

Dysplasia of the GI Tract: Pitfalls and Solutions

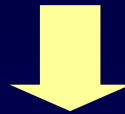
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and Molecular Oncology

University of Utah / ARUP Laboratories

Neoplastic Progression in Chronic Inflammatory GI Dz

Chronic Reflux



GERD



Metaplasia



Dysplasia



Adenocarcinoma

Dysplasia

Definition

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

Case 1

Barrett's Esophagus
with Dysplasia

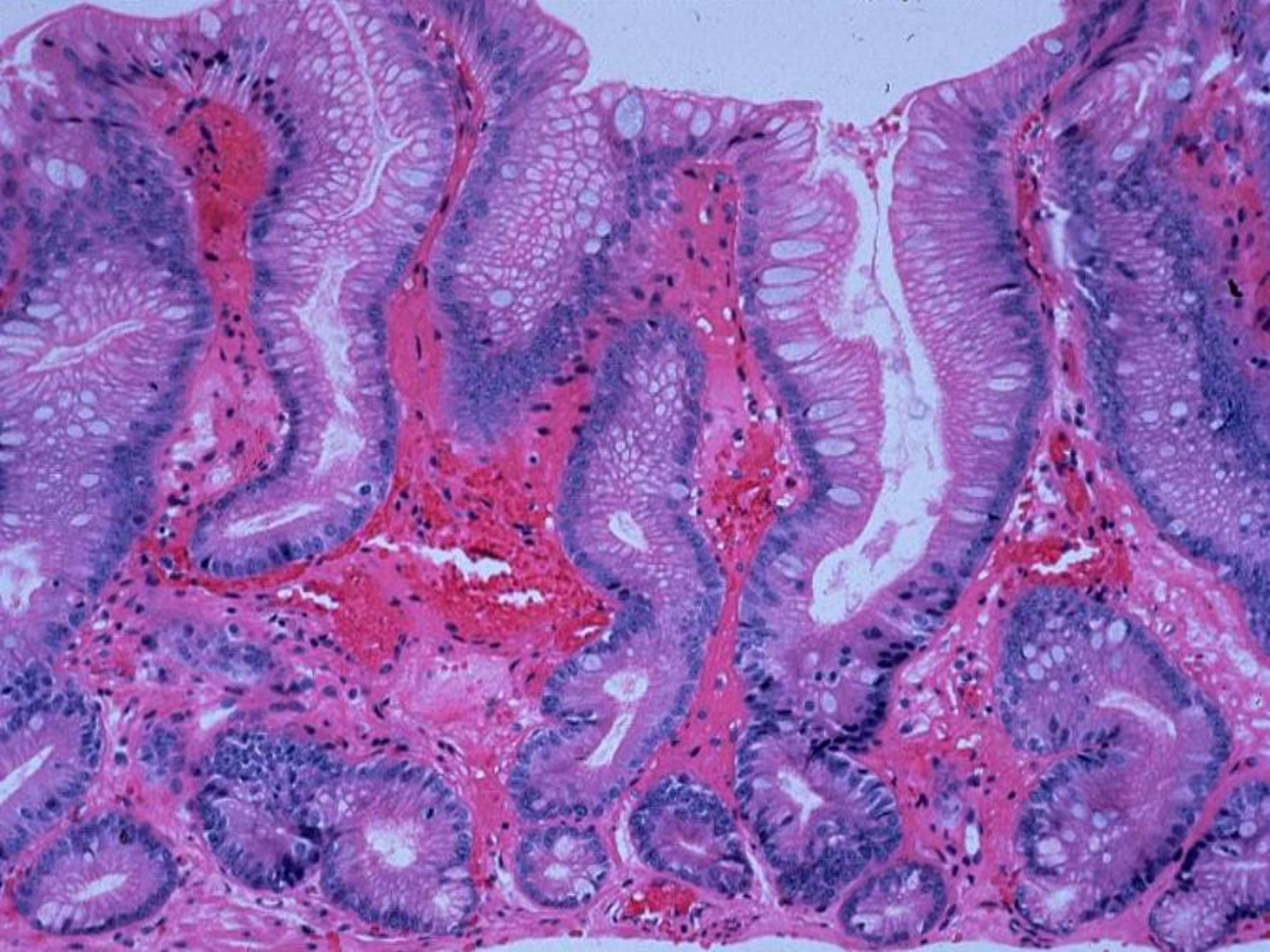
Grading System for GI Dysplasia

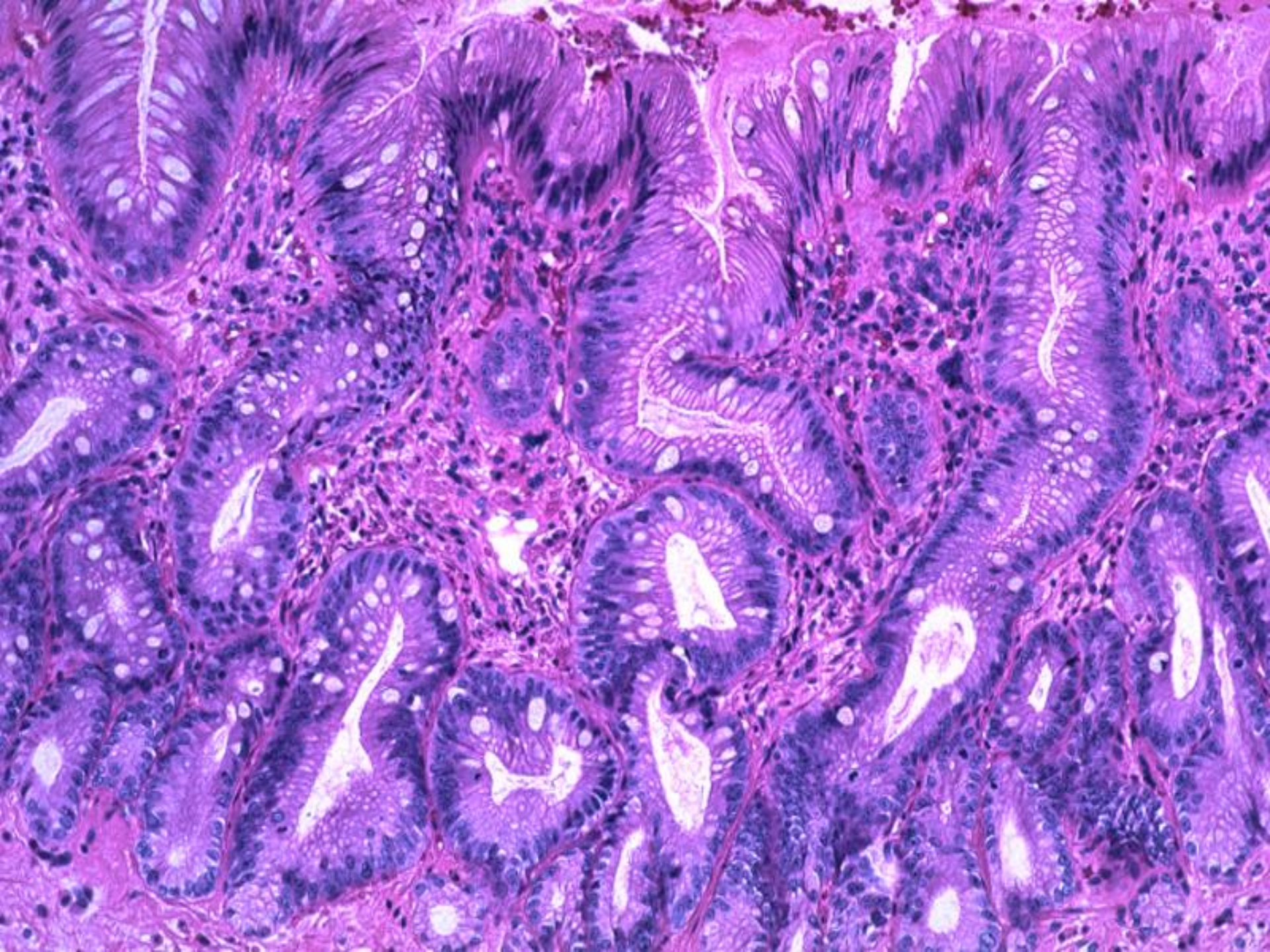
- Negative
- Indefinite
- Positive
 - Low-grade
 - High-grade

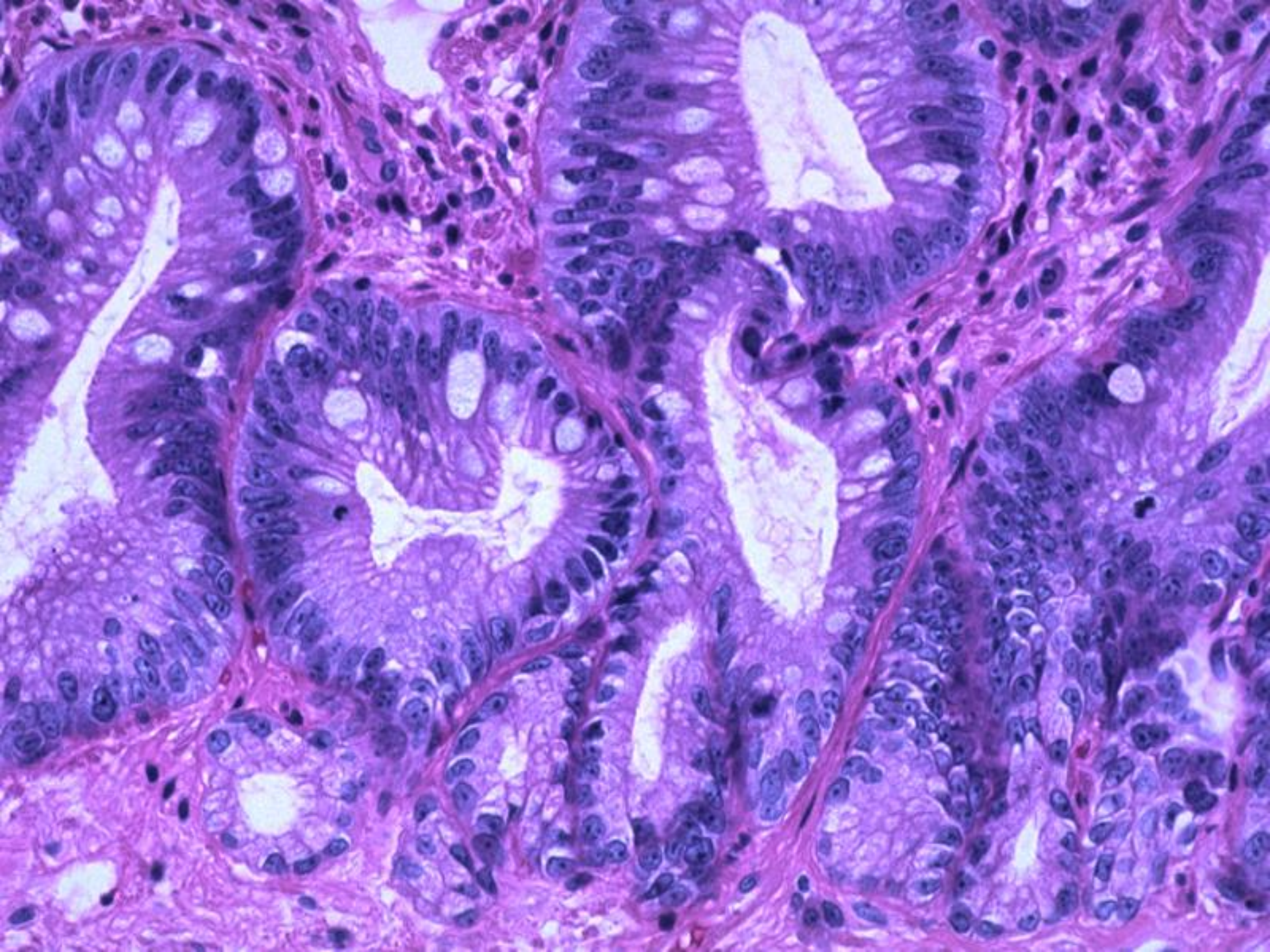
Barrett's Dysplasia

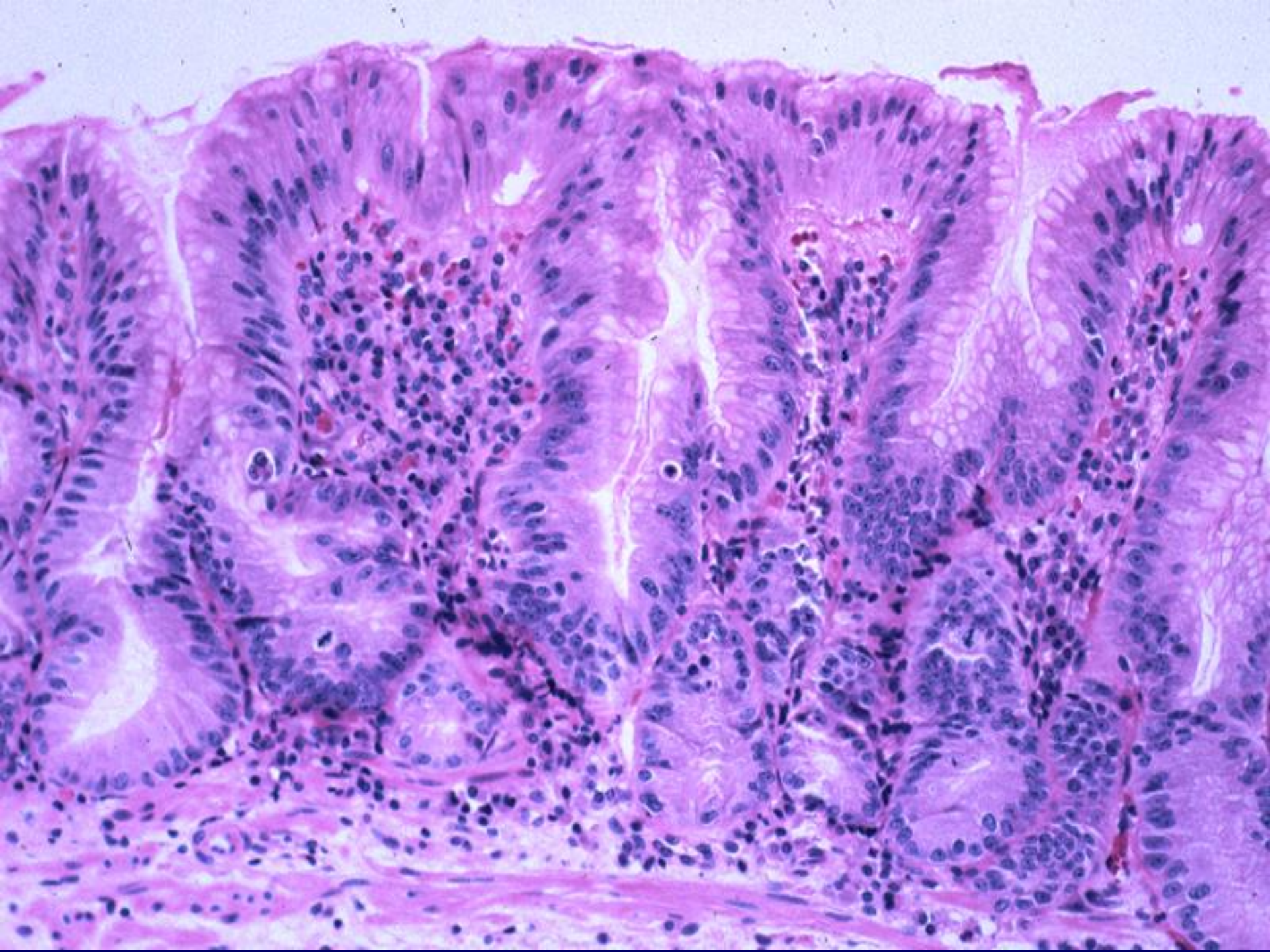
- Two types
 - Intestinal (85%)
 - Gastric Foveolar (15%)

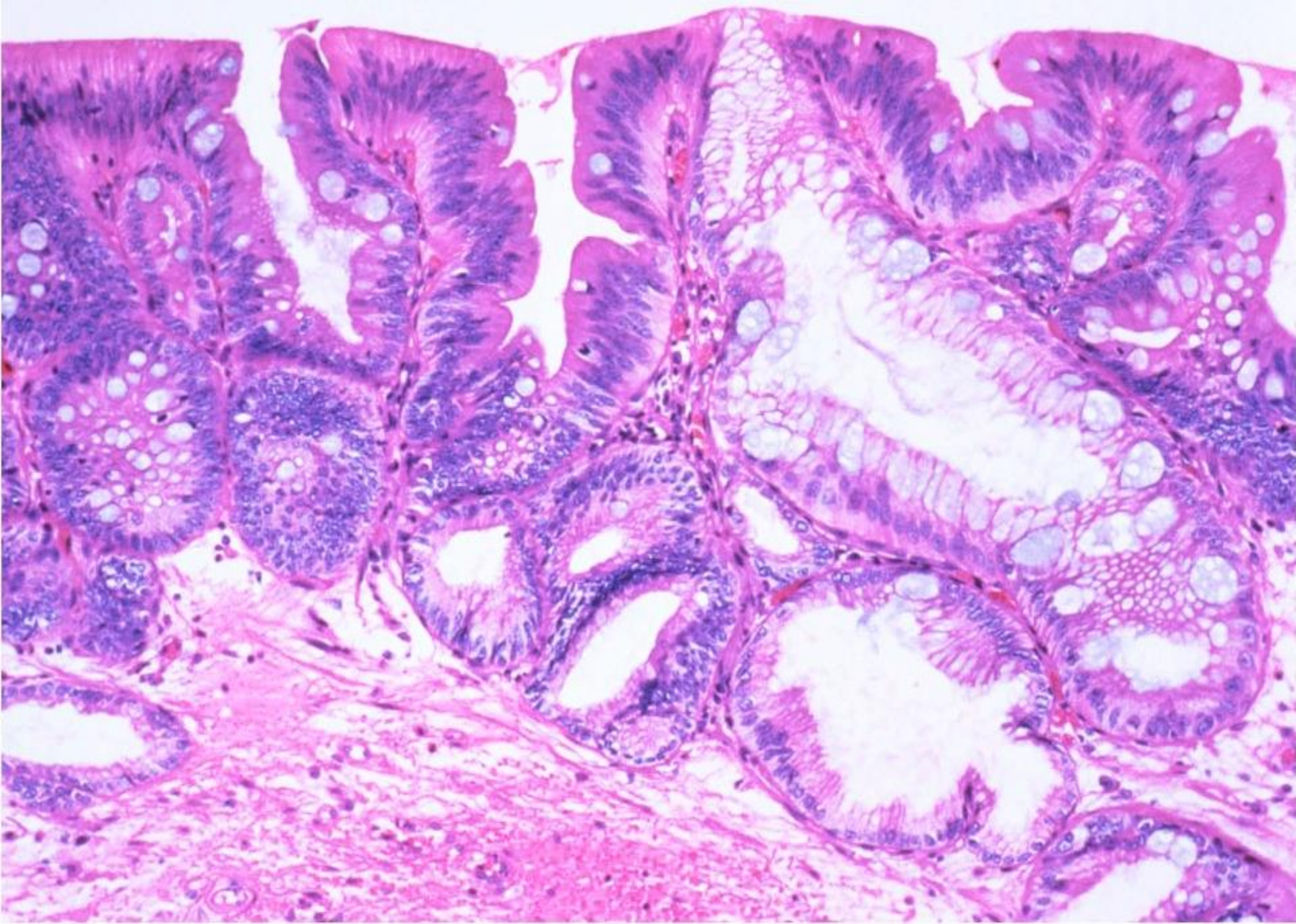
Barrett's Intestinal-type Dysplasia



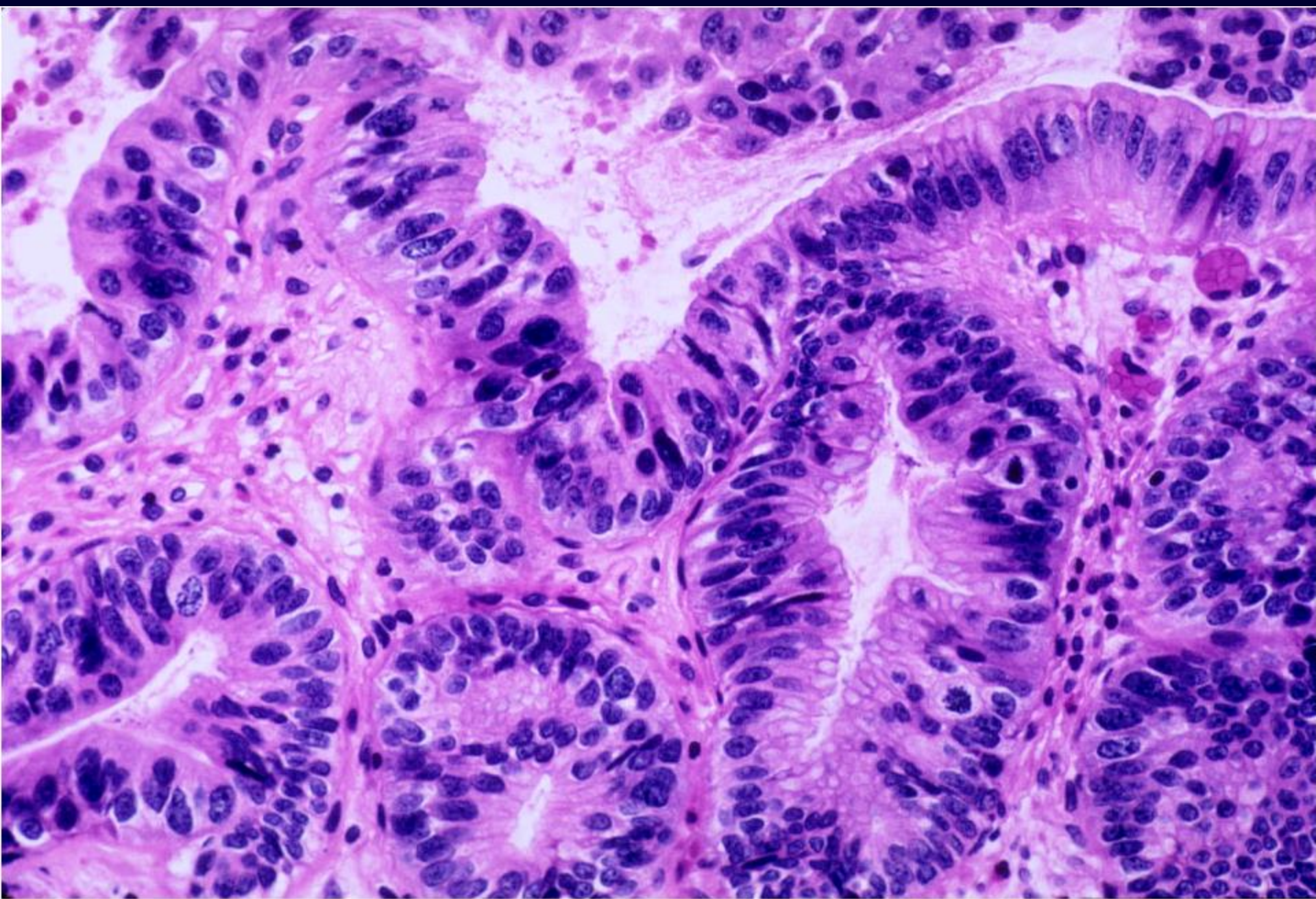


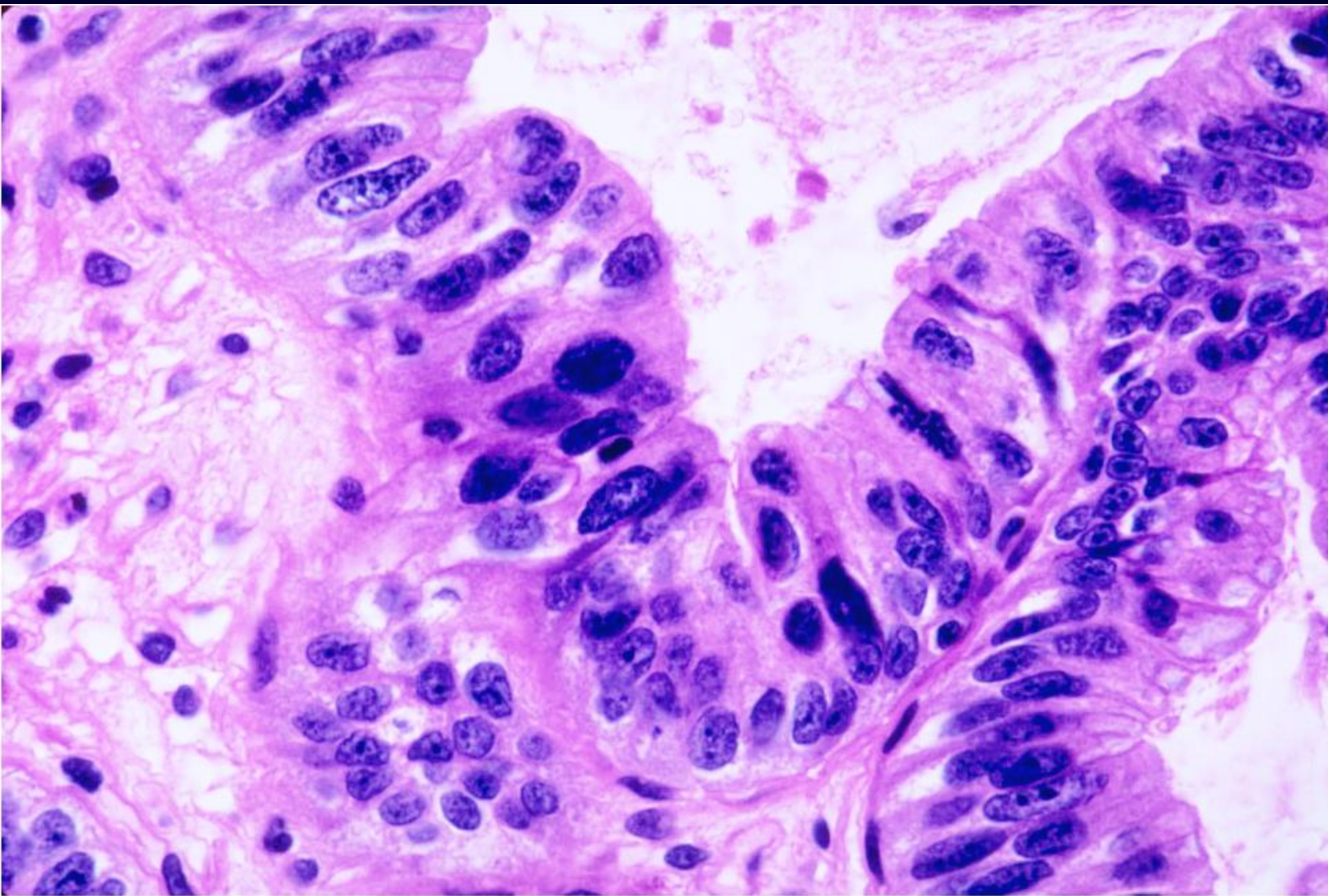


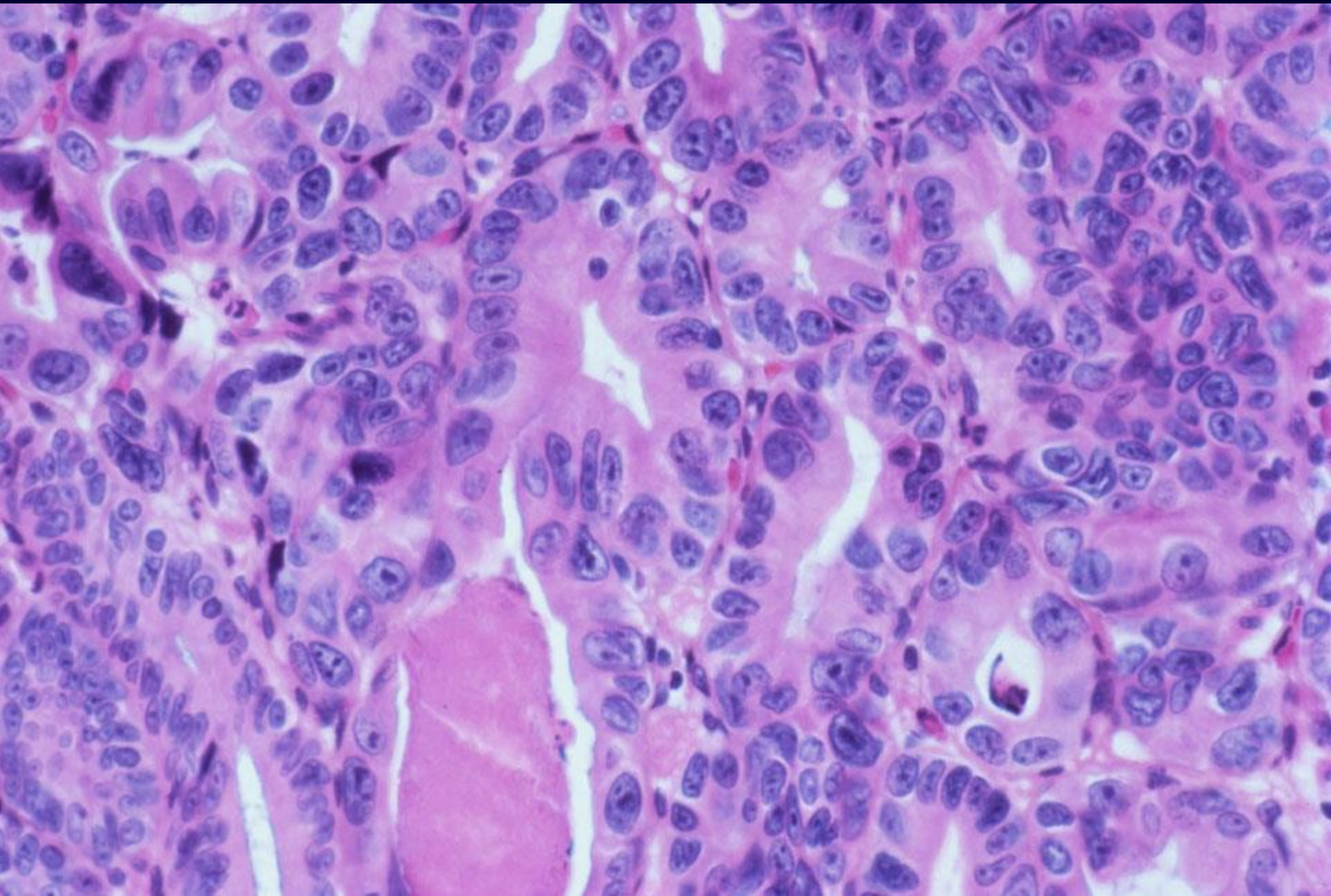






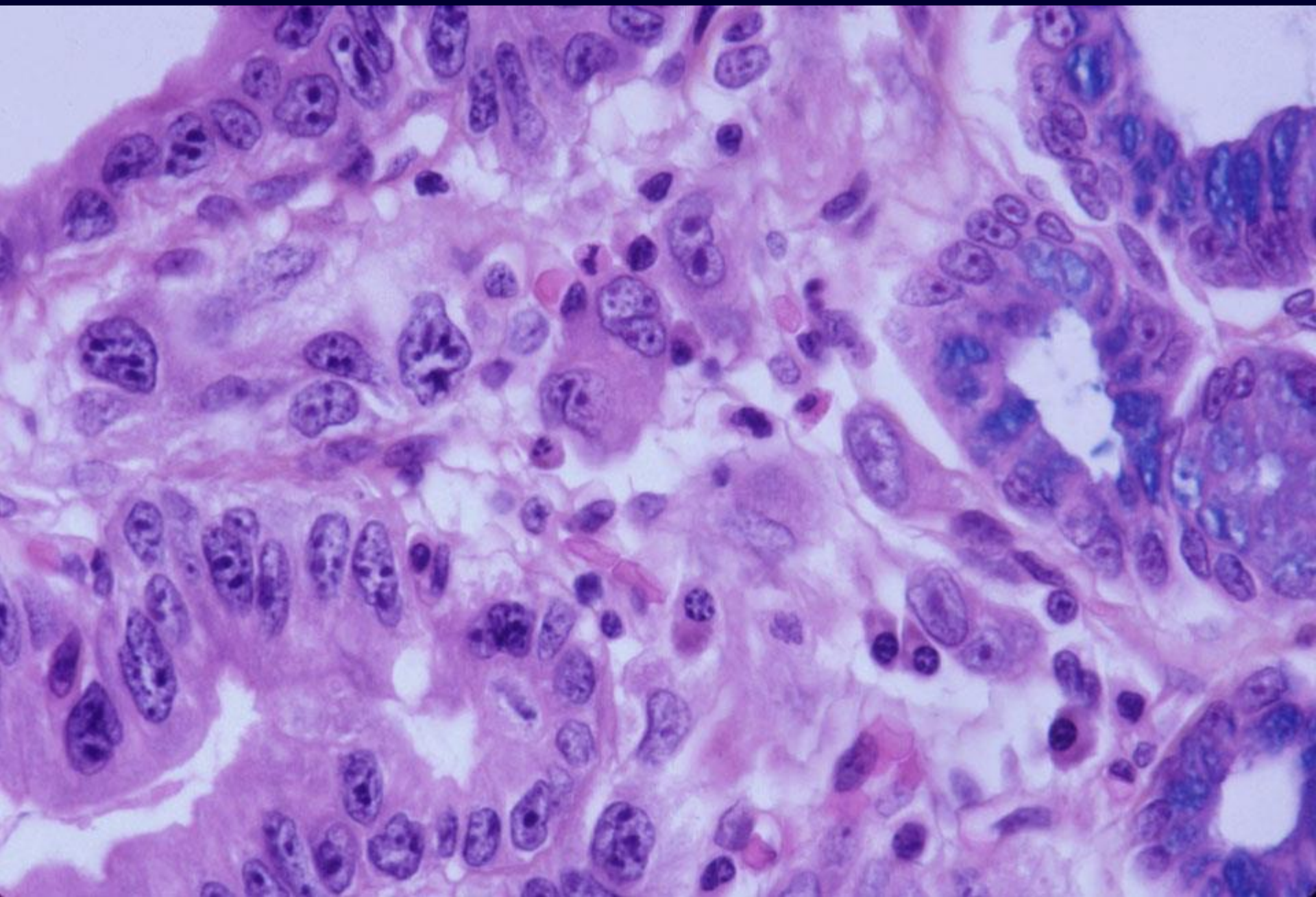


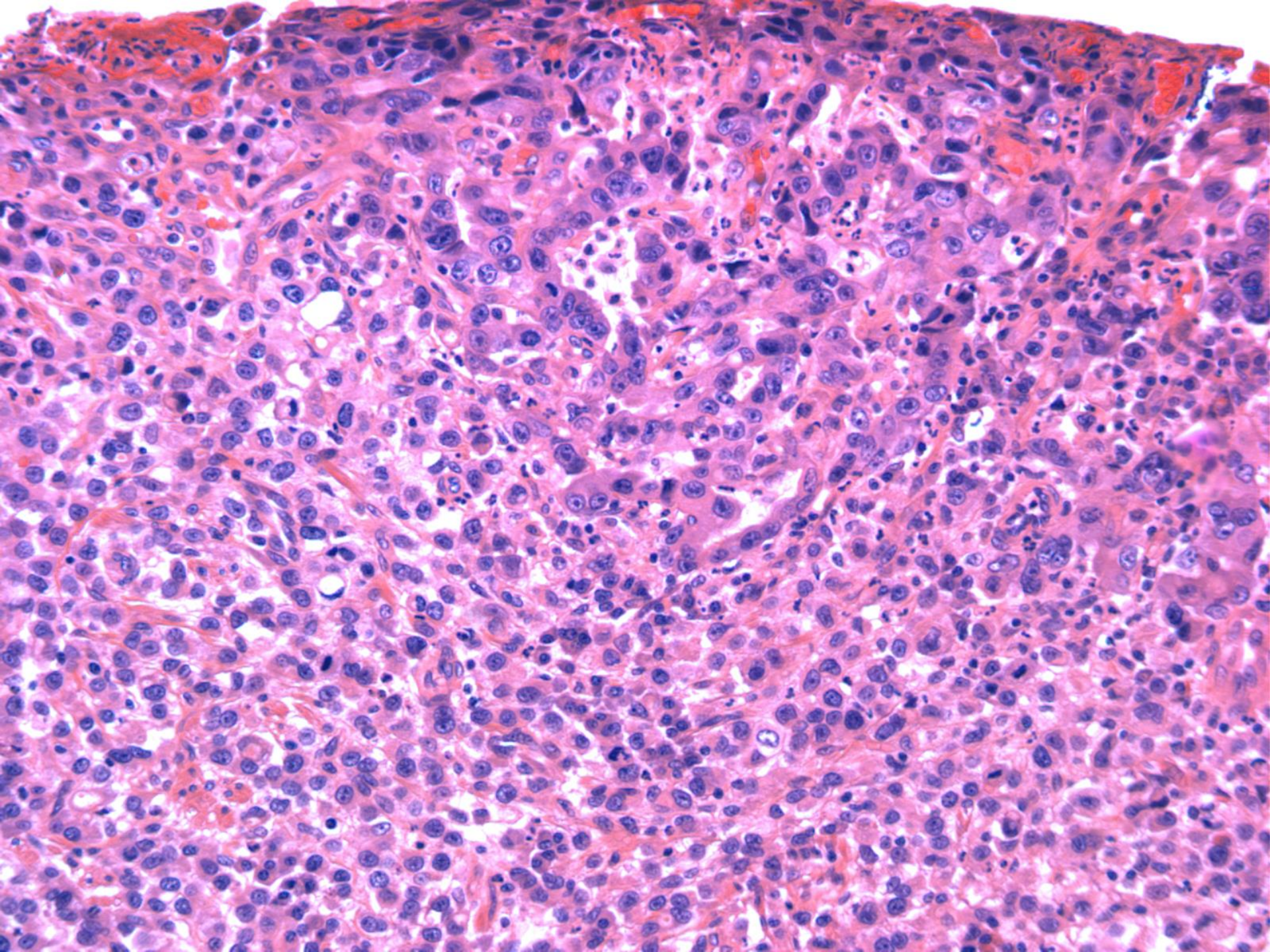


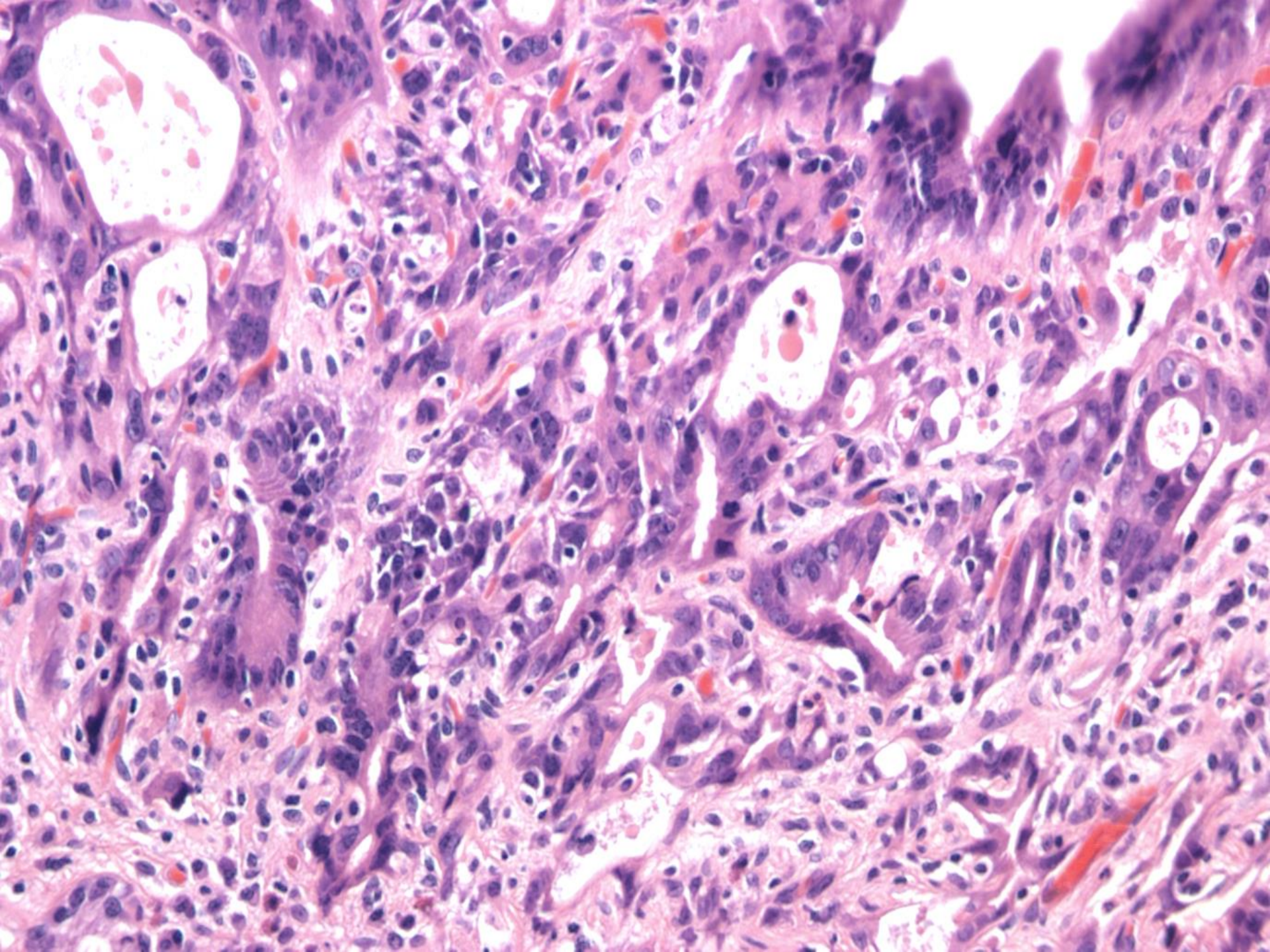


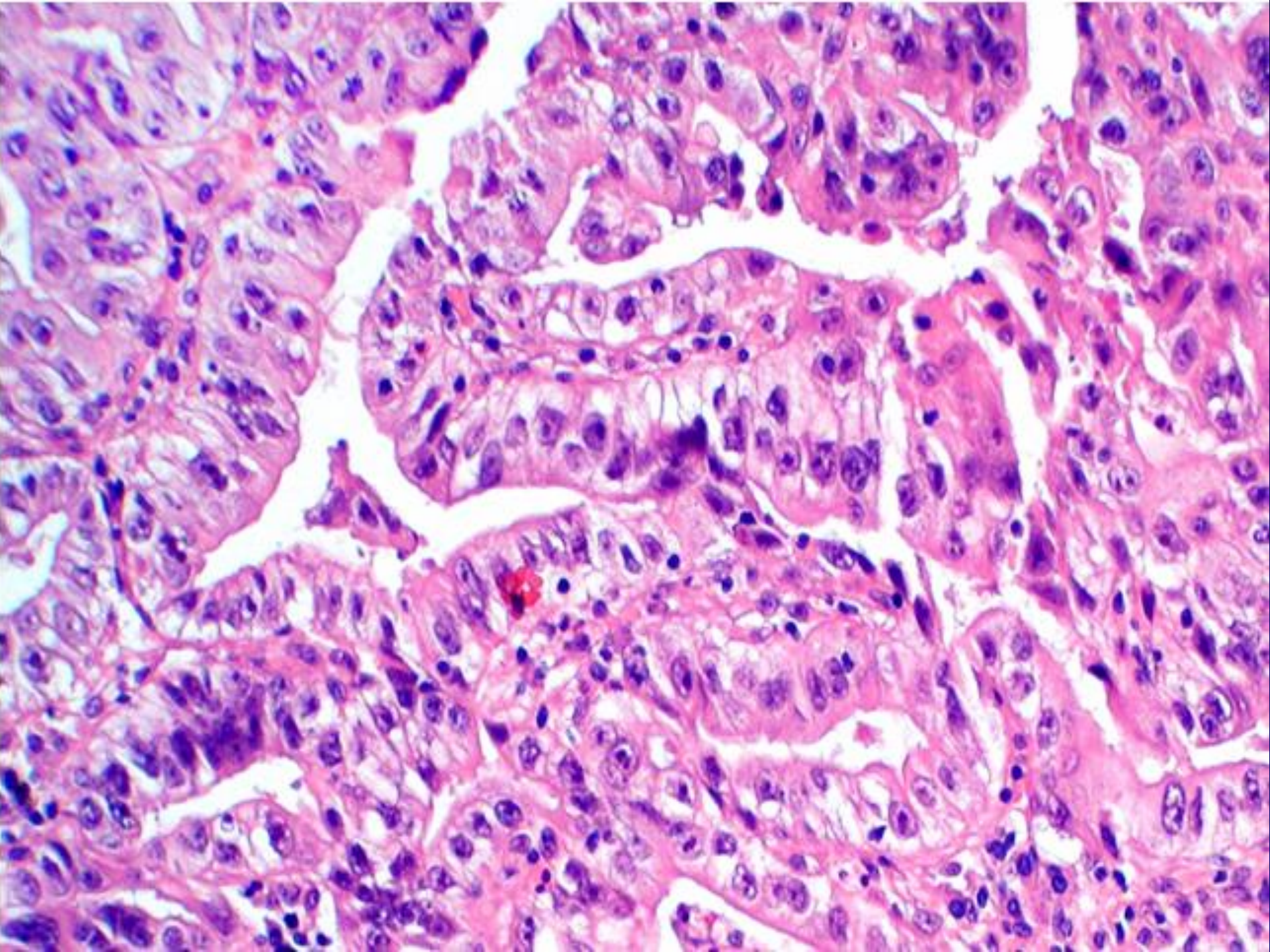
Intramucosal Adenocarcinoma

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









Barrett's
Gastric Foveolar-type
Dysplasia

Gastric-Type Barrett's Dysplasia

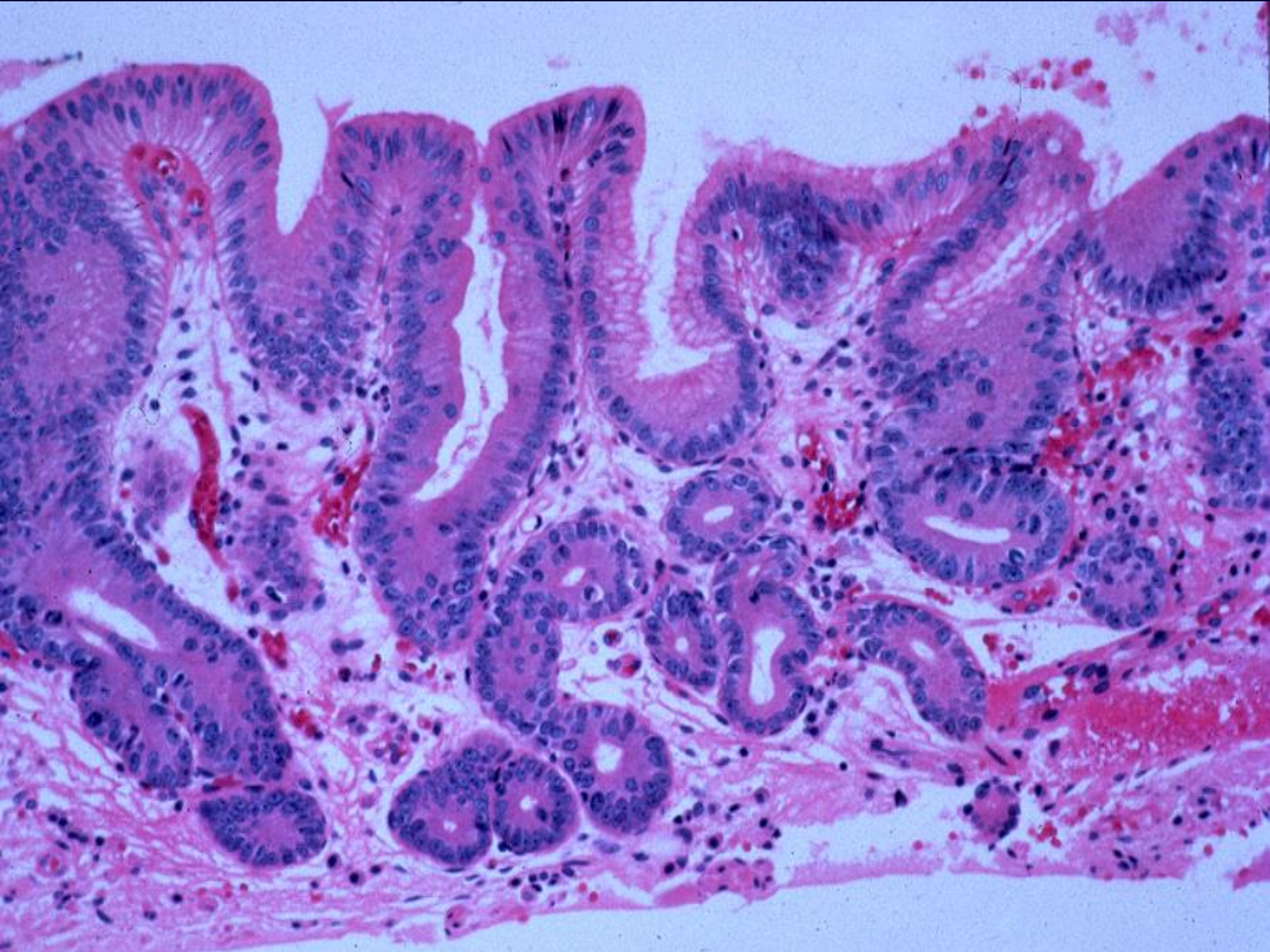
- **Very** different criteria from intestinal-type
- Non-stratified, basal nuclei precludes loss of nuclear polarity criterion

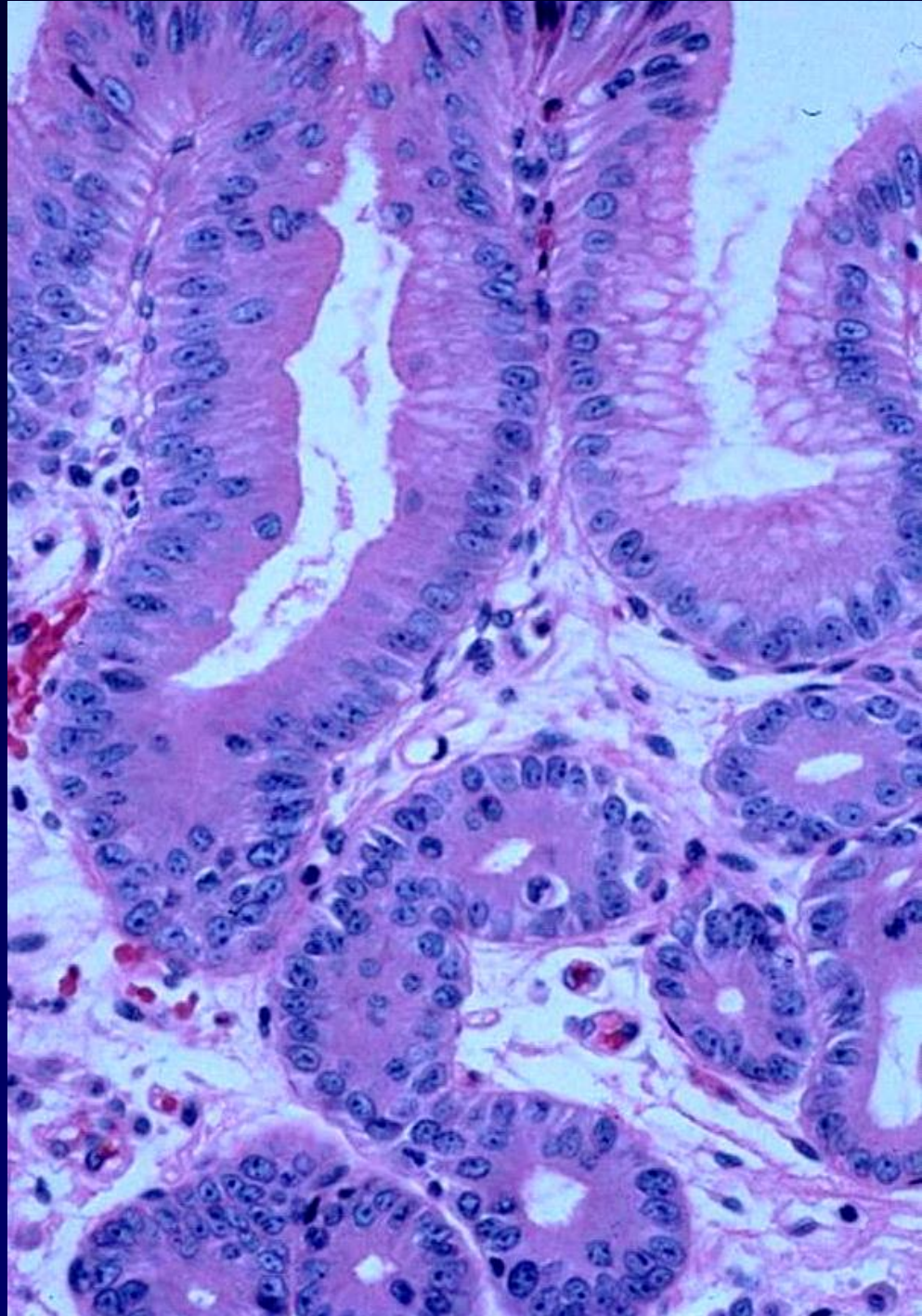
Gastric-Type Barrett's Dysplasia

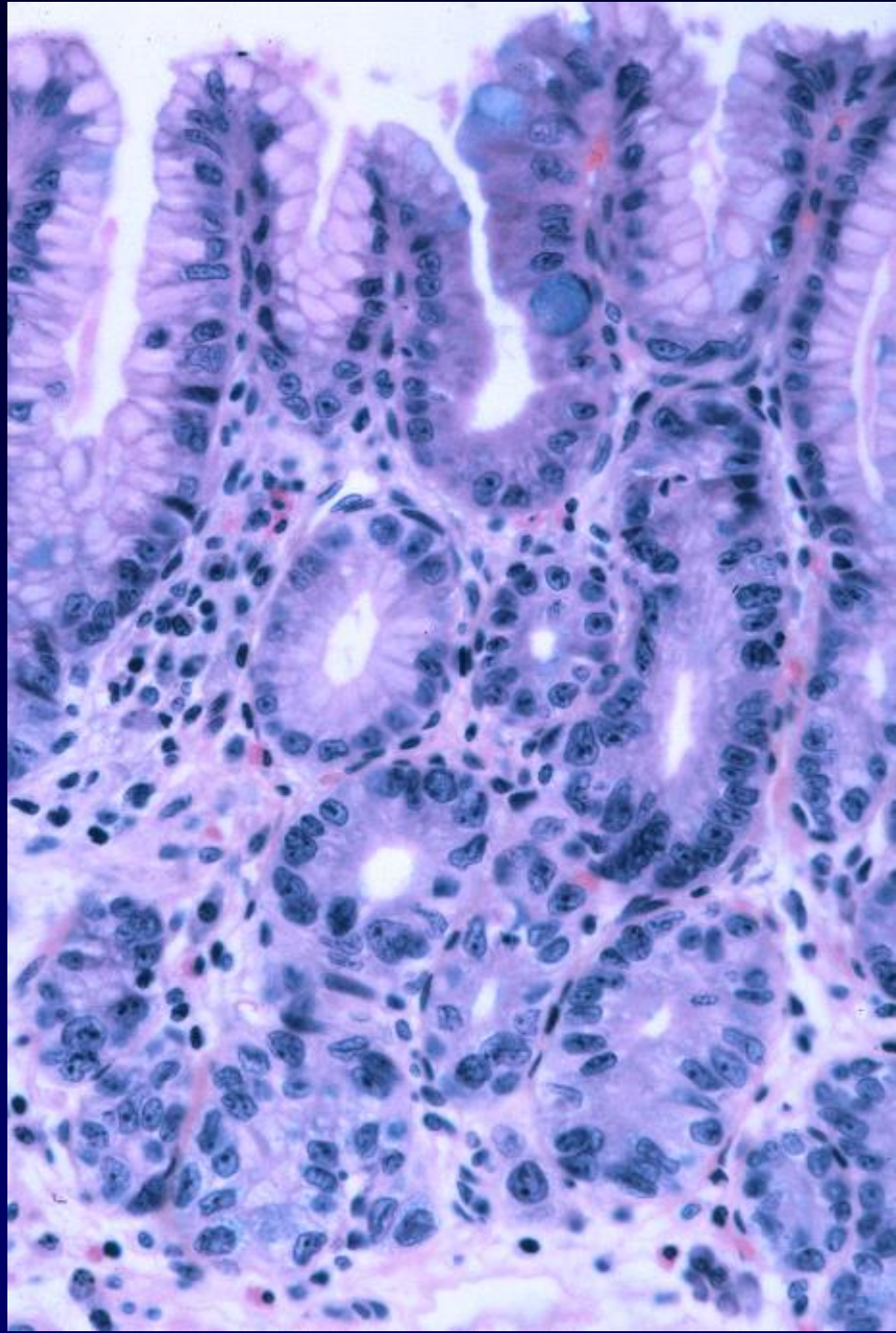
- *Gastric-type* LGD & HGD distinguished by
 - nuclear size cut off of 3-4X small lymph
 - increased but mild pleomorphism
 - prominent nucleoli
 - eosinophilic to oncocytic cytoplasm
 - crowded, irregular glandular architecture

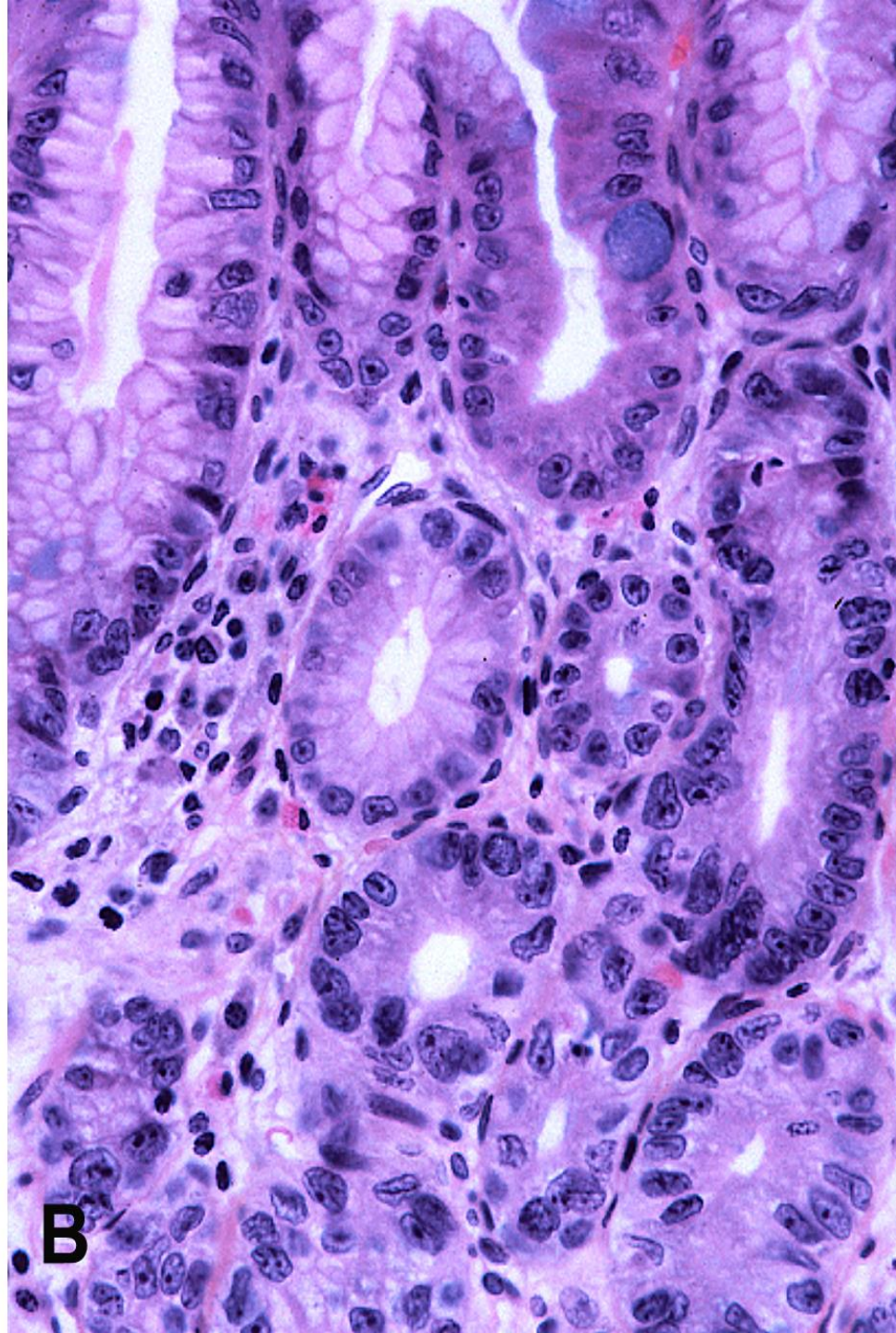
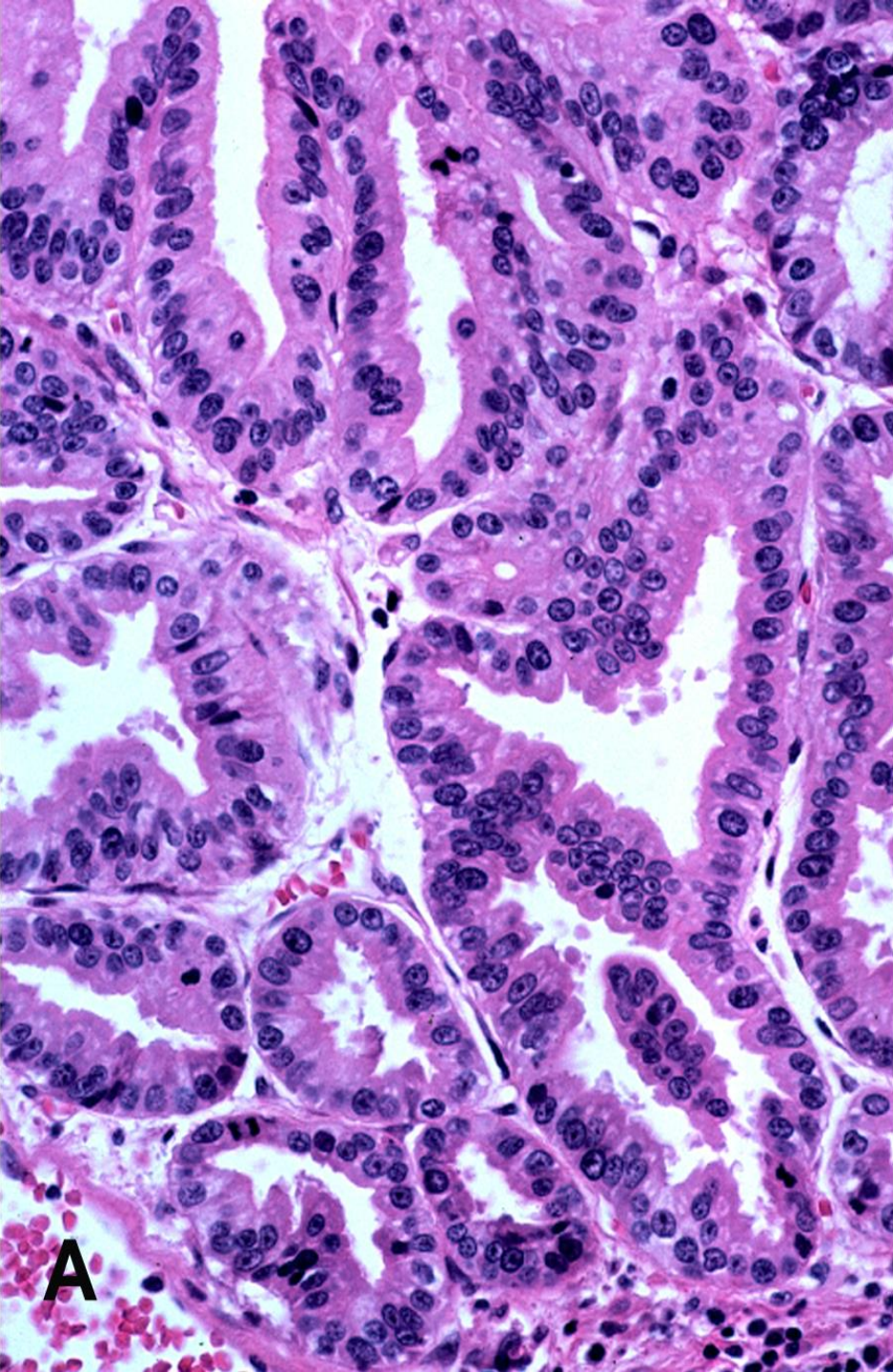
Mahajan D, et al. *Mod Pathol* 23:1, 2010

Serra S, et al. *Path* 49:391, 2017; *J Clin Pathol* 67:898, 2014









Gastric-Type Barrett's Dysplasia

Natural history poorly defined

- <100 pts in composite literature
- F:M = 2.7:1
- Decade older than intestinal 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

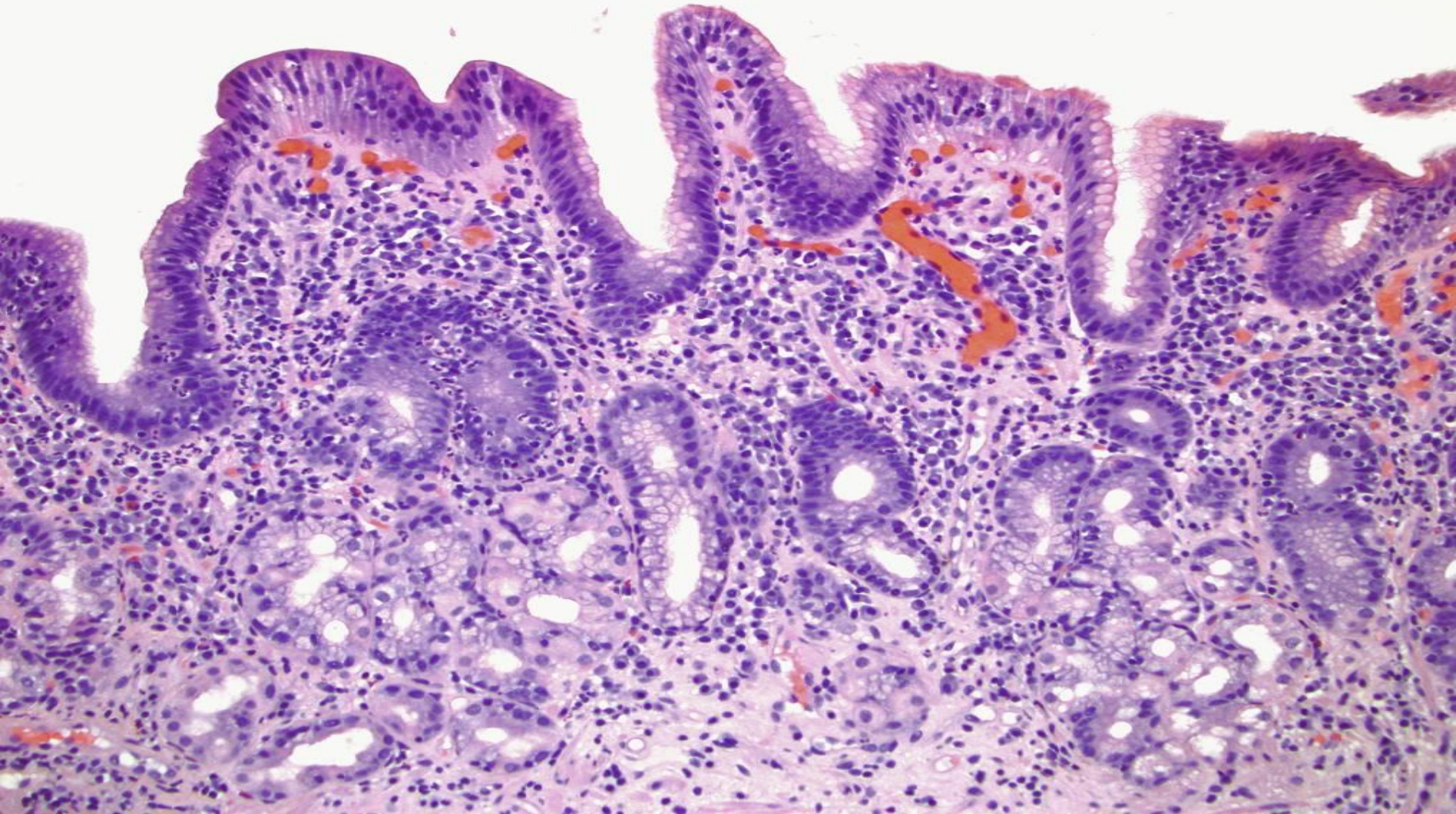
Stefano A, et al. *J Clin Pathol* 67:898, 2014

DDX GERD vs. Foveolar Dysplasia

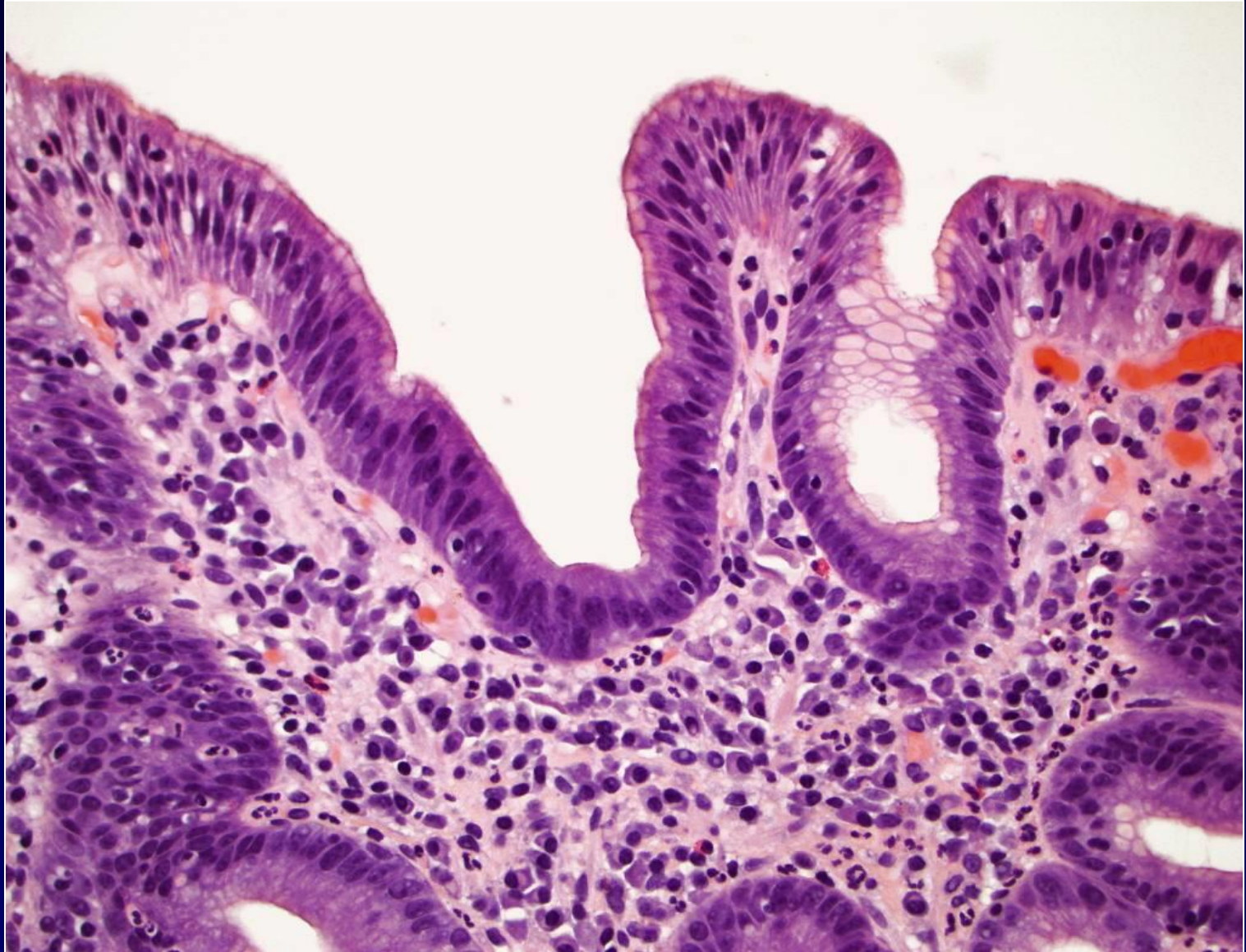
Feature	FOV DYS	GERD	P value	
<i>Nuc Strat</i>	0	80%	<0.00001	•3,698 EGD bxs 461 BE pts
<i>Top-Heavy Atypia</i>	0	80%	<0.00001	
<i>Full Thick Atypia</i>	80%	0	<0.00001	•80 bxs gastric-type dysplasia (13 LGD, 30 HGD)
<i>Villiform</i>	6%	53%	0.0006	
<i>Crowded Glands</i>	78%	0	<0.00001	•60 severe GERD
<i>Nucleoli</i>	79%	33%	0.0003	
<i>Pleomorph Mild</i>	35%	10%	0.09	

Hum Pathol 44:1146-53, 2013

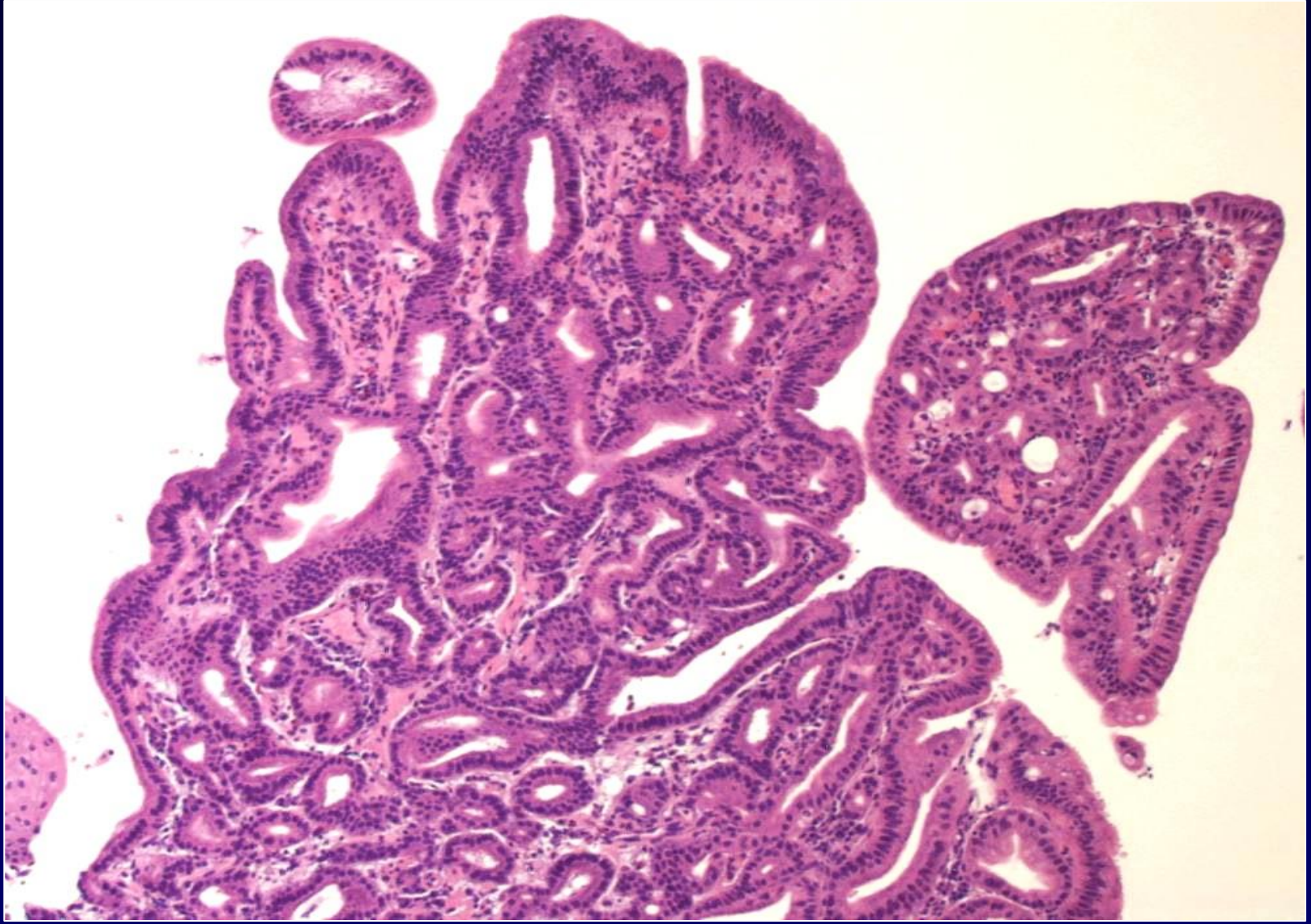
Reactive Cardia/GERD Villiform & 'Top-Heavy' Atypia



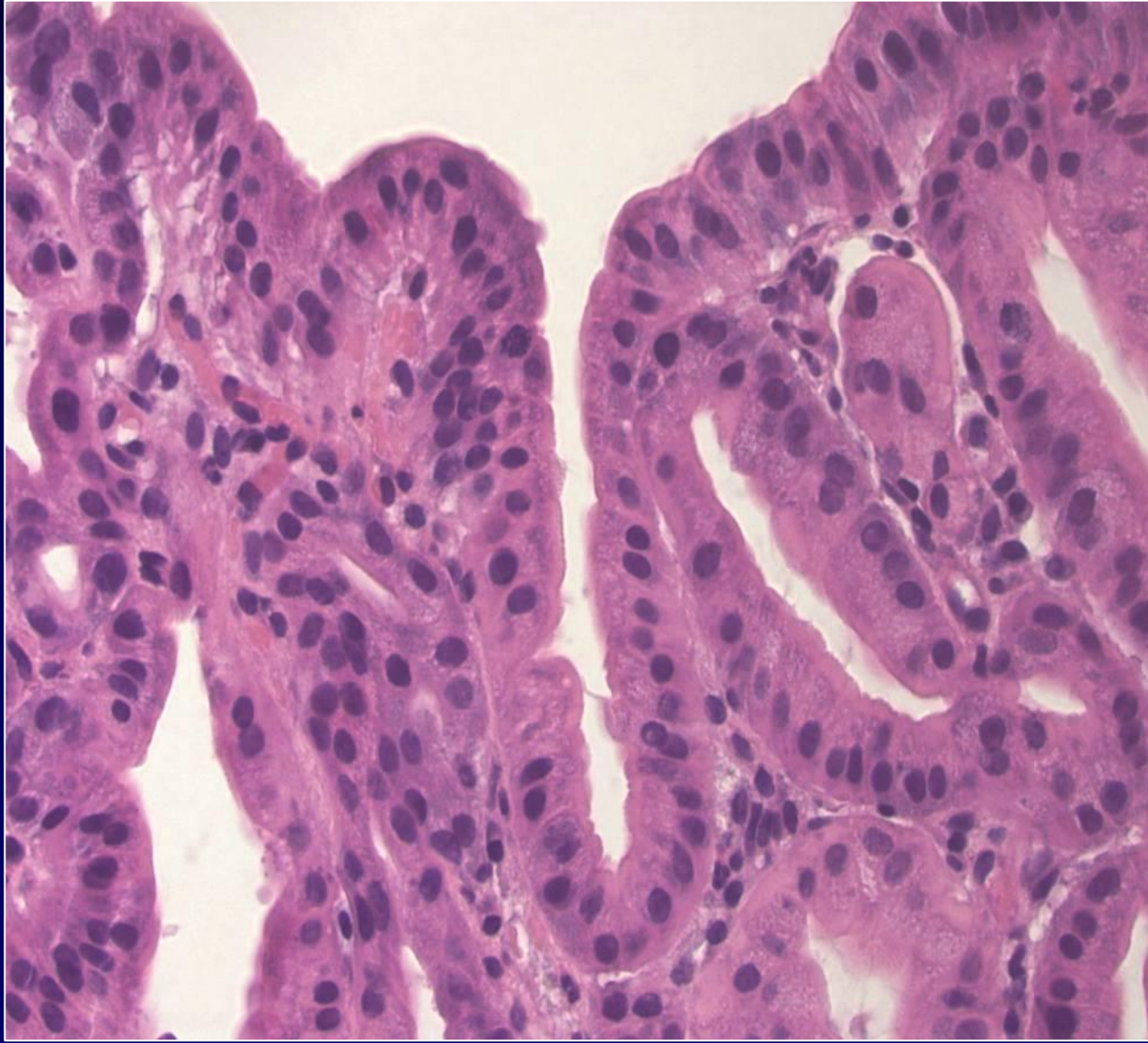
Reactive Cardia/GERD: Stratified Surface Nuclei



Gastric-type Dysplasia: Full-thickness Atypia



Gastric-type Dysplasia: Non-stratified Nuclei



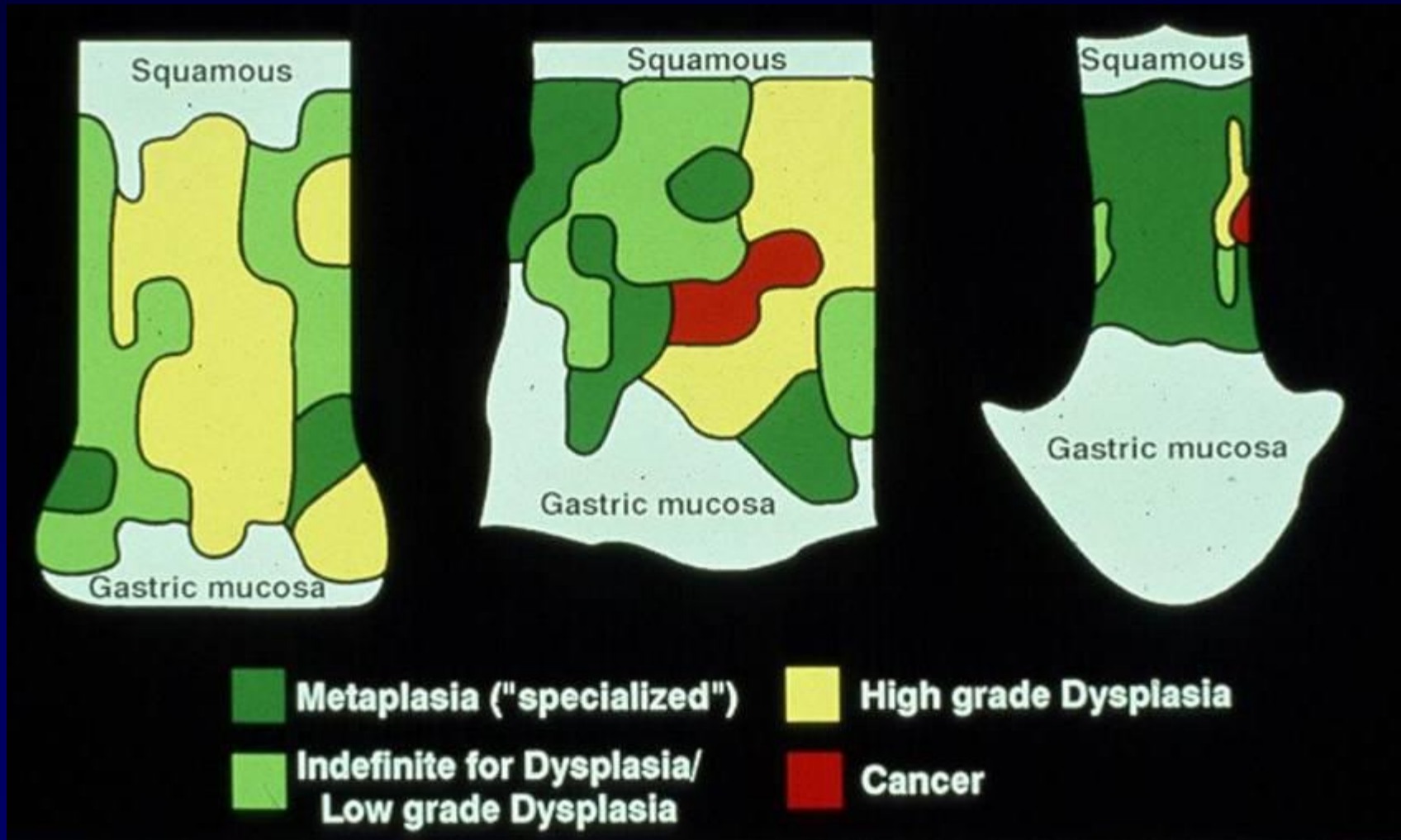
Goblet Cells in 100% of Barrett's with Foveolar Dysplasia

- Goblet cells still required to diagnose Barrett's
- Gastric foveolar dysplasia changes only the *criteria for dysplasia* within Barrett's, *not the definition* of Barrett's itself

GI Dysplasia: Problems

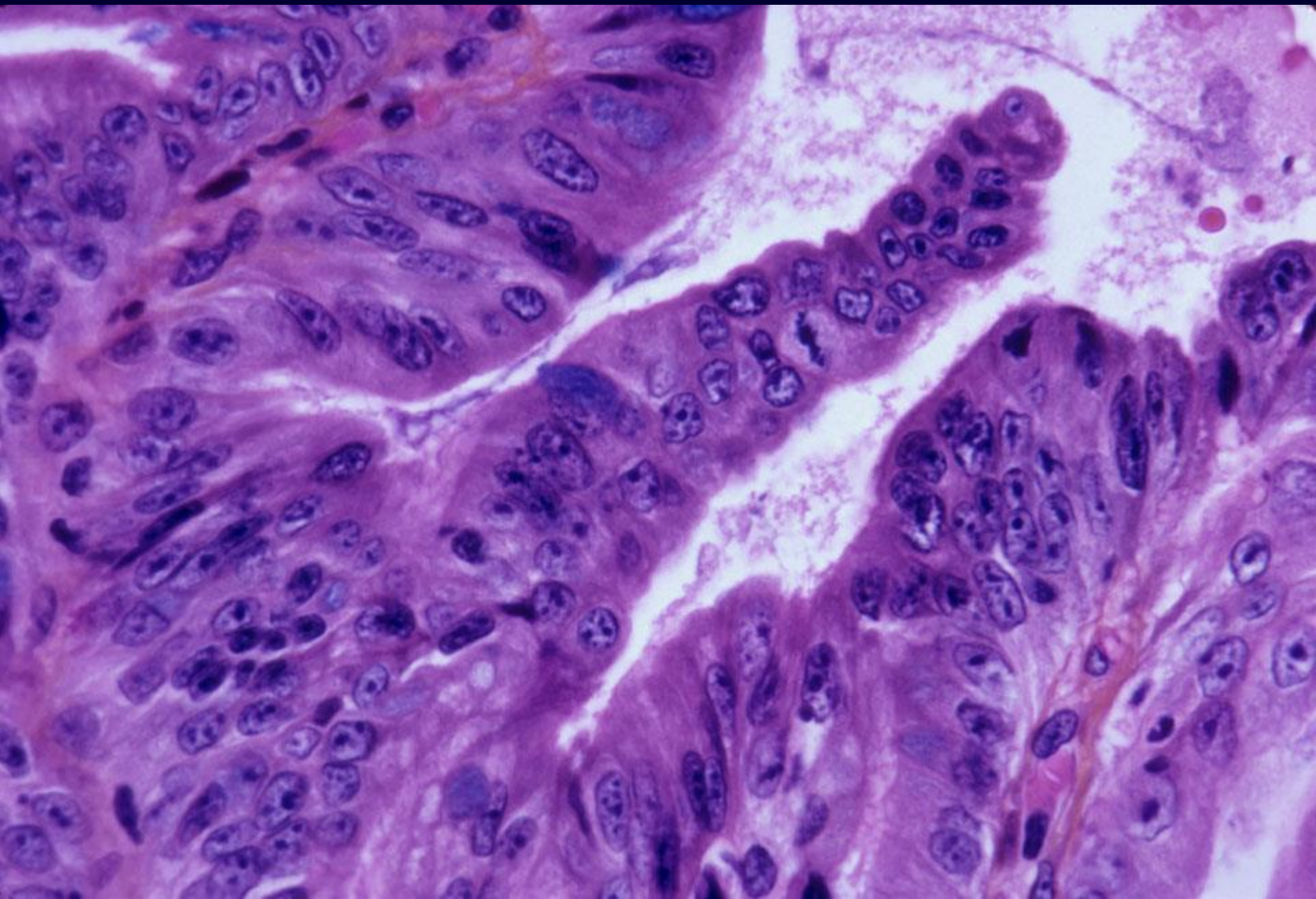
- Sampling
- Distinction from reactive change
- Observer variation
- Squamous overgrowth
- Natural history incompletely understood

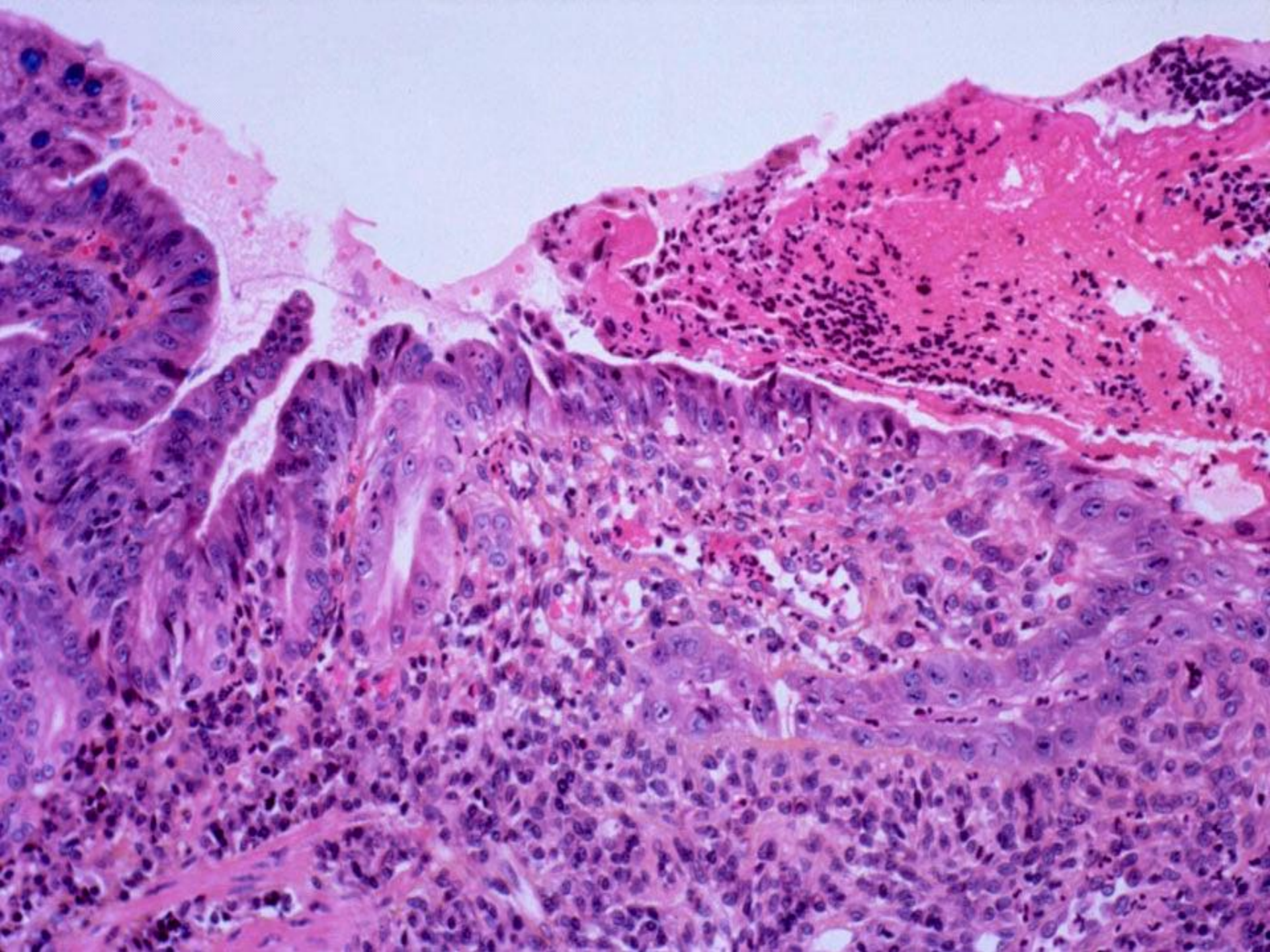
Distribution of Dysplasia



Dysplasia: Problems

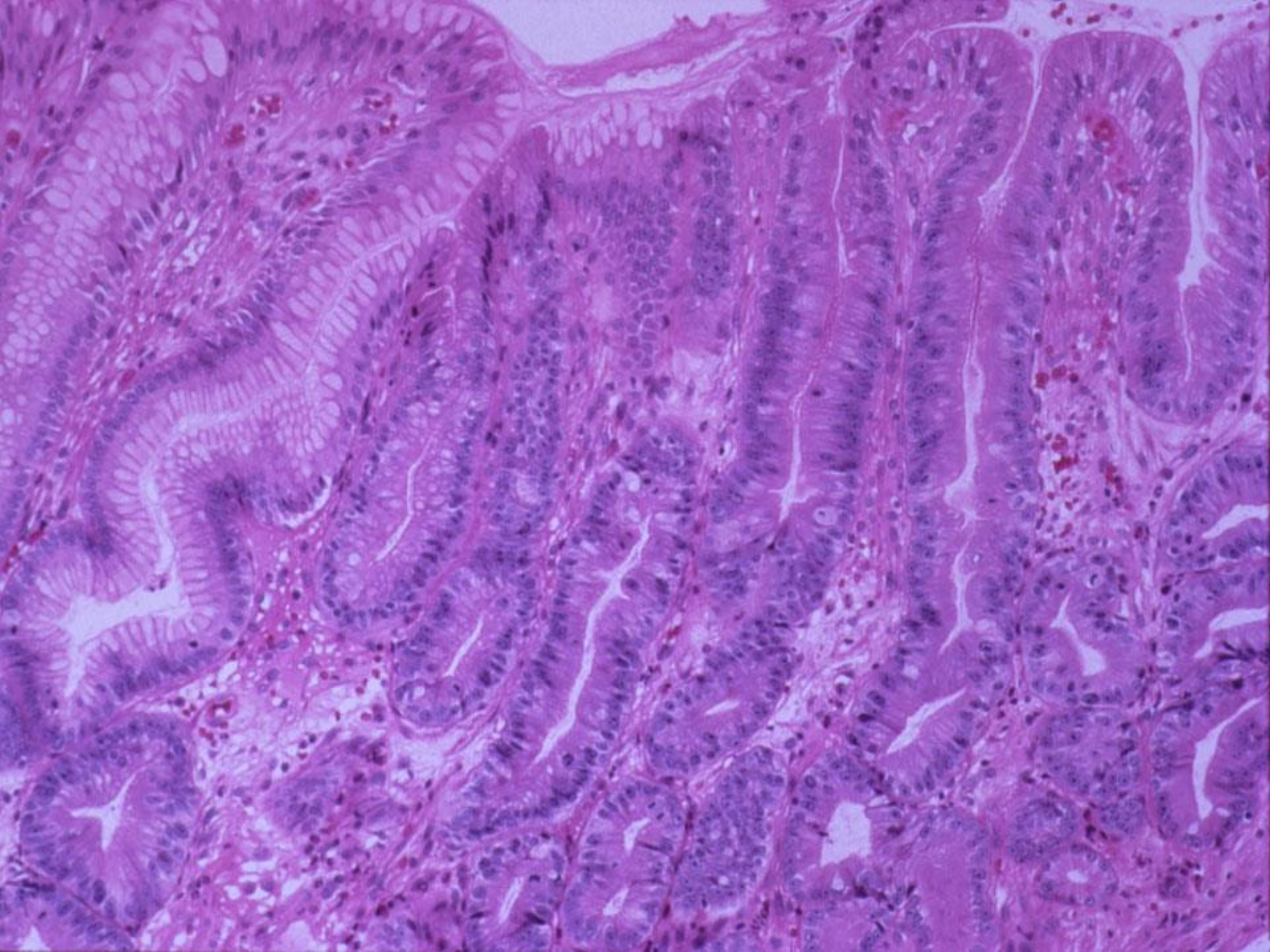
- Sampling
- Distinction from reactive change





Dysplasia: Problems

- Sampling
- Distinction from reactive change
- Observer variation



Spectrum of Dysplasia

Negative

Indefinite

Low Grade

High Grade

Negative

Indefinite

Low Grade

High Grade

Interobserver Agreement: Dysplasia in Barrett's

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

From: Montgomery E, et al. *Hum Pathol* 32:368-78; 2001

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 with HGD
 - 485 patients with "HGD" screened
 - Review original slides
 - Repeat protocol endoscopy 4 quad q2cm
 - 248 with confirmed HGD (51%)
 - 193 patients **downgraded** (40%)

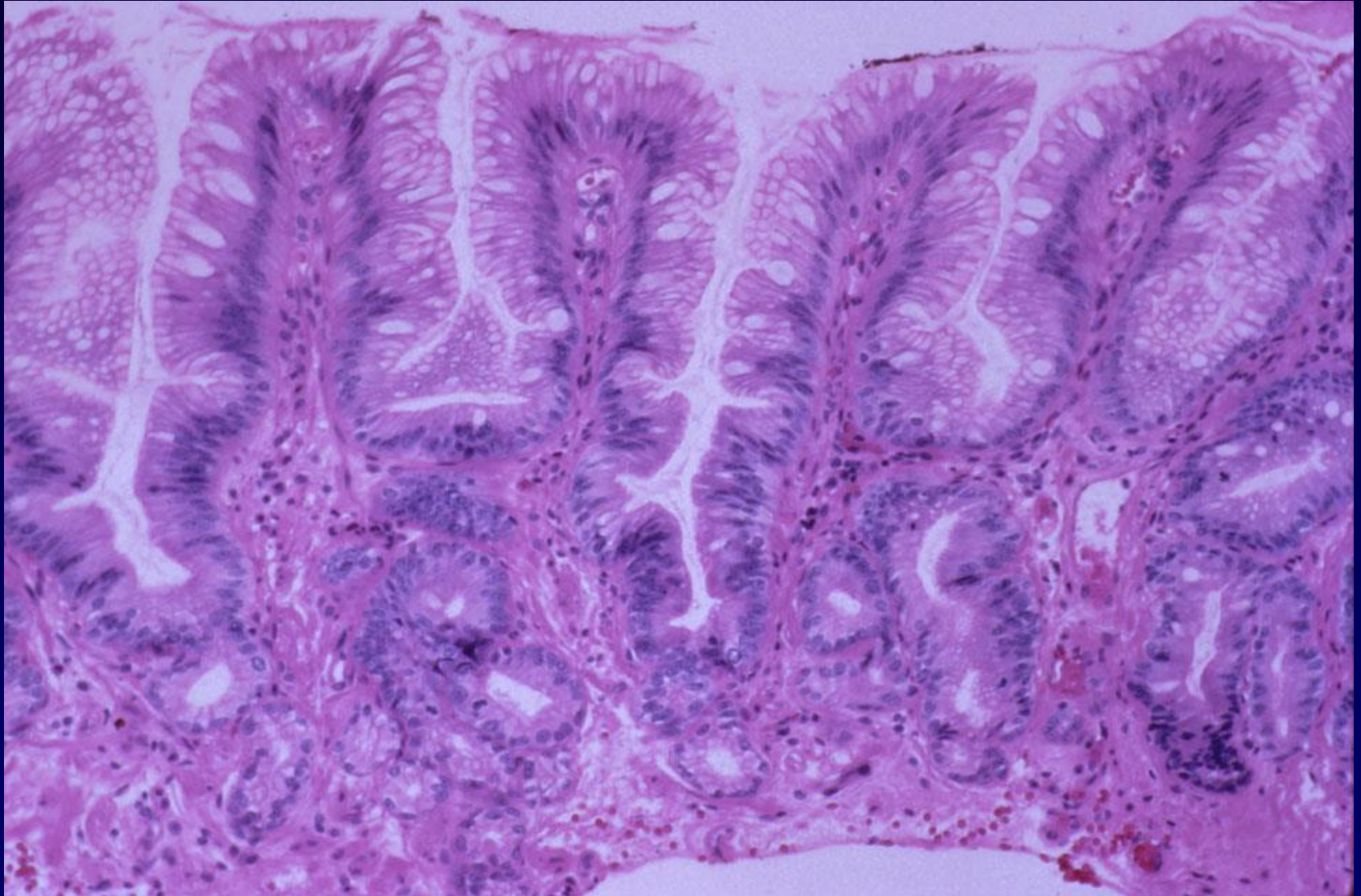
193 Downgraded Patients

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

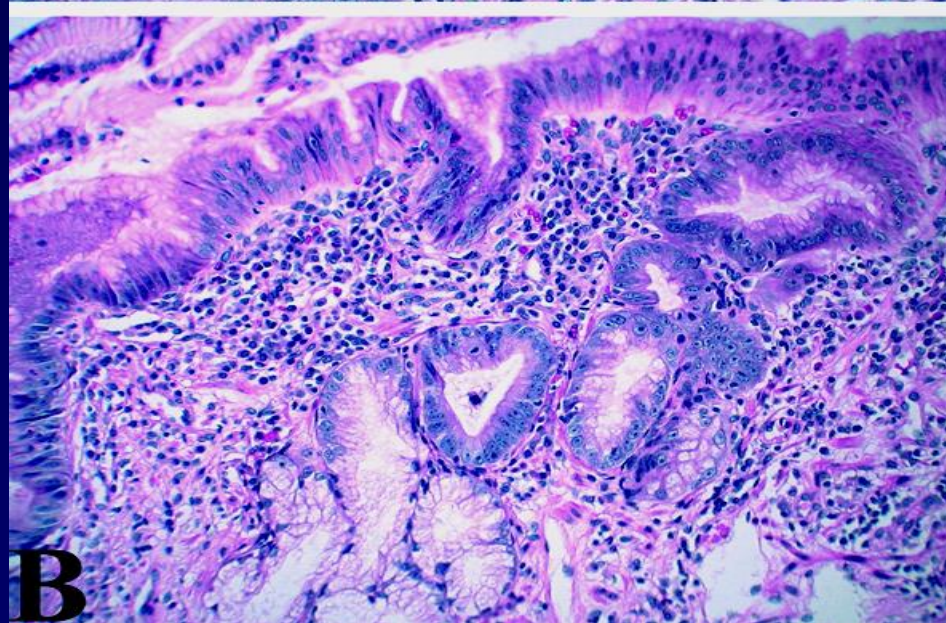
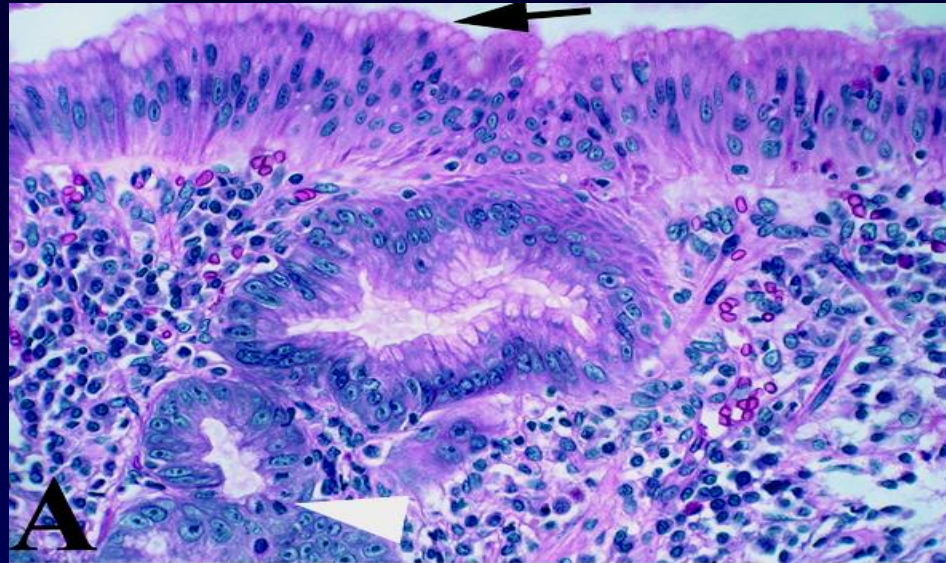
Diagnostic Pitfalls: HGD in Barrett's Esophagus

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

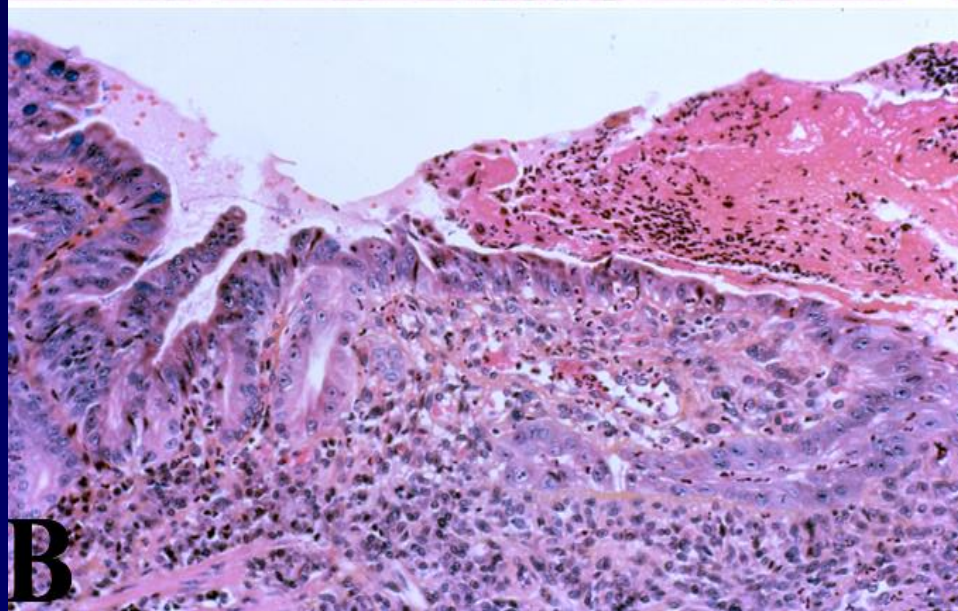
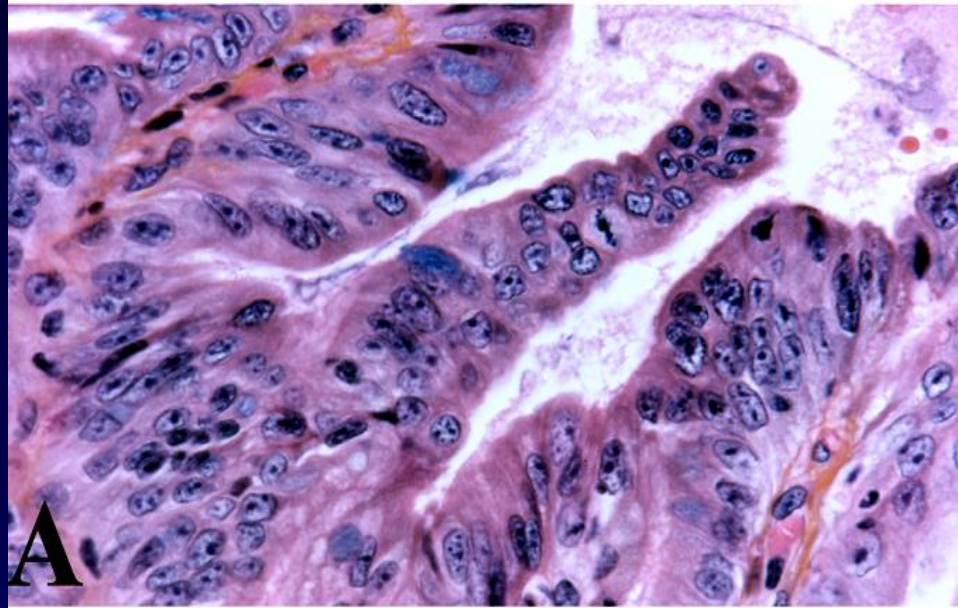
NOT Baseline Glandular Atypia



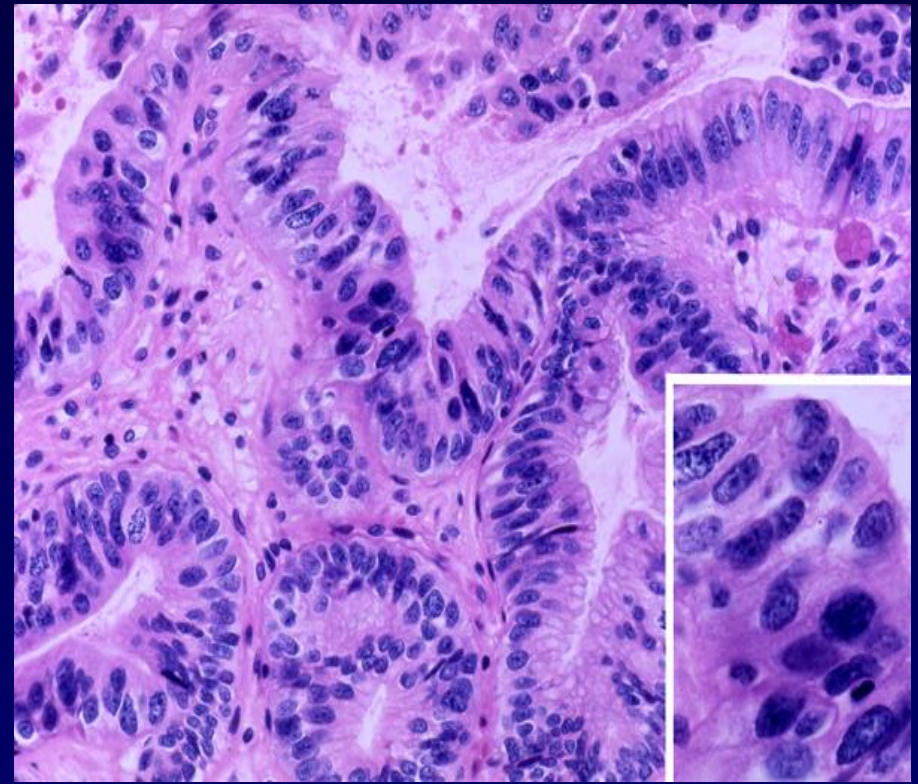
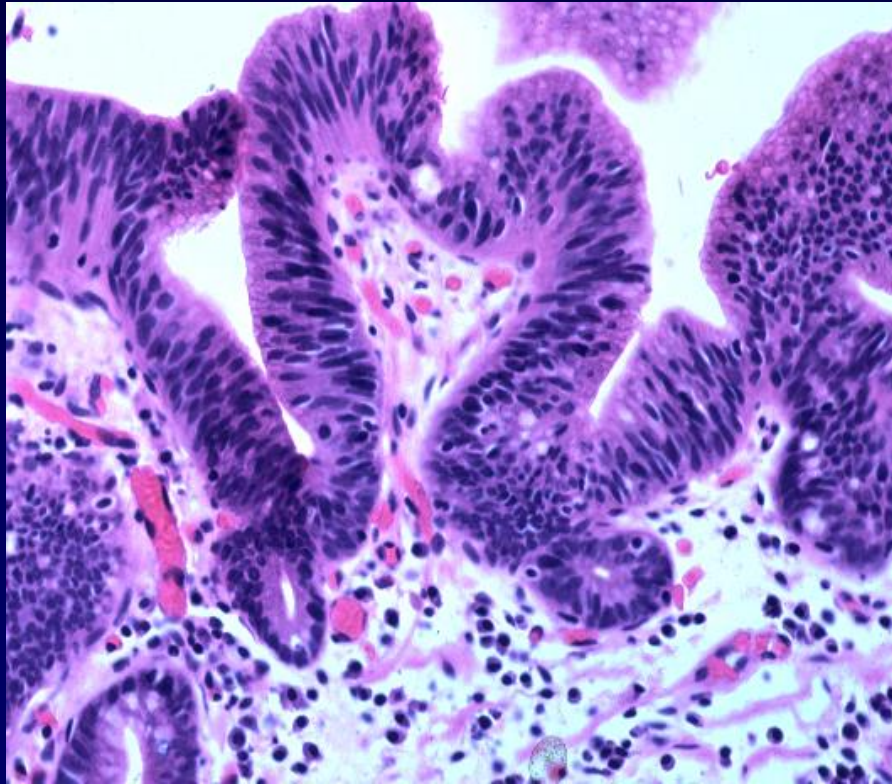
NOT Reactive Gastric Mucosa



NOT Inflammatory Atypia



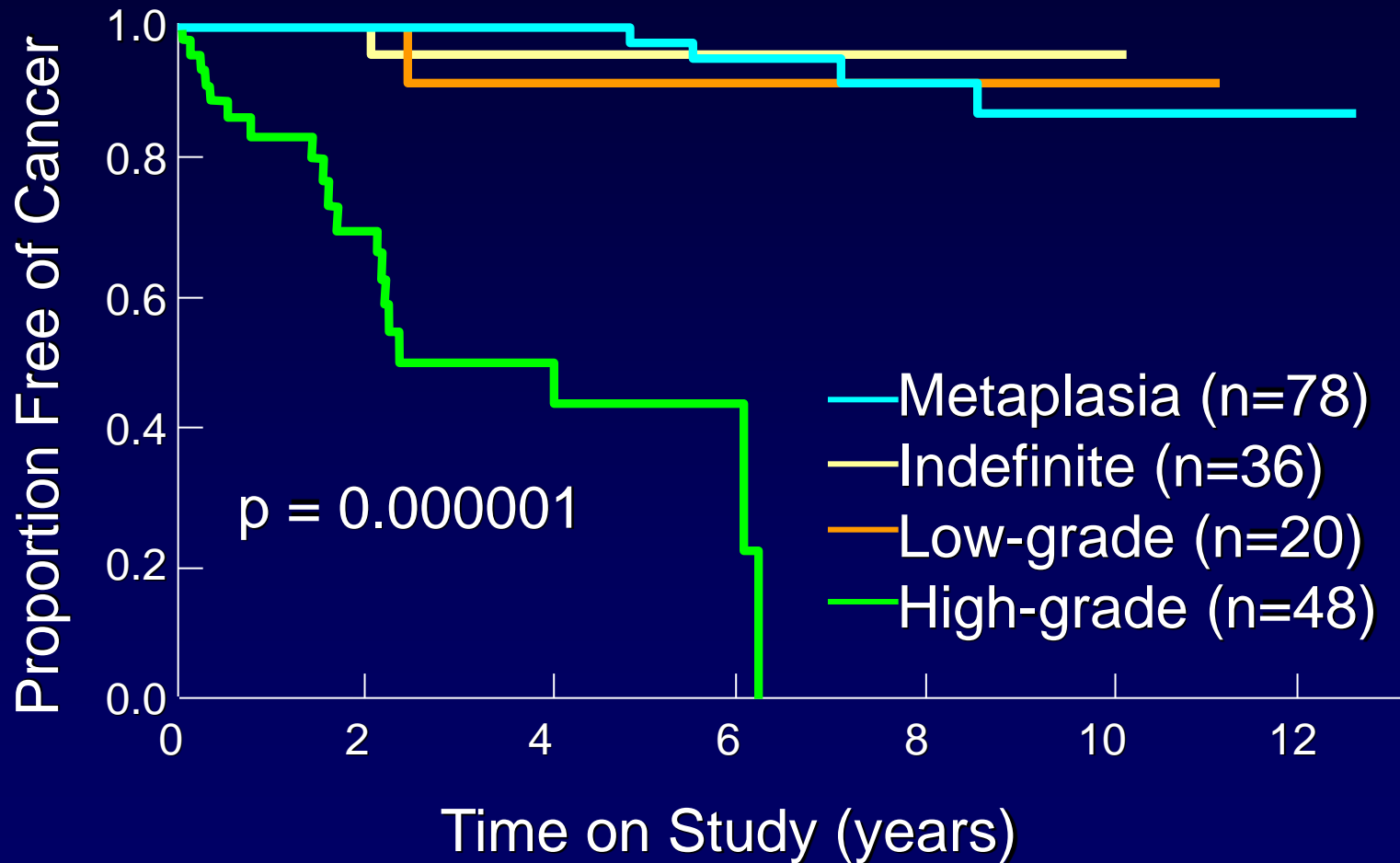
Loss of Nuclear Polarity to DDX Low & High-Grade Dysplasia



Dysplasia: Problems

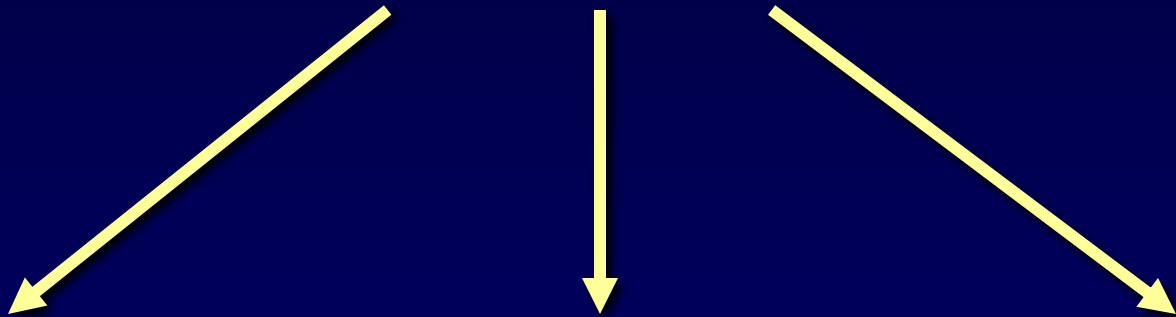
- Sampling
- Distinction from reactive change
- Observer variation
- Squamous overgrowth
- Natural history incompletely understood

BE Progression to Cancer Based on Diagnosis at First Visit



High Grade Dysplasia

Management Options



Surveillance

Ablation/EMR

Surgery

Interobserver Variability: At Least High-grade Dysplasia

Dx	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

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

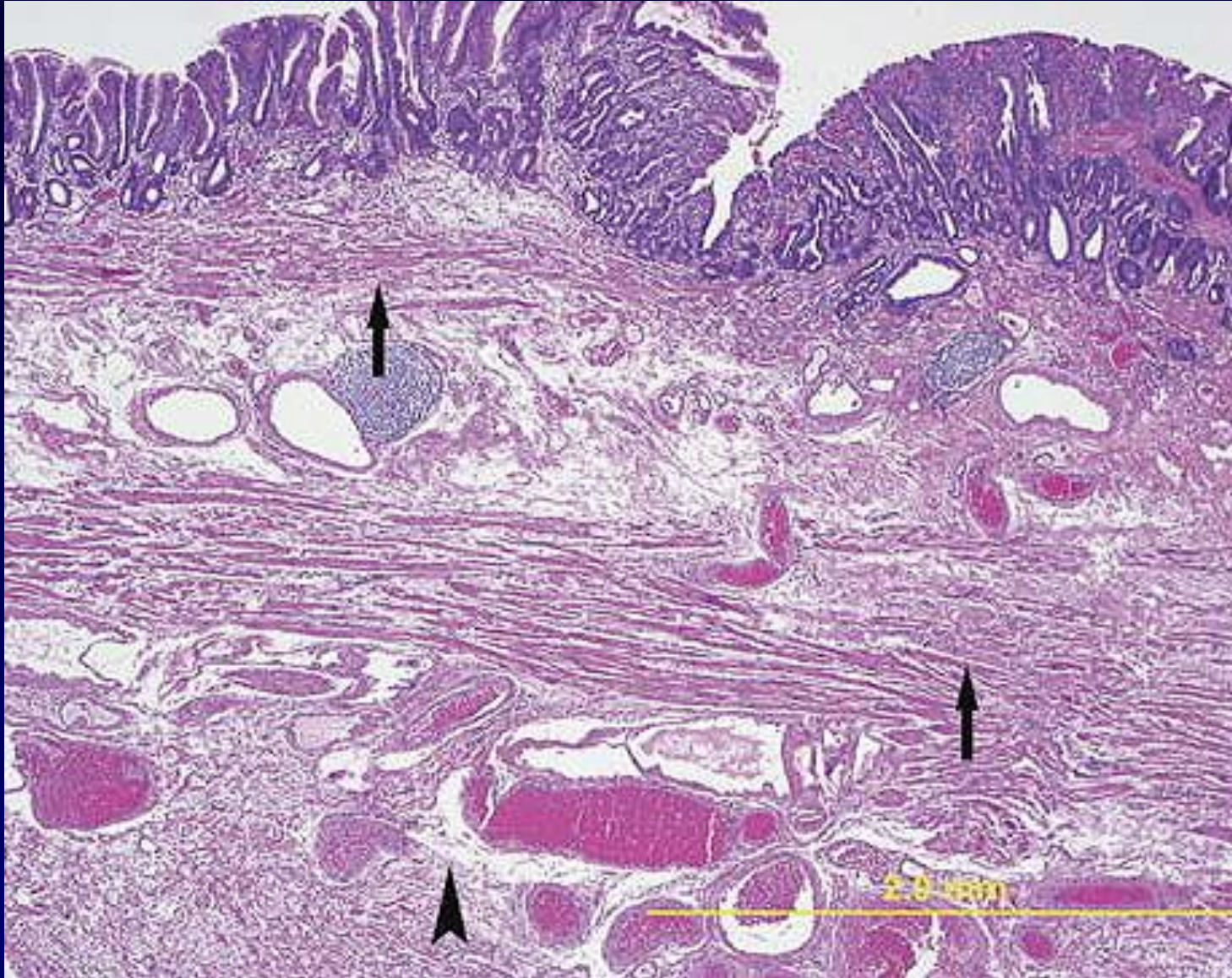
Study	# Pt	Up-stage by EMR	Down-stage by EMR	Total EMR Altered
Larghi '05	48	13%	2%	15%
Hull '06	41	34%	5%	39%
Chennat '09	49	14%	31%	45%
Moss '10	75	20%	28%	48%

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

EMR for T1a (HGD/IMC)

Study	# Pt's	Avg F/U	Compl Resp	Recur/ Metach
May, 2002	70	34 mo	98%	30%
Pech, 2008	279	64 mo	97%	22%
Chennat, 2009 <i>CBE-EMR</i>	32	23 mo	97%	3%
Moss, 2010	75	31 mo	94%	11%
Anders, 2014 <i>CBE-EMR</i>	90	65 mo	90%	6%

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 submucosa (T1b)
- EMR & EUS also overstage
- >60% of IMC cases overstaged

Mandal, et.al. *Am J Surg Path* 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%)

BE Neoplasia Summary

- Intestinal vs gastric foveolar types
- Sampling, observer variation, nat hx
- Over diagnosis of HGD
 - Baseline atypia, cardia atypia, inflammation, nuclear polarity
- HGD options: surveillance, ablation, CBE-EMR, surgery
- Duplicated MM: don't overstage

Case 2

Dysplasia in IBD



Risk Factors for Carcinoma in Ulcerative Colitis

- Extent and duration of disease
- Family history of colorectal cancer
- Age at onset
- Primary sclerosing cholangitis
- Presence of dysplasia
- Relationship to activity?

Options for Managing Cancer Risk in UC

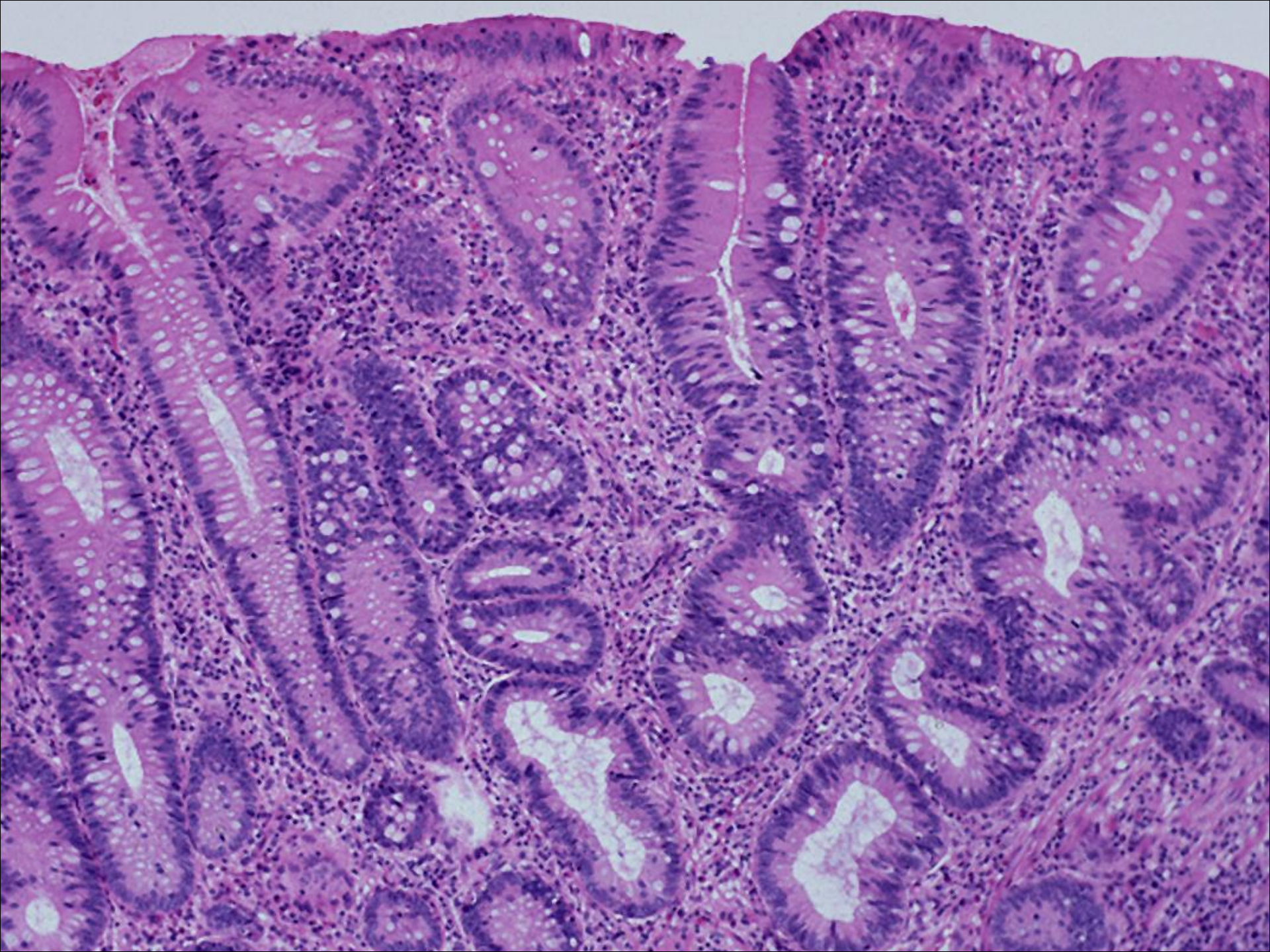
- Ignore it
- “Prophylactic” colectomy
- Colonoscopic surveillance for dysplasia / early carcinoma

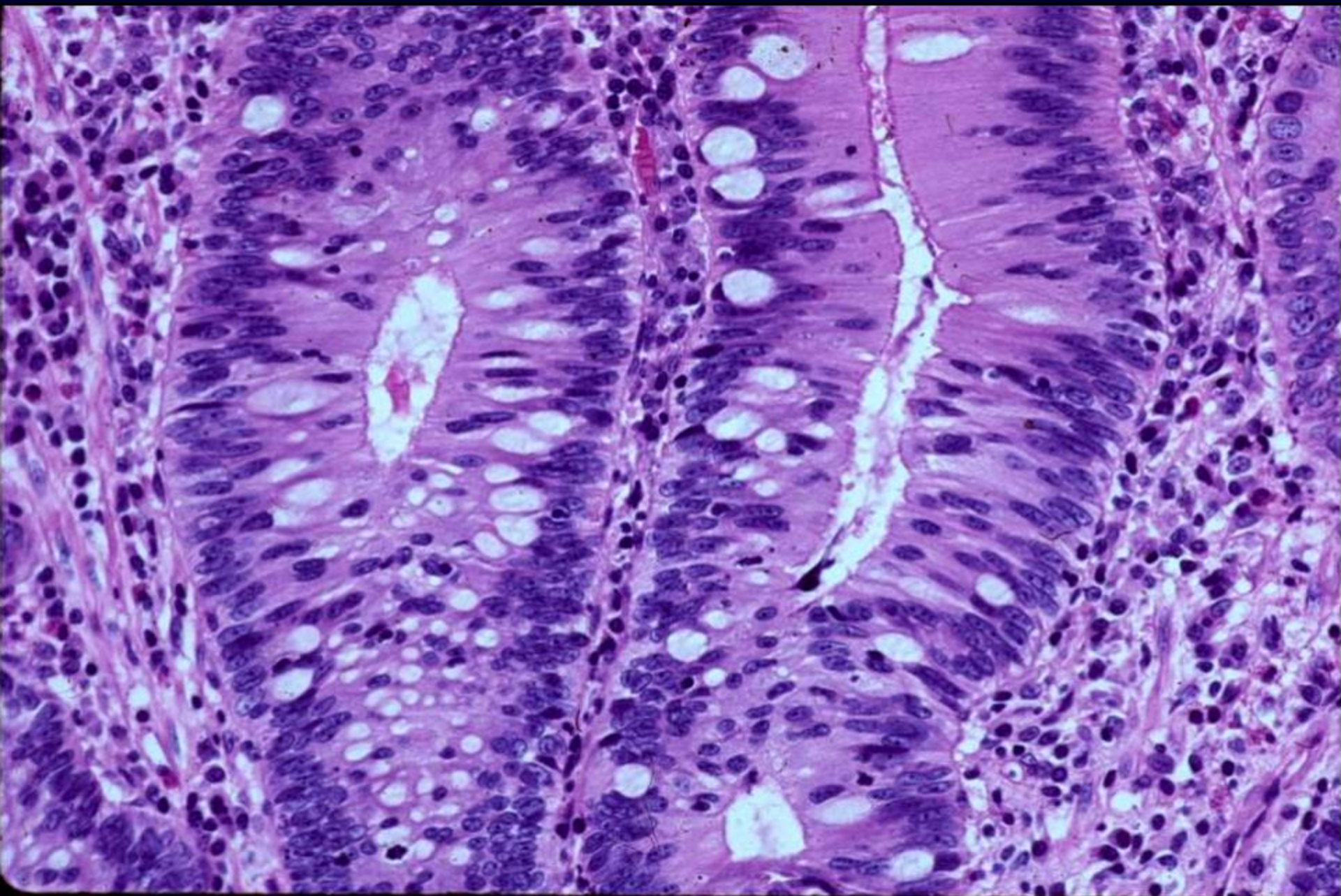
Comparison of IIBD and BE Neoplasia

Similarities	Differences
Definition of Dysplasia	Nomenclature of Cancer (No IMC in Colon)
Grading of Dysplasia	DALM lesions
Reactive Change	Sampling error UC>BE
Observer Variation	Natural History: less known for UC than BE

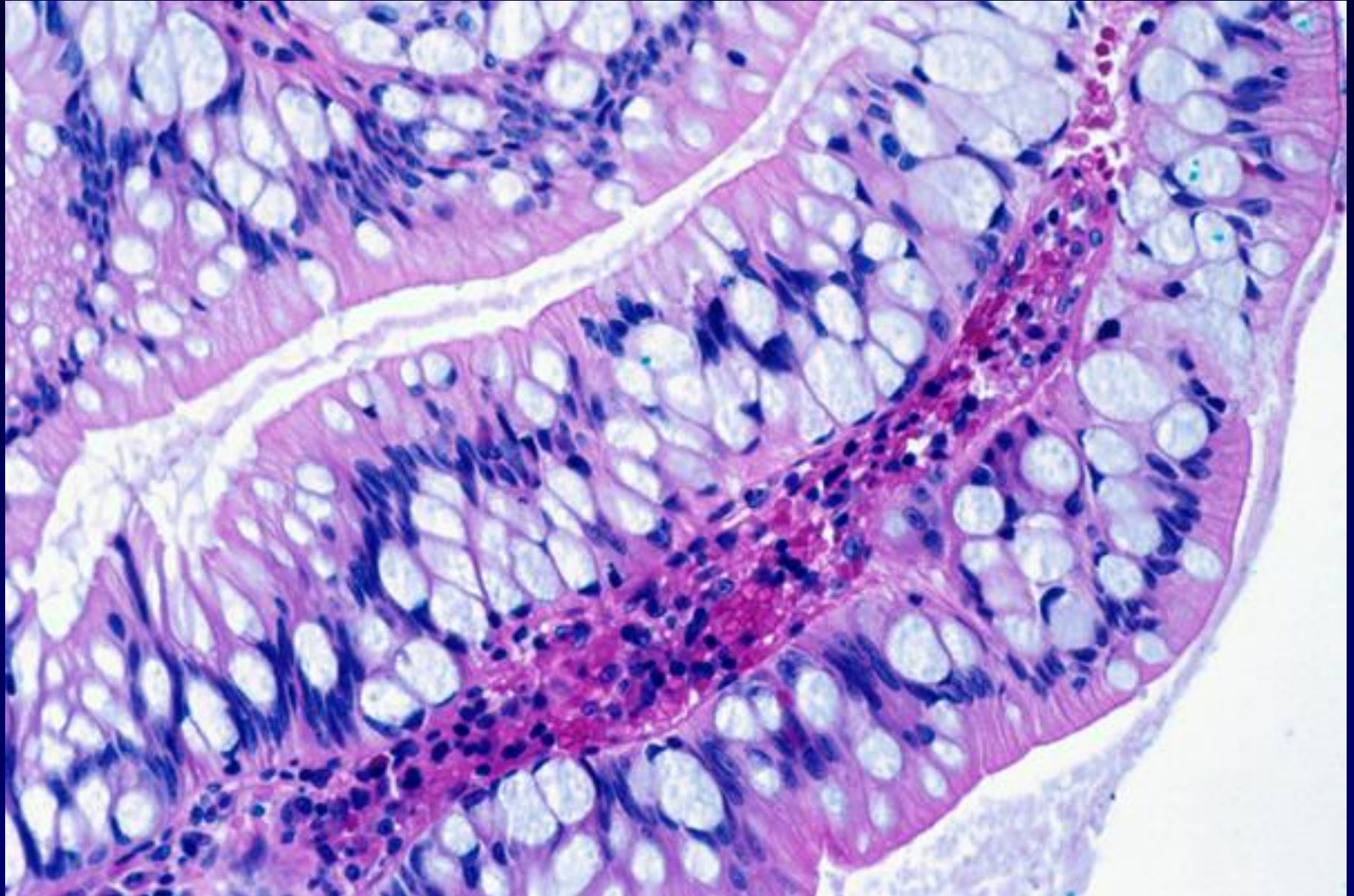
Grading System for Dysplasia

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 - High-grade

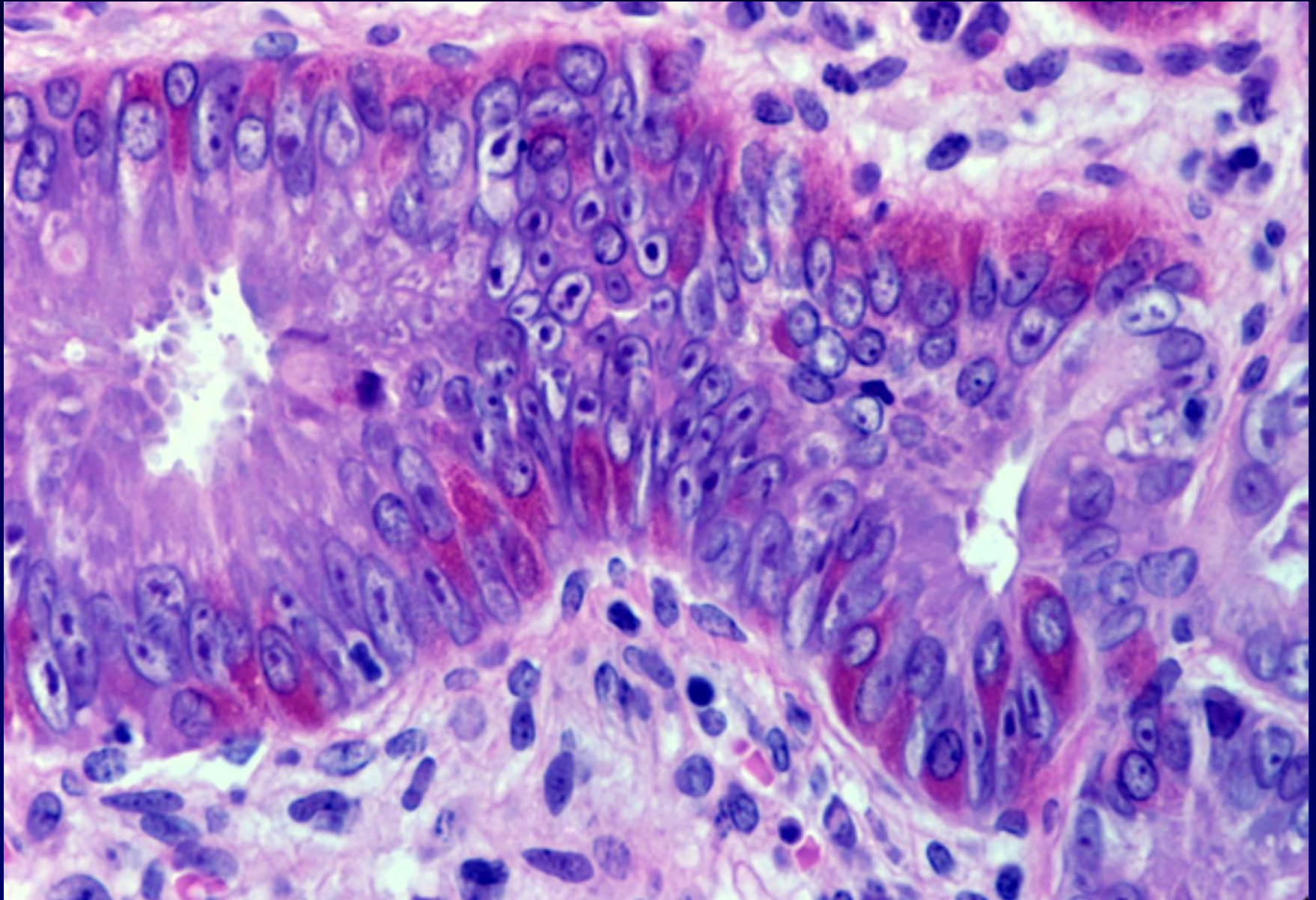


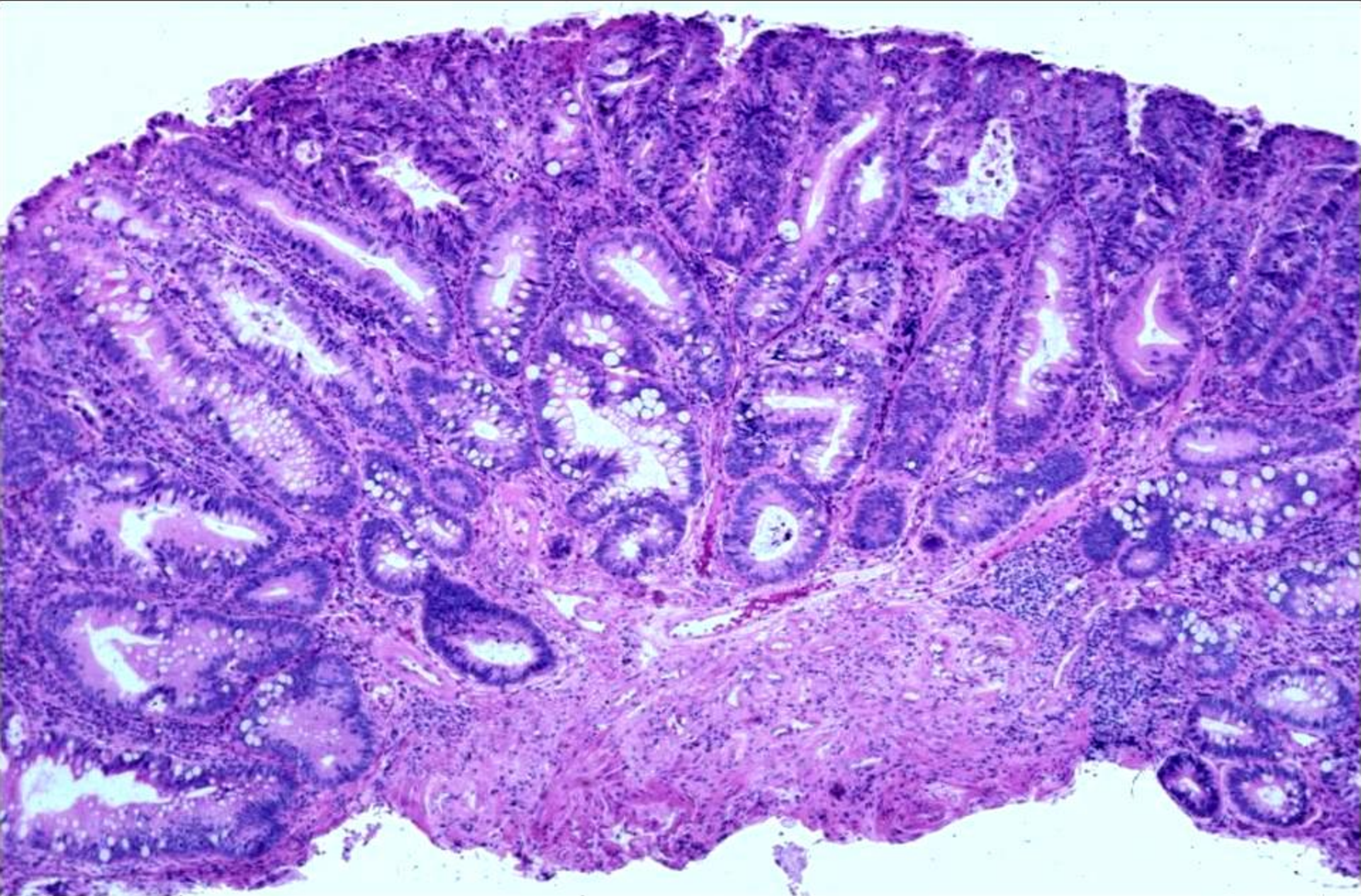


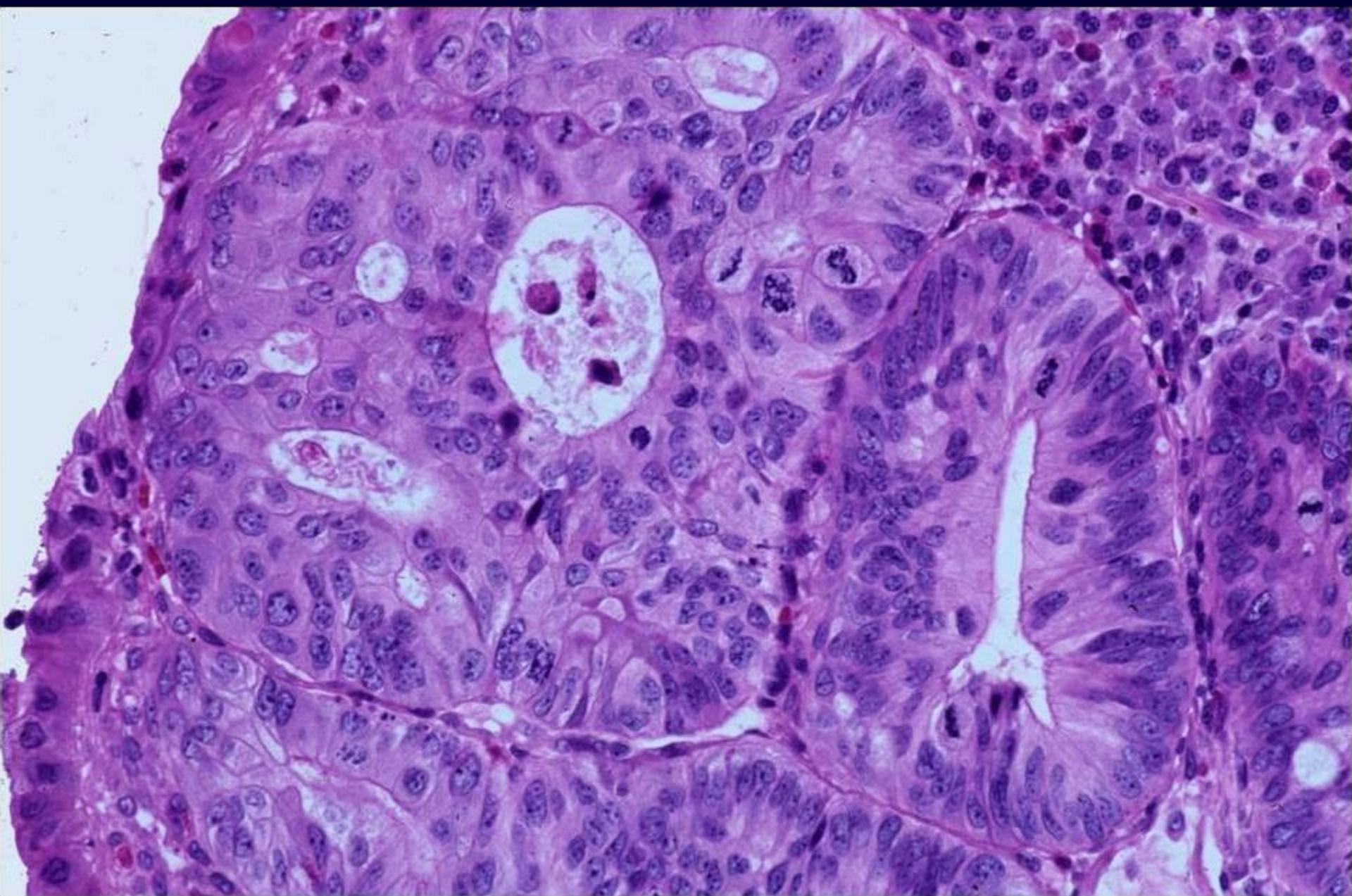
LGD-Dystrophic Goblet Cells



LGD-Increased Endocrine Cells







Adequate Biopsy Sampling - Histology

	Histologic Category	
	Dysplasia	Cancer
No. Bx for 90% confidence	33	34
No. Bx for 95% confidence	56	64

From: Rubin CE, et al. *Gastroenterology* 1992;103:1611

Better Risk Markers Needed!!!

- **Ideal biomarker for IBD cancer risk:**
 - **Pancolonic**
 - **Rectal**
 - **Objective, high Sens/Spec/PPV/NPV**
- **FISH CIN, aneuploidy, numerous single gene alterations (ex: p53), MSI, genomic, transcriptomic and proteomic alterations, and gene hypermethylation**
- **None yet ready for prime time**

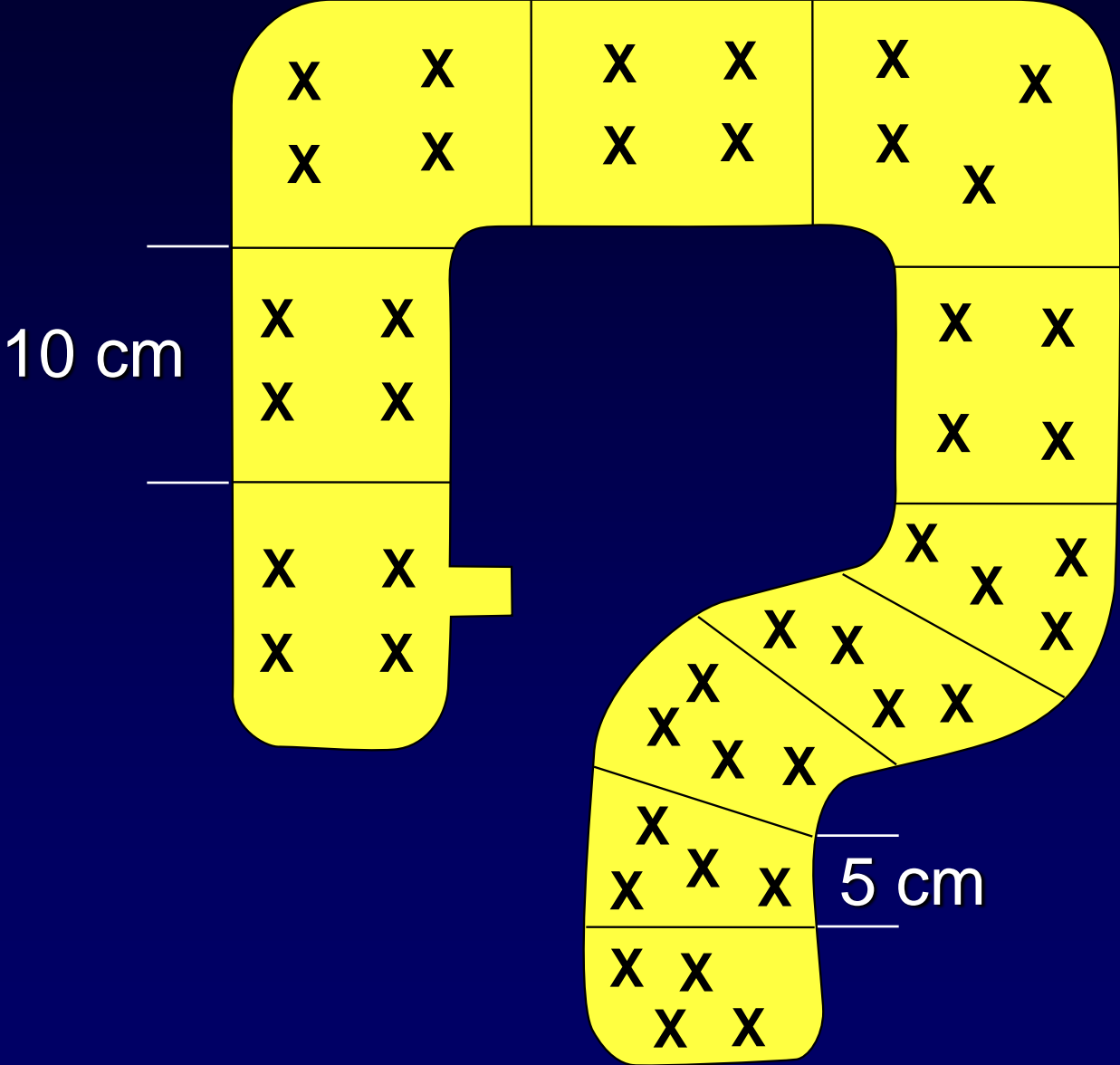
Adequate Biopsy Sampling

Mathematical modeling study:

- 80% confidence- 32 random biopsies
- 90% confidence- 45 biopsies
- 95% confidence- 58 biopsies
- *18 biopsies yields only 60% confidence!*

From: Awais D, et al. Modeling dysplasia detection in UC clinical implications of surveillance intensity. Gut 2009;58:1498-1503

Ulcerative Colitis Surveillance Protocol



Rectosigmoid Predominance of UC Cancer

Location of Colorectal Carcinoma

RS	D	T	A/C
52%	12%	21%	15%

Choi PM. *Gastroenterology* 1993;104:666 Summary of 5 Studies

Outcome of 42 LGD Patients

- 81% *did not progress*, avg f/u 5 y (1-13 y)
 - 7 (17%) LGD
 - 27 (64%) indef, neg
 - 19% *progressed*
 - 6 HGD (avg 1.5 yr)
 - 2 cancer (lost to fu)
 - ≥ 3 biopsies with LGD: 5.8x \uparrow progression
- Only outcome study in literature with *adequate* bx sampling



Dysplasia in UC vs. Adenoma

- No clinical features
- No pathologic features
- No molecular tests

HOWEVER

- If the lesion demonstrably completely resected, and
- If no dysplasia elsewhere, and
- If LGD
- Careful follow-up may be considered

UC Dysplasia Management

Continue Surveillance with adequate sampling:

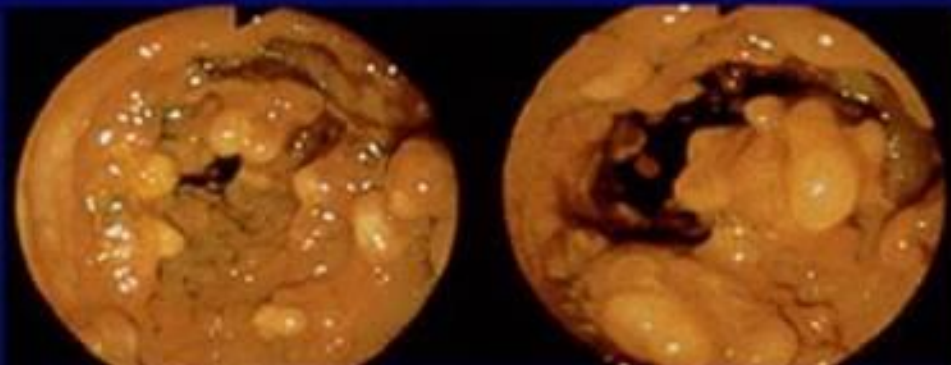
- Single site LGD while in surveillance
- Indefinite for dysplasia
- Negative

UC Dysplasia Management

Consider Colectomy:

- Multiple LGD sites
- LGD on more than one endoscopy
- LGD at initial colonoscopy
- Excessive inflammatory polyps

Inflammatory Polyps



UC Dysplasia Management

Colectomy Indicated:

- HGD
- Endoscopically unresectable dysplastic lesion

Summary: IIBD Dysplasia

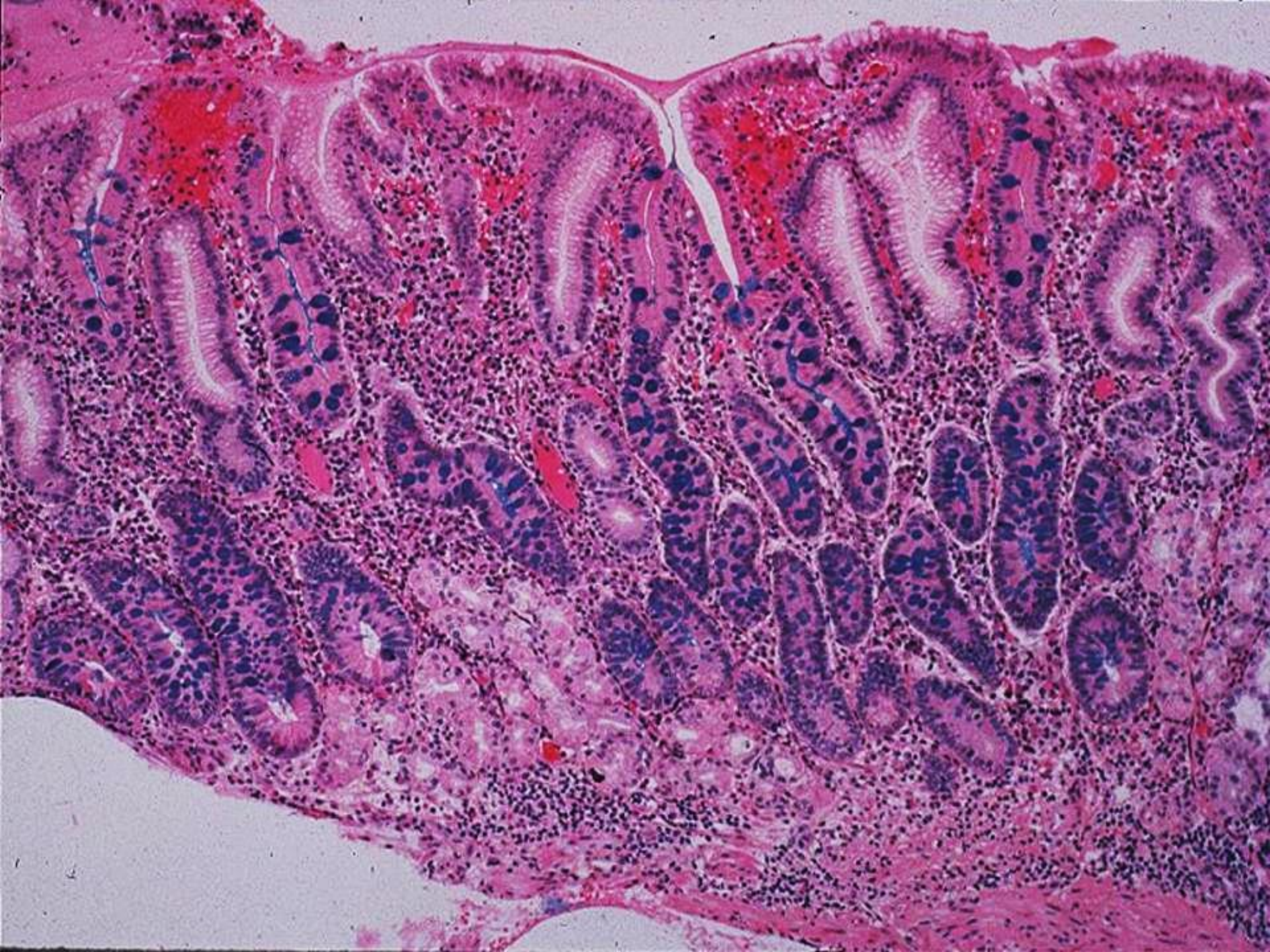
- Nomenclature: No CIS or IMC in colon
- Huge surface area: 33 bxs
- Natural history: limited to one study of 42 pts with LGD: minority progress (>3 LGD bxs)
- Adenoma-like dysplasia: follow but many caveats

Case 3

Gastric Dysplasia in
Multifocal Intestinalized
Pangastritis (MIP)

Gastric Dysplasia

- 3 kinds of gastritis
- 1 with gastric CA risk
 - Multifocal Intestinalized Pangastritis
 - Diagnosed by IM of gastric BODY
 - Type of HP gastritis
 - Linked to ethnicity: Asian, Hispanic
 - 10% risk of dysplasia/CA
 - Same pathology as BE neoplasia



Summary: Gastric Dysplasia

- MIP essentially
 - IM of gastric BODY
 - Caused by HP
 - 2nd most common CA worldwide
- Caveat: Gastric IM mimics dysplasia more due to adjacent totally bland gastric mucosa: DON'T OVER DX:
Use surface maturation

Case 4

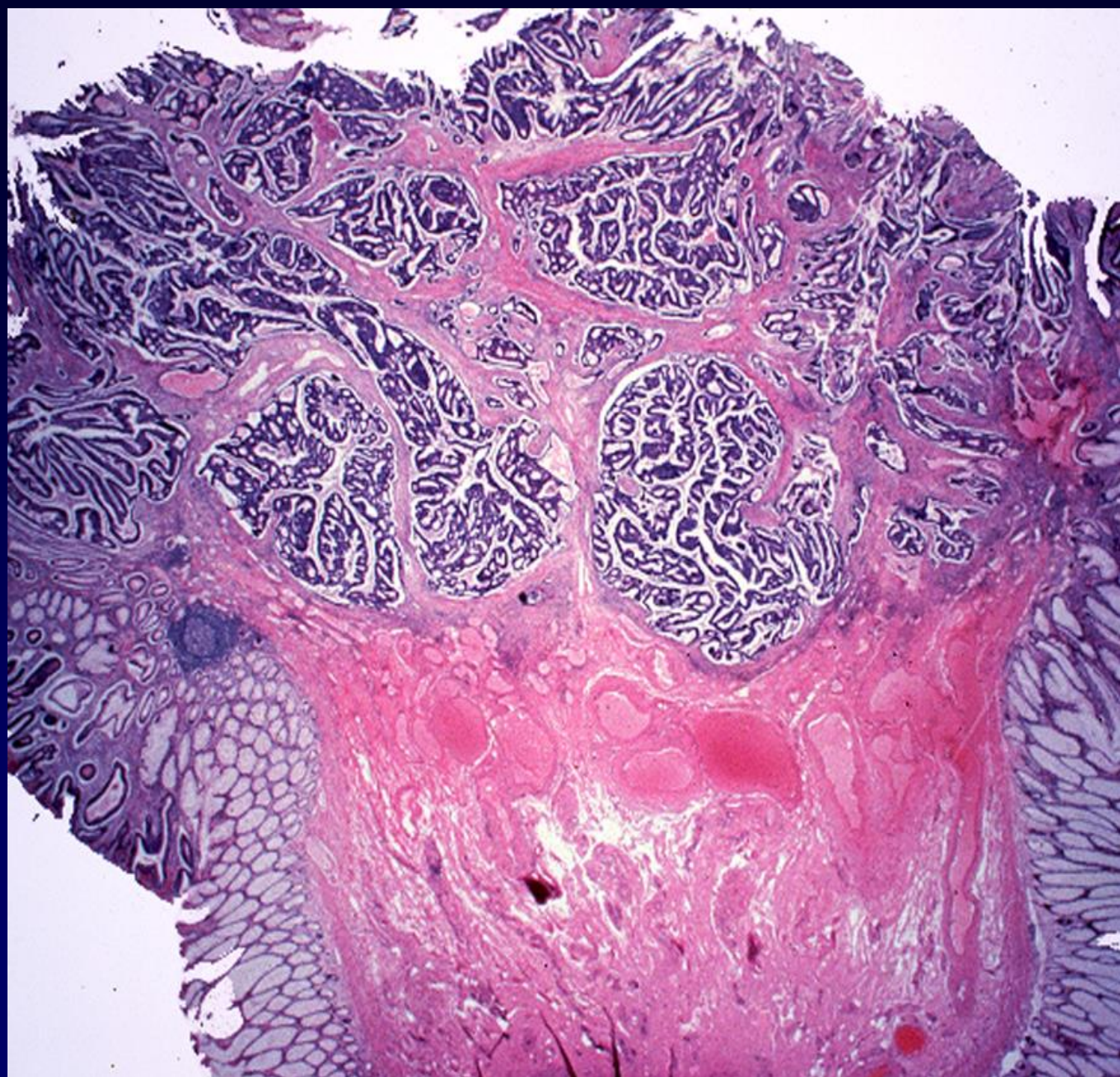
Carcinoma Arising in an
Adenoma: Diagnosis and
Management

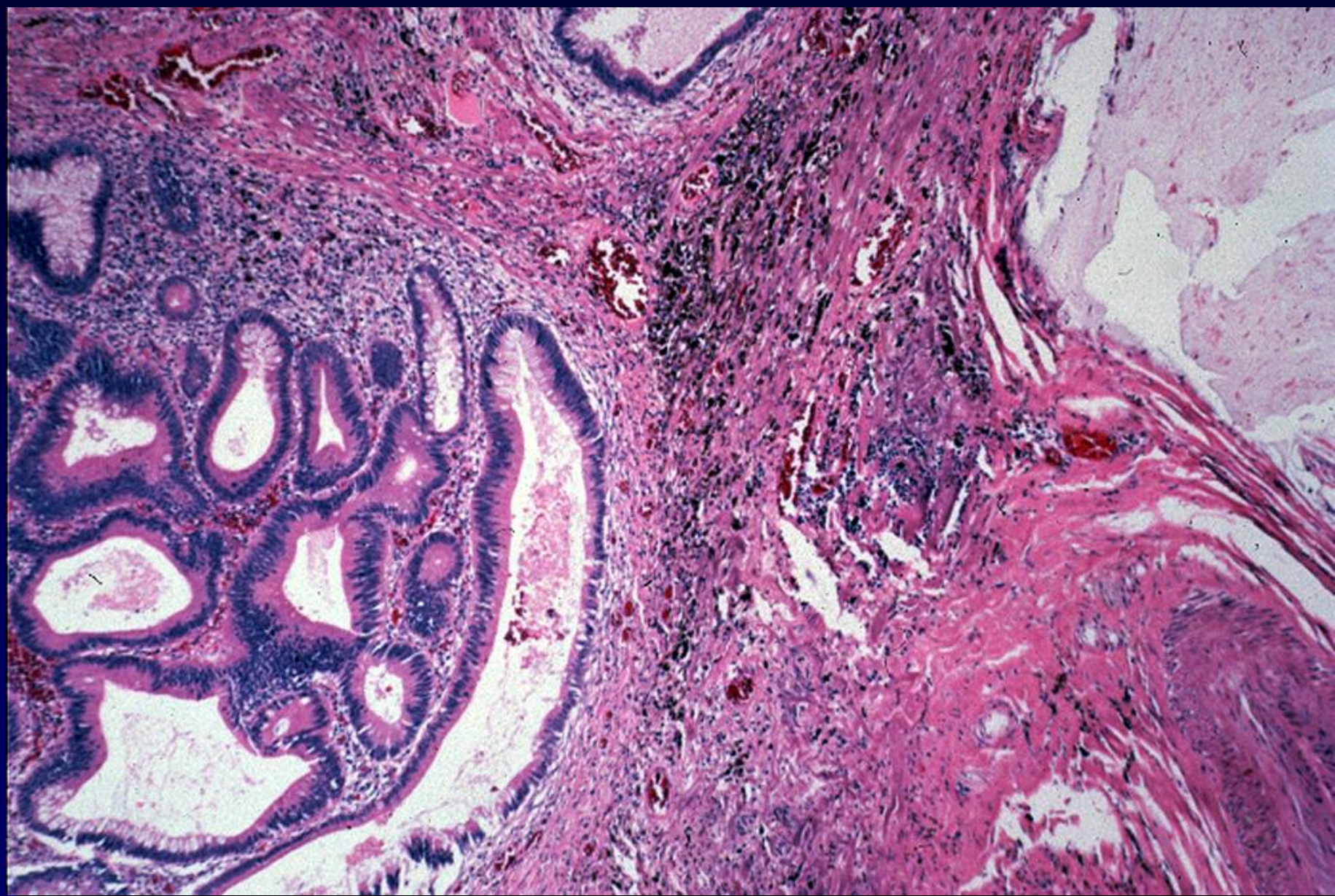
Management of Carcinoma in Adenomas

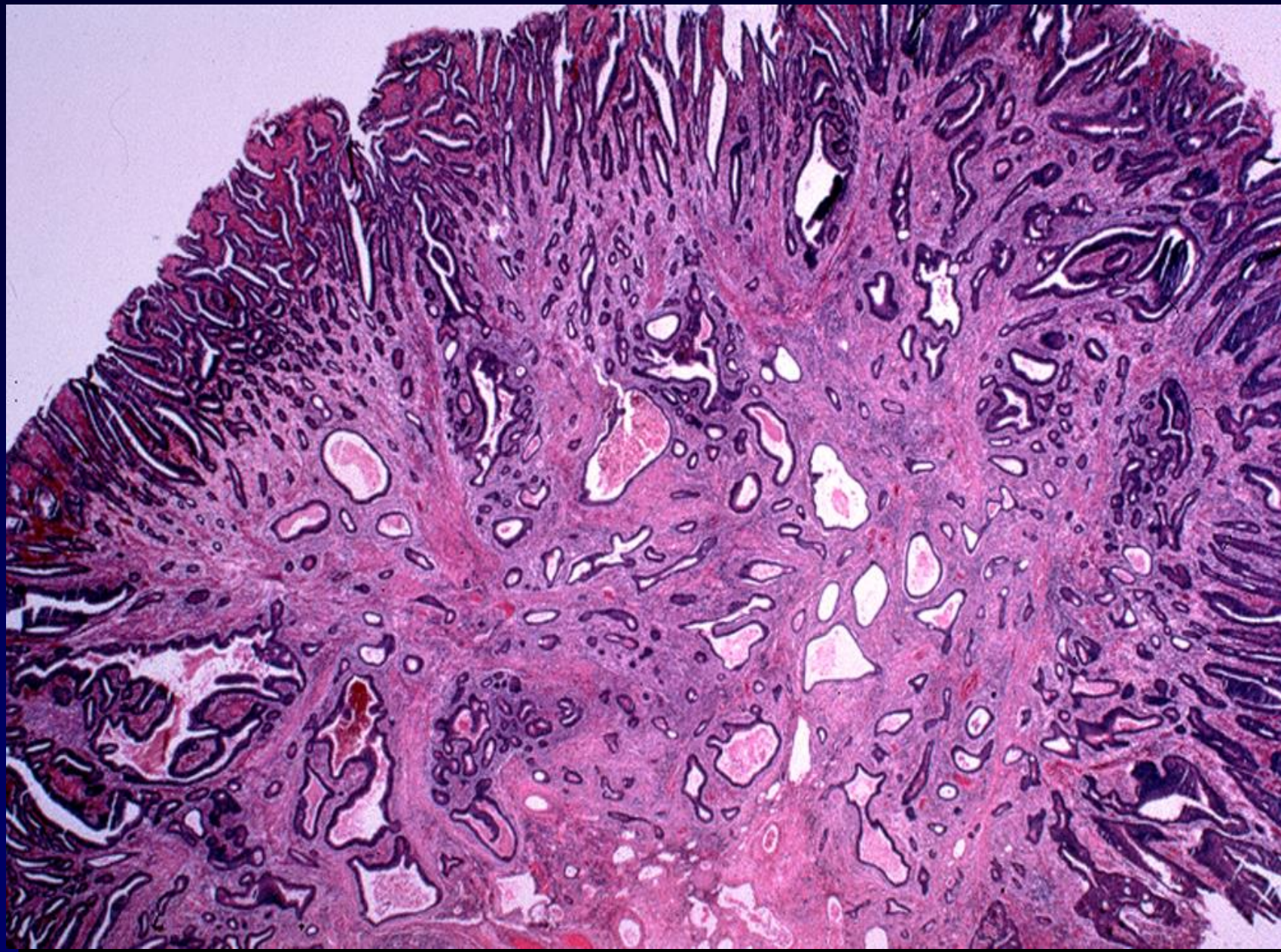
- 1) Establish diagnosis
- 2) Depth of invasion
- 3) Histologic grade
- 4) Angiolymphatic invasion
- 5) Completeness of resection
- 6) Metastatic risk

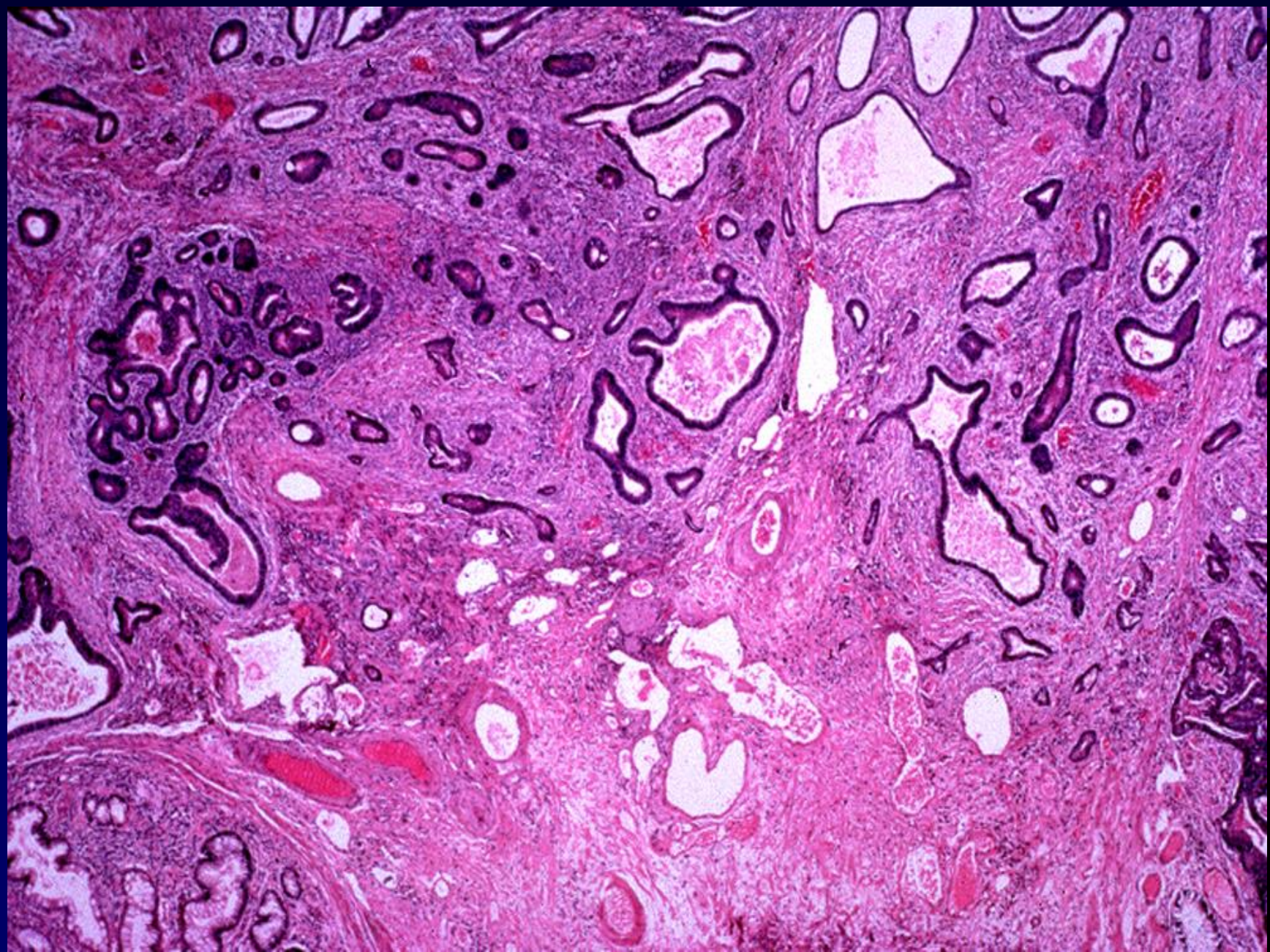
Misplaced Epithelium In Colonic Adenomas

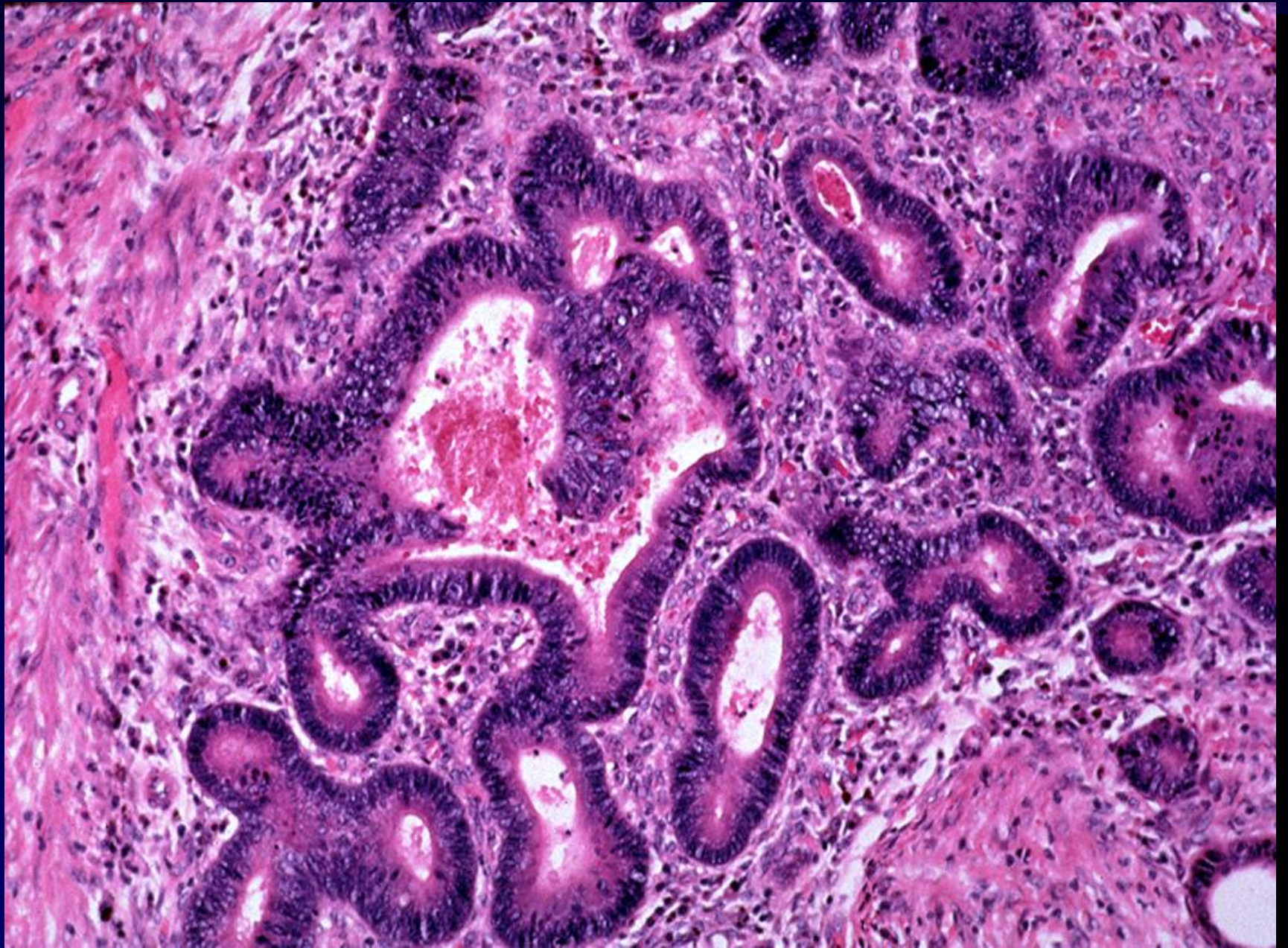
- Low power contour rounded
- Glands invested by lamina propria
- Large, pedunculated adenomas
- Most often sigmoid
- Hemosiderin & dense fibrosis

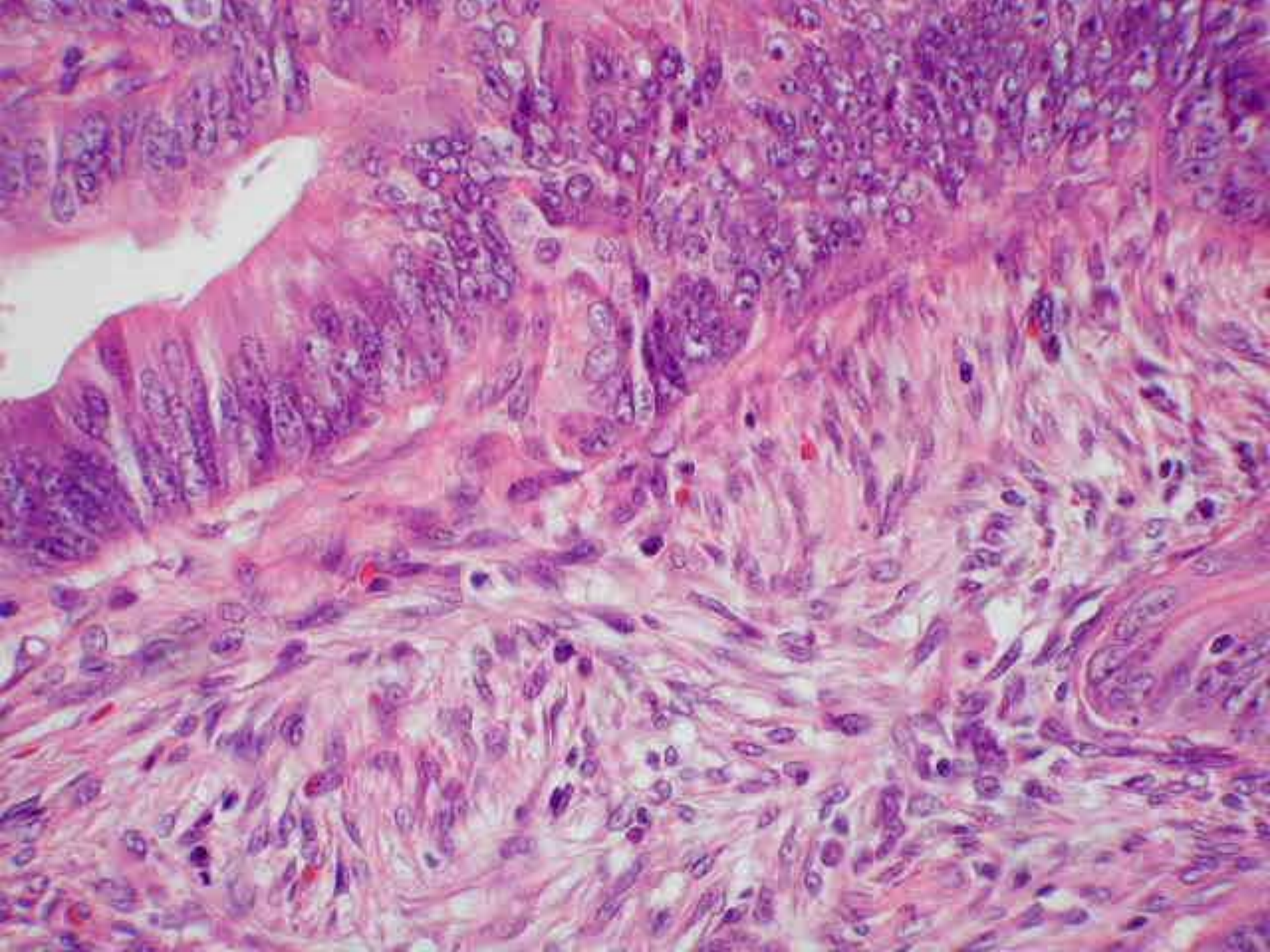


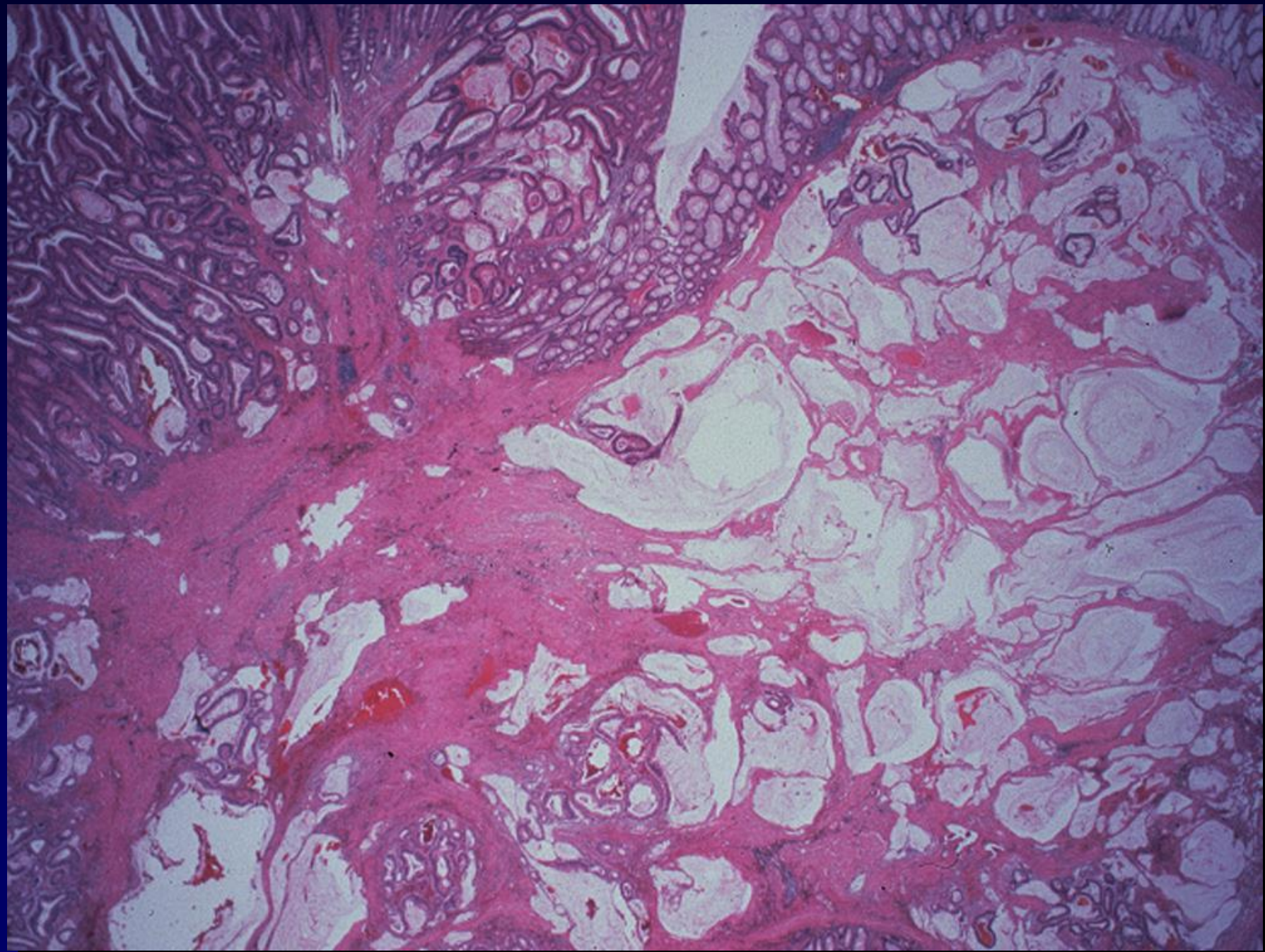




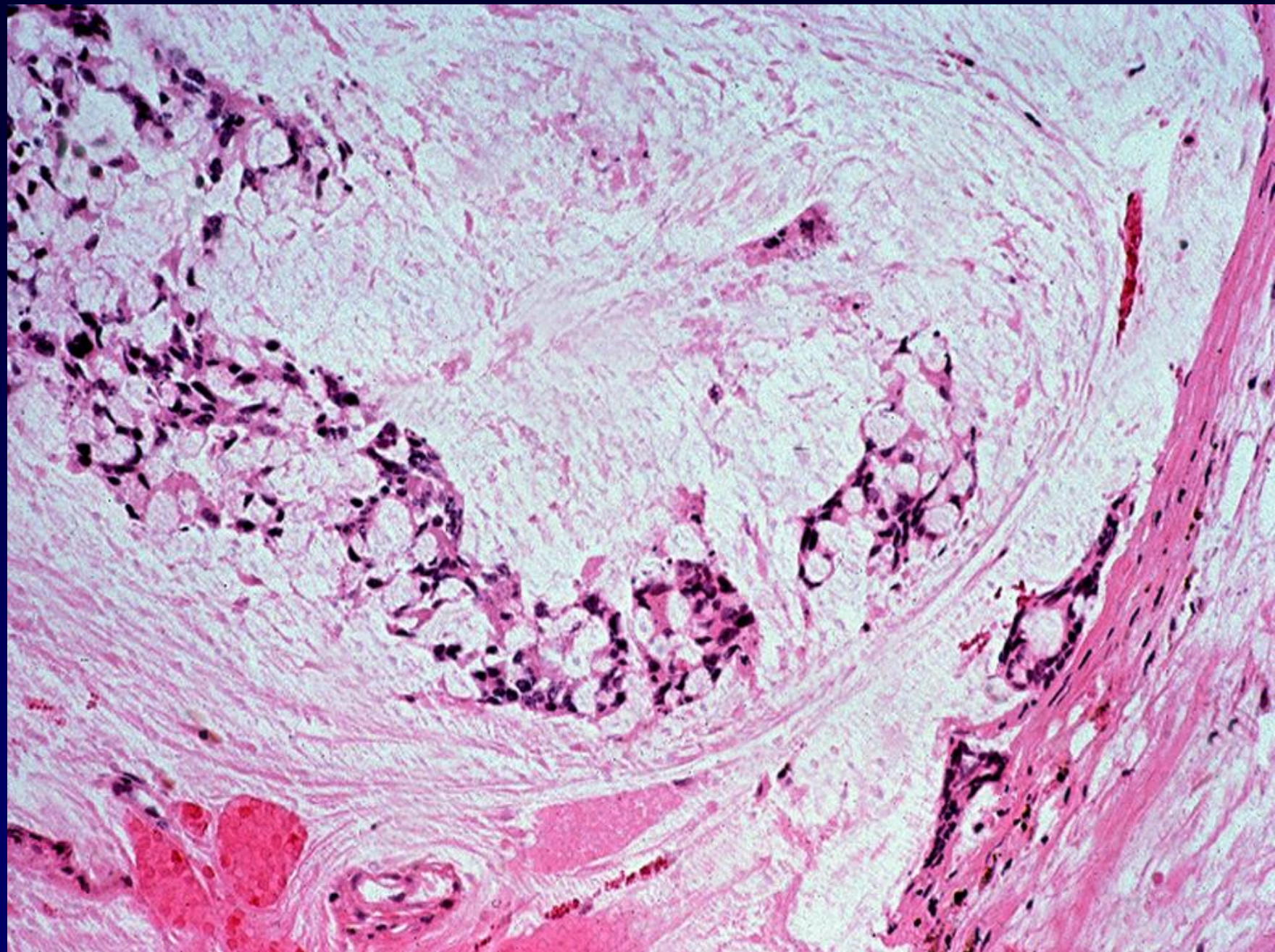


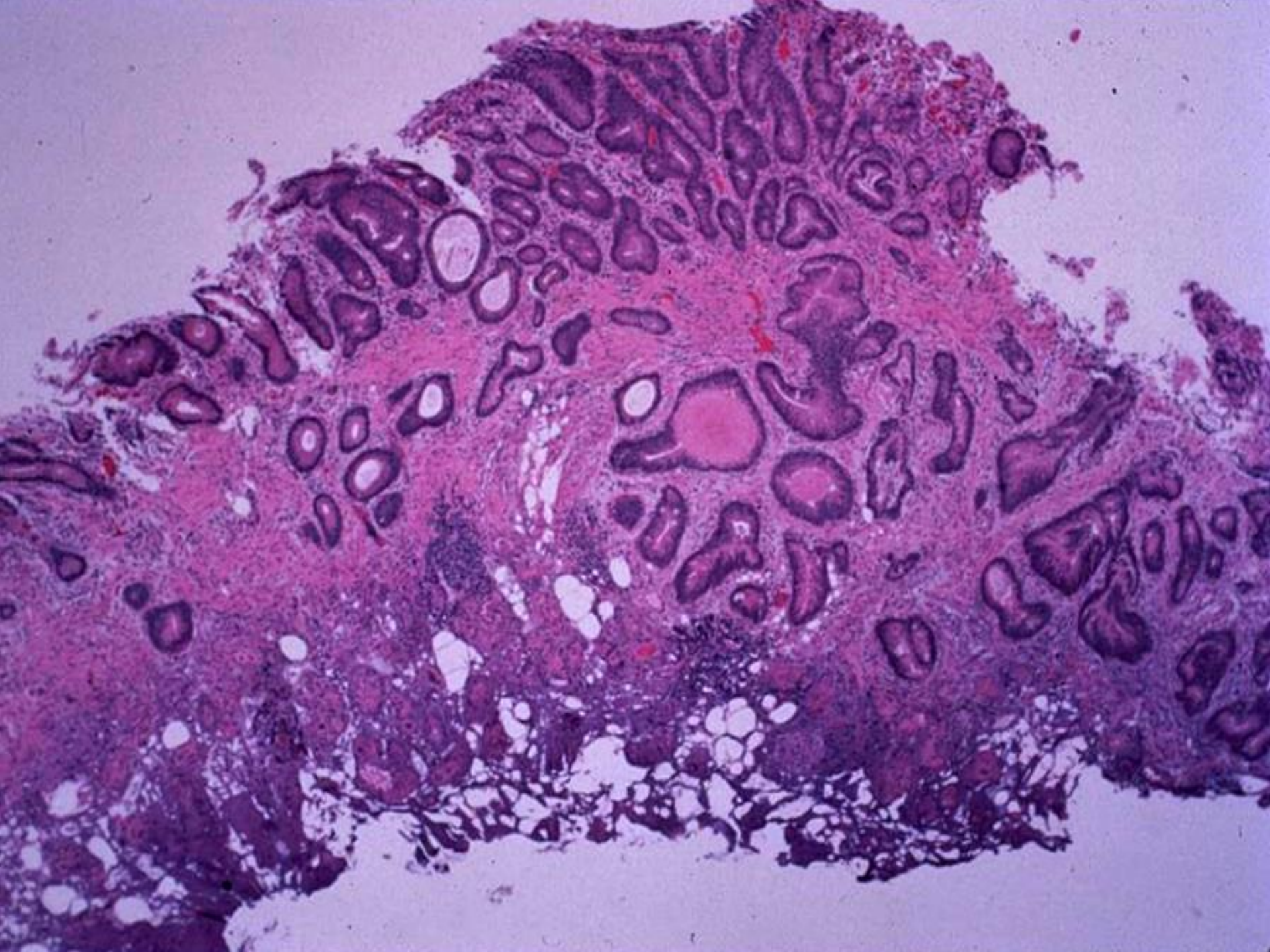


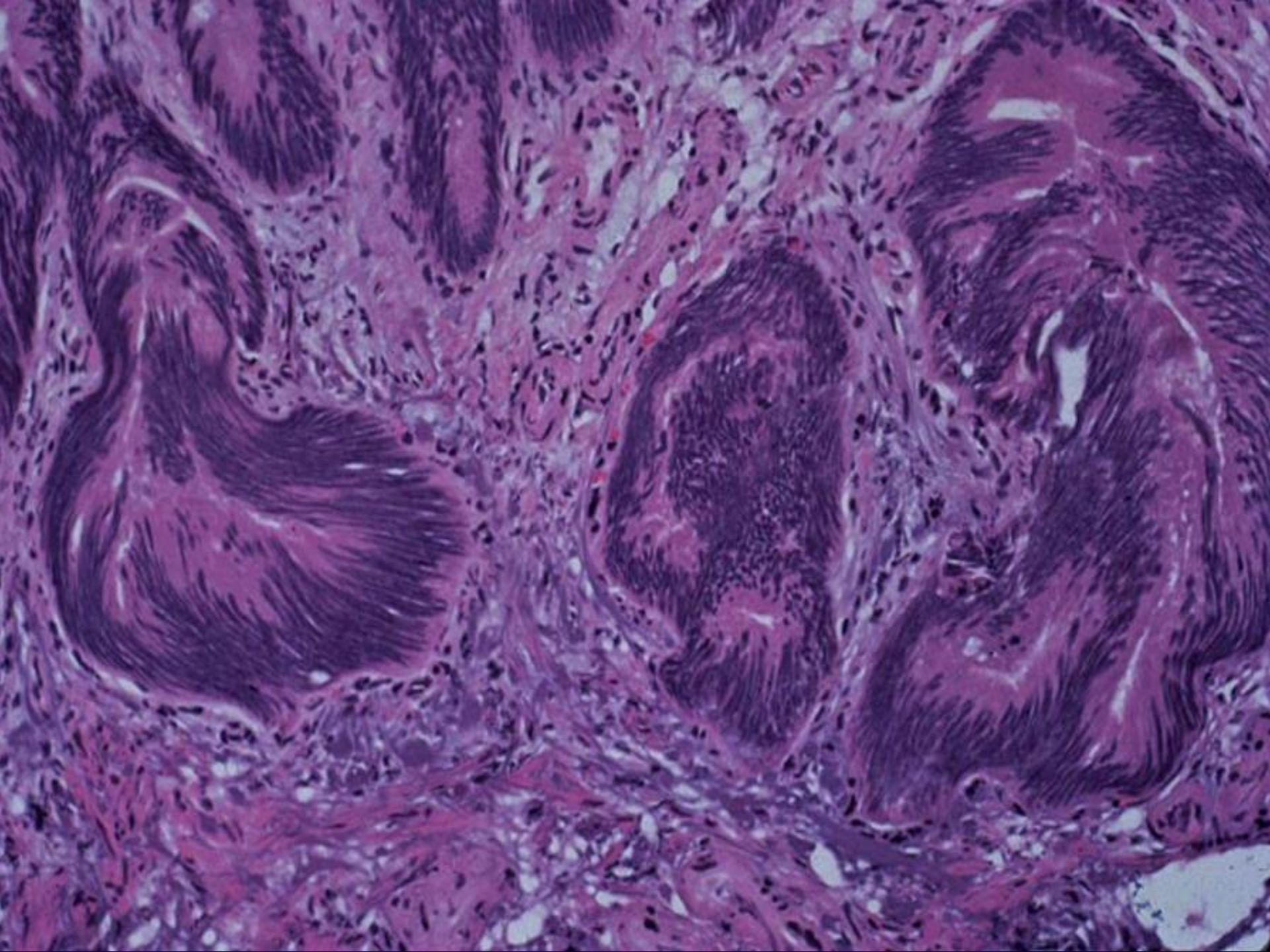








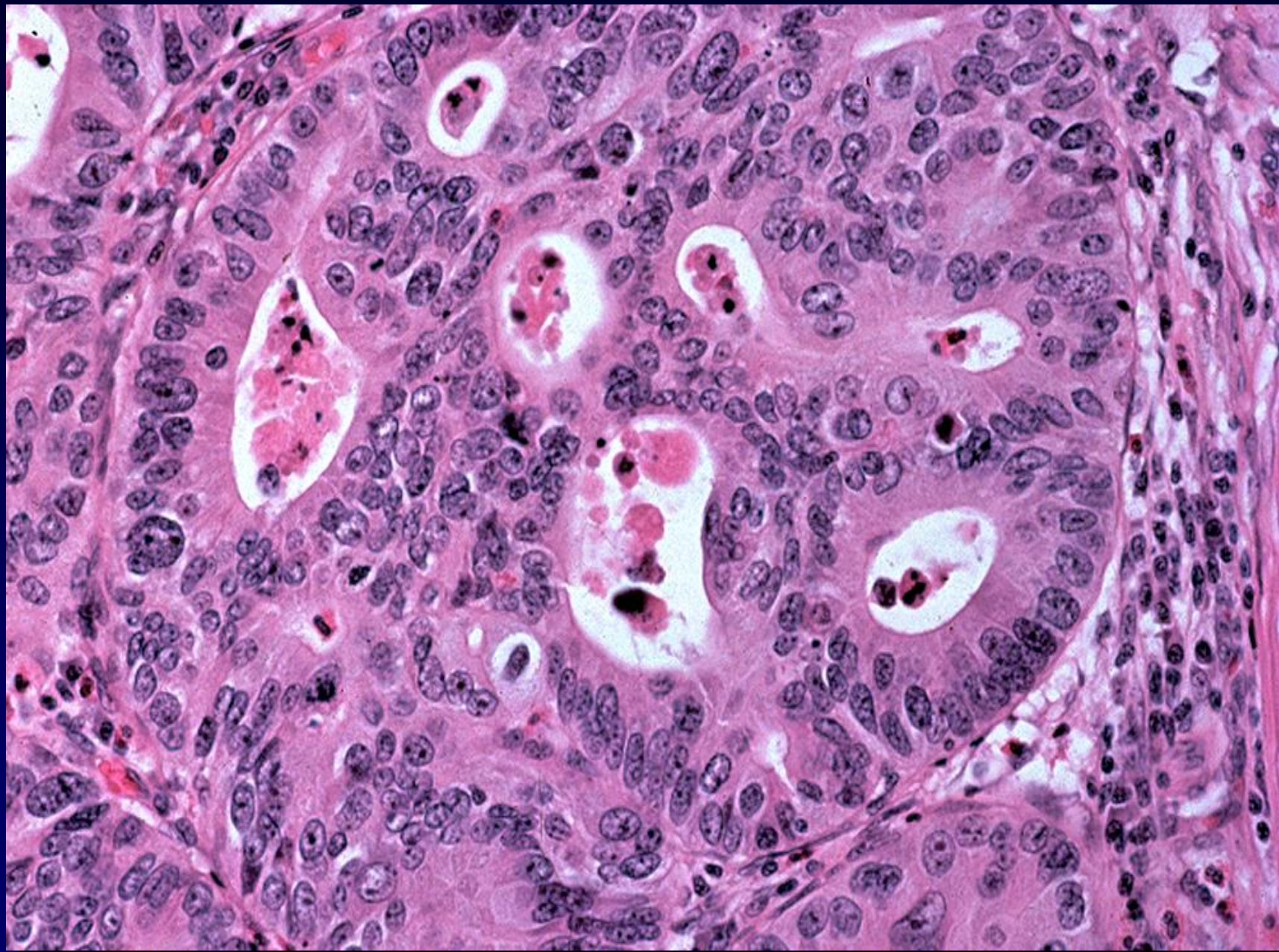




Cancer or Misplaced?

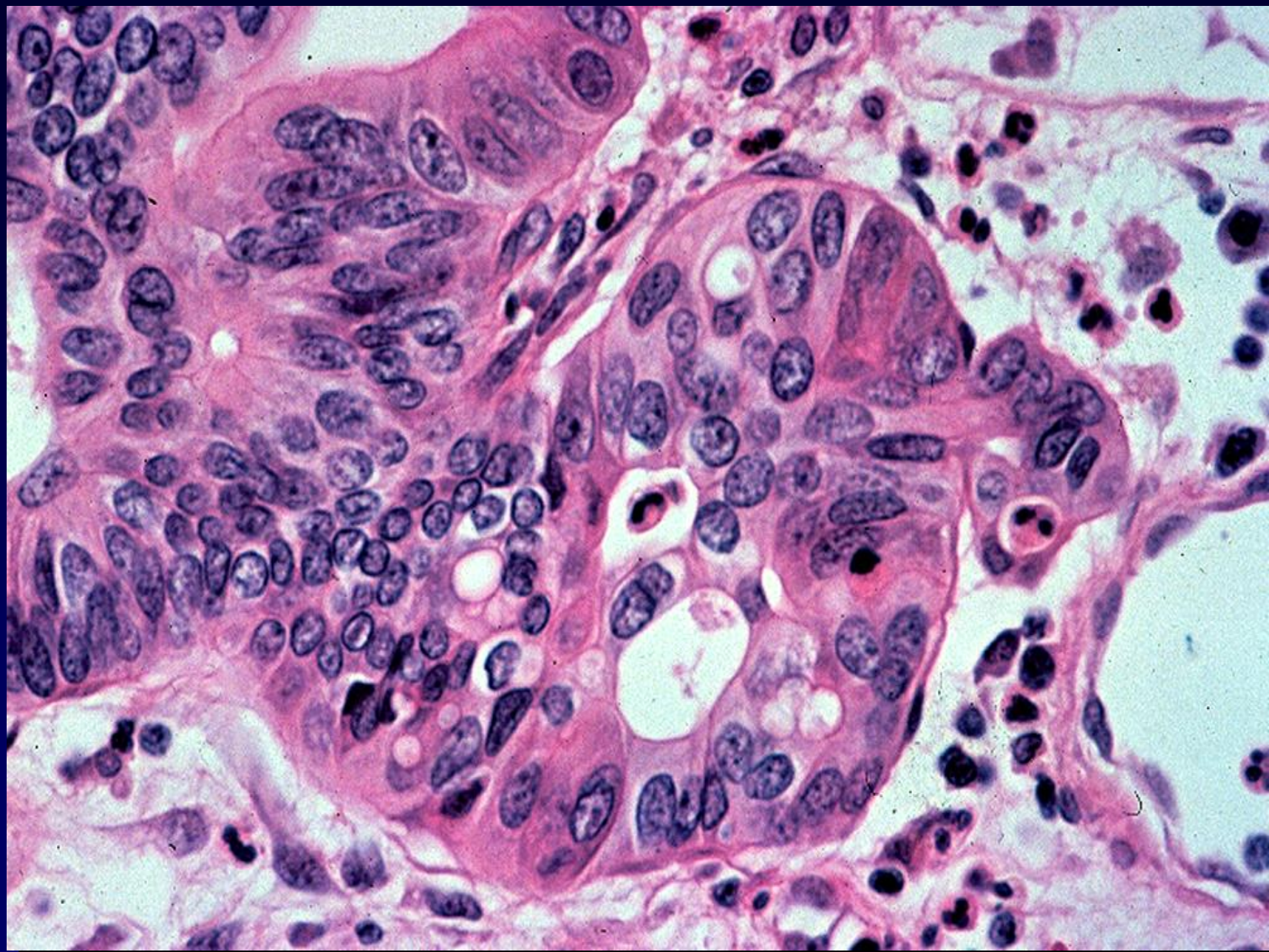
- Inevitable inscrutable cases
- Diagnosis :
“Adenoma with neoplastic submucosal glands of unknown significance”
- **Treatment is the same:** Complete endoscopic excision

Nomenclature of Colorectal Carcinoma



CARCINOMA-IN-SITU

- High grade neoplastic epithelium confined within basement membrane
- Synonymous with high grade dysplasia
- *Cannot* metastasize
- Avoid this term for GI neoplasms!



INTRAMUCOSAL CARCINOMA

- Neoplastic epithelium invading through basement membrane into lamina propria but not through muscularis mucosae
- Metastasis not reported for colon
- Avoid this term for colonic neoplasms!

Diagnosis of Invasive Colorectal Carcinoma

“Invasive carcinoma should only be reported when spread through the muscularis mucosae into the submucosa has been demonstrated. To prevent potential confusion, the term ‘intramucosal carcinoma’ is best avoided in the large bowel.”

From: WHO International Typing of Intestinal Tumors

COLORECTAL ADENOCARCINOMA

- Neoplastic epithelium has invaded through muscularis mucosae into submucosa
- Virtually always desmoplastic stromal reaction
- Capable of metastasis

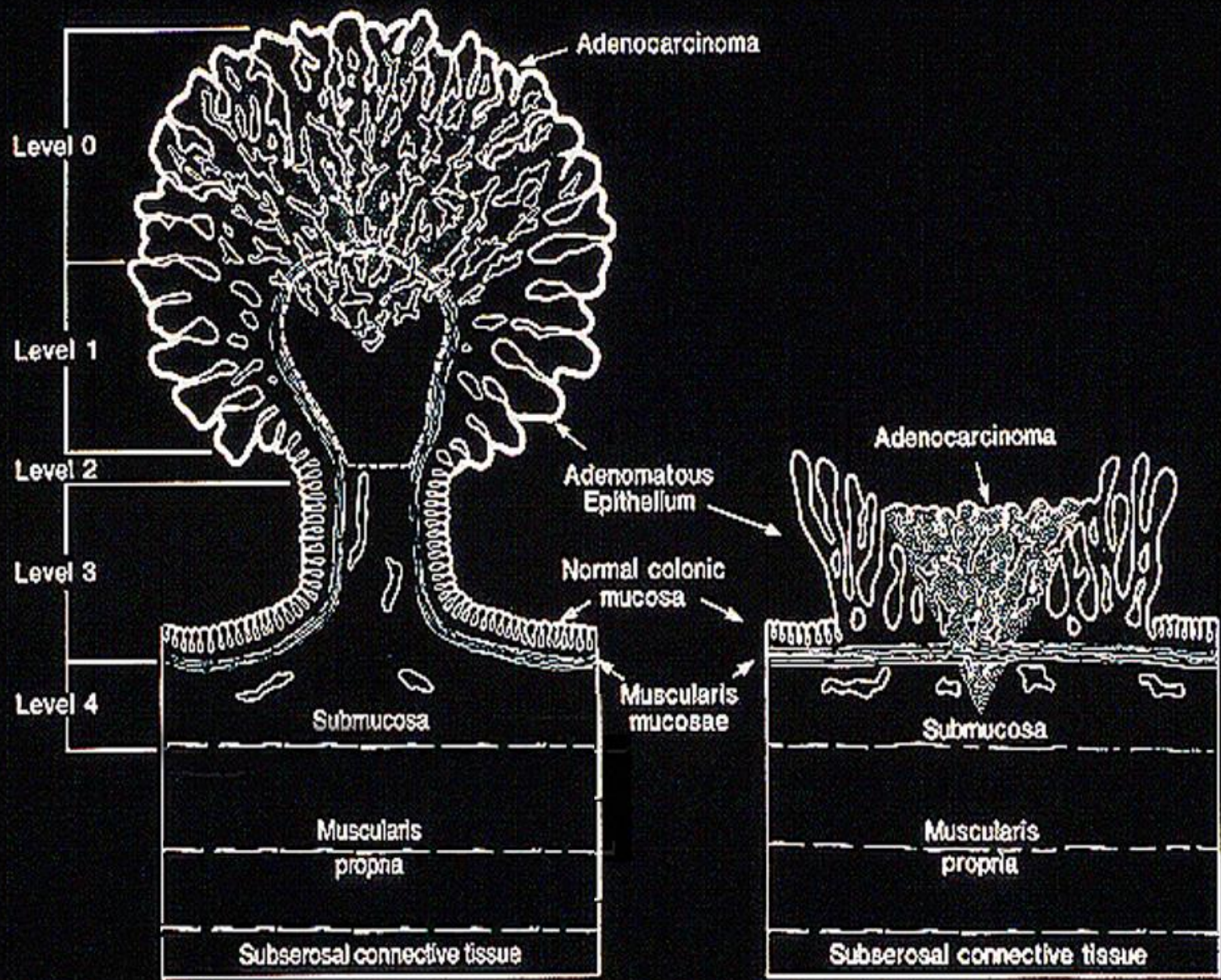
Recommendations for Management??

- A. Do nothing. Patient is cured.
- B. Laparotomy with resection of the polypectomy site.
- C. Laparotomy with wide resection containing polypectomy site and regional lymph nodes.
- D. Follow up periodic colonoscopy.

Steps in Management

2) Determine depth of invasion

- Submucosa polyp head or stalk
- Submucosa bowel wall proper
- Sessile or pedunculated polyp



Pedunculated Adenoma

Sessile Adenoma

Level of Invasion & Nodal Metastases

Level of Invasion	Positive Nodes (44 resections)	Dead of Disease
0	0/18	0/65
1-3	0/13	0/36
4	3/13 (23%)	4/28 (14%)

Includes only well or moderately differentiated tumors without lymphatic invasion. Haggitt RC, et al. Gastroenterology 1985;89:328

Depth of Invasion vs. Positive Nodes

Depth of Invasion	% Positive Lymph Nodes		
	Morson (2084)	Minsky (168)	Grigg (268)
Submucosa	11	0	6.5
M. propria	12	28	-
Thru m.p.	58	39	-

All rectal cancers; all resected by LAR or APR

Steps in Management

3) Assign histologic grade of carcinoma

- Well or Moderately Differentiated
- Poorly Differentiated

Prognostic Significance of Poor Differentiation

Senior Author	Poorly Differentiated	Adverse Outcome	Confounding Factors?
Fenglio	2	2	YES
Colacchio	2	1	NS
Cooper	3	2	NS
Morson	3	1	YES
Haggitt	2	1	YES
Cranley	4	3	YES
TOTALS	16	10 (63%)	

Steps in Management

4) Angiolymphatic invasion

Prognostic Significance of Lymphatic Invasion

Senior Author	Lymphatic Invasion	Adverse Outcome	Confounding Factors?
Fenoglio	2	2	Yes
Colacchio	4	2	NS
Cooper	6	6	NS
Morson	10	5	Yes
Haggitt	2	1	Yes
Cranley	4	1	Yes
TOTALS	28	12 (43%)	

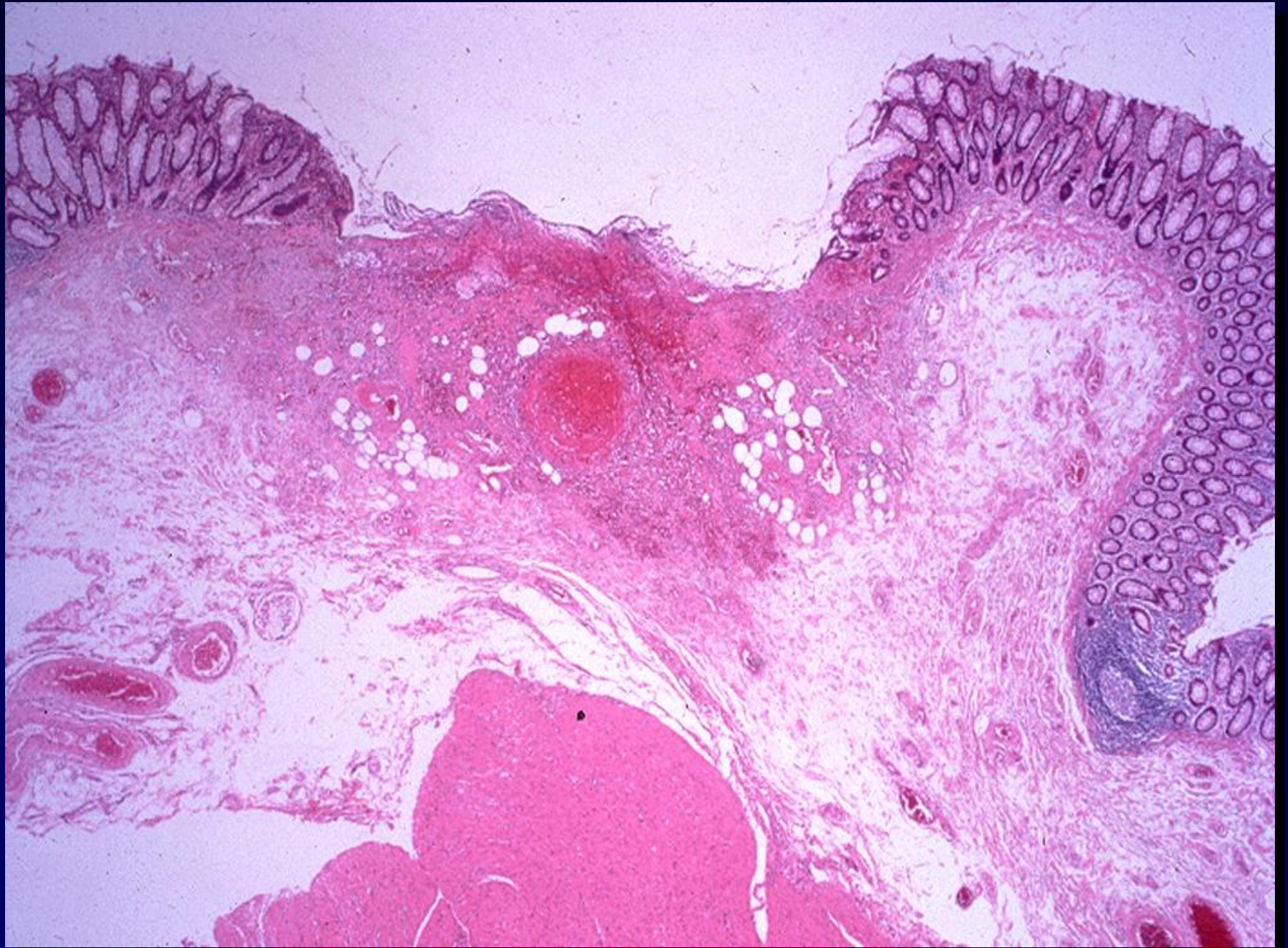
Steps in Management

5) Assess completeness of excision

Completeness of Excision

Endoscopist's opinion is *most* important

- Assesses gross in 3-dimensions
- Cauterizes base: addn 3-5mm destroyed
- If endoscopist thinks excision complete, almost always true
- Addn bxs or EUS for clinical uncertainty



Completeness of Excision

Pathologist's view is limited

- 5 um slice in 2-dimensions
- Histologic distance to margin is arbitrary
- 3 assessments
 - *Appears* completely excised OR
 - Completeness of excision cannot be assessed histologically
 - Neoplasm involved margin

Steps in Management

6) Estimate risk of metastasis

Factors Increasing the Probability of Positive Nodes

- Invasion into submucosa of bowel wall
- Poorly differentiated
- Vascular invasion
- Incomplete resection



Risk of death
from cancer if
no further Rx

Risk of death
from operation
and cancer in
spite of Rx

Surgical Mortality

- Nationwide Survey colorectal CA surgery in 1997 (N=20,862)
- Mortality increase with low-volumes & older age
- Dimick JB, et al. *J Surg Res* 2003

AGE	MORTALITY
<50	0.8%
50-65	1.3%
66-80	2.9%
>80	6.9%

Cancer in *Pedunculated Adenoma*

- Risk of nodal metastasis < 1%
- Mortality segmental resection ~ 5%
- Uniform agreement: Polypectomy
ALONE is adequate treatment

Cancer in *Sessile Adenoma*

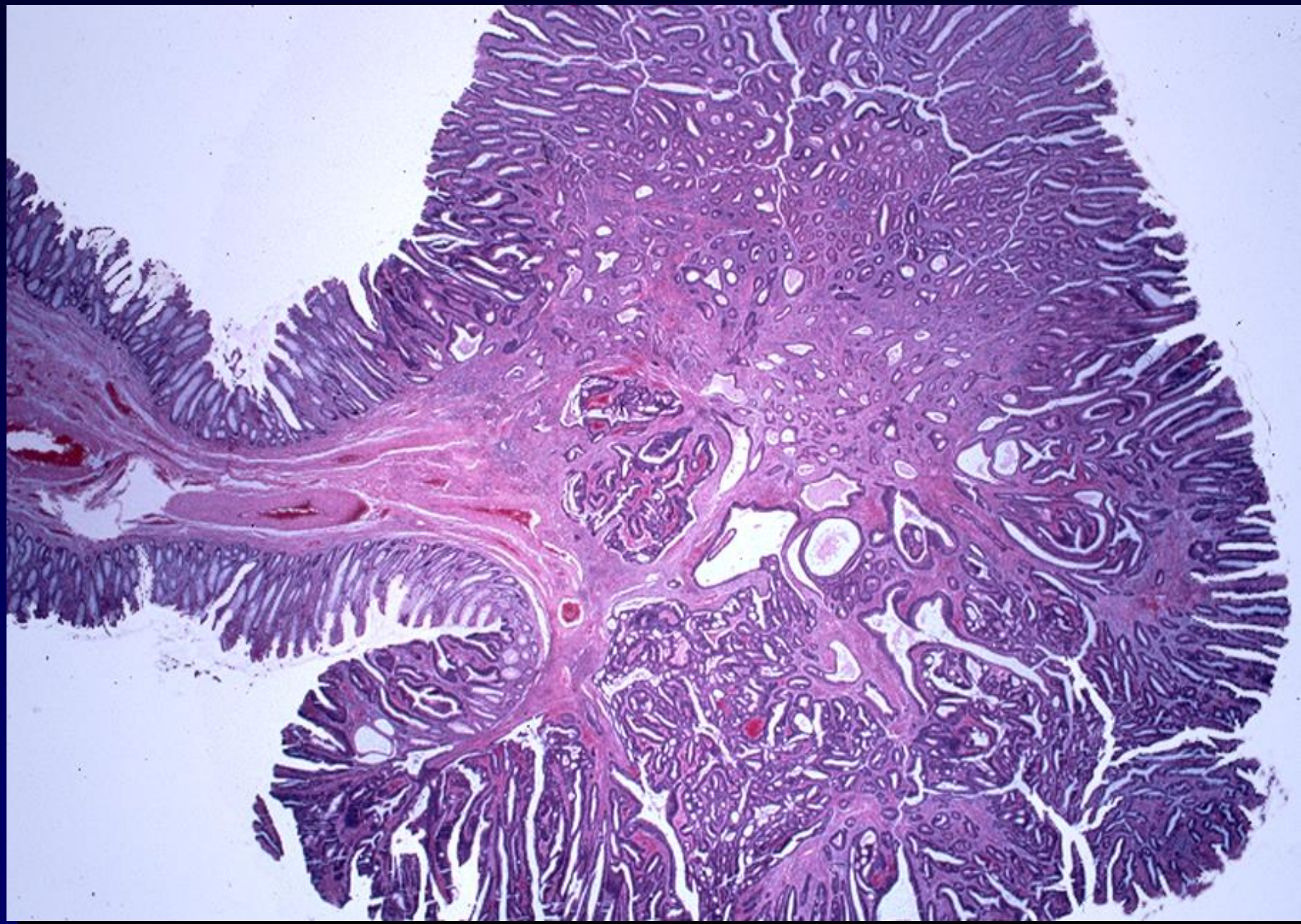
- Risk of LN metastasis ~ 5%
- Mortality at 5 years for Dukes' C > 50%
- Mortality for segmental resection ~ 5%
- Polypectomy alone is PROBABLY STILL adequate treatment, but risk is higher & decisions individual

CAUTION!

All parties, including the patient, must understand the 95% chance or greater of finding nothing in resections done for submucosal invasion in a complete polypectomy

Reporting Cancer in Polyps

- Differentiation: well-mod vs. poor
- Invasion depth: submucosa of polyp head/stalk vs. bowel wall (sessile or pedunculated)
- Angiolymphatic invasion
- Completeness of resection





Summary: BE Neoplasia

- Intestinal vs gastric foveolar types
- Sampling, observer variation, nat hx
- Over diagnosis of HGD
 - Baseline atypia, cardia atypia, inflammation, nuclear polarity
- HGD options: surveillance, ablation, CBE-EMR, surgery
- Duplicated MM: don't overstage

Summary: IIBD Dysplasia

- Nomenclature: No CIS or IMC in colon
- Huge surface area: 33 bxs
- Natural history: limited to one study of 42 pts with LGD: minority progress (>3 LGD bxs)
- Adenoma-like dysplasia: follow but many caveats

Summary: Gastric Dysplasia

- MIP essentially
 - IM of gastric BODY
 - Caused by HP
 - 2nd most common CA worldwide
- Caveat: Gastric IM mimics dysplasia more due to adjacent totally bland gastric mucosa: DON'T OVER DX:
Use surface maturation

Summary: Cancer in *Pedunculated Adenoma*

- Risk of nodal metastasis < 1%
- Mortality segmental resection ~ 5%
- Uniform agreement: Polypectomy
ALONE is adequate treatment

Summary: Cancer in *Sessile Adenoma*

- Risk of LN metastasis ~ 5%
- Mortality at 5 years for Dukes' C > 50%
- Mortality for segmental resection ~ 5%
- Polypectomy alone is PROBABLY STILL adequate treatment, but risk is higher & decisions individual

Summary: Reporting Cancer in Polyps

- Differentiation: well-mod vs. poor
- Invasion depth: submucosa of polyp head/stalk vs. bowel wall (sessile or pedunculated)
- Angiolymphatic invasion
- Completeness of resection