



The Latest on Appendix: LAMN and Goblet cell adenocarcinoma

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Epithelial lesions of the appendix

Adenoma

Low-grade appendiceal mucinous neoplasm

High-grade appendiceal mucinous neoplasm

Adenocarcinoma

Serrated lesions

Goblet cell carcinoid

Adenoma

Adenomatous proliferation resembling colorectal type (pencillate nuclei, pseudostratified, etc).

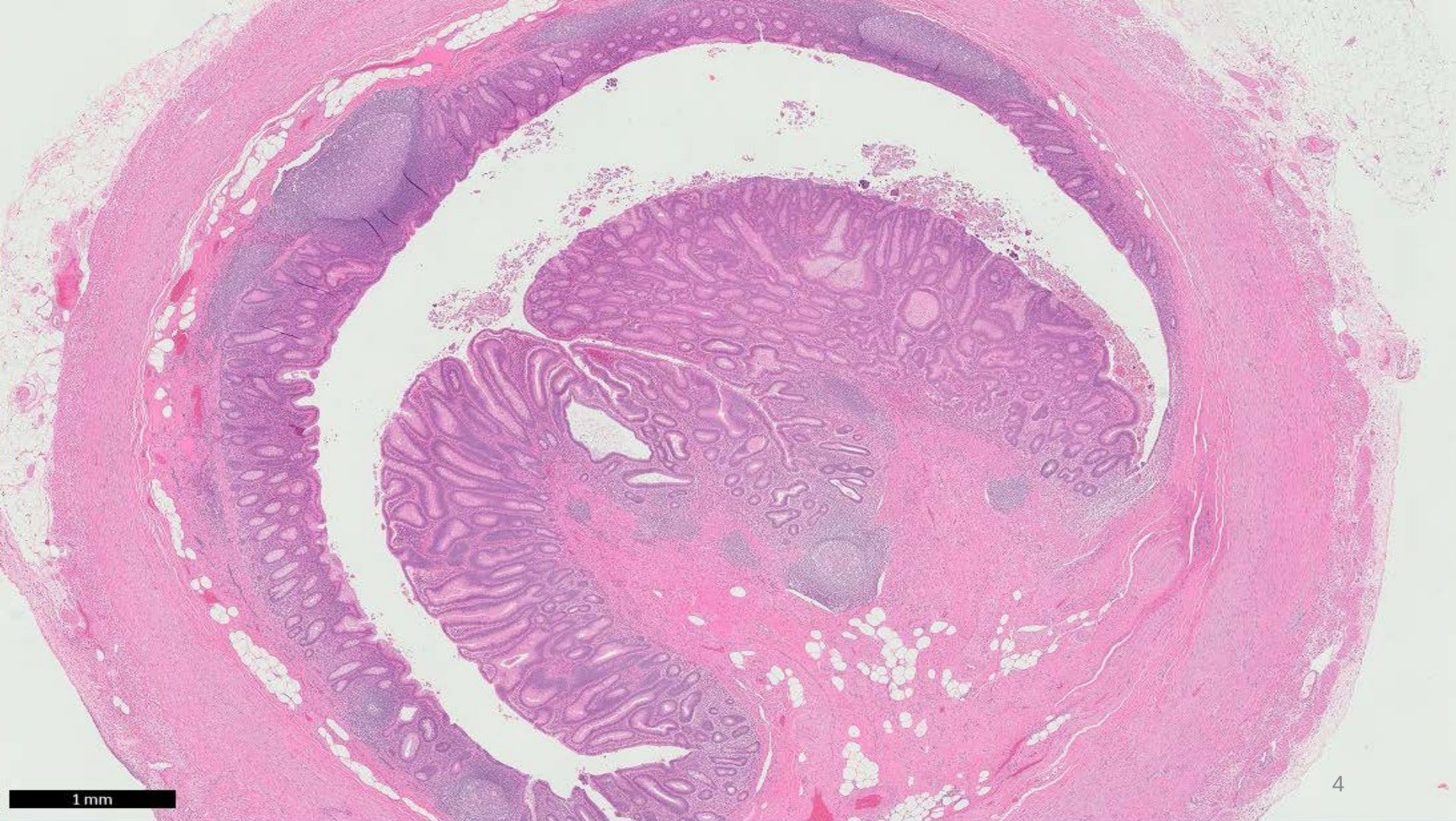
- *Intact muscularis mucosae*
- *No tumor outside appendix*

Can be tubular, tubulovillous, or villous

Dysplasia graded similar to other sites in GI tract

- Low Grade
- High Grade

Defined in this way, an adenoma is benign.



Low Grade Appendiceal Mucinous Neoplasm

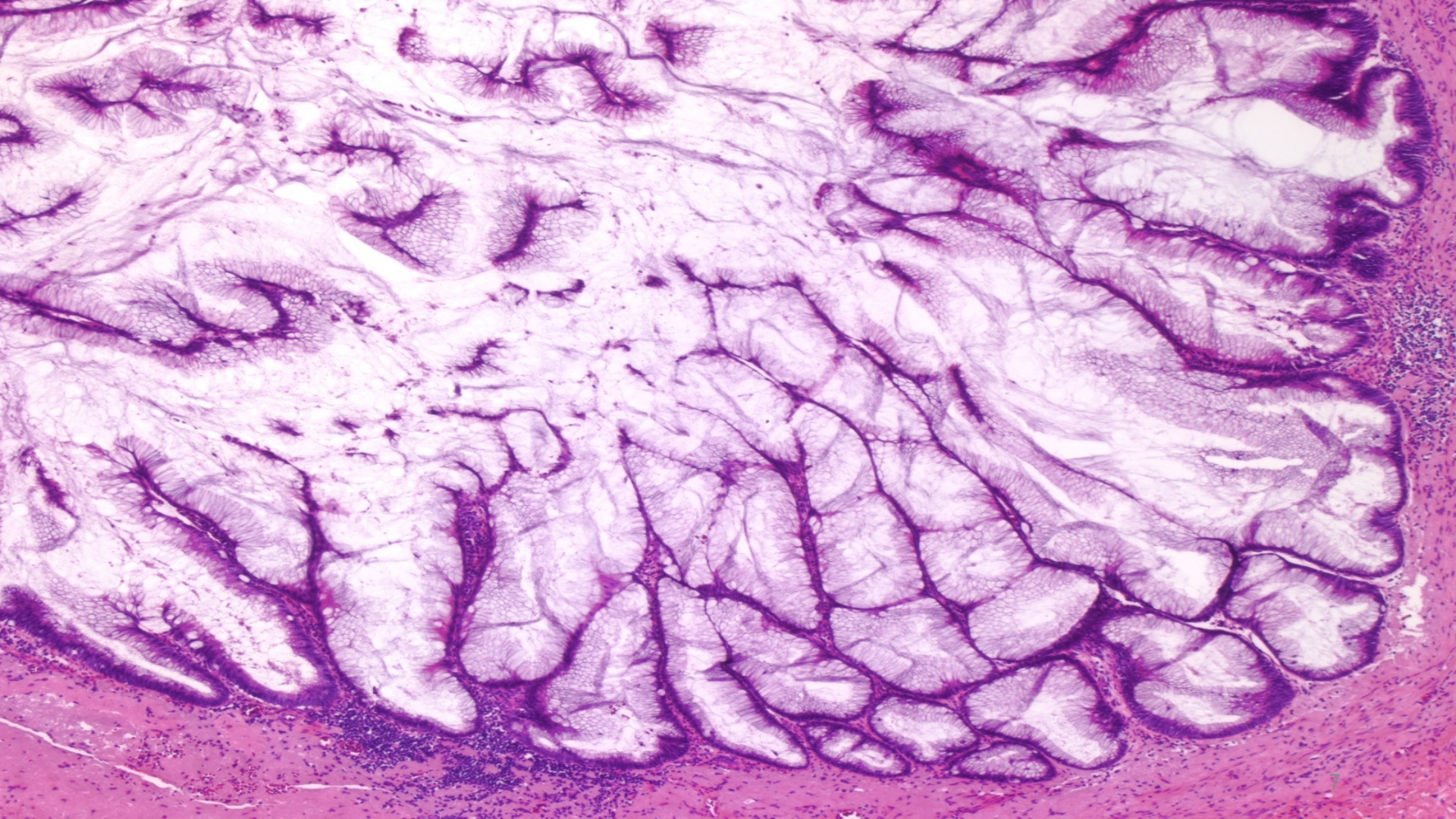
A low grade mucinous epithelial tumor characterized by villiform or undulating growth pattern and tall mucinous epithelial cells.

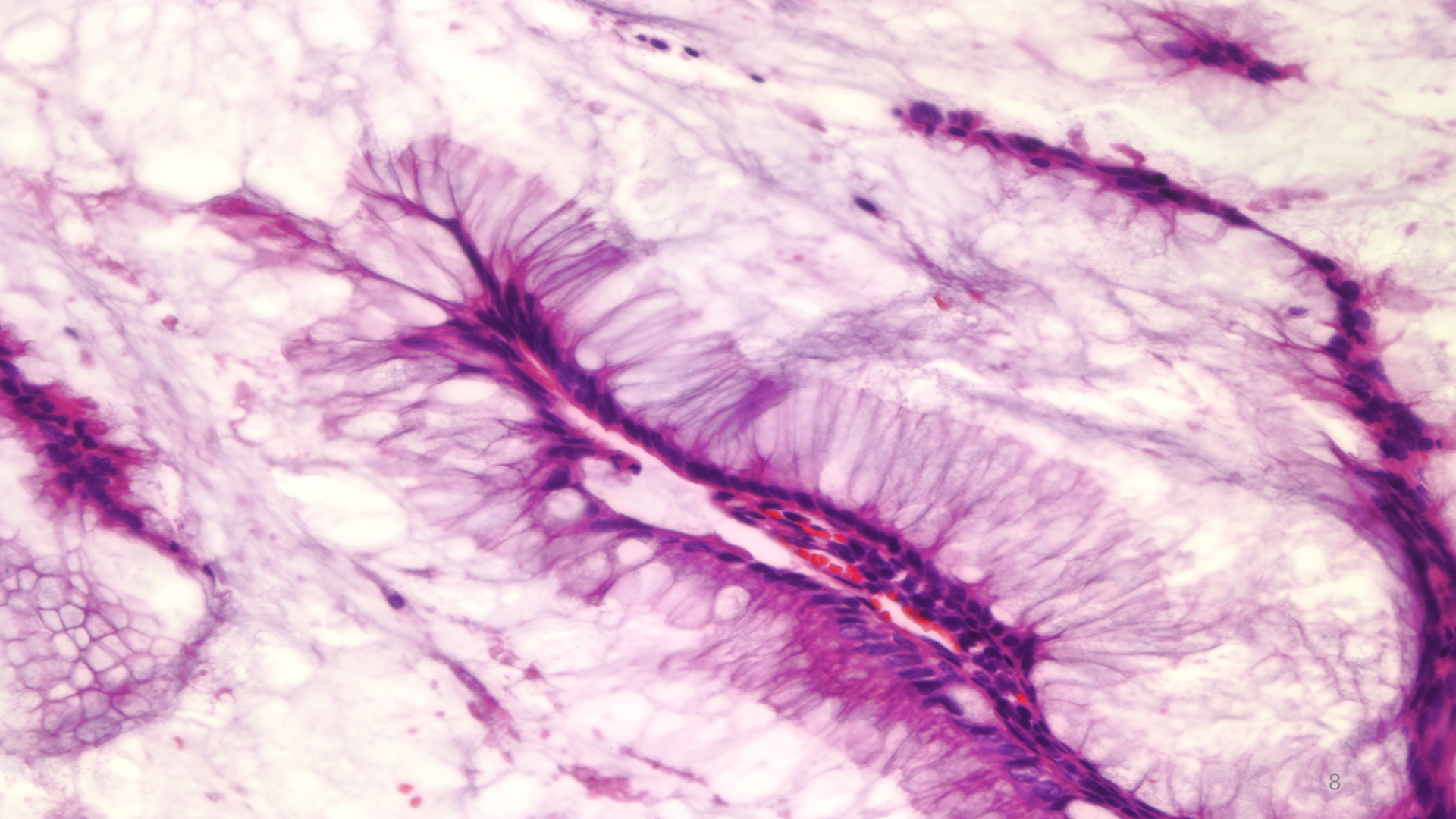
“Pushing” invasion. Destruction of muscularis mucosae with fibrosis, diverticula, herniations, dissections, etc. with possible rupture.

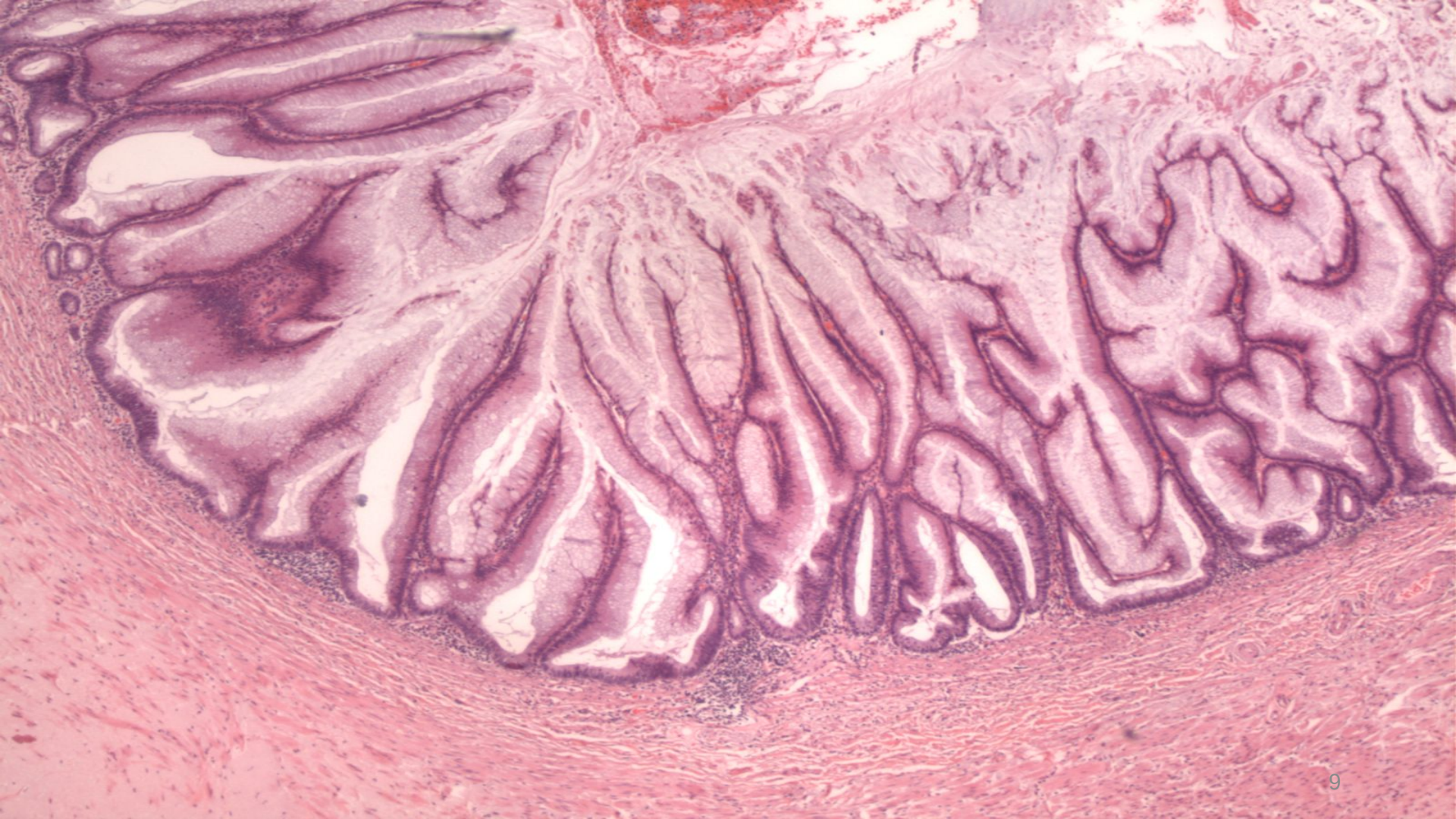


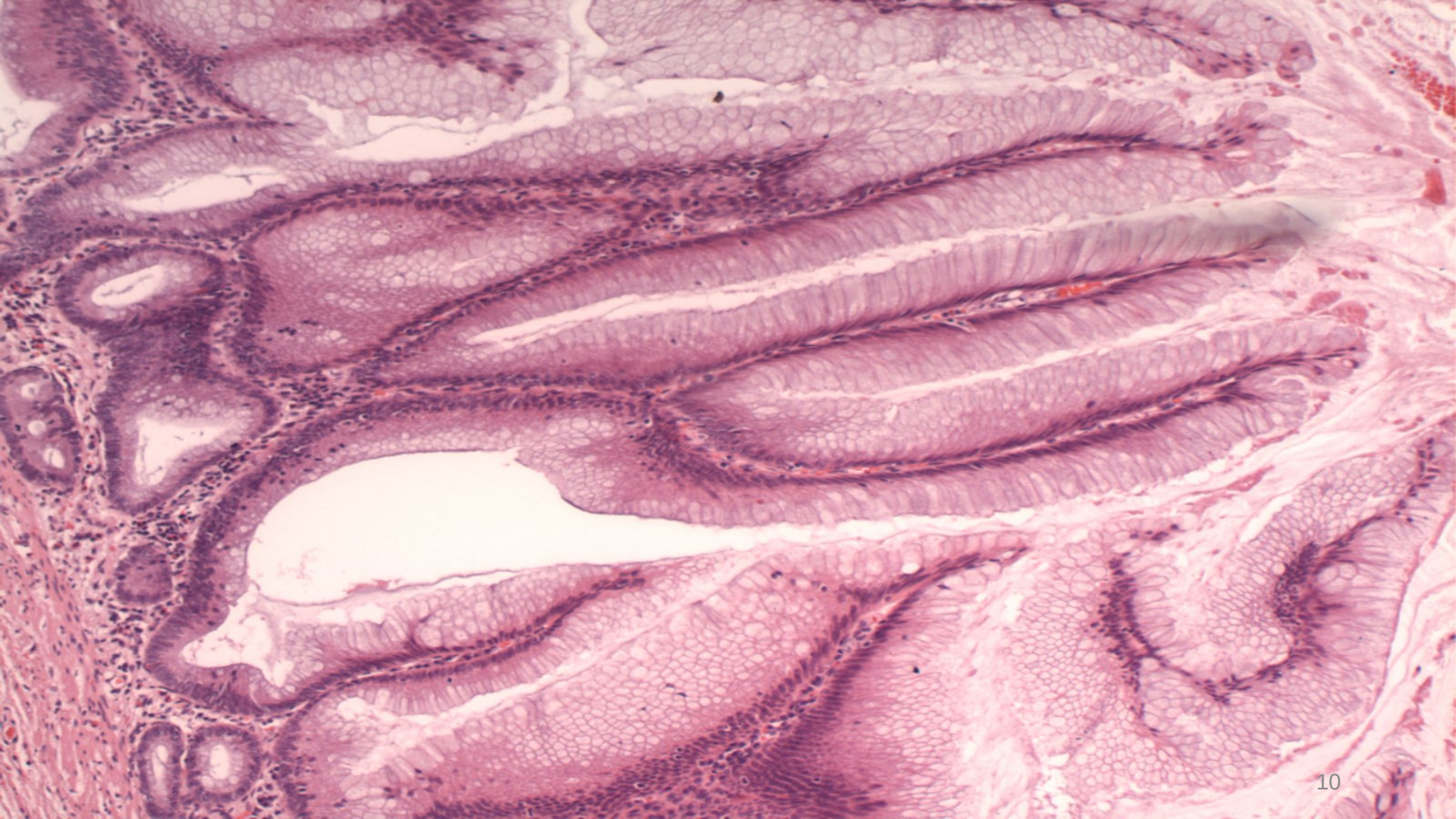
Mass General Hospital Pathology Department

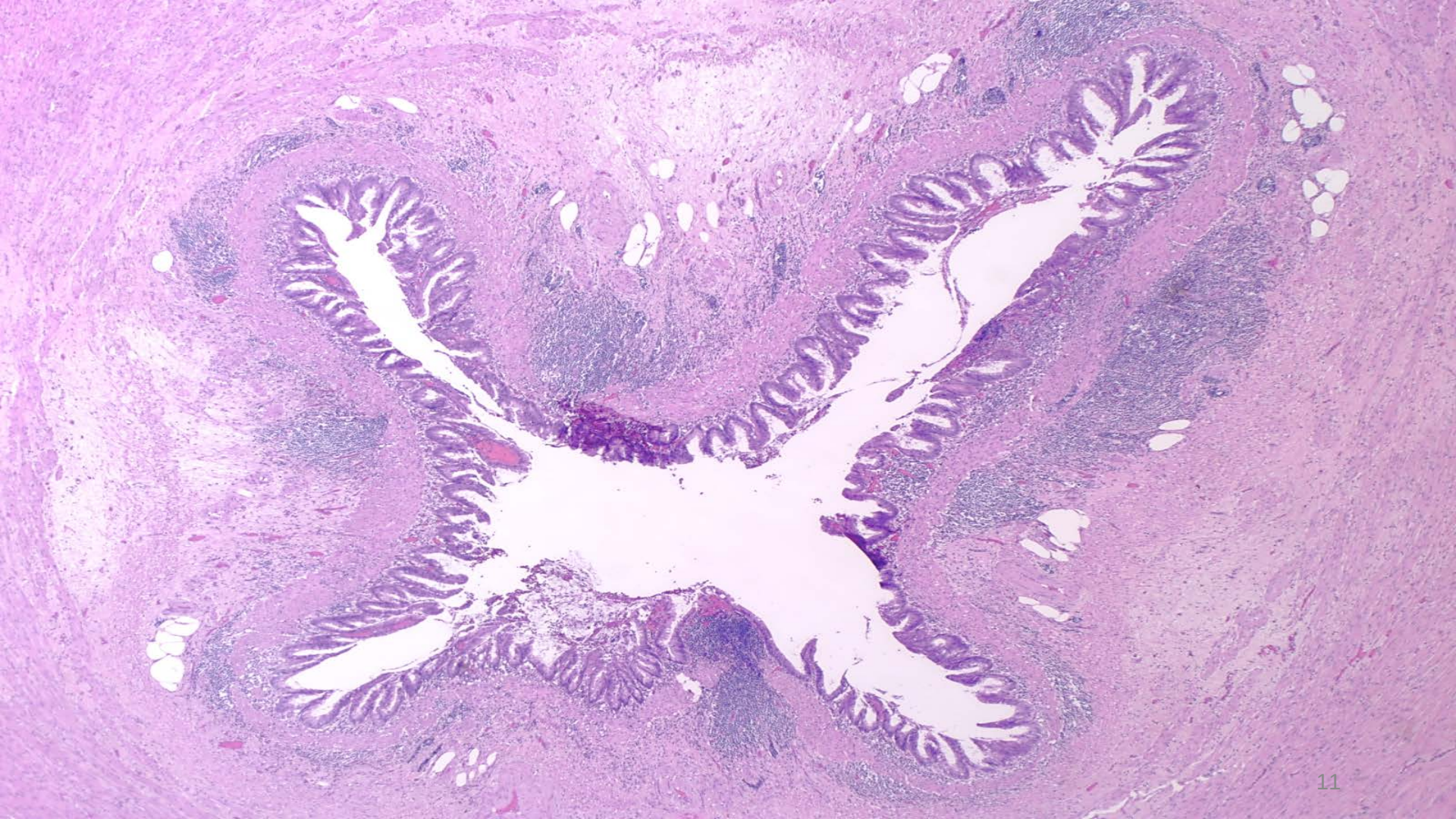


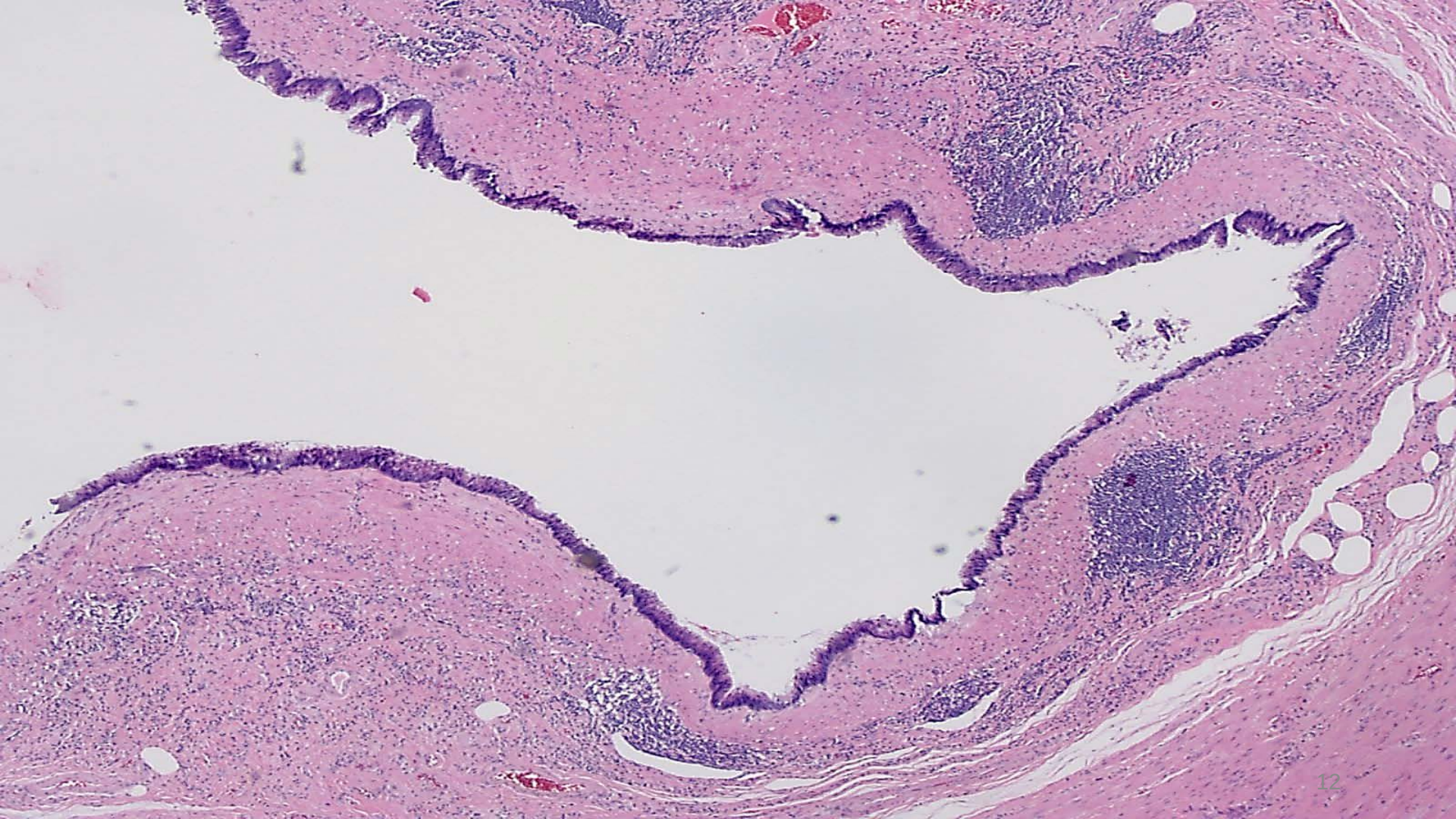


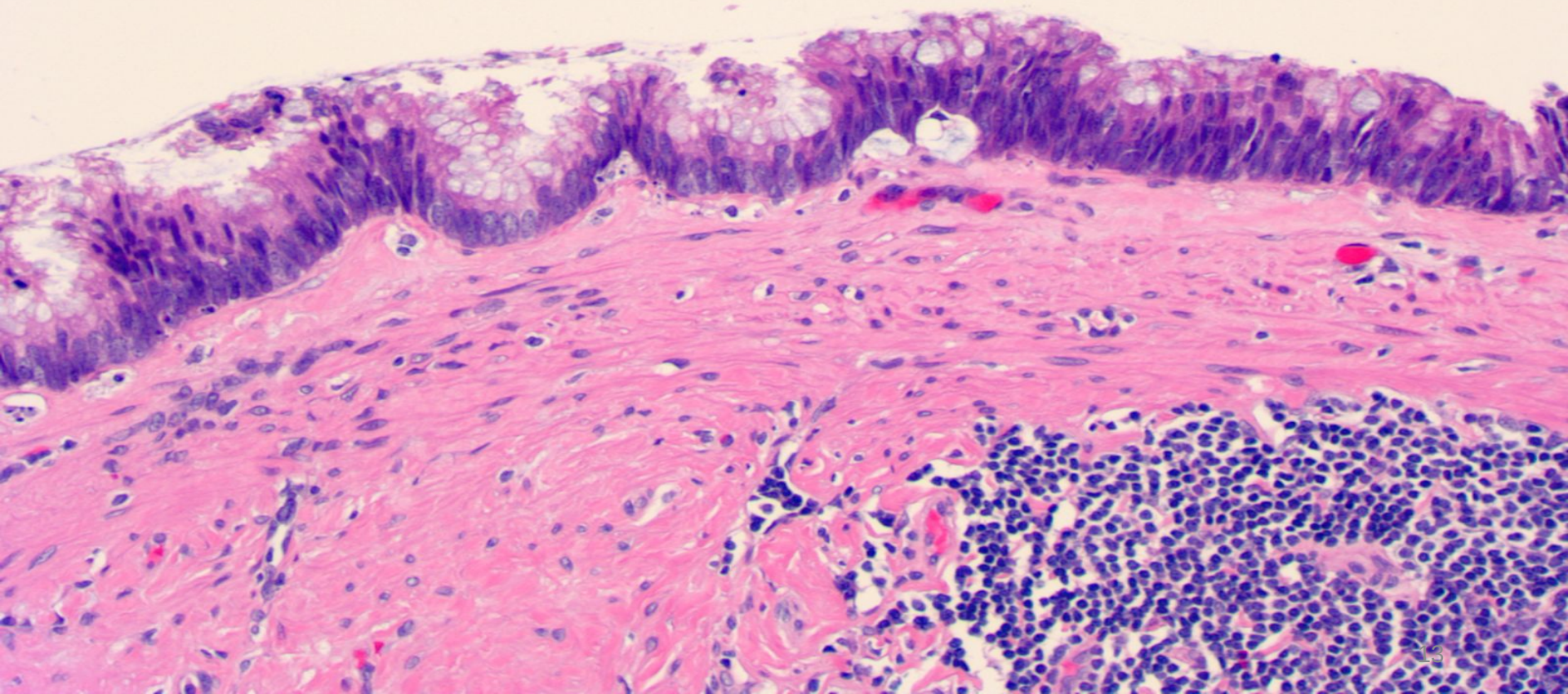


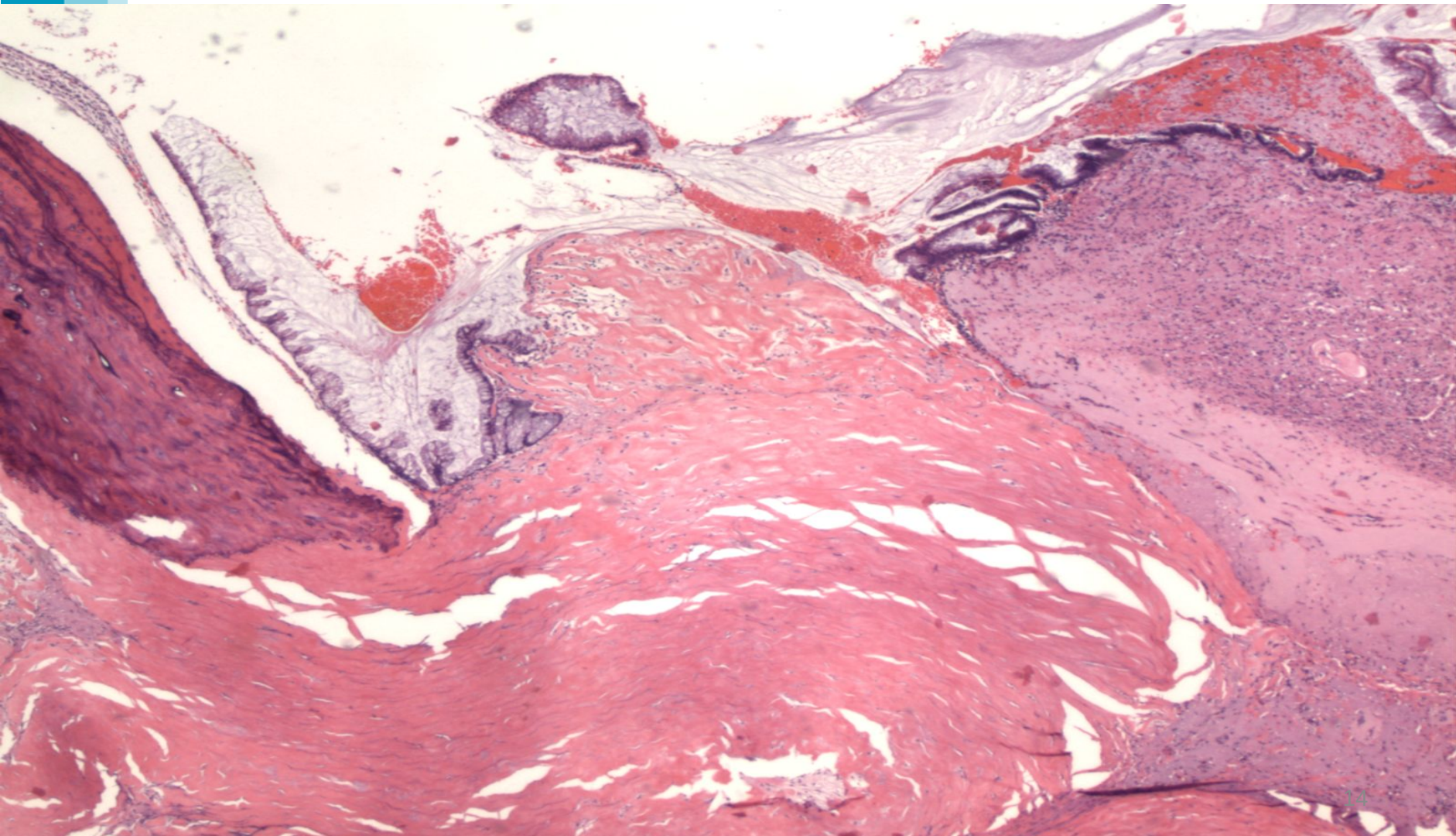


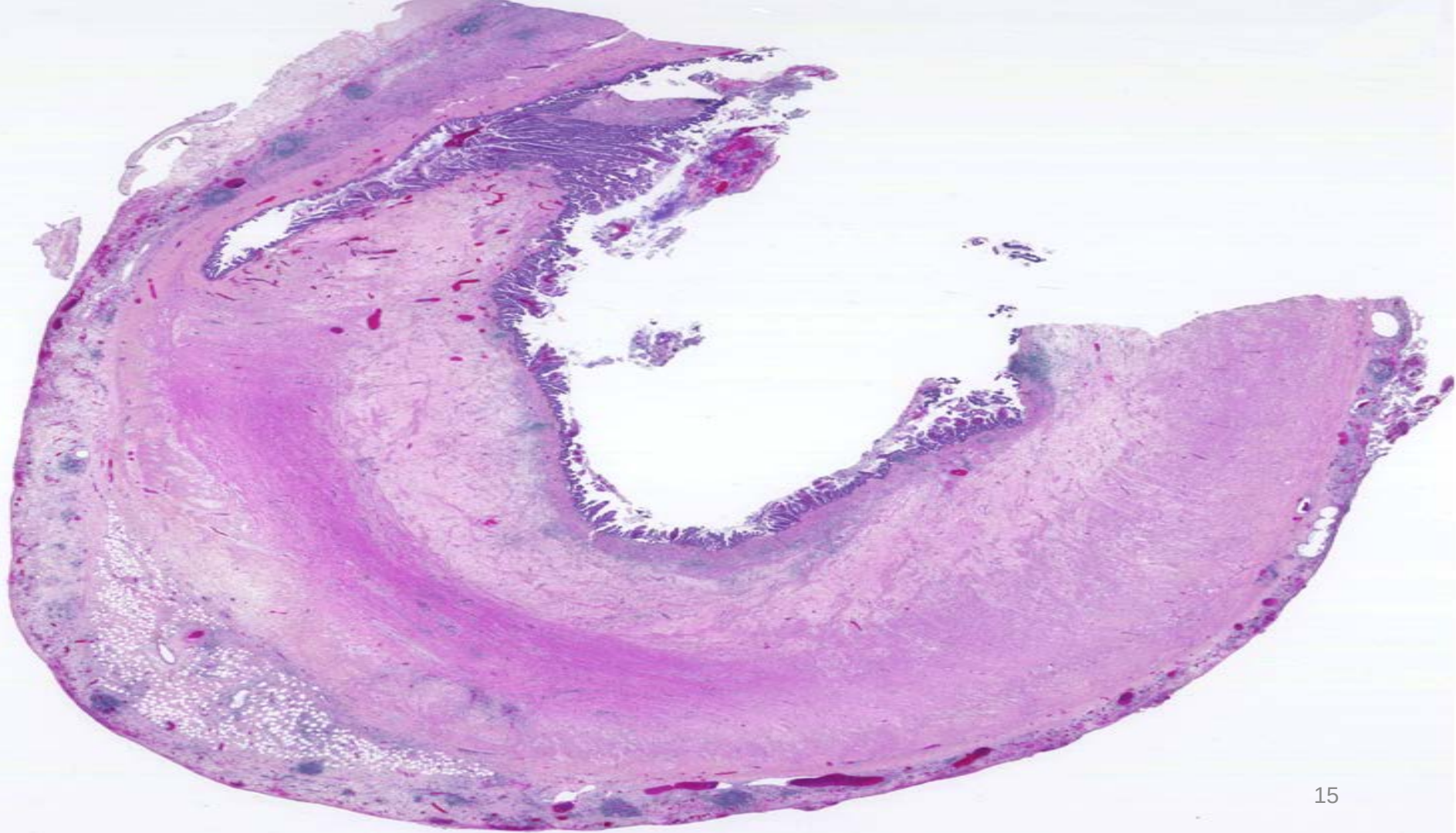


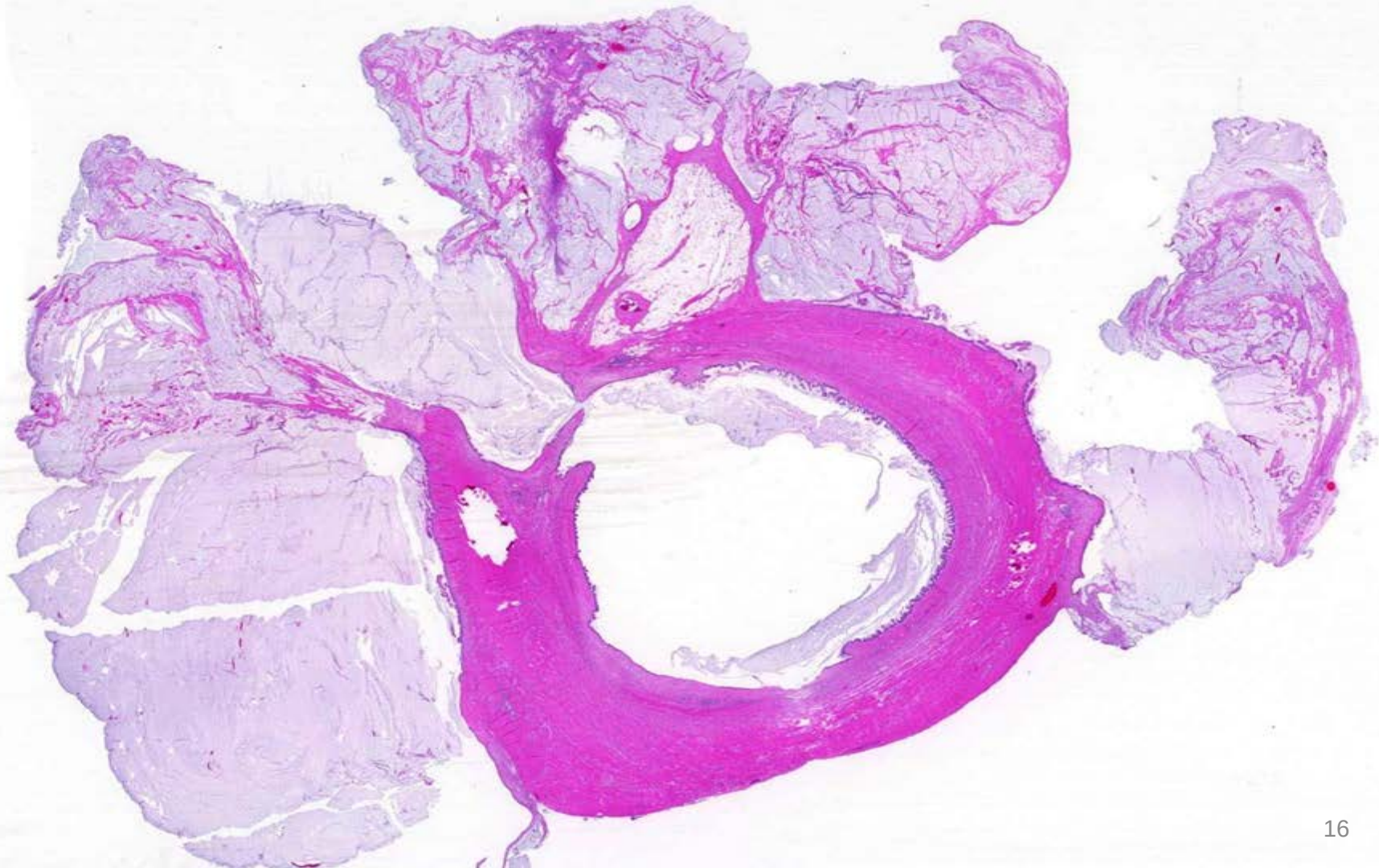


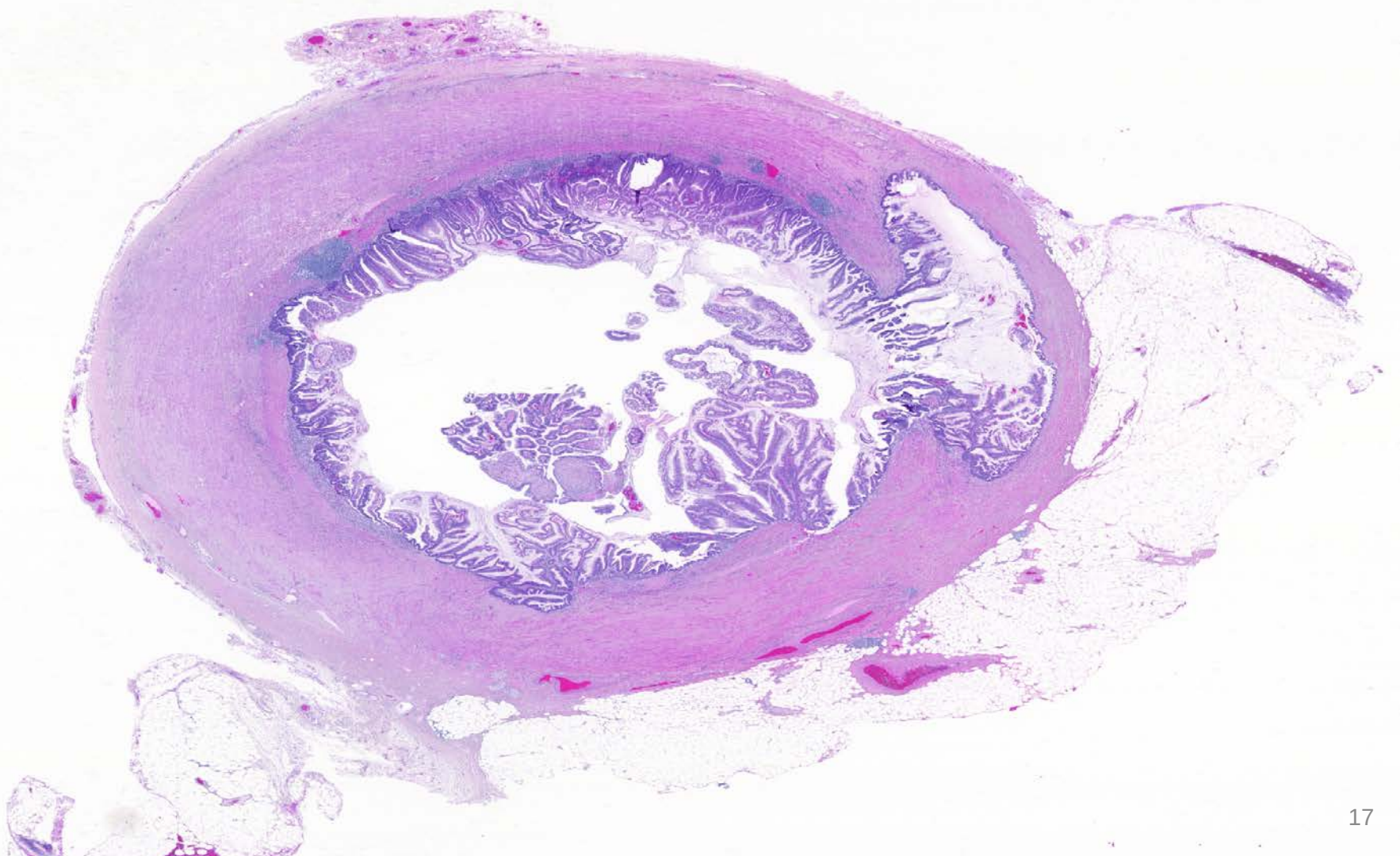


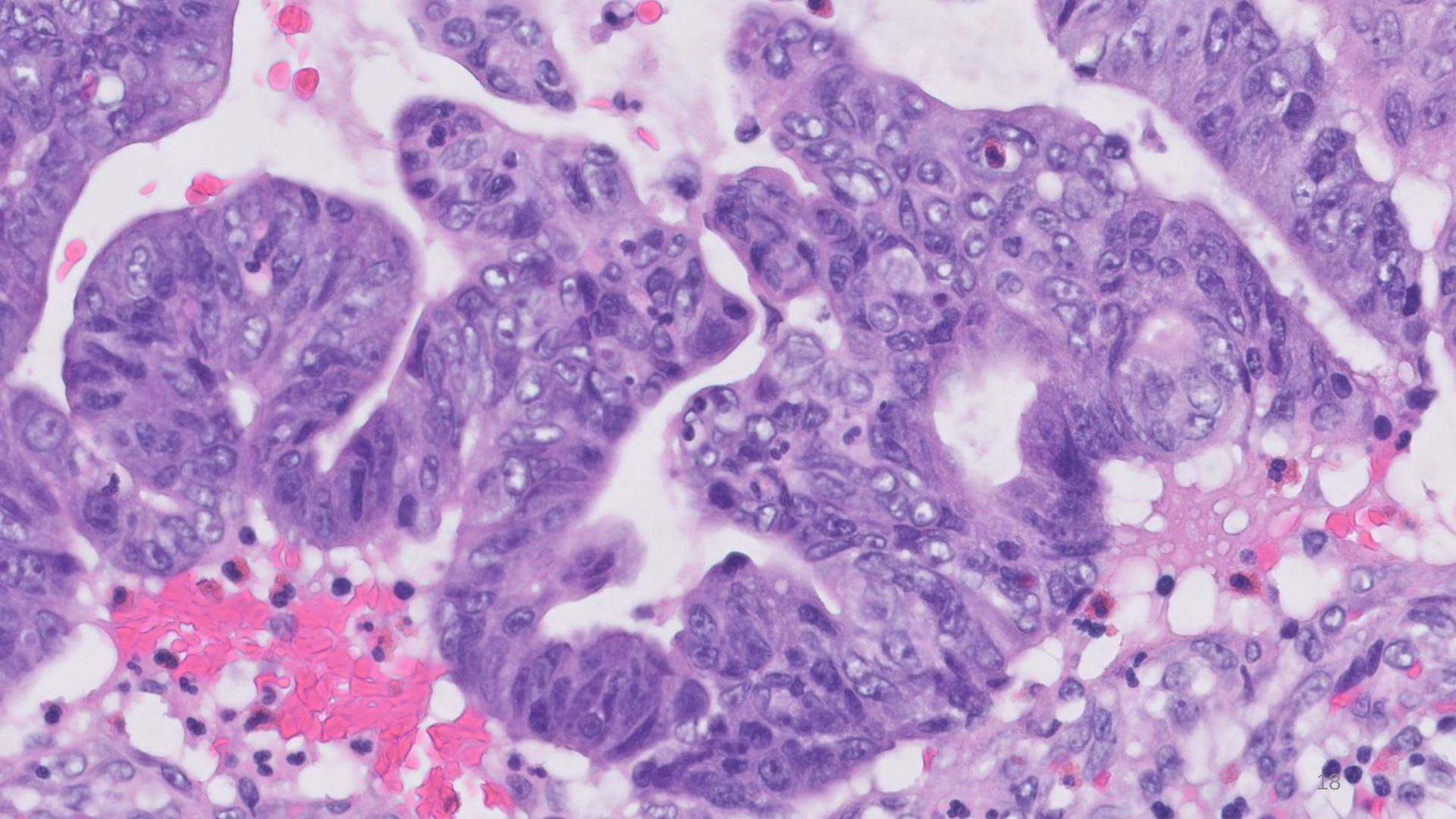












High-grade appendiceal mucinous neoplasm

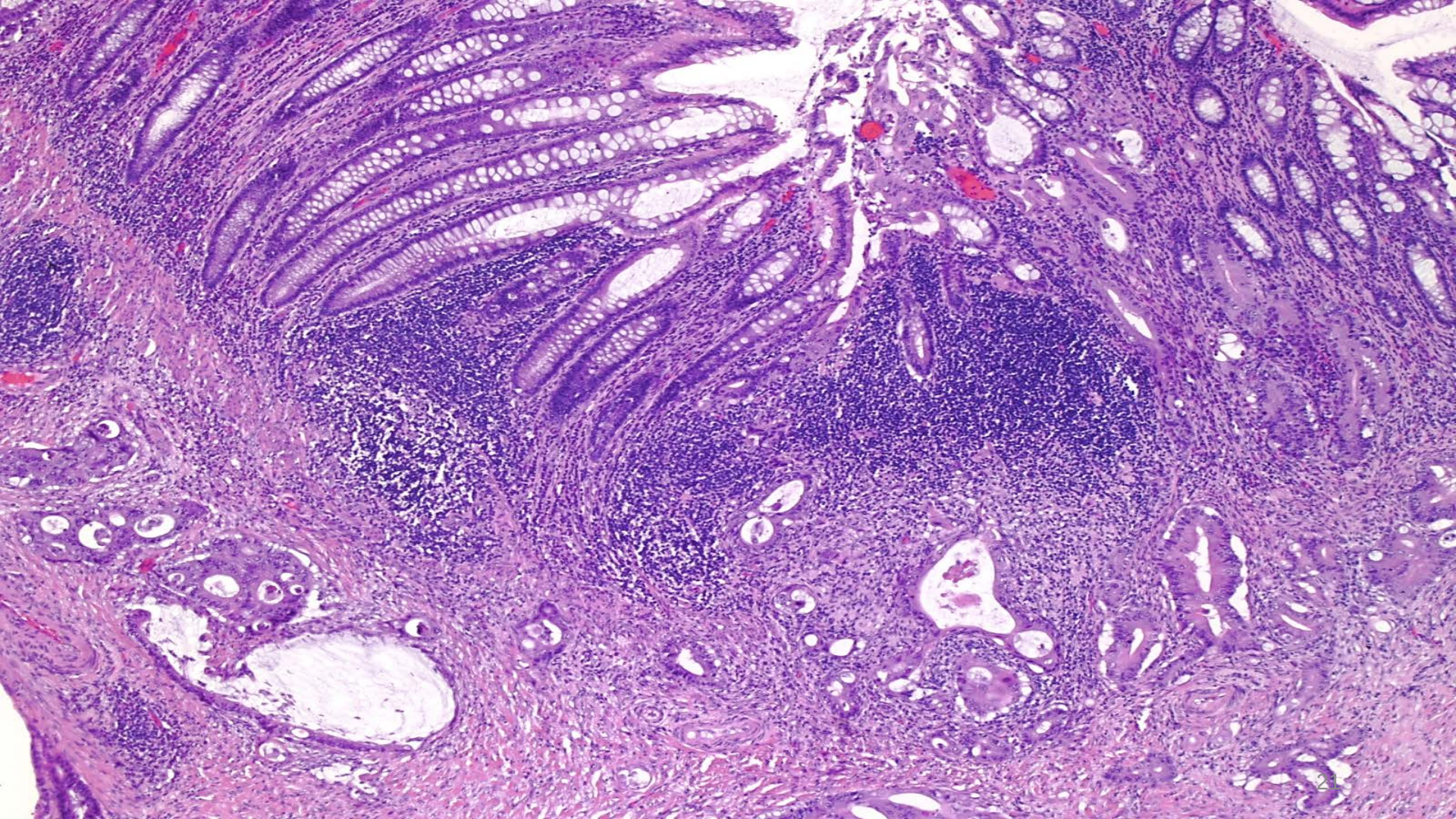
Pushing invasion, like LAMN, but *unequivocal* high-grade cytology. May have complex architecture (micropapillary or cribriform).

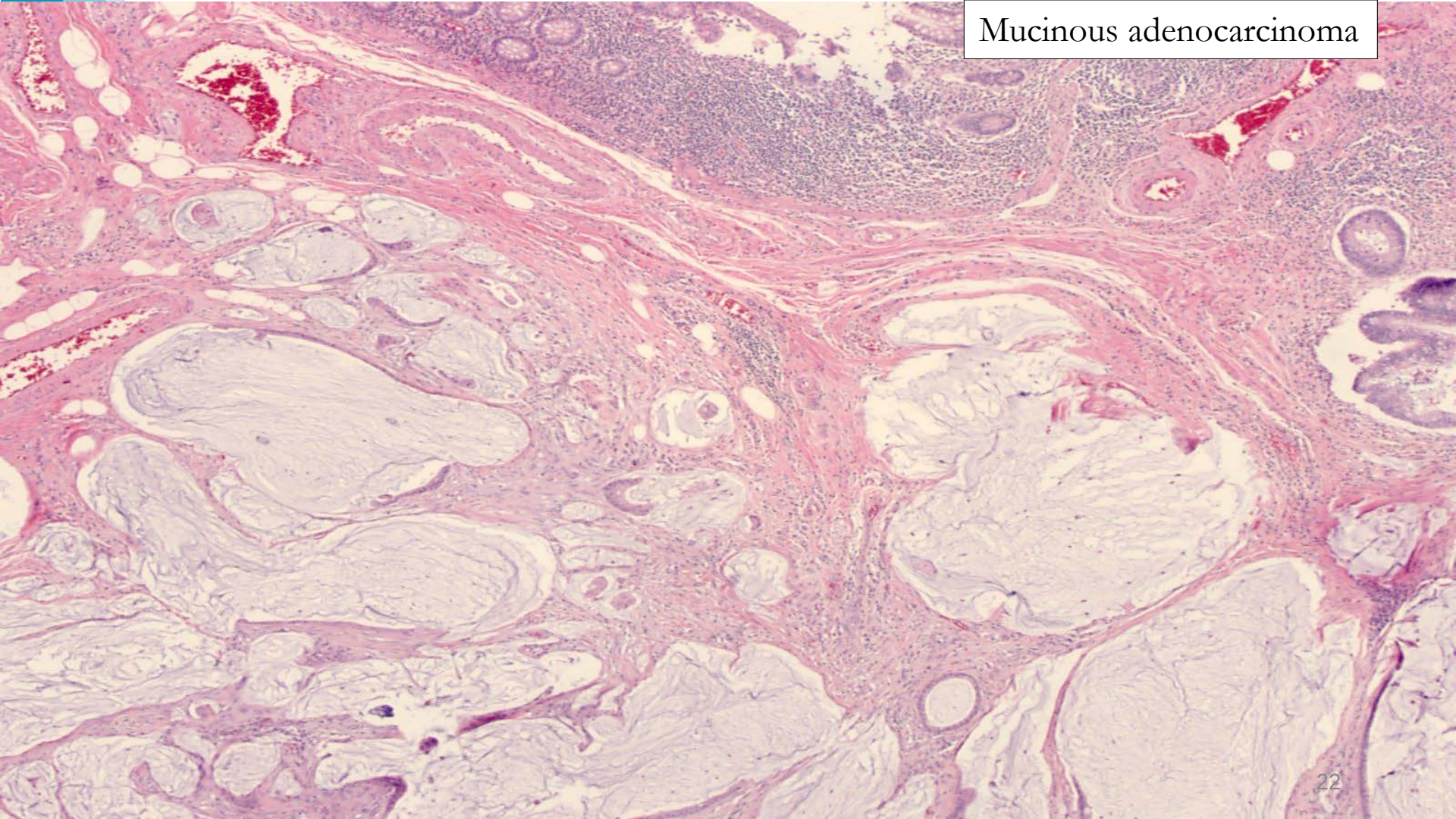
HAMNs are rare. Most tumors with high-grade cytology are invasive cancers; evaluate the entire tumor before concluding it is a HAMN.

Adenocarcinoma

Adenocarcinoma

- Adenocarcinoma, not otherwise specified
- Mucinous adenocarcinoma
- Adenocarcinoma, colonic type
- Signet ring cell adenocarcinoma
- Serrated adenocarcinoma



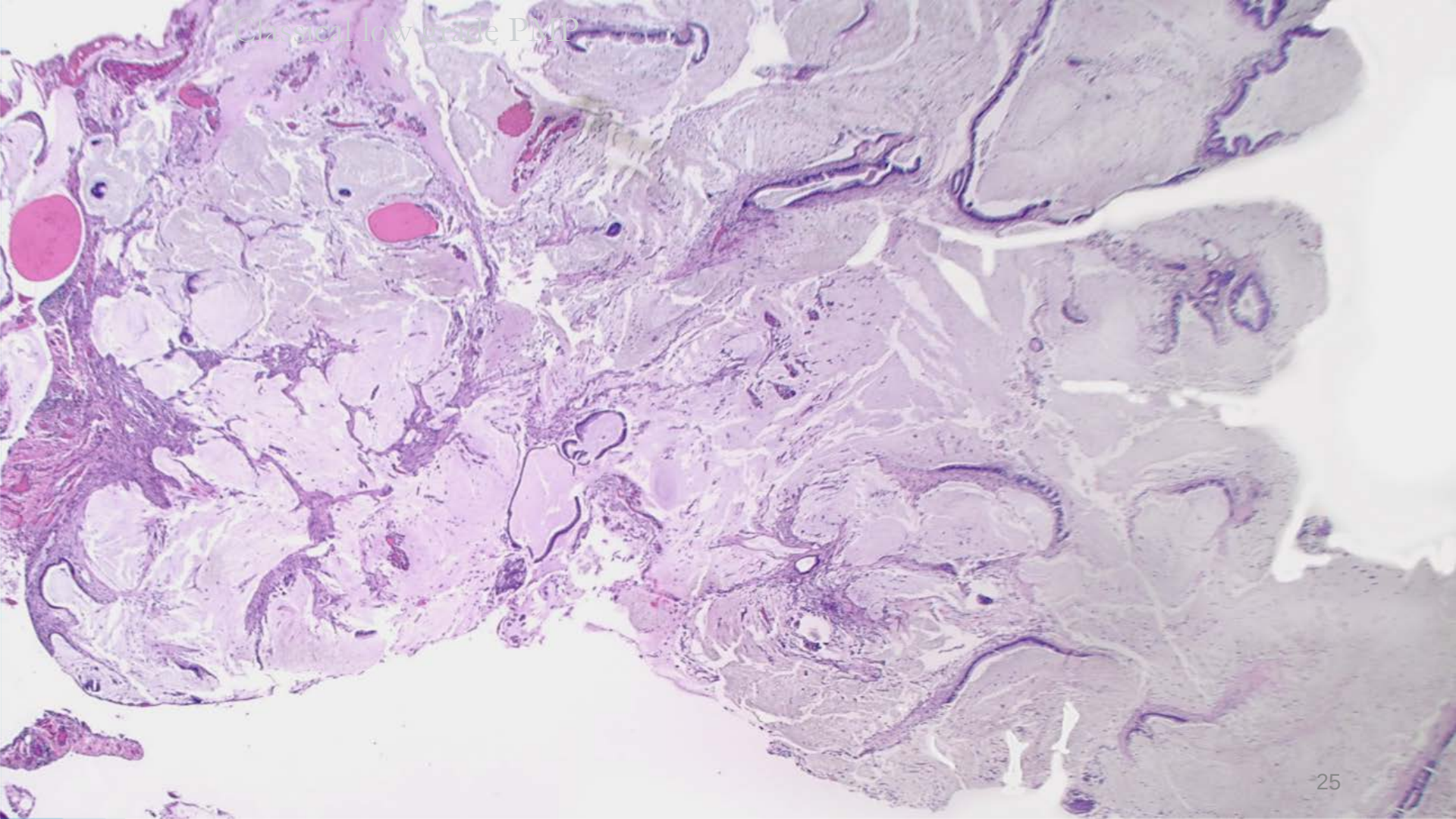


Pseudomyxoma Peritonei

Accumulation of mucin within the peritoneal cavity associated with mucinous tumor implants.

Usually from a mucinous tumor of the appendix, but can arise from pancreas, gallbladder, colon, urachus, and teratoma of the ovary.

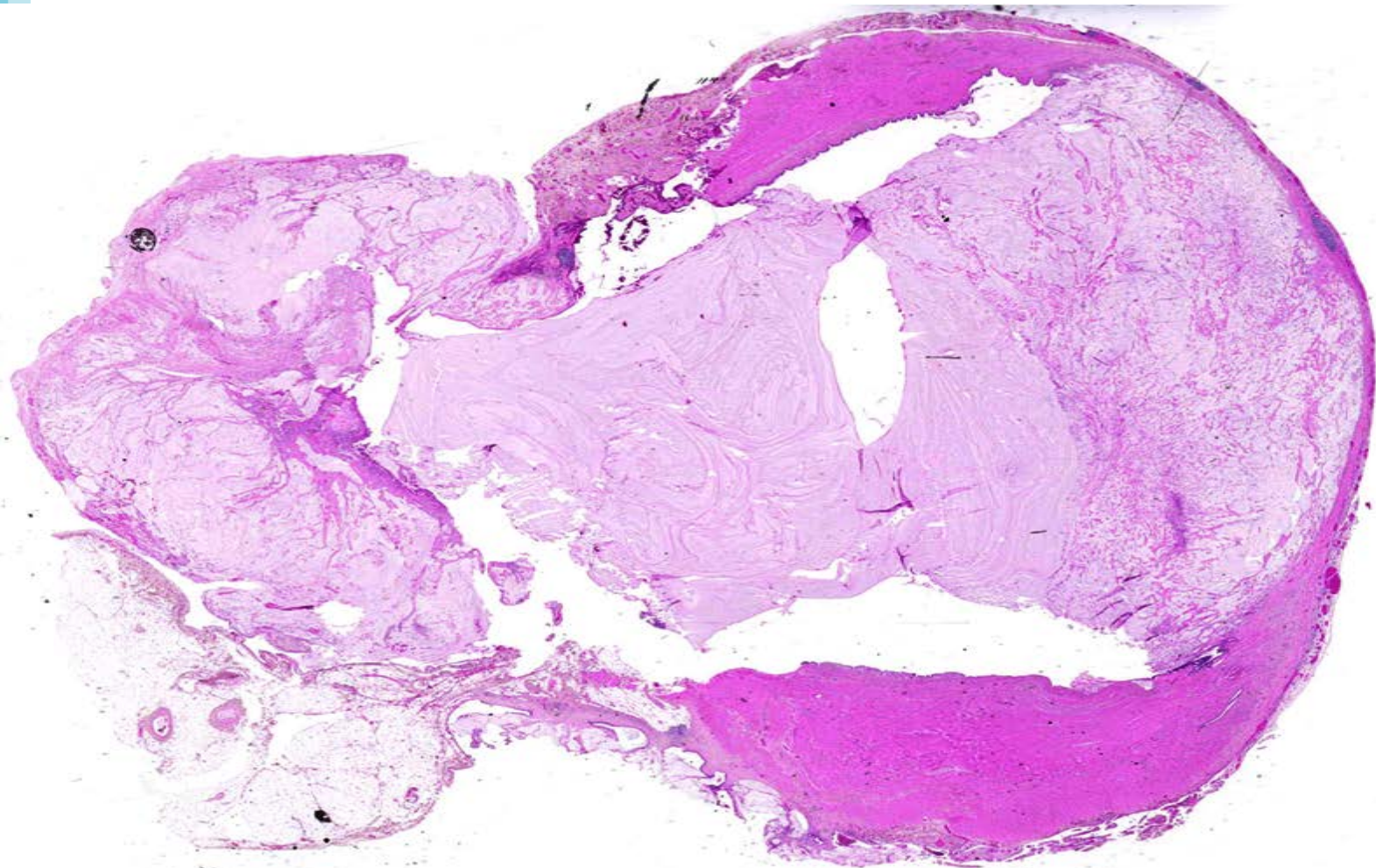




Classical low grade PMP

Classic Pseudomyxoma Peritonei (Grade 1)





Proposed Criteria for Grading PMP

Davison et al. Mod Pathol 2014; 27:1521-39

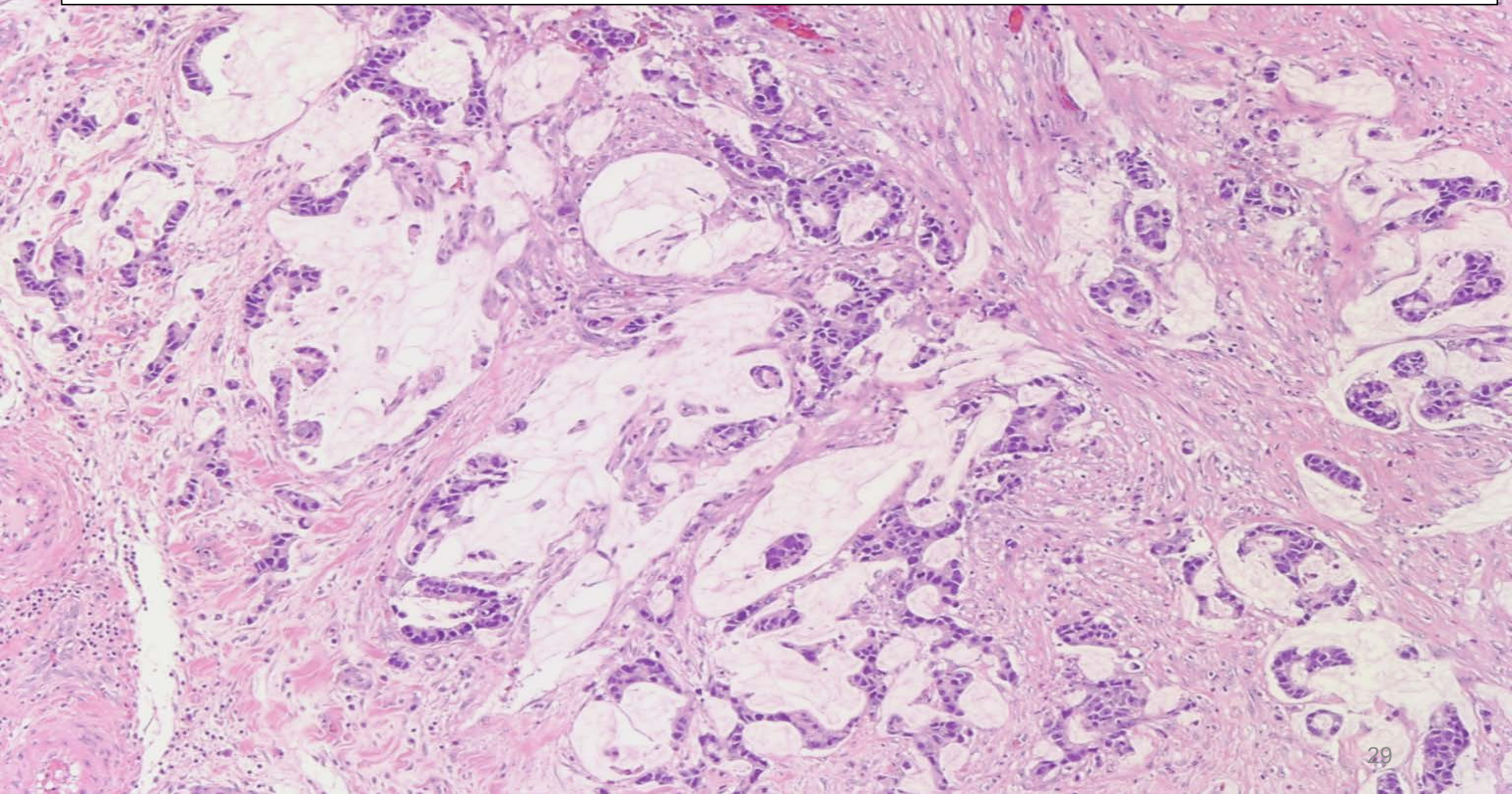
3 grades of mucinous carcinoma peritonei

- ▶ Grade 1: Low cellularity, low grade nuclei, cohesive strips
- ▶ Grade 2
 - ✓ High cytologic grade in >10% of tumor
 - ✓ High tumor cellularity: Neoplastic epithelium in > 20% of mucin pools at 20X
 - ✓ Destructive invasion
 - Infiltrating jagged, irregular glands
 - Expansile/confluent cribriform growth
 - Small nests/glands within small mucin pools ("small mucin pool pattern")
- ▶ Grade 3: Signet ring cells present

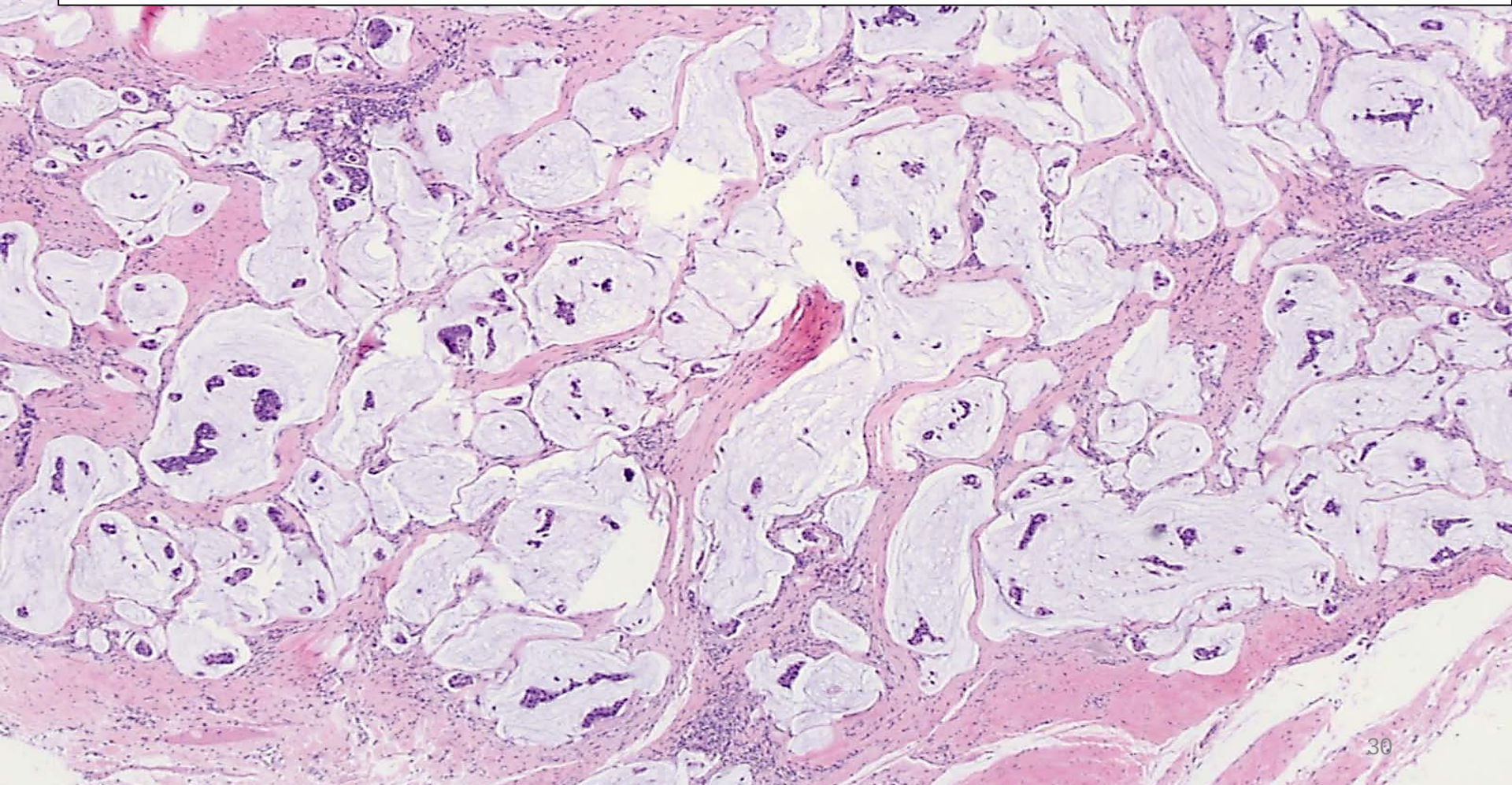
Primary tumor in the appendix

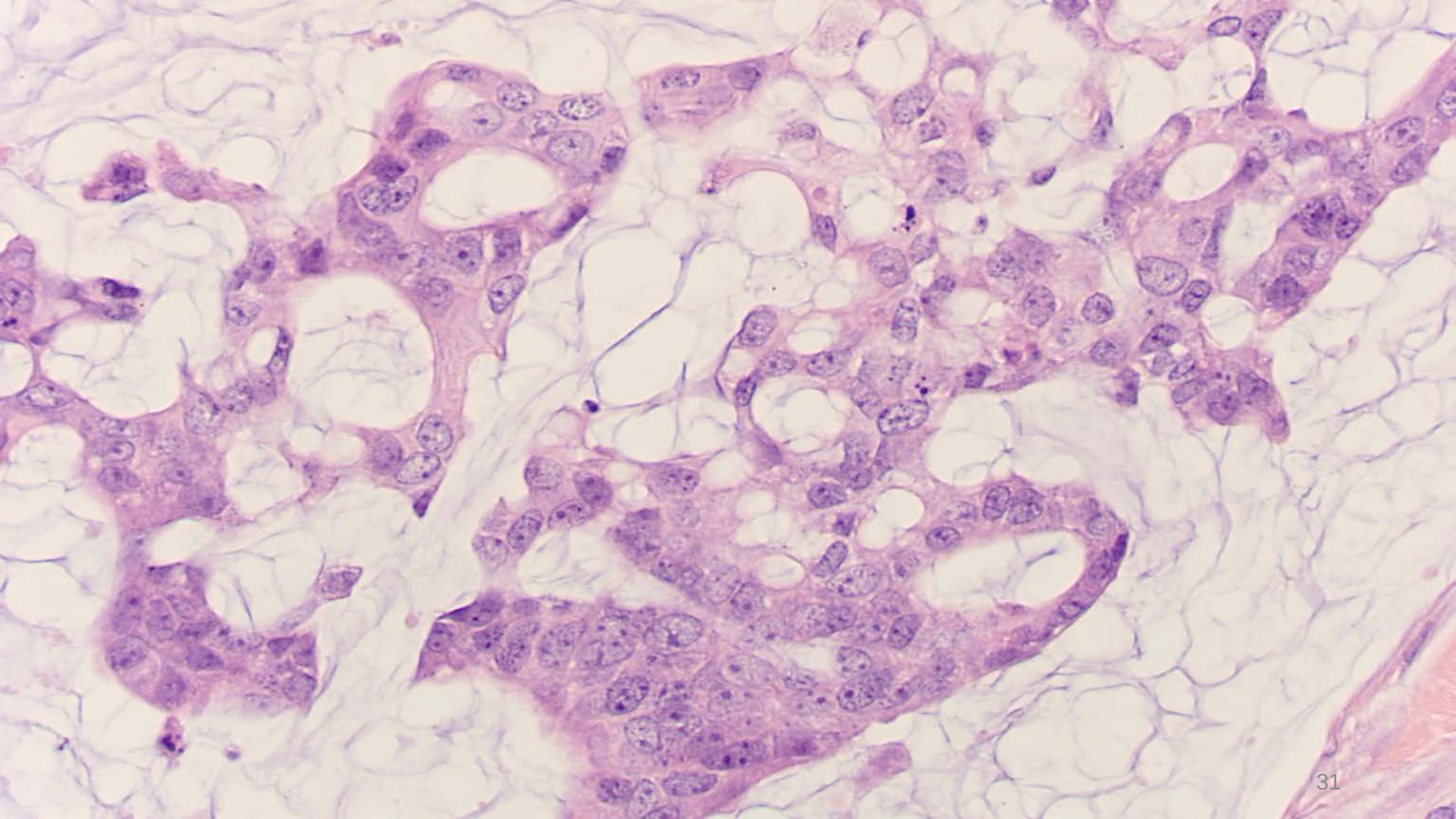
- G1: Usually LAMN, or low-grade invasive mucinous adenocarcinoma
- G2: Usually invasive mucinous adenocarcinoma, rarely HAMN
- G3: Usually signet ring cell adenocarcinoma or high grade goblet cell adenocarcinoma

Grade 2 pseudomyxoma peritonei with desmoplasia, high cellularity, irregular infiltrating glands

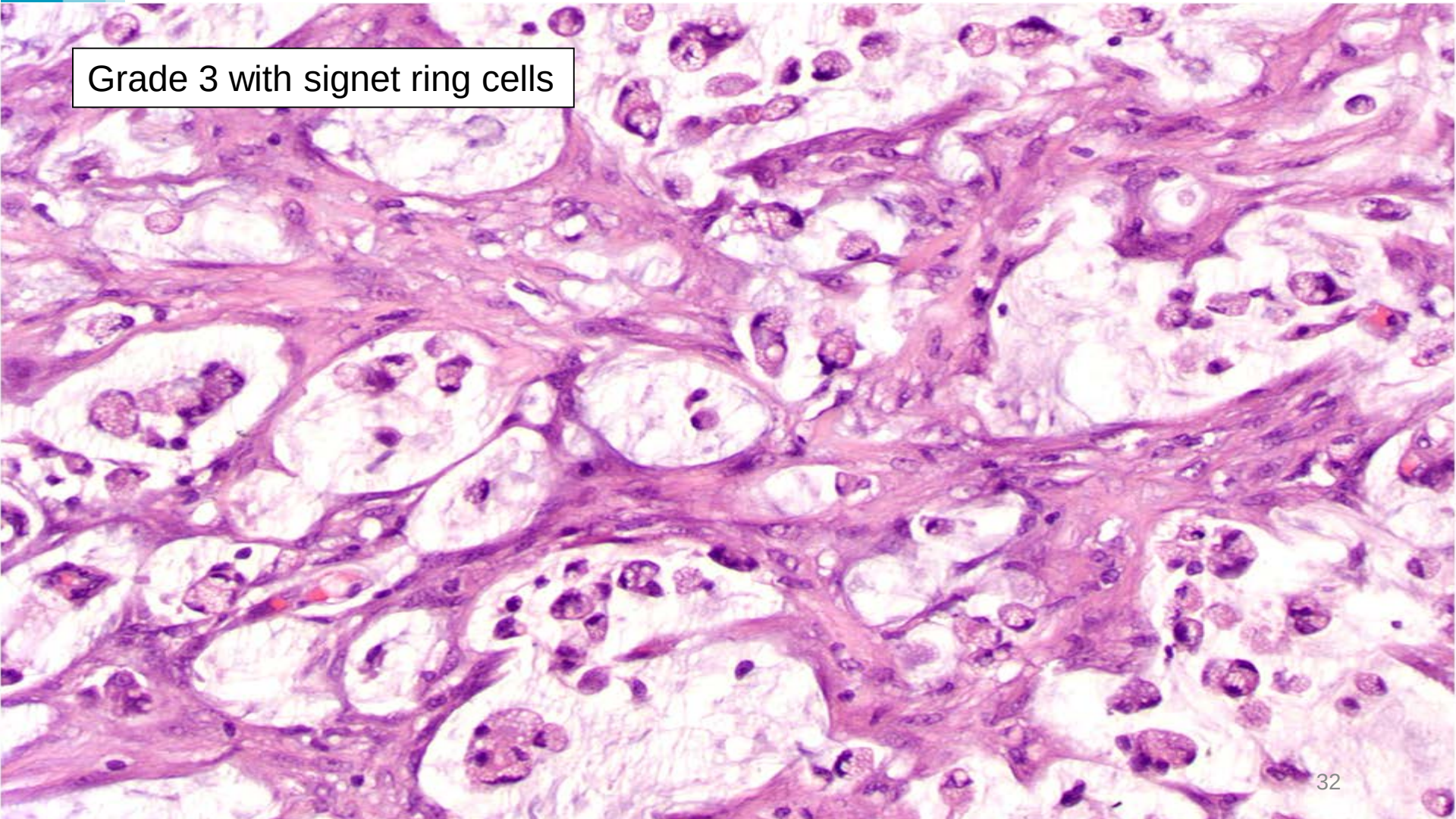


Small mucin pool pattern of grade 2 PMP: Numerous pools of mucin with many tumor clusters

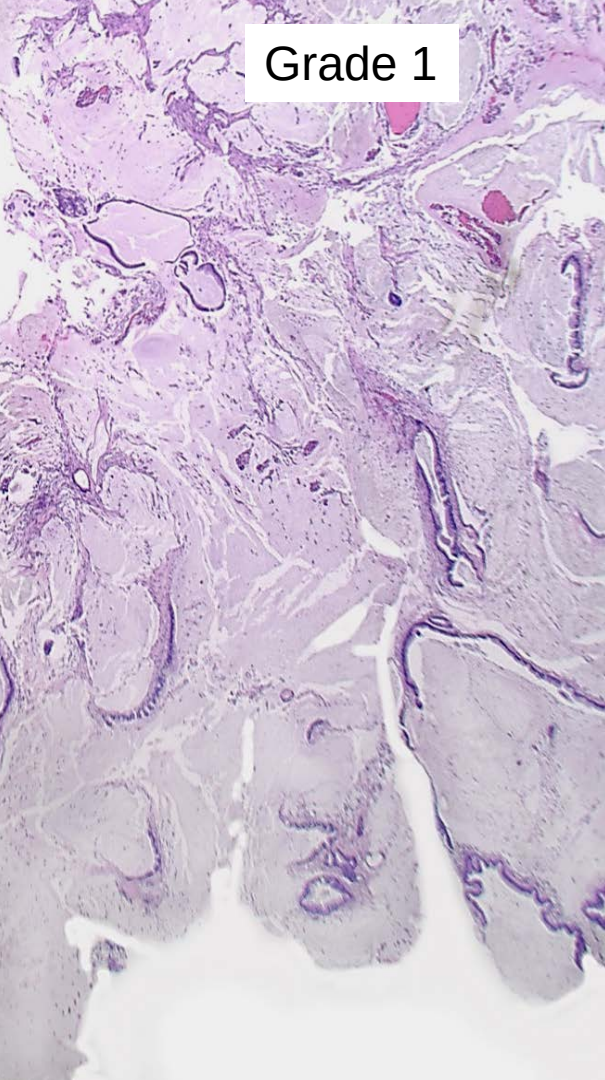




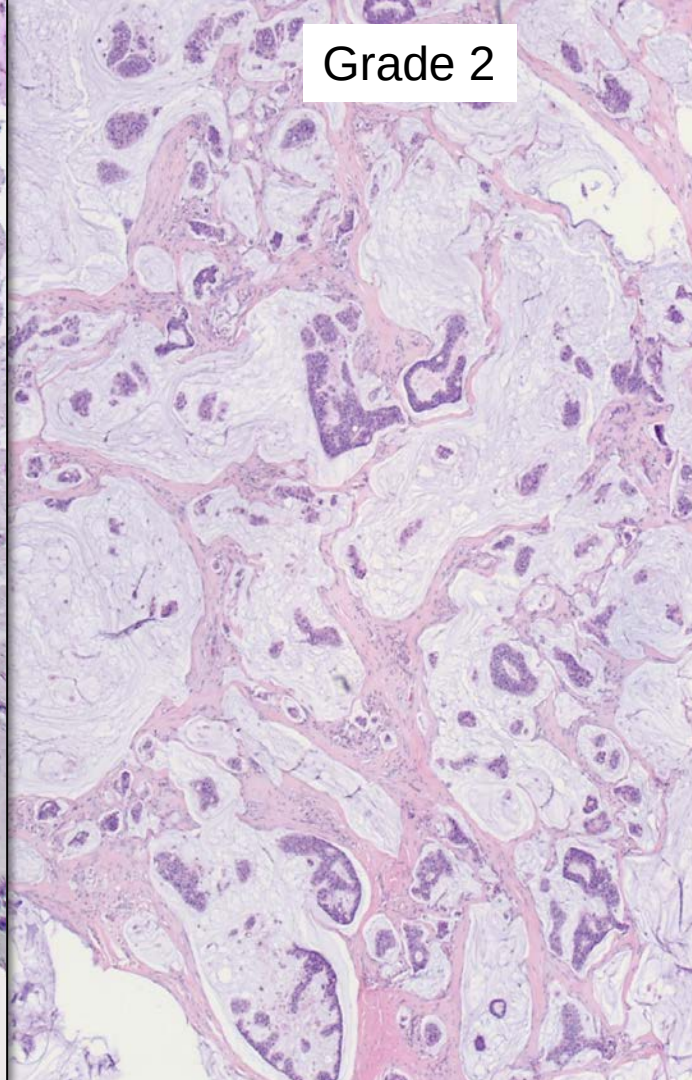
Grade 3 with signet ring cells



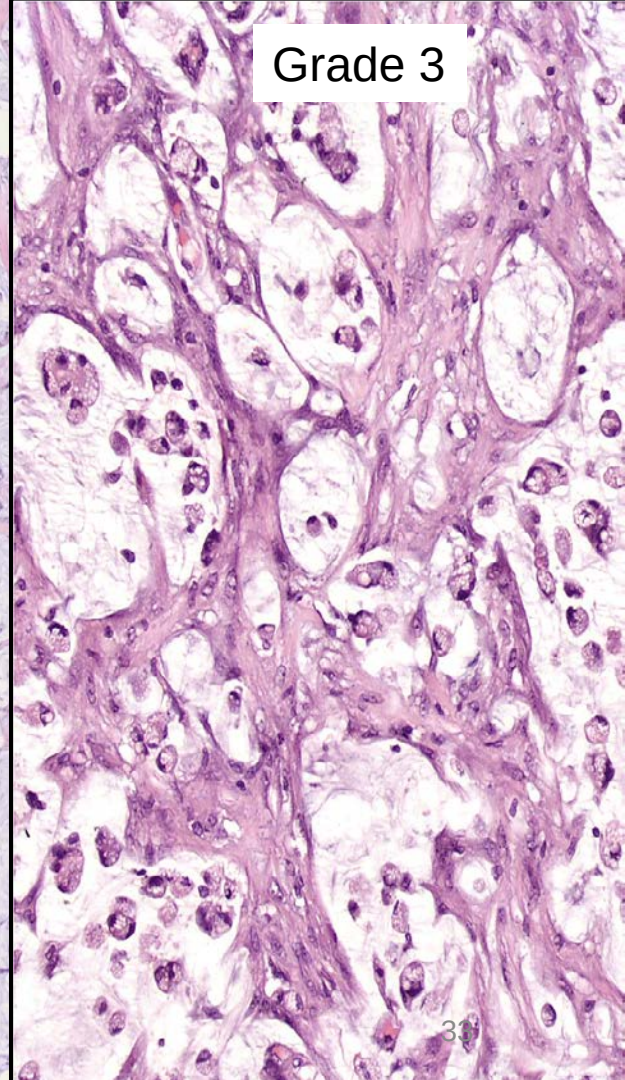
Grade 1



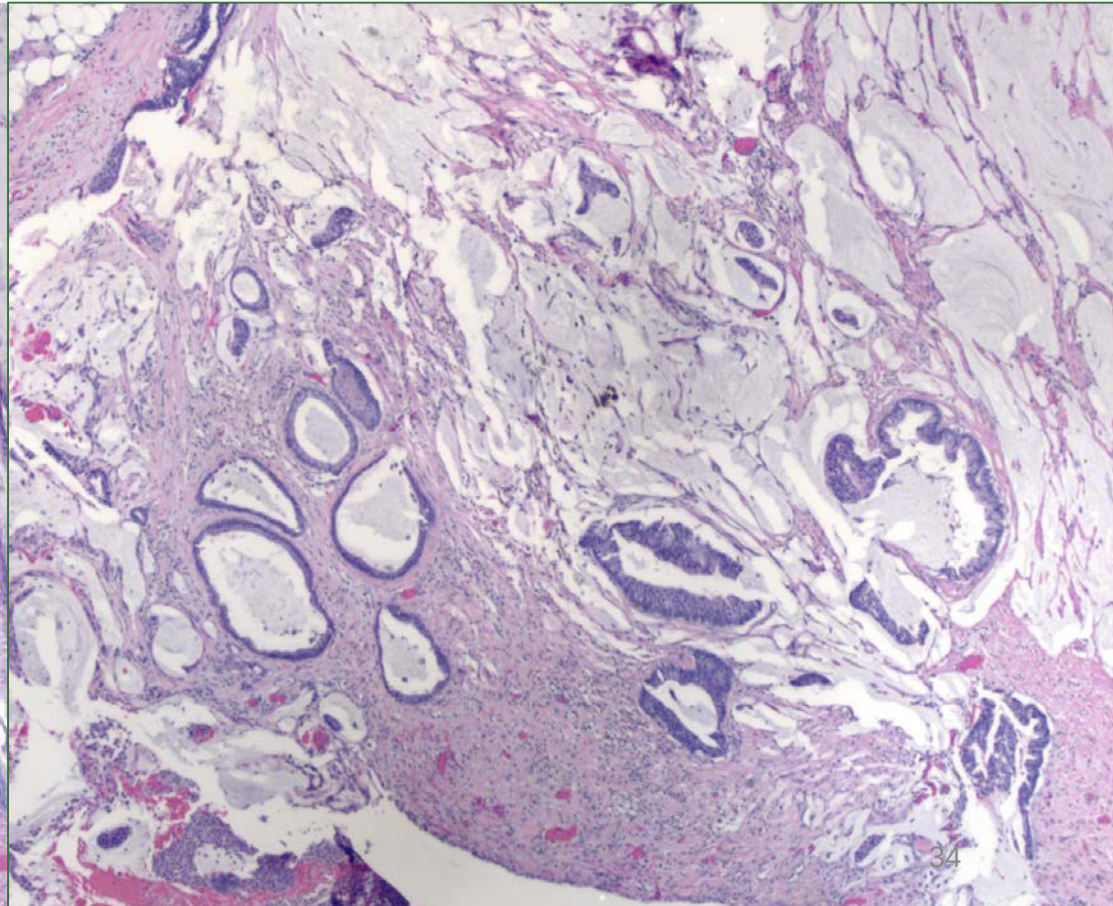
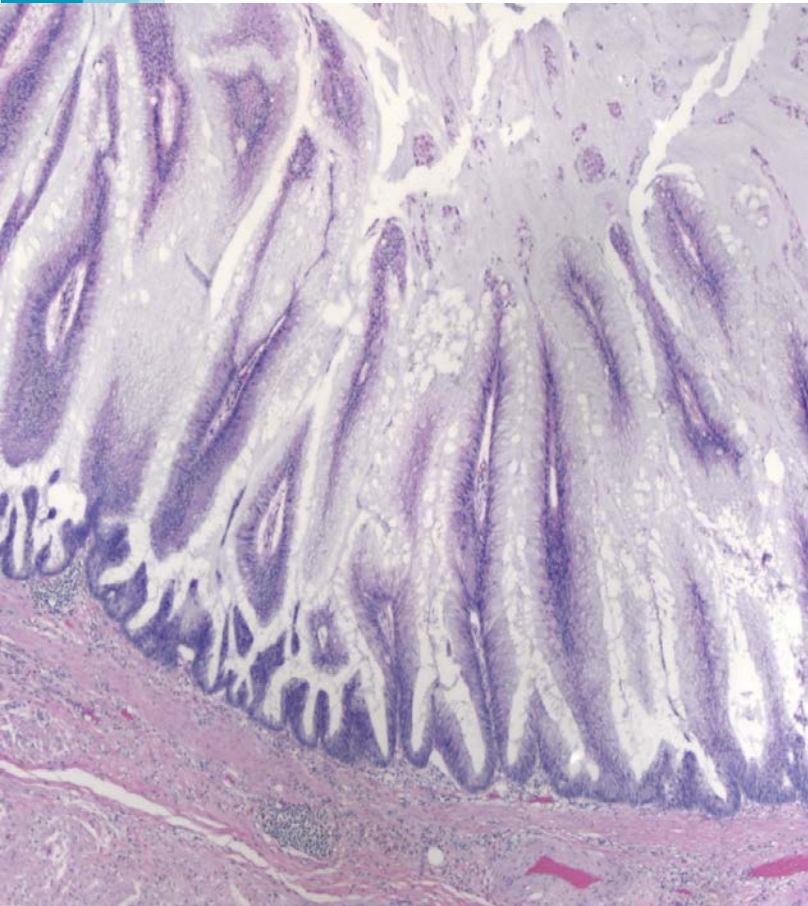
Grade 2



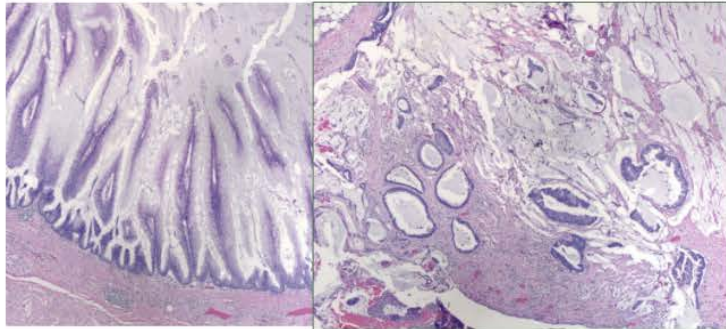
Grade 3



Q: An appendix tumor (left) and the pseudomyxoma (right):



The pathology report should report:



A. The diagnosis of LAMN of the appendix, grade 1, and mucinous carcinoma peritonei, grade 2.

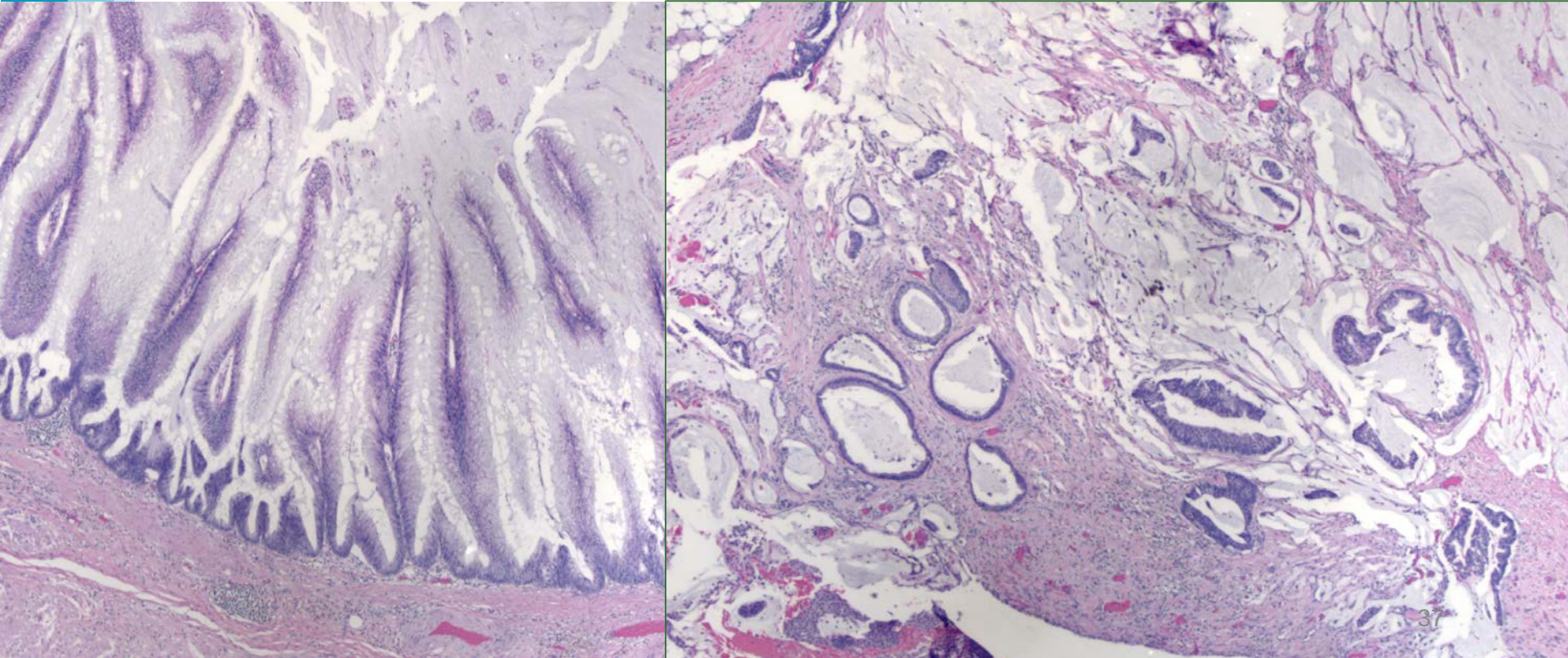
B. The diagnosis as LAMN of the appendix, and grade 1 mucinous carcinoma peritonei.

C. The diagnosis of HAMN of the appendix (to reconcile with the grade of PMP) and mucinous carcinoma peritonei, grade 2.

D. The diagnosis of mucinous adenocarcinoma of the appendix (given the presence of PMP), and grade 2 mucinous carcinoma peritonei.

A. The diagnosis of LAMN of the appendix, grade 1, and mucinous carcinoma peritonei, grade 2.

Discordant grades between the appendix and the PMP are rare but when they occur, document each grade separately. The grade of the mucinous tumor in the peritoneum (PMP) will determine prognosis.



Staging LAMN

T stage

- Tis(LAMN) – LAMN confined by the muscularis propria. Acellular mucin or mucinous epithelium may invade into m. propria.
- T3 – Tumor extends to subserosa. *Includes acellular mucin.*
- T4a - Tumor invades visceral peritoneum, including acellular or cellular mucin on the serosa of the appendix or mesoappendix.

M stage

- M1a: Intraperitoneal acellular mucin
- M1b: Intraperitoneal mucinous deposits containing tumor cells.
- M1c: Metastasis to sites other than peritoneum.

Staging HAMN – the same as invasive cancer*

T stage

- T1 – Tumor invades submucosa
- T2 – Tumor invades muscularis propria
- T3 – Tumor invades subserosa or mesoappendix.
- T4a - Tumor invades visceral peritoneum, including acellular or cellular mucin on the serosa of the appendix or mesoappendix.

M stage

- M1a: Intraperitoneal acellular mucin
- M1b: Intraperitoneal mucinous deposits with tumor cells.
- M1c: Metastasis to sites other than peritoneum.

*Based on the principle that high-grade tumors are more likely to recur. The data to support this is lacking. It may be the case that the outcome is dependent on stage, as it is with LAMN.

Reporting localized disease



Prognostic Significance of Localized Extra-Appendiceal Mucin Deposition in Appendiceal Mucinous Neoplasms

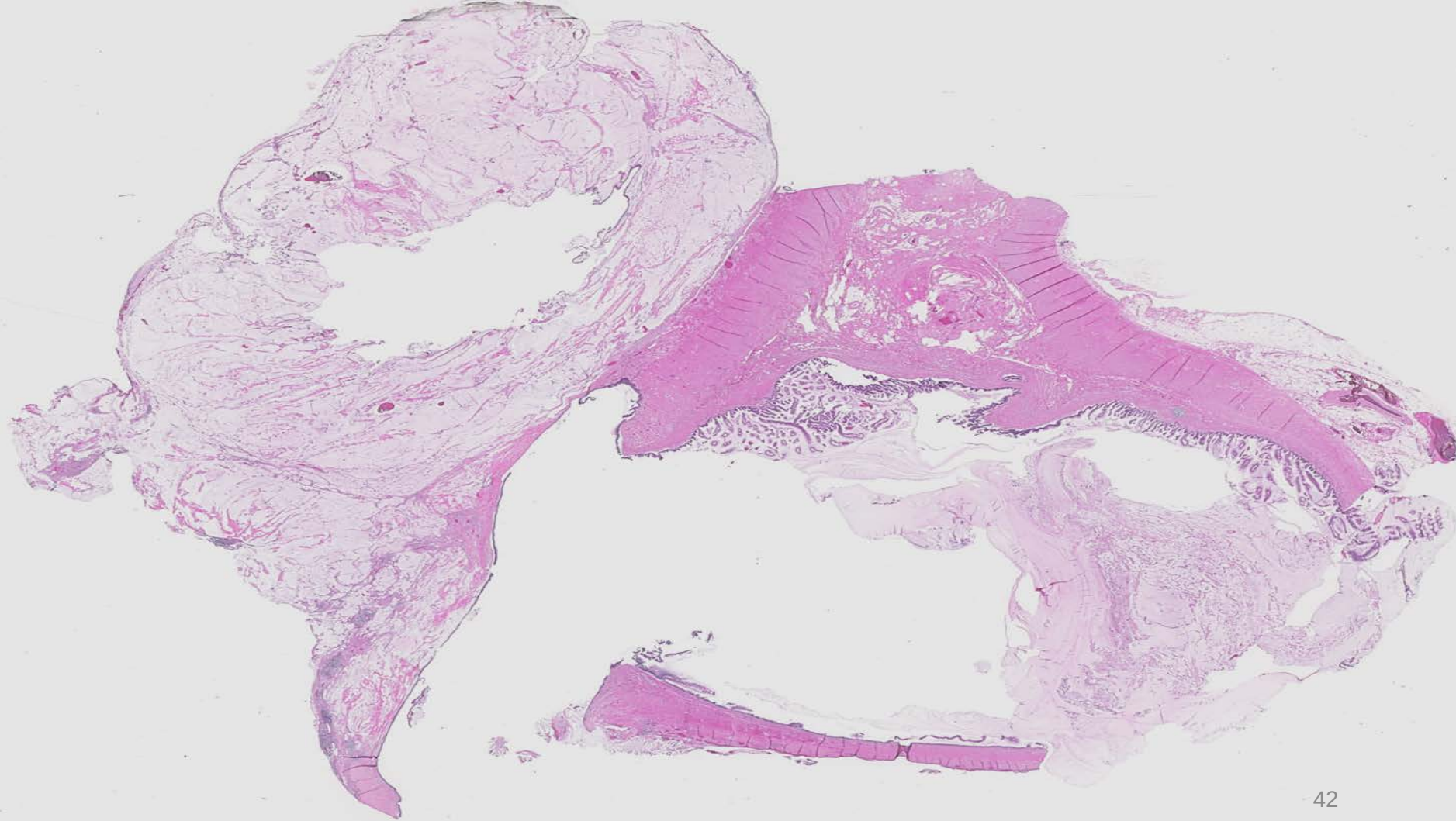
Am J Surg Pathol 2009;33:248-255

50 cases without cells in periappendiceal mucin

- 2 (4%) recurred as pseudomyxoma peritonei
 - Neither was submitted entirely, raising the possibility that epithelial cells were unsampled

15 cases with cells in the periappendiceal mucin

- 5 (33%) recurred ($p=0.03$); 1 died of disease

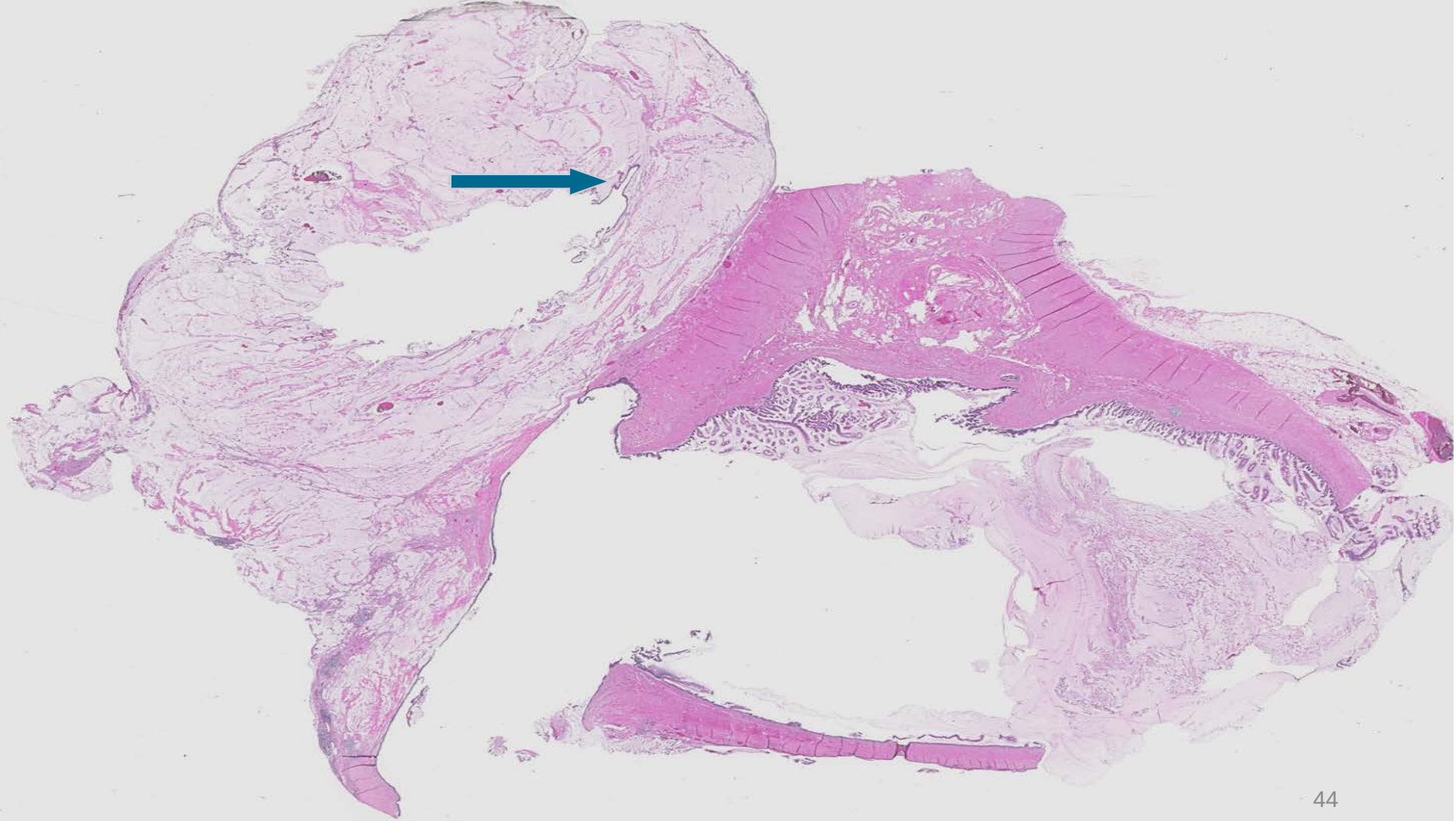


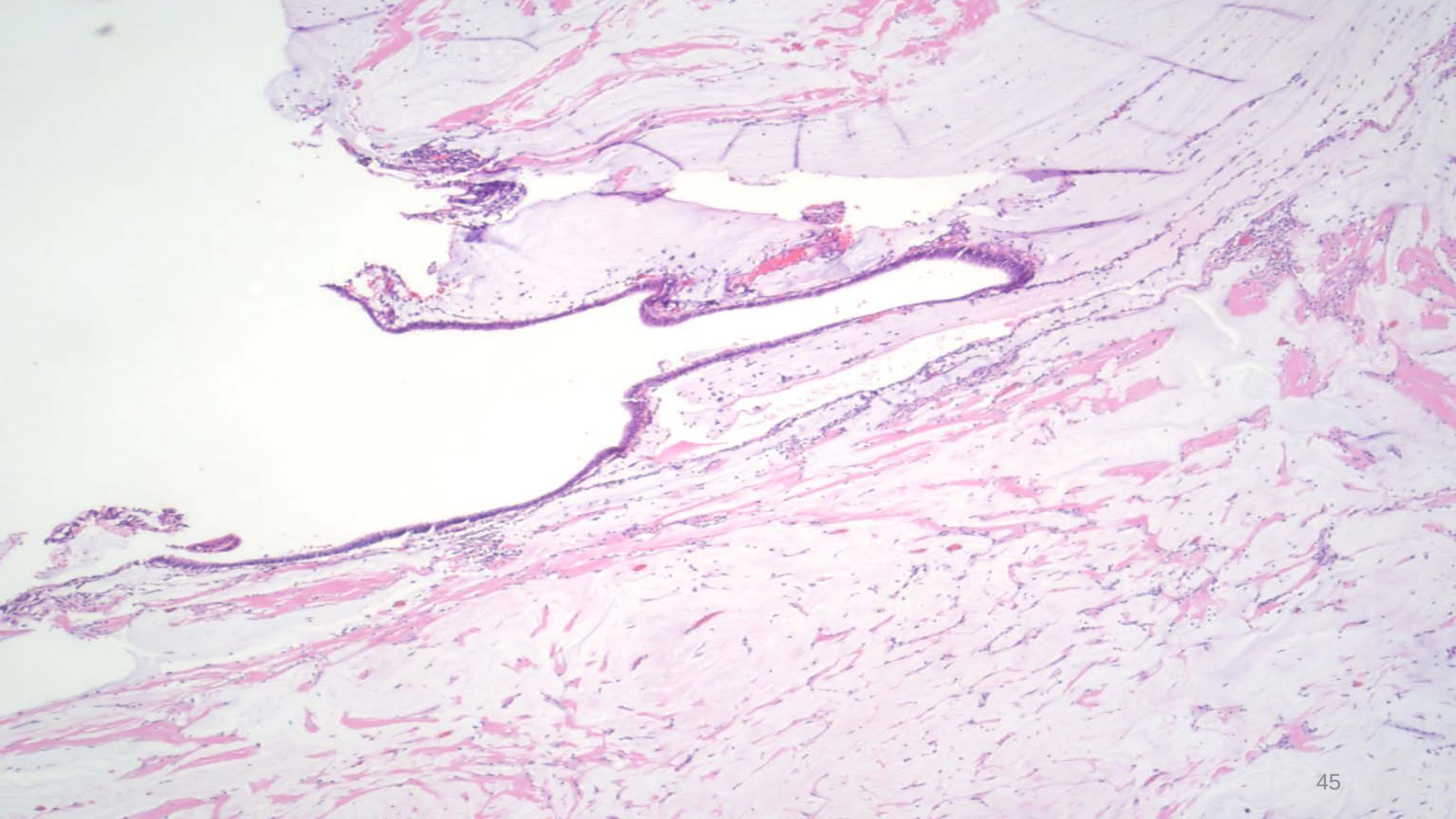
Diagnosis

Low grade appendiceal mucinous neoplasm, ruptured, with extrusion of acellular mucin on the appendiceal serosa.

In the comments:

- Clarify that there is mucin BUT NO mucinous epithelium on the surface of the appendix;
- Rupture of a mucinous neoplasm with extrusion of acellular mucin in the RLQ is associated with a low risk of recurrence as pseudomyxoma peritonei.





Diagnosis

Low grade appendiceal mucinous neoplasm, ruptured, with involvement of the peri-appendiceal serosa (localized pseudomyxoma peritonei).

- Clarify that there is mucin AND low grade mucinous epithelium on the surface of the appendix;
- This is considered high risk of recurrence as PMP;
- Although surgeons who specialize in PMP likely would proceed to evaluate peritoneum and offer HIPEC, a recent paper reports that prognosis for low grade limited peritoneal disease was not affected by watching for radiologic progression (Ann Surg Oncol 2014)

LAMN: Prognosis is stage dependent

(but T stage doesn't stratify patients into distinct prognostic groups)

Extent of tumor spread in appendectomy	Prognosis	TNM stages
Tumor is confined to the appendix: serosa intact, no mucin or tumor outside appendix	Almost certainly cured by appendectomy	Tis(LAMN) or T3
Tumor perforates serosa with acellular mucin on the serosa (or with acellular mucin elsewhere)	Low-risk of recurrence as pseudomyxoma	T4a (and maybe M1a)
Tumor perforates serosa with cellular mucin on the serosa	High-risk of recurrence as pseudomyxoma	T4a

Ultimately, it is critical to describe the extent of spread of tumor and mucin, emphasizing whether there is acellular or cell mucin on the appendix serosa

Serrated lesions in the appendix

Serrated lesions occur in the appendix but it is not clear that the classification used in the colon is applicable.

Serrated lesions only infrequently have BRAF mutations, suggesting a different serrated pathway in the appendix.

KRAS mutations are common in serrated lesions (as they are in LAMN).

True serrated lesions probably do not cause PMP, but may be precursors for invasive cancers of the appendix.

MSI-H cancers are rare in the appendix – 3% of cancers (as opposed to 20% in the right colon).

Classification of Serrated lesions

Colon

Hyperplastic polyp

Sessile serrated adenoma

Traditional serrated adenoma

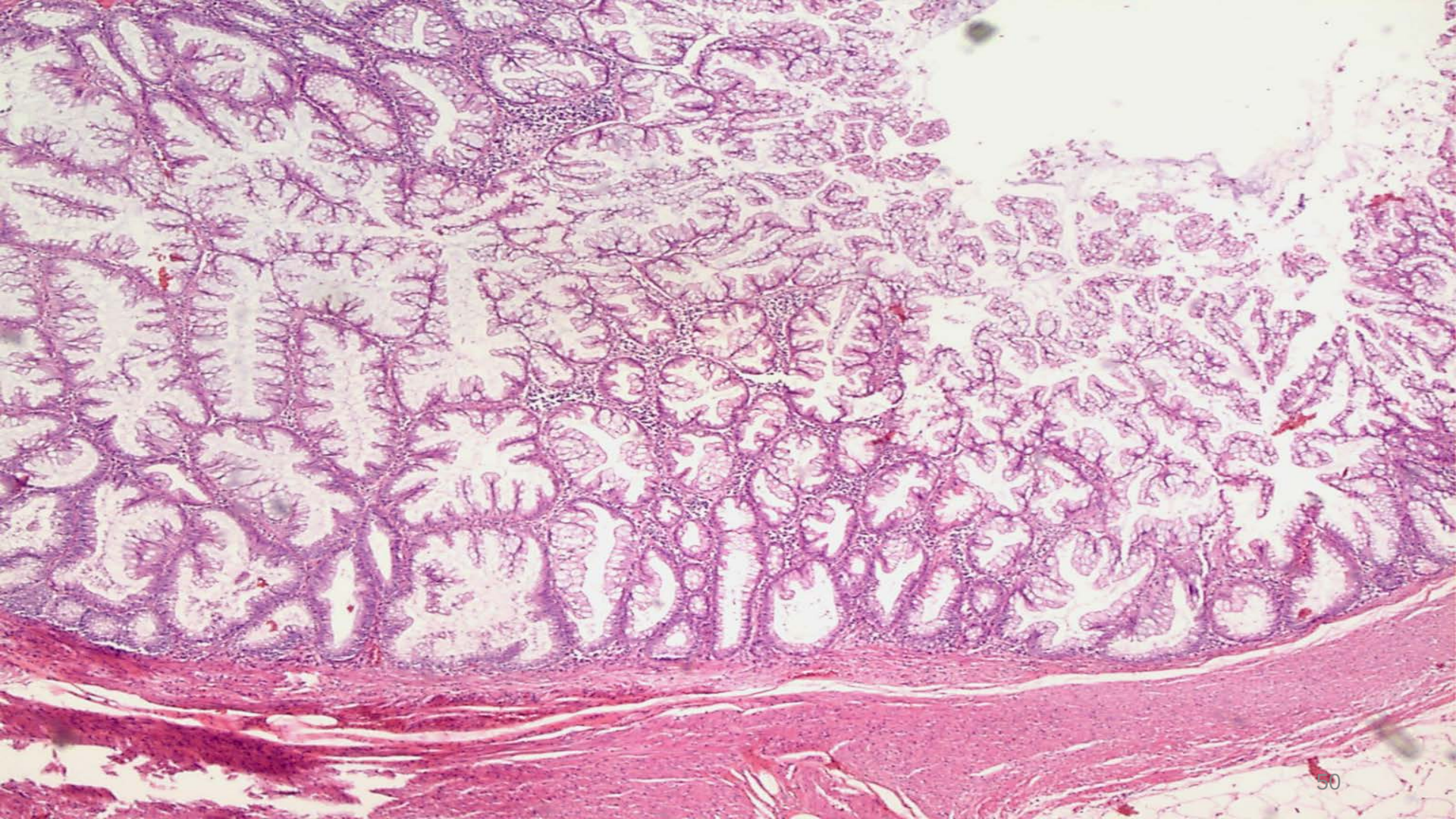
SSA with dysplasia

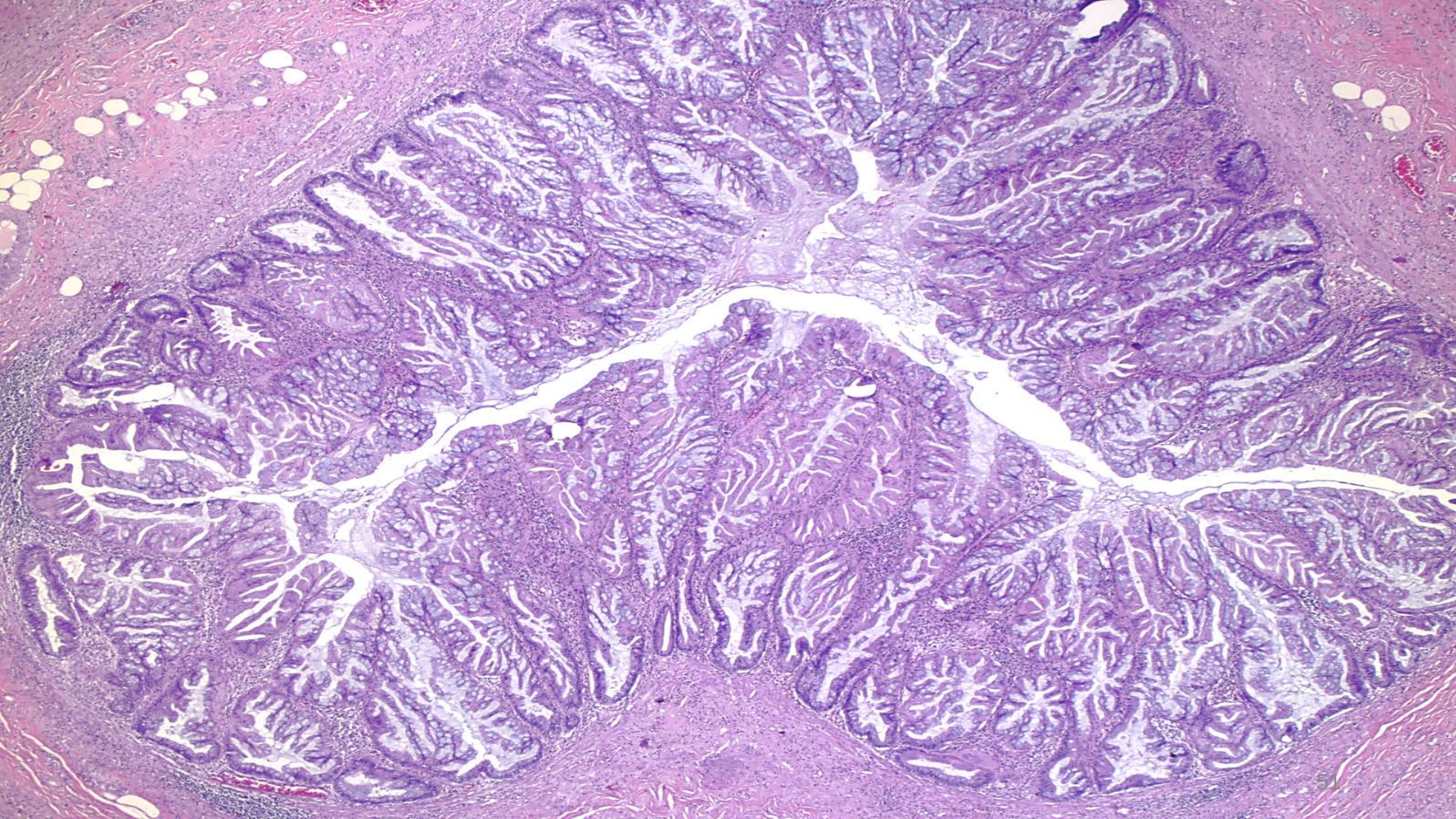
Appendix

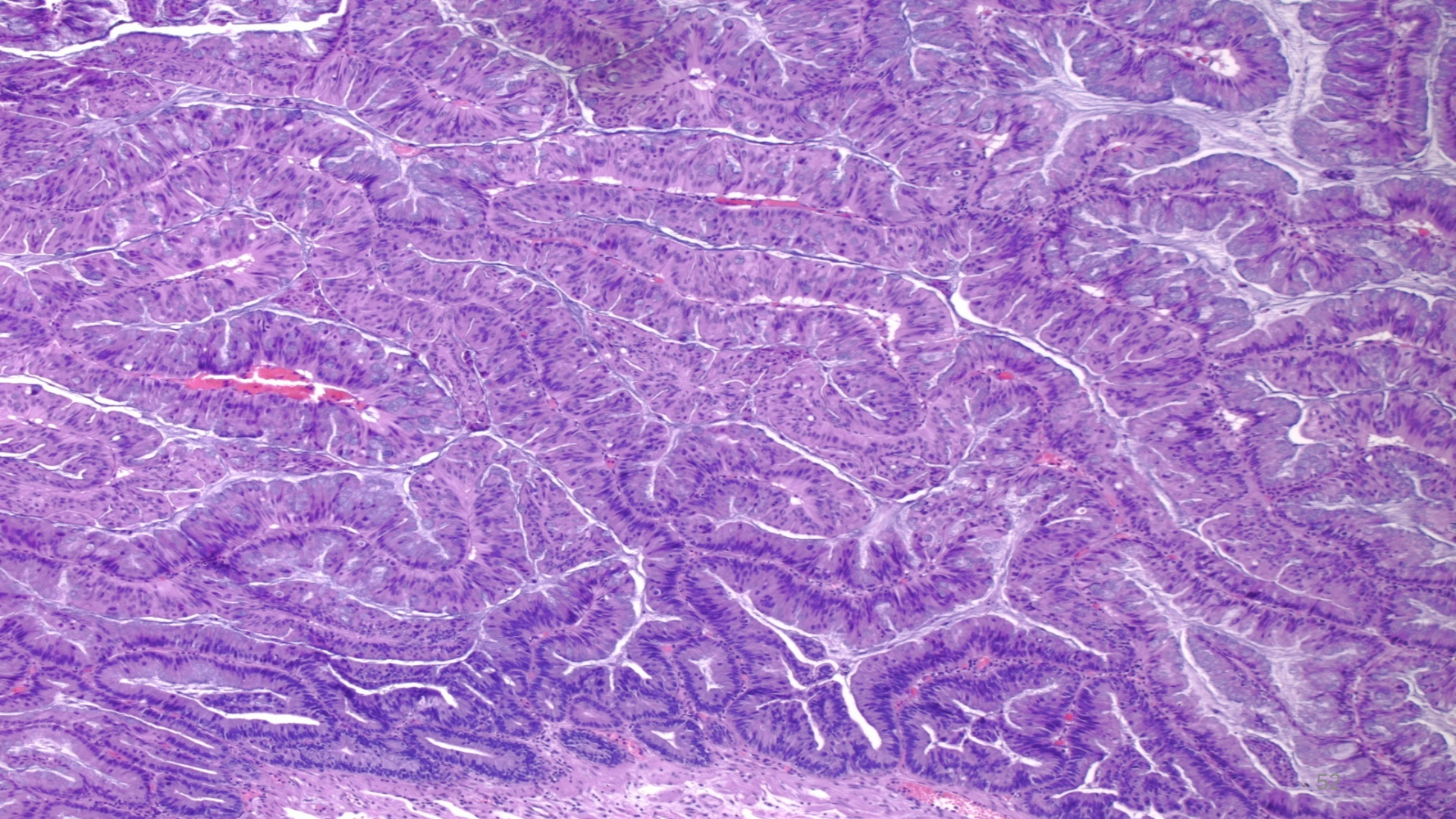
Hyperplastic polyp/mucosal
hyperplasia

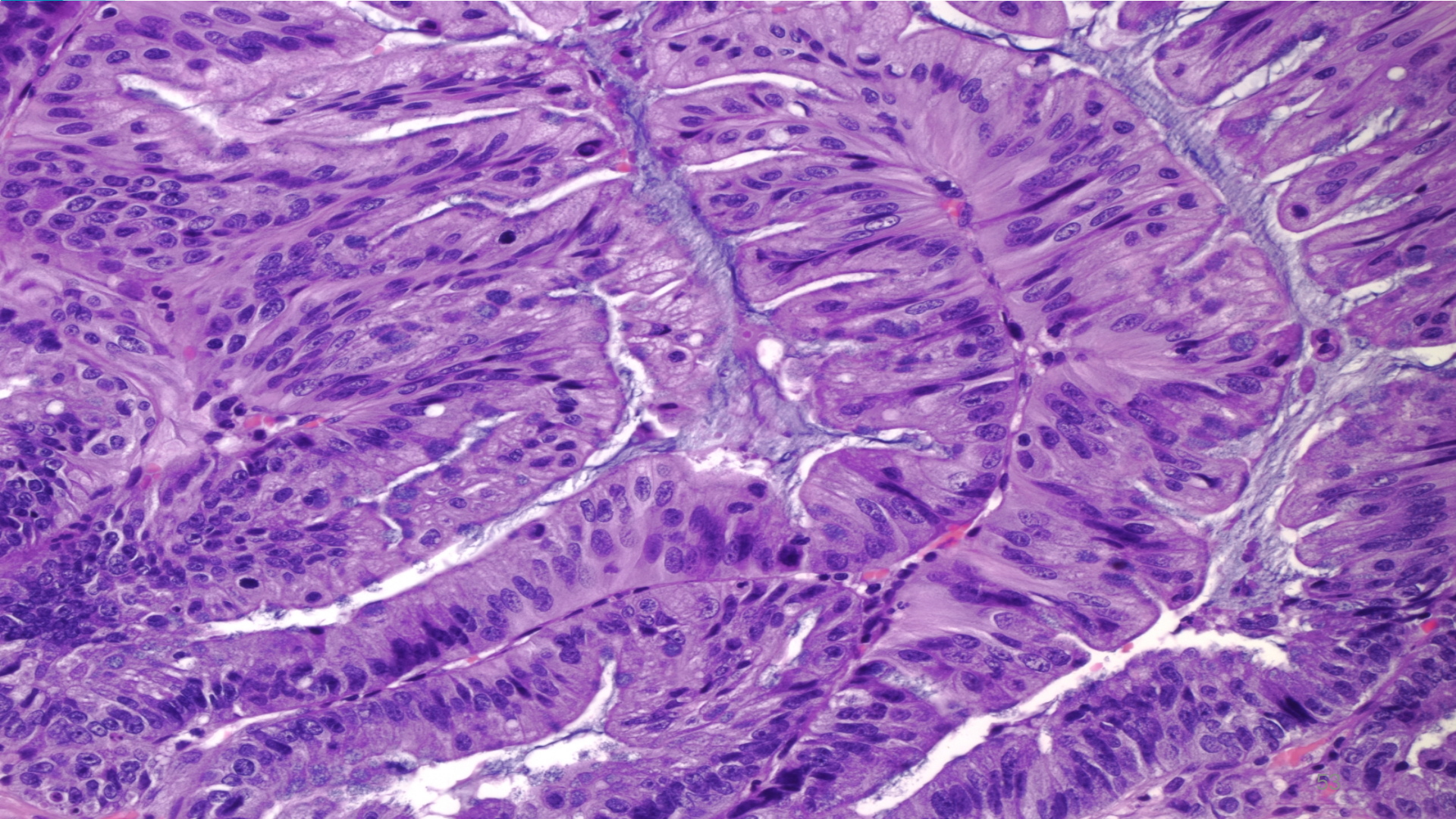
Serrated lesion/polyp without
dysplasia

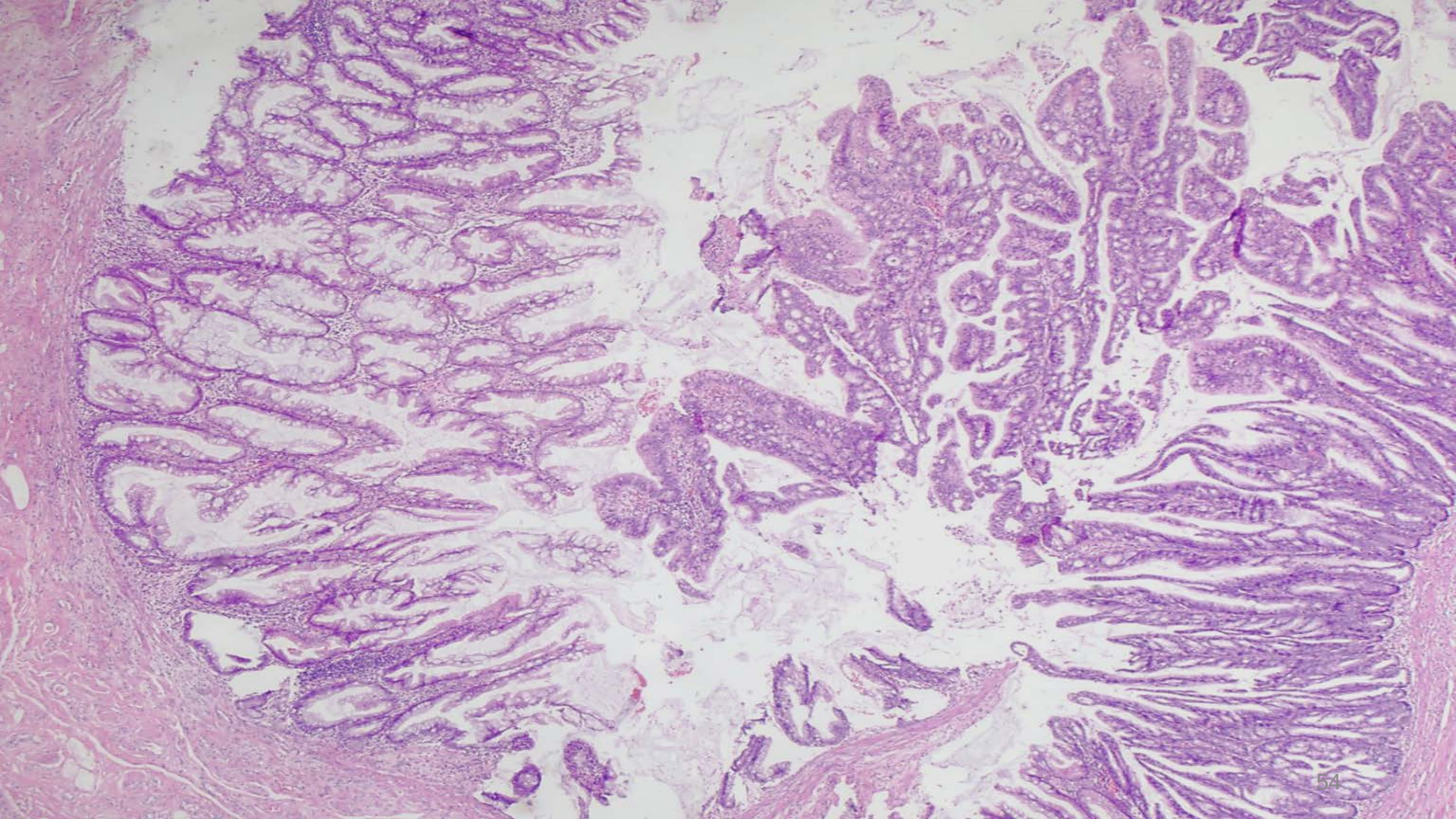
Serrated lesion/polyp with dysplasia

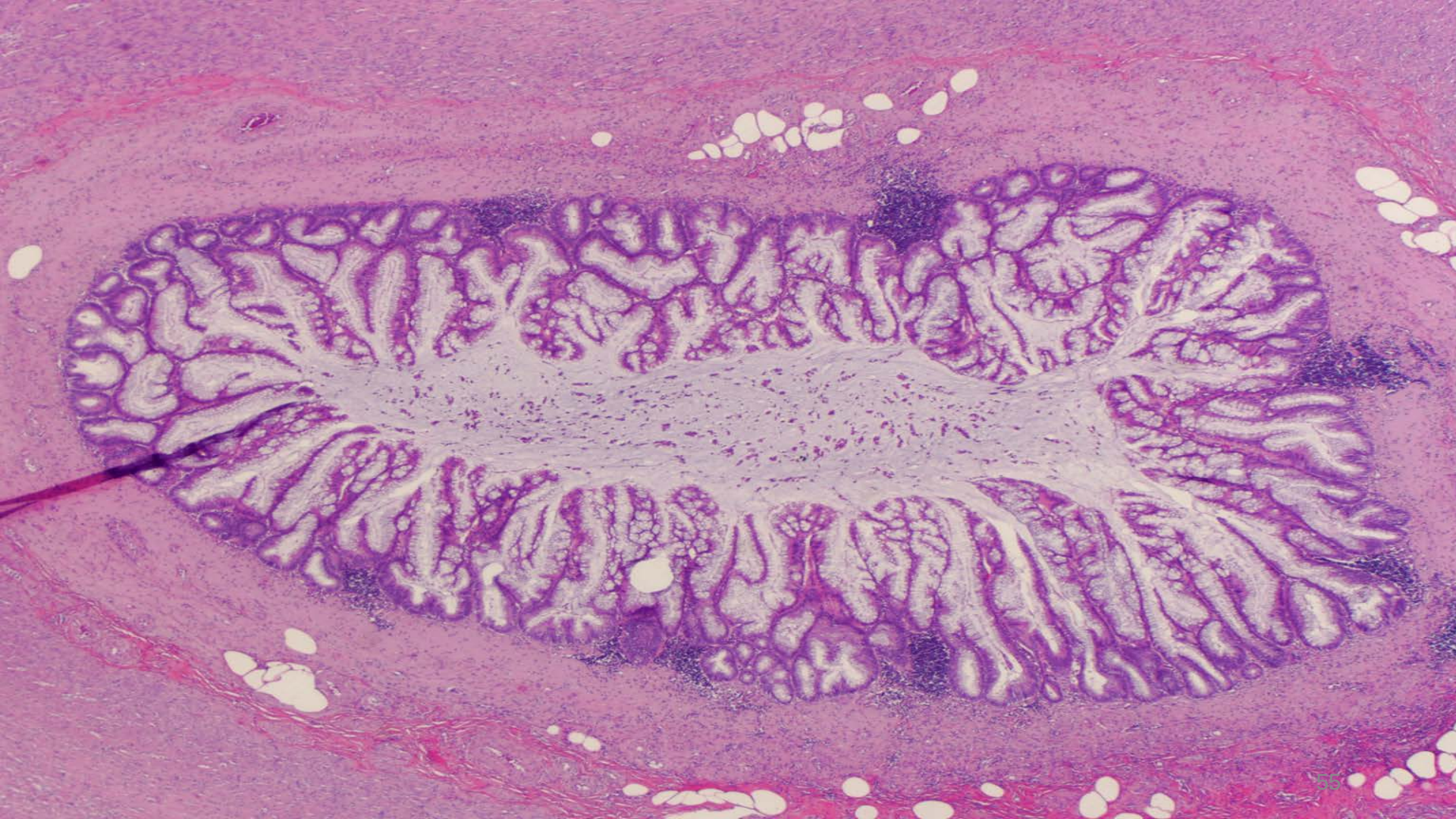


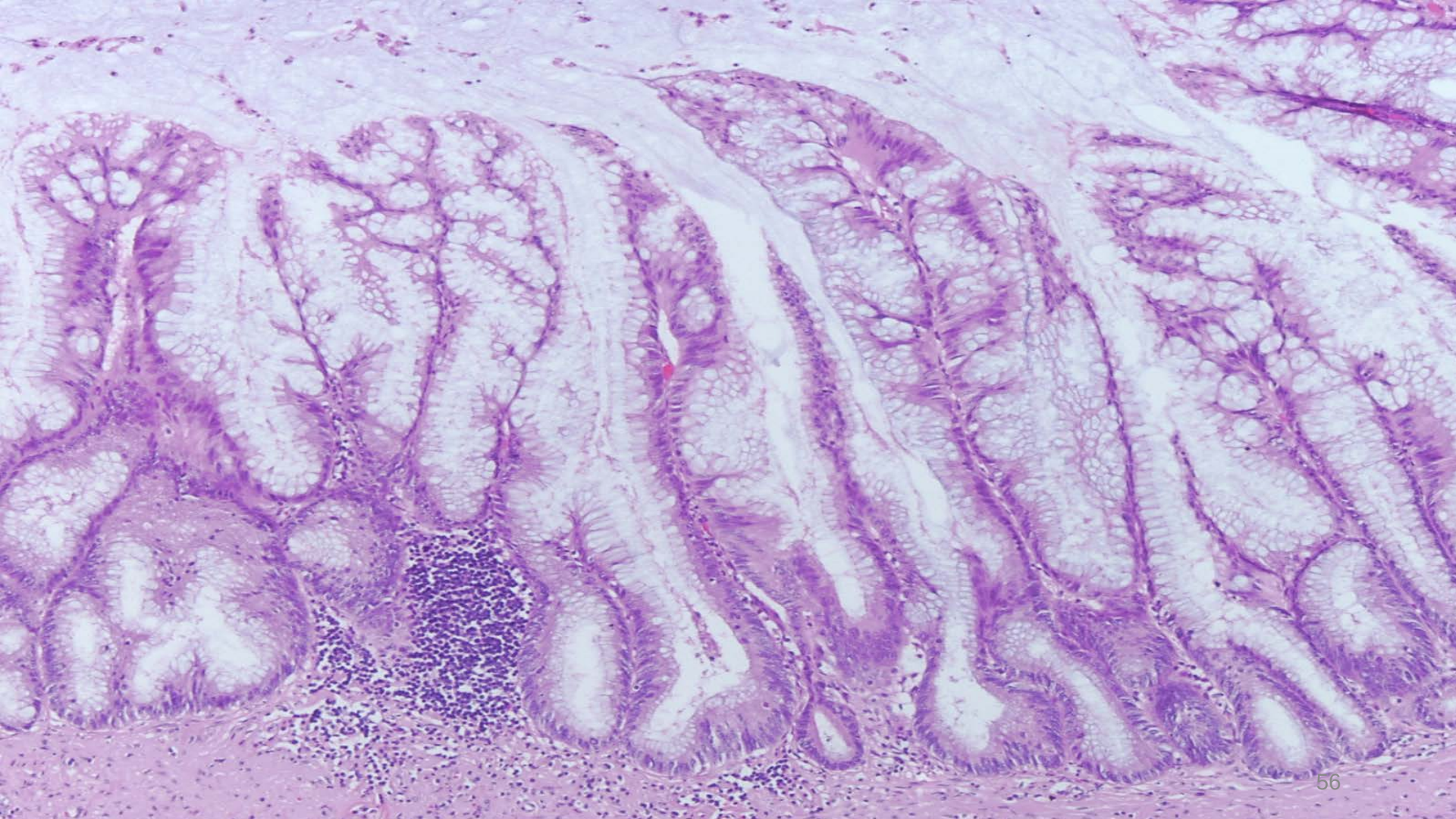










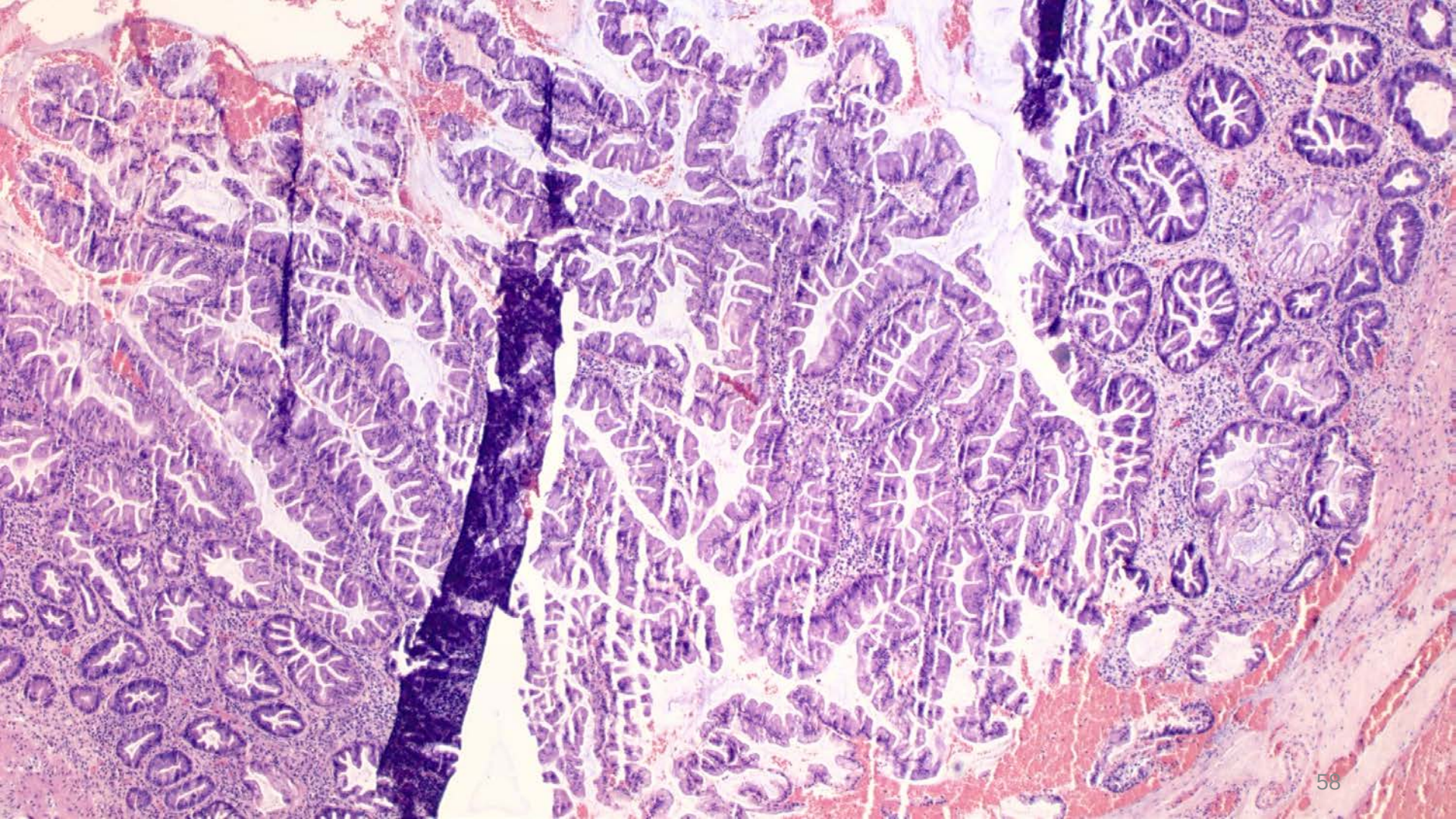


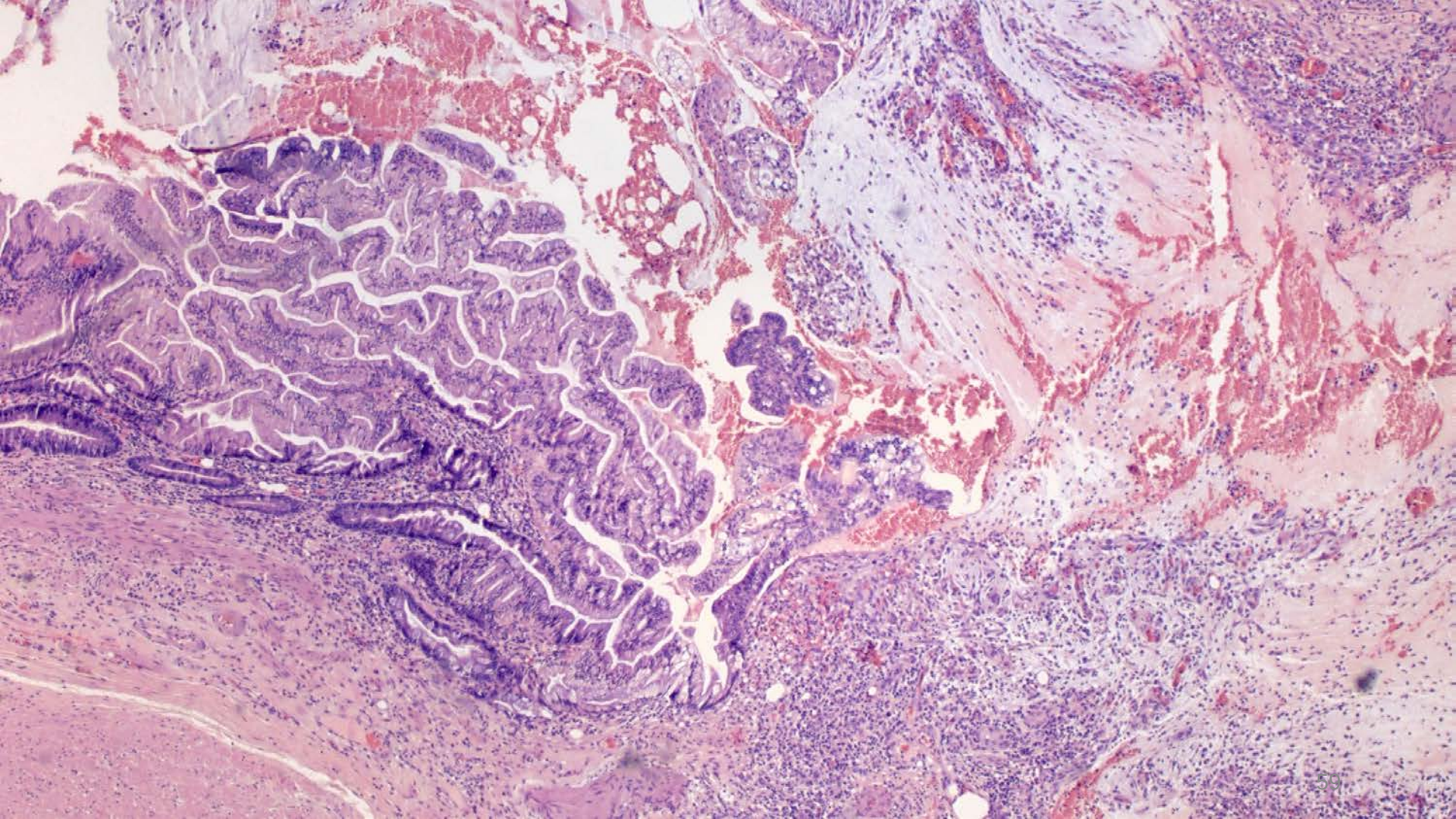
What are the consequences of a diagnosis?

If the appendix is not ruptured, then the distinction between LAMN and serrated lesion is probably academic.

If the appendix is ruptured, then the diagnosis matters.

- LAMN – some patients may be followed radiologically, but others undergo additional surgery and HIPEC on the basis of a ruptured LAMN
- Serrated lesion – Probably, true serrated lesions would not confer risk for pseudomyxoma. Surgeons are not likely to understand what SSA means, so it is unclear what their course of action would be. Avoid confusion by providing guidance as to appropriate follow up (colonoscopy to rule out other serrated lesions).
- If it is unclear, urge radiologic follow up for recurrent mucinous ascites.





My diagnosis: Serrated lesion of the appendix, ruptured, with xanthogranulomatous reaction

Additional information

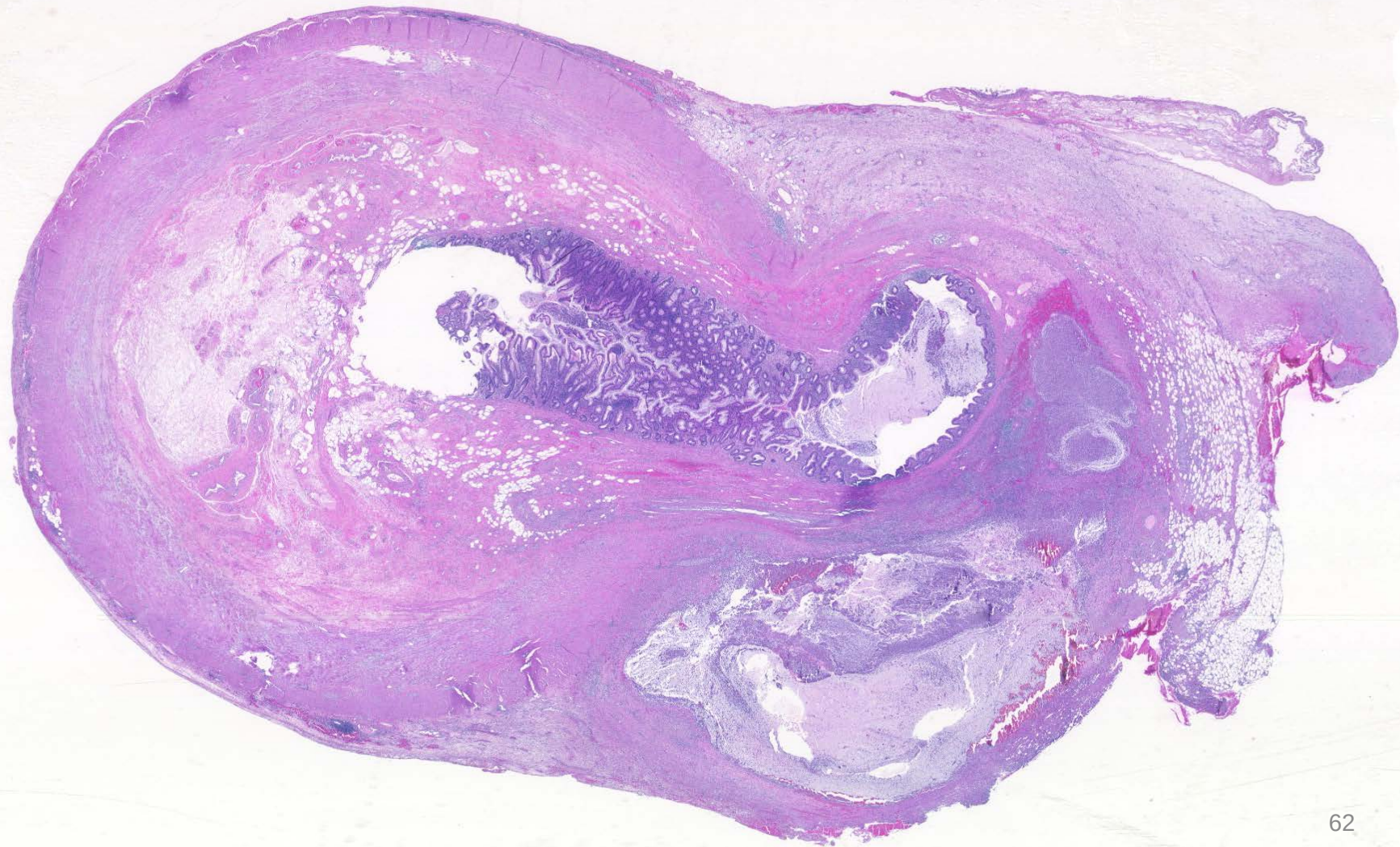
- The proliferation seems too exuberant and hyper serrated for just hyperplasia in the setting of appendicitis.
- Serrated lesions are not presumed to lead to pseudomyxoma so the rupture shouldn't concern us, but...
- Even if I am wrong, the risk of PMP is low given the absence of abundant mucin and absence of epithelium on the serosa, but...
- Maybe it would be prudent to follow this patient radiologically to ensure that mucin does not accumulate in the peritoneal cavity.

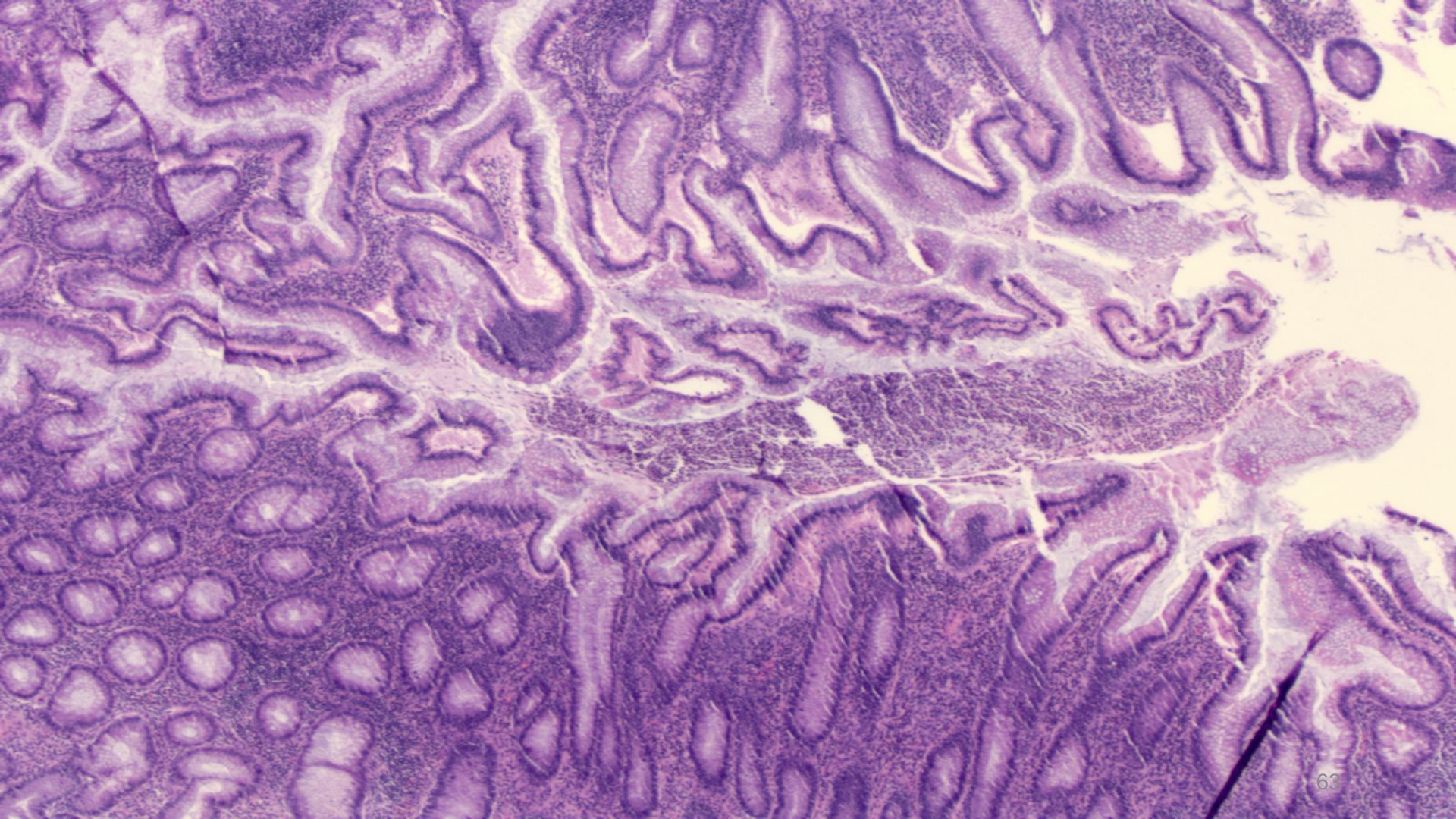
Differential diagnosis of mucinous neoplasms

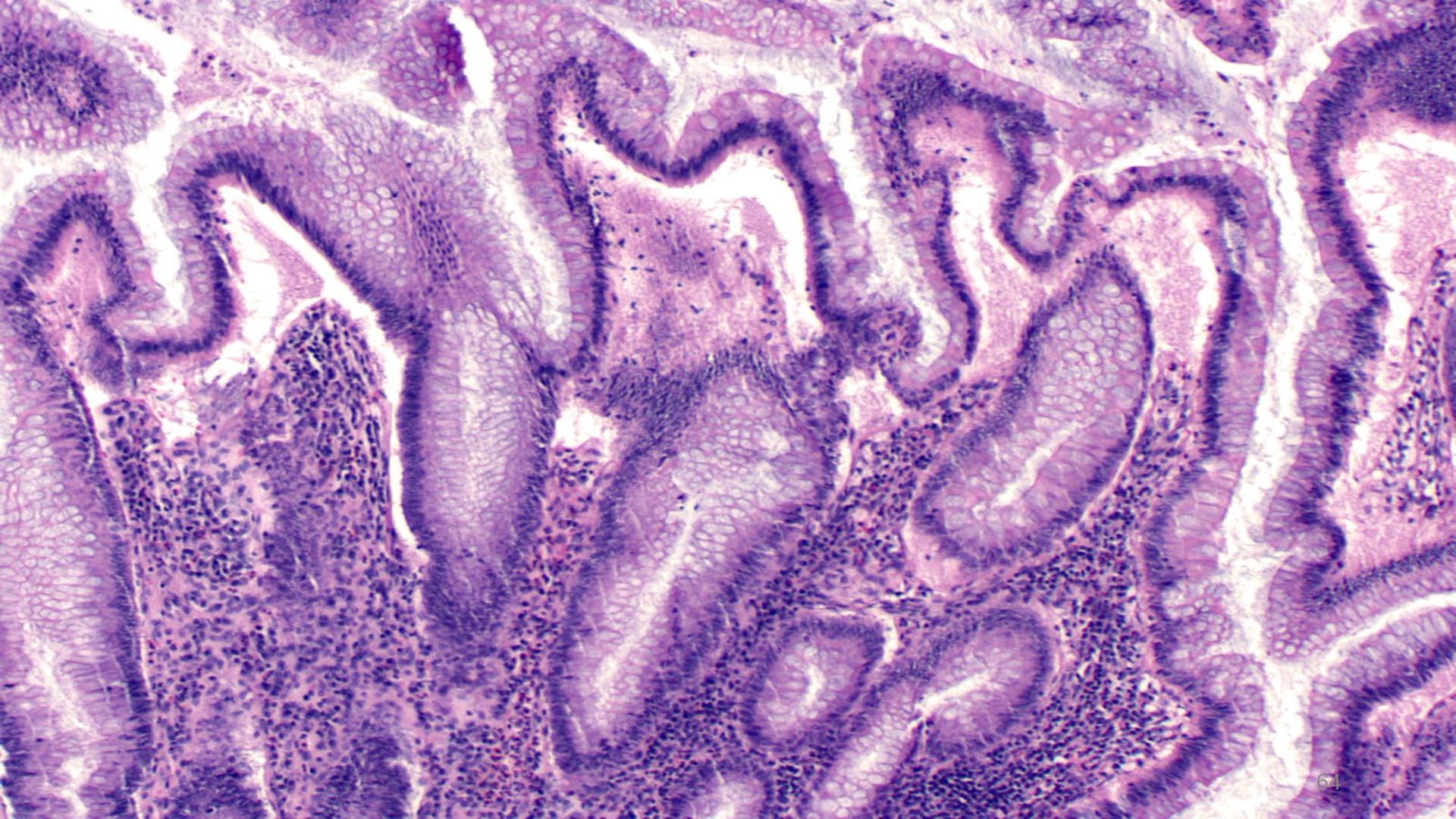
Ruptured appendiceal diverticular disease

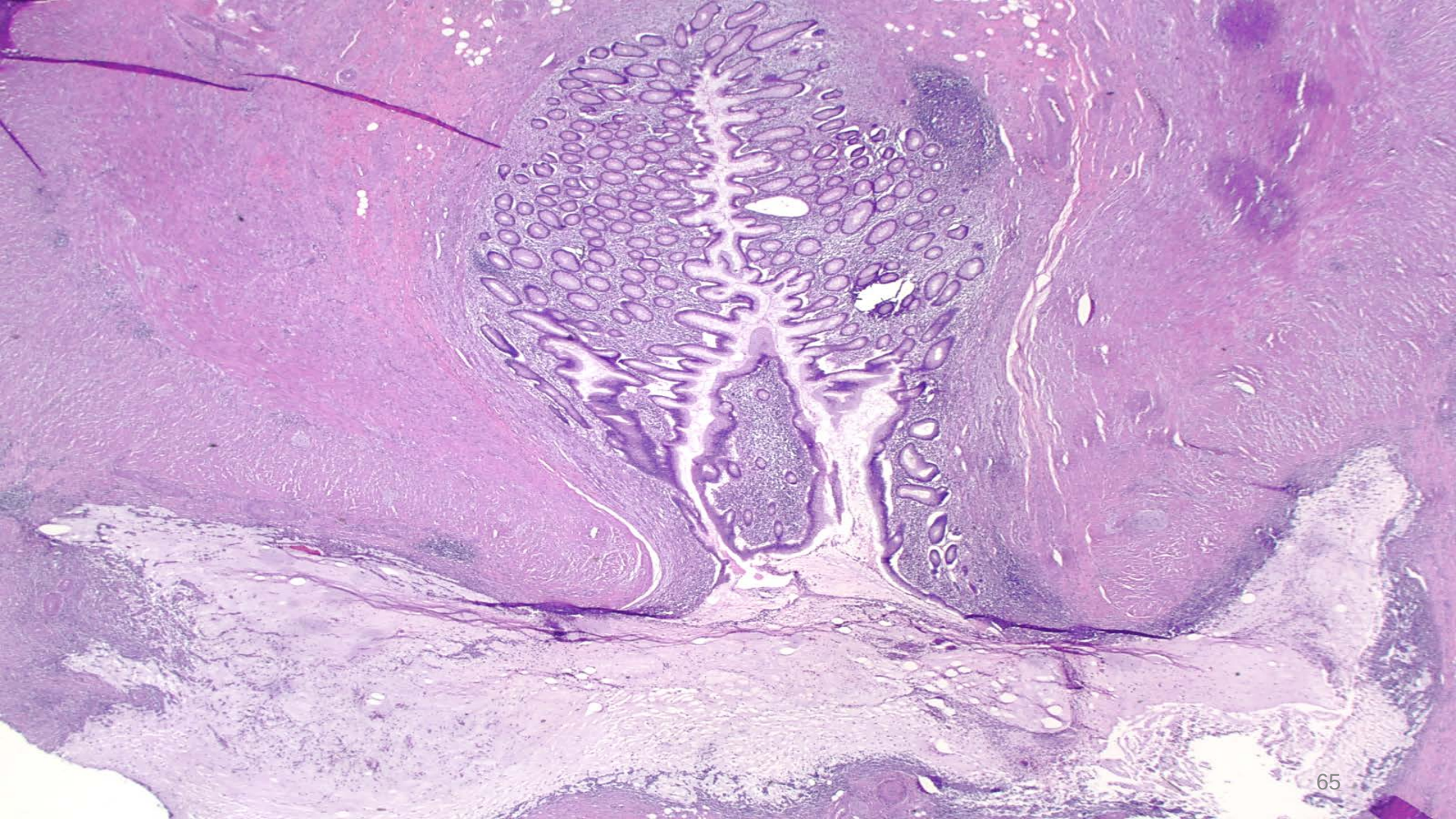
Retention mucocele

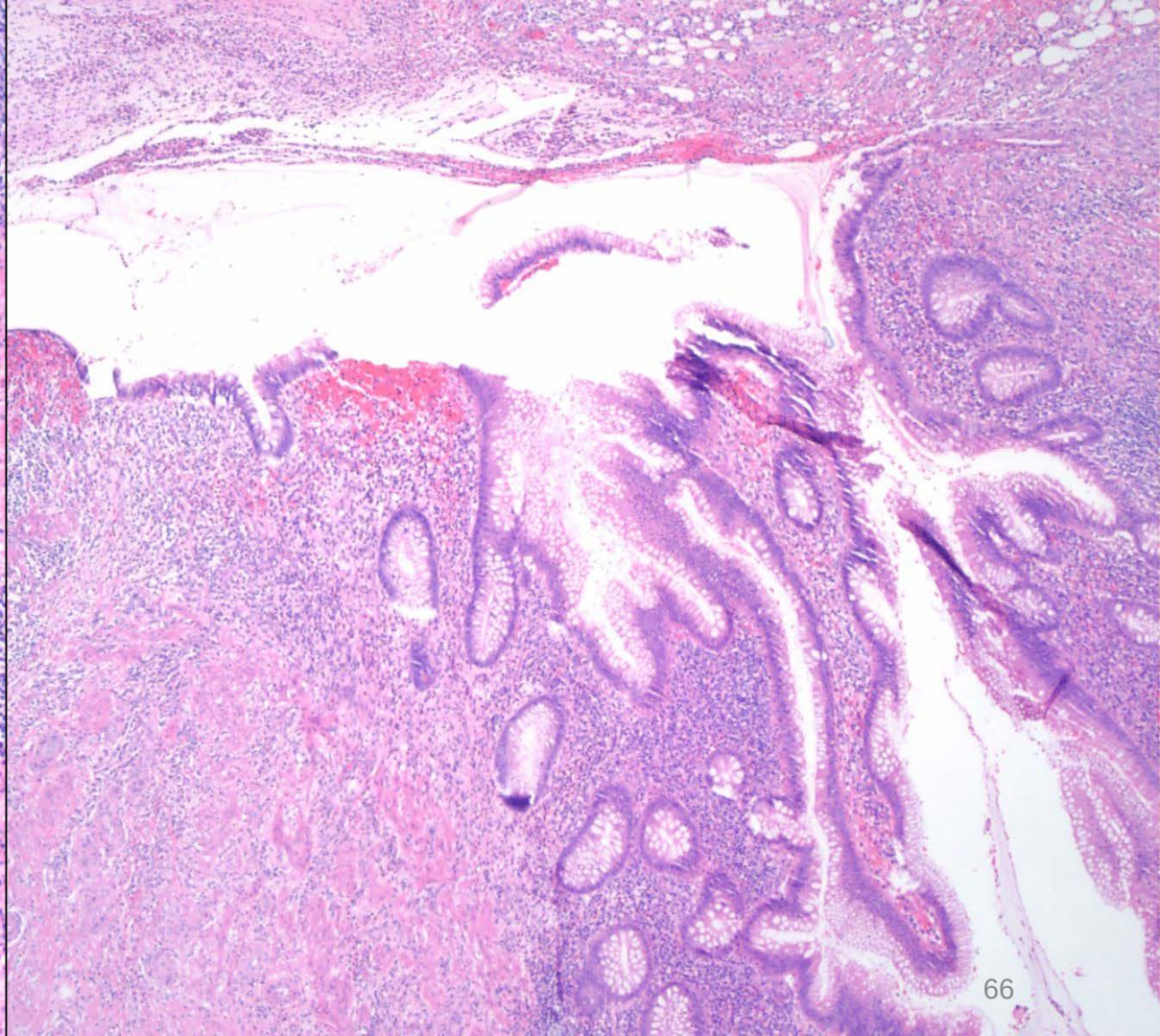
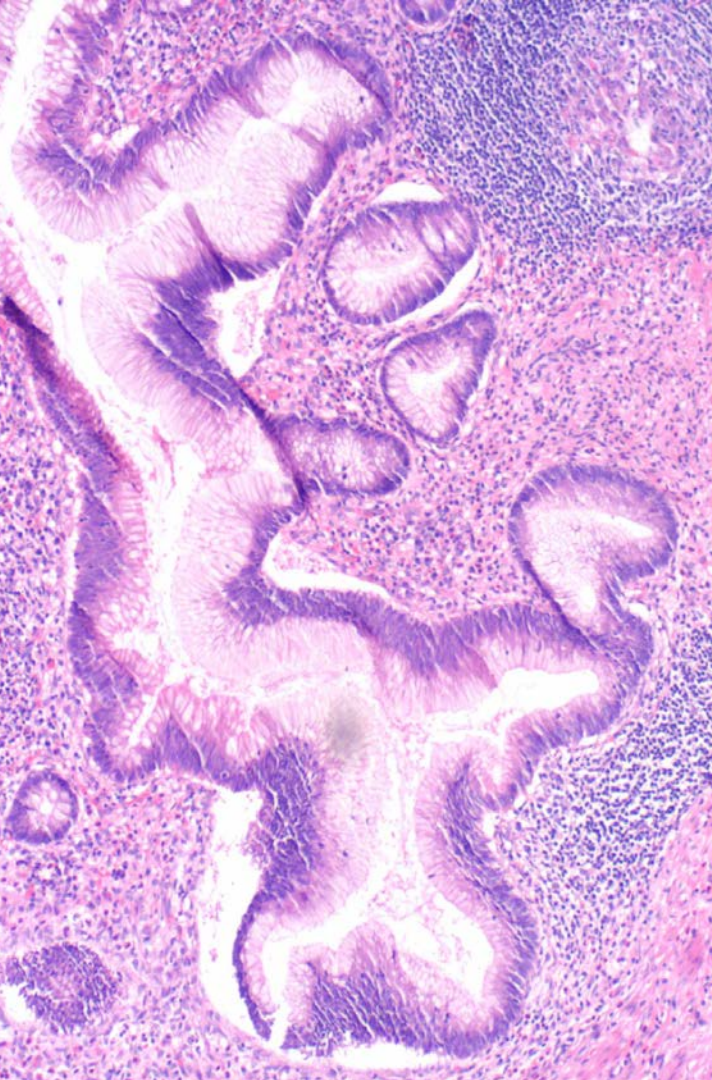
Endometriosis with intestinal metaplasia





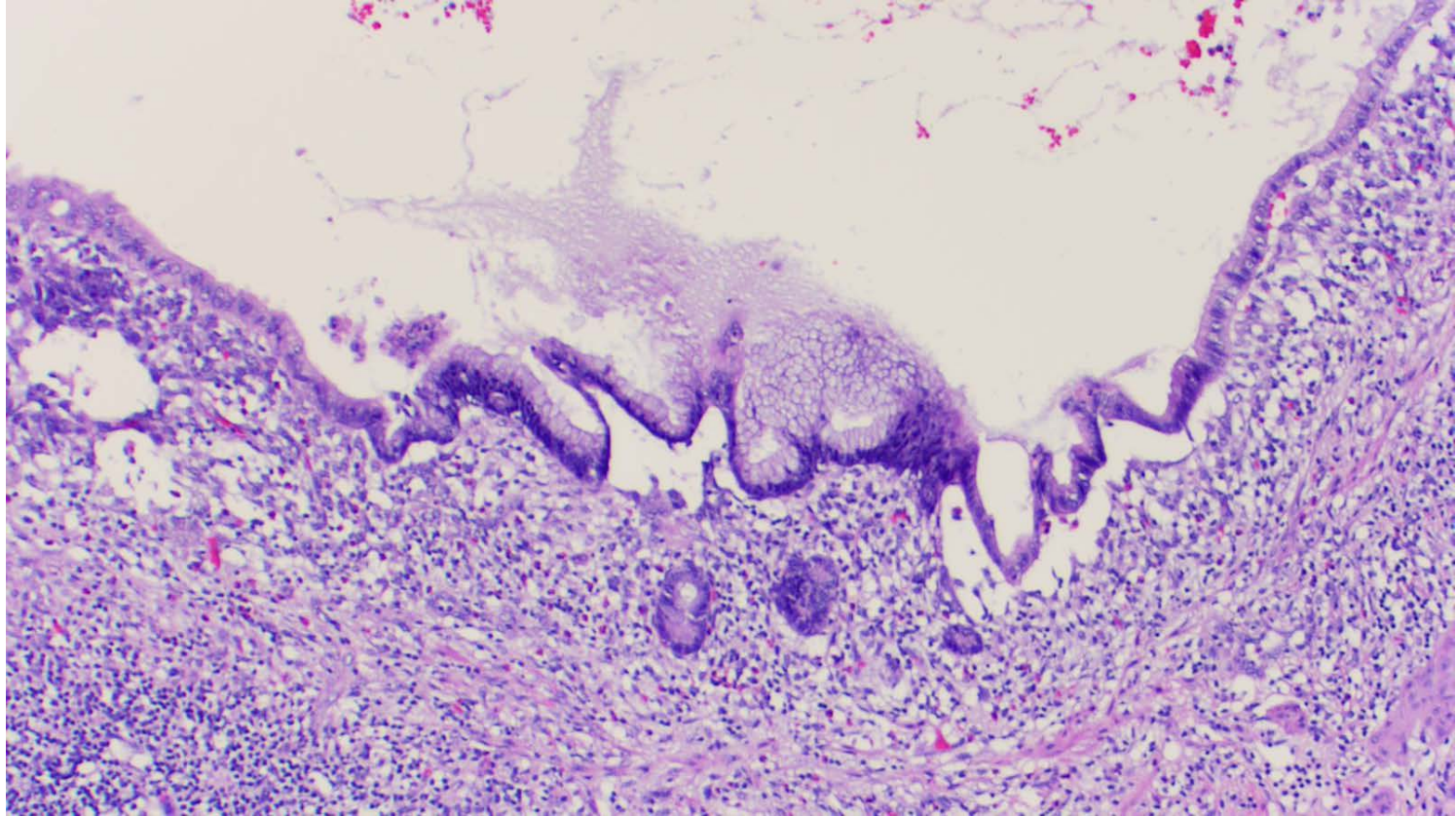




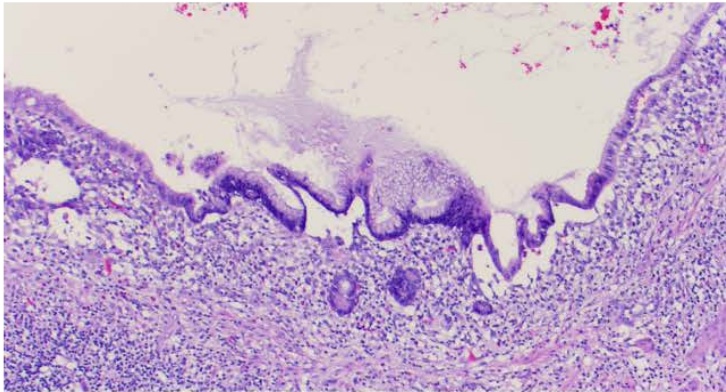




Q: A dilated appendix is lined by epithelium below.



What is your diagnosis?



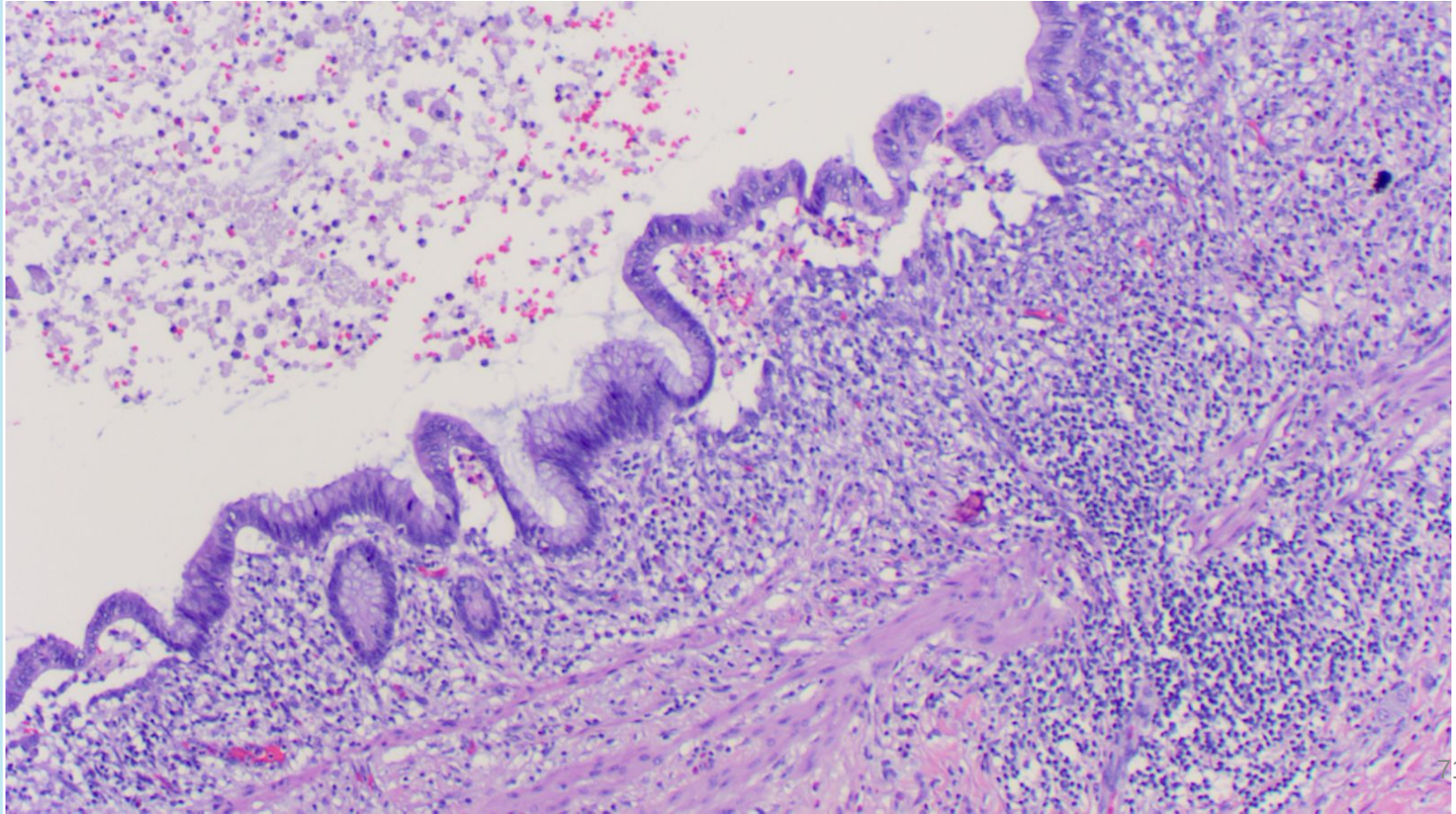
A. LAMN

B. HAMN

C. Retention
mucocele

D. Sessile
serrated lesion

C. Retention mucocele



Goblet cell adenocarcinoma (Formerly goblet cell carcinoid)

Appendiceal tumor with mucinous and neuroendocrine differentiation

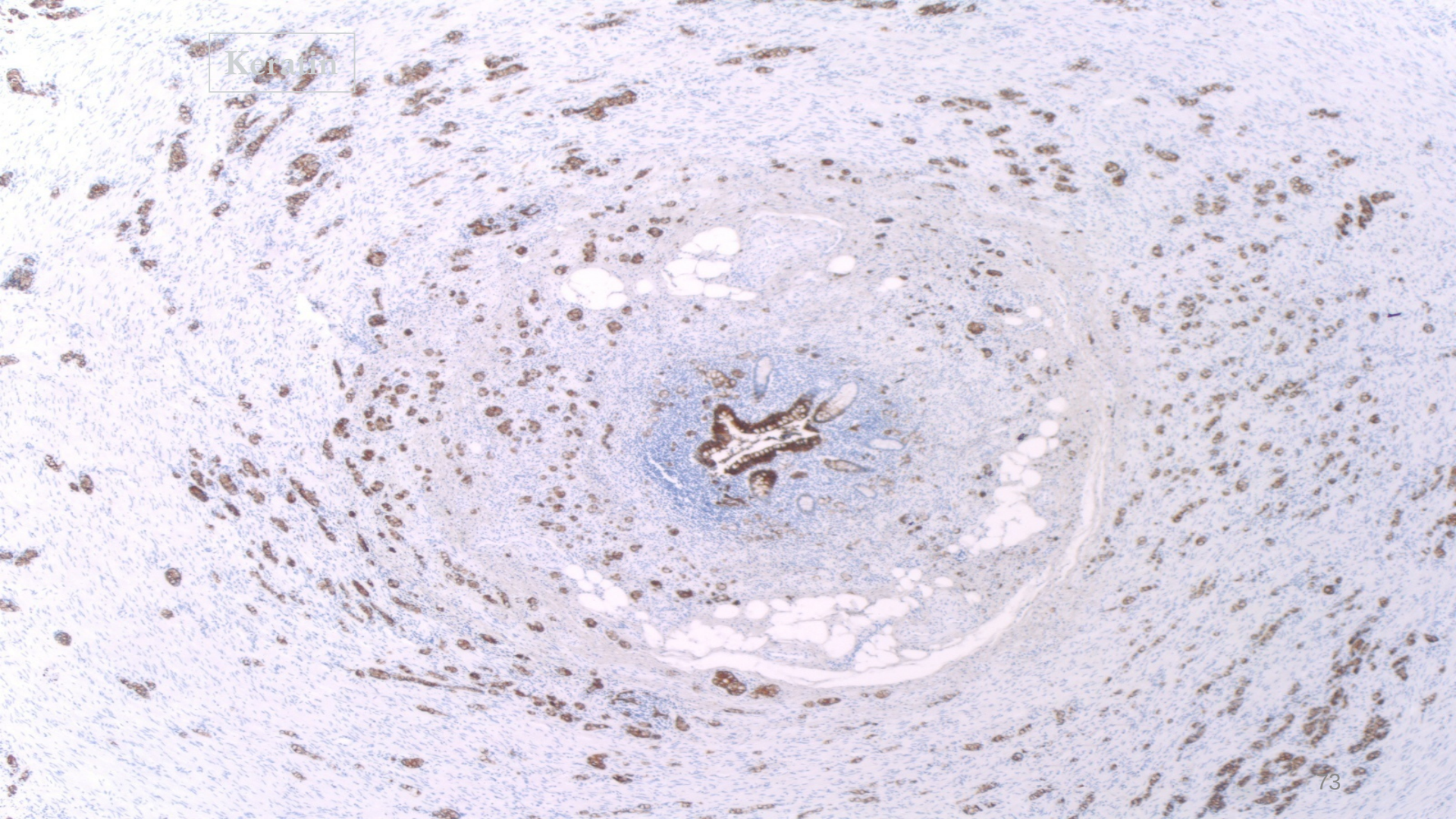
M = F; average 40s

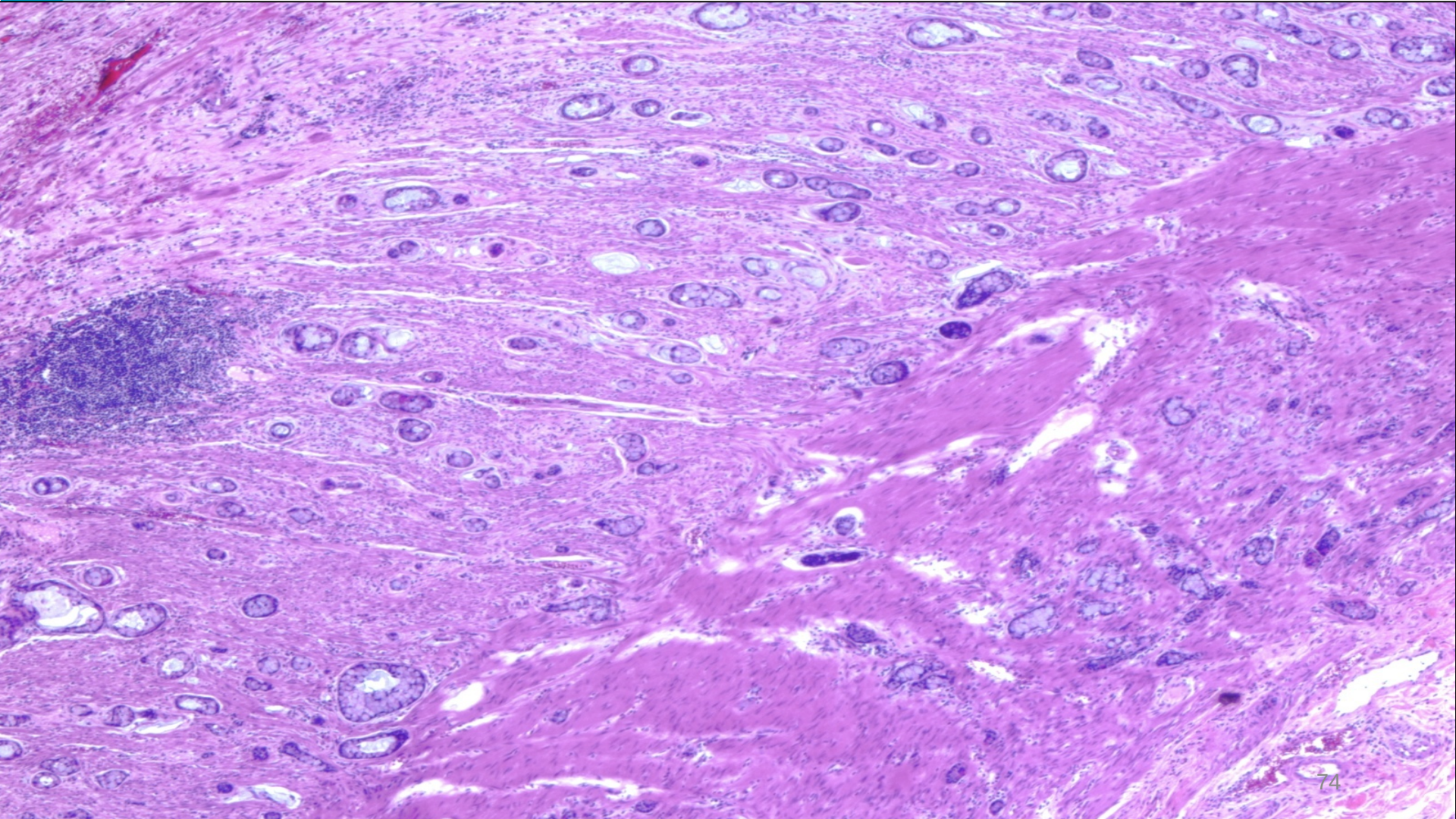
Present with appendicitis, incidentally, or as ovarian metastases
("Krukenberg")

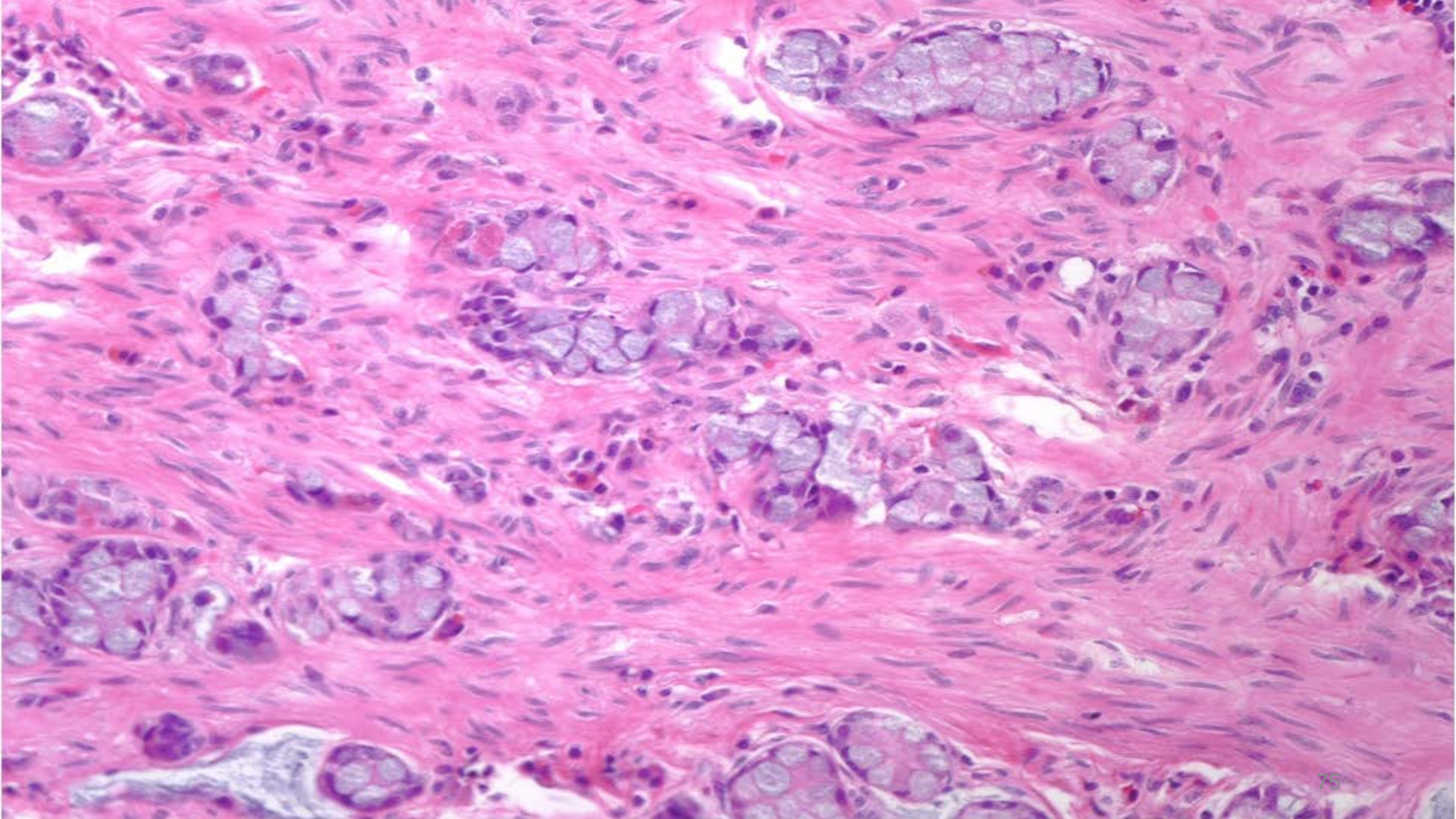
Grossly, normal-appearing or somewhat thickened appendix

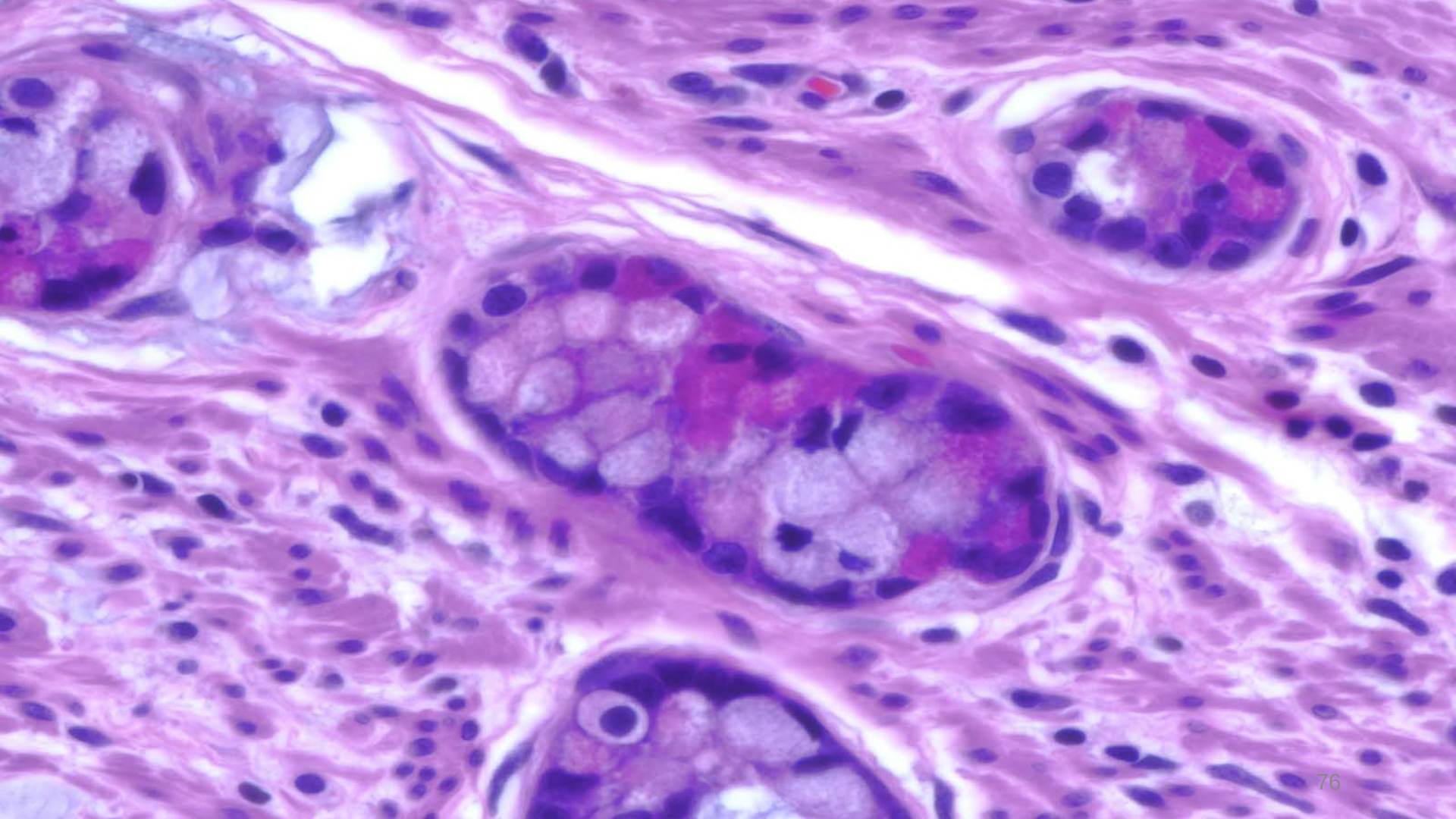
- Size difficult to determine in many cases
- Proximal margin must be identified

Keratin

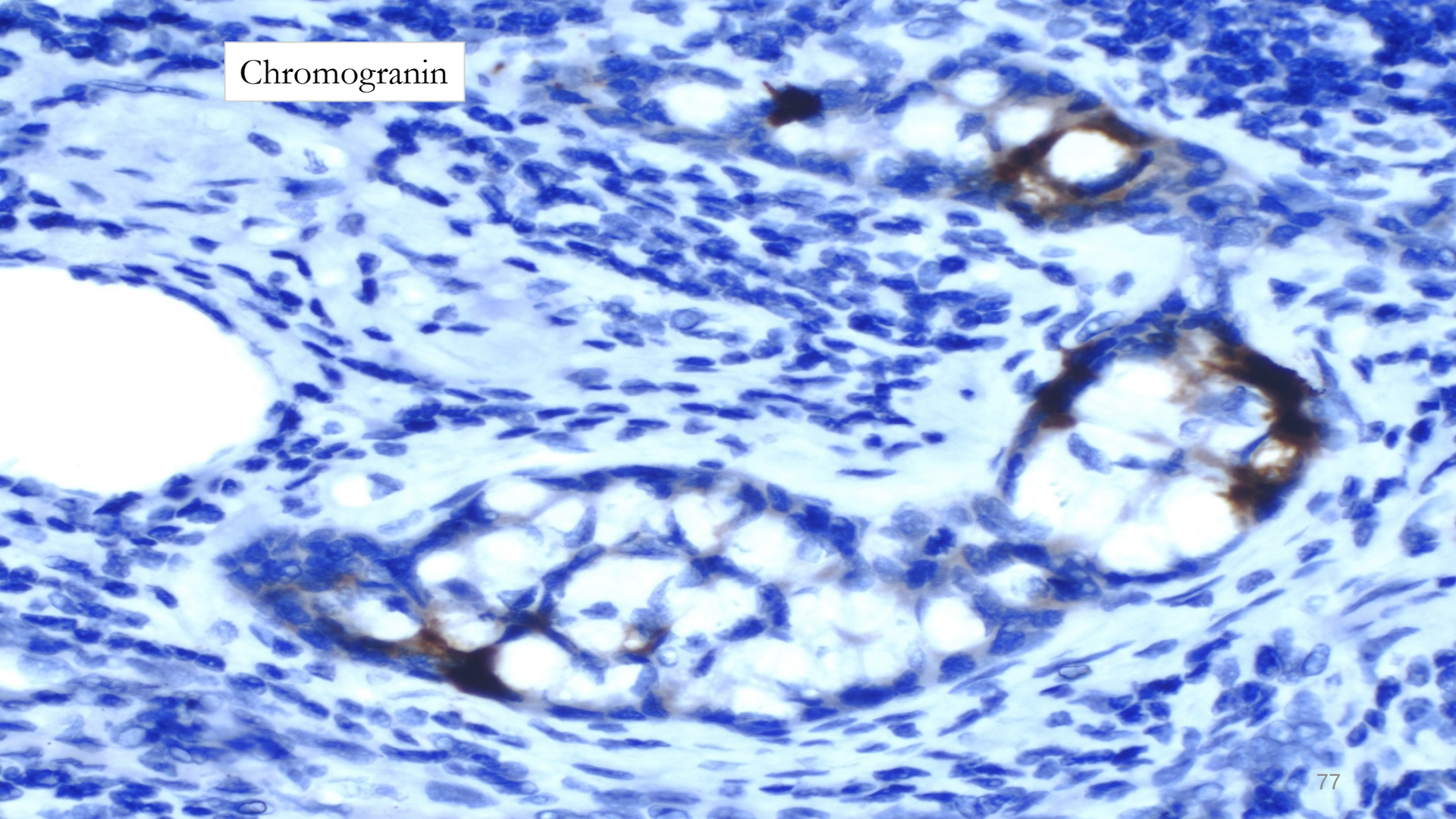


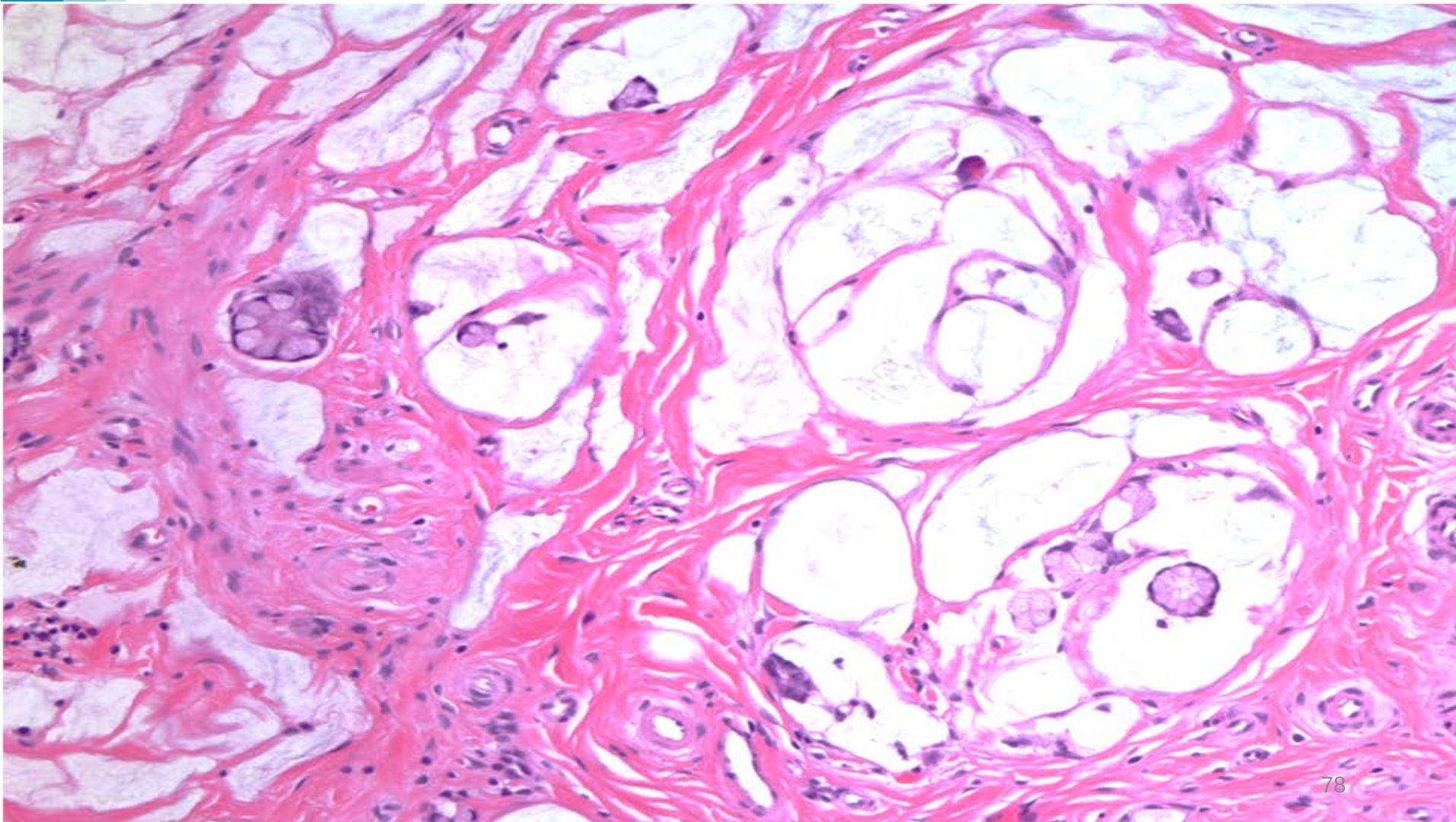






Chromogranin





Goblet cell carcinoids and related tumors of the appendix

Burke. Am J Clin Pathol 1990;94:27-35.

Developed a grading system that is based on identifying carcinomatous growth patterns

Carcinomatous growth patterns

- Fused or cribriform glands
- Single file structures
- Diffusely infiltrating signet ring cells
- Sheets of tumor cells
- Compressed goblet cell nests with little or no stroma
- Extracellular mucin pools harboring epithelium demonstrating gland fusion or the absence of lumens

Goblet cell carcinoid vs. Mixed carcinoid-adenocarcinoma

- ▶ < 25% carcinomatous growth: Goblet cell carcinoid
 - Confined to the appendix
 - Benign behavior
- ▶ > 50% carcinomatous growth: Mixed carcinoid-adenocarcinoma
 - Highly likely to have spread beyond the appendix
 - Aggressive biology

Pathologic Classification and Clinical Behavior of the Spectrum of Goblet Cell Carcinoid Tumors of the Appendix

Tang LH, et al. AJSP 2008

Classification of tumors with at least focal GCC

Goblet cell carcinoid

Adenocarcinoma ex GCC, signet ring cell type

Adenocarcinoma ex GCC, poorly differentiated adenocarcinoma type

Pathologic Classification and Clinical Behavior of the Spectrum of Goblet Cell Carcinoid Tumors of the Appendix

Tang LH, et al. AJSP 2008

Goblet cell carcinoid

Adenocarcinoma ex GCC, signet ring cell type.

- **Partial or nearly complete loss of goblet cell clustered architecture.**
- Signet cells as single cells, irregular clusters, or disordered arrangements but not sheets.
- Cytologic atypia.

Pathologic Classification and Clinical Behavior of the Spectrum of Goblet Cell Carcinoid Tumors of the Appendix

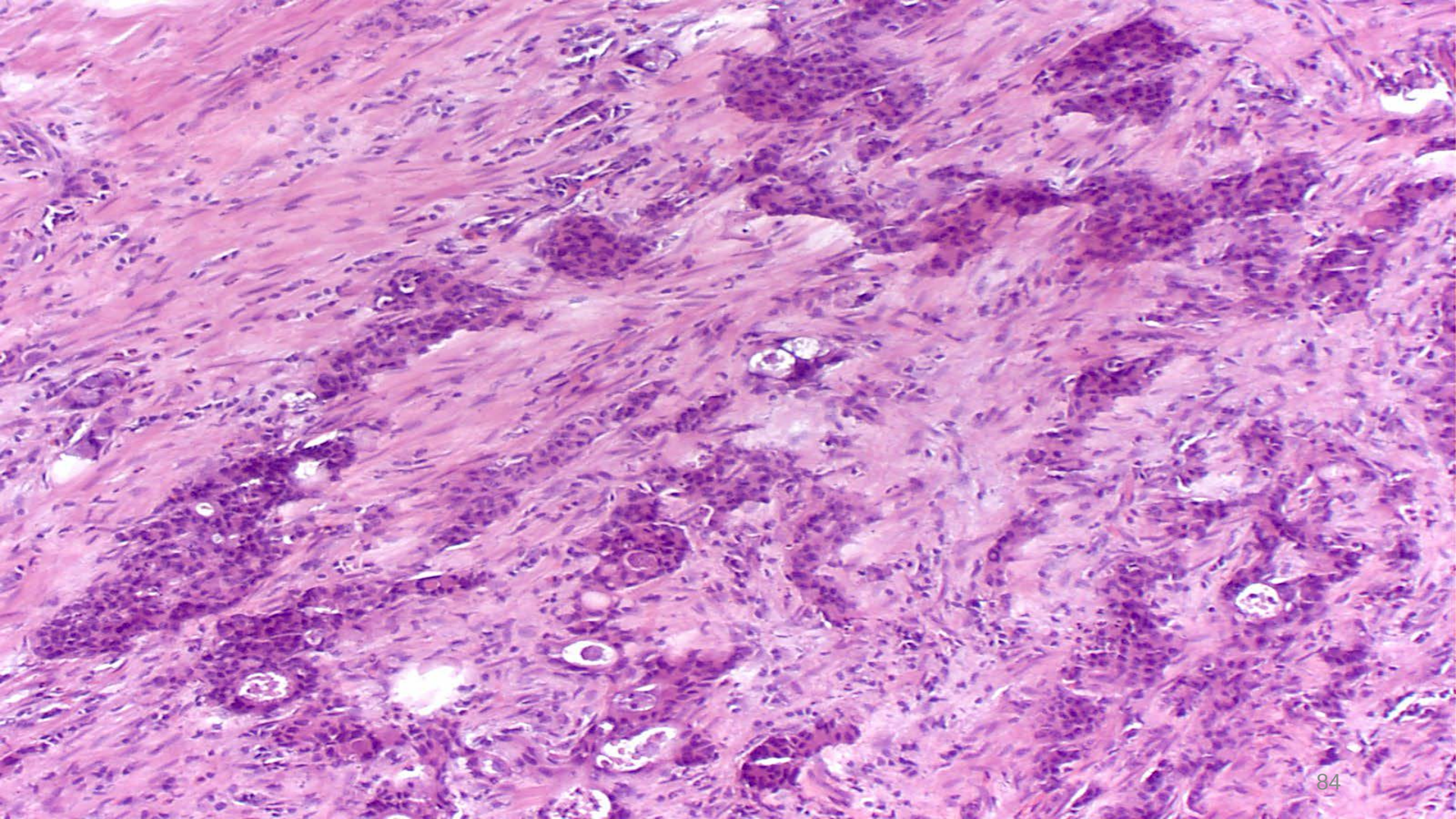
Tang LH, et al. AJSP Oct 2008

Goblet cell carcinoid

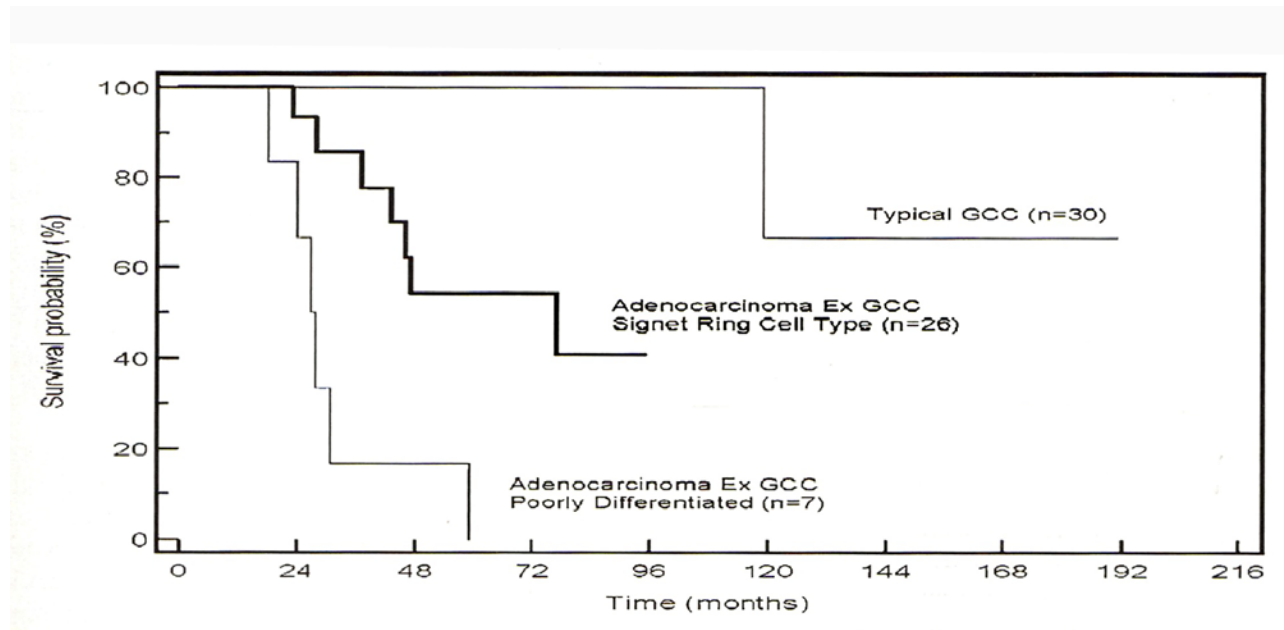
Adenocarcinoma ex GCC, signet ring cell type

Adenocarcinoma ex GCC, poorly differentiated adenocarcinoma type

- At least 1 low power field or 1 mm² indistinguishable from poorly differentiated gland forming adenocarcinoma, signet ring cell adenocarcinoma, neuroendocrine carcinoma, or undifferentiated carcinoma.



Pathologic Classification Correlated with Outcome



GCC, Mixed GCC-Adenocarcinoma, and Adenocarcinoma of the Appendix

Taggart et al. Arch Pathol Lab Med 2015;139:782-790

Burke: 142 tumors classified by the proportion of adenocarcinoma (< 25%, 25-50%, > 50%, pure adenocarcinoma)

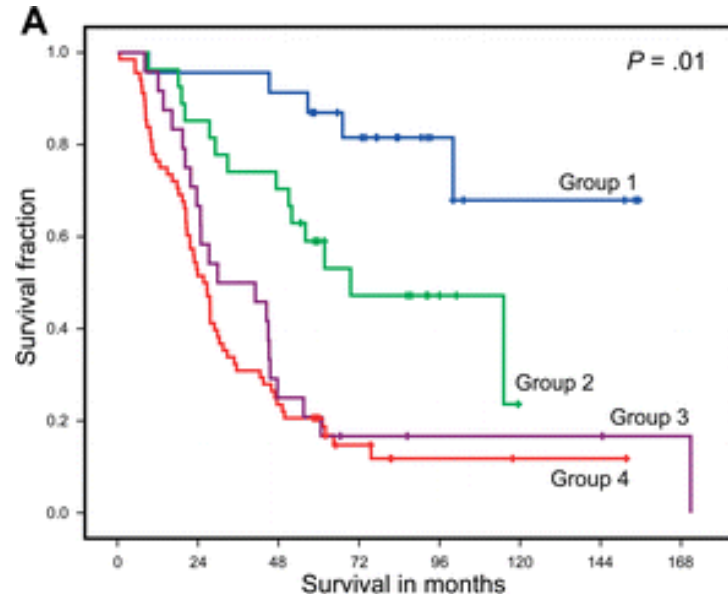
Tang: Adenocarcinoma component classified as either signet ring cell or non-signet ring cell type

GCC, Mixed GCC-Adenocarcinoma, and Adenocarcinoma of the Appendix

Taggart et al. Arch Pathol Lab Med 2015;139:782-790

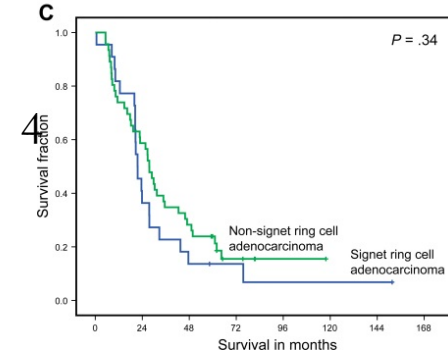
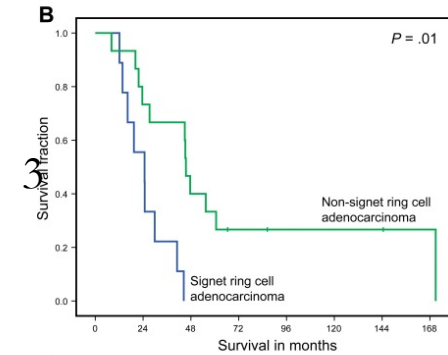
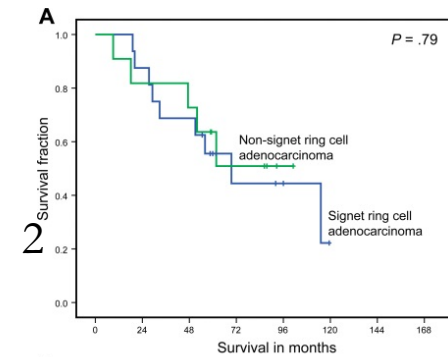
Intermediate group (25-50%)
does somewhat better than > 50%

Once a tumor is >50% adenocarcinoma (group 3), it will behave like a pure adenocarcinoma (group 4)



GCC, Mixed GCC-Adenocarcinoma,
and Adenocarcinoma of the Appendix
Taggart et al. *Arch Pathol Lab Med*
2015;139:782-790

BUT whether the
adenocarcinoma is signet ring
cell type or non-signet ring cell
type is prognostically irrelevant.



Goblet cell “carcinoid”. Problematic nomenclature, problematic grading schemes.

The term “carcinoid” results in pathologists using neuroendocrine staging systems and oncologists considering therapies for endocrine tumors.

“Adenocarcinoma ex GCC” implies that an adenocarcinoma evolves from an endocrine tumor, which is untrue.

Inconsistent terminology for difficult tumors, and only moderate interobserver agreement using Tang system.

Mutational studies have shown that these tumors have a profile distinct from carcinoids and usual adenocarcinomas, indicating that they are a separate entity with a spectrum of grades.

Histologic and Outcome Study Supports Reclassifying Appendiceal Goblet Cell Carcinoids as Goblet Cell Adenocarcinomas, and Grading and Staging Similarly to Colonic Adenocarcinomas

Yozu M, Johncilla ME, Srivastava A, Ryan DP, Cusack JC, Doyle L, Setia N, Yang M, Lauwers GY, Odze RD, Misdraji J.

Am J Surg Pathol 2018;42:898-910

126 tumors studied.

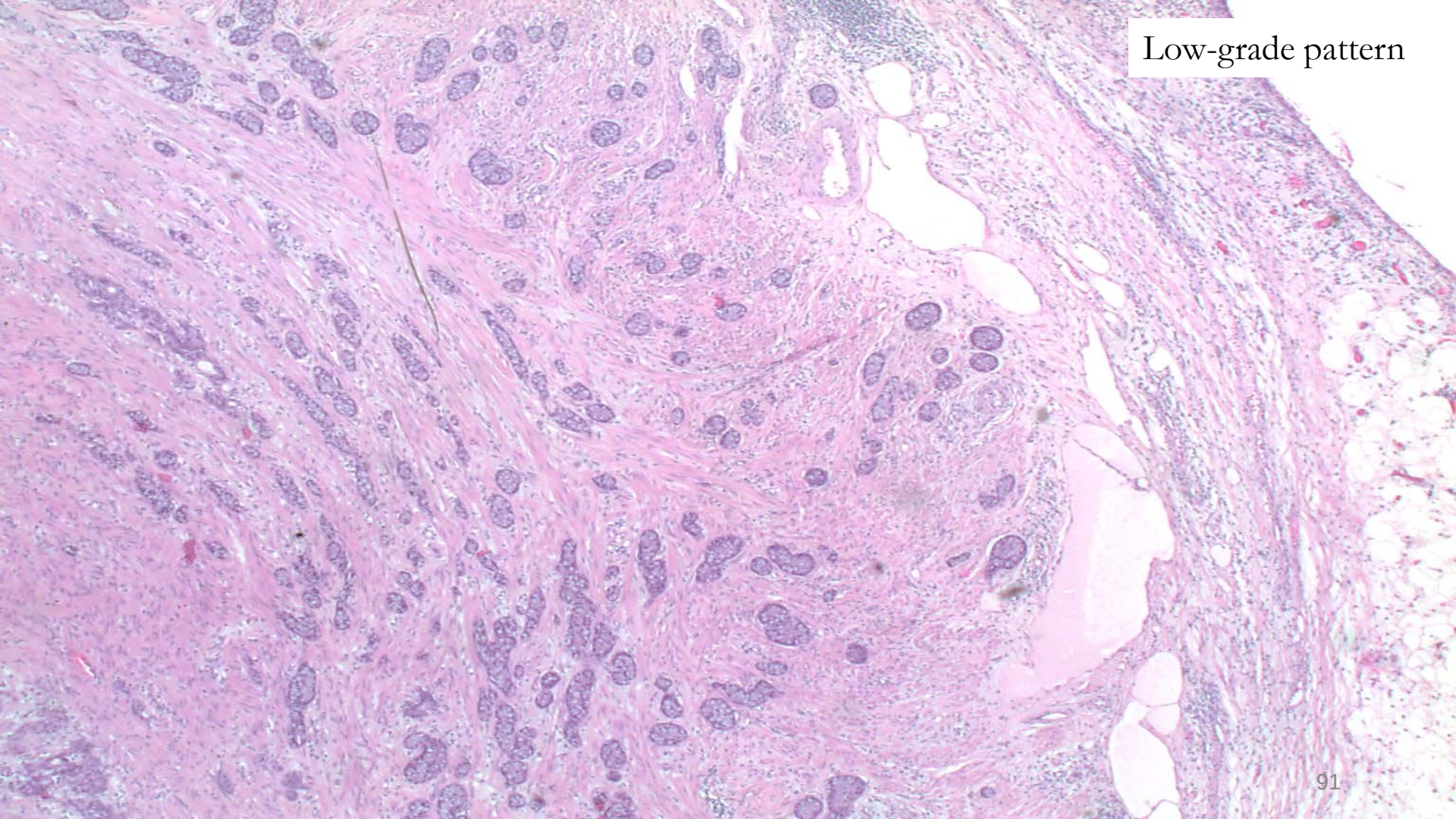
Grading system with parallels in colorectal grading.

- Instead of “% glandular”, use % of tubular/clustered growth.
- Cut off values already established by Burke and Taggart

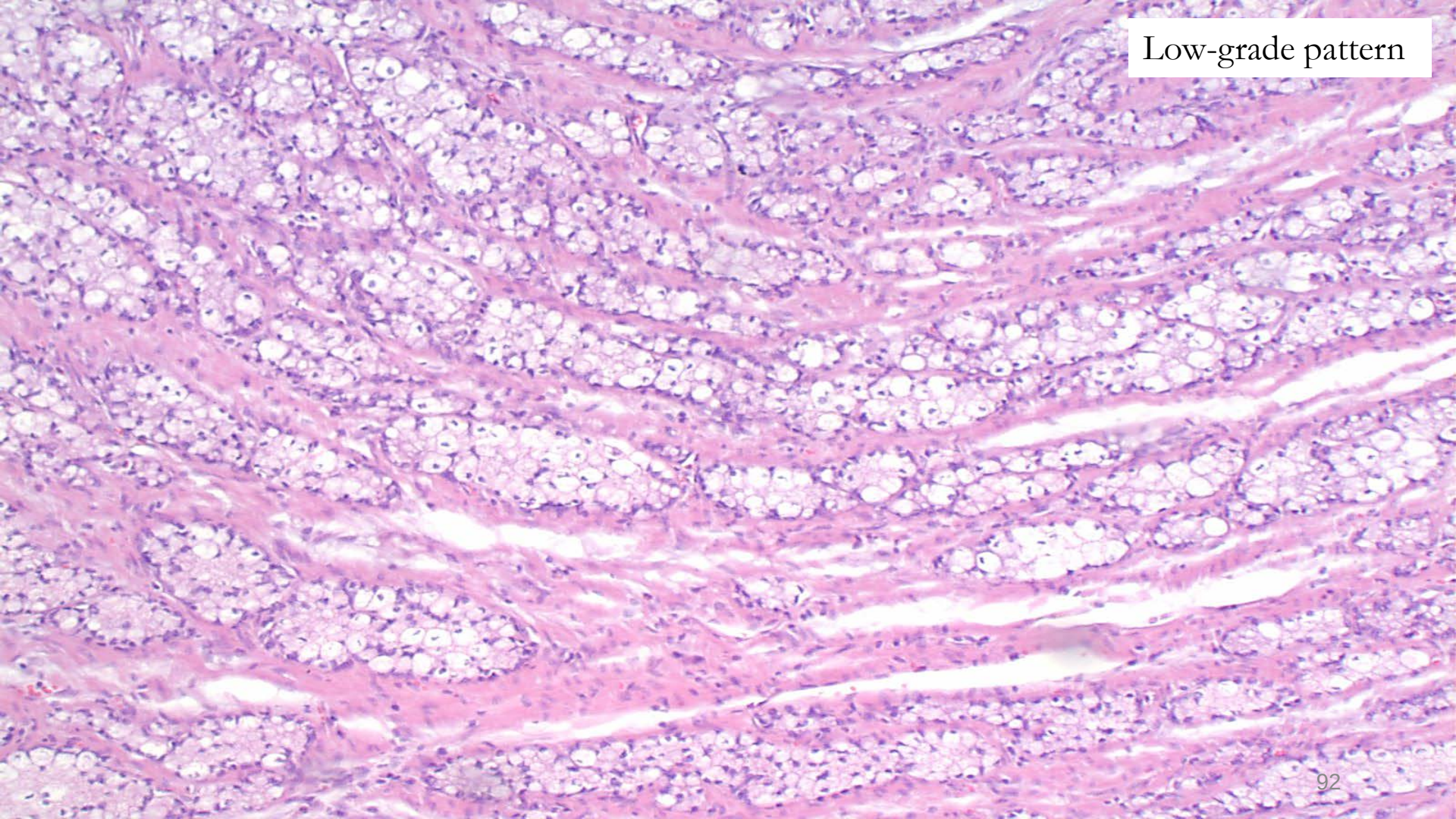
Proposed nomenclature: Goblet cell adenocarcinoma, grade 1-3.

- G1: Tumors > 75 clustered or tubular growth
- G2: Tumors with 50-75% clustered or tubular growth
- G3: Tumors with < 50% tubular or clustered growth.

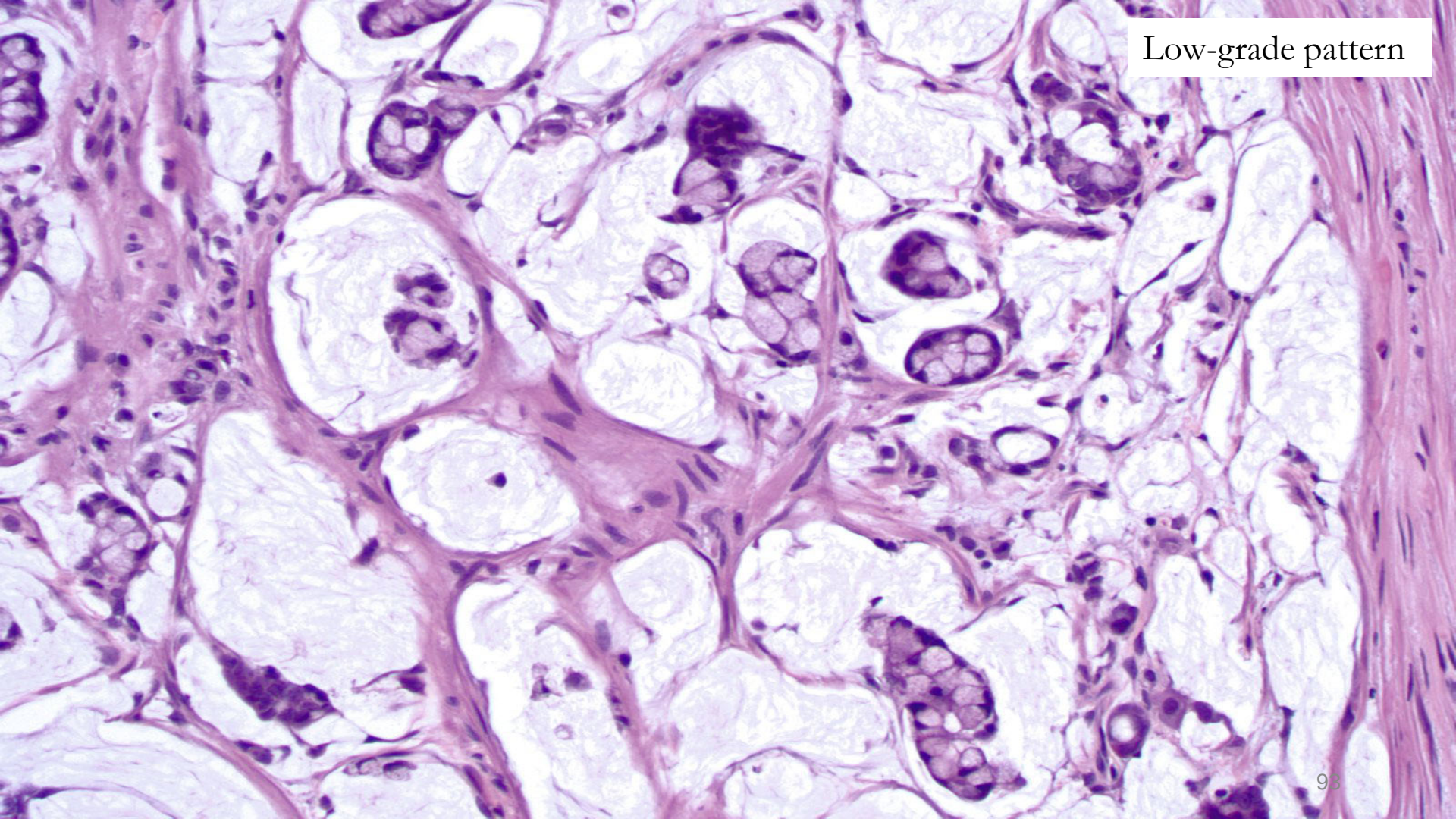
Low-grade pattern



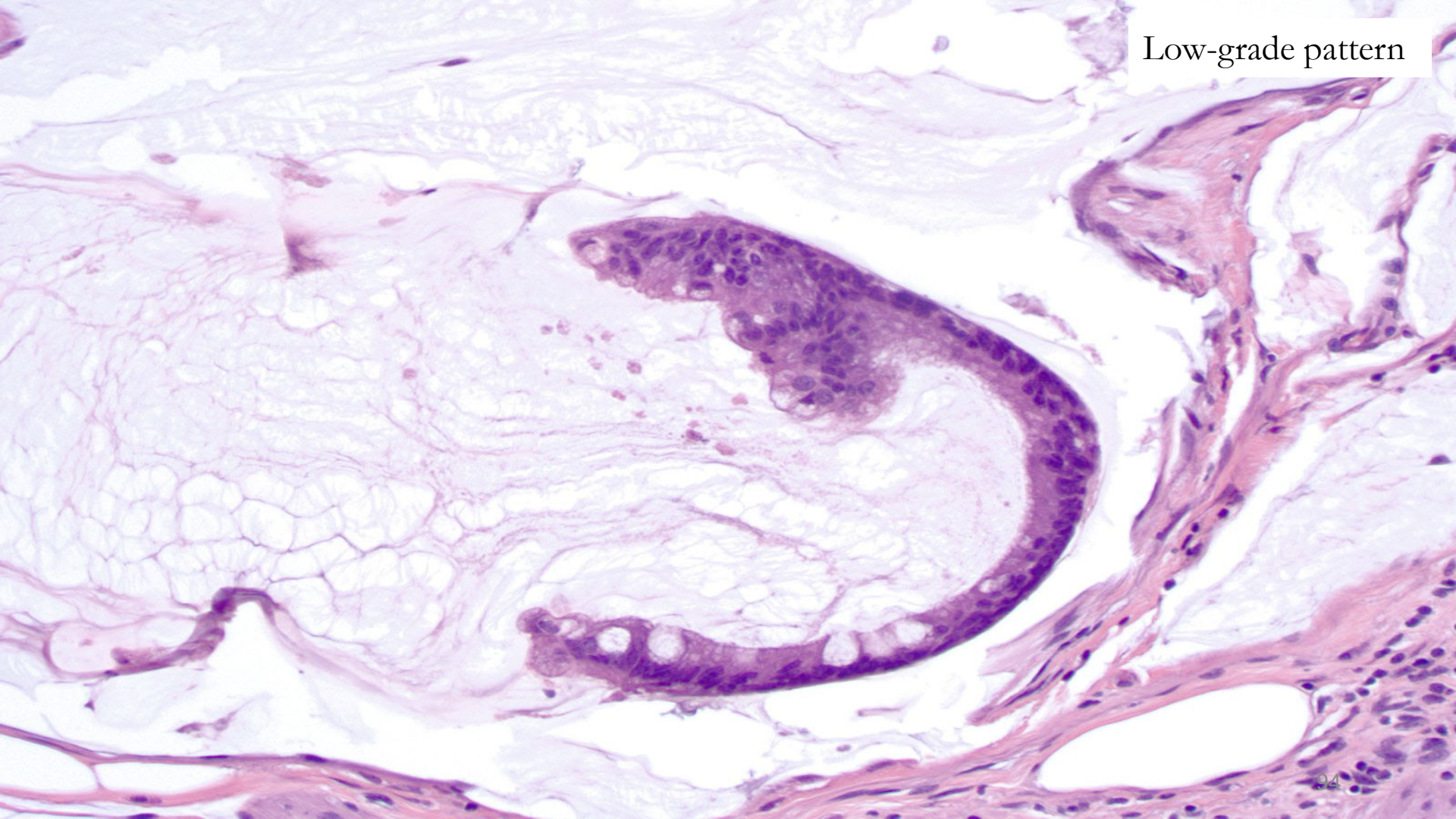
Low-grade pattern



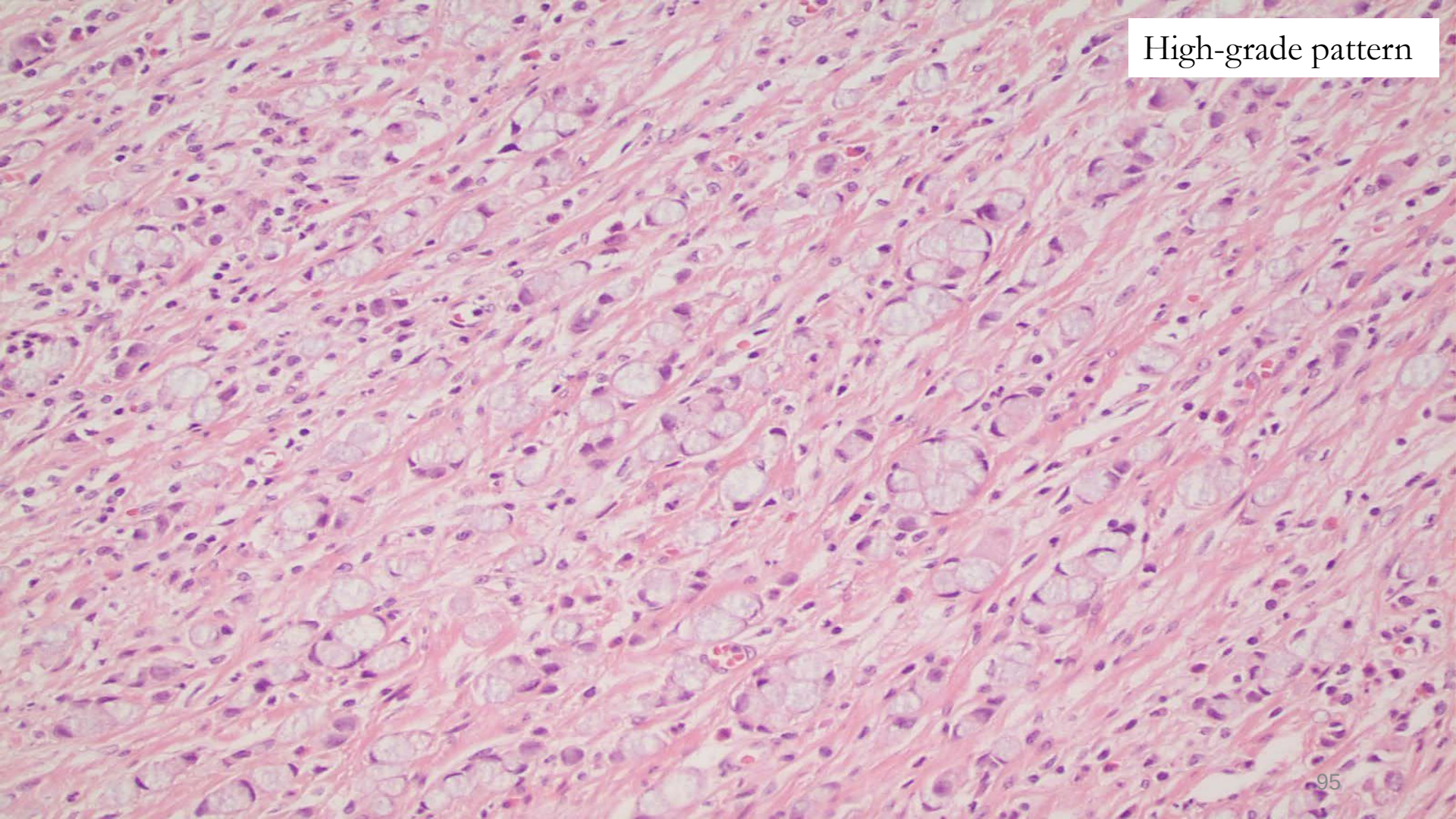
Low-grade pattern



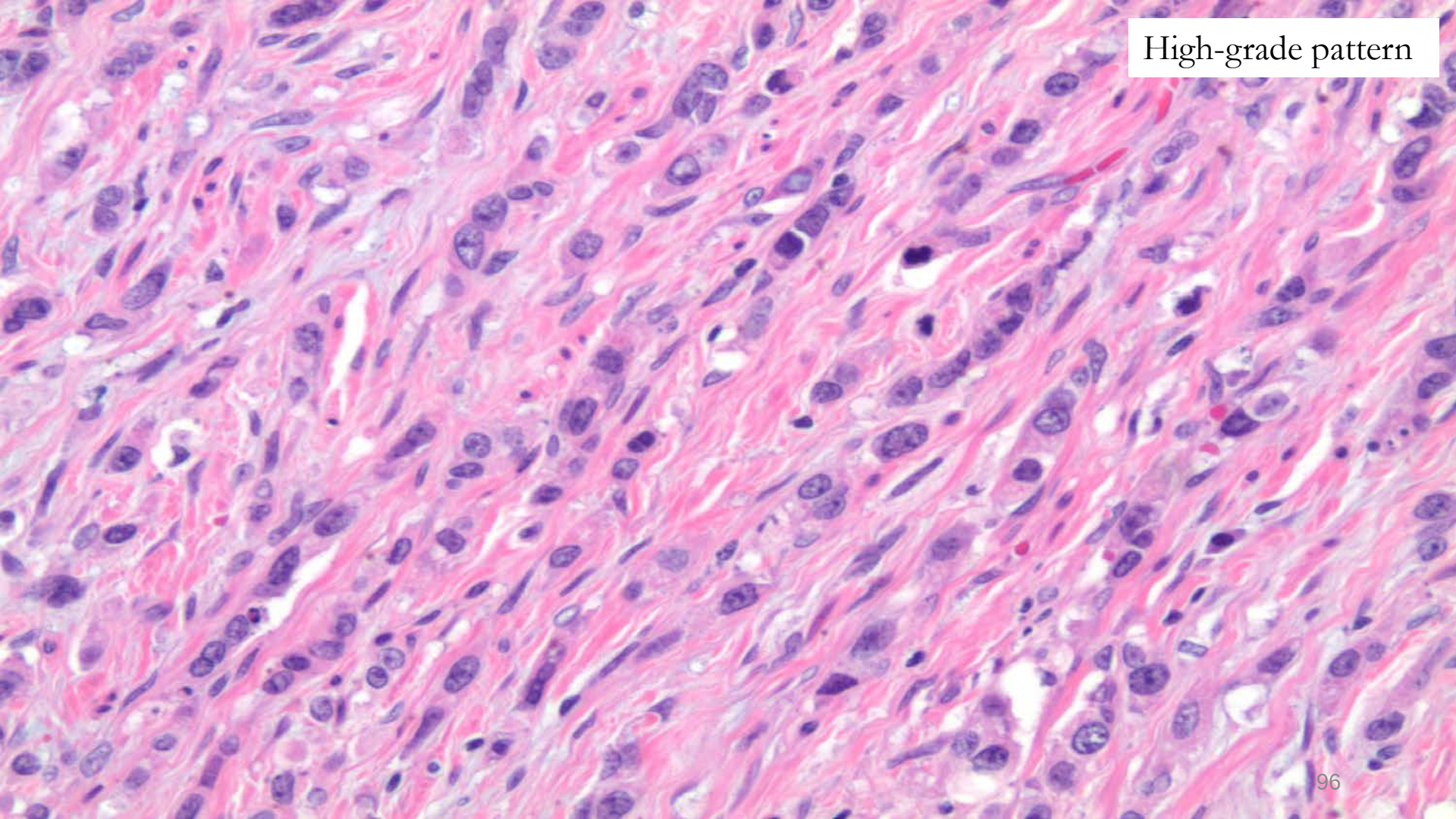
Low-grade pattern



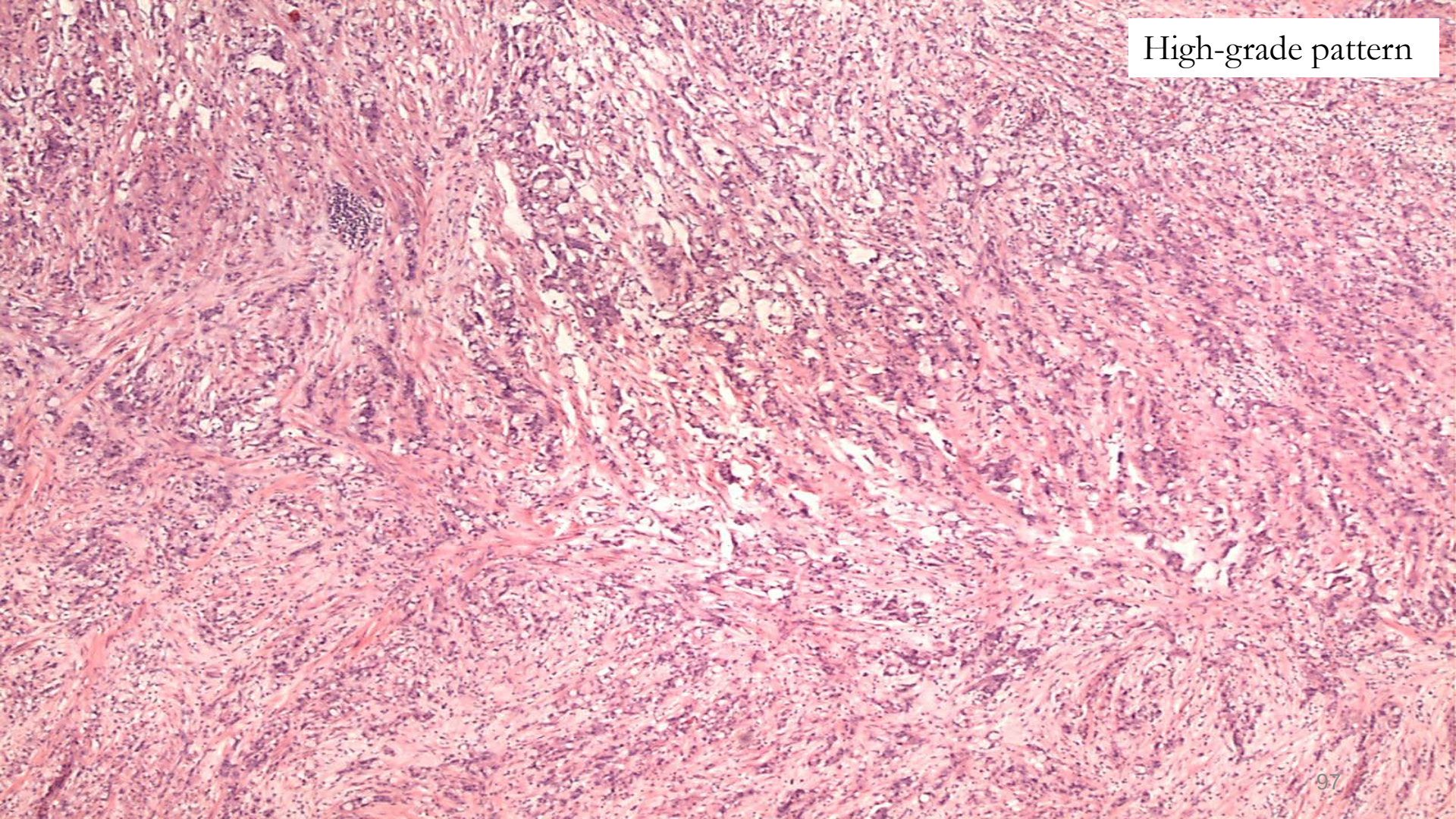
High-grade pattern



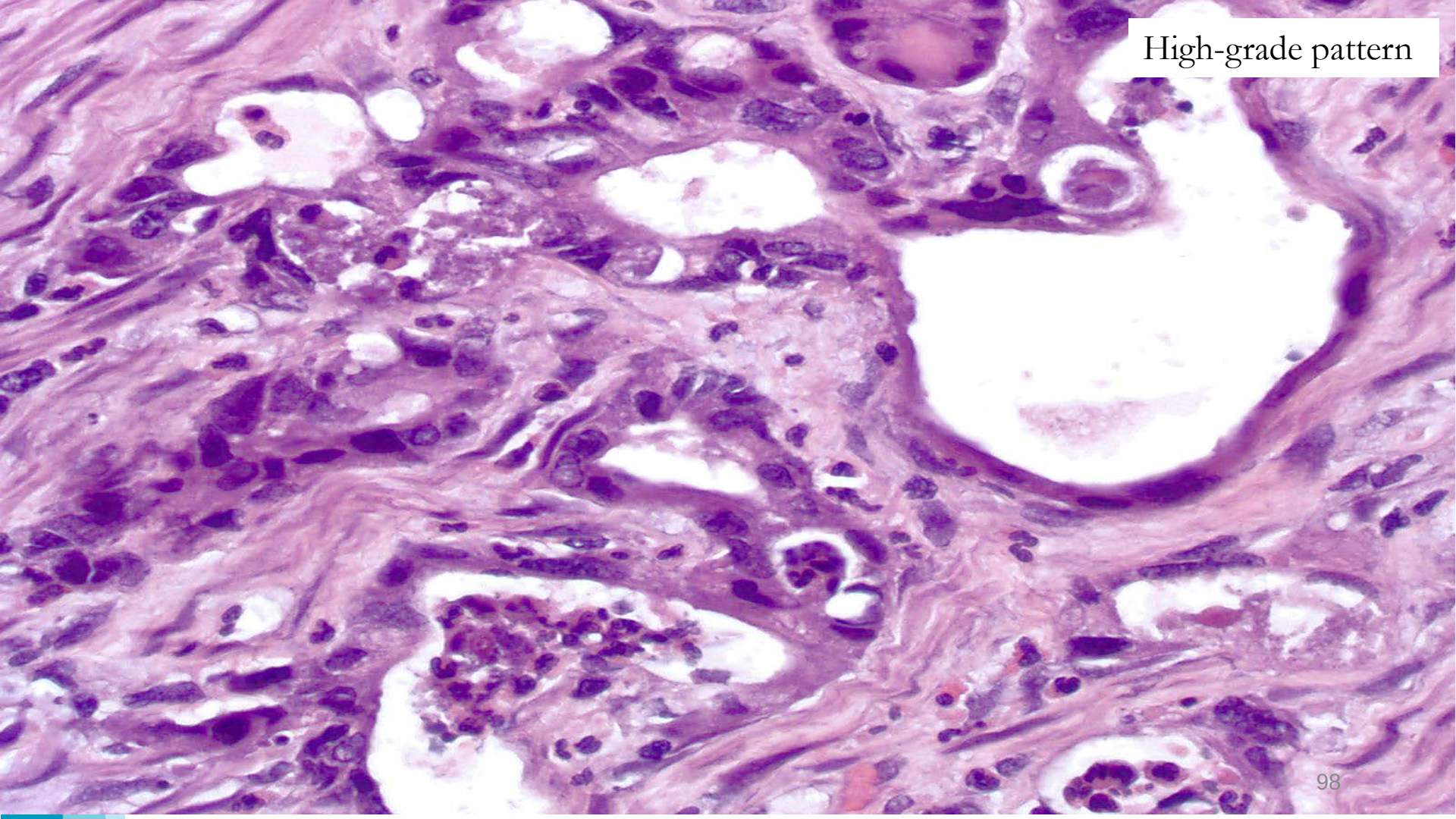
High-grade pattern



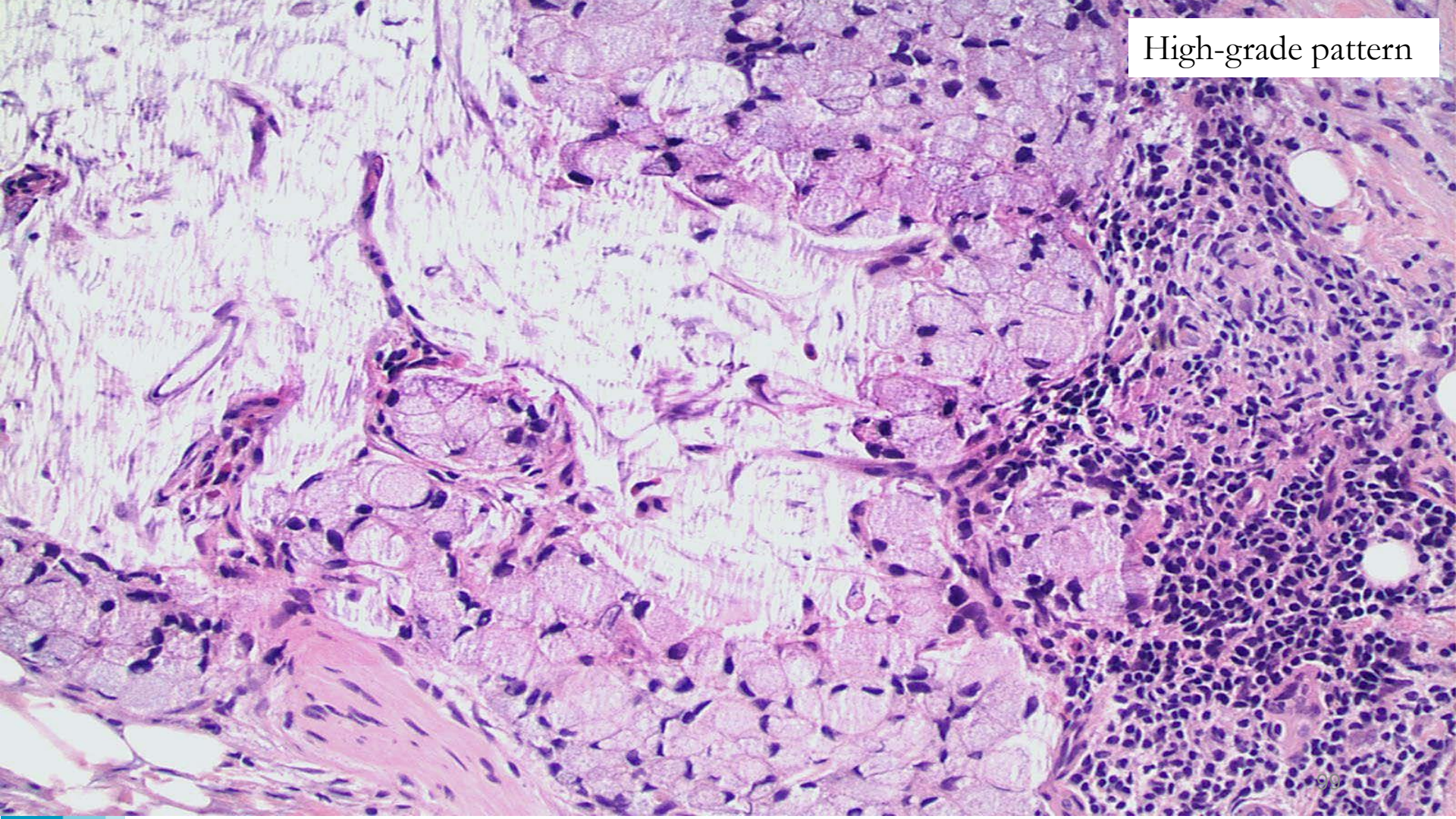
High-grade pattern



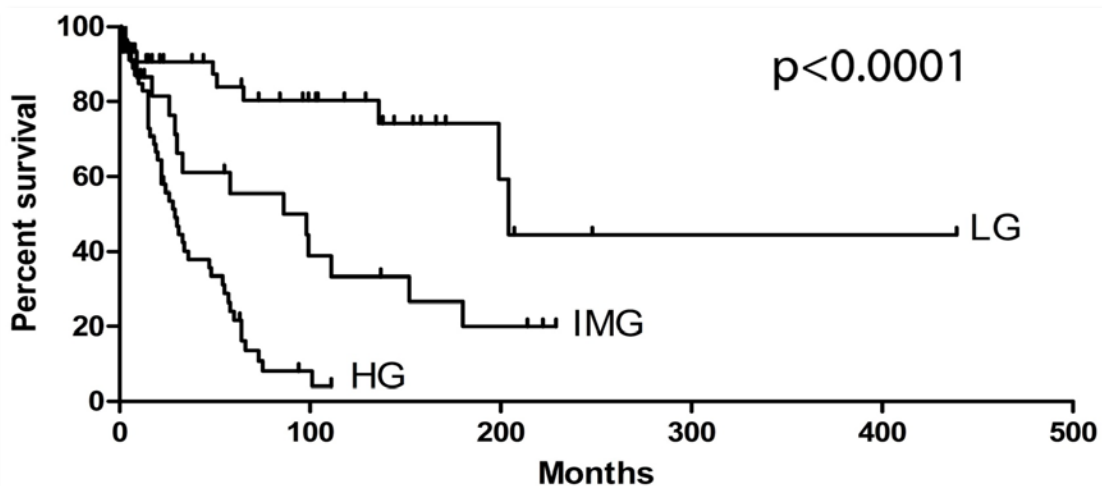
High-grade pattern



High-grade pattern



Overall survival by grade



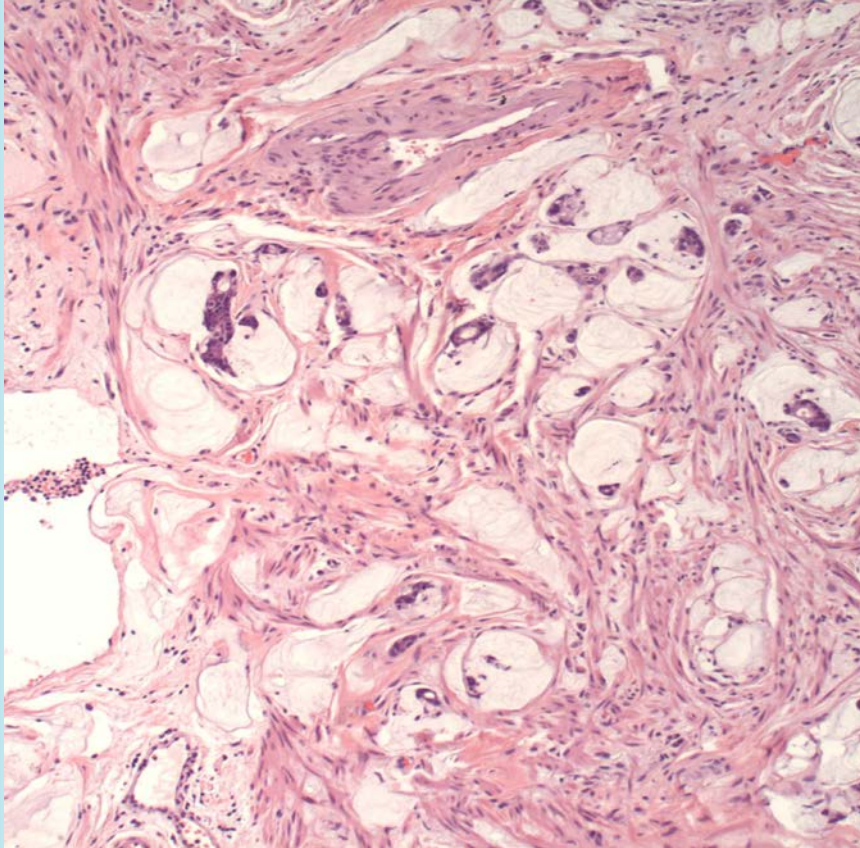
	Median survival (month)	5 year survival (%)	10 year survival (%)
LG (n=45)	204	84	80
IMG (n=23)	86	55	33
HG (n=56)	29	22	4

WHO 5th edition

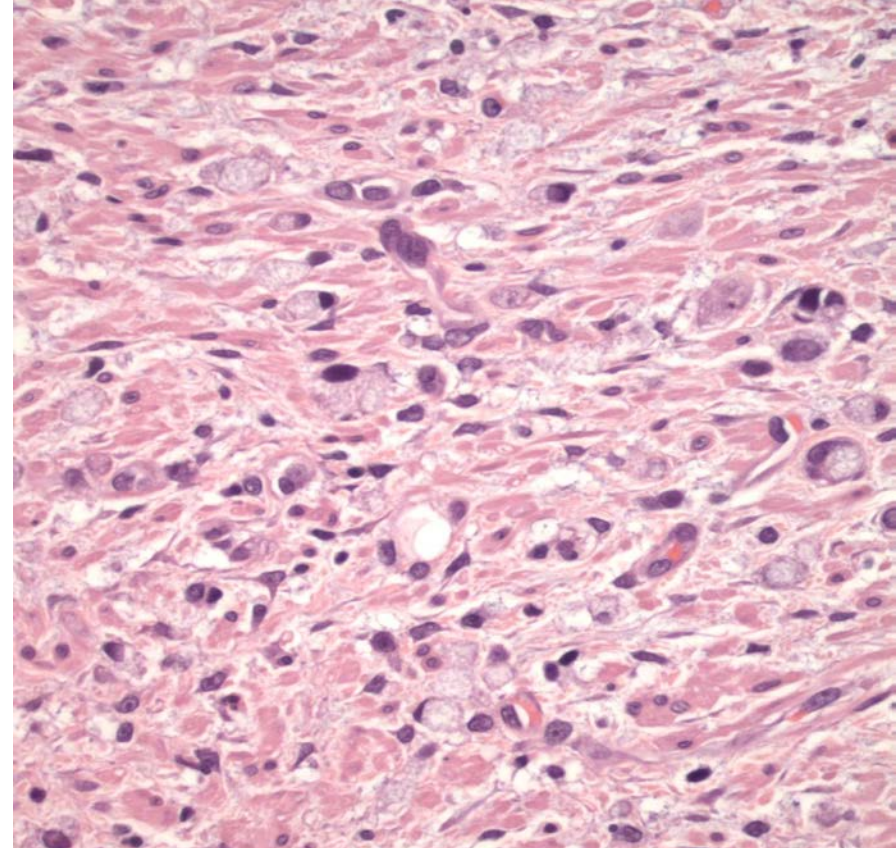
New WHO term	Criteria for grading	Roughly corresponds to
Goblet cell adenocarcinoma, grade 1	➤ 75% low grade patterns ➤ < 25% high grade patterns	Goblet cell carcinoid
Goblet cell adenocarcinoma, grade 2	➤ 50-75% low grade patterns ➤ 25-50% high grade patterns	Adenocarcinoma ex GCC, signet ring cell type
Goblet cell adenocarcinoma, grade 3	➤ < 50% low grade patterns ➤ > 50% high grade patterns	Adenocarcinoma ex GCC, poorly differentiated carcinoma type Mixed carcinoid adenocarcinoma

Q: An appendix tumor has the following appearance

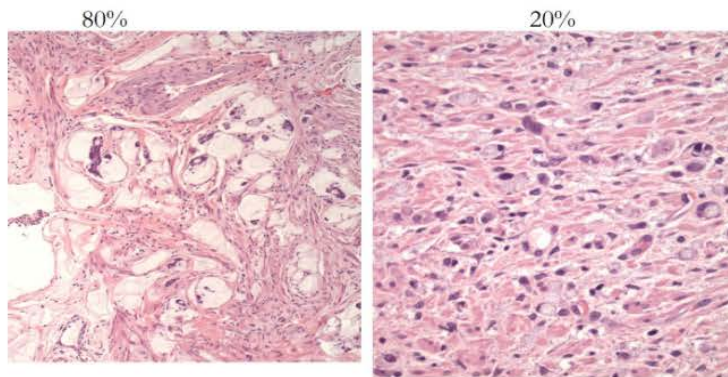
80%



20%



What is your diagnosis?



A. Goblet cell tumor

B. Goblet cell
adenocarcinoma, grade 1

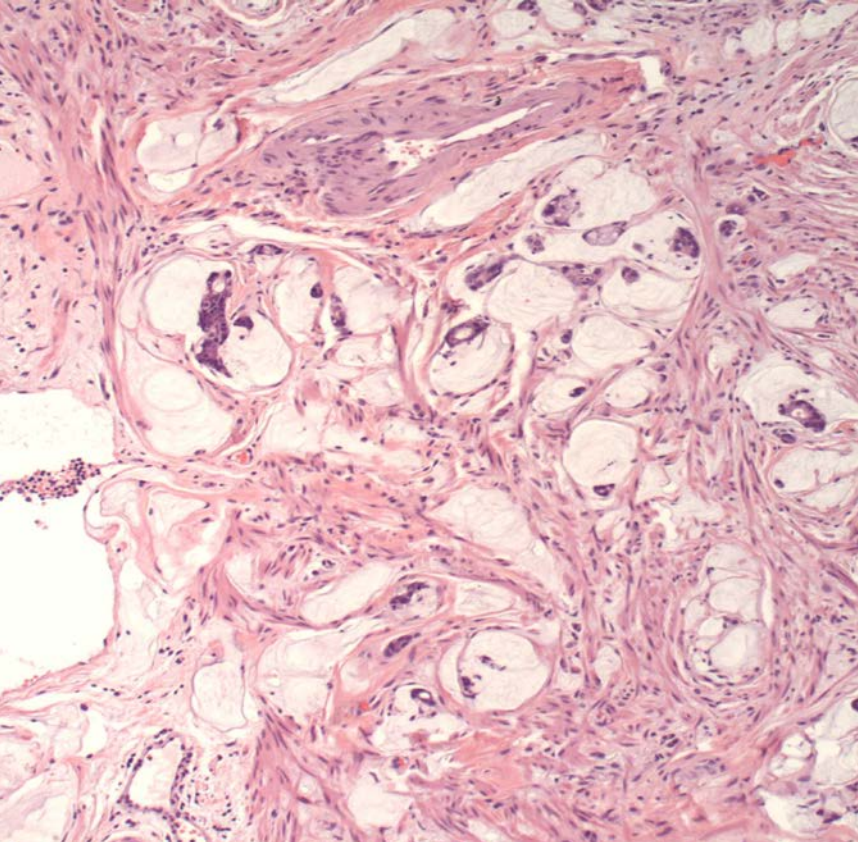
C. Adenocarcinoma ex
goblet cell carcinoid,
signet ring cell type

D. Atypical goblet cell
carcinoid

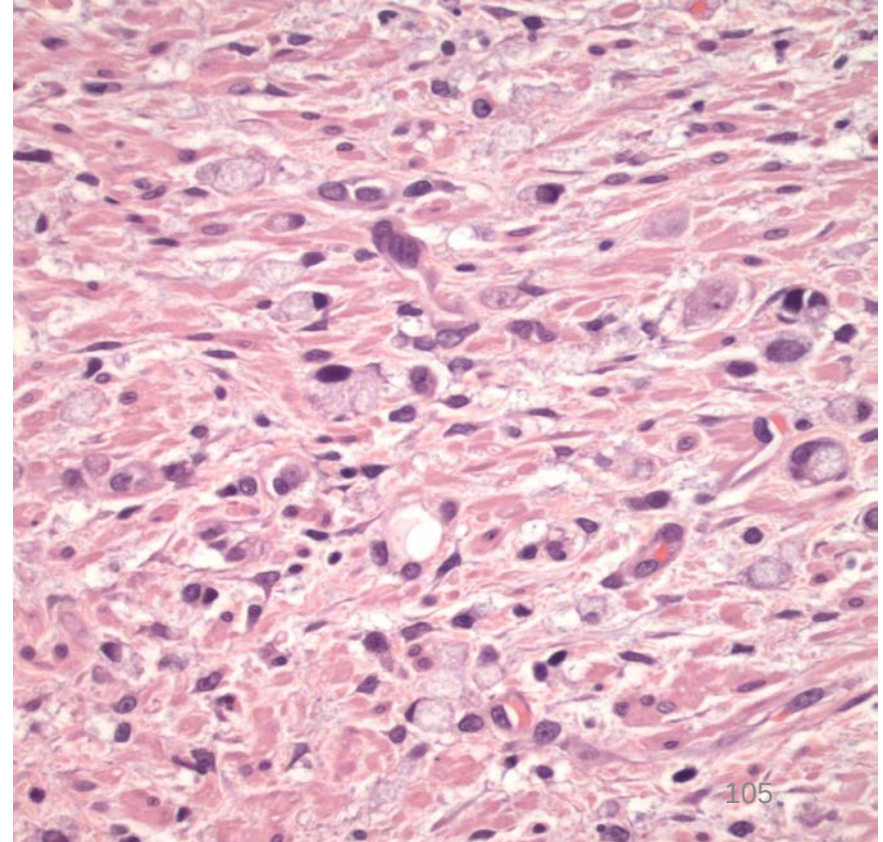
B. Goblet cell adenocarcinoma, grade 1

The “high-grade” component was less than 25% of the tumor

80%



20%



Final thoughts...

When diagnosing goblet cell adenocarcinoma:

- Most tumors that are confined to the appendix at diagnosis will be grade 1.
 - Don't upgrade tumors because of small areas of disorganization.
- In the transition period, educate surgeons and oncologists that GCA grade 1 is formerly known as goblet cell carcinoid.
 - They will not be used to a diagnosis of “adenocarcinoma” for low-grade tumors and will be inclined to over-treat.
 - Use multiple terms in the note of the report and consider contacting them before issuing a report.



Before you go...

Complete the online evaluation!

Take less than 3 minutes to
provide your feedback and help
shape the next annual meeting!

https://www.surveymonkey.com/r/CAP19_S1921C

Thank You





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