

THE FRONTIERS OF APPENDICEAL CONTROVERSIES

PRESENTED BY

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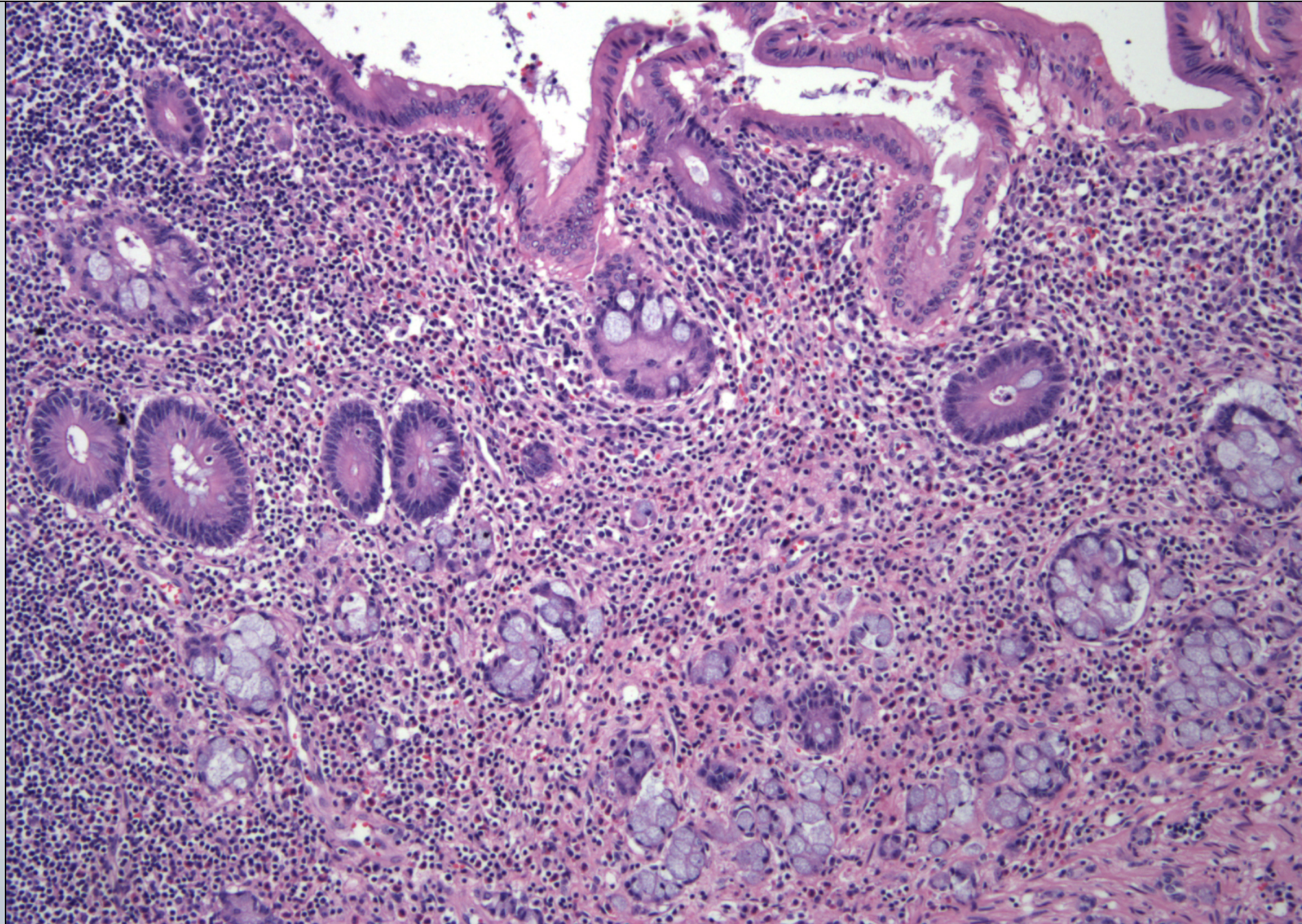
Topics to Discuss

Updates from the WHO

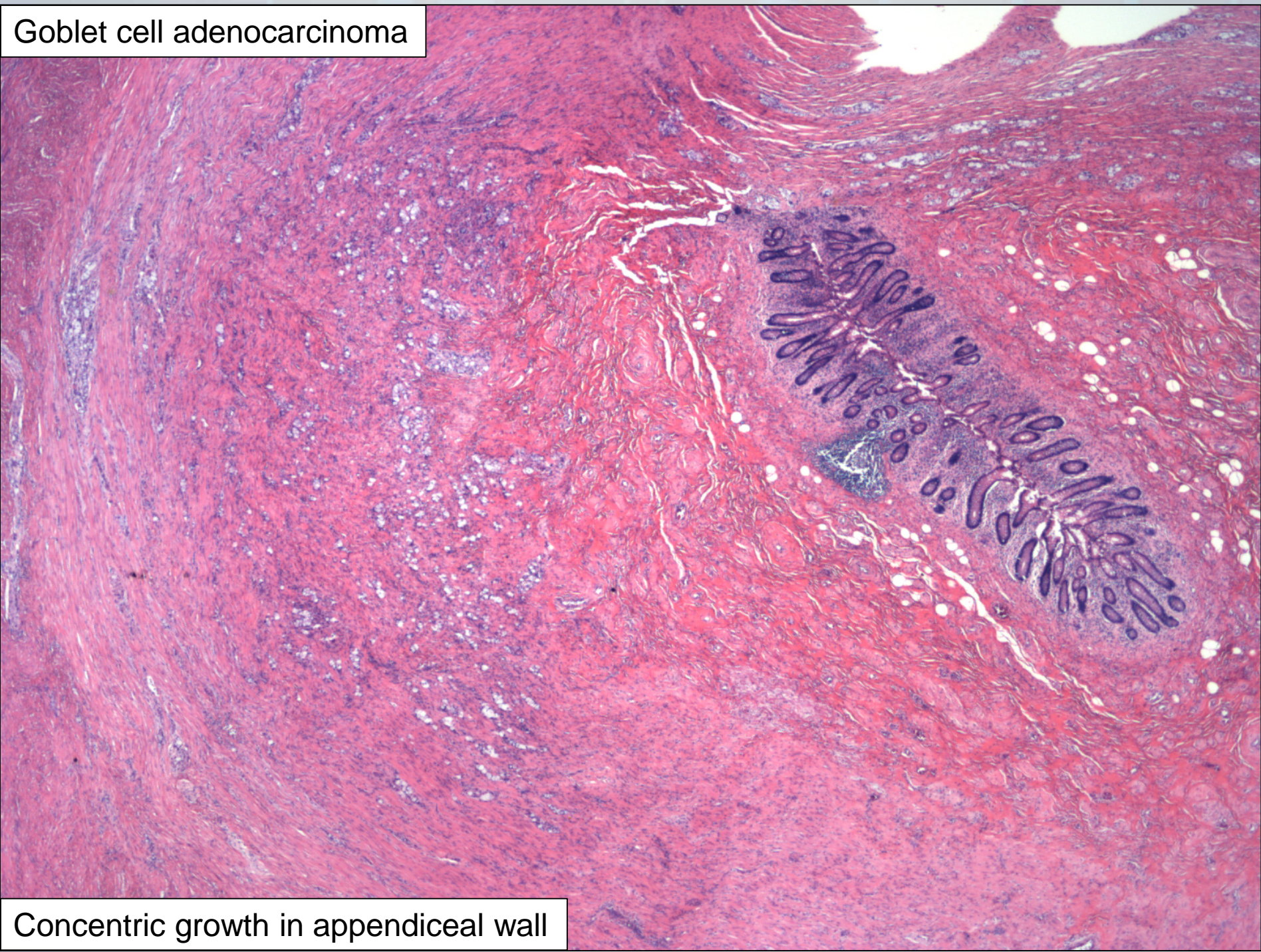
- Goblet cell neoplasia
- A word (or two) on serrated things
- Mucinous tumors and their mimics

Goblet Cell Adenocarcinoma (Not Carcinoid)

Goblet cell adenocarcinoma contains nests and clusters of goblet cells, recapitulating crypts (“crypt cell carcinoma”)

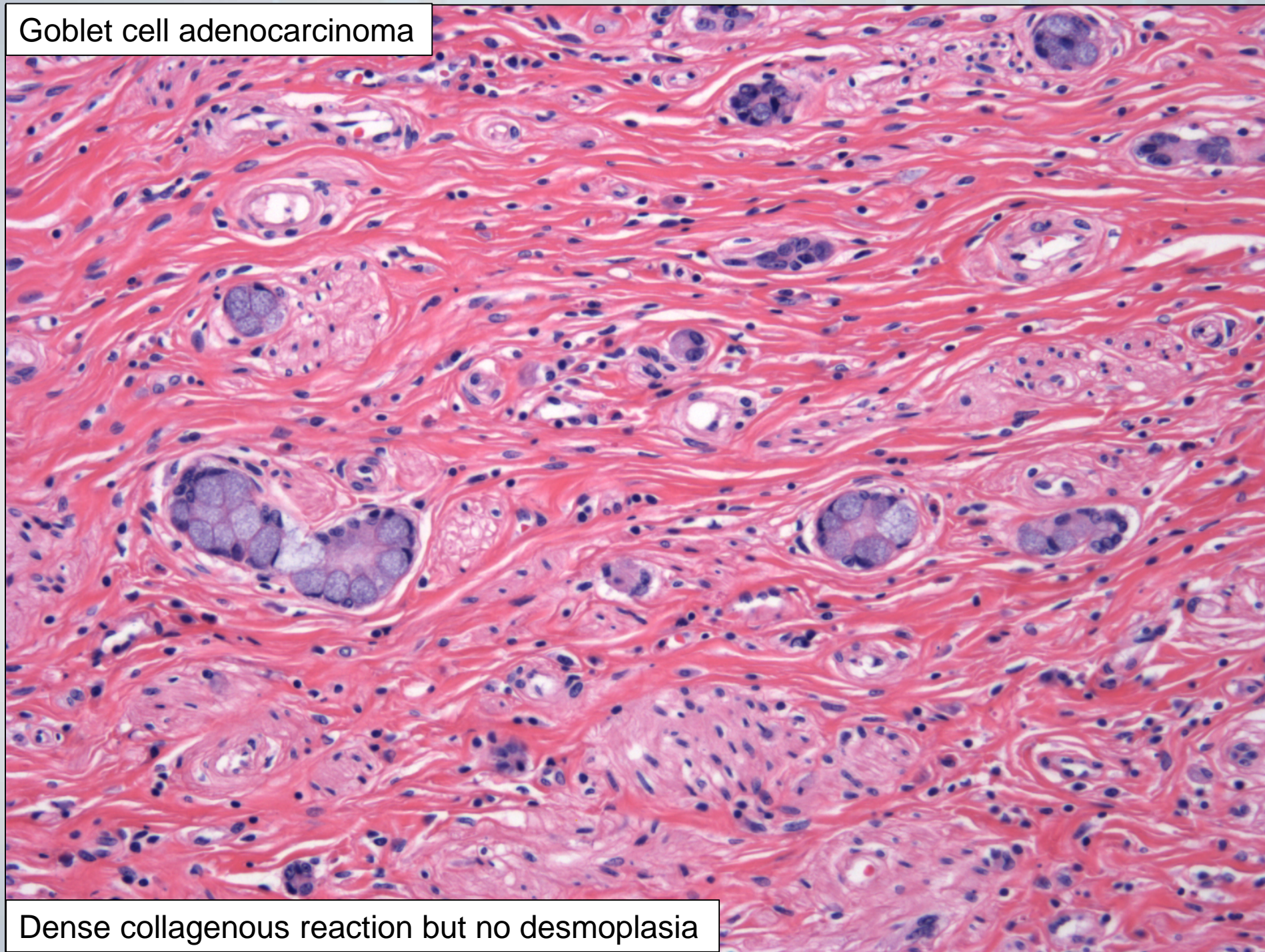


Goblet cell adenocarcinoma



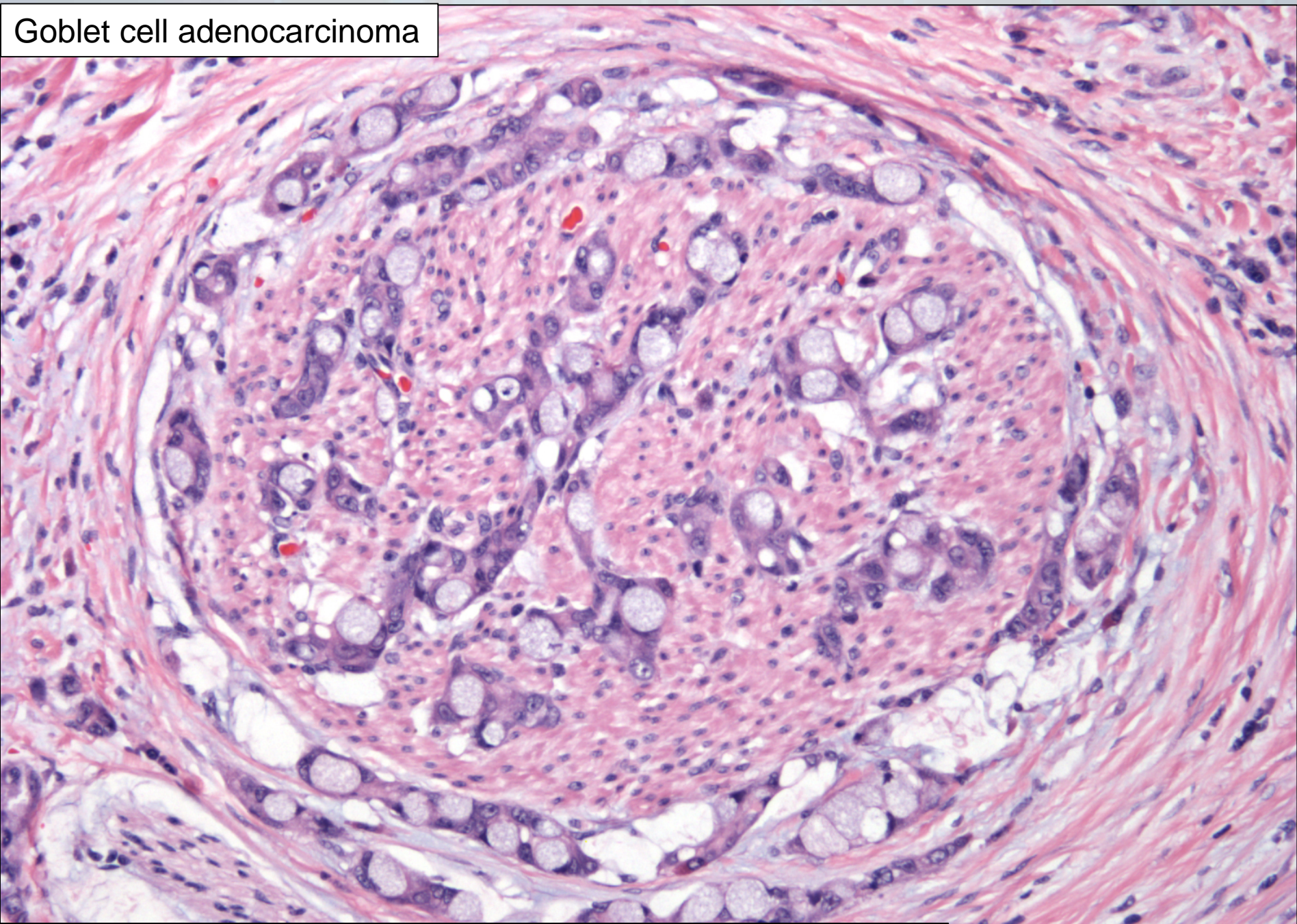
Concentric growth in appendiceal wall

Goblet cell adenocarcinoma

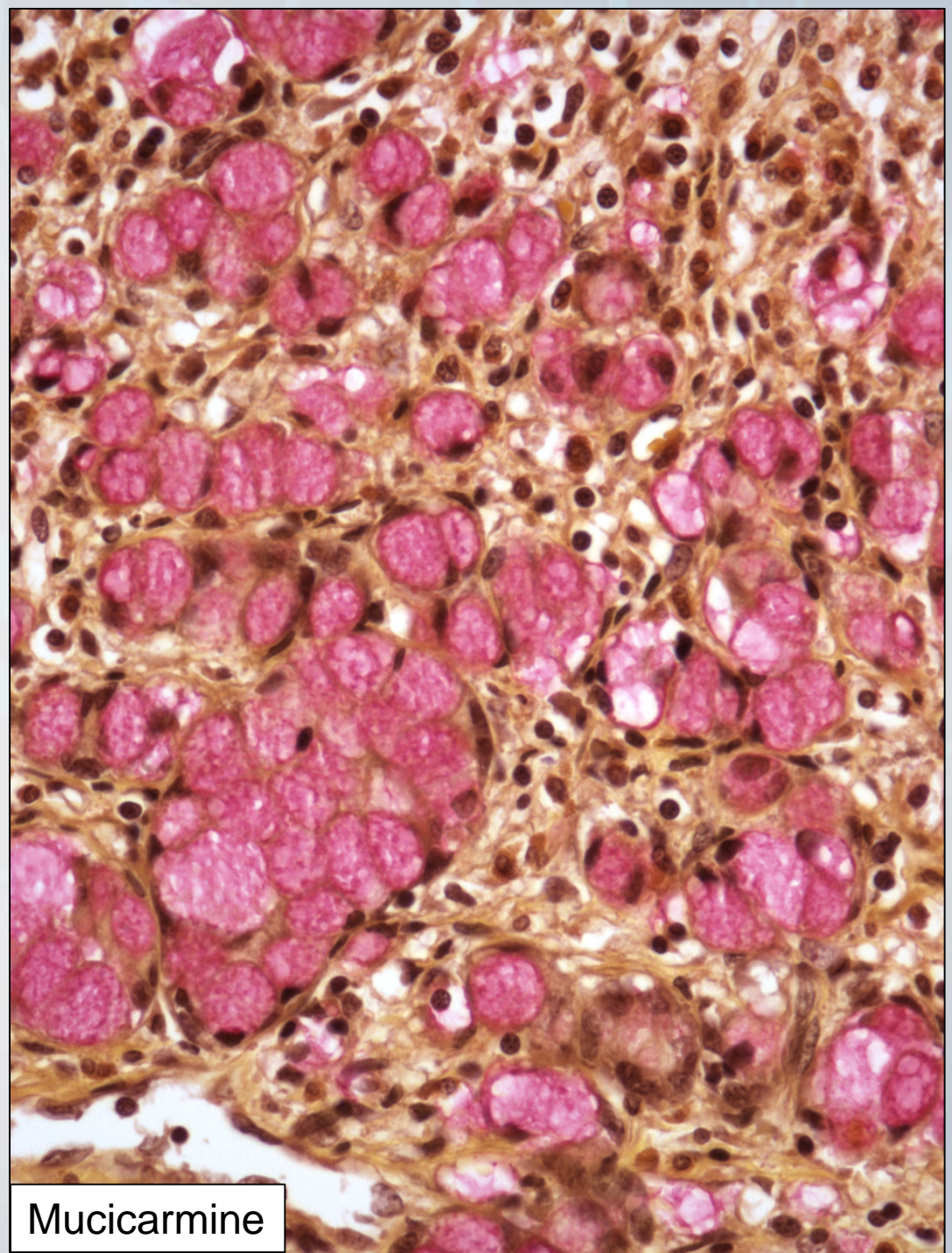
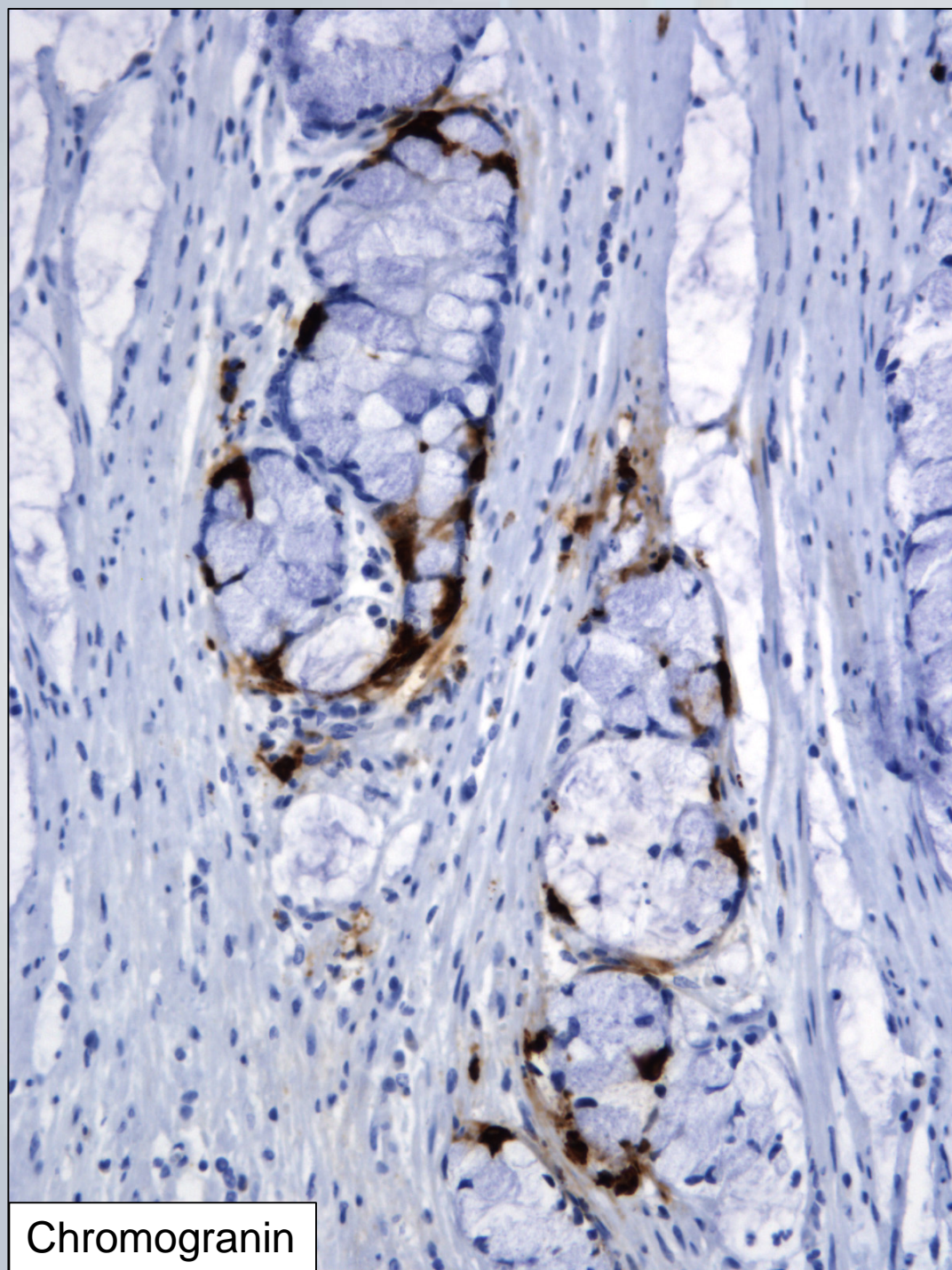


Dense collagenous reaction but no desmoplasia

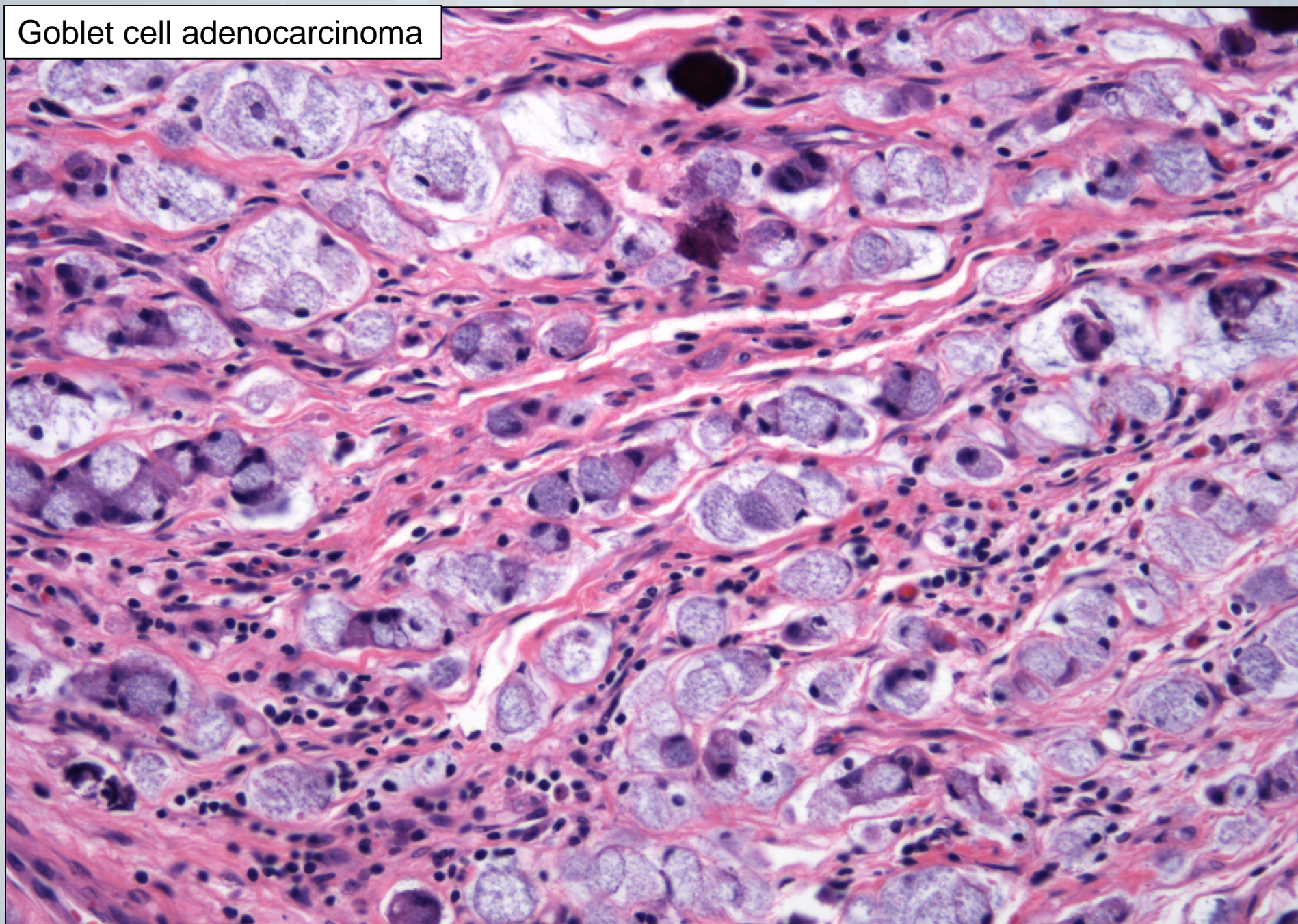
Goblet cell adenocarcinoma



Perineural invasion is common but not prognostically important

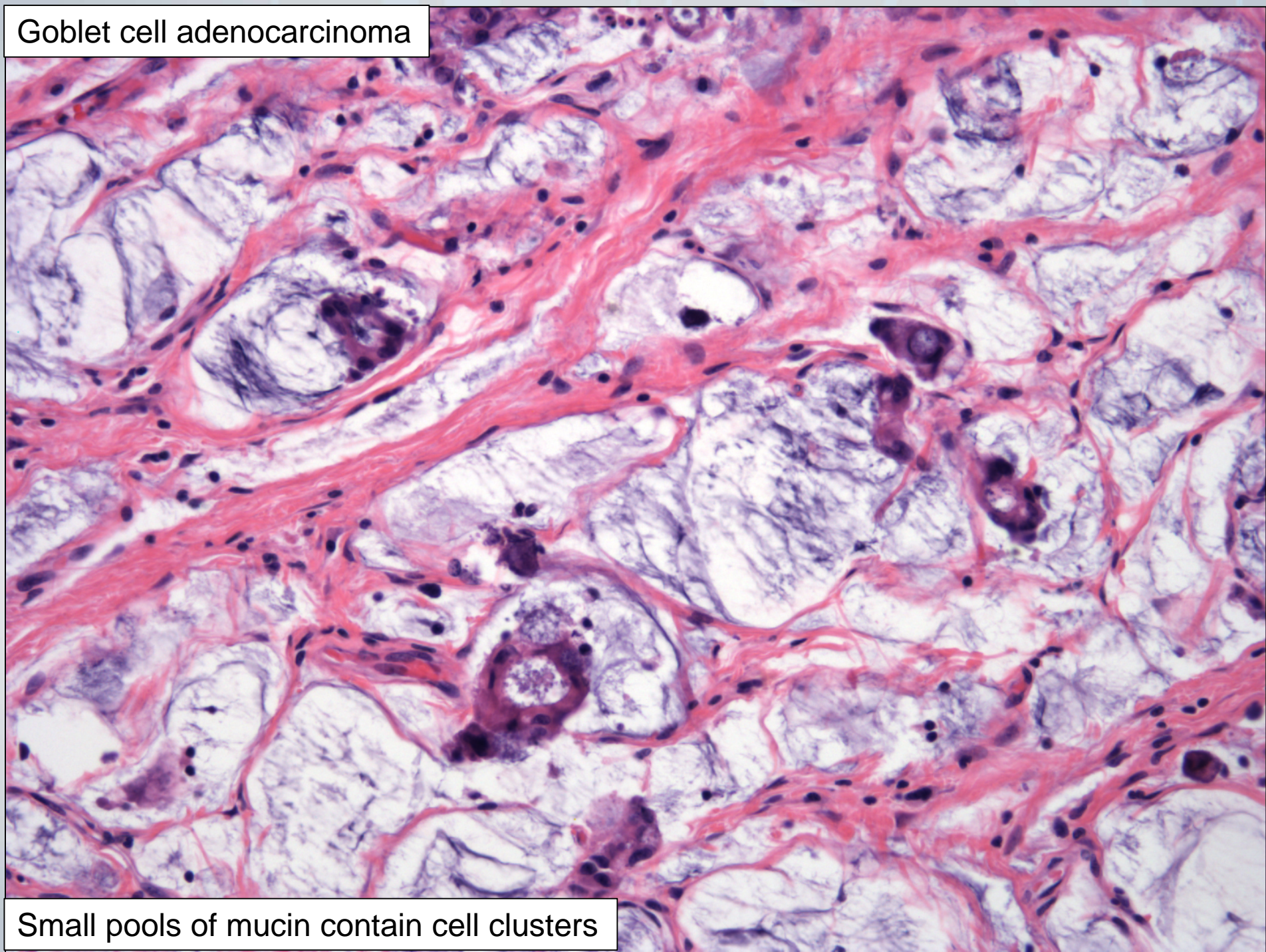


Goblet cell adenocarcinoma



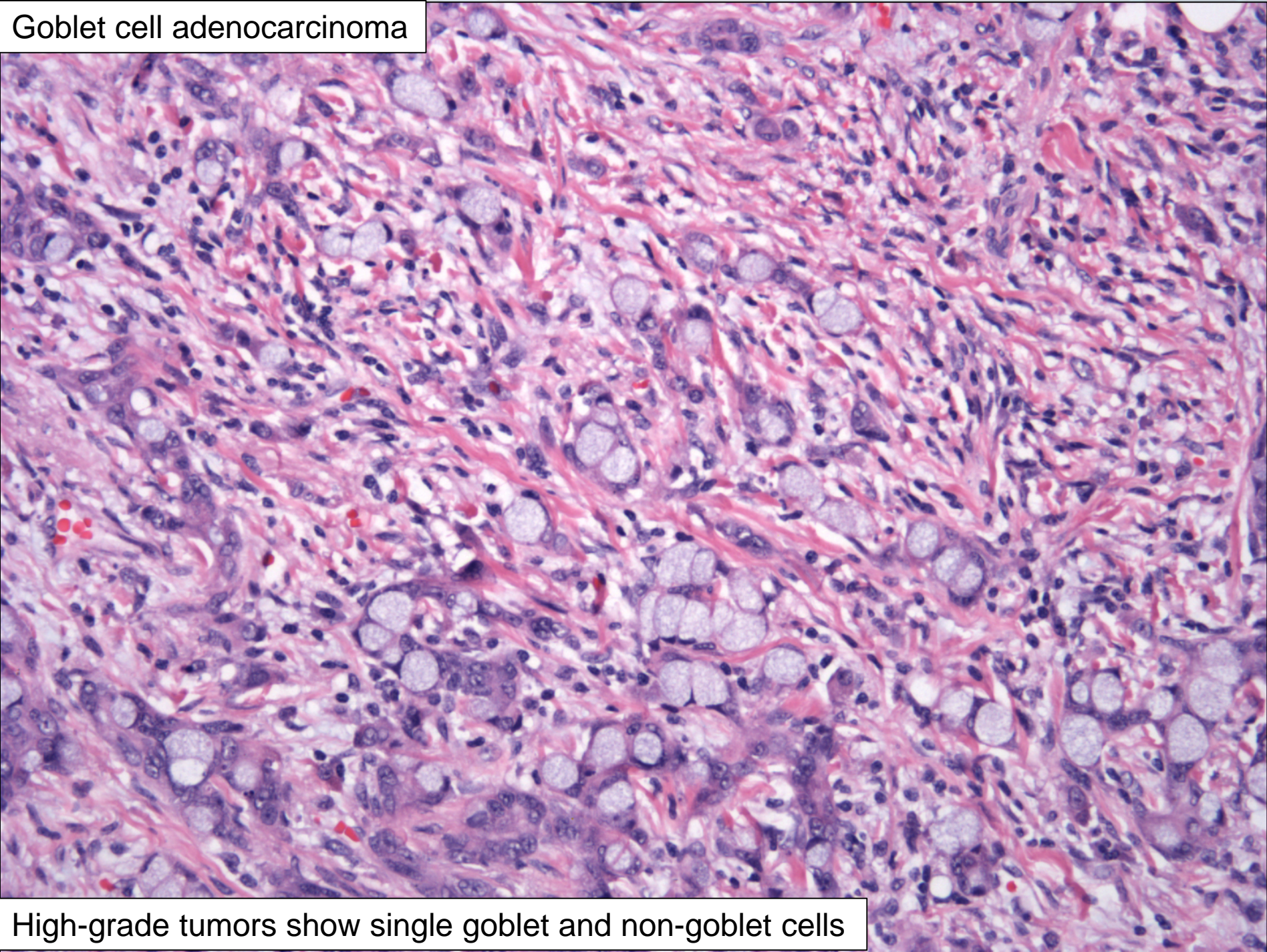
Low-grade tumors can contain squeezed groups that simulate signet ring cells

Goblet cell adenocarcinoma



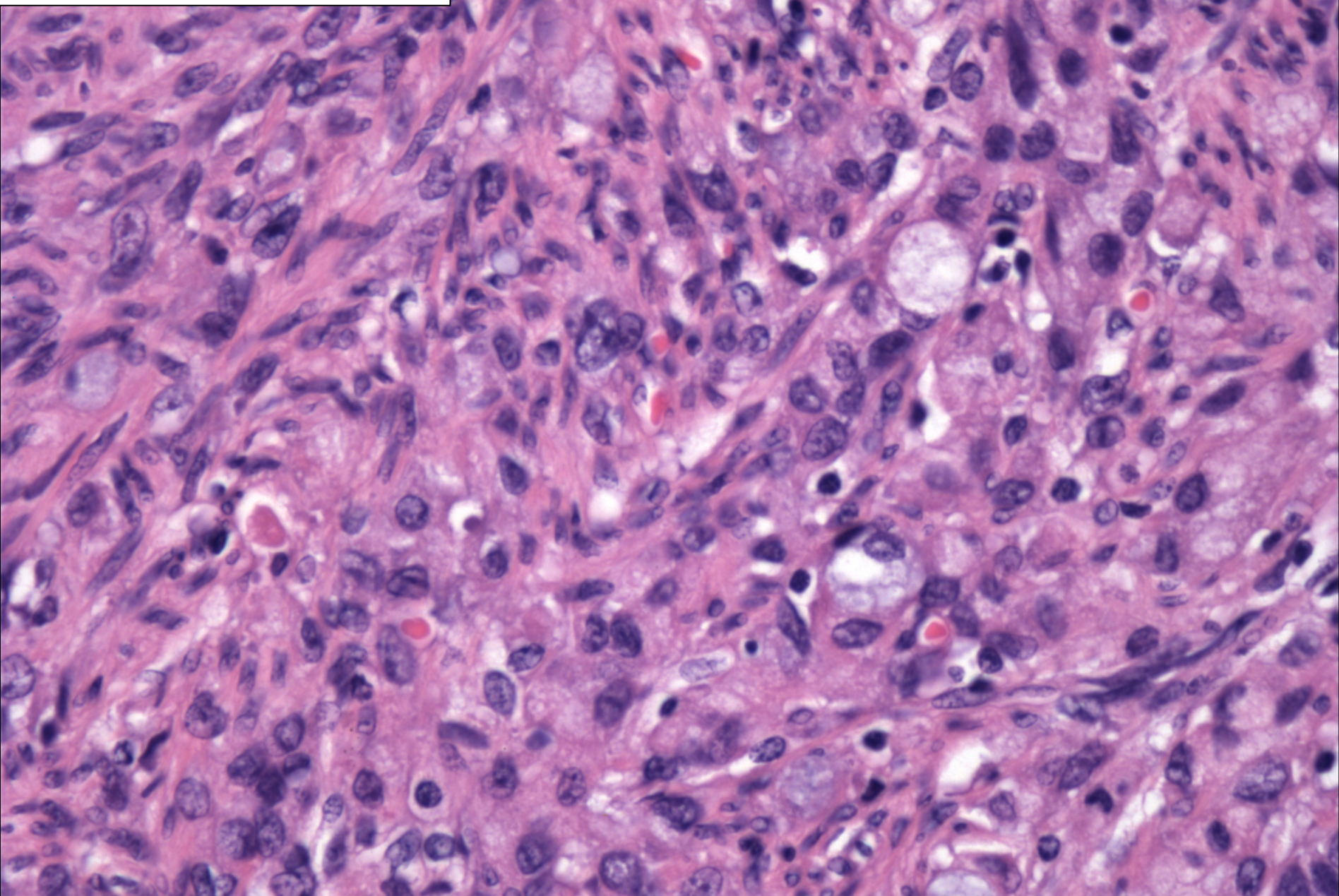
Small pools of mucin contain cell clusters

Goblet cell adenocarcinoma



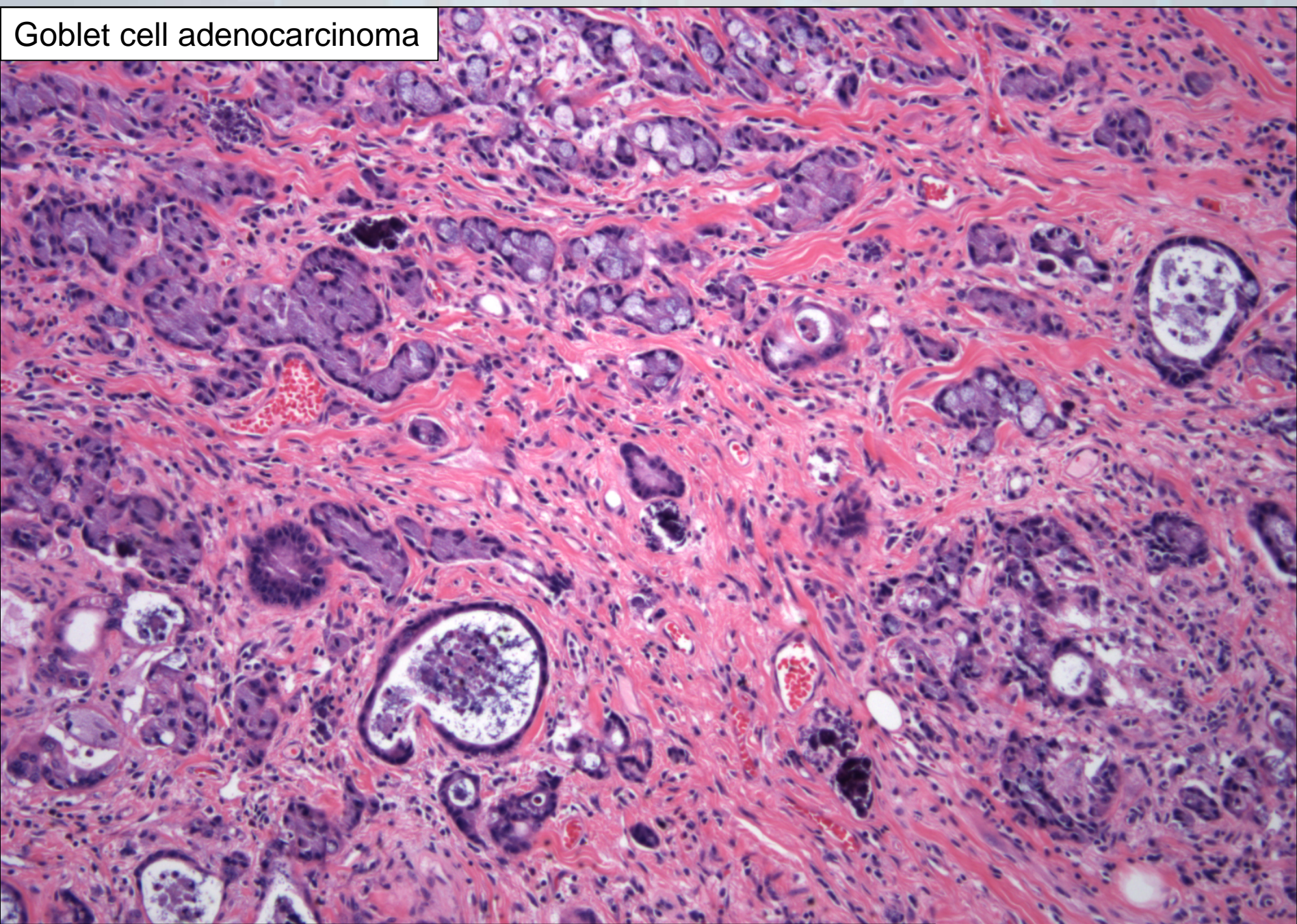
High-grade tumors show single goblet and non-goblet cells

Goblet cell adenocarcinoma



High-grade tumors show malignant cytology

Goblet cell adenocarcinoma



High-grade tumors can show areas of typical adenocarcinoma

Goblet Cell Neoplasms

- Prognosis based on tumor grade and stage
- Grade determined based on extent of low-grade component

Grade	Extent of Tubular or Clustered Growth (Low-Grade)
1	>75%
2	50-75%
3	<50%

- Stage is probably more important
 - Virtually all grade 2 and 3 tumors have spread beyond appendix at diagnosis
 - Most grade 1 tumors confined to the appendix at diagnosis do not recur

Serrated Appendiceal Lesions

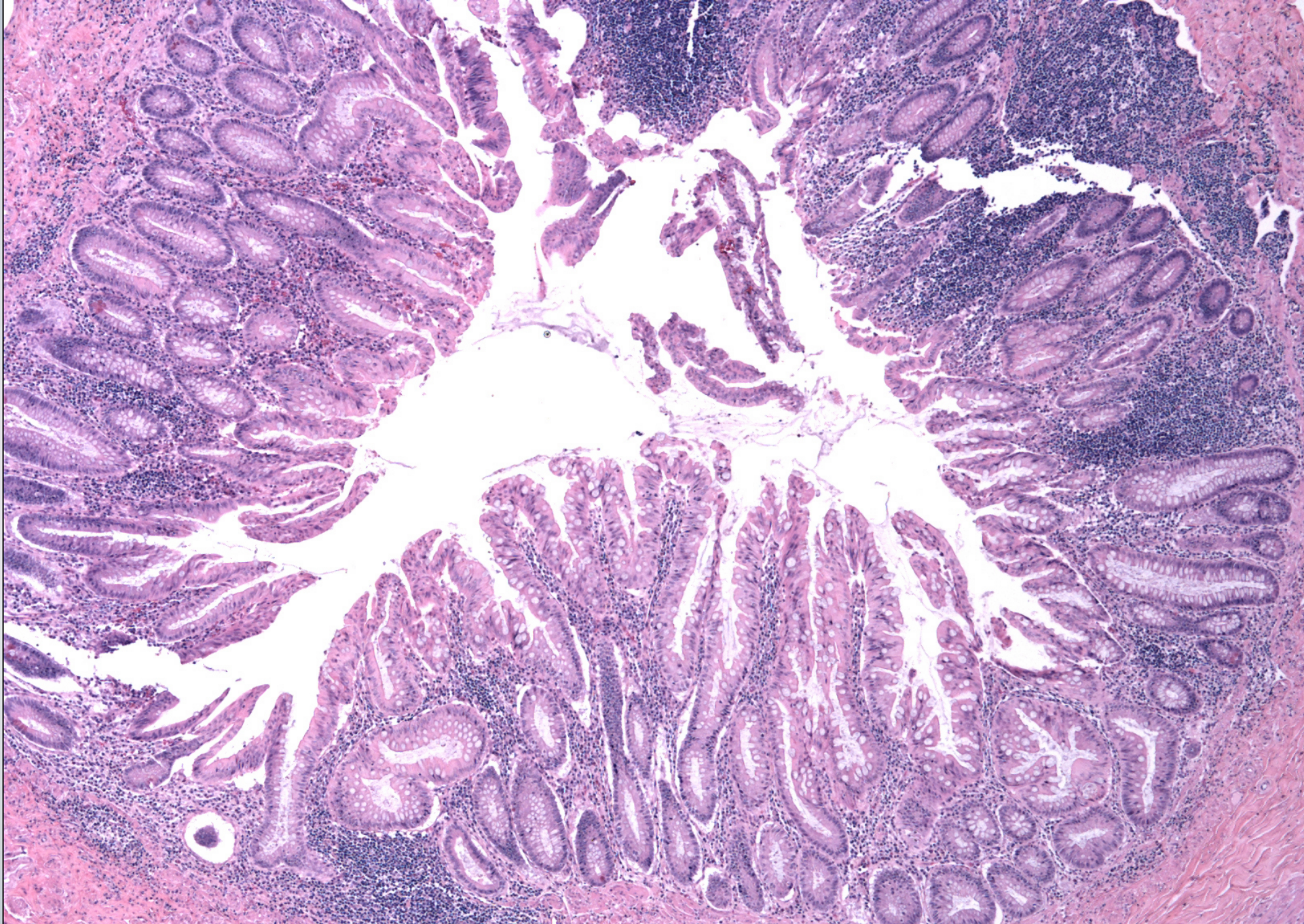
Serrated Appendiceal Lesions

- Hyperplastic polyps
- Non-dysplastic sessile serrated lesions (WHO says “no” to sessile serrated polyp)
 - Sort of look like sessile serrated polyps of the colon
 - Have either *BRAF* or *KRAS* mutations
 - Associated with right-sided colon cancers and serrated polyposis
 - Usually incidental findings so relationships likely influenced by specimen type
- Dysplastic serrated lesions
 - May resemble colonic counterparts
 - *KRAS* mutations more frequent than *BRAF* mutations

Yantiss, et al. Am J Surg Pathol 2007; 31(11): 1742-1753

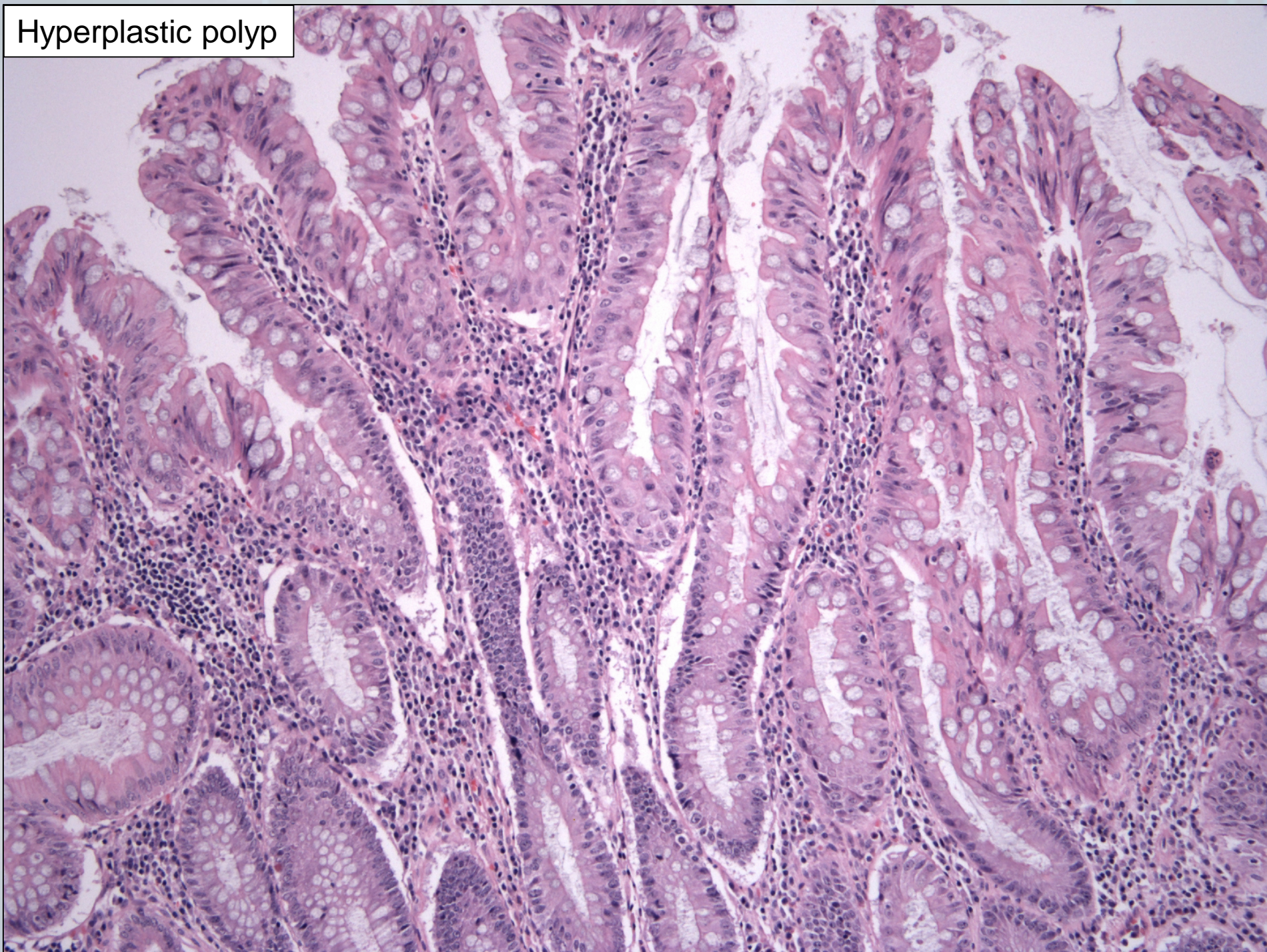
Bettington, et al. Pathology 2016; 48(1): 30-34.

WHO Classification of Tumours Digestive System Tumours, 5th Ed.

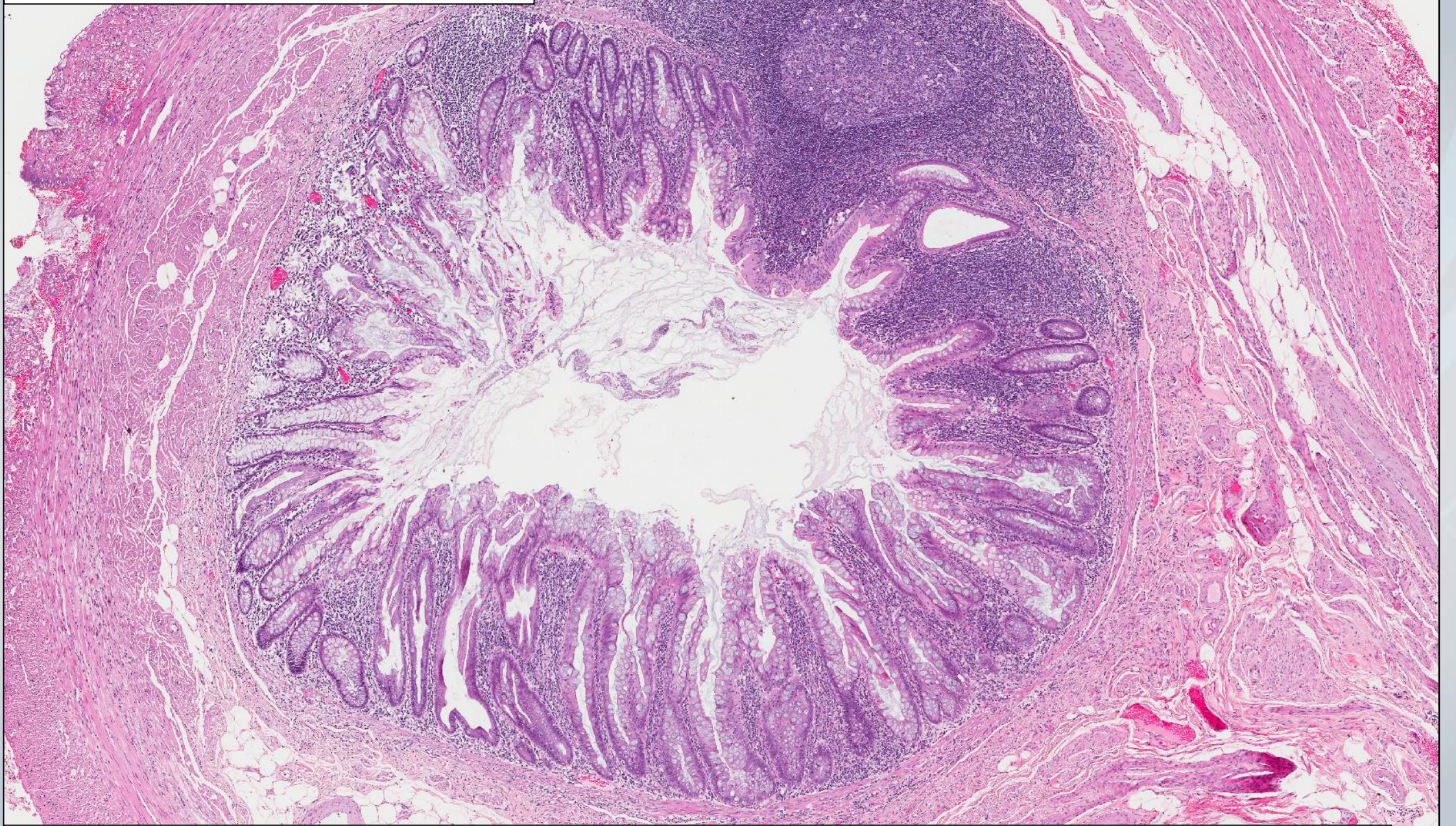


Hyperplastic polyp

Hyperplastic polyp

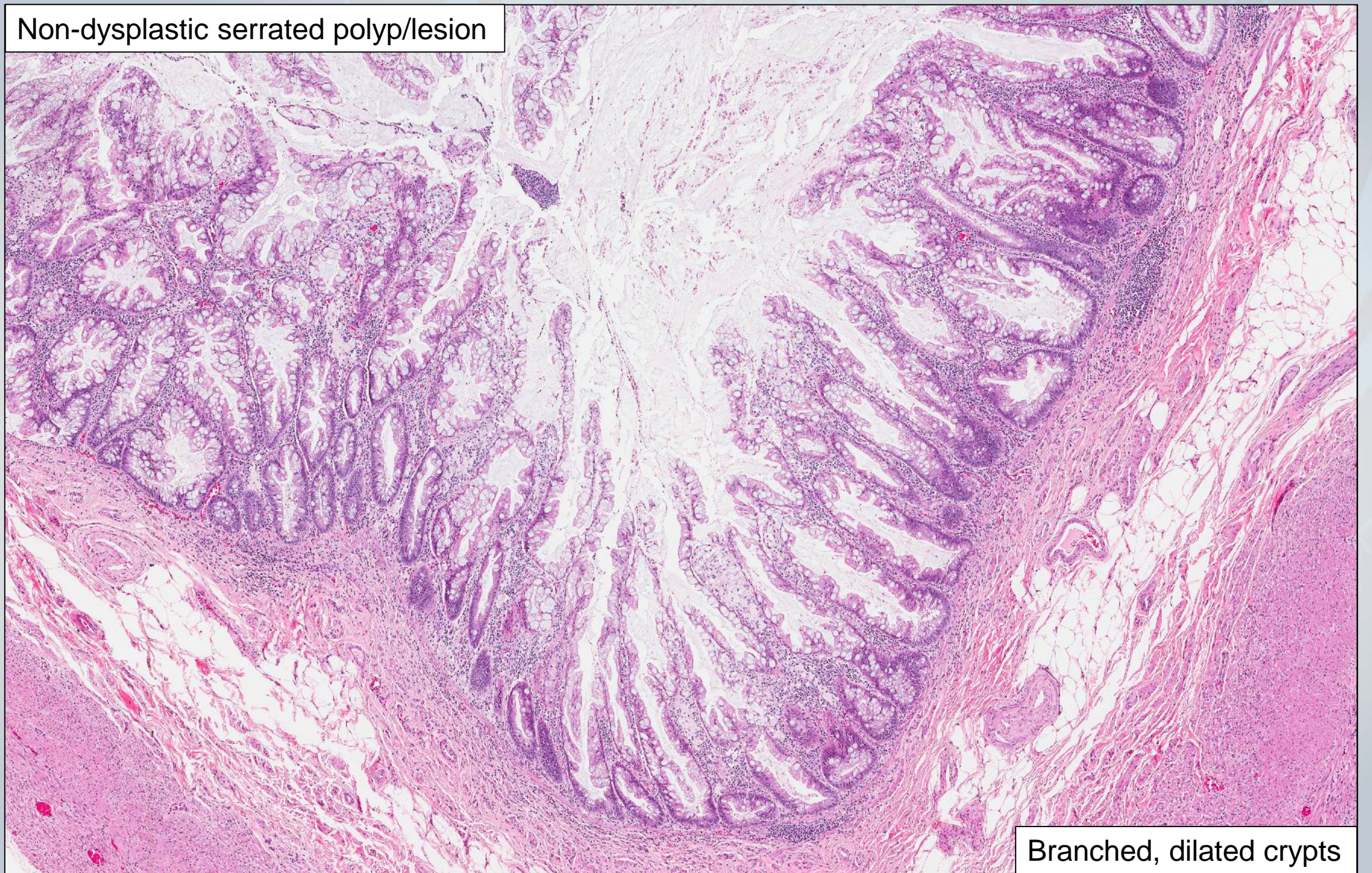


Non-dysplastic serrated lesion/polyp



Circumferential proliferation of epithelium supported by lamina propria; preserved wall architecture

Non-dysplastic serrated polyp/lesion



Branched, dilated crypts

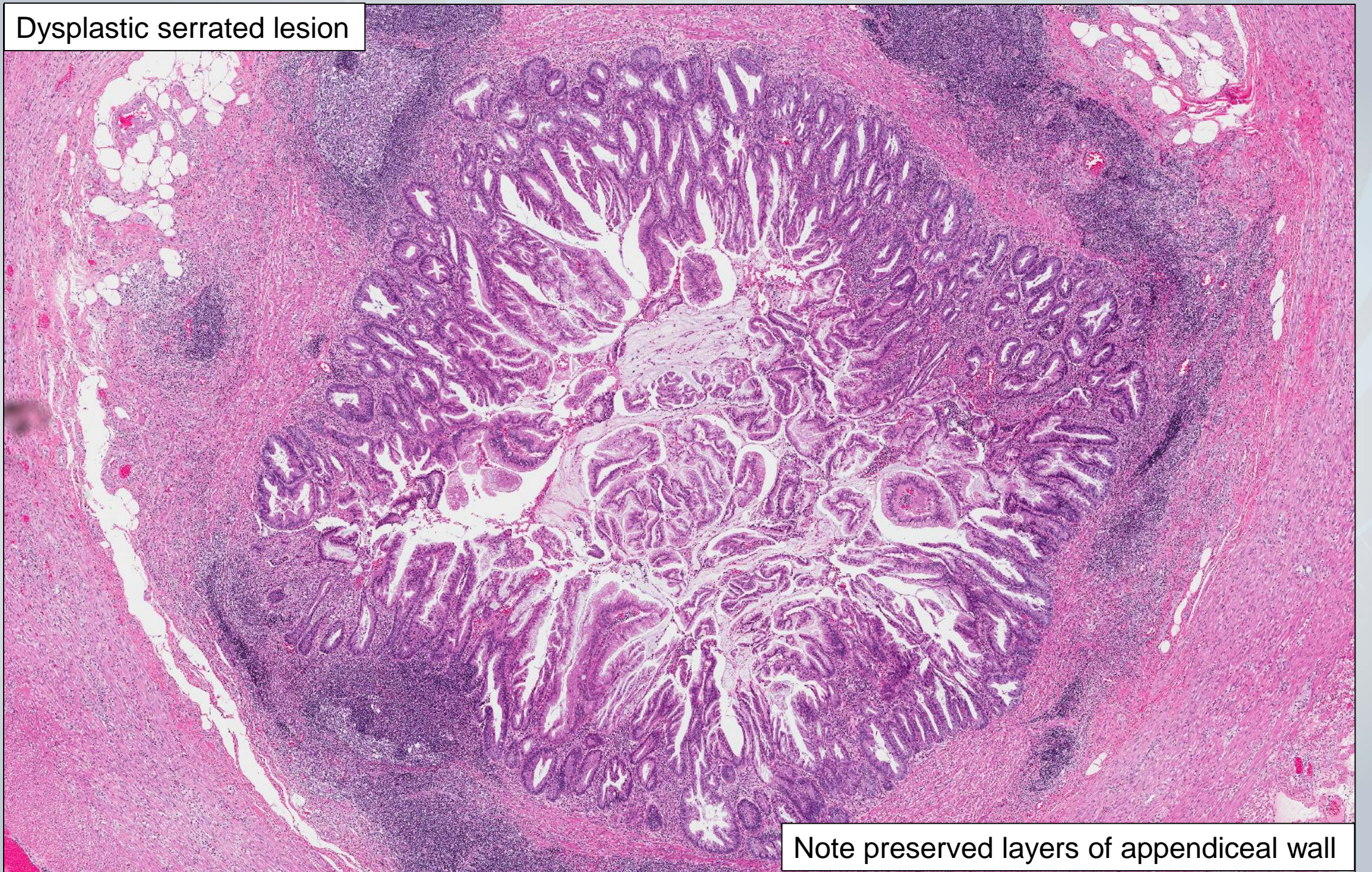
A histological section of a sessile serrated polyp in the colon. The image shows a large, flat, serrated lesion extending from the mucosal surface. The lesion is characterized by elongated, serrated crypts that branch out and extend deep into the mucosa. The crypts are lined by columnar epithelium. The underlying layers of the colon wall, including the muscularis mucosae, submucosa, and muscularis propria, appear normal and are not infiltrated by the lesion. The overall appearance is that of a large, flat, serrated polyp.

More papillary than colonic lesions

Normal muscularis mucosae, submucosa, and muscularis propria

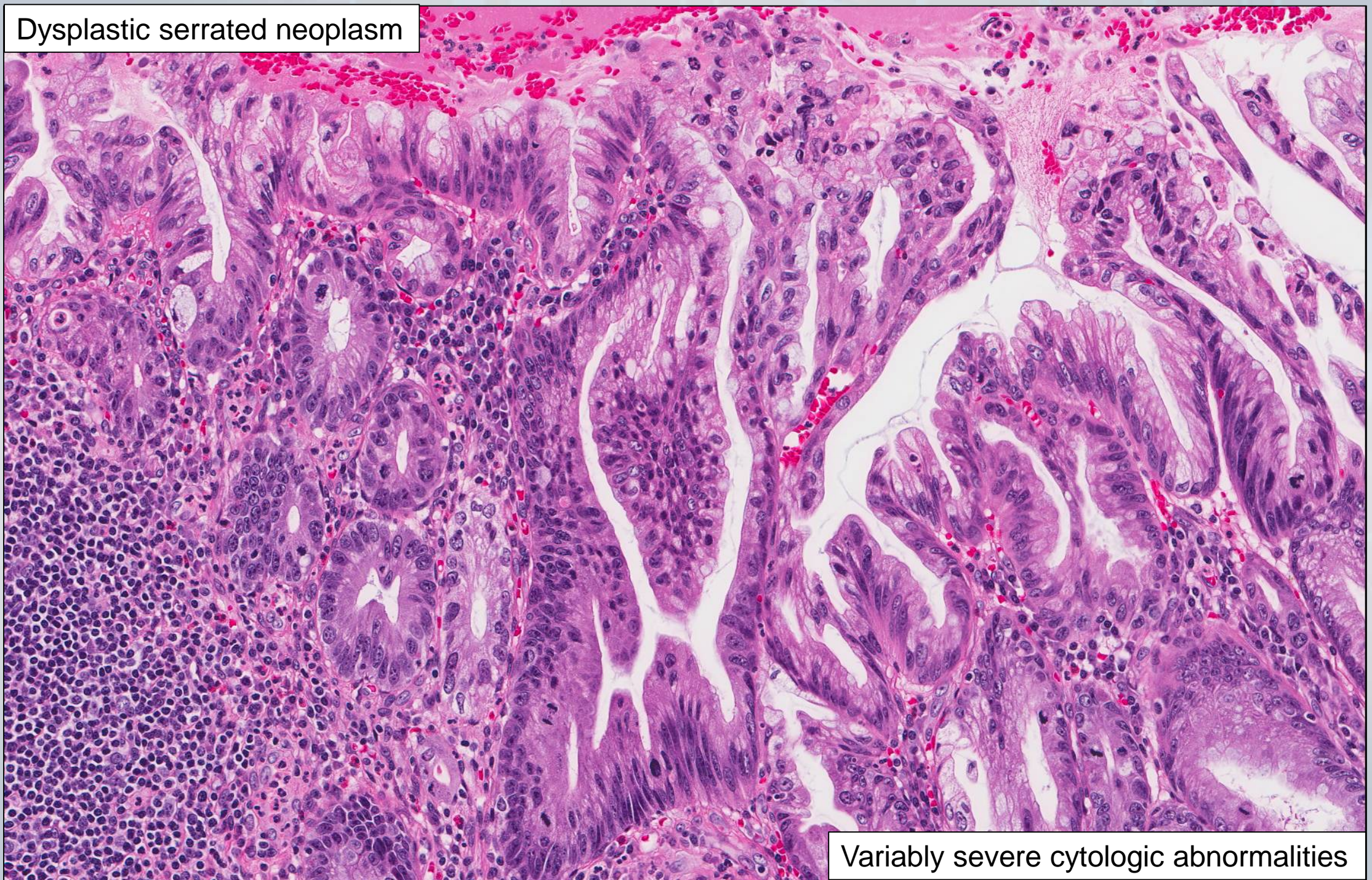
Sessile serrated polyp/lesion

Dysplastic serrated lesion



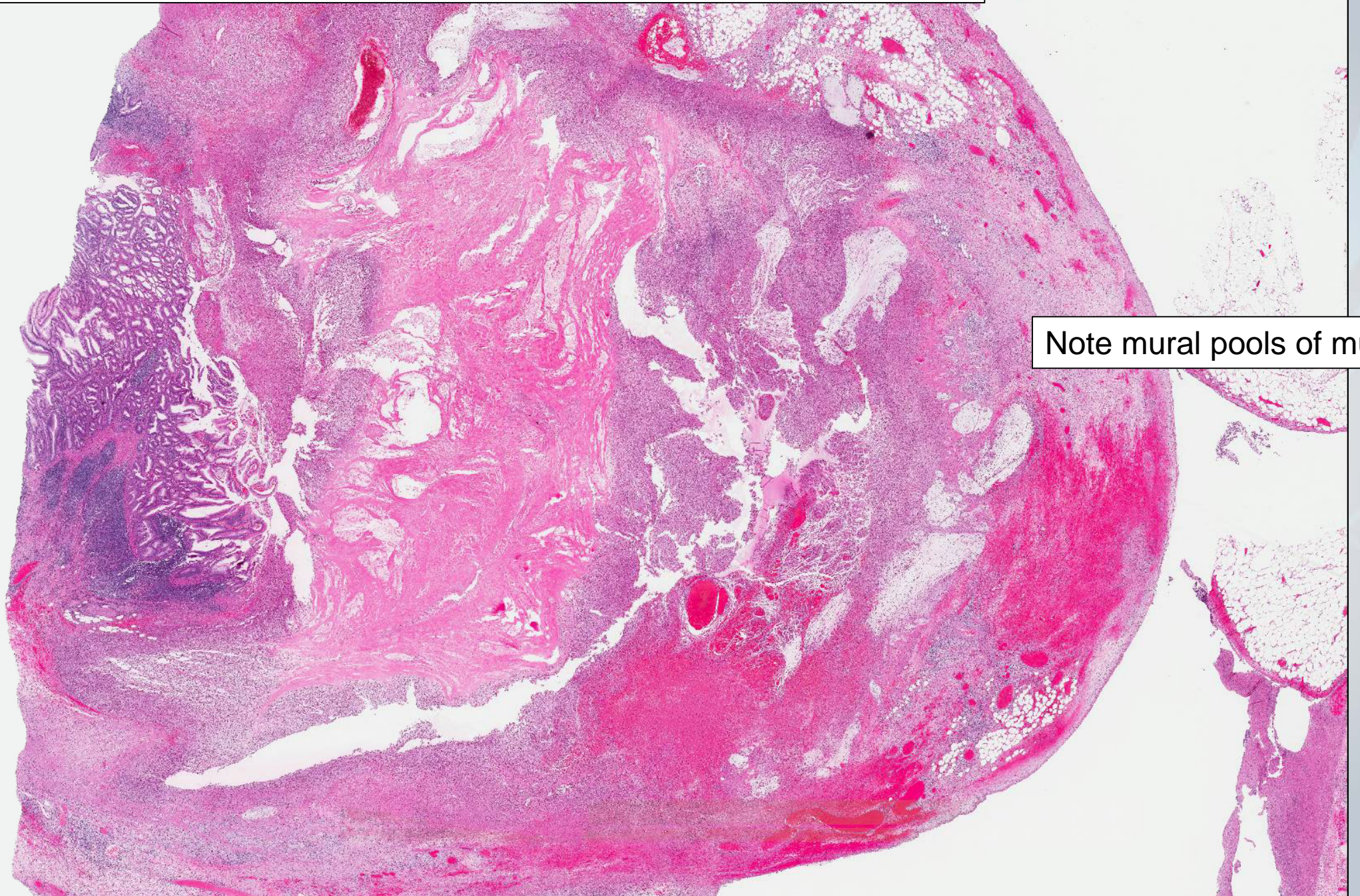
Note preserved layers of appendiceal wall

Dysplastic serrated neoplasm

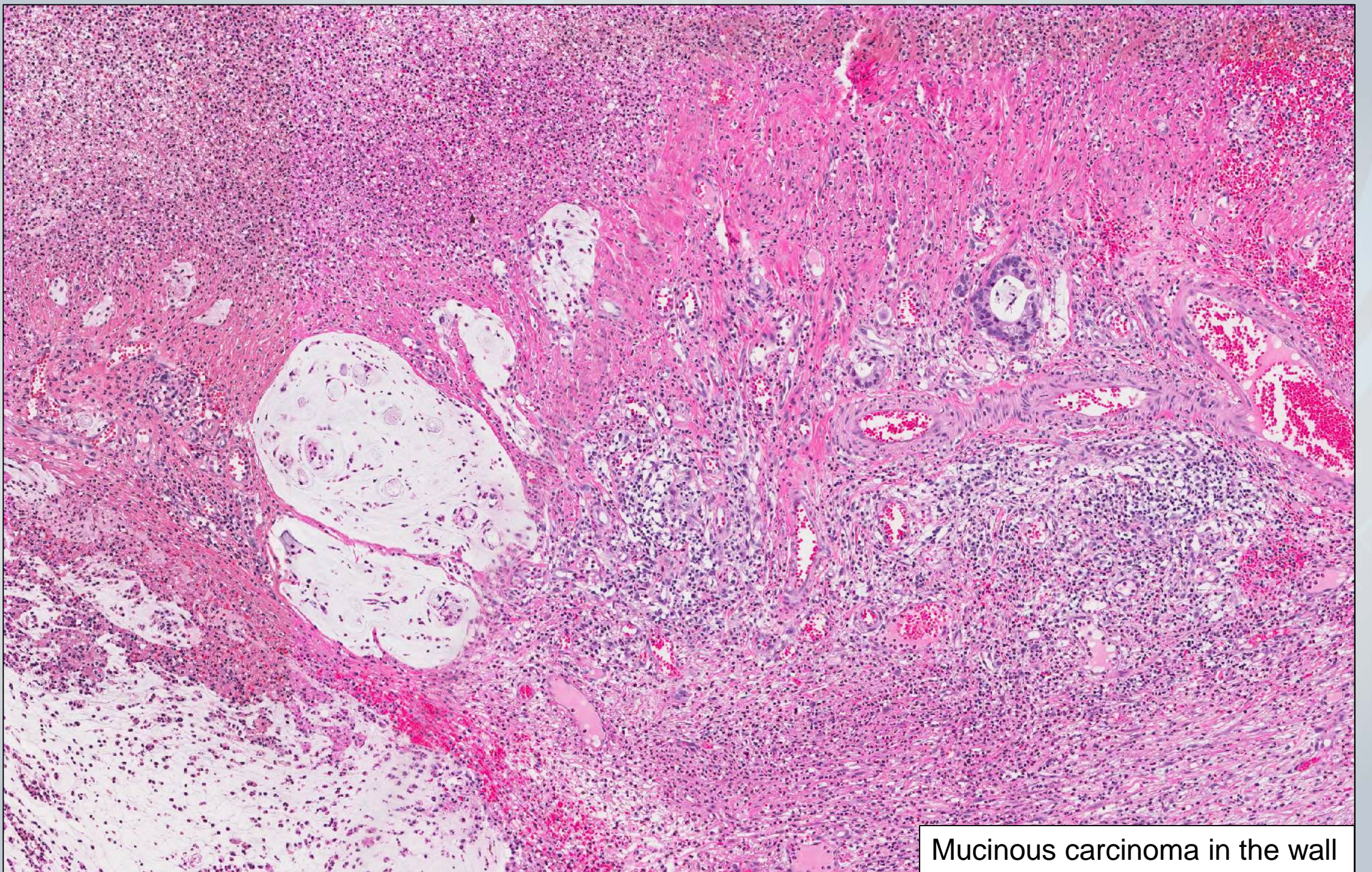


Variably severe cytologic abnormalities

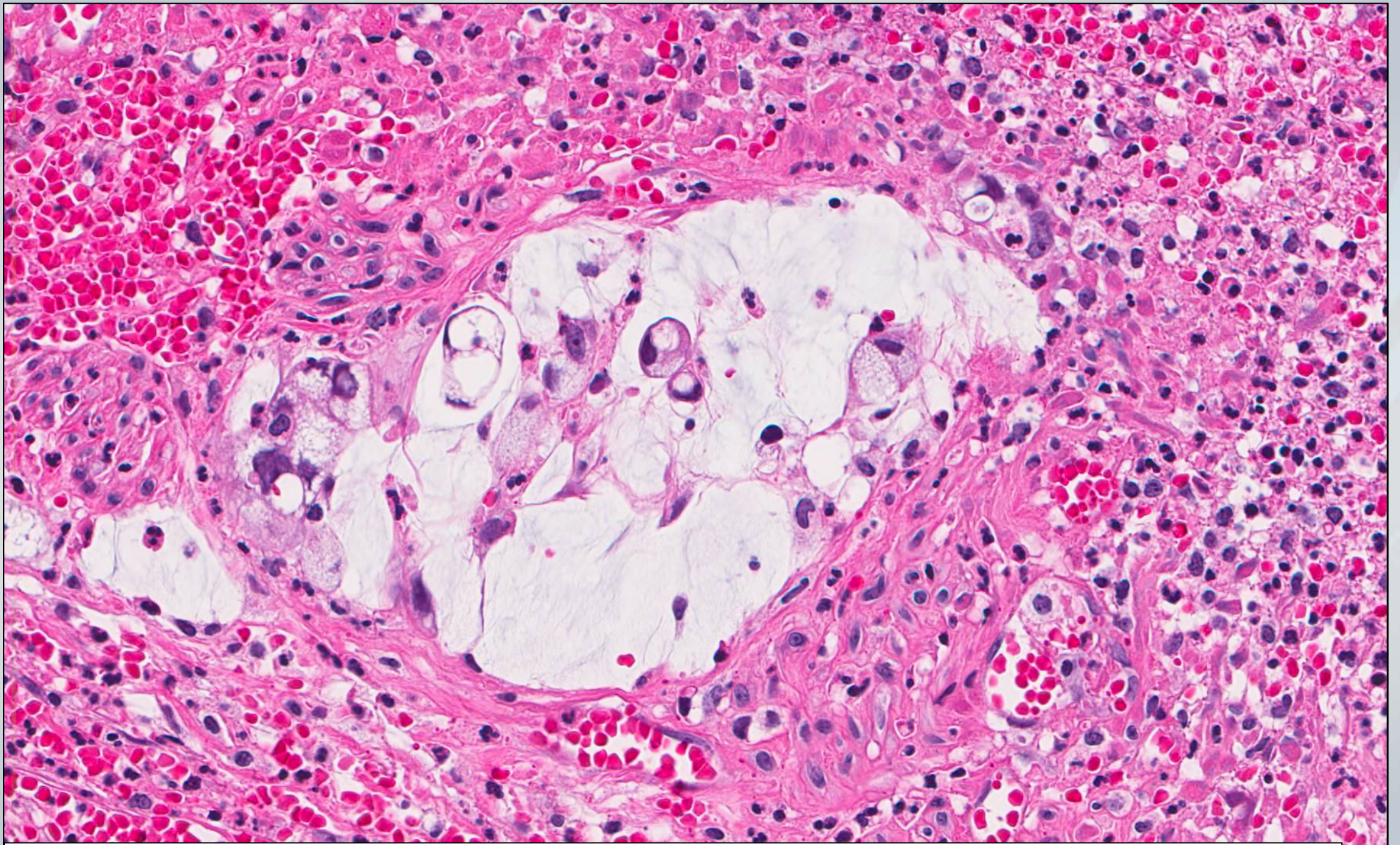
Dysplastic serrated neoplasm in a patient presenting with acute appendicitis



Note mural pools of mucin



Mucinous carcinoma in the wall



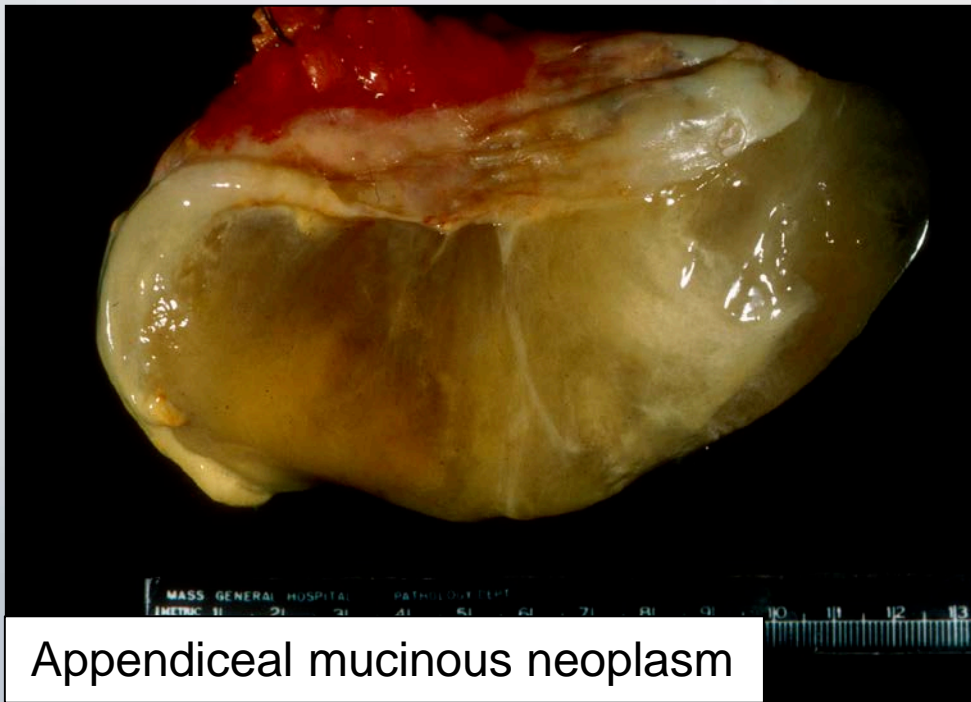
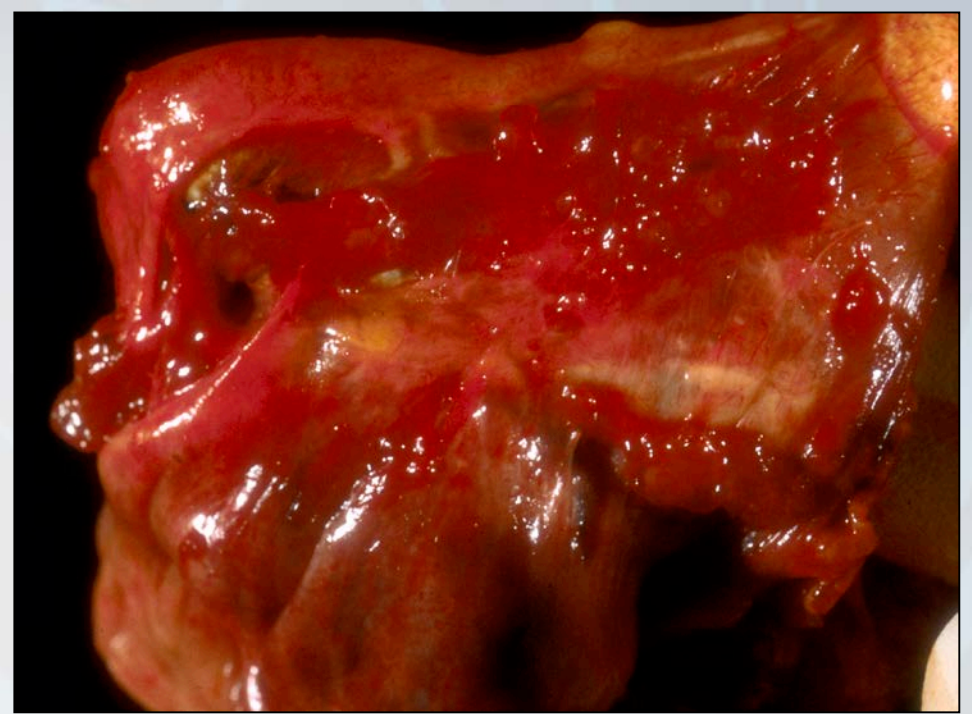
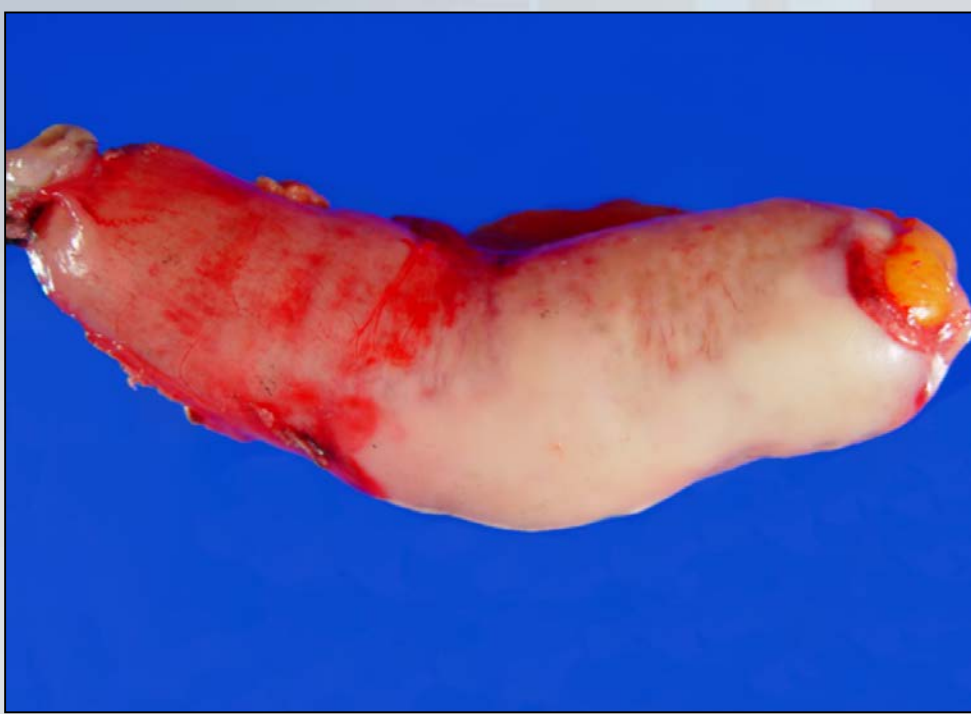
Mucinous carcinoma (most appendiceal cancers show mucinous features regardless of precursor)

Appendiceal Epithelial Neoplasms

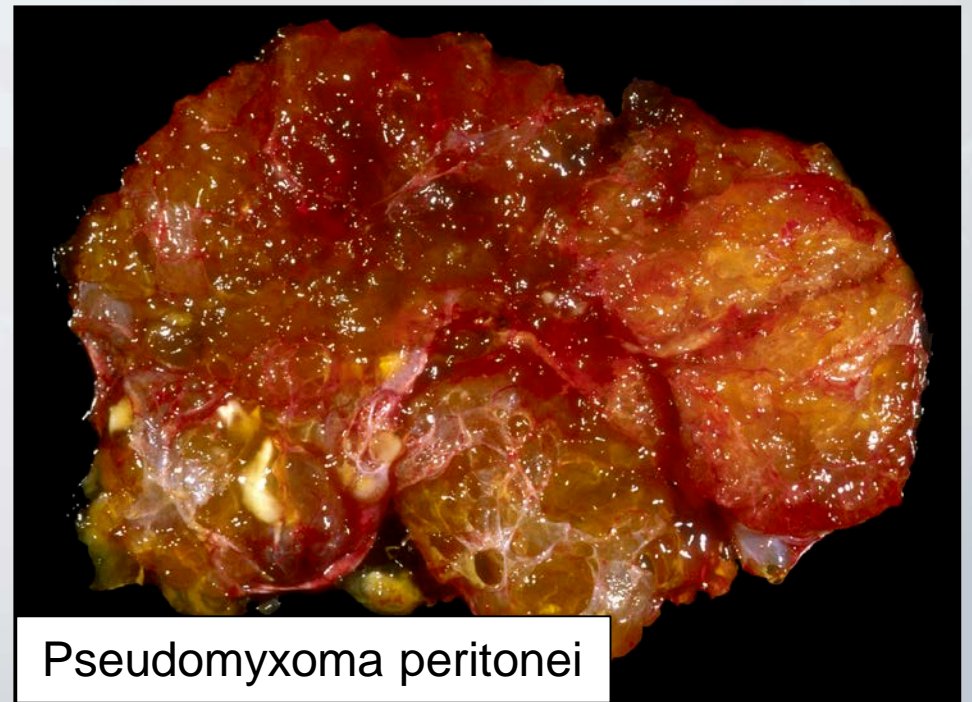
Not Too Controversial So Far

- Goblet cell neoplasia
 - Carcinomas not carcinoids
 - Grade based on extent of nested growth
- Serrated neoplasms
 - Non-dysplastic and dysplastic serrated lesions generally incidental or found in right colectomy specimens
 - Be careful with dysplastic lesions; associated cancers can be sneaky
- Mucinous tumors
 - Nomenclature
 - Distinction from non-neoplastic mimics

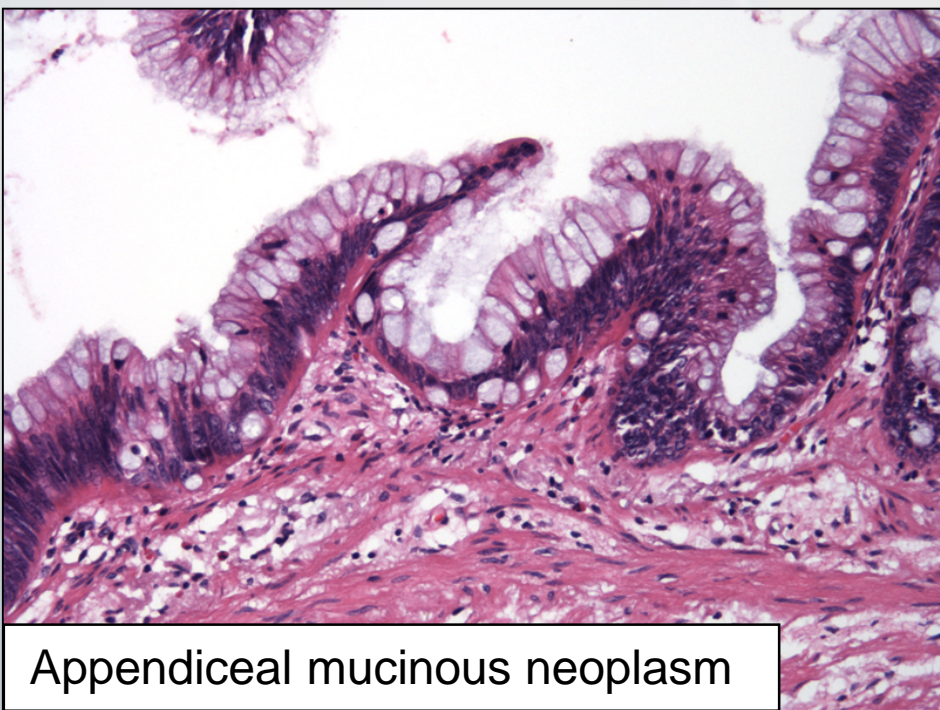
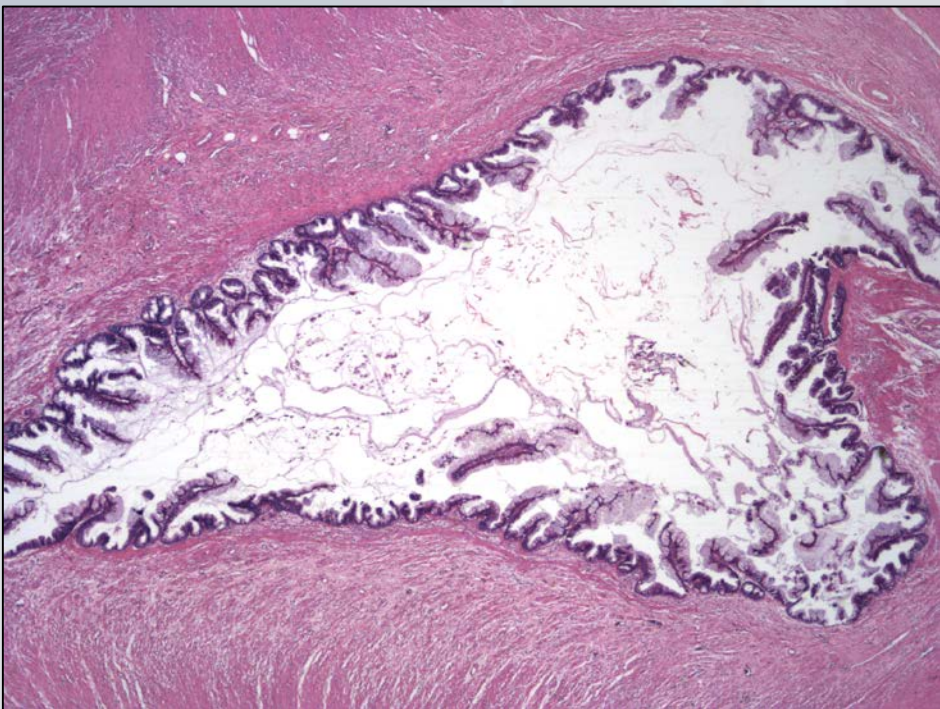
Mucinous Appendiceal Lesions



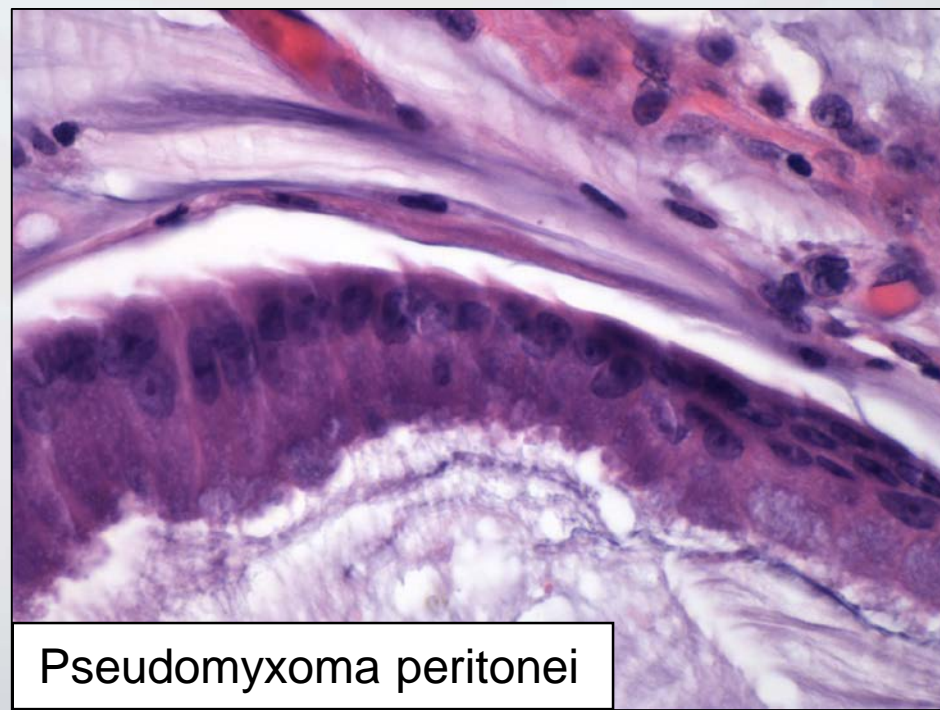
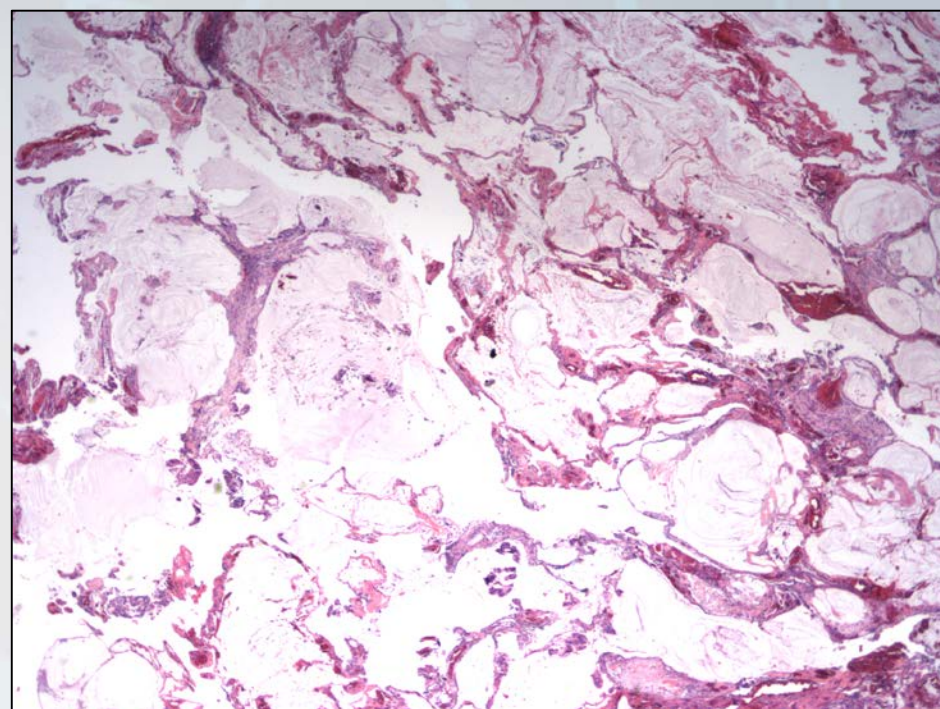
Appendiceal mucinous neoplasm



Pseudomyxoma peritonei

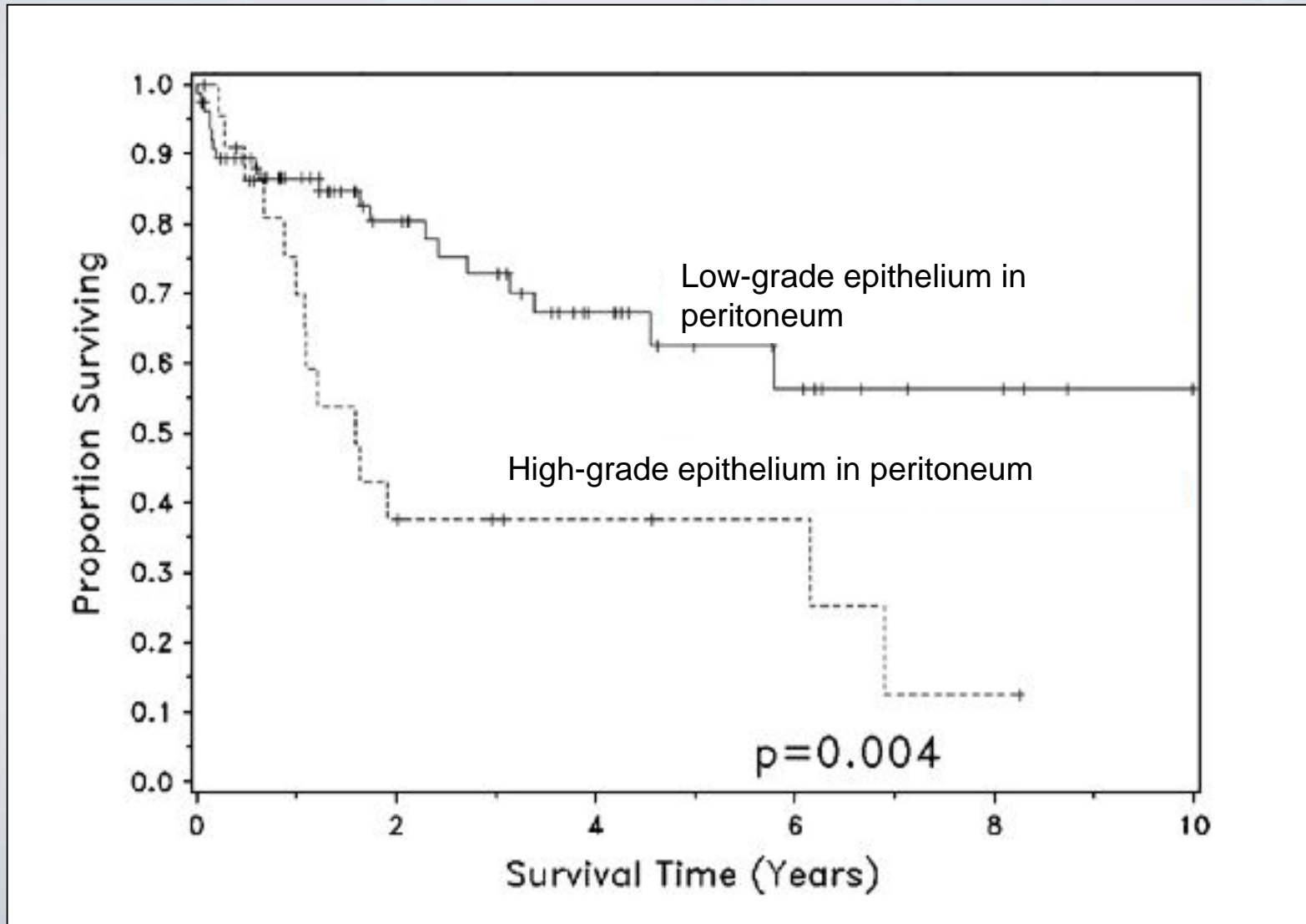


Appendiceal mucinous neoplasm



Pseudomyxoma peritonei

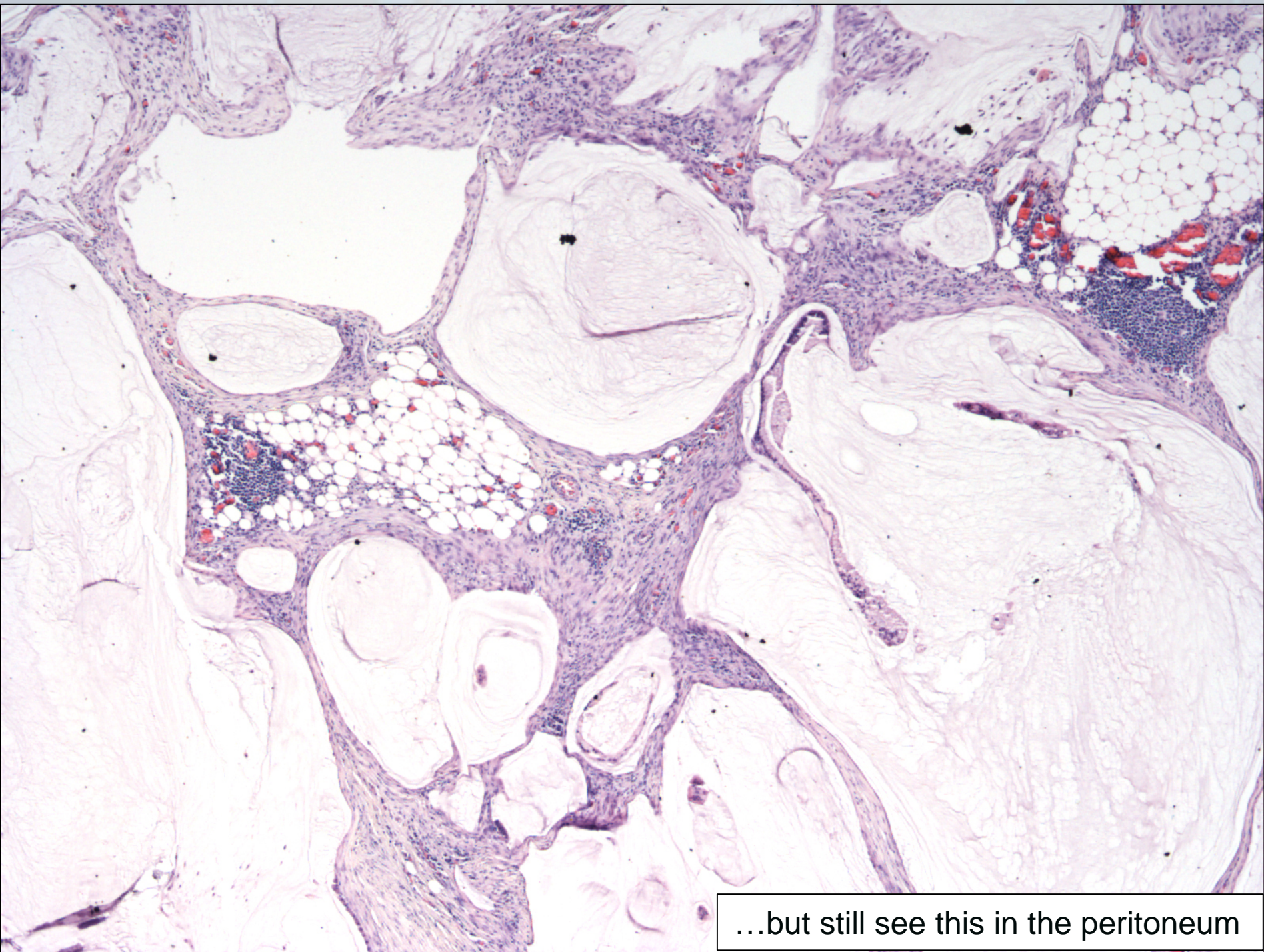
Natural History of Pseudomyxoma Peritonei



Not typical invasive pattern of cancer



Can see this in the appendix....



...but still see this in the peritoneum

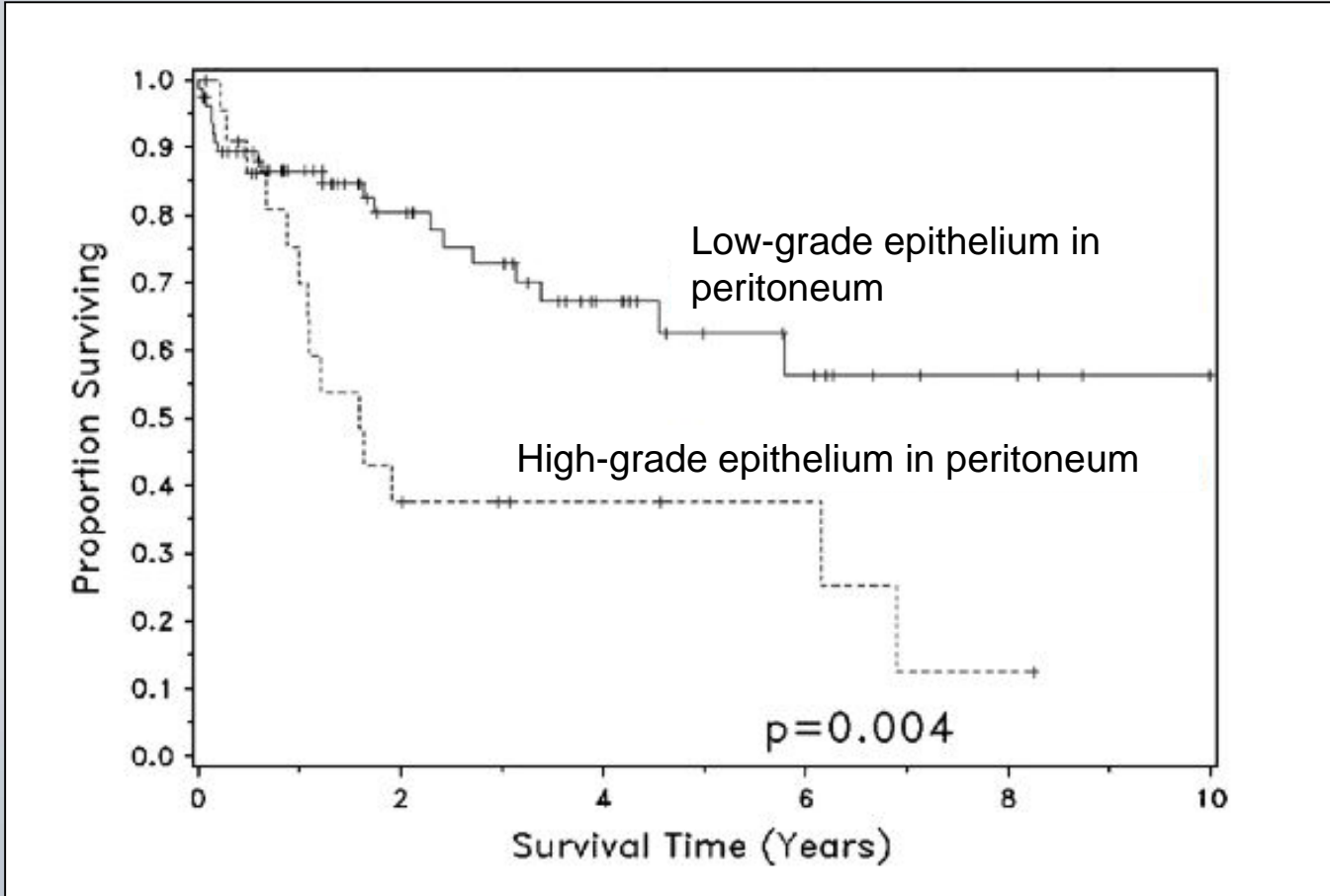
Problematic Issues

- A peritoneal tumor that looks benign, but it isn't
- An appendiceal tumor that doesn't seem invasive, but it is

Mucinous Tumors of Appendix and Peritoneum

- Appendiceal tumor
 - Adenoma
 - Mucinous tumor of uncertain malignant potential
 - Low-grade appendiceal mucinous neoplasm
 - Mucinous adenocarcinoma
 - Invasive mucinous adenocarcinoma
- Peritoneal disease
 - Disseminated peritoneal adenomucinosis
 - Low-grade appendiceal mucinous neoplasm
 - Ruptured mucocele
 - Mucinous adenocarcinoma
 - Disseminated mucinous carcinomatosis

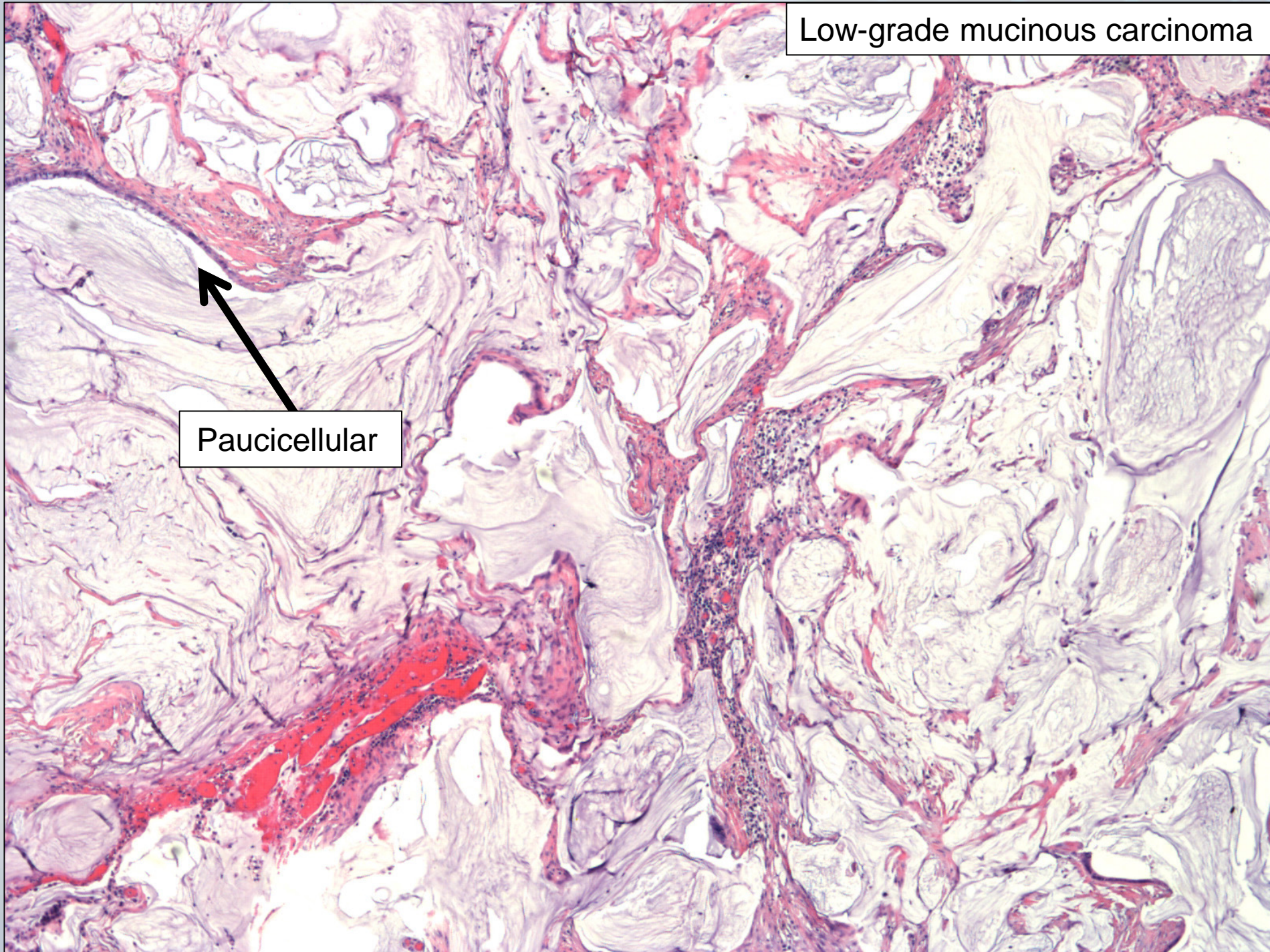
Cytologic Grade of Peritoneal Disease is Important



Malignant behavior justifies terminology

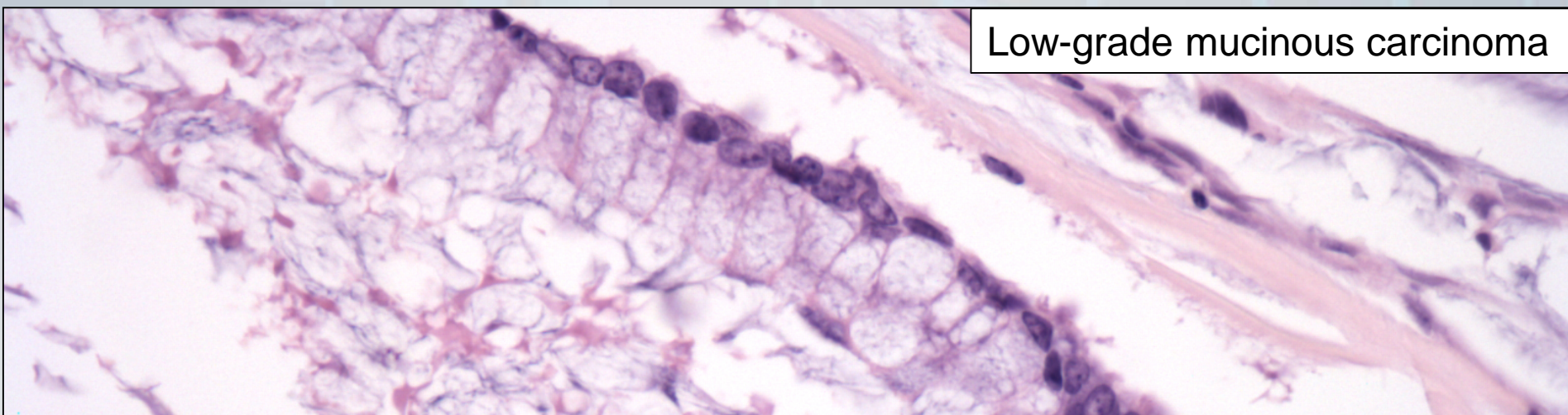
- Low-grade mucinous carcinoma
- High-grade mucinous carcinoma

Low-grade mucinous carcinoma

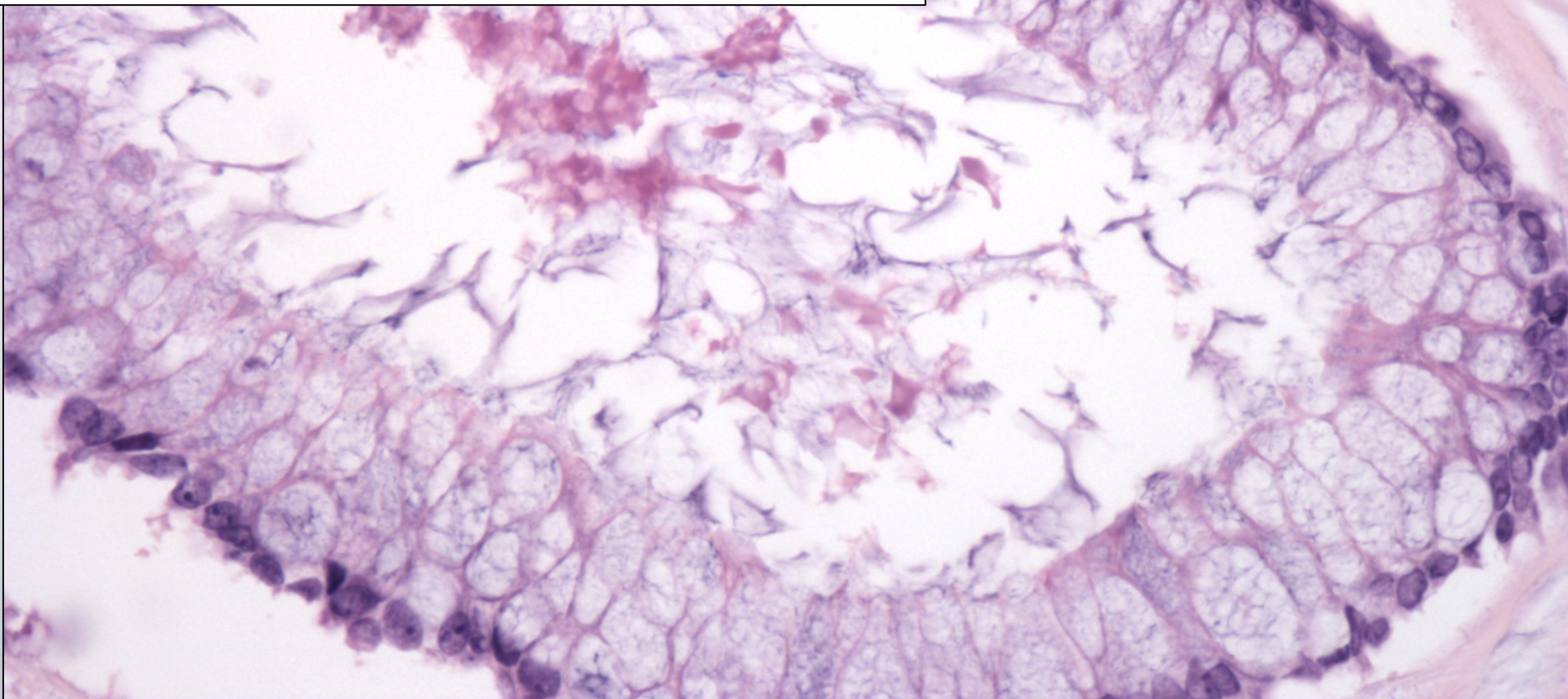


Paucicellular

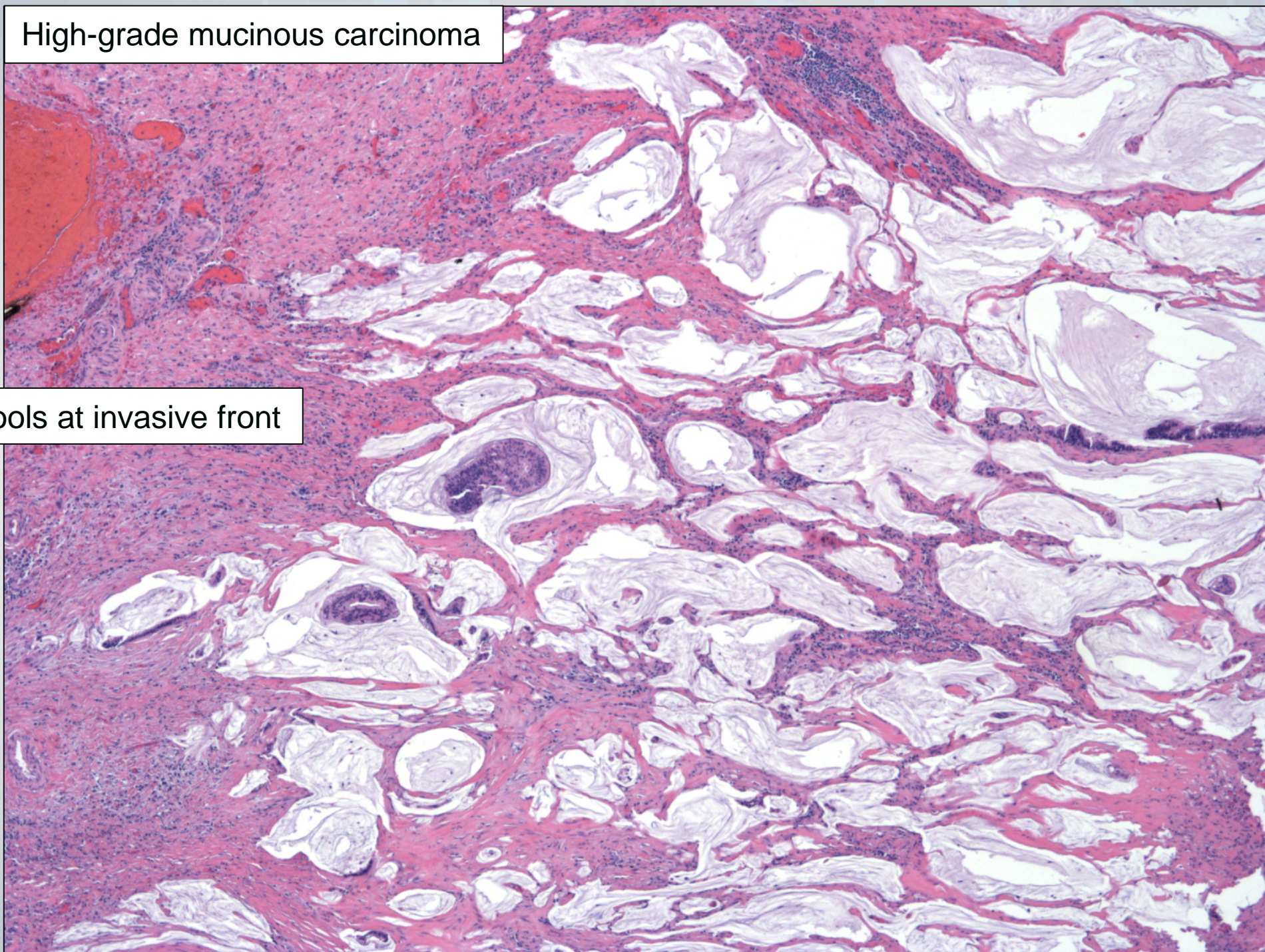
Low-grade mucinous carcinoma



Nucleus located at cell base, occupying bottom one-third of cell

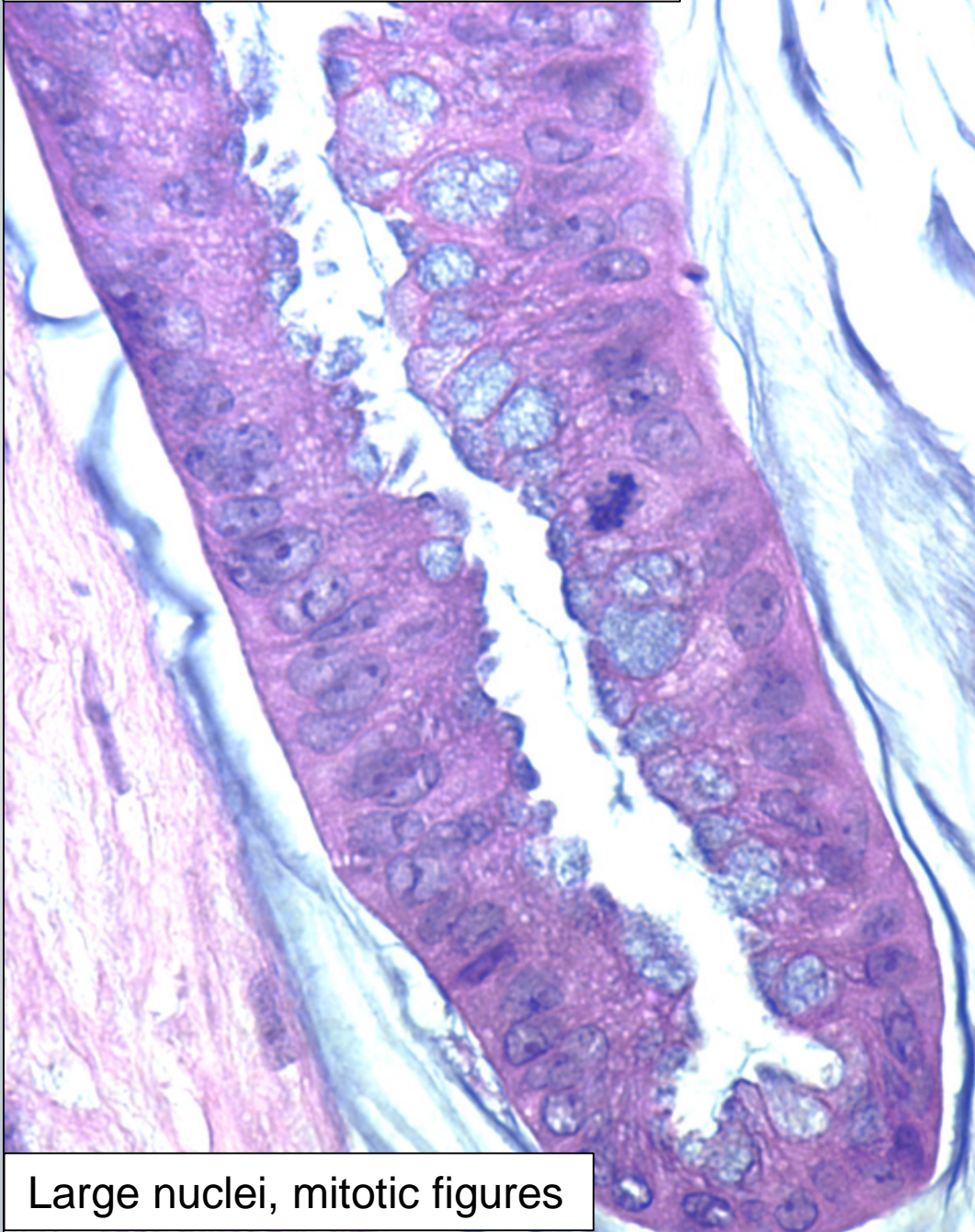


High-grade mucinous carcinoma



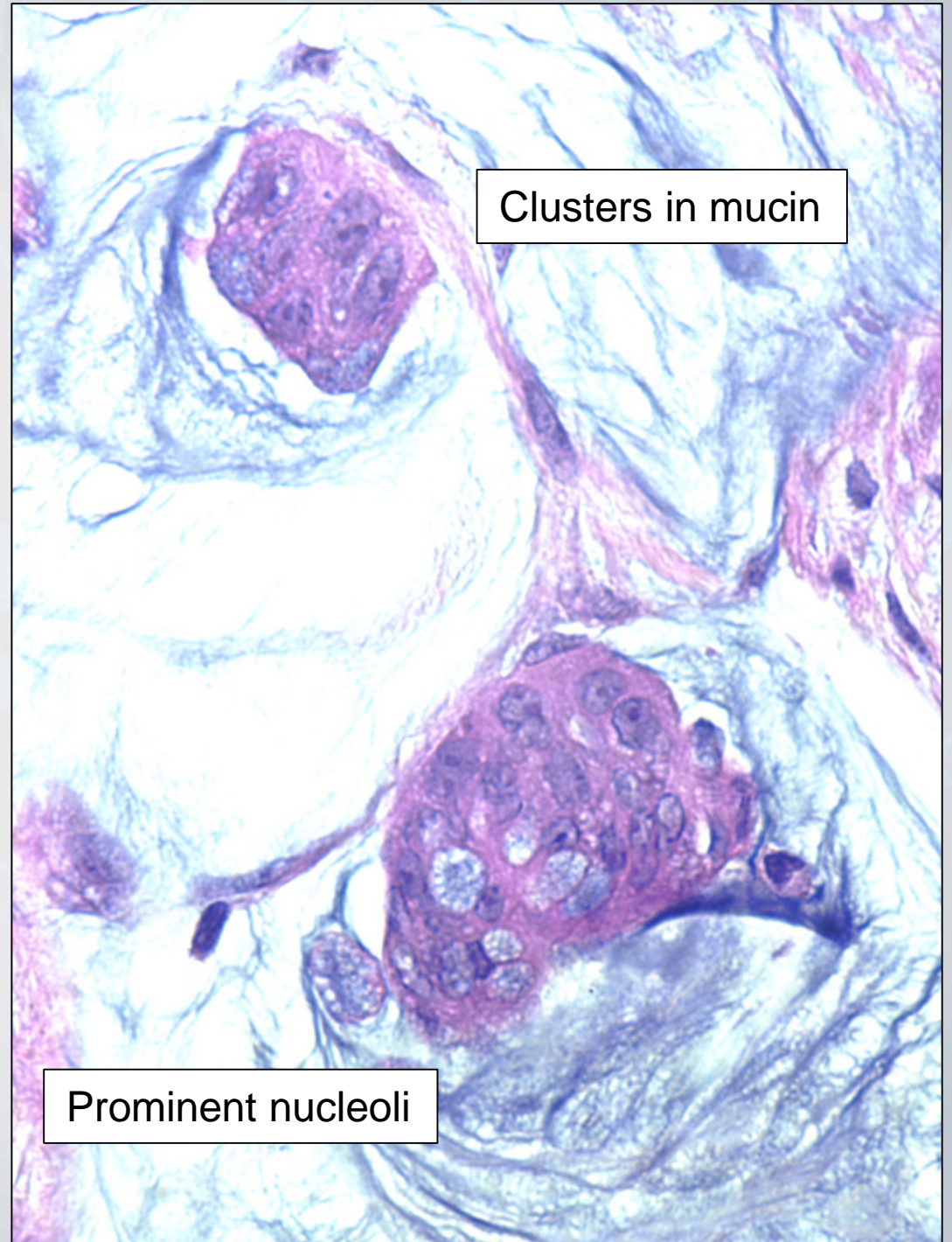
Irregular pools at invasive front

High-grade mucinous carcinoma



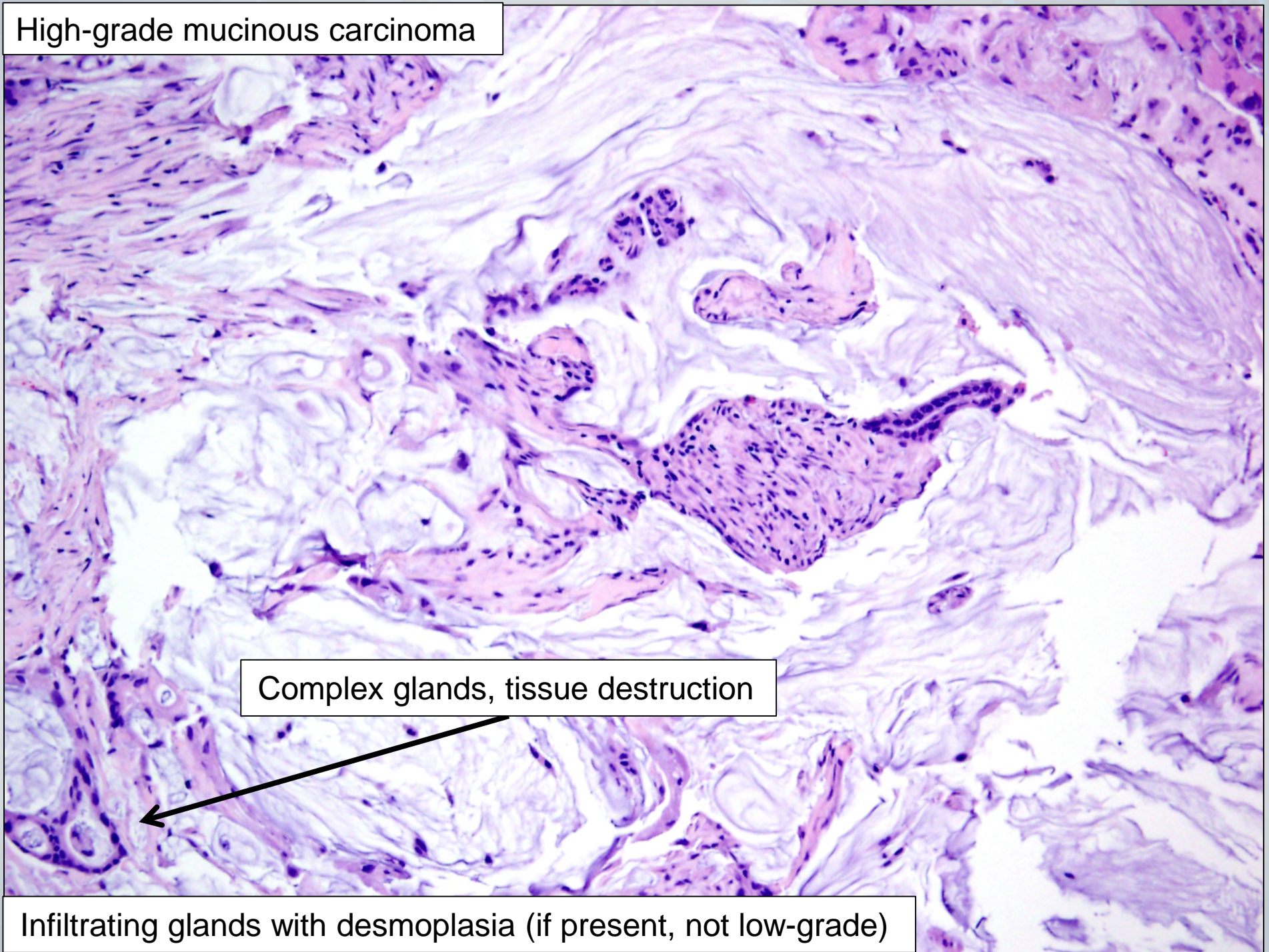
Large nuclei, mitotic figures

Clusters in mucin

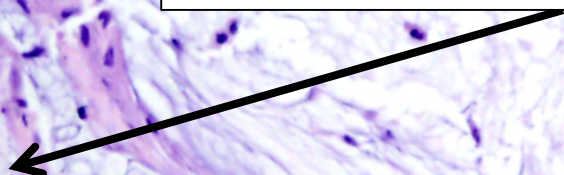


Prominent nucleoli

High-grade mucinous carcinoma

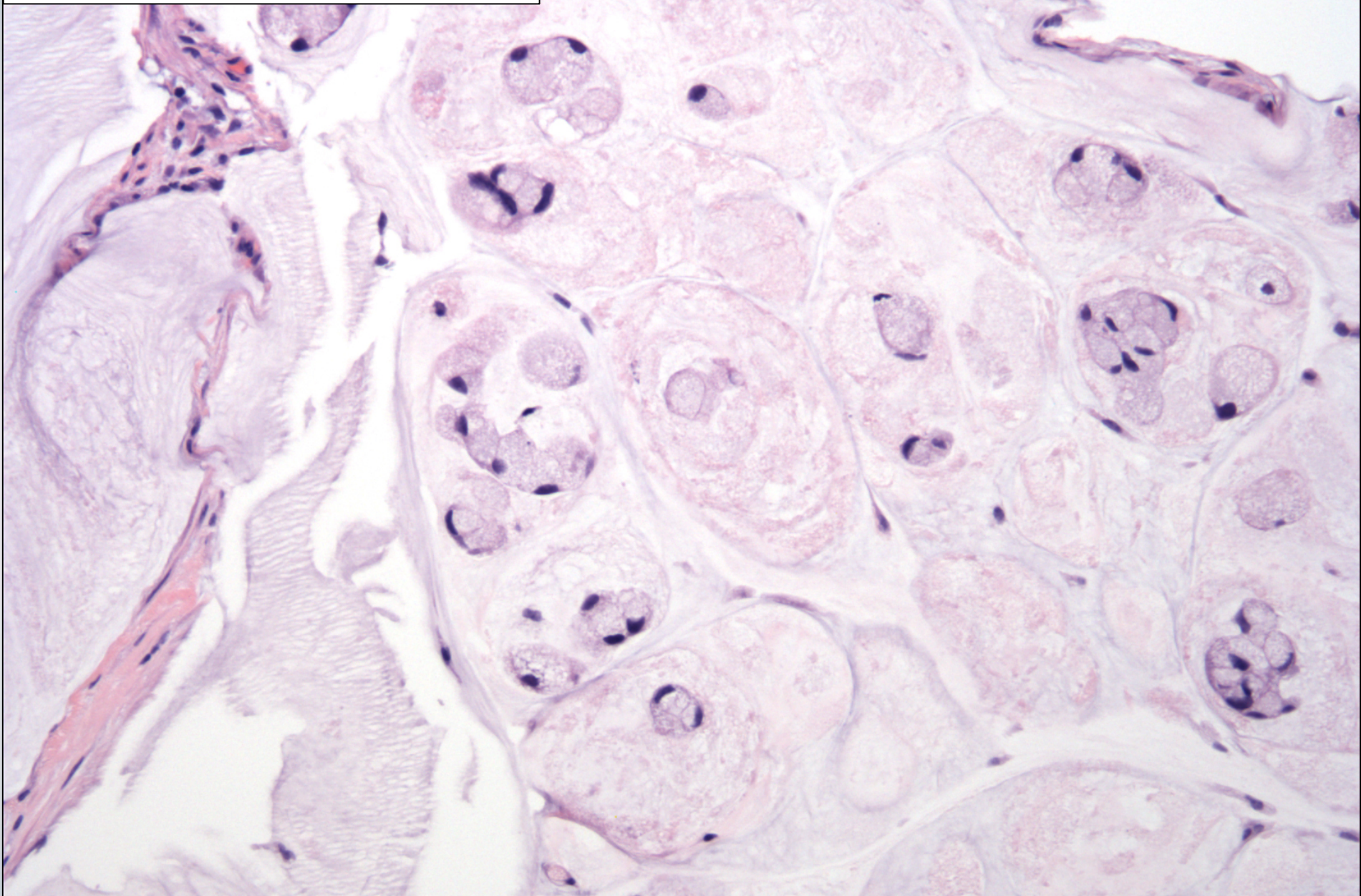


Complex glands, tissue destruction



Infiltrating glands with desmoplasia (if present, not low-grade)

High-grade mucinous carcinoma



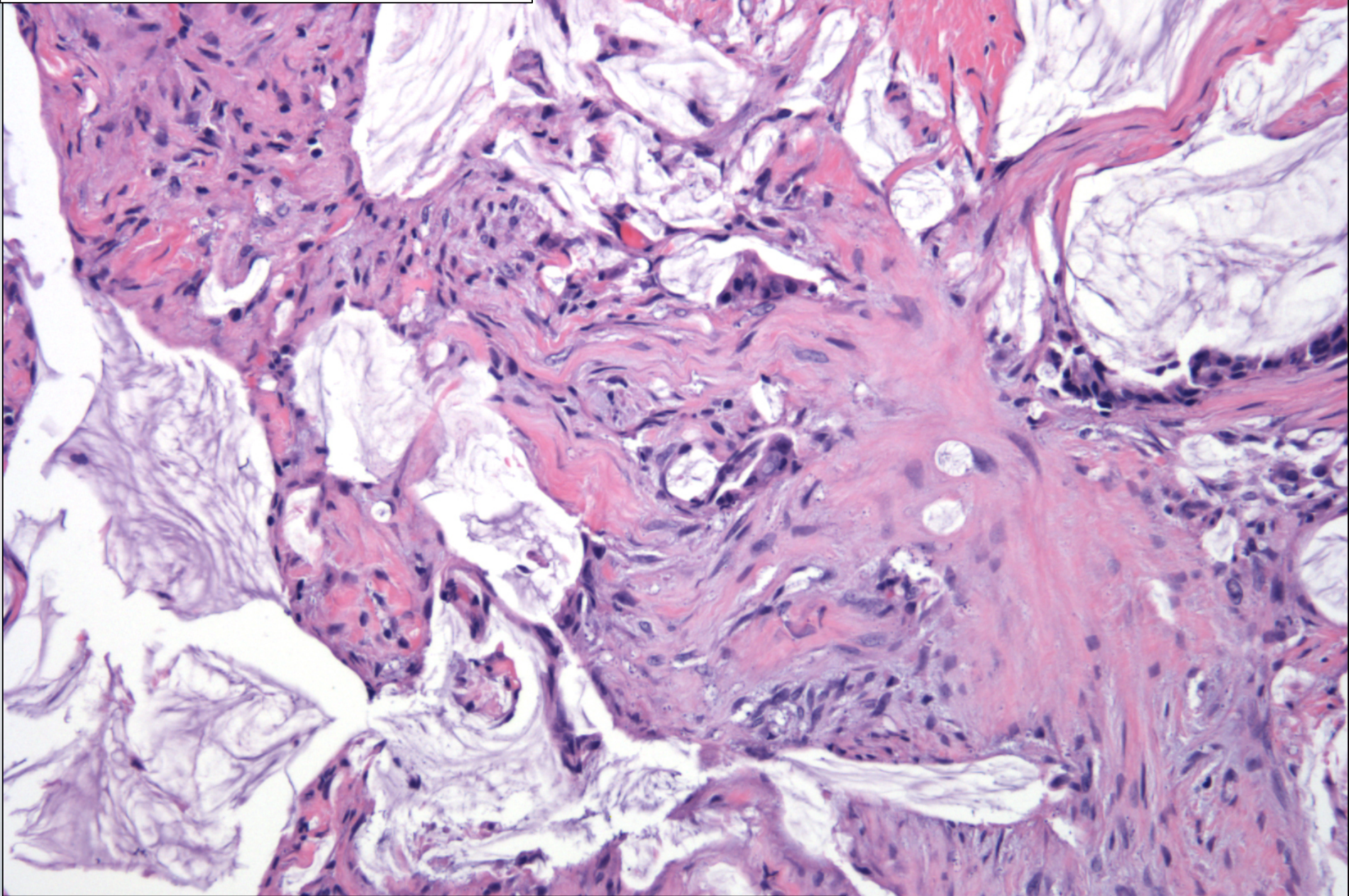
Signet ring cells in mucin pools; not a feature of low-grade disease

Importance of Signet Ring Cells

	Angiolymphatic Invasion	Perineural Invasion	Lymph Node Metastases	5-Year Survival
Grade 1 disease (low-grade cytology)	0%	0%	0%	91%
Grade 2 disease (high-grade cytology)	17%	5%	17%	61%
Grade 3 disease (high-grade cytology with signet ring cells)	70%	70%	72%	23%

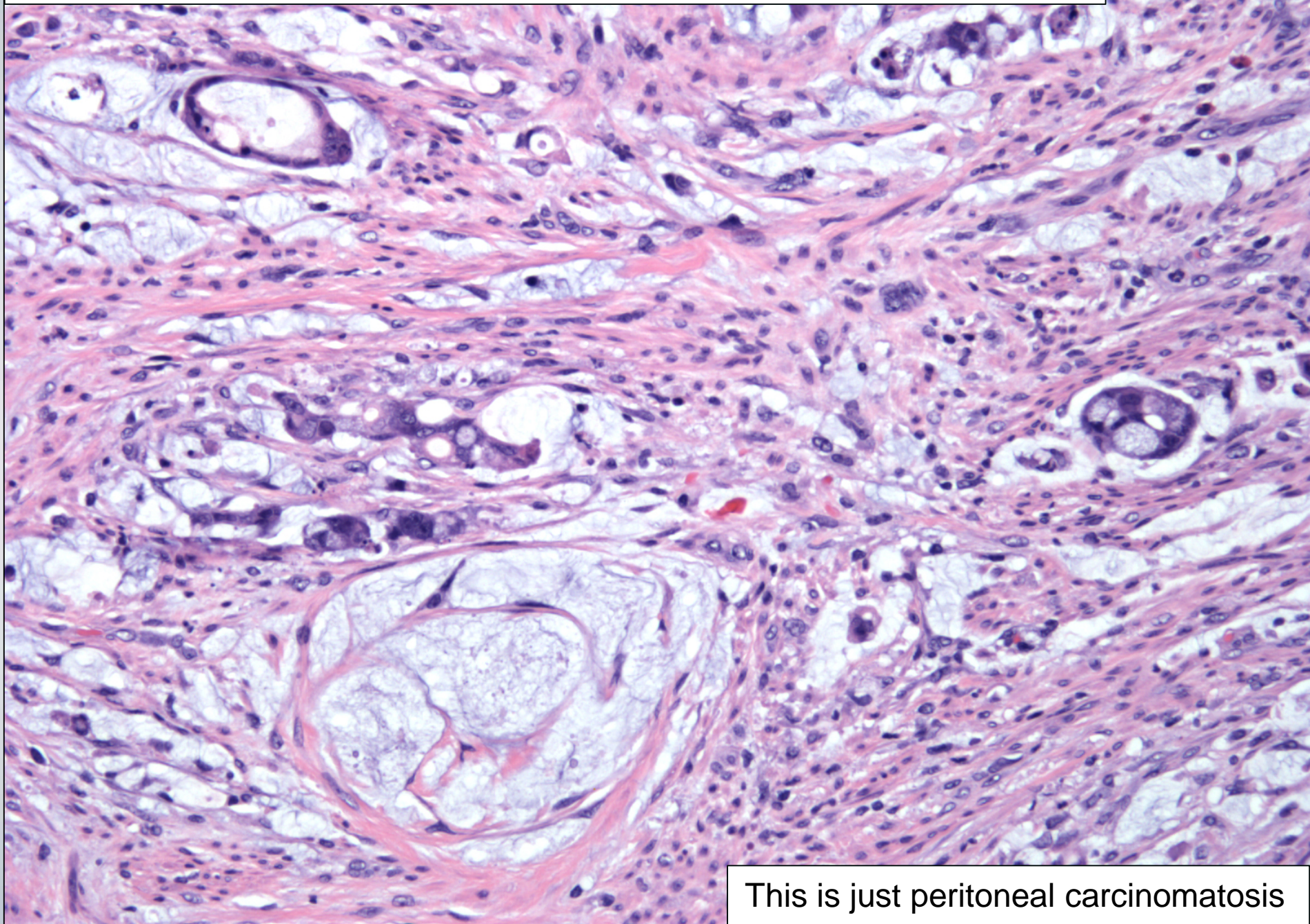
If signet ring cells are present, then classify as high-grade and mention it

High-grade mucinous carcinoma



Infiltrating signet ring cells usually only a focal finding

Goblet cell adenocarcinomas can make mucin when they are high-grade



This is just peritoneal carcinomatosis

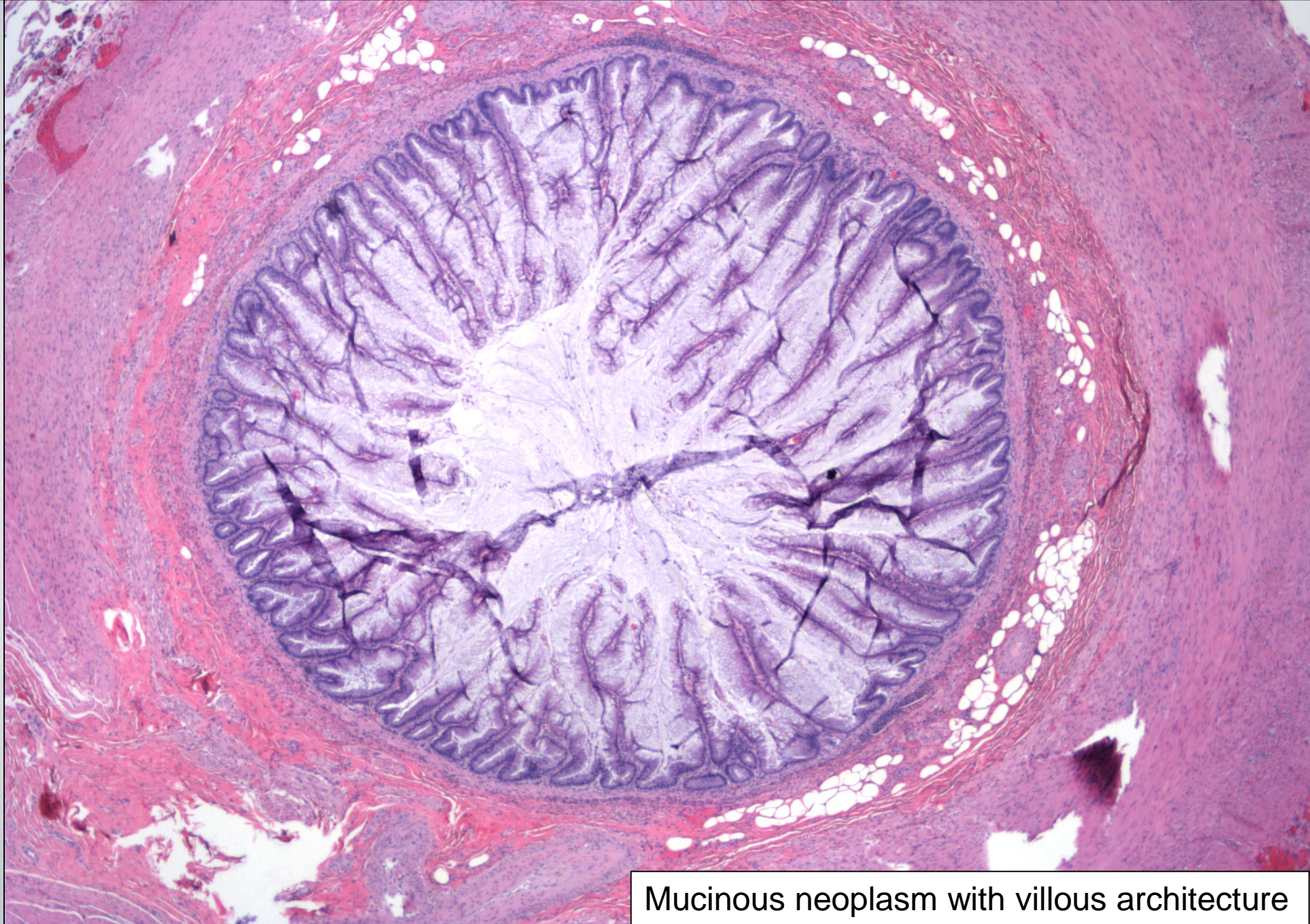
Peritoneal Mucinous Neoplasia

A Quick Summary So Far

- Appendiceal mucinous neoplasms that spread to the peritoneum are malignant and should be classified as mucinous carcinoma
 - Eliminate equivocal terminology, as behavior is not benign or unpredictable
- Overall prognosis and likelihood of response to HIPEC dependent on cytologic grade of peritoneal disease

**Let's focus on the appendix
when patients don't have any
extra-appendiceal disease**

Incidental finding in appendectomy specimen from 54-year-old female (peritoneum free of disease)



Mucinous neoplasm with villous architecture

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: What is the best term for this lesion?

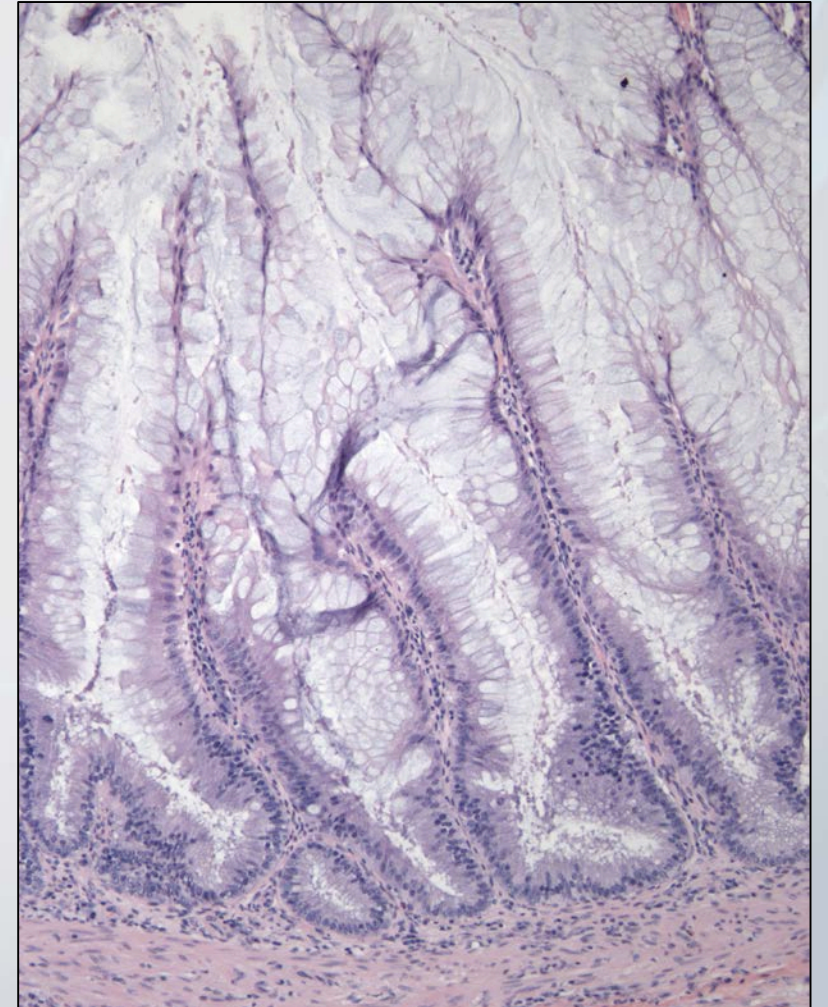
Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: What is the likelihood of peritoneal recurrence of this lesion?

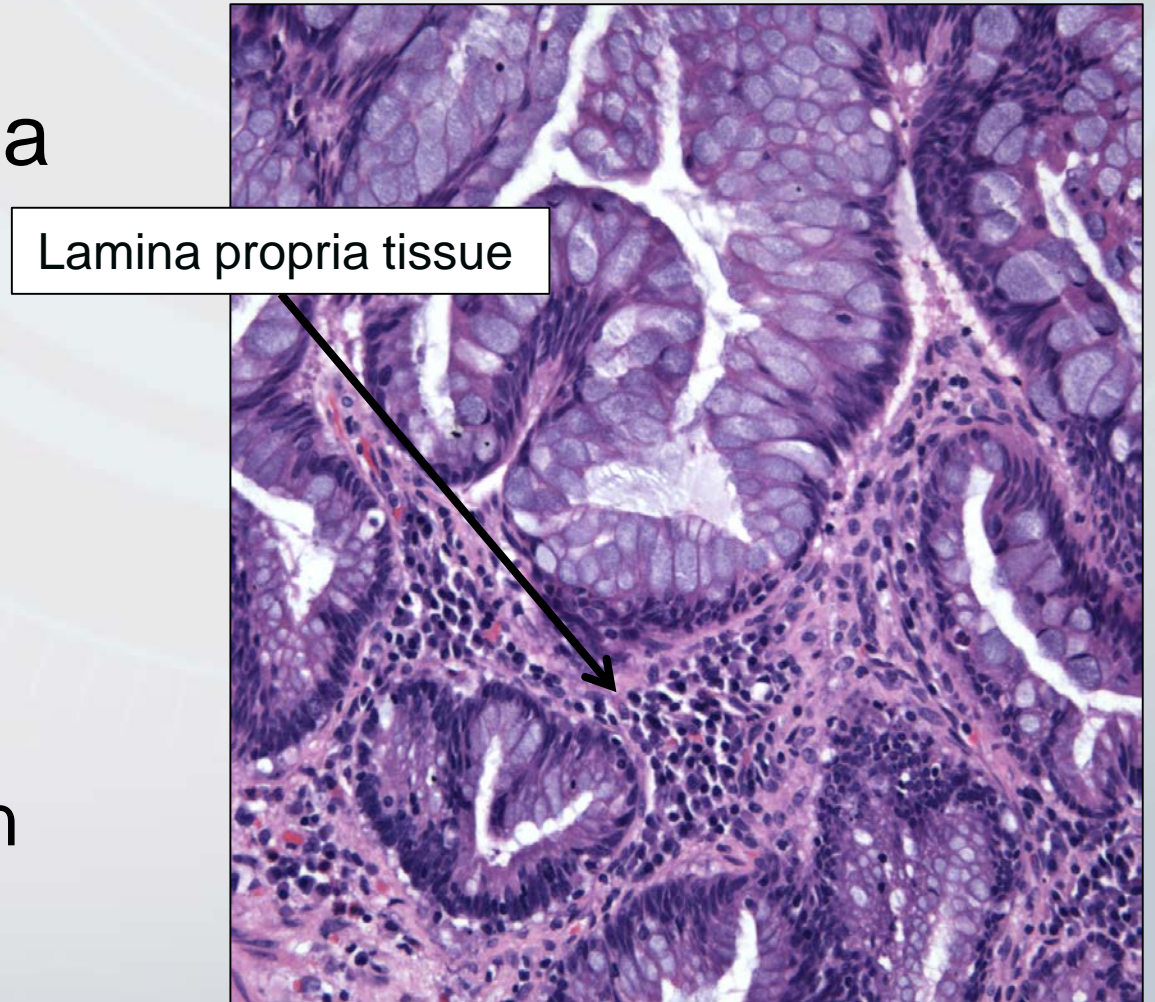
WHO (2010): Adenoma

- Neoplasm limited to mucosa
- Epithelium with low- or high-grade cytologic atypia
- Epithelium flat or undulating, villi, or papillae
- No mucin outside appendix
- Defined in this fashion, uniformly benign
 - Room for “mucinous adenoma” in past years



Adenoma Issues Unique to Appendix

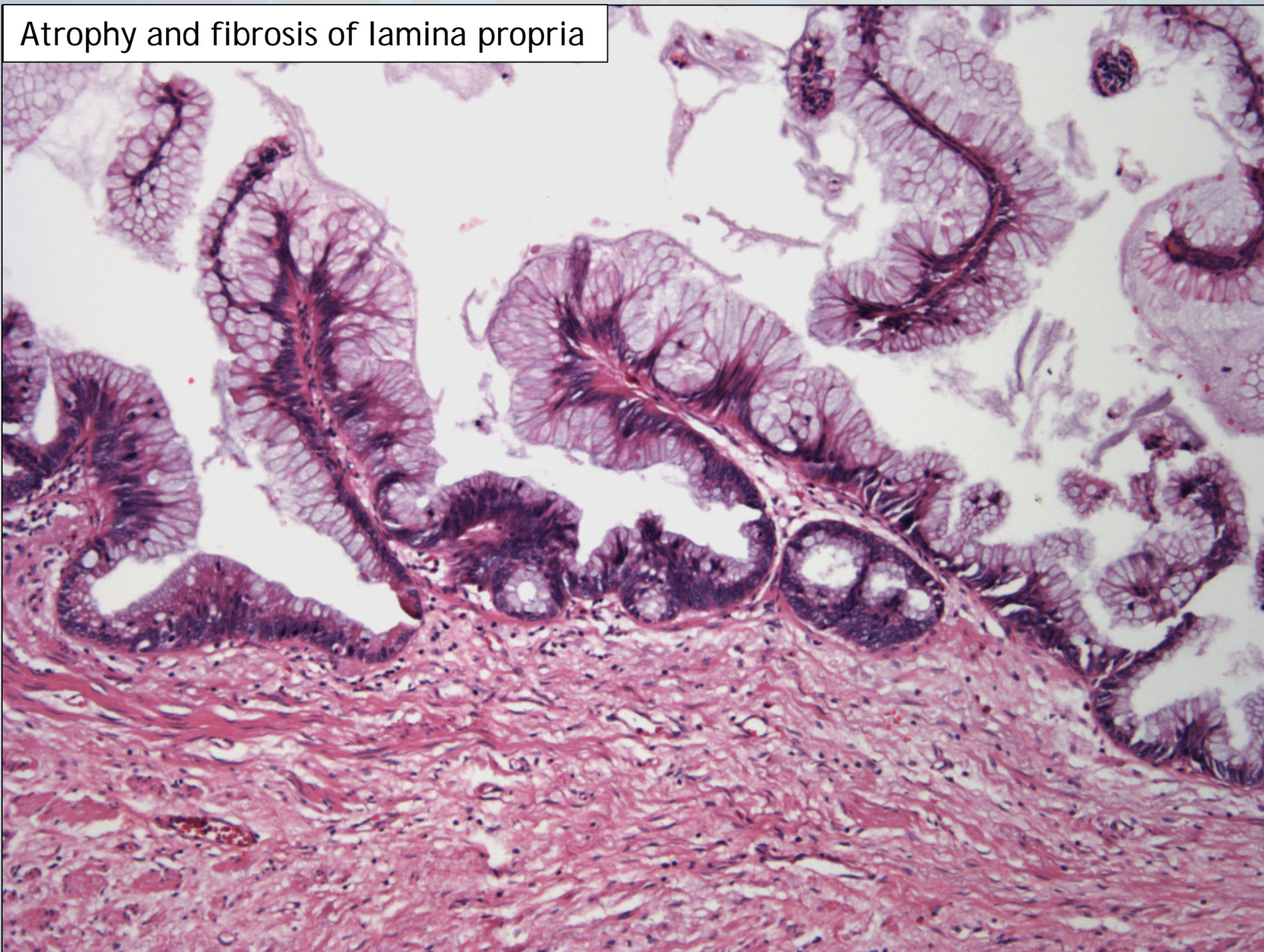
- Elsewhere in GI tract, adenoma is confined to basement membrane
- Mucinous lesions of appendix show mucosal and mural alterations
 - Lamina propria always decreased
 - May be difficult to be sure lesion is confined to mucosa



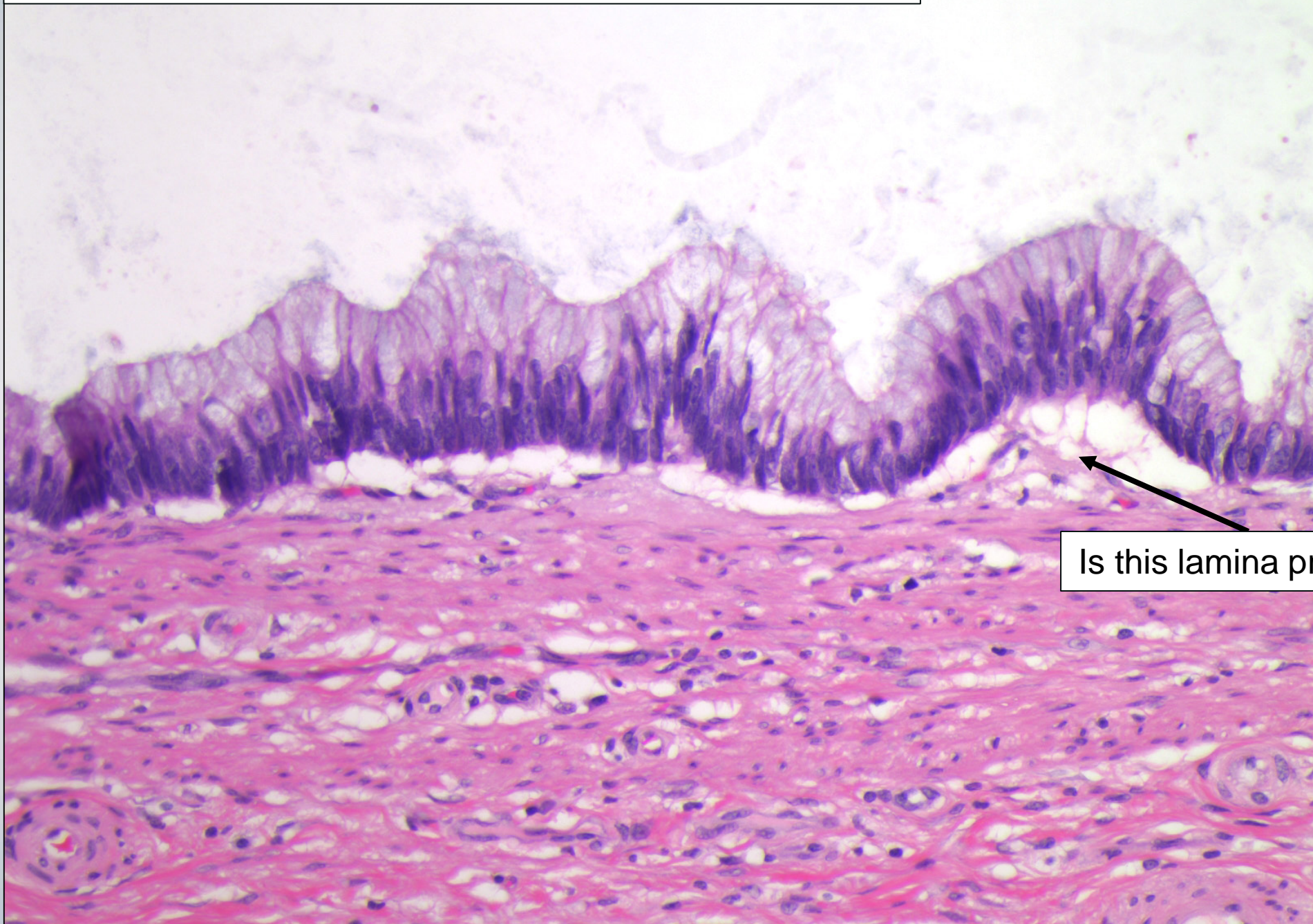
Proliferative epithelium associated with compressed lamina propria



Atrophy and fibrosis of lamina propria



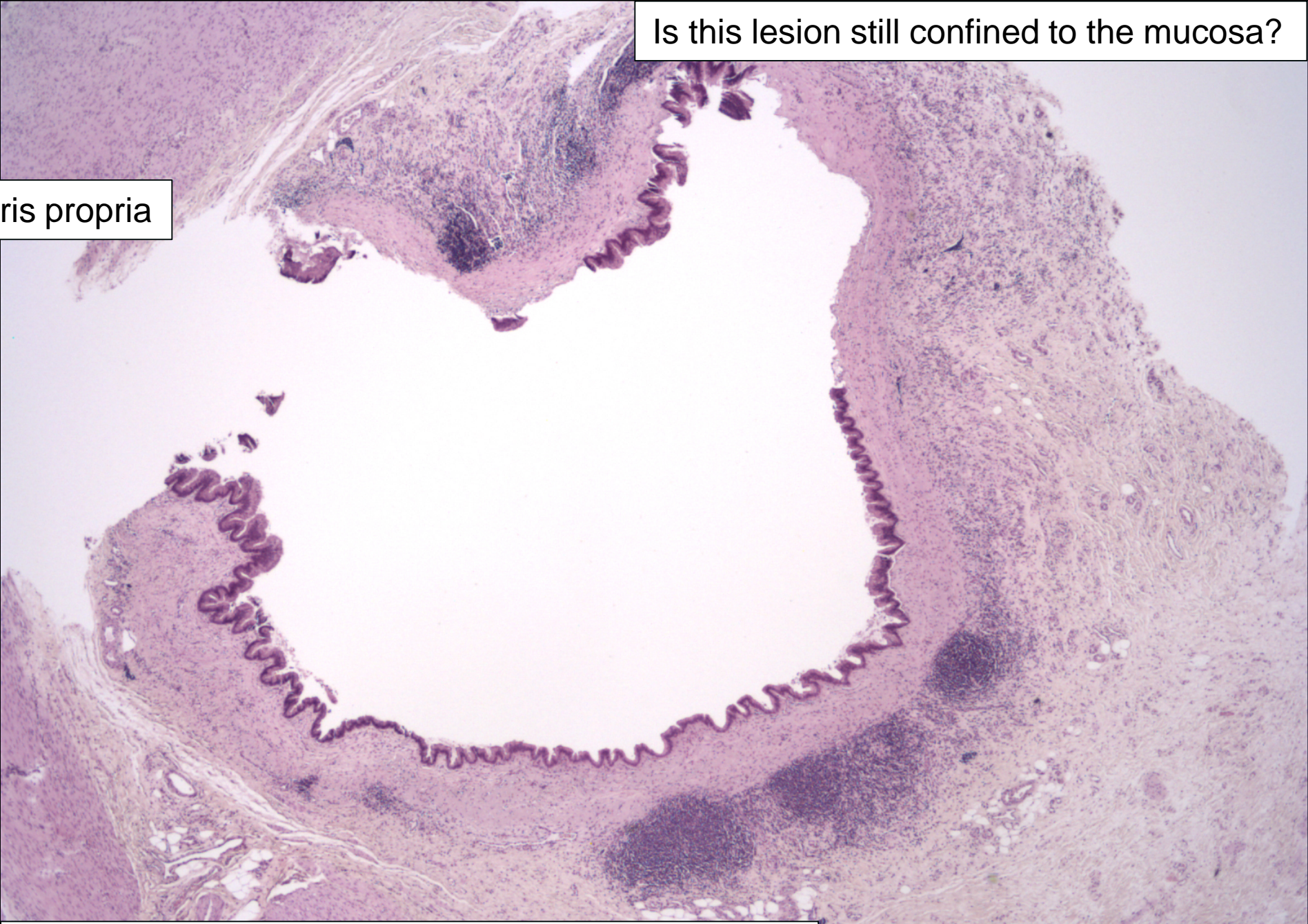
Atrophy and fibrosis of lamina propria, no lymphoid tissue



Is this lamina propria?

Is this lesion still confined to the mucosa?

Muscularis propria



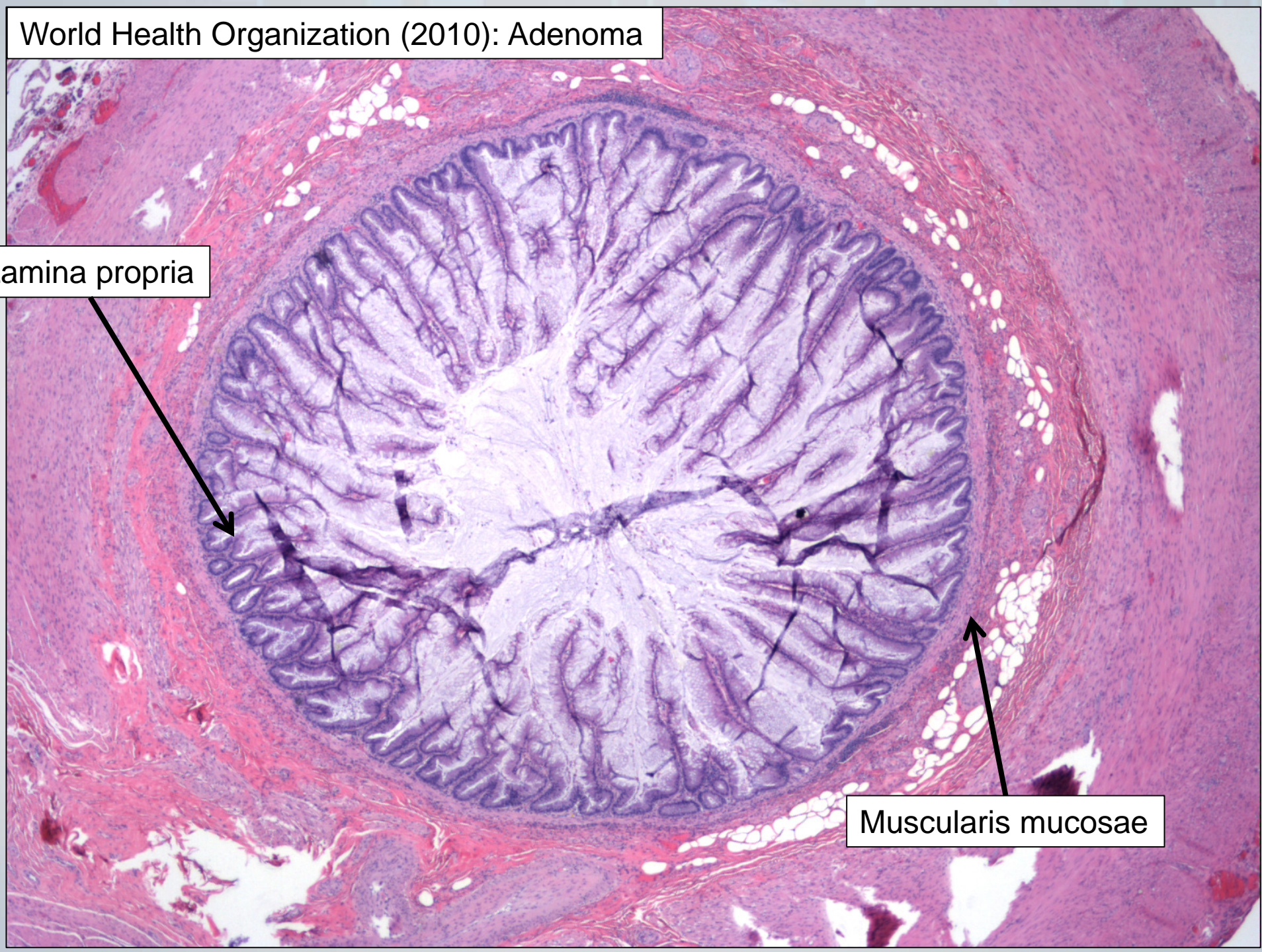
Obliteration of mucosal elements; lymphoid atrophy

WHO (2010) Recommendations *Adenoma vs. LAMN*

- Consider adenoma only when muscularis mucosae intact
- LAMN terminology recommended when there is fibrosis of muscularis mucosae (obliteration of planes between muscularis mucosae and submucosa)

World Health Organization (2010): Adenoma

Lamina propria



Muscularis mucosae

New Recommendations (WHO and Others)

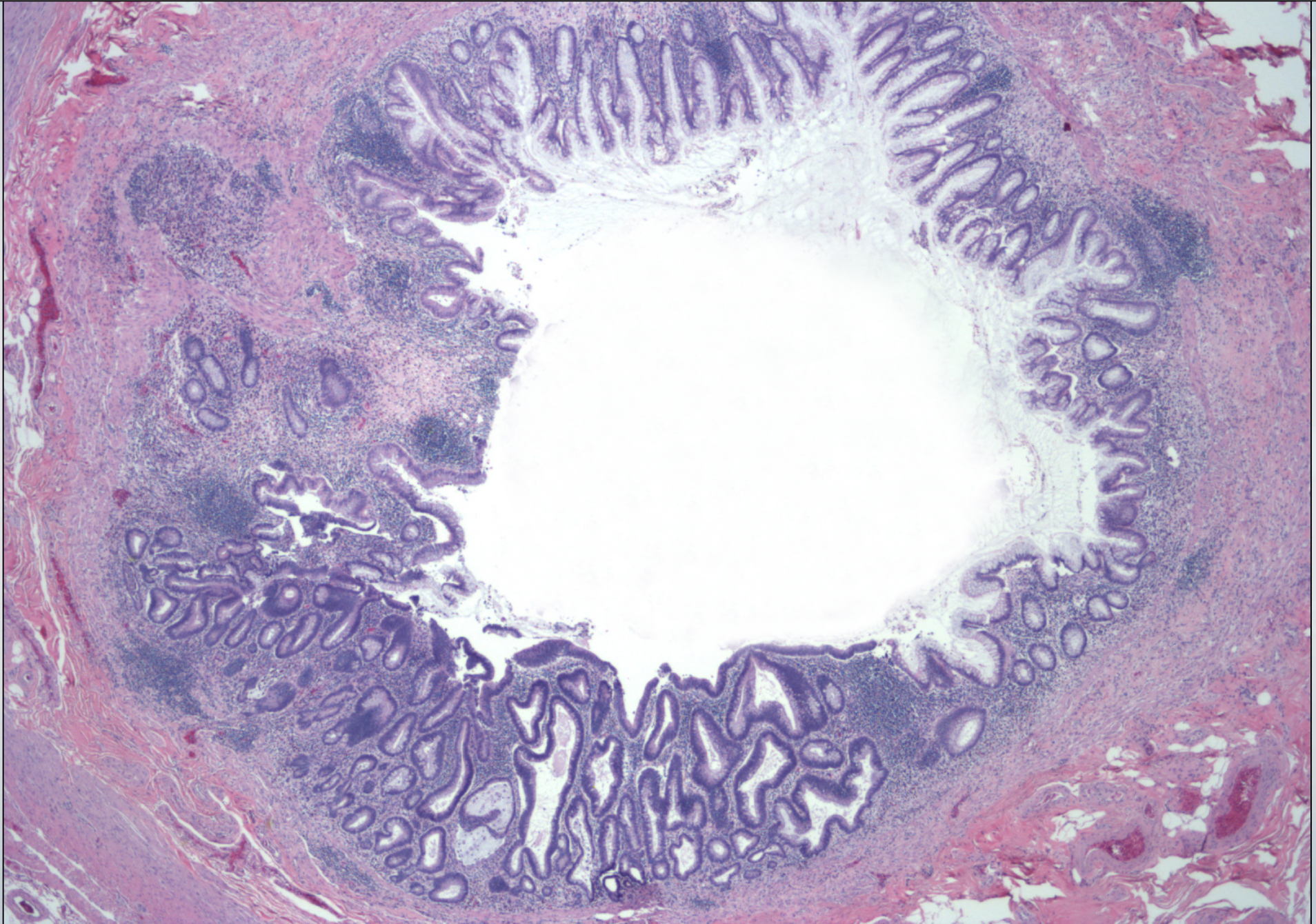
Adenoma vs. LAMN

- Eliminate mucinous adenoma altogether
- Expand criteria for low-grade appendiceal mucinous neoplasm (LAMN)
 - Any mucinous tumor classified as LAMN, or worse
- Adenoma restricted to conventional tubular and villous adenomas of appendix

Carr, et al. Histopathology 2017; 71(6): 847-858.

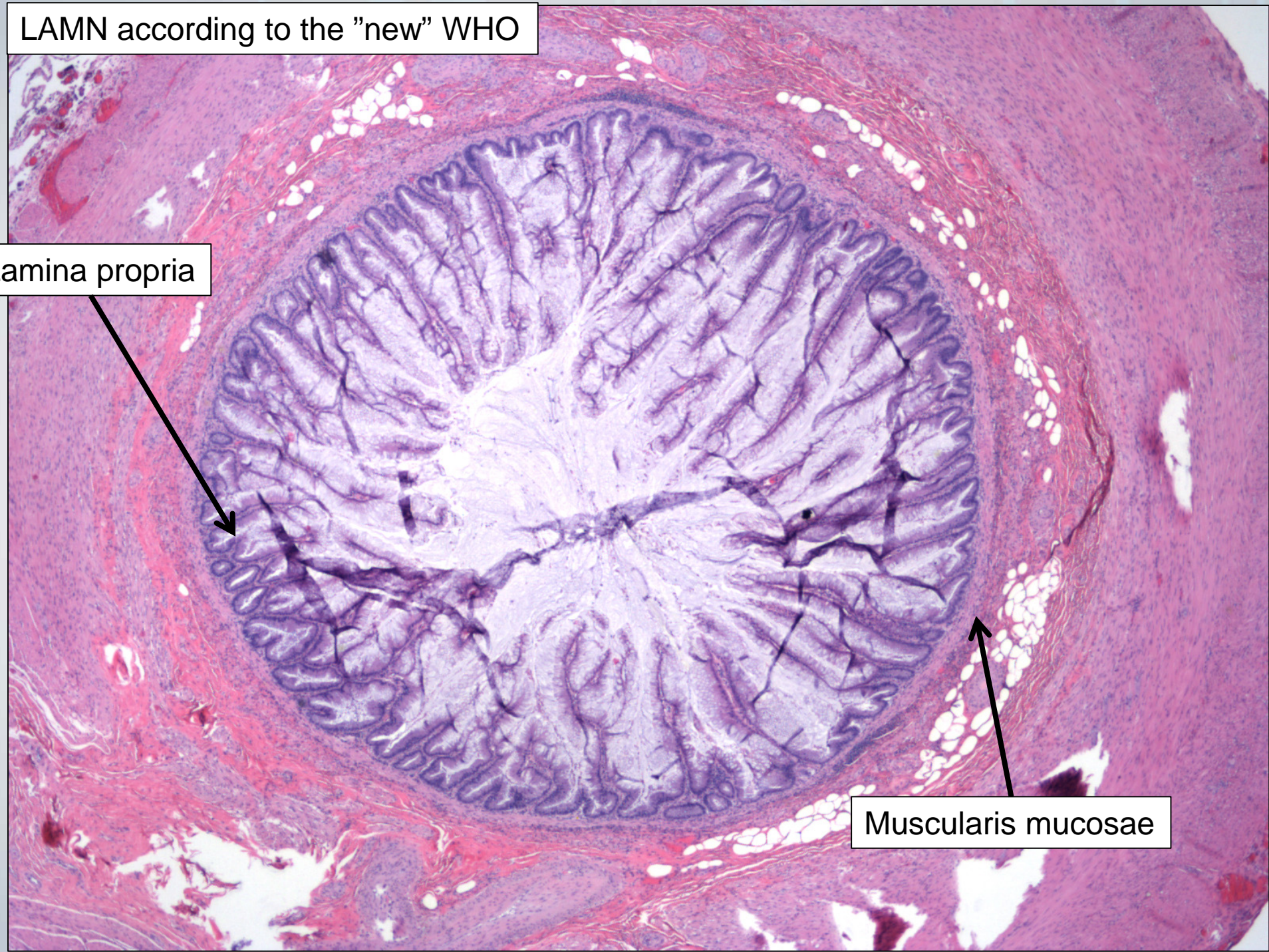
WHO Classification of Tumours Digestive System Tumours, 5th Ed.

Practical implications: "Adenoma" limited to colonic-type lesions, which are uncommon outside setting of FAP



LAMN according to the "new" WHO

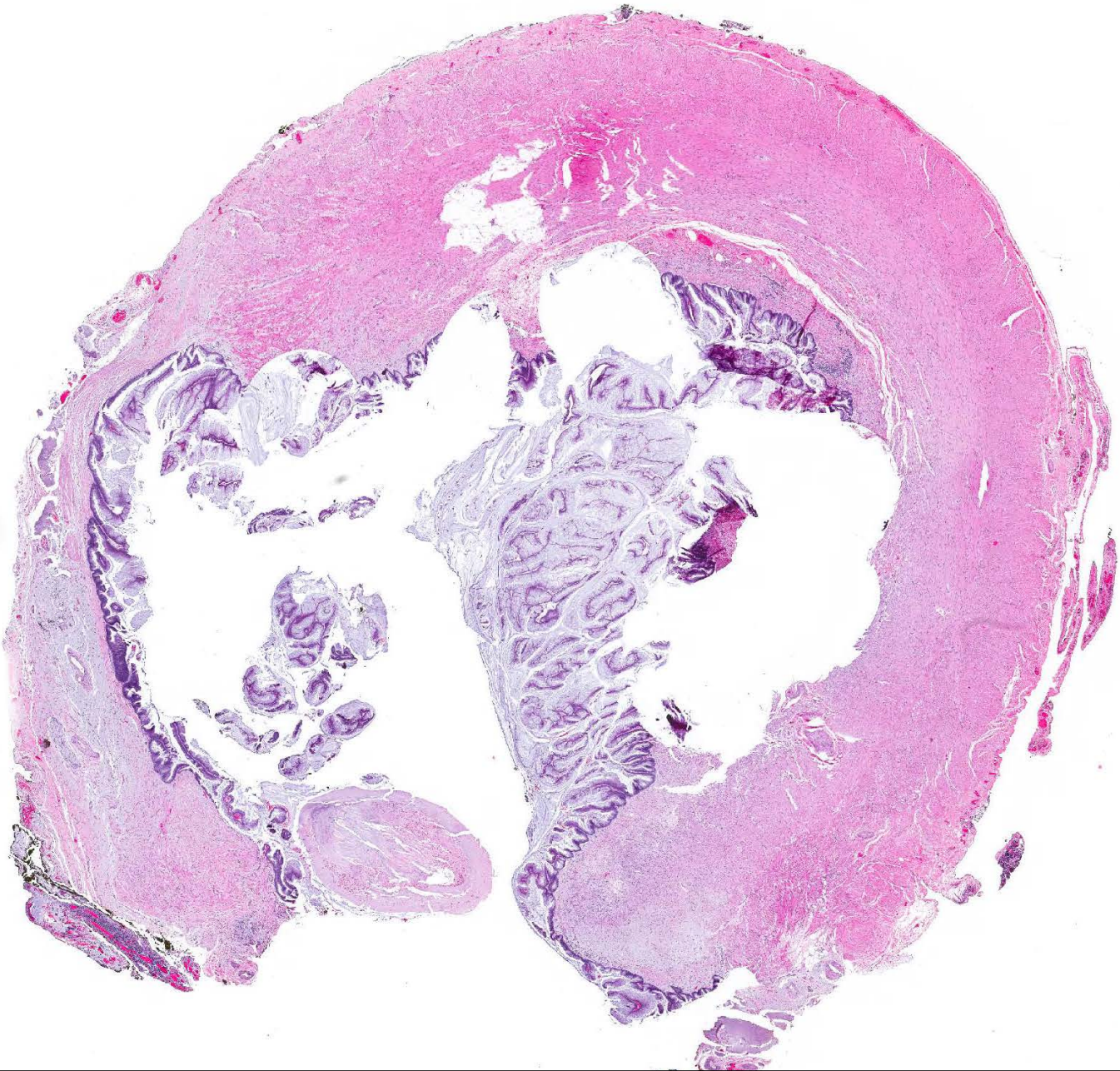
Lamina propria



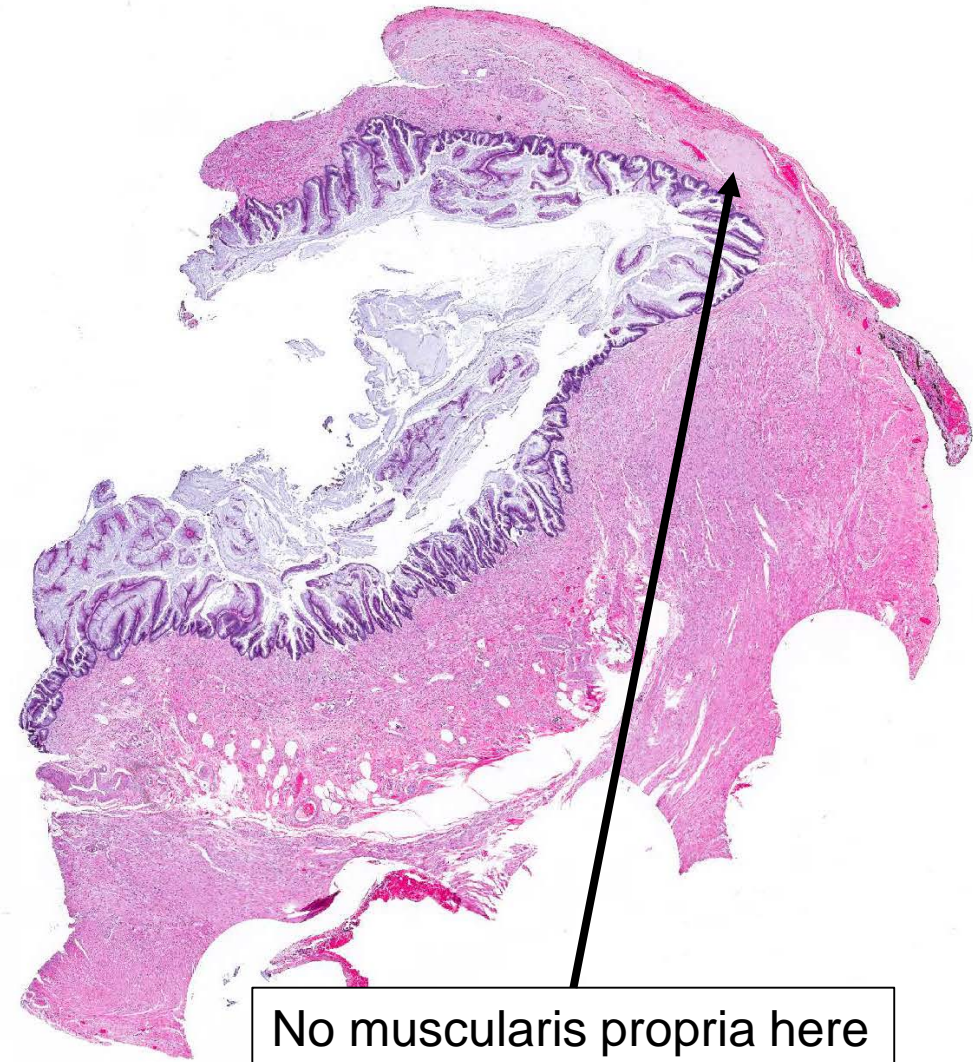
Muscularis mucosae

LAMN: If We Were in the Business of Naming Things, We Could've Done Better

- This term no longer means what we (I) intended
- Introduced LAMN to imply uncertainty regarding behavior
 - One could not predict status of peritoneum based on appendix findings for lesions with diverticulum-like growth



Decreased lamina propria and obliteration of mural elements



No muscularis propria here

Diverticulum-like growth is present

LAMN: If We Were in the Business of Naming Things, We Could've Done Better

- This term no longer means what we (I) intended
- Introduced LAMN to imply uncertainty regarding behavior
 - One could not predict status of peritoneum based on appendix findings for lesions with diverticulum-like growth
 - We recognized that these tumors were essentially benign when confined to appendix

The Truth About LAMN

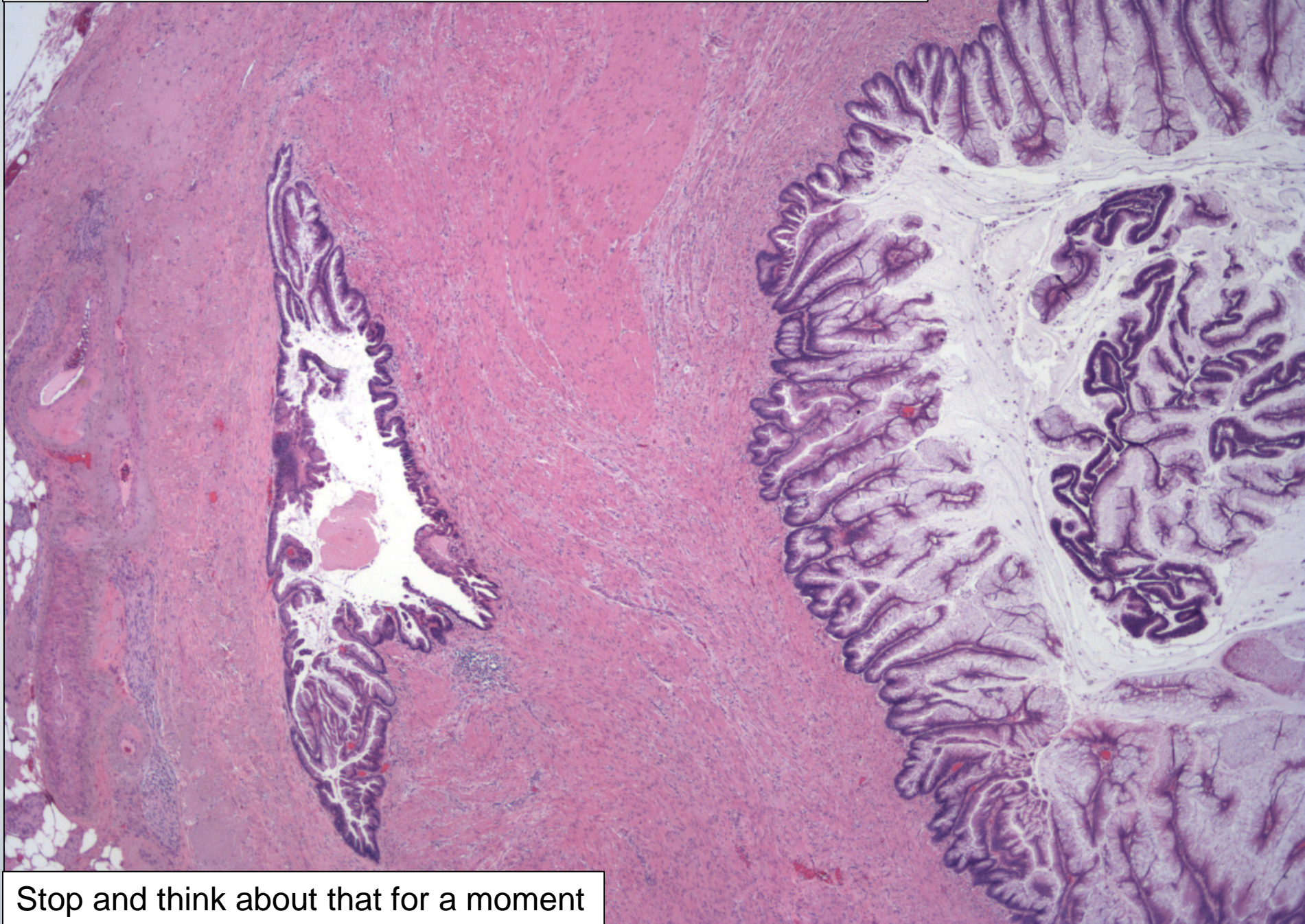
- Reports of progressive disease (i.e. pseudomyxoma peritonei) when the lesion is completely confined to inner appendix (i.e. no peritoneal disease at appendectomy) are anecdotal at best
- There are no well-documented published cases of lesions confined to the muscularis mucosae that progressed to peritoneal disease

Staging Low-Grade Appendiceal Tumors

AJCC 8th Edition

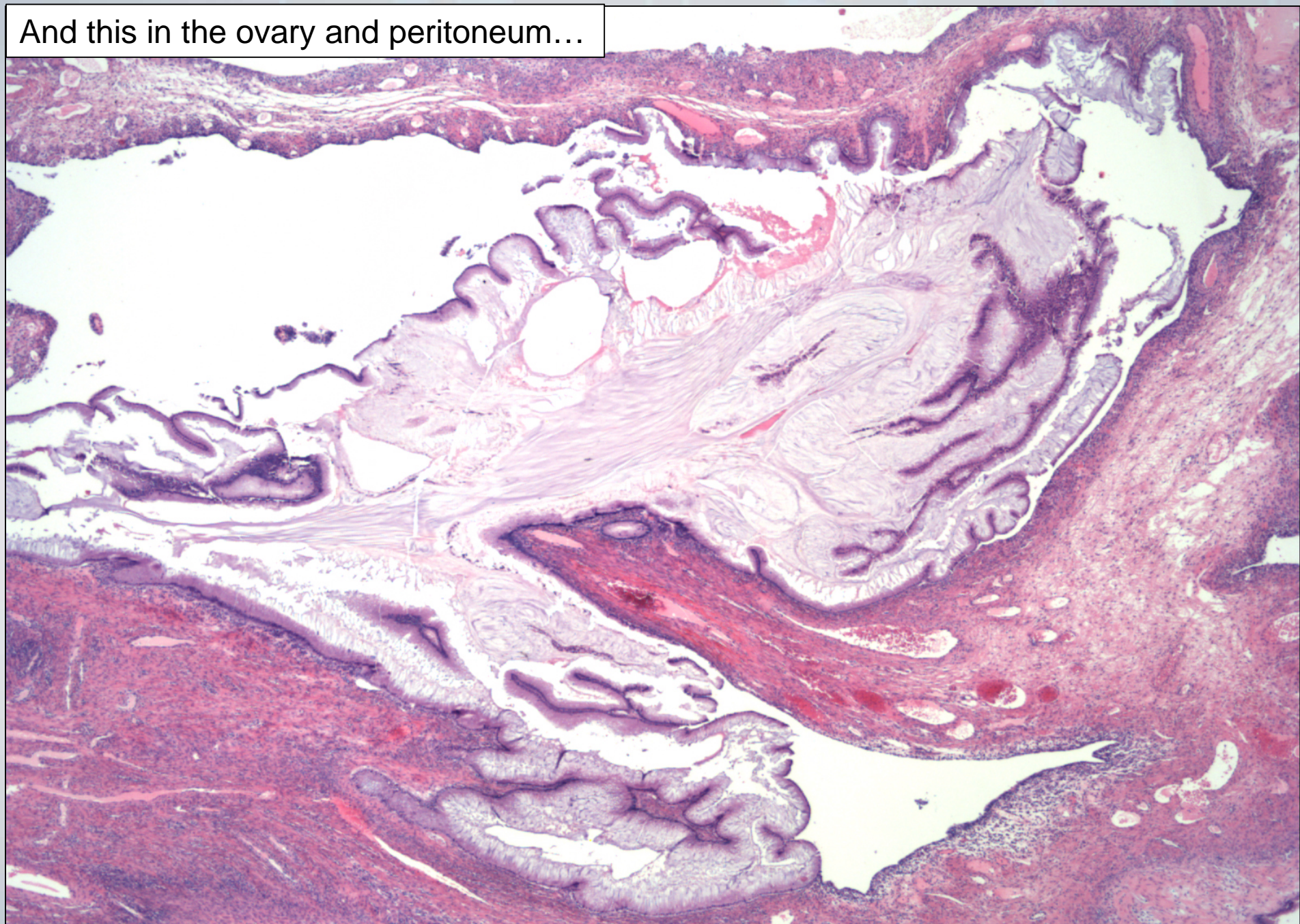
- Skirts the issue of mucinous adenoma
- LAMN *in situ* does not extend beyond muscularis propria (i.e. there is no T1 or T2 LAMN)
 - If epithelium and/or mucin are confined to appendix proper, not a risk factor for recurrence
- Subserosal tumor staged as T3
- Mucin or epithelium on serosa staged as T4a

Mucinous lesion confined to muscularis propria: LAMN *in situ*



Stop and think about that for a moment

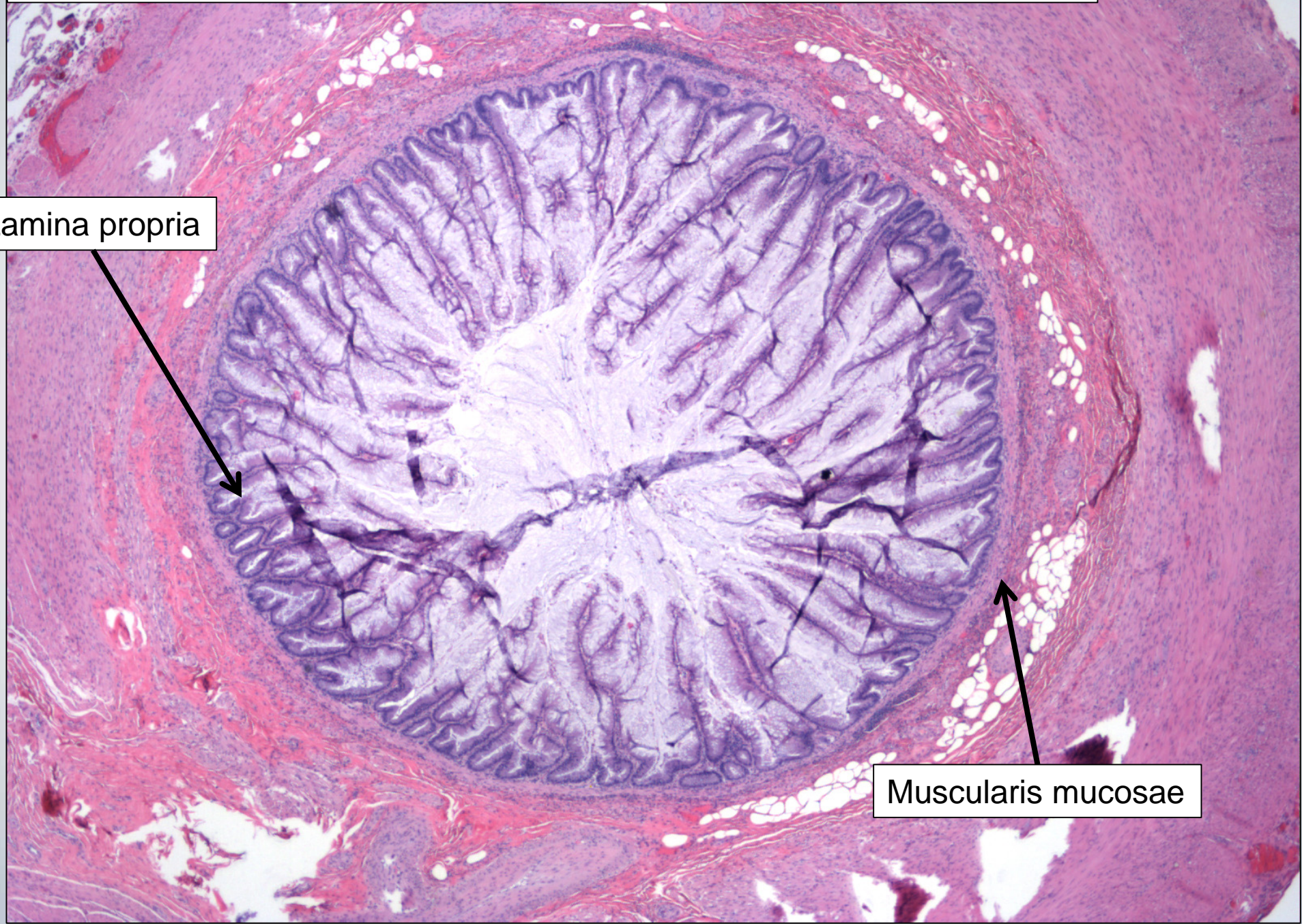
And this in the ovary and peritoneum...



Diagnosis: LAMN *in situ* associated with low-grade mucinous carcinoma in the peritoneum

I would call this a mucinous adenoma today and I will still do it next week

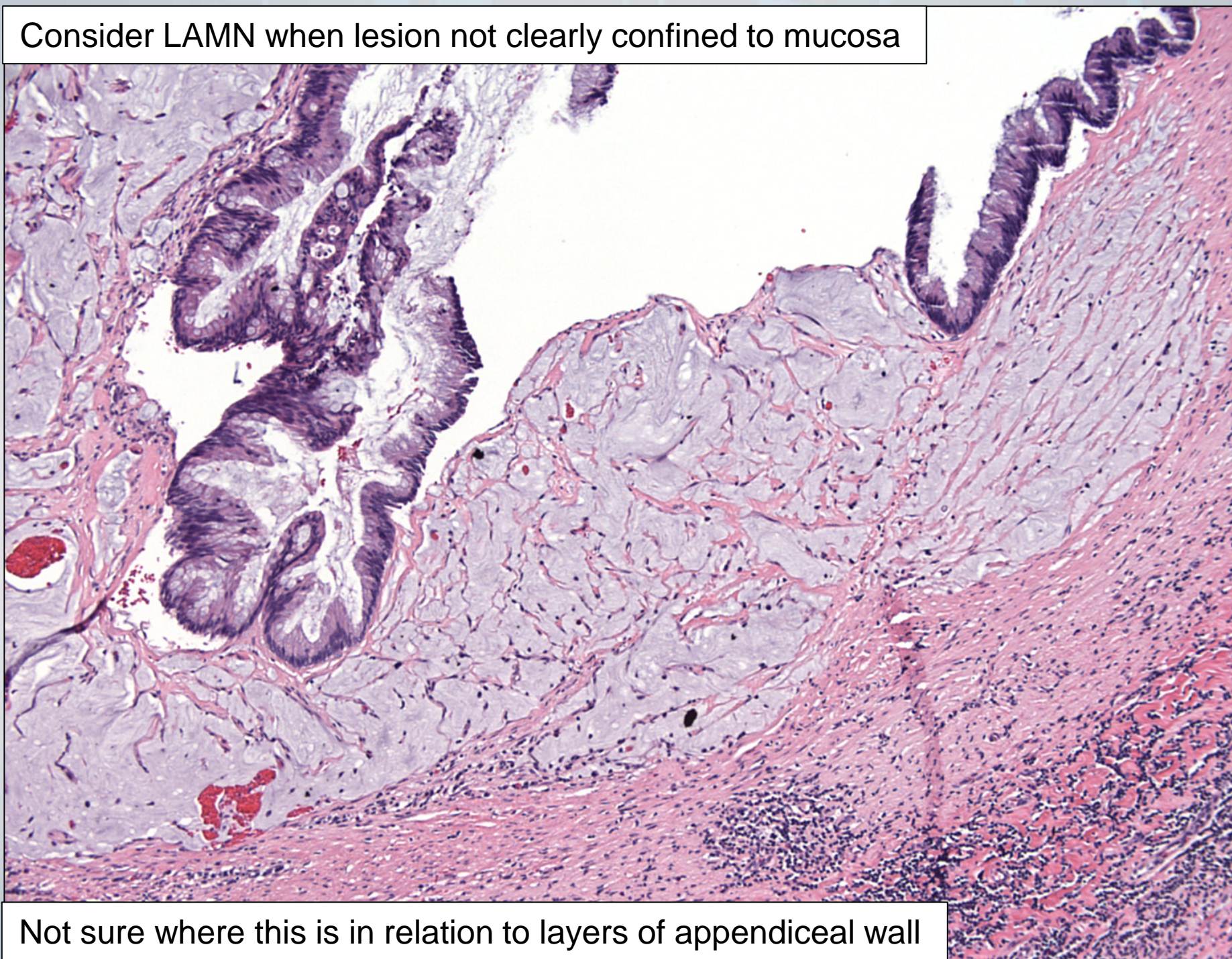
Lamina propria



Muscularis mucosae

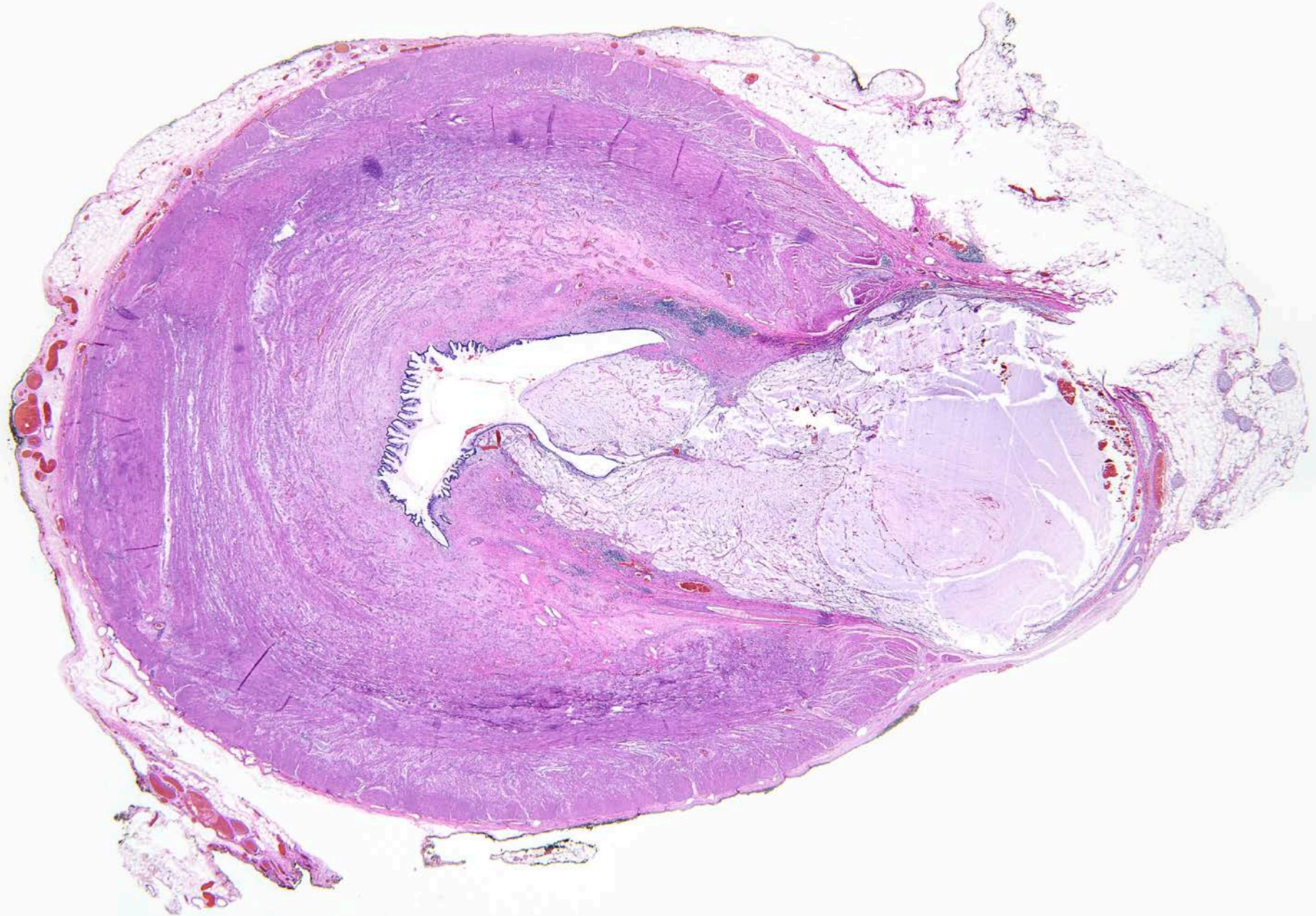
Other situations in which low-grade mucinous neoplasm (LAMN) is the best term

Consider LAMN when lesion not clearly confined to mucosa



Not sure where this is in relation to layers of appendiceal wall

Diverticulum-like protrusions of mucin with or without epithelium



Extra-Appendiceal Mucin

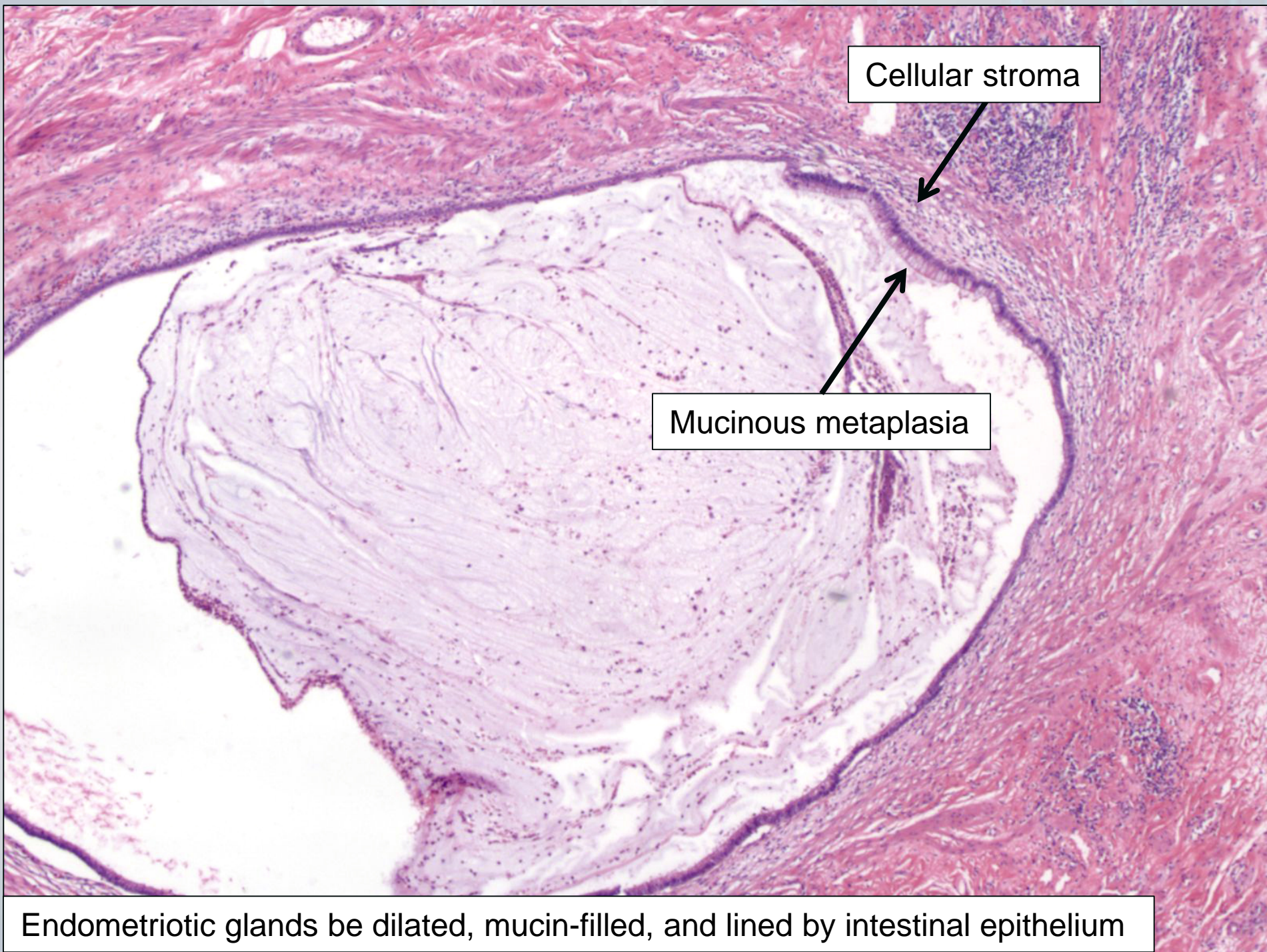
- Any epithelium outside appendix
 - Approximately 1/3 of patients develop peritoneal disease
 - Call this LAMN, or worse (depending on amount of epithelium and degree of atypia)
- No epithelium in extra-appendiceal mucin
 - Submit all of peri-appendiceal mucin
 - If no neoplastic epithelium outside the appendix, still safest to consider this to be LAMN but recurrences are anecdotal

Consider Using LAMN When...

- Cannot determine whether lesion is confined to mucosa
 - Fibrosis, atrophy, dilatation, loss of mural elements
- Diverticulum-like protrusions lined by neoplastic epithelium
- Any neoplastic epithelium beyond the mucosa
- Mucinous neoplasm with mural mucin, or mucin in mesoappendix
- Generally a good idea to make a comment explaining rationale for diagnosis

Mimics of Mucinous Neoplasia

- Endometriosis
 - Can show mucinous metaplasia
 - Decidualized stroma can appear myxoid
 - Characteristic cuff of cellular stroma and non-mucinous epithelium may be obscured
- Diverticulosis
- Post-inflammatory mucosal hyperplasia

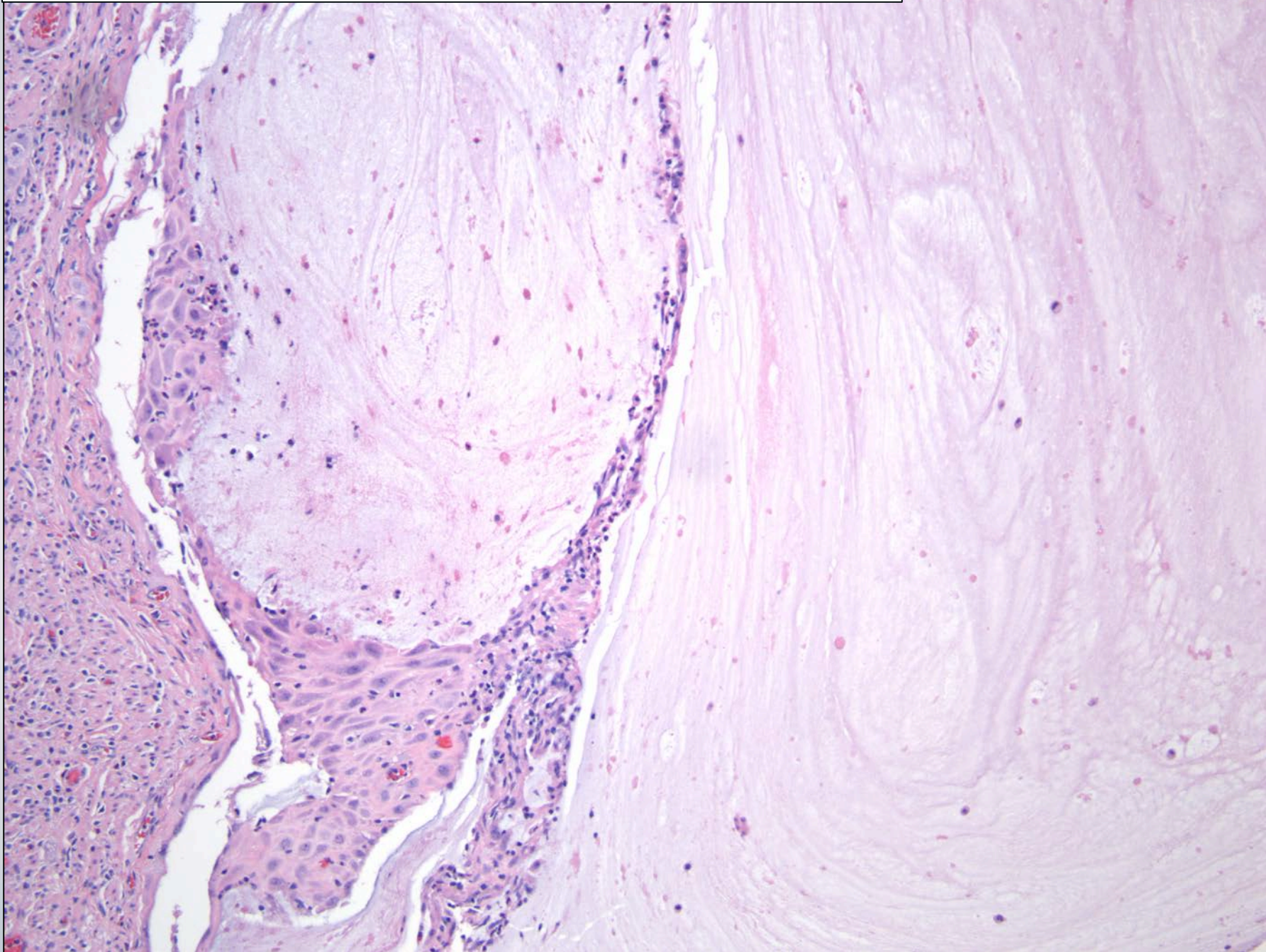


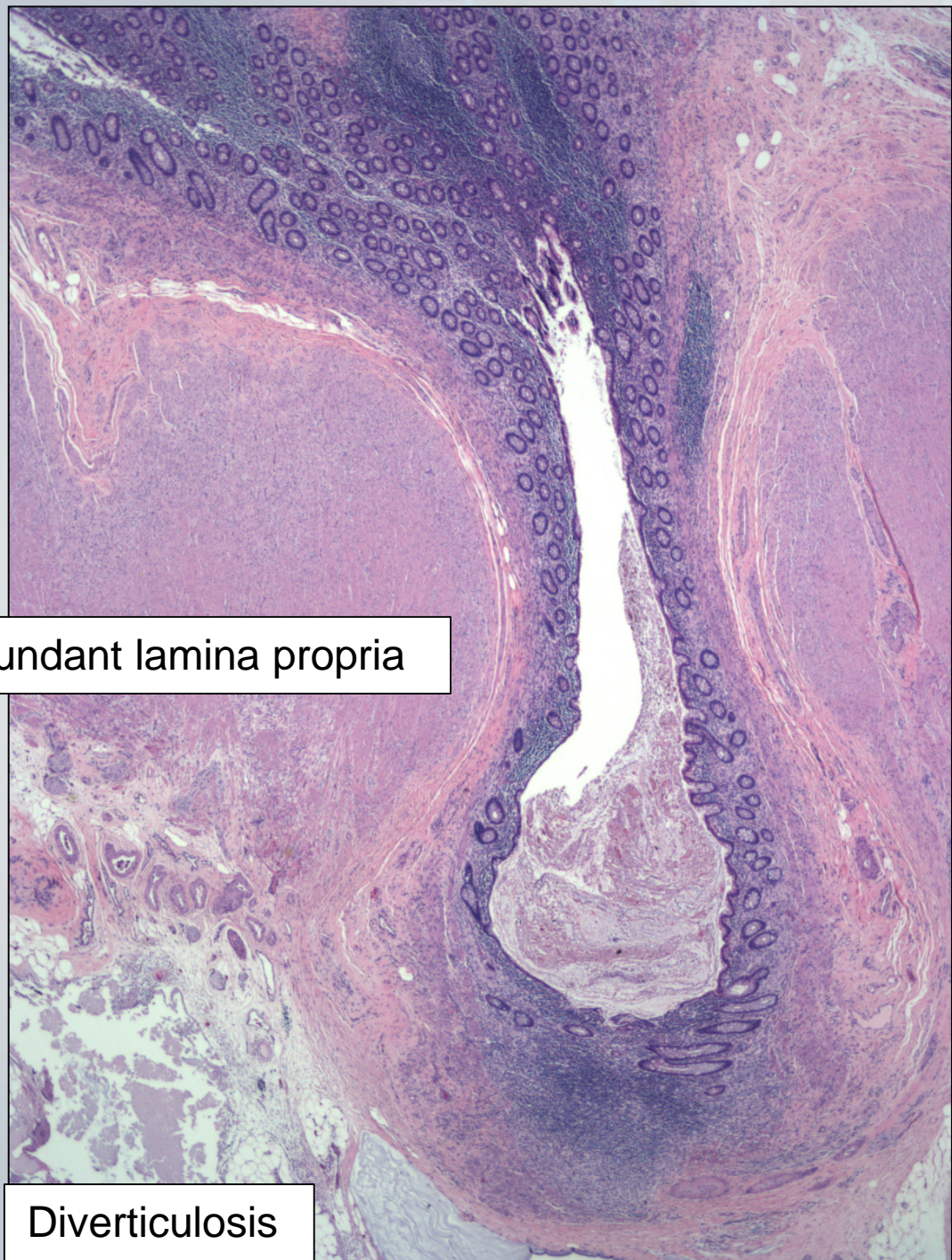
Cellular stroma

Mucinous metaplasia

Endometriotic glands be dilated, mucin-filled, and lined by intestinal epithelium

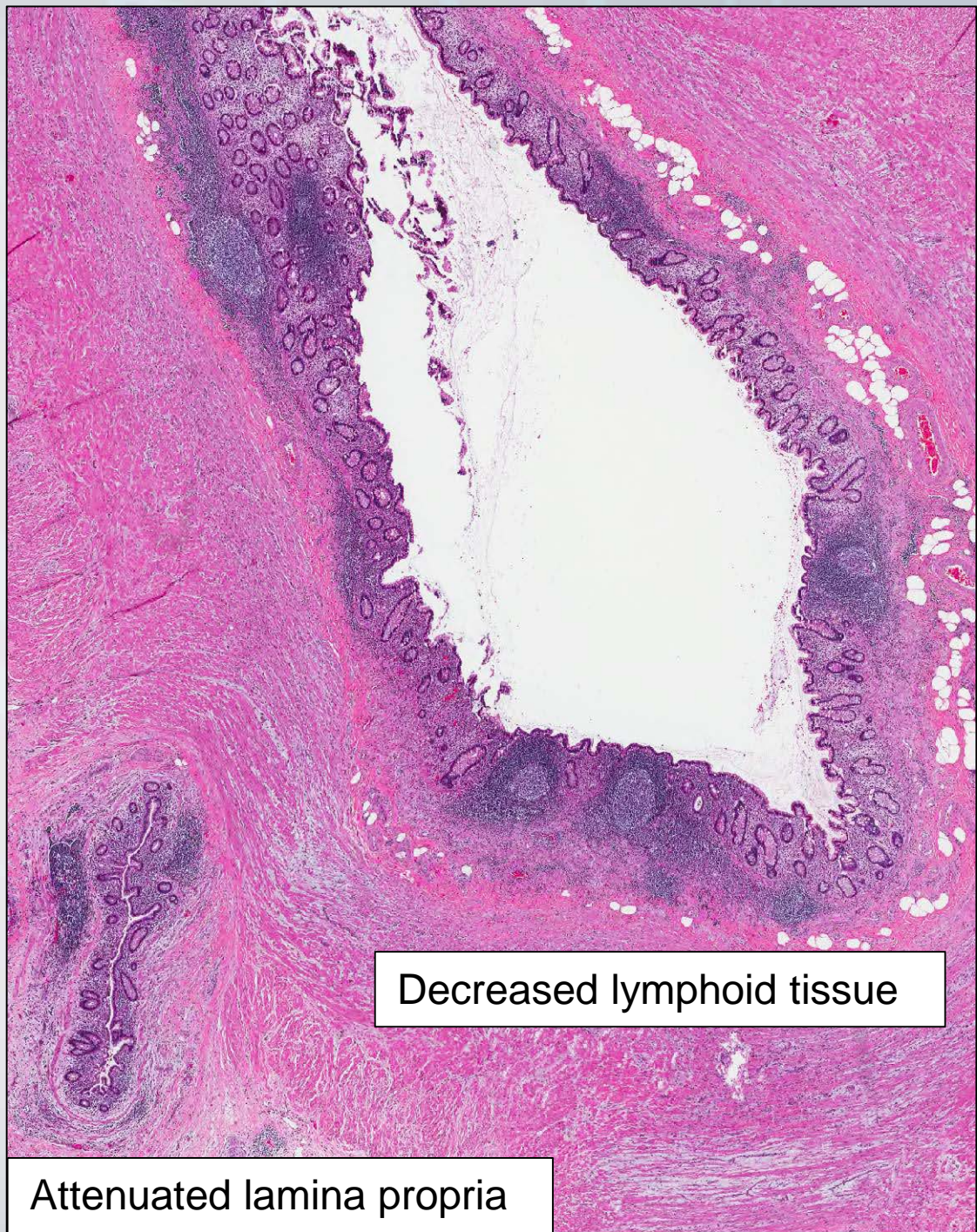
Mucin accumulation associated with decidualized stroma





Abundant lamina propria

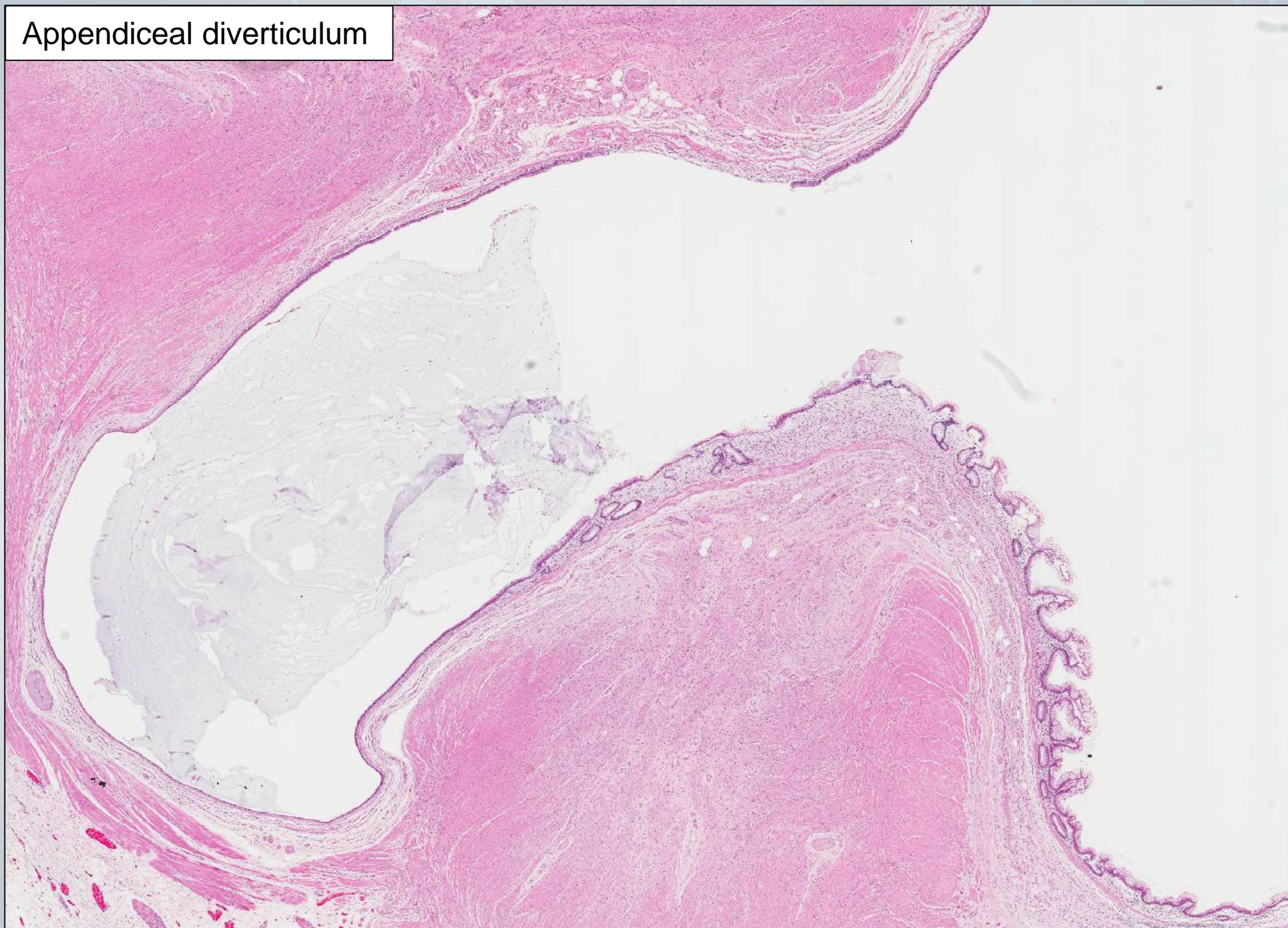
Diverticulosis



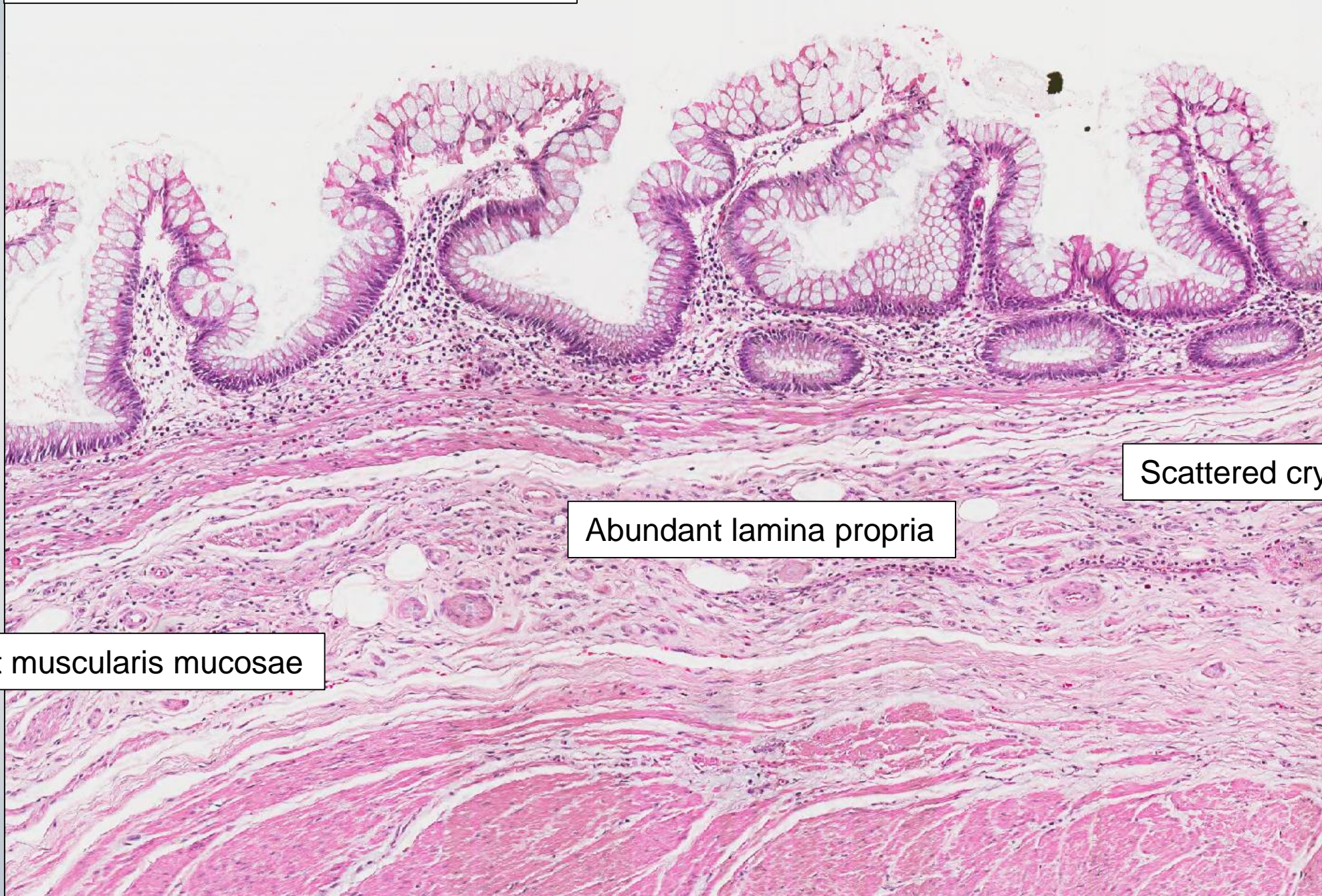
Decreased lymphoid tissue

Attenuated lamina propria

Appendiceal diverticulum



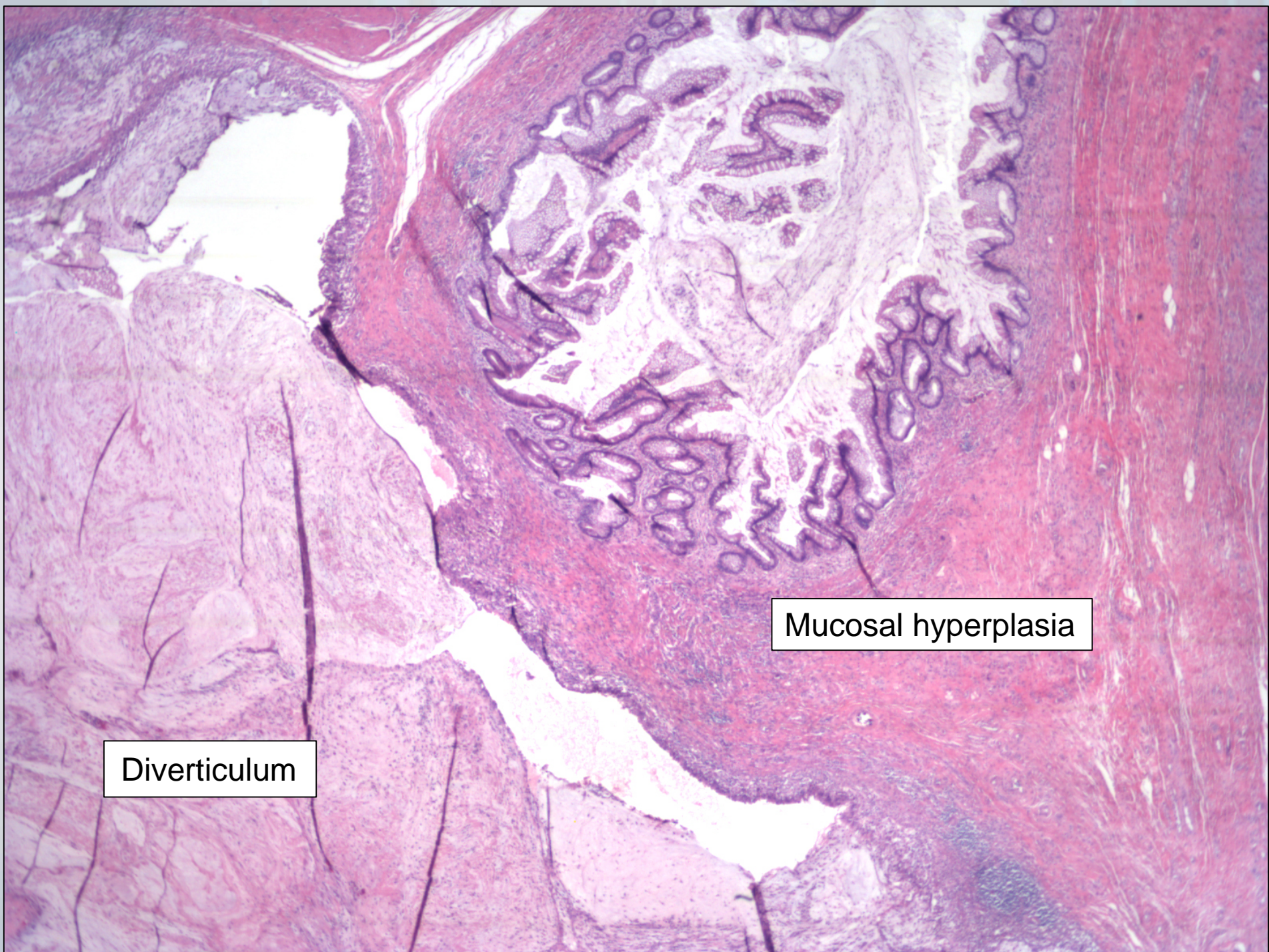
Mucosal hyperplasia in a diverticulum



Scattered crypts

Abundant lamina propria

Intact muscularis mucosae

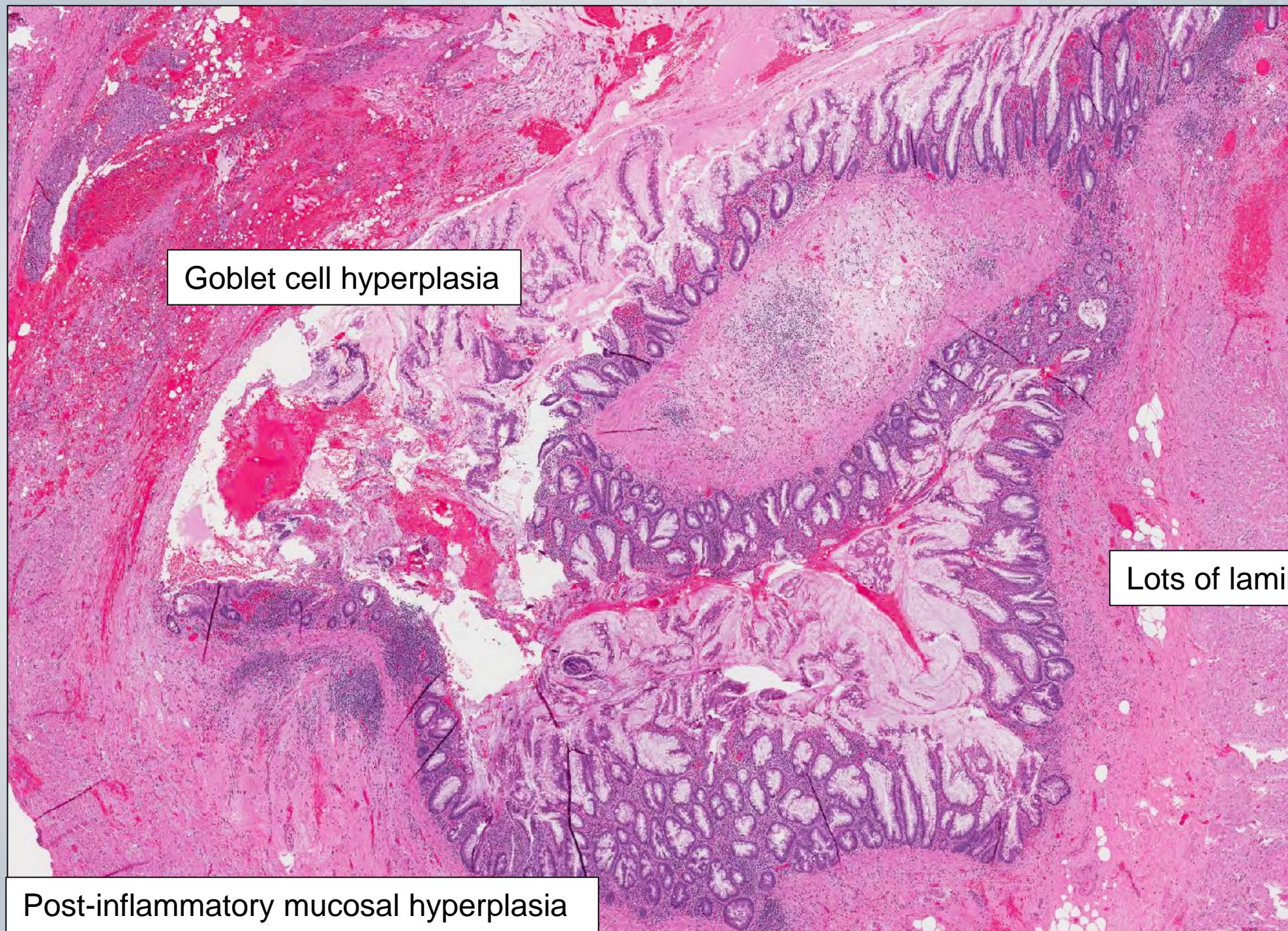


Diverticulum

Mucosal hyperplasia

Post-inflammatory Mucosal Hyperplasia

- Delayed appendectomy increasingly common
 - Especially true among stable patients with walled-off perforated appendicitis
- Surgery can occur weeks to years after symptom onset
- Organization of inflammation accompanied by mucosal regeneration, hyperplasia, and diverticula with extra-appendiceal mucin

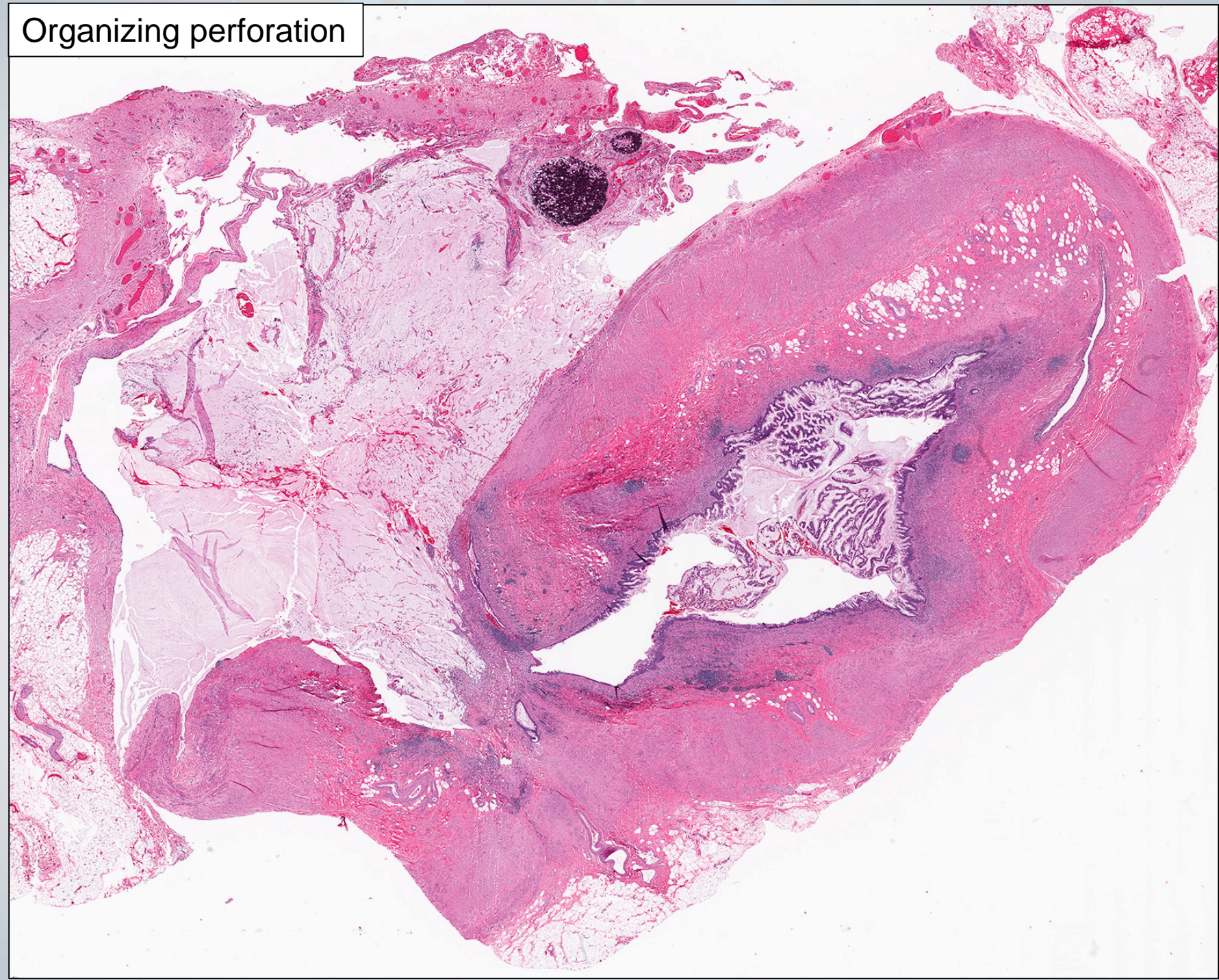


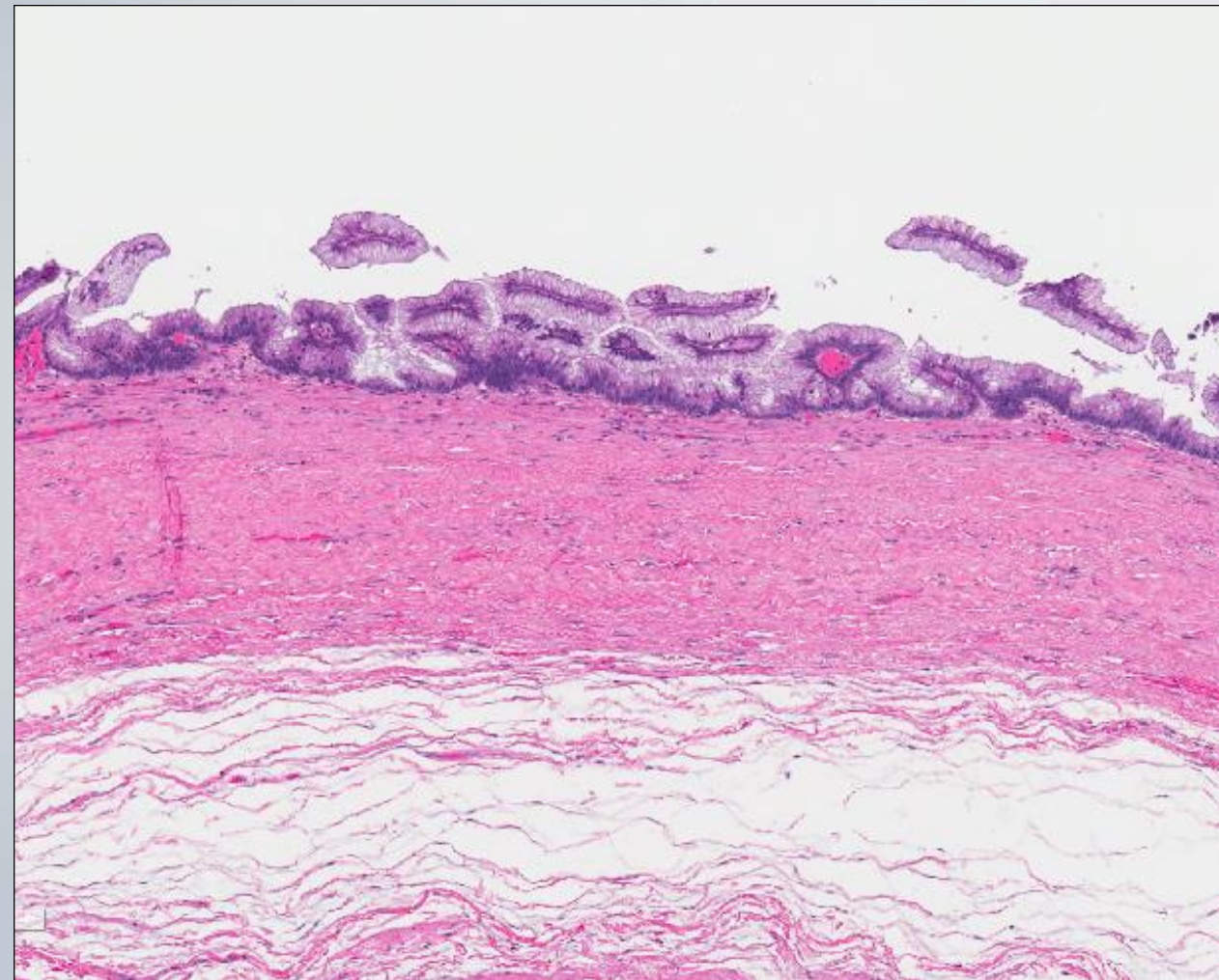
Goblet cell hyperplasia

Lots of lamina propria

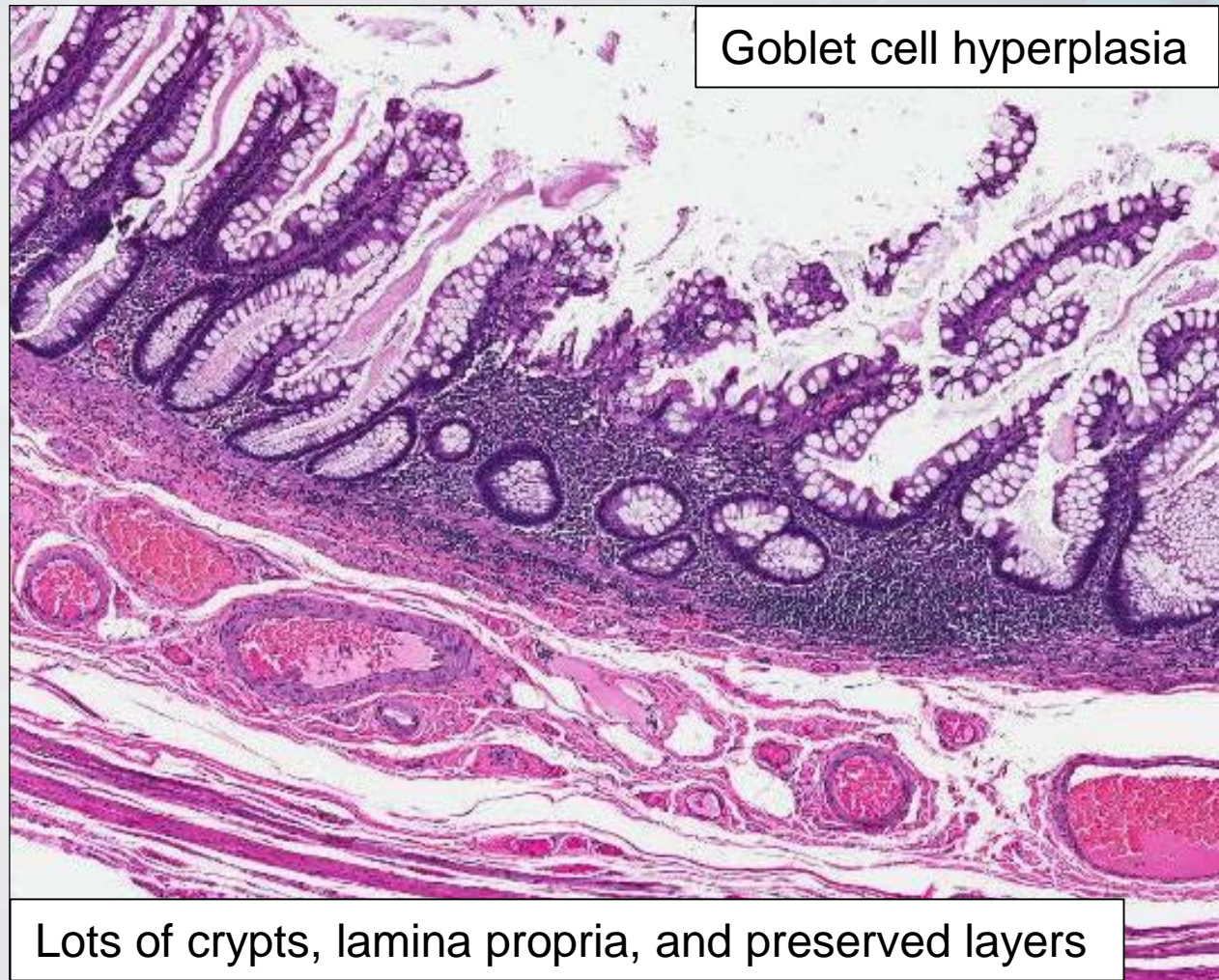
Post-inflammatory mucosal hyperplasia

Organizing perforation





Mucinous neoplasm



Mucosal hyperplasia

Appendiceal Mucinous Lesions

A Few Parting Thoughts

- Strictly defined mucinous adenoma pursues benign course
 - We can learn to recognize it again and we should
- Neoplasms associated with mucin or epithelium beyond muscularis mucosae have risk
 - Reserving LAMN for cases of questionable biologic risk is appropriate
 - Movement to classify all mucinous neoplasms as potentially malignant is not
- Avoid over-interpreting non-neoplastic lesions
 - Abundant lamina propria with preserved layers of wall
 - Mucin or epithelium in wall but luminal surface is normal (think endometriosis, diverticulosis)
 - Dealing with interval appendectomy specimens

THANK YOU!



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