Barrett's Esophagus

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Two Main Problems in Barrett's Pathology

- Over diagnosis of Barrett's esophagus
- Over diagnosis of *high-grade dysplasia*

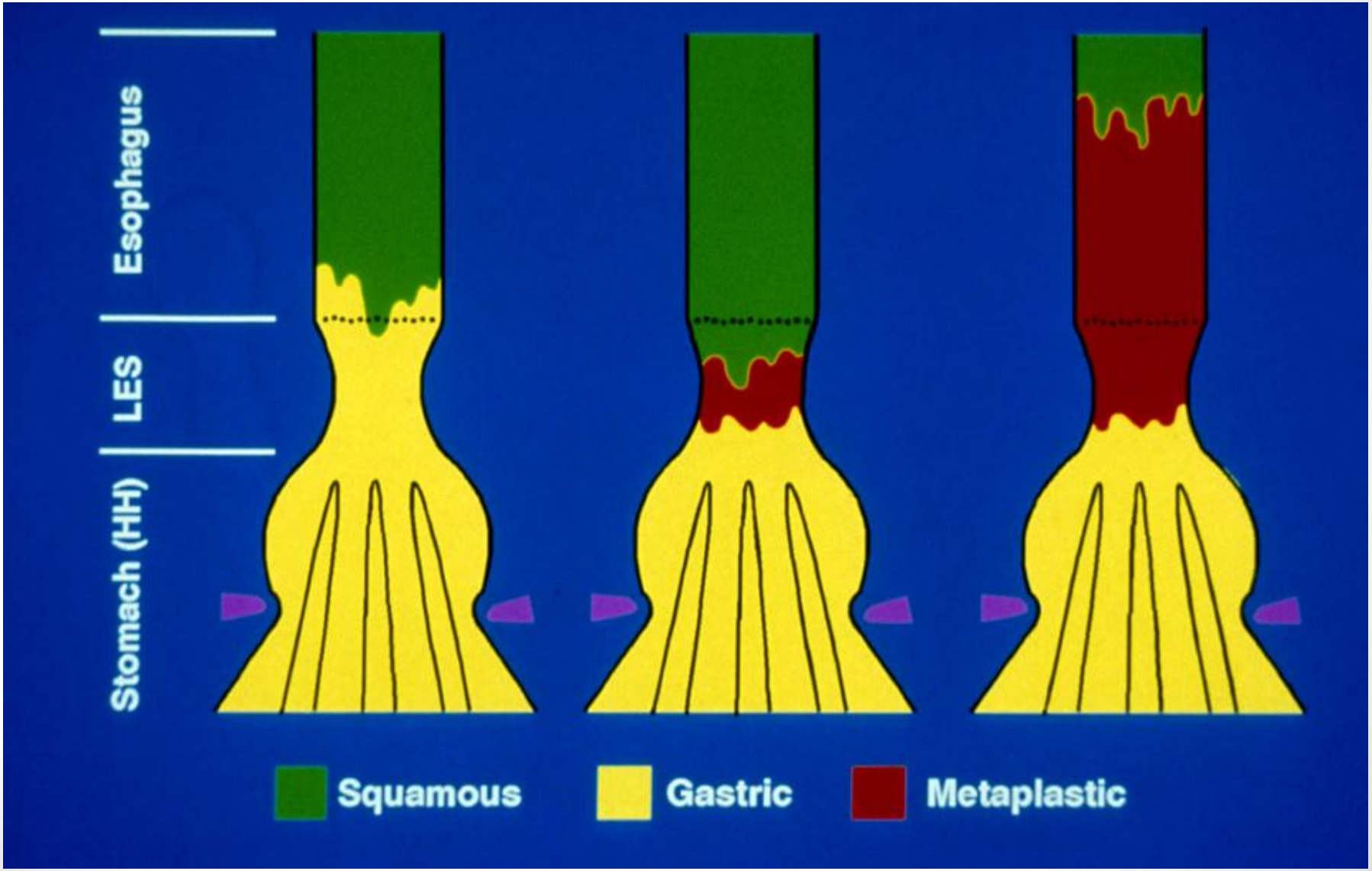
Barrett's Esophagus

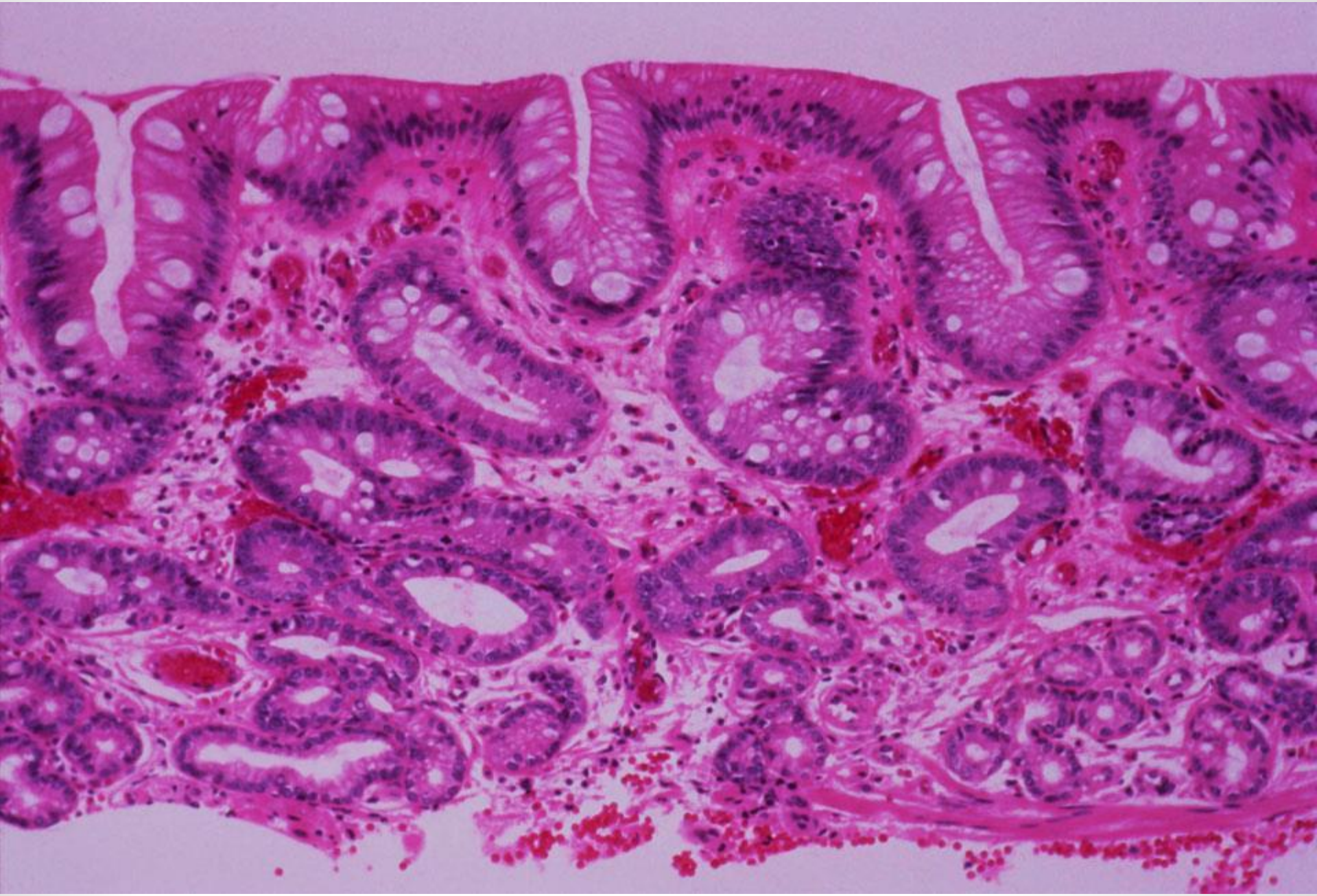
Definition: 2-Fold

- Endoscopically visible columnar epithelium in esophagus that on biopsy has:
- Metaplastic columnar epithelium, defined by goblet cells

ACG Practice guidelines. Am J Gastroenterol 2008;103:788

Barrett's Esophagus





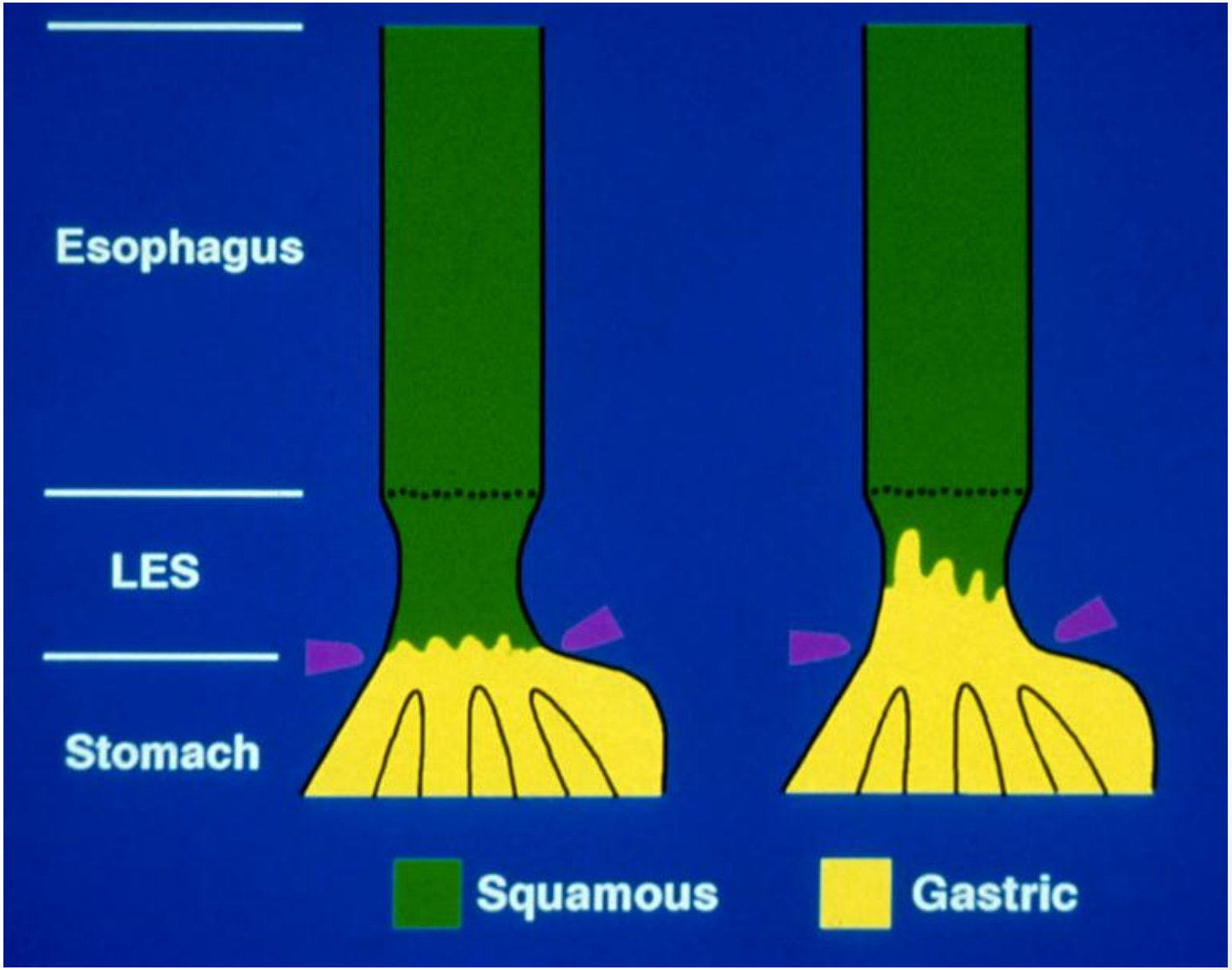
Questions in the Histologic Dx of Barrett's Esophagus

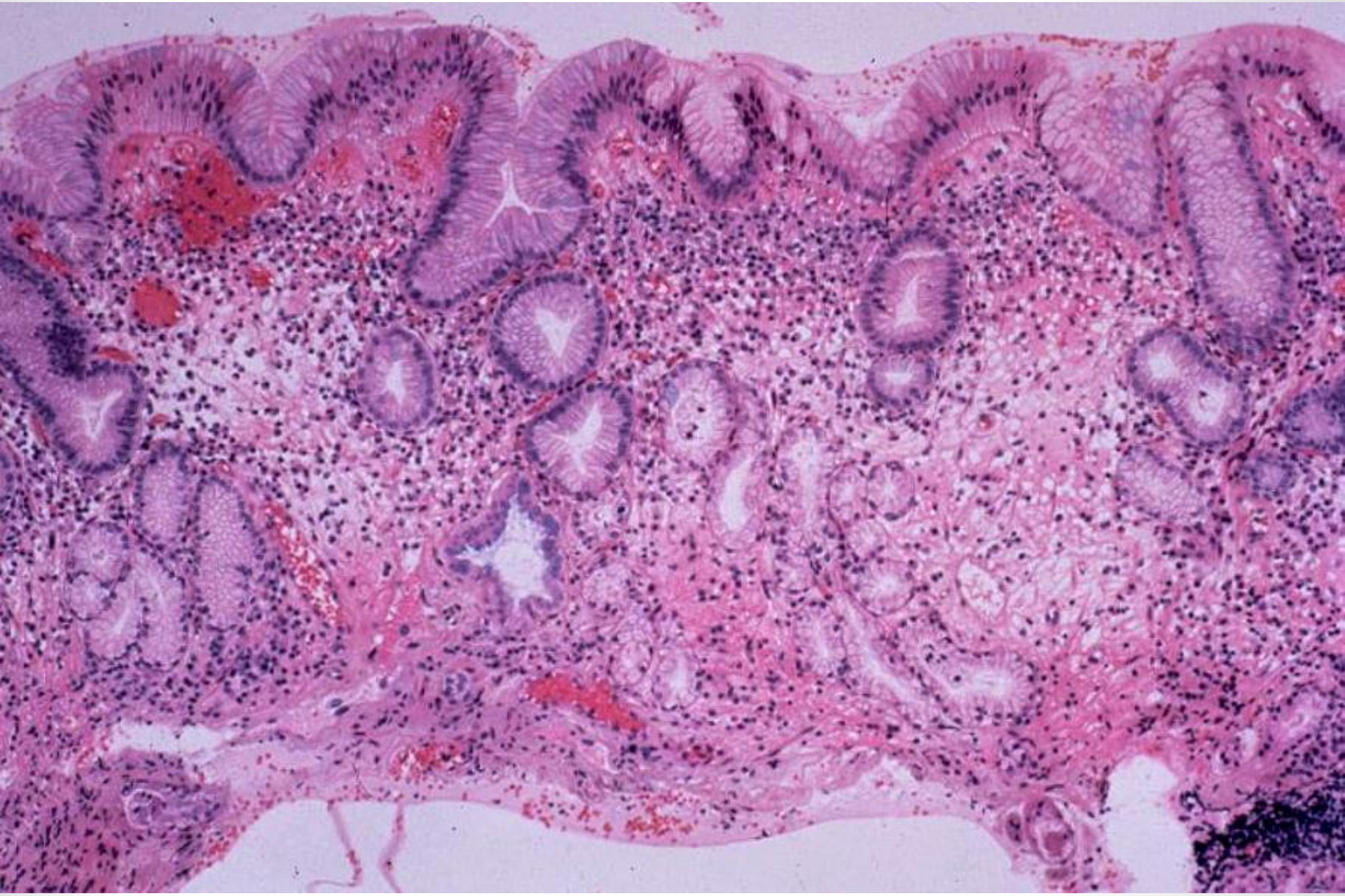
- Is it Barrett's or normal columnar epithelium in the esophagus?
- Are all goblet-like cells metaplastic?
- Does Alcian blue positivity = metaplasia?
- How much metaplastic epithelium is needed to diagnose Barrett's?

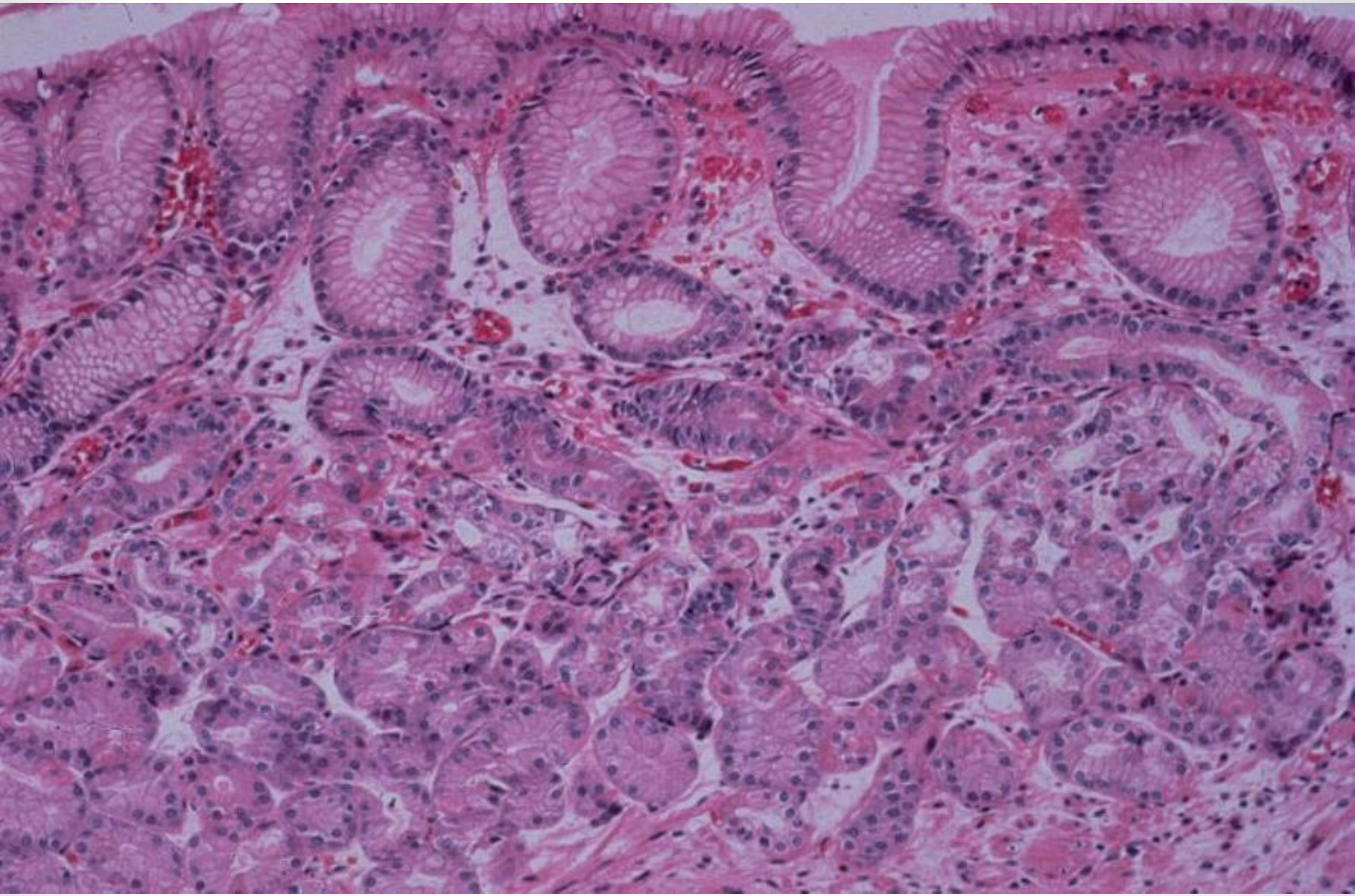
Columnar Epithelium in the Esophagus May Be Normal

- The S-C junction (Z-line) may be irregular with “tongues” of columnar epithelium in the esophagus, or
- The entire S-C junction may lie within the esophagus

Normal Esophagus







Any Columnar vs. Goblet Barrett's??

300,000,000 Americans

100,000,000 GERD

with columnar mucosa

4,000,000 Barrett's with goblets

16,000 annual Barrett's CA

Esophageal Adenocarcinoma

Should we screen

100,000,000 “any columnar/gastric” Barrett’s?

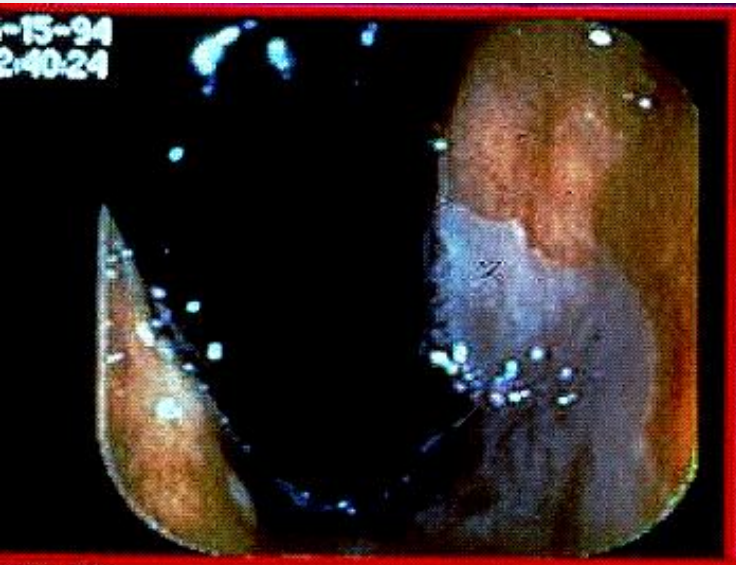
OR

4,000,000 with goblet-cell Barrett’s?

Noto bene: Even using the goblet Barrett’s definition, screening is ineffective!

Questions in the Histologic DX of Barrett's Esophagus

- Is it Barrett's or normal columnar epithelium in the esophagus?
- How much metaplastic epithelium is needed to diagnose Barrett's?



TURNAROUND IN THE STOMACH

FORCEP STRADDLING SQUAMO-
COLUMNAR JUNCTION

Significance of Few Metaplastic Glands Unknown

- Prevalence as high as 30%
- No good evidence of cancer predisposition
- Avoid Barrett's diagnosis, instead use: "Focal Intestinal Metaplasia"

  (personal opinion)

How Much Metaplastic Epithelium is Needed to Diagnose Barrett's?

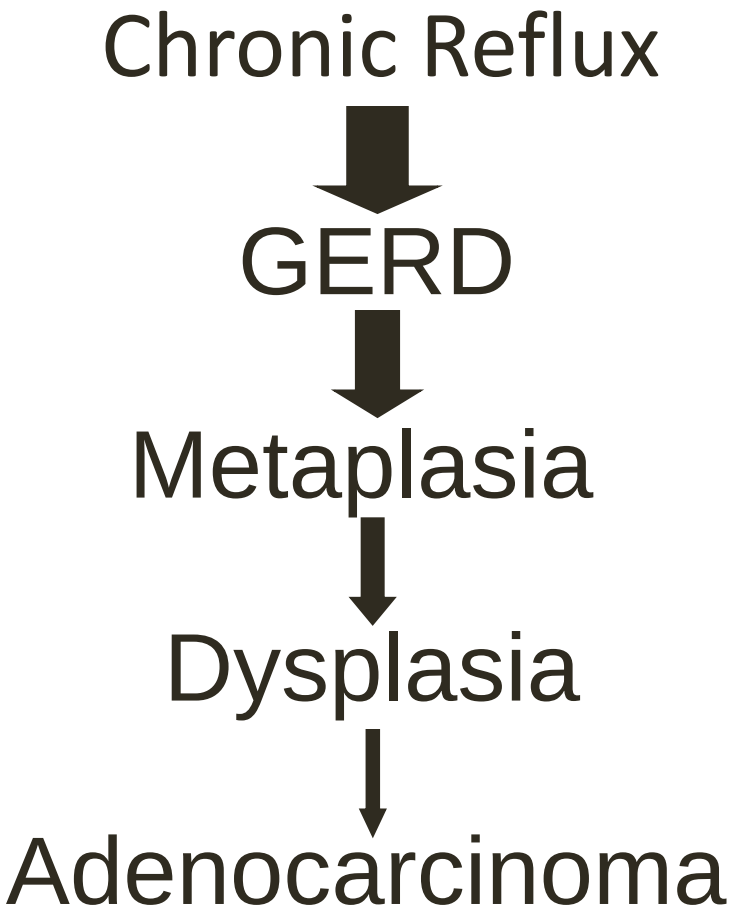
- No one knows! But,
- If only rare glands – I diagnose intestinal metaplasia
- Intestinal glands replacing biopsy -- consider diagnosing Barrett's

Case

- History: 72-yr-old man with long-standing reflux & Barrett's esophagus
- Endosc: 8 cm Barrett's segment; no mass lesions
- Bxs: 4 quadrant every 2 cm to rule out dysplasia

Barrett's Esophagus with Dysplasia

Neoplastic Progression in Barrett's Esophagus



Dysplasia

Definition

Neoplastic epithelium confined within the basement membrane of the gland within which it arose

Grading System for Dysplasia

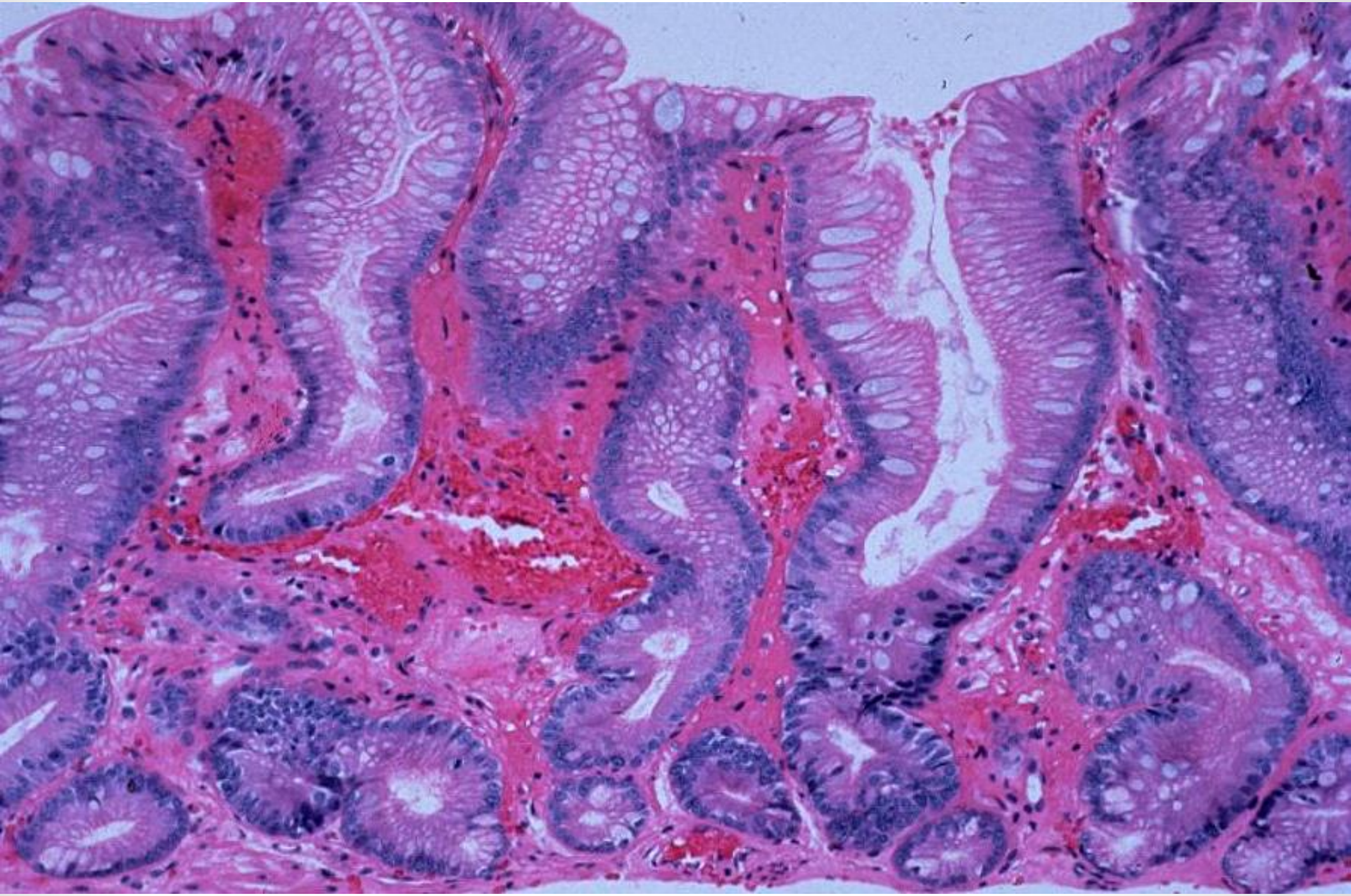
- Negative
- Indefinite
- Positive
  - Low-grade
  - High-grade

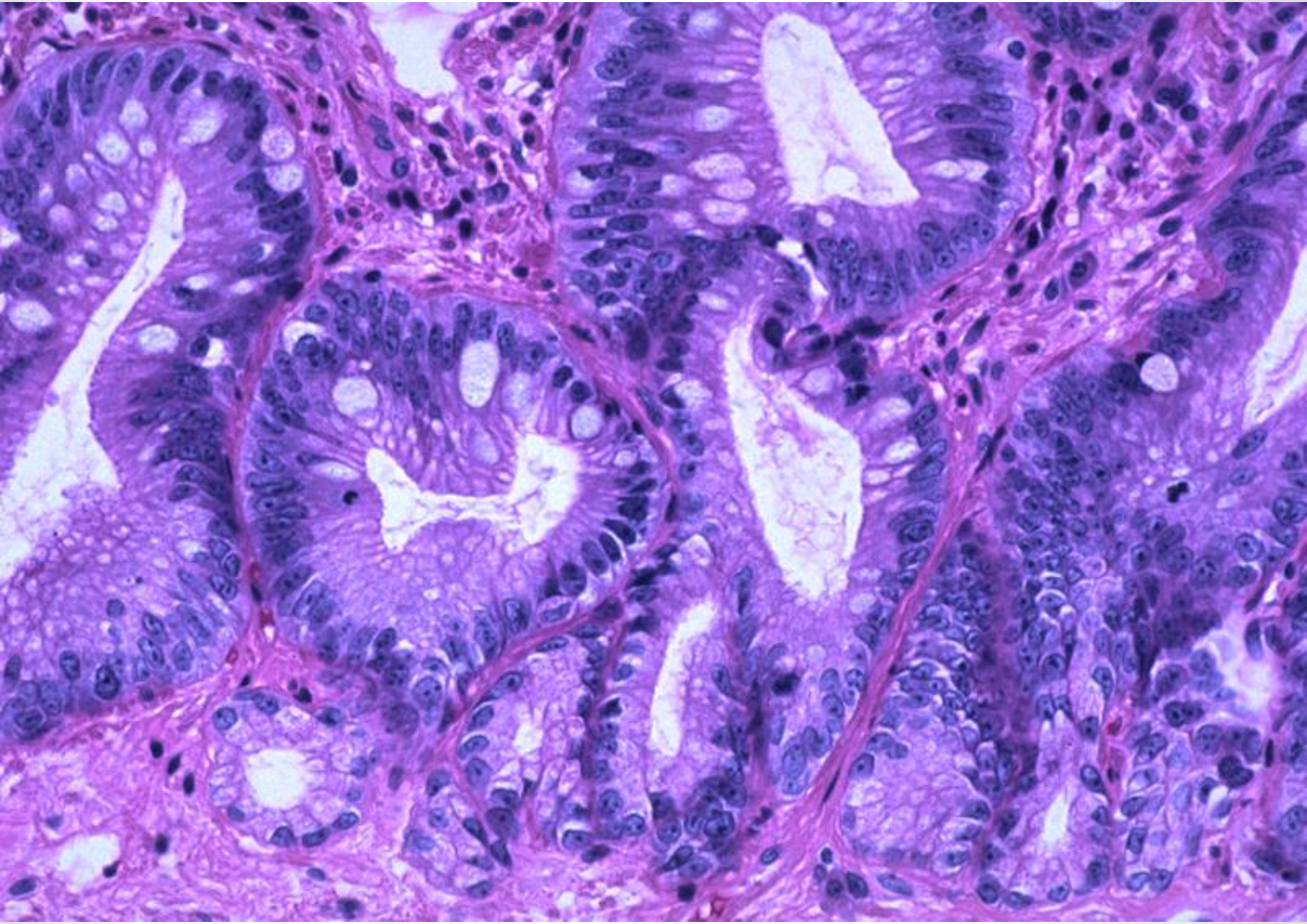
IBD/DMSG Hum Pathol 1983 Pathol 1983;14:831

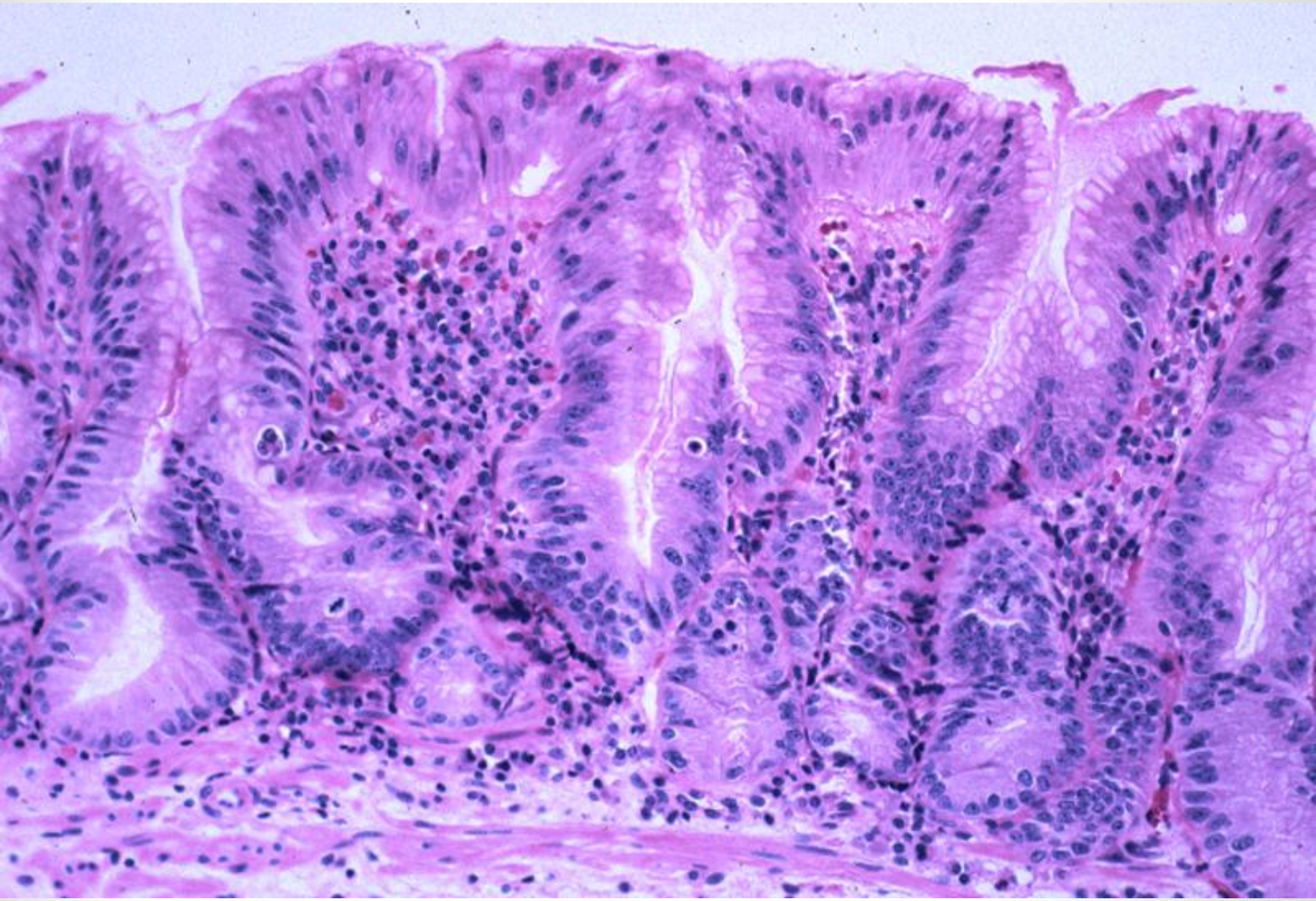
Barrett's Dysplasia

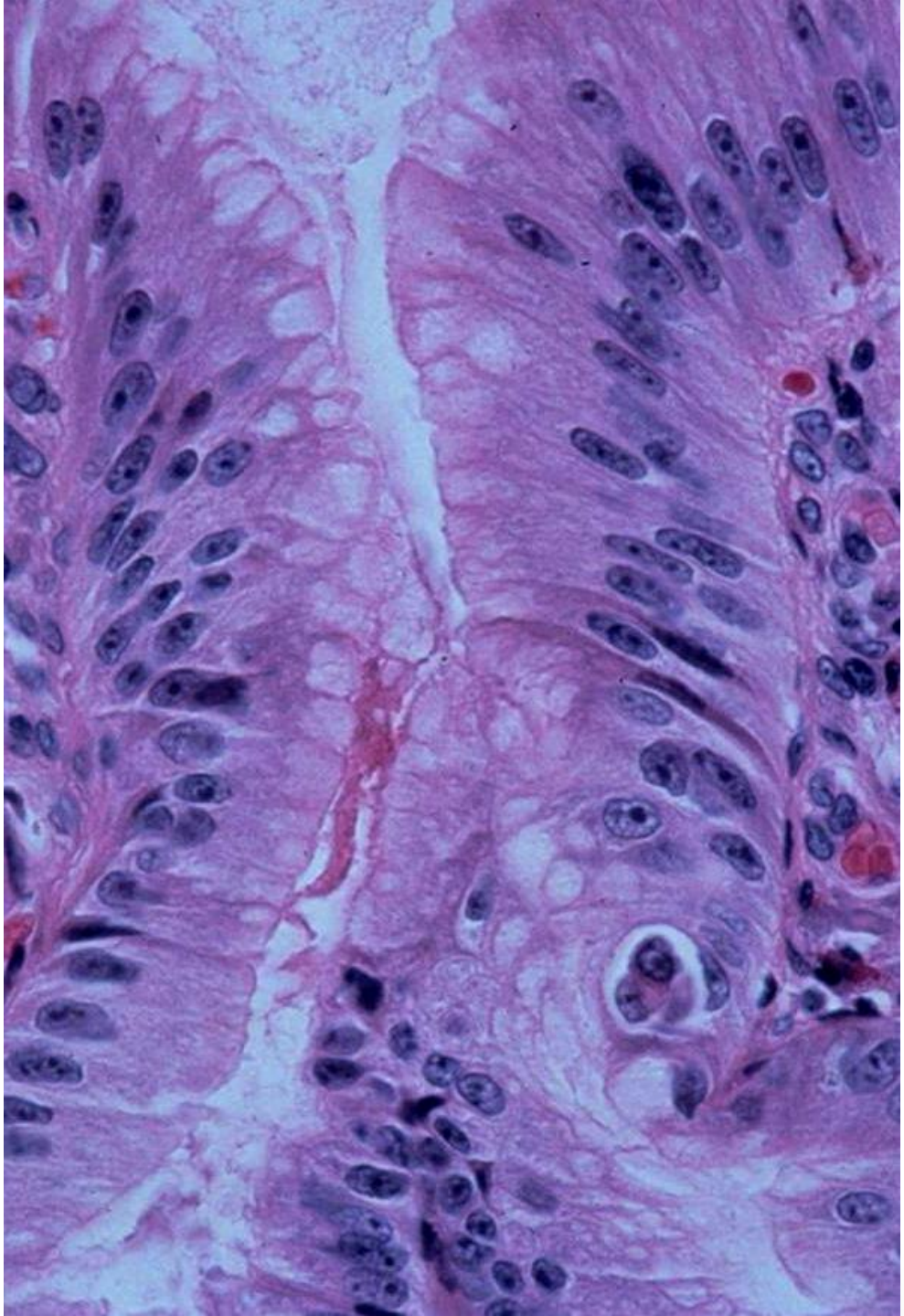
- Two types
  - Intestinal (85%)
  - Gastric Foveolar (15%)

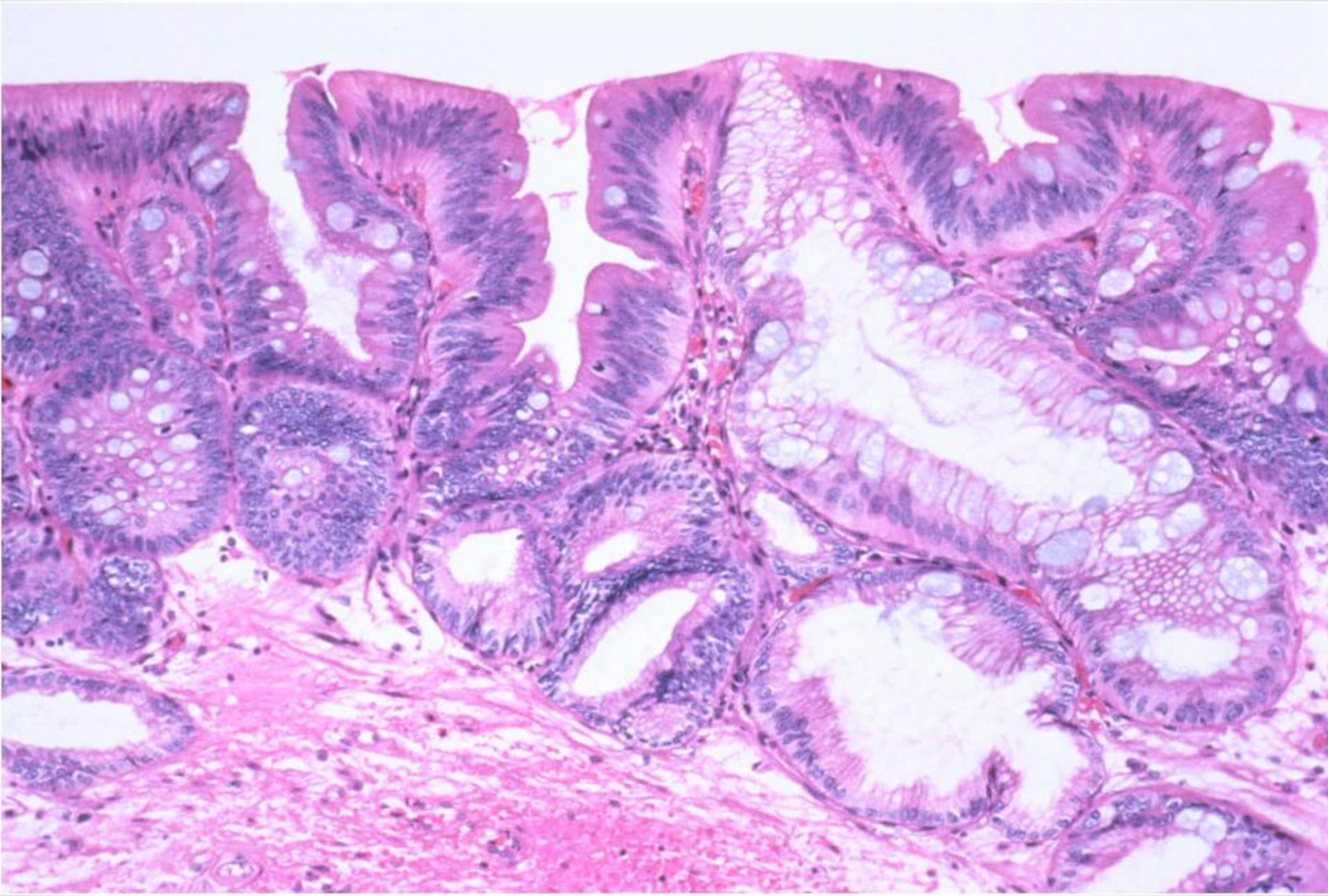
Barrett's Intestinal-type Dysplasia

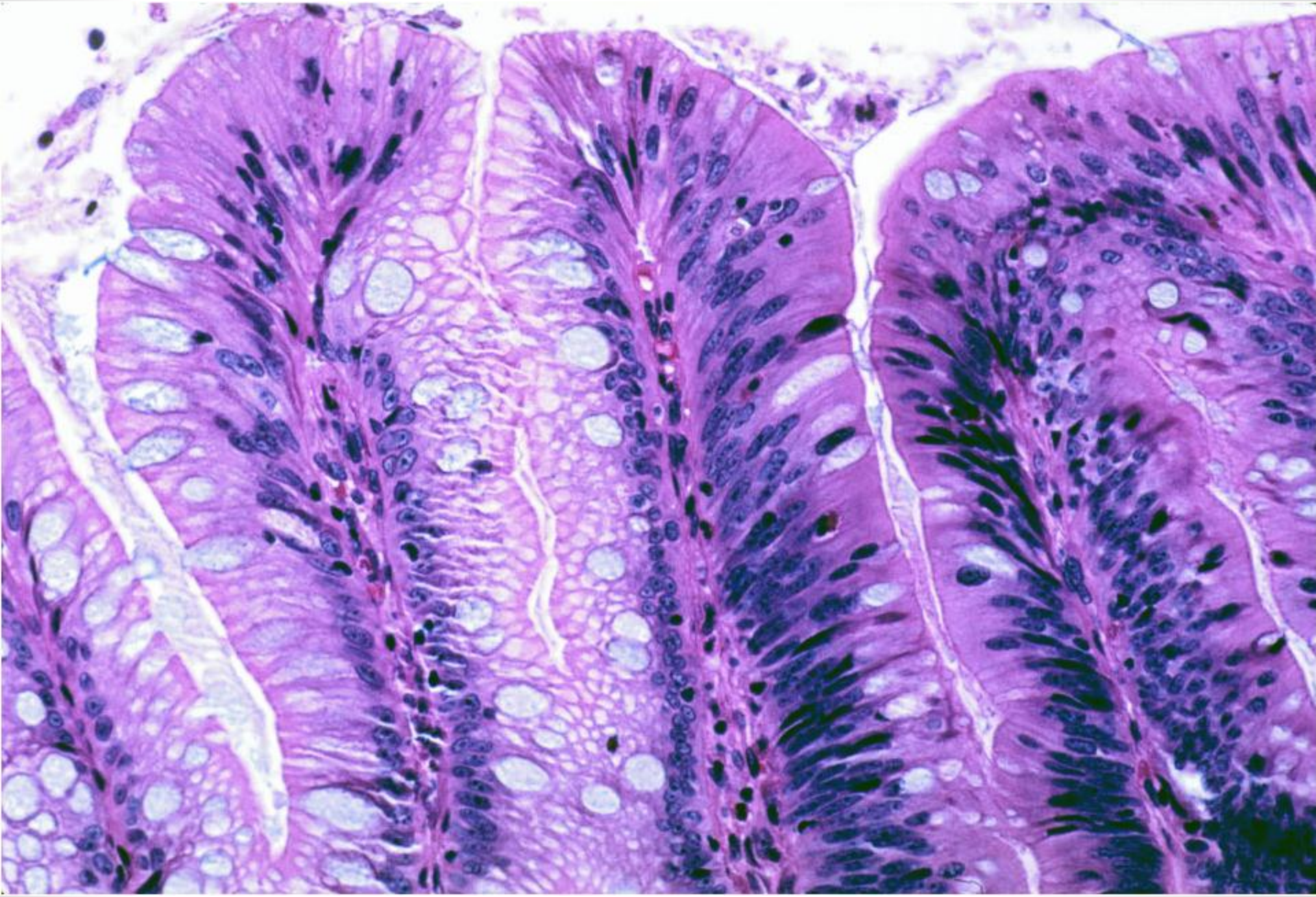


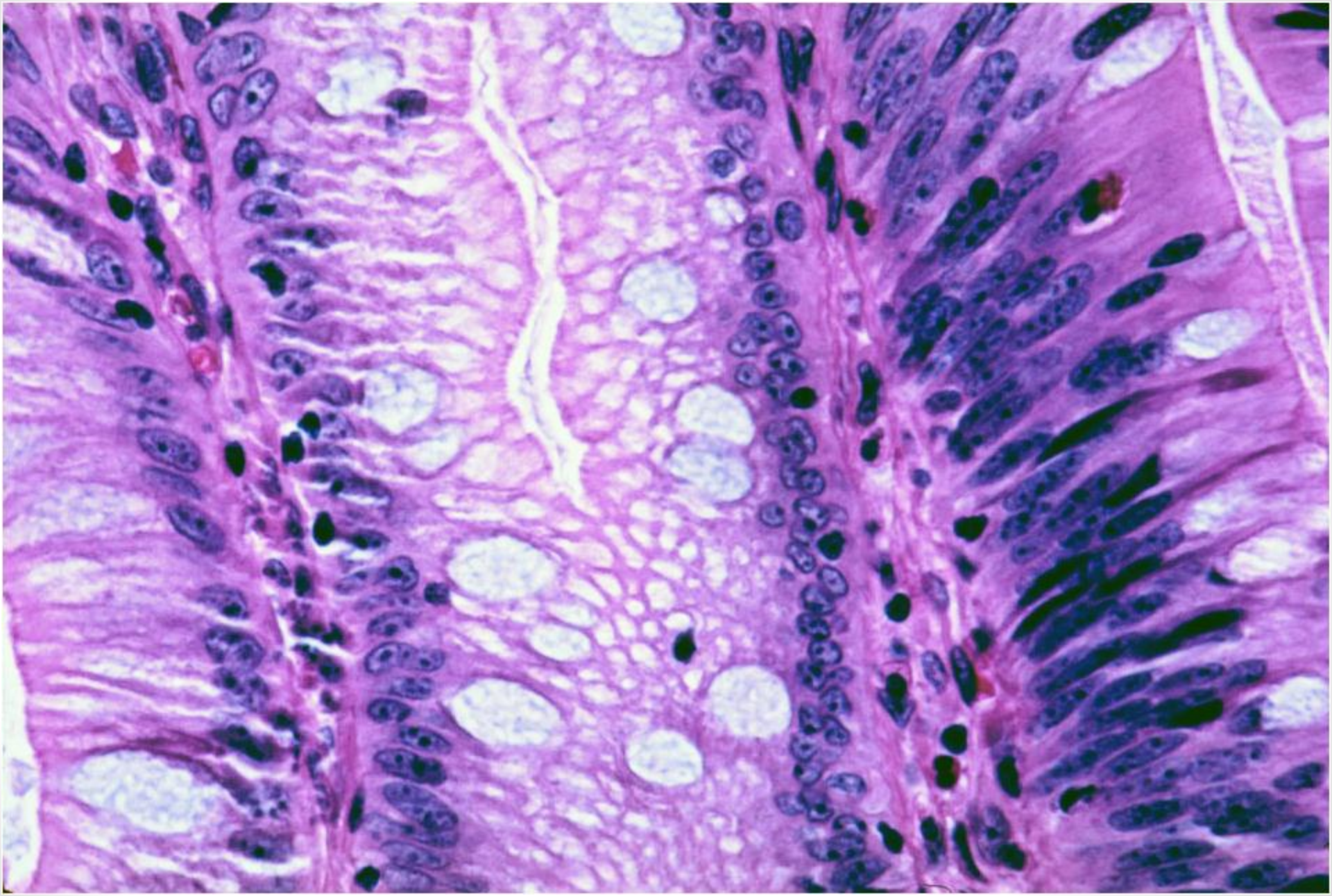


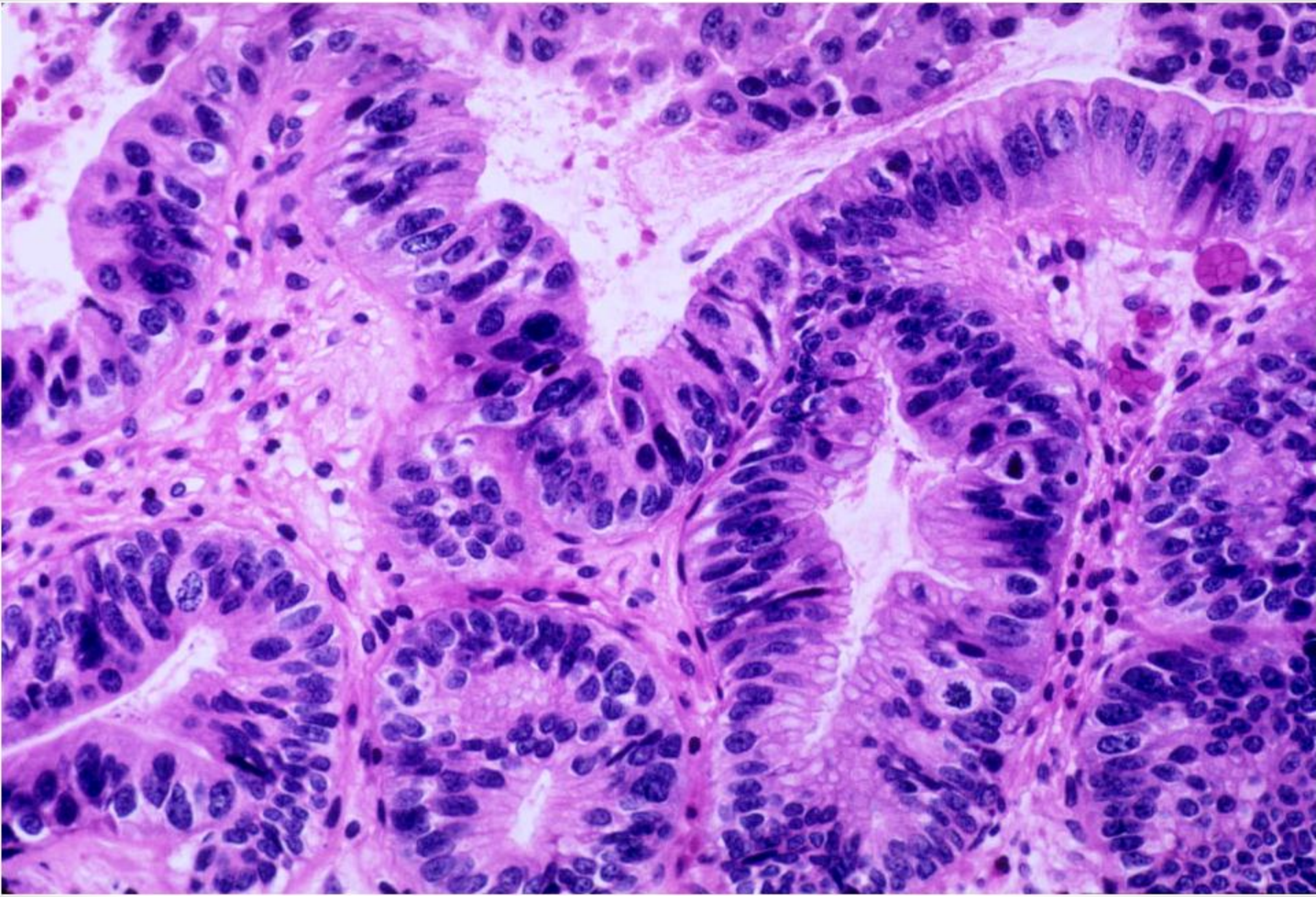


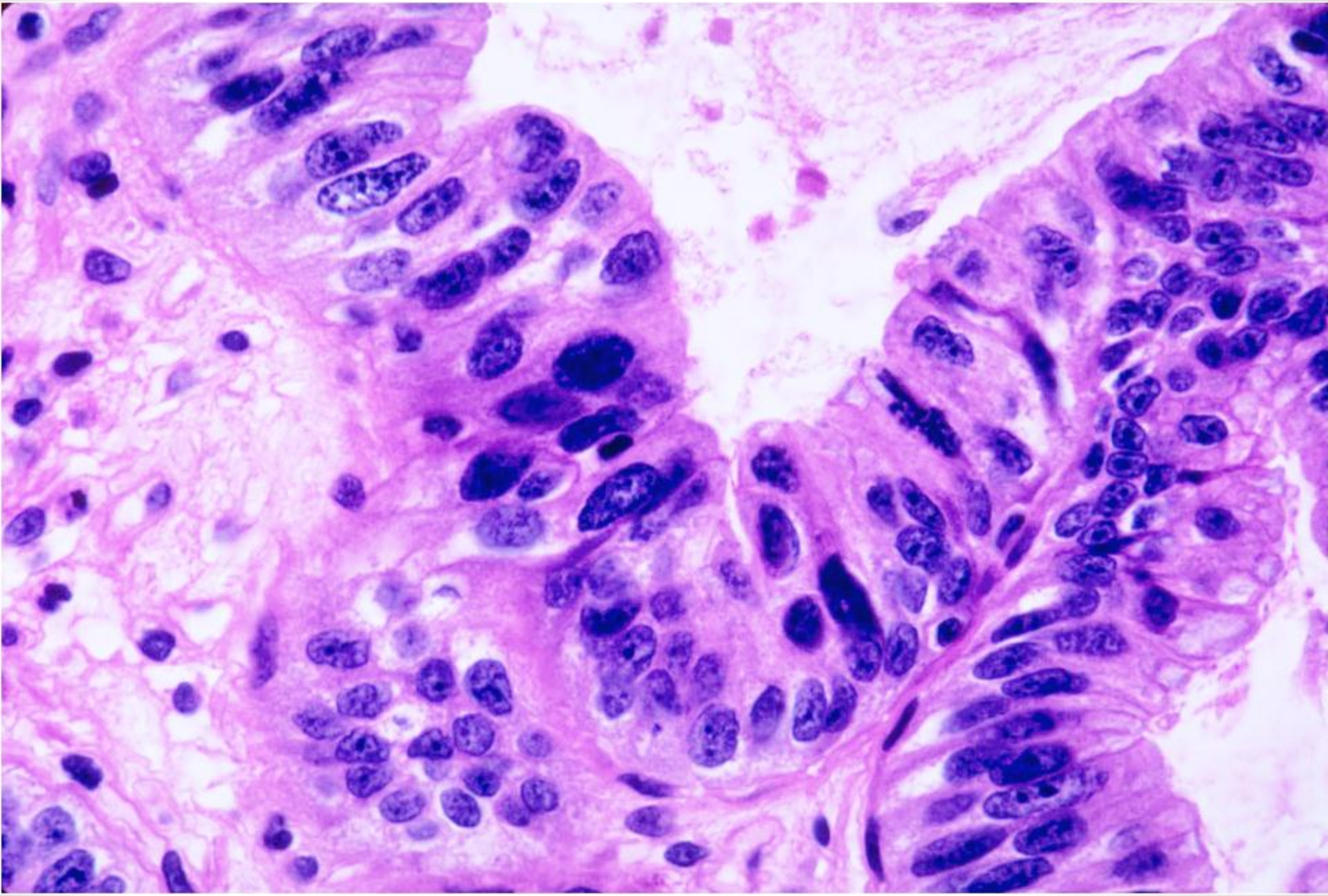


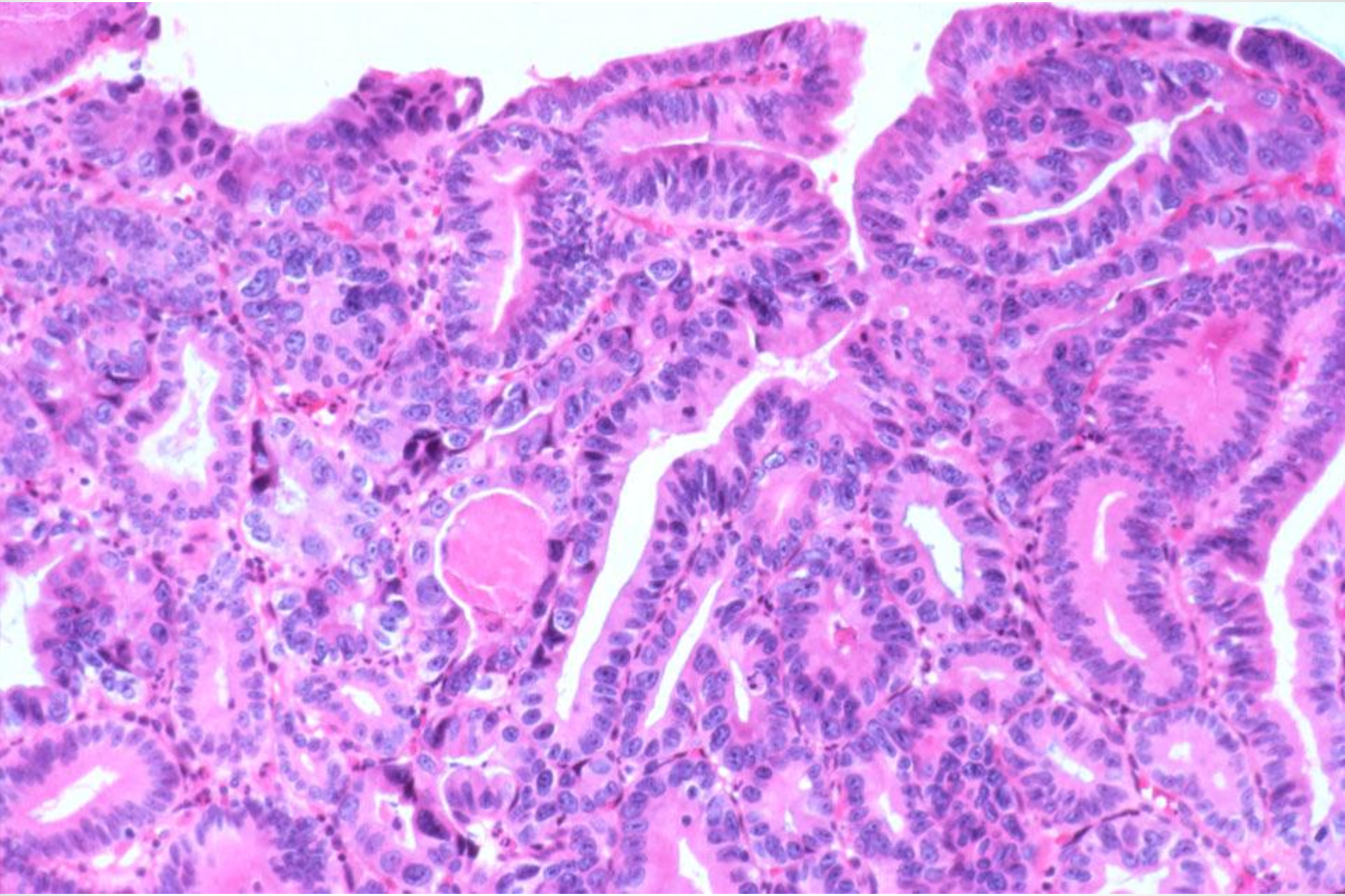


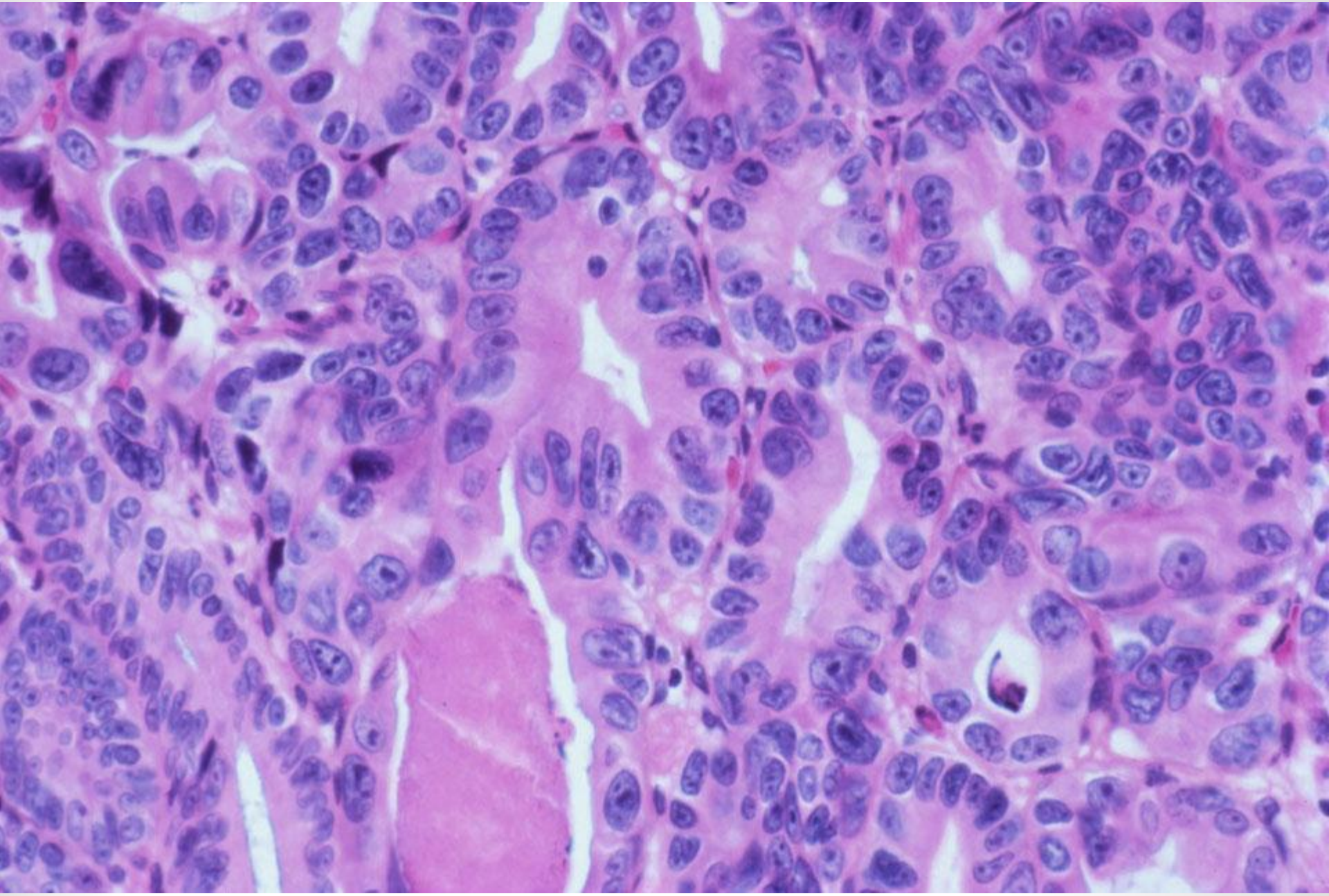






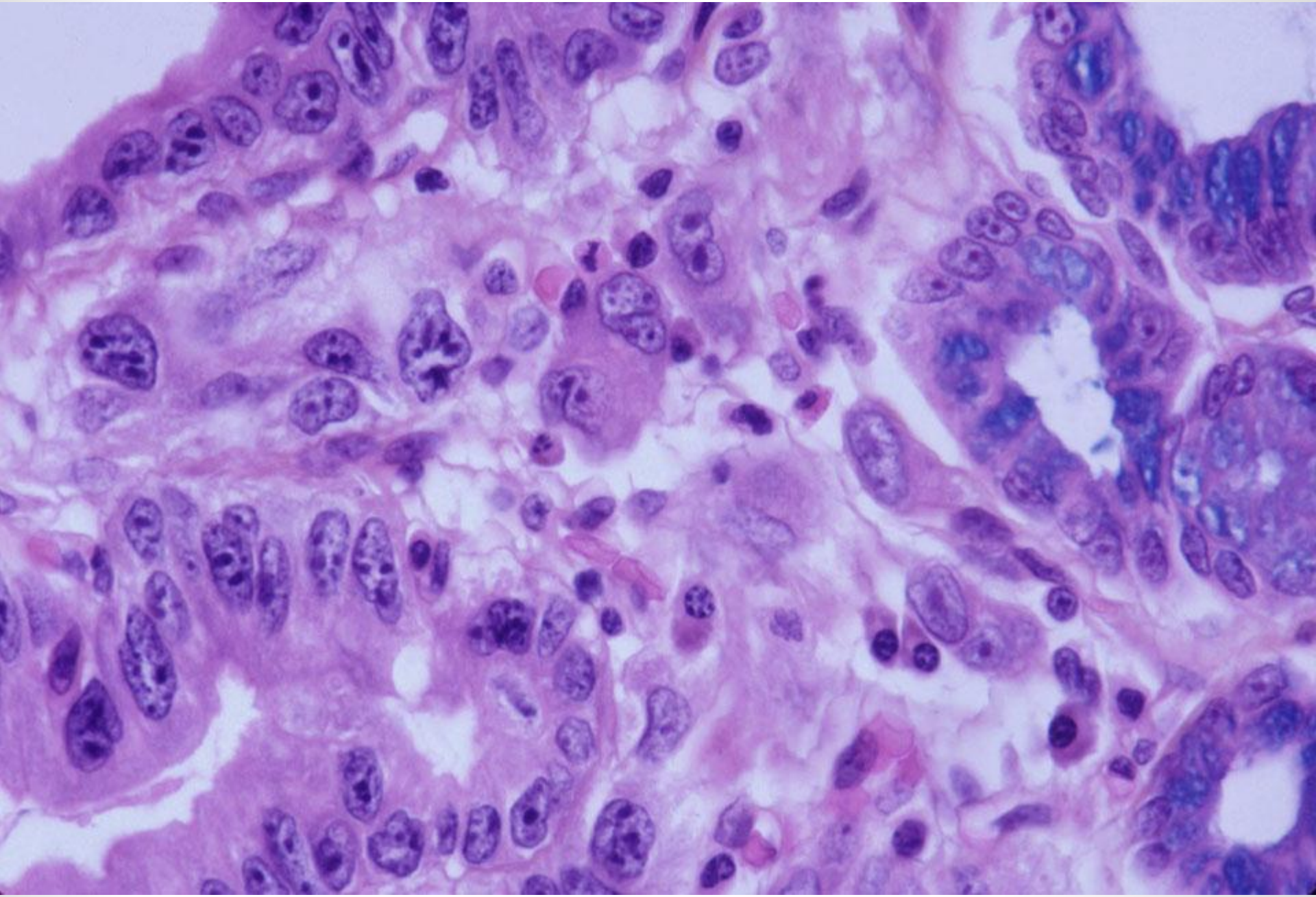


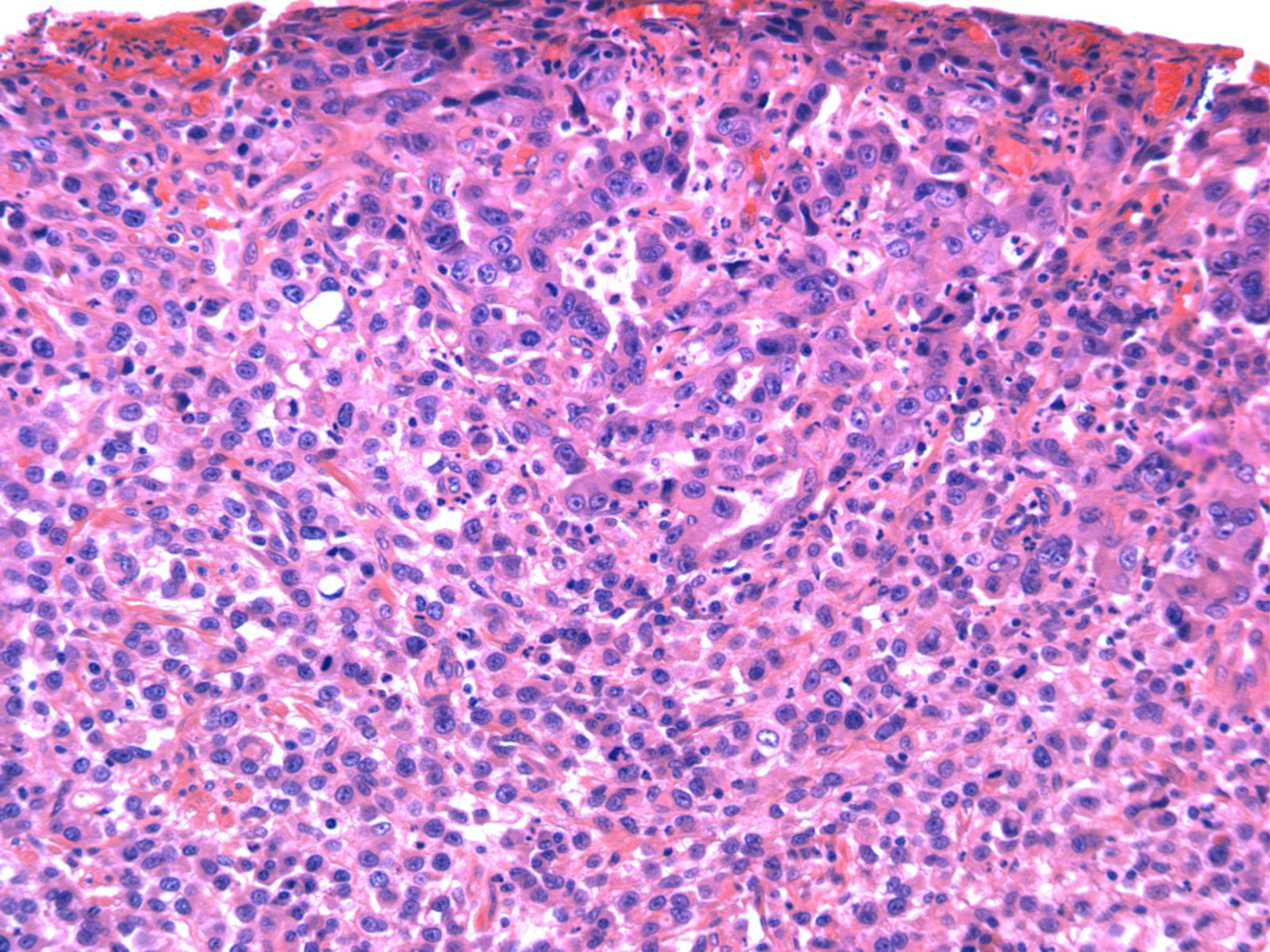


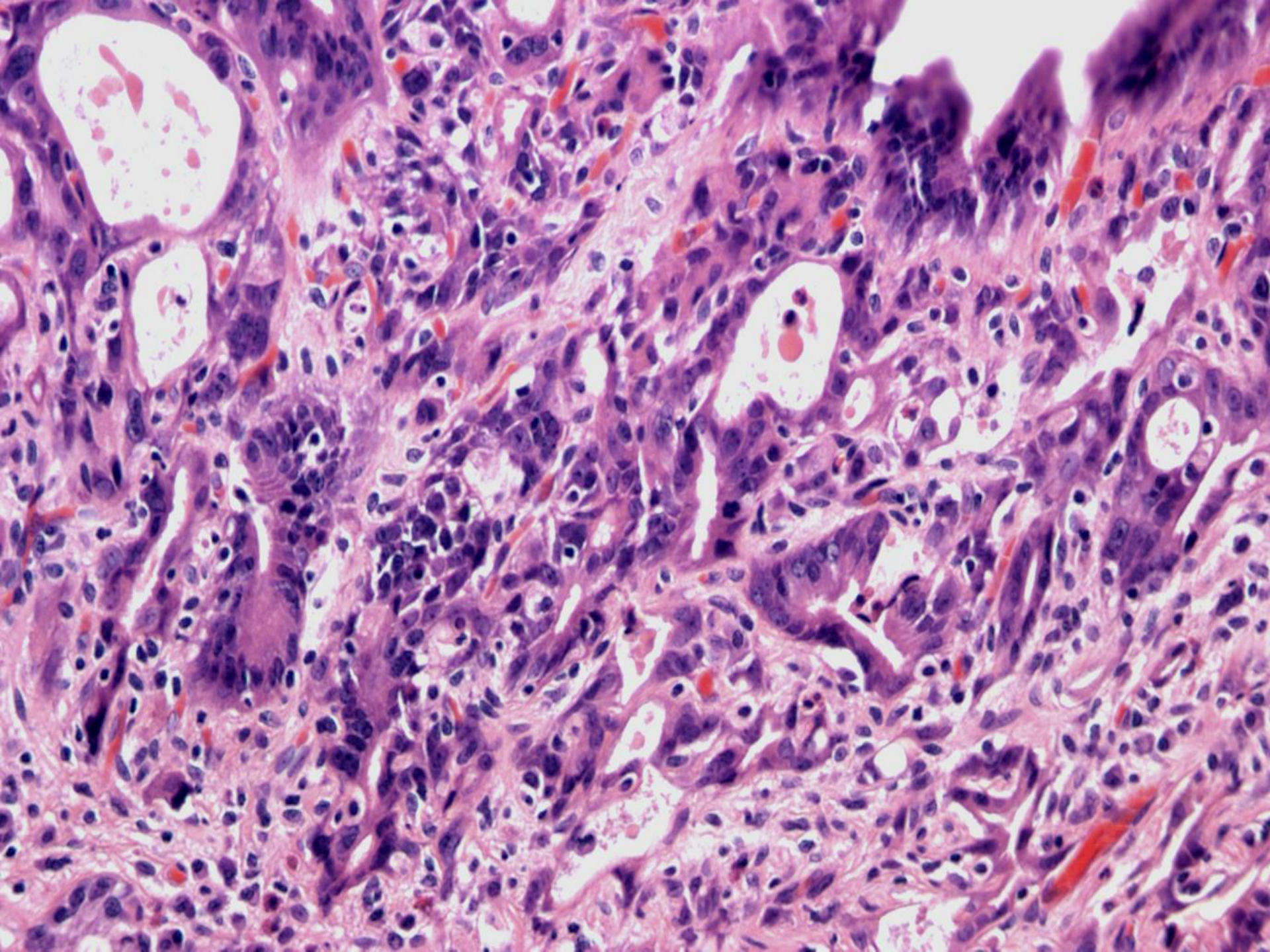


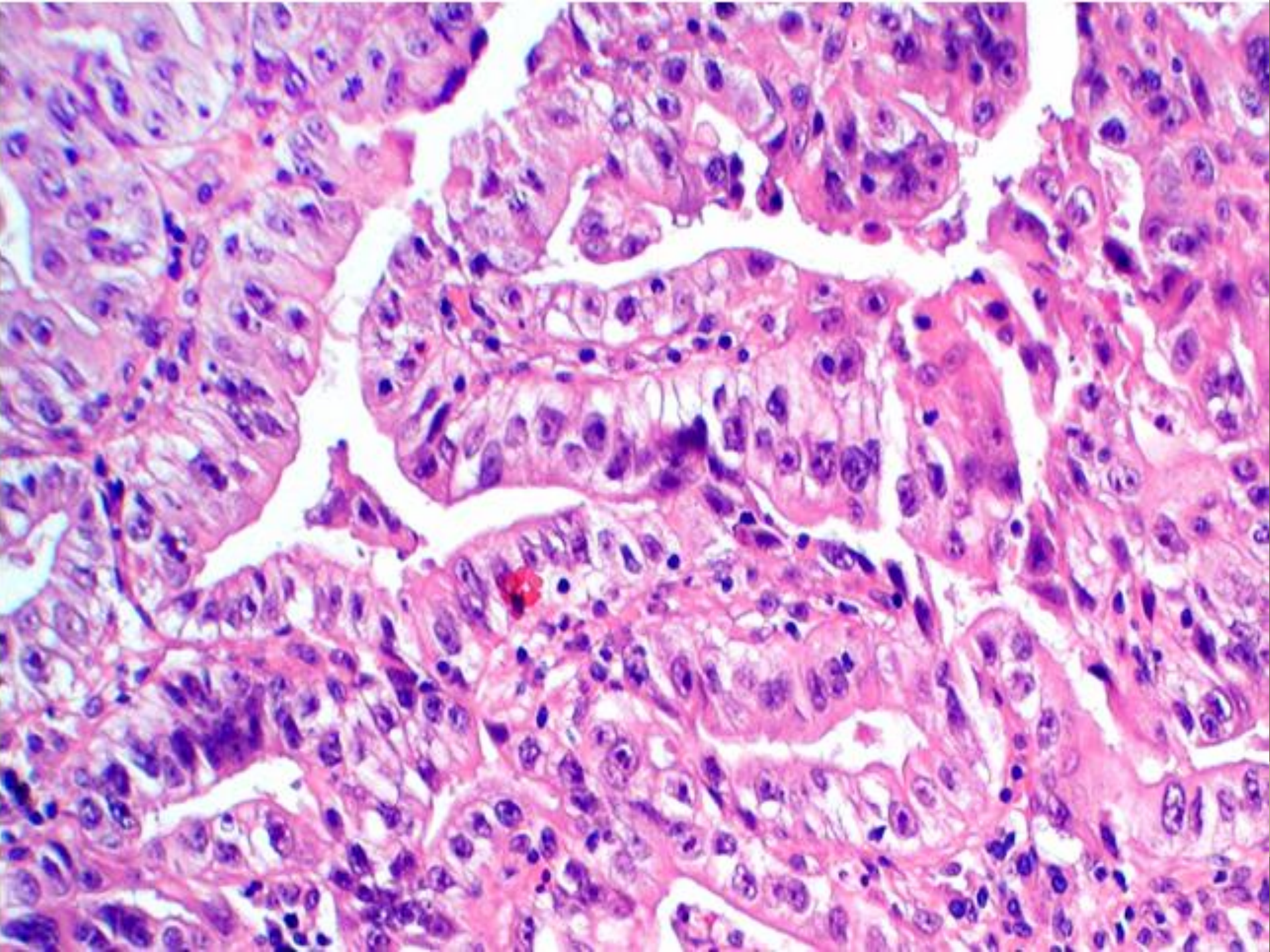
Intramucosal Adenocarcinoma

- Single cell lamina propria invasion
- Sheets of malignant cells
- Abortive angulated glands
- Never ending gland pattern



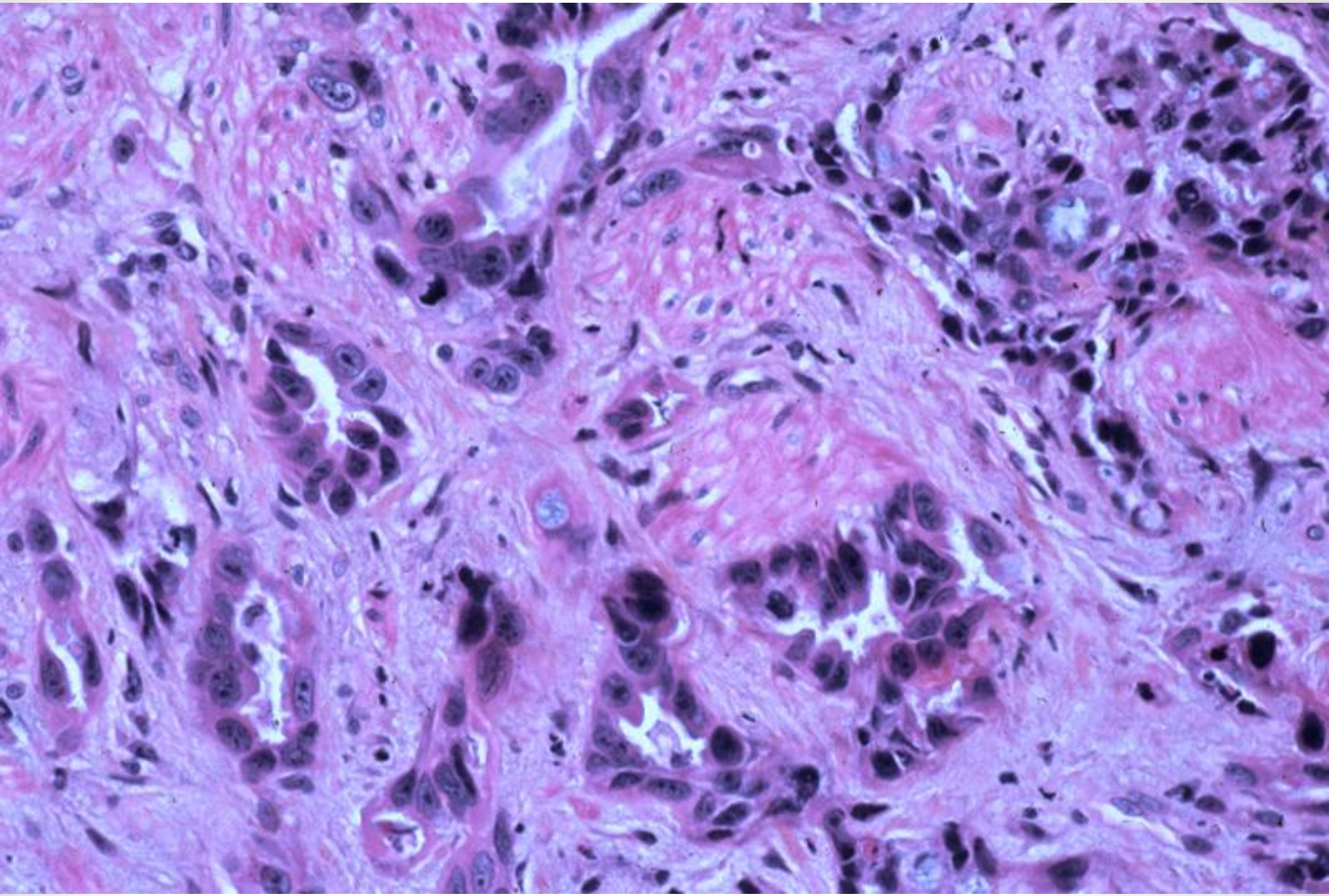






Invasive Adenocarcinoma

- Unequivocal desmoplasia
- Indicates at least submucosal invasion



Barrett's Gastric Foveolar-type Dysplasia

Gastric-Type Barrett's Dysplasia

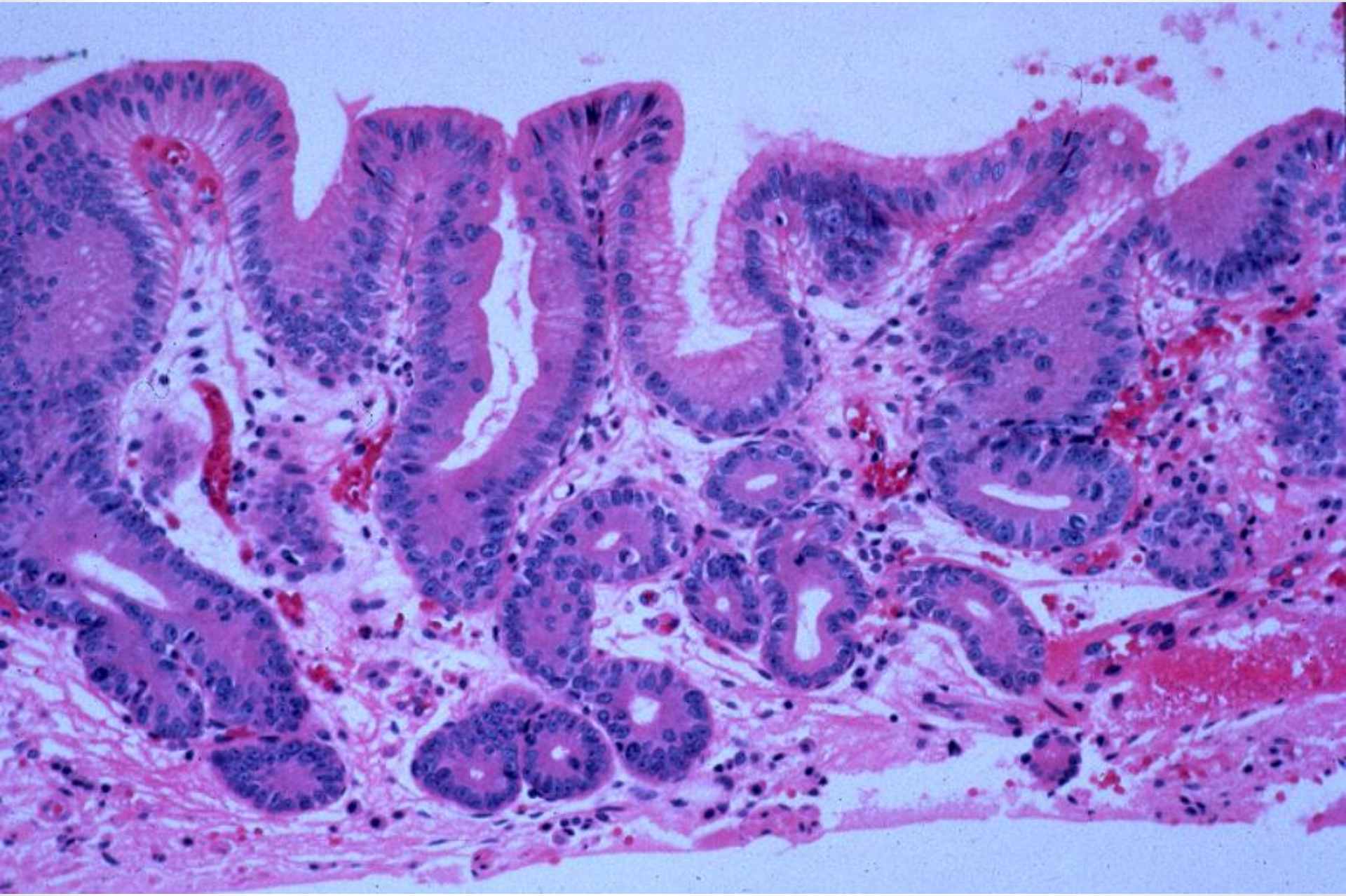
- Very different criteria from intestinal-type dysplasia
- Non-stratified, basal nuclei precludes loss of nuclear polarity criterion

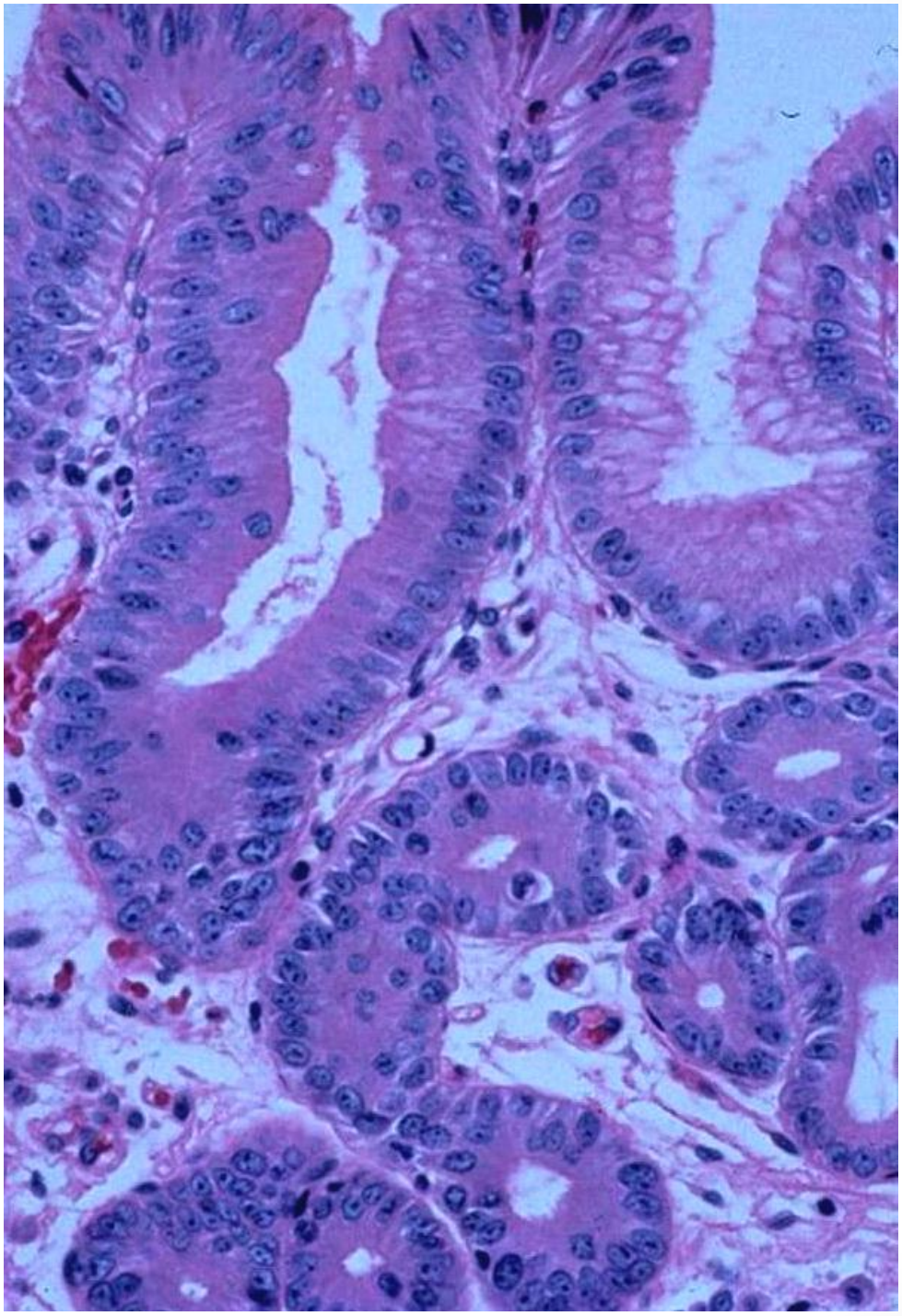
Mahajan D, et al. *Mod Pathol* 23:1-11, 2010

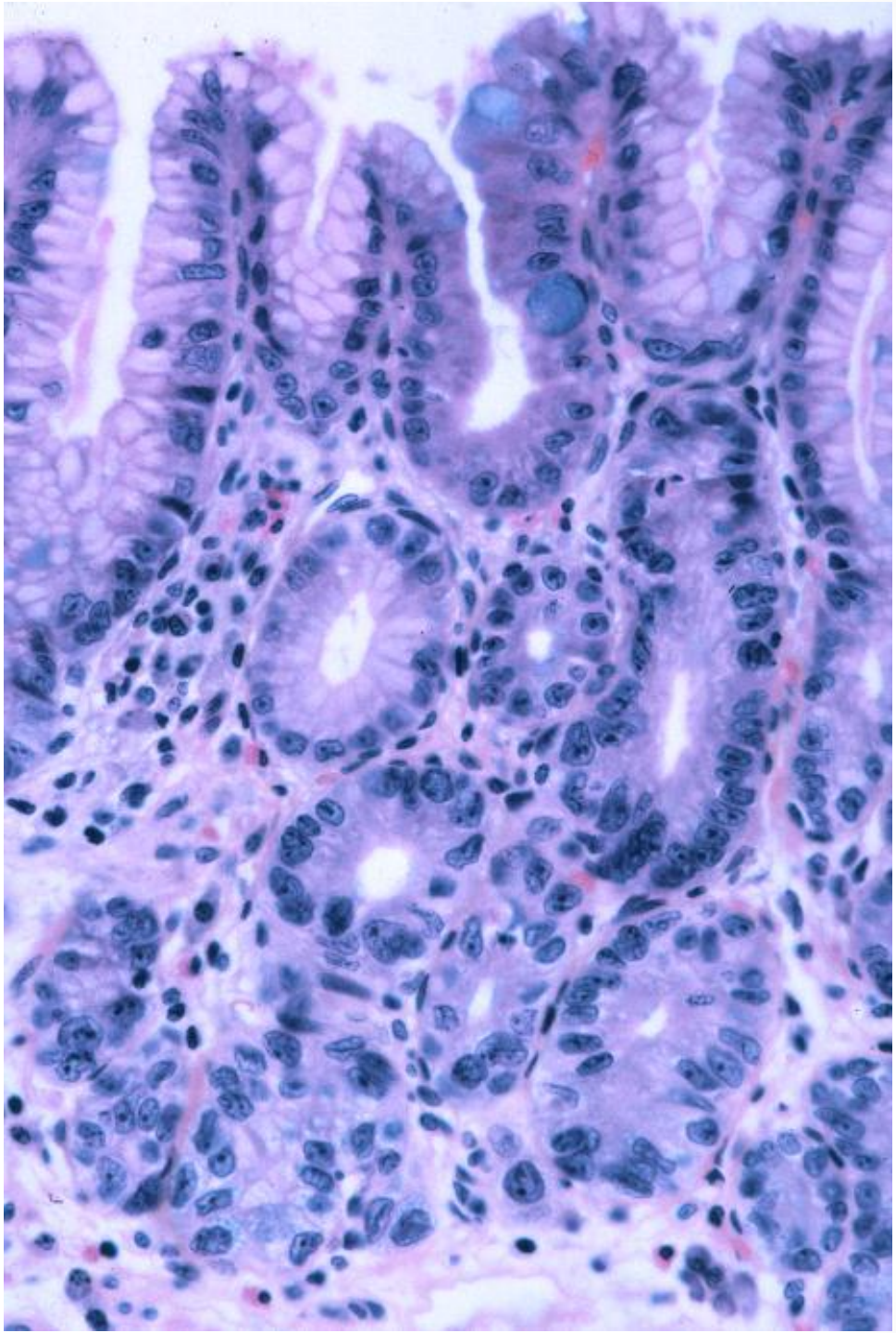
Gastric-Type Barrett's Dysplasia

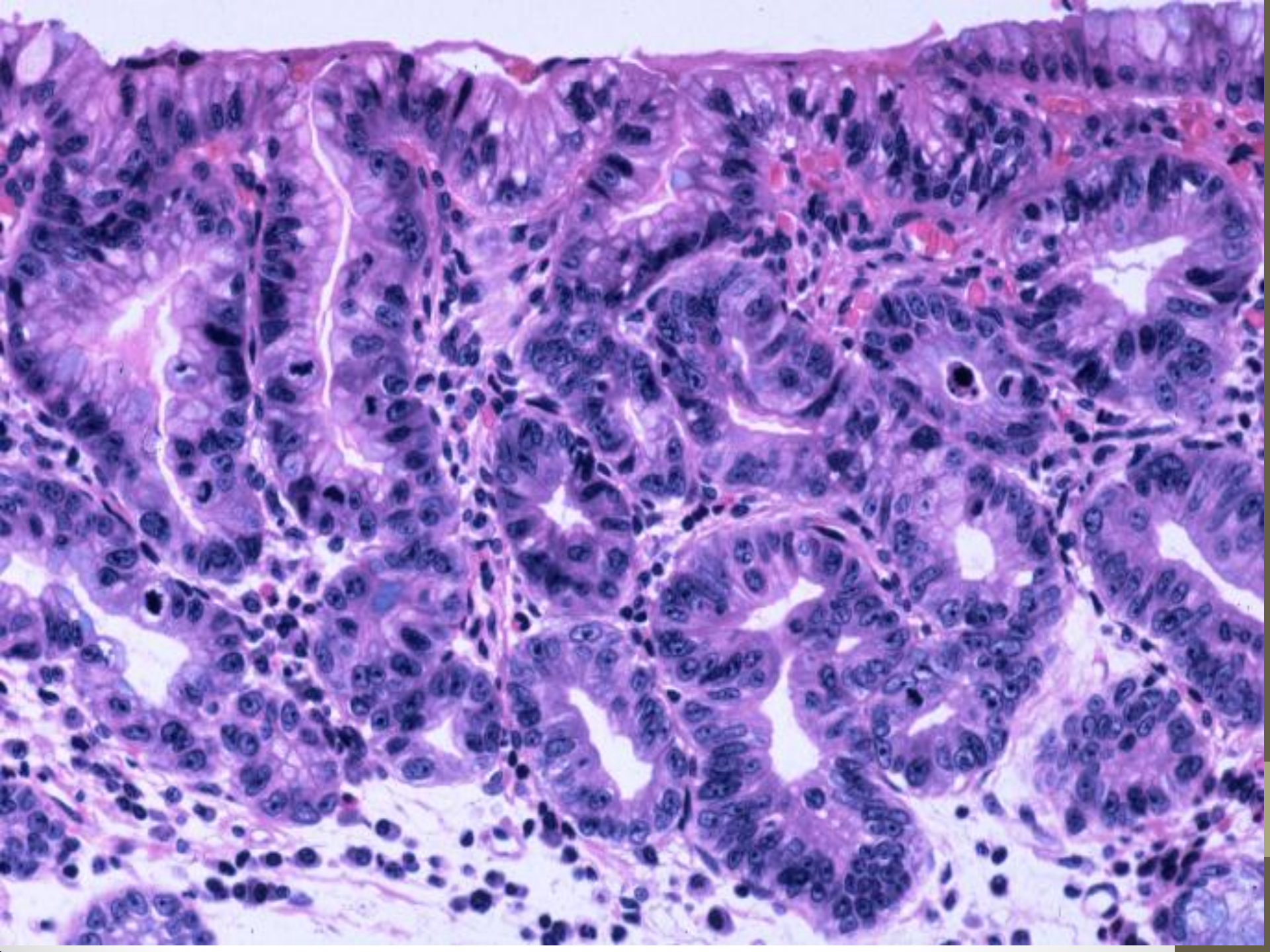
- *Gastric-type* LGD & HGD distinguished by
  - nuclear size cut off of 3-4X small lymph
  - increased but mild pleomorphism
  - prominent nucleoli
  - eosinophilic to oncocytic cytoplasm
  - crowded, irregular gland architecture

Mahajan D, et al. *Mod Pathol* 23:1-11, 2010









Gastric-Type Barrett's Dysplasia

Natural history poorly defined

- 49 patients in present composite literature
- F:M = 2.7:1
- Decade older than intestinal-type dysplasia (73 vs 63 yrs mean age)
- More often high-grade (70%)
- Neoplastic progression in 64% over 8 years of follow-up

Mahajan D, et al. *Mod Pathol* 23:1-11, 2010

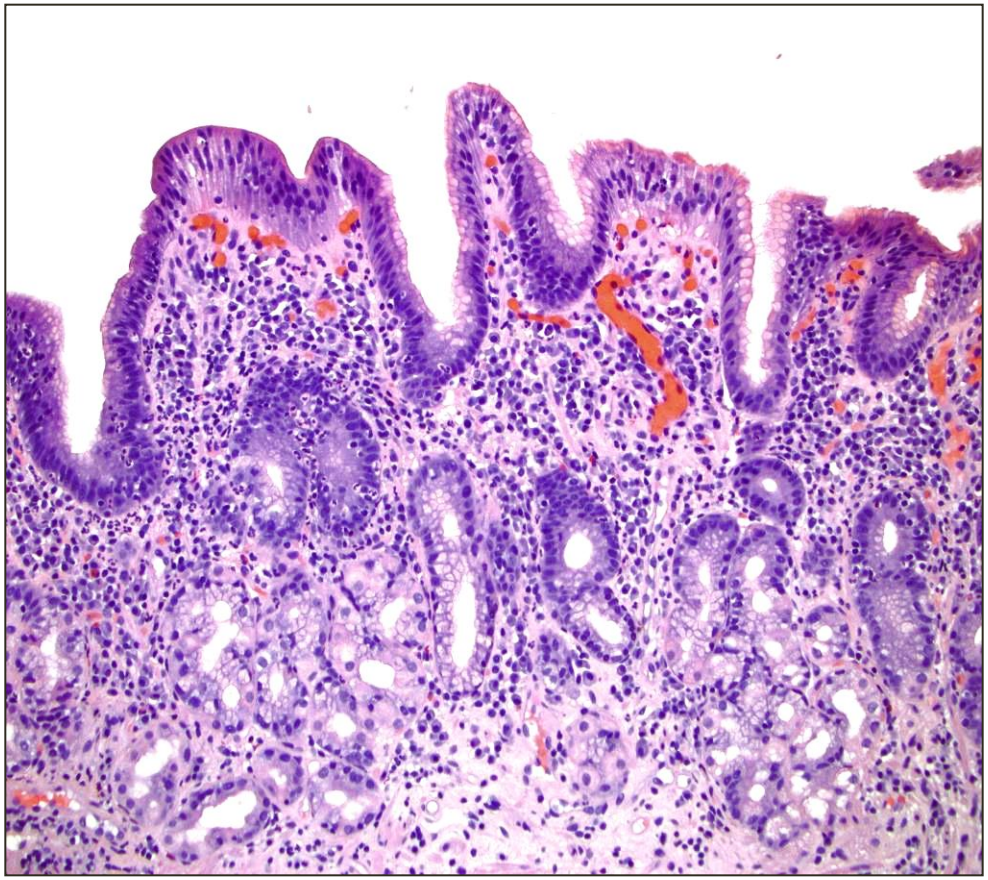
DDX GERD vs. Foveolar Dysplasia

	GERD	FOV DYSP	P-Value
Nuclear stratif	0	80%	<.00001
Top-heavy atypia	0	80%	<.00001
Full thick atypia	80%	0	<.00001
Villiform	6%	53%	0.0006
Crowded glands	78%	0	<.00001
Nucleoli	79%	33%	0.0003
Pleomorph–mild	35%	10%	0.09

- 3,698 EGD bxs from 461 Barrett's patients
- 80 bxs foveolar gastric-type dysplasia (13 LGD, 30 HGD)
- 60 severe GERD

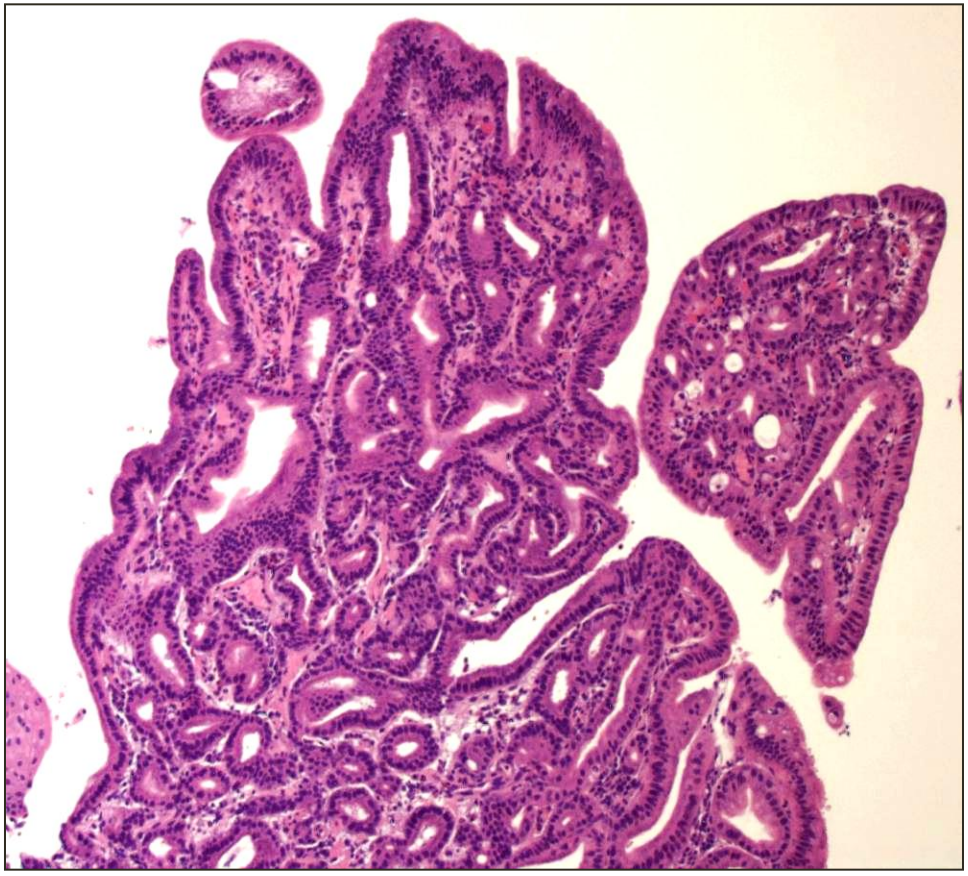
Patil DT, et al. *Hum Pathol 44:1146-53, 2013.*

Reactive Cardia/GERD Villiform Architecture & "Top-Heavy" Atypia

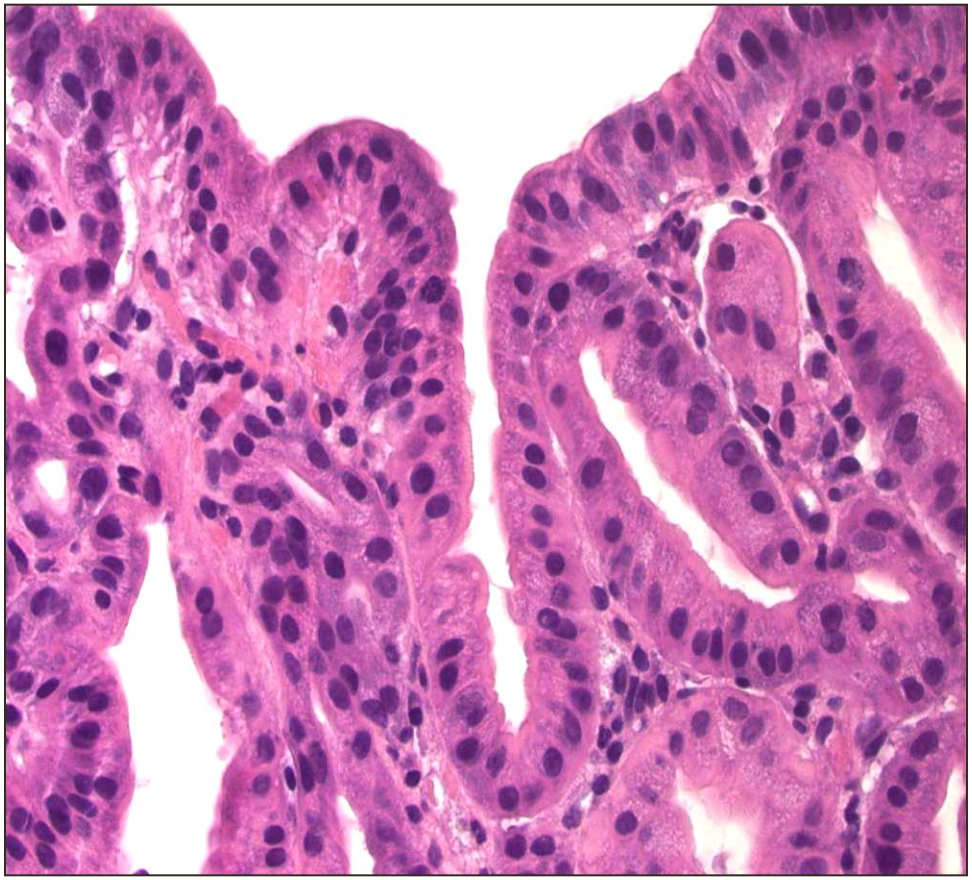


Reactive Cardia/GERD: Stratified Surface Nuclei

Gastric-type Dysplasia: Full-thickness Atypia



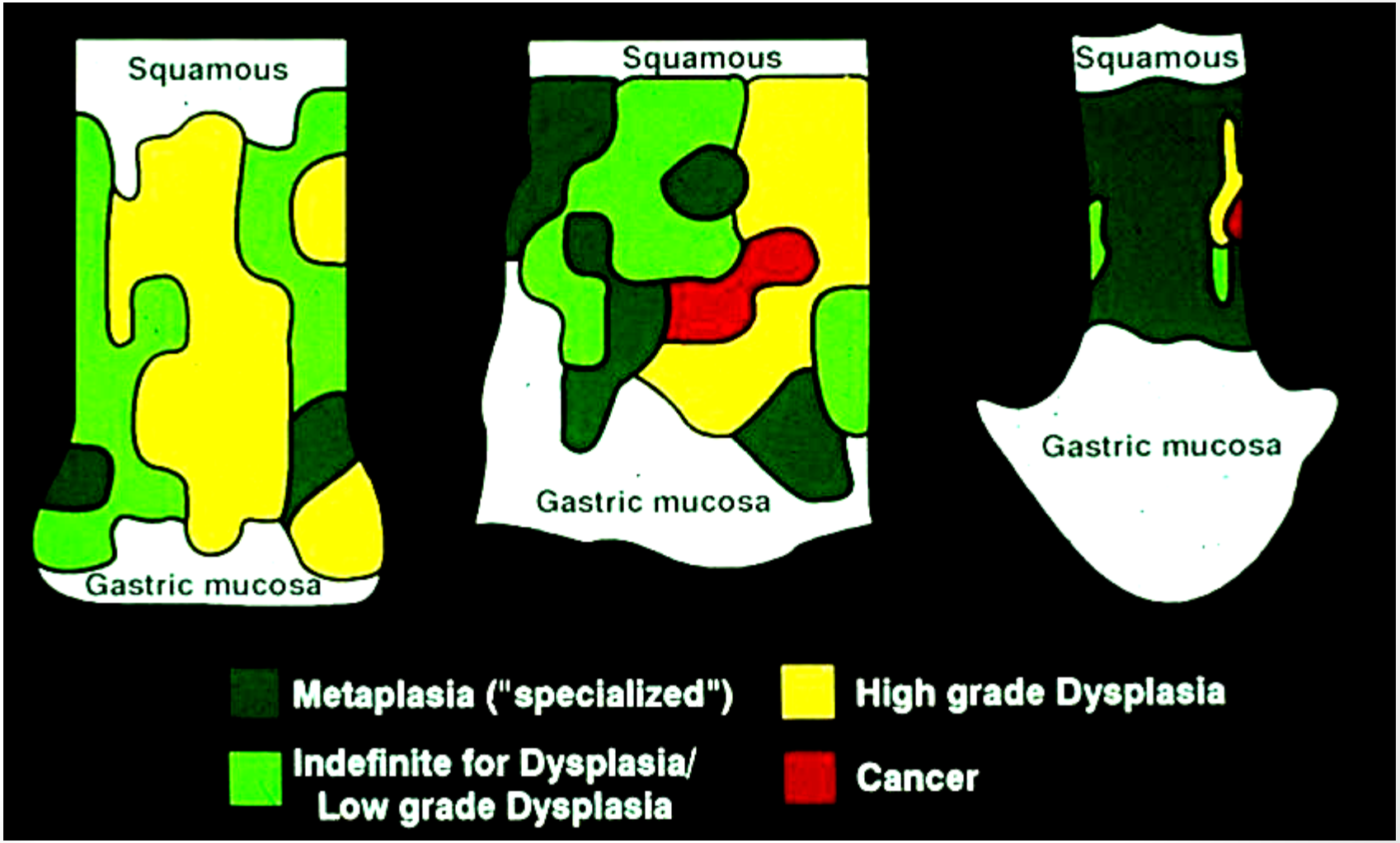
Gastric-type Dysplasia: Non-stratified Nuclei



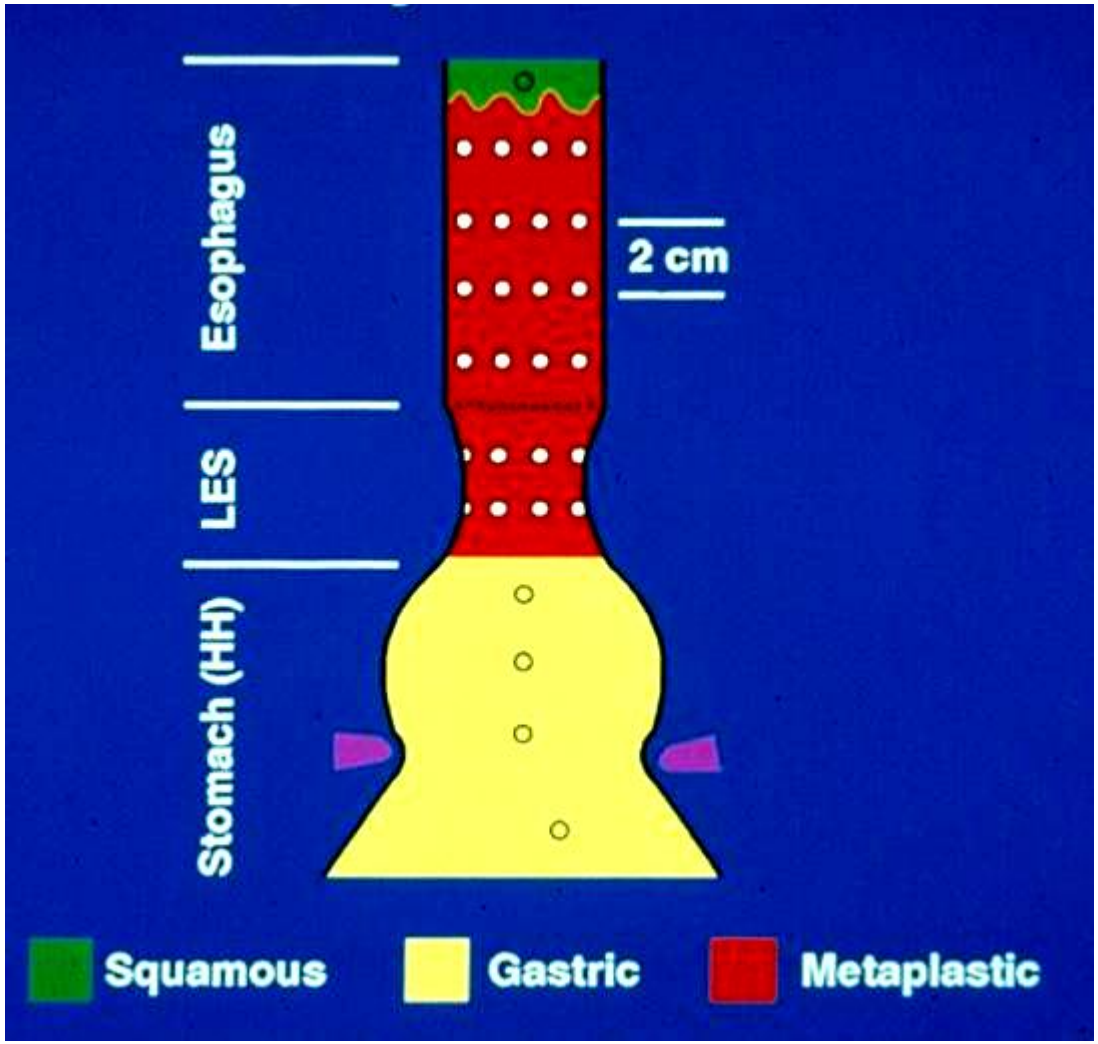
Dysplasia: Problems

- Sampling
- Distinction from reactive change
- Observer variation
- Squamous overgrowth
- Natural history incompletely

Distribution of Dysplasia



Biopsy Protocol



Dysplasia: Problems

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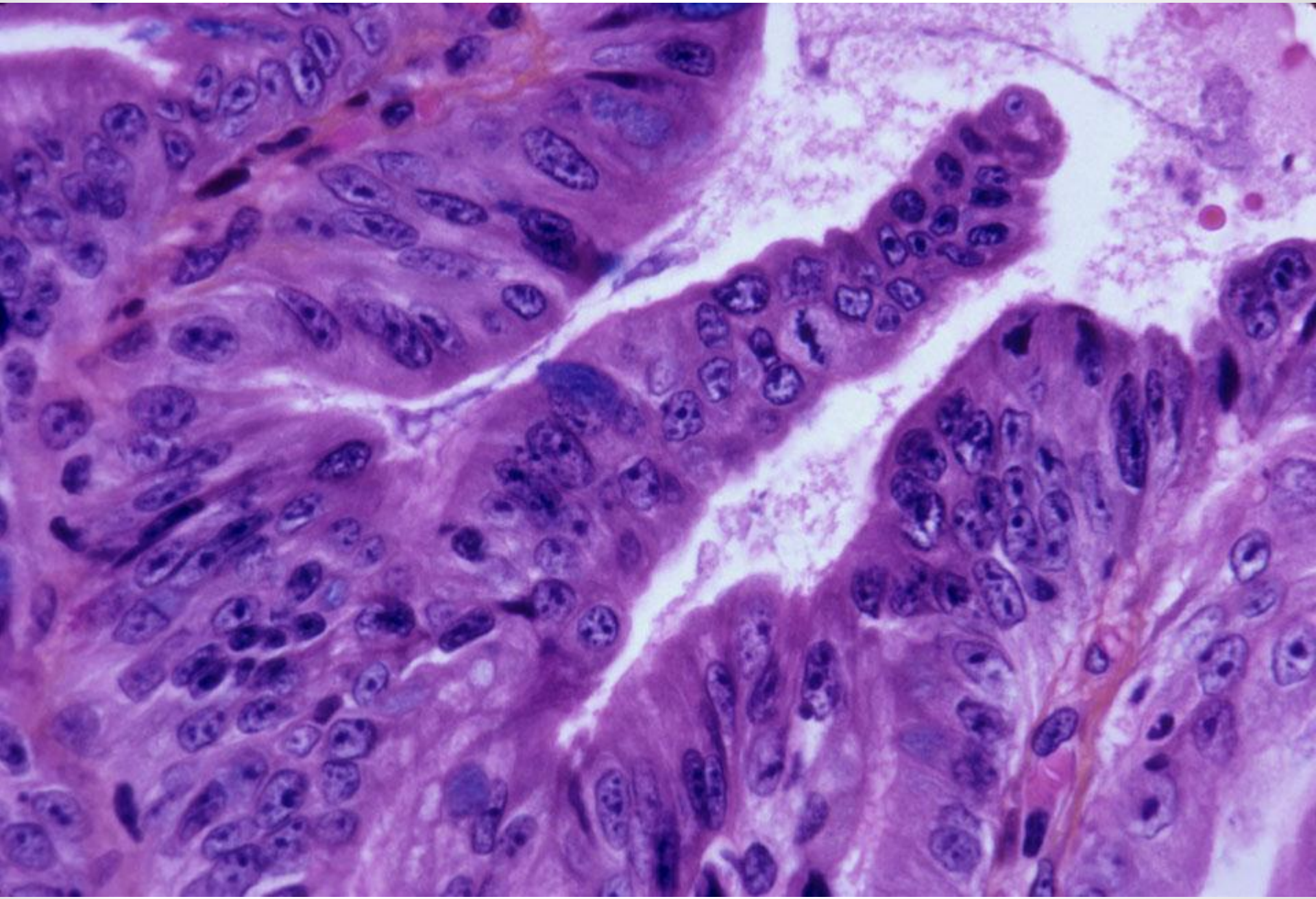
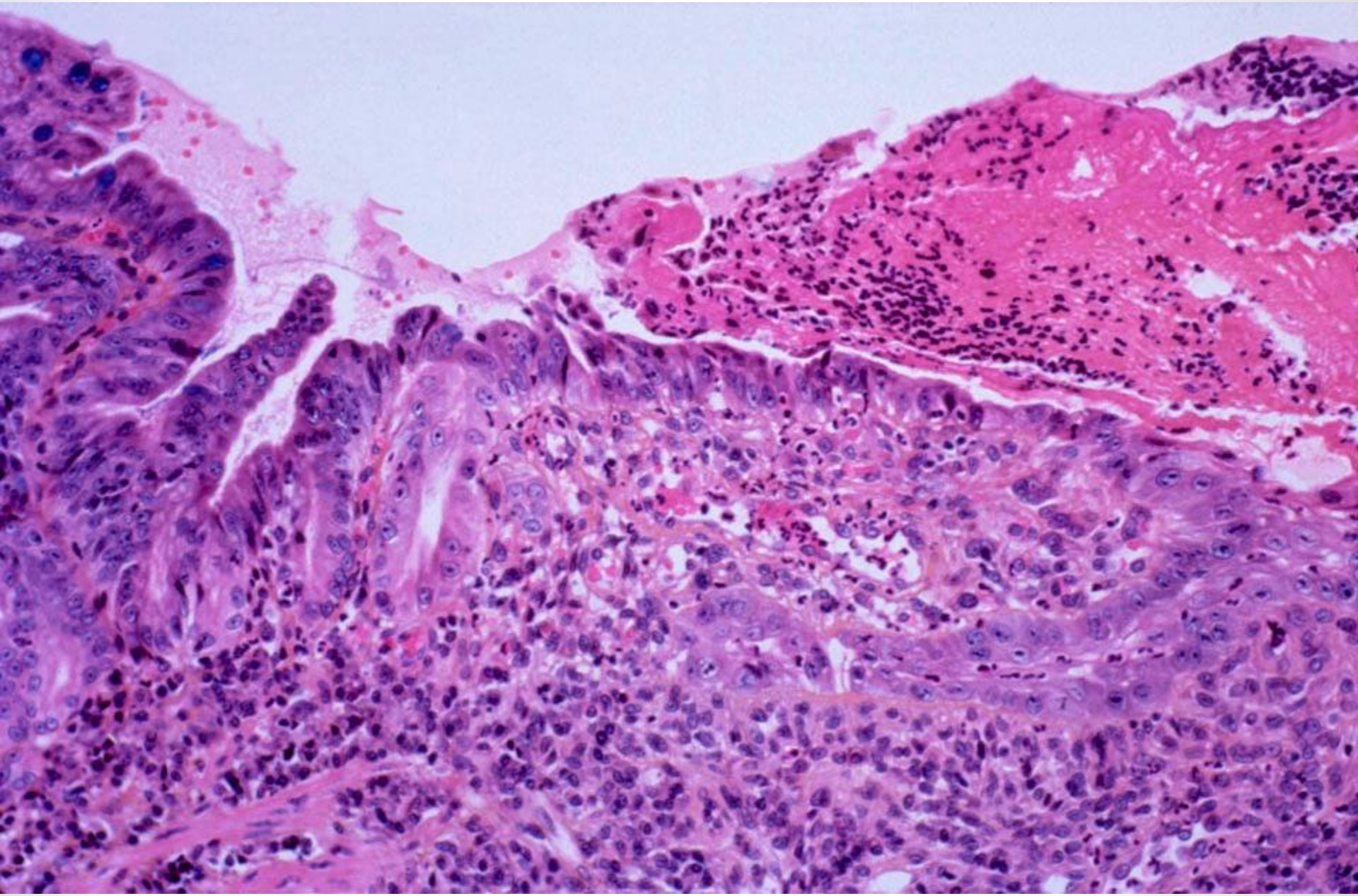
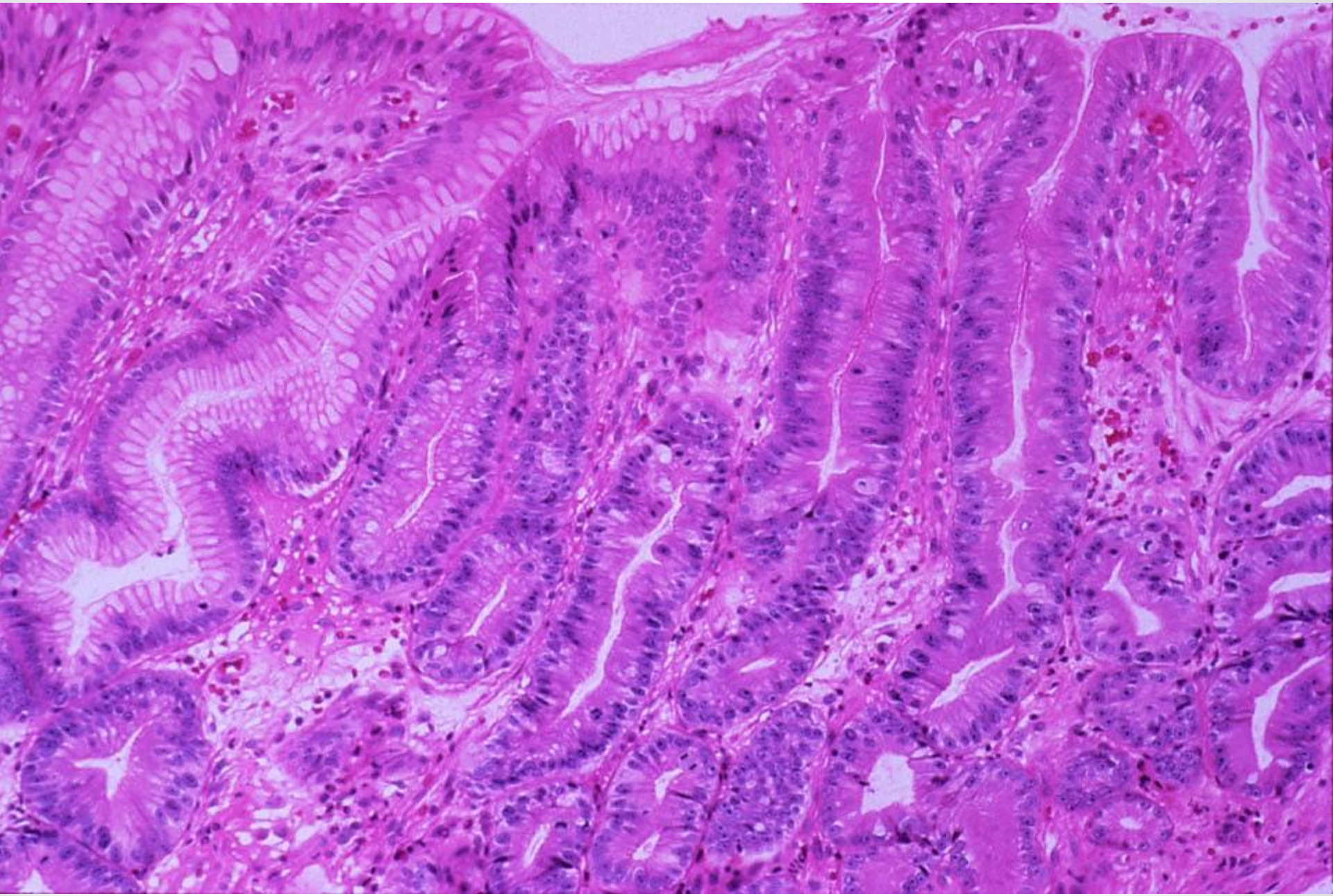


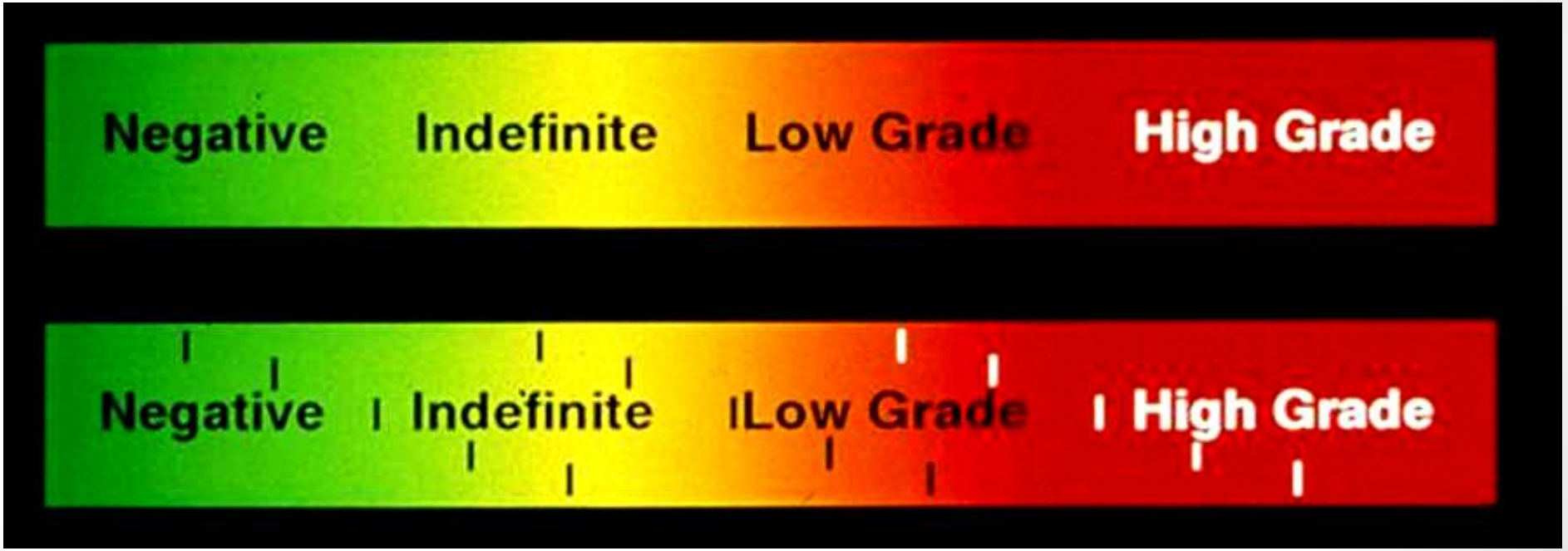


Dysplasia: Problems

- Sampling
- Distinction from reactive change
- Observer variation



Spectrum of Dysplasia



Interobserver Agreement: Dysplasia in Barrett's Esophagus

Diagnosis	Kappa Statistic	Agreement
HGD/CA	0.65	Substantial
LGD	0.32	Fair
Indefinite	0.15	Poor
Negative	0.58	Moderate

Two Main Problems In Barrett's Pathology

- Over diagnosis of Barrett's esophagus
- Over diagnosis of *high-grade dysplasia*

Inaccuracy in the Diagnosis of Barrett's with HGD

- PDT multi-center trial for Barrett's HGD
  - 485 patients with "HGD" screened
    - Review original slides
    - Repeat protocol study endoscopy 4 quad q2cm
  - 248 with confirmed HGD (51%)
  - 193 patients downgraded (40%)

Sangle N, Bronner MP: Mod Pathol, In press 2015

193 Downgraded Patients

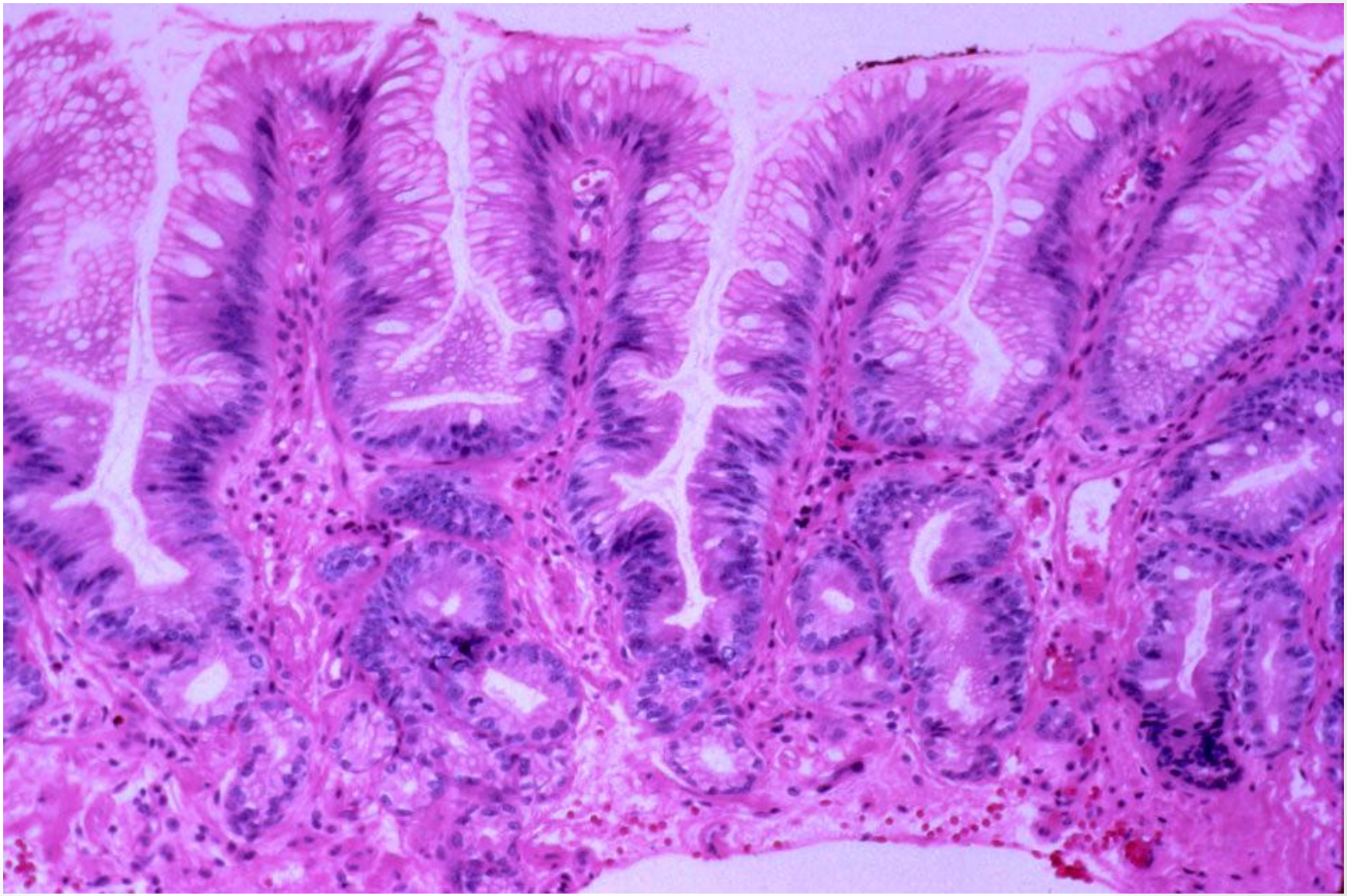
Reinterpretations	No.	Percent
Gastric only	18	9%
Barrett's negative	35	18%
Barrett's indefinite	61	32%
Barrett's LGD	79	41%

Sangle N and Bronner MP: Mod Pathol, In press 2015

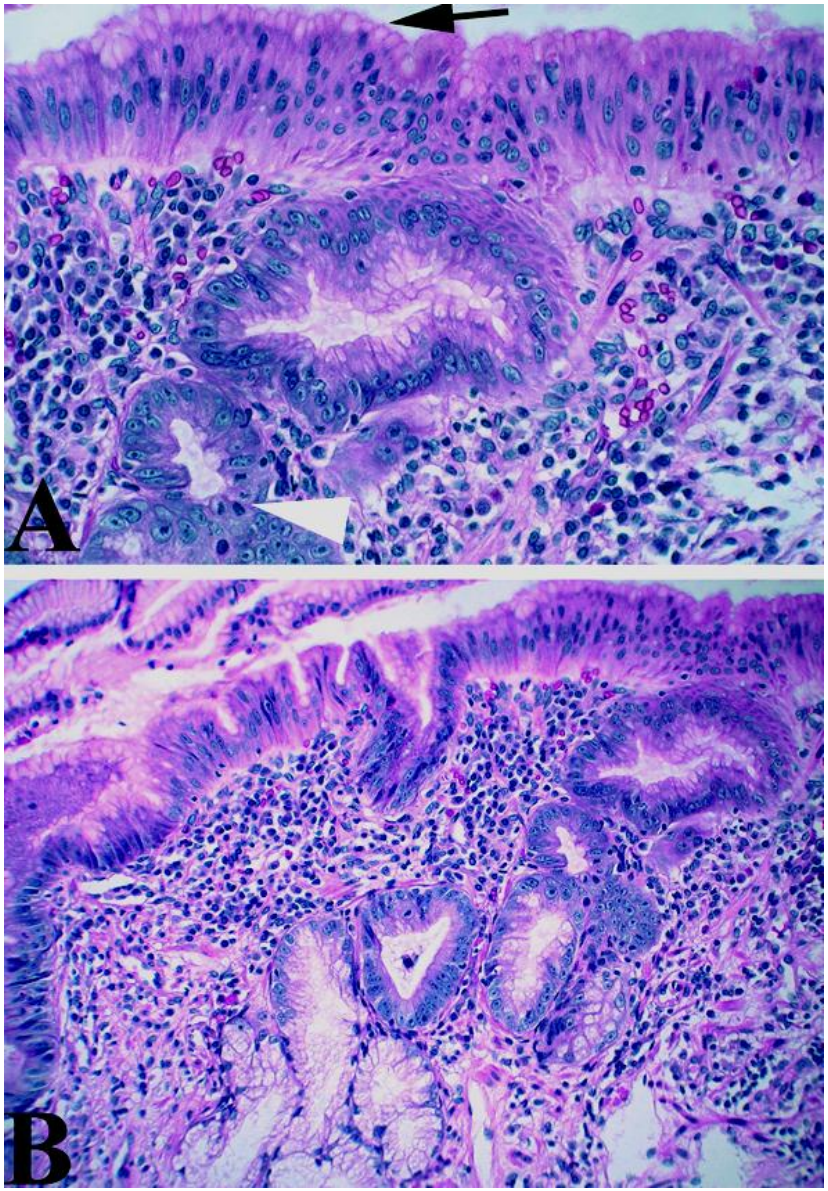
Diagnostic Pitfalls: HGD in Barrett's Esophagus

- NOT atypia limited to basal glands
- NOT reactive gastric cardiac-type mucosa
- NOT inflammatory reactive change
- Sampling error

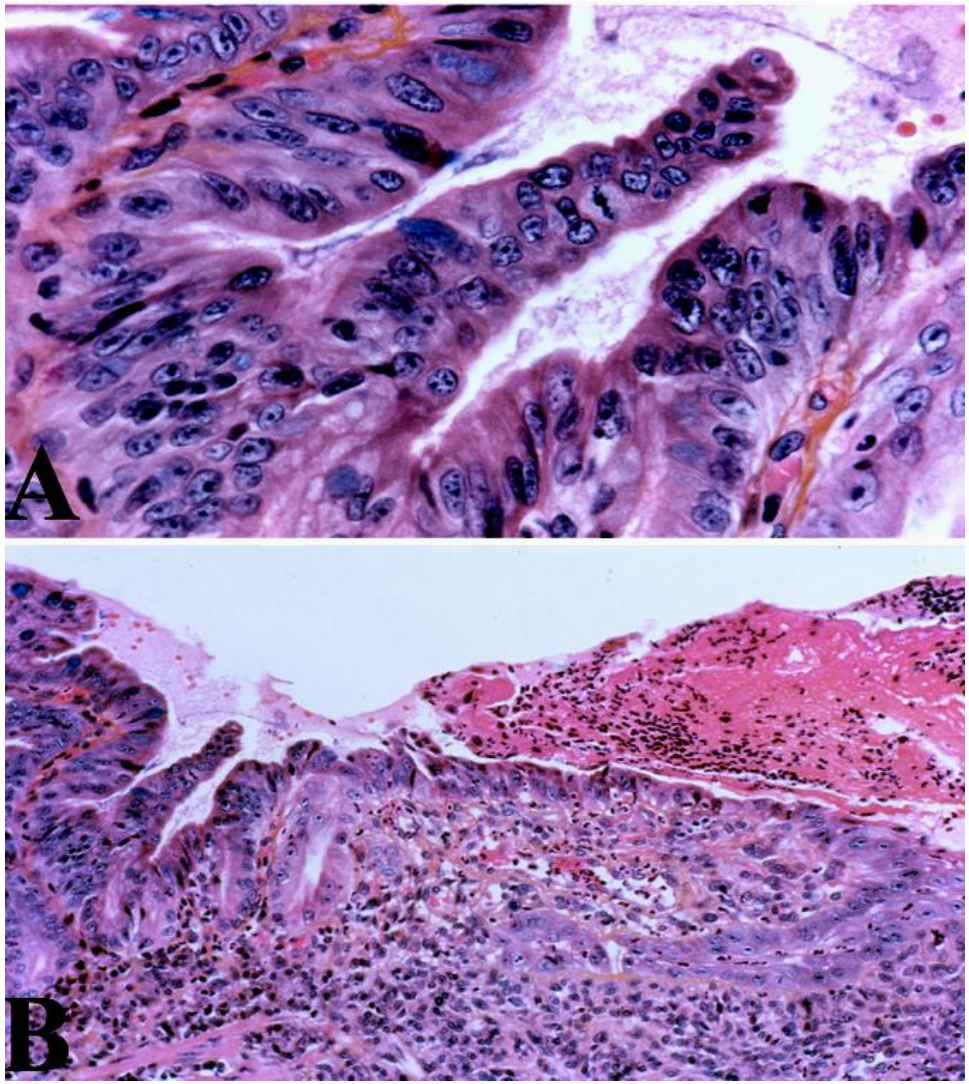
NOT Baseline Glandular Atypia



NOT Reactive Gastric Mucosa



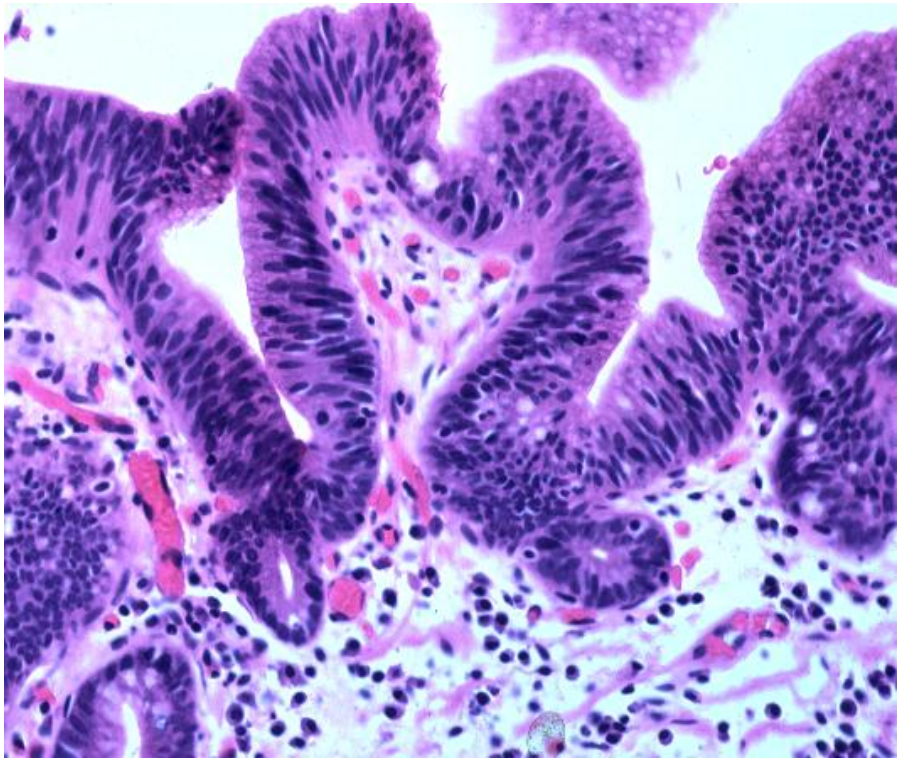
NOT Inflammatory Atypia

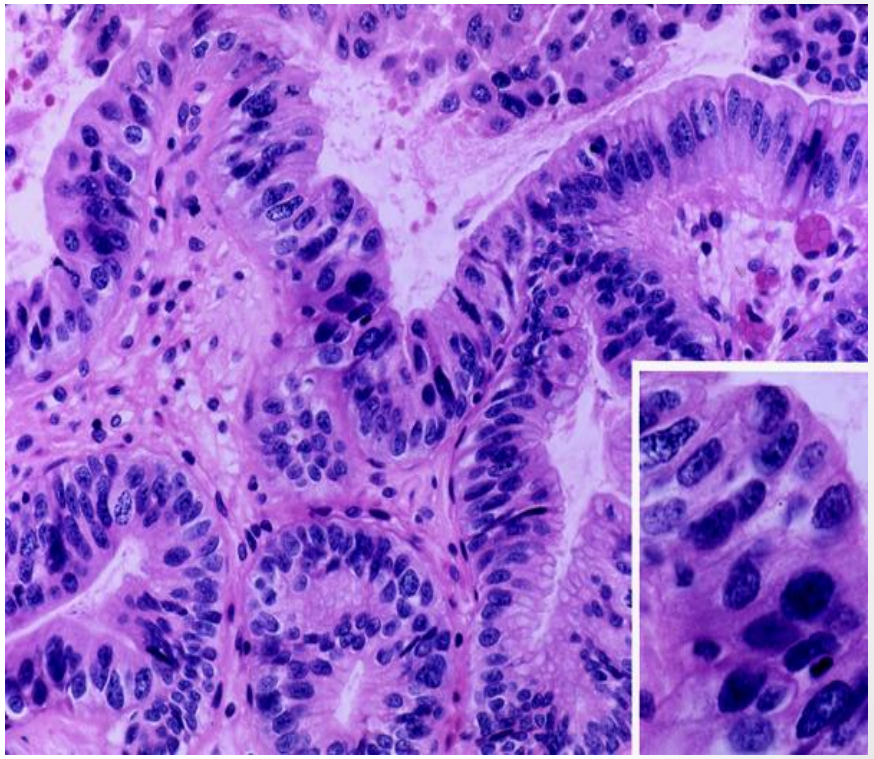


Over Diagnosis of HGD in BE

- Under utilization of loss of nuclear polarity as most objective criterion
- Morphologic spectrum without precise definable boundaries
- Accuracy is experience and volume dependent

Loss of Nuclear Polarity to Distinguish Low and High-Grade Dysplasia



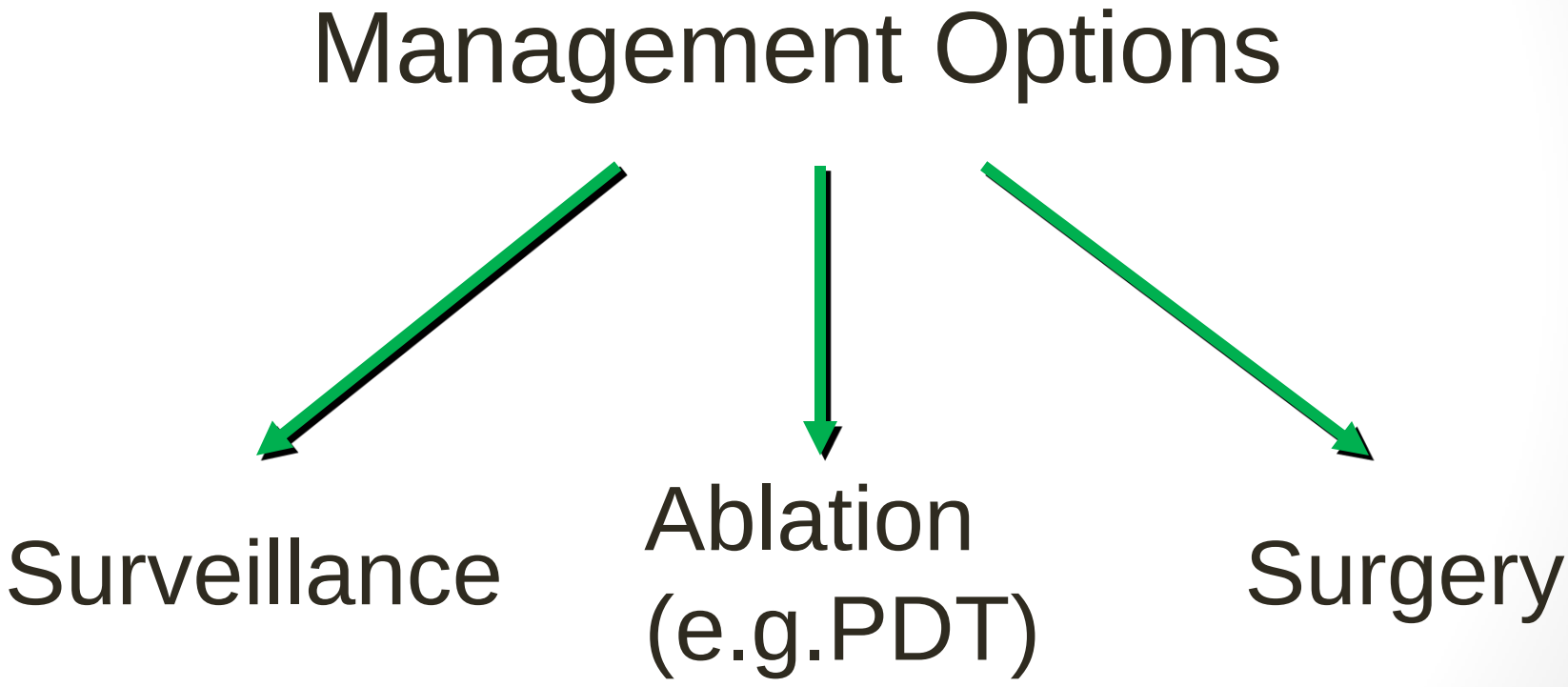


ACG GUIDELINES

High-grade dysplasia in Barrett's esophagus should be confirmed by an expert GI pathologist

Wang KK, Sampliner RE. *Am J Gastroenterol* 2008;103:788.

High Grade Dysplasia



Can we tell BAD from WORSE?

Shaheen NJ. Gastroenterology 2003; 125:260.

Interobserver Variability: At Least High-grade Dysplasia

Diagnosis	Kappa	P-value	95% CI	Interp
ALL	0.30	<0.001	0.28-0.32	Poor
HGD	0.47	<0.001	0.44-0.51	Mod
HGD-MAD	0.21	<0.001	0.18-0.25	Poor
IMC	0.30	<0.001	0.26-0.33	Poor
SMC	0.17	<0.001	0.14-0.21	Poor

Erinn Downs-Kelly, et al. *Am J Gastroenterol* 103:2333-2340, 2008

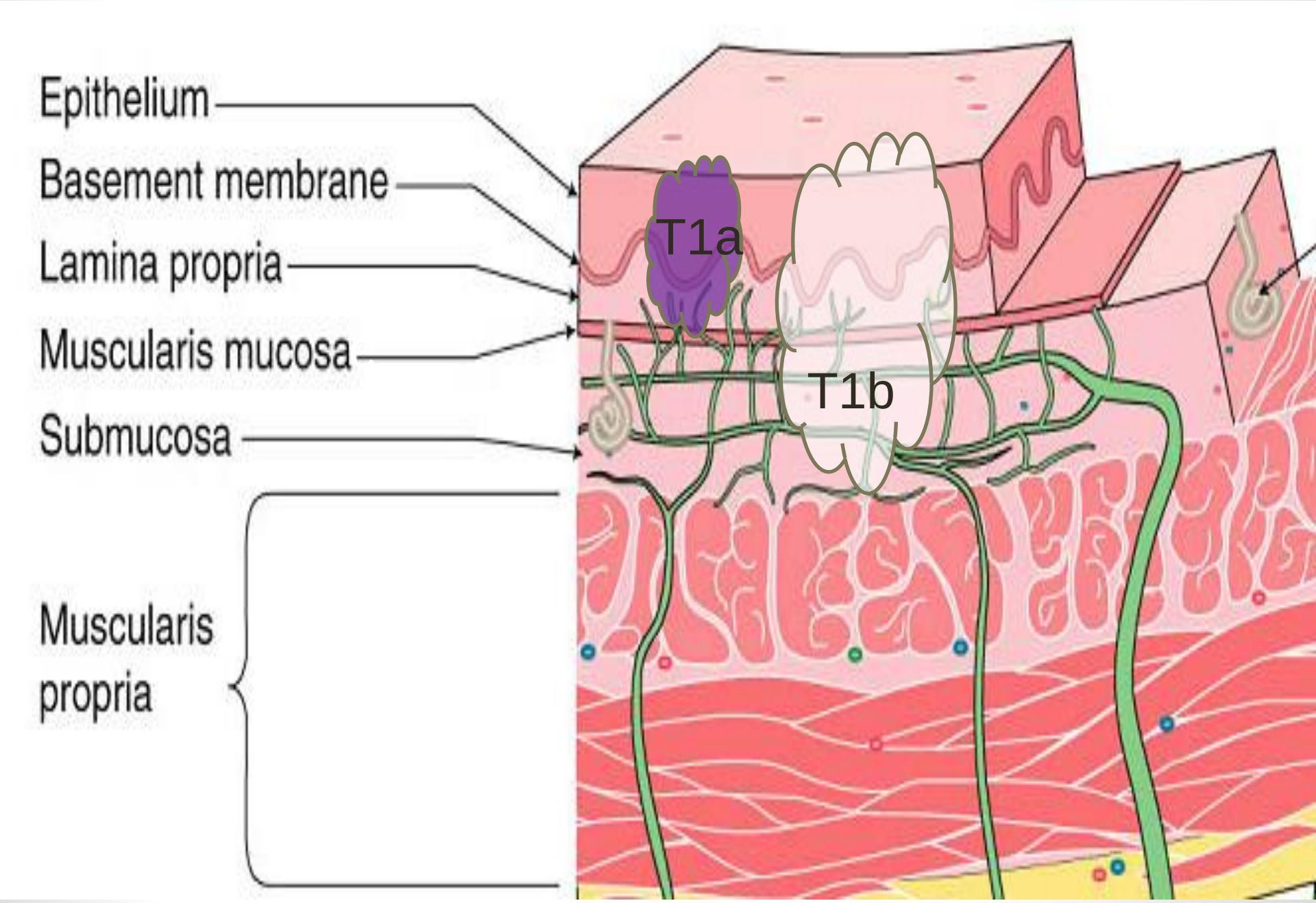
Can we tell BAD from WORSE?

- NO! Not on Biopsies!
- Management based on distinction between HGD, IMC & SMC in *biopsies* is questionable
- What about EMR?

Bx vs. EMR Histology

Study	# of Pt	Up-stage by EMR	Down-stage by EMR	Total EMR Altered
Larghi, 2005	48	13%	2%	15%
Hull, 2006	41	34%	5%	39%
Chennat, 2009	49	14%	31%	45%
Moss, 2010	75	20%	28%	48%

Note: EMR results altered the bx diagnosis 15-48% of the time

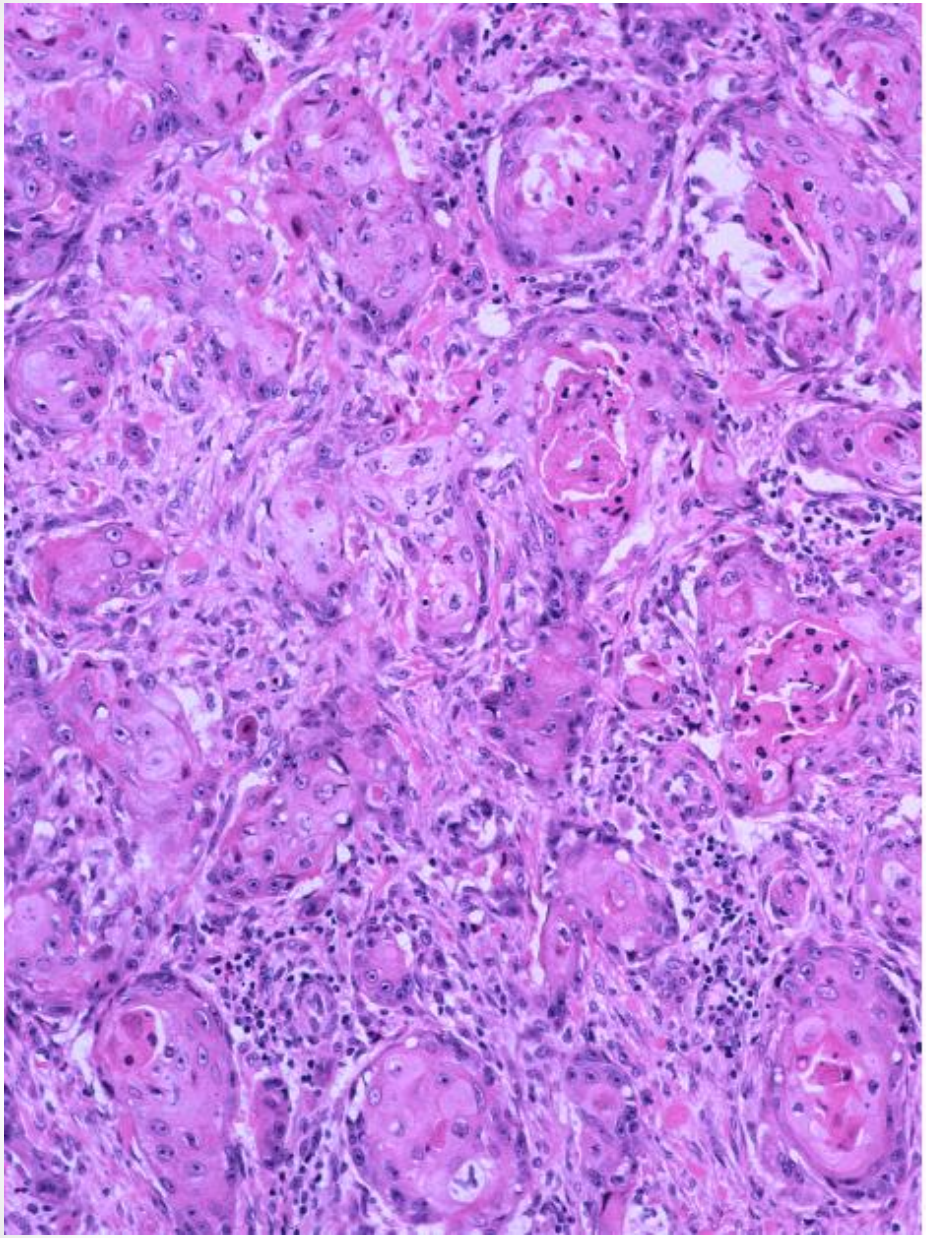

Epithelium
Basement membrane
Lamina propria
Muscularis mucosa
Submucosa
Muscularis propria
T1a
T1b

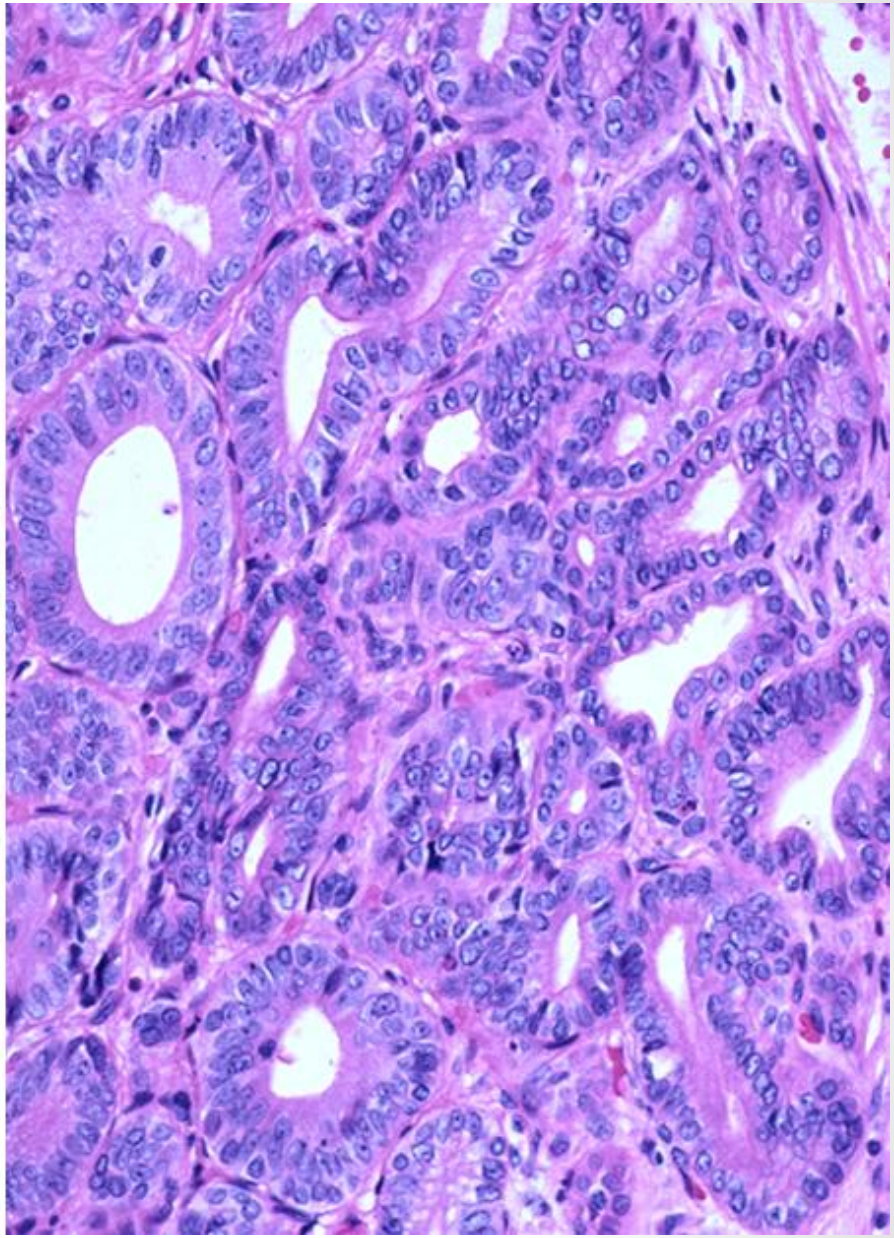
T1a Esophageal CA

- Intramucosal carcinoma
  - Invades into
    - lamina propria
    - muscularis mucosae
- Low metastatic rate 1-2%

T1b Esophageal CA

- Submucosal carcinoma
  - Subdivided into thirds (no reliable significance)
- High metastatic rate ~30%

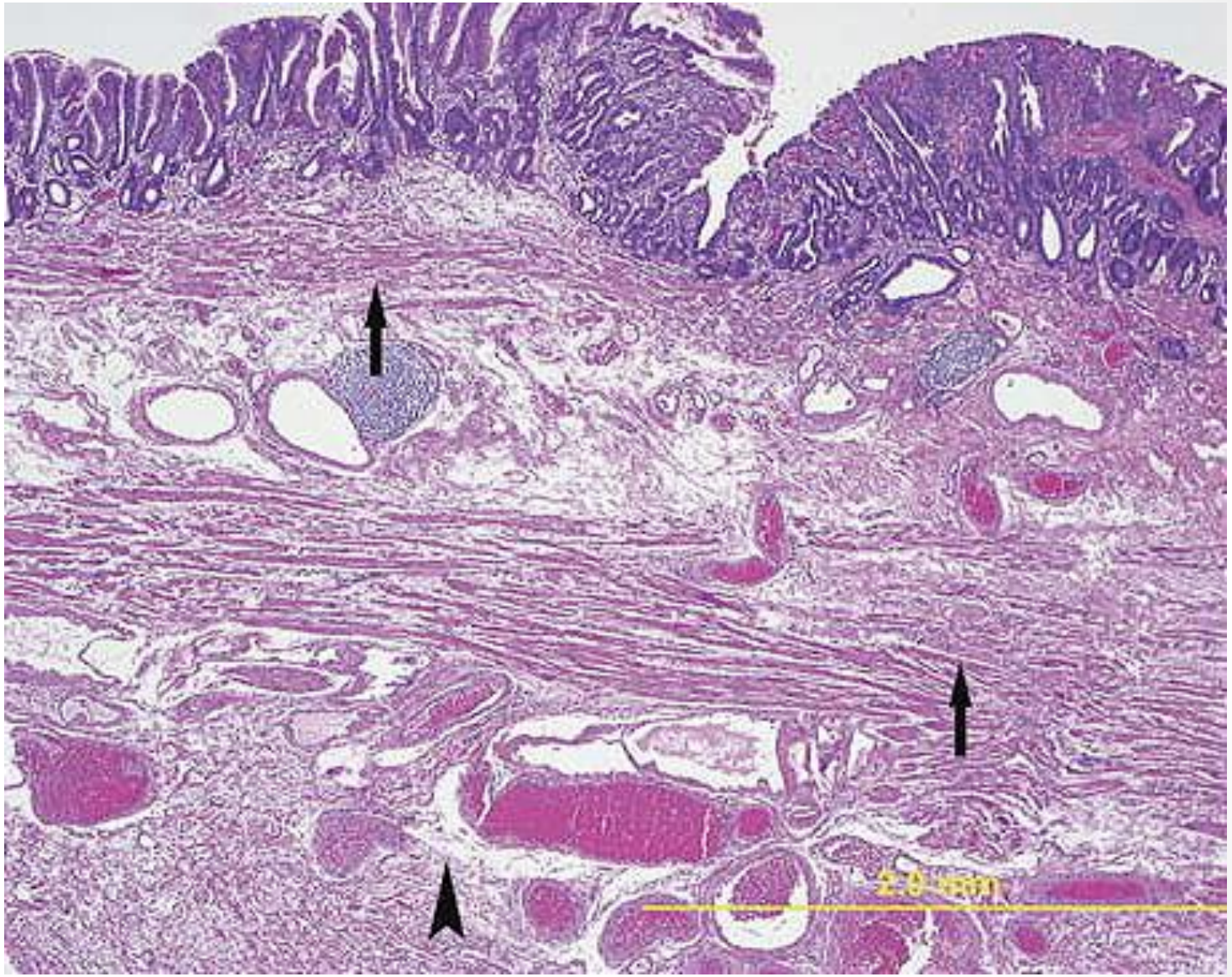




EMR for T1a (HGD/IMC)

Study	# Pt's	Avg F/U	Compl Resp	Recur/ Metachr
Ell, 2000	35	12 mo	97%	14%
May, 2002	70	34 mo	98%	30%
Pech, 2008	279	64 mo	97%	22%
Chennat, 2009 *CBE-EMR*	32	23 mo	97%	***3%***
Moss, 2010	75	31 mo	94%	11%

Duplicated Muscularis Mucosae in Barrett's



Estrella, et.al. *Am J Surg Pathol* 2011; 35:1045

Duplicated Muscularis Mucosae

- Easy to overcall split MM space as submucosal invasion (T1b)
- EMR & EUS also overstage
- >60% of IMC cases overstaged

Mandal, et.al. *AJSP* 2009;33:620

Split MM CA's are T1a

Invasion Depth	Nodal Mets
Mucosa & Dupl MM	1/69 (1.4%)
Submucosa	10/30 (33.3%)

Estrella JS, et.al. *Am J Surg Pathol* 2011; 35:1045

BE Dysplasia Summary-1

- Grading of dysplasia: intestinal & gastric foveolar types
- Problems with dysplasia
  - Sampling
  - Observer variation
  - Natural history: prevalent vs. incident

BE Dysplasia Summary-2

- Over diagnosis of HGD
  - Baseline atypia of metaplasia
  - Reactive cardia
  - Inflammatory change
  - Loss of nuclear polarity
- HGD management options broadening

BE Dysplasia Summary-3

- HGD management options broadening
- Continued surveillance: incident HGD
- Ablation
- CBE-EMR
  - Duplicated muscularis mucosae: beware of overstaging T1a to T1b