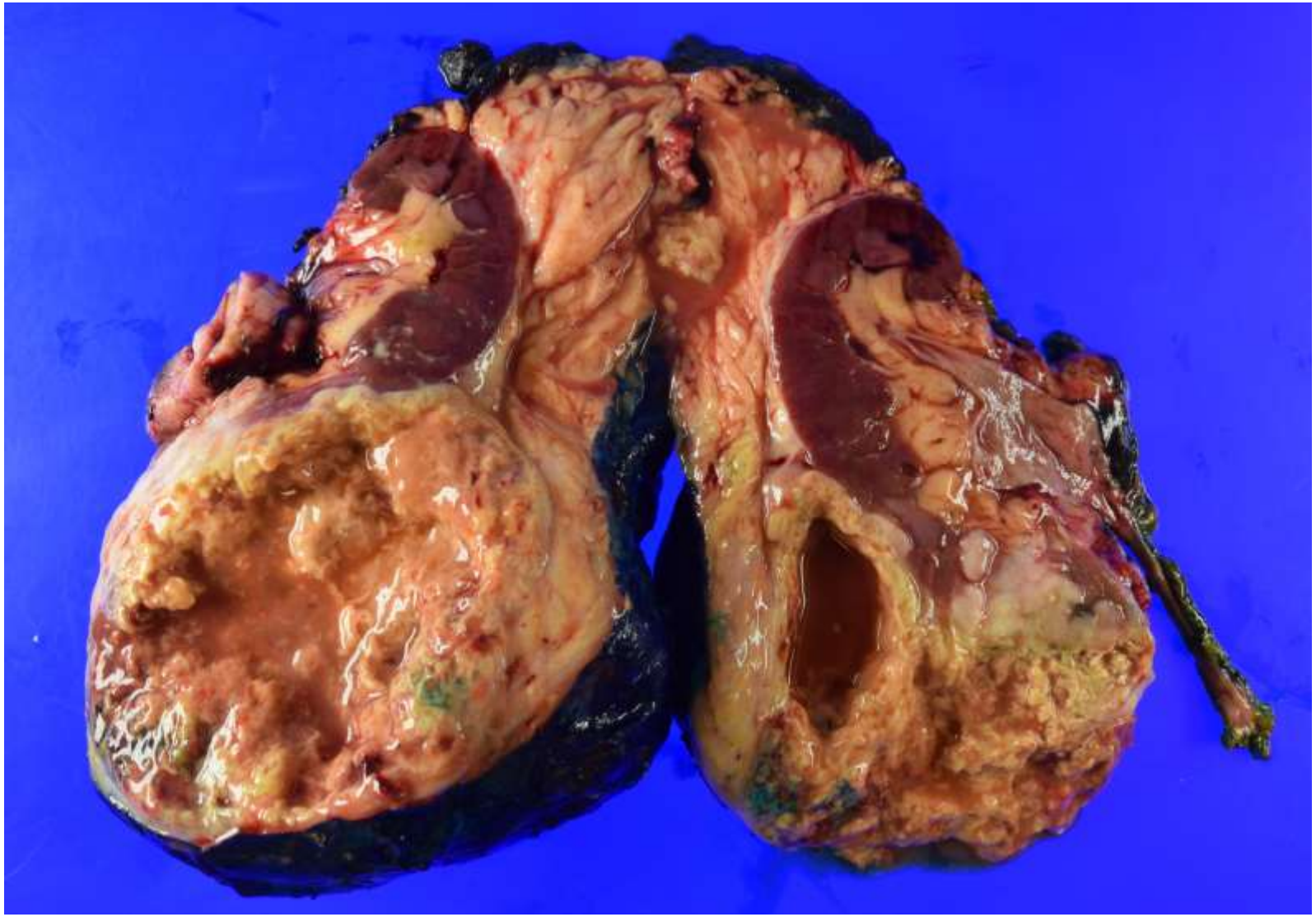
Lisha Wang [1 2], Yuping Zhang [1 2], Ying-Bei Chen [3], Stephanie L Skala [2], Hikmat A Al-Ahmadie [3], Xiaoming Wang [1 2], Xuhong Cao [1 2], Brendan A Veeneman [1 2], Jin Chen [1 2], Marcin Cieślik [1 2], Yuanyuan Qiao [1 2], Fengyun Su [1 2], Pankaj Vats [1 2], Javed Siddiqui [1 2], Hong Xiao [2], Evita T Sadimin [4], Jonathan I Epstein [5], Ming Zhou [6], Ankur R Sangoi [7], Kiril Trpkov [8], Adeboye O Osunkoya [9], Giovanna A Giannico [10], Jesse K McKenney [11], Pedram Argani [5], Satish K Tickoo [3], Victor E Reuter [3], Arul M Chinnaiyan [1 2 12 13 14], Saravana M Dhanasekaran [1 2], Rohit Mehra [1 2 12]



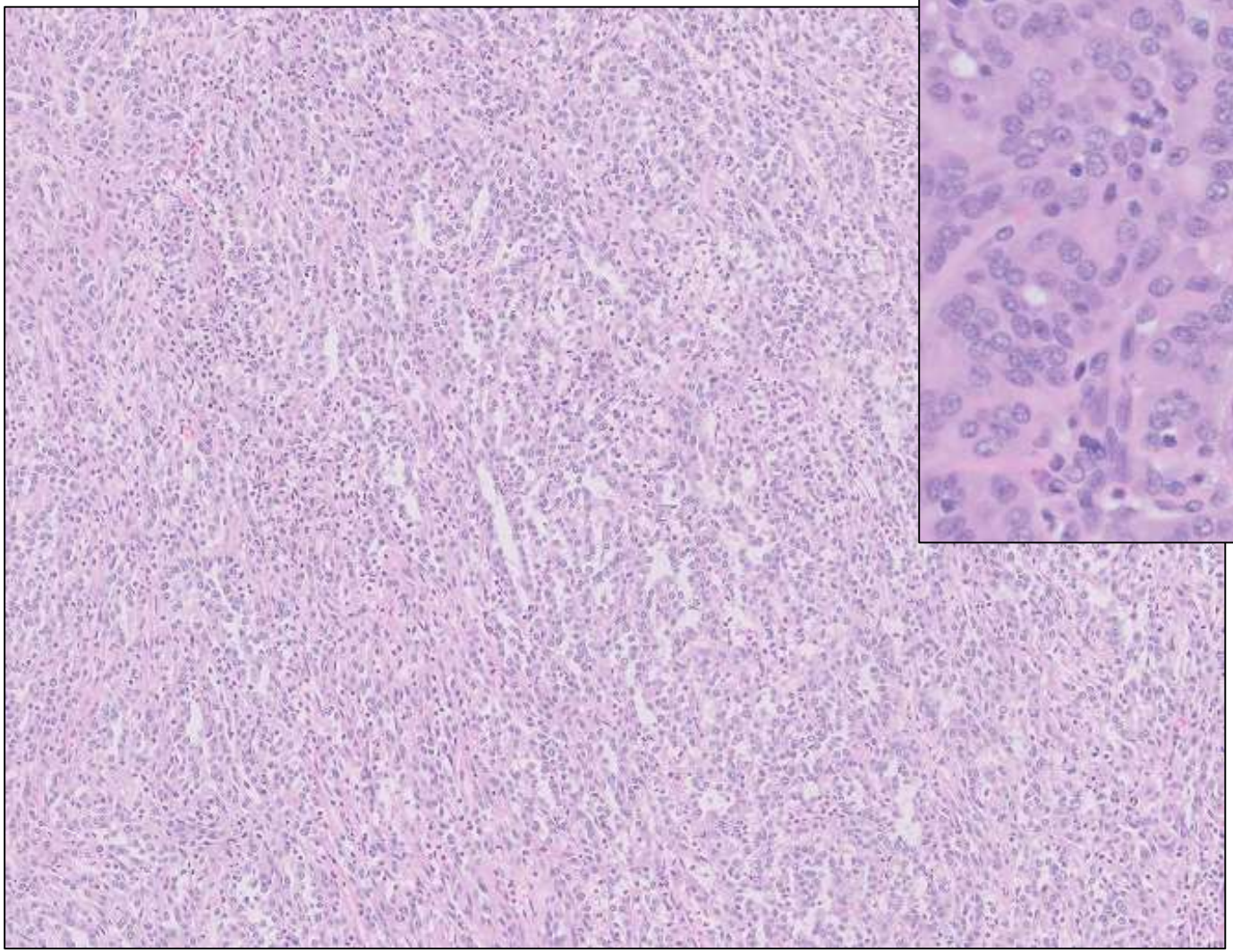


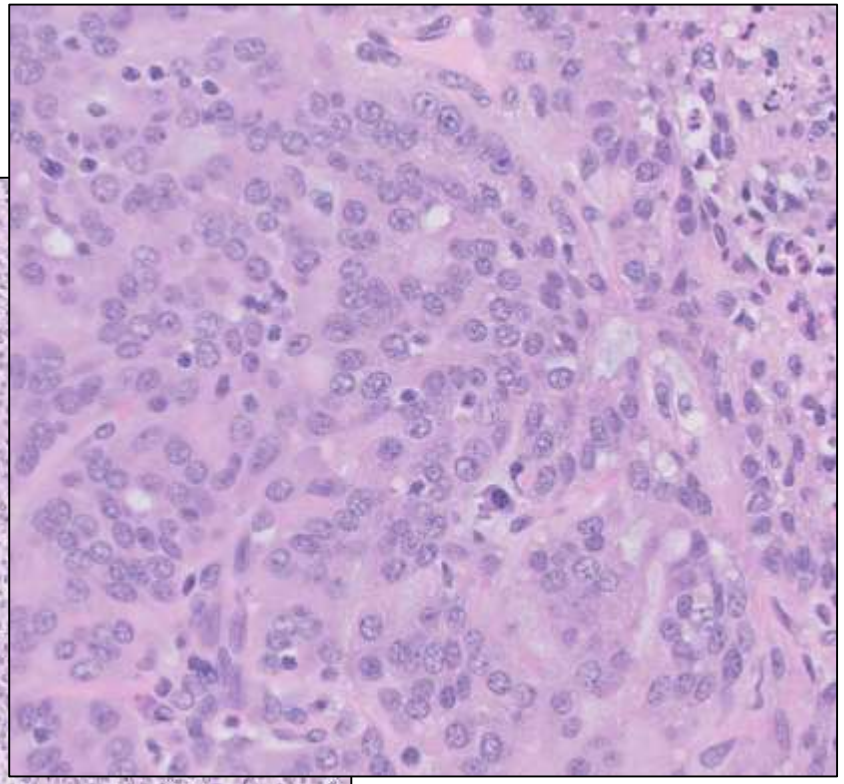


Resection specimen



Resection specimen





Extensive necrosis, lymph nodes and peritoneal metastases

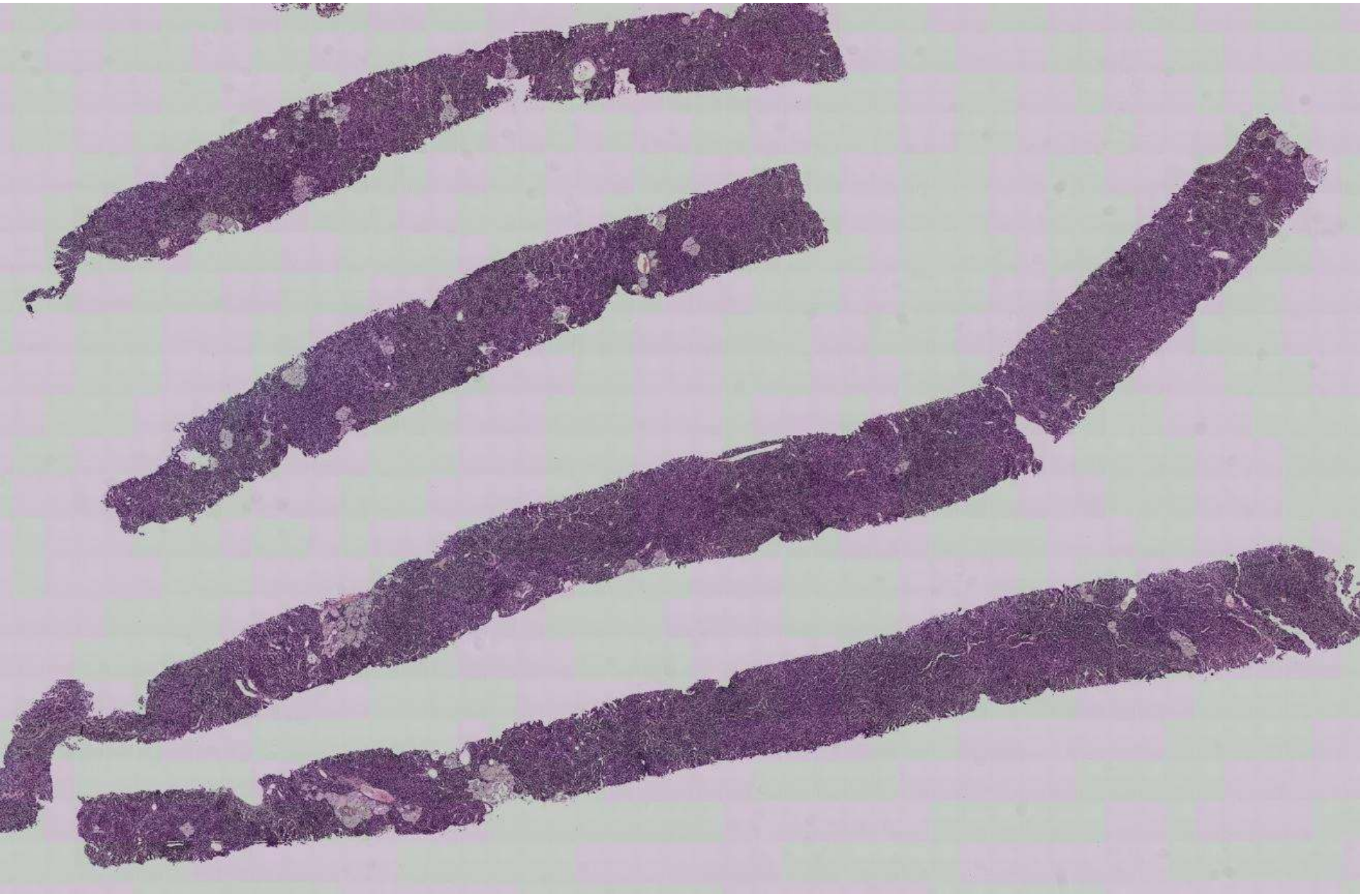
Take home points

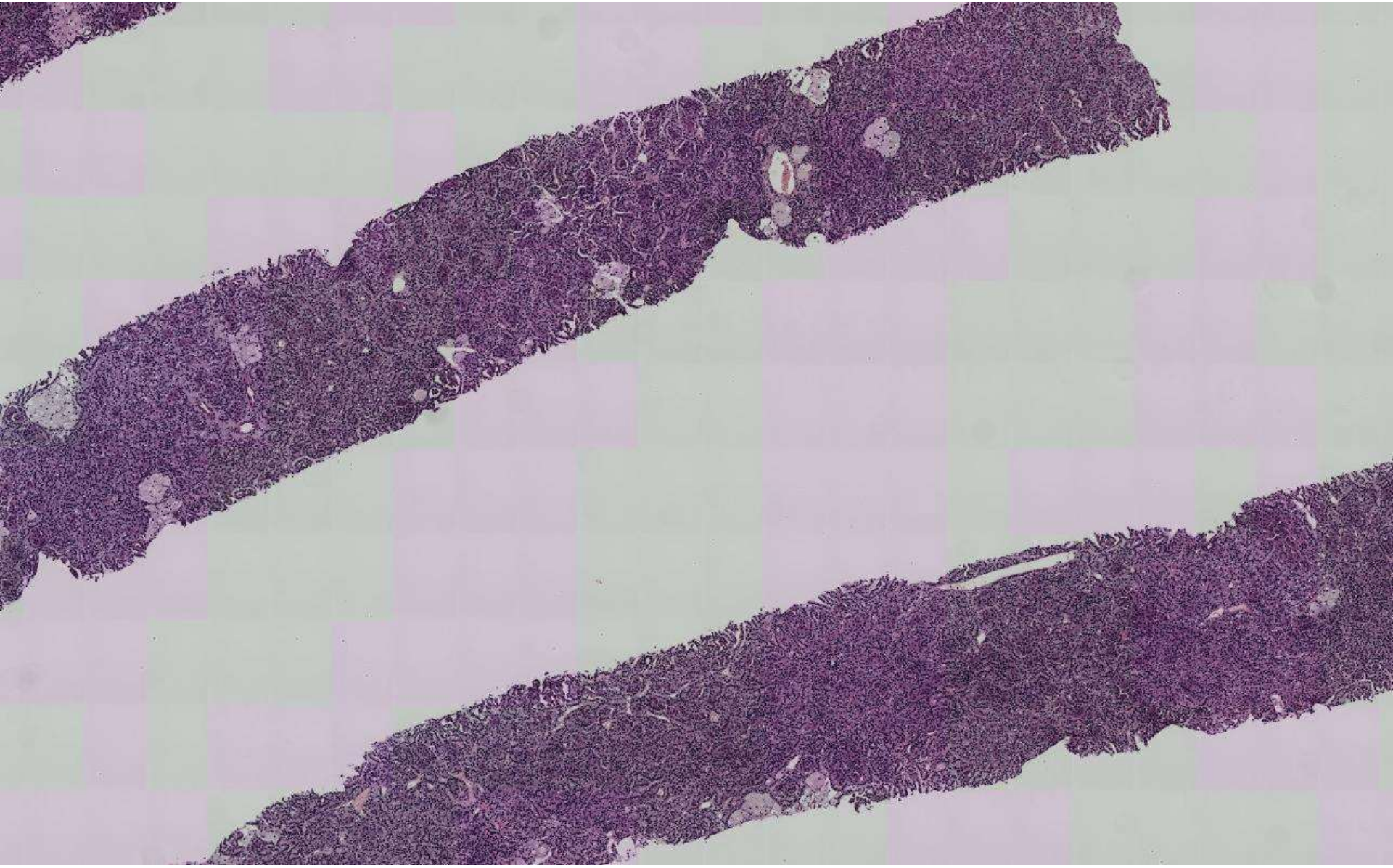
- Consider MTSCC when presented with relatively bland but clinically aggressive tumor
- In small biopsy with “poorly differentiated” features, rather than order the kitchen sink, consider preserving tissue for molecular testing
- For renal tumors, choose a comprehensive molecular test that provides analysis of all kidney tumor associated genes (including those associated with rearrangements), as well as copy number analysis

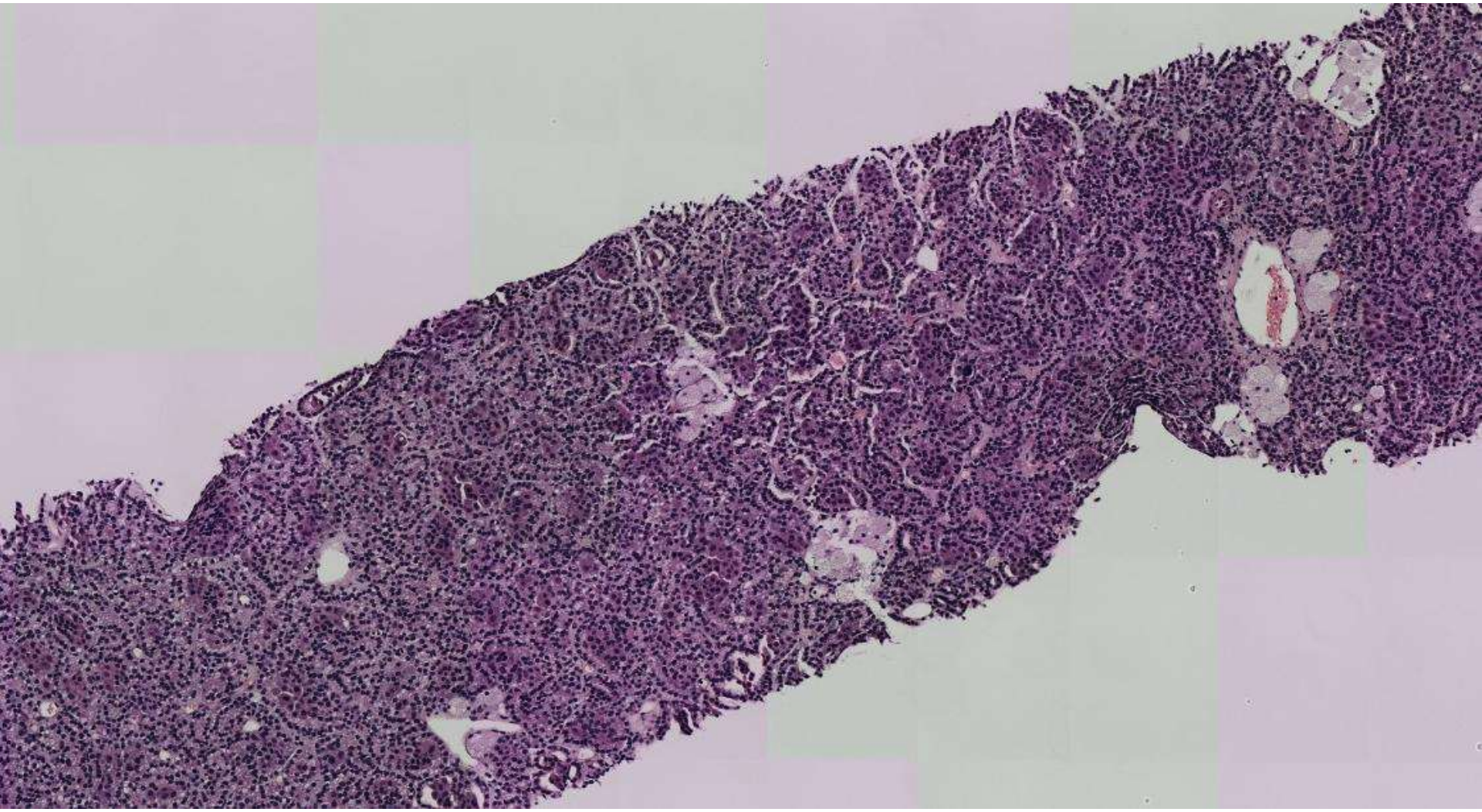
21-0403
scanned slide avail!

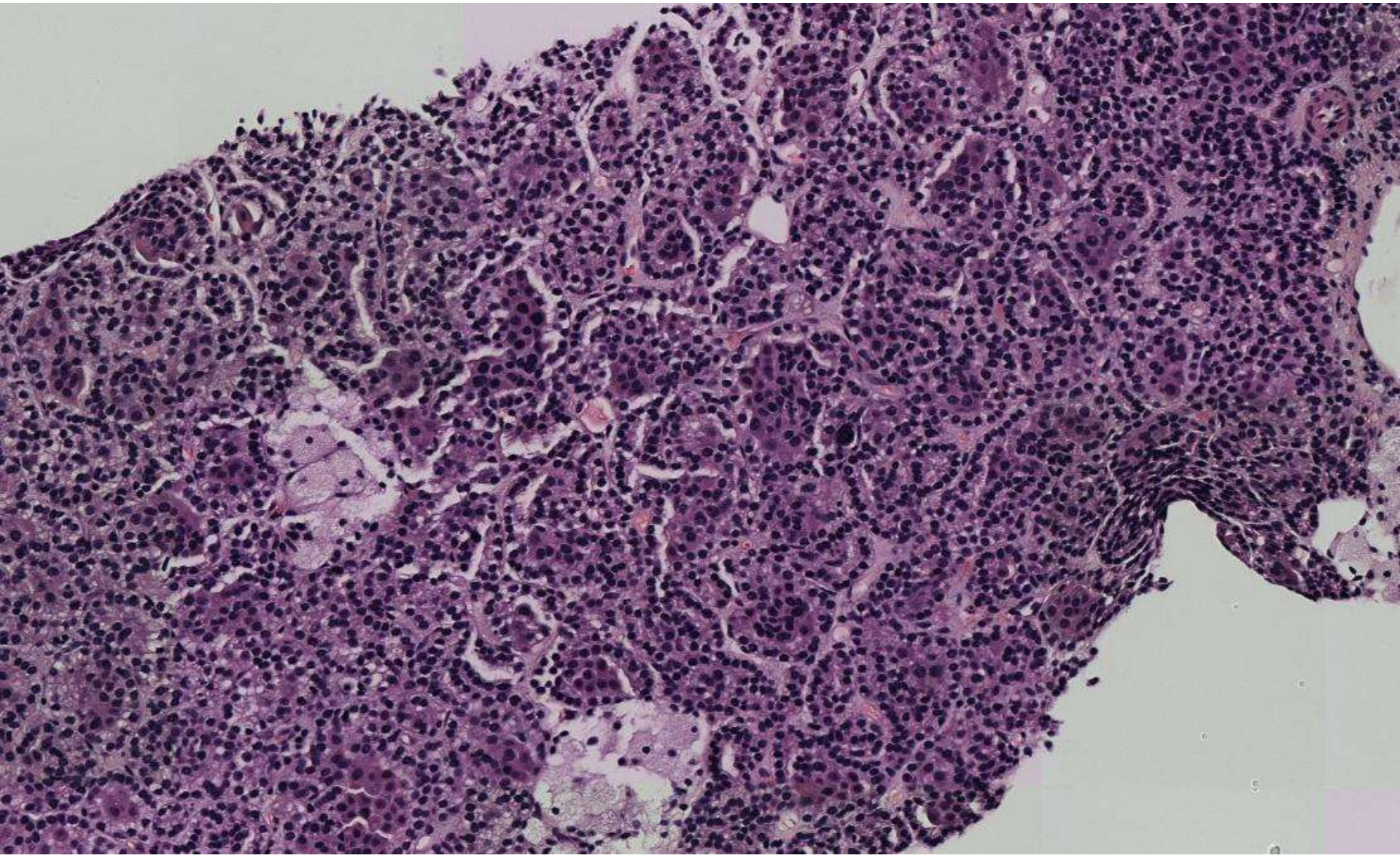
Ankur Sangoi; El Camino Hospital

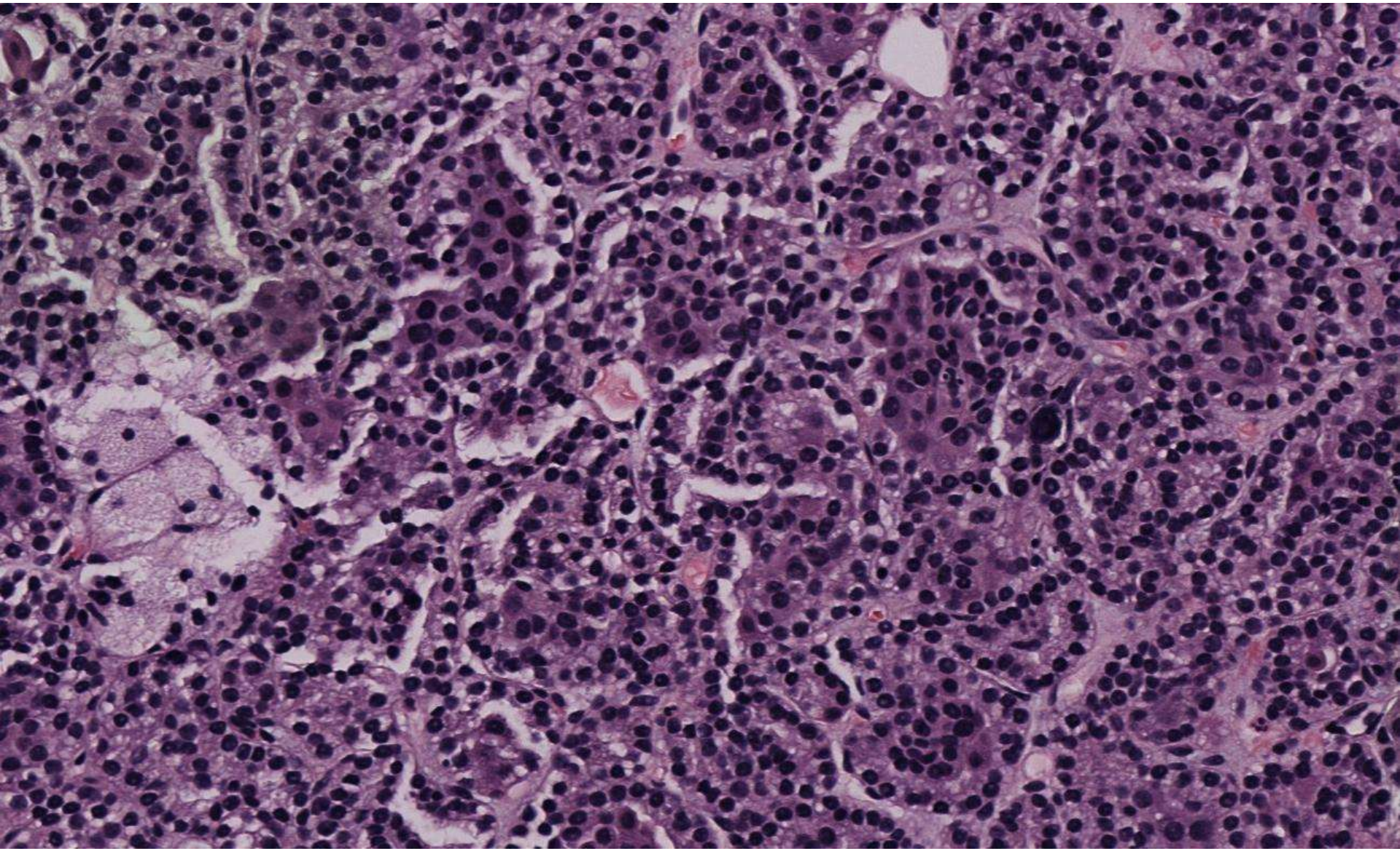
Adult F with kidney mass, core biopsy performed.

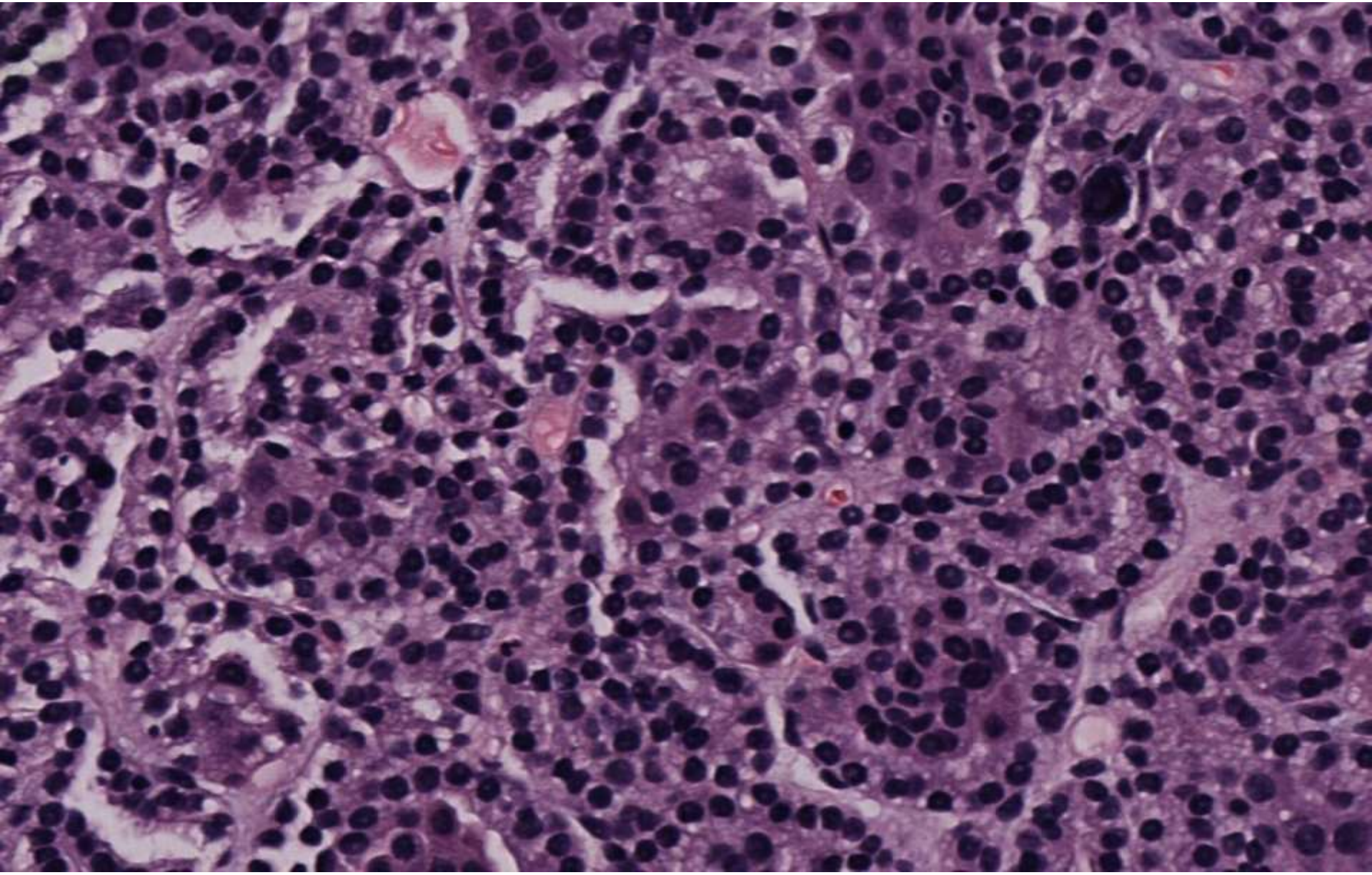






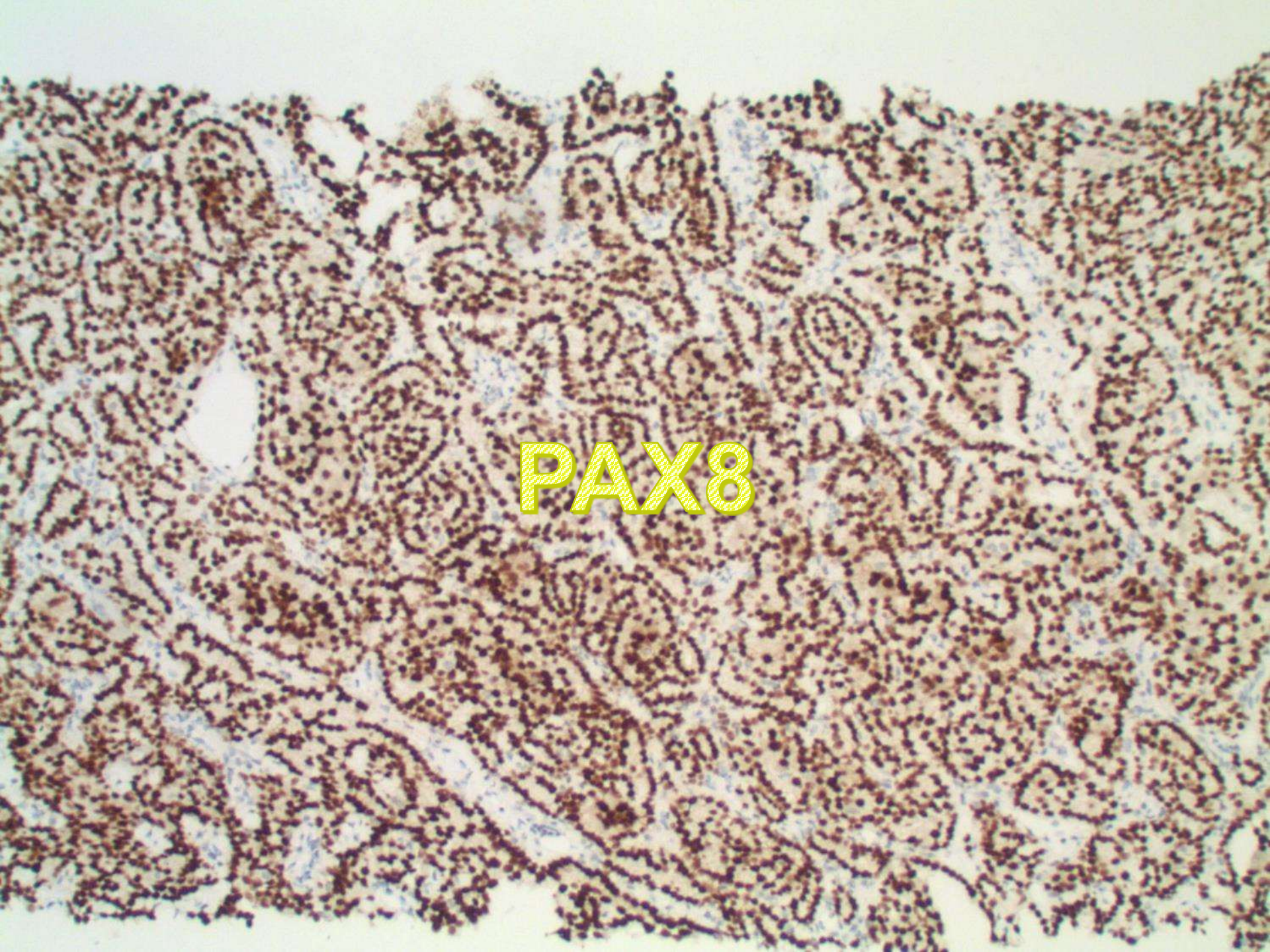


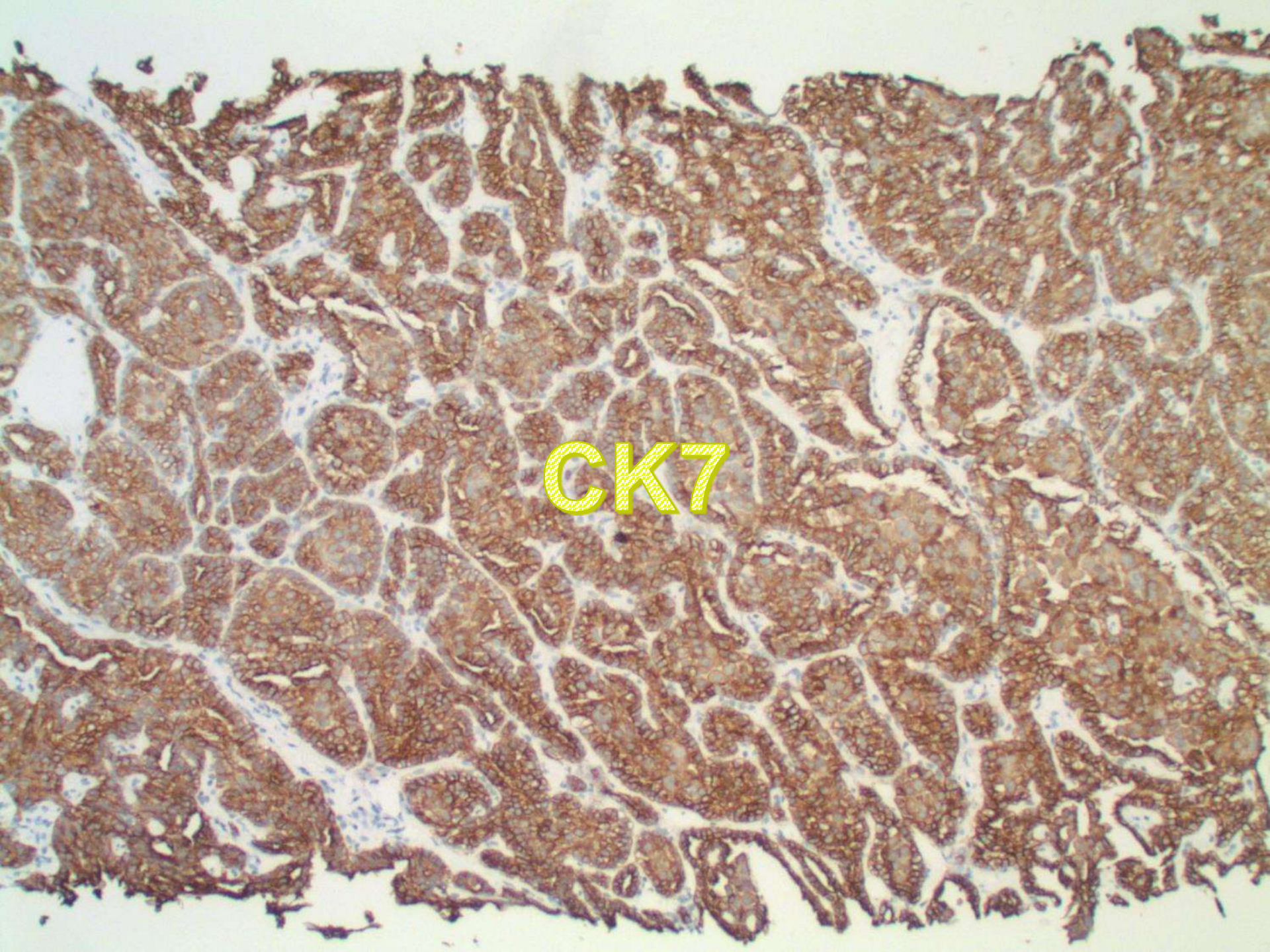


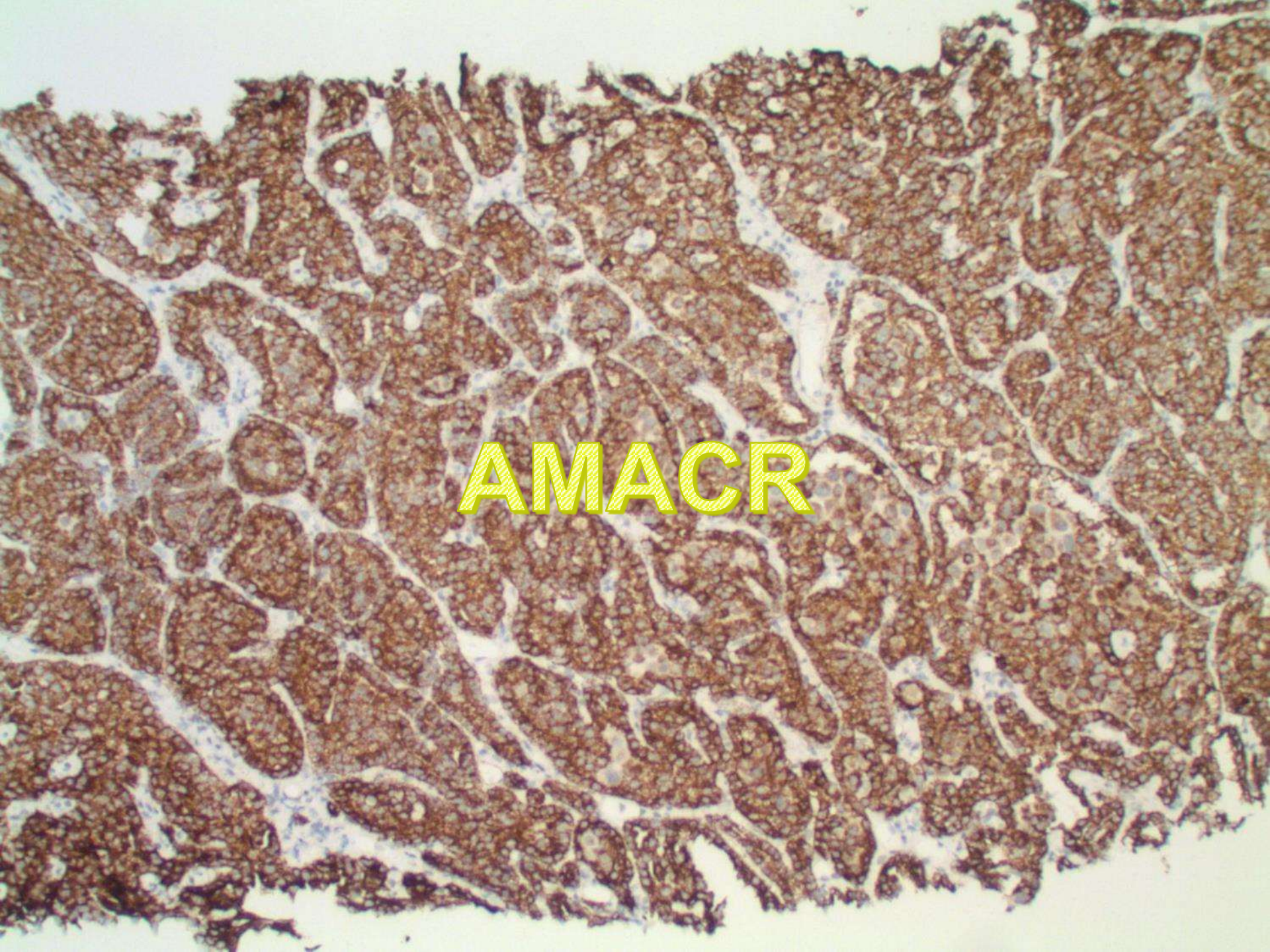


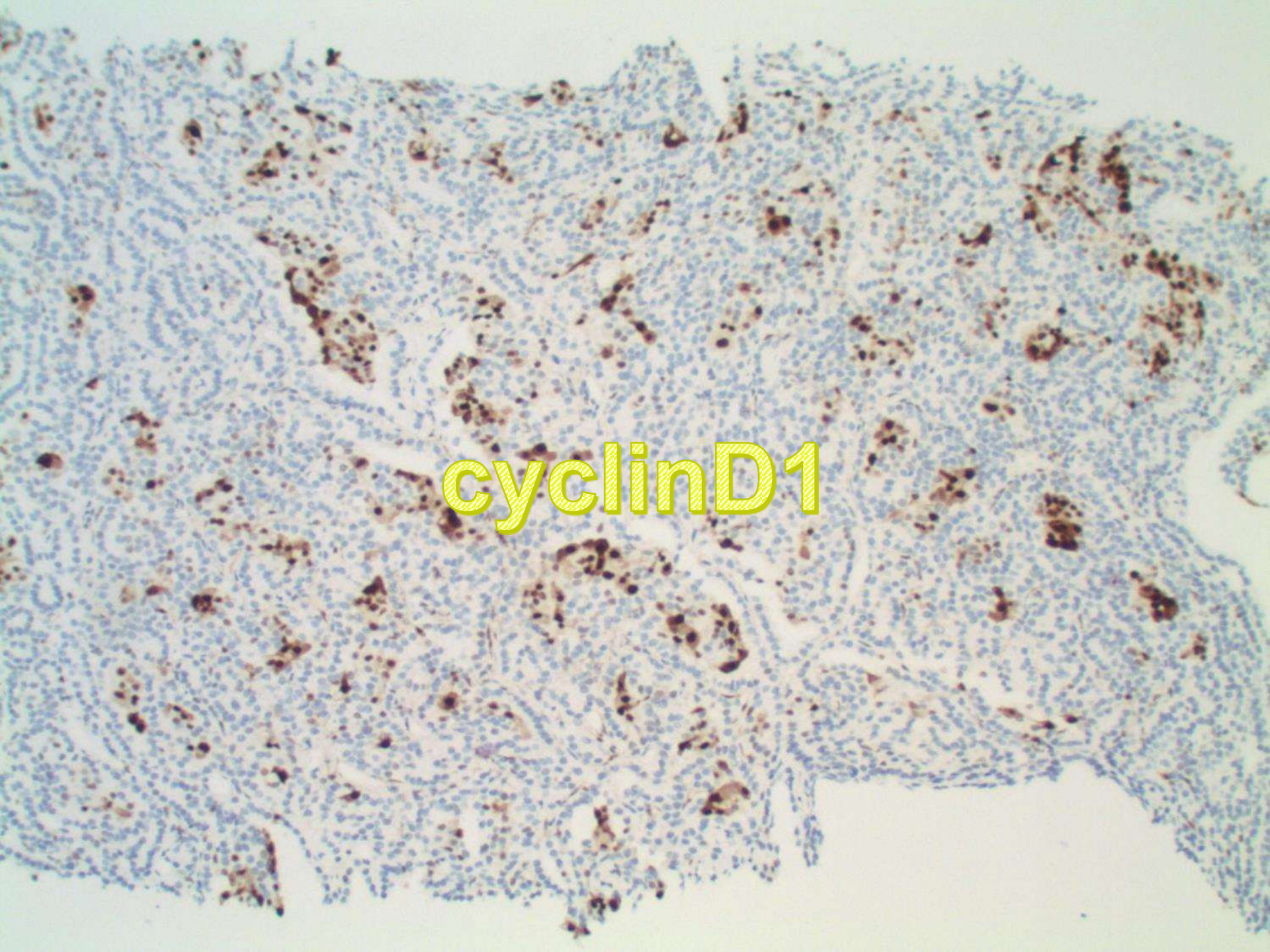
DDx

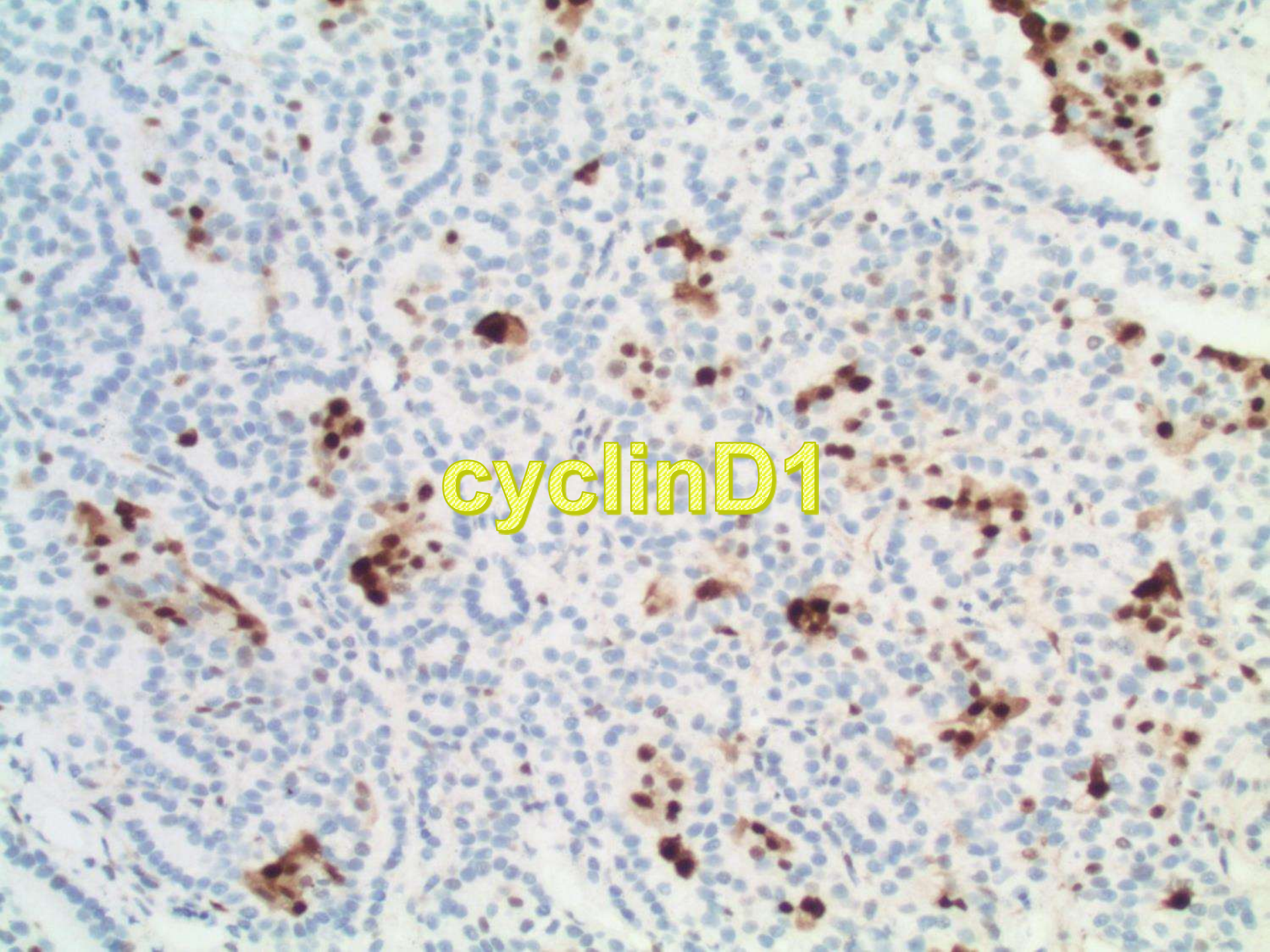
- Biphasic squamoid alveolar RCC
- Papillary RCC
- MiTF family translocation RCC
- Biphasic hyalinizing psammomatous RCC
- Papillary urothelial carcinoma


PAX8


CK7

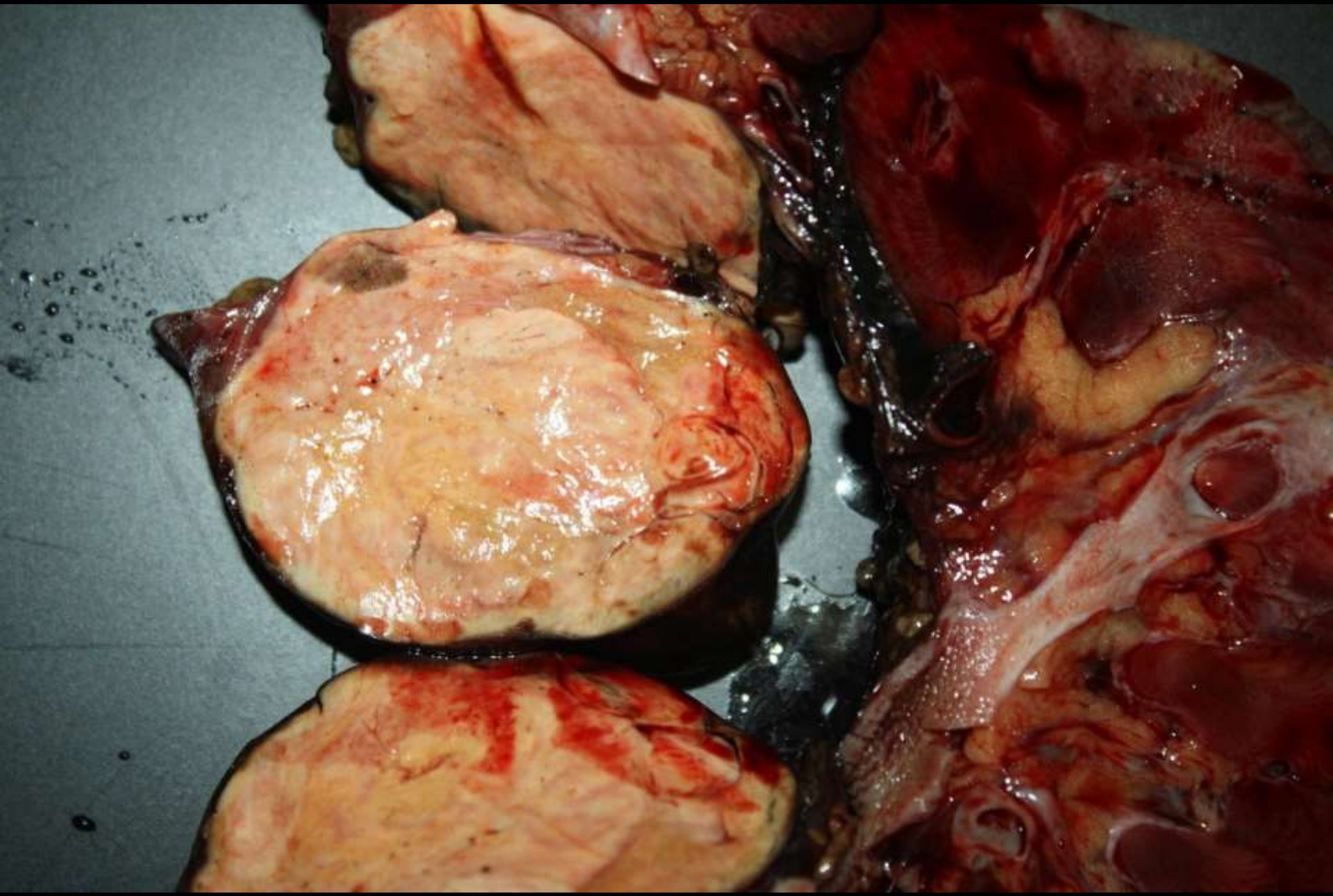

AMACR

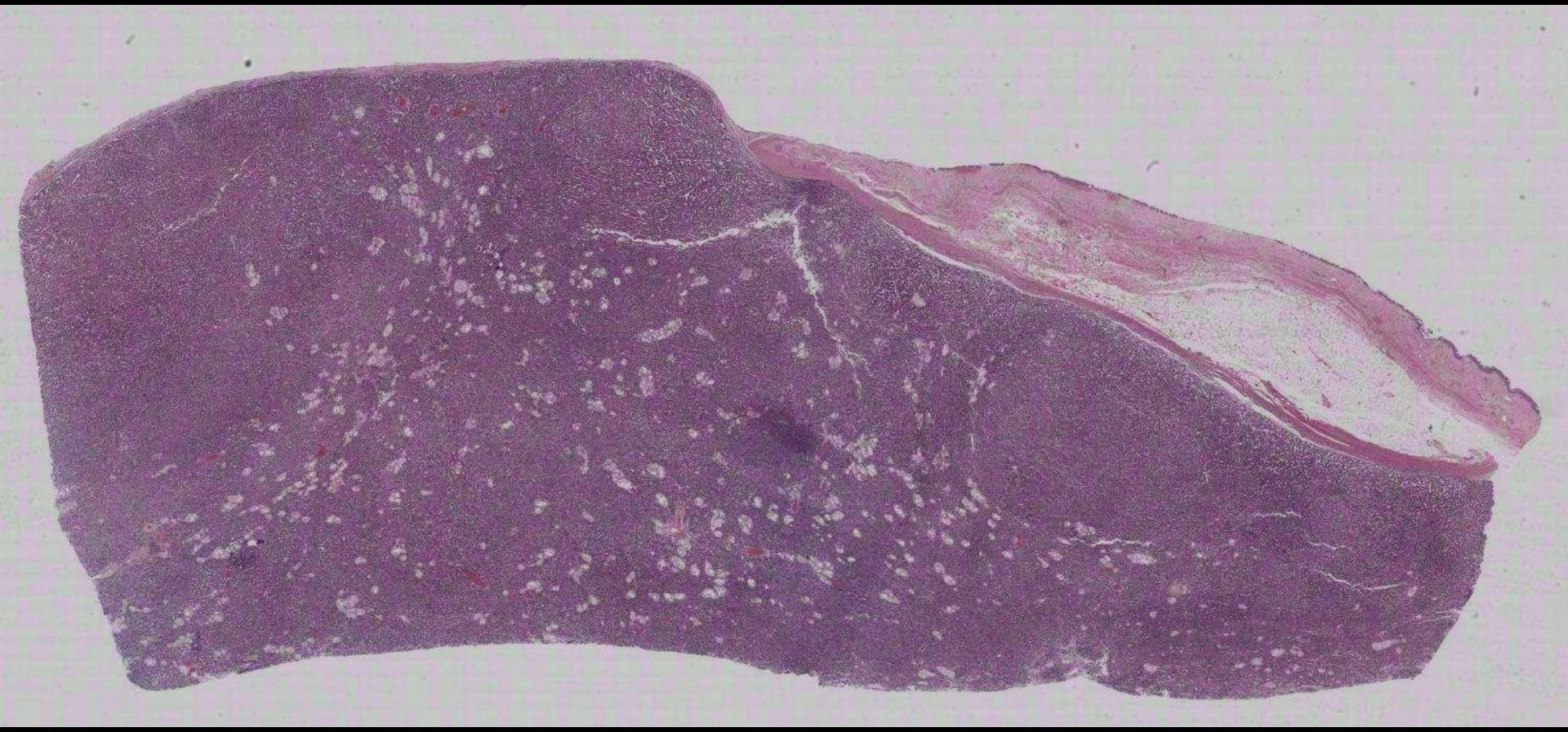

cyclinD1

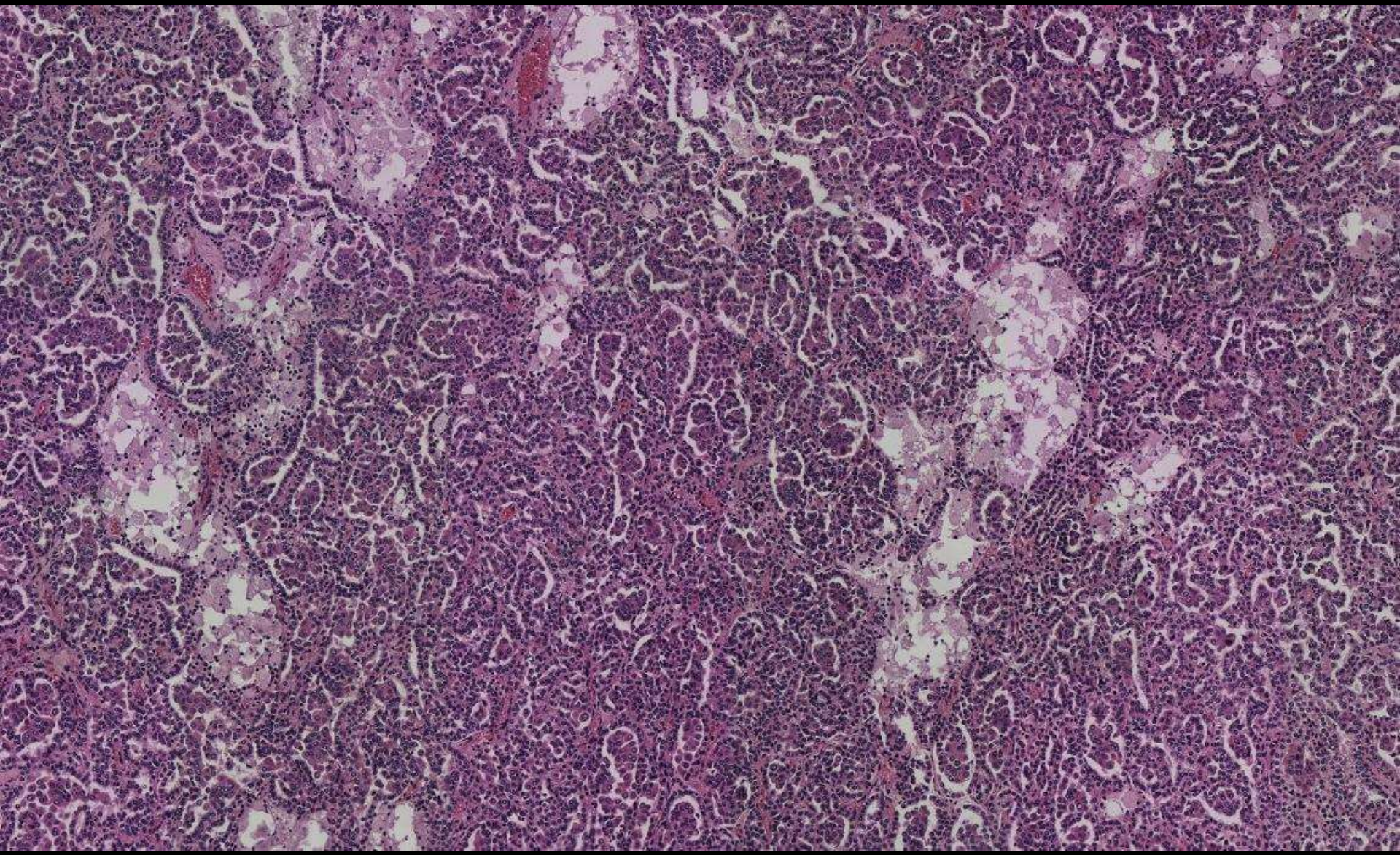

cyclinD1

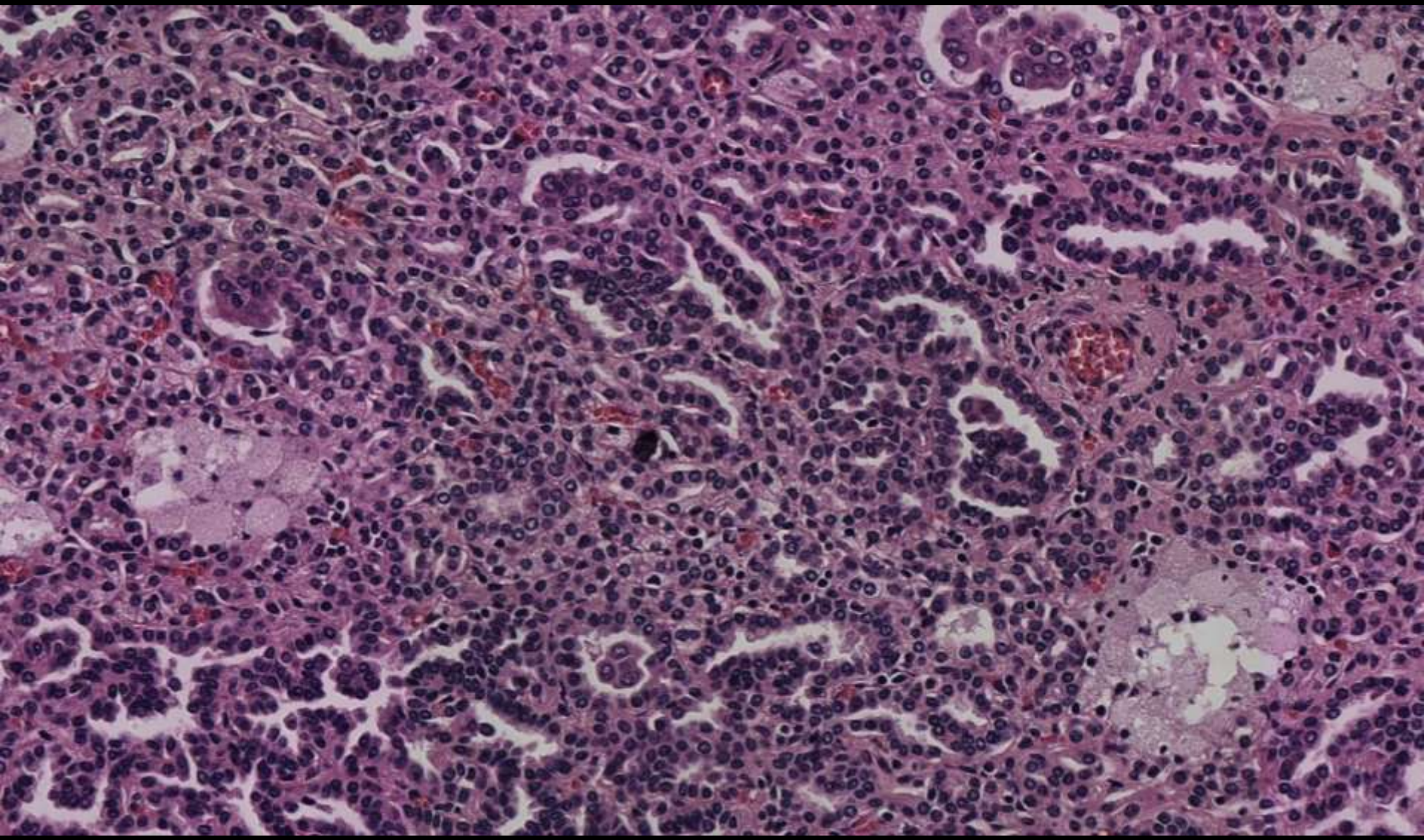
IHC summary

- PAX8+
- cyclinD1+
- CK7+
- AMACR+
- Weak CD10+
- Negative CAIX, TTF1





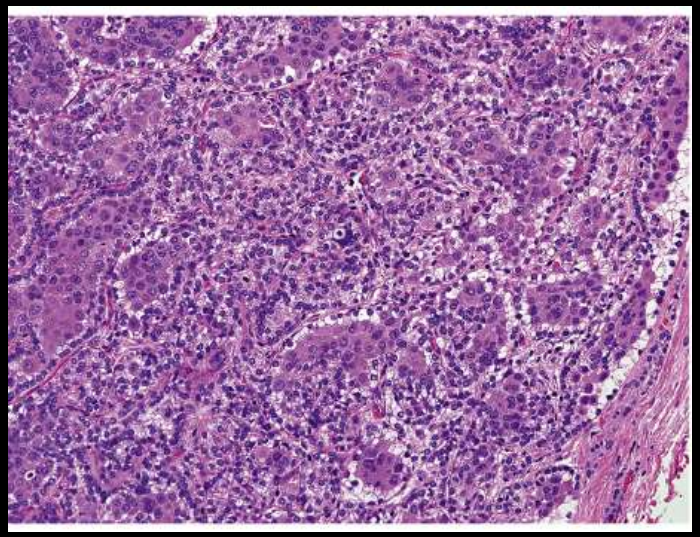




Biphasic alveolosquamoid renal carcinoma: a histomorphological, immunohistochemical, molecular genetic, and ultrastructural study of a distinctive morphologic variant of renal cell carcinoma☆,☆☆

Fredrik Petersson, MD, PhD[a,b], Stela Bulimbasic, MD, PhD[c], Ondrej Hes, MD, PhD[a,*], Pavol Slavik, MD[d], Petr Martínek, MSc[a], Michal Michal, MD[a], Barbora Gomolčáková[e], Milan Hora, MD, PhD[f], Ivan Damjanov, MD, PhD[g]

Annals of Diagnostic Pathology 16 (2012) 459–469



Biphasic Squamoid Alveolar Renal Cell Carcinoma

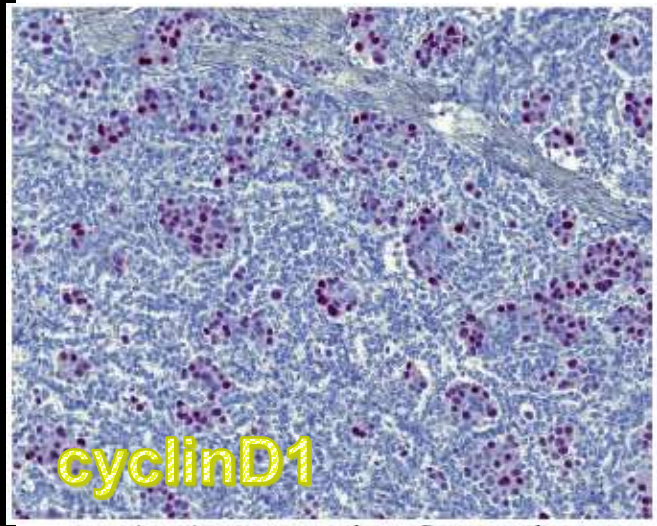
A Distinctive Subtype of Papillary Renal Cell Carcinoma?

Ondrej Hes, MD, PhD, Enric Condom Mundo, MD, PhD,†‡ Kvetoslava Peckova, MD,* Jose I. Lopez, MD,§ Petr Martinek, PhD,* Tomas Vanecek, PhD,* Giovanni Falconieri, MD,‖ Abbas Agaimy, MD,¶ Whitney Davidson, MD,# Fredrik Petersson, MD, PhD,** Stela Bulimbasic, MD, PhD,†† Ivan Damjanov, MD, PhD,# Mireya Jimeno, MD,‡‡ Monika Ulamec, MD, PhD,§§ Miroslav Podhola, MD, PhD,‖‖ Maris Sperga, MD,¶¶ Maria Pane Foix, MD,†‡ Ksenya Shelekhova, MD, PhD,## Kristyna Kalusova, MD,*** Milan Hora, MD, PhD,*** Pavla Rotterova, MD, PhD,* Ondrej Daum, MD, PhD,* Kristyna Pivovarcikova, MD,* and Michal Michal, MD**

Abstract: Biphasic squamoid alveolar renal cell carcinoma (BSARCC) has been recently described as a distinct neoplasm. Twenty-one cases from 12 institutions were analyzed using routine histology, immunohistochemistry, array comparative genomic hybridization (aCGH) and fluorescence in situ hybridization. Tumors were removed from 11 male and 10 female patients, whose age ranged from 53 to 79 years. The size of tumors ranged from 1.5 to 16 cm. Follow-up information was available for 14 patients (range, 1 to 96 mo), and metastatic spread was found in 5 cases. All tumors comprised 2 cell populations arranged in organoid structures: small, low-grade neoplastic cells with scant cytoplasm usually lining the inside of alveolar structures, and larger squamoid cells with more prominent cytoplasm and larger vesicular nuclei arranged in compact nests. In 9/21 tumors there was a visible transition from such solid and alveolar areas into papillary components. Areas composed of large squamoid cells comprised 10% to 80% of total tumor volume. Emperipolesis was present in all (21/21) tumors. Immunohistochemically, all cases were positive for cytokeratin 7, EMA, vimentin, and cyclin D1. aCGH (confirmed by fluorescence in situ hybridization) in 5 analyzable cases revealed multiple numerical chromosomal changes including gains of chromosomes 7 and 17 in all cases. These changes were further disclosed in 6 additional cases, which were unsuitable for aCGH. We conclude that tumors show a morphologic spectrum ranging from RCC with papillary architecture and large squamoid cells to fully developed BSARCC. Emperipolesis in squamoid cells was a constant finding. All BSARCCs expressed CK7, EMA, vimentin, and cyclin D1. Antibody to cyclin D1 showed a unique and previously not recognized pattern of immunohistochemical staining. Multiple chromosomal aberrations were identified in all analyzable cases including gains of chromosomes 7 and 17, indicating that they are akin to papillary RCC. Some BSARCCs were clinically aggressive, but their prognosis could not be predicted from currently available data. Present microscopic, immunohistochemical, and molecular genetic data strongly support the view that BSARCC is a distinctive and peculiar morphologic variant of papillary RCC.

Key Words: kidney, biphasic squamoid alveolar renal cell carcinoma, papillary renal cell carcinoma, immunohistochemistry, aCGH, FISH

(*Am J Surg Pathol* 2016;40:664–675)

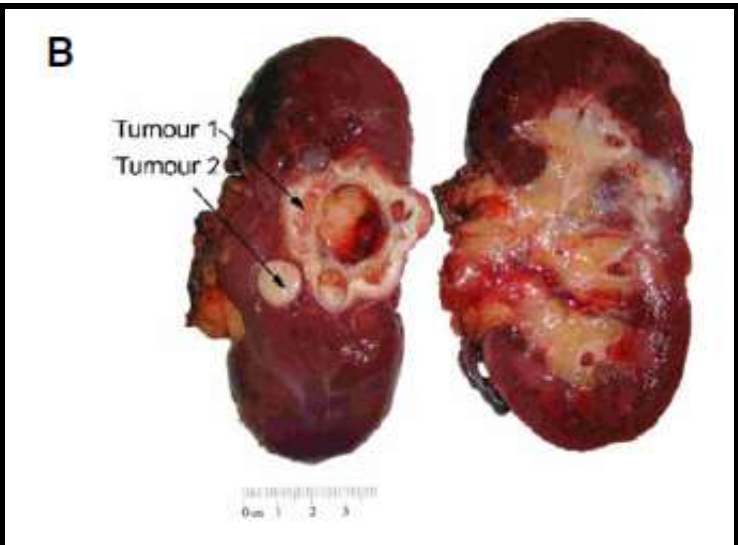


Histopathology 2018, 72, 777–785. DOI: 10.1111/his.13432

Biphasic papillary renal cell carcinoma is a rare morphological variant with frequent multifocality: a study of 28 cases

Kiril Trpkov,[1] Daniel Athanazio,[1,*,†] Cristina Magi-Galluzzi,[2] Helene Yilmaz,[2] David Clouston,[3] Abbas Agaimy,[4] Sean R Williamson,[5] Fadi Brimo,[6] Jose I Lopez,[7] Monika Ulamec,[8] Nathalie Rioux-Leclercq,[9] Maysoun Kassem,[9] Nilesh Gupta,[5] Arndt Hartmann,[4] Xavier Leroy,[10] Samir Al Bashir,[11] Asli Yilmaz[1] & Ondřej Hes[12]

[1]*Calgary Laboratory Services and University of Calgary, Rockyview General Hospital, Calgary, AB, Canada,* [2]*Cleveland Clinic, Cleveland, OH, USA,* [3]*Tissupath, Melbourne, Vic., Australia,* [4]*Friedrich-Alexander-University, Erlangen, Germany,* [5]*Henry Ford Health System, Detroit, MI, USA,* [6]*McGill University, Montreal, QC, Canada,* [7]*Cruces University Hospital, BioCruces Institute, University of the Basque Country (UPV/EHU), Bizkaia, Spain,* [8]*University Clinical Hospital Centre Sestre Milosrdnice, Zagreb, Croatia,* [9]*CHU Pontchaillou, Rennes, France,* [10]*Centre de Biologie Pathologie, Lille, France,* [11]*Jordan University of Science and Technology, Irbid, Jordan, and* [12]*Charles University, Pilsen, Czech Republic*



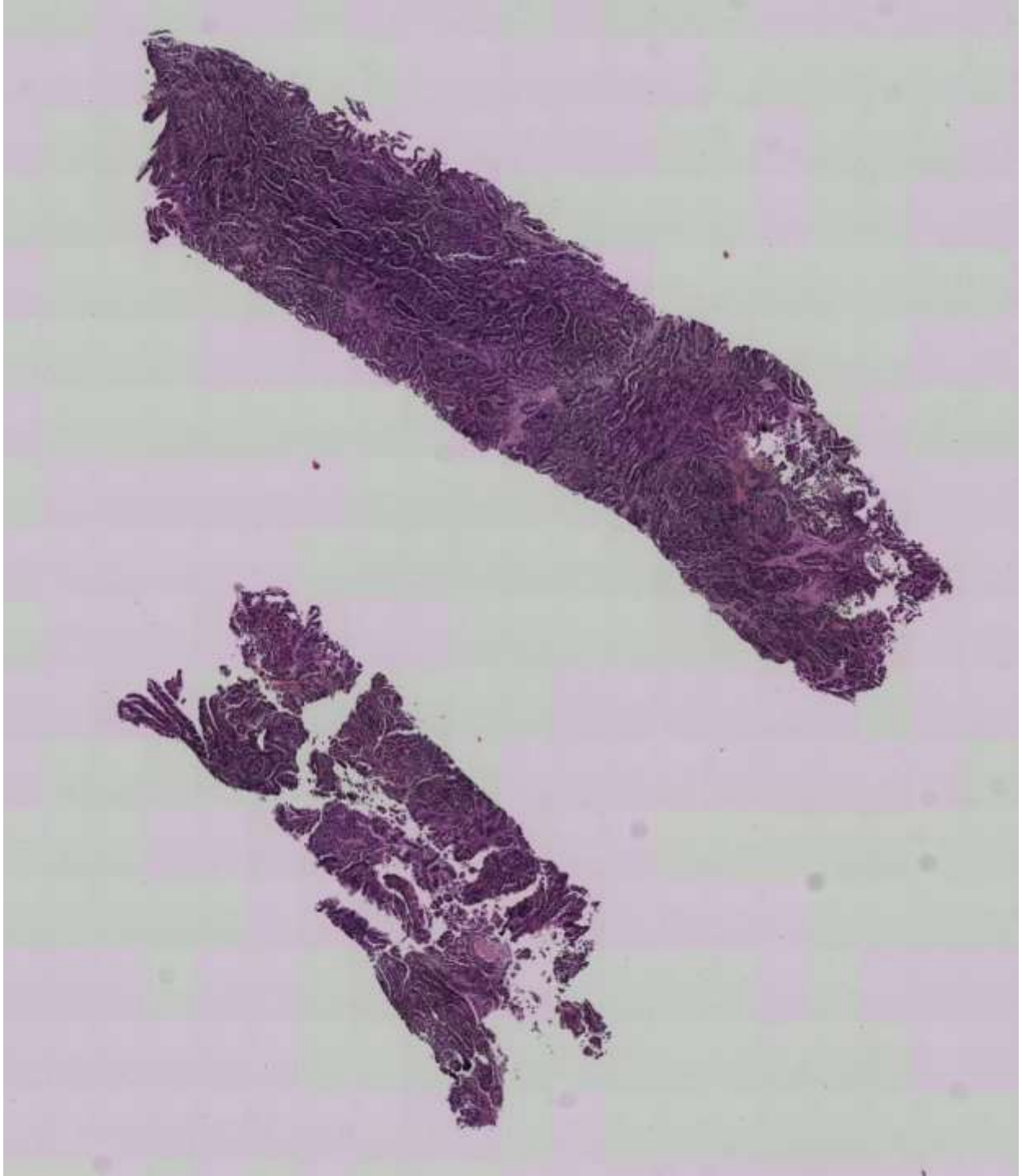
Biphasic alveolosquamoid RCC

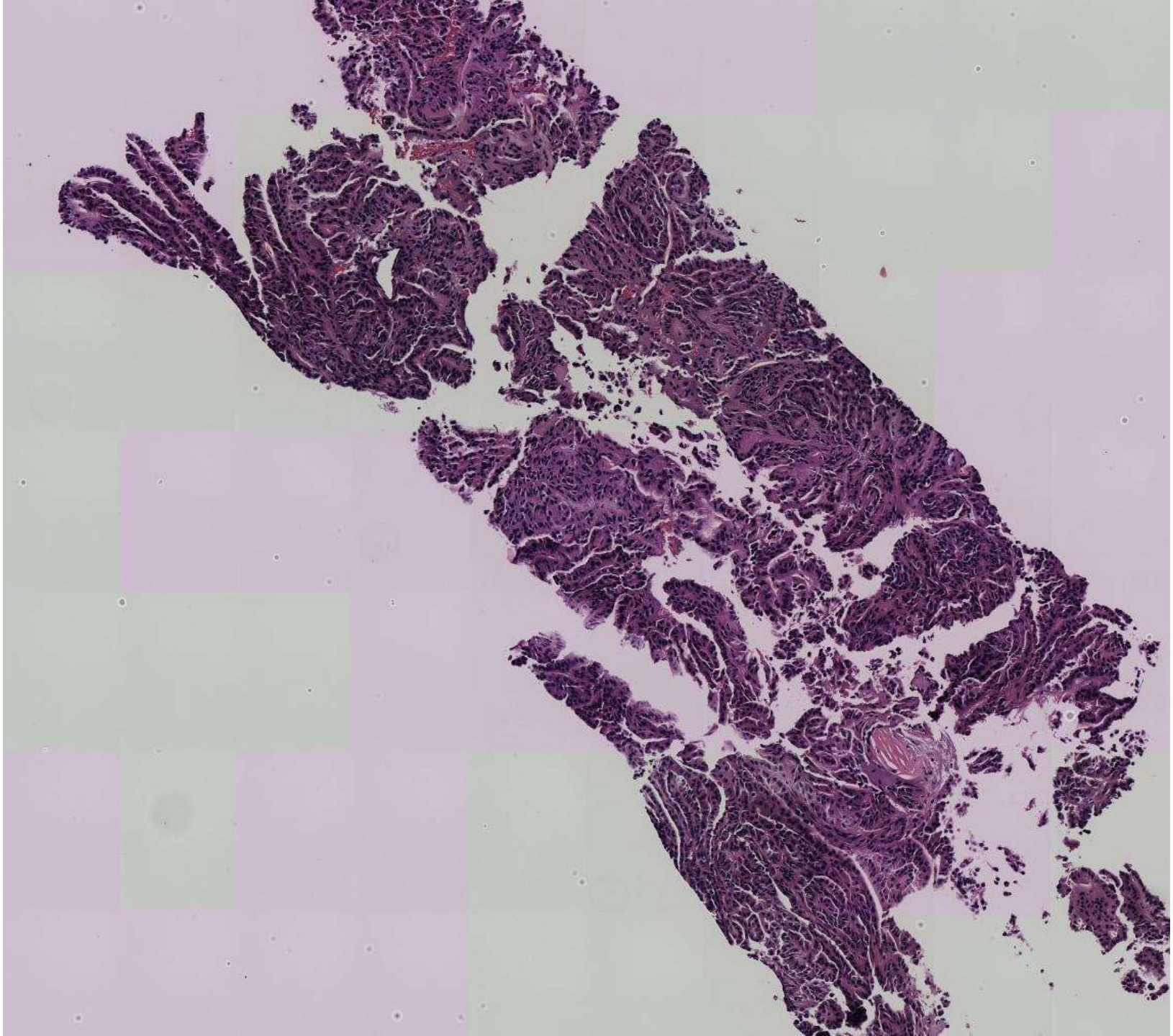
- **Uncommon, likely a variant of papillary RCC**
- **Often multifocal, wide size ranges**
- **Subset can be clinically aggressive**
- **Biphasic+squamoid histology, emperipolesis**
- **Unique cyclinD1+**
  - Also PAX8+ CK7+ AMACR+ vimentin+

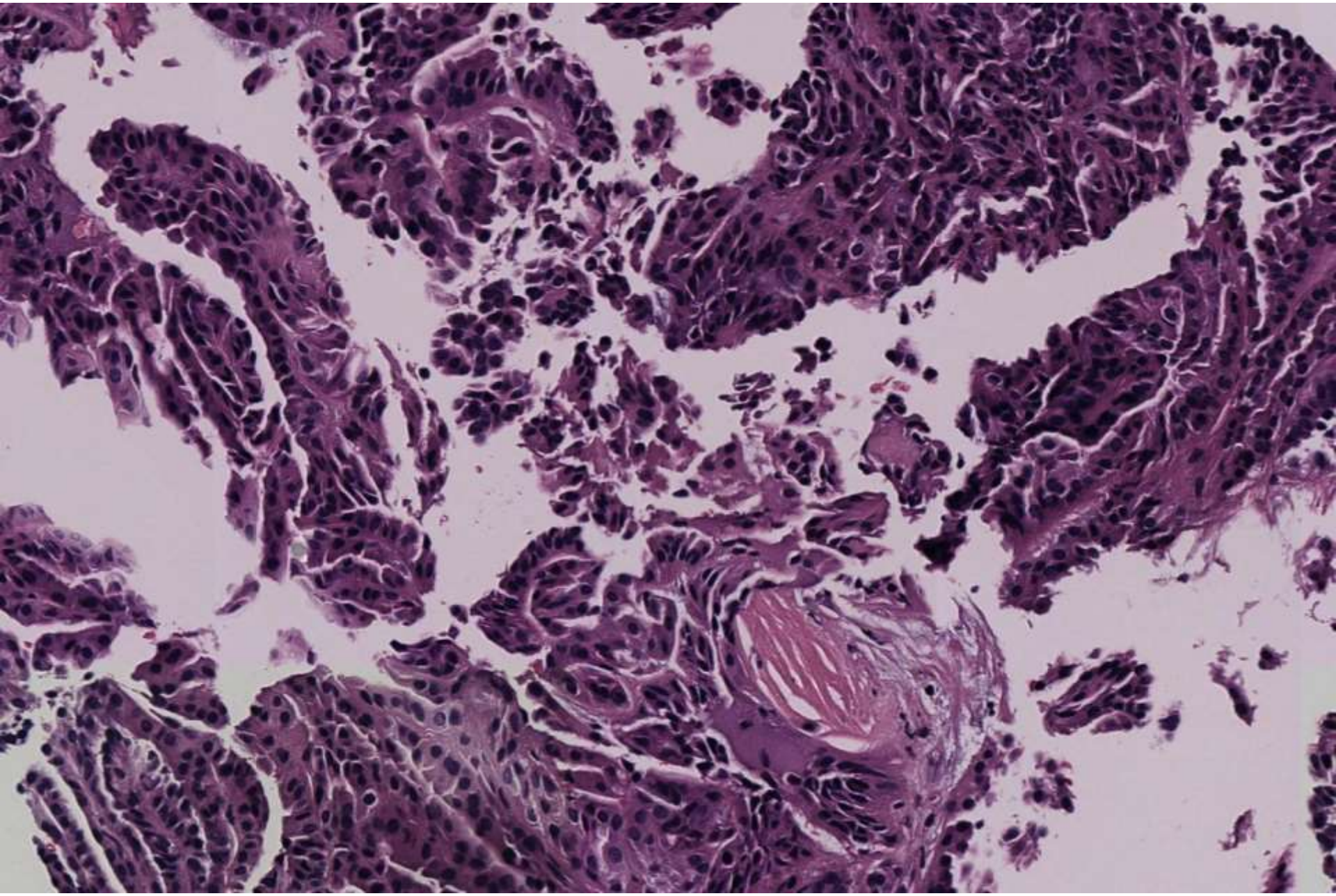
21-0404
scanned slide avail!

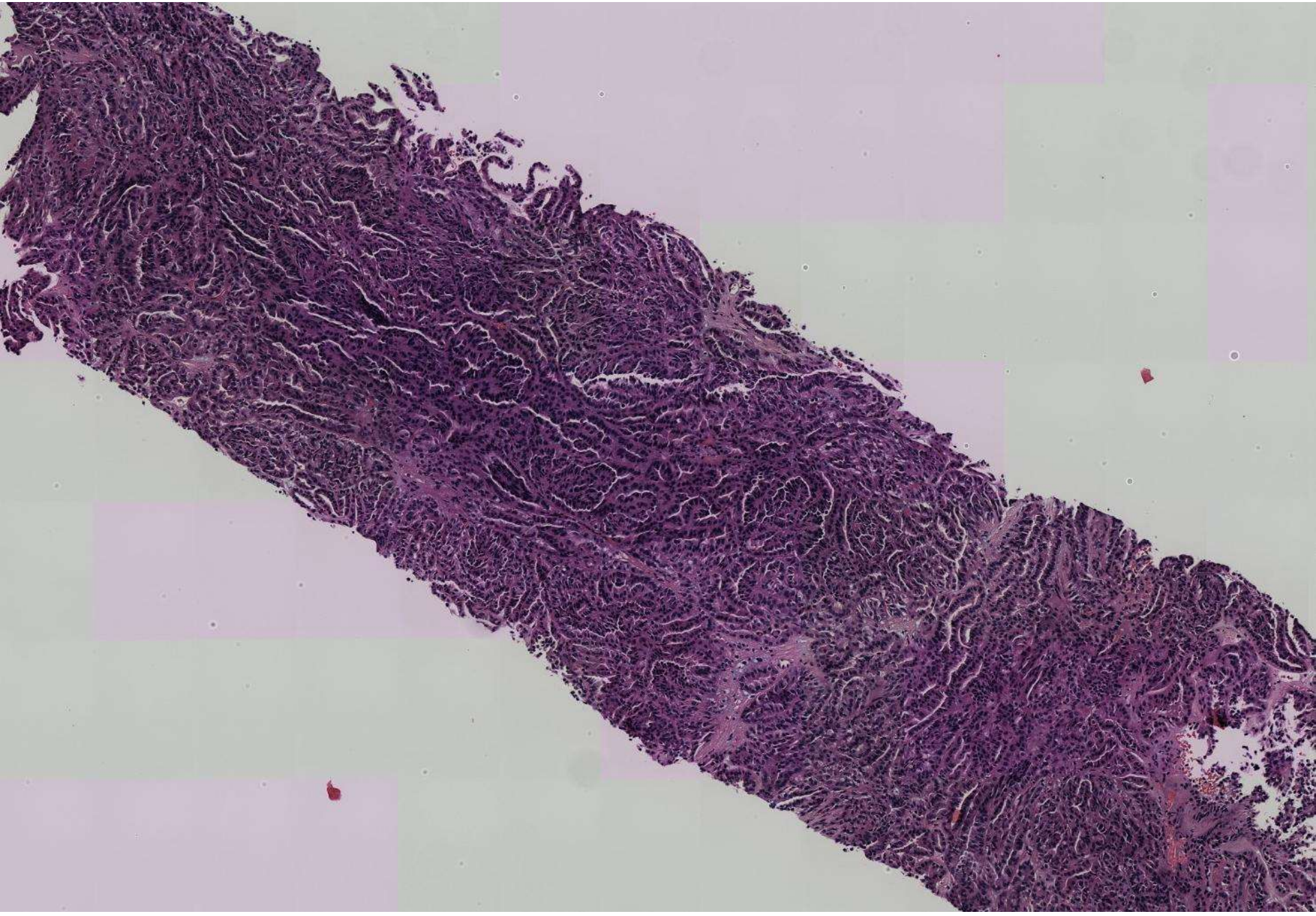
Ankur Sangoi; El Camino Hospital

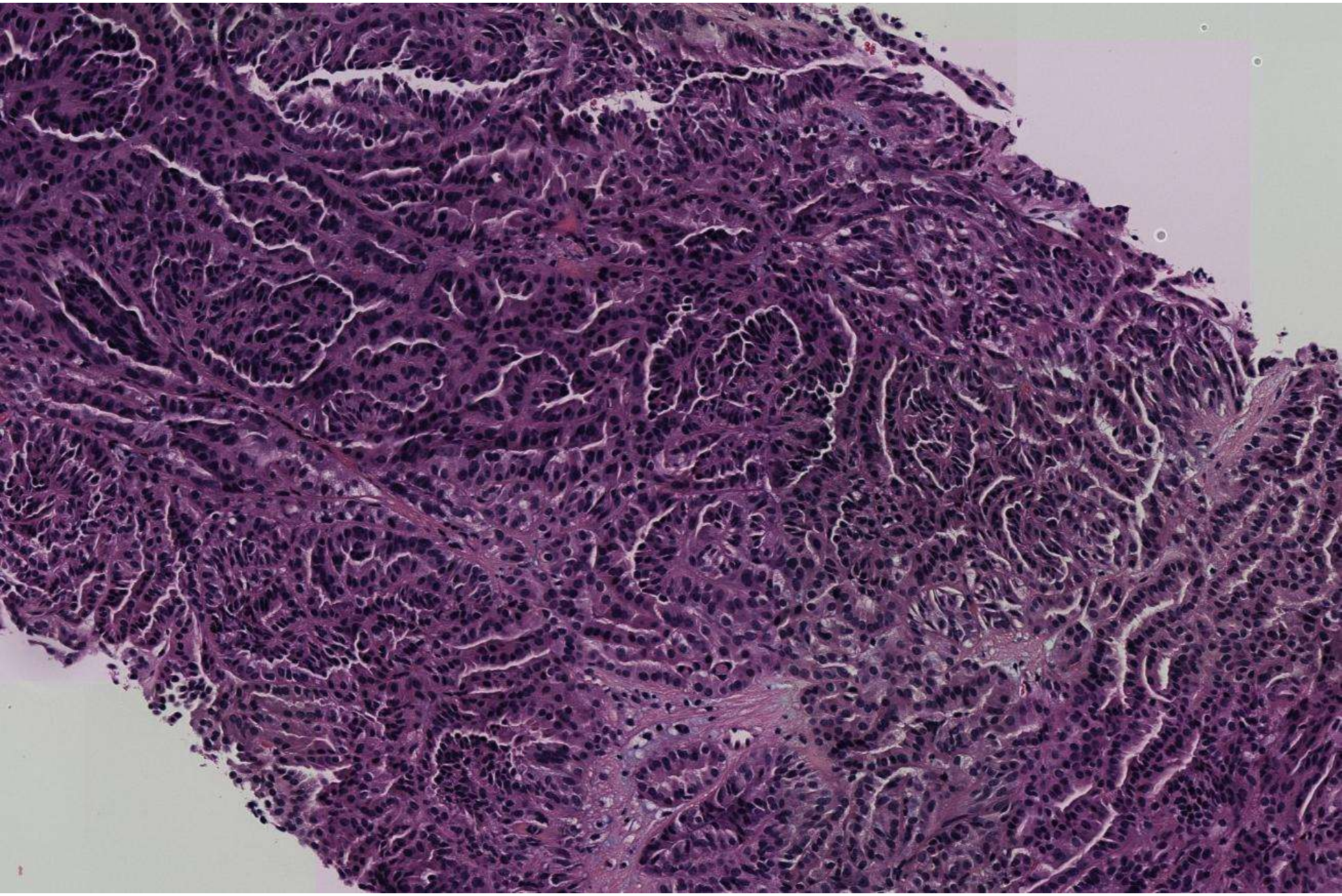
Adult F with kidney mass, h/o enlarged thyroid, core biopsy with ablation performed.

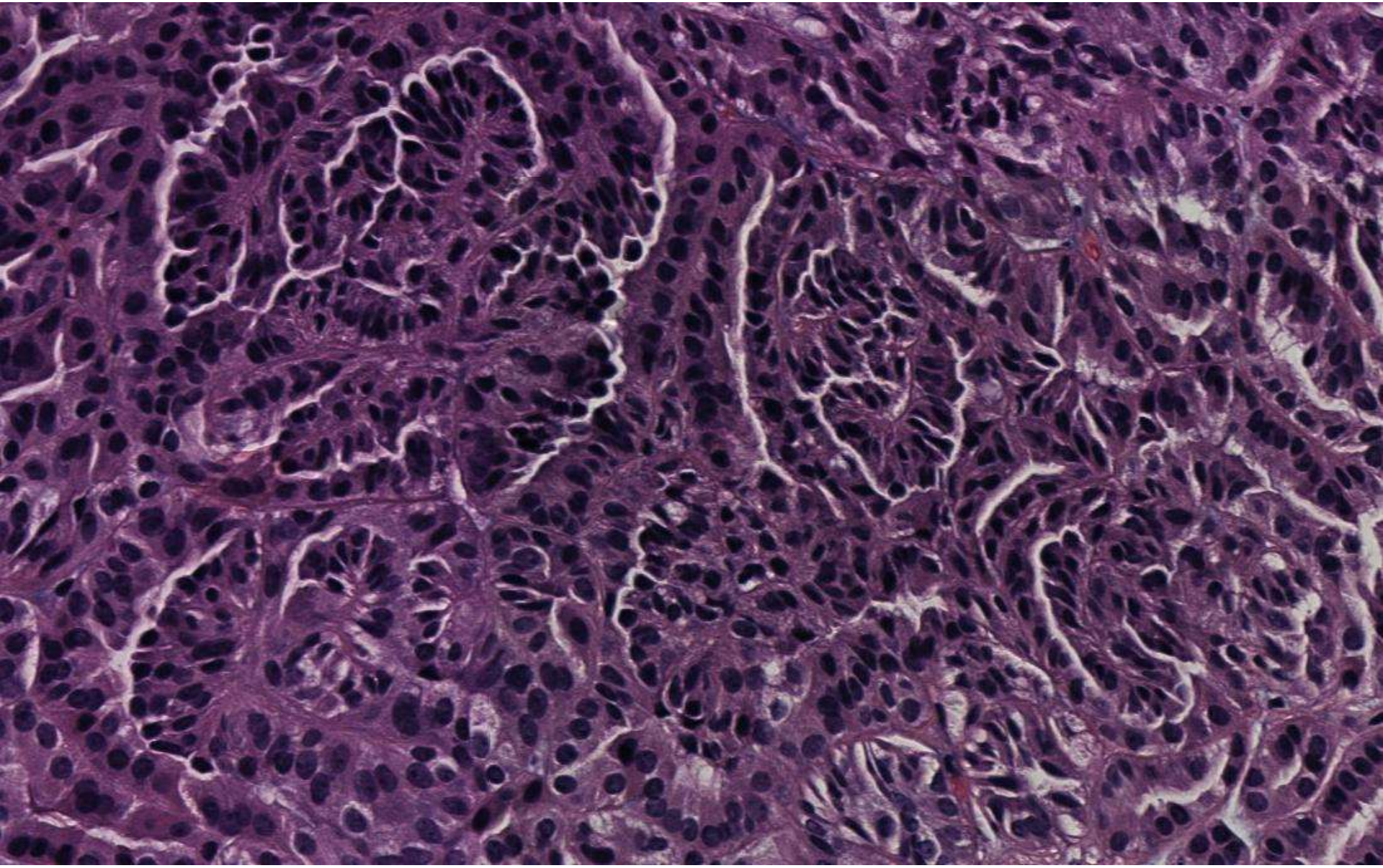


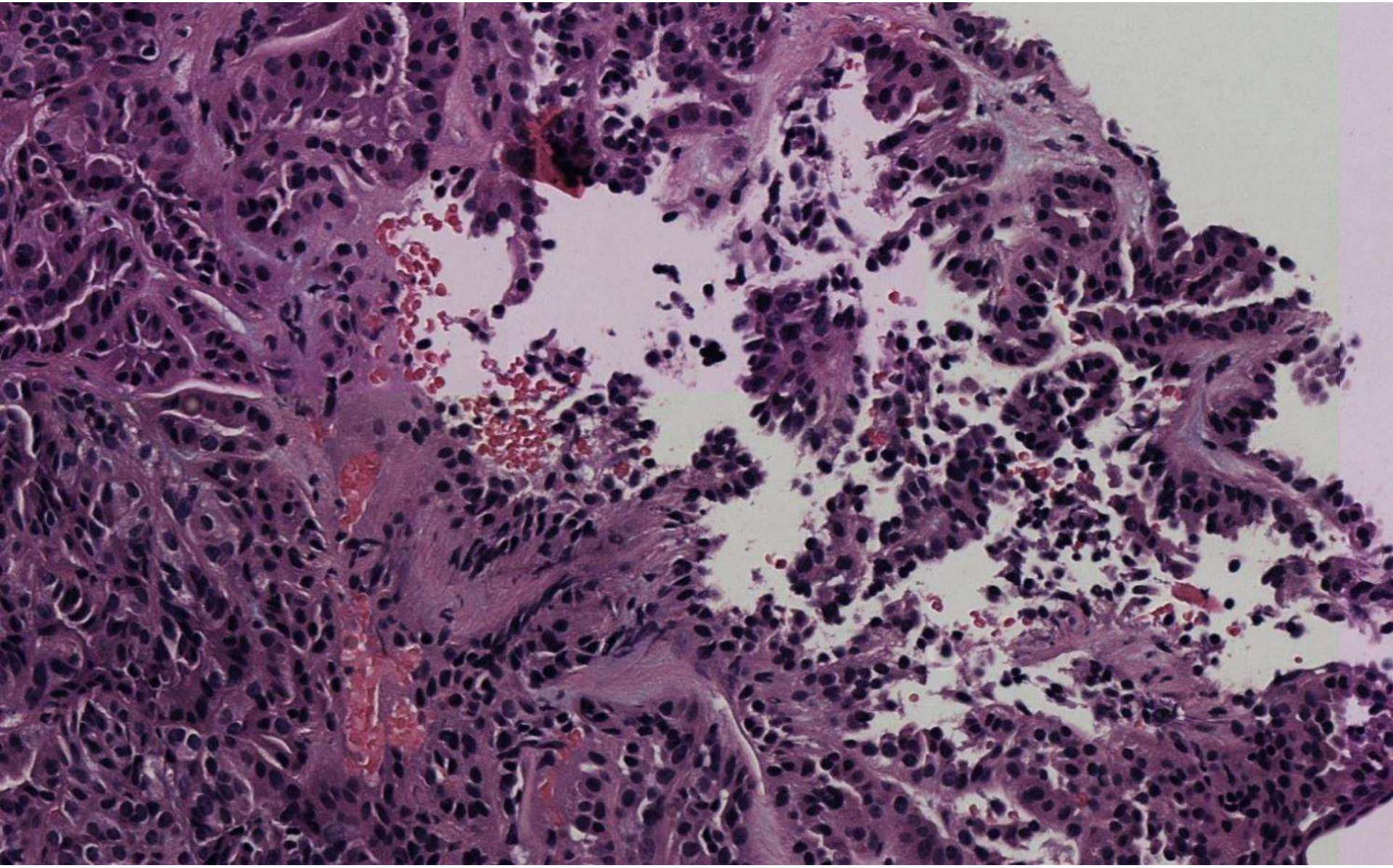






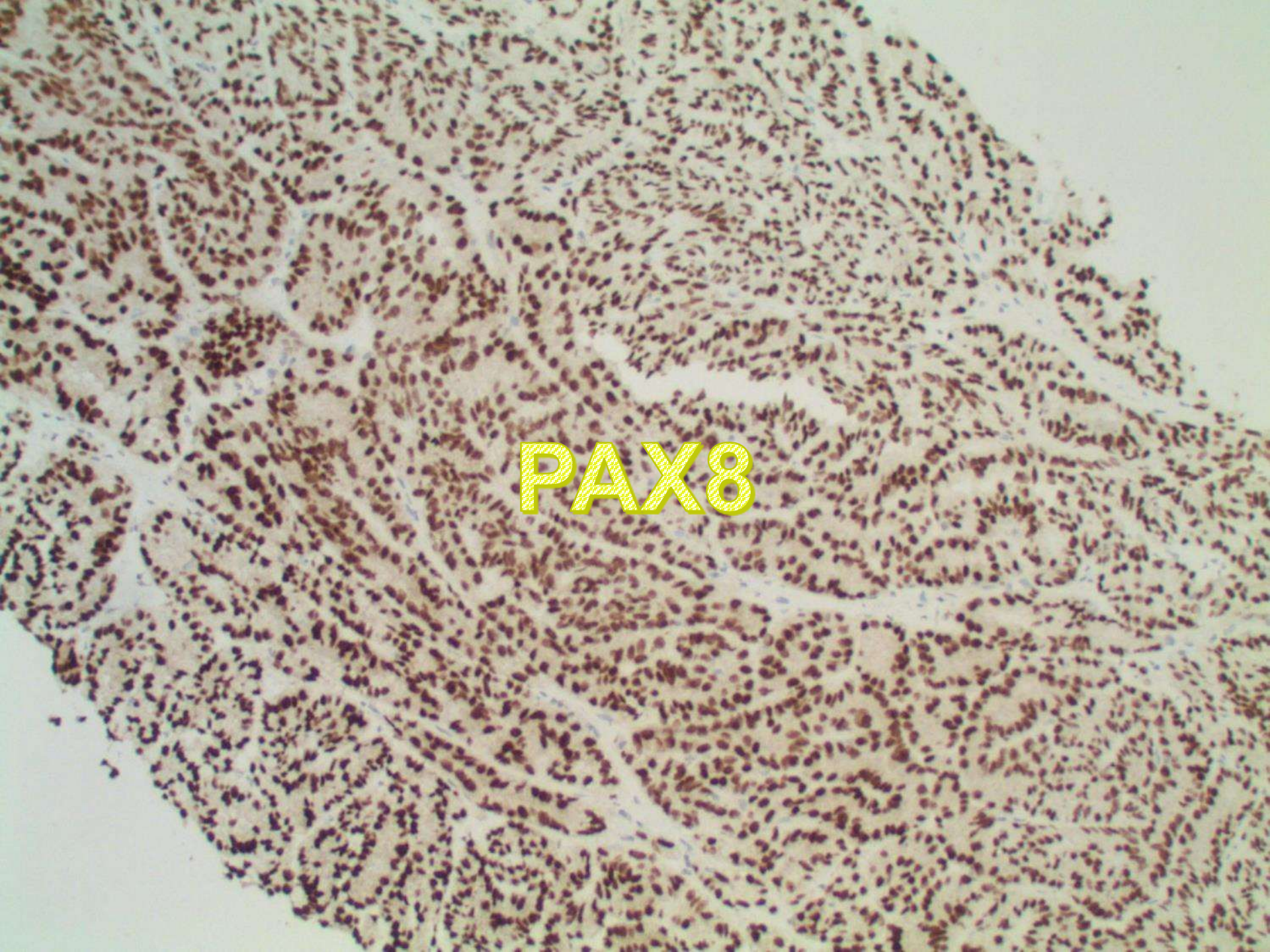


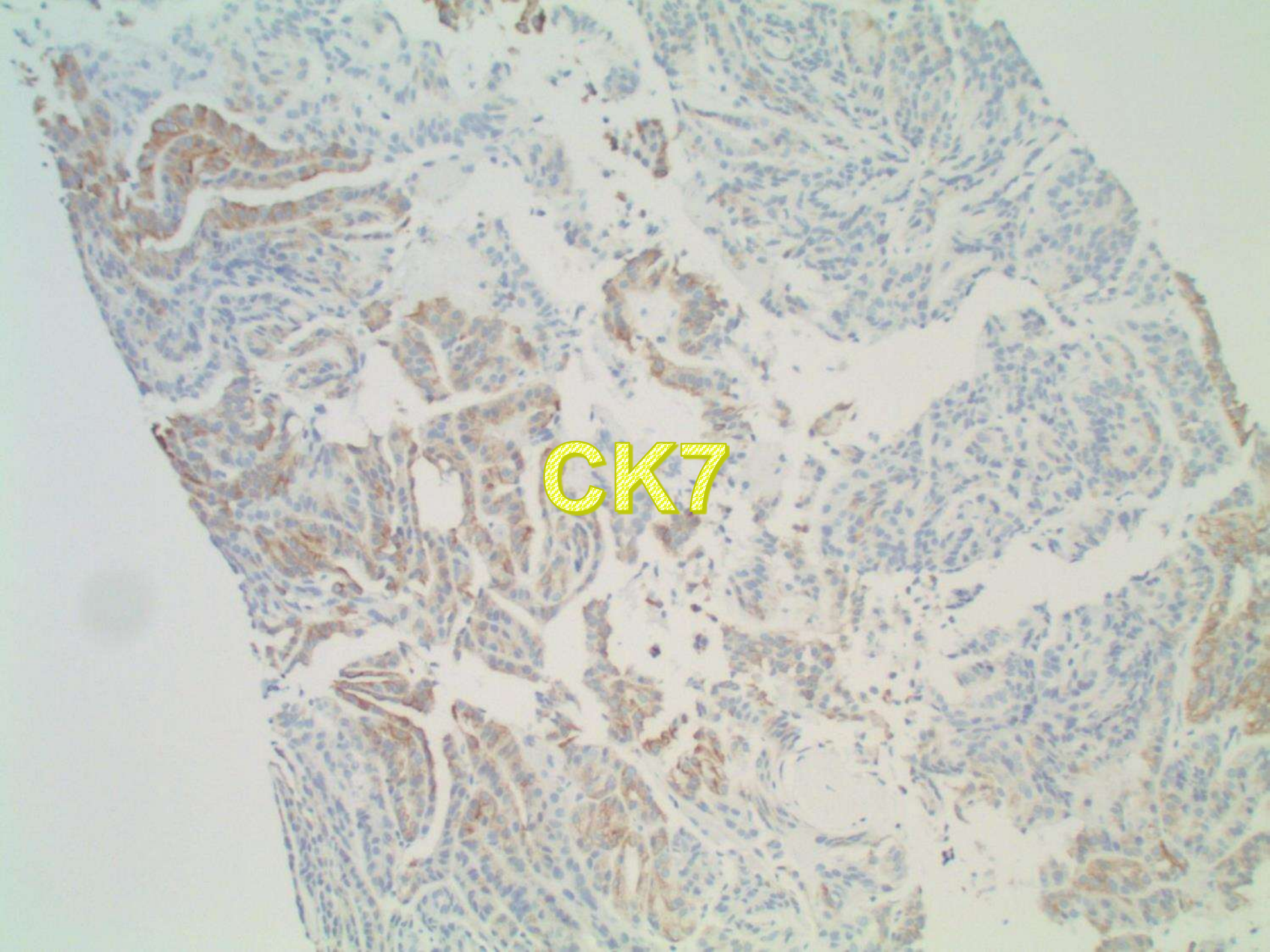


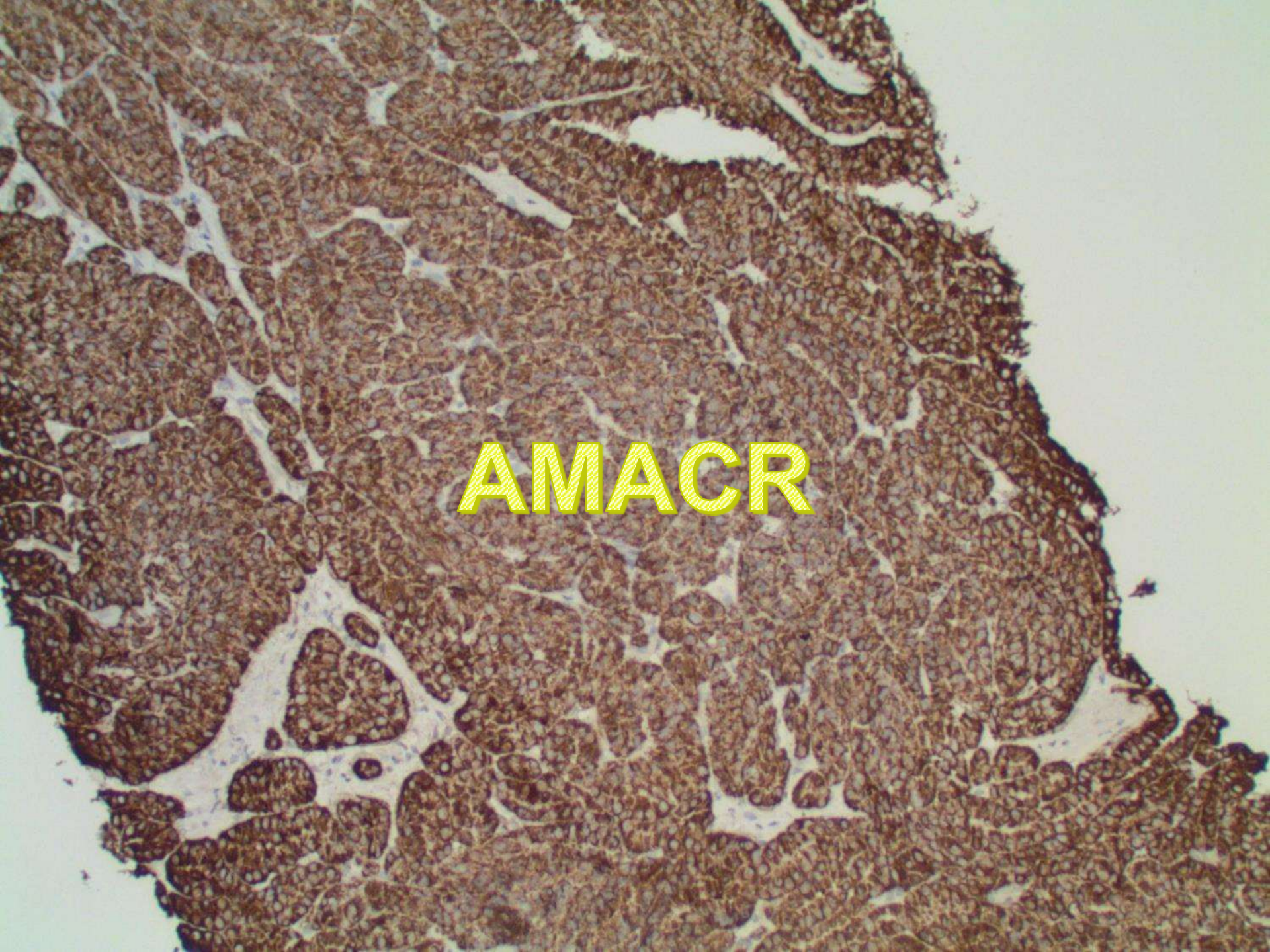


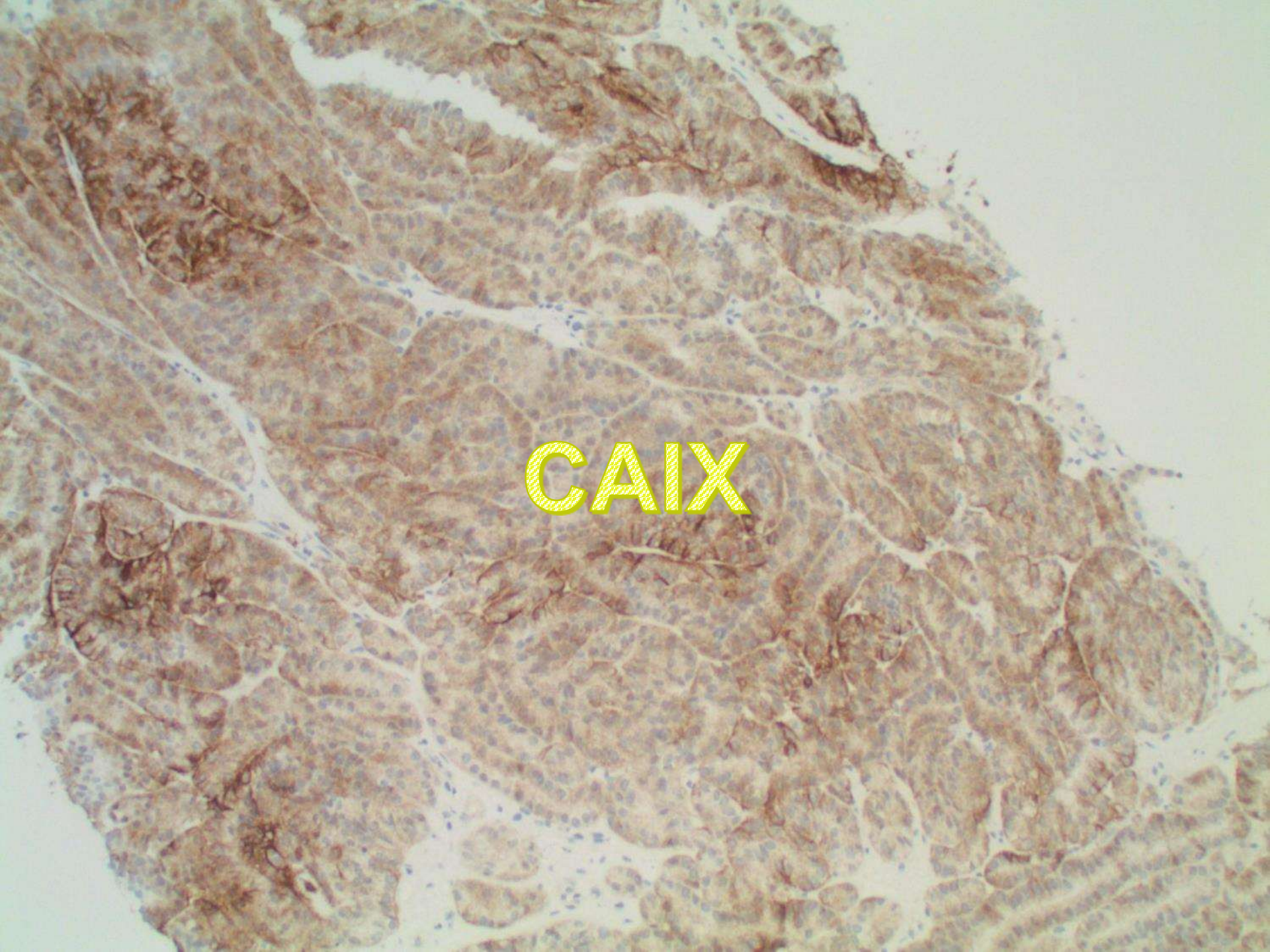
DDx

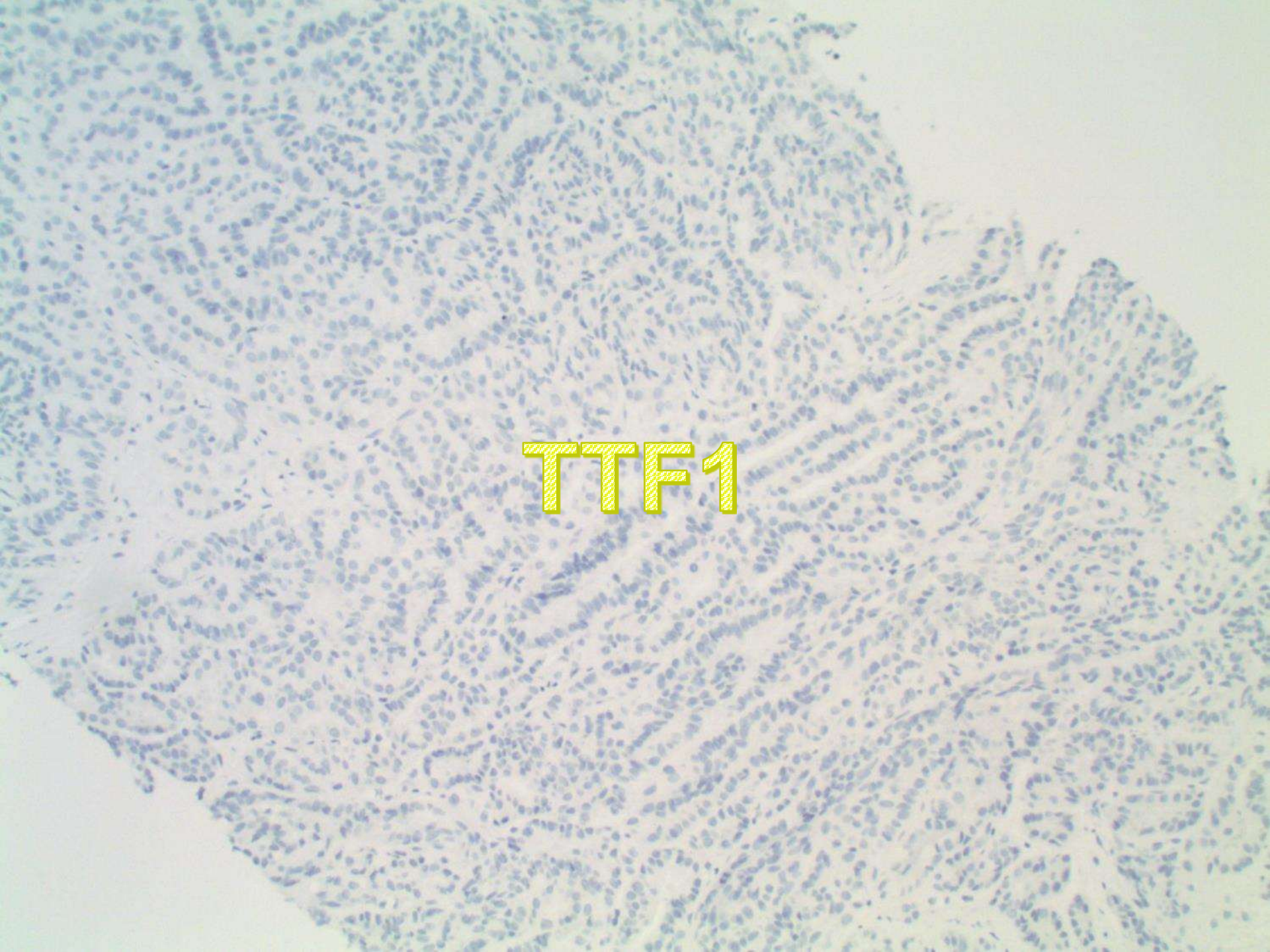
- Papillary renal cell carcinoma
- Mucinous tubular & spindle cell carcinoma
- Clear cell tubulopapillary renal cell carcinoma (“clear cell papillary RCC”)
- Papillary adenoma
- Metastatic carcinoma


PAX8


CK7

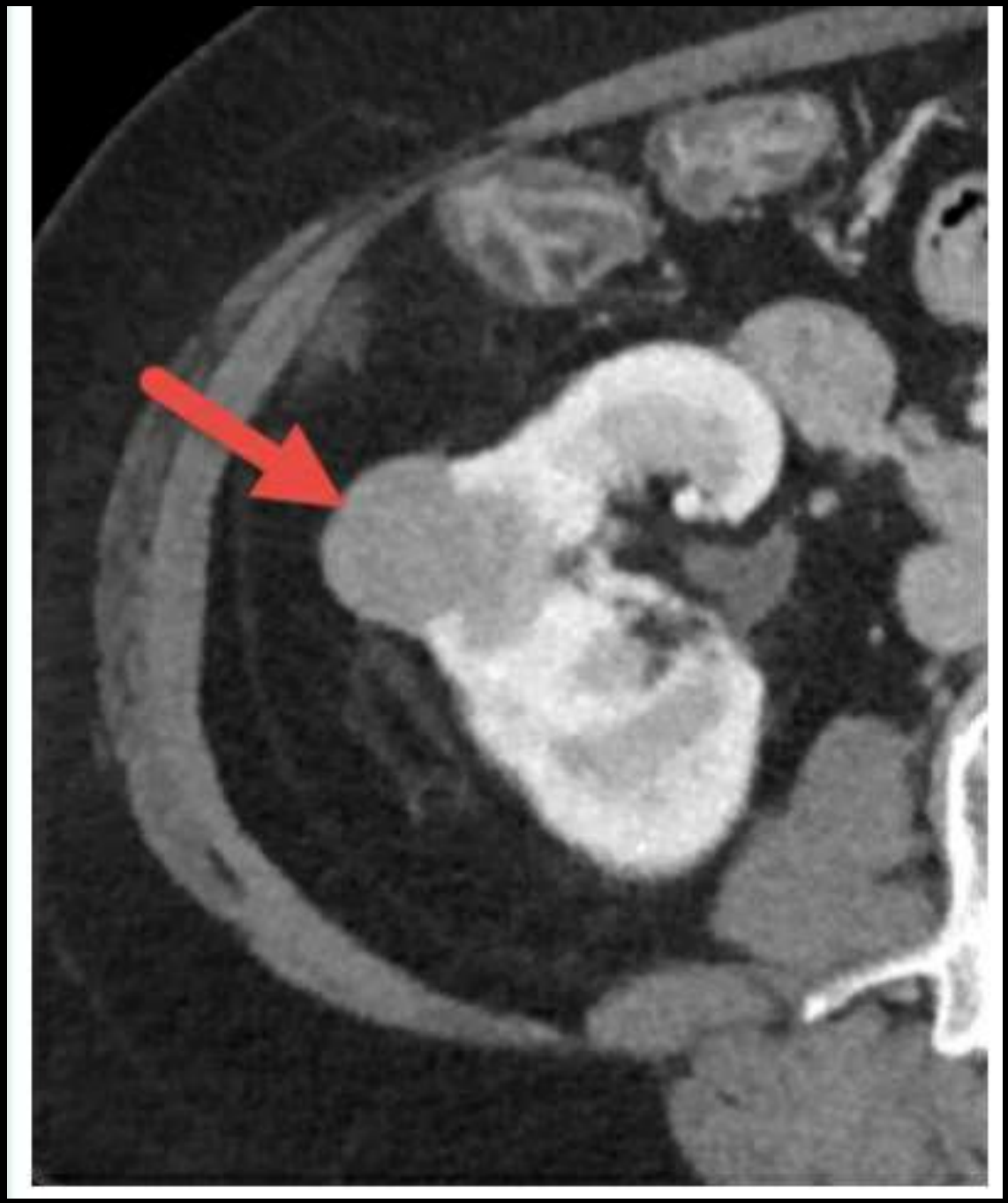

AMACR


CAIX


TTF1

CT:

2.4cm circumscribed renal mass



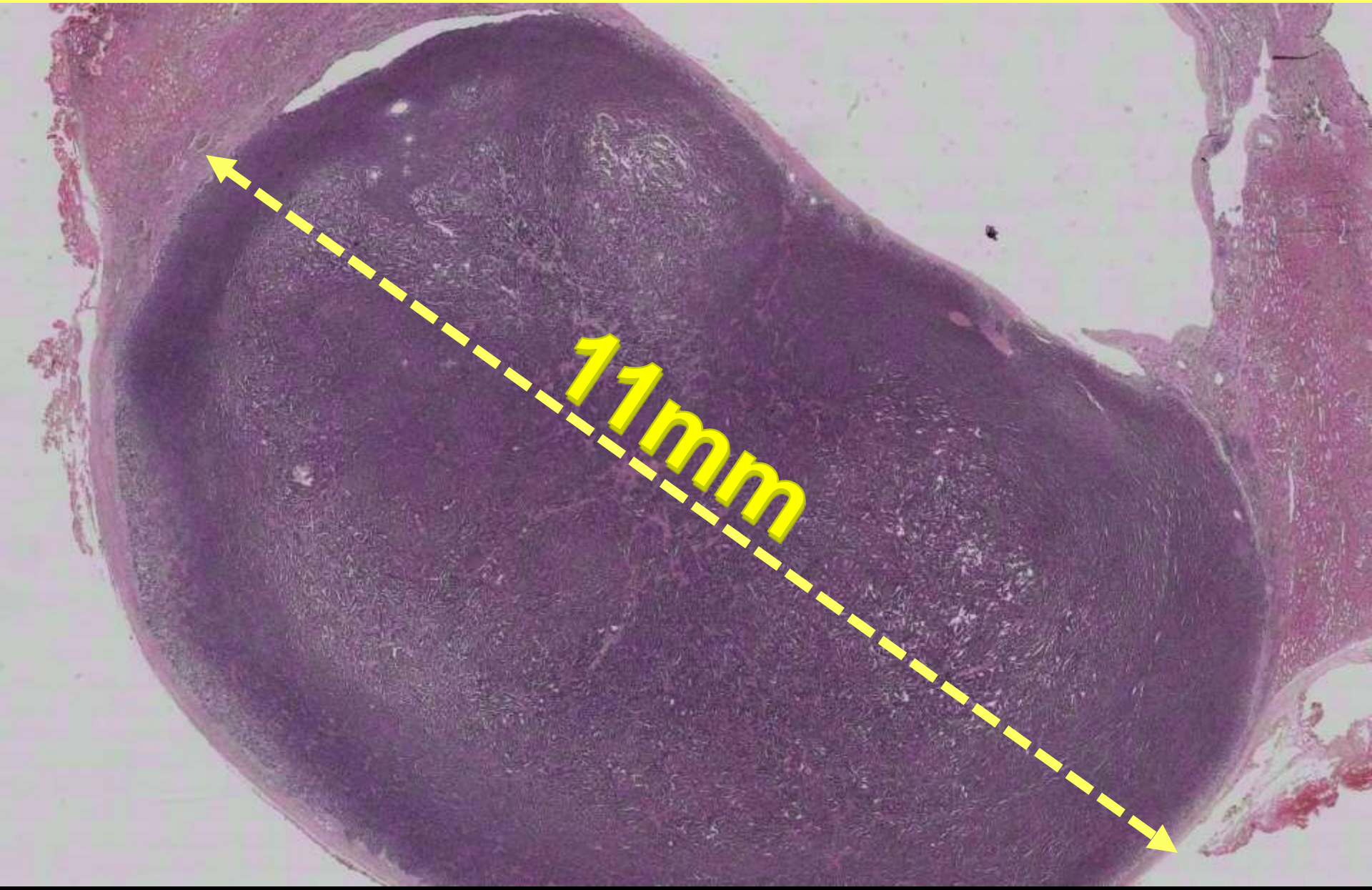
Final diagnosis

- **Right kidney mass, core biopsy with ablation:**
  - Consistent with papillary renal cell carcinoma

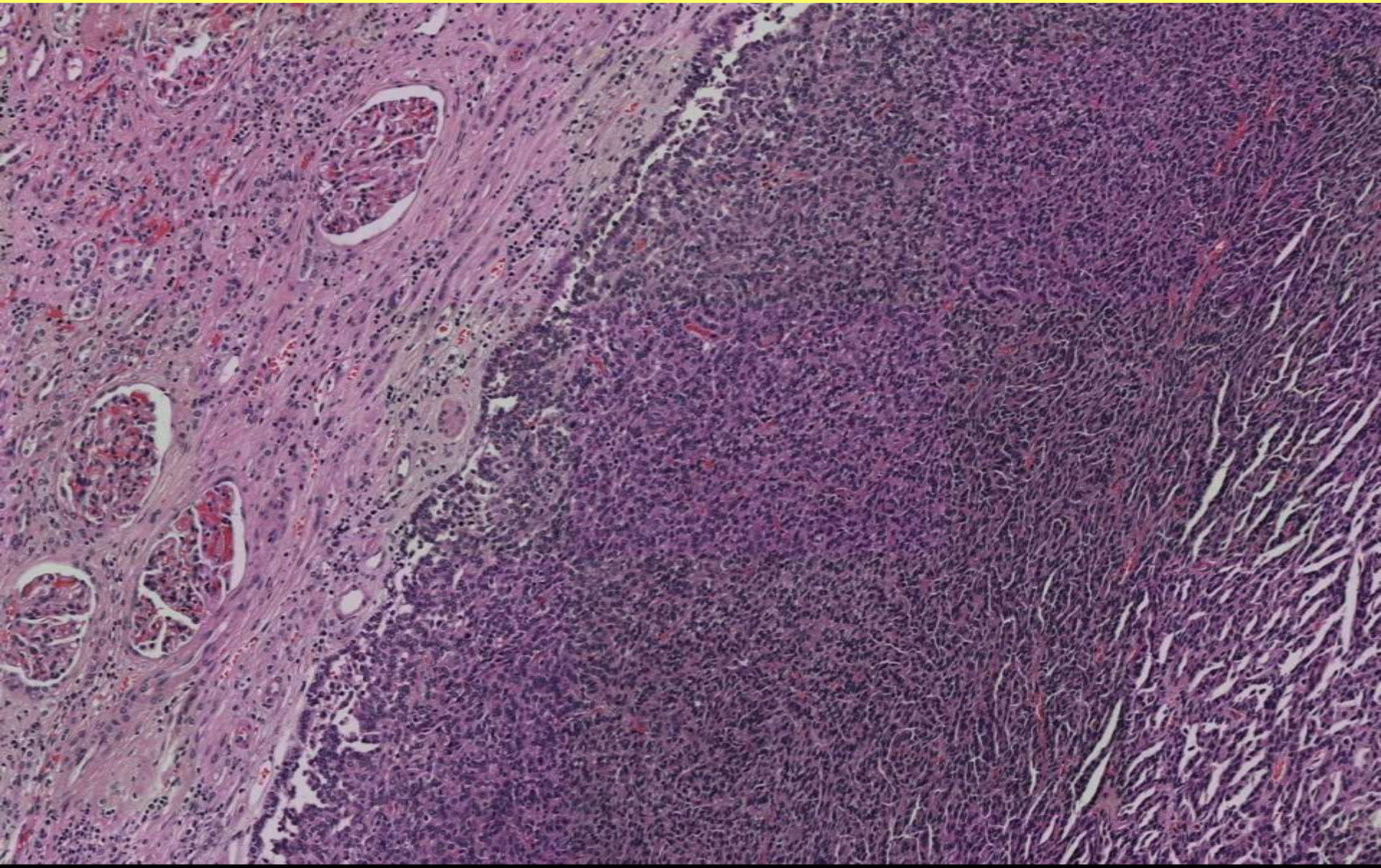
Key DDx: papillary adenoma

- **criteria:**
  - ≤15mm size cut-off
  - WHO/ISUP grade 1-2 nuclei
  - unencapsulated

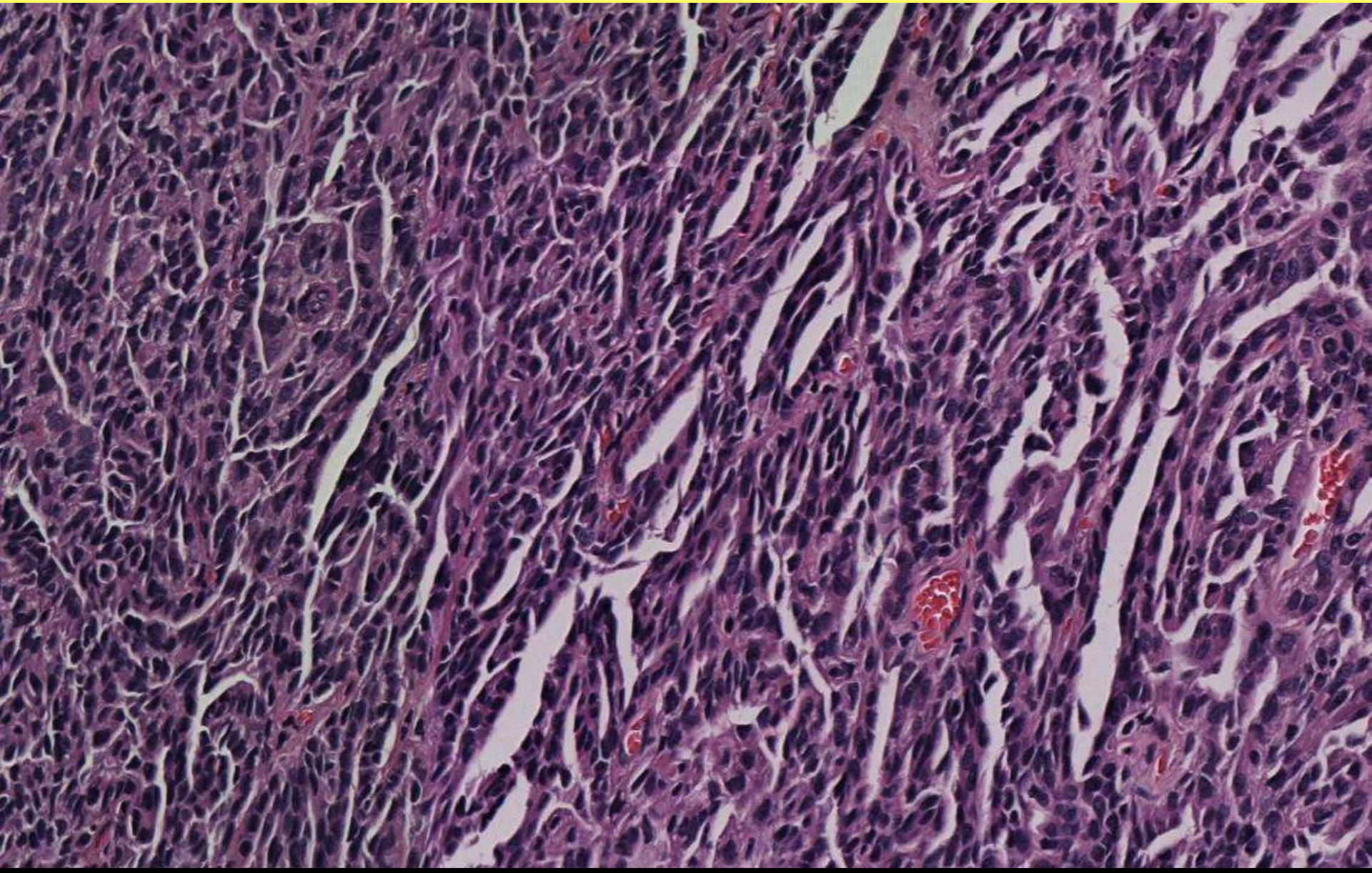
Papillary adenoma



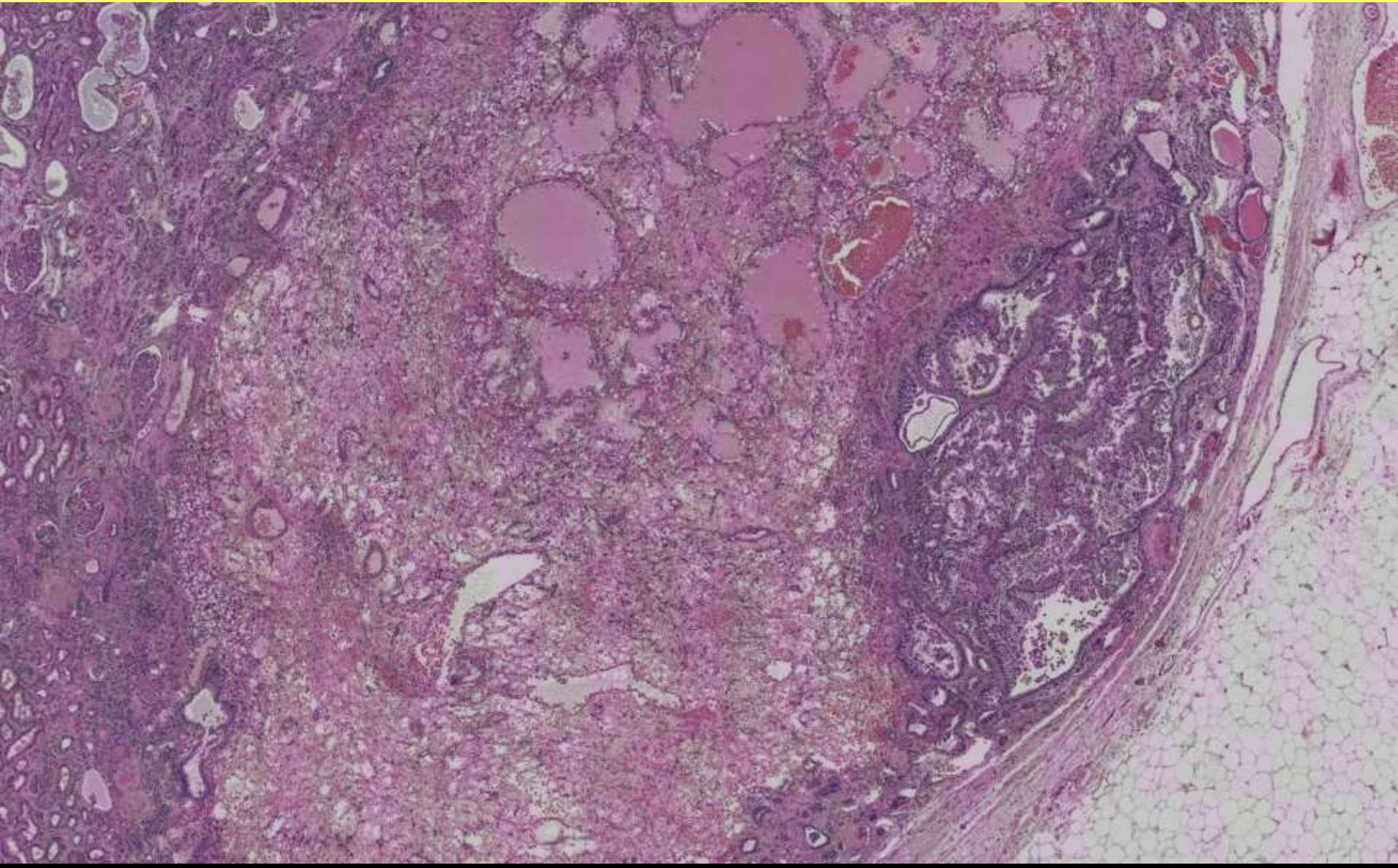
Papillary adenoma



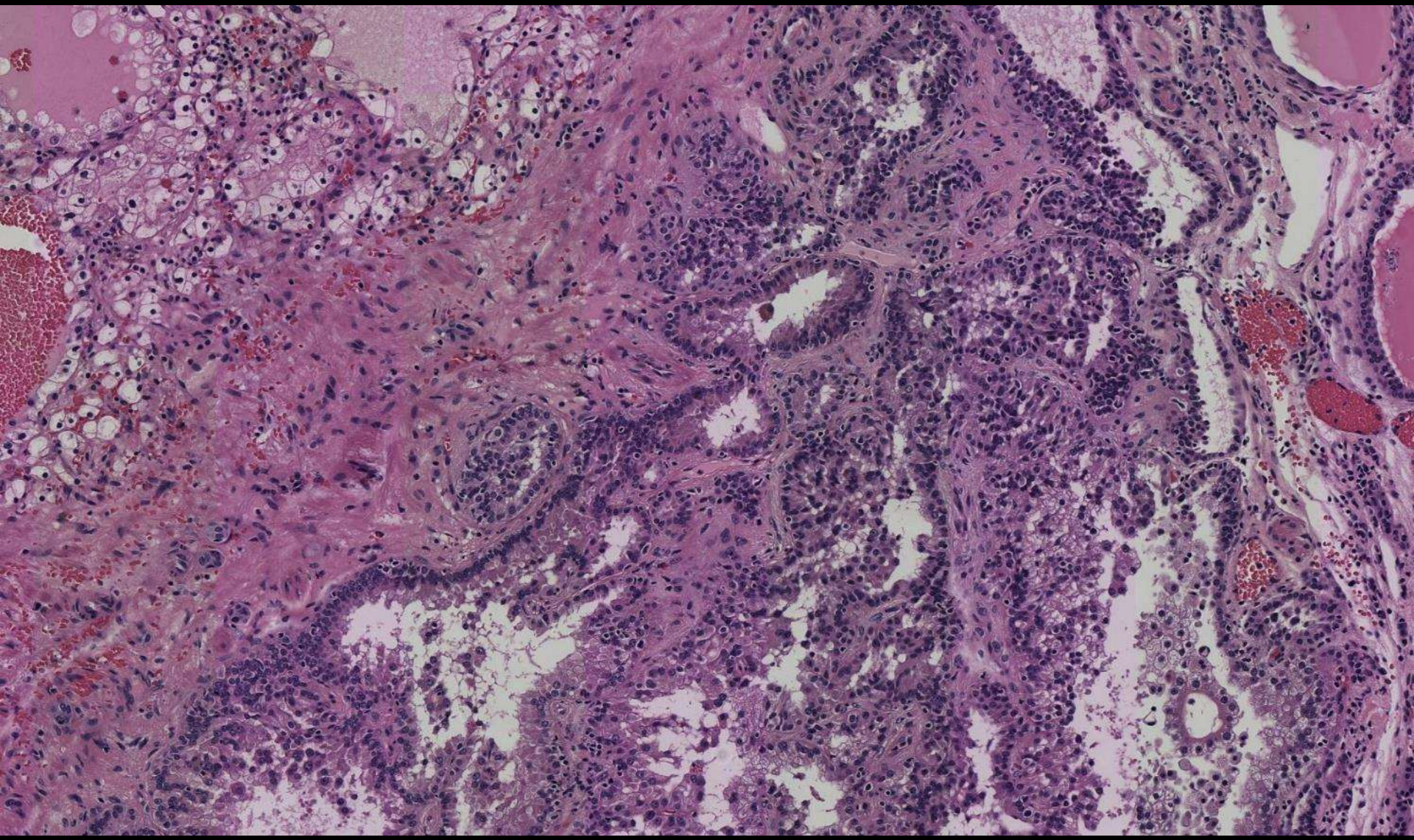
Papillary adenoma



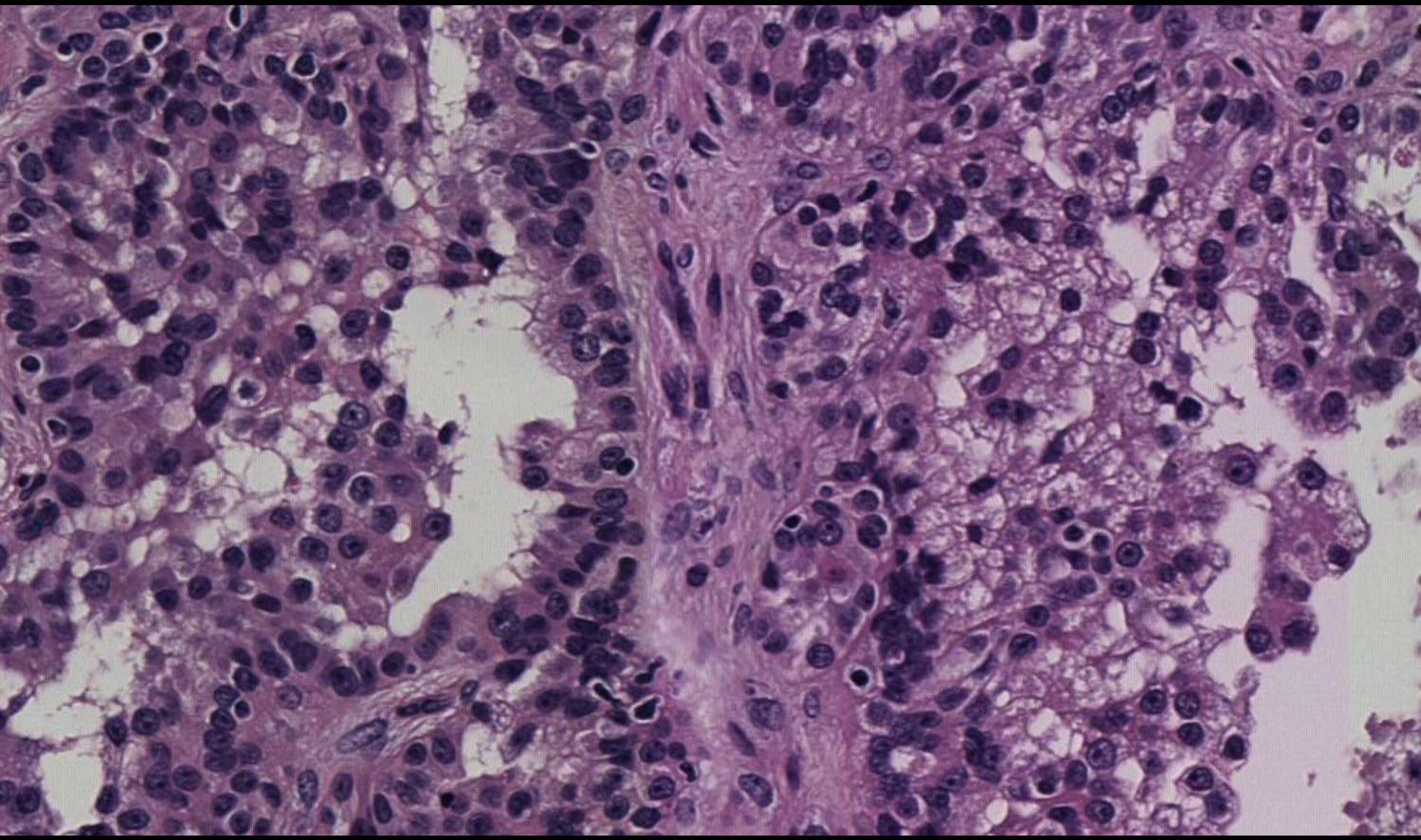
Small papillary RCC
(with adjacent clear cell RCC)



Small papillary RCC



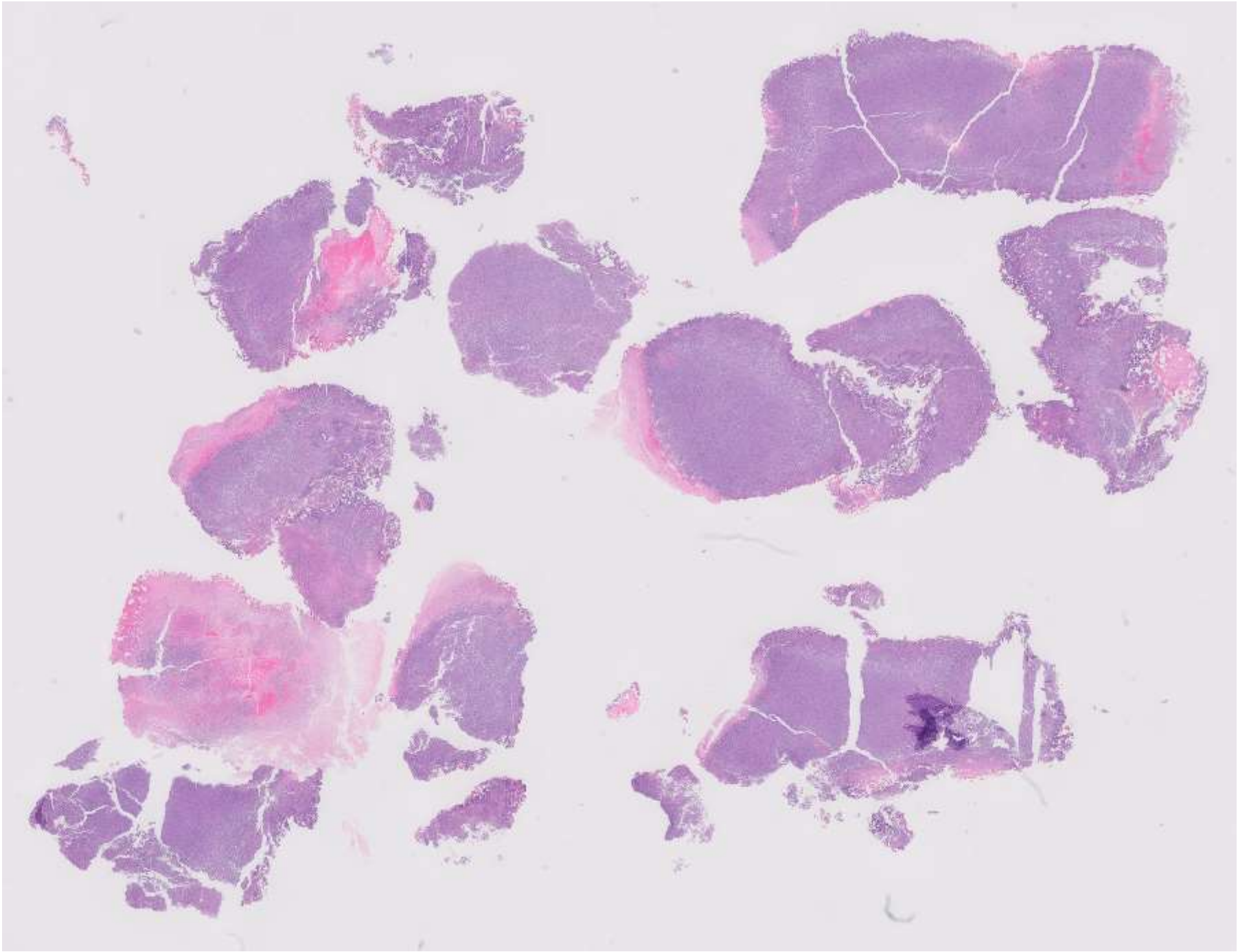
Small papillary RCC

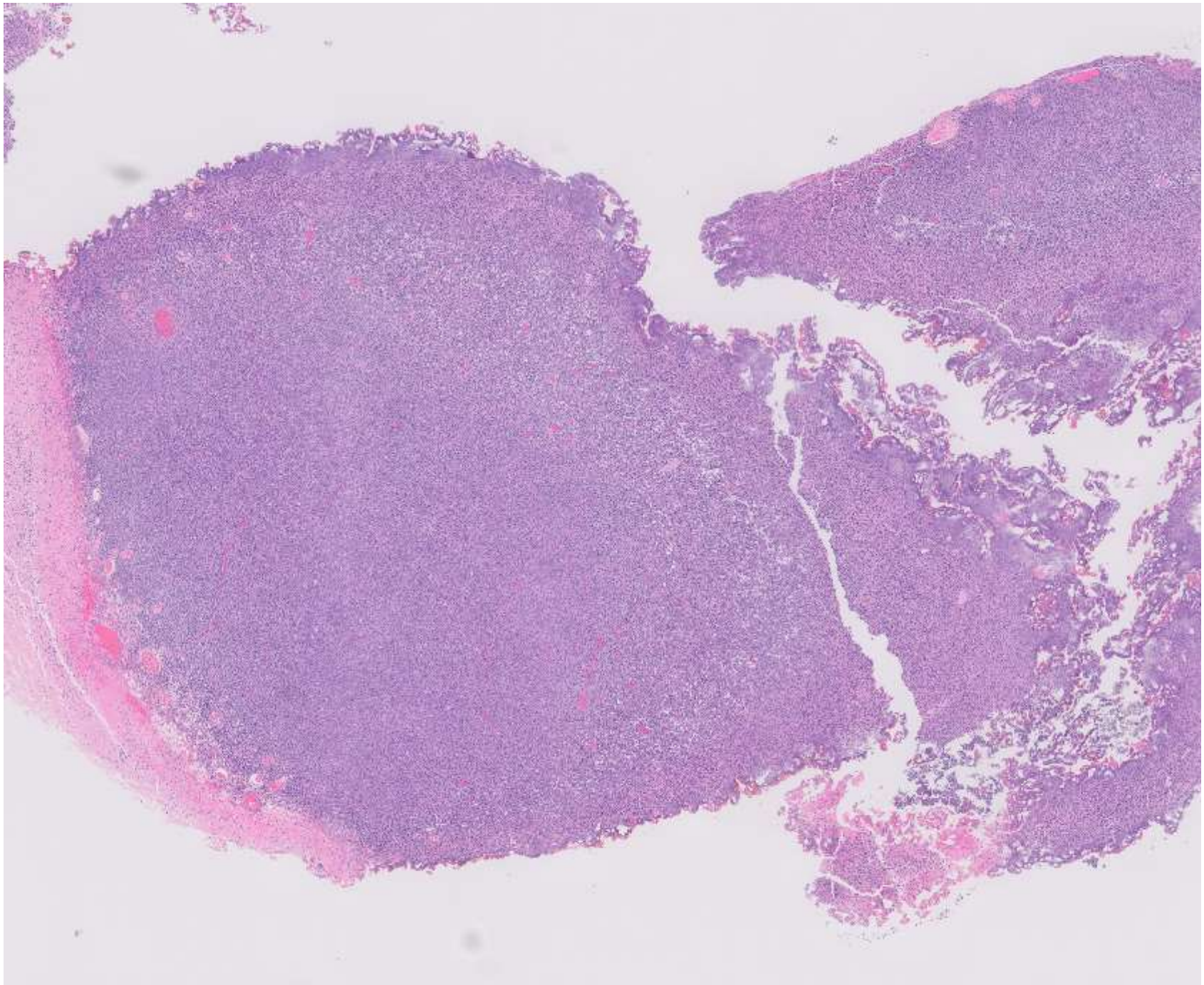


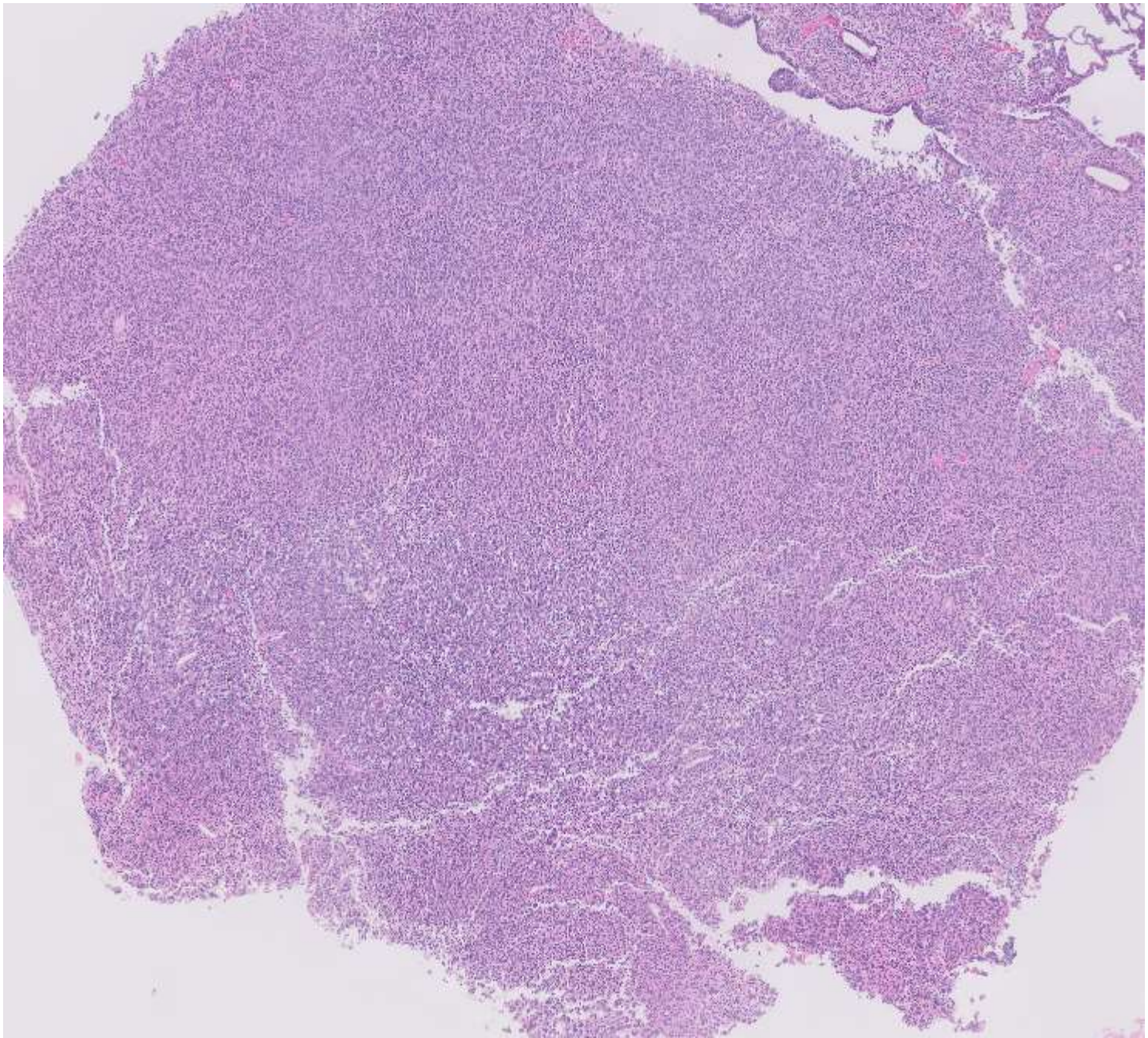
21-0405

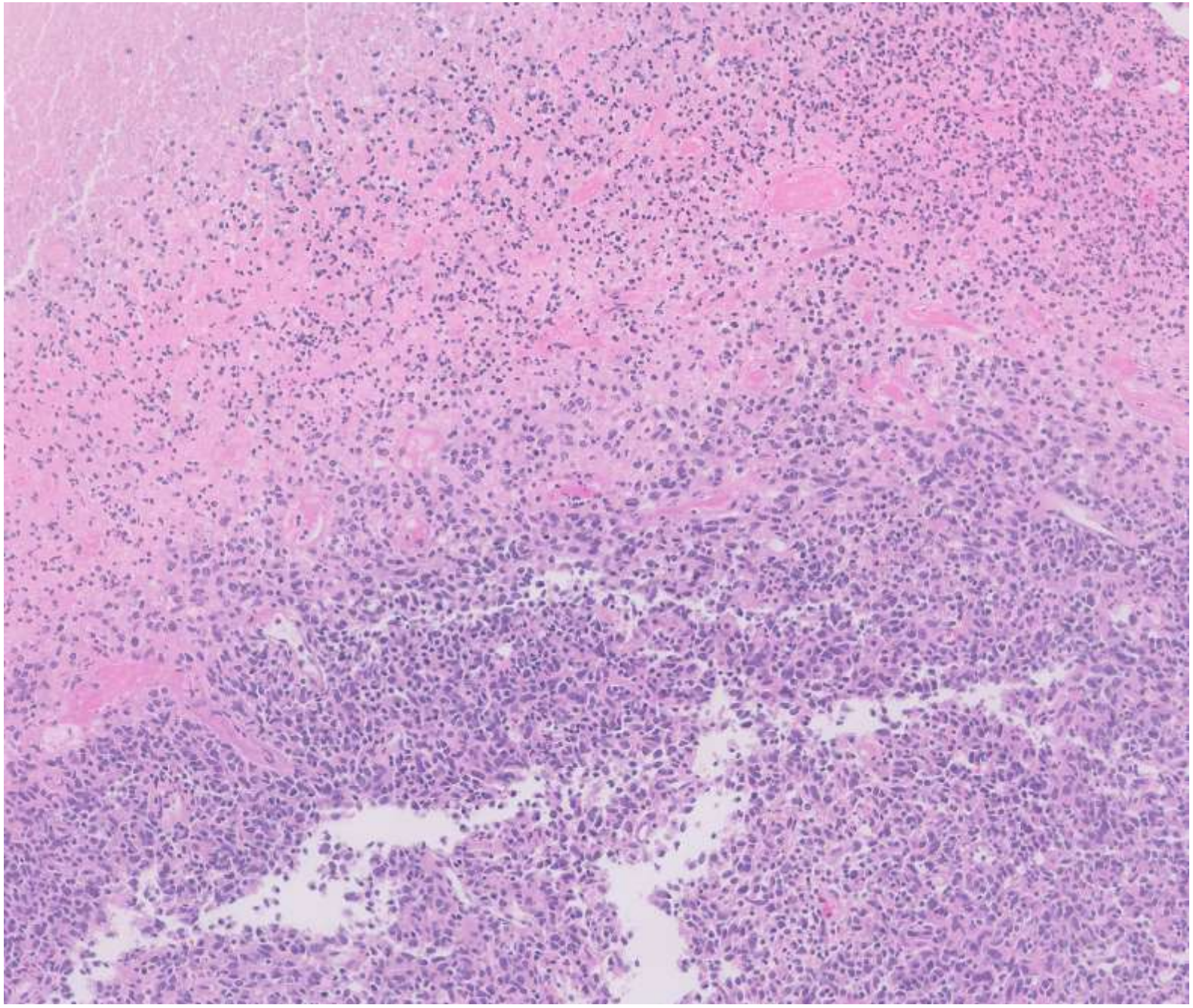
Emily Chan; UCSF

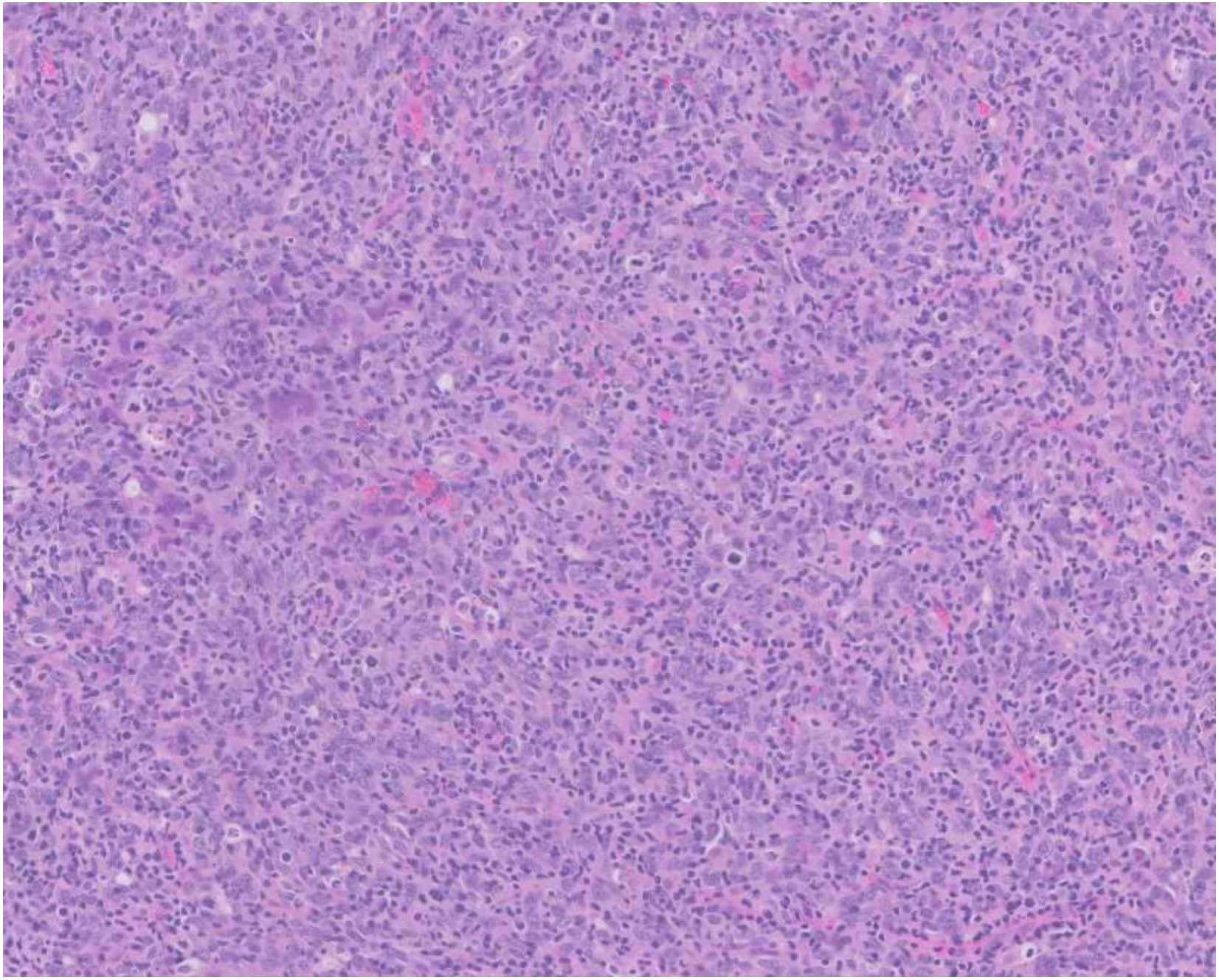
80-year-old F with right distal ureteral mass.

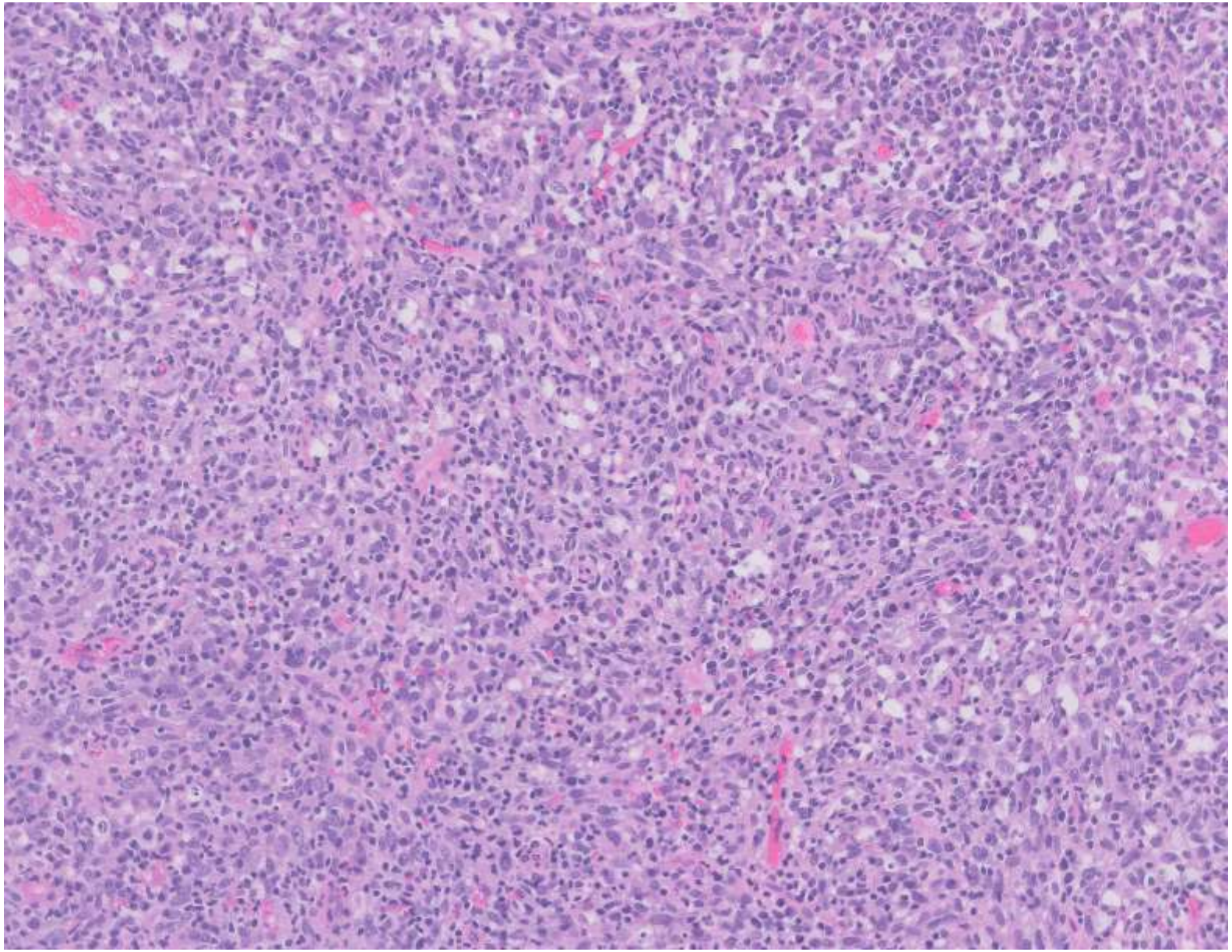


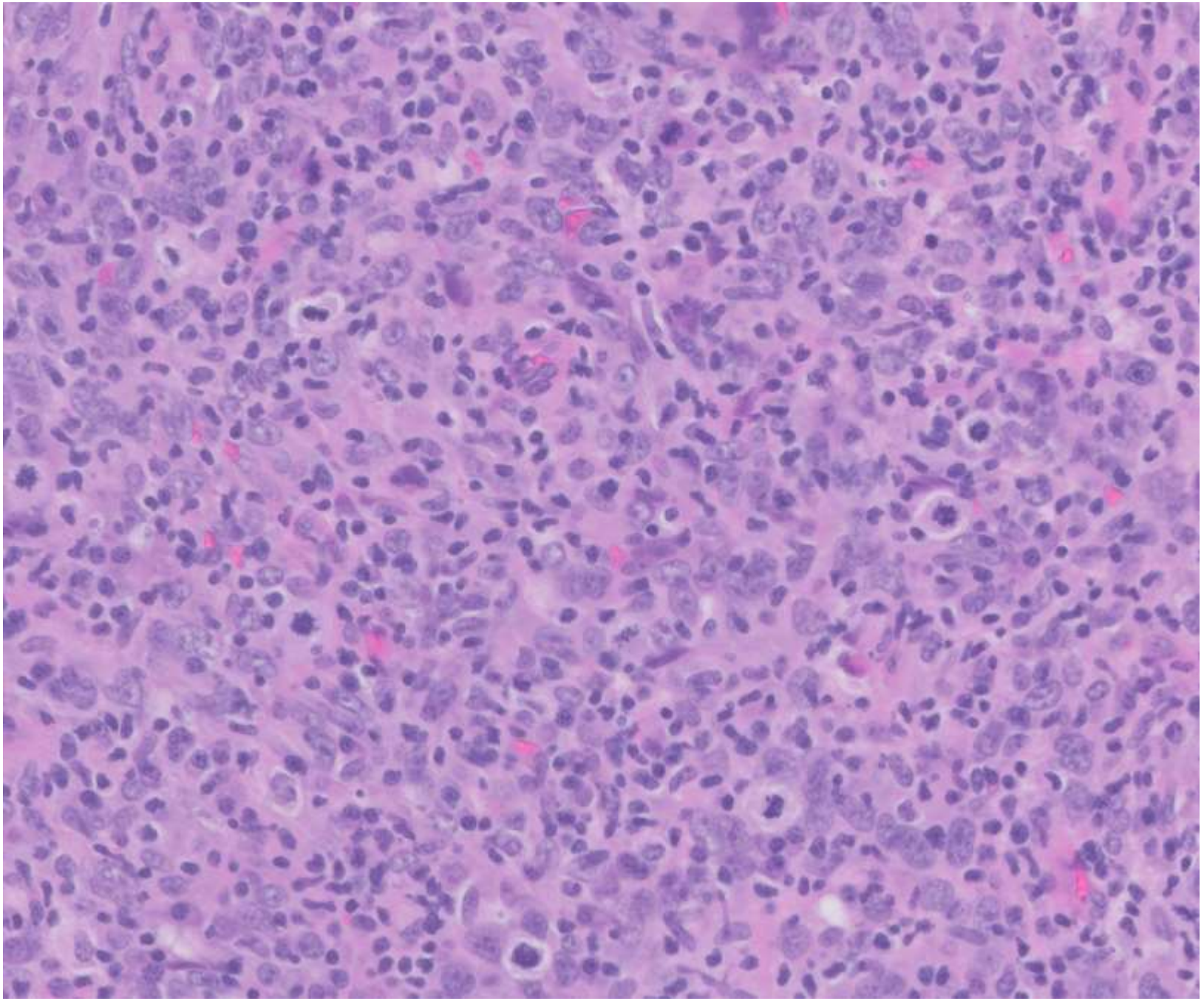


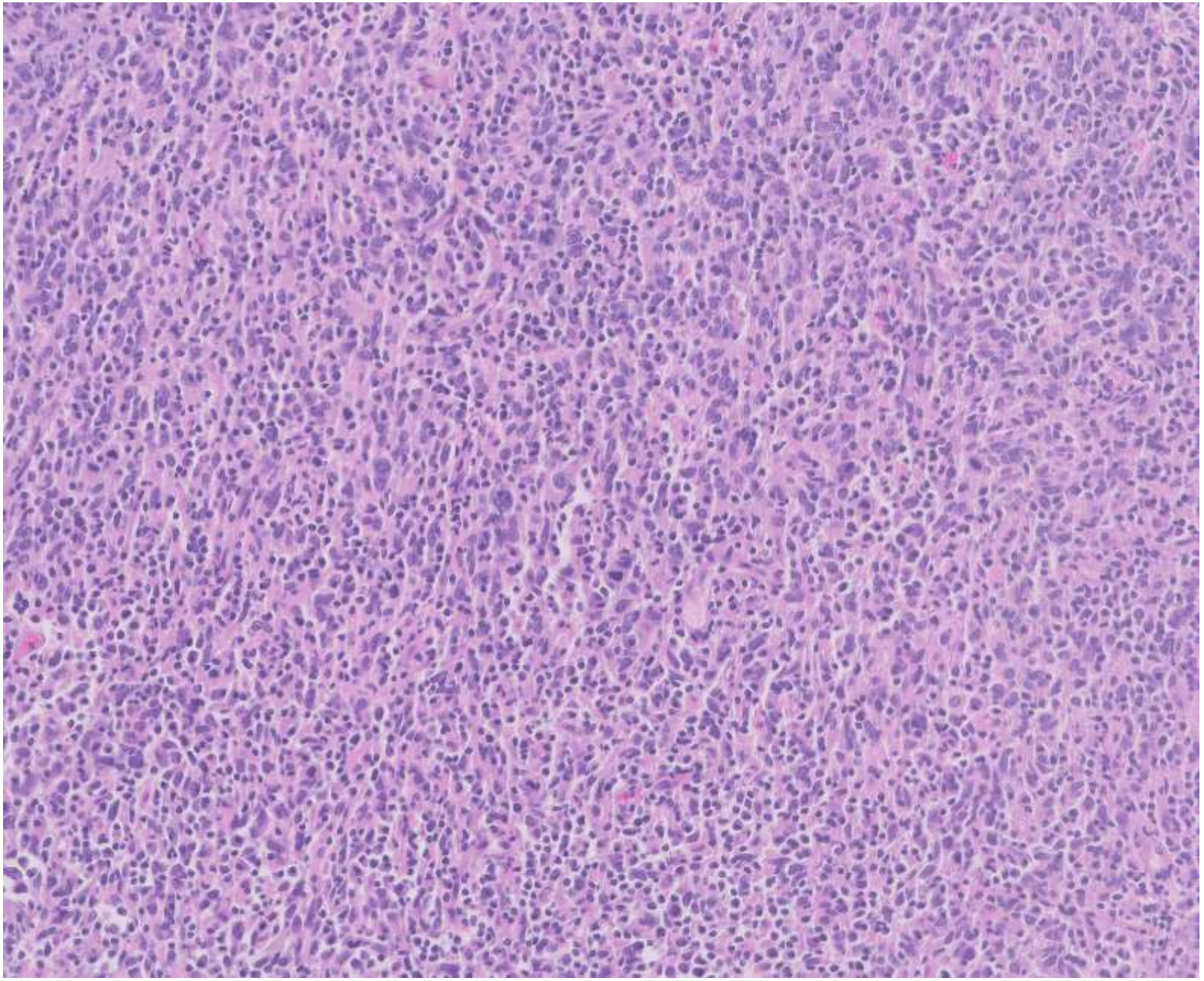


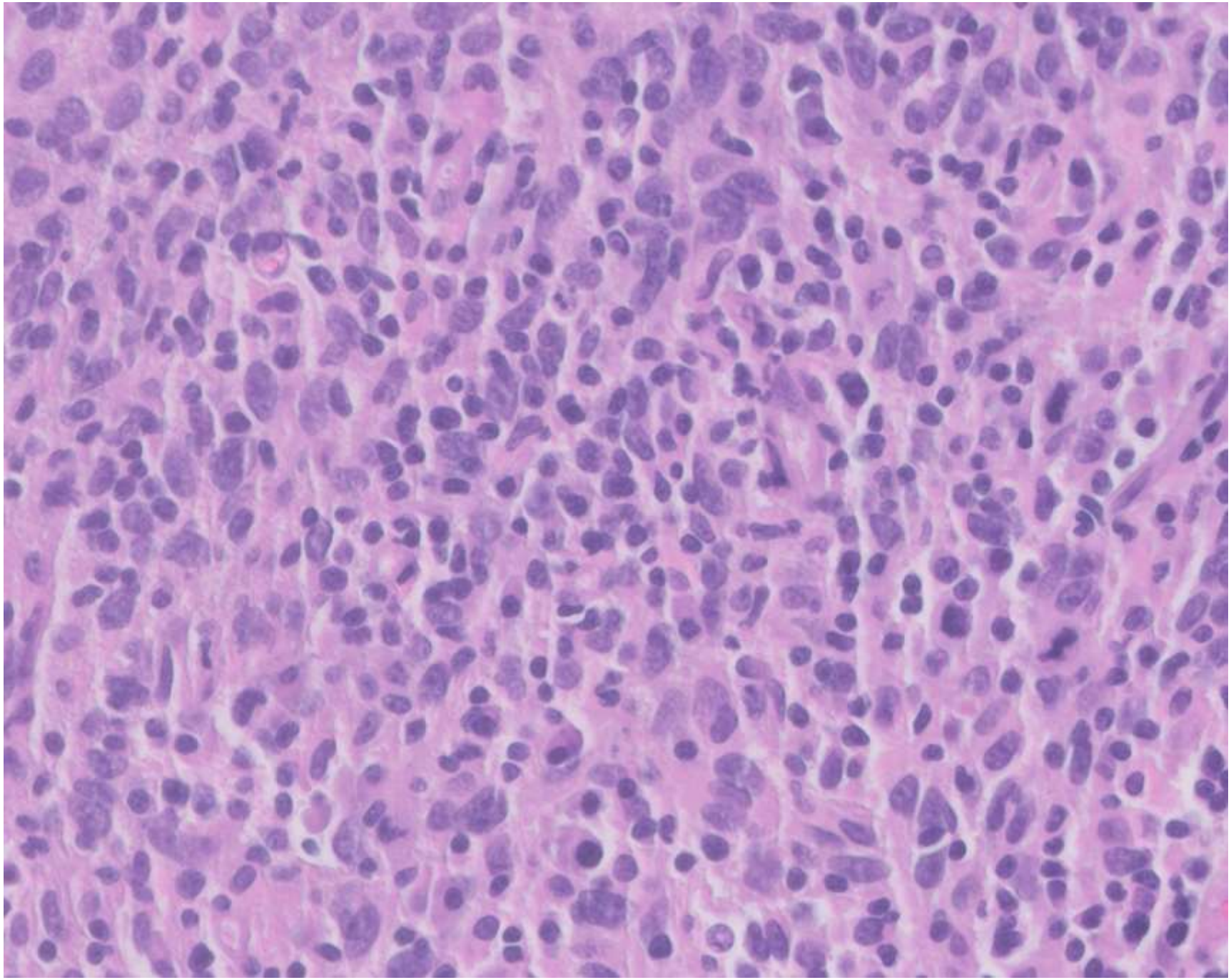






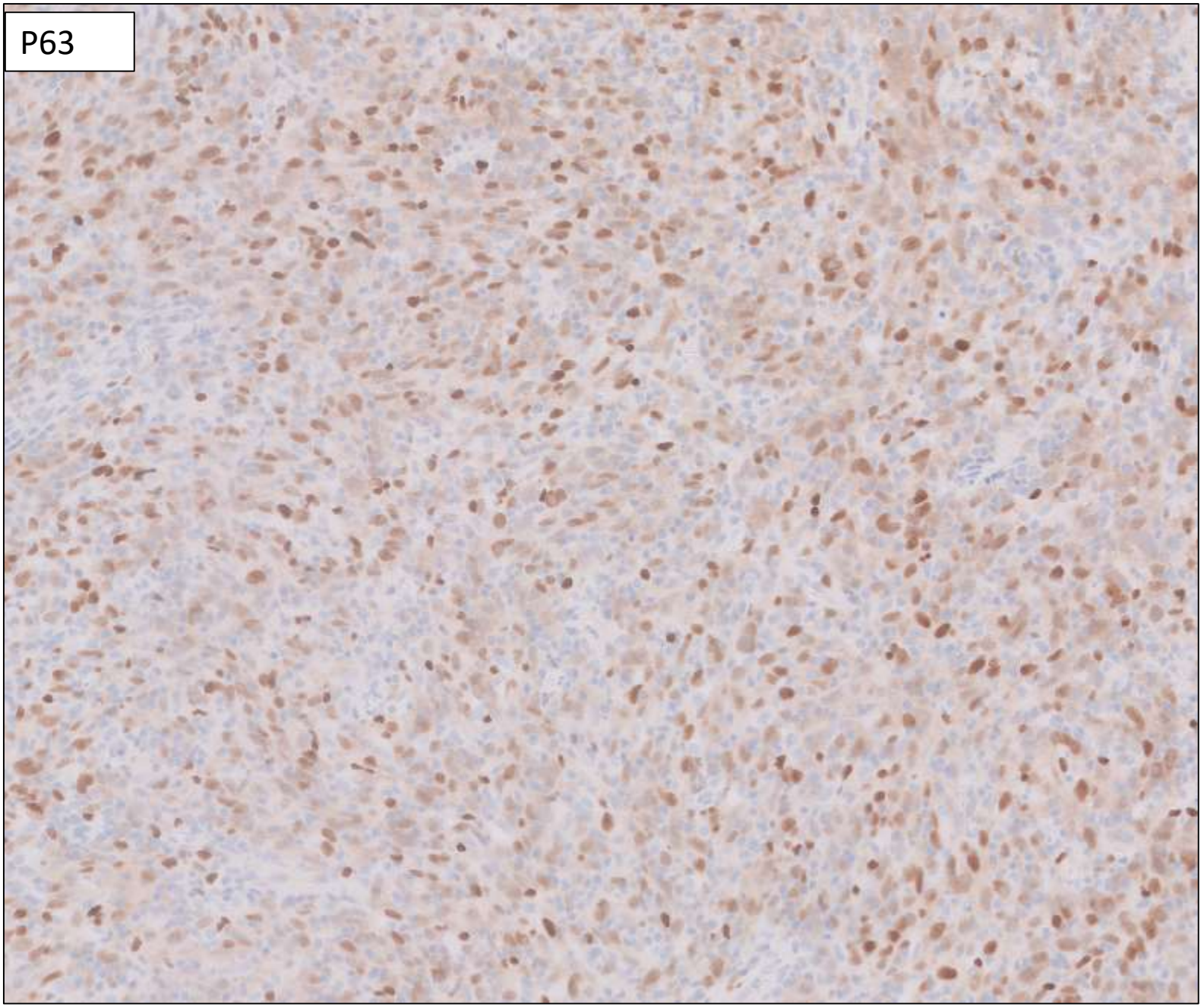


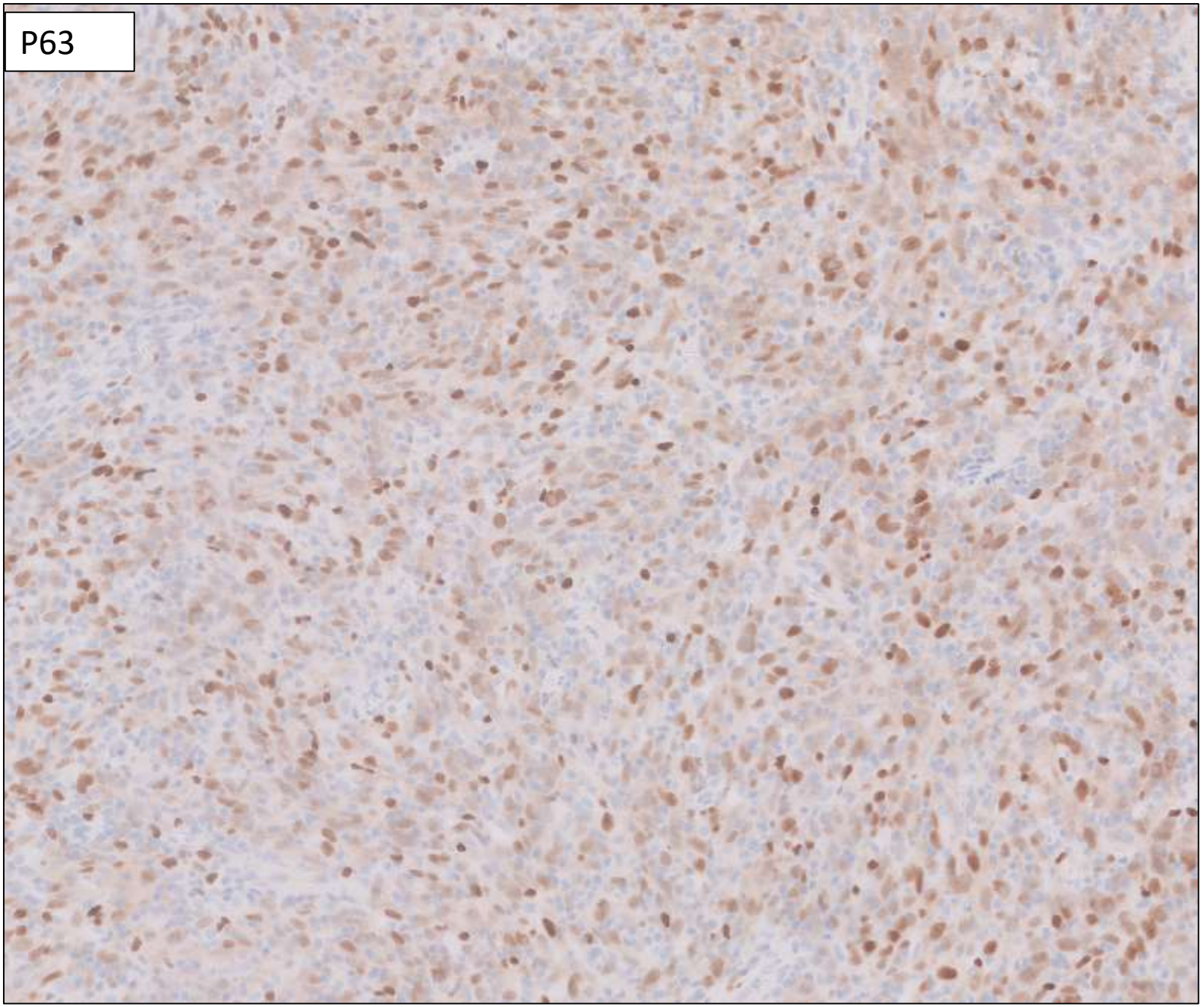


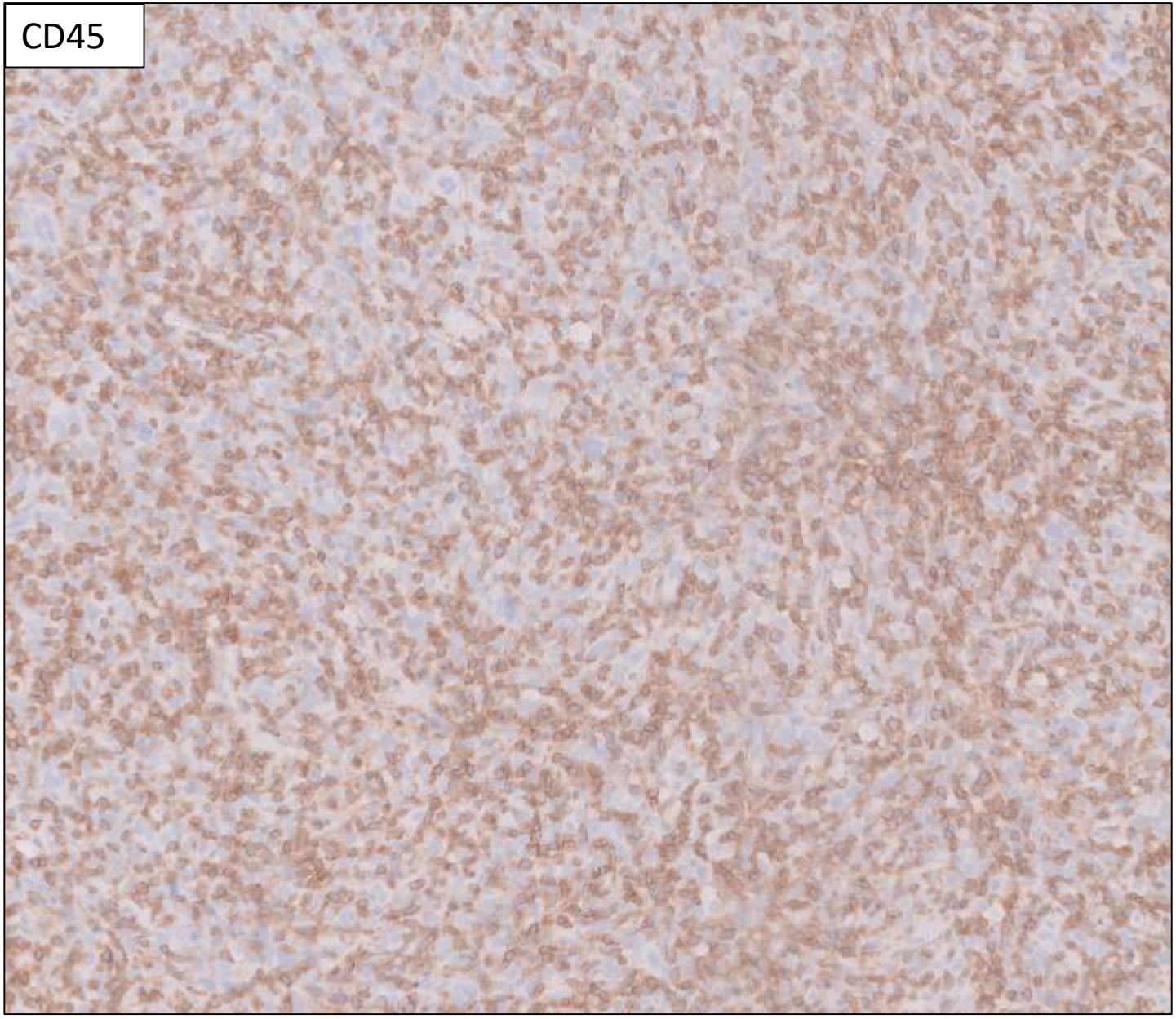


Pankeratin, CK7 and CK20


GATA3


P63


P63

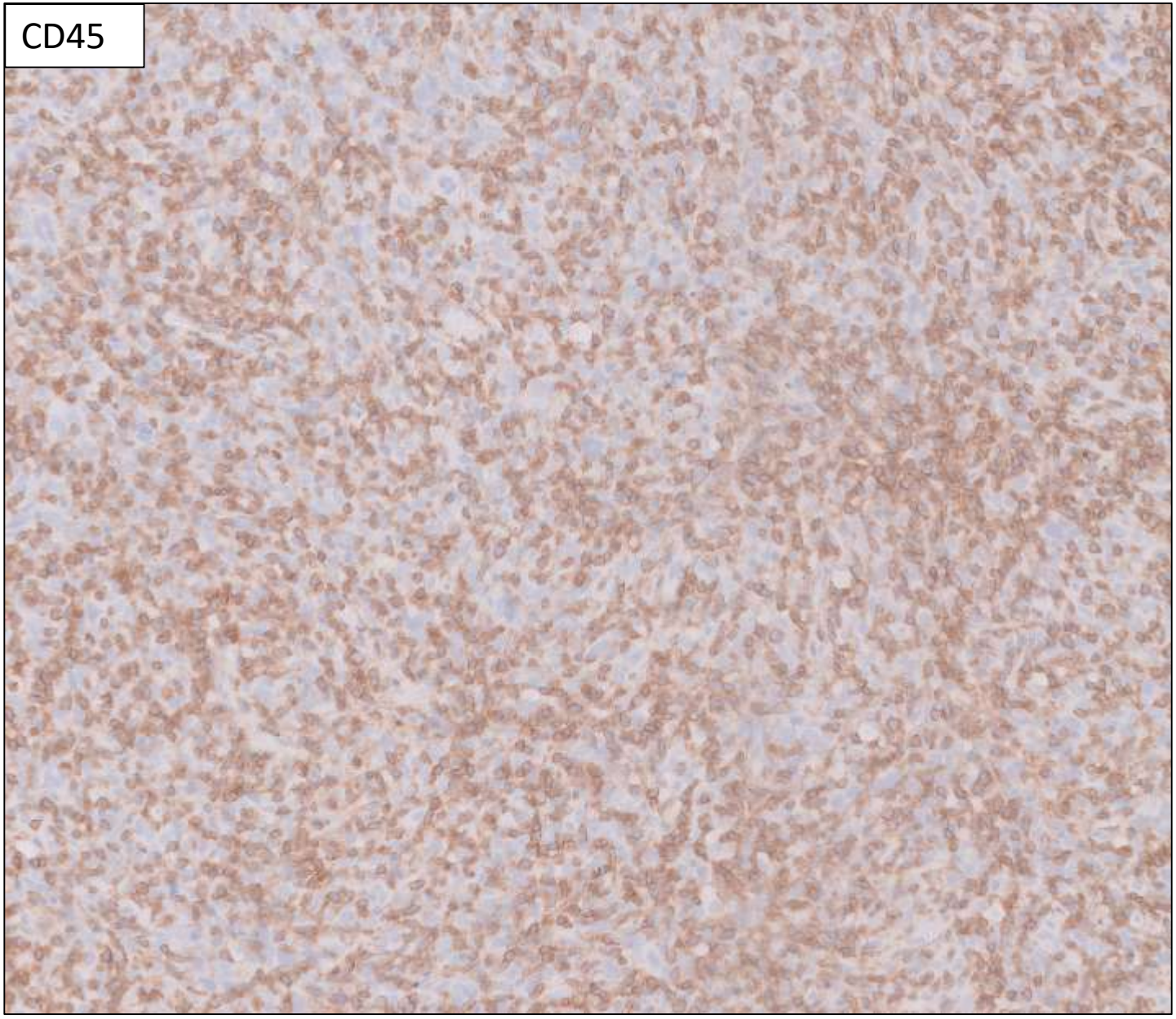

CD45

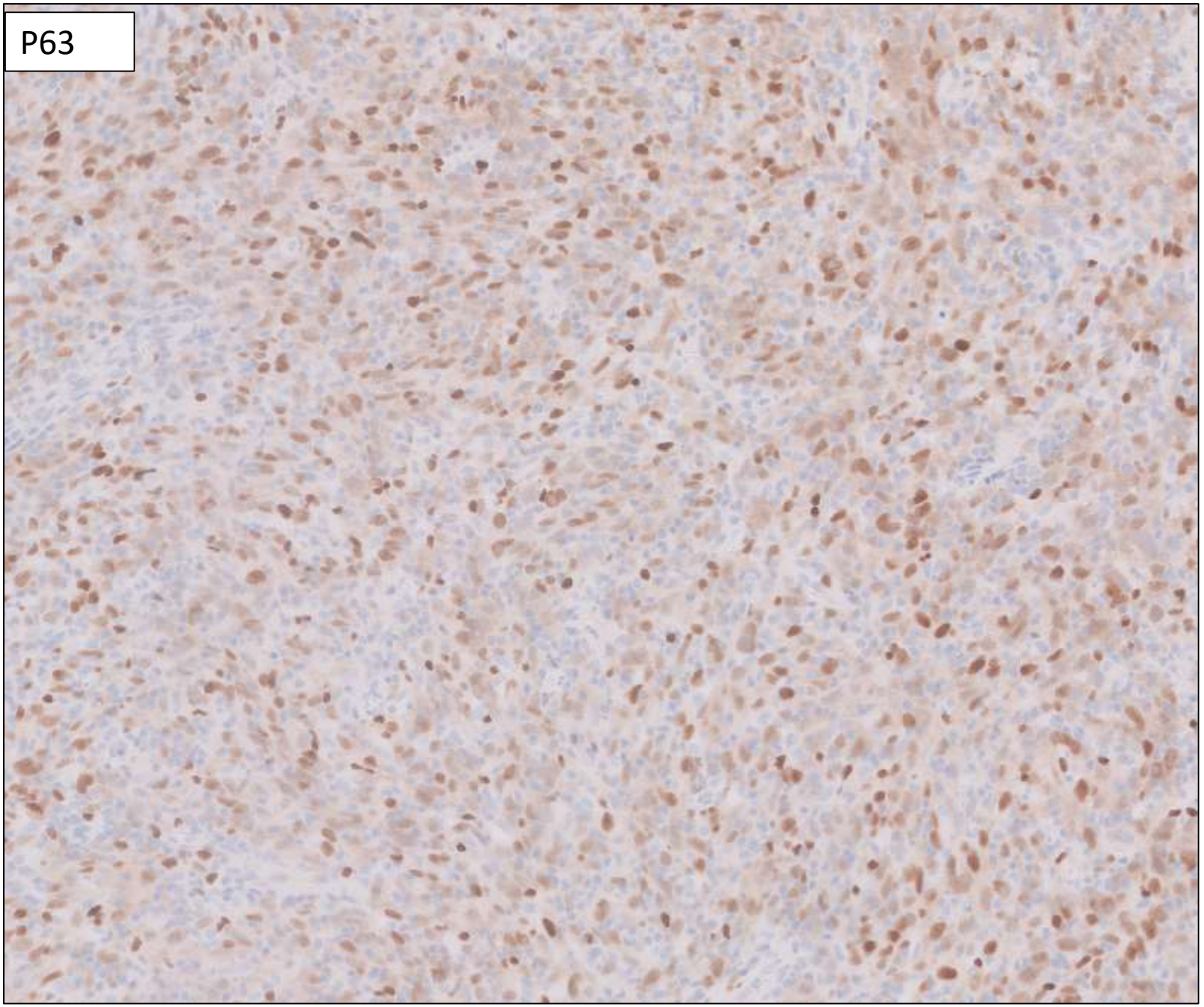
Differential diagnosis

- Poorly differentiated carcinoma
  - Urothelial
  - Metastasis
- Lymphoma
- Prior surgical site changes/reactive/cystitis

IHC summary

- Multiple Keratins: Negative
- GATA3: Negative (staining small inflammatory cells)
- CD45: Negative (staining small inflammatory cells)
- P63: Weak positive in large cells


CD45


P63

Diagnosis:

Malignant neoplasm pending UCSF500

UCSF500 Next Generation Sequencing Assay

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
ARID1A p.Q1066*	NM_006015.4	Pathogenic	666	27%
KDM6A p.I854fs	NM_021140.2	Pathogenic	1201	48%
KMT2D p.S2455*	NM_003482.3	Pathogenic	2167	32%
NBN p.S442fs	NM_002485.4	Pathogenic	663	28%
RB1 p.E184*	NM_000321.2	Pathogenic	257	25%
TERT c.-124C>T	NM_198253.2	Pathogenic	1264	22%
TP53 p.R280T	NM_000546.5	Pathogenic	1133	41%

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.

0 of 85 tested microsatellites (0.00%) were found to be unstable.

Assessment of microsatellite instability (MSI) by percentage of unstable sites:
<20%: MSI absent (MSS) | 20-30%: MSI equivocal | >30%: MSI present (MSI-High)

INTERPRETATION

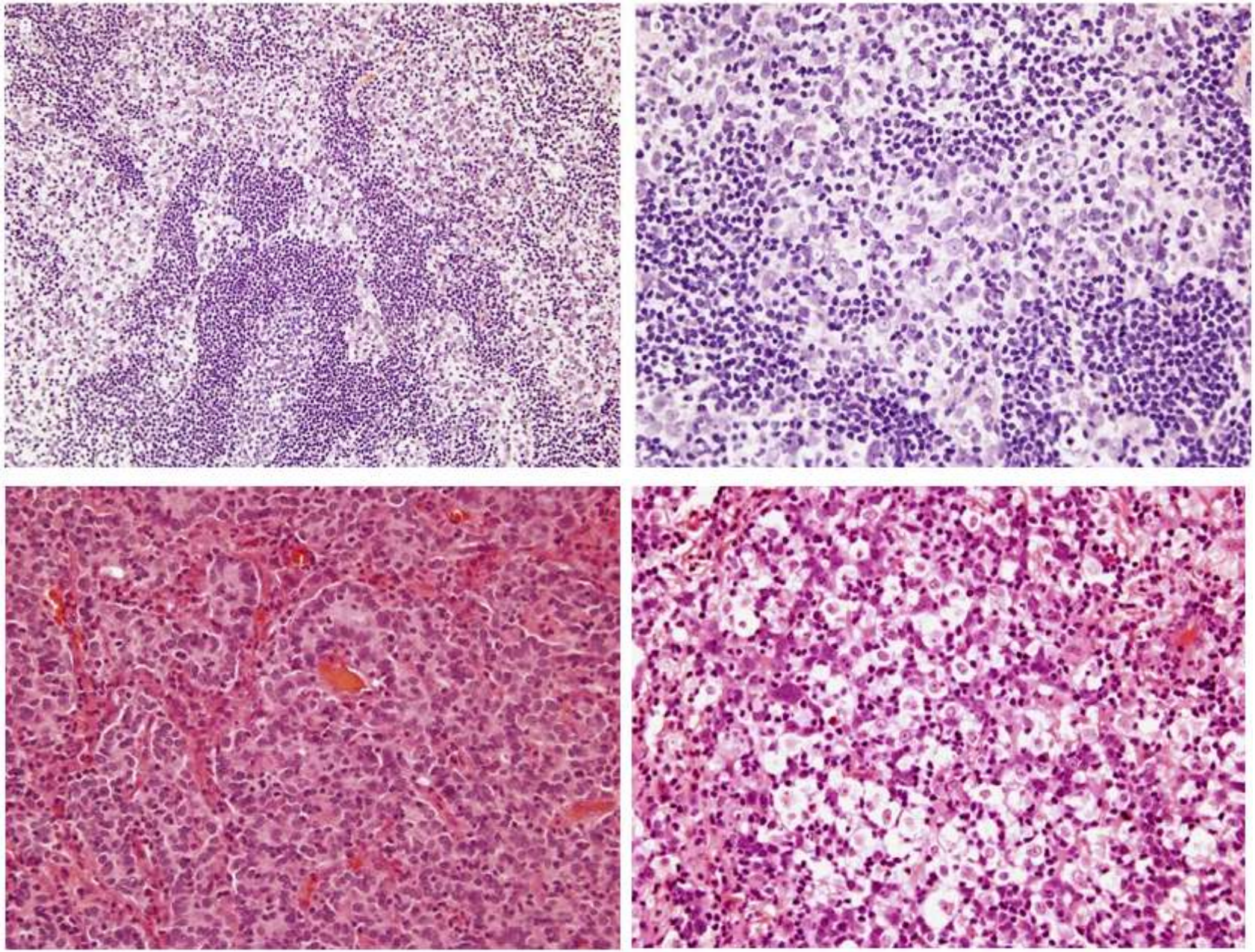
This malignant neoplasm of the ureter demonstrates pathogenic mutations in TERTp, TP53, KMT2D, KDM6A, ARID1A and RB1 (among other alterations). These are all frequently mutated in urothelial carcinoma (Ref. 1). Also present is a frameshift in NBN, involved in DNA repair. NBN mutations may increase tumor response to DNA damaging therapies and PARP inhibition (2).

Revised Diagnosis:

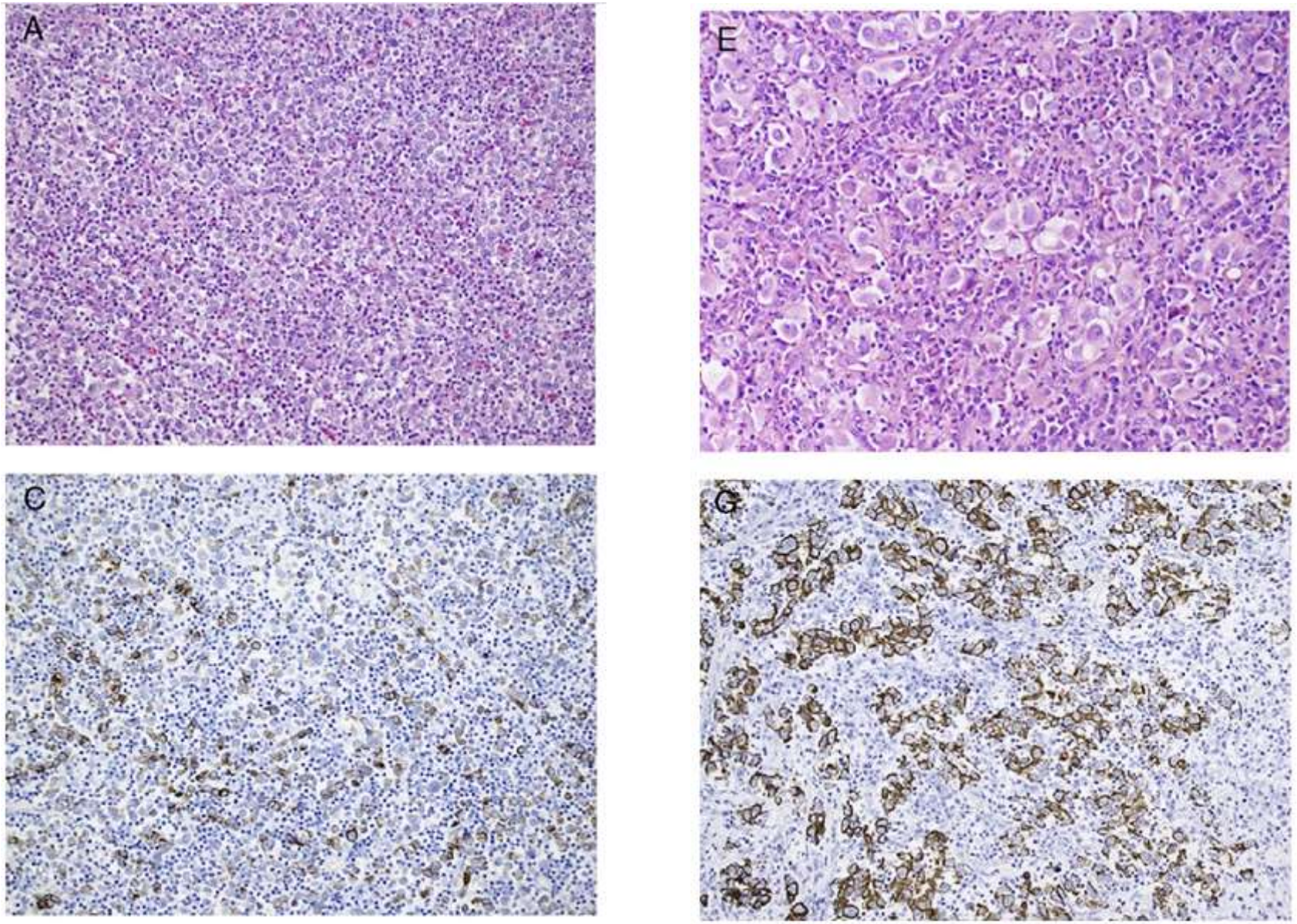
Urothelial carcinoma, lymphoepithelioma-like variant.

Lymphoepithelioma-like urothelial carcinoma (LEL-UC)

- Rare histologic variant of urothelial carcinoma
- Nests and individual cells of undifferentiated carcinoma admixed with prominent often-obscuring inflammatory infiltrate
- Keratins, p63 and GATA3 helpful when positive
- EBV negative
- Approximately 50% in literature have conventional UC component
- Biologic behavior of pure/predominant LEL-UC debated



Tamas et al Modern Path 2007



Williamson et al AJSP 2011

Do pure LEL or LEL-predominant UCs behave better?

- Early literature suggests pure LEL or LEL-predominant UCs has better prognosis than conventional UC or UC with focal LEL
  - Amin MB, et al. AJSP 1994.
  - Lopez-Beltran et al. Virchow Arch, 2001.
- May also respond well to TUR followed by chemotherapy

Do pure LEL or LEL-predominant UCs behave better?

Published: 01 June 2007

Lymphoepithelioma-like carcinoma of the urinary tract: a clinicopathological study of 30 pure and mixed cases

Ecaterina F Tamas, Matthew E Nielsen, Mark P Schoenberg & Jonathan I Epstein

Modern Pathology **20**, 828–834(2007) | Cite this article

- 77% stage T2 or higher at presentation
- 5 year recurrence 59% (62% for pure, 57% for mixed)
- Concluded those treated by cystectomy have similar prognosis to conventional UC (citing large scale study of 1000+ T2/T3 tumors showing 68% 5-year recurrence free)
- One of three pure LEL treated with chemo-only had recurrence

Do pure LEL or LEL-predominant UCs behave better?

› Am J Surg Pathol. 2011 Apr;35(4):474-83. doi: 10.1097/PAS.0b013e31820f709e.

Lymphoepithelioma-like carcinoma of the urinary bladder: clinicopathologic, immunohistochemical, and molecular features

Sean R Williamson [1], Shaobo Zhang, Antonio Lopez-Beltran, Rajal B Shah, Rodolfo Montironi, Puay-Hoon Tan, Mingsheng Wang, Lee Ann Baldridge, Gregory T MacLennan, Liang Cheng

Affiliations + expand

PMID: 21383609 DOI: 10.1097/PAS.0b013e31820f709e

- Concluded their series findings support earlier hypotheses but more data needed

Patient	Sex	Age (y)	Stage	Percent LELC (%)	Other Component	CIS	Treatment	Chemotherapy	Status	Months
1	M	74	T3 N0	100	—	+	CP		ANED	98
2	M	76	T2 N0	100	—	+	CP		ANED	81
3	M	75	T2	100	—	+	TURBT	6 cycles gem/cis/pac	ANED	72
4	F	70	T2	100	—	+	TURBT	6 cycles gem/cis/pac	ANED	61
5	M	65	T2 N0	100	—	+	Cystectomy		ANED	53
6	M	69	T3 N0	100	—	—	BCG, CP	6 cycles gem/cis/pac	ANED	53
7	M	54	T2 N0	100	—	—	CP		ANED	42
8	M	70	T3 N0	100	—	—	CP		ANED	36
9	M	76	T3 N+	100	—	Dys	CP	4 cycles gem/cis	ANED	28
10	M	73	T3 N+	100	—	—	CP		AWD (LN met)	22
11	M	68	T2 N0	100	—	+	CP		ANED	18
12	F	84	T3 N+	100	—	—	Cystectomy, XRT	Yes, unspecified	AWD (LN met)	15
13	F	61	T2 N0	100	—	+	Anterior exenteration		ANED	6
14	M	64	T2	100	—	—	CP		ANED	5
15	F	66	T2 N+	100	—	+	Anterior exenteration		Death medical complications*	2
16	M	75	T2 N0	100	—	—	CP		Unknown	
17	F	73	T2	100	—	—	Unknown		Unknown	
18	M	82	T2	90	Papillary, squamous	—	TURBT		AWD (papillary UC)	61
19	M	73	T2	90	Papillary, squamous	—	TURBT	6 cycles gem/cis/pac	ANED	59
20	M	66	T3 N+	90	Squamous	+	Partial penectomy, XRT	4 cycles gem/carb/tax	ANED	31
21	M	69	T2	90	Papillary	+	TURBT		ANED	22
22	F	67	T2	90	Glandular	—	Unknown		Unknown	
23	F	71	T2	90	Squamous	—	Unknown		Unknown	
24	M	69	T2	80	Papillary, glandular	—	TURBT	6 cycles gem/cis/pac	ANED	25
25	M	71	T2	75	Sarcomatoid, glandular	—	TURBT, XRT	3 cycles gem/cis	ANED	70
26	M	62	T2 N0	60	Invasive UC, sarcomatoid	—	CP		ANED	62
27	M	74	T2	40	Papillary, invasive UC	+	TURBT, BCG	6 cycles gem/cis/pac	DOD	39
28	M	70	T3 N0	40	Invasive UC	—	CP	Yes, unspecified	ANED	19
29	M	54	T2 N0	35	Invasive UC	+	Partial cystectomy		Unknown	
30	F	74	T3 N0	33	Papillary, invasive UC	+	Cystectomy		ANED	12
31	M	67	T3	30	Papillary, invasive UC	+	TURBT	6 cycles gem/cis/pac	AWD (lung met)	34
32	M	72	T4 N+	30	Papillary, invasive UC, squamous	+	CP	6 cycles gem/cis/pac	AWD (lung met)	24
33	F	75	T2	30	Papillary, invasive UC	+	TURBT		AWD	0
34	M	77	T3 N+	15	Papillary, invasive UC	+	CP, Nephrectomy	6 wk local distal urethra	ANED	131

*For patient 15, surgical recovery was complicated by wound dehiscence, infection, and respiratory failure, leading to death at two months after surgery.

ANED indicates alive with no evidence of disease; AWD, alive with disease; carb, carboplatin; BCG, Bacillus Calmette-Guerin; cis, cisplatin; CP, cystoprostatectomy; DOD, died of disease; Dys, urothelial dysplasia; gem, gemcitabine; LN, lymph node; met, metastasis; pac, paclitaxel; tax, taxol; TURBT, transurethral resection of bladder tumor; UC, urothelial carcinoma; XRT, radiation therapy.

Williamson et al AJSP 2011

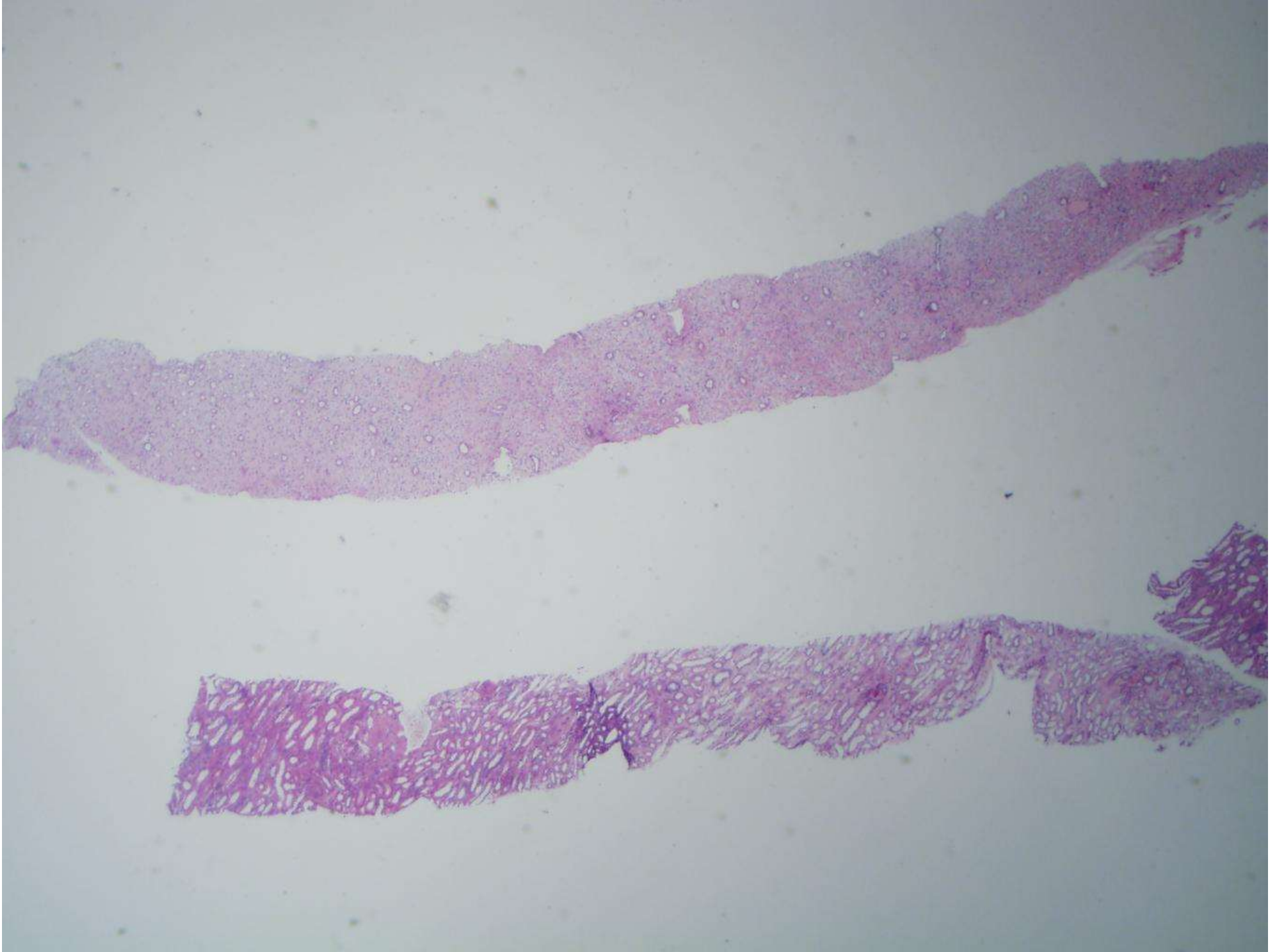
Take home

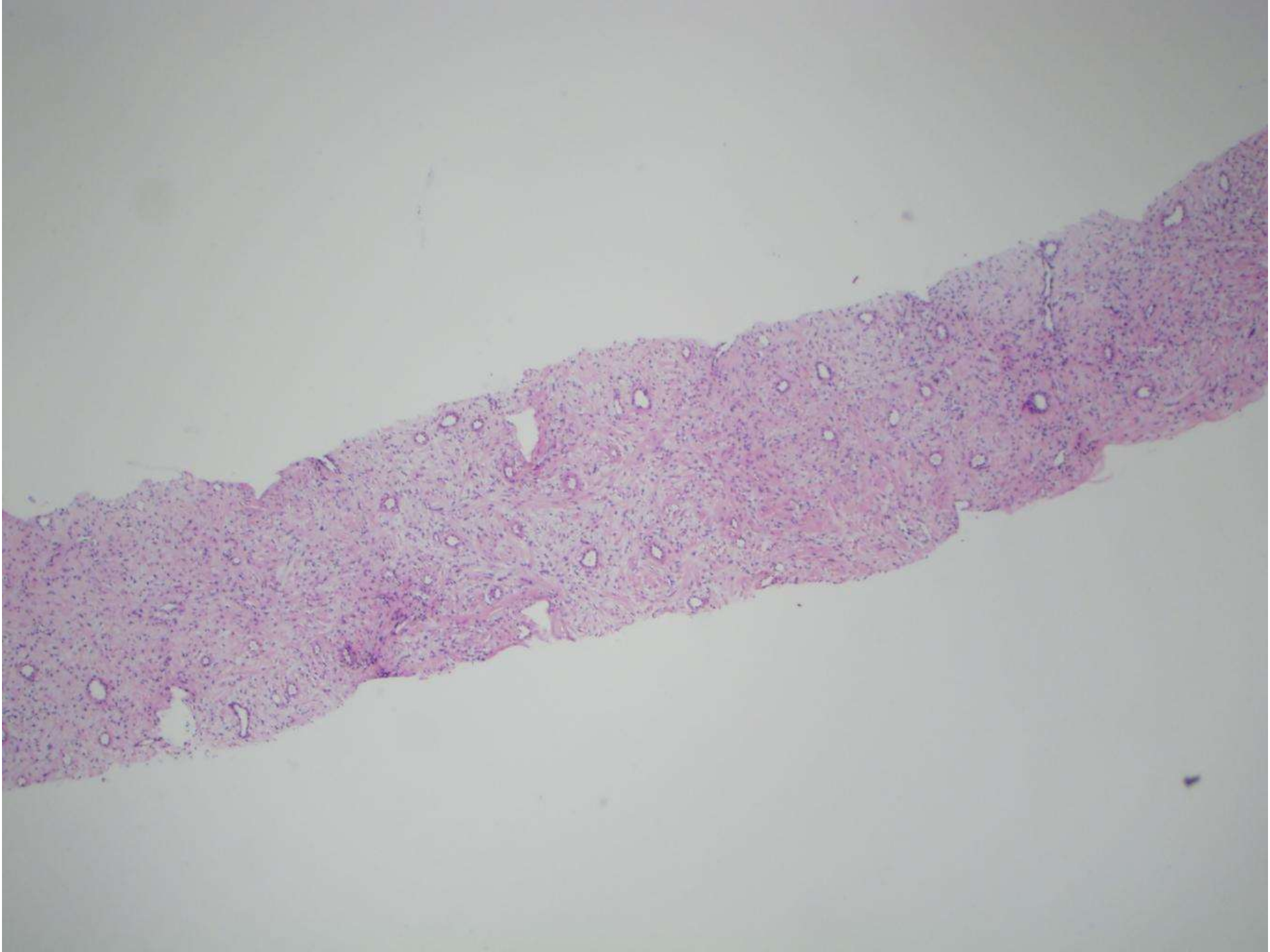
- Lymphoepithelioma-like is a rare variant of urothelial carcinoma
- Can mimic lymphoma or cystitis
  - Broad spectrum keratins can help highlight carcinoma
  - P63/GATA3 or associated urothelial CIS/conventional UC can point to urothelial
- Given potential implications for prognosis and treatment recommendations, report percentage of LEL seen (as you would the presence of all other variants)

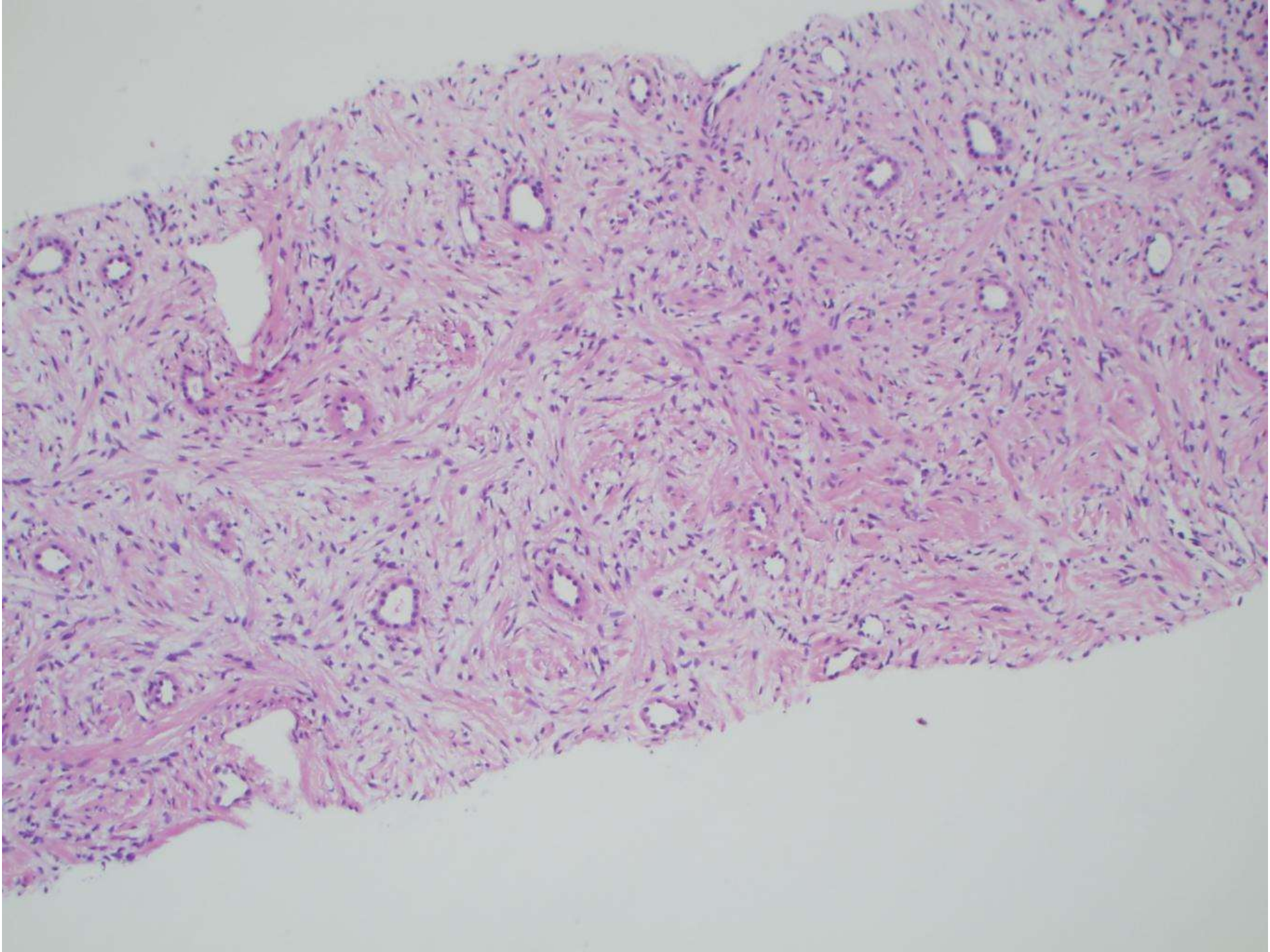
21-0406
scanned slide avail!

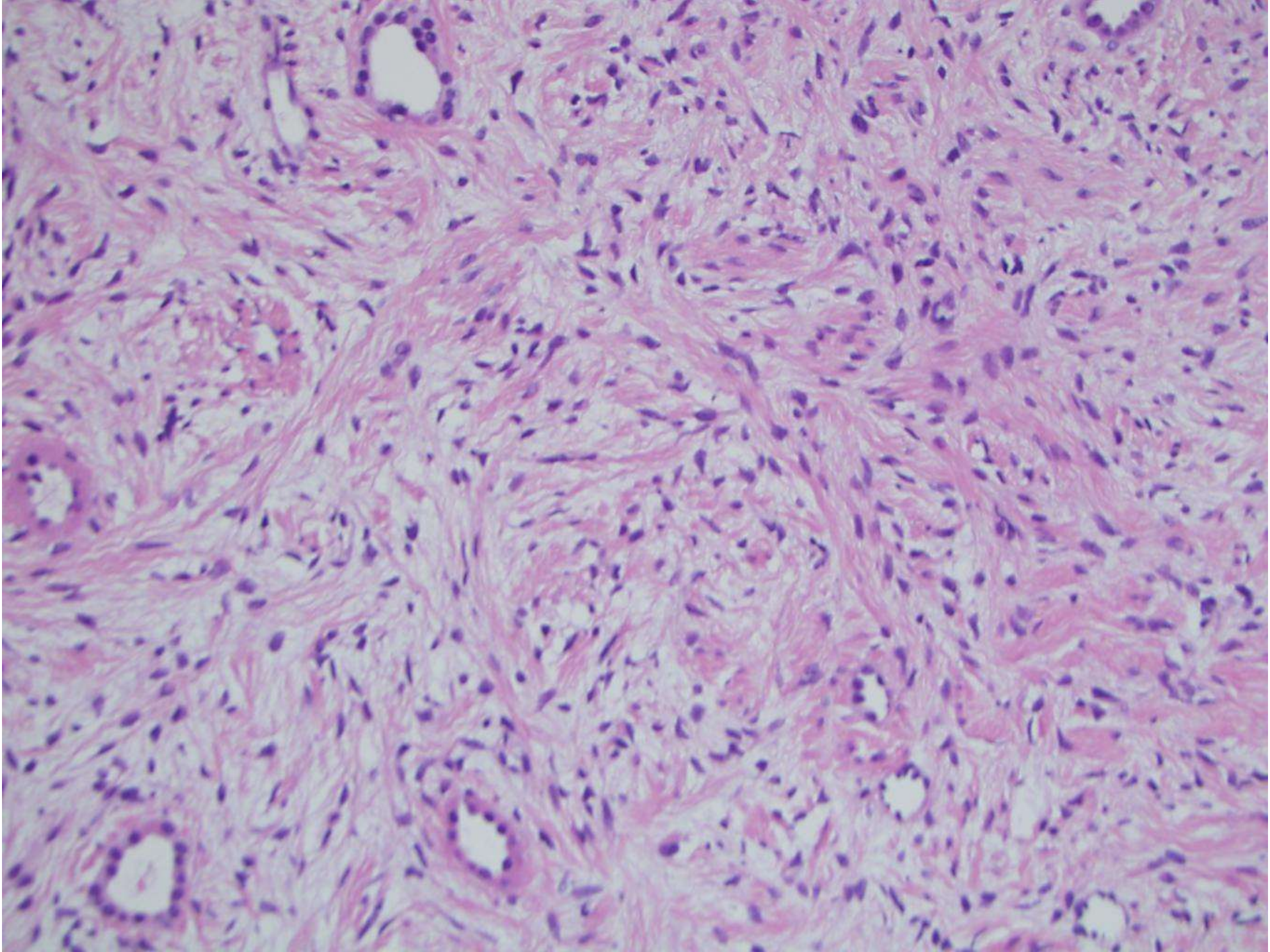
Ankur Sangoi; El Camino Hospital

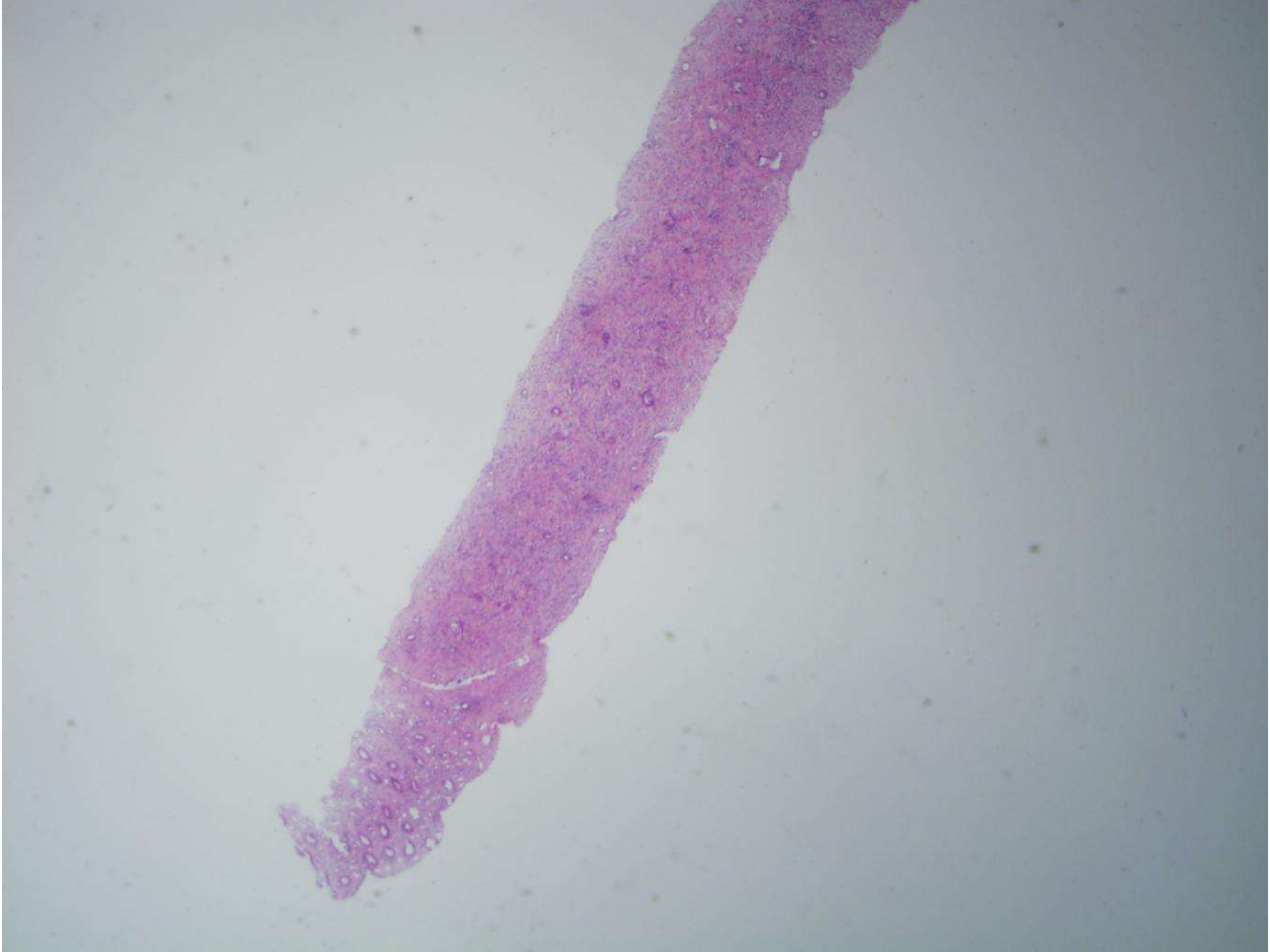
Adult F with kidney mass, core biopsy performed.

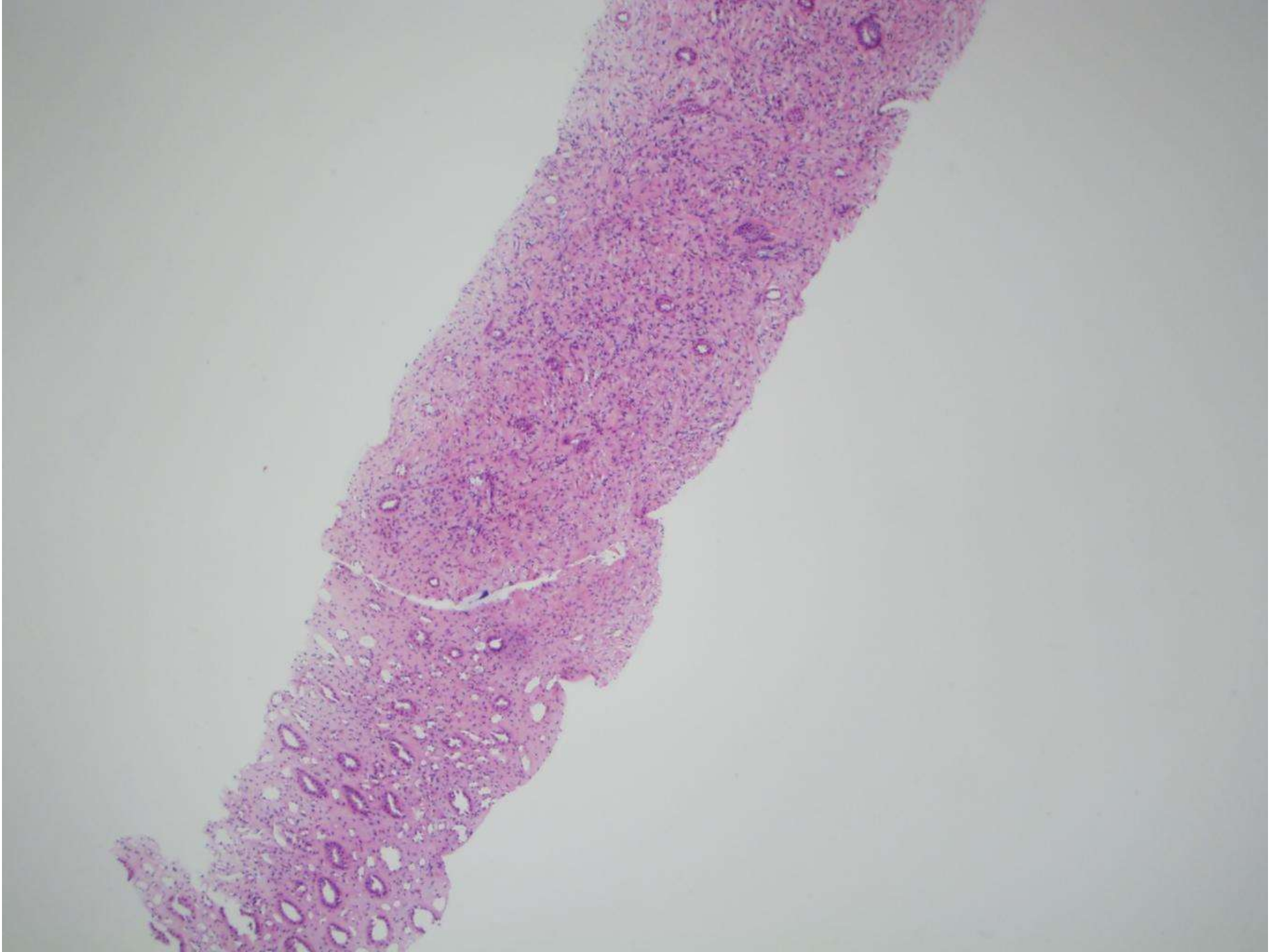


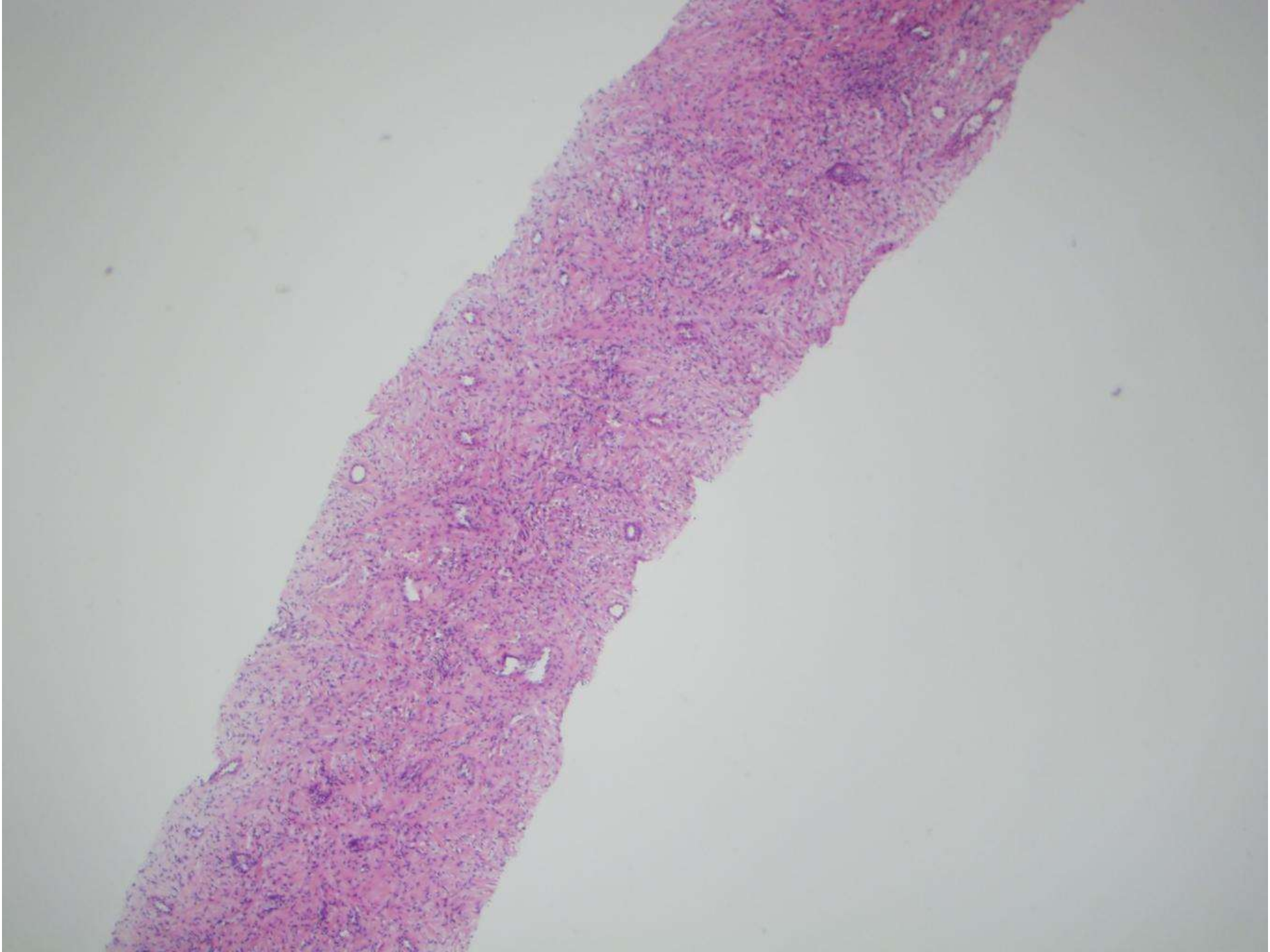


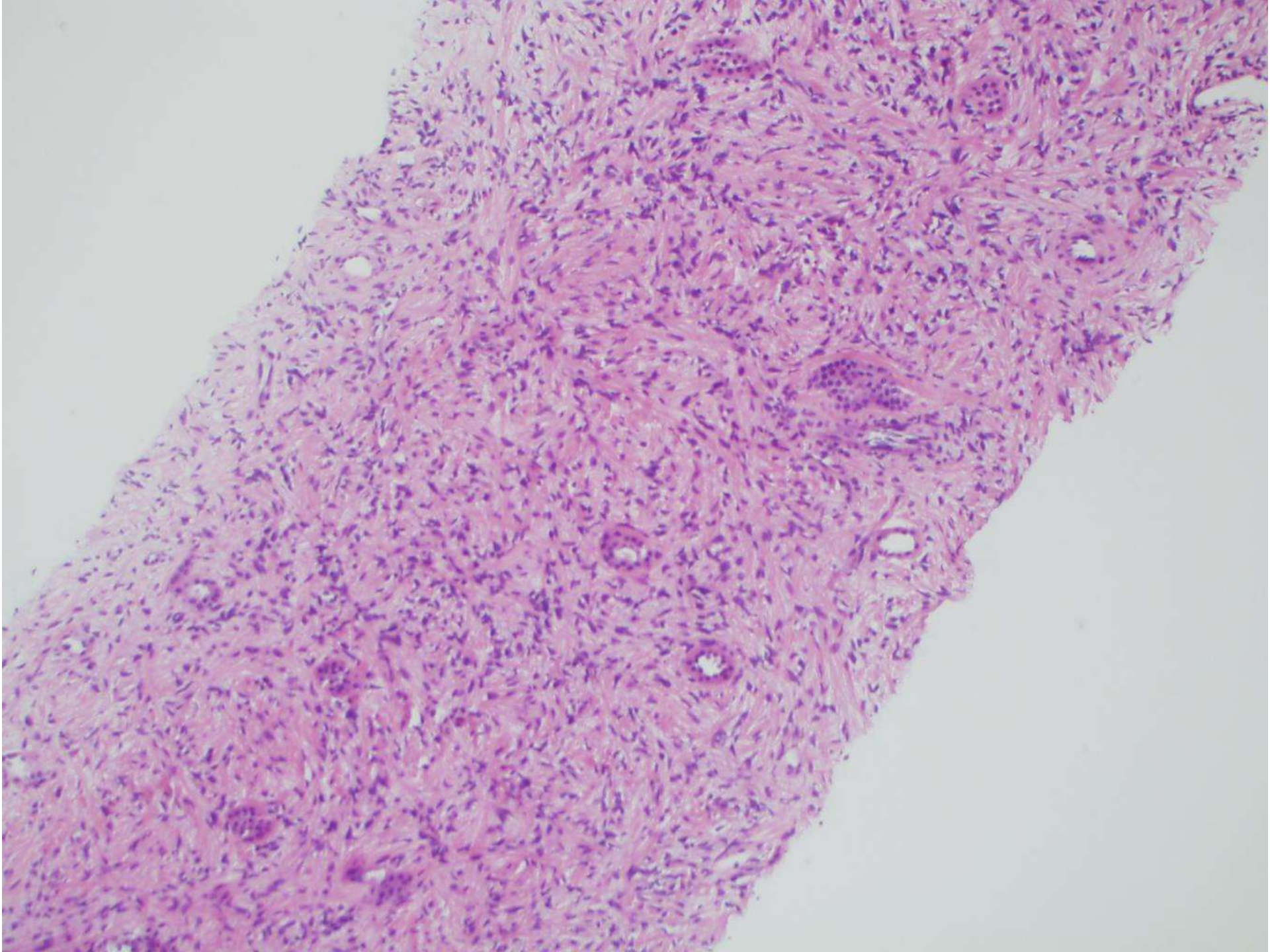


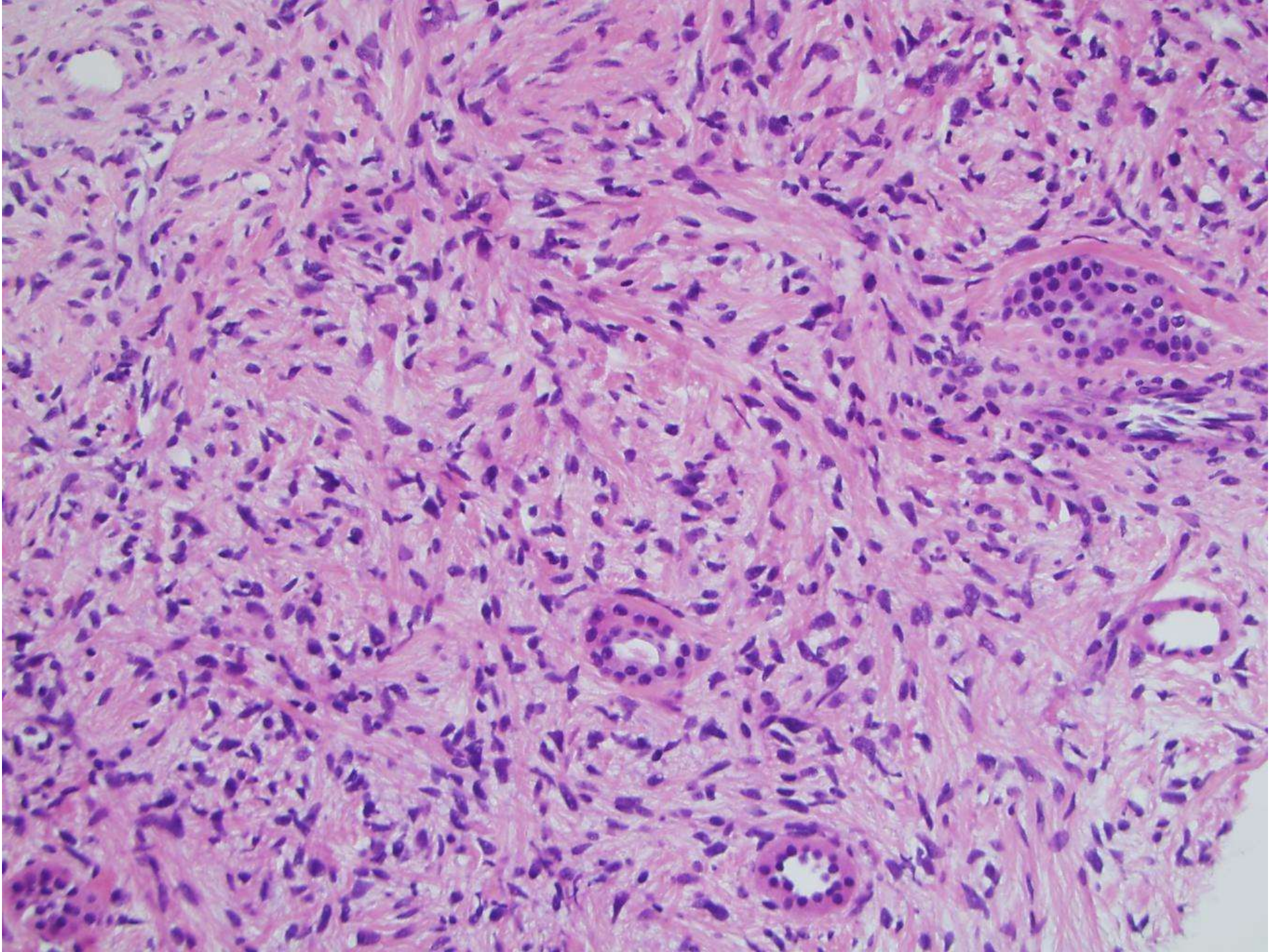








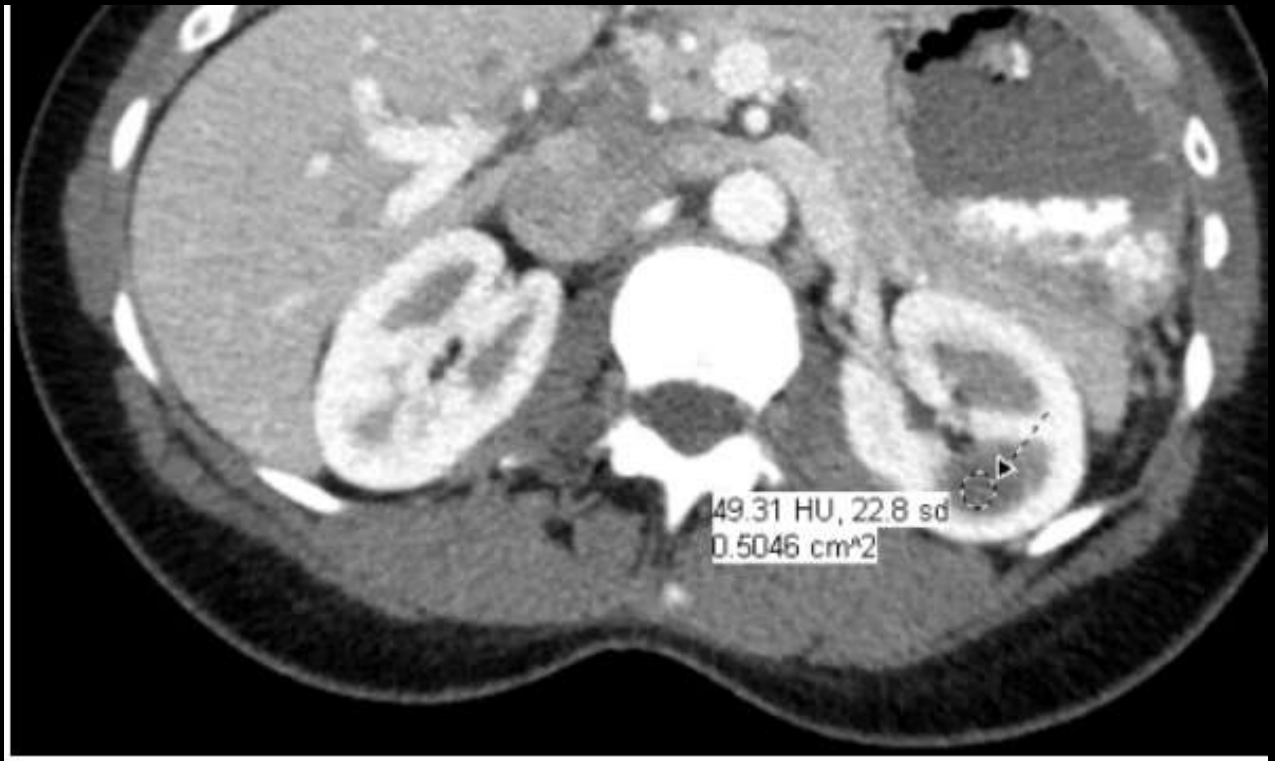


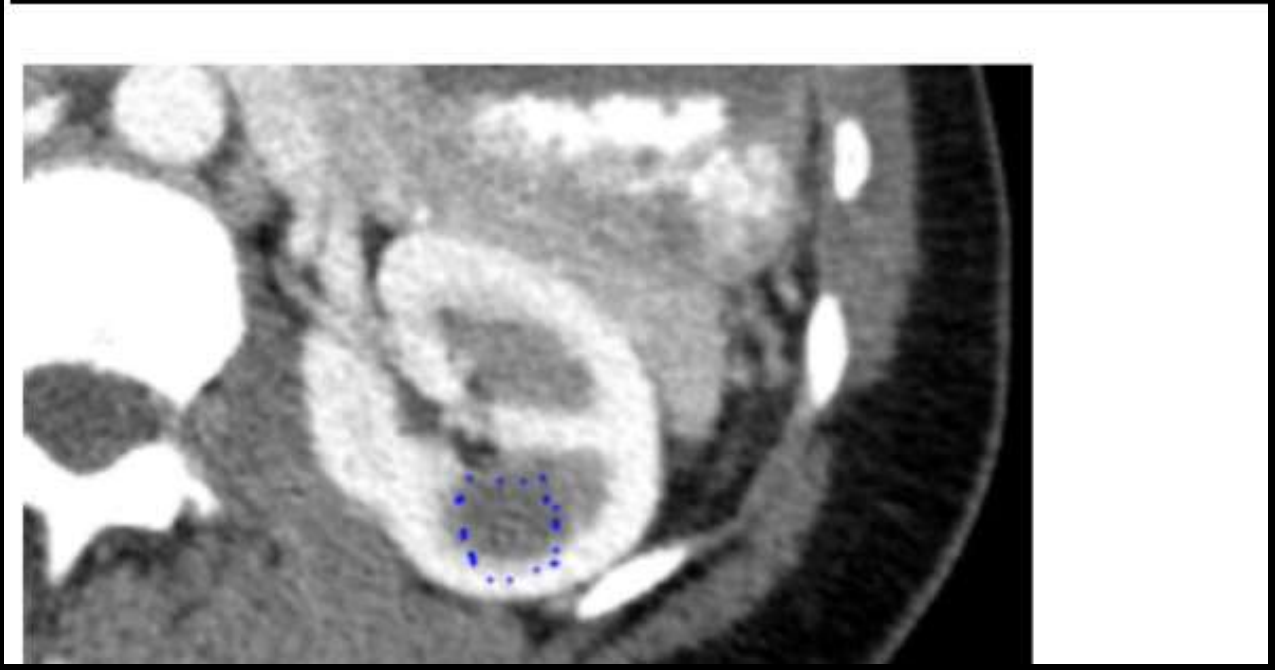


DDx

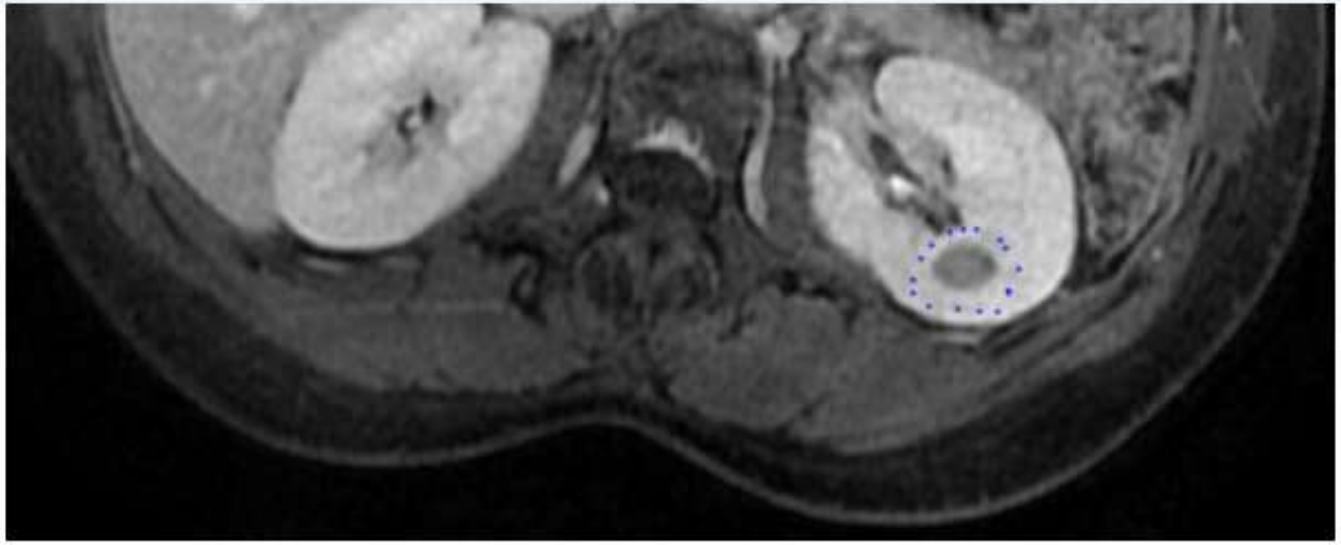
- Renomedullary interstitial tumor ("medullary fibroma")
- Metanephric stromal tumor
- AML
- Renal cell carcinoma
- Urothelial carcinoma

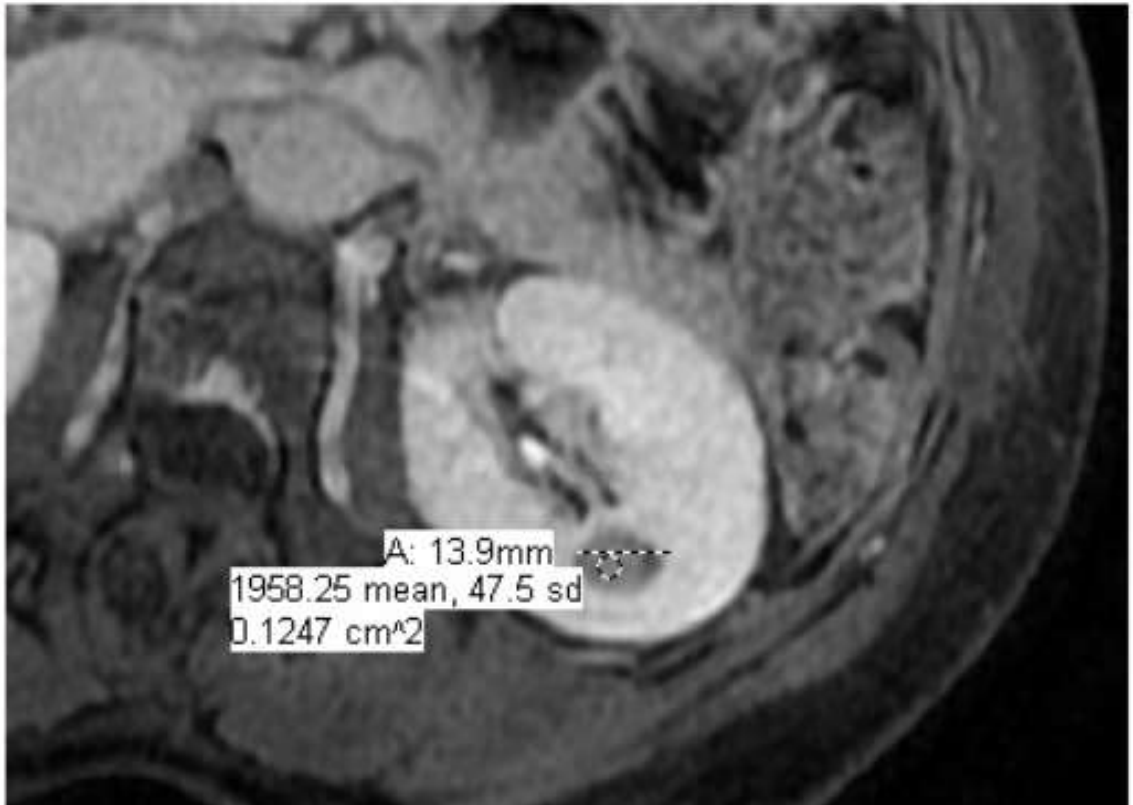
CT





MRI





IMAGING FINDINGS

- **CT/MRI show 1.3cm mass**
  - left upper pole near medulla

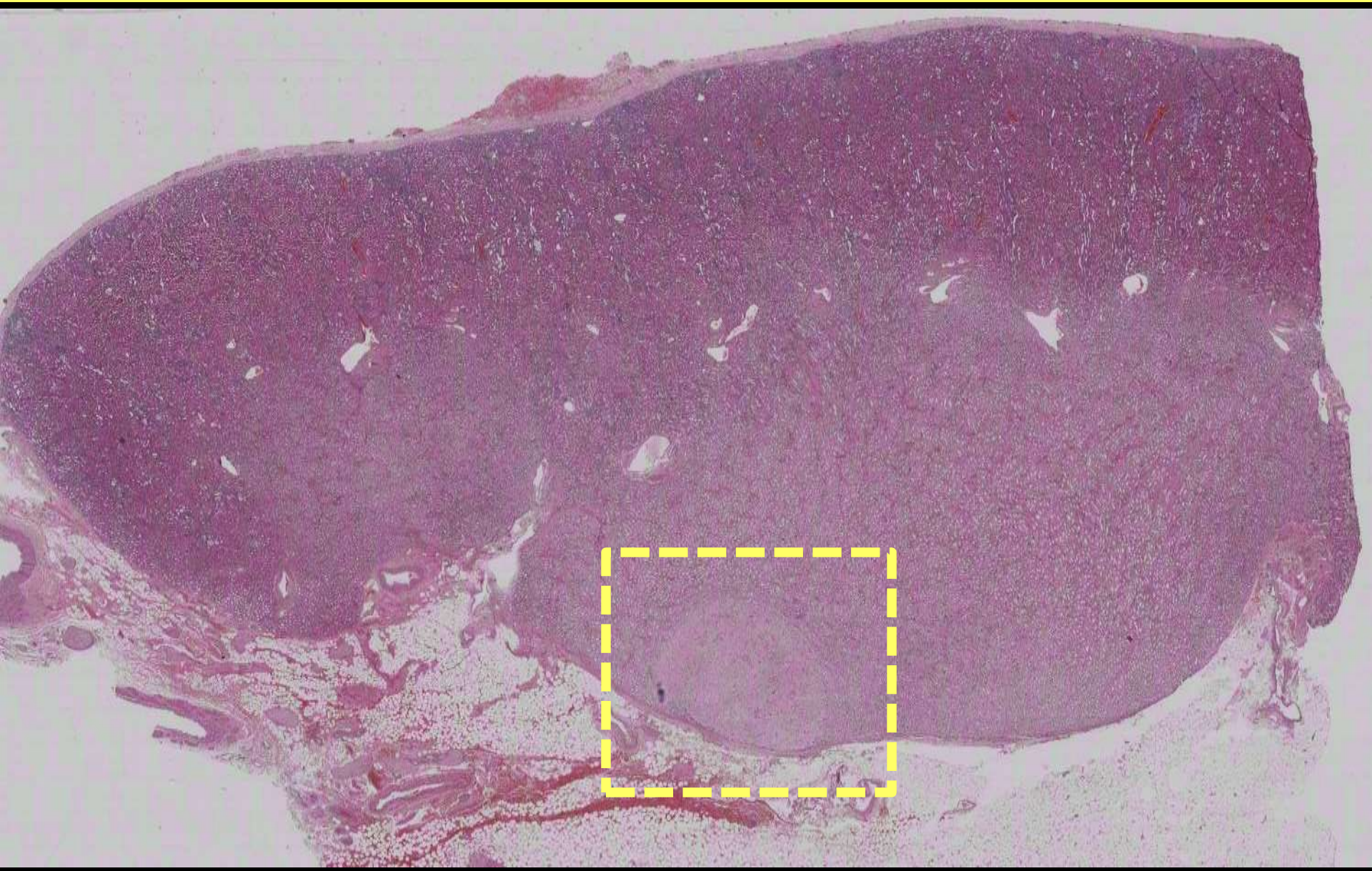
IHC summary

- **NEGATIVE:**
  - pankeratin, PAX8, ALK, cathepsinK

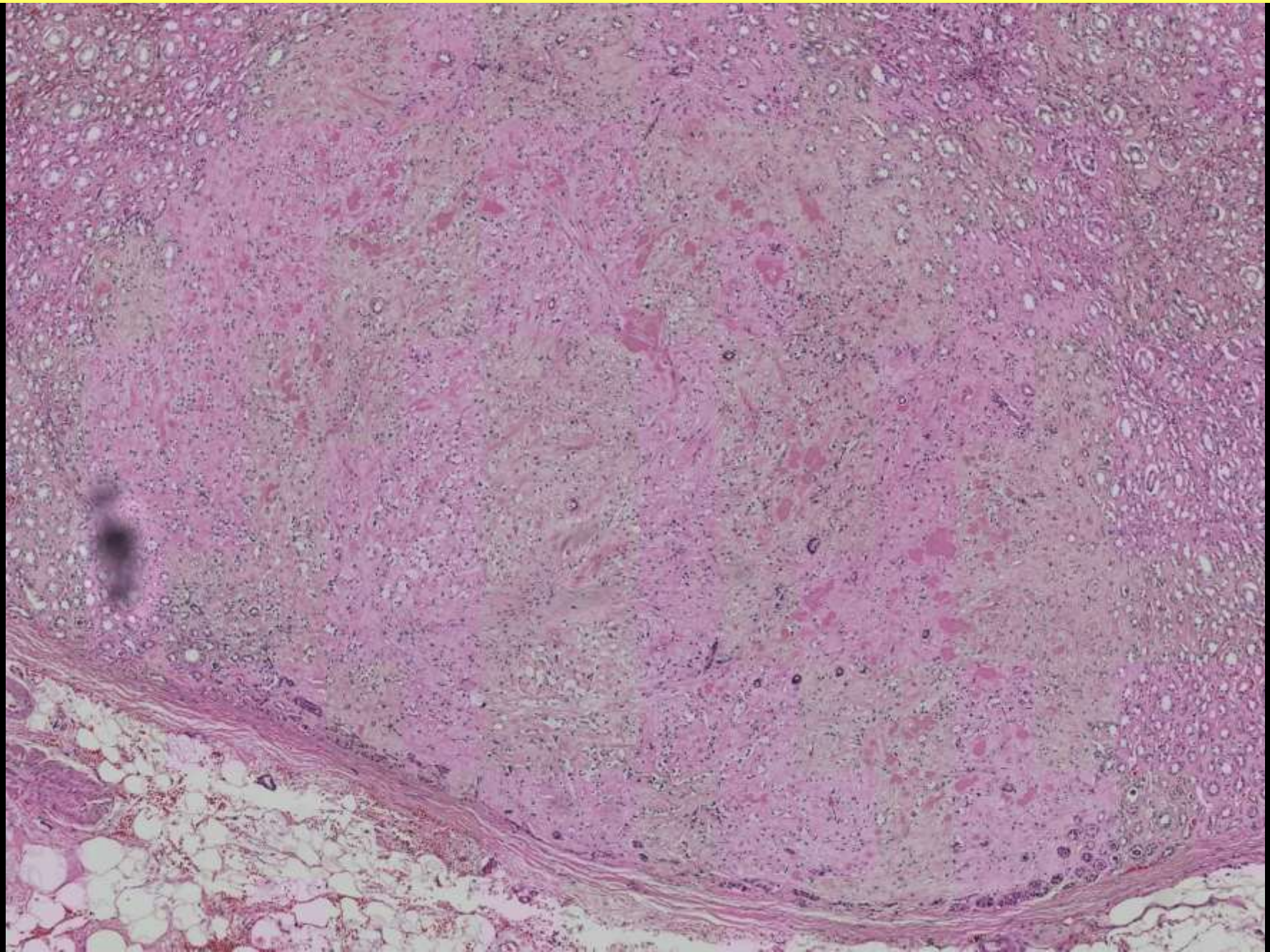
Final Dx

- Consistent with renomedullary interstitial tumor (“medullary fibroma”)

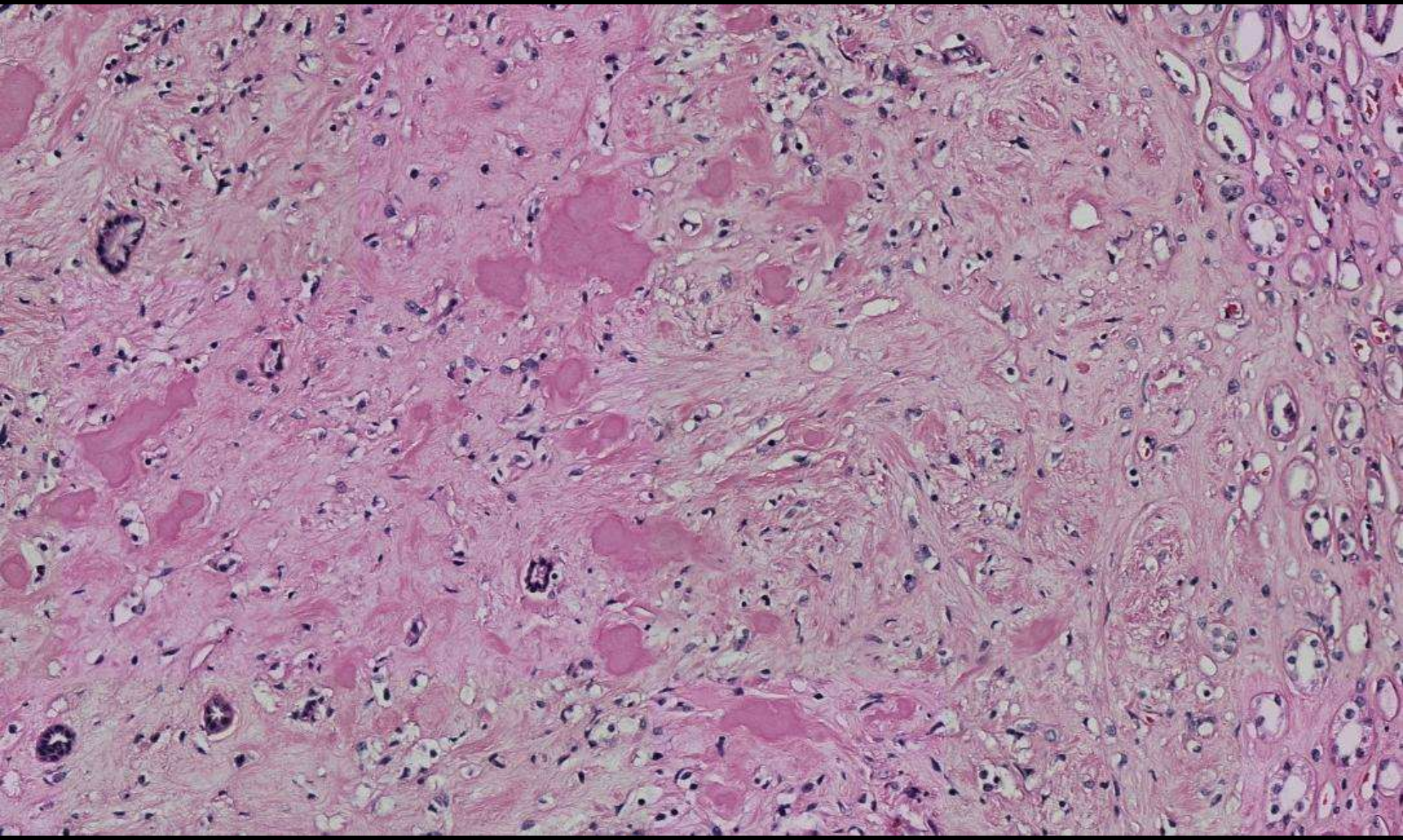
(different case) renomedullary interstitial tumor



(different case) renomedullary interstitial tumor



(different case) renomedullary interstitial tumor



Renomedullary Interstitial Cell Tumors

Pathologic Features and Clinical Correlations

Anna Caliò, MD,† Kathleen A. Warfel, MD,† and John N. Eble, MD†*

Abstract: Renomedullary interstitial cell tumors are common incidental findings in kidney specimens. Despite their frequency, little is known about their morphology and pathogenesis. Kidneys from 402 unselected autopsies were sectioned at 1 to 2 mm intervals, and all lesions were examined histologically. A total of 421 renomedullary interstitial cell tumors were present in 150 patients (37%), ranging from 1 to 23 tumors per patient (mean = 3). There was no statistically significant difference in age, sex, hypertension, heart weight, tobacco smoking, diabetes mellitus, and renal function between patients with renomedullary interstitial cell tumors and those without. Almost half the patients with renomedullary interstitial cell tumors (41%) had bilateral tumors, and they were older than patients with unilateral tumors ($P = 0.0007$). The tumors ranged in size from 0.5 to 6 mm (mean 1.7 mm). The lesions varied in cellularity: fibrous stroma was found in older patients, whereas cellular and hypocellular stroma predominated in younger patients ($P = 0.001$ and $P < 0.0001$, respectively). Entrapped renal tubules were found throughout the tumor in younger patients and smaller tumors, whereas the absence of entrapped tubules or their location only at the periphery of the lesion were common in older patients and larger tumors ($P = 0.02$ and $P < 0.0001$, respectively). Ropey brightly eosinophilic material, found in 26% of tumors, was not amyloid but collagen type III. This material was observed in older patients ($P < 0.0001$) with larger tumors ($P < 0.0001$) and was also correlated to higher heart weight ($P = 0.003$) but not to hypertension ($P = 0.11$). On the basis of our findings, renomedullary interstitial cell tumors appear to originate as a proliferation of renomedullary interstitial cells between medullary tubules. As their size increases, cellularity decreases, ropey eosinophilic material is deposited, and tubules disappear.

Key Words: renomedullary interstitial cell tumor, kidney, autopsy

(*Am J Surg Pathol* 2016;40:1693–1701)

Renomedullary interstitial cell tumors are small lesions frequently found incidentally in kidneys from adults. These tumors arise in the renal medulla, and it has been demonstrated that they are composed of cells with the ultrastructural and, more recently, biochemical features of renomedullary interstitial cells.[1,2] These cells, normal components of the renal medulla, synthesize several vasoactive agents, including prostaglandin, with antihypertensive effects.[3] On this basis, it has been proposed that renomedullary interstitial cell tumors develop in response to hypertension, although a previous study failed to find a causal association.[4] Histologically, the tumors are composed of spindle cells embedded in basophilic or sometimes collagenized stroma with or without amyloid-like material.[5] The description of clinical and morphologic features is limited to case reports and a few studies of limited numbers of tumors.[1,4,6–9] Given the limited information about renomedullary interstitial cell tumors in the literature, the aim of this study is to elucidate their

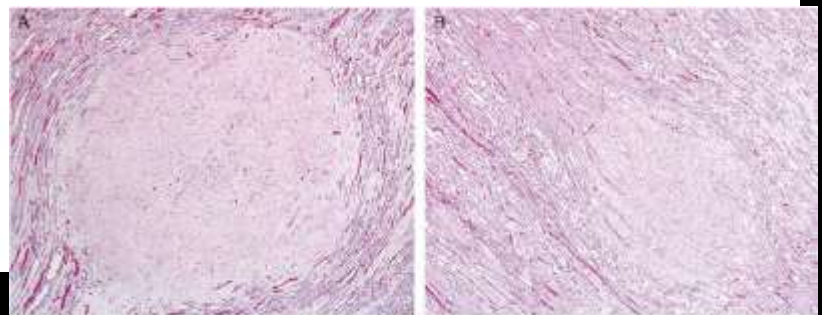


TABLE 1. Comparison of Patients With and Without Renomedullary Interstitial Cell Tumors*

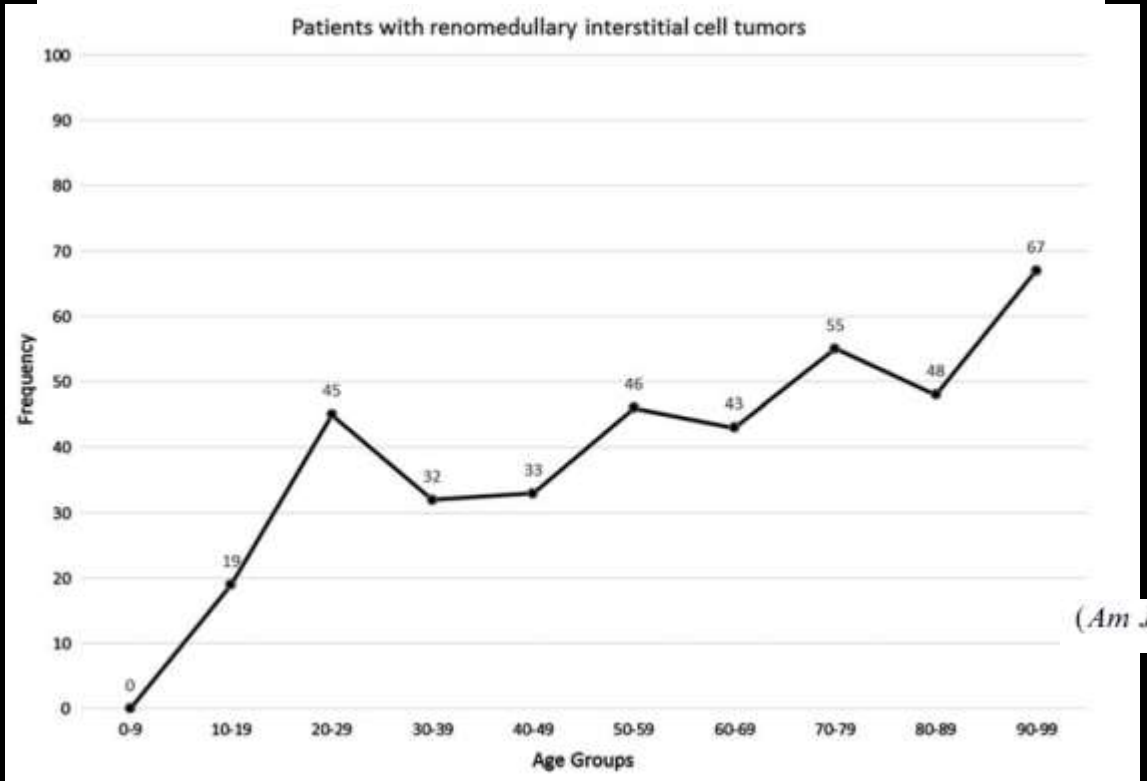
	No RMICT (189)	RMICT (150)	*P*
Age, mean (y)	56	58	0.1
Sex			
Male	141	117	0.44
Female	48	33	
Hypertension			
Yes	25	30	0.11
No	86	62	
Heart weight, mean (g)	435	428	0.64
Smoke			
Yes	90	69	1
No	19	15	
Diabetes mellitus			
Yes	25	18	0.73
No	91	78	
Renal function			
Normal	92	77	1
Abnormal	20	16	

*Excluded patients under 18 years old.
RMICT indicates renomedullary interstitial cell tumor.

(*Am J Surg Pathol* 2016;40:1693–1701)

TABLE 2. Distribution of Number of Renomedullary Interstitial Cell Tumors in Decade Age Groups

	1	2	3	4	5	6	7	8	9	> 10	> 20	Total
0-9	0	0	0	0	0	0	0	0	0	0	0	0
10-19	2	2	0	0	0	0	0	0	0	0	0	4
20-29	9	2	0	1	0	1	0	0	0	0	0	13
30-39	5	1	0	1	0	0	0	0	0	0	0	7
40-49	4	2	0	1	3	1	0	1	1	0	0	13
50-59	16	7	1	3	4	2	2	0	0	1	0	36
60-69	13	7	5	5	3	0	1	1	1	0	0	36
70-79	10	8	4	2	3	0	0	0	0	0	0	27
80-89	3	2	2	0	1	1	2	0	0	0	1	12
90-99	1	1	0	0	0	0	0	0	0	0	0	2
Total	63	32	12	13	14	5	5	2	2	1	1	150



(*Am J Surg Pathol* 2016;40:1693–1701)

TABLE 3. Pathologic Features of Renomedullary Interstitial Cell Tumors

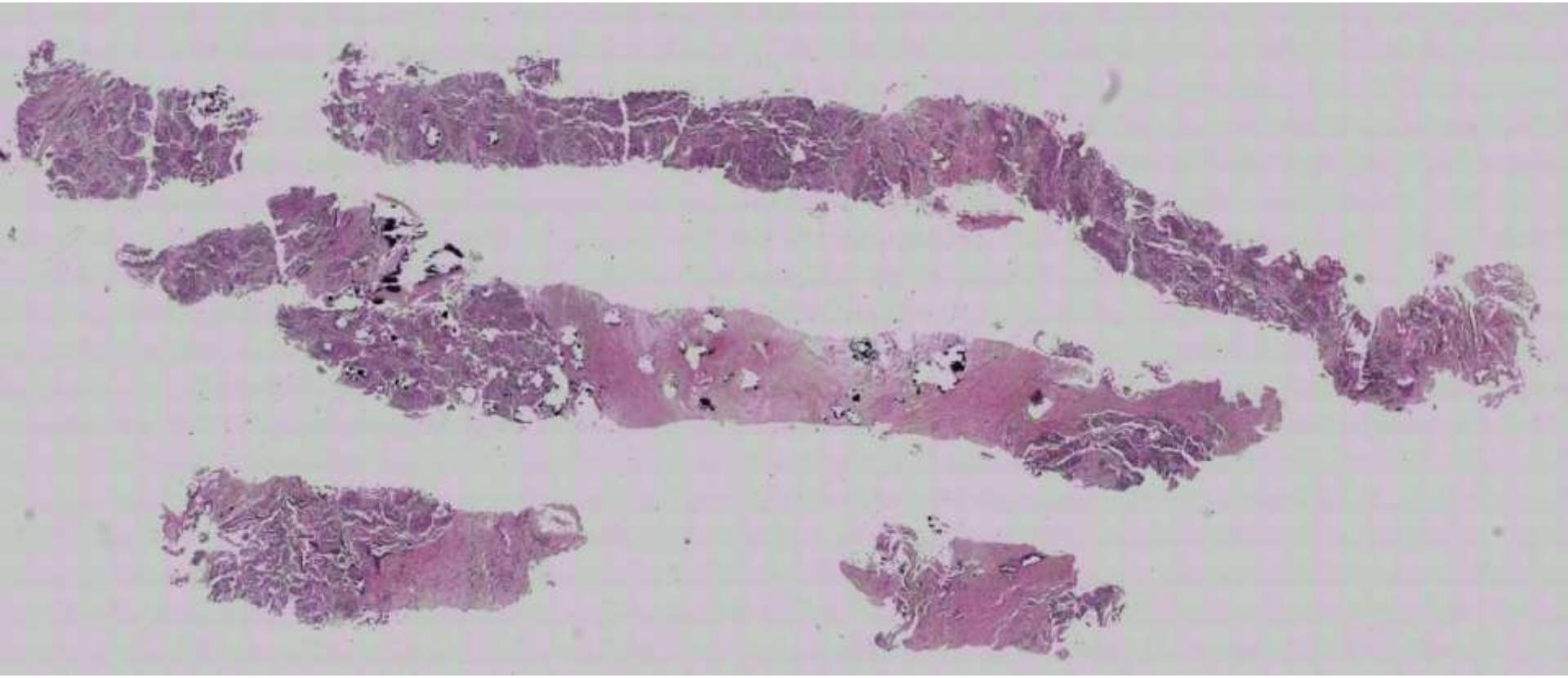
Parameter	N
Laterality	
Right	214
Left	184
Not available	23
Shape	
Round	224
Ovoid	197
Stromal cellularity	
Hypocellular	234
Fibrous	163
Cellular	24
Entrapped tubules	
Everywhere	161
Periphery	183
Center	9
No tubules	68
Amyloid-like material	108
Glomerulosclerosis in the adjacent parenchyma	
Absent	70
Slight	42
Moderate	28
Severe	10

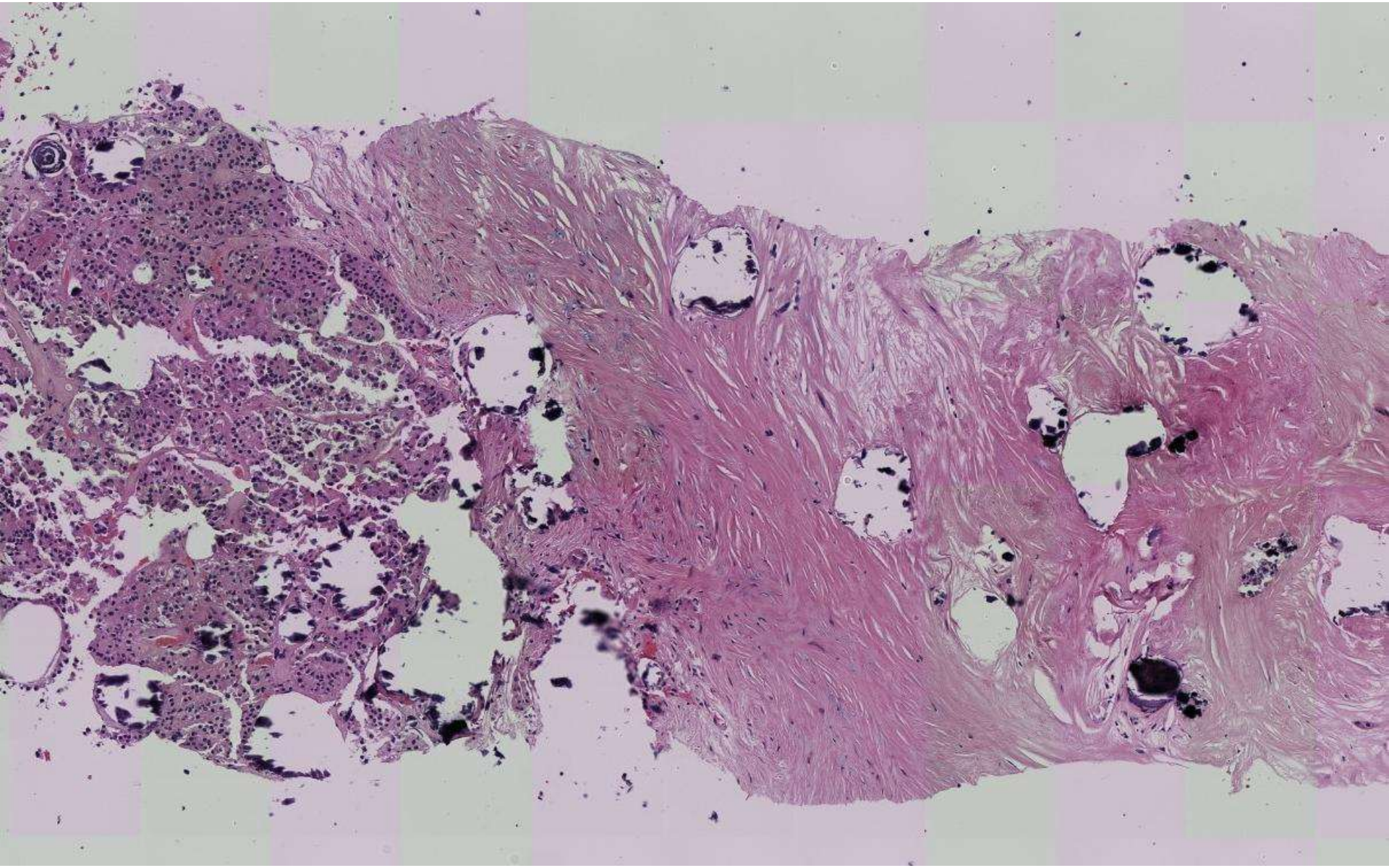
(*Am J Surg Pathol* 2016;40:1693–1701)

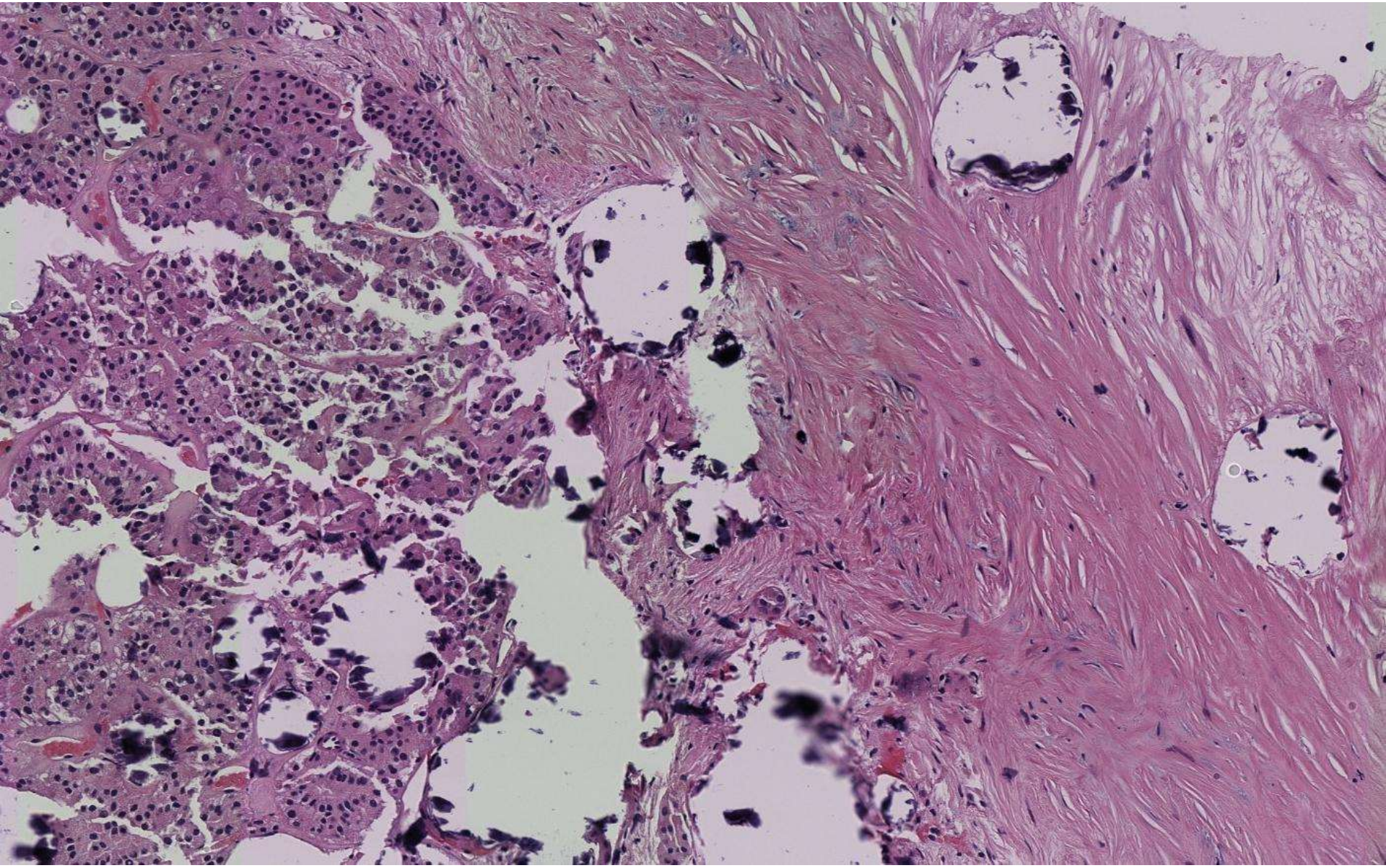
21-0407 scanned slide avail!

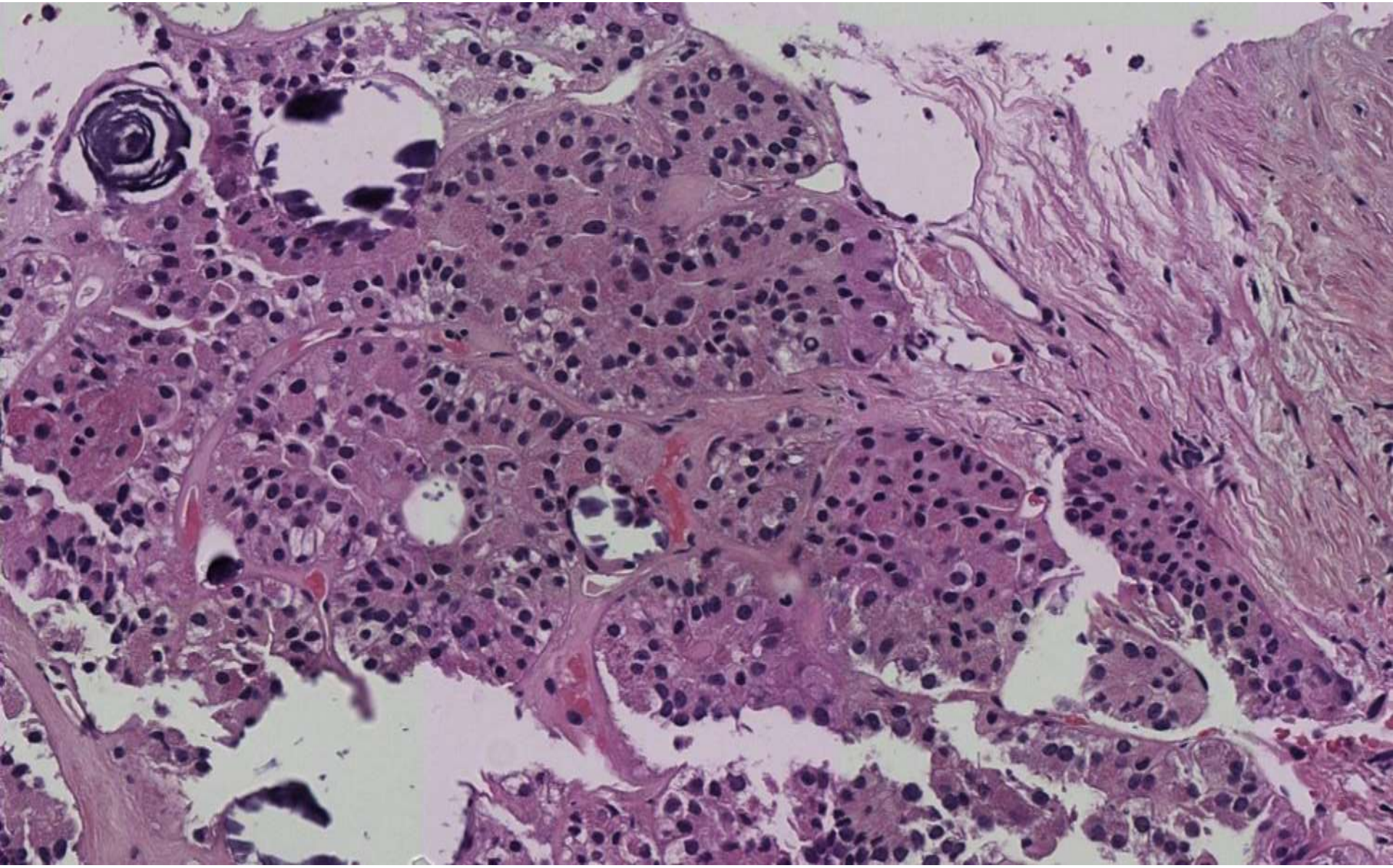
Ankur Sangoi; El Camino Hospital

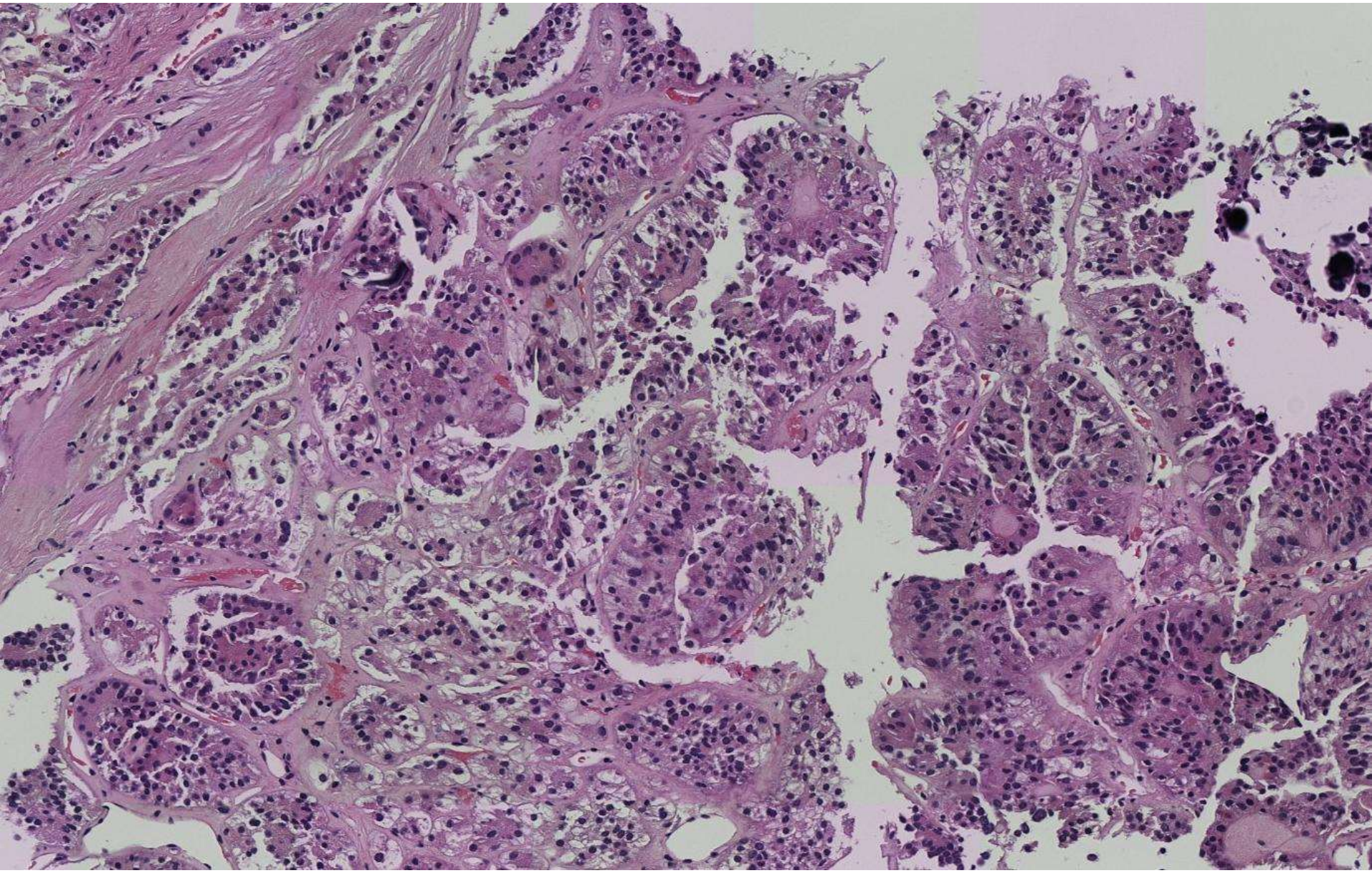
Adult F with long-standing kidney mass followed for many years, thought to be angiomyolipoma, now enlarging; core biopsy performed.

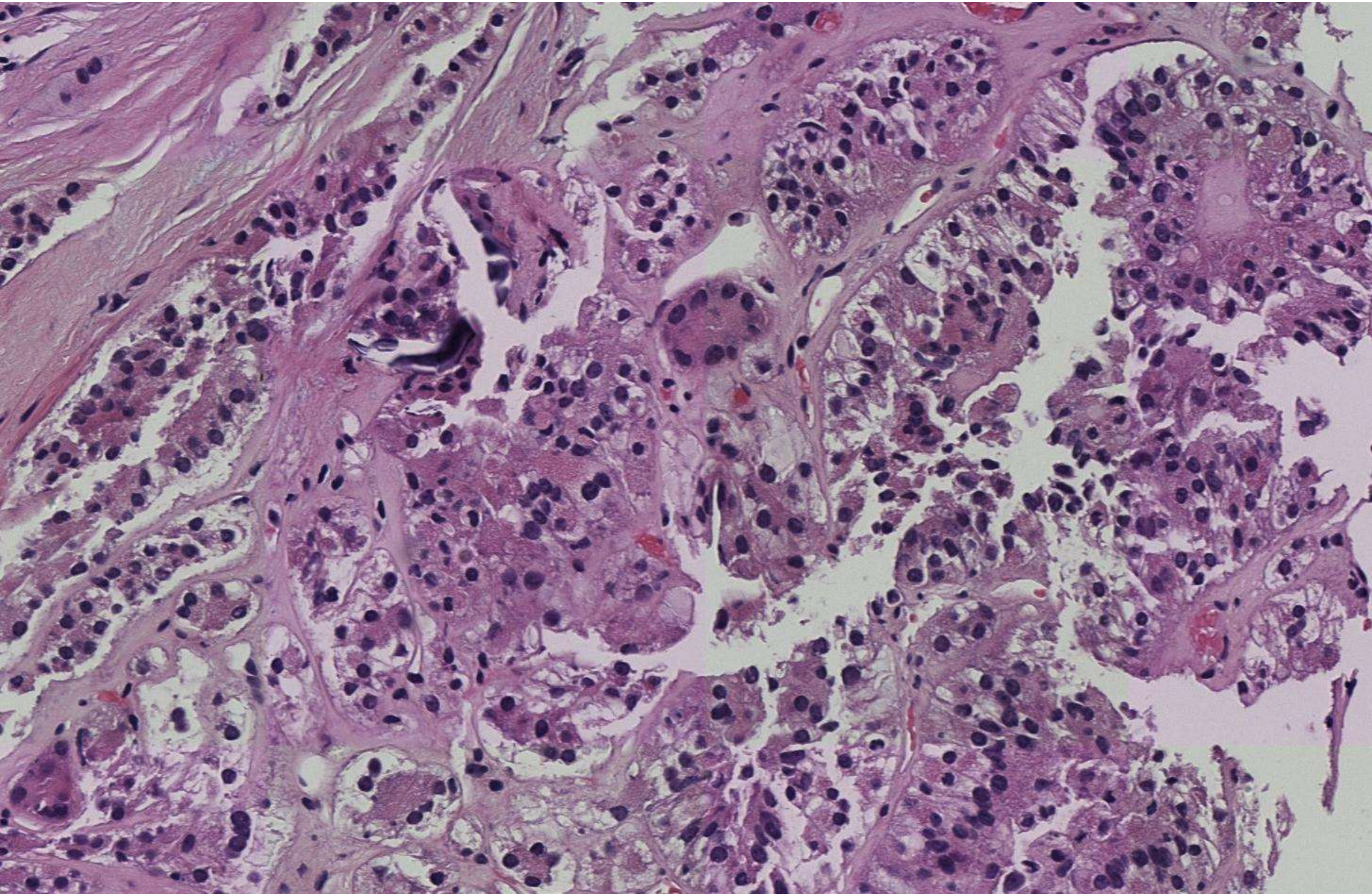


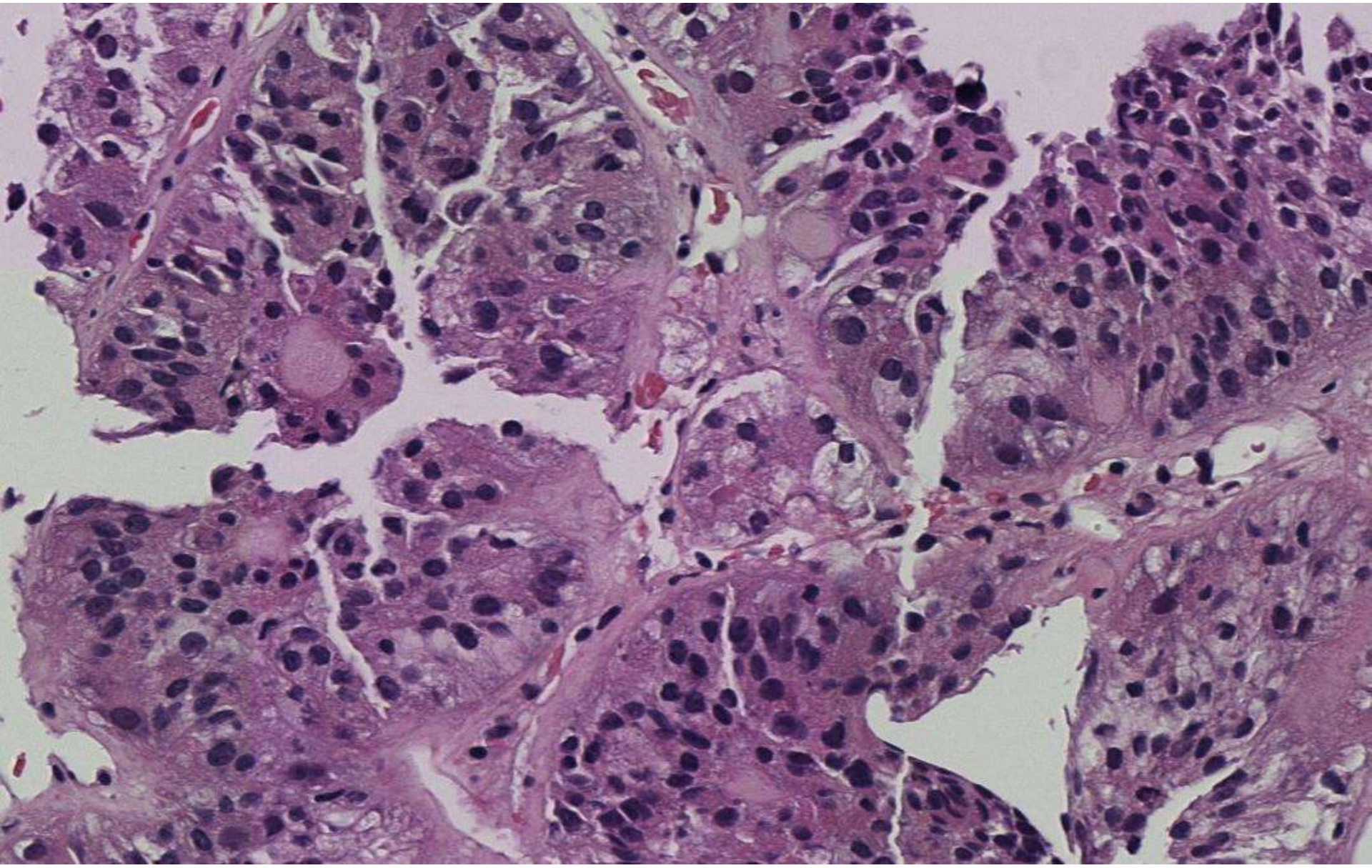


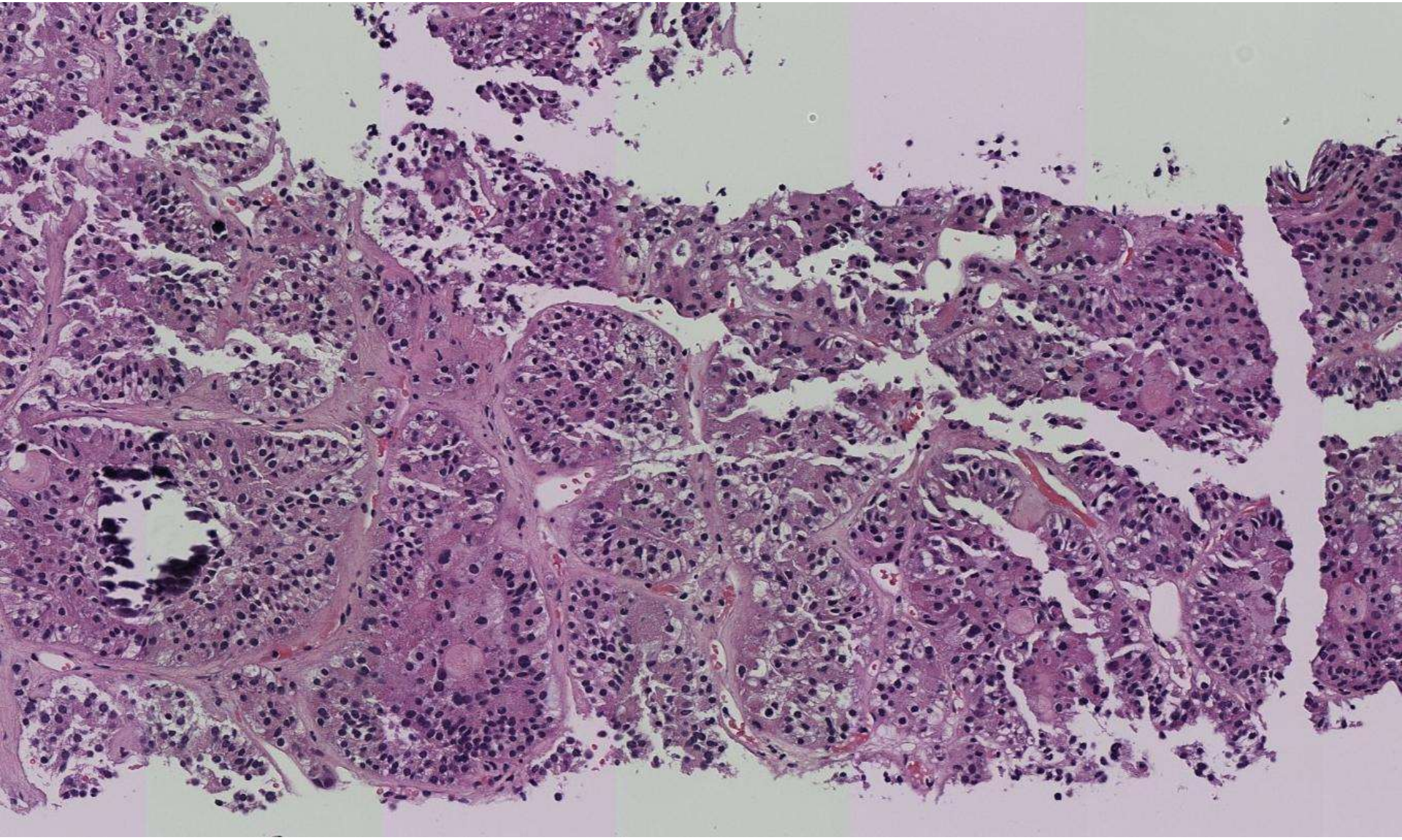


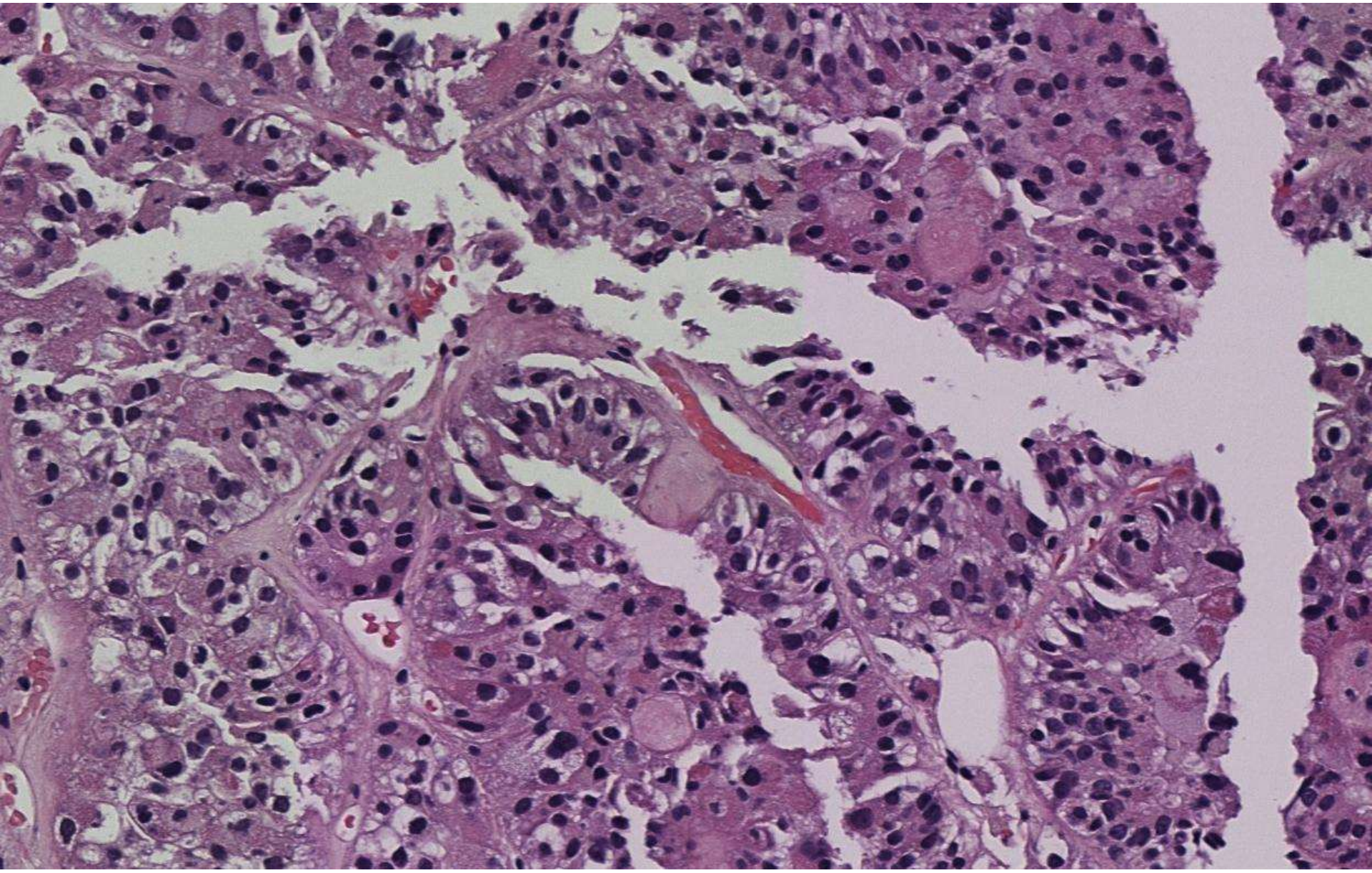






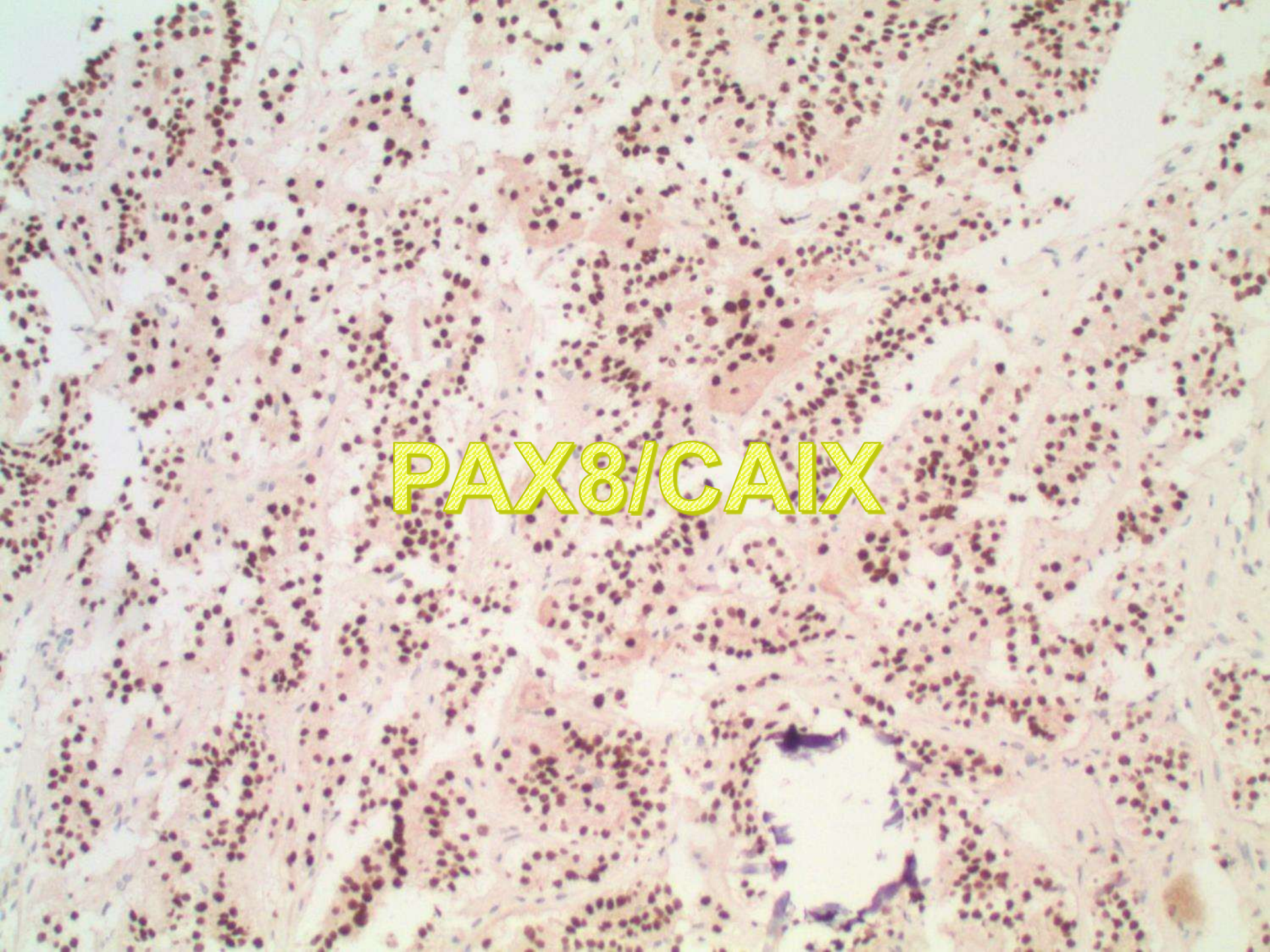


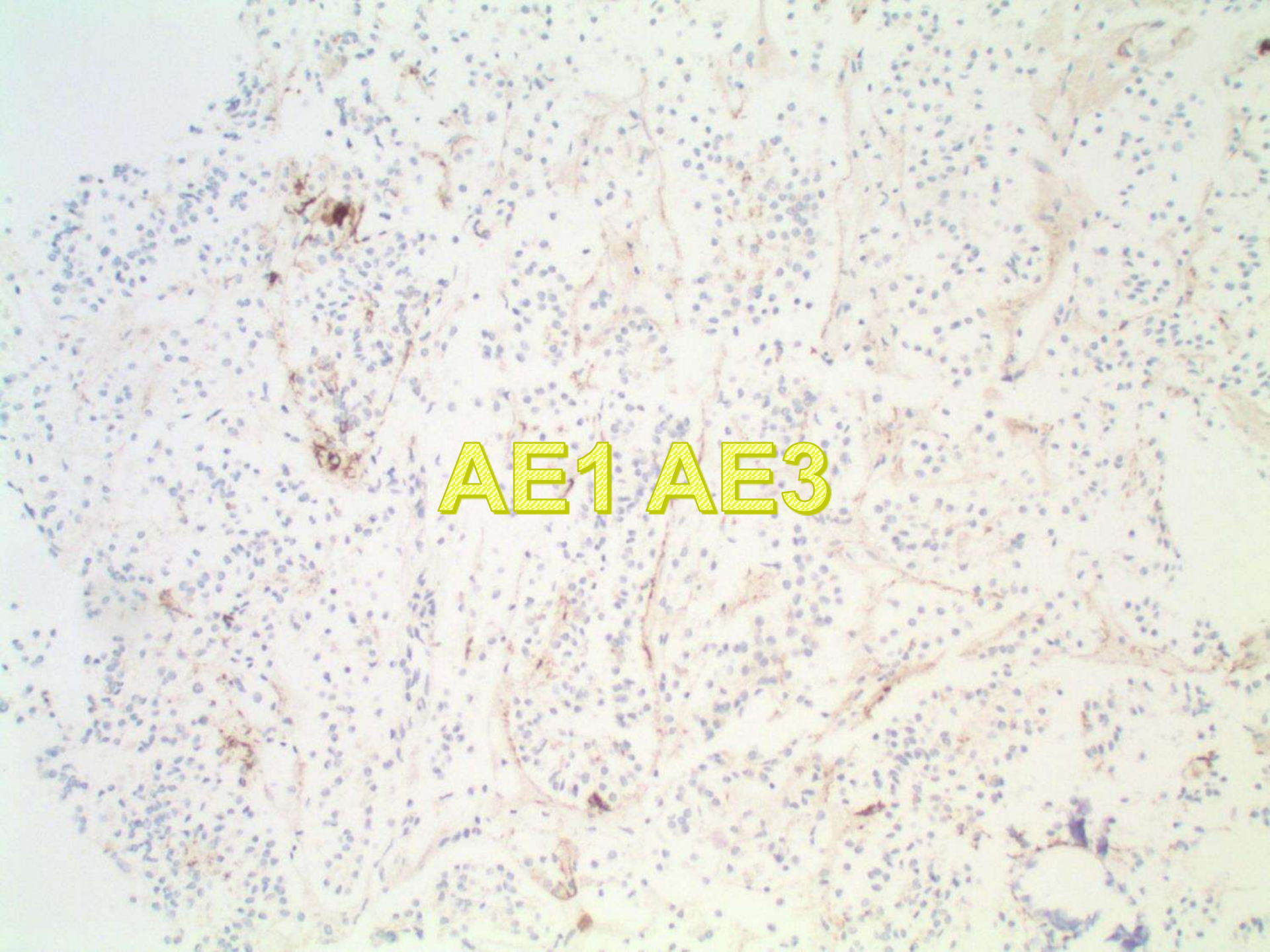


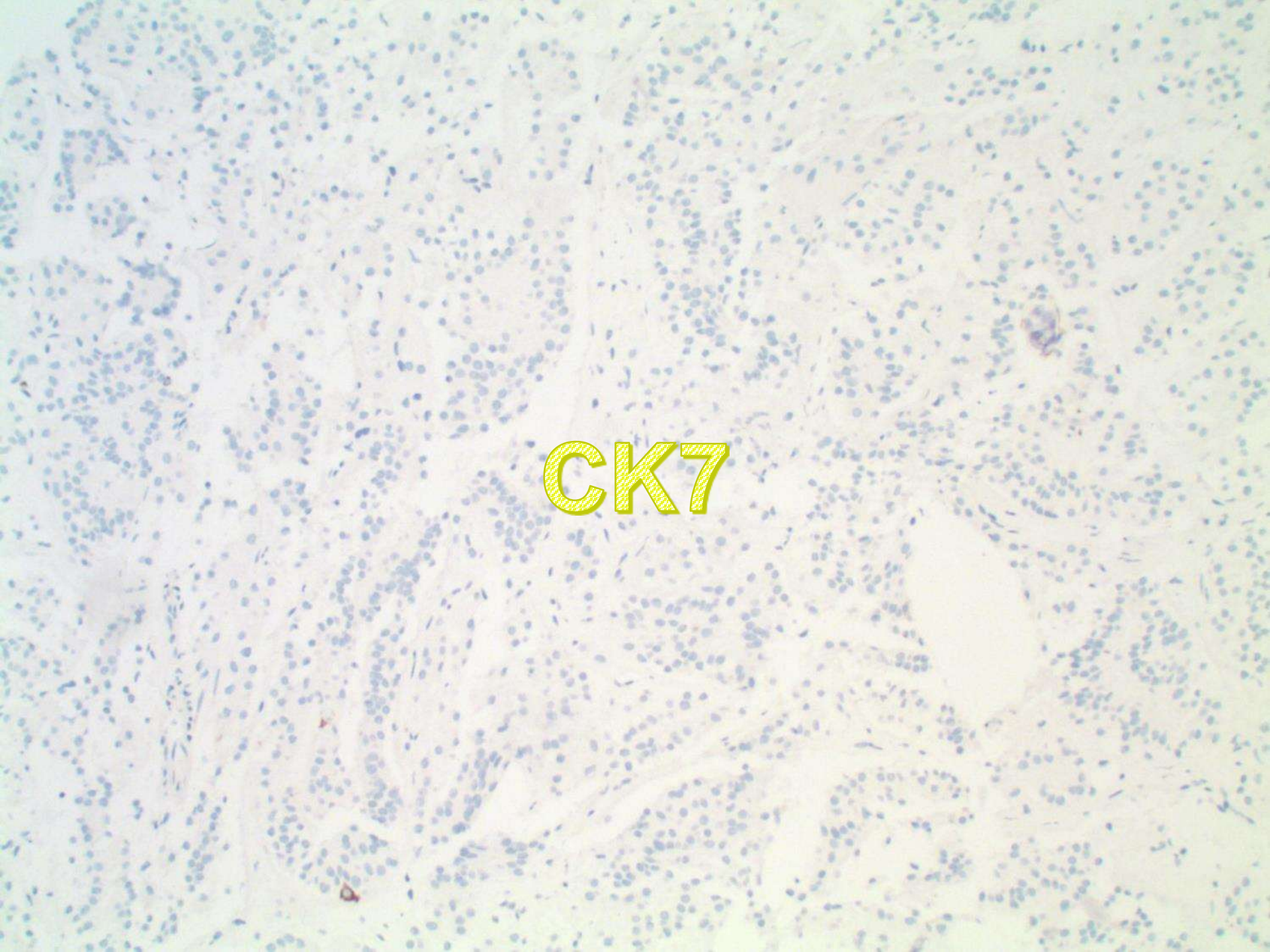


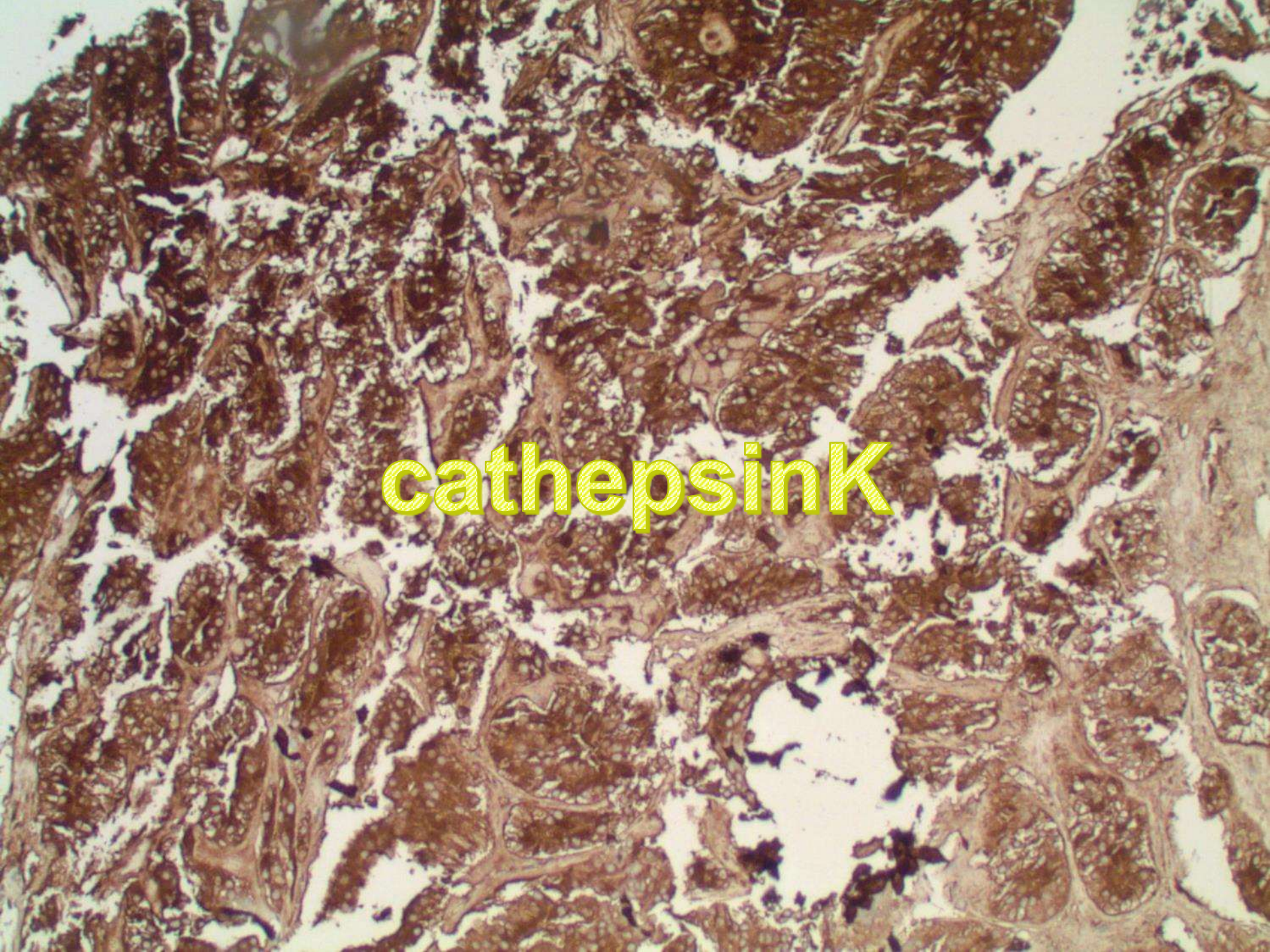
DDx

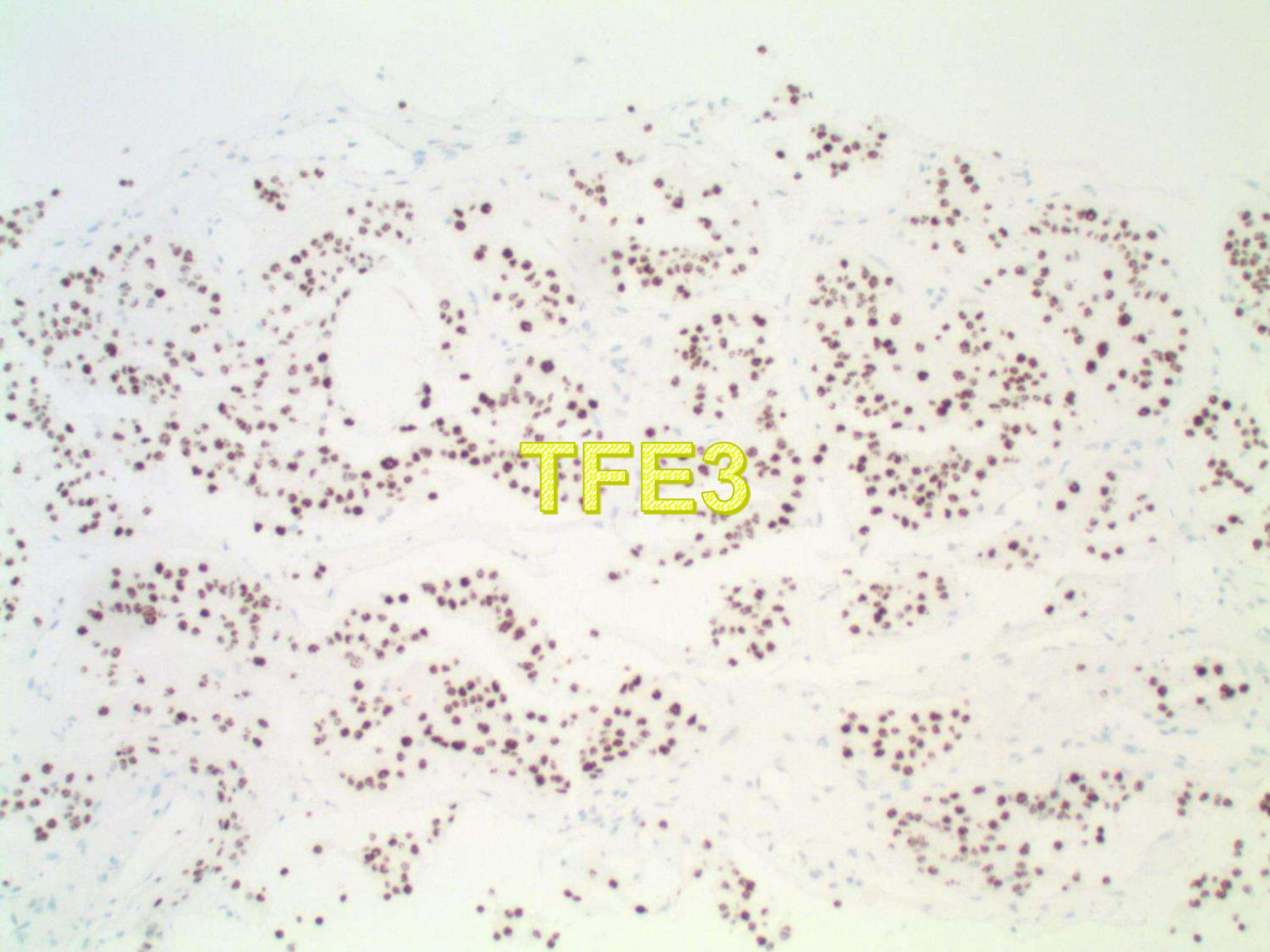
- **MiTF family translocation RCC**
  - TFE3 rearranged
  - TFEB rearranged
  - TFEB amplified
- **Papillary RCC**
  - “type 2”
- **Clear cell RCC**
- **Clear cell tubulopapillary RCC**
- **FH-deficient RCC**
- **ALK RCC**
- **Epithelioid AML**
  - TFE3 rearranged PEComa


PAX8/CAIX


AE1 AE3

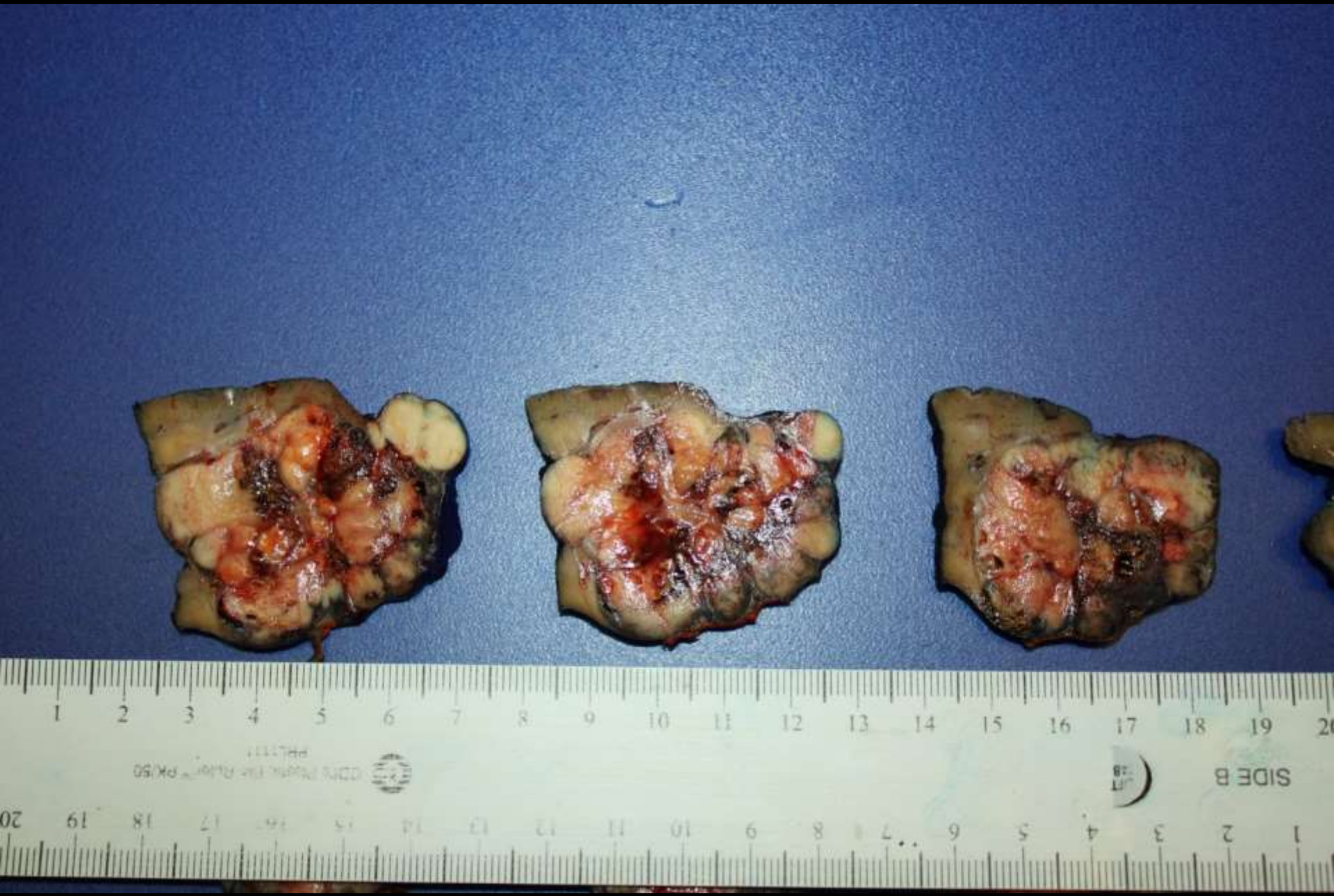

CK7

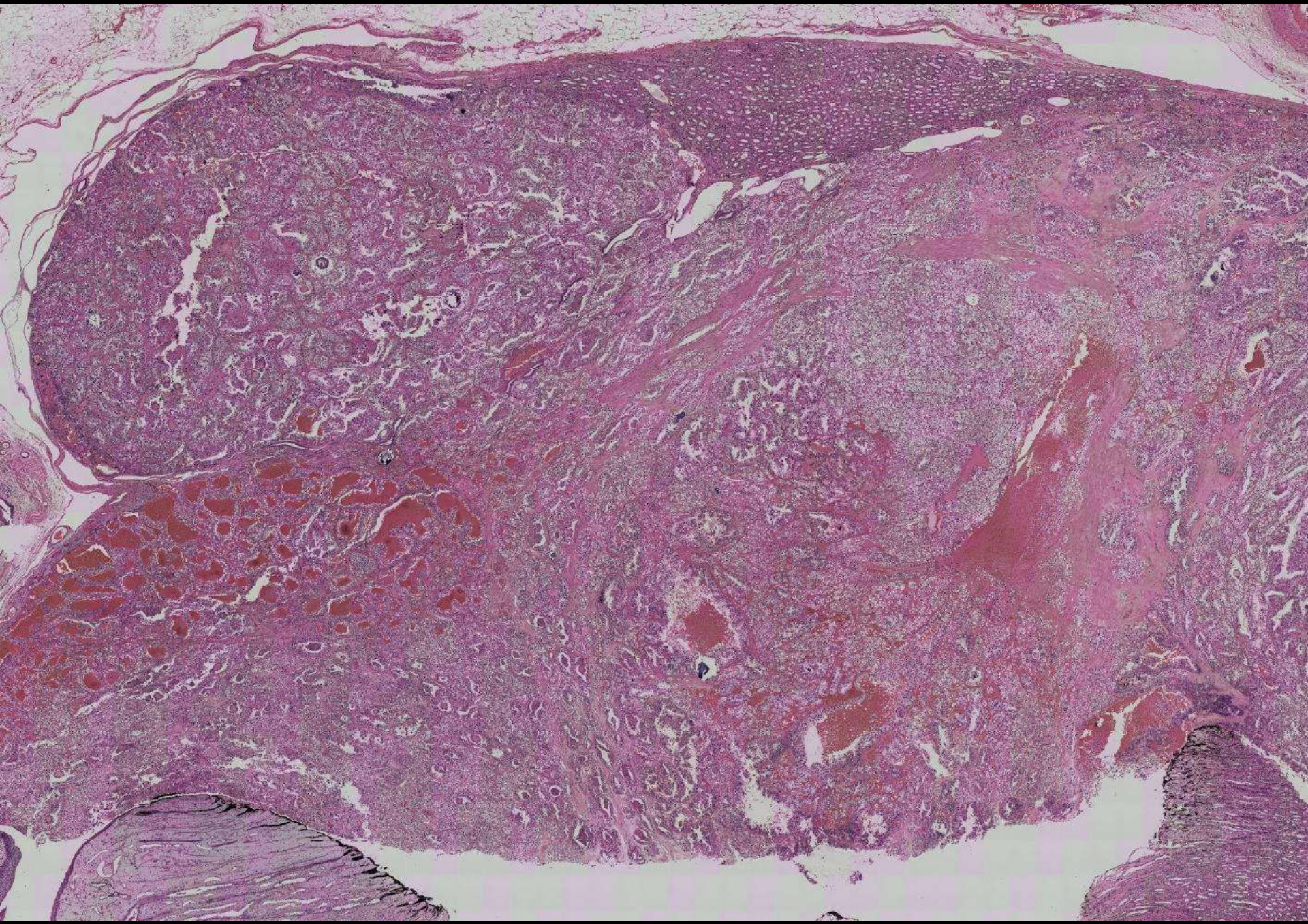

cathepsinK

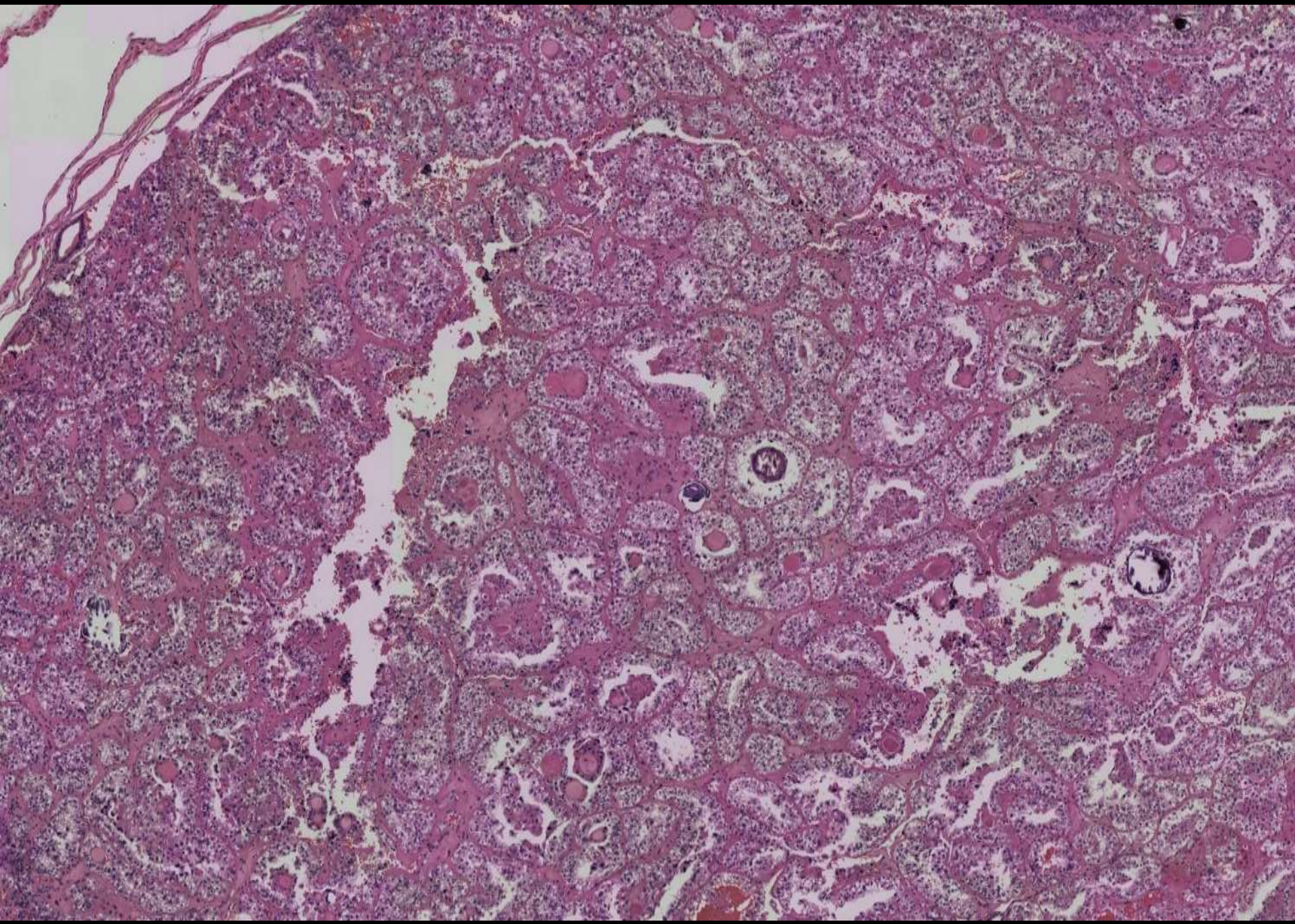

TFE3

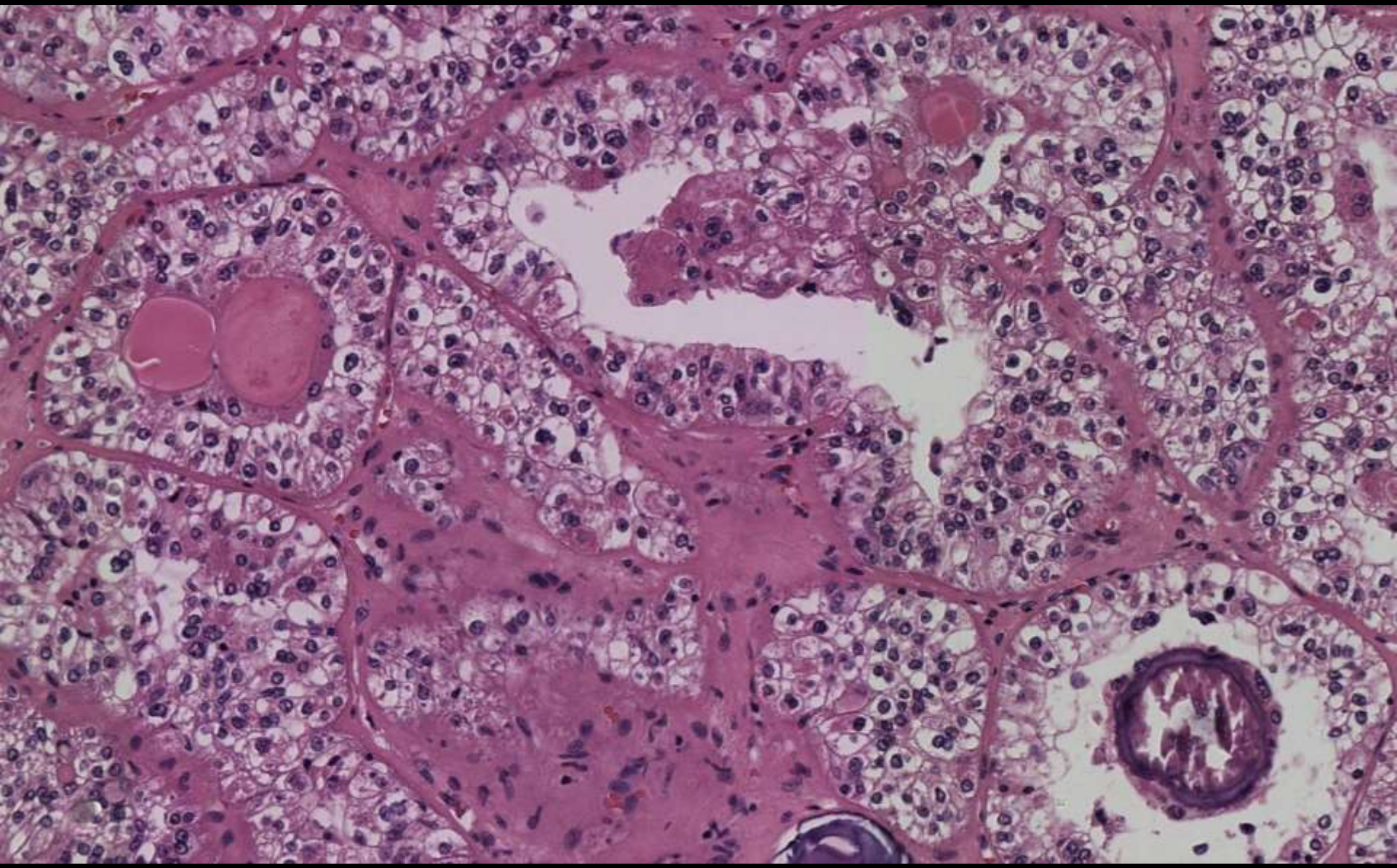
Final Dx

- **MiTF family translocation RCC**


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
SIDE B







When to consider MiTF family translocation RCC

- **“FLK” = funny-looking kidney**

- **Younger age**
  - Older age does not exclude!

Tools to ID MiTF RCC

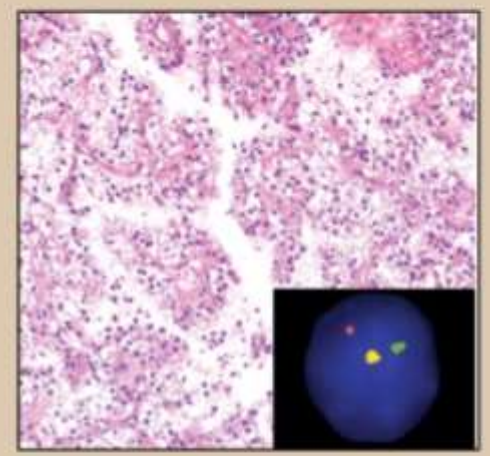
- **IHC**
  - Weak/neg keratin (prob not reliable “screen”)
  - melanA/HMB45+
    - TFEB>TFE3 RCC
  - cathepsinK+
  - TFE3 & TFEB stains often problematic
  - Novel: TRIM63 RNA ISH stain
- **FISH**
  - I usually send for BOTH TFE3 & TFEB FISH
- **PCR, RNA seq**
- **NGS**

TABLE 3. Comparison of Subtypes of *TFE3* Translocation RCCs and t(6;11) RCCs

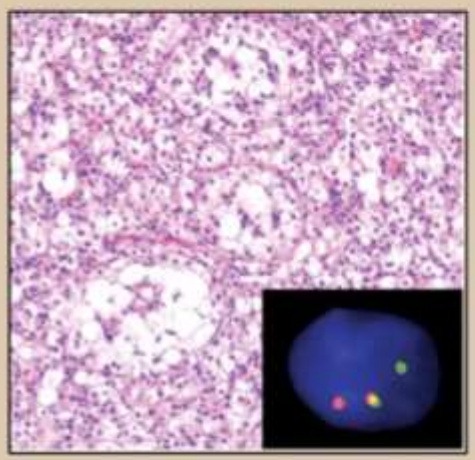
	RBM-TFE3 RCCs[13-15]	*NONO-TFE3* RCCs[10,20]	*ASPSCR1-TFE3* RCCs[2,10]	*PRCC-TFE3* RCCs[3,10]	*SFPQ-TFE3* RCCs[4,10]	t(6;11) RCCs[22-25]
Morphology feature	A biphasic morphology overlapping with t(6;11) RCCs: mixed areas of sheets, nests and papillary patterns of epithelioid cells and pseudorosette-like architecture. Cytoplasmic vacuolization and nuclear grooves were usually observed	A biphasic pattern: sheets of epithelial cells and glandular/tubular or papillary architecture mimicking secretory endometrioid gland or clear cell papillary RCC	Nested to papillary architecture, voluminous clear to eosinophilic cytoplasm, and abundant psammoma bodies	Compact nested to papillary architecture, clear to eosinophilic cytoplasm, and fewer psammoma bodies	Nested or papillary architecture and predominantly clear cytoplasm. Subnuclear vacuoles similar was usually seen. Occasionally present pseudorosette-like architecture	The most distinctive pattern of the t(6;11) RCCs is of a biphasi neoplasm, composed of nests o larger epithelioid cells and smaller cells clustered around basement membrane material
Psammoma bodies	Often present	Usually present	Usually present	Sometimes present	Sometimes present	Often present
Pigment	Occasionally present	Absent	Absent	Absent	Absent	Often present
IHC findings	Positive: TFE3, Cathepsin K and Melan-A (focally expressed) Negative: TFEB, HMB45	Positive: TFE3 Negative: Cathepsin K, Melan-A and HMB45	Positive: TFE3 Negative: Cathepsin K, Melan-A and HMB45	Positive: TFE3, Cathepsin K Negative: Melan-A and HMB45	Positive: TFE3 Negative: Cathepsin K, Melan-A and HMB45	Positive: TFEB, Cathepsin K, HMB45 and Melan-A Negative: TFE3
FISH findings	"False negative" for *TFE3* (split signals with a distance < 1 signal diameter) Negative for *TFEB*	Equivocal results for *TFE3* (split signals with a distance of nearly 2 signal diameters) Negative for *TFEB*	Positive for *TFE3* Negative for *TFEB*	Positive for *TFE3* Negative for *TFEB*	Positive for *TFE3* Negative for *TFEB*	Negative for *TFE3* Positive for *TFEB*

(*Am J Surg Pathol* 2017;41:663–676)

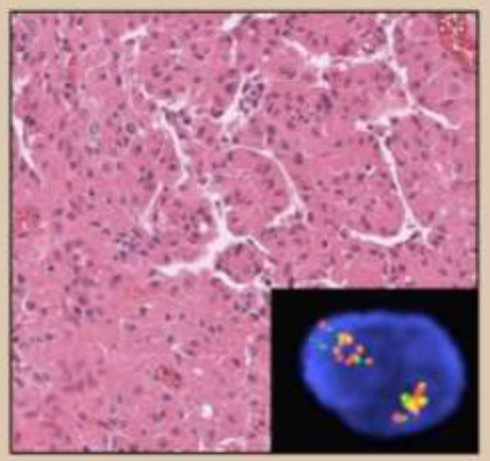
TFE3/TFEB FISH for MiTF RCC



TFE3 translocation RCC



TFEB translocation RCC



TFEB amplification RCC

Table 2. Current Understanding of Diagnostic Biomarkers for MiT Family Aberration–Associated Renal Cell Carcinoma (RCC)

Category	TFE3 RCC or Xp11 RCC	TFEB RCC or t(6;11) RCC	RCC With TFEB Amplification
Genomic aberration	Translocations involving *TFE3* on chr Xp11.2	Translocations involving *TFEB* on chr 6p21	chr 6p21 (*TFEB* locus) amplification
Pancytokeratin, EMA	Underexpressed/positive	Underexpressed/positive	Variably positive
Melan-A, HMB-45	Negative/variably positive	Predominantly positive	Negative/variably positive
FISH	Positive *TFE3* break-apart FISH	Positive *TFEB* break-apart FISH	High-level copy number gain of *TFEB* probe

Abbreviations: chr, chromosome; EMA, epithelial membrane antigen; FISH, fluorescence in situ hybridization; HMB-45, human melanoma black 45; Melan-A, melanoma antigen; *TFEB*, transcription factor EB; v*TFE3*, transcription factor binding to IGHM enhancer 3.

Arch Pathol Lab Med
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Contemporary Renal Tumor Categorization With Biomarker and Translational Updates

A Practical Review

Courtesy of Dr. Rohit Mehra

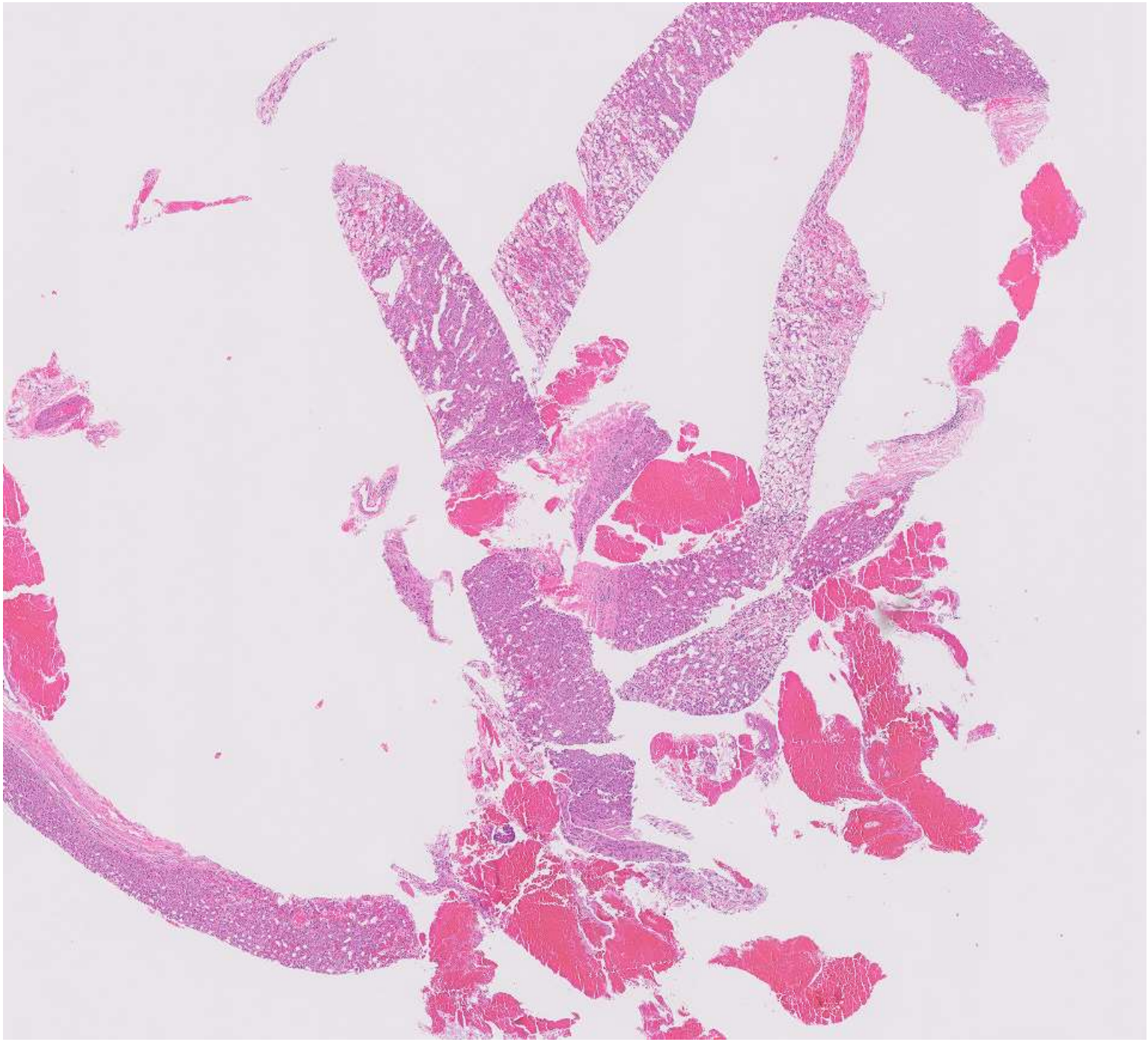
Outcome of MiTF RCC

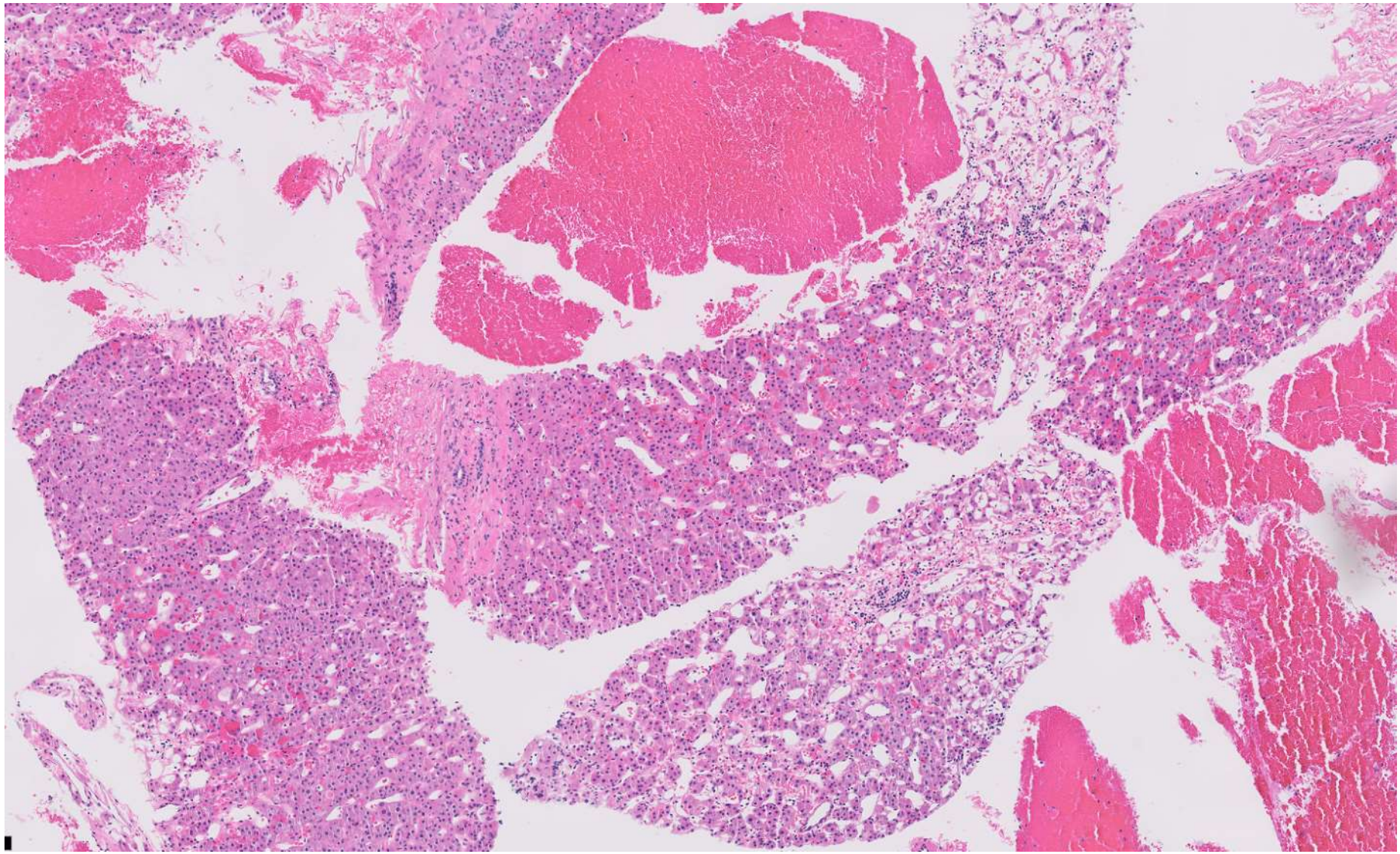
- **TFE3 translocated RCC**
  - Kids: often present at high stage, may still do well
  - Adults: survival similar to clear RCC
- **TFEB translocated RCC**
  - Often low stage, but potential for late recurrences/mets
- **TFEB amplified RCC**
  - Often high stage/high grade

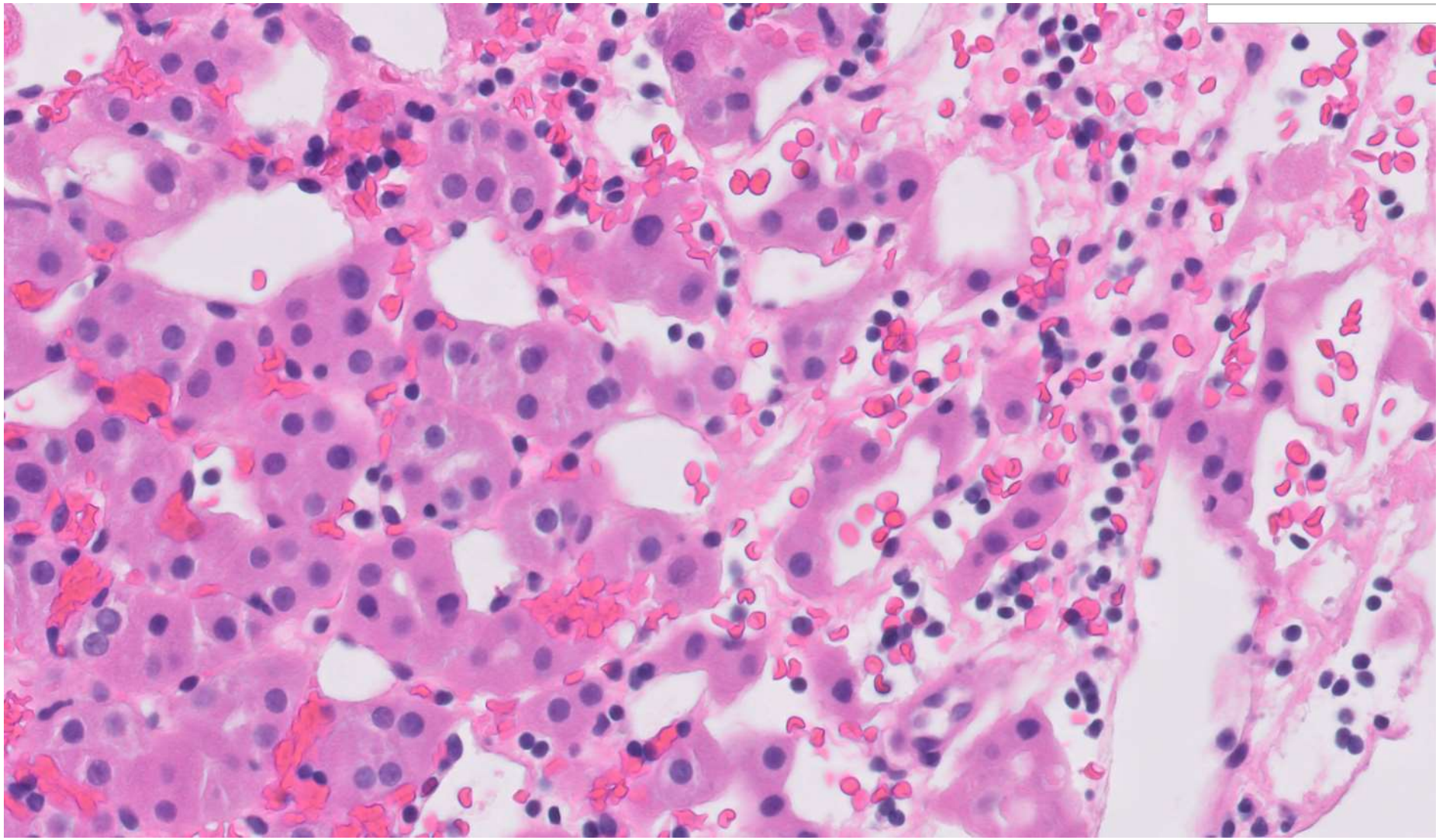
21-0408

Deidre Ongaro/Sunny Kao; Stanford

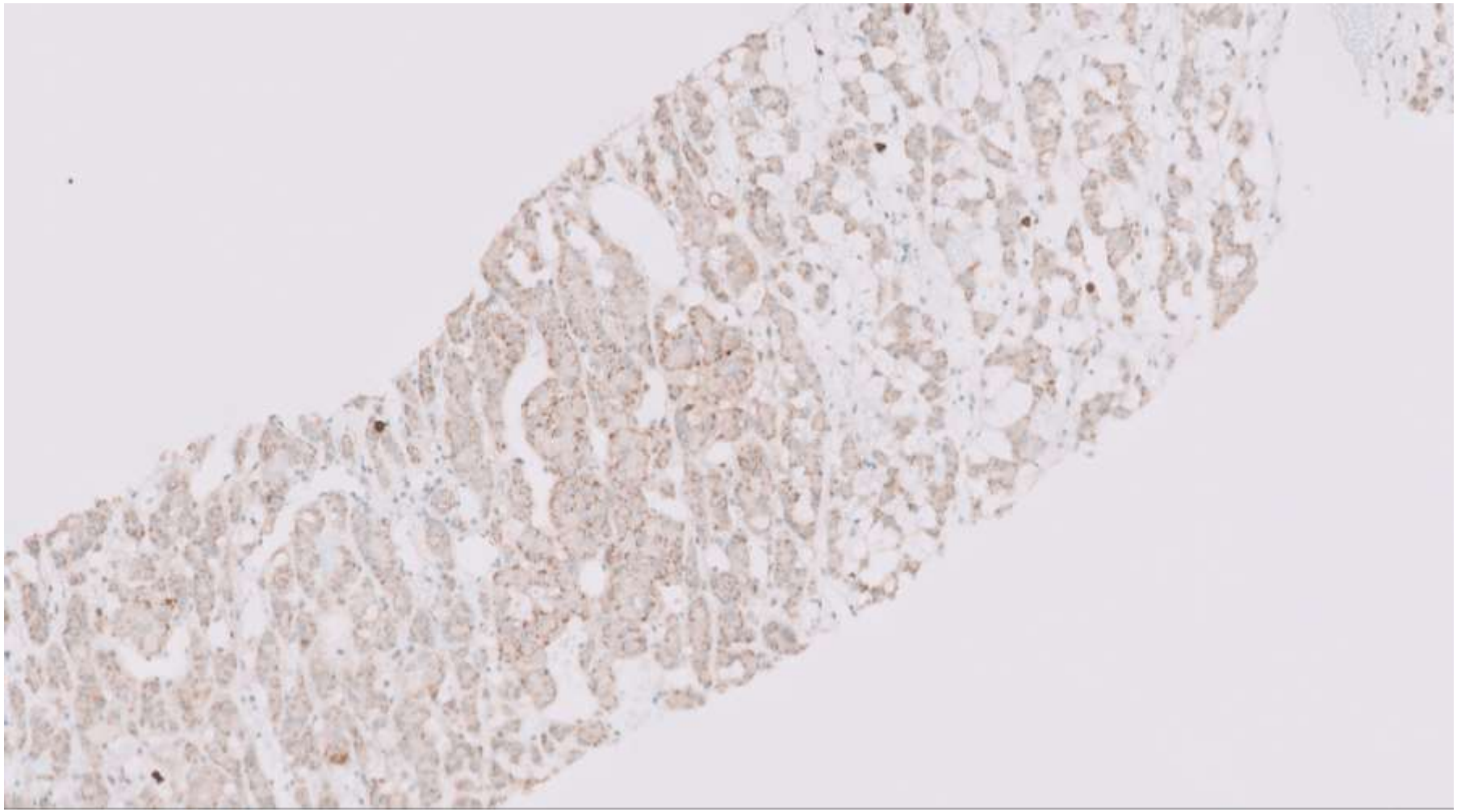
70-year-old F with right kidney mass, core biopsy performed.





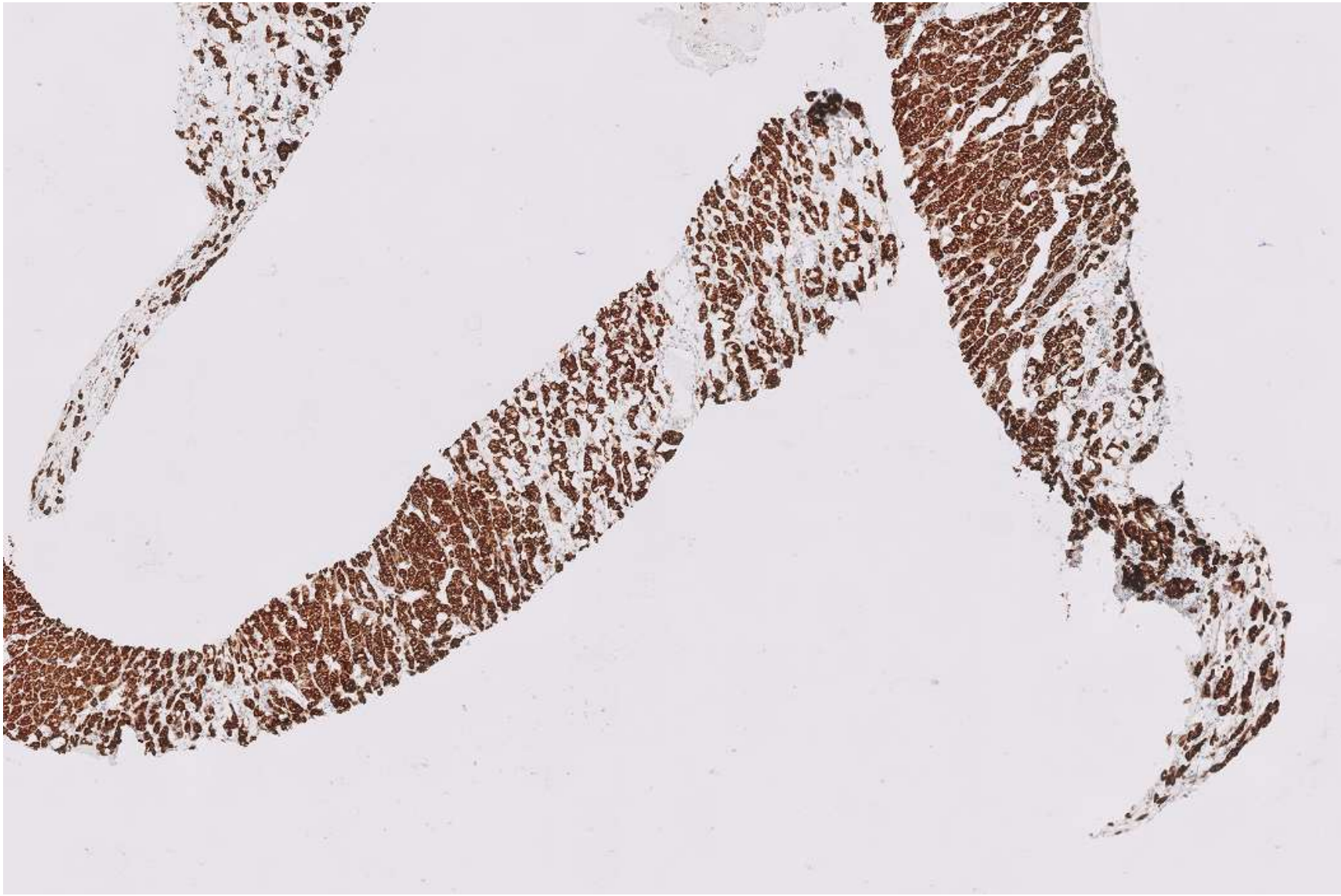


CD117

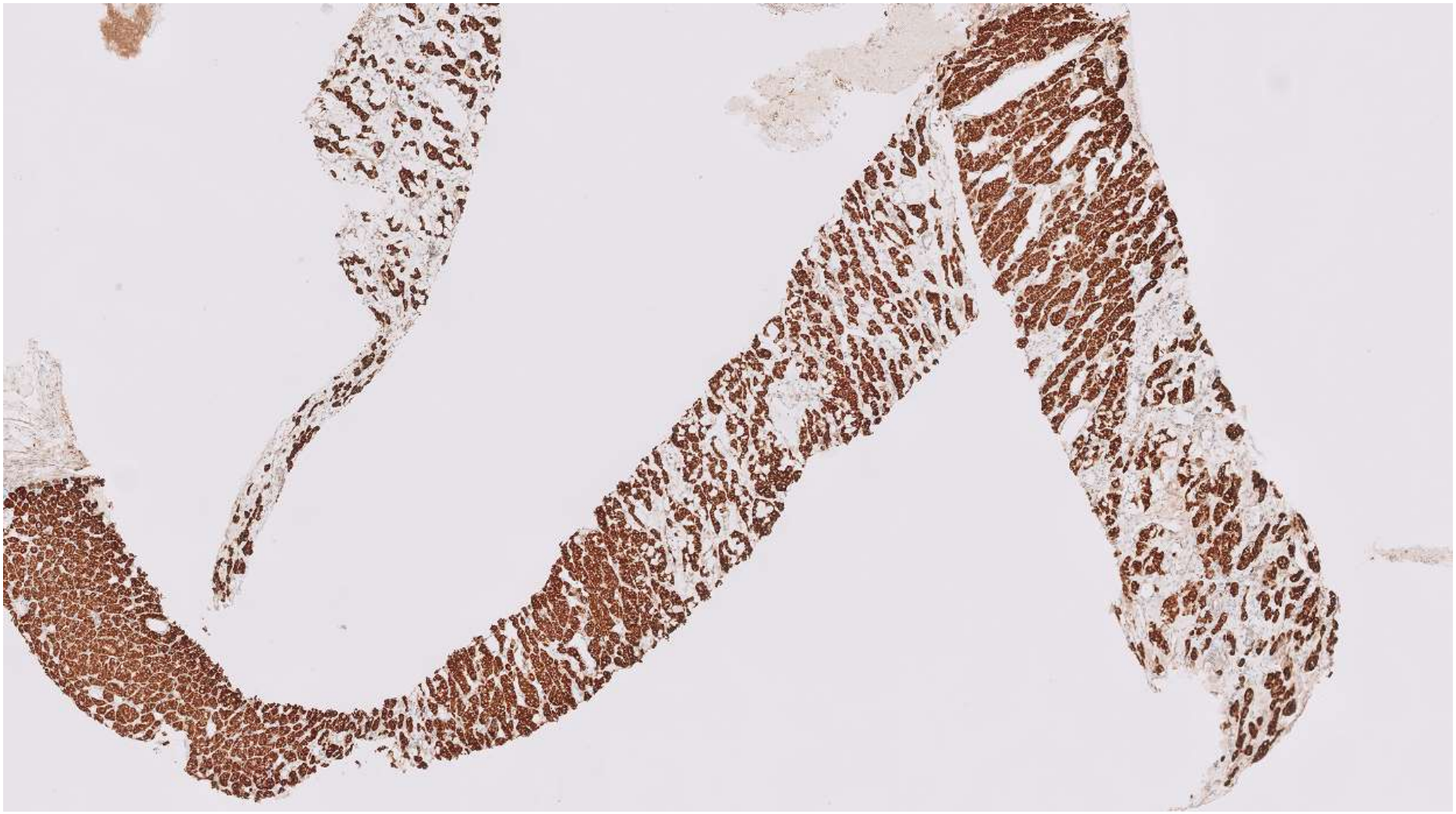


CK7

SDHB



FH



LOW-GRADE ONCOCYTIC TUMOR

Deidre Ongaro/Sunny Kao

Differential Diagnosis

- Oncocytoma
- Chromophobe renal cell carcinoma, eosinophilic variant
- Hybrid oncocytic tumor
- “Oncocytic Renal Neoplasm of Low Malignant Potential, Not Further Classified”
- Low-grade oncocytic tumor (LOT)
- Clear cell renal cell carcinoma
- Succinate dehydrogenase deficient RCC
- Eosinophilic solid and cystic RCC
- Epithelioid angiomyolipoma

Low-Grade Oncocytic Tumor

- Provisional entity (GUPS)
- Single tumors
- Solid tan-brown
- Median tumor size 3 cm, 88% pT1a or pT1b
- No syndromic association
- On follow up, all patients were alive with no disease progression
  - Requires a larger number of cases and longer follow-up to fully characterize these tumors

Low-Grade Oncocytic Tumor: Morphology

- Lack peripheral capsule
- **Solid, compact nested** or focal tubular, tubuloreticular and trabecular growth
- **Edematous stromal areas** that are sharply delineated from solid areas
  - Loosely arranged cords, reticular growth and individual cells
- Cytology:
  - Oncocytic/eosinophilic cytoplasm
  - Uniformly round to oval nuclei without significant irregularities
  - Focal perinuclear halos may be seen
- **Negative CD117 and diffusely positive CK7 reactivity** (caveat: by study design)
- Lack multiple chromosomal losses and gains

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