CHALLENGING LESIONS OF THE GENITOURINARY TRACT: CASE PRESENTATION

Cristina Magi-Galluzzi, MD, PhD

Professor of Pathology
Director of Anatomic Pathology
The C. Bruce Alexander Endowed Professorship in Pathology

GUPS Genitourinary Pathology Society

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UAB HEERSINK SCHOOL OF MEDICINE
The University of Alabama at Birmingham

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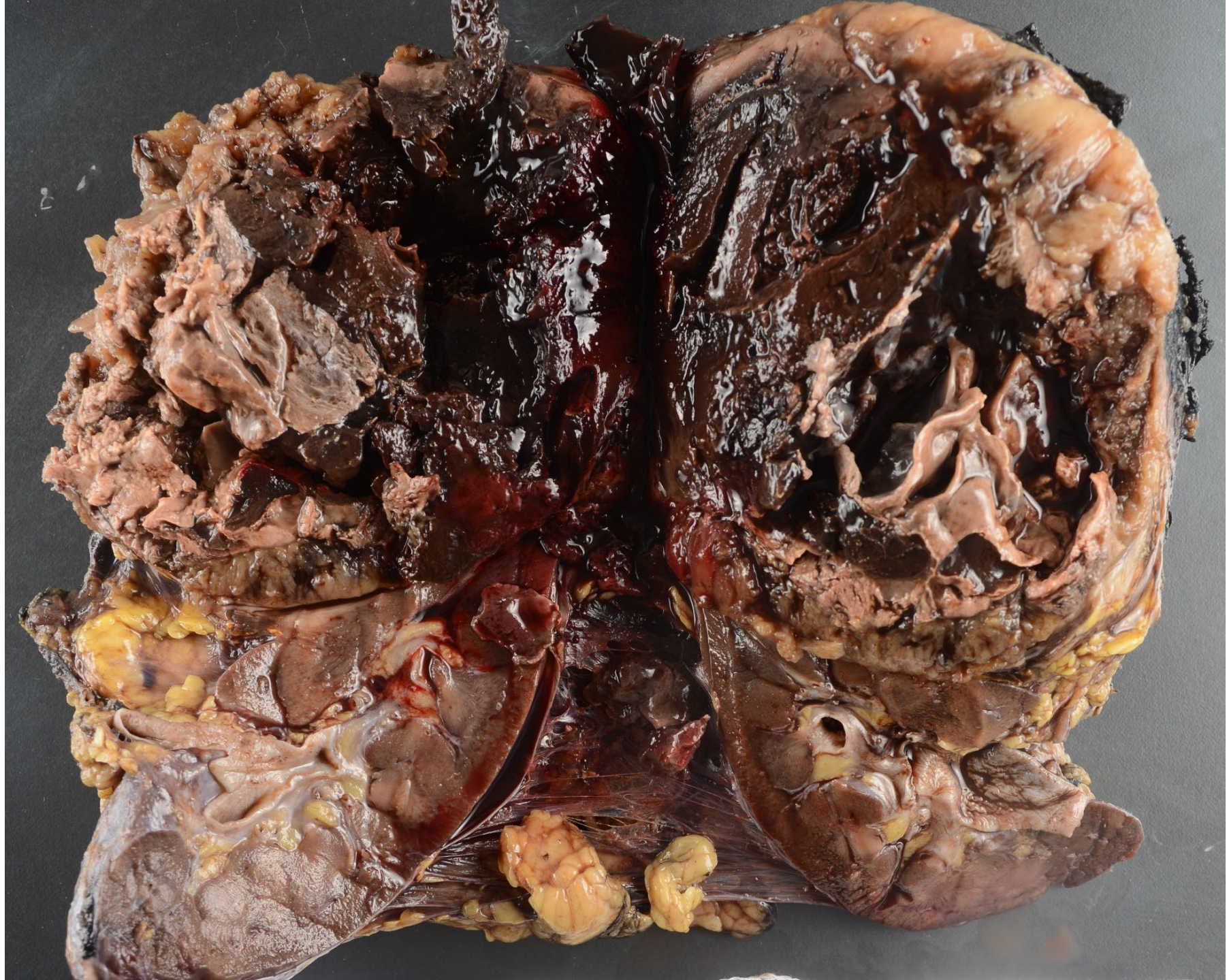
I HAVE NO DISCLOSURES

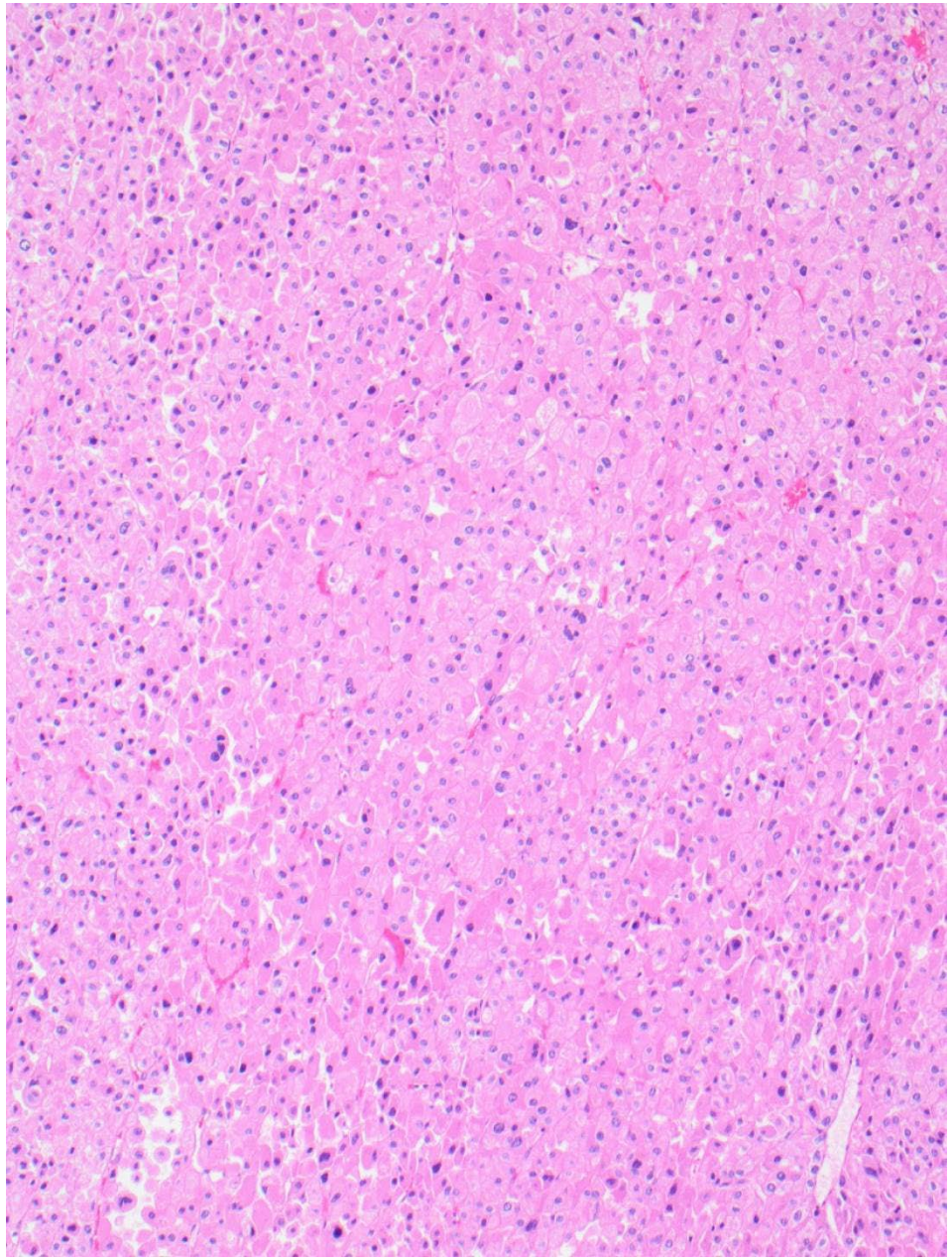
OBJECTIVES

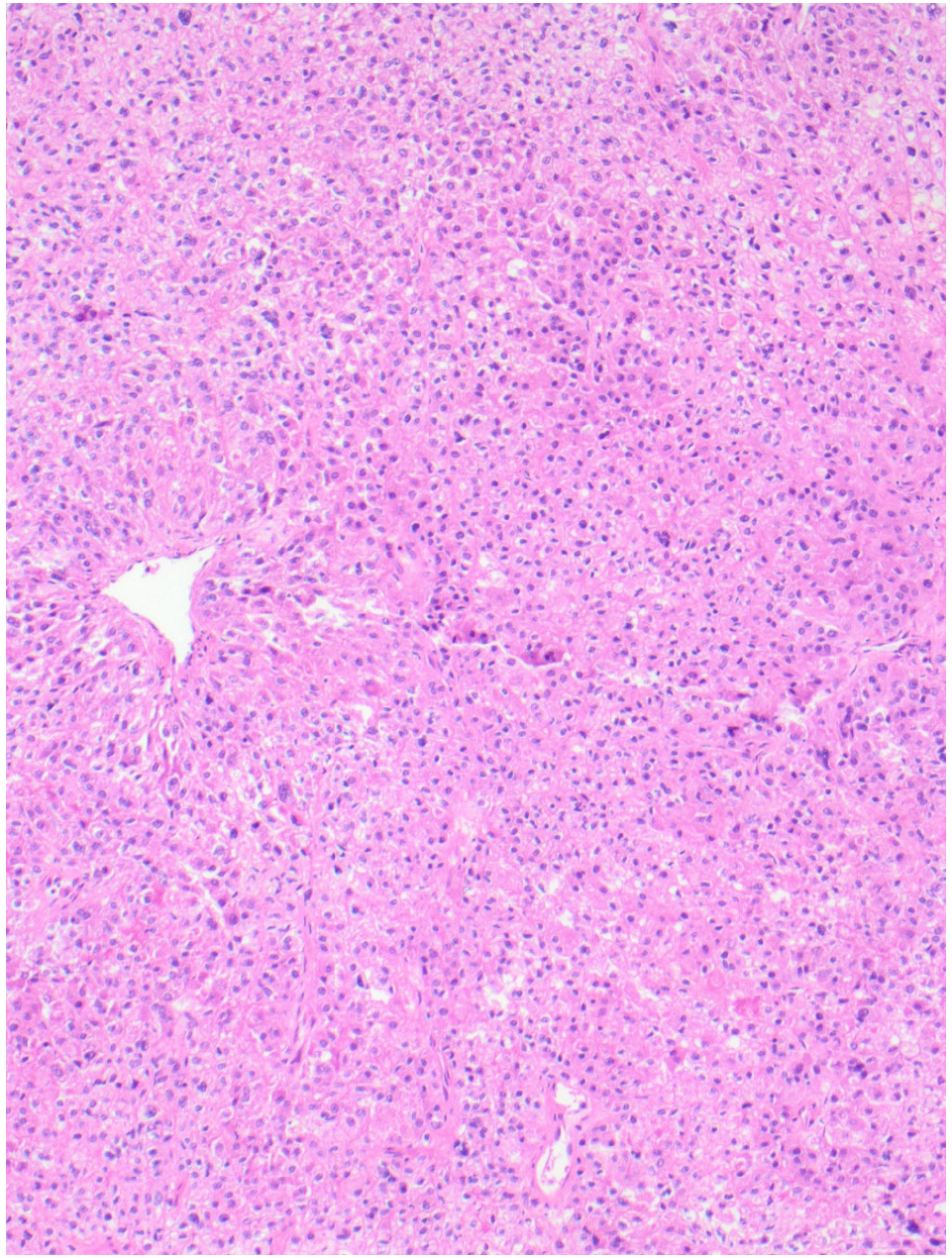
- Review challenging lesions of the genitourinary tract
- Illustrate important differential diagnoses

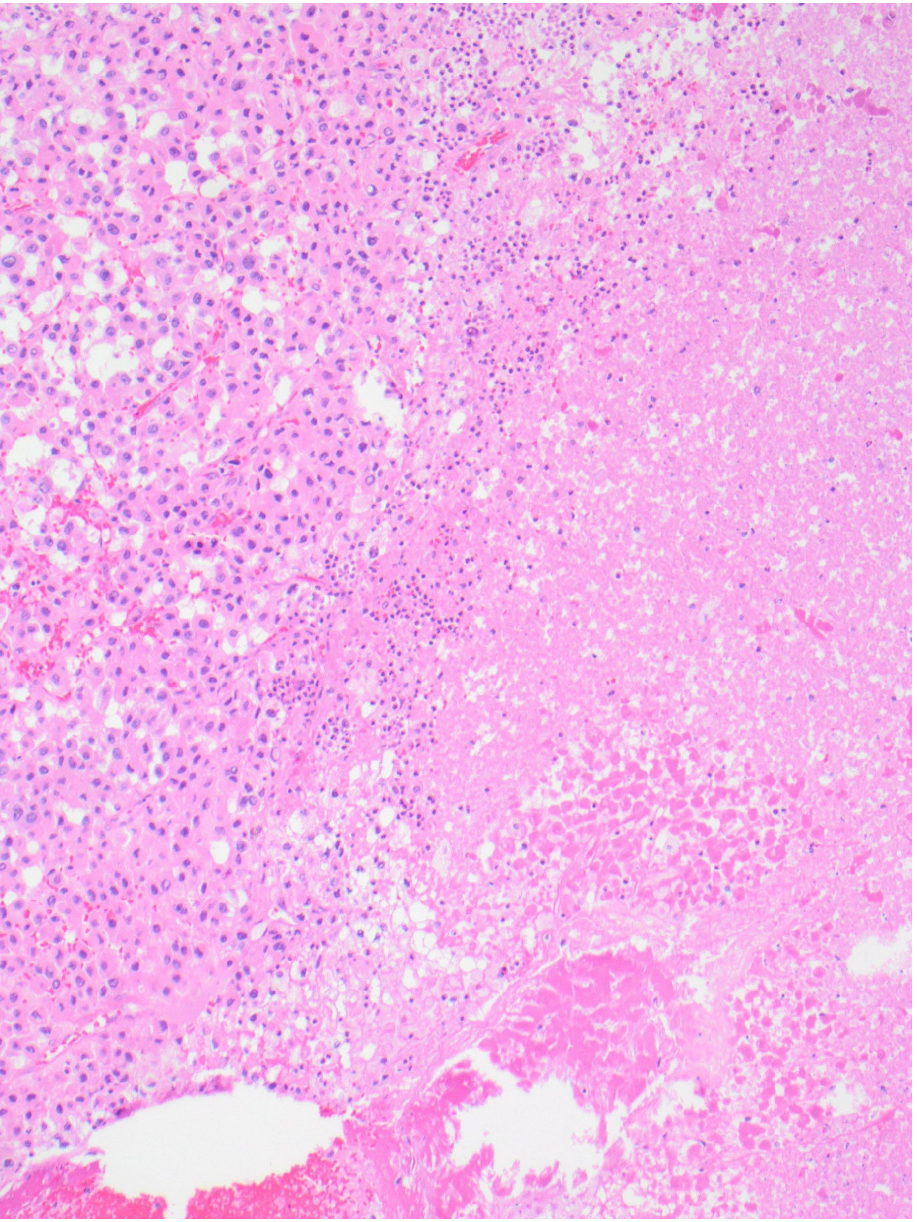
CASE #1

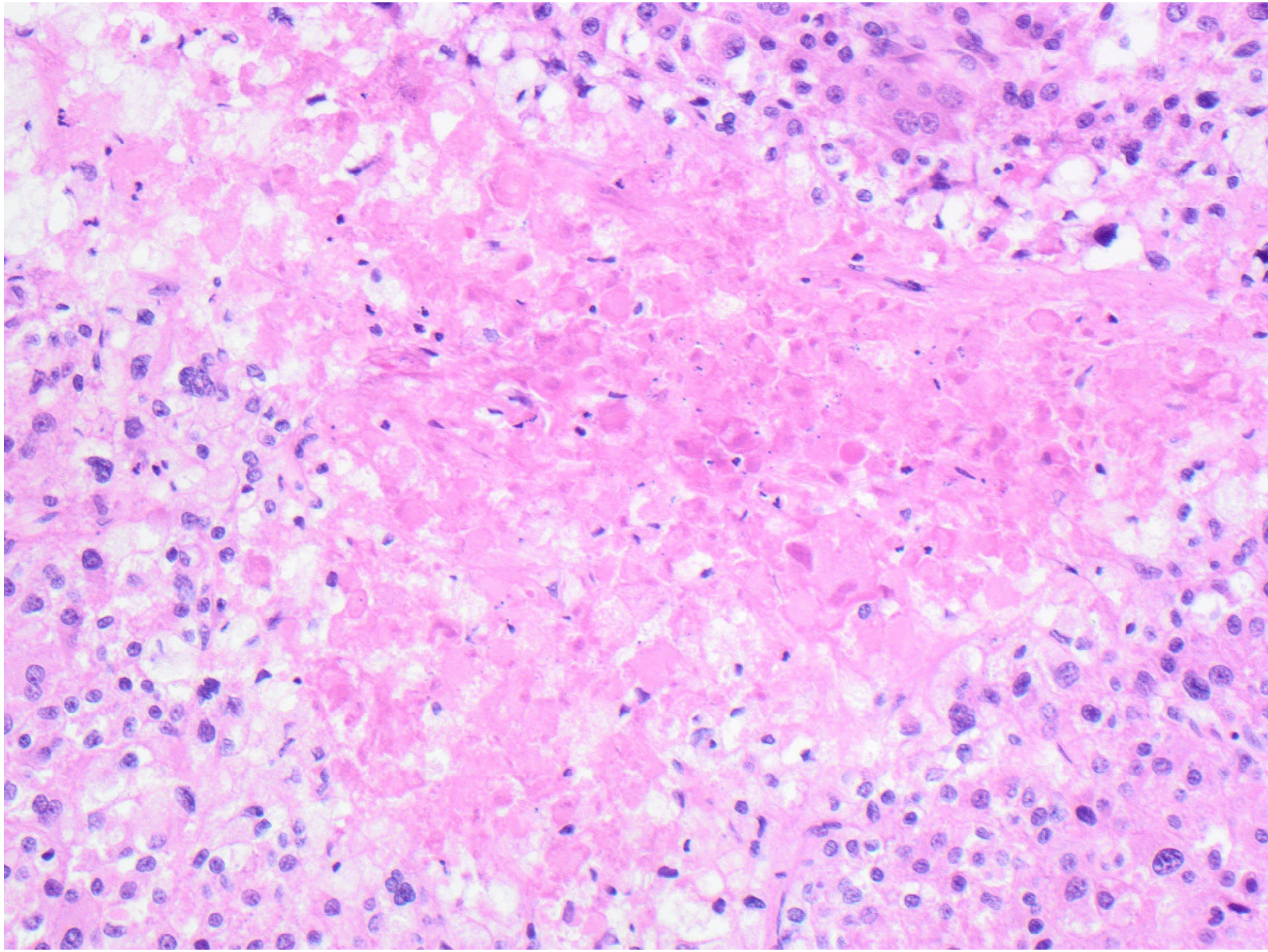
- 32 year-old female with left renal mass
- Nephrectomy specimen measuring 25.5 x 19.5 x 11.5 cm and weighing 4,169 grams
- A 21 x 19 x 17 cm well-circumscribed mass involves upper pole of kidney

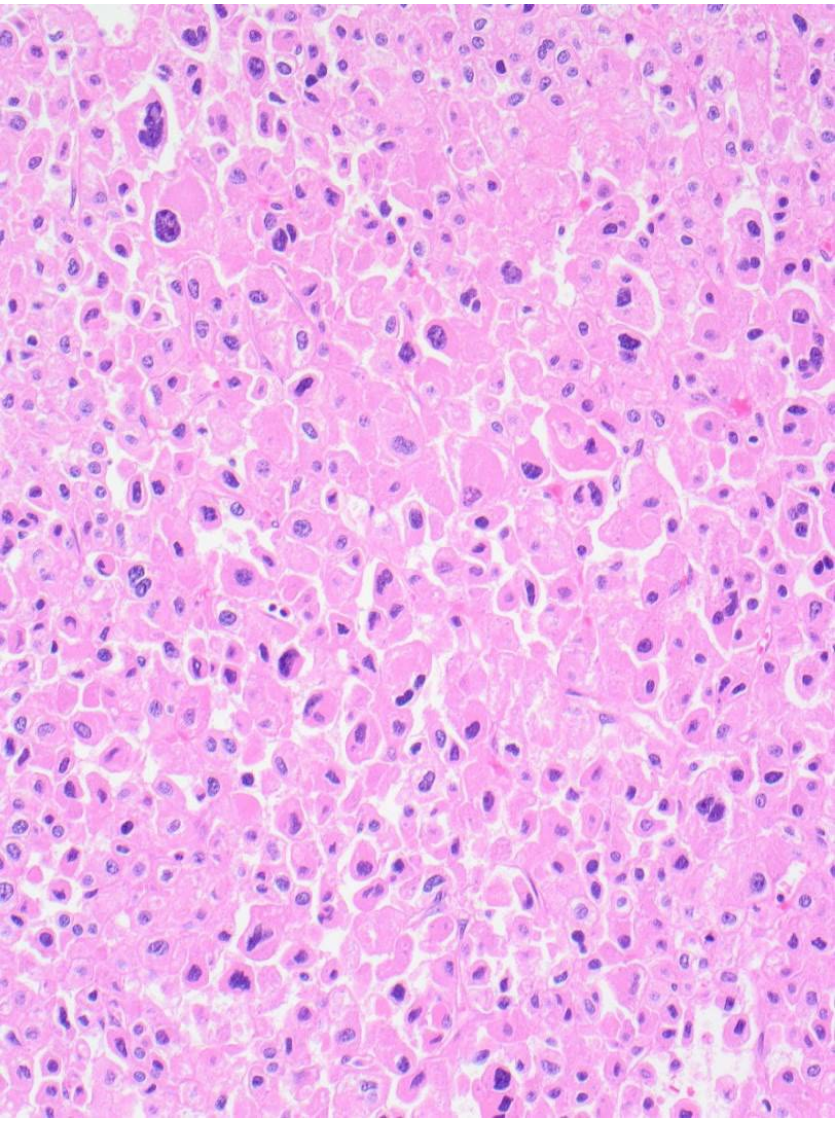
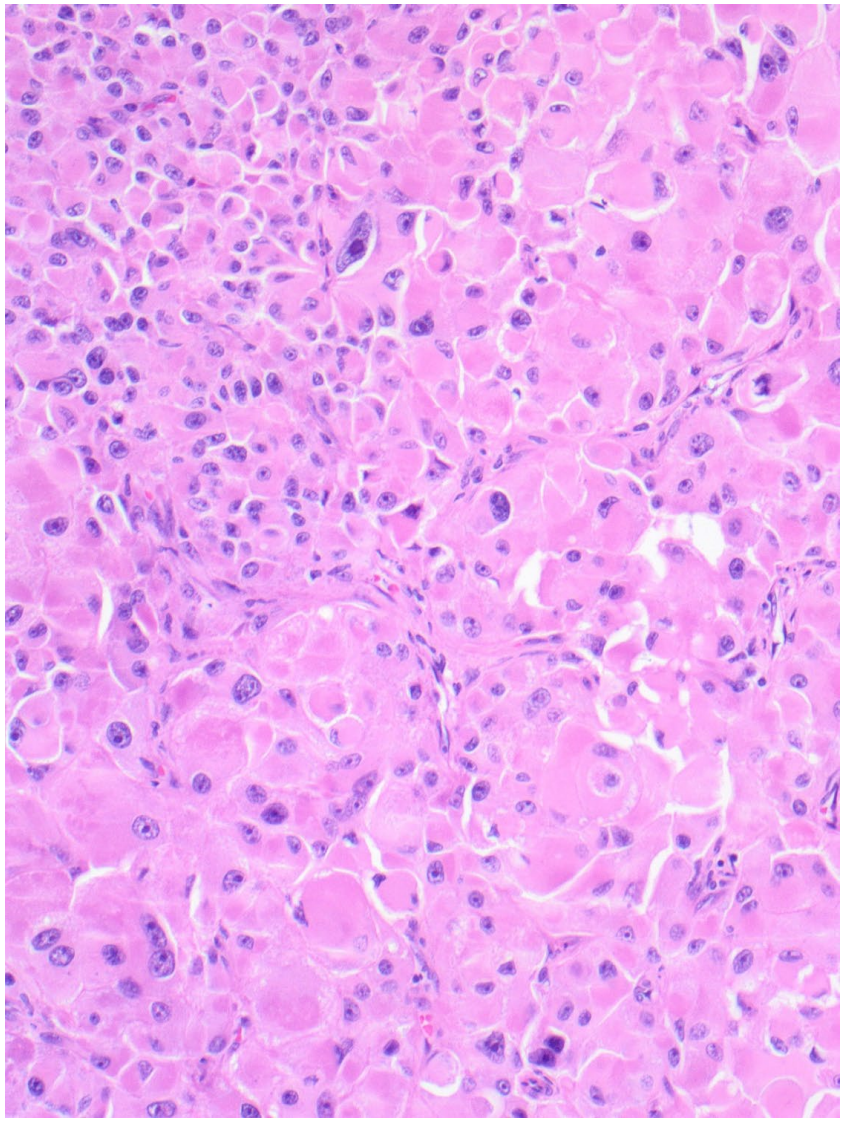
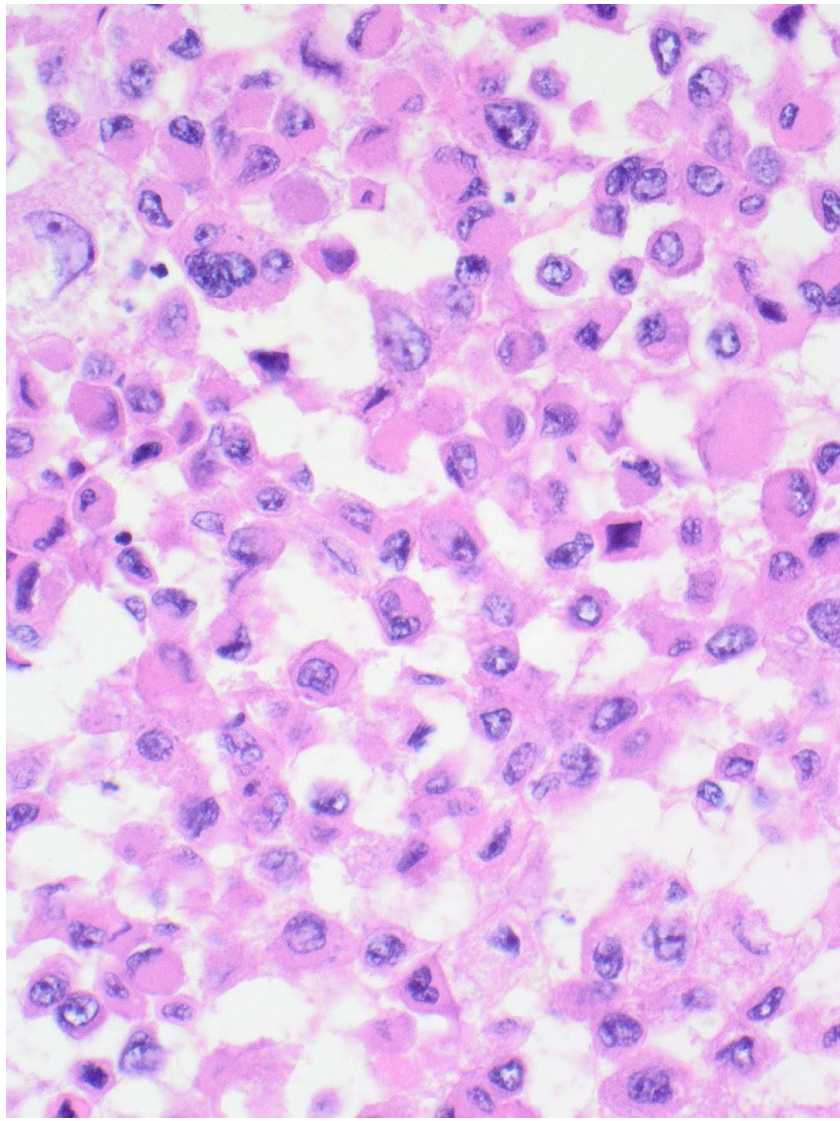


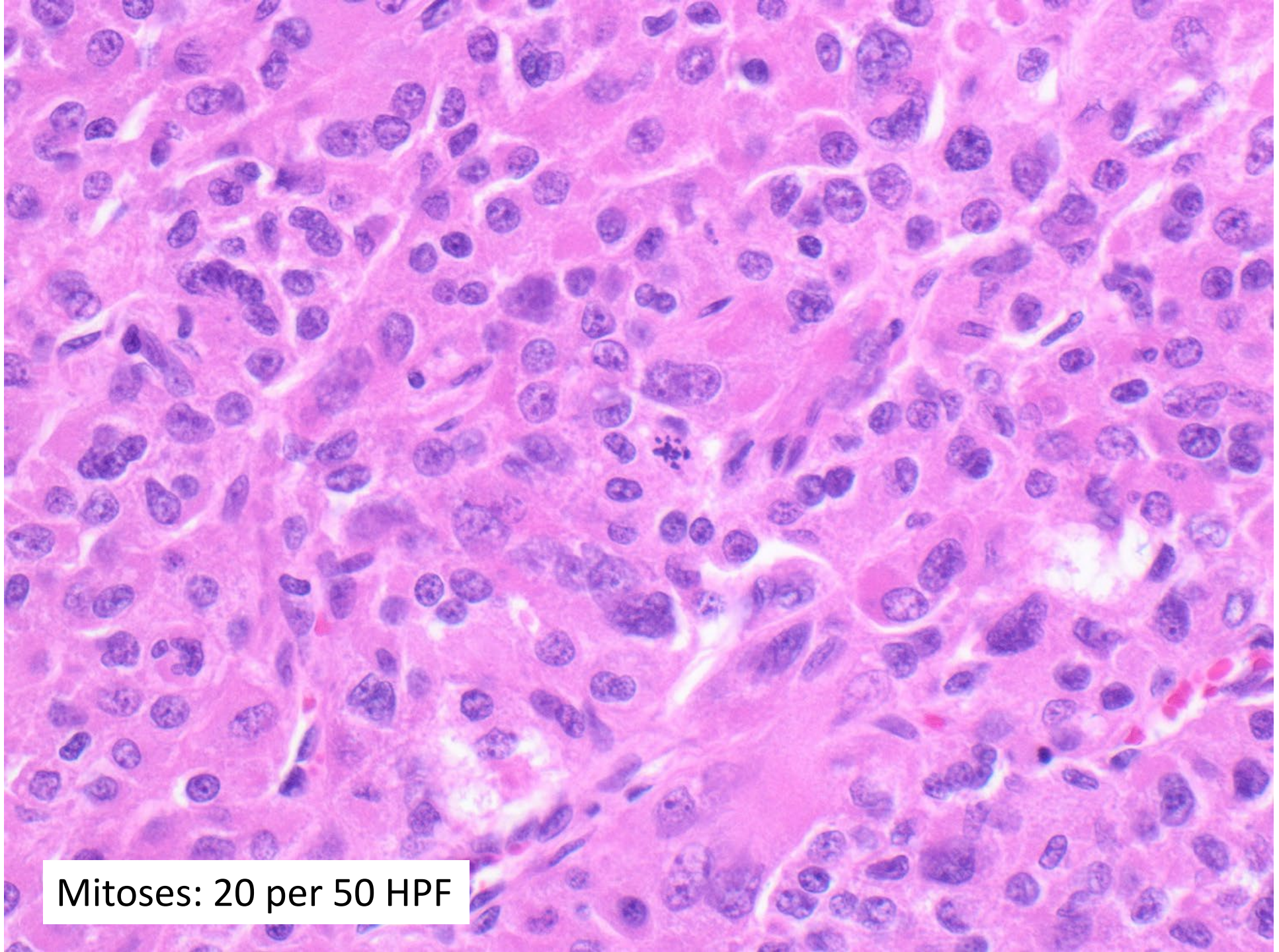






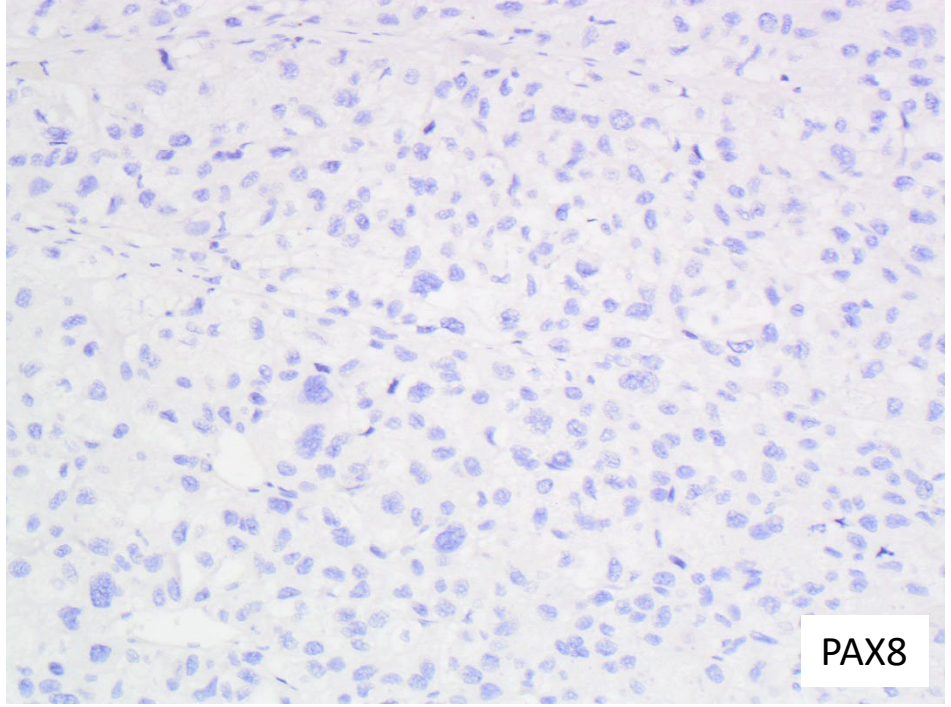


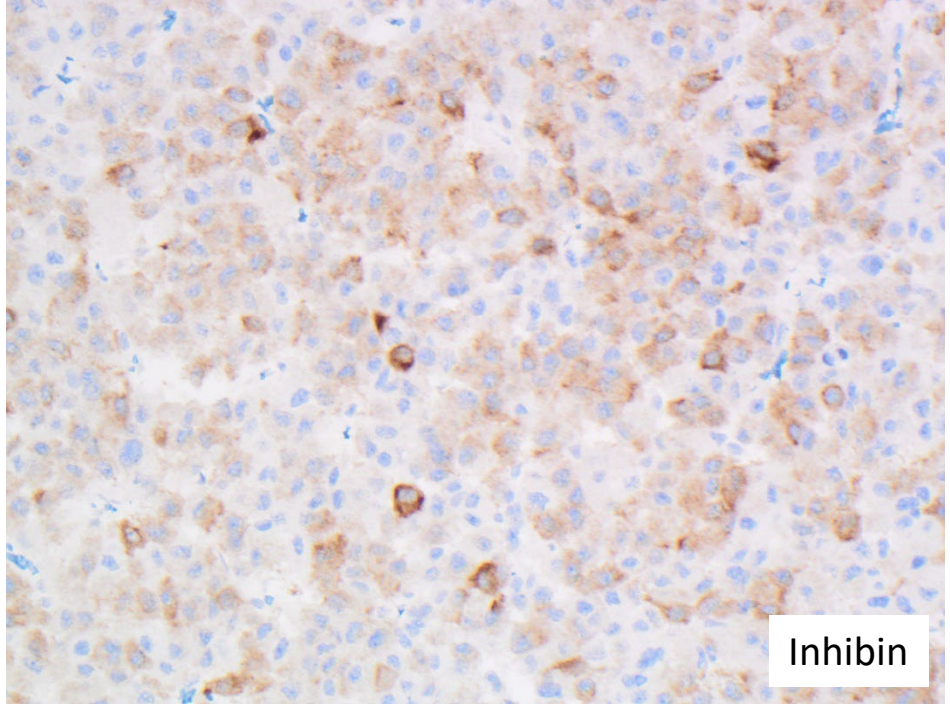




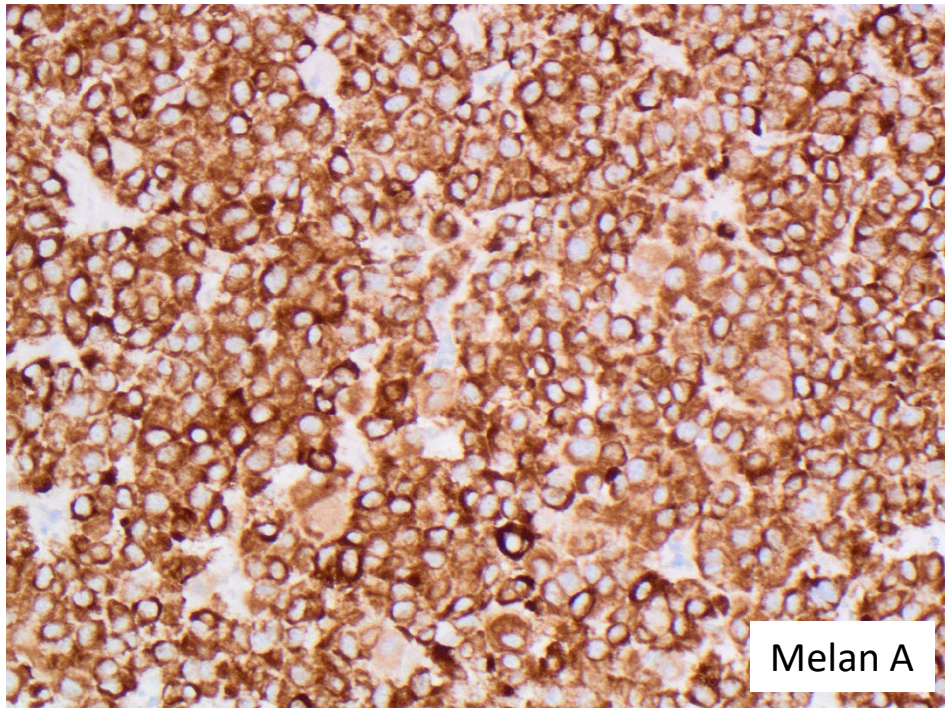

Mitoses: 20 per 50 HPF

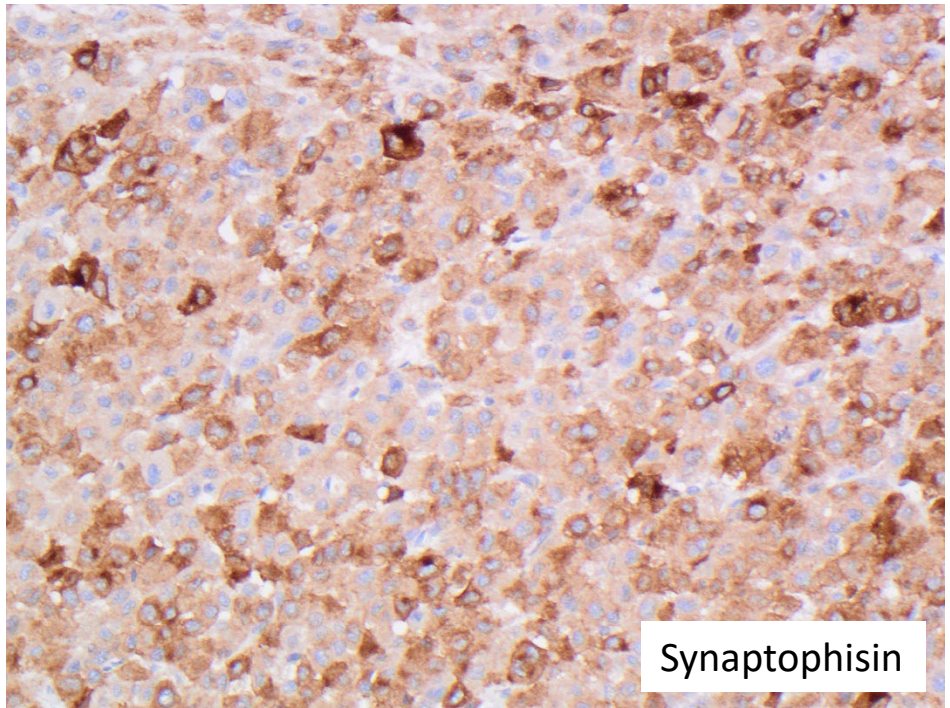
Differential Diagnosis?

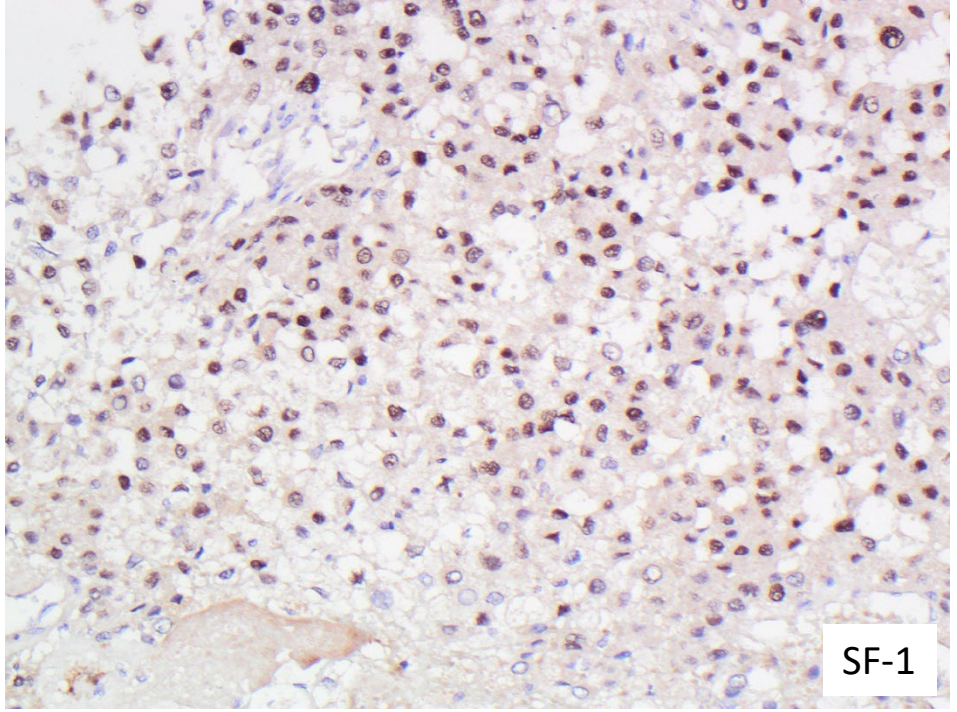
- High-grade renal cell carcinoma with eosinophilic features
- Epithelioid AML
- Adrenocortical carcinoma
- Pheochromocytoma
- Metastatic carcinoma

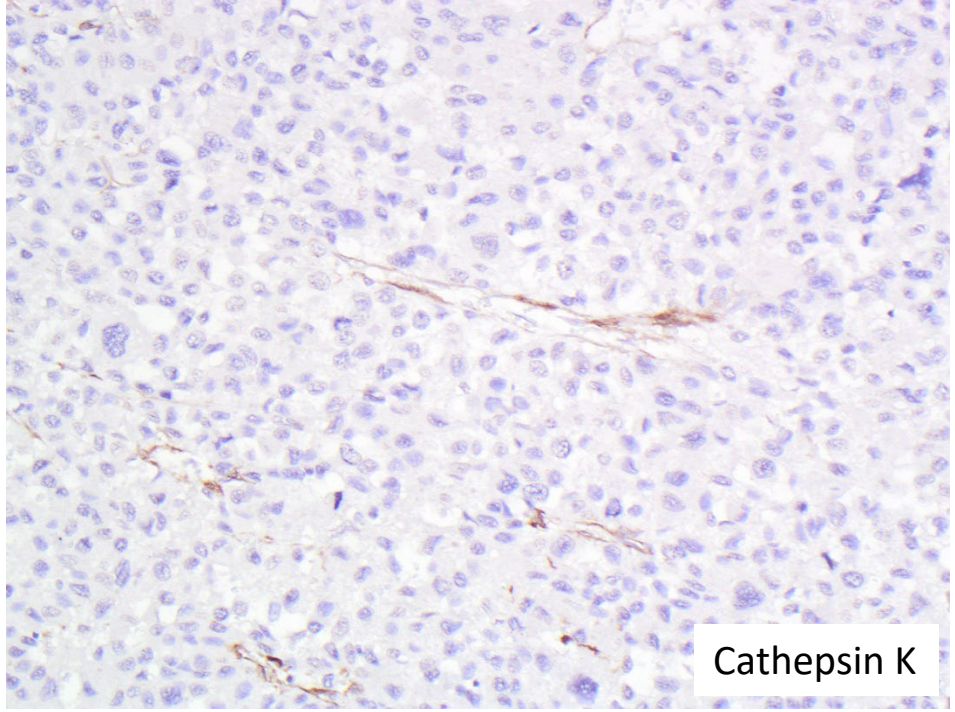

PAX8

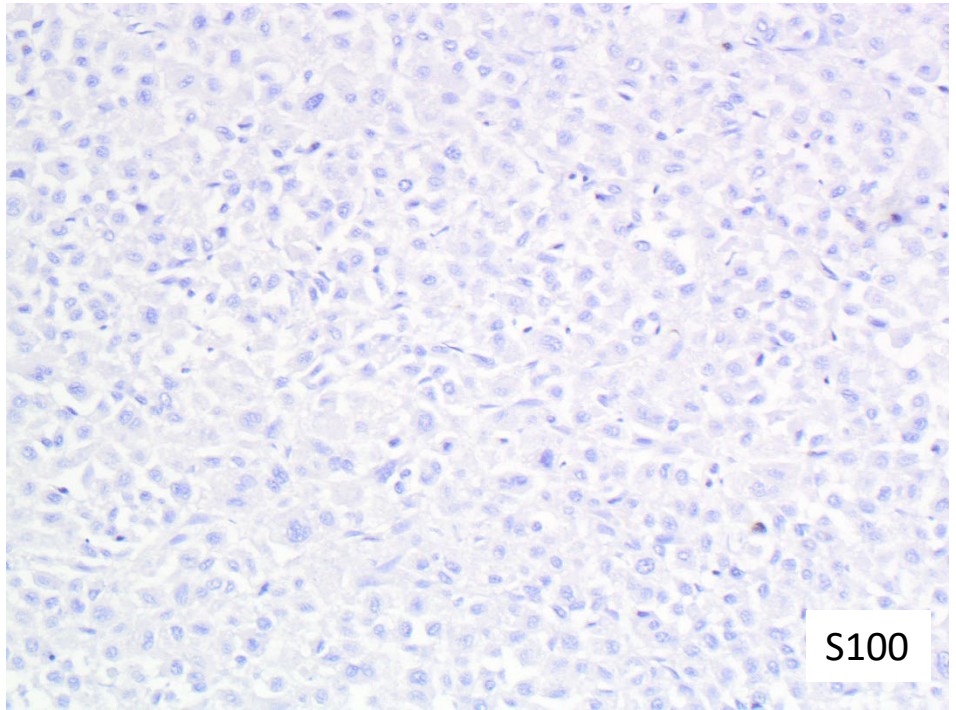

Inhibin

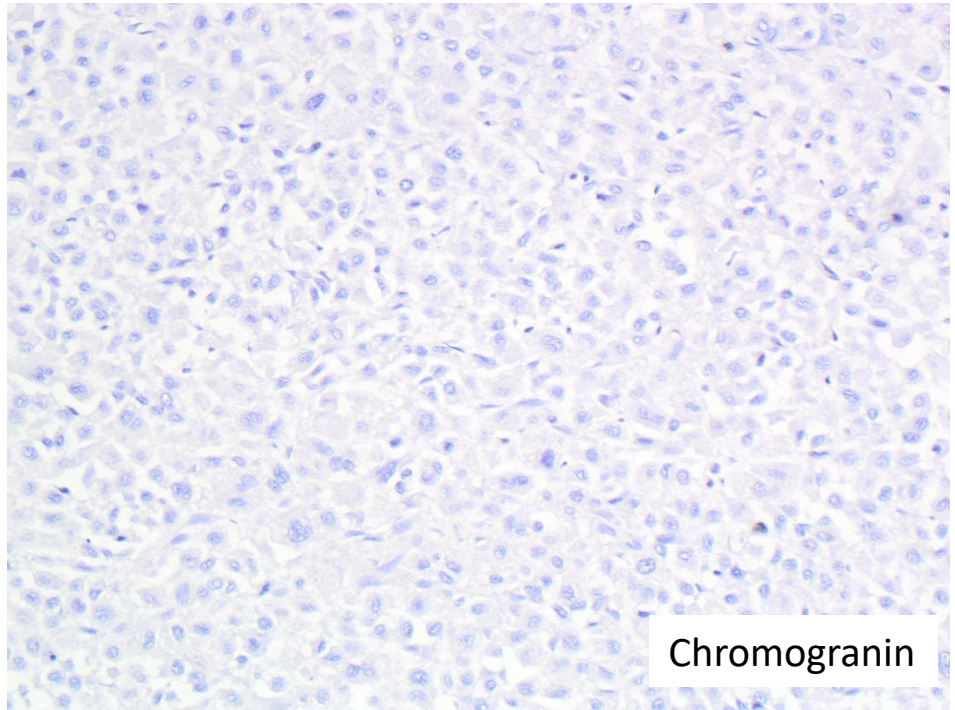

Melan A


Synaptophisin


SF-1


Cathepsin K


S100


Chromogranin

Case #1

Diagnosis

Oncocytic Adrenocortical Carcinoma

Biomarker	ACC	PHEO/PGL	RCC	Metastatic carcinoma	EAML
Pan-cytokeratin	−/(+)	−	+	+	-
Vimentin	+	−/(+)	+	−/+	+
Chromogranin-A	−	+	−	- (+ in NE carcinomas)	
Synaptophysin	+	+	−	- (+ in NE carcinomas)	-
Melan A	+	−	- (+ in some)	-[a]	+
Calretinin	+/−	−	−	−/+	
Alpha-inhibin	+/−	− /(+)	−	−/+	
D2–40	+	−	−	−/+	
Tyrosine hydroxylase	−	+	−	−	
CD10	+/−	NA	+/−	−/+	
SF-1	+	−	−	−	-
PAX8 (monoclonal)	−	−	+	+/−	-

ACC adrenal cortical carcinoma, *PHEO* pheochromocytoma, *PGL* paraganglioma, *RCC* renal cell carcinoma, *NE* neuroendocrine, *NA* not available or limited data

[a] This biomarker is also expressed in several other non-epithelial neoplasms including melanoma and PEComas

Adapted from Mete et al. Endocr Pathol 2018

Criteria for Malignancy in Adrenal Cortical Tumors

- Size and weight >100 gr
- Hemorrhage (extensive)
- Necrosis (extensive)
- Extension into adjacent soft tissue or surroundings organs
- Nuclear atypia
- Atypical and frequent mitoses
- Vascular invasion

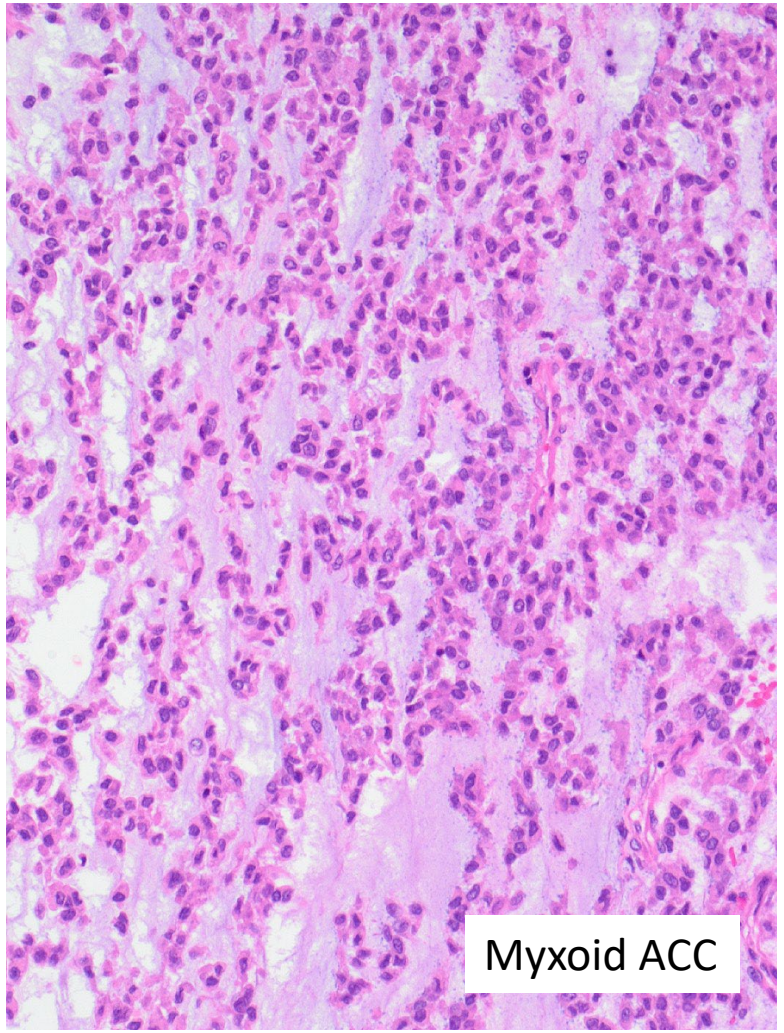
Modified Weiss system

Parameter	Score
Mitotic count > 5 per 50 high-power fields (10 mm^2)	2
Clear cells in ≤ 25%	2
Atypical mitosis	1
Necrosis	1
Capsular invasion	1
Total score	7
A score of ≥ 3 indicates a diagnosis of adrenal cortical carcinoma	

Adrenocortical Carcinomas

Subtyped based on their characteristic cytomorphological features to include:

- conventional
- **oncocytic (oncocytic tumor cells account for >90% of tumor)**
- myxoid (prominent extracellular mucin deposition)
- sarcomatoid



Myxoid ACC

Oncocytic Adrenocortical Neoplasm

- Unusual variant of adrenocortical tumors
- Composed exclusively or predominantly of large polygonal cells with granular eosinophilic cytoplasm
- More frequently found in females
- Biological behavior classified by histological features according to Lin-Weiss-Bisceglia system

Lin-Weiss-Bisceglia System (LWB)

- Major criteria:
  - mitotic rate of >5 mitoses per 50 HPF (10 mm^2)
  - any atypical mitoses
  - venous invasion

- Minor criteria:
  - large size [>10 cm and/or >200gr]
  - necrosis
  - capsular invasion or sinusoidal invasion

Oncocytic adrenal cortical carcinoma: at least **one major criterion**

Oncocytic adrenal cortical neoplasm of uncertain malignant potential: at least one minor criterion

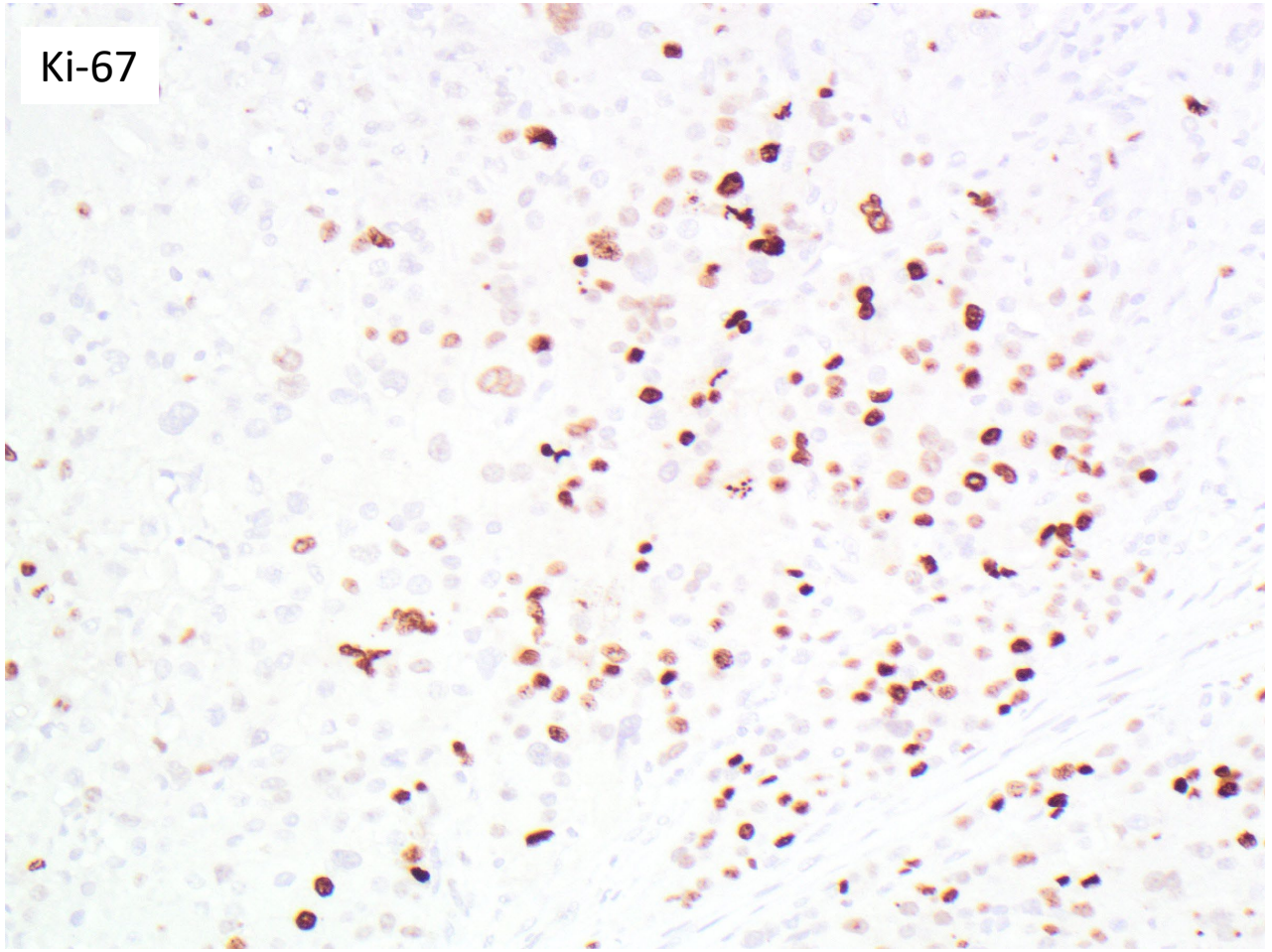
Oncocytic adrenal cortical adenoma: absence of major and minor criteria

Multiparameter diagnostic algorithms

Helsinki scoring system

Parameter	Score
Mitoses > 5 per 50 higher-power fields (10 mm^2)	3
Necrosis	5
Ki67 proliferation index (%)*	Numeric value of the Ki67 index from the highest proliferative area
Score 0 to 8.5: adrenal cortical adenoma	
Score > 8.5: adrenal cortical carcinoma	
Score > 17: adverse prognosis	(predict metastasis)

*The original study used an automated image analysis for the assessment of the Ki67 proliferation index

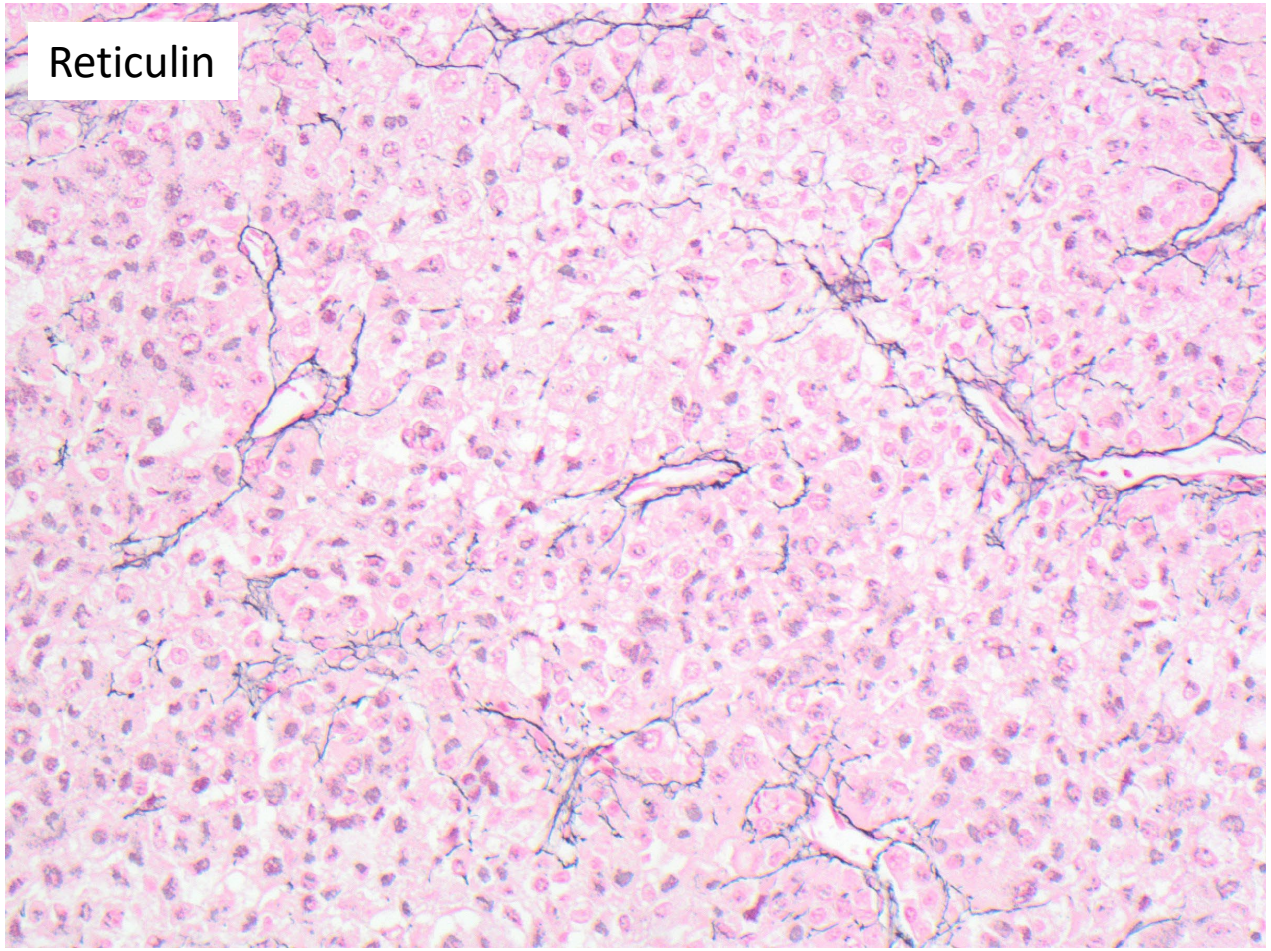


Multiparameter diagnostic algorithms

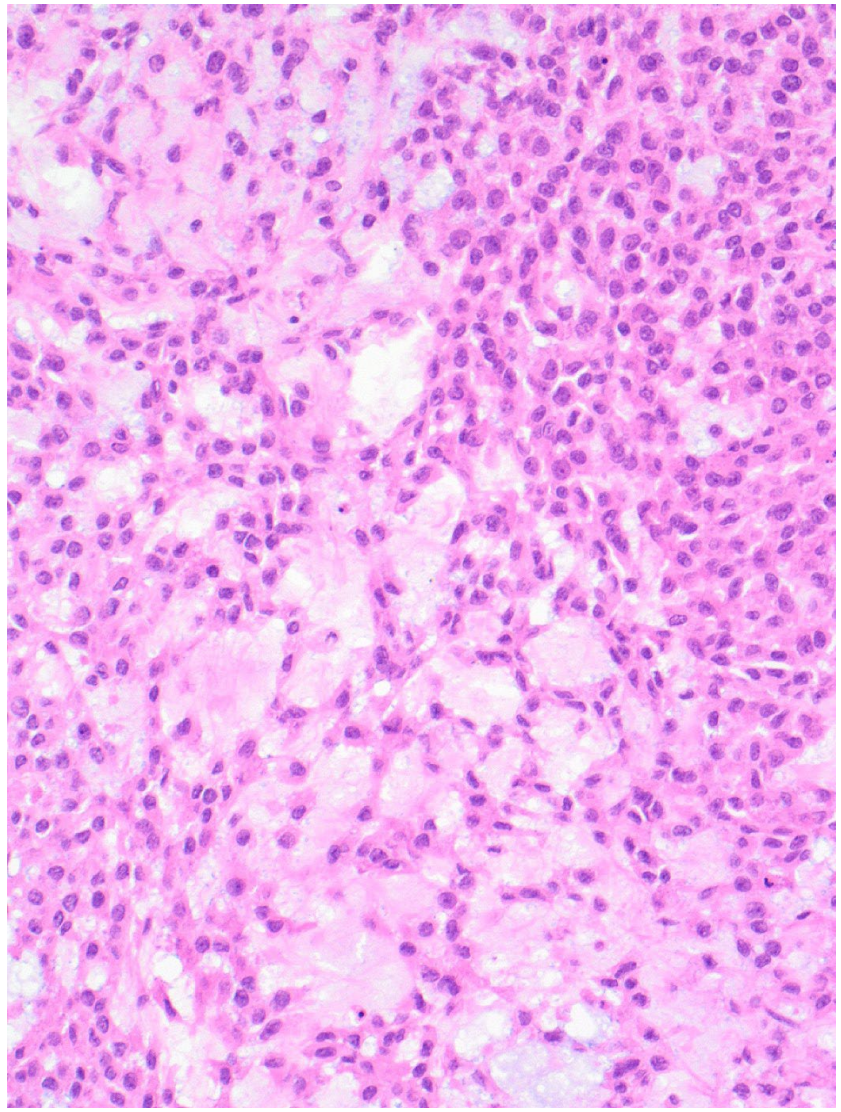
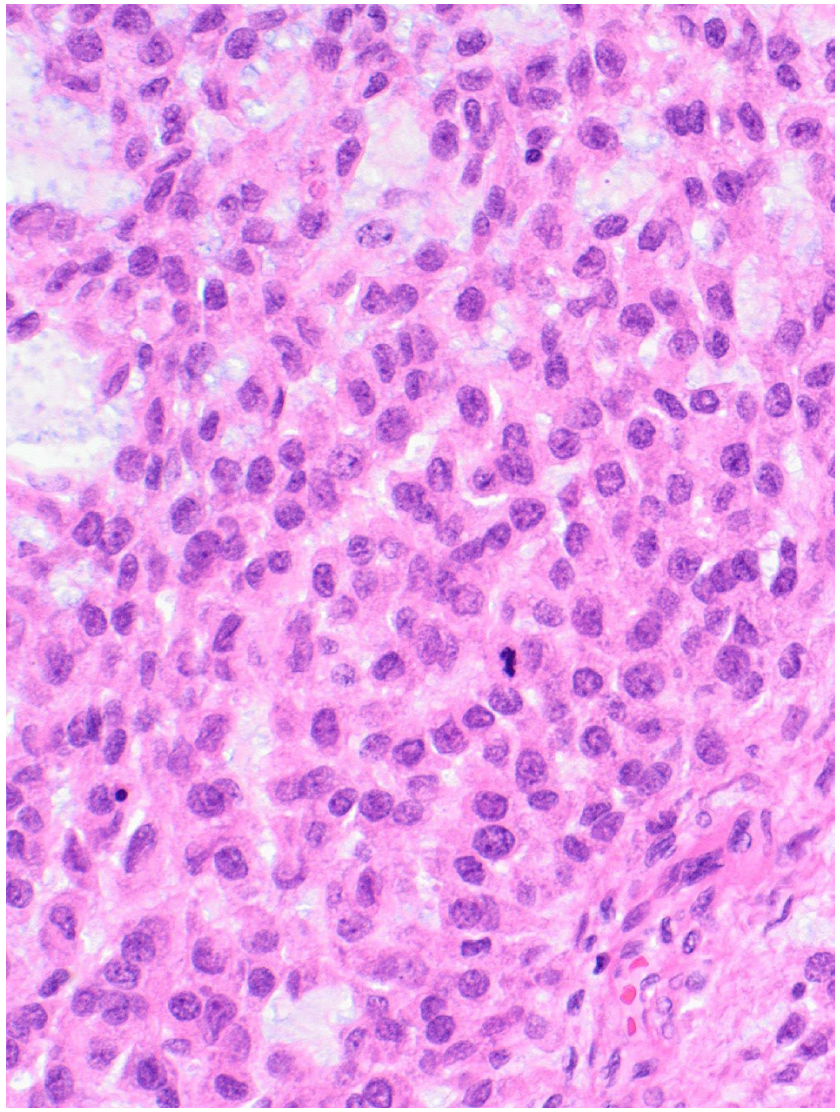
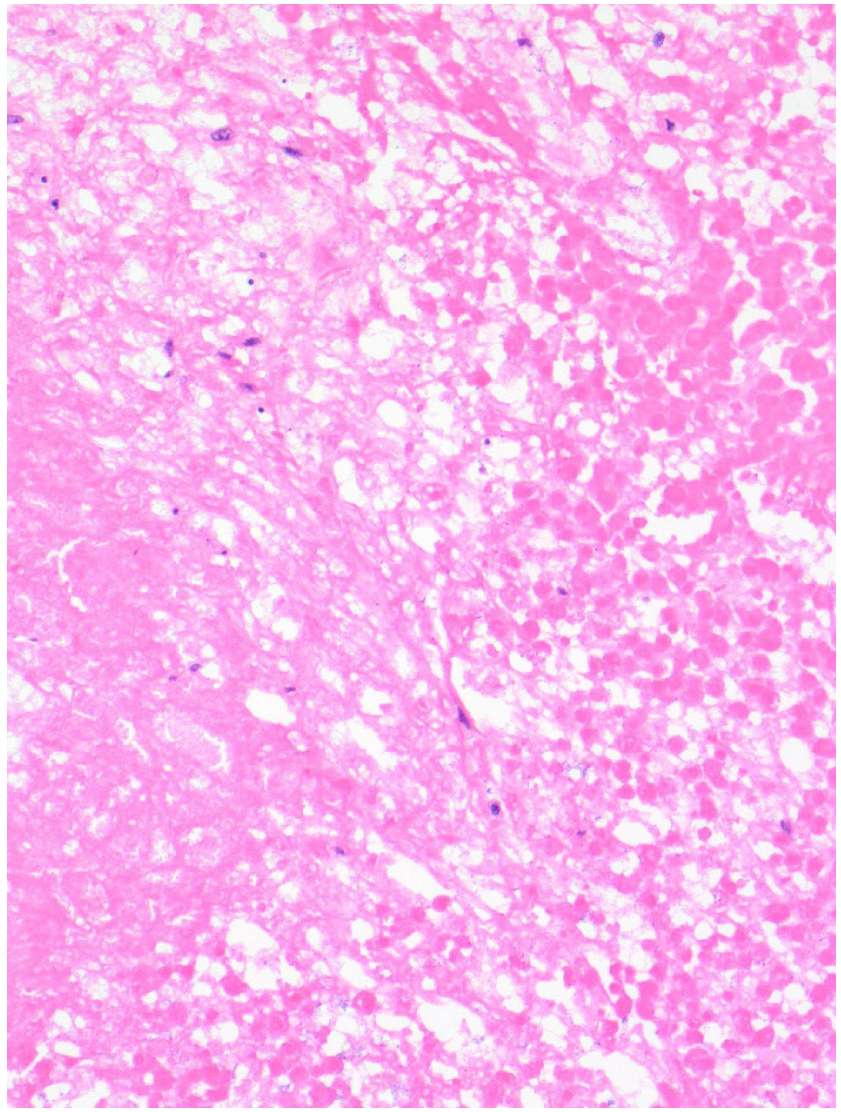
Reticulin algorithm

Criteria
Altered reticulin framework in association with one of the following features indicates malignancy: -Mitotic count > 5 per 50 high-power fields (10 mm^2) -Tumor necrosis -Vascular invasion (angioinvasion)

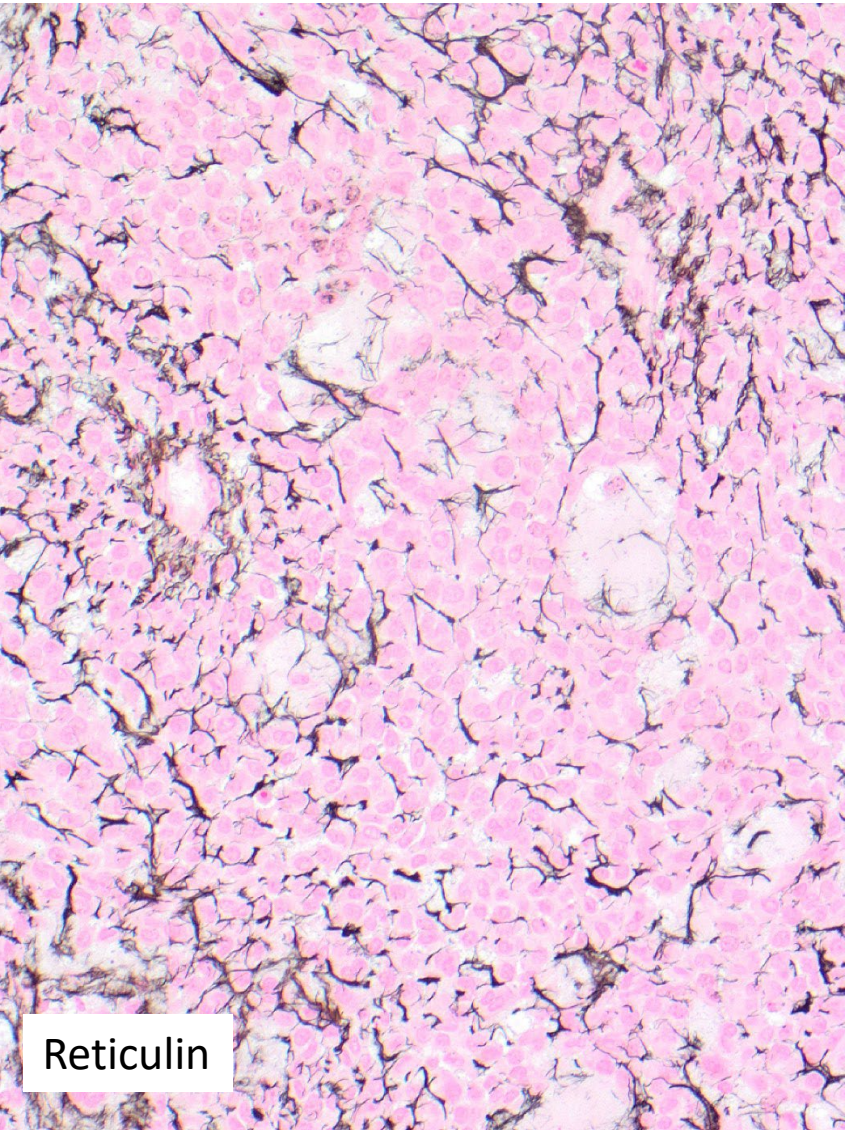
A diagnosis of ACC is rendered when an altered reticulin network is seen in association with **one** of the other parameters

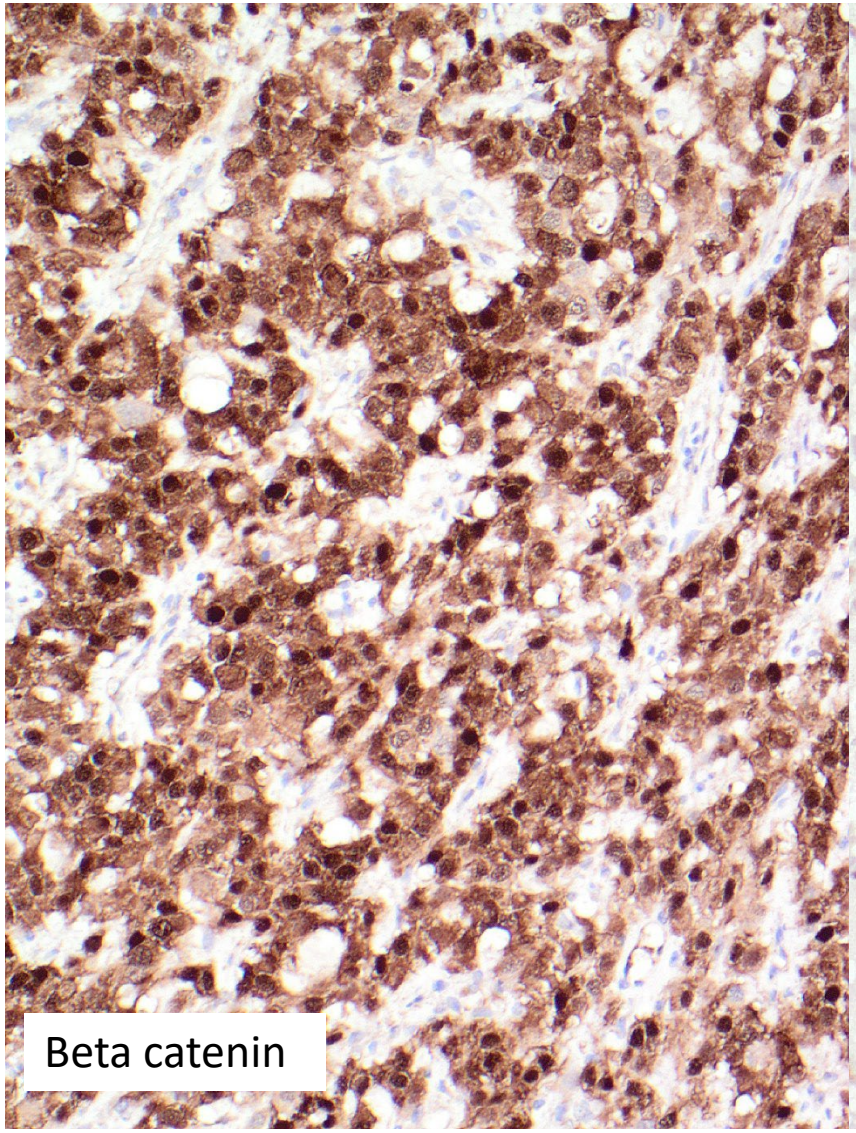


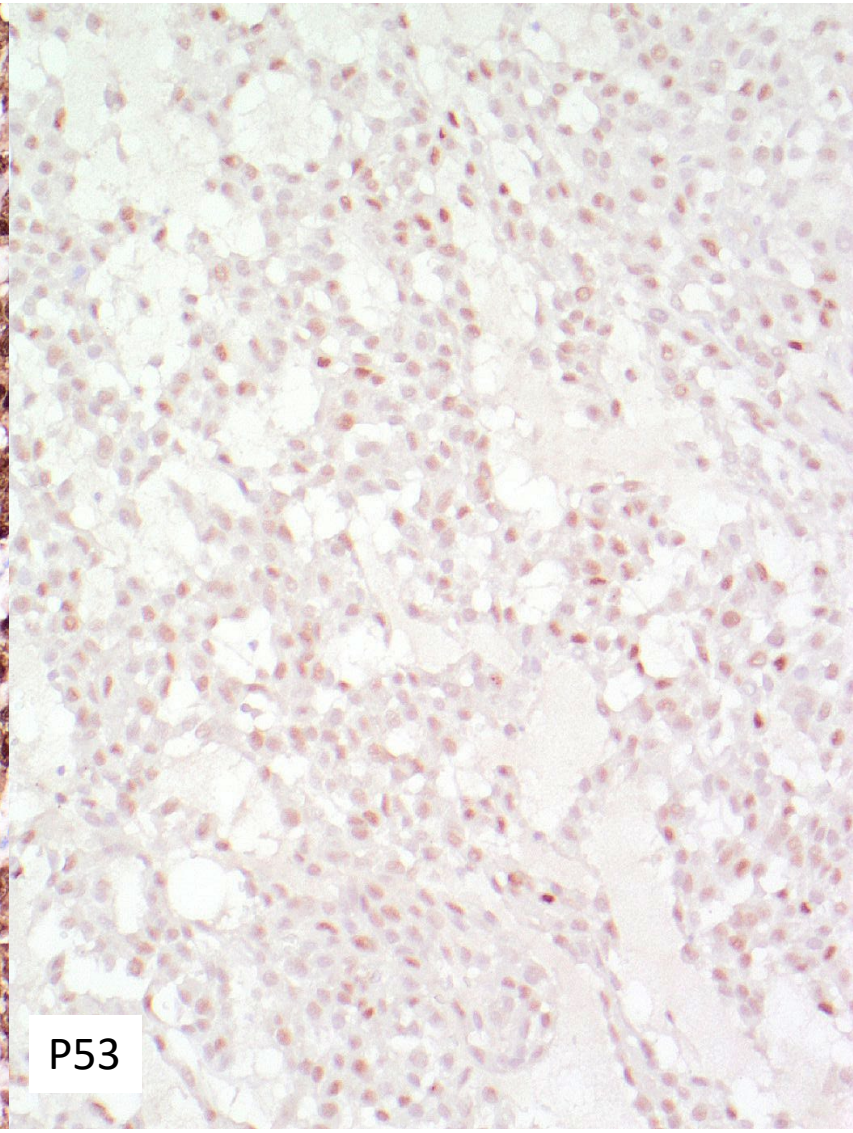
Myxoid Adrenocortical Carcinoma

Poor-prognostic molecular clusters

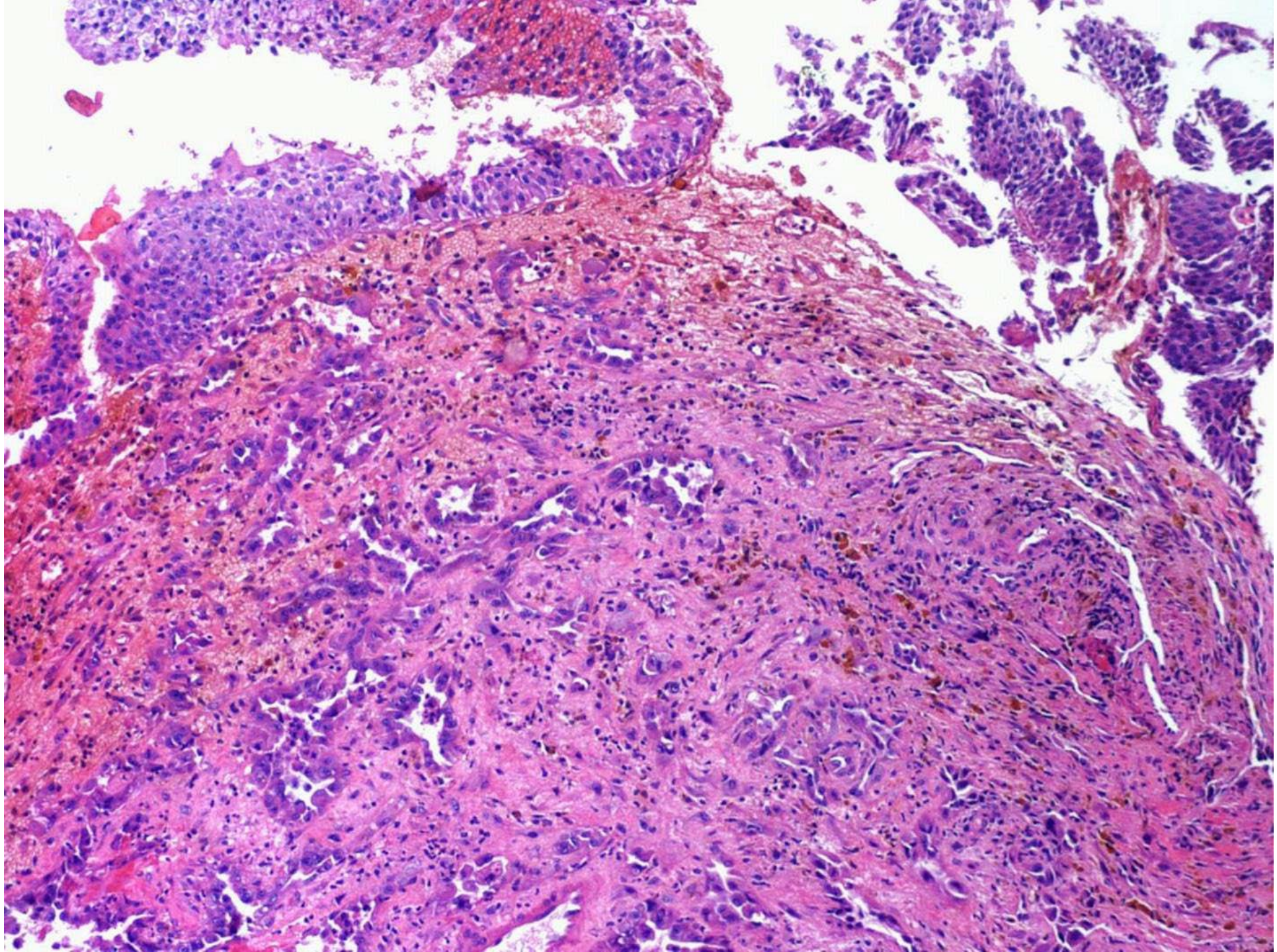


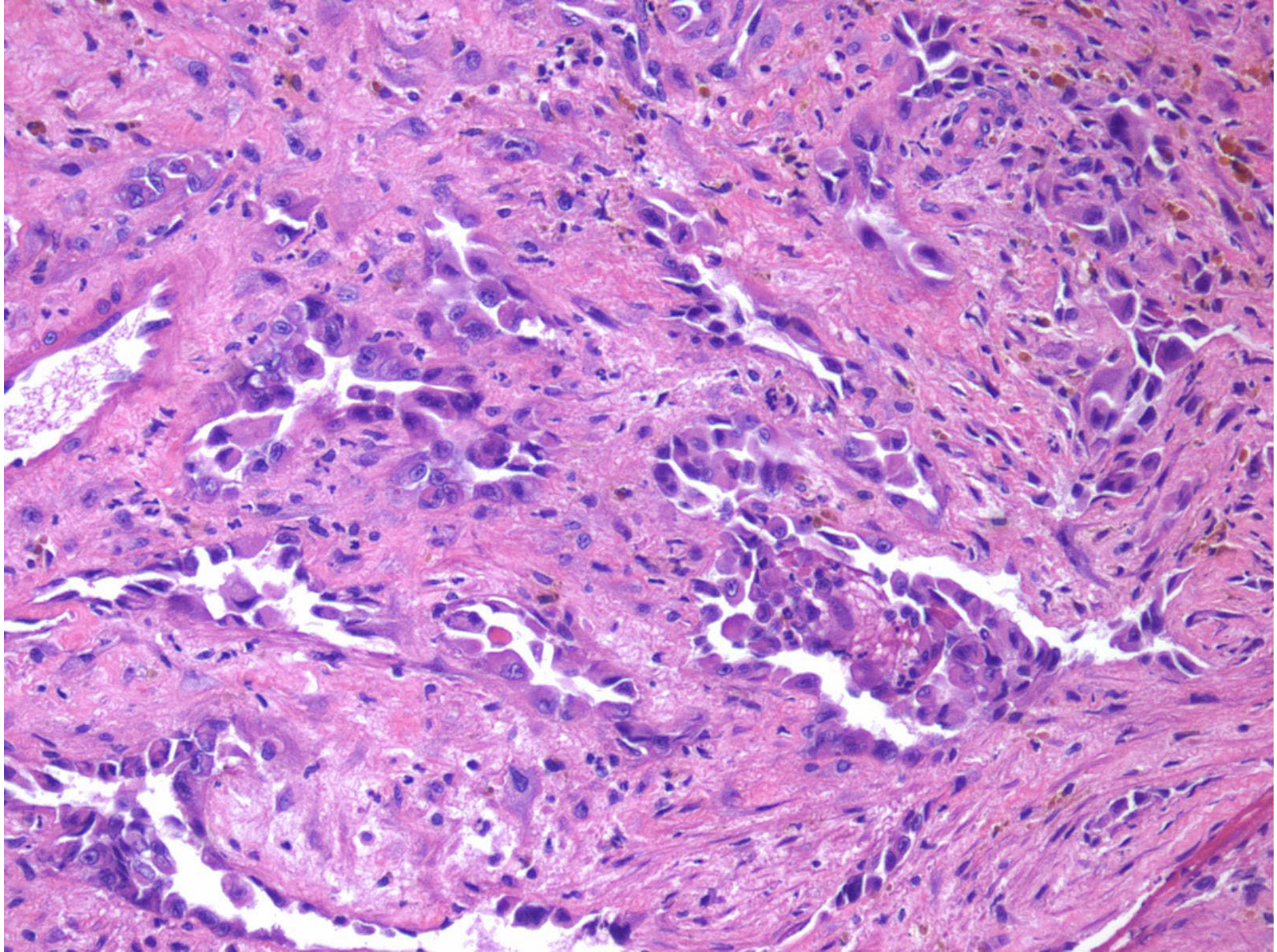


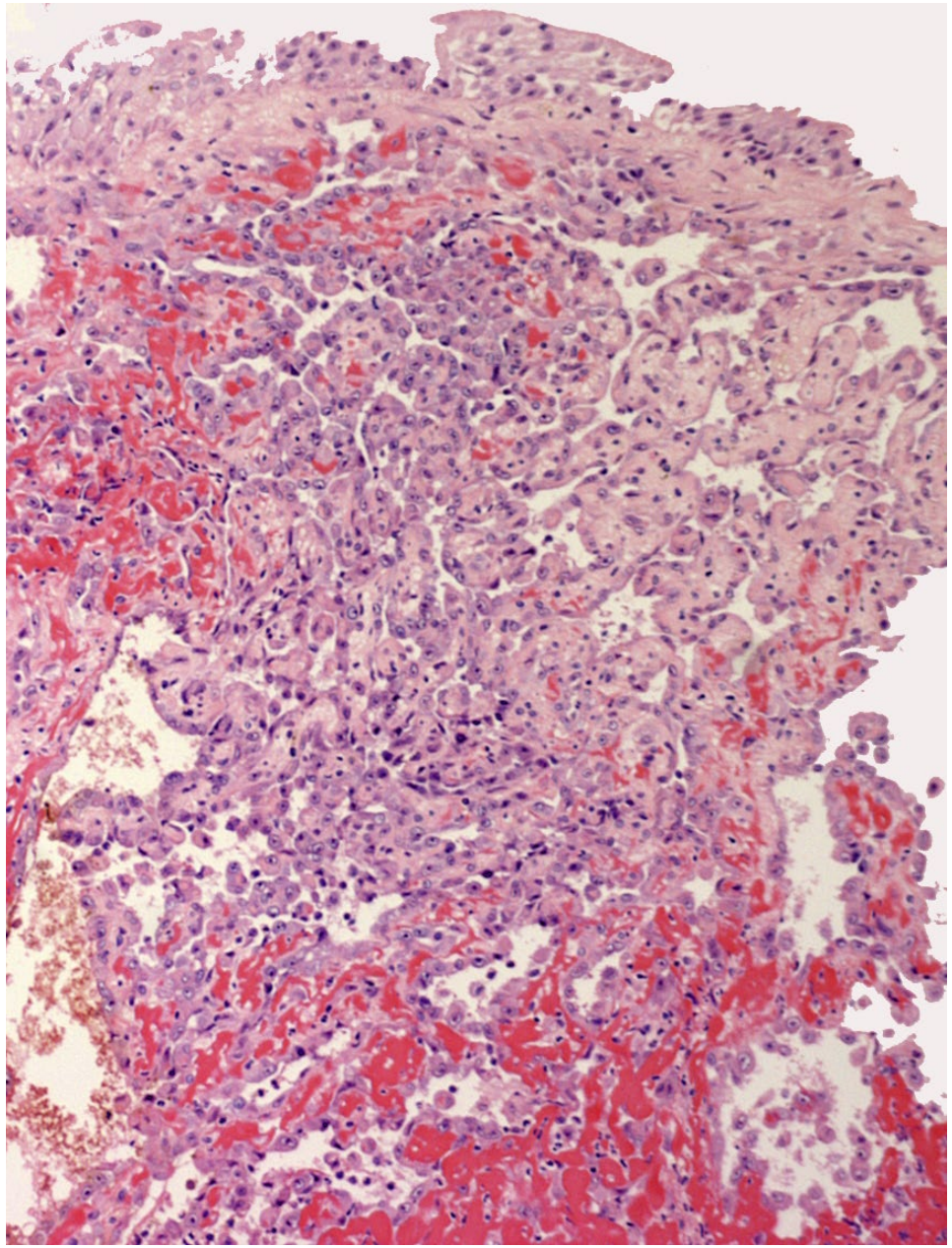


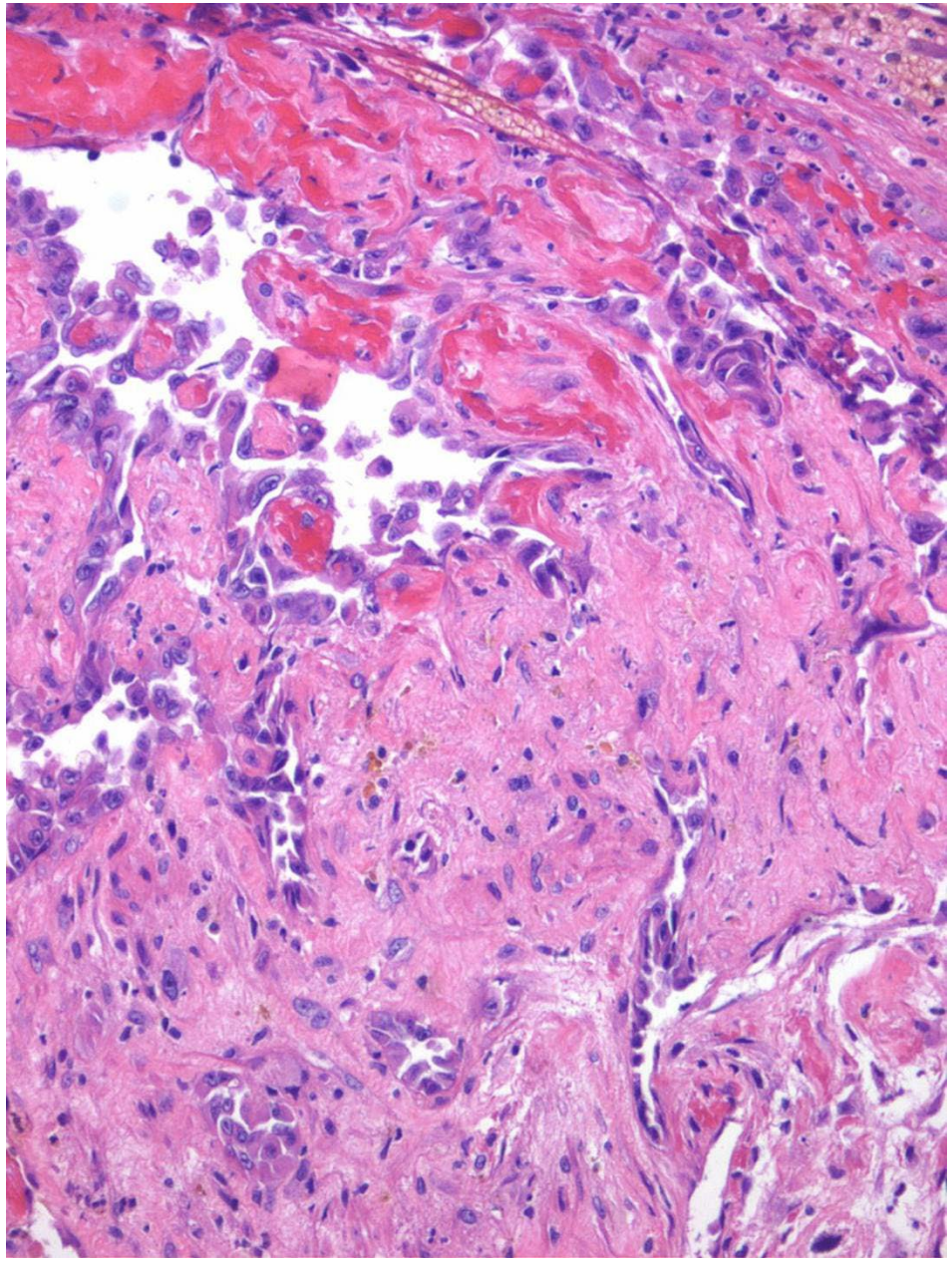
CASE #2

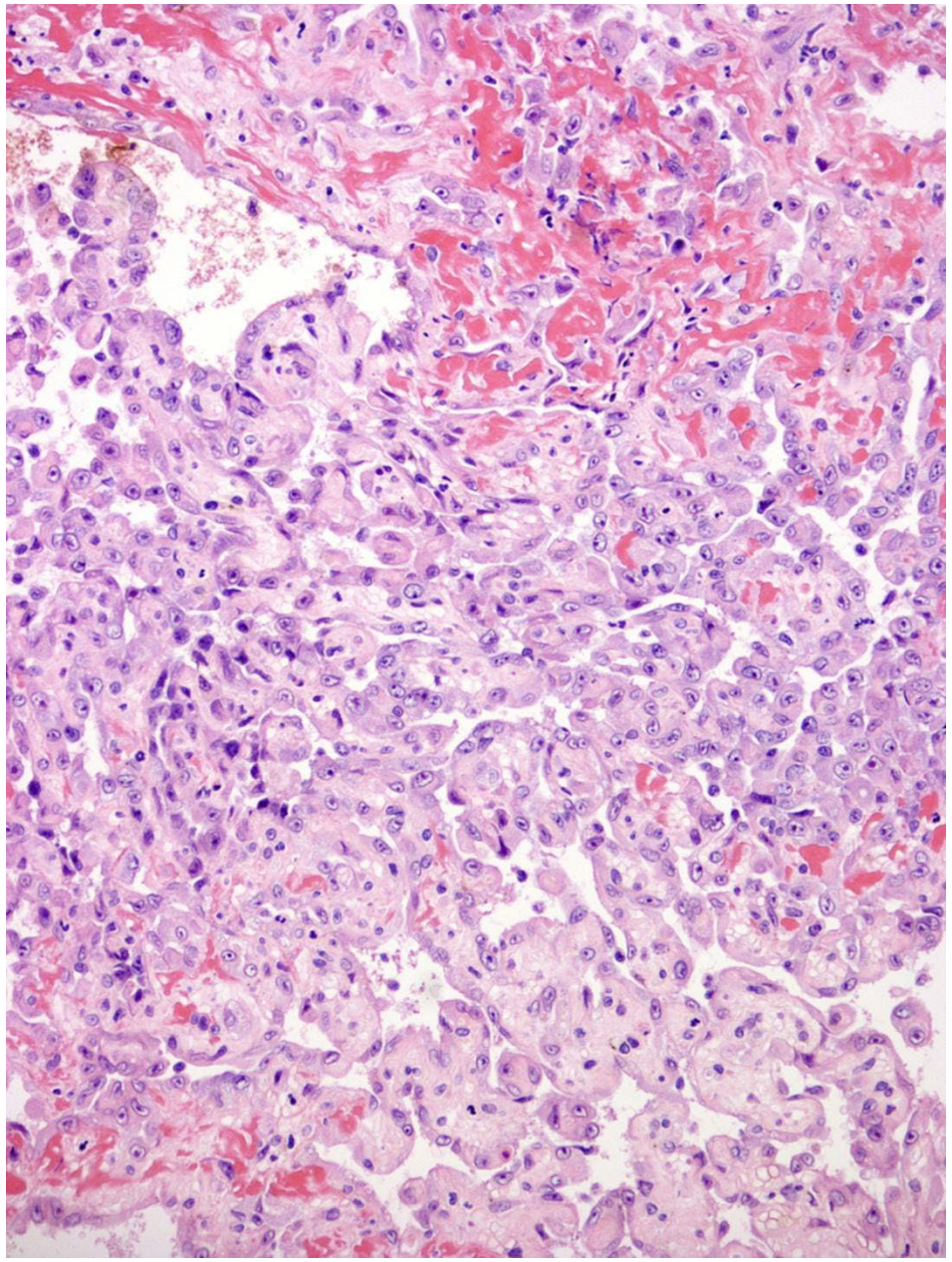
- 73 year-old female with gross hematuria
- Cystoscopy revealed a mass @ dome of bladder
- Patient underwent multiple biopsies
- Pathology review of outside slides

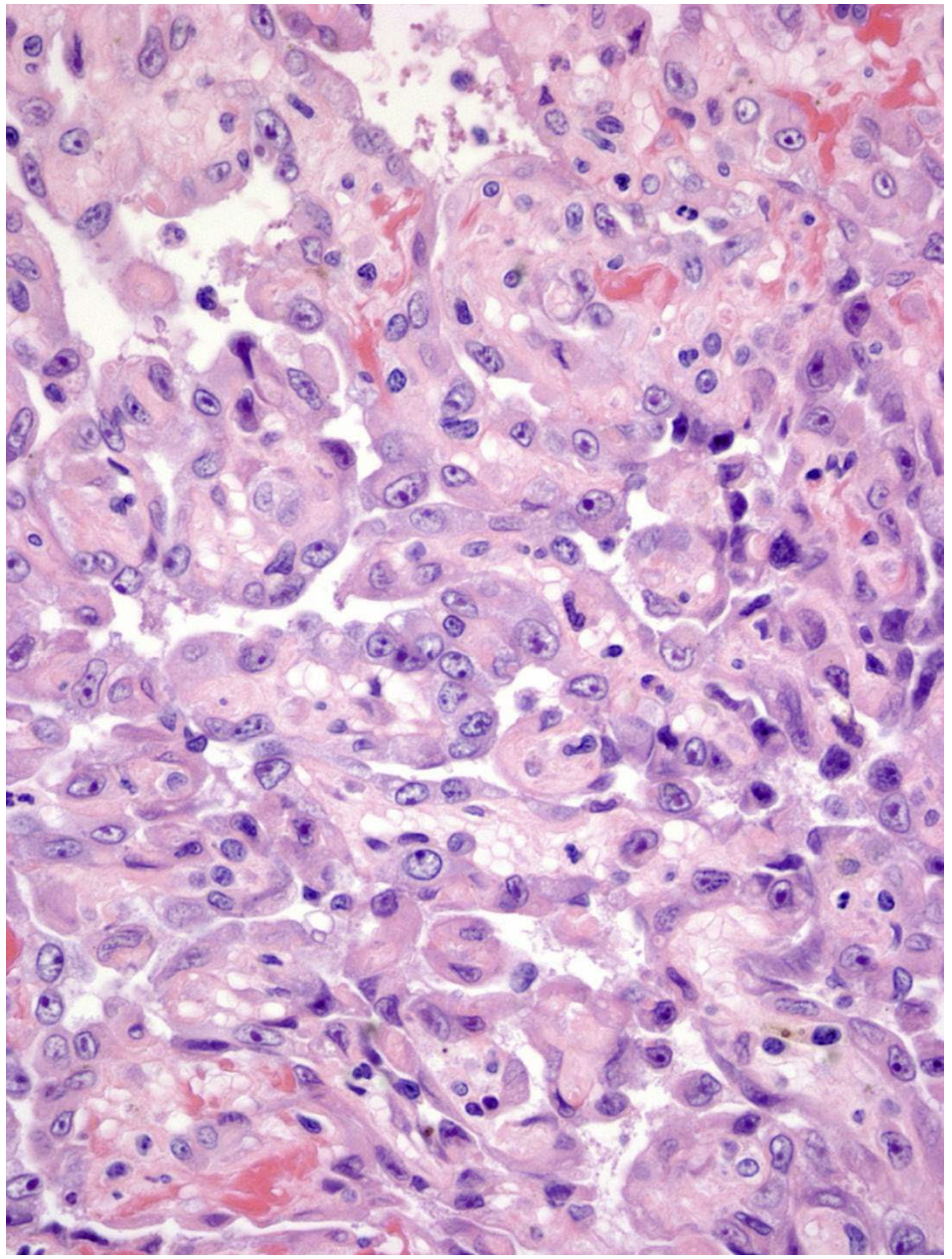






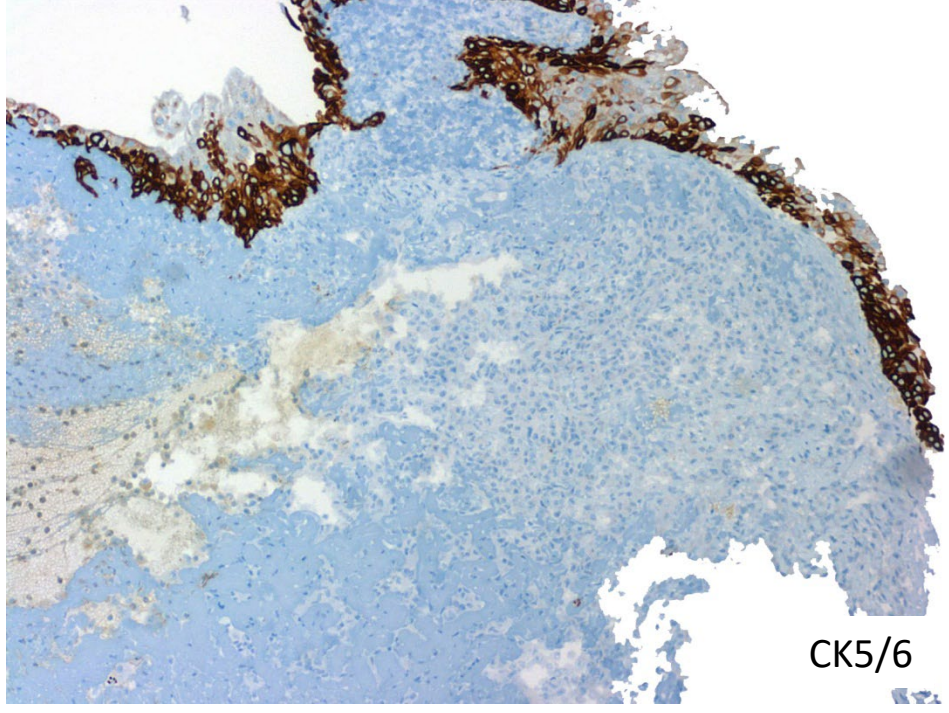


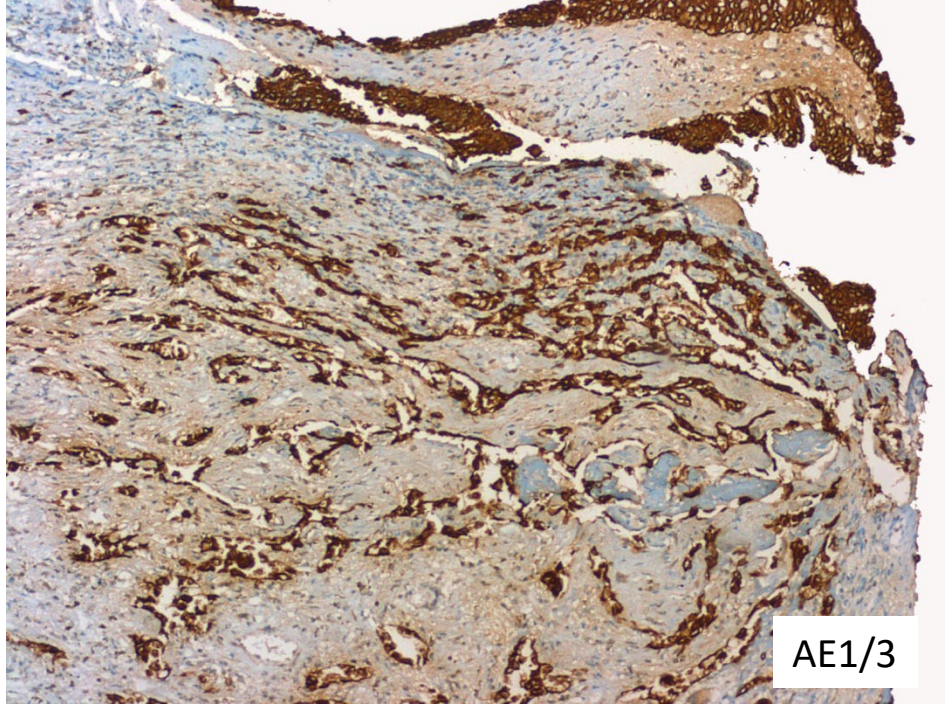


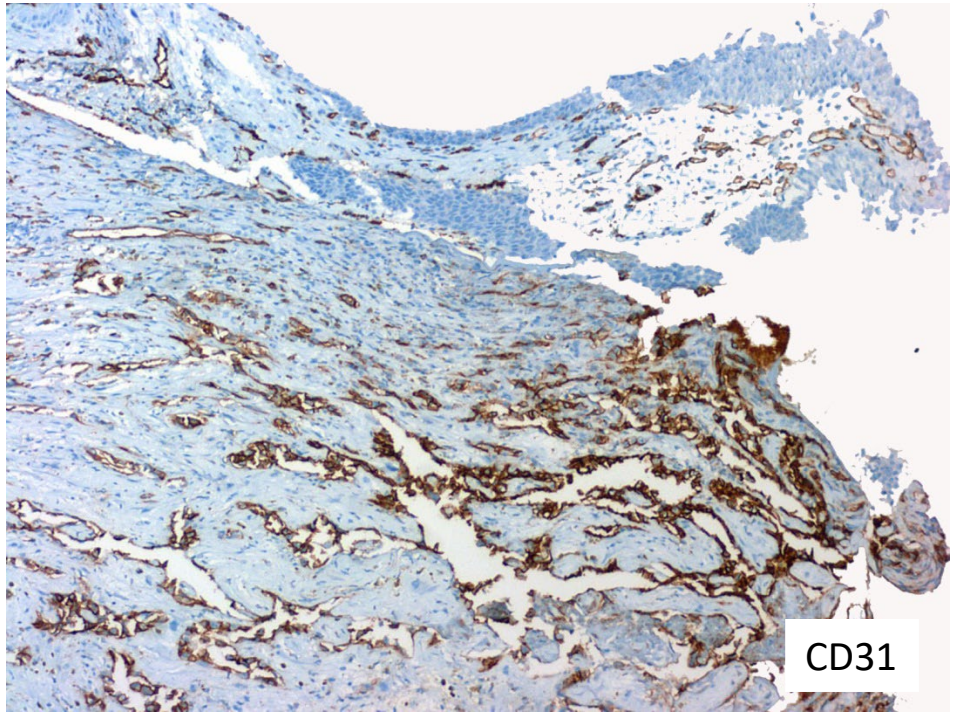


Differential Diagnosis?

- Poorly differentiated carcinoma
- Epithelioid angiosarcoma
- Pseudoangiosarcomatous urothelial carcinoma
- Urothelial carcinoma with glandular features
- Melanoma


CK5/6


AE1/3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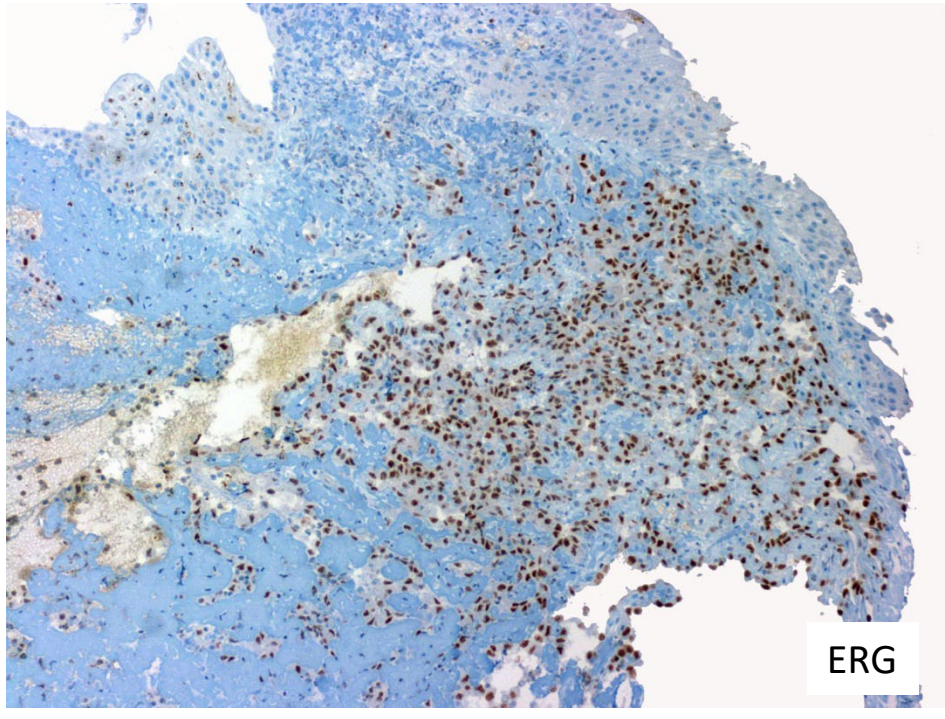

ERG

Case #2

Diagnosis

Epithelioid Angiosarcoma

Angiosarcoma of Urinary Bladder

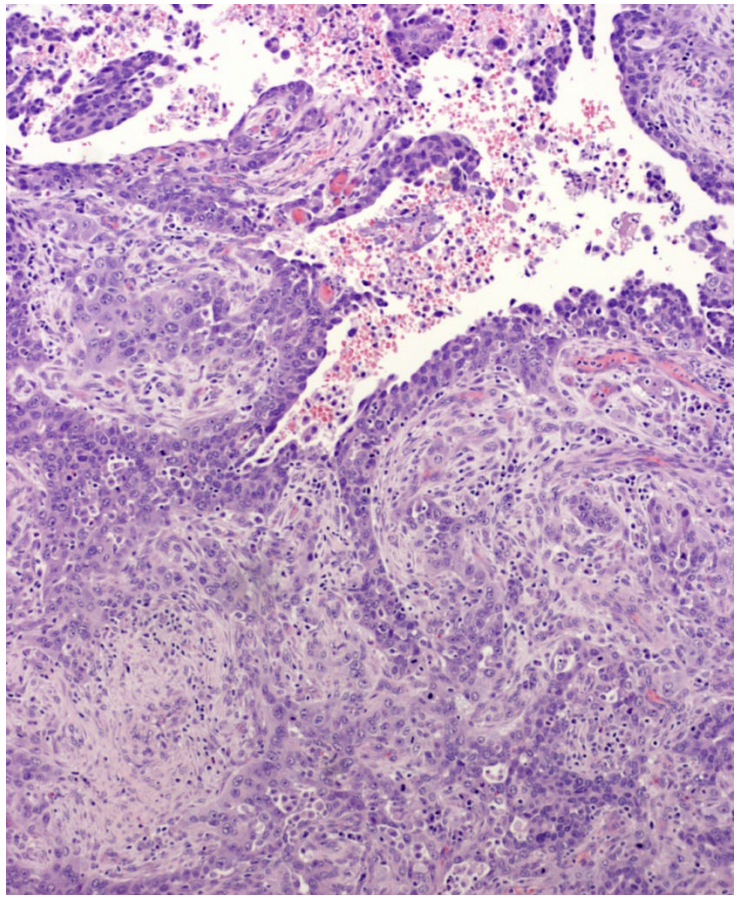
- Rare vascular neoplasm (<1%); visceral involvement is quite uncommon
- Marked male predominance
- Associated with cigarette smoking, exposure to vinyl chlorides, remote history of radiation treatment (for GYN or prostate cancer)
- Highly aggressive tumor
- Despite multimodal therapeutic approach, prognosis is poor (median survival 6 months)

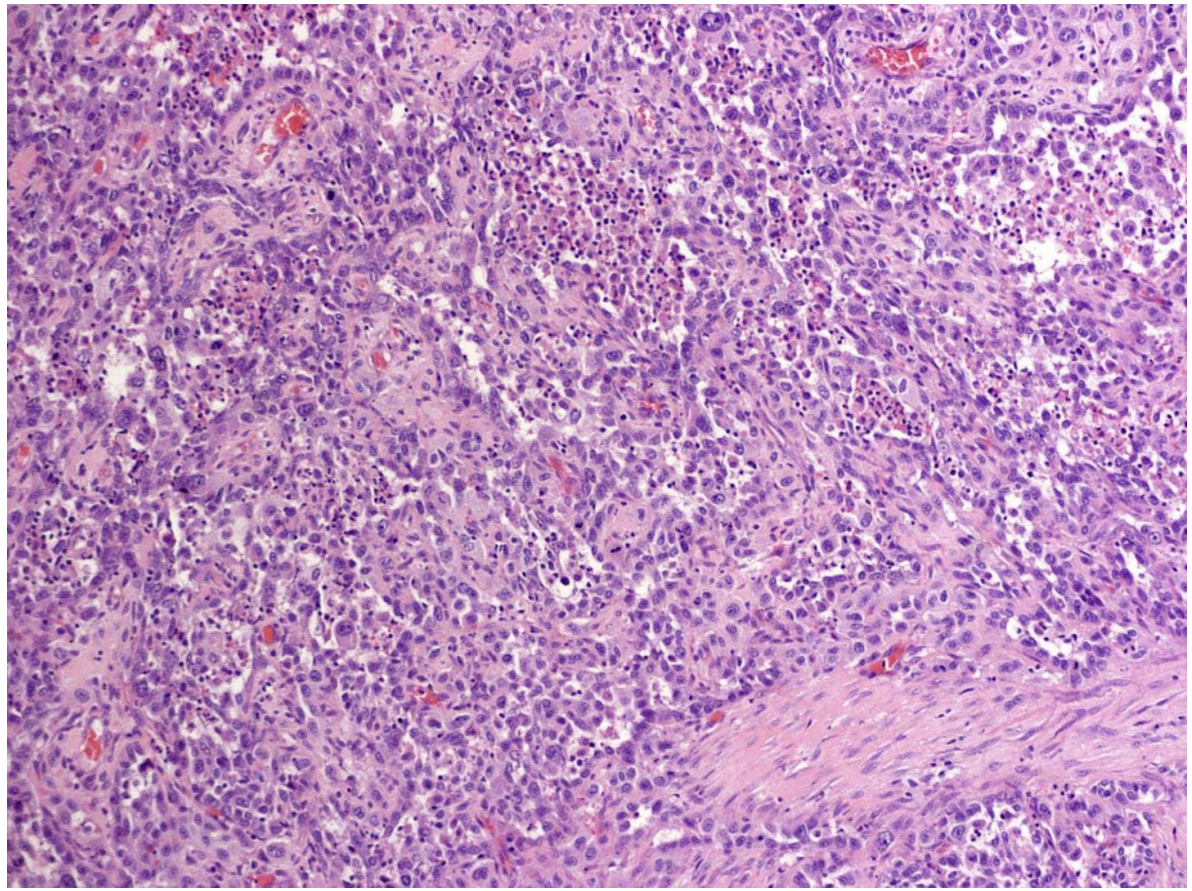
Nizam et al. Clin Genitourin Cancer. 2018

Angiosarcoma of Urinary Bladder

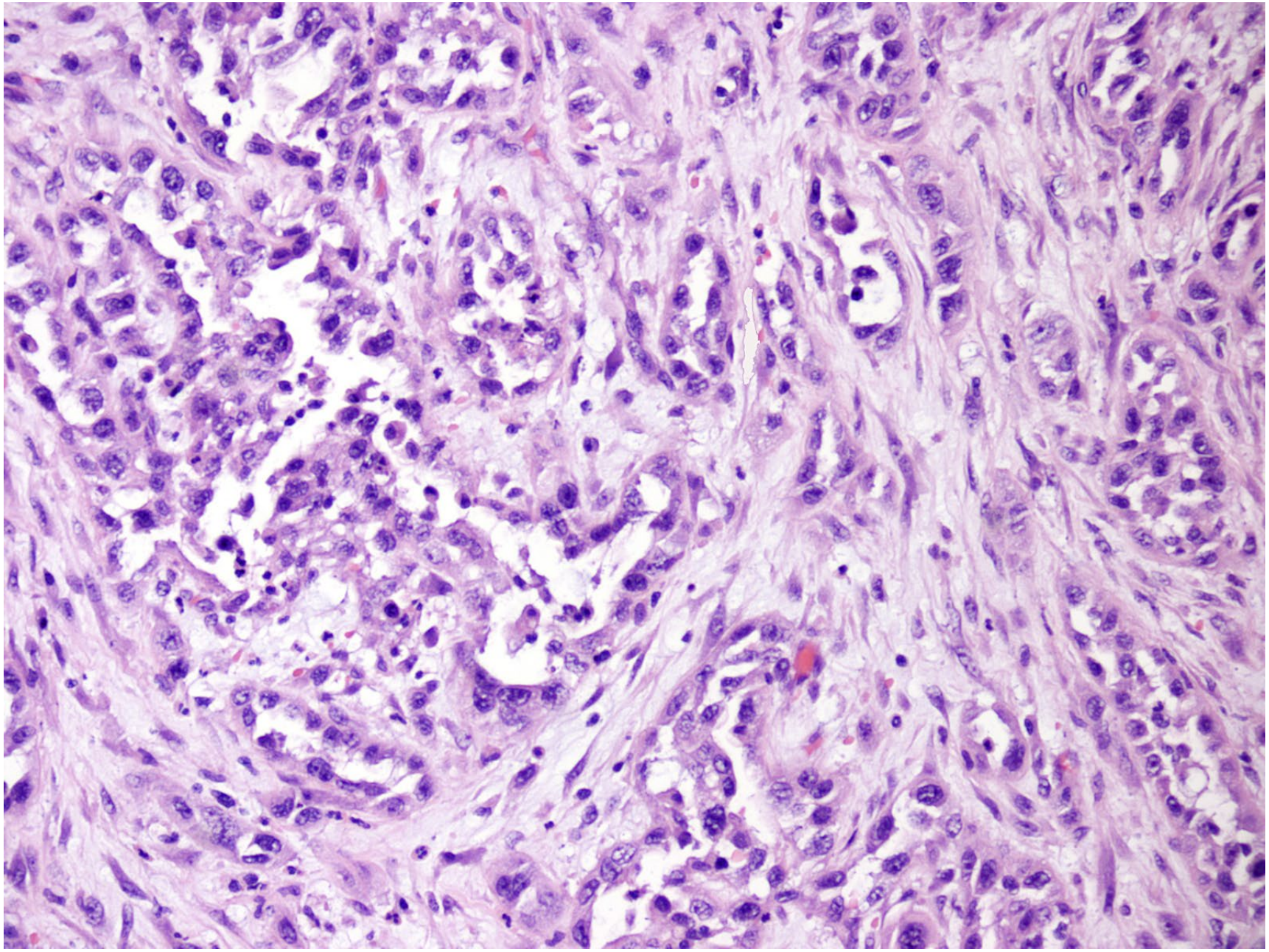
Differential Diagnosis

- Pseudoangiosarcomatous Urothelial Carcinoma





Pseudoangiosarcomatous Urothelial Carcinoma

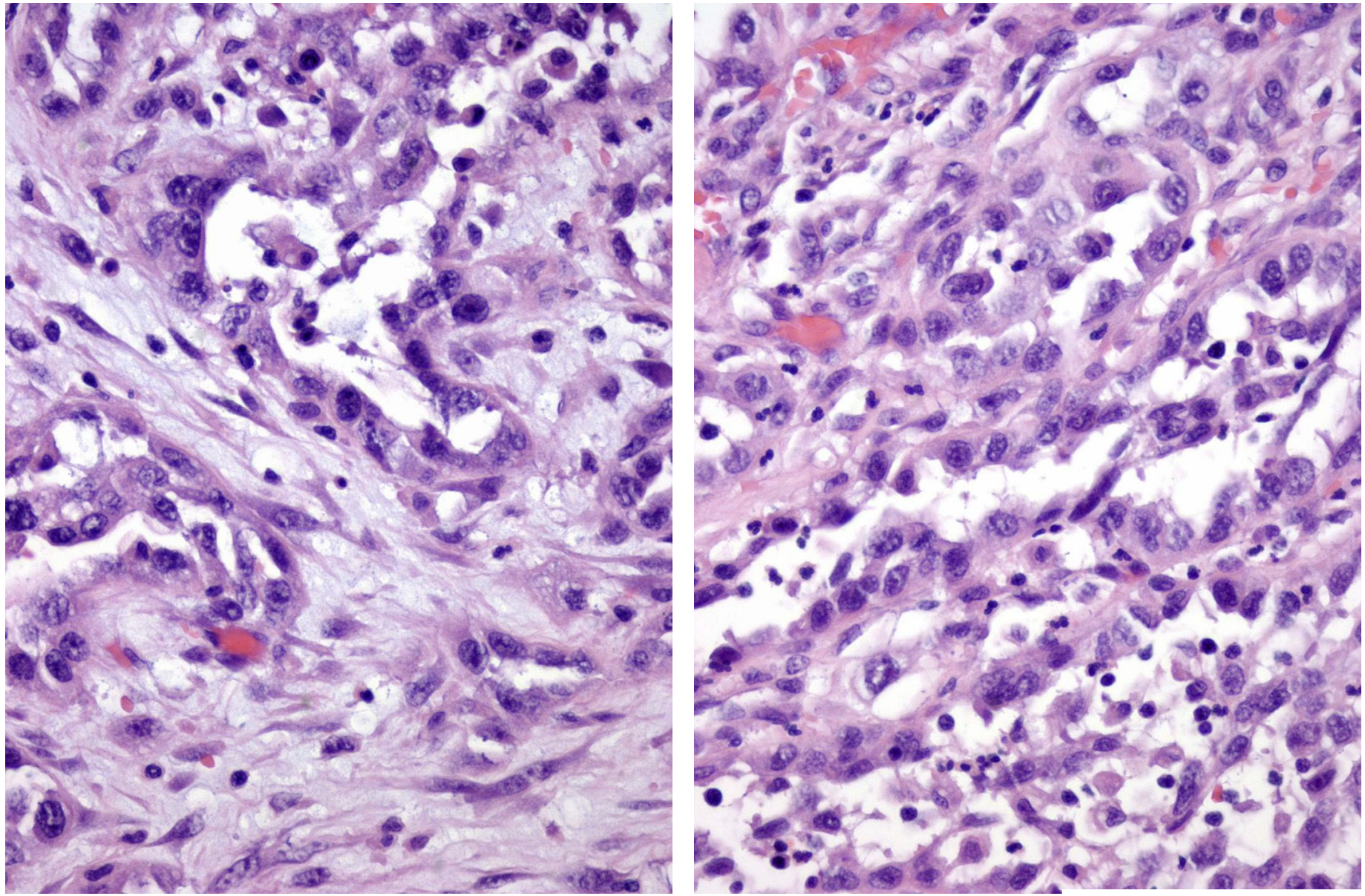


Pseudoangiosarcomatous Urothelial Carcinoma

- 7 pseudoangiosarcomatous UC of urinary bladder
- 6 M and 1 F; median age 70 years (47 to 87 years)
- Pseudoangiosarcomatous morphology comprised 35% to 85% of invasive tumor
- All tumors contained other components: conventional UC, squamous differentiation, sarcomatoid carcinoma, small cell carcinoma, micropapillary carcinoma, and glandular differentiation

Paner at al. AJSP 2014

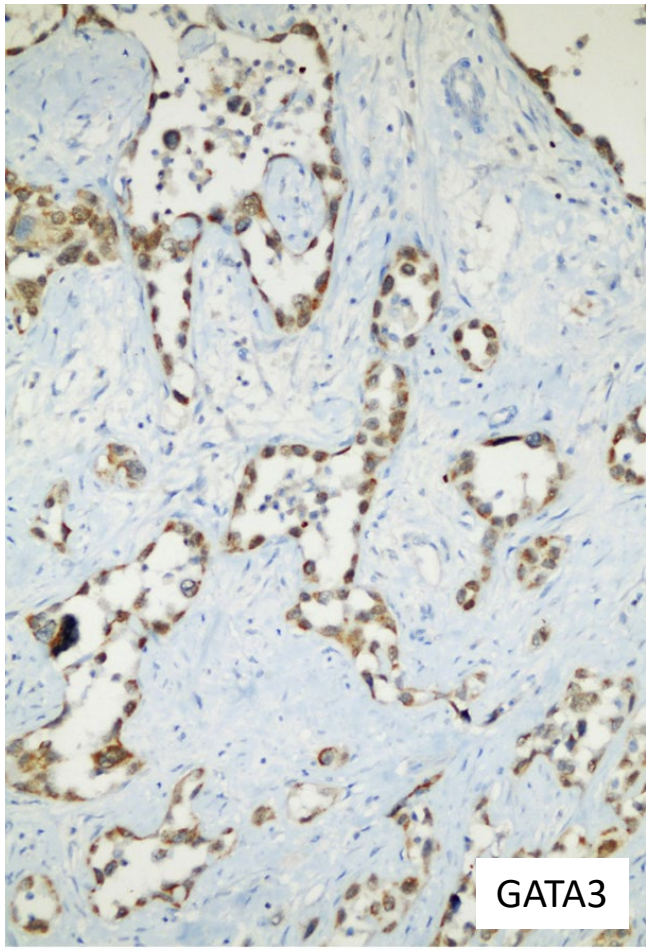
Pseudoangiosarcomatous Urothelial Carcinoma



Paner at al. AJSP 2014

Pseudoangiosarcomatous Urothelial Carcinoma

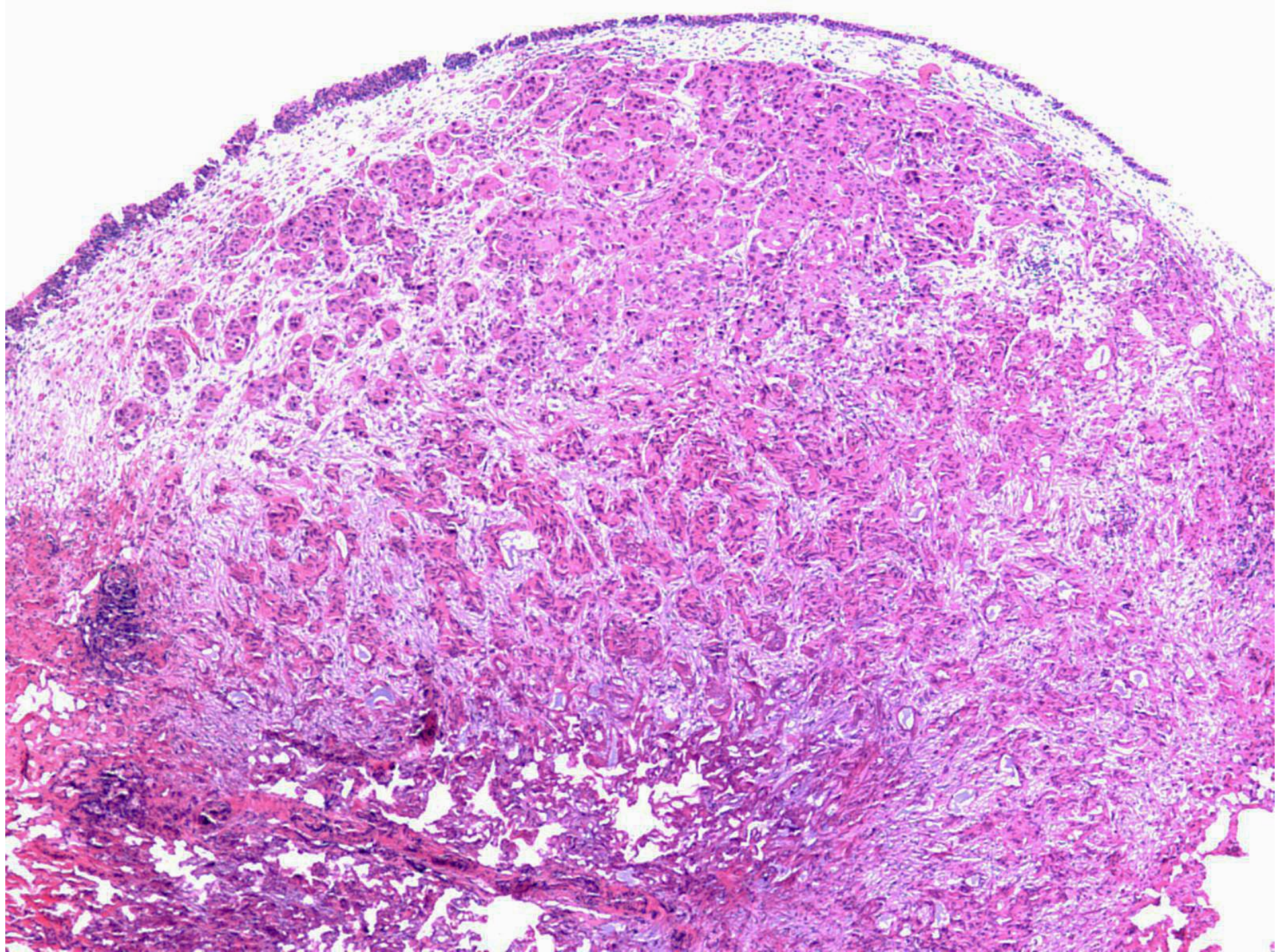
- CK7, GATA3 +
- Vascular-associated markers –
- All tumors were high stage @ cystectomy
- Poor outcome: overall median survival of 8.5 months
- Awareness of this pattern of UC is important to avoid misdiagnosis, particularly in limited tissue samples

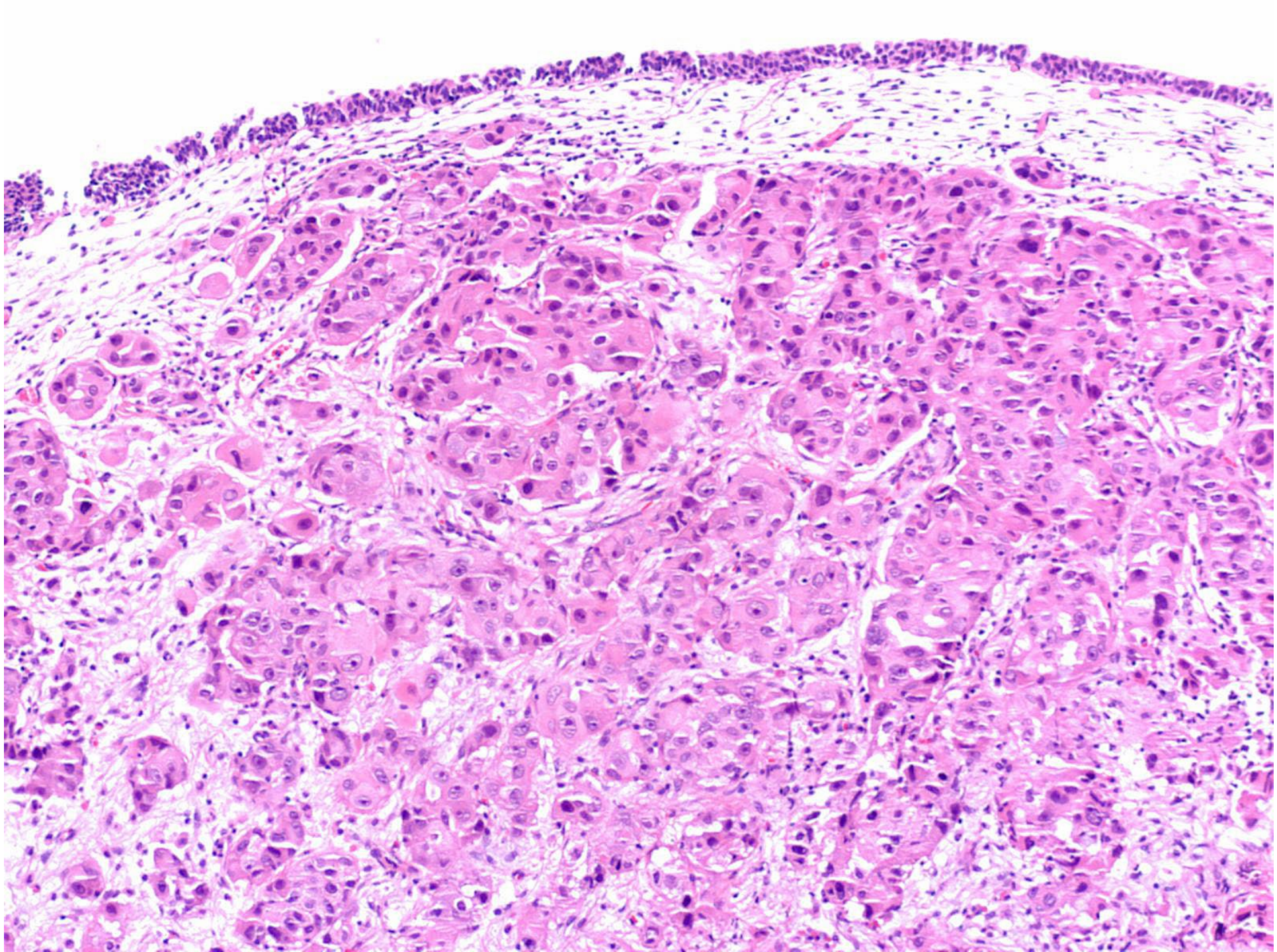


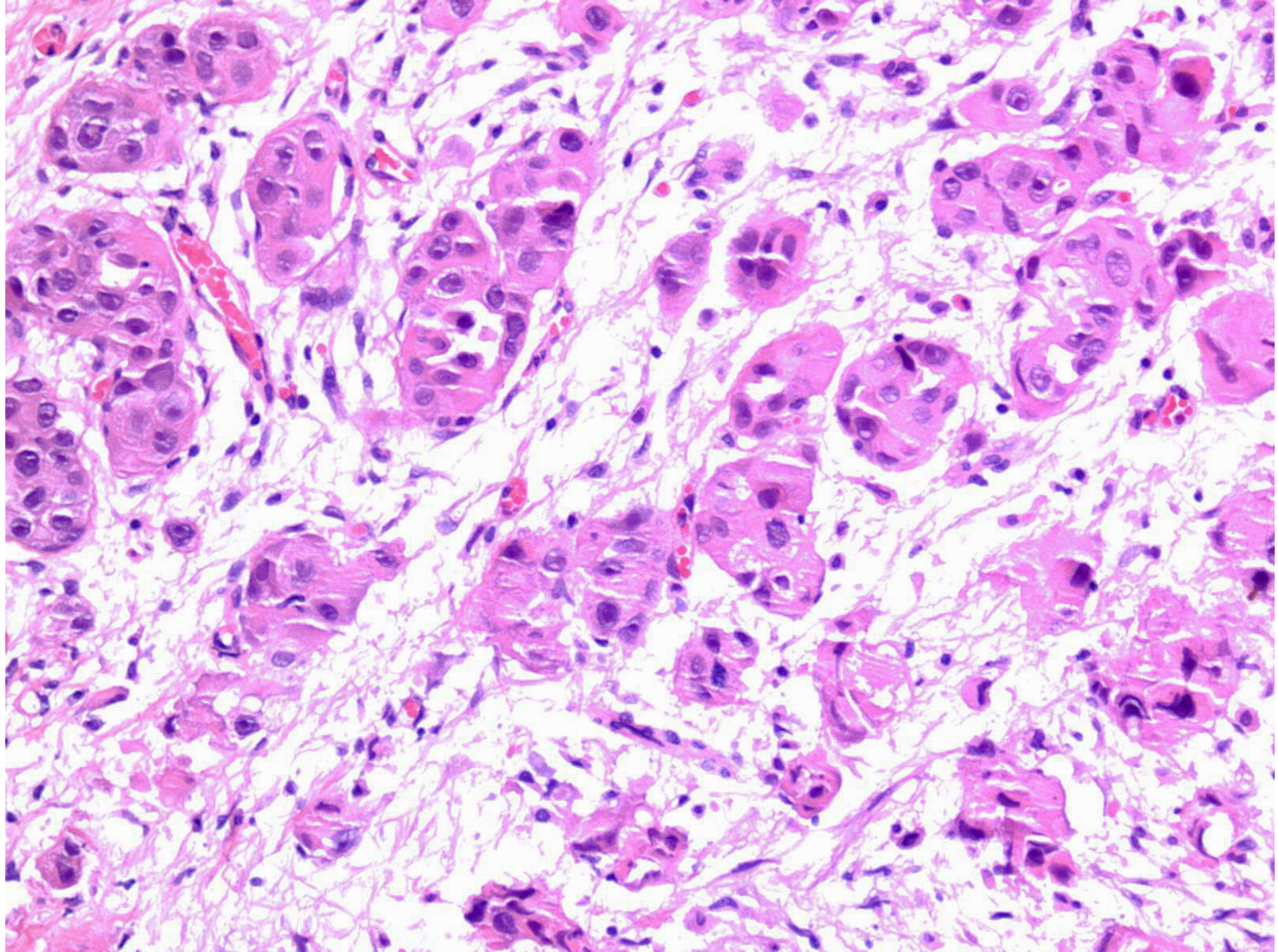
Paner at al. AJSP 2014; Yildiz et al. Ann Diagn Pathol 2017

CASE #3

- 69 y/o female with hematuria; cystoscopy shows 2-3 small lesions at the dome of the bladder



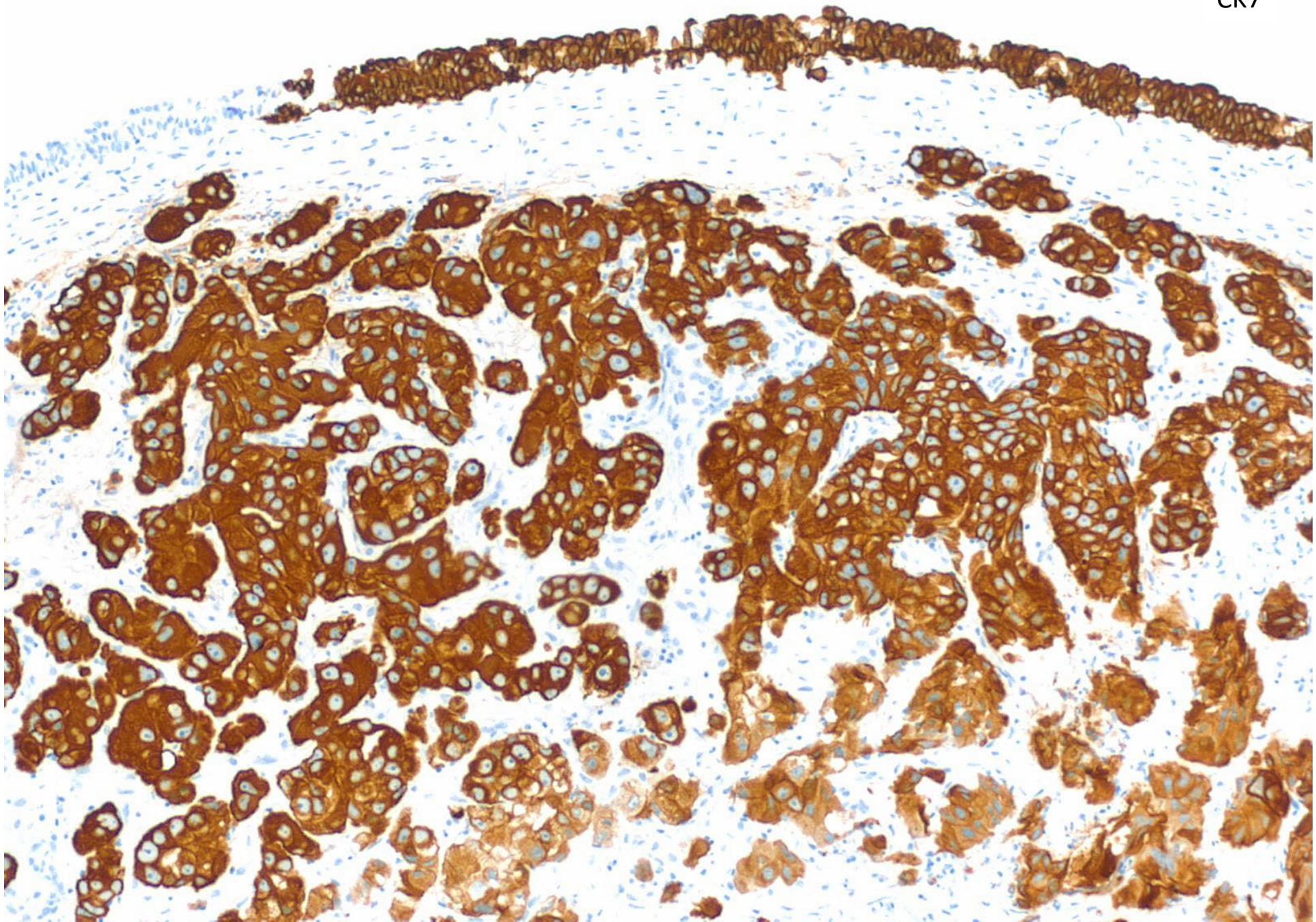


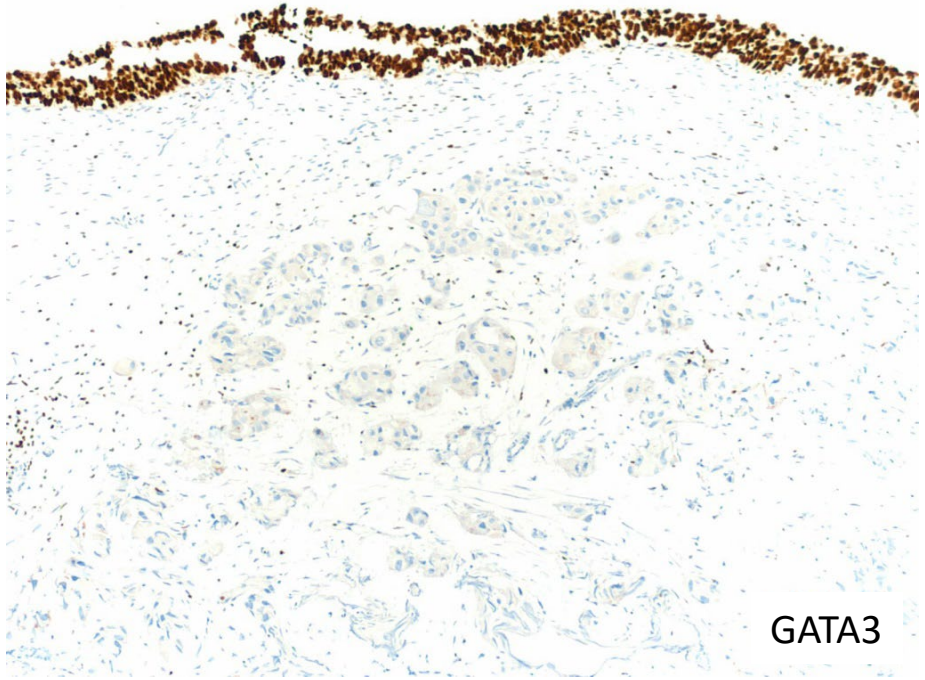


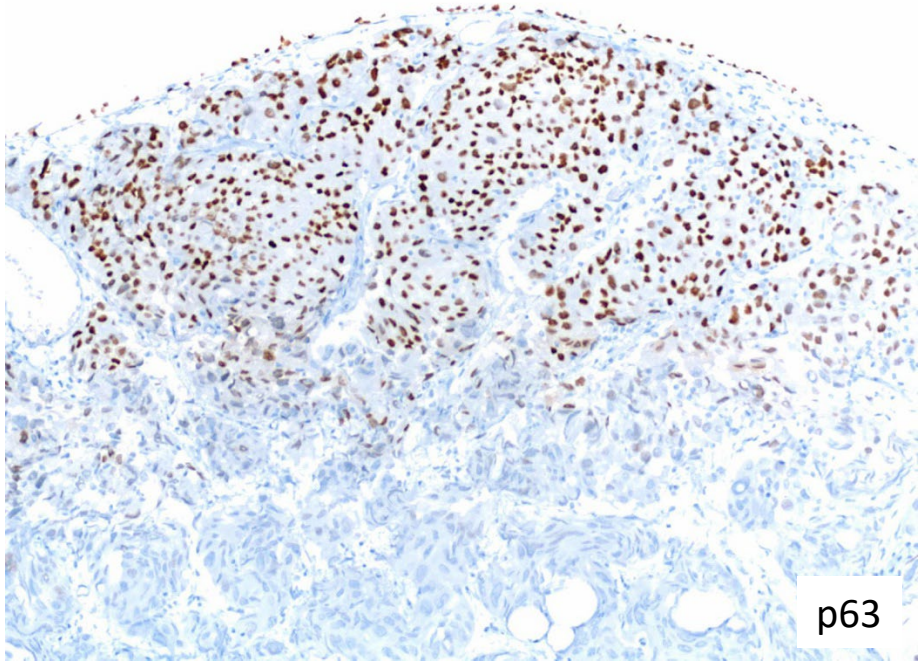
Differential Diagnosis?

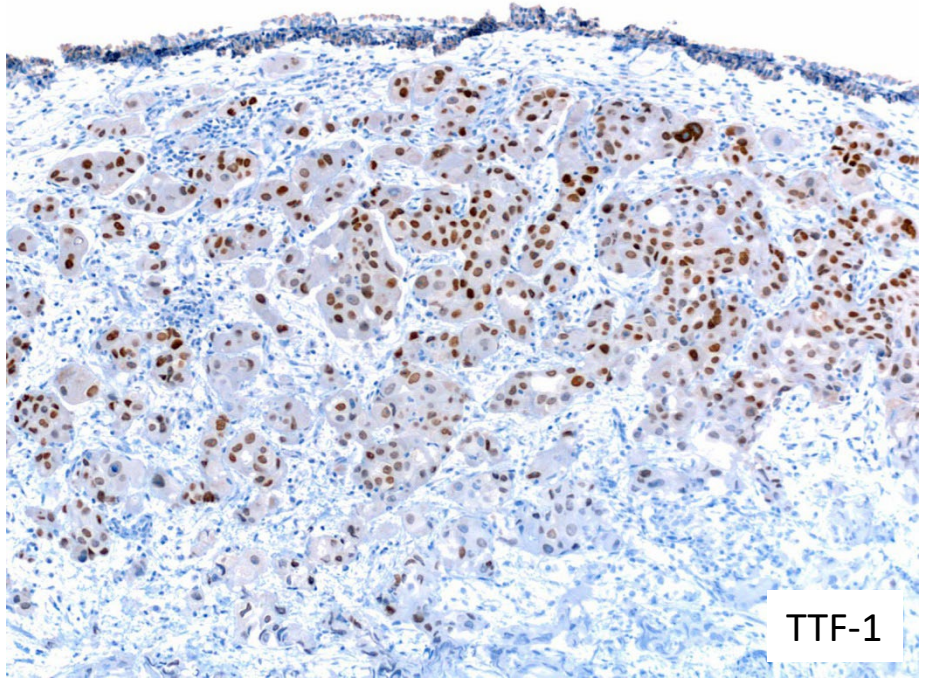
- High-grade urothelial carcinoma with nested features
- Adenocarcinoma (primary vs. secondary)
- Paraganglioma

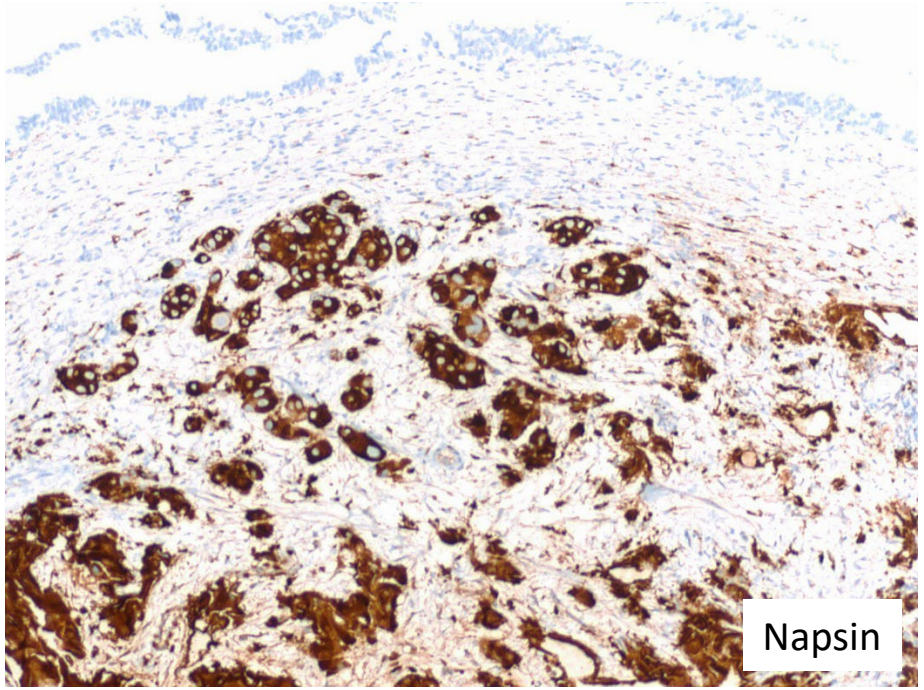
CK7




GATA3


p63


TTF-1


Napsin

Diagnosis

- Immunohistochemical stains:
  - TTF-1, CK7, EMA, p63, napsin +
  - GATA3, CK20, CK5/6 and KER 903 –
- Review of patient's clinical history confirmed a **history** of right lung, lower lobe resection for mixed adenocarcinoma, acinar, solid and papillary type

Case #3

Diagnosis

Invasive poorly differentiated carcinoma, consistent with **metastatic adenocarcinoma** of lung

Adenocarcinoma involving bladder

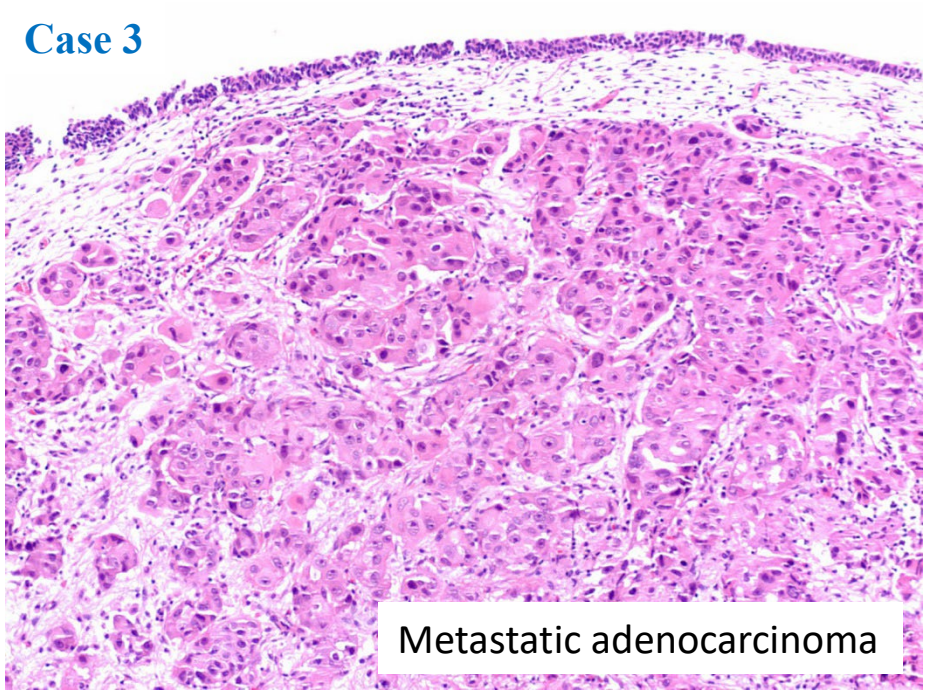
Differential Diagnosis

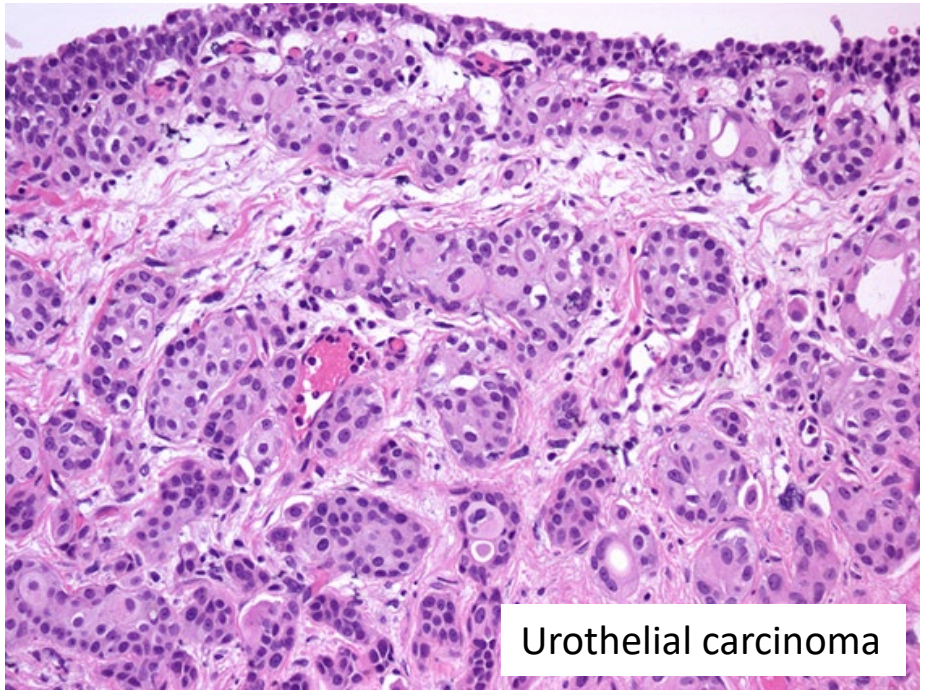
- Differentiating primary from secondary can be difficult (immunophenotypic overlap)
- Clinical history and correlation with imaging is vital
- Possibility of spread of a contiguous-site malignancy should first be sought
- In patients harboring a distant site primary adenocarcinoma, D.D. between primary and metastatic relies on morphology and specific IHC staining
- Intact epithelium overlying tumor is suggestive of a secondary lesion

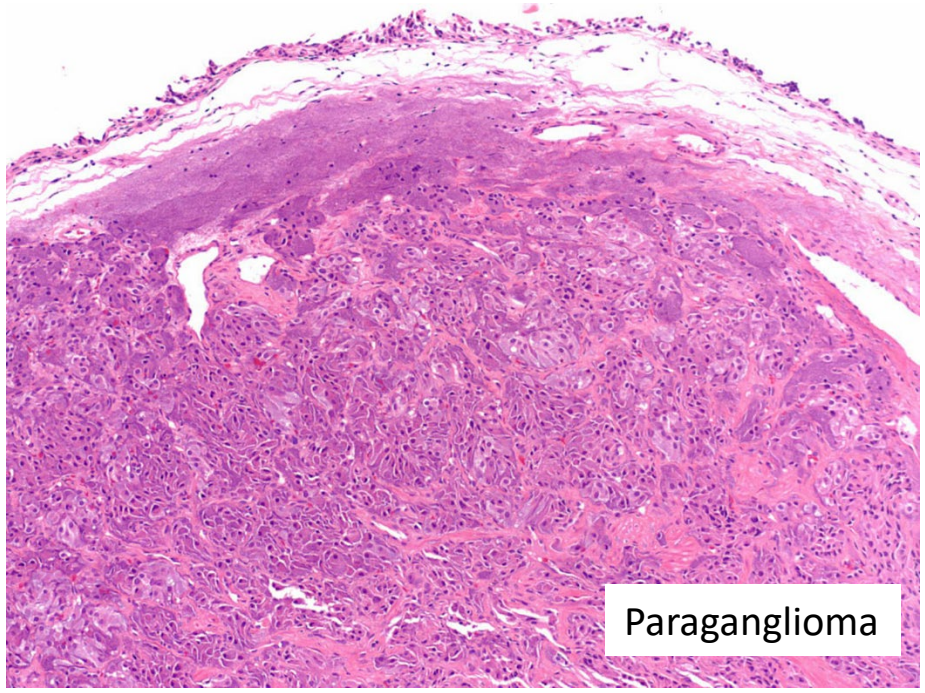
Metastatic adenocarcinoma to bladder

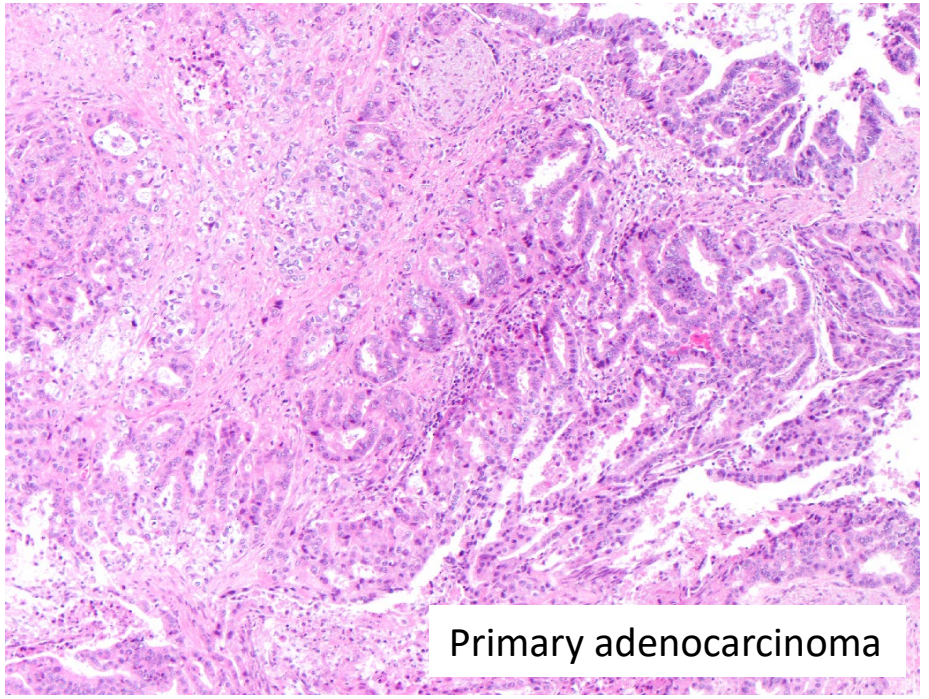
- Metastases from lung cancer are uncommon; from lung adenocarcinoma are extremely rare (< dozen documented cases)
- Secondary cancers to bladder are rare:
  - most result from direct extension from surrounding organs (prostate, colorectal, ovary, cervix)
  - minority are metastasis originating from lymphomas/leukemias or from solid tumors (breast, lung, kidney, skin primaries)
- Bladder metastases are managed with palliative chemotherapy and have worse outcome than primary carcinoma

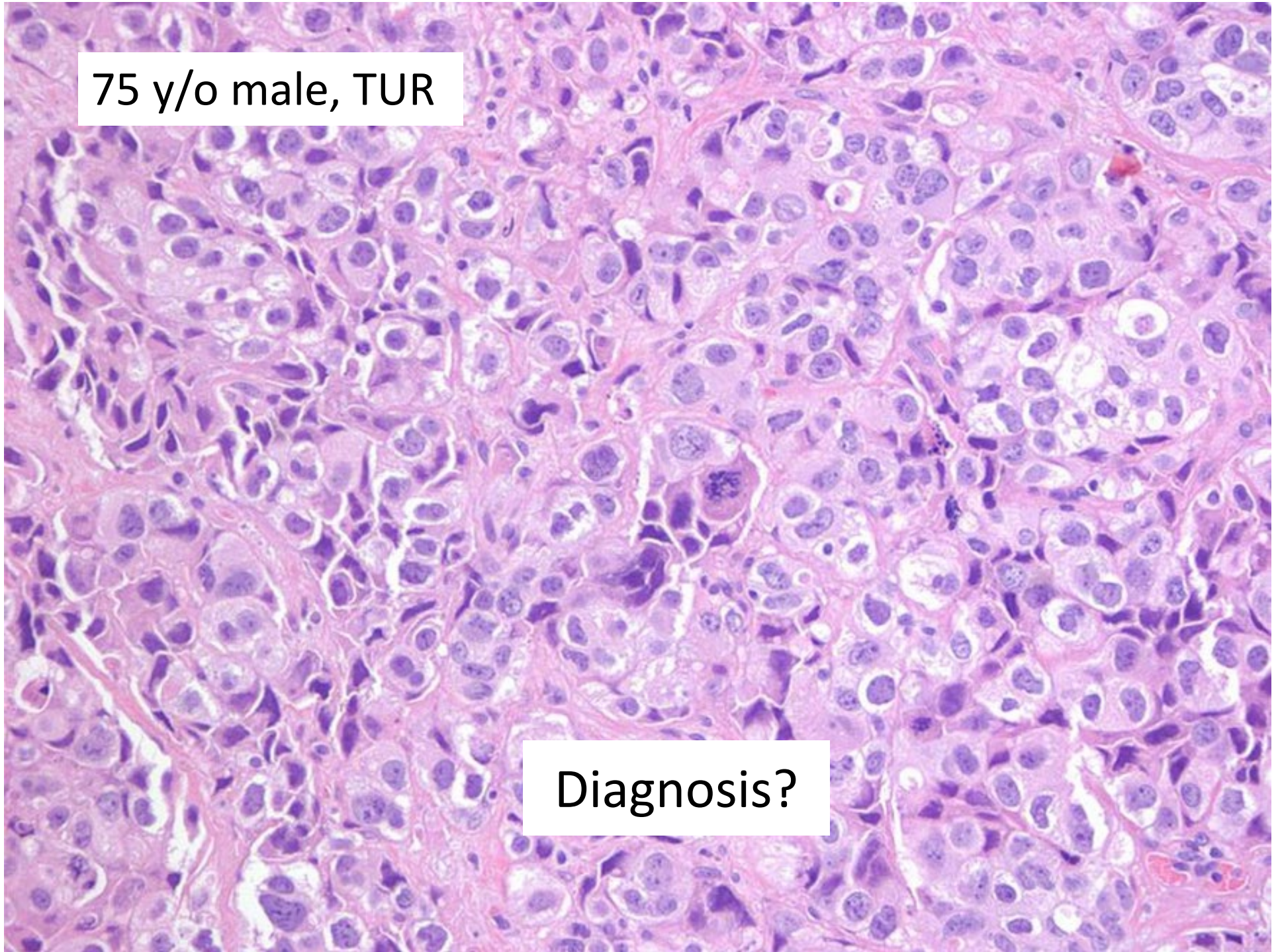
Case 3

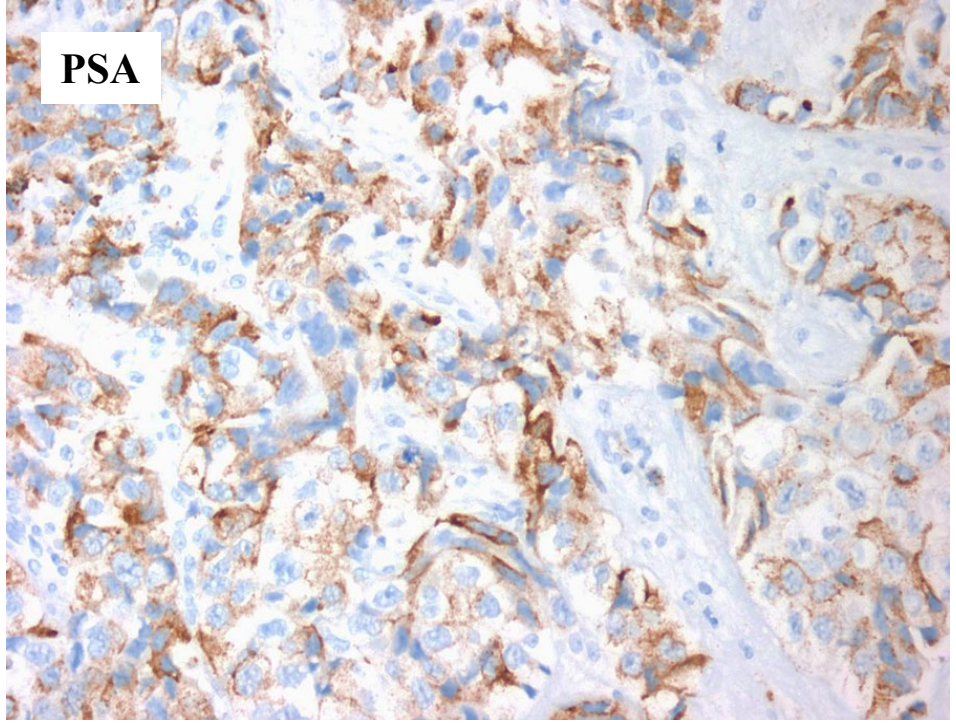

Metastatic adenocarcinoma

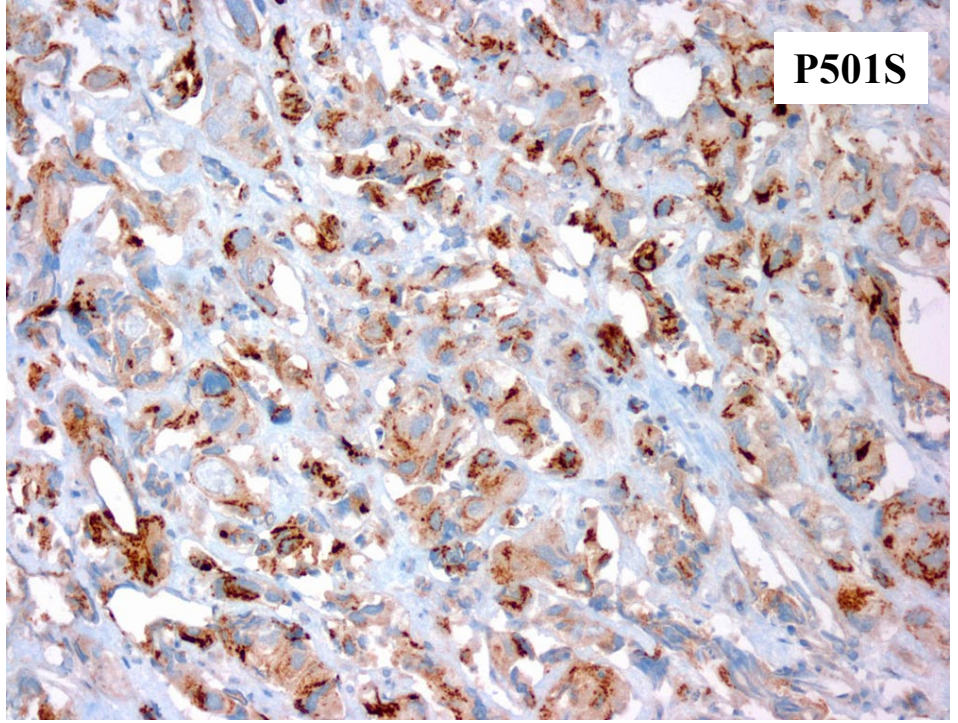

Urothelial carcinoma

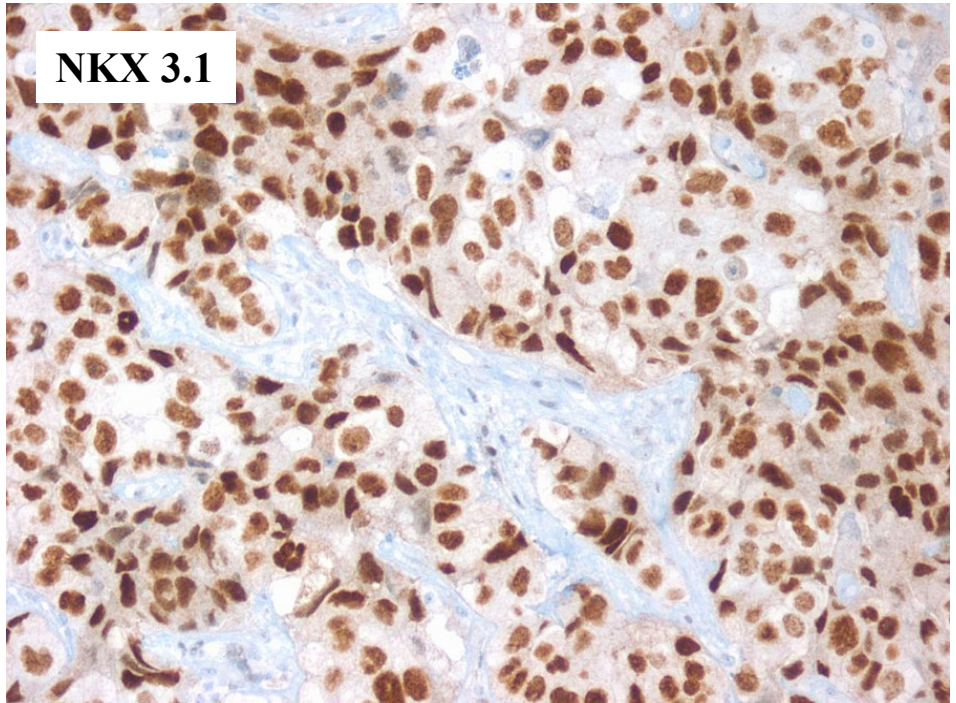

Paraganglioma

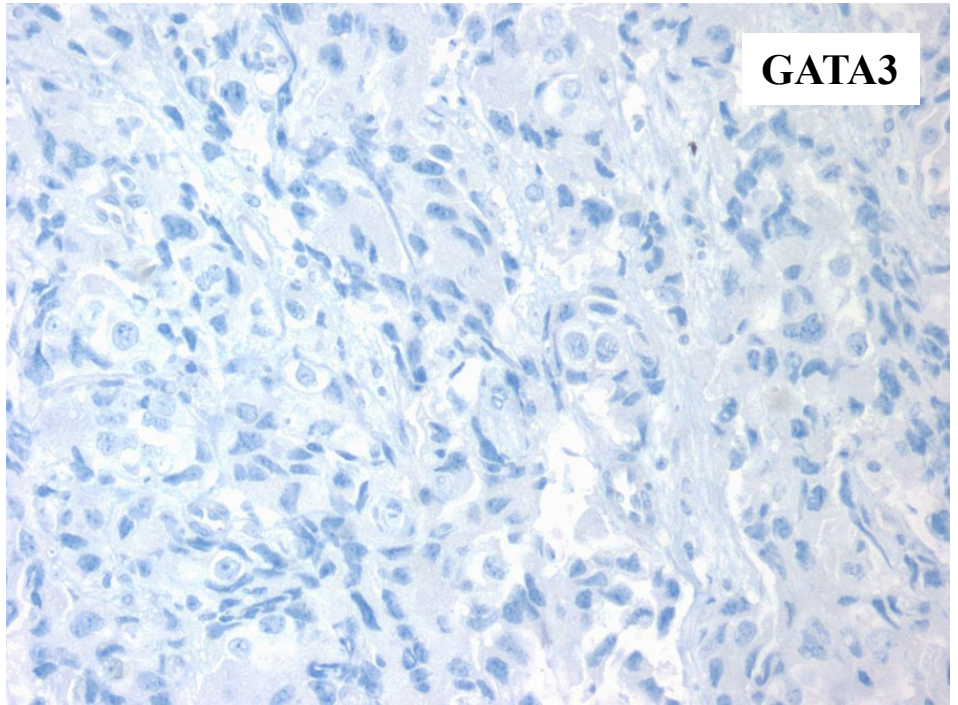

Primary adenocarcinoma

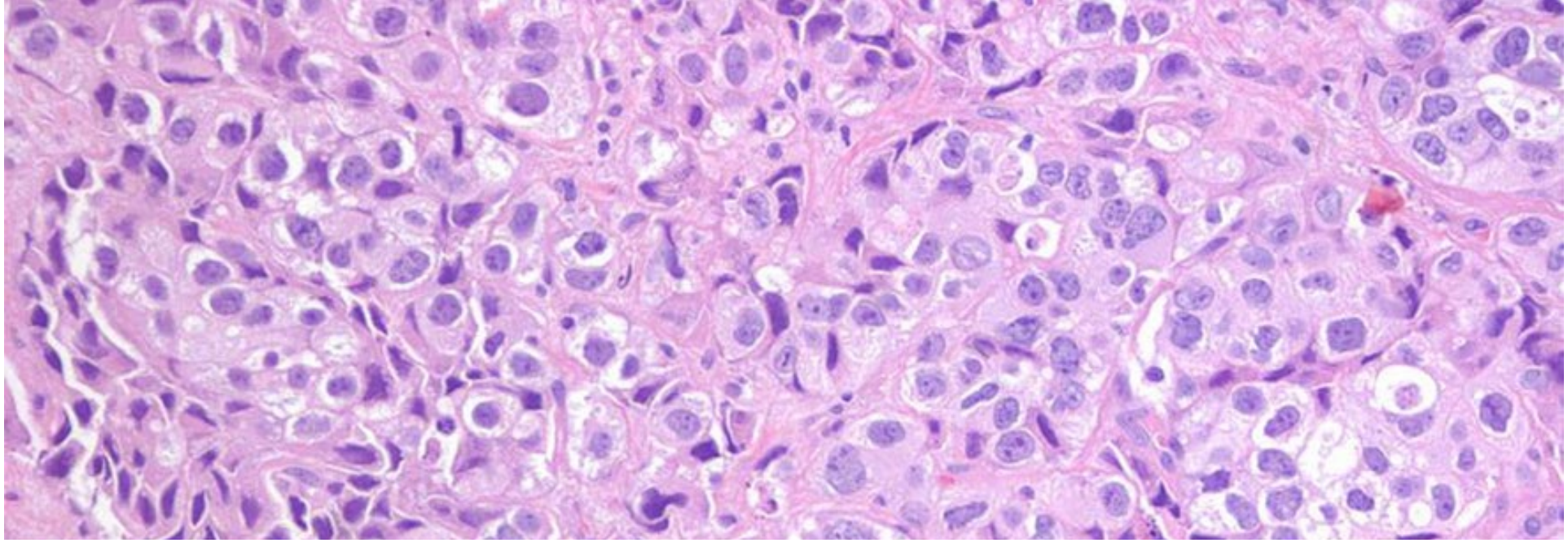

75 y/o male, TUR
Diagnosis?


PSA

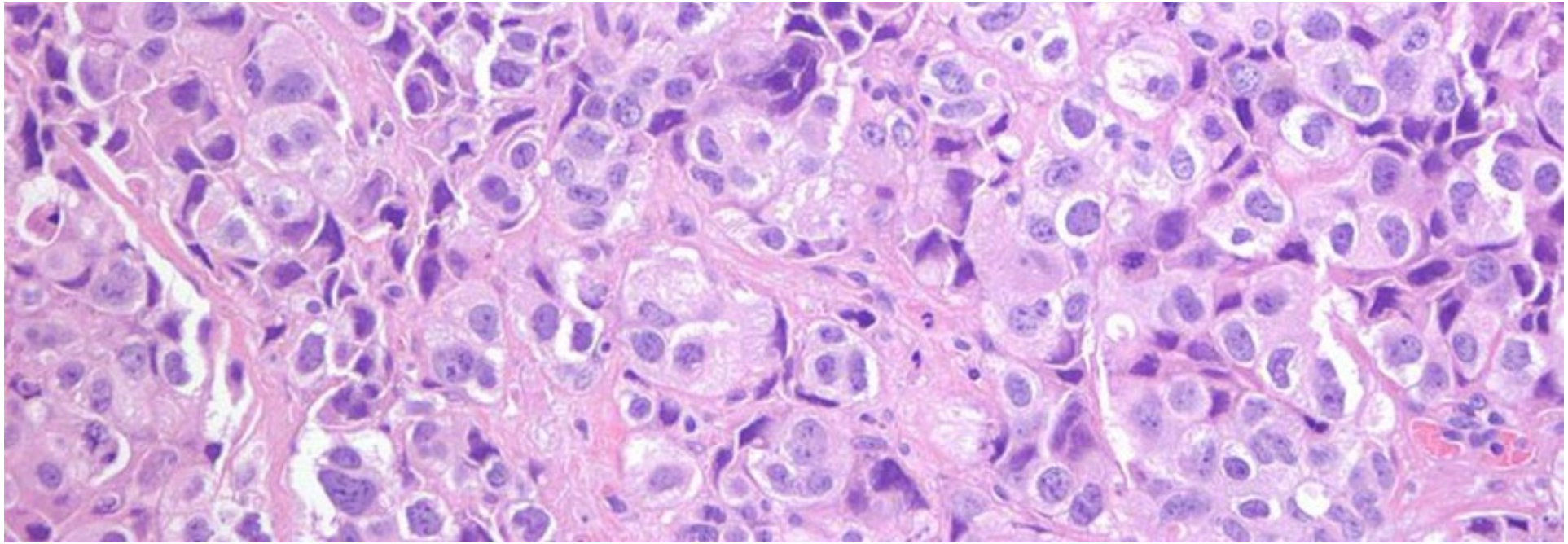

P501S

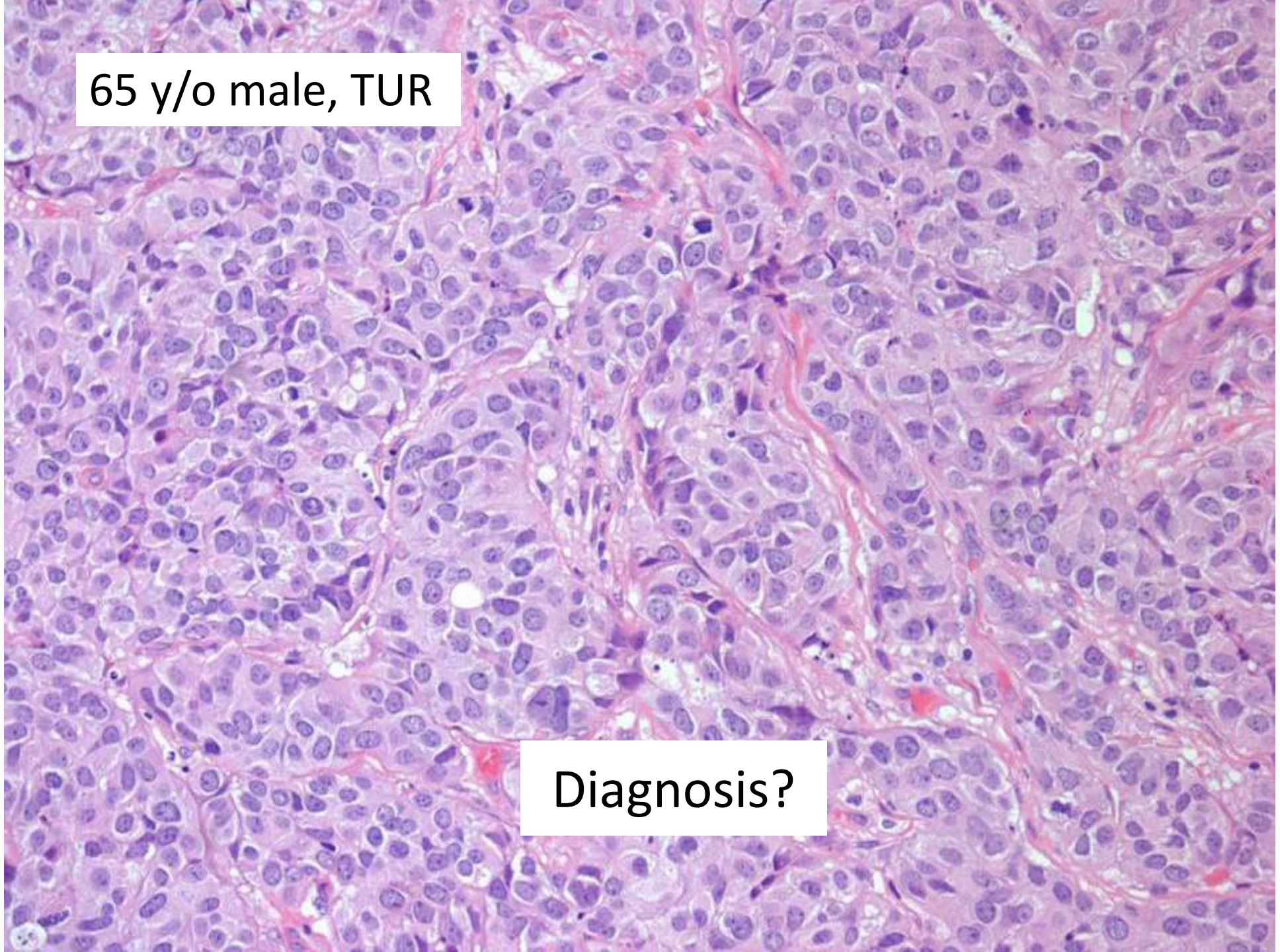

NKX 3.1

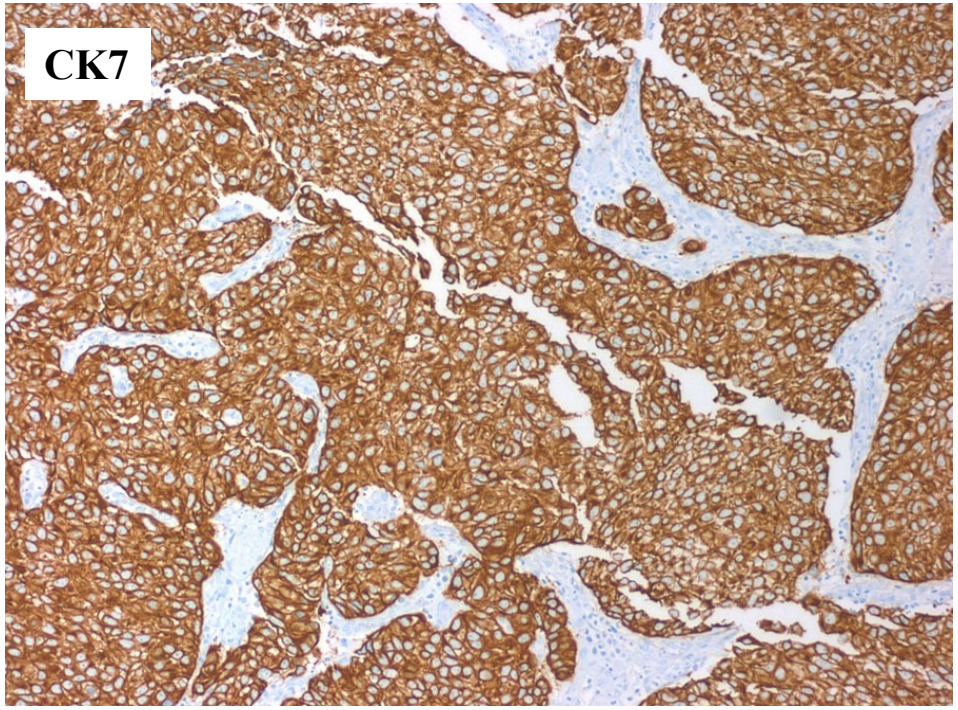

GATA3

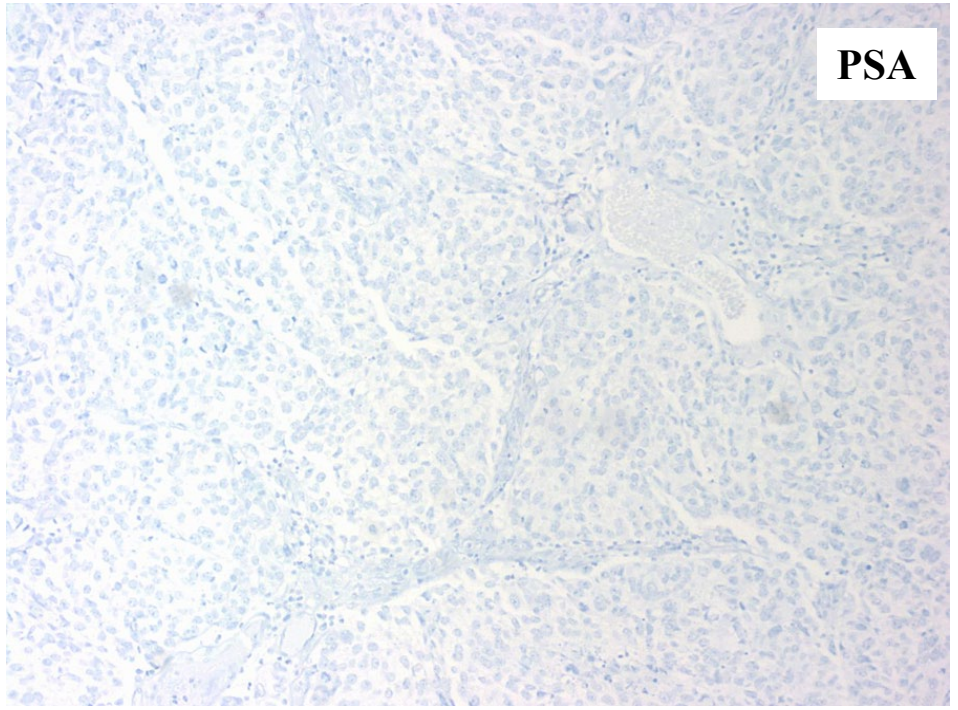


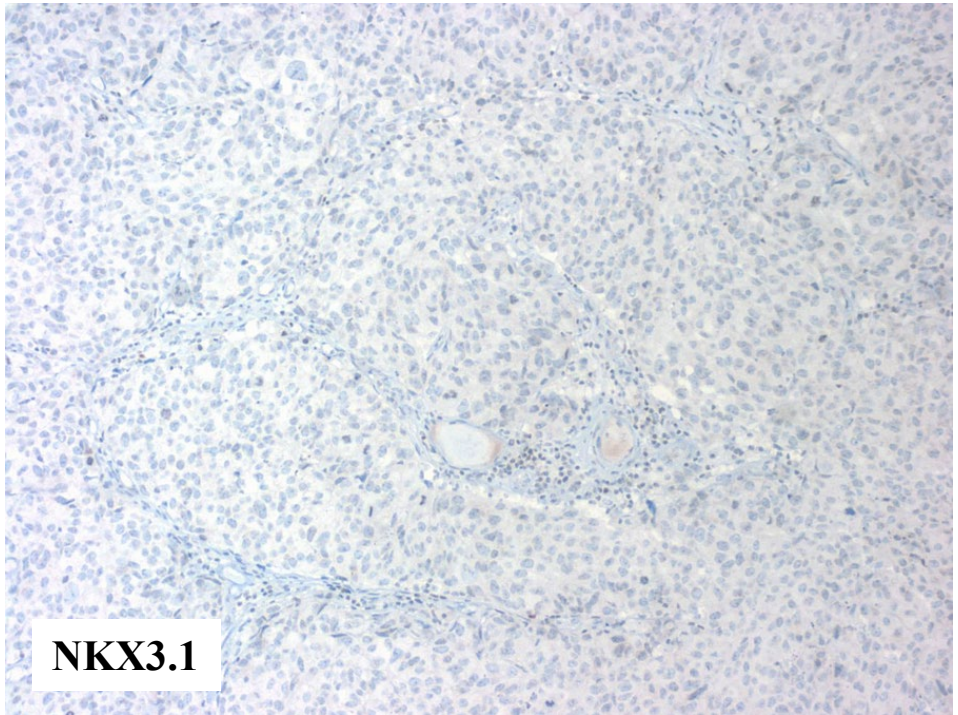
Prostatic adenocarcinoma extending to bladder

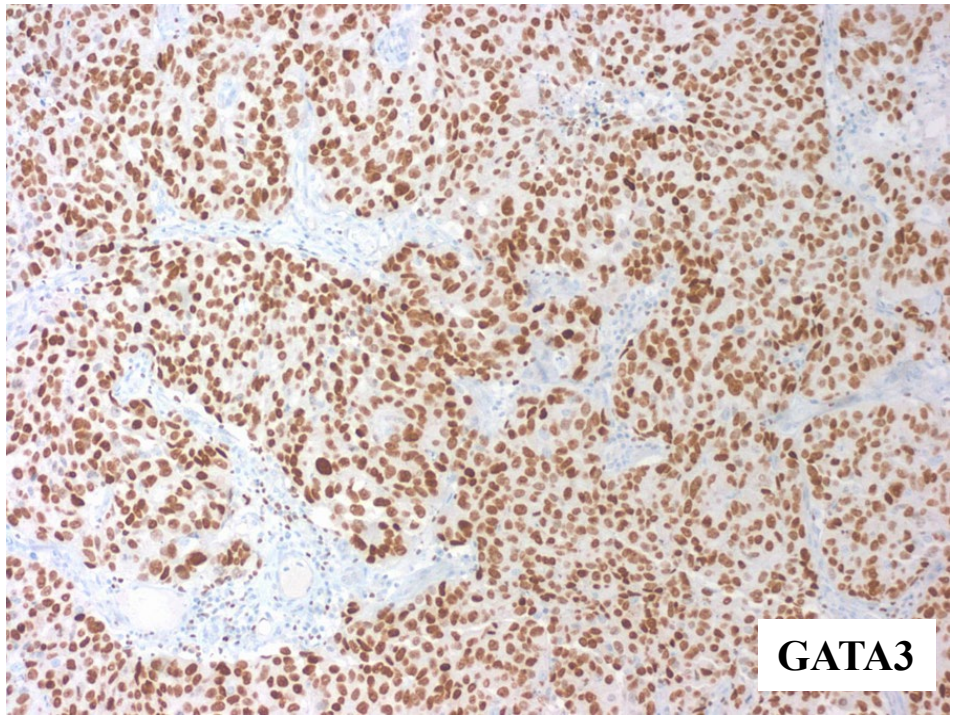


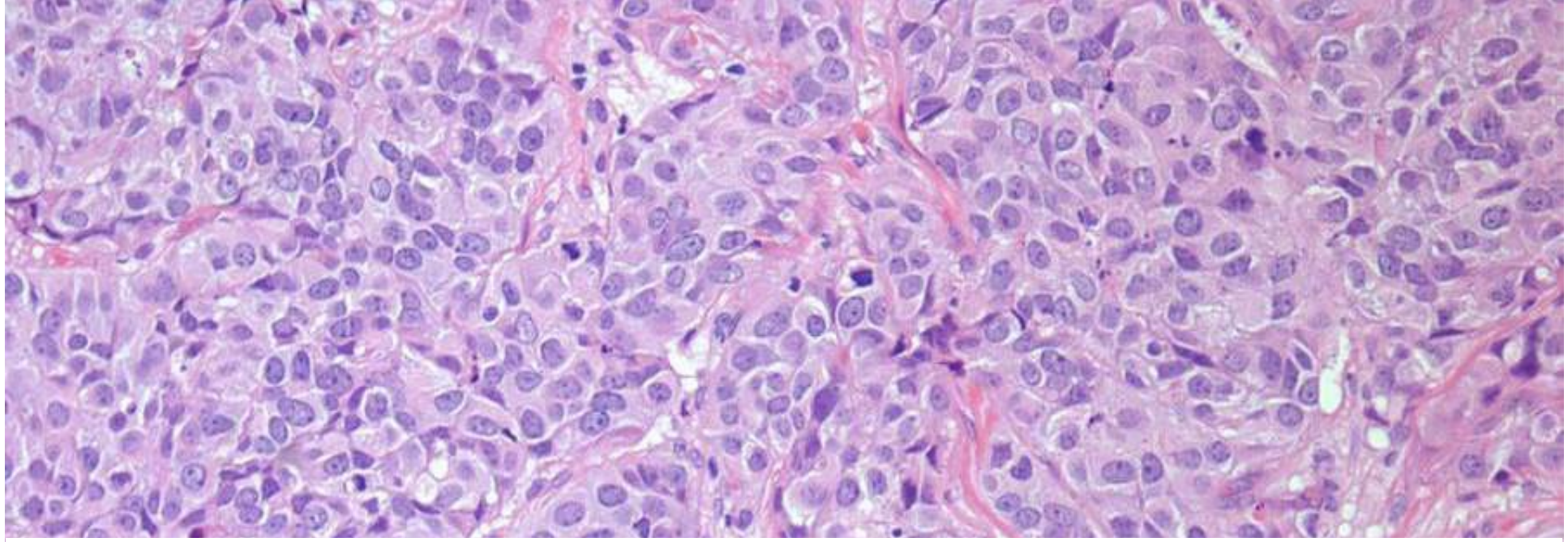

65 y/o male, TUR
Diagnosis?


CK7

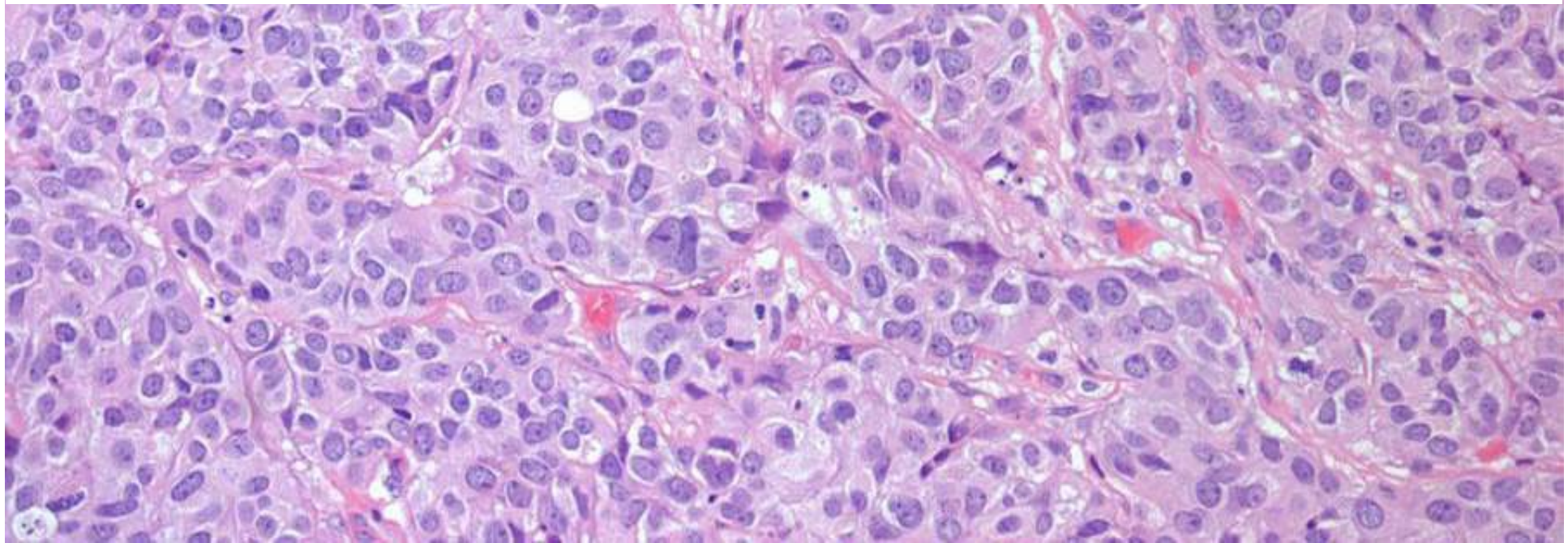

PSA


NKX3.1


GATA3

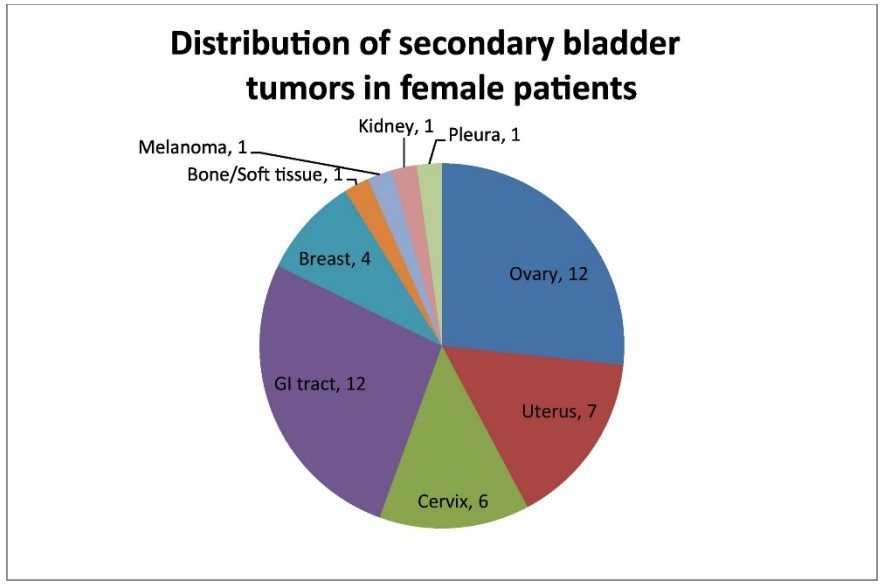


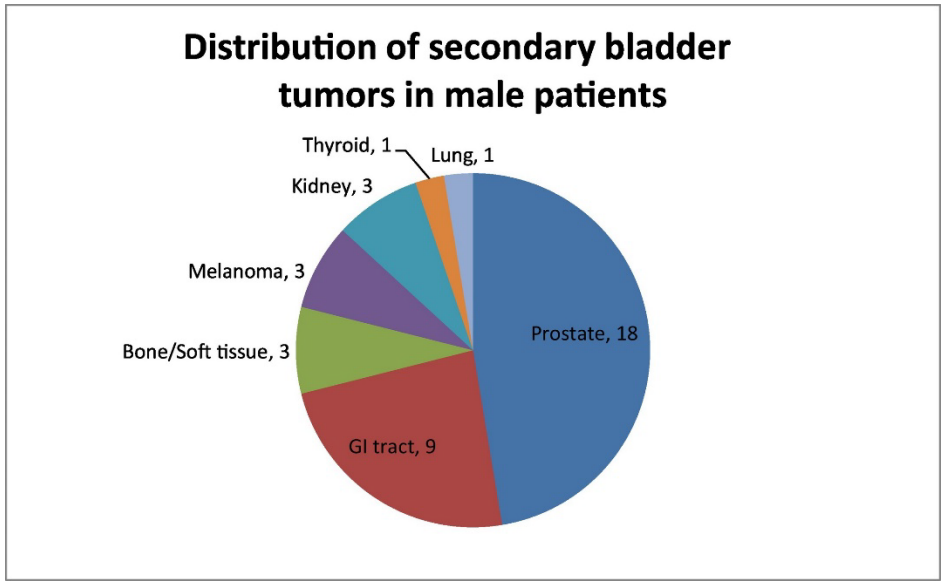
High-grade urothelial carcinoma

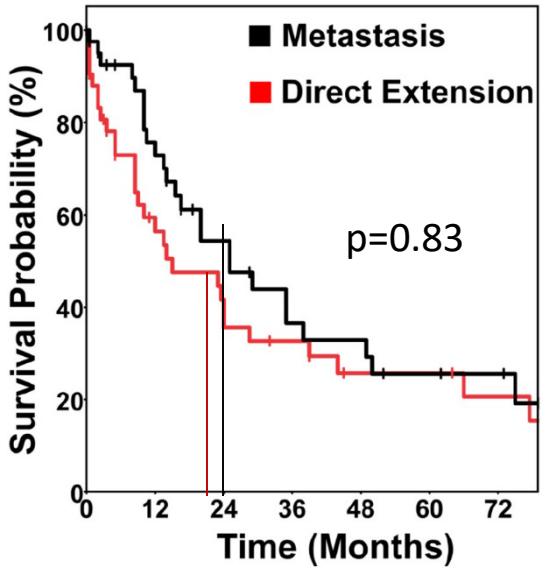


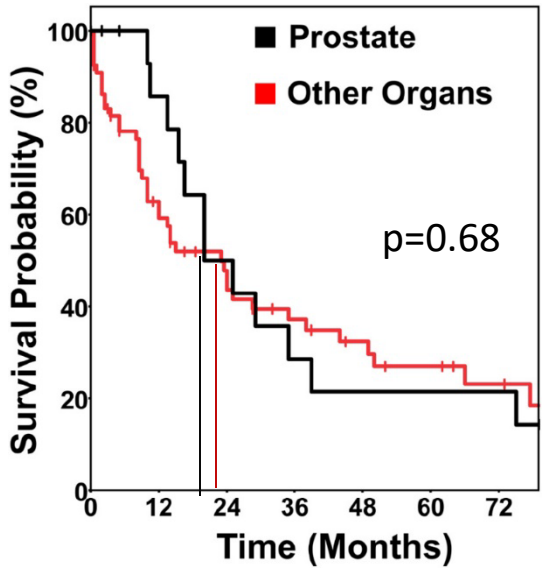
Secondary tumors of the bladder: A survival outcome study

Hamza A, Hwang MJ, Czerniak BA, Guo CC. Ann Diagn Pathol 2020



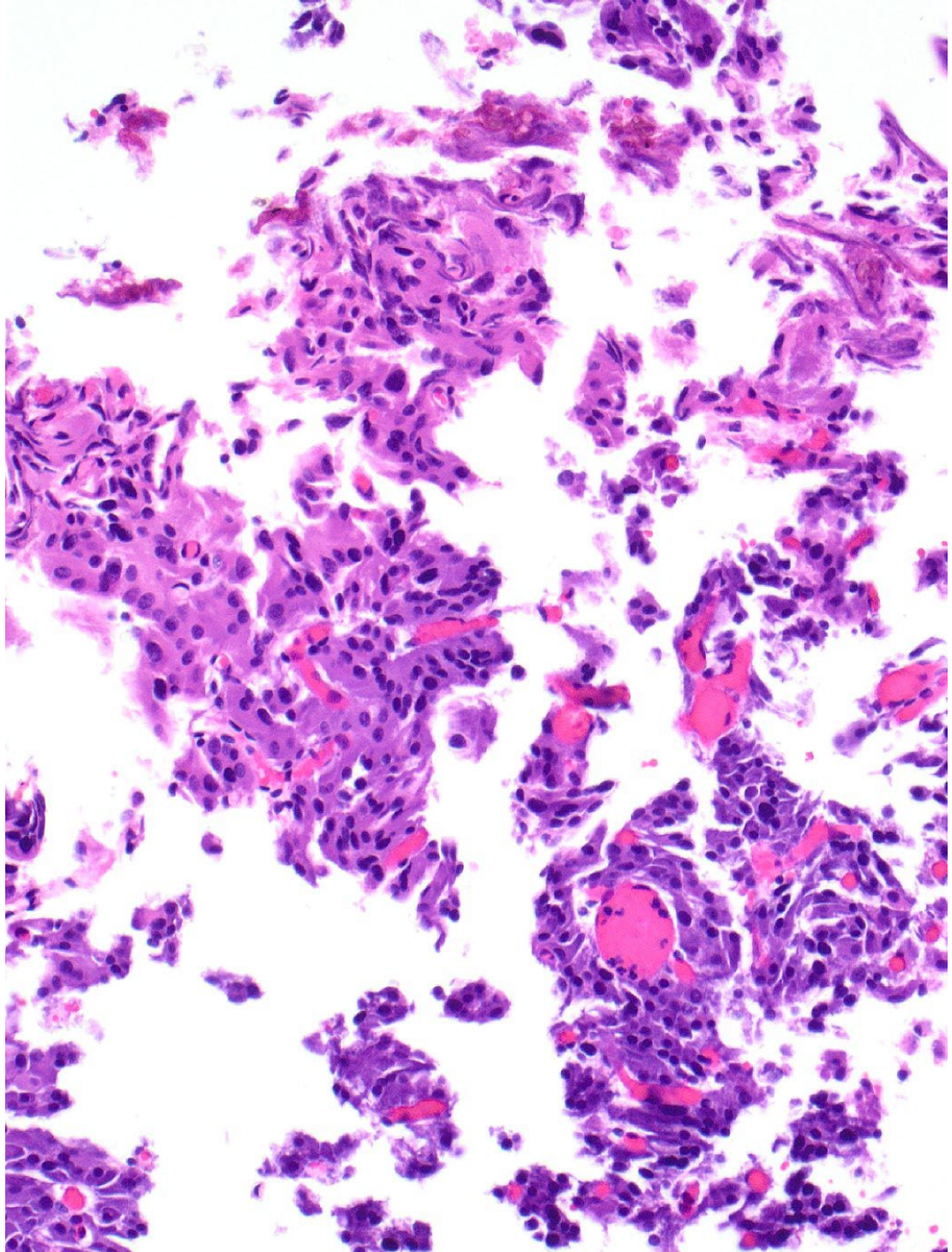


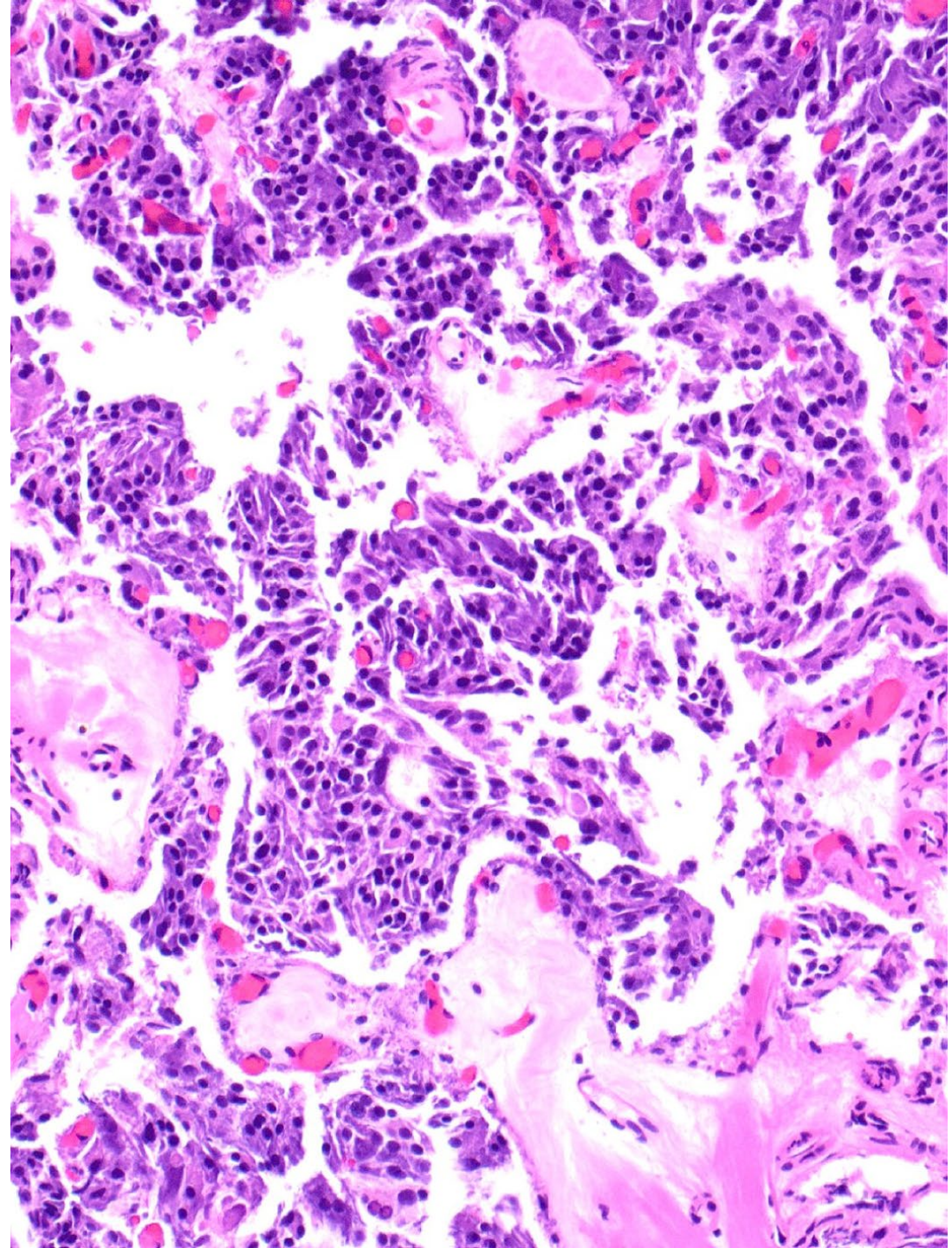


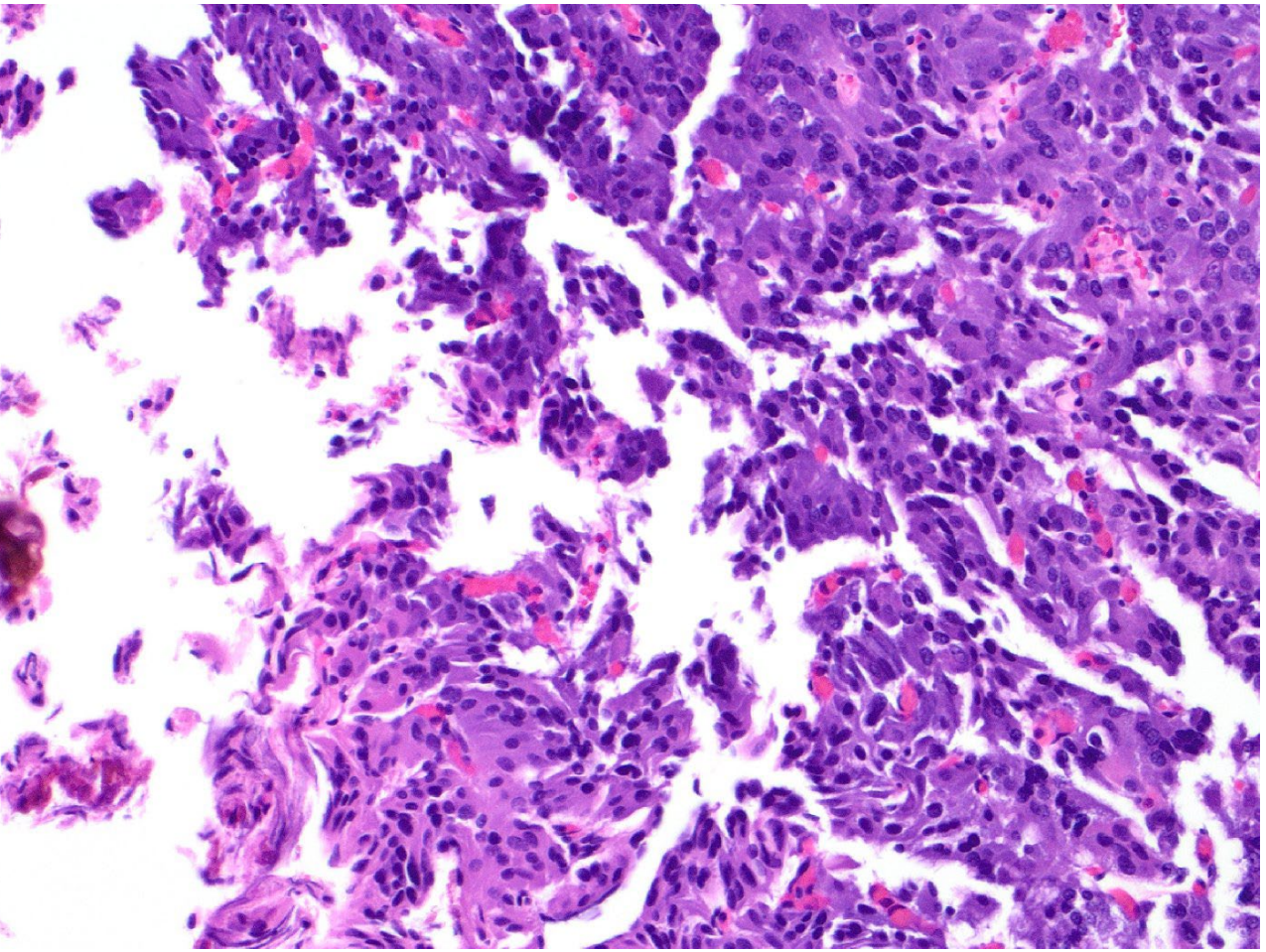


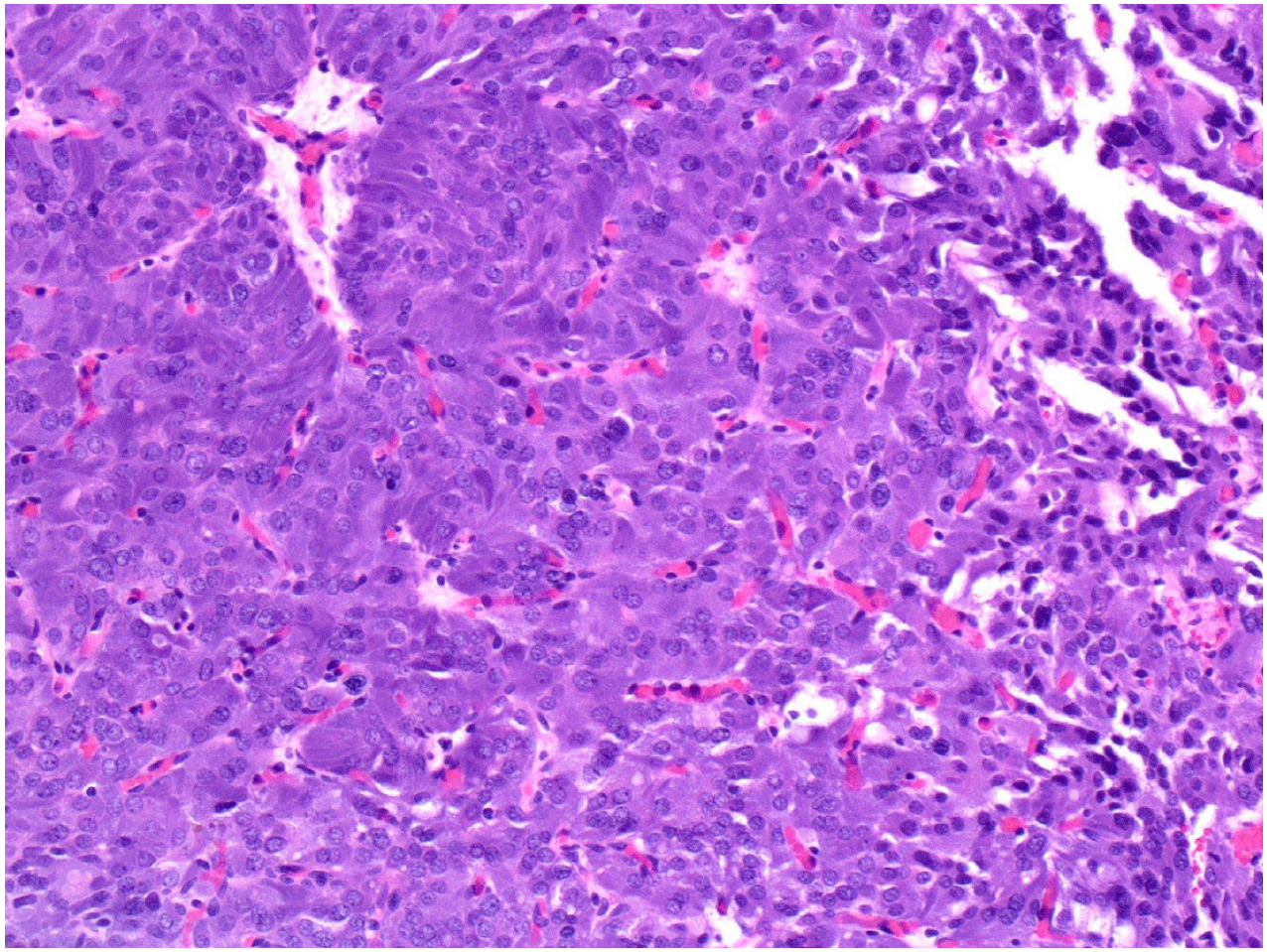
CASE #4

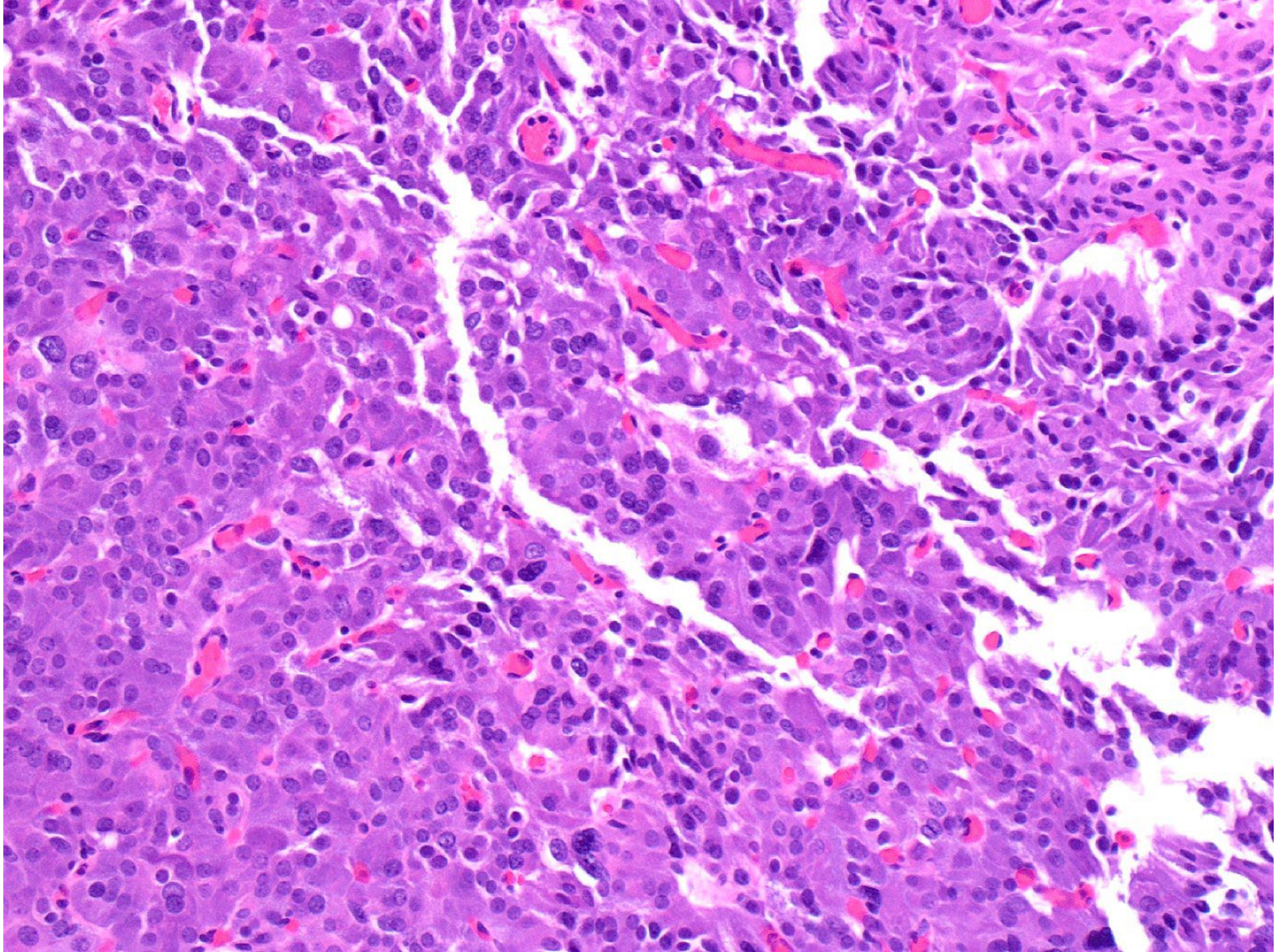
- 89 y/o female with bladder polyp





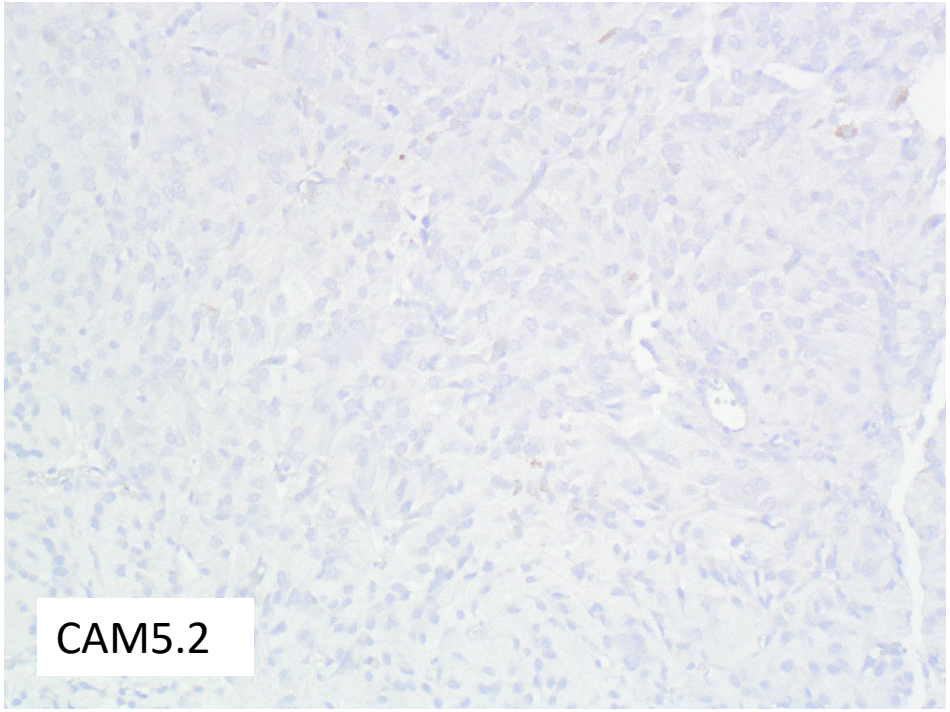


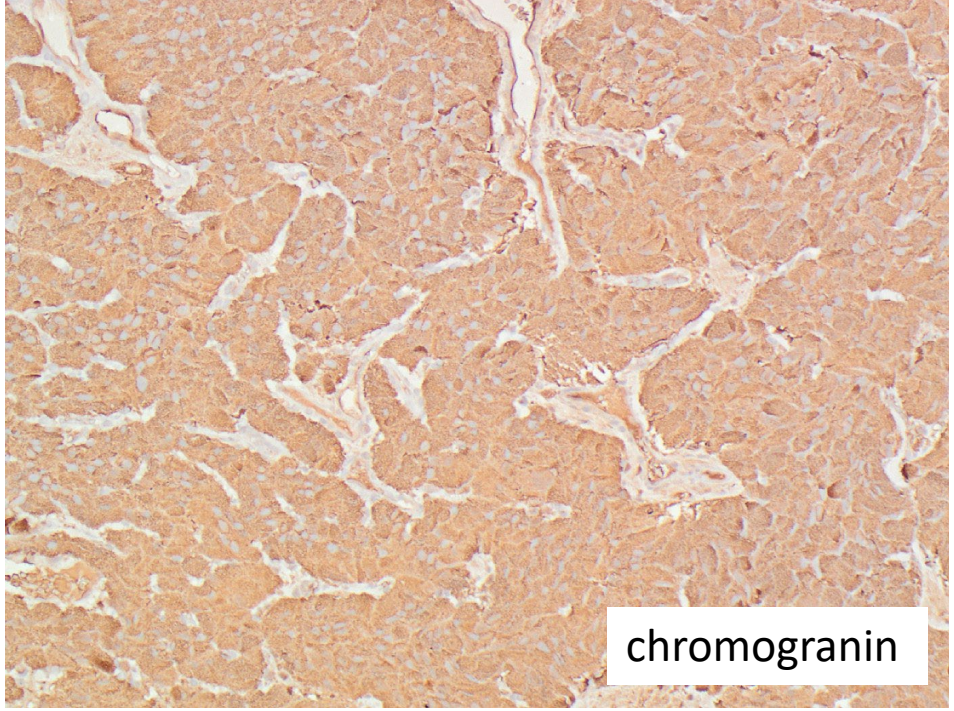


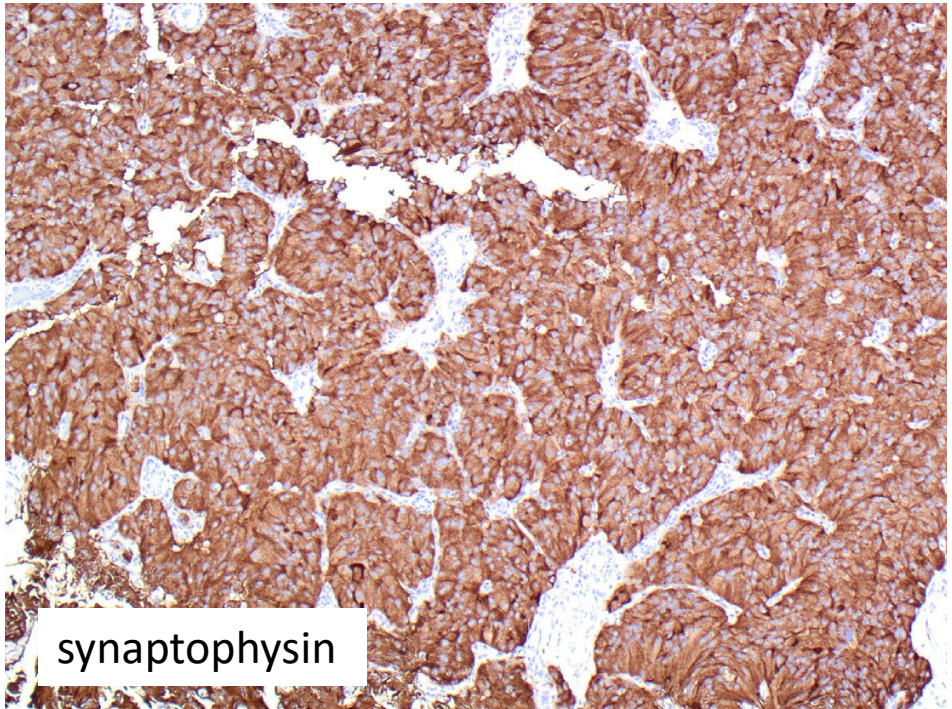


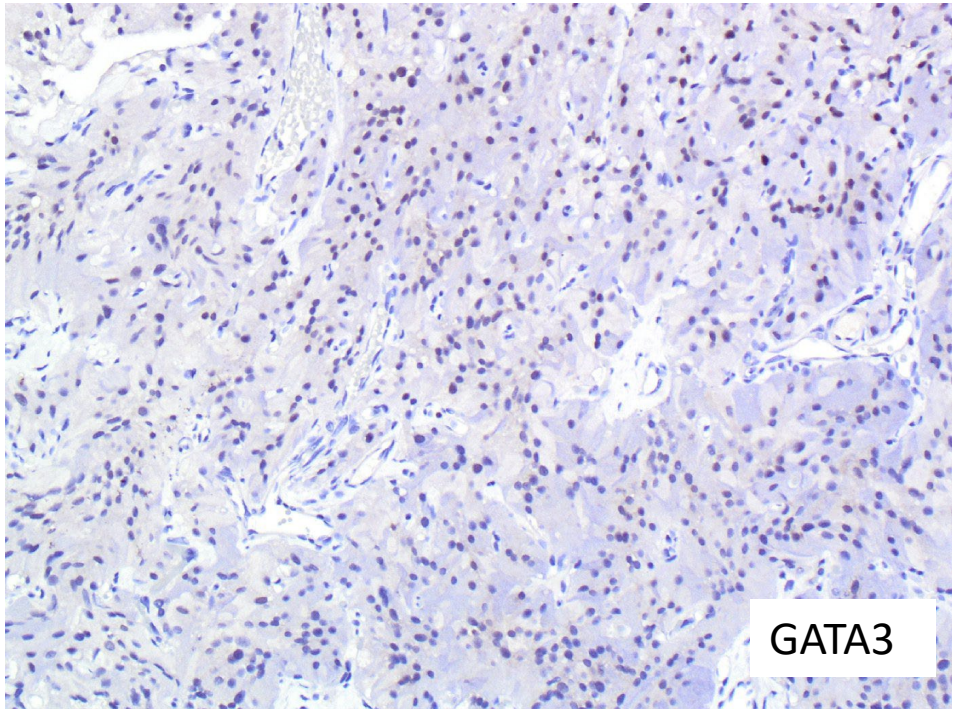
Differential Diagnosis?

- High-grade urothelial carcinoma
- Metastatic carcinoma
- Paraganglioma


CAM5.2


chromogranin


synaptophysin

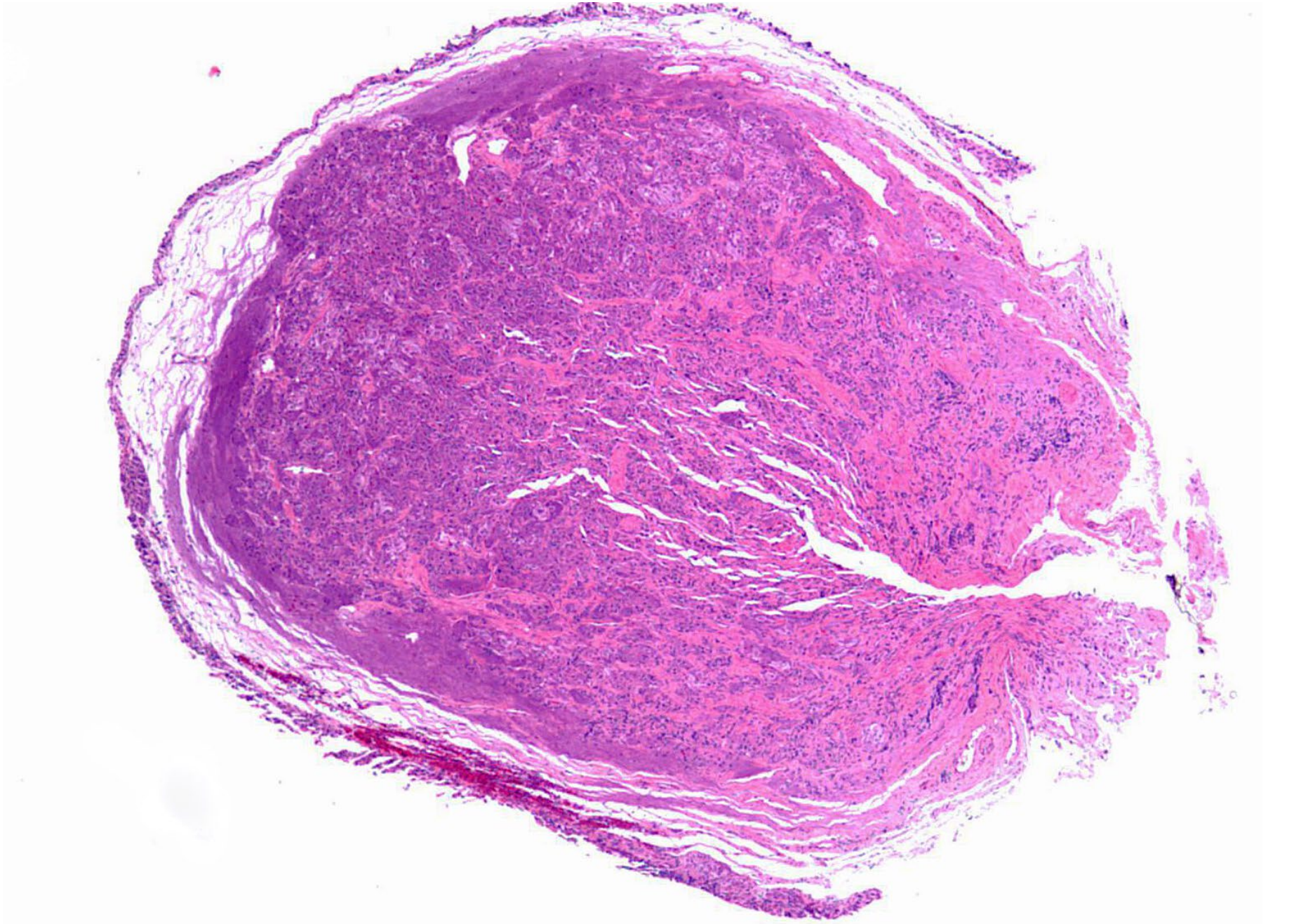

GATA3

Case #4

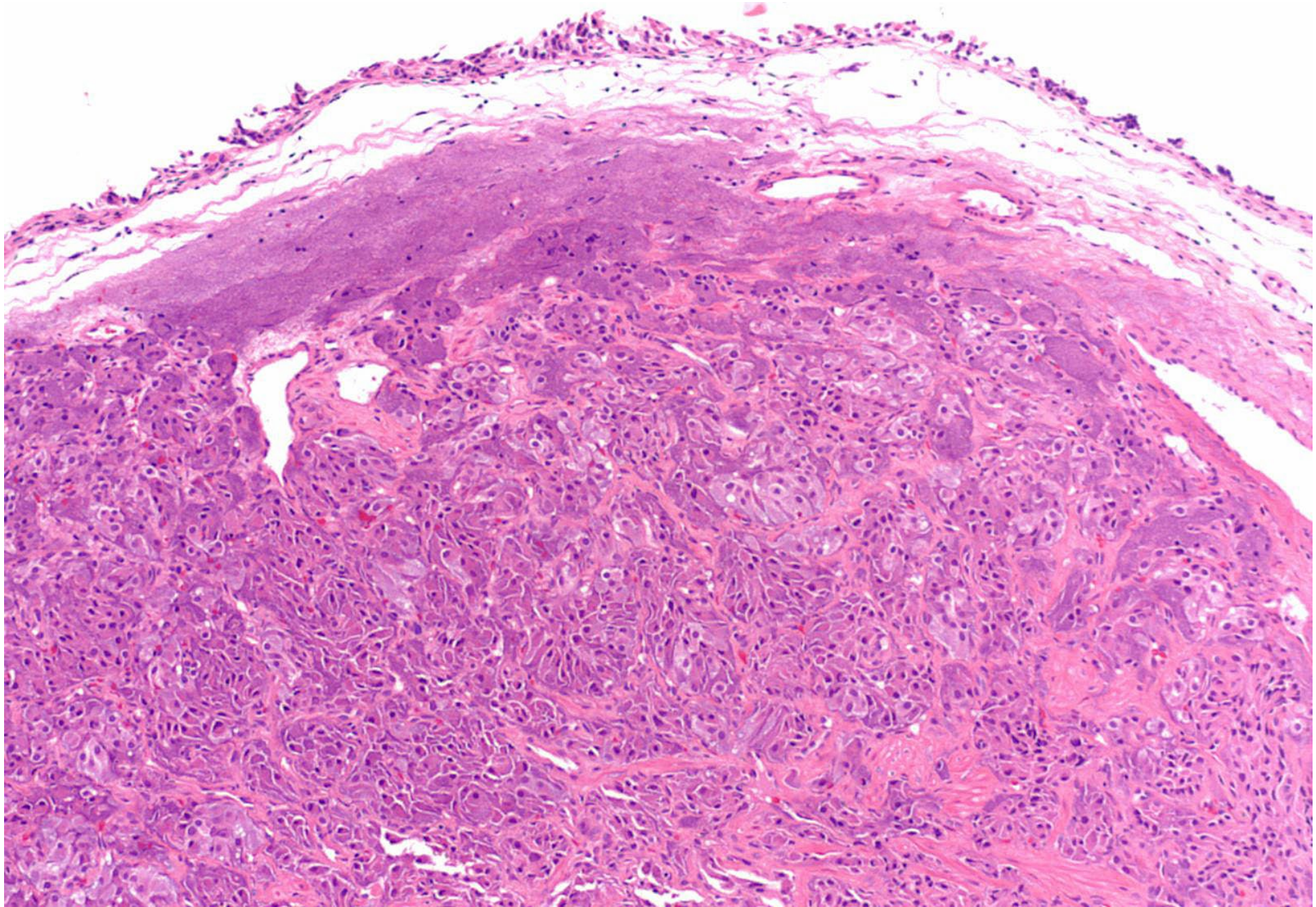
Diagnosis

Paraganglioma

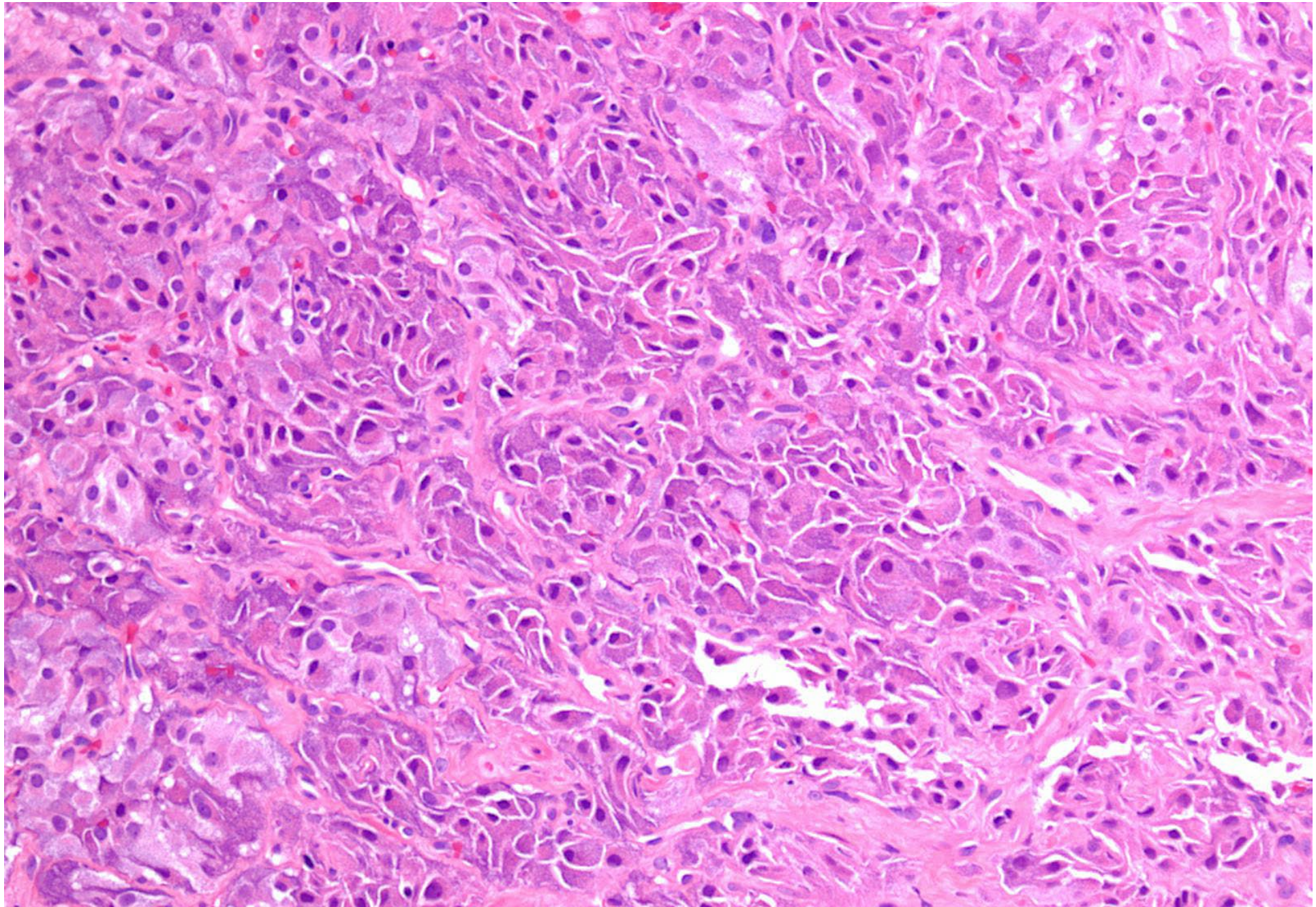
Bladder paraganglioma

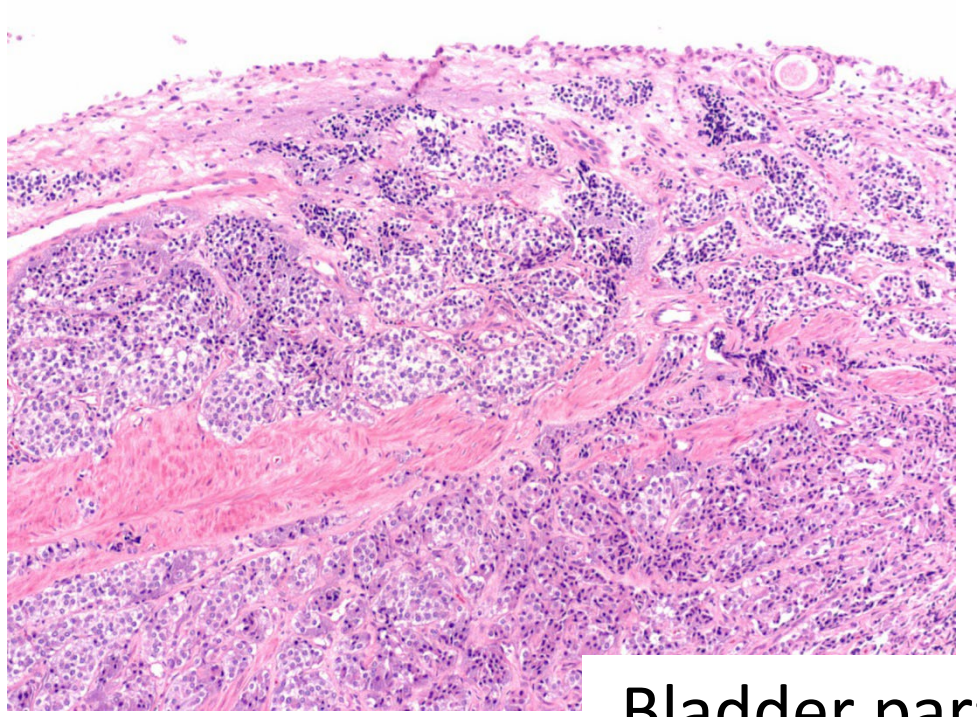


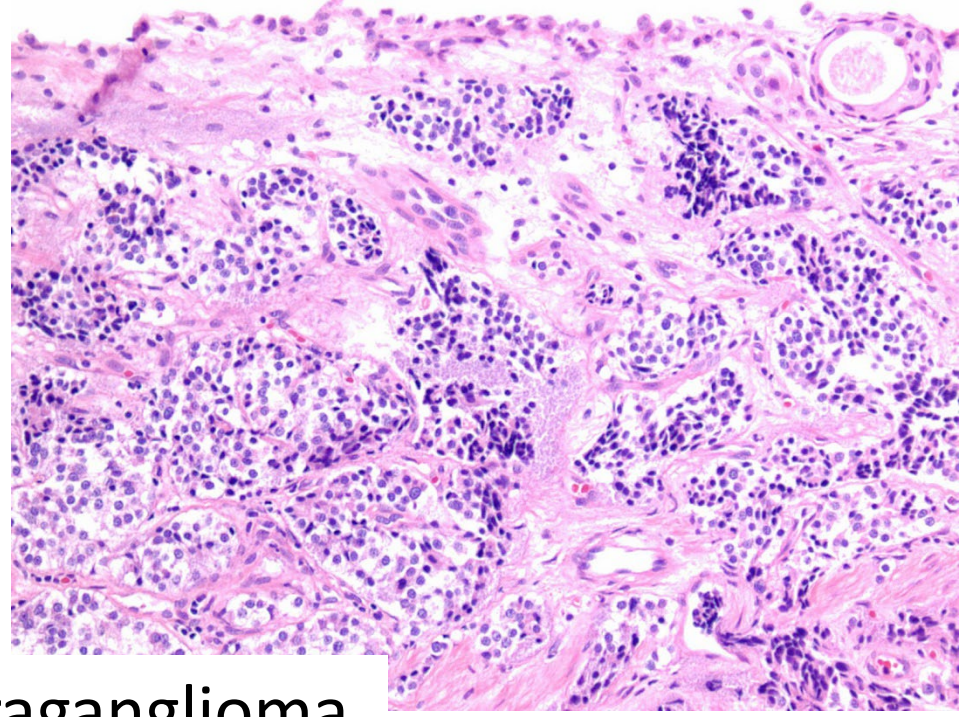
Bladder paraganglioma



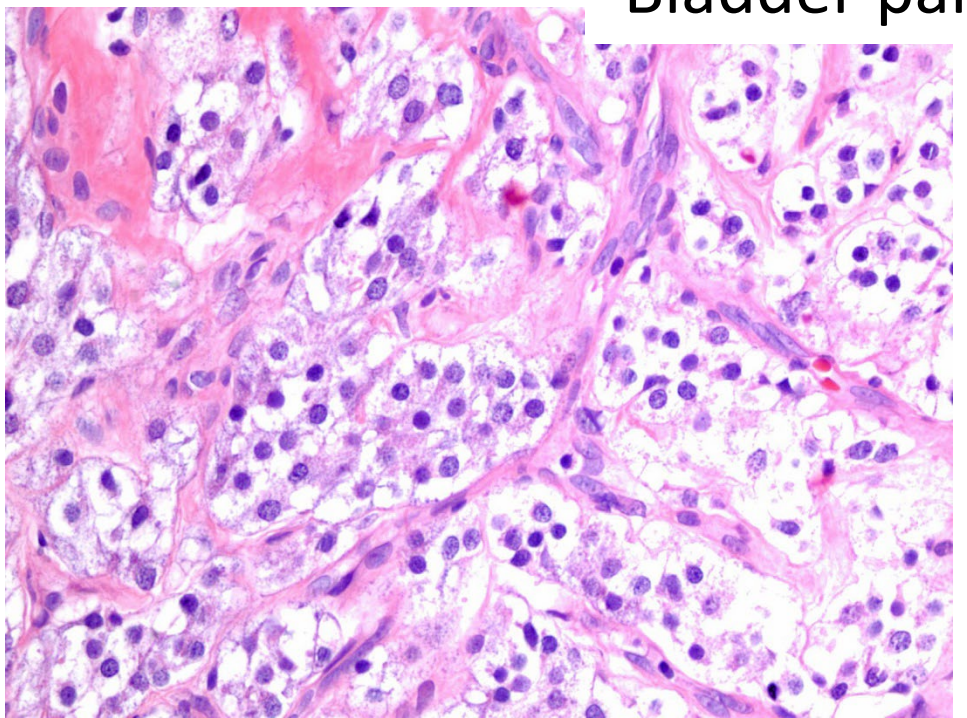
Bladder paraganglioma

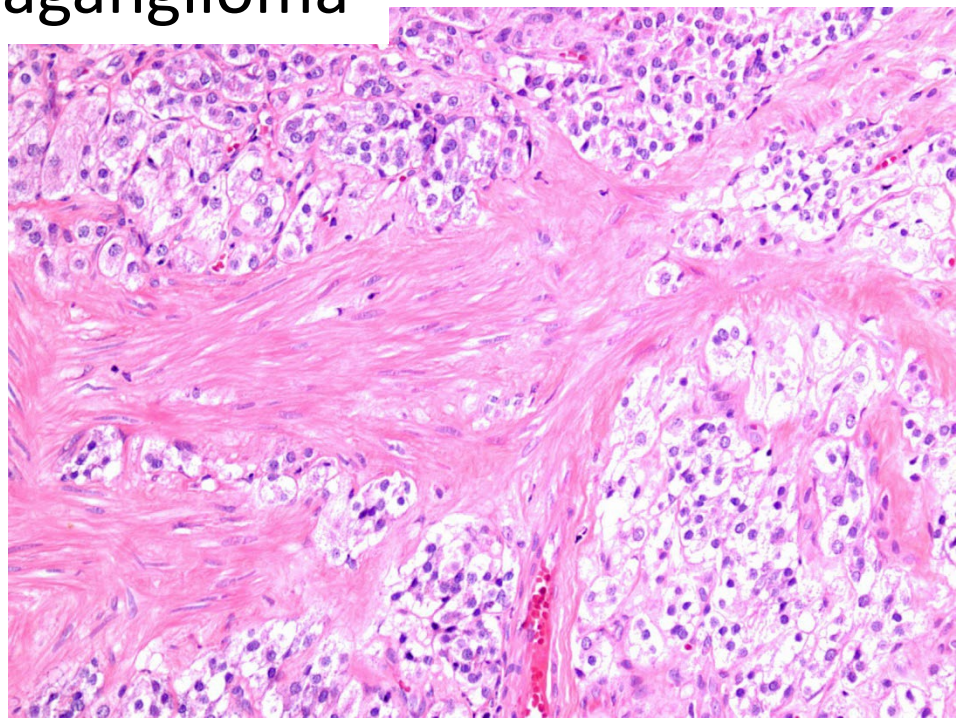




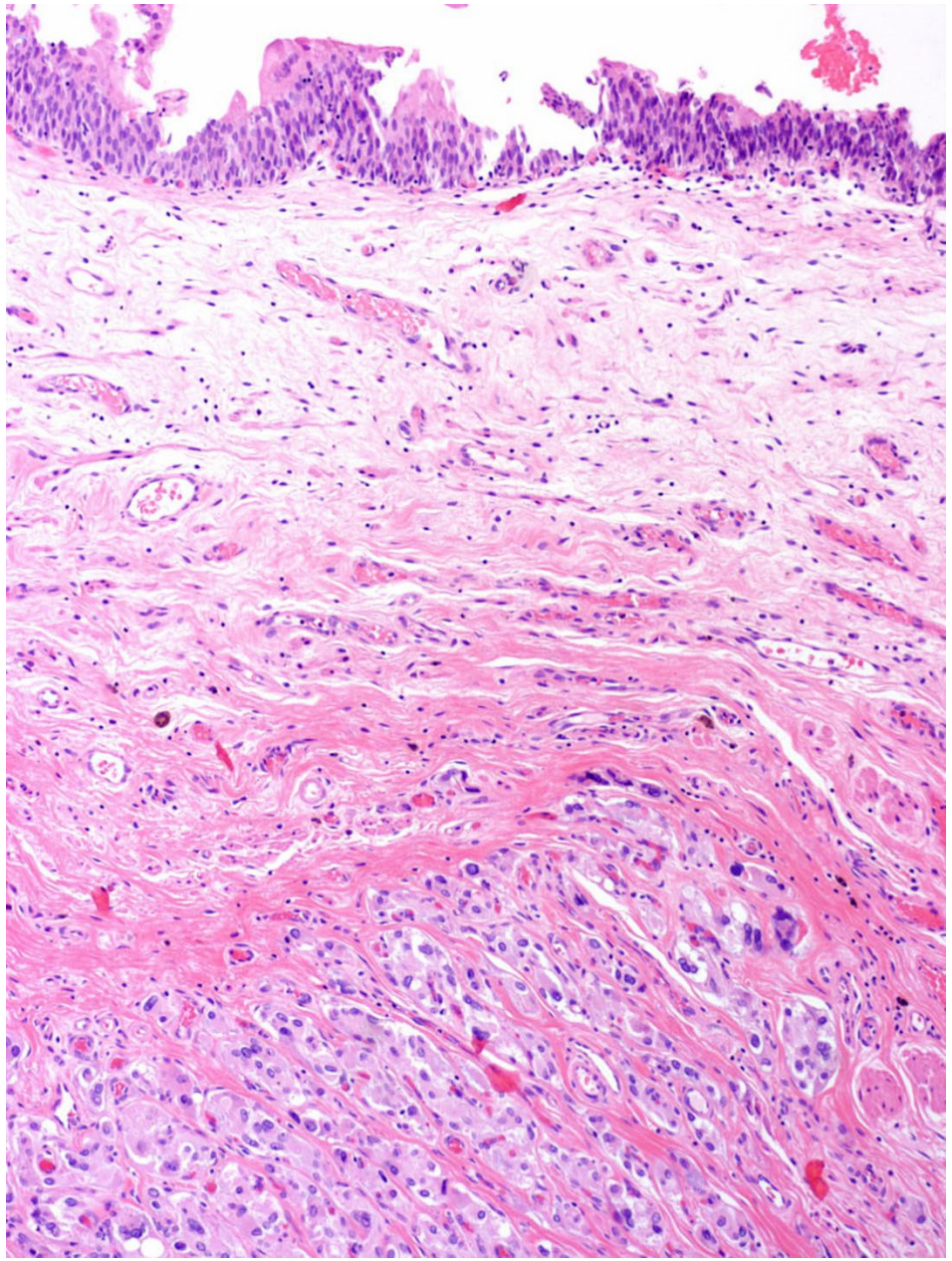


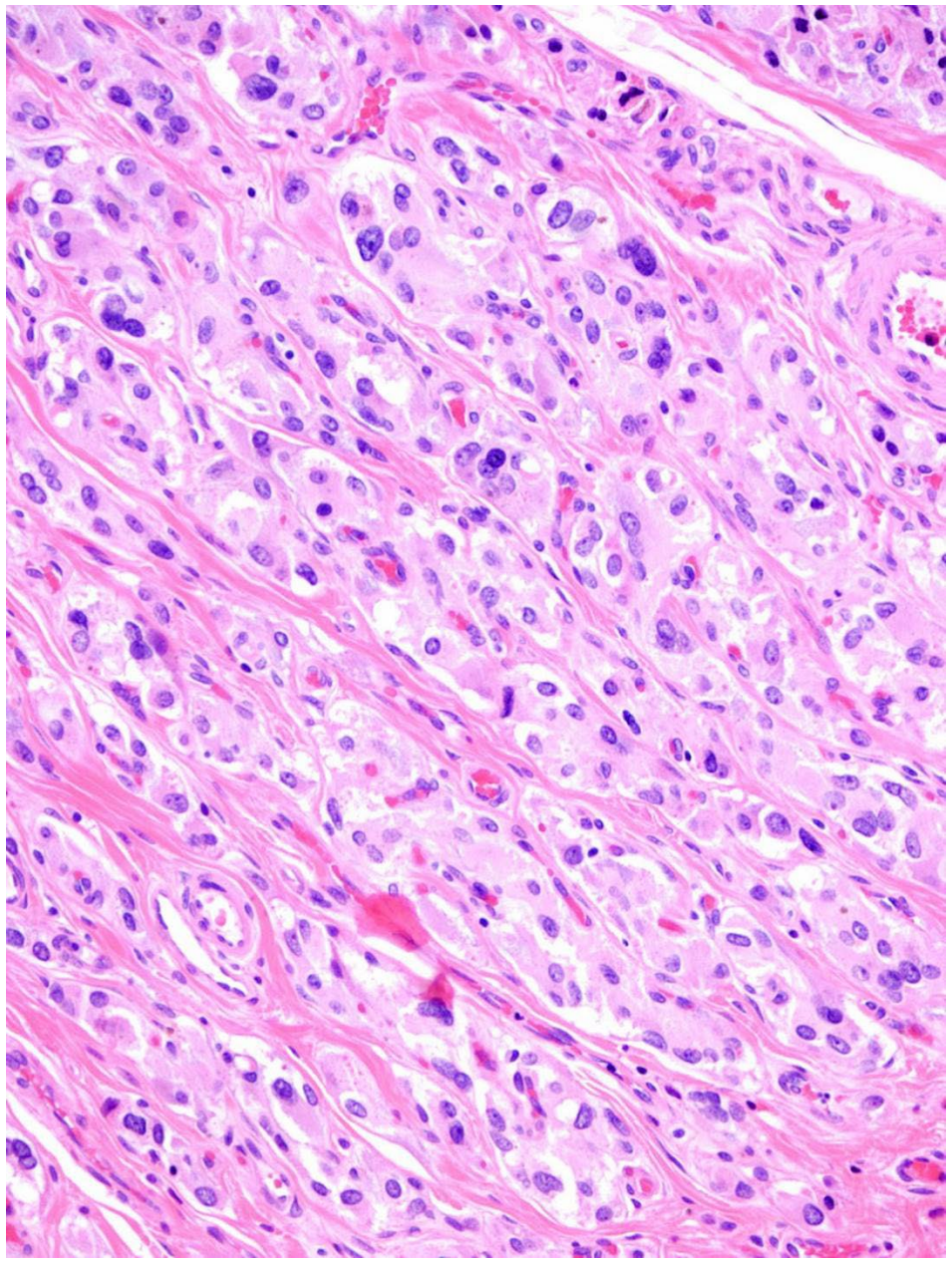
Bladder paraganglioma





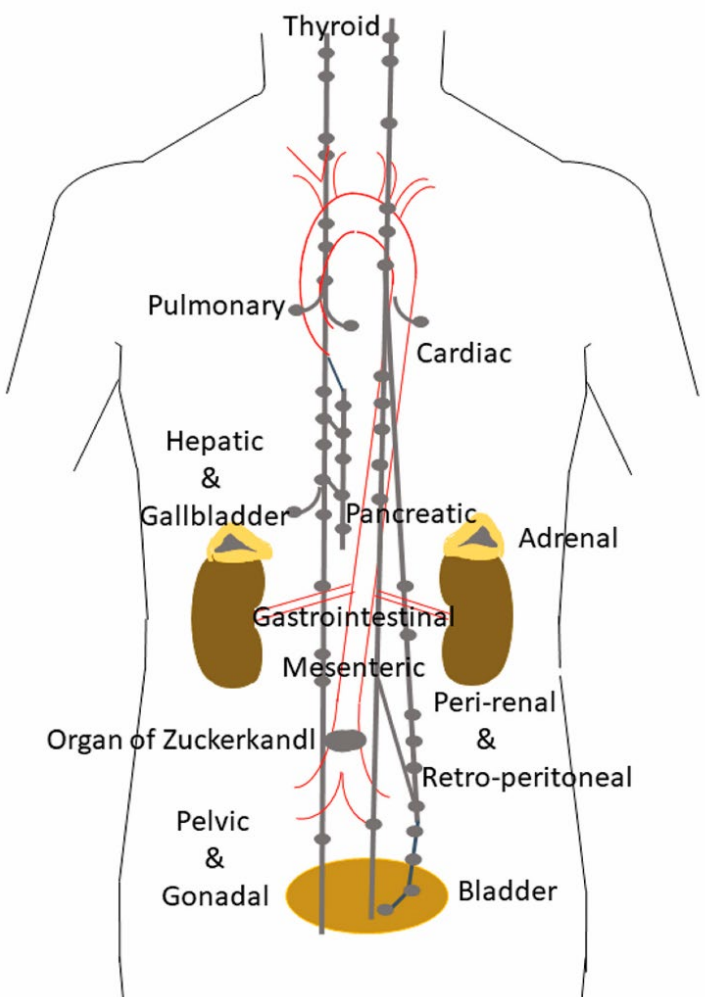
Bladder paraganglioma





Bladder Paraganglioma

- Abdominal sites include urinary bladder tumors that originate in organ of Zuckerkandl
- 0.06% of bladder tumors; 6% of extra-adrenal pheochromocytomas
- GU tract: **urinary bladder** is primary site (~ 80%), followed by urethra, pelvis, ureter



Location of normal paraganglia in neck, thorax, abdomen

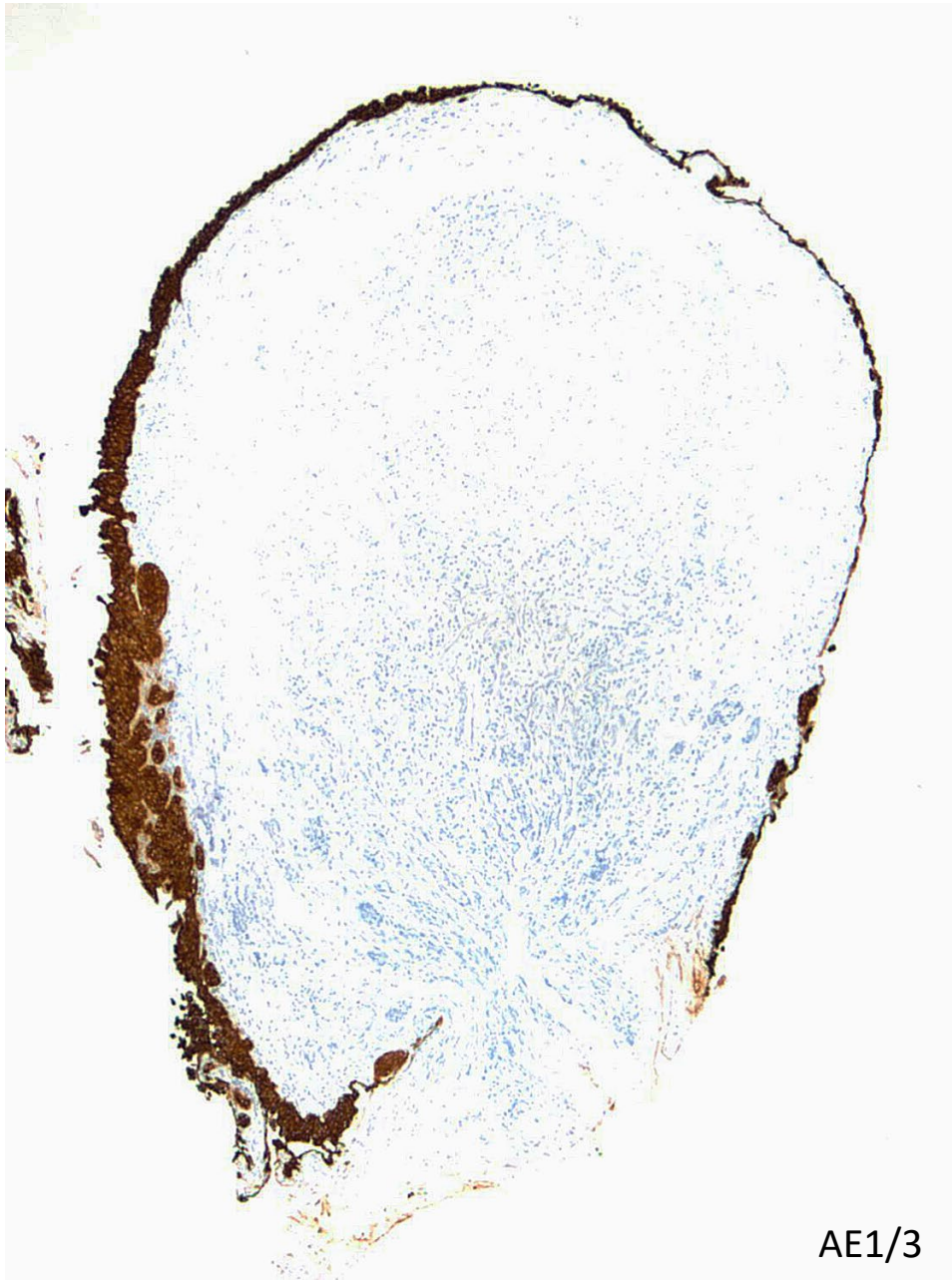
Asa et al. J Clin Med. 2018

Bladder Paraganglioma

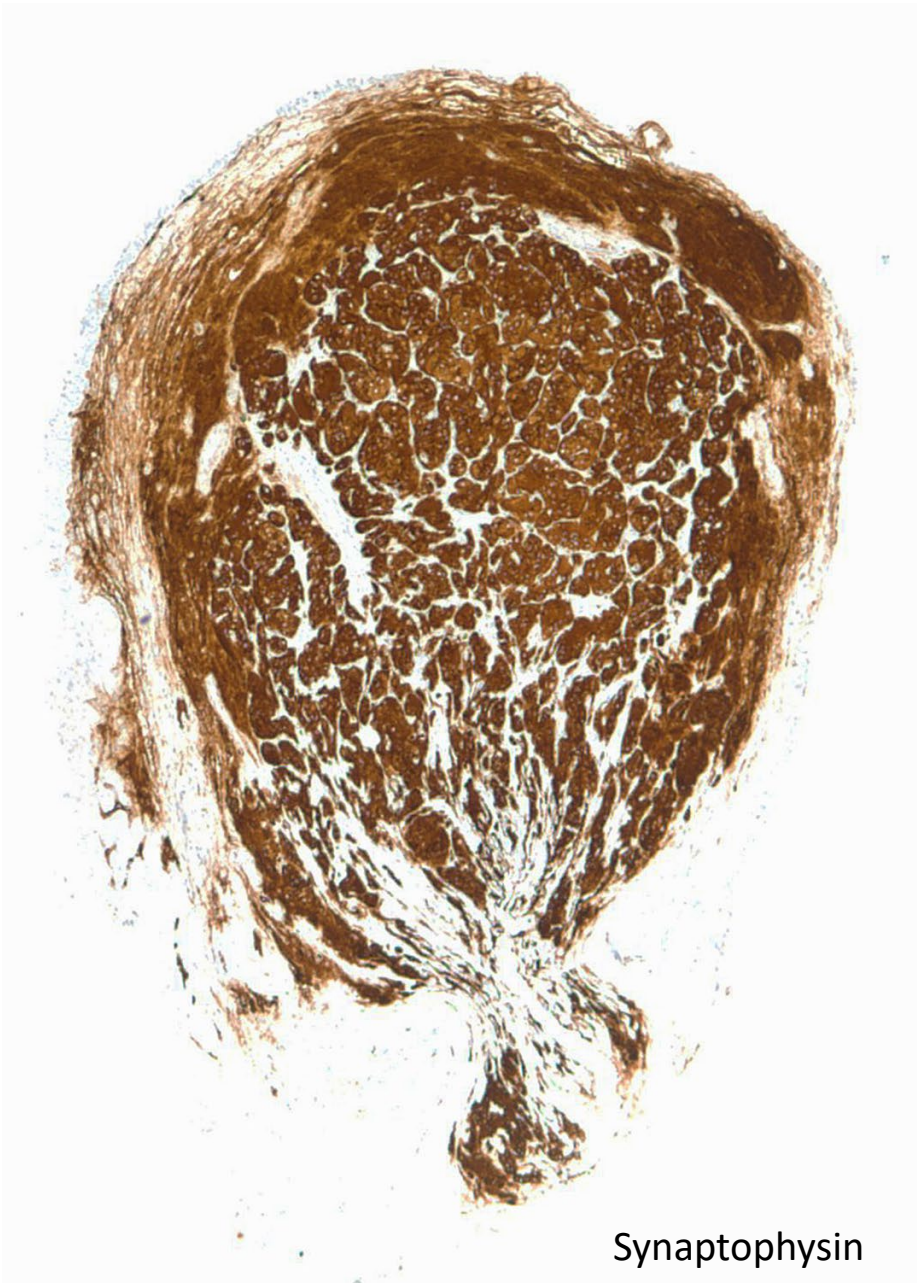
- Classified as functional or nonfunctional
- Present with intermittent hypertensive attacks, headaches, palpitations, micturition, and fainting
- ~10-15% are non-functional; 10% have hormonal activities that do not manifest clinically
- Treated surgically (~3% succumb to their cancer)
- Likelihood of aggressive behavior depends on size, and mutation status
- Tumors with **SDHB** mutations have increased metastatic potential

Asa et al. J Clin Med. 2018

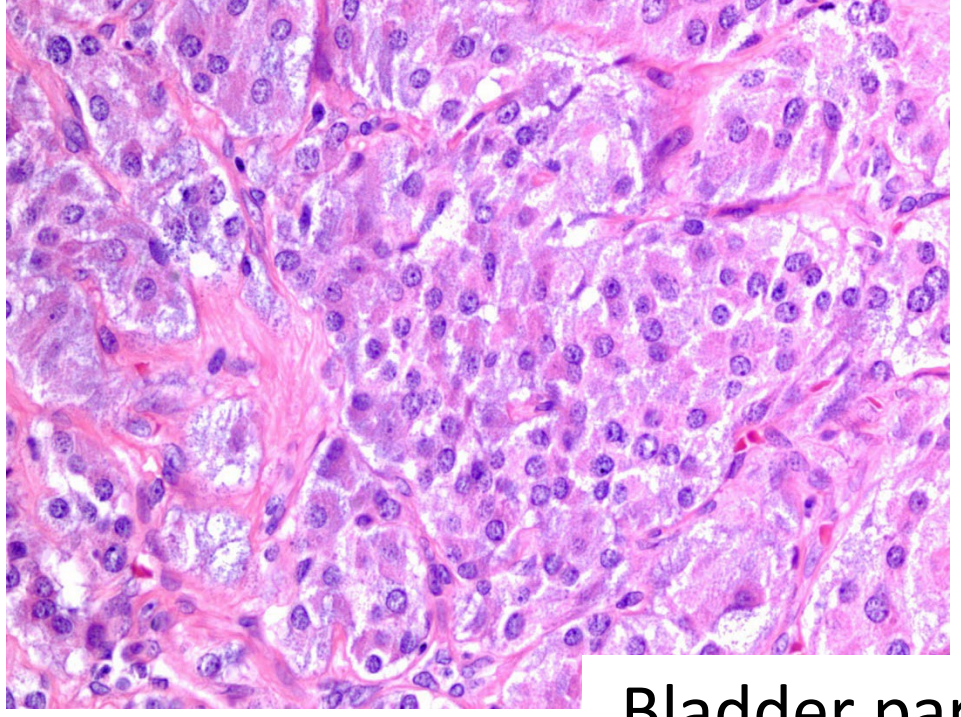
Bladder paraganglioma

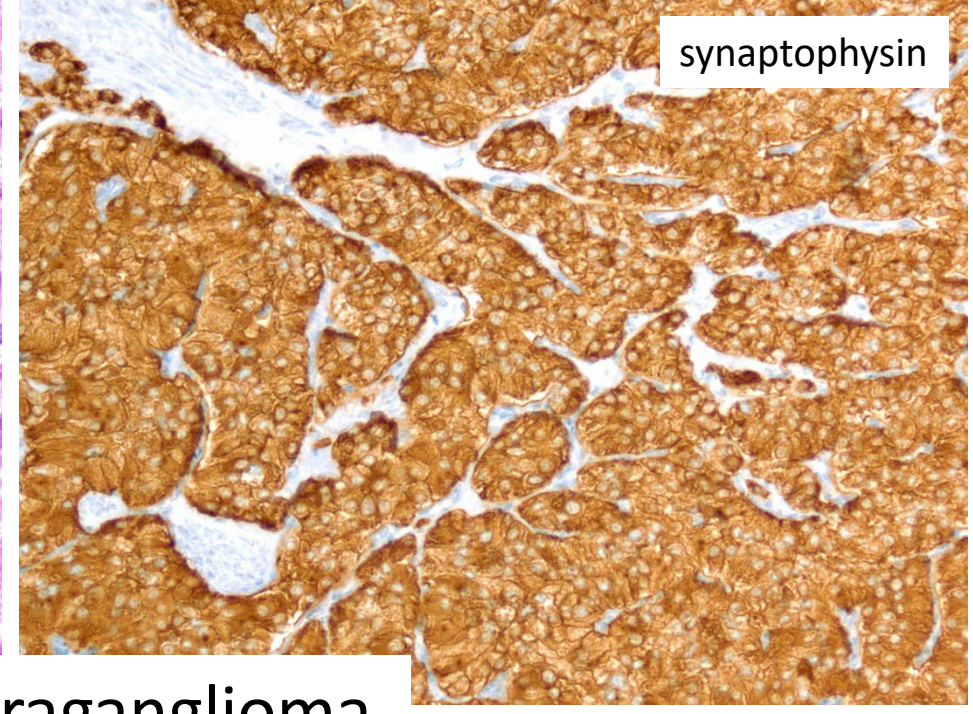


AE1/3

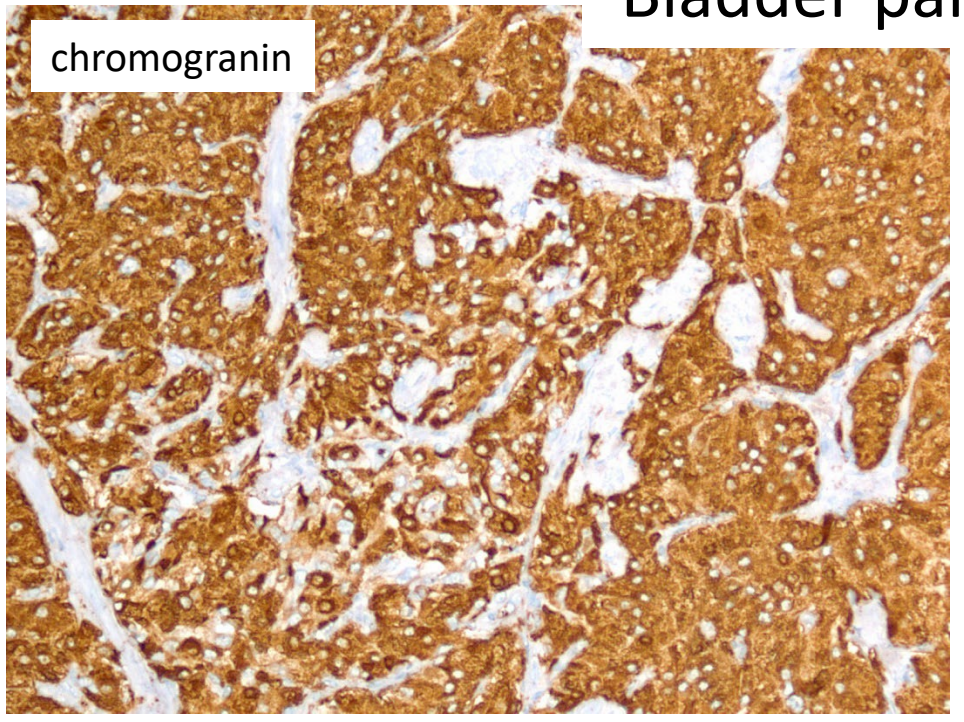


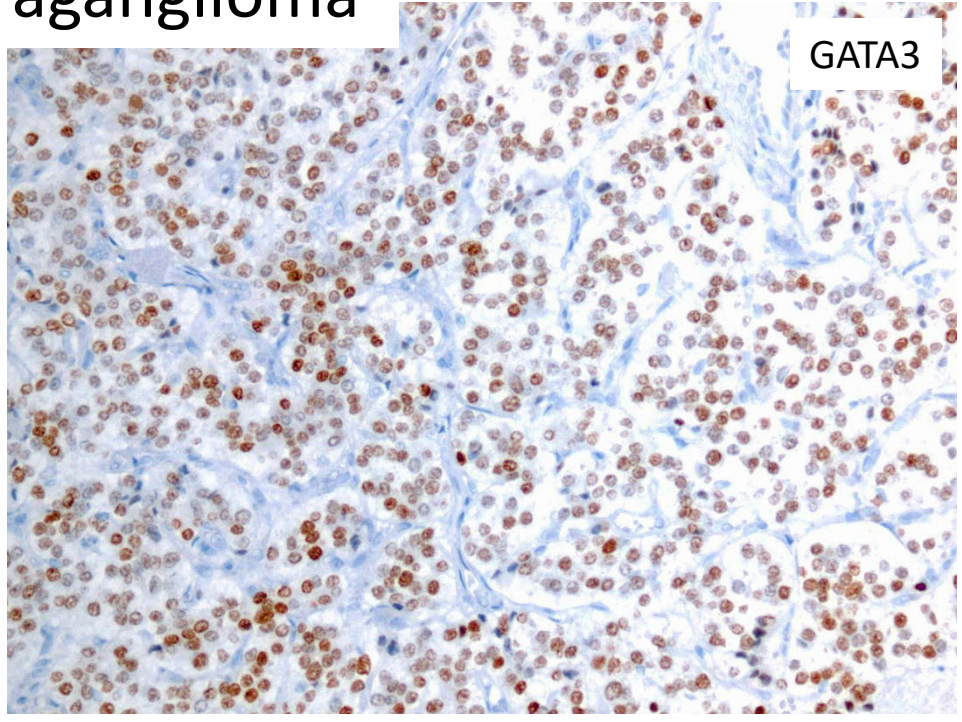
Synaptophysin





Bladder paraganglioma





Bladder Paraganglioma

Immunohistochemistry

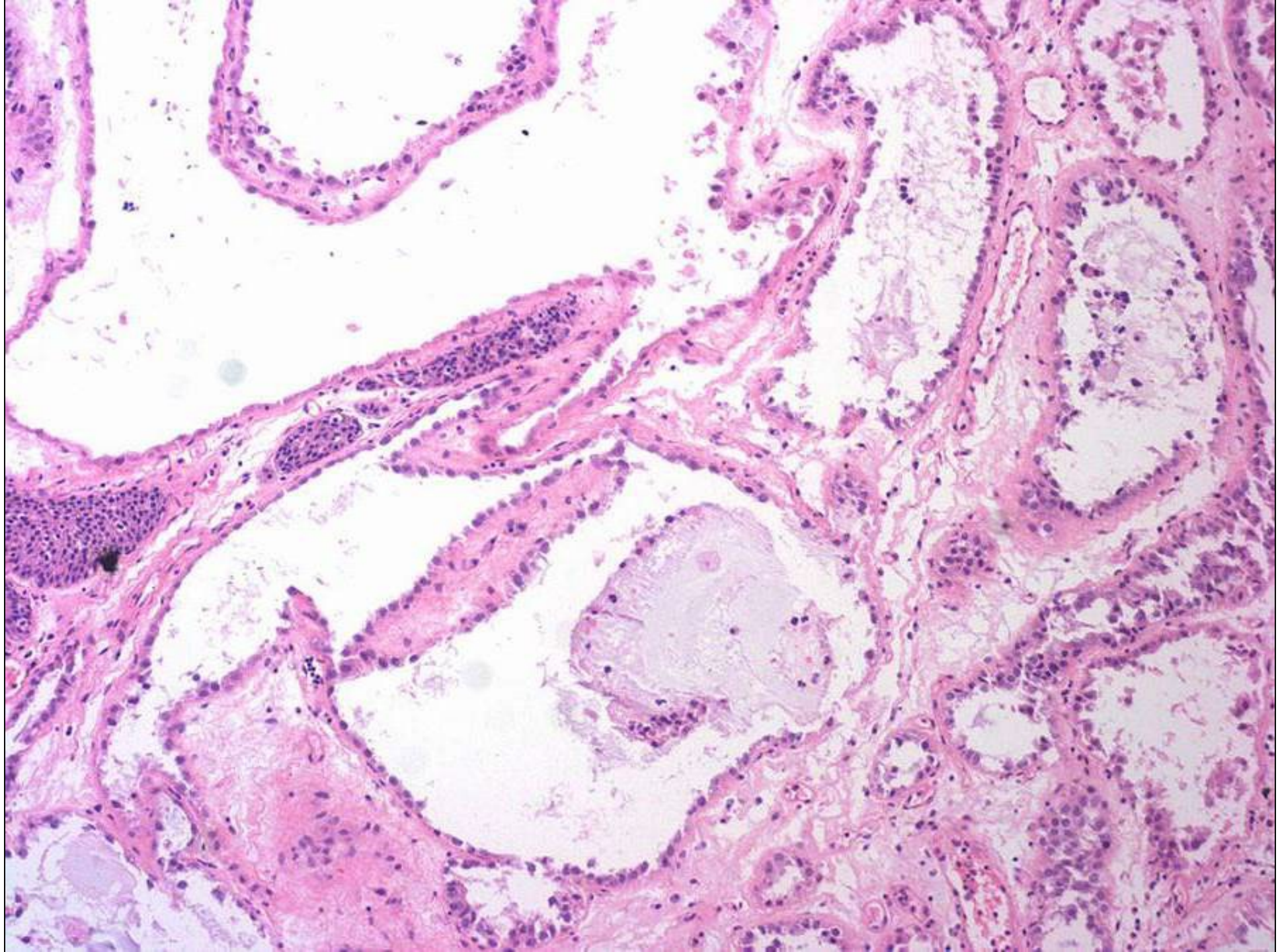
- NSE, chromogranin, synaptophysin +
- Pan cytokeratin, CAM5.2, CK7, EMA –
- S-100 highlighted sustentacular cells

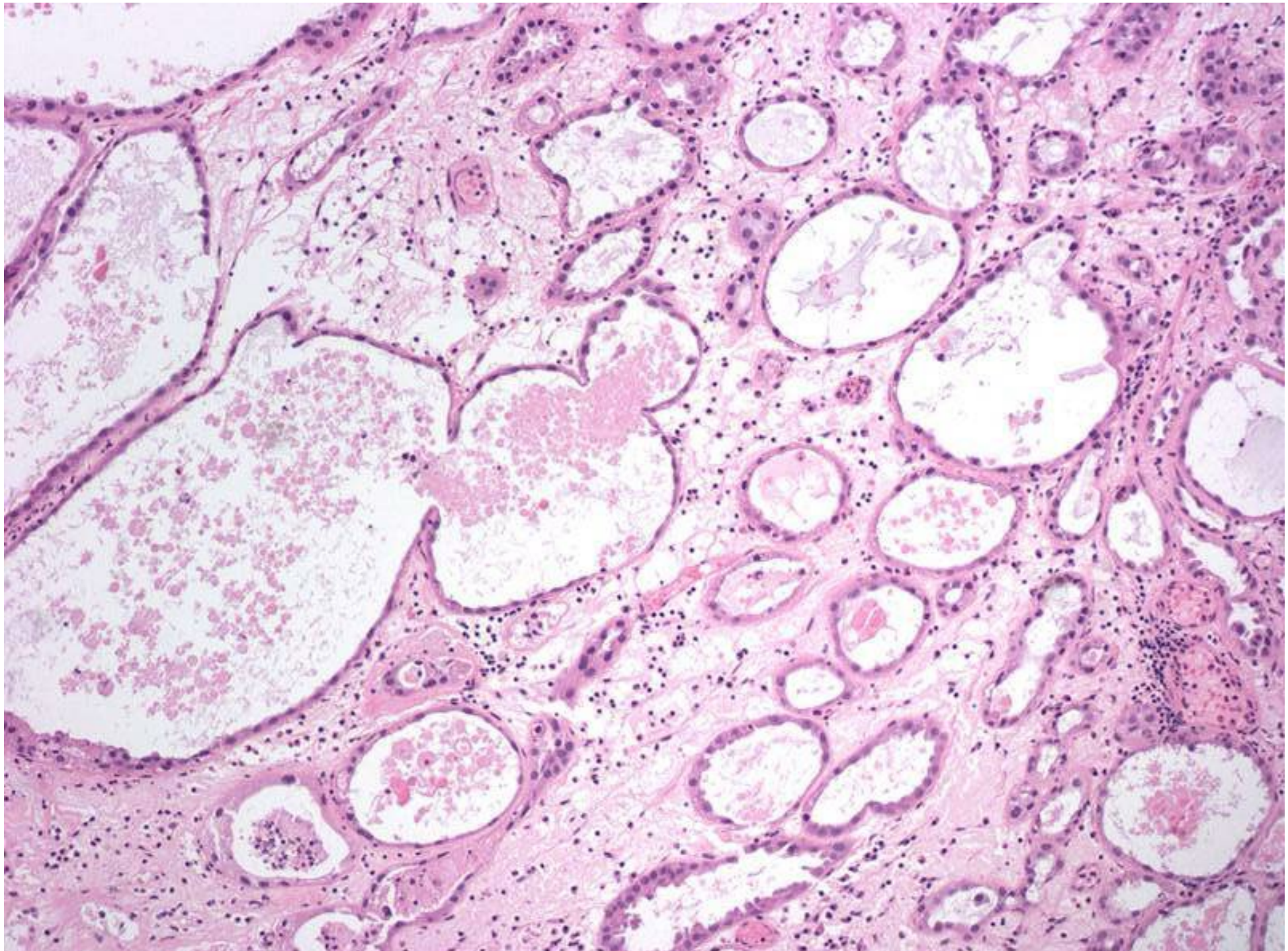
- **GATA3 +** (80% of cases)

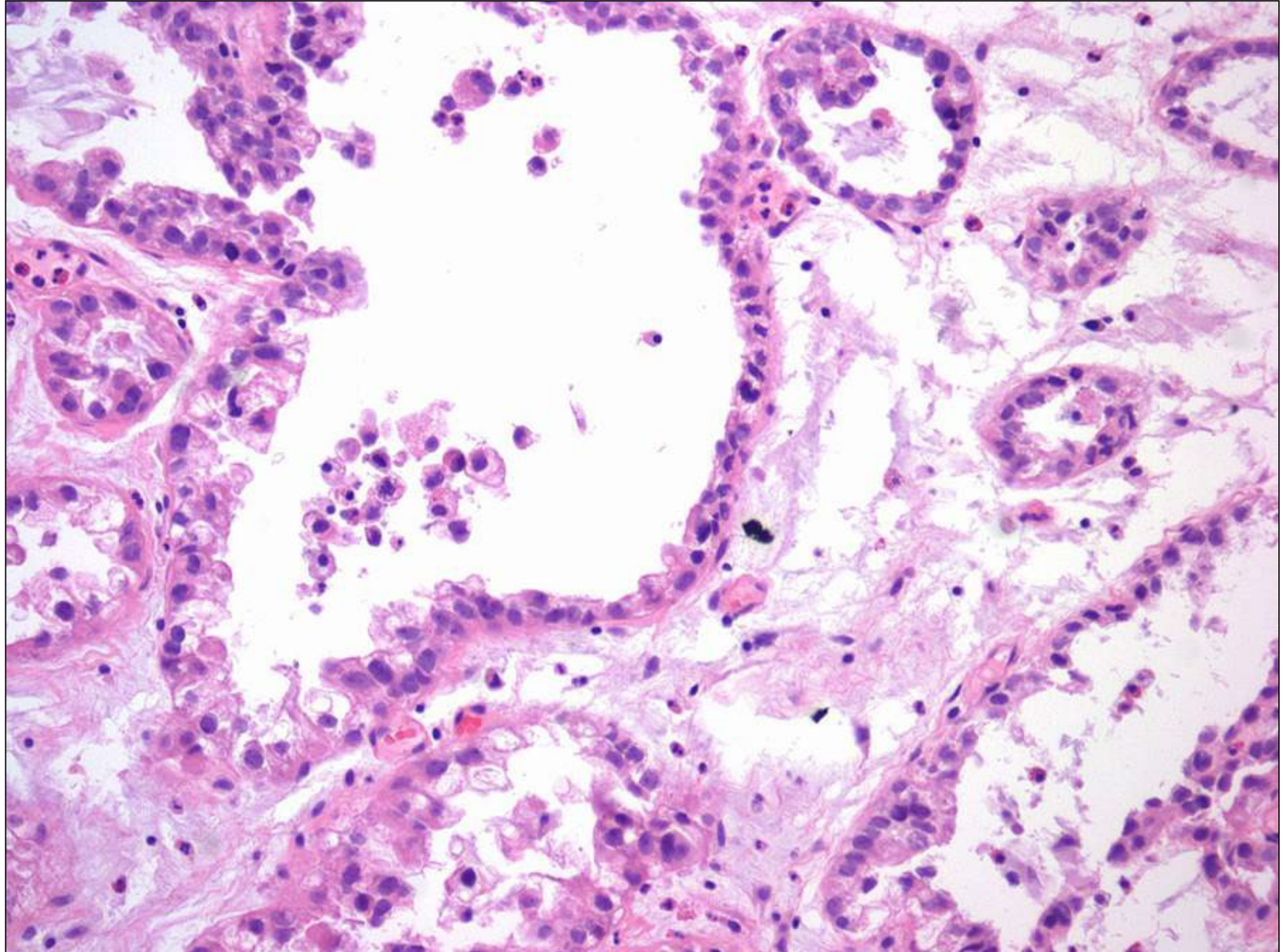
So & Epstein. Mod. Pathol. **2013**

CASE #5

- 55 year old female with UTI and possible stone
- Cystoscopy: 1-2 cm lesion protruding retrograde from urethra into bladder; anterior urethra variably involved with process throughout
- She underwent TURBT

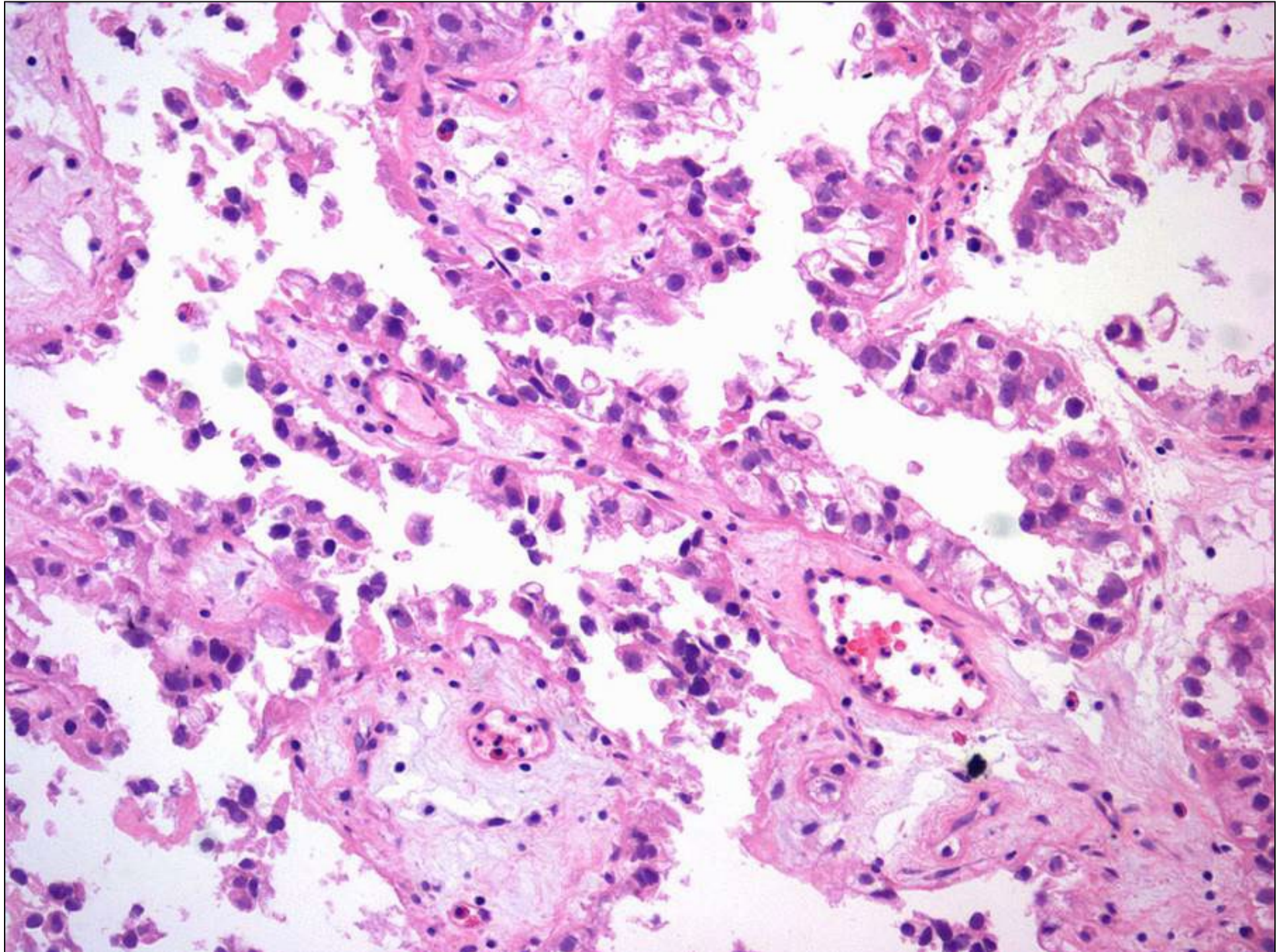


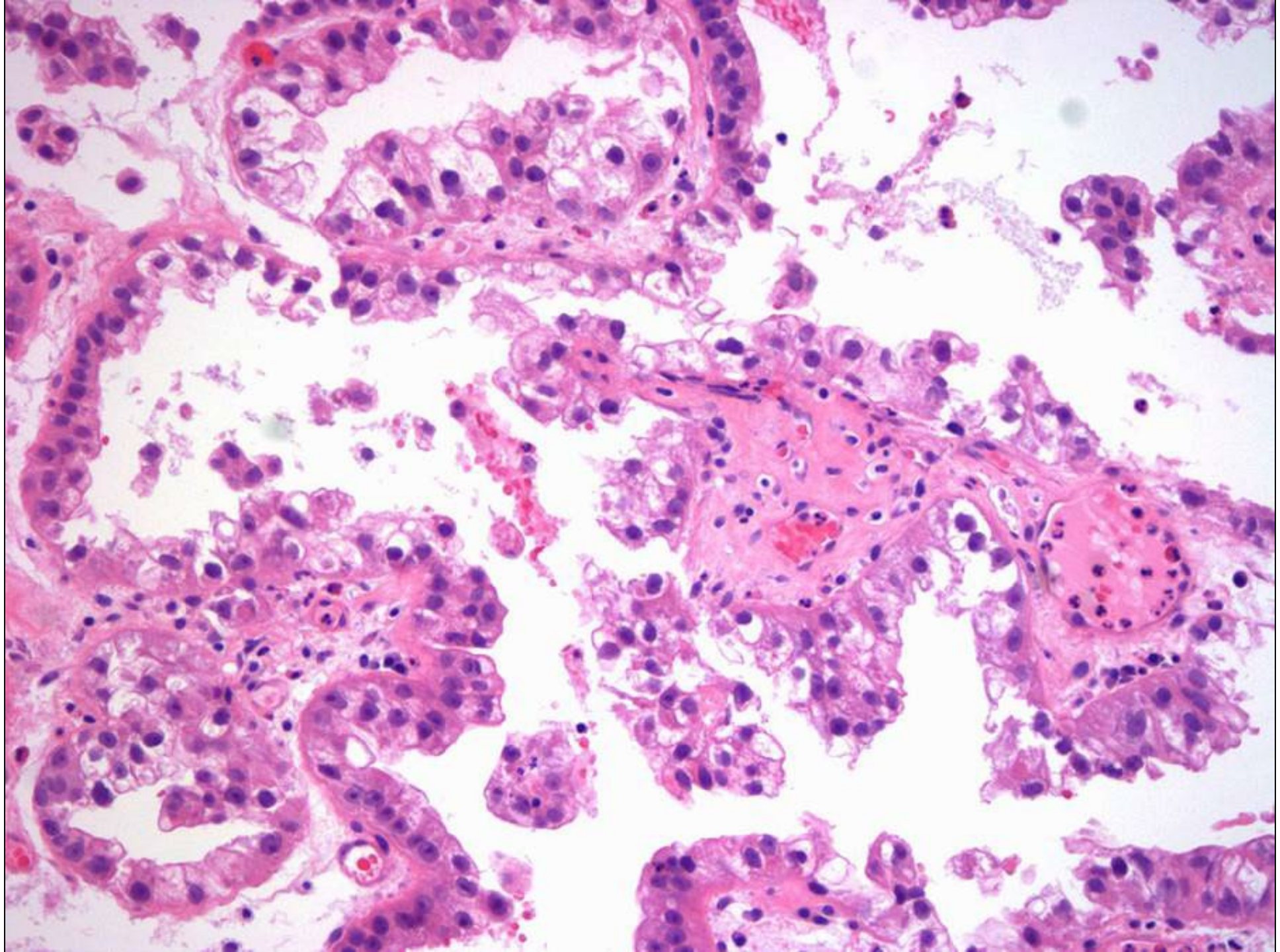




Differential Diagnosis?

- Nephrogenic adenoma
- Clear cell adenocarcinoma
- Urothelial carcinoma with clear cell features
- Metastatic clear cell carcinoma (renal/ovarian)





Case #5

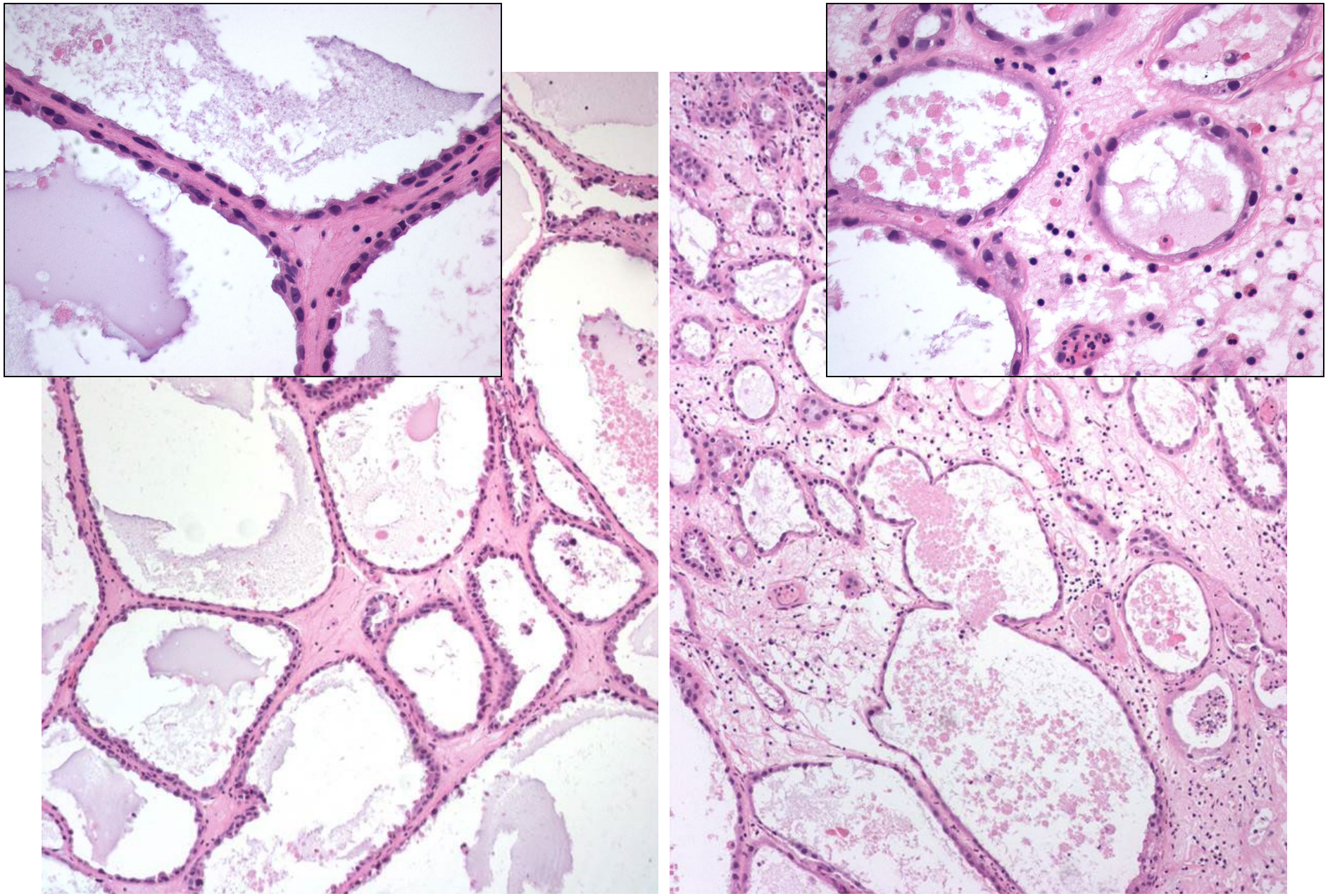
Diagnosis

Clear Cell Adenocarcinoma

Clear Cell Adenocarcinoma

- Rare variant of urinary bladder (urethra) carcinoma resembling its counterpart in ♀ genital tract
- Typically occurs in ♀, but described also in ♂
- 1-7 cm polypoid or papillary mass
- Usually presents with hematuria or dysuria
- Occasionally associated with endometriosis or müllerianosis
- Tend to be aggressive; may infiltrate bladder wall and metastasize to lymph nodes and distant organs

Clear Cell Adenocarcinoma with NA-like areas

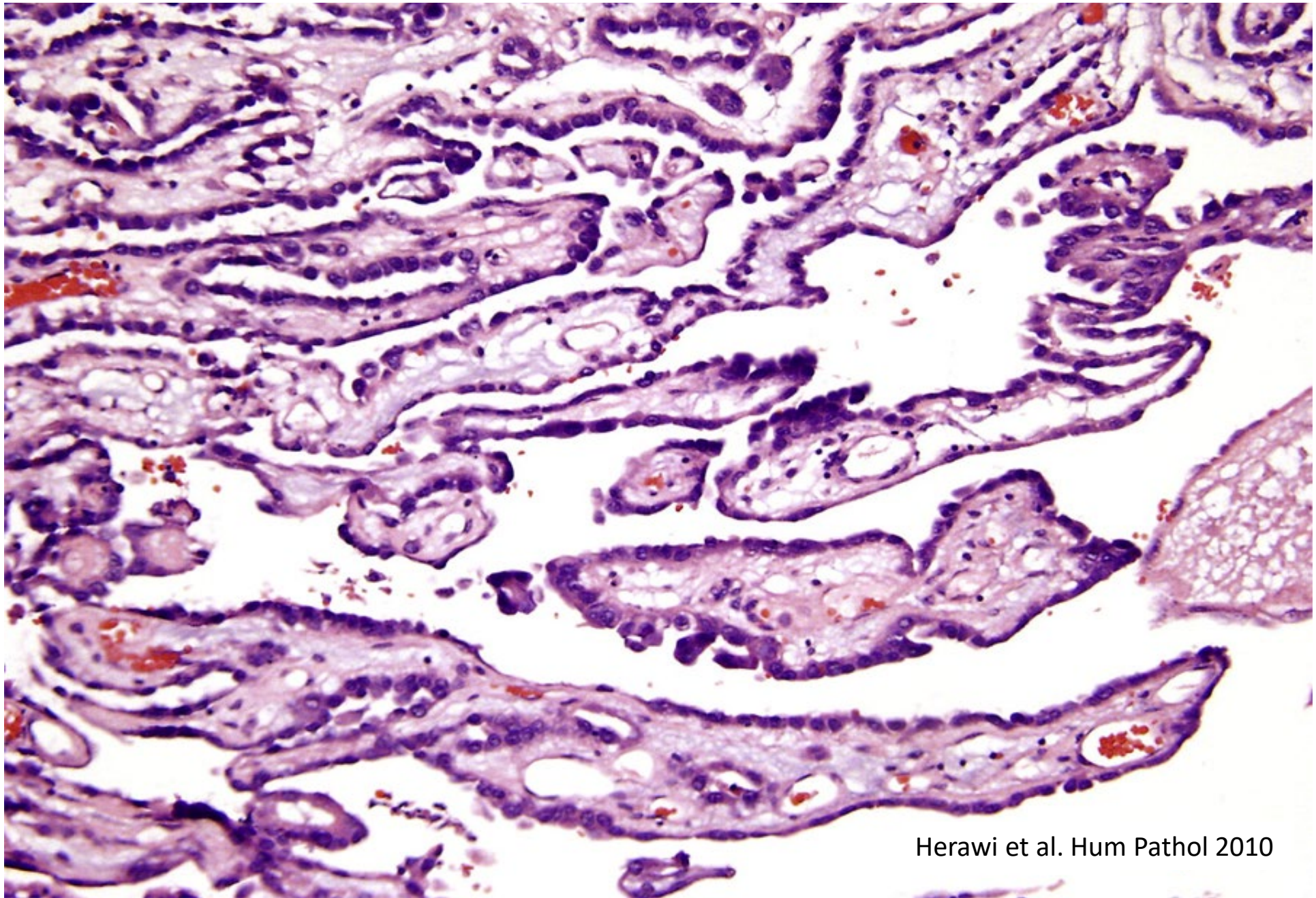


NA-like Clear Cell Adenocarcinoma

- 7 cases of NA-like CCA (4 in urethra, 3 in bladder) compared to 12 classic CCA, and 10 NA
- 4♂, 15♀
- Necrosis was often focal and intraluminal
- No significant solid growth pattern
- Prominent hobnail features were more pronounced
- Muscularis propria invasion in 5/9 classic and 6/6 NA-like CCA
- Discriminating features between NA-like CCA and NA:
  - Occasional clear cells
  - More prominent pleomorphism (hyperchromatic nuclei)
  - Extensive muscularis propria invasion
  - Necrosis, vascular invasion

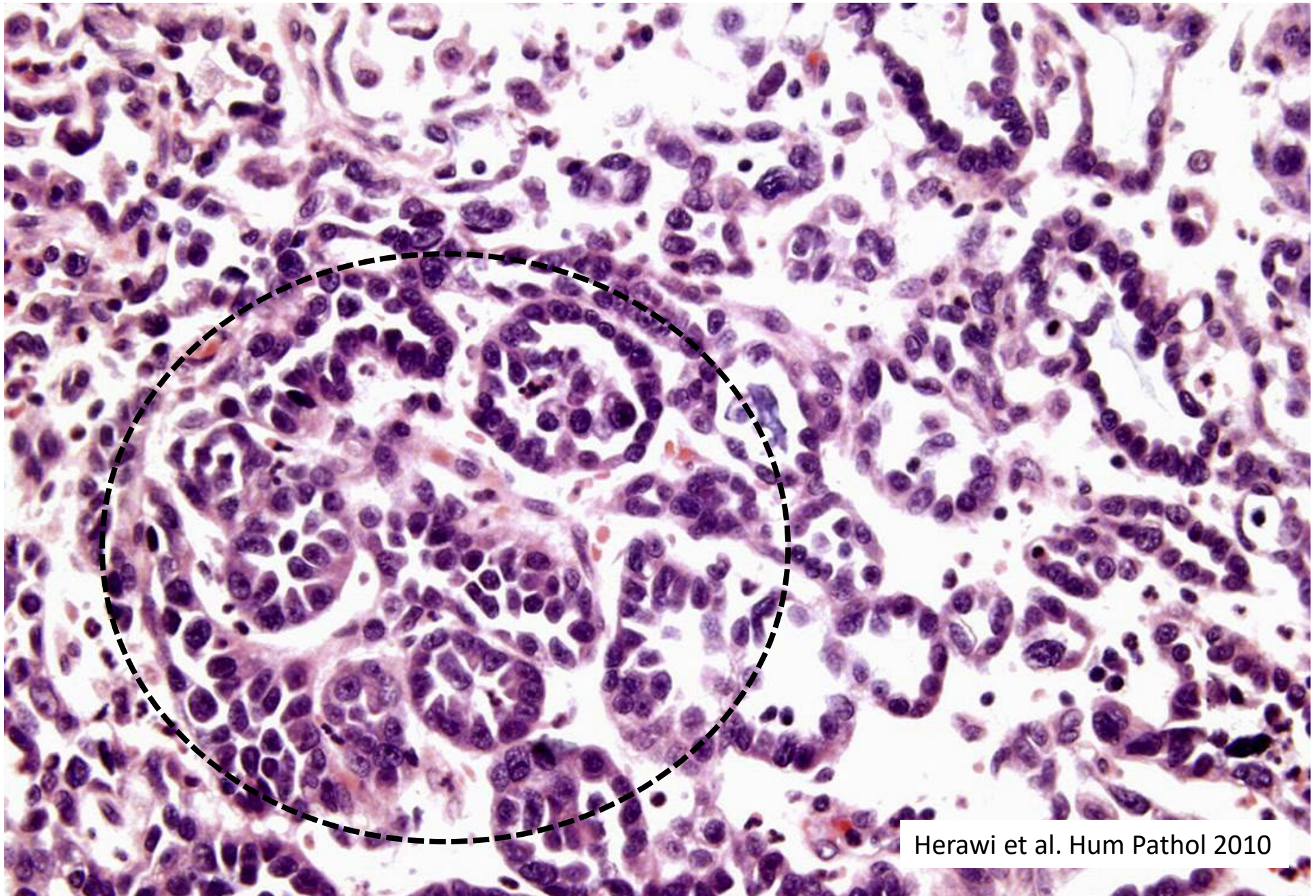
Herawi et al. Hum Pathol 2010

NA-like Clear Cell Adenocarcinoma



Herawi et al. Hum Pathol 2010

NA-like Clear Cell Adenocarcinoma



Comparison of NA and CCA

Characteristics	Nephrogenic adenoma	Clear cell adenocarcinoma
Sex	♂ predominance	♀ predominance
Age	1/3 < 30 years	All > 40 years
Tumor size, focality	< 1 cm, multifocal	mean 3.4 cm, unifocal
Biologic behavior	Benign	Aggressive
Solid growth pattern	Rare	Common
Microscopic findings: • necrosis • mitoses and atypia • stromal edema • clear cell change • infiltrative growth • inflammation	 • absent • absent, rare • common • uncommon • usually absent • invariably present	 • often present (~50%) • common • uncommon • common • present • may be present
p53	- Mean 0-1%	- Mean 4-20%%
MIB-1/Ki-67	- Mean 2%	- Mean 33-50%

Clear Cell Adenocarcinoma

Follow-up

- 24% no clinical evidence of disease
- 40% alive with local recurrence and/or metastasis
- 36% died of disease (8-65 months)
- Classic CCA and NA-like CCA have similar dismal prognosis

Herawi et al. Hum Pathol 2010;
Sung et al. Clin Cancer Res 2008

Clear Cell Adenocarcinoma in Men: A Series of 15 Cases

Grosser et al. Am J Surg Pathol 2020

TABLE 1. Clinicopathologic Findings at Presentation

Case No.	Age (y)	Site	Size (cm)	Extent of Disease at Presentation
1	70	Bladder	0.7	—
2	17	Between bladder and rectum (prostatic utricle cyst)	9.3	Metastases to internal iliac LN and bladder
3	84	Bladder (multifocal)	NA	—
4	68	Bladder	3.8	—
5	61	Prostate	5.3	*Direct extension to SV and periprostatic soft tissue with metastases to pelvic LN and flank
6	29	Membranous urethra and prostatic urethra (multifocal)	NA	Metastases to mediastinal LN, lung, adrenal
7	89	Bladder	NA	—
8	45	Membranous urethra	NA	—
9	60	Prostate	2.1	Extraprostatic extension
10	42	Periprostatic (Müllerian remnant)	2.5	Direct extension to prostate
11	47	Prostatic urethra	8	*Direct extension to bladder and rectum
12	68	Bladder	NA	—
13	78	Prostate	NA	—
14	49	Prostate	NA	*Direct extension to bladder neck with metastases to femoral LN
15	36	Prostatic urethra	1.2	Membranous urethra

LN indicates lymph node; NA, not available; SV, seminal vesicle.

TABLE 2. Treatment and Prognosis

Case No.	Initial Surgical Treatment	Subsequent Therapy	Follow-up (mo)	Status
1	Cystectomy	h/o RT, HT for prostate cancer	18	NED
2	TUR	RT, chemotherapy, gefitinib	12	AWD
3	TUR	RT	23	NED
4	TUR followed by cystoprostatectomy and LND	h/o RT for prostate cancer	17	NED
5	RP and LND	RT, chemotherapy, nivolumab	39	*Dead
6	Urethrectomy	Chemotherapy	36	NED
7	—	—	1	AWD
8	TUR	RT (for recurrent tumor)	36	NED
9	RP and LND	NA	NA	NA
10	RP and LND	RT	138	NED
11	Cystoprostatectomy and LND with resection of sigmoid colon and rectum	—	10	*Dead
12	TUR	BCG	134	NED
13	NA	NA	10	*Dead
14	NA	NA	6	*Dead
15	—	—	3	AWD

BCG indicates Bacillus Calmette-Guerin; h/o, history of; HT, hormonal therapy; LND, lymph node dissection; NA, not available; NED, no evidence of disease; RP, radical prostatectomy; RT, radiation therapy; TUR, transurethral resection.

THANK YOU!

cmagigalluzzi@uabmc.edu

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