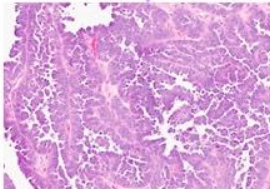
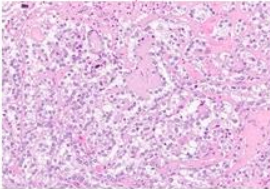
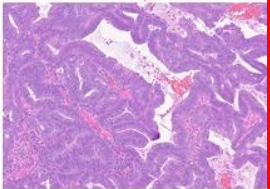
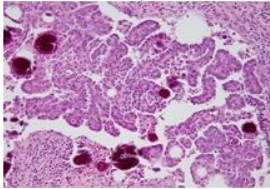
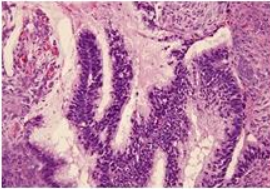


Endometriosis Associated Ovarian Carcinomas

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Harvard Medical School, Boston, MA
gturashvili@mgh.harvard.edu

Ovarian Carcinomas

Origin	Fallopian Tube Epithelium	Endometriosis	Endometriosis	Fallopian Tube Epithelium	?Unknown
					
	High-Grade Serous Carcinoma	Clear Cell Carcinoma	Endometrioid Carcinoma	Low-Grade Serous Carcinoma	Mucinous Carcinoma
% of all Ovarian Carcinomas	~70%	~10%	~10%	<5%	<5%
Precursor Lesions	Serous tubal intraepithelial carcinoma (STIC)	Clear Cell Borderline Tumor	Endometrioid Borderline Tumor	Serous Borderline Tumor	Mucinous Borderline Tumor
Inherited Syndromes	BRCA1/2, Hereditary Breast and Ovarian Cancer (HBOC)	Lynch Syndrome	Lynch Syndrome	?	?
Common Mutations and Molecular Aberrations	TP53 BRCA1/2 and HRD Chromosomal instability Aneuploidy (100%)	ARID1A PIK3CA CTNNB1 PPP2R1A MSI	PTEN CTNNB1 ARID1A PPP2R1A MSI	KRAS BRAF	KRAS HER2 amplification
Potential Molecular Targeted Therapies	PARP inhibitors, immune checkpoint inhibitors	Tyrosine kinase inhibitors	mTOR inhibitors	MEK1/2 inhibitors	Trastuzumab

ENDOMETRIOID CARCINOMA: Definition (WHO)

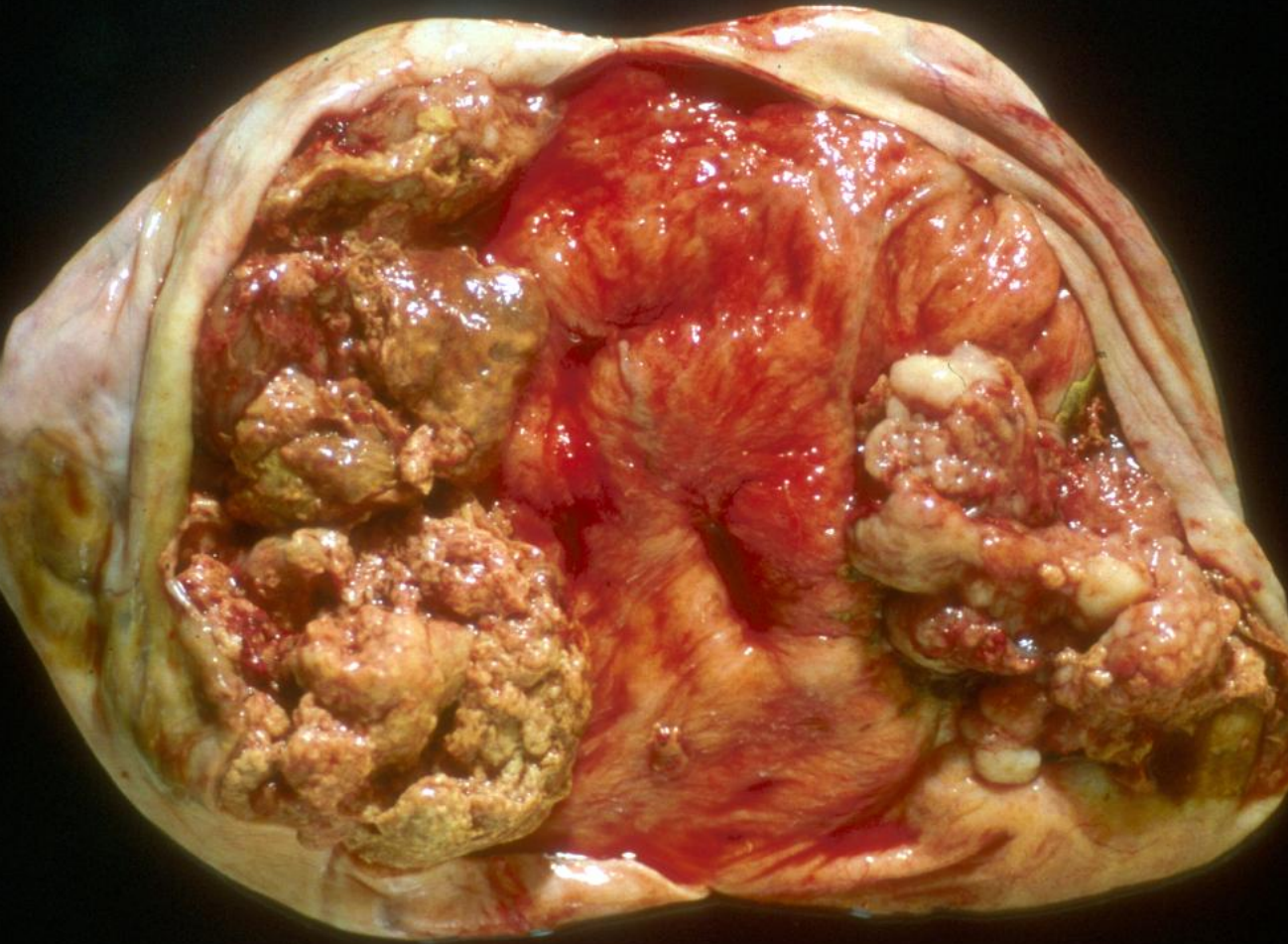
- Malignant epithelial tumor of ovary closely resembling common variants of endometrial endometrioid carcinoma
- Endometriosis (~42%), patients being 5-10 years younger
- Elevated serum CA-125 (>80%)
- Bilateral tumors (~20%)
- Synchronous endometrial carcinoma (15-20%)

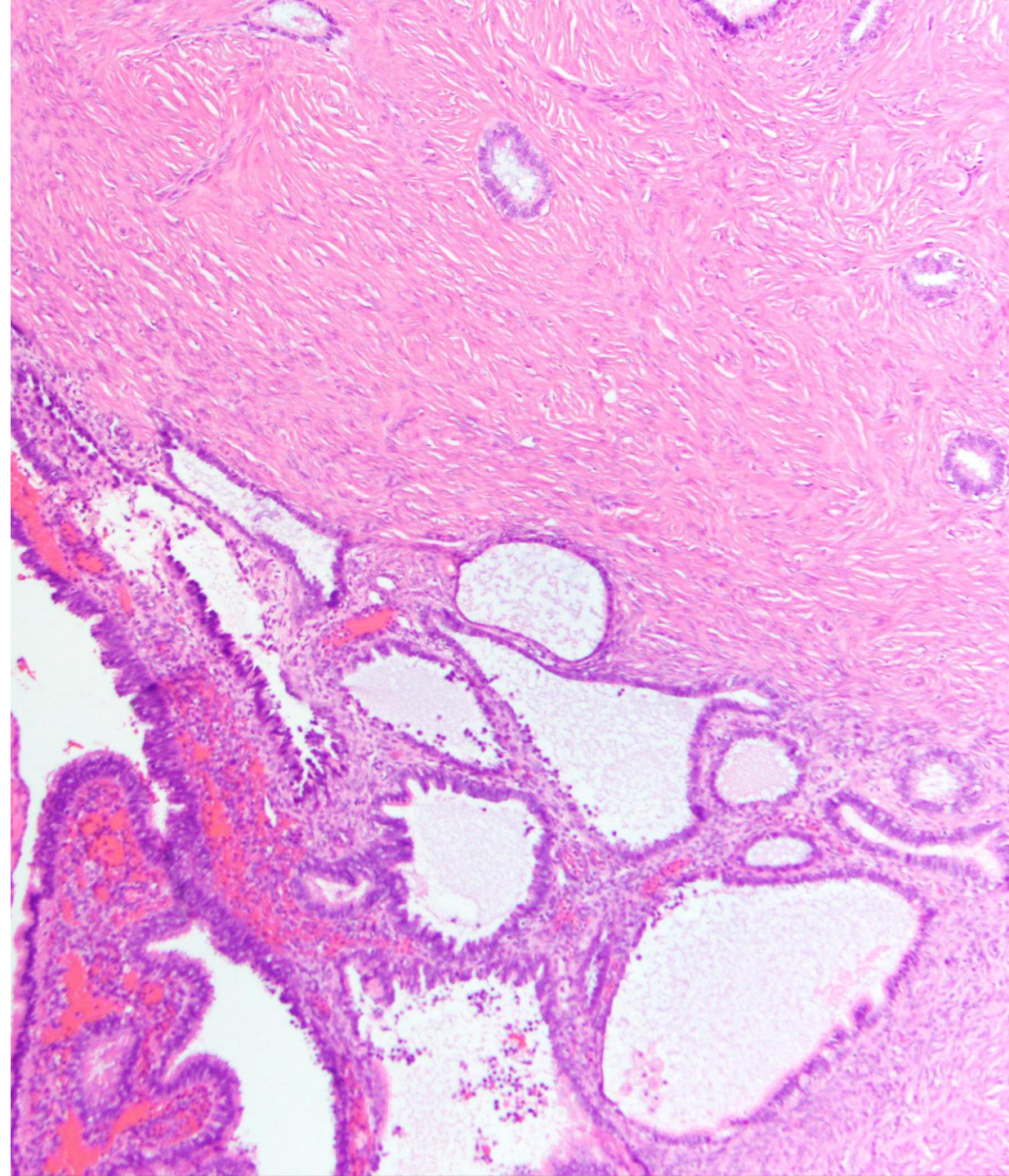
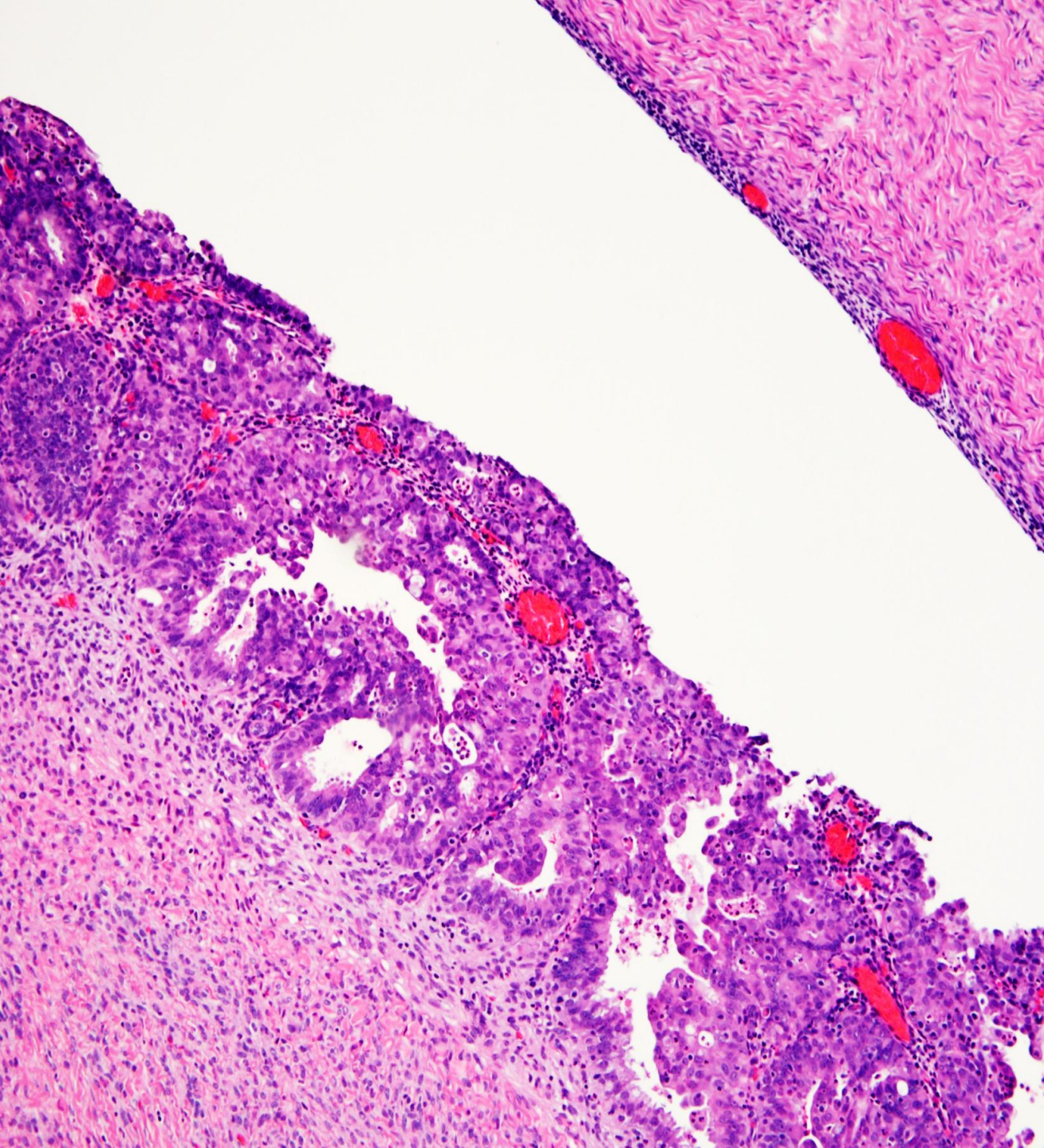
ARISING IN:

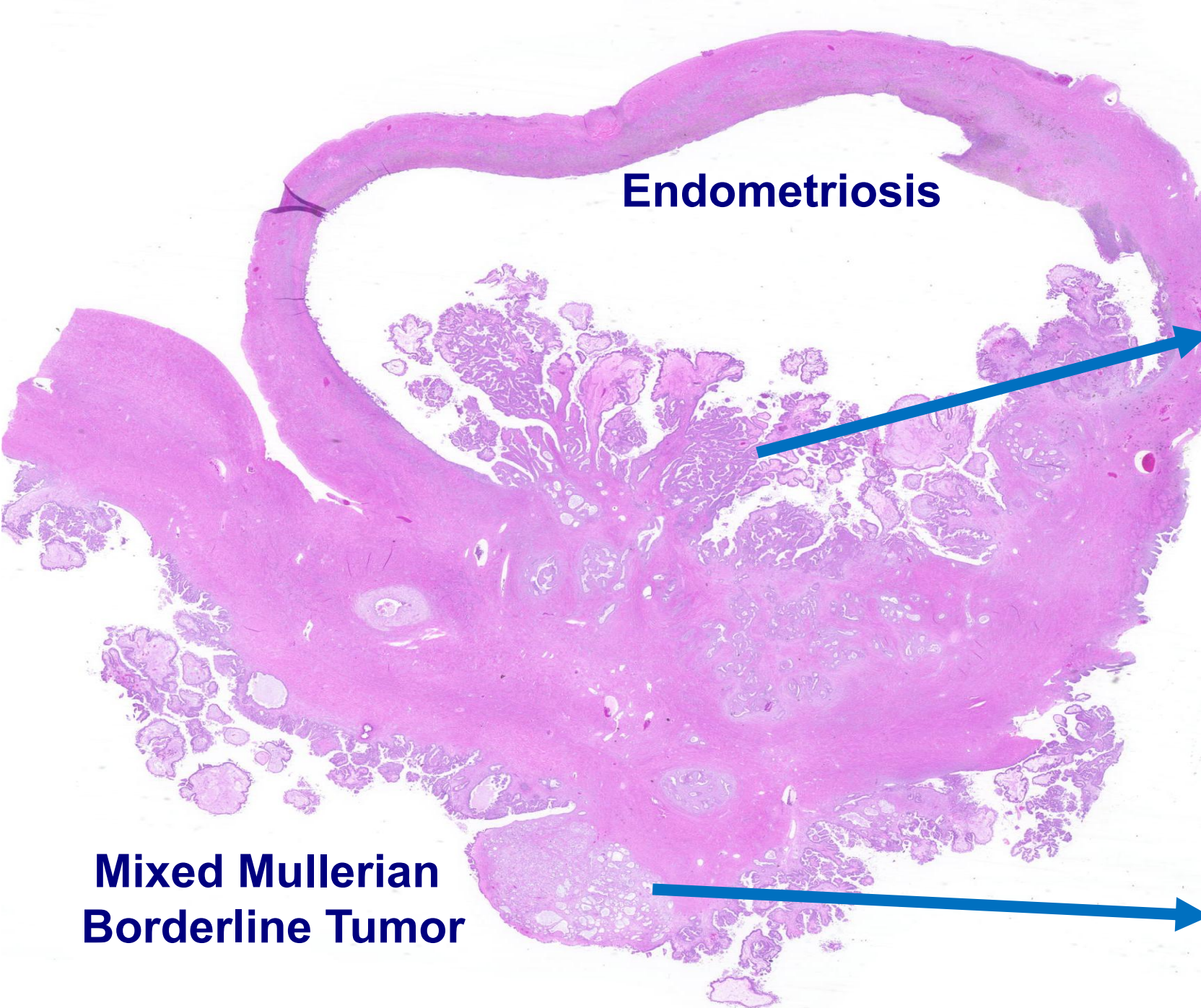
Endometriotic Cyst

OR

Adenofibroma



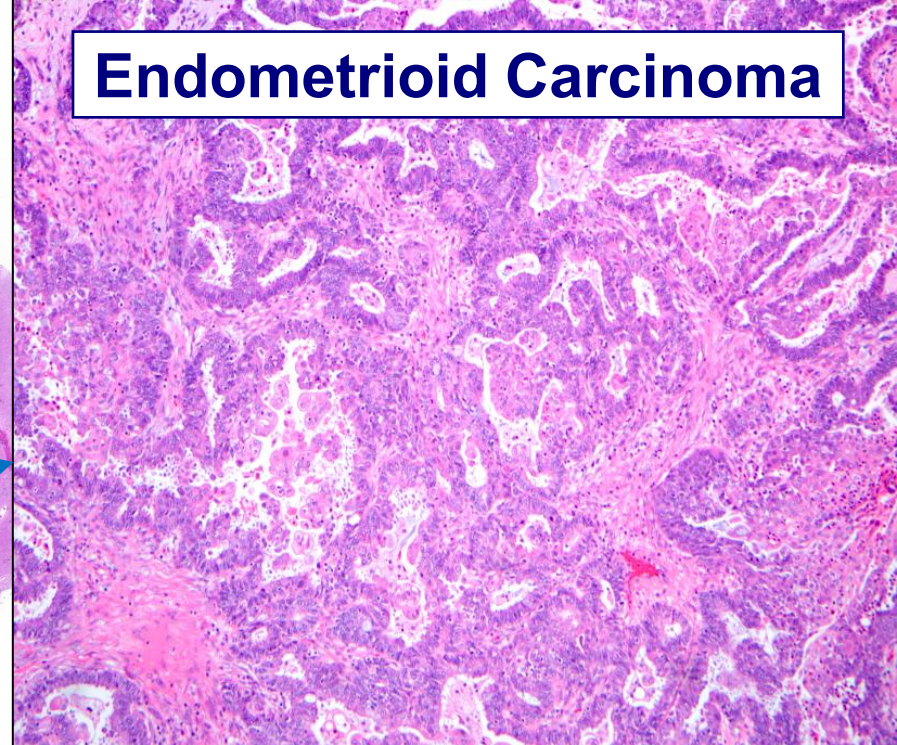




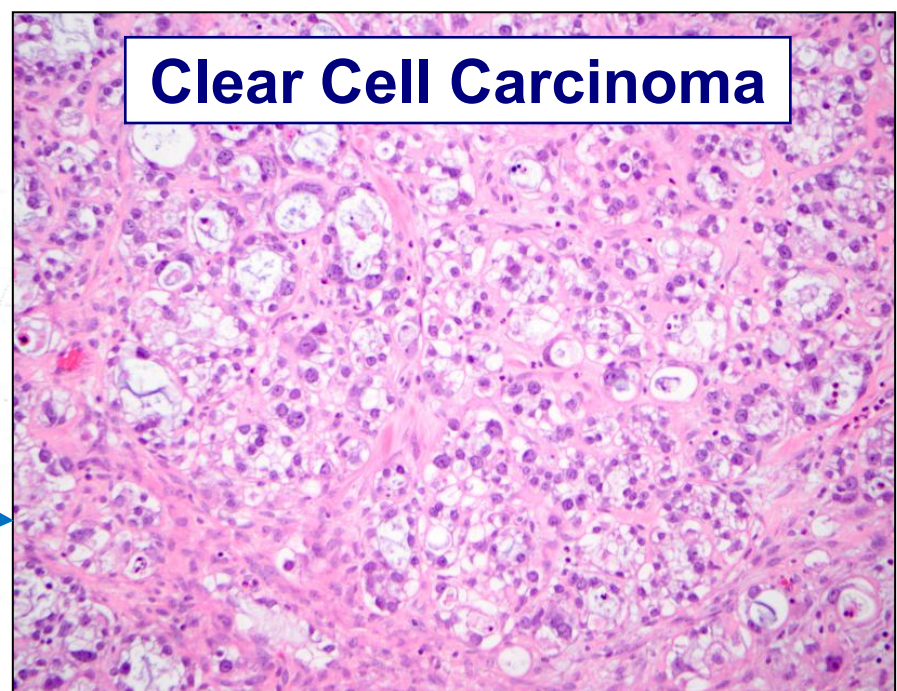
Endometriosis

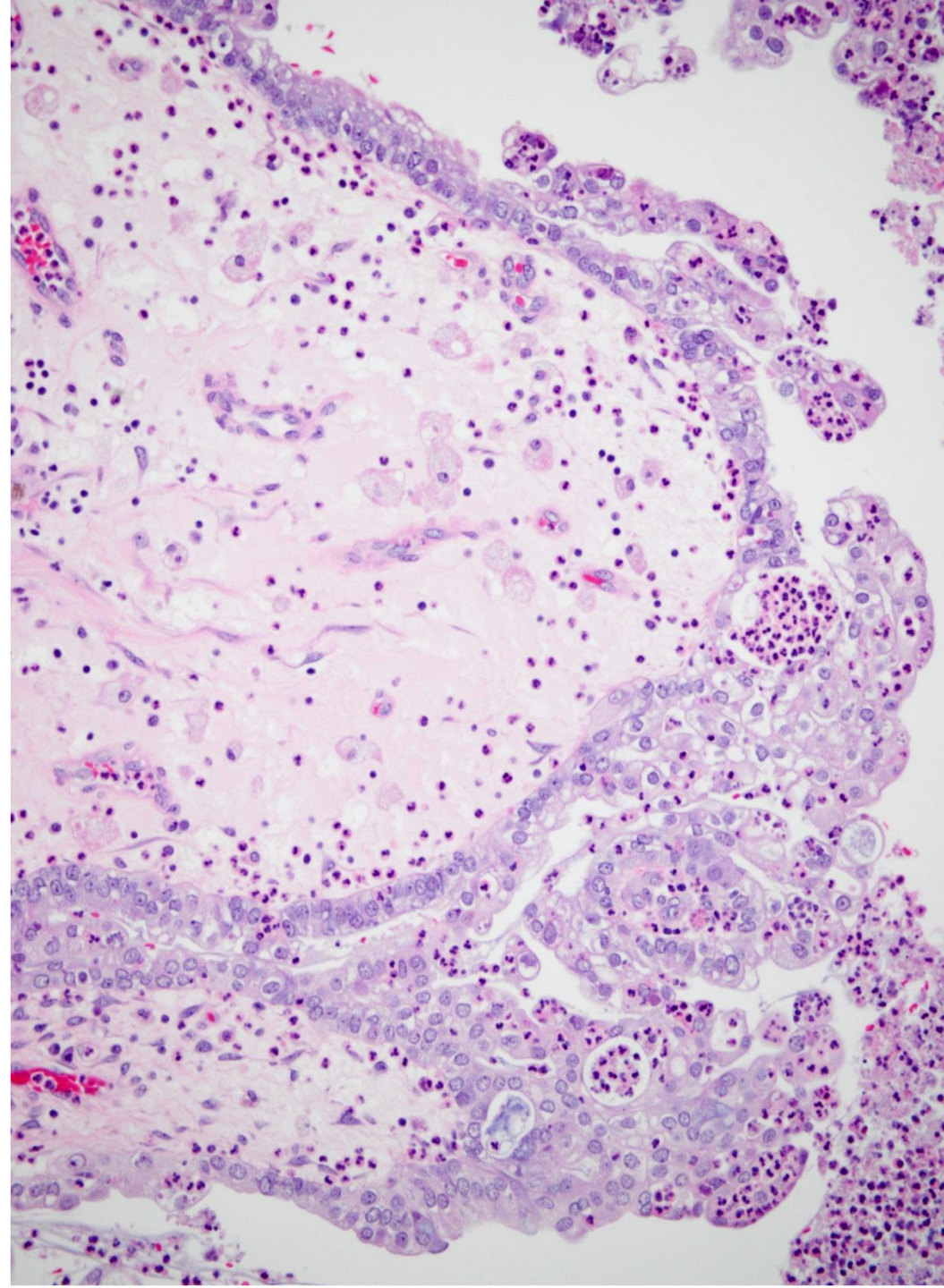
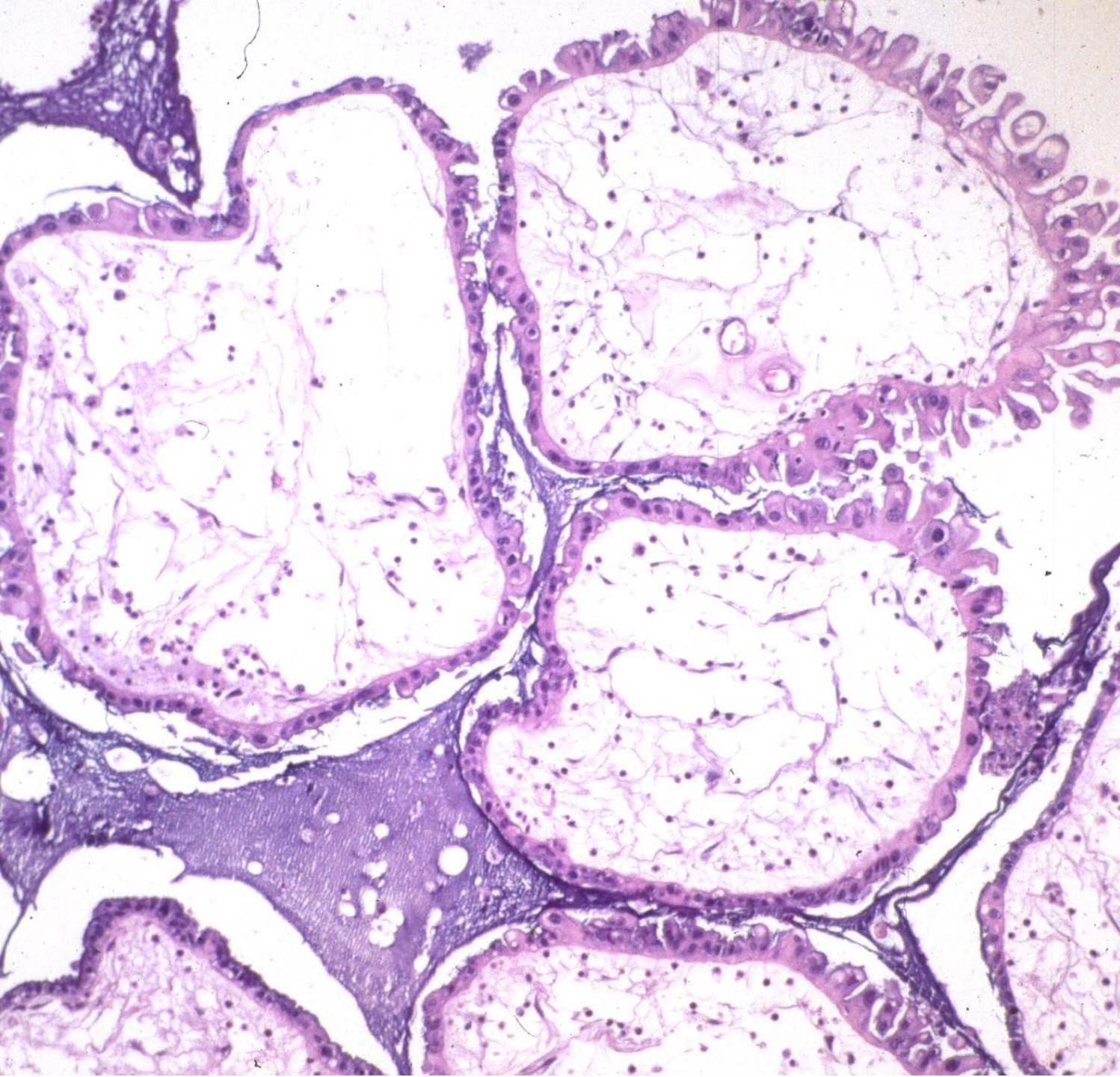
**Mixed Mullerian
Borderline Tumor**

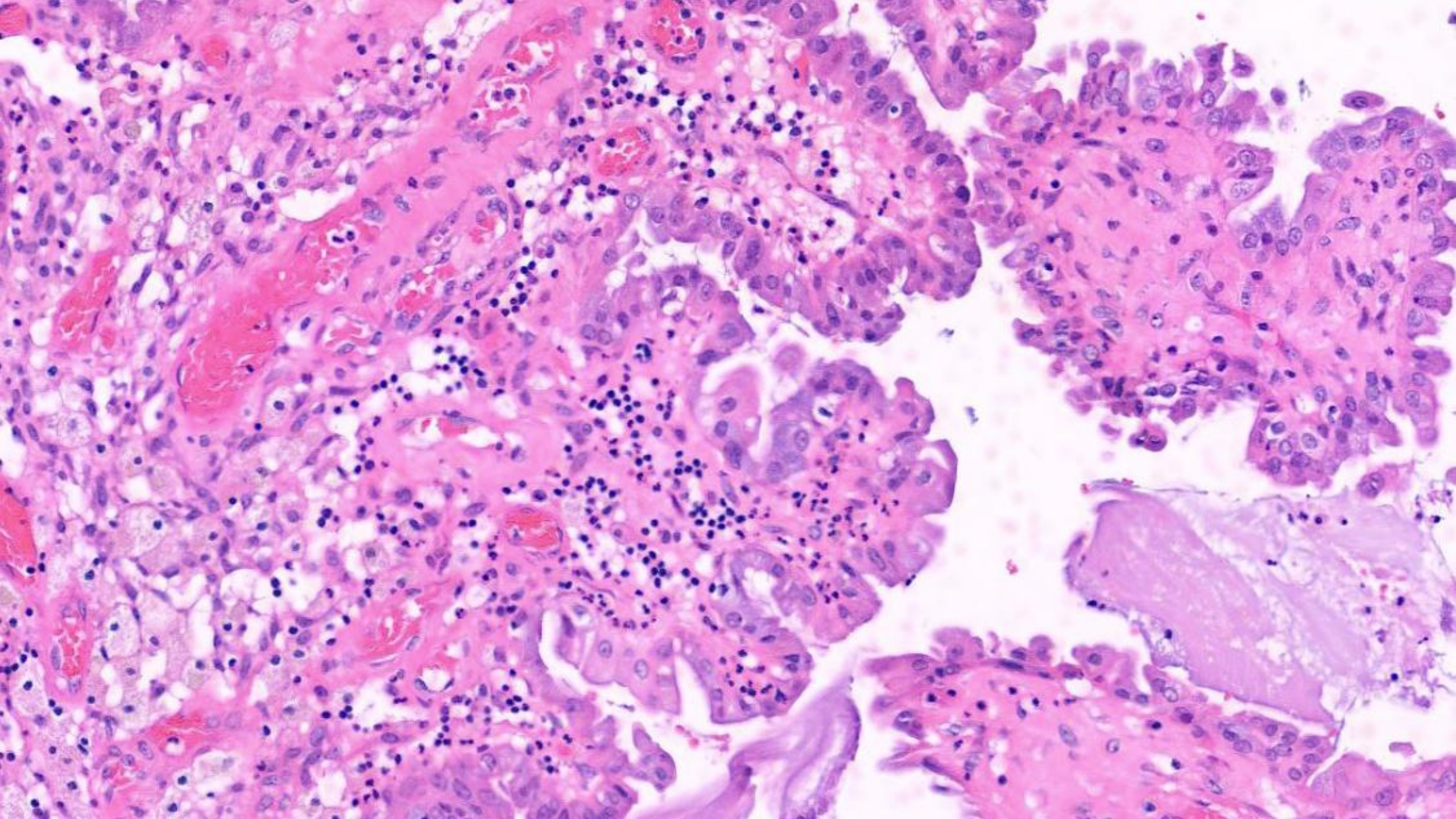
Endometrioid Carcinoma



Clear Cell Carcinoma

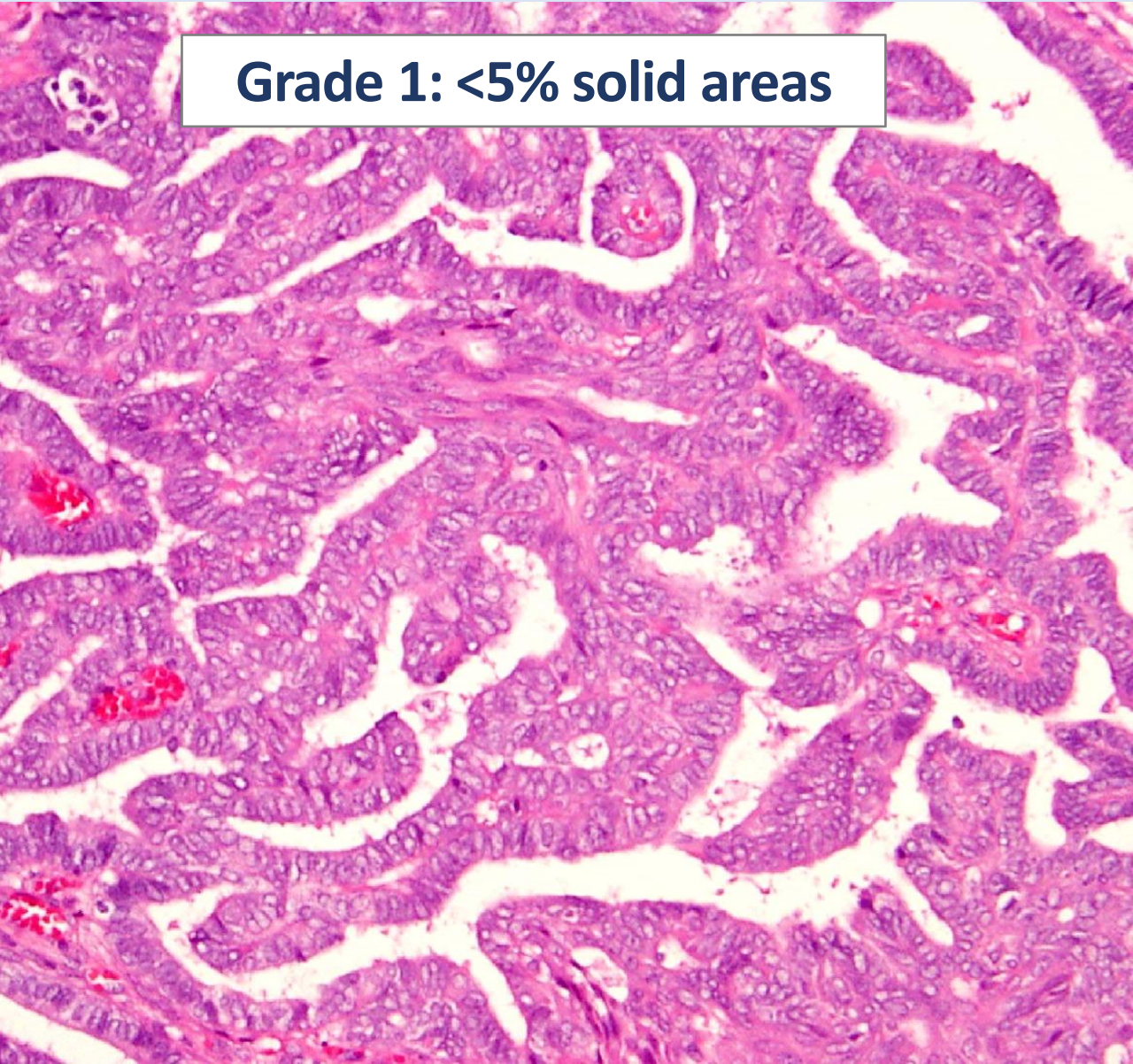




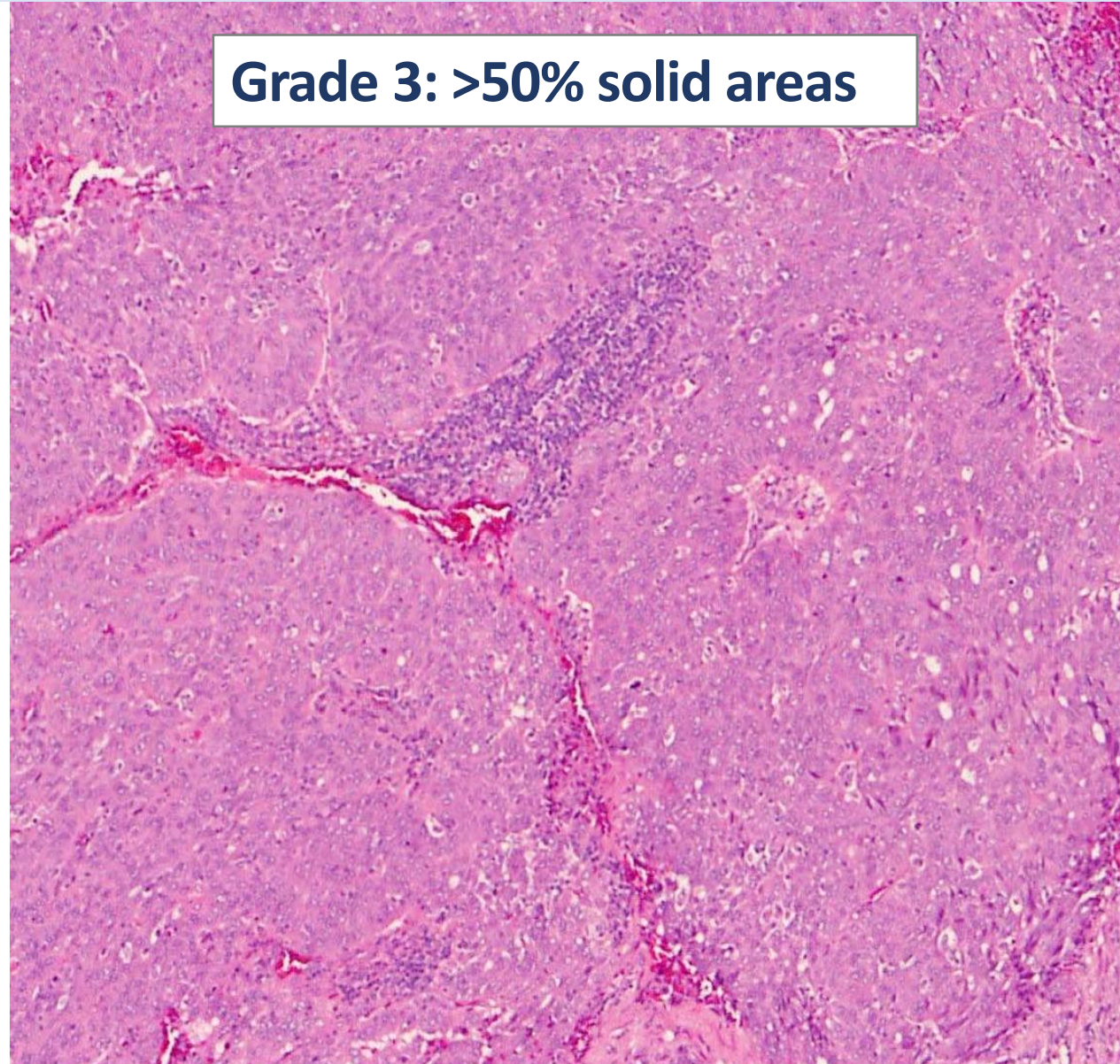


Most Endometrioid Carcinomas Are Low-Grade

Grade 1: <5% solid areas



Grade 3: >50% solid areas



ENDOMETRIOID CARCINOMA: Variants

Architecture

- Squamous differentiation ($\pm$ morular):
 - ✓ Associated keratin granulomas
- Sex cord-like differentiation
- Spindle >>>> corded and hyalinized
- Transitional-like
- Microglandular hyperplasia-like (rare)
- Pilomatrix-like high-grade
- Small non-villous papillae

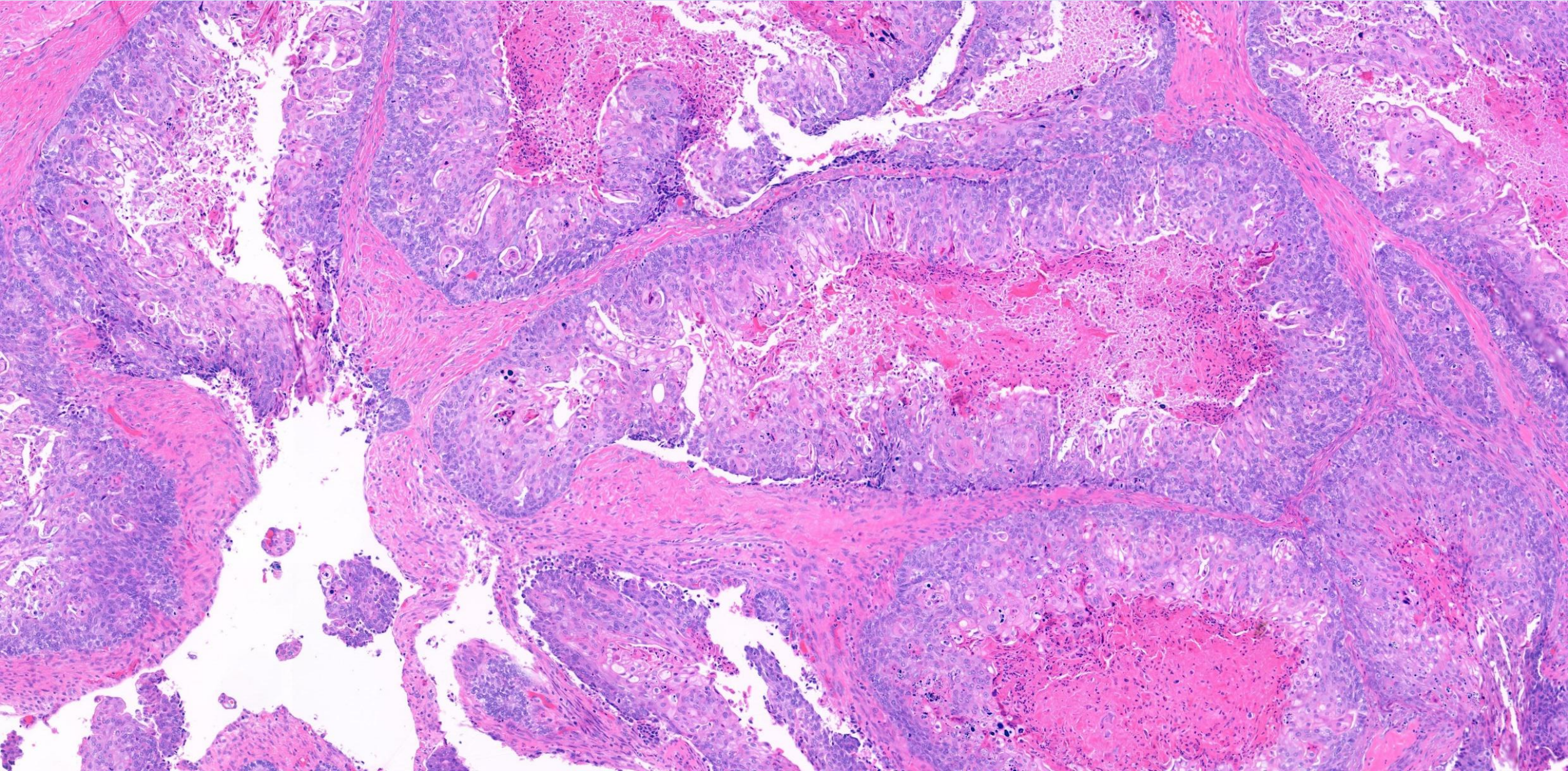
Cytology

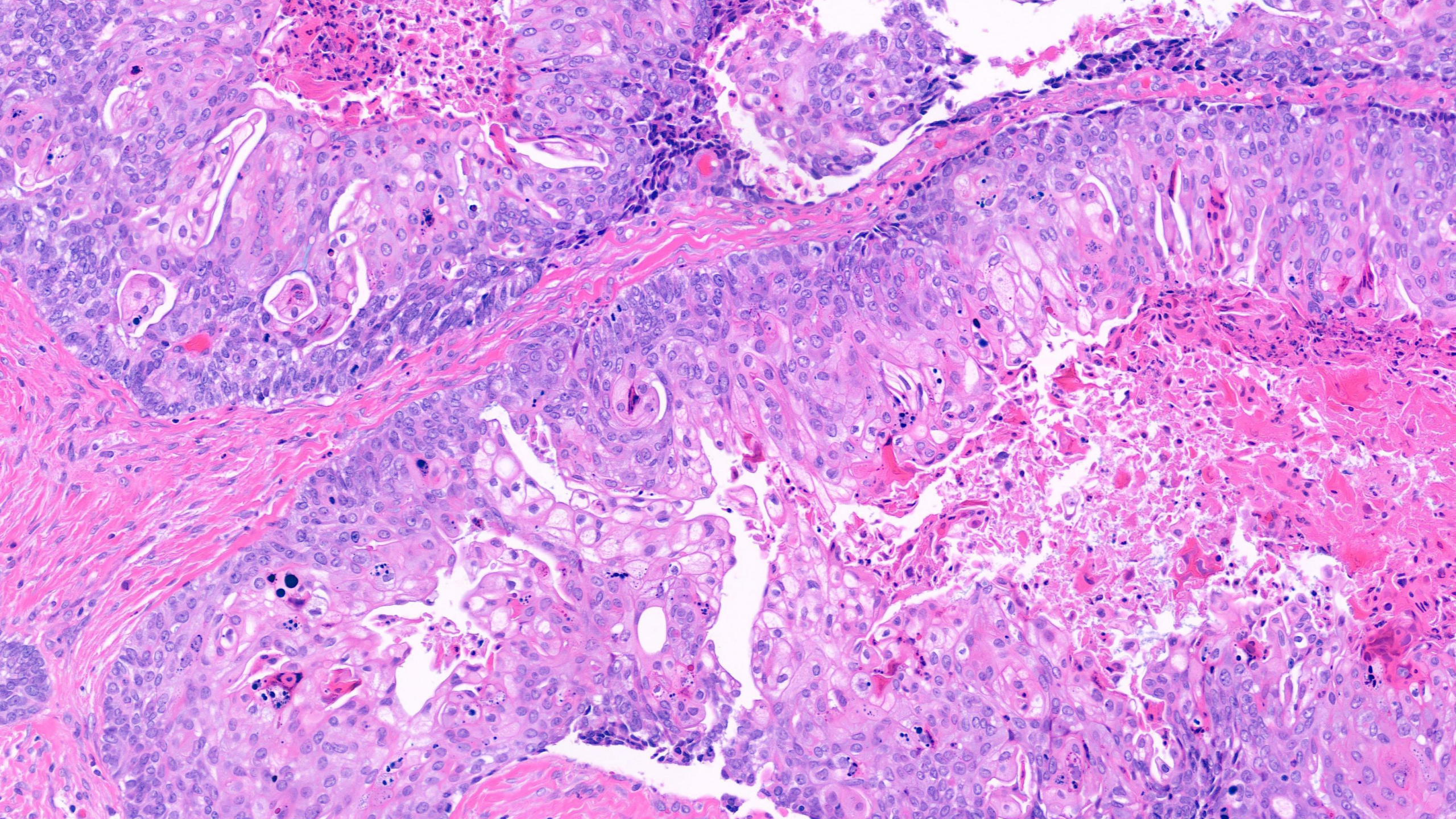
- Clear cells, including secretory
- Mucin-rich
- Oxyphilic and/or ciliated
- Basaloid epithelial cells

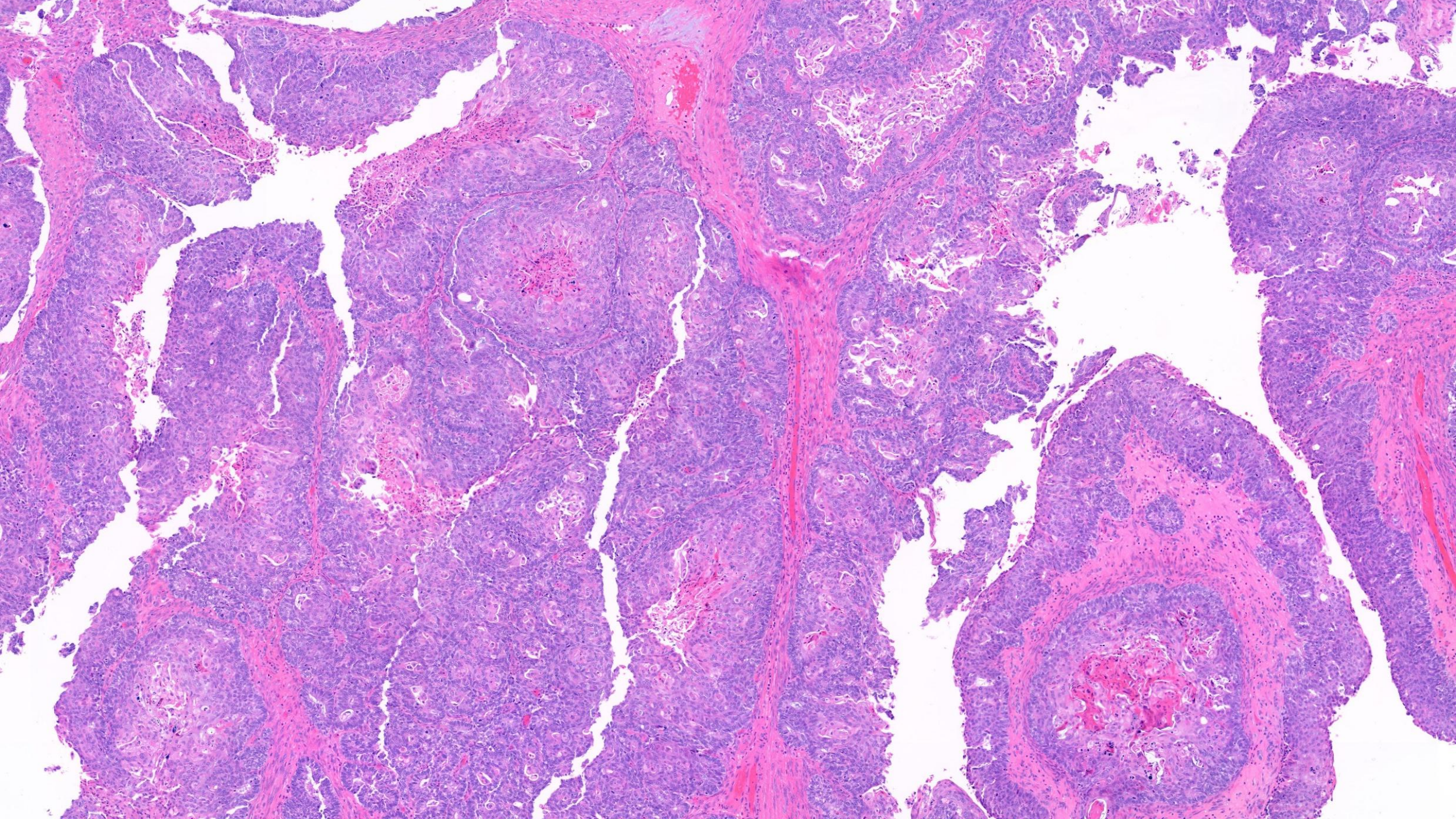
Other

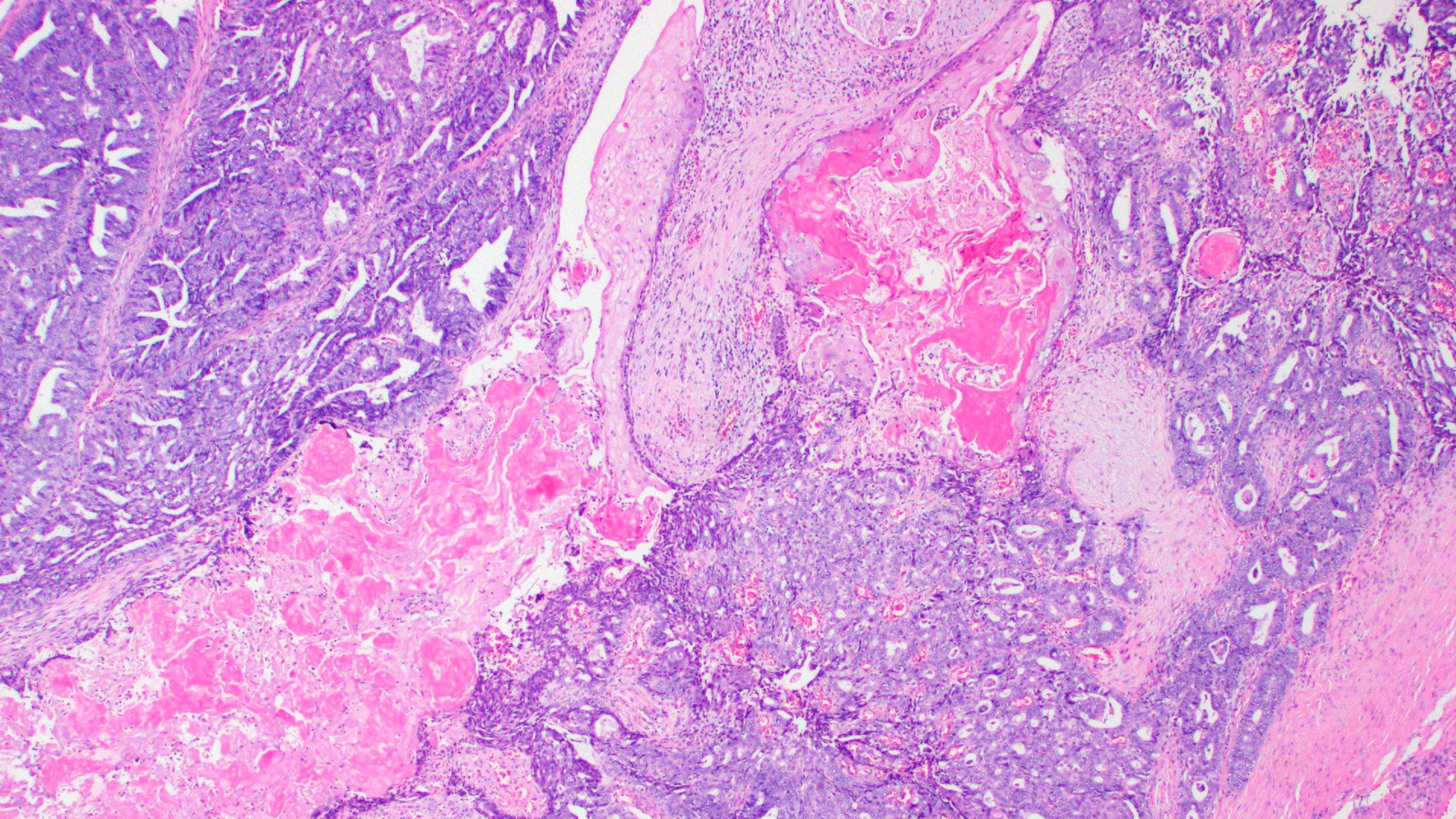
- Associated with somatic yolk sac tumor

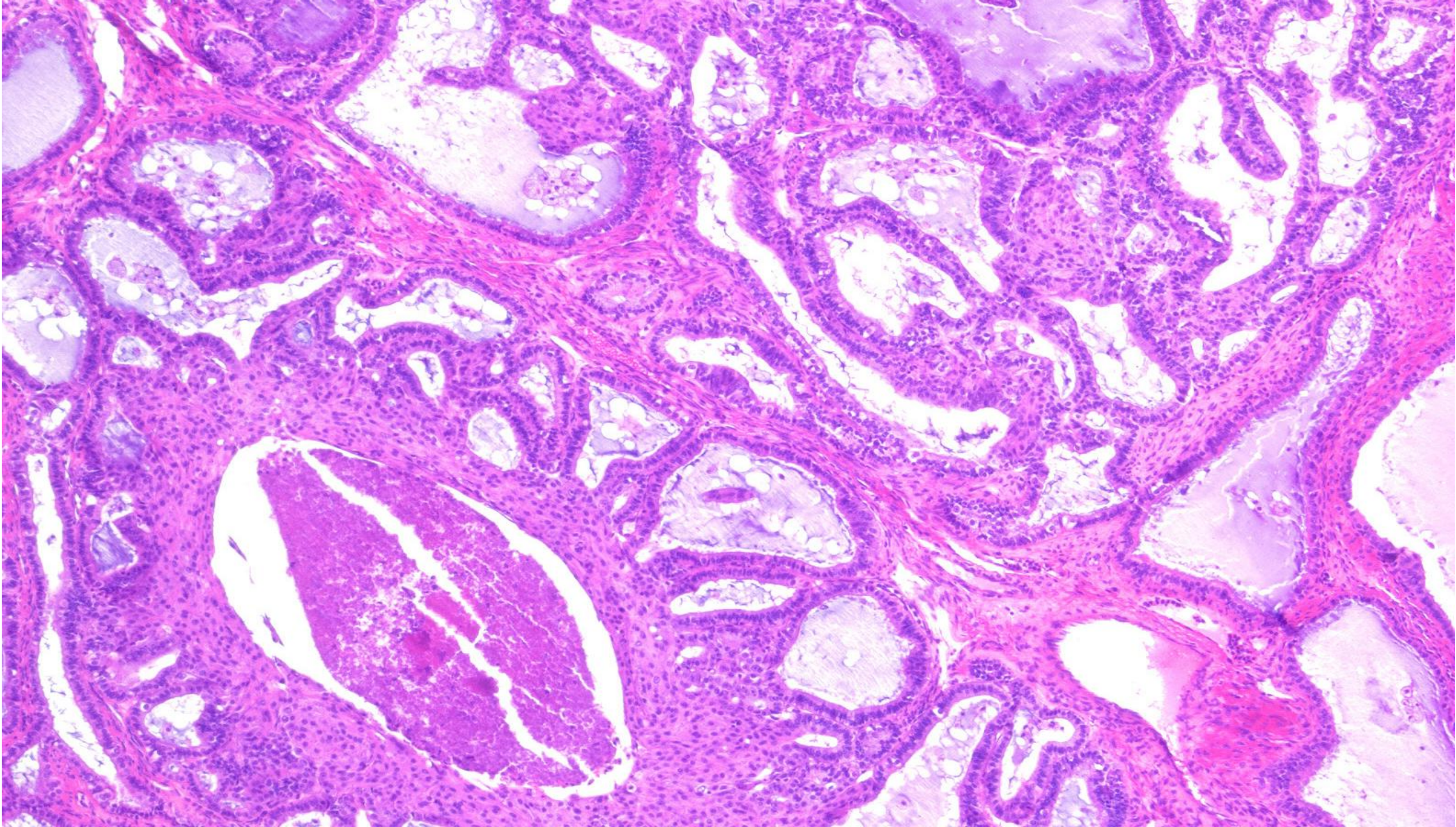
Squamous Differentiation



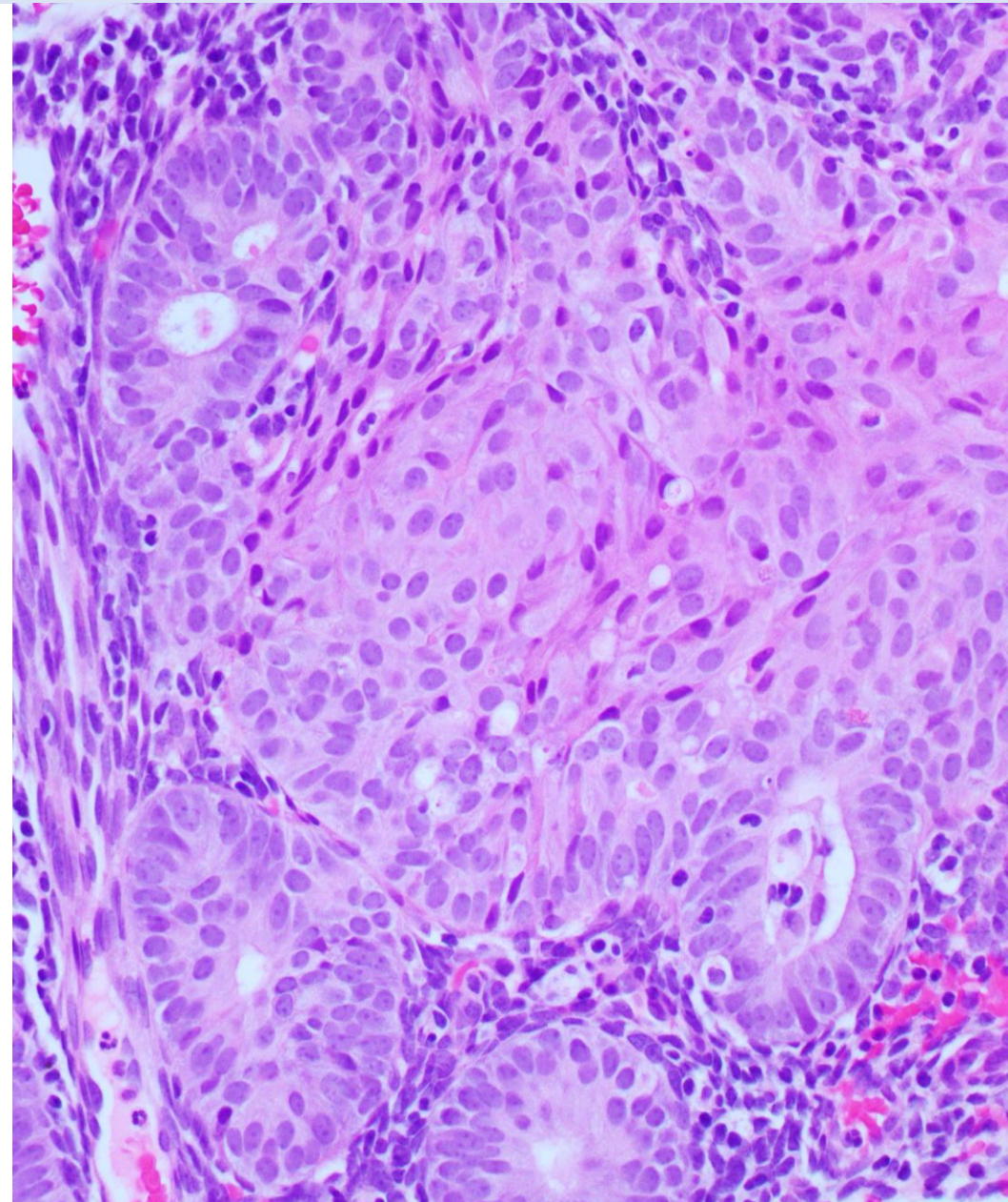
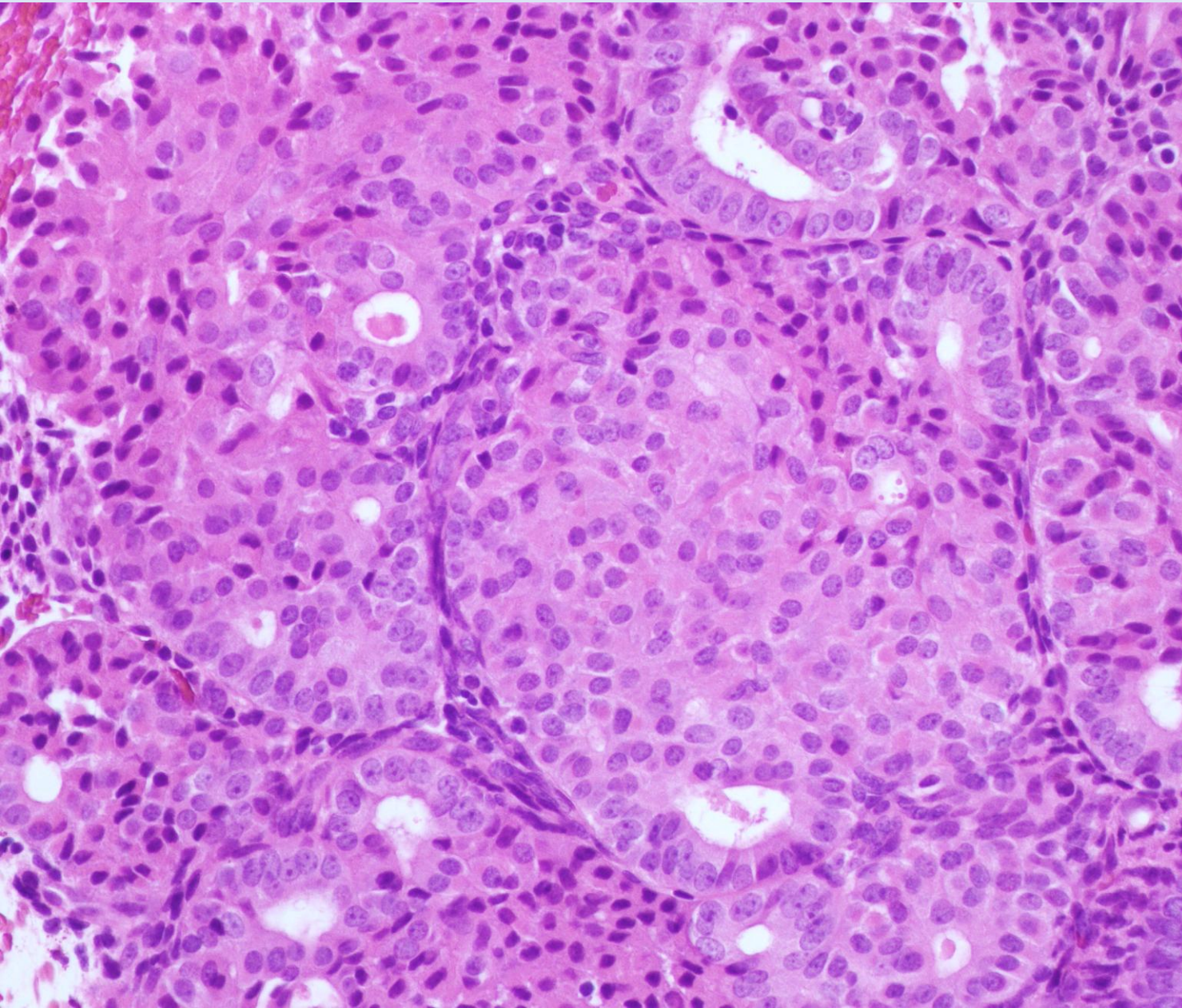




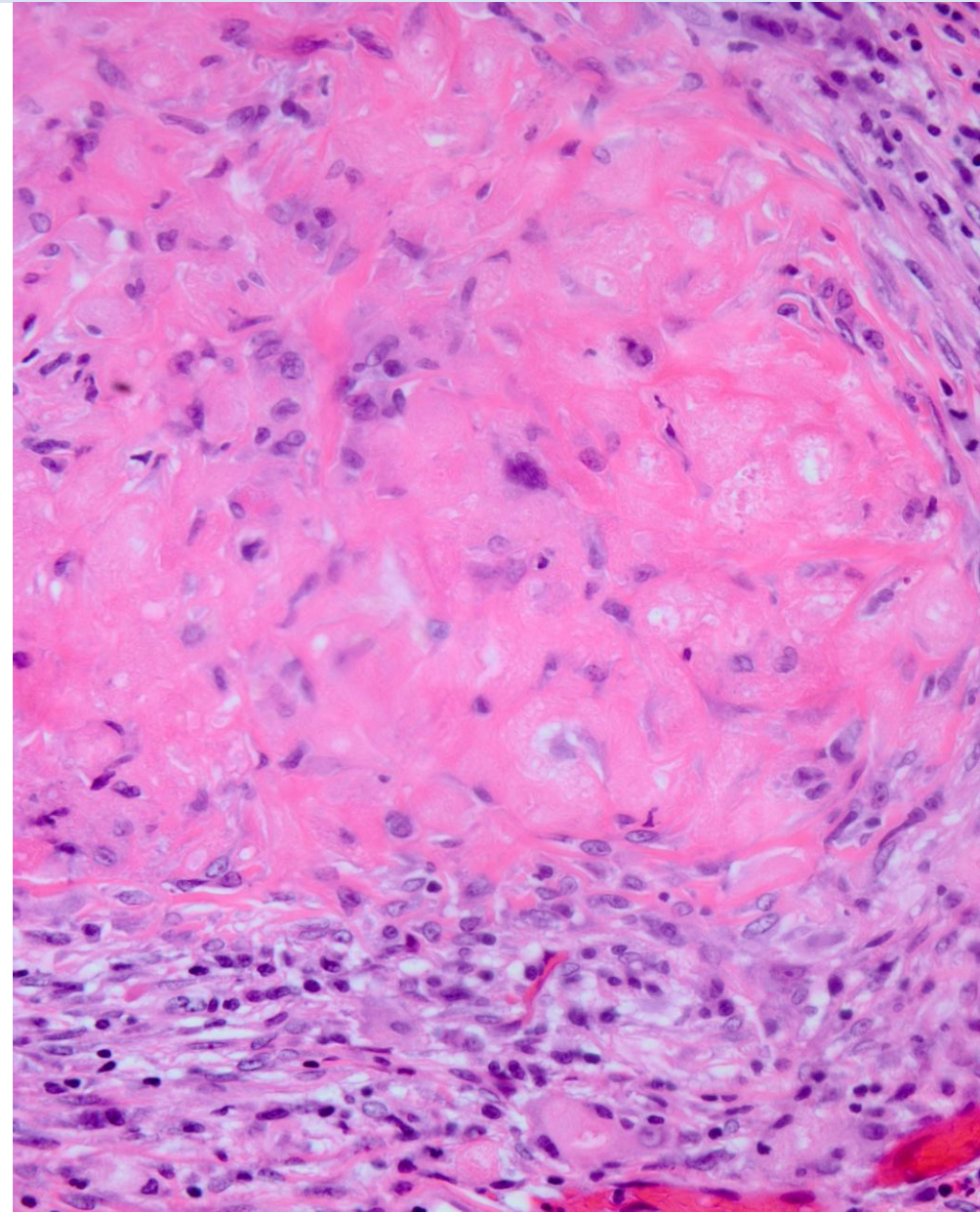
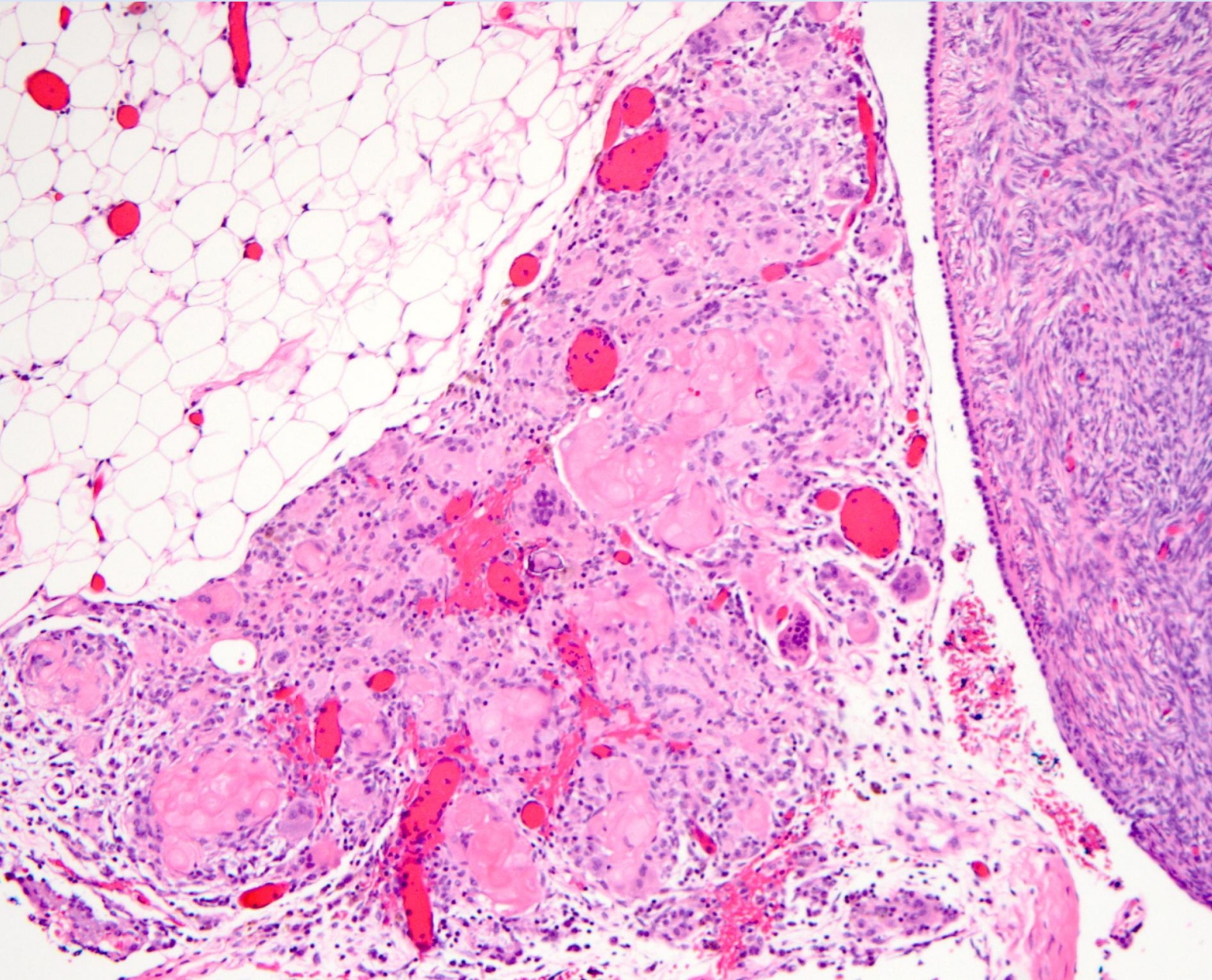




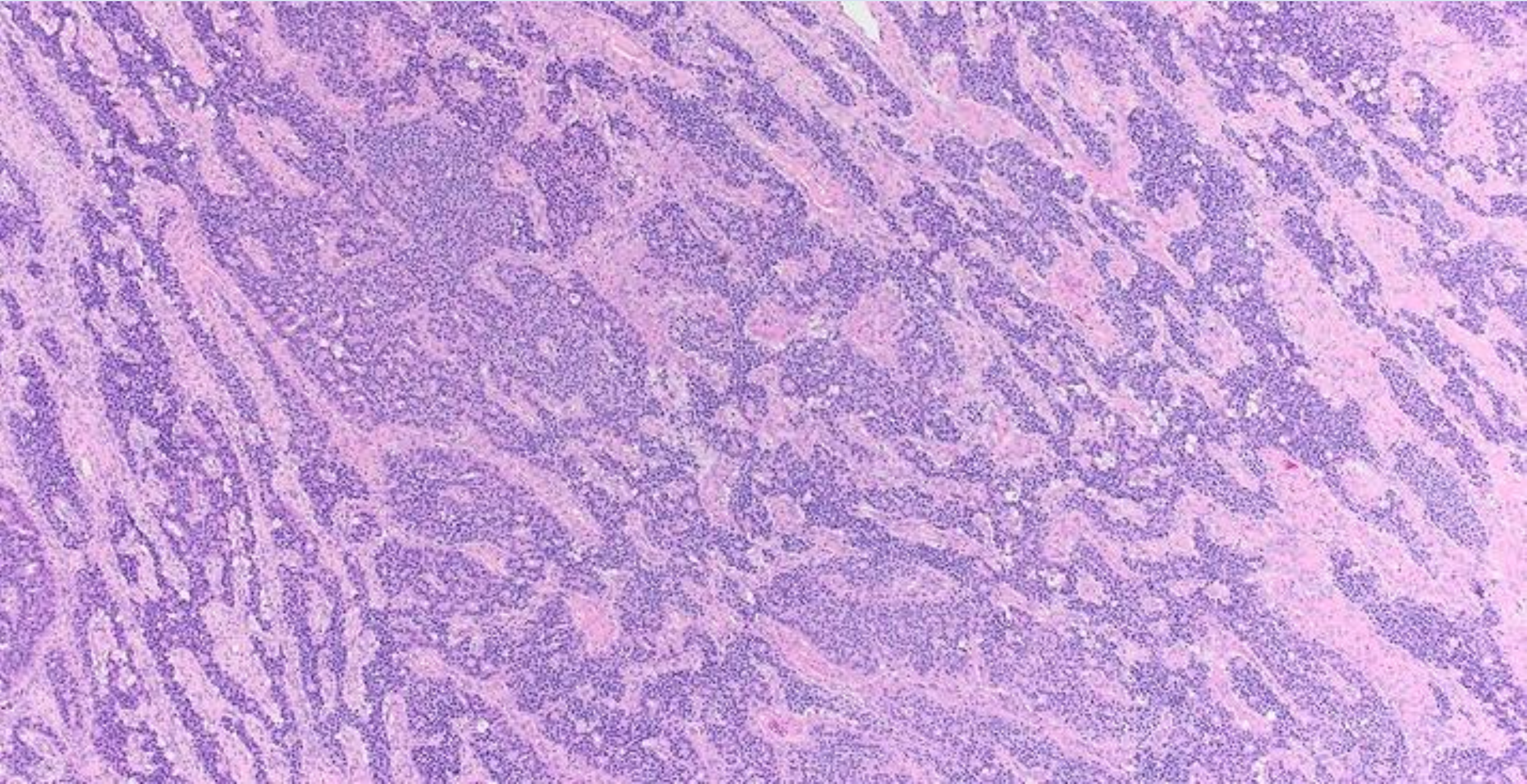
Squamous Morules

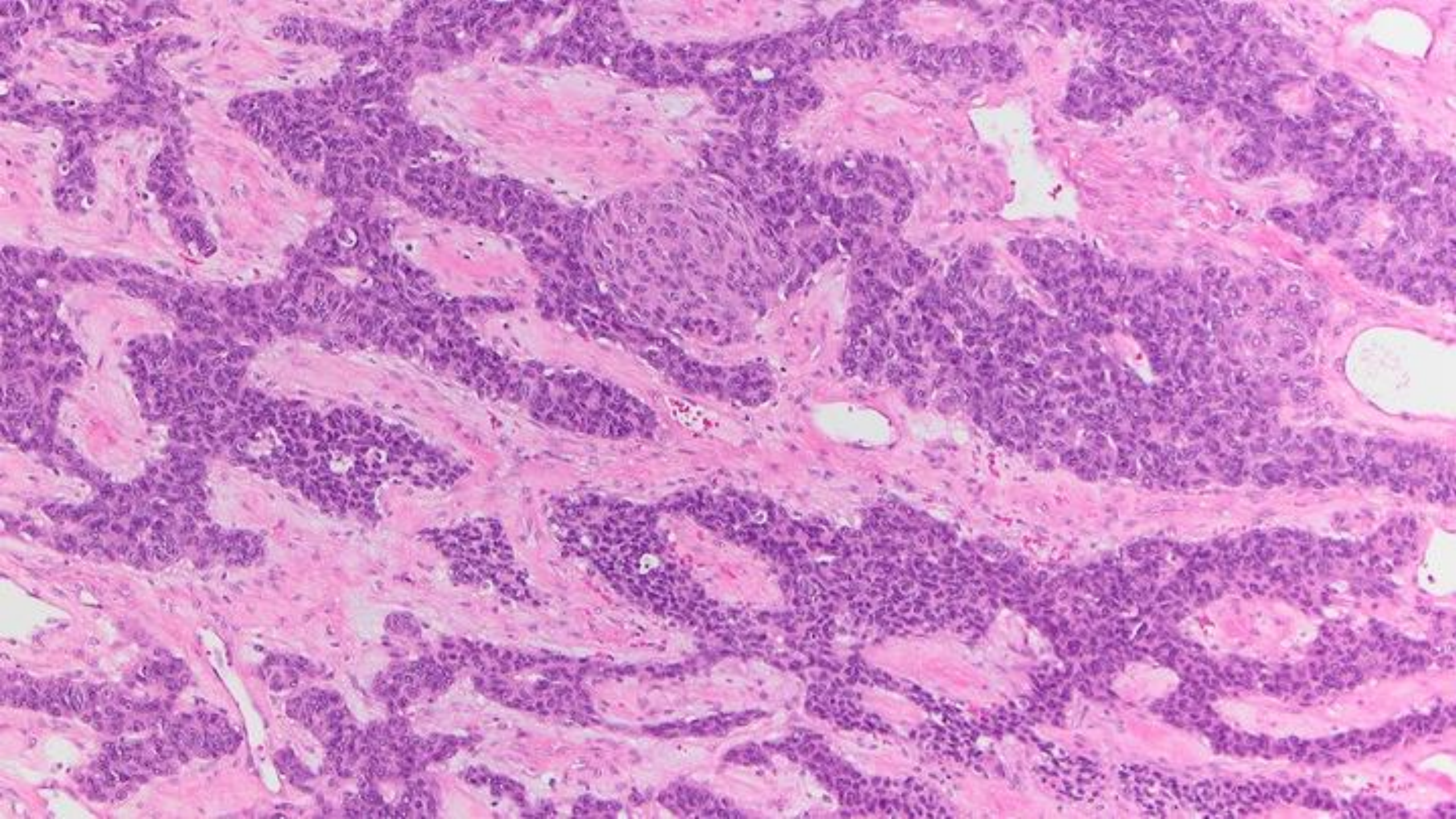


Keratin Granulomas: No Prognostic Significance

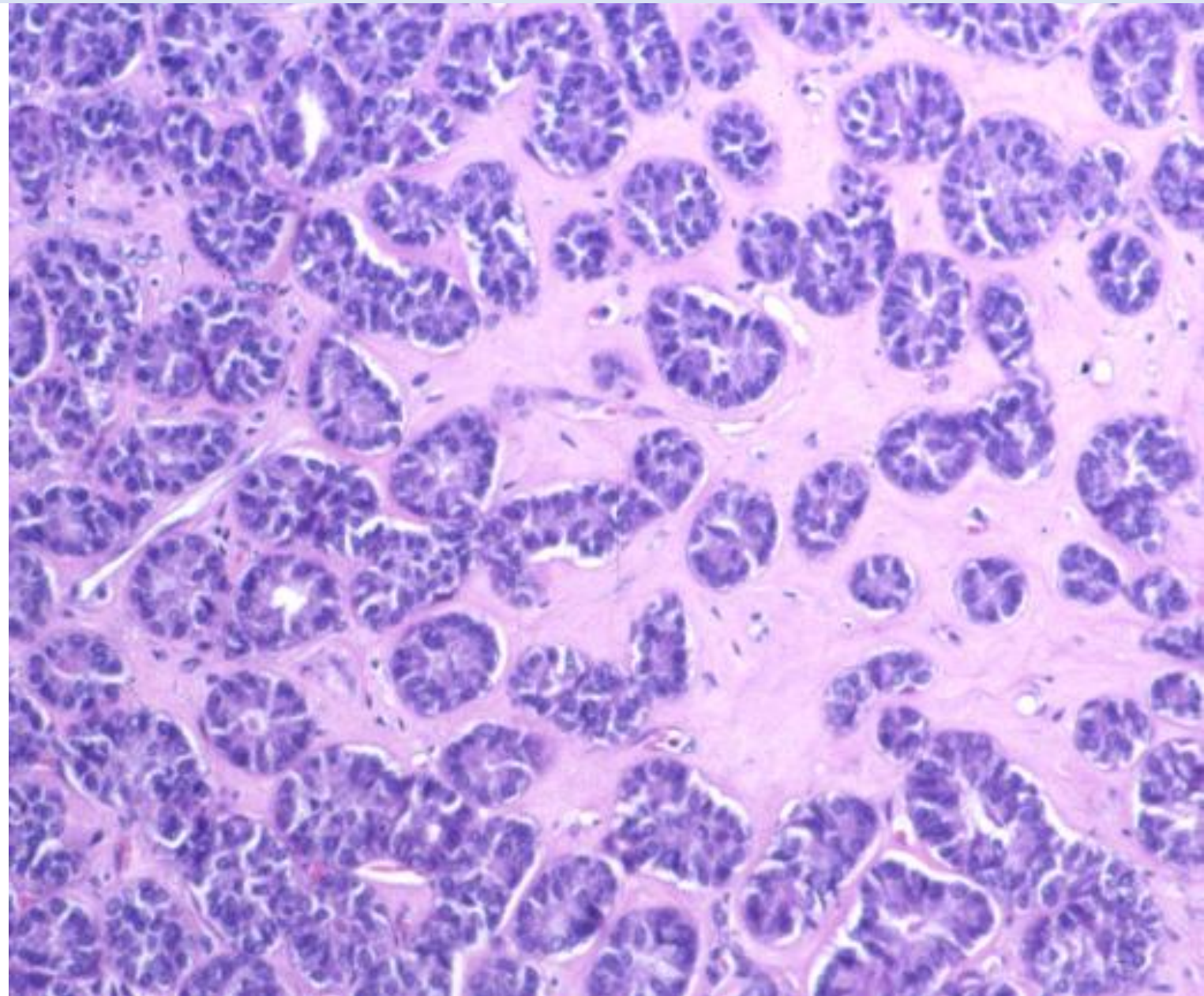
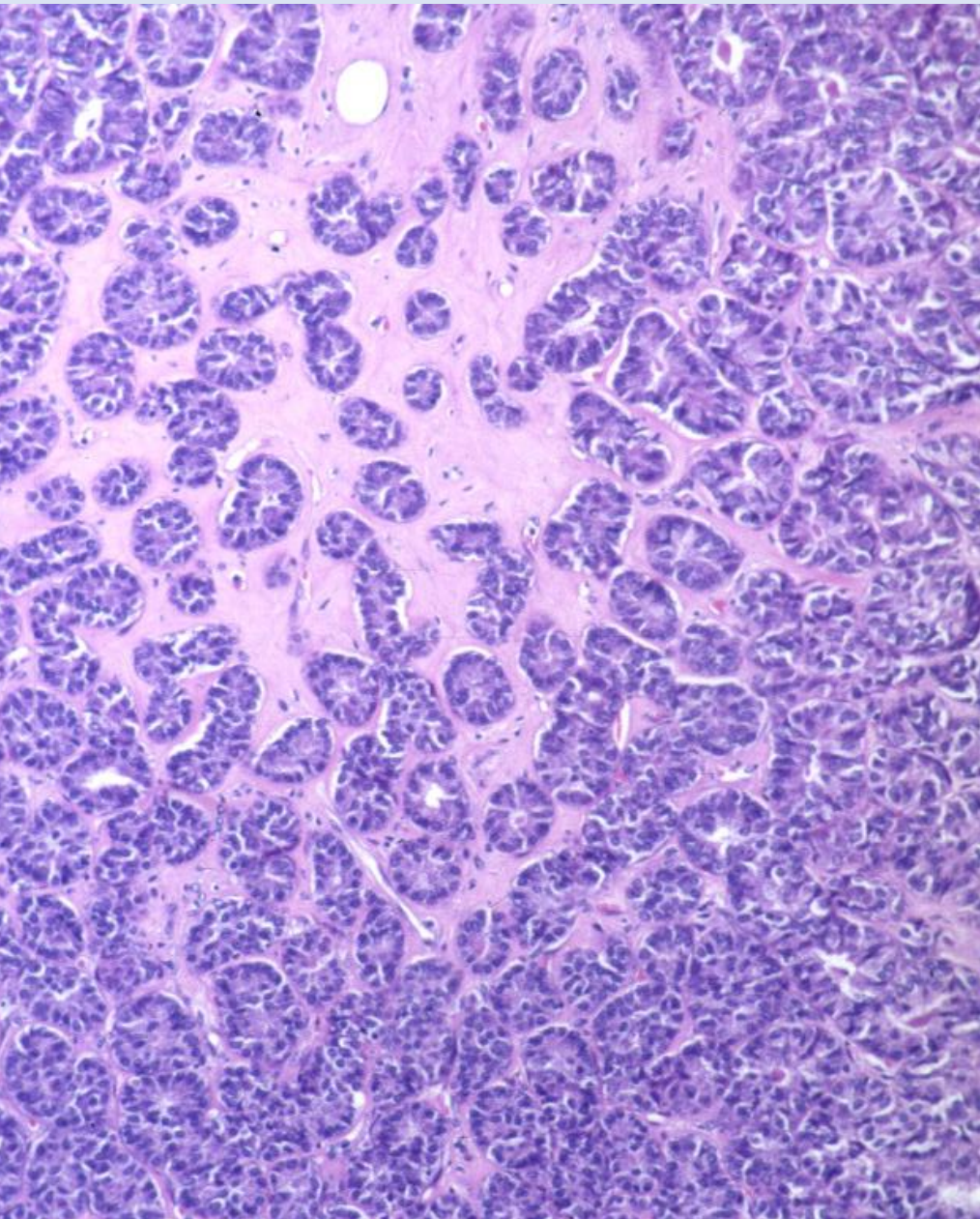


Sex Cord-Like Differentiation

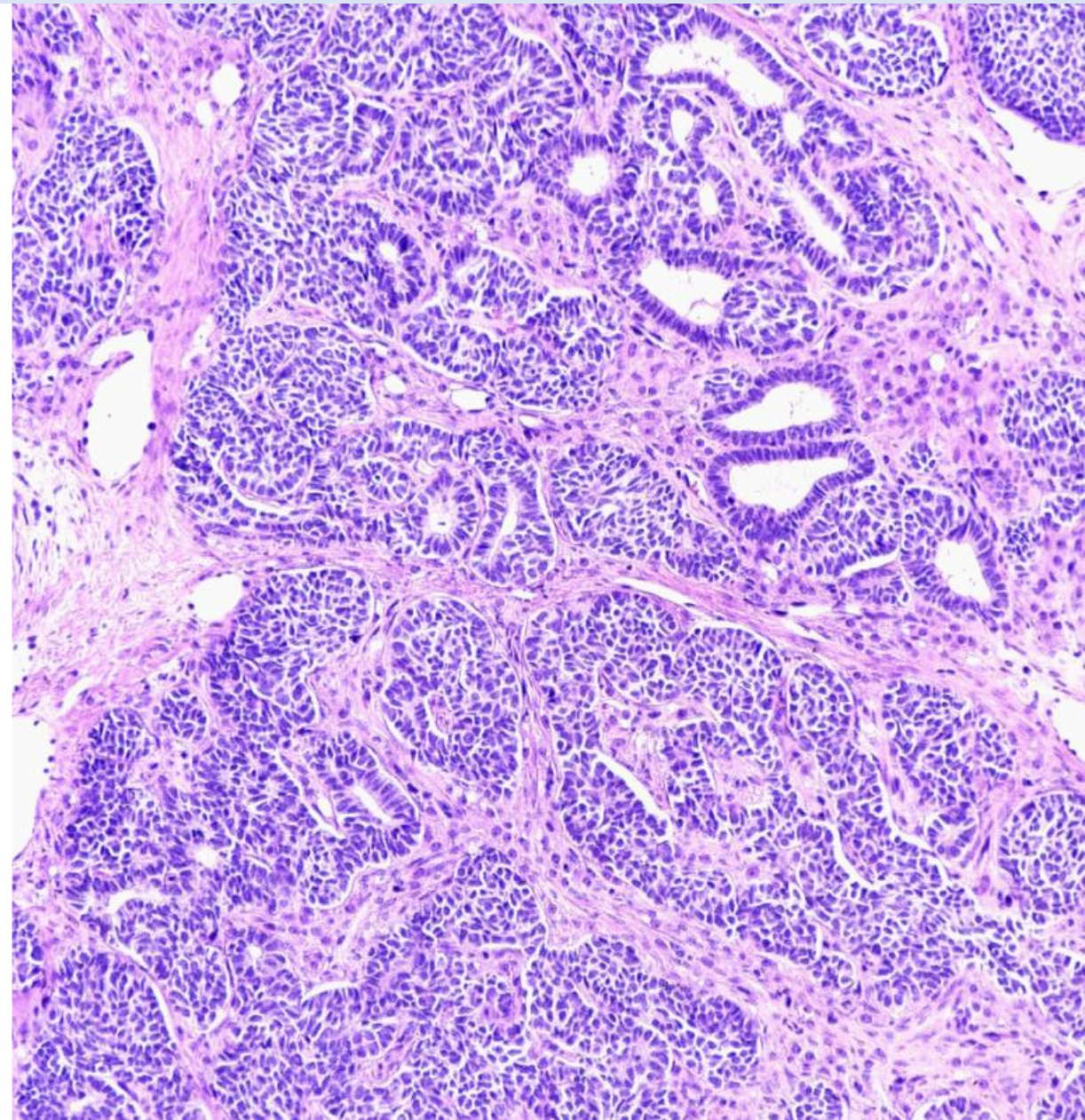
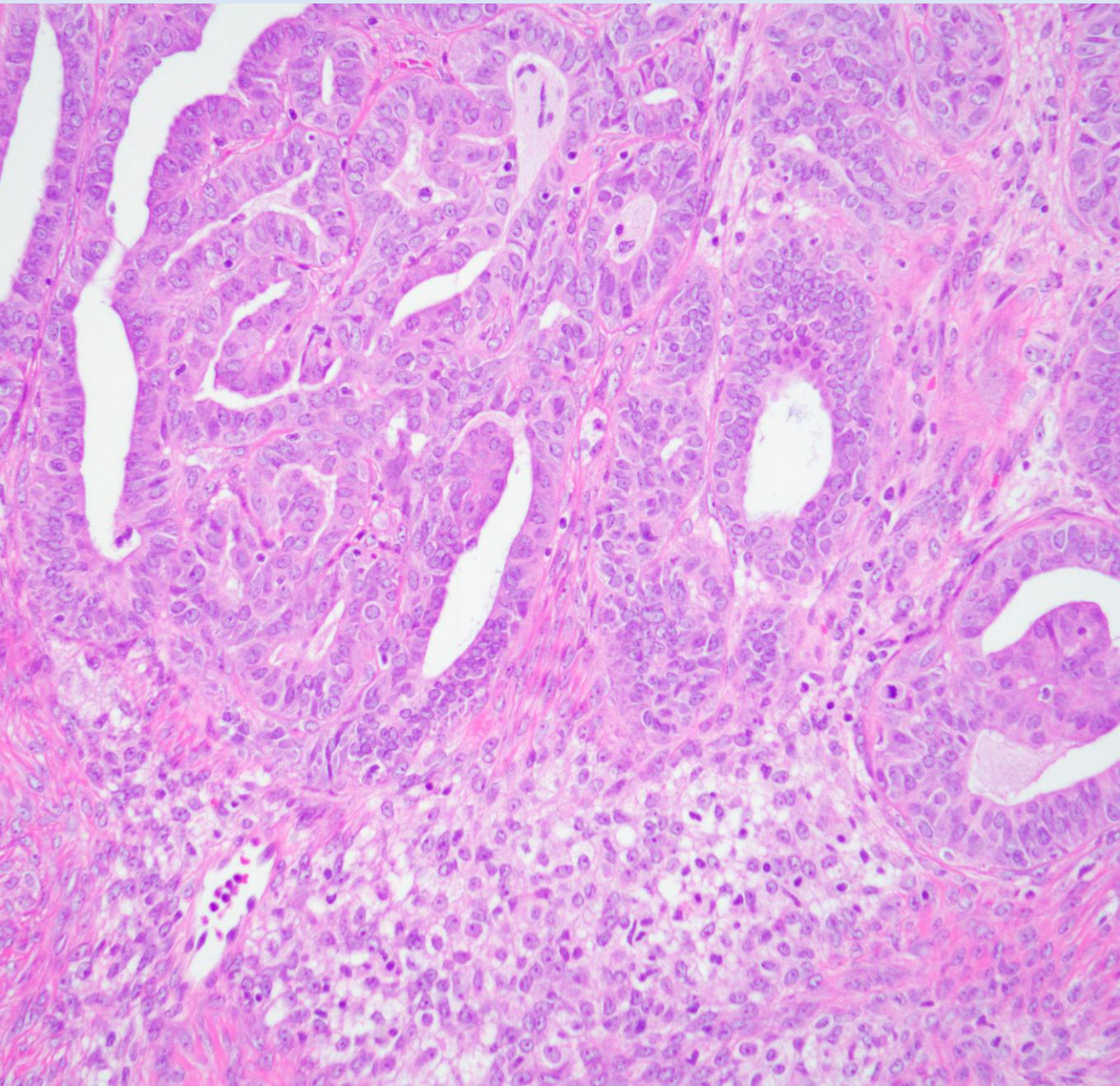


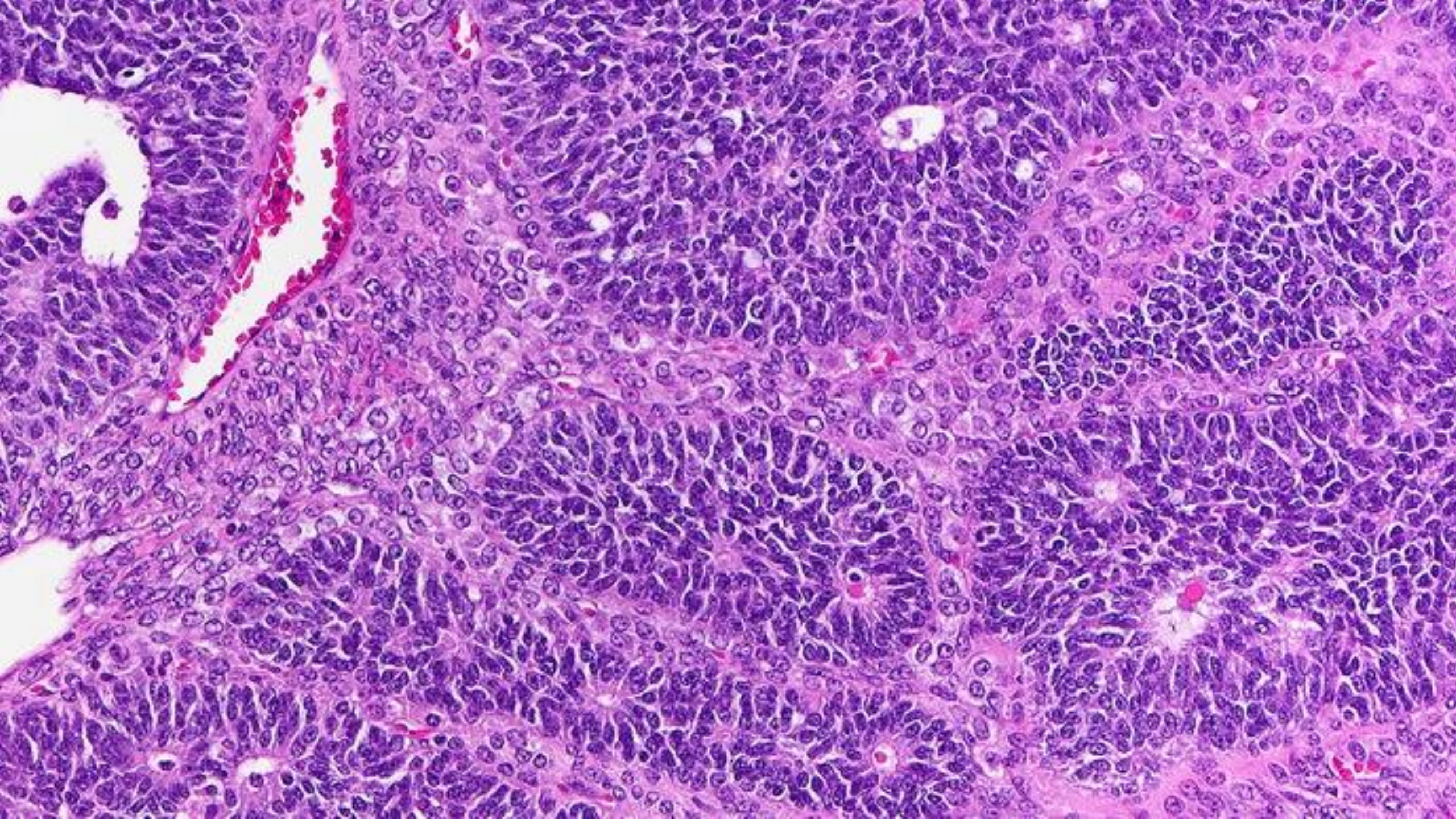


Endometrioid Carcinoma Mimicking Sertoli Cell Tumor

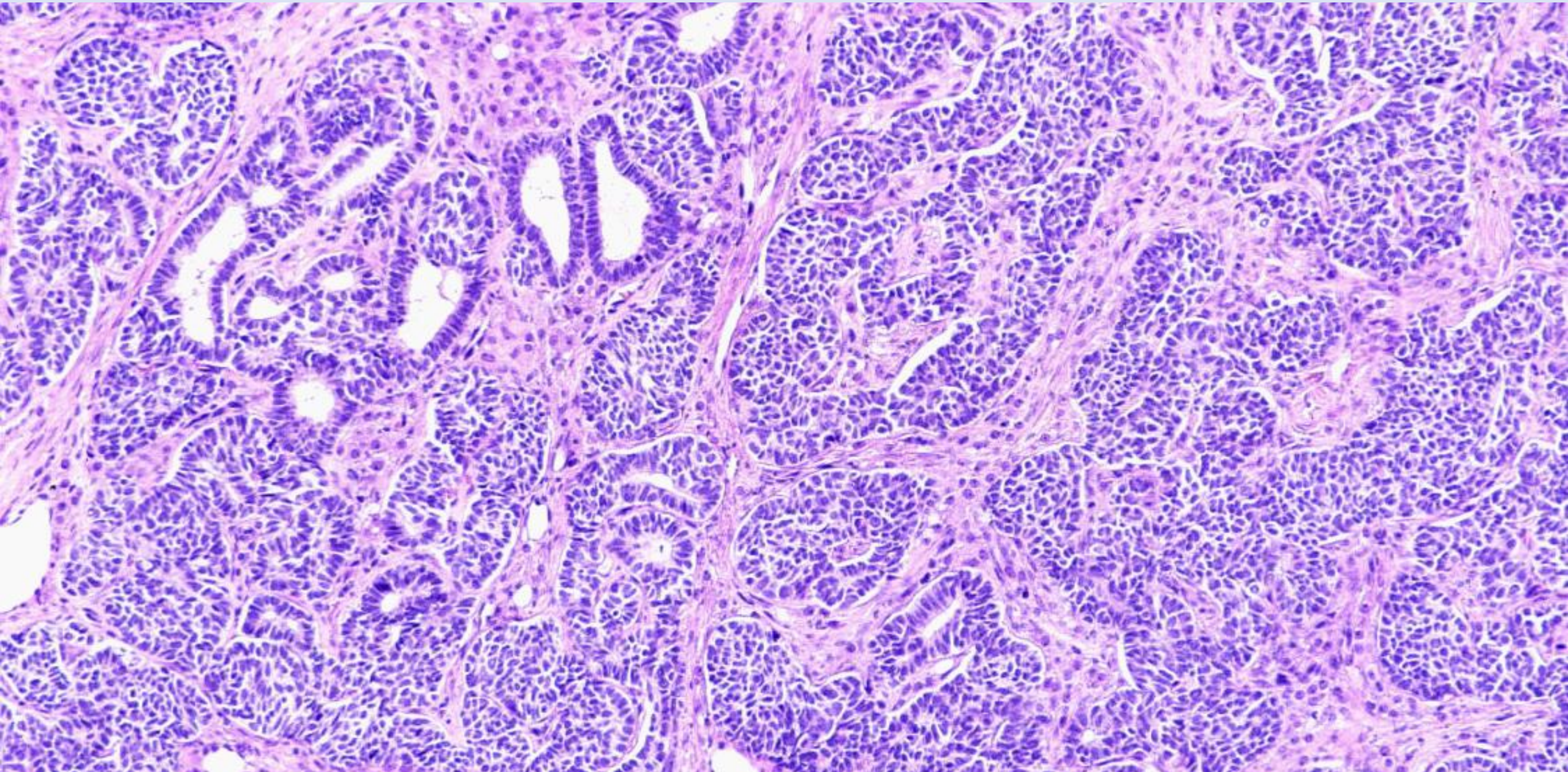


Associated Stromal Luteinization





Sertoli-Leydig Cell Tumor Mimicking Endometrioid Carcinoma

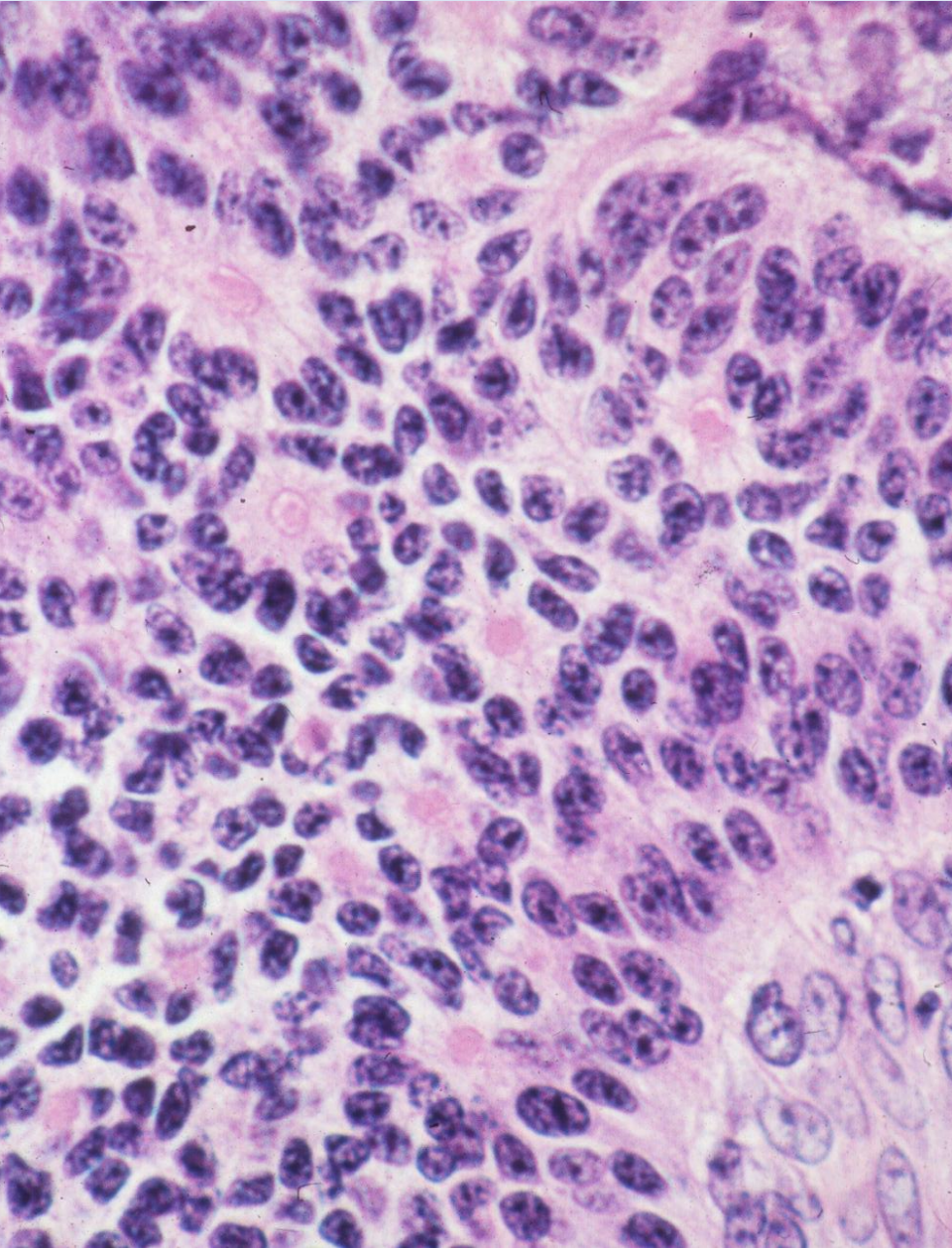


Immunohistochemistry for Differential Diagnosis

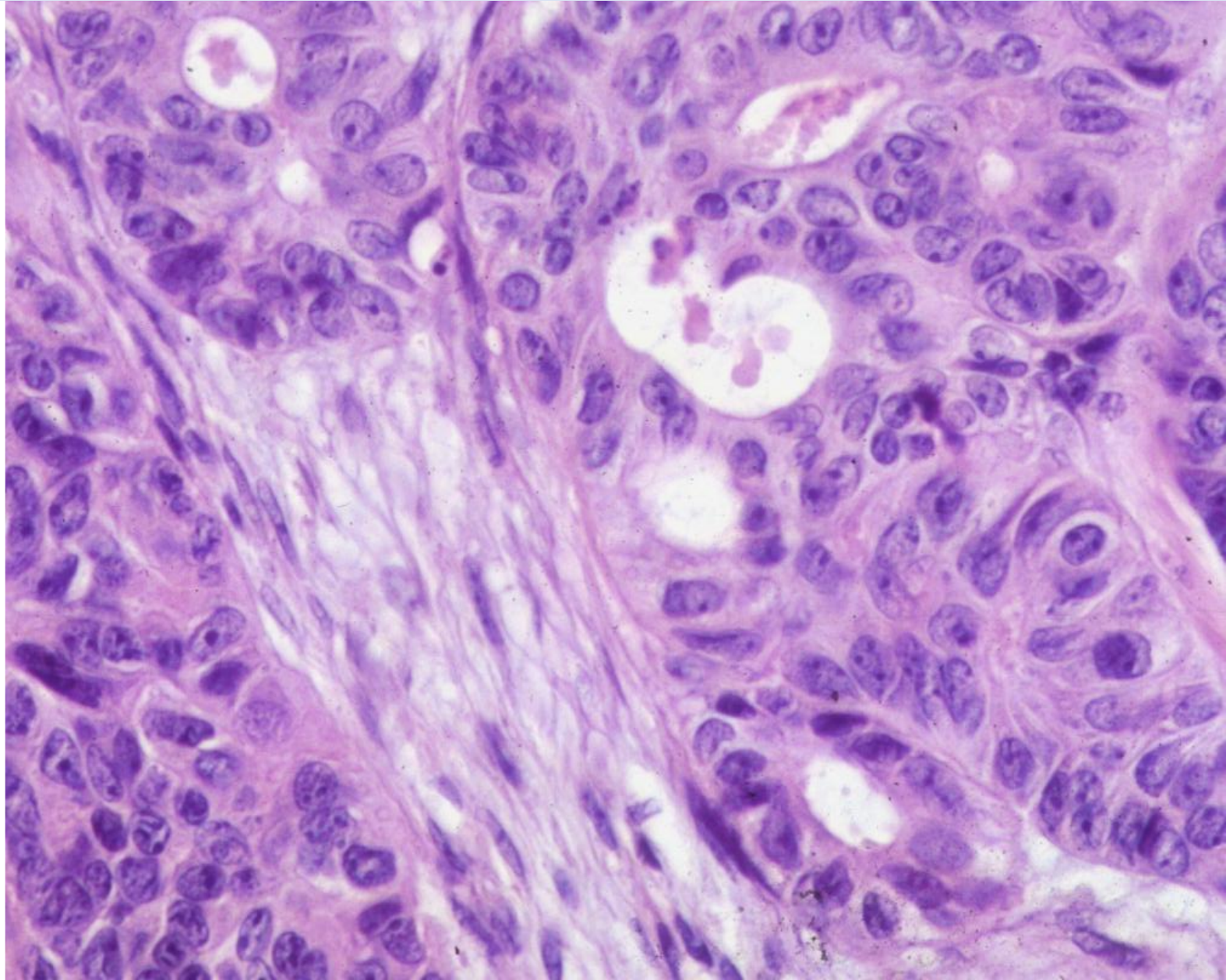
TABLE 2. Overall Positivity for Alternative and Traditional Immunohistochemical Markers

Antigen	Sertoli Cell Tumor	Endometrioid Borderline Tumor	Sertoliform Endometrioid Carcinoma	Well-differentiated Endometrioid Carcinoma	Carcinoid Tumor
Epithelial markers					
CK7*	13%	100%	85%	100%	24%
ER*	8%	87%	85%	89%	2%
PR*	13%	84%	77%	93%	2%
Pan-CK†	65%	100%	100%	100%	98%
CK8/18†	43%	100%	93%	96%	74%
EMA†	0%	100%	100%	100%	12%
Sex cord markers					
CD10*	25%	39%	31%	37%	9%
Inhibin†	98%	0%	0%	4%	2%
Calretinin†	60%	11%	0%	18%	0%
CD99†	68%	16%	23%	33%	40%
Neuroendocrine markers					
CD56*	48%	16%	16%	30%	57%
Synaptophysin†	35%	8%	8%	22%	98%
Chromogranin†	13%	3%	15%	11%	100%

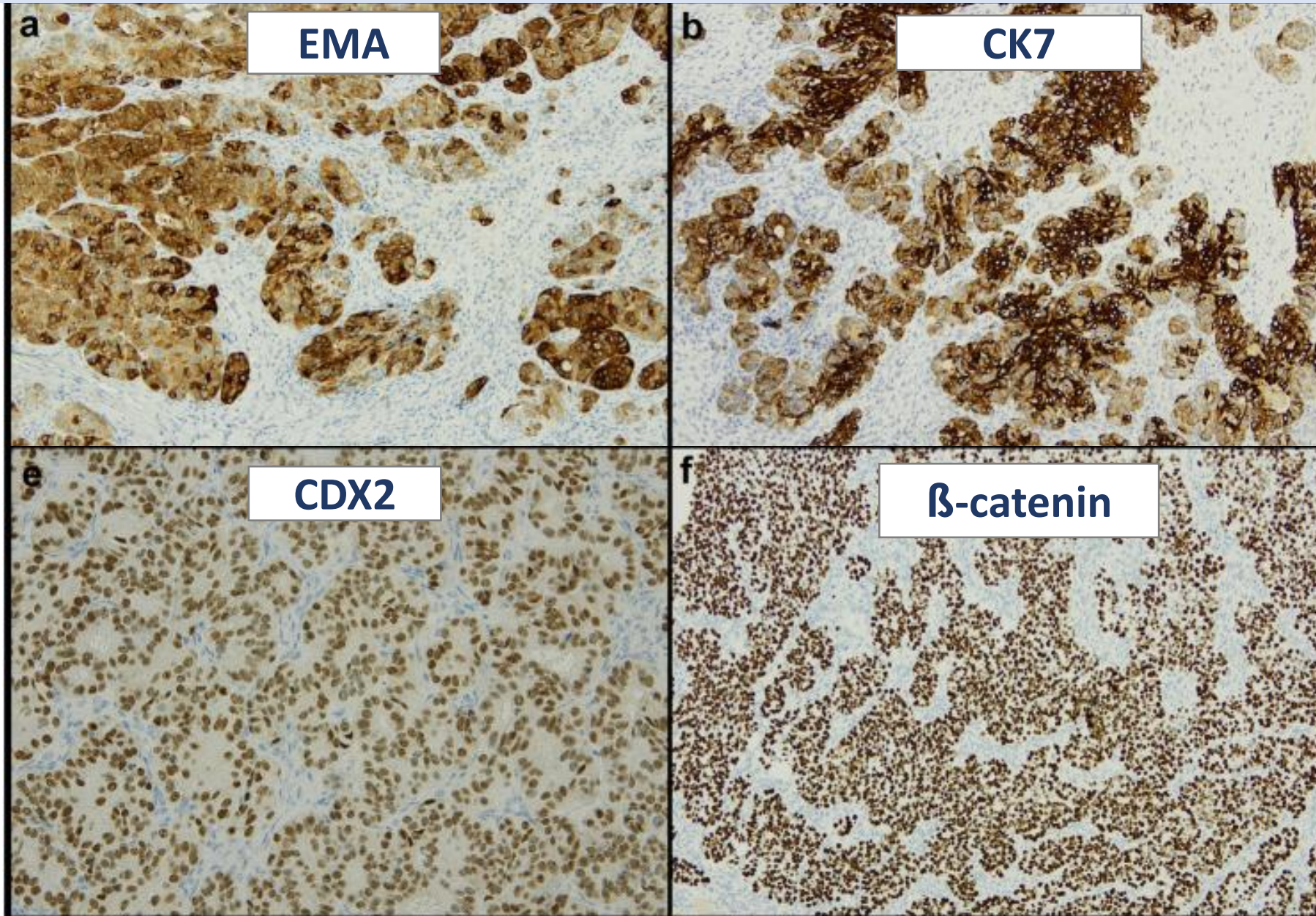
Call-Exner-Like Spaces



Nuclear Grooves



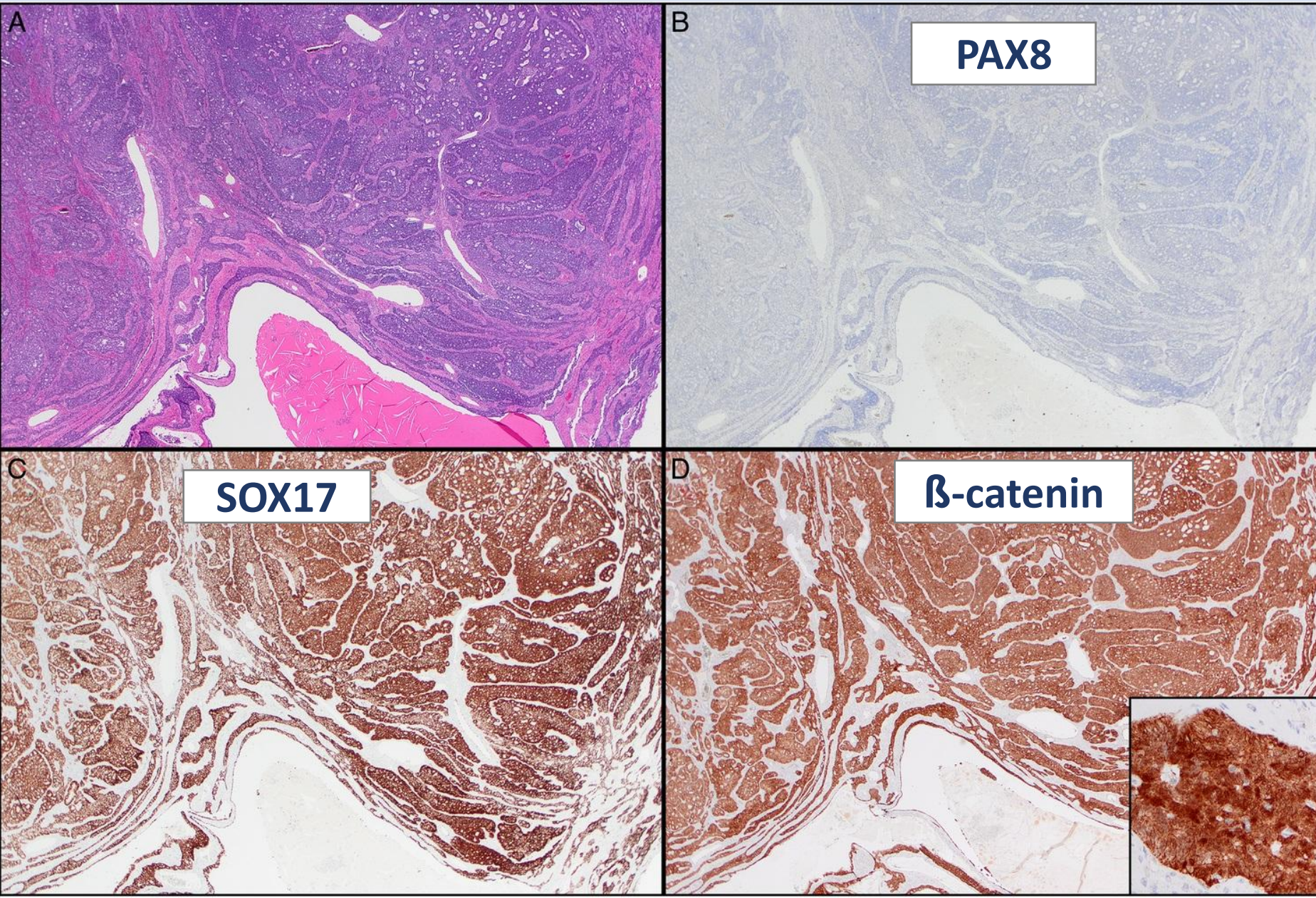
Frequent PAX8 Negativity & *CTNNB1* Mutations (67%)



9 Cases

*Travaglino et al. Virchows
Arch. 2025;486(2):355-63*

Frequent PAX8 Negativity & *CTNNB1* Mutations (90%)



20 Cases

**ALL
SOX17+**

*Lengyel et al. Am J Surg
Pathol. 2026, March 11*

SOX17 Expression in Gynecologic Tumors (on Tissue Microarray)

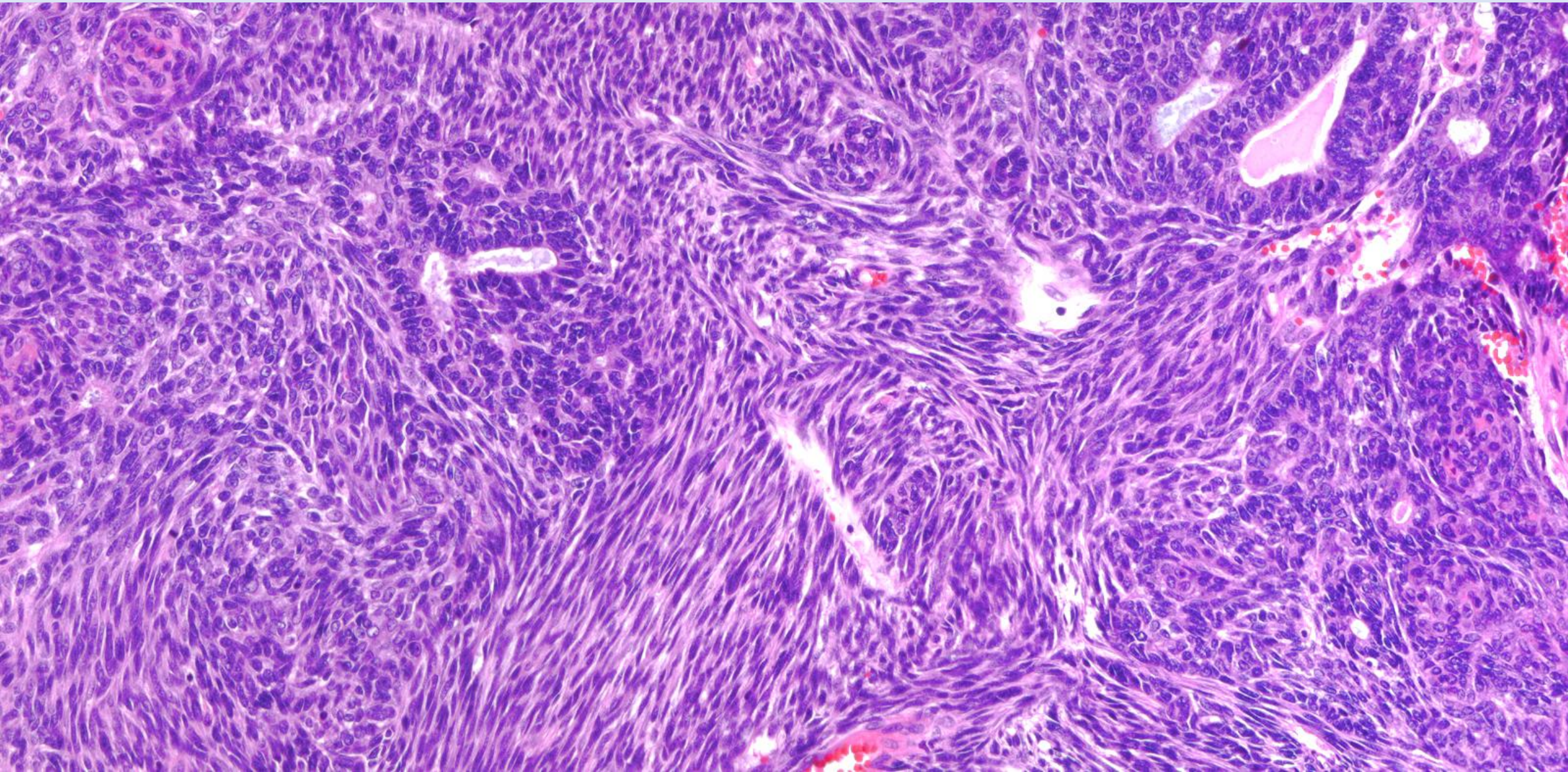
Tumor type	Negative		Low positive (<10%)		Intermediate positive (10%-49%)		High positive (≥50%)		Total positive		Total
	n	%	n	%	n	%	n	%	n	%	
Ovary											
Total	105	26	5	1	16	4	272	68	293	74	398
Serous carcinoma	22	9	5	2	9	4	220	86	234	91	256
Clear cell carcinoma	1	9	0	0	1	9	9	82	10	91	11
Endometrioid carcinoma	5	26	0	0	2	11	12	63	14	74	19
Mucinous carcinoma	51	77	0	0	2	3	13	20	15	23	65
Adenocarcinoma	3	33	0	0	1	11	5	56	6	67	9
Neuroendocrine carcinoma	0	0	0	0	0	0	1	100	1	100	1
Dysgerminoma	2	25	0	0	1	13	5	63	6	75	8
Yolk sac tumor	0	0	0	0	0	0	7	100	7	100	7
Stromal and sex cord tumor	22	100	0	0	0	0	0	0	0	0	22
Uterus											
Total	10	11	0	0	2	2	81	87	83	89	93
Endometrioid carcinoma	10	11	0	0	2	2	81	87	83	89	93
Cervix											
Total	74	93	0	0	0	0	6	8	6	8	80
Adenocarcinoma	34	85	0	0	0	0	6	15	6	15	40
Squamous cell carcinoma	40	100	0	0	0	0	0	0	0	0	40

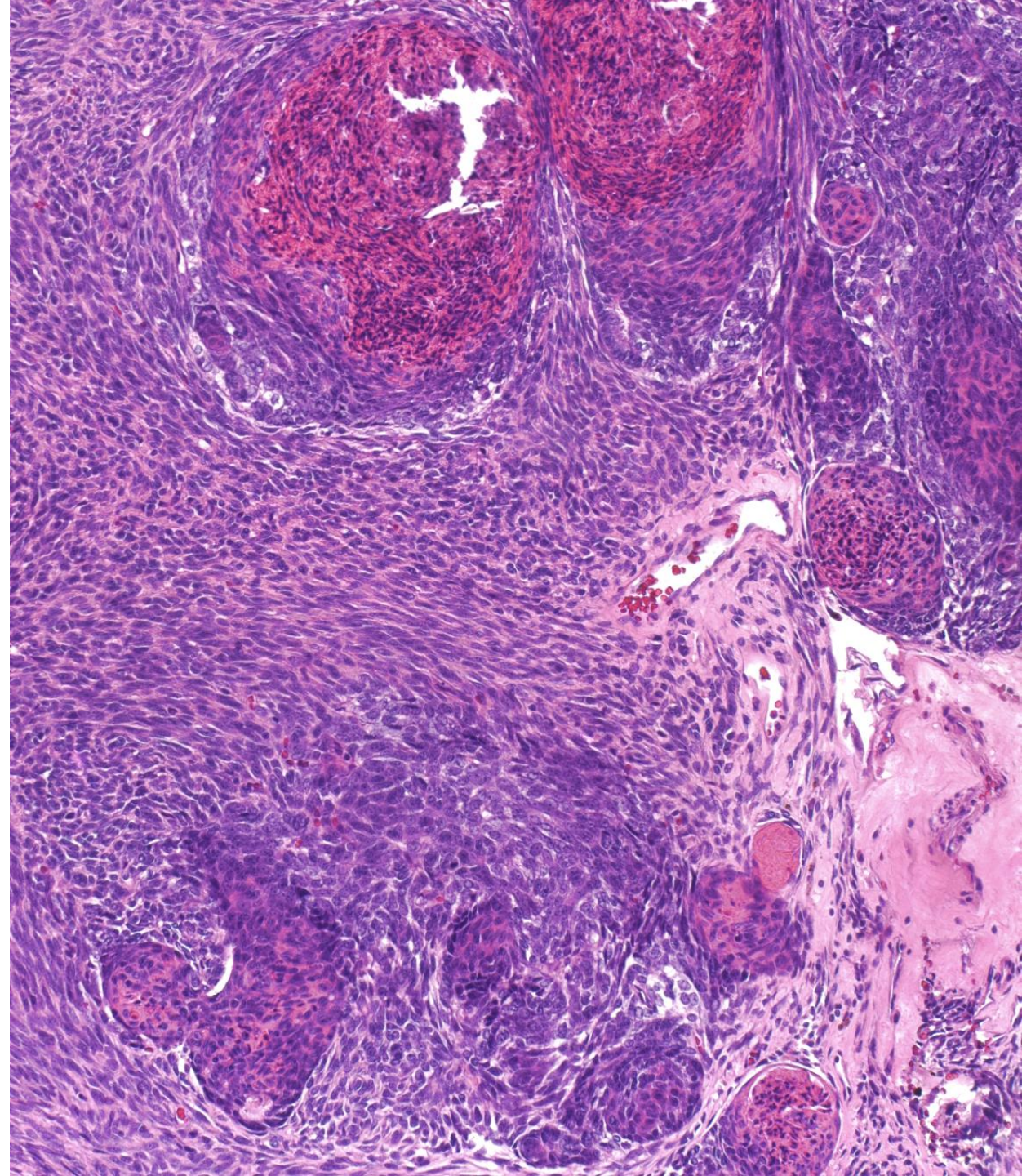
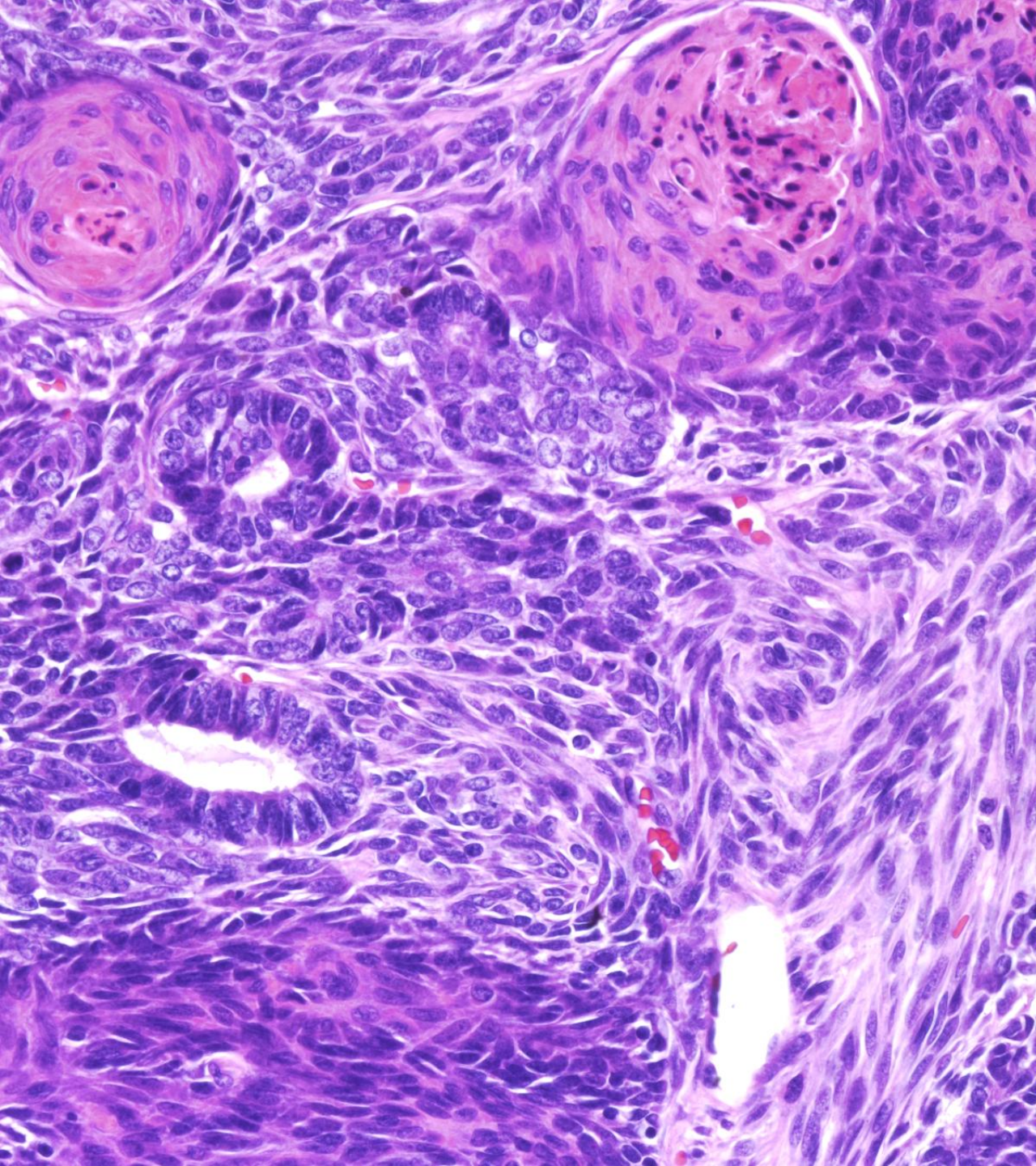
Differential Diagnosis

**Most helpful panel for sex cord tumors:
Inhibin, SF1, and FOXL2**

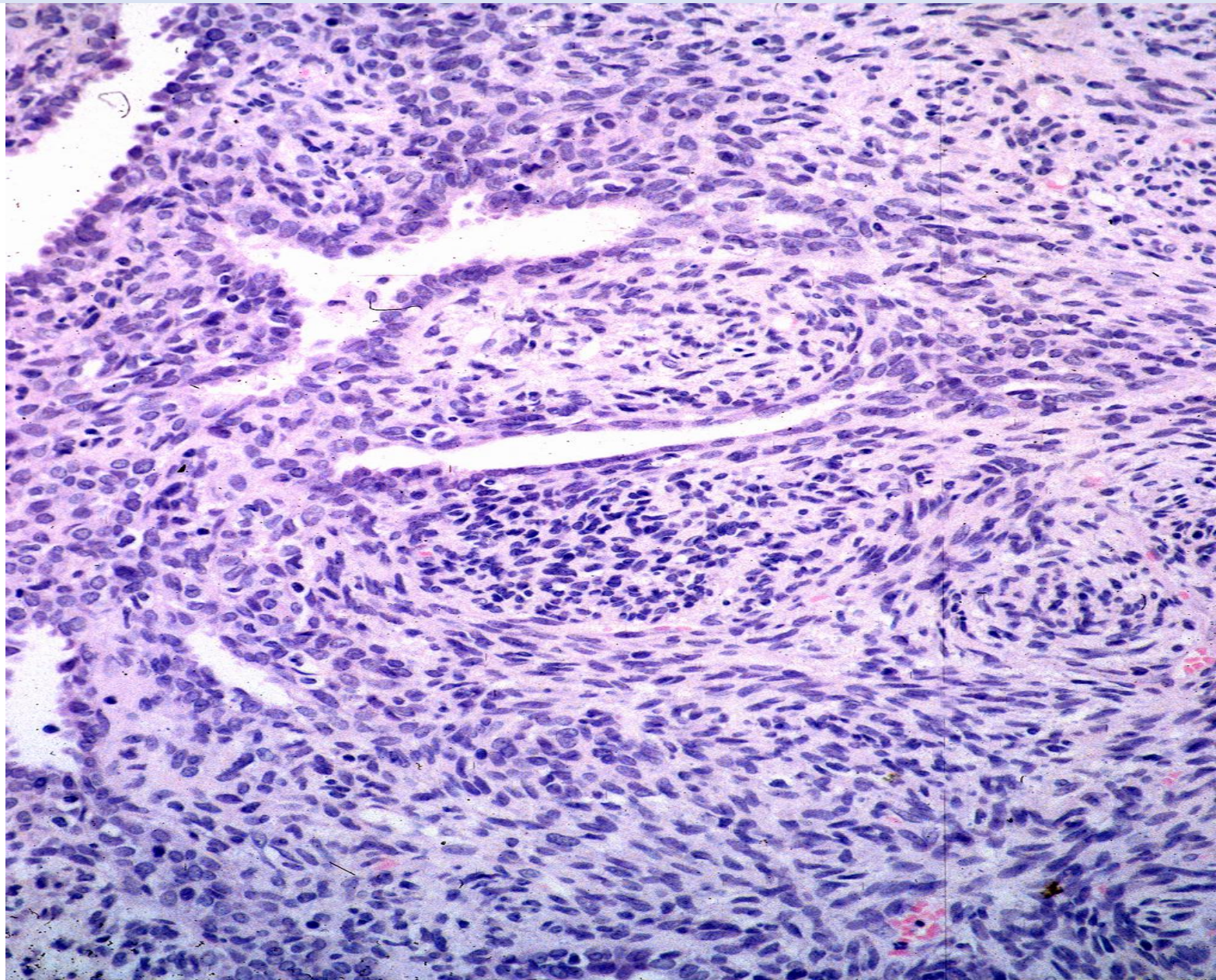
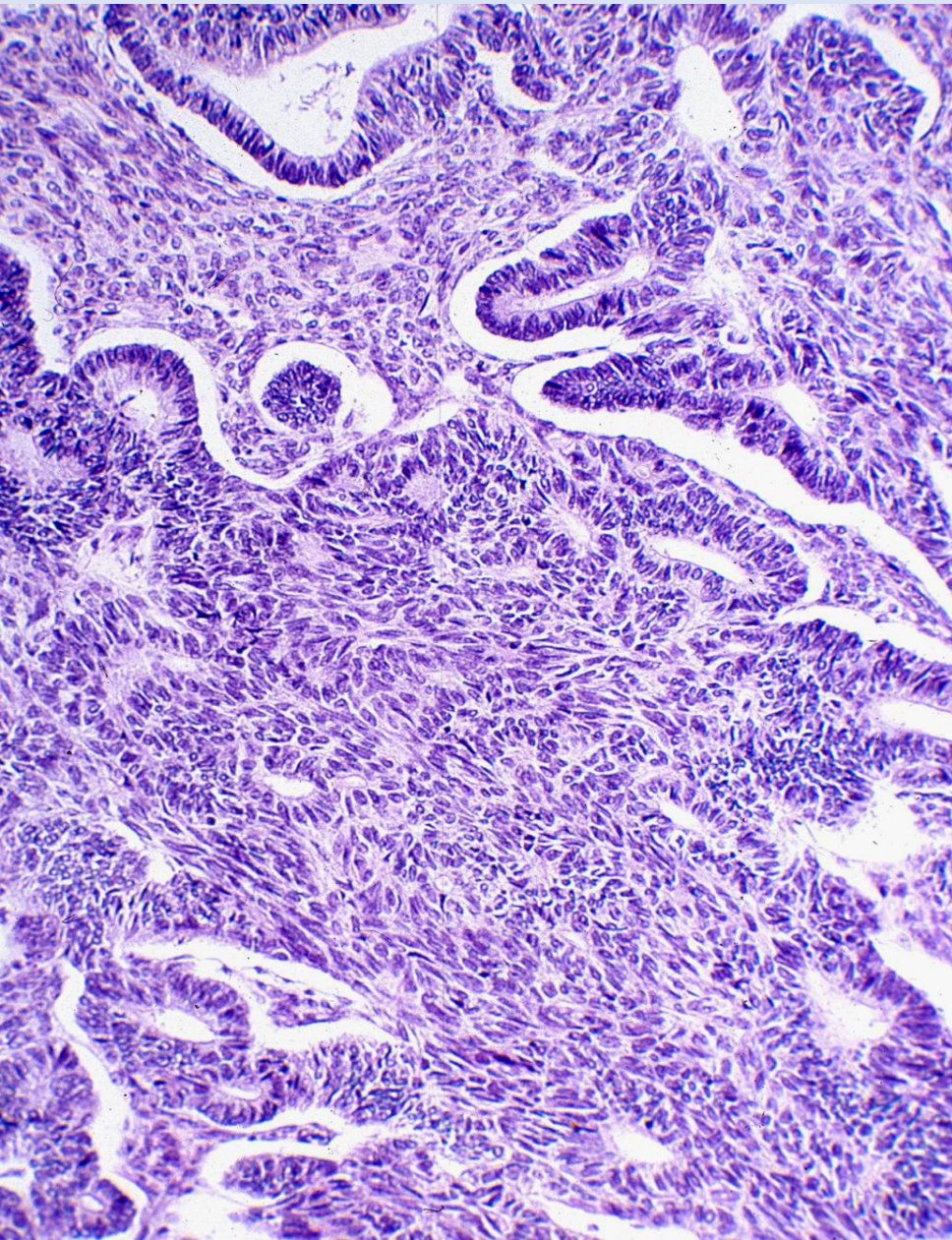
**Calretinin and WT1 *NOT* helpful
in distinction from endometrioid carcinoma**

Endometrioid Carcinoma with Extensive Spindling

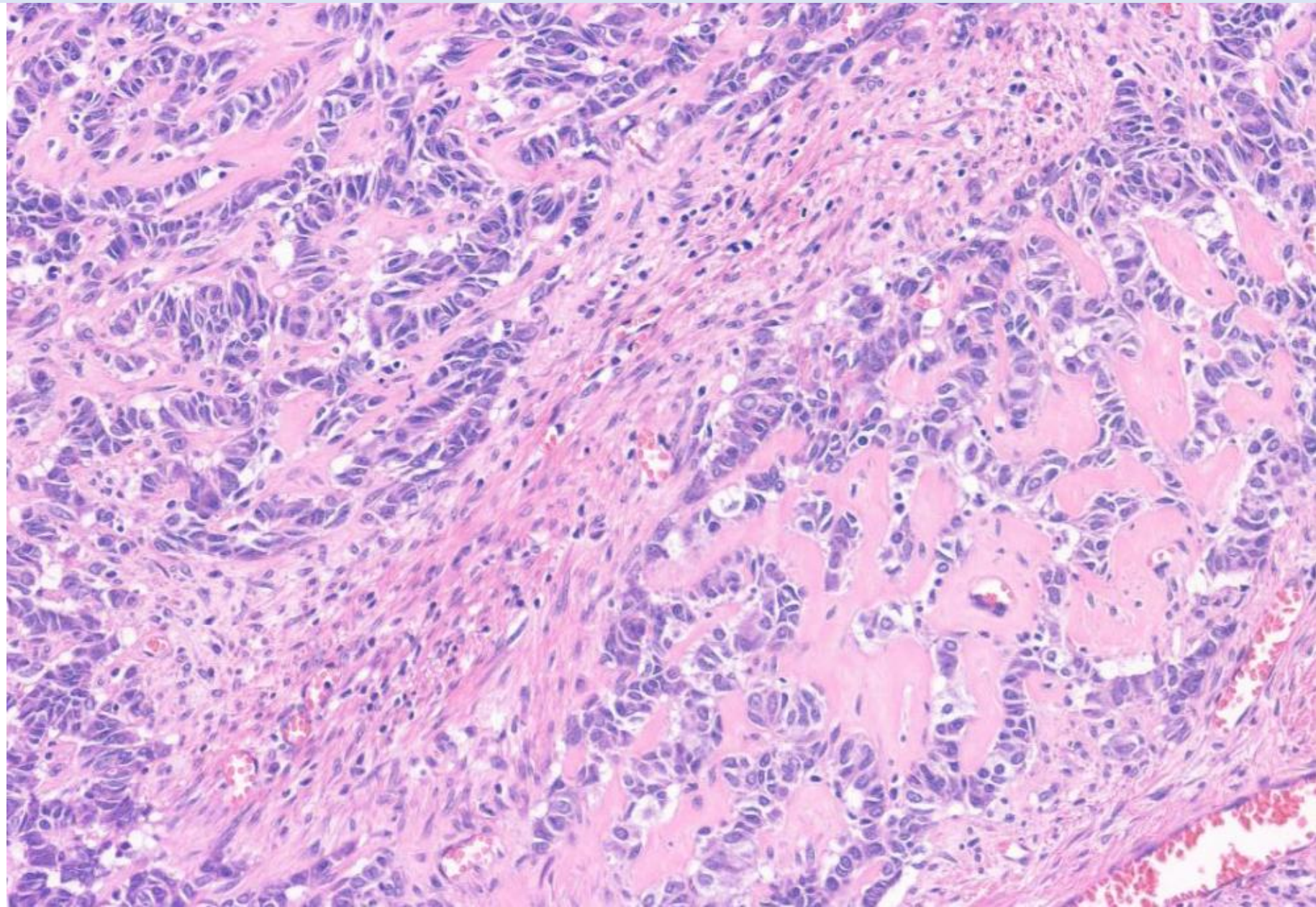
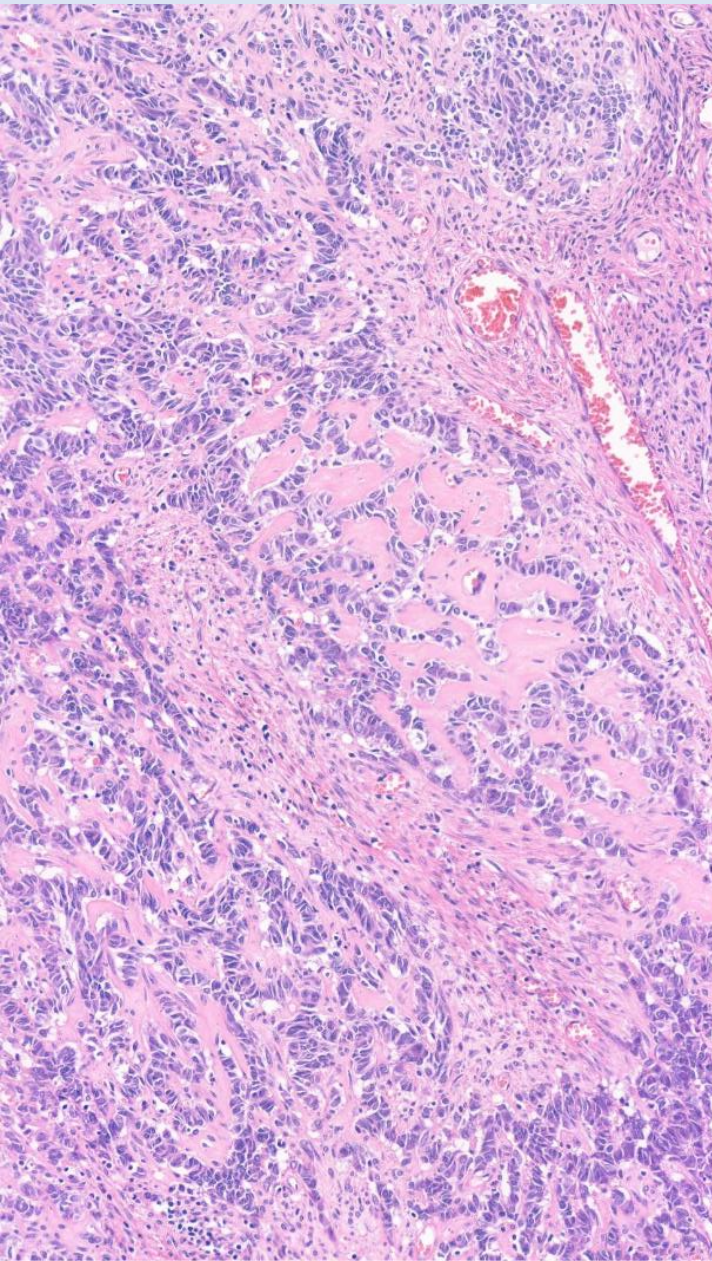




Merging with Glands, Bland Cytologic Features



Corded and Hyalinized Pattern



Endometrioid Carcinoma with Prominent Spindle Cells

Differential Diagnosis

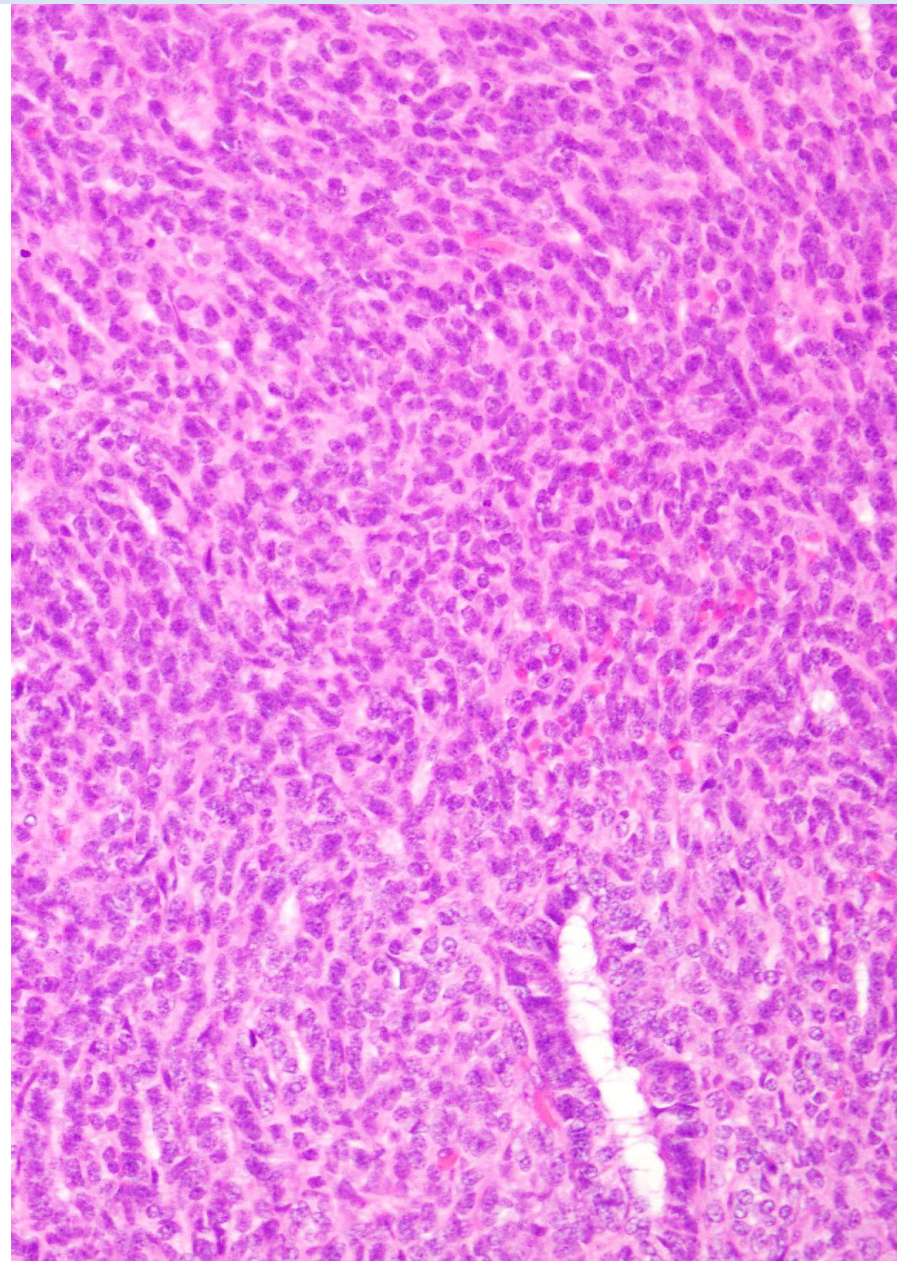
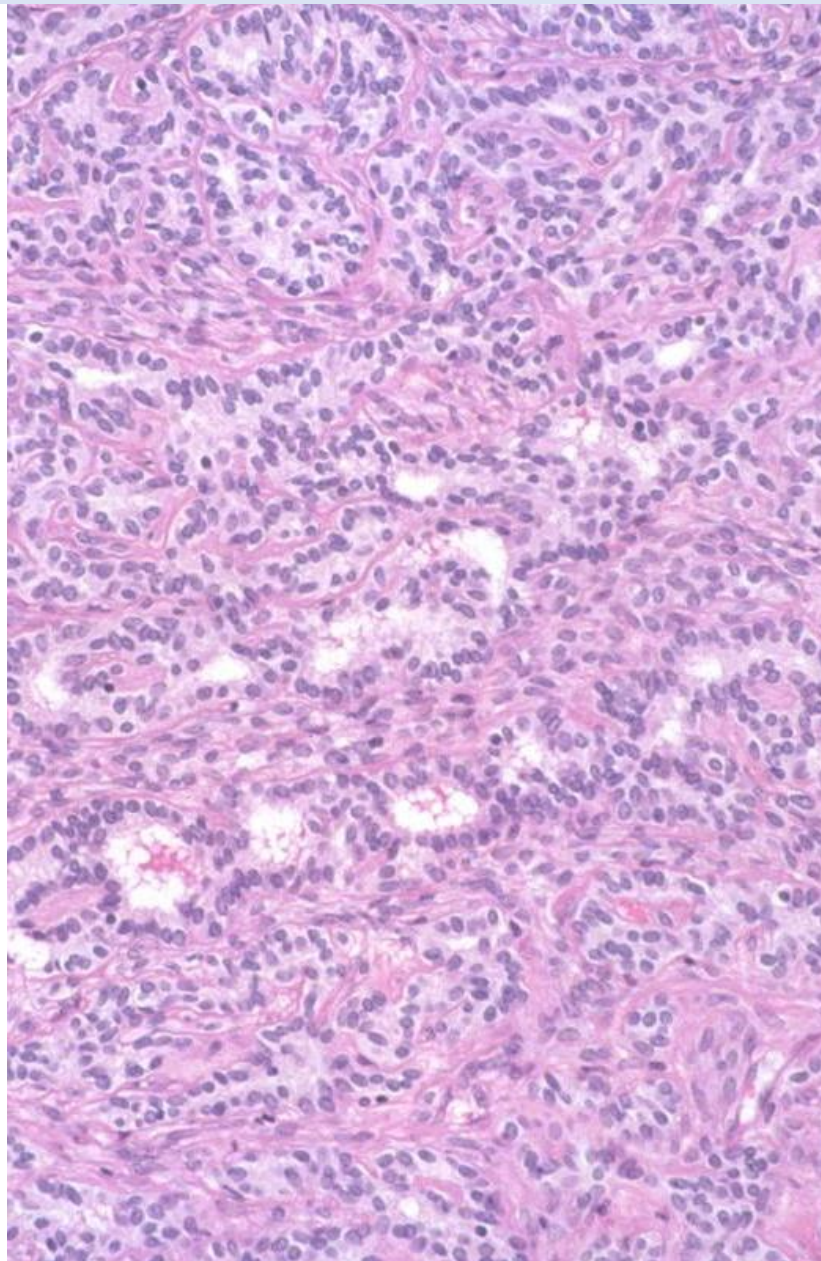
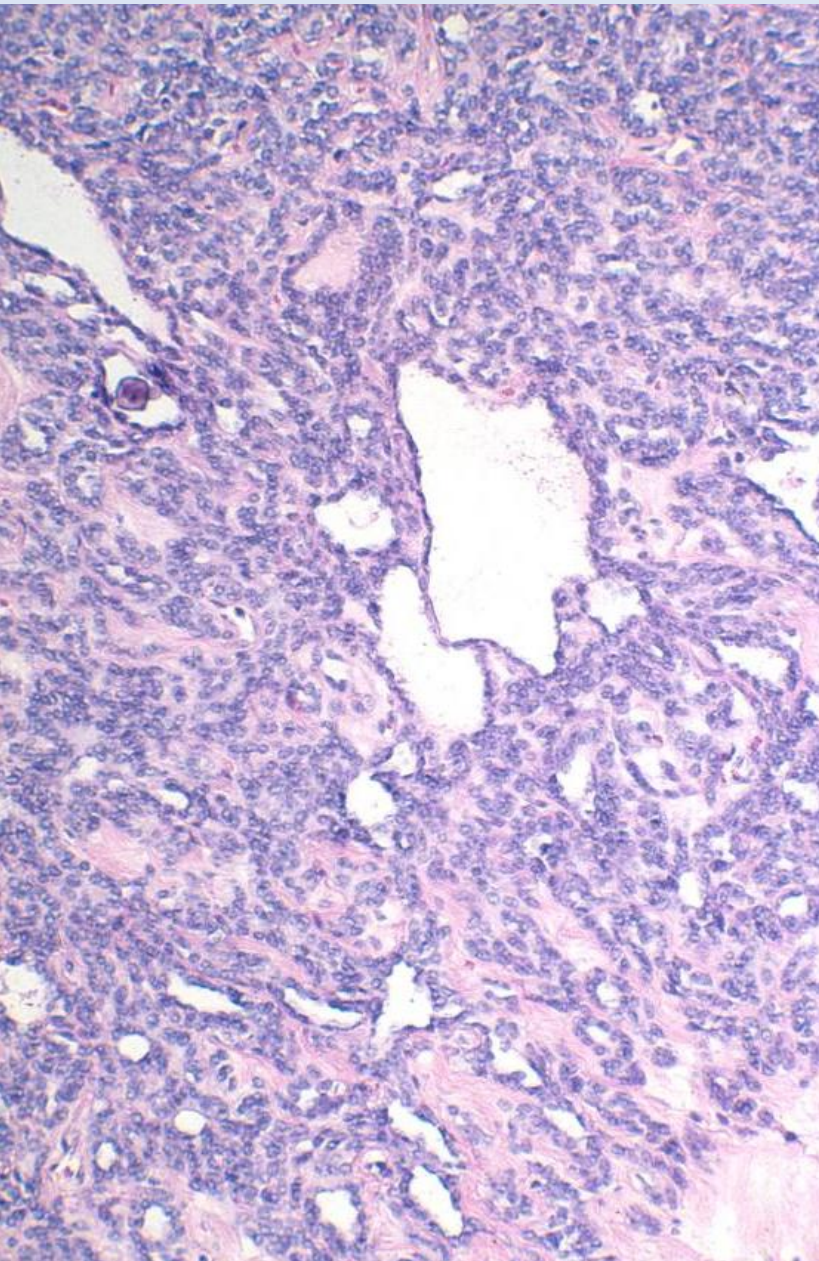
Carcinosarcoma

Sex Cord Stromal Tumor

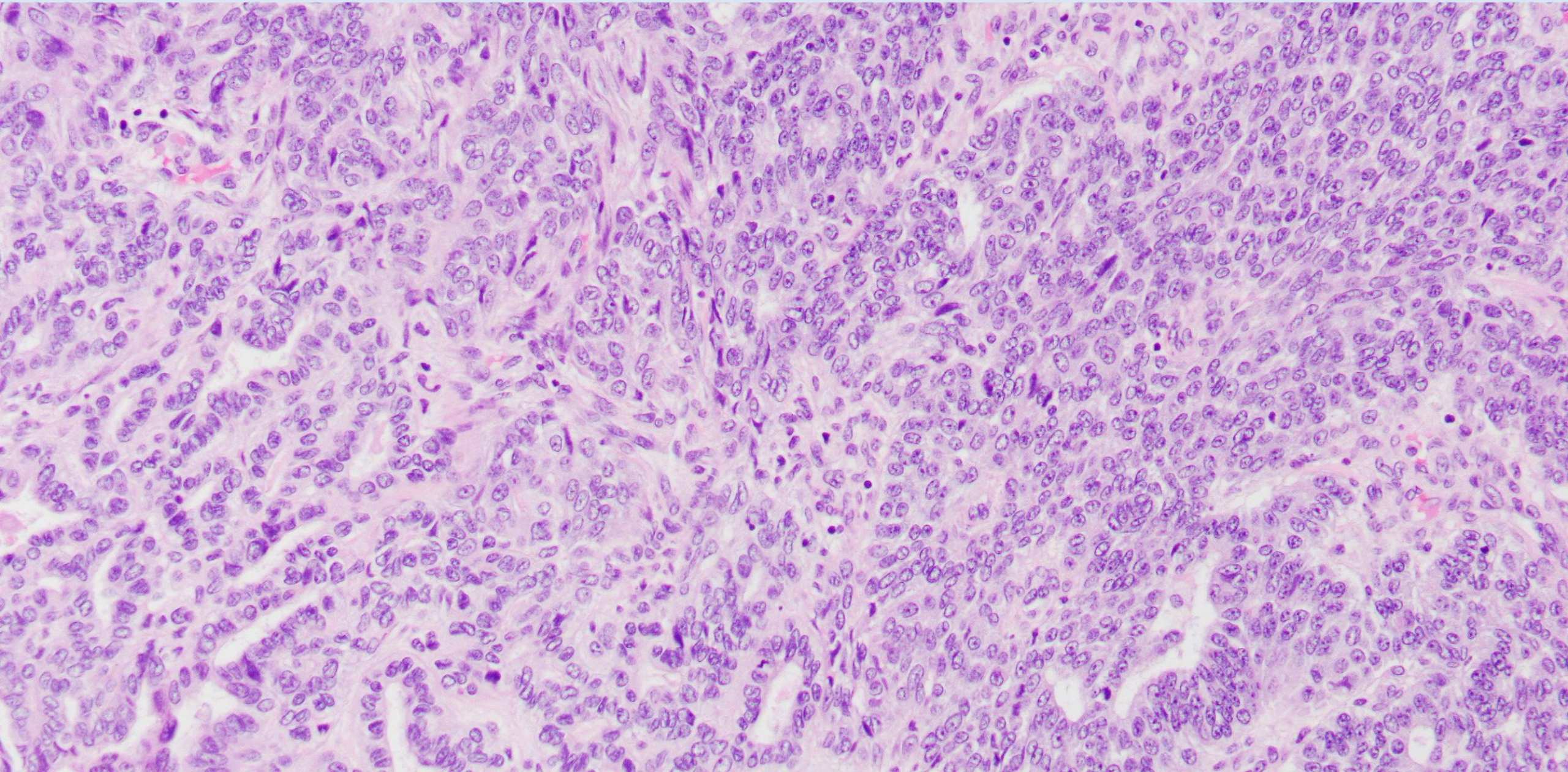
Female Adnexal Tumor of Probable Wolffian Origin (FATWO)

Metastatic Carcinoma

FATWO Patterns



Endometrioid Carcinoma with Wolffian-Like Morphology



Immunoprofile of FATWO

Case	Broad spectrum cytokeratin	EMA	Cytokeratin 7	Vimentin	CD10	Calretinin	Inhibin	ER	PR	WT1	PAX8	GATA3	TTF-1	SF-1
1	++	+	+	—	+	+	—	++	++	NP	—	—	—	—
2	++	—	—	++	—	—	++	+	+	—	—	—	—	++
4	++	NP	NP	++	++	NP	NP	NP	NP	NP	—	+	NP	++
6	++	NP	NP	++	+	—	—	NP	NP	++	—	—	NP	++
7	++	—	NP	++	+	NP	+	NP	NP	NP	—	—	NP	++
8	+	NP	NP	++	+	NP	NP	NP	NP	NP	—	—	NP	+
9	++	—	NP	++	++	++	+	—	—	—	—	—	—	++
10	++	NP	NP	++	+	NP	NP	NP	NP	NP	—	+	NP	++
11	++	—	NP	++	+	NP	+	NP	NP	NP	—	+	NP	++
13	++	NP	—	++	+	+	++	—	—	++	—	—	—	++
14	++	—	++	++	++	—	—	+	—	—	—	—	—	+
15	++	—	NP	++	+	NP	++	NP	NP	NP	—	—	NP	++

ENDOMETRIOID CARCINOMA

Helpful Findings:

Typical endometrioid-type glands

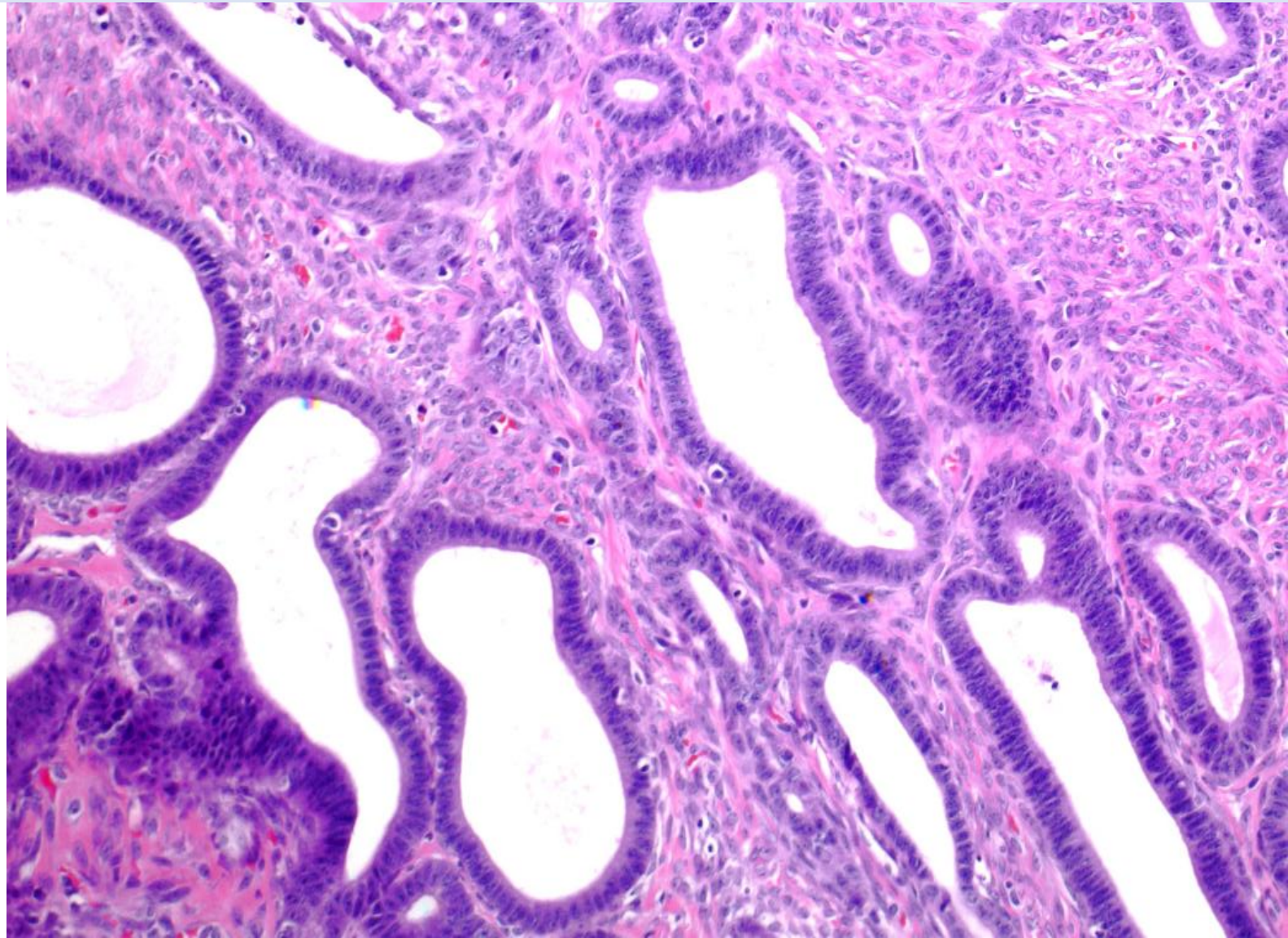
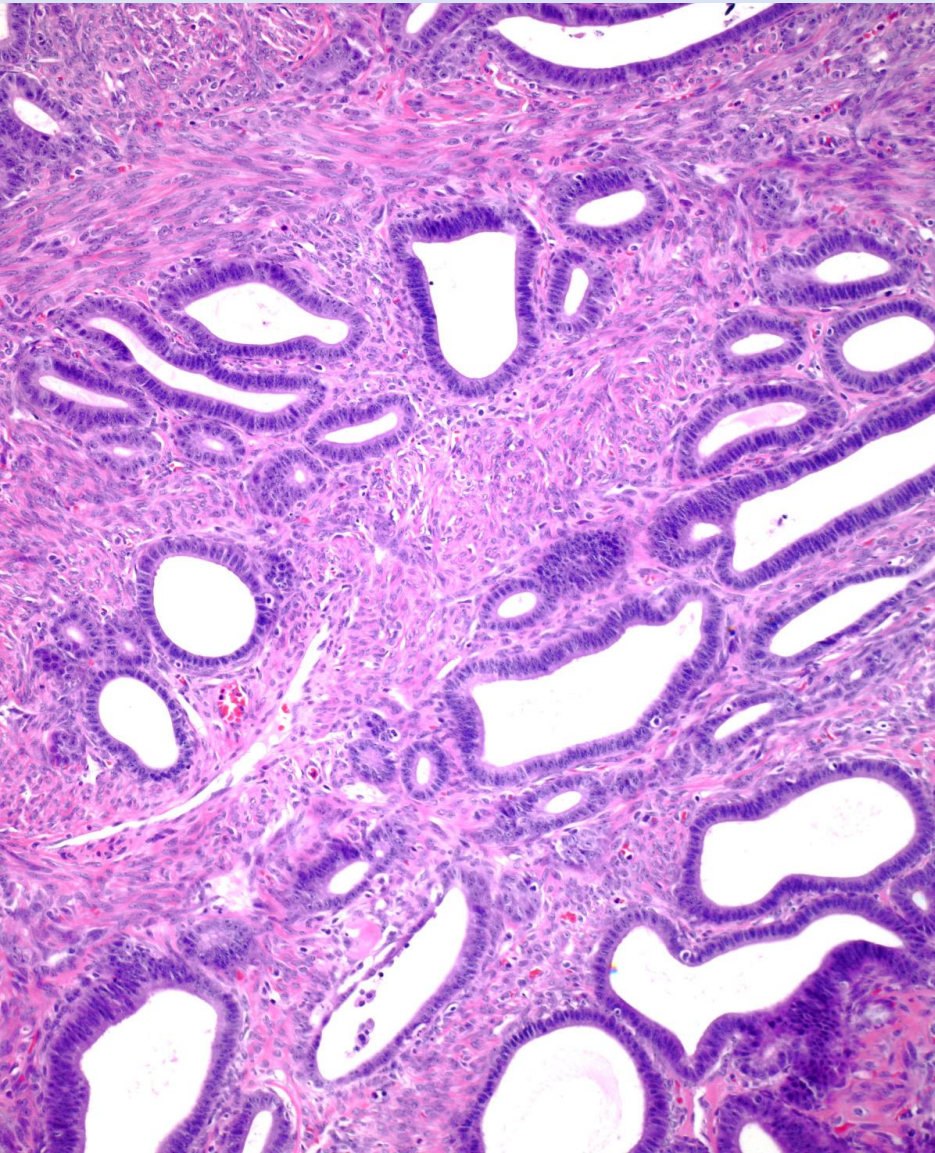
Squamous differentiation

Intraluminal mucin

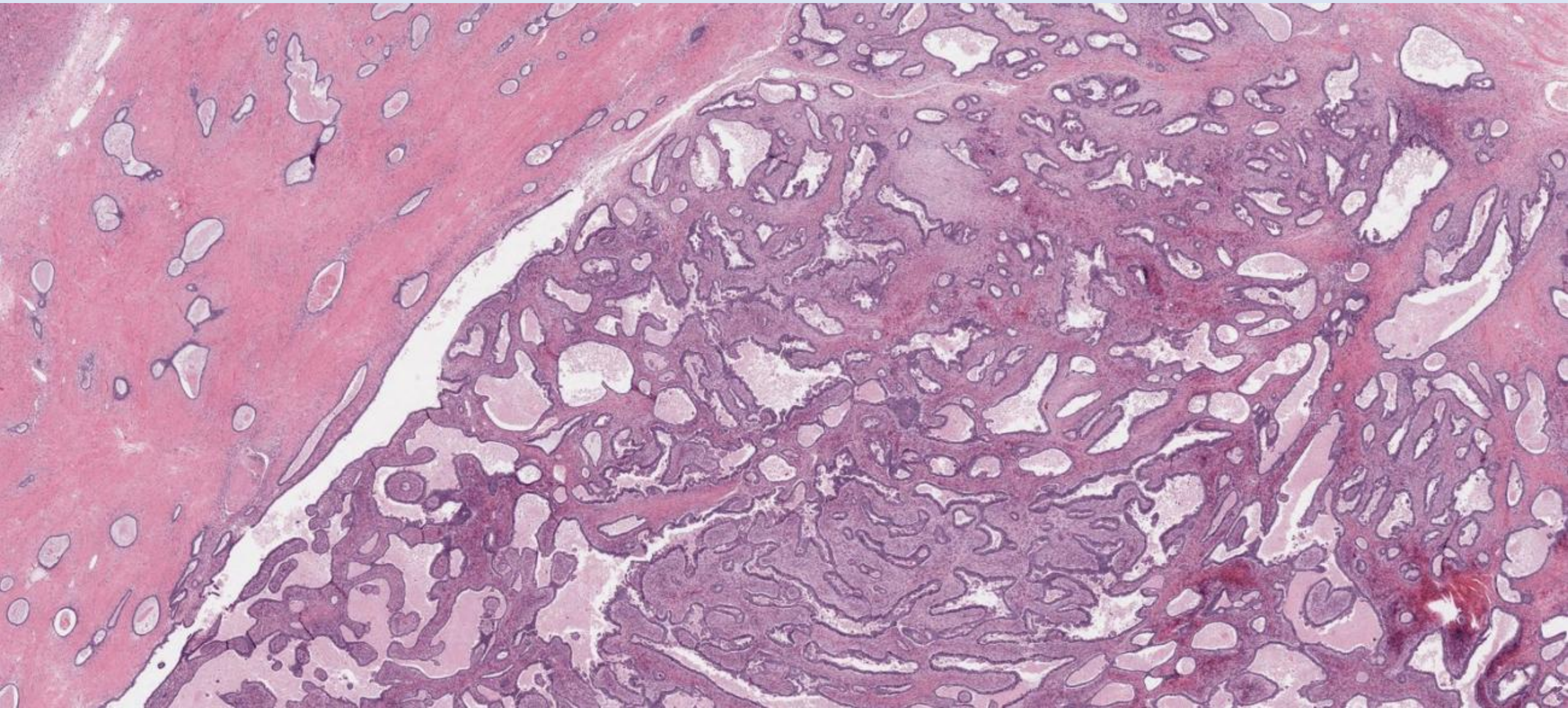
Adenofibromatous background

Endometriosis

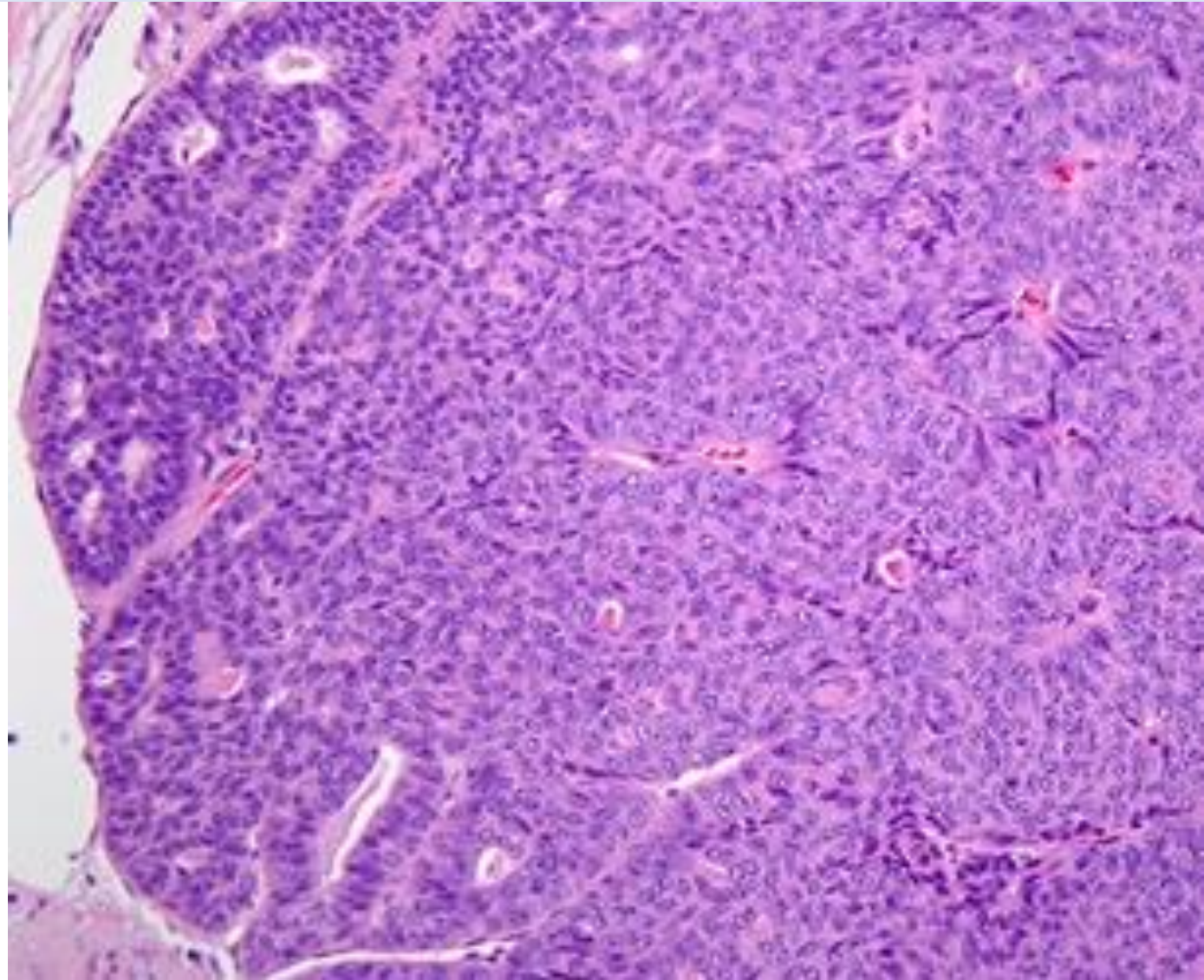
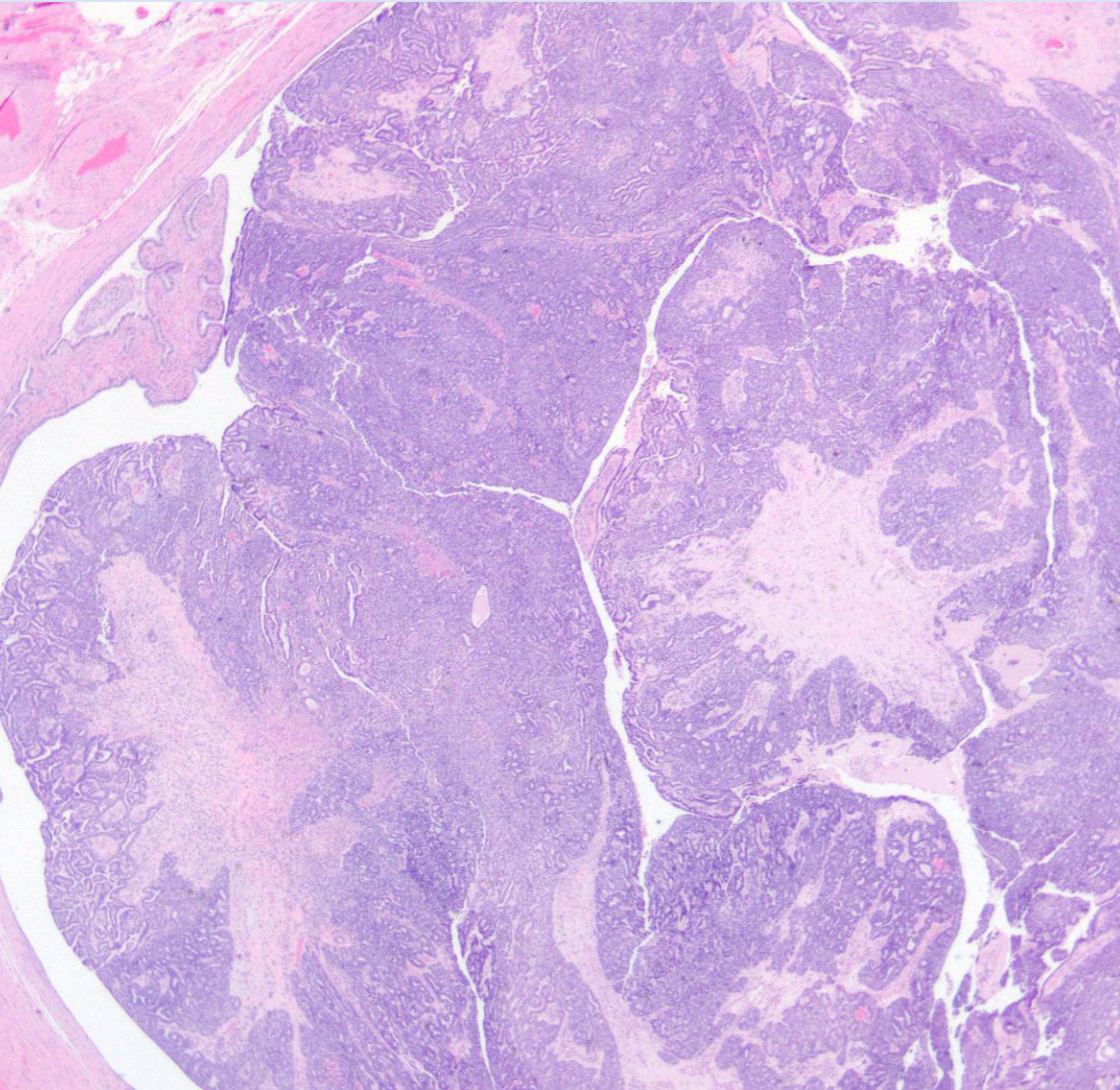
Endometrioid Adenofibroma: Widely Spaced Benign Endometrioid Glands Within Fibromatous Stroma



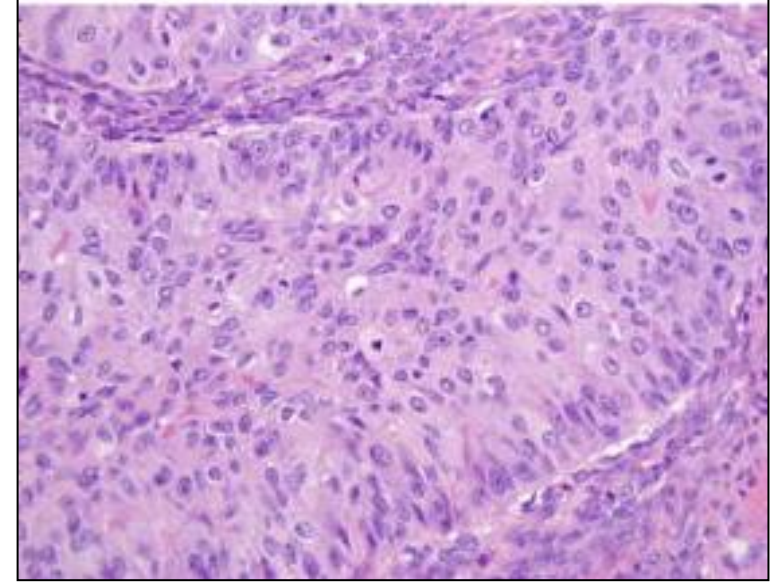
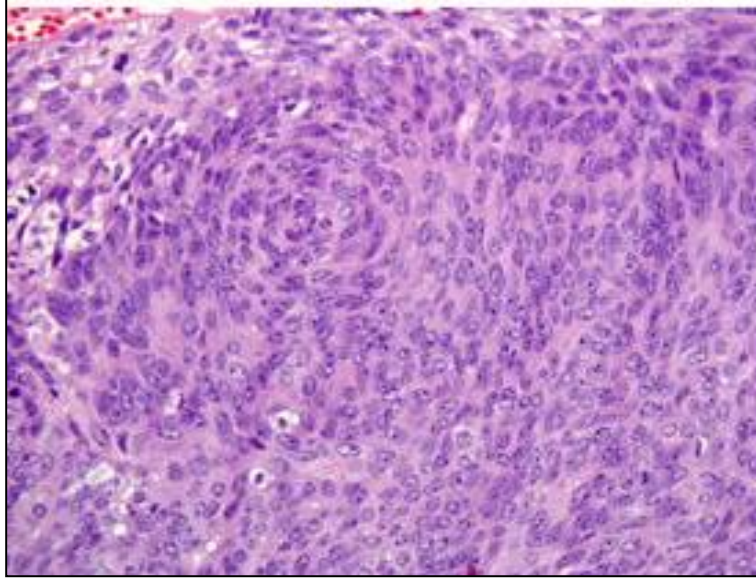
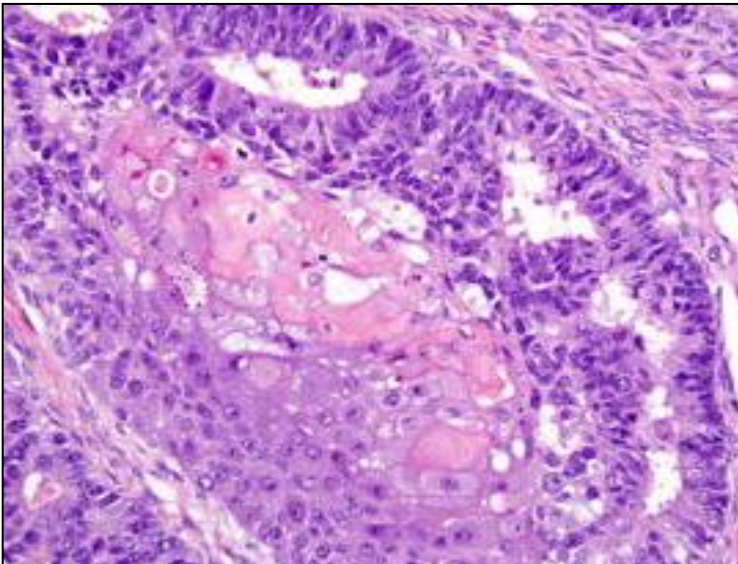
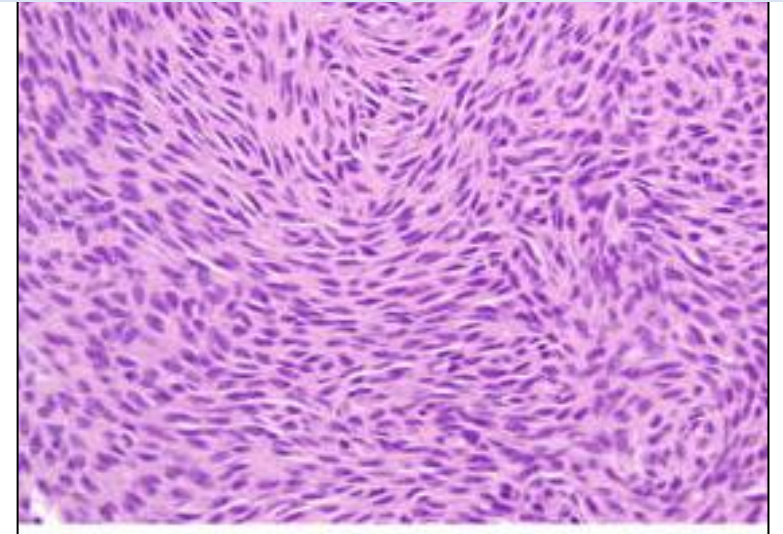
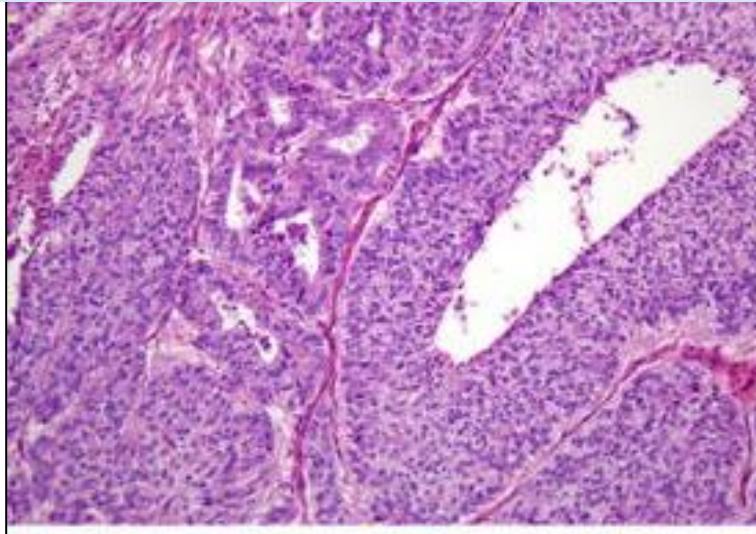
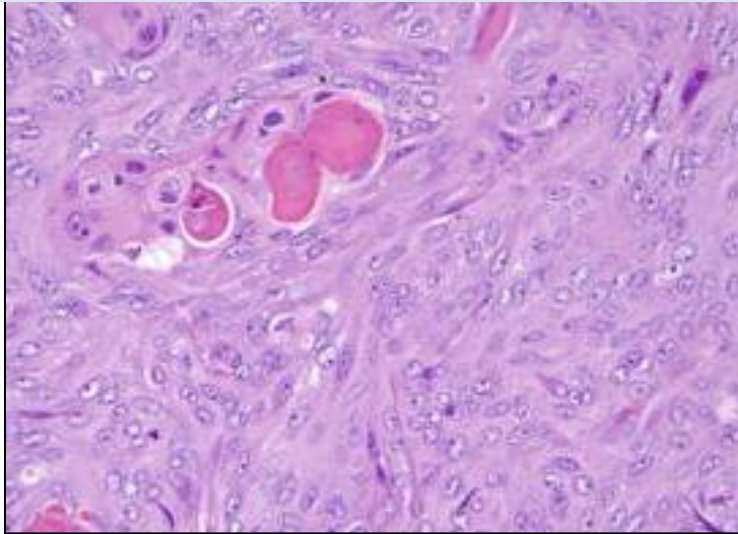
Endometrioid Borderline Tumor with Adenofibromatous Background



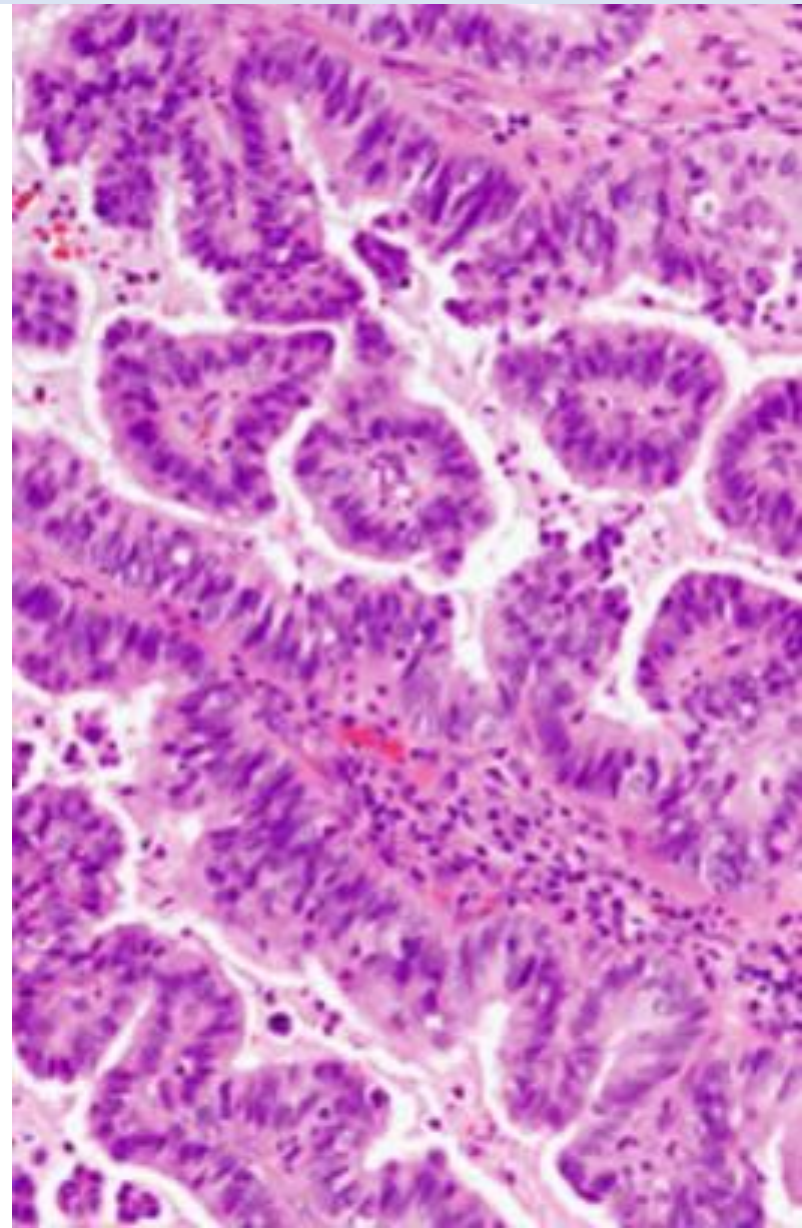
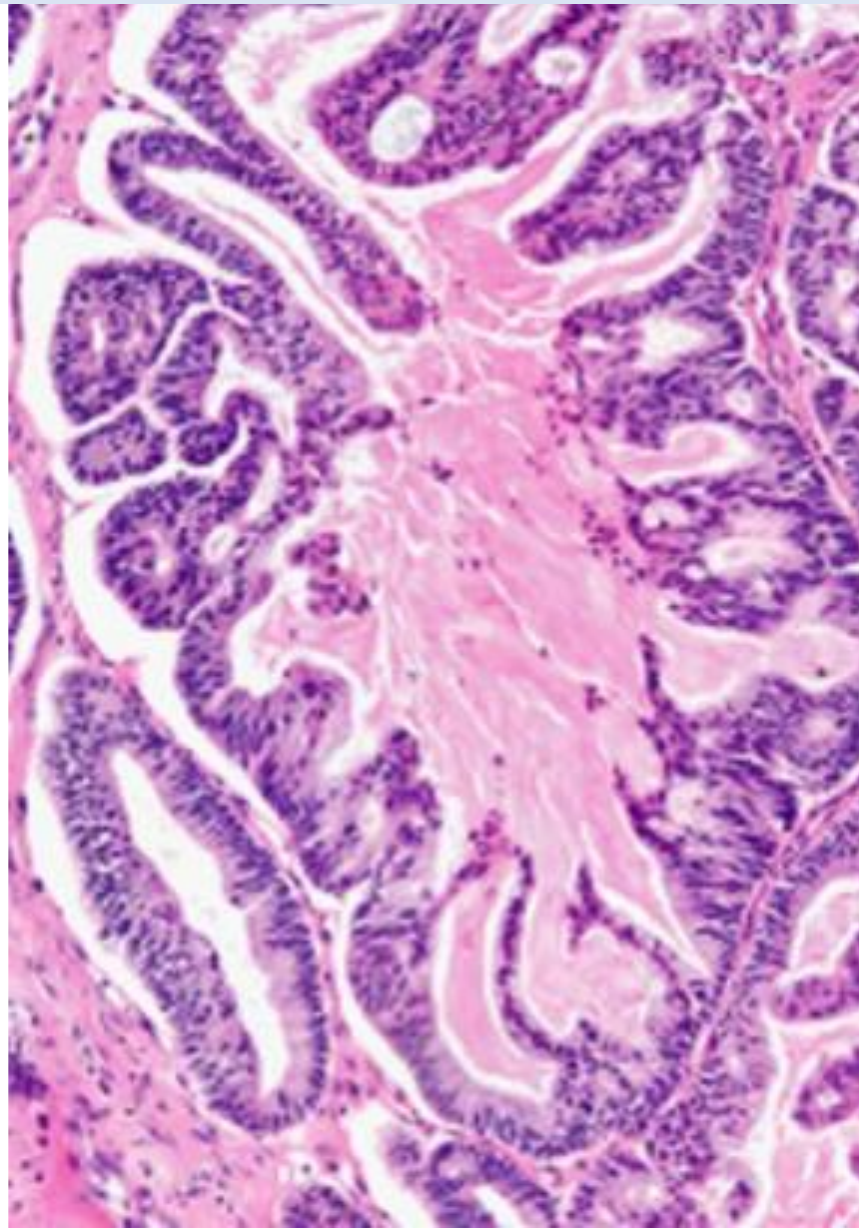
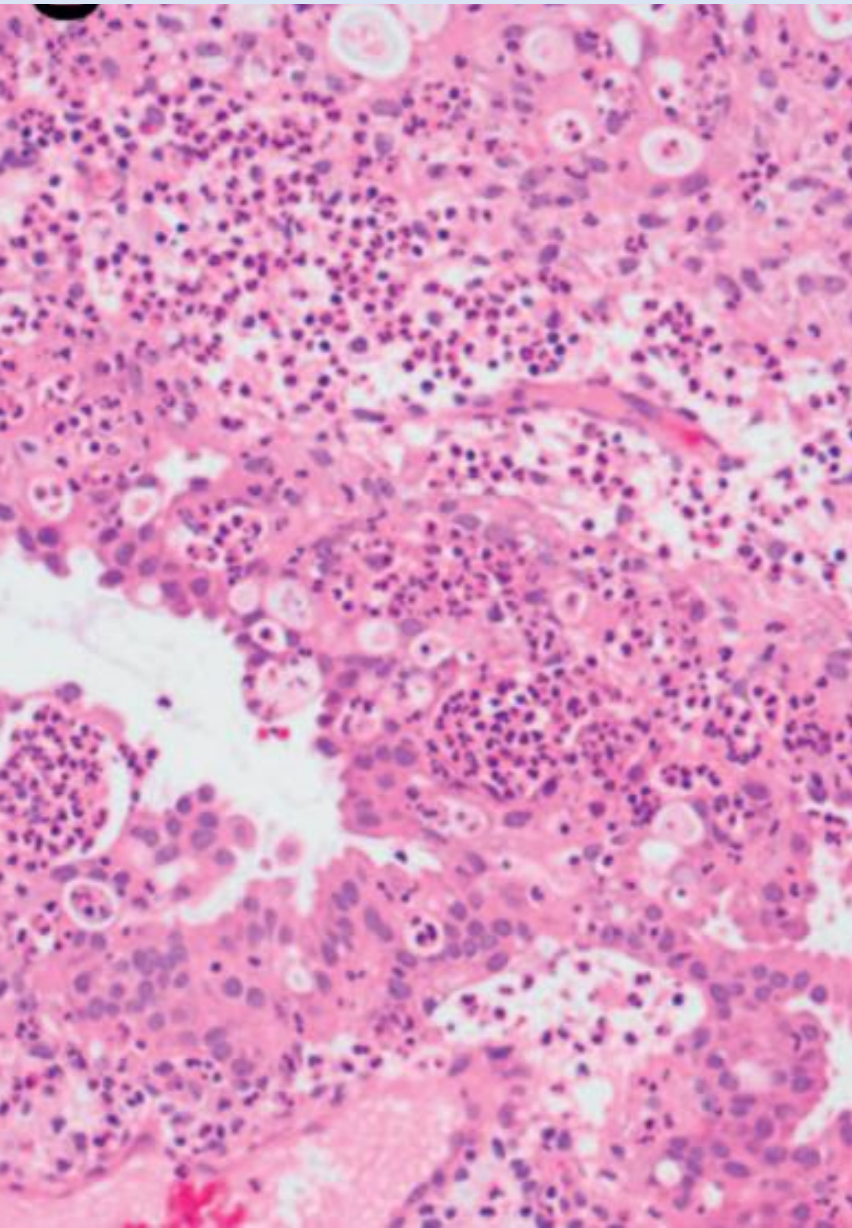
Transitional-Like Morphology



Merges with Typical Endometrioid Carcinoma, Exhibits Squamous Differentiation, and Lacks p53/p16 Abnormal Expression

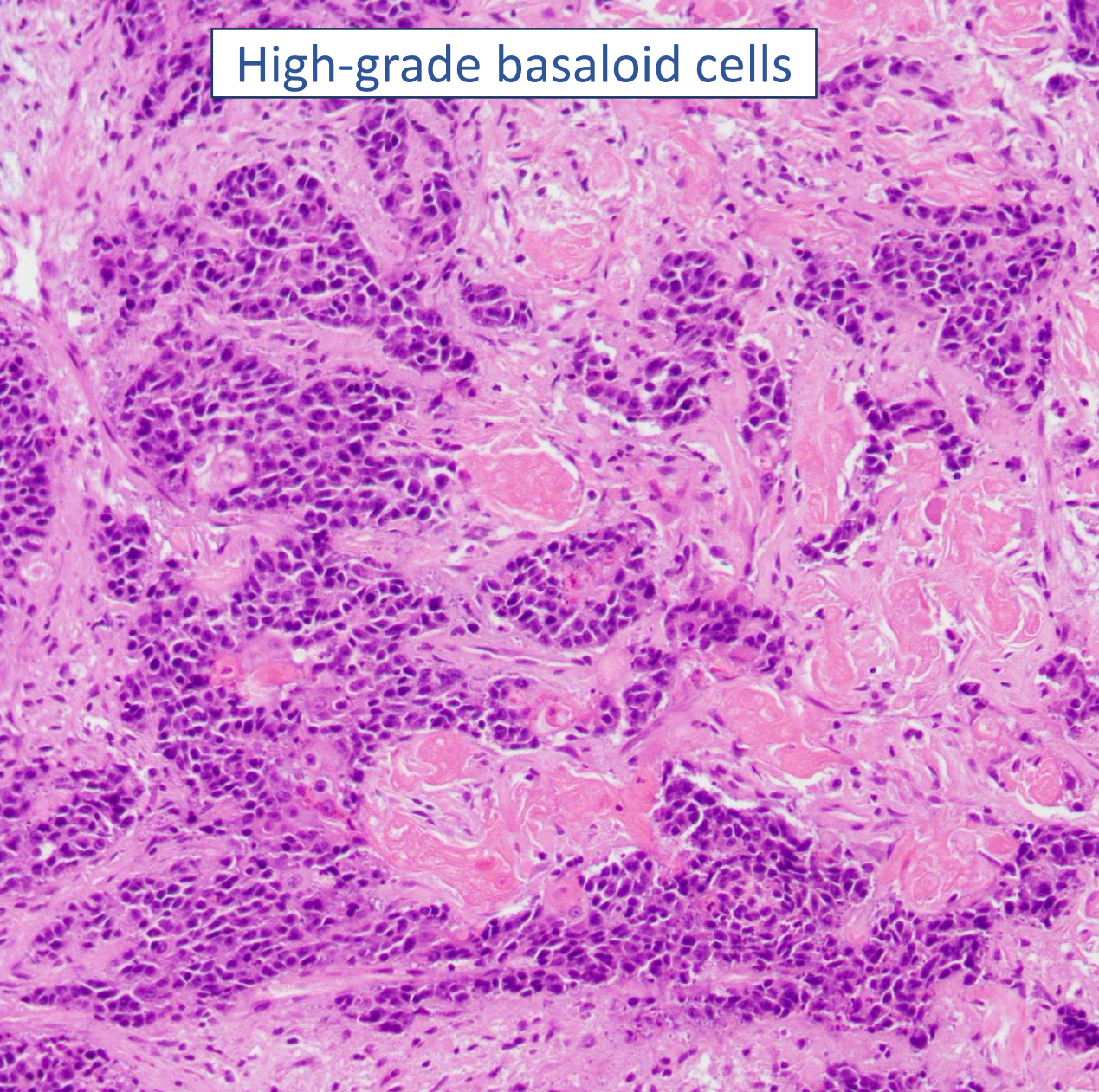


Microglandular Hyperplasia-Like Endometrioid Carcinoma (Rare)

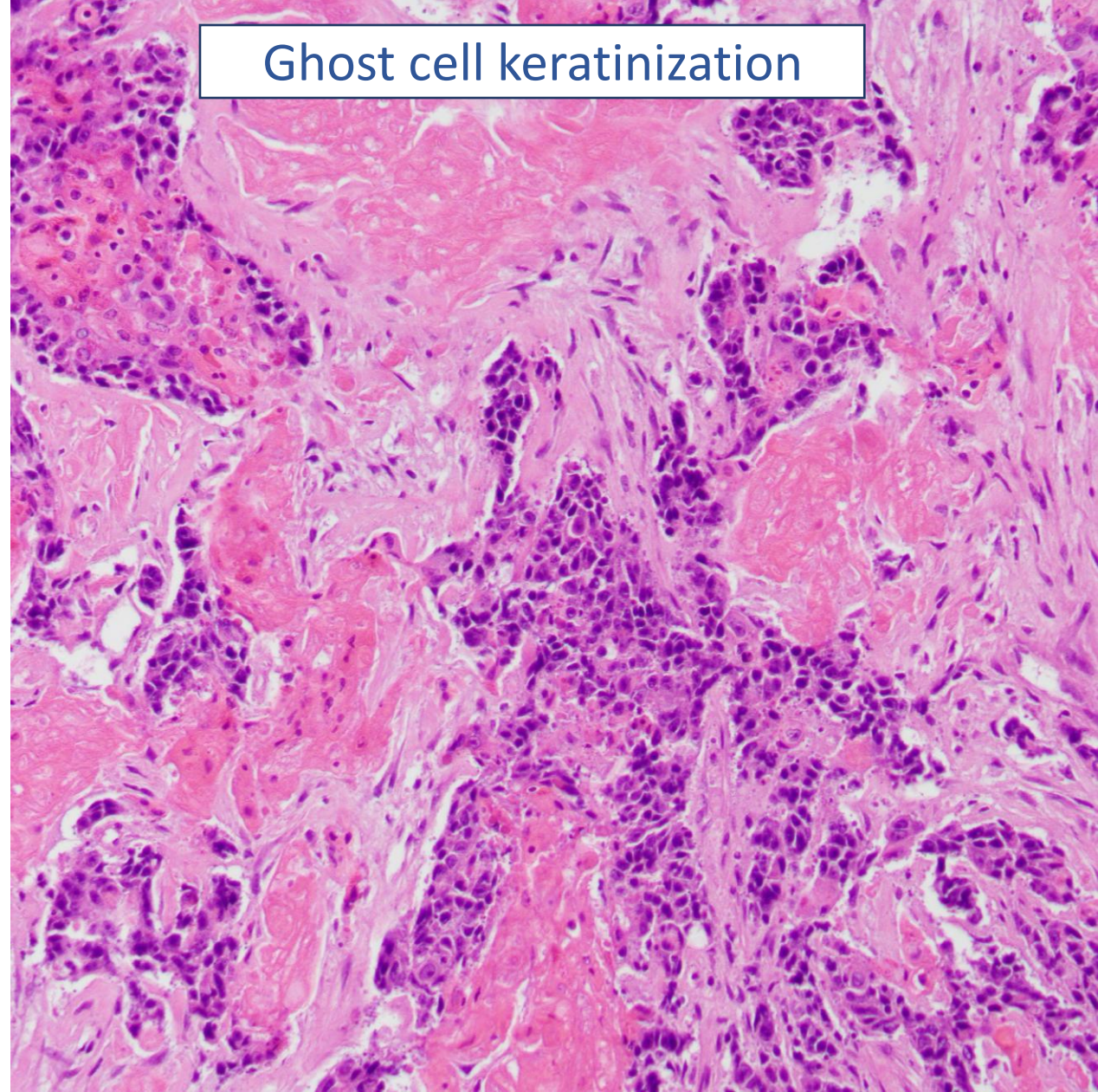


Pilomatrix-Like High-Grade Endometrioid Carcinoma

High-grade basaloid cells

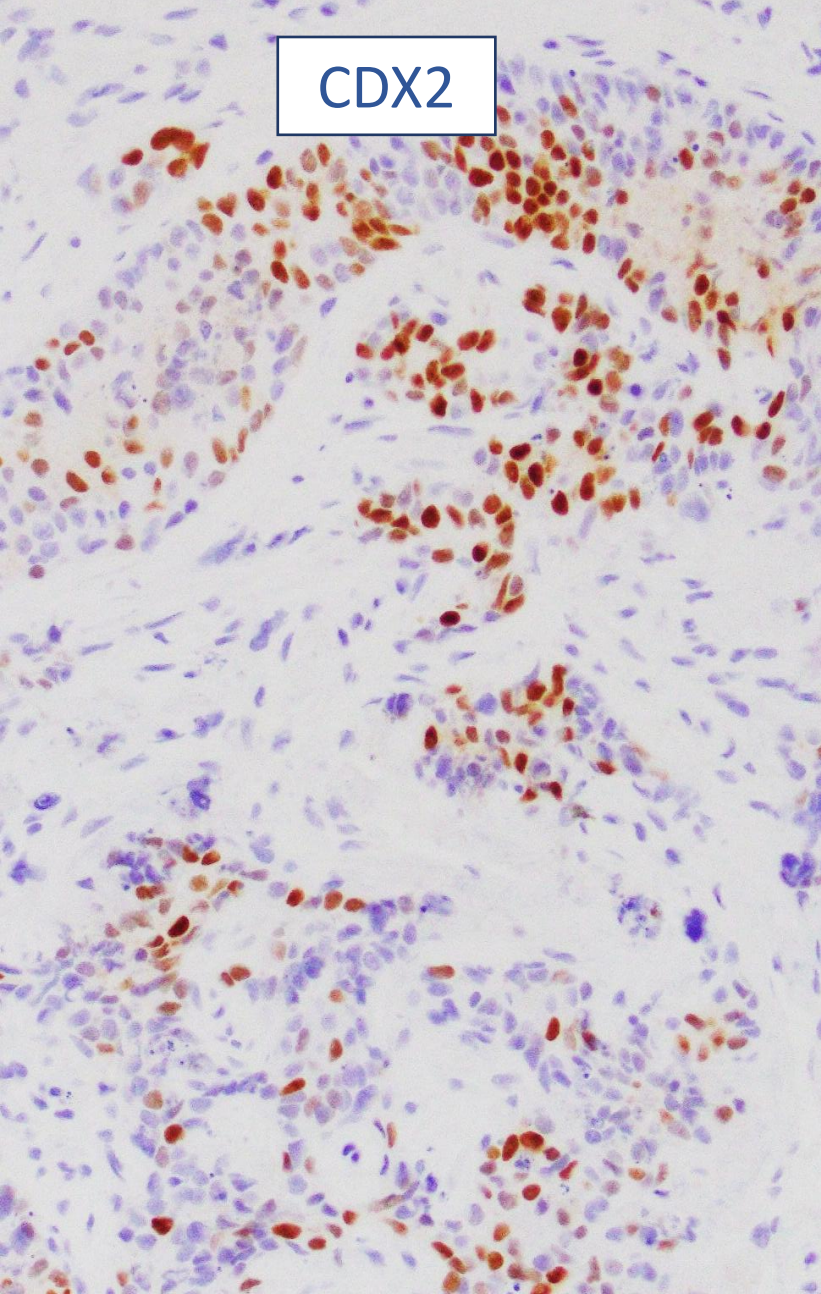


Ghost cell keratinization

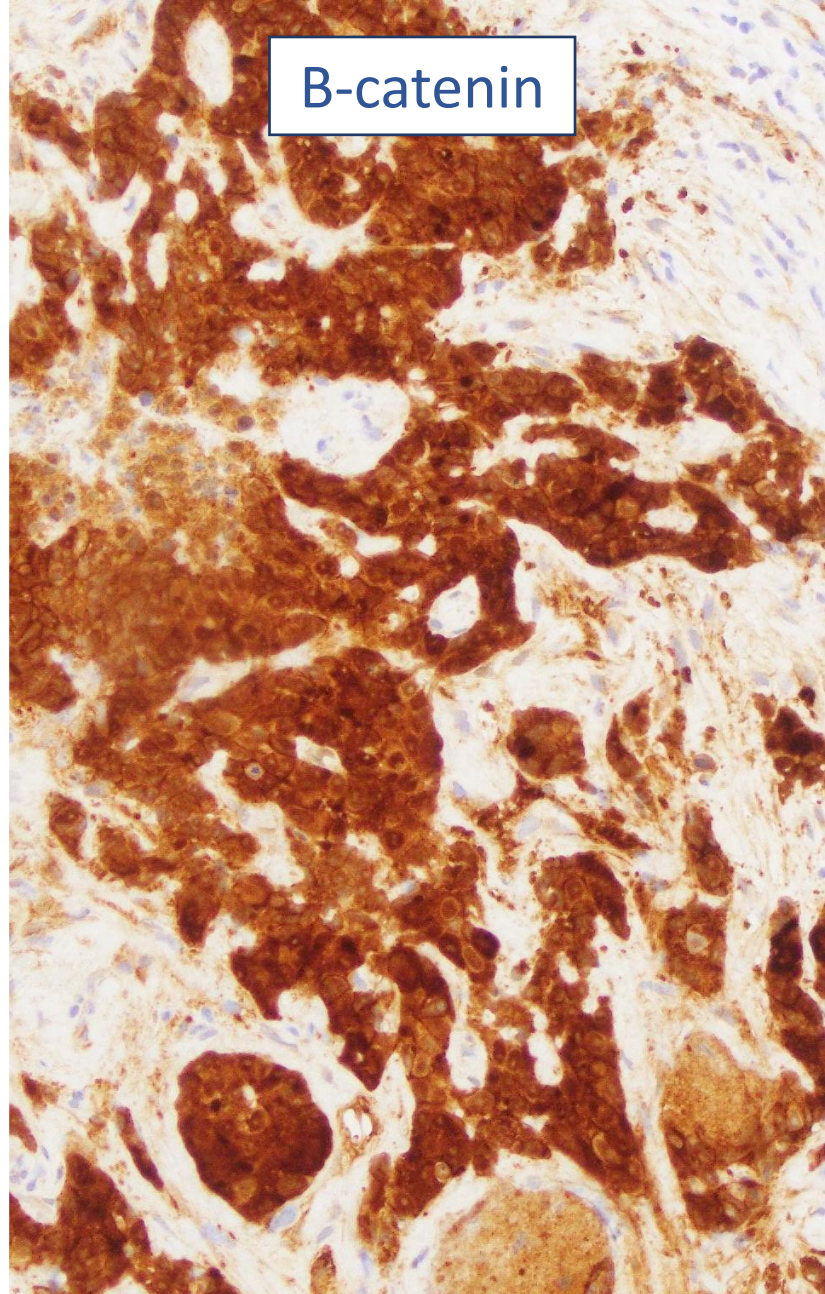


Negative for PAX8 and ER, Variable Synaptophysin

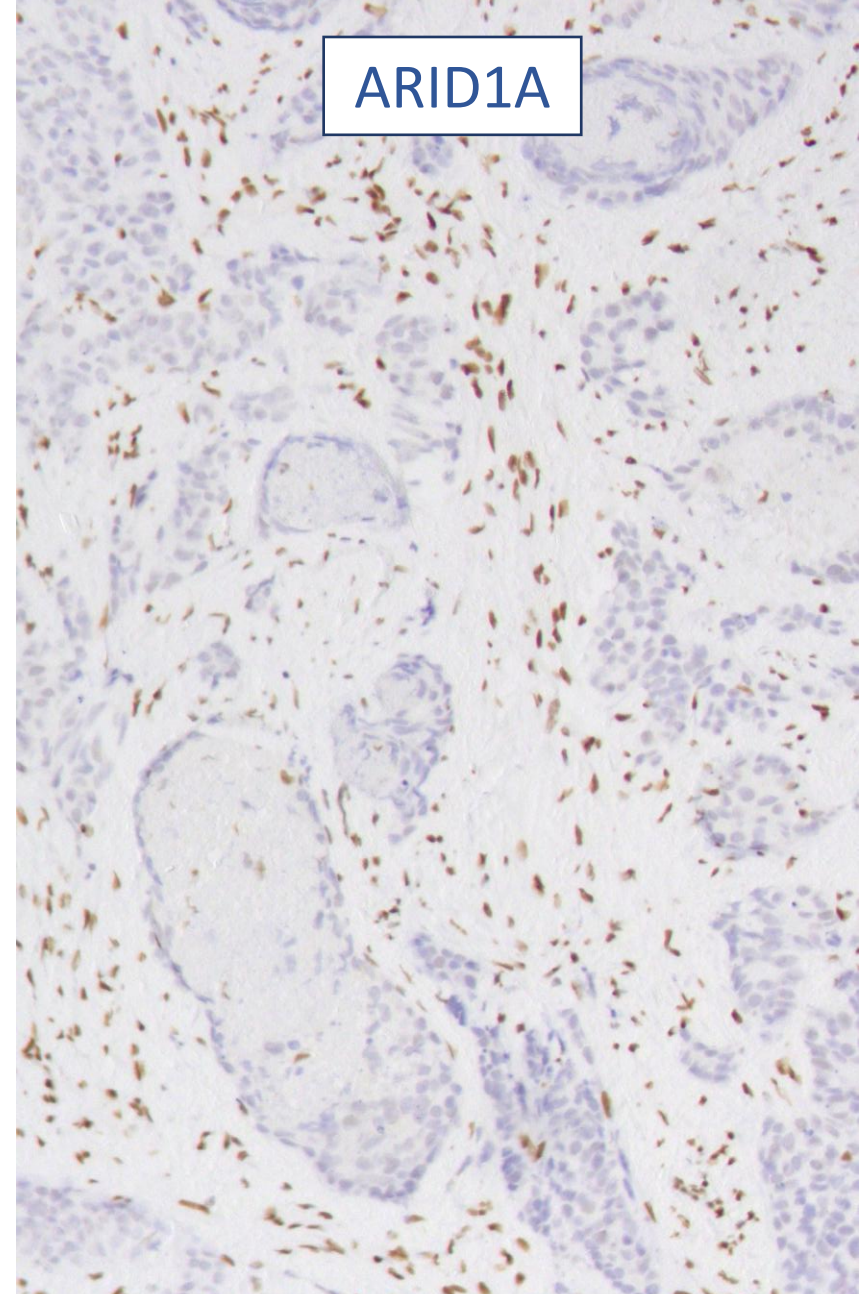
CDX2



B-catenin



ARID1A



FIGO Grade 3 Endometrioid Adenocarcinomas With Diffusely Aberrant β -Catenin Expression: An Aggressive Subset Resembling Cutaneous Pilomatrix Carcinomas

Paul Weisman, M.D., Kay J. Park, M.D., and Jin Xu, M.D.

Int J Gynecol Pathol 2022

Letter to the Editor

An Expanded Series of Pilomatrix-like High-grade Endometrioid Carcinoma (PiMHEC), Including Both MMR Deficient and MMR Proficient Cases

Xu, Jin M.D.; Park, Kay J. M.D.; Weisman, Paul S. M.D.

Pilomatrix-like High-Grade Endometrioid Carcinoma of the Ovary: Case Report, Literature Review, and Differential Diagnosis

by Angela Santoro ¹ , Antonio Travaglino ^{1,2}, Michele Valente ¹, Damiano Arciuolo ^{1,3}, Giulia Scaglione ¹, Nicoletta D'Alessandris ¹, Stefania Sfregola ¹, Francesca Addante ⁴, Caterina Fulgione ⁵, Antonio Raffone ⁶ , Angelo Minucci ⁷ , Frediano Inzani ^{1,*}   and Gian Franco Zannoni ^{1,3} 

Diagnostics 2022

Grade 3 endometrioid carcinoma +/- low-grade component
May be MMR-deficient (usually MLH1/PMS2)
Aggressive behavior - high rate of distant metastases and up to 24 months survival

High-grade Endometrial Carcinomas With Solid Basaloid Morphology and Geographic Necrosis Lacking Definitive Pilomatrix-like Features: Clinicopathologic Characteristics Including Aggressive Behavior and Novel Molecular Events

David K. Carlson, MD, Cheyenne Painter, MS,† Sarah E. Gradecki, MD,* Kari L. Ring, MD,‡
Eli S. Williams, PhD,* and Anne M. Mills, MD**

Basaloid morphology but no shadow cells

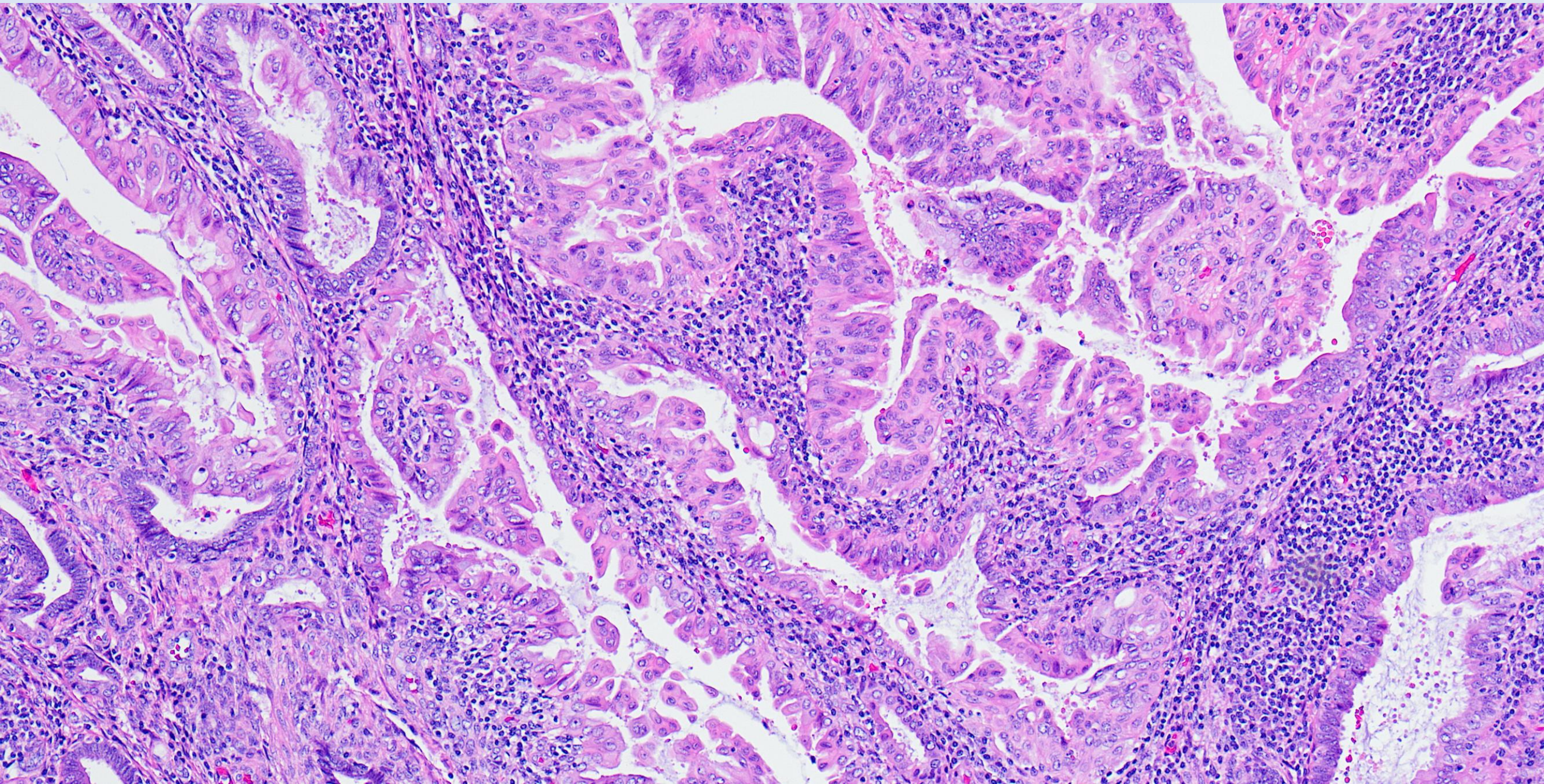
May be CDX2 positive

MMR deficient

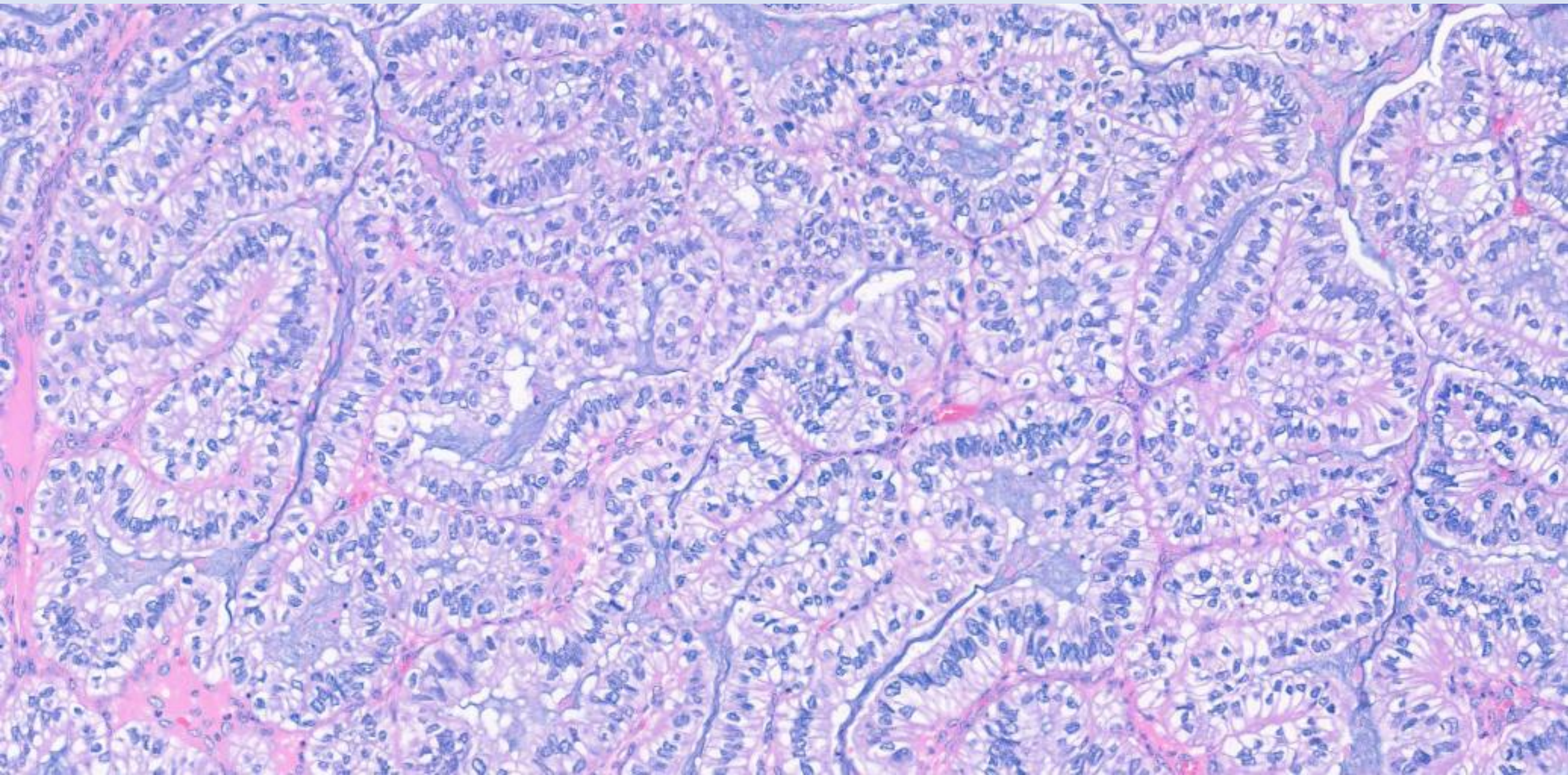
Lack β -catenin positivity and associated mutations

KRAS (1) or oncogenic variants involving pilomatrixoma-associated gene
FGFR2 and somatic Notch pathway (*NOTCH1/NOTCH2/NOTCH3*) variants

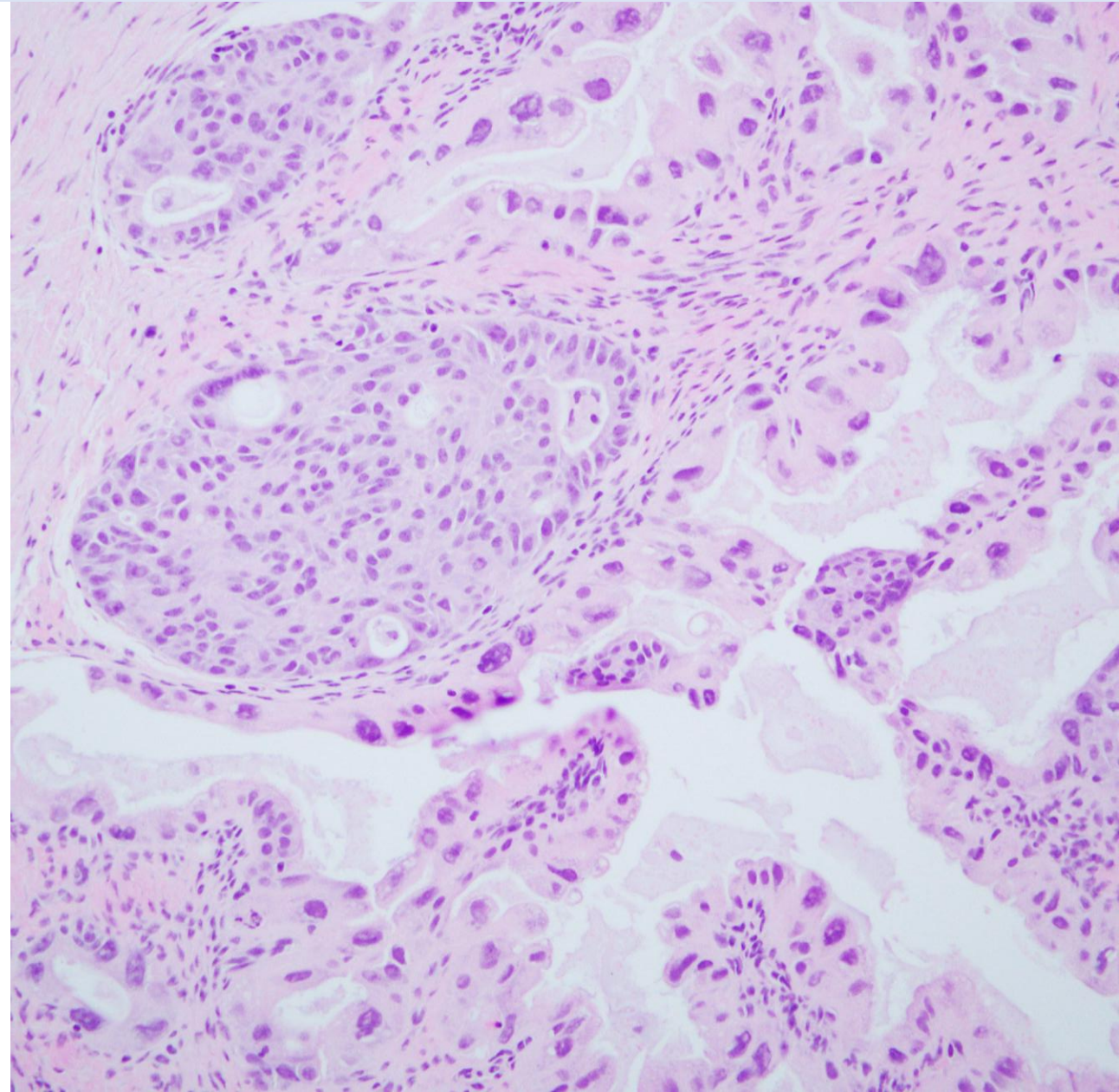
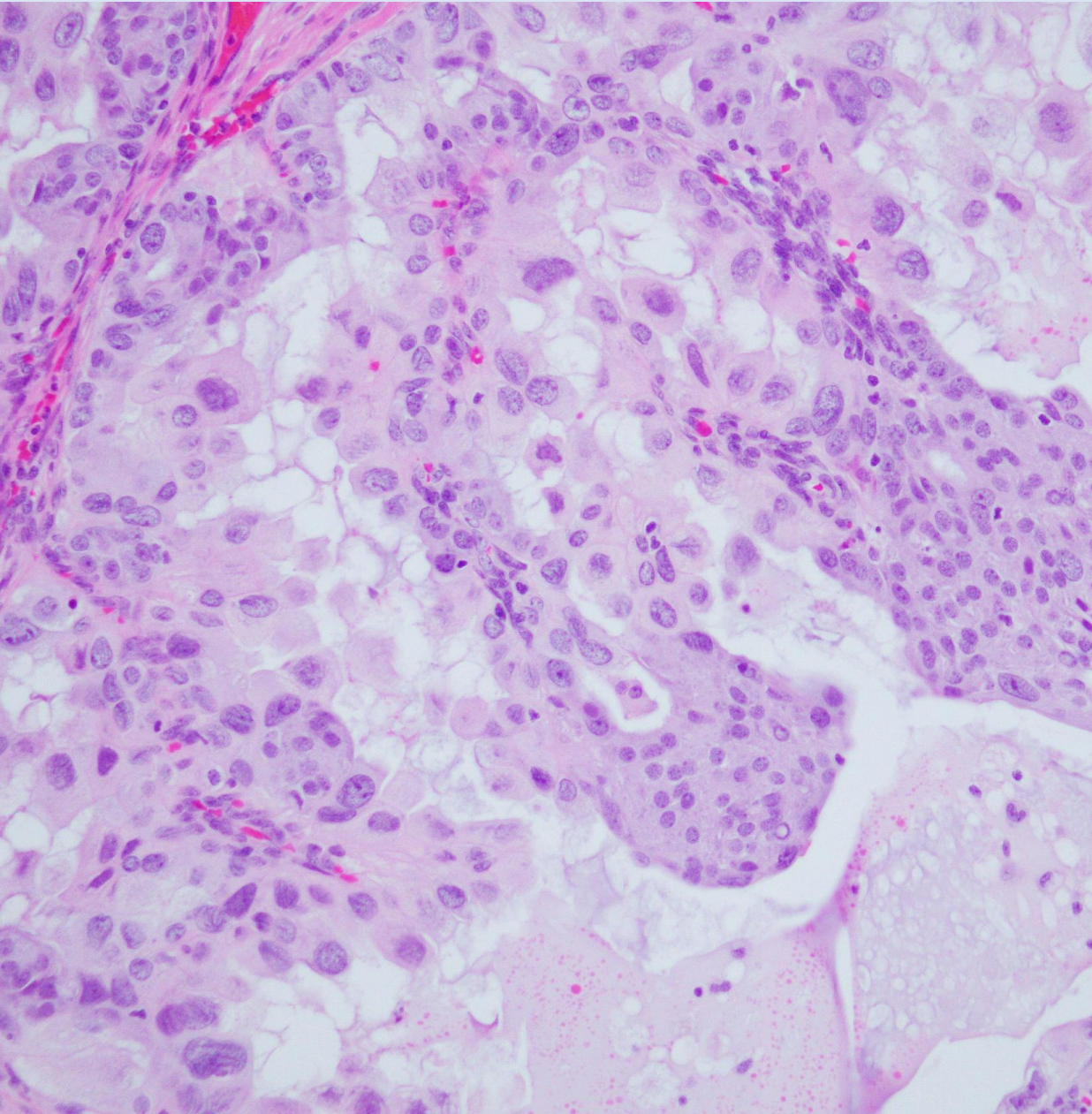
Endometrioid Carcinoma with Small Non-Villous Papillae



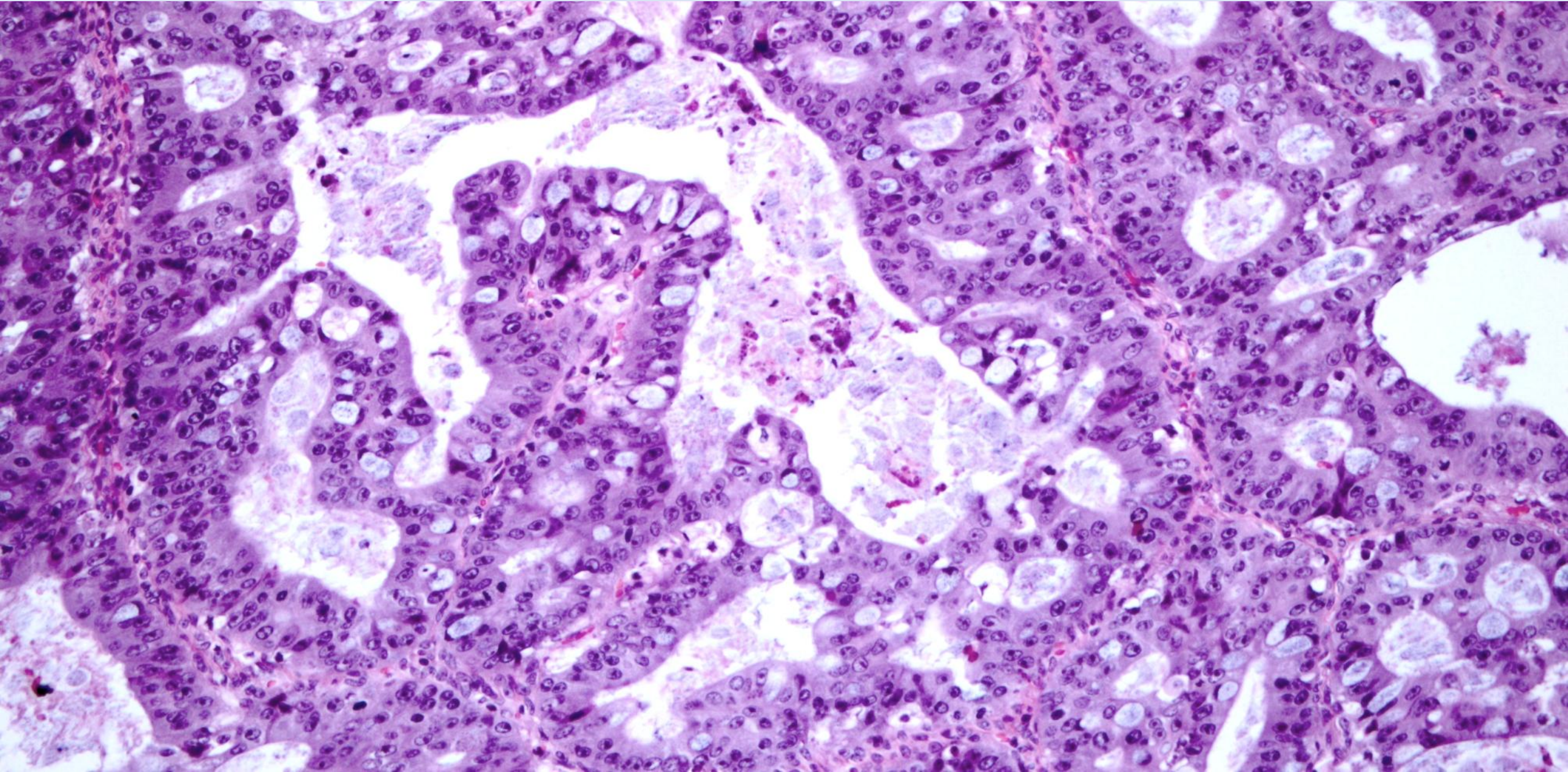
Endometrioid Carcinoma with Secretory Features



Endometrioid Carcinoma with Oxyphilic Cells and Arias-Stella Reaction



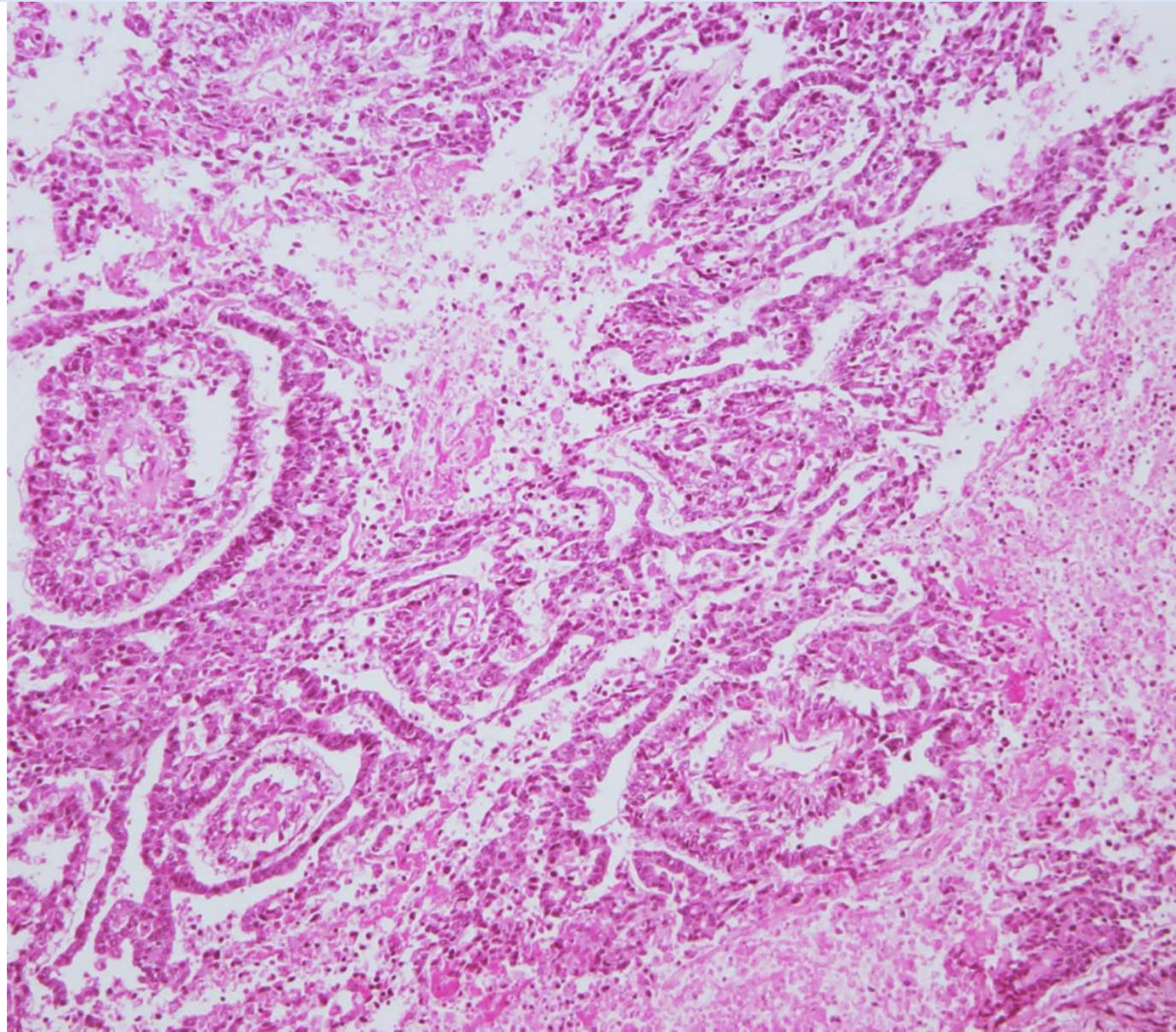
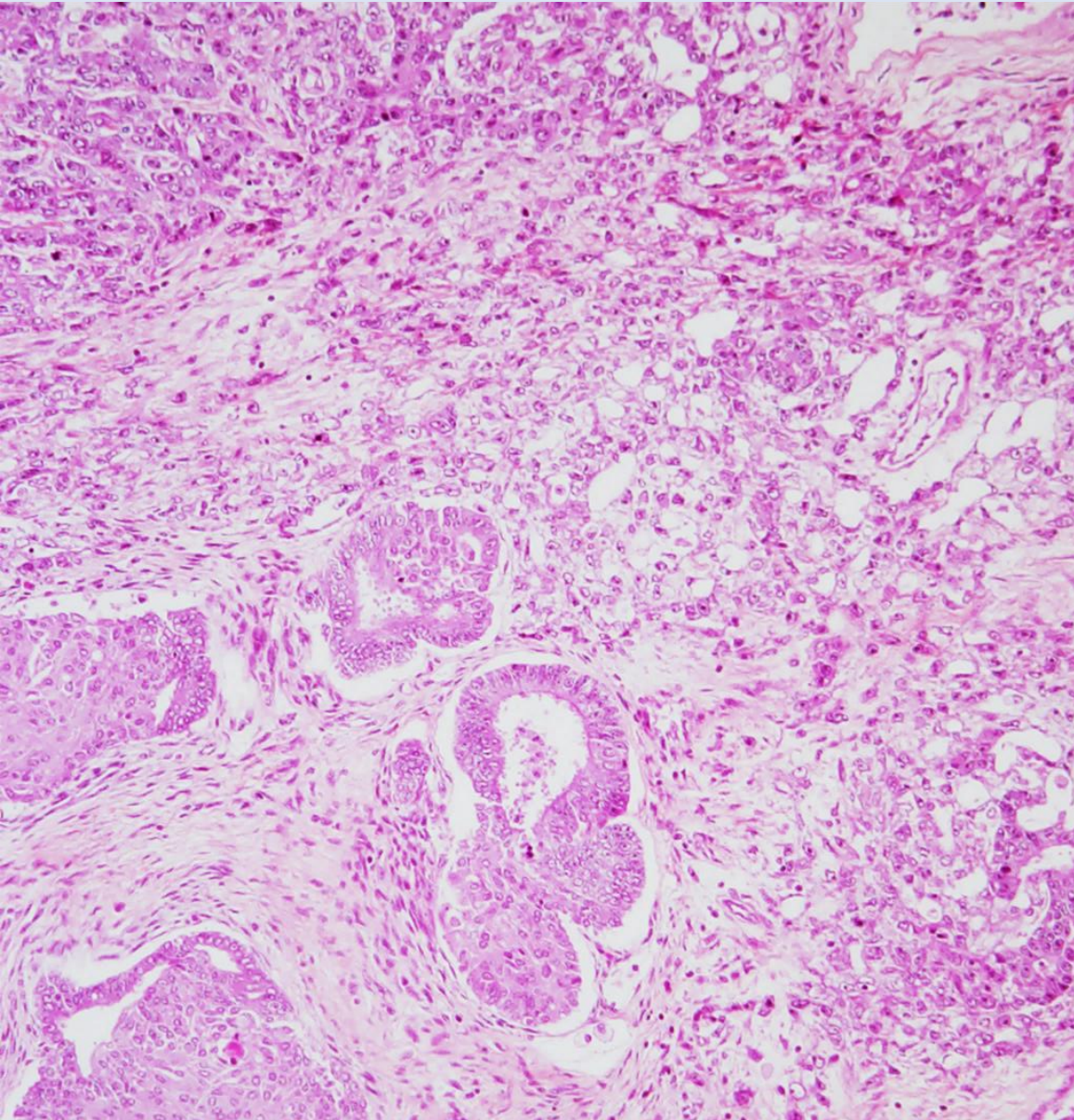
Mucin-Rich Endometrioid Carcinoma: Differentiate from Mucinous Carcinoma



Ovarian Endometrioid Carcinoma with Somatic Yolk Sac Differentiation (Fetal-Type Adenocarcinoma)

- Peri- or postmenopausal women
- Substantial AFP elevation
- Frequent benign endometrioid tumors in ipsilateral or contralateral ovary
- Frequently high stage
- Poor prognosis (poor response to chemotherapy)

Ovarian Endometrioid Carcinoma with Somatic Yolk Sac Differentiation (Fetal-Type Adenocarcinoma)



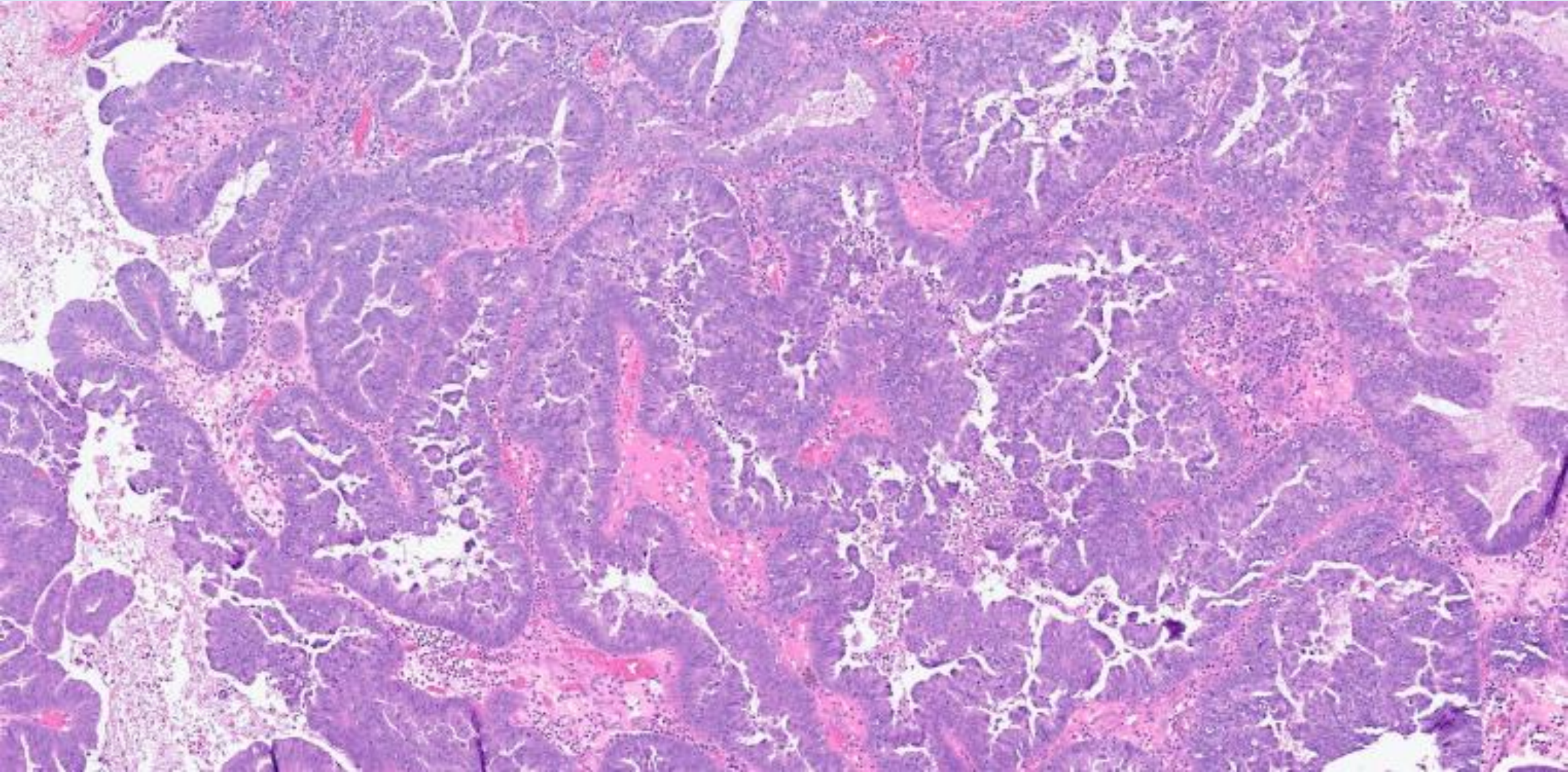
	<u>YST</u>	<u>EndCA</u>
Age	Young	Older
Fibromatous backgr	-	+
Squamous diff.	-	+
Endometriosis	-	+
Primitive nuclei	+	-
CK7	-*	+
EMA	-	+
Glypican-3	+	+/-
SALL4	+	-*
PAX8	- (25% +)	+

ENDOMETRIOID *vs* SEROUS CARCINOMA

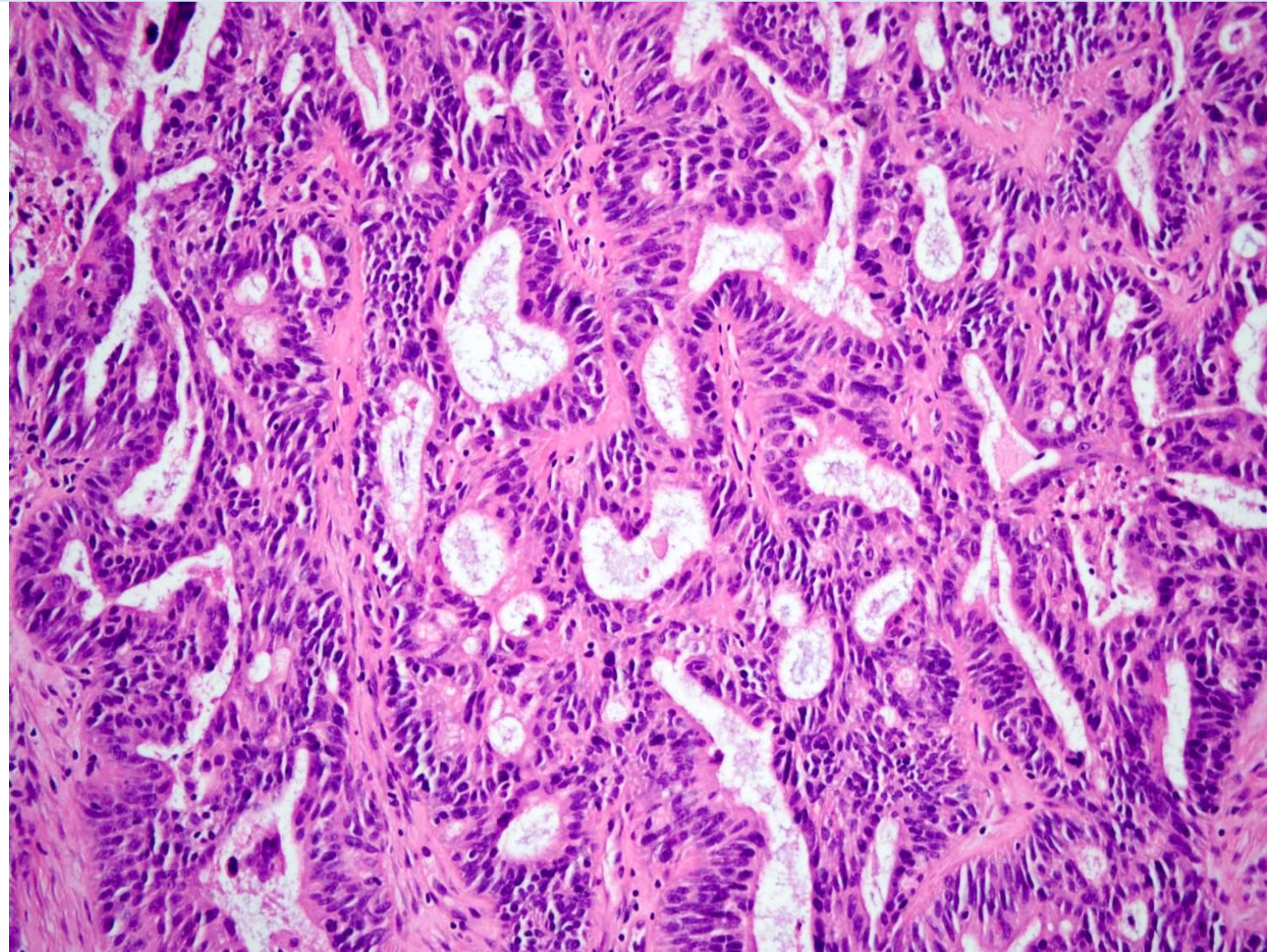
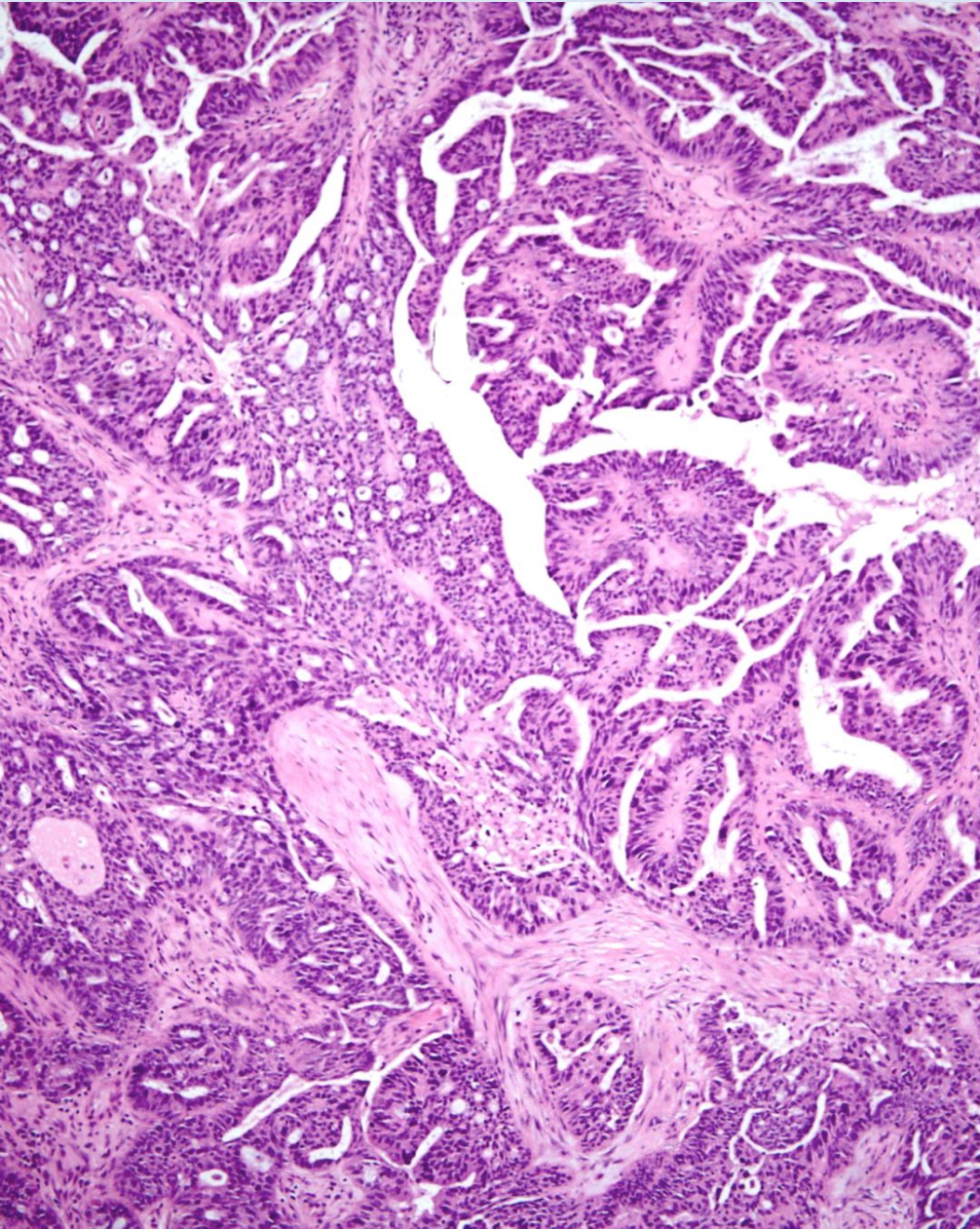
Problems in Differential Diagnosis:

- Endometrioid carcinoma with papillary formation
- Pseudoendometrioid morphology in serous carcinoma
- Solid growth in both

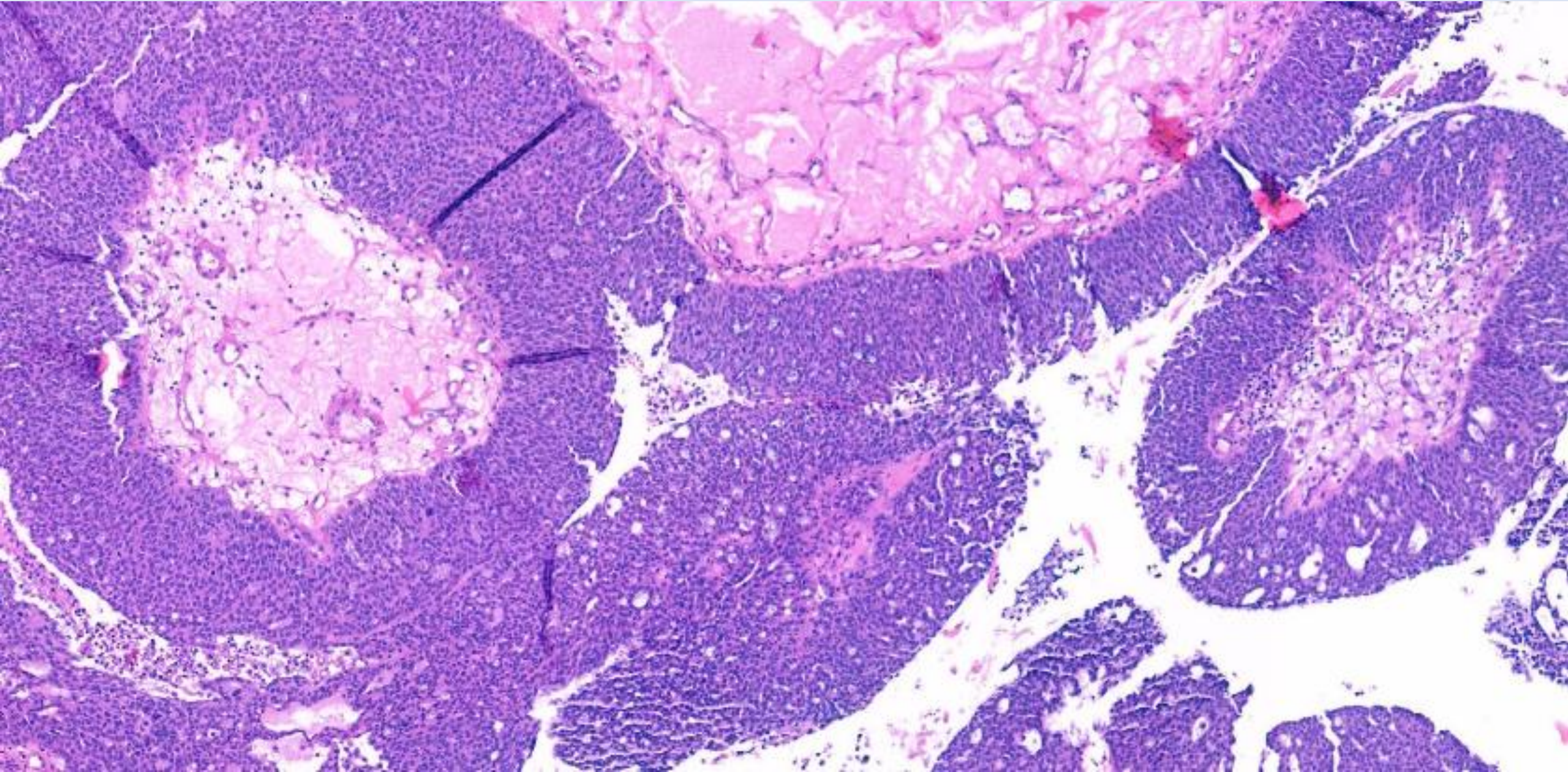
Endometrioid Carcinoma with Papillary Formation



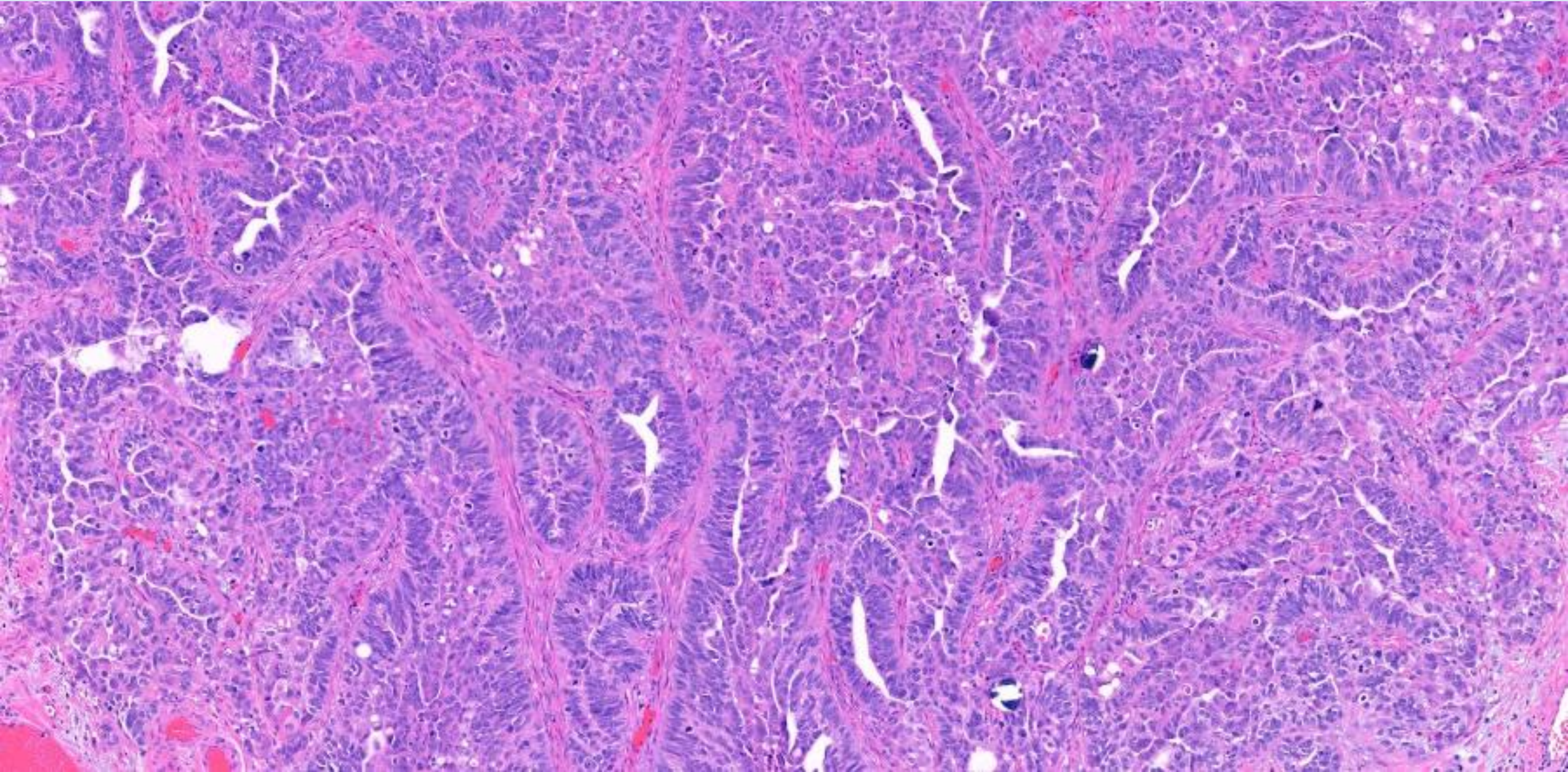
Pseudoendometrioid Morphology in High-Grade Serous Carcinoma



Transitional to Typical Serous Morphology



Transitional to Typical Serous Morphology



High-Grade Serous vs G3 Endometrioid Carcinoma

- PAX8 (both +)
- ER α and PR (both +)
- p16 (diffuse: serous > endometrioid; patchy favors endometrioid)
- p53 mutant pattern (serous: nearly all, endometrioid: subset)
- **WT1:**
 - ✓ Strong and diffuse in serous
 - ✓ Variable but can be extensive in endometrioid
- $\pm$ **MMR, PTEN, or ARID1A** in endometrioid carcinoma

Köbel et al. Histopathology. 2014;64:1004-13

Bennett et al. Am J Surg Pathol. 2016;40:656-63

Köbel et al. Int J Gynecol Pathol. 2019;38(4):353-62

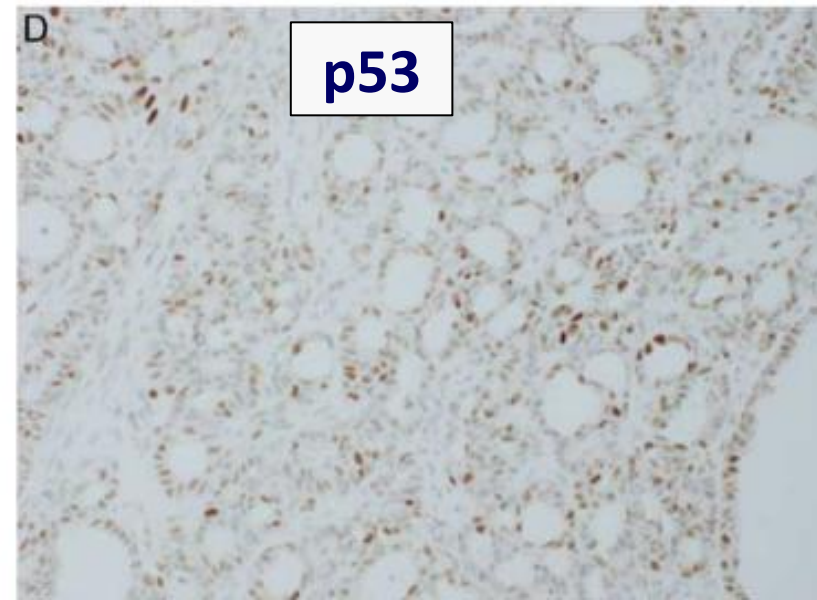
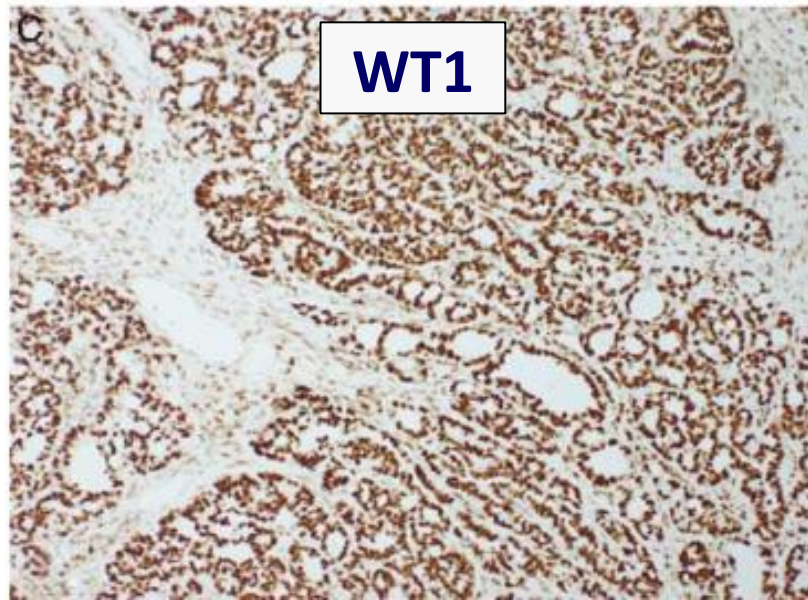
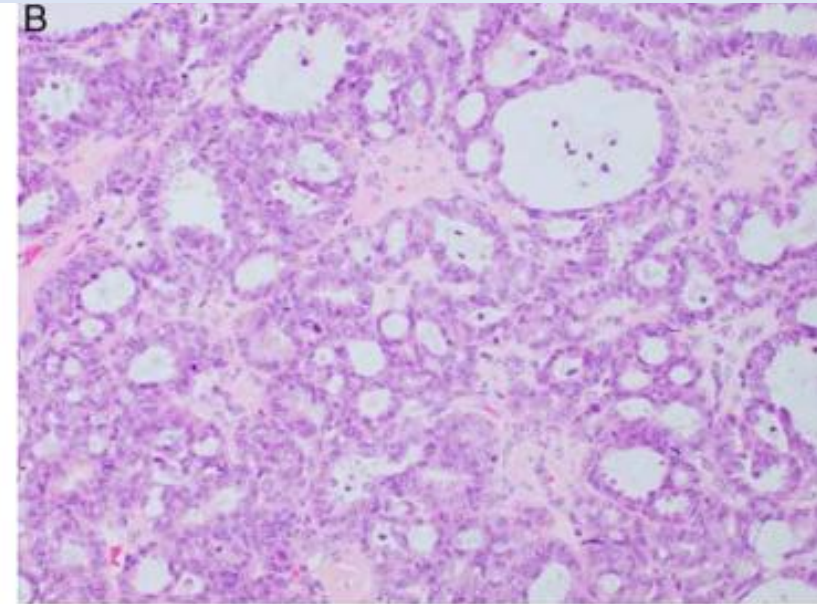
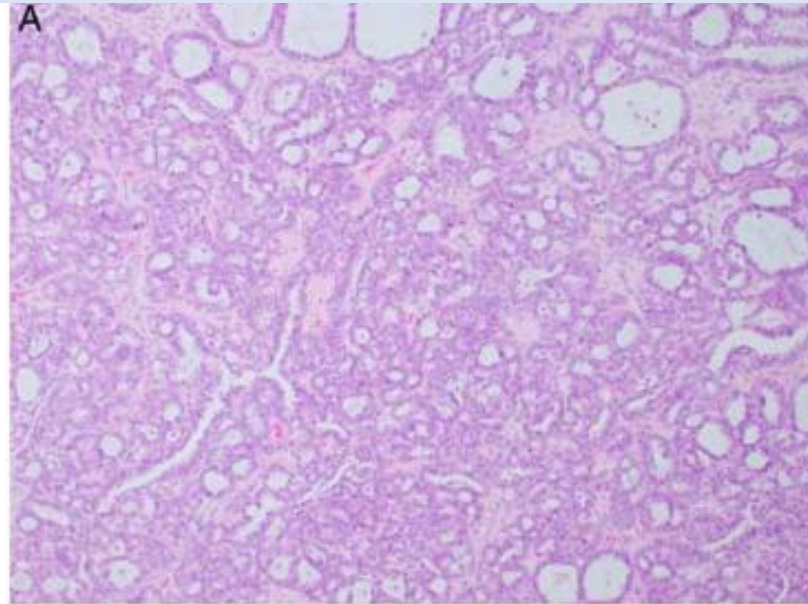
McCluggage & Stewart. Semin Diagn Pathol. 2021;38(3):199-211

Irshaid et al. Mod Pathol. 2023;36(5):100123

WT1-Positive Ovarian Endometrioid Tumors

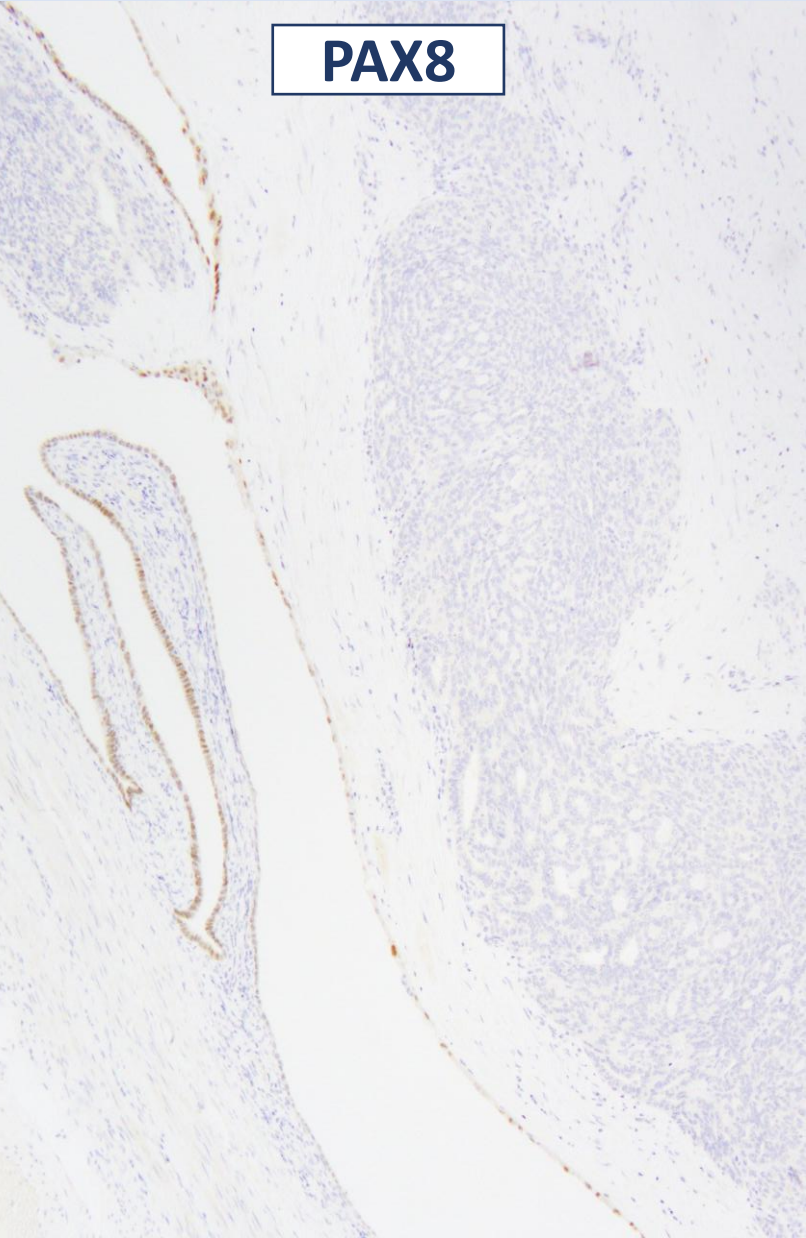
**Diffuse WT1 expression
may be seen in low-
grade tumors**

**Typically, wild-type p53
and patchy p16**

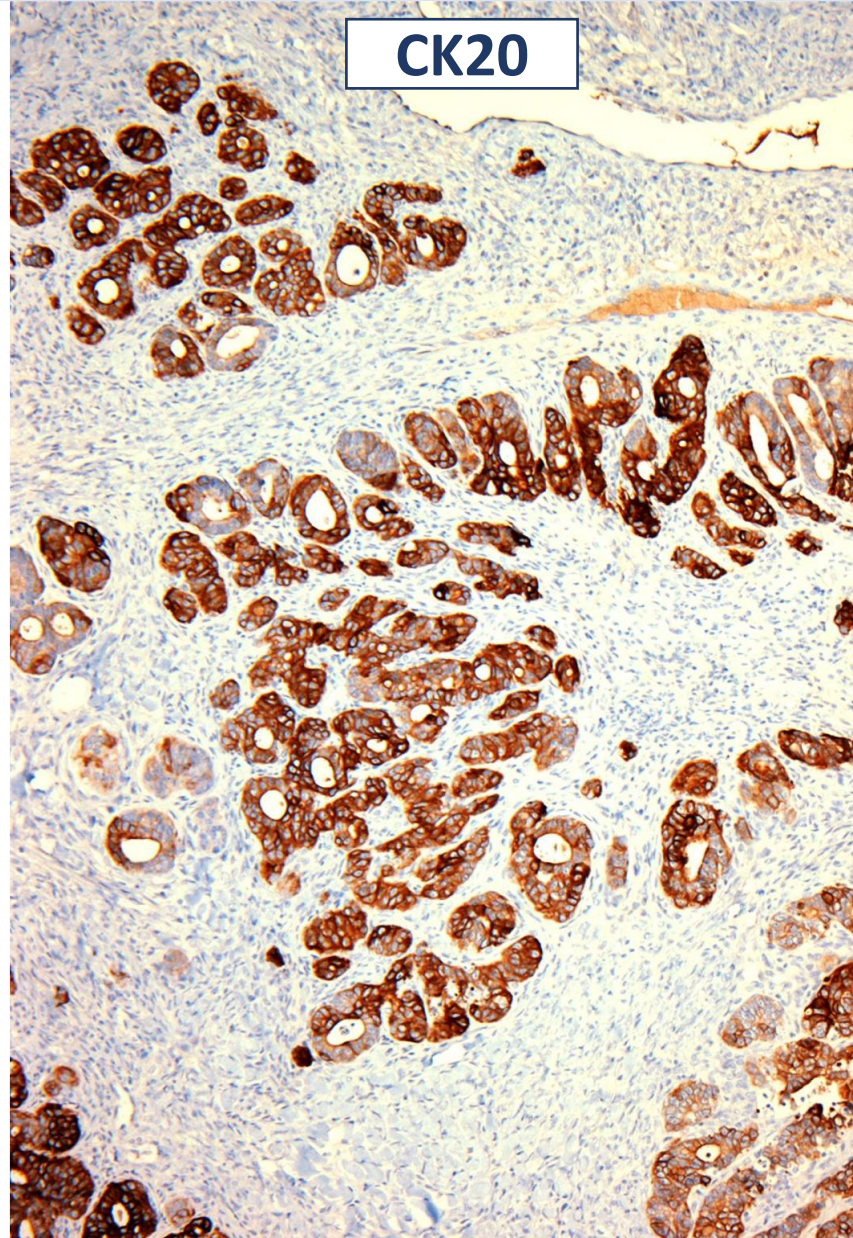


Endometrioid Carcinomas with Aberrant Immunohistochemical Profile

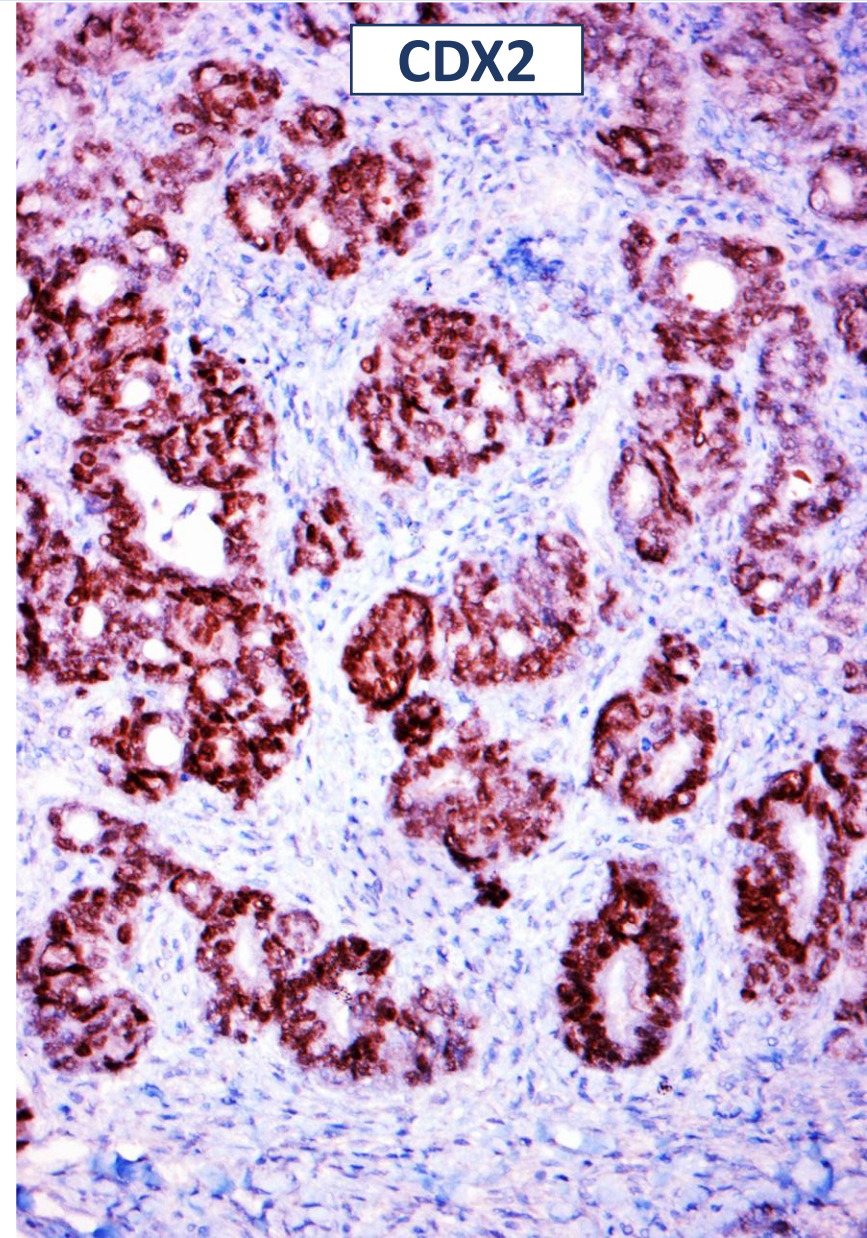
PAX8



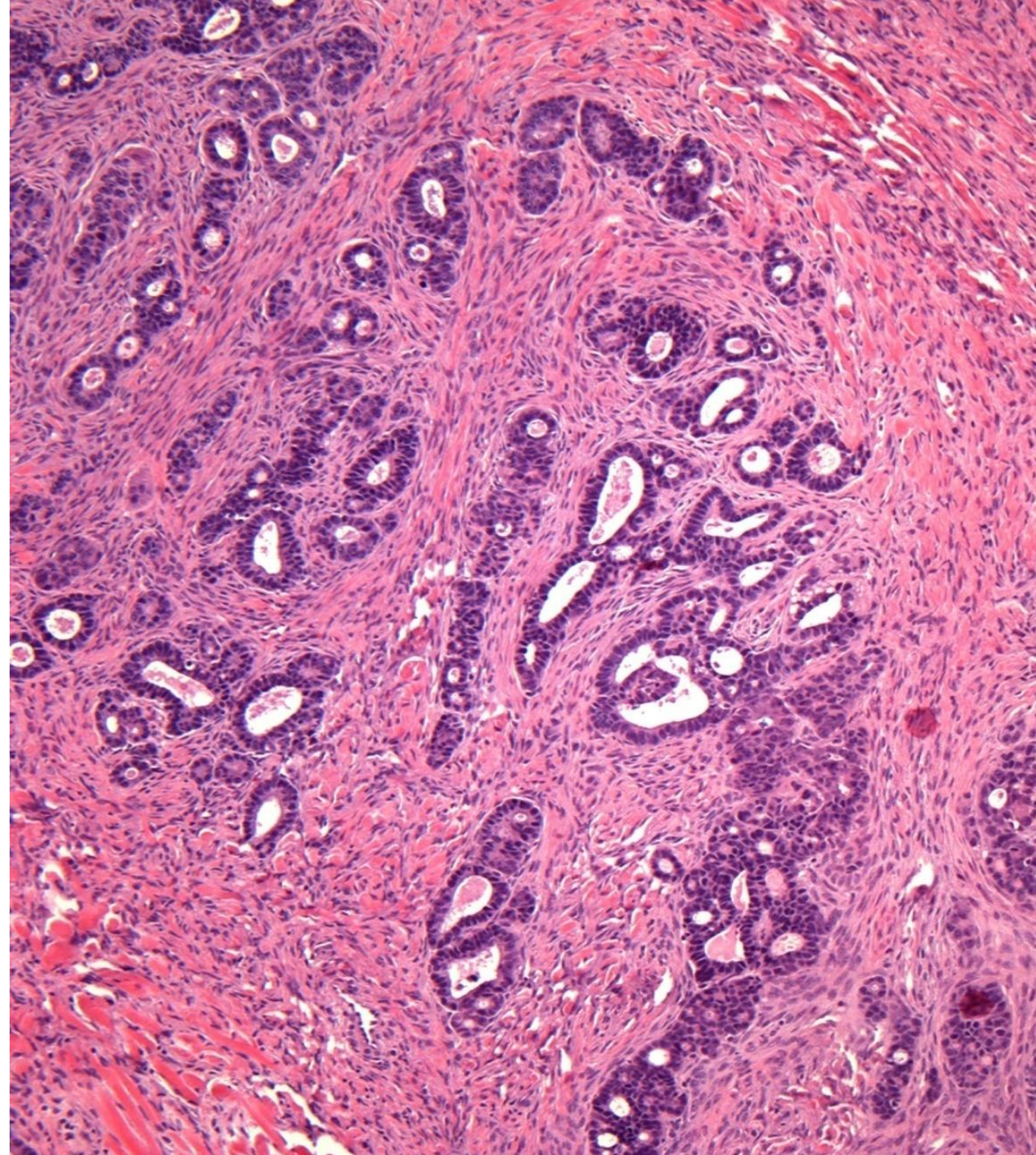
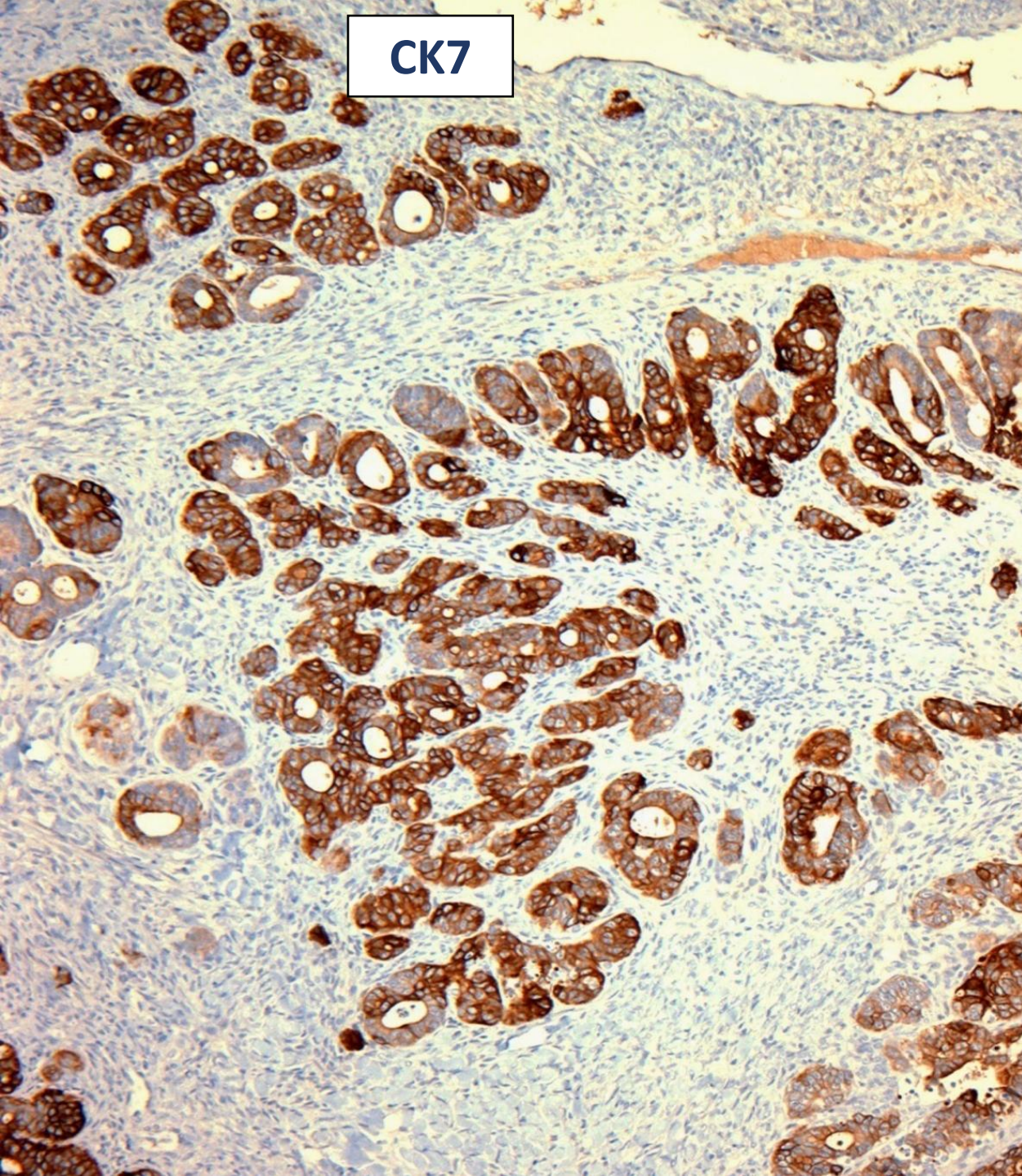
CK20

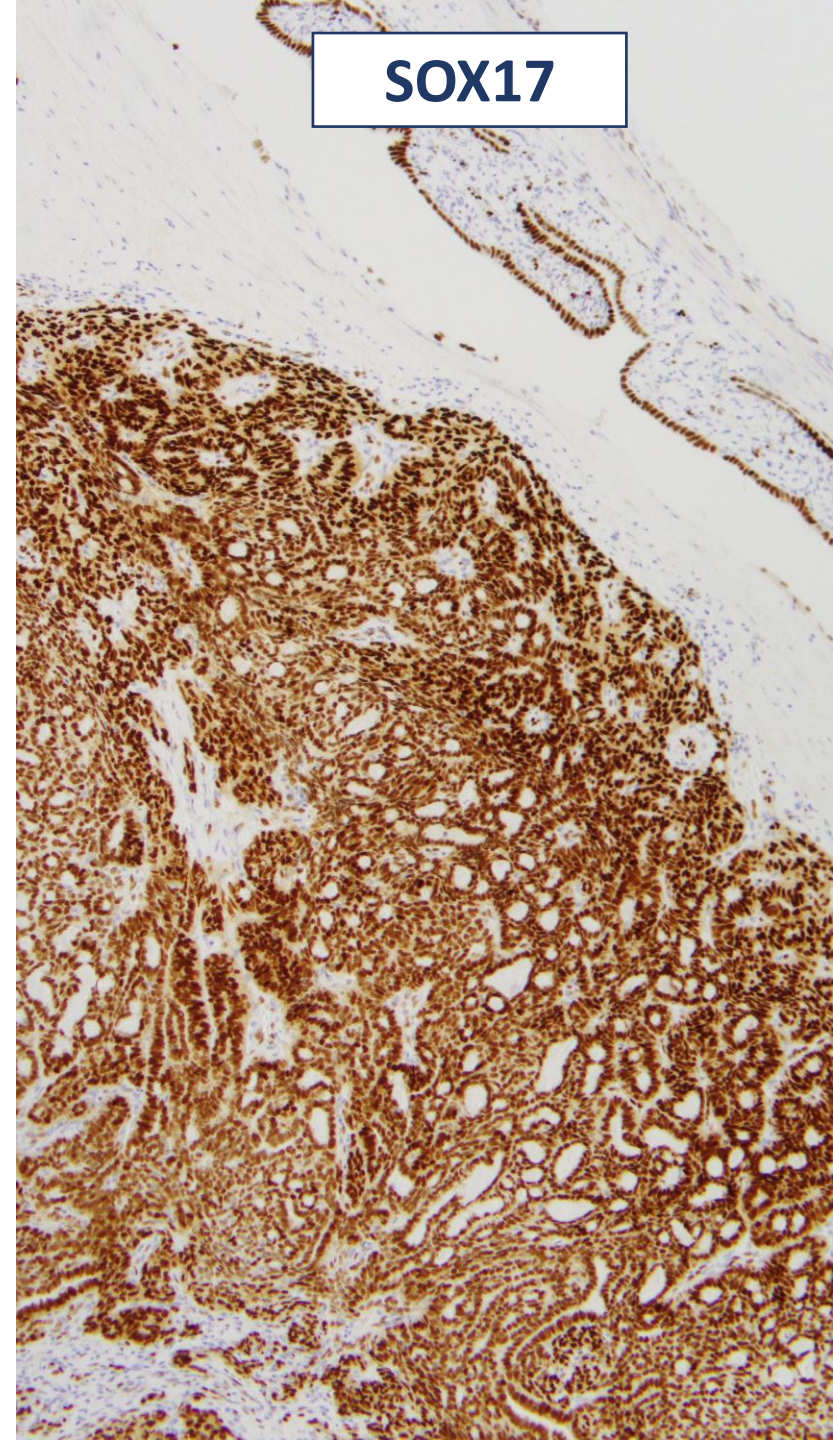
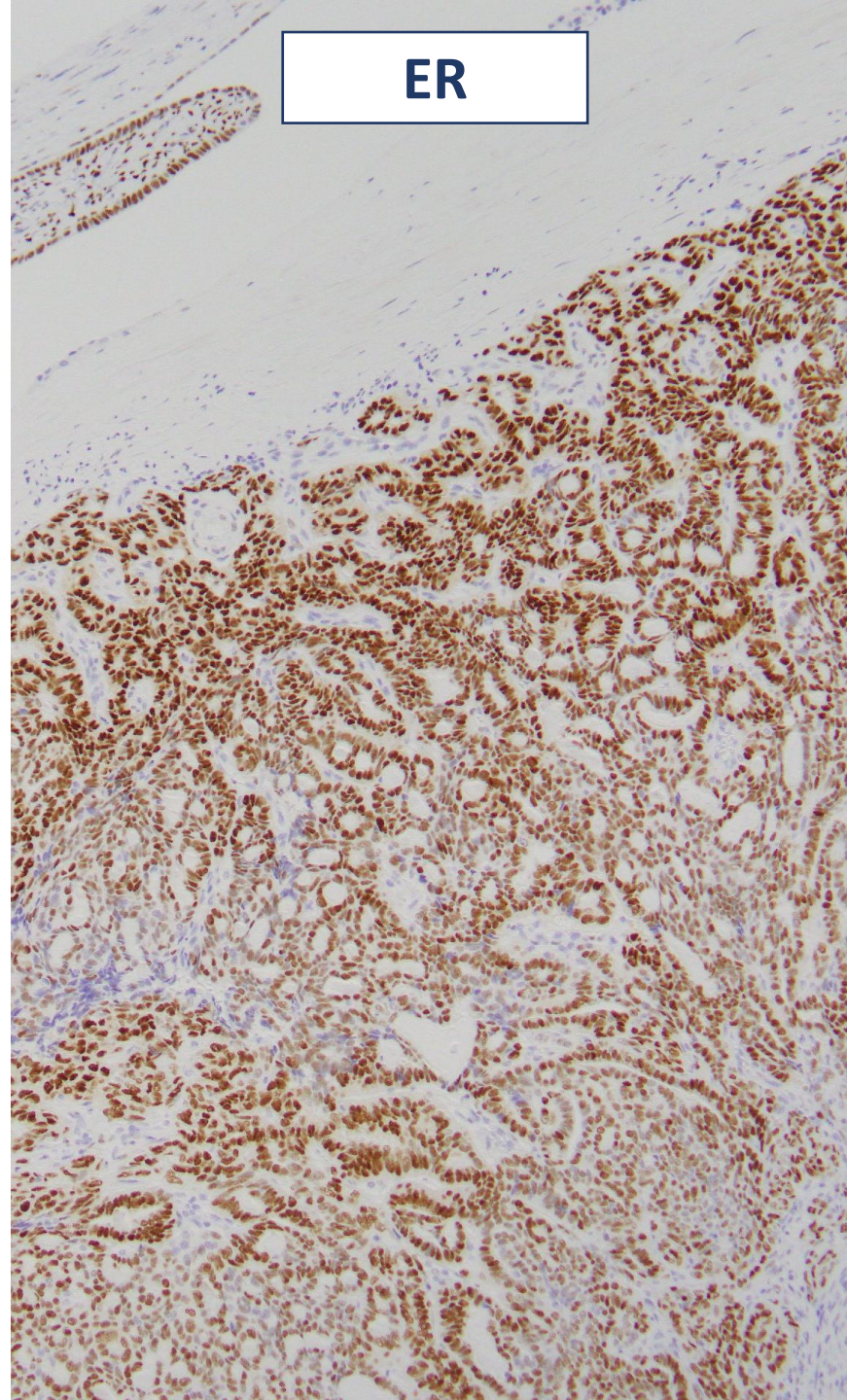
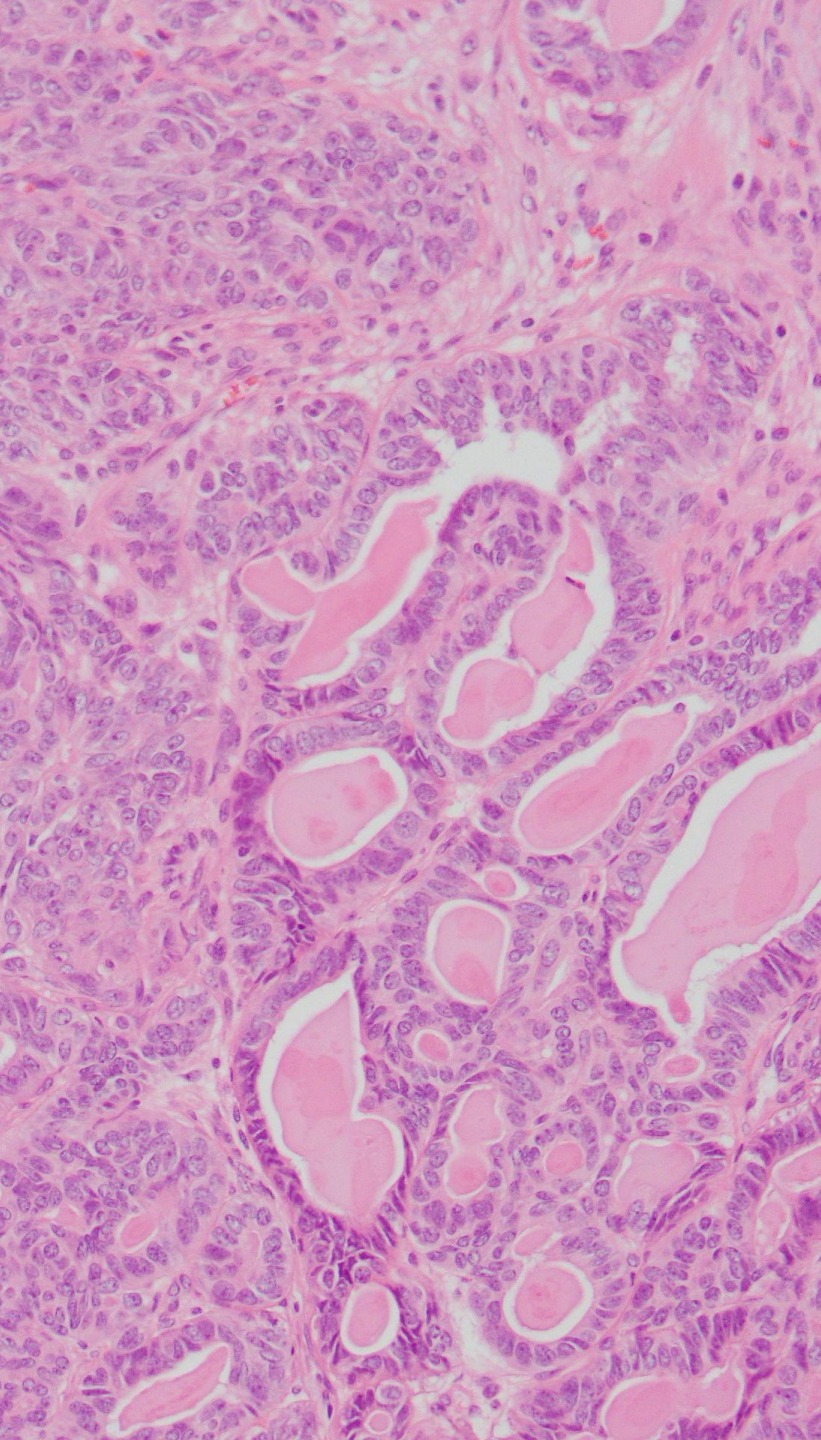


CDX2



CK7

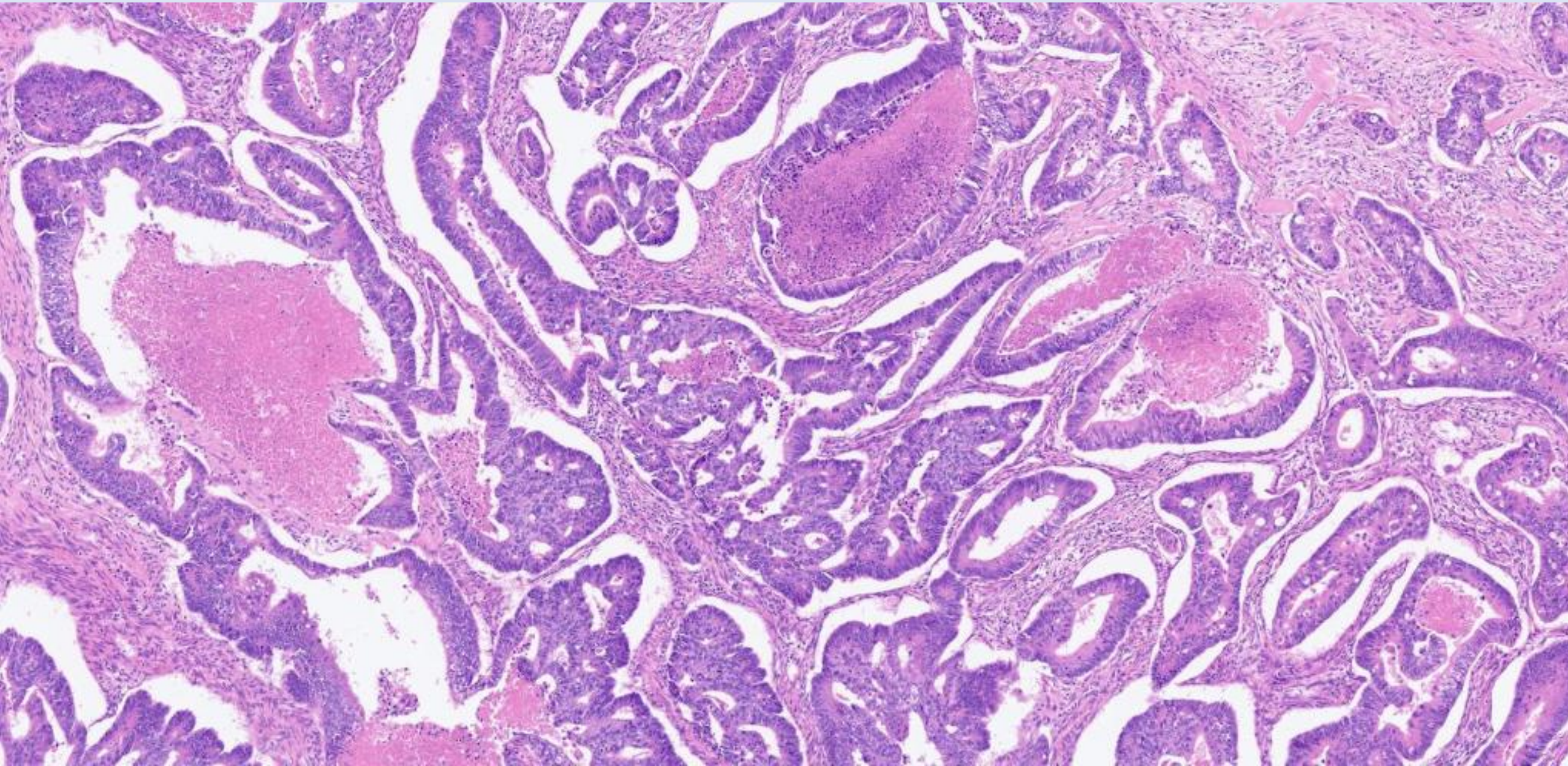


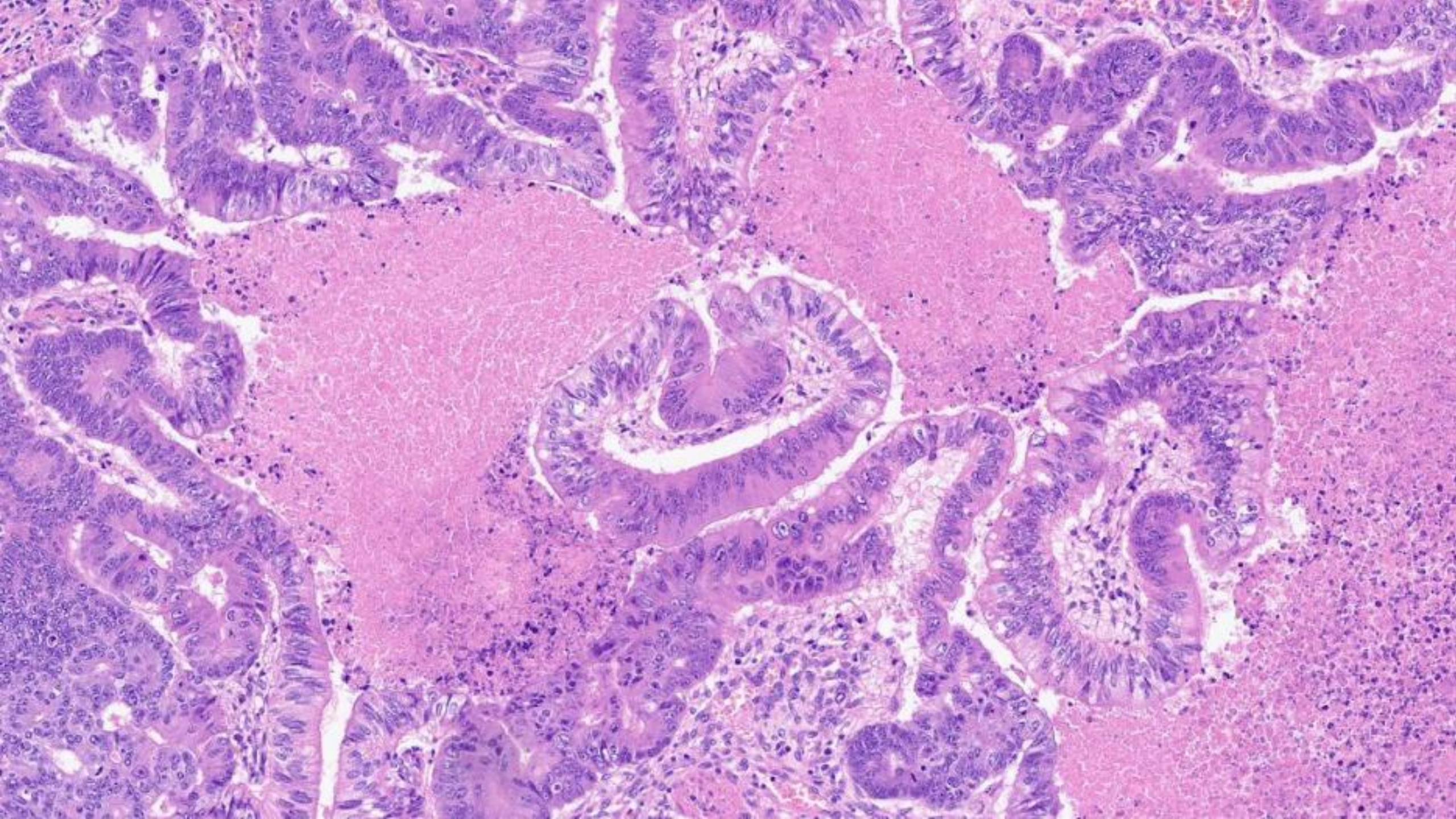


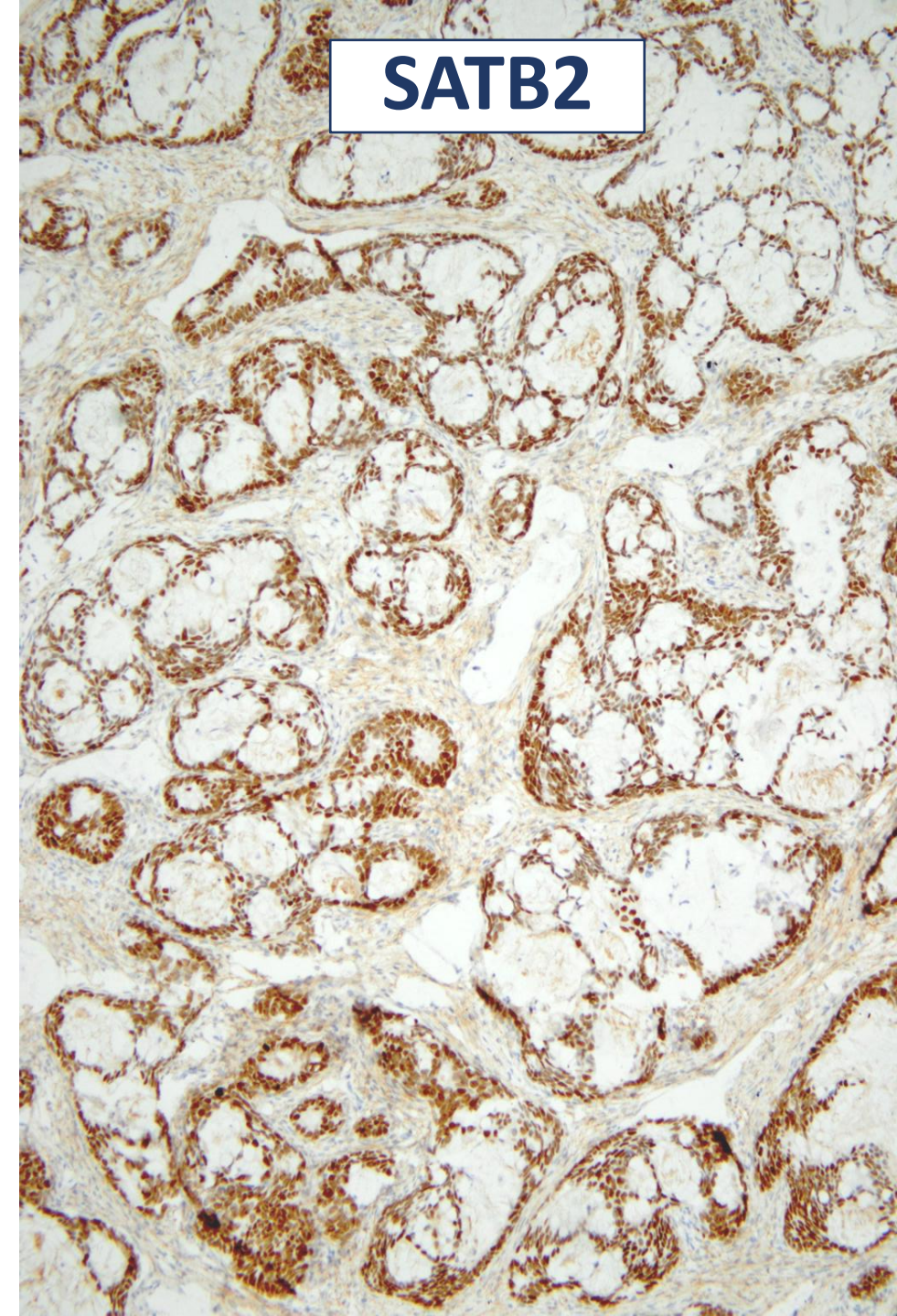
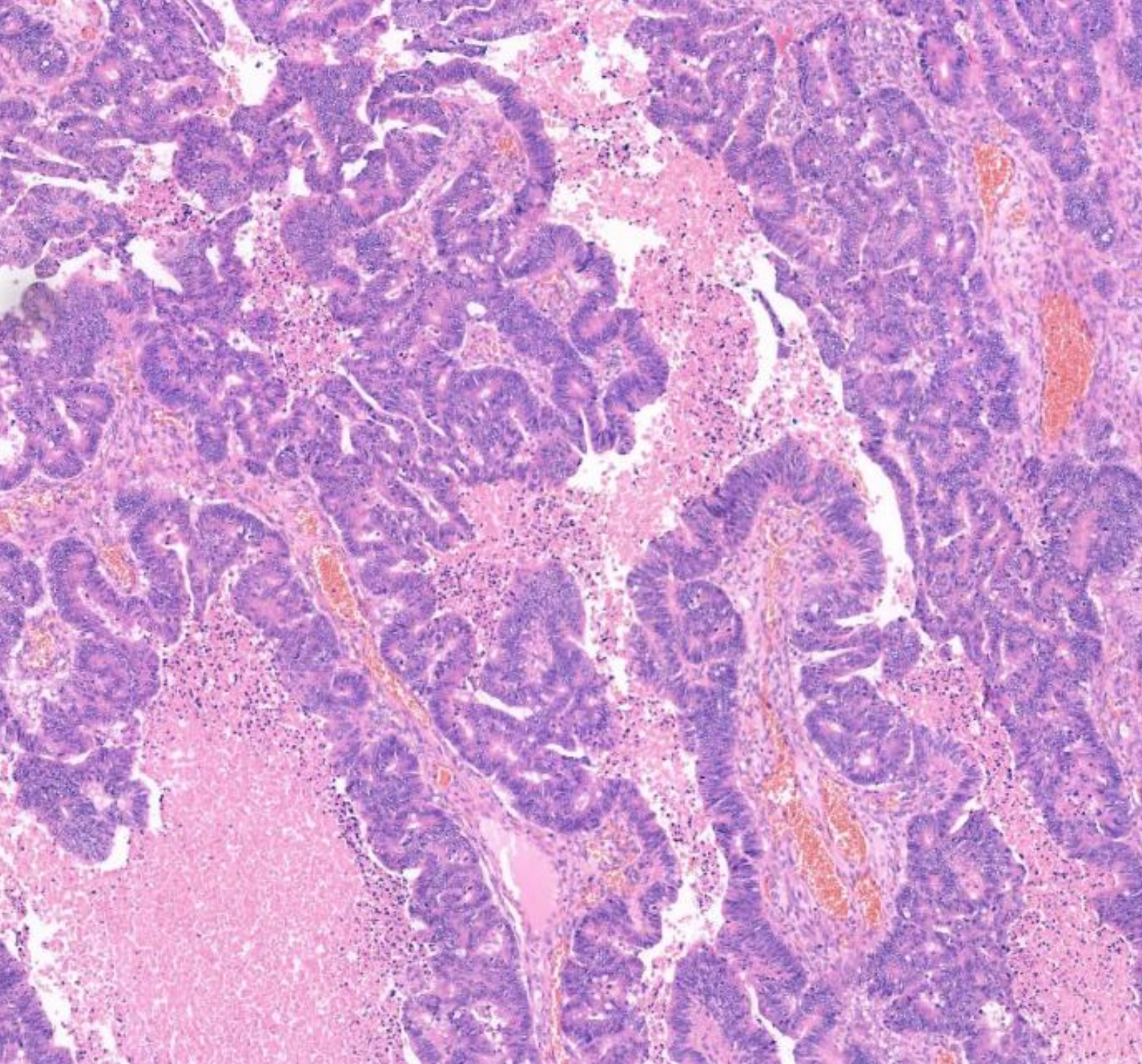
SOX17: A Highly Sensitive and Specific Marker for Ovarian and Endometrial Carcinomas

Cancer type	Negative	Positive			Total
		Low	Intermediate	High	
SOX17					
Serous, total	7 (2.5%)	8 (3%)	42 (15%)	220 (79.5%)	277
Low grade	0	0	4	12	16
High grade	7	8	38	208	261
Mucinous	11 (100%)	0	0	0	11
Endometrioid	2 (10%)	0	3 (15%)	15 (75%)	20
Clear cell	0	0	2 (25%)	6 (75%)	8
Carcinosarcoma	5 (45%)	0	0	6 (55%)	11
PAX8					
Serous, total	9 (3%)	11 (4%)	51 (18%)	206 (74%)	277
Low grade	0	0	5	11	16
High grade	9	11	46	195	261
Mucinous	8 (73%)	1 (9%)	1 (9%)	1 (9%)	11
Endometrioid	2 (10%)	1 (5%)	6 (30%)	11 (55%)	20
Clear cell	0	0	0	8 (100%)	8
Carcinosarcoma	5 (45%)	0	1 (9%)	5 (45%)	11

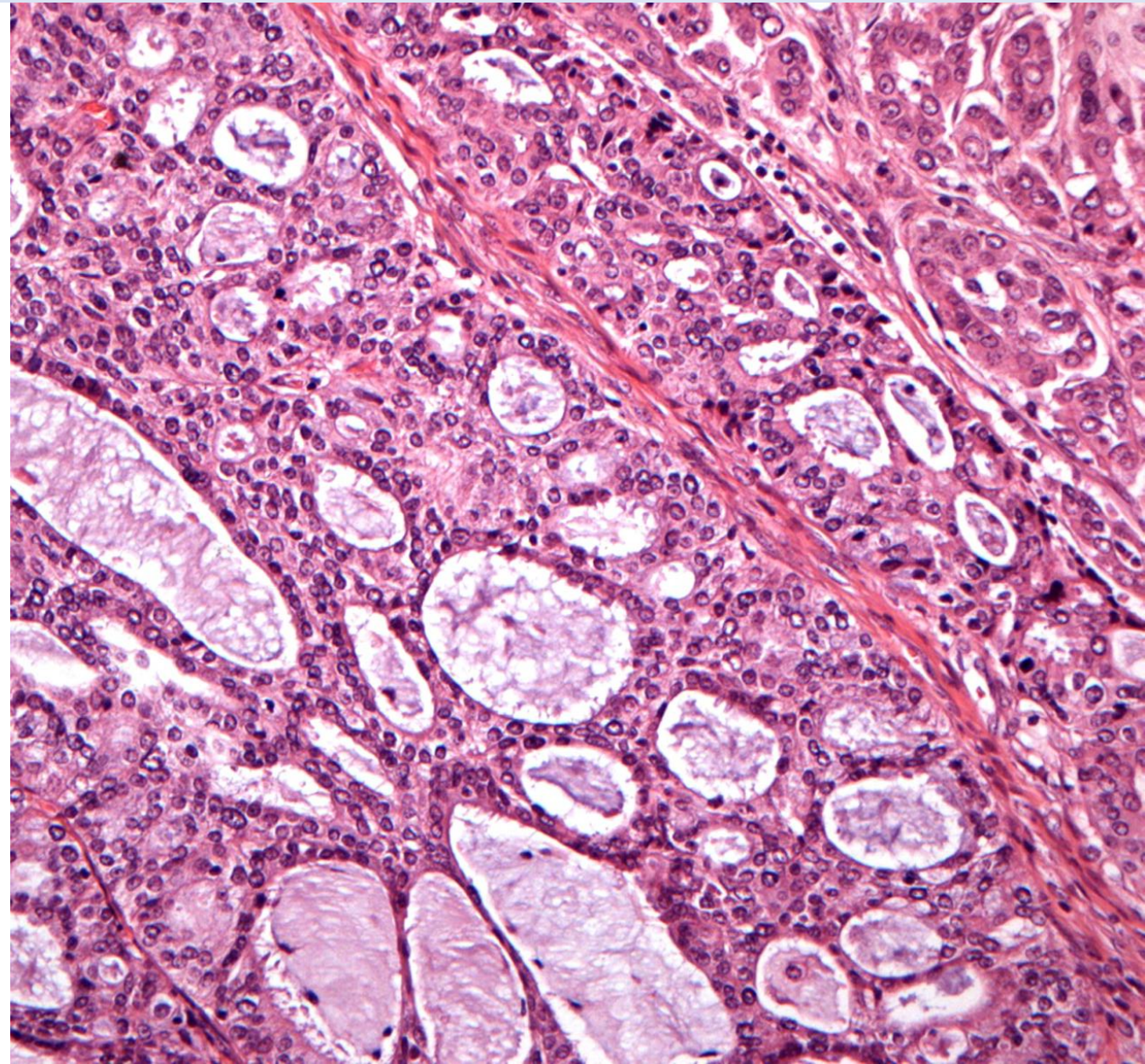
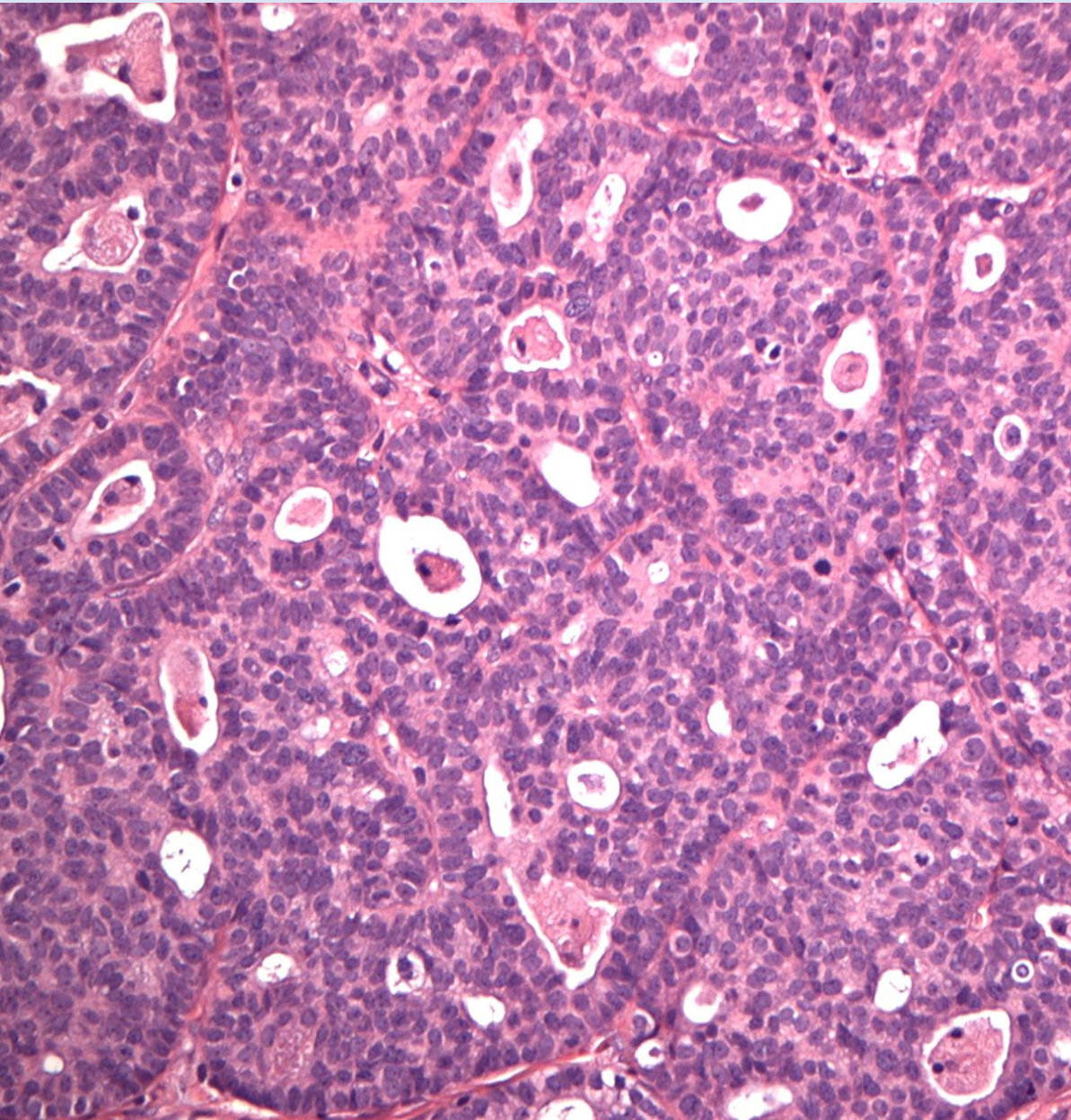
Metastatic Colonic Carcinoma to Ovary







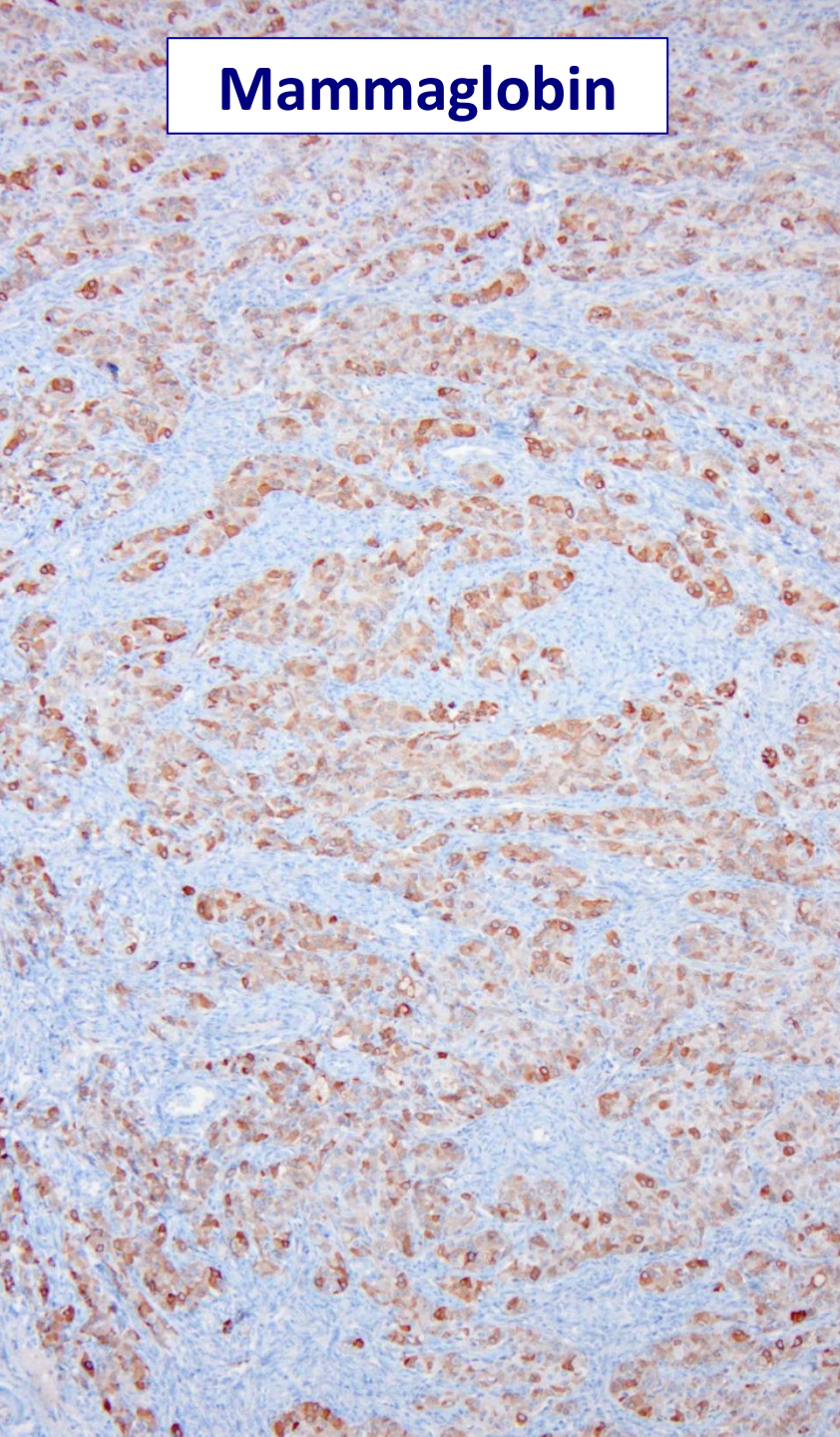
Breast Carcinoma vs Endometrioid Carcinoma



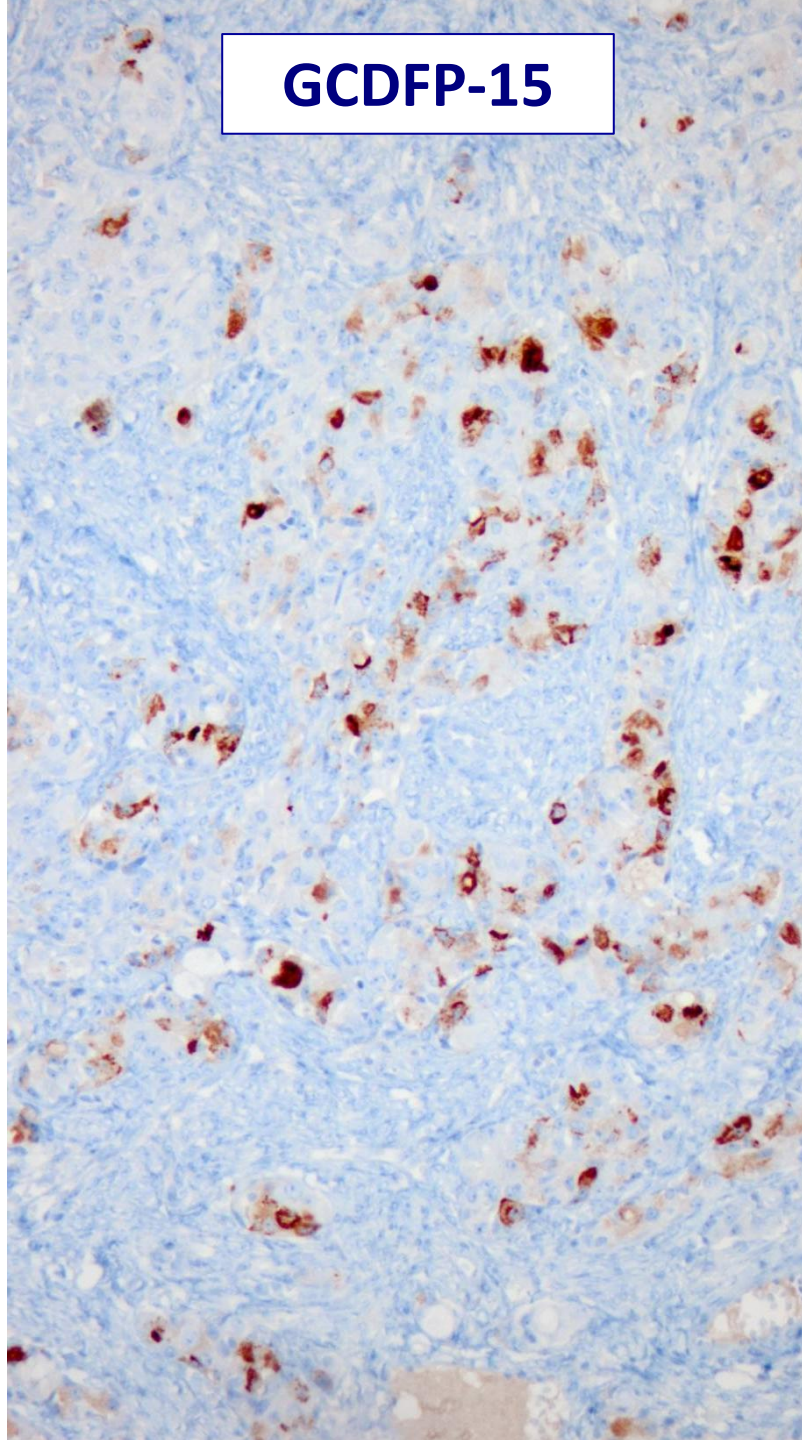
A GCDFP-15+ Tumor in the Ovary Is Almost Certainly of Breast Origin; A GCDFP-15- Tumor Does Not Exclude A Breast Primary

	<u>BREAST</u>	<u>SEROUS</u>	<u>ENDOMETRIAL</u>
CK7	+	+	+
CK20	-	-	-
GCDFP-15	+ (50%)	-	-/+
Mammaglobin	+/- (45%)	-	-/+
GATA3	+	-/focal	- (exceptions)
TRPS1	+	-/+	-/+
WT-1	-/+ (rare)	+	-/+
PAX 8	-	+	+
SOX17	-	+	+

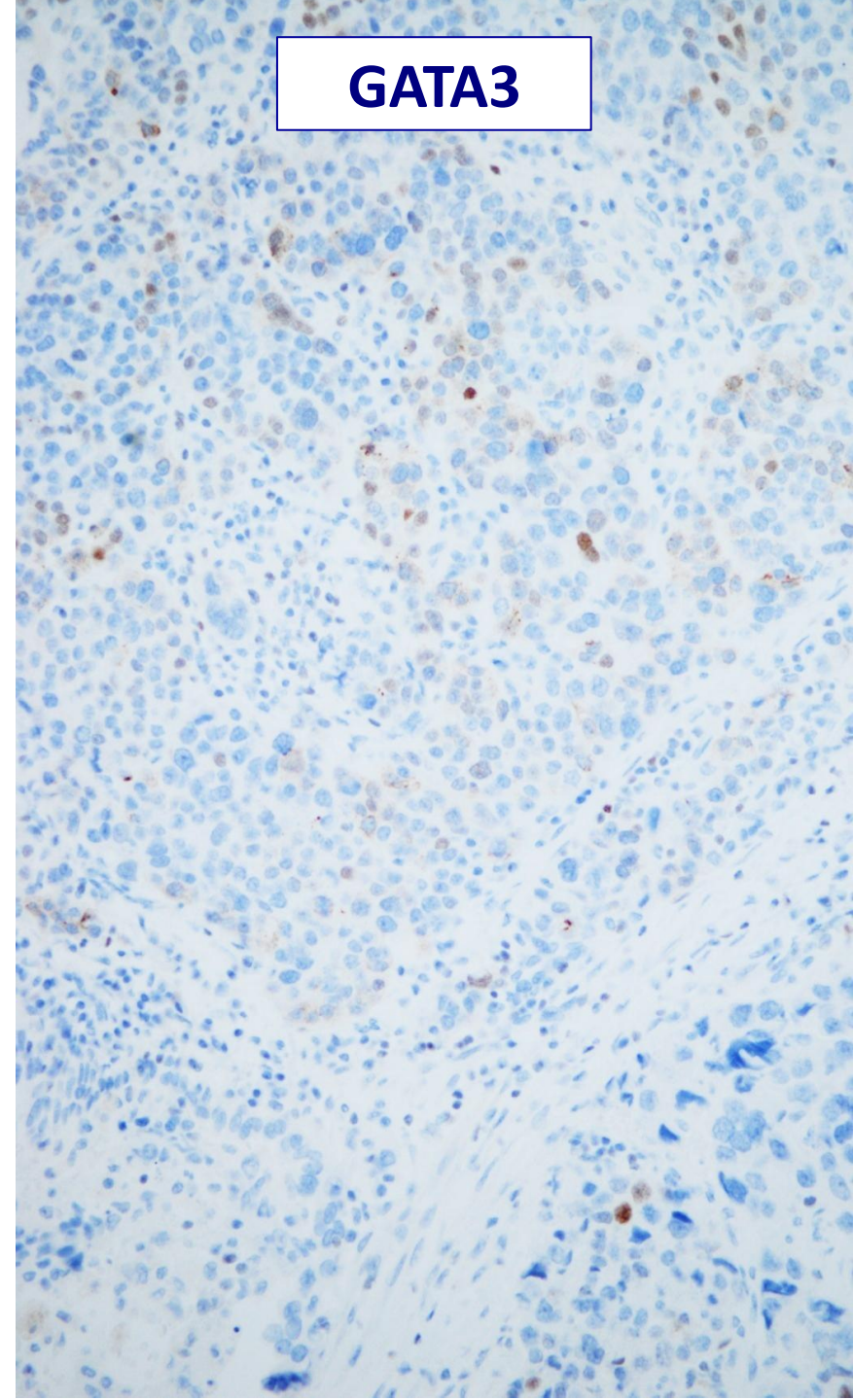
Mammaglobin



GCDFP-15



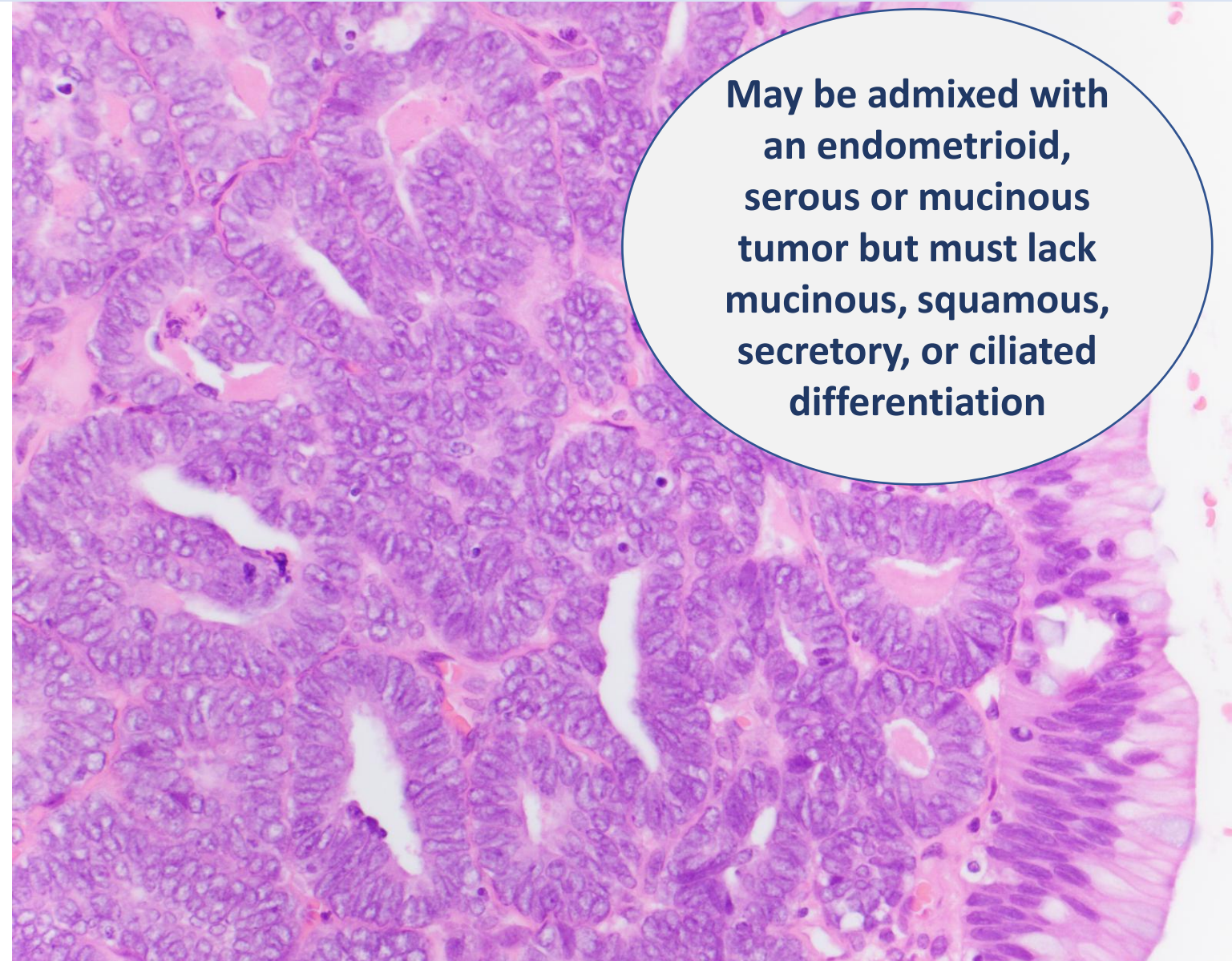
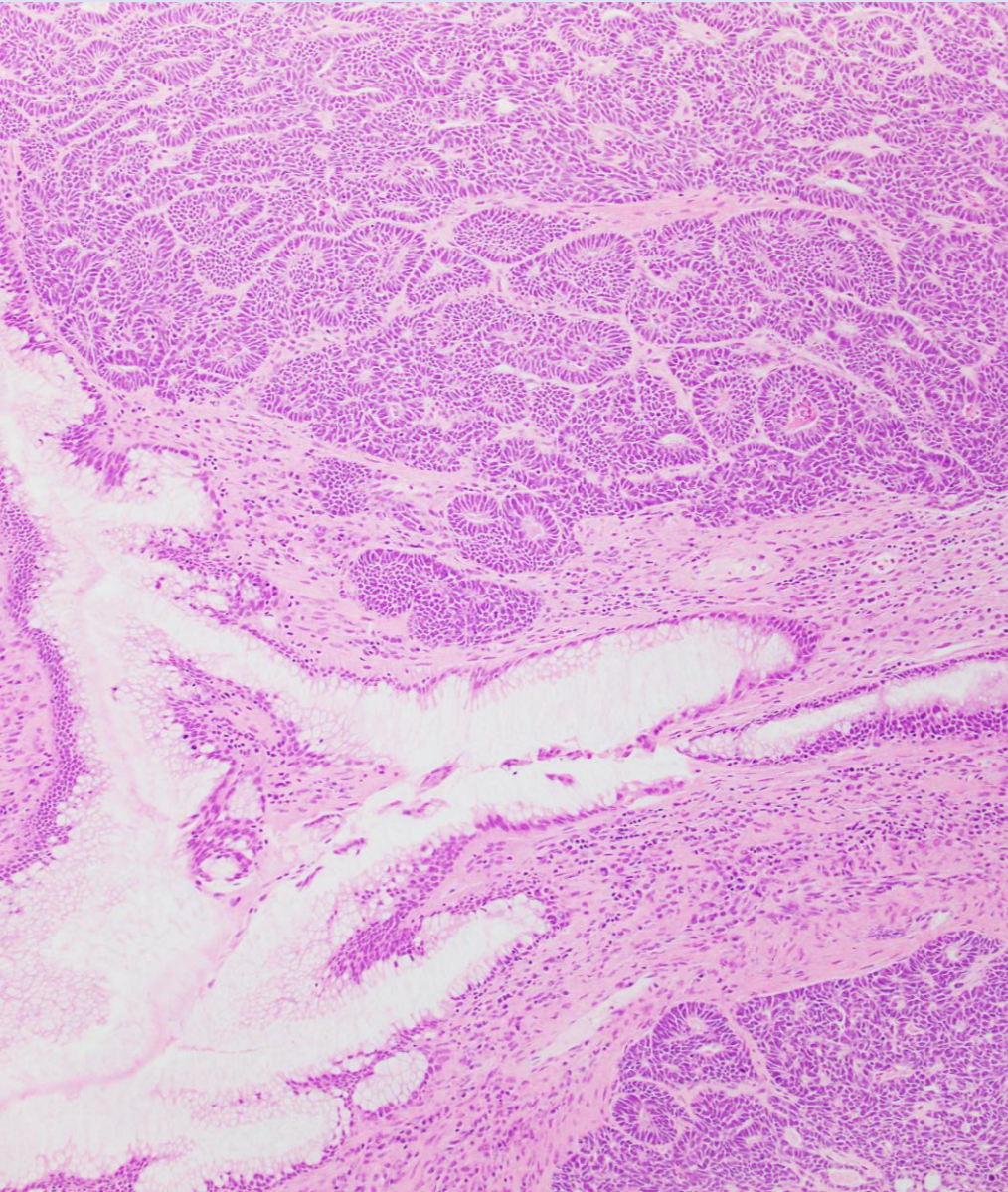
GATA3



Diagnostic Pitfalls

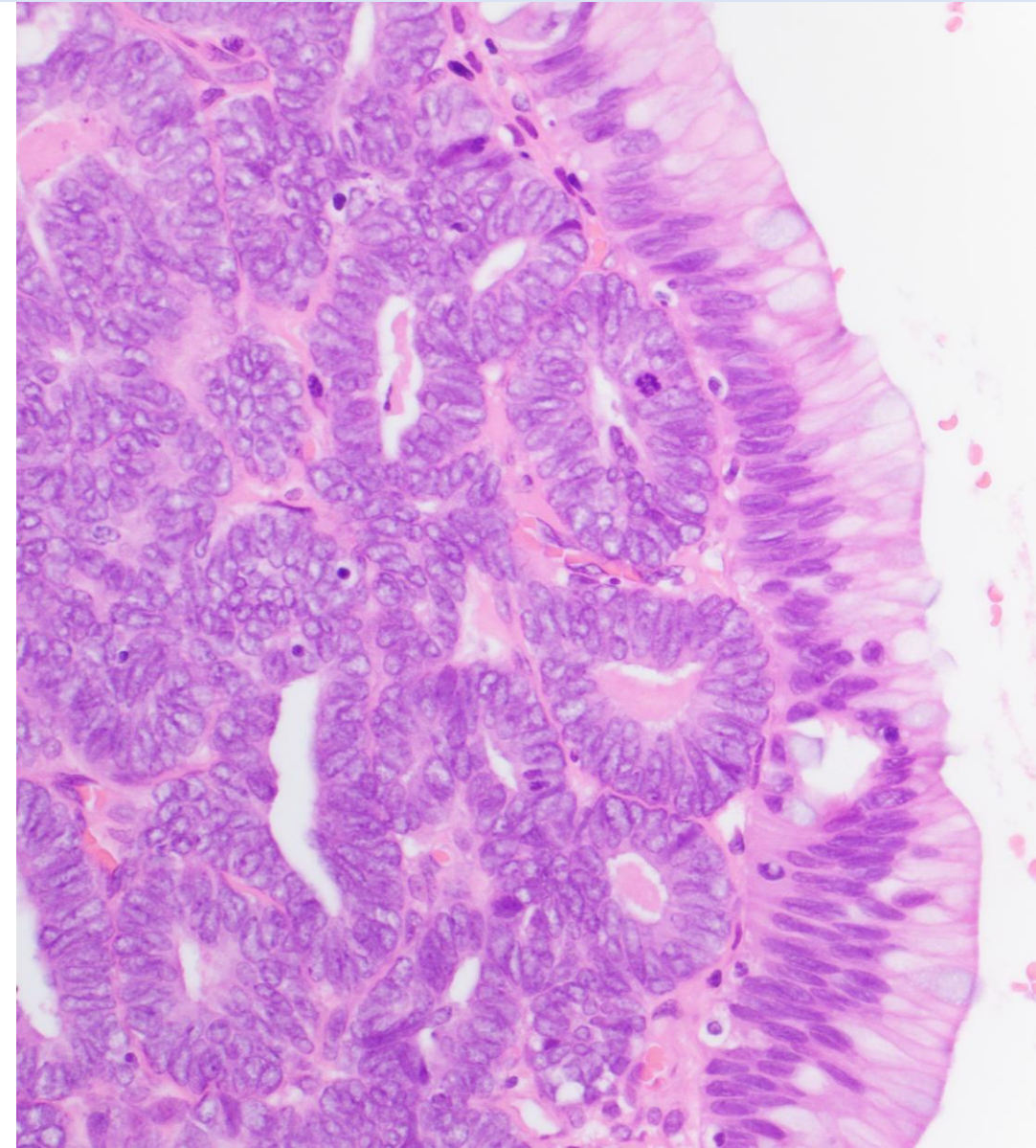
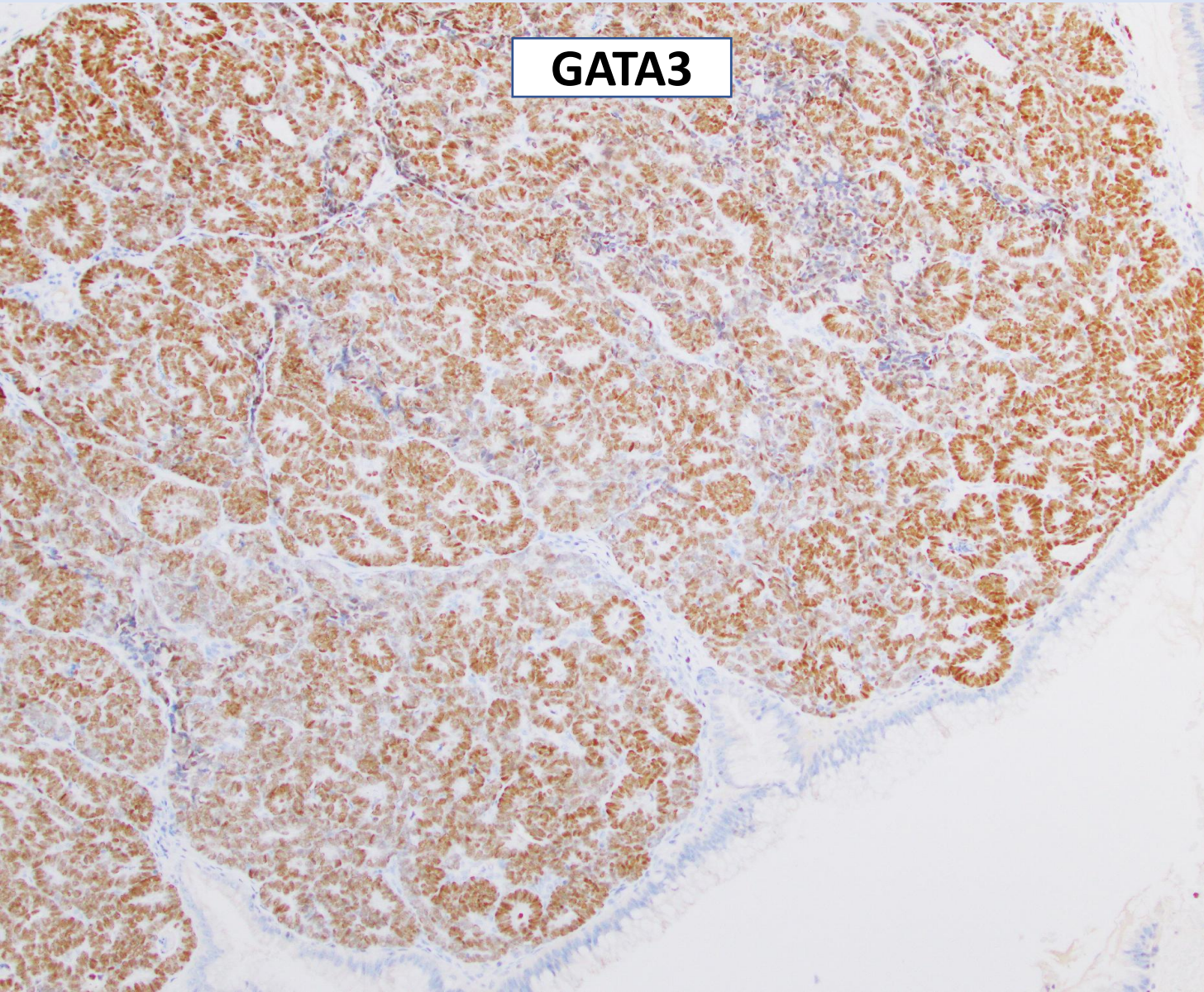
- Endometrioid carcinomas may have an aberrant immunohistochemical profile and besides expressing WT1, they can express CDX2, CK20, SATB2, and TTF1
- Endometrioid carcinomas (even low-grade) may be ER, PAX8, and CK7 negative
- GATA3, mammaglobin, or GCDFP-15 may be focally positive
- PAX8-negative endometrioid carcinomas are positive for SOX17

Intestinal-Type Mucinous Borderline Tumor and Mesonephric-Like Carcinoma



May be admixed with an endometrioid, serous or mucinous tumor but must lack mucinous, squamous, secretory, or ciliated differentiation

Intestinal-Type Mucinous Borderline Tumor and Mesonephric-Like Carcinoma



A Comparison of GATA3, TTF-1, and Calretinin in Identifying Mesonephric and Mesonephric-like Carcinomas

- **GATA3:**
 - ✓ Highest sensitivity and specificity compared to TTF1, CD10, and calretinin
 - ✓ Staining may be weak and very focal, especially in solid/spindled areas
 - ✓ Stains high-grade endometrioid/serous carcinomas (low number and TTF1-negative) and carcinosarcomas (high number but also TTF1-negative)
- **TTF1:**
 - ✓ Typically strong and extensive positivity in mesonephric-like carcinoma but absent or minimal staining in mesonephric carcinoma
 - ✓ Inverse pattern of staining compared to GATA3
 - ✓ No expression in endocervical carcinoma; rare expression in endometrial carcinoma
 - ✓ CALRETININ and CD10 may be used as supplemental stains (+/-)

Classic Immunoprofile



Euscher et al. Am J Surg Pathol. 2020;44:429-43
Kobel et al. J Pathol Clin Res. 2024;10(4):e12389
Zhang et al. Histopathology. 2024;85:820-25

PAX8+ ER-* PR-
Often SOX17-
PAX2+ and GATA3 and/or TTF1+
p16- or patchy
p53 wild-type
MMR preserved

***With
exceptions**

Research Article

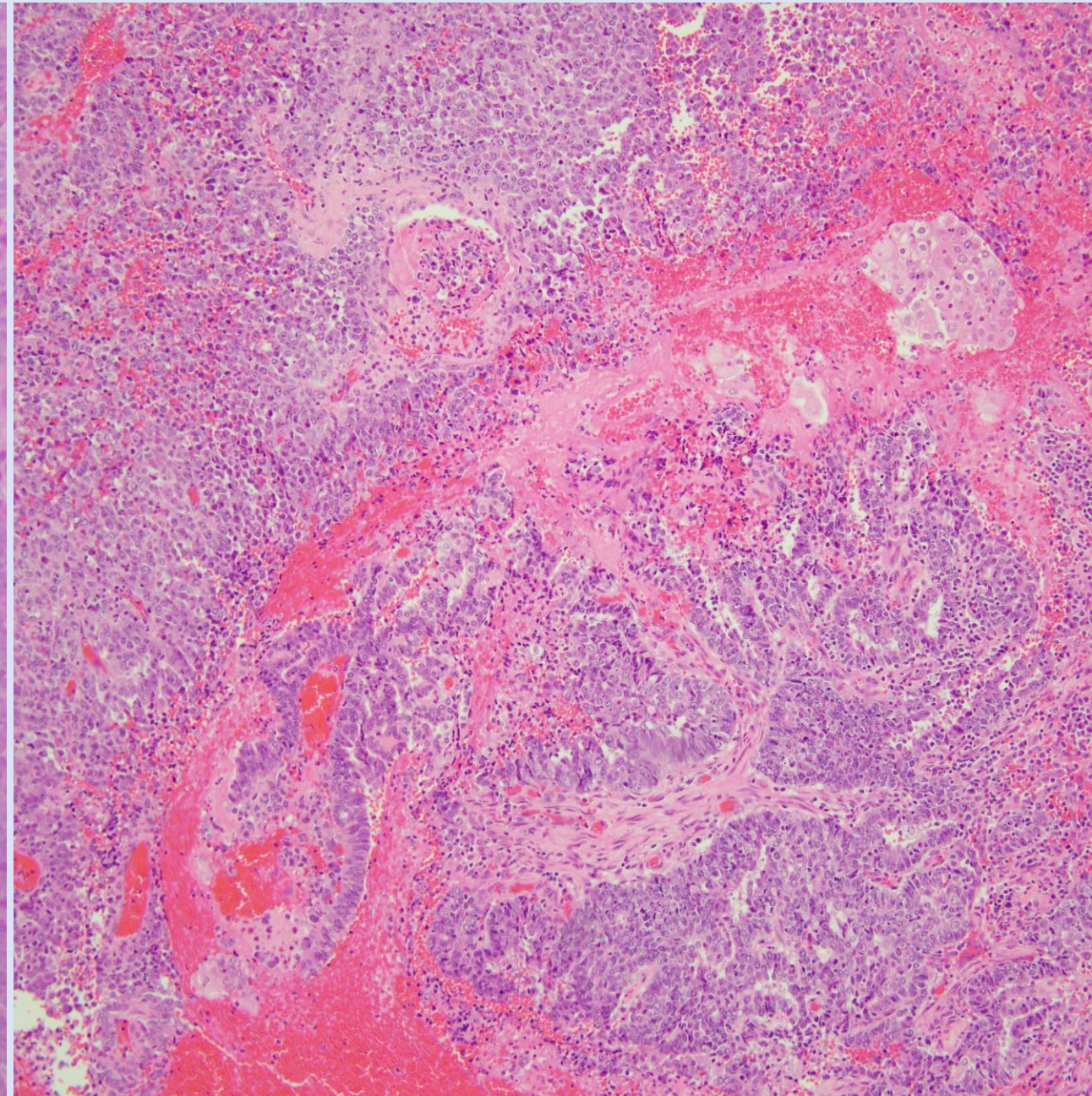
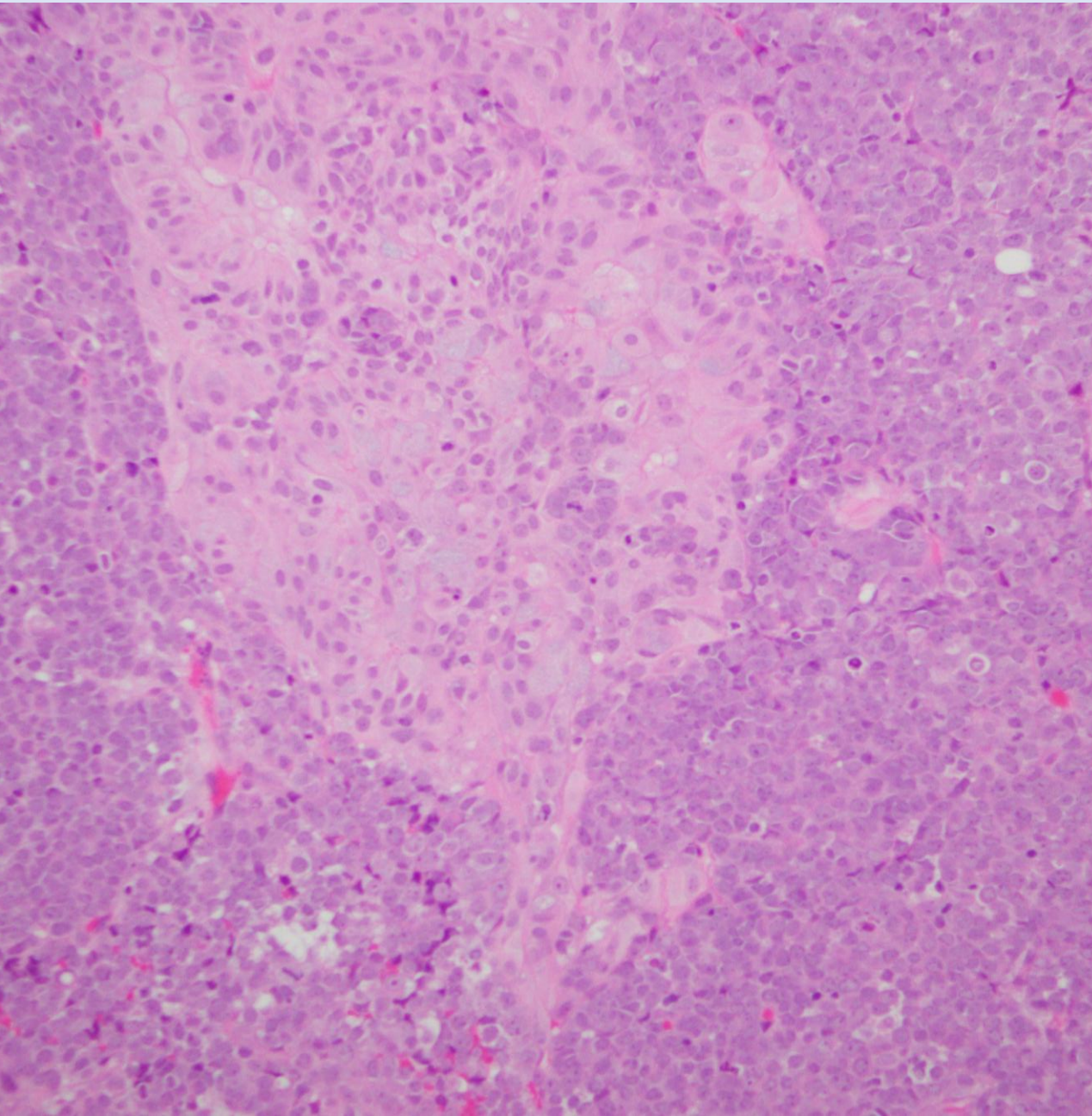
Dedifferentiated and Undifferentiated Ovarian Carcinoma: An Aggressive and Molecularly Distinct Ovarian Tumor Characterized by Frequent SWI/SNF Complex Inactivation

Basile Tessier-Cloutier^a, Felix K.F. Kommoss^b, David L. Kolin^c, Kristýna Němejcová^d, DuPreez Smith^e, Jennifer Pors^f, Colin J.R. Stewart^g, W Glenn McCluggage^h, William D. Foulkesⁱ, Andreas von Deimling^{j,k}, Martin Köbel^l, Cheng-Han Lee^{m,*}

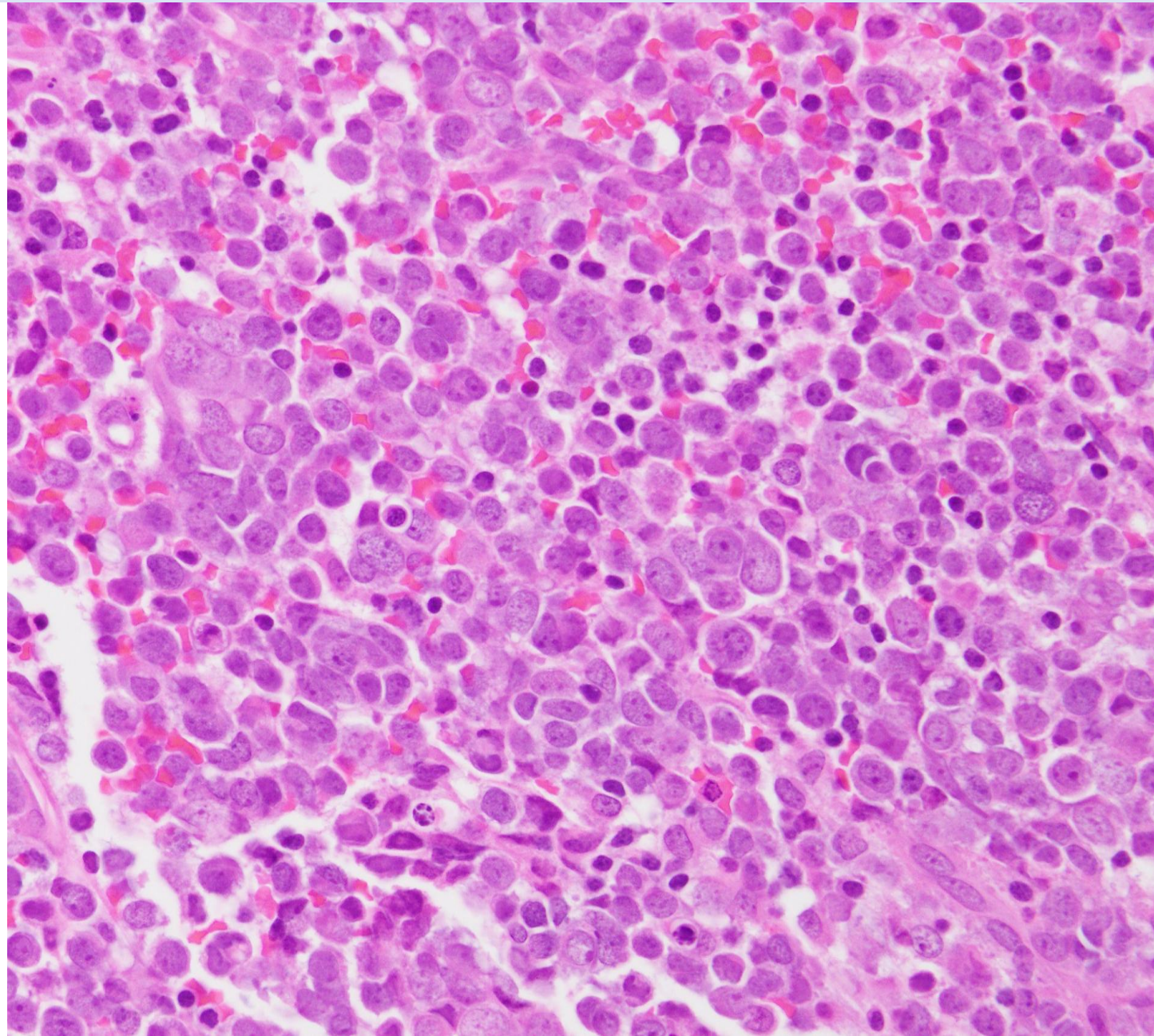
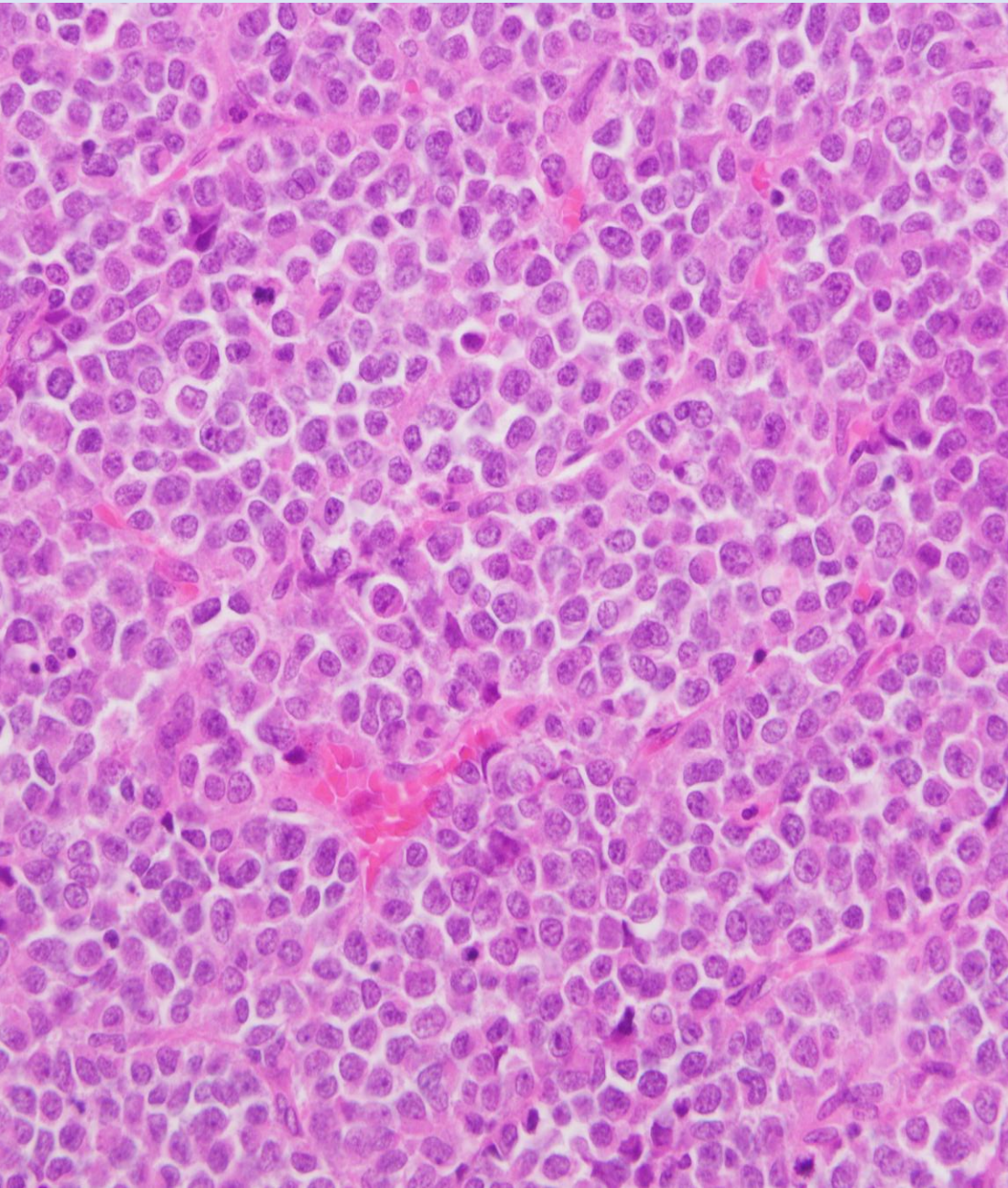
- 22-71 (average 50) years
- 16/23 patients presented with extraovarian disease
- 17/19 patients with follow-up died from disease (median survival 3 years)
- 18/22 tumors with loss of expression of SWI/SNF protein(s):
 - ARID1A and ARID1B (10)
 - SMARCA4 (7); SMARCB1 (1)
- 6/23 **MMR-deficient** tumors
- 2/19 p53-abnormal tumors
- Methylation profiles: co-clustering of DDOC/UDOC with UDEC

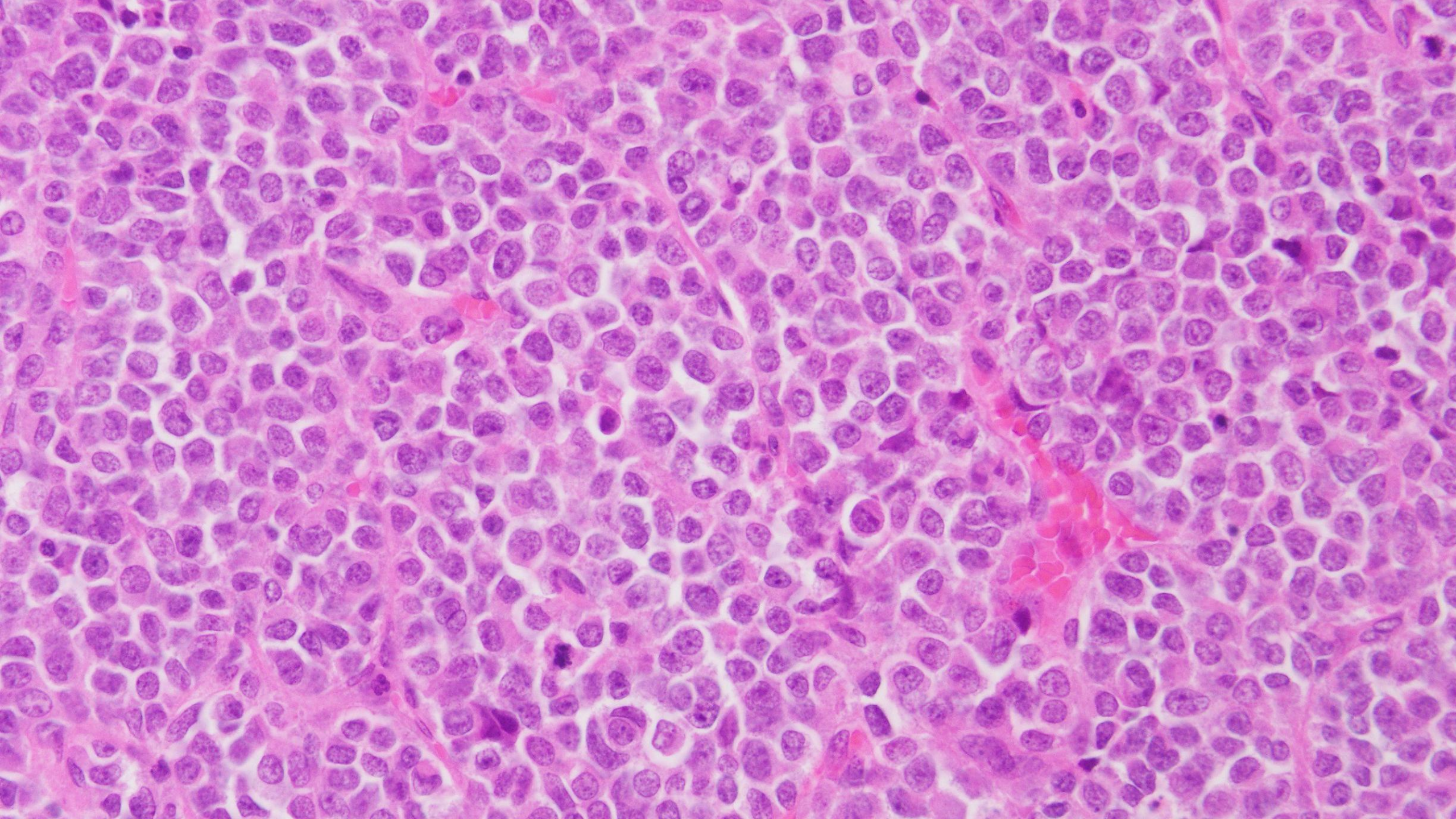
Mod Pathol.
2024;37(1):100374

De differentiated Carcinoma



Range of Morphologic Appearances

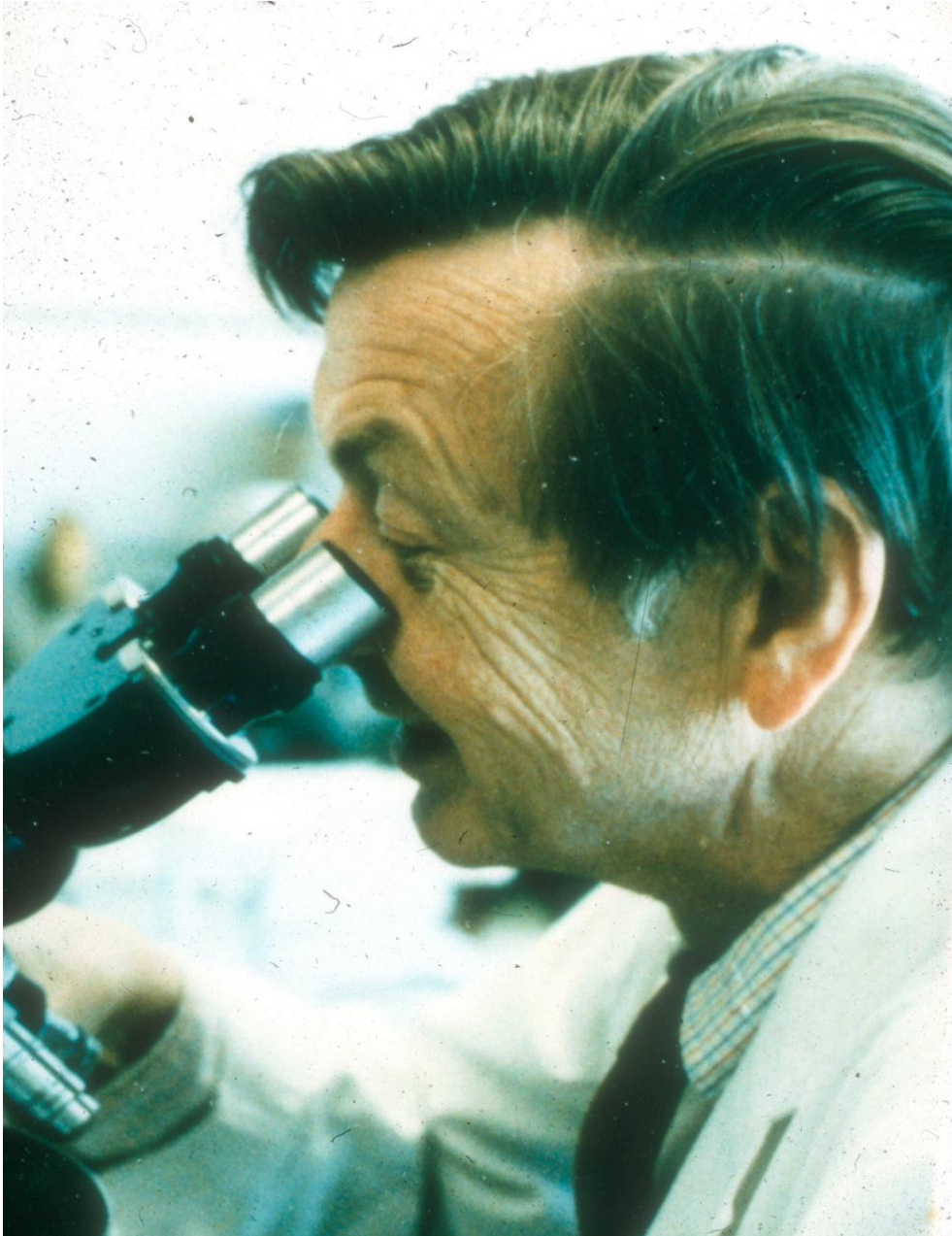




Undifferentiated Carcinoma of the Endometrium

IHC stain	No. cases	n (%)			
		Negative < 5%	Focal 6%–25%	Patchy 26%–75%	Diffuse > 75%
PAX-8	20	17 (85)	0	1 (5)	2 (10)
Keratin cocktail	20	1 (5)	5 (25)	7 (35)	7 (35)
CK8/18	20	2 (10)	4 (20)	5 (25)	9 (45)
CK5/6	13	9 (69)	1 (8)	3 (23)	0
ER	20	17 (85)	2 (10)	0	1 (5)
PR	19	16 (85)	1 (5)	1 (5)	1 (5)
Her-2/neu	19	19 (100)	0	0	0
CD44	20	11 (55)	2 (10)	3 (15)	4 (20)
E-cadherin	20	10 (50)	4 (20)	0	6 (30)
p16	19	0	3 (16)	7 (37)	9 (47)
p53	19	1 (5)	6 (32)	7 (37)	5 (26)
c-Kit	13	13 (100)	0	0	0
EGFR	13	8 (62)	3 (23)	0	2 (15)

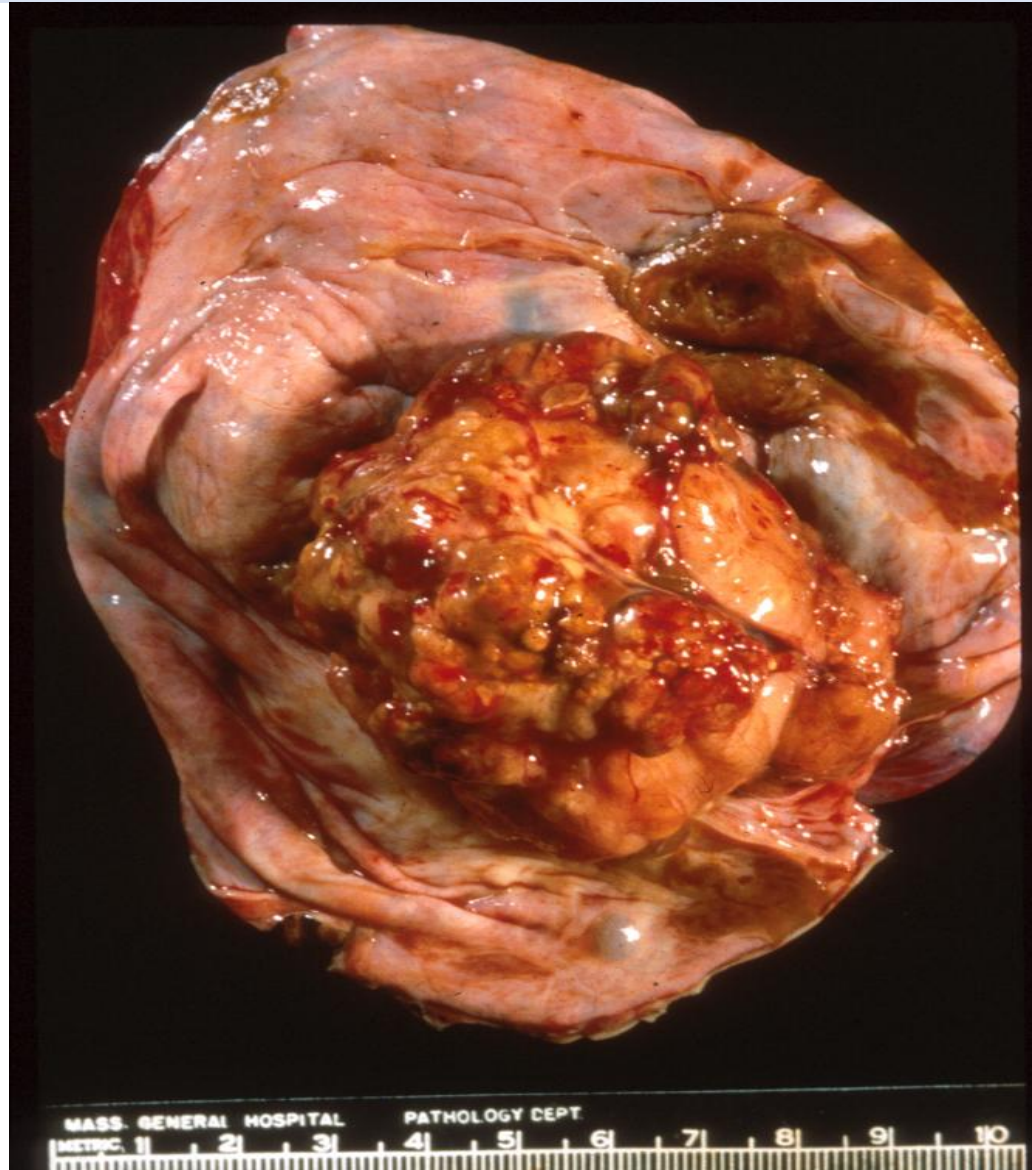
ER indicates estrogen receptor; PR, progesterone receptor.



**“Mesonephroma”
of the ovary, tumor of
Müllerian nature related to
endometrioid carcinoma**

Scully & Barlow. Cancer 1967;29:1405-17

Clear Cell Carcinoma

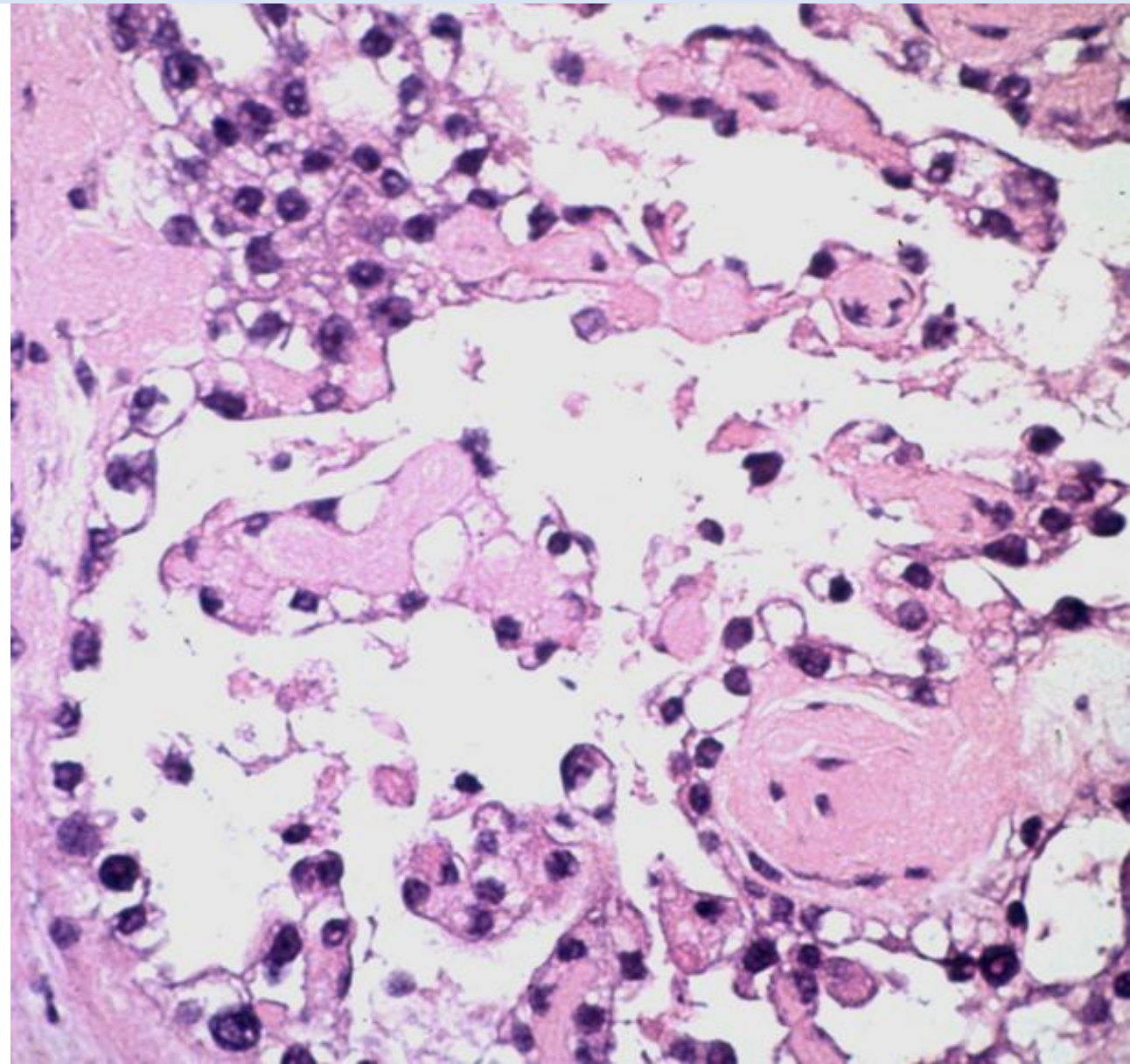
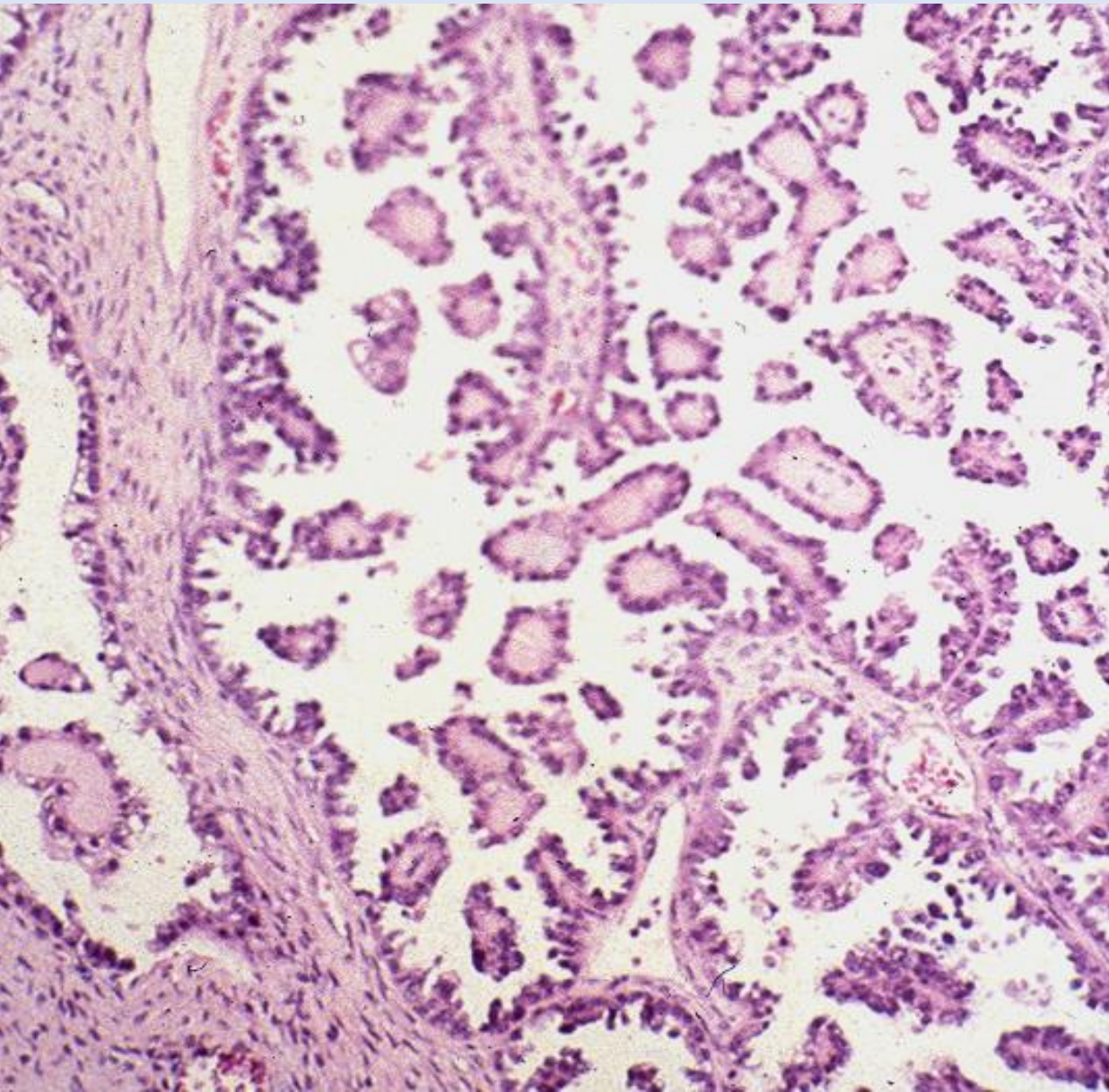


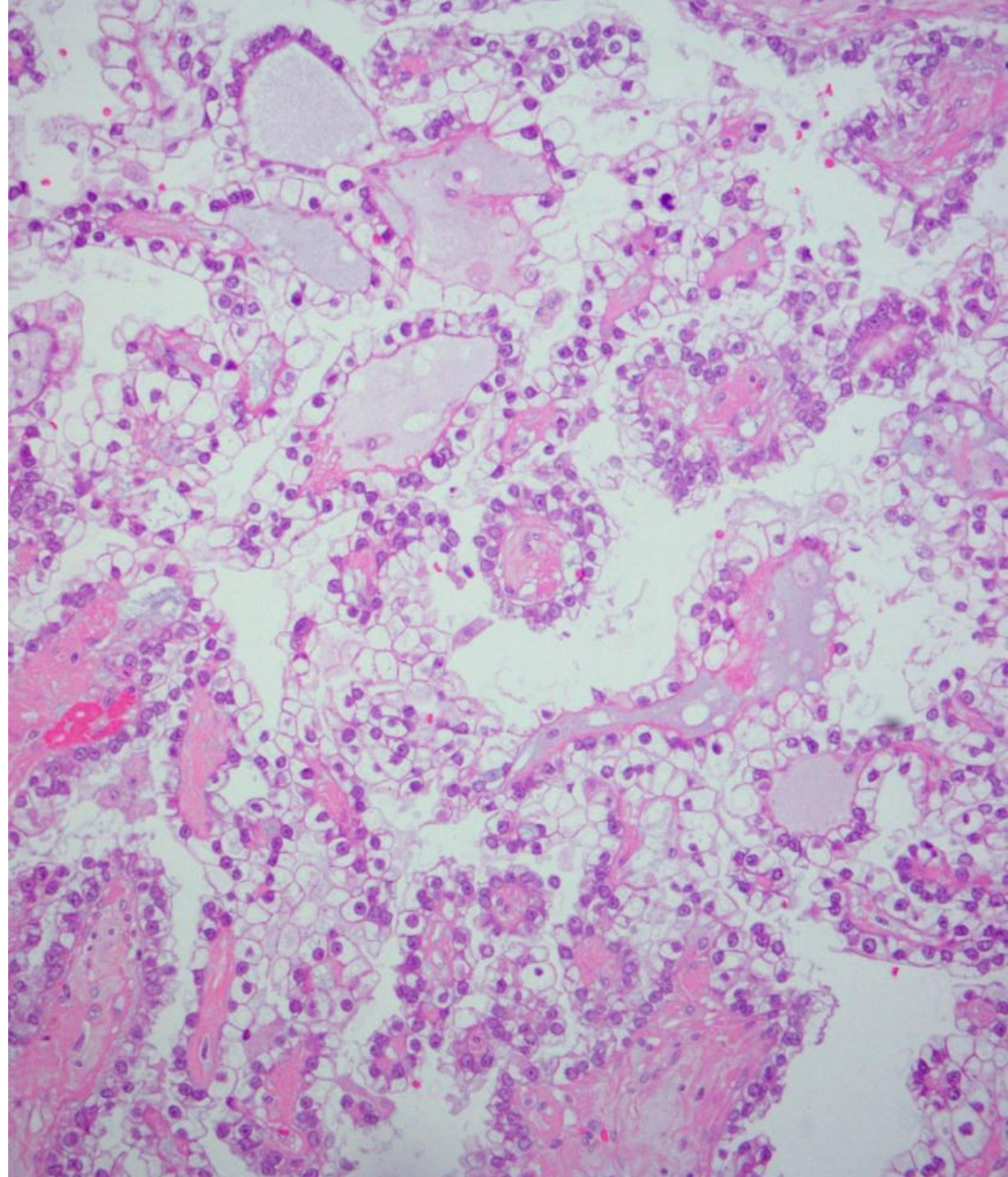
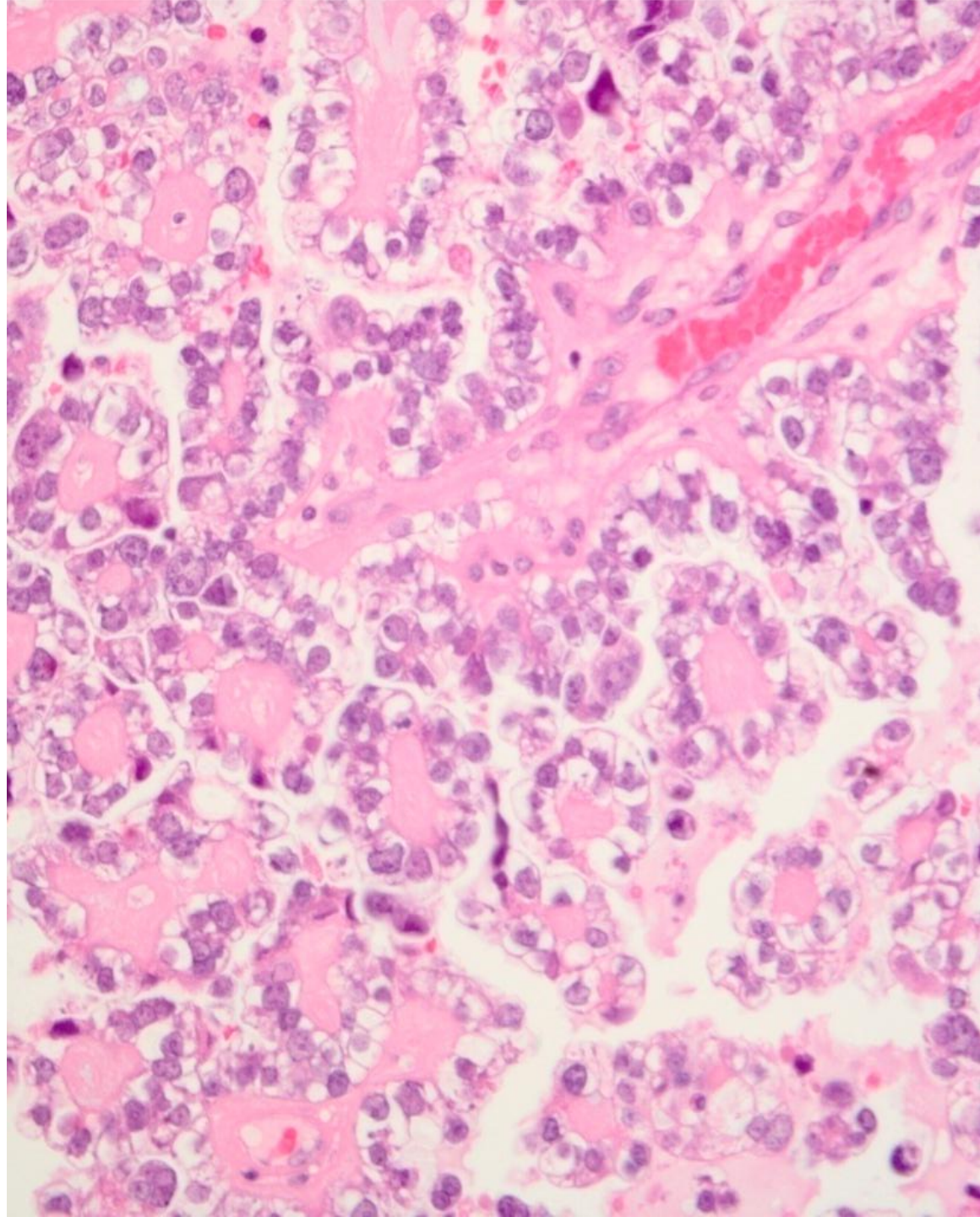
Clear Cell Carcinoma

- Diagnosis based on **TYPICAL ARCHITECTURAL PATTERNS**
- Presentation at early stage
- Highest association with endometriosis among ovarian carcinomas
- Often accompanied by paraneoplastic syndromes:
 - ✓ Hypercalcemia, thromboembolic events, subacute cerebellar degeneration, bilateral diffuse uveal melanocytic proliferation, others

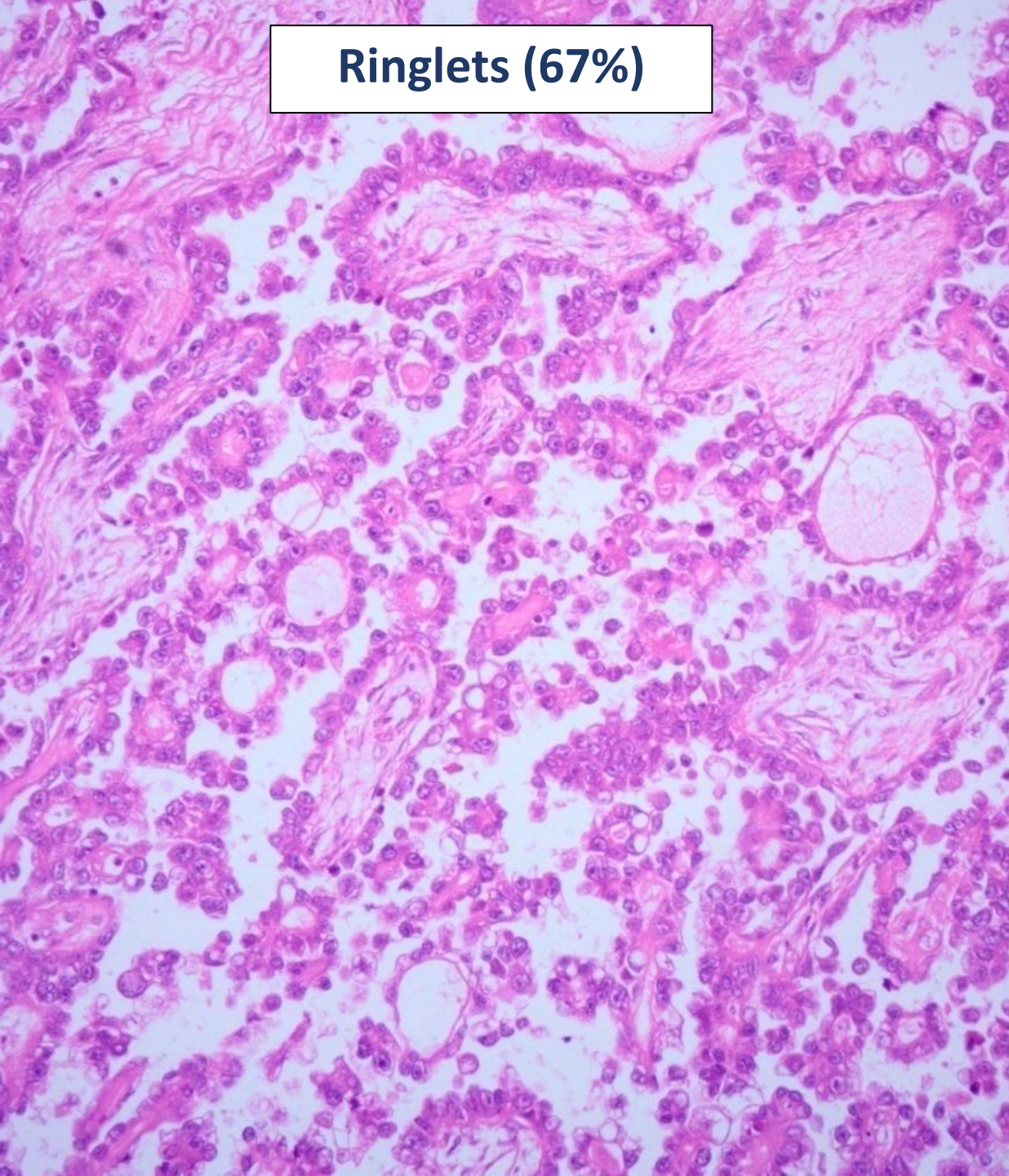
Papillary Architecture Most Common: 70% (Predominant: 50%)

(Bennett et al. Histopathology. 2015;66:808-15)

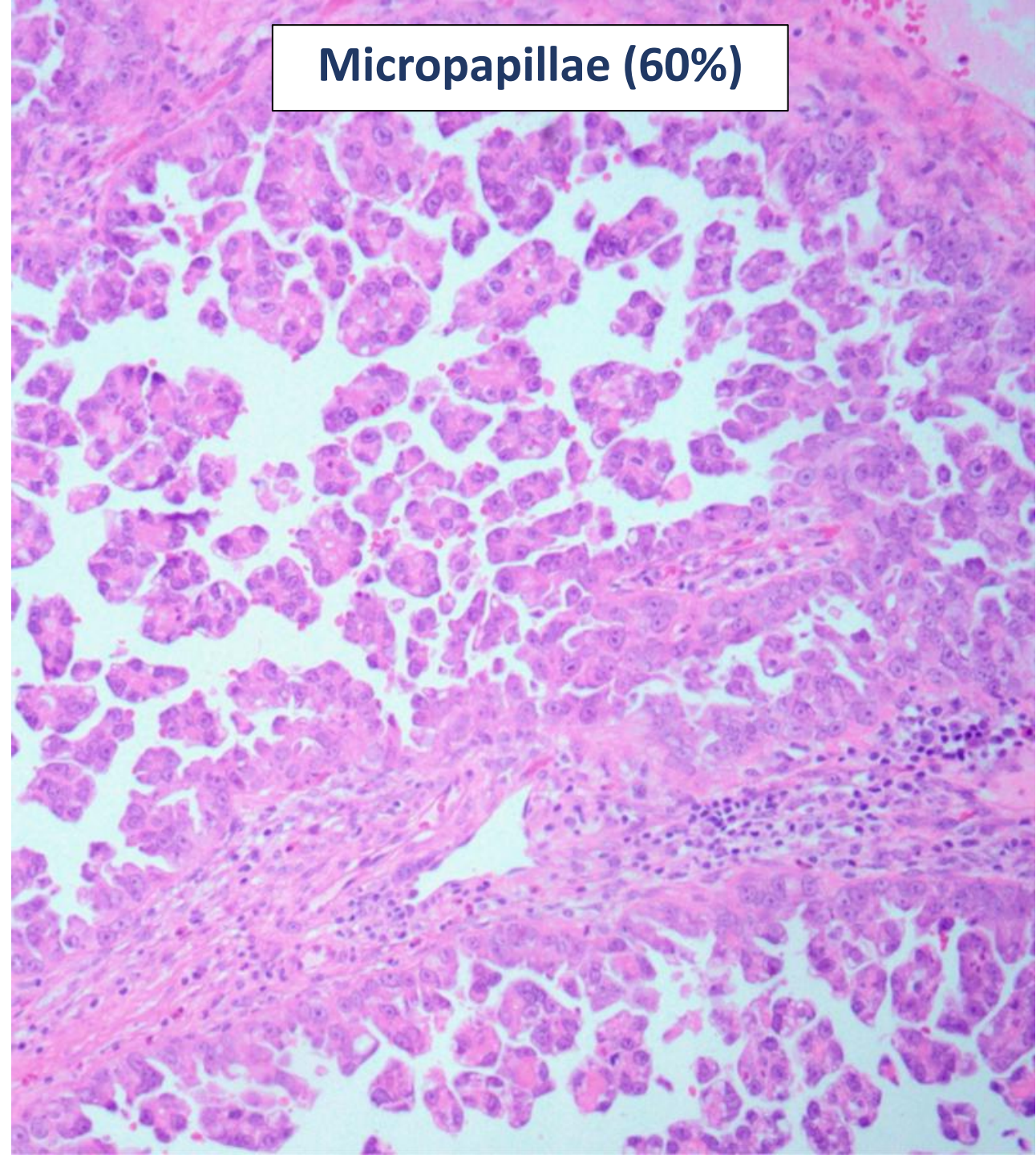




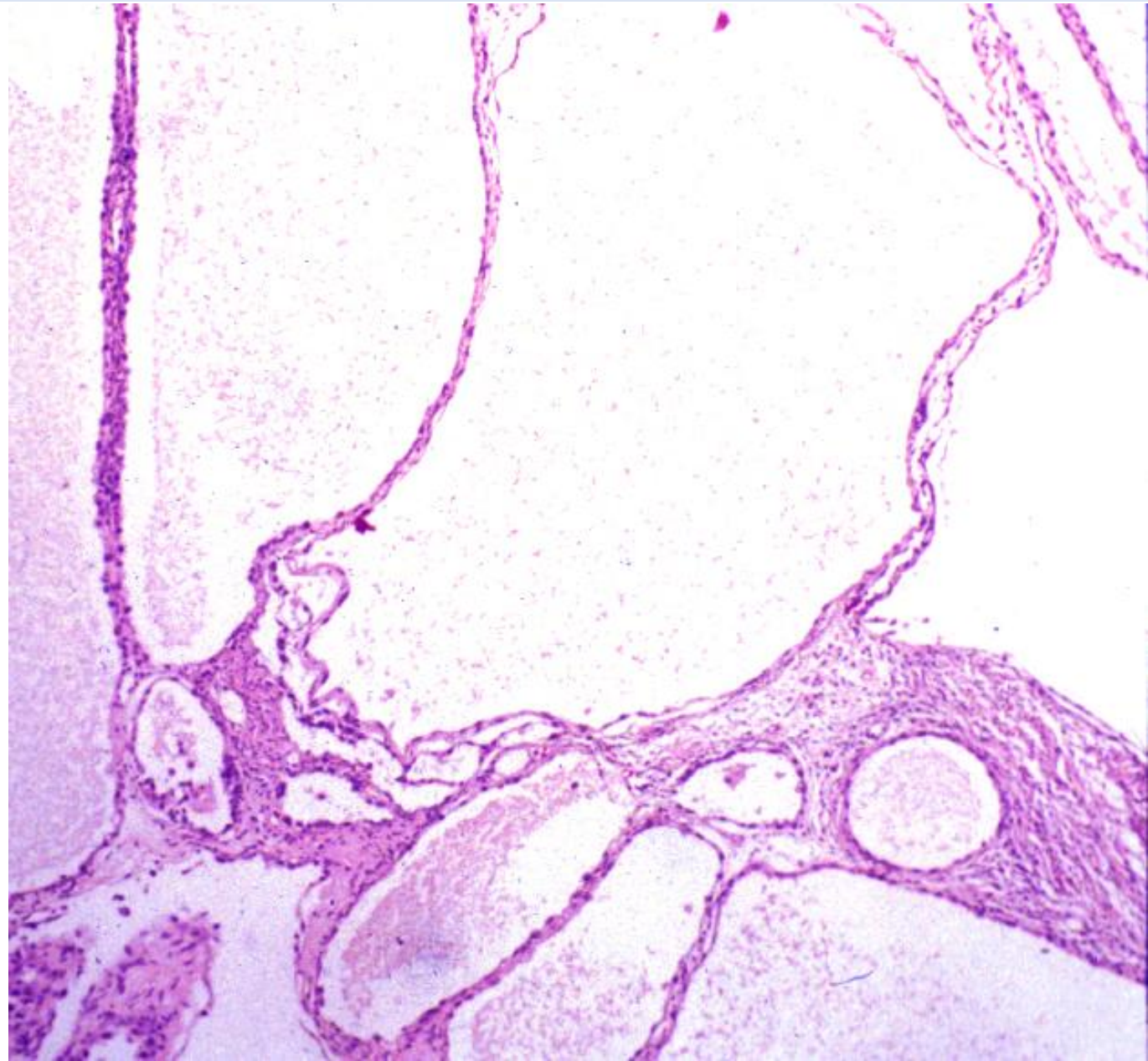
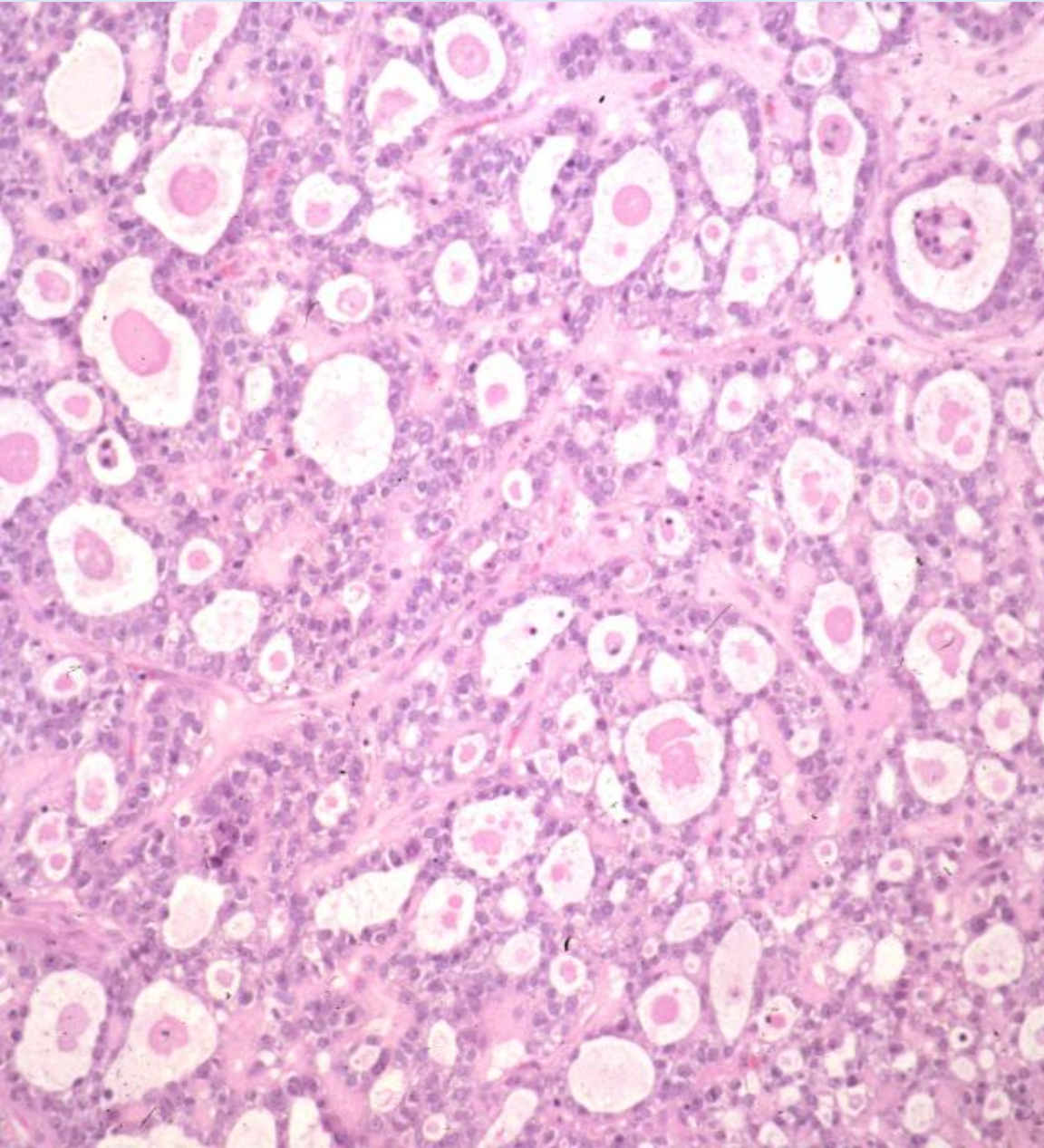
Ringlets (67%)



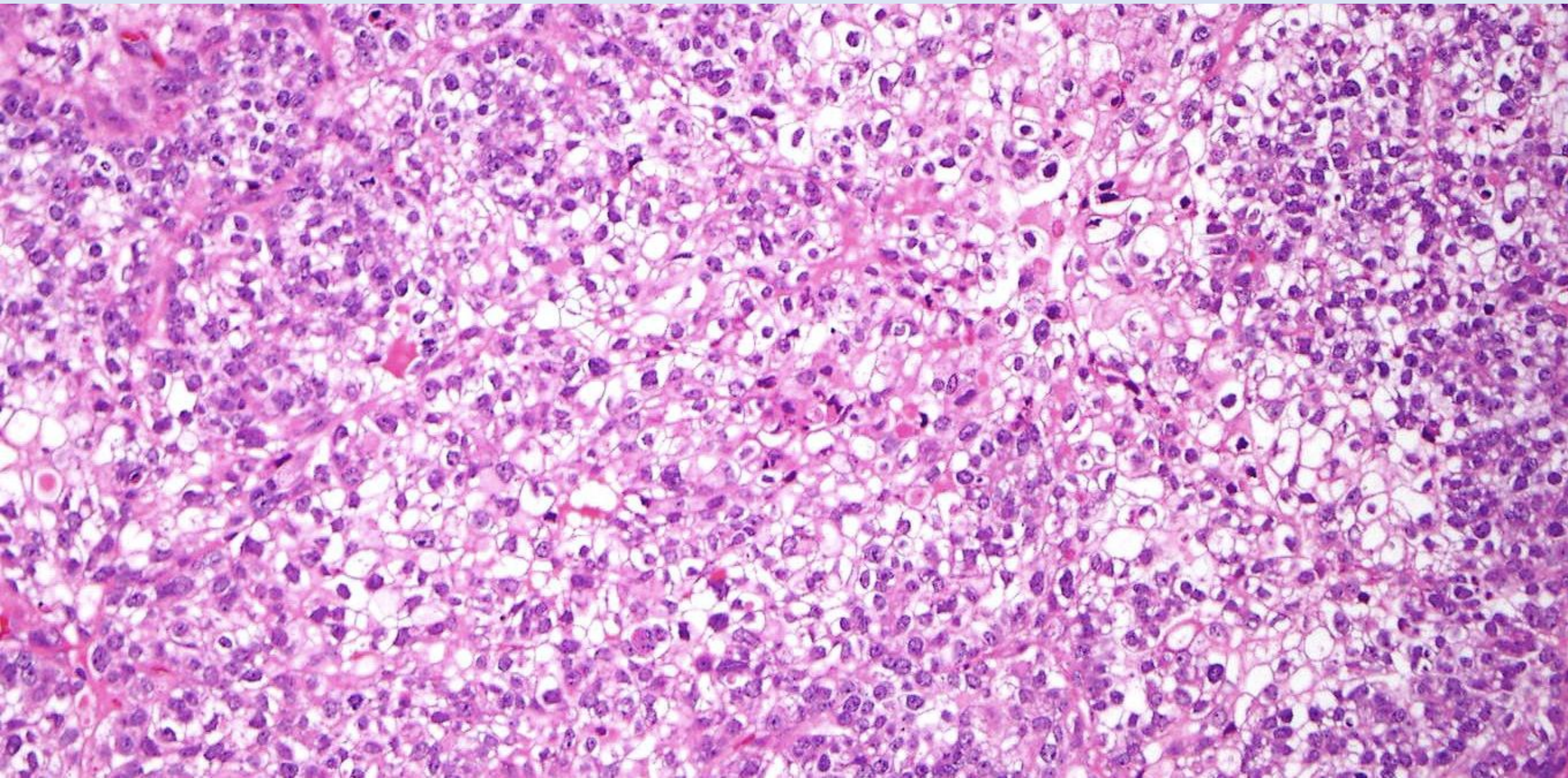
Micropapillae (60%)



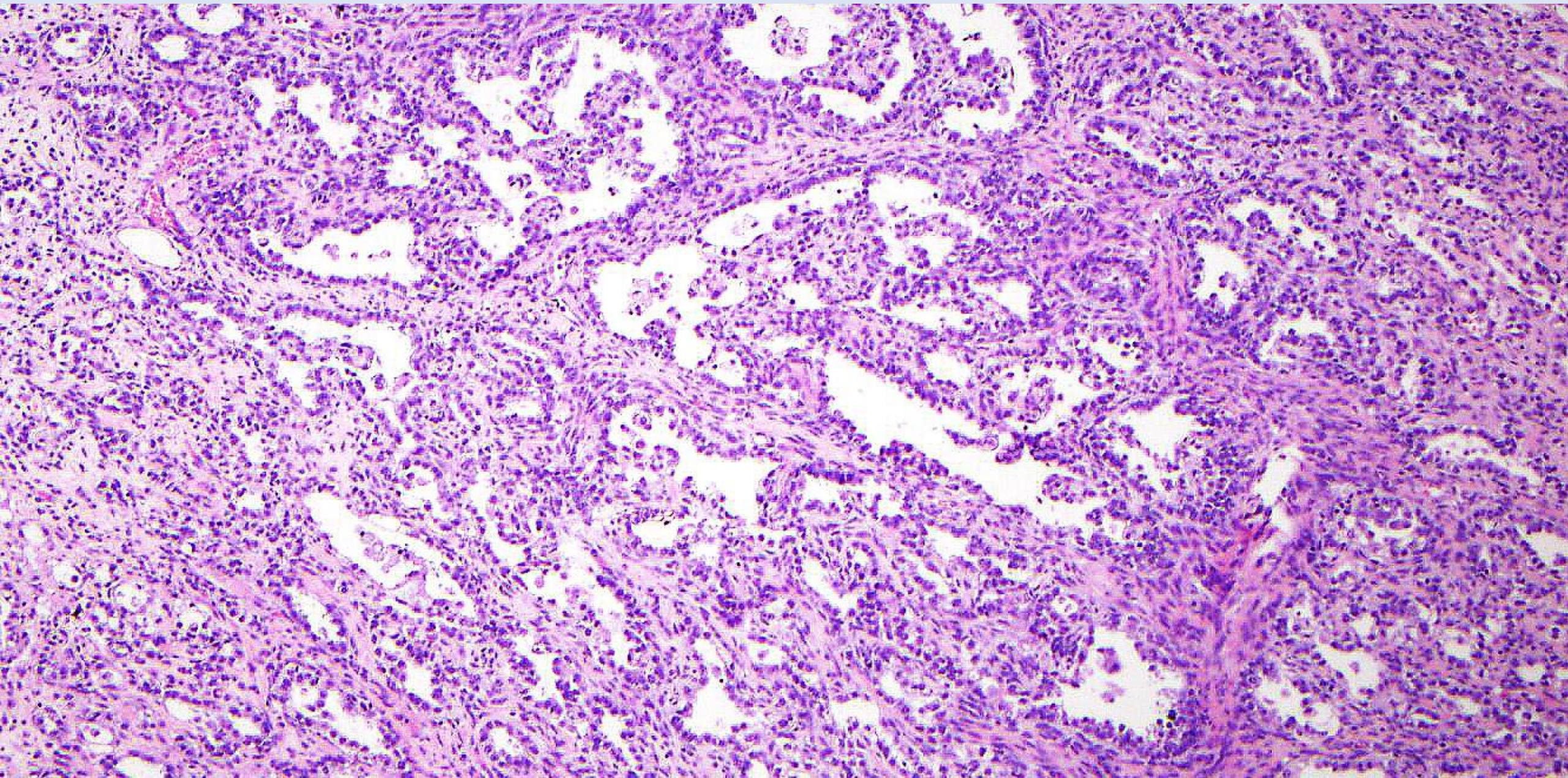
Tubulocystic Pattern (Frequency 65%, Predominant 44%)



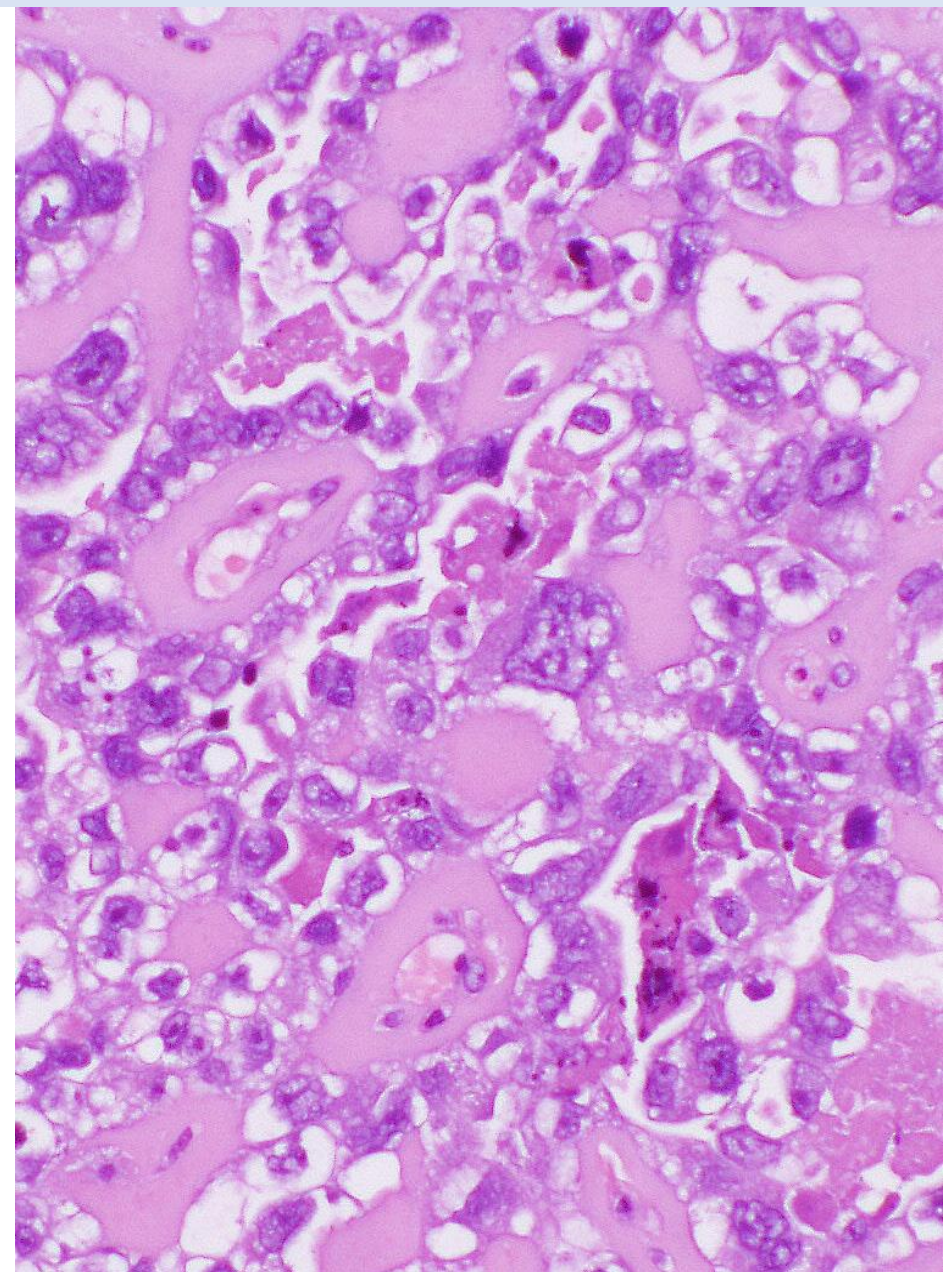
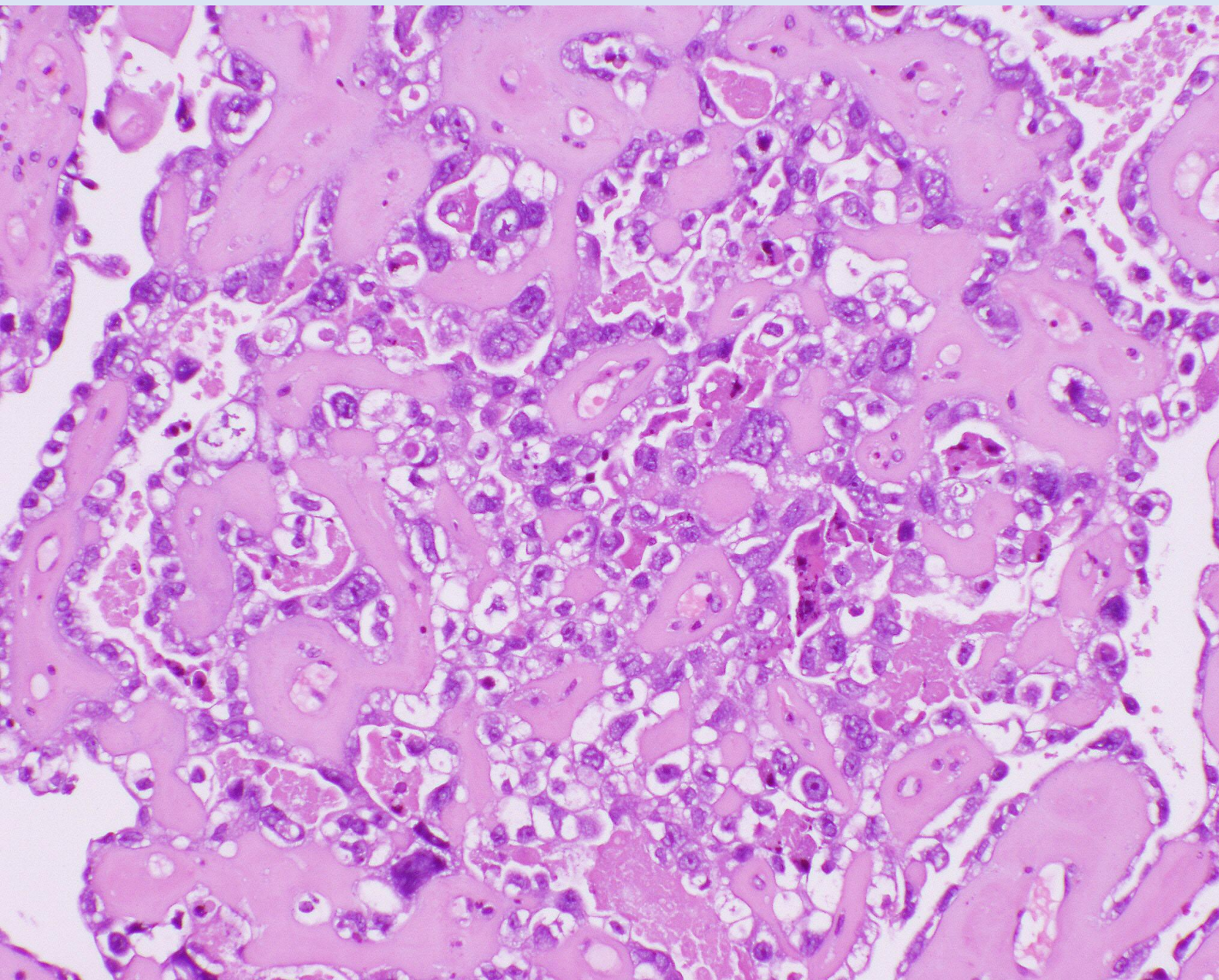
Solid Architecture (Frequency 62%, Predominant 34%)

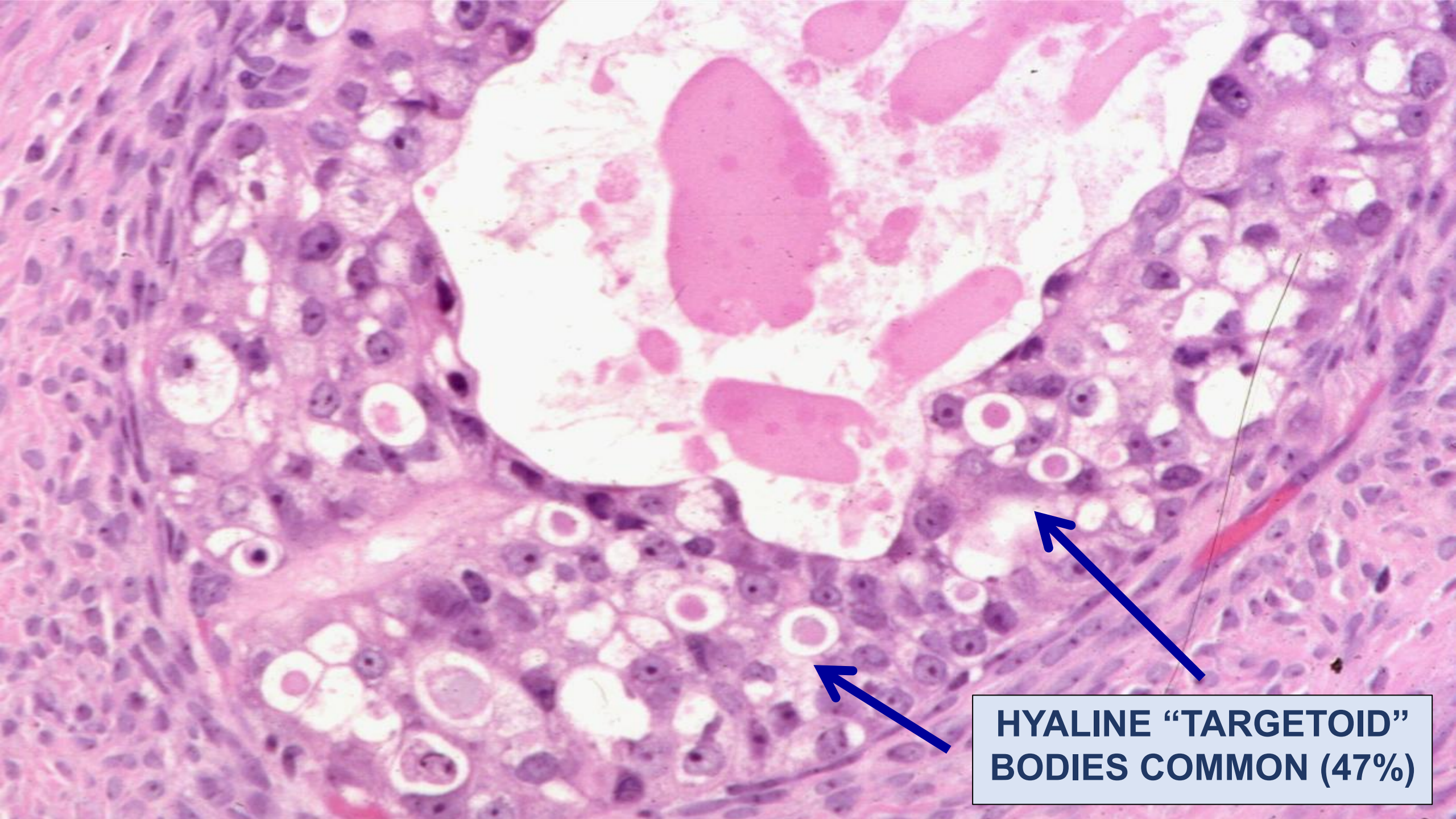


Non-Specific Glands (Frequency 19%, Predominant 11%)



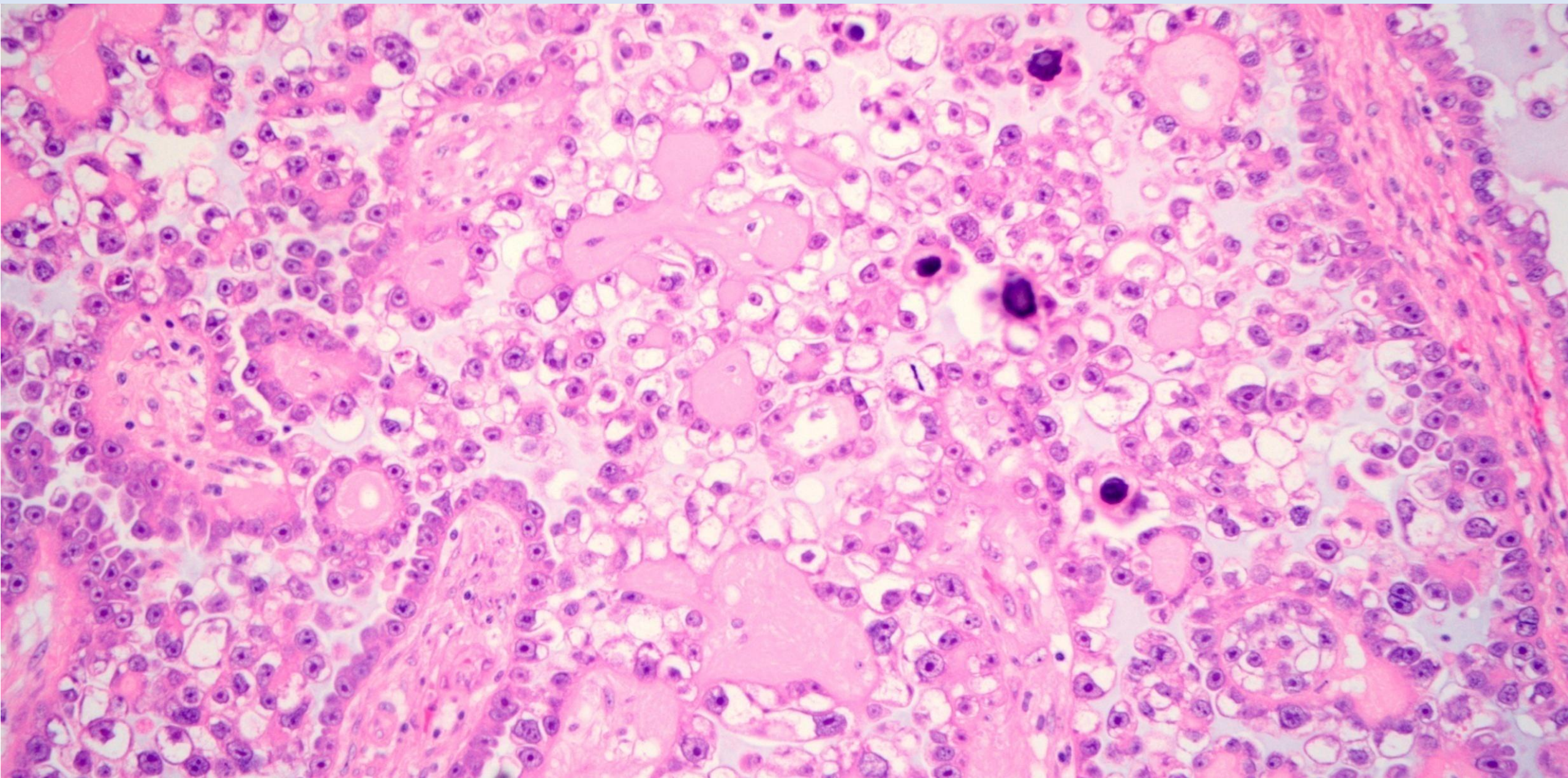
Prominent Stromal Hyalinization



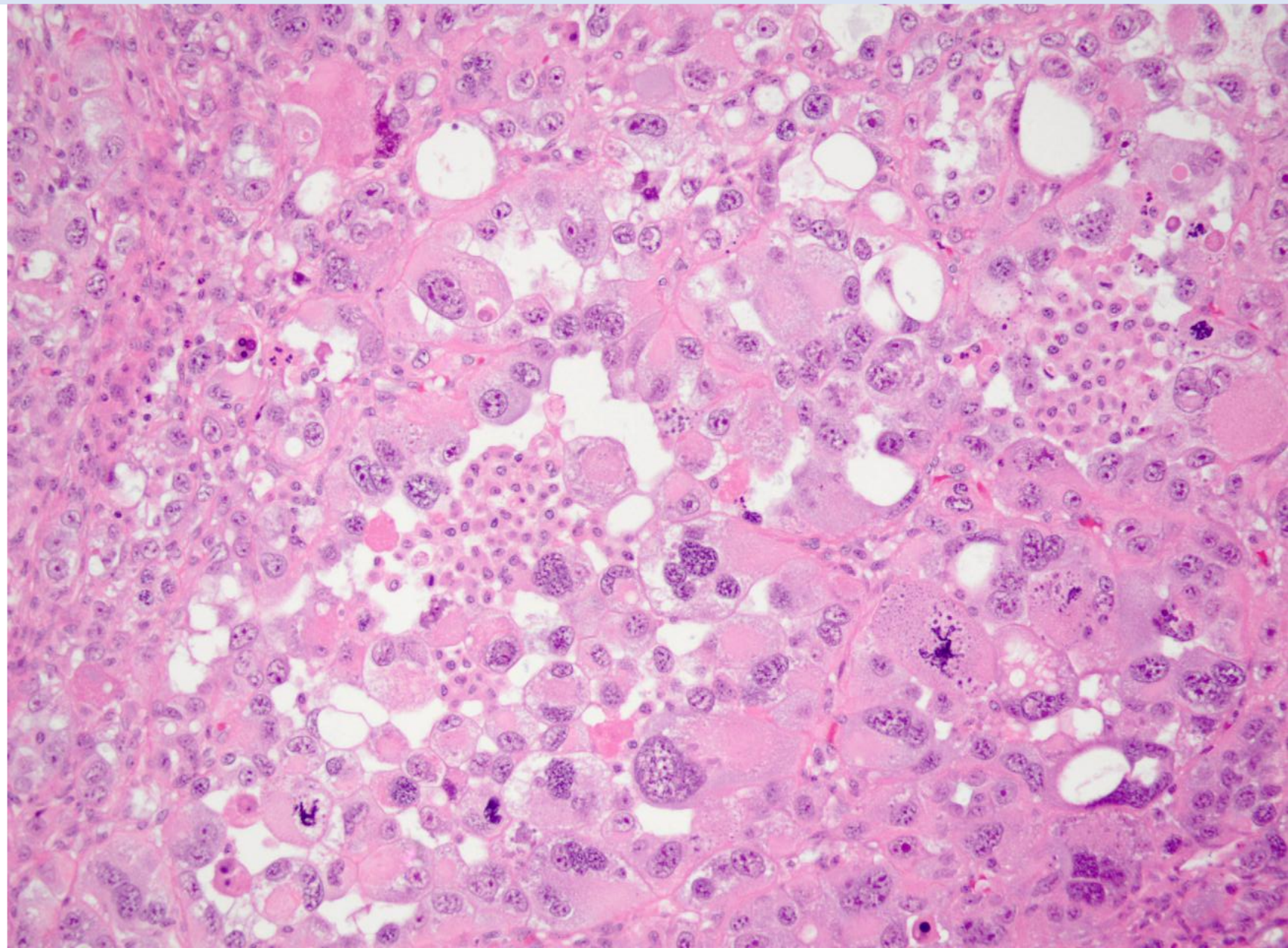
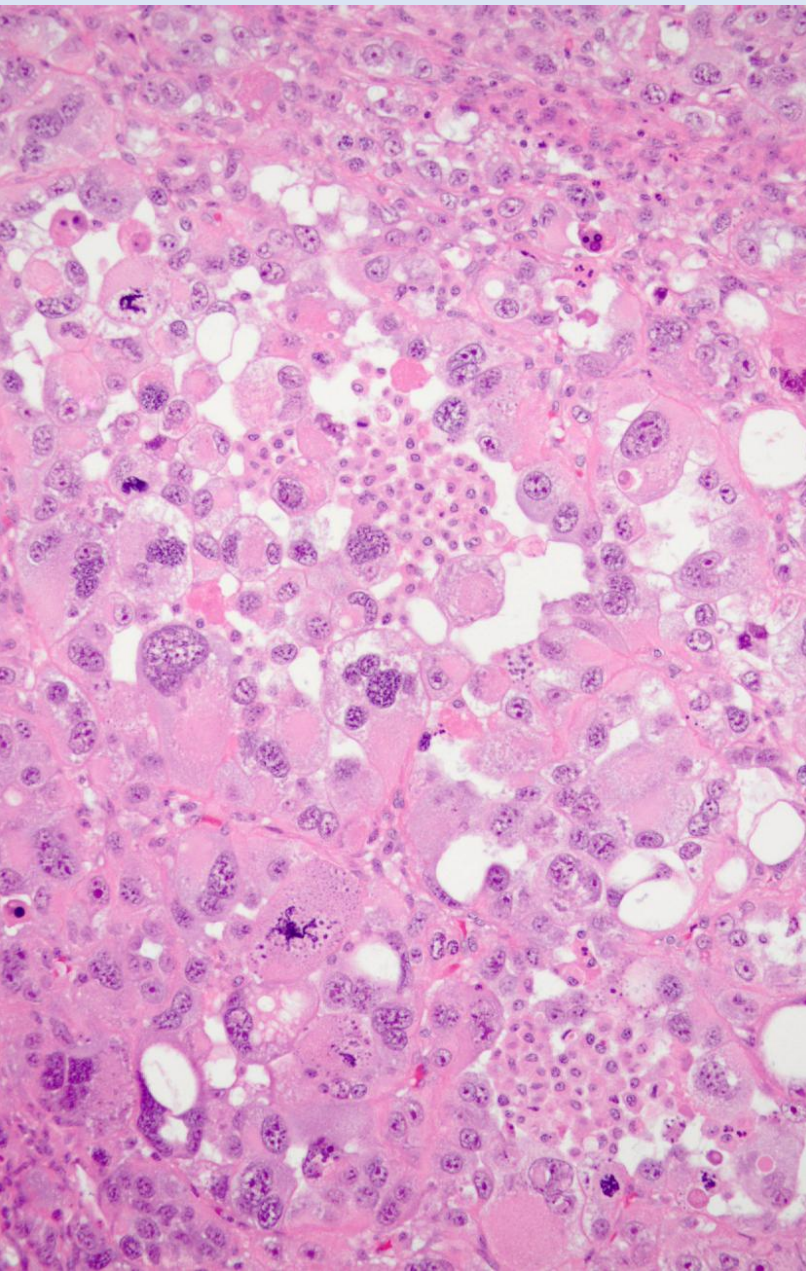


**HYALINE “TARGETOID”
BODIES COMMON (47%)**

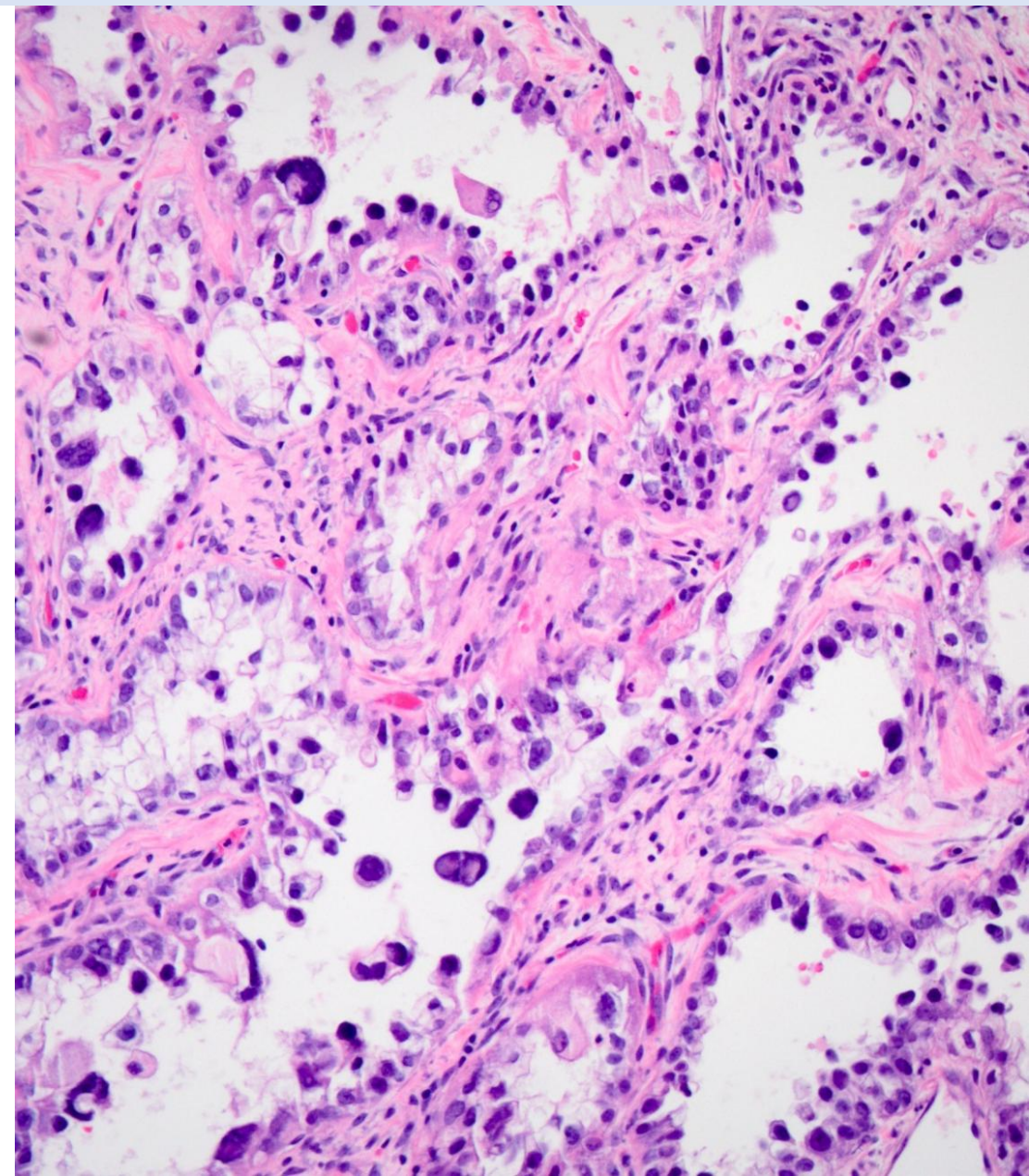
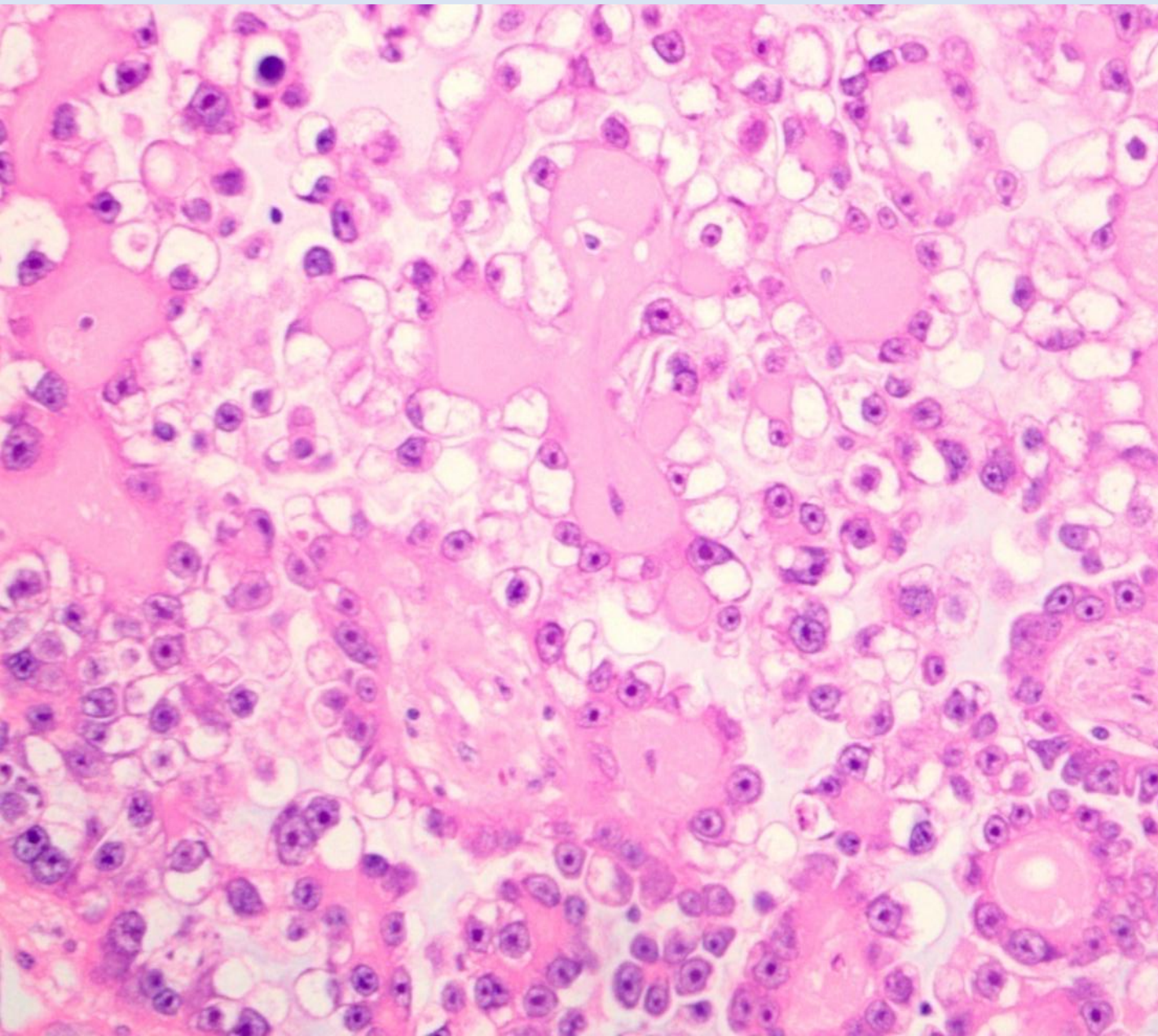
Usually Moderate to Severe BUT Uniform Atypia



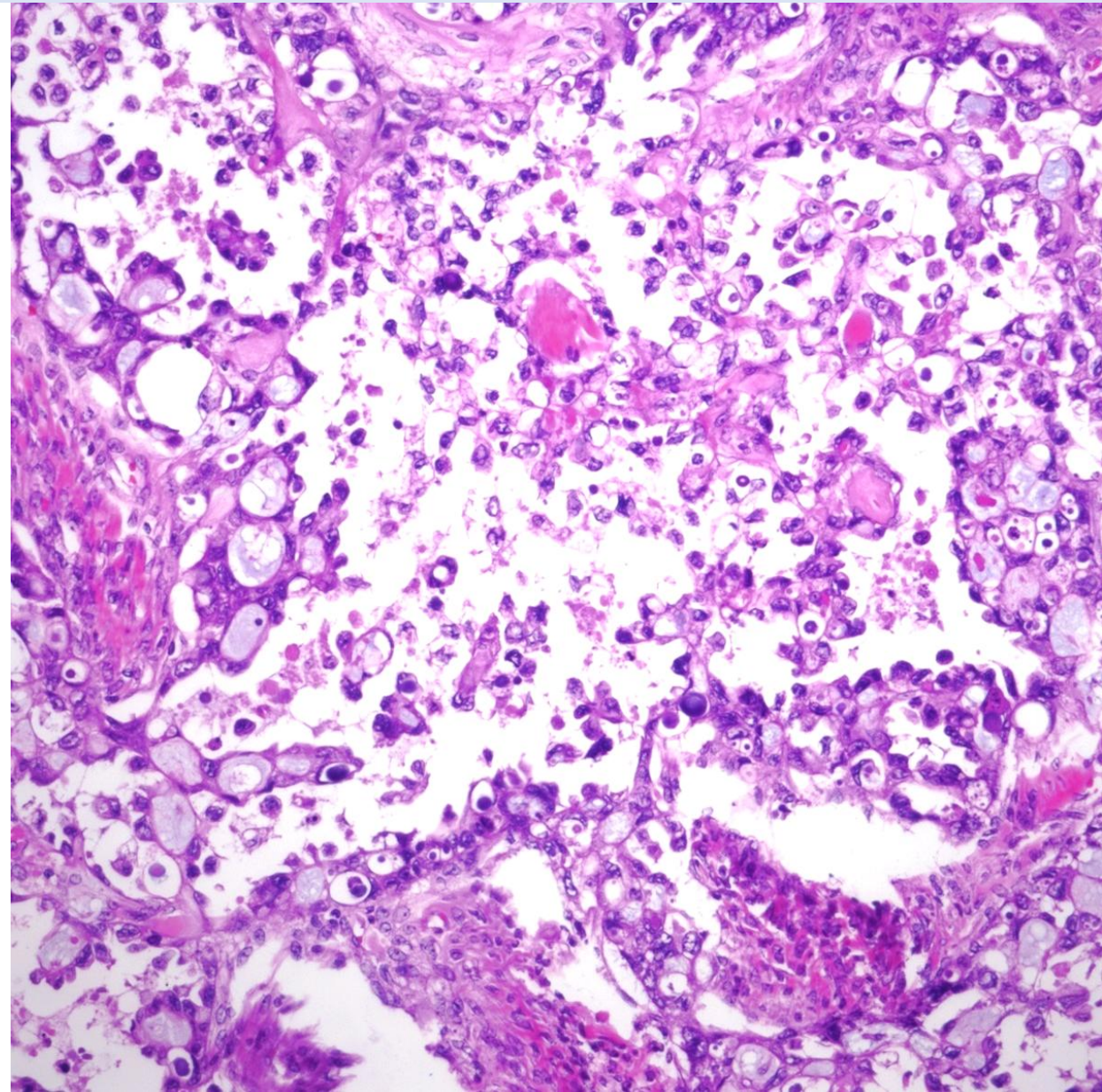
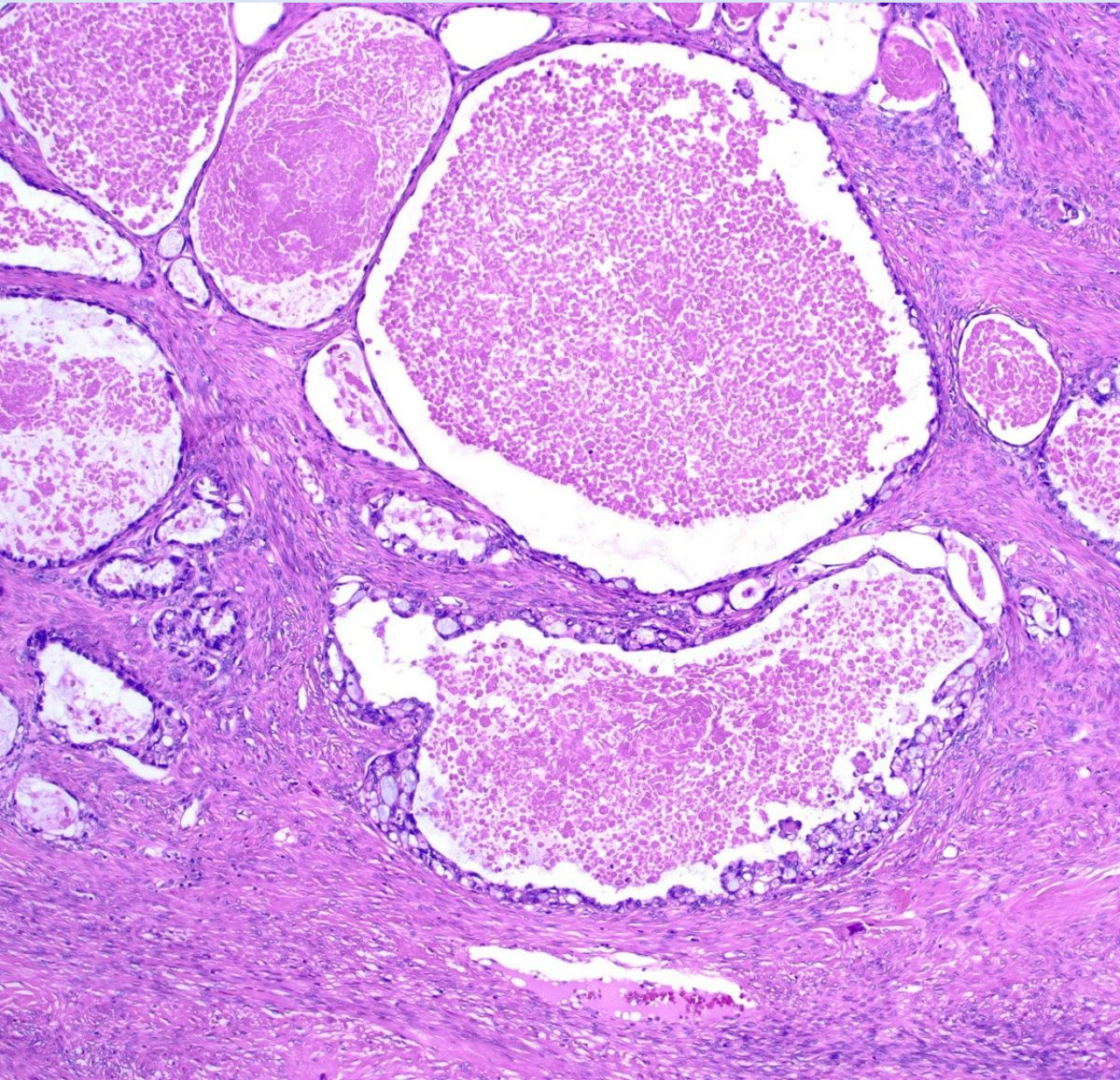
Anaplastic Features Are Uncommon

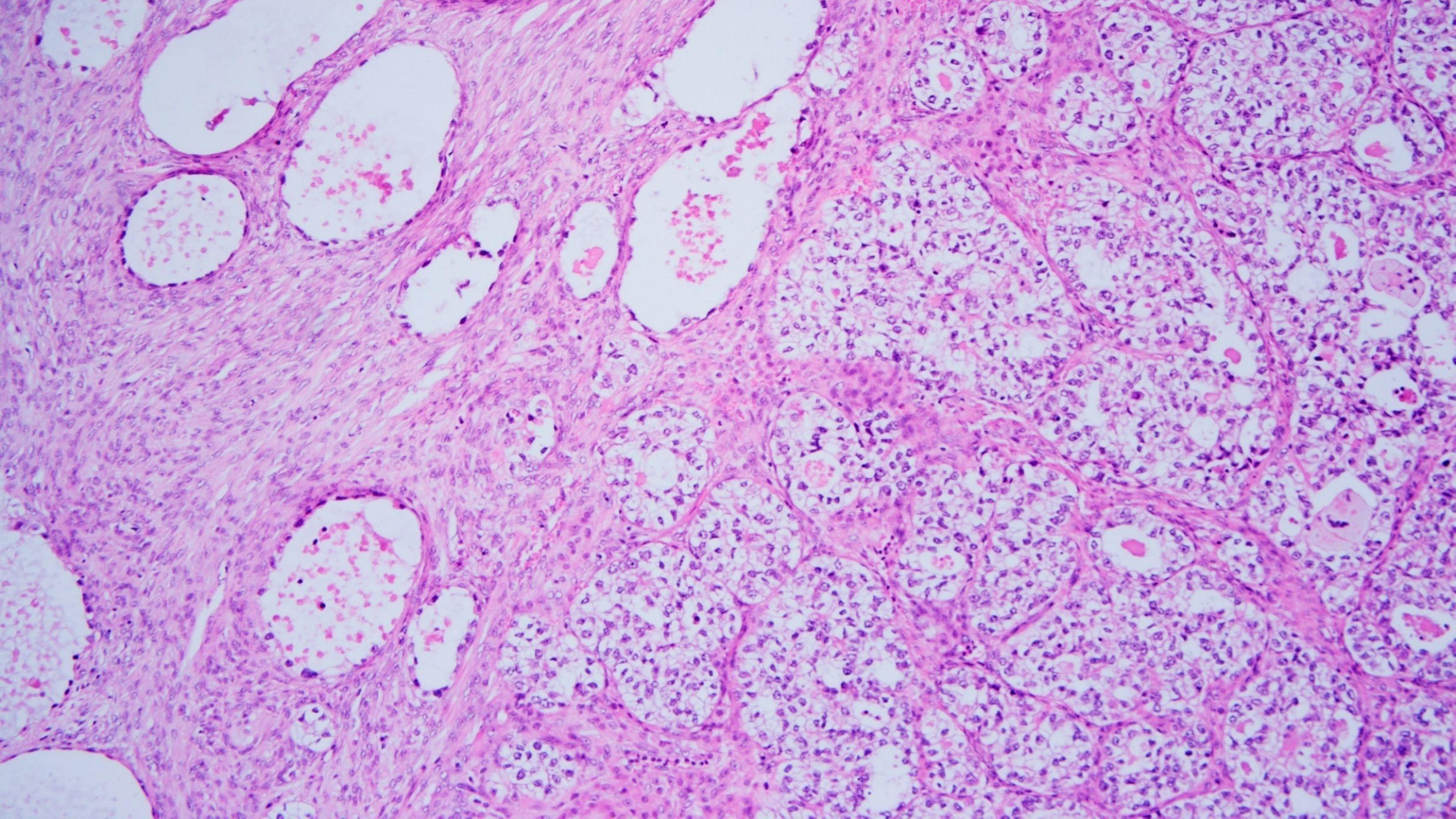


Clear Cells and Hobnail Cells (Not Always Present)



Clear Cell Carcinoma Arising in Adenofibroma





Clear Cell Carcinoma

Importance of correct diagnosis

- Broad differential diagnosis
- Poor response to platinum-based agents
- Association with Lynch Syndrome

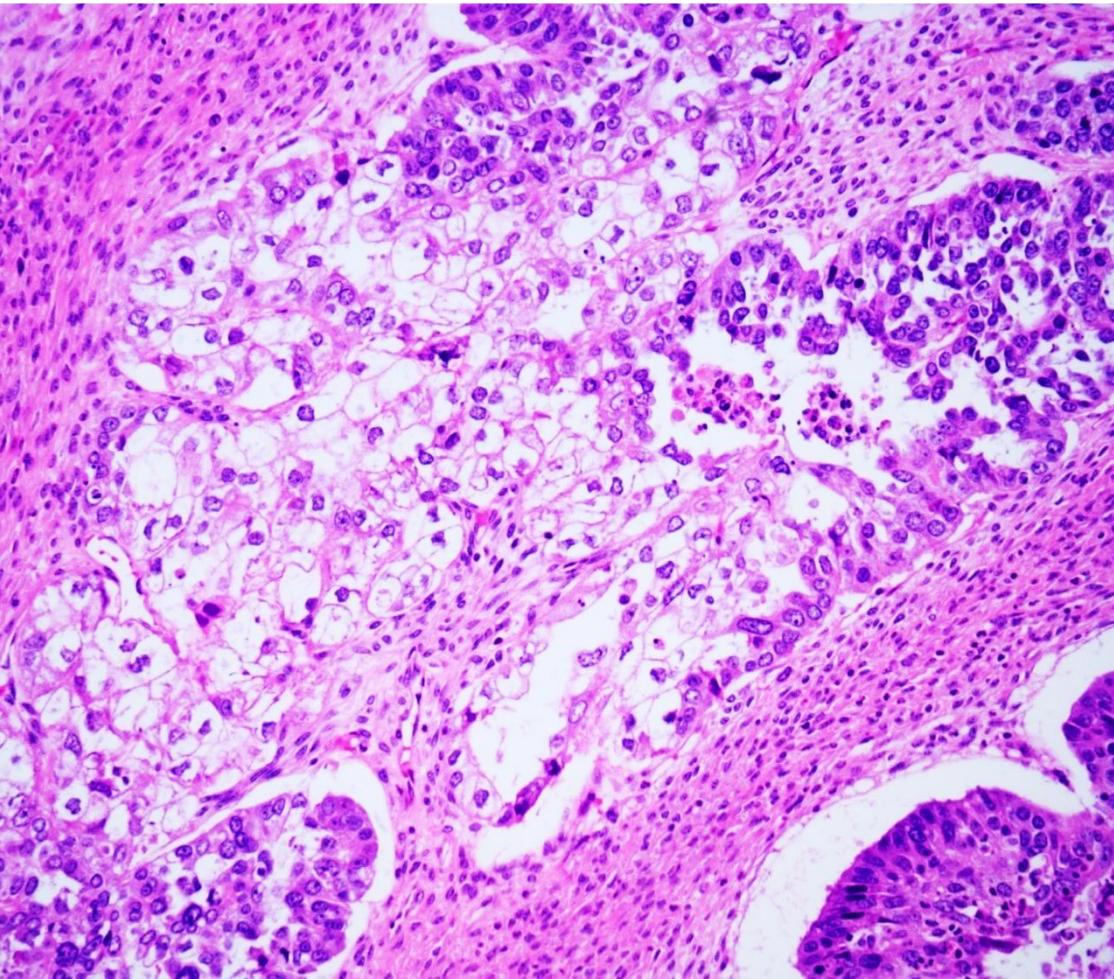
Clear Cell Carcinoma

DIFFERENTIAL DIAGNOSIS

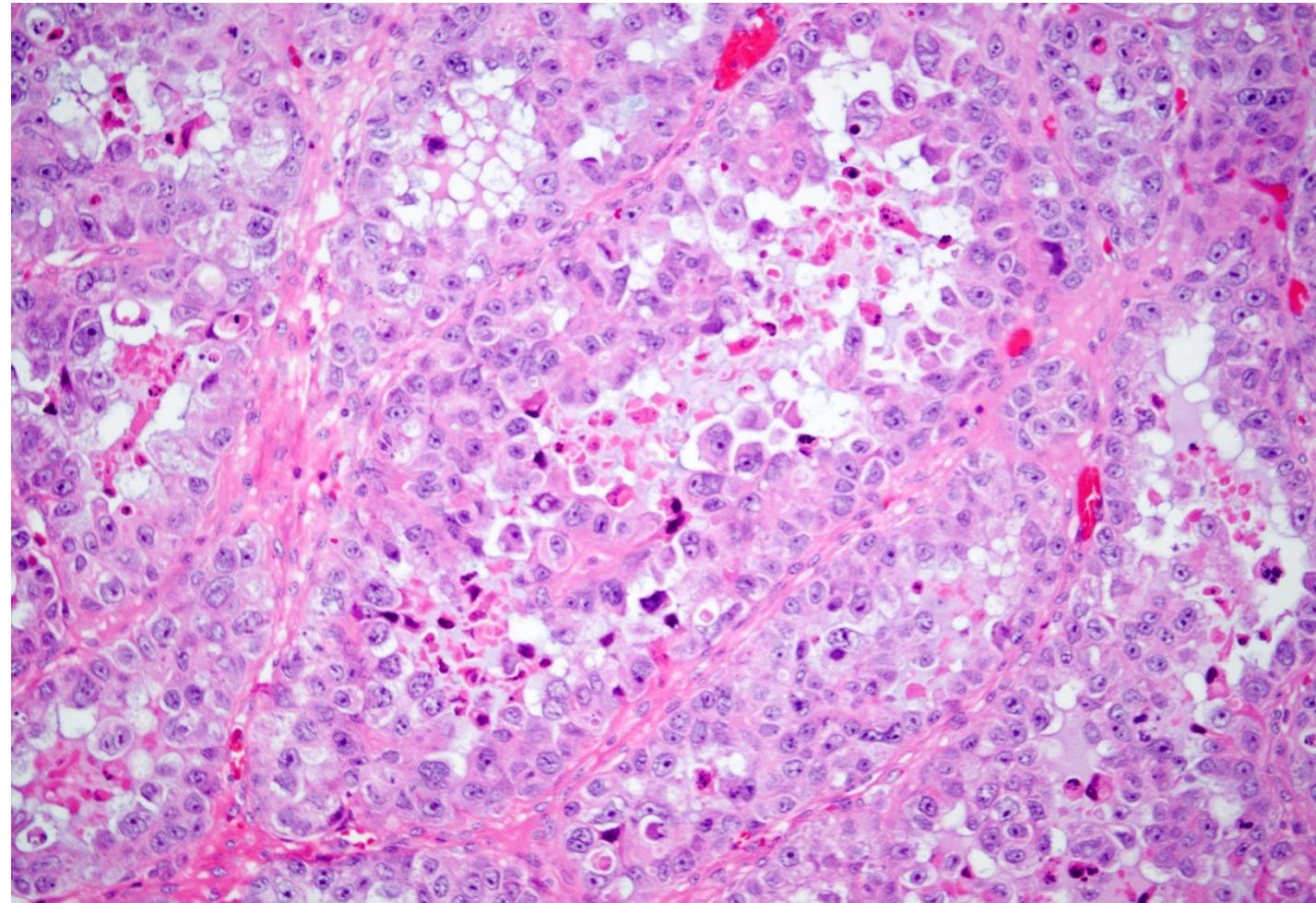
- Arias-Stella Reaction
- Endometrioid & high-grade serous carcinoma with clear cells
- Serous borderline tumor and carcinoma
- Yolk sac tumor
- Dysgerminoma
- Clear cell struma
- Metastatic intestinal / renal cell carcinoma
- Others

Do Not Diagnose Clear Cell Carcinoma Solely Based on the Presence of Clear Cytoplasm

High-grade serous carcinoma



Clear cell carcinoma



SEROUS vs CLEAR CELL CARCINOMA

Importance of correct diagnosis:

- Diagnosis of mixed serous and clear cell carcinoma not reproducible
- Most mixed serous and clear cell carcinomas show stage and immunoprofile similar to those seen in serous carcinoma
- If diagnosed as stage III/IV, clear cell carcinoma has worse prognosis and does not respond to platinum-based chemotherapy

Differences in Tumor Type in Low vs High-Stage Ovarian Cancer

(Köbel et al. *Int J Gynecol Pathol.* 2010;29:203-11)

TABLE 2. *Distribution of primary tumor type by stage from the British Columbia Cohort*

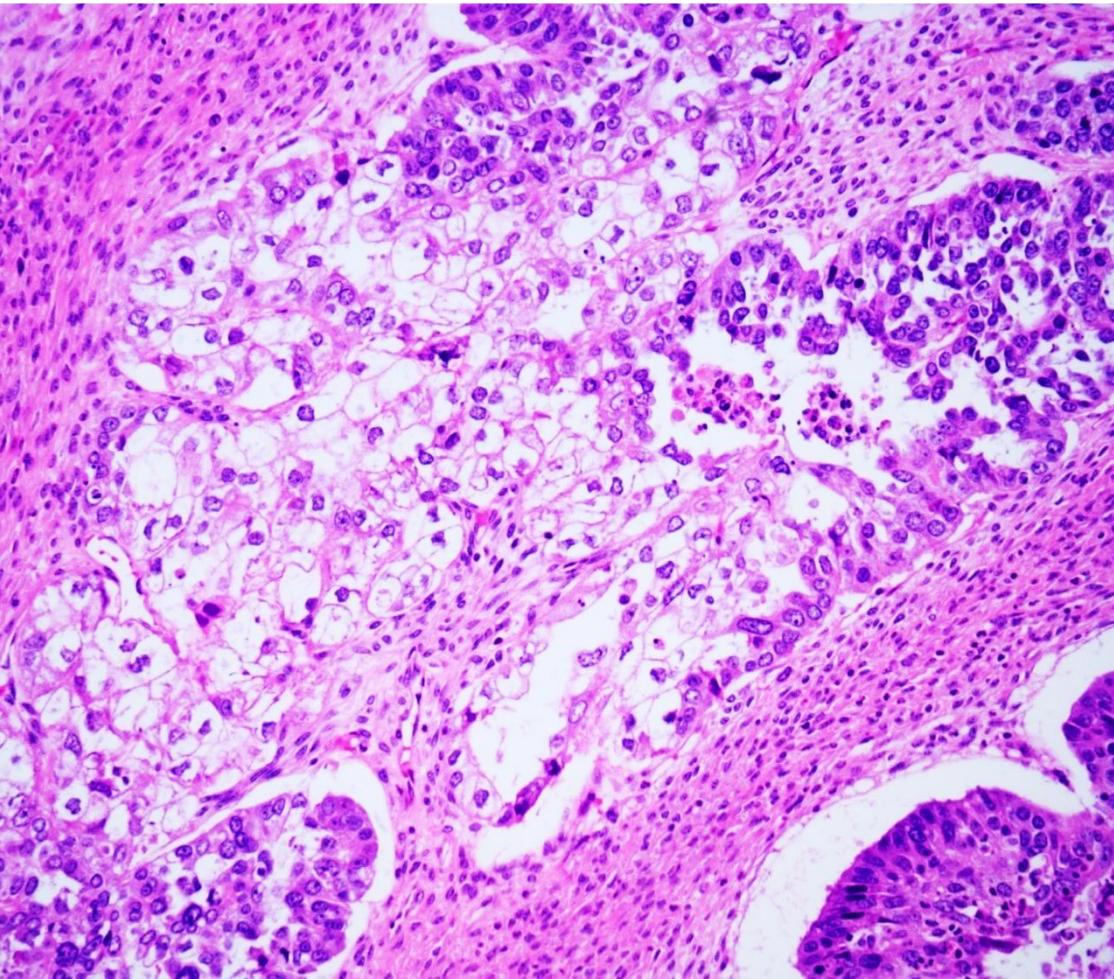
Stage	High-grade serous (%)	Clear cell (%)	Endometrioid (%)	Mucinous (%)	Low-grade serous (%)	Other (%)	All (%)
I/II	35.5	26.2	26.6	7.5	1.9	3.2	37.7
III/IV	87.7	4.5	2.5	1.2	5.3	1.2	62.3
All	68.1	12.2	11.3	3.4	3.4	1.6	100

Stage I - 71%
Stage II - 4%
Stage III - 17%
Stage IV - 8%

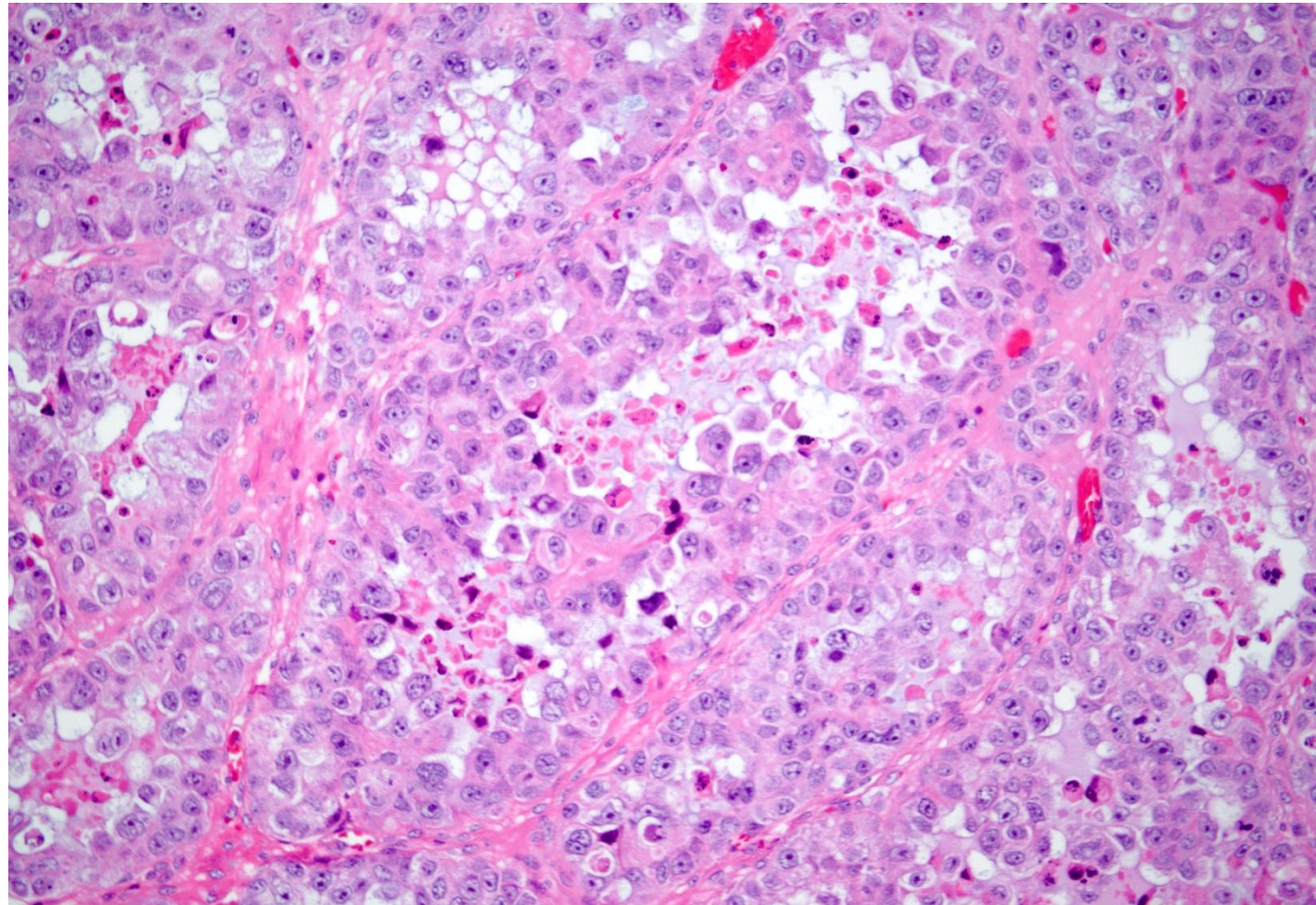
*Bennett et al.
Histopathology.
2015;66:808-15*

Do Not Diagnose Clear Cell Carcinoma Solely Based on the Presence of Clear Cytoplasm

High-grade serous carcinoma



Clear cell carcinoma



SEROUS vs CLEAR CELL CARCINOMA

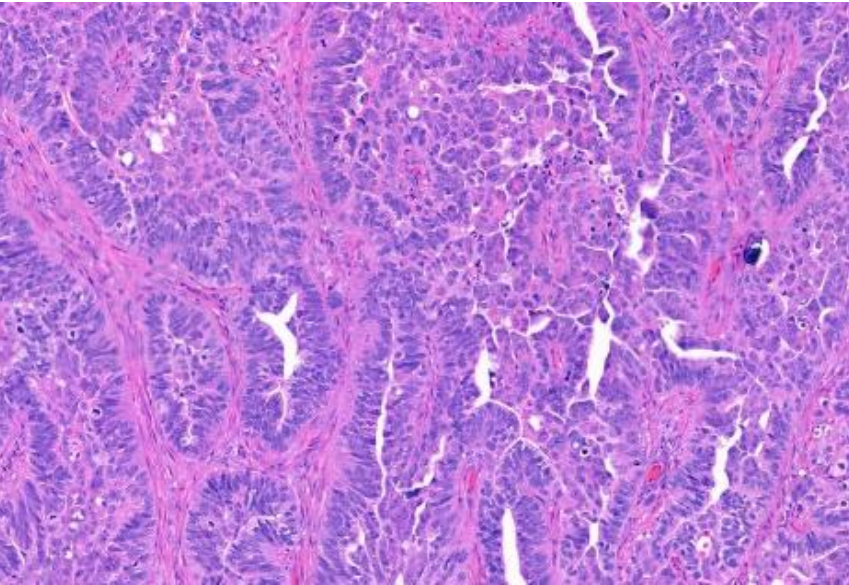
		%					
	N	WT1	p53	ER	p21	Cyclin E	HNF-1 β
CCC	133	3	4.6	11	73.7	81.5	82.8
SerC	200	80	48	76	33.3	51.5	4.8

Napsin-A / Racemase

Features Favoring Different Types of Carcinoma

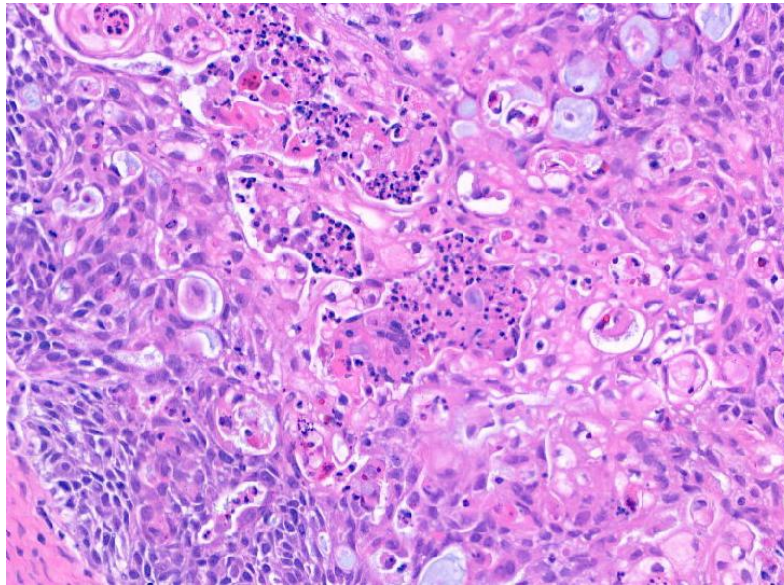
High-grade Serous

- Large cells
- Multinucleated giant cells
- More typical areas (papillary, micropapillary)
- Psammomatous calcs



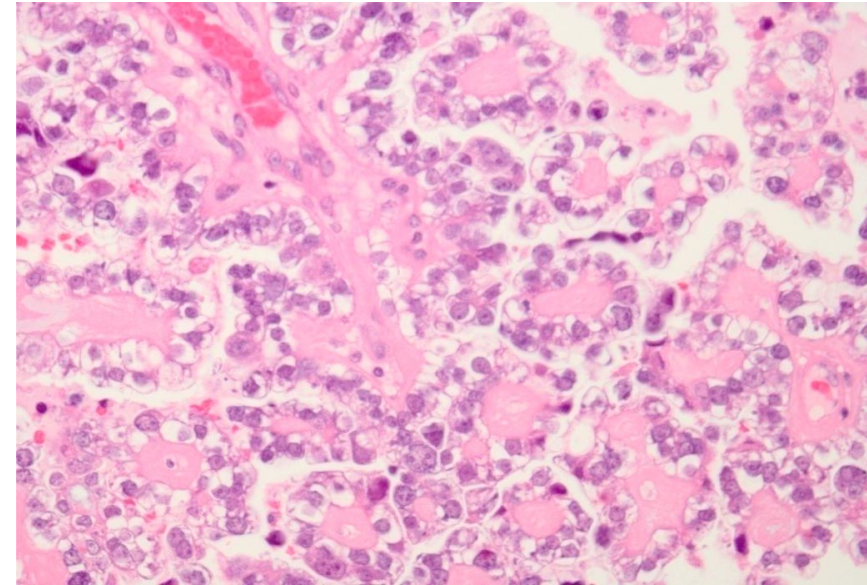
Endometrioid

- Glands with smooth luminal outlines
- Squamous, secretory or mucinous differentiation
- Endometriosis

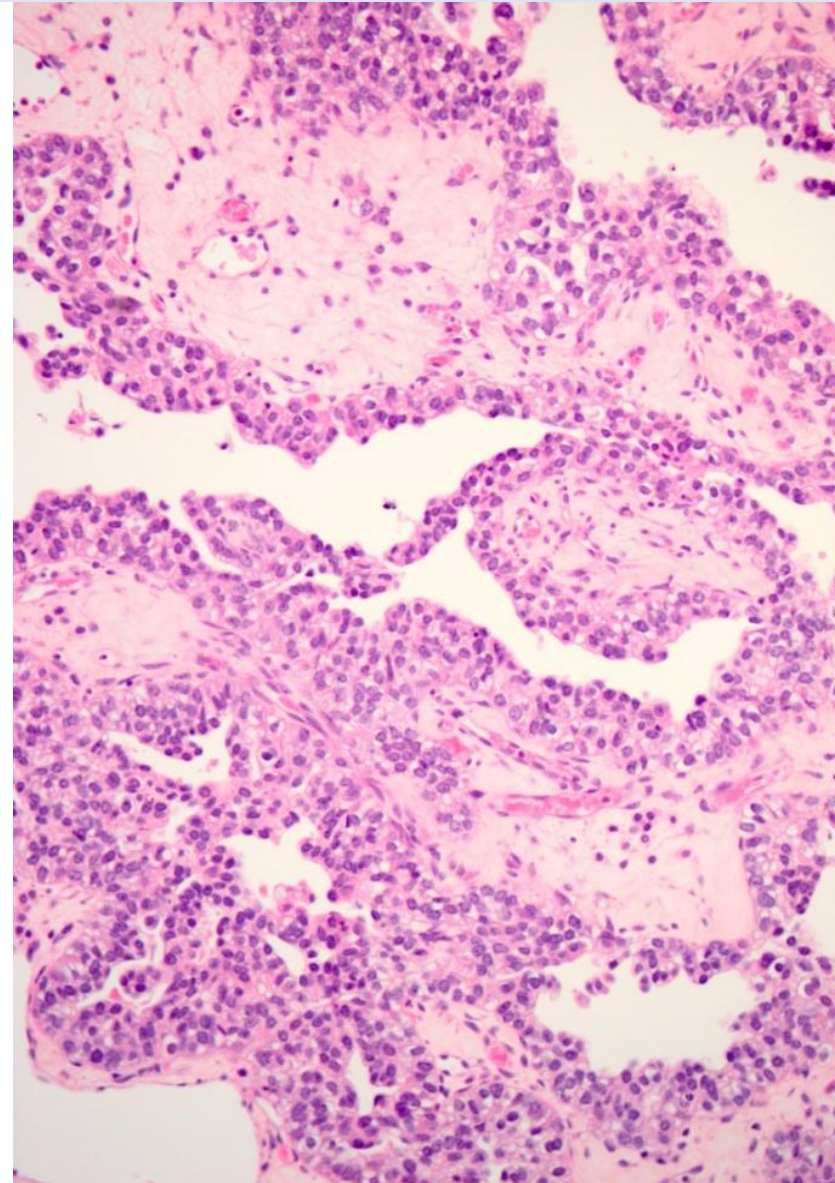
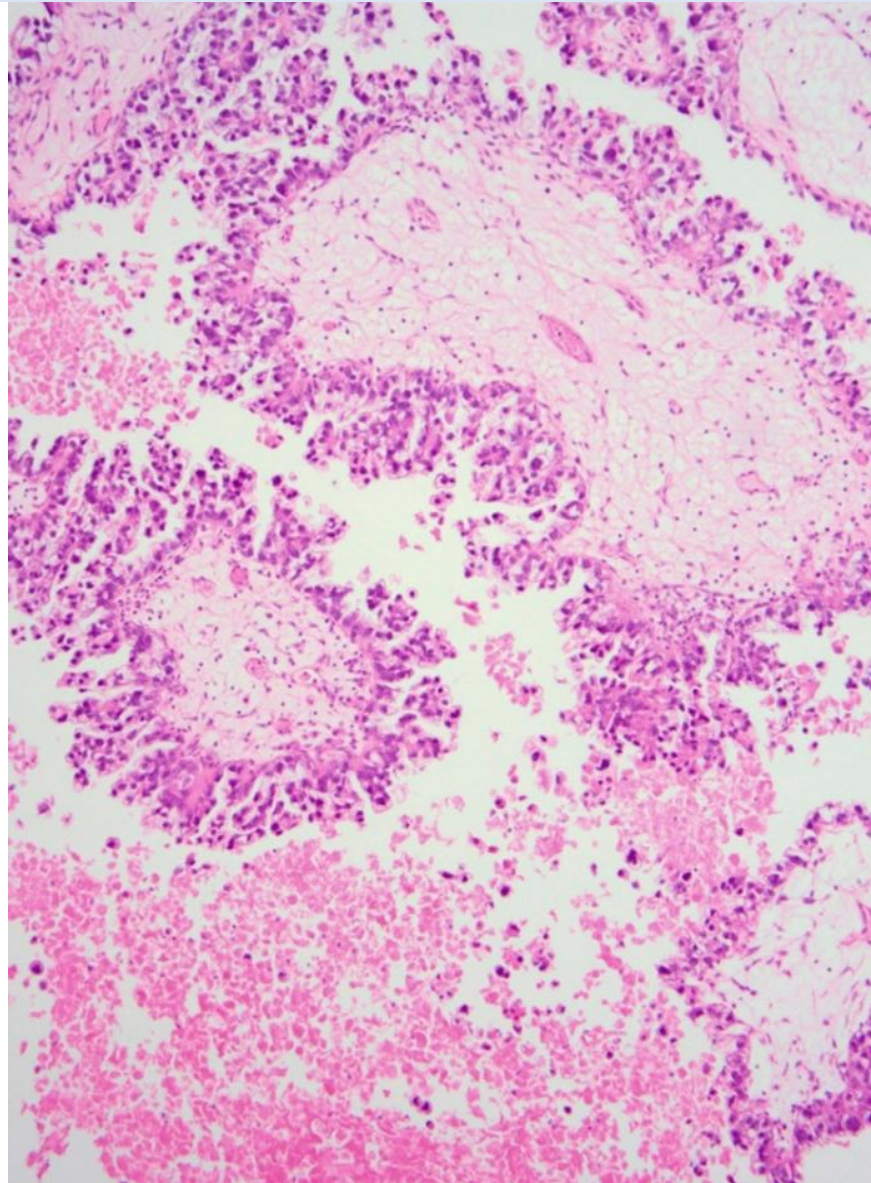
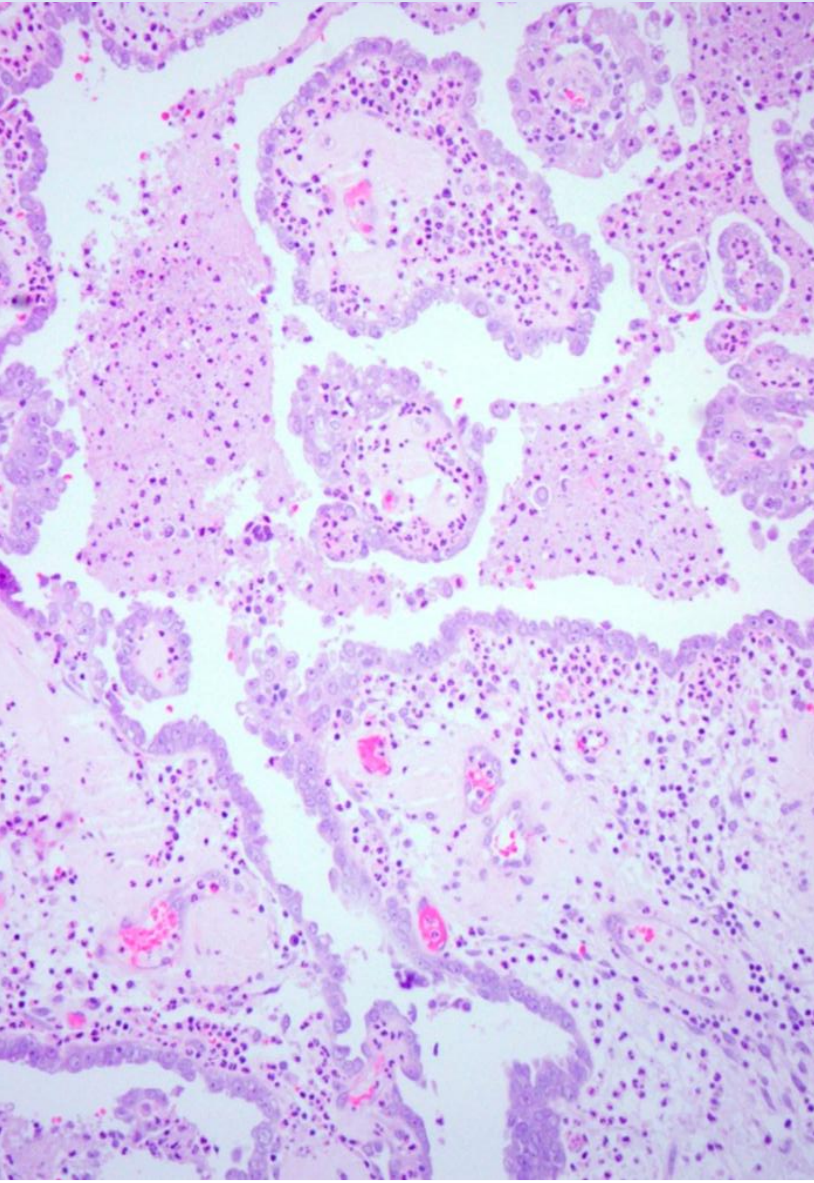


Clear Cell

- Tubulocystic, papillary and/or solid architecture
- Usually no marked cytologic atypia
- Endometriosis



Distinguishing between Clear Cell Carcinoma and Low-Grade Serous Neoplasm Can Be Difficult



Distinguishing between Clear Cell Carcinoma and Low-Grade Serous Neoplasm Can Be Difficult

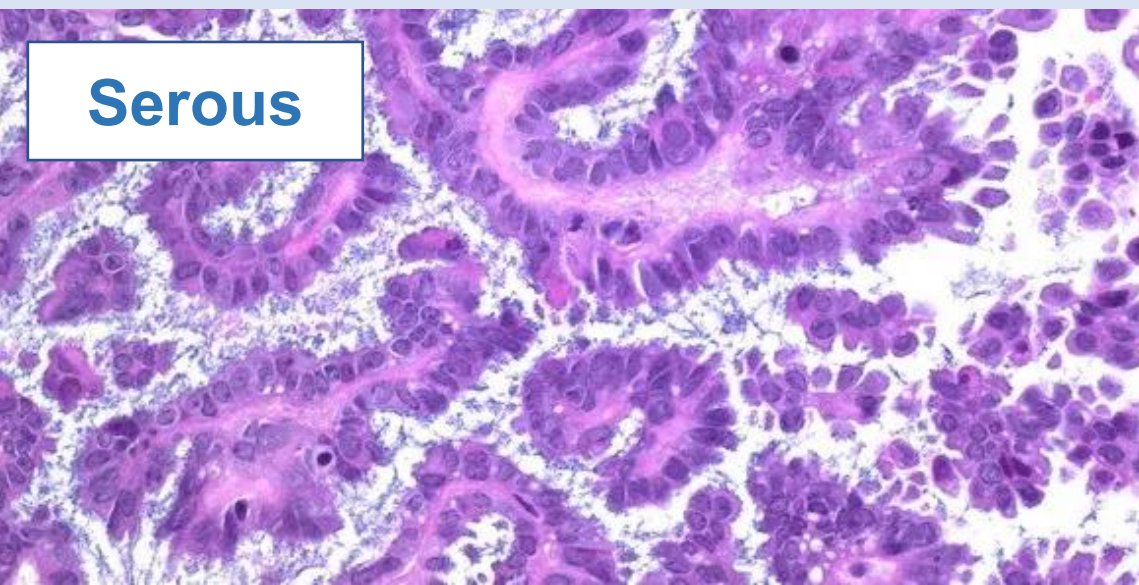
- **Features favoring clear cell carcinoma:**

- ✓ Unilateral
- ✓ Non-hierarchical branching
- ✓ Lack of stratification and tufting
- ✓ Monomorphic cells
- ✓ Other growth patterns
- ✓ Endometriosis

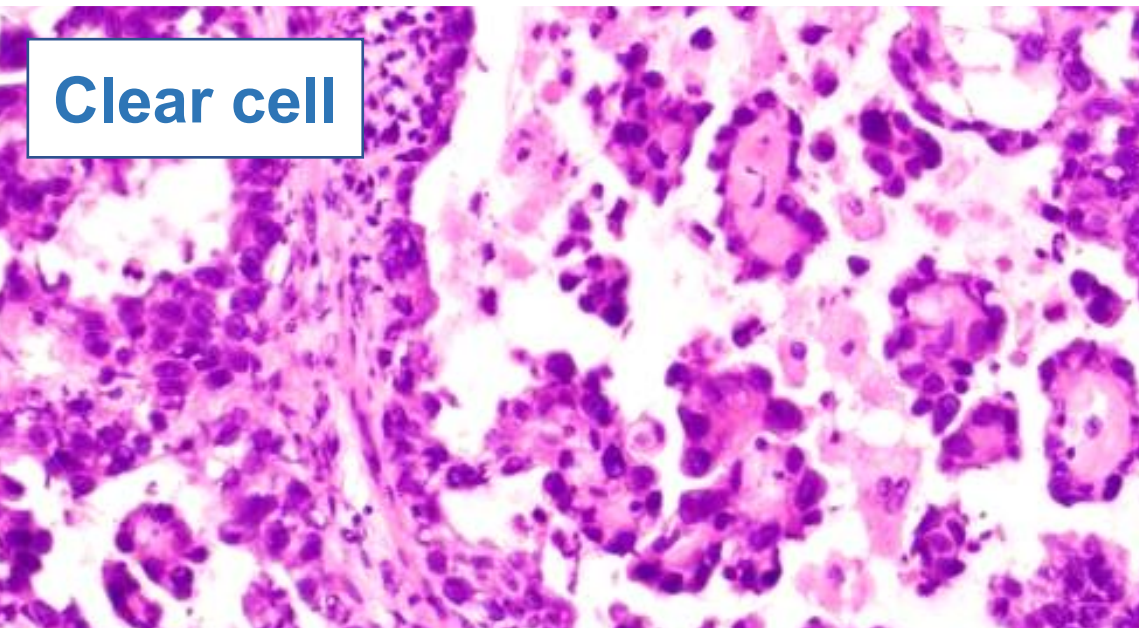
Nature of Papillae

Papillae	Serous	Clear cell
Shape/size	Variable	More uniform
Hyalinization	Rare	Common
Edema	Rare	Common
Tufting	Common	Rare

Clear Cell Carcinoma May Mimic a Low-Grade Serous Neoplasm



Serous



Clear cell

Nature of Papillae

Papillae	Serous	Clear cell
Shape/size	Variable	More uniform
Hyalinization	Rare	Common
Edema	Rare	Common
Tufting	Common	Rare

Molecular Alterations in Clear Cell Carcinoma

Gene	Gene type	Change	Pathways affected	Roles in tumor development
ARID1A	Tumor suppressor	Mutation in ~50%	SWI/SNF chromatin remodeling complex	Modulate accessibility of transcription factors to promoters
PIK3CA	Oncogenic	Mutation in ~40%	PI3K/AKT/mTOR	Proliferation/survival
PPP2R1A	Oncogenic	Mutation in 7%	AKT/MAPK	Proliferation/survival
KRAS	Oncogenic	Mutation in 5%	AKT/MAPK	Proliferation/survival
BRCA1/2	Tumor suppressor	Mutation in 6%	DNA repair	Genomic instability
PTEN	Tumor suppressor	Mutation in 5%	PI3K/AKT/mTOR	Proliferation/survival
CDKN2A/2B	Tumor suppressor	Deletion in 9%	CDK inhibitors (p15/p16)	Cell cycle progression
ZNF217	Oncogenic	Amplification in 36%	ZNF217	Antiapoptosis
PPM1D	Oncogenic	Amplification in 10%	p53 mediated apoptosis	Antiapoptosis
AKT2	Oncogenic	Amplification in 14%	AKT/mTOR	Proliferation/survival
MET	Oncogene	Amplification in 37%	AKT/MAPK	Proliferation/survival

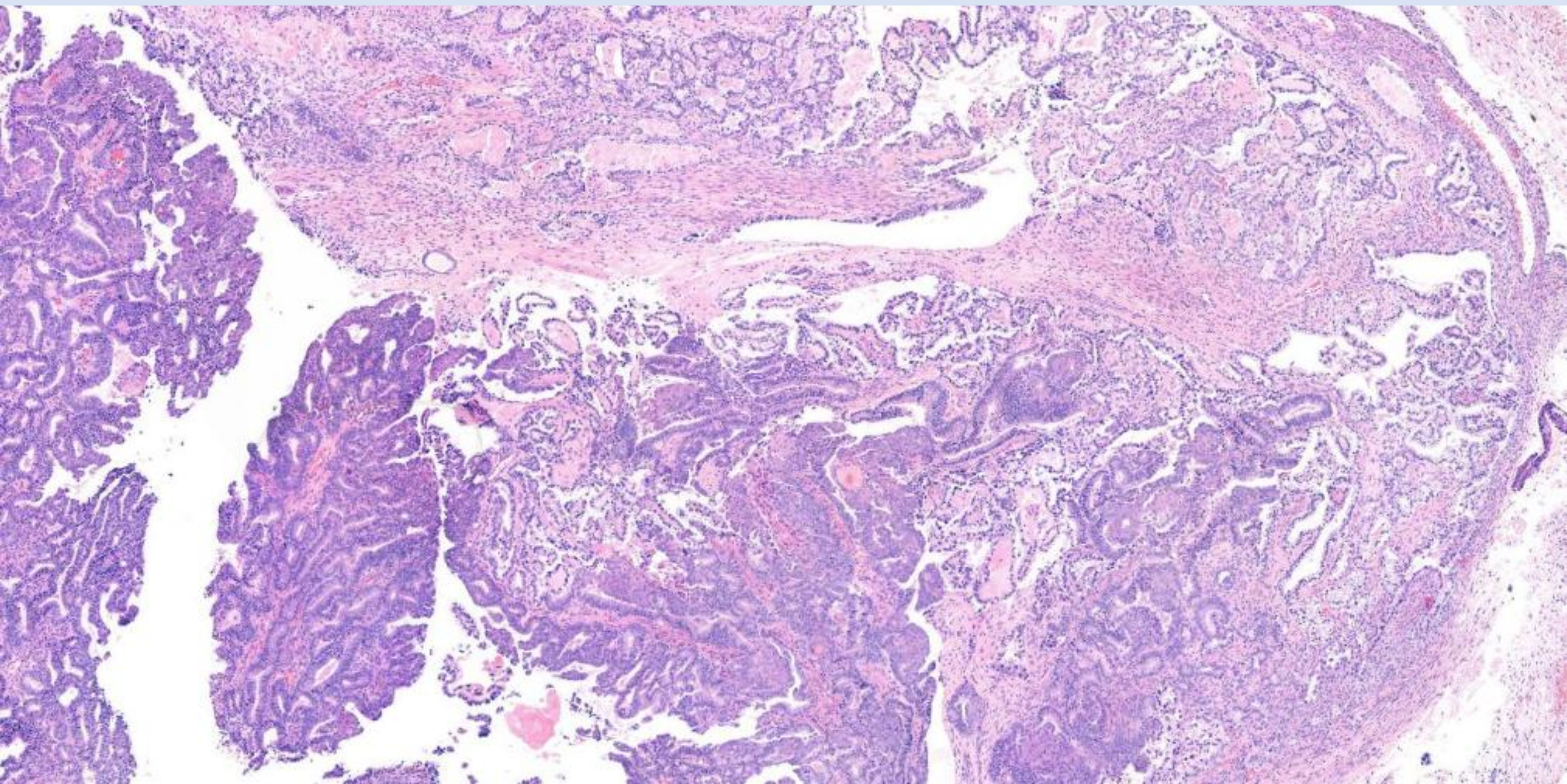
**p53
mutations
in ~25%**

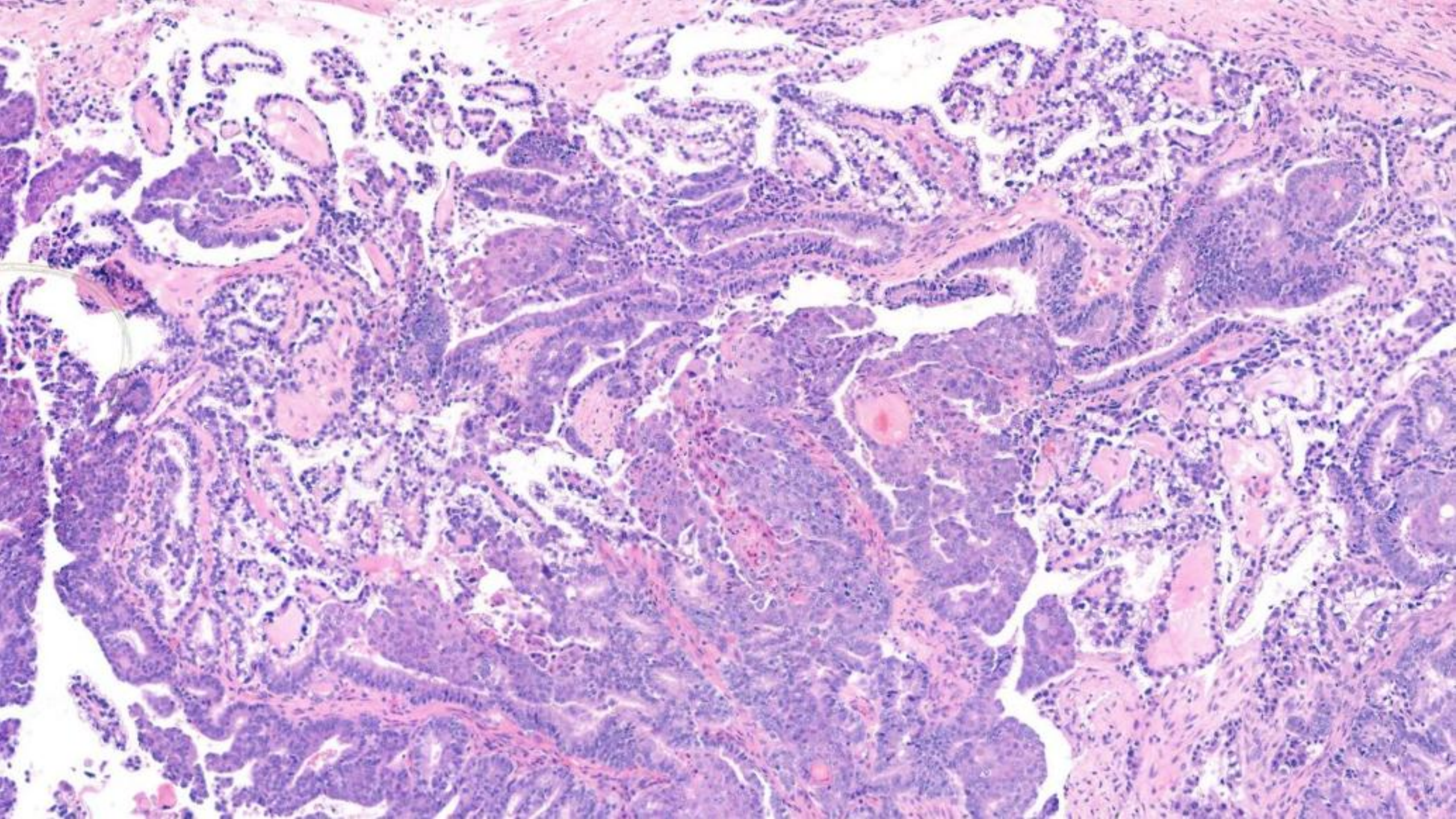
Clear Cell Carcinomas of the Ovary: Evaluation of Prognostic Parameters Based on a Clinicopathologic Analysis of 100 Cases

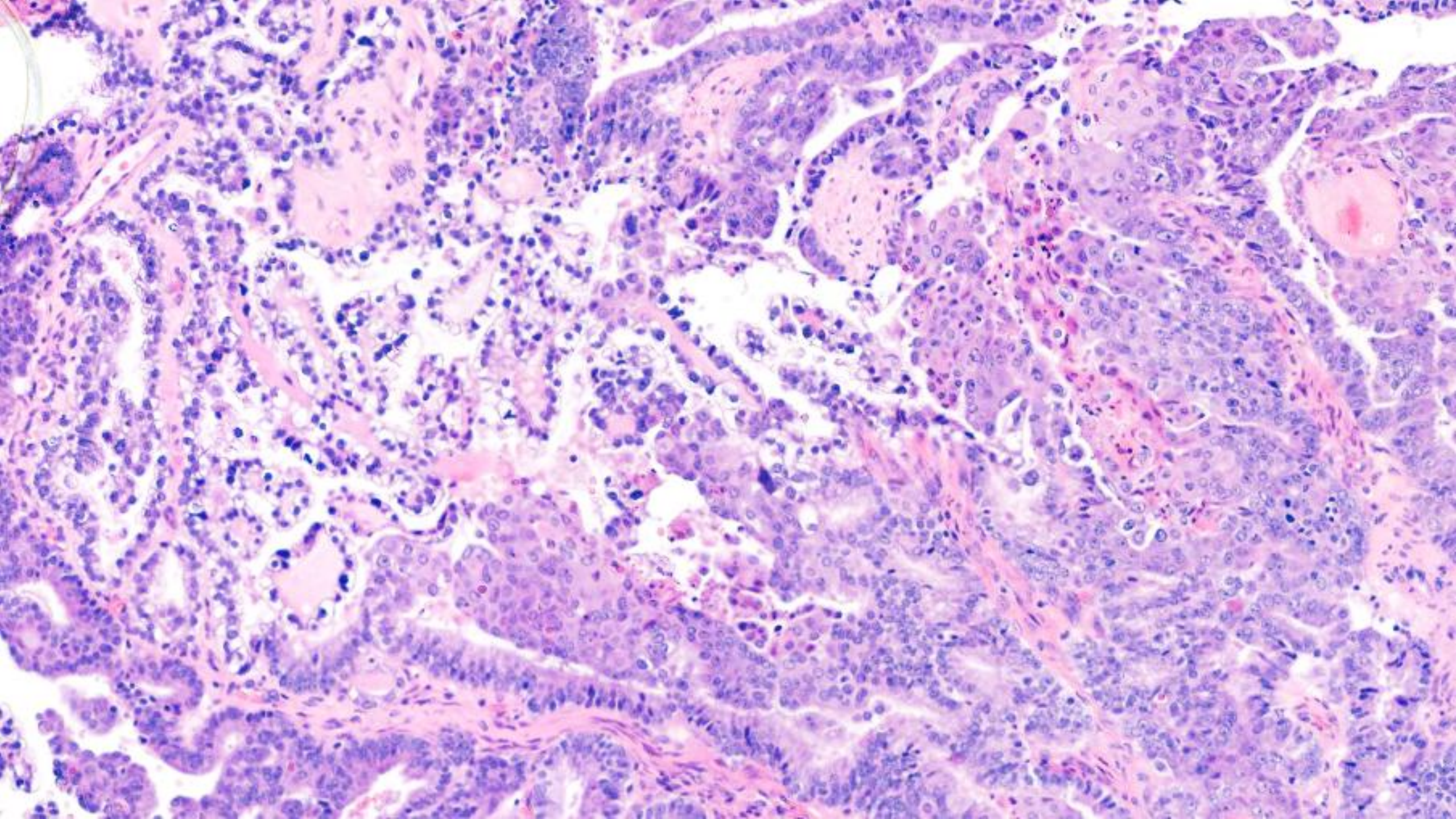
(Bennett et al. Histopathology. 2015;66:808-15)

- Endometriosis vs adenofibroma does not alter prognosis
- When confined to the ovary, favorable prognosis (5 year-survival rates: 14% for stage III, 4% for stage IV)
- Adverse histology as poor response to platinum-based therapy

Mixed Endometrioid and Clear Cell Carcinoma





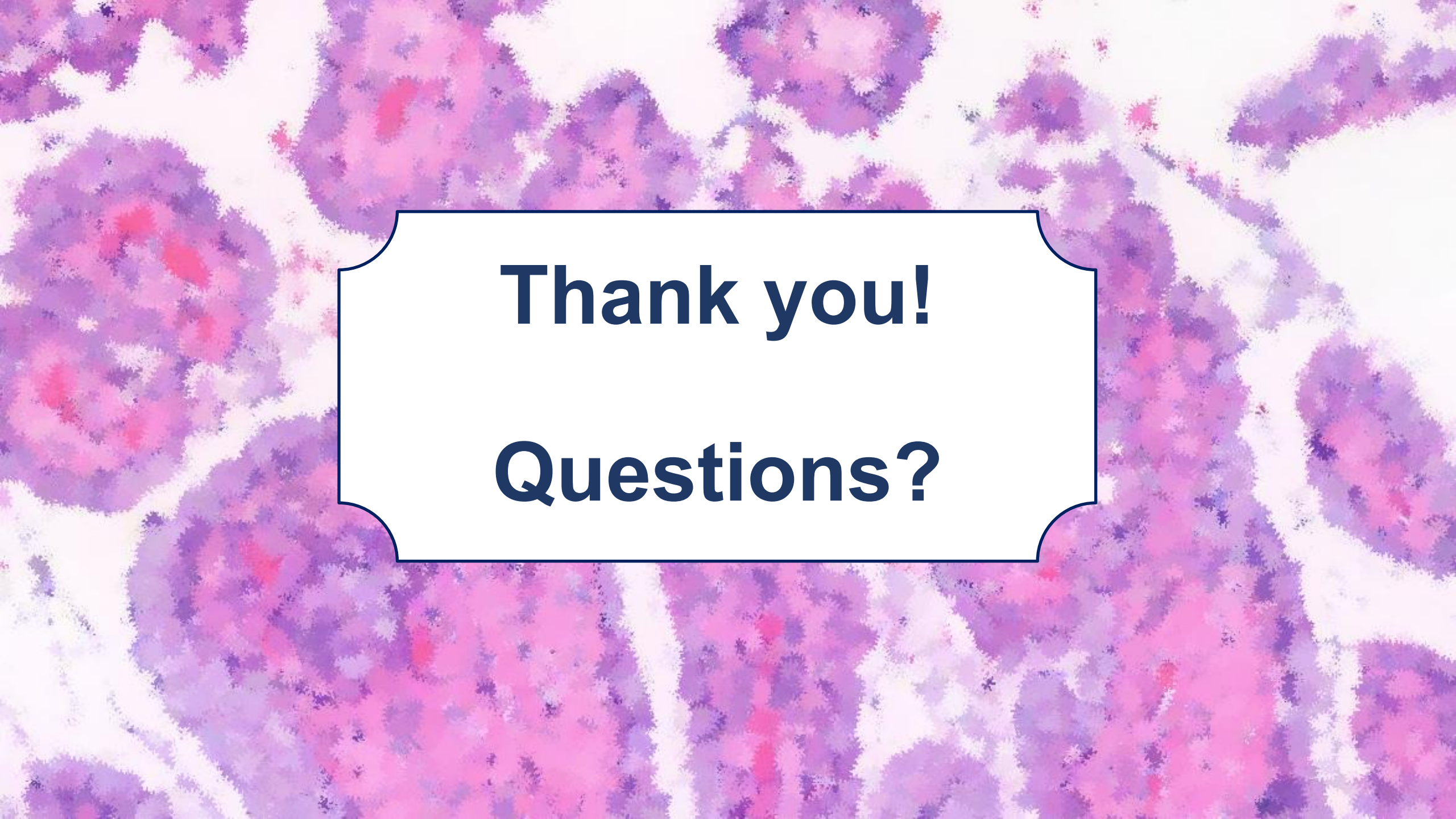


Increased Risk for Ovarian Cancer in Lynch Syndrome Patients

- Risk of endometrial and ovarian cancers is higher than colorectal cancer
- ~10% of endometriosis-associated ovarian carcinomas are MMR-deficient
- **Mismatch repair testing is recommended in:**
 - ✓ Endometrioid carcinoma
 - ✓ De-/undifferentiated carcinoma
 - ✓ Clear cell carcinomas
 - ✓ Carcinomas of mixed cell types

Summary

- Endometriosis associated ovarian carcinomas have a heterogenous morphology and may present diagnostic challenges
- Lynch syndrome screening is recommended in all endometriosis associated ovarian carcinomas:
 - ✓ Endometrioid carcinoma
 - ✓ De-/undifferentiated carcinoma
 - ✓ Clear cell carcinomas
 - ✓ Carcinomas of mixed cell types



Thank you!

Questions?