Cleveland Clinic

DYSPLASIA IN BARRETT'S ESOPHAGUS: IMPACT OF NEW ACG GUIDELINES

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107TH ANNUAL MEETING
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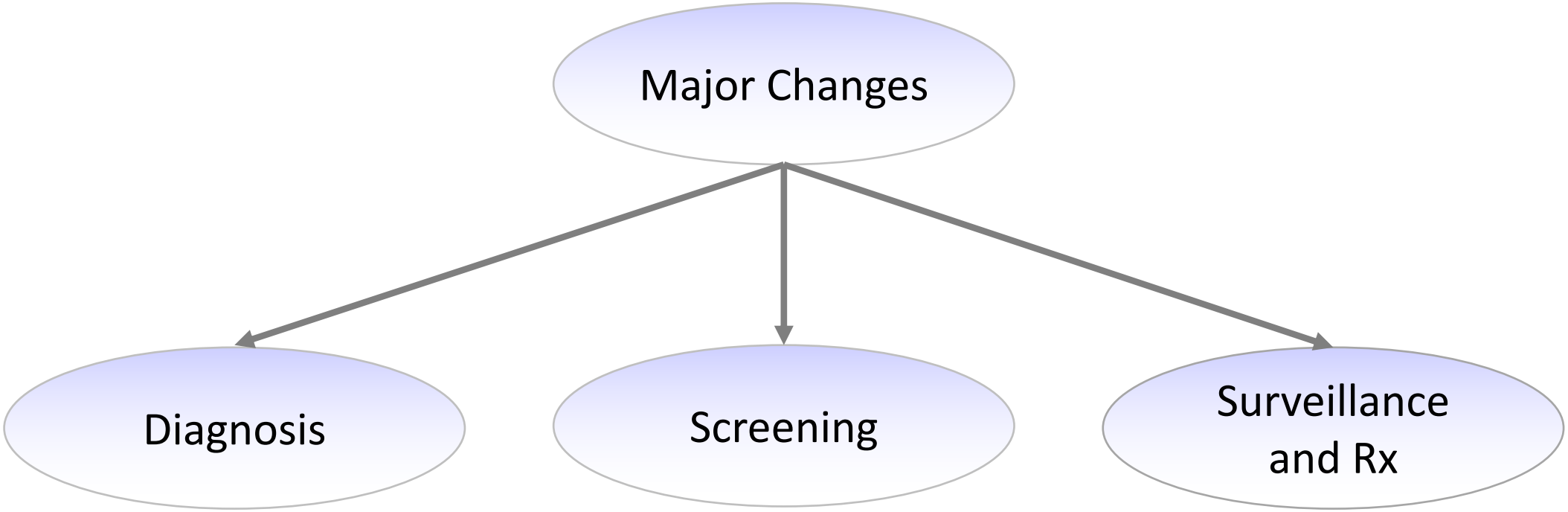
Outline

- 2016 ACG guidelines for BE
- Dysplasia in BE
- Does the new treatment algorithm for BE-related dysplasia change anything for pathologists?

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]

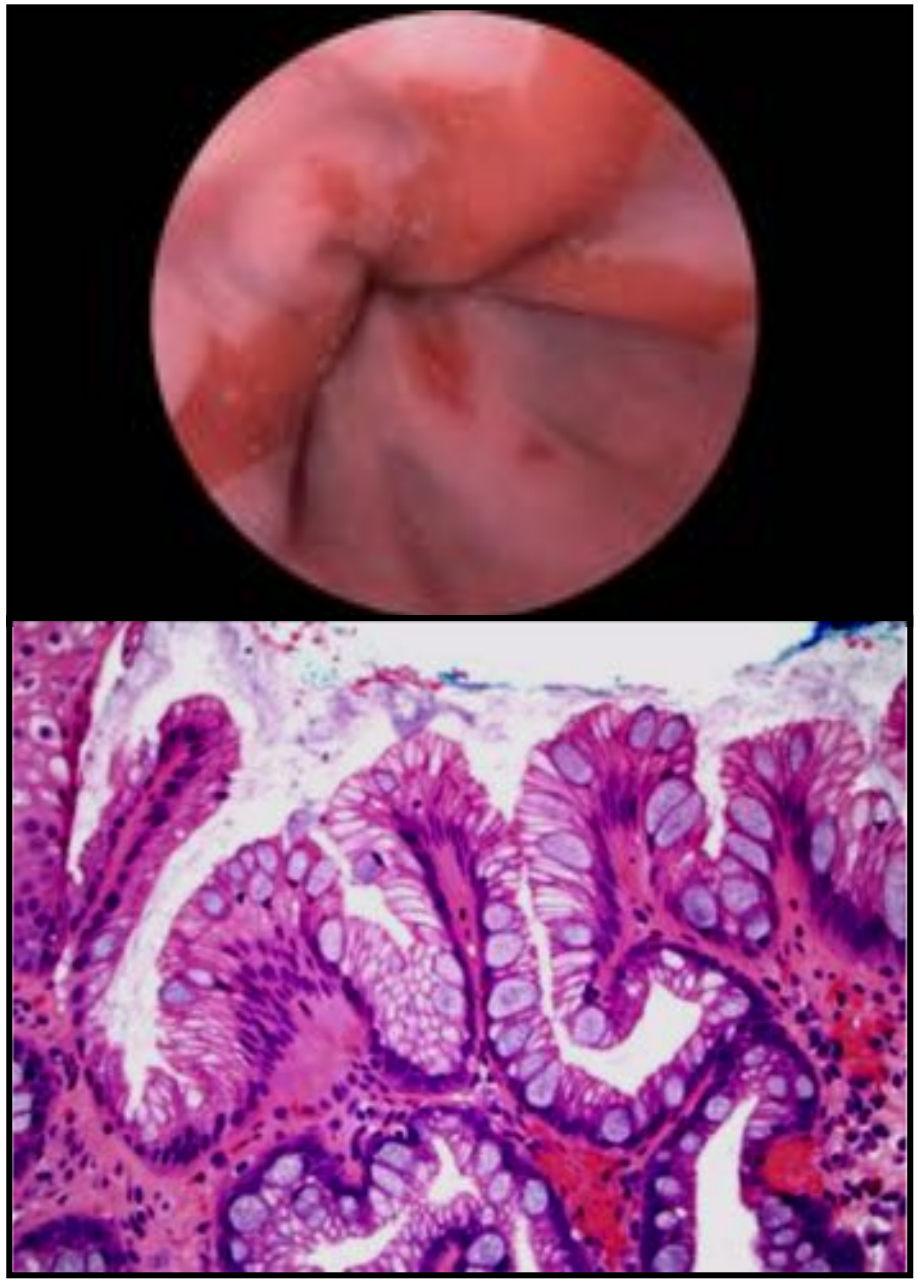
Am J Gastroenterol 2016; 111:30–50



New Definition of BE - 2016

- BE should be diagnosed when there is extension of salmon-colored mucosa (CLE) into the tubular esophagus extending > 1 cm proximal to the EGJ with biopsy confirmation of IM
- At least 8 biopsies should be obtained to maximize yield of goblet cells

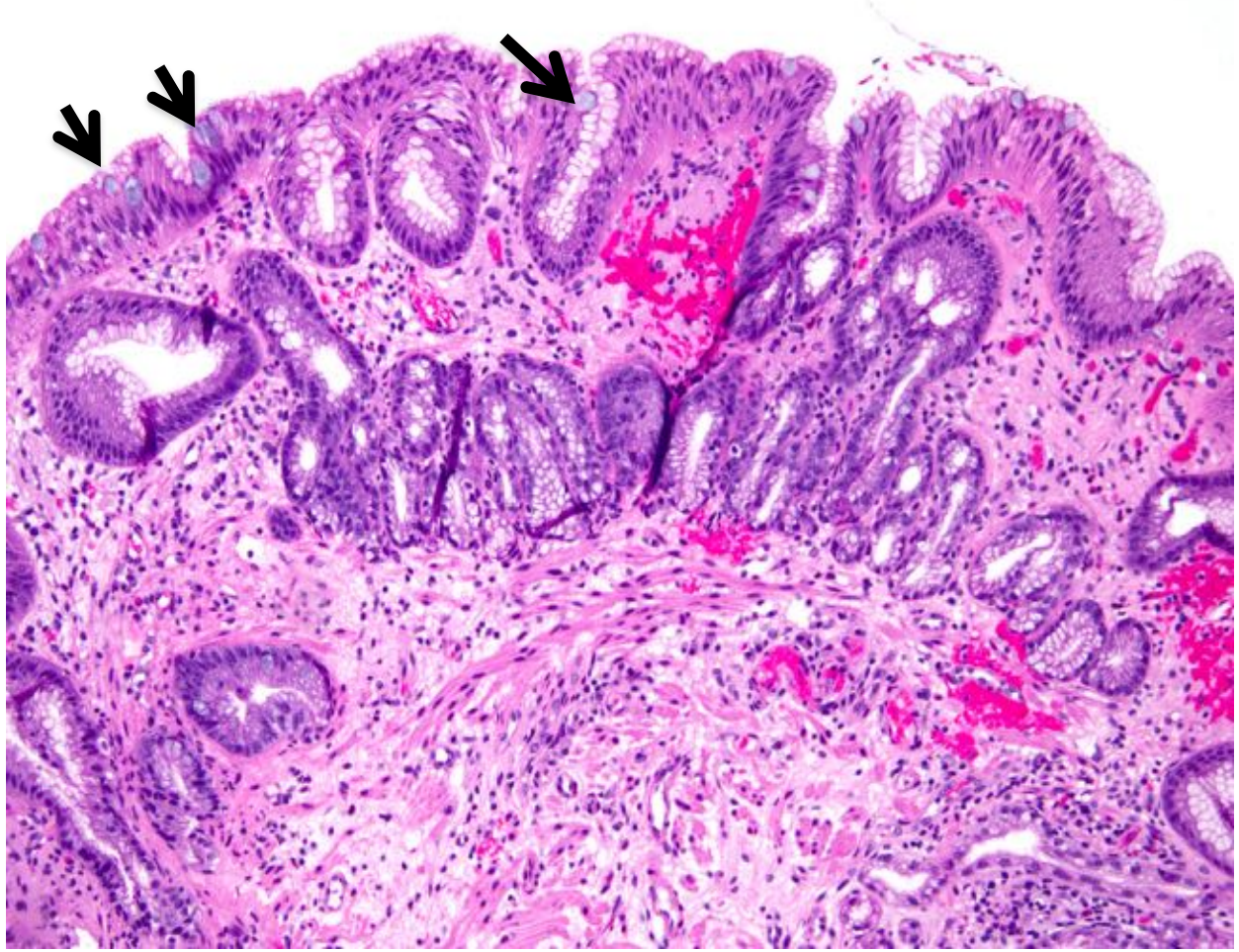
Shaheen N et al. Am J Gastroenterol 2016



IM at GE Junction – Clinical Implications

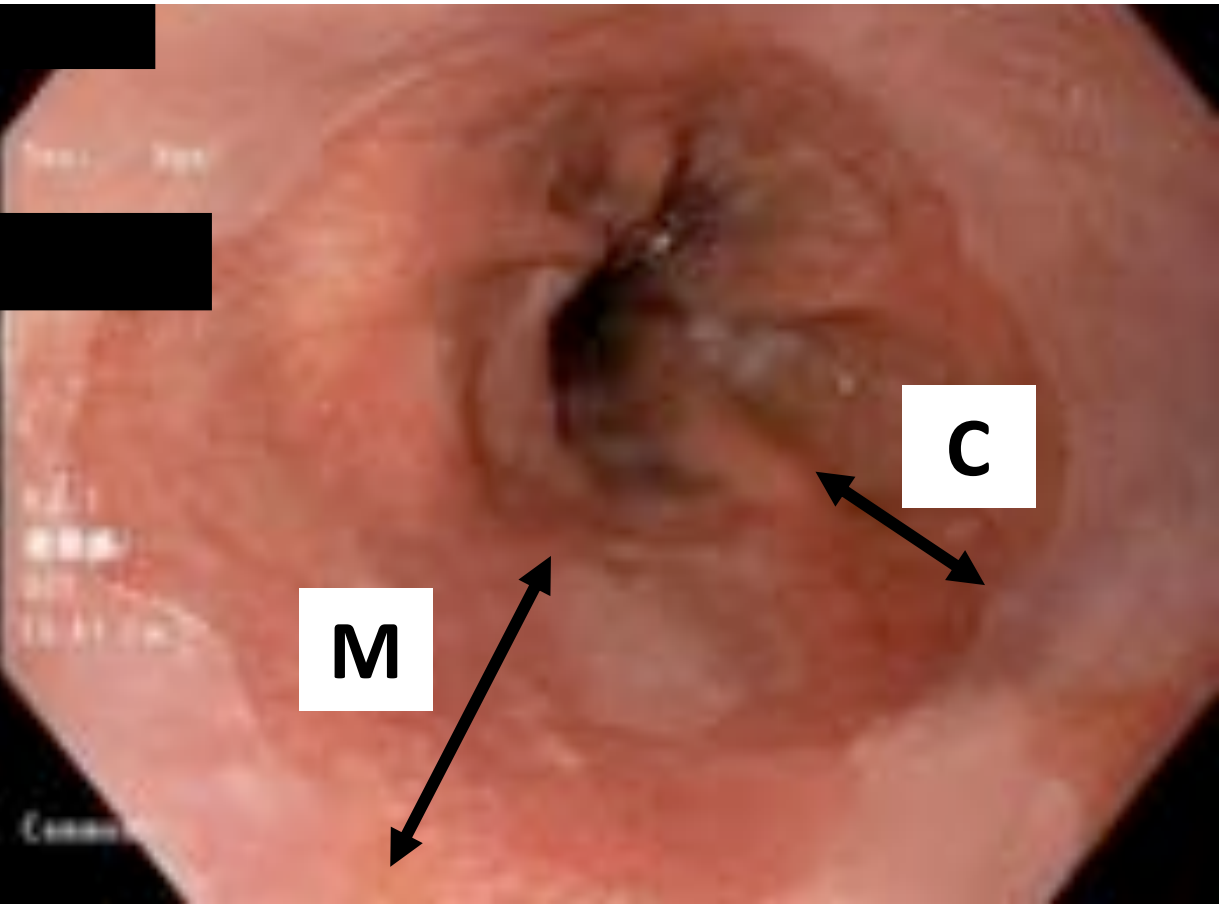
- Cardiac IM has a much lower risk of progression to cancer compared to BE
- Accurate distinction between BE and cardiac IM can be challenging – high interobserver variability
- ACG guidelines - Biopsy should NOT be performed in the presence of a normal Z-line or a Z-line with < 1 cm of variability

GE Junction Biopsy

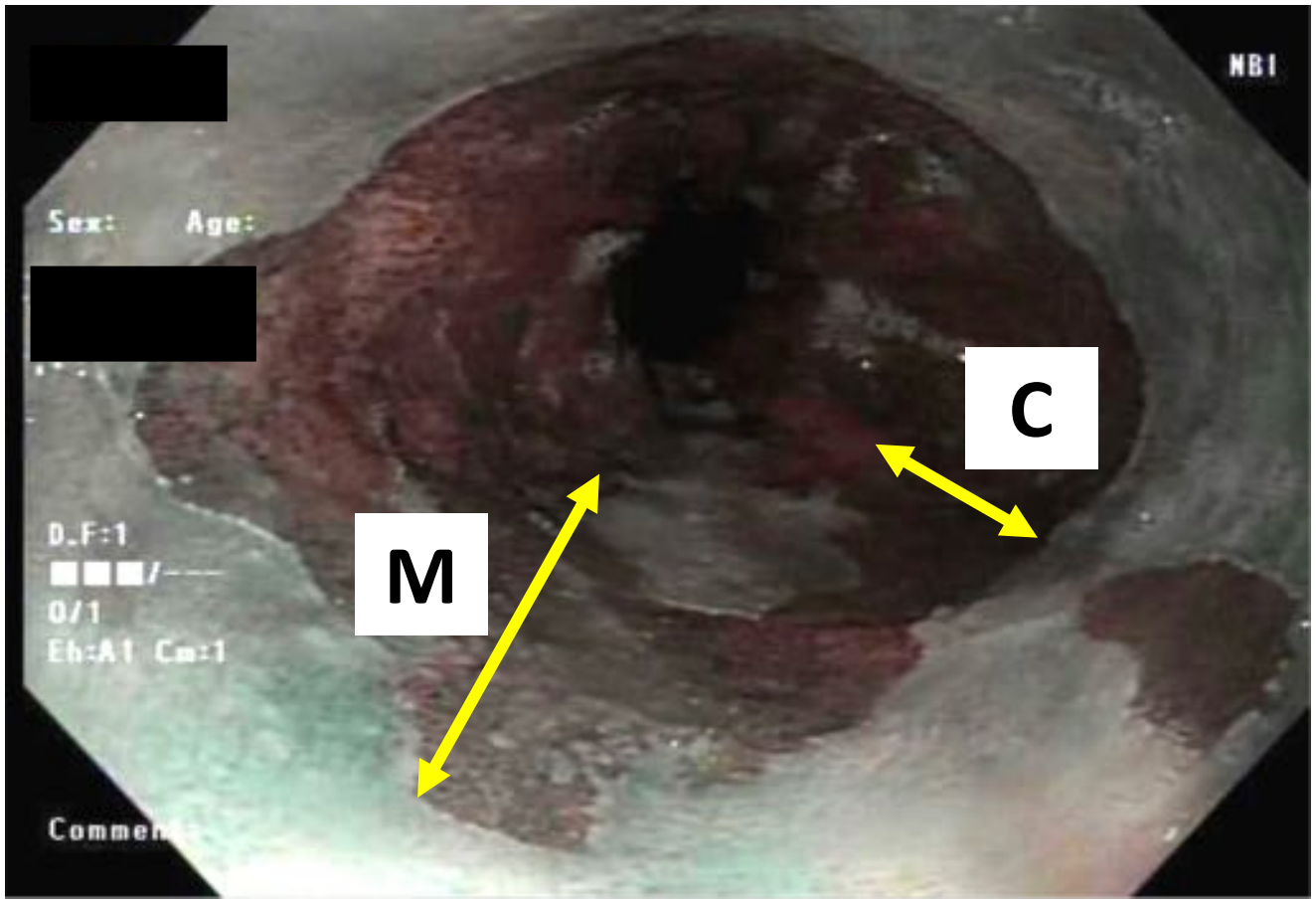


Endoscopic Classification – Prague System

White Light Endoscopy



Narrow Band Imaging



Barrett's Stage: C2-M3

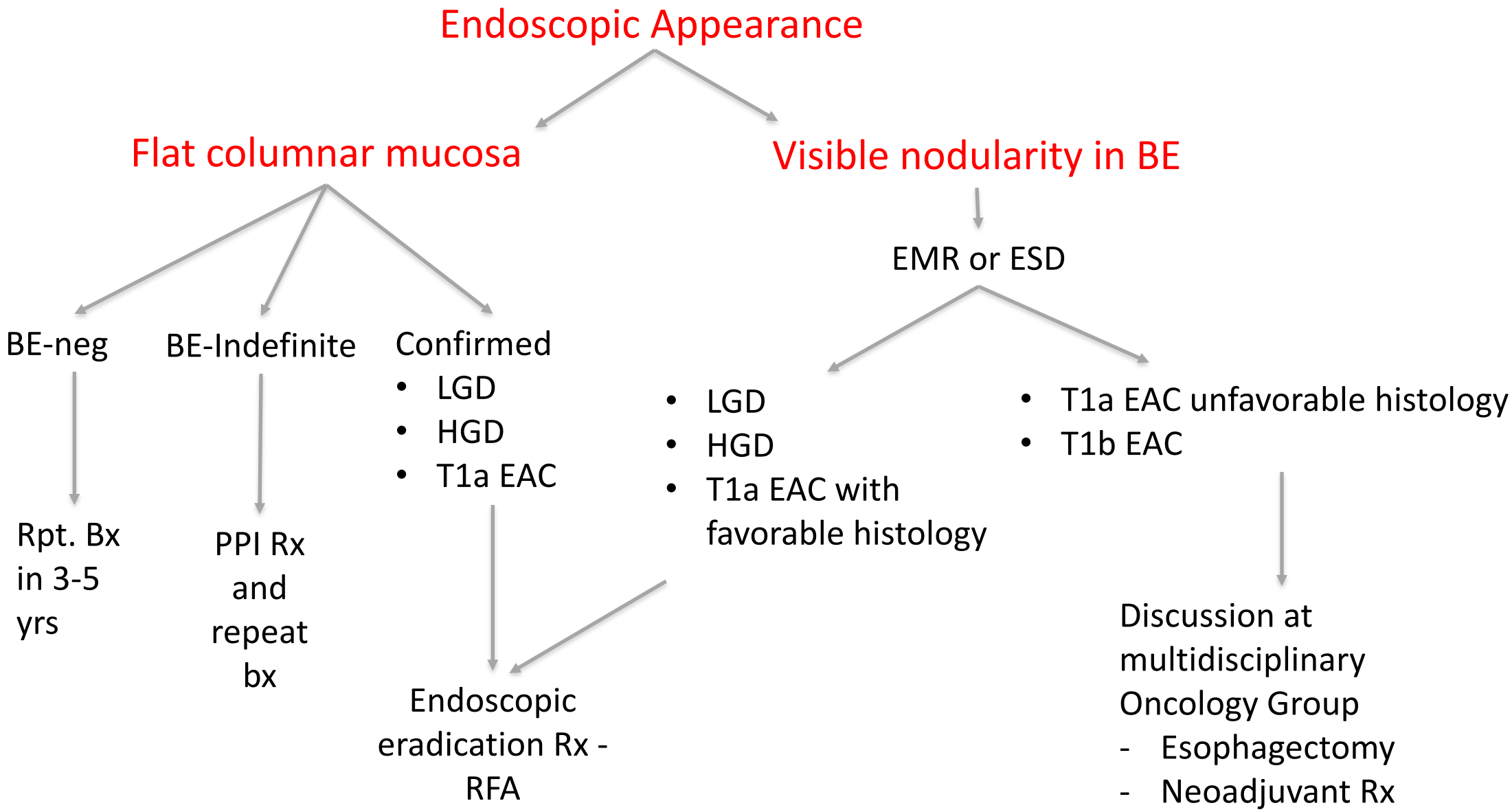
C = Maximum circumferential extent of abnormal mucosa above GEJ

M = Maximum longitudinal extent of abnormal mucosa above GEJ

Screening Recommendations

- Men with chronic (>5 years) symptoms of GERD with at least 2 additional risk factors:
  - Age > 50 yrs
  - White race
  - Central obesity
  - Current or past history of smoking
  - Confirmed family history of BE
- Screening is no longer indicated in women with chronic GERD (may be considered in women with multiple risk factors)
- Erosive esophagitis at baseline endoscopy – repeat endoscopy after 8 – 12 weeks to exclude BE

Surveillance and Treatment Guidelines



Shaheen N et al. Am J Gastroenterol 2016; 111:30–50

Grading BE-related Dysplasia

Dysplasia Morphology Study Group Classification	Revised Vienna Classification
• United States	• Europe and Asia
• Negative for dysplasia	• Negative for dysplasia
• Indefinite for dysplasia	• Indefinite for dysplasia
• Low-grade dysplasia	• Noninvasive low-grade neoplasia (low-grade adenoma/dysplasia)
• High-grade dysplasia	• Noninvasive high-grade dysplasia
	• High-grade adenoma/dysplasia
	• Noninvasive carcinoma (CIS)
	• Suspicious for invasive carcinoma
	• Invasive neoplasia
• Intramucosal adenocarcinoma	• Intramucosal carcinoma
• Submucosal adenocarcinoma	• Submucosal carcinoma or beyond

Problems with BE-related Dysplasia

- Sampling error
  - Dysplastic mucosa cannot be easily distinguished from non-dysplastic BE endoscopically
  - "Seattle protocol" – systematic 4-quadrant biopsies using jumbo biopsy forceps, every 1-2 cm throughout the BE segment is recommended
  - Any mucosal irregularities must be biopsied

Problems with BE-related Dysplasia

- Diagnostic Interpretation

Negative Low-grade High-grade Adenocarcinoma

Per American College of Gastroenterology and American Cancer Society - Diagnosis of dysplasia must be confirmed by an expert GI pathologist

BE-related Dysplasia

Reproducibility of the Diagnosis of Dysplasia in Barrett Esophagus: A Reaffirmation

ELIZABETH MONTGOMERY, MD, MARY P. BRONNER, MD, JOHN R. GOLDBLUM, MD, JOEL K. GREENSON, MD, MARIAN M. HABER, MD, JOHN HART, MD, LAURA W. LAMPS, MD, GREGORY Y. LAUWERS, MD, AUDREY J. LAZENBY, MD, DAVID N. LEWIN, MD, MARIE E. ROBERT, MD, ALICIA Y. TOLEDANO, ScD, YU SHYR, PhD, AND KAY WASHINGTON, MD, PhD

Hum Pathol 2001; 32:368-378

- Interobserver agreement:
  - HGD/Ca – 0.64 (substantial)
  - BE-Neg – 0.58 (mod to substantial)
  - LGD – 0.32 (fair)
  - IND – 0.15 (slight)

Poor Interobserver Agreement in the Distinction of High-Grade Dysplasia and Adenocarcinoma in Pretreatment Barrett's Esophagus Biopsies

Erinn Downs-Kelly, D.O.,[1] Joel E. Mendelin, M.D.,[1] Ana E. Bennett, M.D.,[1] Elias Castilla, M.D.,[1] Walter H. Henricks,[1] Lynn Schoenfield, M.D.,[1] Marek Skacel, M.D.,[1] Lisa Yerian, M.D.,[1] Thomas W. Rice, M.D.,[2] Lisa A. Rybicki, M.S.,[3] Mary P. Bronner, M.D.,[1] and John R. Goldblum, M.D.[1]

[1]*Cleveland Clinic Departments of Anatomic Pathology,* [2]*Thoracic Surgery, and* [3]*Quantitative Health Sciences, Cleveland, Ohio*

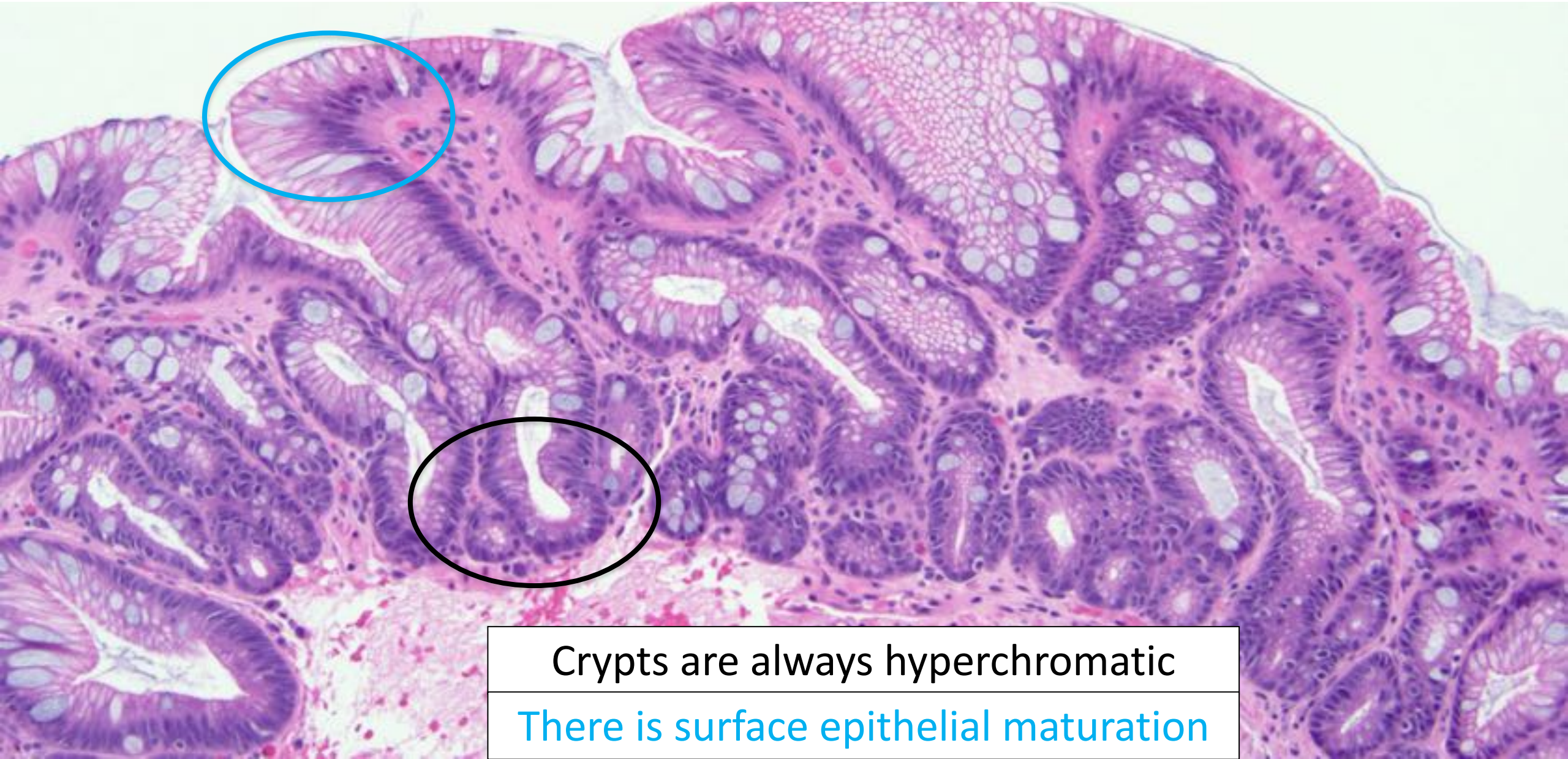
Am J Gastroenterol 2008;103:2333–2340

Diagnosis	Kappa	*p* value	95% CI	Interobserver Agreement
HGD	0.47	<0.001	0.42 - 0.50	Moderate
HGD-MAD	0.21	<0.001	0.17 - 0.25	Fair
IMC	0.30	<0.001	0.27 - 0.35	Fair
SMC	0.14	<0.001	0.10 - 0.18	Poor

General Pathologists Vs. Expert Pathologists

- BE-LGD
  - Pech et al. 2007
    - 25/50 LGD (50% confirmed); 21 (42%):BE-NEG, 4 (8%): BE-HGD
  - Curvers et al. 2010
    - 22/147 LGD (15% confirmed); 110 (74.8%):BE-NEG, 1 (0.7%): BE-HGD, 14 (9.5%): IND
    - Cumulative risk of progression to HGD/Ca:
      - 85% (109.1 mo) with consensus diagnosis vs 4.6% (107.4 mo) for pts. downstaged to BE-NEG
  - Duits et al. 2015
    - 79/293 LGD (29% confirmed); 174 (59%): BE-NEG, 40 (14%): IND
    - Risk of HGD/Ca
      - 9.1% / pt-yr for confirmed LGD vs 0.6% for pts. downstaged to BE-NEG
- BE-HGD
  - Sangle et al. 2015
    - Academic and Private centers from 25 study sites across US, Canada (2), UK (2) and France (1)
    - 248/485 (51% confirmed); 43 (18%): Ca, 79 (33%): LGD, 61 (26%): IND, 35 (15):BE- NEG, 18 (7%): Inflamed gastric cardia

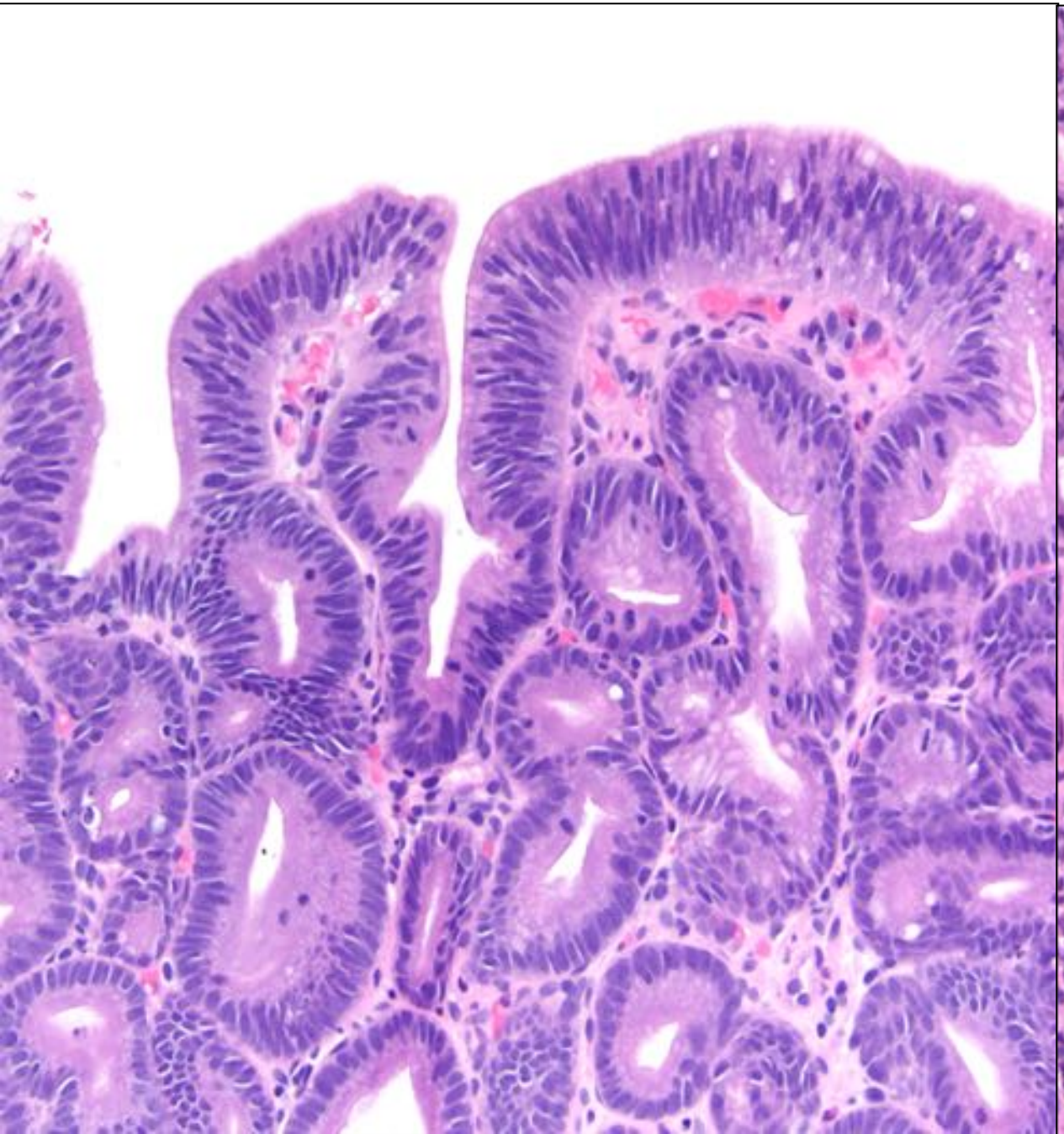
BE - Negative for Dysplasia
"Baseline Atypia of Barrett's Mucosa"



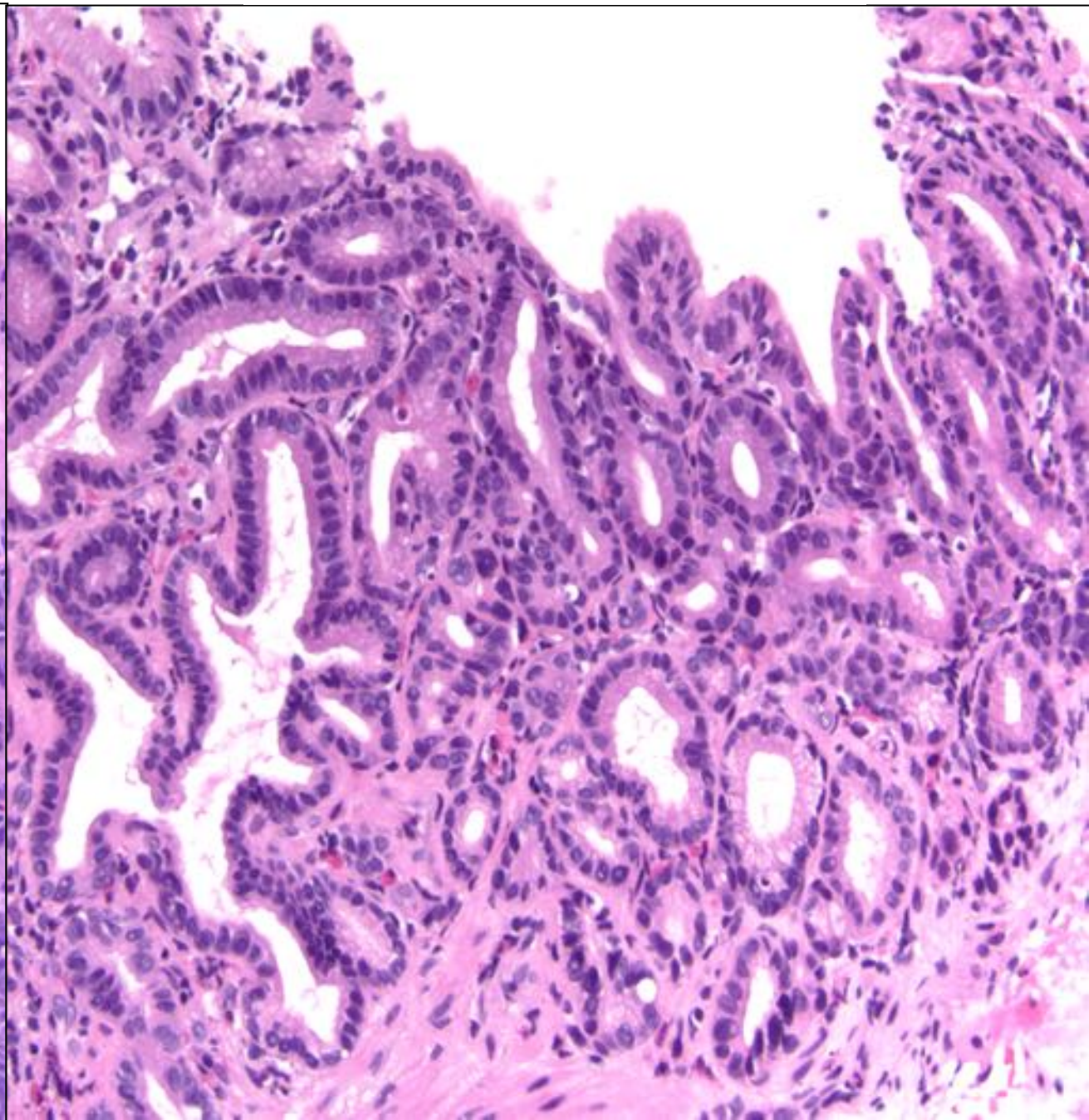
Crypts are always hyperchromatic

There is surface epithelial maturation

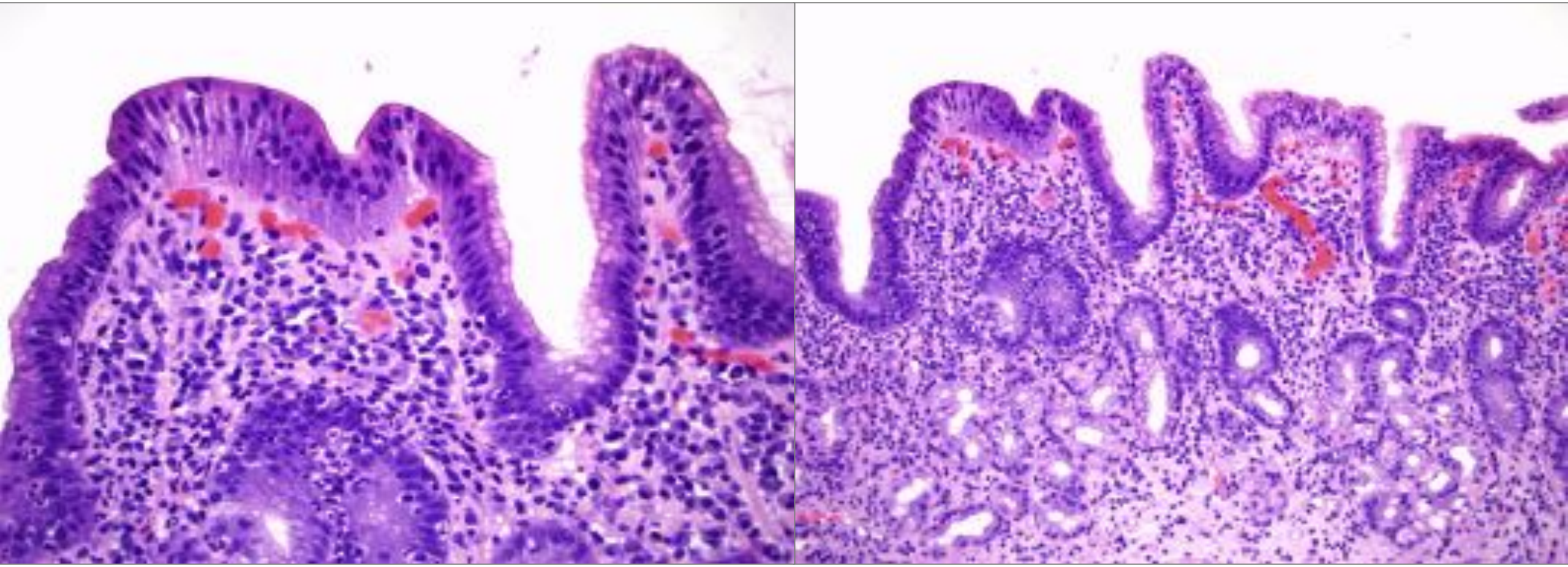
Intestinal-Type Dysplasia



Foveolar-Type Dysplasia

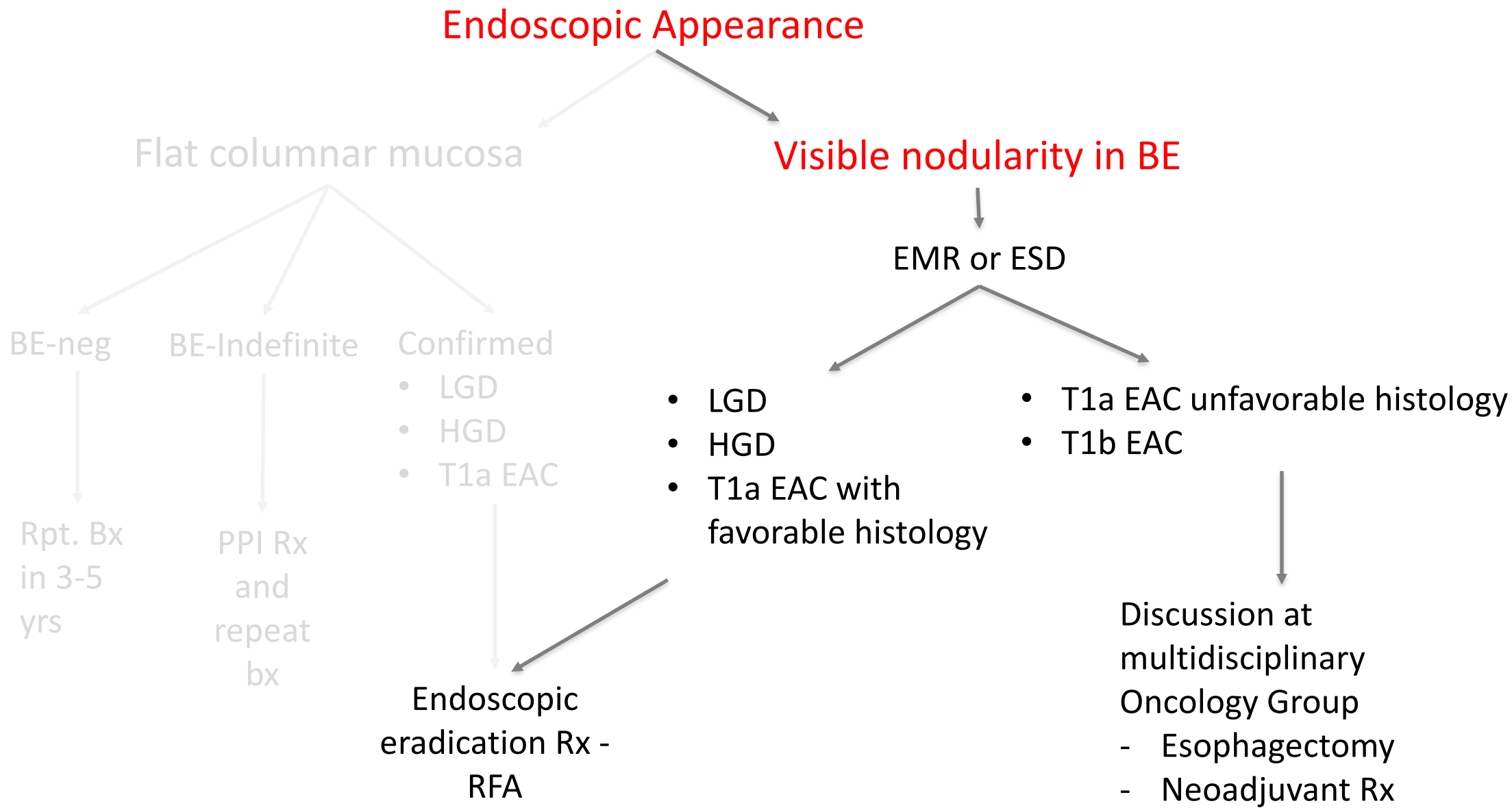


Reactive Cardiac Mucosa



Patil DT et al. Hum Pathol 2013

Surveillance and Treatment Guidelines

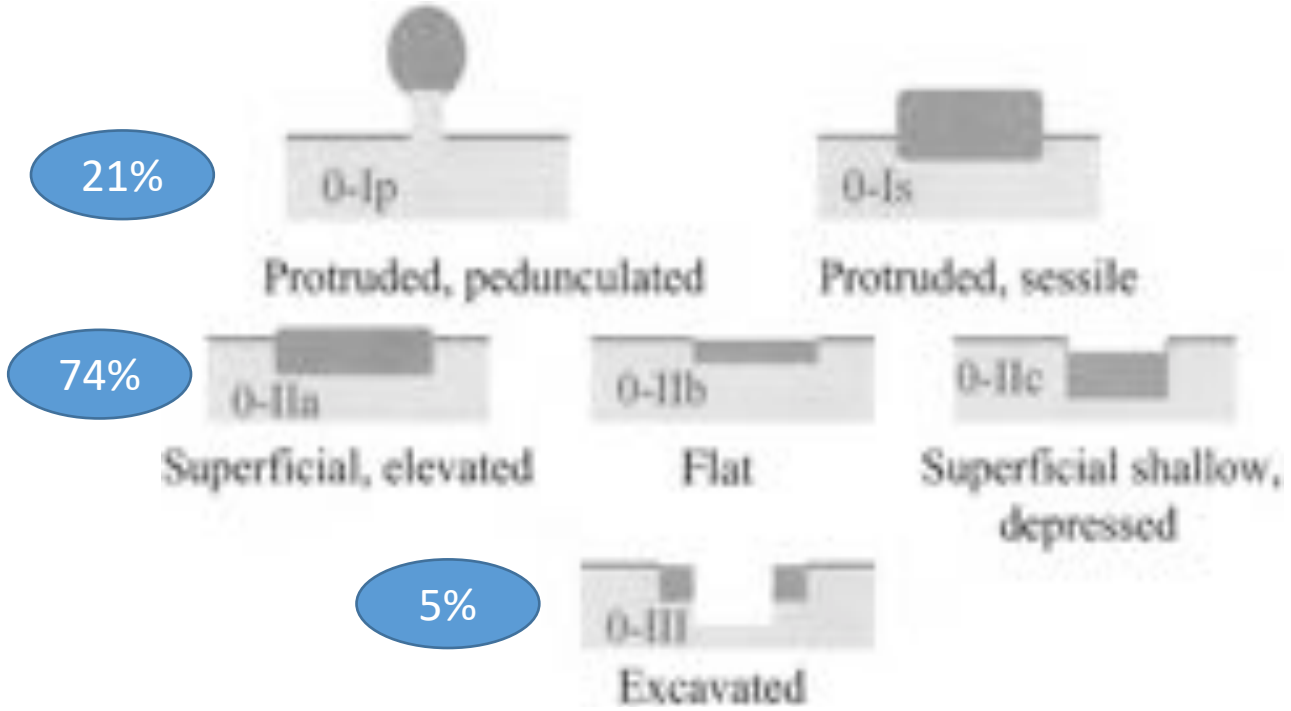


Shaheen N et al. Am J Gastroenterol 2016; 111:30–50

Visible Lesions In BE

- Nodules, ulcers, depressions and abnormal surface patterns are more likely to harbor dysplasia and early neoplasia
- EMR/ESD
  - Better interobserver diagnostic reproducibility
  - Better accuracy in staging early neoplasia
  - Upstaging or downstaging neoplasia in 20 – 30% cases

PARIS ENDOSCOPIC CLASSIFICATION

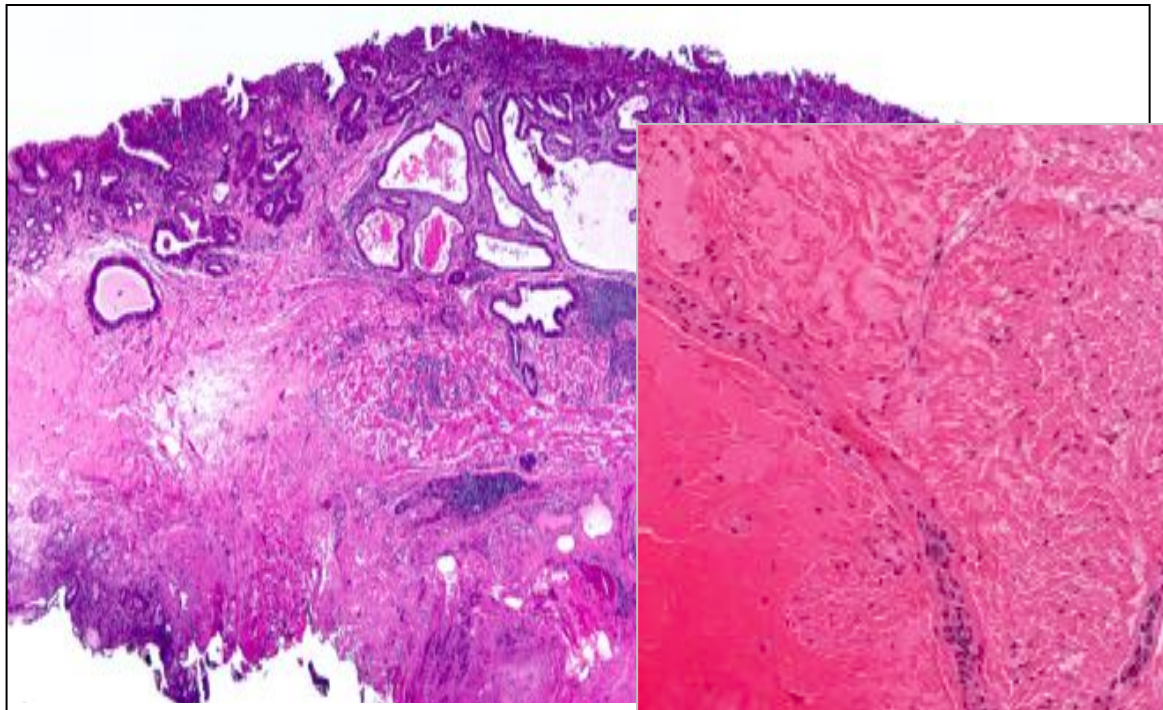


Ell C Gastroenterology 2000

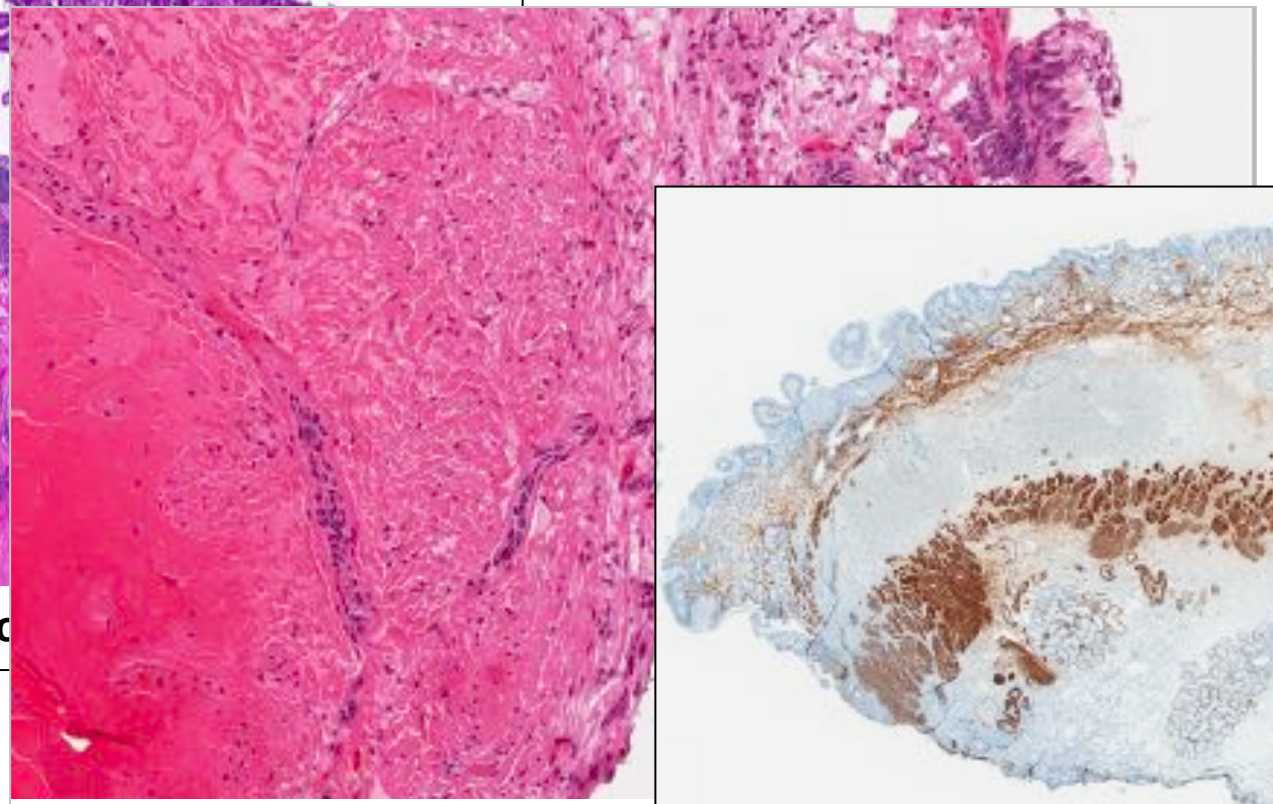
Levine DS 1993
Buttar NS Gastroenterology 2001
Montogomery E Am J Gastroenterol 2002
Konda V Clin Gastroenterol and Hepatol 2008
Wang V 2009

Endoscopic Resection of Visible Lesions – What does this mean for Pathologists?

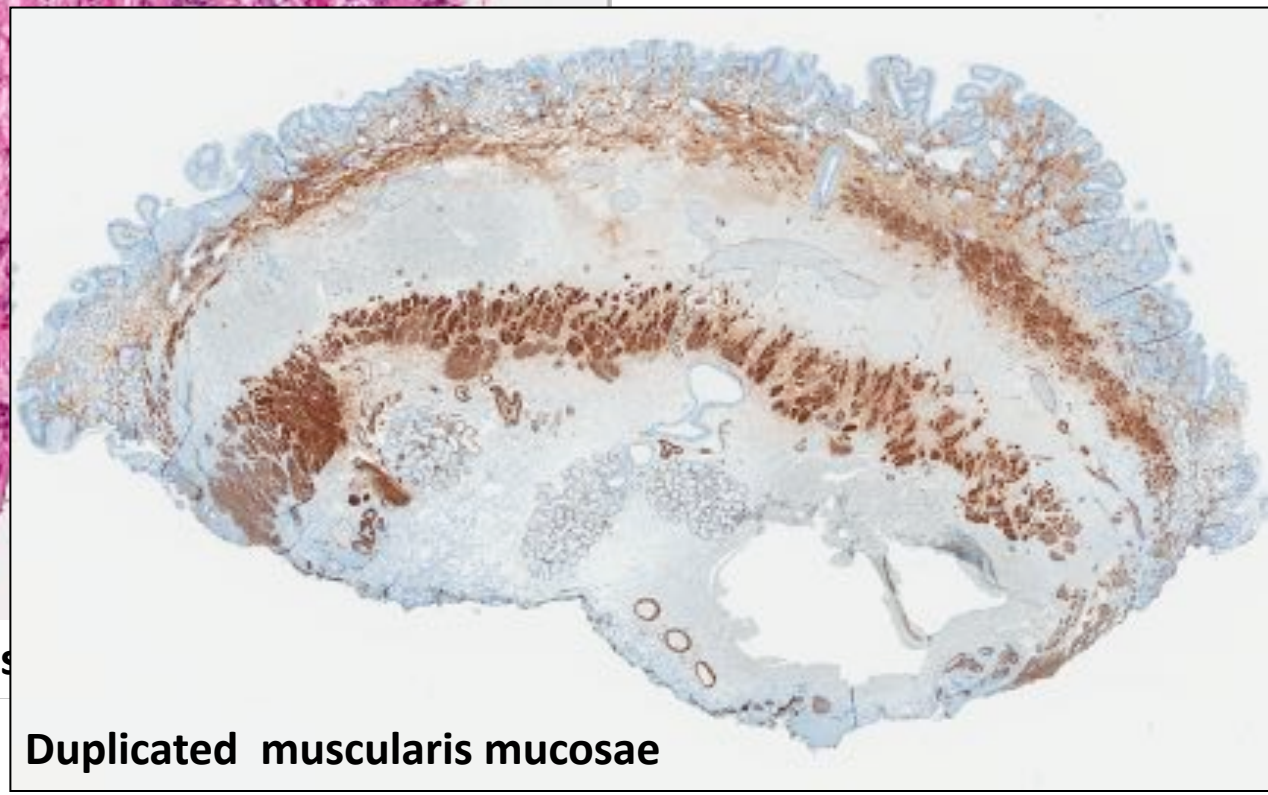
EMR



Optimal fixation and orientatic

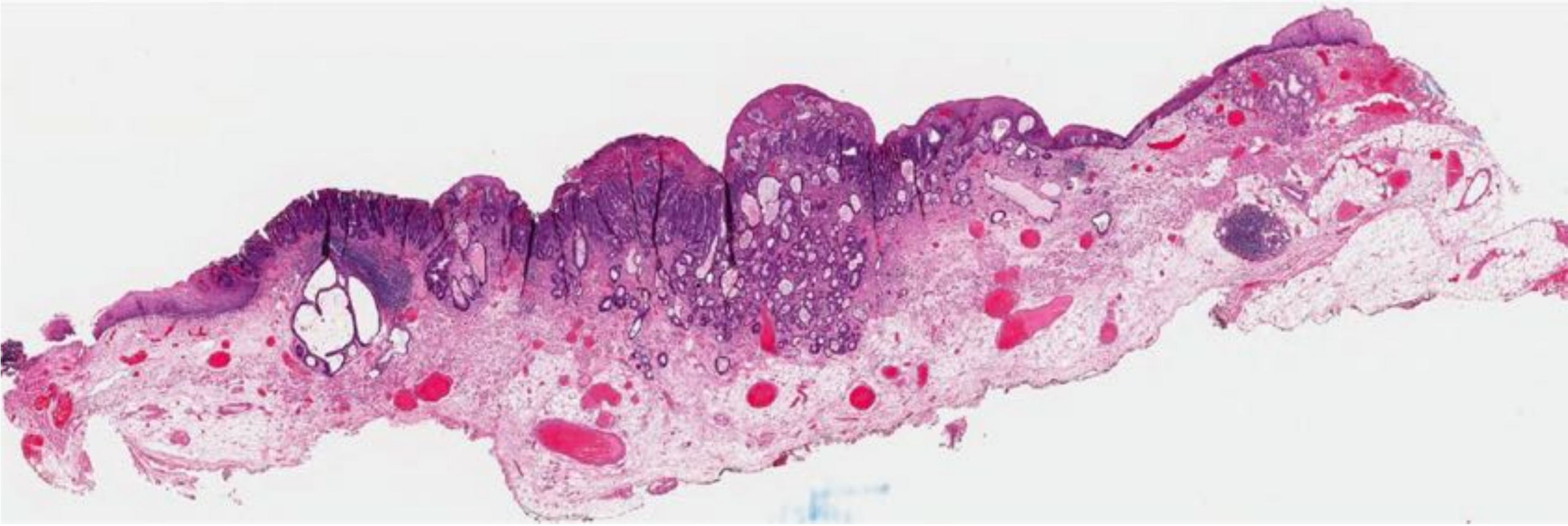


Thermal artifact at lateral edges



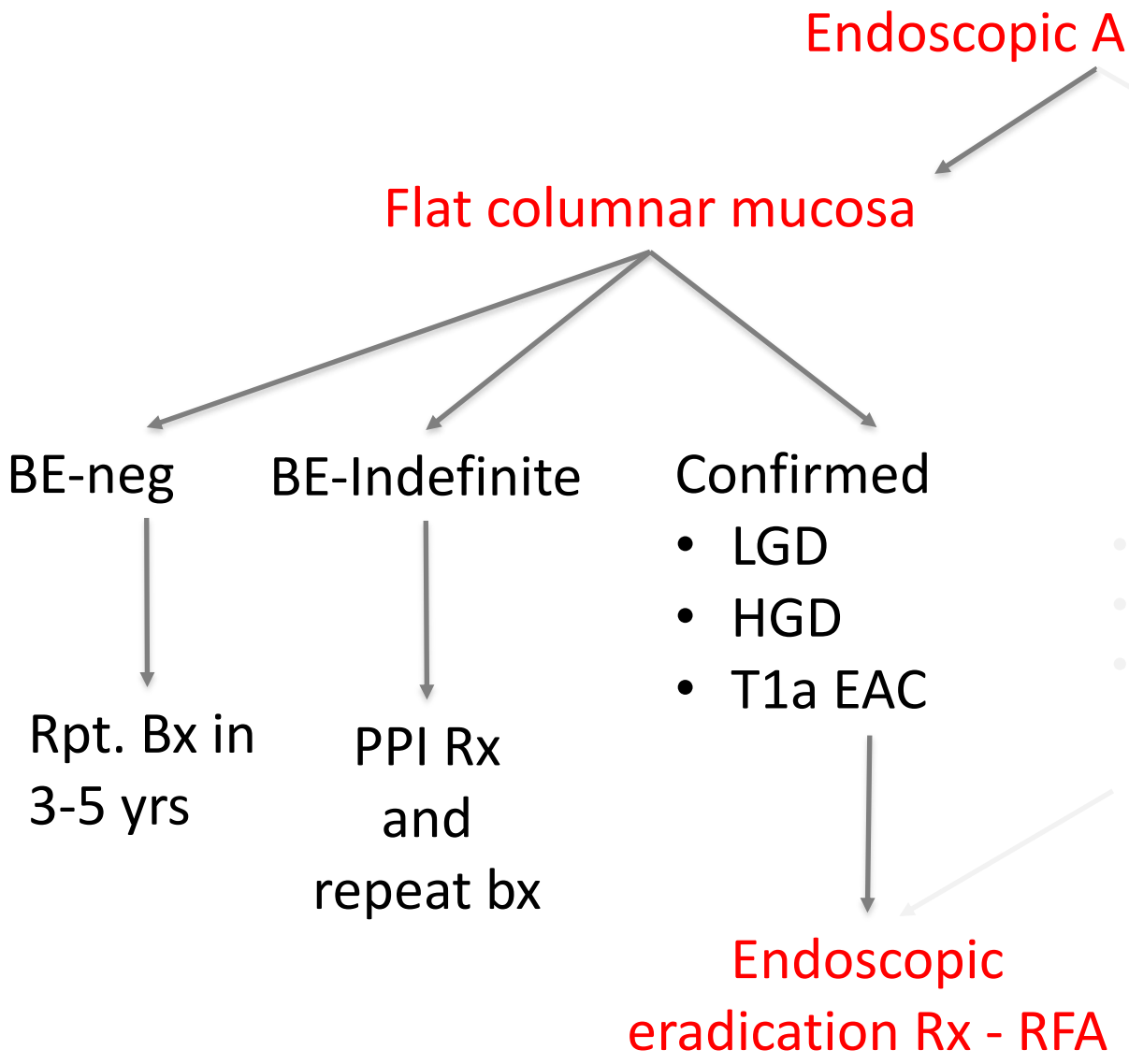
Duplicated muscularis mucosae

Endoscopic Submucosal Dissection



- Indications: Larger lesion (> 2cm), nodular lesion involving < 2/3rd the circumference of esophagus, Paris type I or II lesion with possible submucosal invasion
- T1b cancer: Documenting depth of submucosal invasion in microns (<500 microns – low risk of LN mets)

Surveillance and Treatment Guidelines



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RFA for Flat Neoplasia

- U.S-based multicenter, prospective, randomized, sham-controlled trial
- 127 patients (64 with LGD) were randomized (84-RFA, 43 Sham)
- 1 yr follow-up: Complete eradication of LGD RFA- 90% vs Sham-23% ($p<0.001$)

Table 2. Two- and Three-Year Outcomes of the AIM Dysplasia Trial

	CE-IM (entire cohort)		CE-D (HGD cohort)		CE-D (LGD cohort)	
	n	%	n	%	n	%
Year 2	99/106	93	50/54	95	51/52	98
Year 3	51/56	91	23/24	96	32/32	100

CE-IM and CE-D, allowing for interim focal touch-up RFA.

Shaheen N Gastroenterology 2011

RFA for Flat Neoplasia

- European multicenter randomized control trial (Surveillance vs RFA study)
- 136 patients with BE-LGD

Phoa KN JAMA 2014

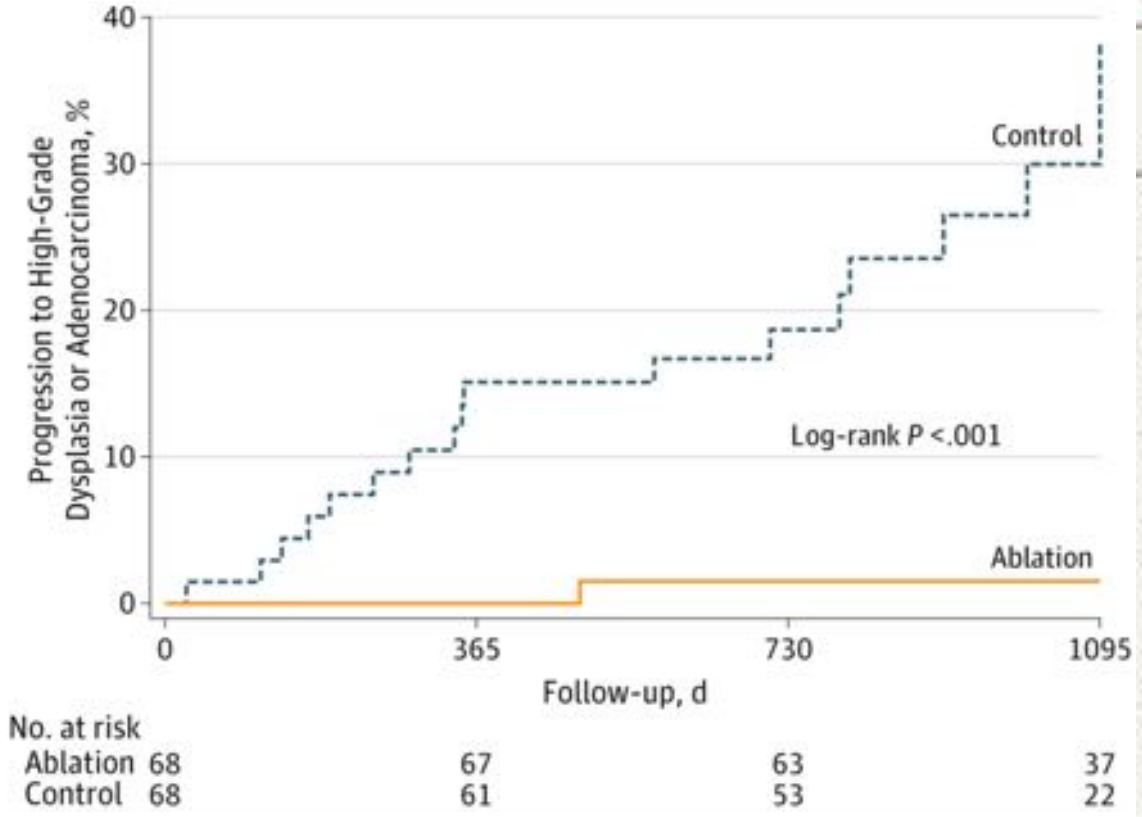


Table 2. Primary and Secondary Efficacy Outcomes

Efficacy Outcomes	No. of Patients (%) Ablation Group (n = 68)	Control Group (n = 68)	Risk Difference, % (95% CI)	P Value
Progression to high-grade dysplasia or cancer	1 (1.5)	18 (26.5)	25.0 (14.1-35.9)	<.001[a]
Progression to cancer	1 (1.5)	6 (8.8)	7.4 (0.0-14.7)	.03[a]
Complete eradication of dysplasia at the end of endoscopic treatment	63/68 (92.6)[b]			NA
Complete eradication of IM at the end of endoscopic treatment	60/68 (88.2)[b]			NA
Complete eradication of dysplasia during follow-up, No. of events/total patients (%)[c]	62/63 (98.4)[b]	19/68 (27.9)	70.5 (59.4-81.6)	<.001
Complete eradication of IM during follow-up, No. of events/total patients (%)[c]	54/60 (90.0)[b]	0/68 (0.0)	90.0 (82.4-97.6)	<.001

Provocative Questions:

- Since therapy for LGD and HGD is converging and the apparent poor diagnostic reproducibility, do we need to grade dysplasia?
- Should we categorize dysplasia into negative, indefinite and positive for dysplasia (simplified grading system)?

Simplified Grading System - Pros

- Improve diagnostic reproducibility among expert and community pathologists
- Efficient triaging of patients for endoscopic therapy, potentially reducing time to treat neoplasia

Improved Diagnostic Reproducibility

- Montgomery et al. 2001
  - Grouped as 3 categories: NEG, IND/LGD and HGD/Ca
  - Intraobserver agreement: 0.67 (substantial)
  - Interobserver agreement: 0.48 (moderate)
- Salomao et al. 2017

Diagnosis	Kappa (by pt)	Kappa (by biopsy jar)	Diagnosis	Kappa (by pt)	Kappa (by biopsy jar)
Overall	0.54	0.48	Overall	0.59	0.55
NEG	0.66	0.61	NEG	0.66	0.61
IND	0.21	0.08	IND	0.21	0.08
LGD	0.31	0.30	Positive for Dysplasia	0.70	0.65
HGD	0.76	0.66			

Simplified Grading System - Cons

- Impact on outcome-based studies
- Post-RFA surveillance – ACG guidelines
- Post-RFA – Sampling and diagnostic issues
- Post-RFA – Unanswered questions

Simplified Grading System – Cons: Outcome-based Studies

- Outcome based studies (progressors vs non-progressors) are defined based on HGD/Ca as the end-point
- IND is often combined with LGD
- Inability to compare data across studies that have allowed us to study natural history of BE and neoplastic progression

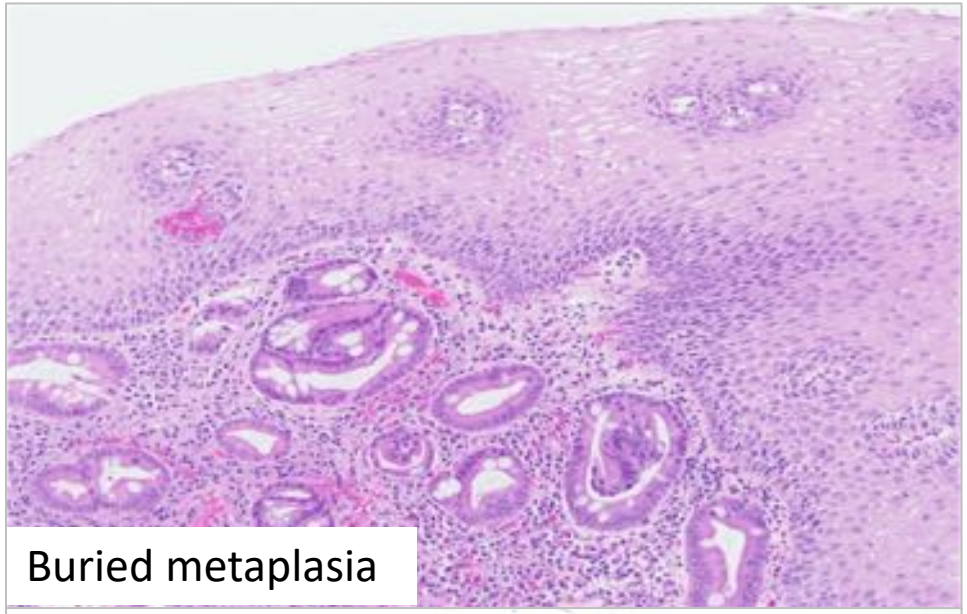
Biomarker	Category	Clinical Trial	Outcome	Comment
Trefoil factor -3	Diagnosis	Phase 4	Promising data	
FISH	Risk stratification Response to Rx	Phase 3 and 4	Promising data	C-MYC, HER2, p53, ZNF-11, p16
DNA content abnormalities/ Aneuploidy	Risk stratification	No clinical trial	Potential biomarker	
Methylation	Risk stratification	Phase 2, 3, 4	Inconsistent data	p16, RUNX3, MGMT, SFRP1, TIMP3, and CDH13
MicroRNA	Diagnosis	Phase 2	Promising data	miRNAs -192, -215, -194, -205, and -203
P53	Diagnosis Response to Rx	Phase 4	Promising data, Not helpful for predicting response	
Clonal diversity	Risk stratification	Phase 2	Promising data	Computationally challenging
Proliferation markers	Risk stratification	No trial	Limited use	

Simplified Grading System – Cons: Post-RFA Surveillance

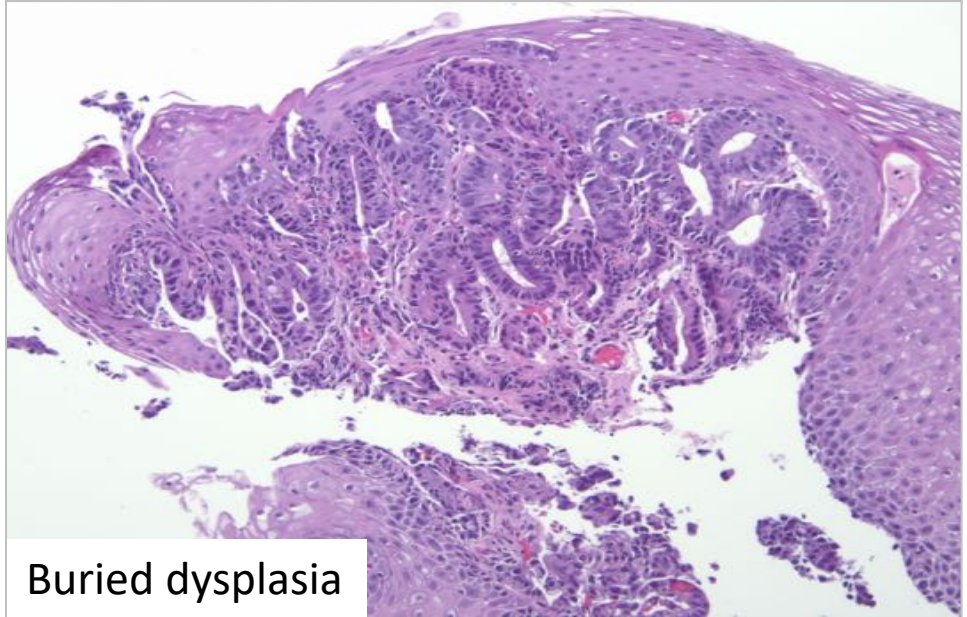
- Post-RFA surveillance
  - Recurrence rate of IM 20% - 39.5%
  - Recurrence rate of dysplasia – up to 25%
- ACG guidelines surveillance recommendation is based on baseline grade of dysplasia
  - Baseline HGD – every 3 months in 1st year, 6 months in 2nd year and annually thereafter
  - Baseline LGD – 6 months in 1st year and annually thereafter

Post-RFA: Sampling and Diagnostic Issues

- Inadequate amount of lamina propria
- Lack of endoscopic features that d/d neosquamous from native squamous epithelium
- Potential for increased interobserver variability in diagnosing buried metaplasia and dysplasia
- Recurrence of IM is more common at GEJ post-RFA – change in surveillance?
- Therapy?



Buried metaplasia



Buried dysplasia

Simplified Grading System – Cons: Unanswered Questions

- Does persistent LGD following ablation therapy carry similar prognosis to persistent HGD/Ca?
- What about molecular alterations in residual BE and residual dysplasia? Are these similar to native BE and native dysplasia?
- What are the predictors of recurrence of LGD and HGD/Ca post-RFA?

THANK YOU