Appendiceal Tumors: An Update

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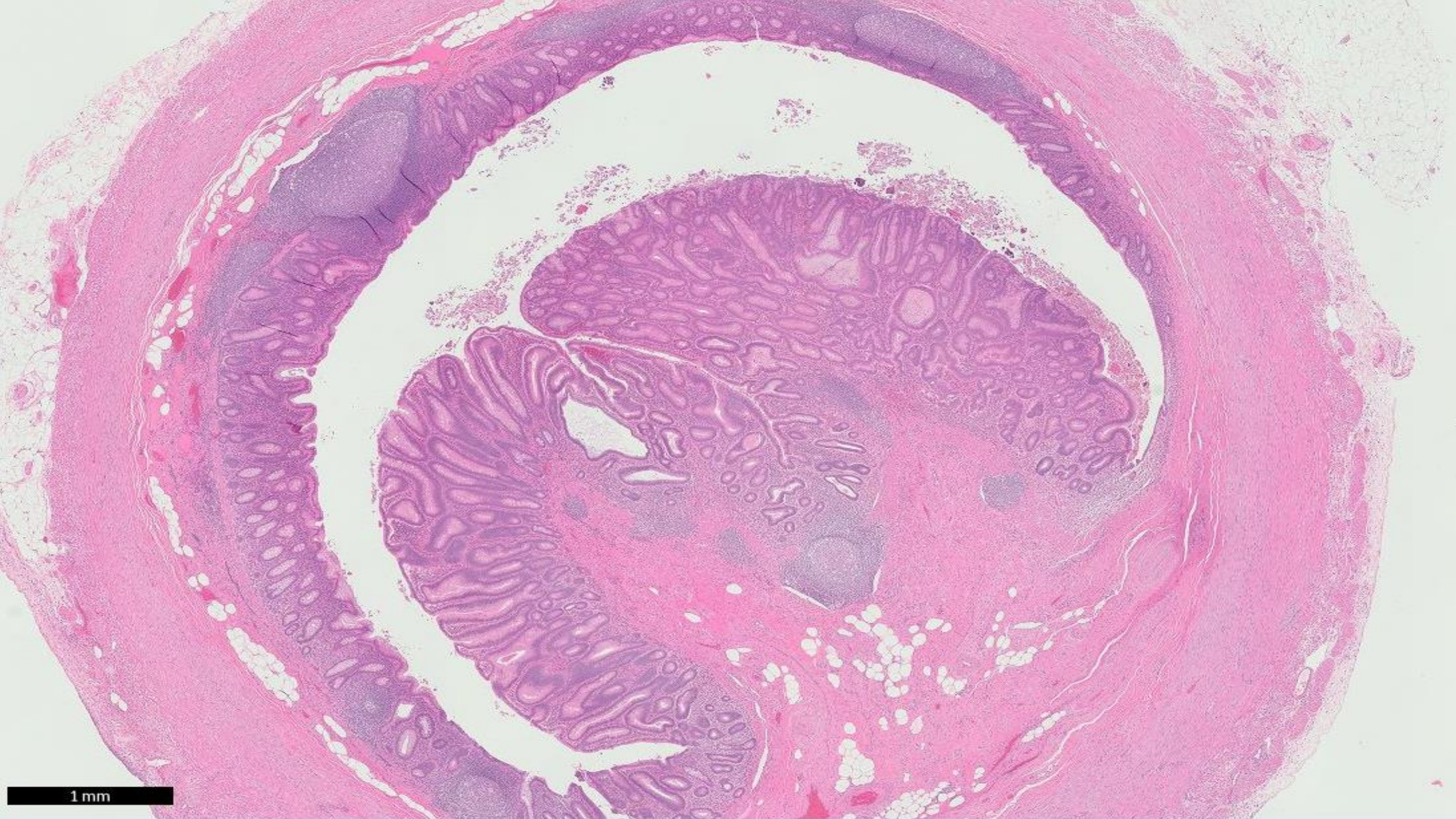
Epithelial neoplasms of the appendix

- Adenoma
- Low-grade appendiceal mucinous neoplasm
- High-grade appendiceal mucinous neoplasm
- Adenocarcinoma
- Serrated lesions or polyps
- Goblet cell tumors

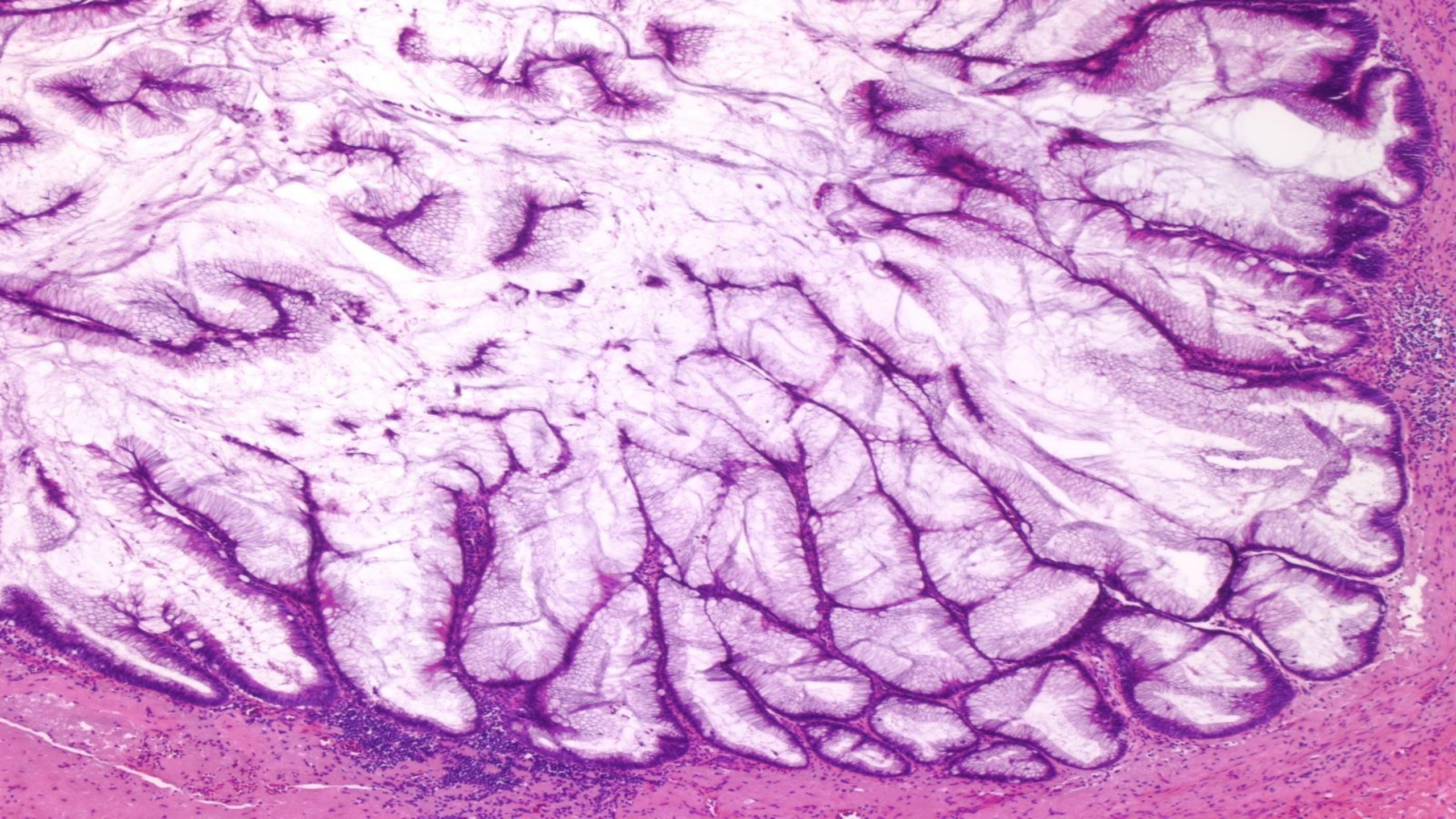
Adenoma

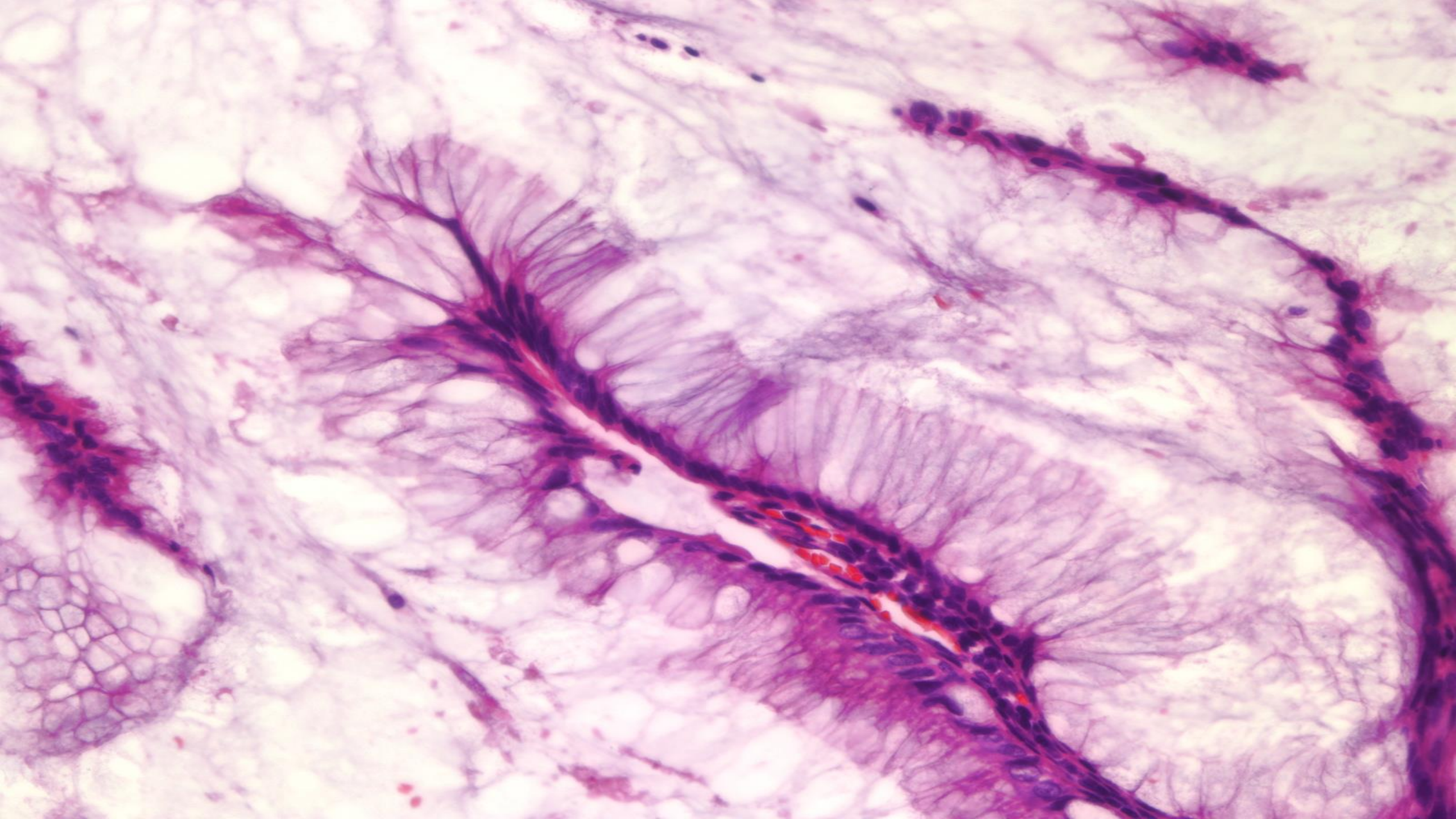
- Adenomatous proliferation *resembling colorectal type* (pencillate nuclei, pseudostratified, etc).
  - Intact muscularis mucosae
  - No tumor outside appendix
- Can be tubular, tubulovillous, or villous
- Dysplasia graded similar to other sites in GI tract
  - Low Grade
  - High Grade
- Defined in this way, an adenoma is benign.

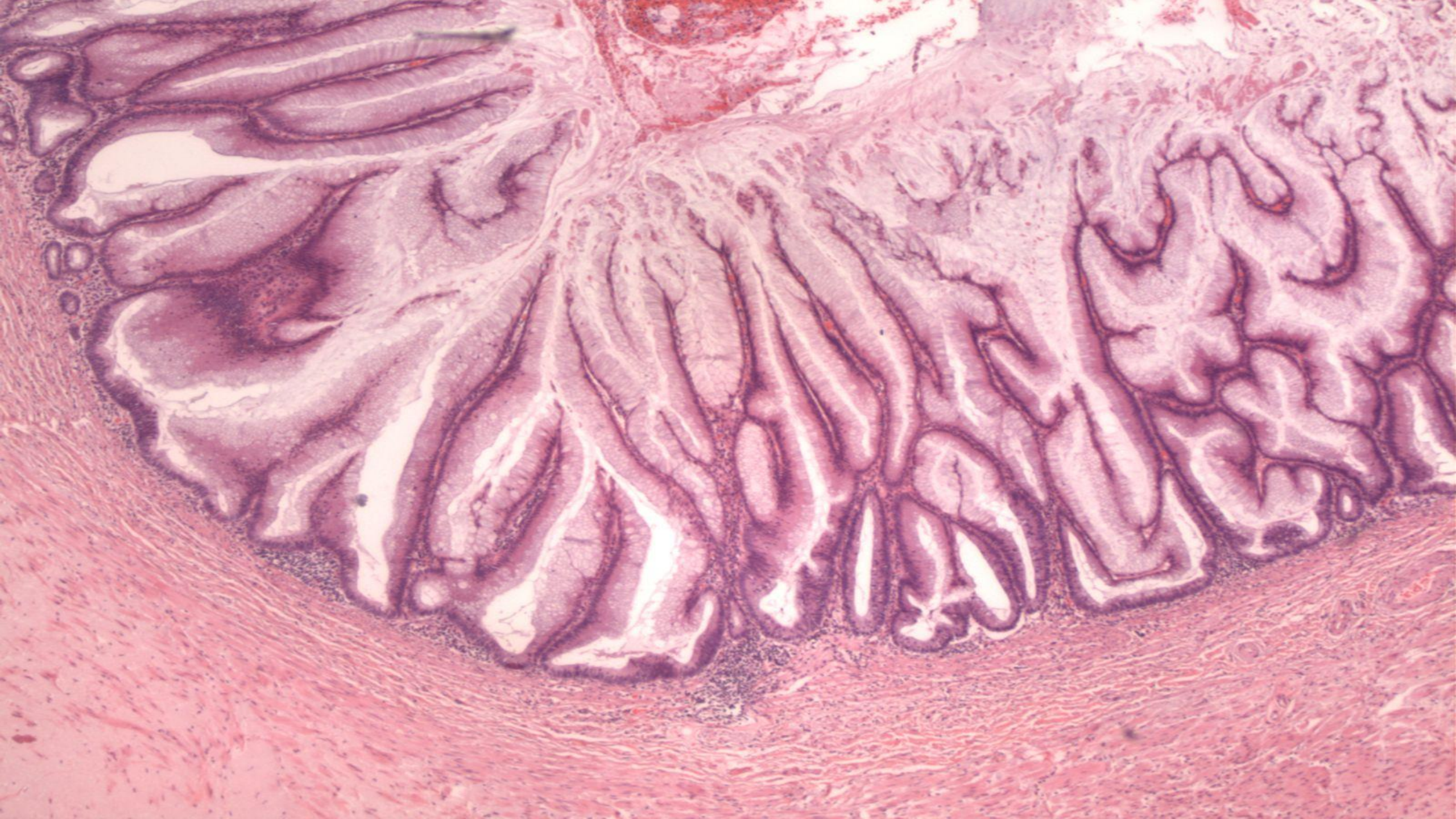

1 mm

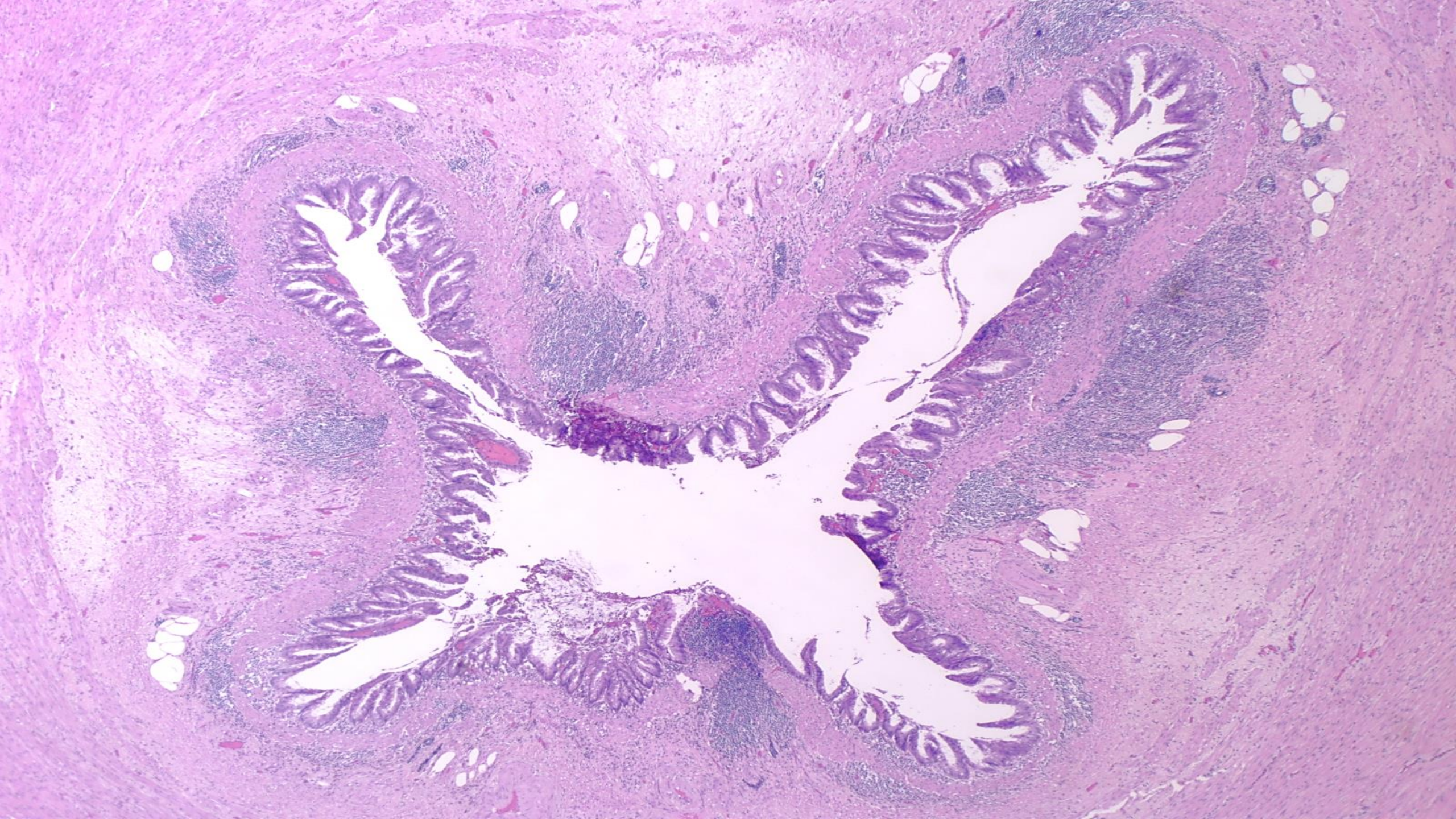
Low Grade Appendiceal Mucinous Neoplasm

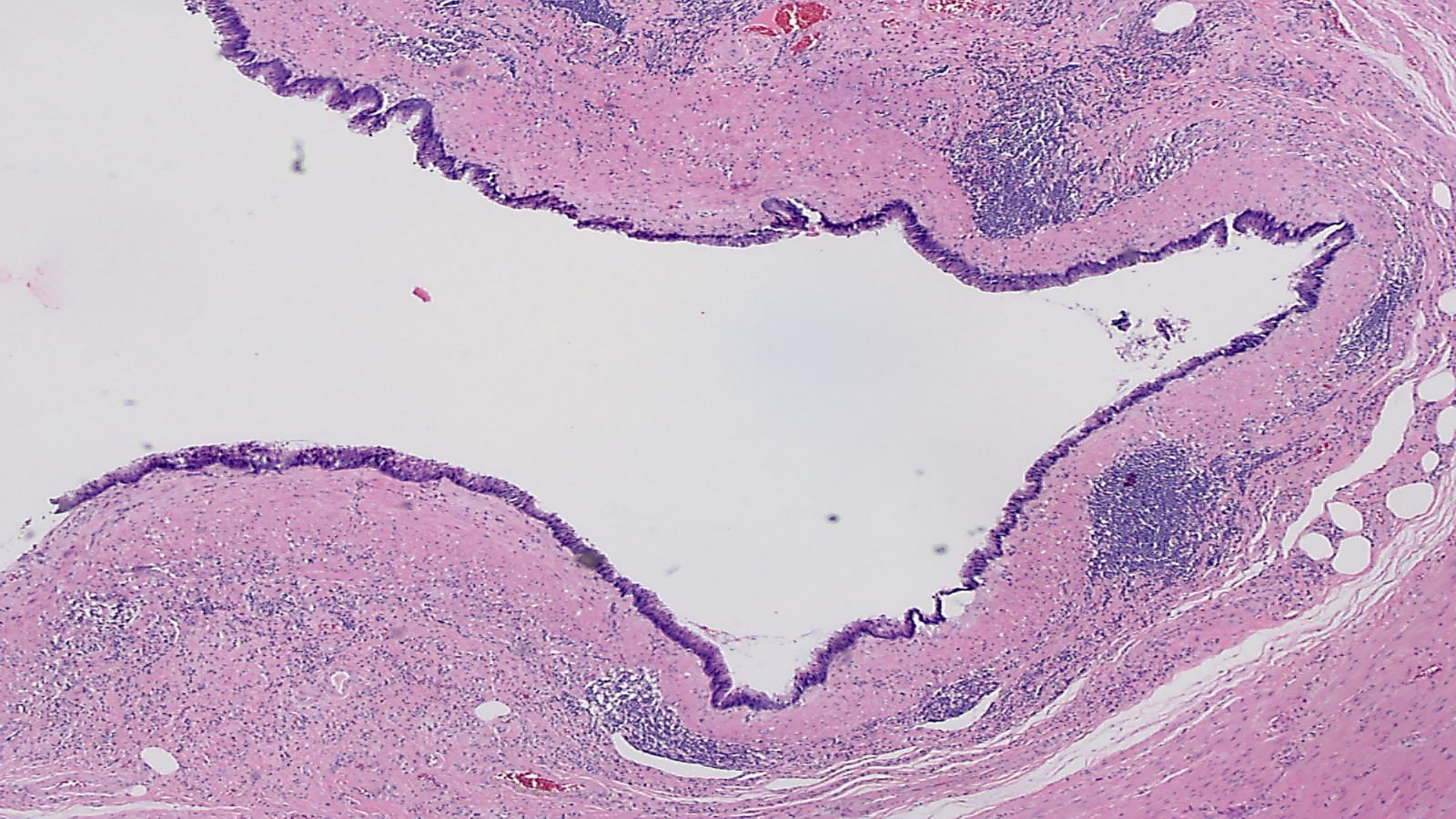
- A low grade mucinous epithelial tumor characterized by villiform or undulating growth pattern and tall mucinous epithelial cells.
- “Pushing” invasion. Destruction of muscularis mucosae with fibrosis, diverticula, herniations, dissections, etc. with possible rupture.

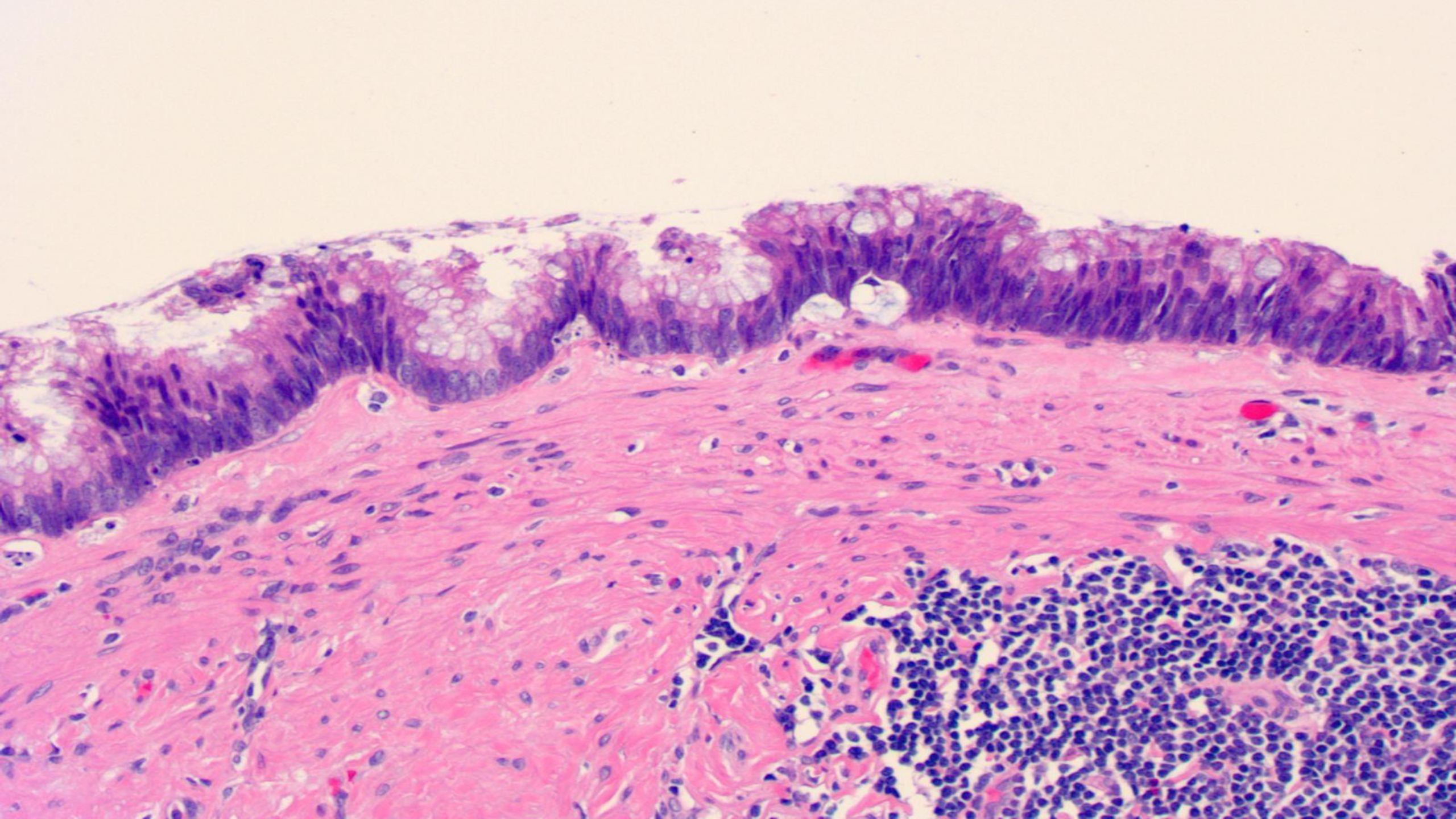


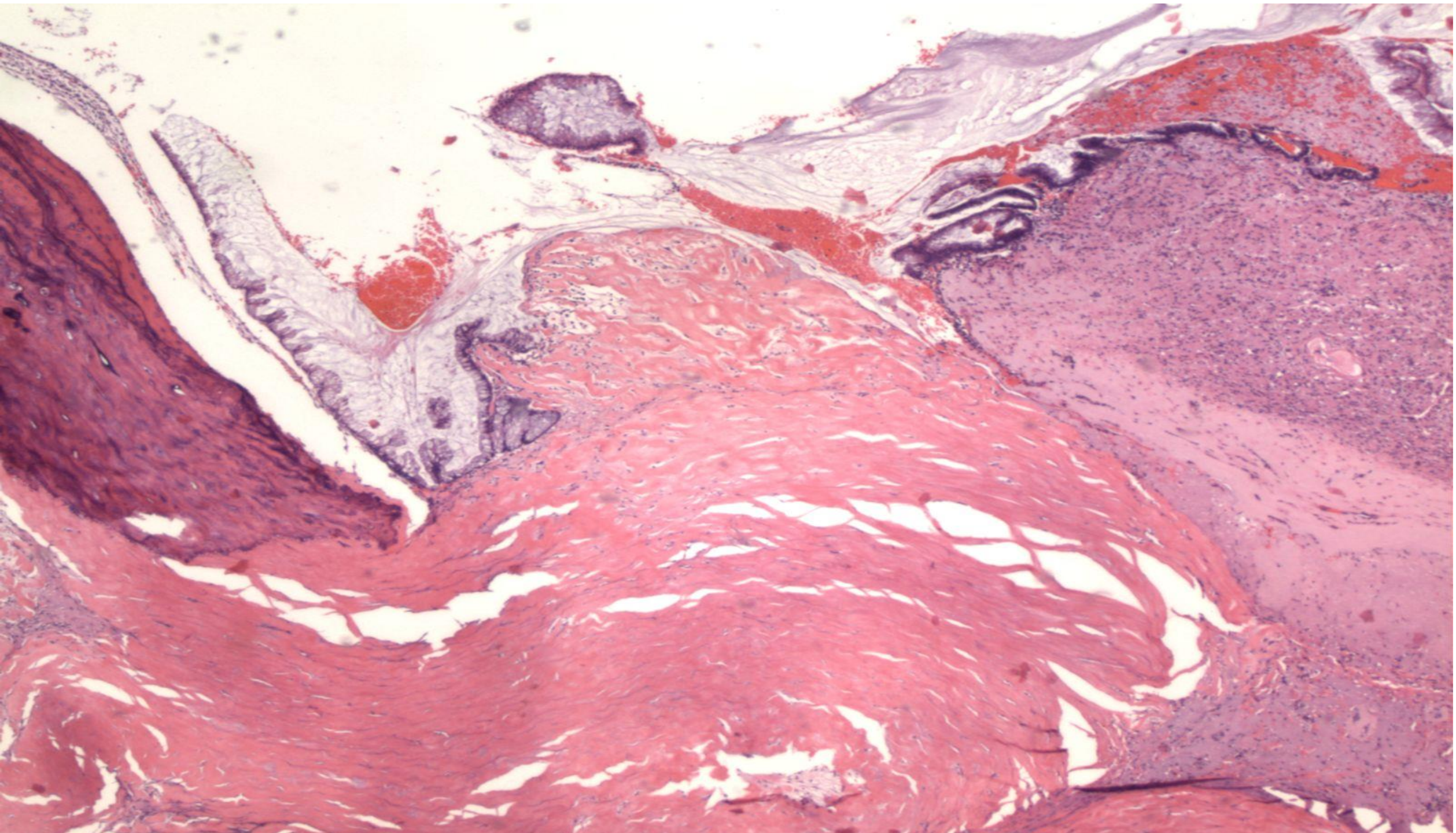


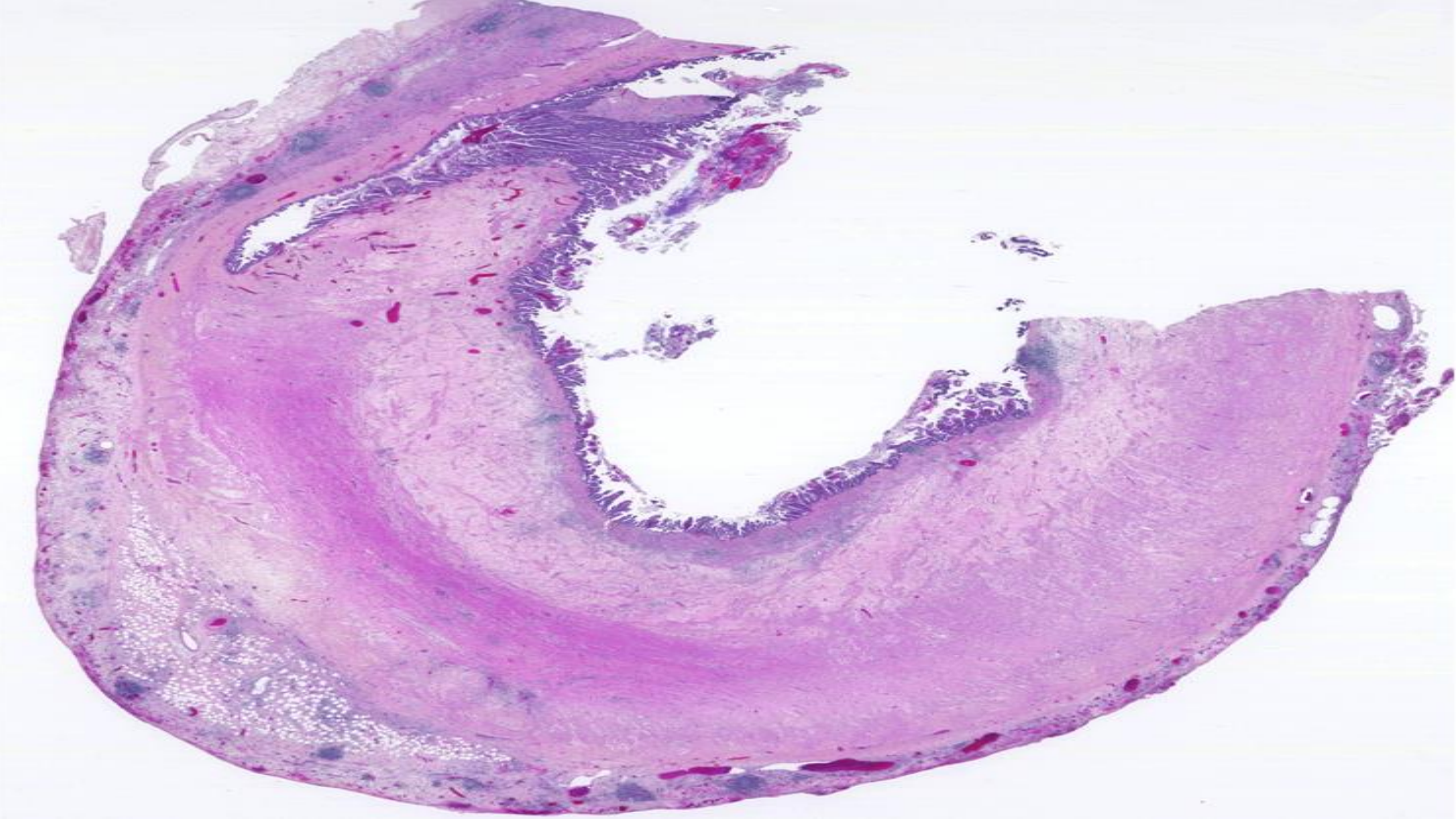


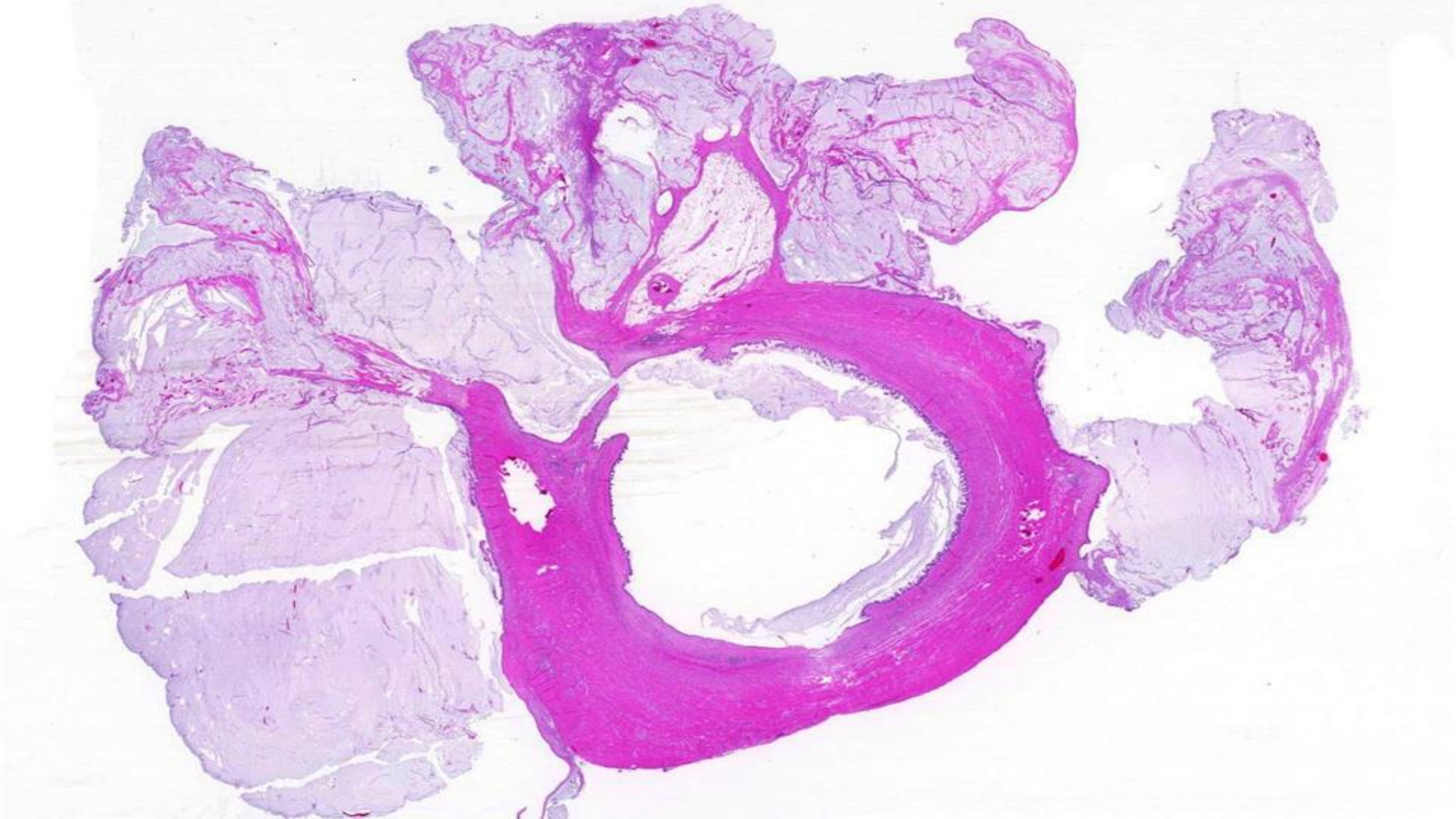


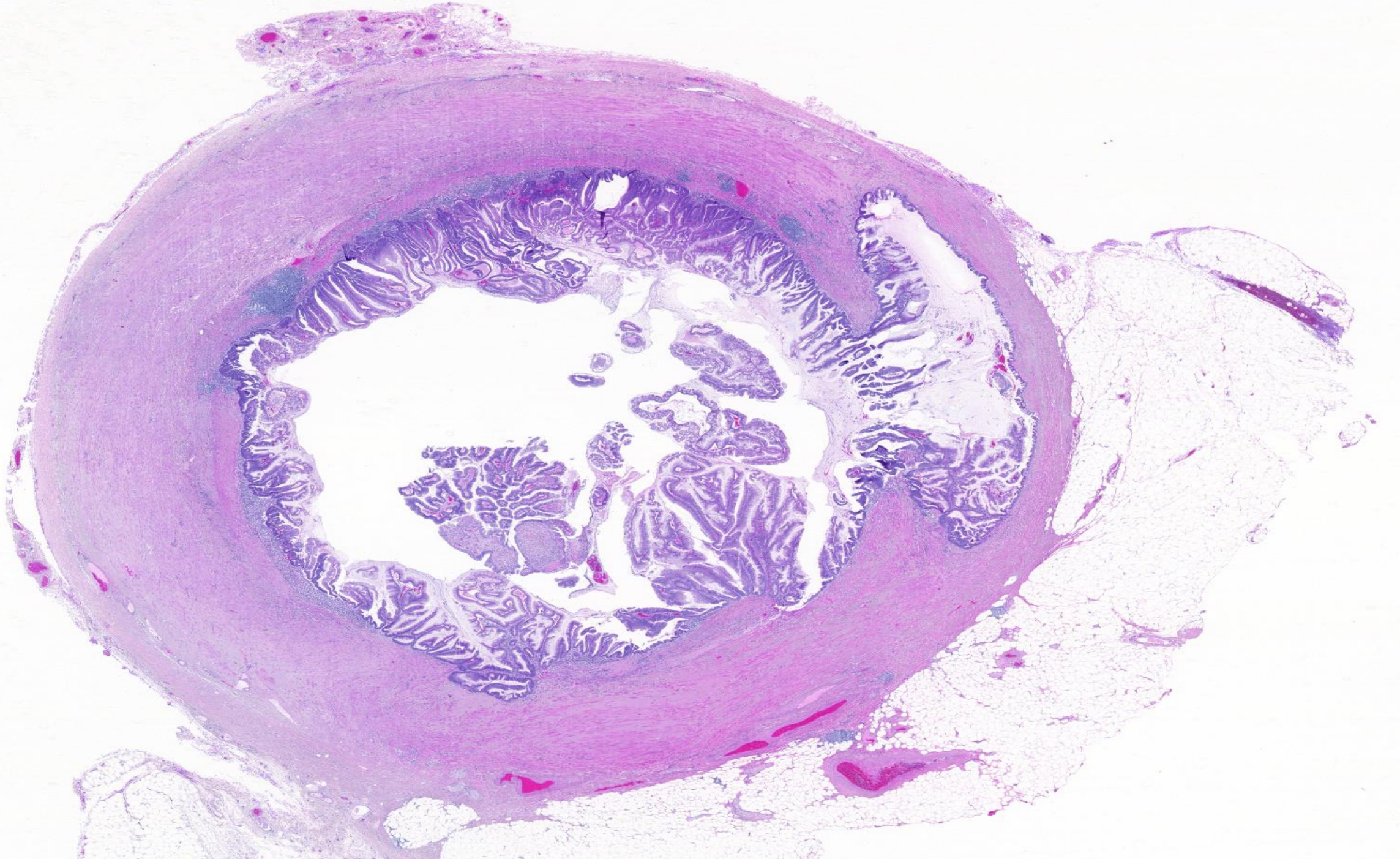


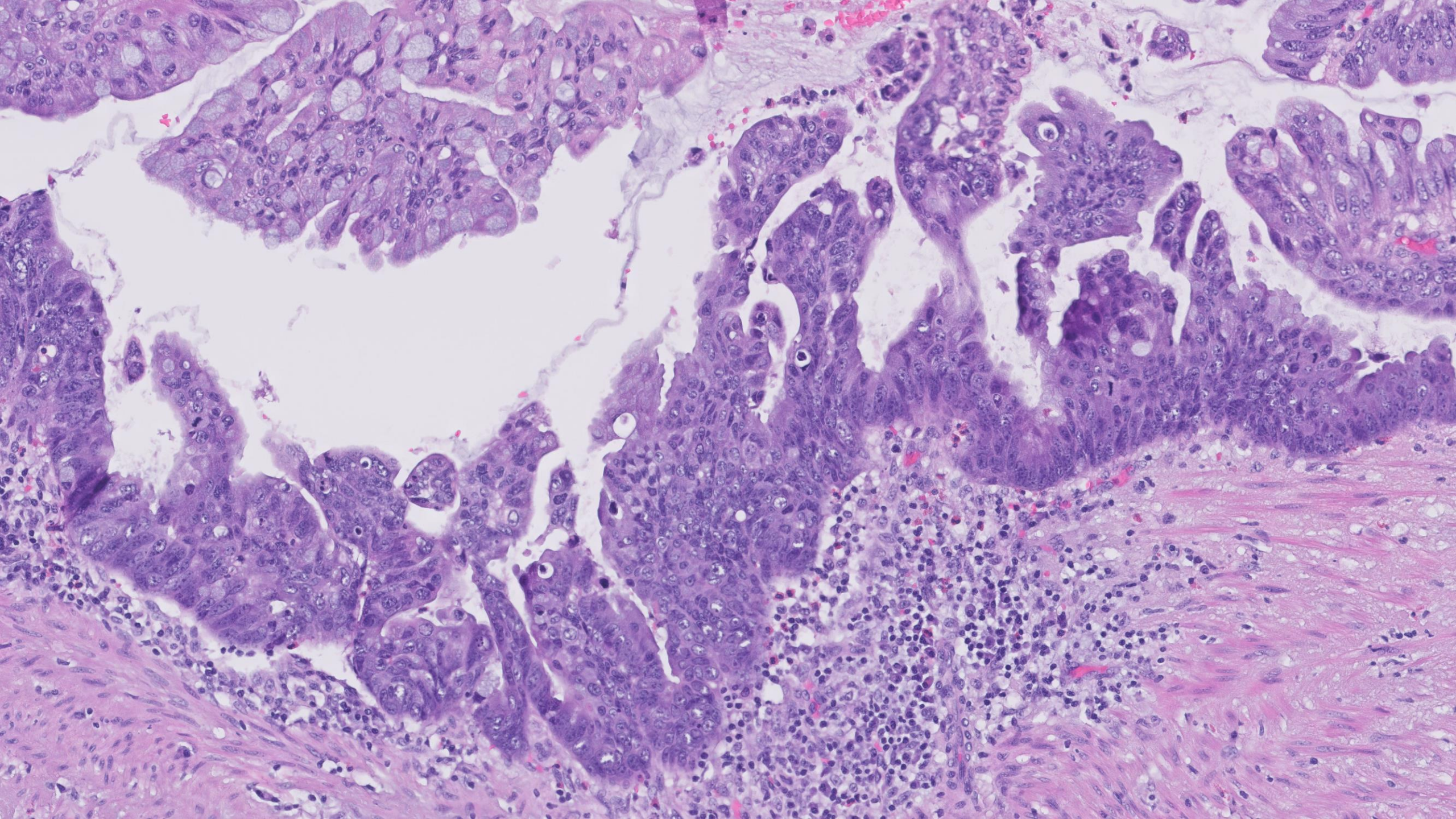


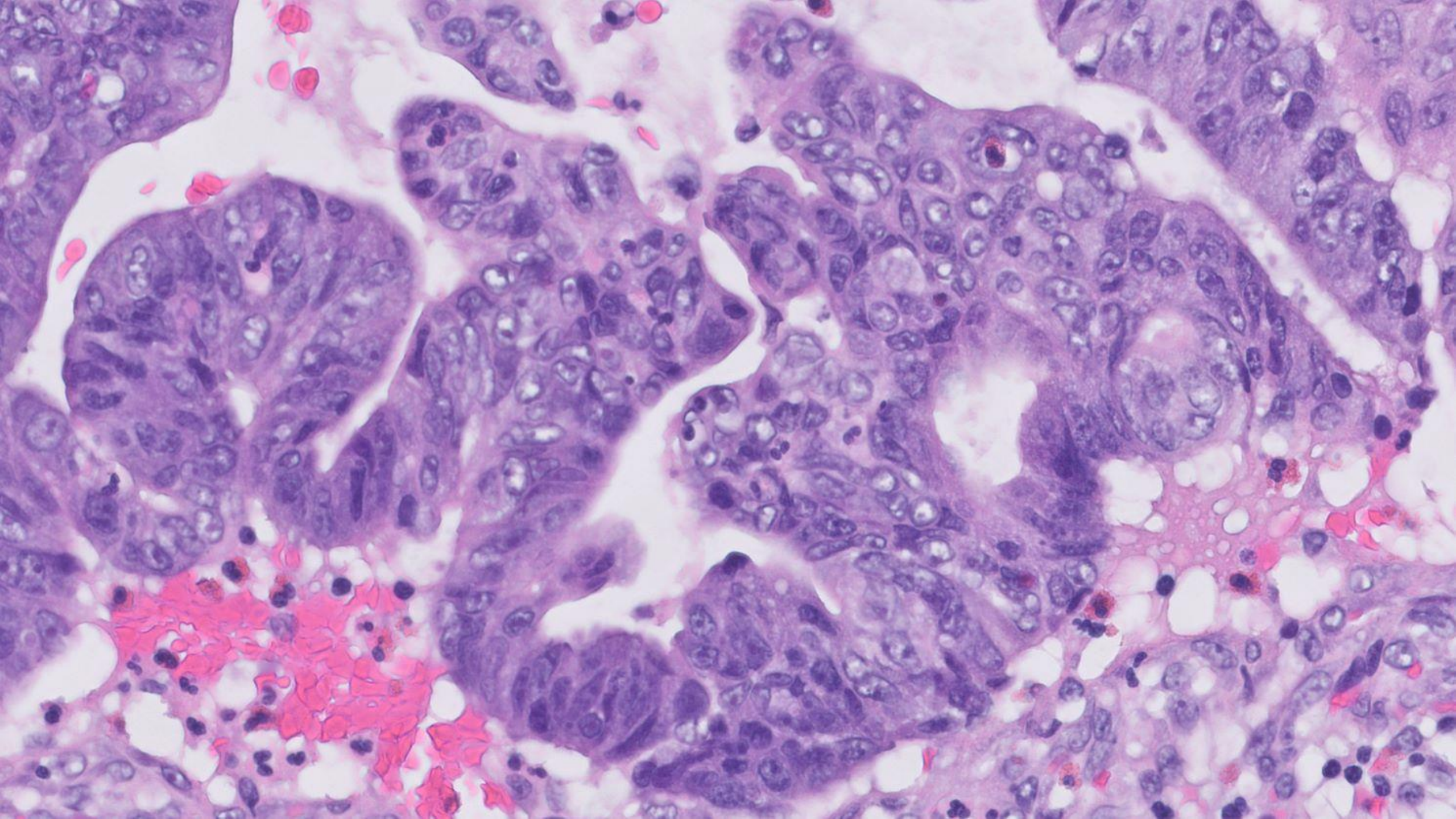










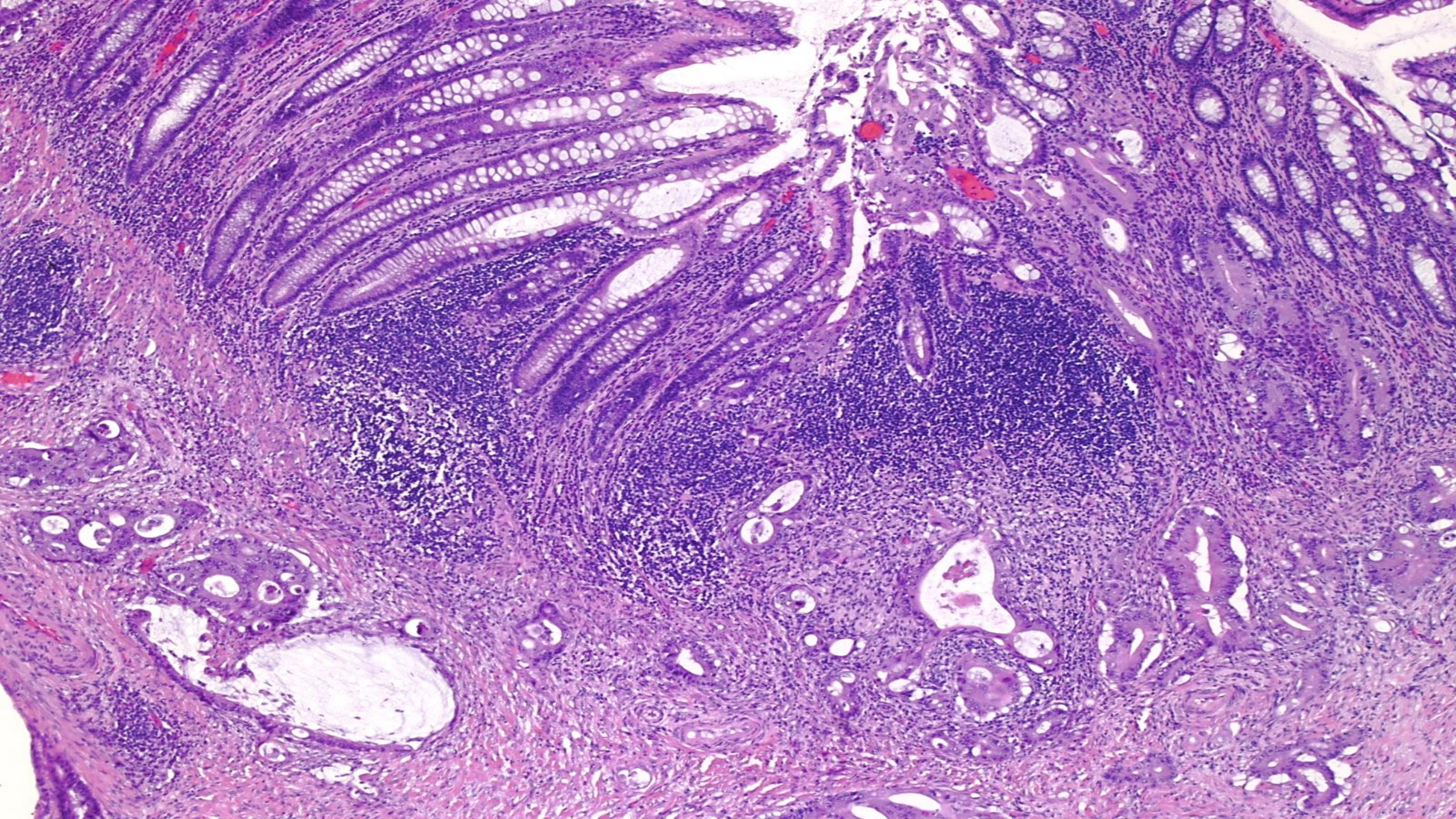


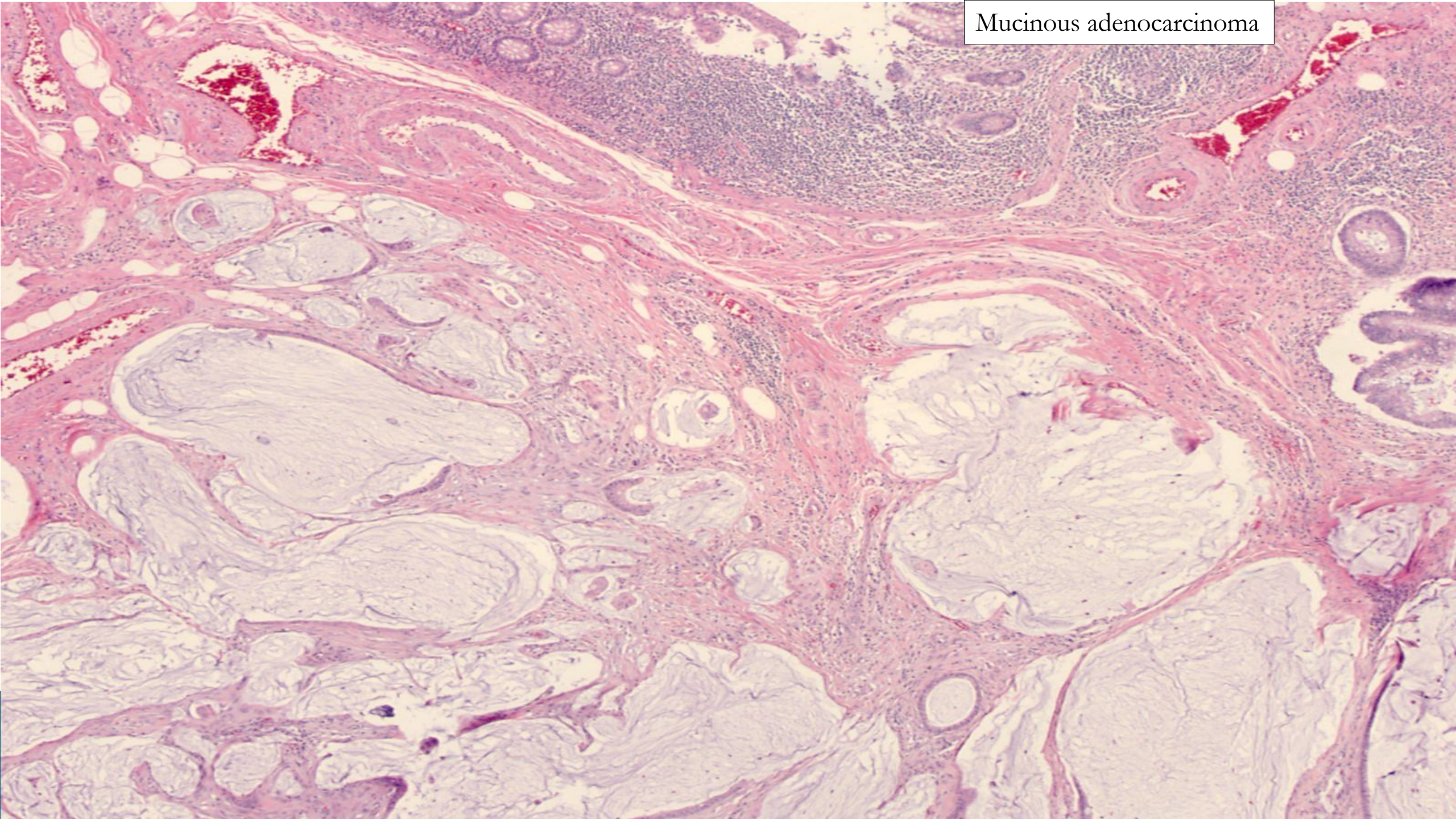
High-grade appendiceal mucinous neoplasm

- Pushing invasion 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.
- T stages the same as adenocarcinoma! Tis(HAMN) does not exist. Tumor into muscle is T2.
  - But there is no data to support that HAMN is more likely than LAMN to disseminate.

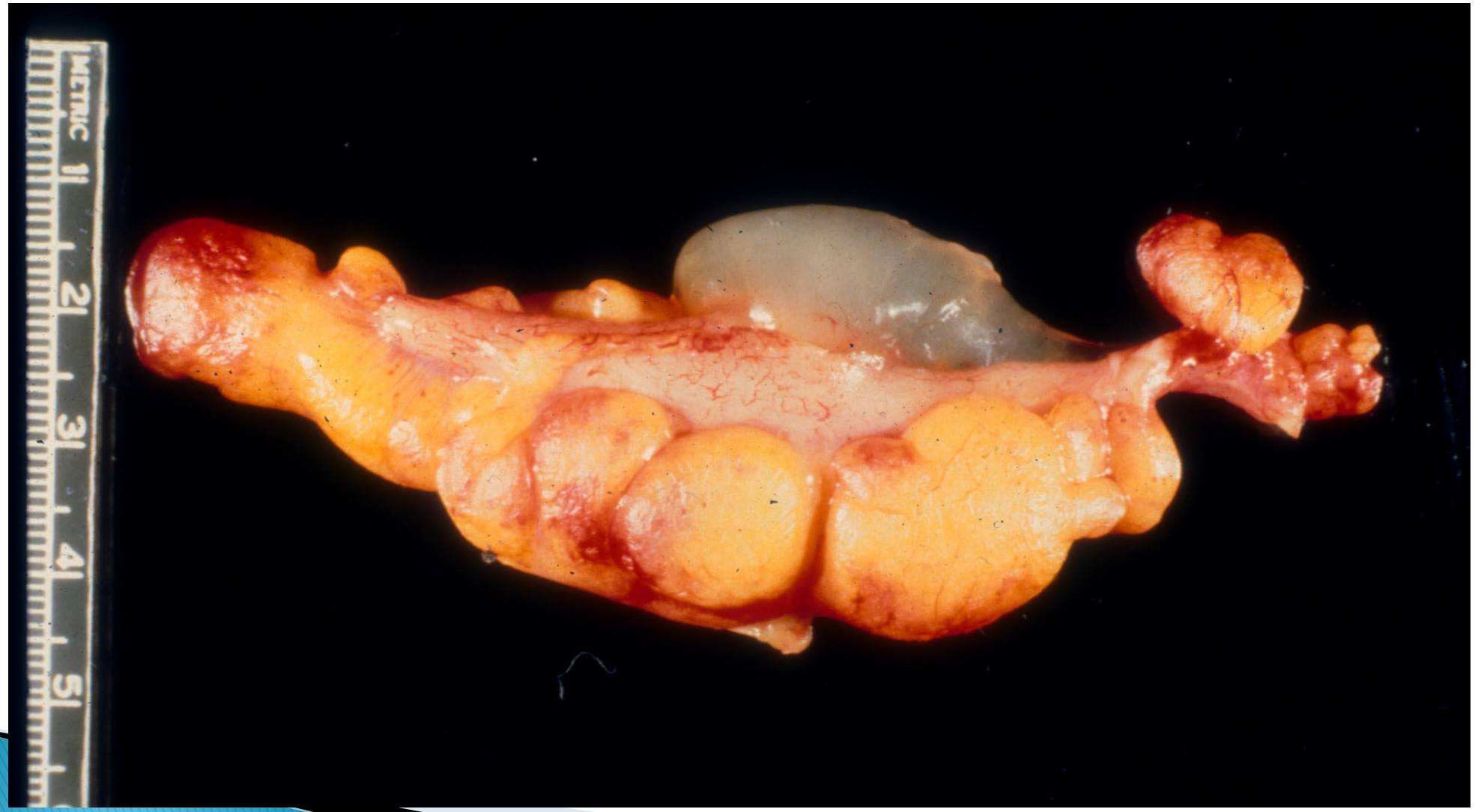
Adenocarcinoma

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




Mucinous adenocarcinoma

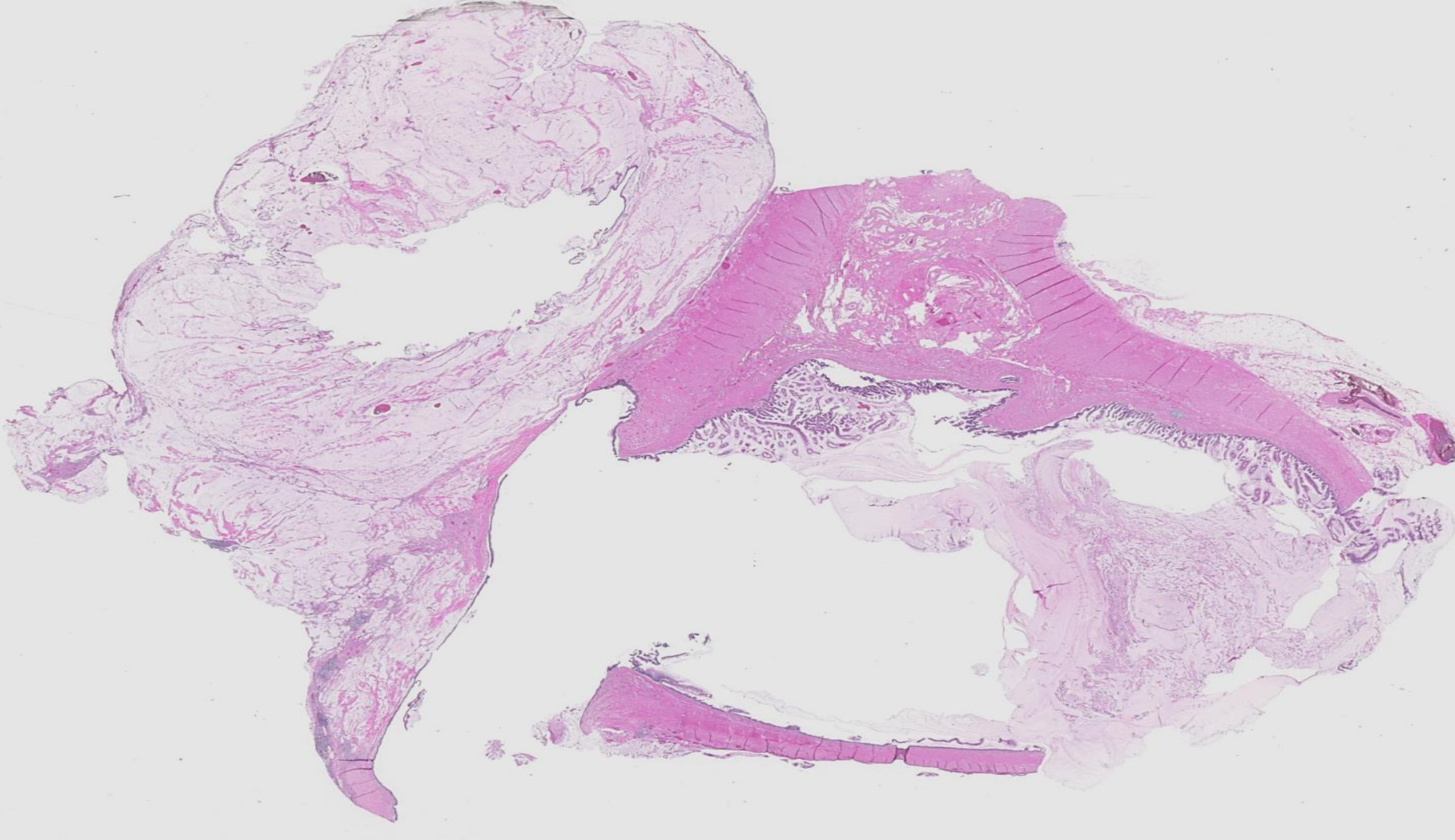
Reporting localized disease



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

Am J Surg Pathol 2009;33:248-255

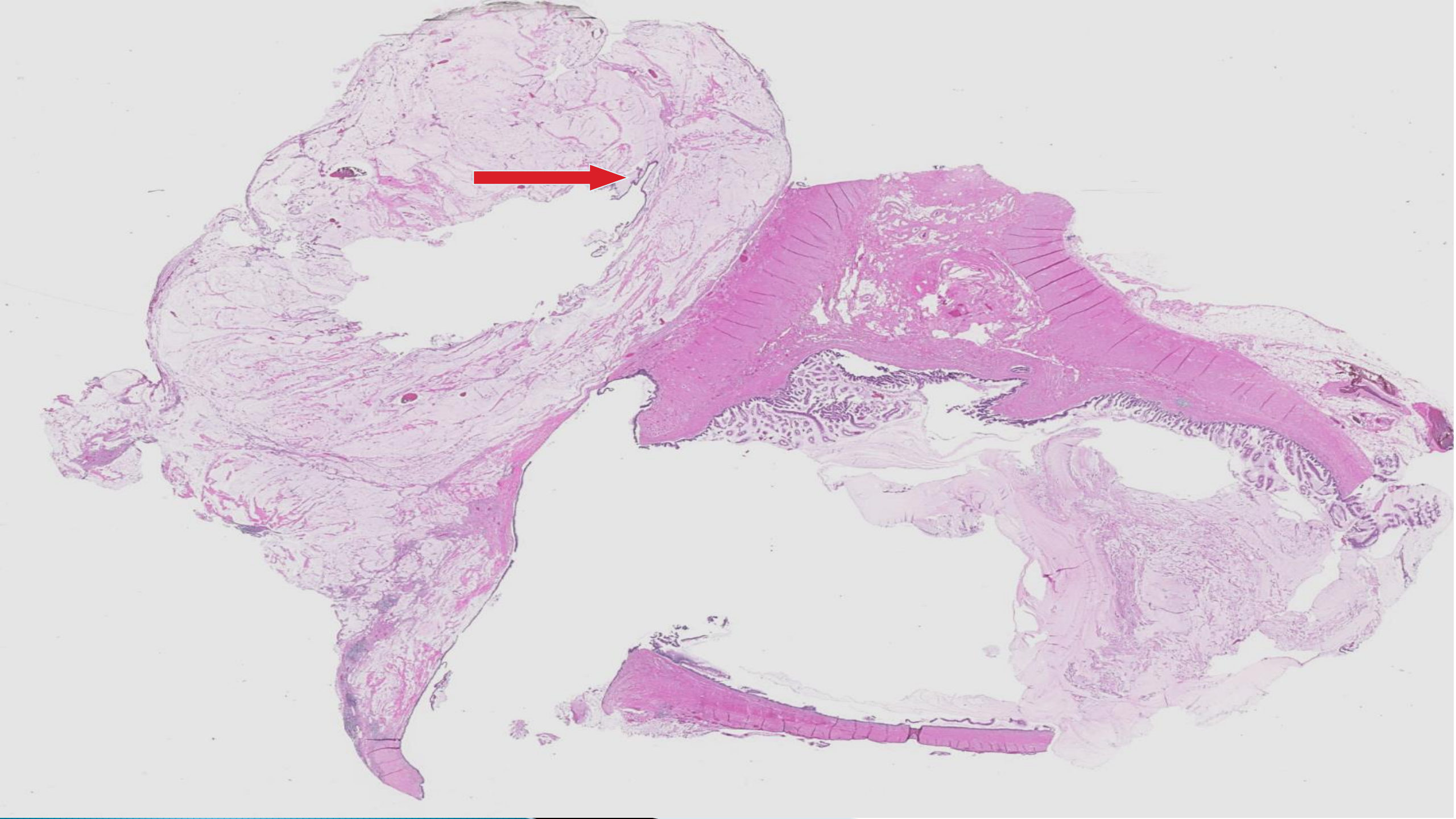
- 50 cases without cells in periappendiceal mucin
  - 2 (4%) recurred as pseudomyxoma peritonei
    - Neither was submitted entirely, raising the possibility that epithelial cells were unsampled
- 15 cases with cells in the periappendiceal mucin
  - 5 (33%) recurred (p=0.03); 1 died of disease

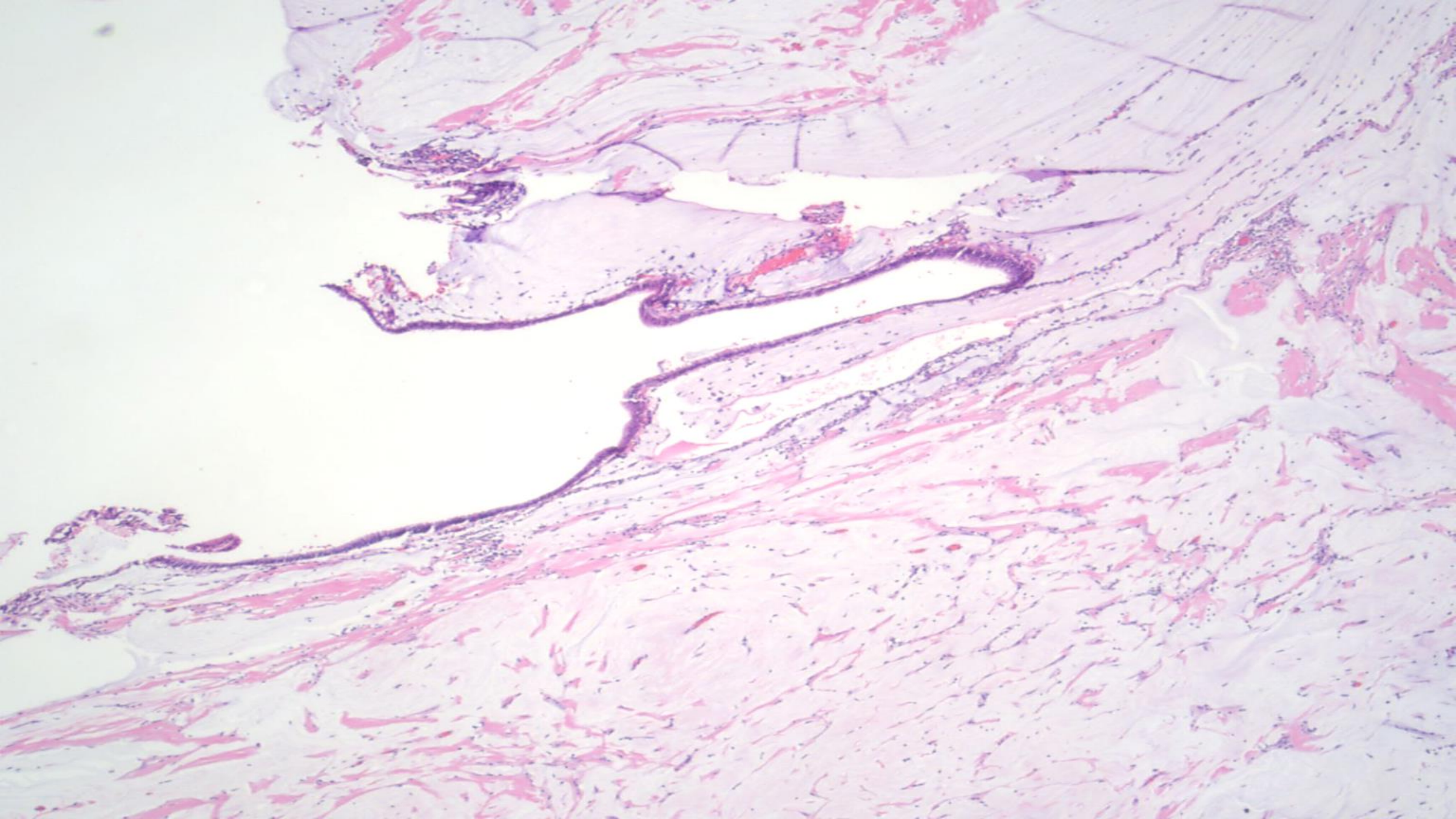


Diagnosis

- 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.





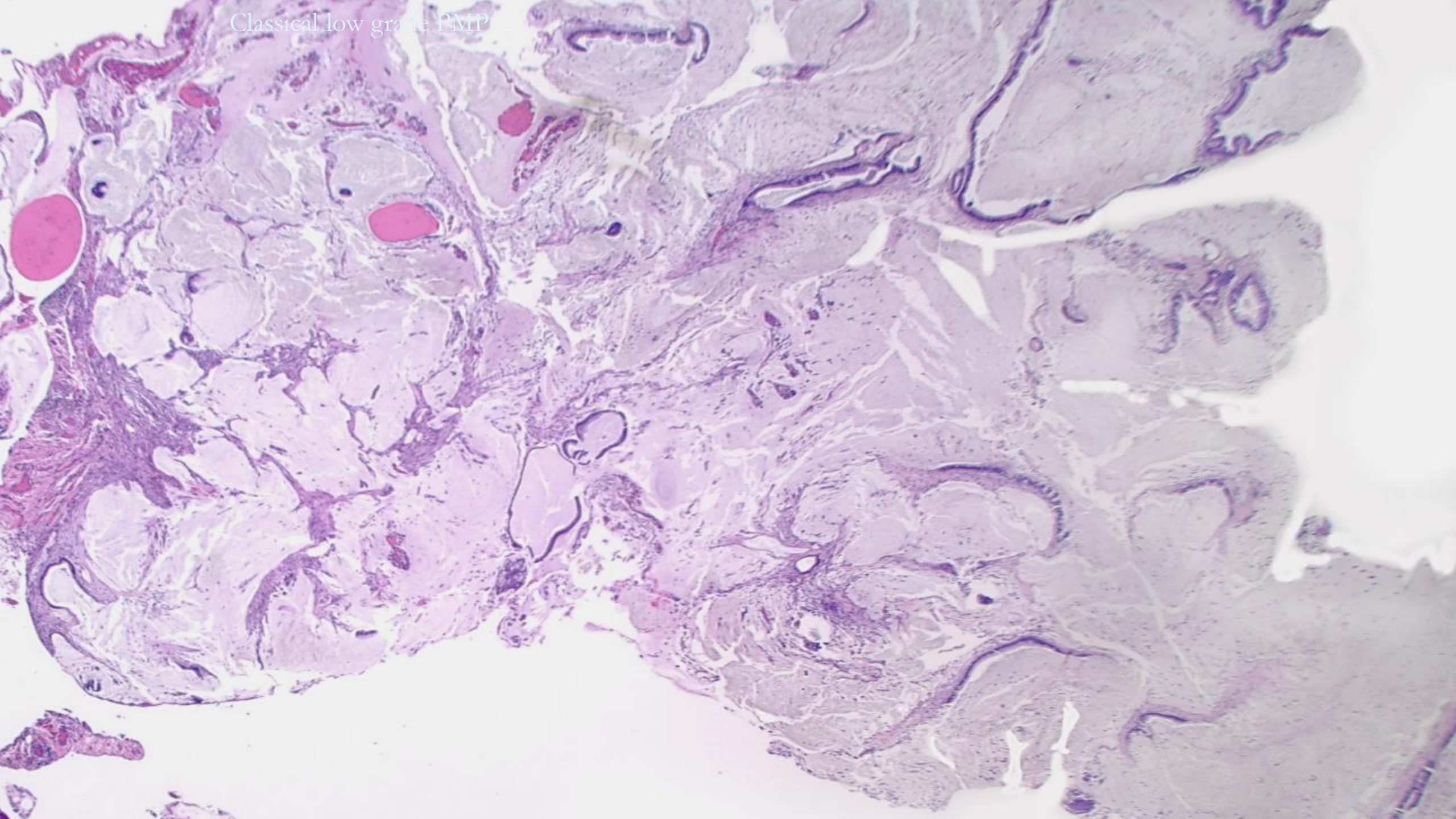
Diagnosis

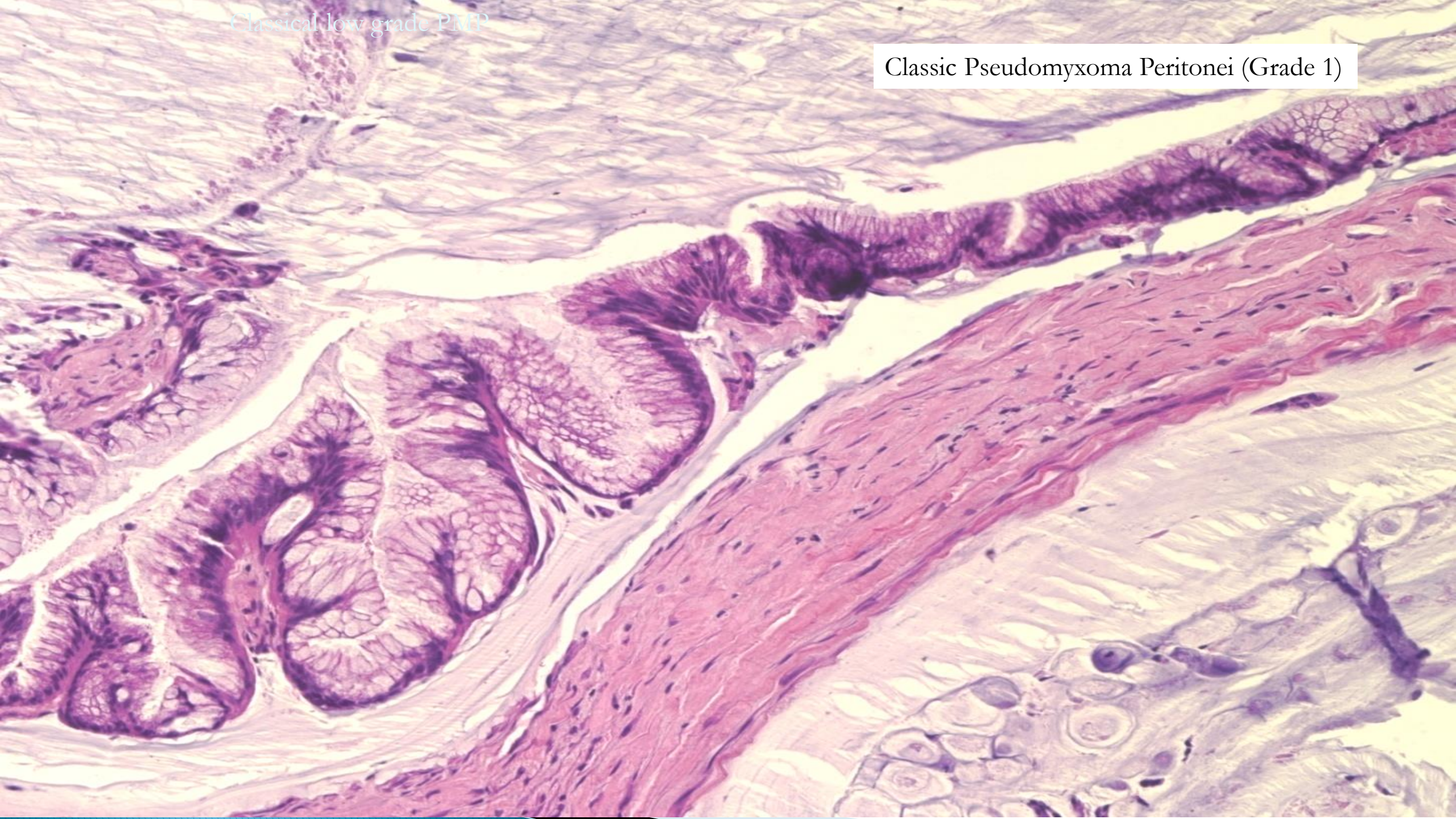
- Low grade appendiceal mucinous neoplasm, ruptured, with involvement of the peri-appendiceal serosa (localized pseudomyxoma peritonei).
  - Clarify that there is mucin AND low grade mucinous epithelium on the surface of the appendix;
  - This is considered high risk of recurrence as PMP;
  - Management varies. One paper reports that prognosis for low grade limited peritoneal disease was not affected by watching for radiologic progression (Ann Surg Oncol 2014)

Pseudomyxoma Peritonei

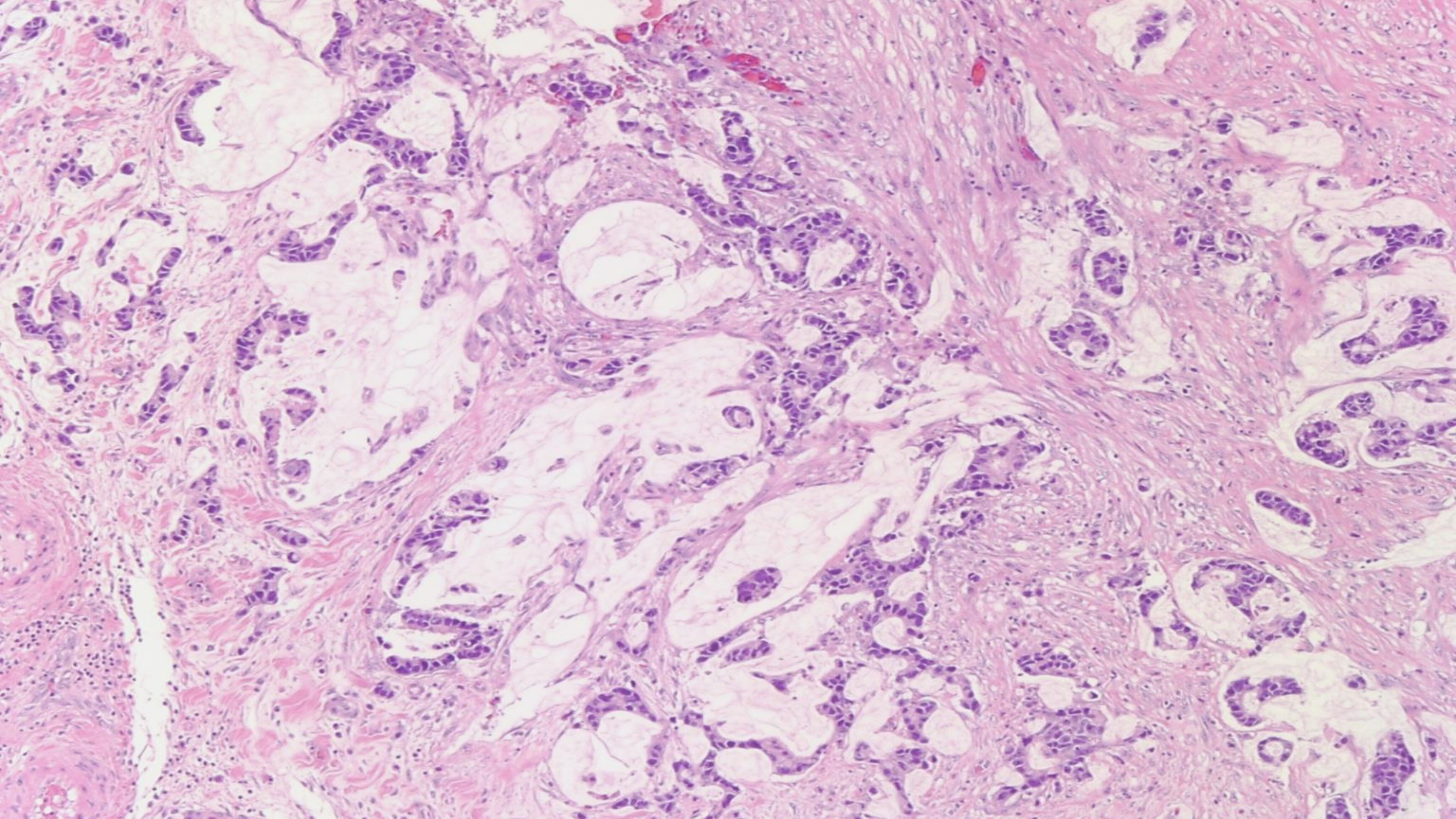
- Accumulation of mucin within the peritoneal cavity associated with mucinous tumor implants.
- Usually from a mucinous tumor of the appendix, but can arise from pancreas, gallbladder, colon, urachus, and teratoma of the ovary.

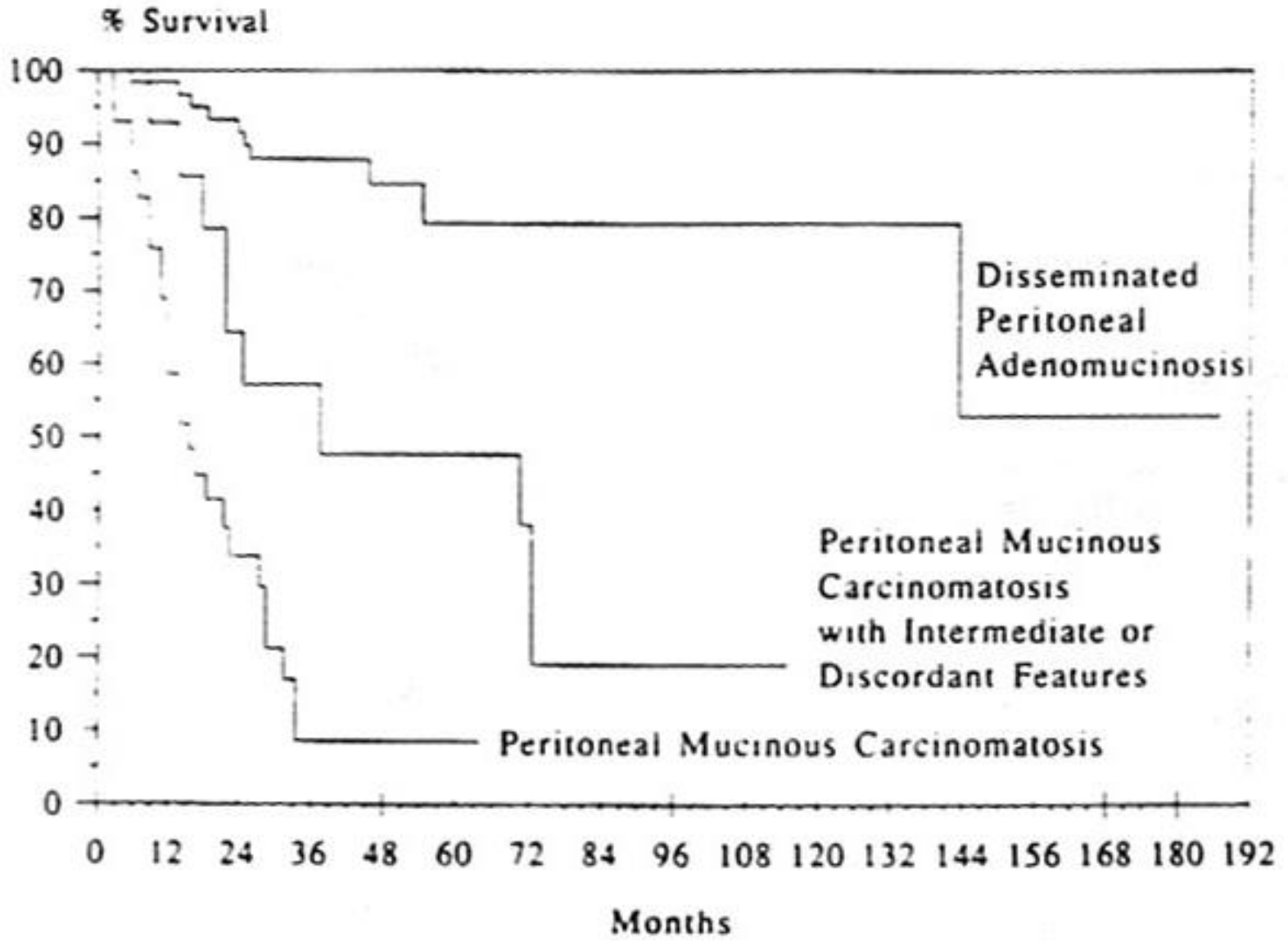
Classical low grade PMP





Classic Pseudomyxoma Peritonei (Grade 1)





Ronnett et al. Am J Surg Pathol 1995
Ronnett et al. Cancer 2001

Pseudomyxoma Peritonei of Appendiceal Origin: A Clinicopathologic Analysis of 101 Patients Uniformly Treated at a Single Institution, With Literature Review

Robert F. Bradley, MD, John H. Stewart, IV, MD,† Gregory B. Russell, MS,‡ Edward A. Levine, MD,† and Kim R. Geisinger, MD**

Am J Surg Pathol 2006;30:551-559

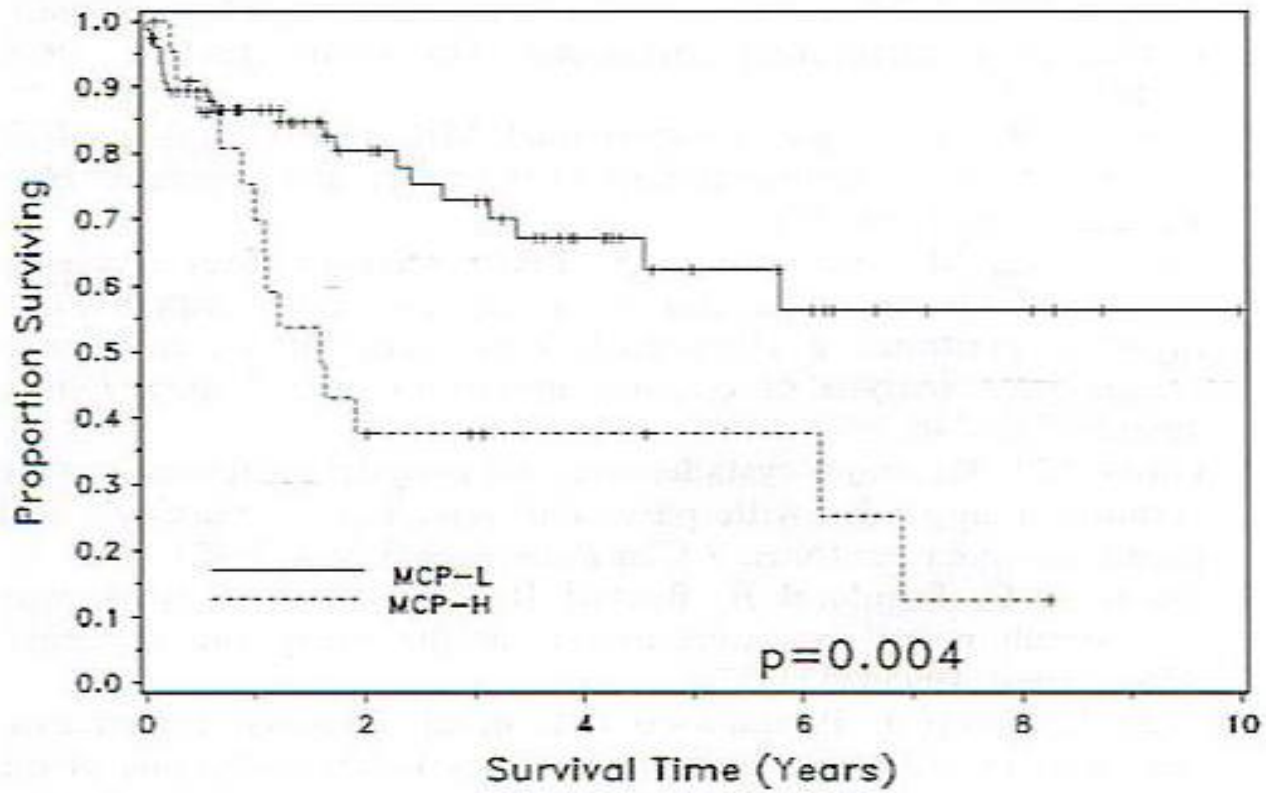
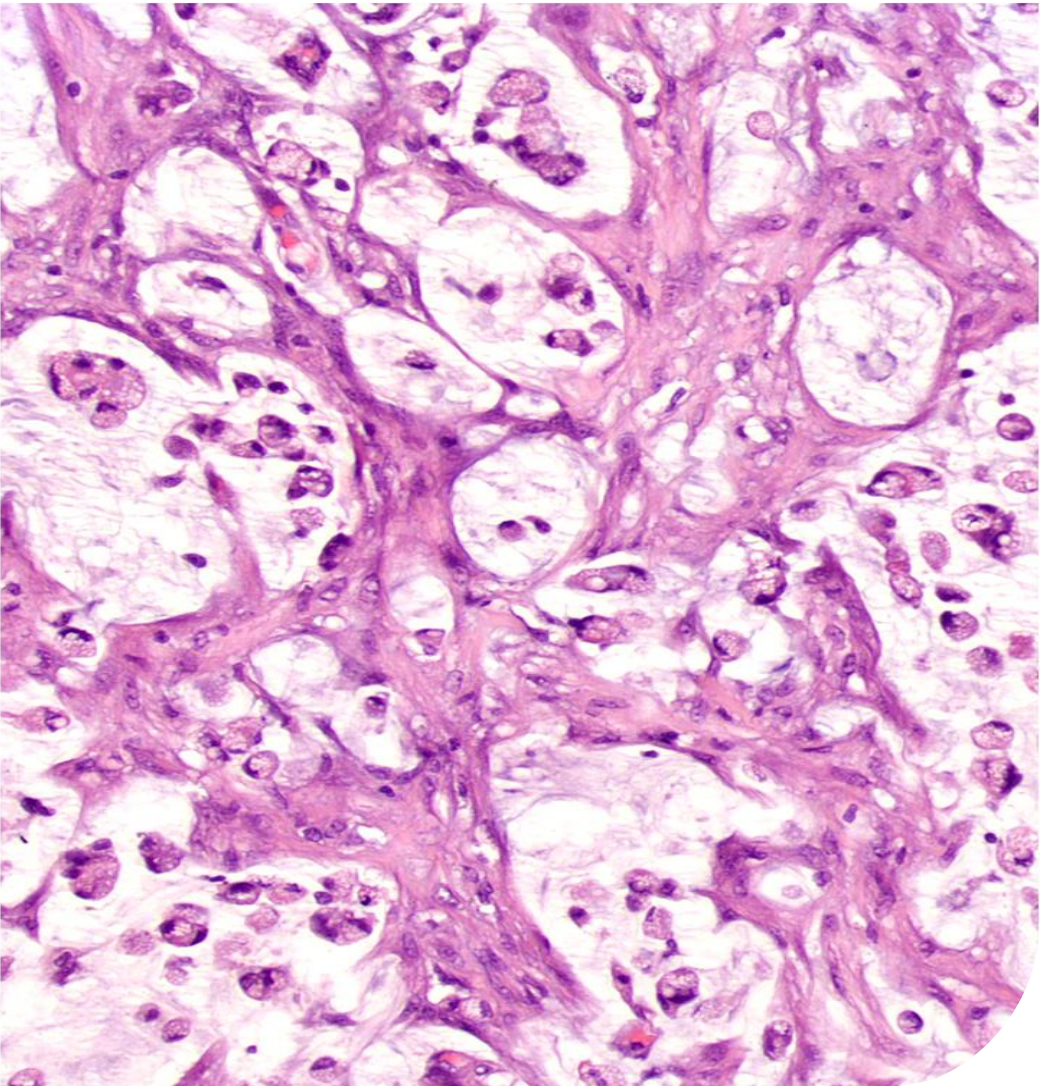
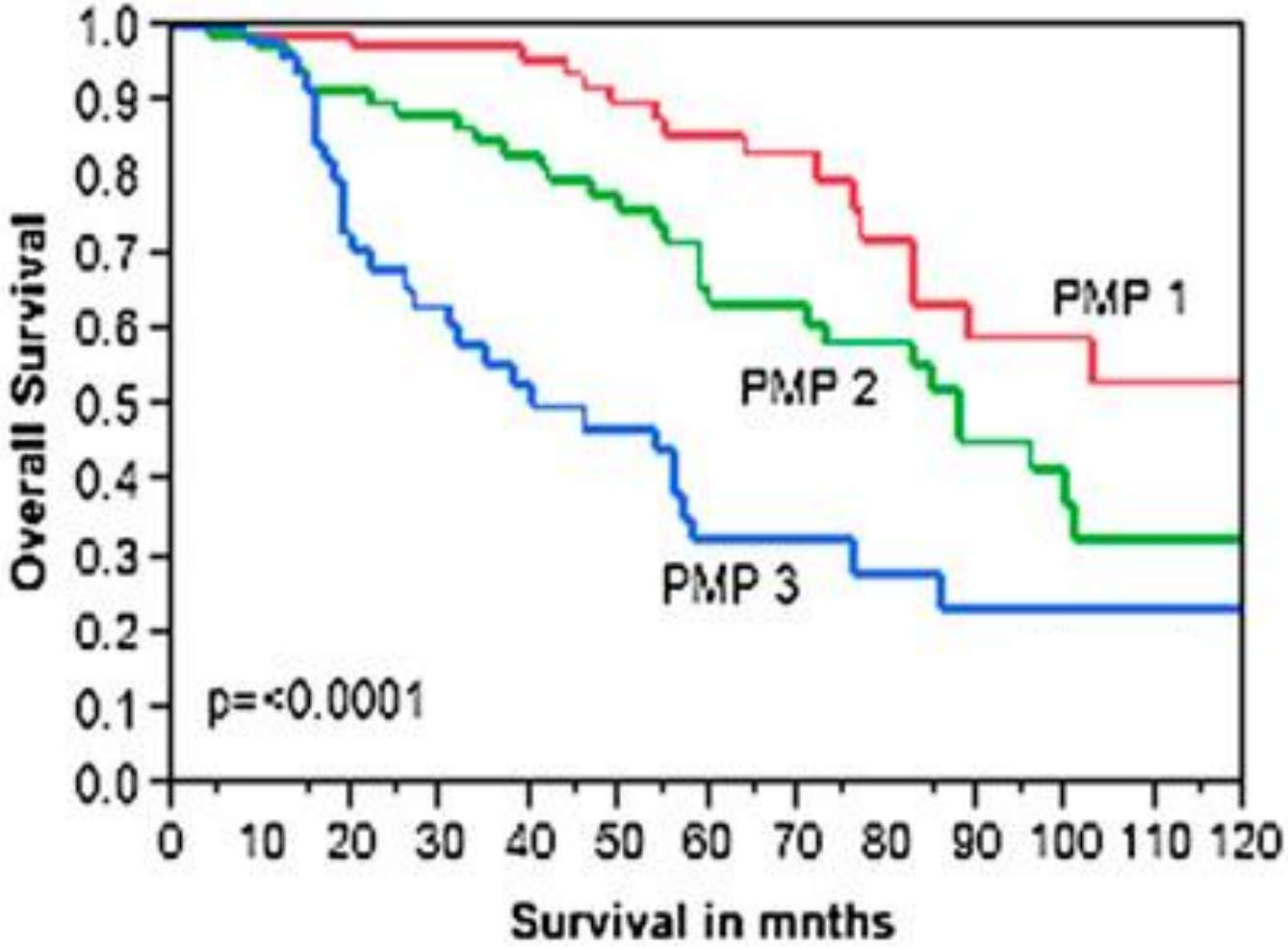


FIGURE 6. Kaplan-Meier curves comparing survival between the low-grade (MCP-L) and high-grade (MCP-H) variants of MCP.

Proposed Classification of Pseudomyxoma Peritonei: Influence of Signet Ring Cells on Survival

Shetty et al. *American Surgeon* Nov 2013





Proposed Criteria for Grading PMP

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

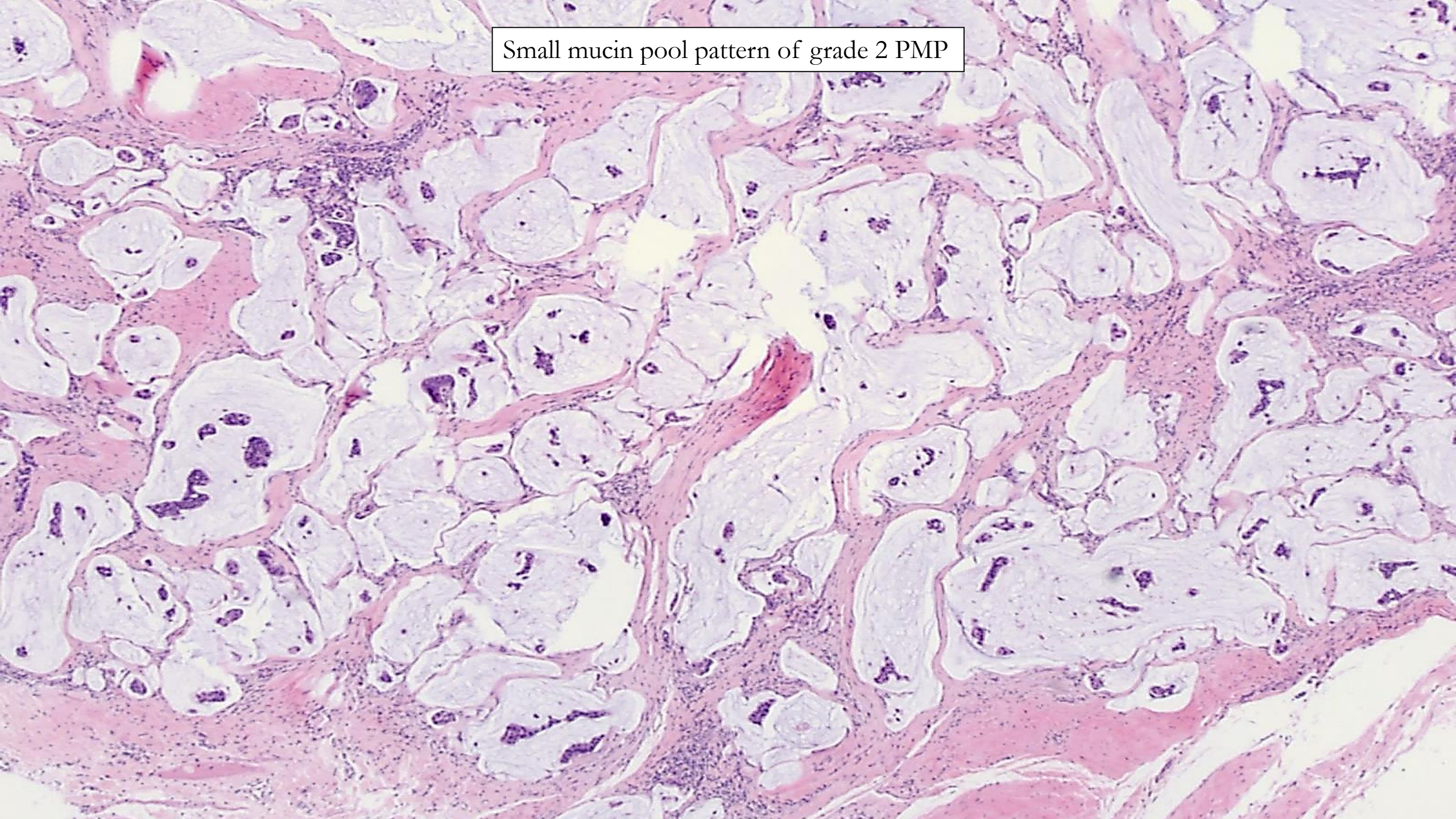
3 grades of pseudomyxoma peritonei

- Grade 1: Abundant mucin, scant cells, low-grade cytology
- Grade 2: Distinguished from grade 1 by:
  - High cytologic grade (>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

Usual primary tumor

- LAMN, rarely HAMN
- Invasive adenocarcinoma, rarely HAMN

- Signet ring cell carcinoma or goblet cell adenocarcinoma


Small mucin pool pattern of grade 2 PMP

AJCC 8th edition: T and M stage for LAMN

- Tis(LAMN) – LAMN confined by the muscularis propria
  - No T1 or T2 for LAMN
- T3 – LAMN that extends to subserosa.
- T4a – Tumor invades visceral peritoneum.
  - 7th edition: Tumor penetrates visceral peritoneum, *including mucinous tumors within the right lower quadrant.*

- M1a – Intraperitoneal acellular mucin
- M1b – Intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells
- M1c – Metastasis to sites other than peritoneum

LAMN: Prognosis is stage dependent
(but T stage doesn't communicate prognosis effectively)

Extent of tumor spread in appendectomy	TNM stages	Prognosis
Tumor is confined to the appendix: serosa intact, no mucin or tumor outside appendix	Tis(LAMN) or T3	Almost certainly cured by appendectomy
Tumor perforates serosa with acellular mucin on the serosa or in the peritoneum	T4	Low-risk of recurrence as pseudomyxoma
Tumor perforates serosa with cellular mucin on the serosa	T4	High-risk of recurrence as pseudomyxoma

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

Genetic landscape of appendiceal mucinous tumors.

- LAMNs show frequent KRAS mutations (90%) and GNAS mutations (>50%).
- LAMNs express DNA mismatch repair proteins and are MSS.
- Mutations typical of colorectal carcinoma (APC, p53, and SMAD4) are not common in appendiceal mucinous neoplasms, but are more common in high-grade tumors.

Misdraji J, Burgart LJ, Lauwers GY. Modern Pathology 2004;17:1447-1452.
Zauber P, Berman E, Marotta S, et al. Scandinavian J Gastroenterol 2011;46:869-74.
Nishikawa G, Sekine S, Ogawa R, et al. British J Cancer 2013;108:951-8.
Hara K, Saito T, Hayashi T, et al. Pathology, Research and Practice. 2013;211:657-64.

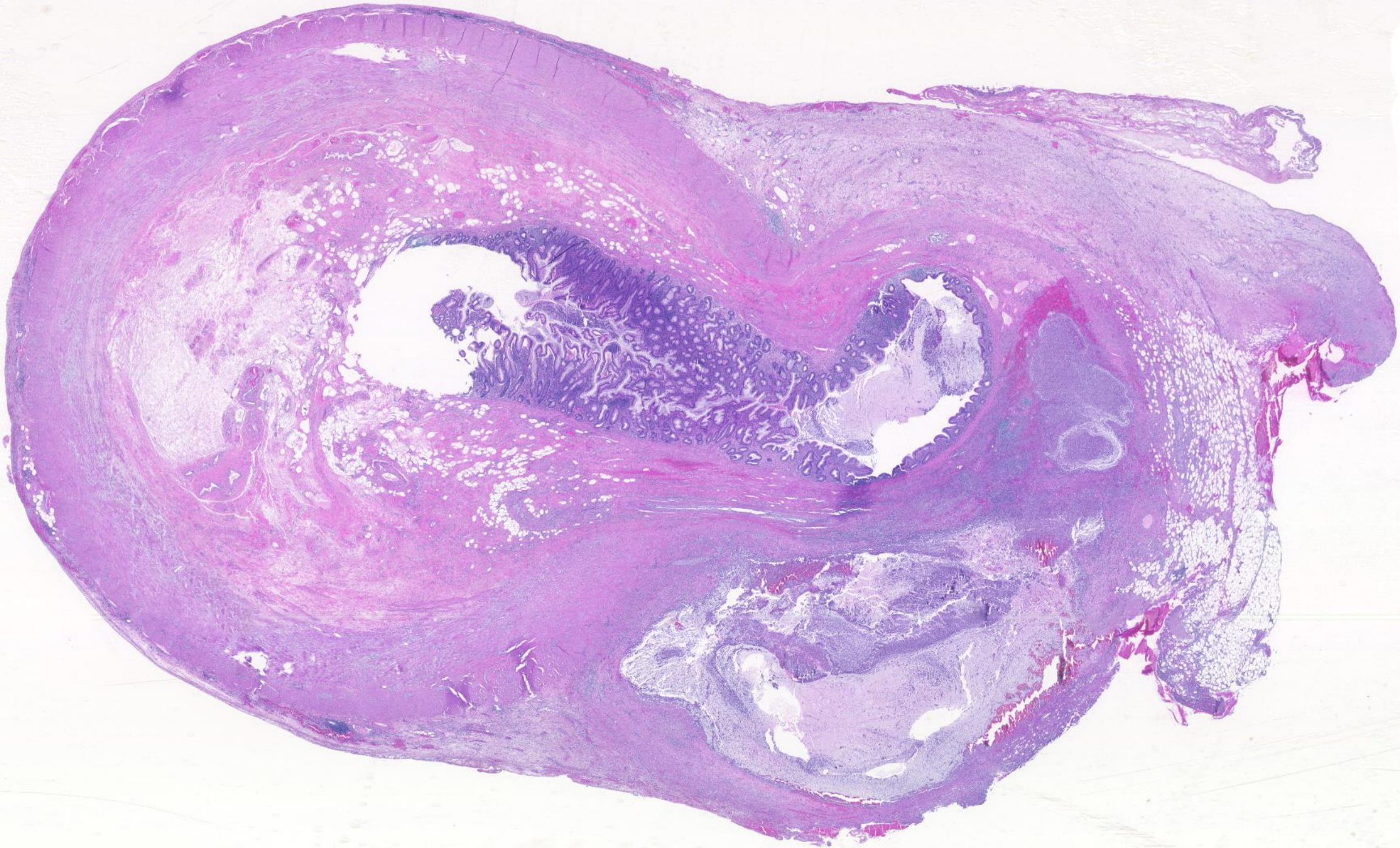
Genetic landscape of appendiceal adenocarcinoma.

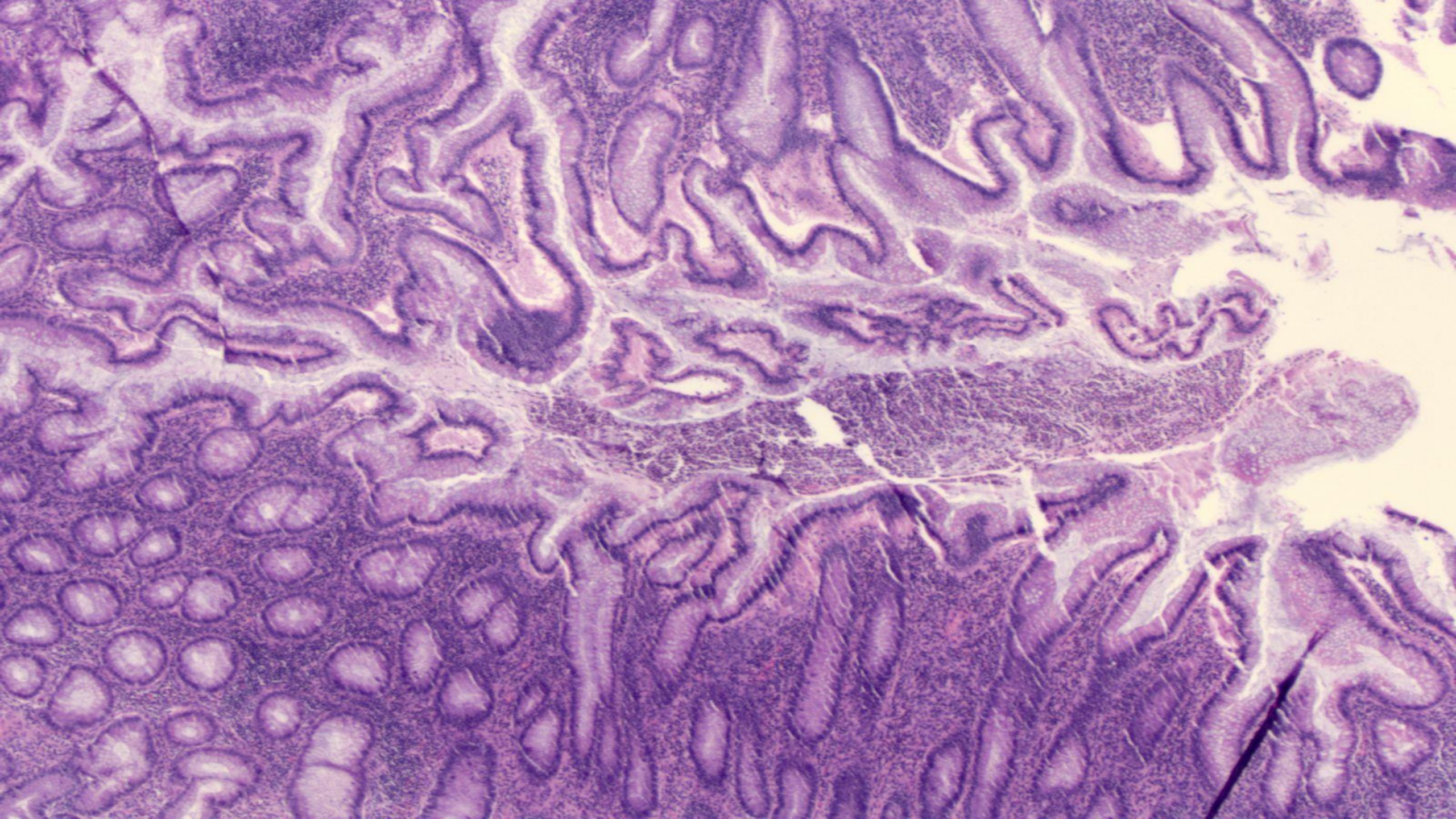
- Mucinous adenocarcinomas commonly have KRAS mutations and 35% have GNAS
- Occasional mucinous adenocarcinomas demonstrate mutations in TP53, PIK3CA, SMAD4, AKT1, and APC.
- Only 3% of appendix cancers show MSI (as opposed to 20% in the right colon and 15% of colon overall).
- MSI cancers may be more likely to show loss of MSH2/MSH6 expression than MLH1 promoter methylation.

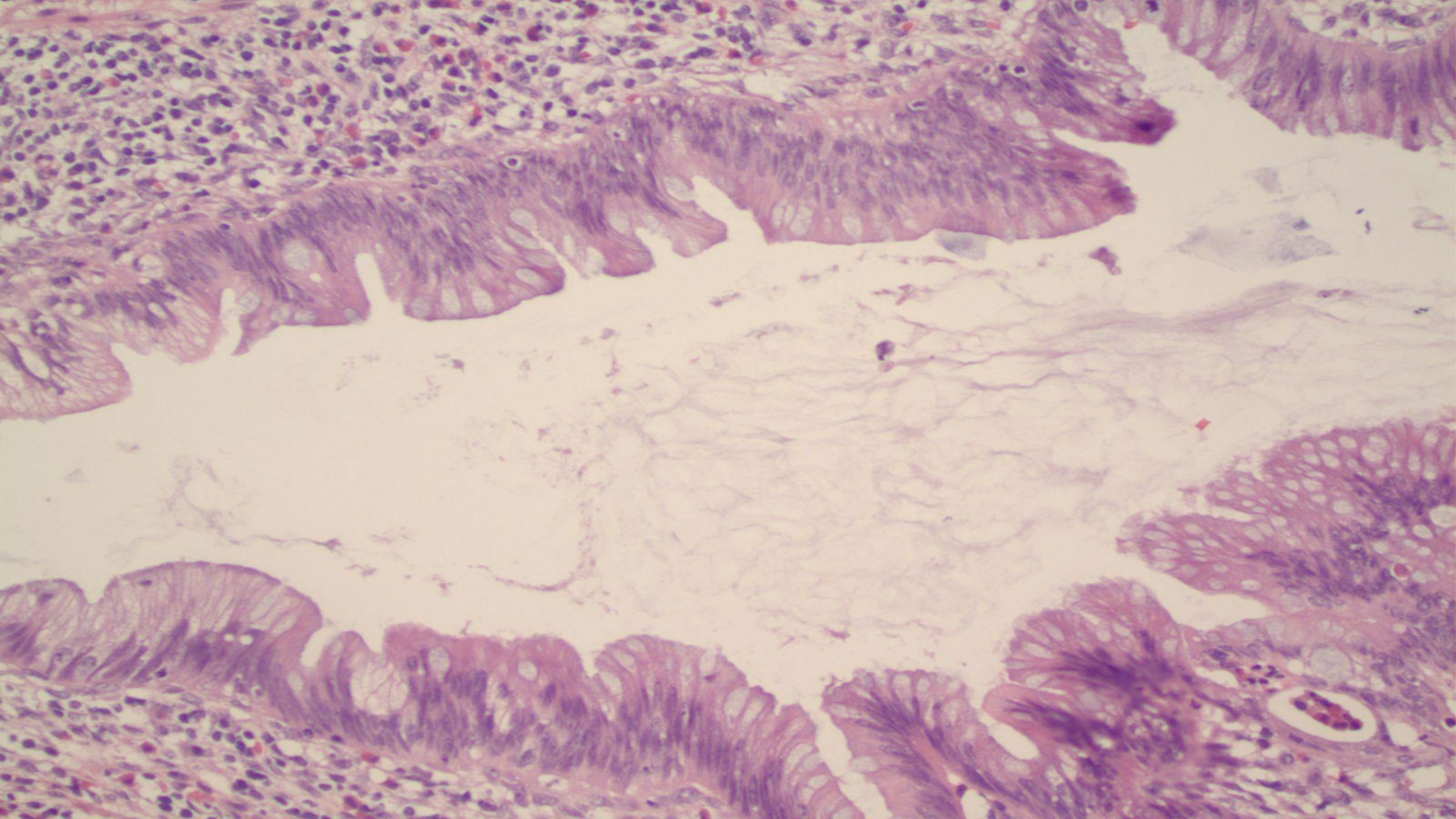
Kabbani W, Houlihan PS, Luthra R, et al. Modern Pathology 2002;15:599-605
Misdraji J, Burgart LJ, Lauwers GY. Modern Pathology 2004;17:1447-1452.
Hara K, Saito T, Hayashi T, et al. Pathology, Research and Practice. 2013;211:657-64.
Taggart MW, Galbincea J, Mansfield PF, et al. AJSP 2013;37:1192-200.

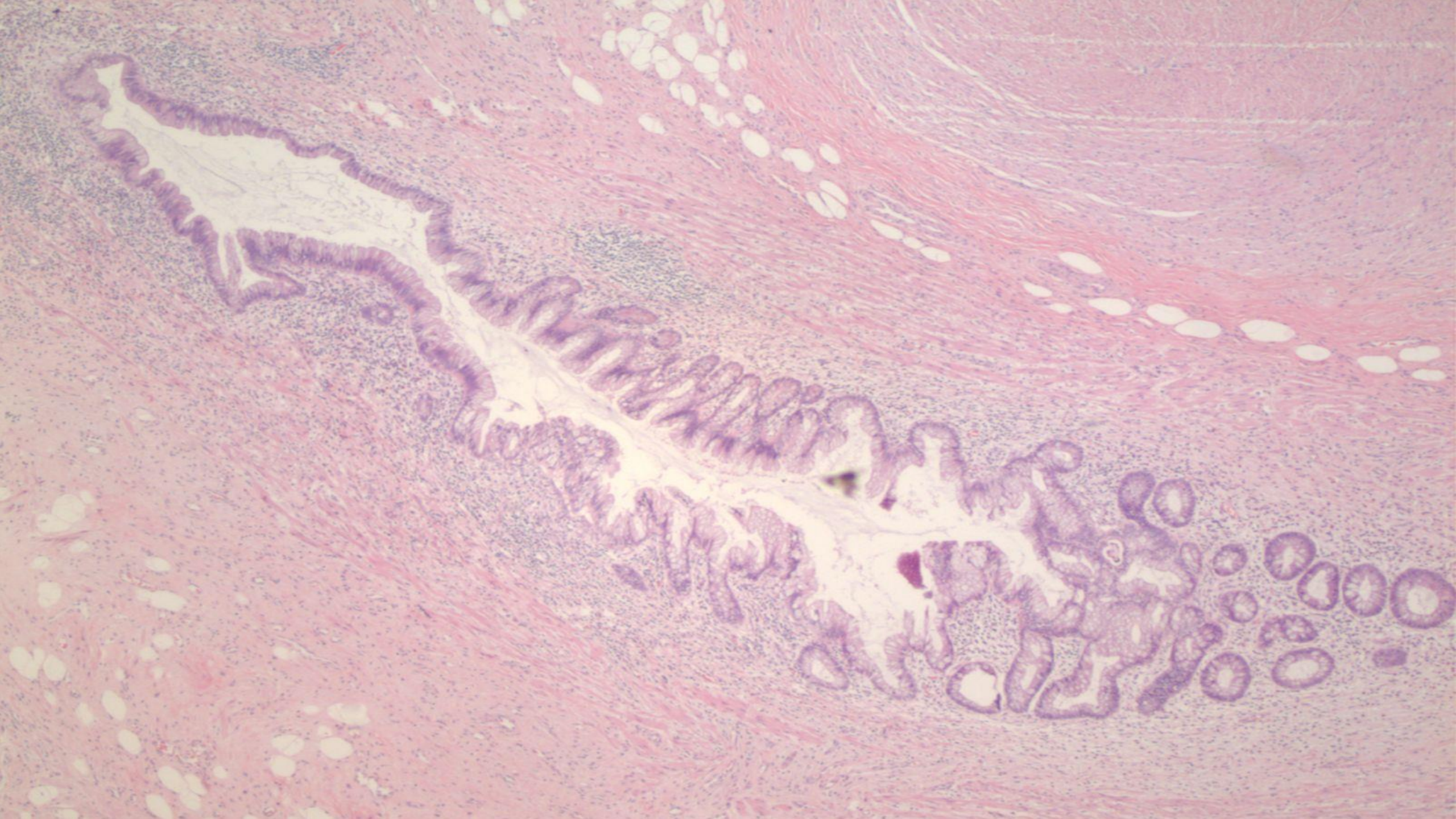
Differential diagnosis of mucinous neoplasia

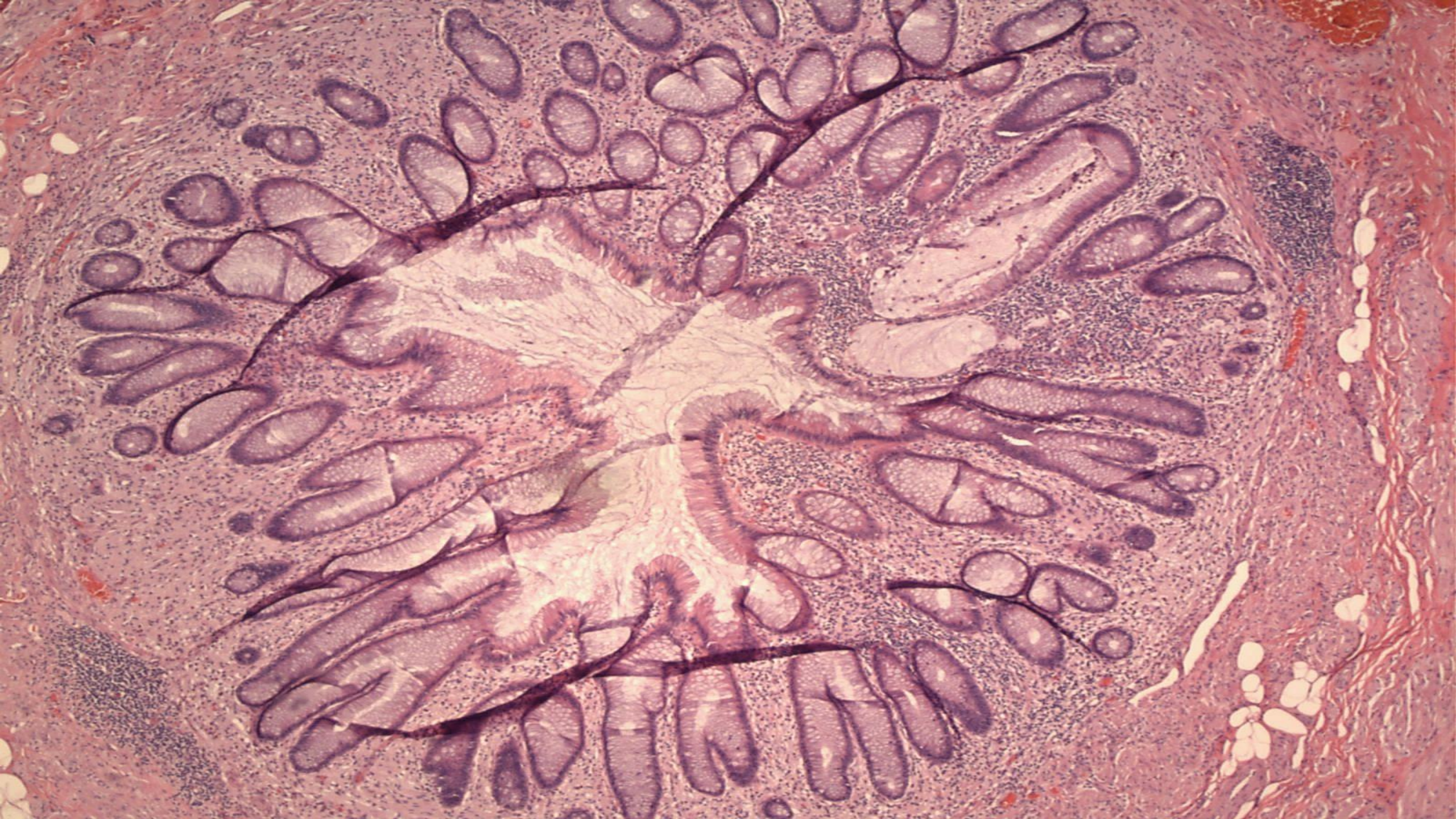
- Ruptured appendiceal diverticular disease
- Retention mucocele
- Endometriosis with intestinal metaplasia

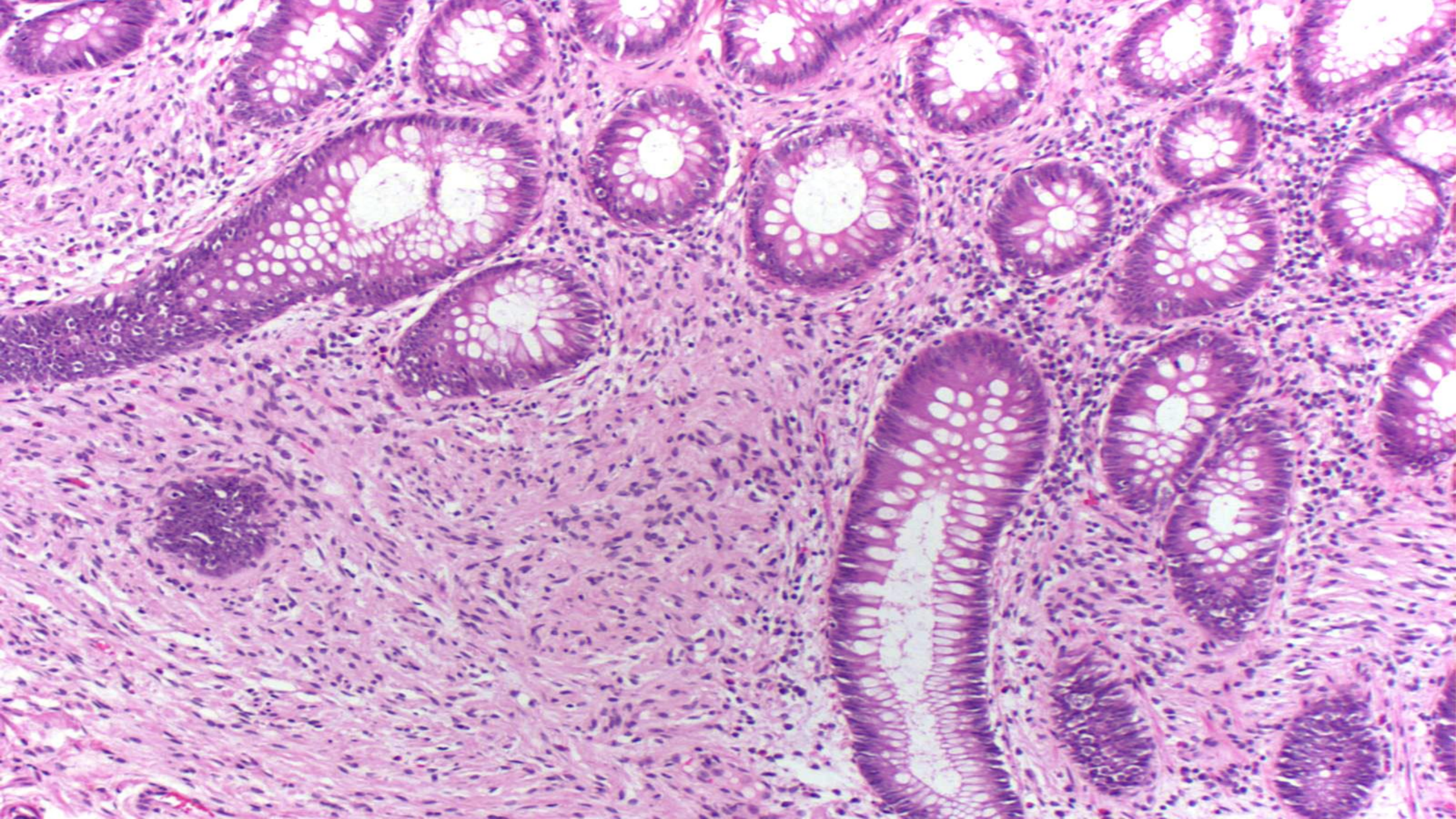












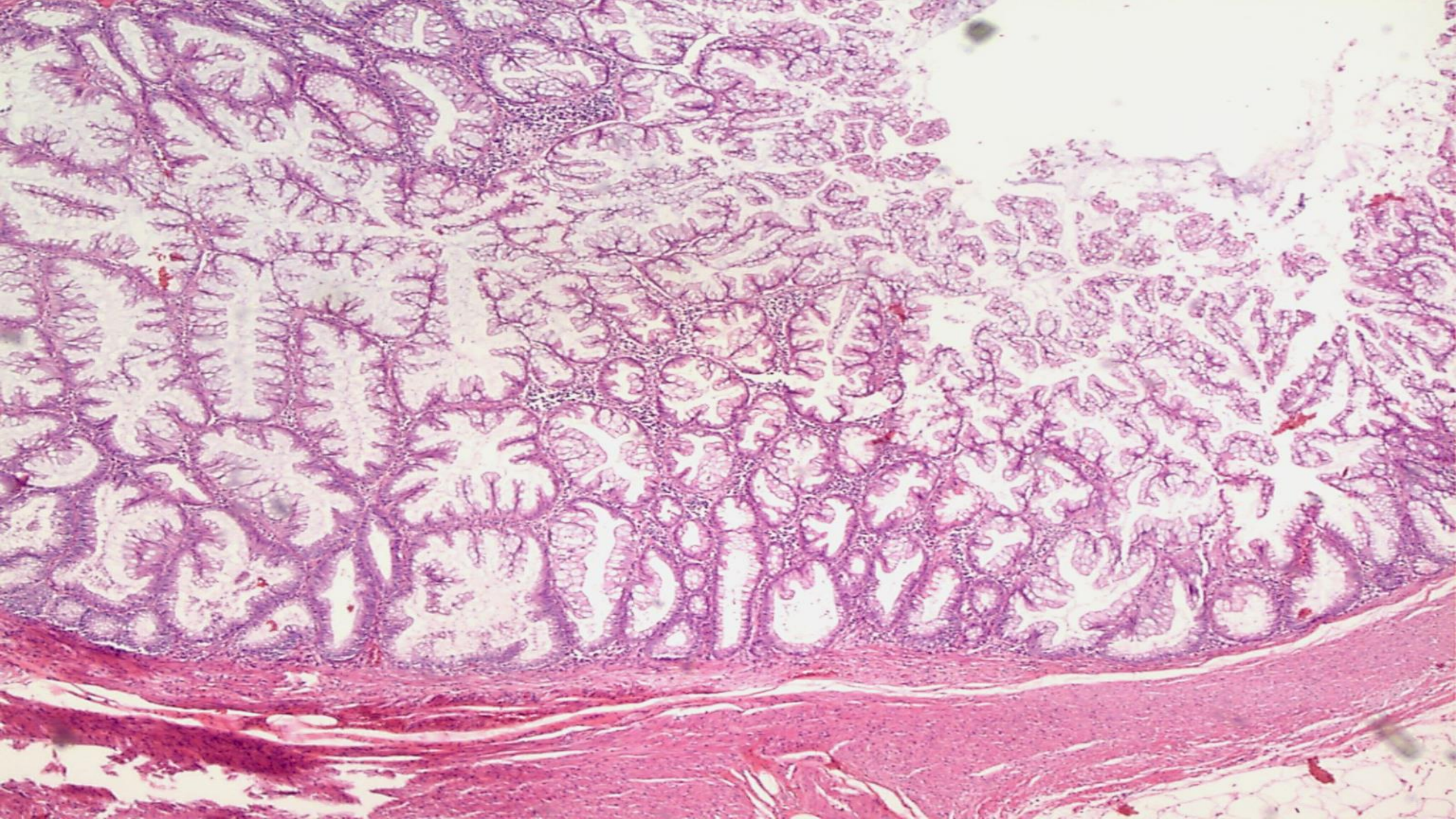
Serrated polyps in the colon vs. appendix

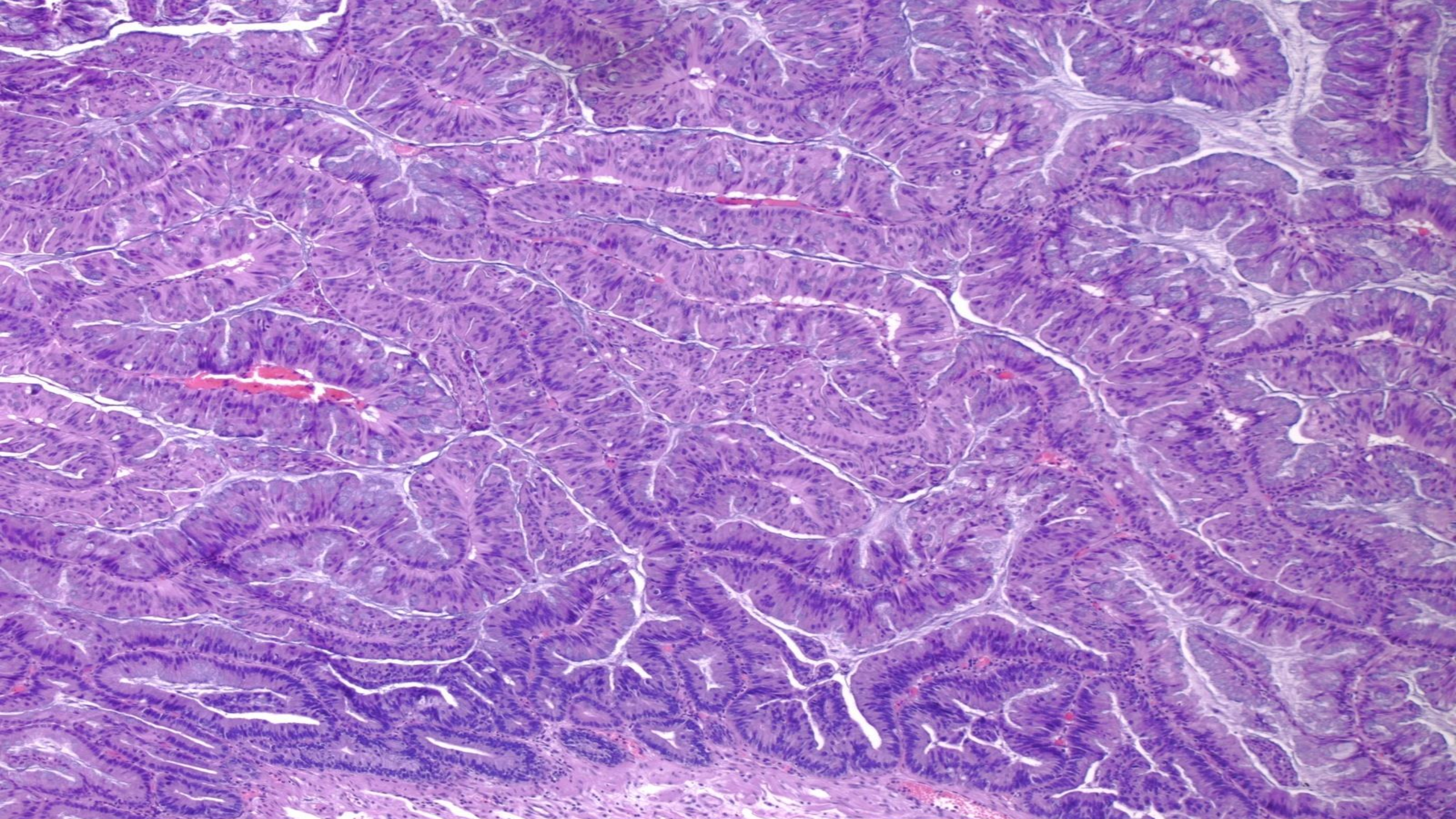
Colon

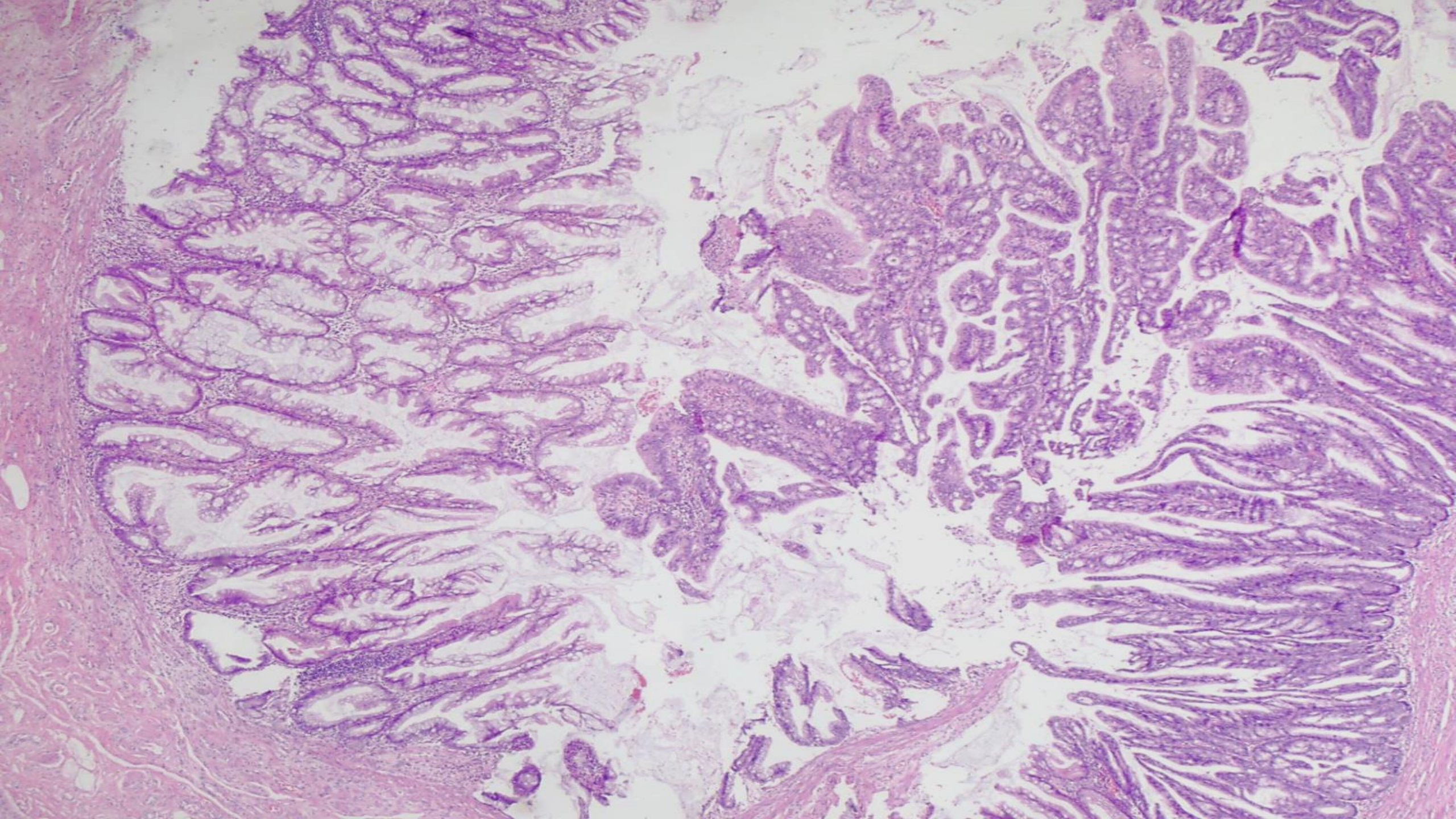
- Hyperplastic polyp
- Sessile serrated adenoma/polyp
- SSA/P with dysplasia
- Traditional serrated adenoma
- Mixed polyp

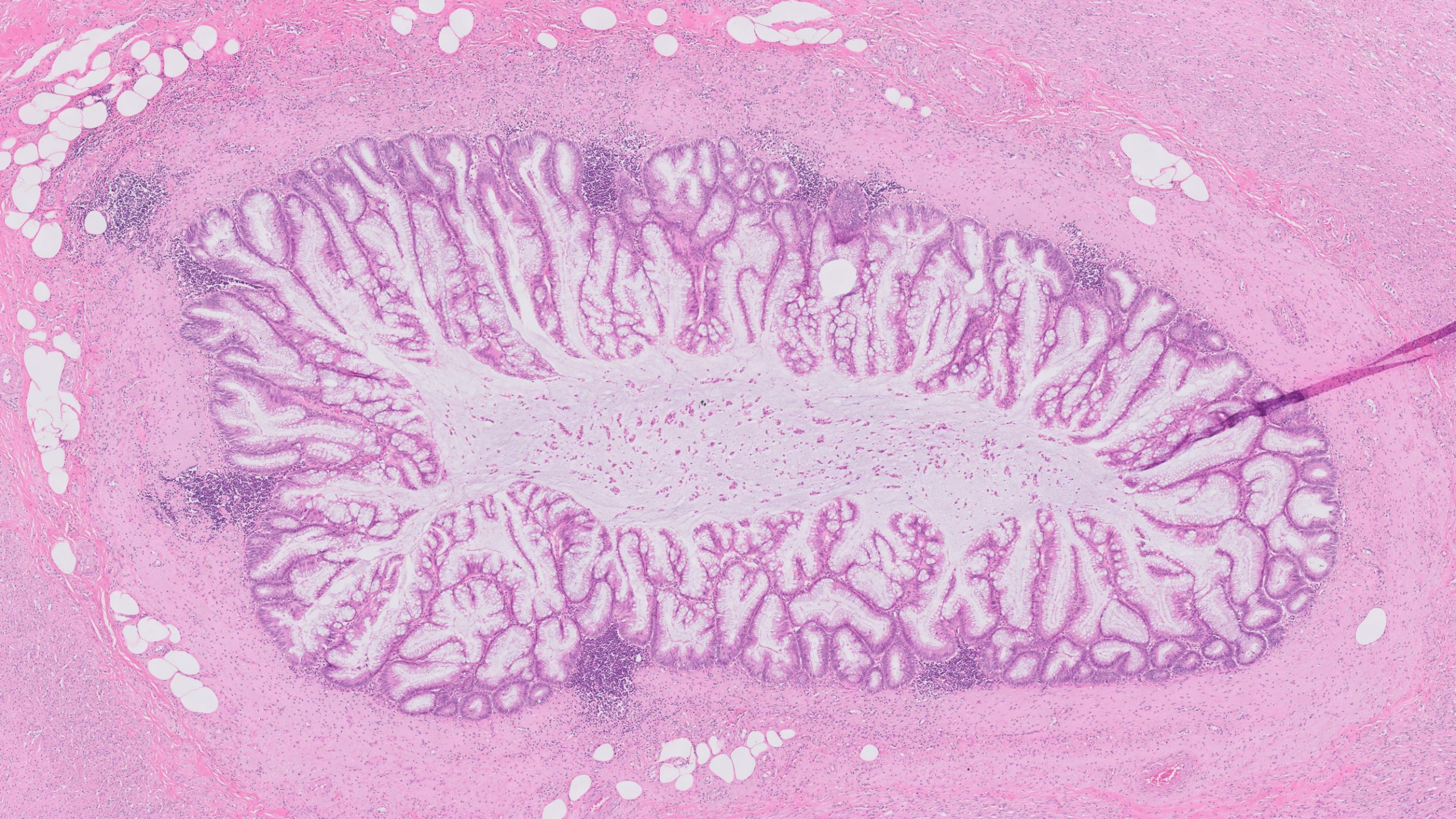
Appendix

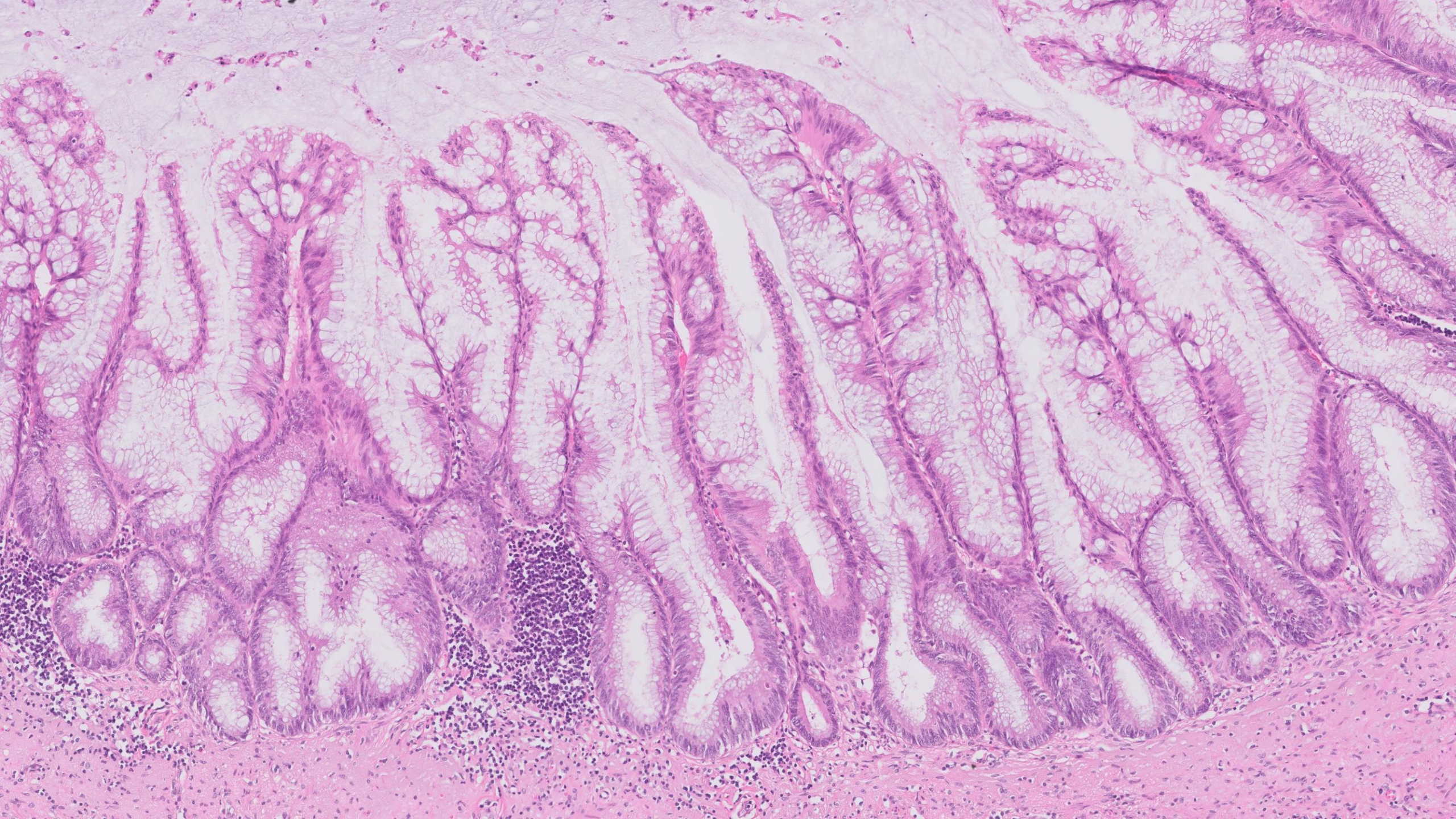
- Hyperplastic polyp/mucosal hyperplasia
- Serrated polyp/lesion without dysplasia
- Serrated polyp/lesion with dysplasia

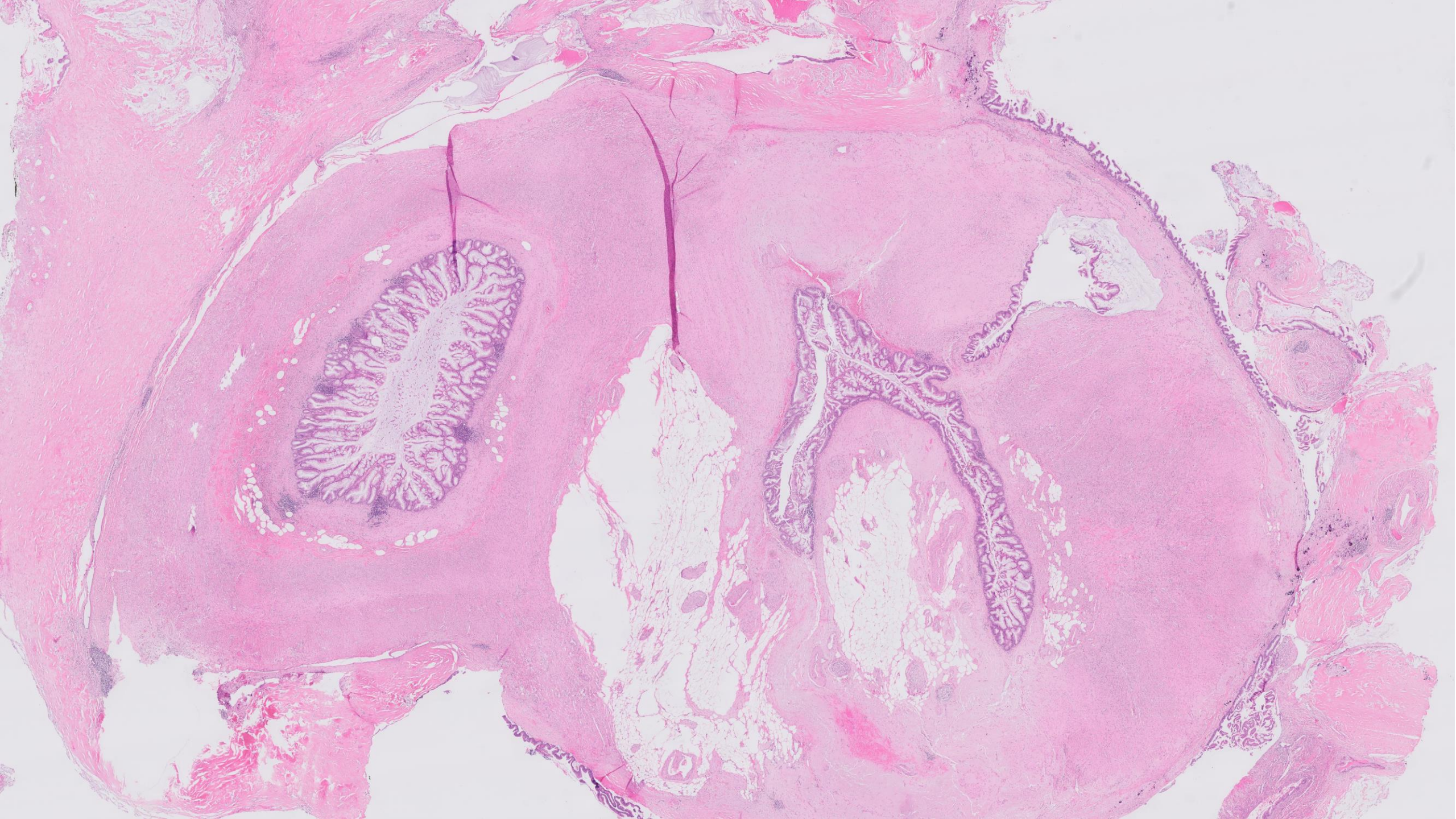












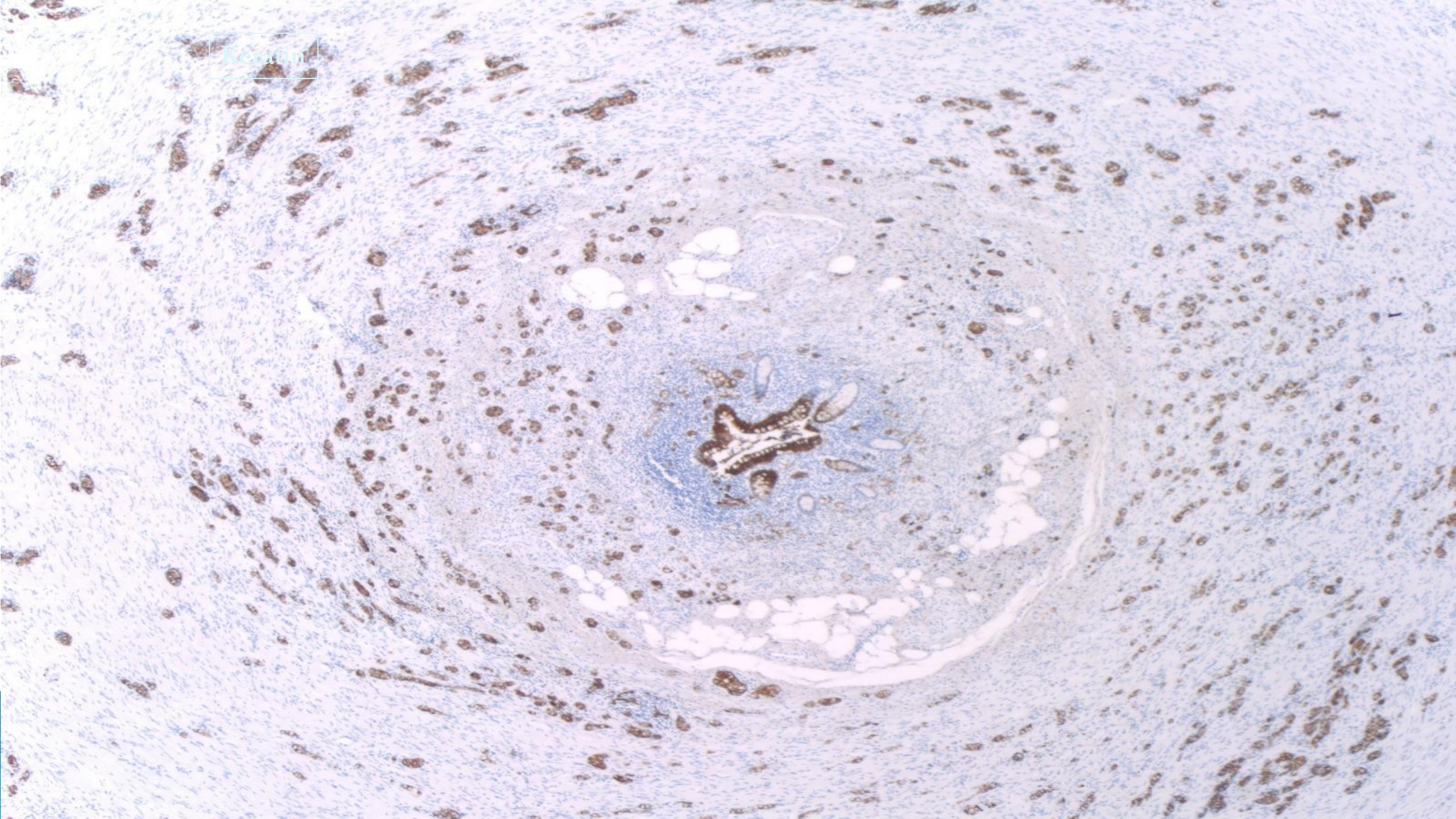
Genetic landscape of appendiceal serrated lesions.

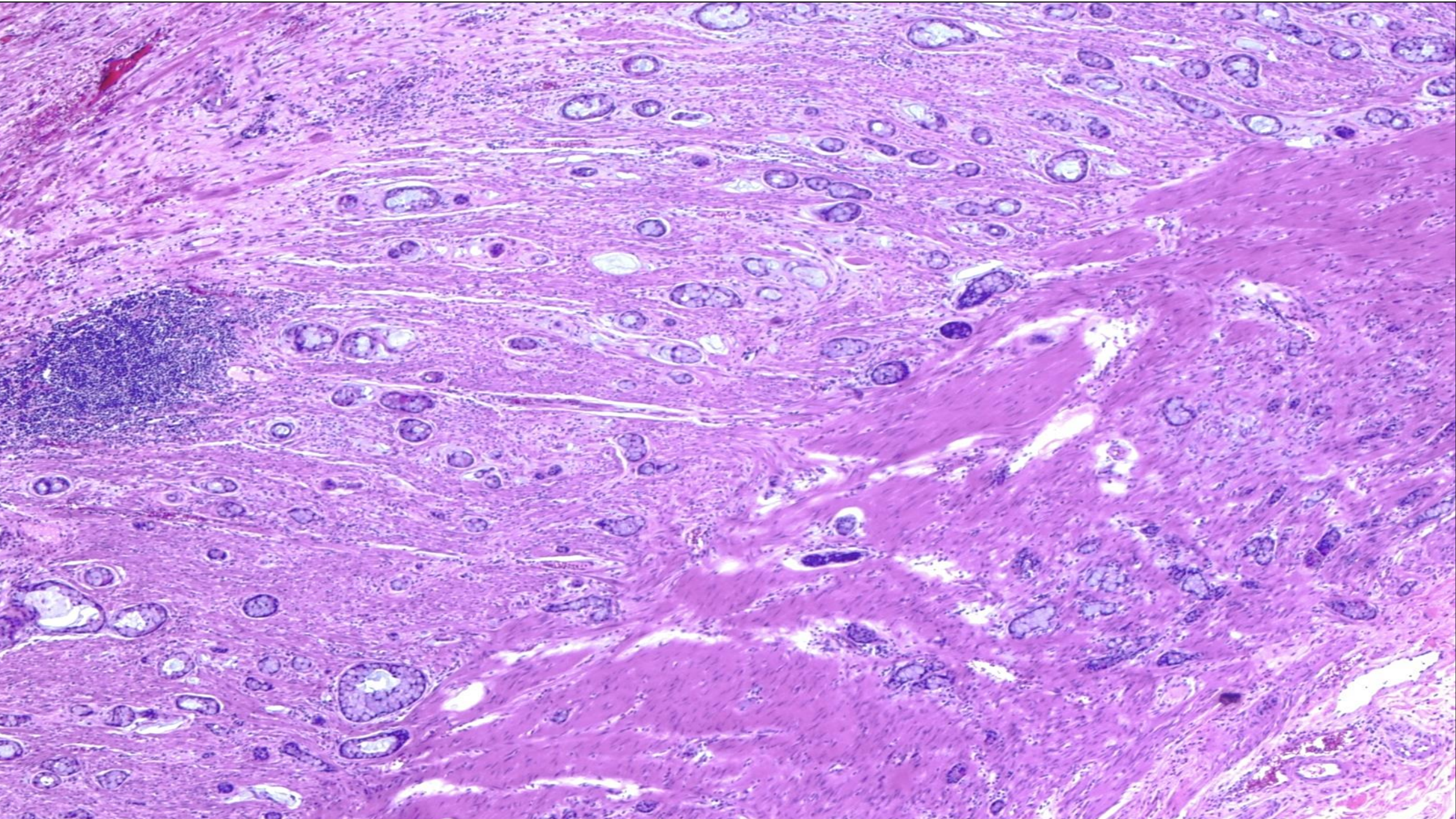
- Appendix serrated polyps often have KRAS mutations (50%), particularly those with dysplasia.
- They infrequently have BRAF mutations (10-20%).
- KRAS may be more biologically important in the appendix than BRAF, and the serrated pathway of carcinogenesis may have less relevance in the appendix than in the colon.

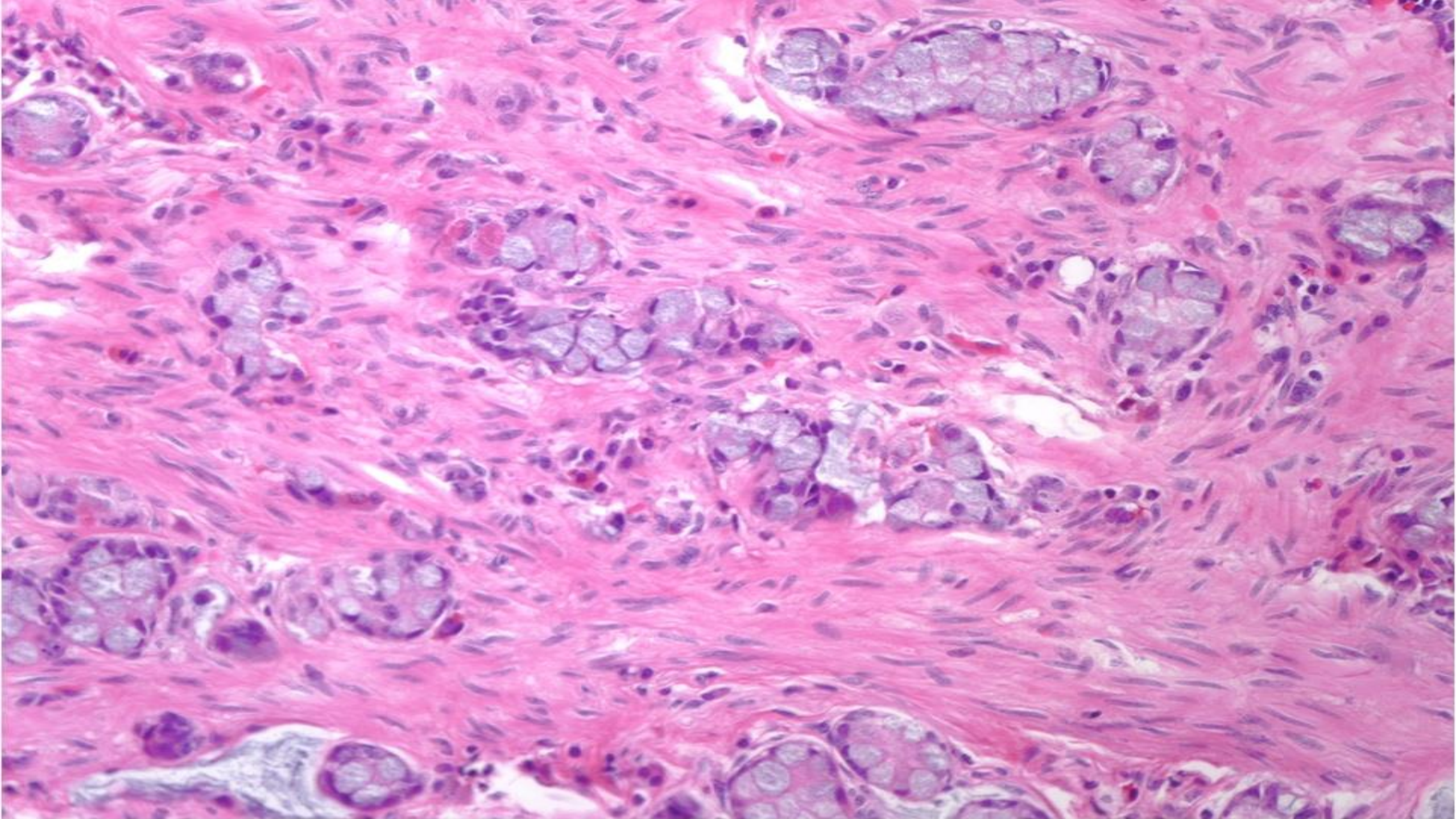
Yantiss RK, Panczykowski A, Misdraji J, et al. AJSP 2007;31:1742-53
Pai RK, Hartman DJ, Gonzalo DH, et al. Human pathology. 2014;45:227-35

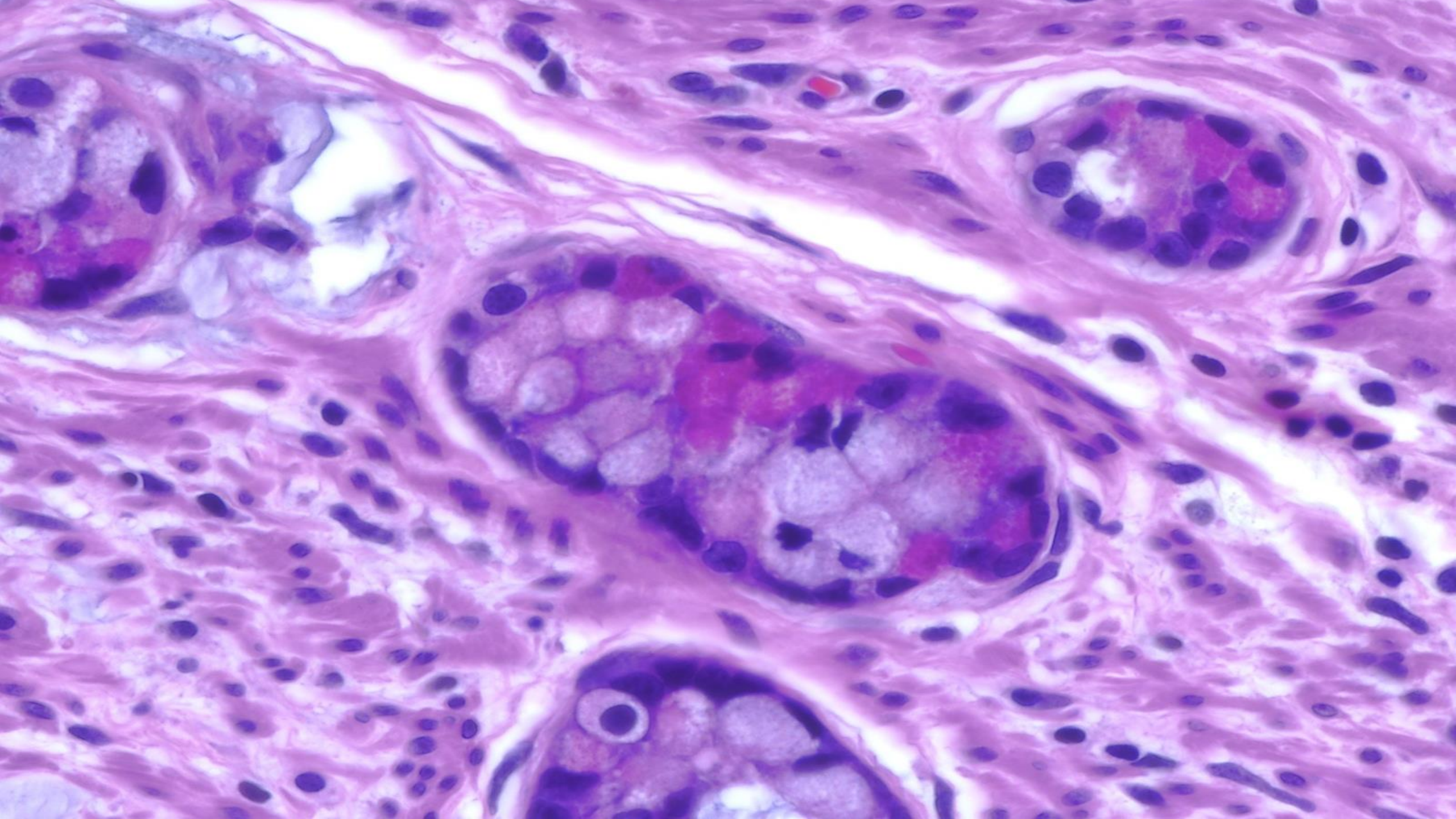
Goblet cell “carcinoid”

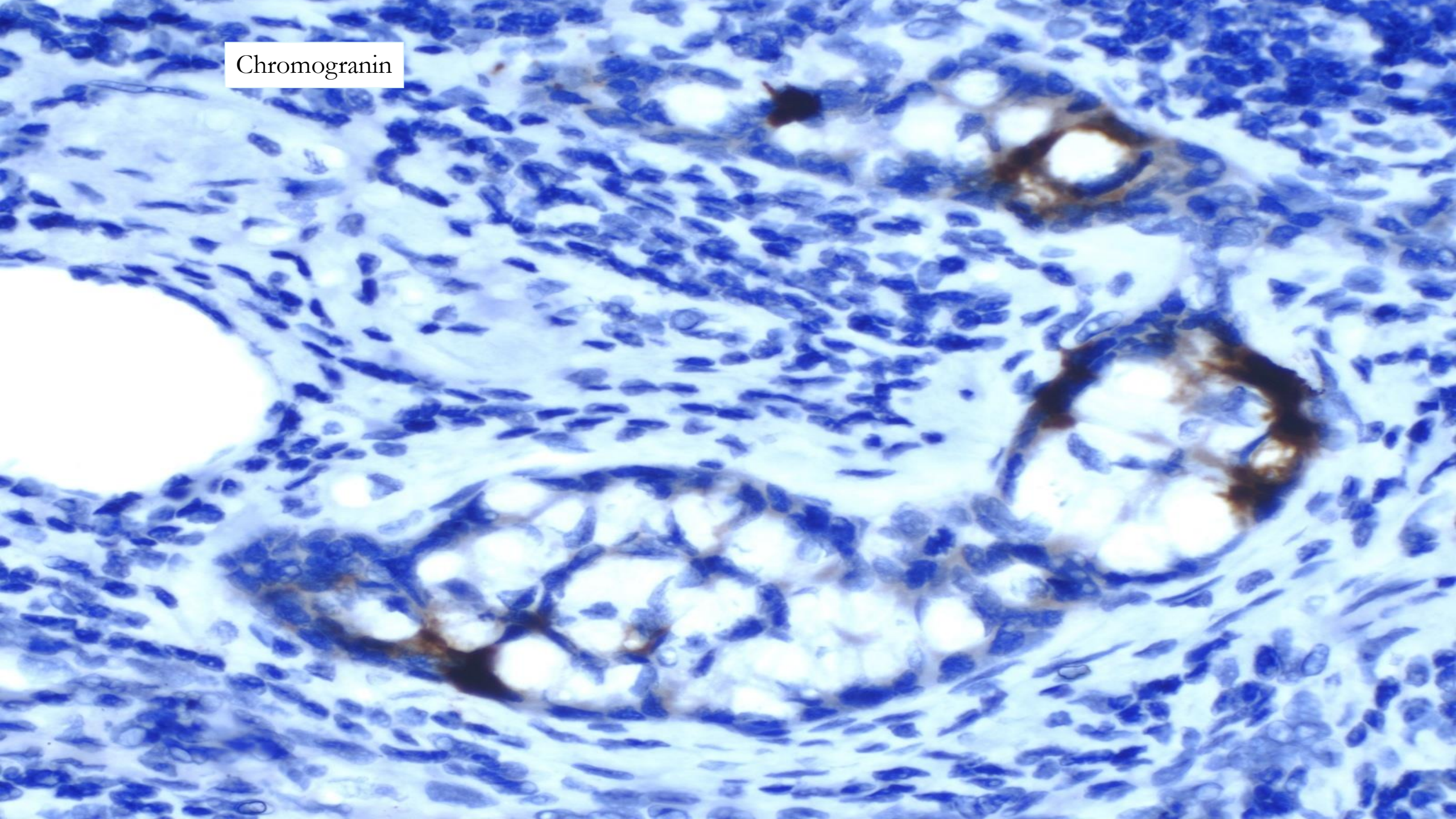
- Appendiceal tumor with mucinous and neuroendocrine differentiation
- M = F; average 40s
- Present with appendicitis, incidentally, or as ovarian metastases (“Krukenberg”)
- Grossly, normal-appearing or somewhat thickened appendix
  - Size difficult to determine in many cases
  - Proximal margin must be identified

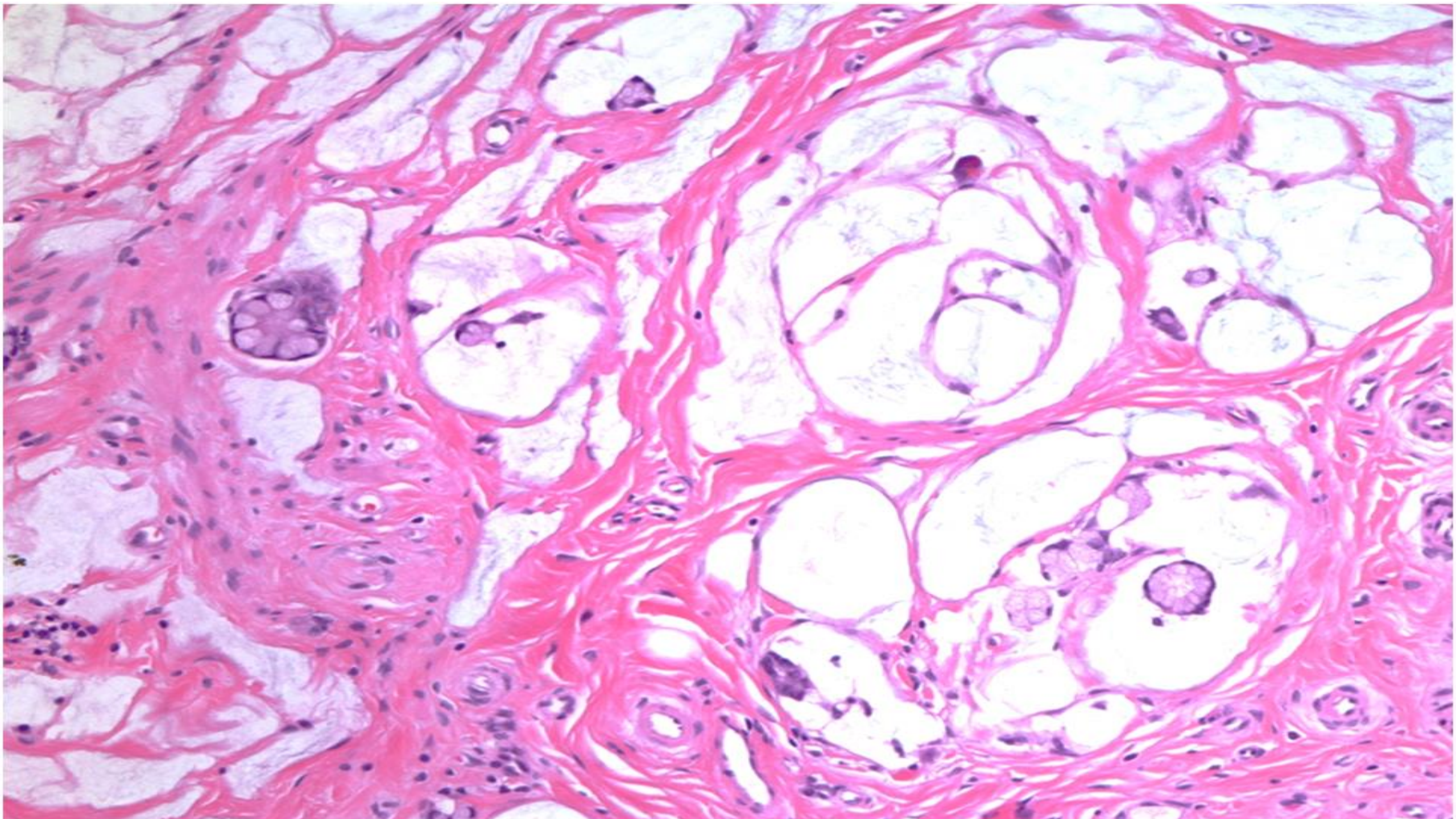

Keratin








Chromogranin



Adenocarcinoma ex Goblet Cell Carcinoid
Burke Am J Clin Pathol 1990

- 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 Oct 2008

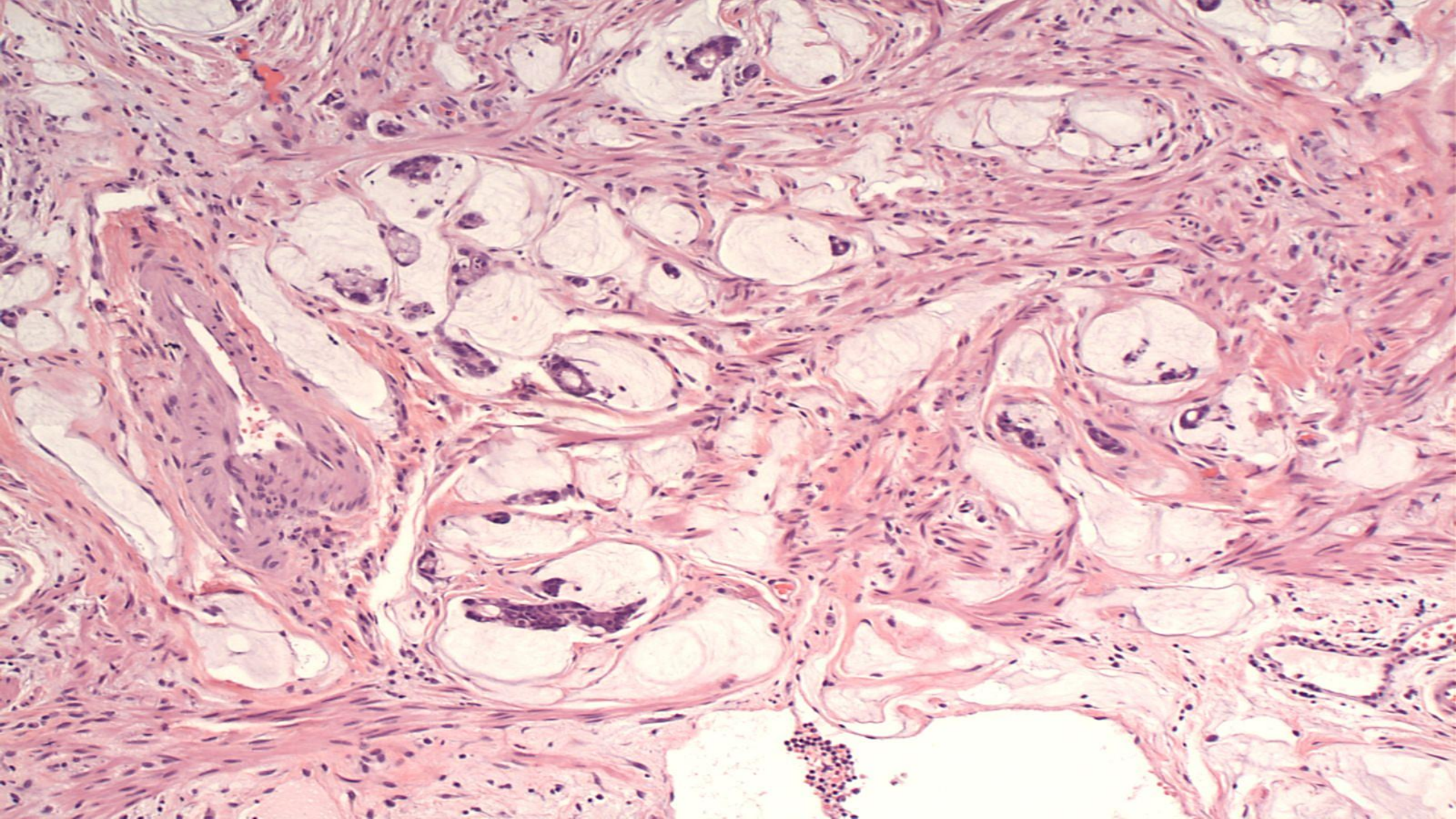
Classification of tumors with at least focal GCC

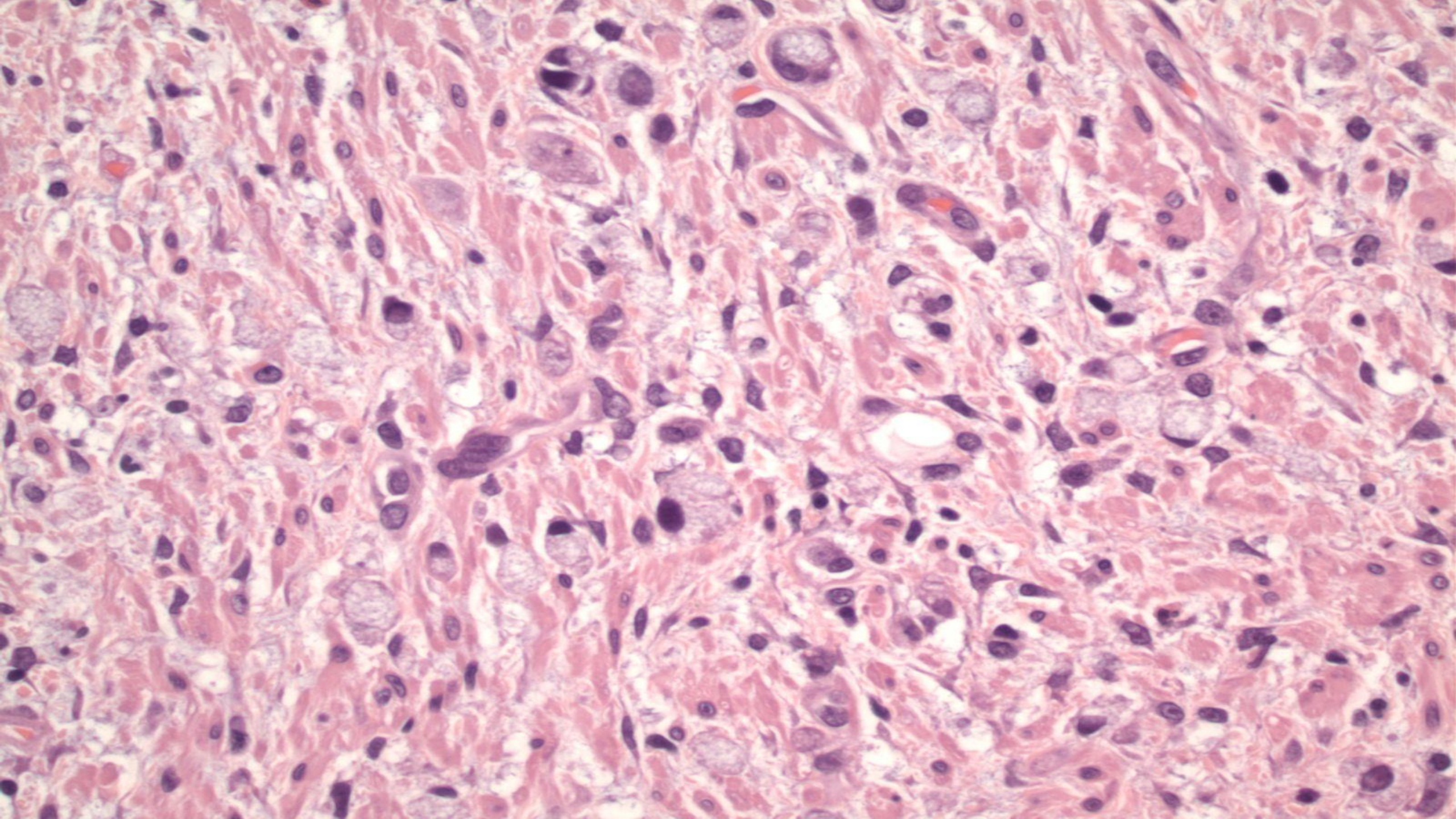
- Goblet cell carcinoid
- Adenocarcinoma ex GCC, signet ring cell type
- Adenocarcinoma ex GCC, poorly differentiated adenocarcinoma type

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

Tang LH, et al. AJSP Oct 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.

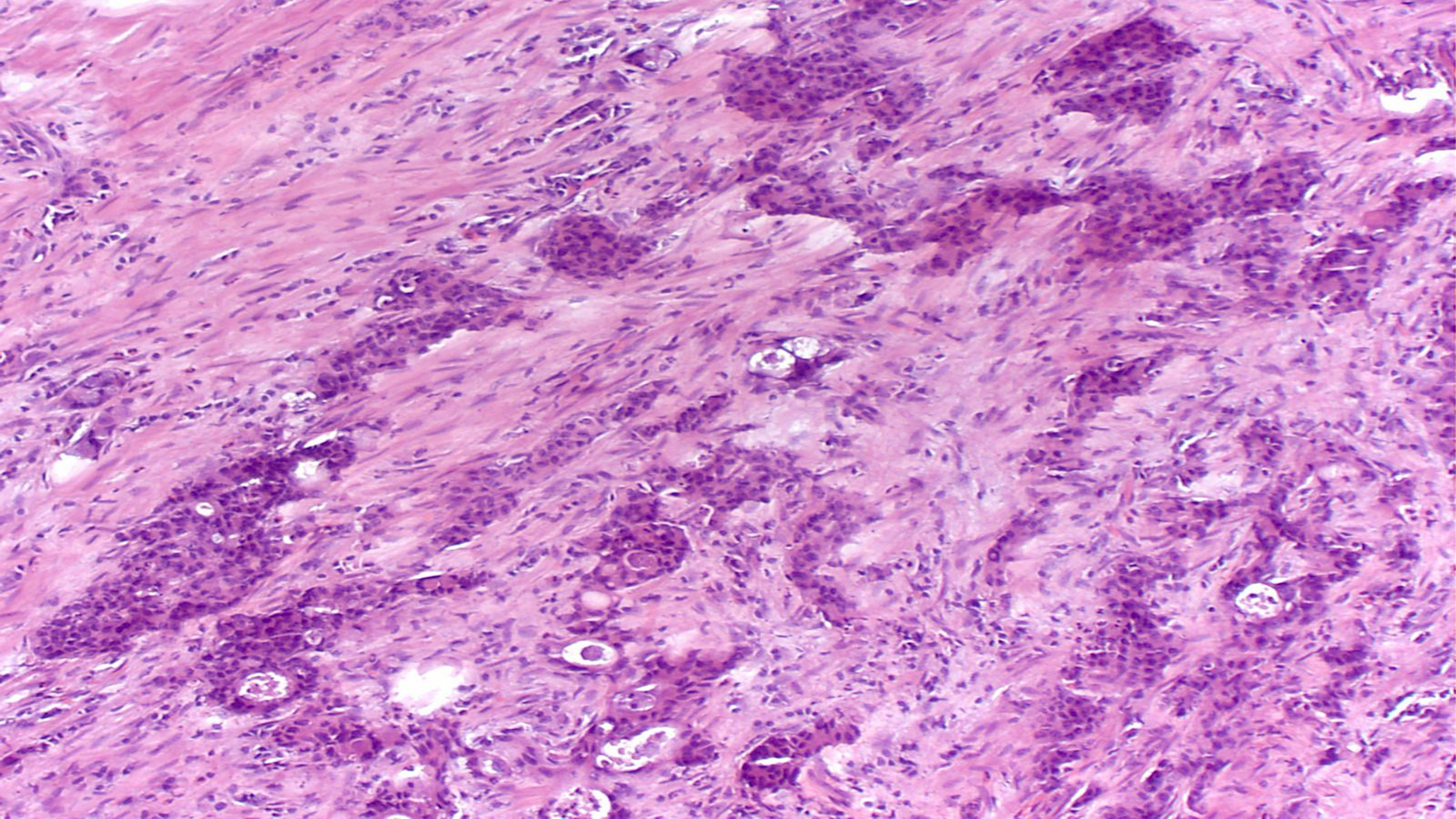




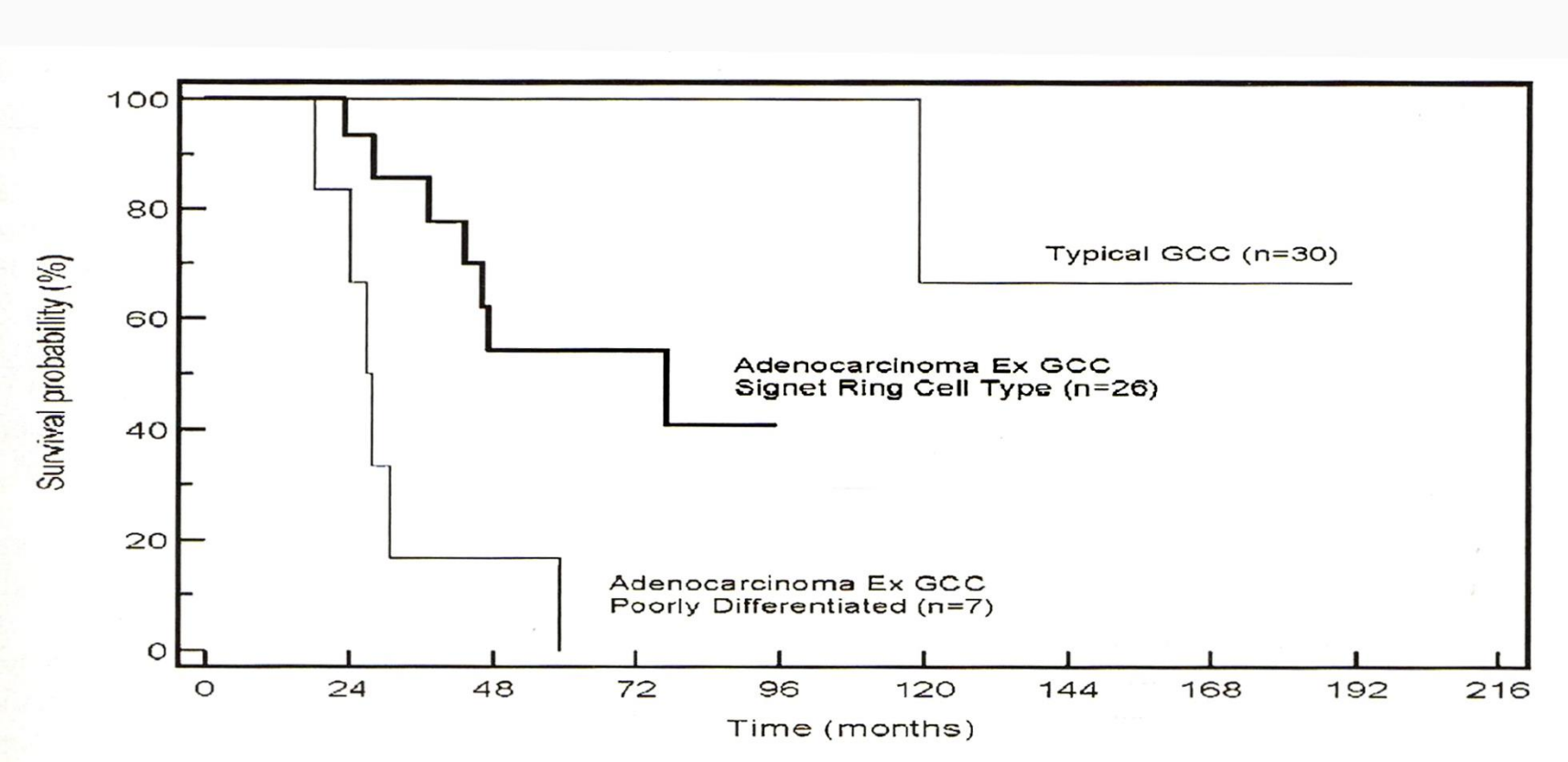
Pathologic Classification and Clinical Behavior of the Spectrum of Goblet Cell Carcinoid Tumors of the Appendix

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 mm^2 indistinguishable from poorly differentiated gland forming adenocarcinoma, signet ring cell adenocarcinoma, neuroendocrine carcinoma, or undifferentiated carcinoma.



Pathologic Classification Correlated with Outcome



Goblet cell carcinoid, Mixed Goblet cell carcinoid-Adenocarcinoma, and Adenocarcinoma of the Appendix

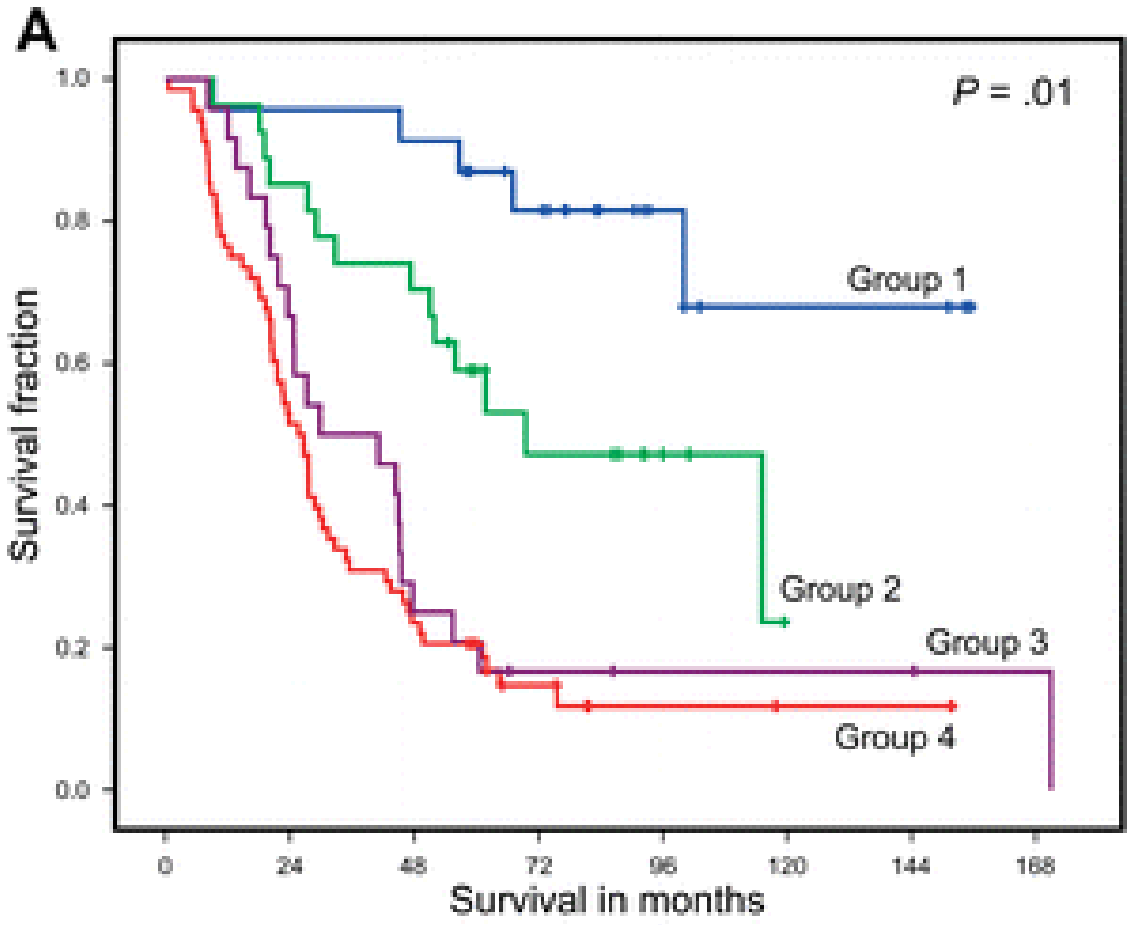
Taggart et al. Arch Pathol Lab Med 2015;139:782-790

- 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 (Group 2; 25-50%) does somewhat better than > 50% (group 3).
- Tumors with >50% adenocarcinoma (group 3) behave like adenocarcinoma (group 4)



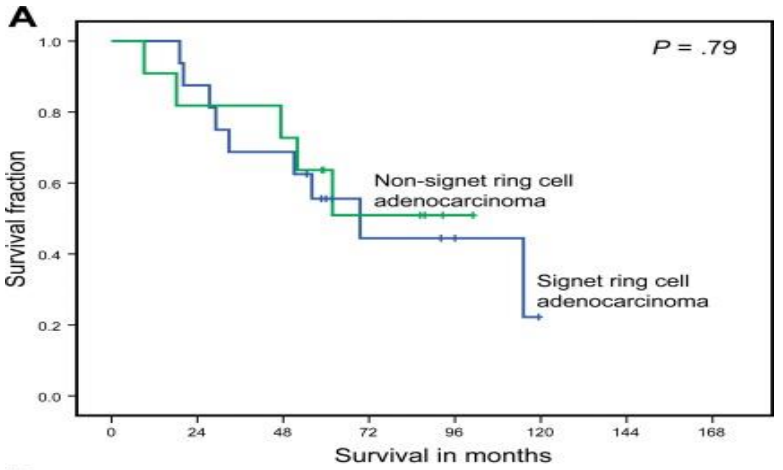
GCC, Mixed GCC–Adenocarcinoma, and Adenocarcinoma of the Appendix

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

- Signet ring cell type and non–signet ring cell type behave similarly.

Group

2



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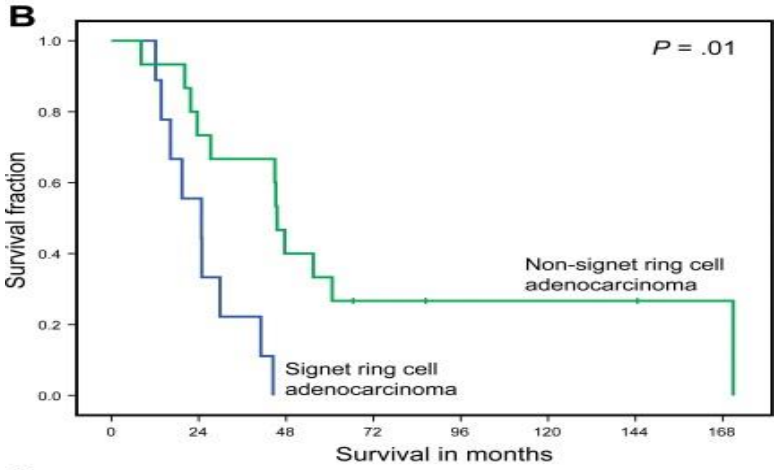

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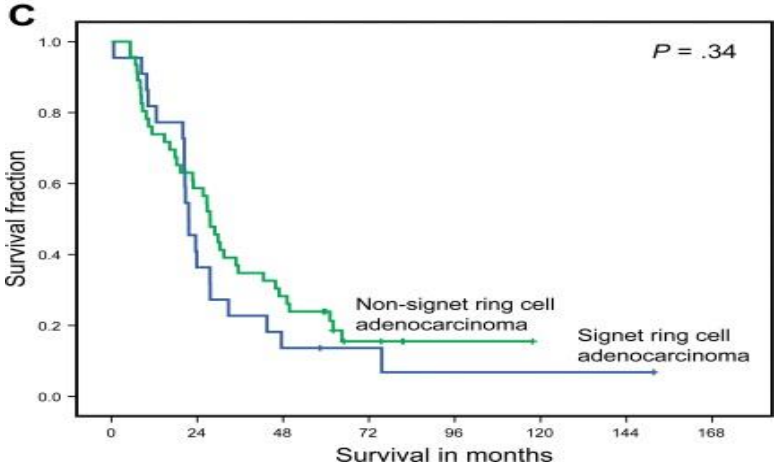


Goblet cell “carcinoid”: Misleading nomenclature, confusing grading schemes.

- The term “carcinoid” misleads pathologists to inappropriately use neuroendocrine staging systems and oncologists to consider therapies for endocrine tumors.
- “Adenocarcinoma ex GCC” implies that an adenocarcinoma evolves from an endocrine tumor, which is confusing and untrue.
- Studies have noted inconsistent use of terminology for difficult or high-grade tumors, and only moderate interobserver agreement using Tang systems.

Mutations landscape of goblet cell tumors

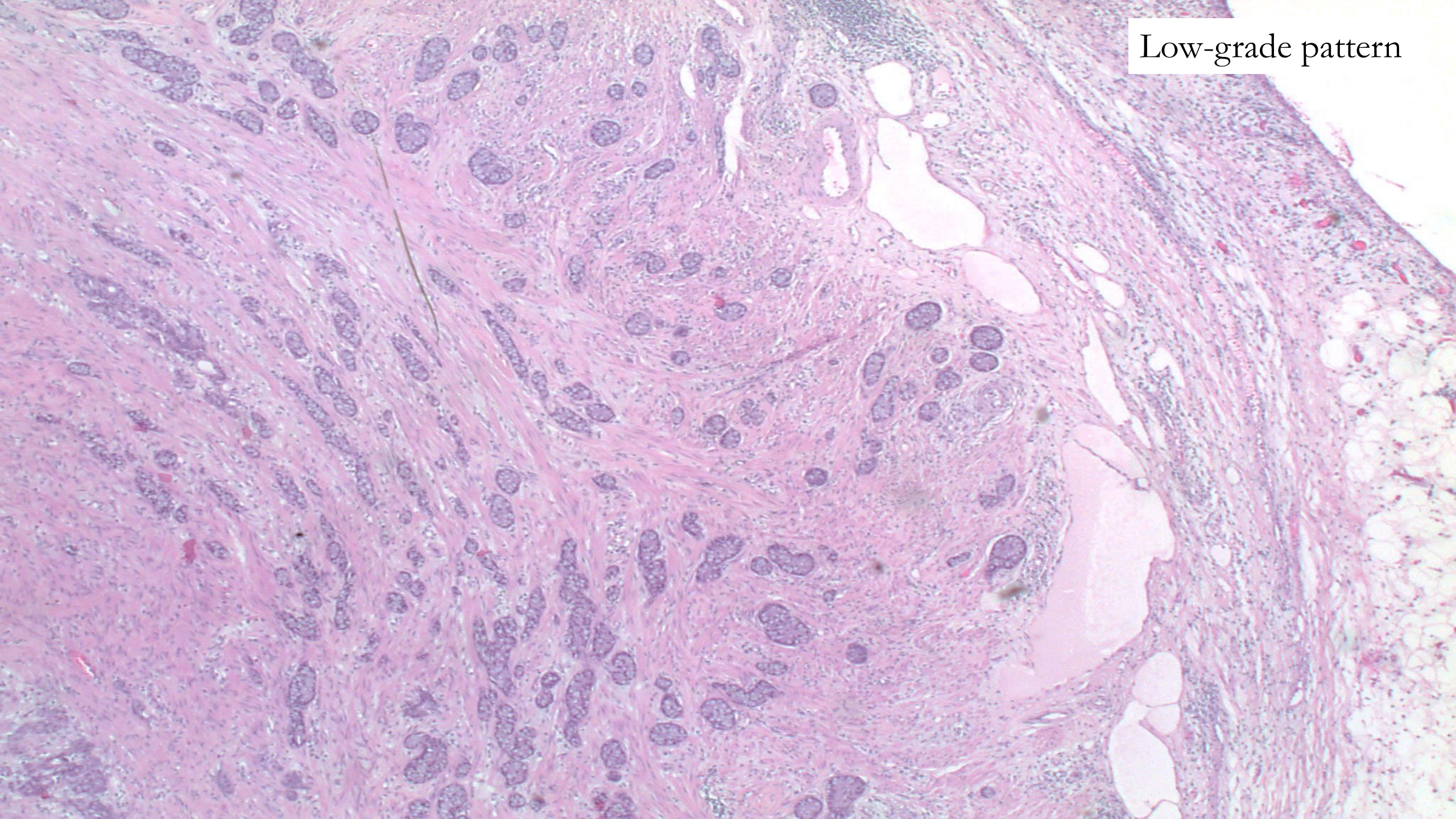
- Mutations in chromatin remodeling genes (ARID2, ARID1A, KMT2D) occur in relatively high proportion of GCC (suggests epigenetic modification in the early stage of tumor formation).
- Mutations typical of CRC adenocarcinoma occur at low frequency (KRAS, P53, BRAF); usually in high-grade tumors.
- A subset have mutations that occur in signet ring cell gastric cancer (e-cadherin, RHOA).
- The overlap between GCC and adenoca-ex-GCC suggests a distinct tumor with a spectrum of grades.

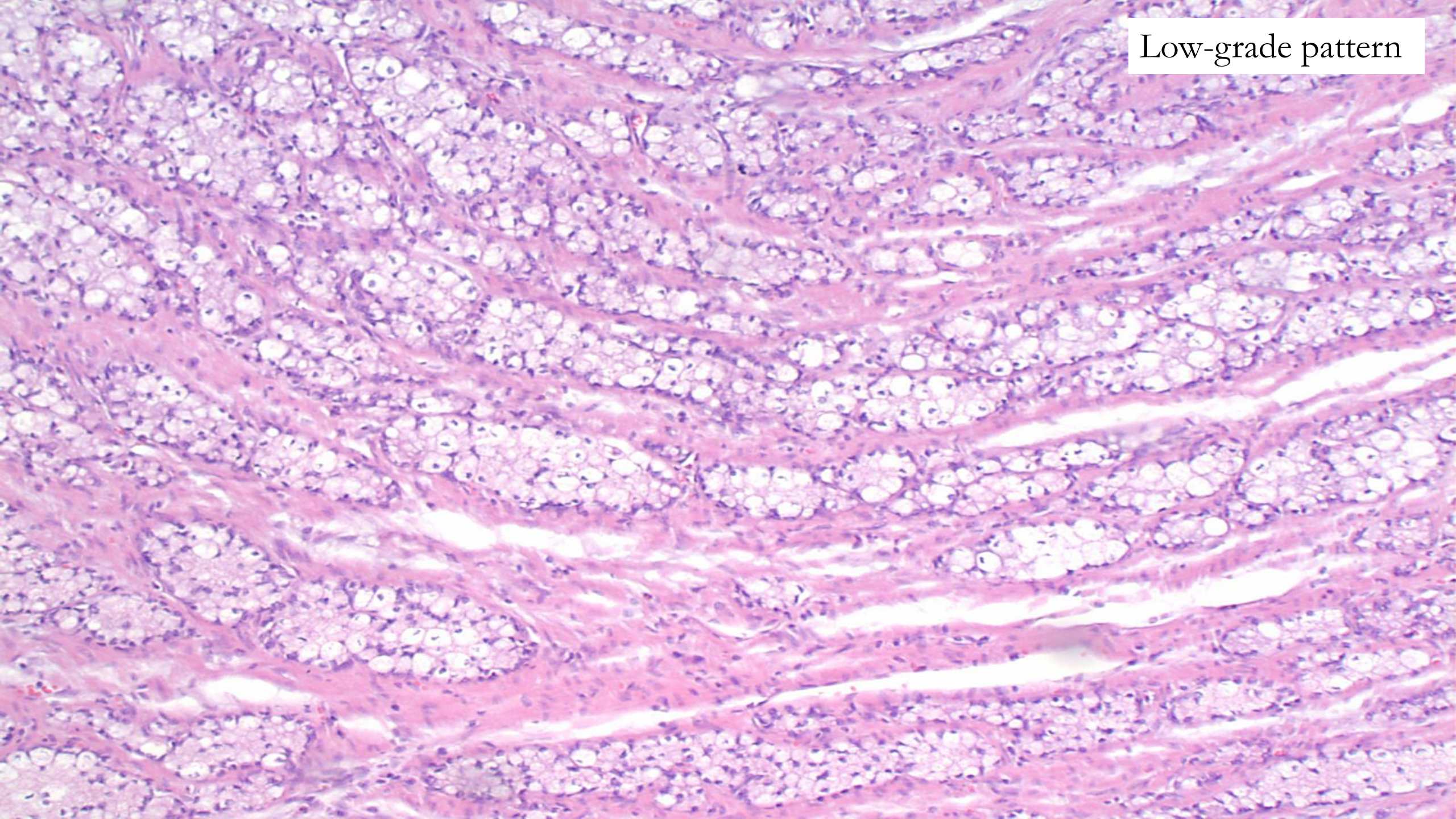
Johncilla M, Stachler M, Misdraji J, et al. Modern Pathology 2018;31: 989-996.
Jesinghaus M, Konukiewitz B, Foersch S, et al. Modern Pathology 2018;31:829-839.

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 "% gland formation", we used % of tubular/clustered growth.
  - Cut off values 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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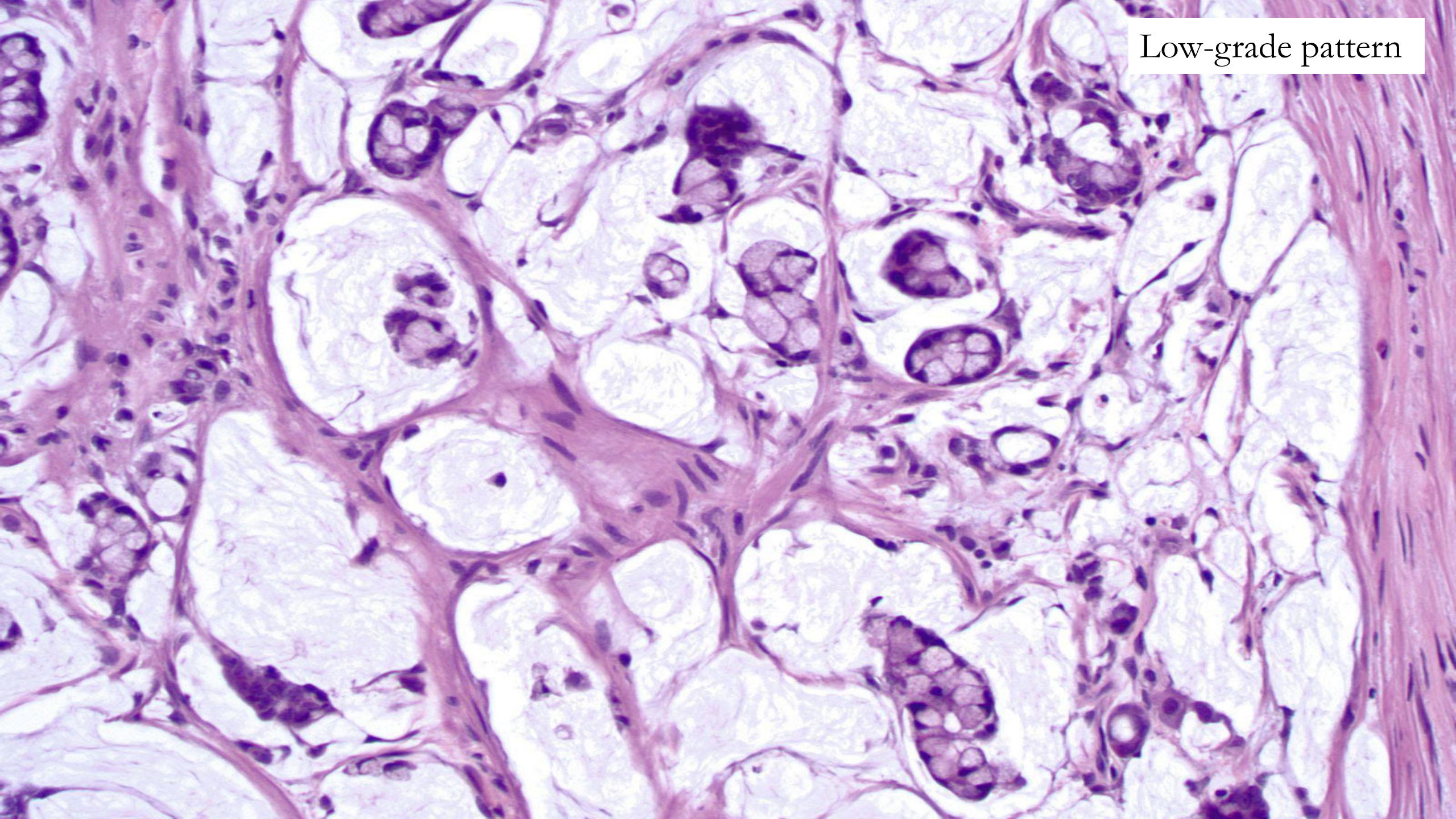
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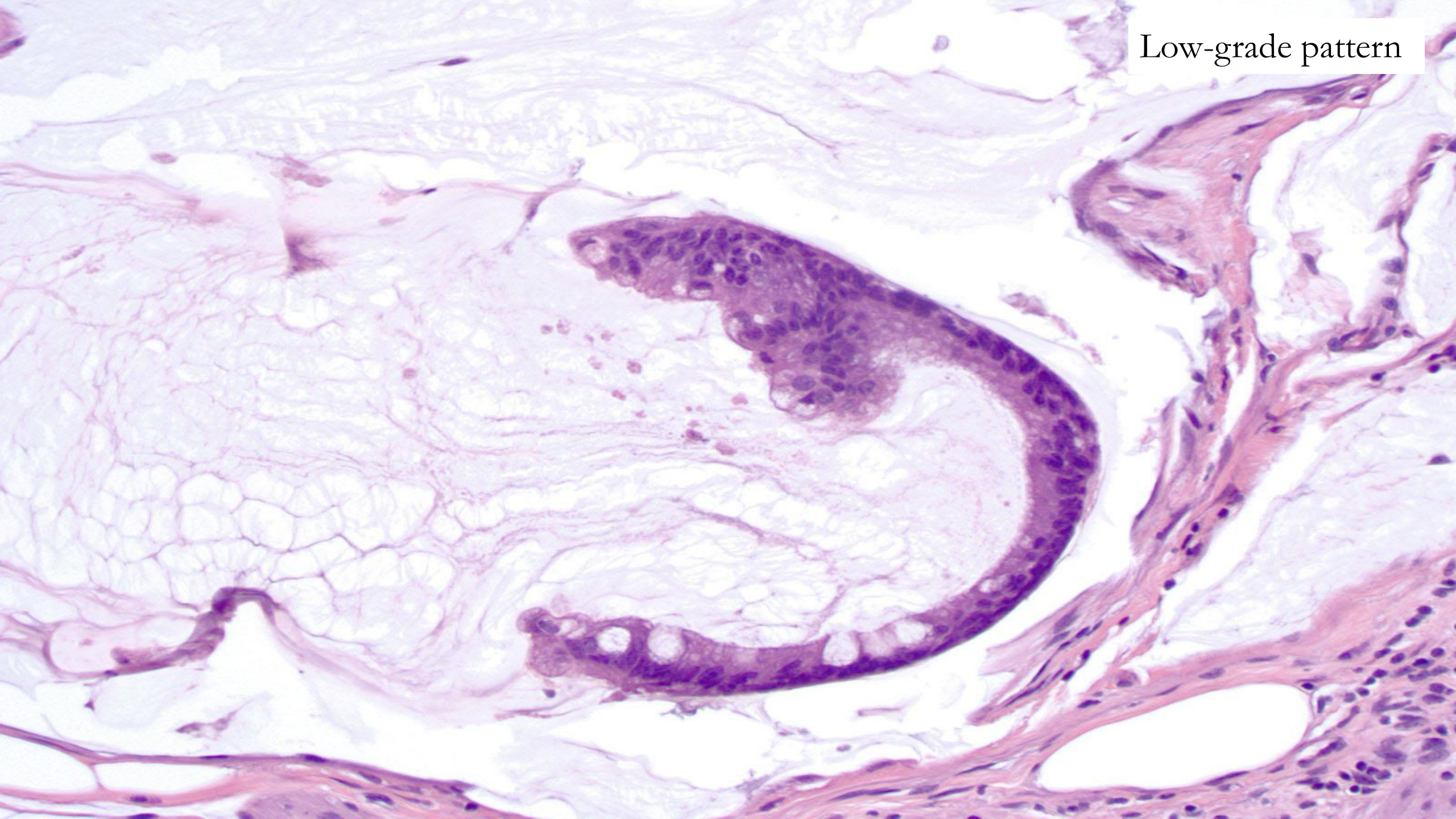
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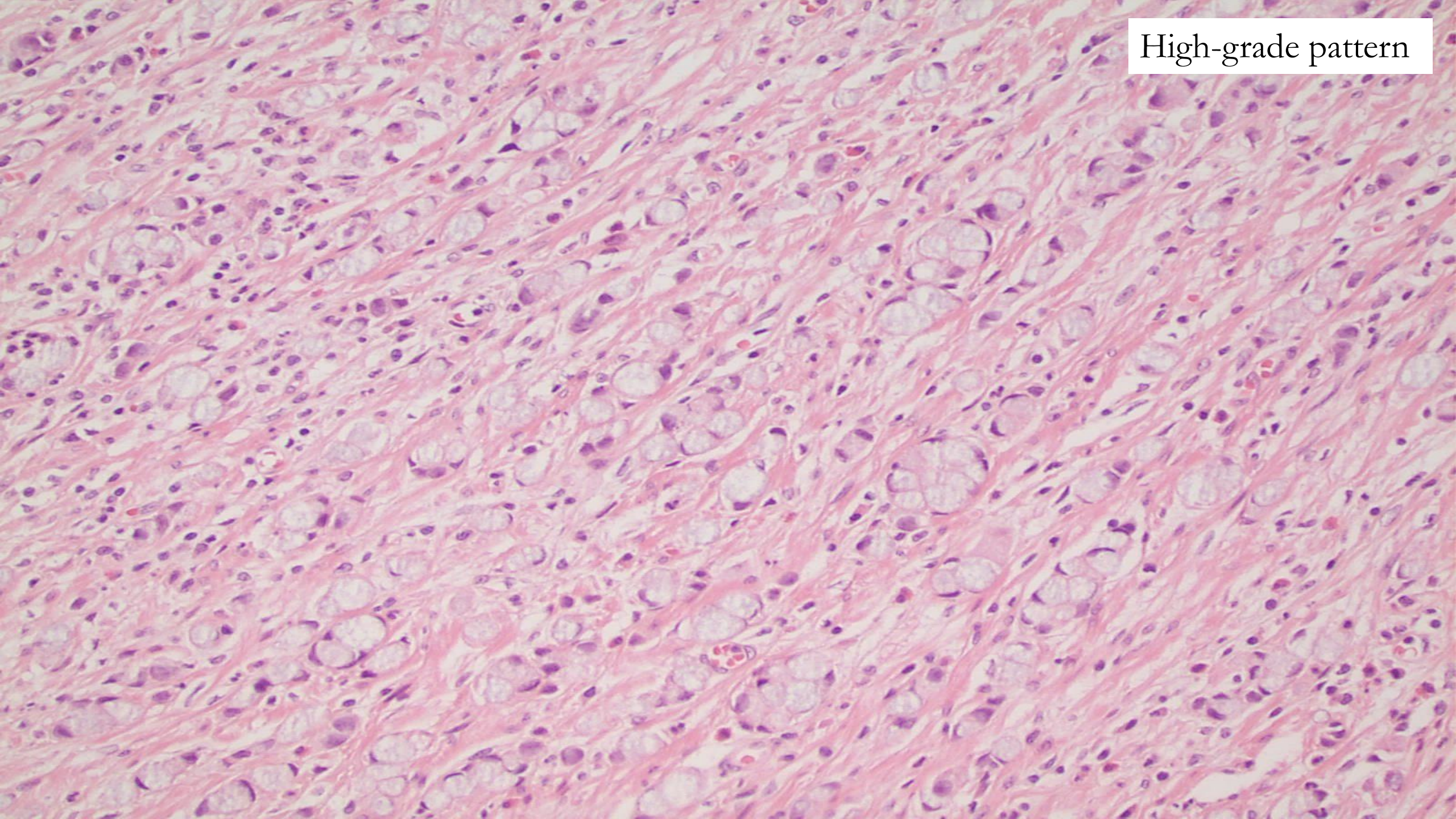
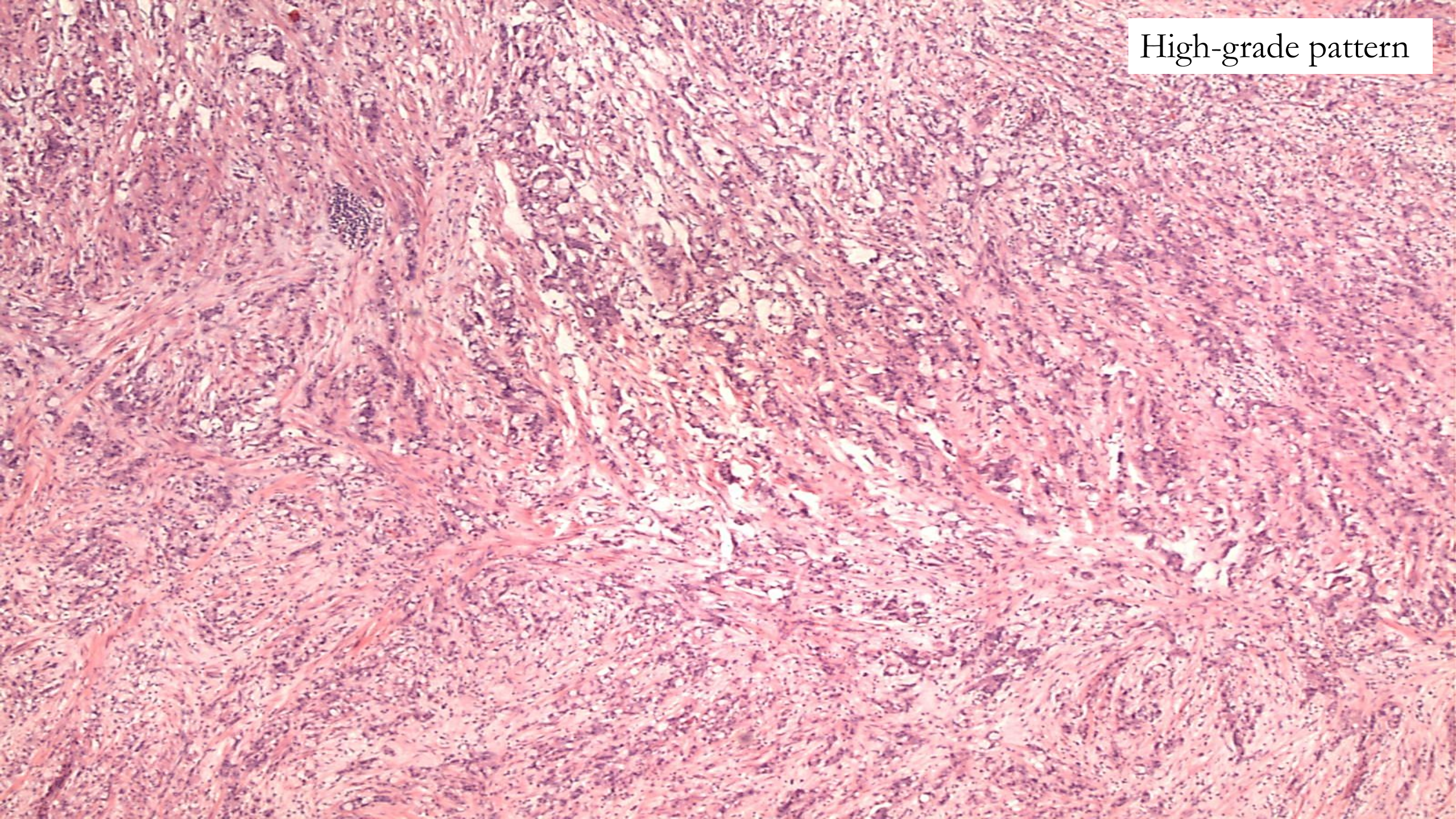
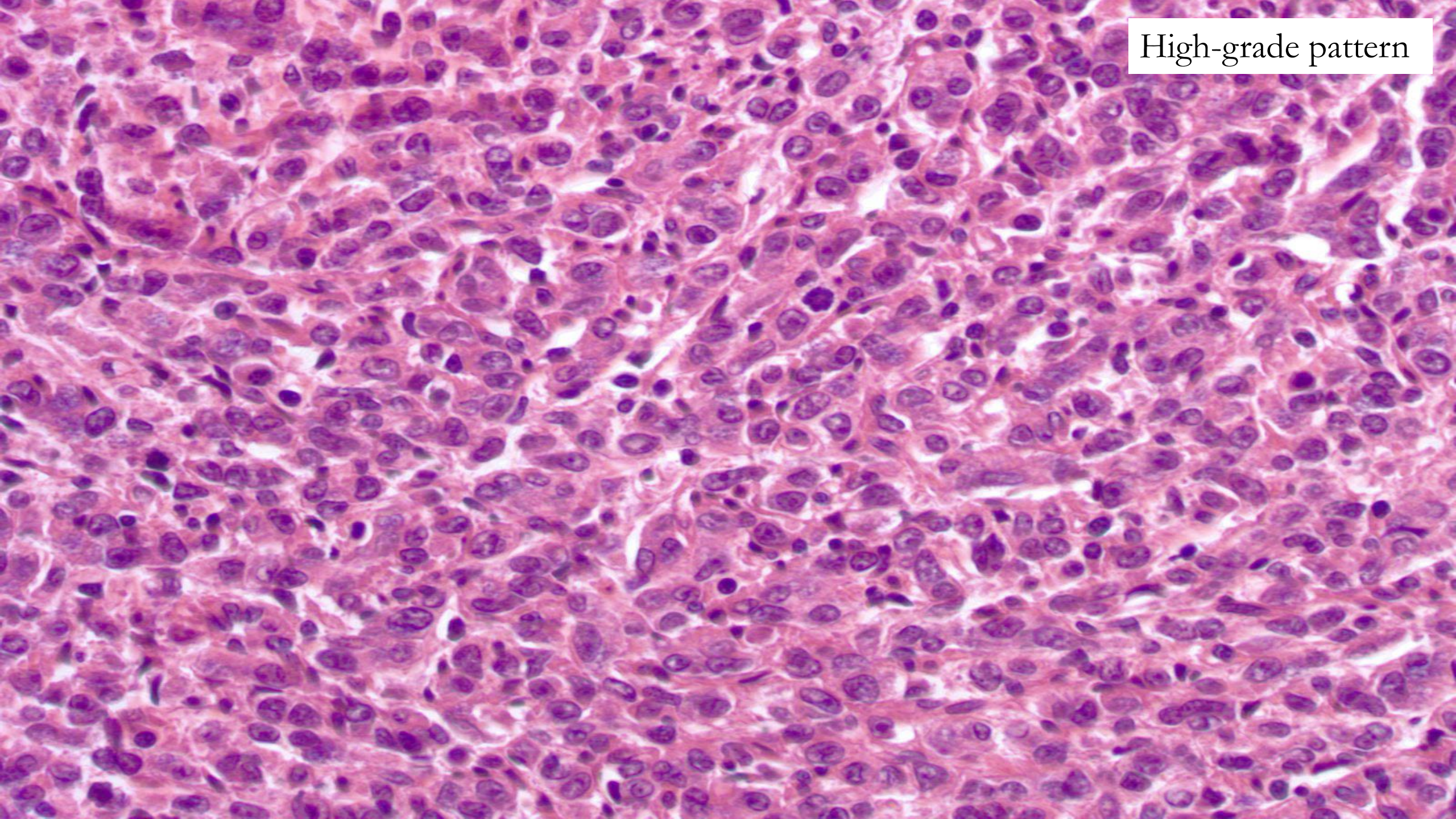

High-grade pattern


High-grade pattern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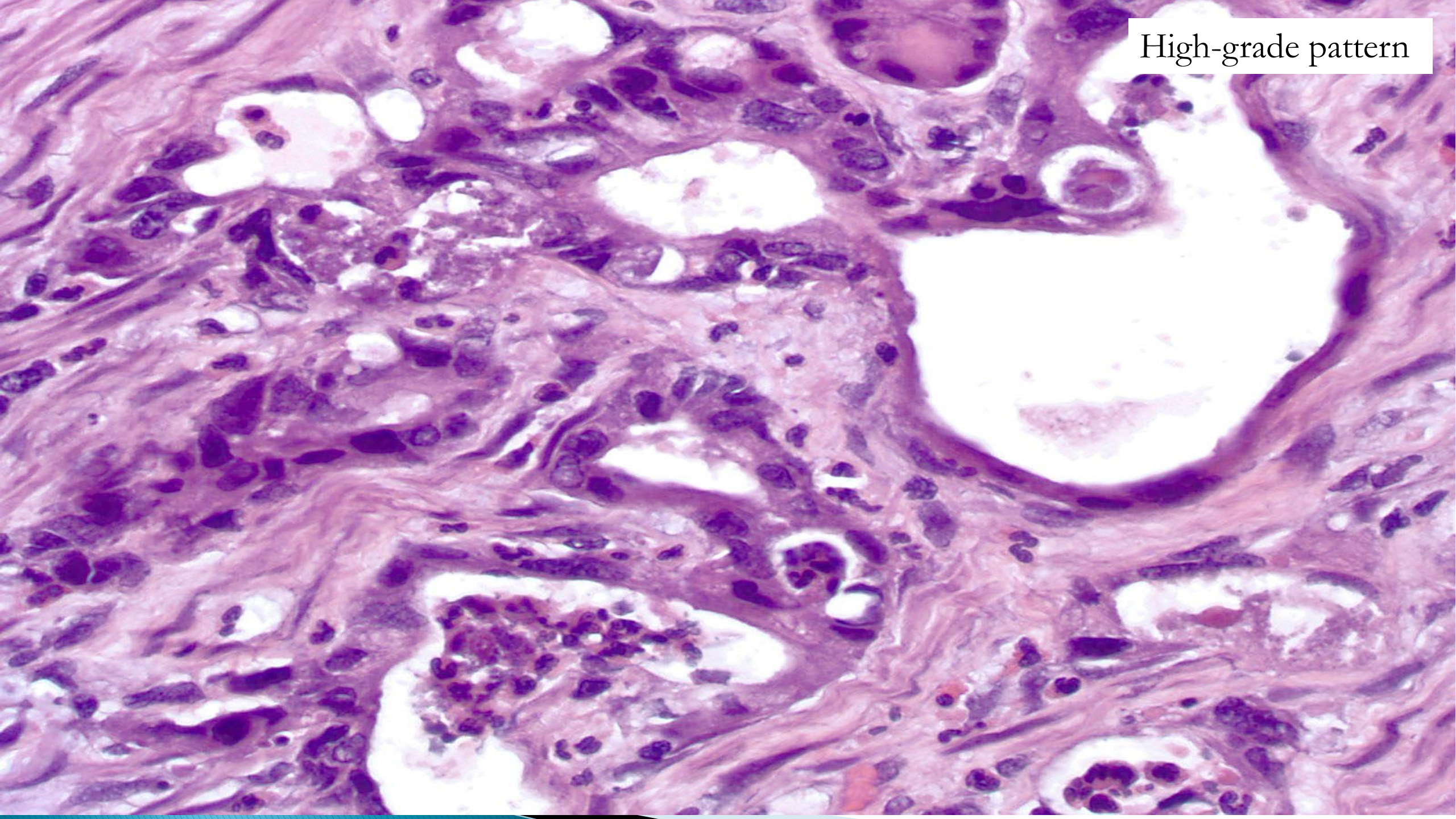
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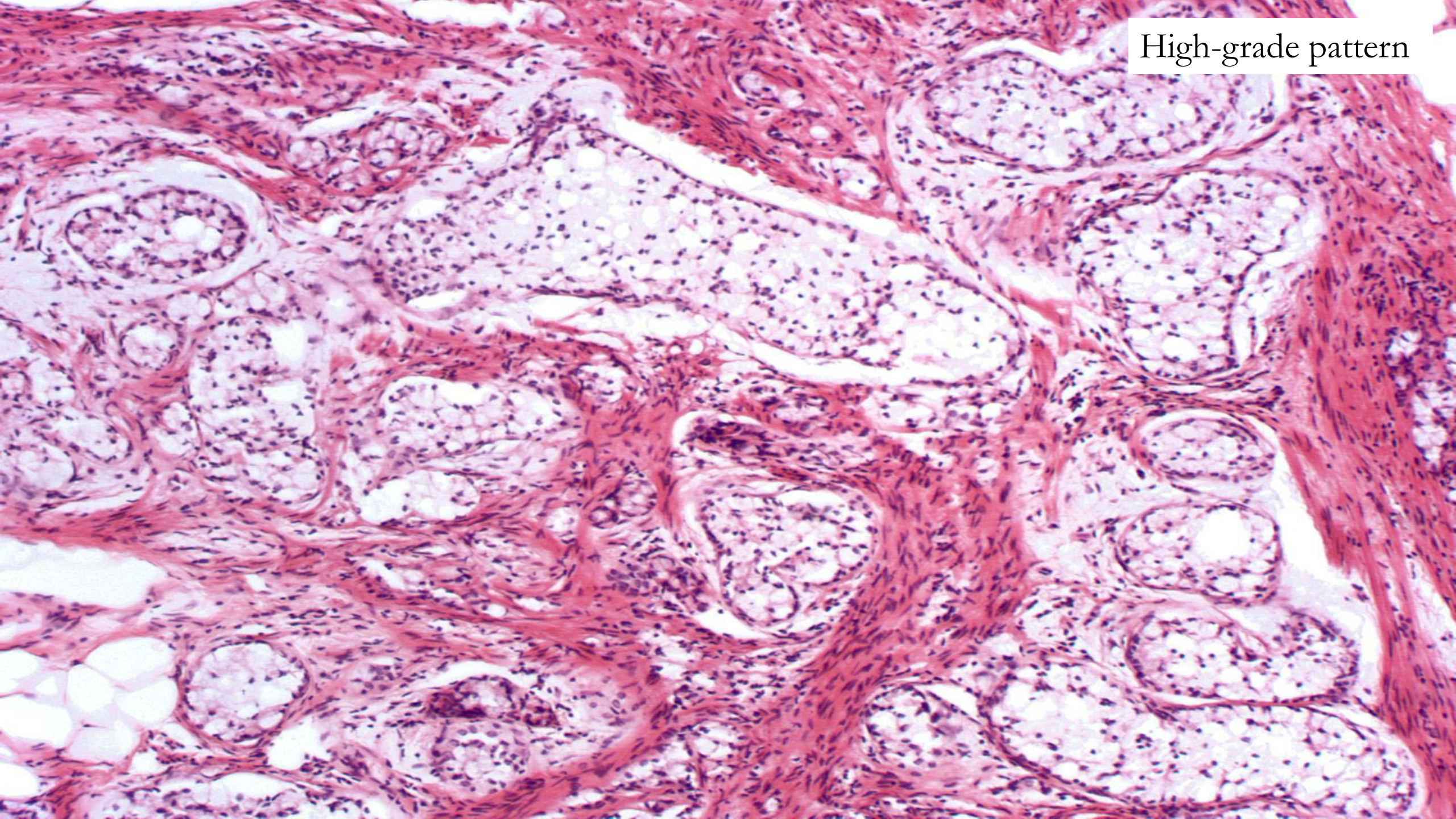
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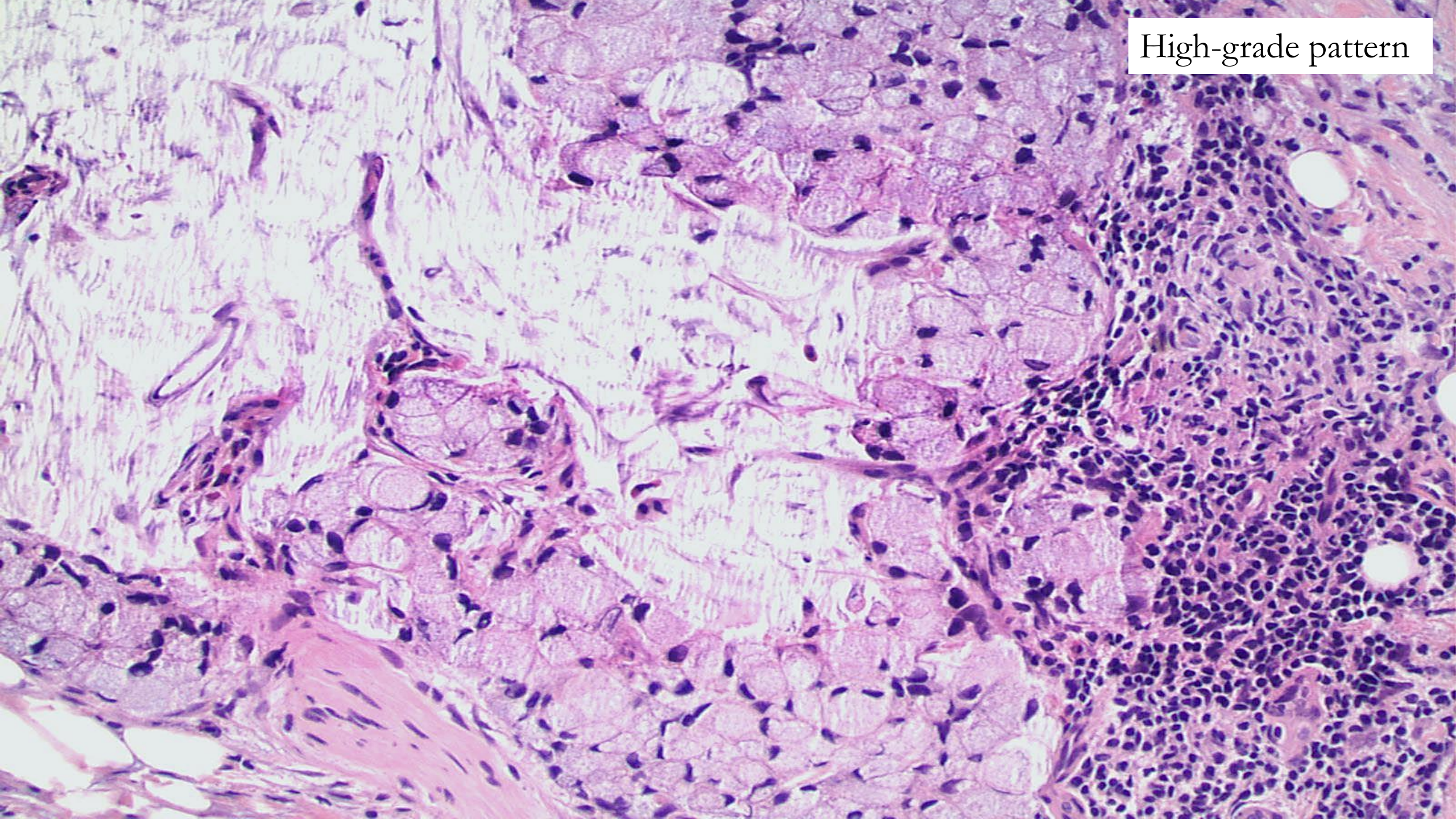
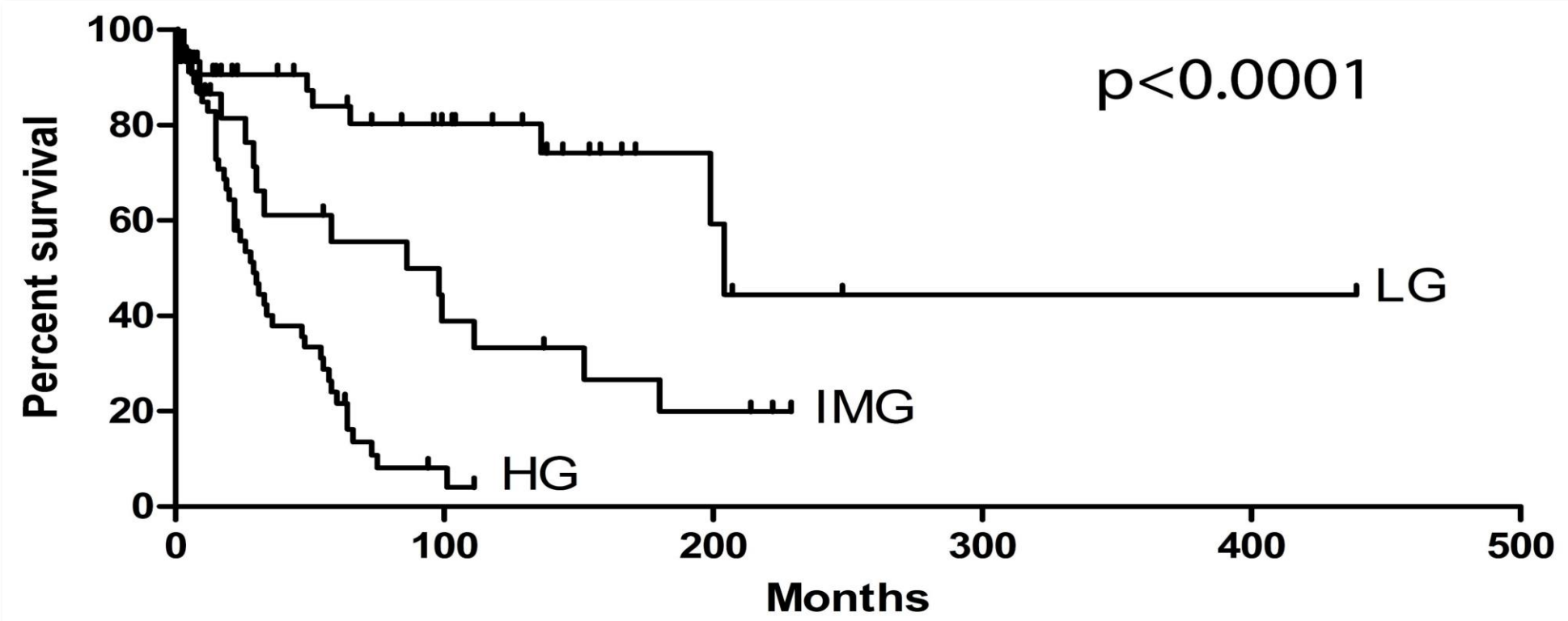

High-grade pattern

Goblet cell adenocarcinoma, Low grade: > 75% low grade patterns; < 25% high grade patterns
Goblet cell adenocarcinoma, Intermediate grade: 50-75% low grade patterns; 25-50% high grade patterns
Goblet cell adenocarcinoma, High grade: < 50% low grade patterns; > 50% high grade patterns

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