Gynecologic and Gastrointestinal Pathology: Pitfalls and Pearls in Frozen Section Diagnosis

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32nd Annual Park City Anatomic Pathology Update
Deer Valley Resort, Park City, UT
February 13, 2019

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Gynecologic Pathology

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OBJECTIVES

Not an "all inclusive" presentation

- Discuss goals of frozen section analysis in gynecologic pathology
- Discuss common diagnostic difficulties and sources of error in frozen section analysis of ovarian neoplasms
- Discuss diagnostic difficulties and sources of error in frozen section analysis of endometrial lesions

OVARIAN NEOPLASMS

Pearls…

GUIDING PRINCIPALS *(before you look at the slides)*

1. Know the patient's history

- Age
- Previous history of malignancy

2. Know the clinical presentation

- Radiology (and/or operative findings)
  - Where is the mass arising from?
  - Laterality – Unilateral or bilateral?
  - Extraovarian disease?
- Serum tumor markers
  - CA125
  - CEA
  - AFP
  - Etc.

3. Look at the gross specimen

- Size
- Surface growth?
- Cut surface consistency: Solid? Cystic? Papillary excrecences?
- Cyst contents/fluid
- Color

KNOW THE DECISION POINT(S)

How far should I "stick my neck out"?
What does the surgeon need to know?

ULTIMATE GOAL:

Facilitate the appropriate
selection of women requiring surgical staging

DECISION POINTS

1

Is the neoplasm a primary ovarian neoplasm or a metastasis?

2

3

EPITHELIAL OVARIAN NEOPLASMS

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Ovarian Cancer
NCCN Evidence Blocks™

WHO HISTOLOGIC CLASSIFICATION[1,2]

Serous Tumors	
• Serous cystadenoma	Benign
• Serous adenofibroma	Benign
• Serous surface papilloma	Benign
• Serous borderline tumor/atypical proliferative serous tumor	Borderline
• Serous borderline tumor-micropapillary variant/non-invasive low-grade serous carcinoma	Carcinoma in-situ/ grade III intraepithelial neoplasia
• Low-grade serous	Malignant
• High-grade serous	Malignant
Mucinous Tumors	
• Mucinous cystadenoma	Benign
• Mucinous adenofibroma	Benign
• Mucinous borderline tumor/atypical proliferative mucinous tumor	Borderline
• Mucinous carcinoma	Malignant
Endometrioid Tumors	
• Endometriotic cyst	Benign
• Endometriotic cystadenoma	Benign
• Endometriotic adenofibroma	Benign
• Endometrioid borderline tumor/atypical proliferative endometrioid tumor	Borderline
• Endometrioid carcinoma	Malignant
Clear Cell Tumors	
• Clear cell cystadenoma	Benign
• Clear cell adenofibroma	Benign
• Clear cell borderline tumor/atypical proliferative clear cell tumor	Borderline
• Clear cell carcinoma	Malignant

Brenner Tumors	
• Brenner tumor	Benign
• Borderline Brenner tumor/atypical proliferative Brenner tumor	Borderline
• Malignant Brenner tumor	Malignant
Seromucinous Tumors	
• Seromucinous cystadenoma	Benign
• Seromucinous adenofibroma	Benign
• Seromucinous borderline tumor/atypical proliferative seromucinous tumor	Borderline
• Seromucinous carcinoma	Malignant
Undifferentiated carcinoma	Malignant
Mesenchymal Tumors	
• Low-grade endometrioid stromal sarcoma	Malignant
• High-grade endometrioid stromal sarcoma	Malignant
Mixed Epithelial & Mesenchymal Tumors	
• Adenosarcoma	Malignant
• Carcinosarcoma	Malignant

NCCN: Reproduced with permission from Kurman RJ, Carcangiu ML, Herrington CS, Young RH. World Health Organization Classification of Tumours of the Female Reproductive Organs. IARC. Lyon, 2014.

CRITICAL POINT: ATYPICAL PROLIFERATIVE (BORDERLINE)

Epithelial ovarian neoplasms (serous, mucinous, endometrioid, transitional cell/Brenner) with uncertain biologic behavior

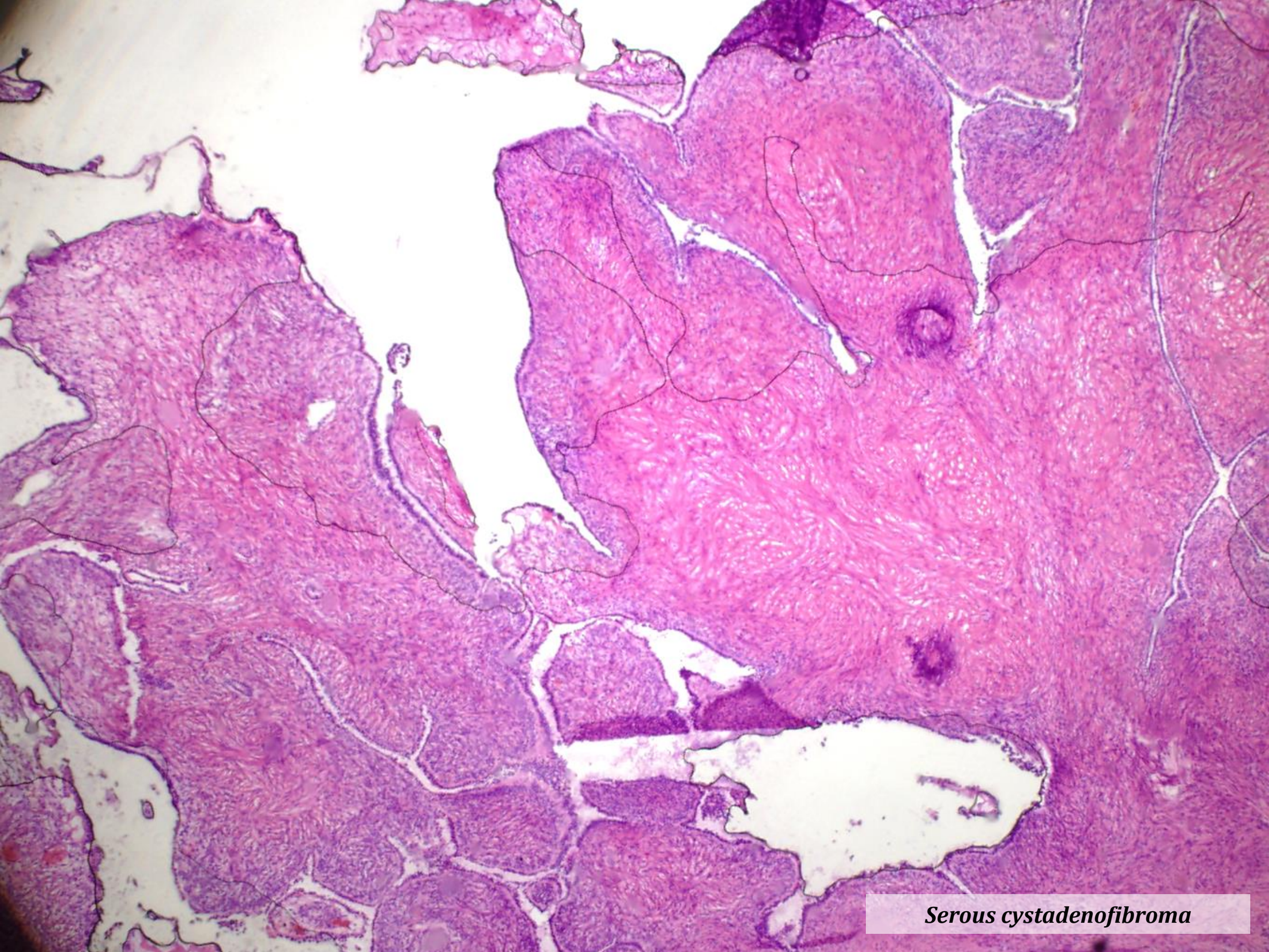
- Most behave in a benign/indolent fashion
- But… a small proportion (predominantly serous) can recur and progress

- **Getting to the correct diagnosis**
  - **Under diagnosis**
    - Sampling errors
    - Interpretive errors
  - **Over diagnosis**

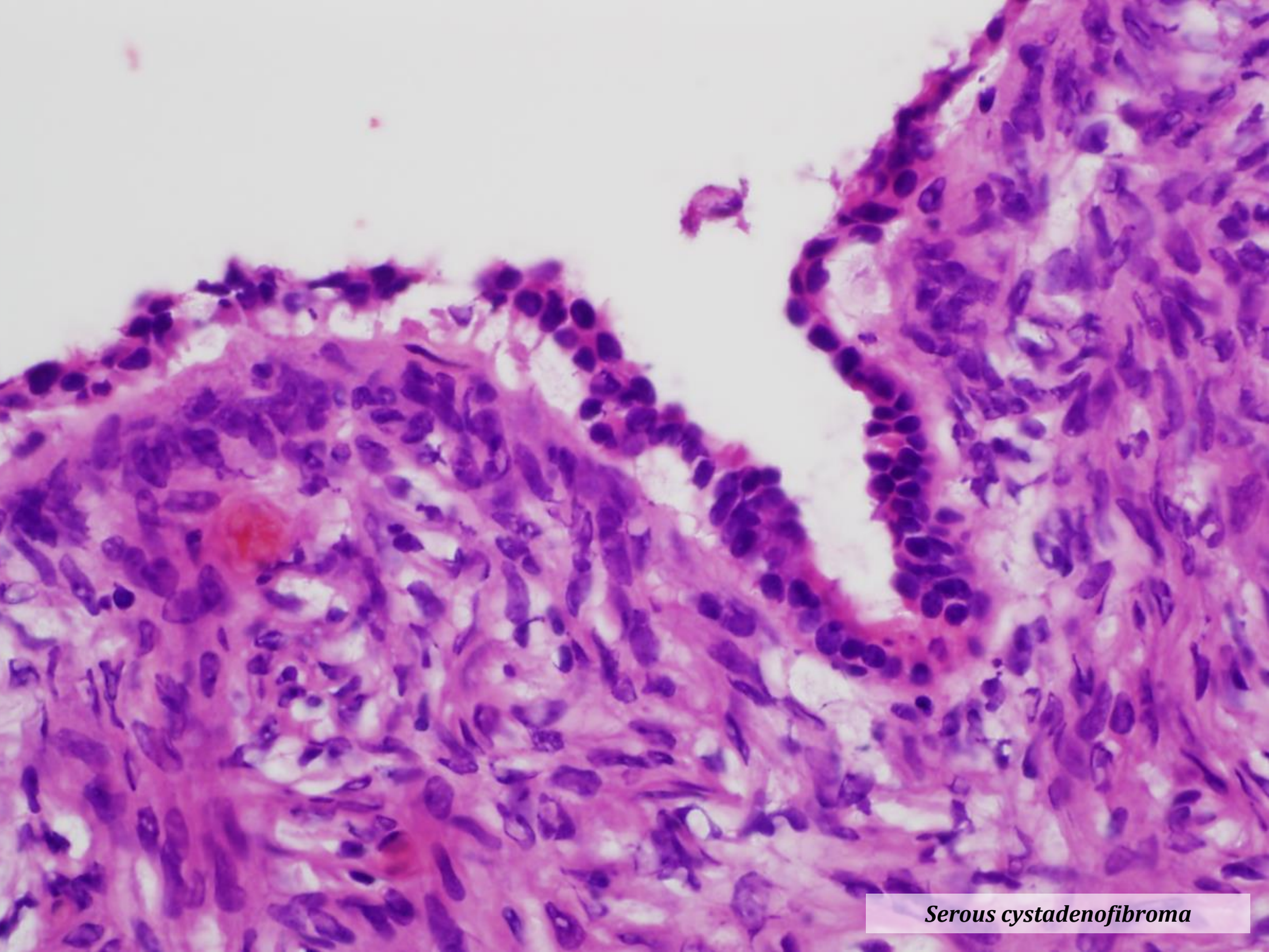
- **Should I completely stage the patient?**
- **Should I perform some type of modified staging?**
  - ✓ Frozen section diagnosis
  - ✓ Age
  - ✓ Fertility desires
  - ✓ Other operative findings

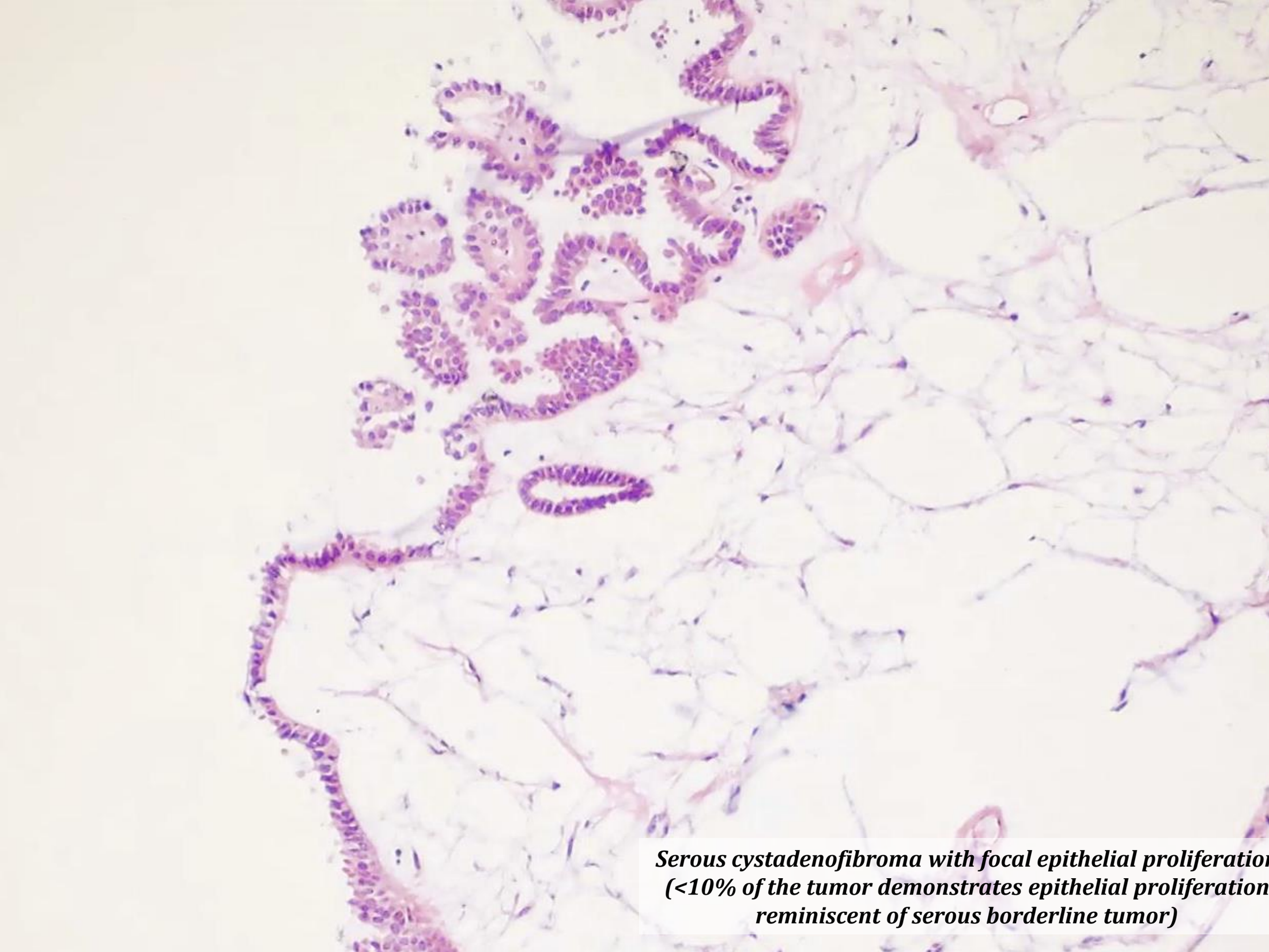
Serous Neoplasms

https://www.humpath.com/spip.php?article6693



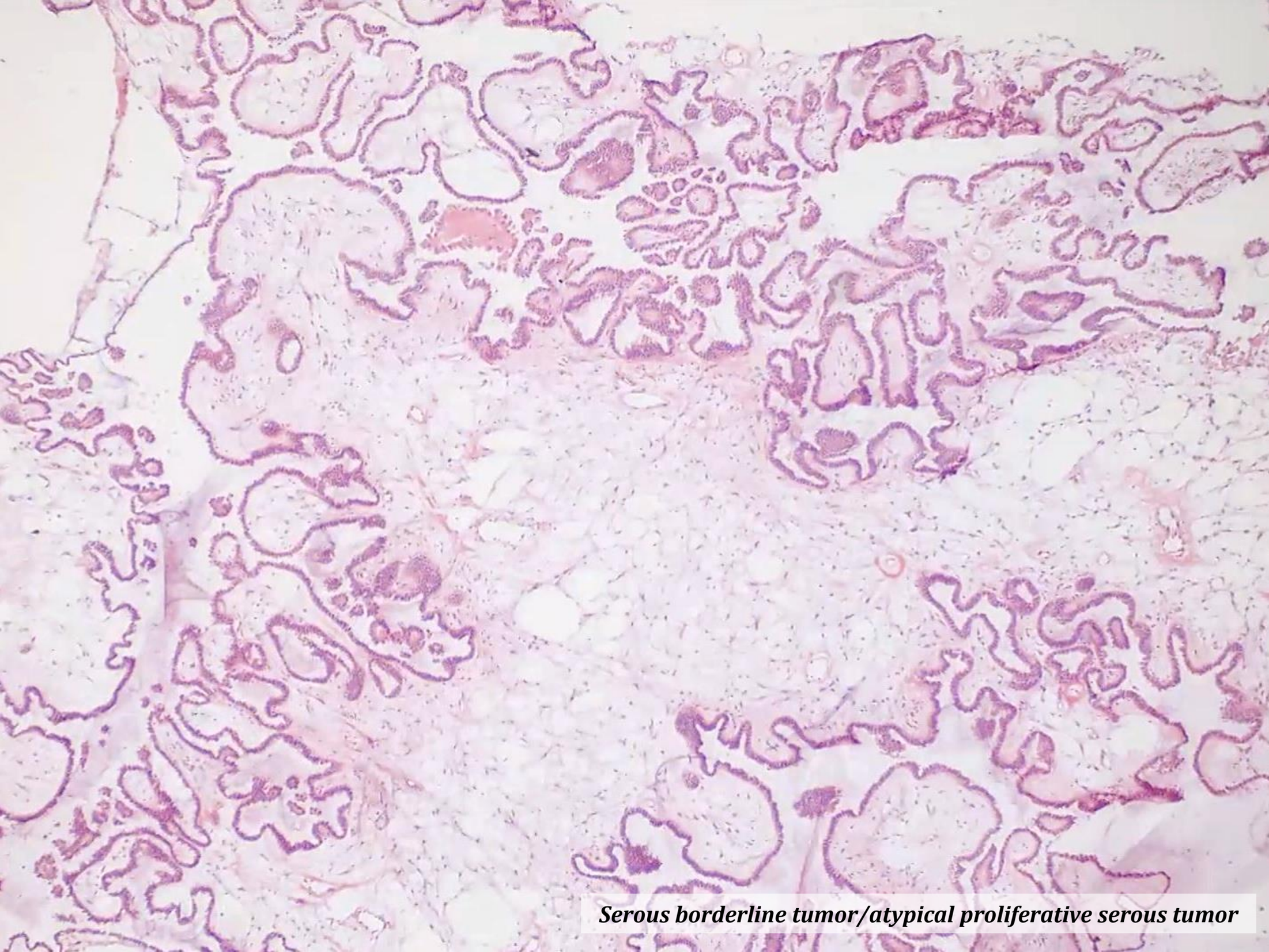
Serous cystadenofibroma


Serous cystadenofibroma

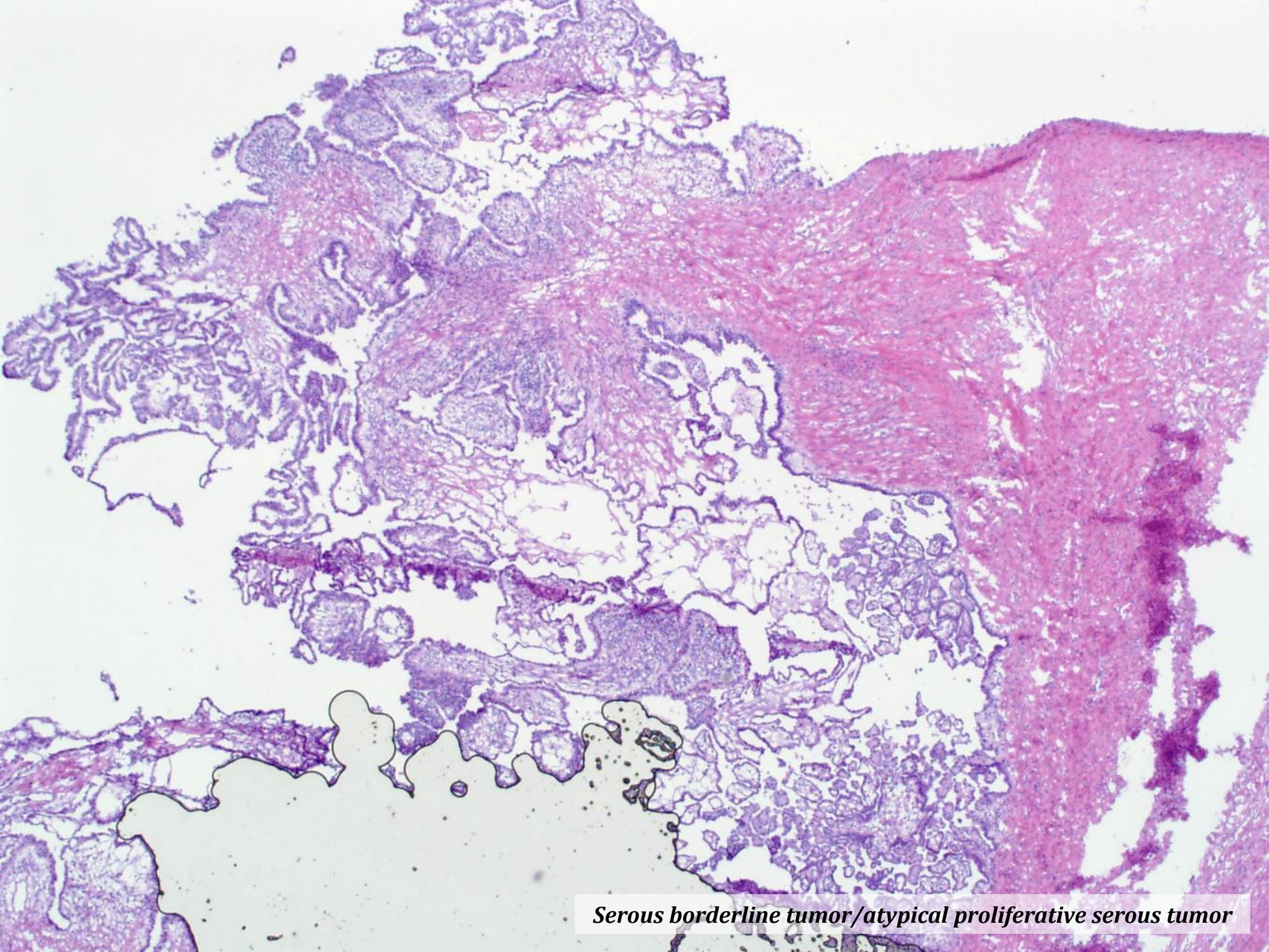


Serous cystadenofibroma with focal epithelial proliferation (<10% of the tumor demonstrates epithelial proliferation reminiscent of serous borderline tumor)

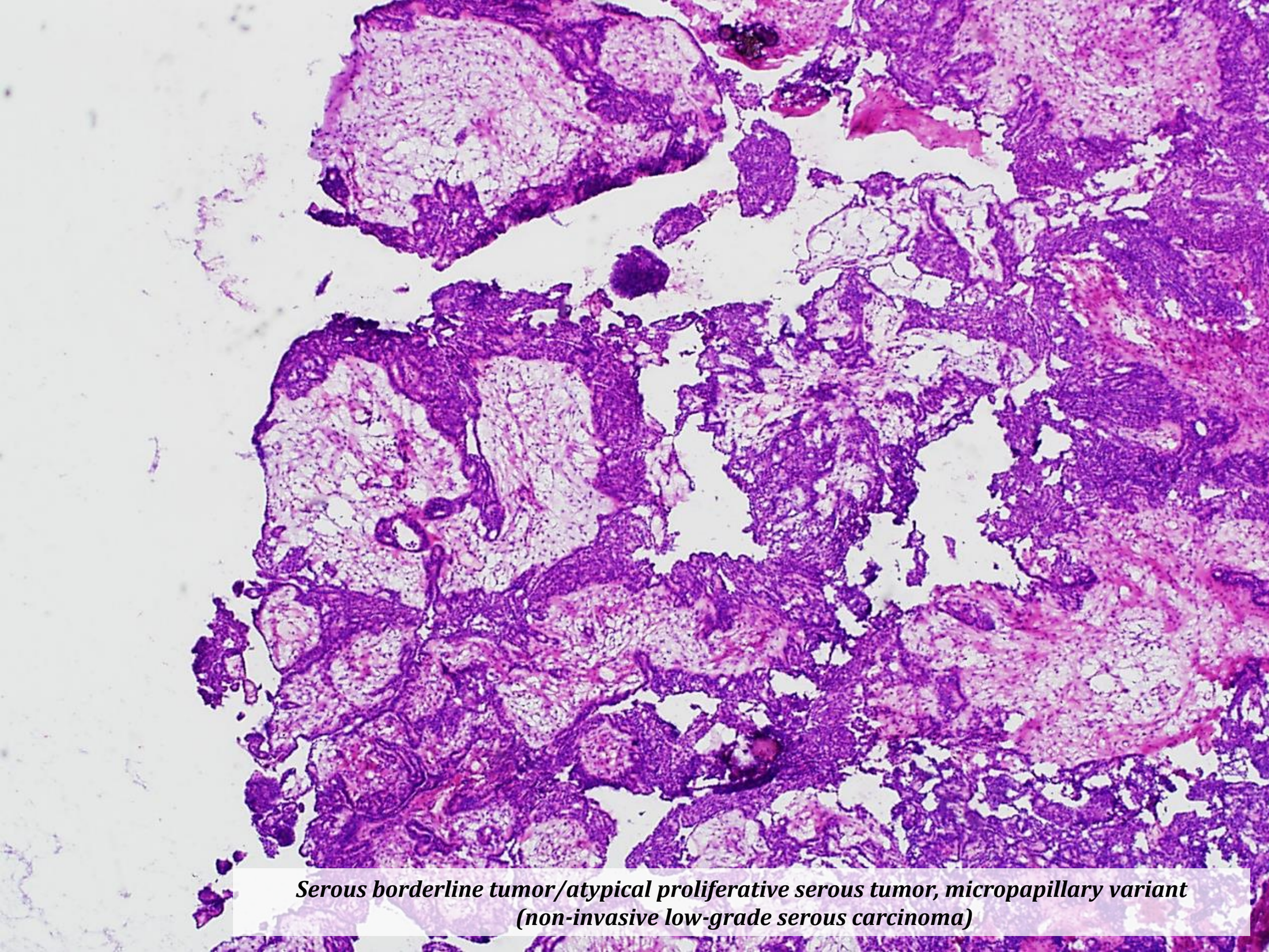
0cm 1 2 3 4 5



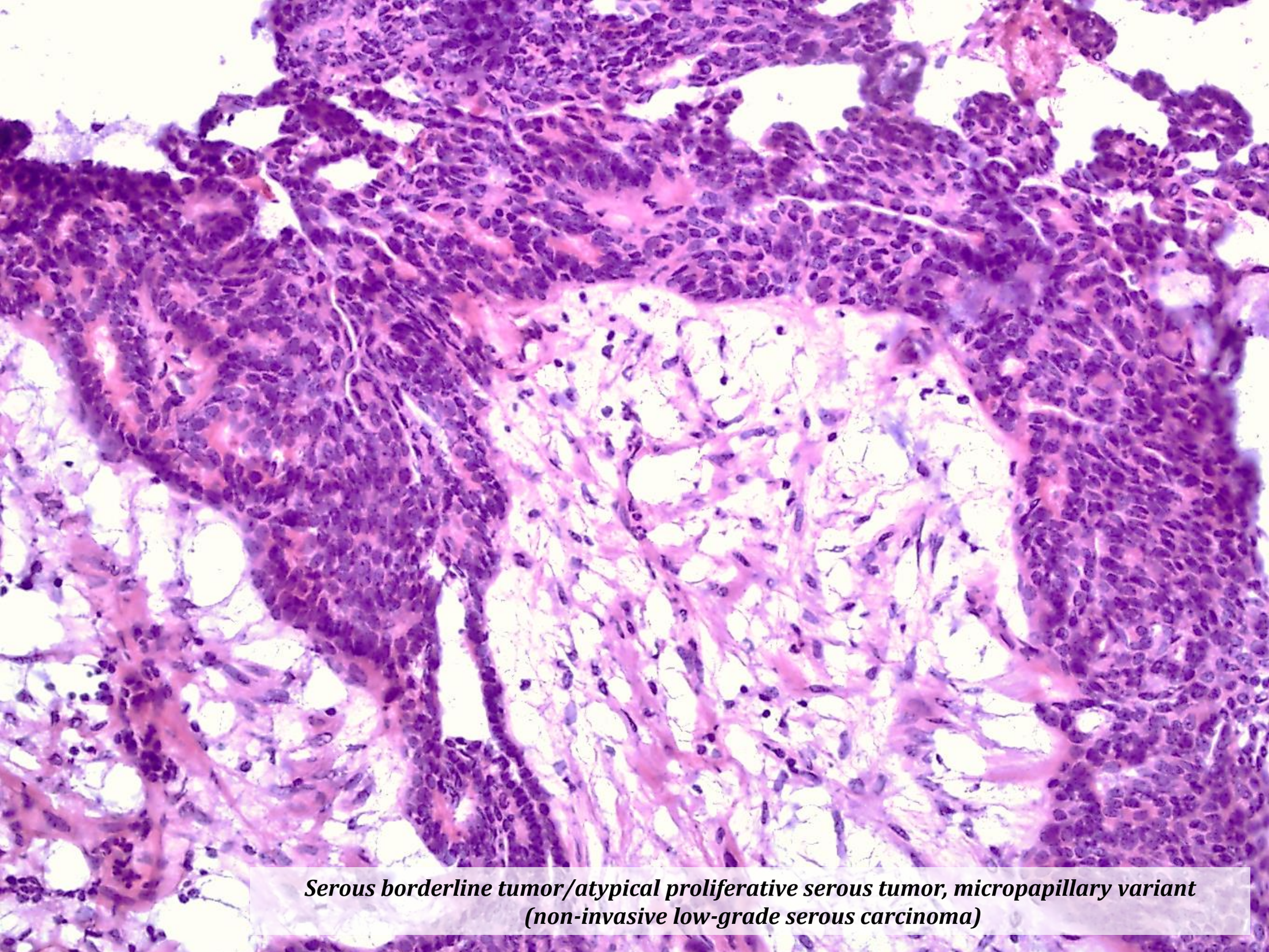
Serous borderline tumor/atypical proliferative serous tumor



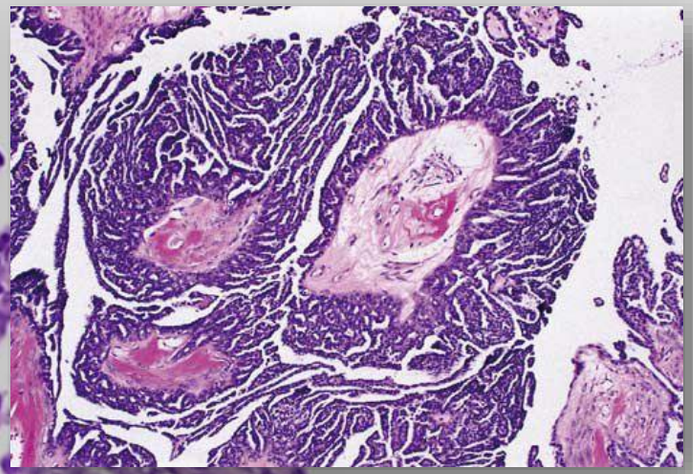
Serous borderline tumor/atypical proliferative serous tumor



Serous borderline tumor/atypical proliferative serous tumor, micropapillary variant (non-invasive low-grade serous carcinoma)



Serous borderline tumor/atypical proliferative serous tumor, micropapillary variant (non-invasive low-grade serous carcinoma)



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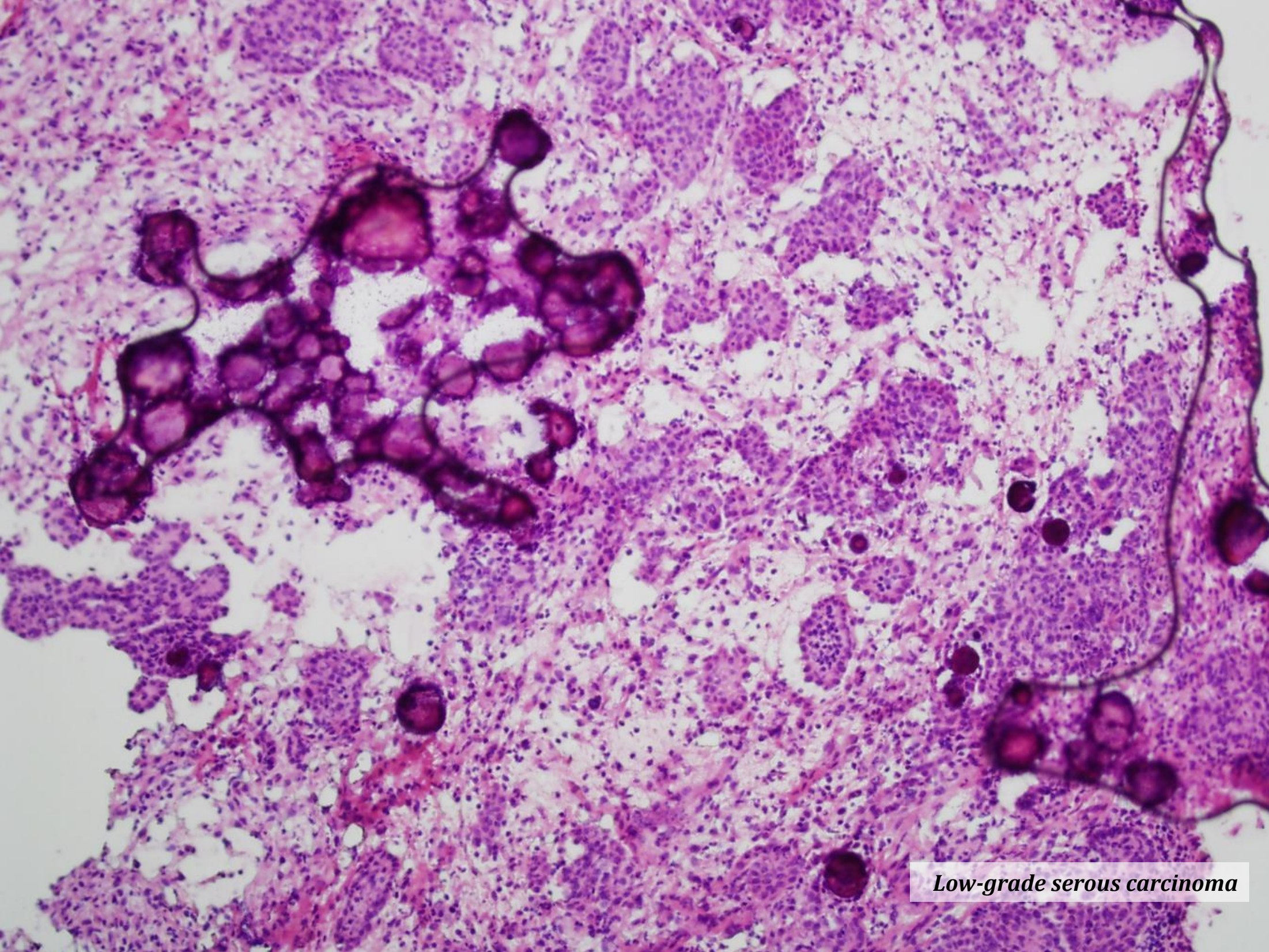
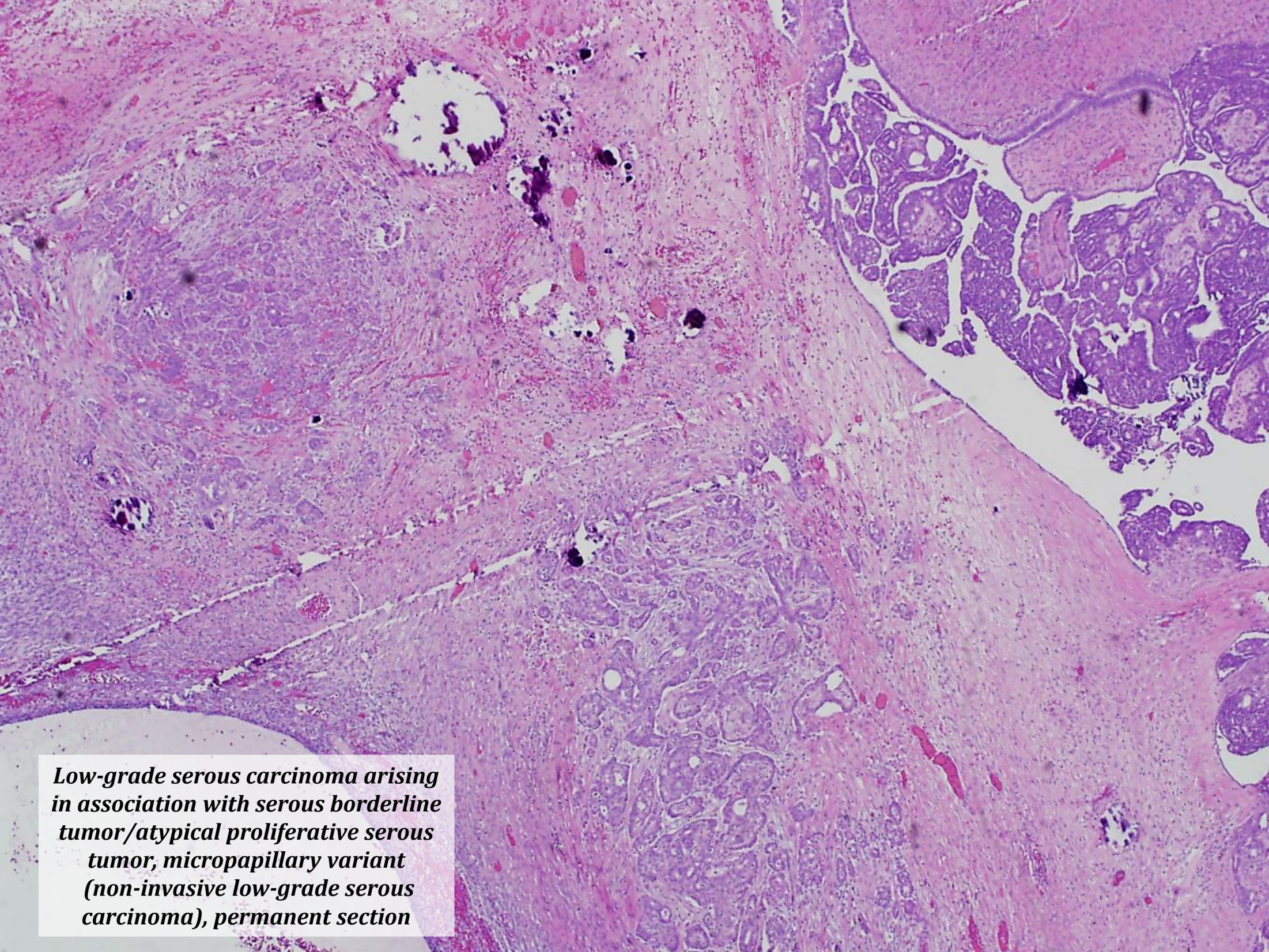
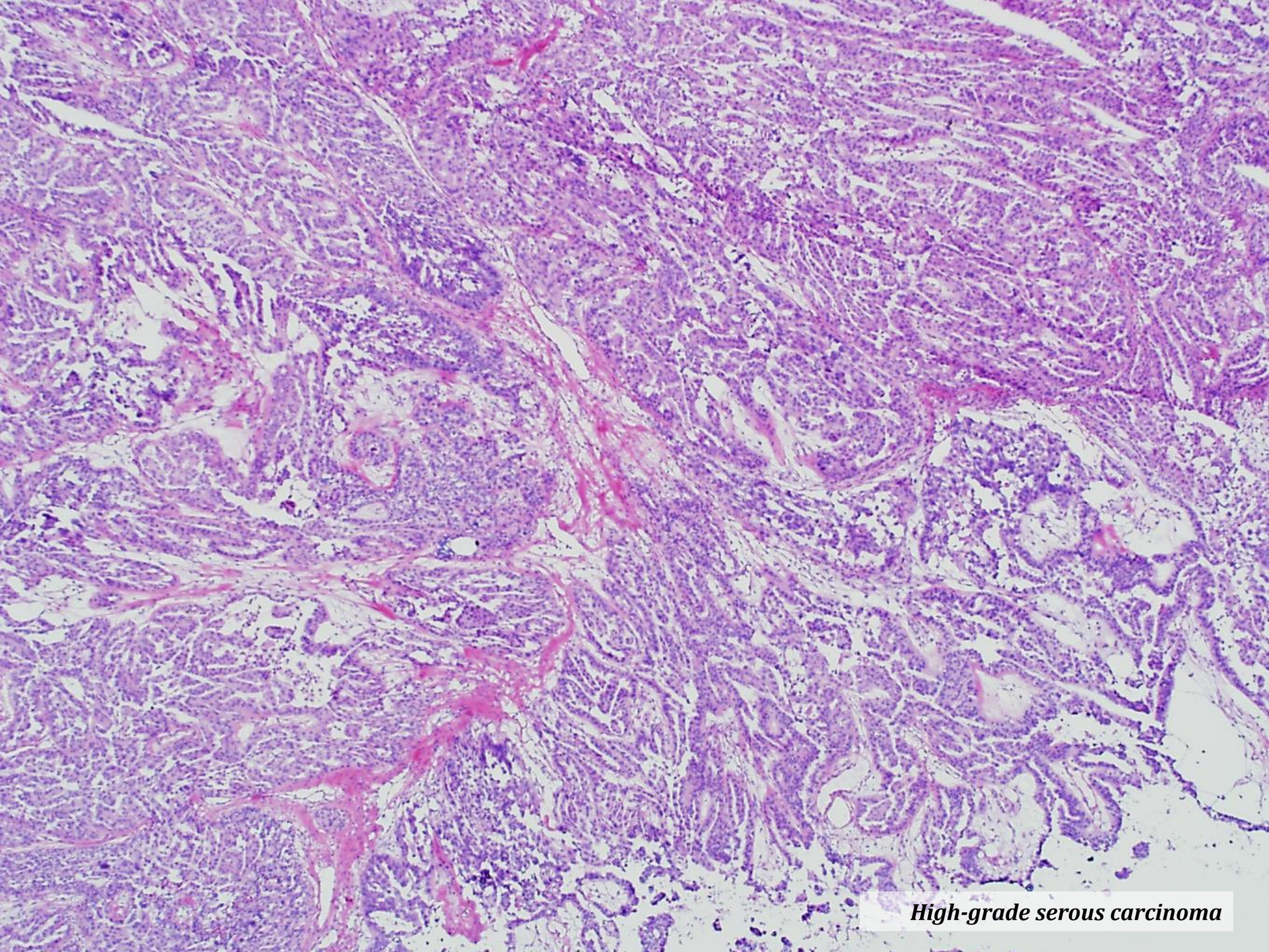
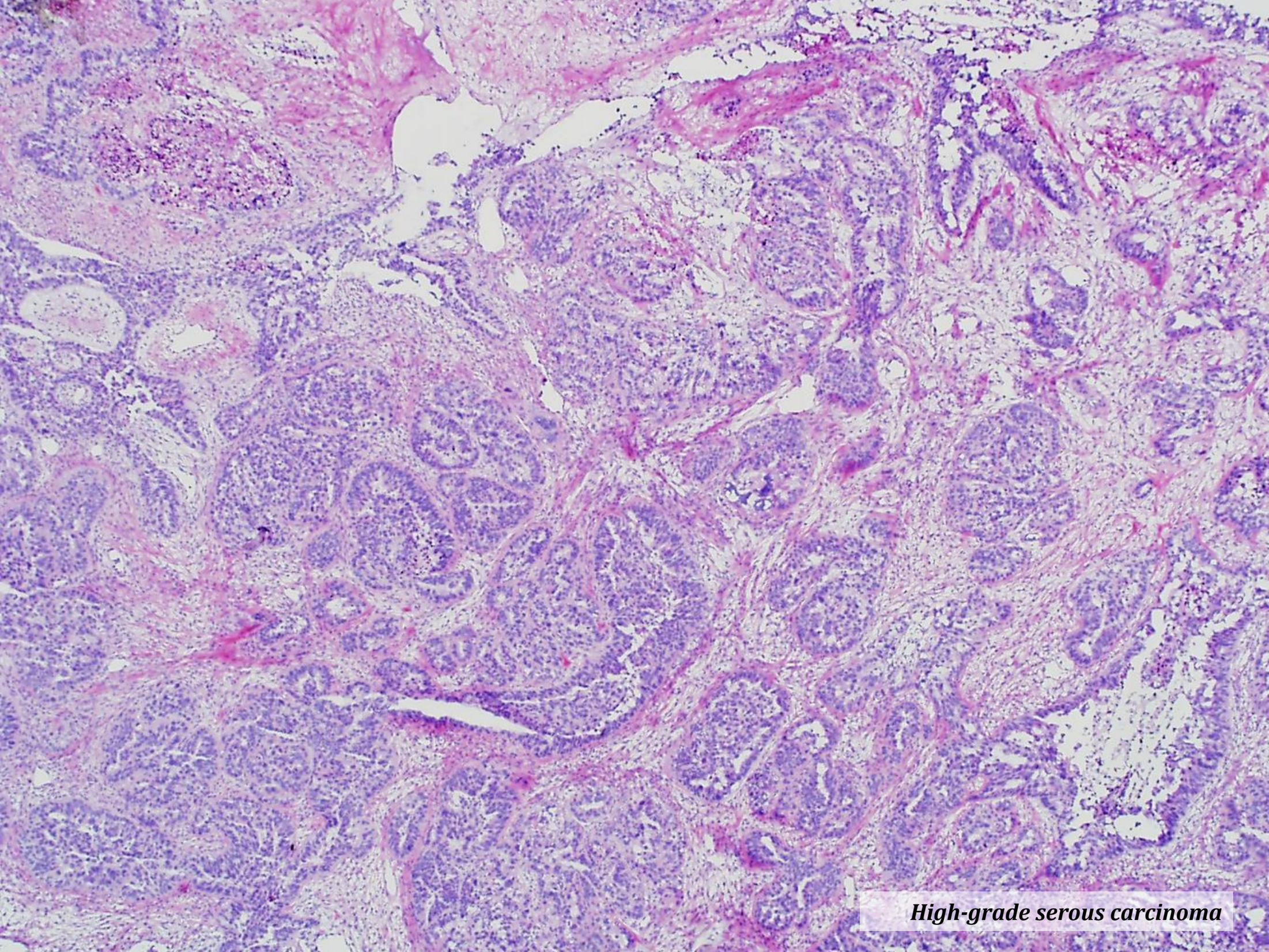
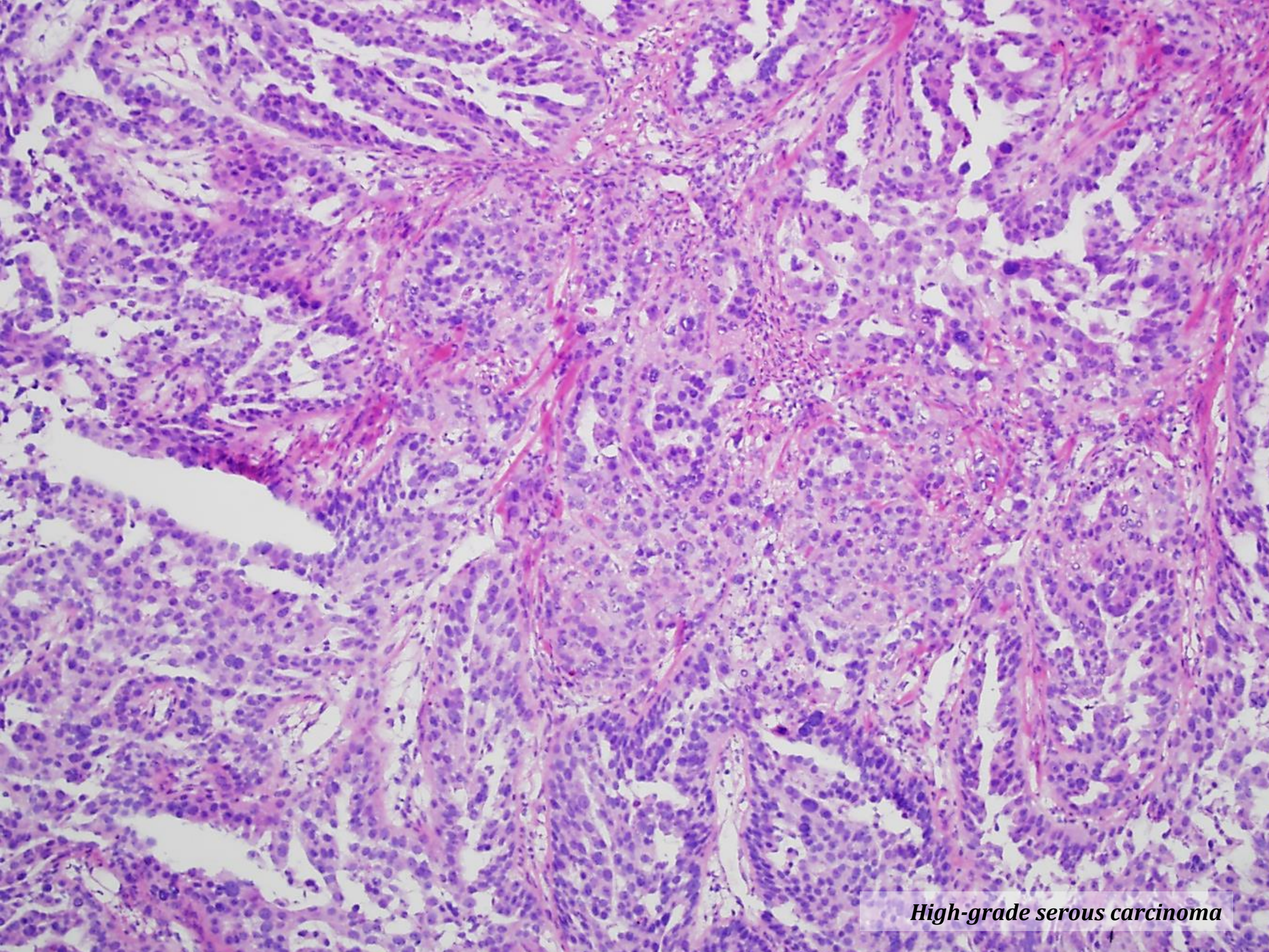

Low-grade serous carcinoma



Low-grade serous carcinoma arising in association with serous borderline tumor/atypical proliferative serous tumor, micropapillary variant (non-invasive low-grade serous carcinoma), permanent section


High-grade serous carcinoma


High-grade serous carcinoma


High-grade serous carcinoma

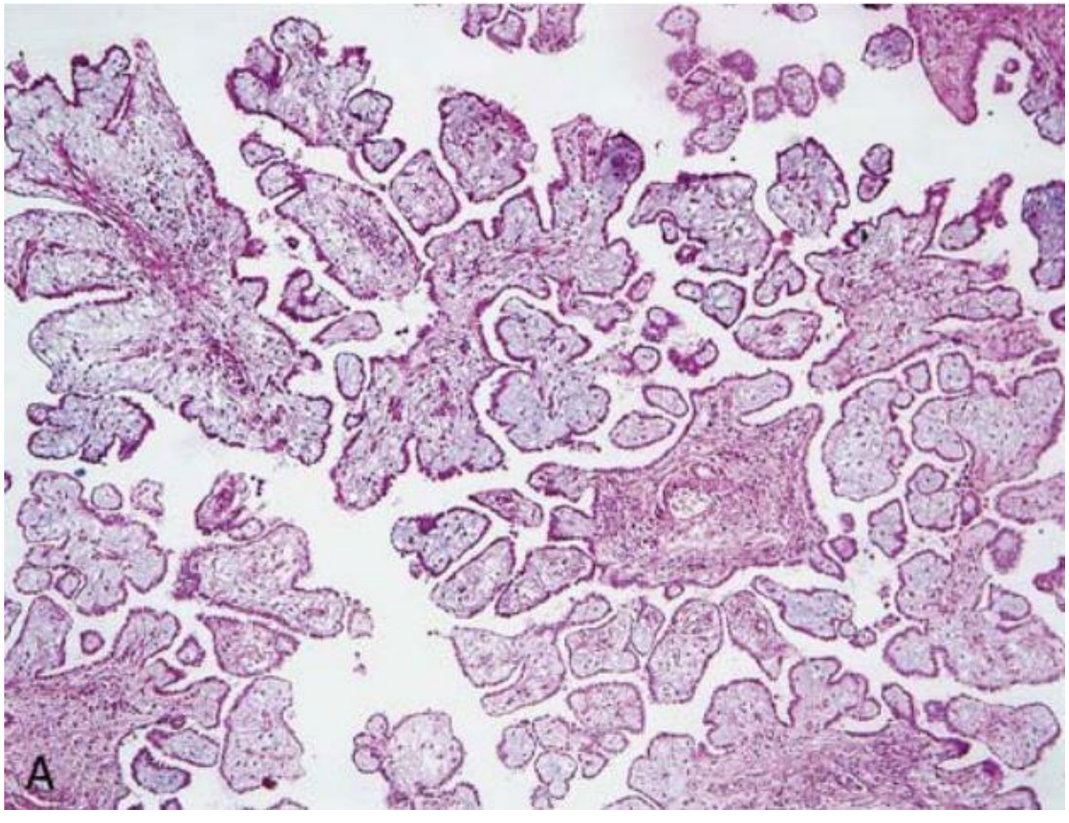
Pitfalls #1 and #2

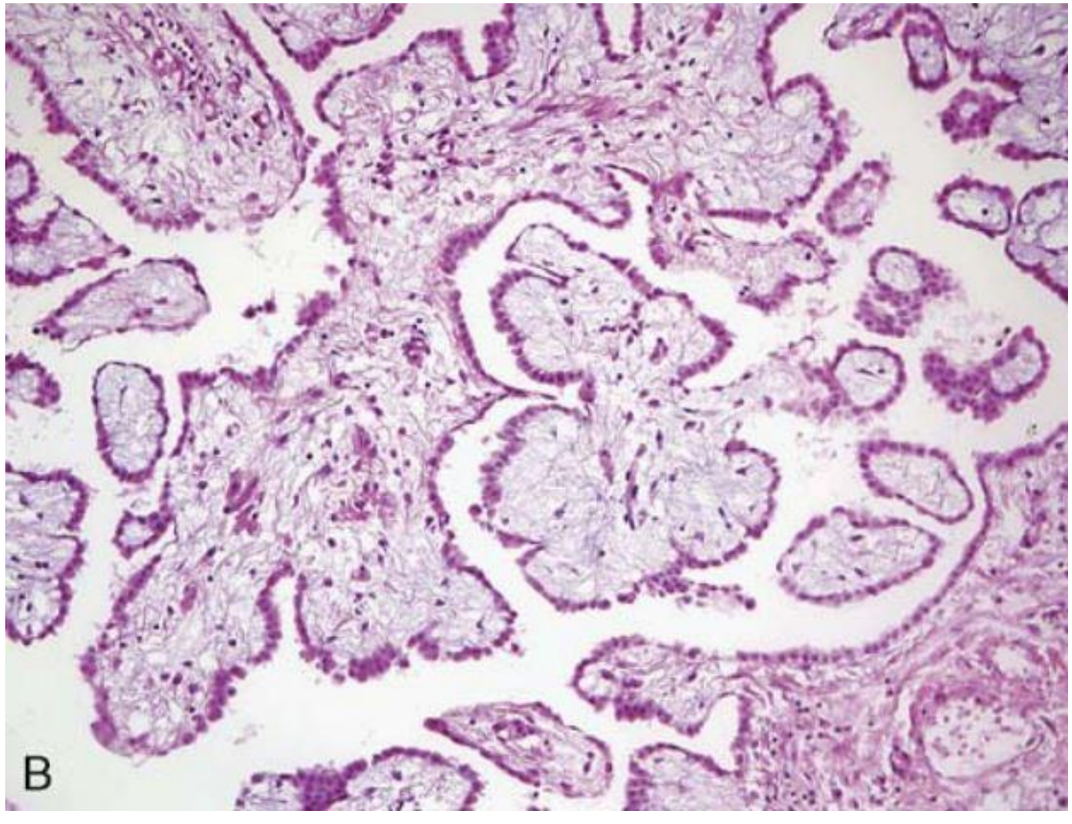
SCENARIO:

Woman with a complex ovarian mass is taken to surgery for salpingo-oophorectomy and possible staging. The ovary was sent for frozen section analysis and a diagnosis of "at least atypical proliferative (borderline) serous tumor" was rendered. As the surgery progressed, the surgeon sends down what is labeled "peritoneal lesion" for frozen section.

OR

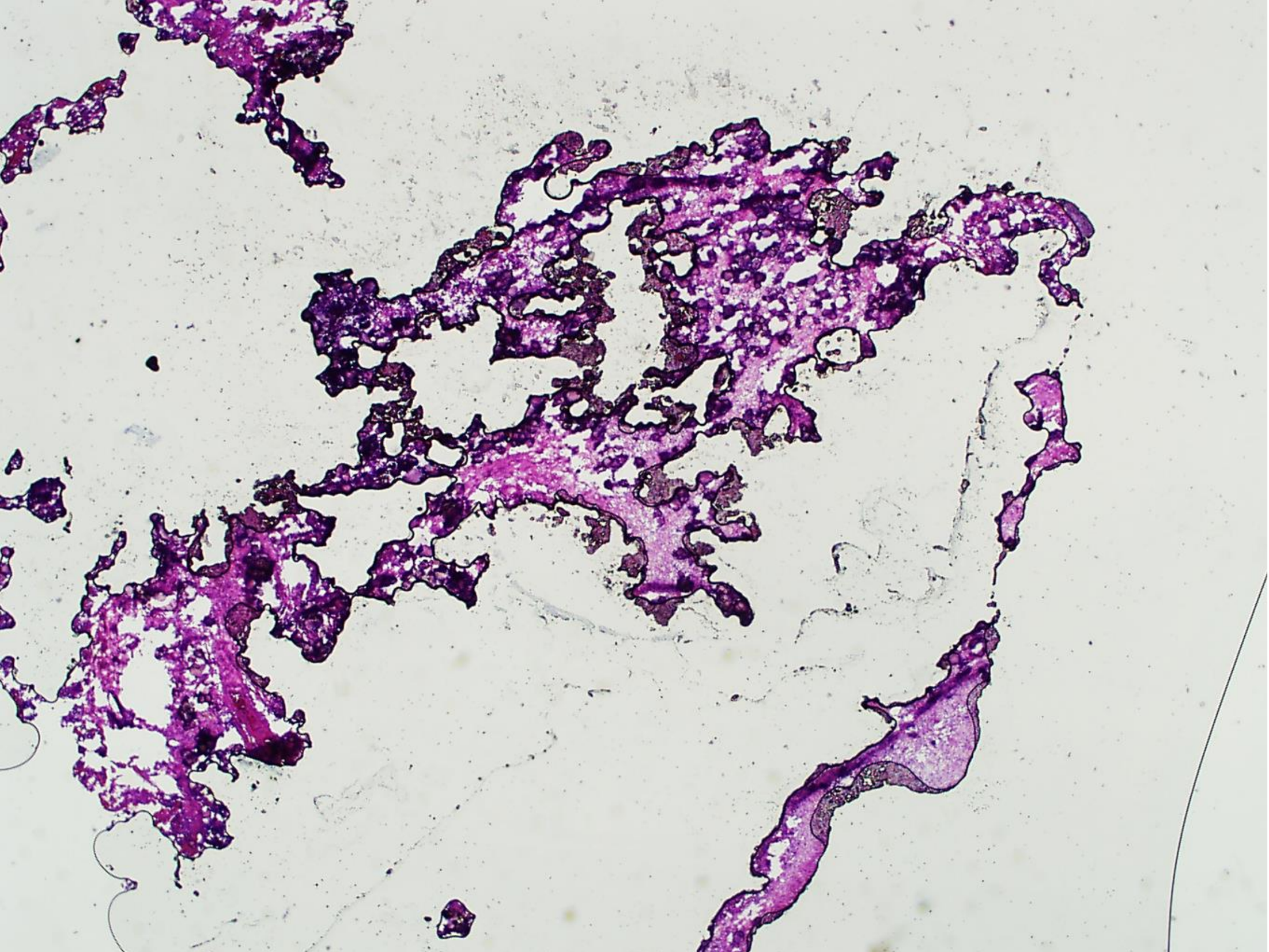
Woman with a complex ovarian mass is taken to surgery for salpingo-oophorectomy and possible staging. Upon entering the peritoneum, the surgeon notes a peritoneal lesion and sends it down for frozen section analysis.

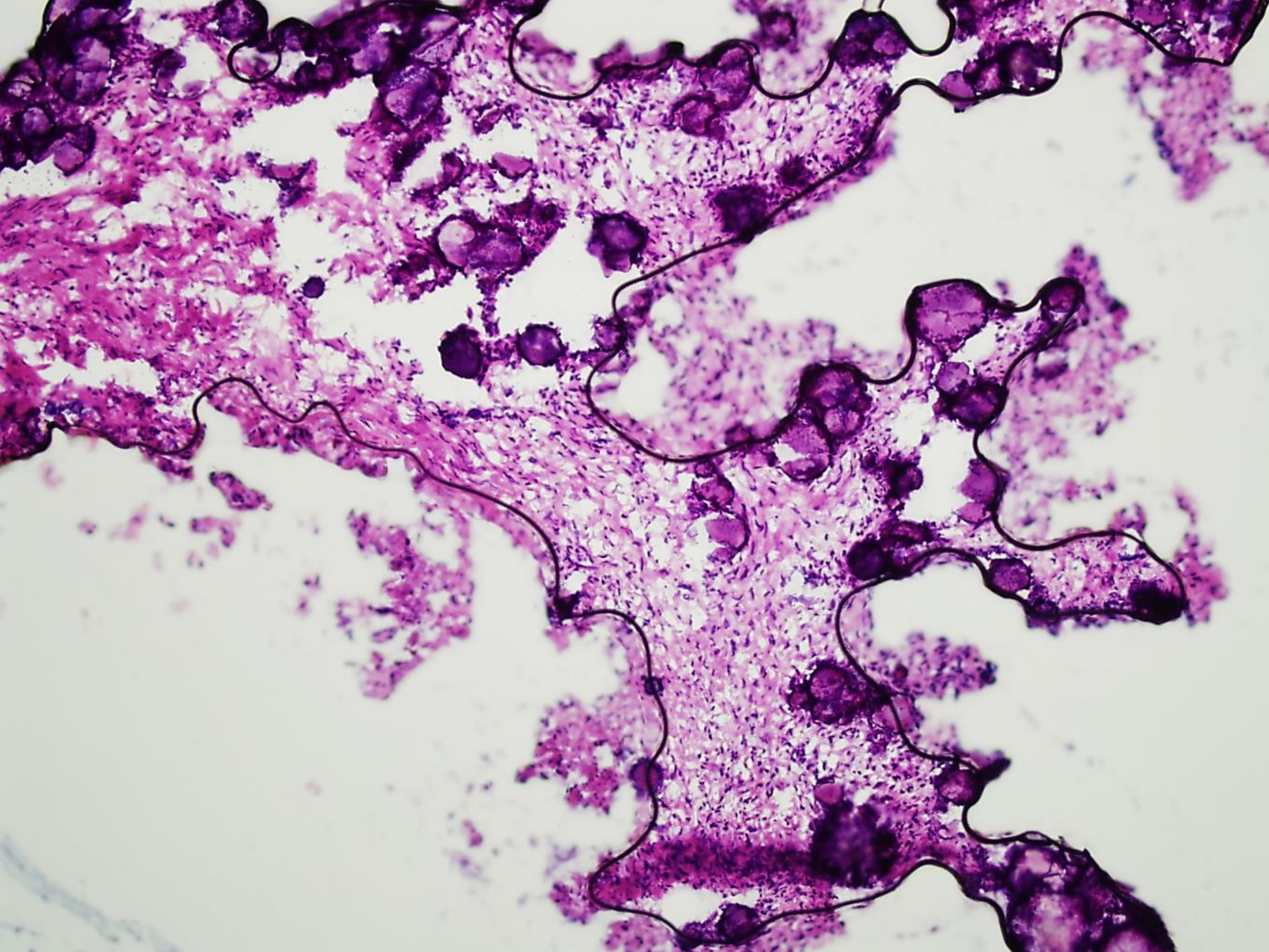


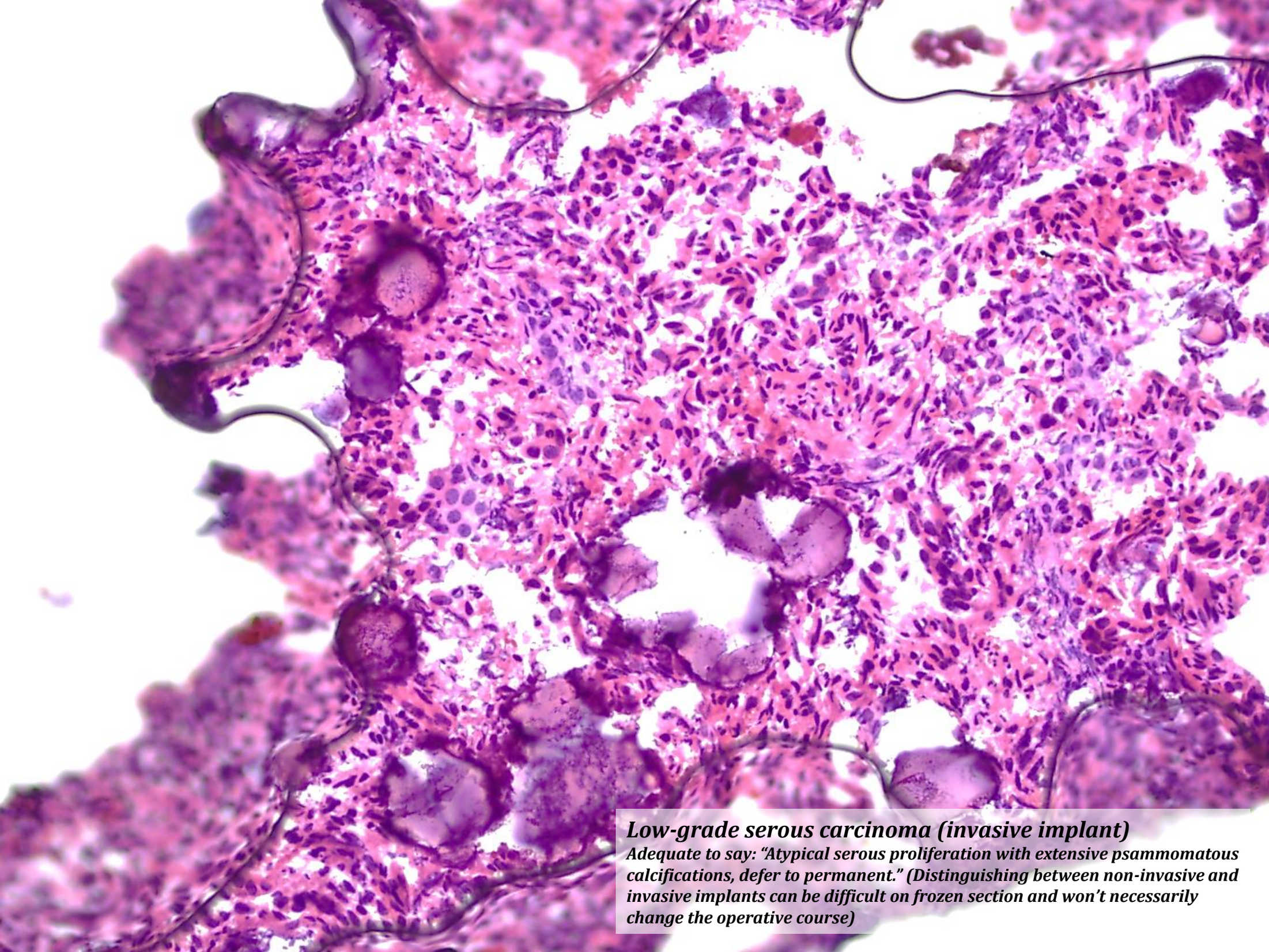


Well-differentiated papillary mesothelioma (WDPM)

Malpica A, Sant'Abrogio S, Deavers MT, Silva EG. Well-differentiated Papillary Mesothelioma of the Female Peritoneum: A Clinicopathologic Study of 26 Cases. Am J Surg Pathol. 2012;36:117-127.







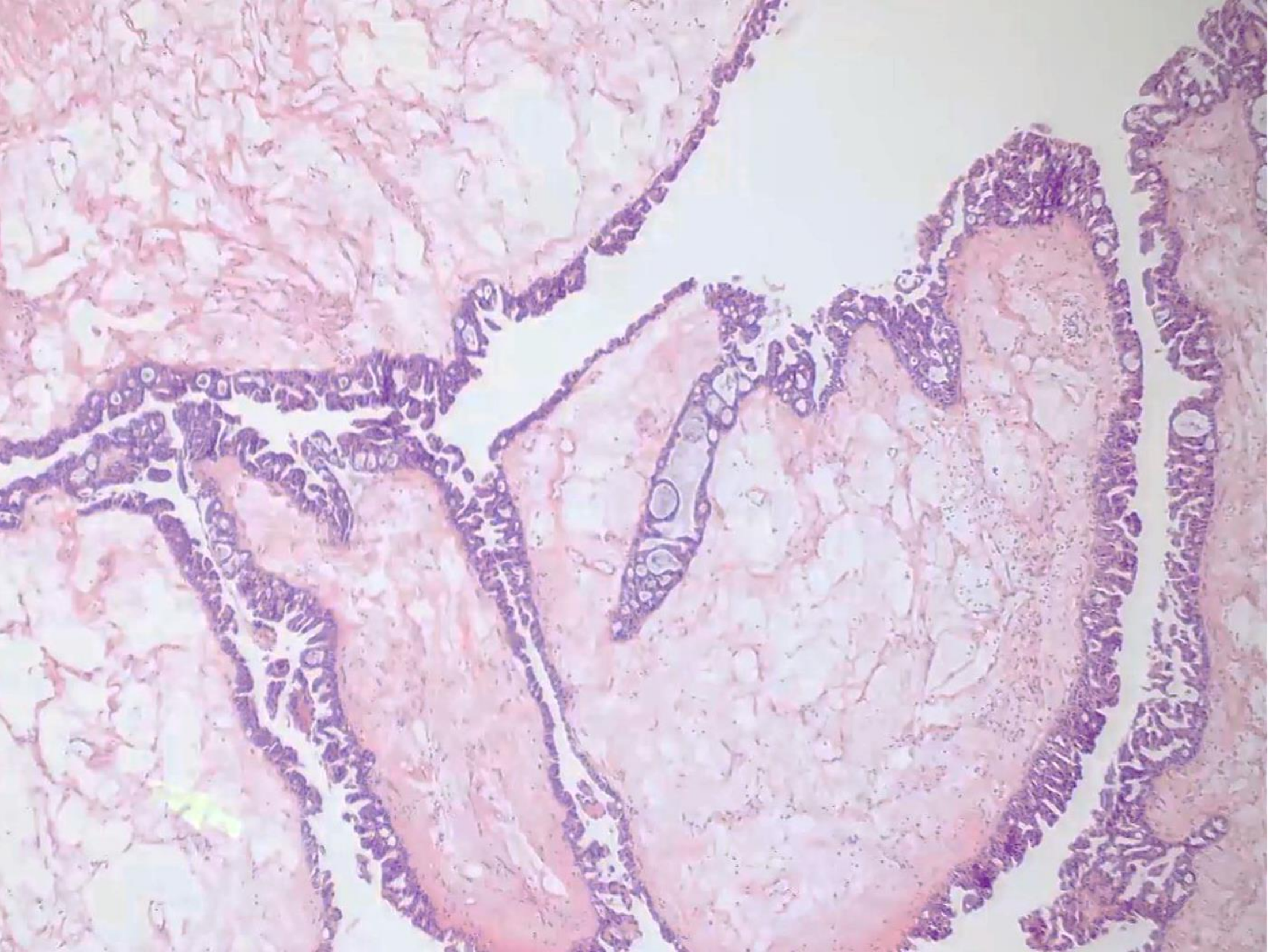
Low-grade serous carcinoma (invasive implant)

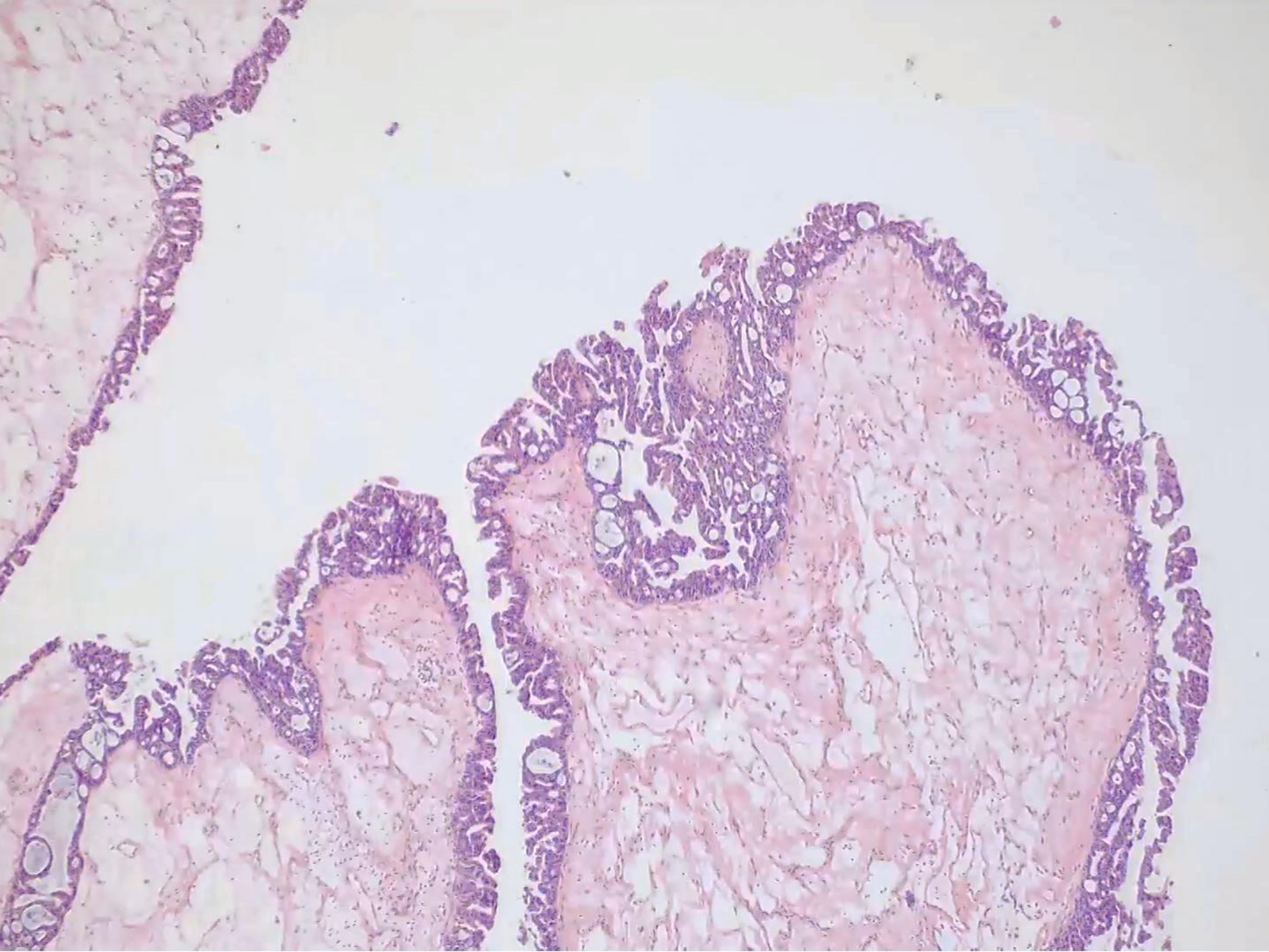
Adequate to say: "Atypical serous proliferation with extensive psammomatous calcifications, defer to permanent." (Distinguishing between non-invasive and invasive implants can be difficult on frozen section and won't necessarily change the operative course)

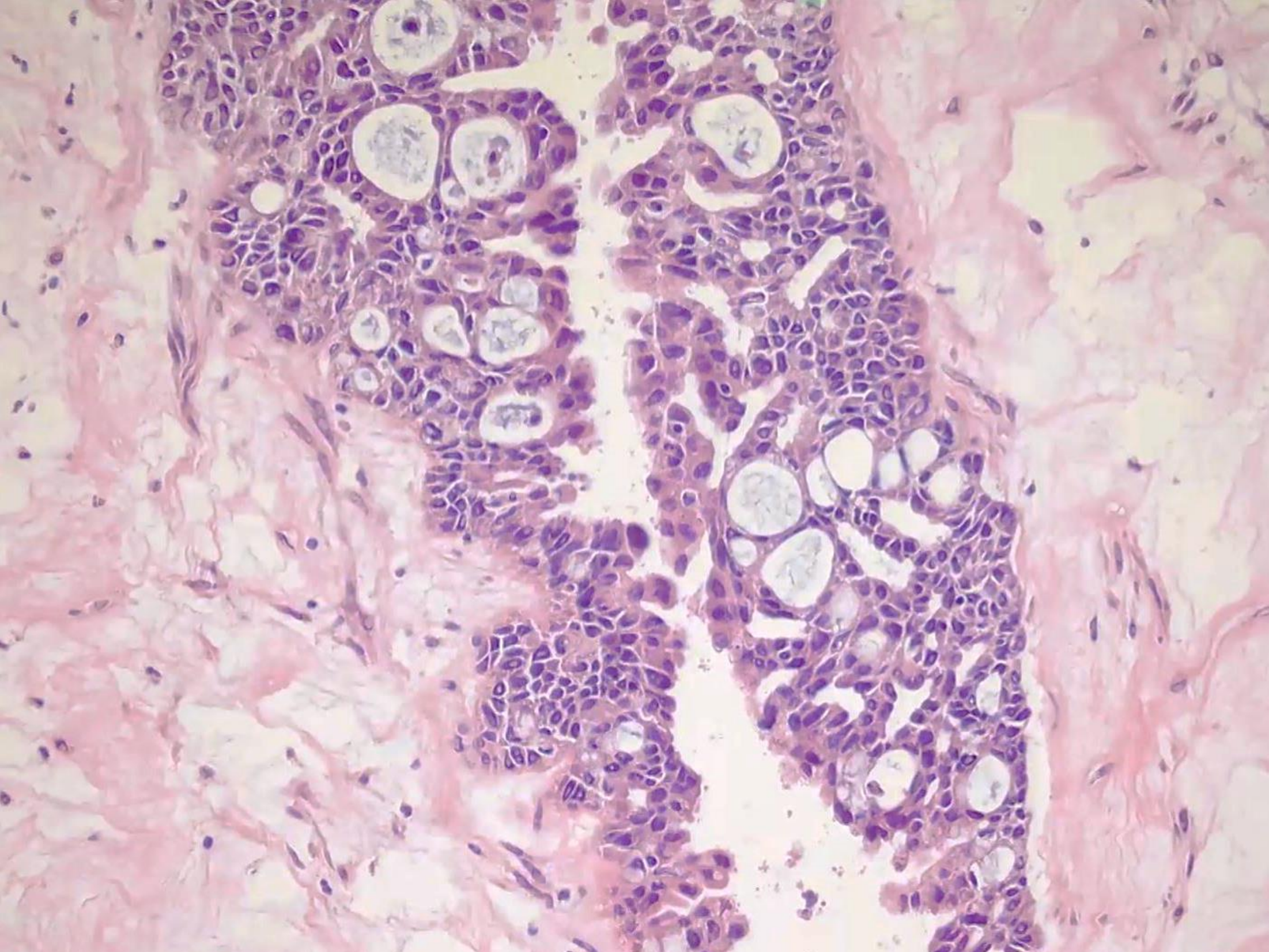
Pitfall #3

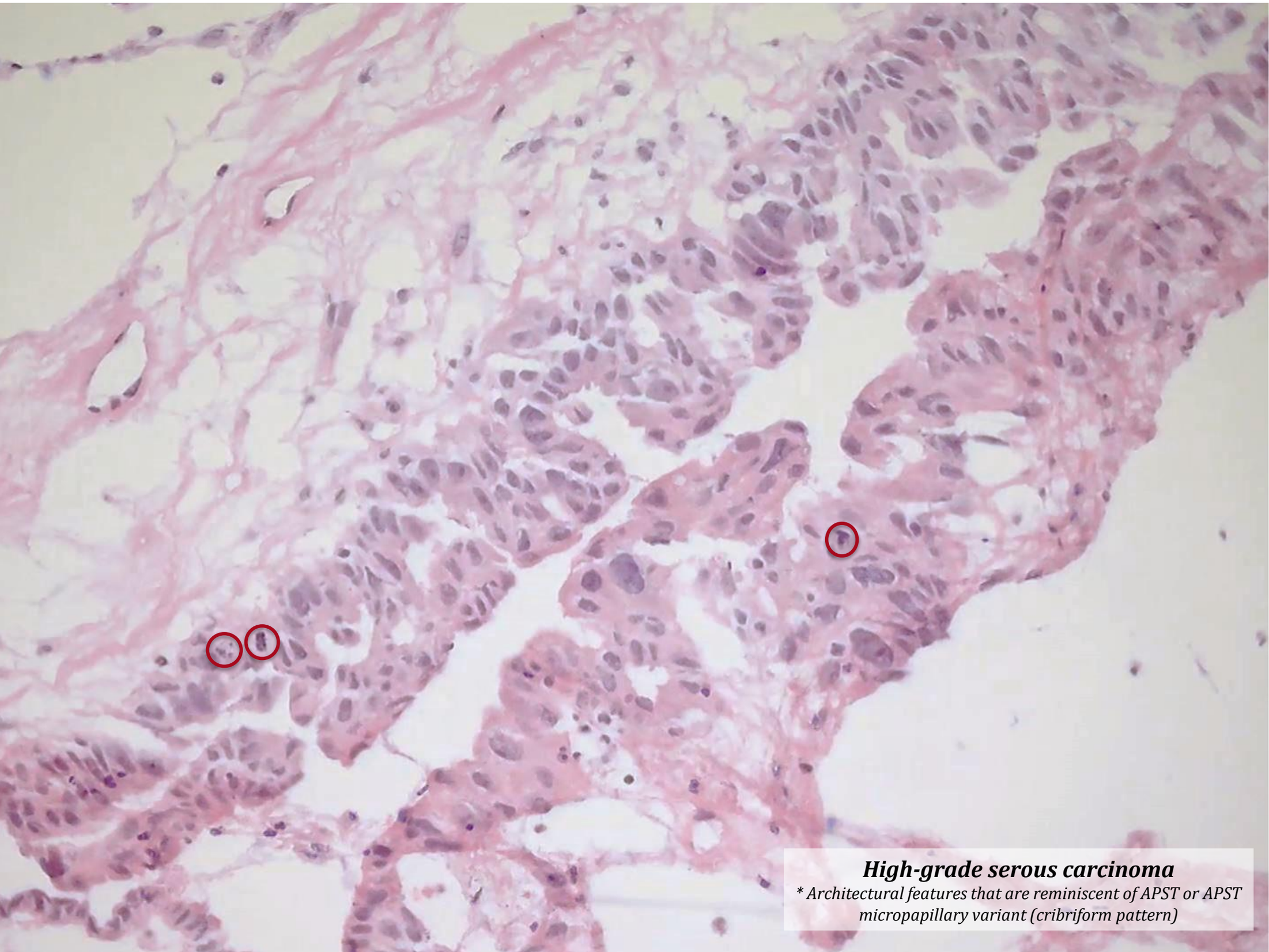
SCENARIO:

Postmenopausal woman with a complex cystic ovarian mass undergoing salpingo-oophorectomy. Frozen section requested on the ovary.









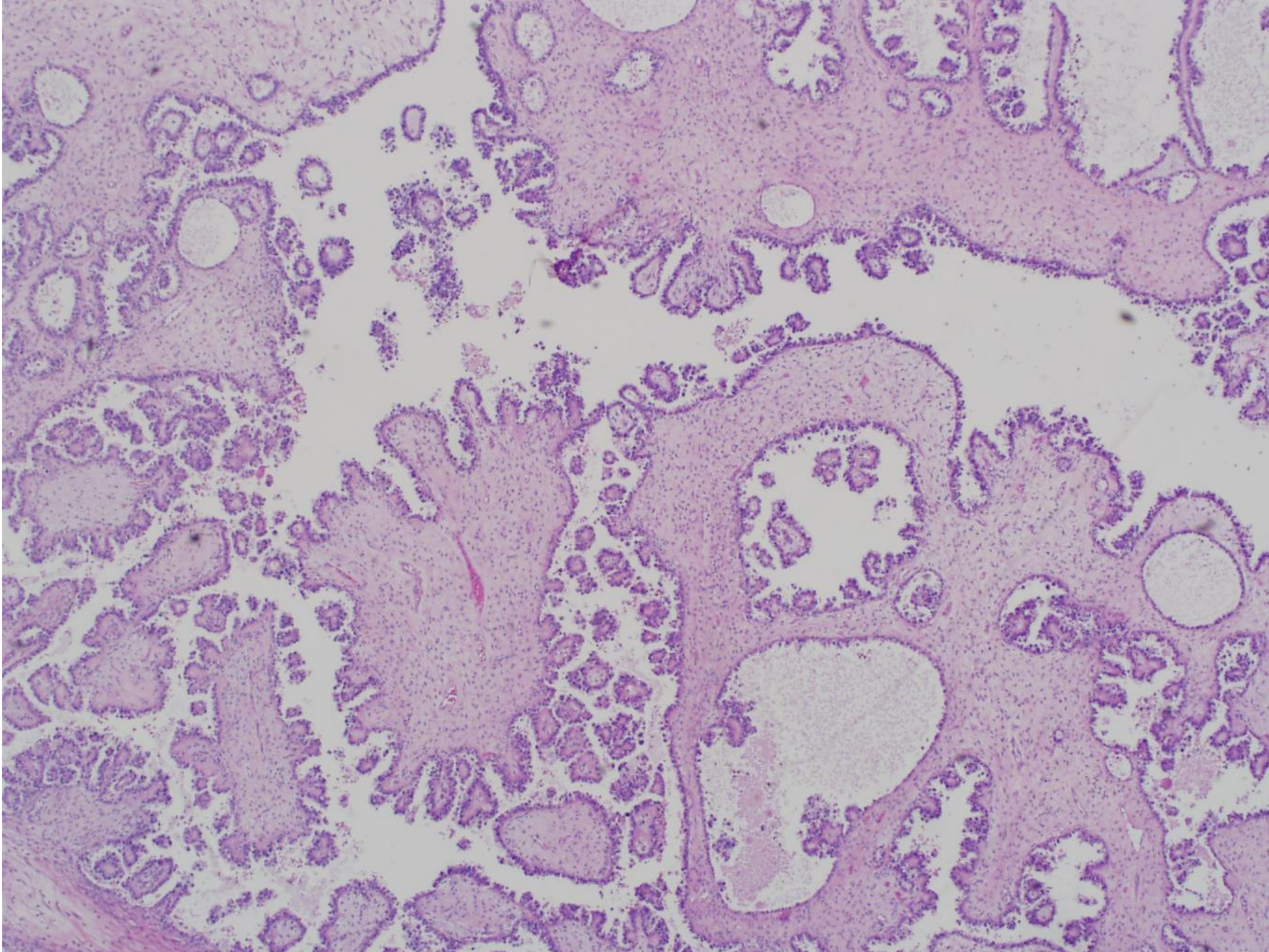
High-grade serous carcinoma

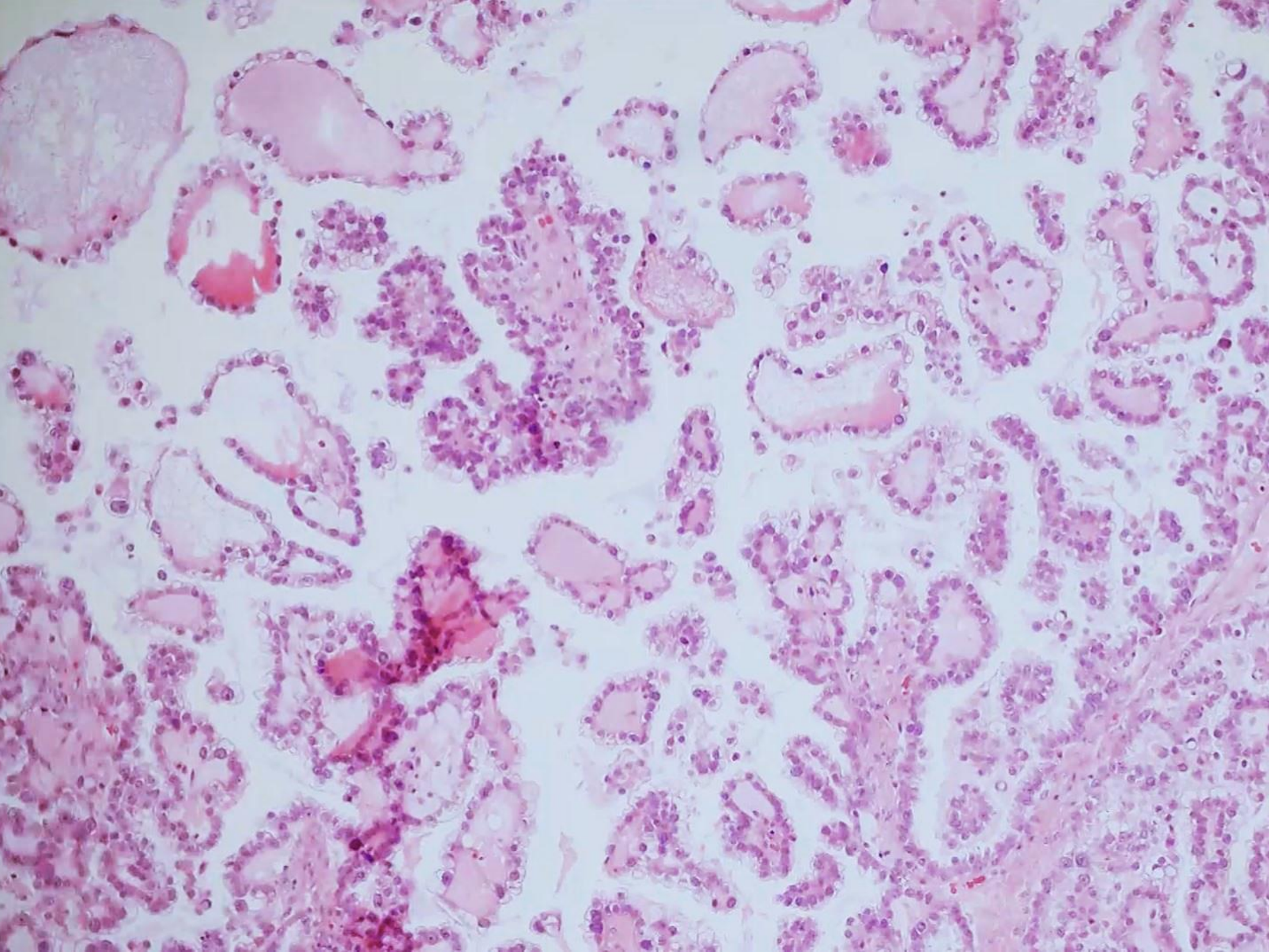
** Architectural features that are reminiscent of APST or APST micropapillary variant (cribriform pattern)*

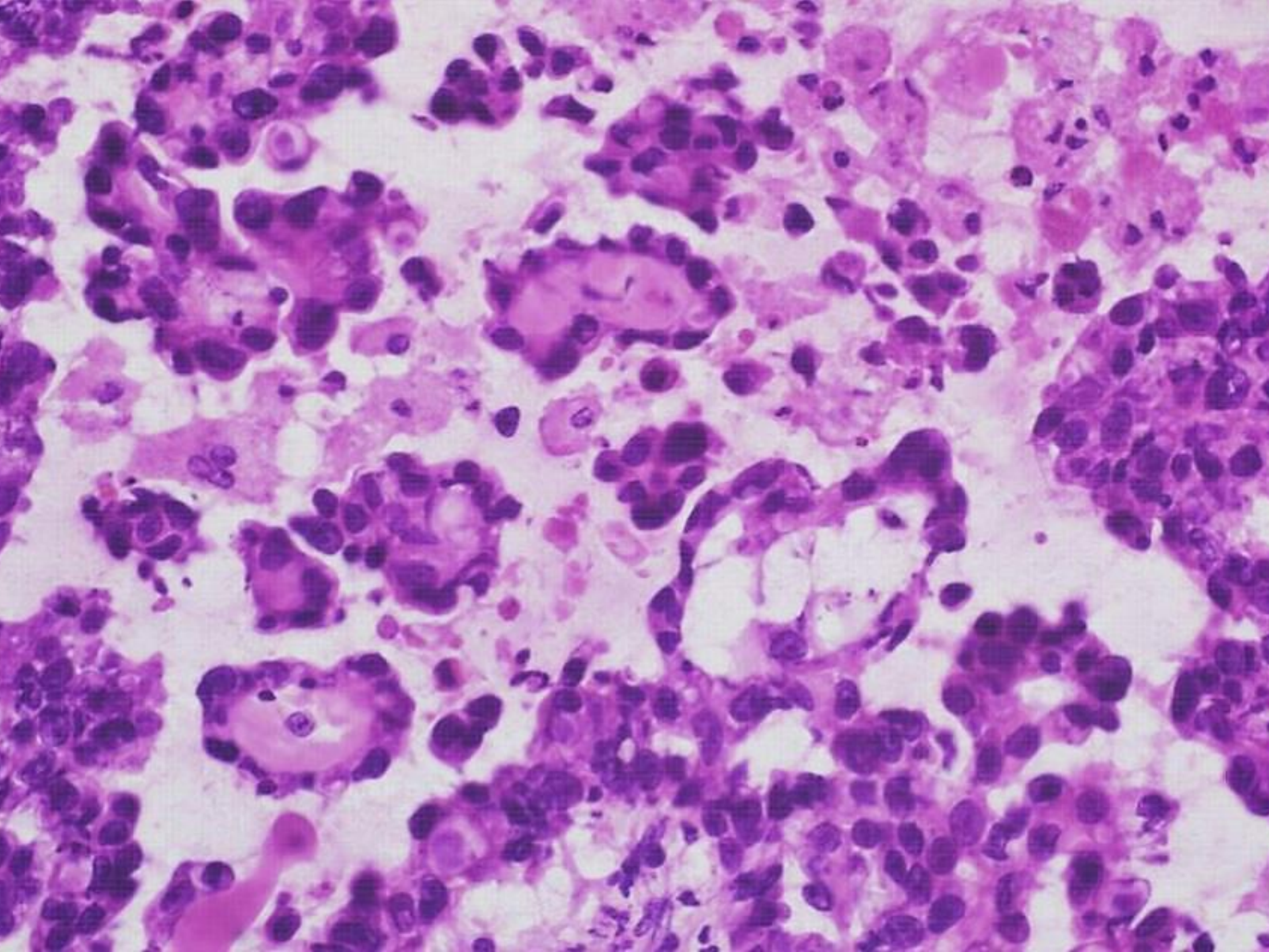
Pitfall #4

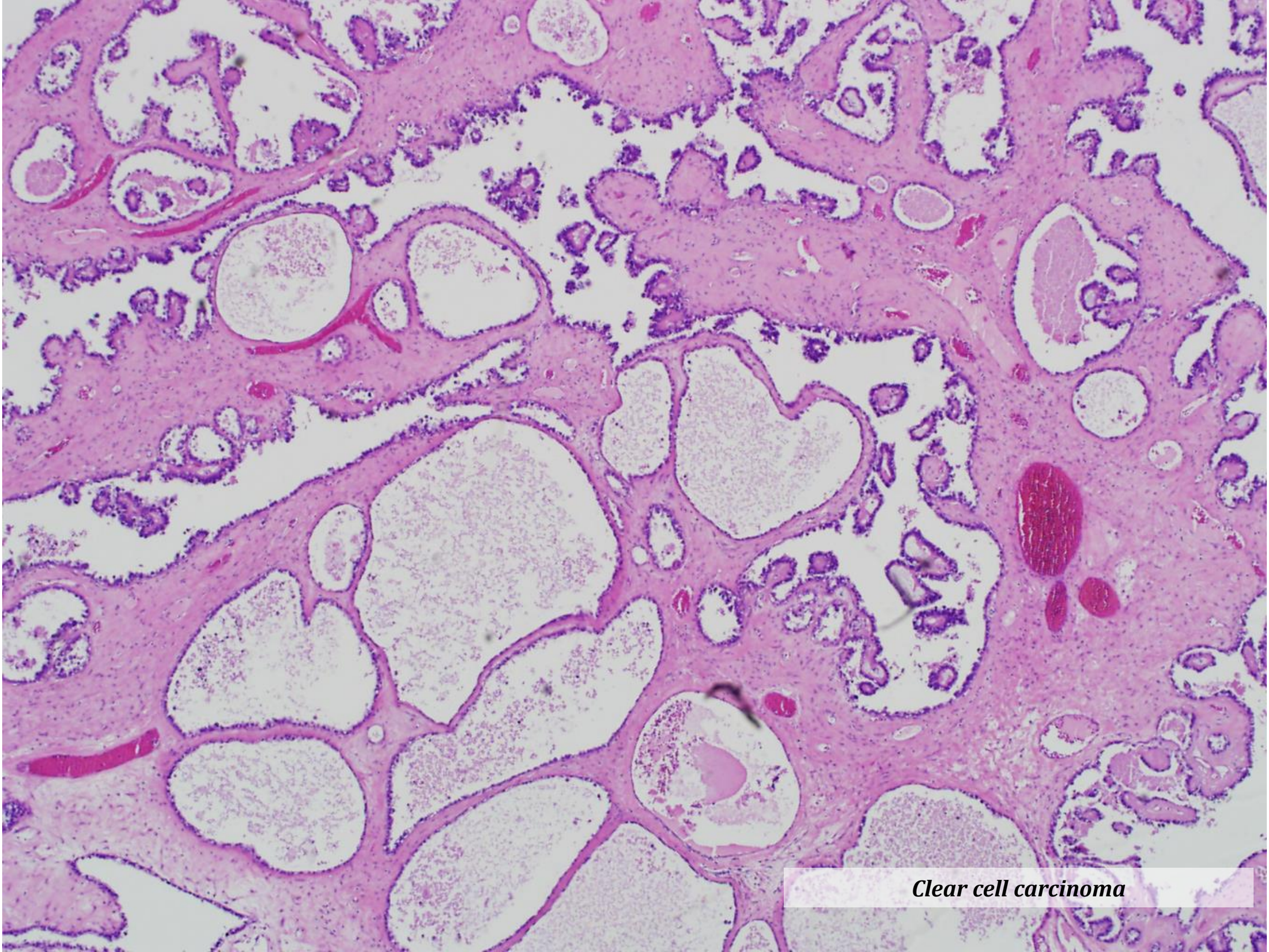
SCENARIO:

Postmenopausal woman with a complex cystic ovarian mass undergoing salpingo-oophorectomy. Frozen section requested on the ovary.

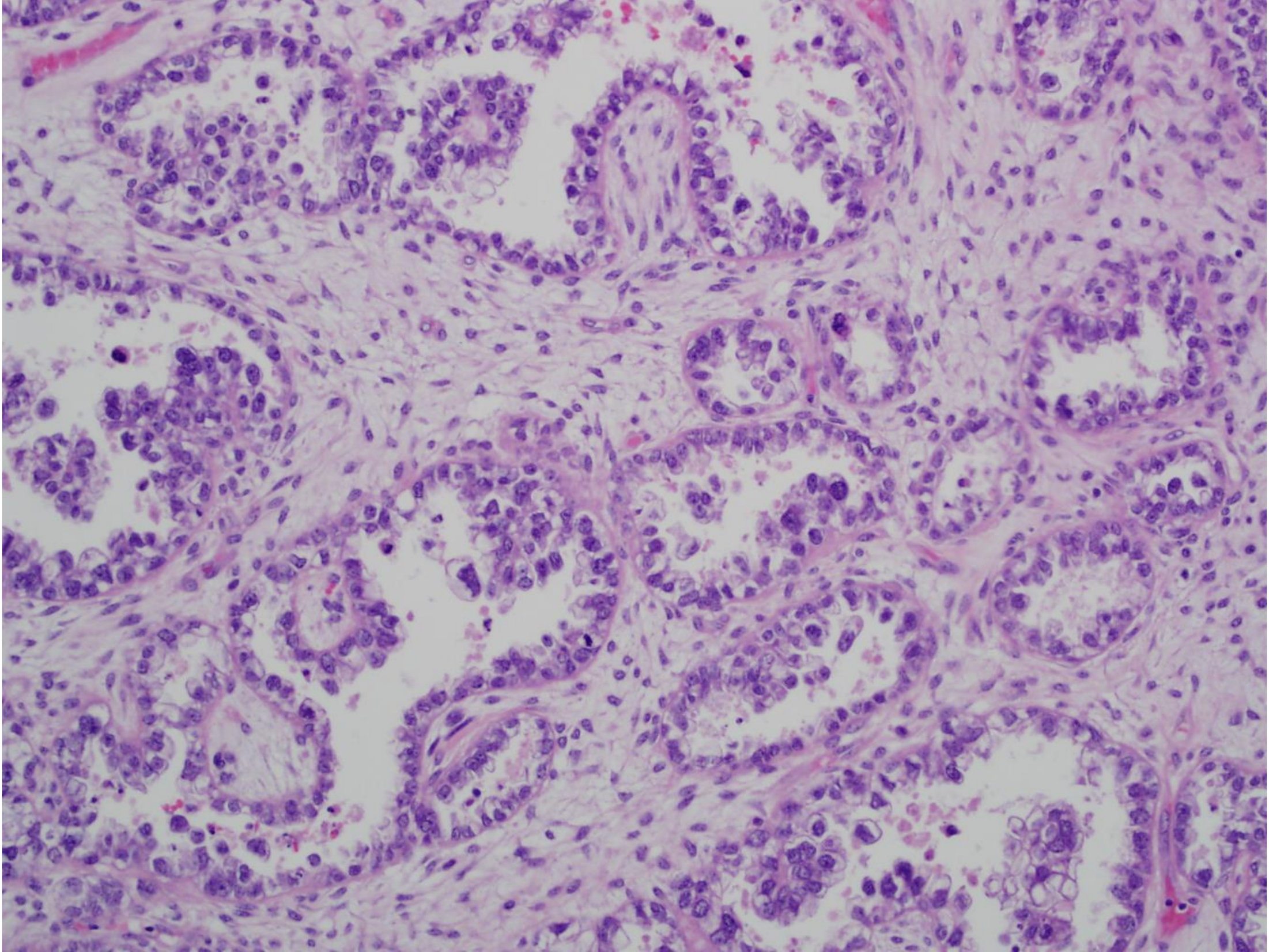








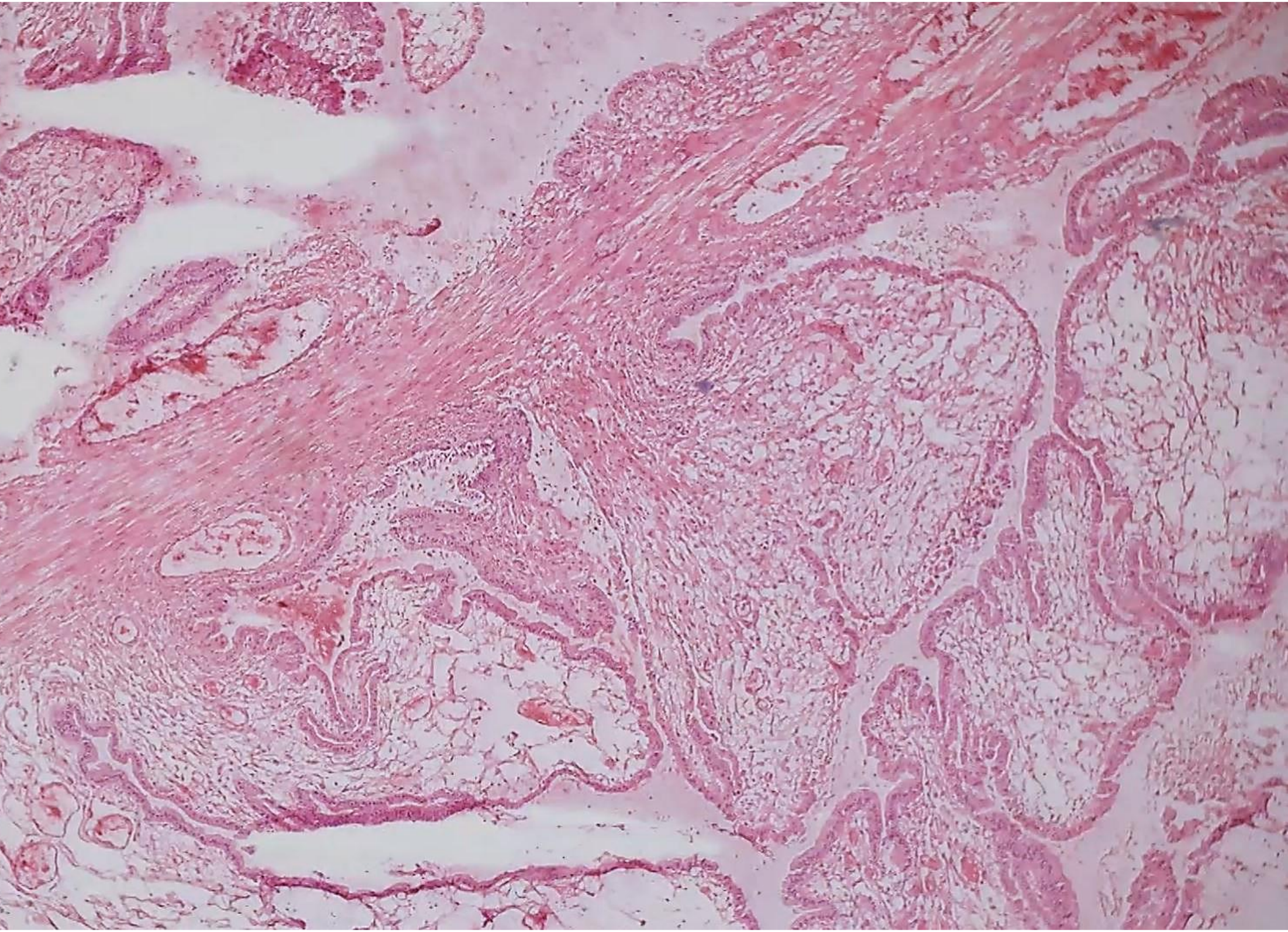
Clear cell carcinoma

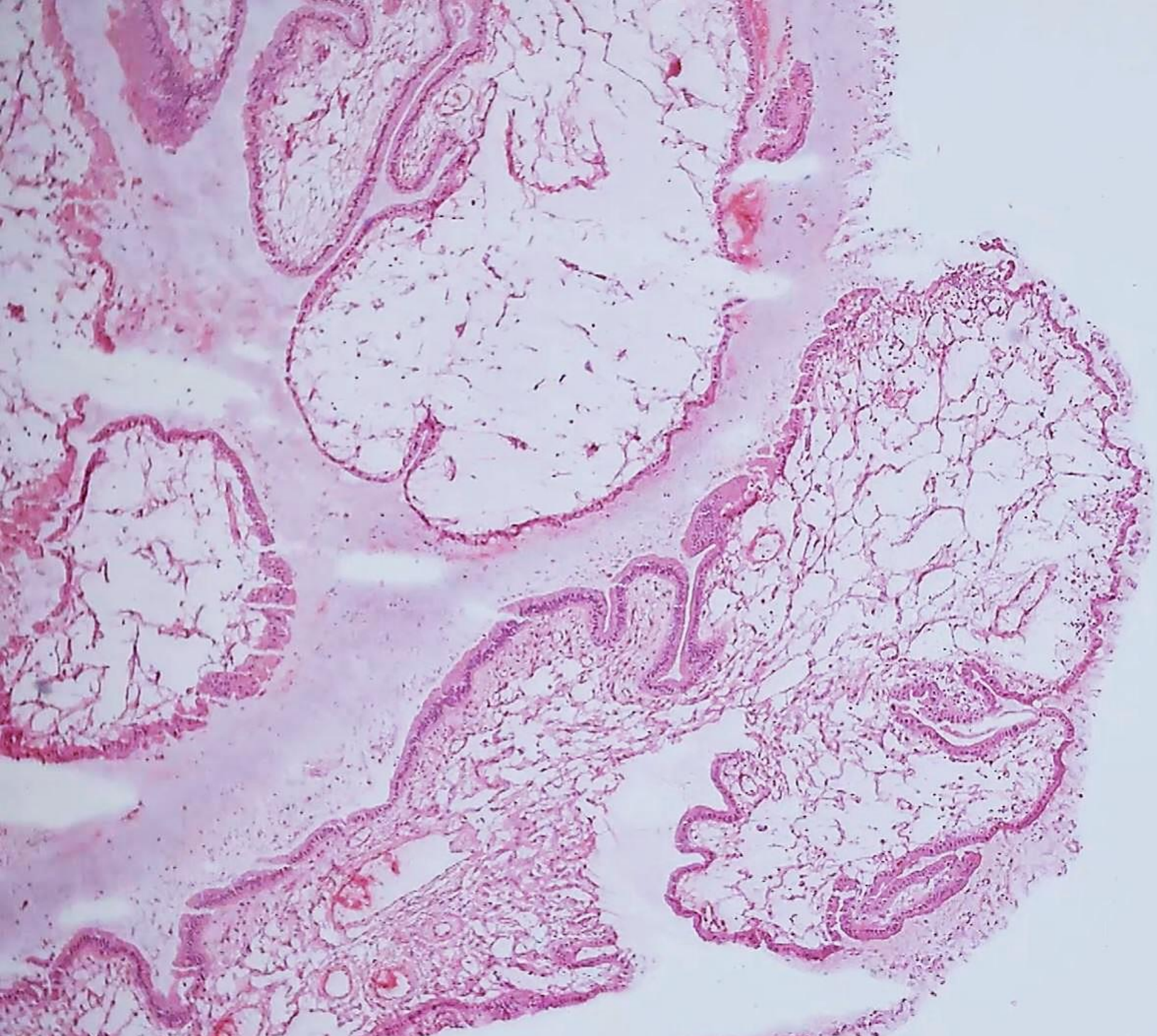


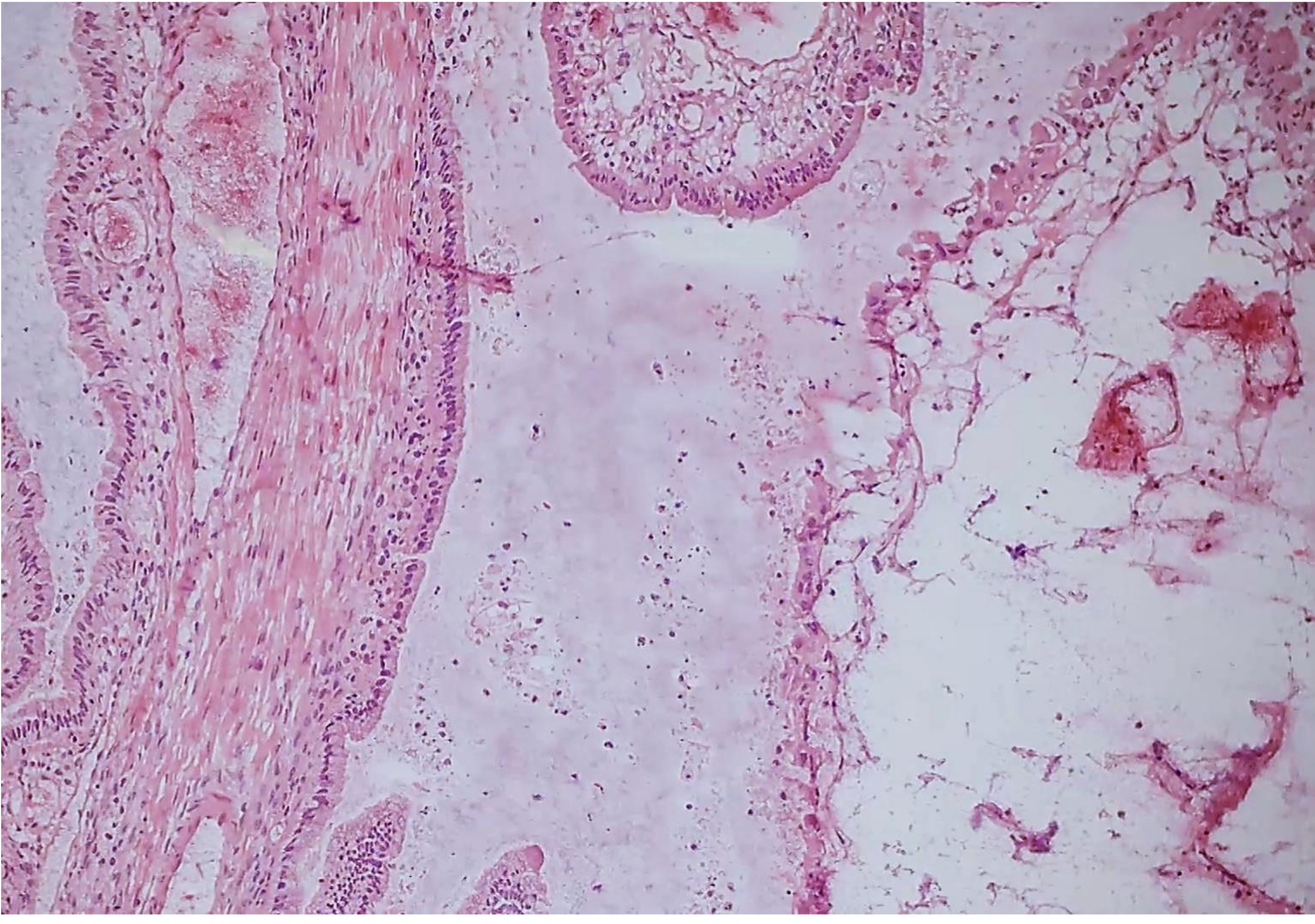
Pitfall #5

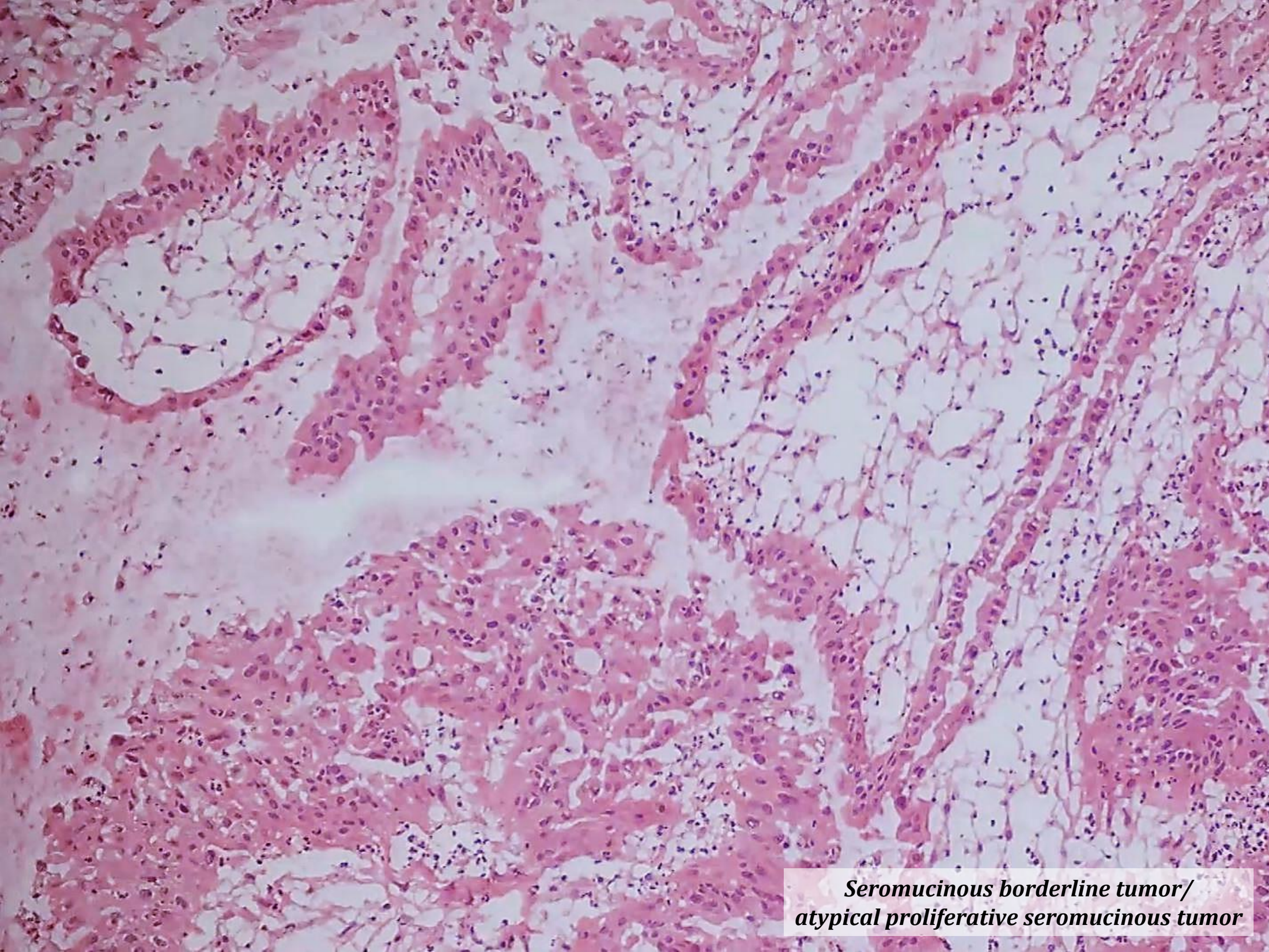
SCENARIO

Premenopausal female with a history of endometriosis, presents with a unilateral complex ovarian mass.



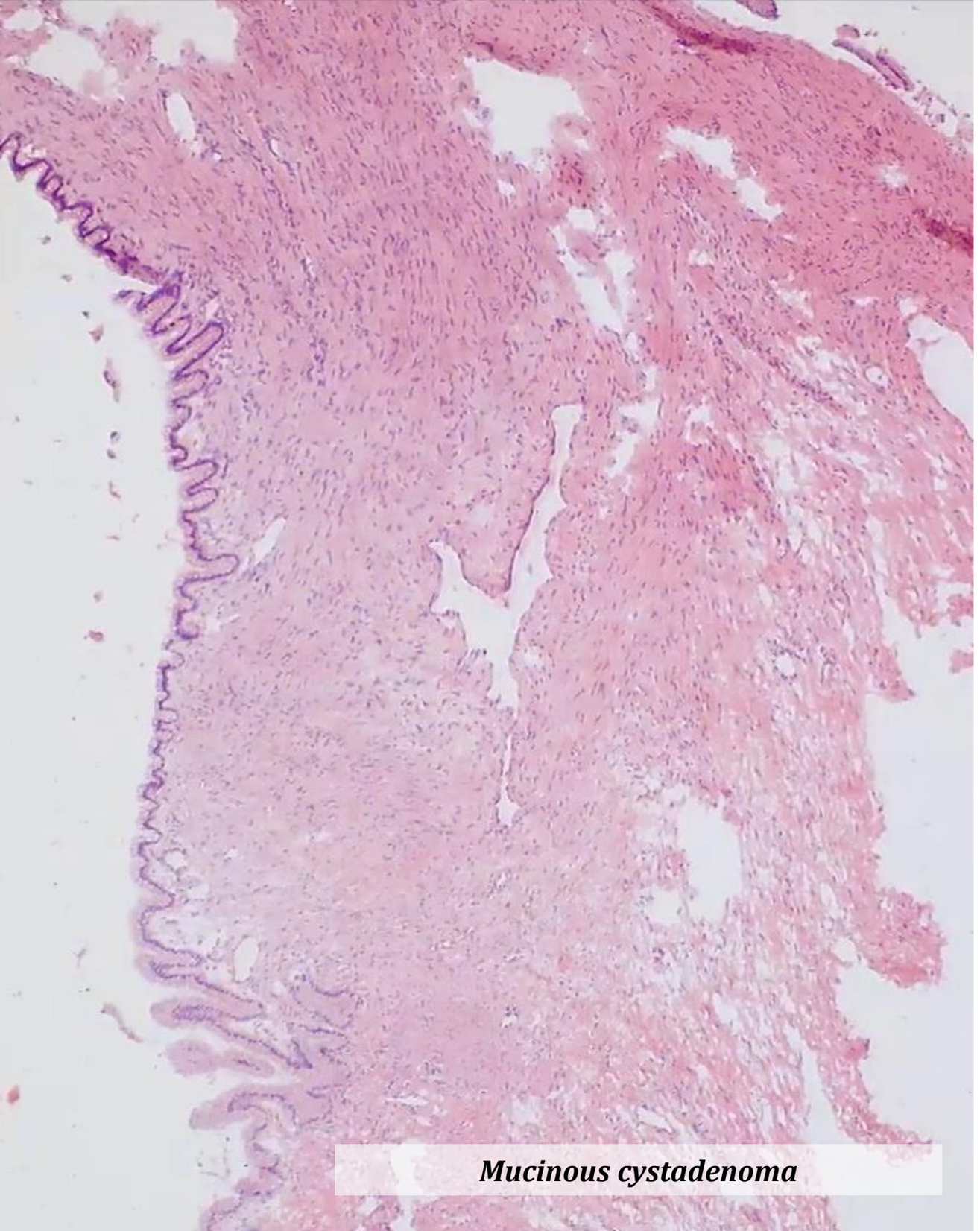




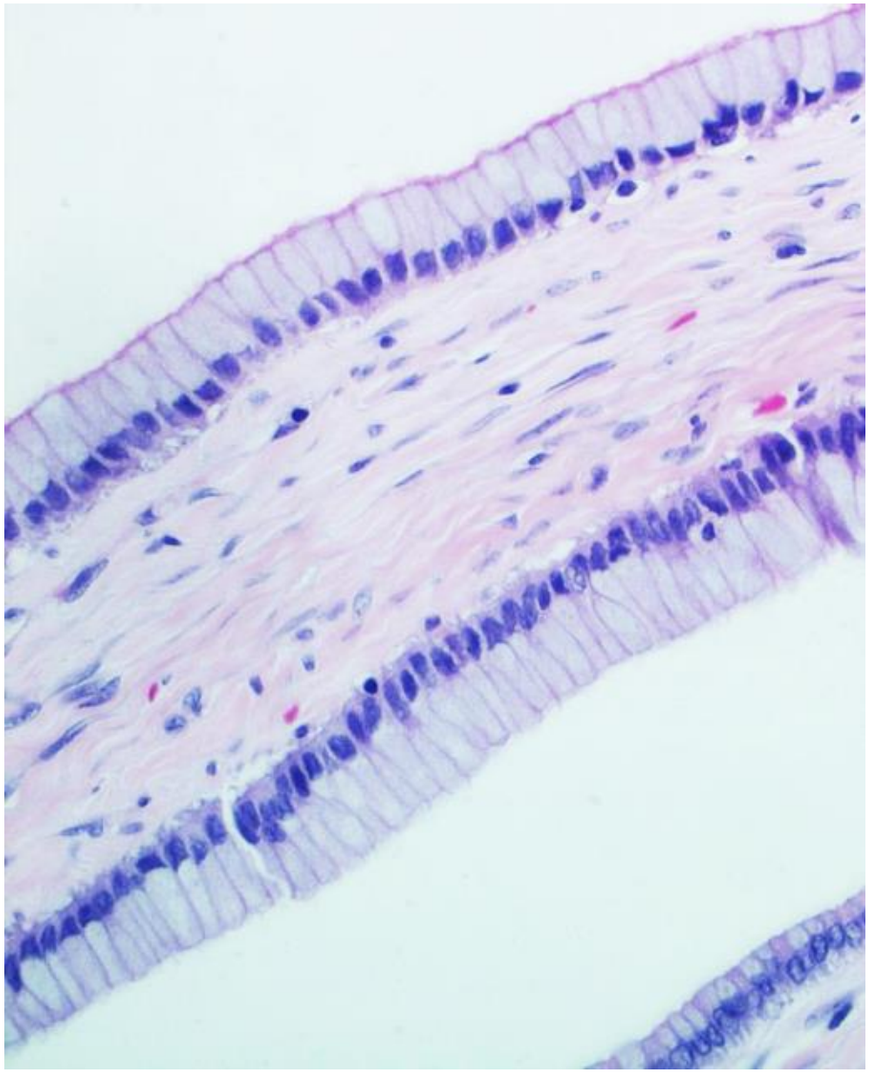


Seromucinous borderline tumor/ atypical proliferative seromucinous tumor

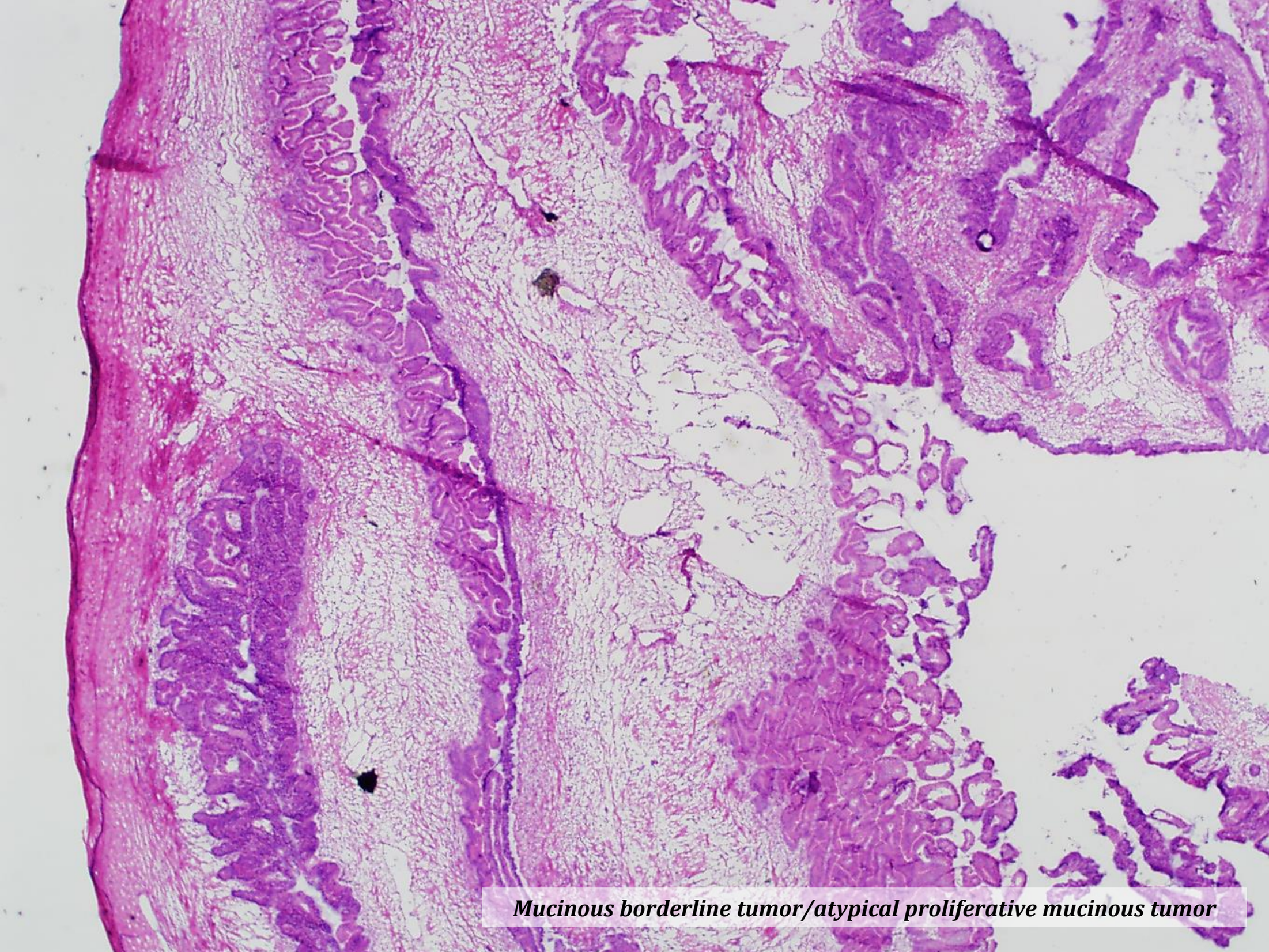
Mucinous Neoplasms



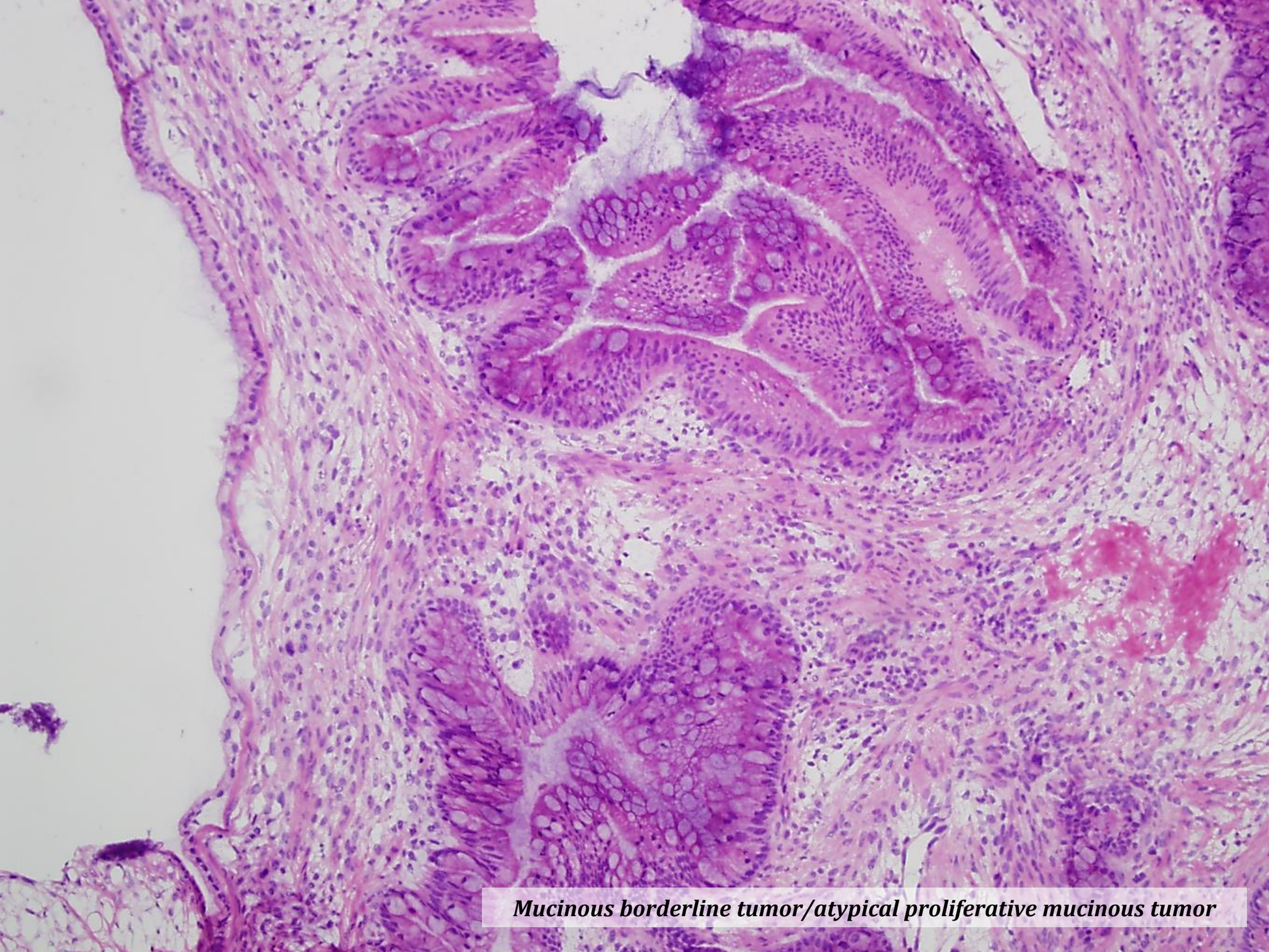
Mucinous cystadenoma



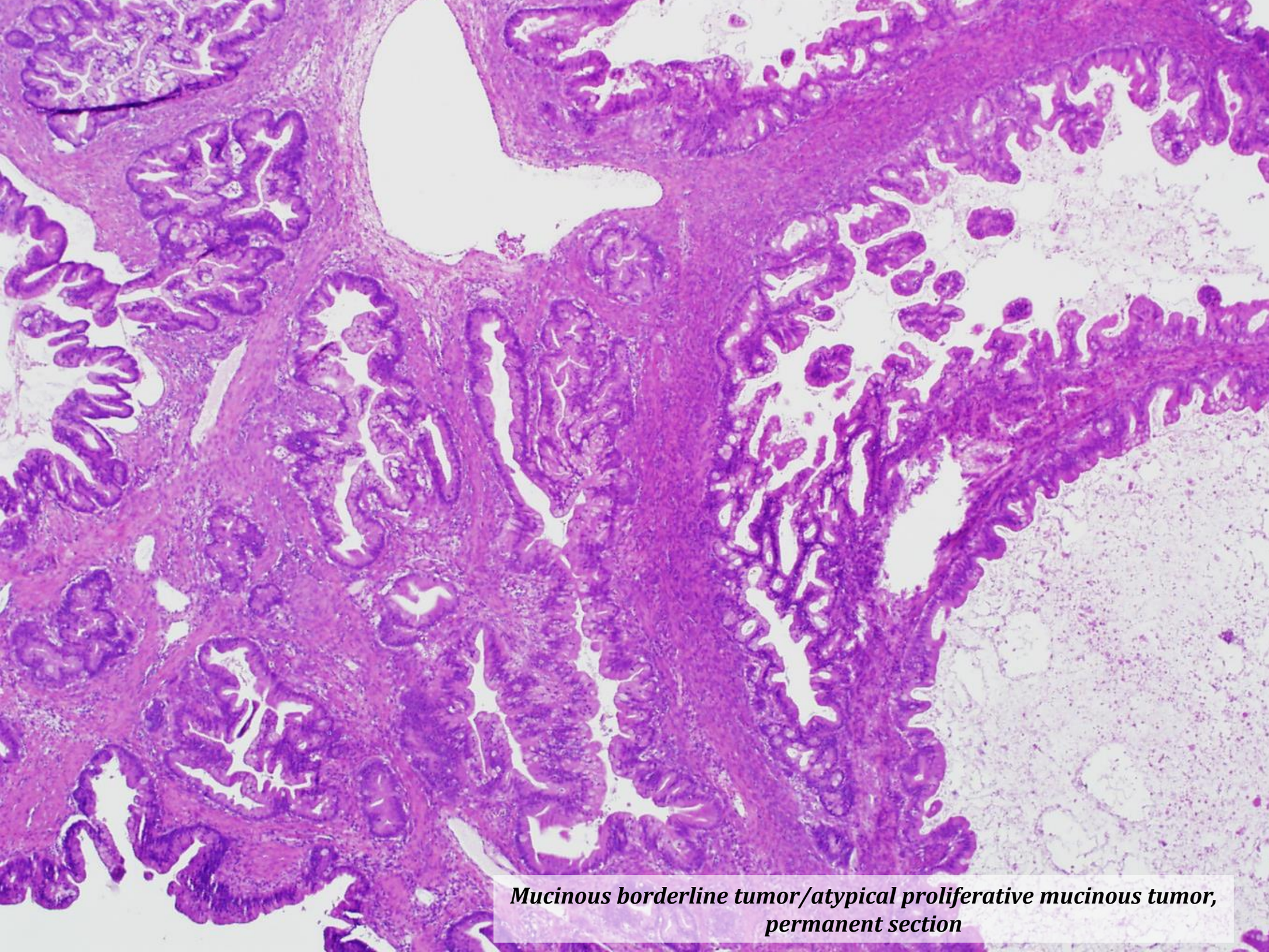
Mucinous borderline tumor/atypical proliferative mucinous tumor



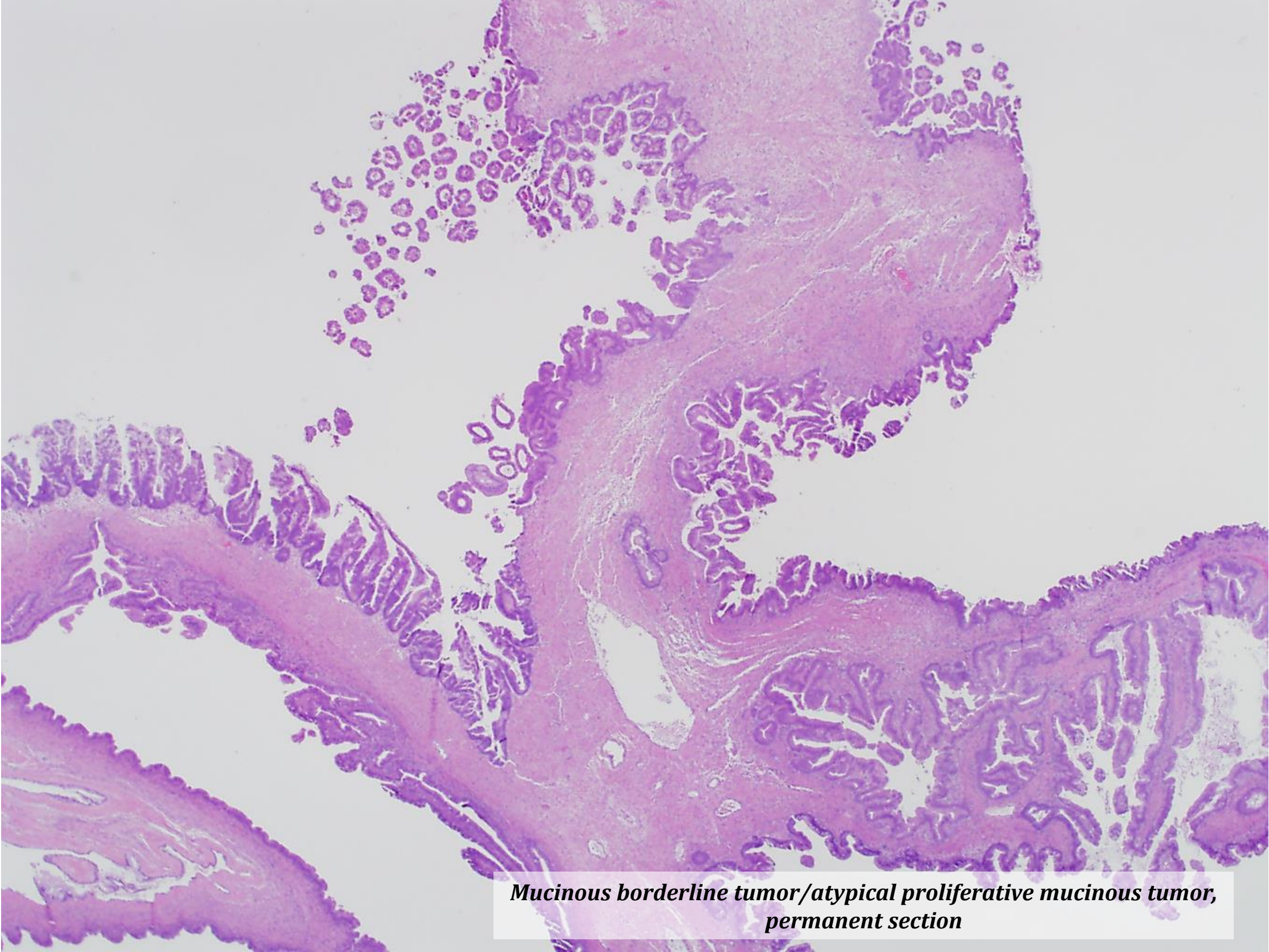
Mucinous borderline tumor/atypical proliferative mucinous tumor



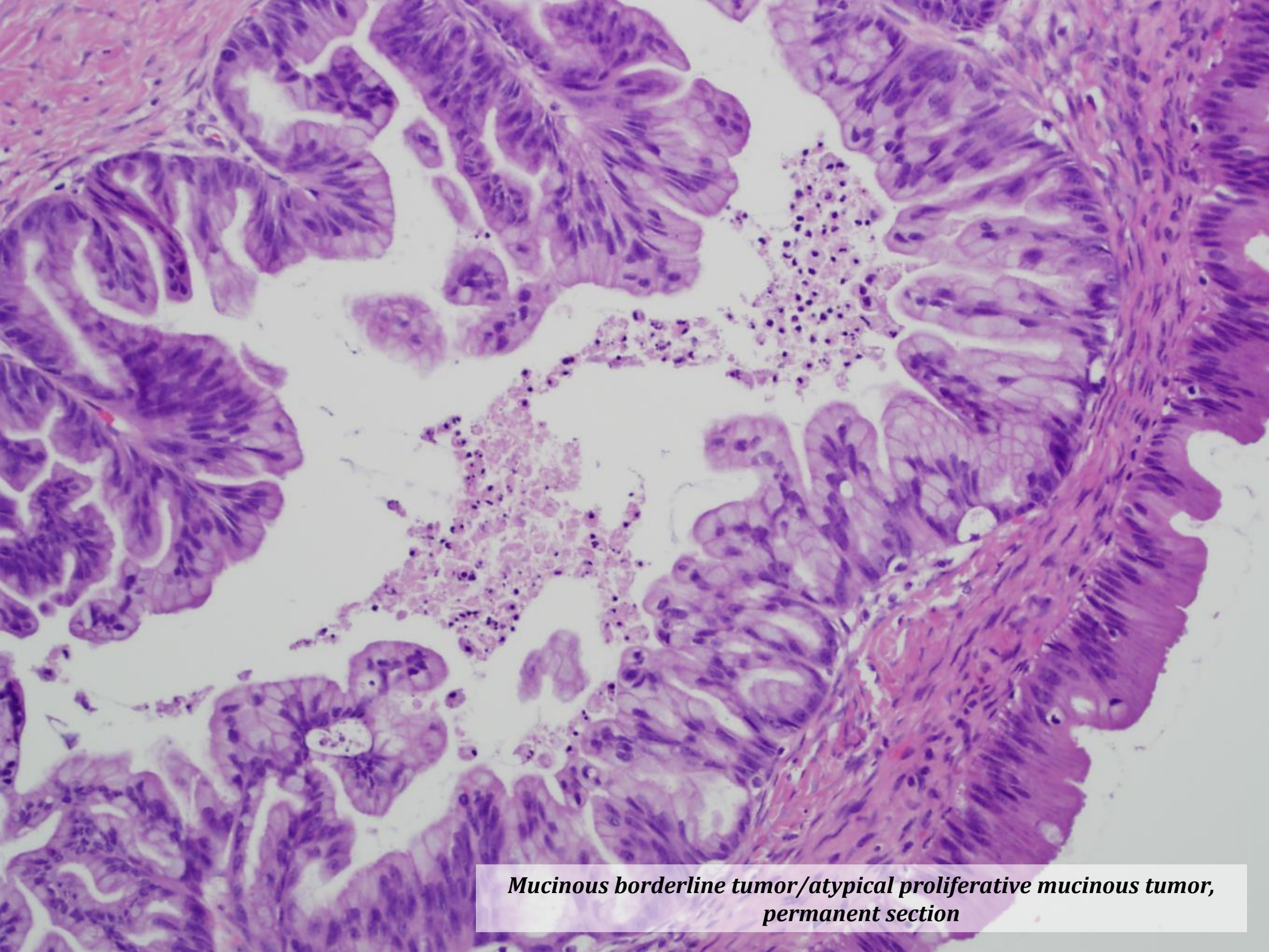
Mucinous borderline tumor/atypical proliferative mucinous tumor



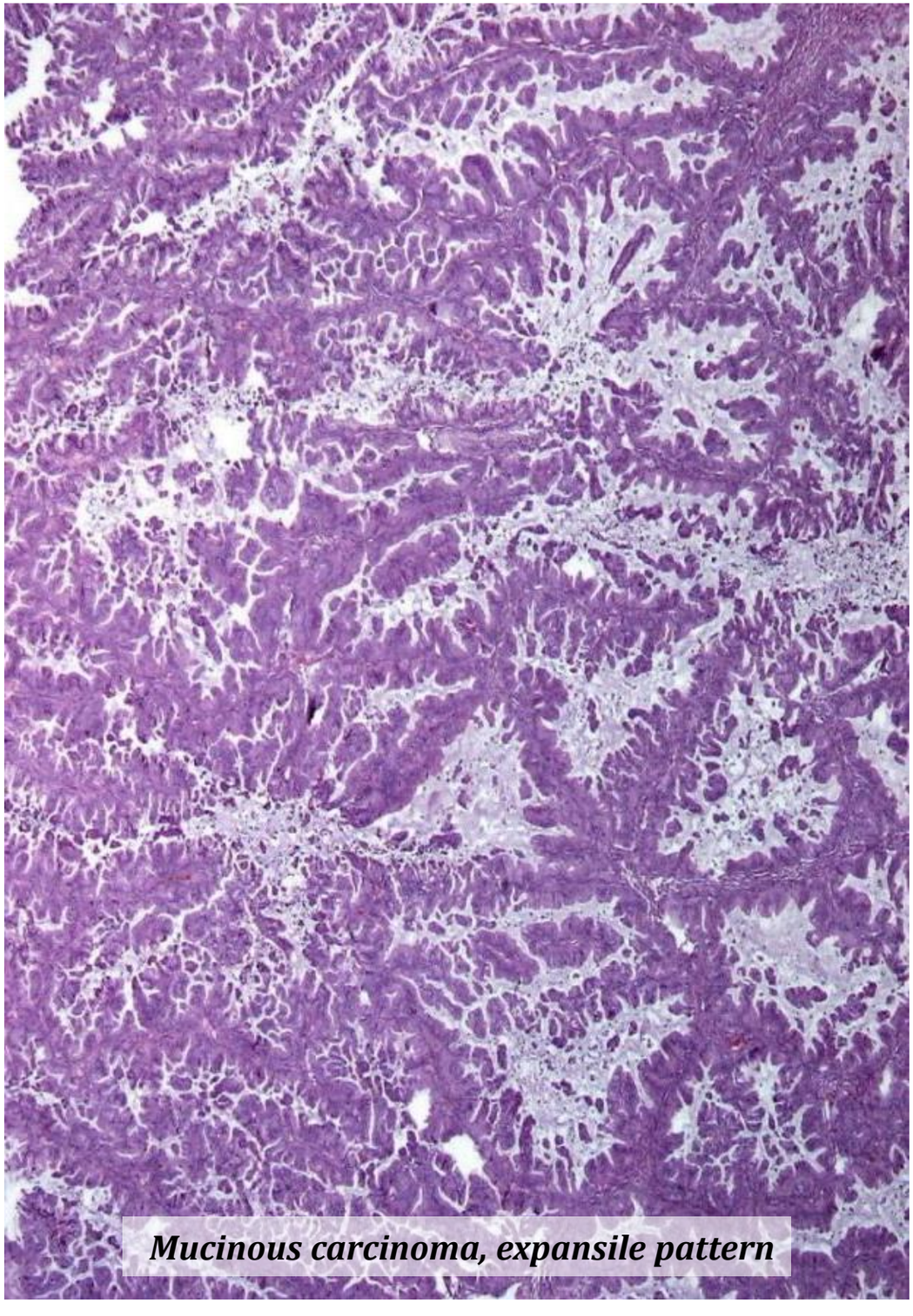
Mucinous borderline tumor/atypical proliferative mucinous tumor, permanent section



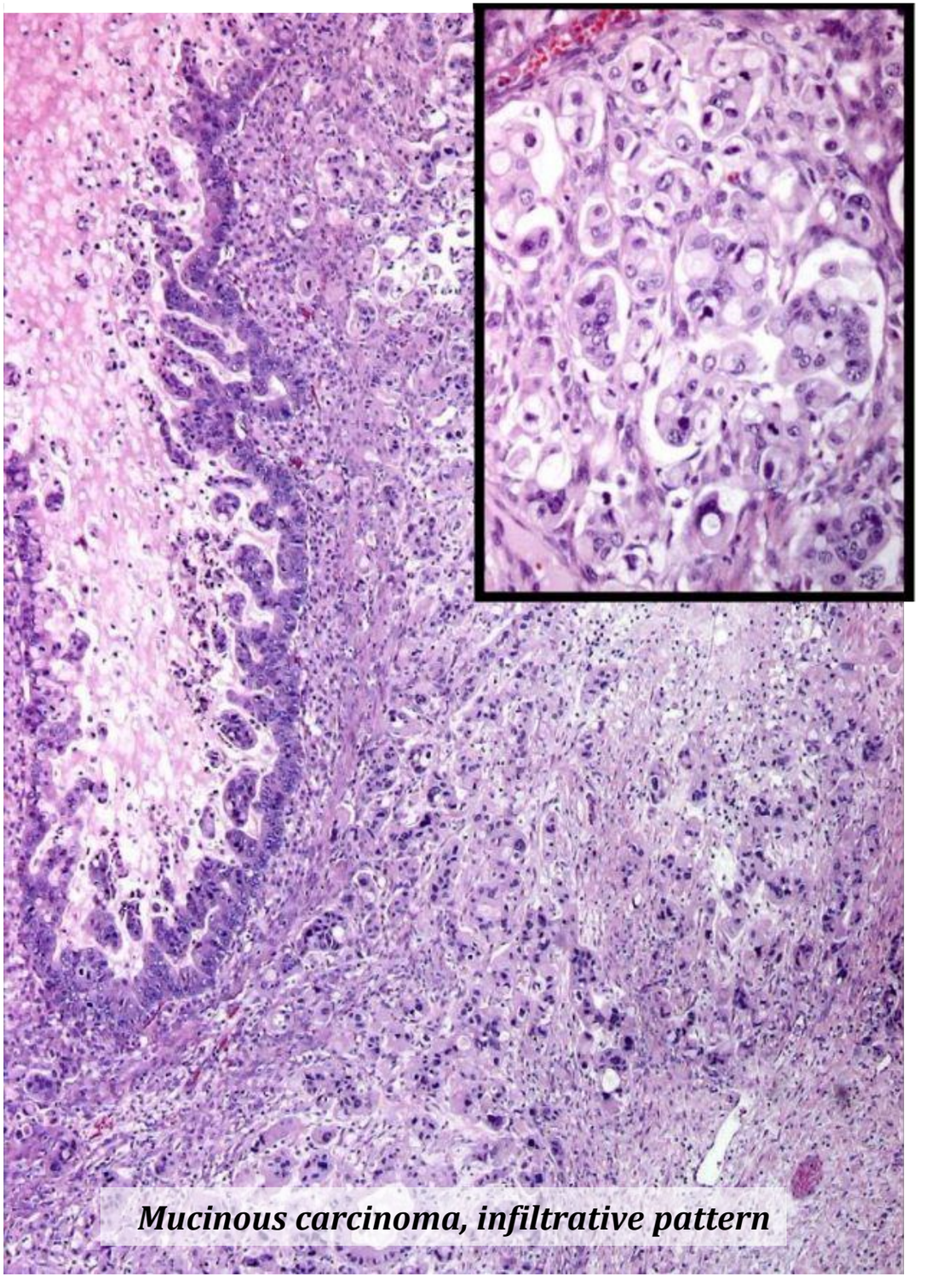
Mucinous borderline tumor/atypical proliferative mucinous tumor, permanent section



Mucinous borderline tumor/atypical proliferative mucinous tumor, permanent section



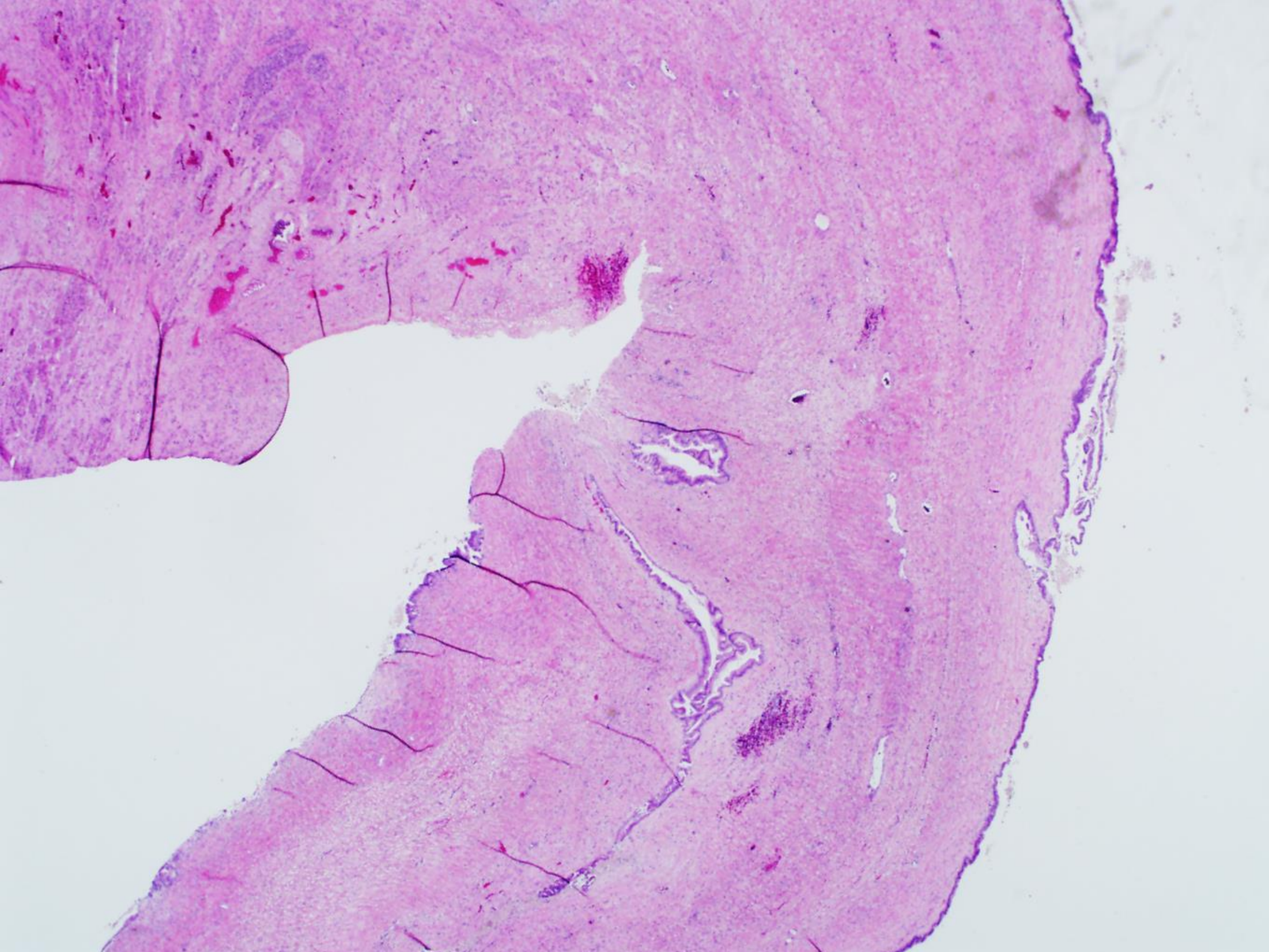
Mucinous carcinoma, expansile pattern

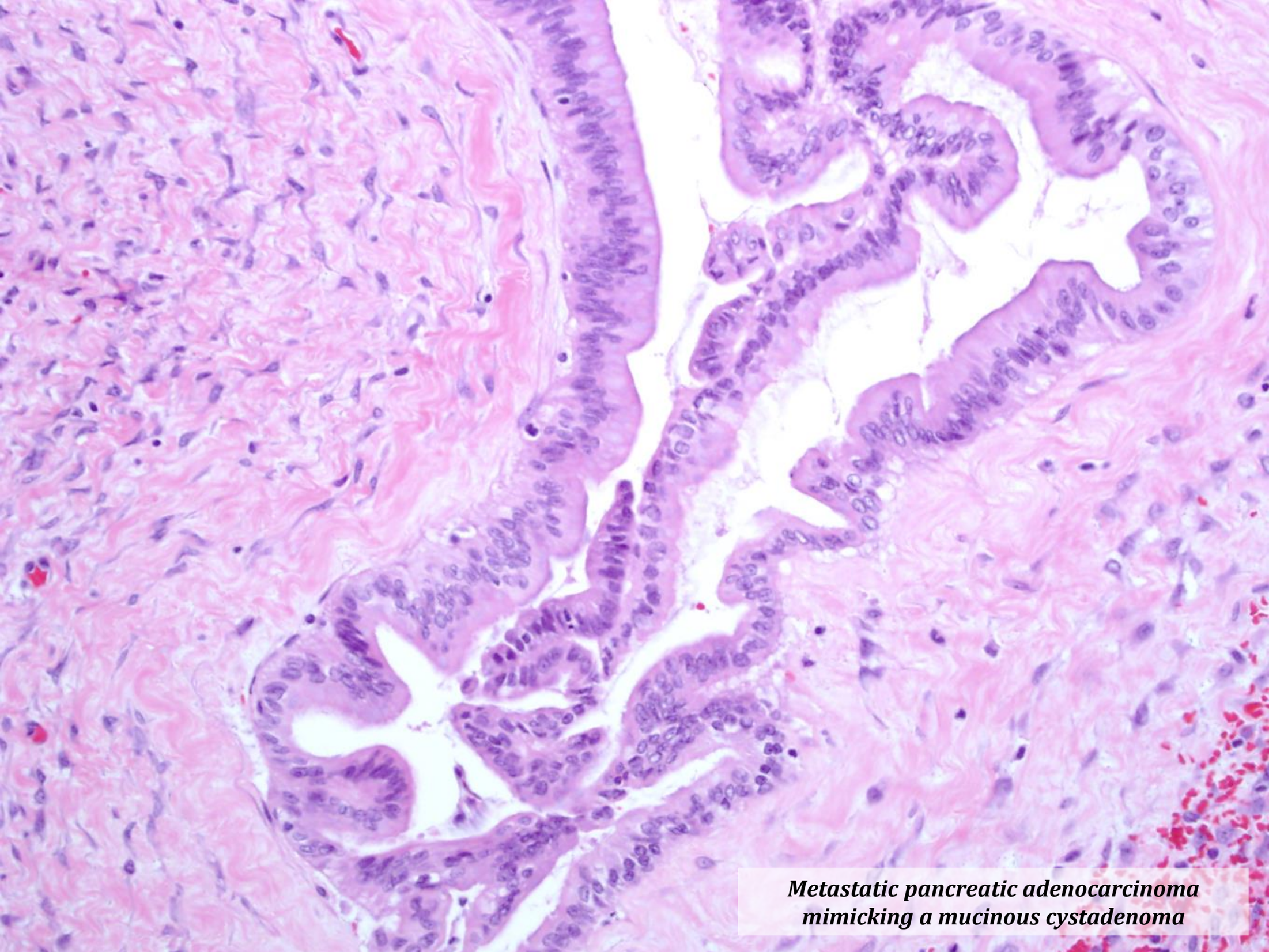


Mucinous carcinoma, infiltrative pattern

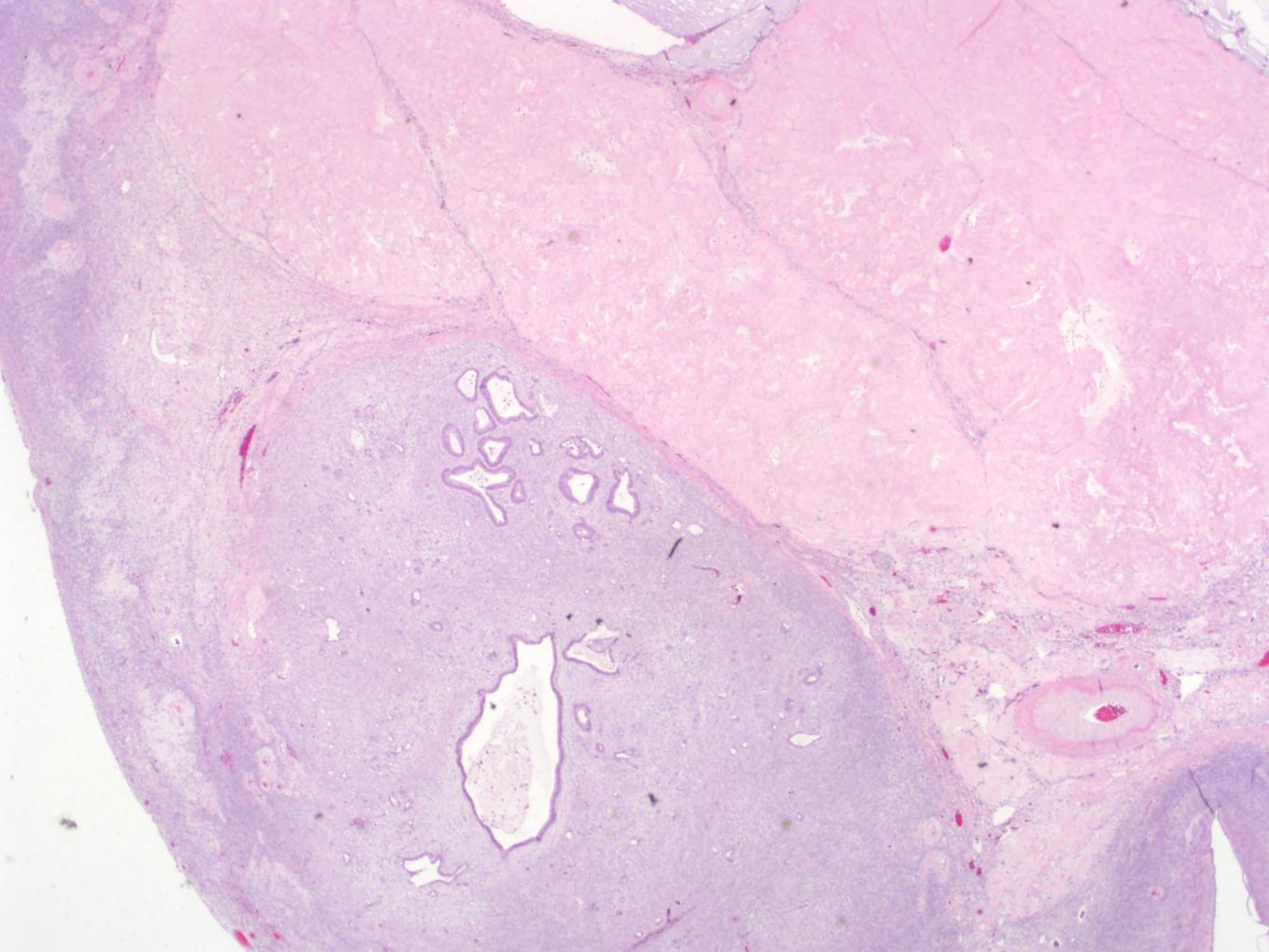
Photo credits: Anis Malpica, MD

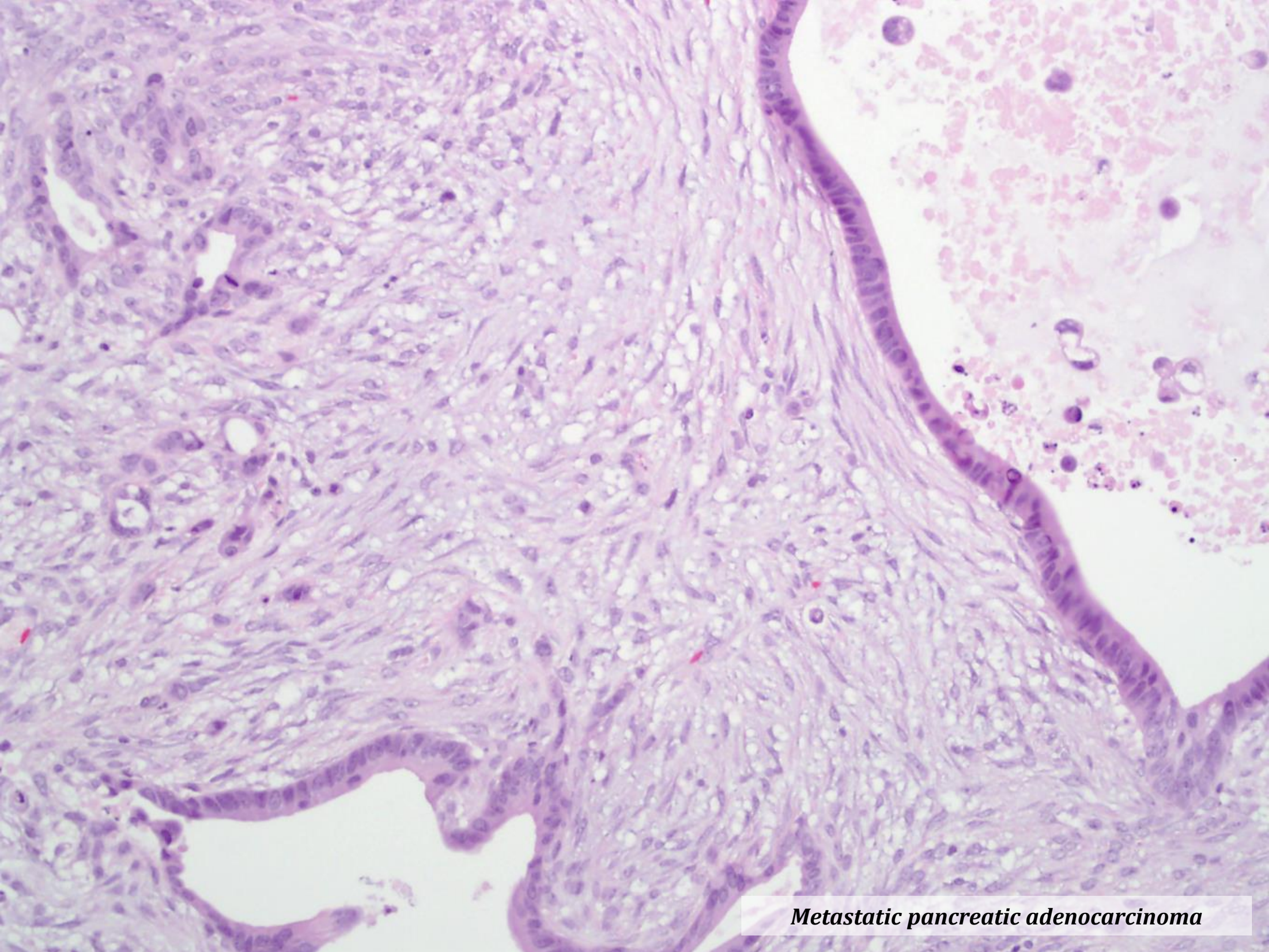
Pitfall #6



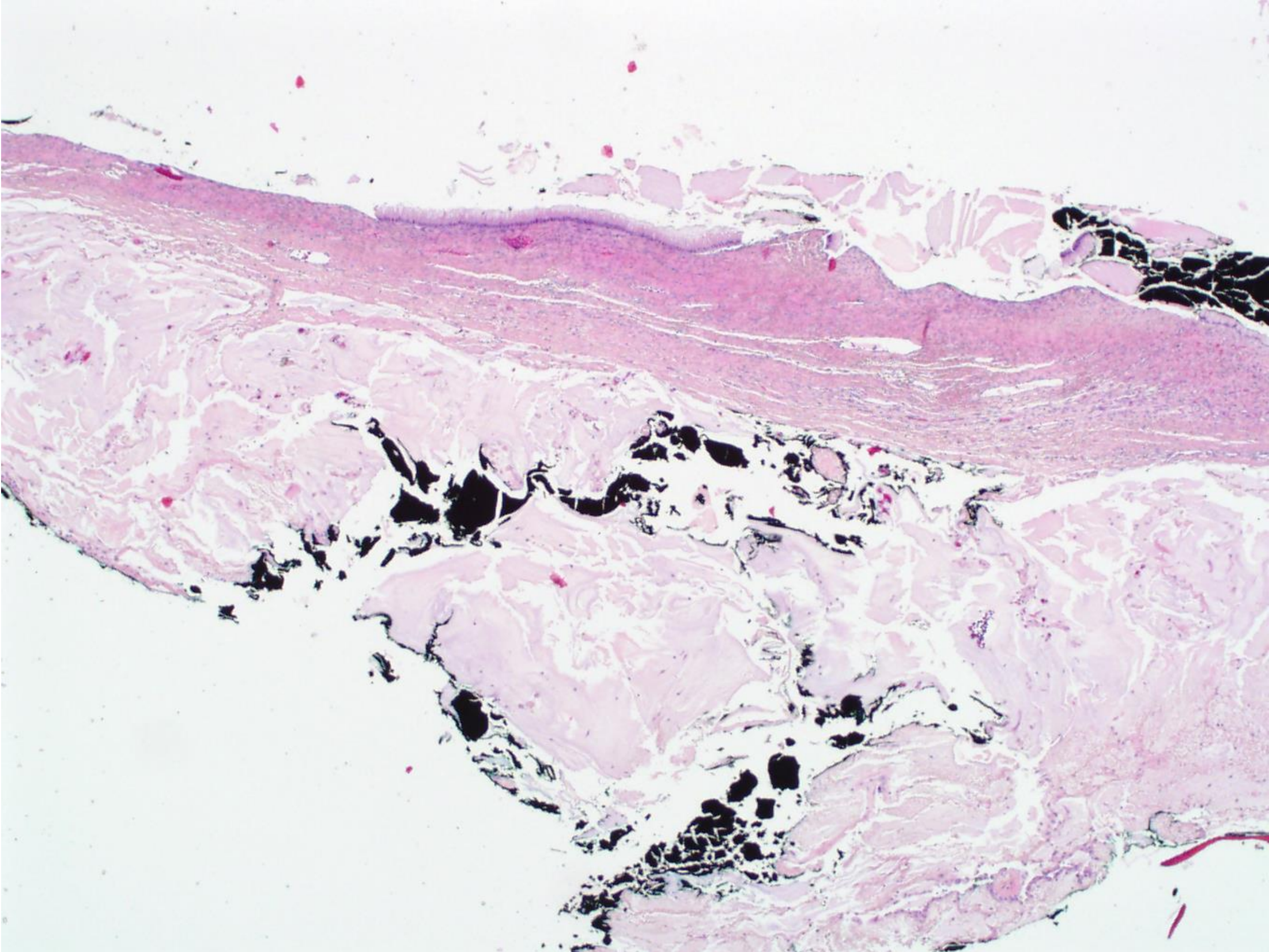


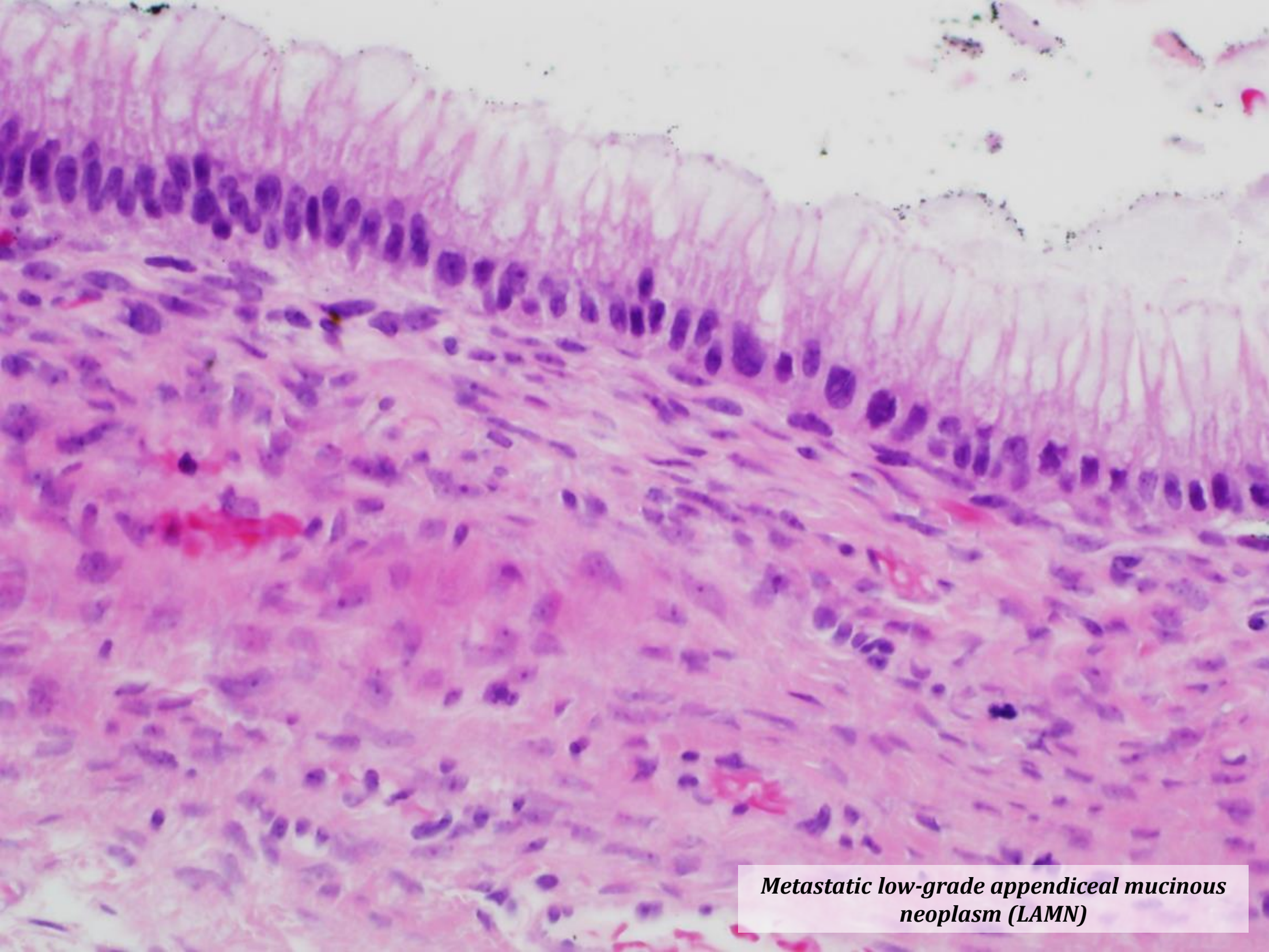
Metastatic pancreatic adenocarcinoma mimicking a mucinous cystadenoma



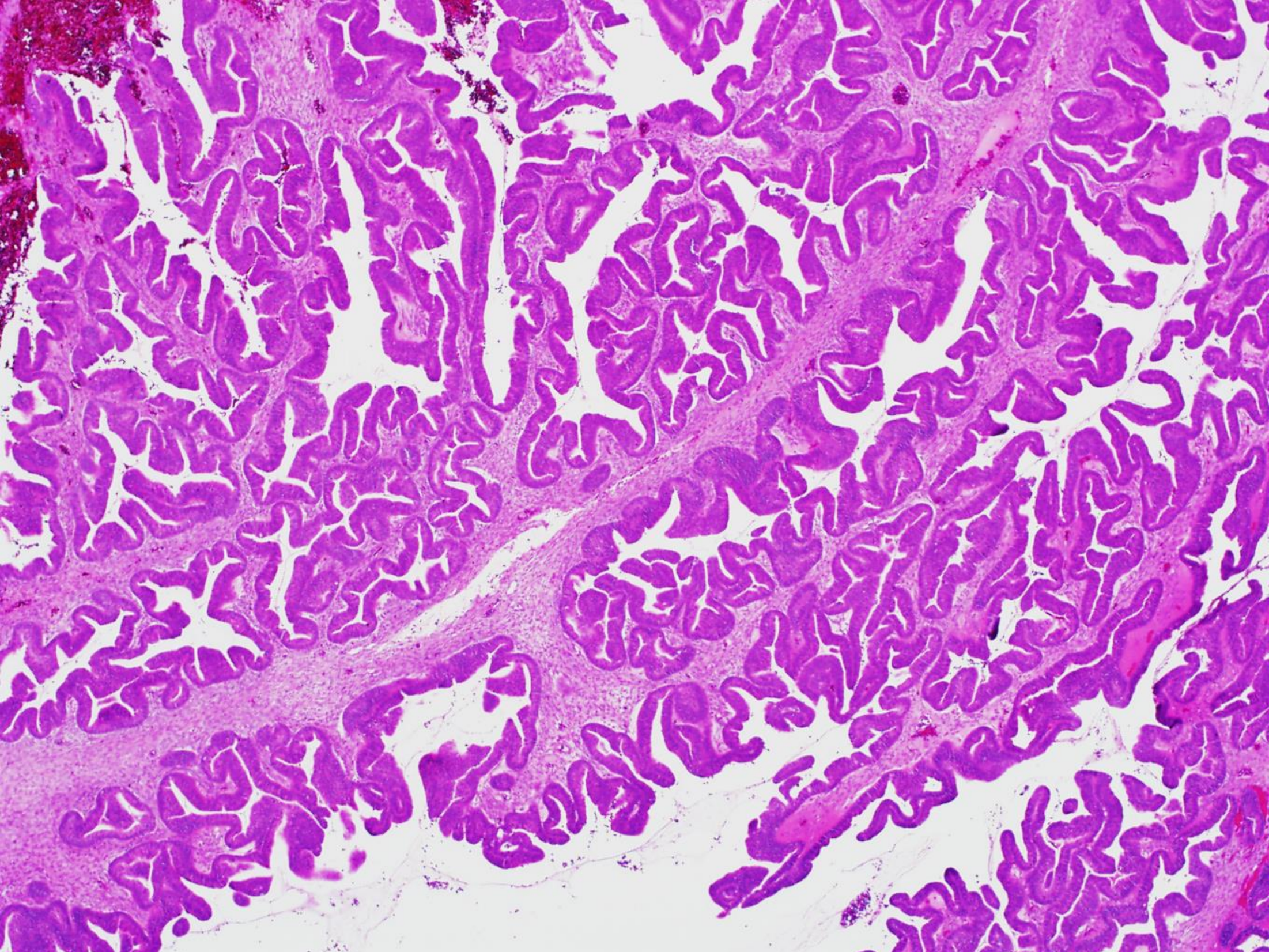


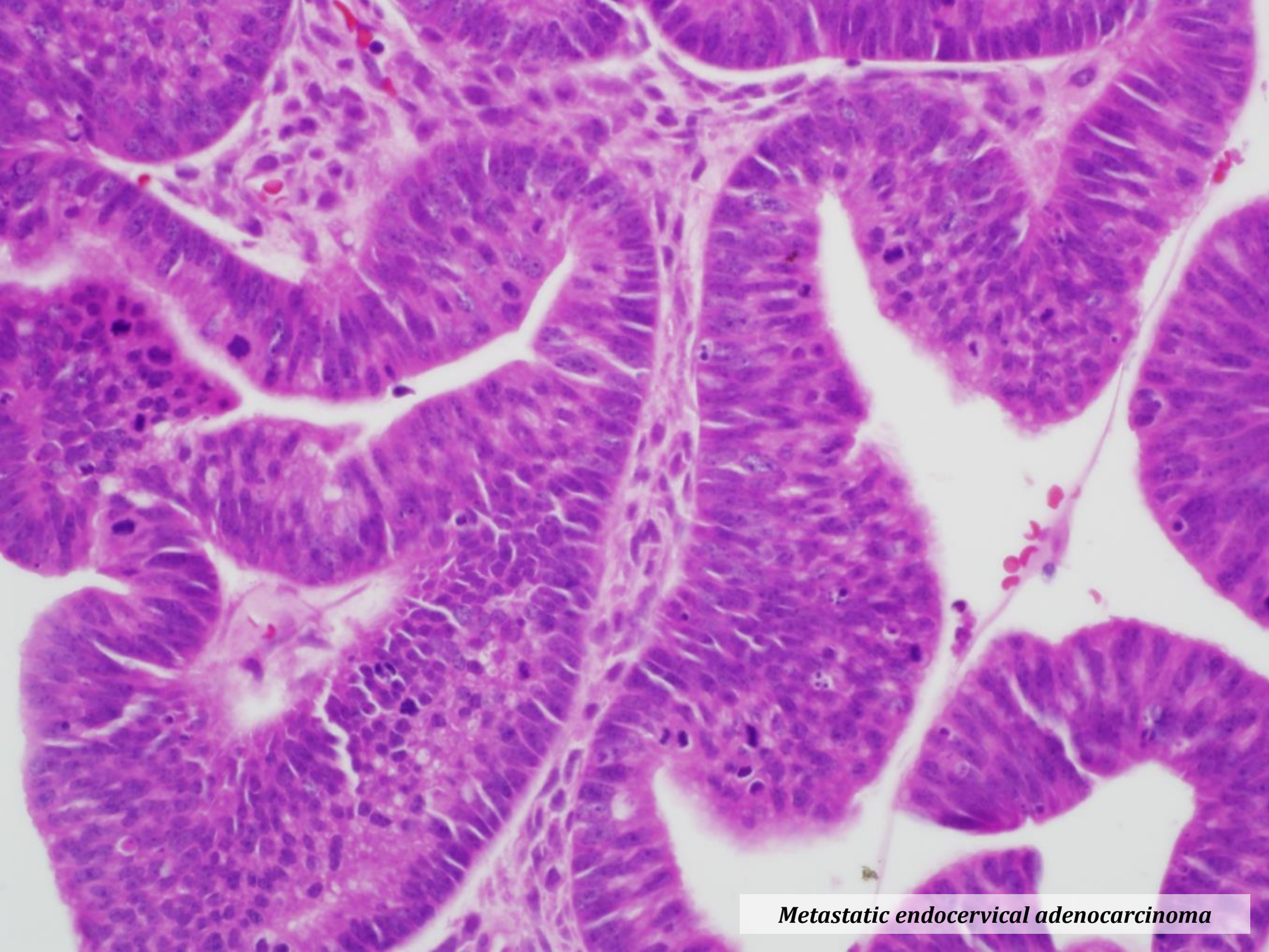
Metastatic pancreatic adenocarcinoma





Metastatic low-grade appendiceal mucinous neoplasm (LAMN)





Metastatic endocervical adenocarcinoma

MUCINOUS TUMORS

GROSS CHARACTERISTICS

- Laterality of the tumor
- Size of the tumor
- Appearance

TABLE 2. *Distribution of primary/metastatic tumors based on size of largest ovary and laterality*

A	<10 cm	≥10 cm
Unilateral	13% primary 87% metastatic	82% primary 18% metastatic
Bilateral	5% primary 95% metastatic	8% primary 92% metastatic

B	Primary	Metastatic
Unilateral ≥10 cm	9	2
Unilateral <10 cm	1	7
Bilateral ≥10 cm	1	11
Bilateral <10 cm	1	18

Note: The above data do not include two tumors with unknown laterality or unknown size (both metastatic).

TABLE 4. Primary and Metastatic Mucinous Tumors: Size and Laterality Data (All Cases Combined)

Tumor Type	n	Size (cm)			Bilateral (%)
		Mean	Median	Range	
Primary ovarian mucinous tumors (total)	52	21.9	21.0	12.0-36.0	0
Atypical proliferative (borderline) mucinous tumors	31	22.1	22.0	12.0-35.0	0
Mucinous carcinomas	21	21.5	20.0	13.0-36.0	0
Metastatic mucinous tumors (total)	142	13.0	12.0	2.1-45.0	65
Colorectal carcinomas	46	13.6	13.0	2.5-45.0	57
Appendiceal tumors					
Low-grade tumors	28	16.0	18.0	3.0-30.0	75
Carcinomas	20	12.0	10.9	3.5-24.0	90
Pancreaticobiliary tract carcinomas	20	9.8	9.8	2.5-21.0	90
Small intestinal carcinomas	3	15.8	15.0	12.5-20.0	33
Gastric carcinomas	5	9.9	9.0	6.0-15.0	40
Endocervical carcinomas	20	12.2	12.3	2.1-30.0	35

Seidman J, Kurman R, Ronnett B. Primary and Metastatic Mucinous Adenocarcinomas in the Ovaries: Incidence in Routine Practice With a New Approach to Improve Intraoperative Diagnosis. Am J Surg Pathol. 2003;27(7):985-993.

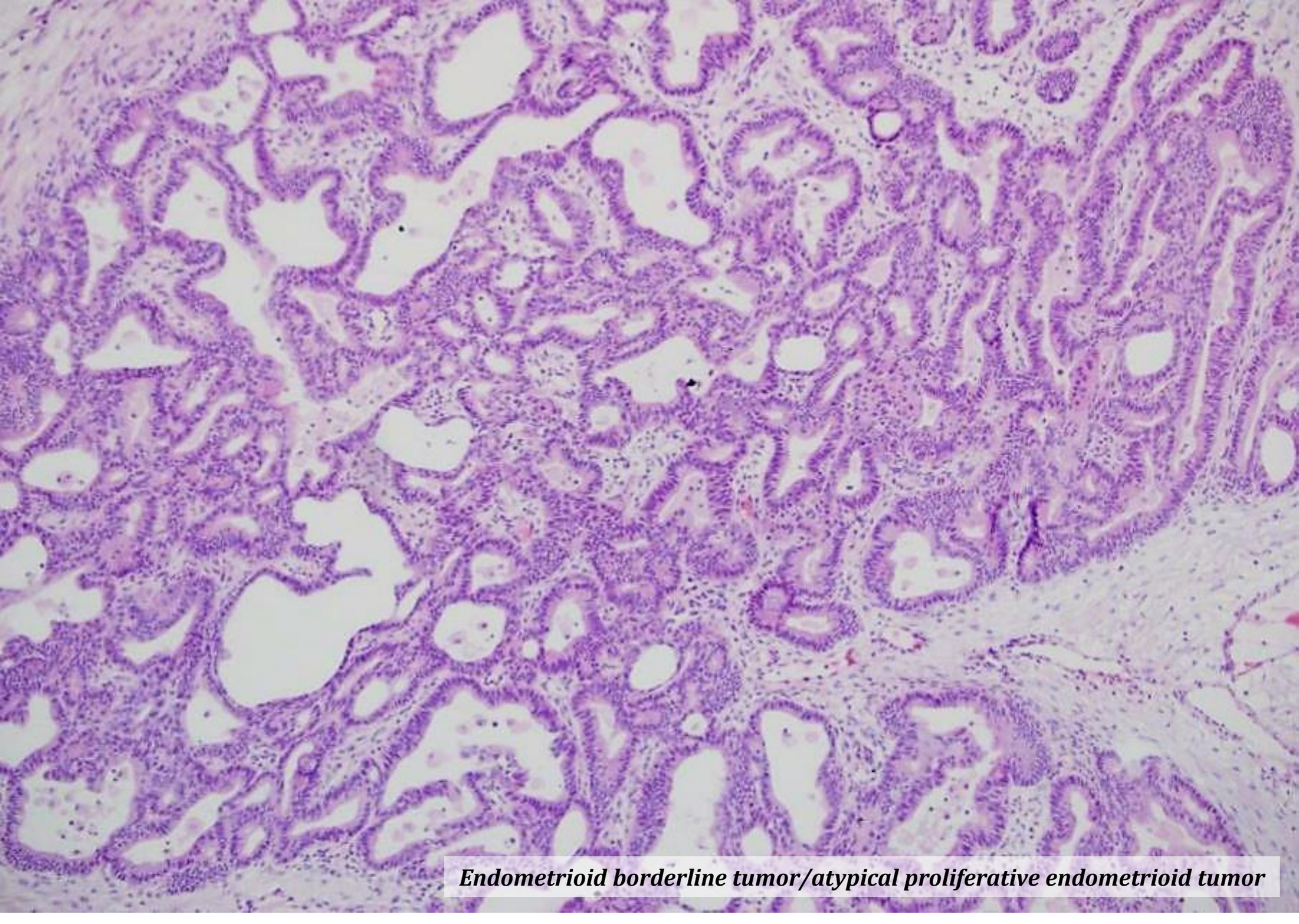
Yemelyanova AV, Vang R, Judson K, Wu L-S-F, Ronnett BM. 2008. Distinction of Primary and Metastatic Mucinous Tumors Involving the Ovary: Analysis of Size and Laterality Data by Primary Site with Reevaluation of an Algorithm for Tumor classification. Am J Surg Pathol. 2008;32:128-138.

METASTASIS

ARCHITECTURAL AND HISTOLOGIC CHARACTERISTICS

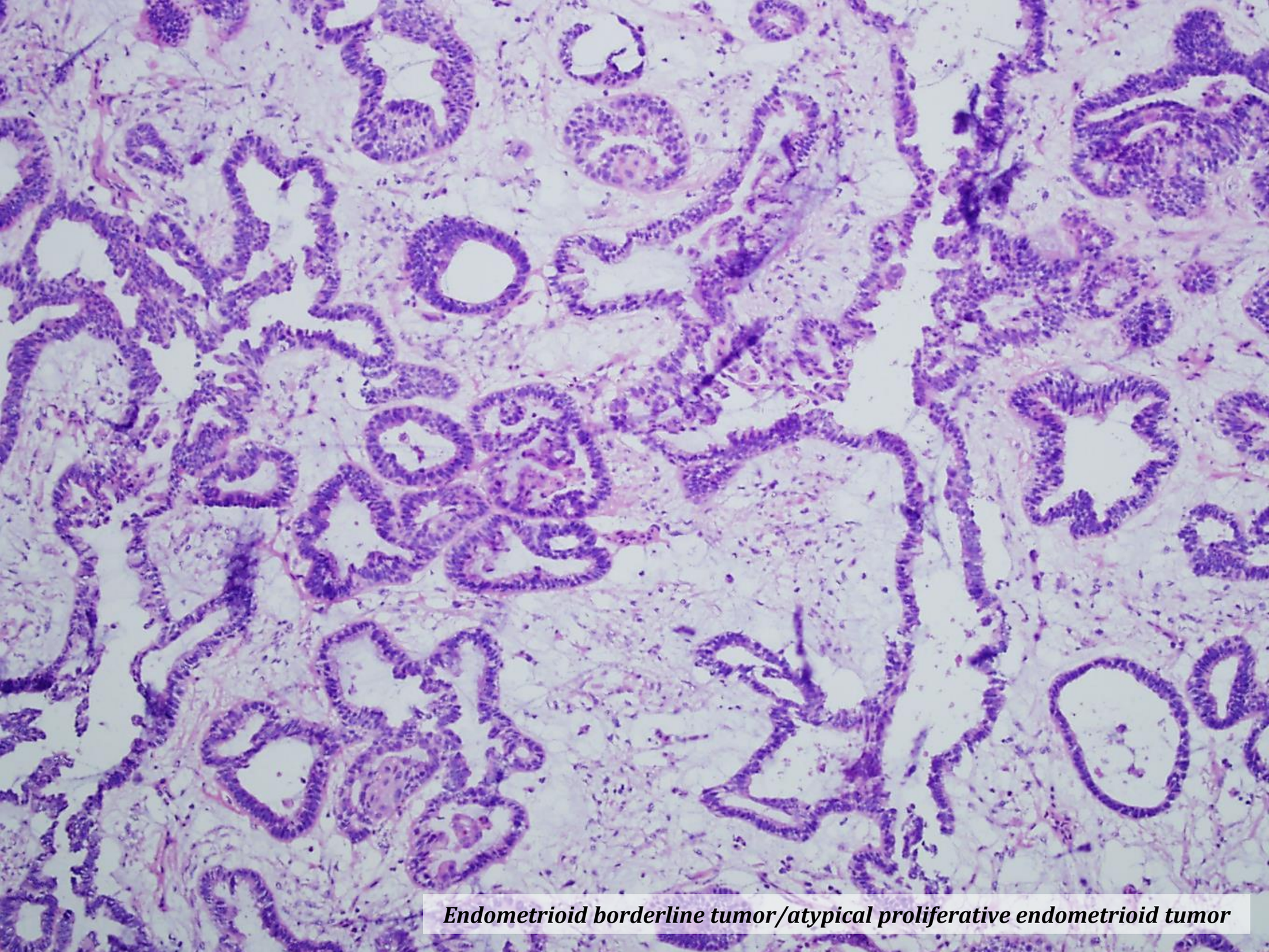
- Multinodular growth
- “Hypermucinous”, pseudomyxoma ovarii
- Discrepant cytology:architecture
  - i.e. high-grade cytology with well differentiated architecture

Endometrioid Neoplasms

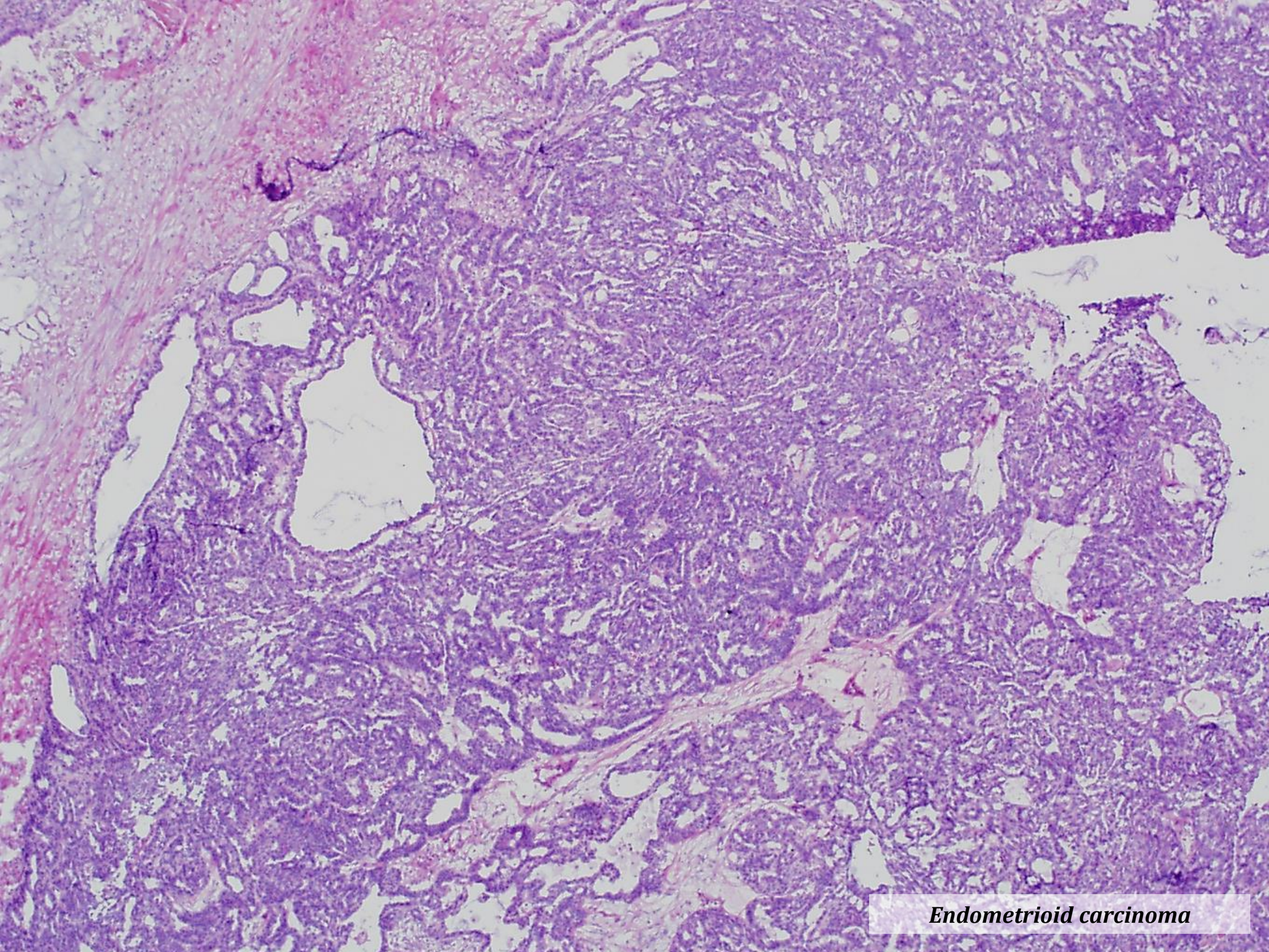


Endometrioid borderline tumor/atypical proliferative endometrioid tumor

Photo credit: Karuna Garg, MD UCSF



Endometrioid borderline tumor/atypical proliferative endometrioid tumor



Endometrioid carcinoma

Reasonable Approaches to the Diagnostic Line

Don't overcommit, but give the surgeon enough information to proceed

CYST WITHOUT AN EPITHELIAL LINING

- "Denuded simple cyst; no evidence of malignancy on limited sectioning. Defer to permanent section."

- "Denuded hemorrhagic cyst; no evidence of malignancy on limited sectioning. Defer to permanent section."

Not uncommon

- *First step: Take a few additional sections for frozen section analysis*
  - *Often encounter this situation with endometriotic cysts (you may find some additional clues in the stroma that would suggest this diagnosis)*
  - *May also occur with serous and mucinous cysts*

- *If, after additional sampling, you still can't classify the lesion … be descriptive and discuss that there are no overt malignant features in these sections.*

BENIGN CYSTS

- Serous neoplasms:
  - “Serous cystadenoma on limited sampling.”
- Mucinous neoplasms:
  - “Mucinous cystic neoplasm, consistent with/favor mucinous cystadenoma on limited sampling”
- Endometrial neoplasms:
  - “Endometriotic cyst/endometrioma, on limited sampling.”
  - “Hemorrhagic cyst with features suggestive of endometriotic cyst, on limited sampling.”

MINIMAL/FOCAL EPITHELIAL PROLIFERATION OR ATYPIA

- "_____ (serous/mucinous) cystadenoma with focal epithelial proliferation/atypia, defer to permanent."

Uncommon scenario

- *First step: Take a few additional sections for frozen section analysis*

- *If, after additional sampling, you are still in the same diagnostic category… discuss your findings with the surgeon. You can state that while you favor a benign lesion, you cannot exclude a borderline tumor and that additional sectioning is needed for definitive characterization.*

In one study, approximately 25% went from benign to borderline tumor on final diagnosis

UNEQUIVOCAL FEATURES OF A BORDERLINE TUMOR

- "**At least** _____ (serous/mucinous/endometrioid) borderline tumor, on limited sampling."

Most surgeons will proceed with staging if a frozen section is called "borderline" or "adenocarcinoma".

However, depending on the patient's age, fertility desires, operative findings, etc., some surgeons may chose to do some degree of modified staging.

If you see clear micropapillary architectural features, mentioning this to the surgeon at the time of frozen section can be helpful (especially in younger patients)

MUCINOUS CARCINOMA

- "Adenocarcinoma with mucinous features."
- "Mucinous adenocarcinoma, favor ovarian primary on limited sampling."
- "Mucinous adenocarcinoma, favor metastatic adenocarcinoma on limited sampling."
- "Mucinous adenocarcinoma, defer to permanent section."

Discuss with the surgeon your impression regarding the histologic features that are present and if you can favor a site of origin. Often asking about the appearance of the peritoneum, bowel, appendix, etc. can be helpful to assess the probability of a primary or metastatic lesion.

MULLERIAN CARCINOMA (SEROUS, CLEAR CELL, ENDOMETRIOID)

- "High-grade carcinoma/adenocarcinoma, compatible with ovarian primary on limited sampling."

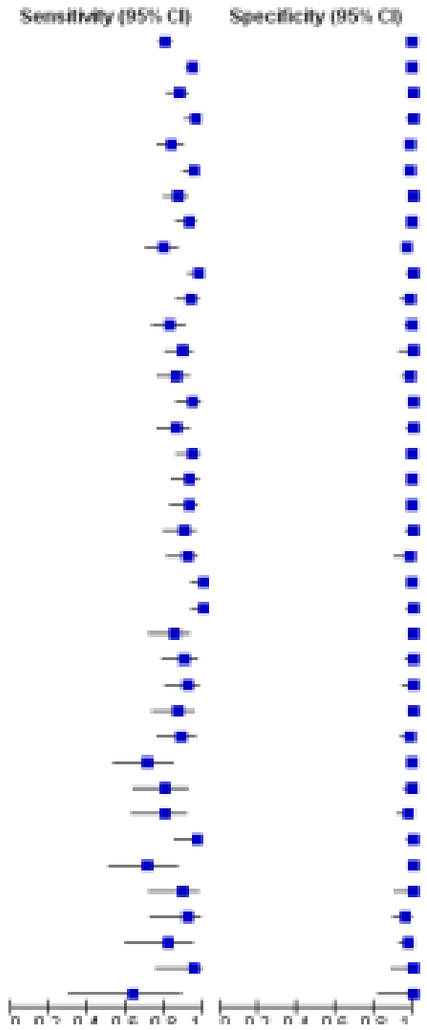
- "High-grade carcinoma/adenocarcinoma, compatible with ovarian primary with _____ (serous, clear cell, endometrioid) features) on limited sampling."

For operative purposes, the type of carcinoma (serous, clear cell, endometrioid) doesn't make a difference

If you see endometrioid carcinoma, you may or may not be able to determine whether the lesion is primary vs. metastatic (look for precursor lesions in the background)

SENSITIVITY AND SPECIFICITY

Study	TP	FP	FN	TN	% Ben study	# DP	% BOT study	% Mal study	Sensitivity (95% CI)	Specificity (95% CI)
Cross 2012	415	5	101	918	54.0	516.0	10.0	36.0	0.80 [0.77, 0.84]	0.99 [0.99, 1.00]
Stewart 2006	251	4	15	644	60.0	266.0	11.0	29.0	0.94 [0.91, 0.97]	0.99 [0.98, 1.00]
Pavlakis 2009	135	0	19	691	70.0	154.0	11.0	18.0	0.88 [0.81, 0.92]	1.00 [0.99, 1.00]
Acikalin 2014	132	0	6	144	43.0	138.0	9.0	49.0	0.96 [0.91, 0.98]	1.00 [0.97, 1.00]
Fanfani 2007	106	2	21	182	41.0	127.0	18.0	41.0	0.83 [0.76, 0.89]	0.99 [0.96, 1.00]
Bige 2011	115	5	6	393	71.0	121.0	5.0	23.0	0.95 [0.90, 0.98]	0.99 [0.97, 1.00]
Ilvan 2005	104	0	16	394	69.0	120.0	8.0	24.0	0.87 [0.79, 0.92]	1.00 [0.99, 1.00]
Rose 1994	111	1	9	262	61.0	120.0	8.0	31.0	0.93 [0.86, 0.97]	1.00 [0.98, 1.00]
Wasinghon 2008	82	8	21	265	58.0	103.0	15.0	27.0	0.80 [0.71, 0.87]	0.97 [0.94, 0.99]
Taskiran 2008	90	0	2	112	48.0	92.0	7.0	45.0	0.98 [0.92, 1.00]	1.00 [0.97, 1.00]
Maheshwari 2006	86	2	6	116	51.0	92.0	5.0	44.0	0.93 [0.86, 0.98]	0.98 [0.94, 1.00]
Sukumaran 2014	73	1	15	144	51.0	88.0	11.0	38.0	0.83 [0.73, 0.90]	0.99 [0.96, 1.00]
Gorisek 2009	73	0	9	49	2.0	82.0	35.0	63.0	0.89 [0.80, 0.95]	1.00 [0.93, 1.00]
Wootipoom 2006	68	2	11	132	53.0	79.0	10.0	37.0	0.86 [0.76, 0.93]	0.99 [0.95, 1.00]
Wang 1998	69	0	4	223	68.0	73.0	8.0	25.0	0.95 [0.87, 0.98]	1.00 [0.98, 1.00]
Tangjitgamol 2004	62	0	10	127	57.0	72.0	7.0	36.0	0.86 [0.76, 0.93]	1.00 [0.97, 1.00]
Cuello 1999	67	3	4	415	81.0	71.0	5.0	15.0	0.94 [0.86, 0.98]	0.99 [0.98, 1.00]
Pinto 2001	64	1	5	173	64.0	69.0	7.0	28.0	0.93 [0.84, 0.98]	0.99 [0.97, 1.00]
Rakhshan 2009	60	1	5	216	72.0	65.0	5.0	23.0	0.92 [0.83, 0.97]	1.00 [0.97, 1.00]
Twaalfhoven 1991	54	0	6	105	55.0	60.0	8.0	36.0	0.90 [0.79, 0.96]	1.00 [0.97, 1.00]
Subbian 2013	55	1	5	56	35.0	60.0	14.0	51.0	0.92 [0.82, 0.97]	0.98 [0.91, 1.00]
Hamed 1993	55	1	0	268	80.0	55.0	3.0	17.0	1.00 [0.94, 1.00]	1.00 [0.98, 1.00]
Wakahara 2001	54	0	0	133	63.0	54.0	8.0	29.0	1.00 [0.93, 1.00]	1.00 [0.97, 1.00]
Mallipatil 2013	45	0	8	165	69.0	53.0	7.0	24.0	0.85 [0.72, 0.93]	1.00 [0.98, 1.00]
Boriboonhirunsarn 2004	47	0	5	95	61.0	52.0	4.0	35.0	0.90 [0.79, 0.97]	1.00 [0.96, 1.00]
Suprasert 2008	46	0	4	62	38.0	50.0	17.0	45.0	0.92 [0.81, 0.98]	1.00 [0.94, 1.00]
Yeo 1998	40	0	6	270	79.0	46.0	6.0	15.0	0.87 [0.74, 0.95]	1.00 [0.99, 1.00]
Naik 2006	40	1	5	83	57.0	45.0	9.0	35.0	0.89 [0.76, 0.96]	0.99 [0.94, 1.00]
Puls 1997	27	1	11	255	73.0	38.0	14.0	13.0	0.71 [0.54, 0.85]	1.00 [0.98, 1.00]
Bazot 2006	29	1	7	114	62.0	36.0	15.0	24.0	0.81 [0.64, 0.92]	0.99 [0.95, 1.00]
Torres 1998	28	2	7	86	63.0	35.0	8.0	28.0	0.80 [0.63, 0.92]	0.98 [0.92, 1.00]
Lim 1997	34	0	1	136	75.0	35.0	5.0	20.0	0.97 [0.85, 1.00]	1.00 [0.97, 1.00]
Iker 2011	20	0	8	238	86.0	28.0	3.0	11.0	0.71 [0.51, 0.87]	1.00 [0.98, 1.00]
Toneva 2012	25	0	3	38	27.0	28.0	30.0	42.0	0.89 [0.72, 0.98]	1.00 [0.91, 1.00]
Yarandi 2008	22	3	2	79	74.0	24.0	4.0	23.0	0.92 [0.73, 0.99]	0.96 [0.90, 0.99]
Canis 2004	18	3	4	111	64.0	22.0	20.0	16.0	0.82 [0.60, 0.95]	0.97 [0.93, 0.99]
Kokka 2009	19	0	1	30	40.0	20.0	20.0	40.0	0.95 [0.75, 1.00]	1.00 [0.88, 1.00]
Garcia 1997	7	0	4	19	53.0	11.0	10.0	37.0	0.64 [0.31, 0.89]	1.00 [0.82, 1.00]



Forest plot: frozen section threshold malignant vs borderline or benign

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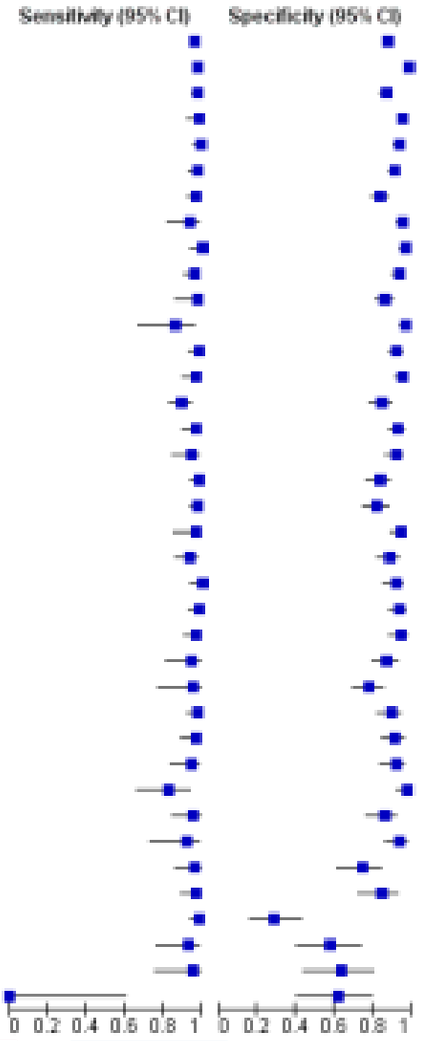
SENSITIVITY AND SPECIFICITY

Study	TP	FP	FN	TN	% Ben study	% BOT study	% Mal study	# DN	Sensitivity (95% CI)	Specificity (95% CI)
Cross 2012	497	115	19	808	54.0	10.0	36.0	923.0	0.96 [0.94, 0.98]	0.88 [0.85, 0.90]
Pavlakis 2009	246	7	5	587	70.0	11.0	18.0	691.0	0.98 [0.95, 0.99]	0.99 [0.98, 1.00]
Stewart 2006	259	87	7	561	60.0	11.0	29.0	648.0	0.97 [0.95, 0.99]	0.87 [0.84, 0.89]
Cuello 1999	70	20	1	398	81.0	5.0	15.0	418.0	0.99 [0.92, 1.00]	0.95 [0.93, 0.97]
Bige 2011	120	27	1	371	71.0	5.0	23.0	398.0	0.99 [0.95, 1.00]	0.93 [0.90, 0.95]
Ilvan 2005	117	33	3	351	69.0	8.0	24.0	384.0	0.97 [0.93, 0.99]	0.91 [0.88, 0.94]
Wasinghon 2008	100	44	3	229	58.0	15.0	27.0	273.0	0.97 [0.92, 0.99]	0.84 [0.79, 0.88]
Yeo 1998	43	13	3	257	79.0	6.0	15.0	270.0	0.93 [0.82, 0.99]	0.95 [0.92, 0.97]
Hamed 1993	55	9	0	260	80.0	3.0	17.0	269.0	1.00 [0.94, 1.00]	0.97 [0.94, 0.98]
Rose 1994	115	17	5	246	61.0	8.0	31.0	263.0	0.96 [0.91, 0.99]	0.94 [0.90, 0.96]
Puls 1997	37	35	1	221	73.0	14.0	13.0	256.0	0.97 [0.86, 1.00]	0.86 [0.82, 0.90]
Iker 2011	24	7	4	231	86.0	3.0	11.0	238.0	0.86 [0.67, 0.96]	0.97 [0.94, 0.99]
Wang 1998	72	18	1	205	68.0	8.0	25.0	223.0	0.99 [0.93, 1.00]	0.92 [0.88, 0.95]
Rakhshan 2009	63	11	2	206	72.0	5.0	23.0	217.0	0.97 [0.89, 1.00]	0.95 [0.91, 0.97]
Fanfani 2007	114	29	13	155	41.0	18.0	41.0	184.0	0.90 [0.83, 0.94]	0.84 [0.78, 0.89]
Pinto 2001	87	12	2	162	64.0	7.0	28.0	174.0	0.97 [0.90, 1.00]	0.93 [0.88, 0.96]
Malipatil 2013	50	14	3	151	69.0	7.0	24.0	165.0	0.94 [0.84, 0.99]	0.92 [0.86, 0.95]
Sukumaran 2014	87	24	1	121	51.0	11.0	38.0	145.0	0.99 [0.94, 1.00]	0.83 [0.76, 0.89]
Acikalin 2014	135	26	3	118	43.0	9.0	49.0	144.0	0.98 [0.94, 1.00]	0.82 [0.75, 0.88]
Lim 1997	34	8	1	128	75.0	5.0	20.0	136.0	0.97 [0.85, 1.00]	0.94 [0.89, 0.97]
Wootipoom 2006	74	15	5	119	53.0	10.0	37.0	134.0	0.94 [0.86, 0.98]	0.89 [0.82, 0.94]
Wakahara 2001	54	11	0	122	83.0	8.0	29.0	133.0	1.00 [0.93, 1.00]	0.92 [0.86, 0.96]
Tangjitgamol 2004	71	8	1	119	57.0	7.0	36.0	127.0	0.99 [0.93, 1.00]	0.94 [0.88, 0.97]
Maheshwari 2006	89	7	3	111	51.0	5.0	44.0	118.0	0.97 [0.91, 0.99]	0.94 [0.88, 0.98]
Bazot 2006	34	15	2	100	62.0	15.0	24.0	115.0	0.94 [0.81, 0.99]	0.87 [0.79, 0.93]
Canis 2004	21	25	1	89	64.0	20.0	16.0	114.0	0.95 [0.77, 1.00]	0.78 [0.69, 0.85]
Taskiran 2008	90	12	2	100	48.0	7.0	45.0	112.0	0.98 [0.92, 1.00]	0.89 [0.82, 0.94]
Twaalfhoven 1991	58	9	2	96	55.0	8.0	36.0	105.0	0.97 [0.88, 1.00]	0.91 [0.84, 0.96]
Boriboonhirunsarn 2004	49	8	3	87	61.0	4.0	35.0	95.0	0.94 [0.84, 0.99]	0.92 [0.84, 0.96]
Torres 1998	29	2	6	86	63.0	8.0	28.0	88.0	0.83 [0.66, 0.93]	0.98 [0.92, 1.00]
Naik 2006	43	12	2	72	57.0	9.0	35.0	84.0	0.96 [0.85, 0.99]	0.86 [0.76, 0.92]
Yarandi 2008	22	5	2	77	74.0	4.0	23.0	82.0	0.92 [0.73, 0.99]	0.94 [0.86, 0.98]
Suprasert 2008	48	16	2	46	38.0	17.0	45.0	62.0	0.96 [0.86, 1.00]	0.74 [0.62, 0.84]
Subbian 2013	58	9	2	48	35.0	14.0	51.0	57.0	0.97 [0.88, 1.00]	0.84 [0.72, 0.93]
Gorisek 2009	81	35	1	14	2.0	35.0	63.0	49.0	0.99 [0.93, 1.00]	0.29 [0.17, 0.43]
Toneva 2012	26	16	2	22	27.0	30.0	42.0	38.0	0.93 [0.76, 0.99]	0.58 [0.41, 0.74]
Kokka 2009	19	11	1	19	40.0	20.0	40.0	30.0	0.95 [0.75, 1.00]	0.63 [0.44, 0.80]
Garcia 1997	0	10	4	16	53.0	10.0	37.0	19.0	0.00 [0.00, 0.60]	0.62 [0.41, 0.80]



Forest plot: frozen section threshold malignant or borderline vs benign

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FACTORS AFFECTING FS ACCURACY

- Histologic subtype
- Tumor size
  - Various cut-offs proposed: 10, 13, 15, 20 cm
- Expertise of the pathologist?
- Technical limitations
  - Frozen section artifact

Table 1
The relationship between clinicopathological parameters and the concordance of frozen section diagnoses.

Characteristic	Concordance (%)	*p* Value
Patient age[1]		0.17
≤42 years	82	
>42 years	82	
Tumor histology		<0.001
Serous	92	
Mucinous	62	
Others	55	
Tumor diameter[1]		0.001
≤100 mm	90	
>100 mm	68	
Ca-125 level[1]		0.19
≤44 IU/ml	75	
>44 IU/ml	85	
Menopausal status		0.50
Premenopausal	82	
Postmenopausal	71	
Laterality of tumor		0.50
Unilateral	75	
Bilateral	85	

[1] Median value.

Ureyen I, Turan T, Akdag Cirik D, Tasci T, Boran N, Bulbul D, Tulunay G. Frozen section in borderline tumors: is it reliable? European Journal of Obstetrics and Gynecology and Reproductive Bioplogy 2014;181:115-118.

UTERINE ENDOMETRIAL NEOPLASMS

Pearls…

KNOW THE DECISION POINT

What does the surgeon need to know?

ULTIMATE GOAL:

Facilitate the appropriate ***selection of women requiring surgical staging***

- ***Principally – which patients need a lymph node dissection?***

Incidence of lymph node metastases correlates with the depth of invasion and grade of tumor

DO YOU NEED A FROZEN?

Preoperative biopsy grade:

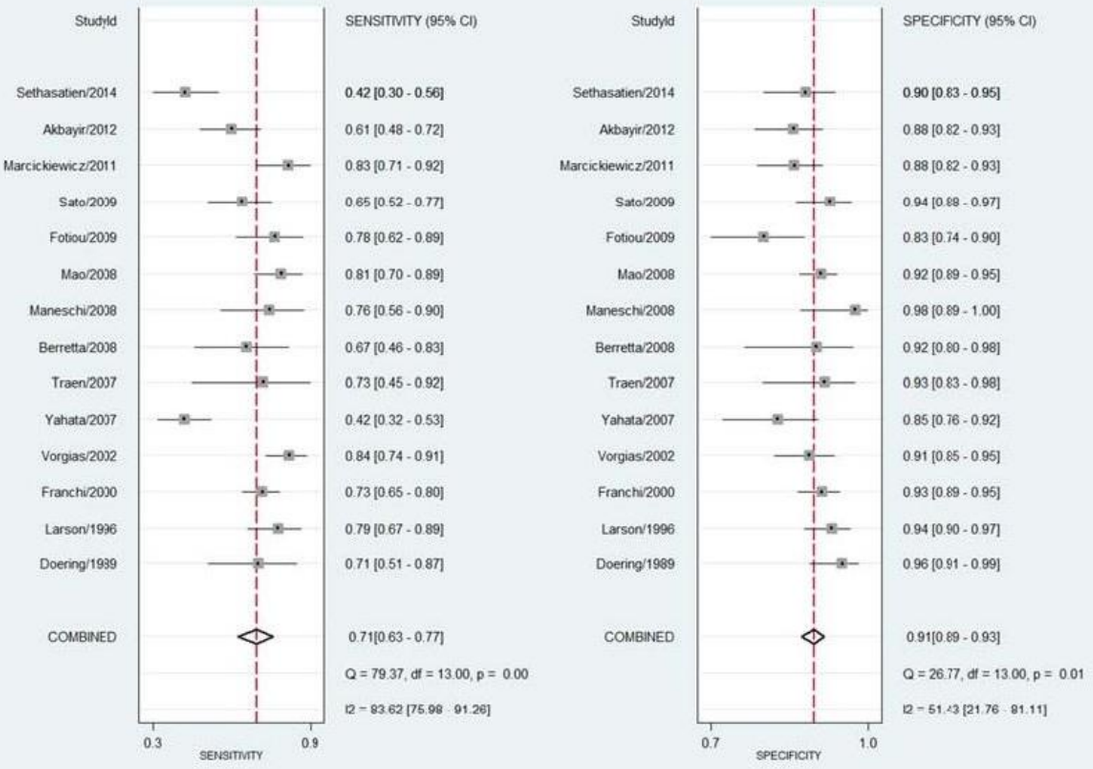
- Variable correlation between preoperative biopsy/curettage and final pathology

Depth of invasion:

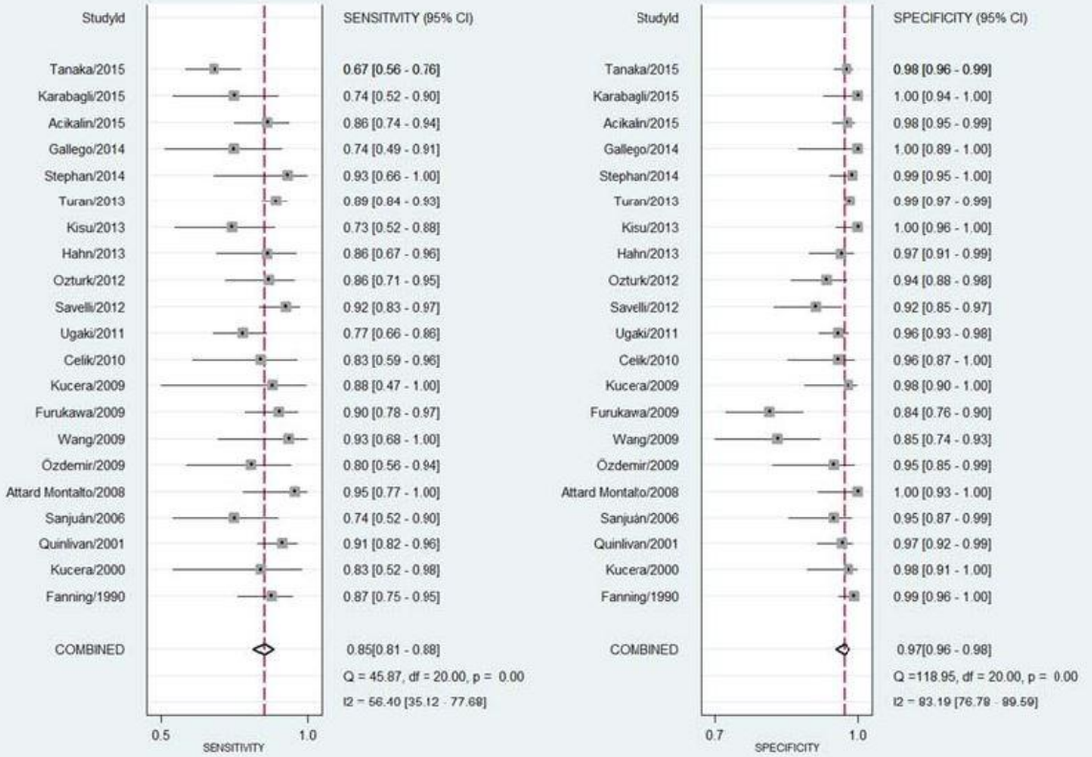
Is a gross assessment adequate?

- In some cases -- Yes
- HOWEVER…
  - Gross assessment of depth of invasion becomes less accurate as the grade of the tumor increases
  - Some patterns of invasion may be difficult to grossly identify
    - i.e. MELF pattern (Microcystic Elongated and Fragmented)
  - Benign mimics of invasion
    - i.e. Adenomyosis (may or may not be involved by tumor)

Intraoperative Gross Examination



Intraoperative Frozen Section



Alcazar JL, Dominguez-Piriz J, Juez L, Caparros M, Jurado M. Intraoperative Gross Examination and Intraoperative Frozen Section in Patients with Endometrial Cancer for Detecting Deep Myometrial Invasion: A Systematic Review and Meta-analysis. Int J Gynecol Cancer 2016;26:407-415.

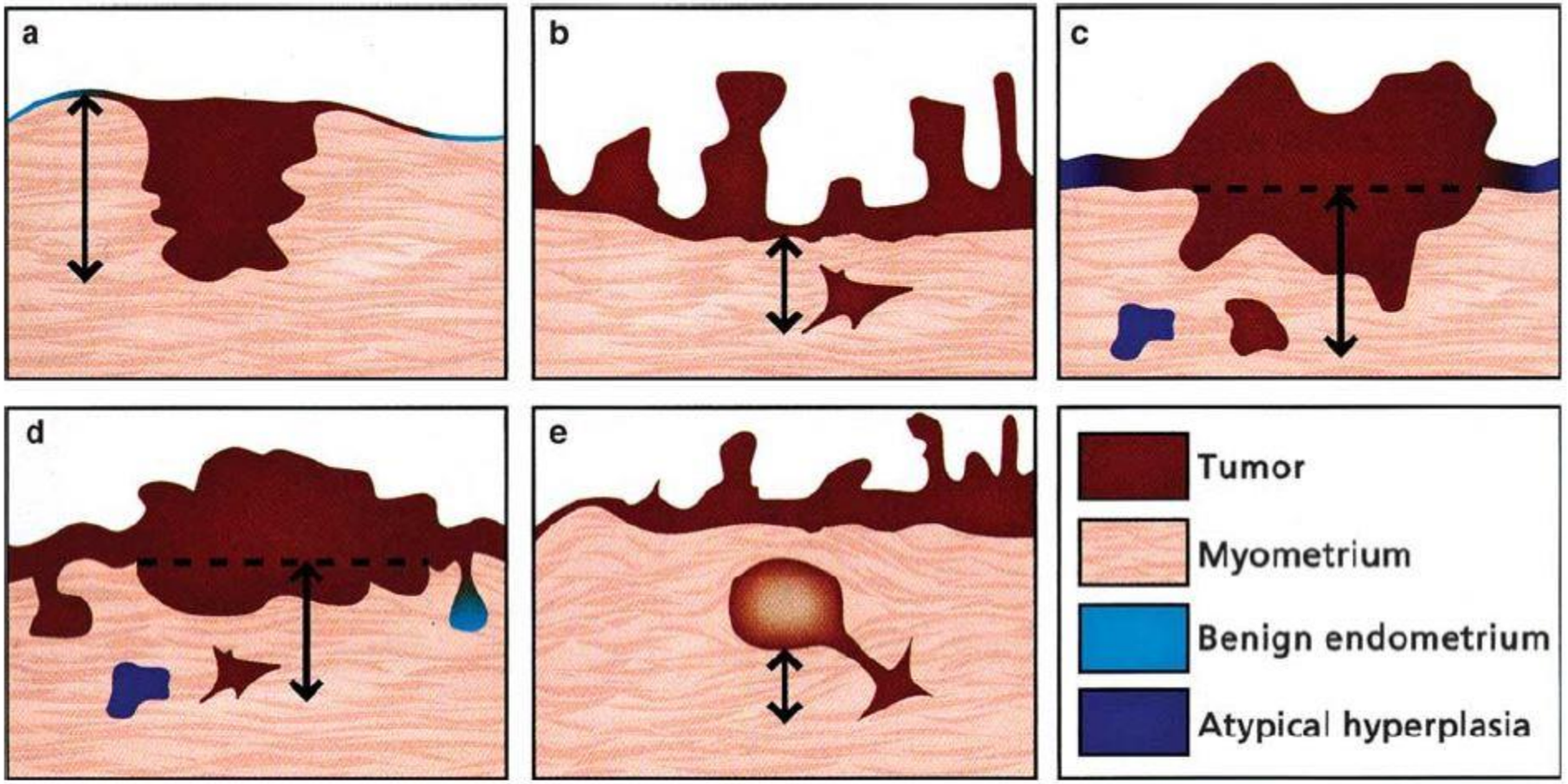


Figure 2 Assessment of myometrial invasion. (**a**) Direct invasion from the endometrium is the most recognizable and reproducible form of invasion, particularly when the advancing front is jagged and associated with a stromal response. In this situation, the depth of invasion is measured from the nearest adjacent uninvolved endomyometrial junction to the deepest focus of invasion. (**b**) Discontinuous myometrial invasion; ensure the discontinuous focus is invasive (illustrated by spiculated contours), not adenomyosis colonized by carcinoma (illustrated by rounded contours in **c**–**e**). (**c** and **d**) Depth of invasion in these cases is measured from a virtual plane whose location is estimated from the adjacent endomyometrial junction. In **c**, the invasive focus is represented by a broad, pushing front, a pattern that is difficult to evaluate. Pushing invasion can often be recognized by the presence of a stromal response at the leading edge. In **d**, the invasive focus is mostly discontinuous; the discontinuous focus of myometrial invasion can be distinguished from adenomyosis because of its spiculated shape. Histologically, the lack of endometrial stroma and the presence of surrounding desmoplasia are the two most helpful features that indicate myometrial invasion is present. (**e**) Rarely, carcinoma may arise in adenomyosis or invade from a deep focus of adenomyosis. In this situation, the depth of invasion should be measured from the junction of the adenomyosis and myometrium to the deepest area of invasive carcinoma. (This figure was published in Uterine Pathology, Copyright Cambridge University Press, 2012).

Soslow R. Practical issues related to uterine pathology: staging, frozen section, artifacts, and Lynch syndrome. Mod Pathol. 2016;29:S59-S77.

Table 1
Guidelines for surgical management of endometrial cancer at Mayo Clinic, Rochester, Minnesota (2004–2006)

Hysterectomy
Bilateral salpingo-oophorectomy
Peritoneal cytology
Bilateral pelvic and para-aortic lymphadenectomy
Para-aortic dissection up to renal vessels
Excision of gonadal vessels at insertions (optional)
Omit lymphadenectomy if no disease beyond corpus and
(1) Endometrioid (grade 1 or 2), MI ≤50%, and PTD ≤2 cm; or
(2) Endometrioid and no MI (independent of grade and PTD)
Omentectomy, staging biopsies, or cytoreduction for nonendometrioid or advanced disease

Abbreviations: MI, myometrial invasion; PTD, primary tumor diameter.
Data from Mariani et al. [28].

Table 1. Description of the risk-stratification models

Criteria	Low-risk	High-risk
Mayo criteria	· Grade 1 or 2, MMI ≤50%, and PTD ≤2 cm · No MMI (independent of grade and PTD)	· Grade 1 or 2, MMI ≤50%, and PTD >2 cm · Grade 3 · MMI ≥50%, any grade or PTD
Mayo-modified criteria	· Grade 1 or 2, MMI ≤50%, regardless of PTD · Grade 2 tumors with PTD <3 cm and MMI ≤50% · Grade 3 tumors with no MMI	· Grade 2, MMI ≤50%, and PTD ≥3 cm · Grade 3, MMI ≤50% · MMI ≥50%, any grade or PTD
GOG-99 criteria	· Grade 1 or 2, ECs confined to the endometrium, stage IA · Age ≤50 years + ≤2 pathologic risk factors · Age 50–69 years + ≤1 pathologic risk factor · Age ≥70 years + no pathologic risk factors · Risk factors: 1) grade 2 or 3 histology; 2) positive LVSI; and 3) MMI to outer 1/3	· Any age ≥3 pathologic risk factors · Age 50–69 years + ≥2 pathologic risk factors · Age ≥70 years + ≥1 pathologic risk factor · Risk factors: 1) grade 2 or 3 histology; 2) positive LVSI; and 3) MMI to outer 1/3
ESMO-modified criteria	· Stage IA (grades 1 and 2) with endometrioid type, LVSI negative · Stage IB (grades 1 and 2) with endometrioid type, LVSI negative	· Stage IA, grade 3 (regardless of LVSI) · Stage I, grade 1 or 2, LVSI positive (regardless of MMI) · Stage IB, grade 3 with endometrioid type (regardless of LVSI)

EC, endometrial cancer; ESMO, European Society for Medical Oncology; GOG-99, Gynecologic Oncology Group-99; LVSI, lymphovascular space invasion; MMI, myometrial invasion; PTD, primary tumor diameter.

Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, Podratz KC. Prospective assessment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging. Gynecologic Oncology 2008;109:11-18.

Korkmaz V, Meydanli MM, Yalcin I, Sari ME, Sahin H, Kocaman E, Haberal A, Dursun P, Gungor T, Ayhan A. Comparison of three different risk-stratification models for predicting lymph node involvement in endometrioid endometrial cancer clinically confined to the uterus. J Gynecol Oncol. 2017;28(6):e78.

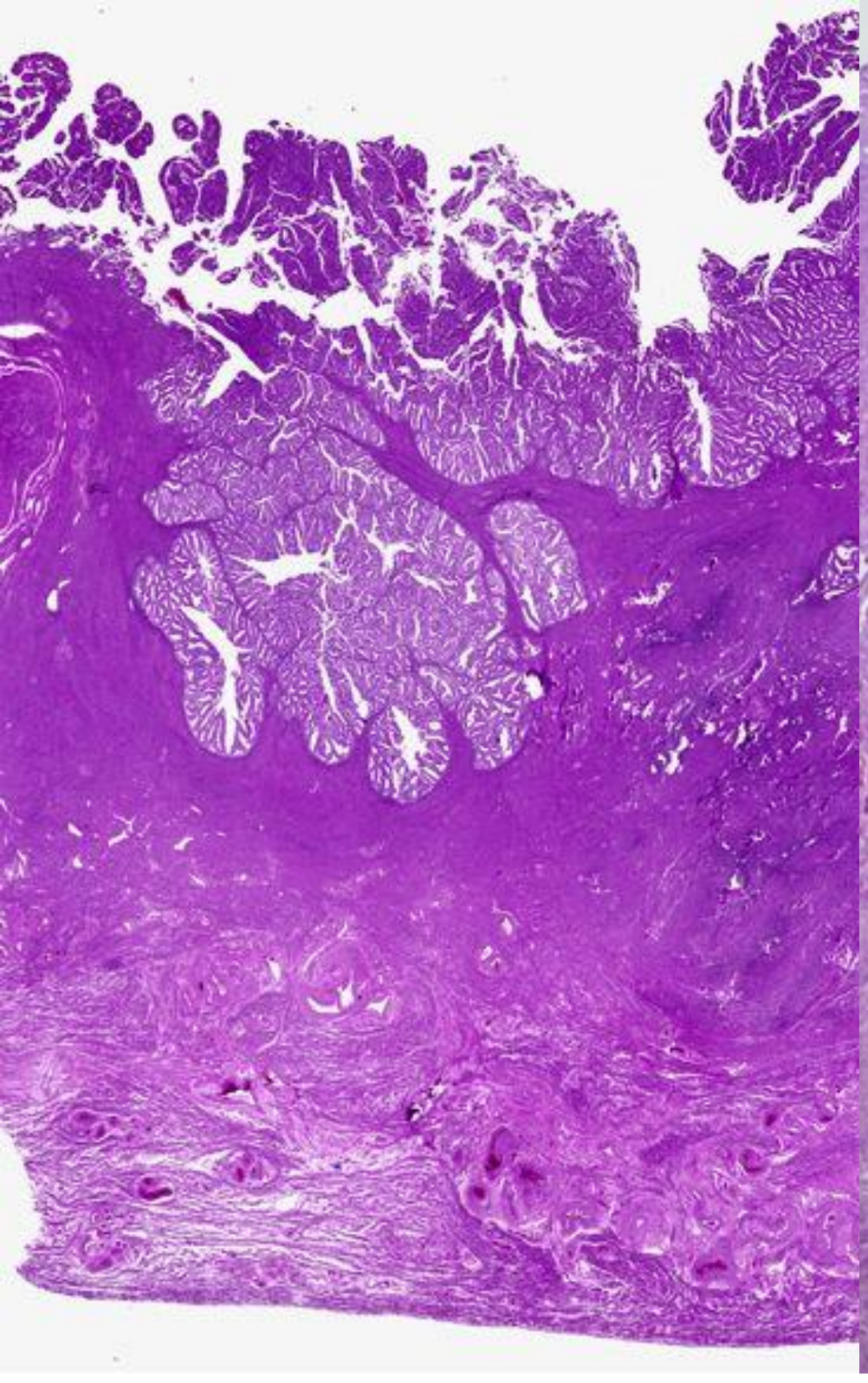
CONTROVERSIAL ELEMENTS

- Variability in surgeon request for frozen section

- No consensus on what constitutes an adequate lymph node dissection
  - Number of nodes?
  - Pelvic vs. pelvic and para-aortic?

- Sentinel lymph nodes?

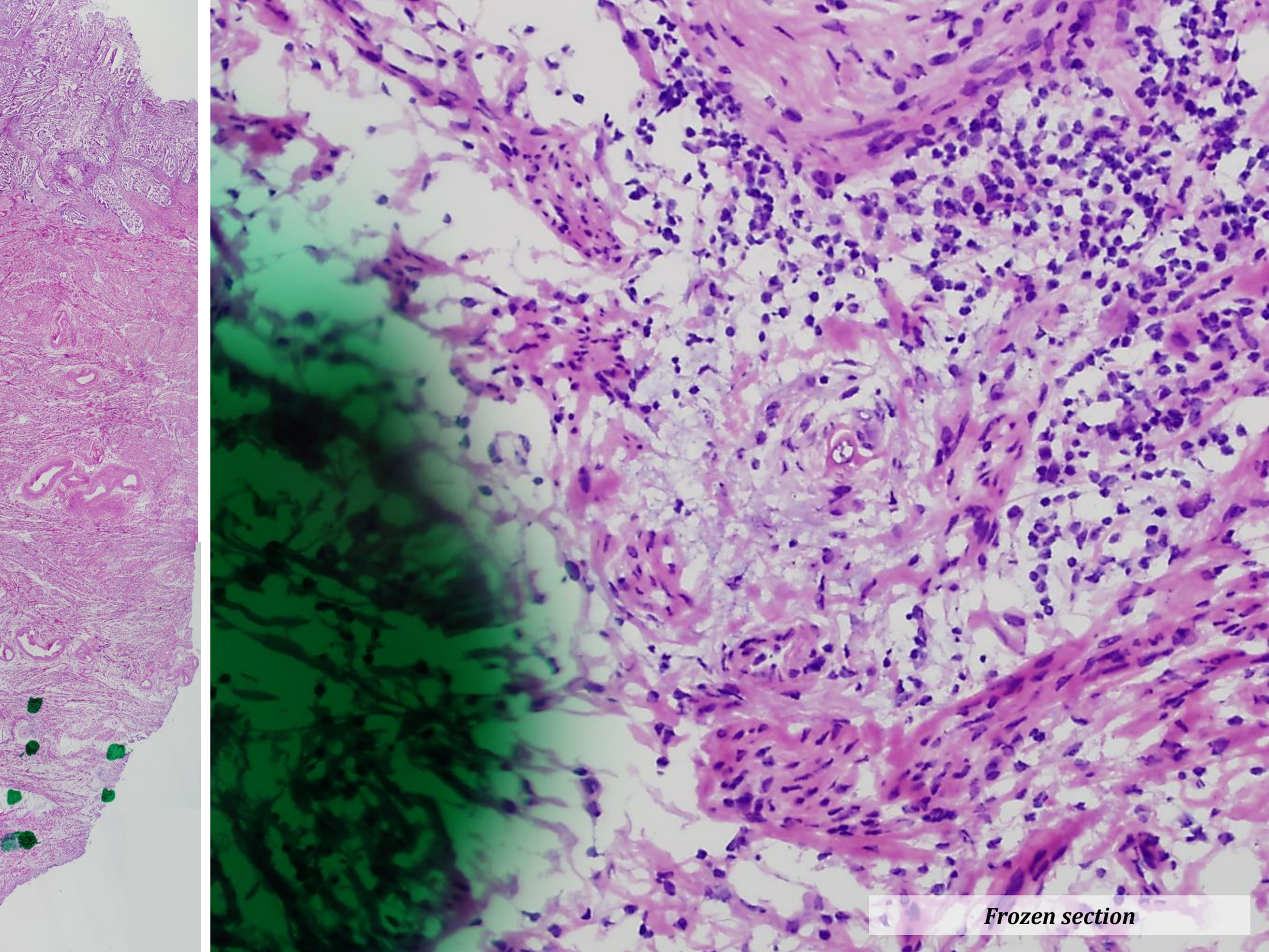
Pitfall #1…

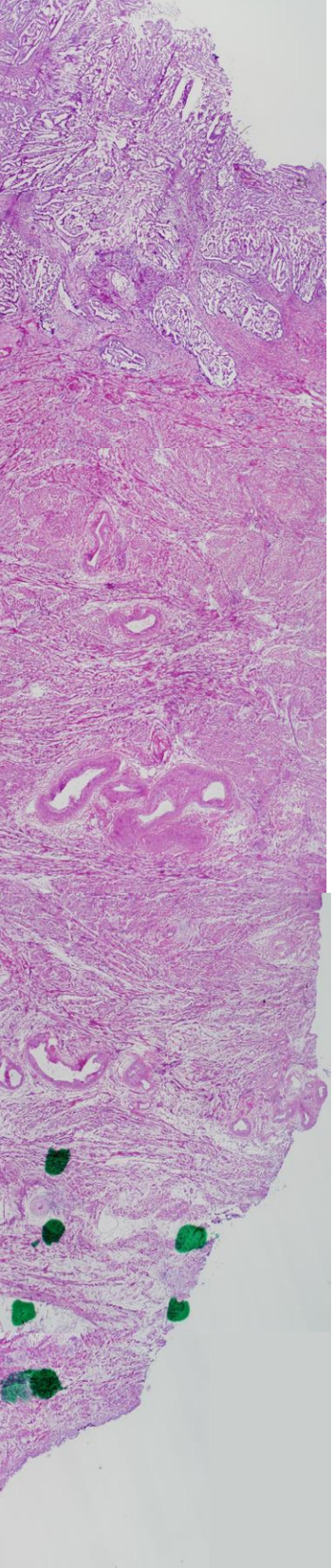


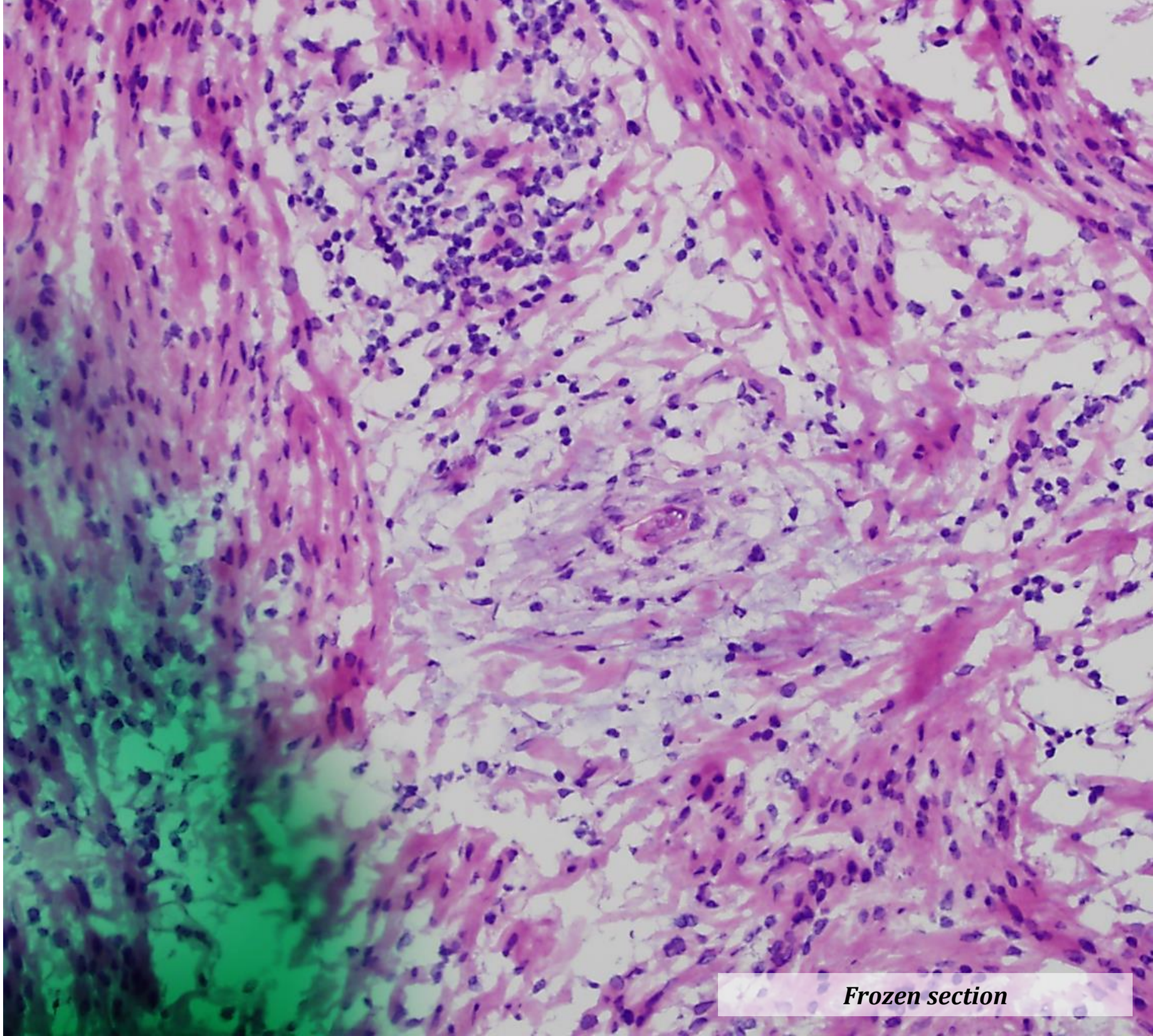
Soslow R. Practical issues related to uterine pathology: staging, frozen section, artifacts, and Lynch syndrome. Mod Pathol. 2016;29:S59-S77.

Photo credit: Karuna Garg, MD UCSF

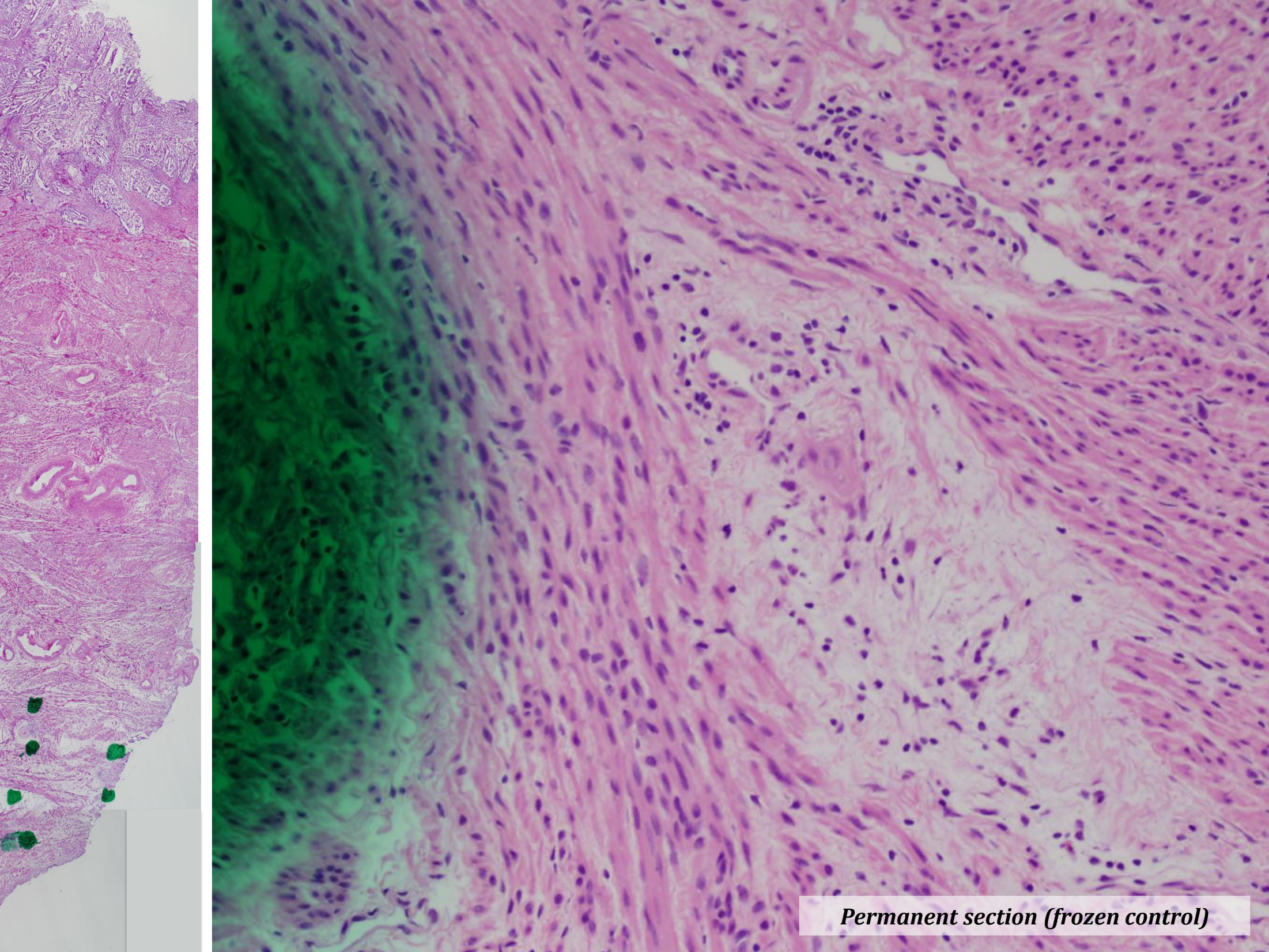
Pitfall #2…

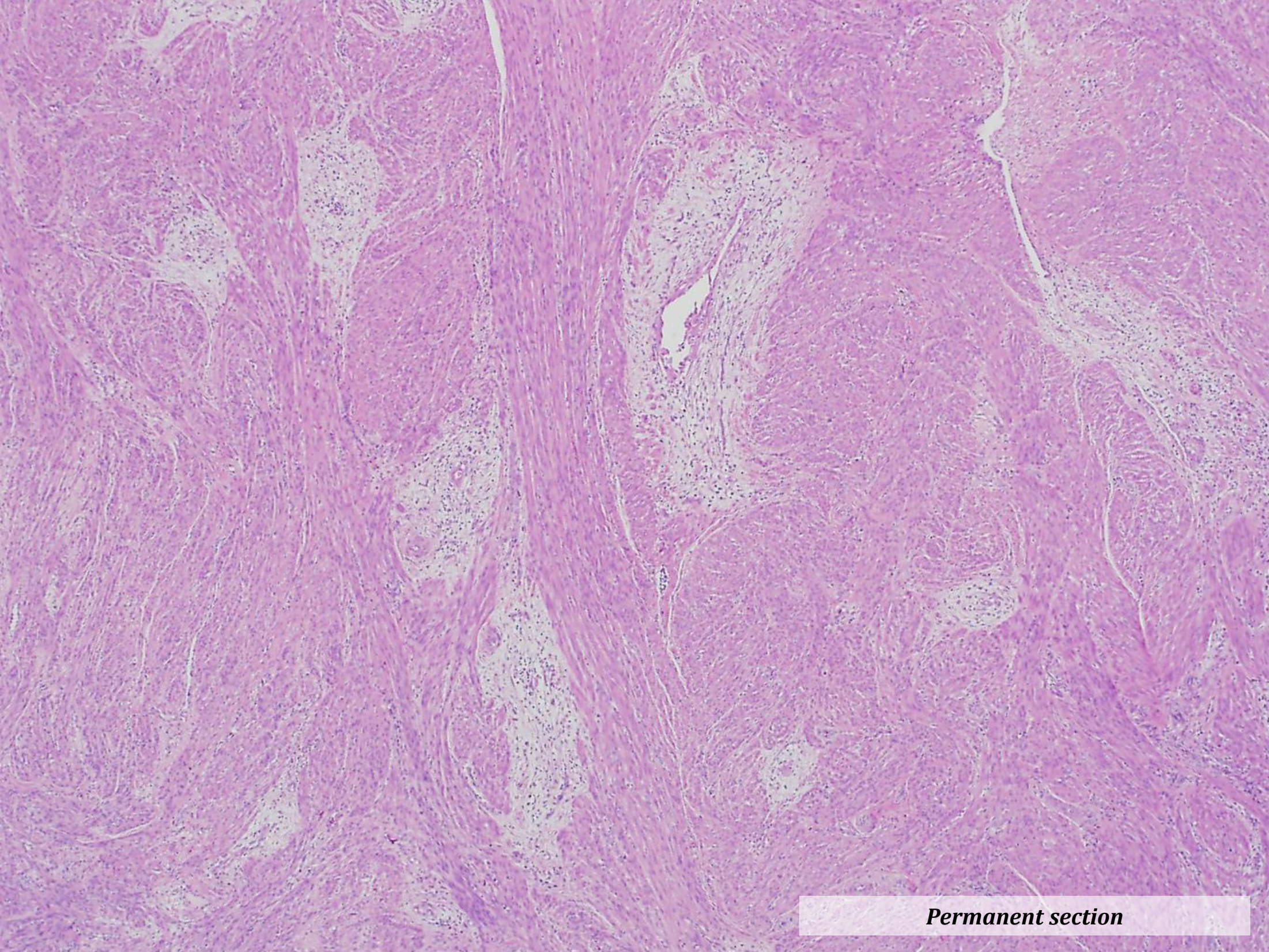

Frozen section



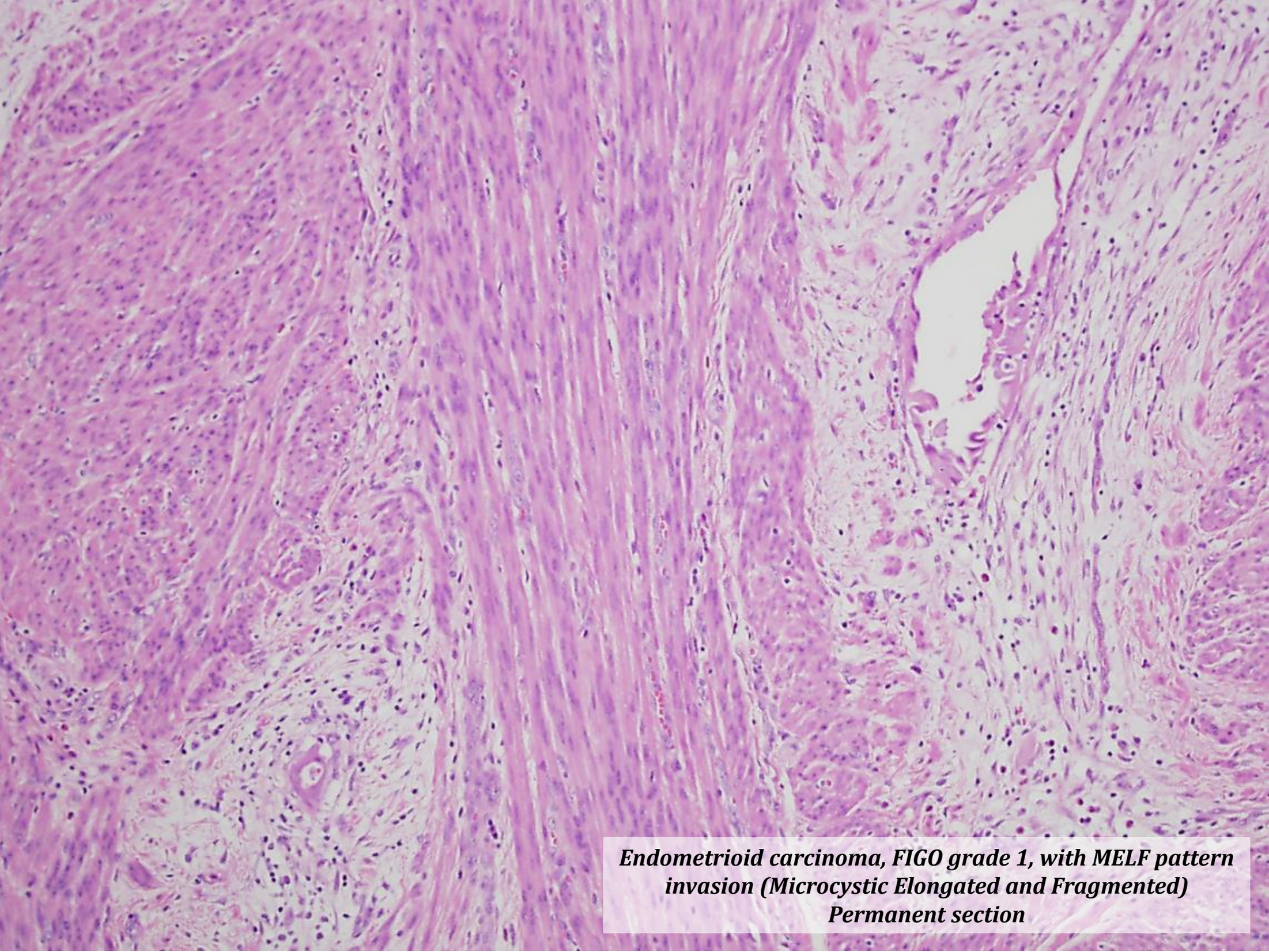


Frozen section


Permanent section (frozen control)



Permanent section



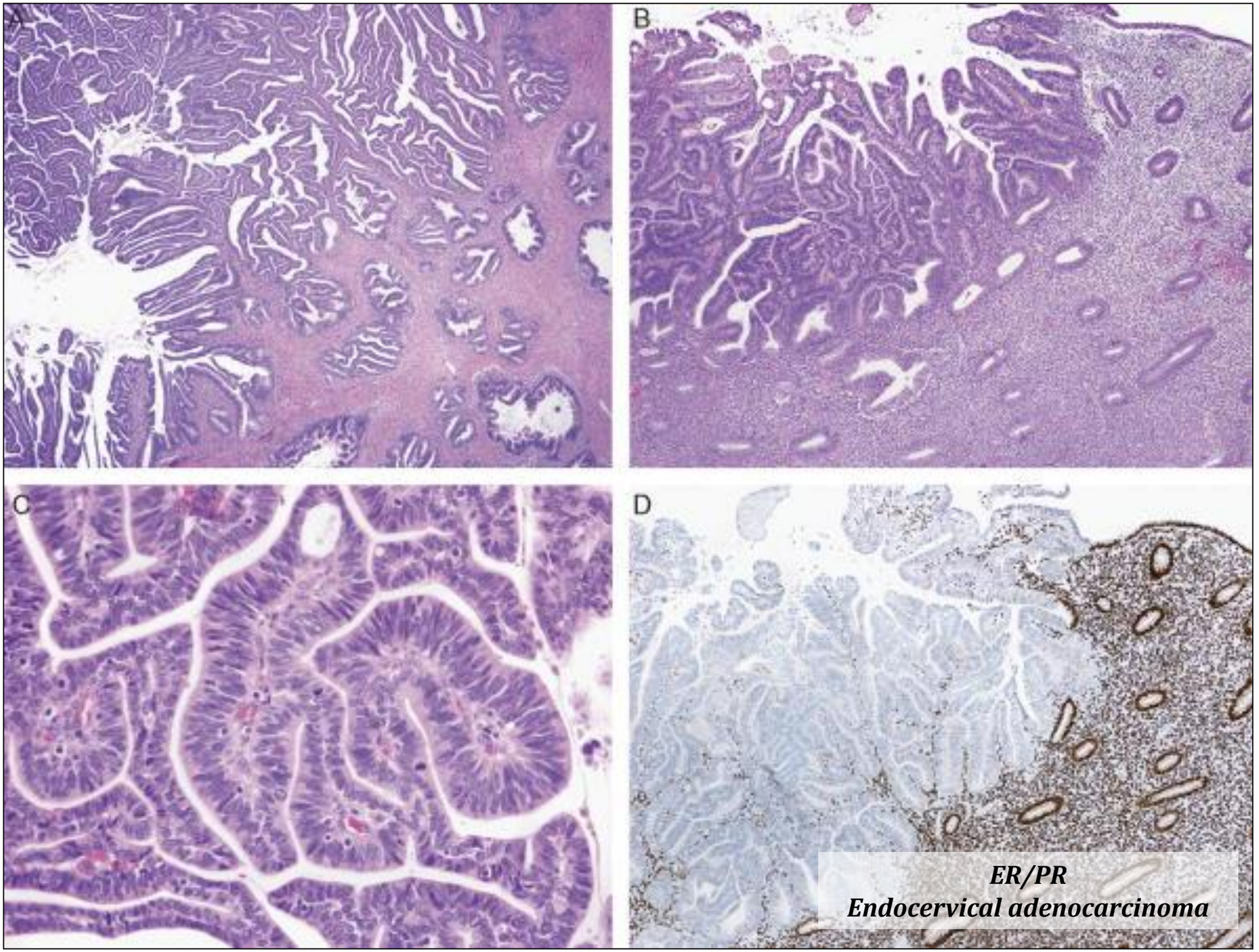
Endometrioid carcinoma, FIGO grade 1, with MELF pattern invasion (Microcystic Elongated and Fragmented) Permanent section

Pitfall #3…

SCENARIO

Premenopausal woman with an history of abnormal pap smears presents with an “endometrial mass” and vaginal bleeding that required numerous blood transfusions. The clinical team was unable to get a preoperative biopsy due to the bleeding and proceeded with hysterectomy.

Grossly, mass centered at lower uterine segment/upper endocervix with involvement of the endometrial fundus.



Yemelyanova A, Vang R, Seidman J, Gravitt P, Ronnett R. Endocervical Adenocarcinomas With Prominent Endometrial or Endomyometrial Involvement Simulating Primary Endometrial Carcinomas: Utility of HPV DNA Detection and Immunohistochemical Expression of p16 and Hormone Receptors to Confirm the Cervical Origin of the Corpus Tumor. Am J Surg Pathol. 2009;33(6):914-924/

Photo Credit: Johnny Adophson