Appendiceal Mucinous Neoplasms: Diagnosis, Staging, and Outcomes

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Carr et al. Am J Surg Pathol 2016;40:14-26

Classification Systems for Appendiceal Tumors

- Peritoneal Surface Oncology Group International (PSOGI)

Lesion	Terminology
Adenoma resembling traditional colorectal type, confined to mucosa, muscularis mucosae intact	Tubular, tubulovillous or villous adenoma, low-grade or high-grade dysplasia
Tumor with serrated features, confined to mucosa, muscularis mucosae intact	Serrated polyp with or without dysplasia (low grade or high grade)
Mucinous neoplasm with low-grade cytologic atypia and any of: Loss of muscularis mucosae Fibrosis of submucosa "Pushing invasion" (expansile or diverticulum-like growth) Dissection of acellular mucin in wall Undulating or flattened epithelial growth Rupture of appendix Mucin and/or cells outside appendix	Low grade appendiceal mucinous neoplasm

Lesion	Terminology
Mucinous neoplasm with the architectural features of LAMN and no infiltrative invasion, but with high-grade cytologic atypia	High grade appendiceal mucinous neoplasm
Mucinous neoplasm with infiltrative invasion*	Mucinous adenocarcinoma—well, moderately, or poorly differentiated
Neoplasm with signet ring cells (≤50% of cells)	Poorly differentiated (mucinous) adenocarcinoma with signet ring cells
Neoplasm with signet ring cells (> 50% of cells)	(Mucinous) signet ring cell carcinoma
Nonmucinous adenocarcinoma resembling traditional colorectal type	Adenocarcinoma—well, moderately, or poorly differentiated

*Features of infiltrative invasion include tumor budding (discohesive single cells or clusters of up to 5 cells) and/or small, irregular glands, typically within a desmoplastic stroma characterized by a proteoglycan-rich extracellular matrix with activated fibroblasts/myofibroblasts with vesicular nuclei.

Classification Systems for Appendiceal Tumors

WHO classification of tumours of the appendix

Epithelial tumours	
	Hyperplastic polyp
	Sessile serrated lesion without dysplasia
8213/0*	Serrated dysplasia, low grade
8213/2*	Serrated dysplasia, high grade
8480/1	Low-grade appendiceal mucinous neoplasm
8480/2*	High-grade appendiceal mucinous neoplasm
8140/3	Adenocarcinoma NOS
8480/3	Mucinous adenocarcinoma
8490/3	Signet-ring cell adenocarcinoma
8020/3	Carcinoma, undifferentiated, NOS
8243/3*	Goblet cell adenocarcinoma
8240/3	Neuroendocrine tumour NOS
8240/3	Neuroendocrine tumour, grade 1
8249/3	Neuroendocrine tumour, grade 2
8249/3	Neuroendocrine tumour, grade 3
8152/3	L-cell tumour
8152/3	Glucagon-like peptide-producing tumour
8152/3	PP/PYY-producing tumour
8241/3	Enterochromaffin-cell carcinoid
8241/3	Serotonin-producing carcinoid
8246/3	Neuroendocrine carcinoma NOS
8013/3	Large cell neuroendocrine carcinoma
8041/3	Small cell neuroendocrine carcinoma
8154/3	Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)

Mucinous Malignancies of the Appendix

Low-grade Appendiceal Mucinous Neoplasm

- LAMN is a low-grade proliferation that grows via expansion and can burst the appendix, seeding the peritoneum and leading to pseudomyxoma peritonei (PMP)
- May cause fibrosis and distortion of the wall of the appendix

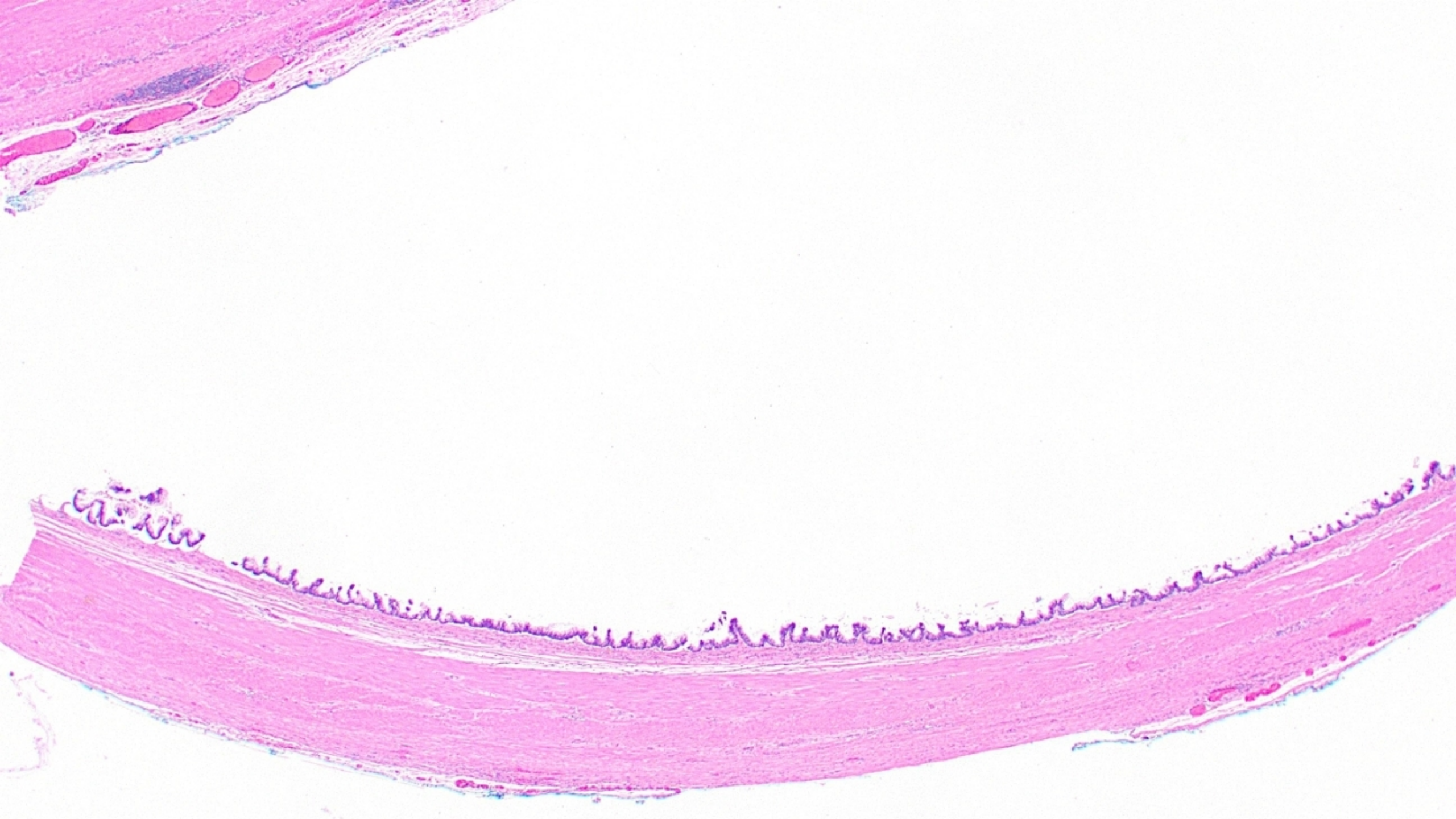
- Only metastasizes via direct spread
  - CANNOT penetrate into lymphatics or blood vessels, and therefore does not spread this way

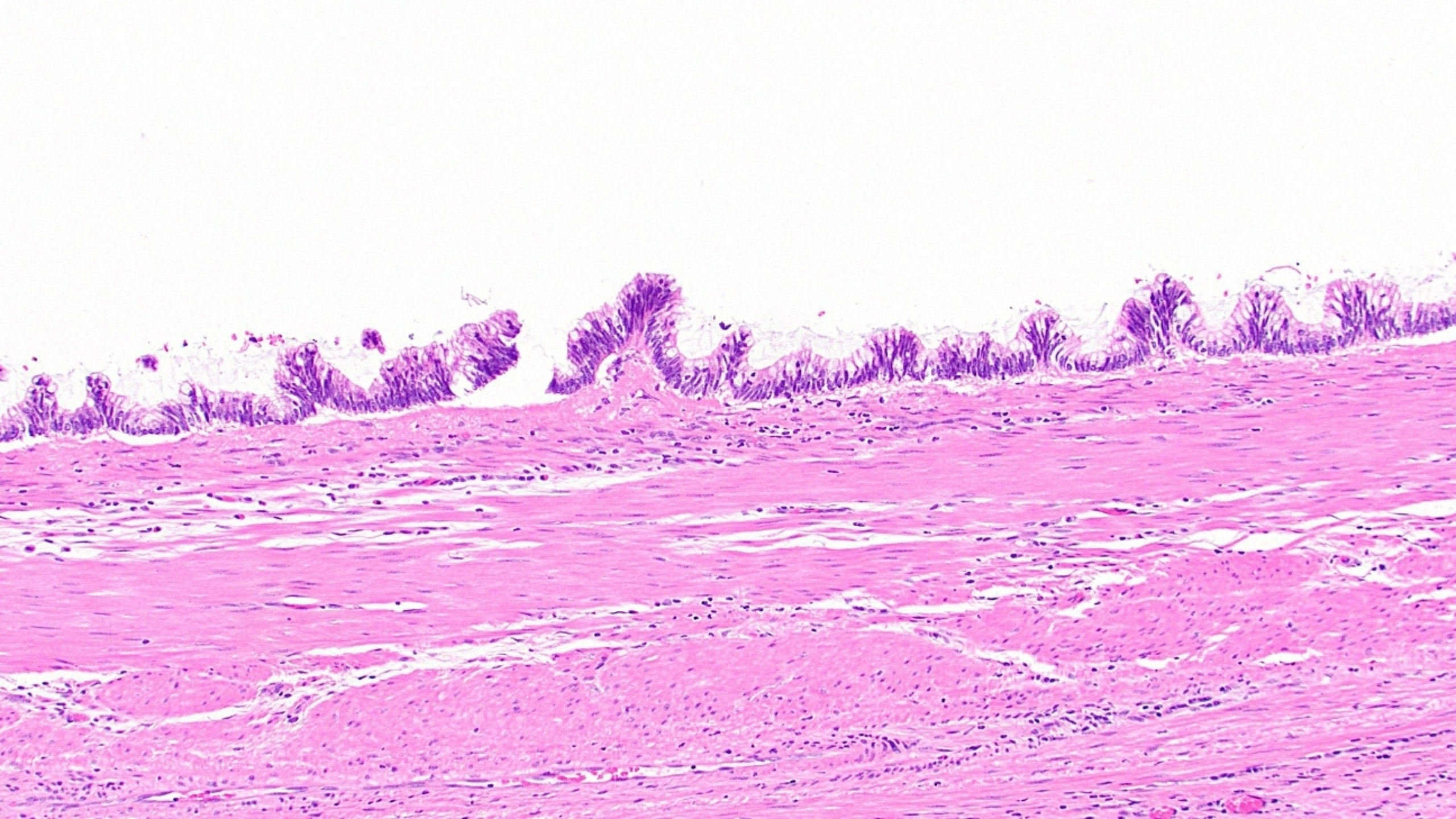
- Technically an “adenocarcinoma,” but best to consider LAMN its own, enigmatic entity
- Former names: cystadenoma, mucinous adenoma, mucinous neoplasm of uncertain malignant potential

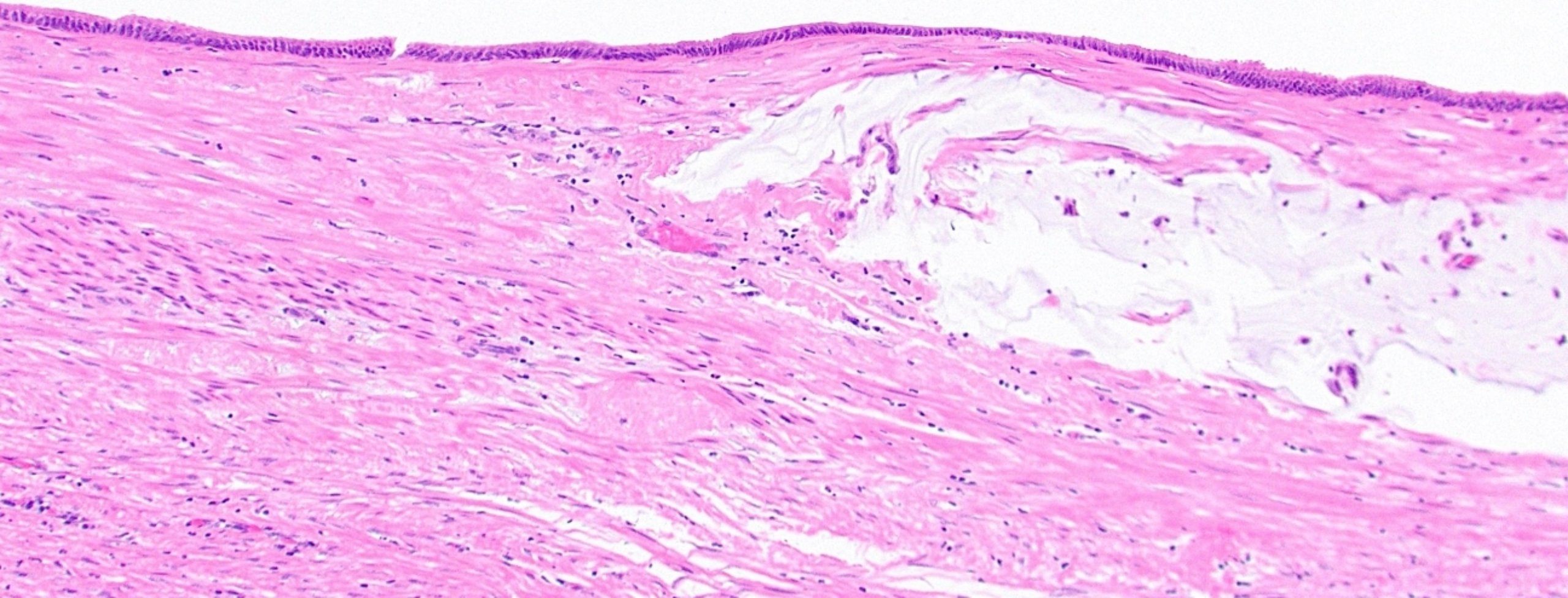
Low-grade Appendiceal Mucinous Neoplasm

- PSOGI criteria:
- 1. Must be a neoplasm
  - Should have low-grade dysplasia but may be subtle
- 2. Must show at least one of these 7 things:
  - Loss of muscularis mucosae; Fibrosis of submucosa; Pushing invasion; Dissection of acellular mucin in wall; Undulating or flattened epithelium; Rupture of appendix; Mucin and/or cells outside appendix


CM
1 2 3 4 5 6 7

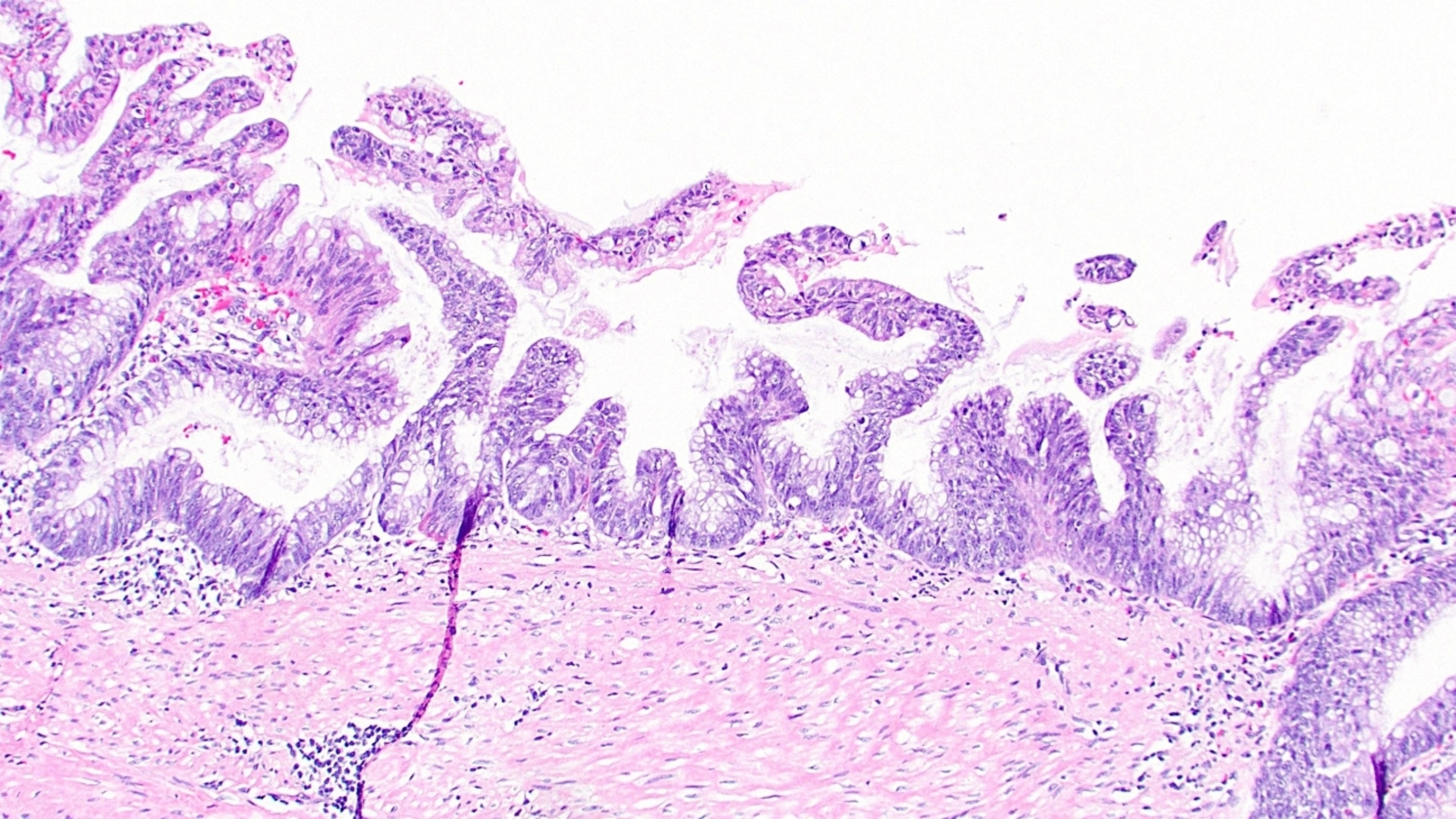






High-grade Appendiceal Mucinous Neoplasm

- HAMN is basically the same as LAMN, but with high-grade cytology and/or architecture under the microscope
- If appendix perforates, HAMN has higher rates of high-grade PMP



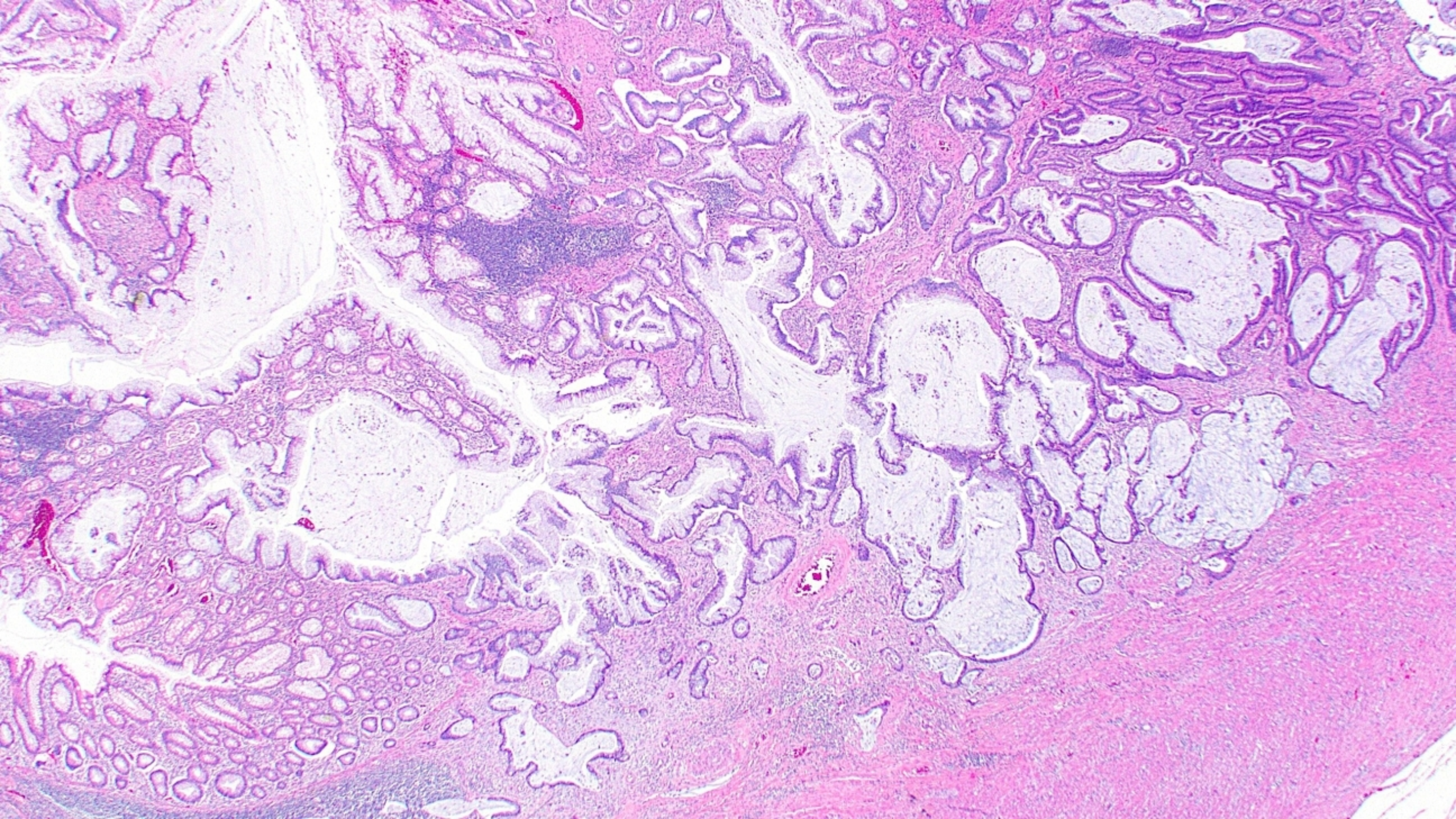
Adenocarcinoma

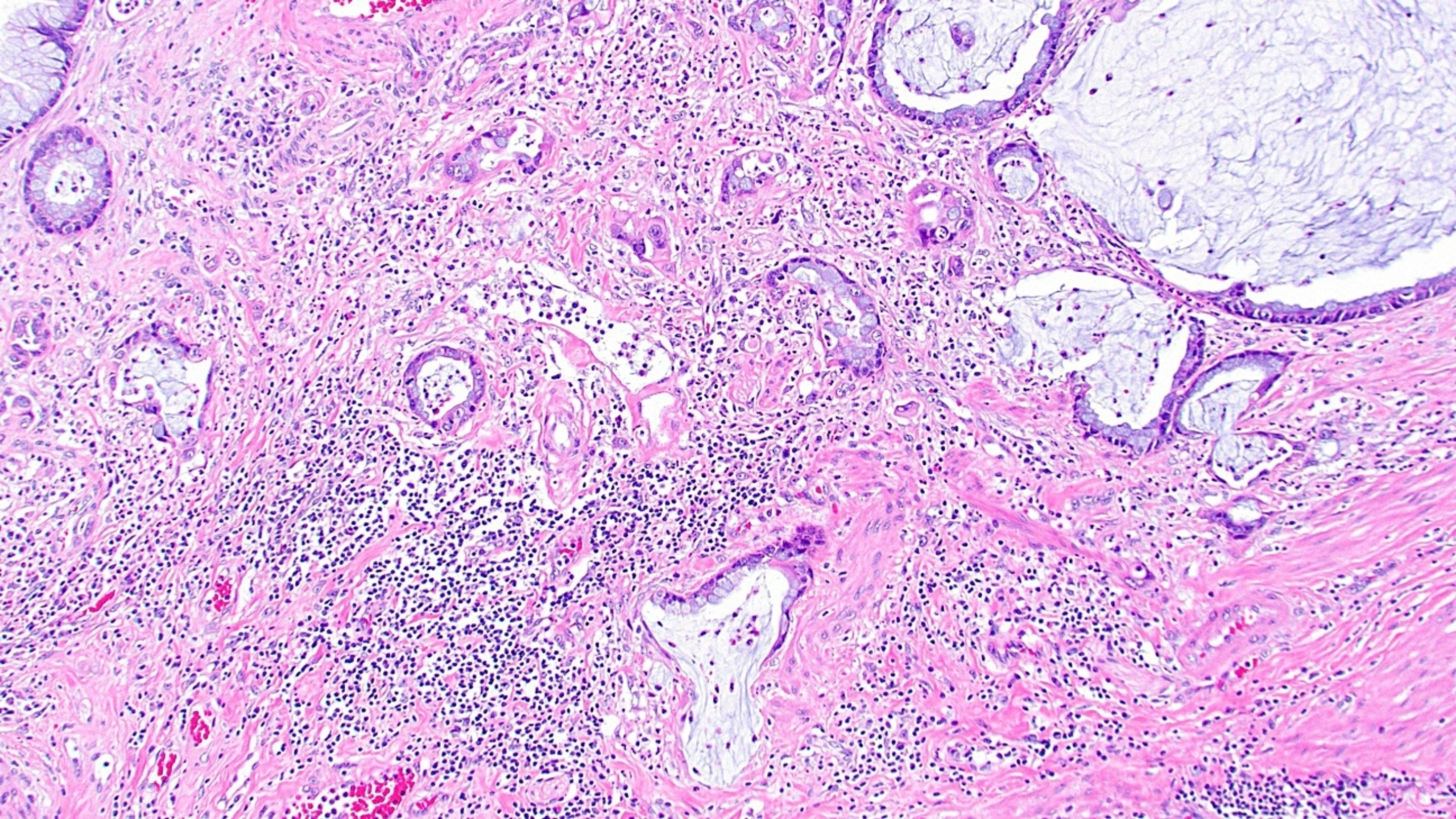
- Less common than LAMN, more common than HAMN
- Basically analogous to colorectal adenocarcinoma
  - Histology shows trickling invasion, desmoplasia, single cells, etc.
  - Adjuvant therapy is the same
- Can be hard to rule out advanced cecal cancers “next door”

Adenocarcinoma

- Most examples are intestinal-type/NOS but a high percentage are mucinous (30-40%)
- Very low-grade examples can be difficult to distinguish from LAMN
- May also be signet ring cell carcinoma (more aggressive)

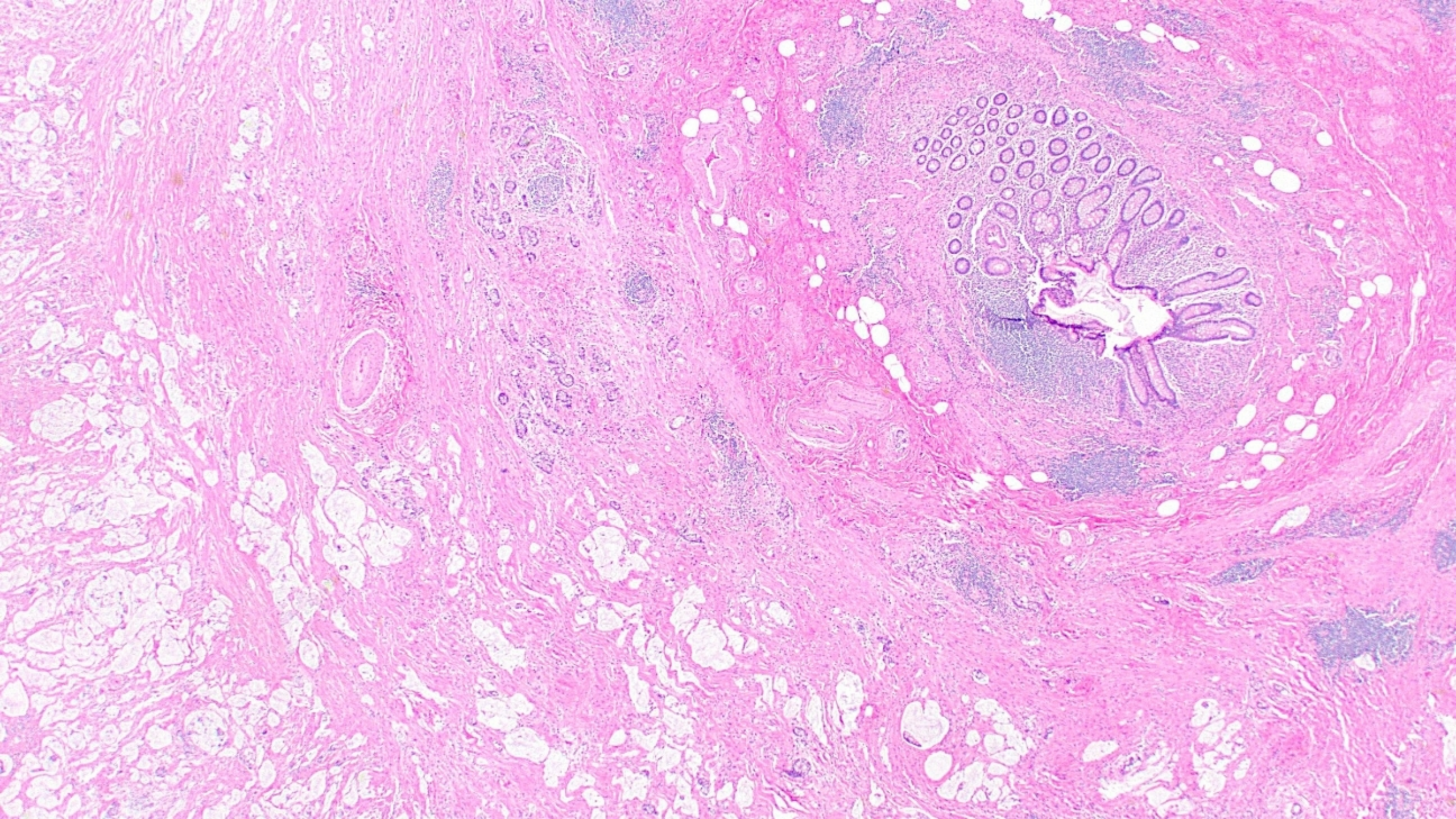
- Often presents as pT4 disease
- Can metastasize to peritoneum but also lymph nodes and (rarely) distant organs

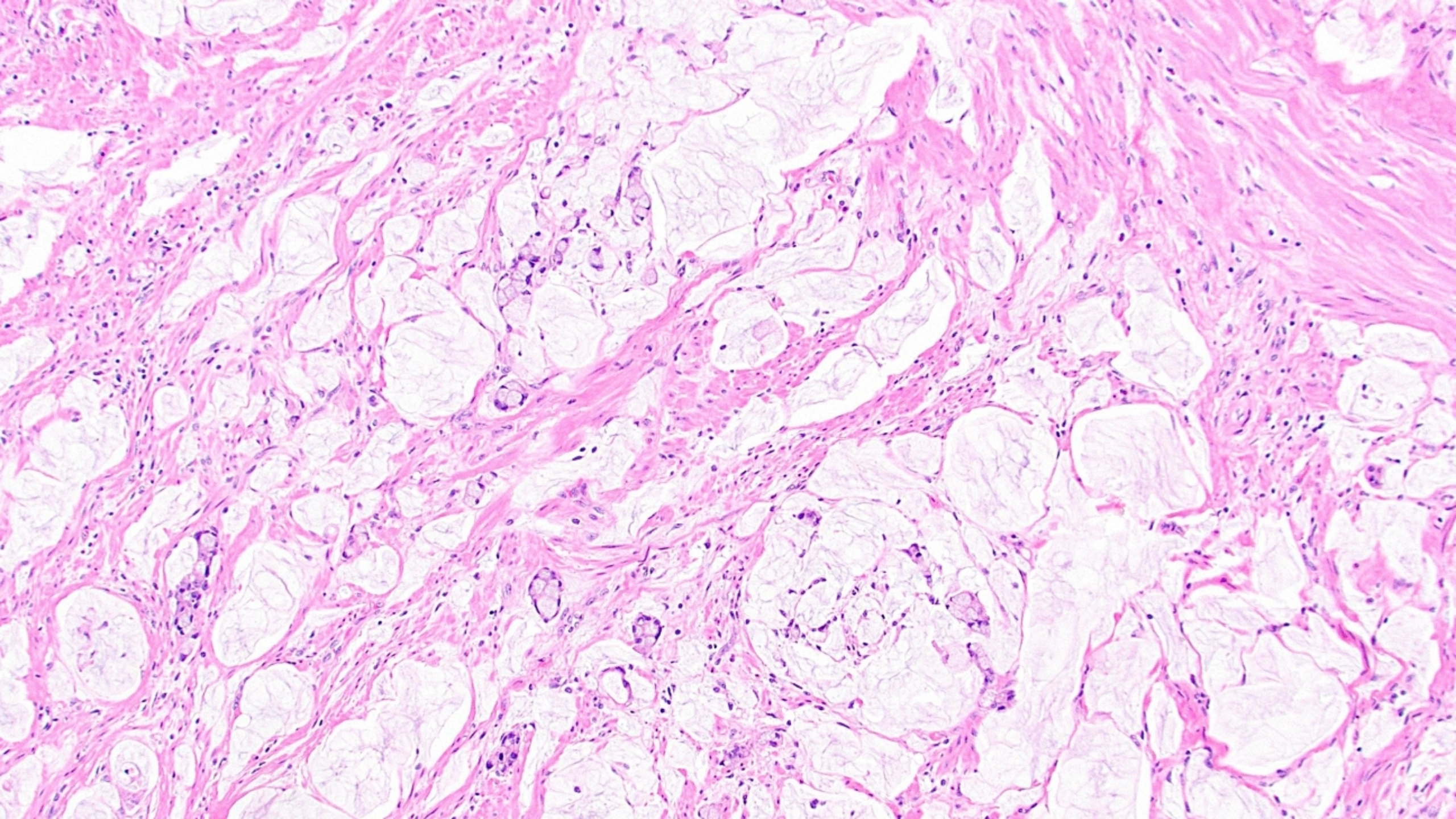




Goblet Cell Adenocarcinoma

- Unusual neoplasm that has had several names
  - Most notably “goblet cell carcinoid,” causing confusion with ‘classic’ carcinoids (well-differentiated neuroendocrine tumors)
- 2019 WHO uses grading scheme based on % of high-grade features
- Diagnosed by finding a component of classic low-grade GCA
  - Bland goblet cell-rich glands or amphophilic tubules of tumor
- May show abundant extracellular mucin





50TH ANNIVERSARY SEER

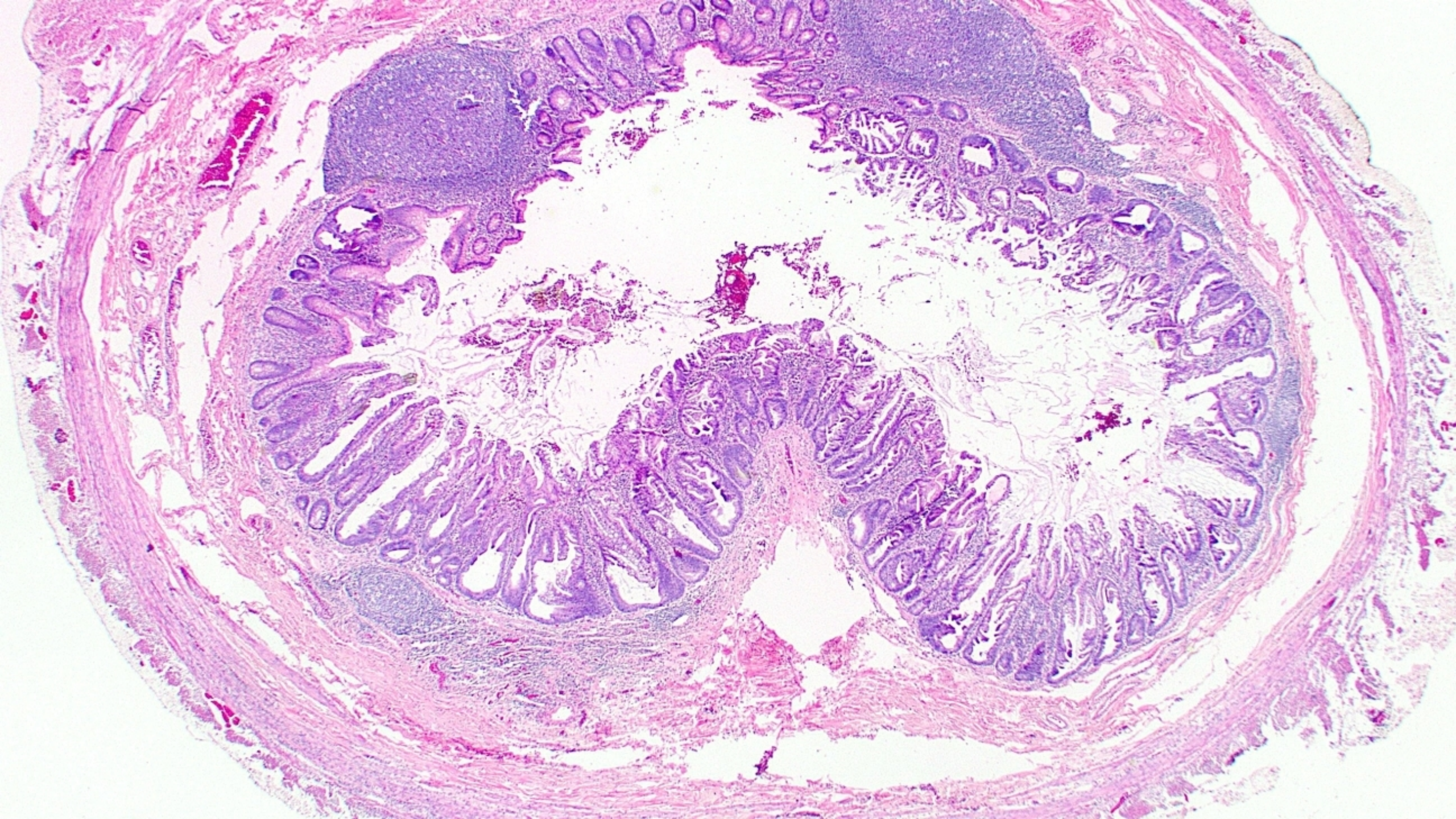
TURNING CANCER DATA INTO DISCOVERY

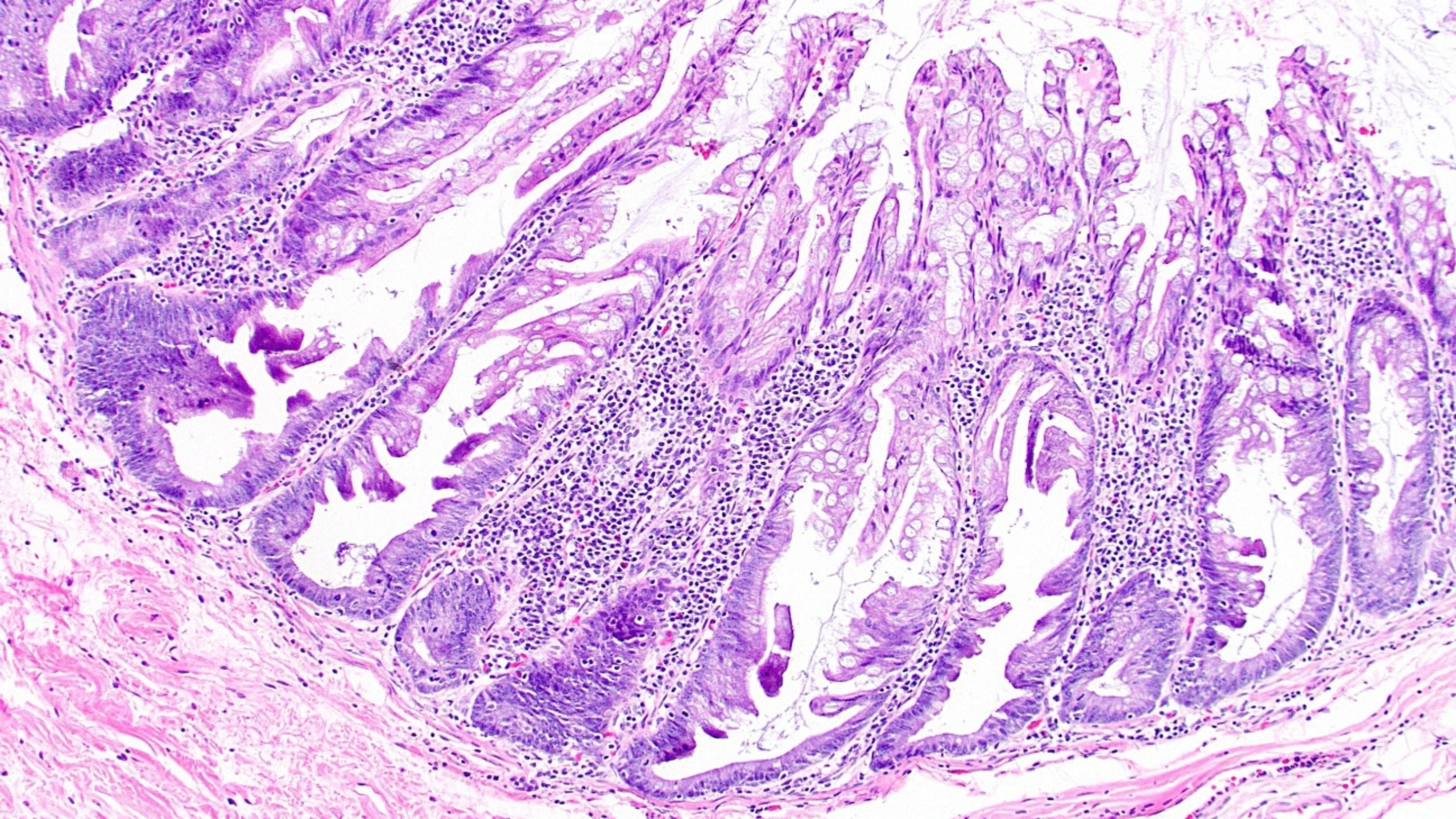
Non-Malignant Mucinous Lesions of the Appendix (mimics)

Serrated Polyp / Sessile Serrated Lesion

- Neoplastic polyp
- Same morphology as sessile serrated lesion (SSL) in the colorectum
  - Bland cytology, mix of enterocytes and goblet cells, serration to base, “booting” shape of crypts
- Also maintains crypts, lamina propria, and muscularis mucosae (does not breach mucosa)
- Sometimes can progress to invasive adenocarcinoma (different problem)

- Some of these probably get reported as LAMN

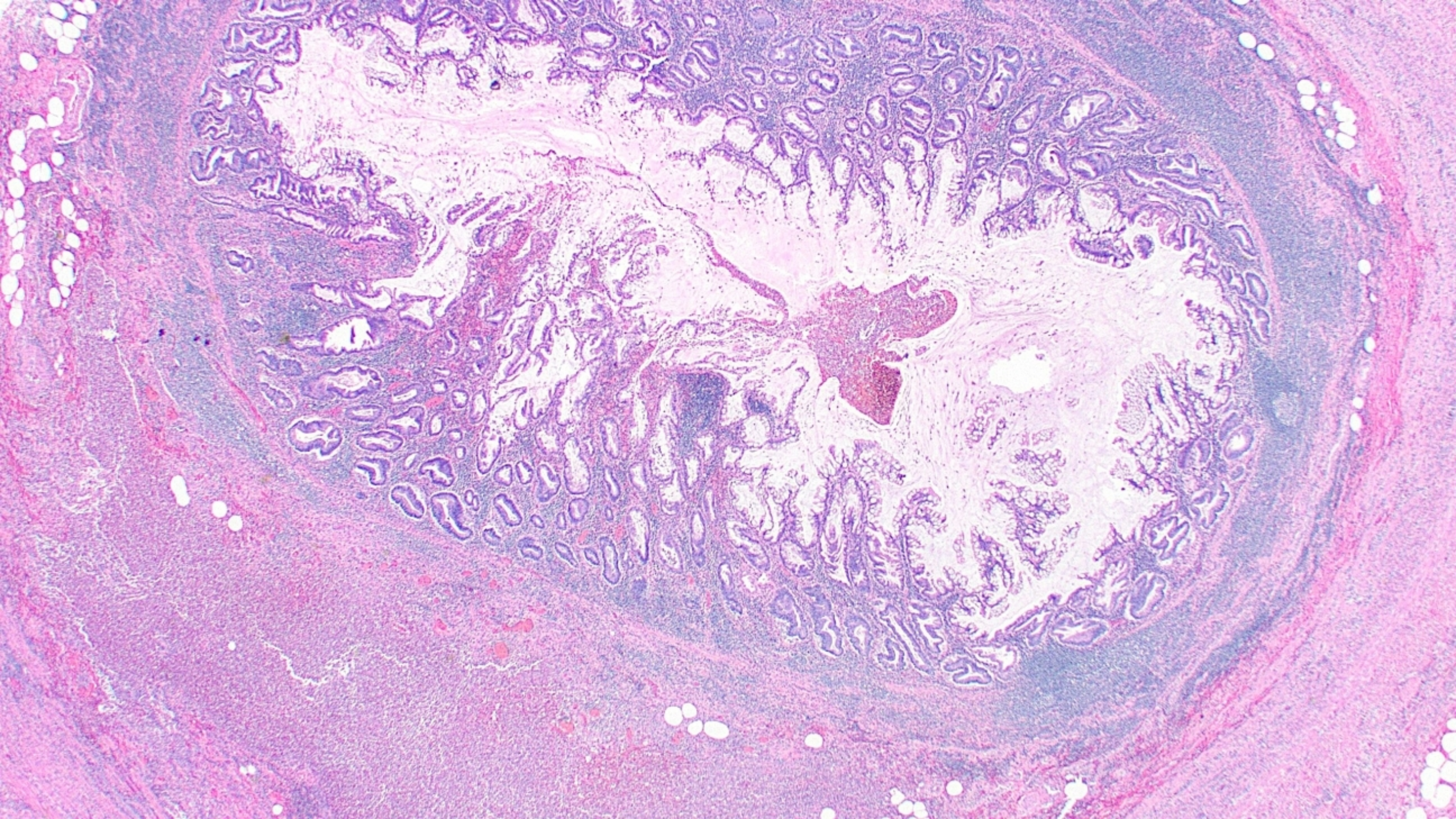




Appendiceal Reactive Hyperplasia

- Mucosal change in response to obstruction and/or appendicitis
- Can really look like serrated polyp, though “booting” is rare
- Mucosa may be flattened but generally maintains crypts, lamina propria, and muscularis mucosae
- Acute inflammation and reactive atypia may be present
- Not a neoplasm

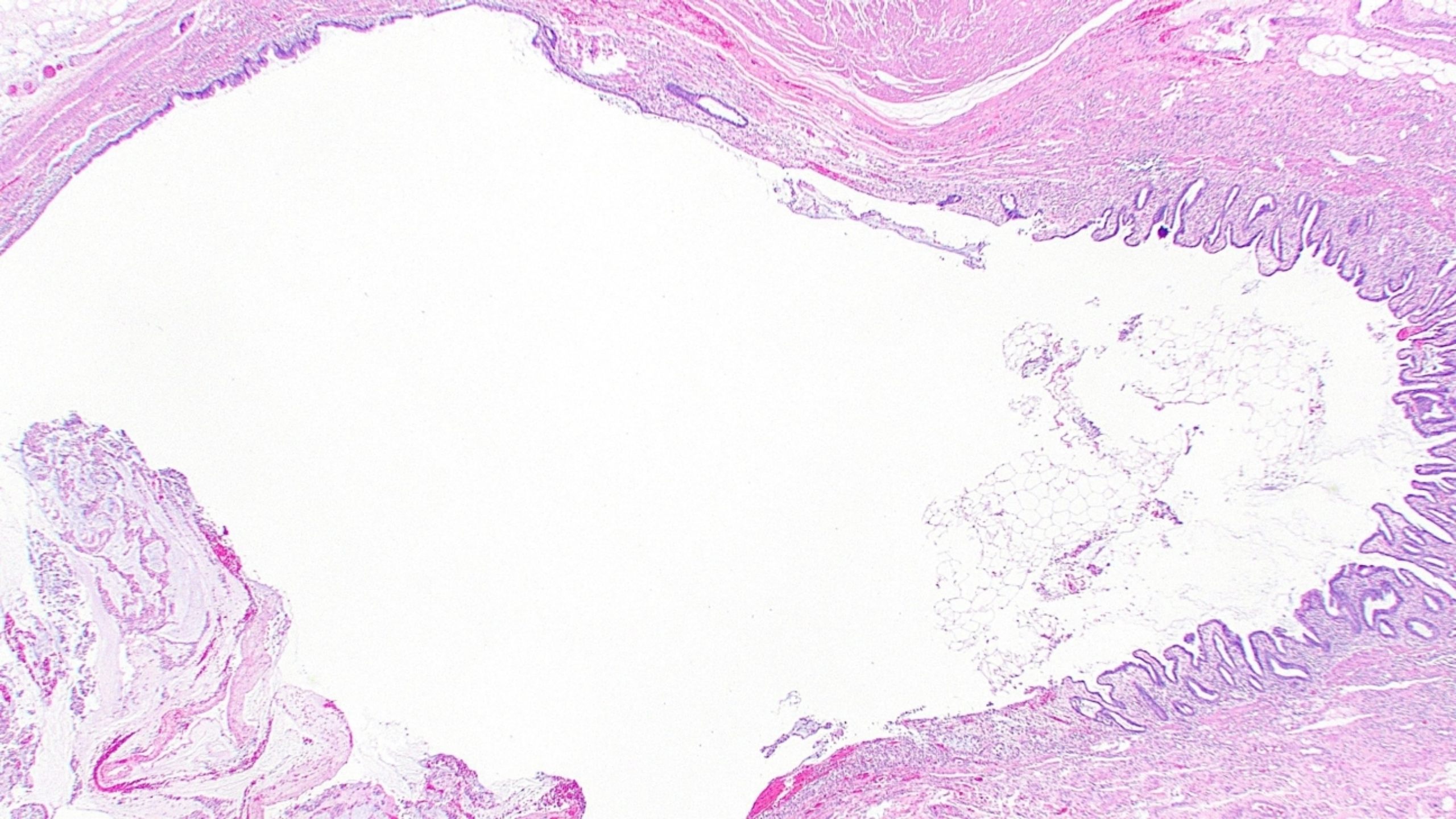
- Some of these probably get reported as LAMN or SP

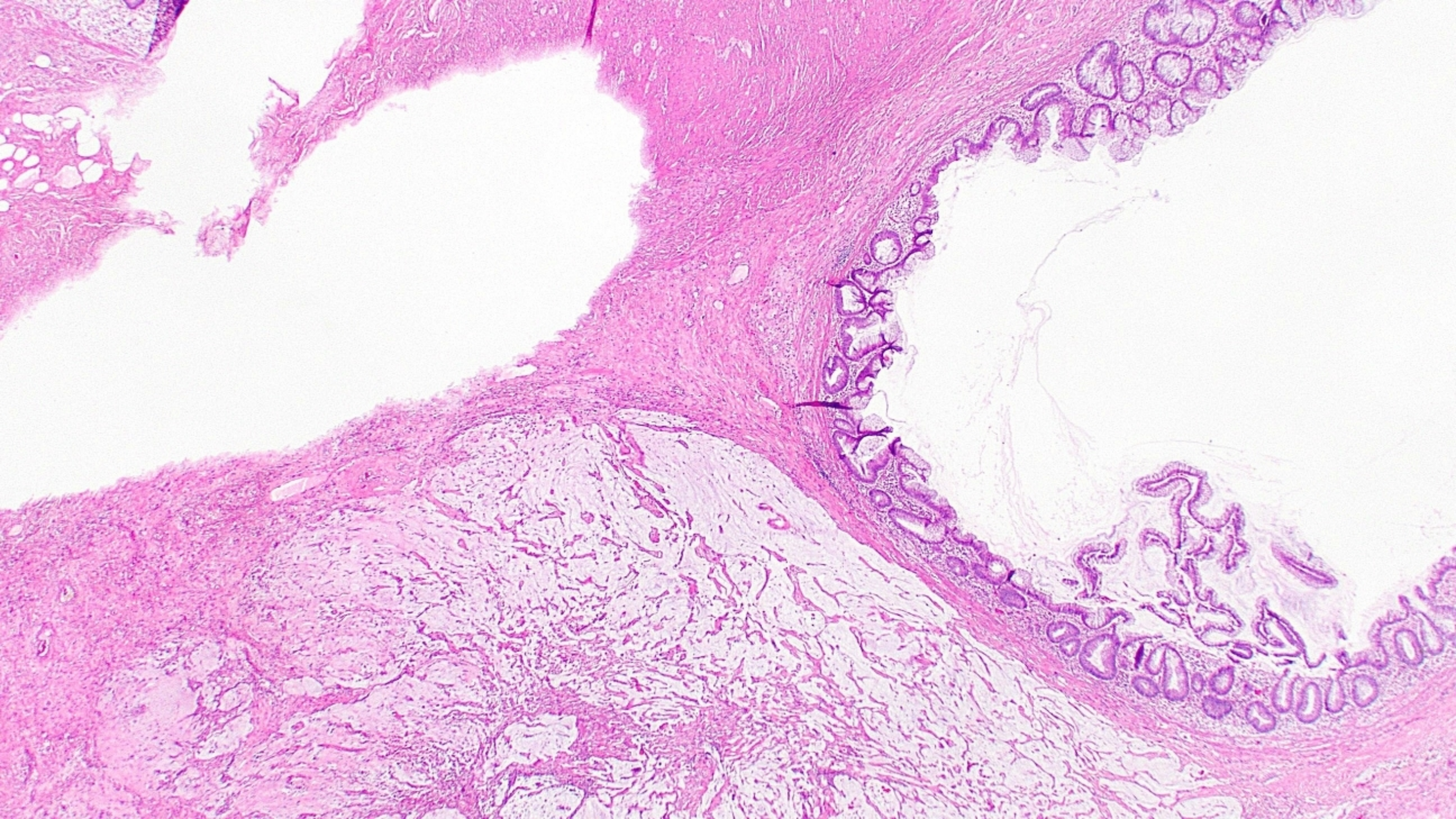


Appendiceal Diverticula

- Outpouchings/extensions of appendiceal mucosa into wall
- Often show reactive or hyperplastic change
- Should (mostly) maintain crypts, lamina propria, muscularis mucosae
- Can rupture, like in the colon (and like LAMN)
- Not a neoplasm, and its epithelium cannot seed the peritoneum

- Some of these probably get reported as LAMN





50TH ANNIVERSARY SEER

TURNING CANCER DATA INTO DISCOVERY

Peritoneal Lesions Originating in the Appendix

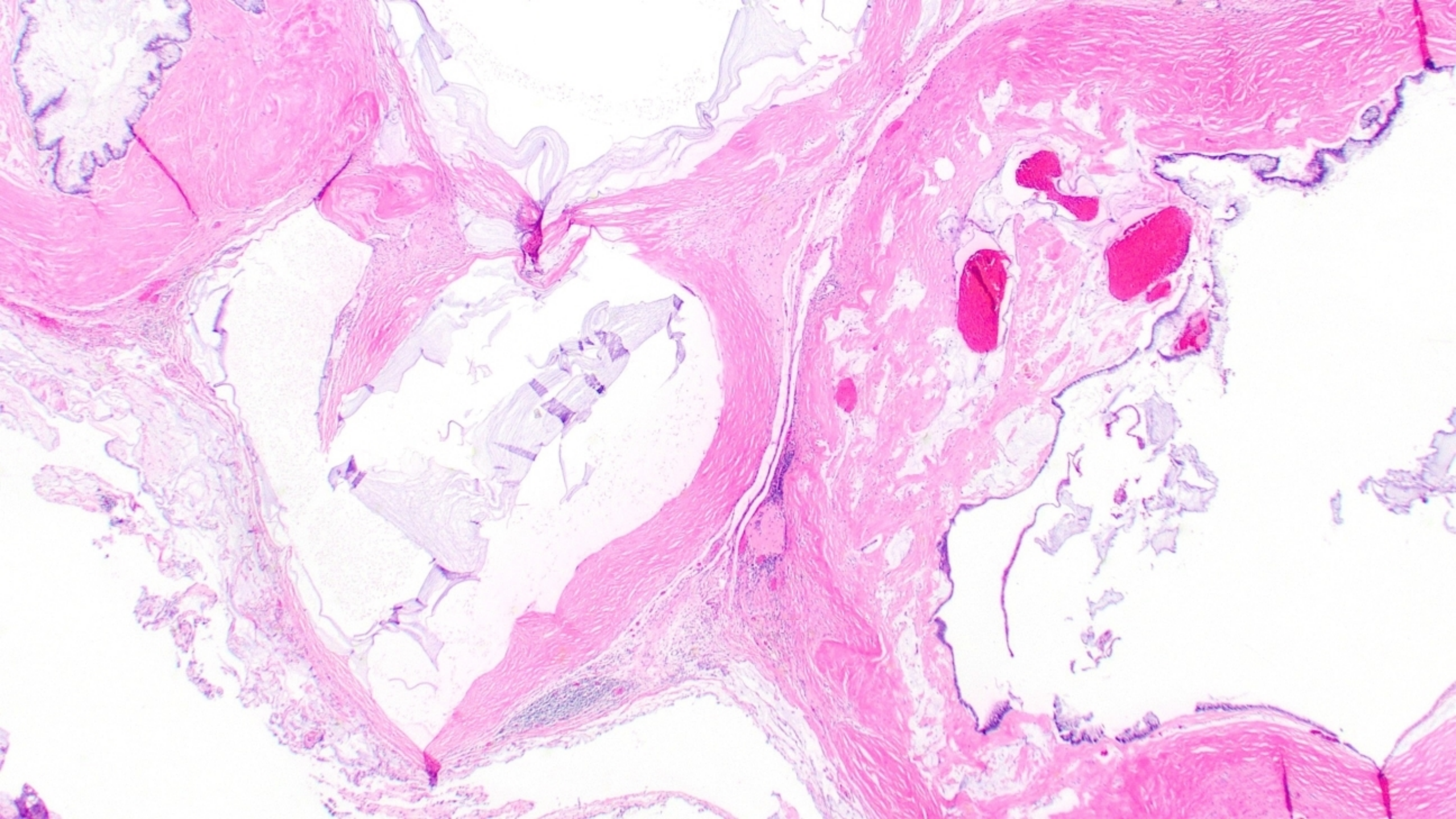
Pseudomyxoma Peritonei

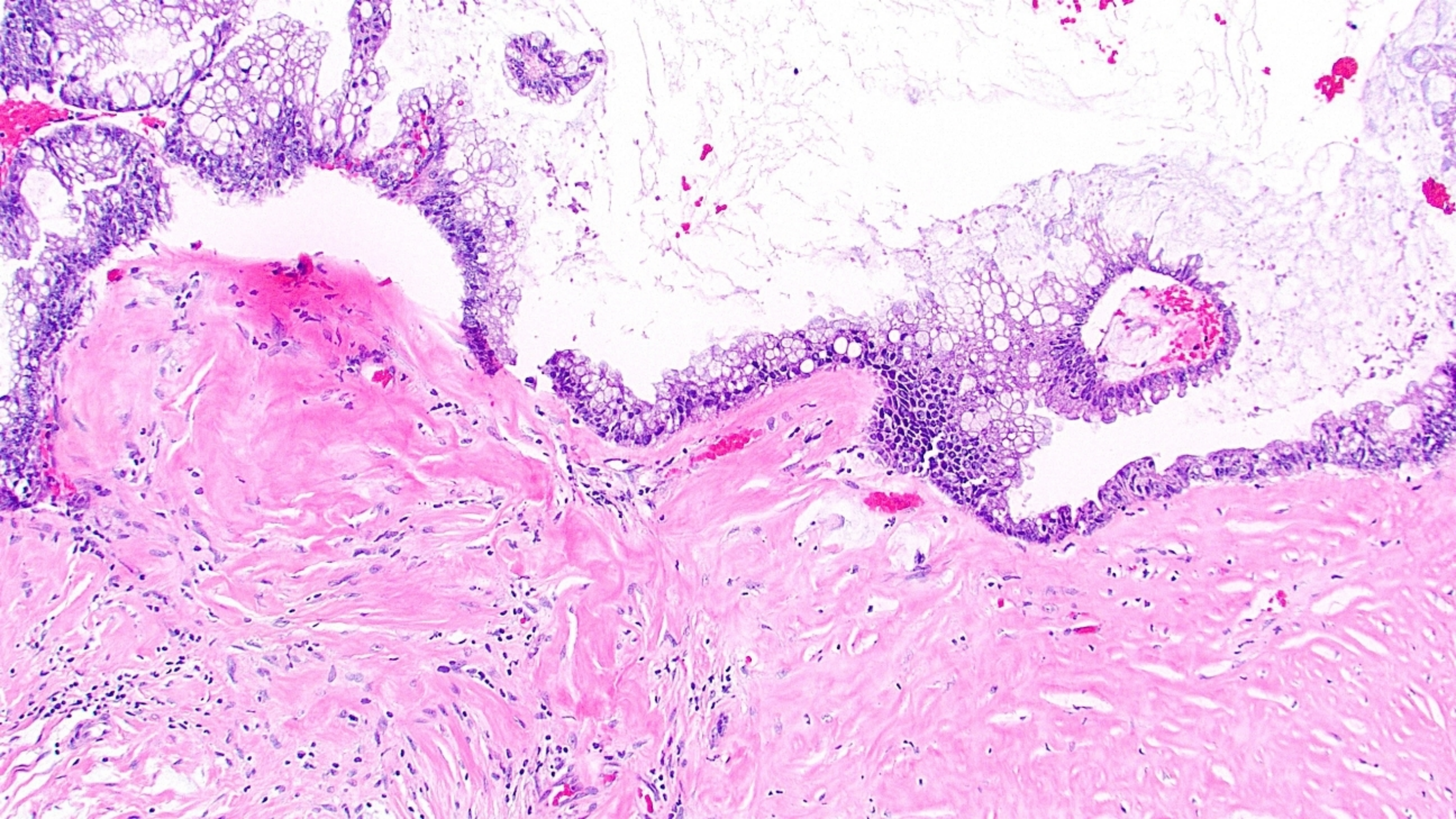
- Intraperitoneal disease of disseminated mucin-producing neoplastic epithelium
  - “Jelly belly”
- Can involve peritoneal surfaces, ovaries, other organs
- Small fragments of epithelium embed in the surfaces and/or float freely and produce copious mucin

- Should NOT spread above the diaphragm

Pseudomyxoma Peritonei

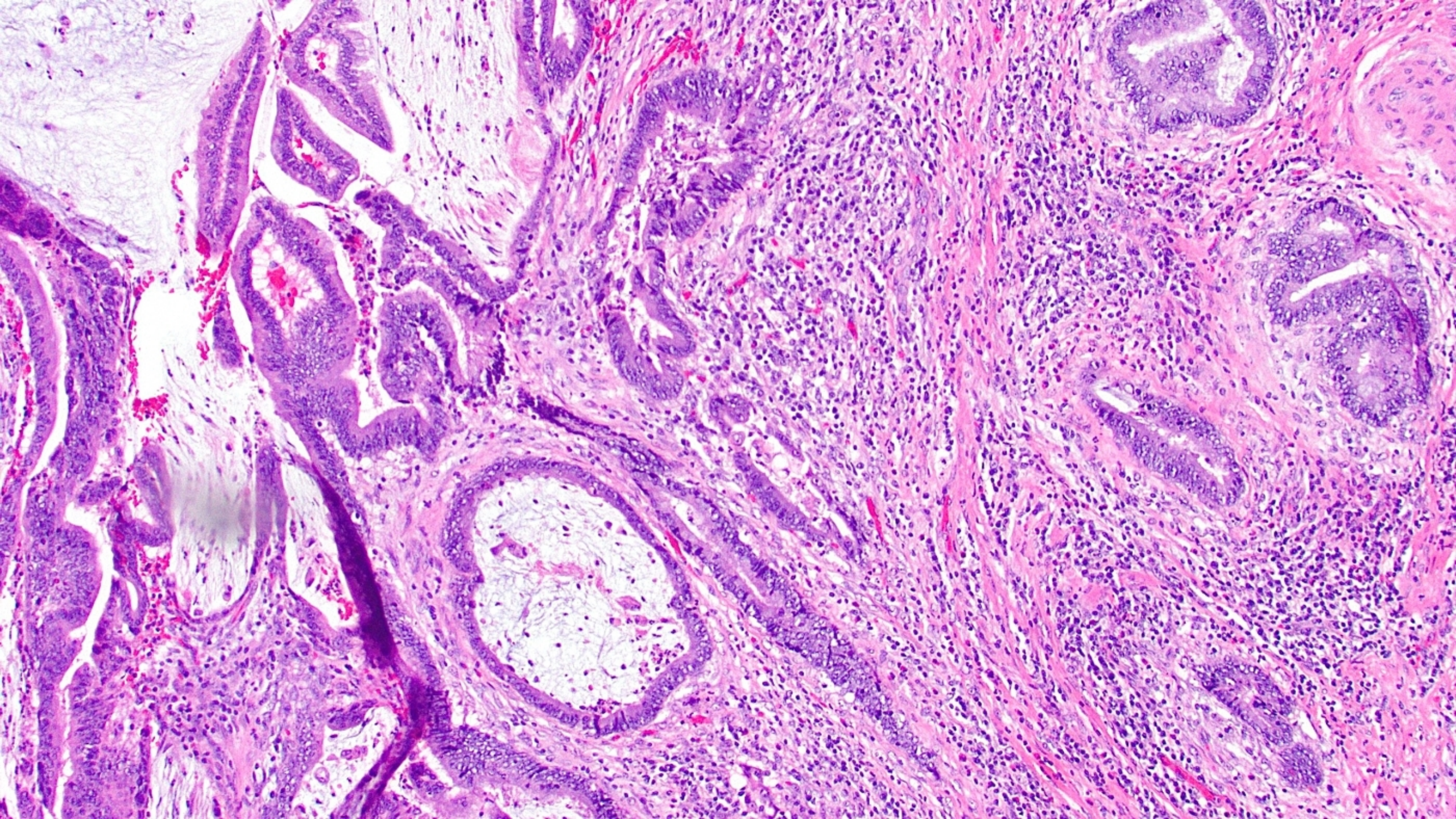
- True PMP almost always arises from LAMN/HAMN
  - Compared to “intra-abdominal carcinomatosis” from adenocarcinomas
- True gyn origin (mucinous ovarian tumors) exceedingly rare
  - Decades ago, it was believed that PMP almost always arose from ovaries
  - Microscopic appearance is unfortunately the exact same
  - Can use SATB2 IHC to confirm GI origin
- Davison criteria most widely used for grading
  - Acellular (some people do not call this PMP)
  - Grade 1: hypocellular, no destructive growth
  - Grade 2: hypercellular and/or destructive growth
  - Grade 3: signet ring cells





Carcinomatosis

- Spread of a true adenocarcinoma throughout the peritoneum
- Usually at least intermediate grade
- Less often produces copious mucin
- More destructive



Staging Malignancies of the Appendix

AJCC 8th (and 9th) Edition Staging

- LAMN, HAMN, adenocarcinoma, and pseudomyxoma peritonei all use the same TNM appendix staging classification
  - LAMN has some caveats
  - LAMN and HAMN staging include extent of both cells and mucin
- Very similar to the staging system for colorectal adenocarcinoma

AJCC 8th Edition pT-Category Staging

- **Tis**: carcinoma in situ (intramucosal carcinoma; invasion of the lamina propria or extension into but not through the muscularis mucosae)
- **Tis(LAMN)**: low grade appendiceal mucinous neoplasm confined by the muscularis propria; acellular mucin or mucinous epithelium may invade into the muscularis propria
- **T1**: tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria) **[not applicable to LAMN]**
- **T2**: tumor invades the muscularis propria **[not applicable to LAMN]**
- **T3**: tumor invades through the muscularis propria into the subserosa or the mesoappendix
- **T4**: tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix or directly invades adjacent organs or structures
  - **T4a**: tumor invades through the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or serosa of the mesoappendix
  - **T4b**: tumor directly invades or adheres to adjacent organs or structures

AJCC 8th Edition pN-Category Staging

- **N0**: no lymph node metastasis
- **N1a:** tumor involvement of one regional lymph node
- **N1b:** tumor involvement of two or three regional lymph nodes
- **N1c:** no tumor involvement of nodes, but tumor deposits present
- **N2:** tumor involvement of four or more regional lymph nodes

AJCC 8th Edition pM-Category Staging

- **M0**: no distant metastasis
- **M1**: distant metastasis
  - **M1a**: intraperitoneal acellular mucin, without identifiable tumor cells in the disseminated peritoneal mucinous deposits
  - **M1b**: intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells
  - **M1c**: metastasis to sites other than peritoneum

AJCC 8th Edition Stage Grouping

• Stage 0:	Tis	N0	M0		[including Tis(LAMN)]
• Stage I:	T1-2	N0	M0		
• Stage IIA:	T3	N0	M0		
• Stage IIB:	T4a	N0	M0		
• Stage IIC:	T4b	N0	M0		
• Stage IIIA:	T1-T2	N1	M0		
• Stage IIIB:	T3-T4	N1	M0		
• Stage IIIC:	any T	N2	M0		
• Stage IVA:	any T	any N	M1a		[from LAMN, basically]
	any T	any N	M1b	G1	[from LAMN, basically]
• Stage IVB:	any T	any N	M1b	G2, G3, GX	[from adenocarcinoma, or rarely LAMN]
• Stage IVC:	any T	any N	M1c	any G	[has to be from adenocarcinoma]

Issues With Staging

- How do you stage LAMNs within a fibrotic wall?
  - pT-category staging depends on level of invasion
  - If muscularis propria is obliterated by fibrosis, how do you know if the LAMN has extended beyond the wall?
- Does pT3 really apply to LAMNs?
  - Rare, perhaps unconvincing reports of pT3 cases that led to PMP
  - Biologically, it makes sense that a LAMN within an intact appendix should be fine
- Should HAMN have the same “carve-outs” as LAMN?
  - Preliminary data say yes
  - However, HAMN is currently staged the same as adenocarcinoma

Issues With Staging

- What if an appendix ruptured and allowed disease to access the peritoneum (PMP), but then the appendix healed?
  - I have seen such cases of pTis(LAMN)N0M1b with appendiceal scarring

- pN1, pN2, and pM1c do not apply to LAMN
  - Not an “issue” but somewhat awkward

Treatment and Prognosis of Appendiceal Lesions

(just the basics; I am not an oncologist)

Treatment of Non-Malignant Lesions

- Reactive change and diverticula (even if ruptured) do not need oncologic follow-up
- Excellent prognosis

- Sessile serrated lesions probably do not need increased follow-up unless they progress to adenocarcinoma
  - Should patients get increased colonoscopy screening?
  - What happens if the appendix ruptures (say, from appendicitis) and a sessile serrated lesion gains access to the peritoneum?
- Excellent prognosis

Treatment of Confined Malignant Lesions

- If LAMN or HAMN is confined to the appendix, should not need any follow-up
- Very good prognosis (pseudomyxoma may very rarely still occur)

- If LAMN or HAMN is found in a ruptured appendix (+/- localized but not disseminated peritoneal mucin), patient needs surveillance
- Good prognosis (pseudomyxoma may rarely still occur)

- Early-stage, non-metastatic adenocarcinoma and goblet cell adenocarcinoma can perhaps be managed with careful surveillance
- Good prognosis (progression may still occur)

Treatment of Pseudomyxoma Peritonei

- From LAMN/HAMN

- Surgical and oncologic treatment necessary
- Cytoreductive surgery (CRS) = surgeon debulks tumor (removing all mucin) and strips away any peritoneal irregularities
- Heated intraperitoneal chemotherapy (HIPEC) = surgeon pumps heated chemotherapy into the abdomen, where it circulates for 1-2 hours
- No need for systemic chemotherapy (unless maybe high-grade cases)

- Moderate prognosis with proper treatment
  - Worse Davison grade = worse prognosis

Treatment of Carcinomatosis / pM1c Cancer

- From adenocarcinoma/goblet cell adenocarcinoma

- Surgical and oncologic treatment necessary
- CRS and HIPEC may be employed
- Systemic chemotherapy also necessary

- Poor prognosis

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Questions?