Selected Topics in Barrett's Esophagus (And Not A Focus on Dysplasia!)

GIPS Companion Society – USCAP 2019

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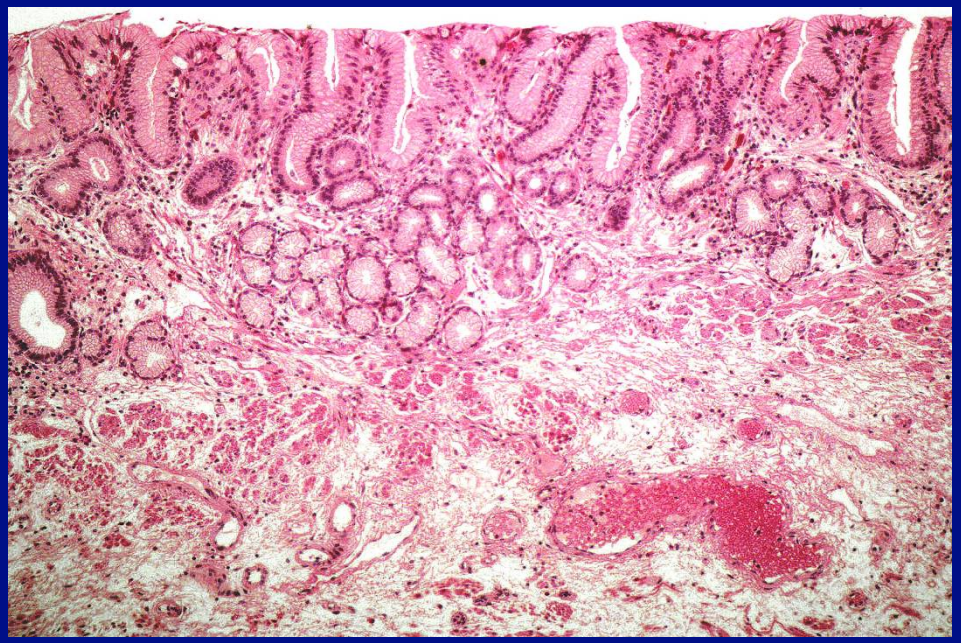
Topics of Discussion

- Definition(s) of Barrett's esophagus
- The necessity of goblet cells for a diagnosis of BE?
- Post-radiofrequency ablation (RFA) biopsies

This biopsy is from the “esophagus at 38;” which of the following statements is true?



A. In the US, this is diagnostic of BE
B. Goblet cells are the predominant columnar cell type depicted
C. This mucosa type may be seen in a patient with BE

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

Barrett's Esophagus ACG Definition

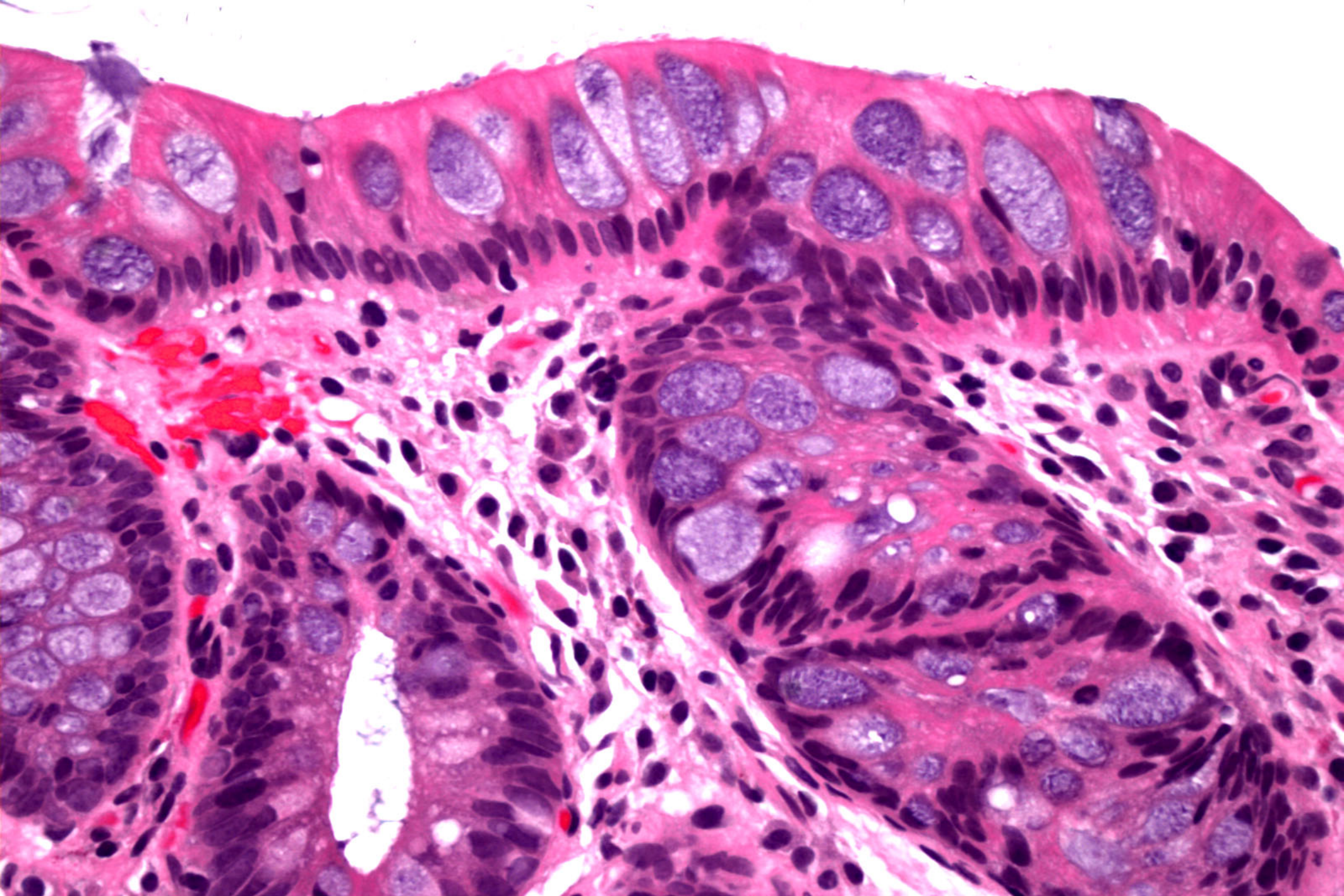
- A change in the esophageal epithelium of any length that can be
  - recognized at endoscopy
  - confirmed to have intestinal metaplasia by biopsy

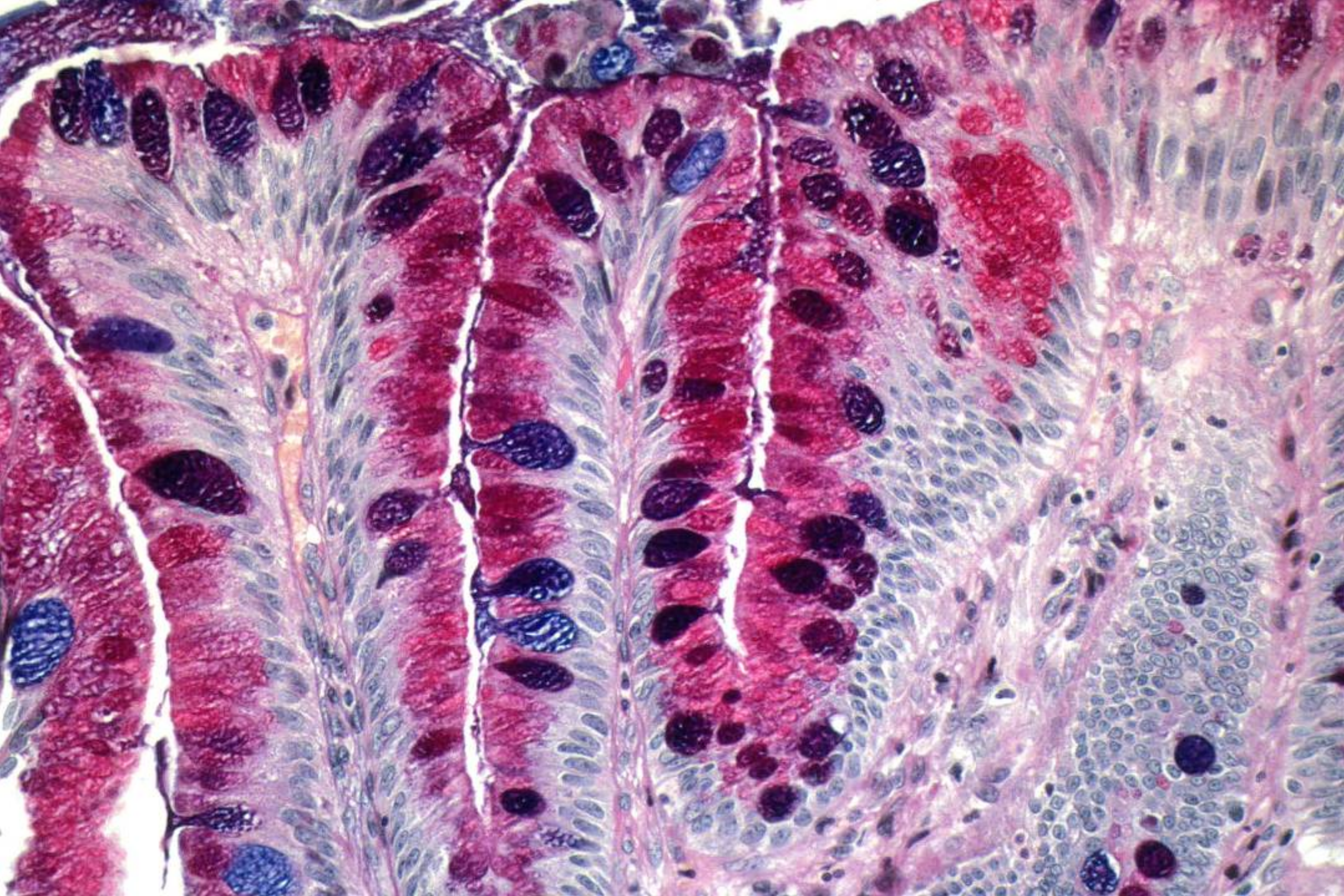
Sampliner RE et al. Am J Gastroenterol 2008

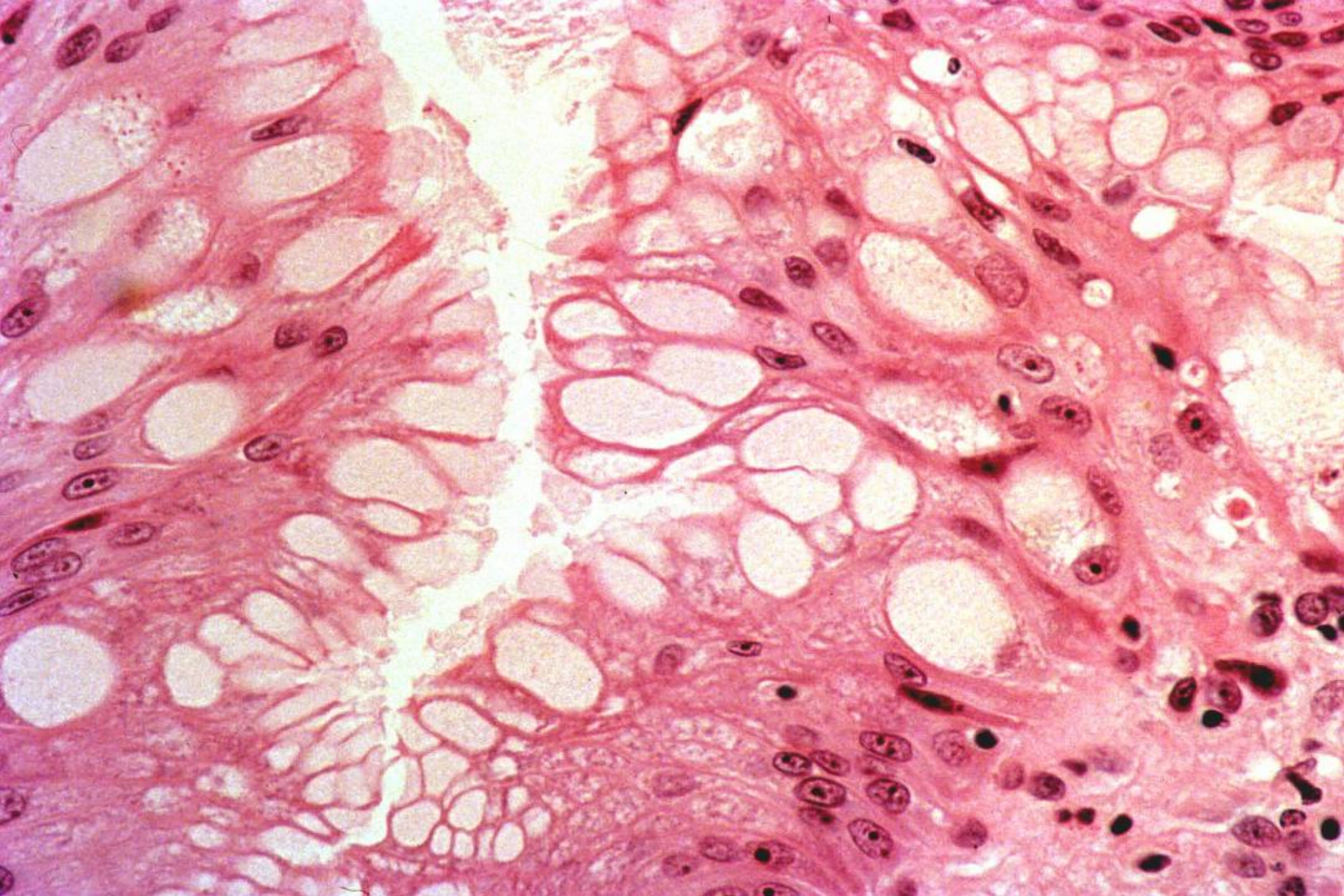
Newest Definition of BE: ACG 2016

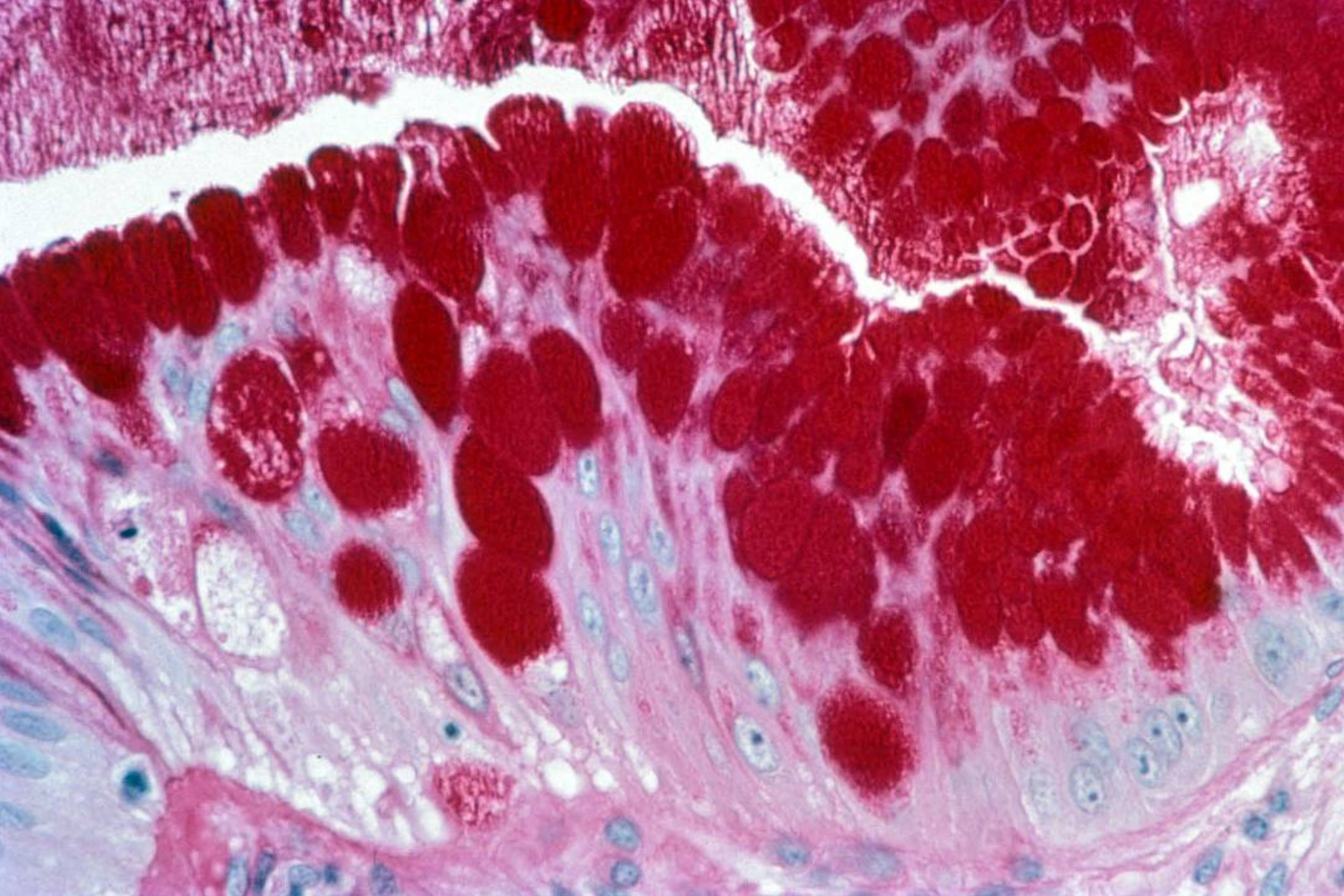
- BE should be diagnosed when there is extension of salmon-colored mucosa (CLE) into the tubular esophagus extending ≥ 1 cm proximal to the EGJ with biopsy confirmation of IM
  - Biopsy should NOT be performed in the presence of a normal Z-line or a Z-line with < 1 cm of variability

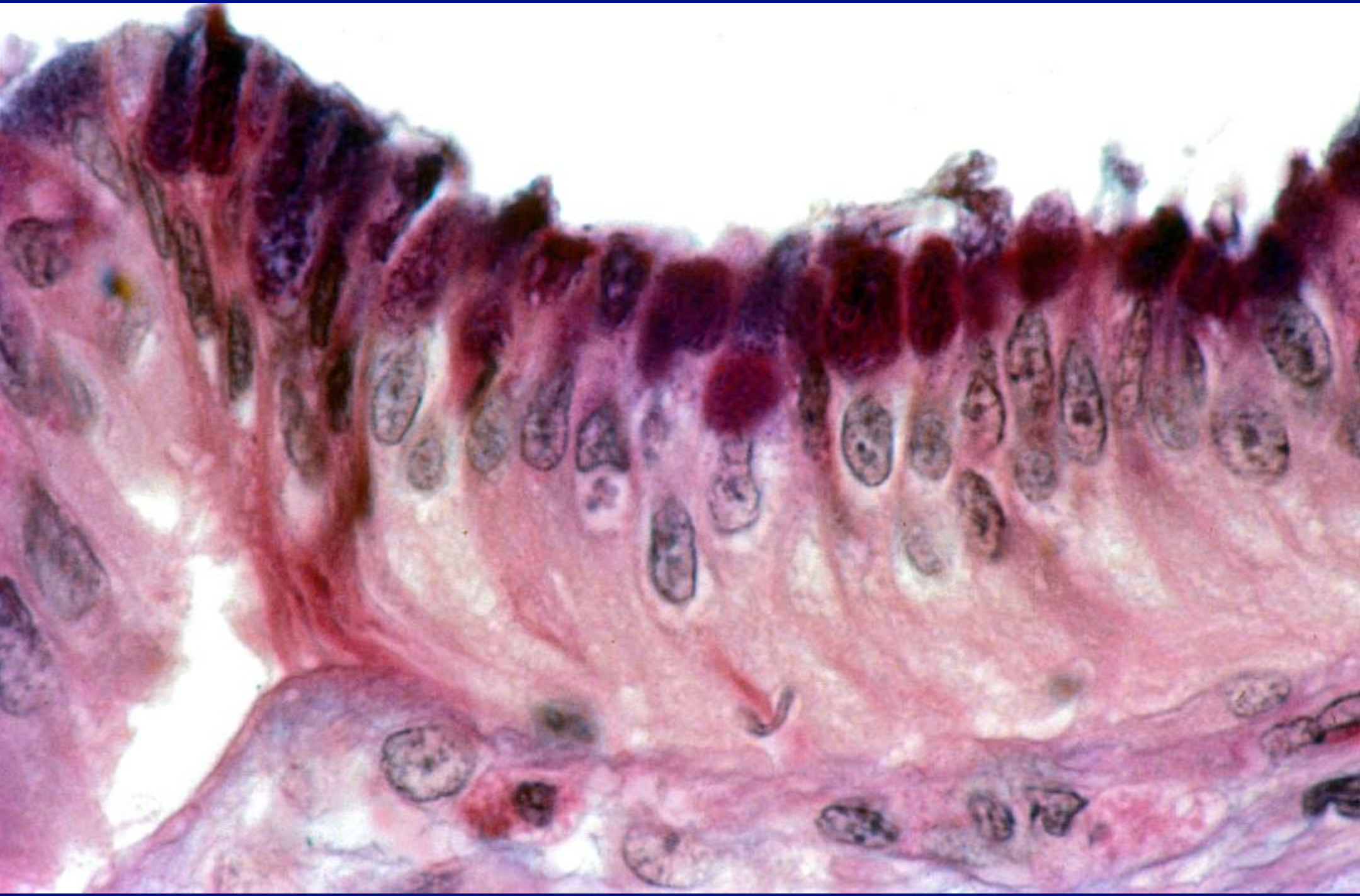
Shaheen N et al. AJG 2016





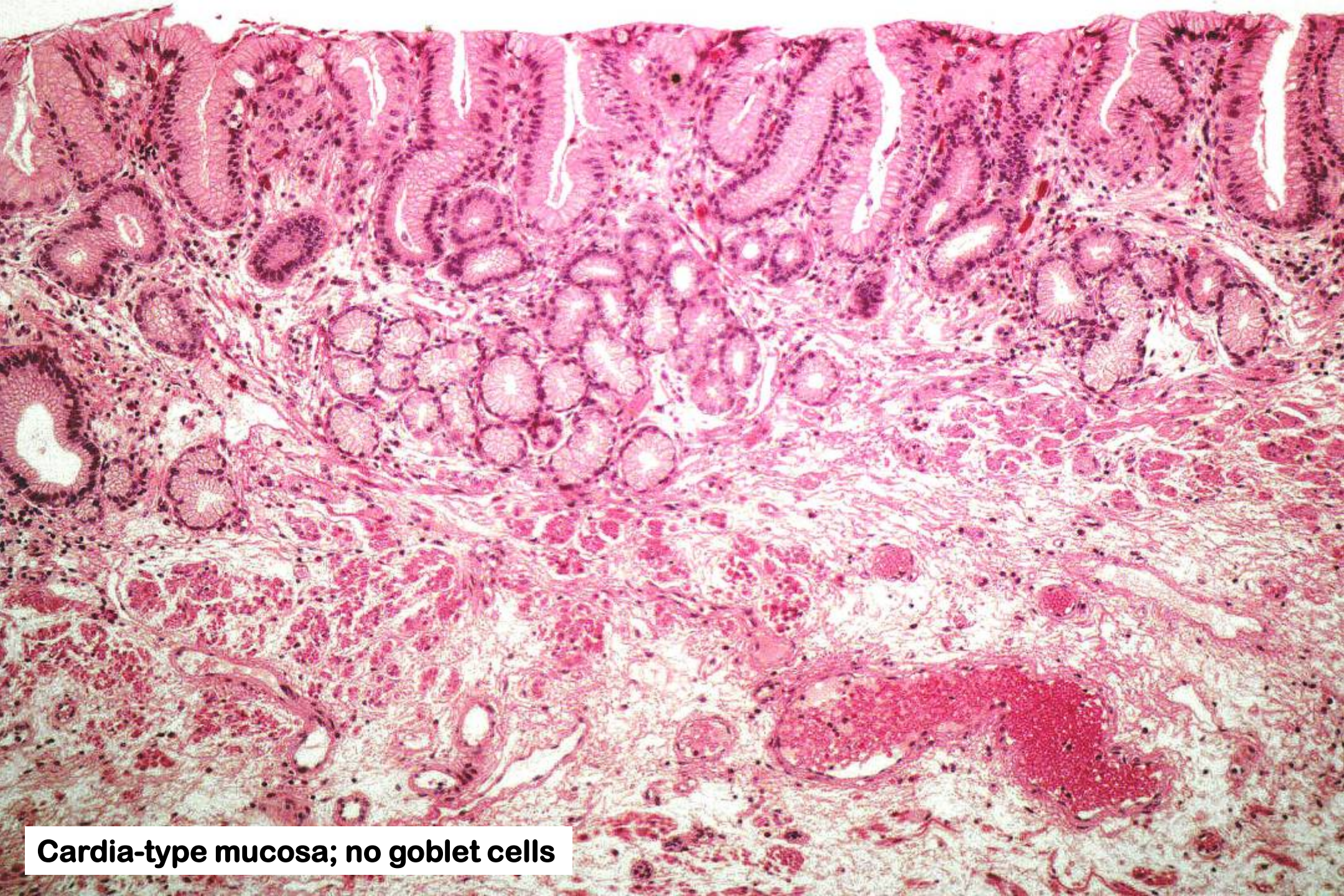






Types of Epithelium in BE

- Intestinalized type (goblet cells)
- Cardiac-type (resembles native gastric cardia)
- Fundic-type (resembles native gastric fundus)


Cardia-type mucosa; no goblet cells

ACG: Why are goblet cells required for BE?

- BE should be defined by the type of mucosa which actually predisposes to dysplasia/cancer

- Historical date (mostly from esophagectomies) suggest it is INTESTINALIZED MUCOSA which predisposes to dysplasia/cancer

    - Older US studies ⟶ IM virtually always found in esophagectomy done for esophageal adenocarcinoma

Esophagectomy Studies
Prevalence of IM

Author	Year	Country	No of patients	IM
Skinner	1983	US	20	20/20
Cameron	1995	US	9	9/9
Rosenberg	1985	US	9	9/9
Van Sandick	2000	Netherlands	32	32/32
Ruol	2000	Italy	26	25/26
Paraf	1995	France	67	66/67
Total				161/163 (98.8%)

Endoscopic Mucosal Resection Studies

- 27 EMRs in 21 patients
  - HGD only N=1
  - IMC N=17
  - SMC N=9
- 17/27 EMRs had IM
  - Non-dysplastic CLE adjacent to cancer N=14
  - Surrounding CLE but not adjacent to cancer N=1
  - Beneath squamous mucosa or cancer N=2

Smith J et al. AJSP, 2016

Endoscopic Mucosal Resection Studies

What about the other 10 EMRs without IM?

- **3 had IM in another EMR done at same endoscopy**
- **4 had IM in biopsies done prior to the EMR**
- **2 had IM in esophagectomy done after the EMR**

***1 patient had**

- **No IM in EMR specimen**
- **No IM in biopsies done prior to the EMR**
- **No IM in the esophagectomy done after the EMR**

Smith J et al. AJSP, 2016

Definition of BE in the US: Necessity of Goblet Cells

- 139 consecutive patients with esophageal adenocarcinoma at Johns Hopkins (EMR/resection)
- Assessment for goblet cells around the cancer (at interface; not totally submitted)
  - Goblet cells: 79/139 (70%)
    - Goblet cells identified: 31% pT3 or greater
    - No goblet cells identified: 57% pT3 or greater

    } p=0.02
- 39 “treatment naïve” patients
  - Goblet cells: 34/39 (87%)
    - 2 additional patients had goblet cells on prior biopsies

      ➡ 36/39 (92%)
    - 2 patients with pT3 (possible overgrowth of goblet cells)

Conclusion: The US definition of BE should continue to require goblet cells

Salimian KJ et al. AJSP 2018

Definition of BE (UK)
British Society of Gastroenterology

“Barrett’s oesophagus is an oesophagus in which any portion of the normal squamous lining has been replaced by a metaplastic columnar epithelium which is visible macroscopically”

Fitzgerald et al. Gut, 2014

BSG: Why are goblet cells not required for BE?

- CLE without IM has biologic characteristics similar to CLE with IM
  - Immunohistochemical similarities (CDX2, villin, DAS-1)
  - DNA flow cytometric similarities

- Esophageal adenocarcinoma may arise without identification of IM and therefore IM is not a required step
  - Biopsy studies
  - EMR studies
  - Esophagectomy studies

Endoscopic Mucosal Resection Studies Takubo et al

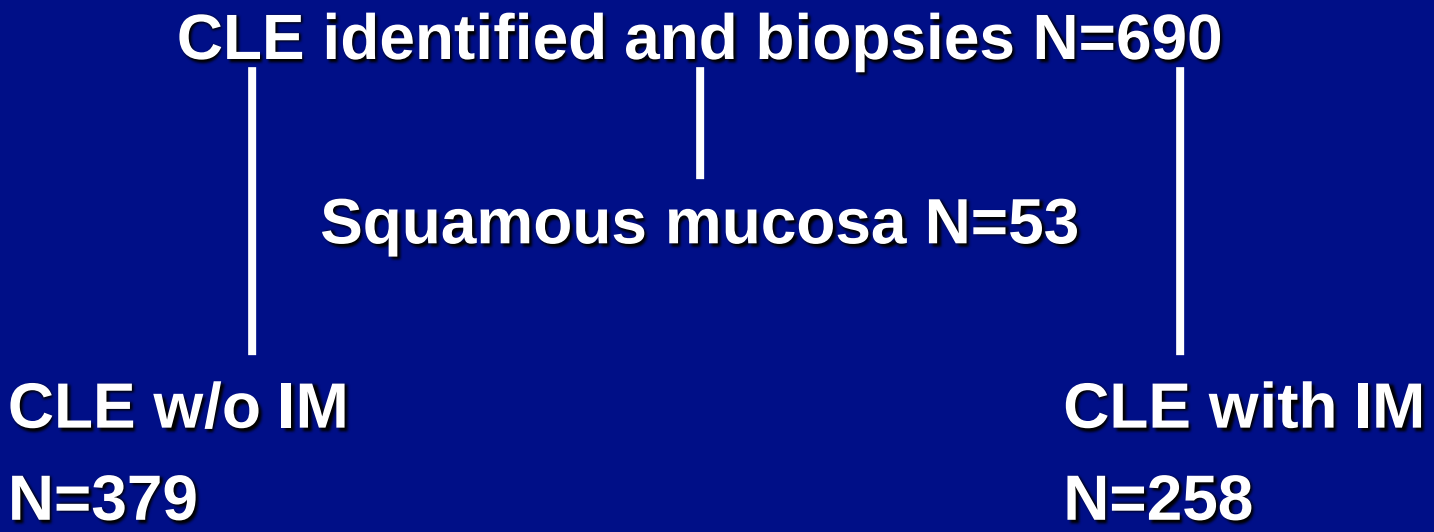
- 141 esophageal adenocarcinomas resected by EMR (all <2 cm tumors)
    - IM adjacent to the tumor 22%
    - IM anywhere in EMR 56%

Takubo et al. Hum Pathol, 2009

Why IM May Not Be Found Near Cancers Potential Explanations

- Sampling error
- Overgrowth of IM by dysplasia or tumor
- Truly not present

Effect of Dropping IM from BE Definition



BE definition with IM: 258/690 (37%) patients with CLE

BE definition without IM: 637/690 (92.3%) patients with CLE

***diagnosis of BE ↑ by 147% !!**

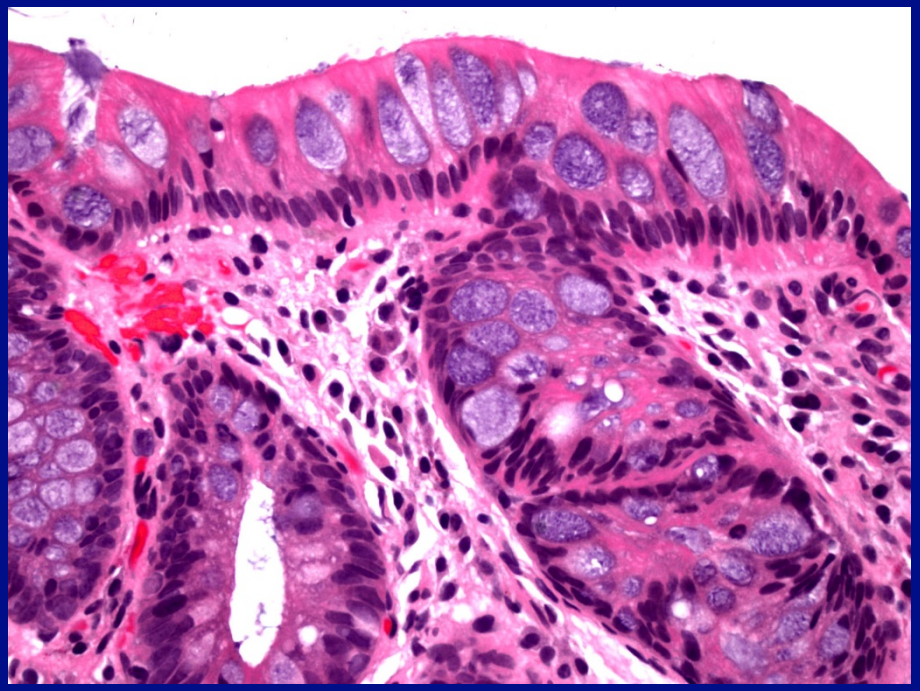
Westerhoff et al. Clin Gastroenterol Hepatol, 2012

My Conclusions

- CLE without IM: may not be completely benign, but no convincing evidence that risk is identical to CLE with IM
- With extensive sampling (and evaluation of a series of specimens over time), almost all patients with esophageal adenocarcinoma have evidence of IM

Smith et al: “Because of its potentially serious consequence, any change in the definition of BE should require persuasive and strong evidence.”

The Pathology Report



“Pathologists should avoid terms like ‘consistent with BE’ in their reports since this is a combined histologic/endoscopic diagnosis and most pathologists don’t receive adequate information about the EGD findings.”

“They may inadvertently handcuff their endoscopists and make them act in an overly aggressive manner, especially now that patients see their report in the EMR.”

Dr. Nicholas Shaheen

UNC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 28, 2009 VOL. 360 NO. 22

Radiofrequency Ablation in Barrett's Esophagus with Dysplasia

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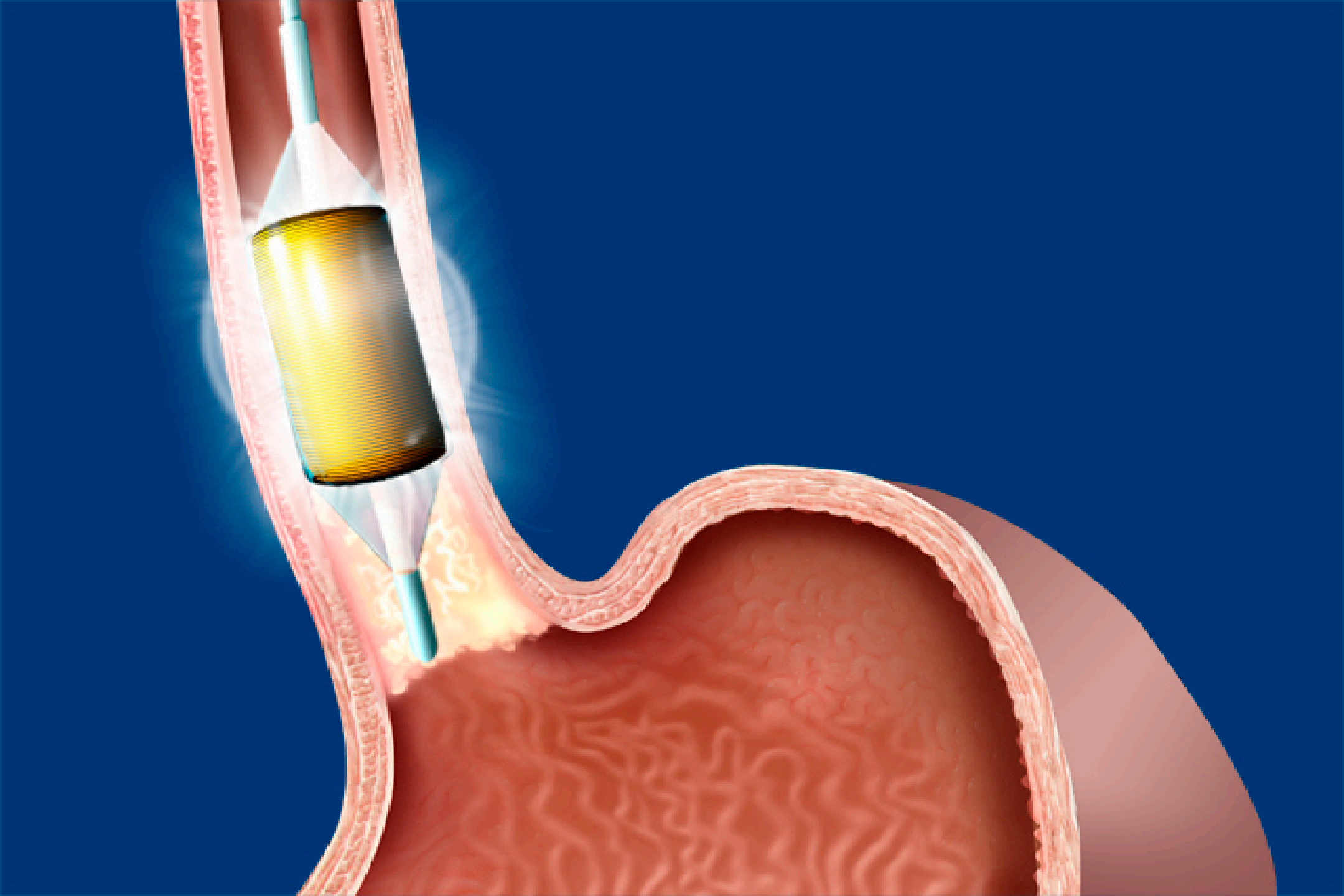
ABSTRACT

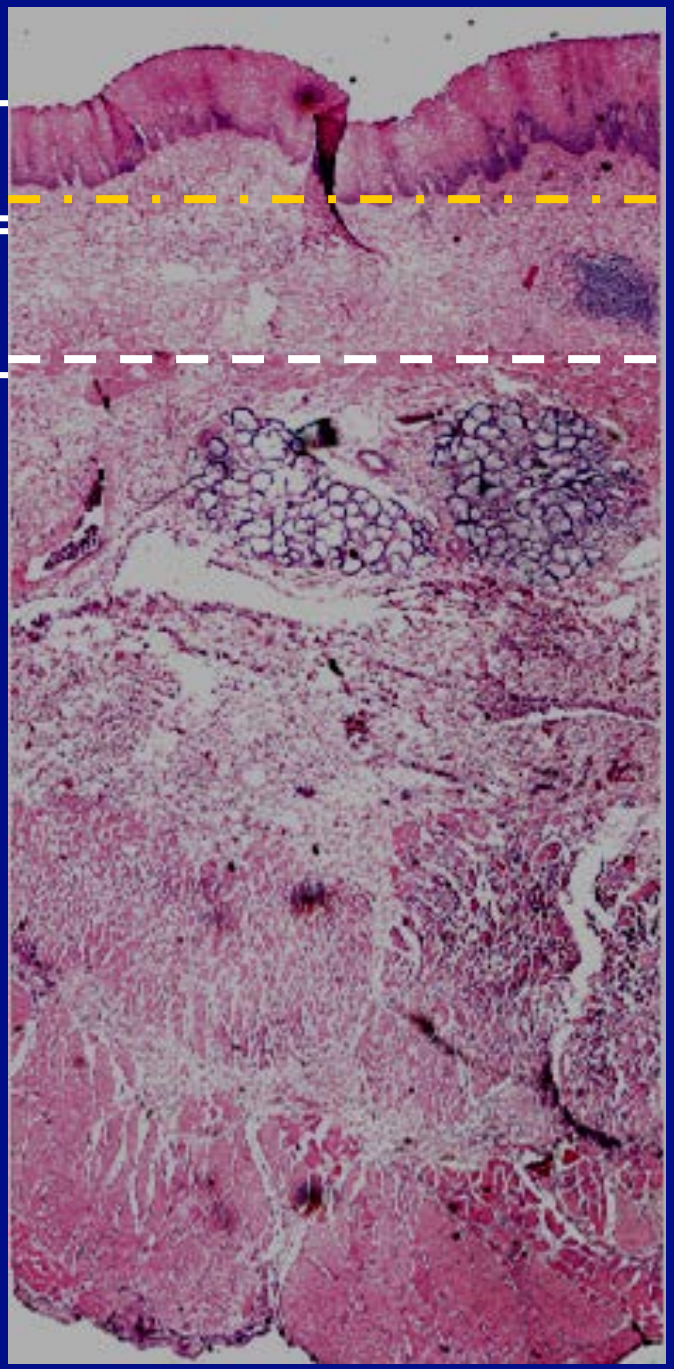


Anatomy and RFA

Targeted Epithelium
Thickness ~500µm

RFA
Ablation depth 500-1,000µm

Approximate EMR Depth



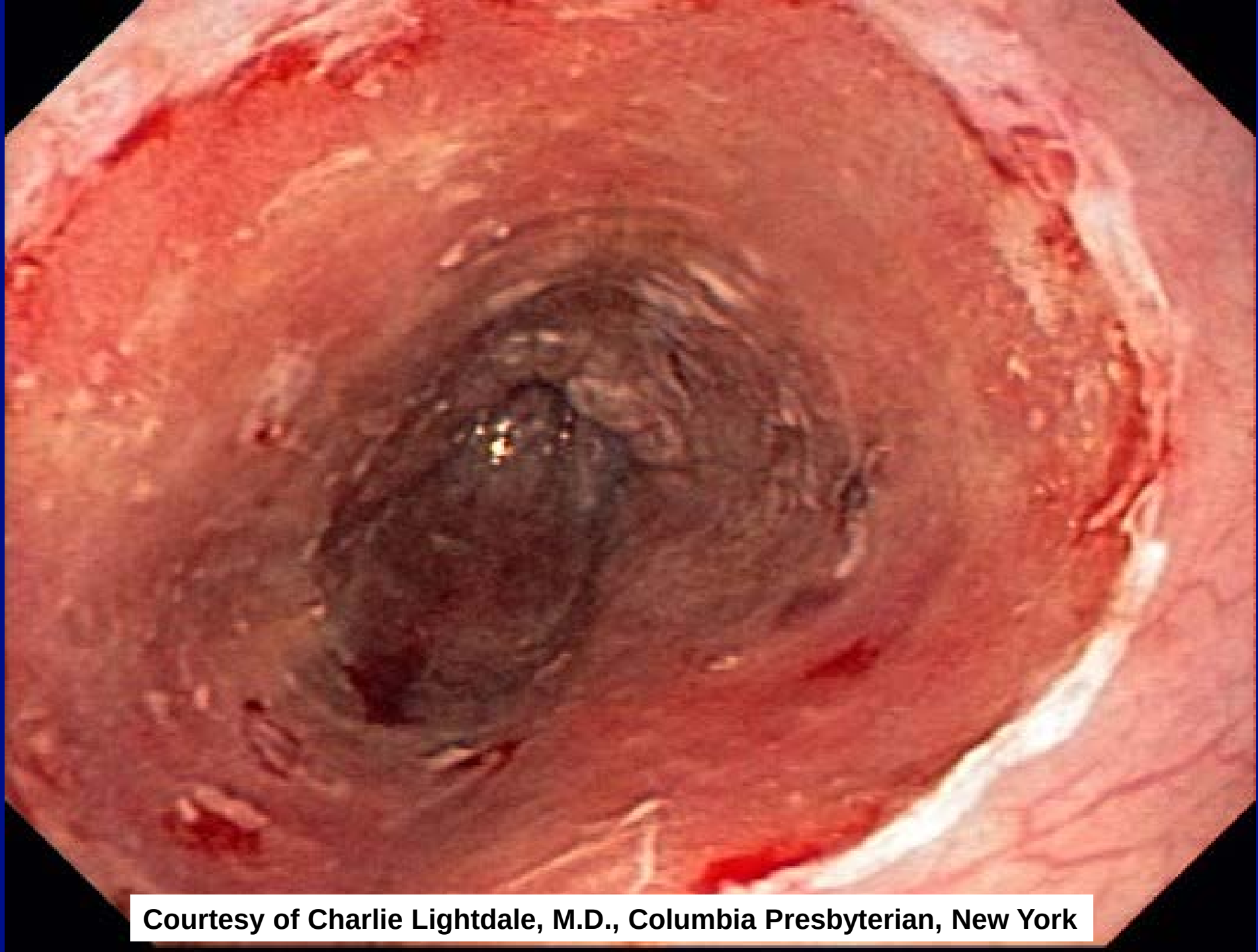
Esophageal epithelium ~500µm

Lamina Propria

Muscularis Mucosae

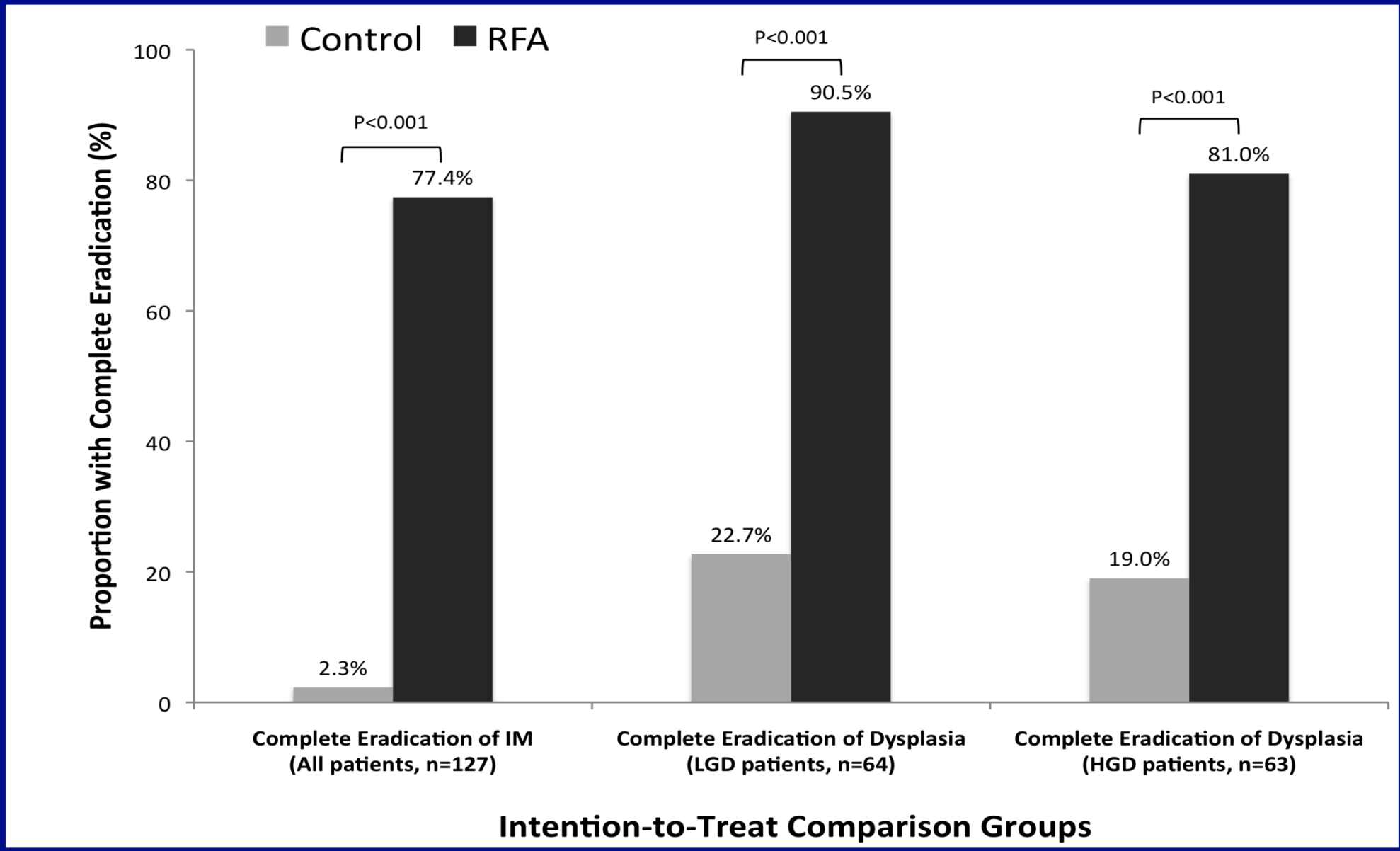
Submucosa

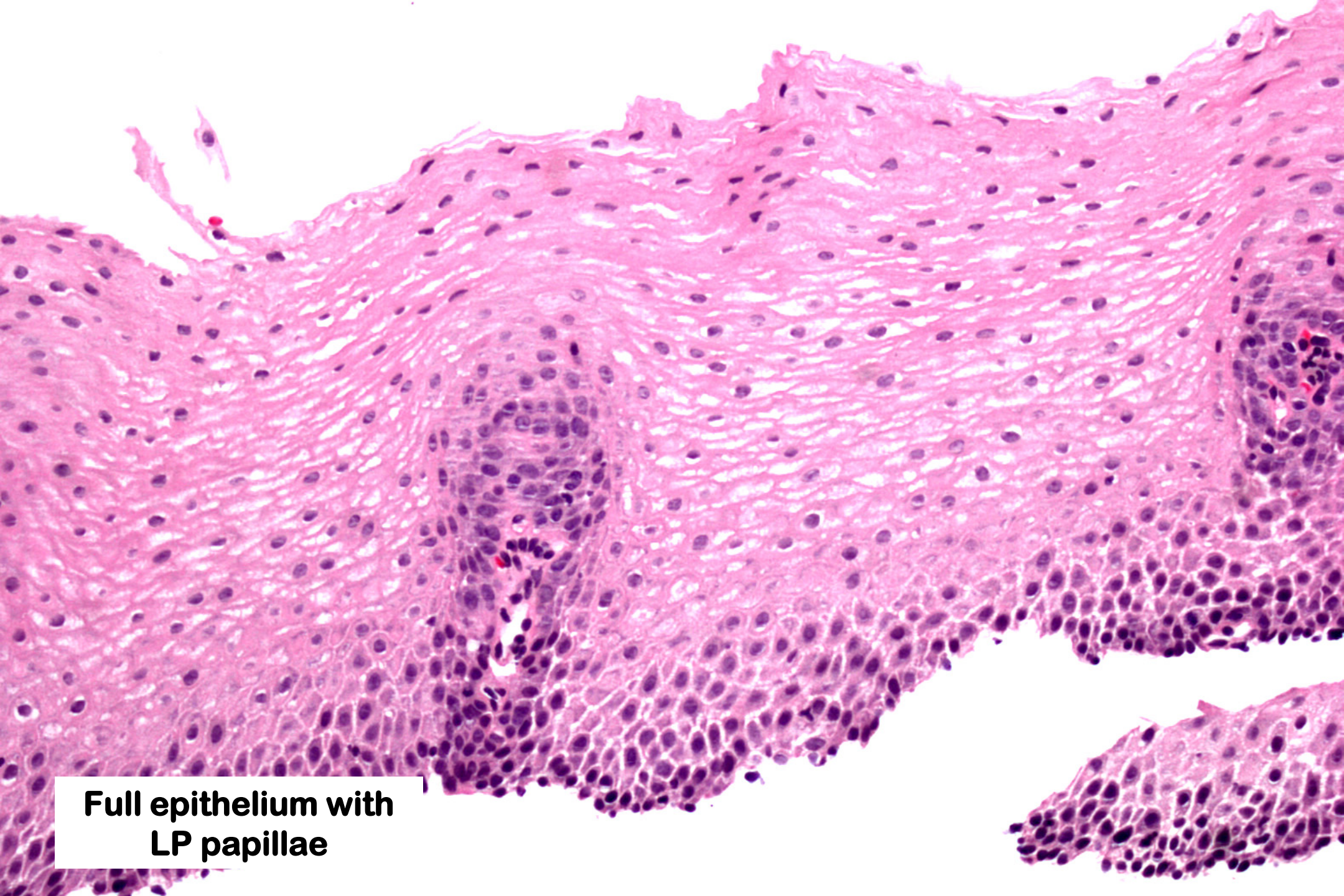
Muscularis Propria

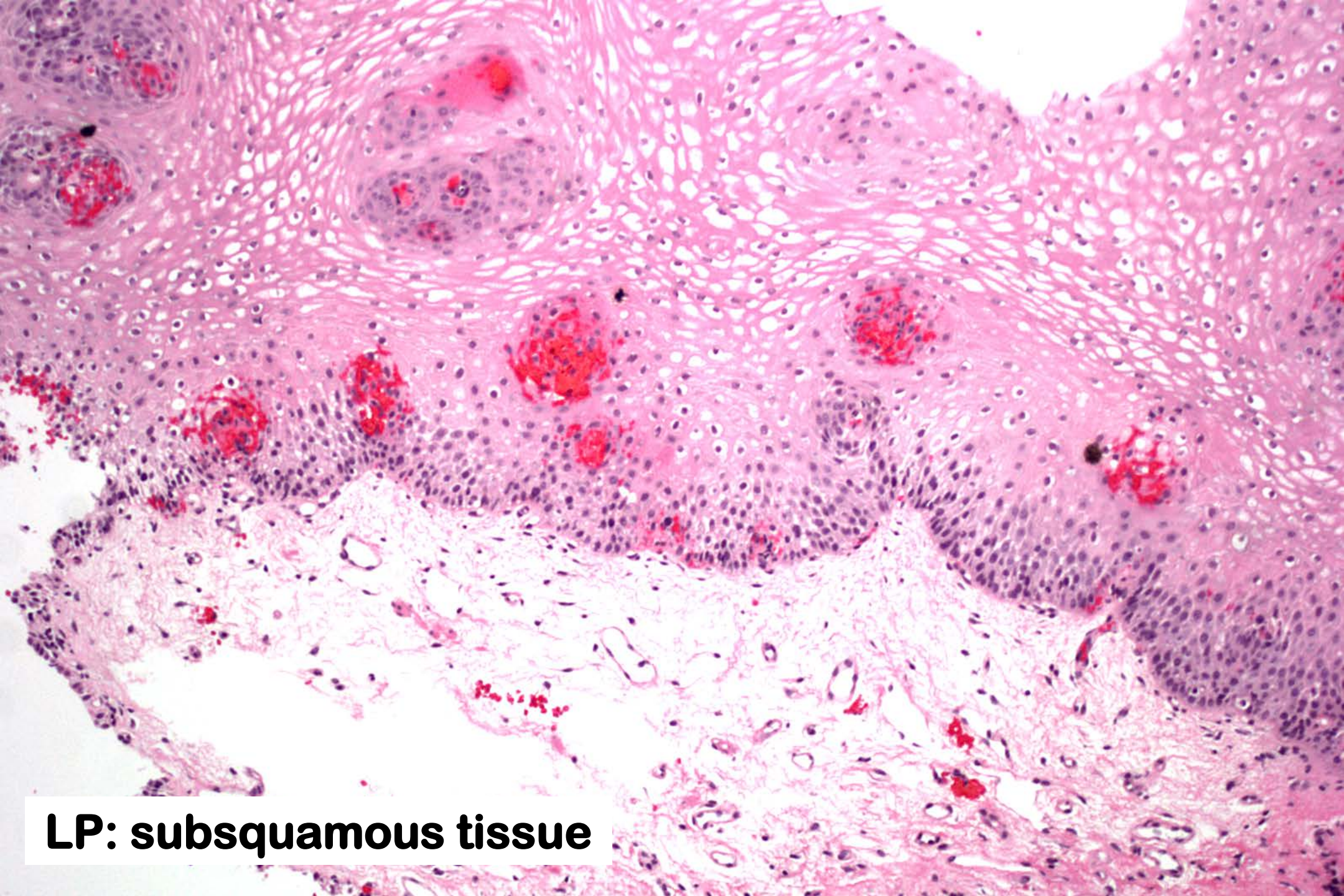


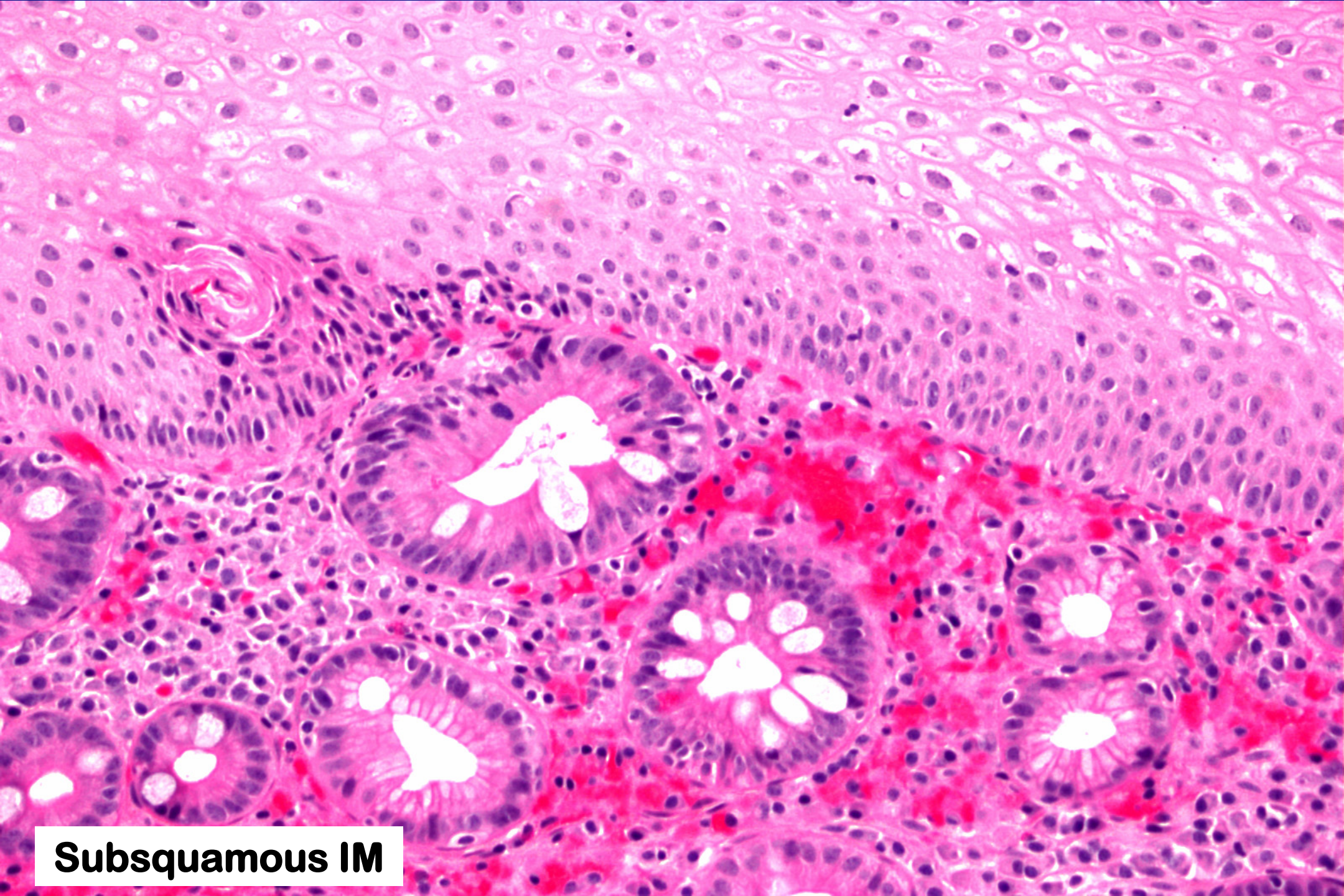
Courtesy of Charlie Lightdale, M.D., Columbia Presbyterian, New York

Complete Eradication (ITT)




Full epithelium with
LP papillae


LP: subsquamous tissue

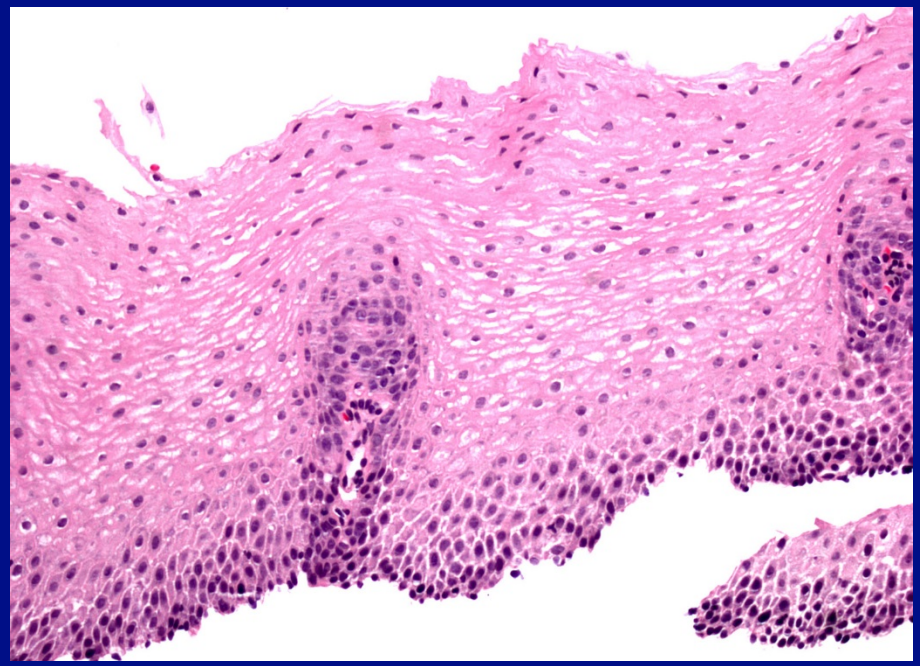

Subsquamous IM

Post-EMR Biopsy Depth

	Native Squamous (N=115)	Neo-Squamous (N=135)	p-value
Partial thickness epithelium	51%	10.7%	0.03
Full thickness epithelium	75.5%	77.5%	0.65
Lamina propria	19.4%	11.7%	0.07

Gupta N et al, AGA, 2018

Post-RFA Biopsies



“It is important to report whether there is any subsquamous tissue in the biopsies. Obviously, if the biopsies are really superficial, we can’t feel real good that we are assessing for subsquamous disease.”

Dr. Nicholas Shaheen
UNC

Post-Ablation Esophageal Eosinophilia

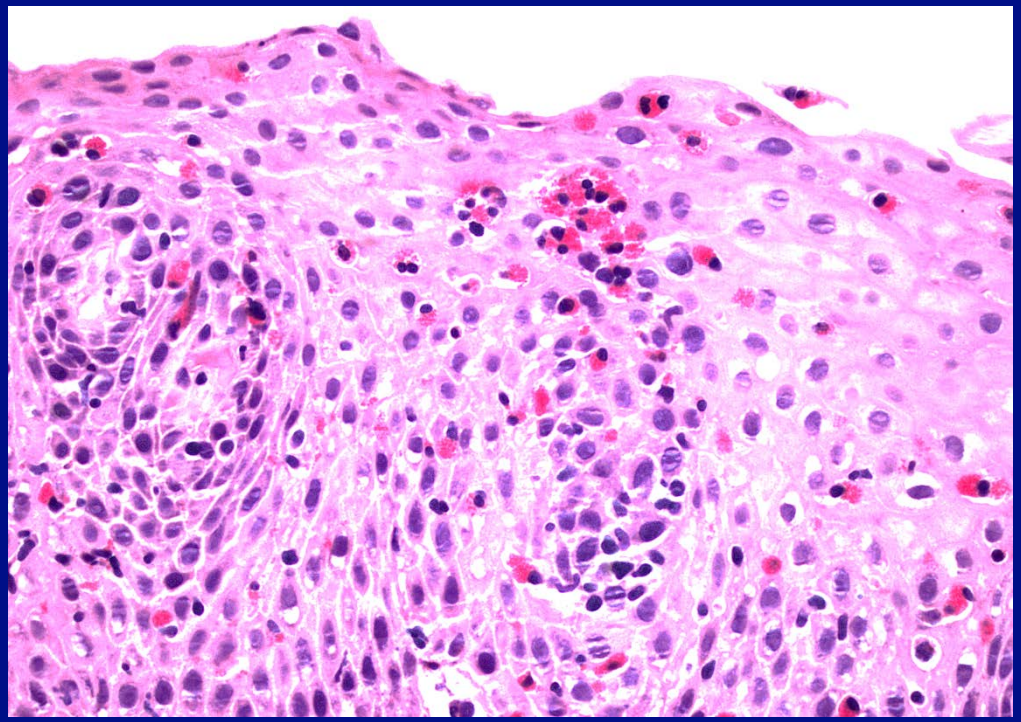
- **Post-ablation eosinophilia**

  Defined as ≥5 eosinophils/HPF found during post-treatment surveillance (in patients without eosinophilia identified on pre-ablation biopsies)

- **Found in 10/122 (16%) patients**
  - **8/77 (10%) treated with RFA**
  - **12/44 (27%) treated with cryotherapy**
- **No patients had clinical/endoscopic findings of or risk factors for EOE**
- **BE segment length found to be only independent risk factor**

Halsey KD et al. Dis Esoph 2013;16:113-116

Post-Ablation Esophageal Eosinophilia



“Stress that esophageal eosinophilia is an extremely common finding in post-ablation tissue; avoid the temptation to say “consistent with EOE” in this setting. It would be a shame to have docs giving these patients steroids and other treatments due to an overcall!”

Dr. Nicholas Shaheen

UNC

Summary

- Pros and cons of requiring goblet cells for diagnosis of BE

- Post-RFA biopsies
  - Most are superficial and inadequate to exclude subsquamous IM
  - Eosinophilia resembling EOE is not uncommon

Cleveland Clinic

Every life deserves world class care.