

***Arthur Purdy Stout Society
at Spanish Society of Pathology***

***“Unusual Patterns of Ulcerative Colitis
and IBD-Related Dysplasia”***

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Ulcerative Colitis vs. Crohn's Disease Who Cares?

- **Ileal pouch-anal anastomosis (IPAA)**
 - **continence-restoring operation**
 - **use of ileum to create a reservoir**
 - **generally contraindicated in patients with preoperative diagnosis of Crohn's disease**

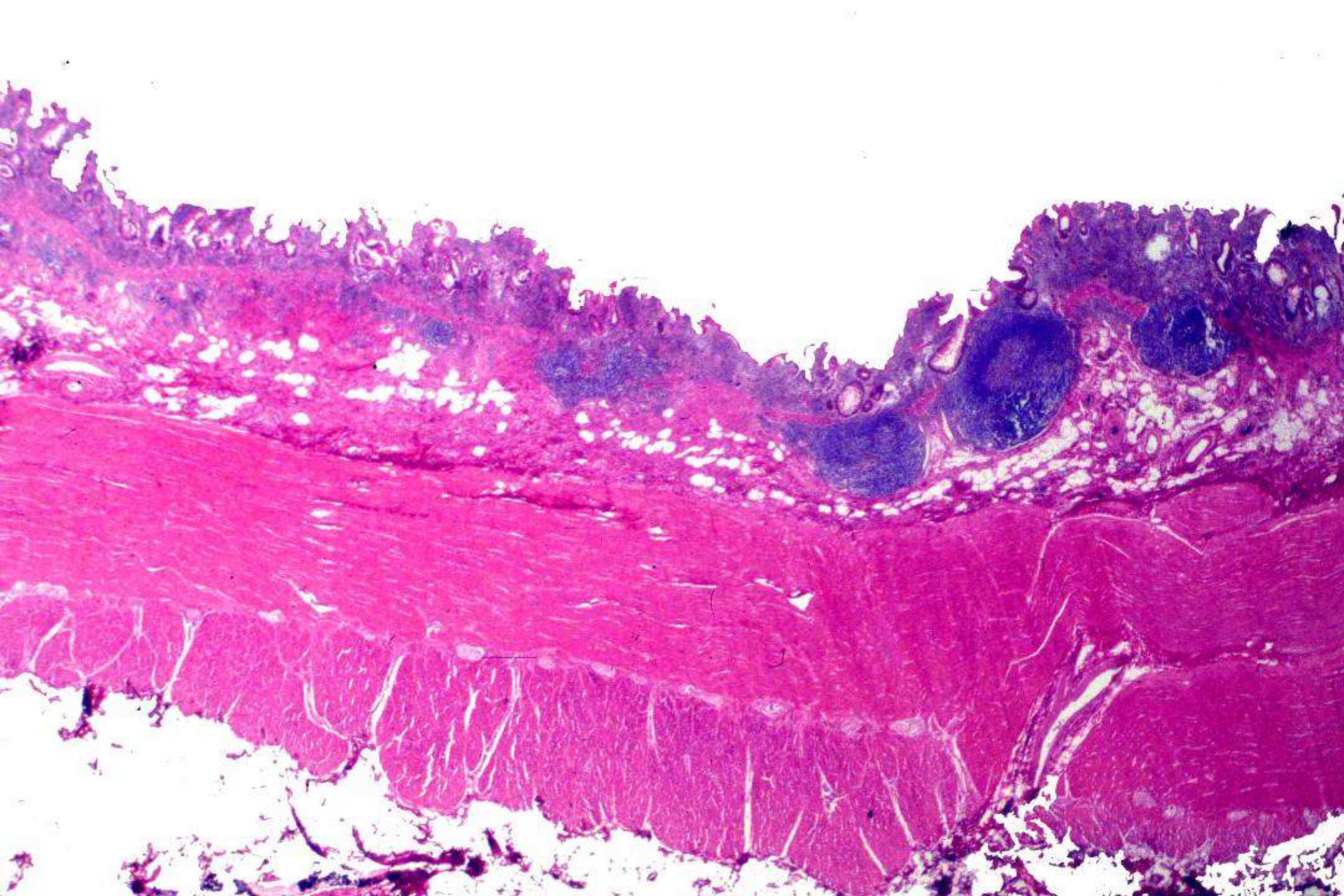
“There is nothing like a pouch to bring out the Crohn's in someone.”

Pouches and Crohn's Disease

- Pouch failure
- Fistulas
- Pelvis sepsis
 - may require resection of pouch and variable length of small bowel → short bowel syndrome

Untreated Ulcerative Colitis

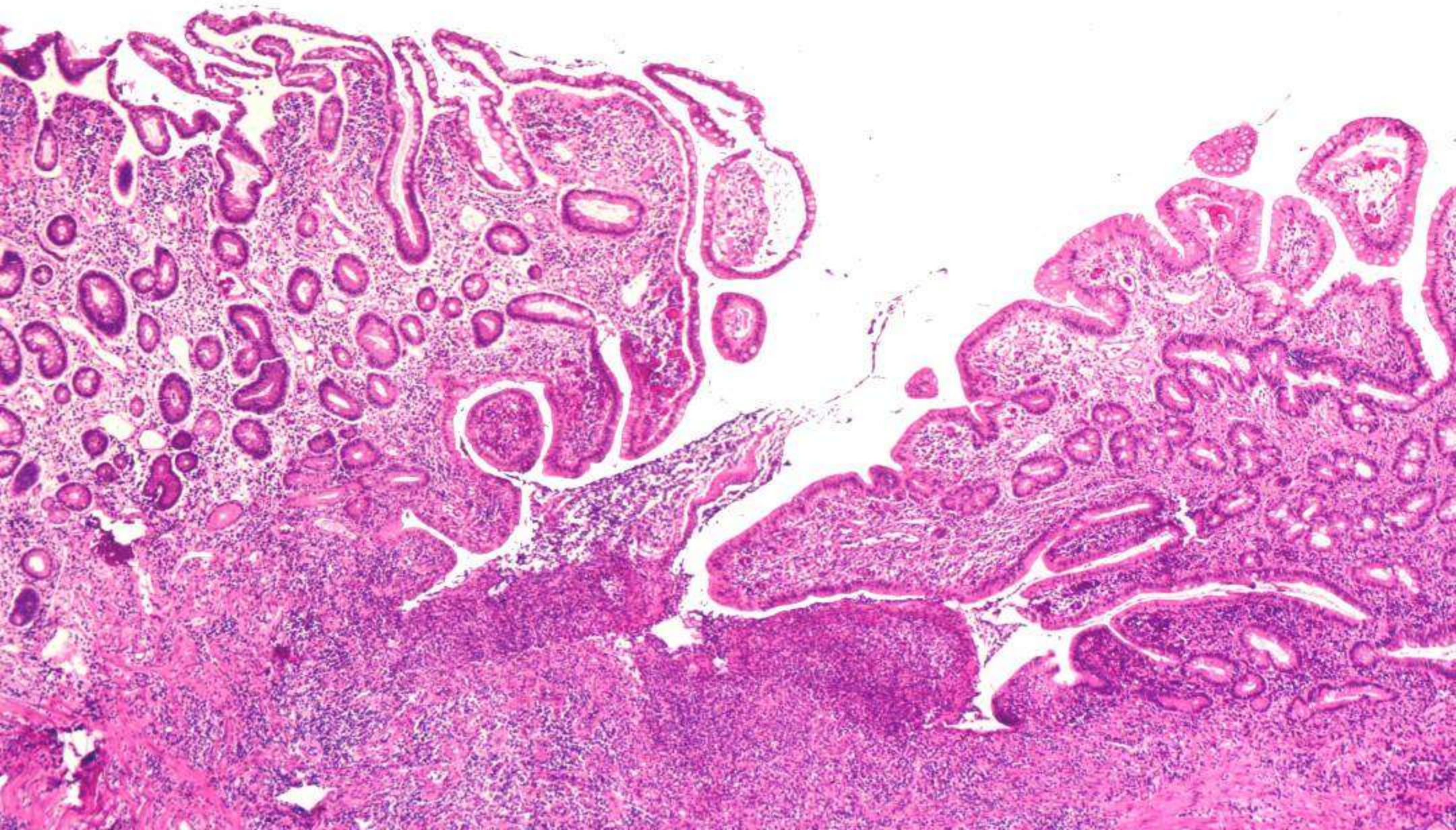
- Diffuse continuous disease
- Rectal involvement
- Disease worse distally
- No fissures
- No transmural aggregates
- No upper GI tract involvement
(except for “BWI”)
- No granulomas
(except for crypt rupture granulomas)

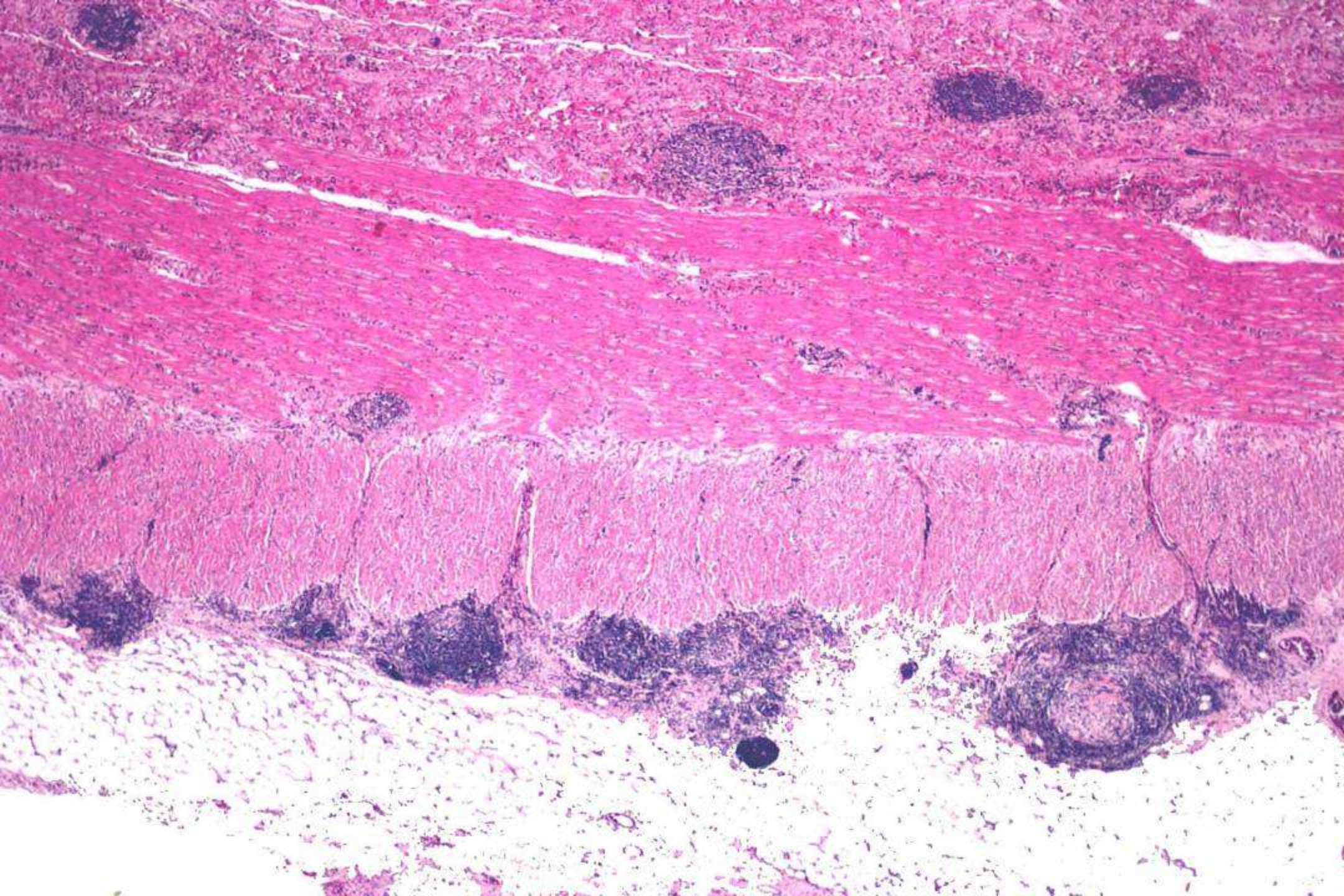


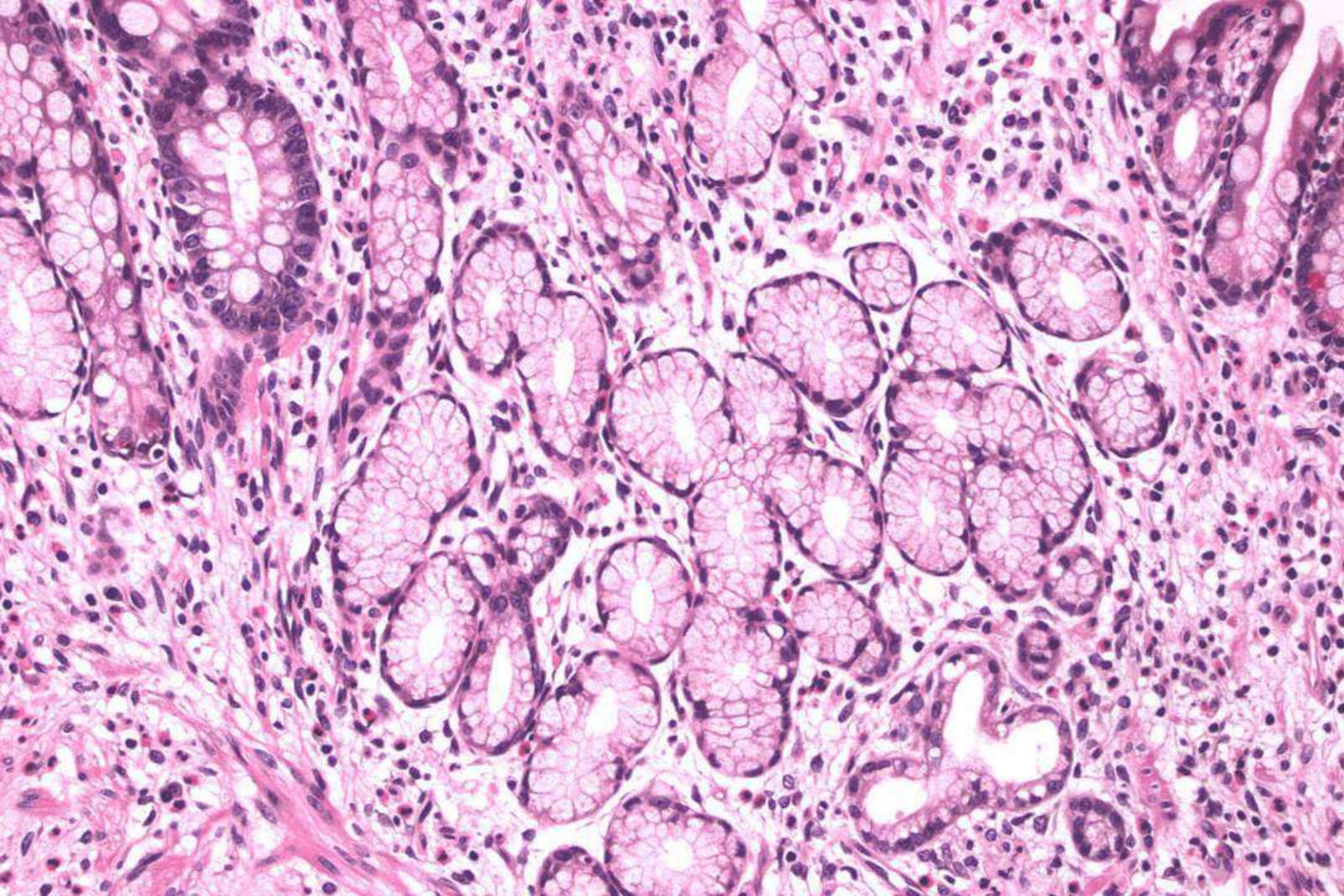


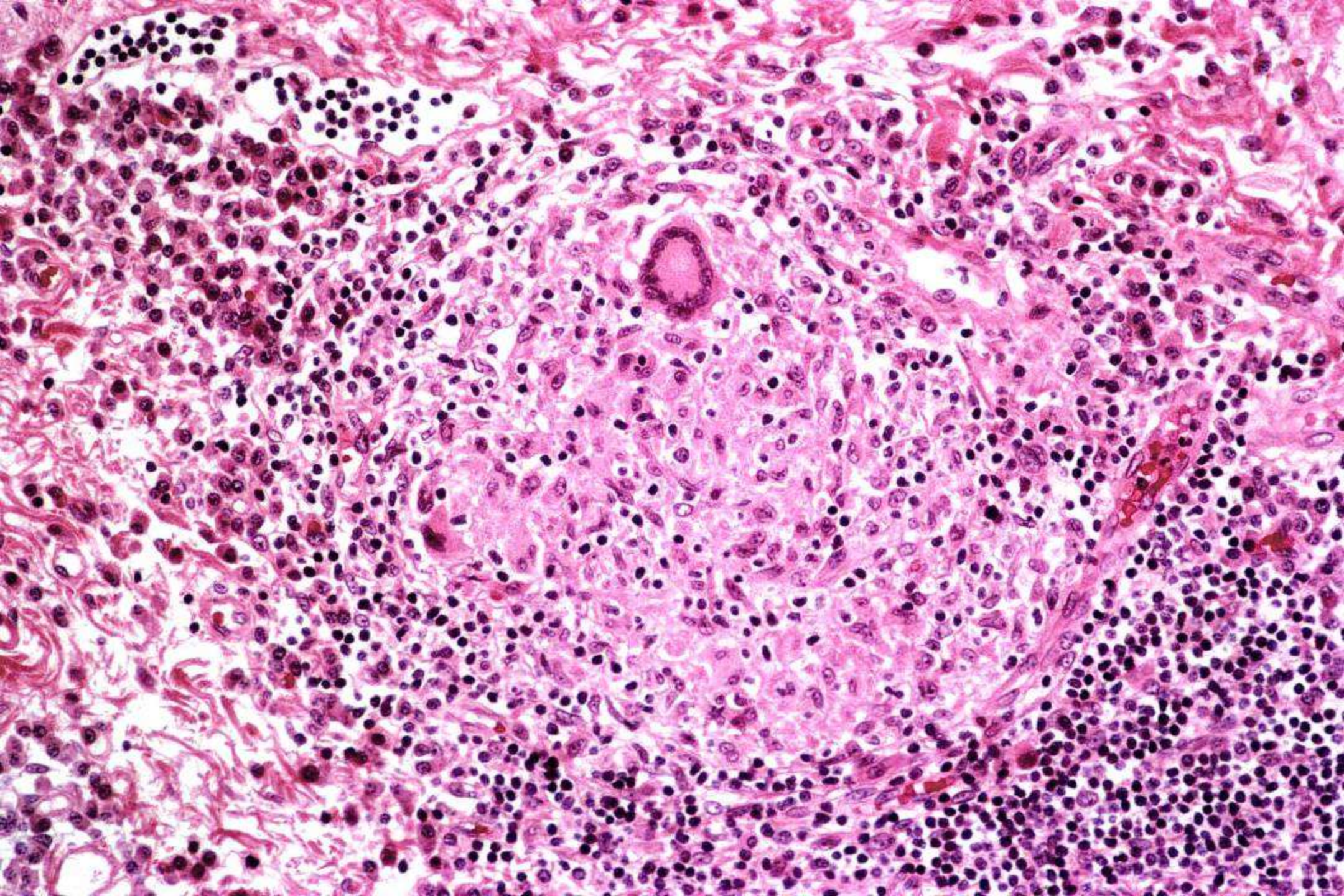
Untreated Crohn's Disease

- Segmental disease
- Variable rectal involvement
- Variable disease severity
- Fissures, sinuses, fistula tracts
- Transmural lymphoid aggregates
- Upper GI tract involvement
- Epithelioid granulomas unrelated to crypt rupture









Unusual Patterns of Disease in UC

- Effects of oral/topical therapy
- Right colon/appendix involvement in subtotal colitis
- Pediatric UC at initial presentation
- Ileitis in UC (“backwash ileitis”)
- Upper GI tract involvement (diffuse duodenitis)
- Granulomas in UC (crypt rupture)
- Fulminant UC

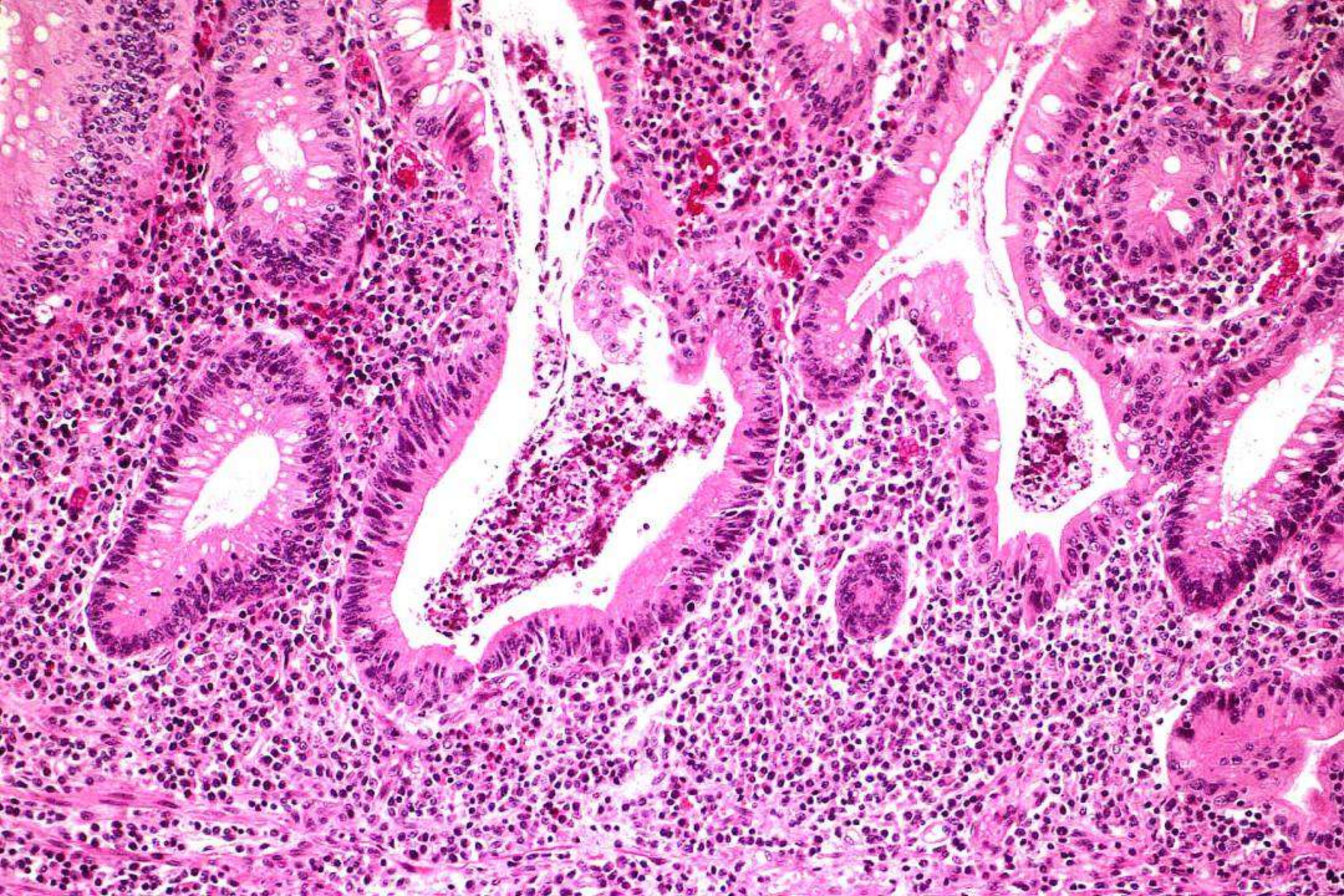
Treatment Effects

- 14 patients with UC
 - 11 ASA enemas
 - 3 placebo enemas
- Rectal biopsies at 1-month intervals
- Evaluated features of activity and chronicity

Treatment Effects

<u>Diagnosis</u>	<u>No. Biopsies (N=123)</u>	
Chronic inactive	53	(43%)
Chronic active	32	(26%)
Active	2	(2%)
Normal	36	(29%)





Treatment Effects Summary

- Patchiness and/or rectal sparing in 30 - 50% of patients with UC
- Does not imply Crohn's disease
- Best chance to distinguish UC from CD is in the initial **pre-treatment** biopsy specimens.



“Skip” Lesions in Subtotal UC

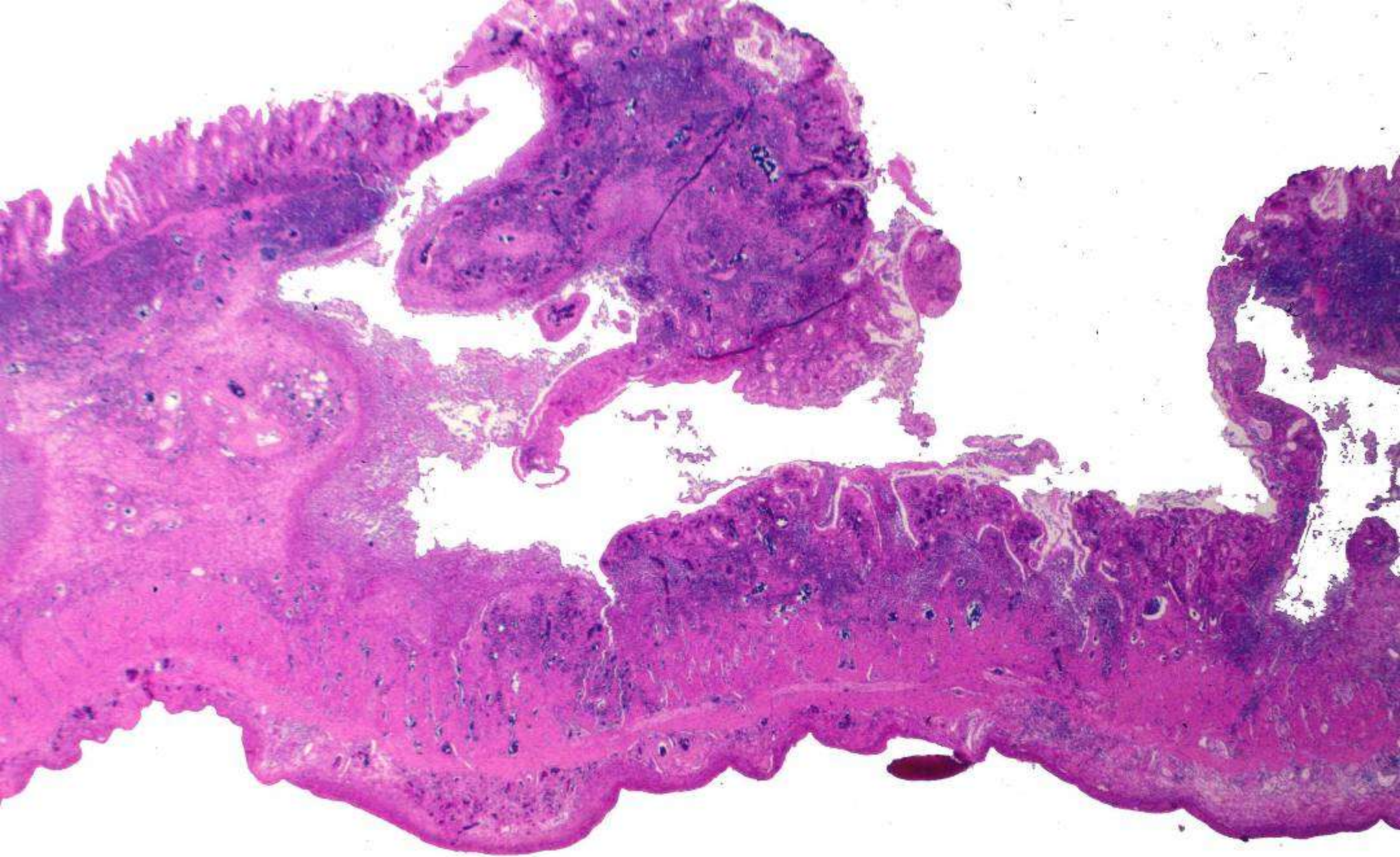
- Appendiceal 21-86 %**
- Ascending colon 4%**
- Cecum/periappendix 10-75%**

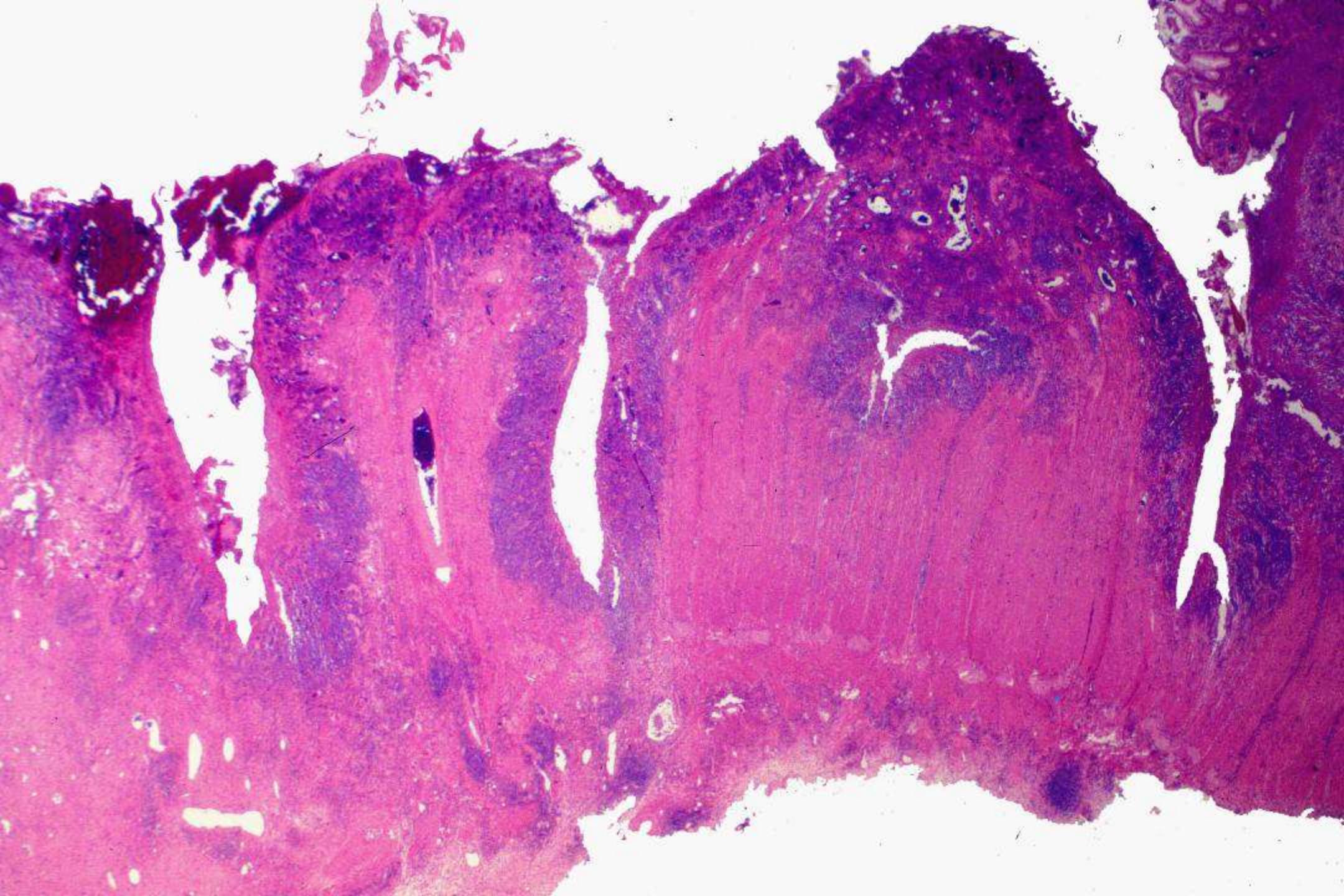
“Backwash Ileitis”

- **Poorly defined criteria**
- **Involvement of TI in continuity with cecum**
- **How much is too much (1 cm? 2 cm? more?)**











Ulcerative Colitis & Carcinoma Risk Factors

- **Extensive colitis**
- **Long duration (>7-10 yrs)**
- **Primary sclerosing cholangitis**
- **Dysplasia**
- **Family history of colon cancer**

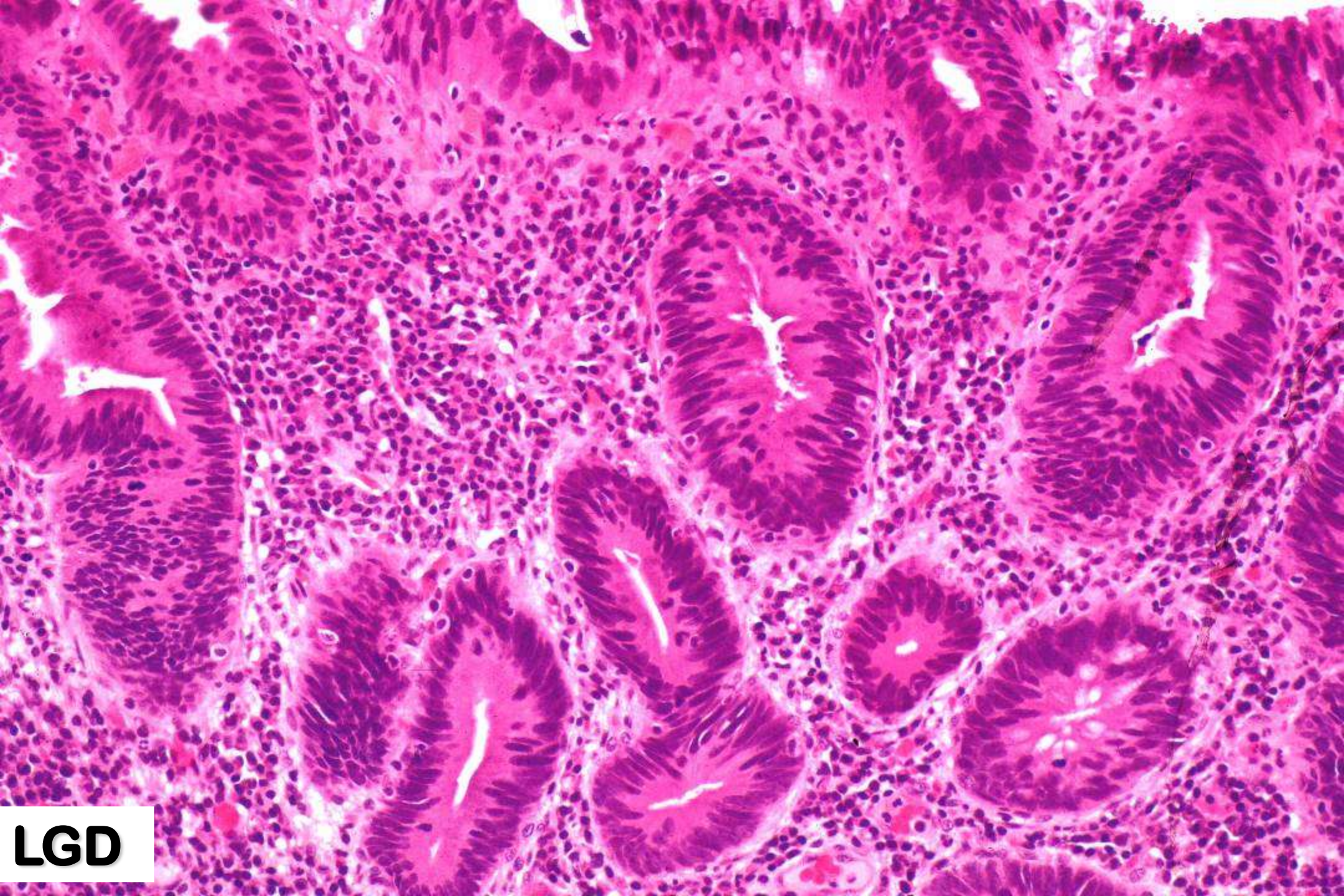
IBD-related Dysplasia Classification

- Negative for dysplasia
- Positive for dysplasia
 - Low-grade dysplasia
 - High-grade dysplasia
- Indefinite for dysplasia

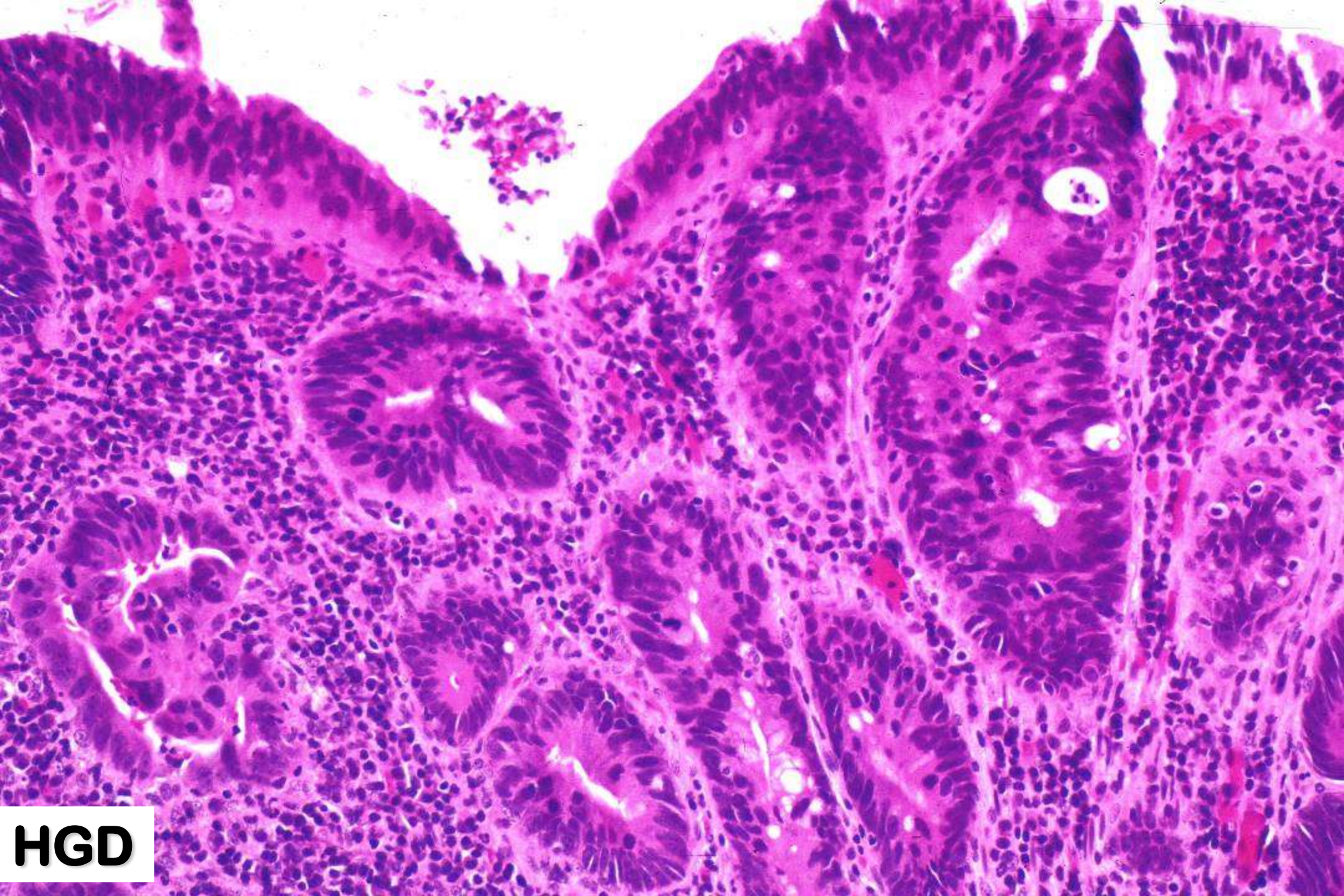
The Problem with Dysplasia

- **Sampling error**
- **Intra/interobserver variation**
 - **reactive vs. dysplasia**
 - **low-grade vs. high-grade**

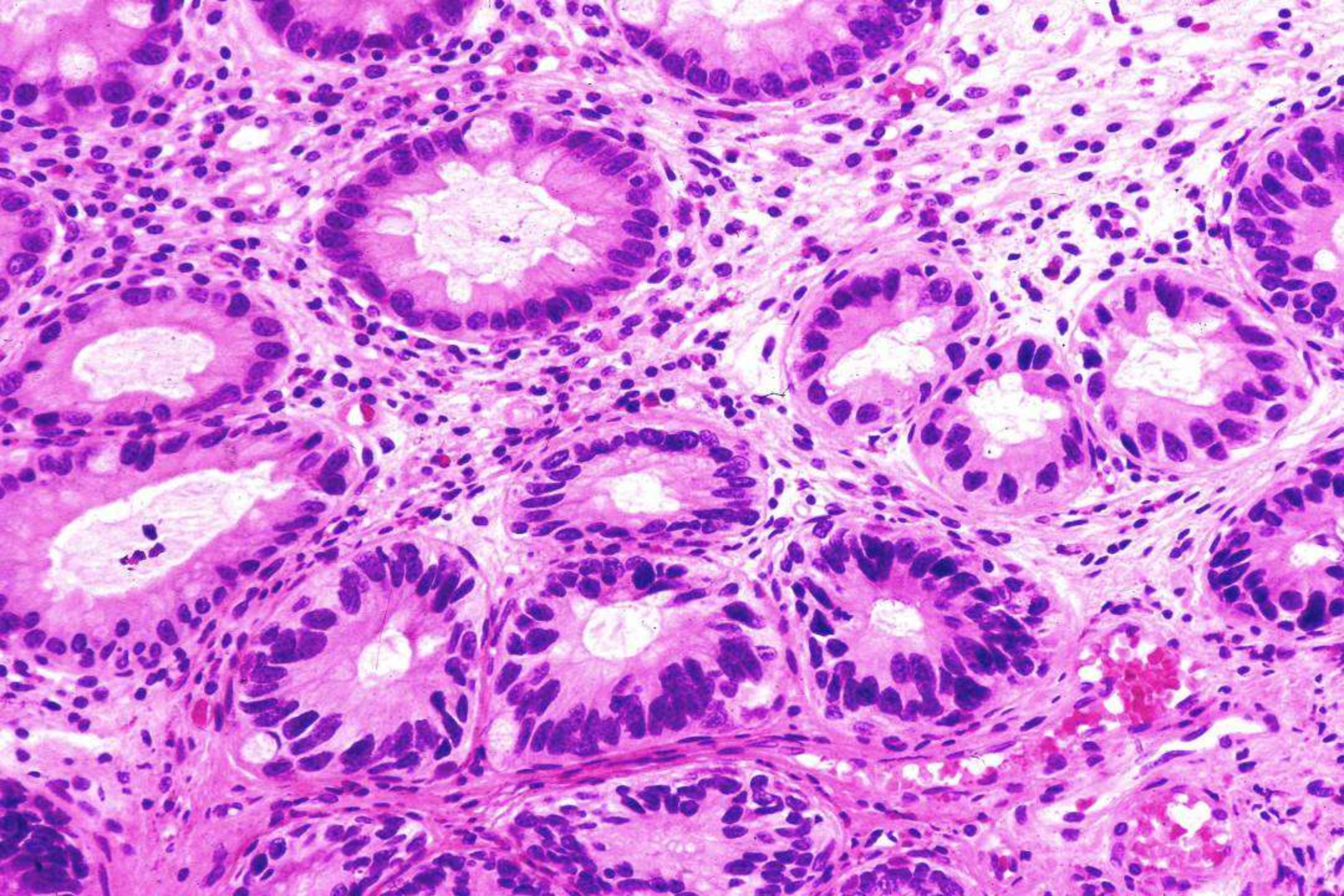




LGD



HGD



IBD-Related Flat Dysplasia

- **Low-Grade**
 - **Coexistent carcinoma** 9%
 - **Progression to HGD/CA** 30-54% at 5 yrs
- **High-Grade**
 - **Coexistent carcinoma** 40-67%
 - **Progression to CA** 40-90% at 5 yrs

The Dreaded “DALM”

	<u># Patients</u>	<u>%DALM</u>	<u>%Cancer w/DALM</u>
Blackstone (1981)	112	11%	58%
Butt (1983)	62	29%	83%
Rosenstock (1985)	248	5%	38%
Lennert-Jones (1990)	401	1.5%	83%
Bernstein (1994)	1225 (meta)	3.2%	43%

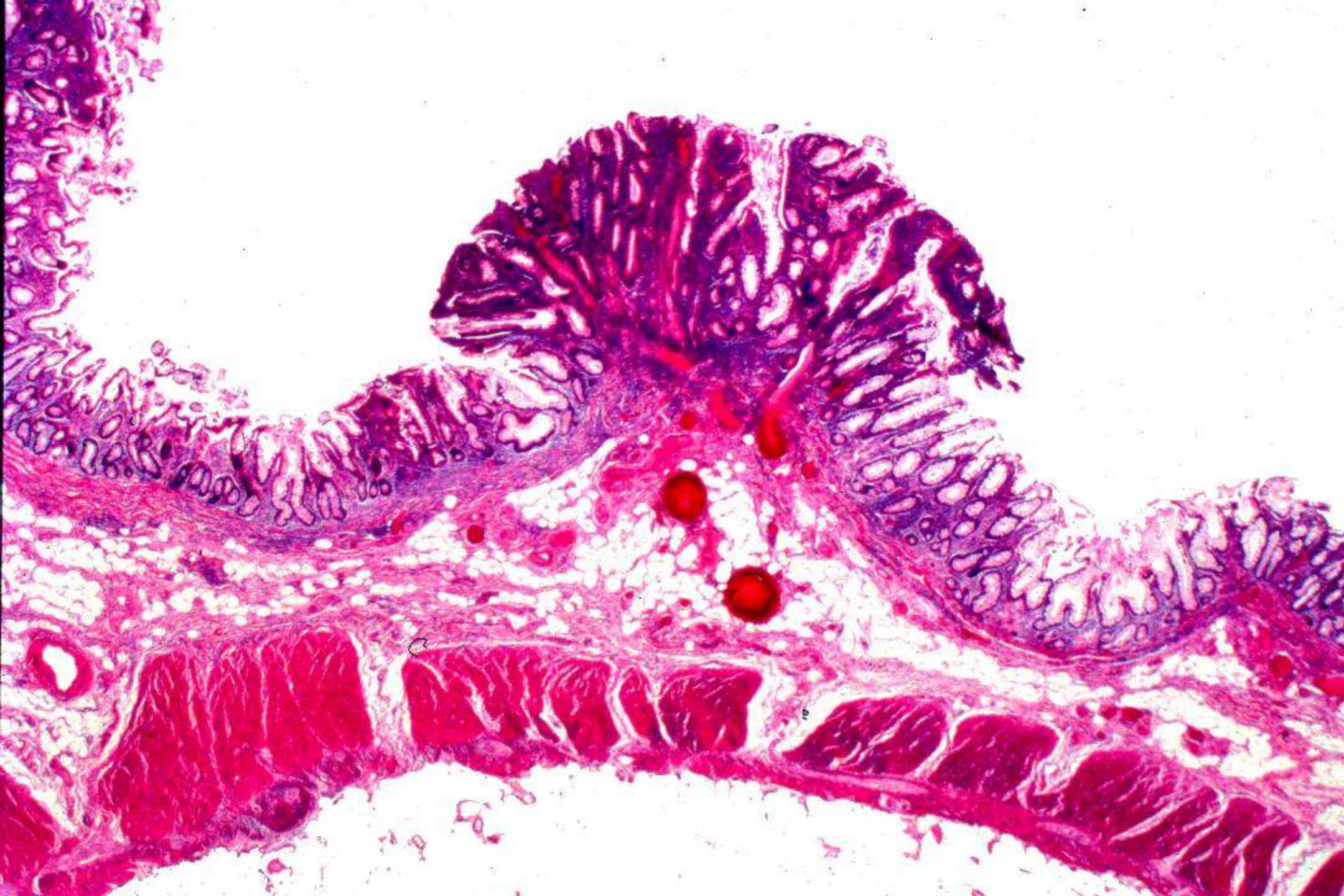
What is a DALM?

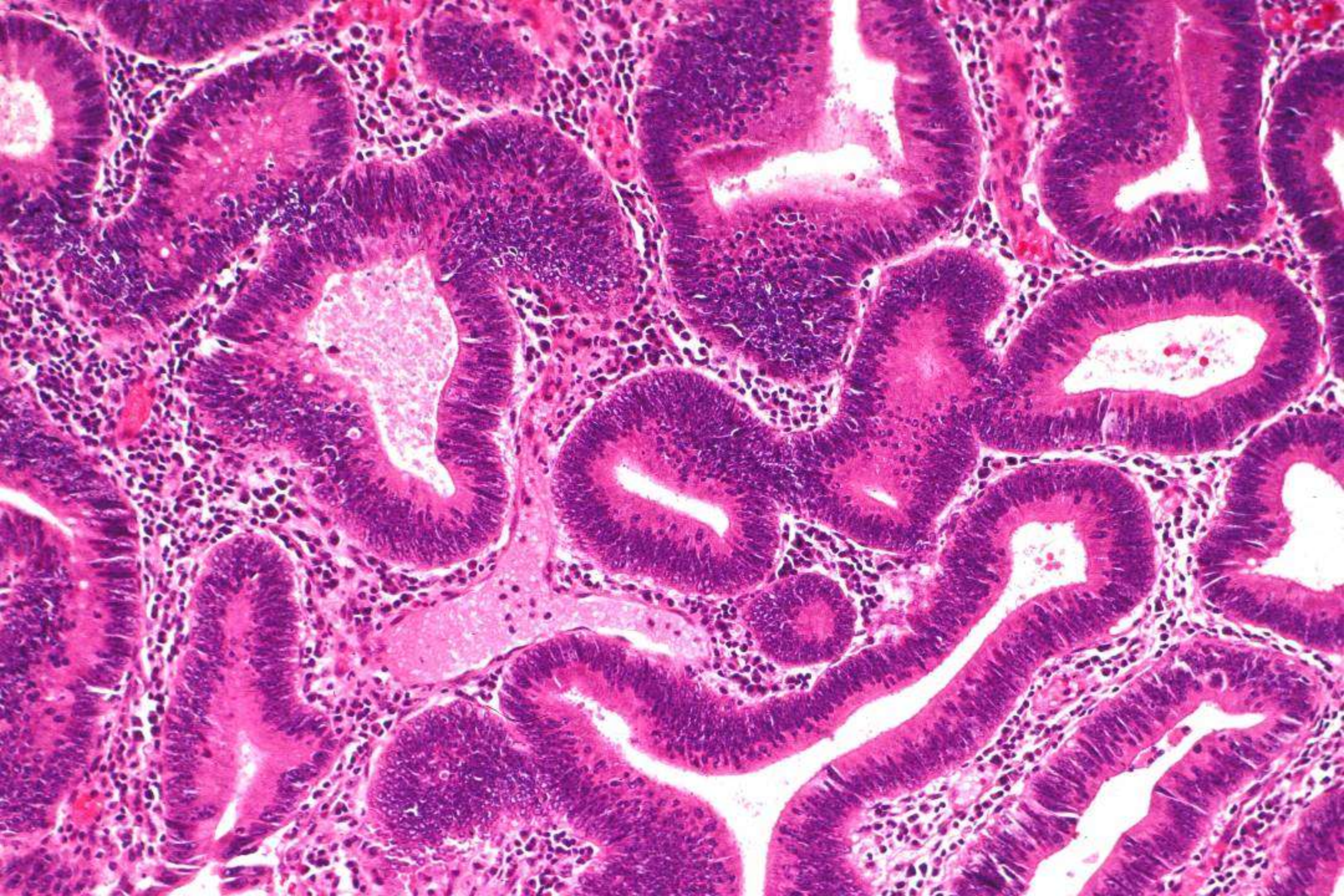
- **Obvious mass**
- **Elevated plaque-like lesion**
- **Sessile / pedunculated polyp**

Adenoma vs. Polypoid Dysplasia

How Can You Tell?

- **Location relative to distribution of IBD**
- **Histology**
- **Molecular profile**
- **You can't tell!**





Adenoma vs. IBD-Related Dysplasia

	<u>Adenoma</u>	<u>IBD-dysplasia</u>
Macroscopic	polyp	plaque
Glands	regular, round	irregular
Mucin	regularly distributed	variable
Nuclei	elongated	round
Stroma	sparse	variable
Proliferation	luminal	basal
Transition	sharp	gradual

*based on **PRE-DETERMINED ARBITRARY** criteria

Adenoma vs. IBD-Related Dysplasia

Molecular Genetic Features

- p53 staining
- β -catenin staining
- LOH 3p21 (vHL)
- LOH 5q (APC)
- LOH 9p (p16)

Polypectomy May Be Adequate Treatment for Adenoma-like Dysplastic Lesions in Chronic Ulcerative Colitis

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See editorial on page 1488.

Background & Aims: Chronic ulcerative colitis (CUC)-associated adenoma-like DALMs (dysplasia-associated lesions or masses) pose a difficult clinical problem to both gastroenterologists and pathologists because they are difficult to distinguish endoscopically and pathologically from sporadic adenomas that develop coincidentally in patients with CUC. The aim of this study was to evaluate the outcome of CUC patients with an adenoma-like DALM treated conservatively and to compare the findings with CUC patients with a coincidental sporadic adenoma. **Methods:** Clinical, endoscopic, and pathological features and outcome of 24 CUC patients with an adenoma-like DALM were compared with those of 10 CUC patients with a coincidental sporadic adenoma and 49 non-CUC (control) patients with a sporadic adenoma. Patients were followed up for a mean of 42.4 and 41.2 months for the 2 CUC groups, respectively, and 37.0 months for the non-CUC controls by endoscopic surveillance. **Results:** Of the 24 CUC patients with adenoma-like DALMs (male/female ratio, 14/10; mean age, 61.5 years; mean duration of colitis, 10.4 years), 14 (58%) developed further adenoma-like DALMs within the follow-up interval. Only 1 patient (4%) developed an isolated focus of low-grade dysplasia, and none developed adenocarcinoma. Five of 10 (50%) CUC patients with sporadic adenomas developed further adenomas, and none of the patients in this group developed either dysplasia or adenocarcinoma. Of the 49 non-CUC control patients, 39% developed further adenomas. **Conclusions:** CUC patients who develop an adenoma-like DALM that endoscopically and histologically resembles a sporadic adenoma, regardless of its location (either within or outside areas of documented colitis), may be treated with polypectomy and endoscopic surveillance because of its relatively benign course.

Patients with chronic ulcerative colitis (CUC) have an increased risk of malignancy that develops through a dysplasia-carcinoma sequence.¹⁻³ Dysplasia, defined as

unequivocal neoplastic epithelium, is the most important risk marker of malignancy.^{1,4} Dysplasia is broadly categorized as flat (endoscopically invisible) or raised (endoscopically visible), in which case the term dysplasia-associated lesion or mass (DALM) is applied.^{5,6} Previous studies on DALMs indicate a high association (up to 50%) with adenocarcinoma.^{4,6-10} However, after a careful appraisal of the literature, it is apparent that DALMs are a heterogeneous population of lesions that may appear as various gross subtypes, such as a plaque, mass, stricture, or, more commonly, as a discrete sessile nodule or pedunculated polyp that endoscopically resembles a sporadic adenoma.^{4,5} Recent data suggest that not all subtypes carry a high risk of malignancy.^{4,11-13}

CUC-associated adenoma-like DALMs pose a difficult diagnostic challenge to both clinicians and pathologists because they are difficult to distinguish endoscopically and pathologically from sporadic adenomas that develop coincidentally in patients with CUC.^{4,5,14,15} This is a critical distinction because a CUC-related adenoma-like DALM is a tumor that develops as a result of the underlying chronic inflammation; thus, its presence has traditionally been considered an indication for colectomy.^{1,4,5} This treatment plan is based on the presumption that these patients have a high risk of progression to malignancy within a short (<5 year) period.^{1,4,16} However, this hypothesis has never been evaluated in a controlled fashion. Because little is known about the natural history of adenoma-like DALMs in CUC, it is unclear if colectomy is necessarily required in all cases. In contrast, sporadic adenomas occurring coincidentally in patients with CUC, whose development is presumably unrelated to the underlying colitis, are usually treated by simple polypectomy.^{4,5} Both CUC and sporadic adenomas are common disorders; thus, gastroenterologists and pathologists often encounter patients with both conditions.

Abbreviations used in this paper: CUC, chronic ulcerative colitis; DALM, dysplasia-associated lesion or mass.
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0016-5085/99/\$10.00

Colonoscopic Polypectomy in Chronic Colitis: Conservative Management After Endoscopic Resection of Dysplastic Polyps

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See editorial on page 1488.

Background & Aims: Adenomatous polyps are by definition dysplastic and pathologically indistinguishable from the dysplasia-associated lesion or mass (DALM) described in 1981. Yet, adenomatous polyps in noncolitic colons are usually removed definitively endoscopically, whereas DALMs are regarded as harbingers of colon cancer, mandating colectomy. **Methods:** Since 1988, all of our patients with chronic ulcerative or Crohn's colitis and dysplastic polyps and no coexistent dysplasia in flat mucosa underwent colonoscopic polypectomy. Biopsy specimens were obtained also adjacent to polypectomy sites, from strictures, and throughout the colon at 10-cm intervals. Follow-up colonoscopies and biopsies were performed within 6 months after polypectomy and yearly thereafter. **Results:** Colonoscopy in 48 patients with chronic colitis (mean duration, 25.4 years) resected 70 polyps (60 in colitic and 10 in noncolitic mucosa). Polyps were detected on screening colonoscopies (29%) and on surveillance (71%). Pathology was tubular adenoma in all polyps from noncolitic mucosa and low-grade dysplasia (57), high-grade dysplasia (2), or carcinoma (1) in polyps from colitic mucosa. Subsequent colonoscopies (mean follow-up, 4.1 years) revealed additional polyps in 48% but no carcinomas. Surgical resection (6 patients) for recurrent polyps confirmed colonoscopic findings. No dysplasia or cancers in flat mucosa were found at surgery or on follow-up colonoscopies. **Conclusions:** In patients with chronic colitis who have no dysplasia in flat mucosa, colonoscopic resection of dysplastic polyps can be performed effectively, just as in noncolitic colons.

It is generally agreed that patients with both chronic ulcerative colitis¹⁻¹⁰ and Crohn's colitis^{3,11-20} are at increased risk of developing colorectal cancer. Colonoscopy with biopsy to detect dysplasia remains the mainstay and most widely used means of cancer prevention in patients with chronic colitis,²⁰⁻²⁴ despite its shortcomings.²⁵⁻³¹

In 1981 Blackstone et al.³² described a series of patients with chronic colitis who had single or multiple discrete polypoid, nodular, or plaque-like colonic dysplastic lesions. These were called dysplasia-associated lesions or mass (DALMs) and identified as markers for colonic cancer. Since then, the discovery on colonoscopy of one or more DALMs has been considered by many as an indication for colectomy.^{32,33}

In contrast to DALMs, adenomatous polyps encountered in patients without colitis usually are not considered indications for surgery. Sporadic adenomatous polyps are frequent findings at colonoscopy, with a prevalence estimated as high as 30% in middle-aged asymptomatic adults.^{34,35} Although adenomatous polyps arising in noncolitic mucosa are, by definition, dysplastic and potentially premalignant, it is widely accepted that they can usually be removed definitively by colonoscopic means.³⁶ Surgery is reserved for adenomas that cannot be removed colonoscopically or for adenomas that are found to have invasive carcinoma.

Despite the differences in the approach to DALMs in colitis and adenomas in noncolitic colon, the 2 lesions are often indistinguishable pathologically. The differentiation between DALM and adenoma is made on clinical grounds. If the polyp originates within colitic mucosa, it is presumed to be a DALM; if it develops in noncolitic mucosa, the diagnosis is adenoma.

This radically different approach to lesions that are pathologically indistinguishable has stimulated us to ask whether some dysplastic polyps arising in colitic mucosa can be managed effectively by colonoscopic resection without incurring a subsequent increased risk of colonic cancer. To address this issue we have studied a large series of patients with chronic colitis observed after colonoscopic removal of dysplastic polyps.

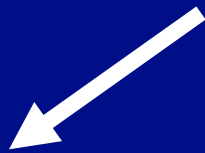
Abbreviation used in this paper: DALM, dysplasia-associated lesion or mass.
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Polypoid Dysplasia in IBD

- Lesion arises in mucosa with histologically confirmed UC
- discrete sessile/pedunculated polyp
 - endoscopically identical to sporadic adenoma
 - histologically identical to sporadic adenoma
- no flat dysplasia or carcinoma elsewhere
- complete polypectomy
- close surveillance (4 quadrant/10 cm)

Polypoid Dysplasia in IBD

24 UC patients with adenoma-like lesion
(follow-up: 17-156 mos; mean 82 mos)



no further dysplasia: 9

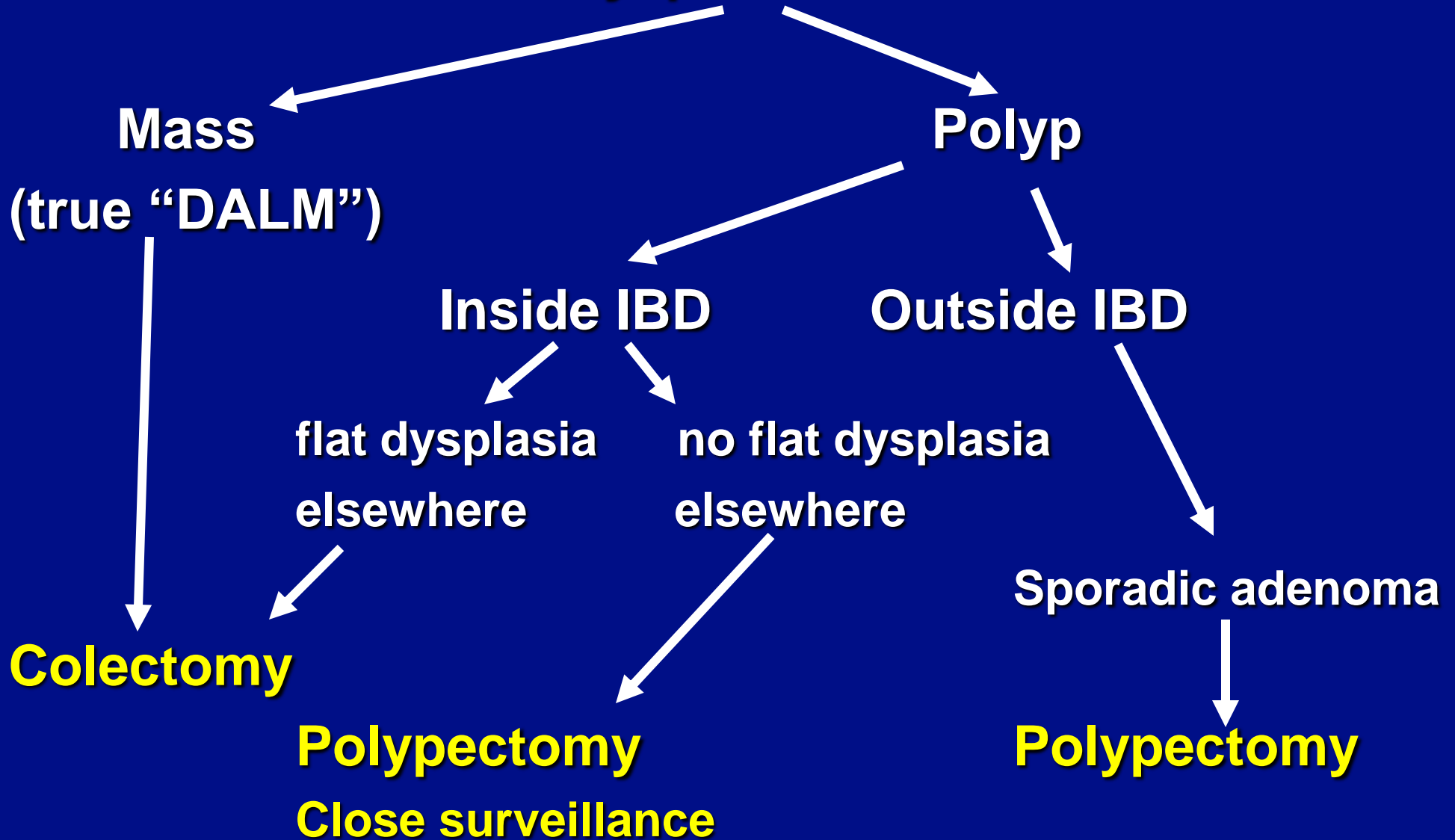


further dysplasia: 15



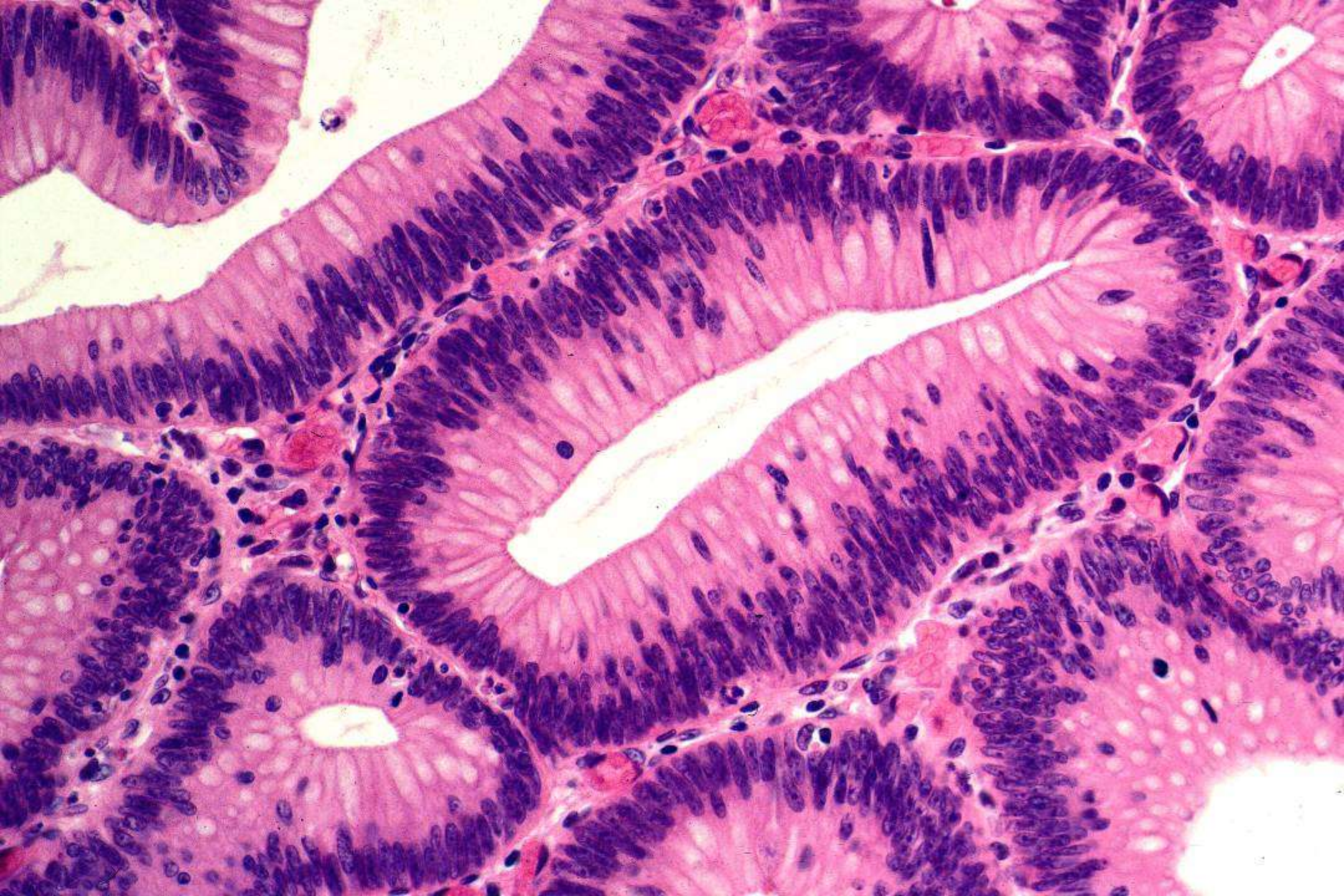
none developed flat dysplasia/ADC (except 1)

Dysplasia in IBD



Colorectal Polyps

- Hyperplastic polyp
- Traditional adenomatous polyp
- “Sessile serrated polyp” (or SSA)
- Traditional serrated adenoma
- Mixed-type polyp
- Hamartomatous polyp
- Lymphoid aggregate (misc)
- Cauterized beyond recognition

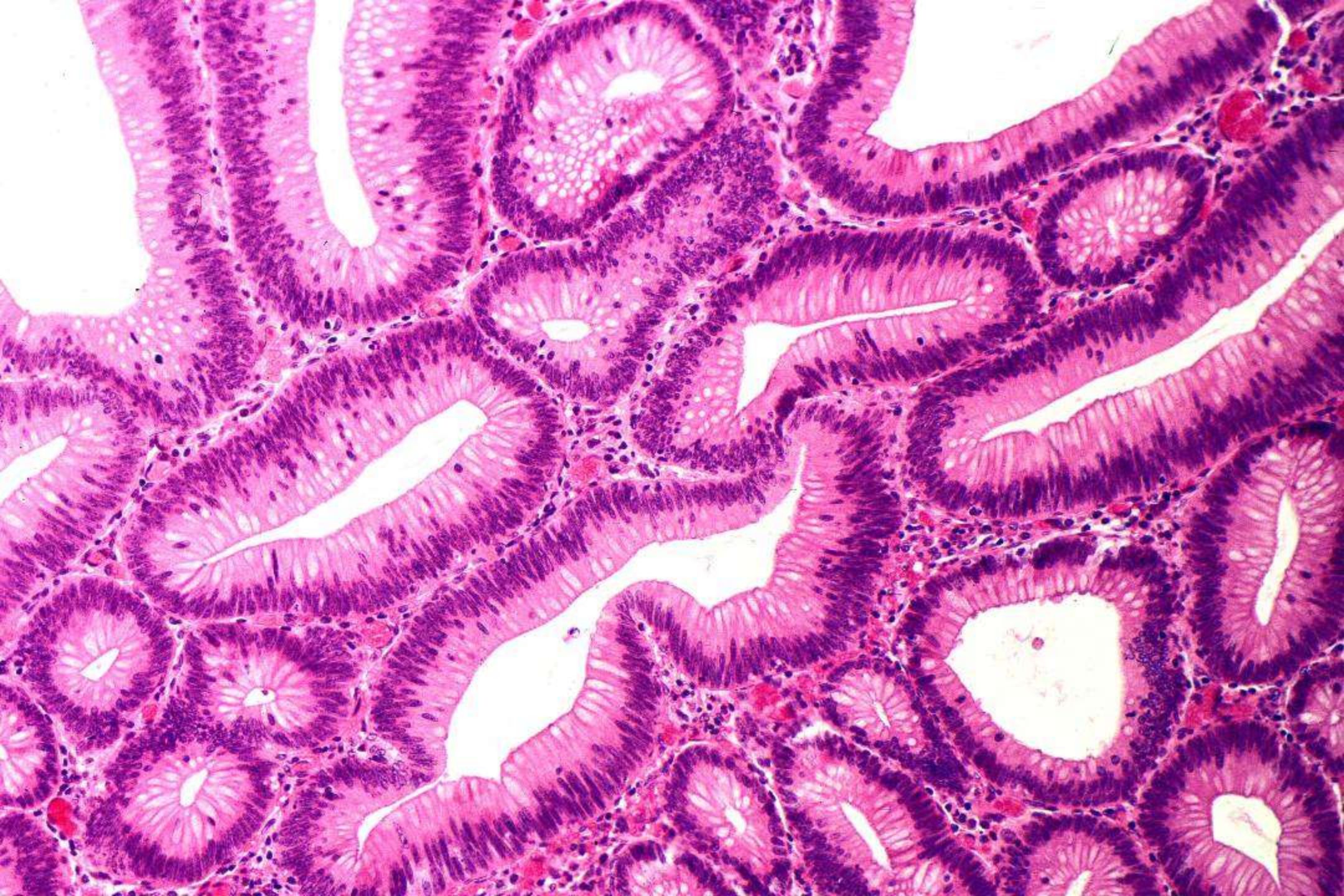


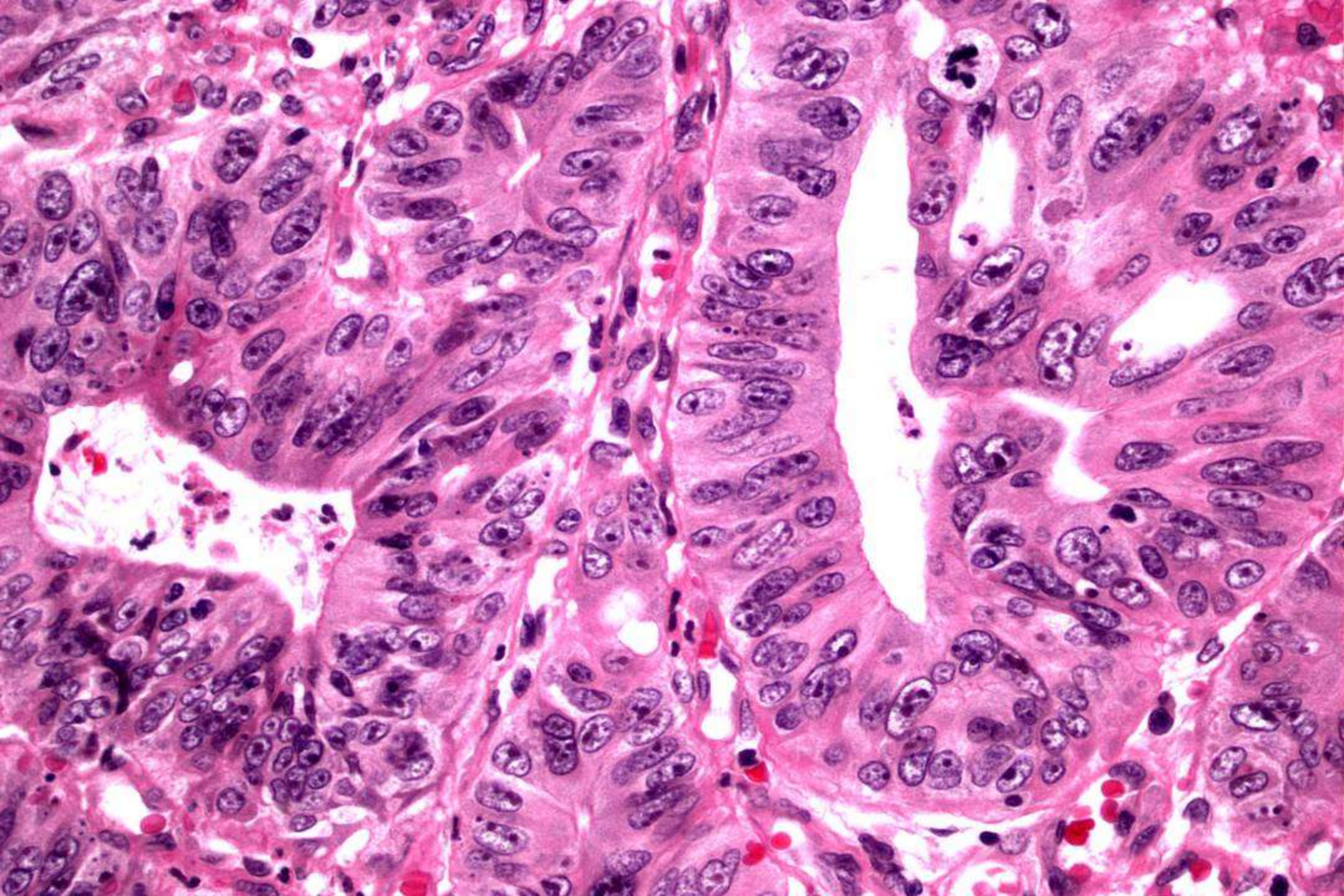
Terminology

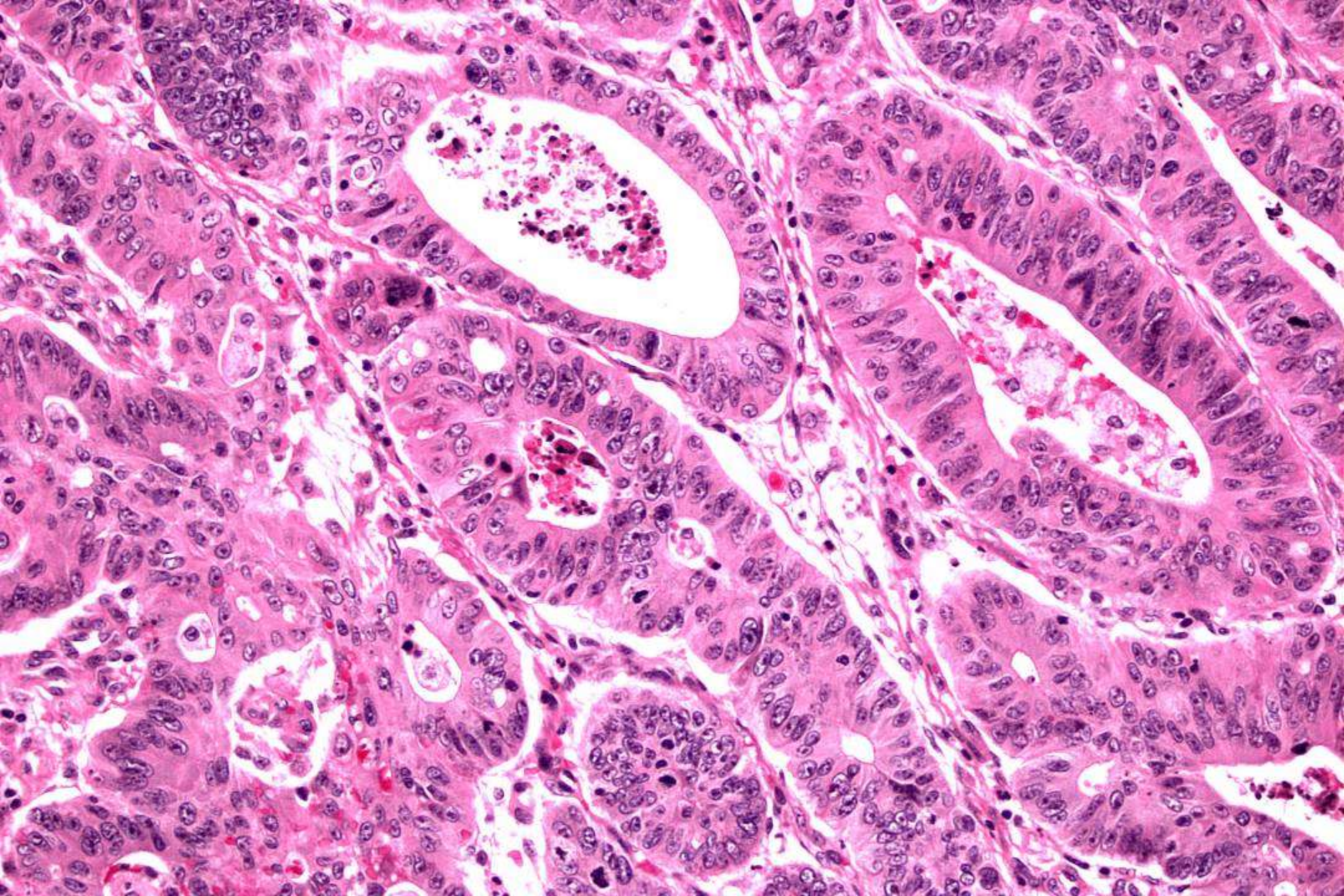
- **Adenoma (implies at least LGD)**
- **Adenoma with high-grade dysplasia**
- **Intramucosal adenocarcinoma**
- **Invasive adenocarcinoma**

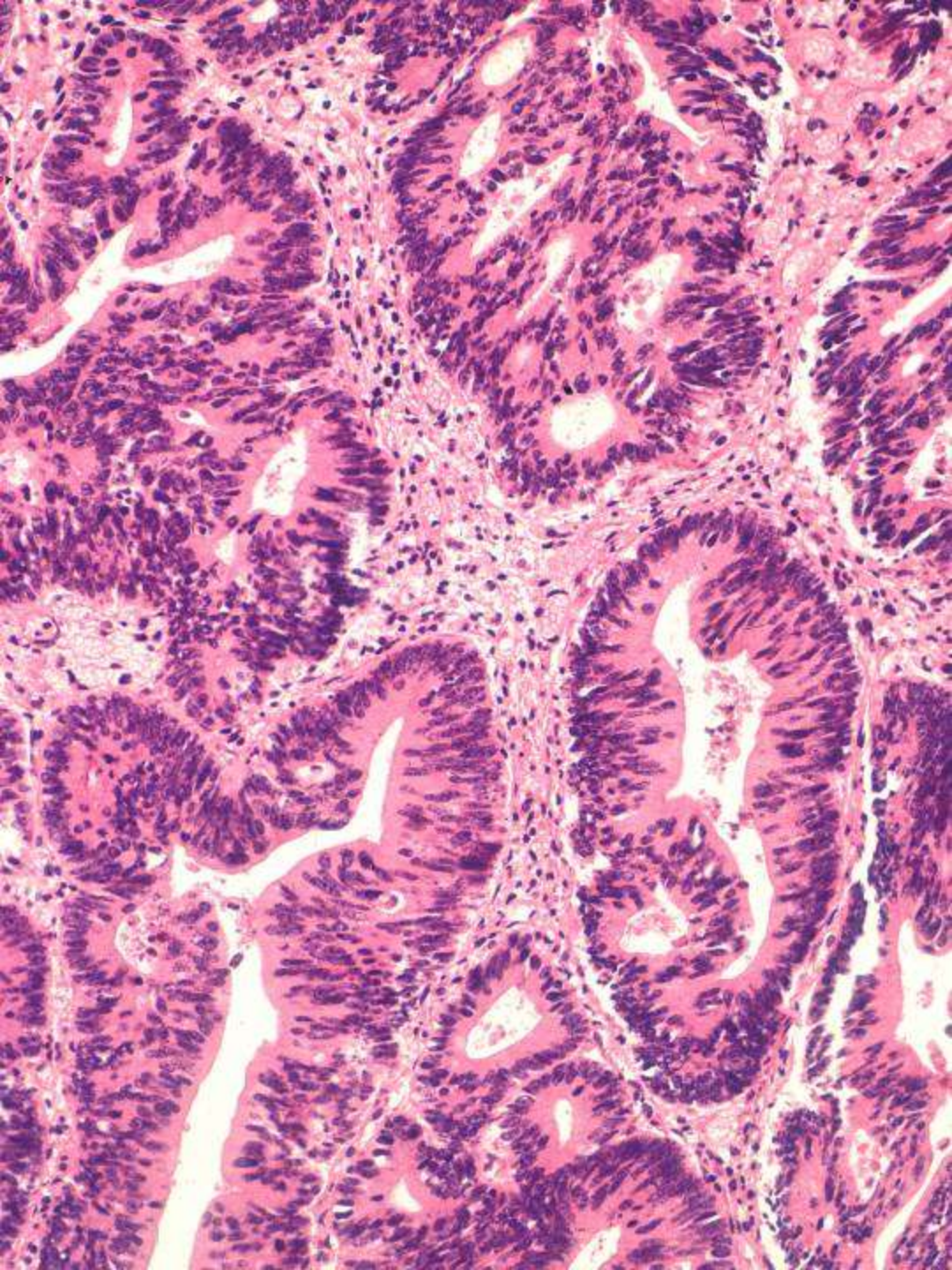
Terms To Avoid

- Adenoma with dysplasia
- Atypia
- Moderate dysplasia
- Carcinoma in situ



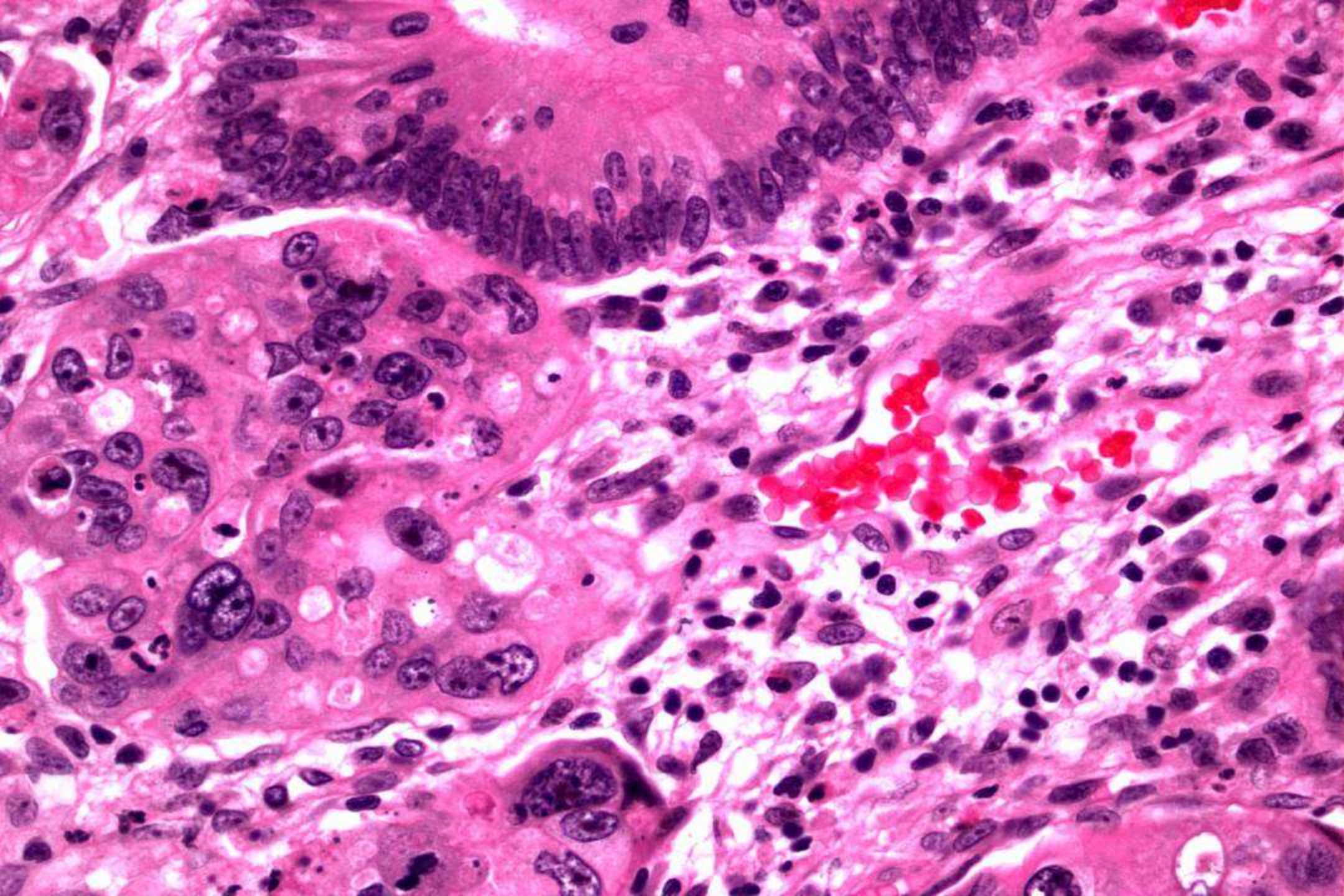


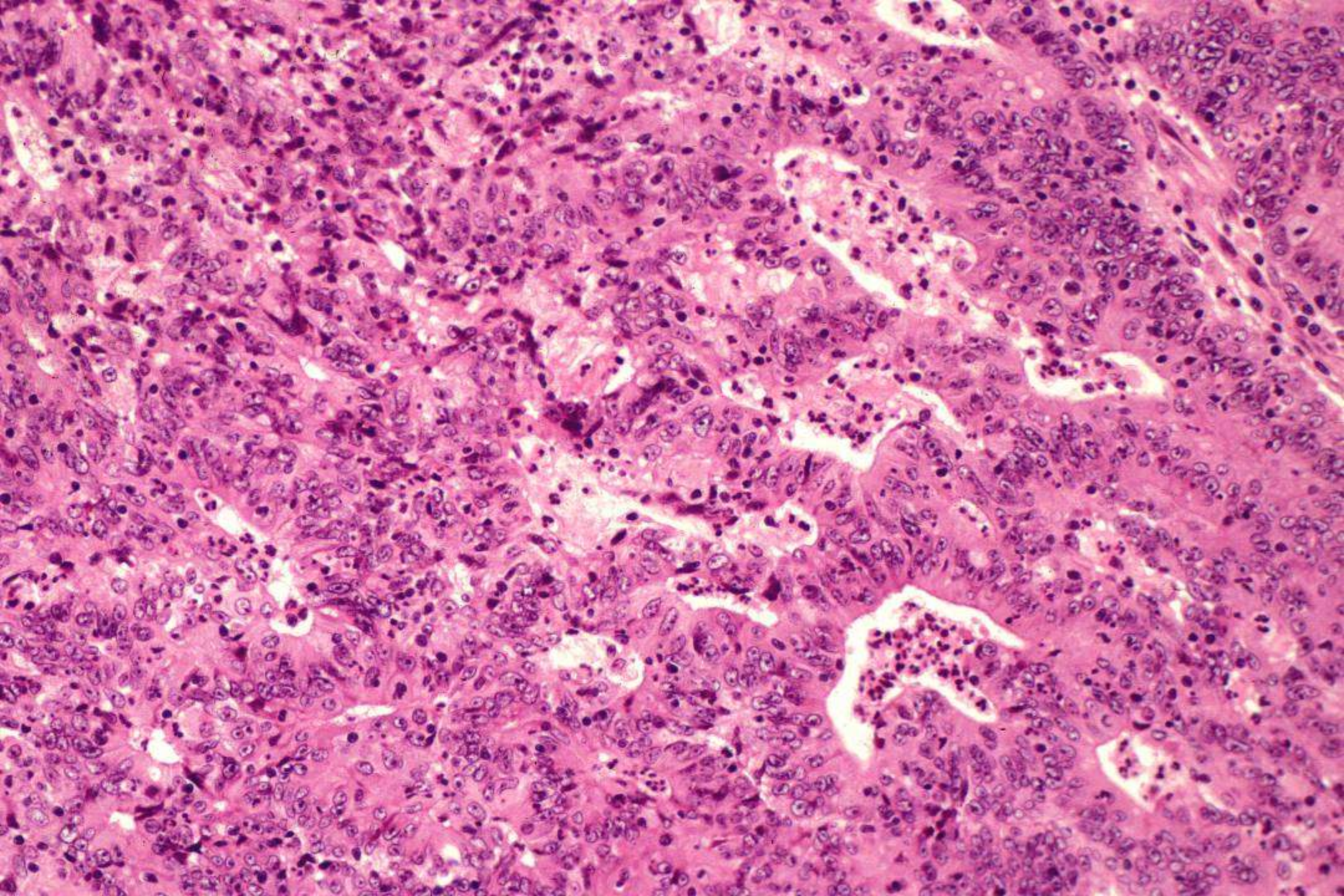


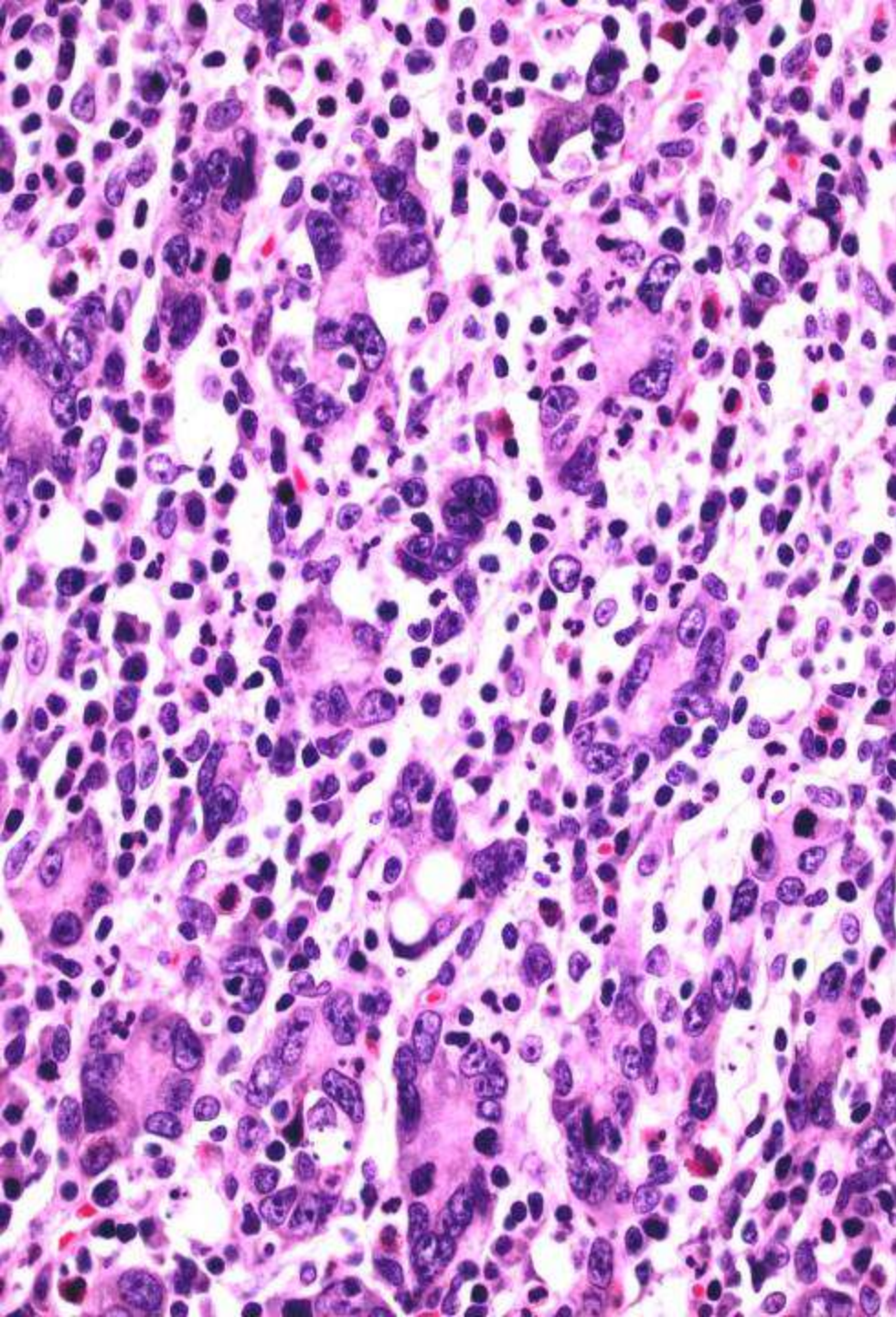


“Carcinoma In Situ”

- **Intraepithelial neoplasia**
- **No penetration of basement membrane**
- **Most severe form of high-grade dysplasia**

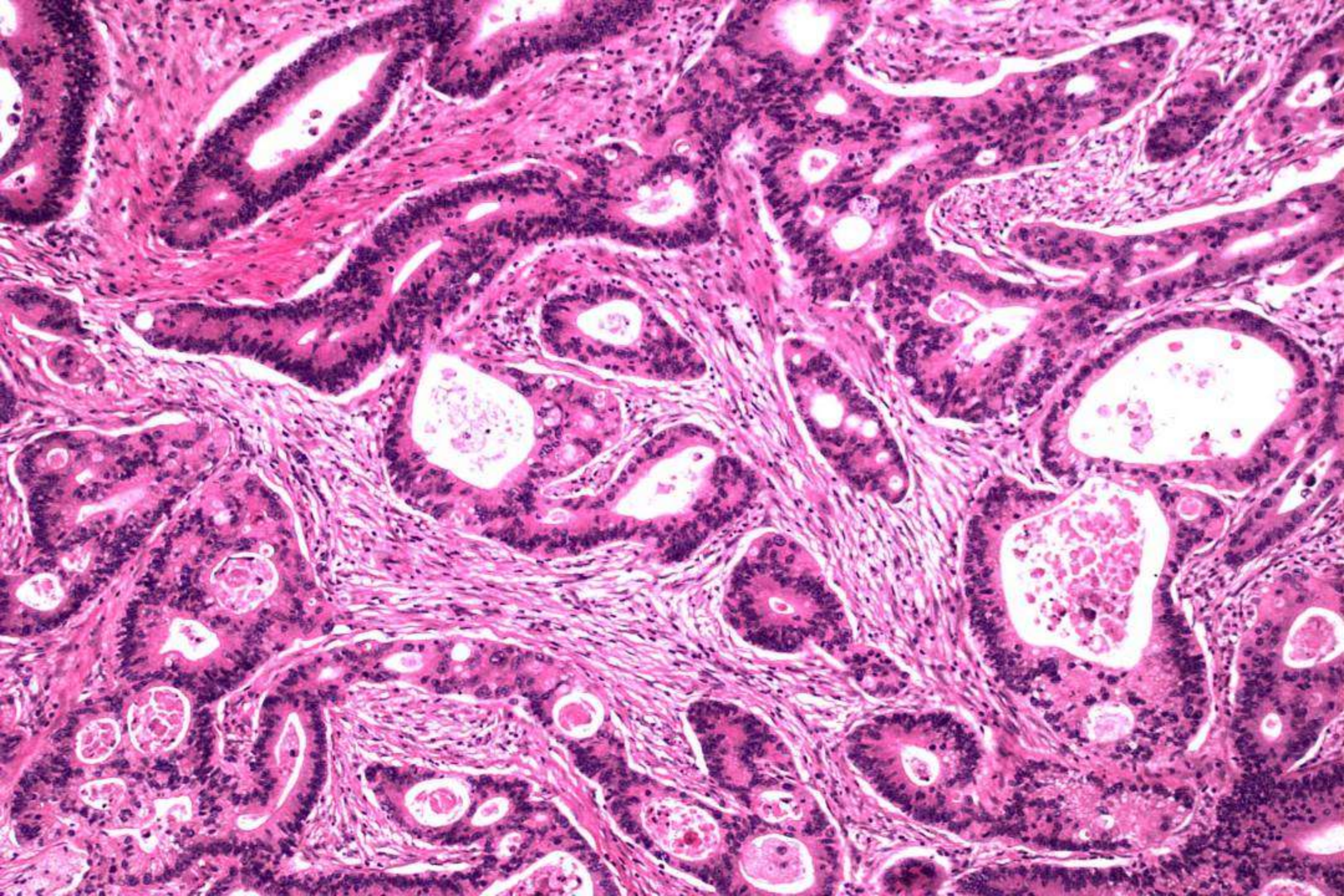






Intramucosal Adenocarcinoma

- **Penetration of BM**
 - **Lamina propria**
 - **Muscularis mucosae**
- **No stromal desmoplasia**
- **Recognized by architecture**
- **No lymphatics in colonic mucosa**

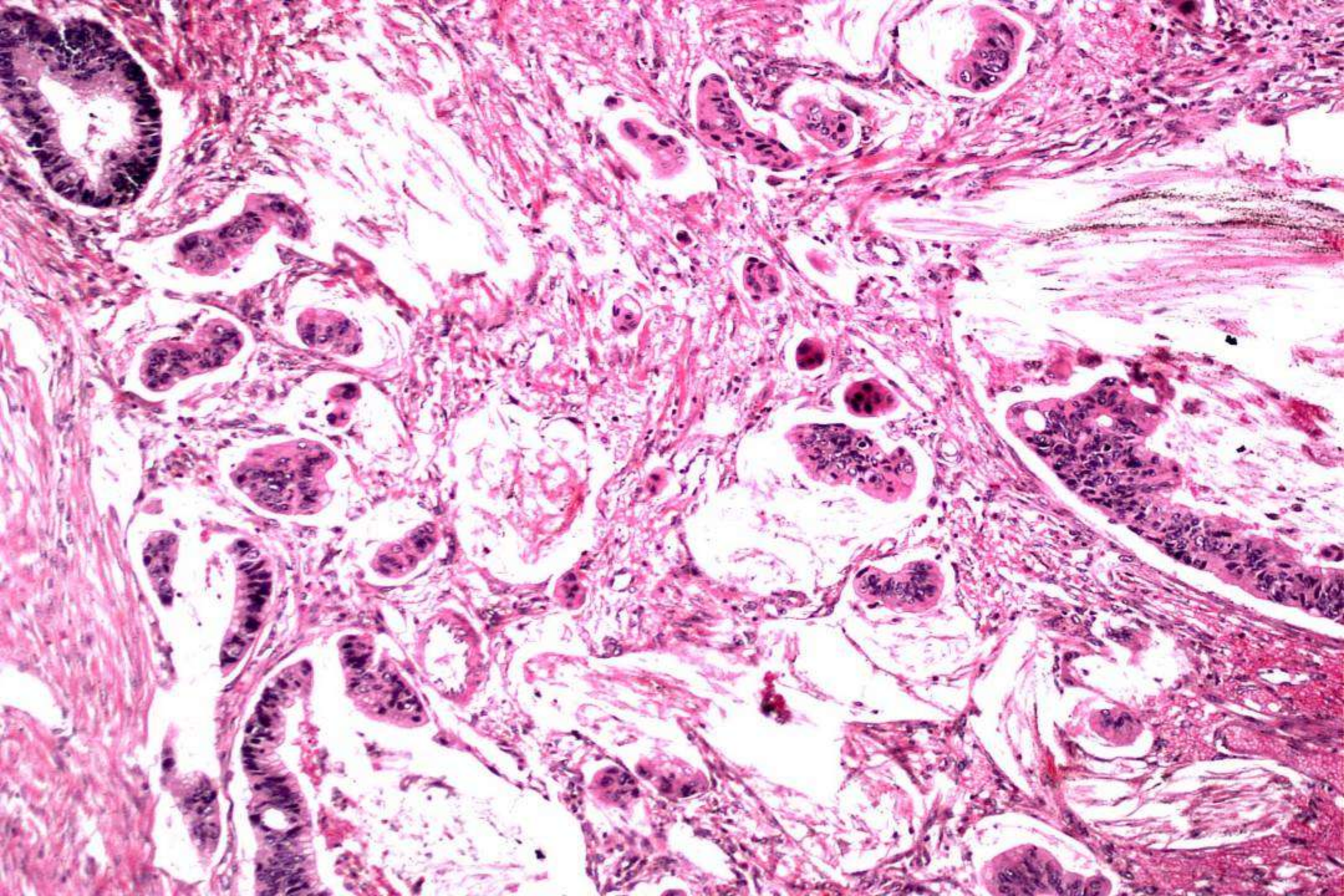




Malignant Colorectal Polyps

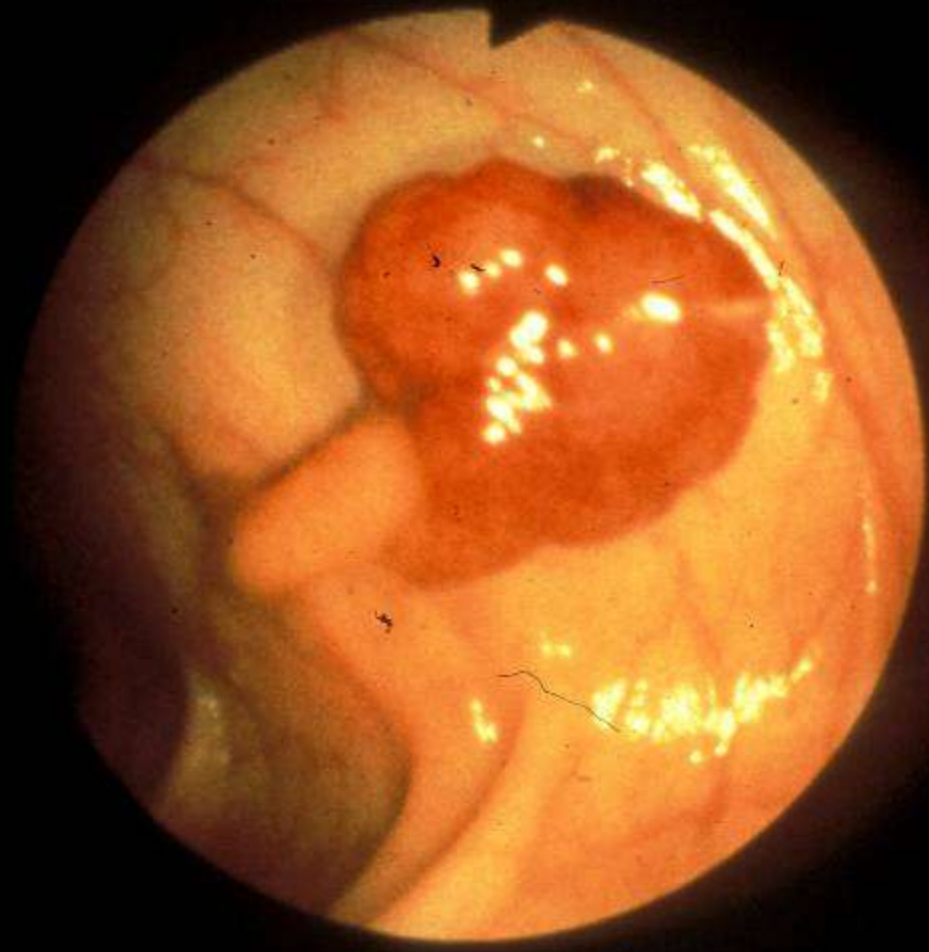
Critical Parameters

- **Differentiation of tumor**
- **Lymphatic invasion**
 - **too subjective (?CD31; ?deeper sections)**
 - **correlates with tumor differentiation and excision margin**
- **Polypectomy margin**
 - **can it be evaluated?**
 - **how close is too close? (2 mm, 1 mm, at margin)**



Completeness of Excision

- Pathologist has a **LIMITED ABILITY** to assess adequacy of excision
 - 5 μm slides viewed in 2 dimensions
 - Depends in large part on proper handling at time of gross evaluation











Completeness of Excision

- The endoscopist's opinion is the **MOST important**
 - **Assesses gross in 3 dimensions**
 - **Cauterizes base: additional 3-5 mm destroyed**
 - **Additional biopsies or EUS warranted in certain cases**

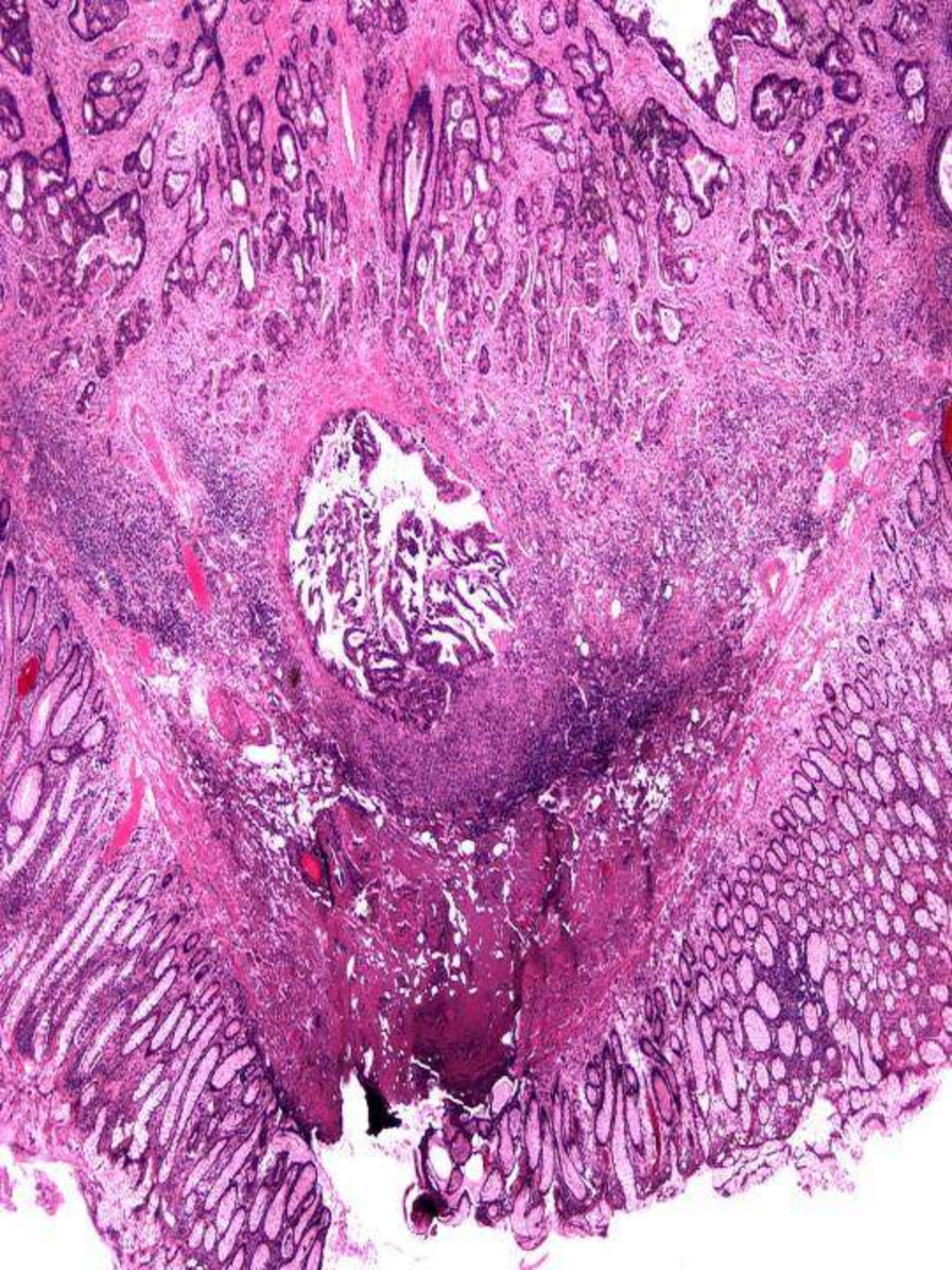
Predictive Factors of Nodal Metastasis

- **Poor differentiation**
- **Angiolymphatic invasion**
- **Incomplete resection**



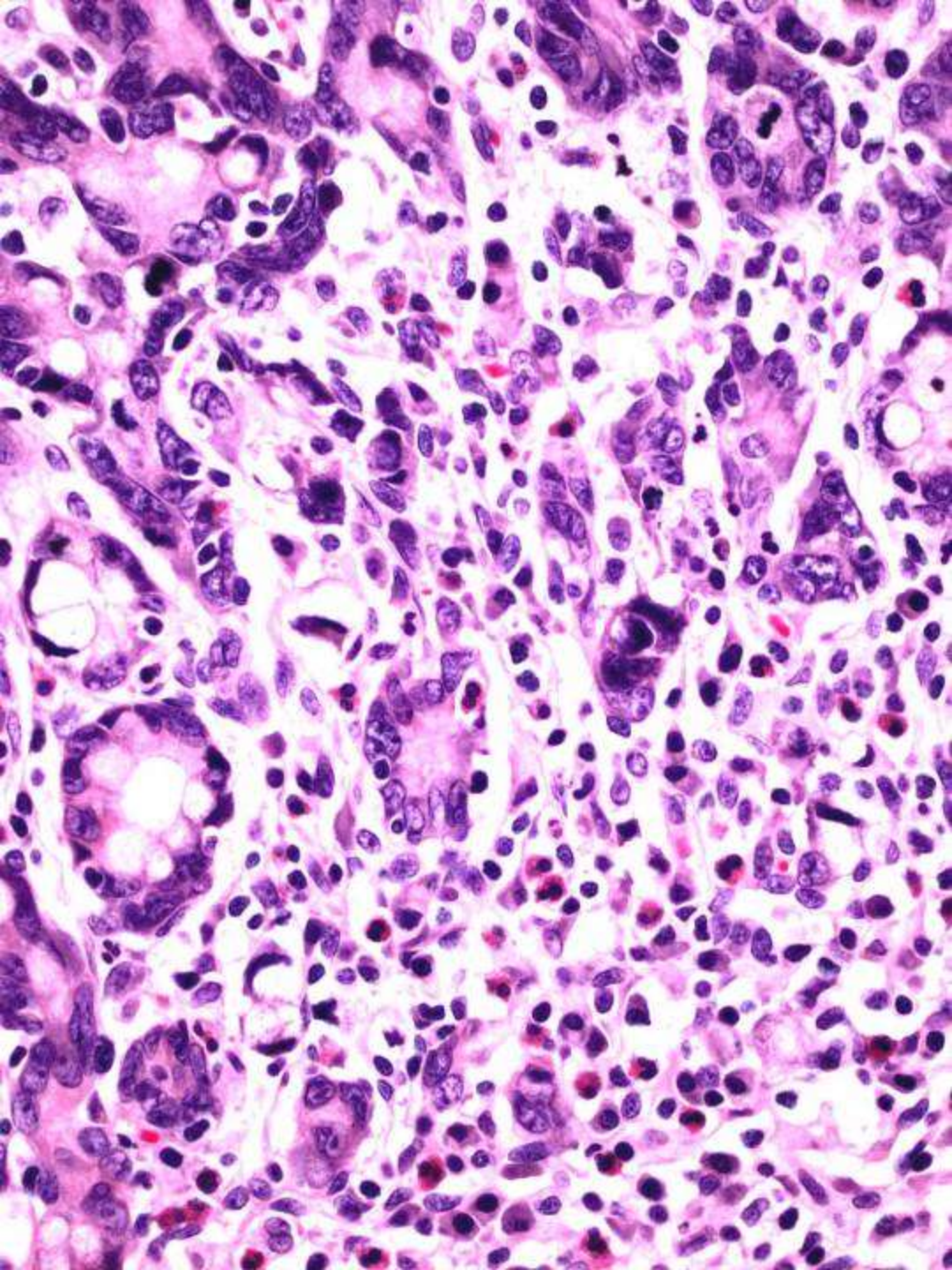
“Polyp at 40 cm”

- **Invasive moderately differentiated adenocarcinoma arising in an adenoma with high-grade dysplasia**
 - **Margin clearly visualized**
 - **Tumor approximately 2.2 mm from cauterized margin**
 - **No angiolymphatic invasion**



“Polyp at 40 cm”

- **Invasive moderately differentiated adenocarcinoma arising in an adenoma with high-grade dysplasia, incompletely excised**
 - **Margin clearly visualized**
 - **Tumor immediately at cauterized margin**
 - **No angiolymphatic invasion**



“Mass at 50 cm”

- **Diagnosis: at least intramucosal adenocarcinoma**
- **Comment: Although submucosal invasion is not seen in this specimen, the severity of the cytologic and architectural features, in conjunction with the endoscopic appearance of a mass, strongly suggest this could be adjacent to an invasive component.**

Conclusions

- Adenoma = dysplasia
- Simplify terminology
- Call it if you see it
- Don't call it if you don't see it
- Communicate with the endoscopist

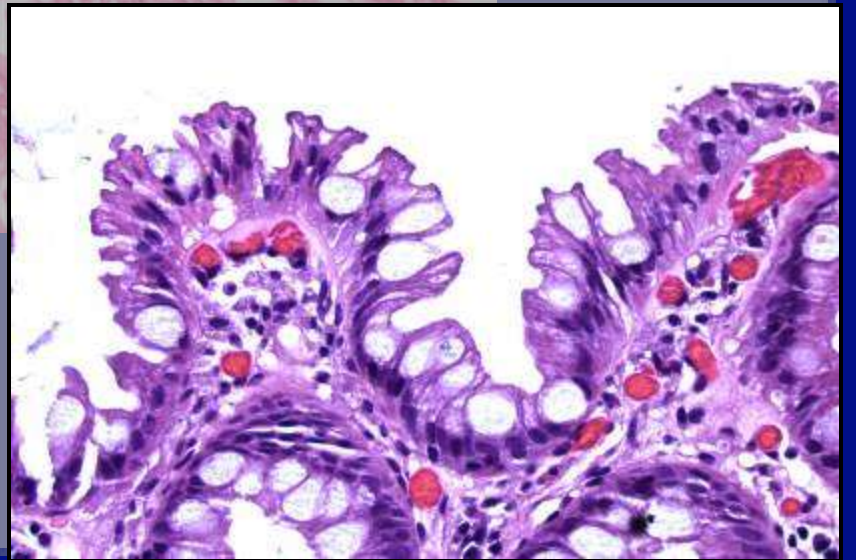
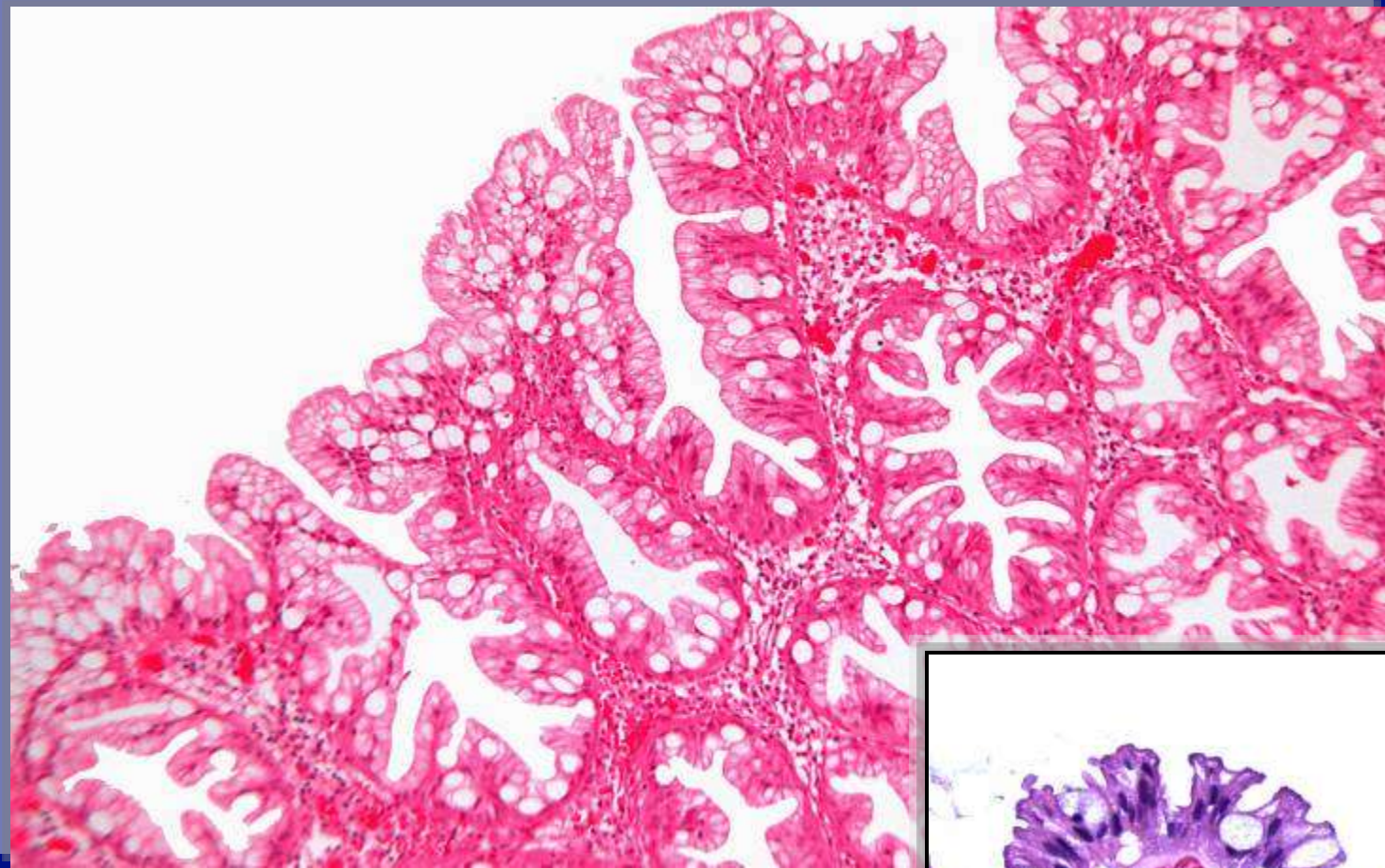
Serrated Polyps: WHO 2010

- **Hyperplastic polyp**
- **Sessile serrated polyp / adenoma (SSP/SSA)**
 - **SSP/SSA with cytological dysplasia**
- **Traditional serrated adenoma**

Terms To Avoid

- **Giant HP**
- **Atypical HP**
- **Large HP**
- **Mixed polyp**
- **Serrated adenoma**



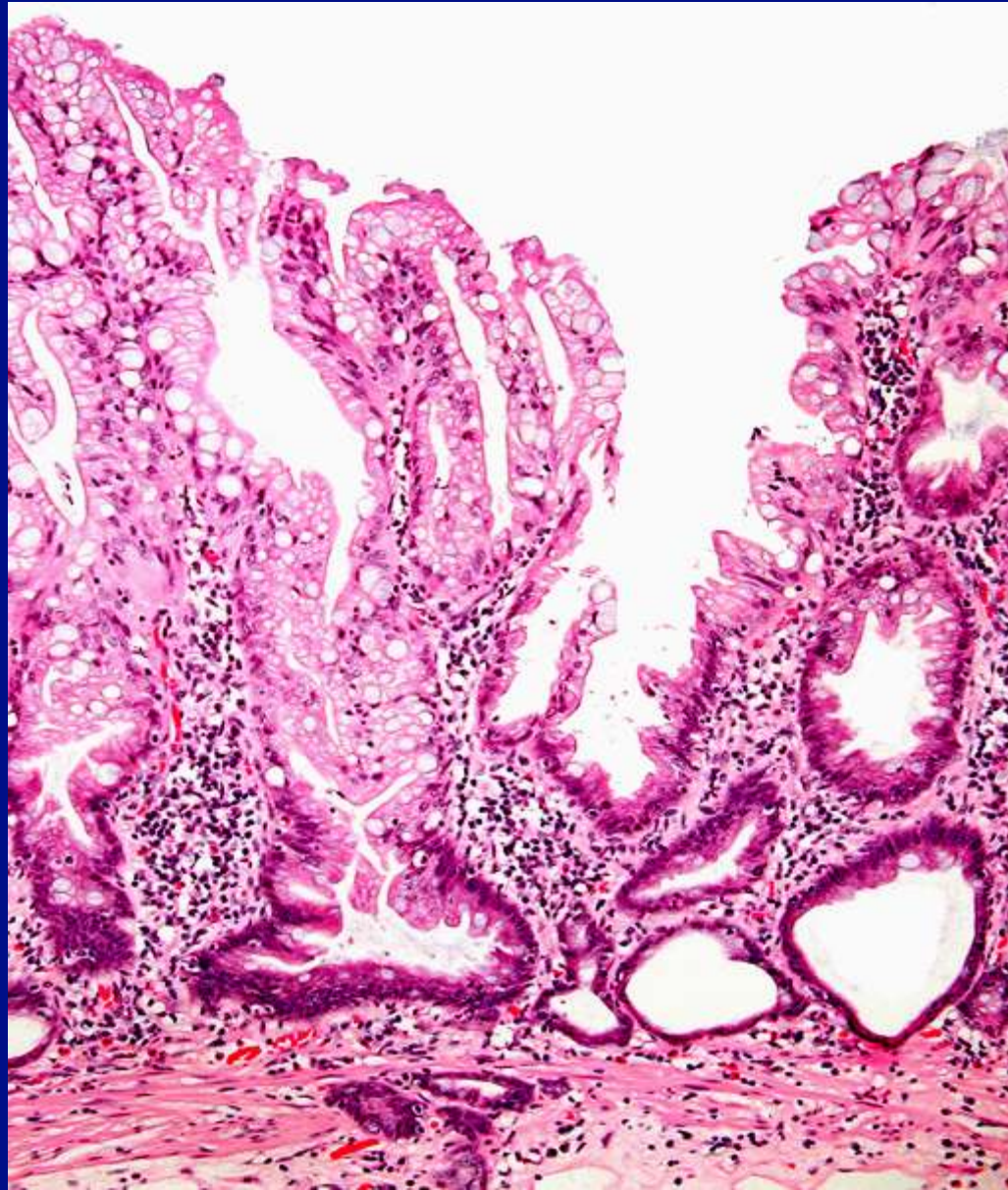


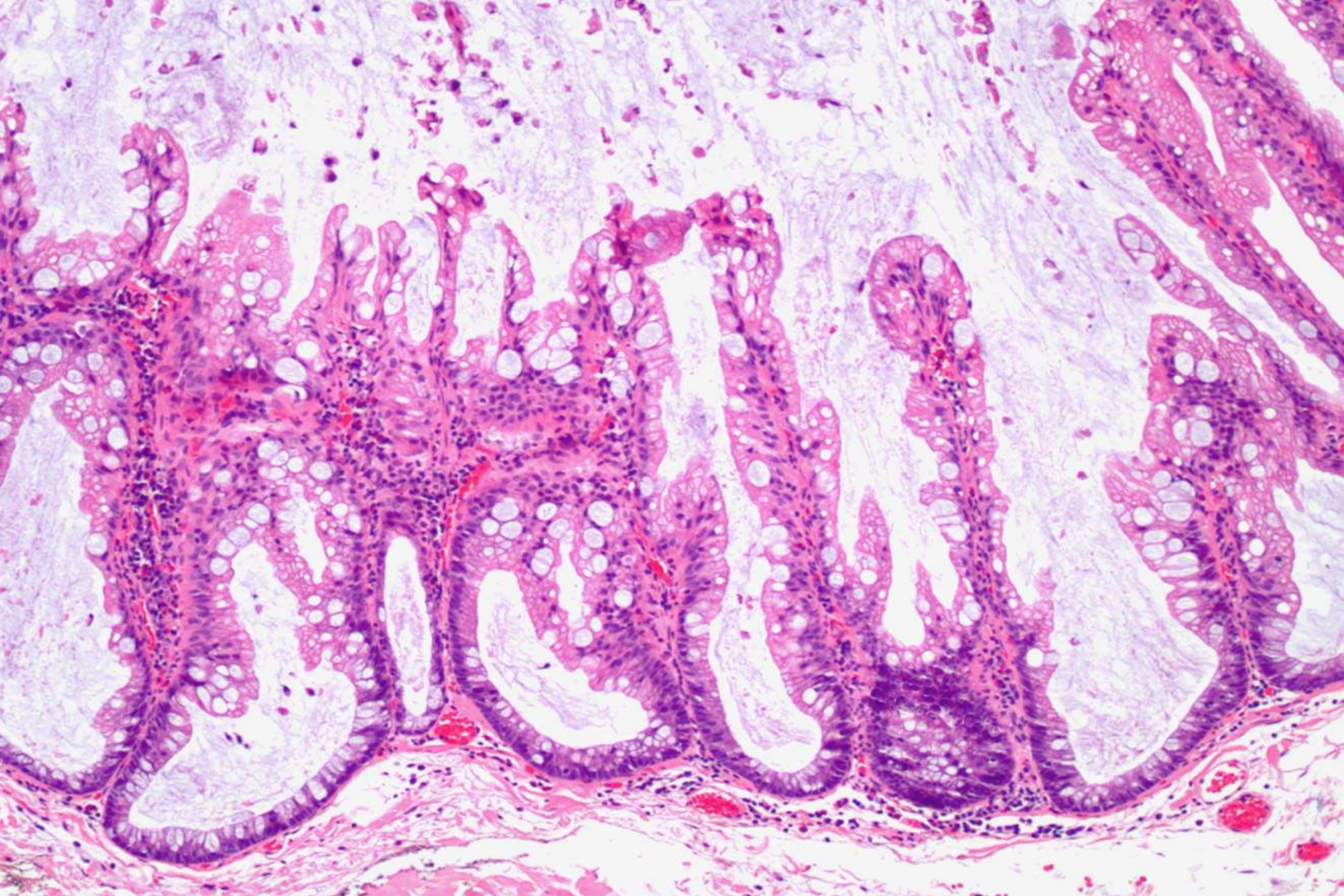
Sessile Serrated Polyp

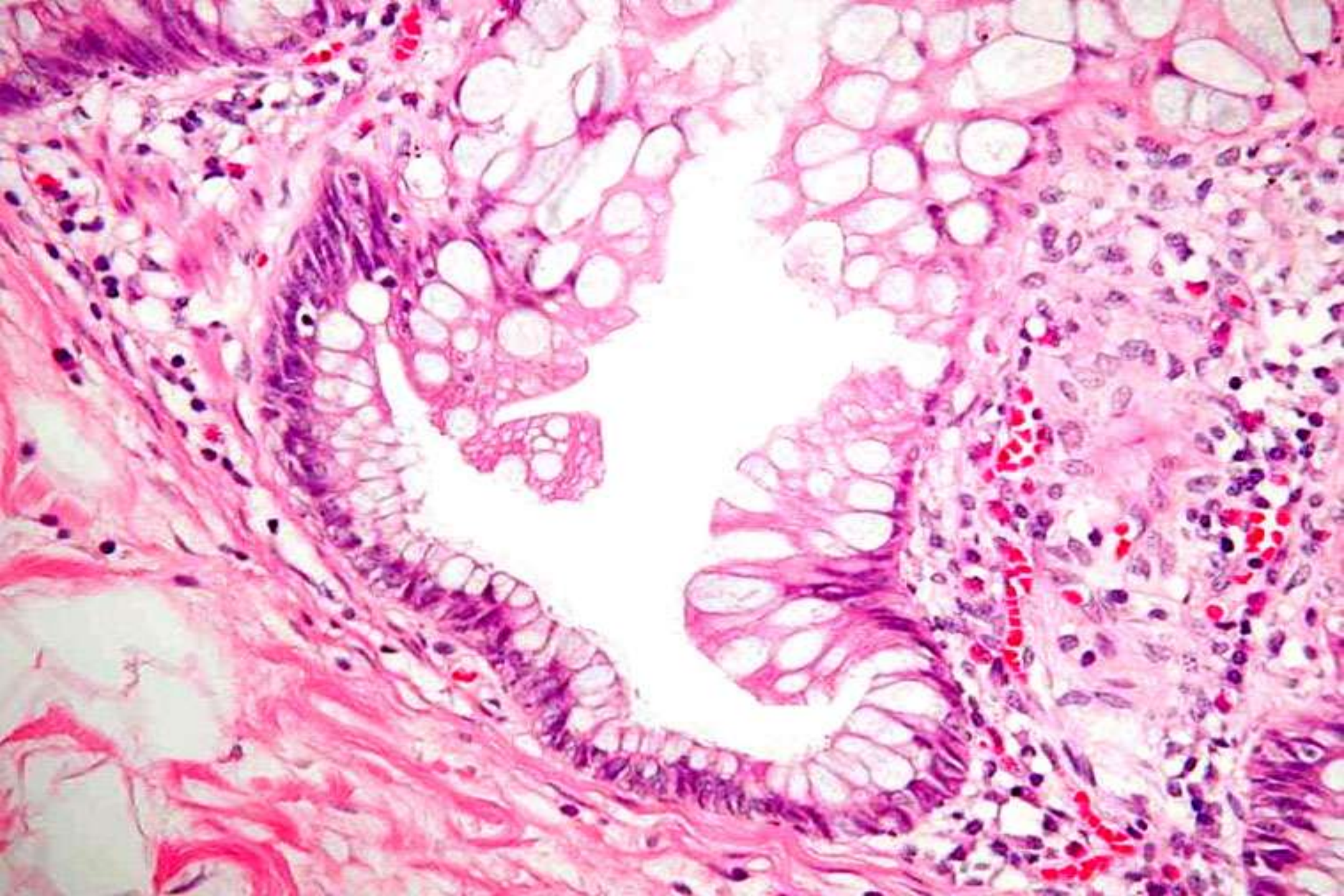
- Endoscopy
 - 9% screening colonoscopy
 - Smooth surface
 - Often mucus covered
 - Sessile growth pattern
 - Size
 - **50% >5mm**
 - **15-20% >10mm**



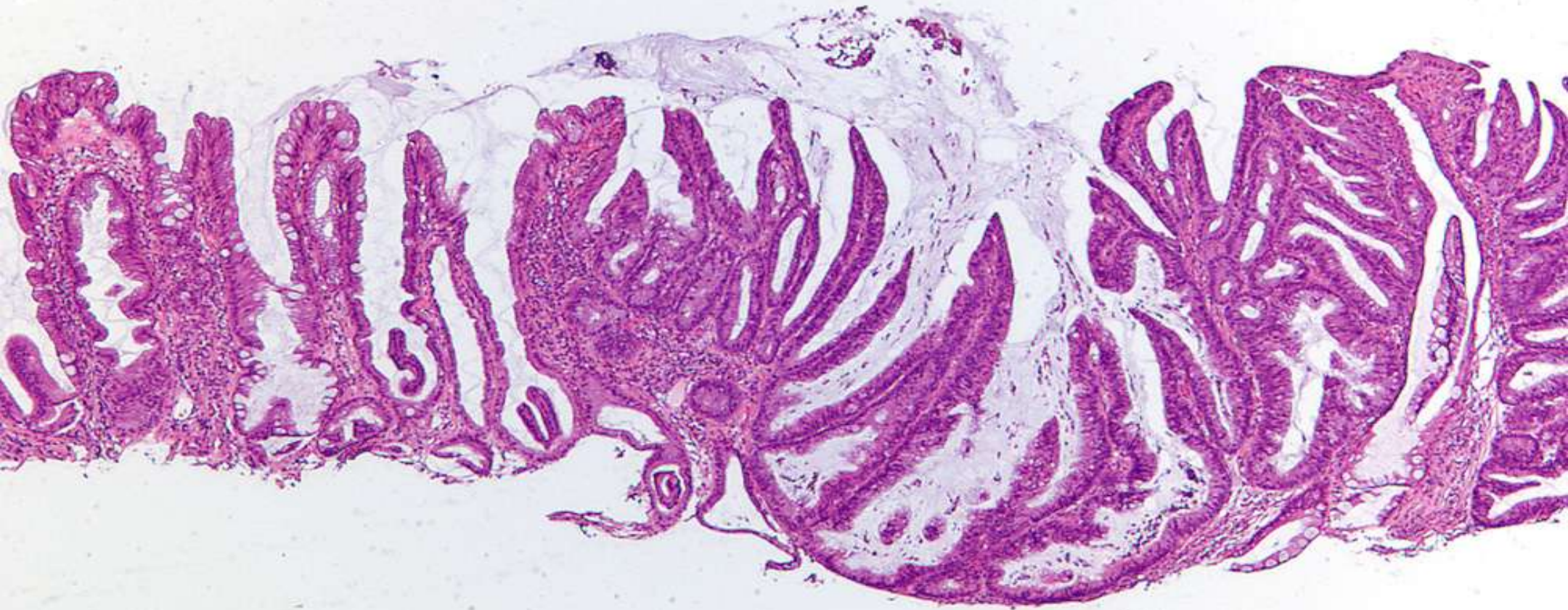
SSP: Architectural Alterations







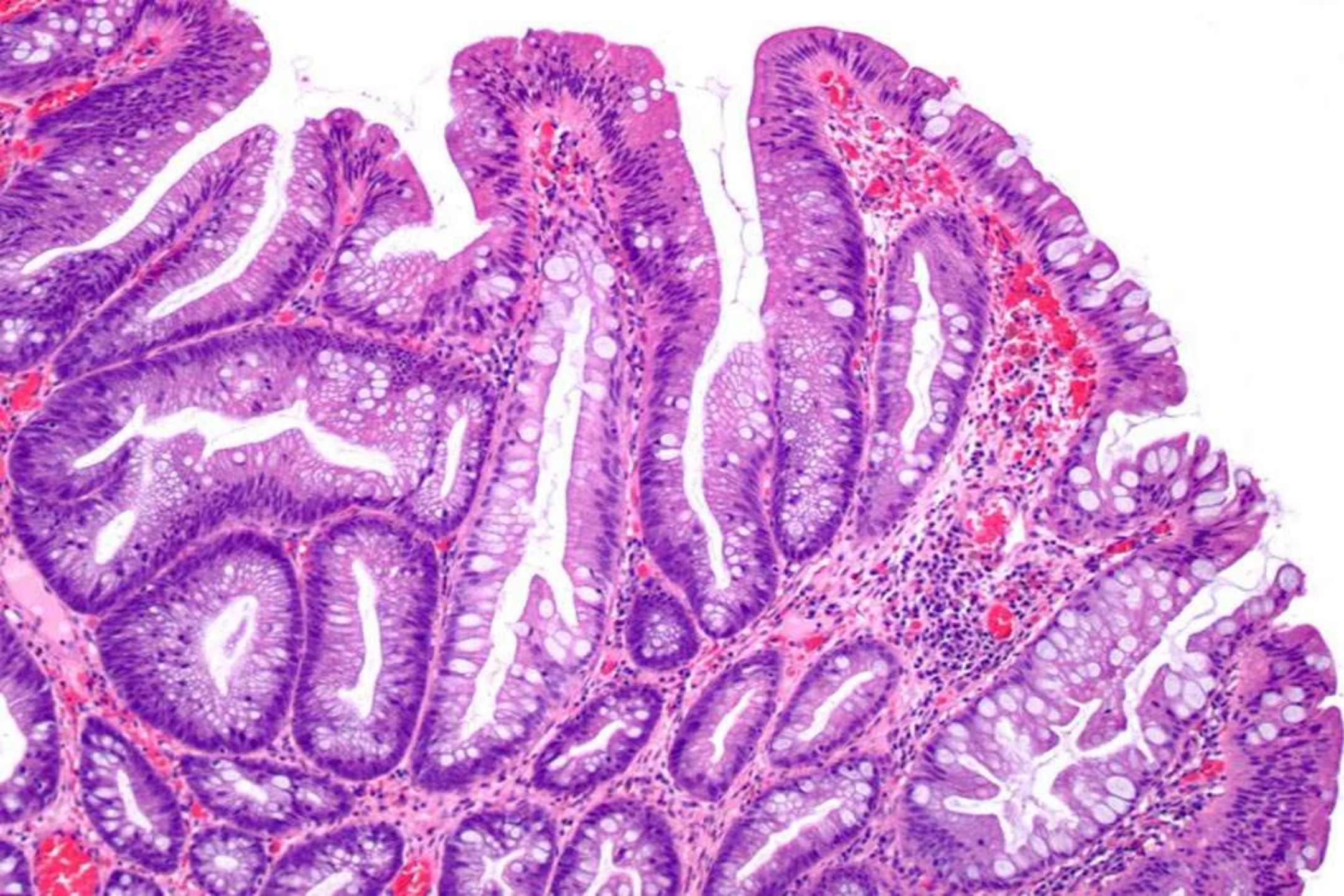
SSP with cytological dysplasia (Low-grade)

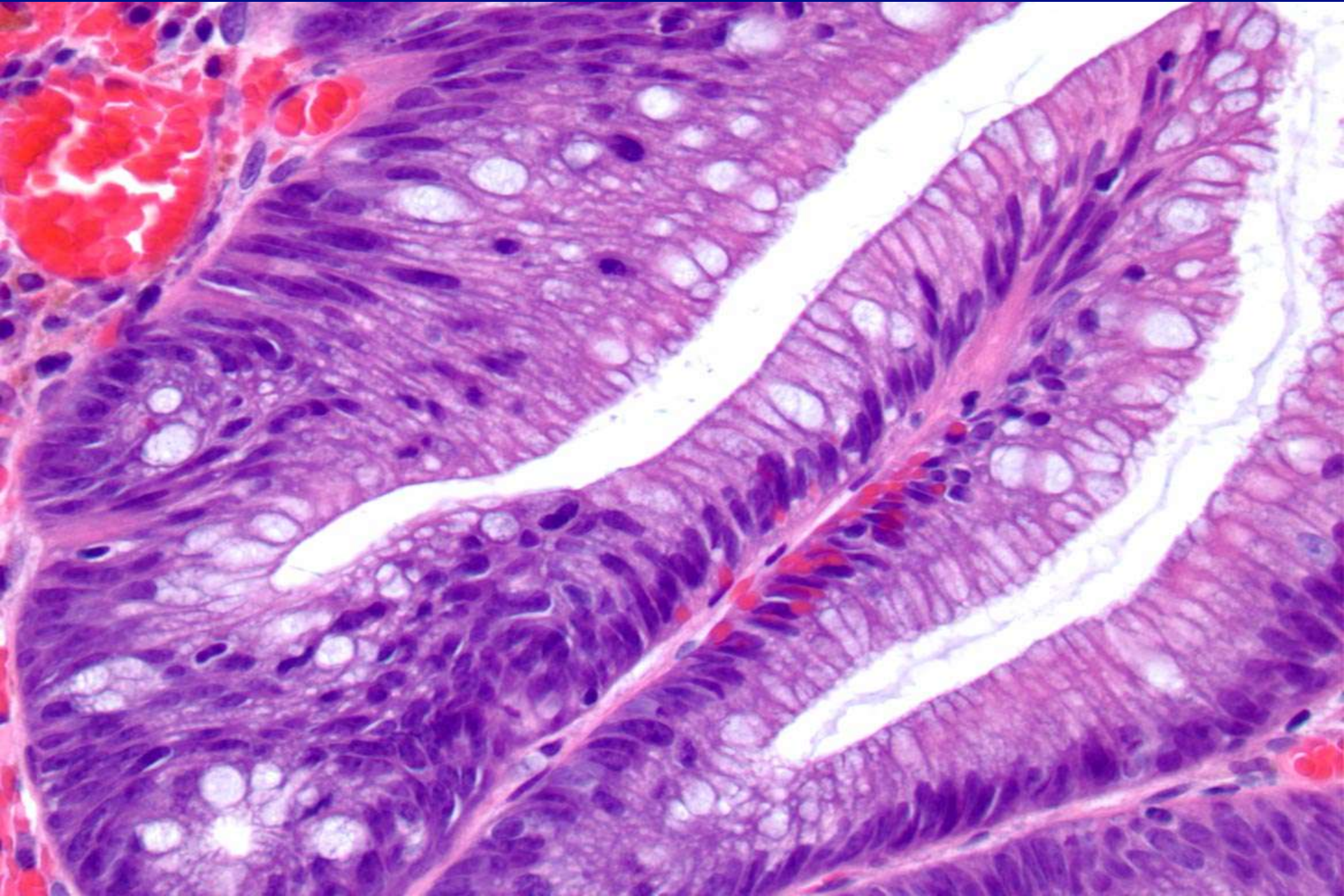


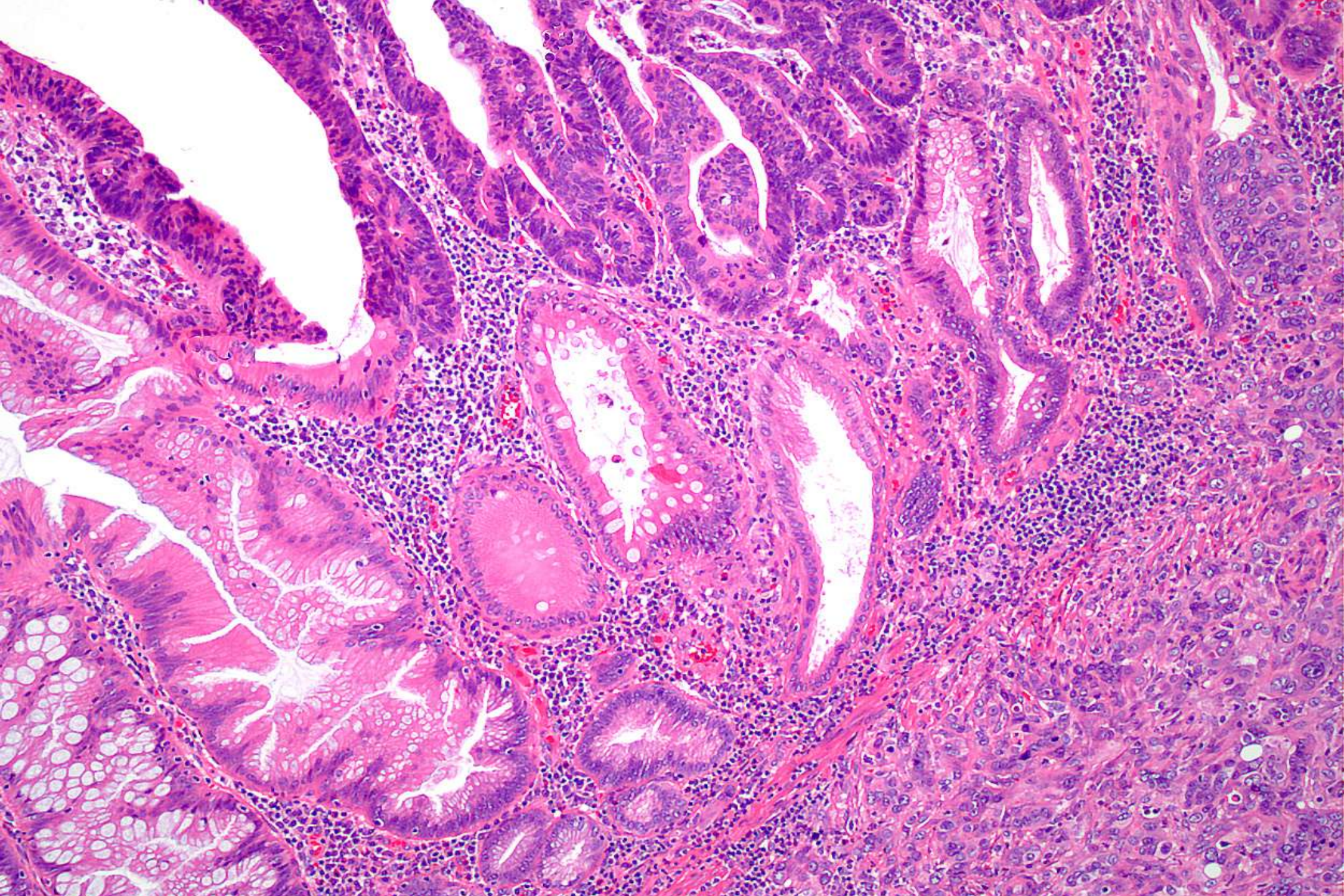
**Dysplasia resembles
conventional adenoma**

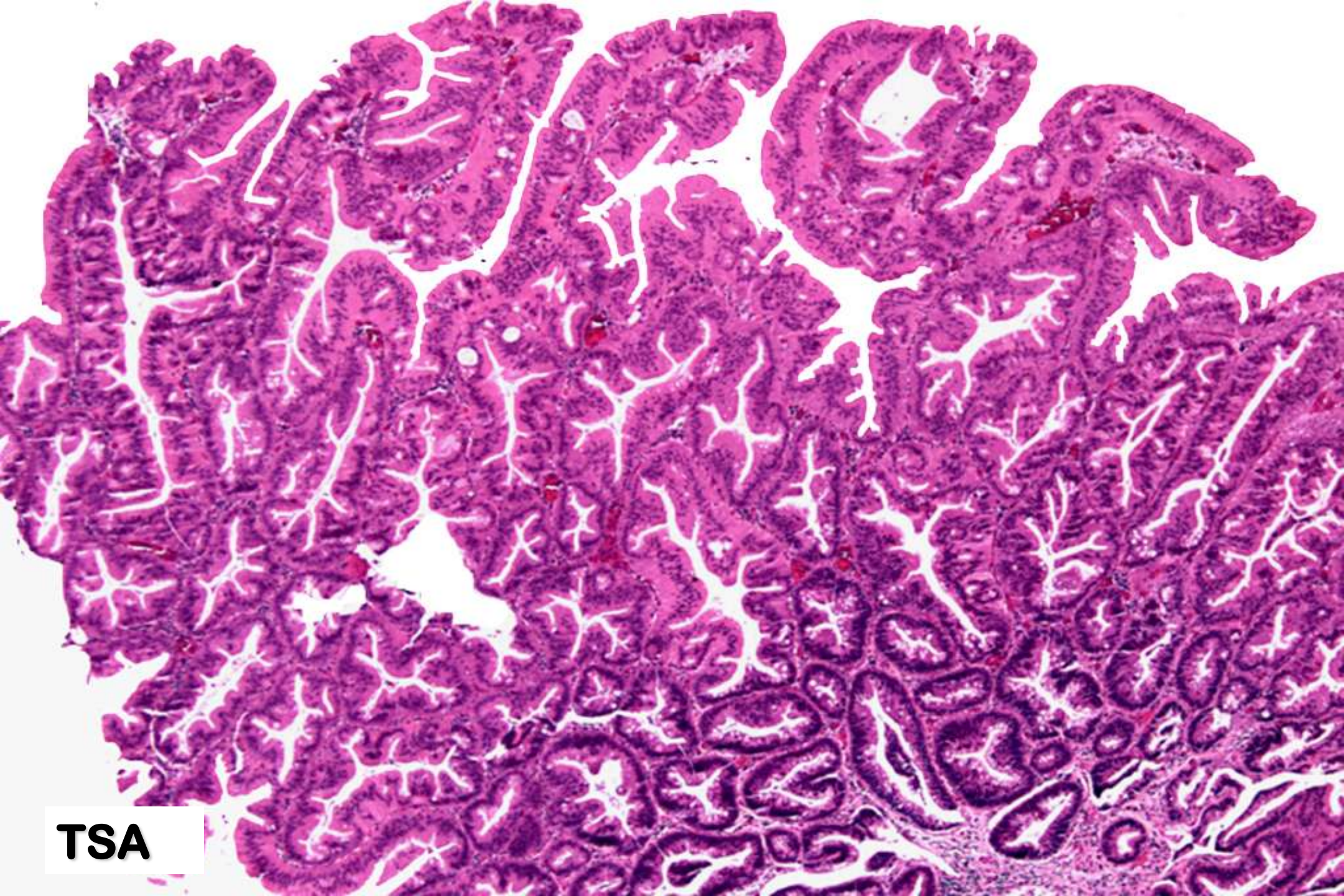
OR

“Serrated dysplasia”

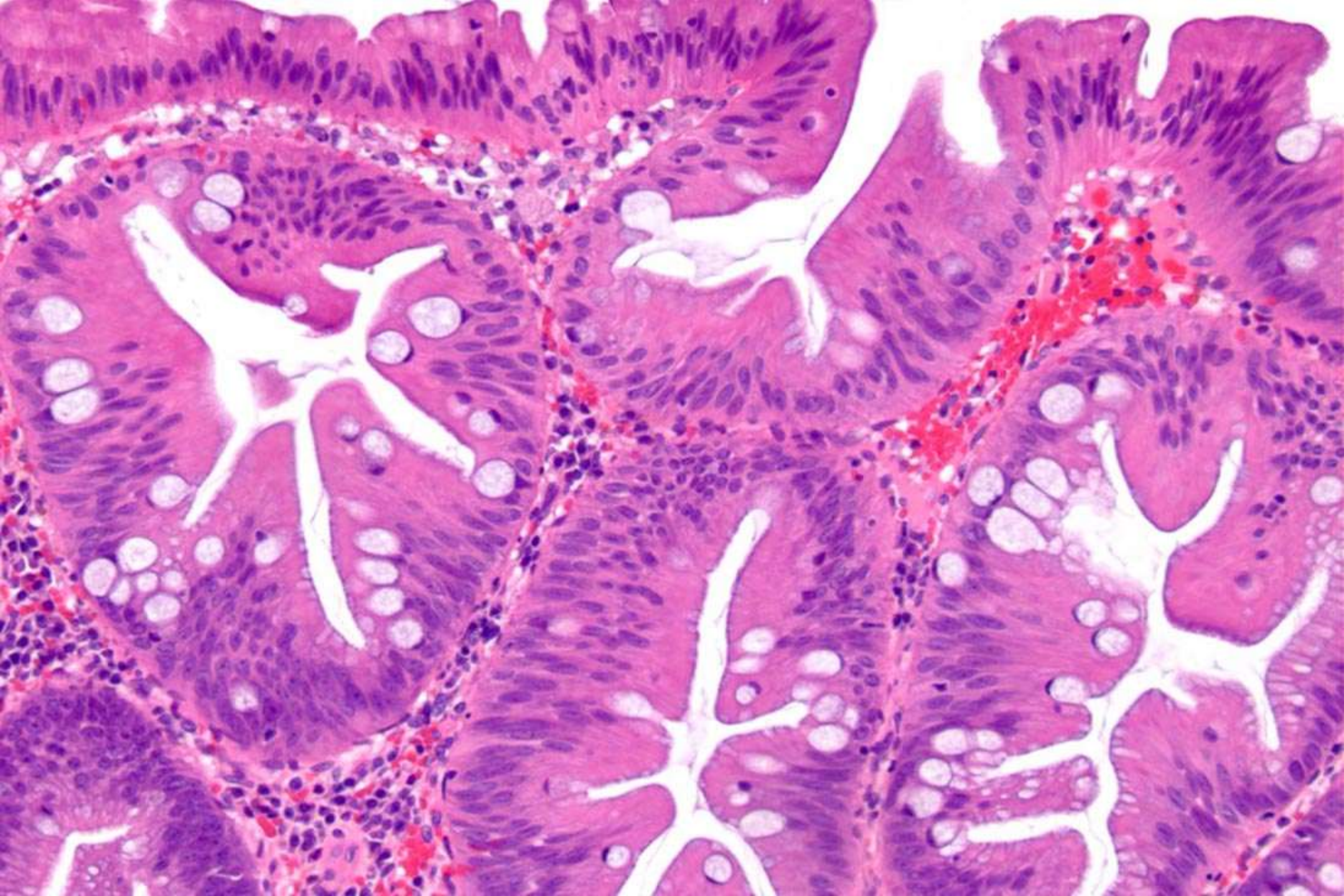








TSA



SSP Diagnosis Interobserver Concordance

Concordance on each category (κ value)			
Category	First round	Second	Third
TSA	0.81	0.78	0.83
SSP	0.45	0.32	0.49
HP	0.52	0.42	0.52
Overall	0.56	0.47	0.58

