

Urothelial Carcinoma of the Urinary Bladder

Issues

- Mayo Clinic Cystectomy Registry
- Urothelial carcinoma variants
- Evaluation of depth of invasion in transurethral resection specimens
- Issues in staging
- Prostatic versus urothelial carcinoma
- Diagnostic errors resulting in cystectomy

Survival Predication After Radical Cystectomy: SPARC

- 1776 patients
- 1980-2006
- Complete clinical and pathologic data collected
- Long term follow-up

TNM

TIS

T_a

T₁

T_{2A}

T_{2B}

T_{3B}

T_{4A}

JSM

0

0

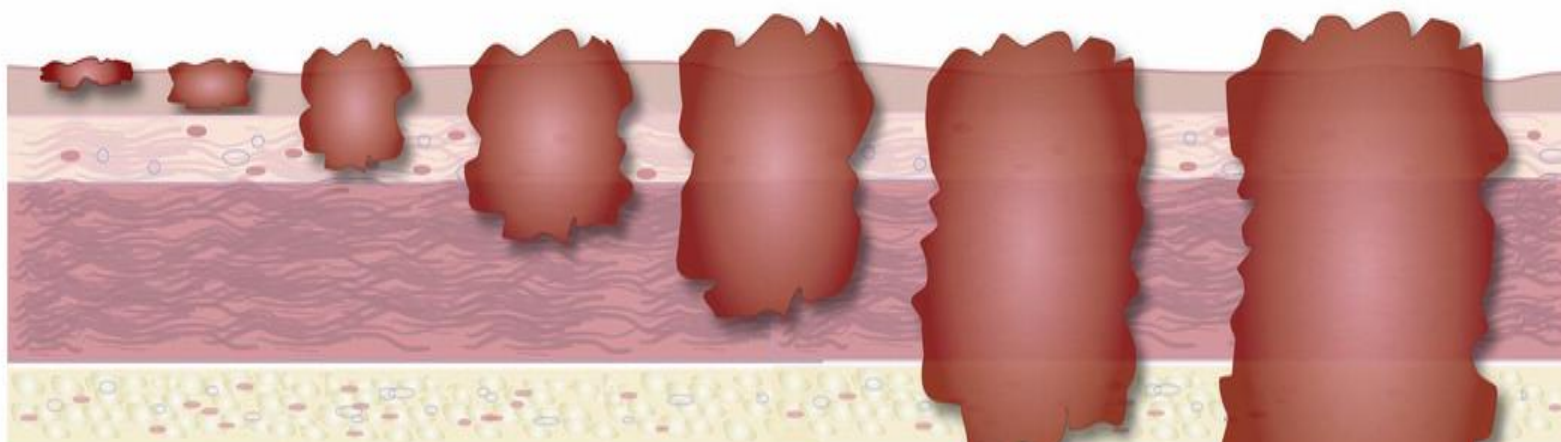
A

B₁

B₂

C

D₁



Mucosa
Submucosa

Muscular Layer
(Detrusor)

Perivesical Fat

Prostate or
other adjacent
organ (uterus,
vagina)

Univariate Associations

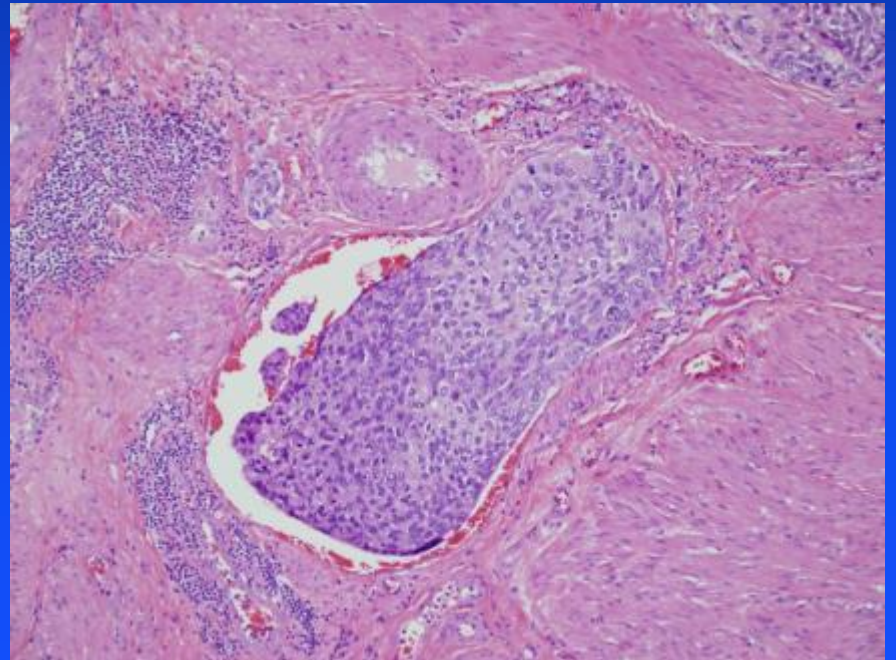
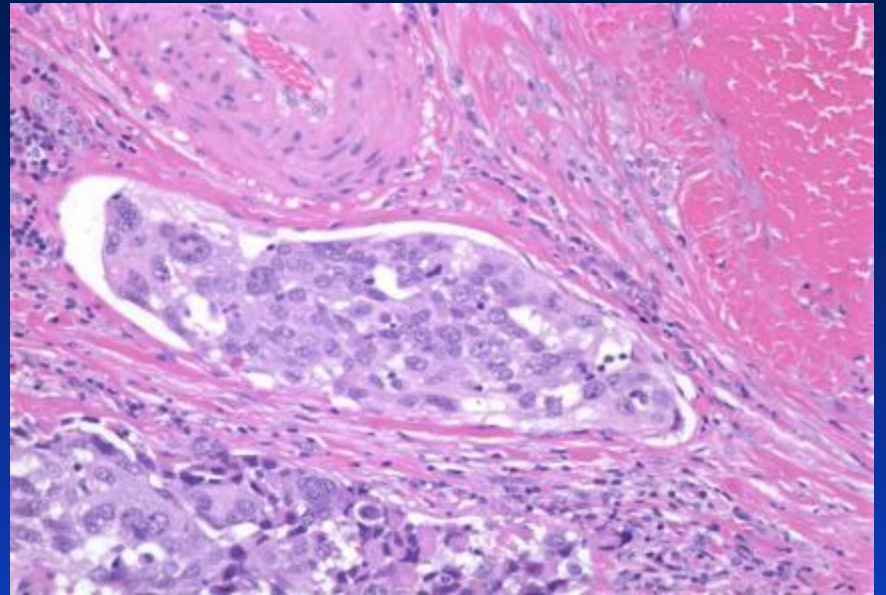
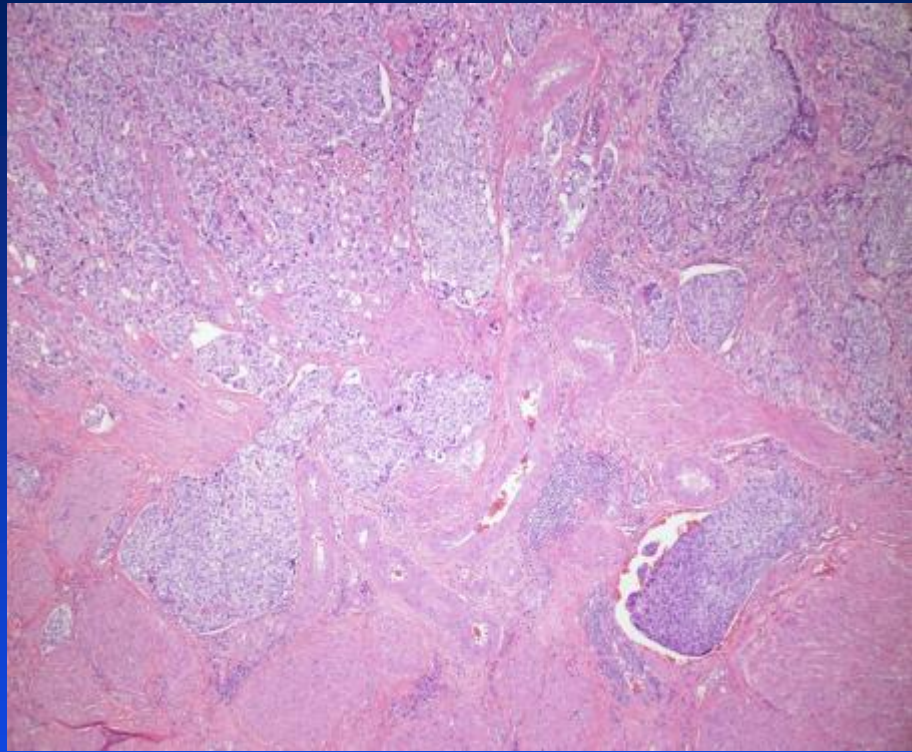
	HR	p-value
Charlson index ≥3	2.8	<0.0001
ECOG ≥2	2.6	<0.0001
Hydronephrosis	1.8	<0.0001
Current smoker	1.1	<0.004
Tumor grade	1.7	<0.0001
Tumor stage		
pT2 (ref ≤pT1)	1.2	<0.0001
pT3a	2.2	<0.0001
pT3b	3.0	<0.0001
pT4	5	<0.0001

Univariate Associations

	HR	p-value
pN (ref N0)	2.5	<0.0001
Tumor size	1.9	<0.0001
Multifocal invasive tumors	1.3	0.08
Necrosis	2.0	<0.0001
LVI	3.1	<0.0001
Upstaging	3.2	<0.0001
Radial margin +	3.2	<0.0001
No adjuvant chemo	0.49	<0.0001
Adjuvant XRT	2.9	<0.001

Multivariate Associations

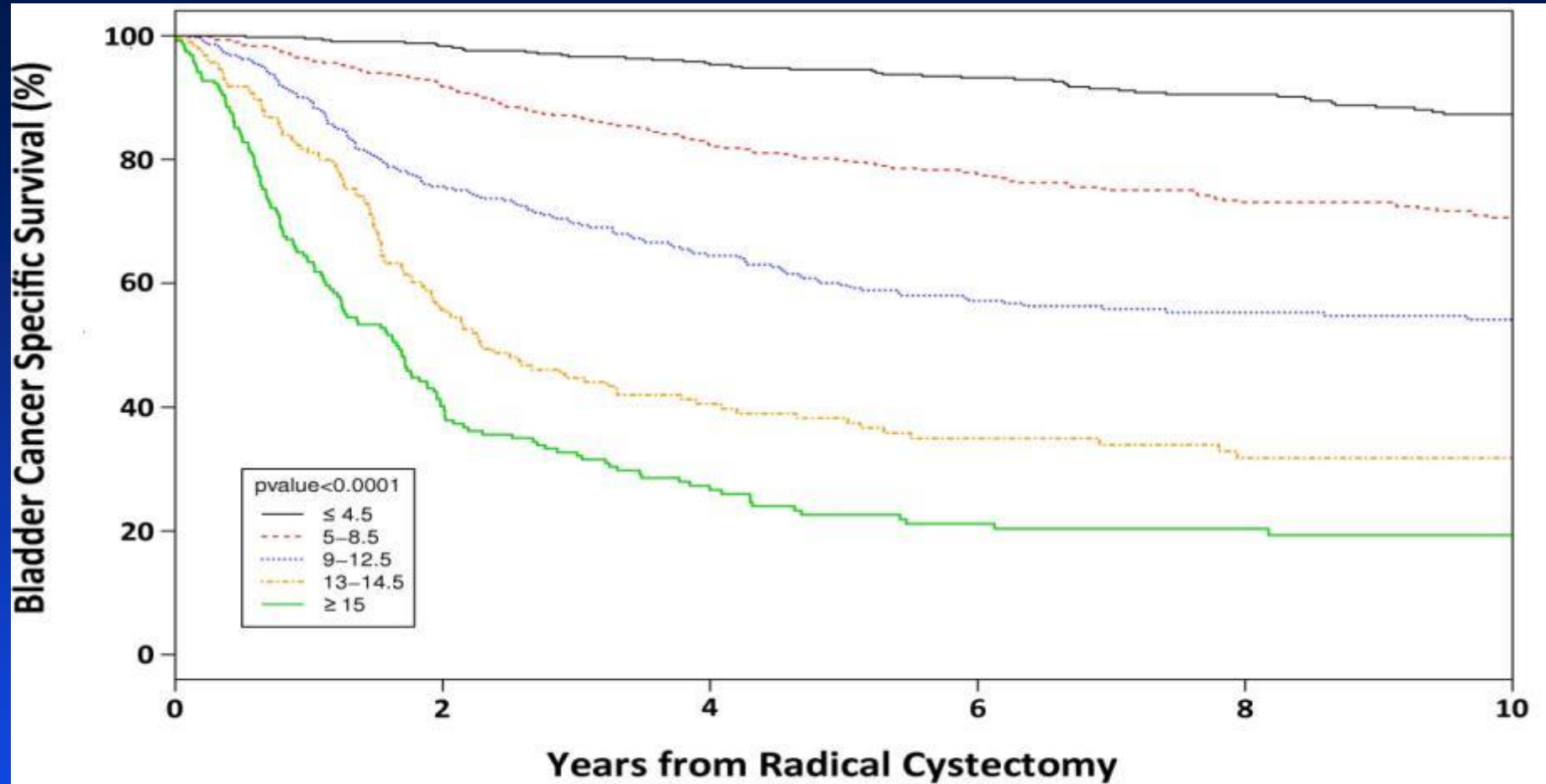
	HR	p-value
Charlson index	1.9	<0.0001
ECOG status	2.1	<0.0001
Smoker	1.3	0.004
Hydronephrosis	1.2	0.04
Tumor stage		
pT2	2.0	<0.0001
pT3a	2.9	<0.0001
pT3b	3.8	<0.0001
pT4	5.8	<0.0001
Multifocal tumors	1.4	0.02
LVI	1.4	0.02
No adjuvant chemo	1.5	0.006



SPARC Scoring

Variable	Points
Charlson Index	
0-2	0
≥ 3	3.5
ECOG status	
0-1	0
≥ 2	4
Hydronephrosis	
No	0
Yes	1
Smoking status	
Never	0
Current	1.5

Variable	Points
Tumor stage	
$\leq pT1$	0
pT2	3.5
pT3a	6
pT3b	7.5
pT4	9.5
LVI	
Absent	0
Present	2
Multifocality	
Unifocal	0
Multifocal	2
Adjuvant chemo	
Received	0
Not received	2



Risk Group	SPARC Score	Bladder cancer specific survival (number at risk)				
		No. Pts	2 years	5 years	8 years	10 years
I	≤ 4.5	414	98% (400)	95% (358)	91% (274)	87% (214)
II	5 – 8.5	590	92% (501)	80% (378)	73% (253)	71% (184)
III	9 – 12.5	357	76% (239)	60% (153)	55% (107)	54% (80)
IV	13 – 14.5	191	56% (88)	38% (49)	32% (30)	32% (22)
V	≥ 15	224	40% (70)	23% (31)	20% (20)	19% (14)

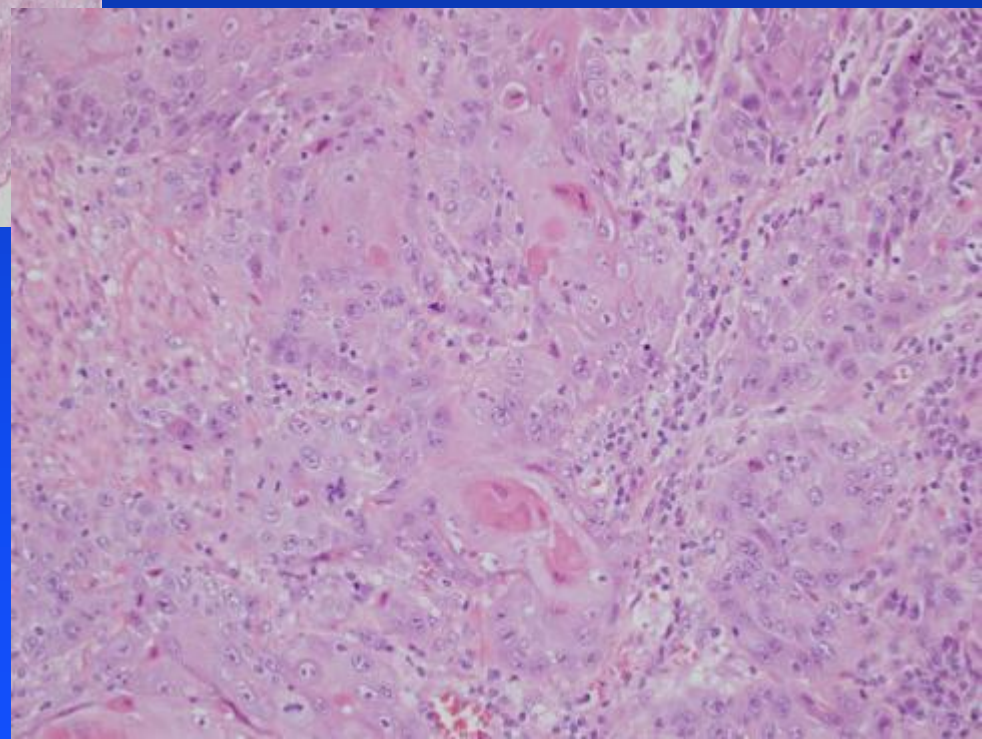
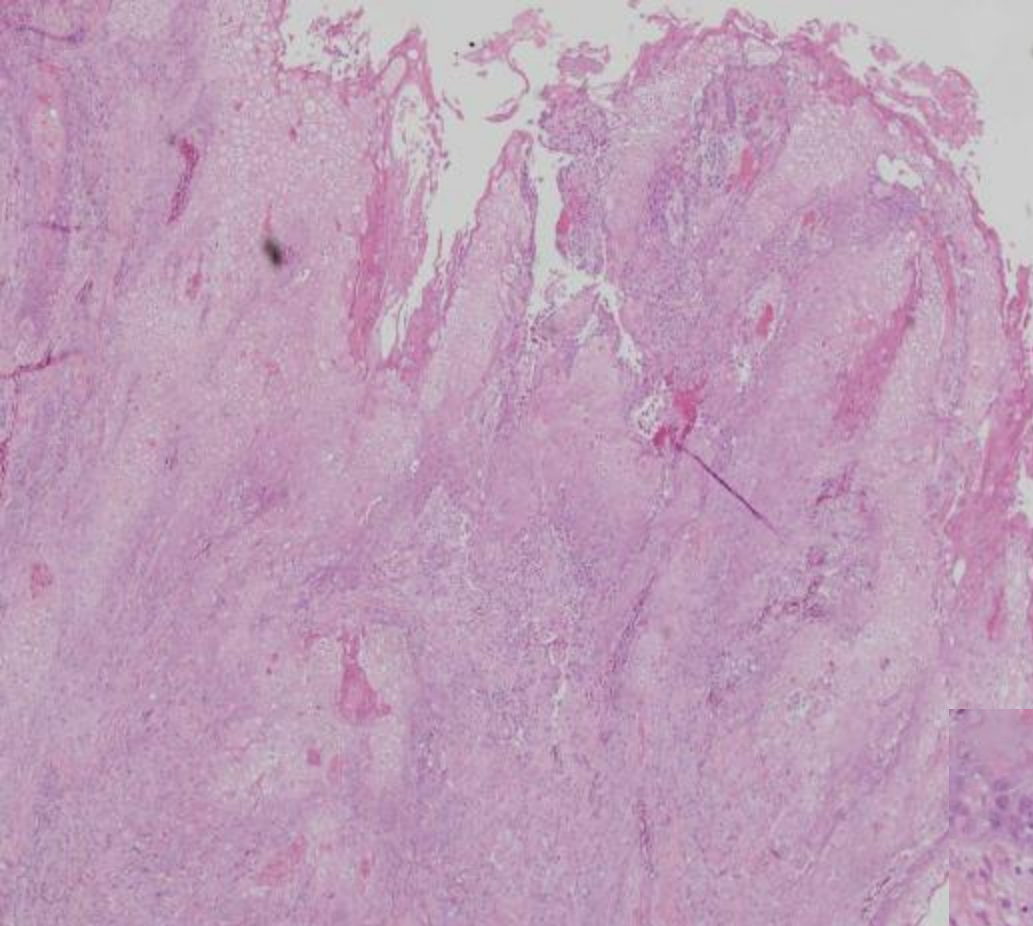
Variants

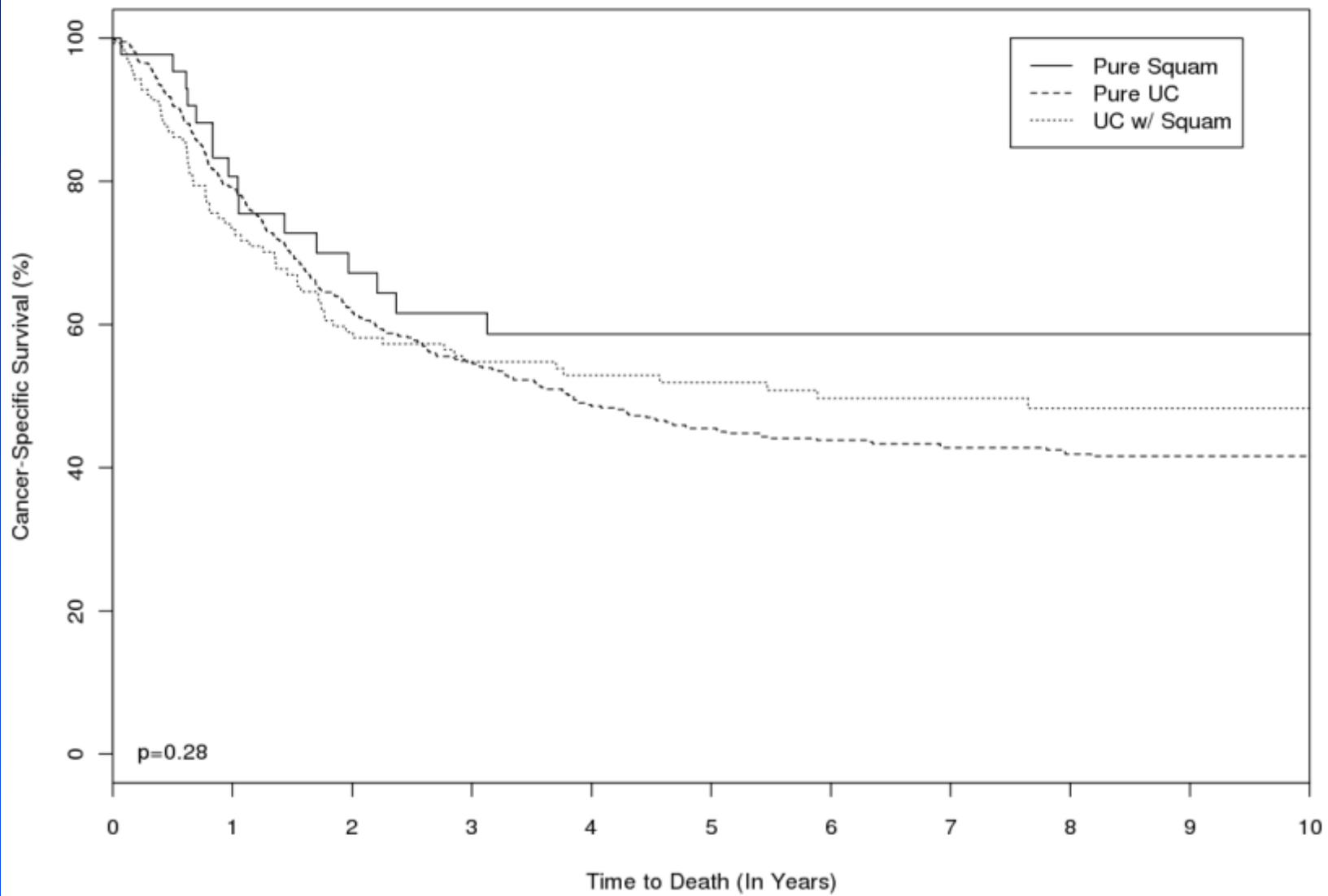
- Squamous cell carcinoma 6%
- Micropapillary 5.5%
- Small cell 5%
- Adenocarcinoma 4.5%
- Nested/microcystic 3.8%
- Plasmacytoid carcinoma 3%
- Sarcomatoid 2%
- Trophoblastic, Lymphoepithelioma-like, lymphoma-like

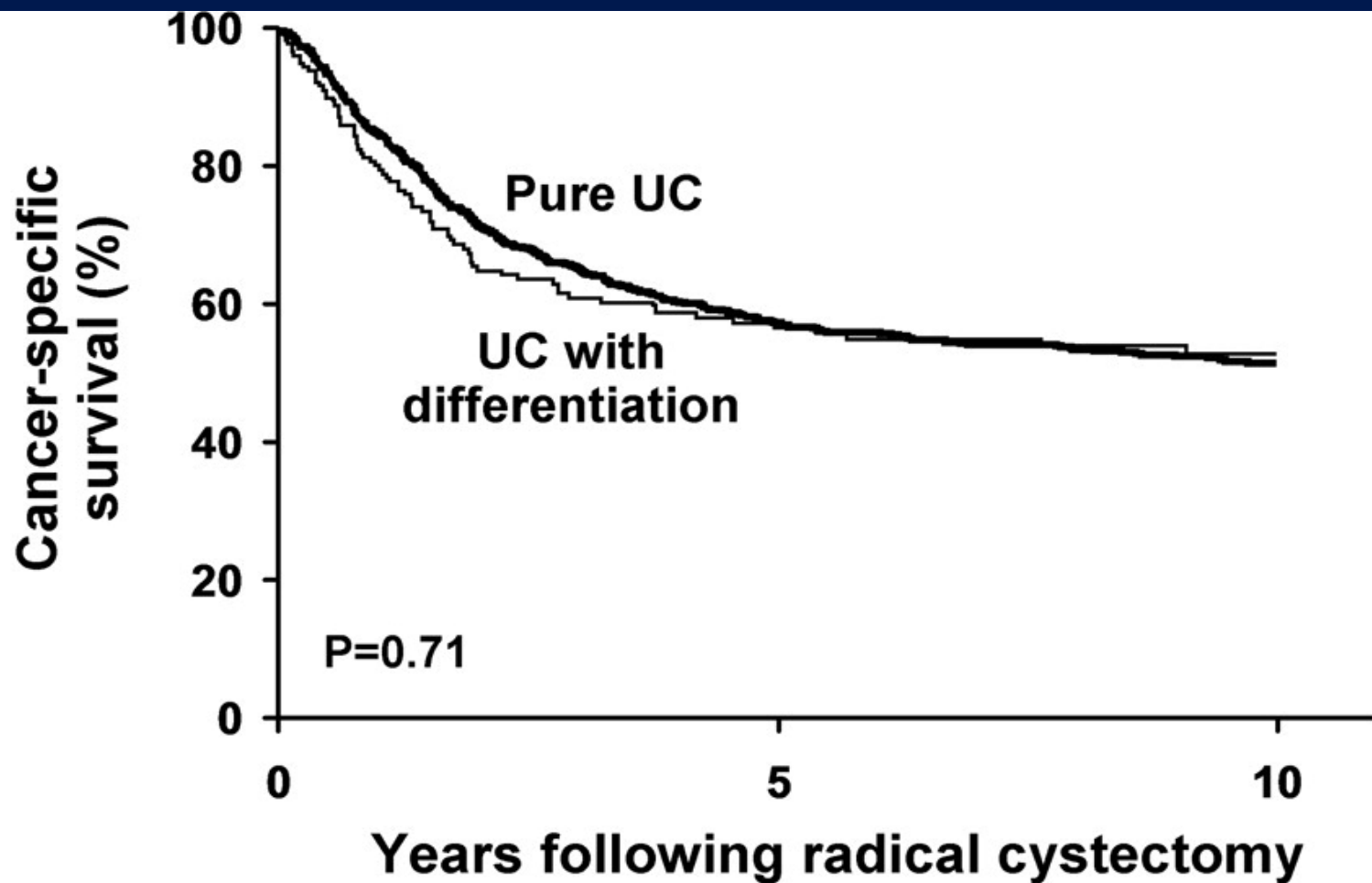
29.8%

Variants- Does it matter?

- Neo-adjuvant Chemotherapy
 - Less effective in patients with squamous cell carcinoma
 - Altered regimen in patients with small cell carcinoma (or component of)
 - Not enough information in other variants although patient may be less likely to receive neo-adjuvant chemotherapy with aggressive variants

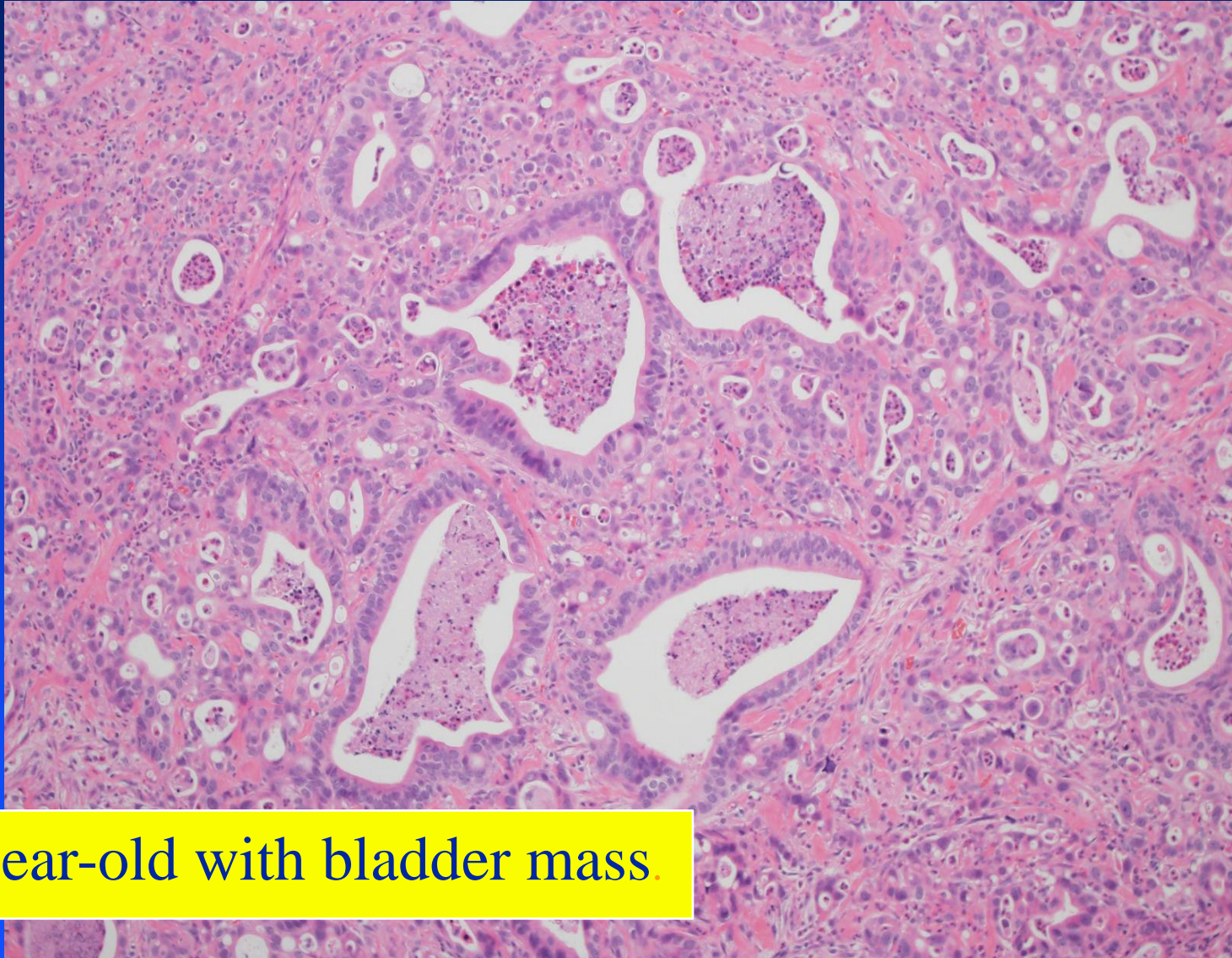




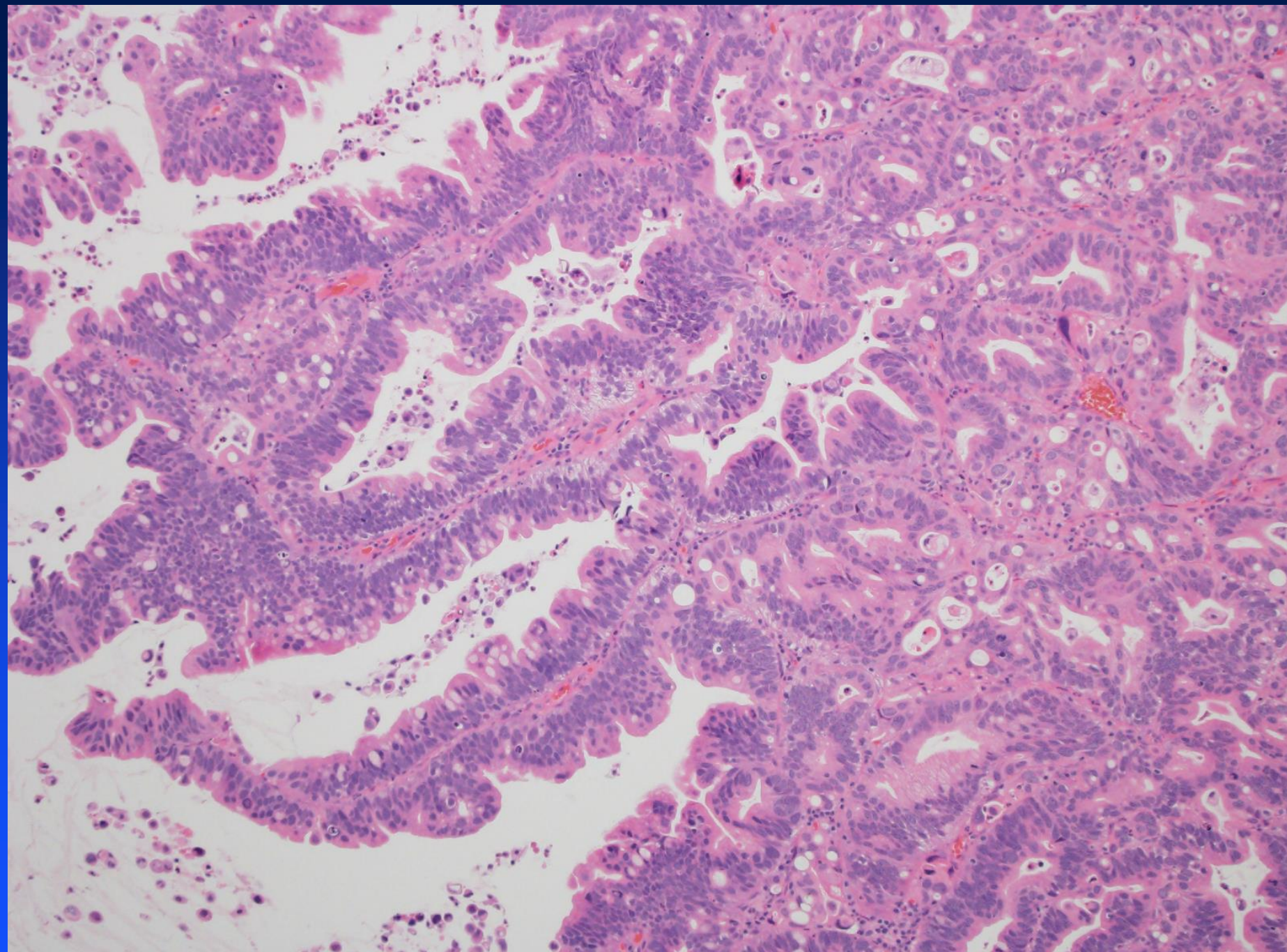


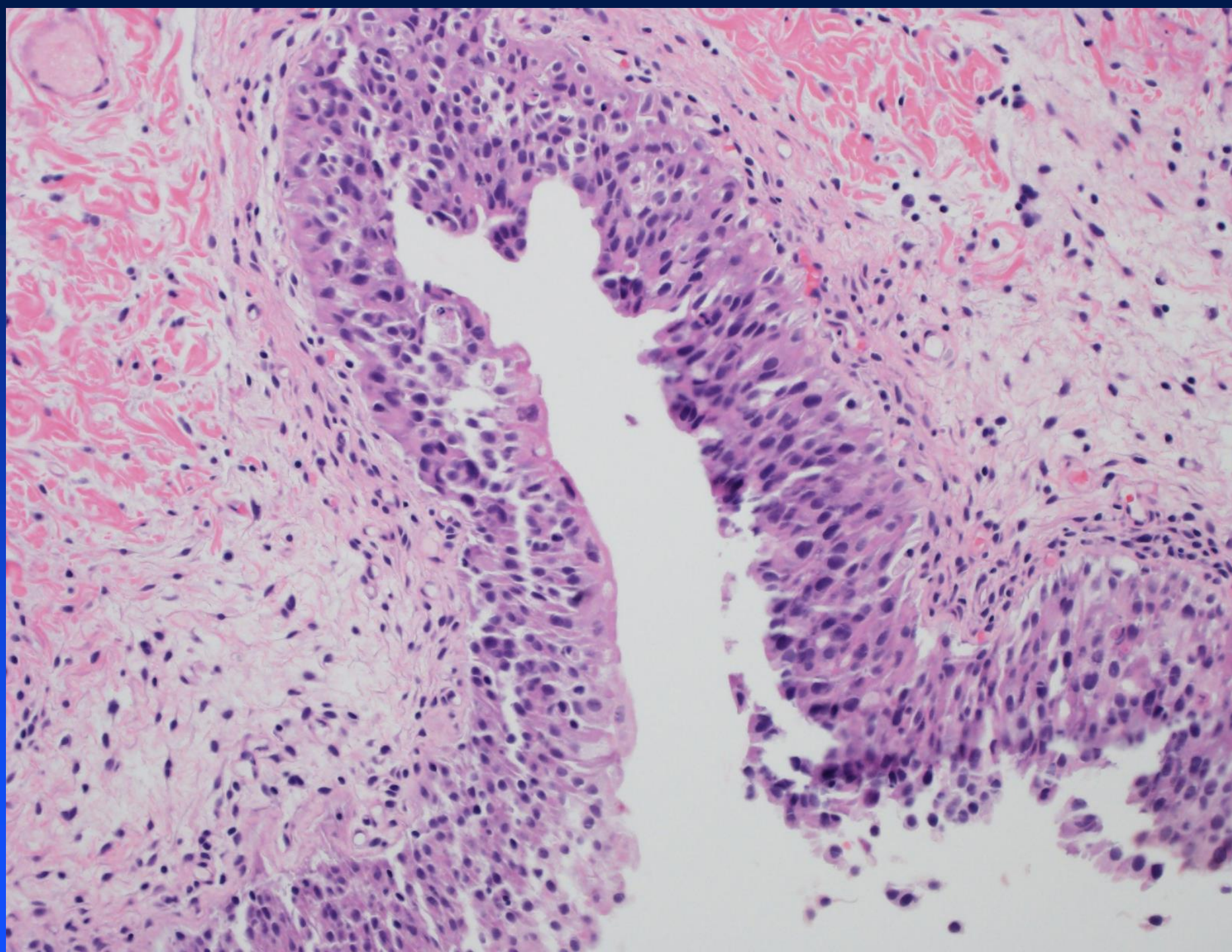
Group	% survival (no. at risk)		
— Pure UC	100 (827)	57 (362)	51 (194)
— UC with differentiation	100 (186)	56 (71)	53 (36)

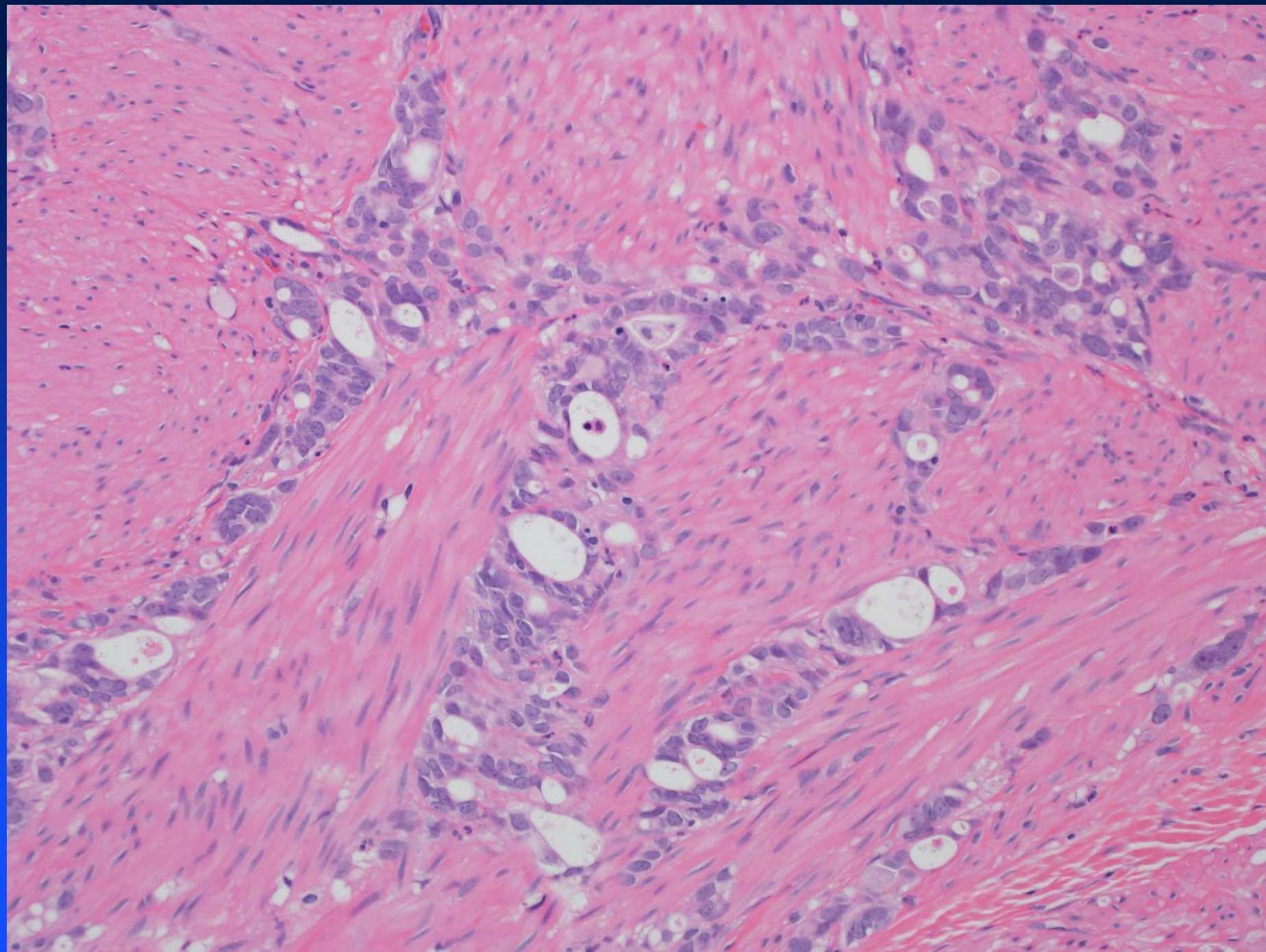
Primary vs Metastatic Adenocarcinoma

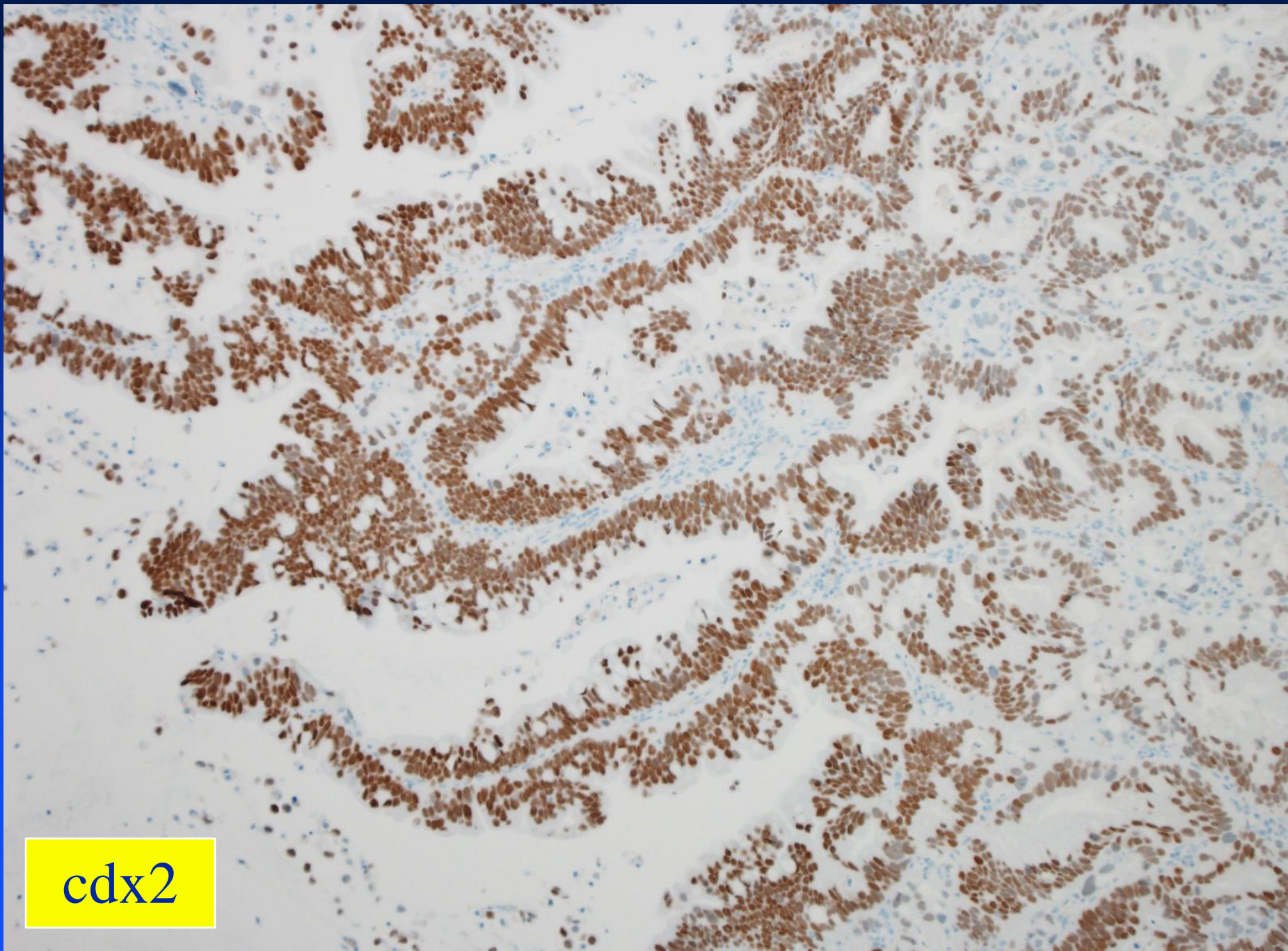


74-year-old with bladder mass.

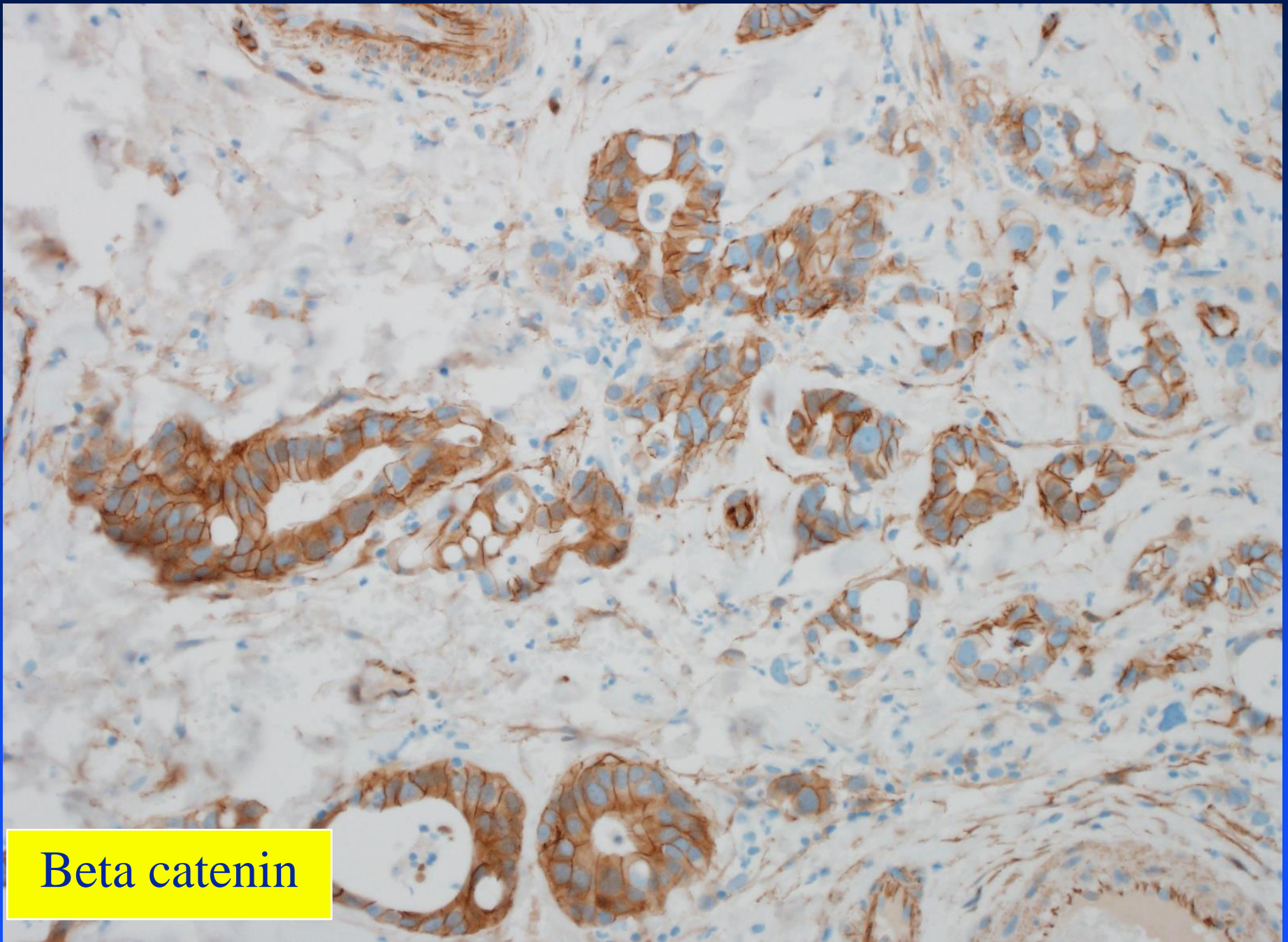








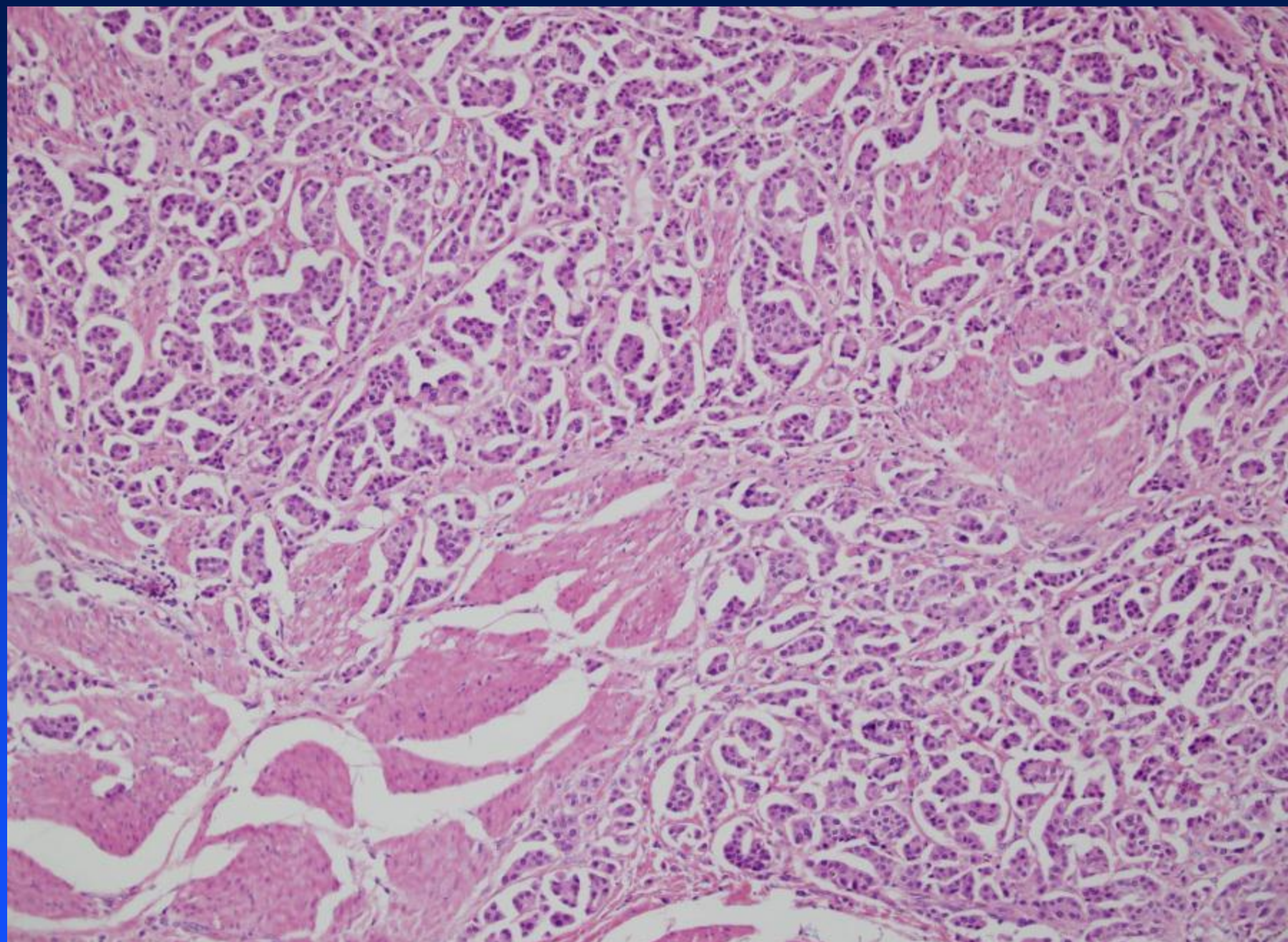
cdx2

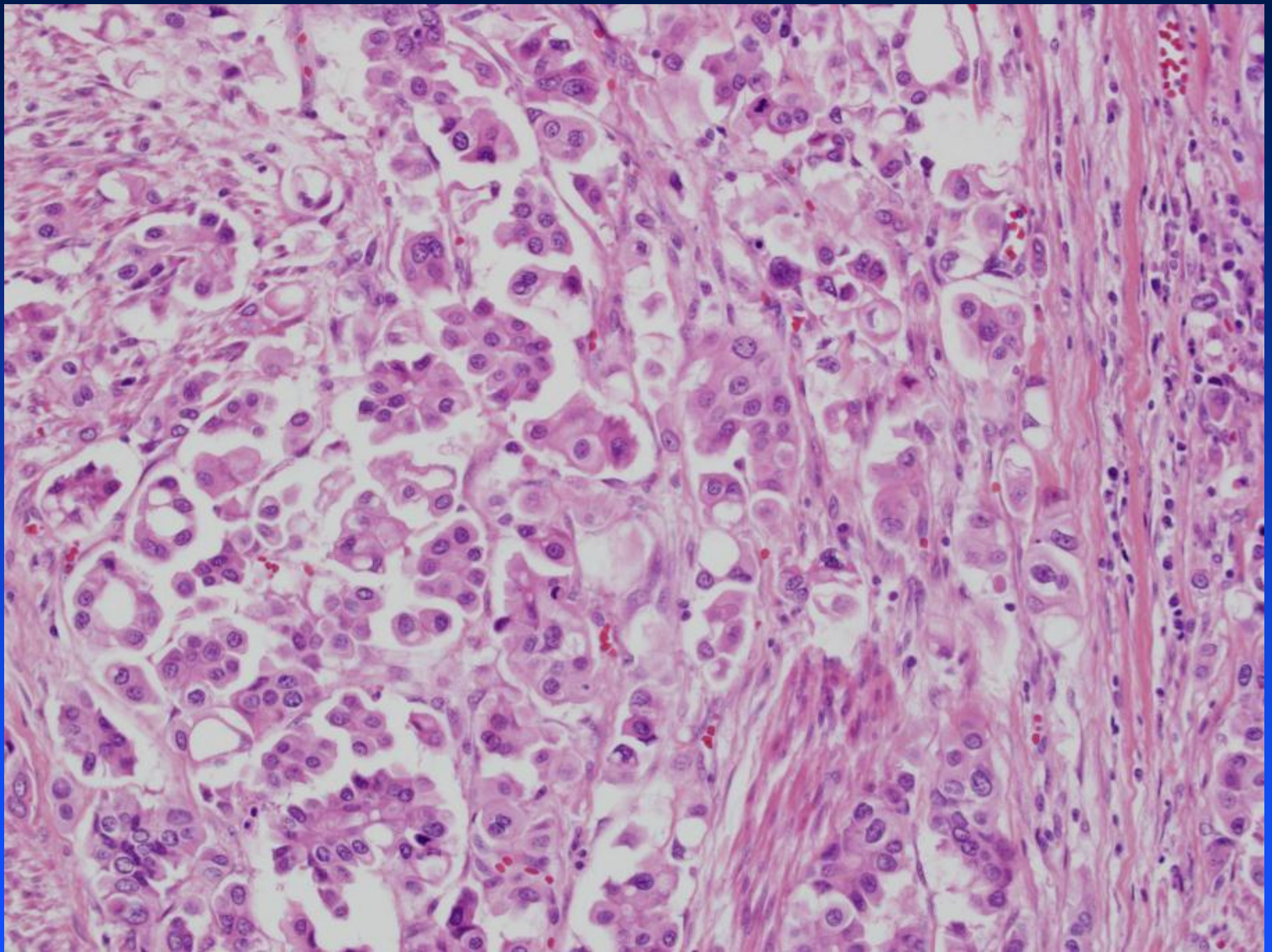


Beta catenin

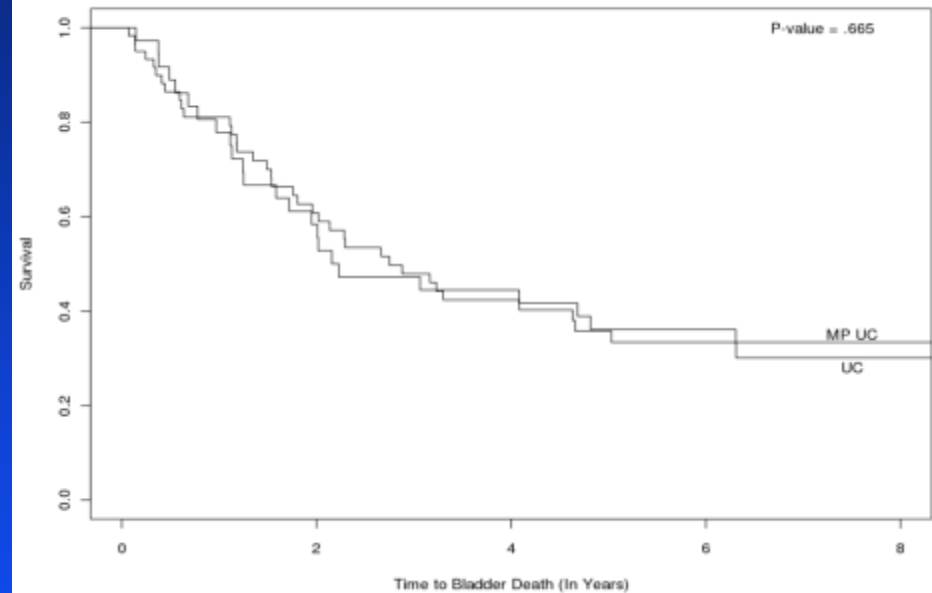
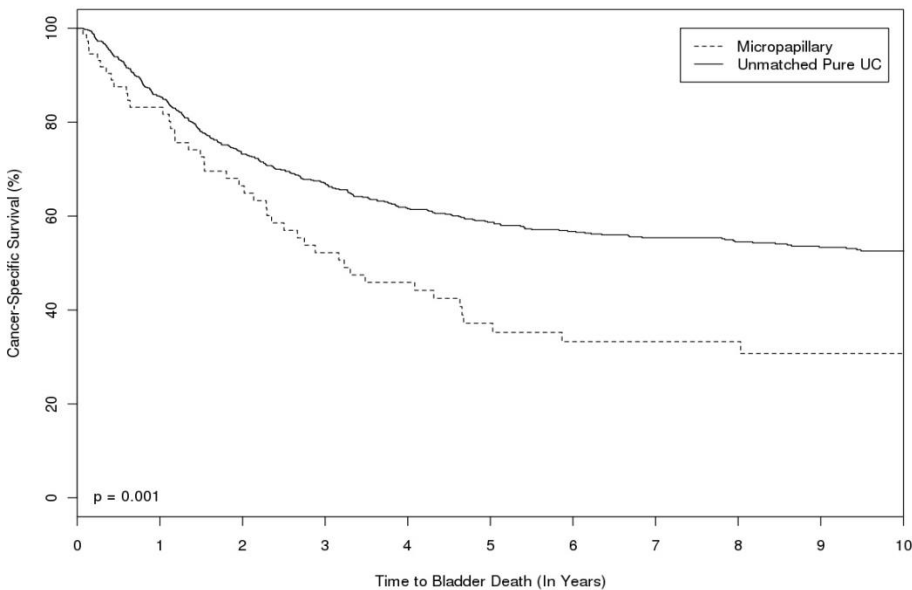
Primary *versus* Metastatic

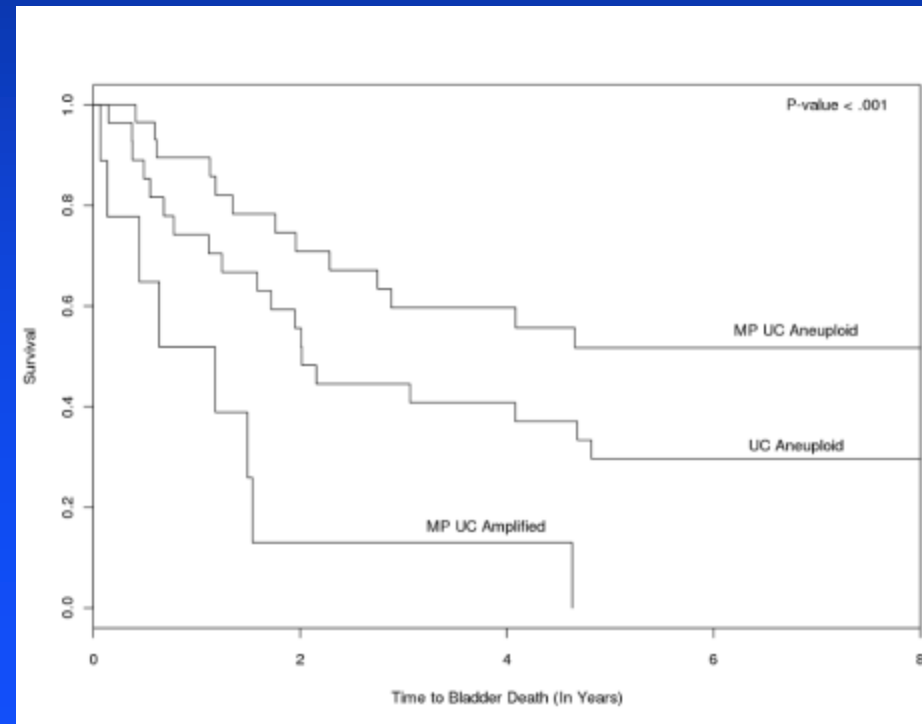
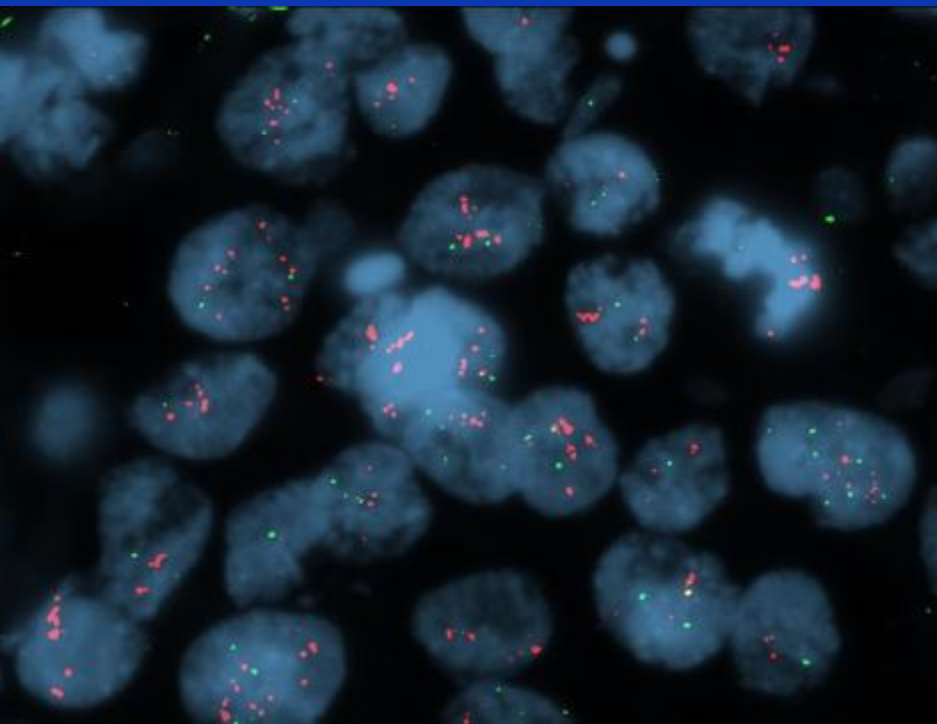
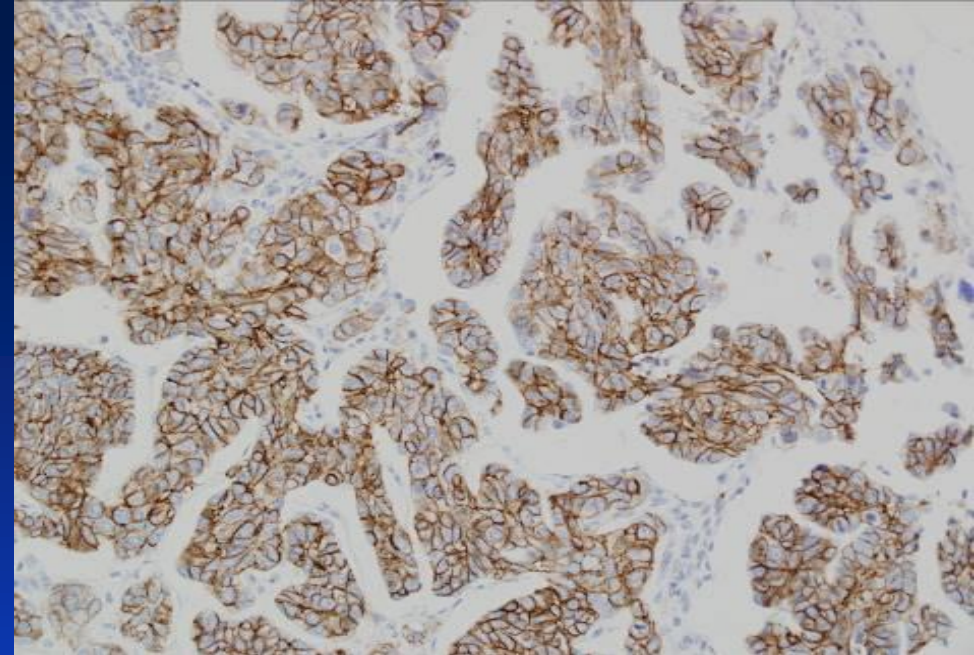
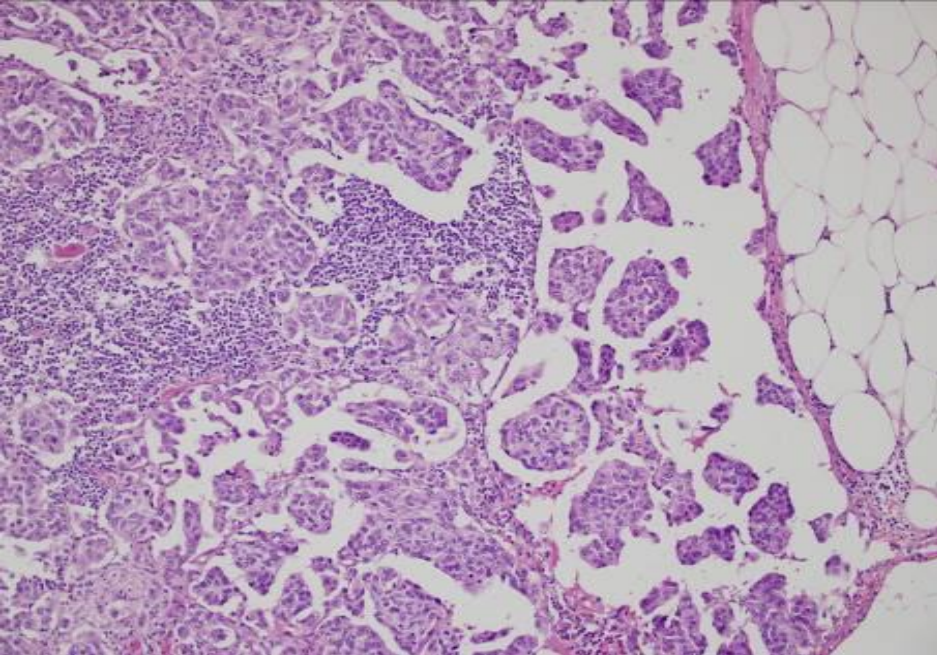
- Primary tumor elsewhere
- In situ component
- Immunostains
 - Pelvic mass- cannot determine site of origin

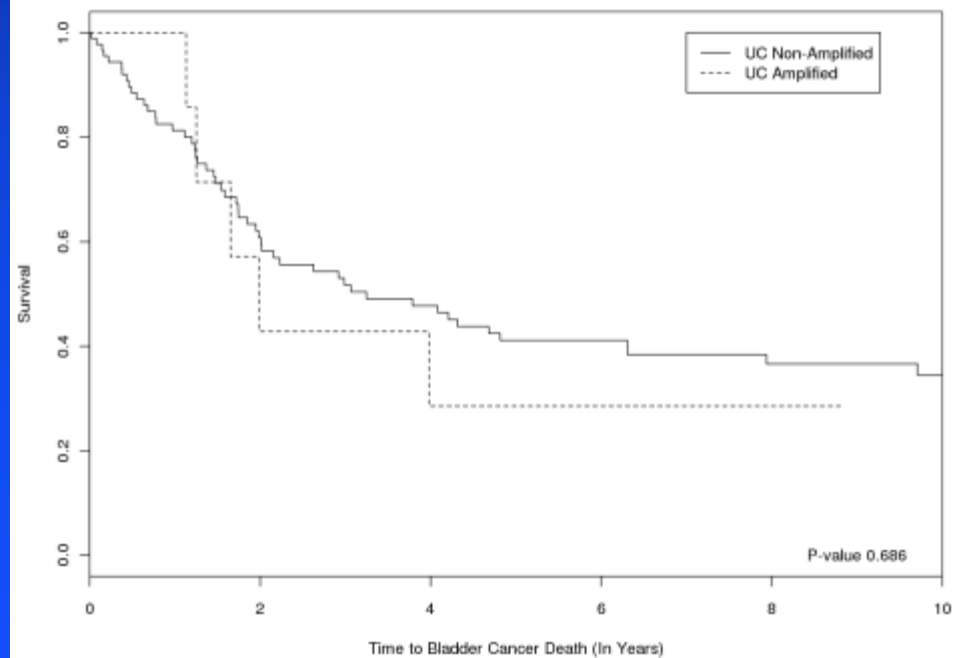
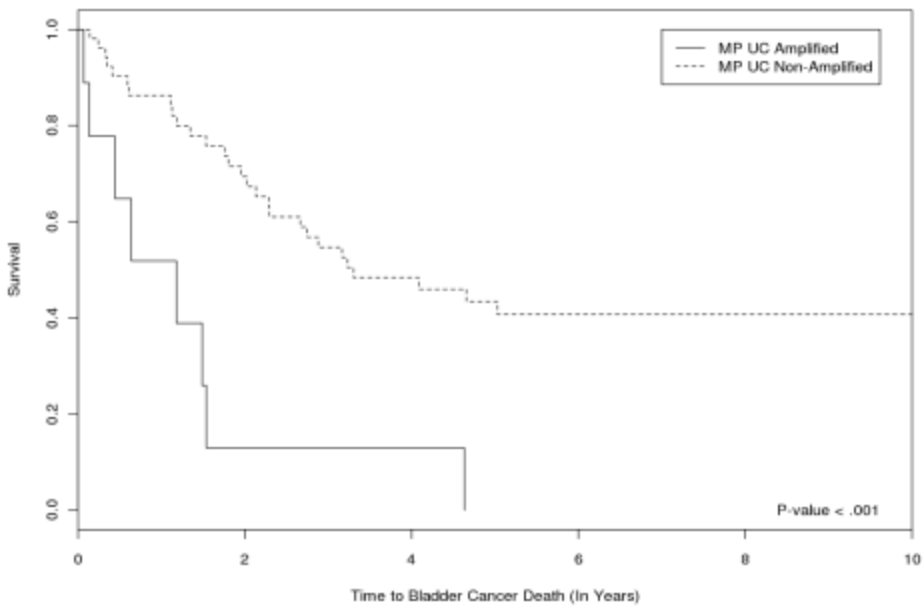




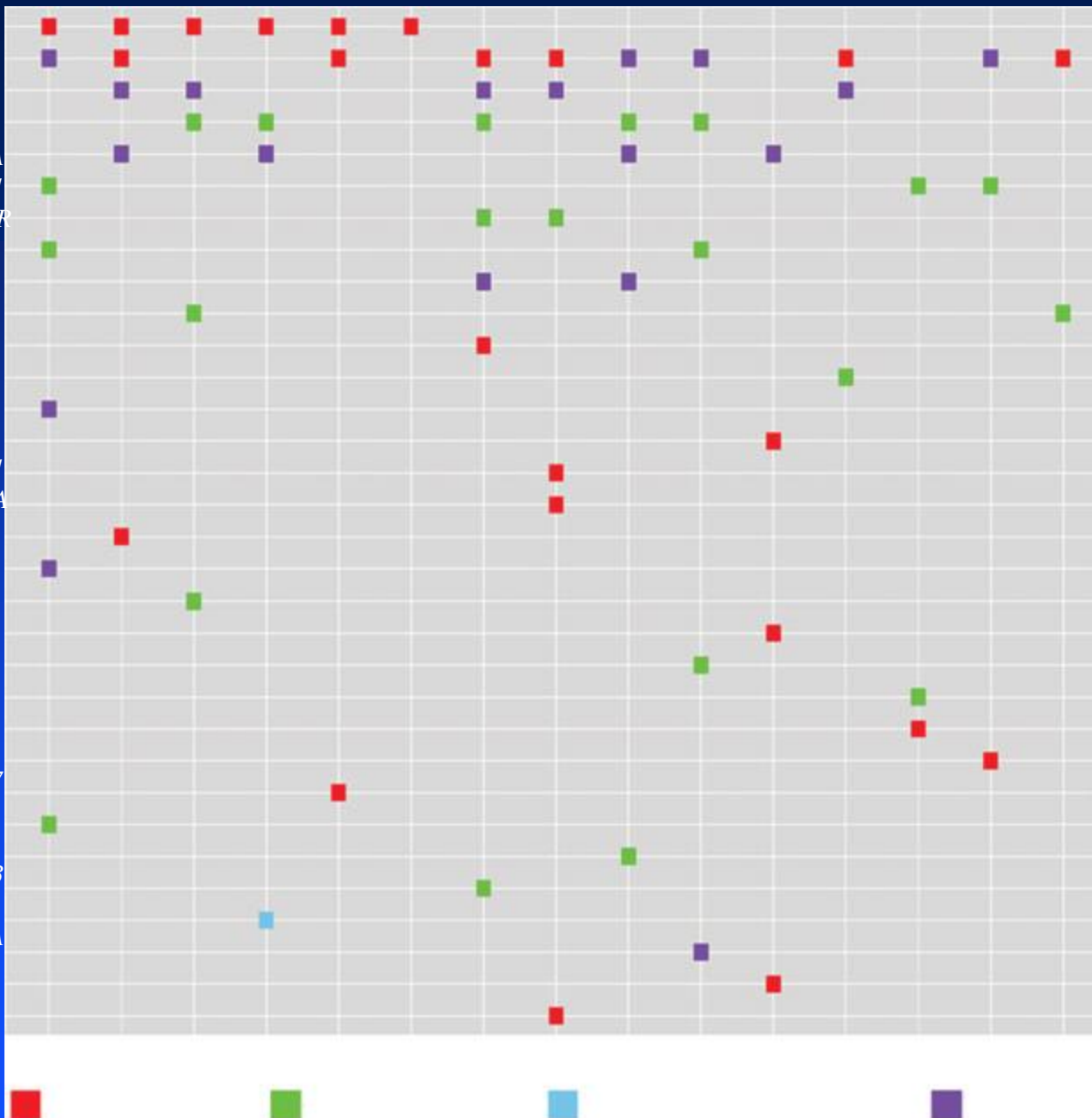
Micropapillary Carcinoma: Cancer-specific survival







ERBB2
TP53
RB1
MCL1
ARID1A
CCND1
RICTOR
MYCL1
MLL2
EGFR
RUNX1
RAF1
PTEN
PTCH1
PIK3R1
PIK3CA
NF2
MSH2
MDM2
KRAS
JAK2
IRS2
IDH2
HRAS
FBXW7
EPHA3
CCNE1
CCND3
BAP1
AURKA
AKT2
AKT1



Substitution/Indel

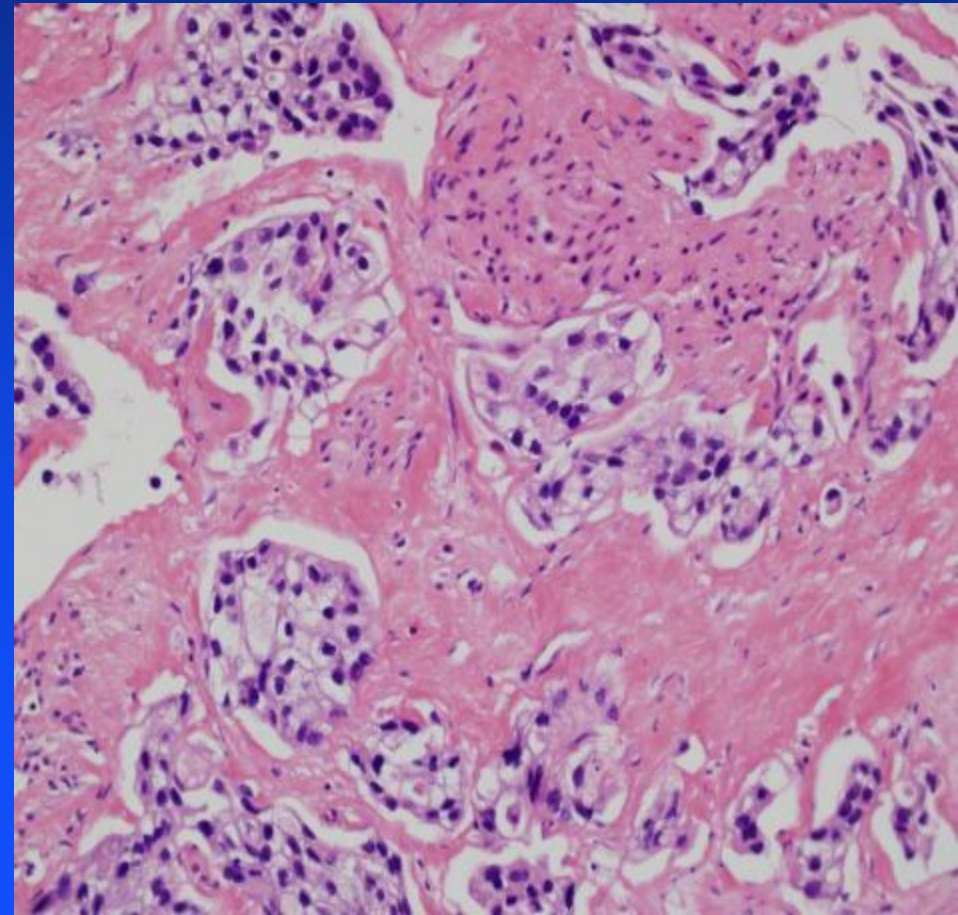
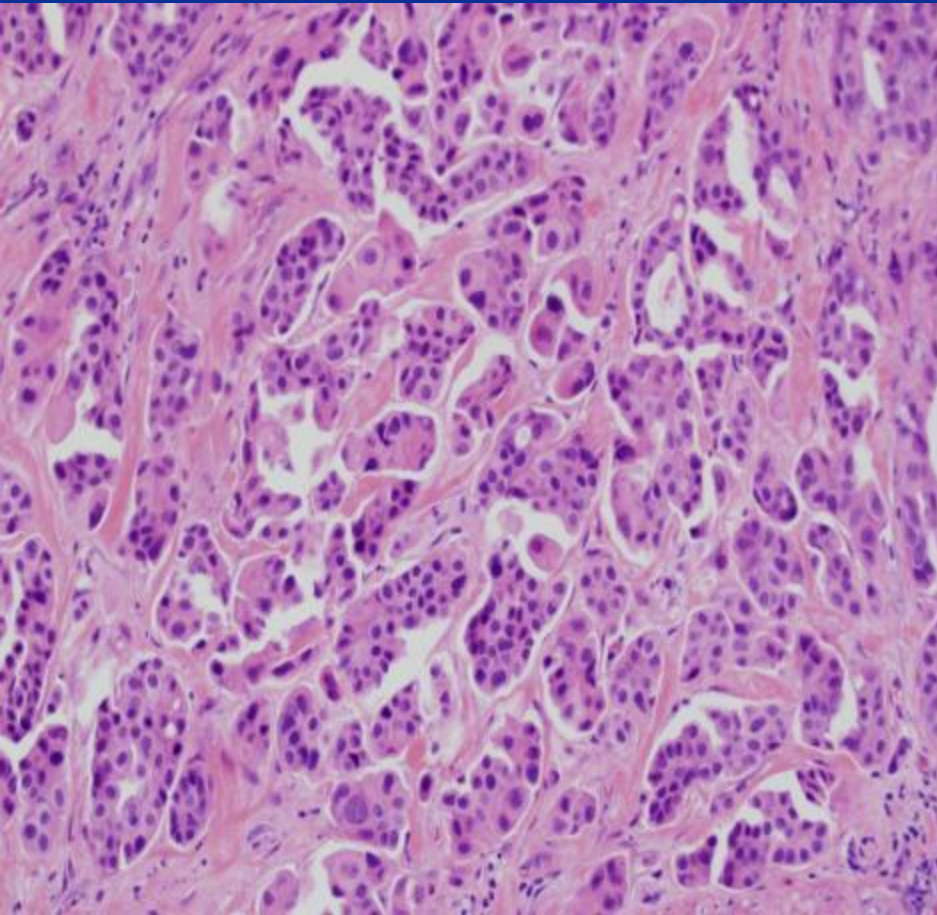
Amplification

Homozygous del

Truncation

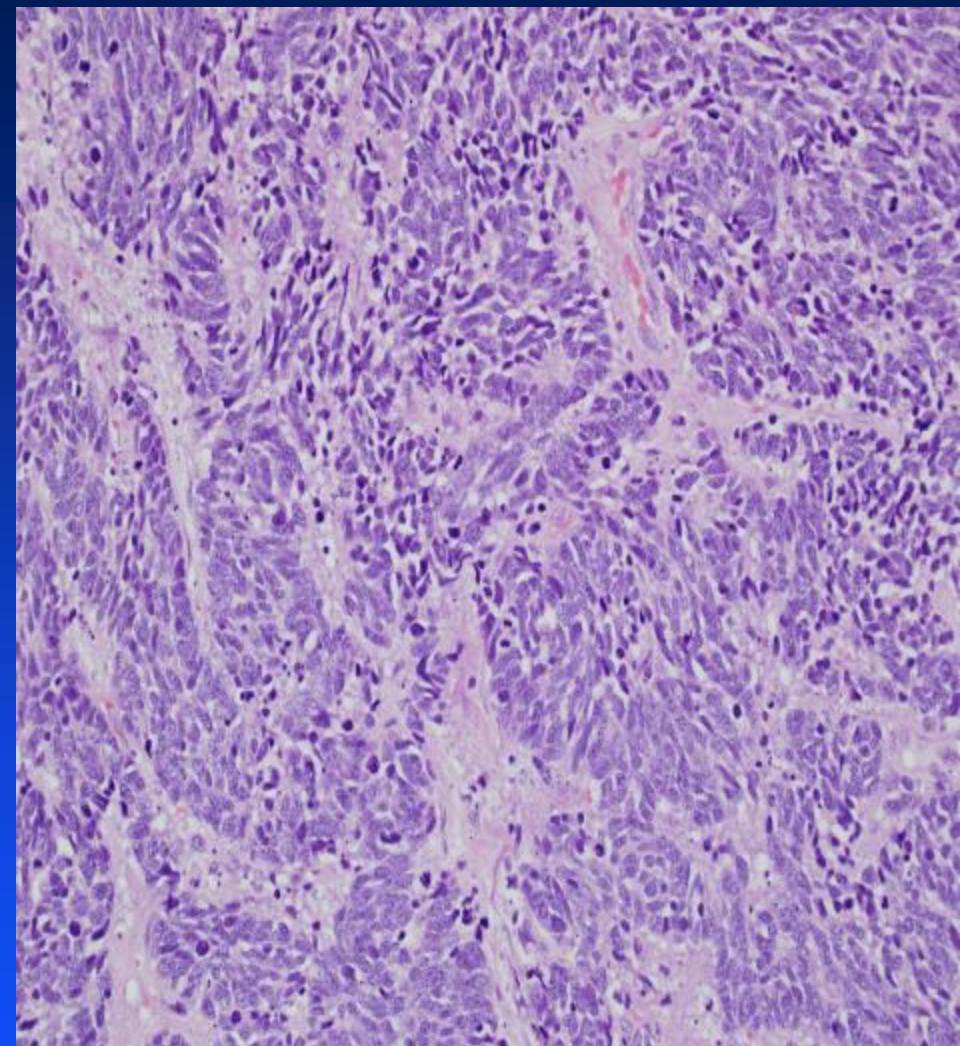
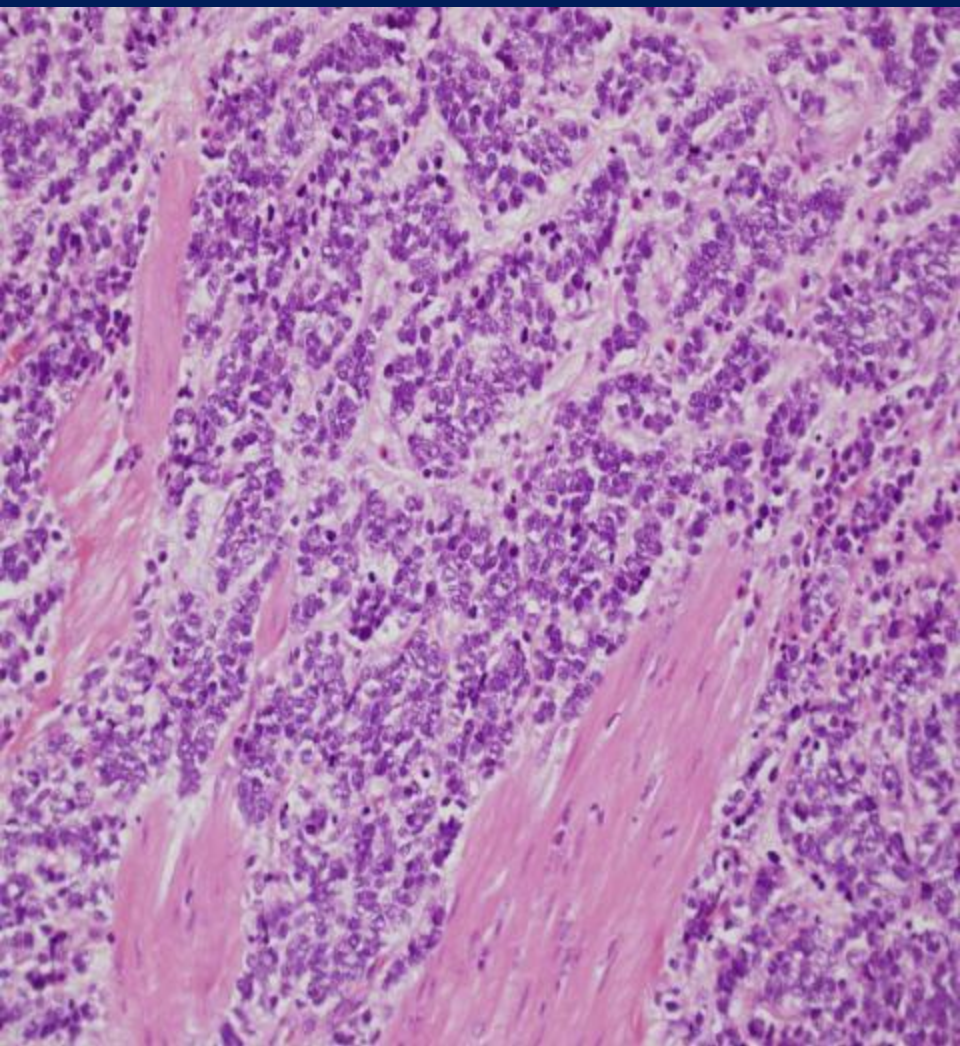
Interobserver Reproducibility in the Diagnosis of Invasive Micropapillary Carcinoma of the Urinary Tract Among Urologic Pathologists

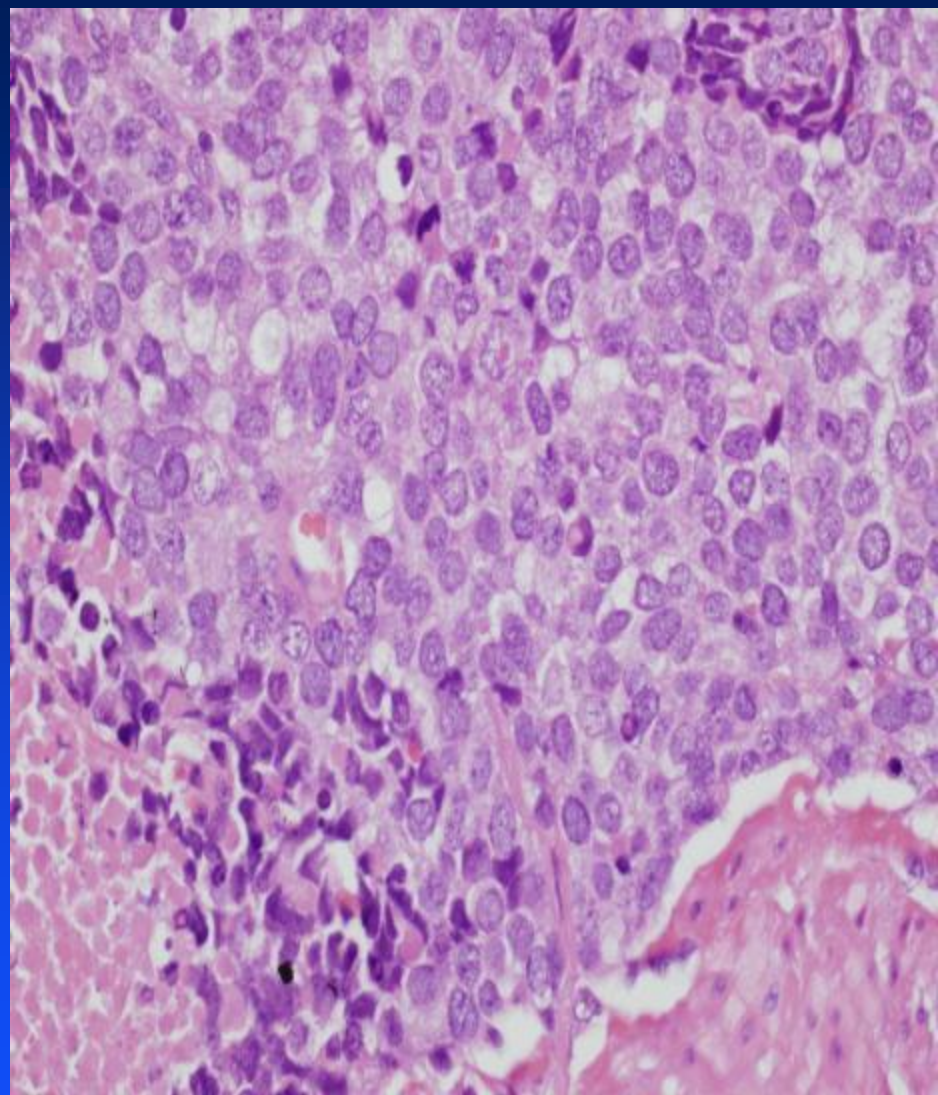
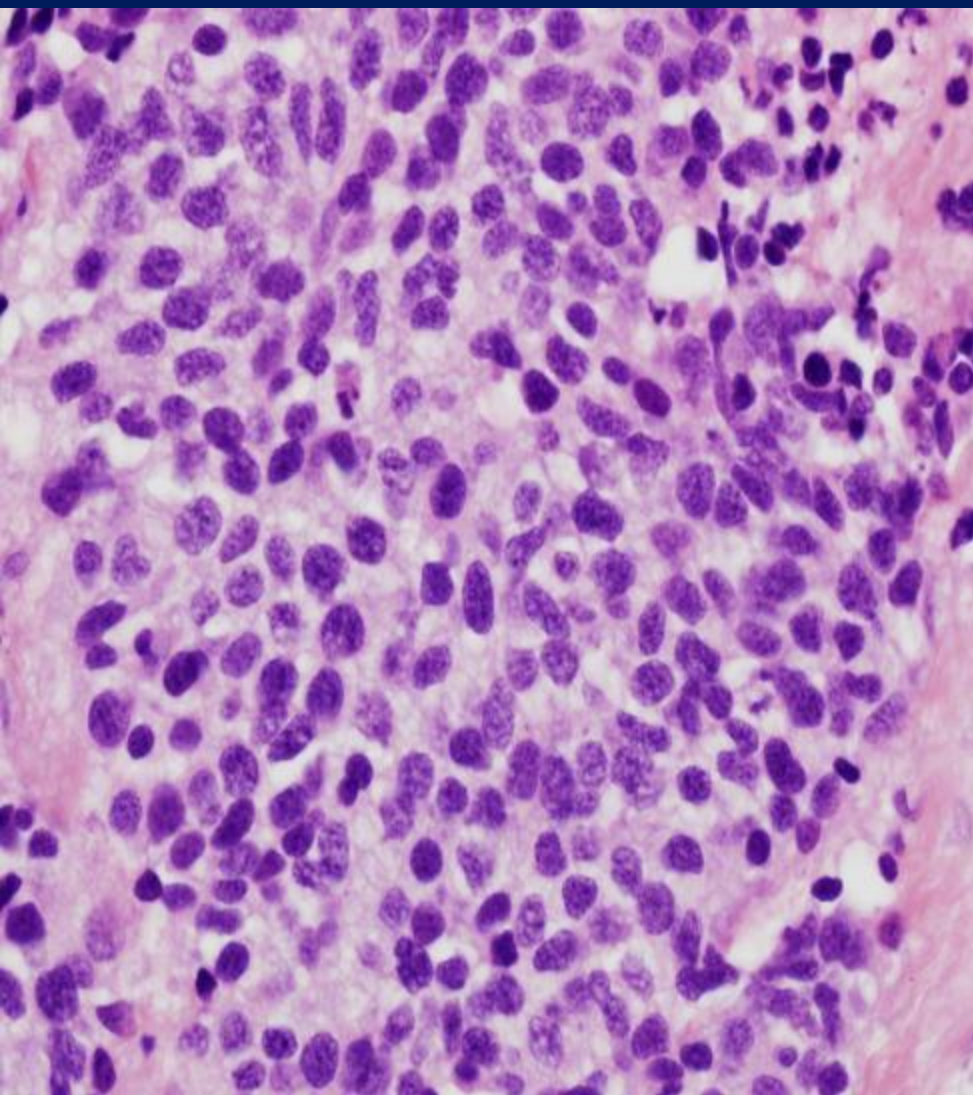
Ankur R. Sangoi, MD,† Andrew H. Beck, MD,* Mahul B. Amin, MD,‡ Liang Cheng, MD,§ Jonathan I. Epstein, MD,|| Donna E. Hansel, MD, PhD,¶ Kenneth A. Iczkowski, MD,# Antonio Lopez-Beltran, MD, PhD,** Esther Oliva, MD, † † Gladell P. Paner, MD,‡‡ Victor E. Reuter, MD,§§ Jae Y. Ro, MD, PhD,||| Rajal B. Shah, MD,¶¶ Steven S. Shen, MD, PhD,||| Pheroze Tamboli, MD,### and Jesse K. McKenney, MD**

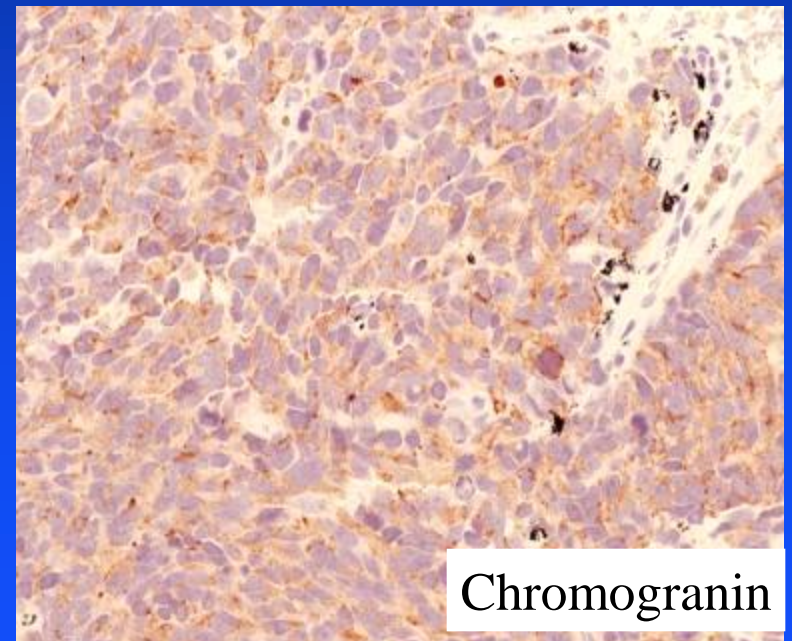
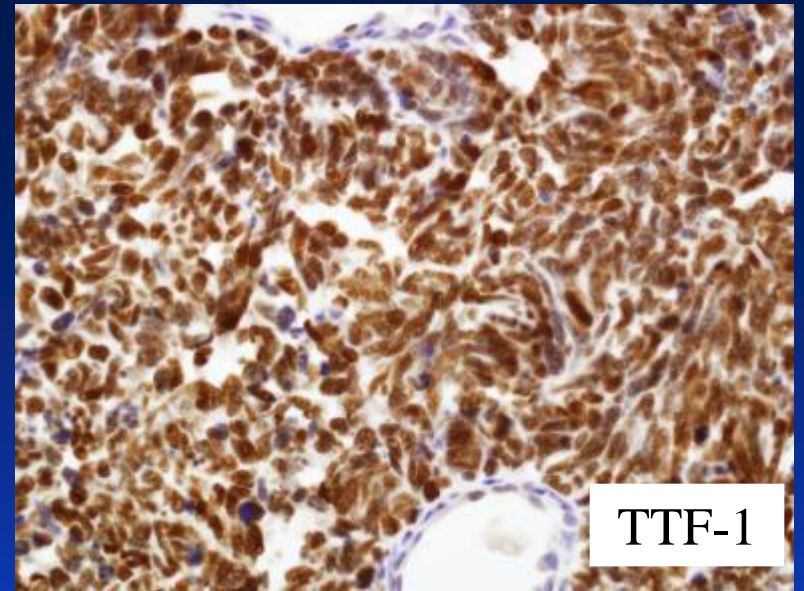
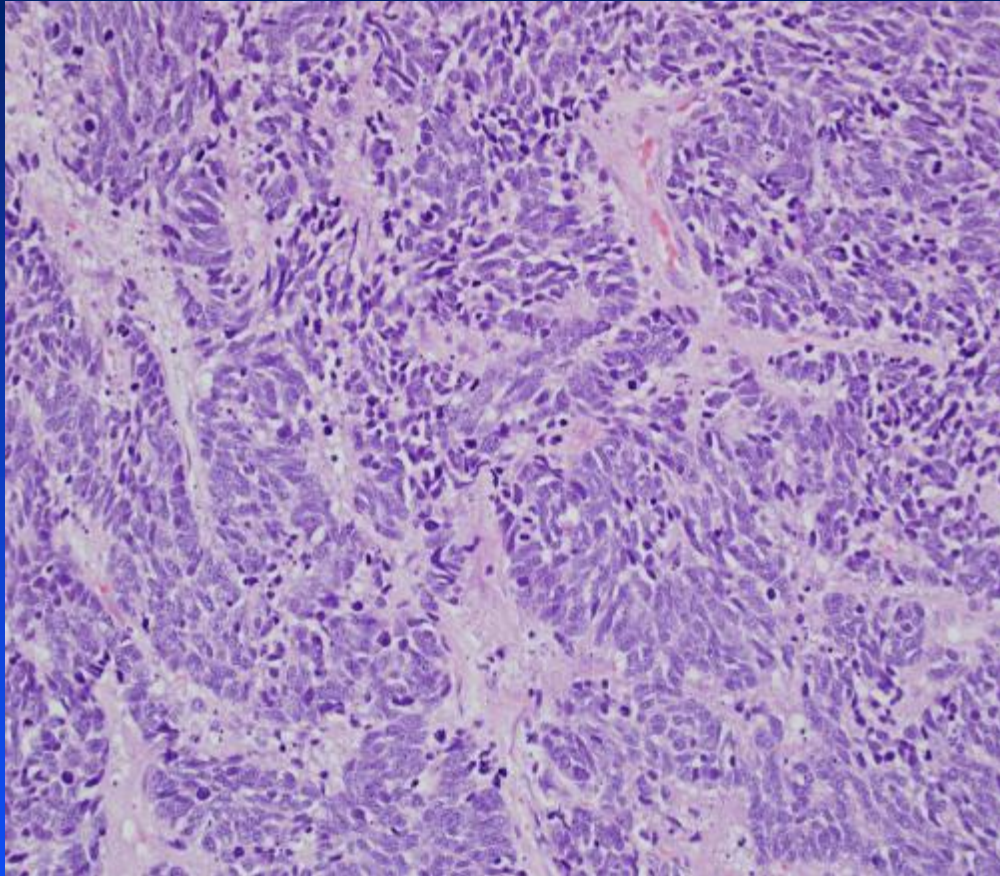


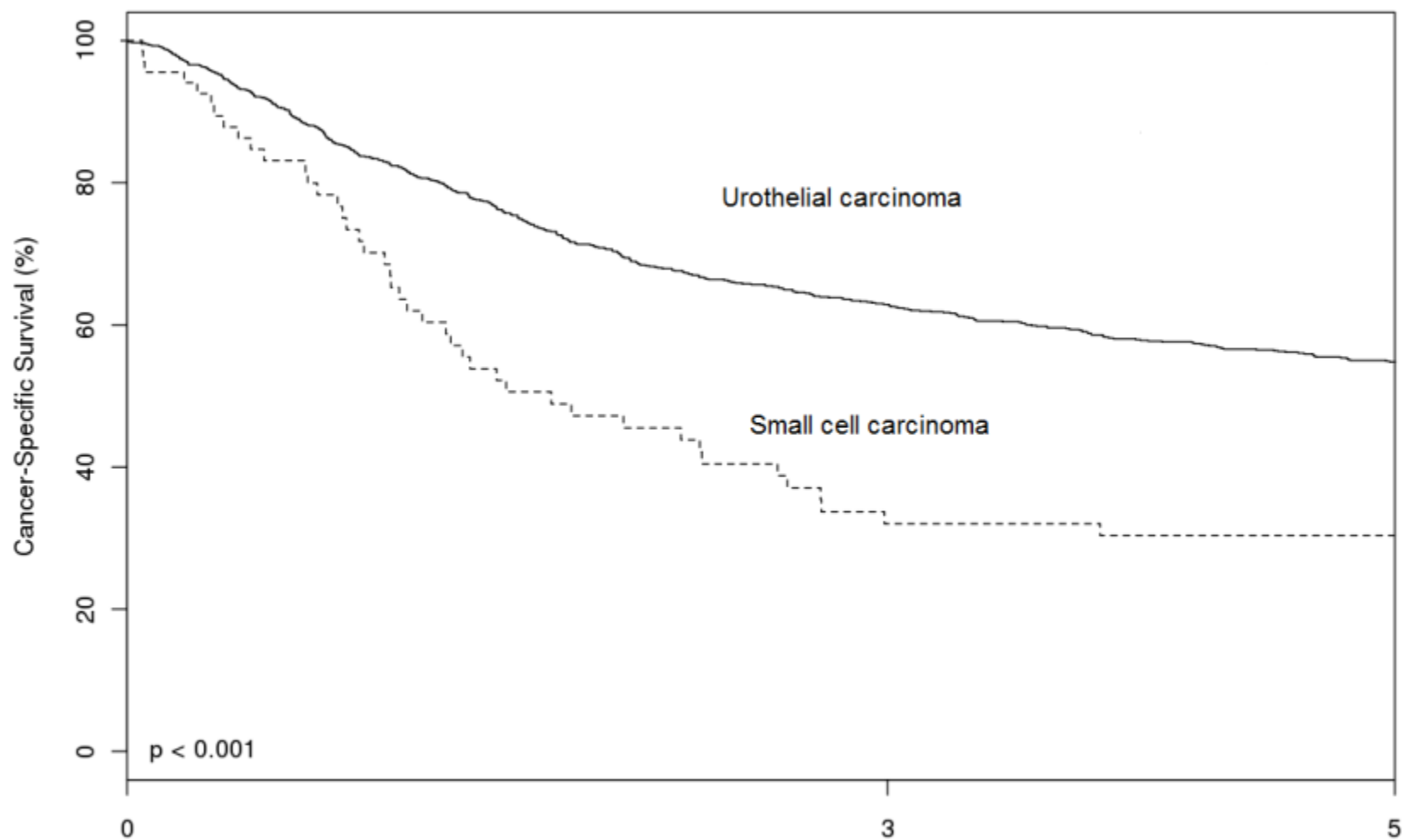
Small Cell Carcinoma

- 2.8% of all patients undergoing cystectomy (68 of 2427 patients)
- 77% of all cases were pure small cell carcinoma
- 84% were advanced stage pT3/T4
- Only 25% of patients had an original diagnosis of small cell carcinoma
- **Diagnostic criteria not well established**

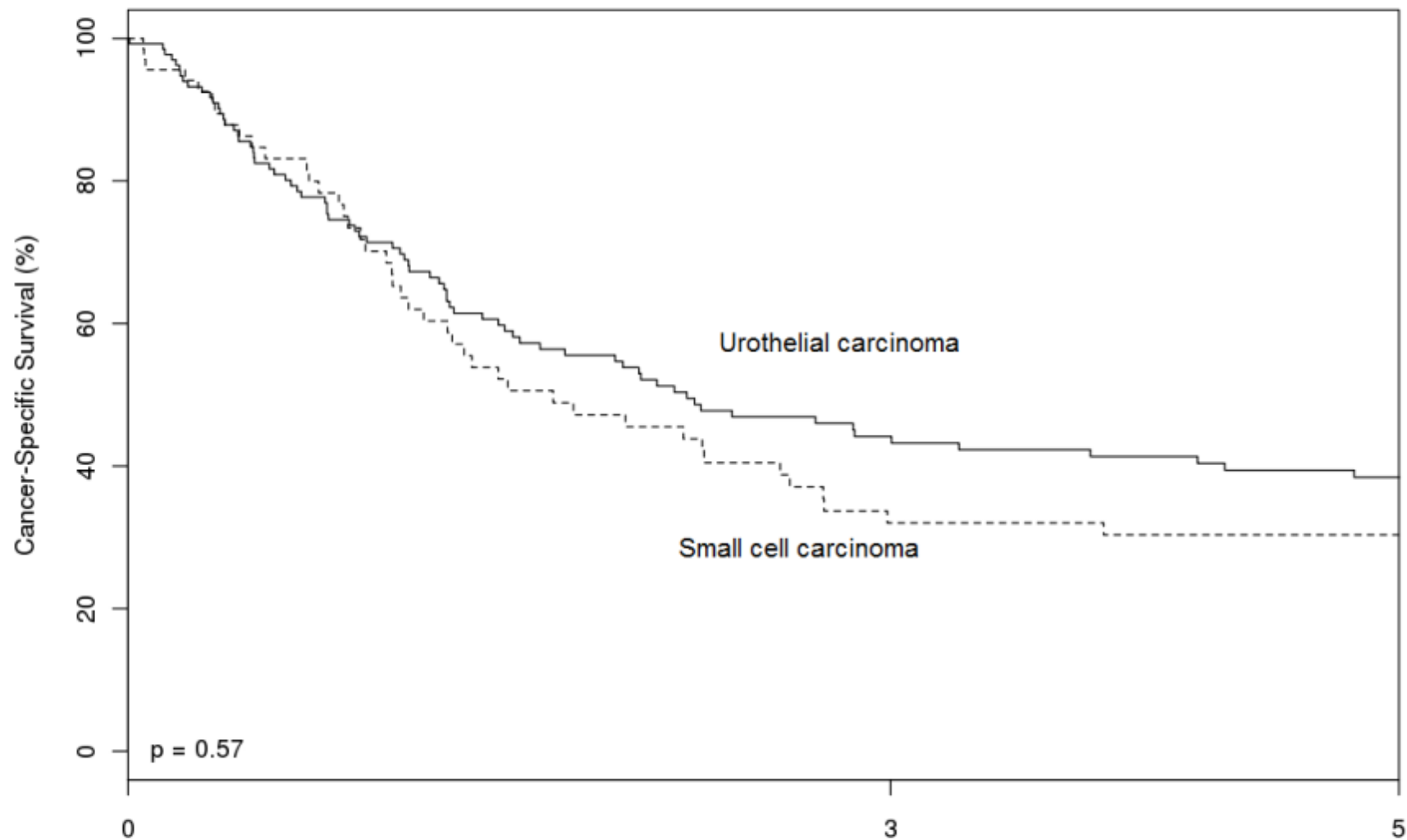




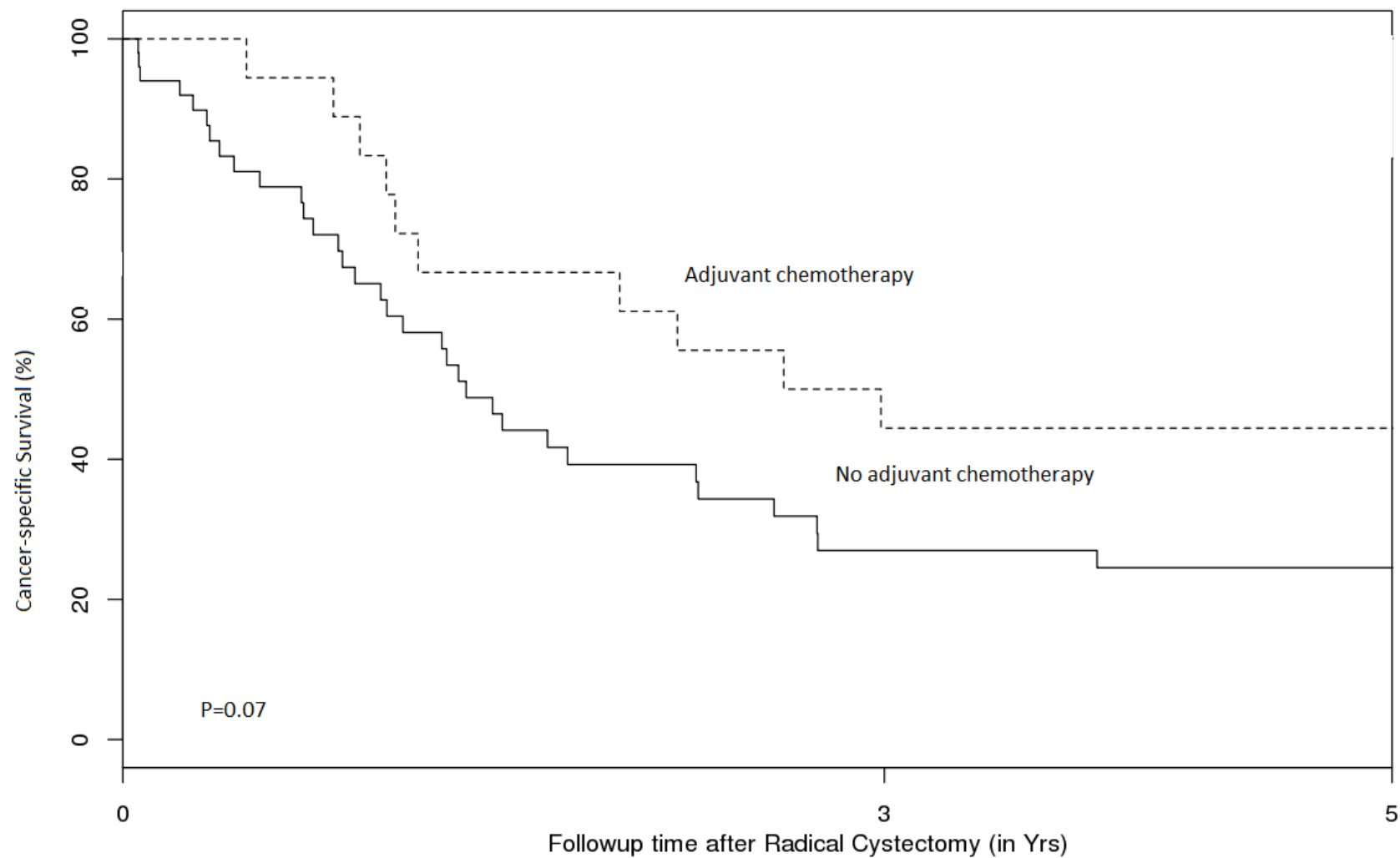




	Survival (%)	Time to Bladder Death (In Years)		
	(No. at Risk)			
Urothelial	100 (1115)	63 (600)	55 (474)	
Small Cell	100 (68)	32 (19)	30 (18)	



	Survival (%)			
	(No. at Risk)			
UC	100 (136)		44 (48)	38 (39)
Small Cell	100 (68)		32 (19)	30 (18)



Survival free of CS death (%)

(No. at Risk)

No adjuvant 100 (49)

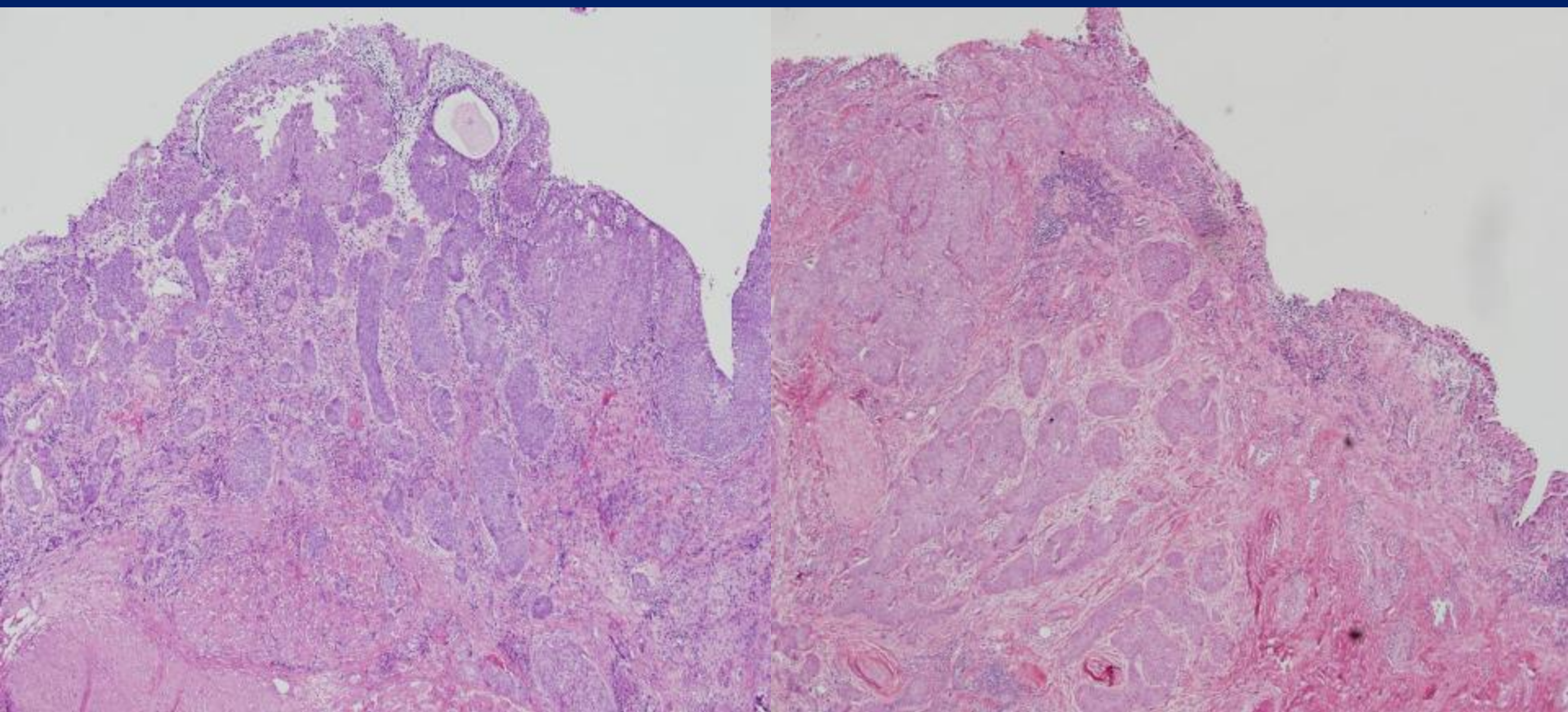
Adjuvant 100 (17)

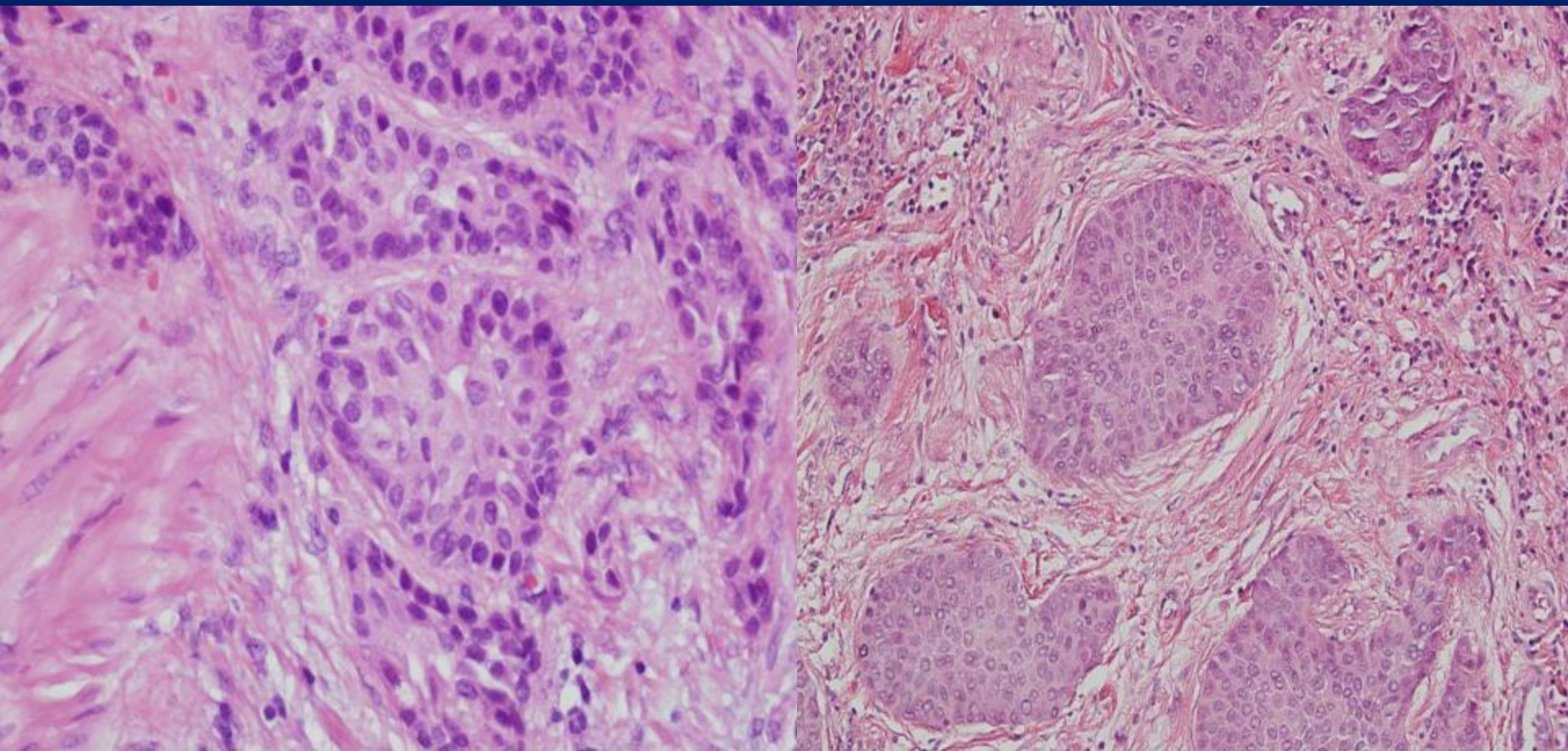
11 (27)

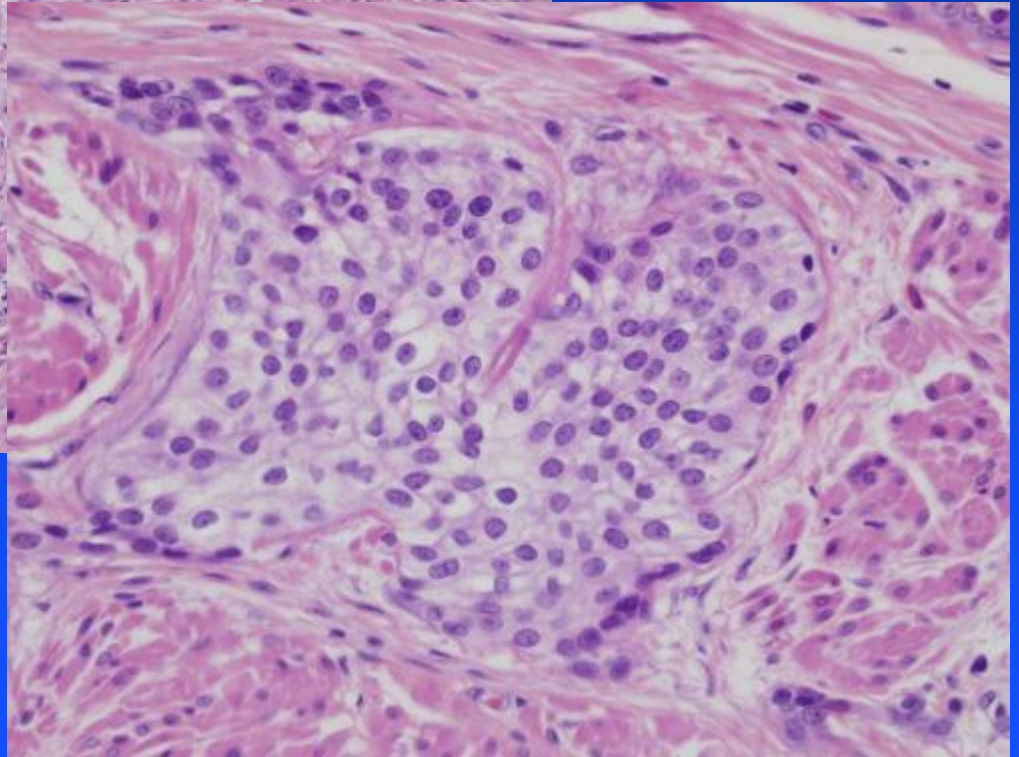
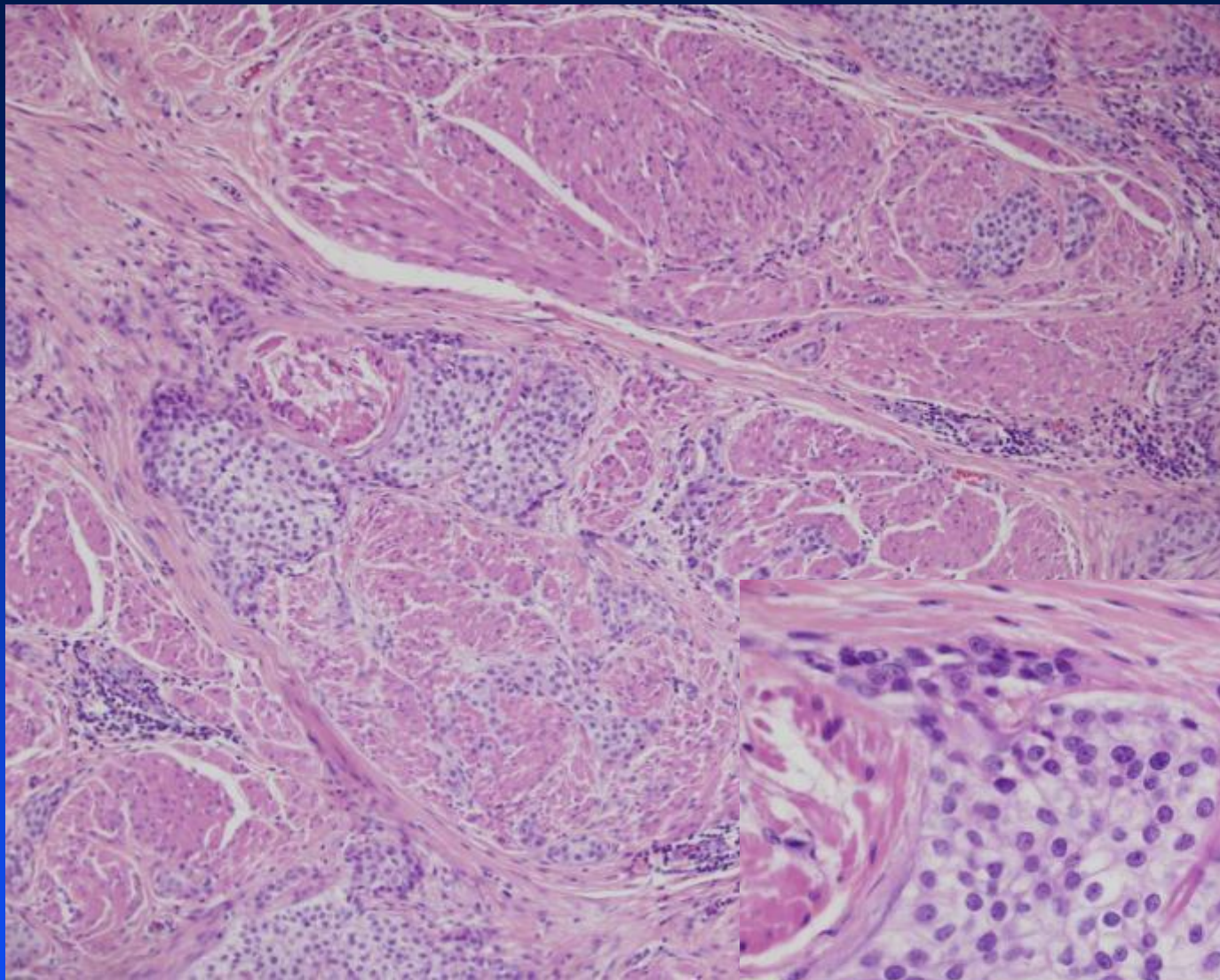
47 (8)

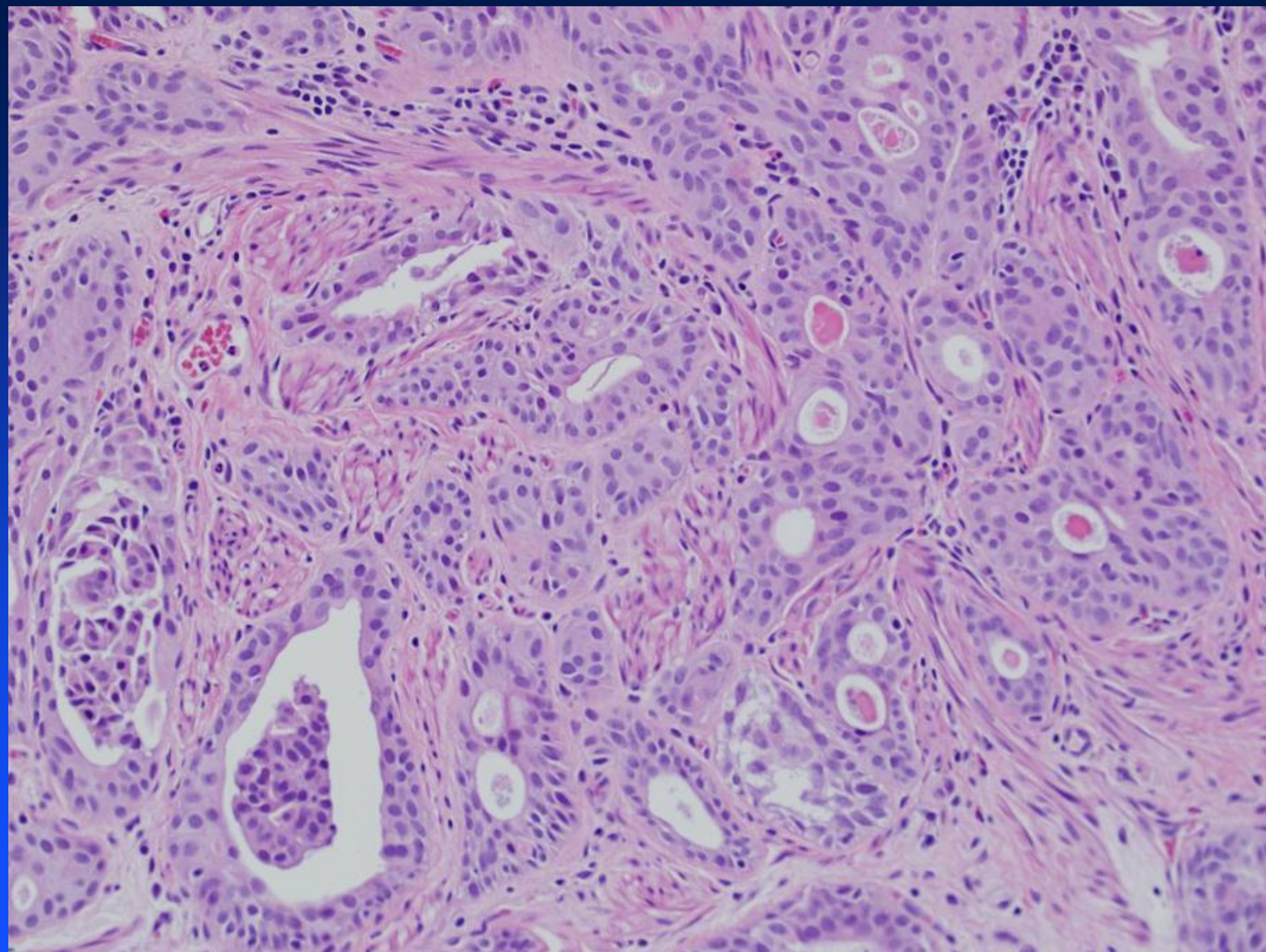
10 (25)

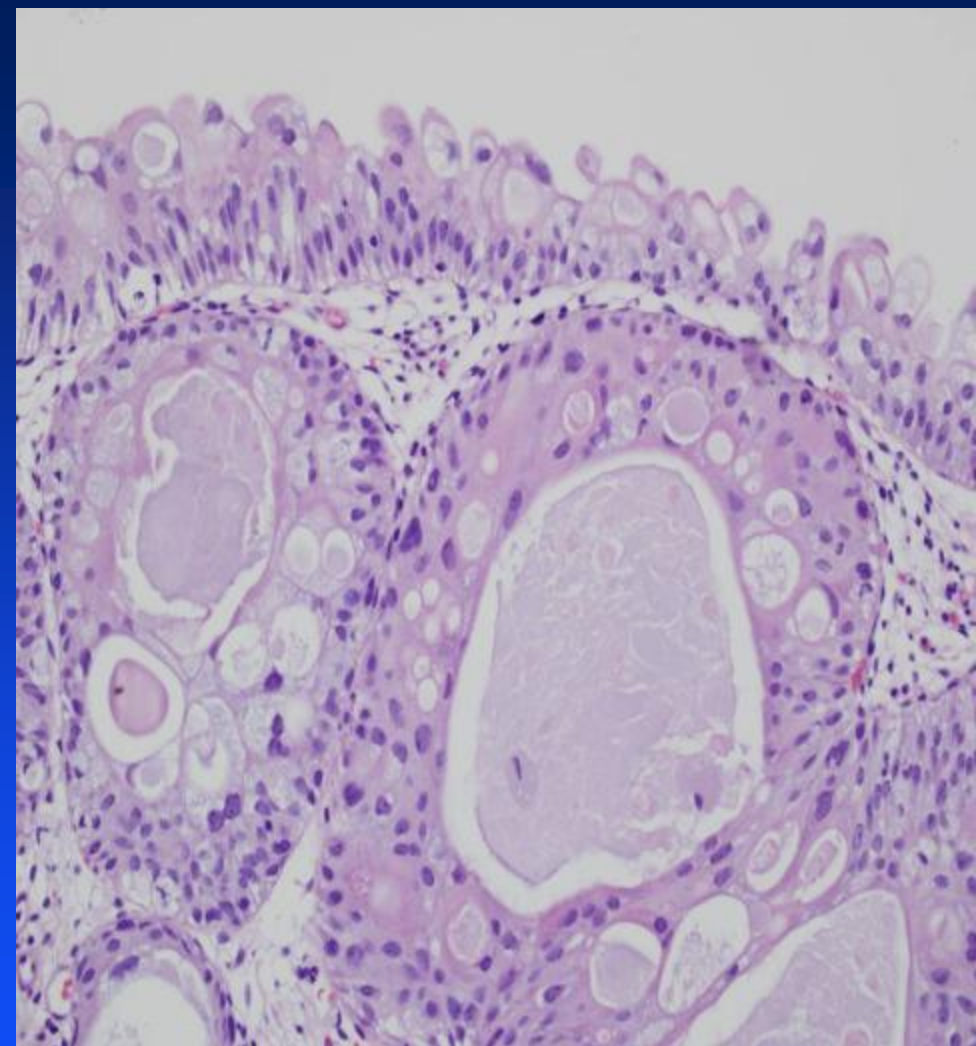
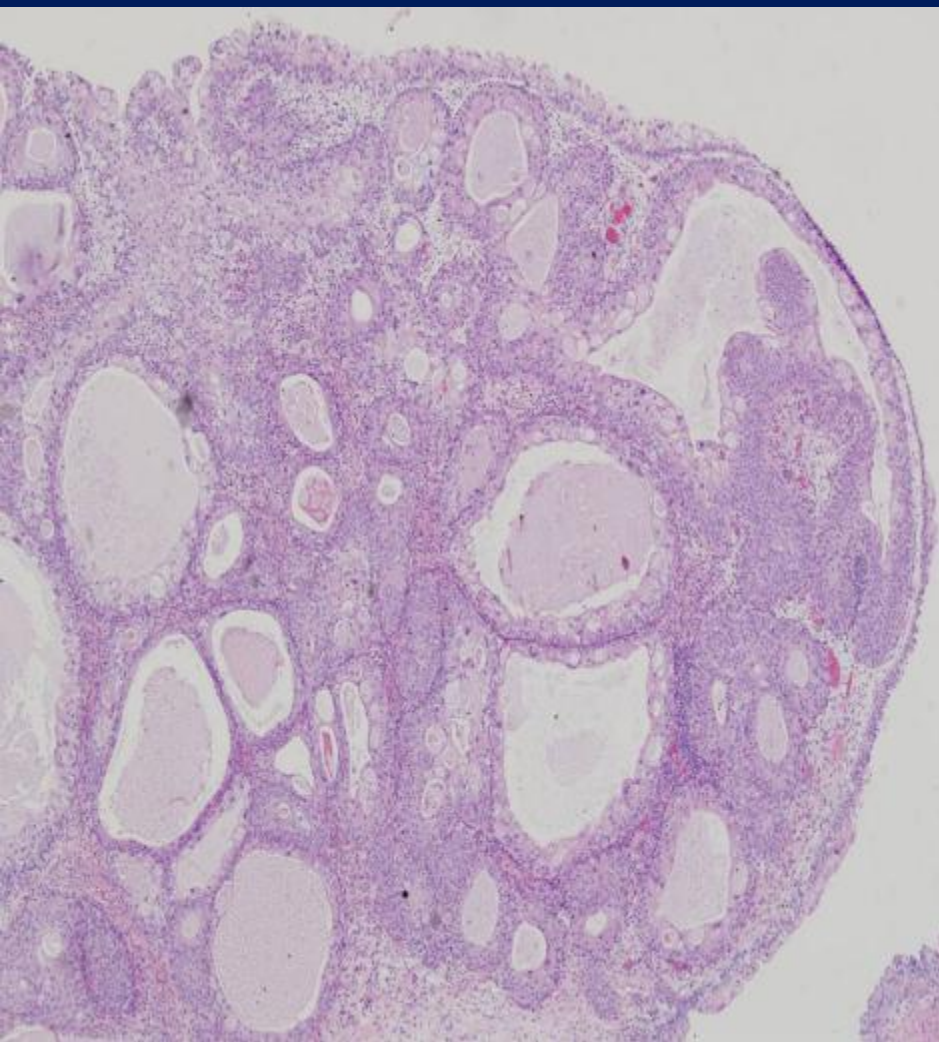
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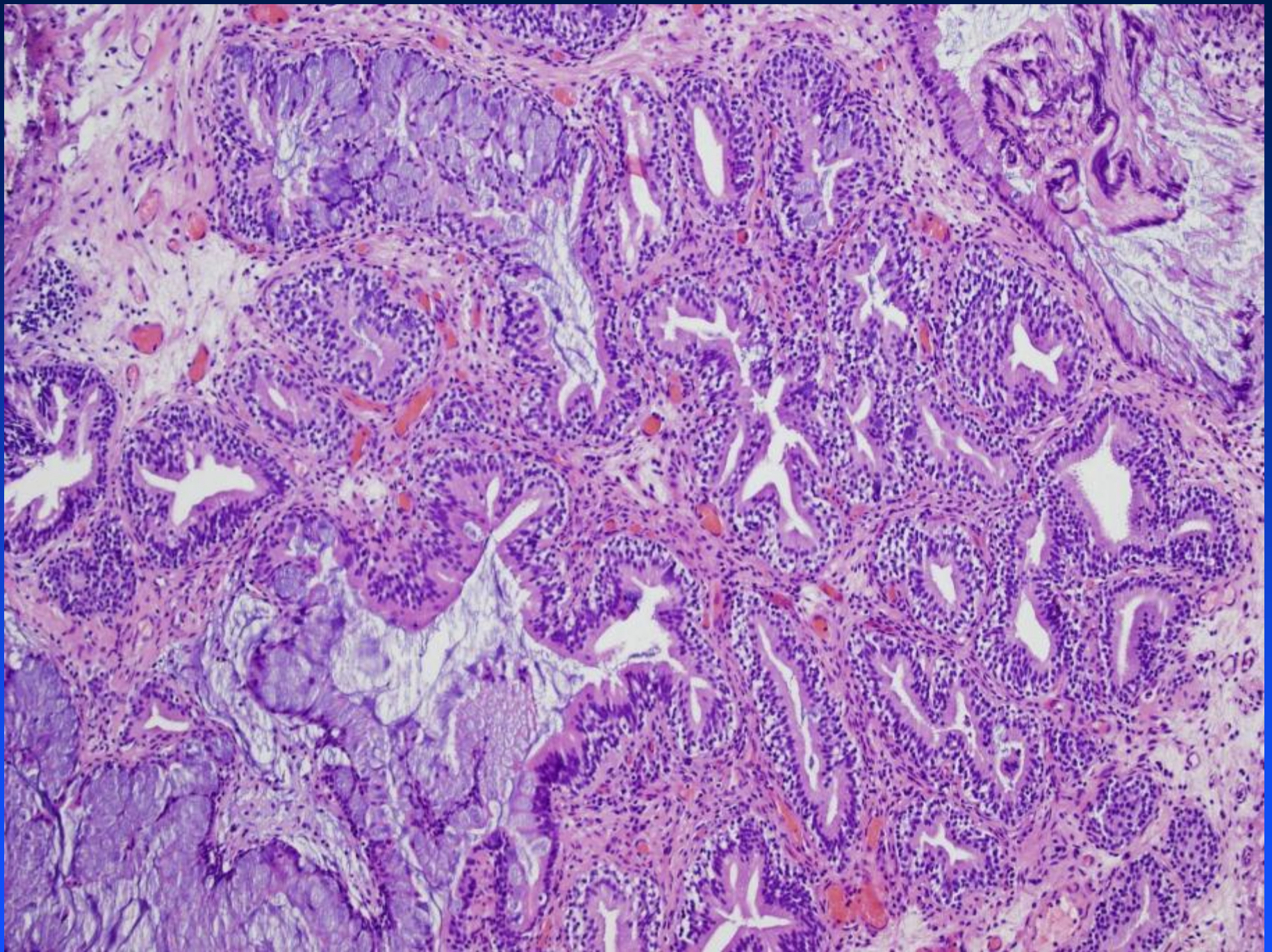


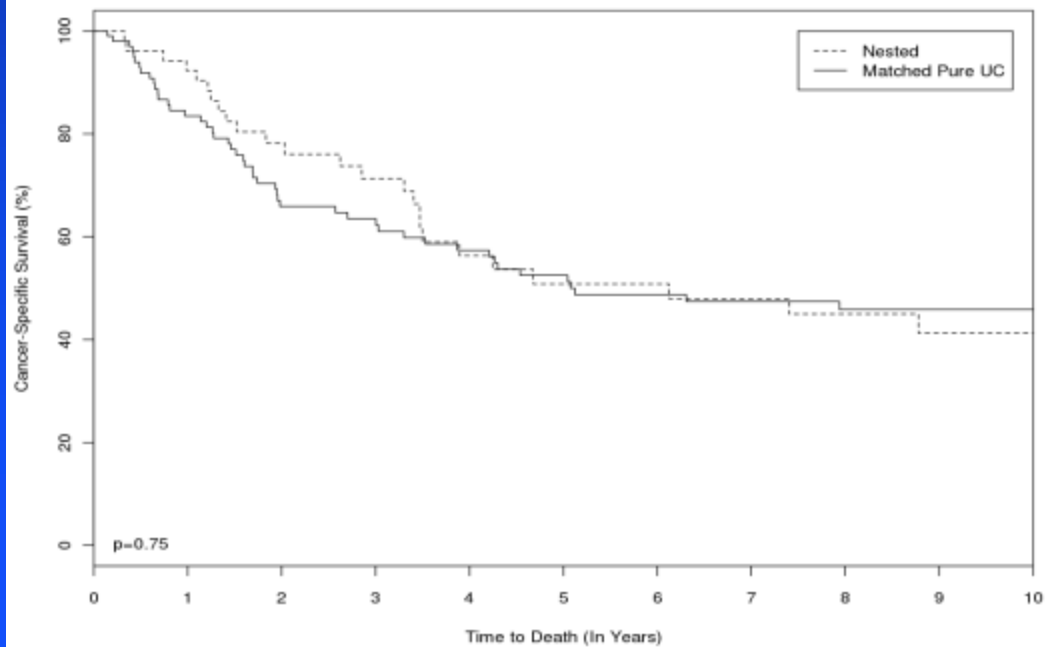
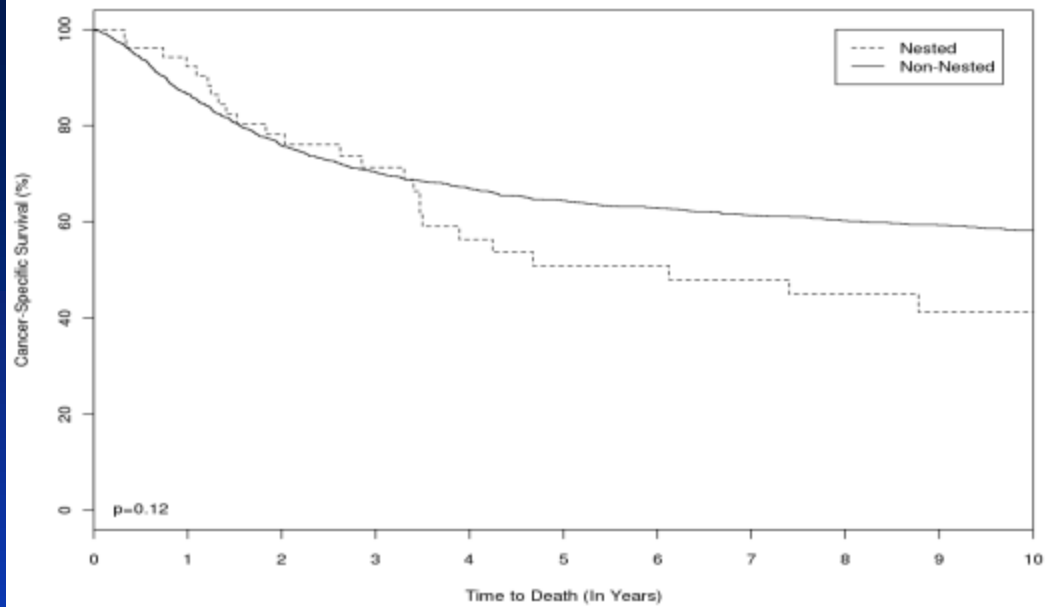


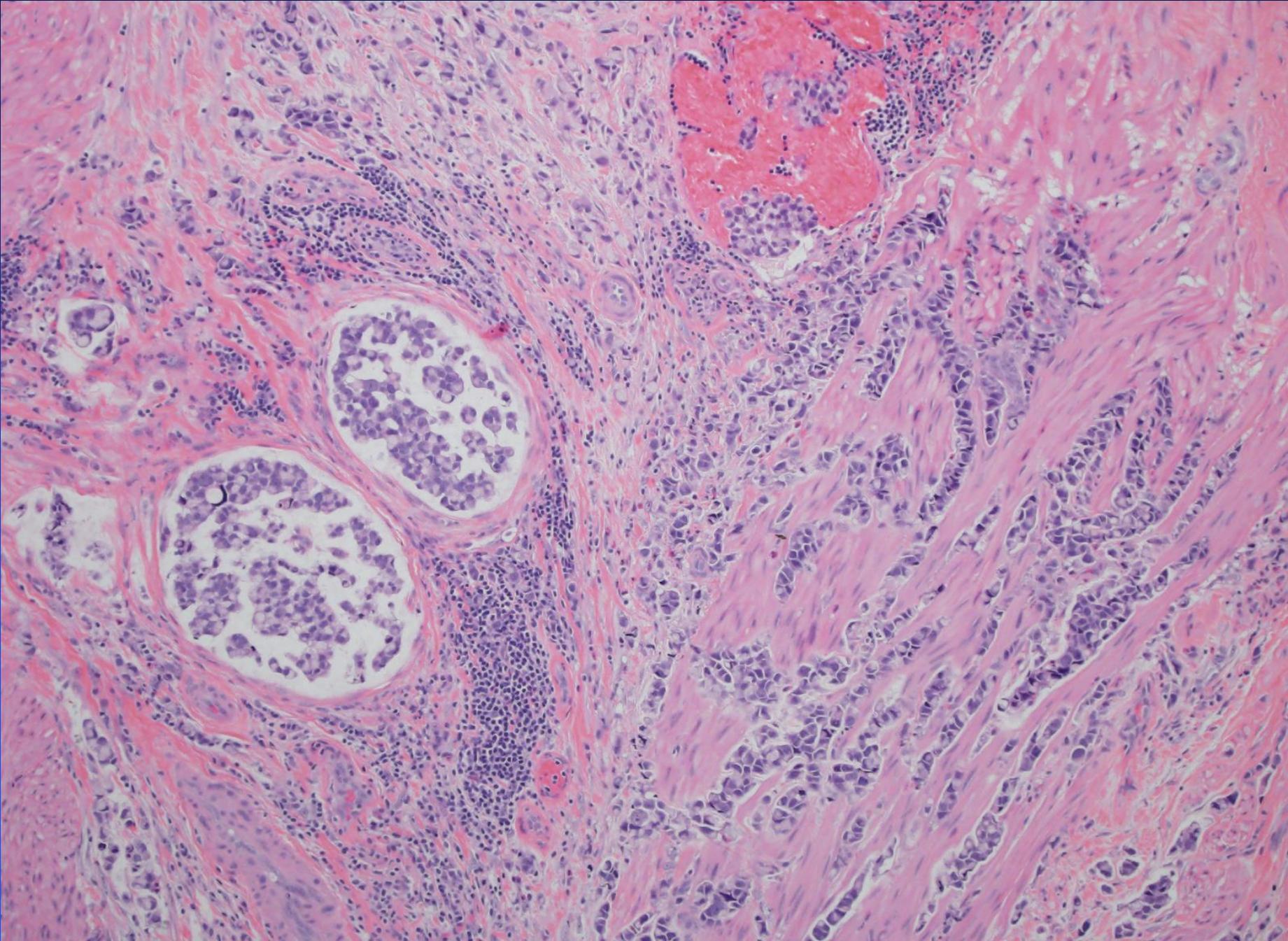


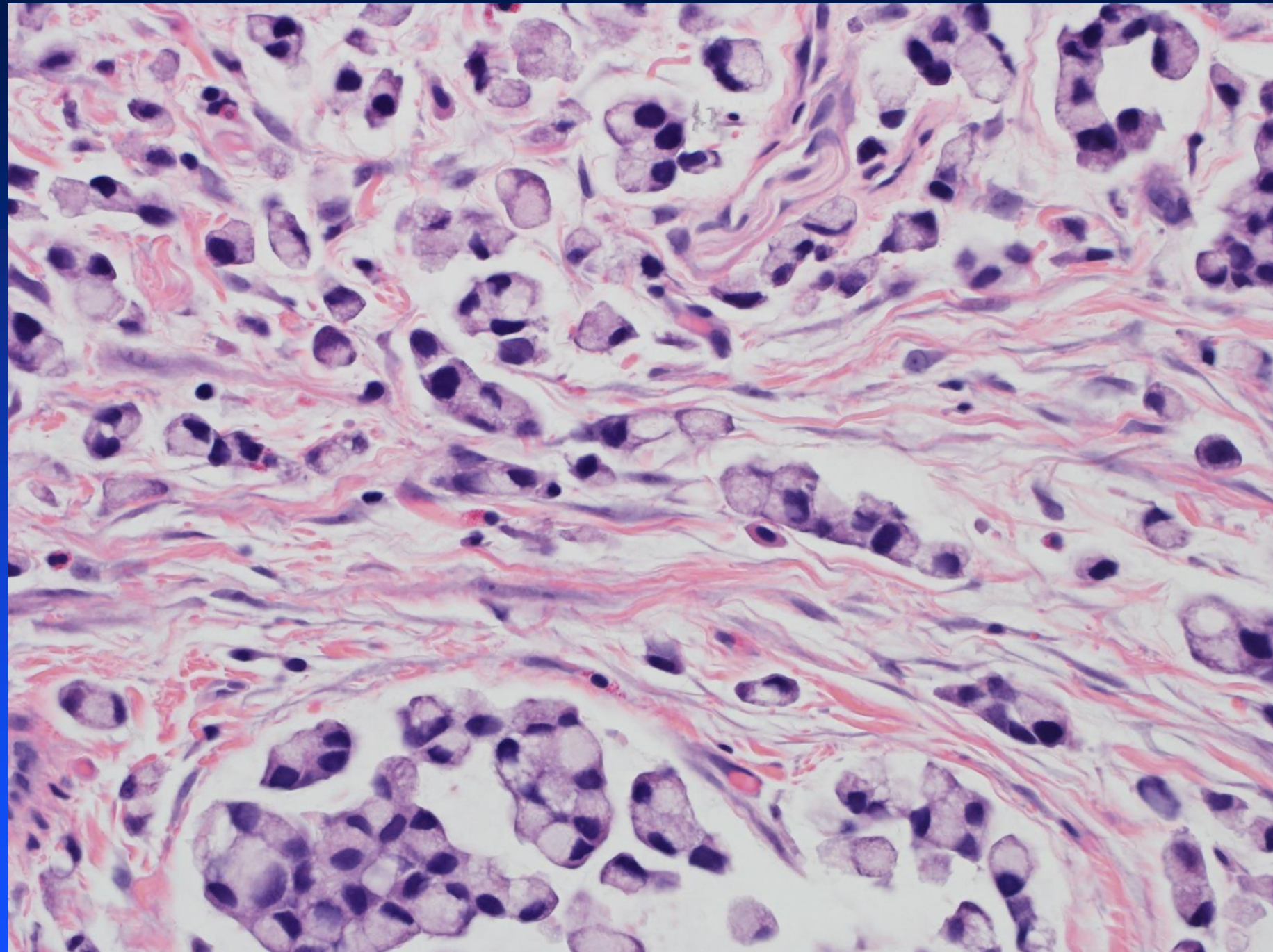


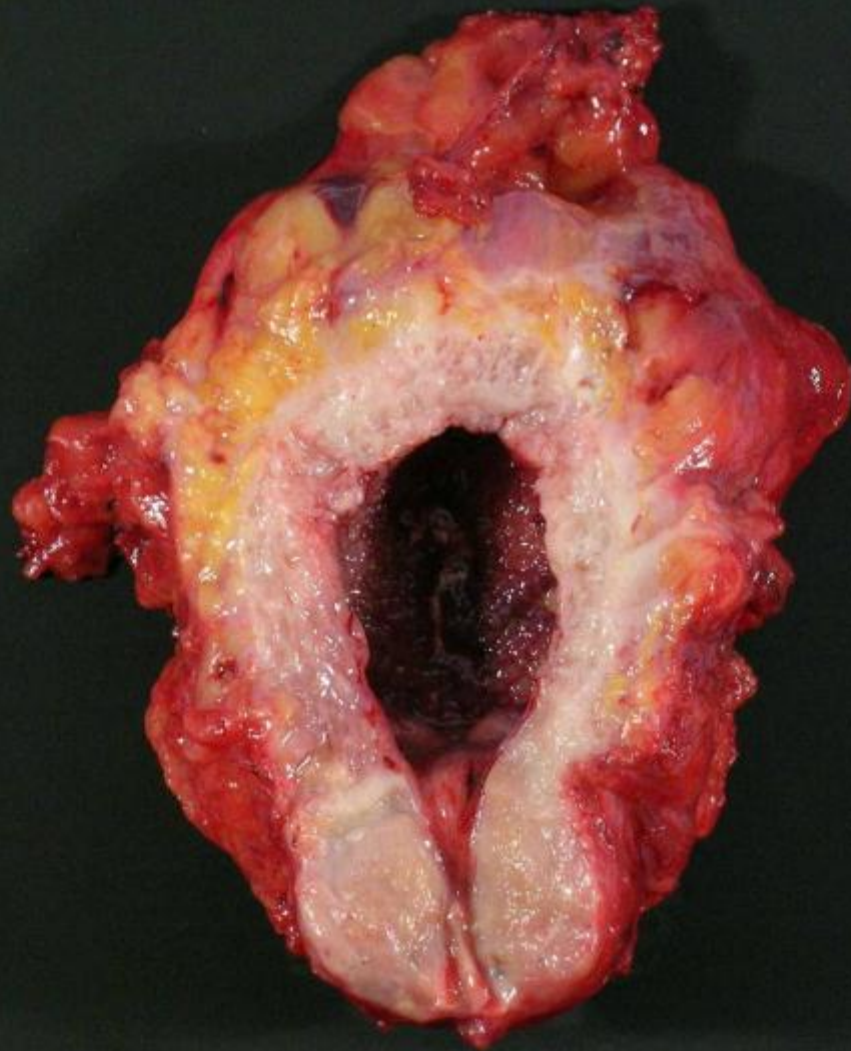


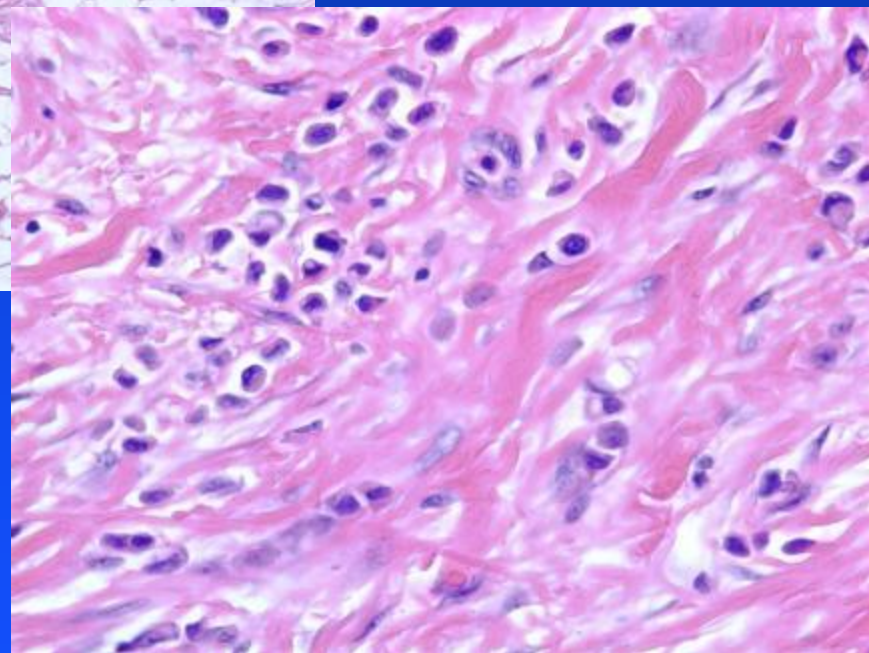
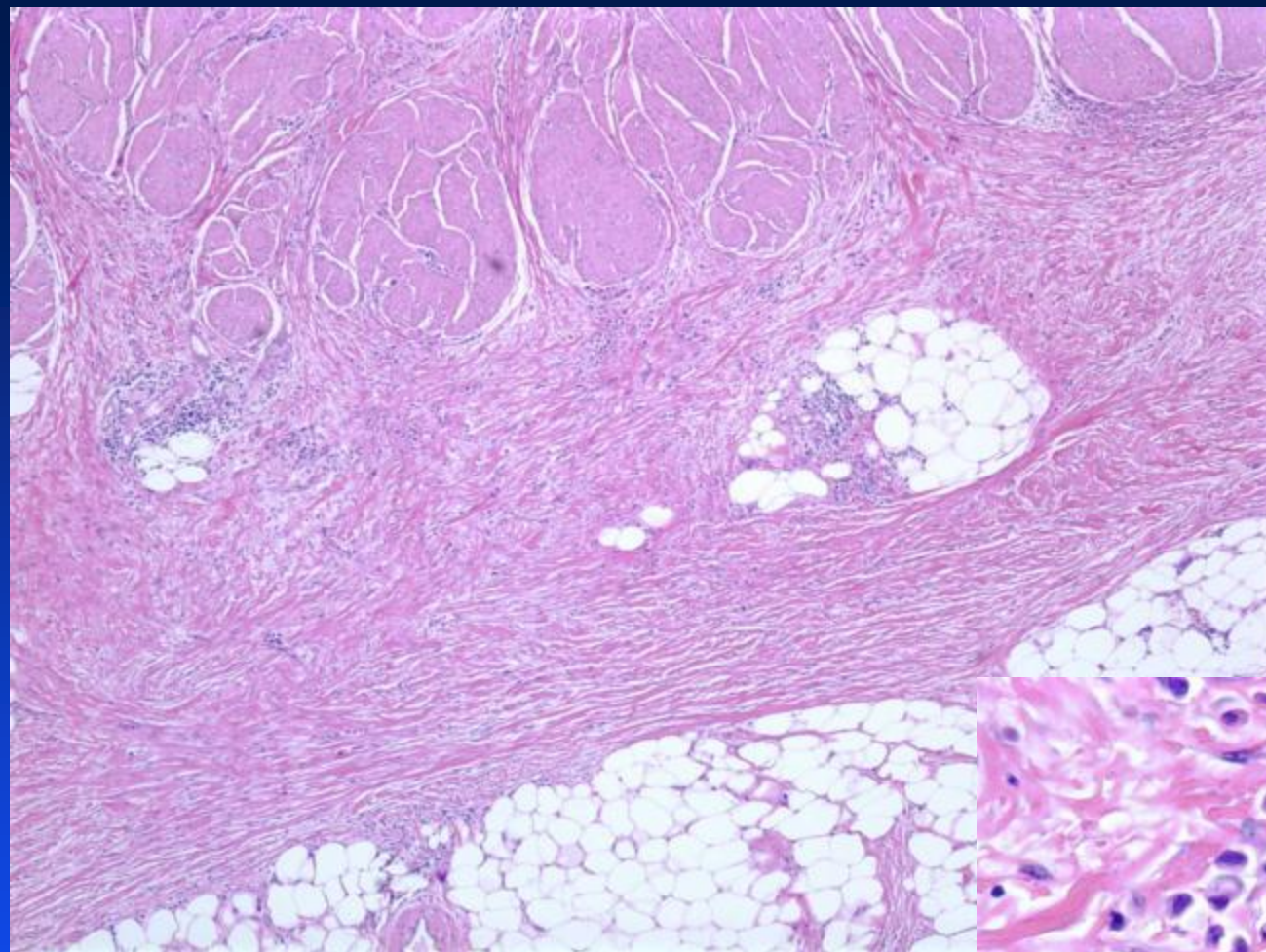


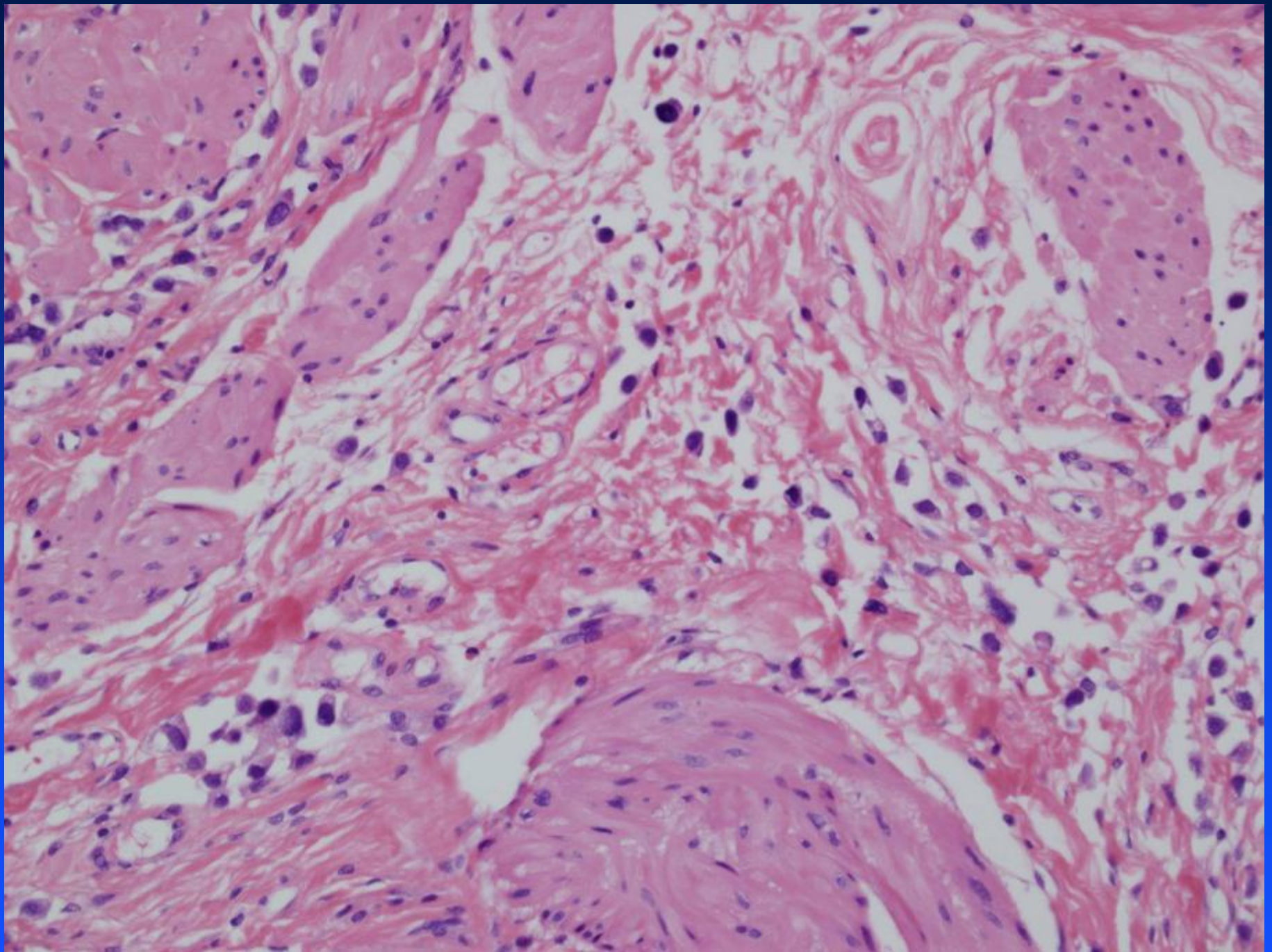


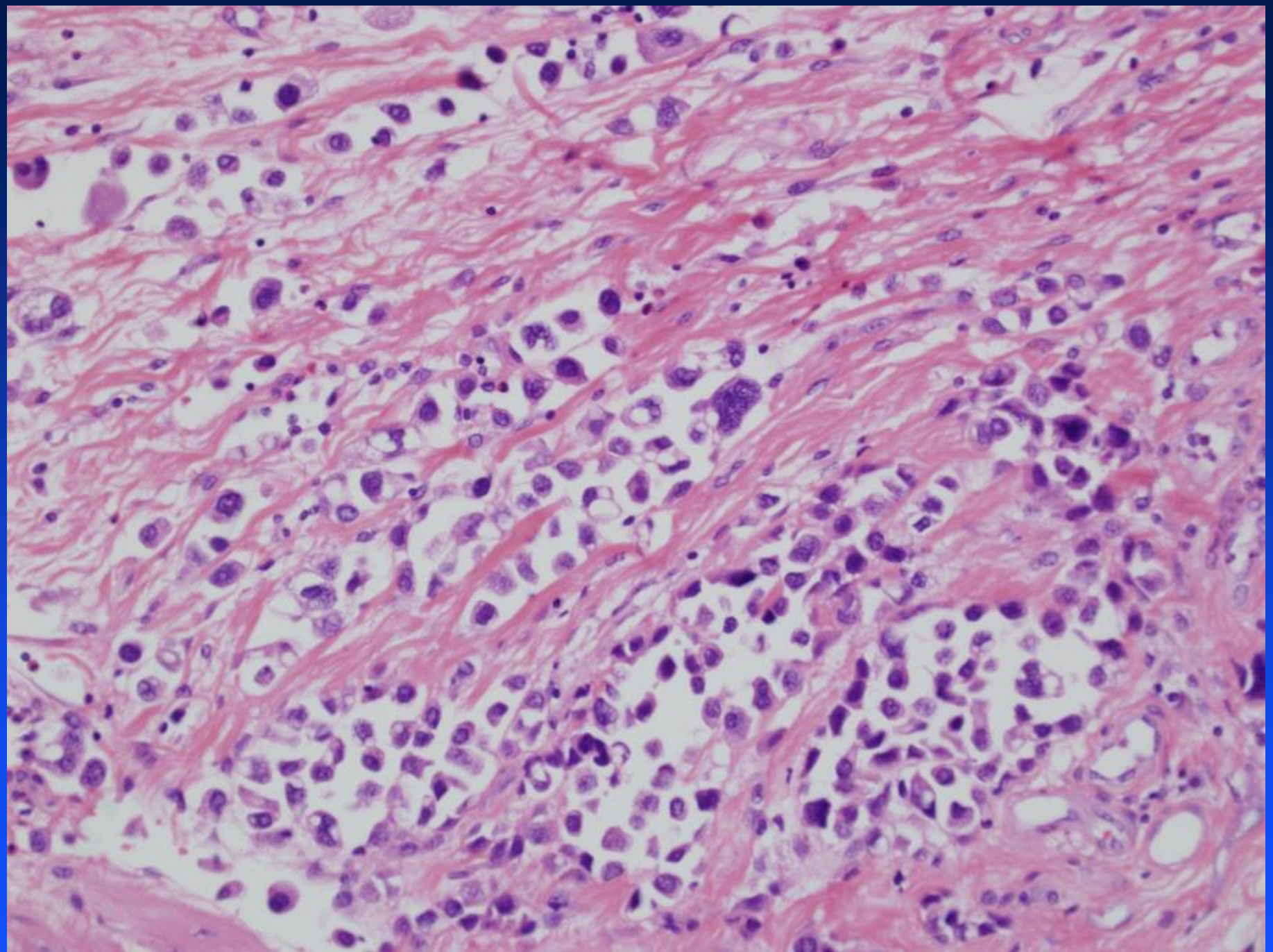


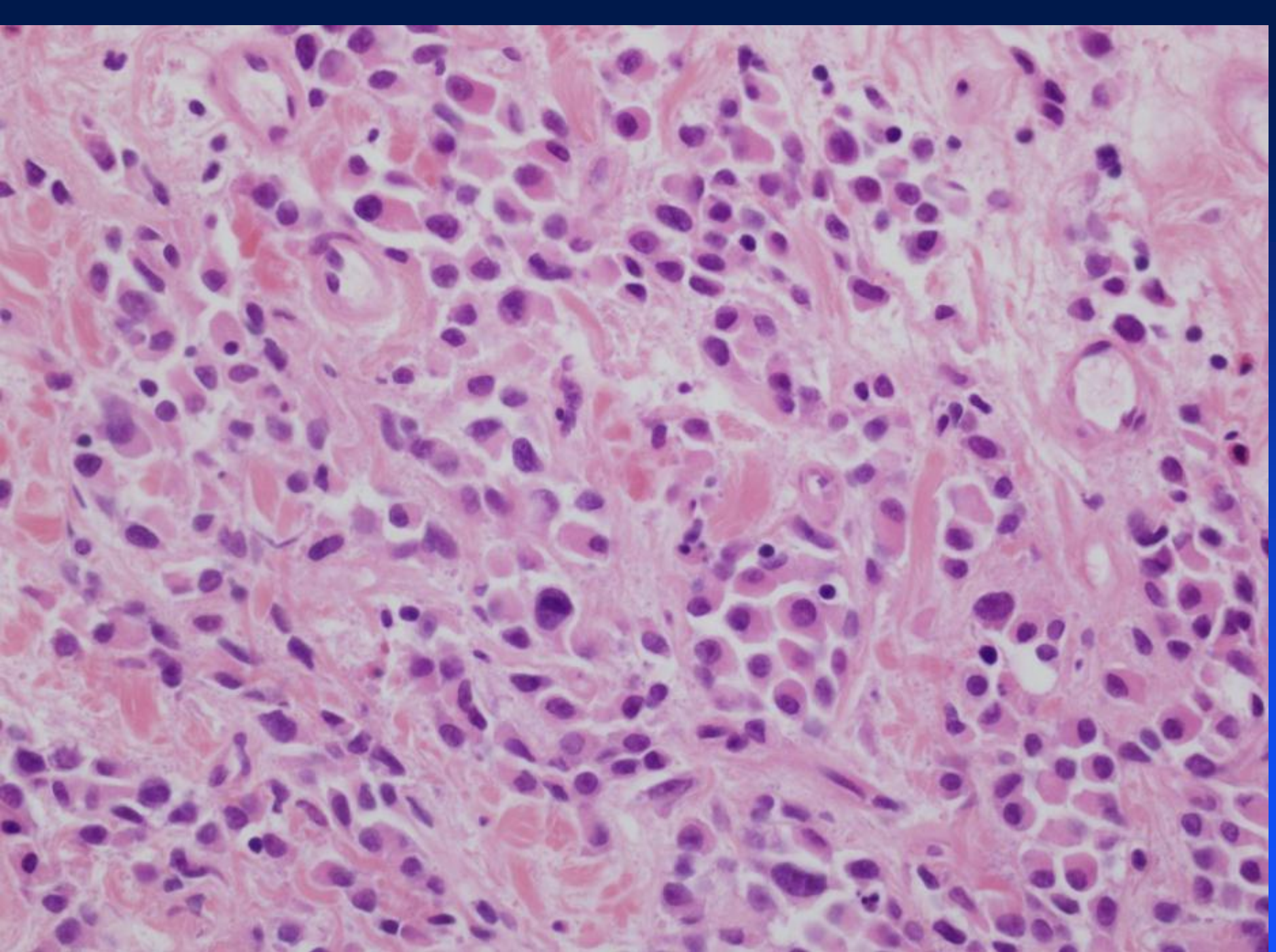


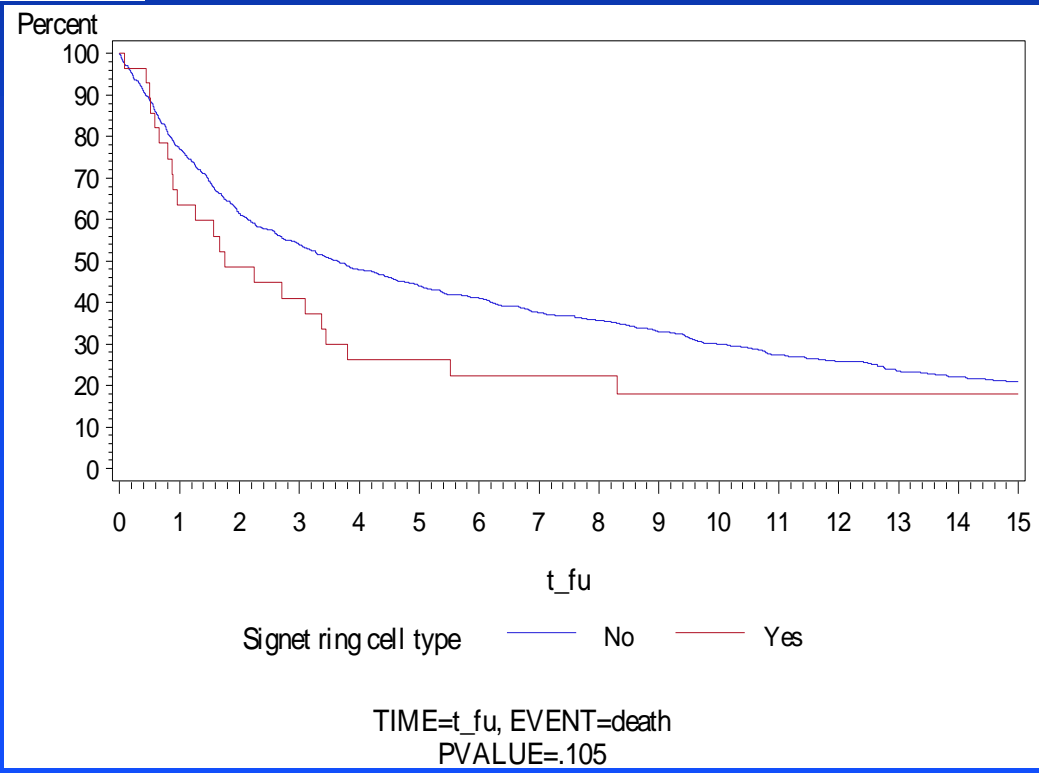
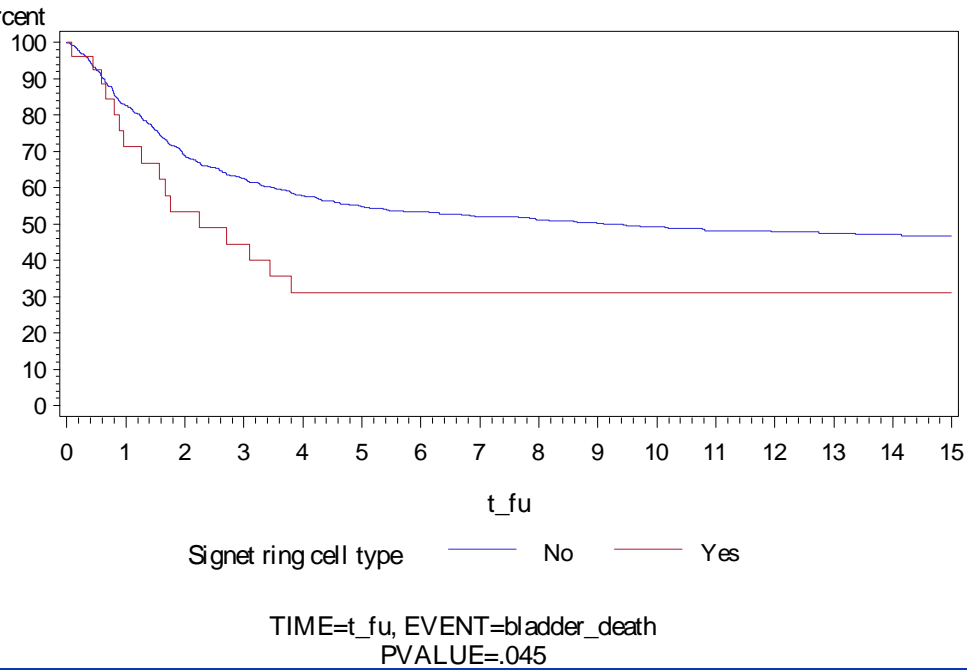


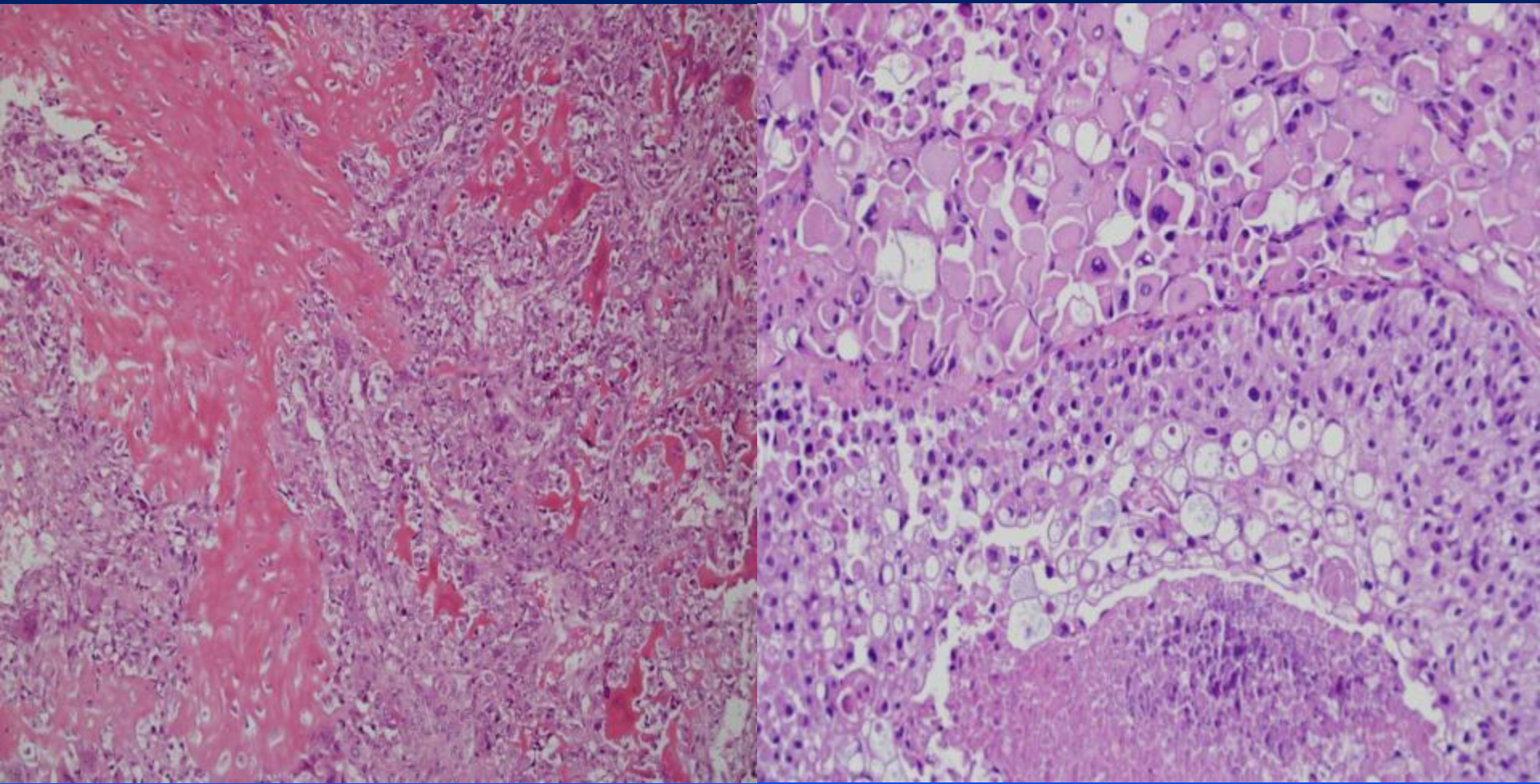






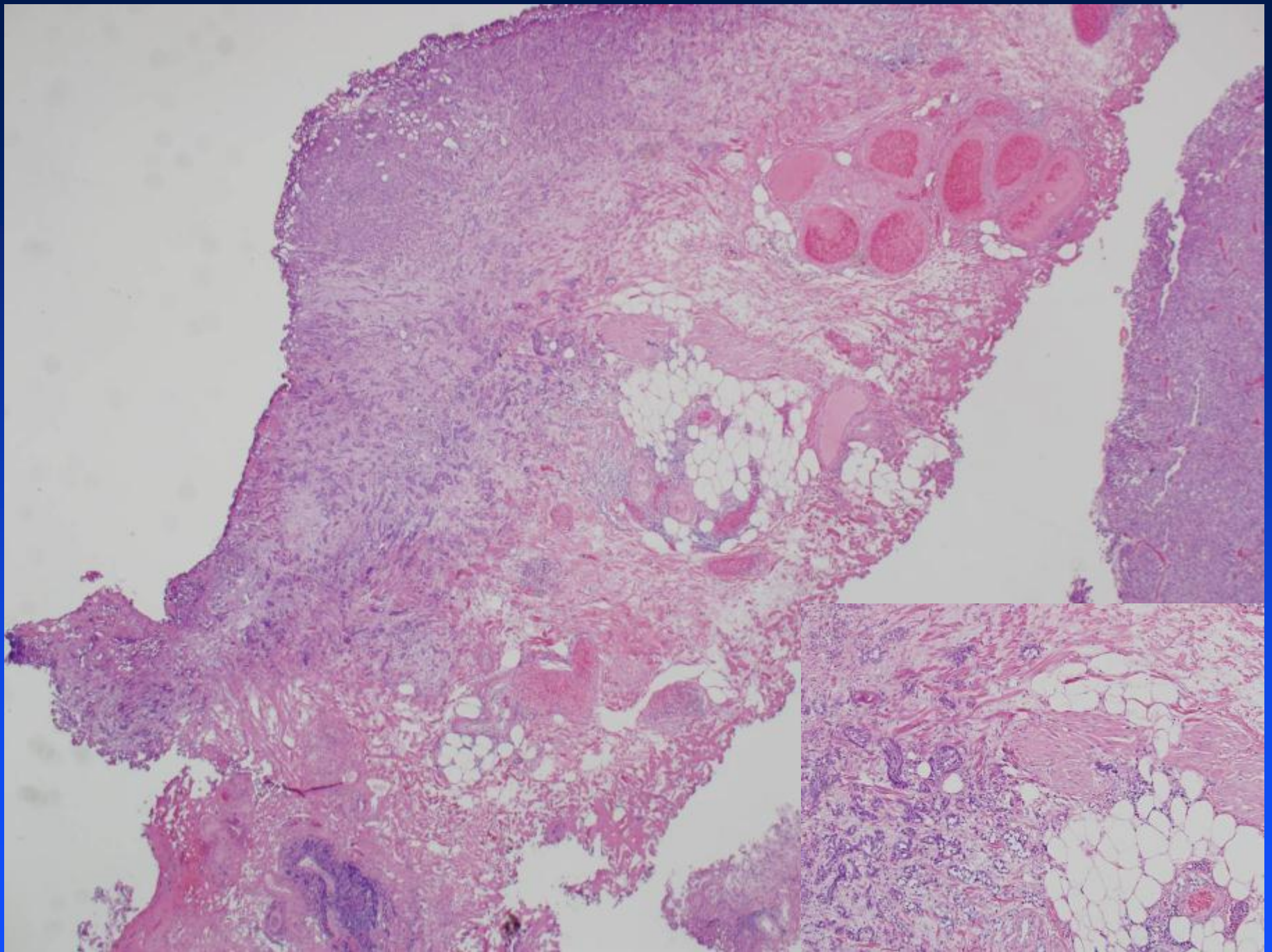




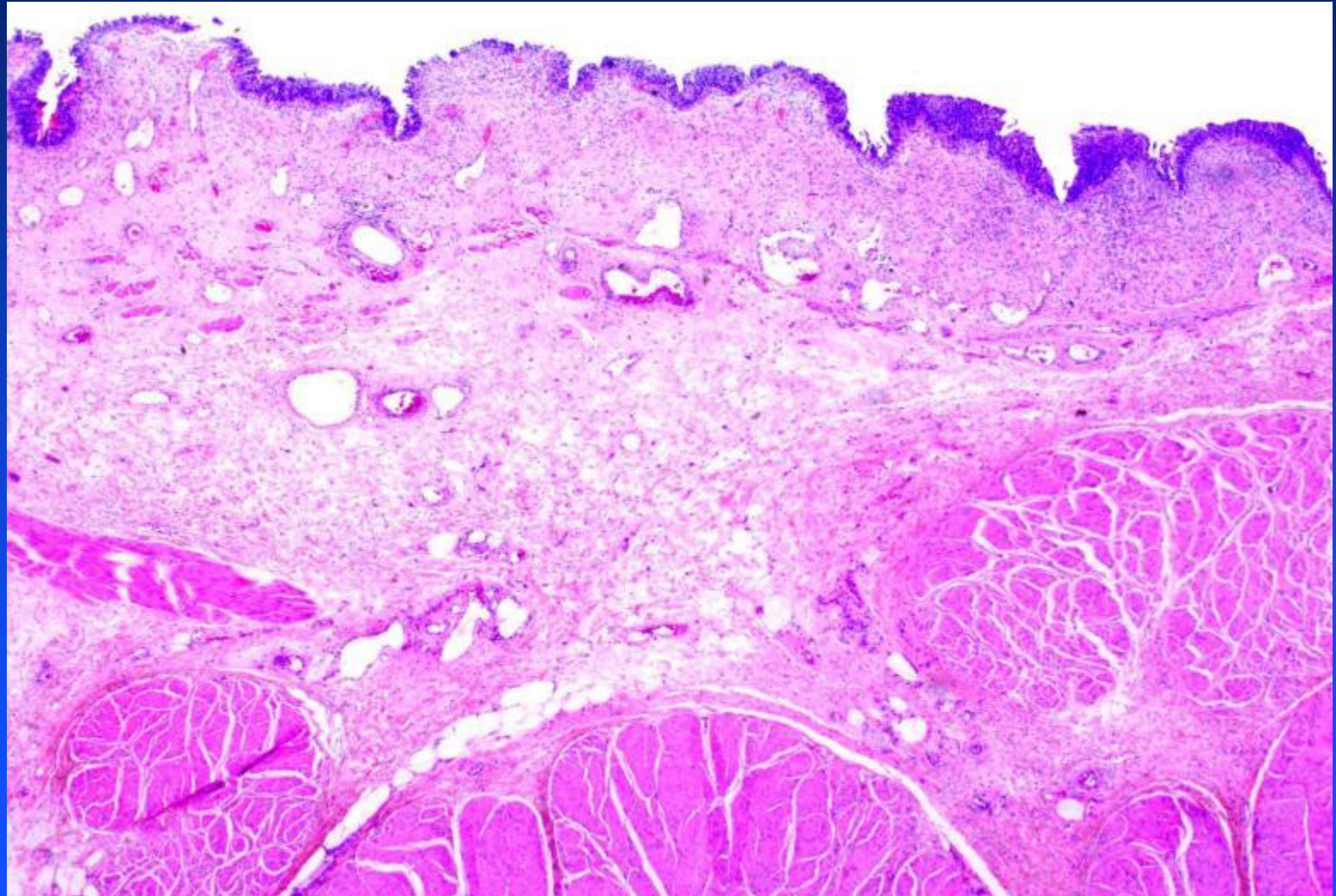


Issues in Staging

- Perivesical fat invasion in TUR specimens
- Muscularis propria invasion in TUR specimens
- pT2 and pT3 substaging in cystectomy specimens
- Substaging pT1 disease
- Prostatic involvement- primary versus pT4 disease



Depth of Invasion in Bladder Cancer

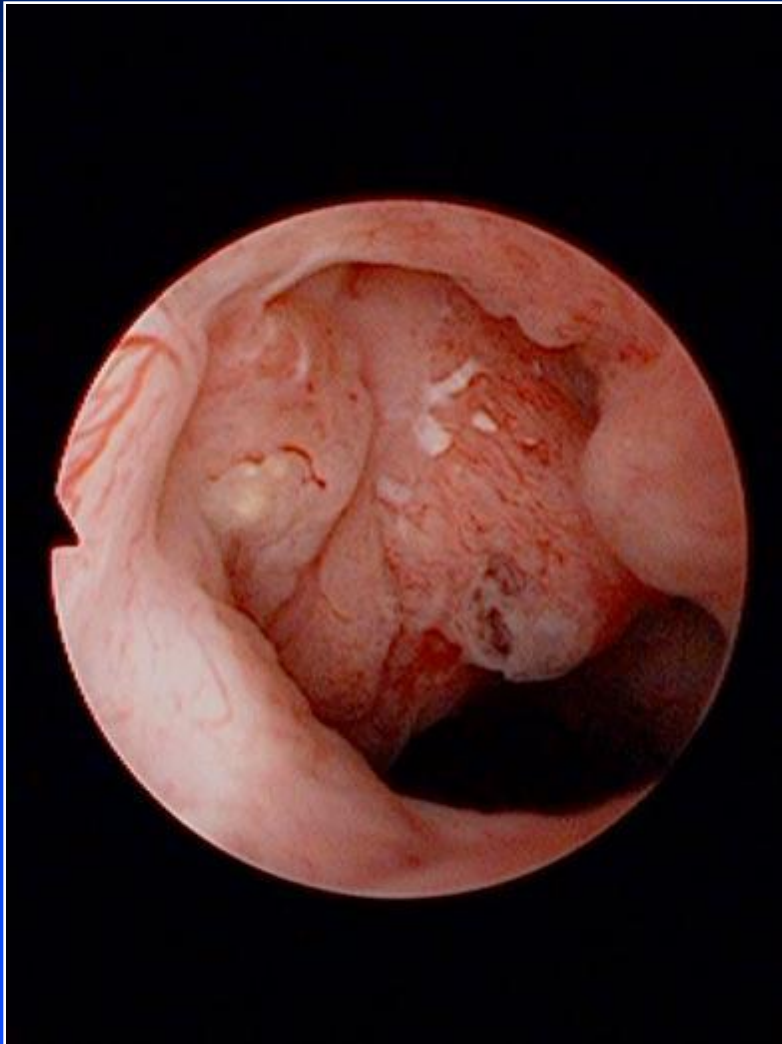


Terminology

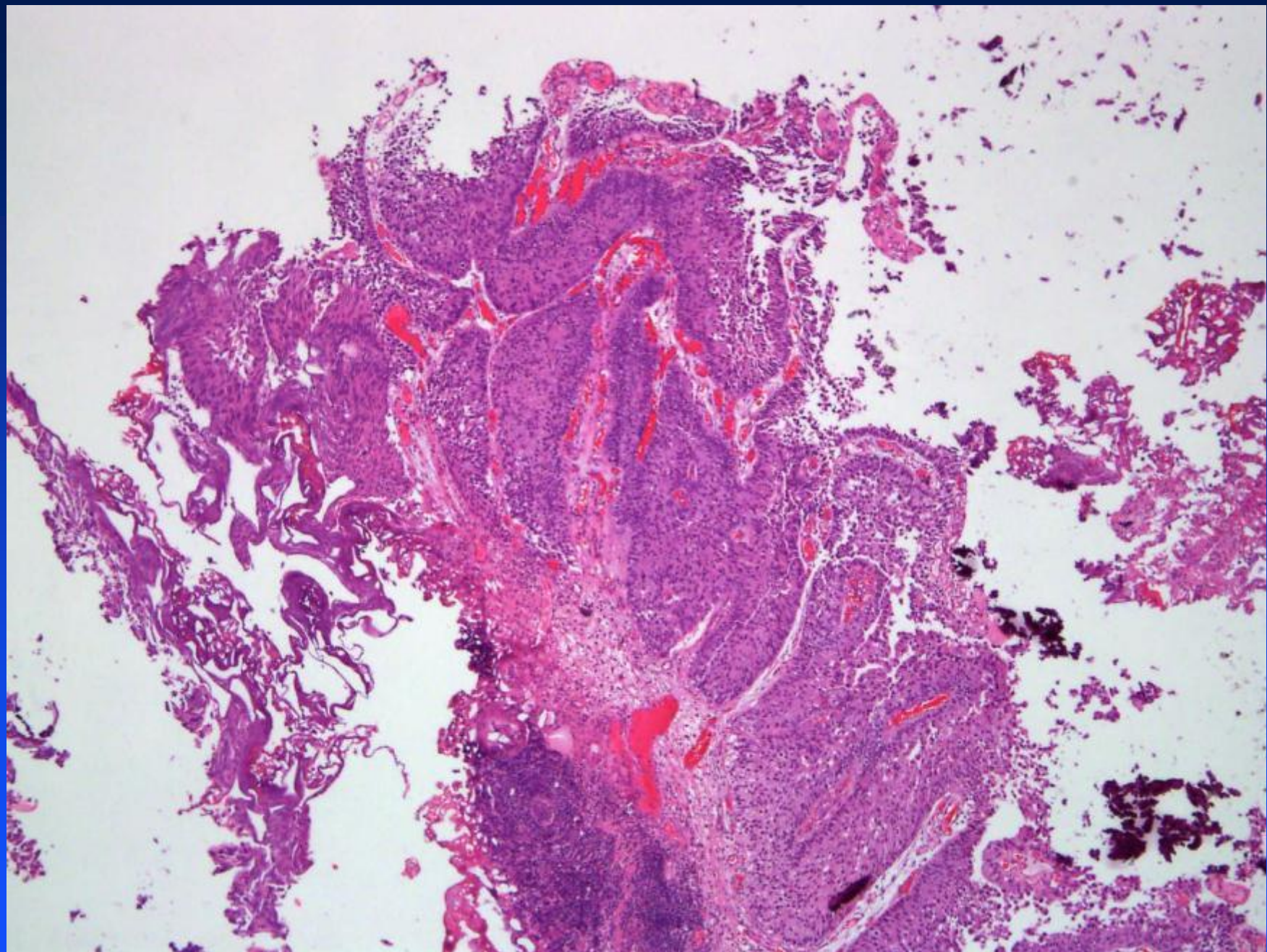
TNM	Clinical- Managerial	
pTis	“Superficial”	Non muscle- invasive
pTa		
pT1		
pT2+	“Invasive”	Muscle- Invasive

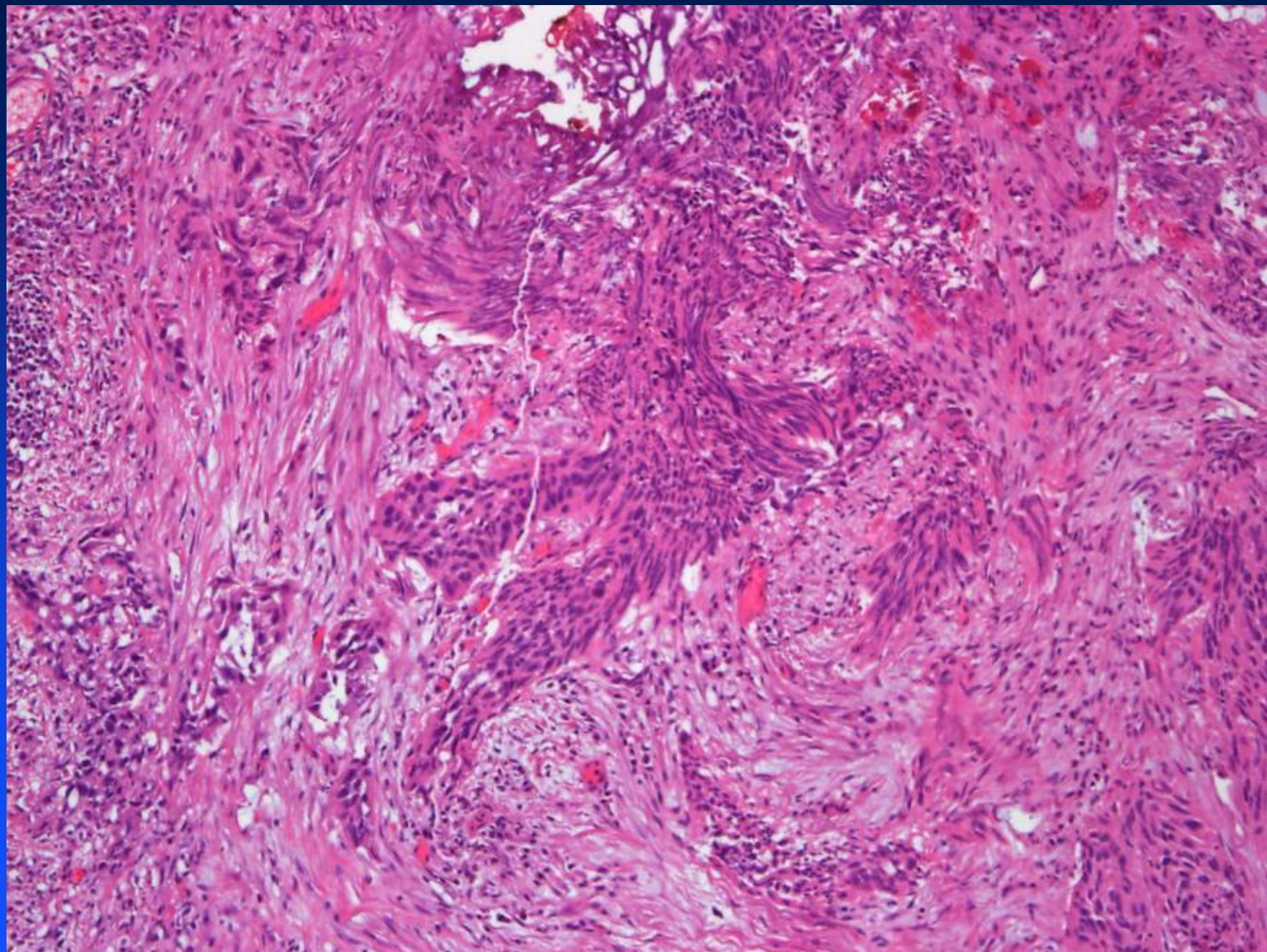
Clinical Management

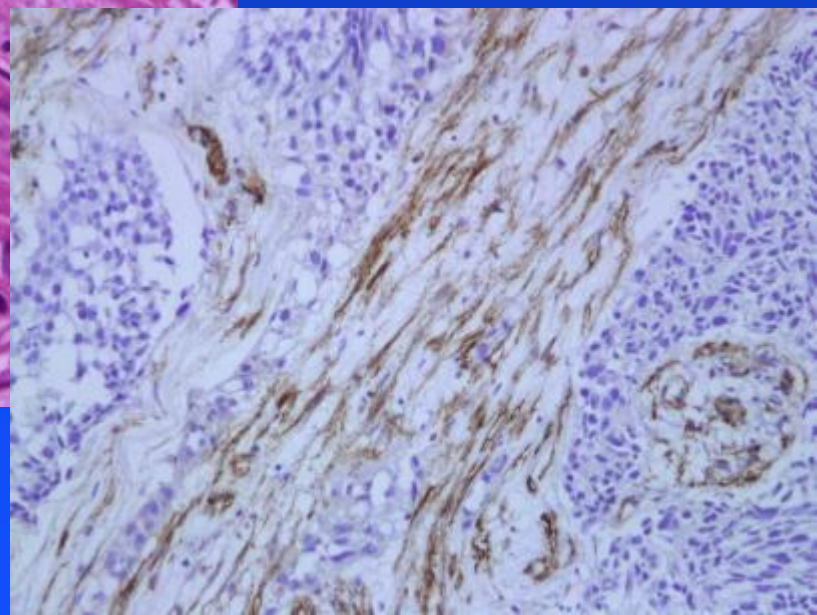
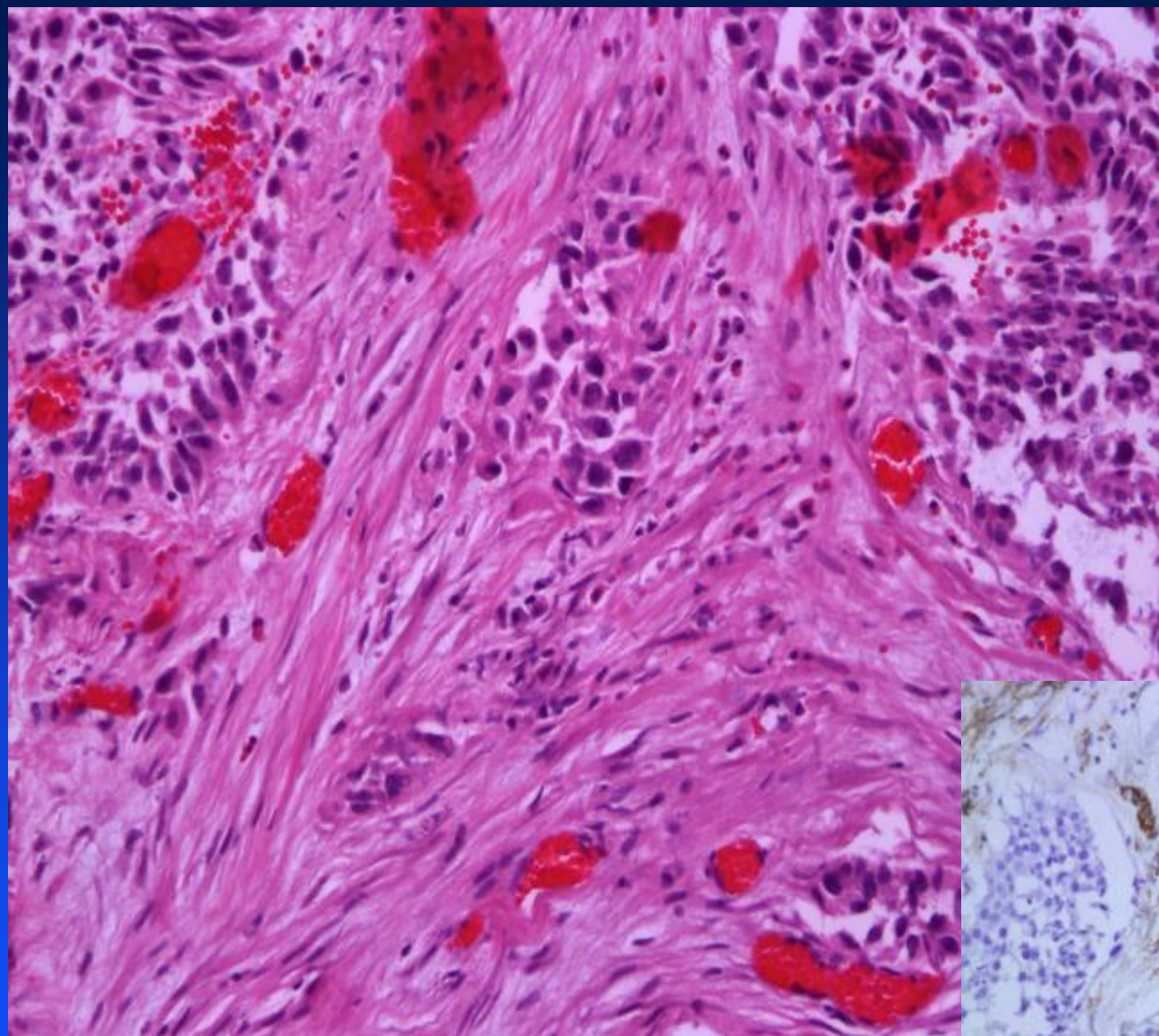
Baseline treatment

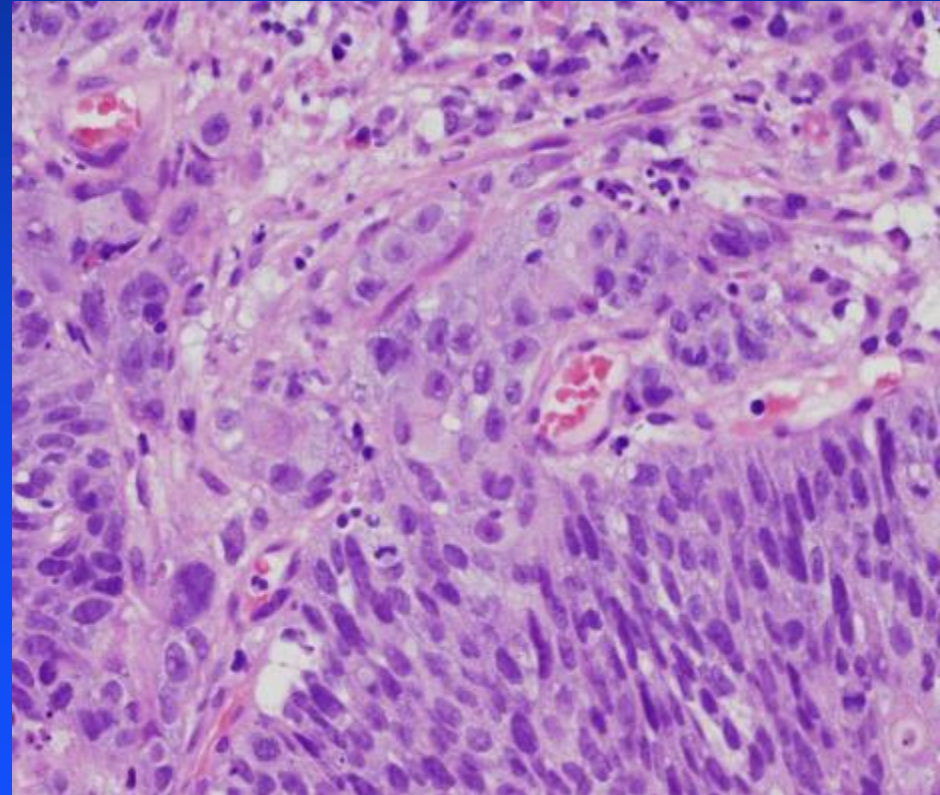
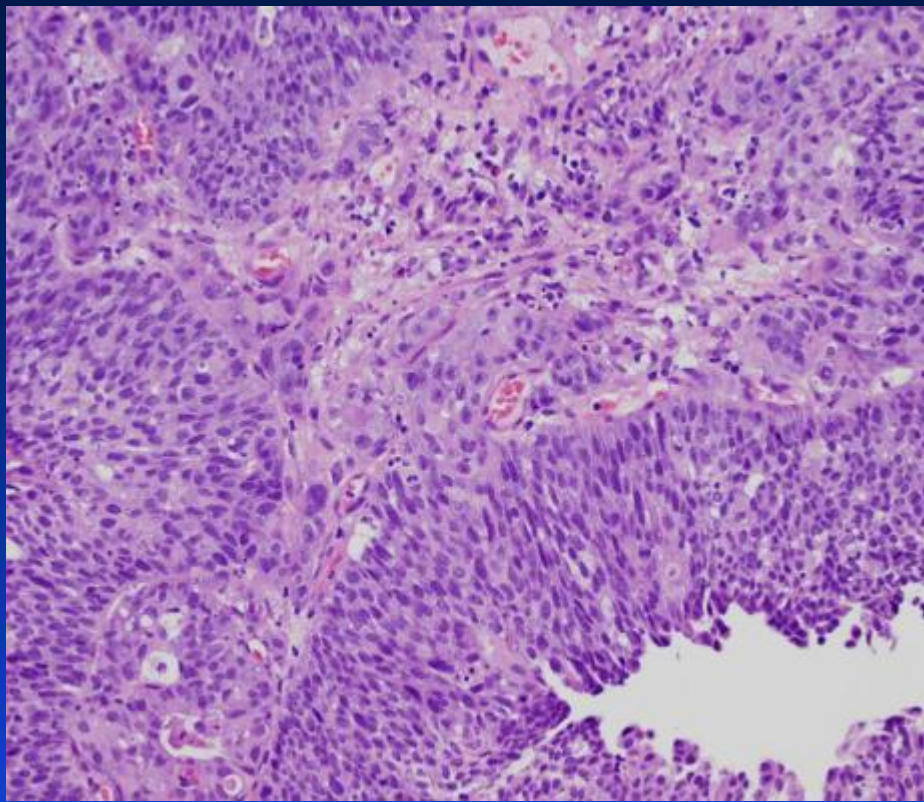


- Transurethral resection of tumor:
 - Provide adequate tissue for pathologic analysis
 - Remove all visible disease
 - Provide tissue from MP for adequate staging.
 - » Repeat resection if no MP identified in the sample
 - » Up to 51% of TUR lack muscularis propria.
- Maruniak et al. J Urol, 2002

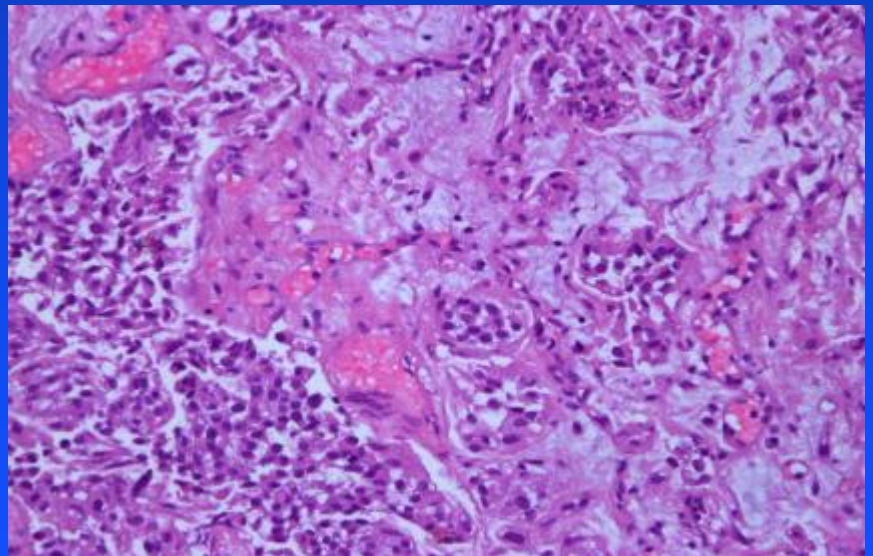
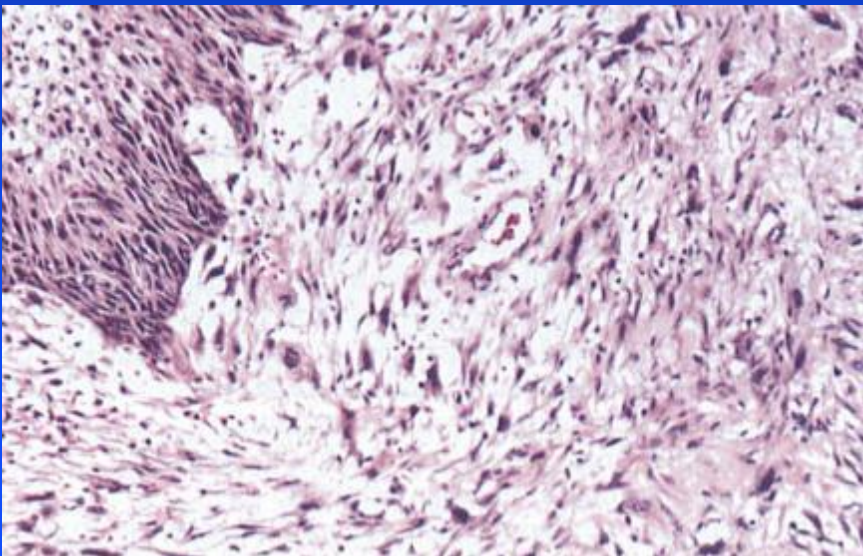
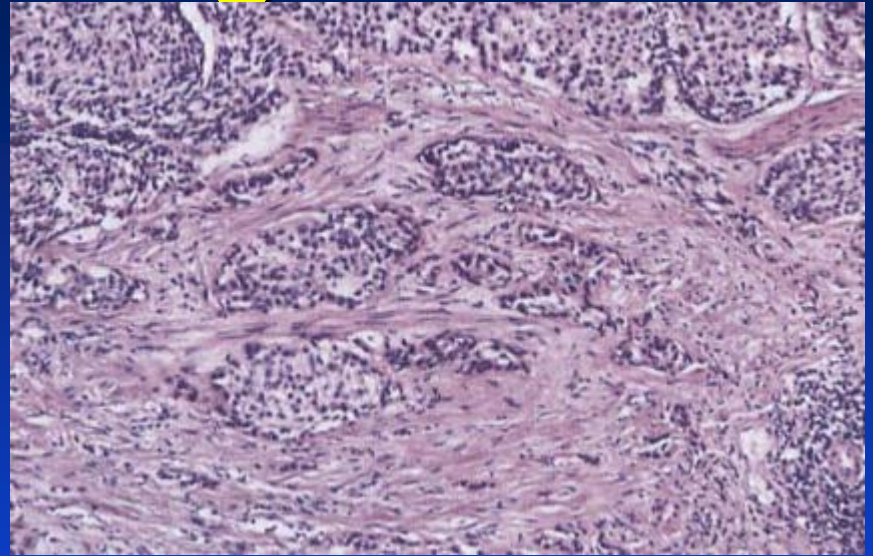
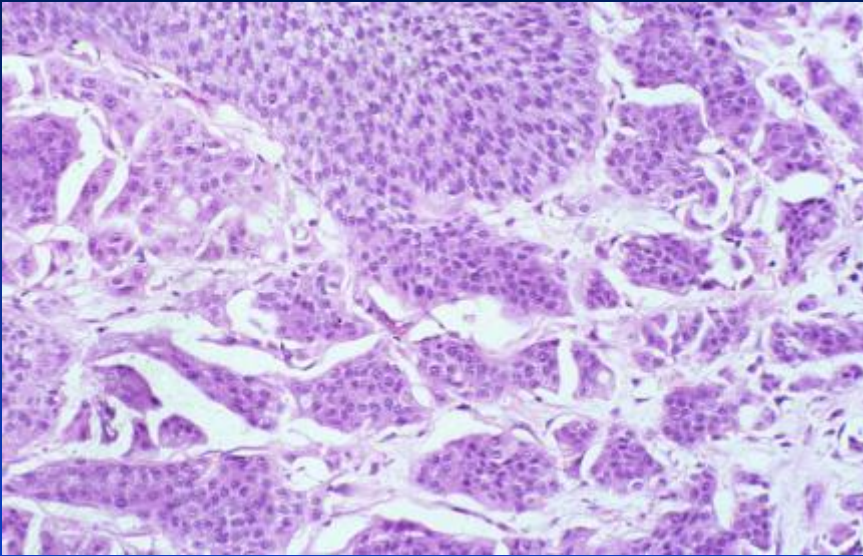




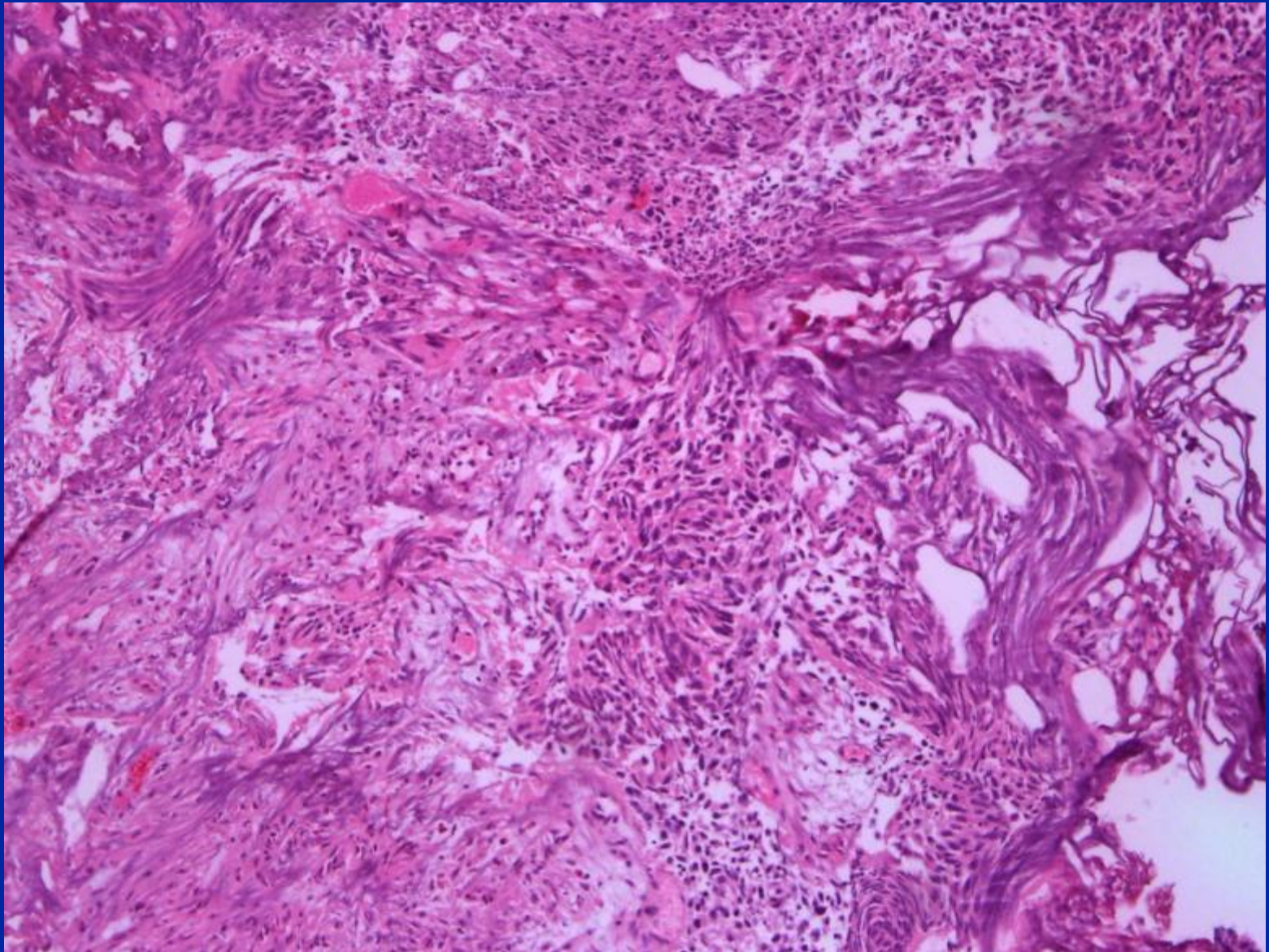




Stromal changes



The Real World



Overcalling invasion

- LP invasion frequently overcalled.
- Interpretation differences:
 - Tangential sectioning
 - Tissue fragmentation
 - Cauterization artifacts

Stage	Original	Consensus
pTa	51.6	78.7
pT1	48.4	21.3

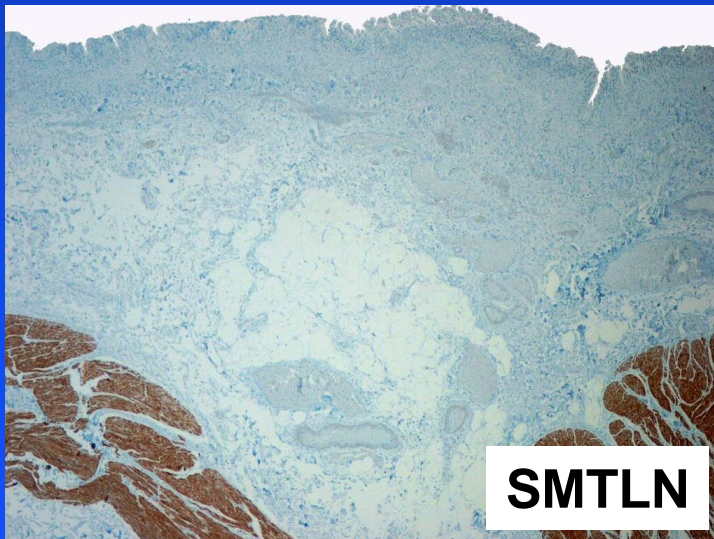
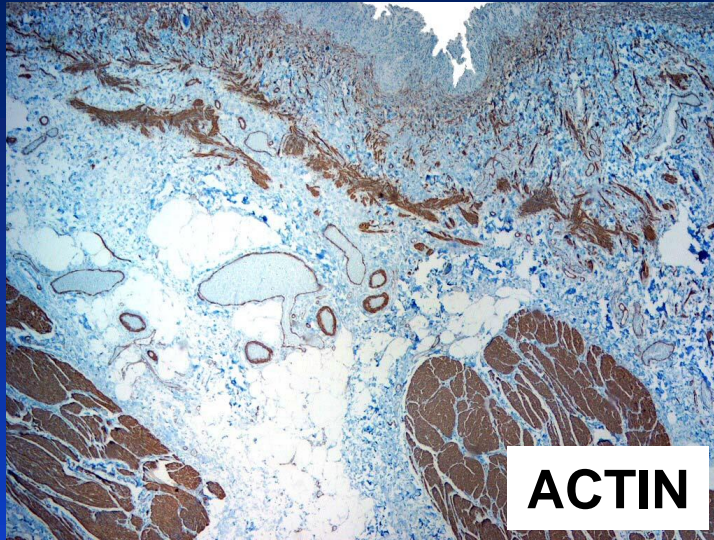
Bol et al. J Urol 169, 1291-1294, 2003.

Understaging

	Cystectomy Stage					
TURB	Ta	T1	T2	T3	T4	Total
Ta	3	7	2	0	3	15
T1	2	10	9	24	10	55
T2	0	2	8	22	3	35
Total	5	19	19	46	16	105

- 43 of 55 cases (78%) were upstaged on cystectomy

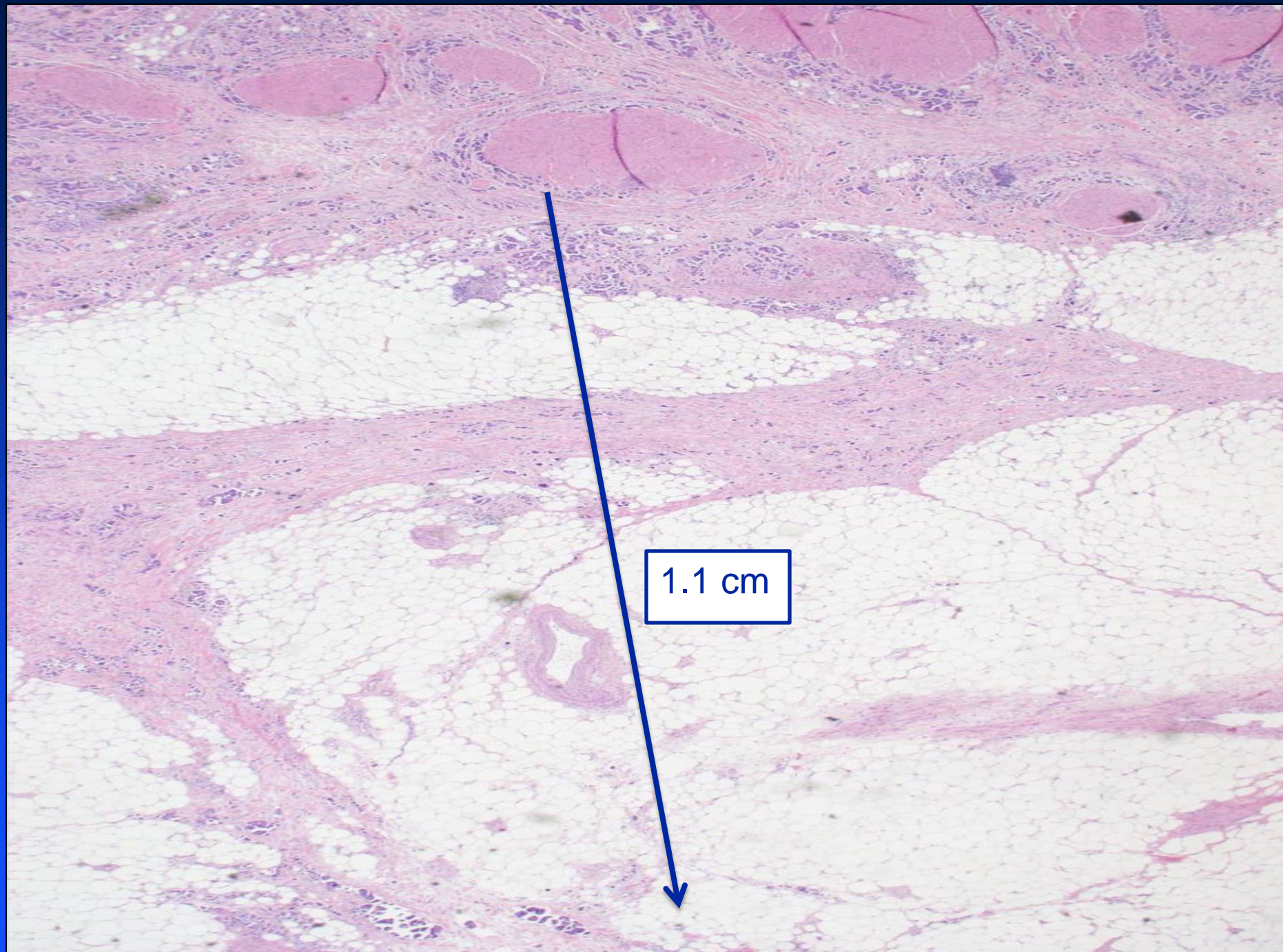
Smoothelin

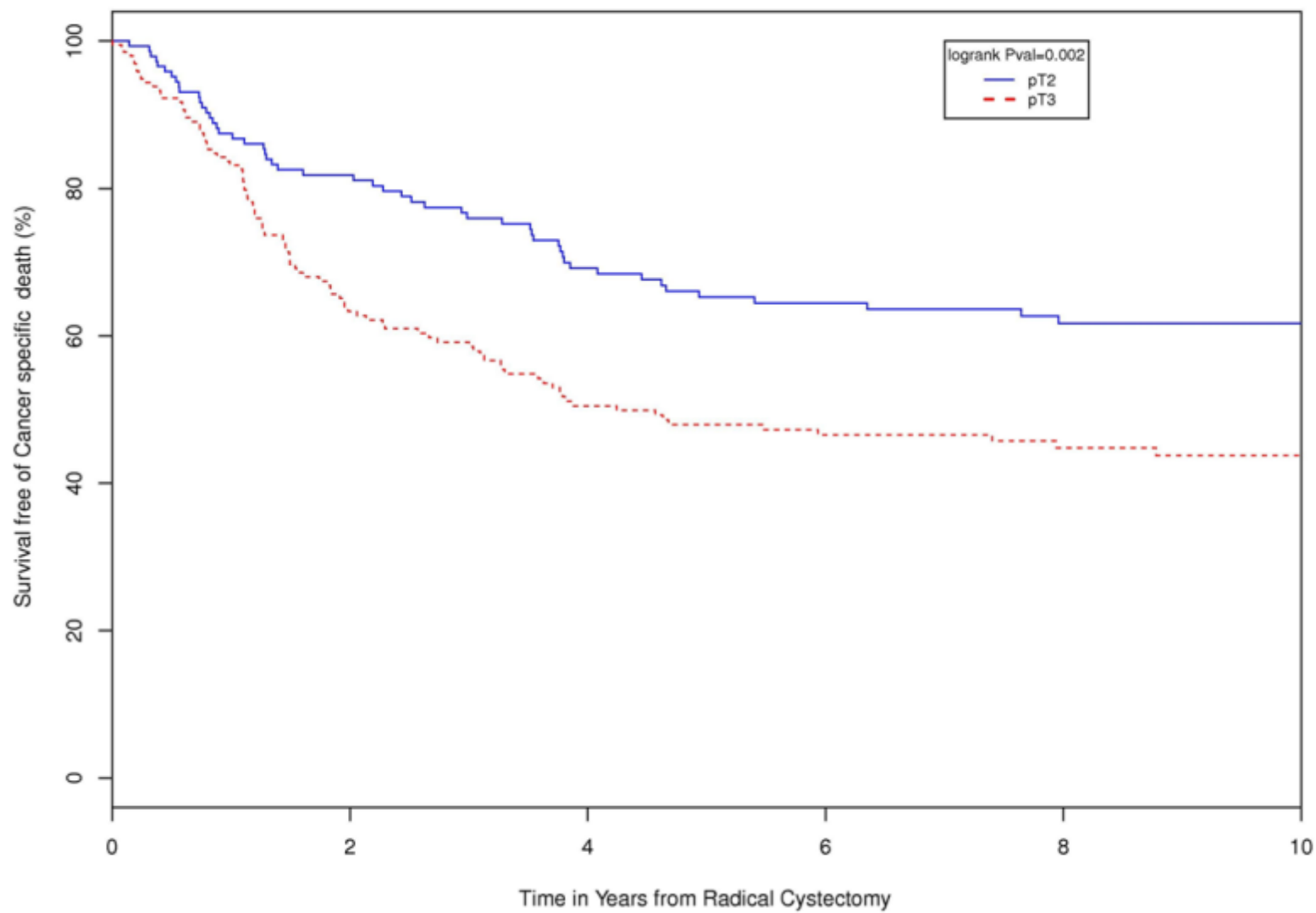


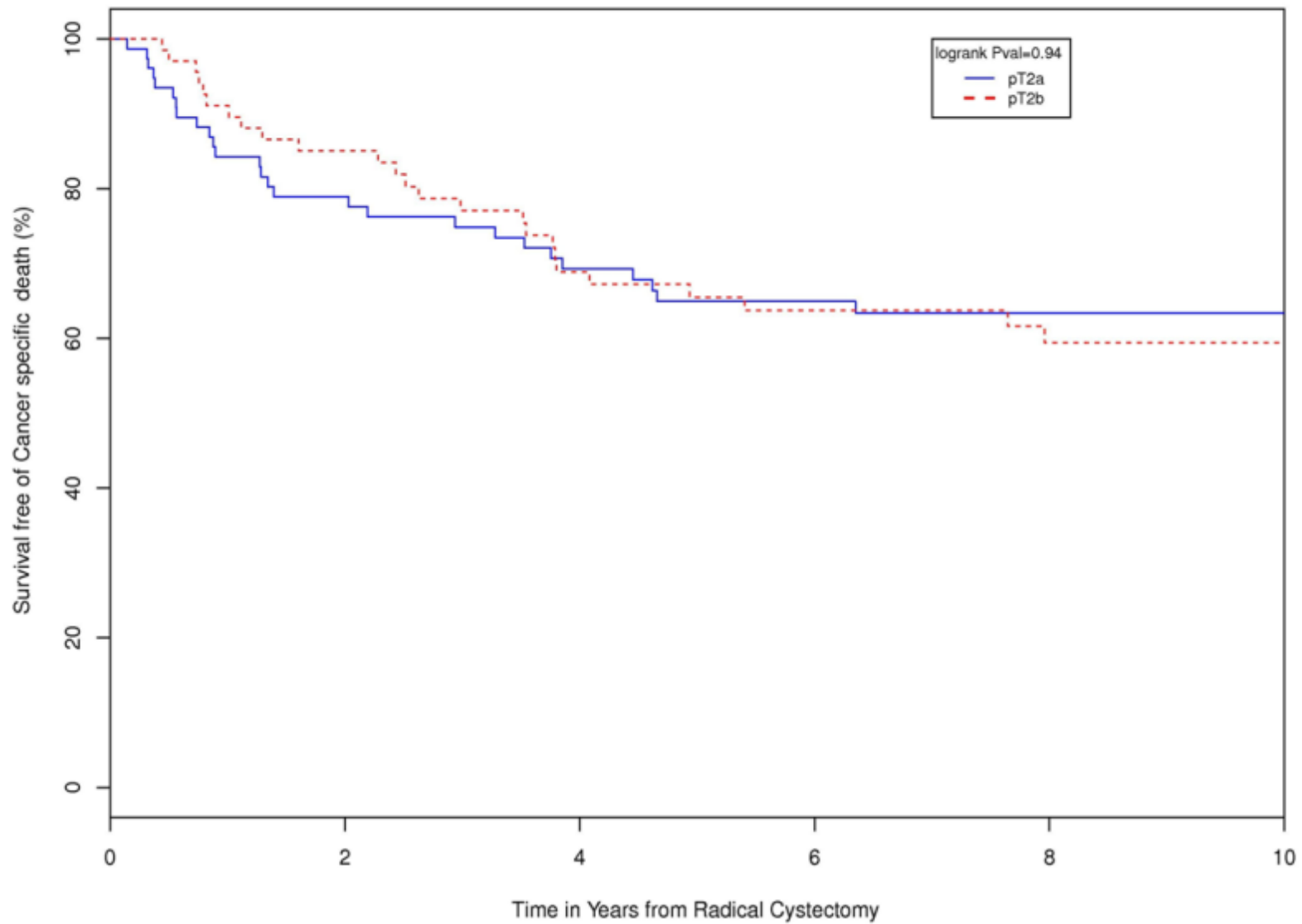
- 100% specificity and positive predictive value in identifying MP vs. MM.
- 10 TURBT cases with perfect correlation between smoothelin results and H&E impression.

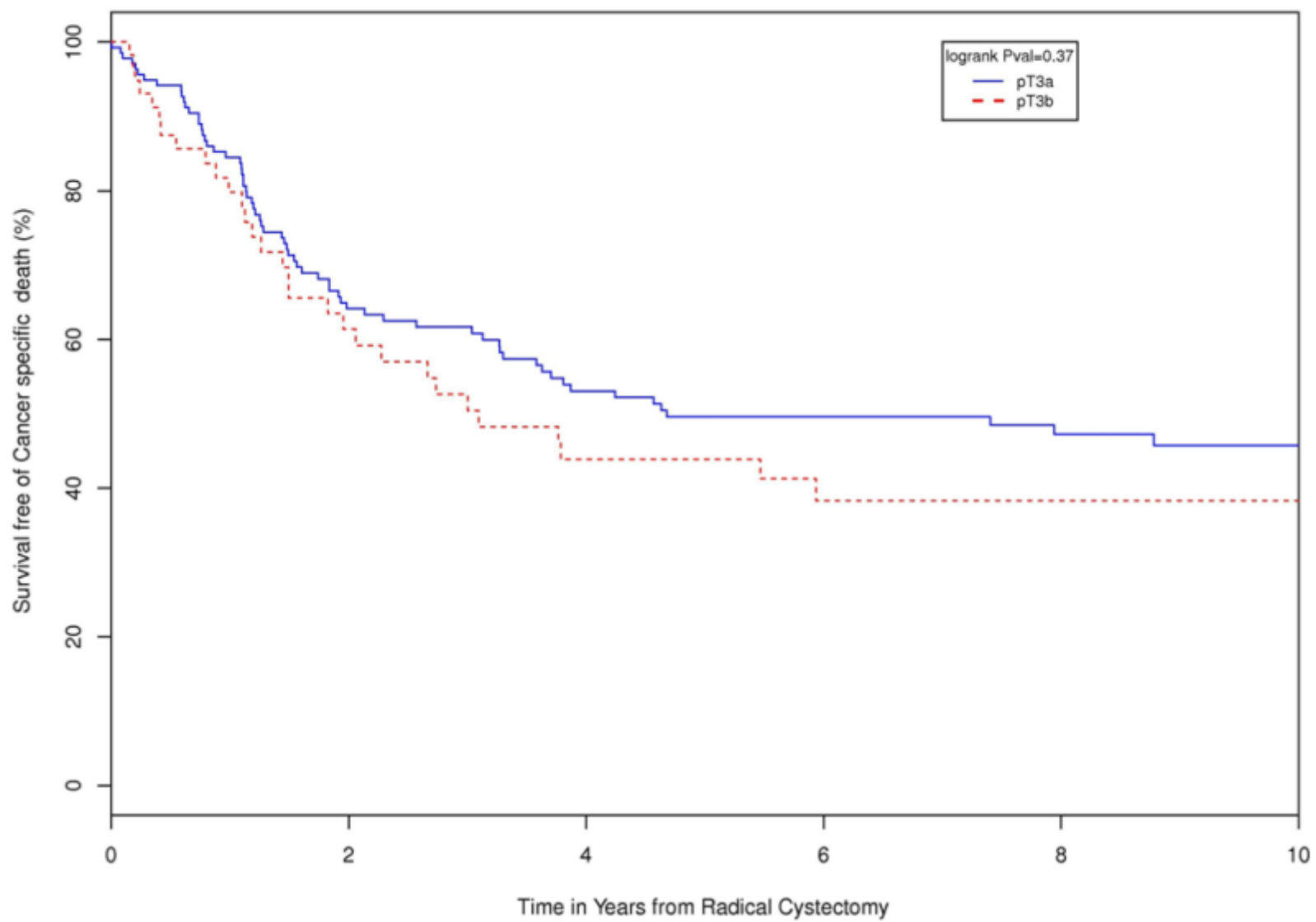
pT2 and pT3 Staging

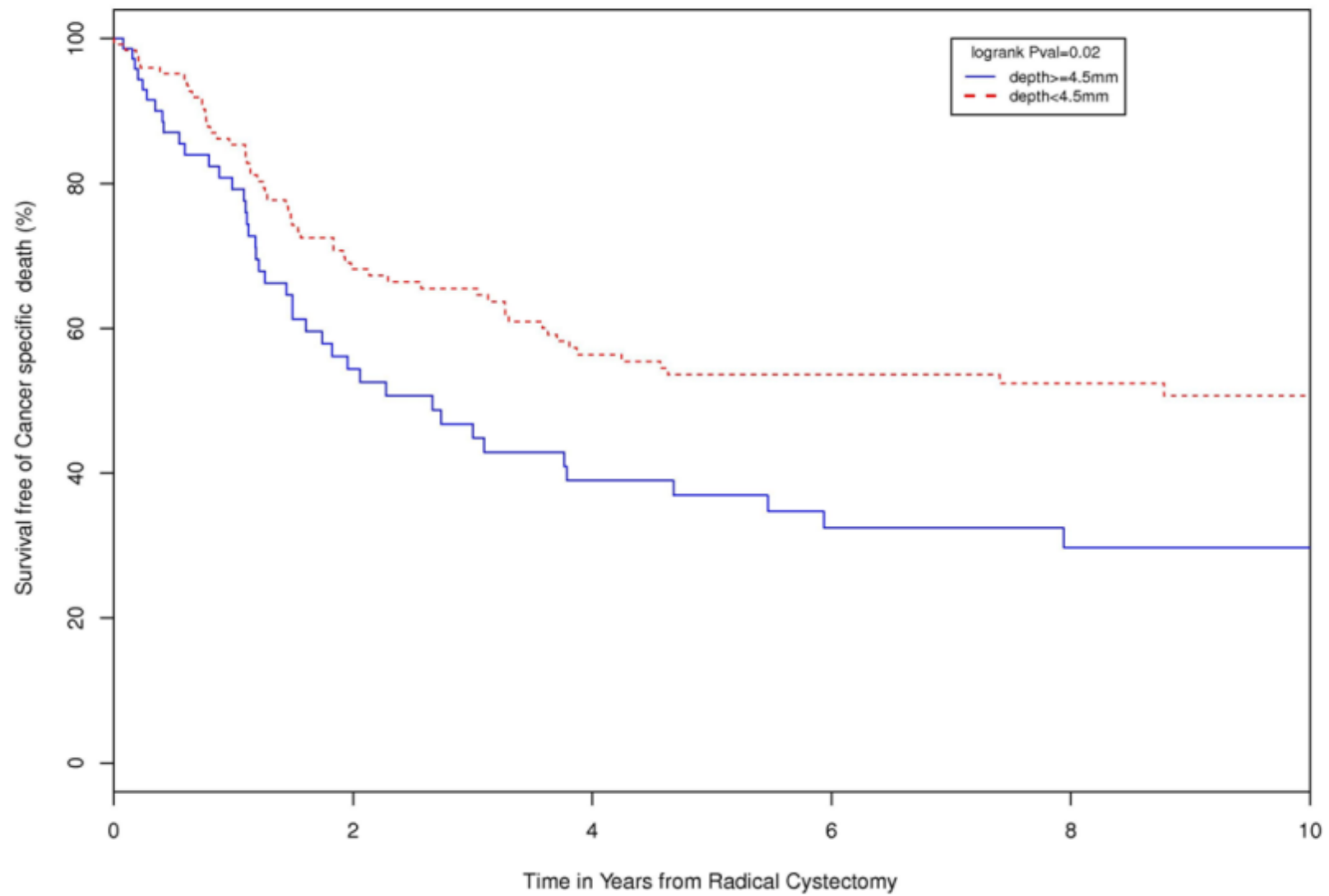
- pT2a - inner half of muscularis propria
- pT2b - outer half of muscularis propria
- pT3a - microscopic fat invasion
- pT3b - macroscopic (mass forming) invasion





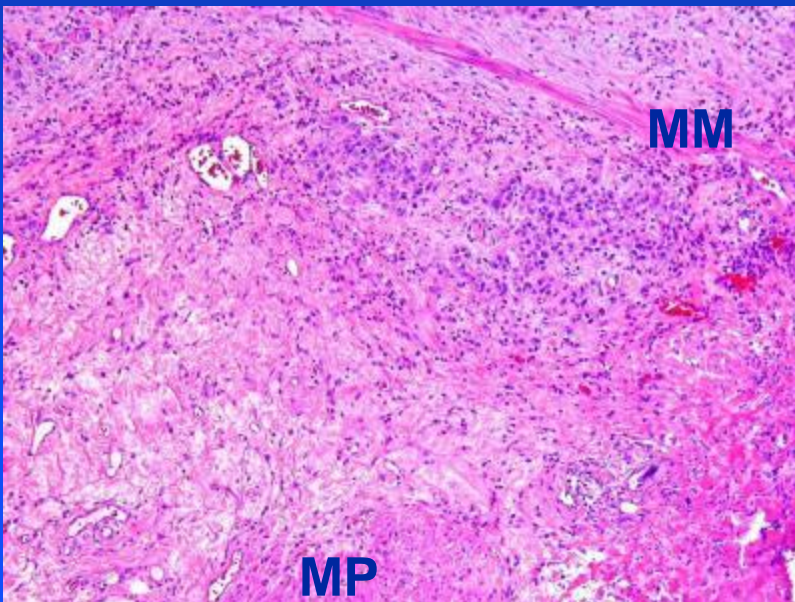
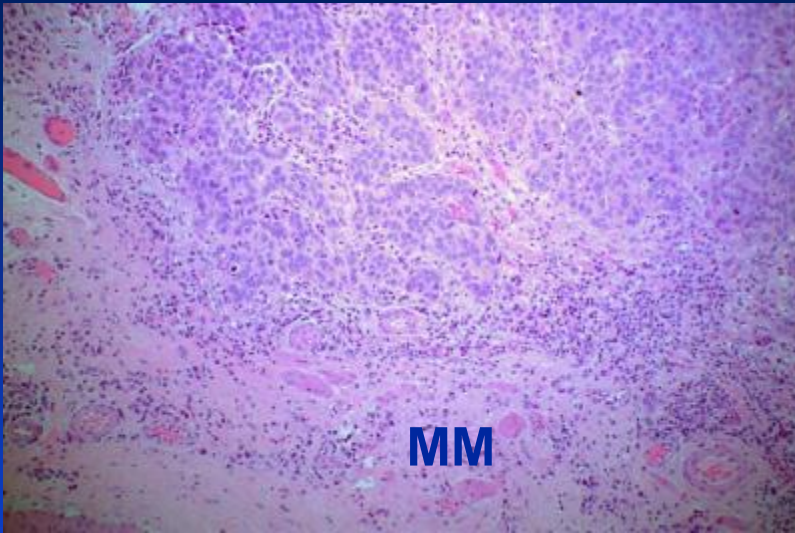






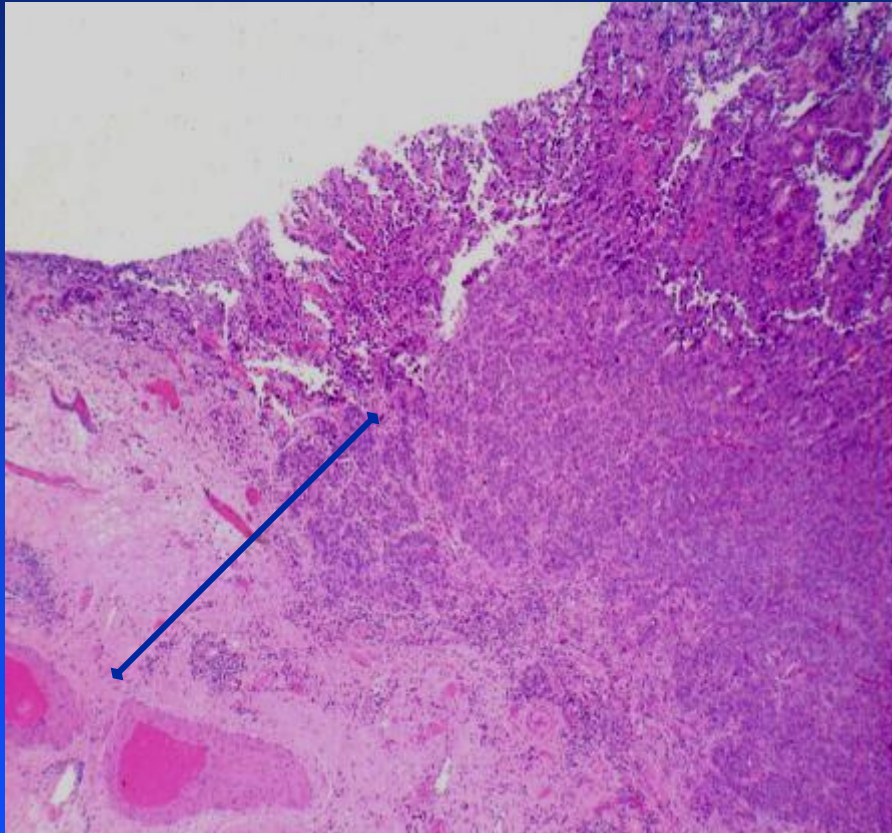
Substaging of pT1 disease

- Relationship to muscularis mucosa



Authors	Categories	Outcome	Endpoint
Younes 1990	T1a	75%	5 year all-cause survival
	T1b		
	T1c	11%	
Hasui 1994	T1a	7%	Progression rate
	T1b	54%	
Angulo 1995	T1a	86%	5-year all-cause survival
	T1b	52%	
Platz 1996	T1a	65%	10-year cancer-specific survival
	T1b	54%	
	T1c	60%	
Holmang 1997	T1a	23%	Disease-specific demise
	T1b	45%	
Hermann 1998	T1a	78%	5-year all cause survival
	T1b	75%	
	T1c	55%	

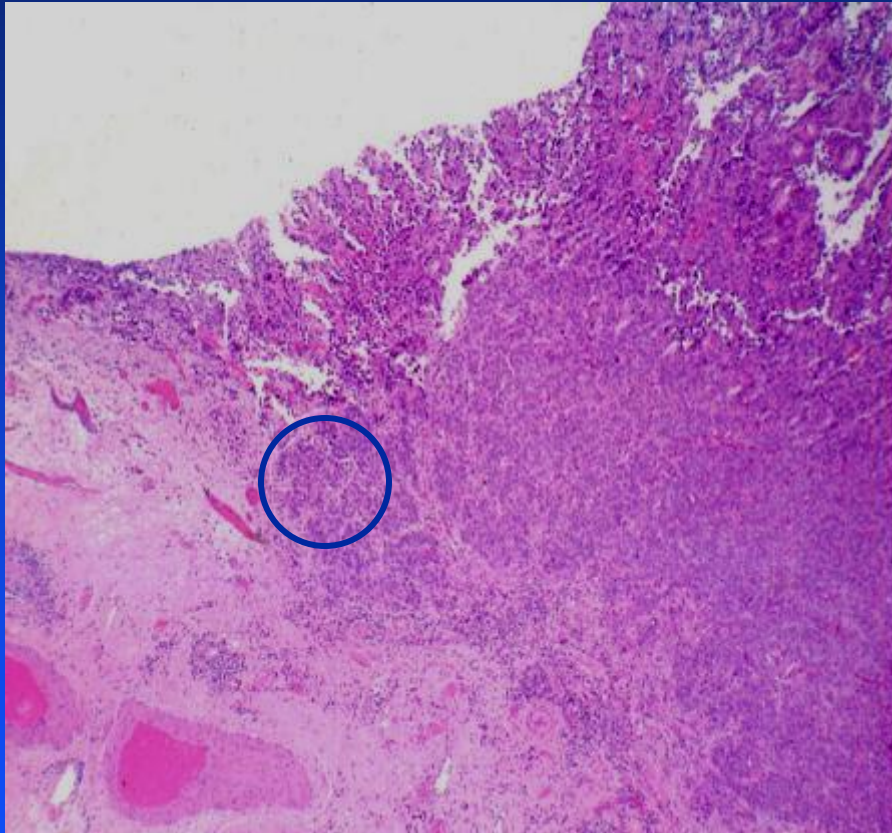
Substaging of pT1 disease



- Depth of Invasion measured by micrometer:

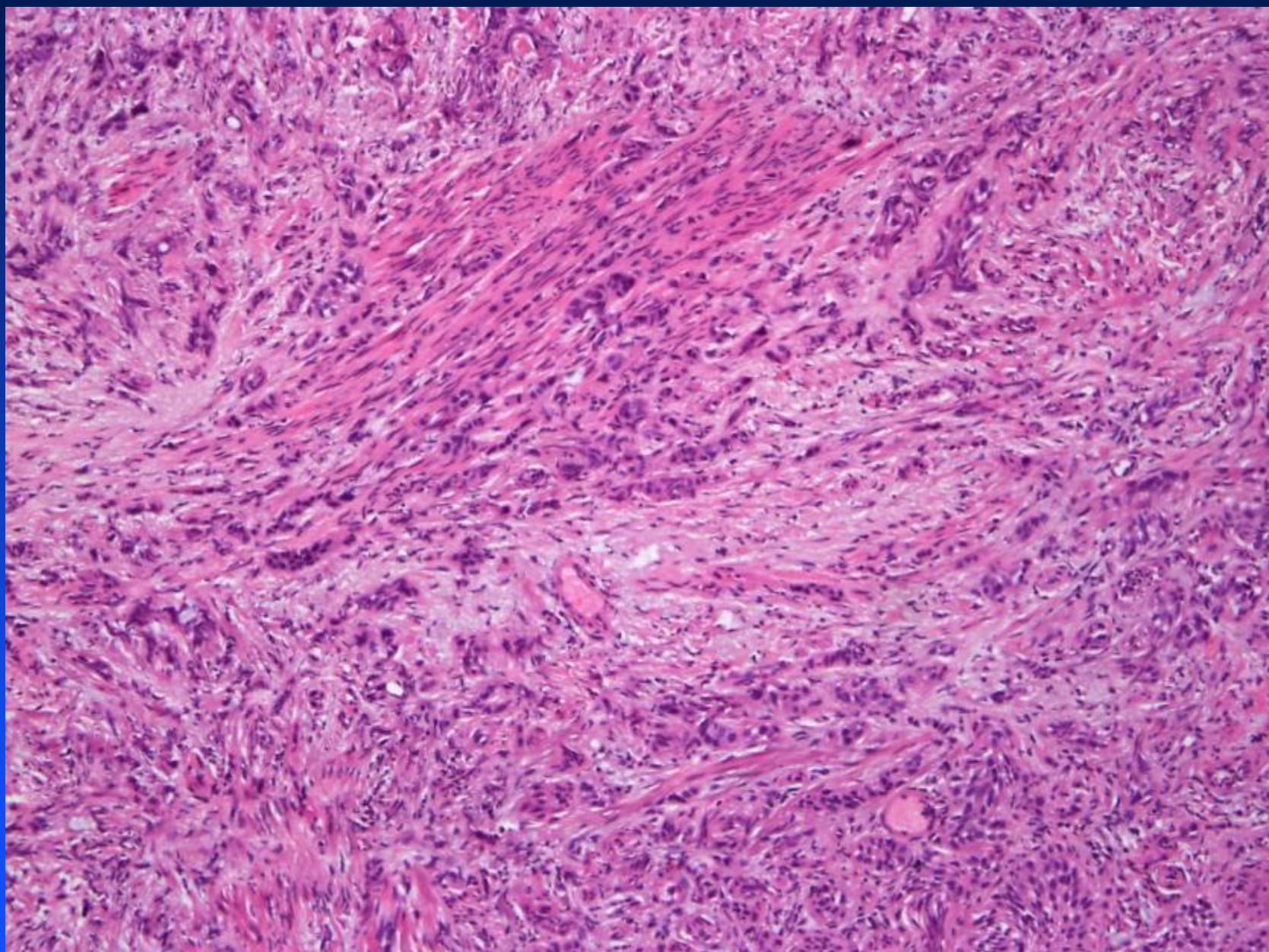
Author	Categories	Outcome	Endpoint
Cheng 1999	<1.5 mm	93%	5-year PFS
	>1.5 mm	67%	

Substaging of pT1 disease



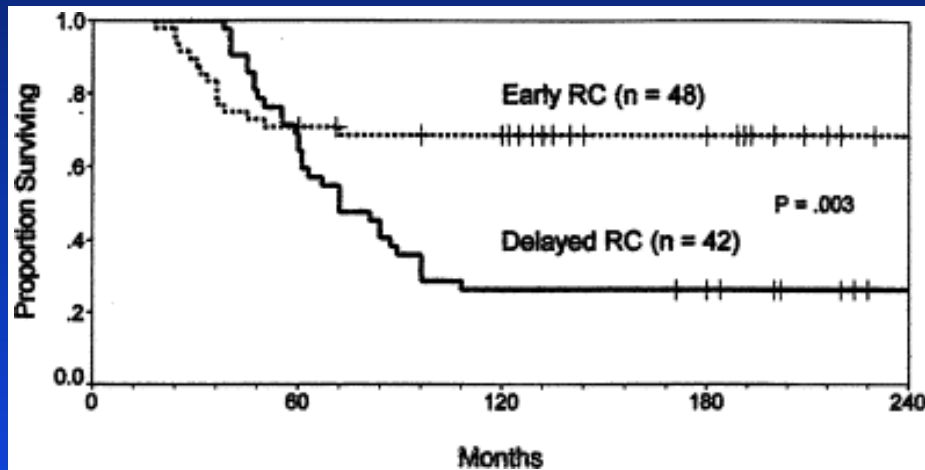
- Maximum linear size of invasive front:

Author	Categories	Outcome	Endpoint
Van der AA 2005	<0.5 mm (1 hpf diameter)	69%	5-year PFS
	>0.5 mm	50%	



Clinical Management

Cystectomy

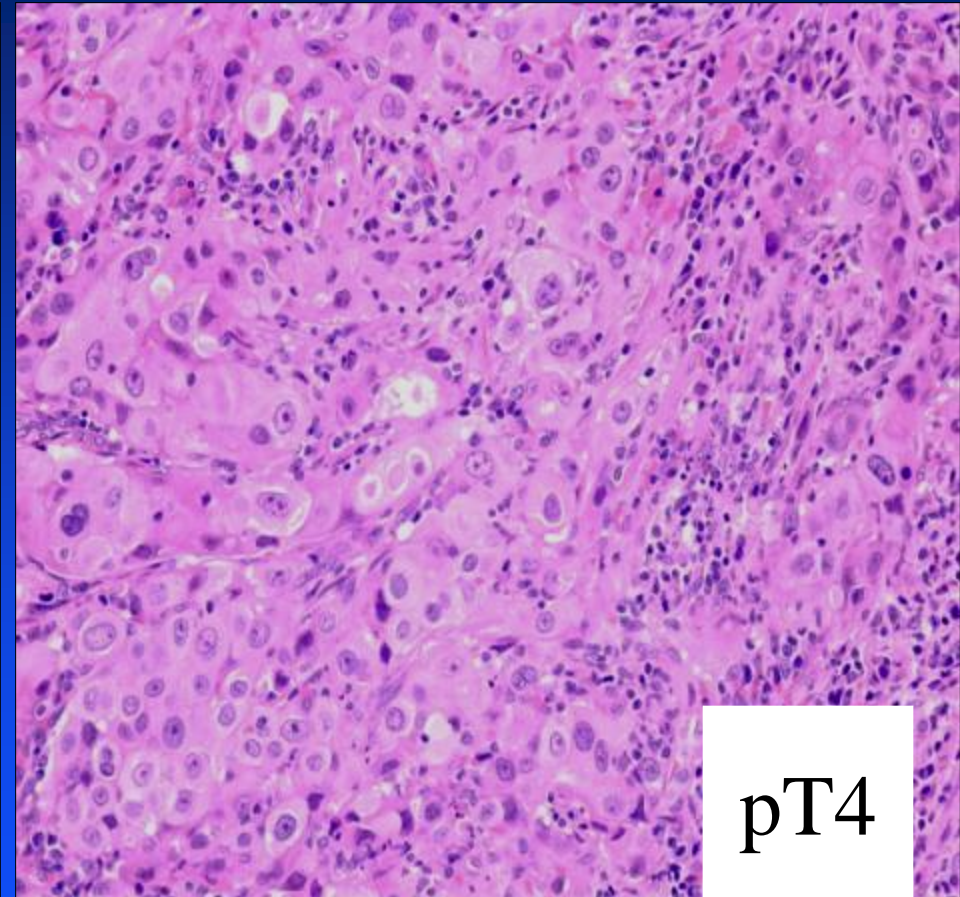
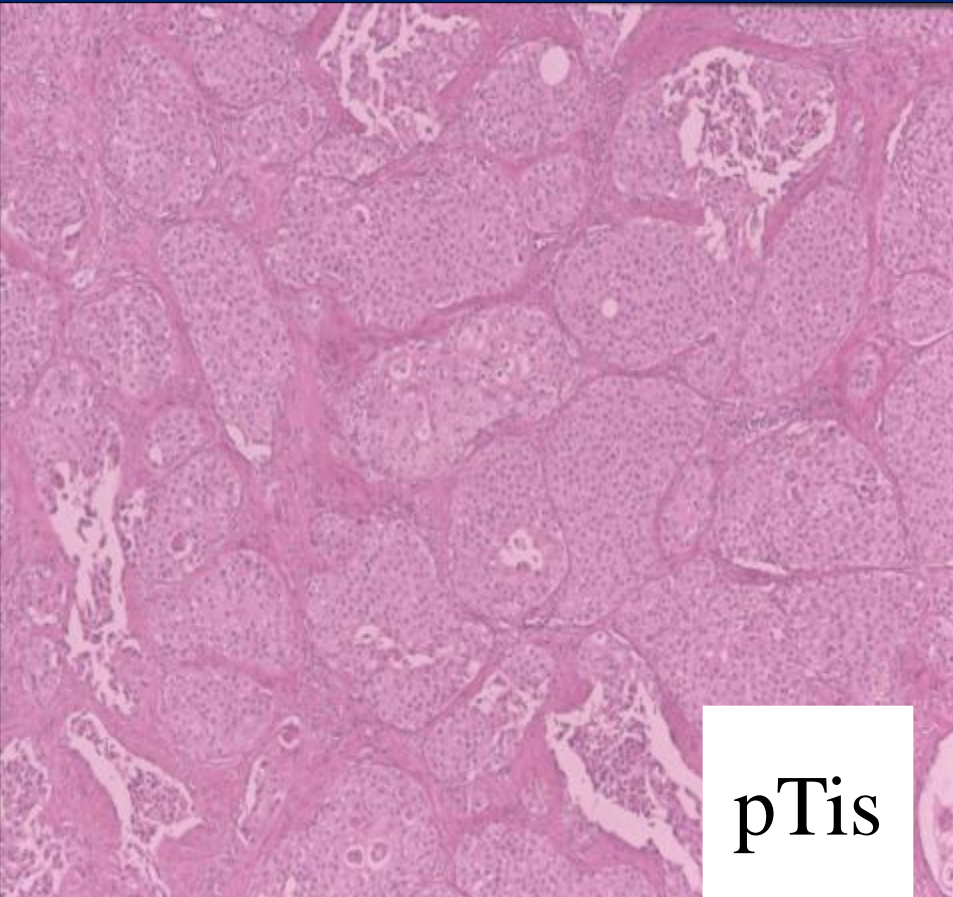


Disease specific survival

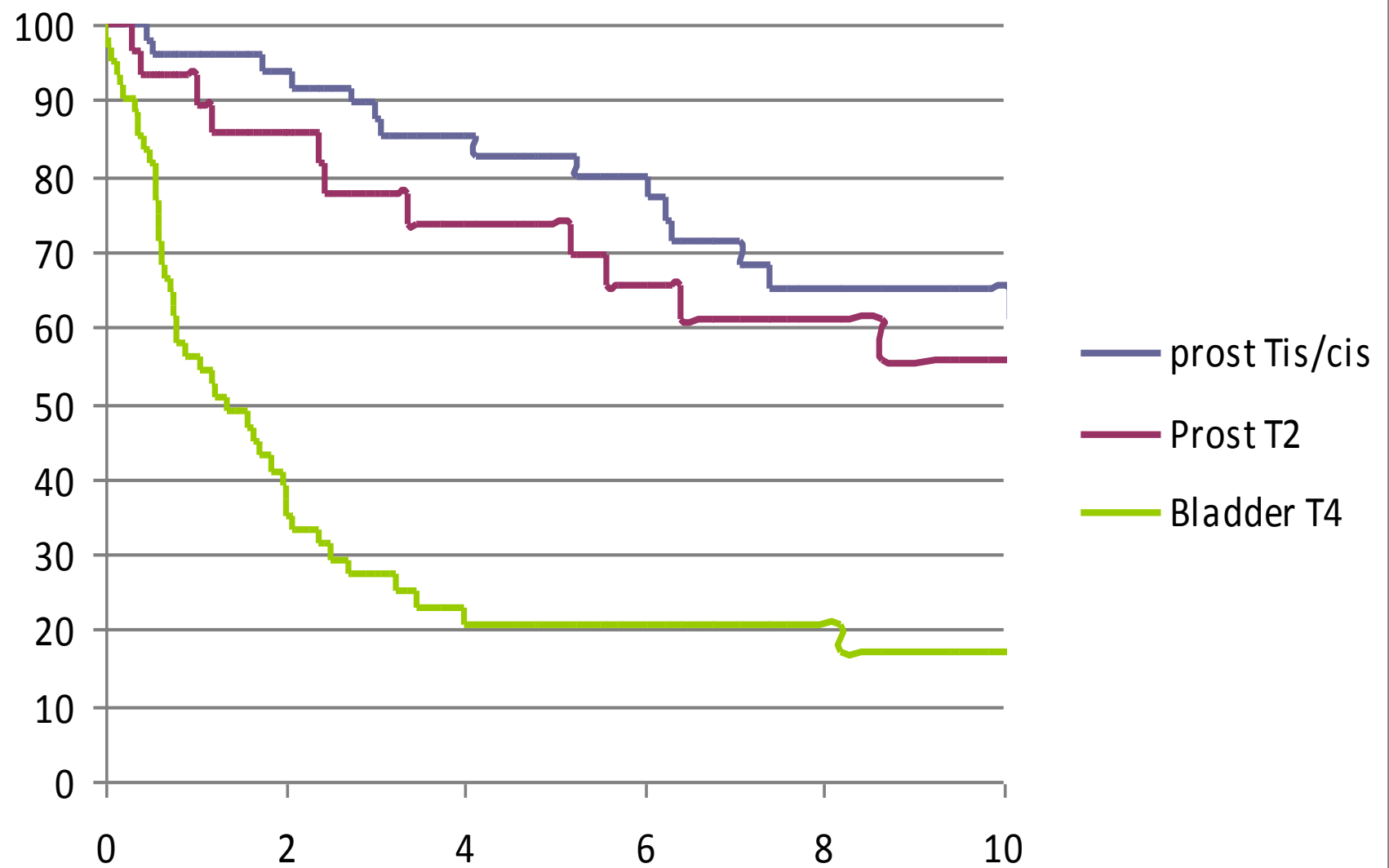
Herr and Sogani. J Urol 2001; 166:231

- High risk of understaging in TUR
- High rate of progression
- High cure rate associated with cystectomy
- Strongly considered in patients with recurrent pT1 tumors after TUR and intravesical therapy.

Urothelial Carcinoma Involving the Prostate

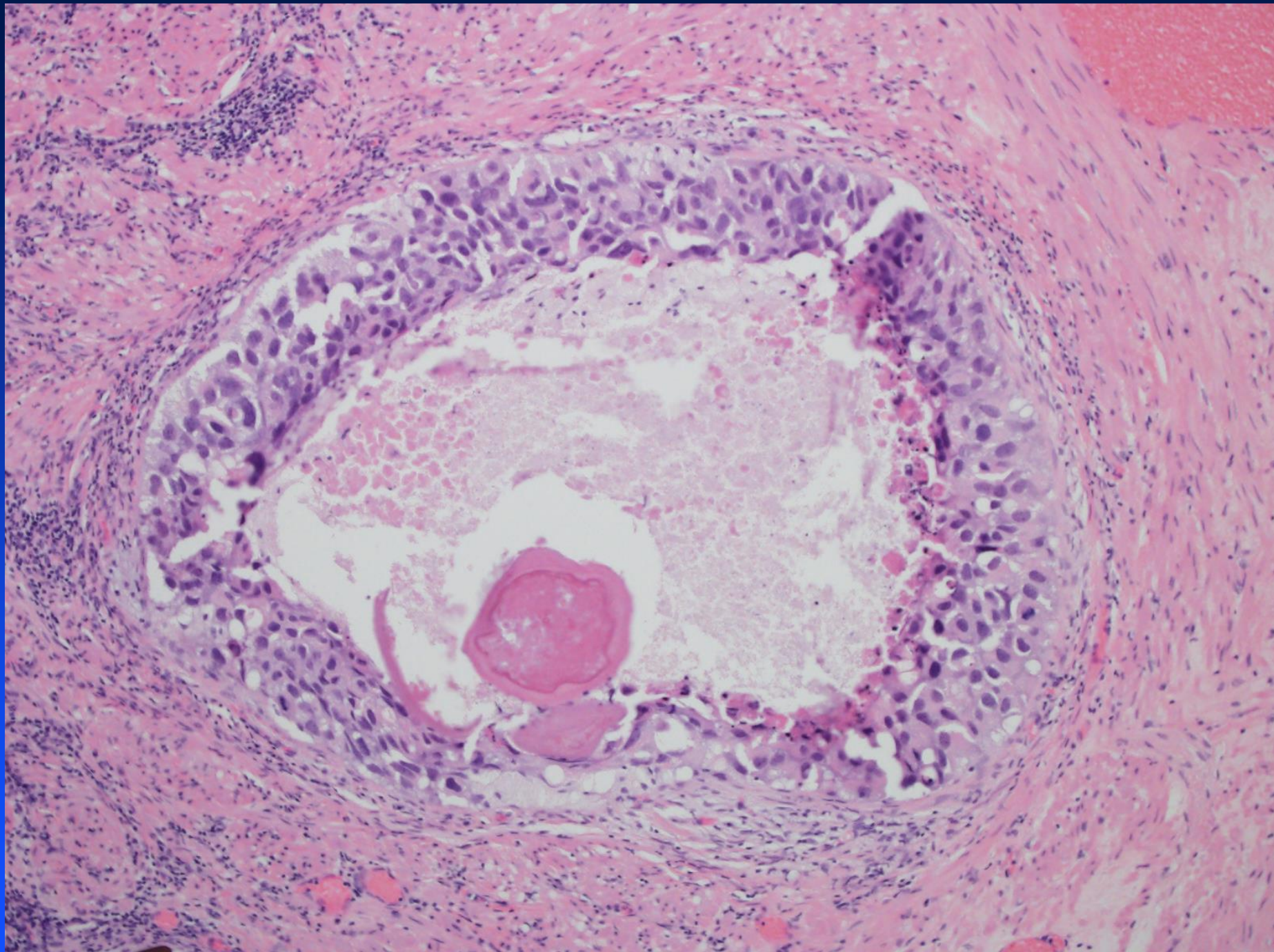


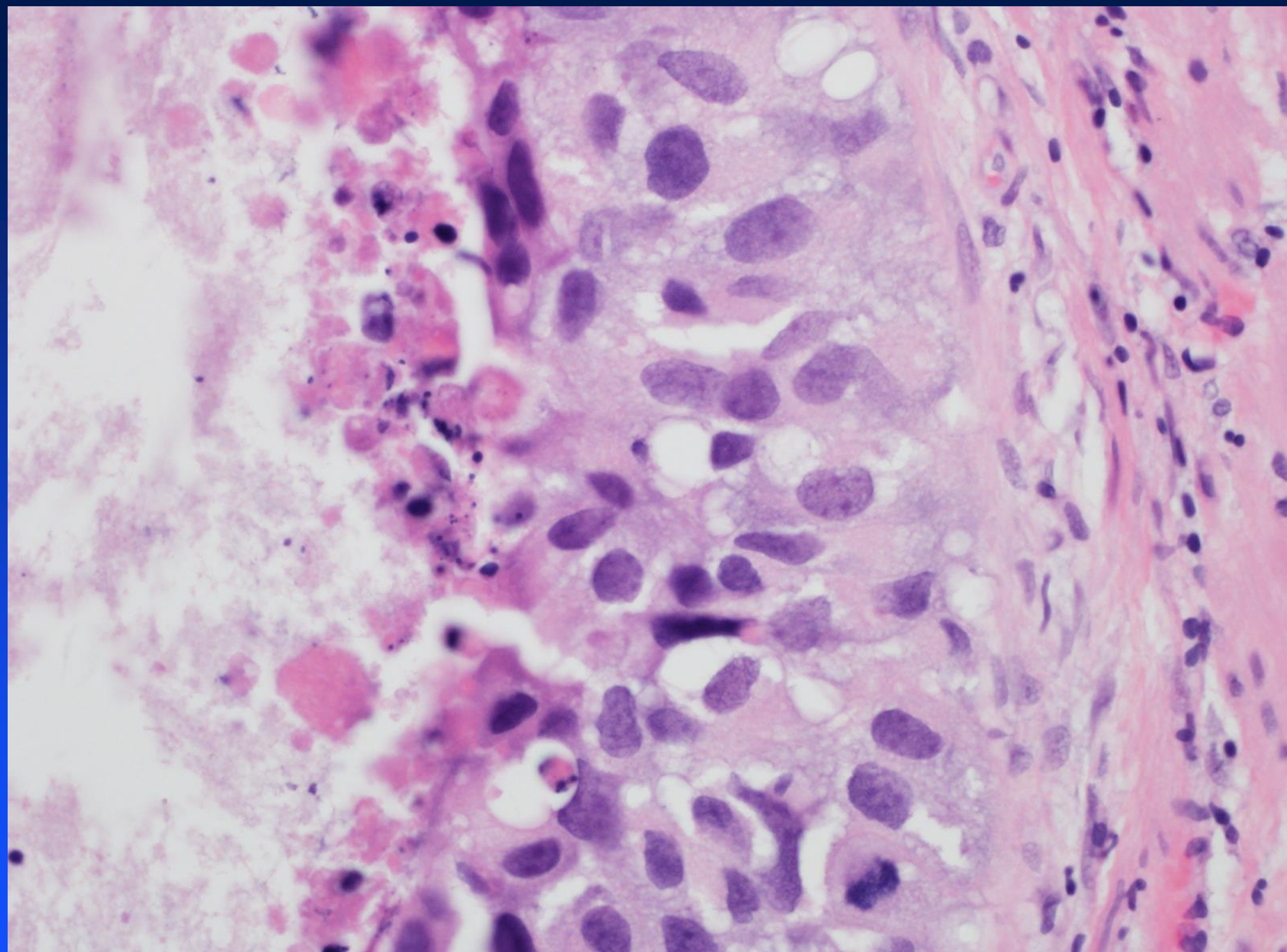


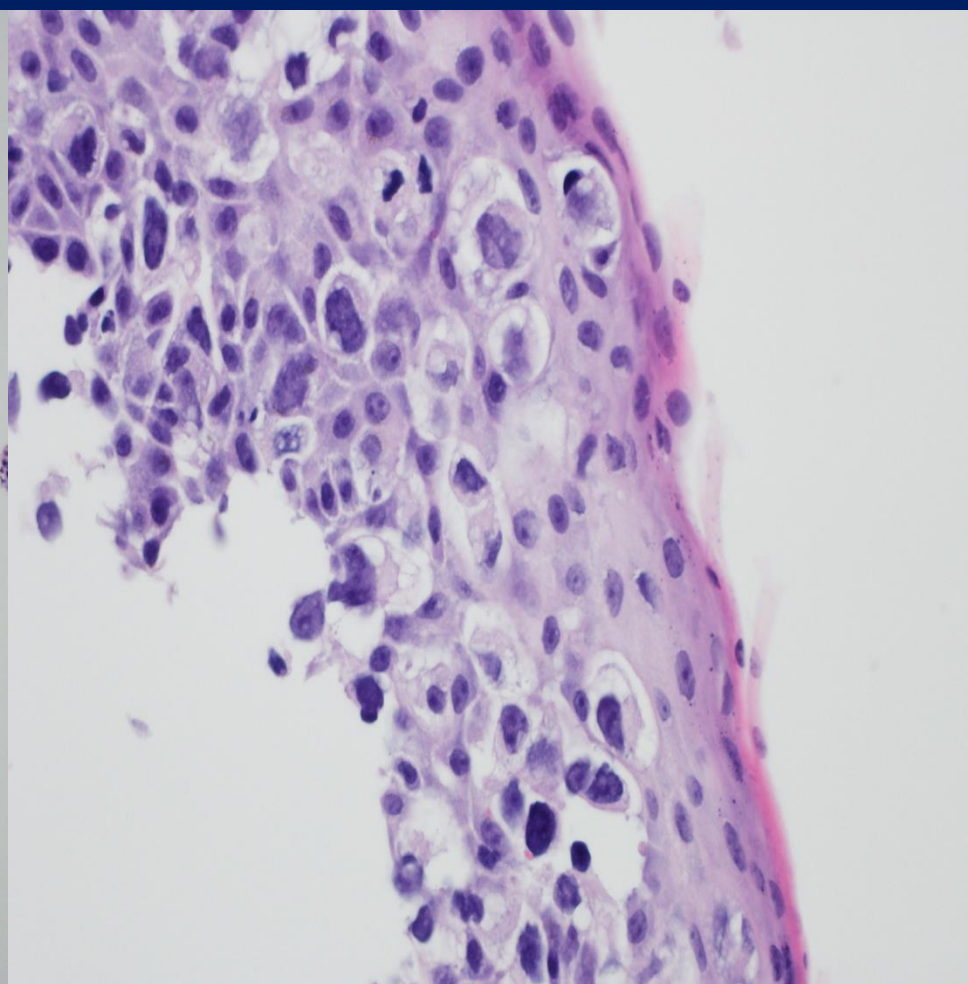
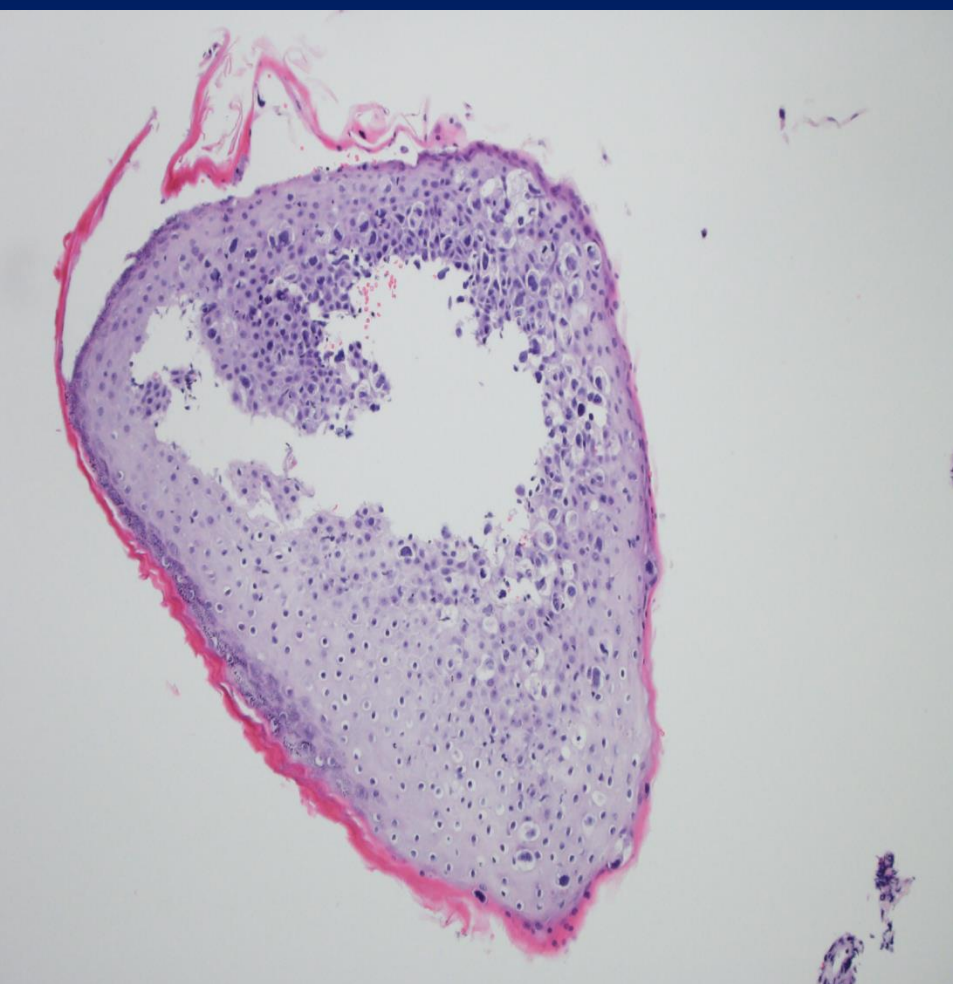


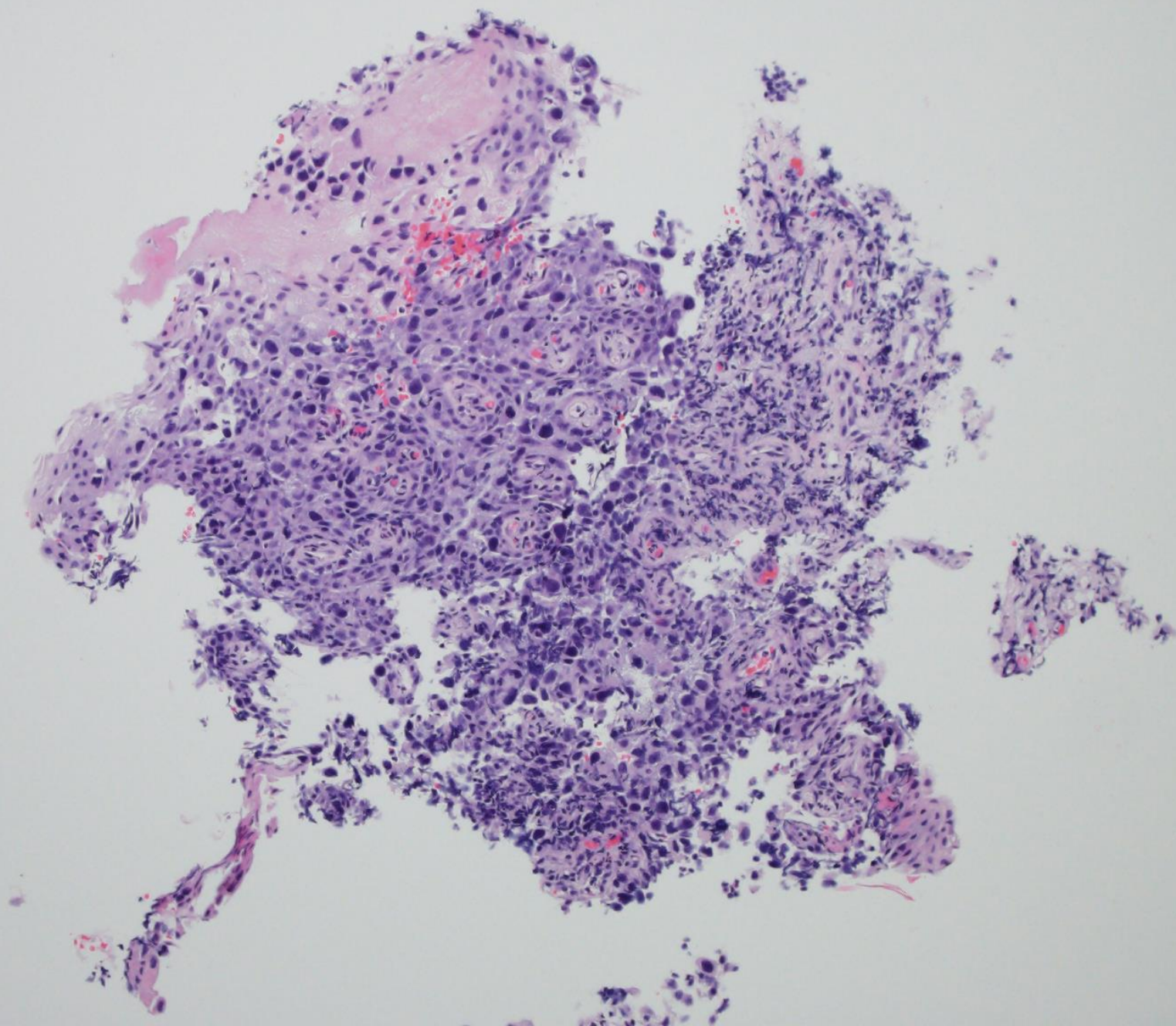


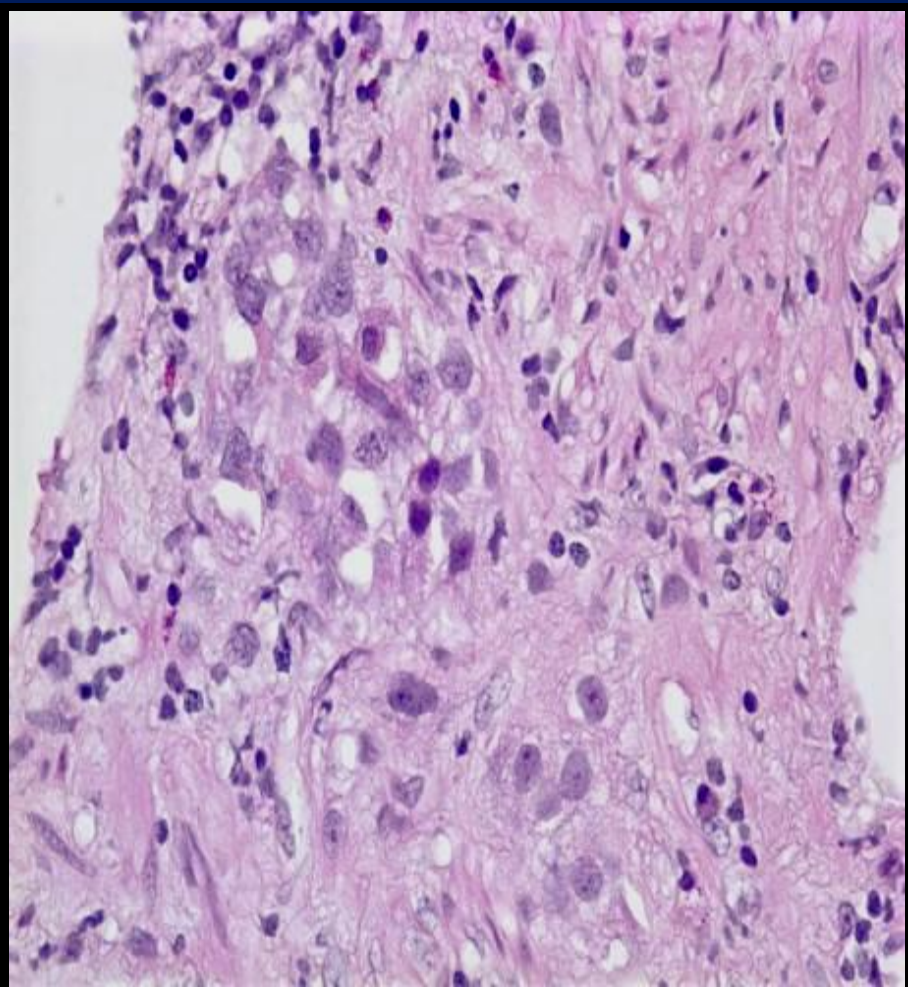
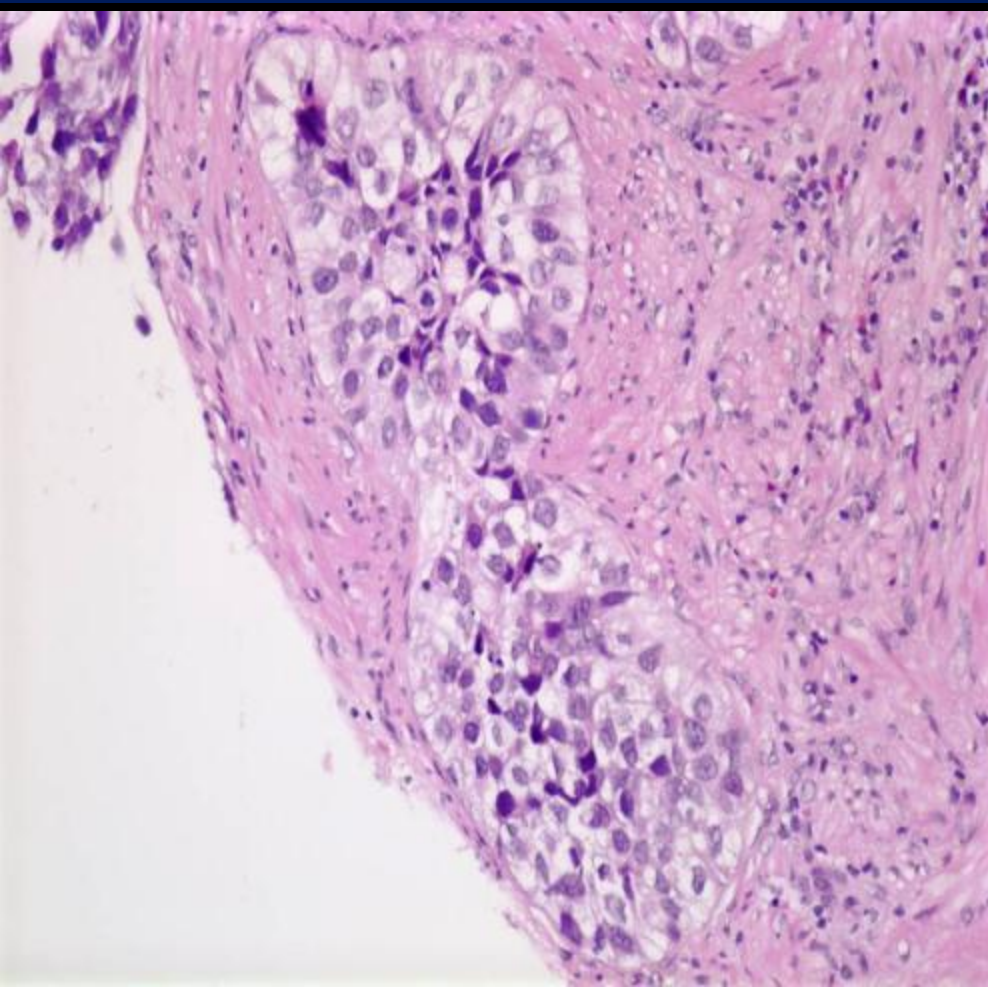
90 year-old with hematuria and erythema of the glans

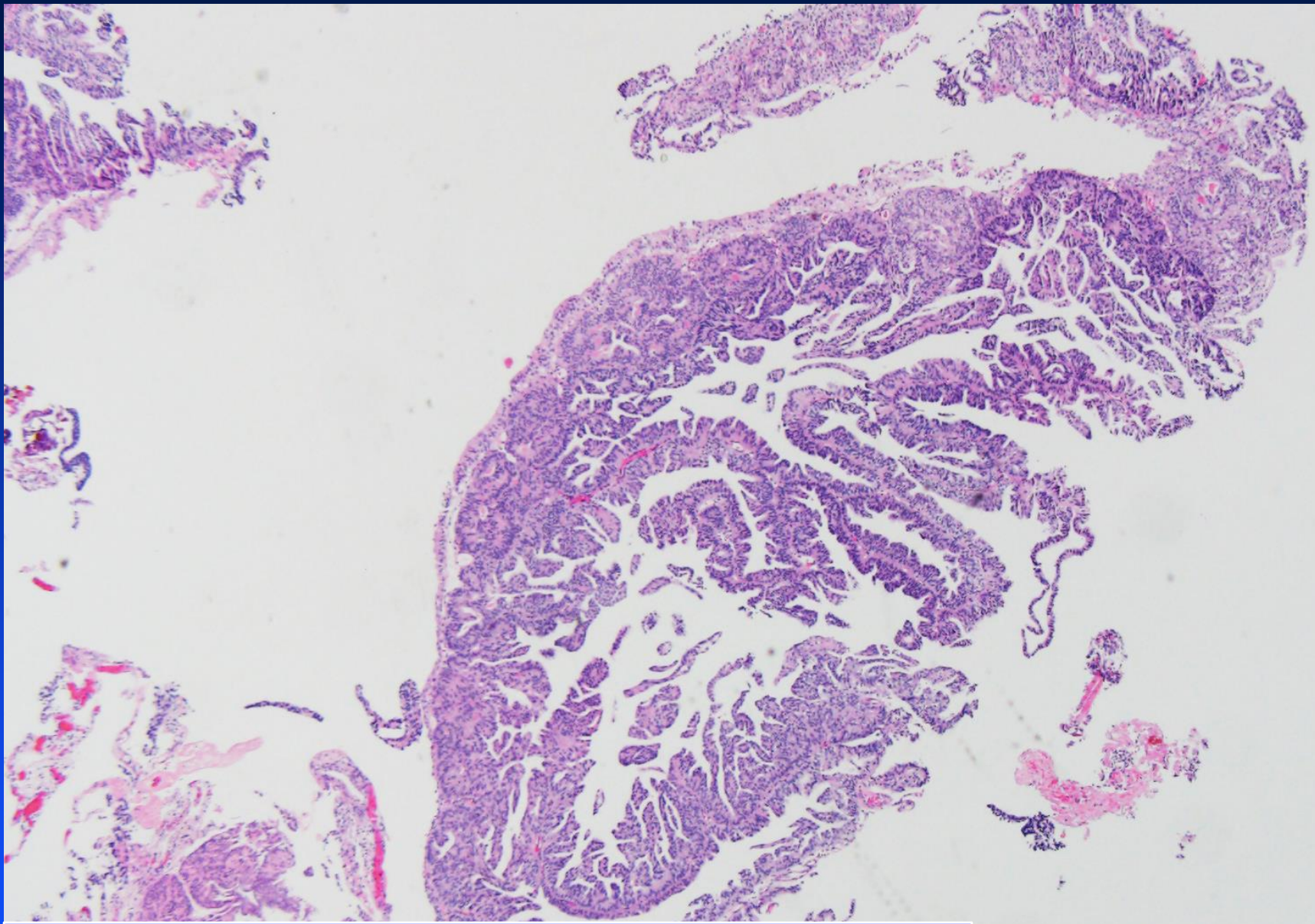




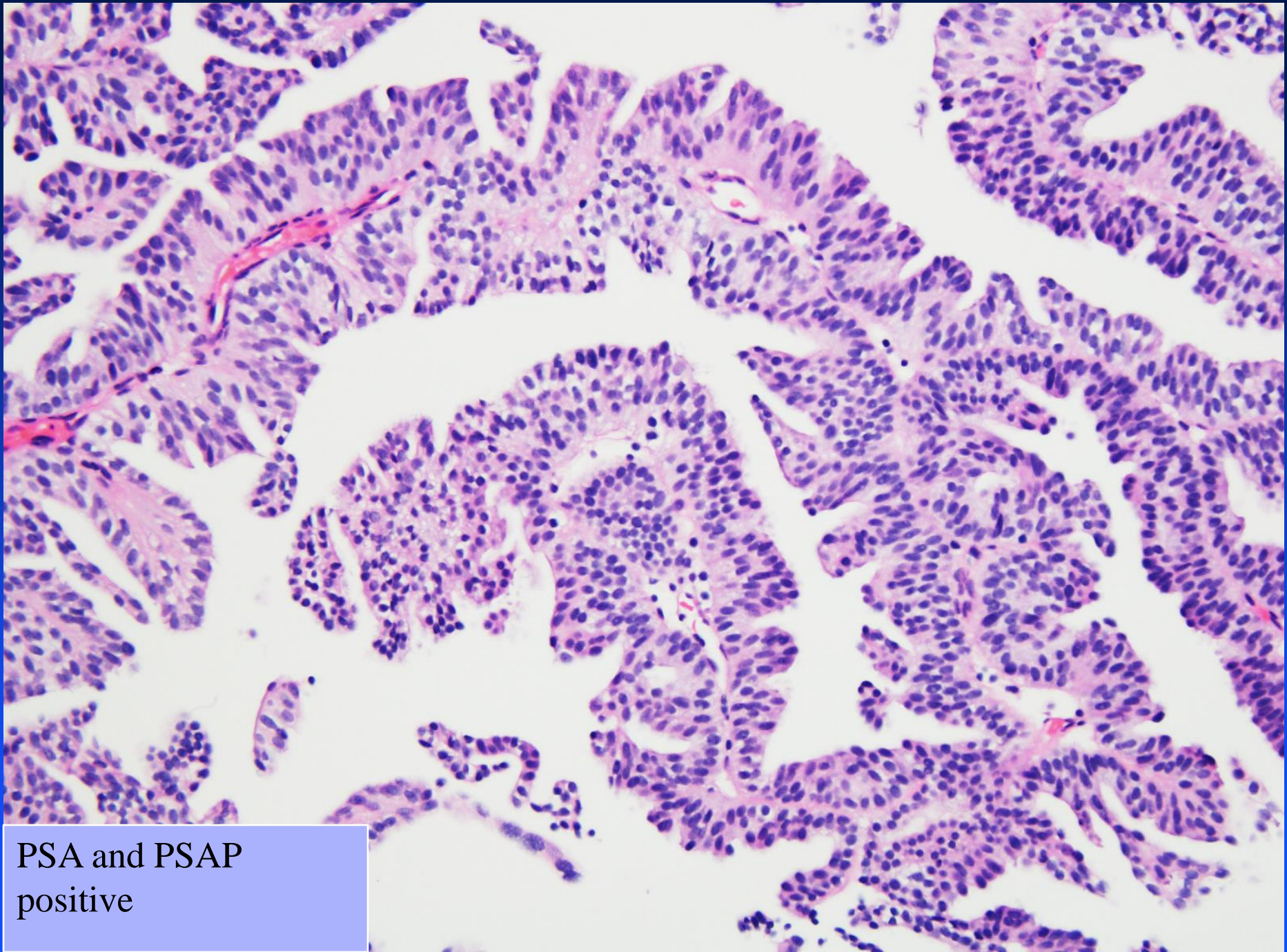






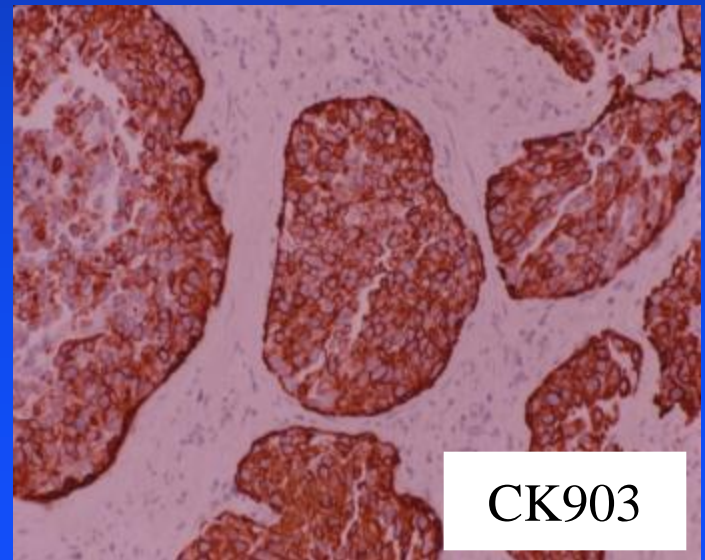


65-year-old with hematuria and “papillary tumor” of bladder base/proximal prostatic urethra



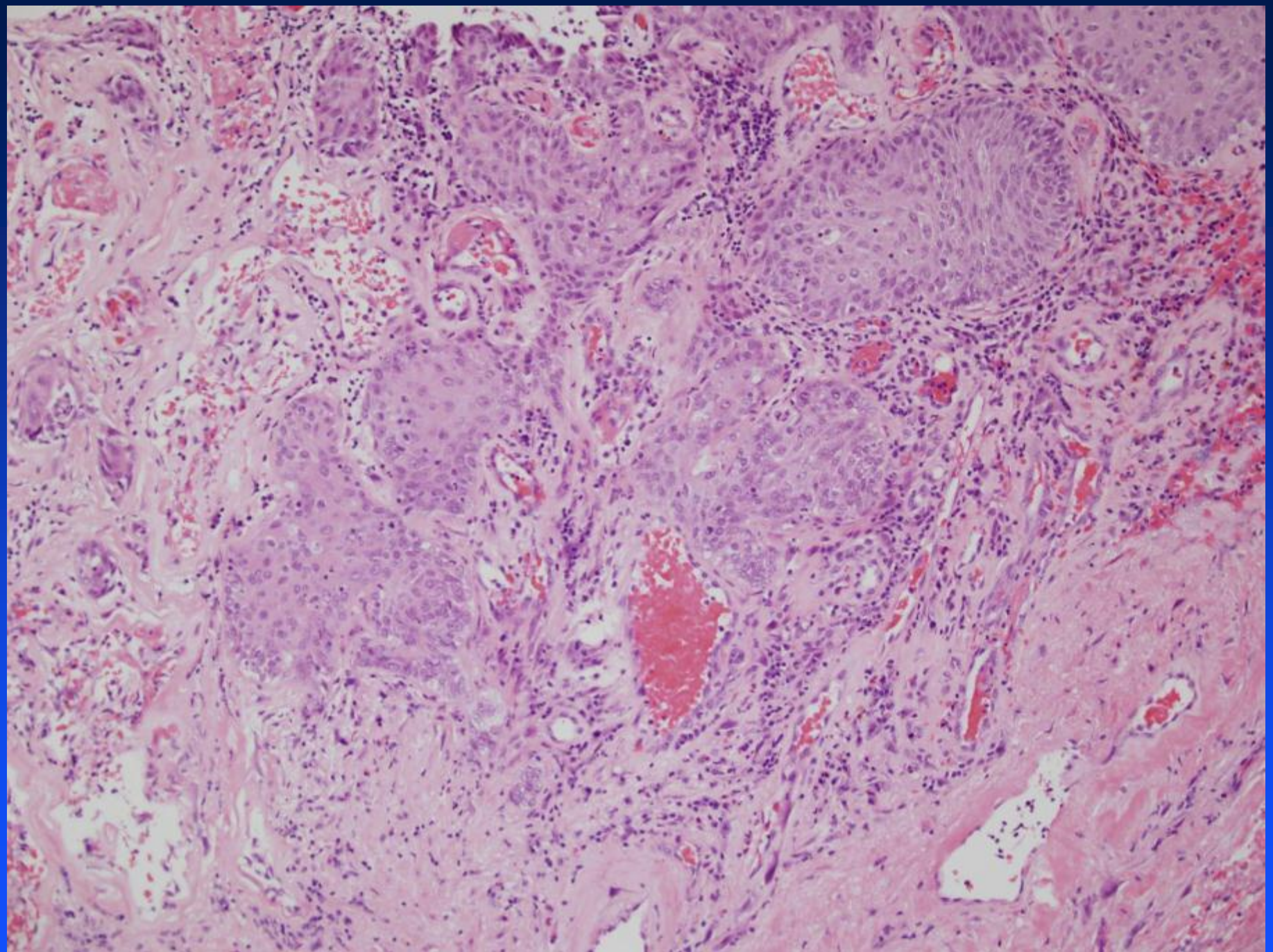
PSA and PSAP
positive

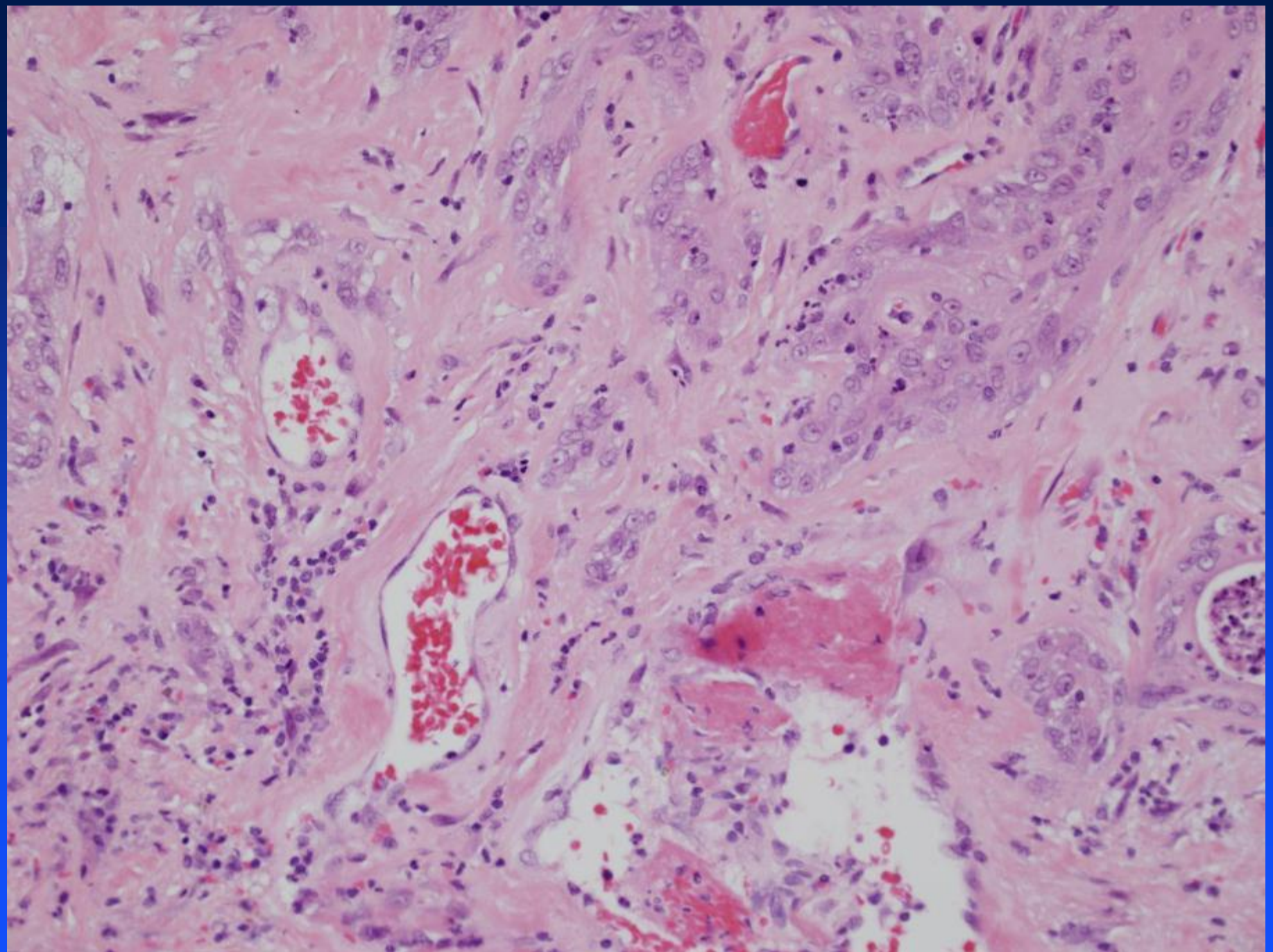
	PSA	PACP	Keratin 903	p63	ERG
UCa	-	-	+	+	-
PCa	+	+	-	-	+/-

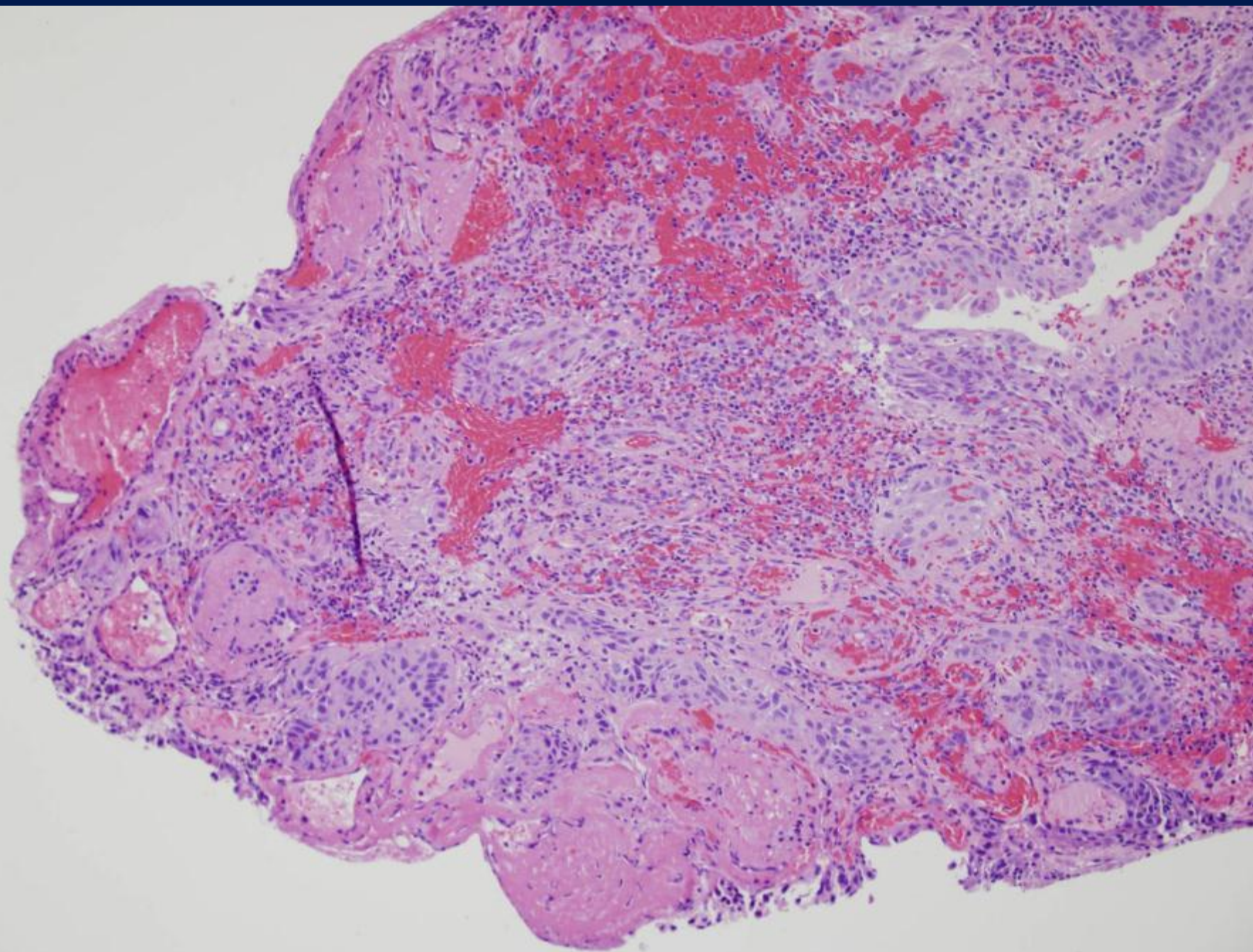


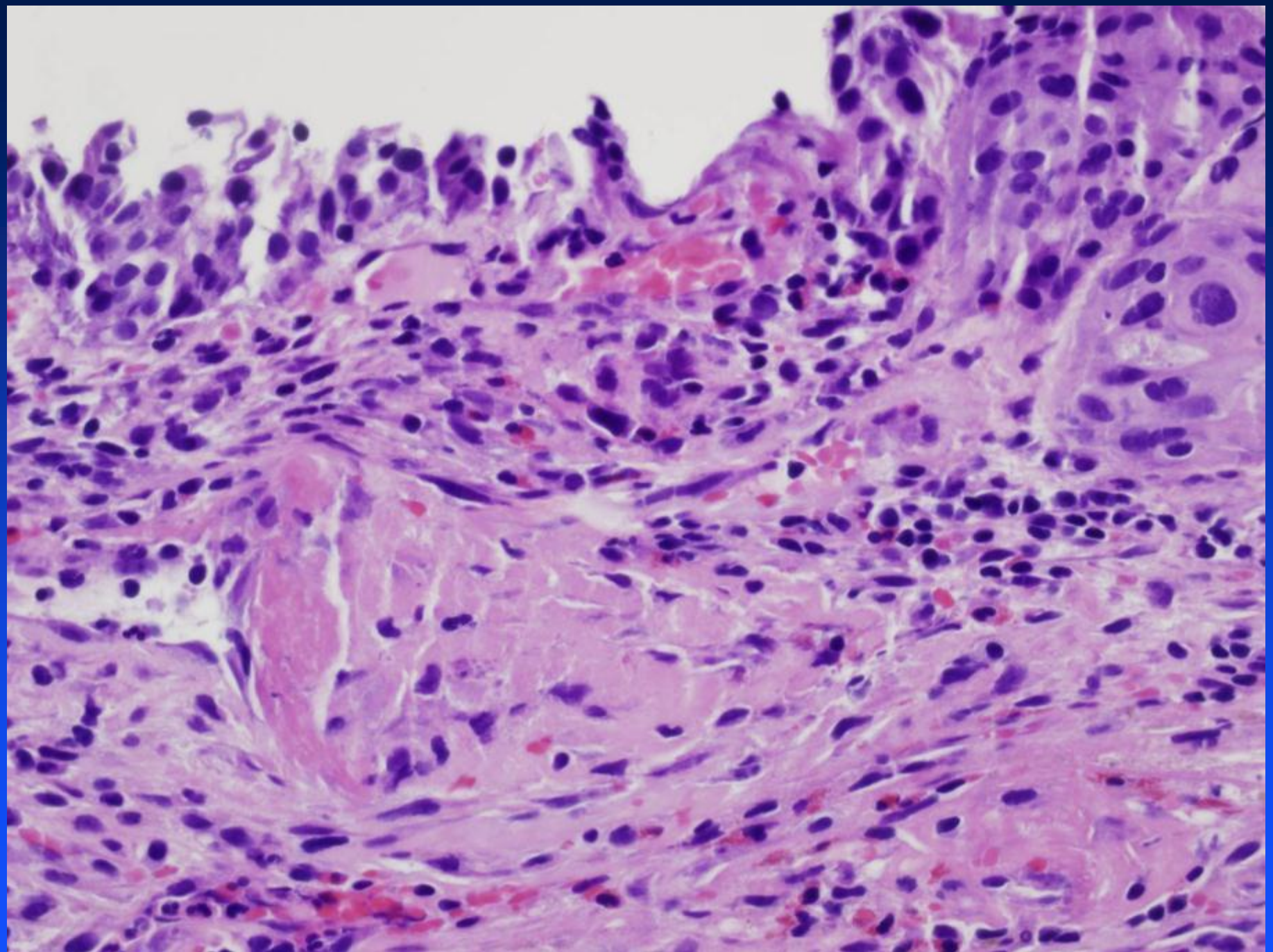
Diagnostic Errors Resulting in Cystectomy

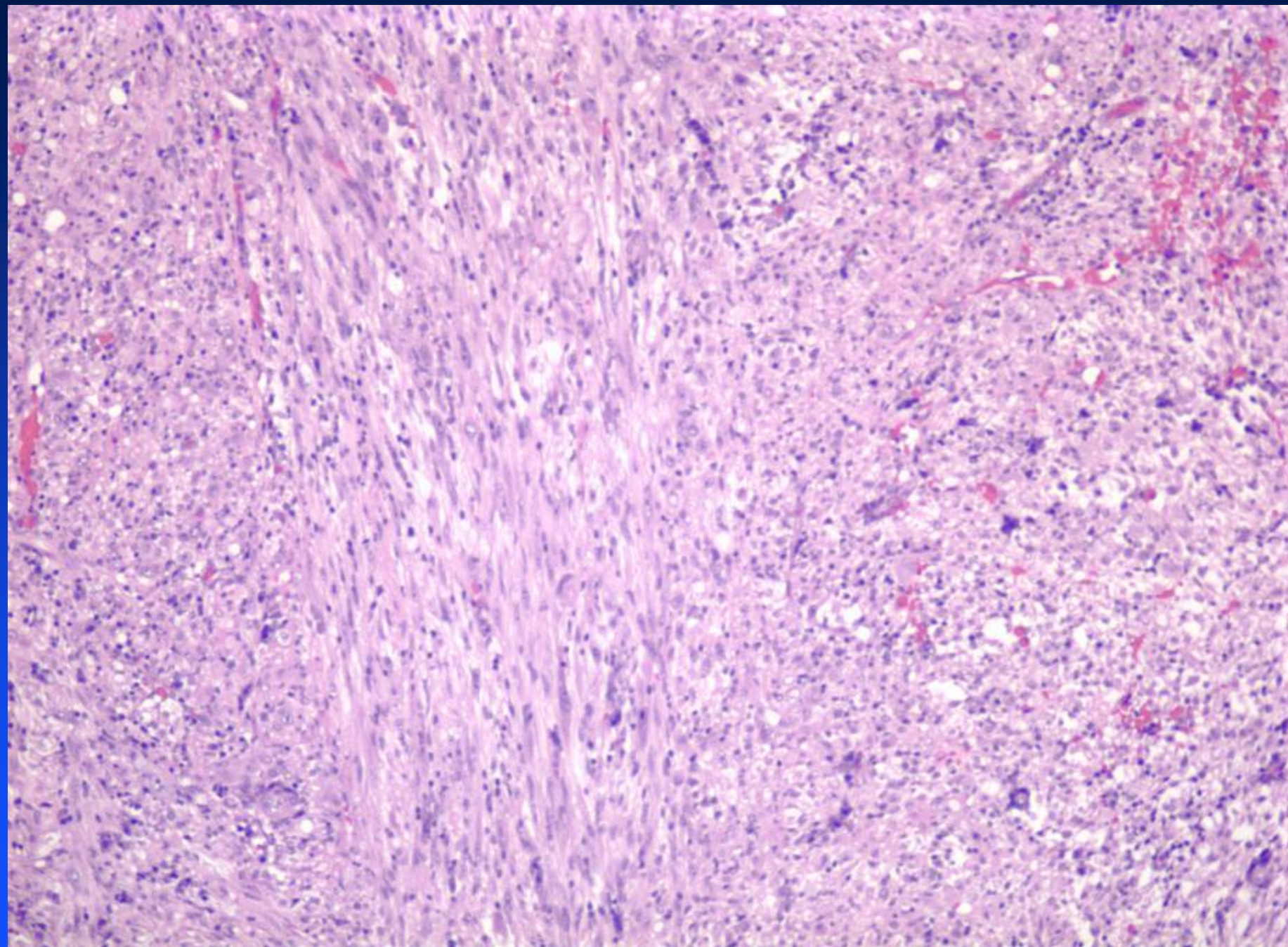
- Radiation injury
- Inflammatory myofibroblastic tumor
- Paraganglioma

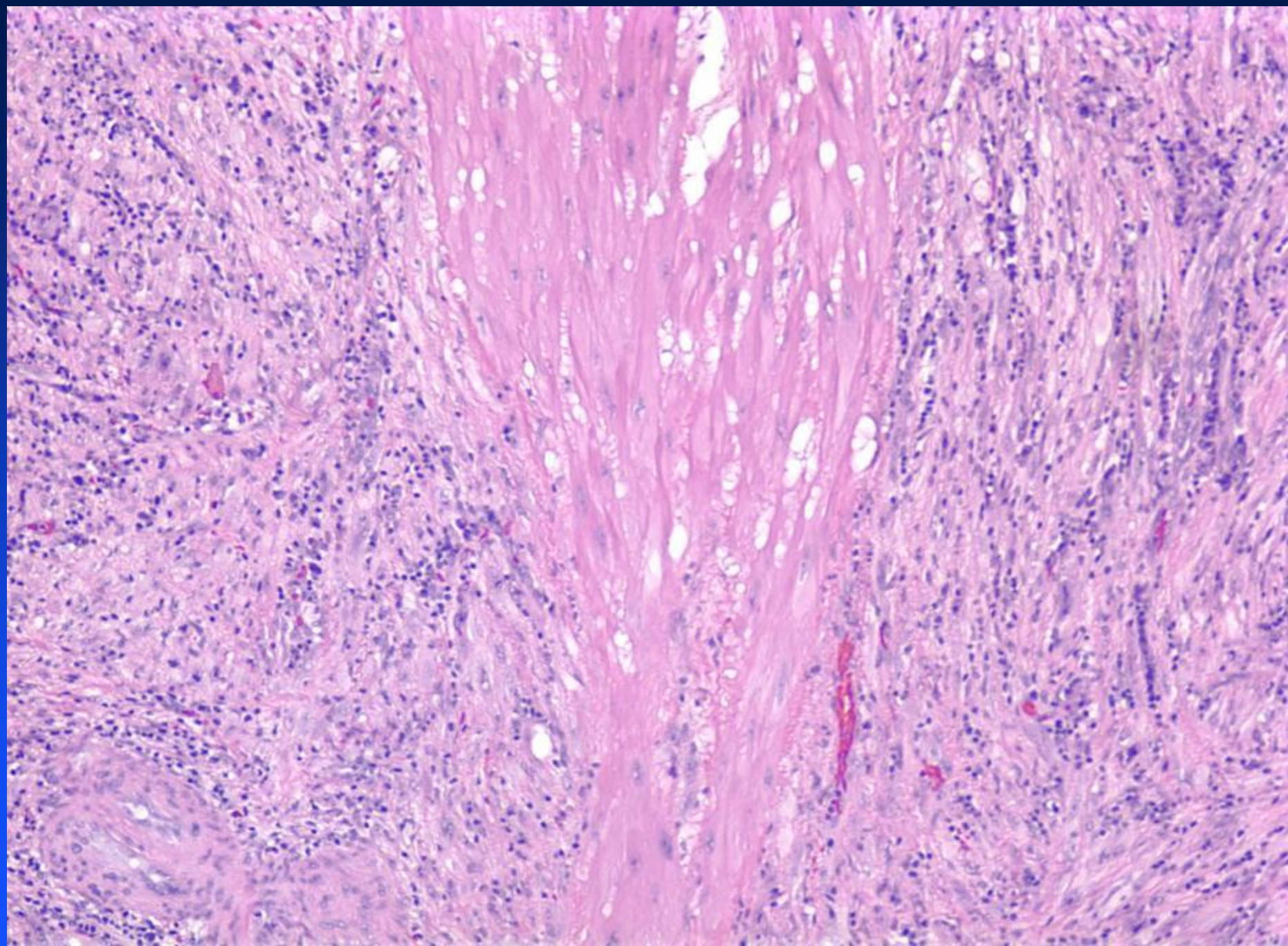


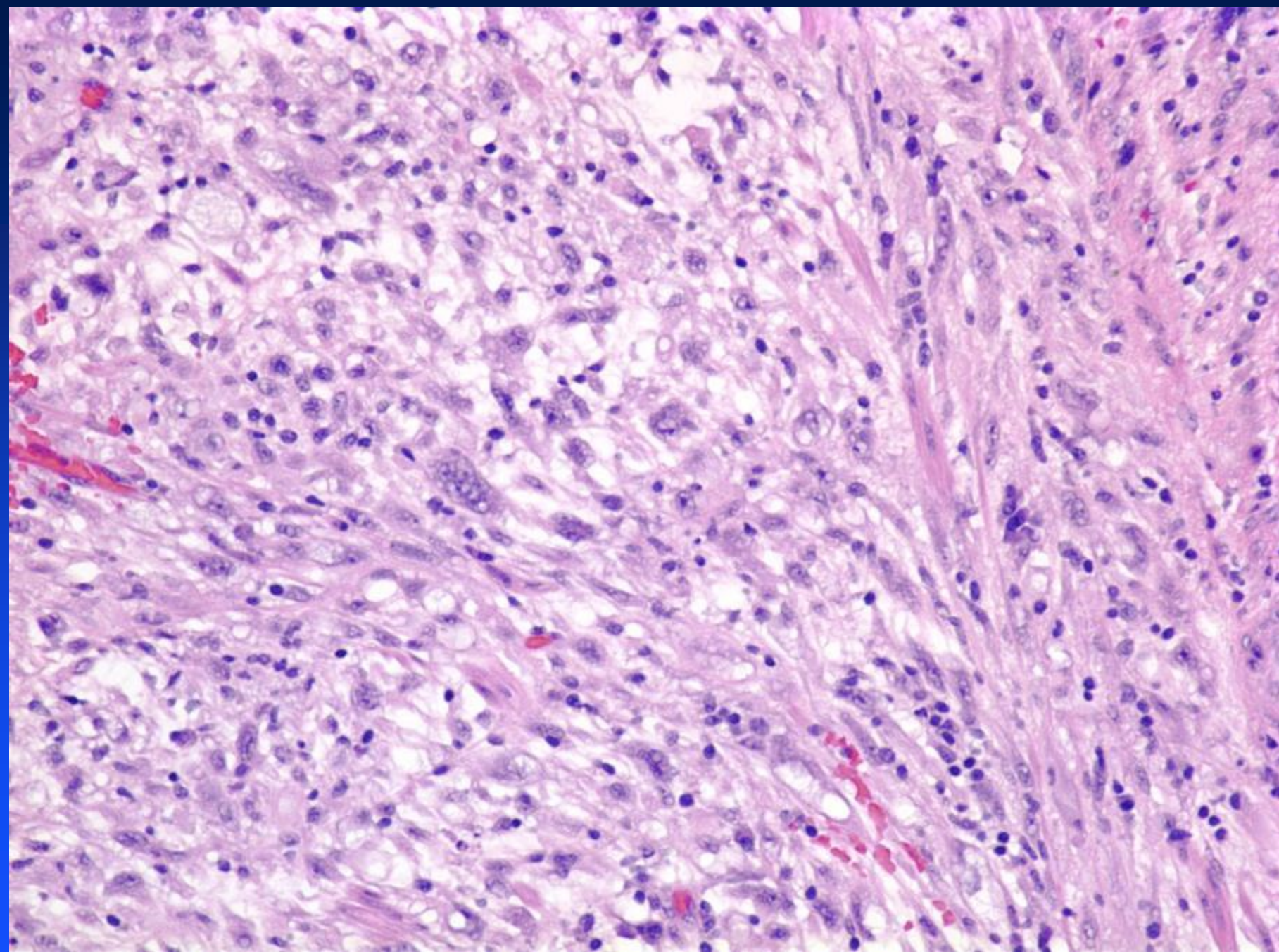


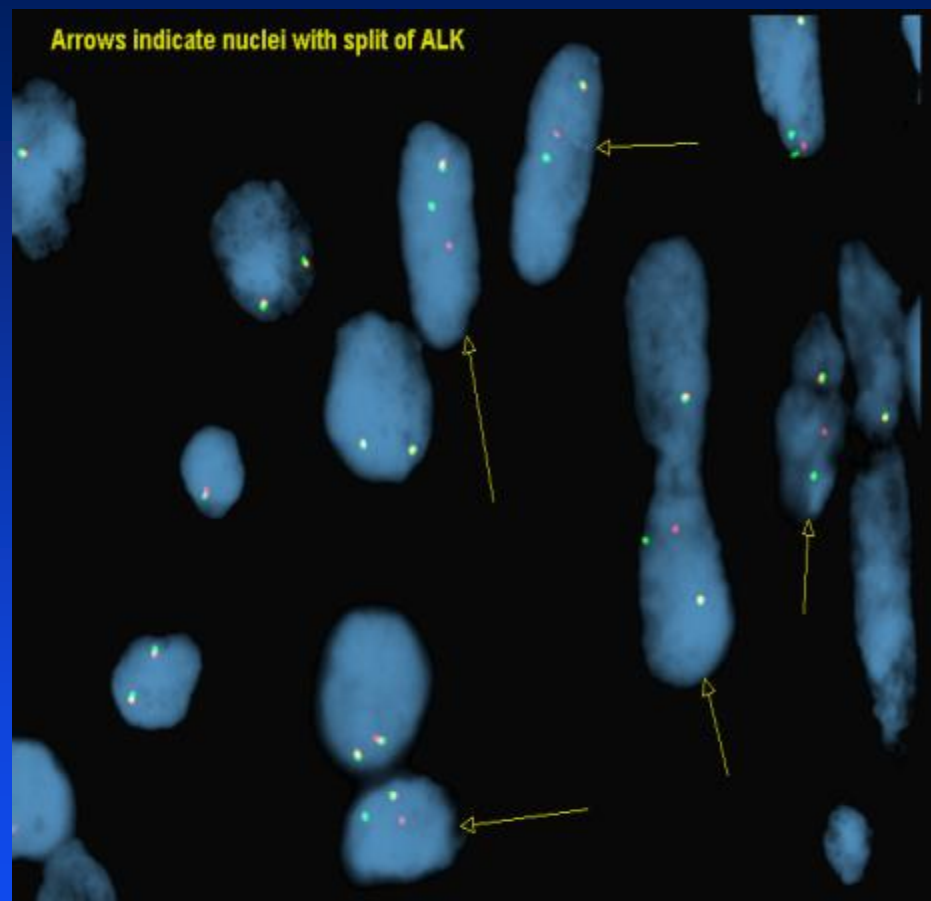
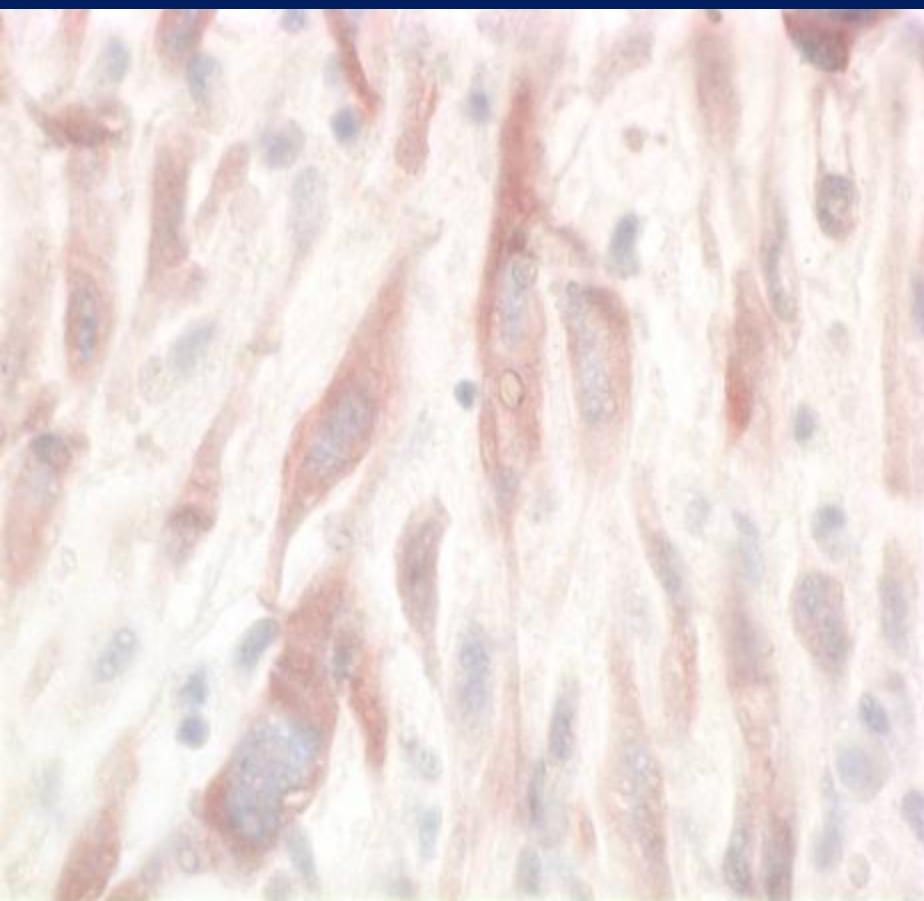


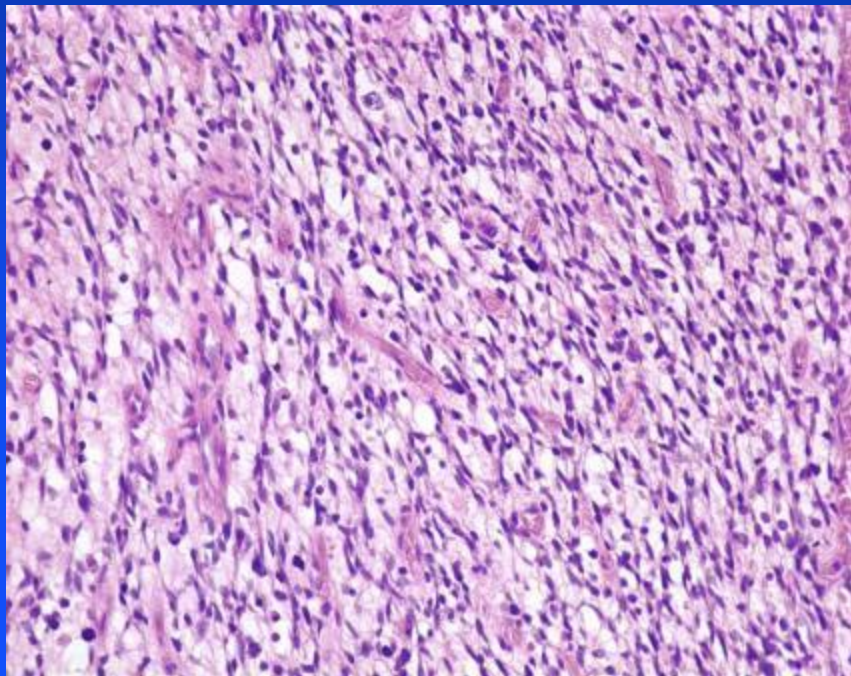
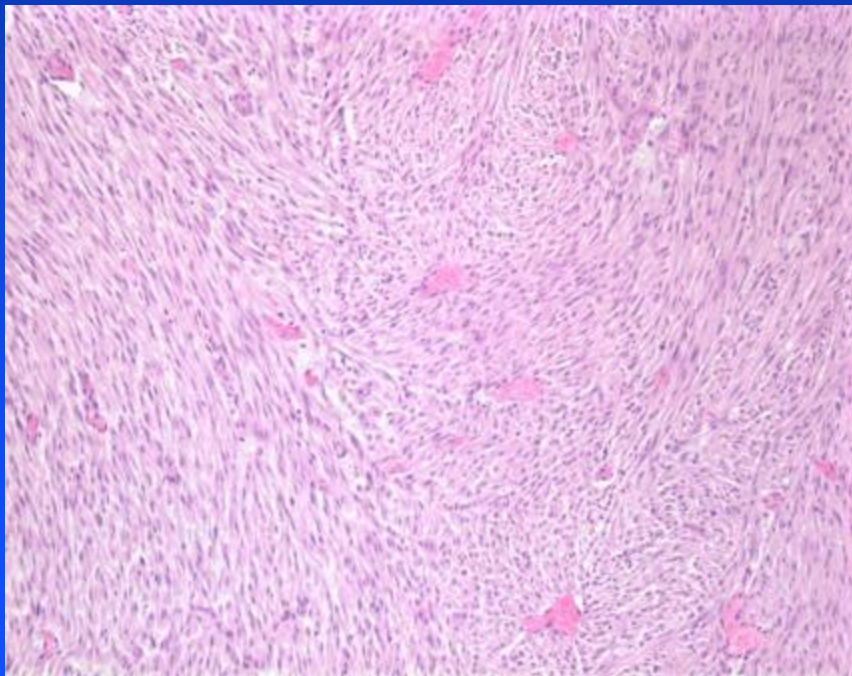
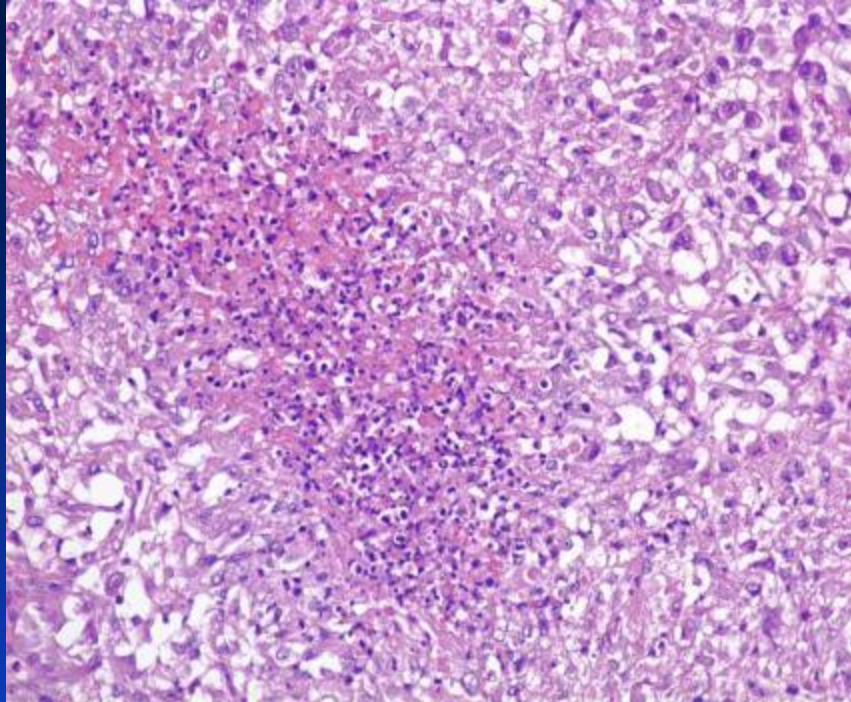
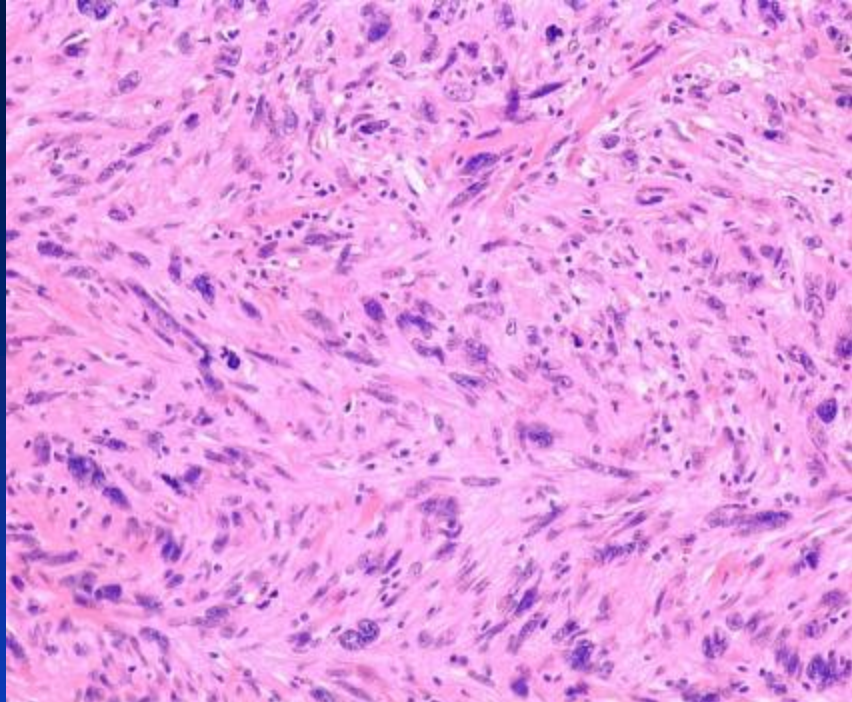


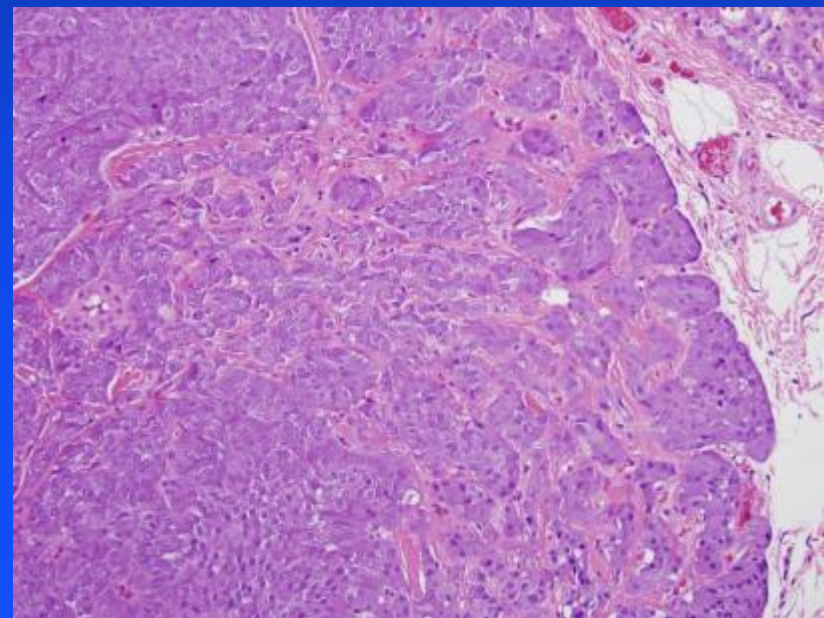
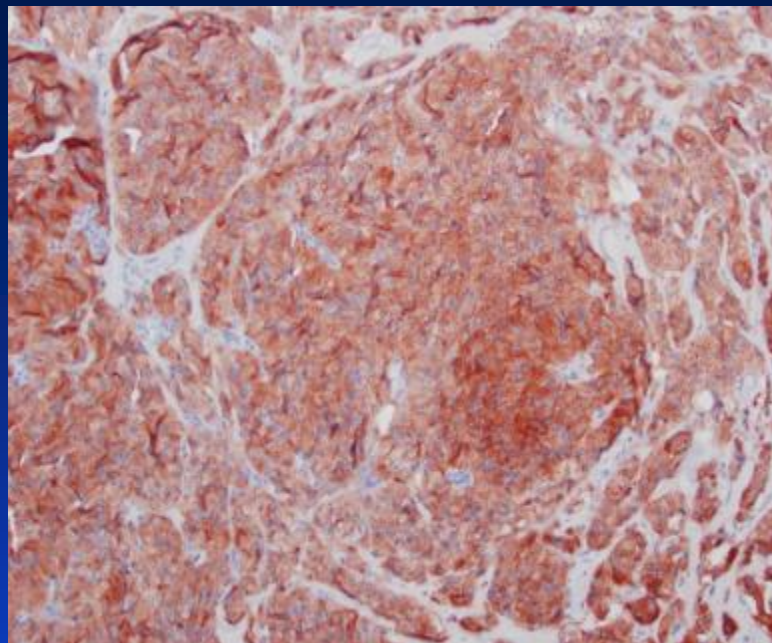
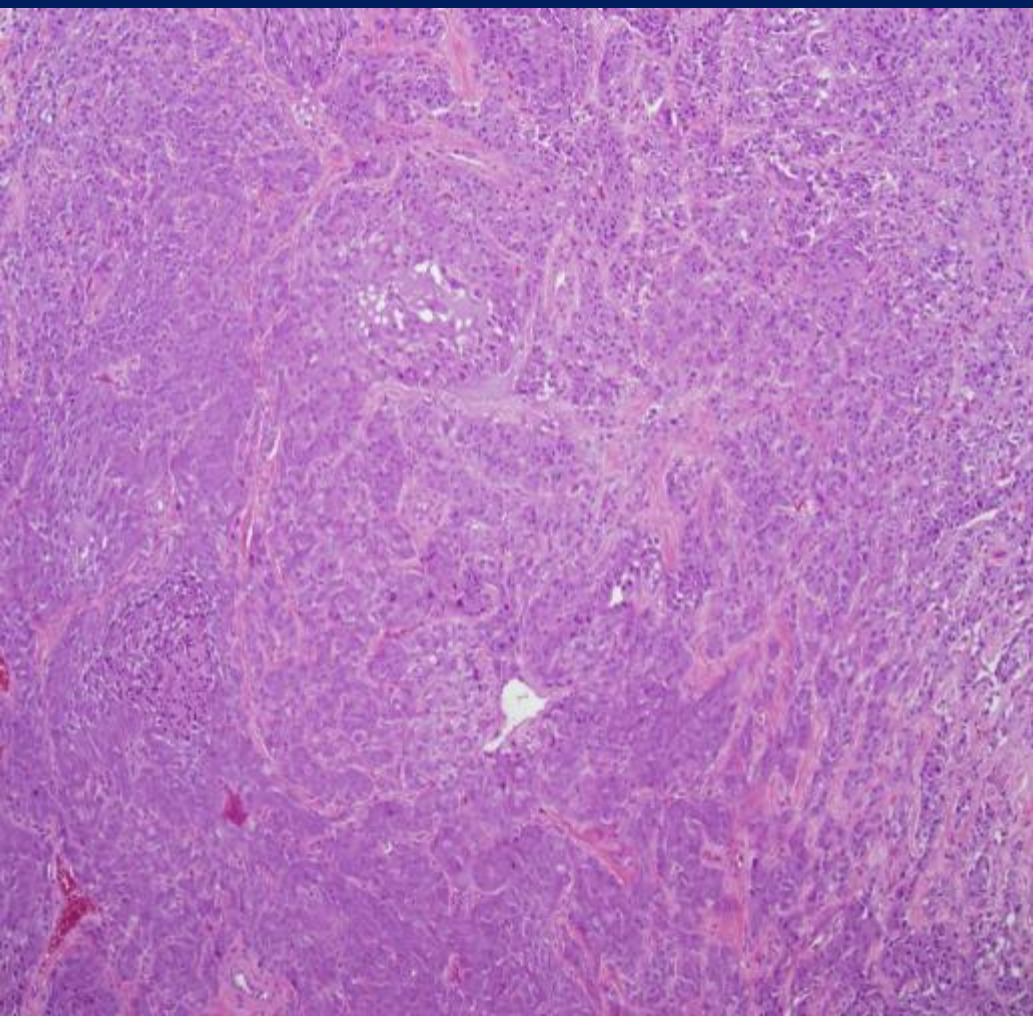














Questions and Cases