MAYO CLINIC

AUSTRALASIAN GASTROINTESTINAL PATHOLOGY SOCIETY

Update on Barrett's Esophagus and Early Esophageal Adenocarcinoma

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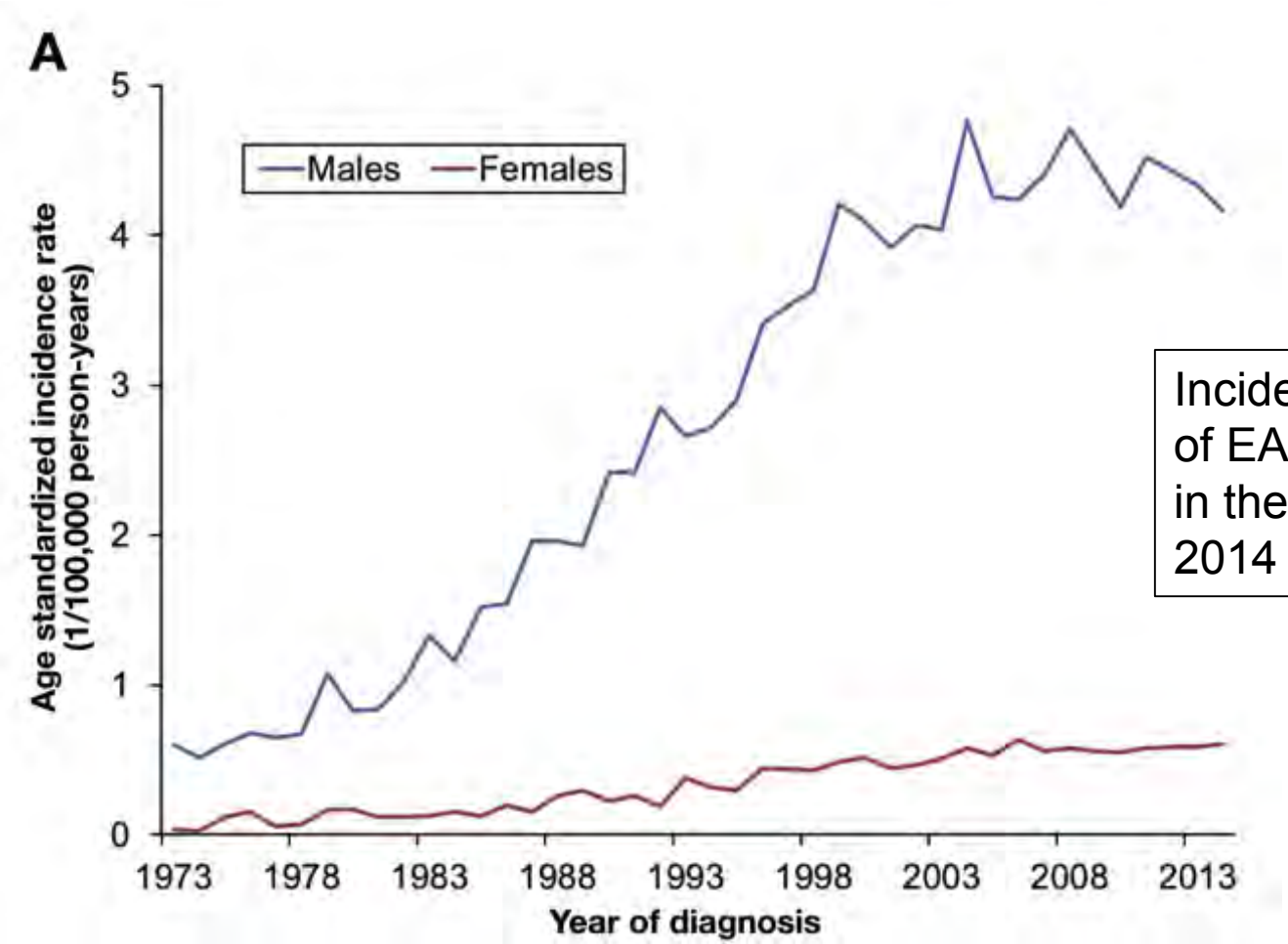
Outline

- Barrett's esophagus clinical decision tree
  - Pathologic diagnoses that guide clinical decision making
- Basic principles in the evaluation of BE-related dysplasia
  - Issues in interpretation
- Role of ancillary diagnostic tests (p53)
- Evaluation of endoscopic mucosal resection/endoscopic submucosal dissection specimens

The Problem: Rising Incidence in Esophageal Adenocarcinoma



Incidence trends of EAC in whites in the US, 1973–2014

Gastroenterology 2018;154:390–405

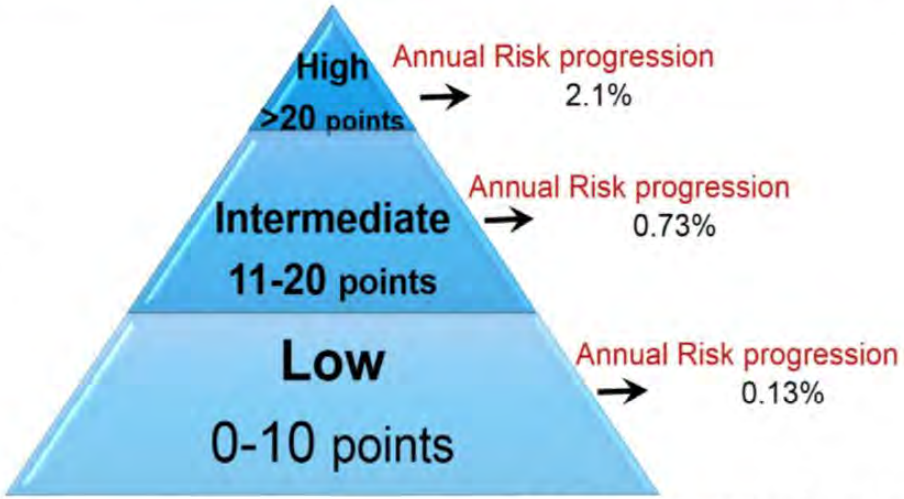
Factors that Predict HGD and Esophageal Adenocarcinoma

PIB Risk Score

- Male Sex - 9 points
- Cigarette Smoking - 5 points
- 

BE length - 1 point / cm length
- 
Confirmed Low Grade Dysplasia - 11points

Risk Pyramid for Progression in Barrett's



Gastroenterology

Parasa, S. et al. Gastro 2018; 154:1281

Question 1:

- Which is true regarding Barrett's esophagus related dysplasia?
  A. Low-grade dysplasia is overdiagnosed.
  B. Complex glandular architecture is a feature of low-grade dysplasia.
  C. High-grade dysplasia is underdiagnosed.
  D. Lack of surface maturation is not a feature of dysplasia.

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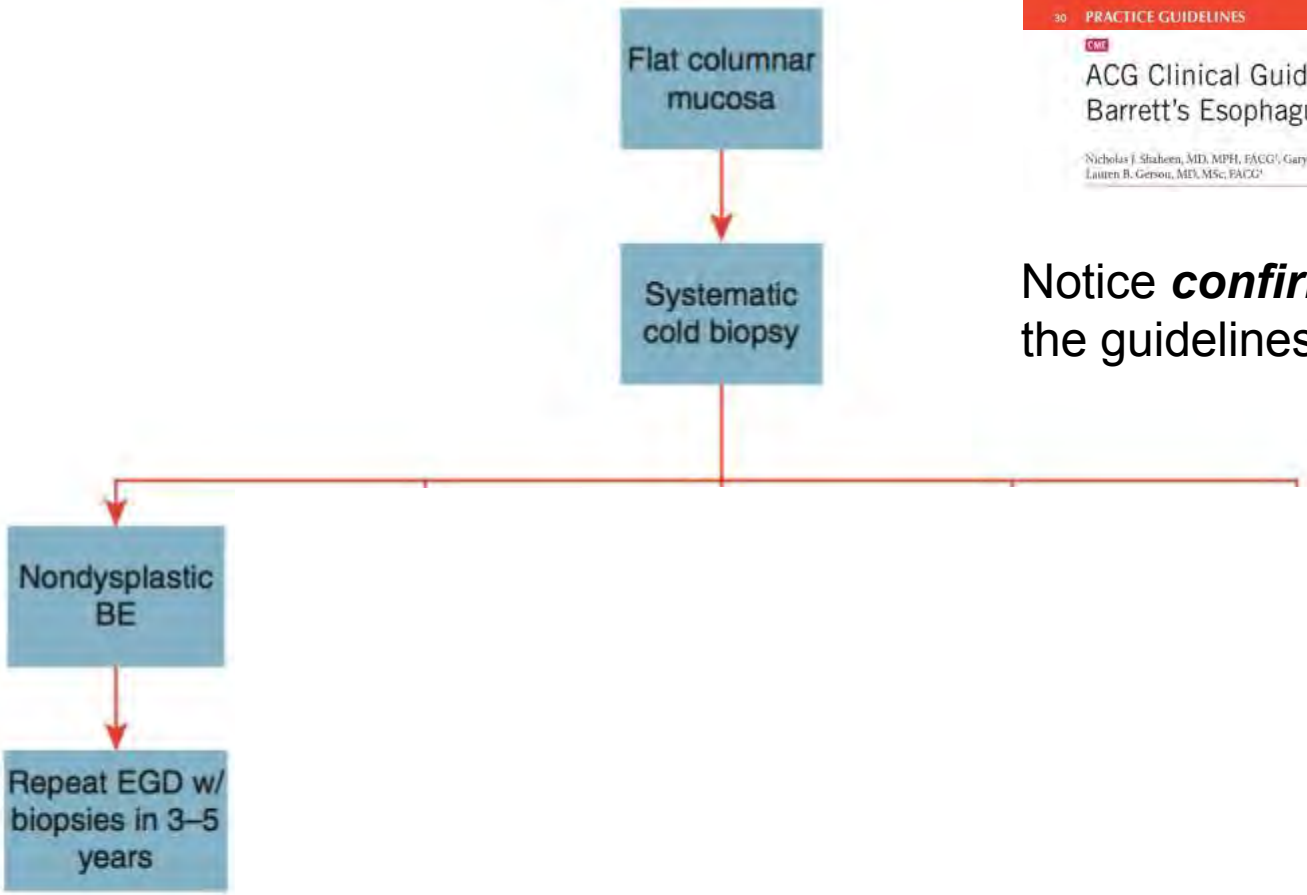
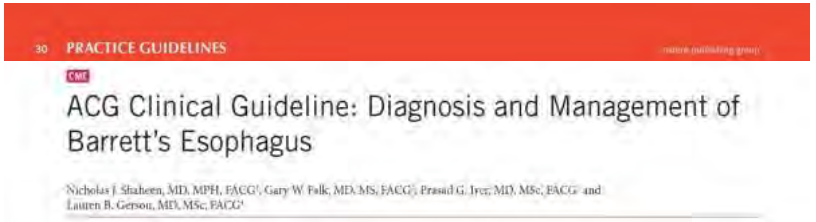
Important facts regarding BE and dysplasia

- BE is relatively common.
  - Is present ~2% of unselected individuals (up to 5.6% in US adults)
  - Prevalence of 5-15% in adults with reflux
- BE-related neoplasia is uncommon.
  - Annual rate of progression from NDBE to adenocarcinoma is 0.1% to 0.3%
- BE-related dysplasia has only moderate interobserver agreement
  - **Low-grade dysplasia** is the most difficult diagnosis
- Despite these issues, the presence of dysplasia is the BEST marker of neoplastic progression
  - Used to risk stratify patients

Flat "Non-Visible" Dysplasia




30 PRACTICE GUIDELINES

CME

ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus

Nicholas J. Shaheen, MD, MPH, FACG[1], Gary W. Falk, MD, MS, FACG[2], Prasad G. Iyer, MD, MSc, FACG[3] and Lauren B. Gerson, MD, MSc, FACG[4]

Notice ***confirmed*** dysplasia in the guidelines

Shaheen, NJ et al. Am J Gastroenterol. 2016;111(1):30-50

Society Guidelines

Table 1. Guideline Recommended Surveillance Intervals for Barrett's Esophagus

	Nondysplastic	Confirmed low-grade dysplasia	High-grade dysplasia
American College of Gastroenterology	3–5 y	Repeat EGD after optimizing proton pump inhibitor therapy For confirmed LGD without life-limiting comorbidity, the preferred treatment modality is endoscopic therapy, however, an acceptable alternative is endoscopic surveillance every 12 mo	Endoscopic eradication therapy
American Gastroenterological Association	3–5 y	Perform surveillance every 6–12 mo Radiofrequency ablation is an option if LGD is confirmed	3 mo in the absence of eradication therapy
American Society for Gastrointestinal Endoscopy	3–5 y	Repeat EGD within 6 mo to confirm the diagnosis Consider ablation in select patients or perform annual surveillance	3 mo; consider endoscopic eradication therapy
British Society of Gastroenterology	≥3 cm, 2–3 y <3 cm, 3–5 y	Perform EGD every 6 months until 2 in a row have negative findings Radiofrequency ablation may be used in patients with LGD	Endoscopic eradication therapy
Australian clinical practice guidelines	≥3 cm, 2–3 y <3 cm, 3–5 y	Perform surveillance every 6–12 mo	Endoscopic eradication therapy

EGD, esophagogastroduodenoscopy; LGD, low-grade dysplasia.

Dysplasia in BE is Overdiagnosed

Low-Grade Dysplasia in Barrett's Esophagus: Overdiagnosed and Underestimated

Am J Gastroenterol. 2010 Jul;105(7):1523-30.

Wouter L. Curvers, MD[1,12], Fiebo J. ten Kate, MD, PhD[2,12,13], Kausilia K. Krishnadath, MD, PhD[1,12], Mike Visser, MD, PhD[2,13], Brenda Elzer, MSc[1], Lubertus C. Baak, MD, PhD[3,12], Clarisse Bohmer, MD, PhD[4,12], Rosalie C. Mallant-Hent, MD, PhD[5,12], Arnout van Oijen, MD[6,12], Anton H. Naber, MD, PhD[7,12], Pieter Scholten, MD[8,12], Olivier R. Busch, MD, PhD[9,13], Harriët G.T. Blaauwgeers, MD, PhD[10,13], Gerrit A. Meijer, MD, PhD[11,13] and Jacques J.G.H.M. Bergman, MD, PhD[1,12,13]

Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel

Gut. 2015 May;64(5):700-6.

Lucas C Duits,[1] K Nadine Phoa,[1] Wouter L Curvers,[1] Fiebo J W ten Kate,[2,3] Gerrit A Meijer,[4] Cees A Seldenrijk,[5] G Johan Offerhaus,[2,3] Mike Visser,[2] Sybren L Meijer,[2] Kausilia K Krishnadath,[1] Jan G P Tijssen,[6] Rosalie C Mallant-Hent,[1,7] Jacques J G H M Bergman[1]

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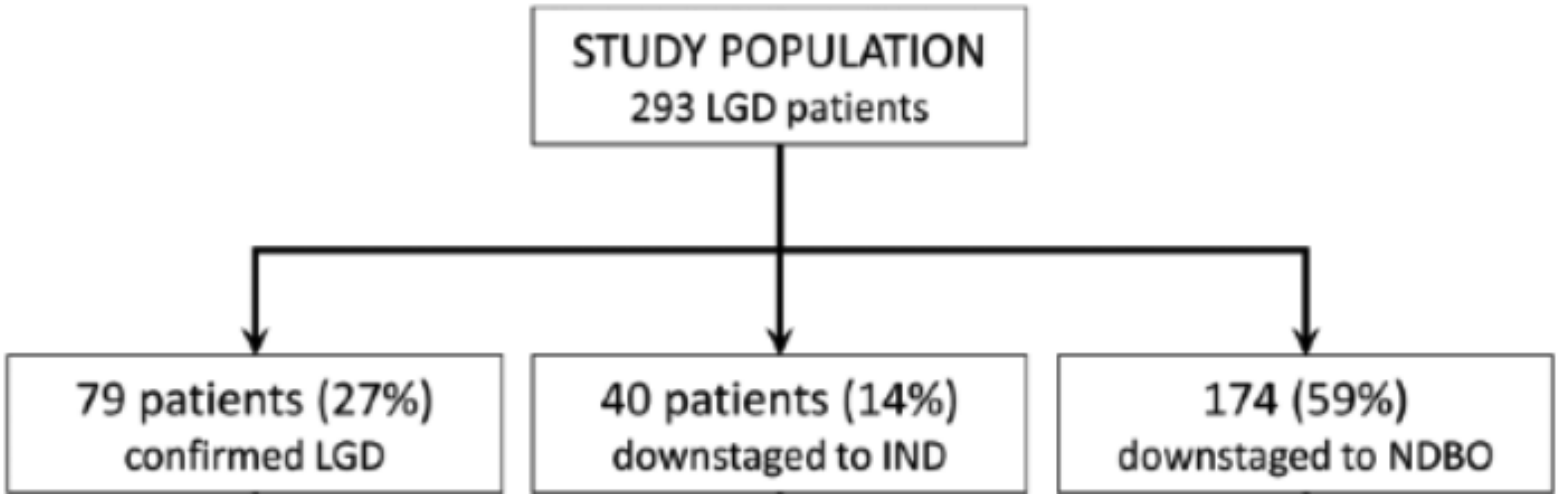
293 patients with LGD diagnosed throughout the Netherlands were enrolled in the study

- **Only 79 (27%) were confirmed to have LGD after central review**



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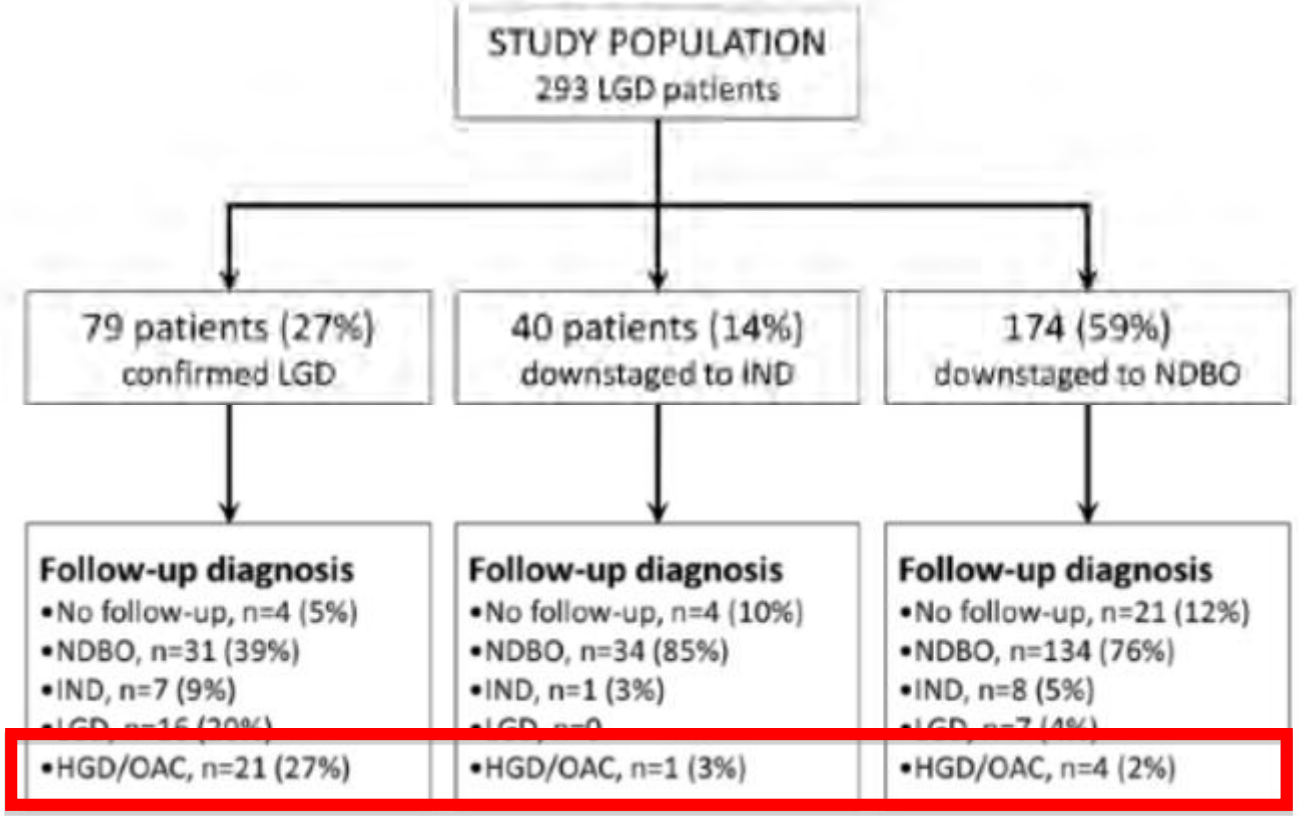
Was the central review diagnosis better?



Patients With Barrett's Esophagus and Confirmed Persistent Low-Grade Dysplasia Are at Increased Risk for Progression to Neoplasia

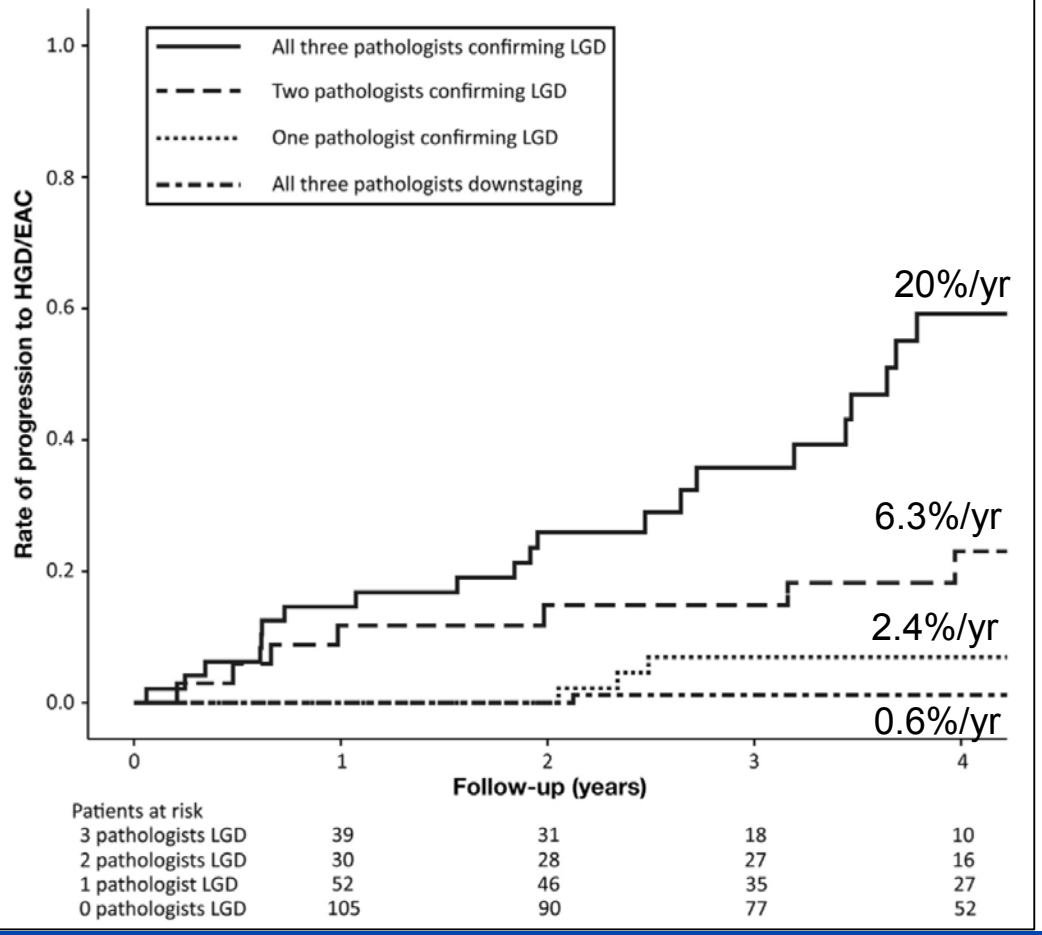
Gastroenterology 2017;152:993–1001

Lucas C. Duits,[1] Myrtle J. van der Wel,[1,2] Cary C. Cotton,[3] K. Nadine Phoa,[1] Fiebo J. W. ten Kate,[3,4] Cees A. Seldenrijk,[5] G. Johan A. Offerhaus,[3,4] Mike Visser,[3] Sybren L. Meijer,[3] Rosalie C. Mallant-Hent,[1,6] Kausilia K. Krishnadath,[1] Roos E. Pouw,[1] Jan G. P. Tijssen,[7] Nicholas J. Shaheen,[3] and Jacques J. G. H. M. Bergman[1]

Patients recruited to a clinical trial of surveillance vs. RFA (SURF) for LGD

Table 1. Demographic and Clinical Characteristics

Characteristic	All patients (N = 255)
Age, *y*, mean ± SD	63.0 ± 10.2
Male, n (%)	199 (78)
Time since Barrett's diagnosis, *y*, median (IQR)	3.4 (0–8)
Length of Barrett's segment, *cm*, median (IQR)	4 (3–7)
Circumferential Barrett's extent, *cm*, median (IQR)	2 (1–5)
No. of pathologists confirming LGD, n (%)	
0	113 (44)
1	60 (24)
2	34 (13)
3	48 (19)



- Persistence of LGD on at least one subsequent endoscopies increased risk of HGD/EAC (9-fold)
- Extent of LGD was not predictive

Overdiagnosis of high-grade dysplasia in Barrett's esophagus: a multicenter, international study

Nikhil A Sangle[1], Shari L Taylor[2], Mary J Emond[3], Michelle Depot[4], Bergein F Overholt[5], Mary P Bronner[1,6] and On behalf of the International Photodynamic Group for High-Grade Dysplasia in Barrett's Esophagus

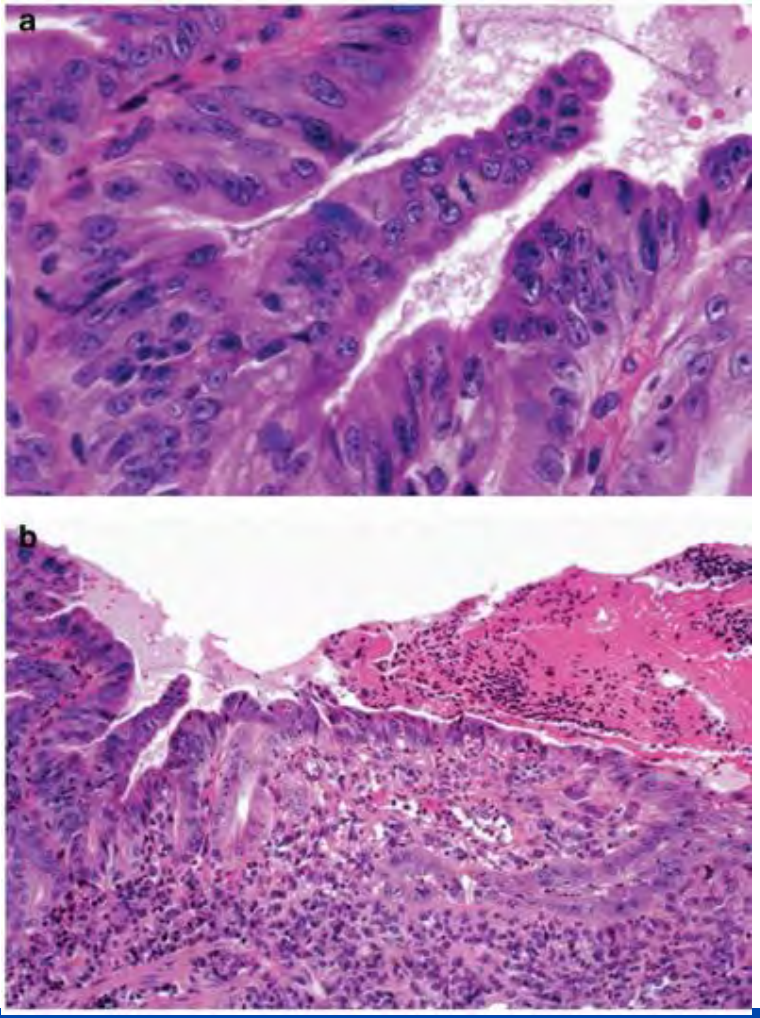
437 referred to study with HGD, only 248 (51%) were confirmed to have HGD

Table 1 Reinterpreted diagnoses in 485 patients originally diagnosed with Barrett's high-grade dysplasia.

Reinterpreted diagnoses from high-grade dysplasia	*# Patients*	*Percentages (%)*
Reactive gastric cardia mucosa only	18	7
Barrett's esophagus, negative for dysplasia	35	15
Barrett's esophagus, indefinite for dysplasia	61	26
Barrett's esophagus, low-grade dysplasia	79	33
Other (squamous neoplasia)	1	1
Barrett's adenocarcinoma	43	18
Total	237	100

Sangle NA et al. Mod Pathol. 2015;38:758-765.

Overdiagnosis of High-Grade Dysplasia

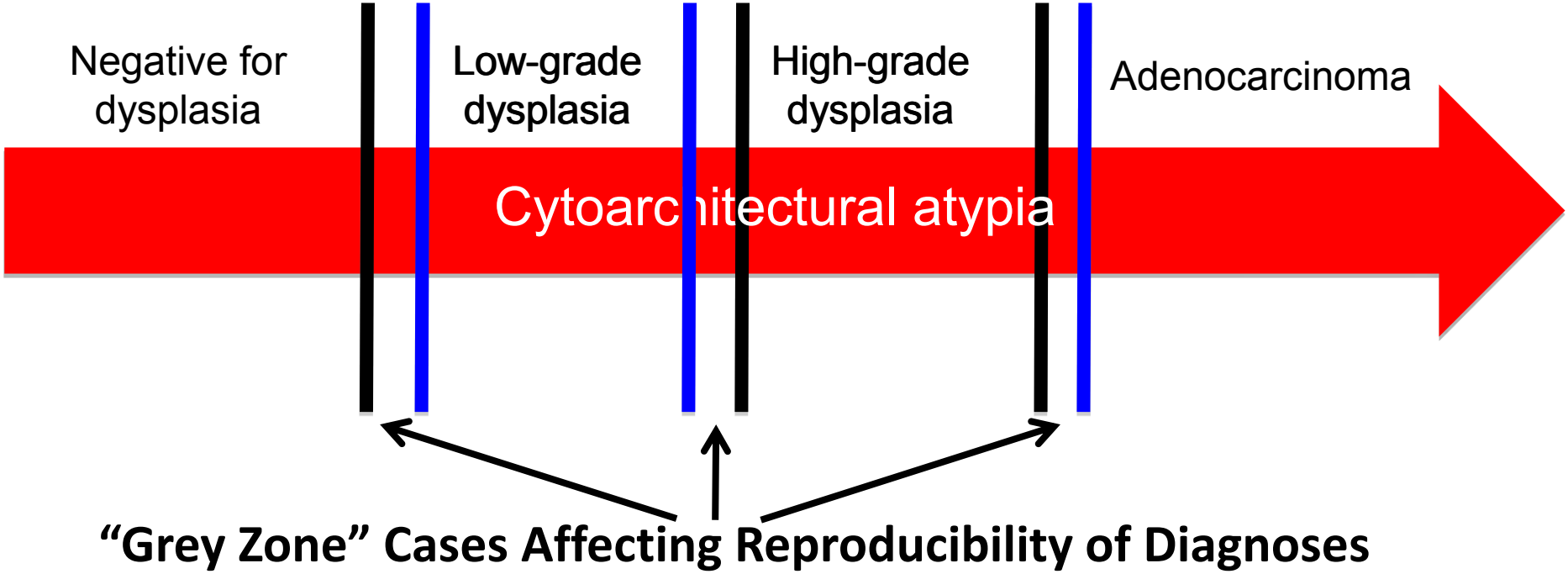


- Epithelial atypia in the presence of intense inflammation, erosion, ulceration can mimic dysplasia.
- On the other hand, ulcers in true dysplasia are worrisome for adenocarcinoma
- If the sample is limited, then a diagnosis of “indefinite for dysplasia” is prudent.
  - Re-biopsy is recommended

Sangle NA et al. Mod Pathol. 2015;38:758-765.

Improving reproducibility in BE

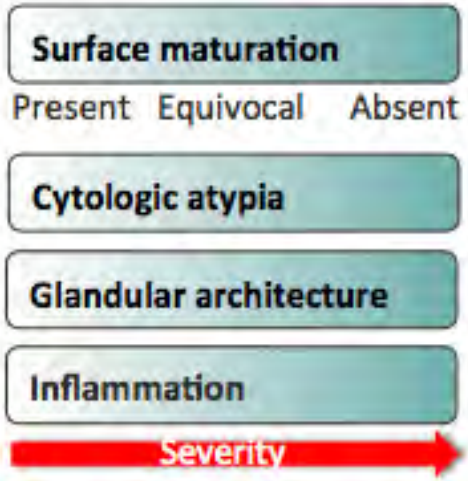
- Agreement in the grade of dysplasia is essential in risk stratifying BE patients
- The problem:
  - Cytoarchitectural atypia occurs on a continuum.
  - How we divide cytoarchitectural atypia into various grades of dysplasia is observer dependent.



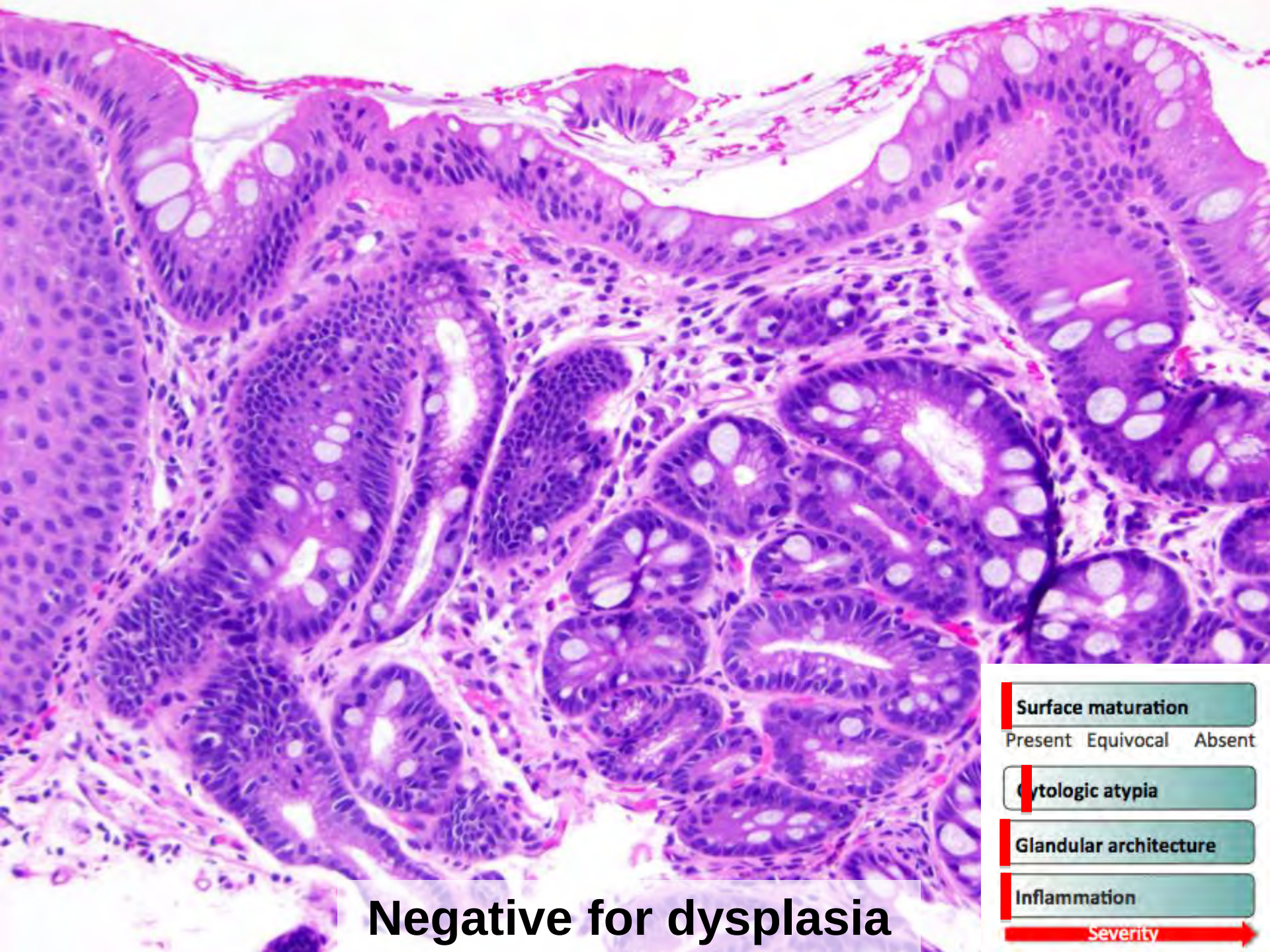
Dysplasia in BE: My approach

Features that should guide the diagnosis

- **Surface maturation** (most important)
  - Present, absent, or equivocal
- **Cytologic atypia**
  - Abrupt cytologic transition, nuclear size, nuclear stratification, nuclear hyperchromasia, nuclear membrane irregularities, nuclear polarity, N:C ratio
- **Glandular architecture**
  - Normal, crowded, complex (focal cribriforming, villiform, glandular budding, papillary growth)
- **Inflammation**
  - Acute inflammation, erosion, ulceration



- These changes occur on a continuum
- It's the overall combination of these factors that determines the grade of dysplasia

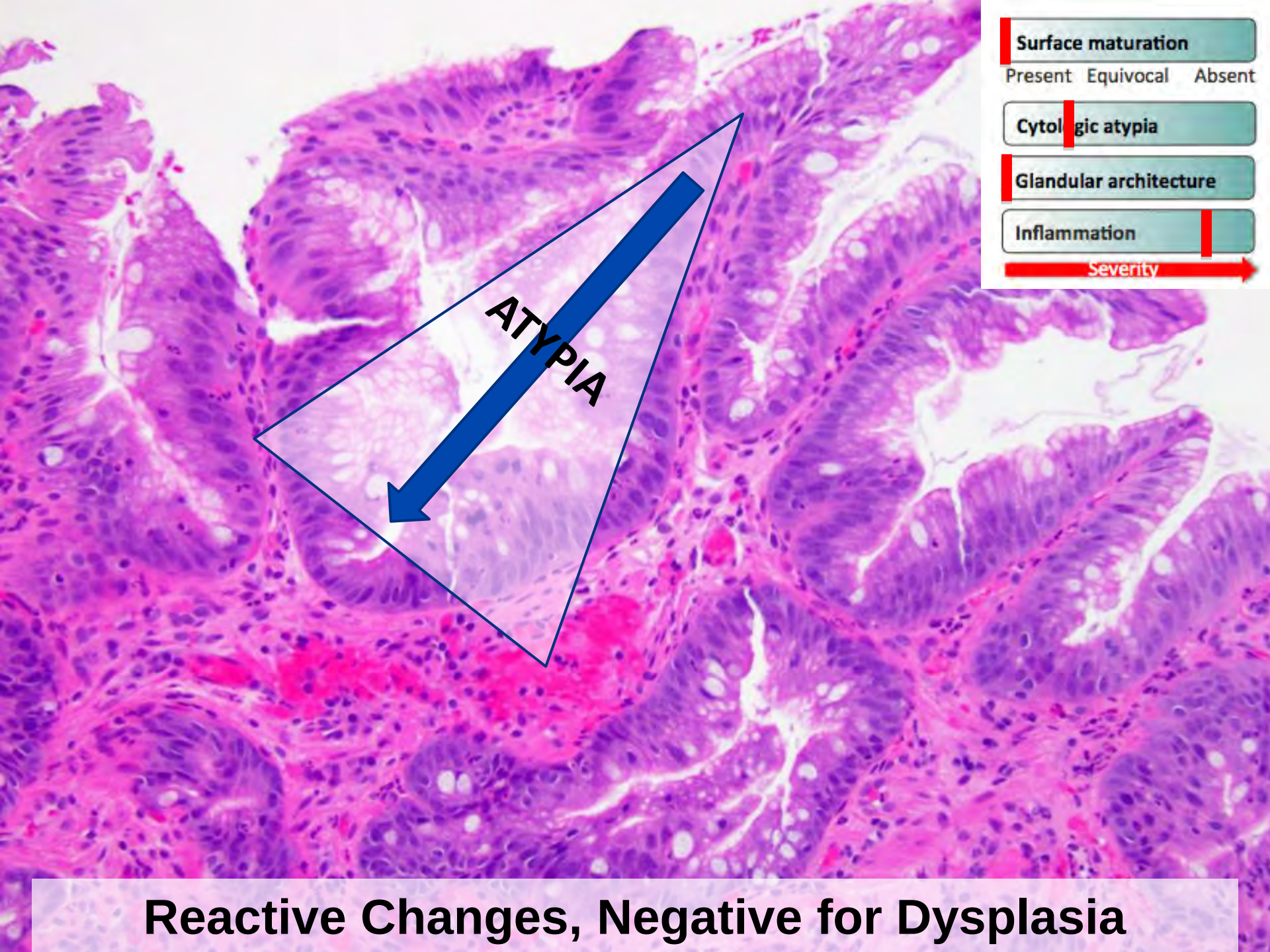


Negative for dysplasia

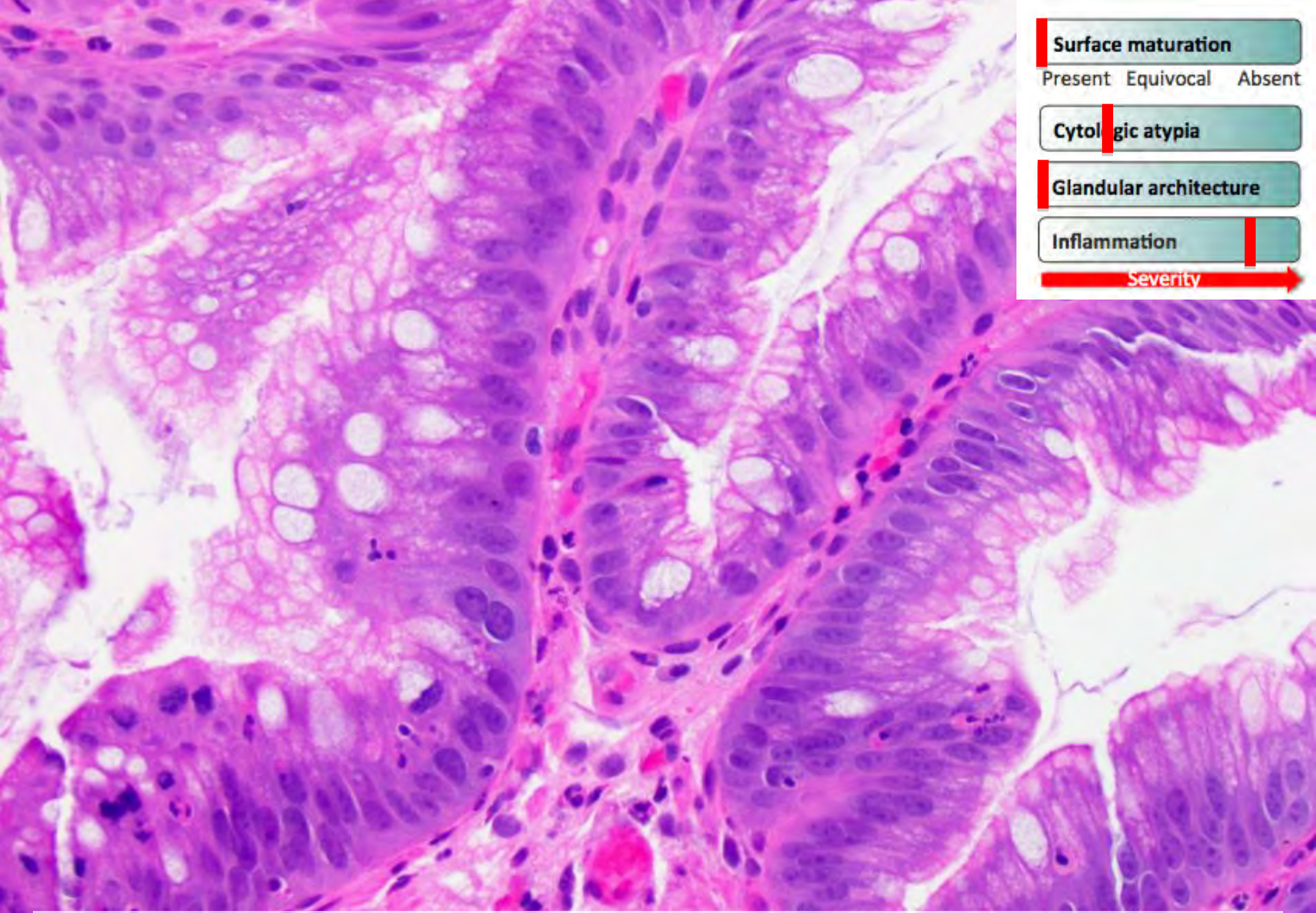

Negative for dysplasia

Reactive Changes vs. Low-Grade Dysplasia

Histologic Features	Reactive Changes, Negative for Dysplasia	Low-Grade Dysplasia
Histologic similarities	• Mitotic activity • Nuclear hyperchromasia • Nuclear enlargement • Nuclear crowding and stratification	• Mitotic activity • Nuclear hyperchromasia • Nuclear enlargement • Nuclear crowding and stratification
Histologic differences	• **Surface maturation present** • **Uniform, diffuse atypia across biopsy fragments** • **Inflammation**	• **Surface maturation absent** • **Non-uniform atypia across biopsy fragments** • **Minimal inflammation**



Reactive Changes, Negative for Dysplasia



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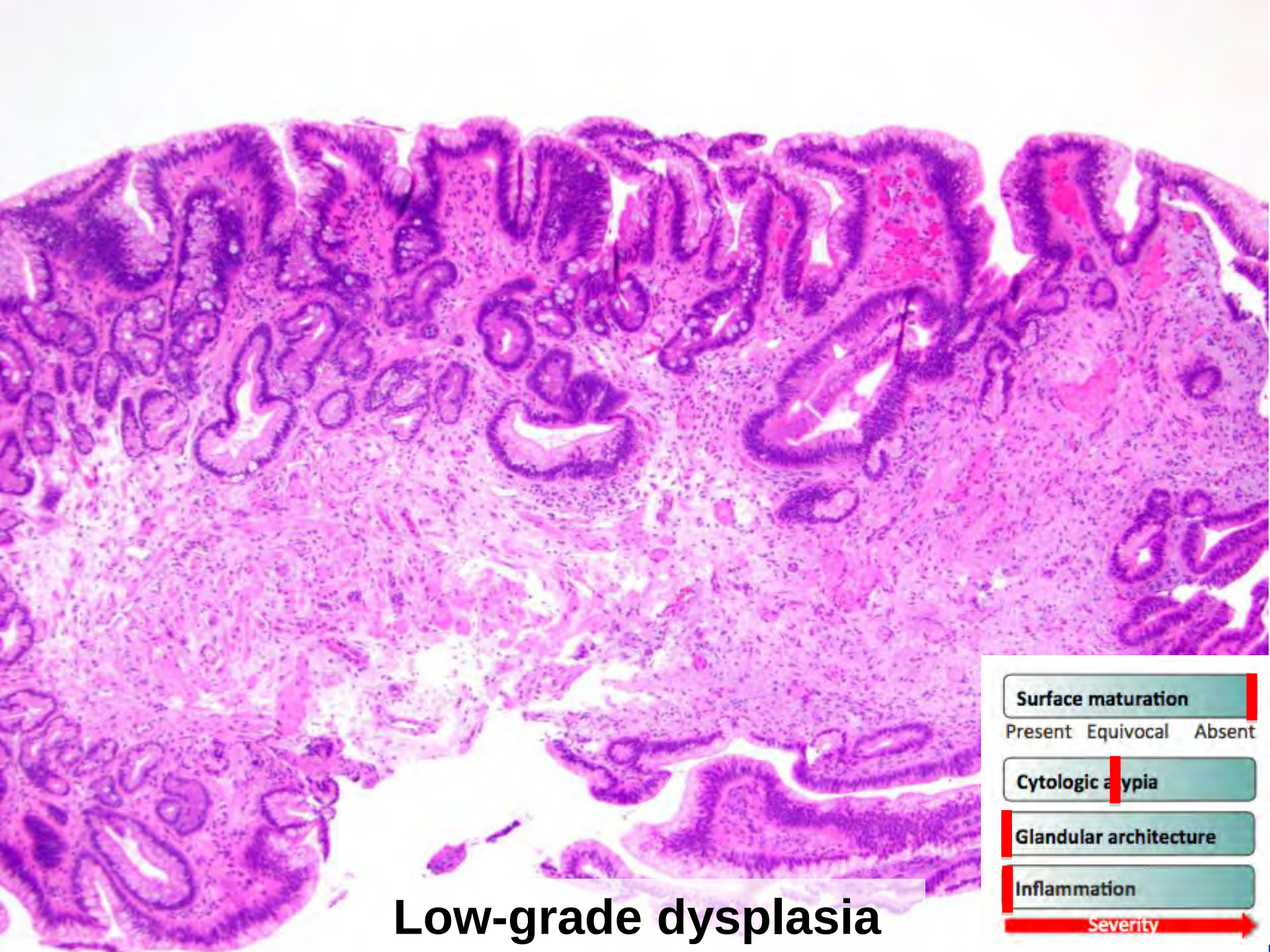
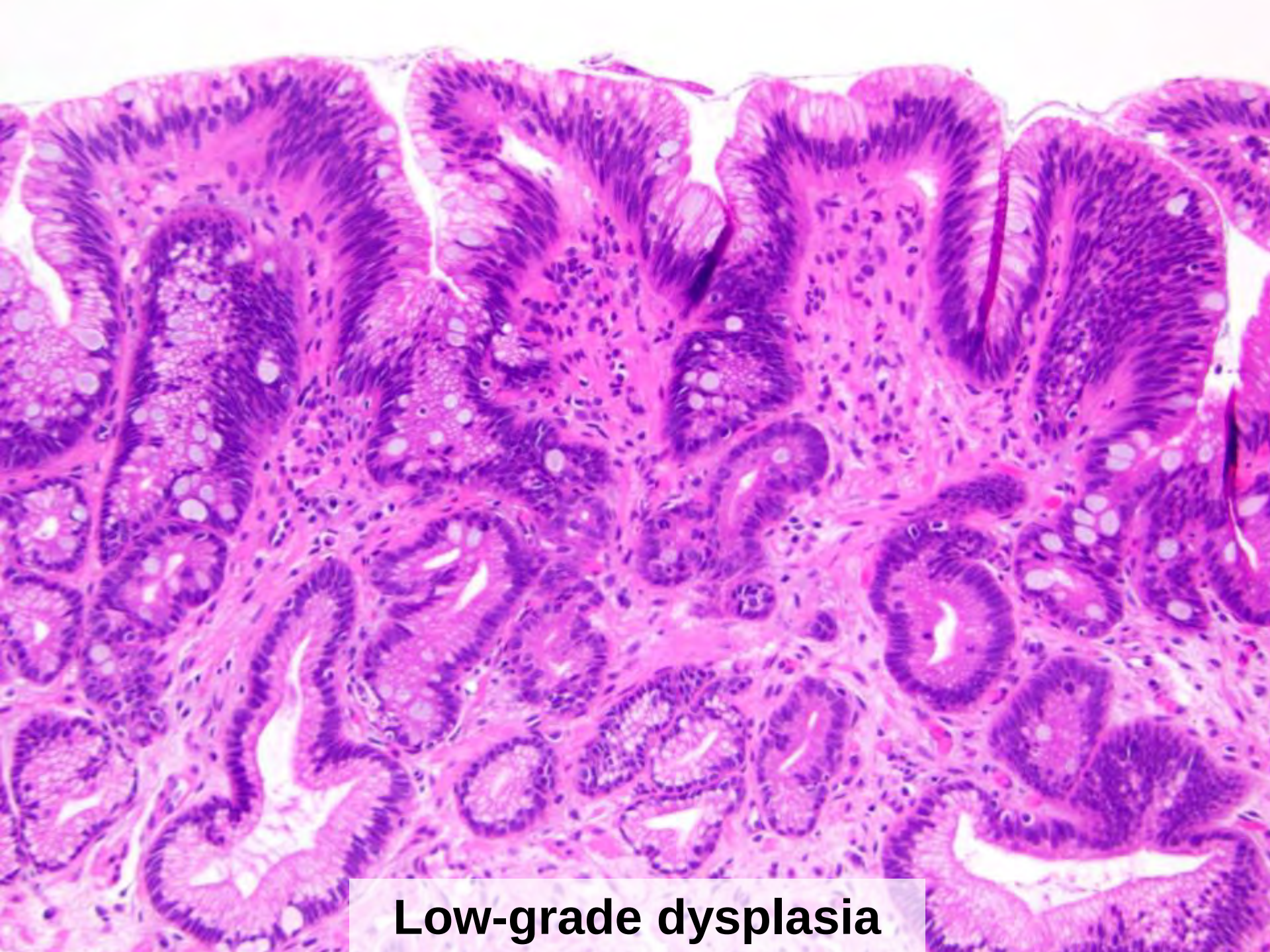
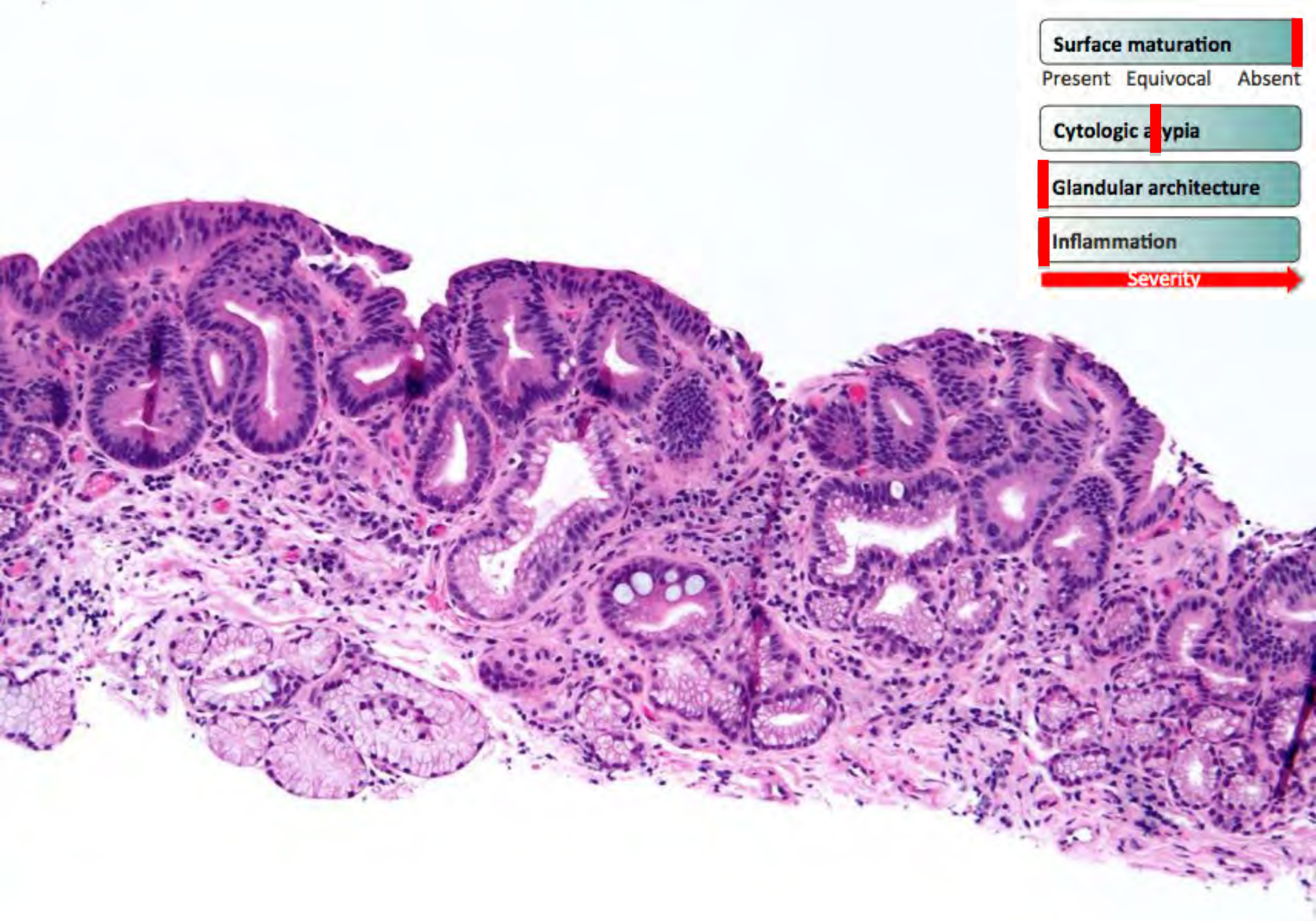
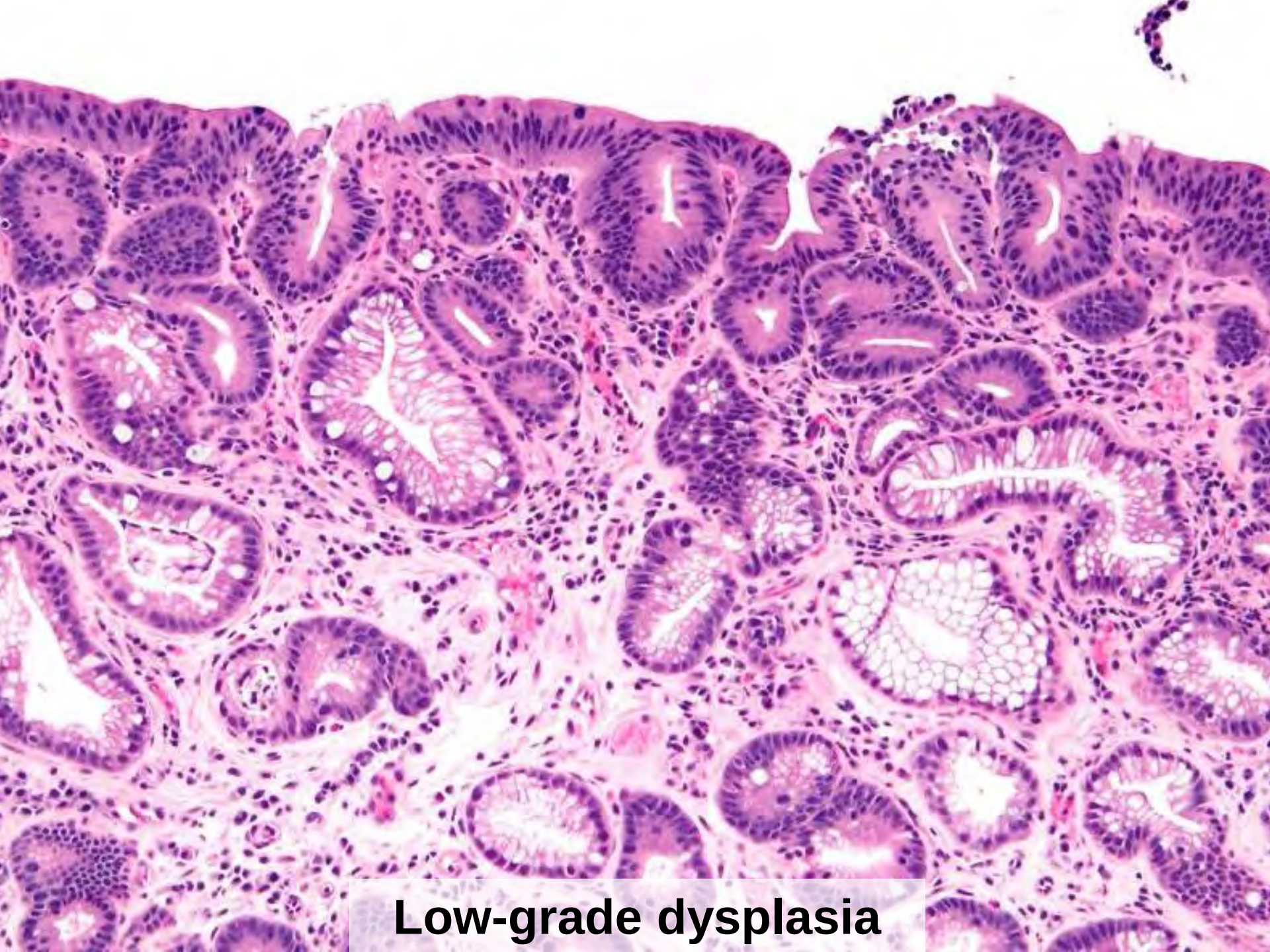


Low-grade dysplasia


Low-grade dysplasia

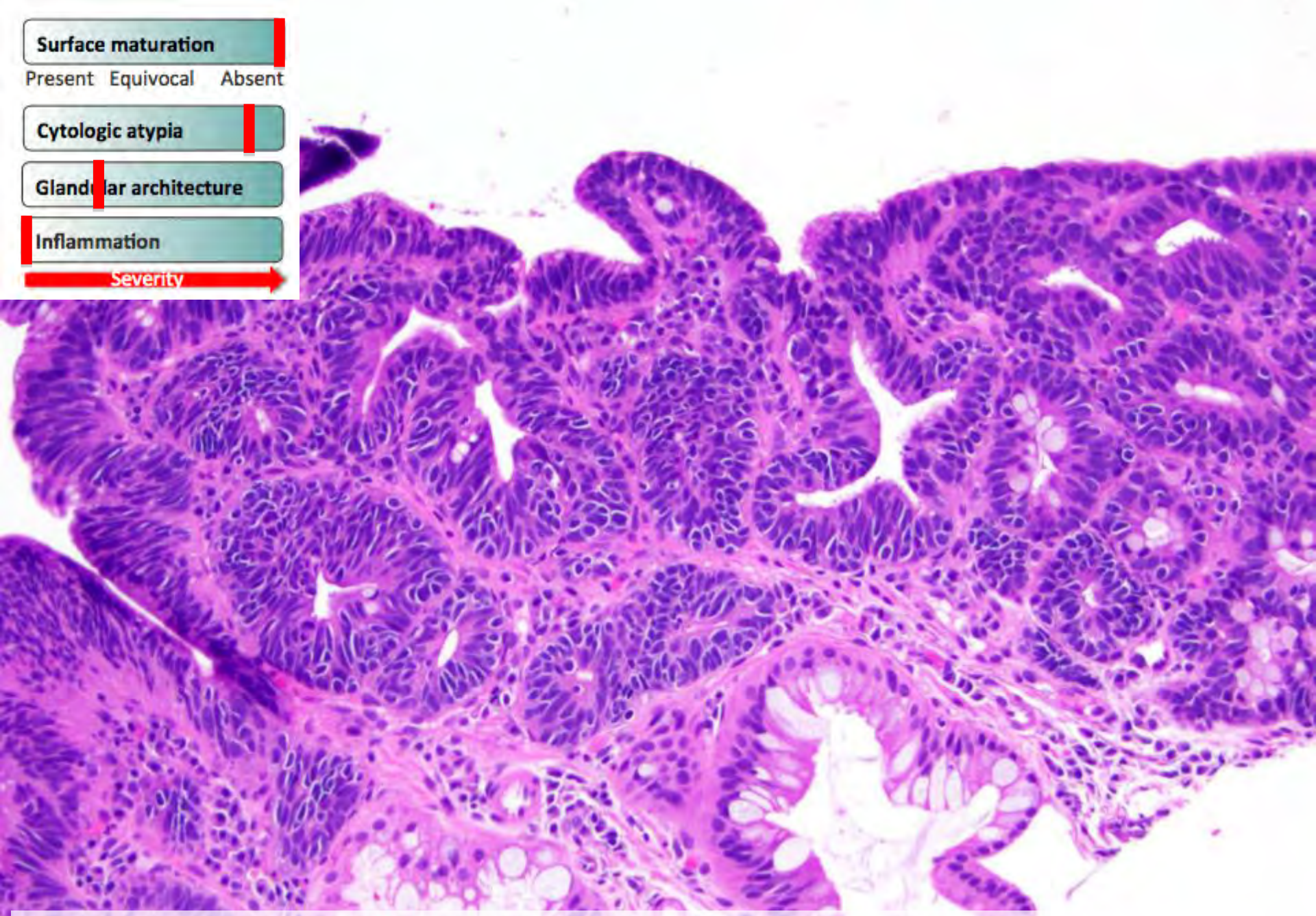


Low-grade dysplasia

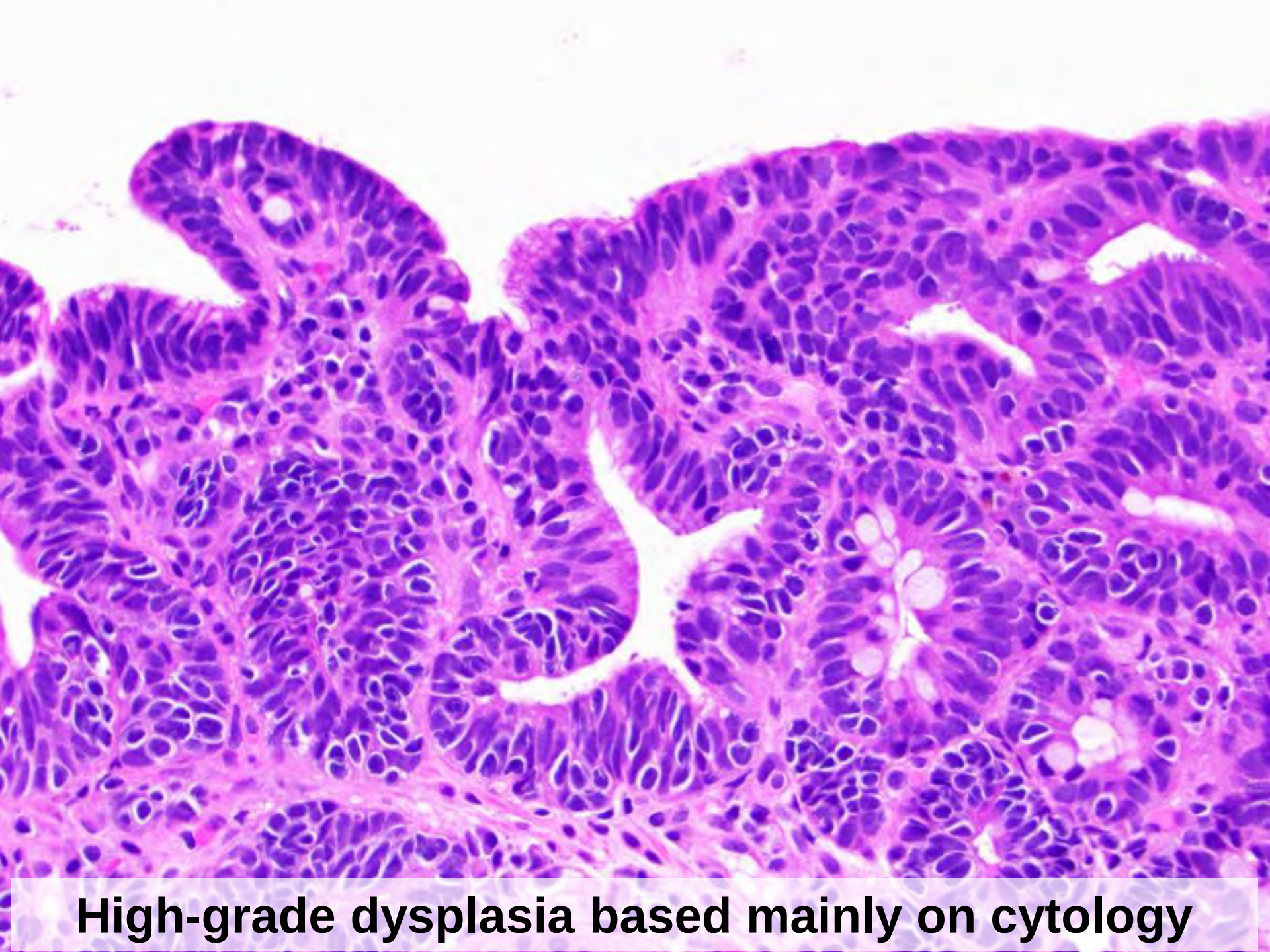

Low-grade dysplasia

Low-Grade vs. High-Grade Dysplasia

Histologic Features	Low-Grade Dysplasia	High-Grade Dysplasia
Cytology	• Uniform nuclear atypia • Uniform nuclear polarity • Nuclei limited to the basal 2/3 of the cell • Small nucleoli, if present	• Marked nuclear pleomorphism • Loss of nuclear polarity • Full-thickness nuclear stratification extending to surface of cell • Prominent nucleoli may be present
Architecture	• Dysplastic epithelium conforms to the shape of the background glands.	• Glandular crowding (not required) • Cribriform architecture (not required)



High-grade dysplasia based mainly on cytology



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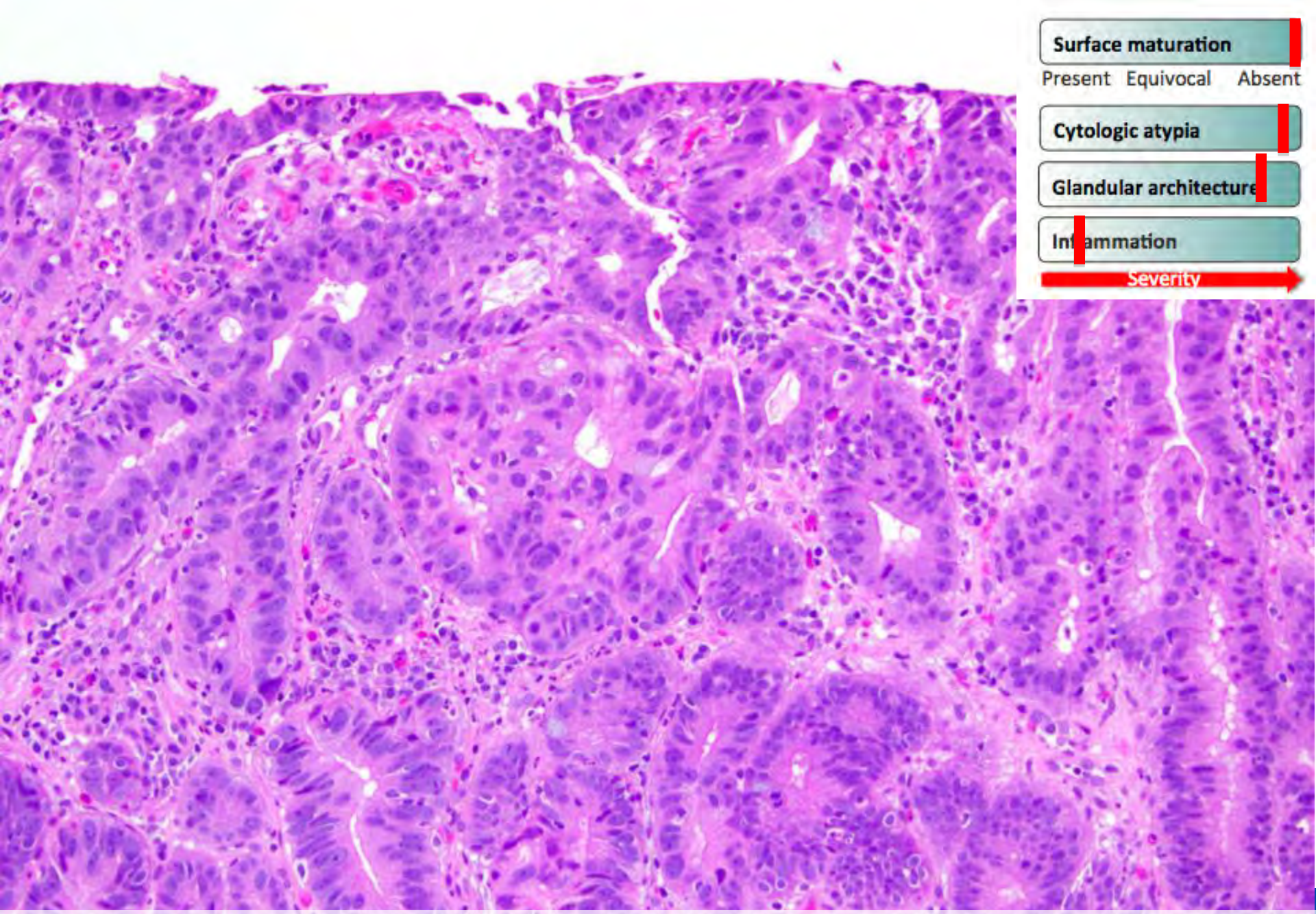


High-grade dysplasia based on cytology & architecture

Agreement studies and 2nd opinion

Discordance Among Pathologists in the United States and Europe in Diagnosis of Low-Grade Dysplasia for Patients With Barrett's Esophagus

Gastroenterology 2017;152:564–570

Prashanth Vennalaganti,[1,2] Vijay Kanakadandi,[1,2] John R. Goldblum,[3] Sharad C. Mathur,[4] Deepa T. Patil,[3] G. Johan Offerhaus,[5] Sybren L. Meijer,[6] Michael Vieth,[7] Robert D. Odze,[8] Saligram Shreyas,[1,2] Sravanthi Parasa,[1,2] Neil Gupta,[9] Alessandro Repici,[10] Ajay Bansal,[1,2] Titi Mohammad,[1,2] and Prateek Sharma[1,2]

7 Pathologists (4 US, 3 Europe) reviewed 79 individual slides

Table 1. κ Values for Inter-observer Agreement Among All 7 Pathologists From the United States and Europe

Histologic diagnosis (no. of slides)	Overall κ (95% CI)
Overall (79)	0.43 (0.42–0.48)
NDBE (23)	0.22 (0.11–0.29)
LGD (22)	0.11 (0.004–0.15)
HGD (34)	0.43 (0.36–0.46)

Slight agreement in the diagnosis of LGD
Fair agreement in the diagnosis of NDBE
Moderate agreement in the diagnosis of HGD

Agreement studies and 2nd opinion

- Most have multiple pathologists review individual glass slides and provide diagnosis. **This is not what is done in clinical practice.**
- Clinical practice: All biopsy slides from a given patient are reviewed together. Comparison between different biopsy parts/jars is useful to identify fragments that are clearly abnormal. Overall diagnosis taking into account all biopsies drives treatment.

Diagnosis per patient (n=129)	Kappa
Overall	0.54
NDBE	0.66
LGD	0.31
HGD	0.76
Diagnosis per biopsy jar (n=549)	
Overall	0.48
NDBE	0.61
LGD	0.30
HGD	0.66

129 patients with BE and no visible lesions

If sending for second opinion, send all biopsy slides from that endoscopic procedure, not just the slide in question.

Salomao MA, Lam-Himlin D, Pai RK. Am J Surg Pathol. 2018;42:376-81.

Setting benchmarks: Individual level

Adherence to pre-set benchmark quality criteria to qualify as expert assessor of dysplasia in Barrett's esophagus biopsies – towards digital review of Barrett's esophagus

United European Gastroenterology Journal
2019, Vol. 7(7) 889–896

MJ van der Wel[1,2], E Klaver[2], LC Duits[2], RE Pouw[2], CA Seldenrijk[3], GJA Offerhaus[4], M Visser[5], FJW ten Kate[4], K Biermann[6], LAA Brosens[4], M Doukas[6], C Huysentruyt[7], A Karrenbeld[8], G Kats-Ugurlu[8], JS van der Laan[9], G van Lijnschoten[7], FCP Moll[10], AHAG Ooms[11], JG Tijssen[12], JJGHM Bergman[2] and SL Meijer[1]

- 10 GI pathologists from BE centers in the Netherlands
- Only 3 met all benchmark criteria

Table 1. Values for benchmark quality criteria based on 95% prediction interval (PI) of five core pathologists.[16]

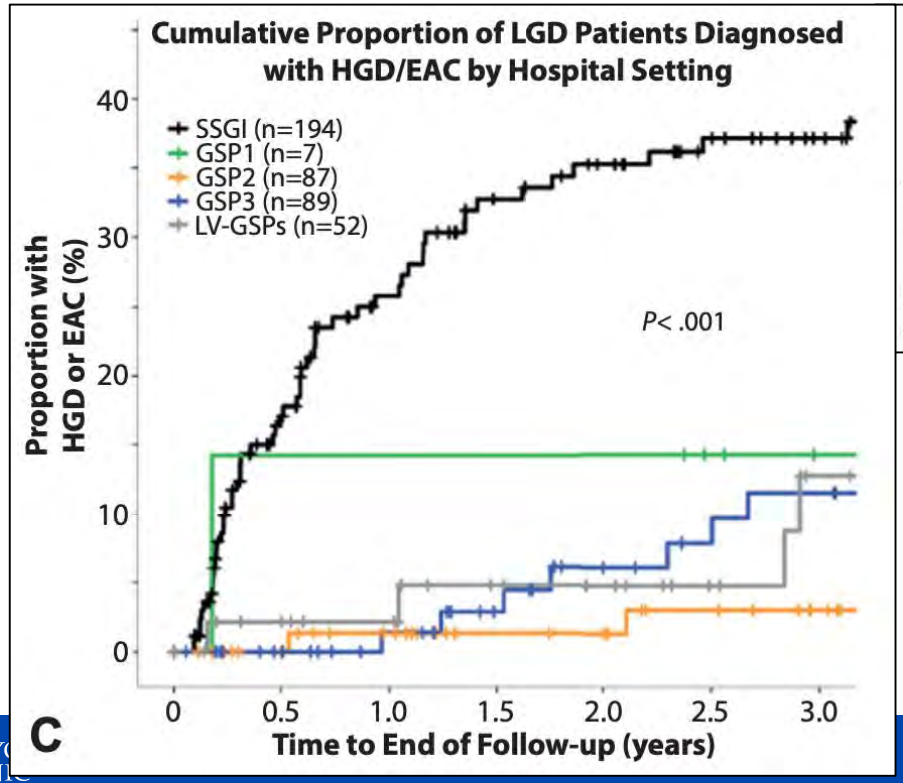
Quality criterion	95% PI core pathologists all cases ($n = 60$)	Benchmark value	95% PI core pathologists dysplastic cases ($n = 39$)	Benchmark value
Percentage of IND* cases (%)	3–14%	≤14%	−2–16%	≤16%
Intra-observer agreement in 3 categories (K)	0.66–1.02	≥0.66	0.39–0.73	≥0.39
Agreement with consensus gold standard diagnosis (%)	82–98%	≥82%	73–104%	≥73%
Consensus HGD† cases misdiagnosed as NDBE‡ (%; fraction)	0.8% (1/120 assessments)	≤0.8% (1/120 assessments)	≤1.3% (1/78 assessments)	≤1.3% (1/78 assessments)

*IND: indefinite for dysplasia; †HGD: high-grade dysplasia, ‡NDBE: non-dysplastic Barrett's esophagus

All slides from 60 cases (21 NDBE, 20 LGD, 19 HGD) were read twice

Setting benchmarks: Group practice

Case type (annual)	SSGI 1999-2016	GSP1 2009-2016	GSP2 2004-2016	GSP3 1999-2016	LV-GSPs 1999-2016
All BE cases	161.7 ± 33.9	78.8 ± 21.3	69.8 ± 19.4	56.1 ± 18.6	10.6 ± 3.9
HGD cases	14.6 ± 4.7	1.3 ± .5	1.4 ± .5	.8 ± .7	.3 ± .2
EAC cases	17 ± 8.6	1.0 ± .6	1.8 ± .8	1.1 ± .8	.3 ± .3
# of Pathologists	5.2 ± 1	3.9 ± 0.6	5.9 ± 0.7	4.0 ± 1.5	13.0 ± 2.5



Cumulative Proportion of Patients with HGD or EAC by Hospital Setting (%)

	SSGI	GSPI	GSP2	GSP3	LV-GSPs	*P* value
2 yr from 1st LGD	35.3	14.3	1.4	6.1	4.8	< .001
5 yr from 1st NDBE	2.6	0.8	0.1	0.6	3.7	< .001

Best predictor of progression is high volume sub-specialty practice

Gastrointest Endosc 2018;88:807-15.

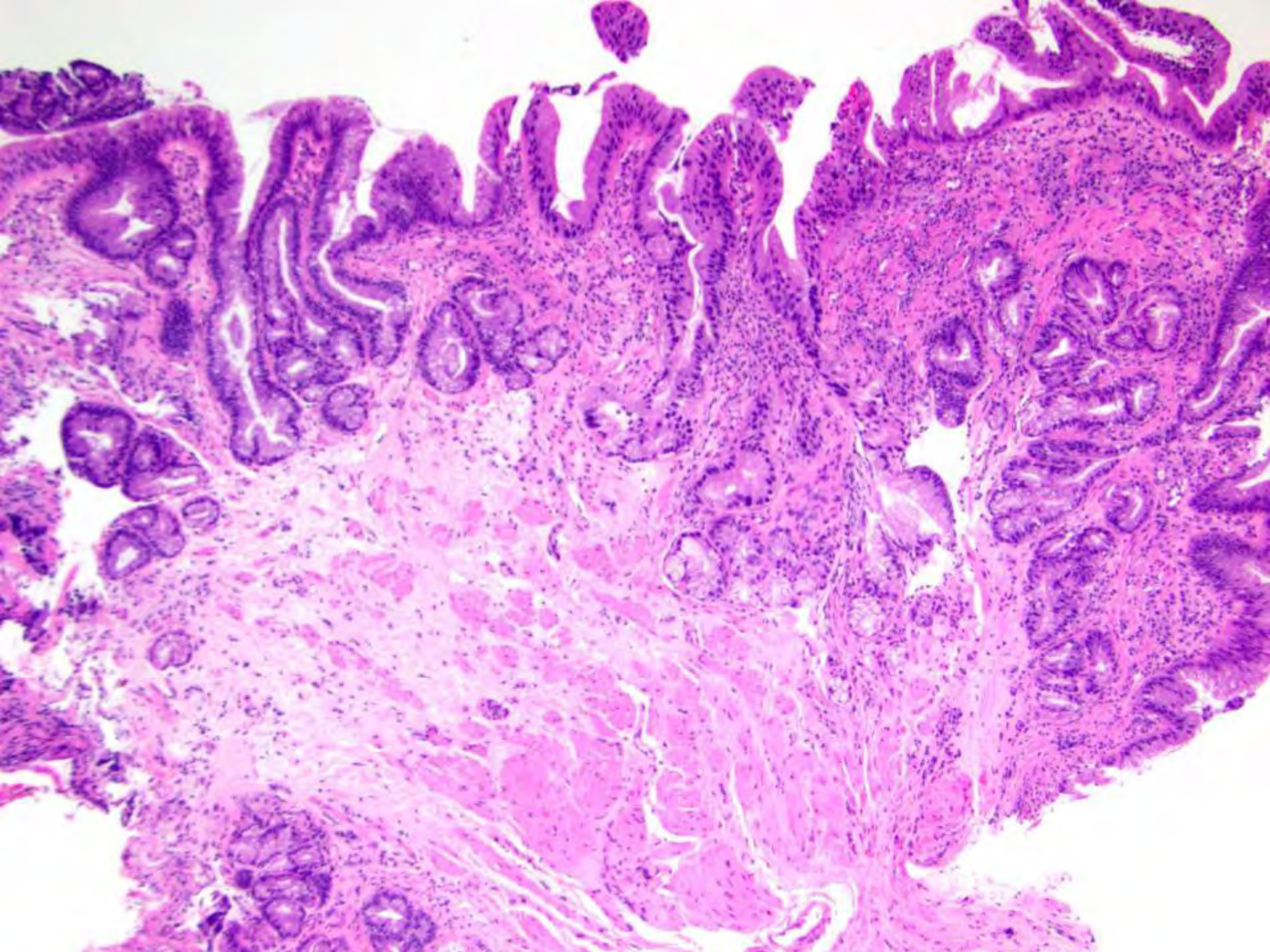
Common Diagnostic Dilemmas

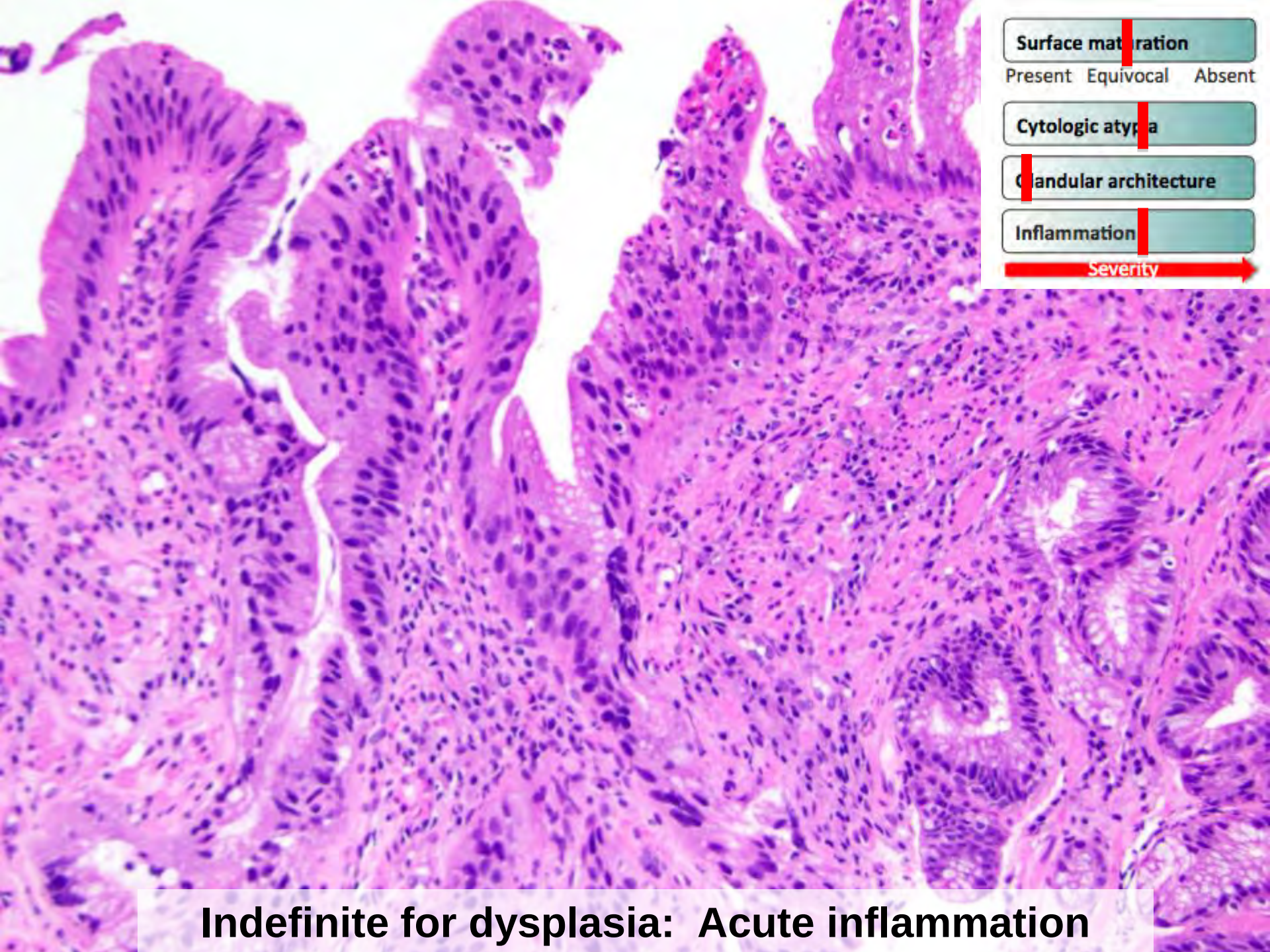
- Indefinite for dysplasia.
- Gastric foveolar type dysplasia (non-intestinal dysplasia).
- Biopsy diagnosis of Barrett's esophagus-associated adenocarcinoma, including intramucosal adenocarcinoma

Indefinite for Dysplasia

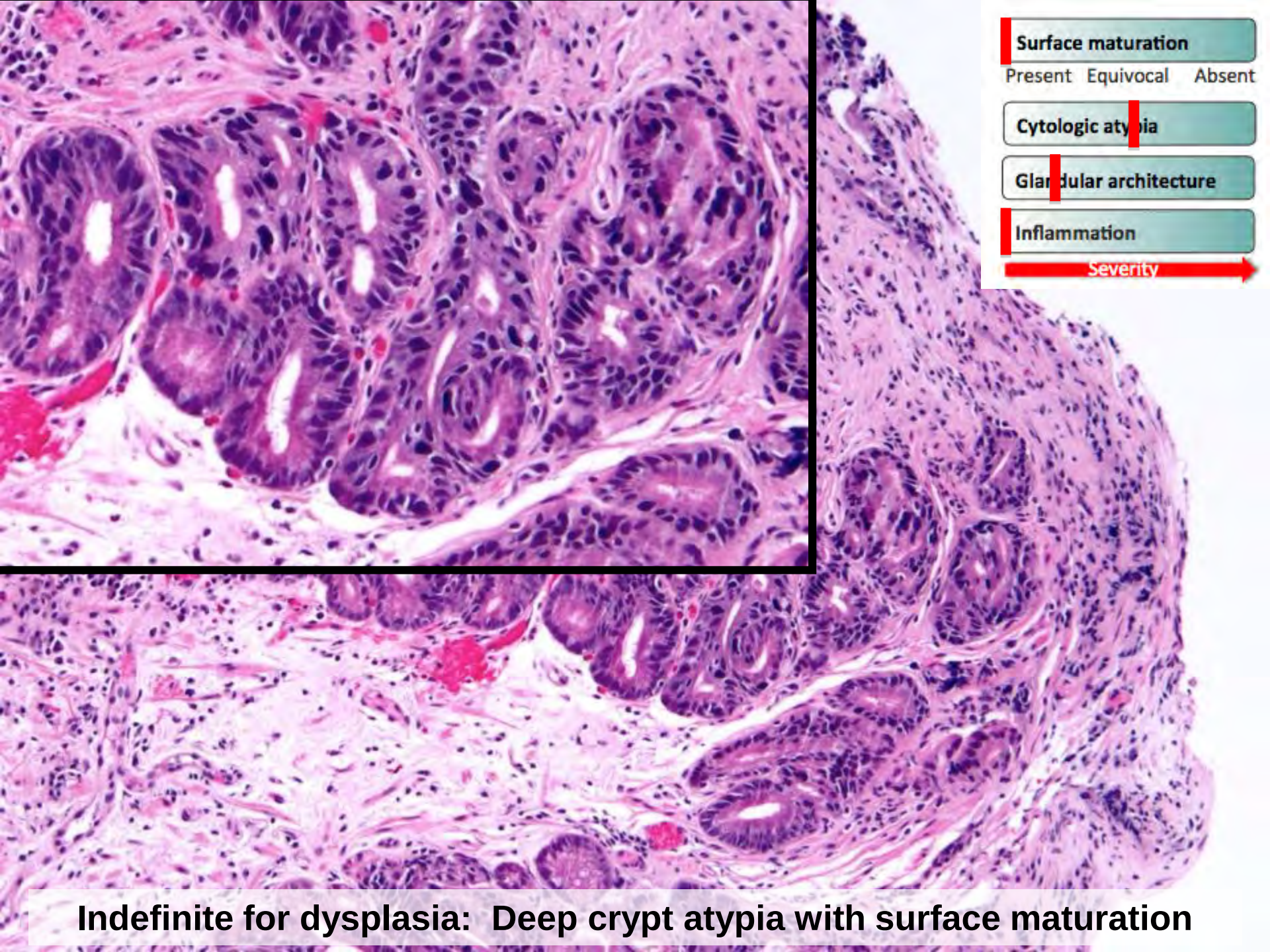
- **Scenario #1**: When the presence of inflammation precludes accurate evaluation for cytoarchitectural features.
  - Caveat: You can still diagnose dysplasia in the presence of active inflammation if the cytoarchitectural features are more severe than the inflammatory infiltrate.

- **Scenario #2**: Where is prominent deep crypt atypia in the presence of surface maturation
  - Some use the term crypt dysplasia in this setting, but this term is not recognized in the ACG guidelines (in British guidelines).





Indefinite for dysplasia: Acute inflammation



Indefinite for dysplasia: Deep crypt atypia with surface maturation

Ancillary tests?

- p53 immunohistochemistry (clone DO-7) is the most well studied. This detects both mutant and wild-type TP53.
- British Society guidelines:

  "The addition of p53 immunostaining to the histopathological assessment may improve the diagnostic reproducibility of a diagnosis of dysplasia in Barrett's oesophagus and should be considered as an adjunct to routine clinical diagnosis (Recommendation grade C)"
- p53 may be useful in select cases.

Question 2:

- Which of the following is true of p53 immunohistochemistry in Barrett's esophagus-associated dysplasia?
  - A. Abnormal p53 is only seen in high-grade dysplasia.
  - B. Abnormal p53 only refers to strong nuclear expression.
  - C. Abnormal p53 is useful for distinguishing low-grade dysplasia from high-grade dysplasia.
  - D. Abnormal p53 expression includes complete loss of expression.

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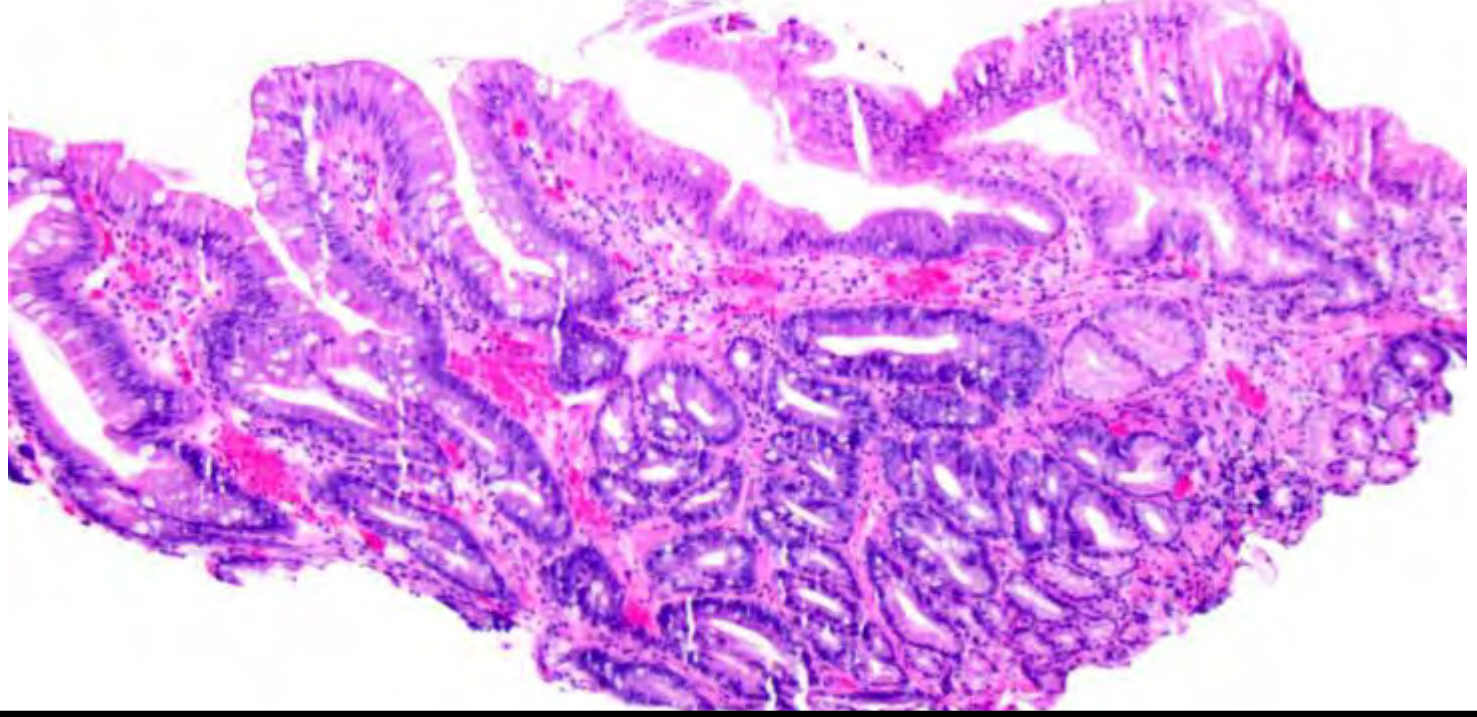
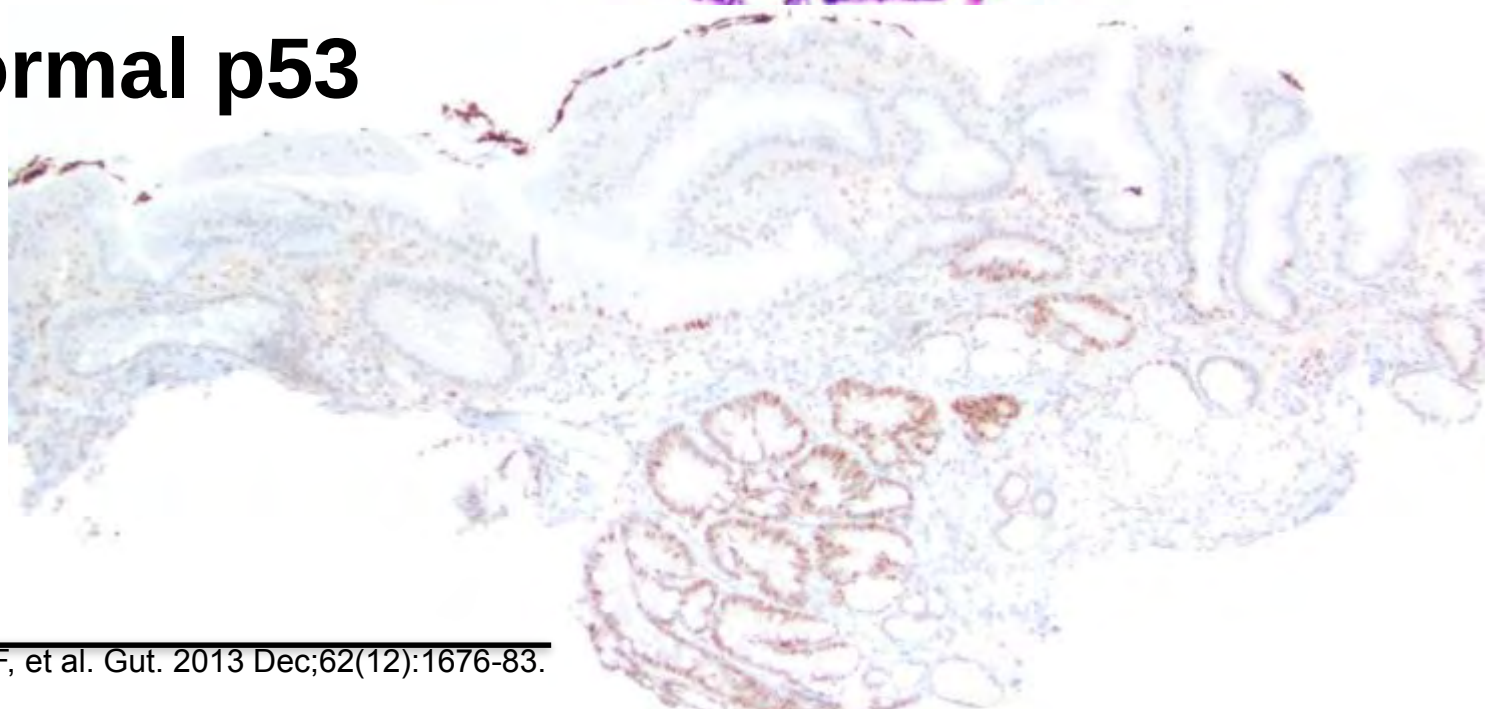
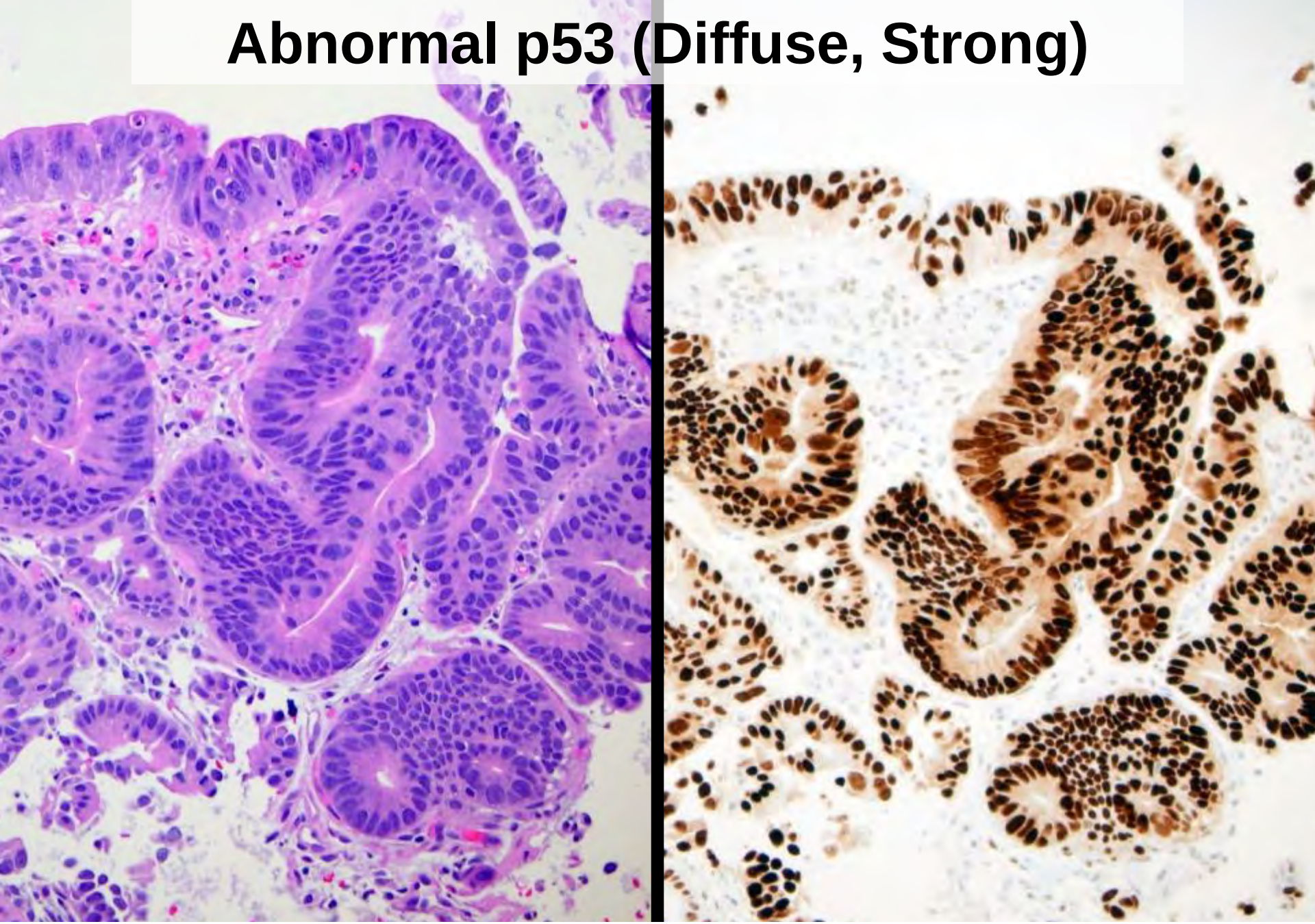


Normal p53



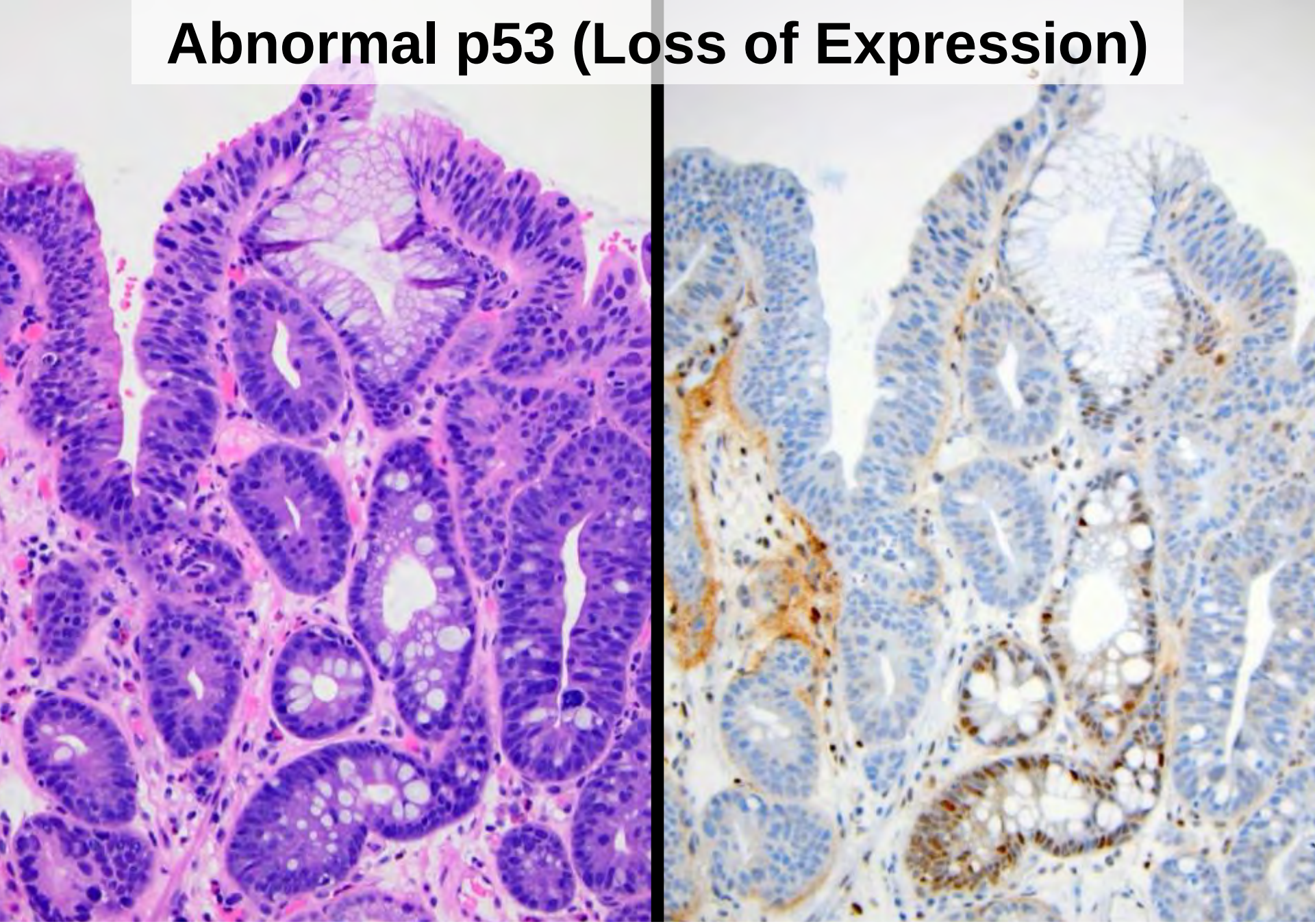
Kastelein F, et al. Gut. 2013 Dec;62(12):1676-83.

Abnormal p53 (Diffuse, Strong)



Activating *TP53* mutations result in p53 stability and accumulation in the nucleus.

Abnormal p53 (Loss of Expression)



Truncating nonsense *TP53* mutations result in lack of p53 expression.

Rate of Abnormal p53 Expression by Histologic Diagnosis

- 720 patients with BE of at least 2 cm and no history of HGD or Carcinoma
- Patients had 1481 endoscopies
  - Histology and p53 expression was performed on all (>12,000 biopsies)

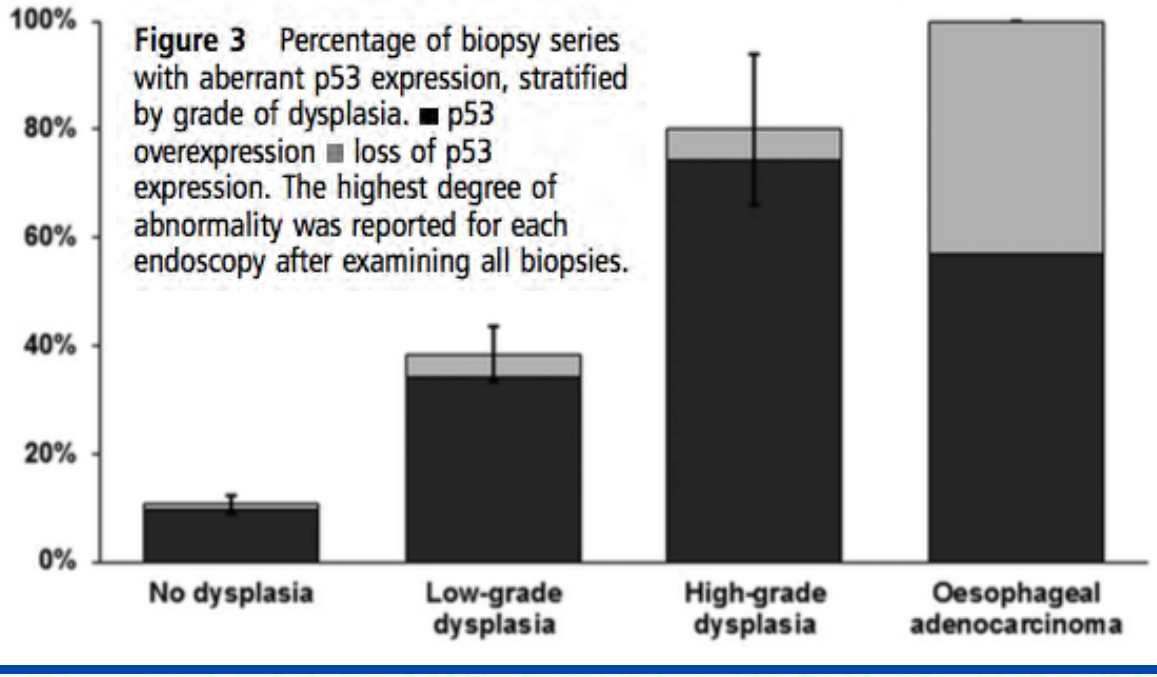


Figure 3 Percentage of biopsy series with aberrant p53 expression, stratified by grade of dysplasia. ■ p53 overexpression ■ loss of p53 expression. The highest degree of abnormality was reported for each endoscopy after examining all biopsies.

Kastelein F, *et al*. *Gut* 2013;**62**:1676–1683. doi:10.1136/gutjnl-2012-303594

Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with Barrett's oesophagus

Kastelein F, et al. Gut. 2013 Dec;62(12):1676-83.

LGD as a predictor of progression to HGD/Ca	Aberrant p53 as a predictor of progression to HGD/Ca
• 223/635 had LGD	• 118/635 had aberrant p53 IHC
• 34/223 (15%) progressed	• 31/118 (26%) progressed
• Relative Risk of 4.0	• Relative risk of 5.6
• Sensitivity: 44%	• Sensitivity: 49%
• Specificity: 78%	• Specificity: 86%

Histology and p53 immunohistochemistry	Relative Risk of progression to HGD/Ca
ND and normal p53 expression	Reference
LGD and normal p53 expression	2.4 (0.9 to 6.0)
ND and aberrant p53 expression	4.5 (2.0 to 10.0)
LGD and aberrant p53 expression	11.2 (5.7 to 22.0)

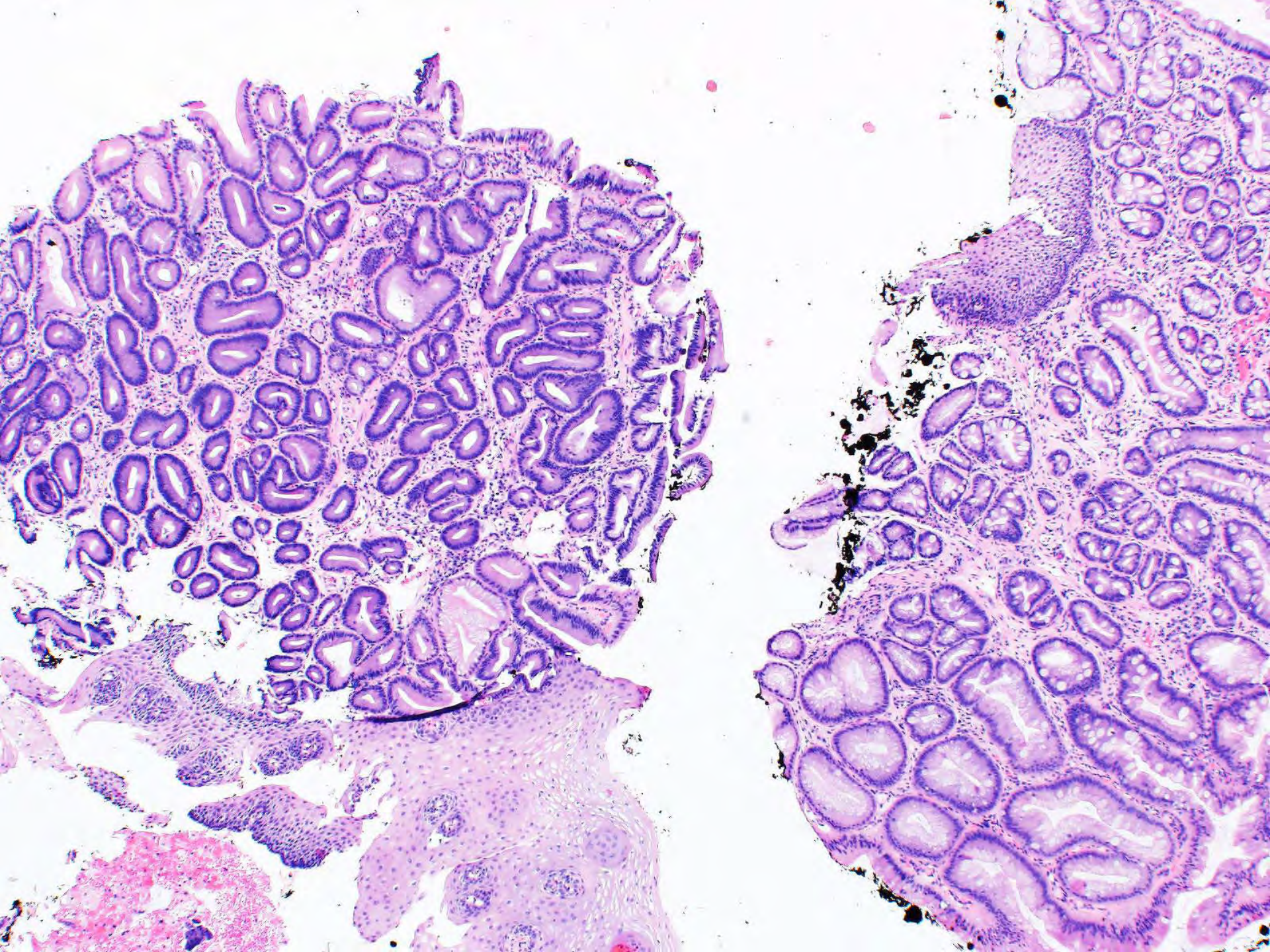
How to use p53 IHC

- **Should not be used on all cases**
- **Should not be routinely used to determine the diagnosis of LGD and HGD**
  - If it is definitive LGD or HGD diagnose as such
- **Three common scenarios to consider p53 IHC**:
  - I really think HGD is present but marked inflammation.
  - HGD present mostly in base of glands with limited surface involvement present.
  - Focal HGD (only 1 involved biopsy fragment with ≤5 glands).
- **p53 may stratify patients with histologic diagnosis of LGD (not validated and do not routinely perform IHC on LGD)**
  - LGD without abnormal p53 has a lower risk of progression
  - LGD with abnormal p53 has a very high risk of progression

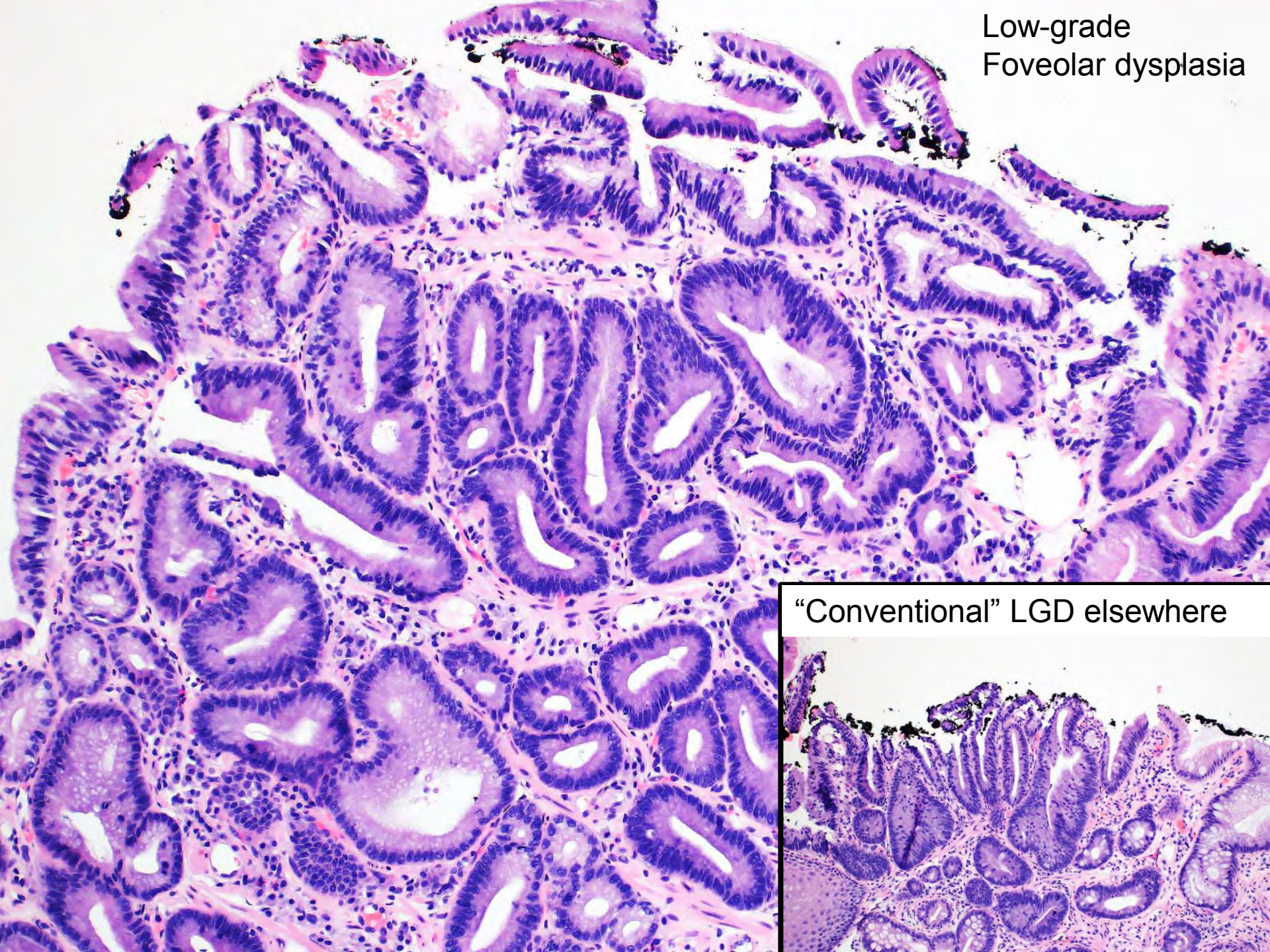
Gastric Foveolar-Type Dysplasia

- Study by Mahajan et al. at Cleveland Clinic in 2010.
- Accounts for ~6% of patients with dysplasia.
- Definition:
  - Predominantly non-stratified, basal nuclei.
  - Typically *does not* have prominent nuclear stratification typical of intestinal-type dysplasia.
  - Often with mucinous or eosinophilic / oncocytic cytoplasm.
- Grading based primarily on nuclear size and glandular architecture.

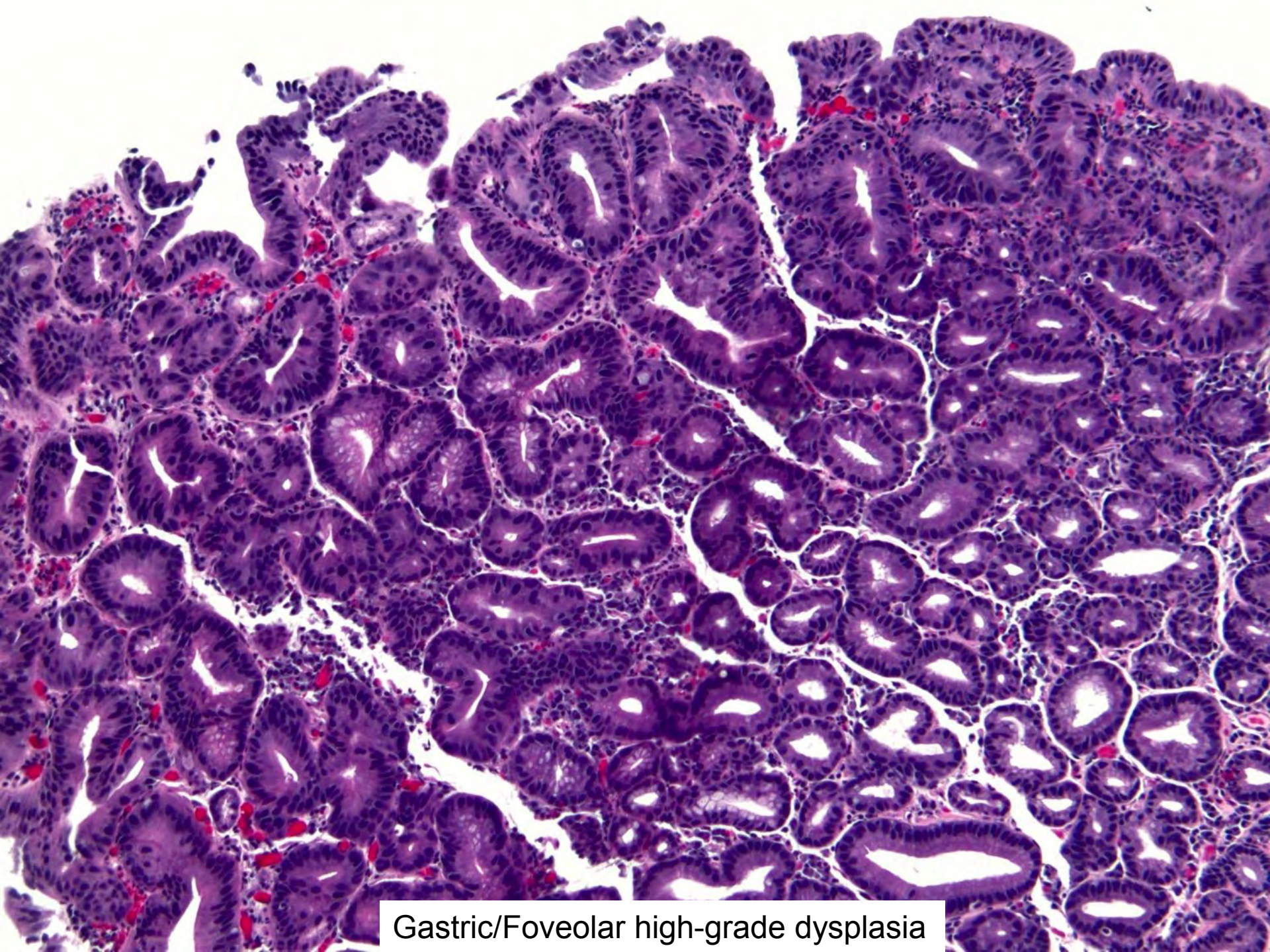
Mahajan D, et al. Mod Pathol 2010;23:1–11.



Low-grade
Foveolar dysplasia



“Conventional” LGD elsewhere


Gastric/Foveolar high-grade dysplasia

Biopsy Diagnosis of BE-associated Adenocarcinoma

- My typical diagnostic lines:
  - High-grade dysplasia with features suspicious for intramucosal carcinoma
  - At least intramucosal carcinoma
  - Invasive adenocarcinoma (with grade)
- Correlation with EUS is very helpful
- Overcall of adenocarcinoma may result in unnecessary treatment **(Be cautious!)**
  - All visible lesions should be endoscopically resected for accurate staging, followed by ablation of remaining BE segment.

Intramucosal Adenocarcinoma (IMC): Suspicious versus Definite IMC

Definitive Intramucosal Adenocarcinoma

- >1 focus of single cell invasion
- Sheets of cells obliterating lamina propria
- Never-ending/anastomosing gland pattern
- Abortive, angulated glands

Cleveland Clinic

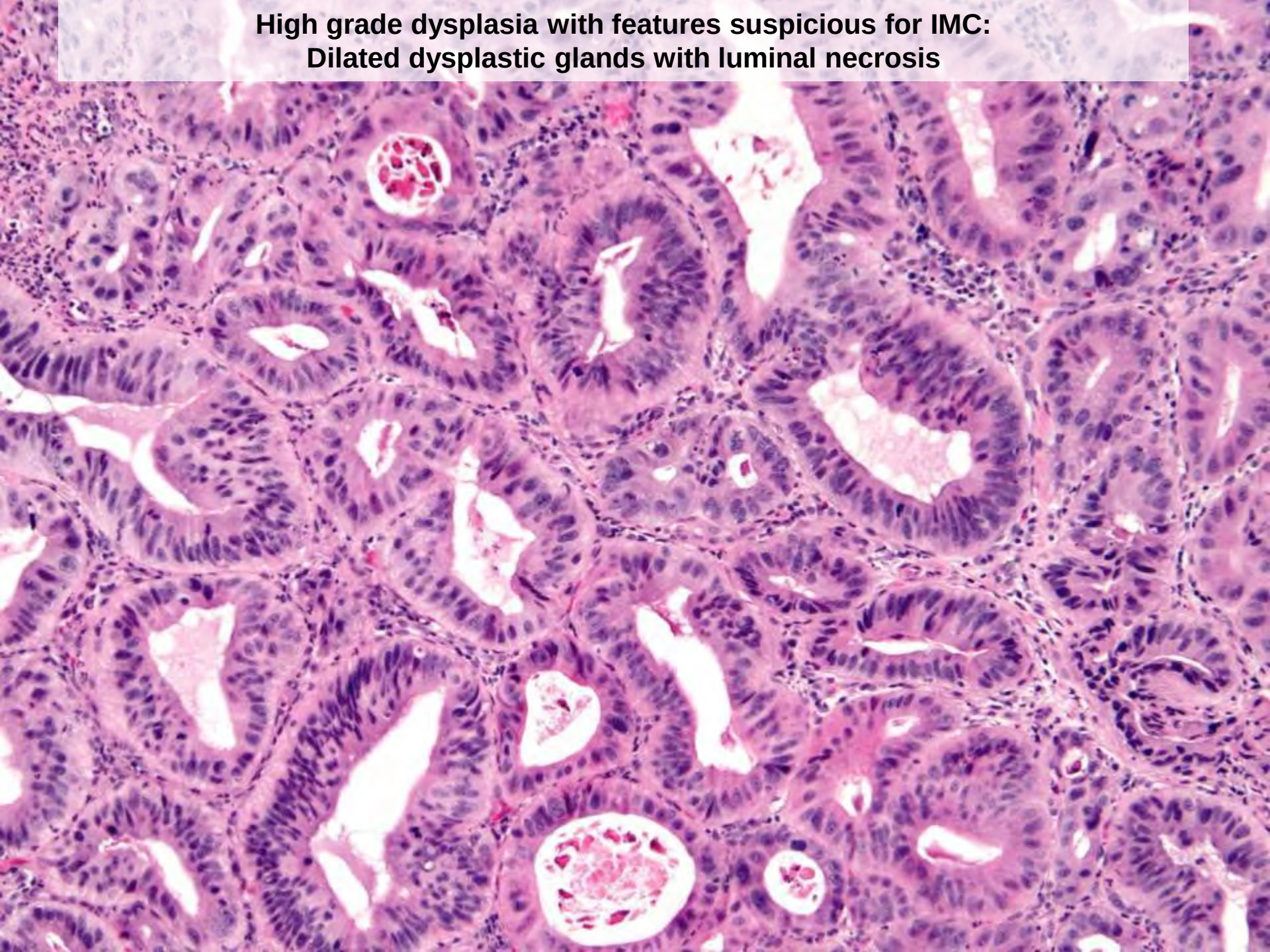
- Suspicious for IMC
  - Marked glandular crowding with only an intervening fibroblast
  - Prominent cribriforming
  - ≥ 3 dilated glands with intraluminal debris

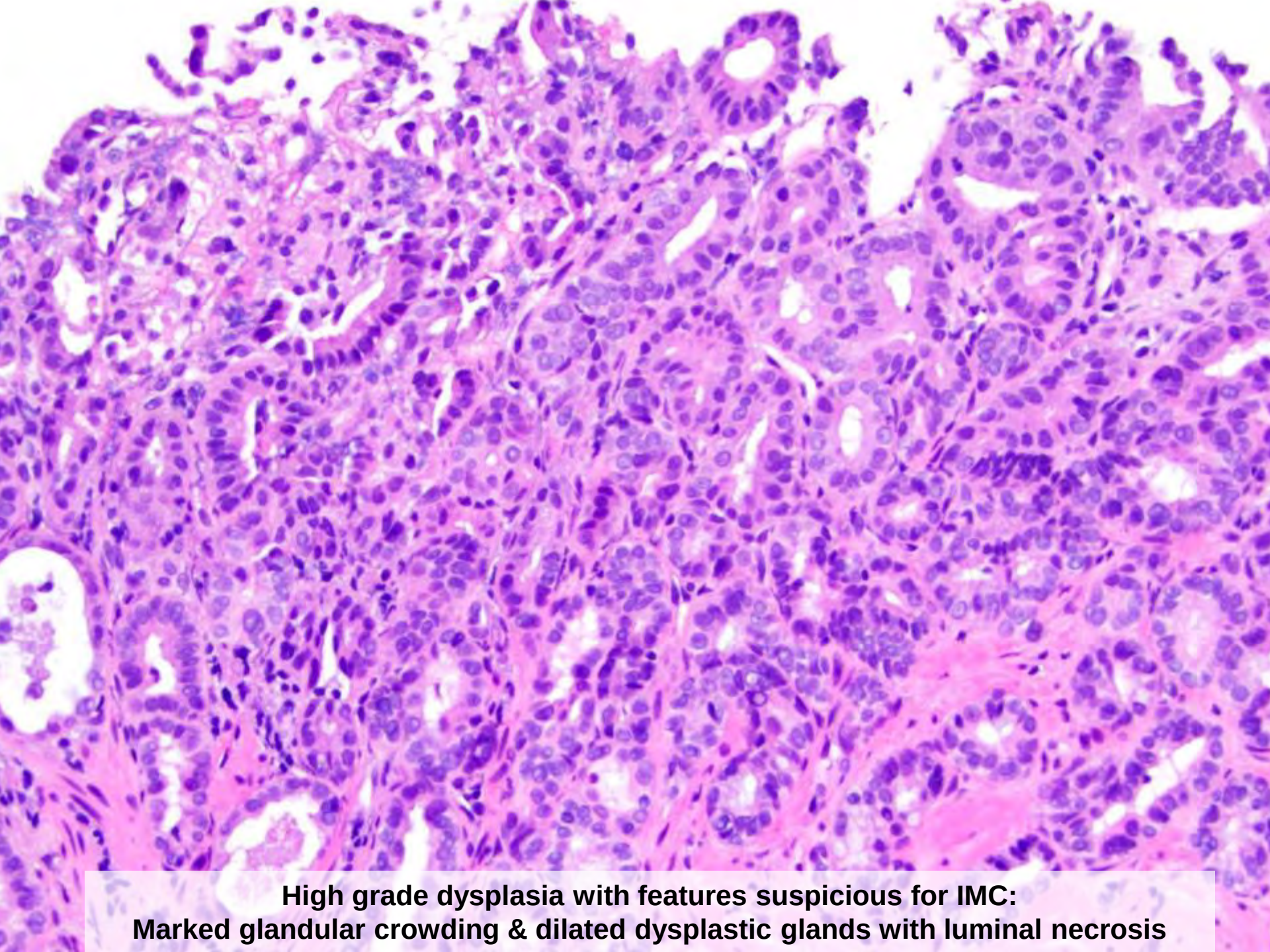
University of Michigan

- Suspicious for IMC
  - Solid or prominent cribriform growth
  - Dilated dysplastic tubules with necrotic debris
  - Ulcerated HGD
  - Dysplastic glands within squamous epithelium

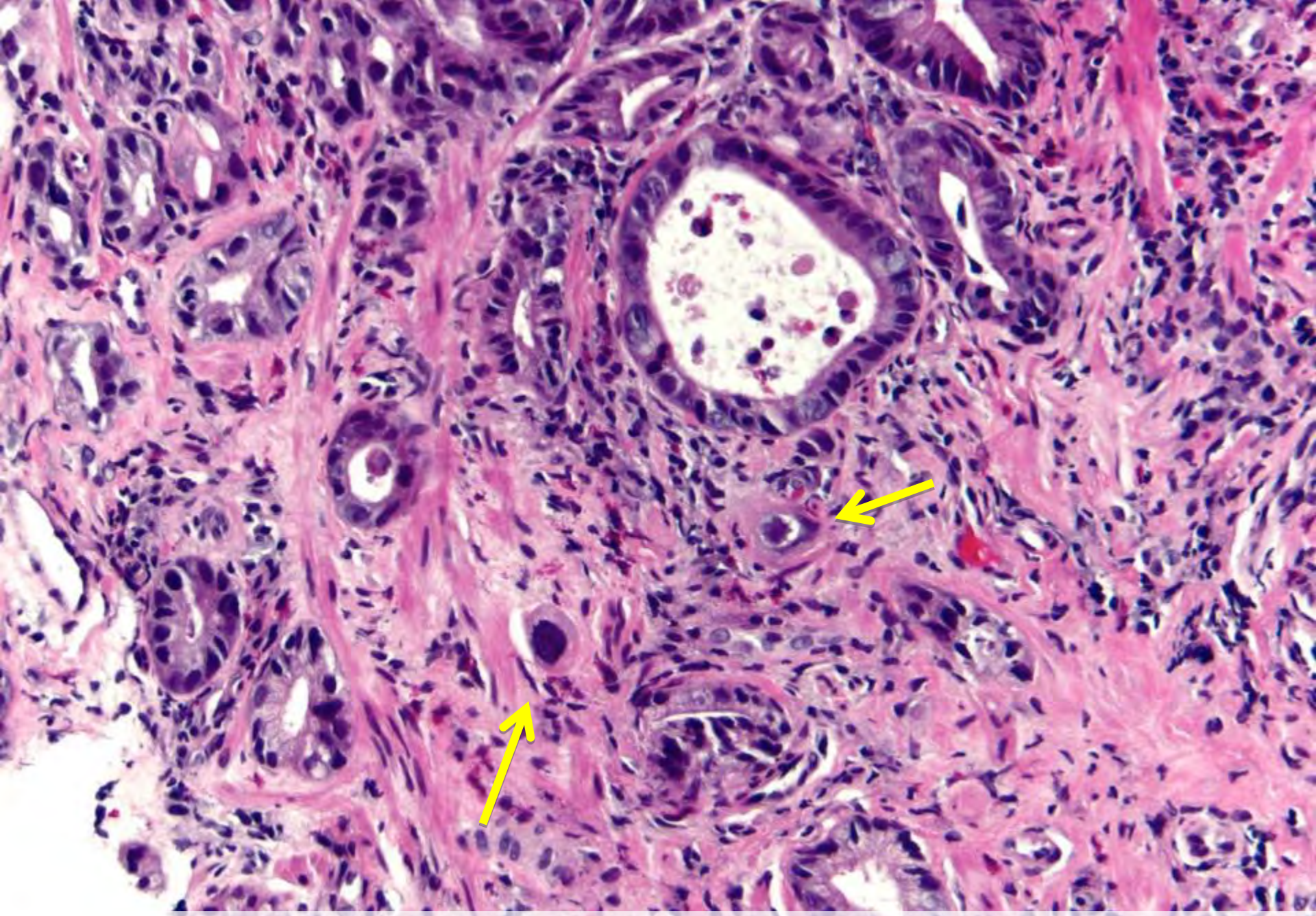
Downs-Kelly E, et al. Am J Gastroenterol. 2008 Sep;103(9):2333-40
Zhu W, A, et al. Am J Clin Pathol. 2009 Jul;132(1):94-100.
Patil DT, et al. Am J Surg Pathol. 2012 Jan;36(1):134-41.

High grade dysplasia with features suspicious for IMC:
Dilated dysplastic glands with luminal necrosis

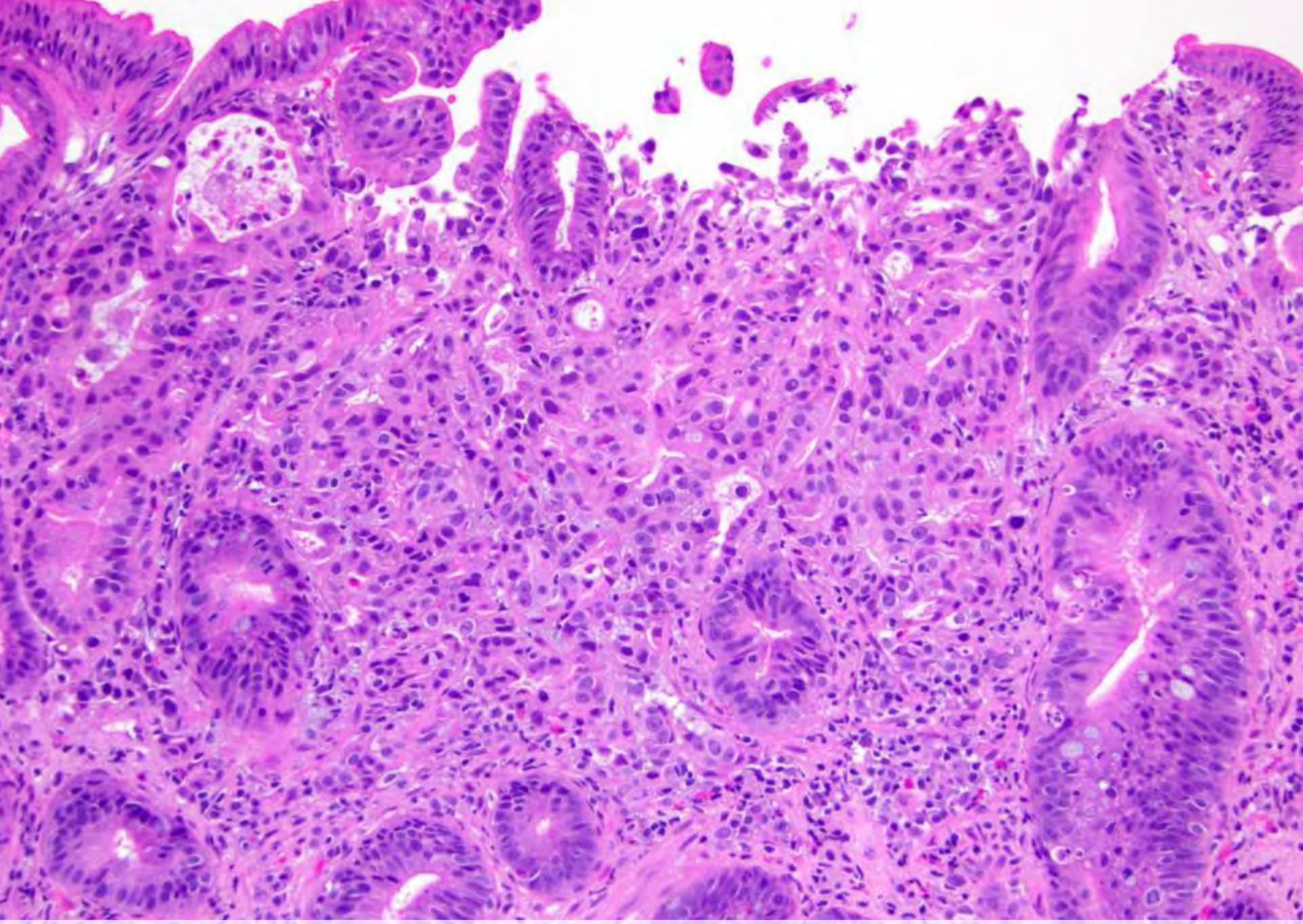




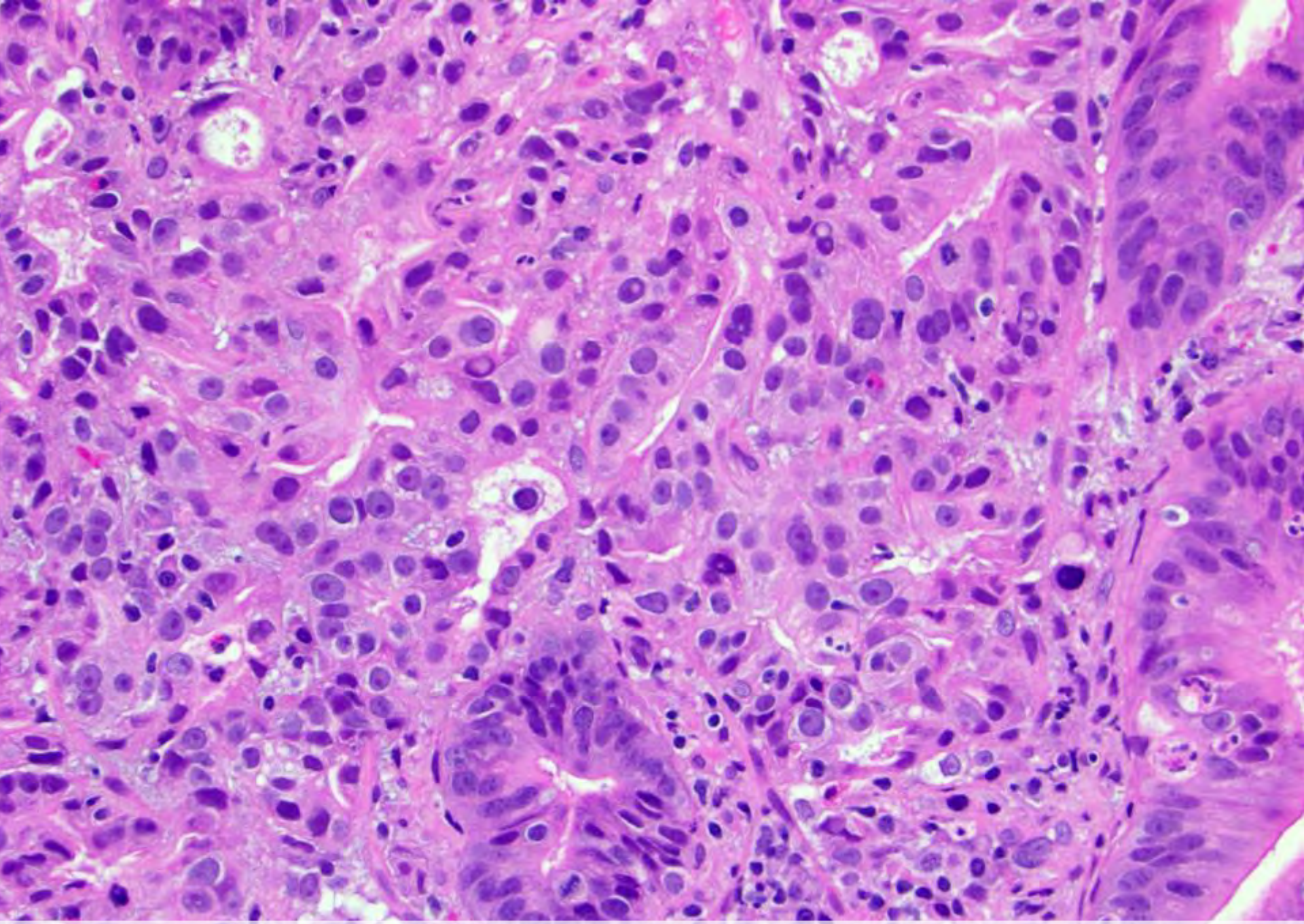
High grade dysplasia with features suspicious for IMC:
Marked glandular crowding & dilated dysplastic glands with luminal necrosis



Intramucosal Adenocarcinoma: Single cell invasion



Intramucosal Adenocarcinoma: Anastomosing growth



Intramucosal Adenocarcinoma: Anastomosing growth

Question 3:

- Which of the following is true of endoscopic resections in Barrett's esophagus related dysplasia?
  - A. Intramucosal adenocarcinoma cannot be treated by endoscopic resection.
  - B. Invasion beyond smooth muscle fibers always indicates submucosal invasion
  - C. Essential histologic features to report include grade of tumor, extent/depth of invasion, margin status, and lymphovascular invasion.
  - D. Nodular lesions in the esophagus should never undergo EMR.

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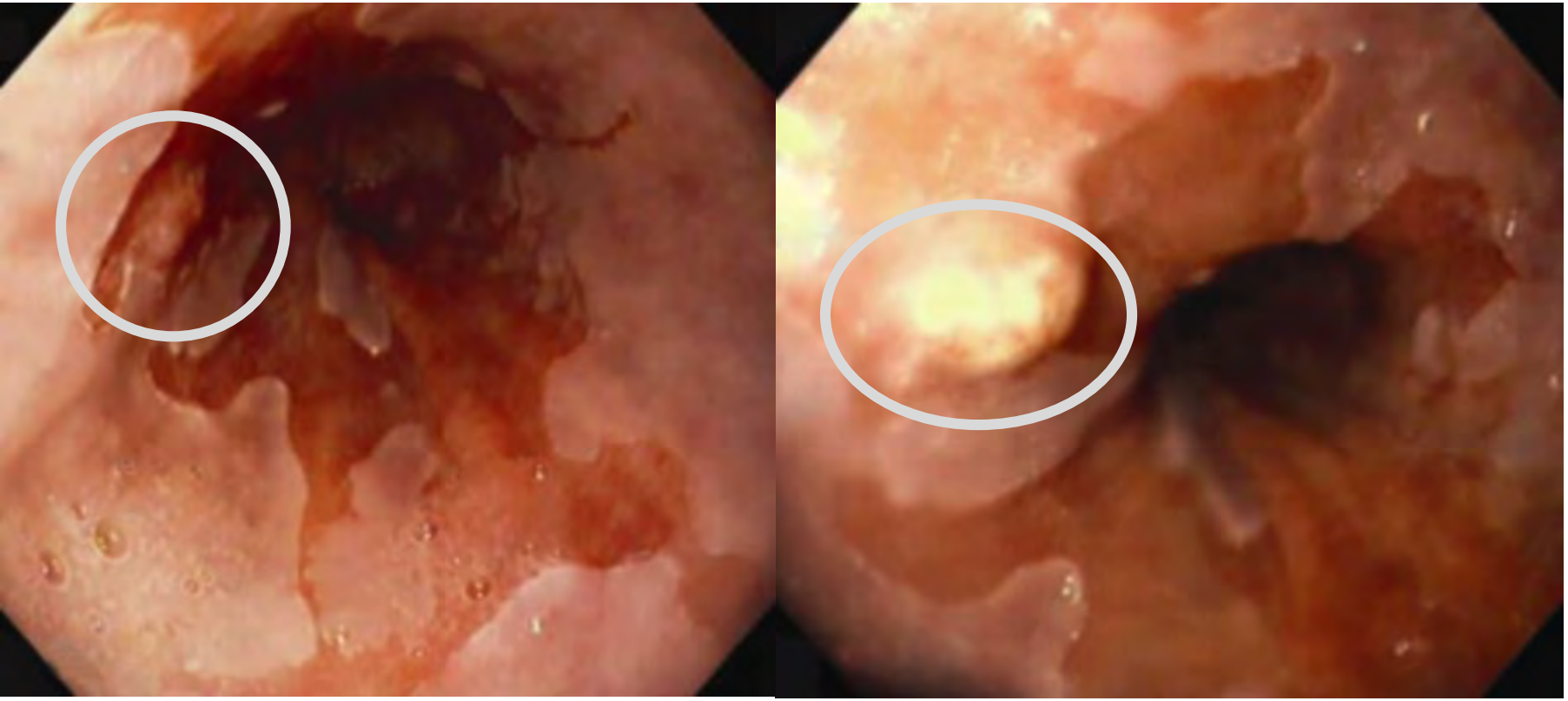
Visible Lesions in BE

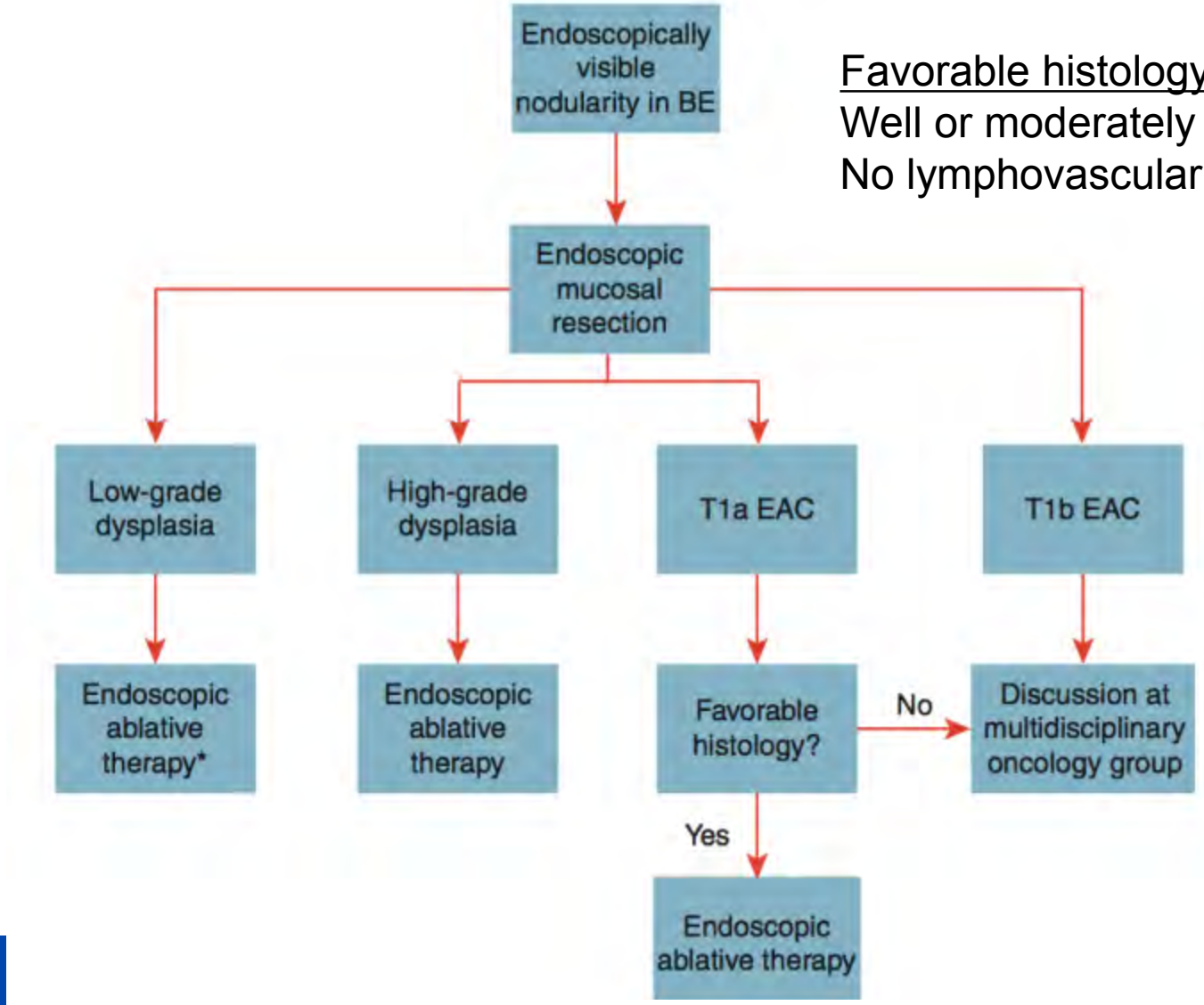


"Patients with nodularity in the BE segment should undergo EMR of the nodular lesion(s) as the initial diagnostic and therapeutic maneuver. Histologic assessment of the EMR specimen should guide further therapy."

Shaheen, NC et al. Am J Gastro. 2016 Jan;111(1):30-50

MAYO CLINIC

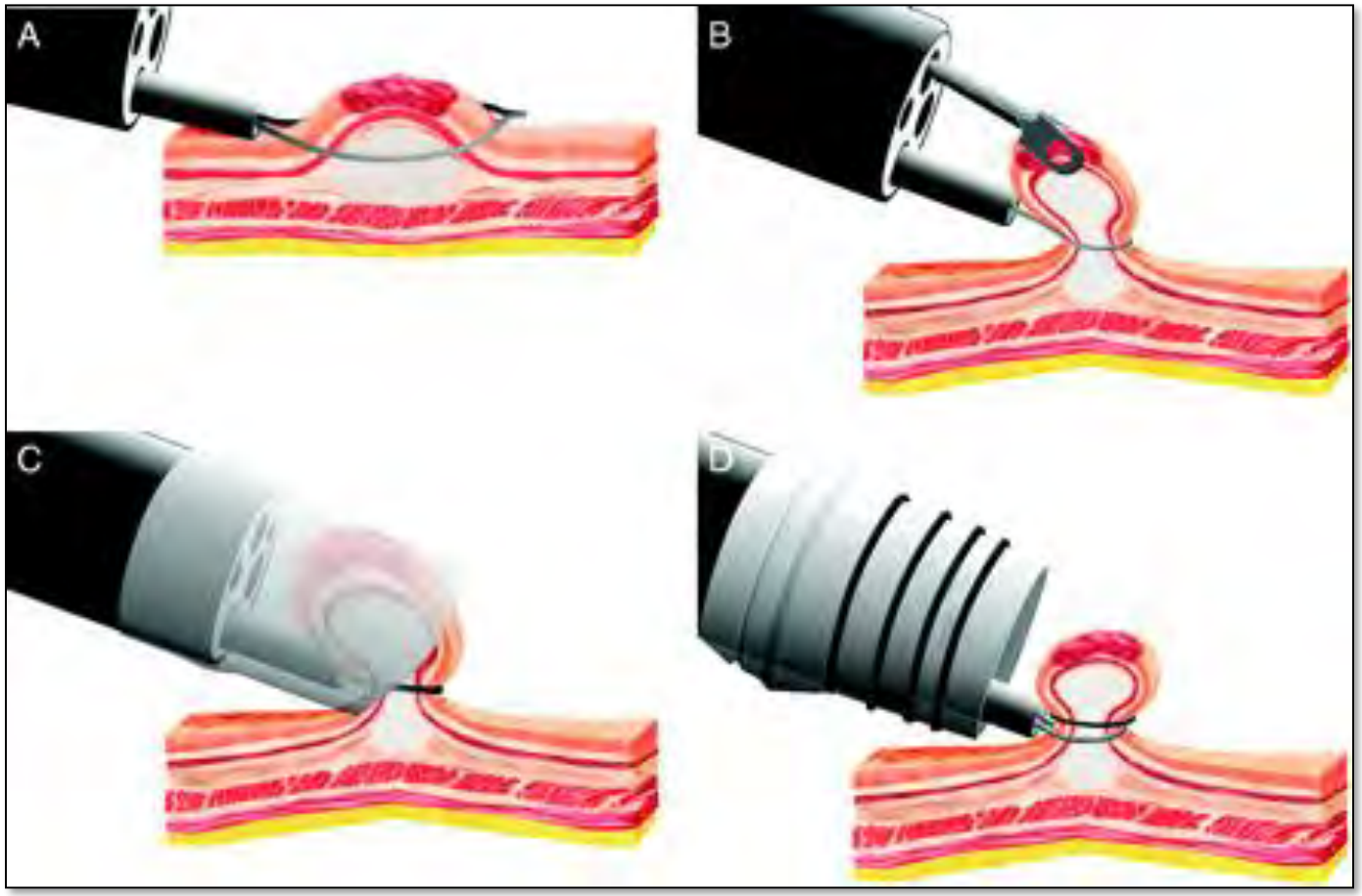
Visible Lesions in BE



Favorable histology:
Well or moderately differentiated
No lymphovascular space invasion

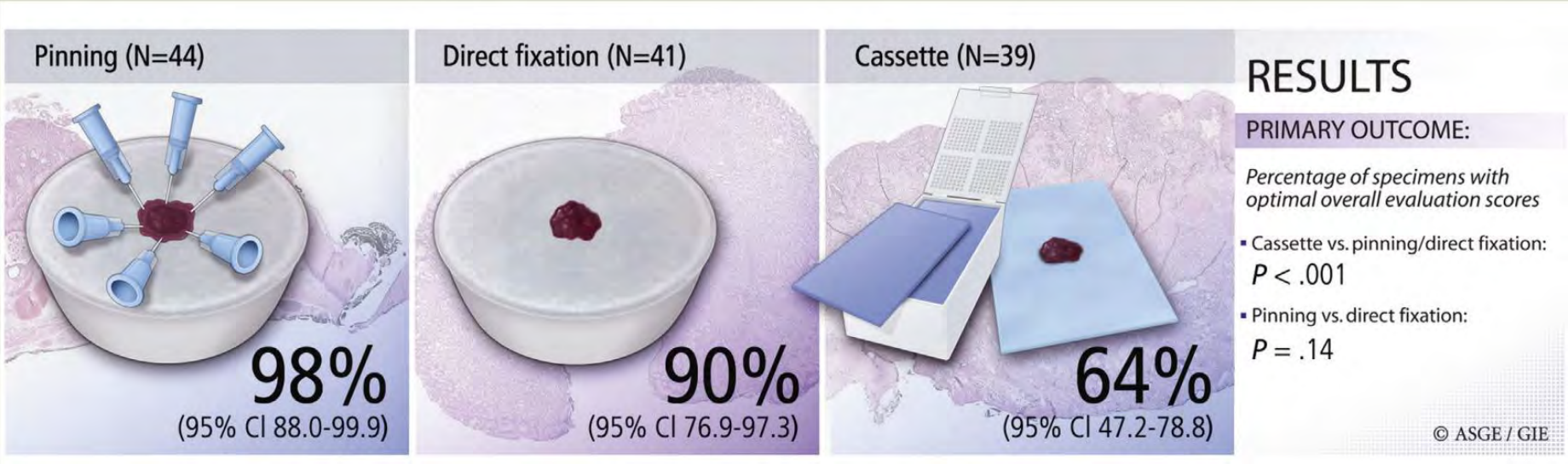
Shaheen, NC et al. Am J Gastro. 2016 Jan;111(1):30-50

EMR Techniques



Soetikno R et al. J Clin Oncol 2005;23:4490-4498.

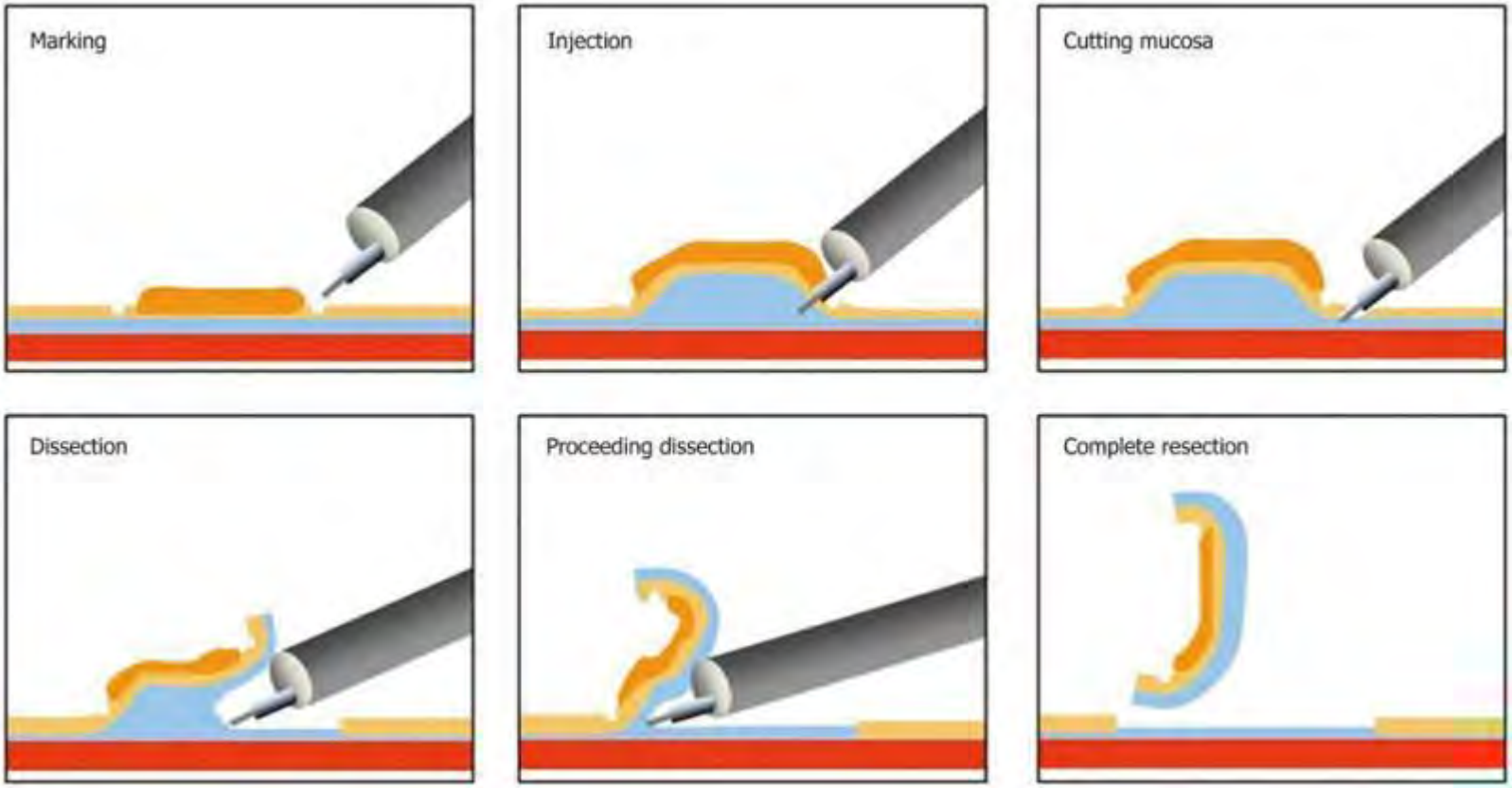
Gross Evaluation of the EMR Specimen



- No need to pin or cassette, place directly in formalin is ok
- Difficult to visualize lesion most of the time
- Ink deep/vertical margin
- Serially section in ~2 mm intervals.
- Lateral margins are usually less important in EMR (often multiple EMRs are done so individual lateral margins are not relevant)

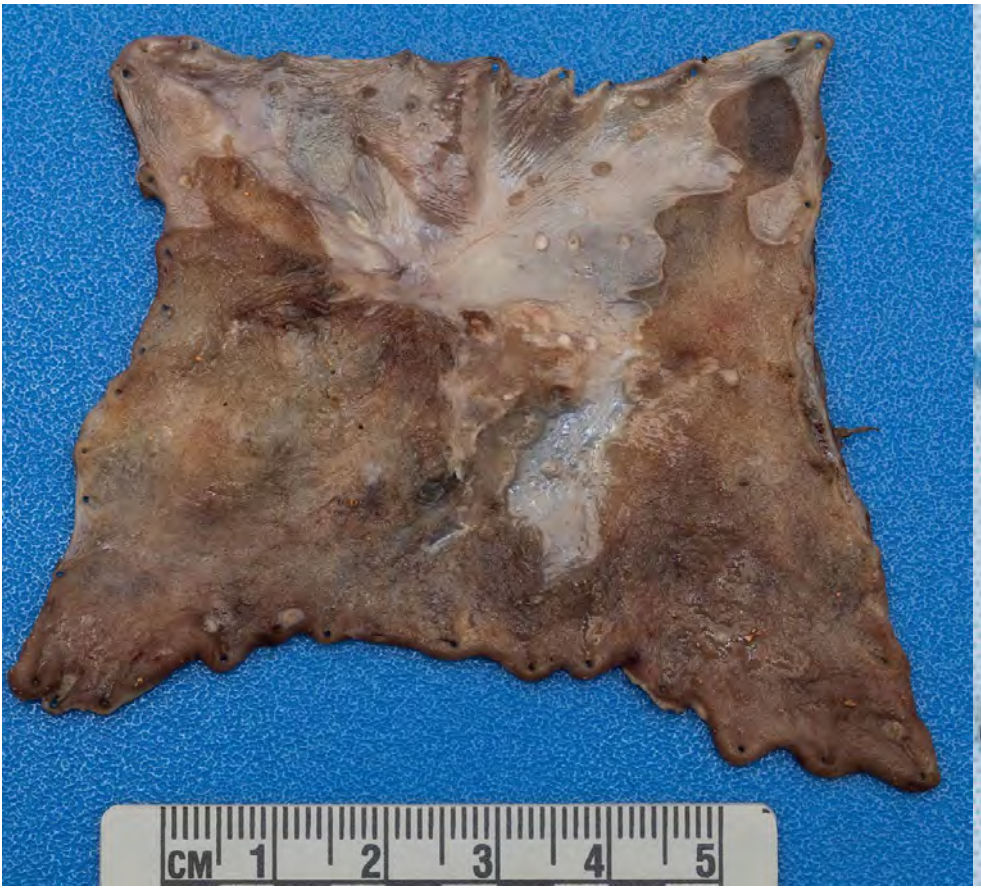
Lauwers GY, et al. Mod Pathol. 2009 Apr;22(4):489-98.
Overwater, et al. Gastrointest Endosc. 2019 Sep;90(3):384-392.

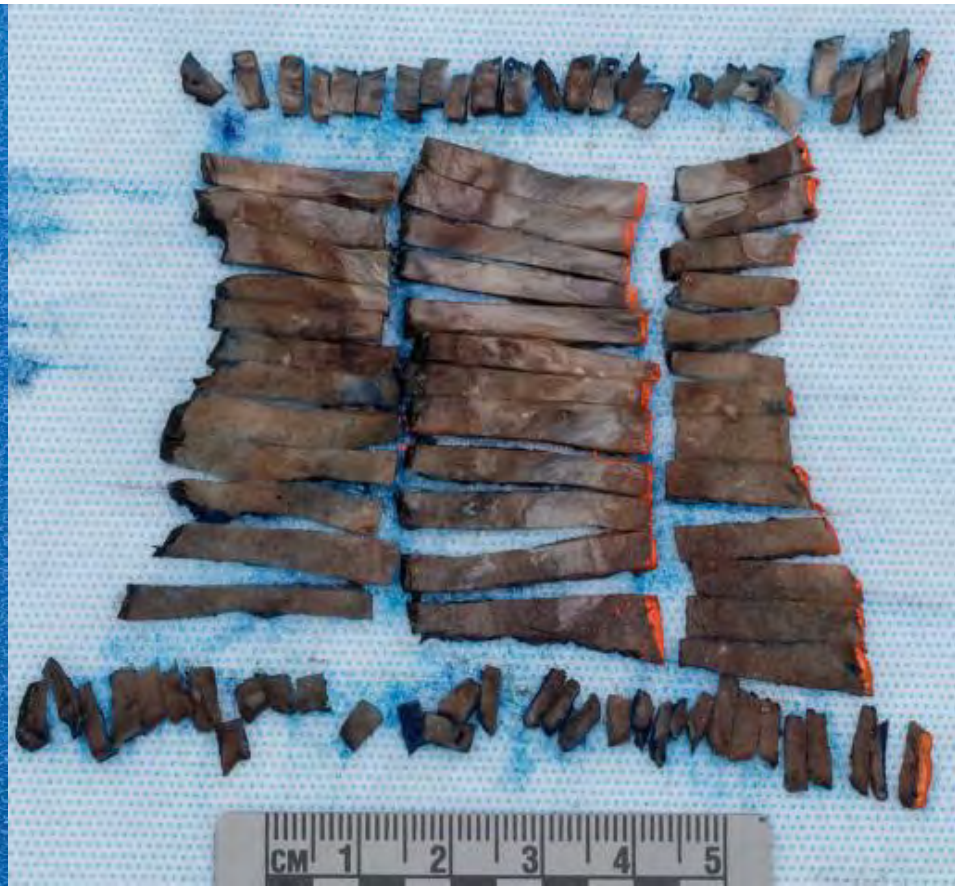
Endoscopic Submucosal Dissection



ESD: requires pinning, orientation by endoscopist and careful evaluation of all margins by perpendicular sectioning.

Proximal



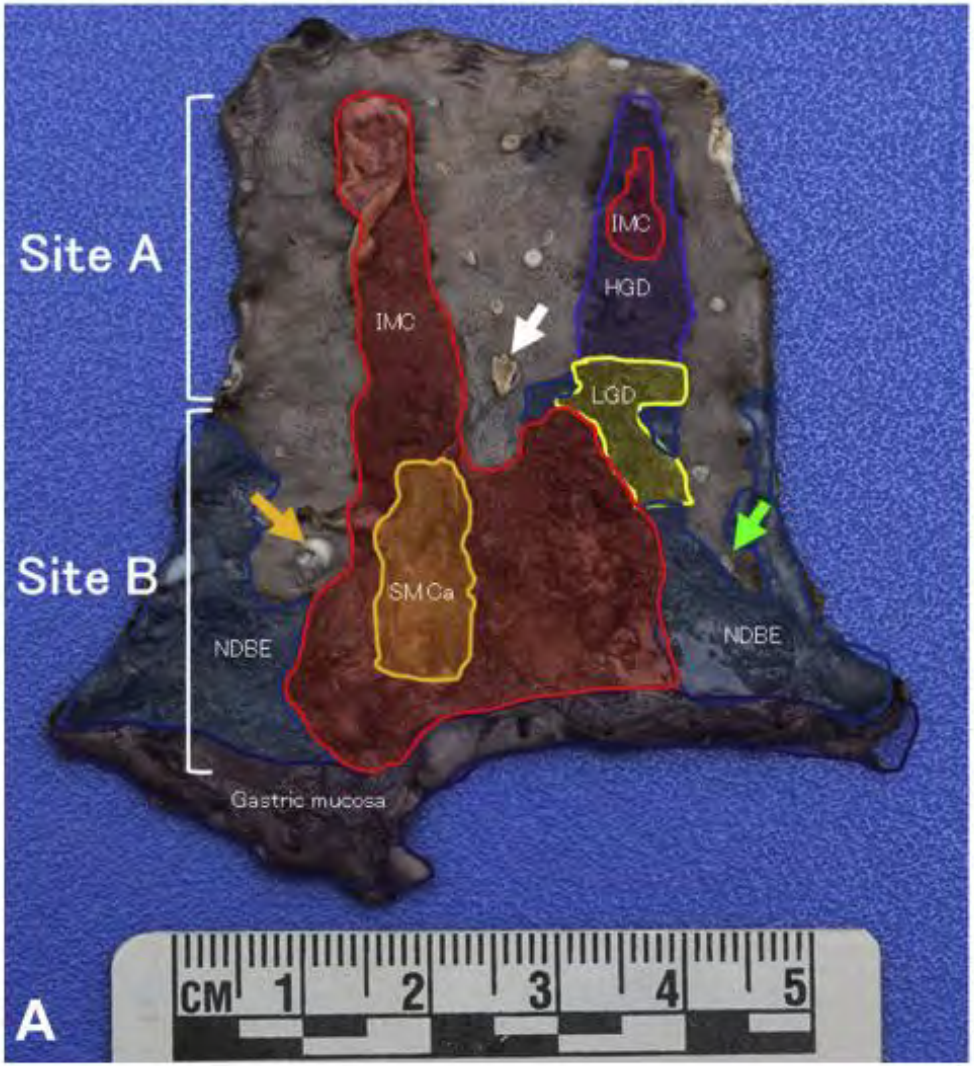


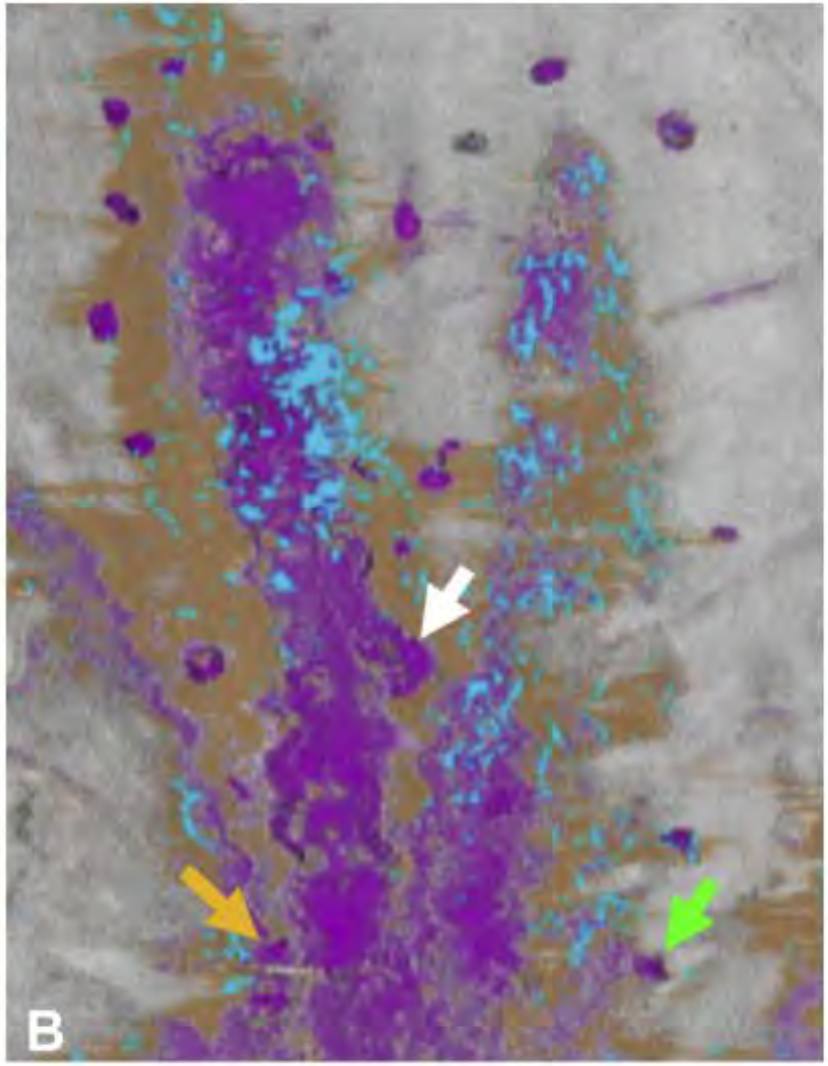
Distal


Carcinoma
HGD
LGD
Non-dysplastic BE
Squamous
Subsquamous Ca
Mix of Ca and HGD
CM 1 2 3 4 5

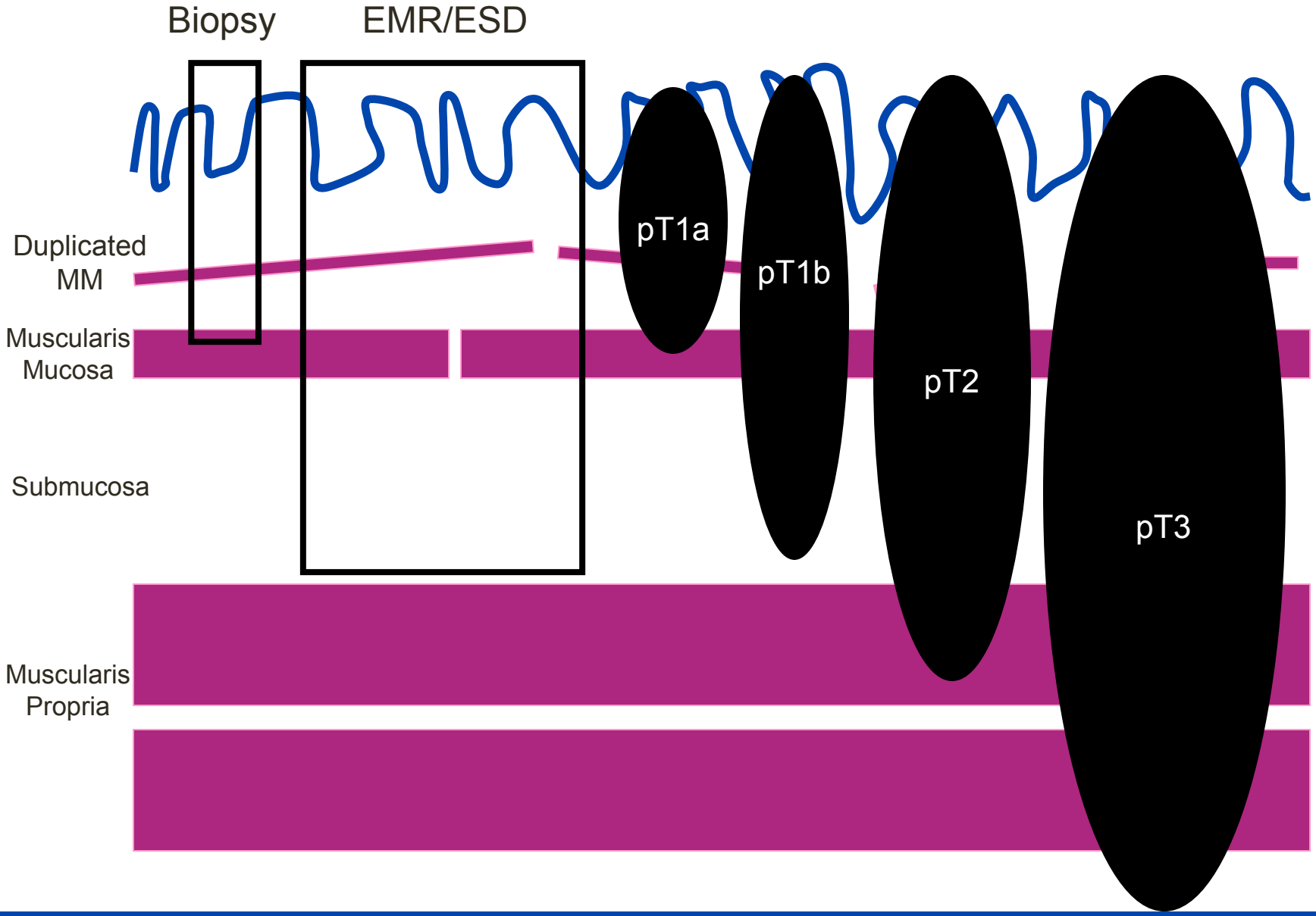
Histologic mapping

Volumetric laser endomicroscopy

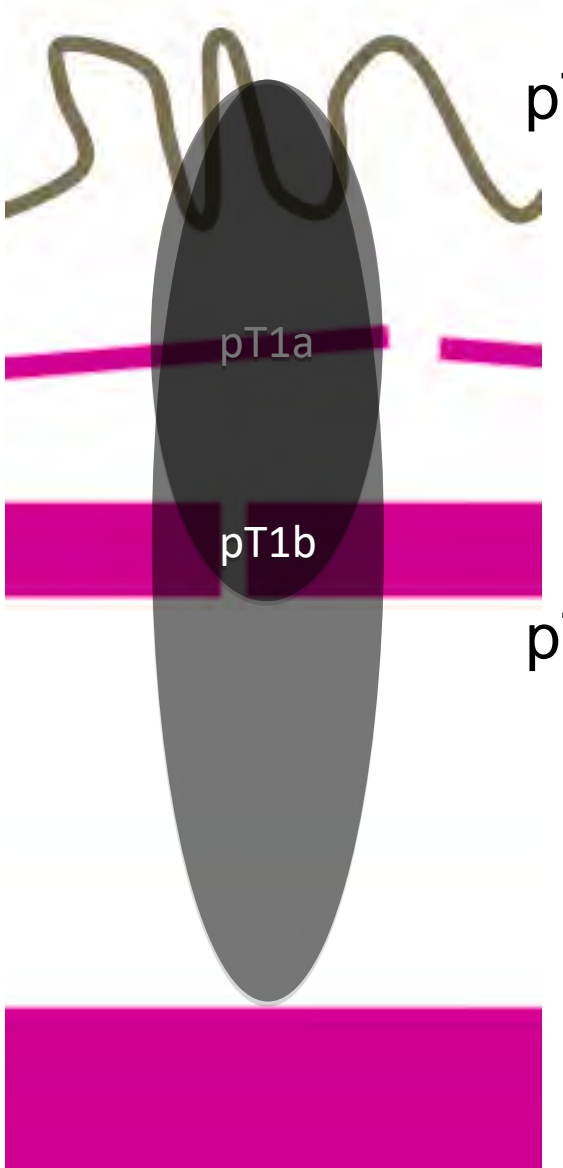




Esophageal Adenocarcinoma



Depth of invasion



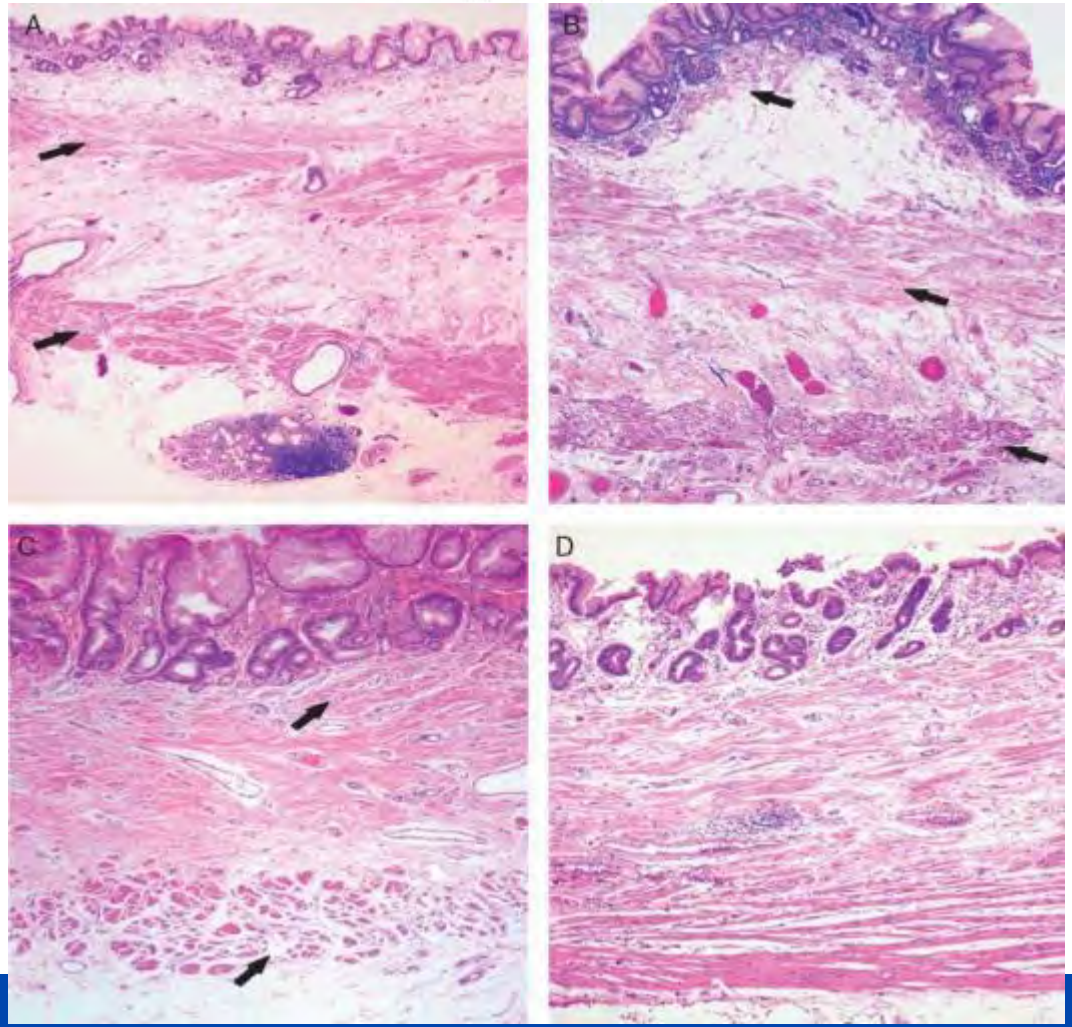
pT1a: Intramucosal adenocarcinoma
Lamina propria only (m1)
Inner muscularis mucosa (m2)
Space between MM layers (m3)
Outer muscularis mucosa (m4)

pT1b: Submucosally invasive
Inner third (sm1)
Middle third (sm2)
Outer third (sm3)

sm levels cannot be reliably evaluated in EMR/ESD specimens as muscularis propria is not sampled. Provide depth of invasion (microns).

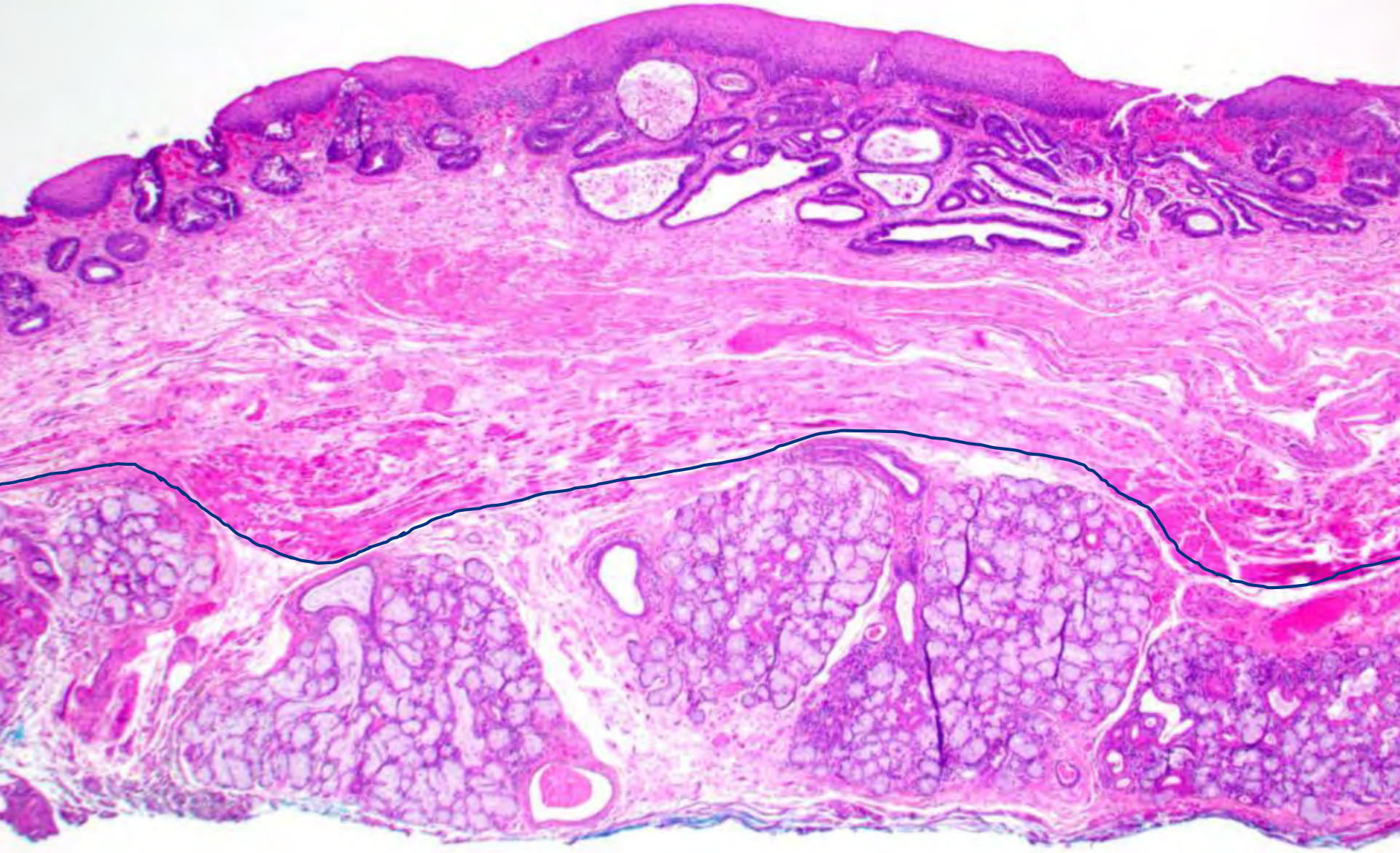
Duplication of the Muscularis Mucosae in Barrett Esophagus: An Underrecognized Feature and Its Implication for Staging of Adenocarcinoma

Susan C. Abraham, MD, Alyssa M. Krasinskas, MD,† Arlene M. Correa, PhD,‡ Wayne L. Hofstetter, MD,‡ Jaffer A. Ajani, MD,§ Stephen G. Swisher, MD,‡ and Tsung-Teh Wu, MD, PhD‖*

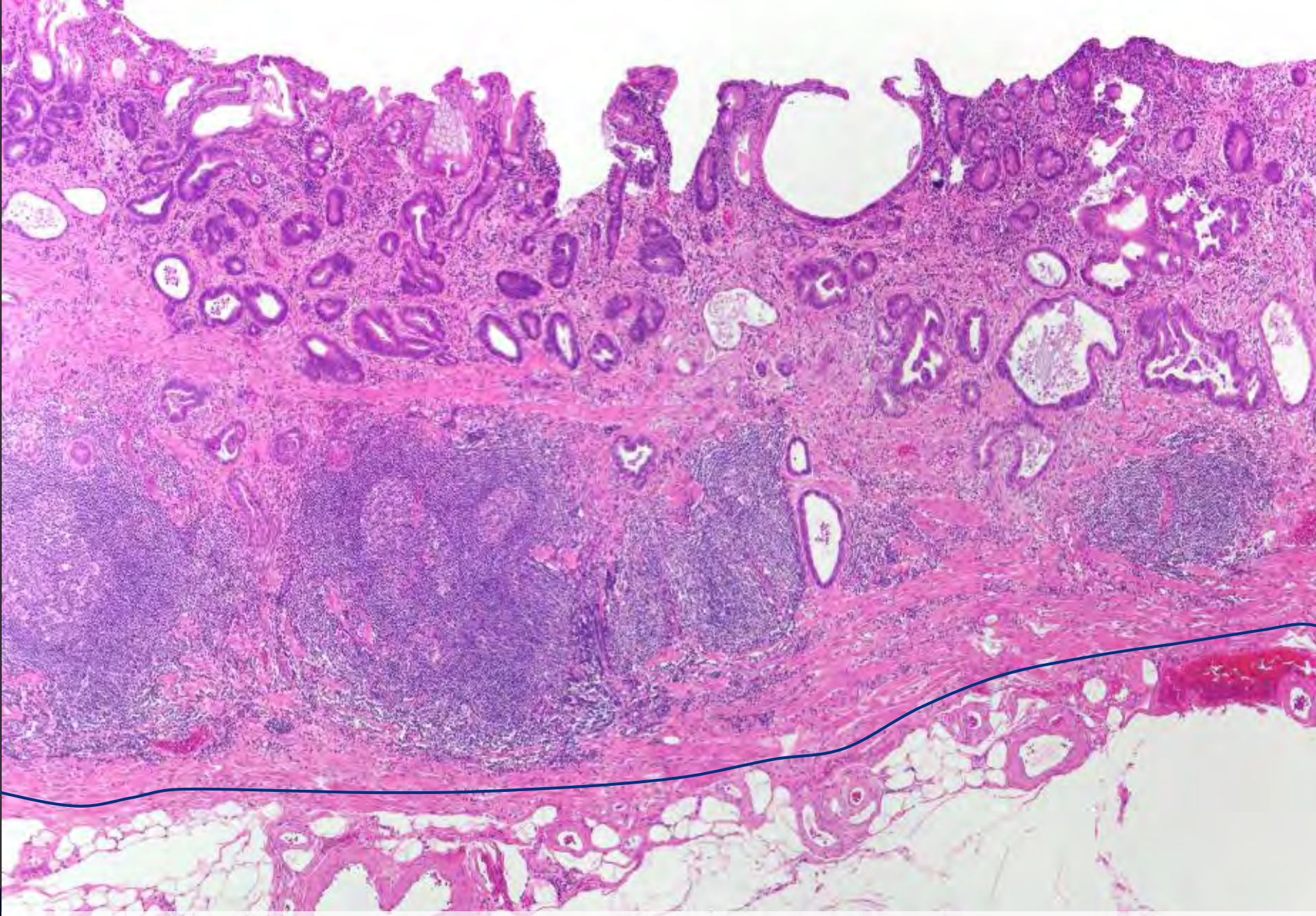


Abraham S, et al. Am J Surg Pathol 2007;31:1719-1725.

EMR with duplicated muscularis mucosae

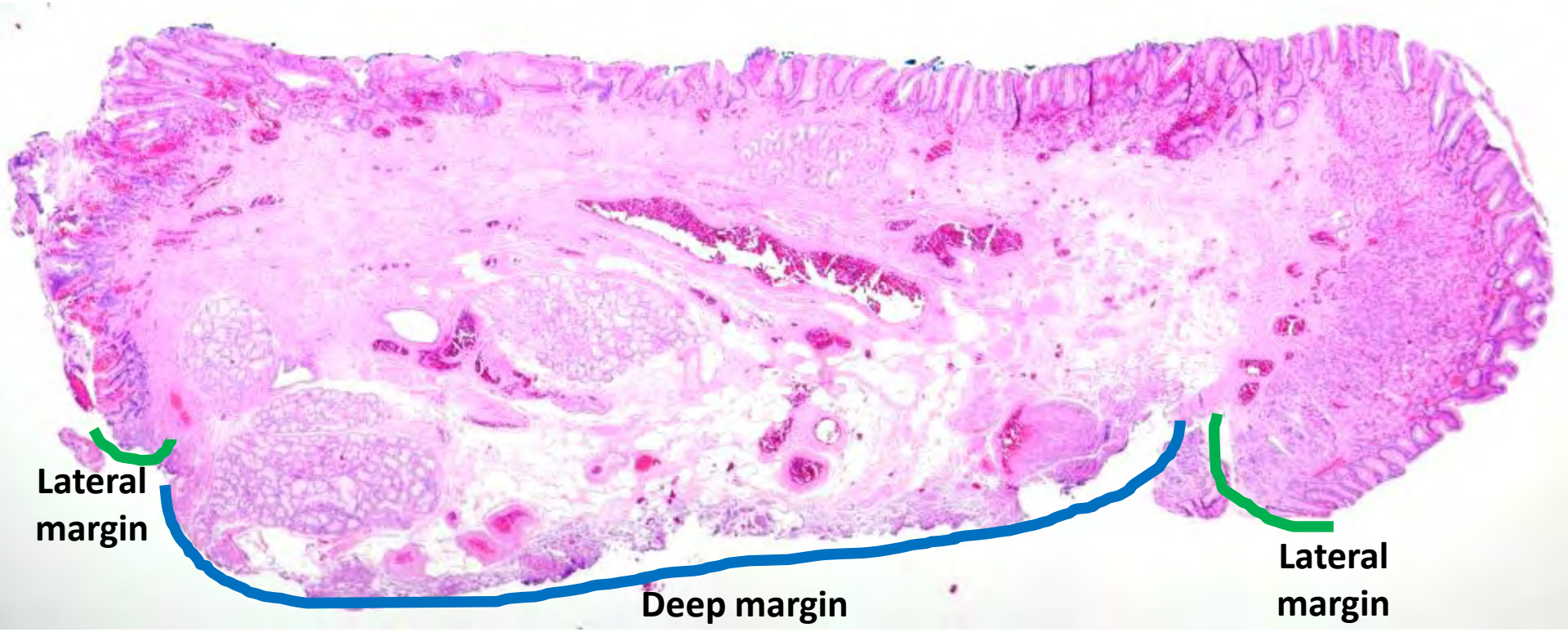


pT1a: well differentiated adenocarcinoma



pT1a Adenocarcinoma: note the duplicated muscularis mucosa

Lateral Margins vs Deep Margin in an EMR Specimen



ESD is less prone to curling of the edges

Risk of LN metastasis

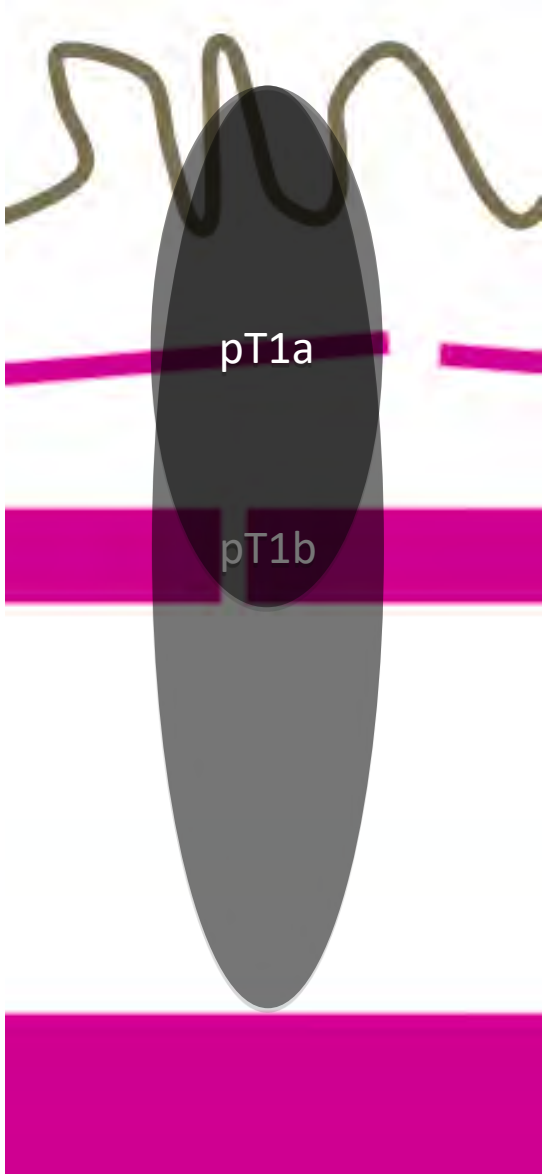


Table 4. Tumor Characteristics and Estimated Probability of Nodal Metastasis With Observed Rate of Nodal Metastasis

Clin Gastroenterol Hepatol. 2016 Mar;14(3):369-377

Tumor characteristics	Model estimated probability of nodal metastasis	Observed rate of nodal metastasis
T1a with no other risk factors	Very low (<5%)	2/57 (3.5%)
T1a with 1 or more risk factors[a]	Estimated >5%[a]	1/15 (6.7%)[a]
T1b with no other risk factors	Low (5%–10%)	2/27 (7.4%)
T1b with ALI or >2 cm alone	Intermediate (15%–20%)	6/38 (15.8%)
T1b with high grade alone	High (~20%)	3/13 (23.1%)
T1b with 2 or more additional risk factors[b]	High (30%–60%)	27/60 (45.0%)

[a]Most tumors in this category had a single risk factor (tumor size >2 cm, n = 10; high grade, n = 3) and would have a low (5%–10%) estimated probability. T1a cancers with 2 risk factors were rare (n = 2); estimated probability in this group was intermediate (15%–20%), which could not be confirmed because of the rarity of these cases.

[b]These tumors invaded the submucosa and had at least 2 additional risk factors (ALI, high tumor grade, and/or tumor size >2 cm).

1. Most pT1a tumors can successfully treated by endoscopic resection
2. pT1b tumors can be potentially be treated by endoscopic resection if:
   - Well to moderately differentiated, no high-grade budding
   - No LVSI
   - < 2 cm

Efficacy, Safety, and Long-term Results of Endoscopic Treatment for Early Stage Adenocarcinoma of the Esophagus With Low-risk sm1 Invasion

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013;11:630–635

HENDRIK MANNER,* OLIVER PECH,‡ YVONNE HELDMANN,* ANDREA MAY,* JUERGEN POHL,* ANGELIKA BEHRENS,* LIEBWIN GOSSNER,§ MANFRED STOLTE,‖ MICHAEL VIETH,¶ and CHRISTIAN ELL*

Table 1. Overview of Patients With LR sm1 EAC (n = 66) Who Underwent ET

Mean age (*y*)	63.2 ± 9.9 (range, 44–81)
BE type	
LSBE	29 (43.9%)
SSBE	37 (56.1%)
Mean BE length (*cm*)	3.4 ± 3 (range, 1–17)
Sex	
Male	58 (87.9%)
Female	8 (12.1%)
Size of hiatal hernia	
Large	9 (13.9%)
Medium	29 (43.9%)
Small	28 (42.4%)
Gross tumor type	
I	12 (18.2%)
IIa	16 (24.2%)
IIb	4 (6.1%)
IIc	6 (9.1%)
IIa + c	21 (31.8%)
I + II	7 (10.6%)
Macroscopic tumor size (*cm*)	
≤2	36 (54.5%)
>2	30 (45.5%)
Focality	
Focal	49 (74.2%)
Bifocal	3 (4.5%)
Multifocal	14 (21.2%)
Tumor differentiation	
G1	19 (28.8%)
G2	47 (71.2%)

BE, Barrett's esophagus; LSBE, long-segment Barrett's esophagus; SSBE, short-segment Barrett's esophagus.

Low-risk lesions:

- Macroscopically polypoid or flat (types I/II).
- Submucosal invasion (sm1) ~ ≤500um
- Good-to-moderate tumor differentiation (G1–2)
- No tumor invasion into lymphatic vessels (L0 situation) or blood vessels (V0 situation).

- Only 1 (1.5%) patient had LN metastasis during follow-up
- No patient died from BE related complications

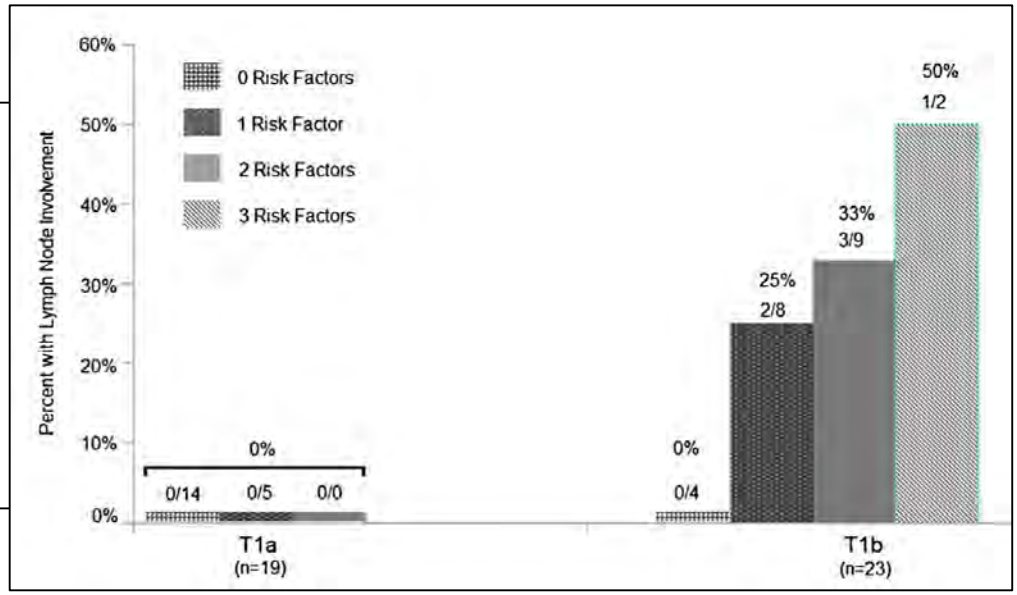
Depth of submucosal invasion

- pT1b with invasion ≤500um is considered low-risk as long as other high risk factors are not present
- What does sm1 translate to on EMR/ESD?

Table 1 Tumor characteristics by depth of invasion

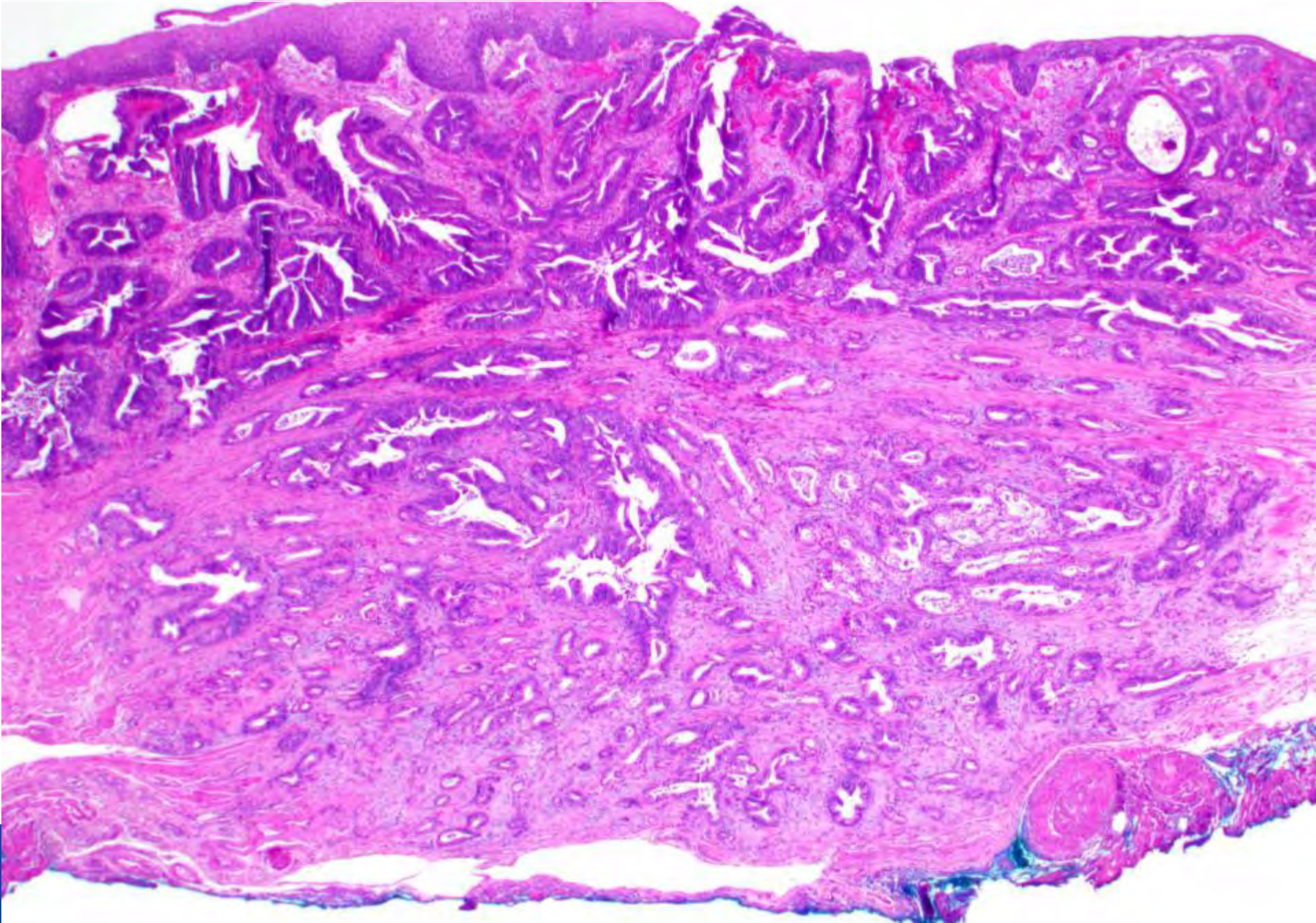
	LVI	Poor differentiation	None	Both
T1A (*n*=19)	1 (5 %)	4 (21 %)	14 (74 %)	0
T1B (*n*=23)				
≤500 μm	1 (4 %)	0	4 (17 %)	0
>500 μm	3 (13 %)	6 (26 %)	7 (30 %)	2 (9 %)

LVI lymphovascular invasion

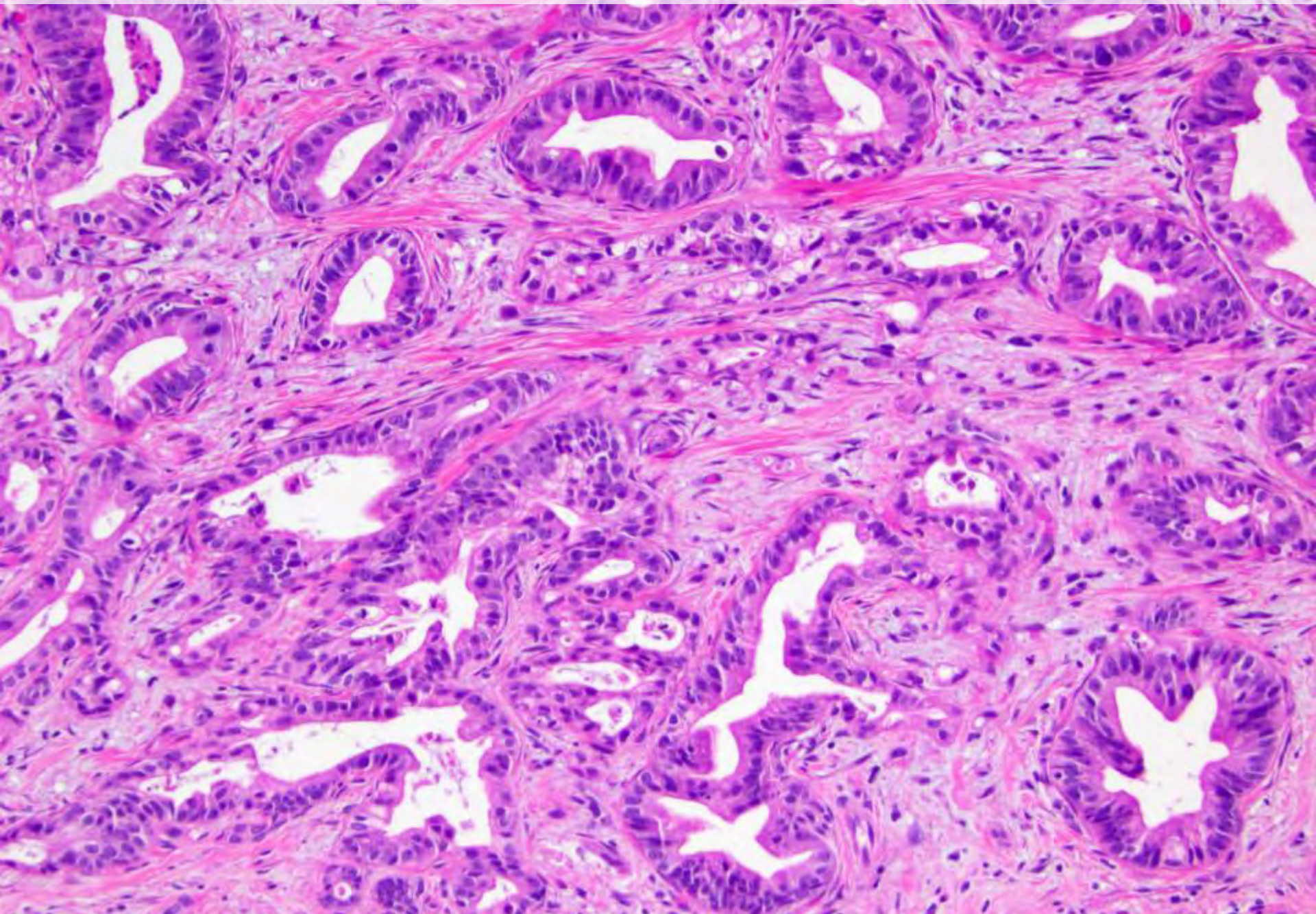


Of the 6 cases with LN met, 5 had depth >500 um, although p-value was n.s.

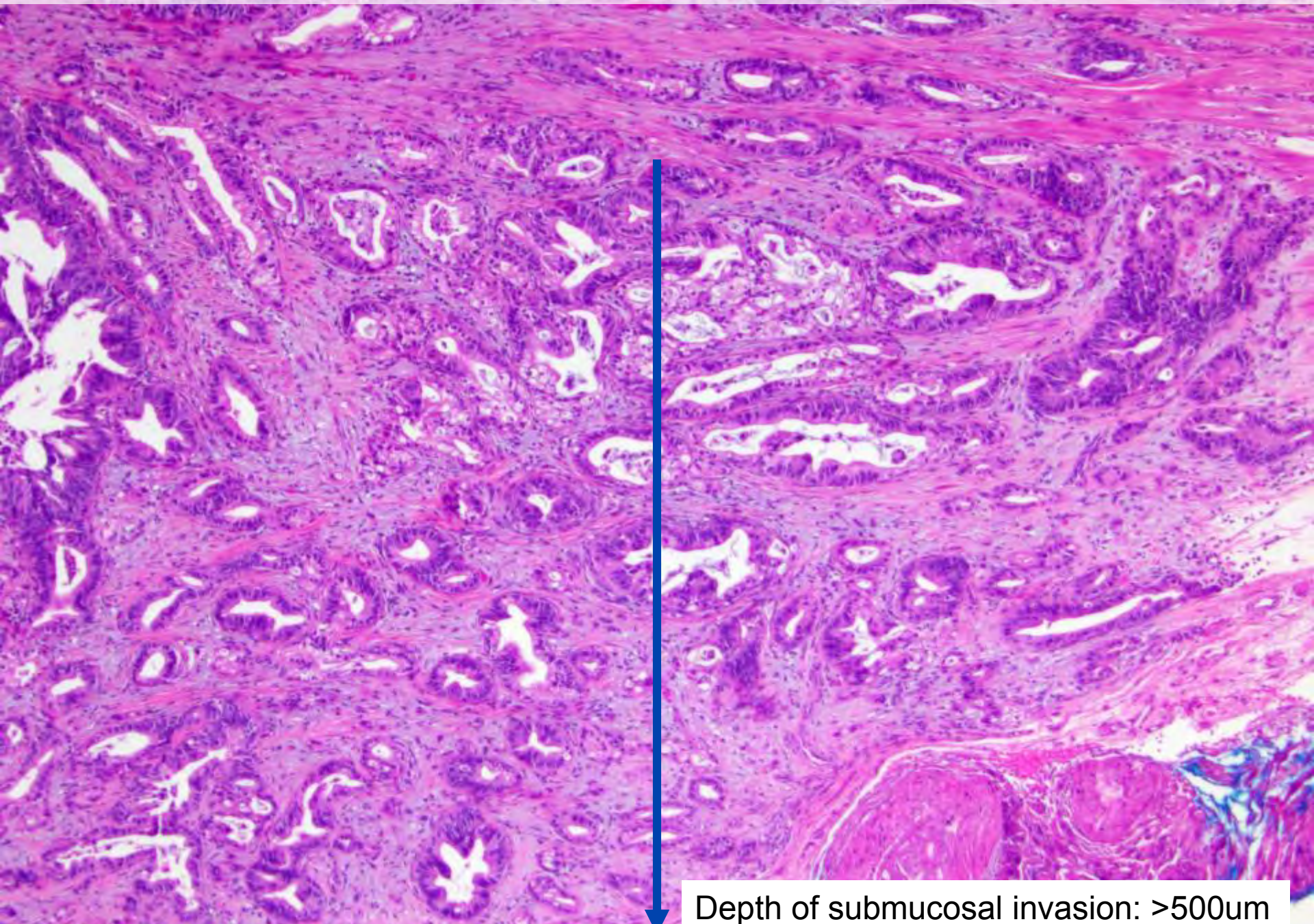
pT1b Adenocarcinoma: Invasion into submucosa

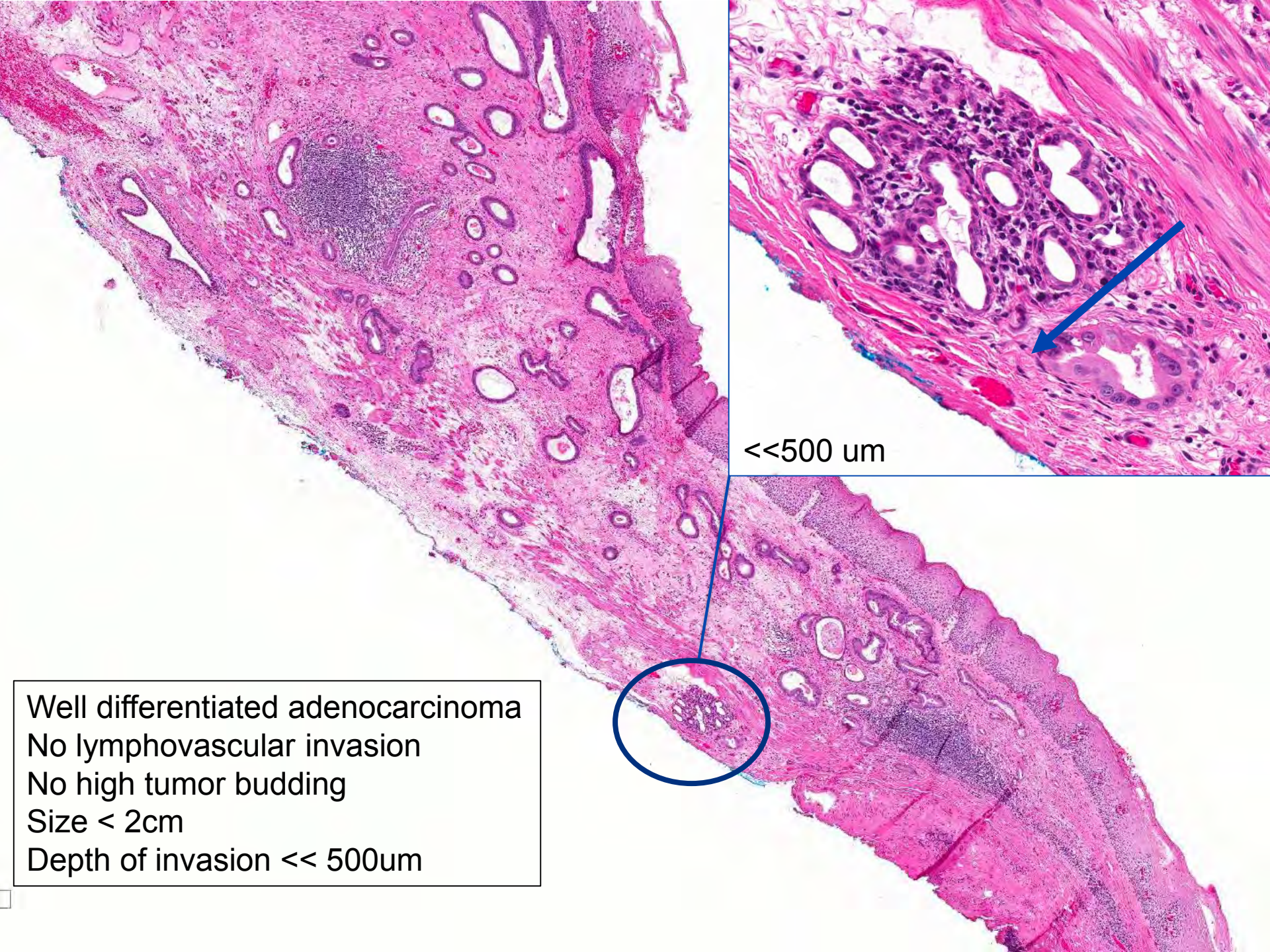


pT1b Adenocarcinoma: Stromal Desmoplasia (75%)



pT1b Adenocarcinoma: Invasion into submucosa





Well differentiated adenocarcinoma
No lymphovascular invasion
No high tumor budding
Size < 2cm
Depth of invasion << 500um

Take Home Points

- Visible and flat dysplasia are handled very differently by gastroenterologists
- Evaluating for dysplasia in biopsies of flat mucosa requires a systematic approach
  - Surface maturation, cytologic atypia, architectural complexity, inflammation
  - Keep in mind that LGD and HGD are often overdiagnosed
  - As a group we should take steps to improve diagnostic accuracy (training on a standardized slide set, high volume BE practice)
  - Send all slides when getting a second opinion
- Important elements to report in EMR/ESD specimens include tumor stage, histologic grade, vascular invasion, deep margin status,
  - Lateral margins on ESD or if only one EMR is done

