Barrett's Ablation Update

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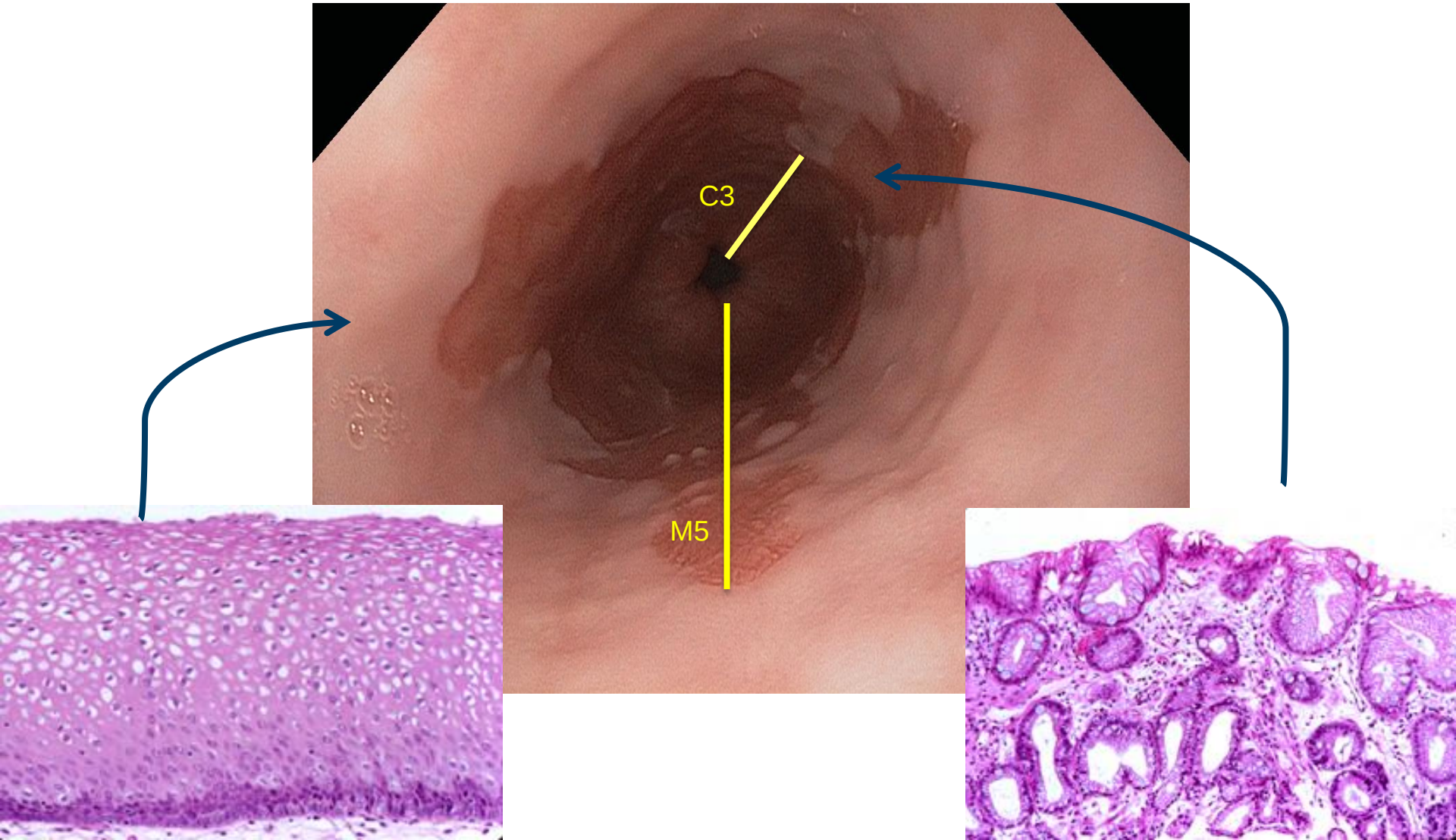
2016 State-of-the-Art In Gastroenterology Course

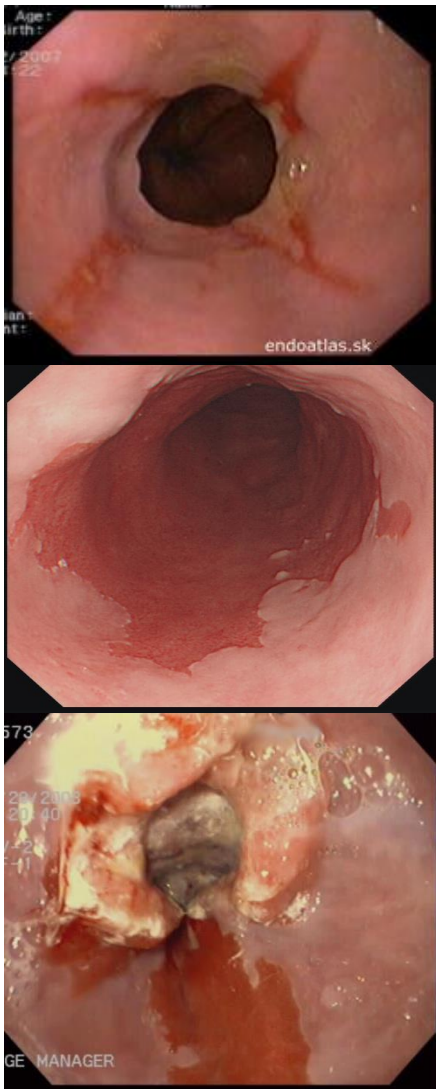
Objectives

- Discuss the indications for ablation in the setting of Barrett's Esophagus (BE)
- Describe the available ablative therapies for BE
- Review the current literature on these ablative therapies

Endoscopic Appearance



Why do we care about BE?



Squamous esophagus

Chronic inflammation

Barrett's metaplasia

Low-grade dysplasia

High-grade dysplasia

Invasive Adenocarcinoma

Injury
Acid & bile reflux
nitrous oxide

Genetics
Gender, race,
? other factors (cox-2)

Accumulate Genetic Changes

Loss of heterozygosity in tumor suppressor genes
53, APC, DCC, MTS1

METAPLASIA

DYSPLASIA

ADENOCA

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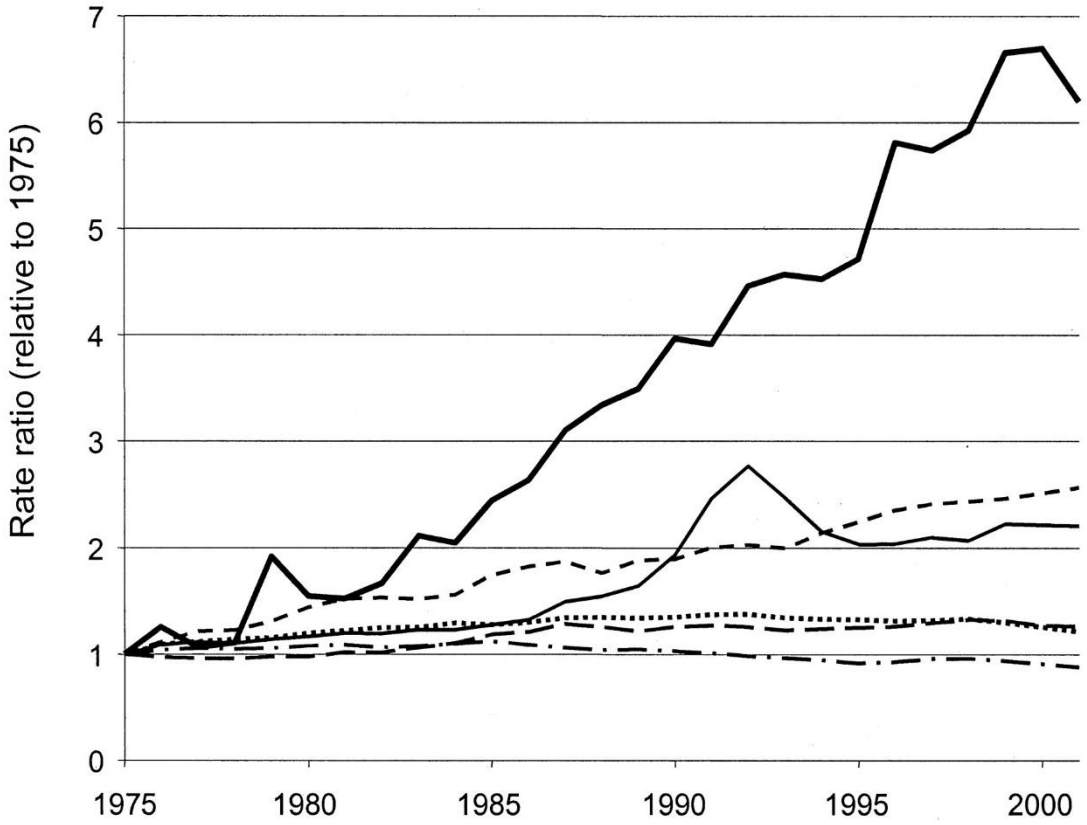
Relative change in incidence of esophageal adenocarcinoma and other malignancies



Esophageal AdenoCA

Melanoma
Prostate Cancer

Breast Cancer
Lung Cancer
CRC

Pohl H , Welch H G JNCI J Natl Cancer Inst 2005;97:142-146

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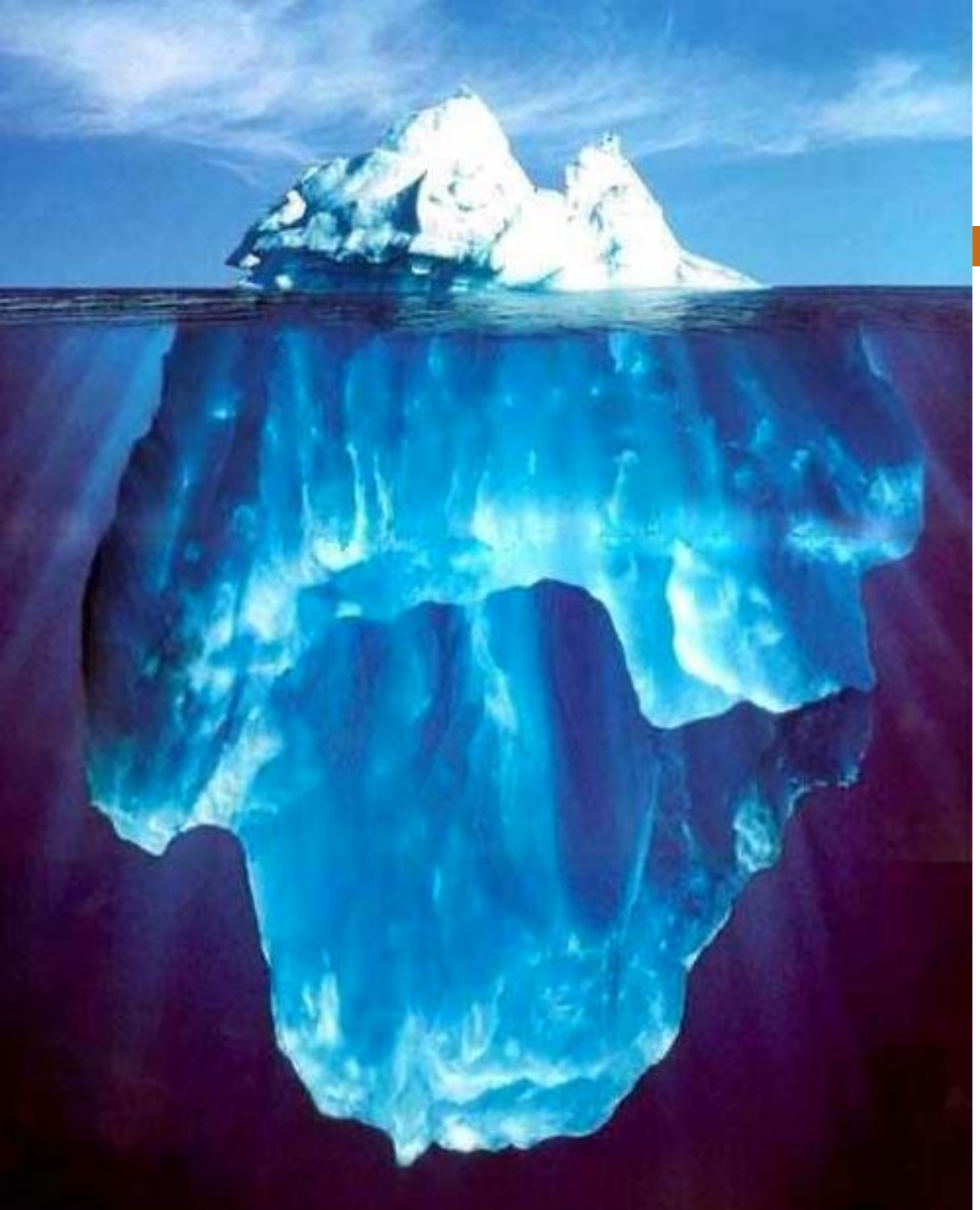

Most people diagnosed with esophageal cancer do NOT have a *known* history of Barrett's esophagus

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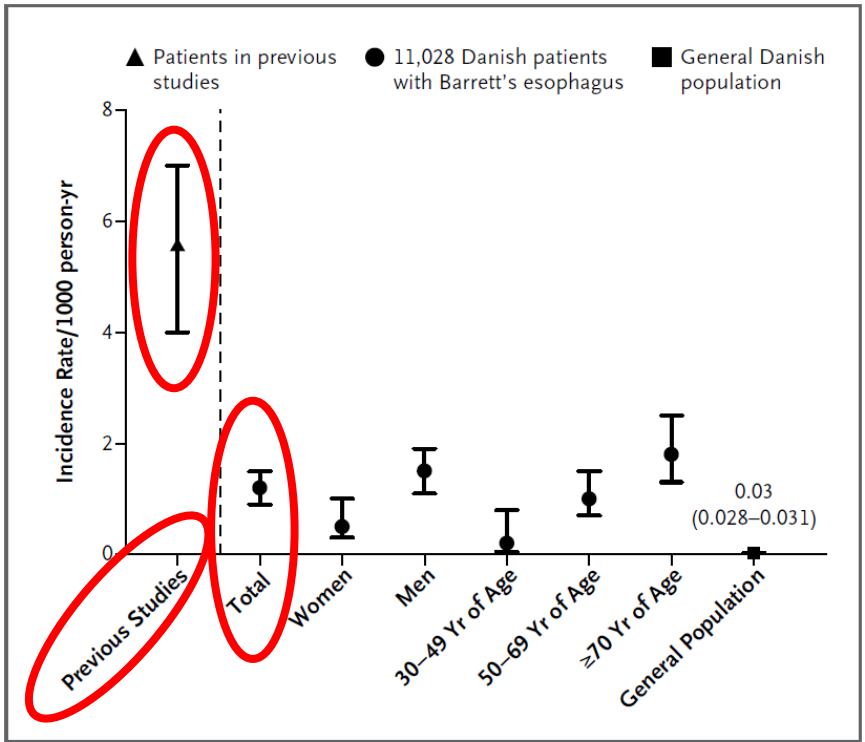
What is the risk of cancer in BE?

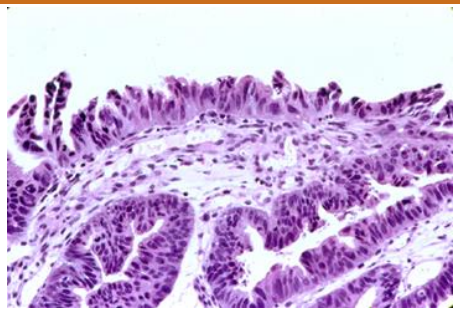
- Annual incidence “historically” has been quoted at 0.5%
- Meta-analysis (51 studies), pooled estimates for:
  - Esoph adenoCA: 0.6% annually (1% if include HGD)
  - Mortality: 0.3% annually (19 studies)
- Largest Population based study: 11,028 pts in Denmark
  - AdenoCA: 0.12% annually
  - 197 cancers in BE cohort
  - 2602 cancers in non-BE cohort
  - Patients with known BE only represented 7.6% of all cases



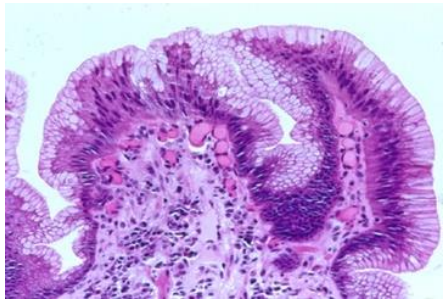
Sikkema et al. CGH 2010, Hvid-Jensen et al. NEJM 2011

Soooo…. Who to ablate in 2016?

- HGD
  - Standard of care



- LGD
  - *Small et al. Gastroenterology 2015*



- Non-dysplastic BE
  - Not routinely recommended

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Endoscopic Ablative Therapies for Barrett's in 2016

- Ablation
  - BURN
    - Thermal (MPEC, LASER, APBC)
    - Cytotoxic (PDT)
    - Radiofrequency ablation (RFA)
  - FREEZE
    - Cryotherapy
- In presence of an-acid environment, re-squamation occurs

But… Don’t forget…

- Resection
  - Endoscopic Mucosal Resection (EMR)
    - Provides histologic specimen for inspection (prognosticators)

Photodynamic Therapy

- Photosensitizer injected and produces cytotoxicity in the presence of appropriate wavelength light
- Superior to omeprazole in eradicating dysplasia (77% vs 39%)
- Superior to omeprazole in preventing cancer in BE (15% vs 29%)
- Significant complications:
  - esophageal stricture—30%
  - photosensitivity (sunburn)

Overholt et al. GIE 2007

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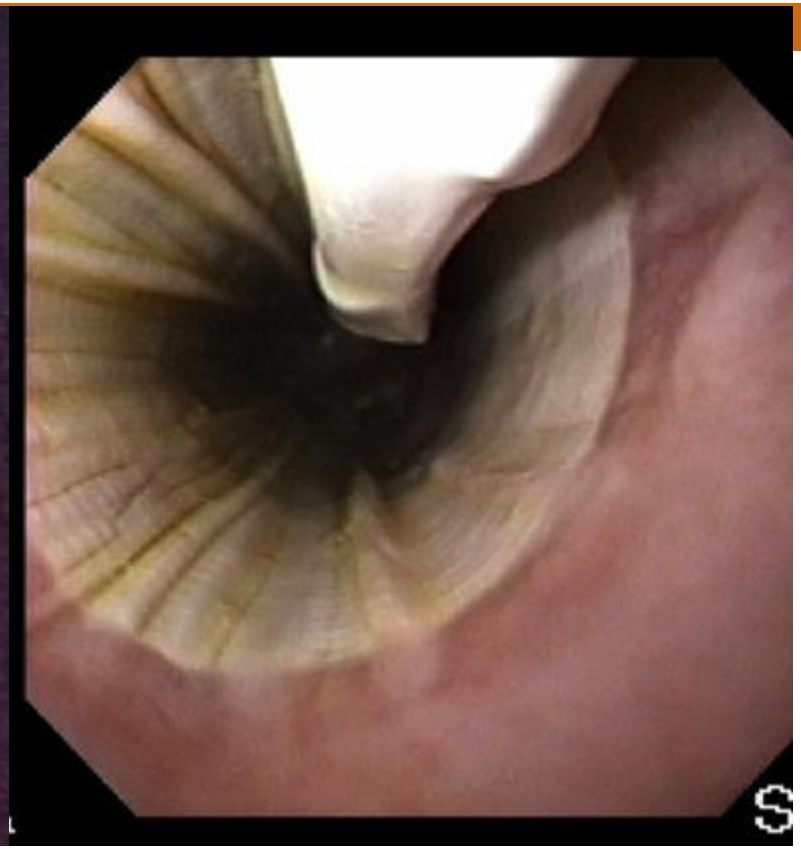
Radiofrequency Ablation Therapy



- Uniform circumferential ablation
- 3 cm in length
- Individualized with sizing balloon
- Precise energy delivery in < 1 sec

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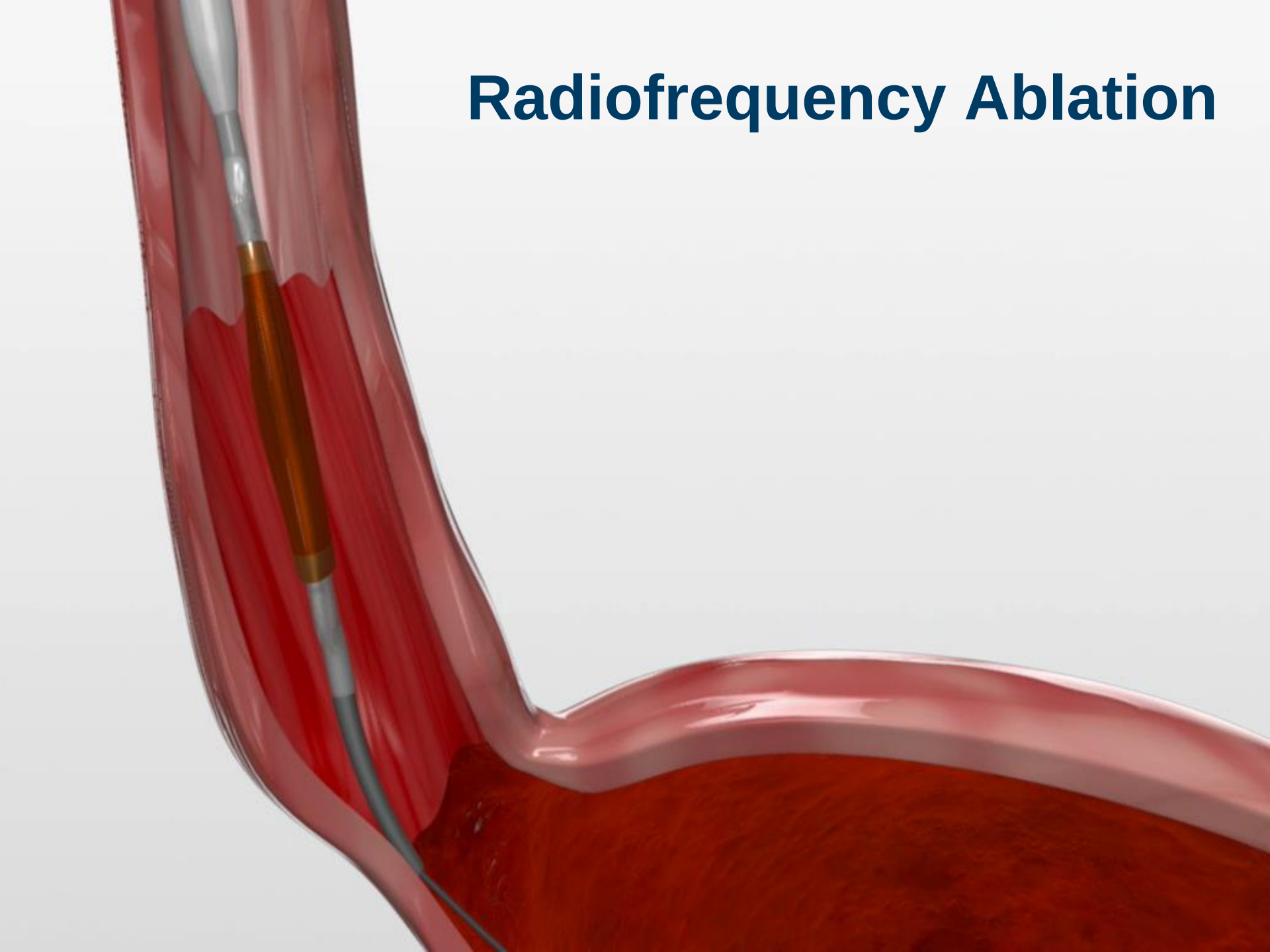
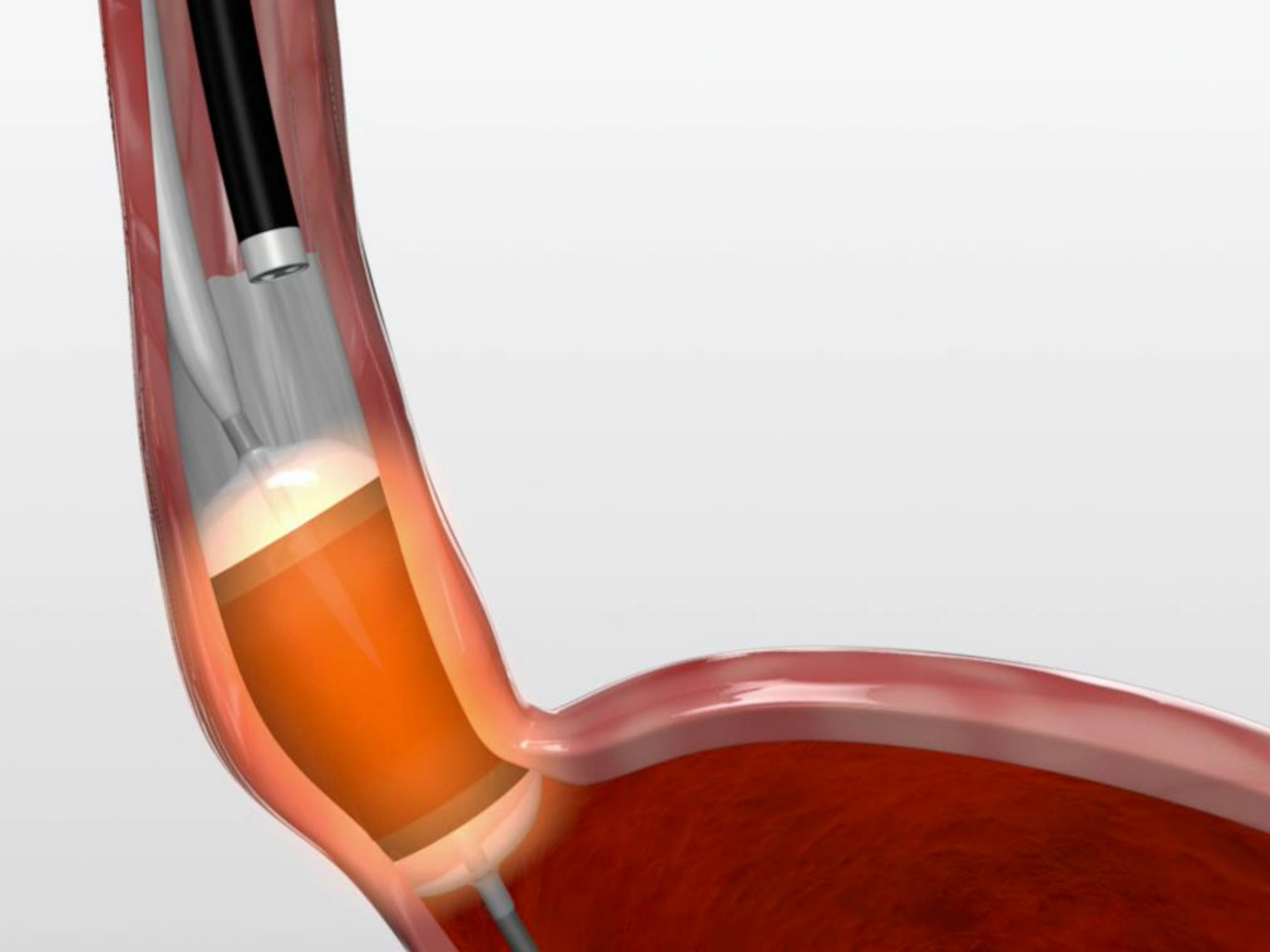
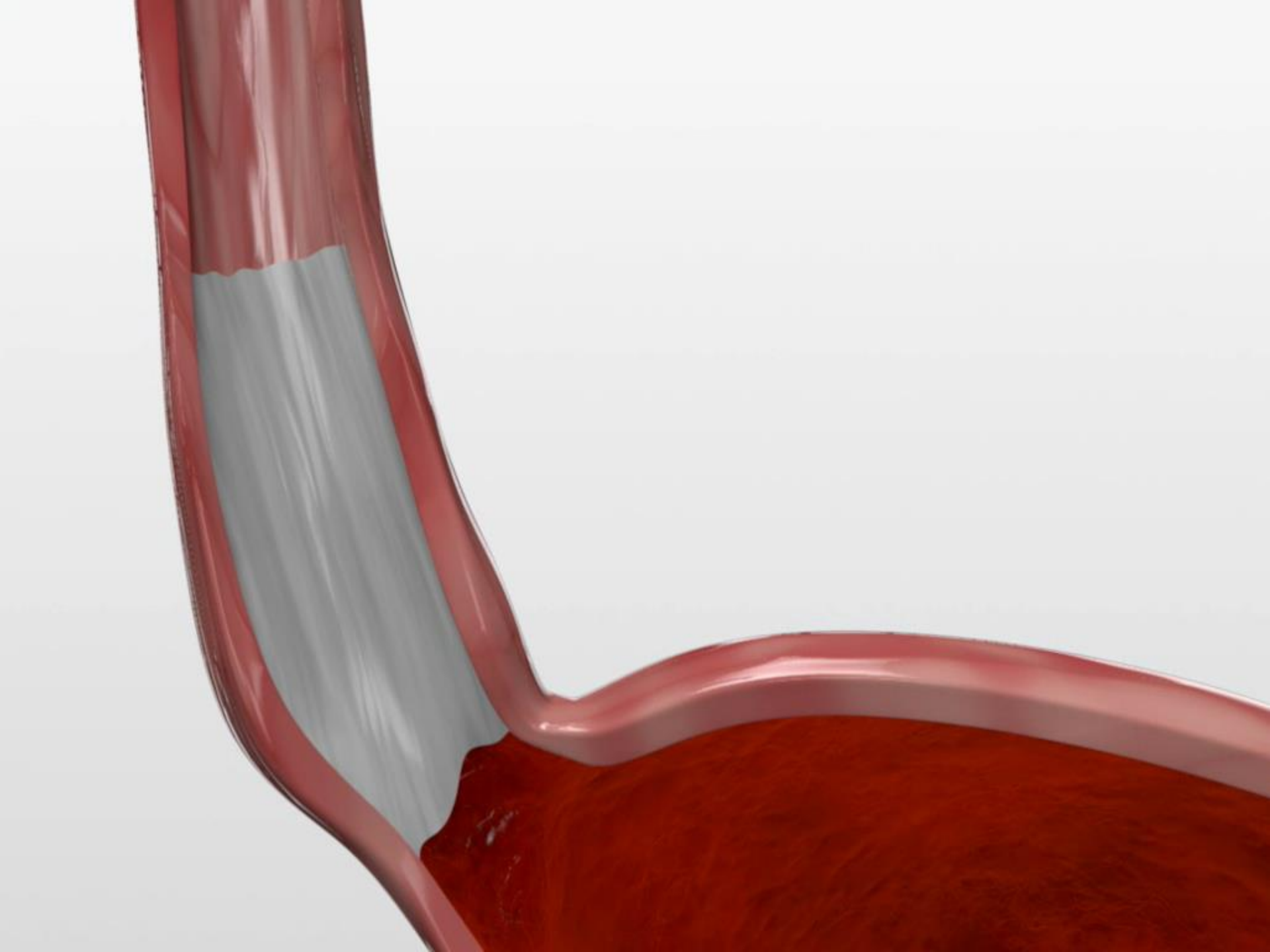
Radiofrequency Ablation

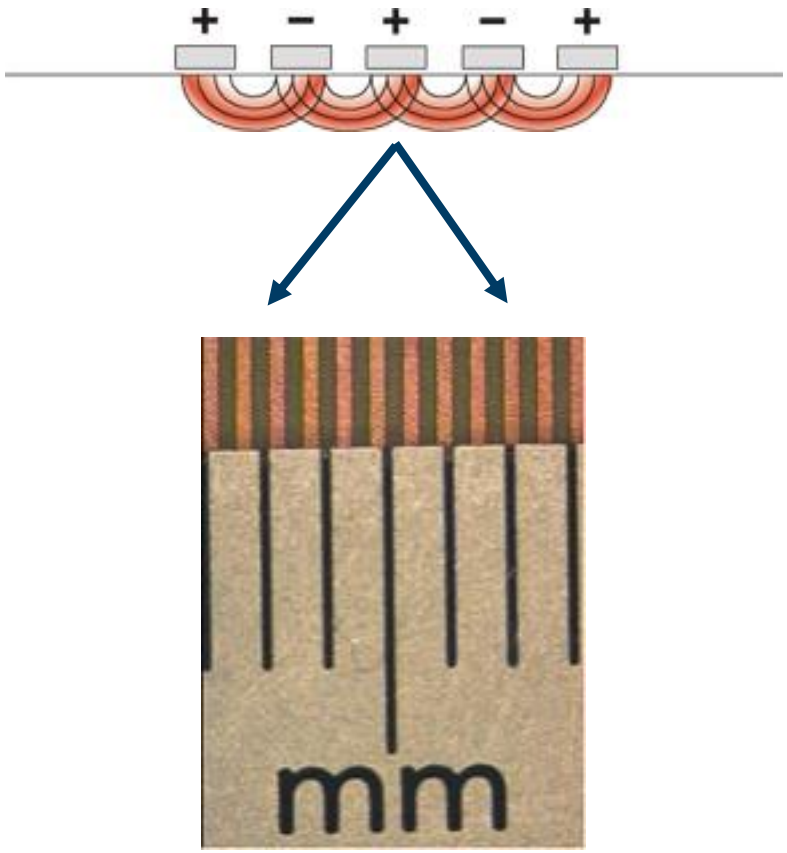


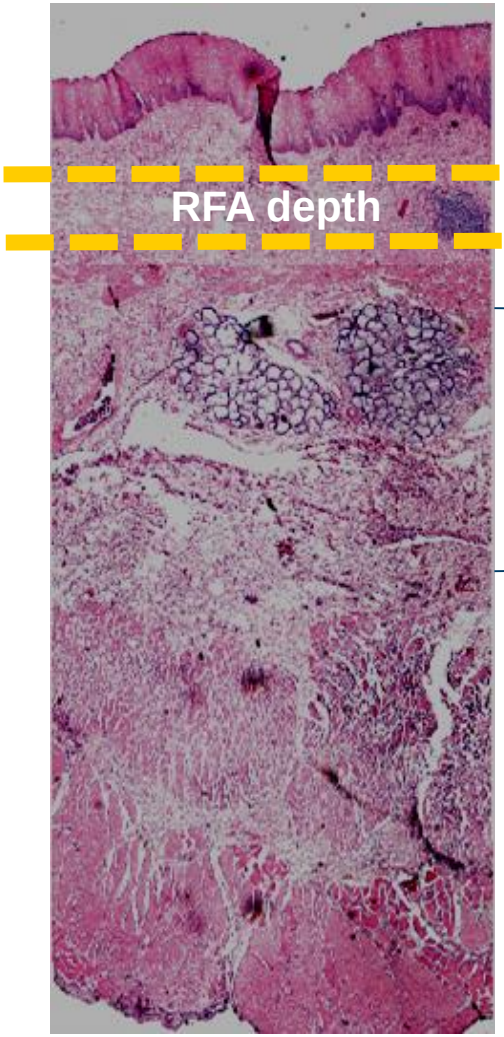




Ablation Depth Control—RFA

Micro-array at Tissue Interface





Esophagus

Epithelium

Lamina Propria

Muscularis Mucosae

Submucosa

Muscularis Propria

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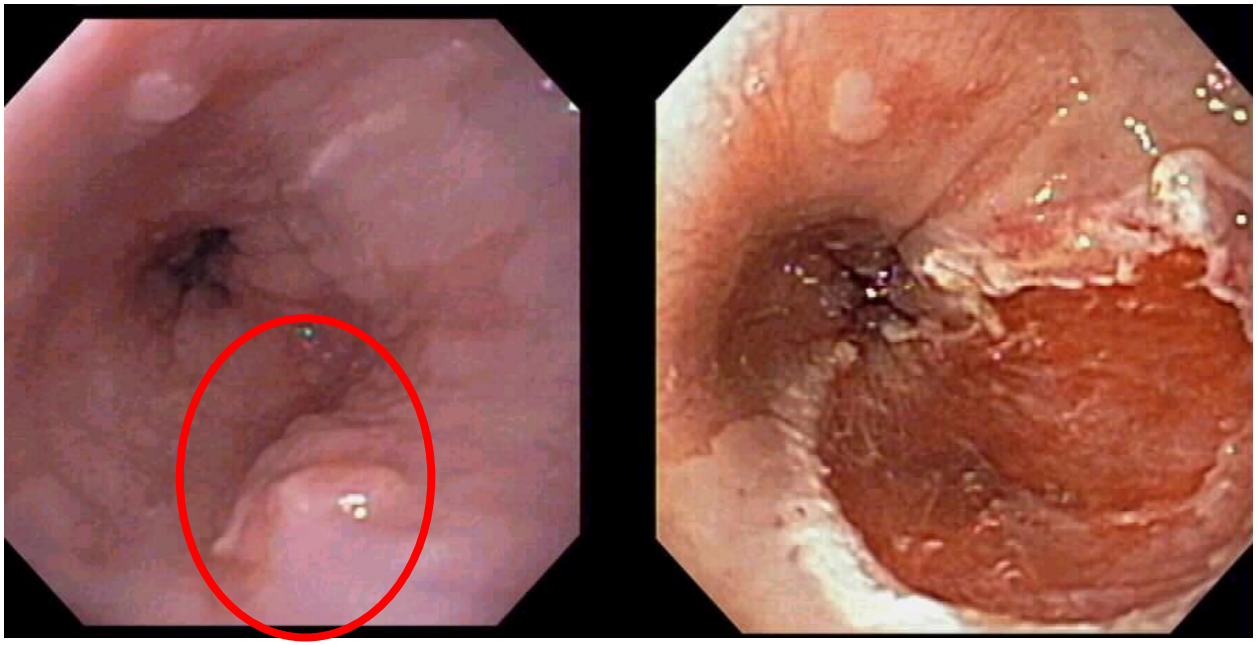
Radiofrequency Ablation Therapy

- ONLY INDICATED IN FLAT BARRETT'S!

- If NODULAR, EMR FIRST, THEN ABLATE ANY RESIDUAL FLAT BARRETT'S



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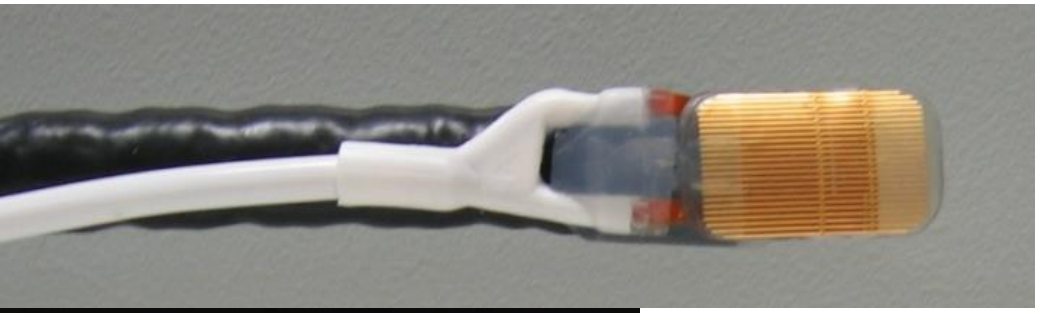
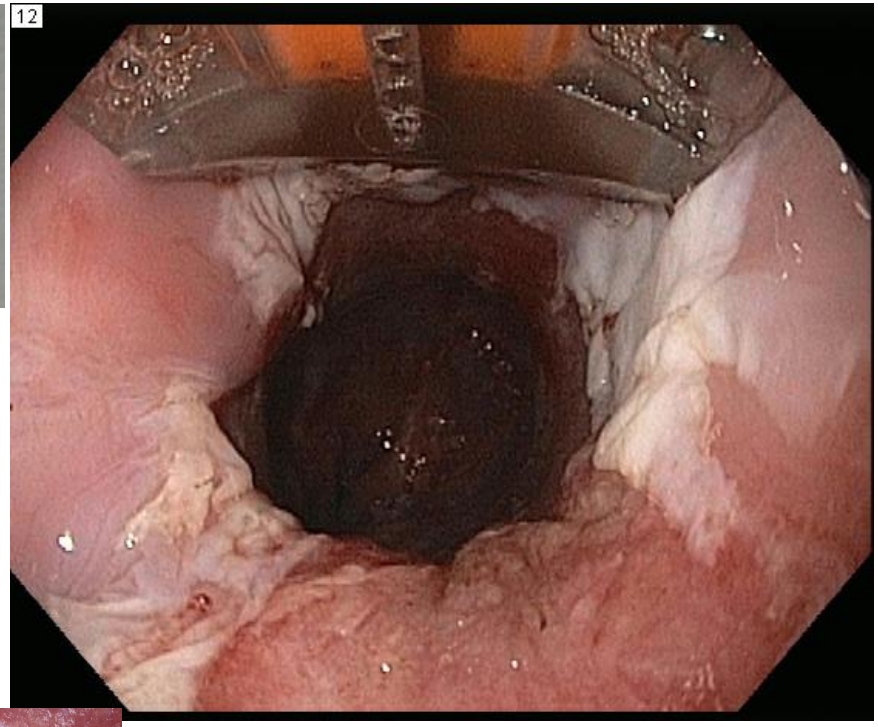
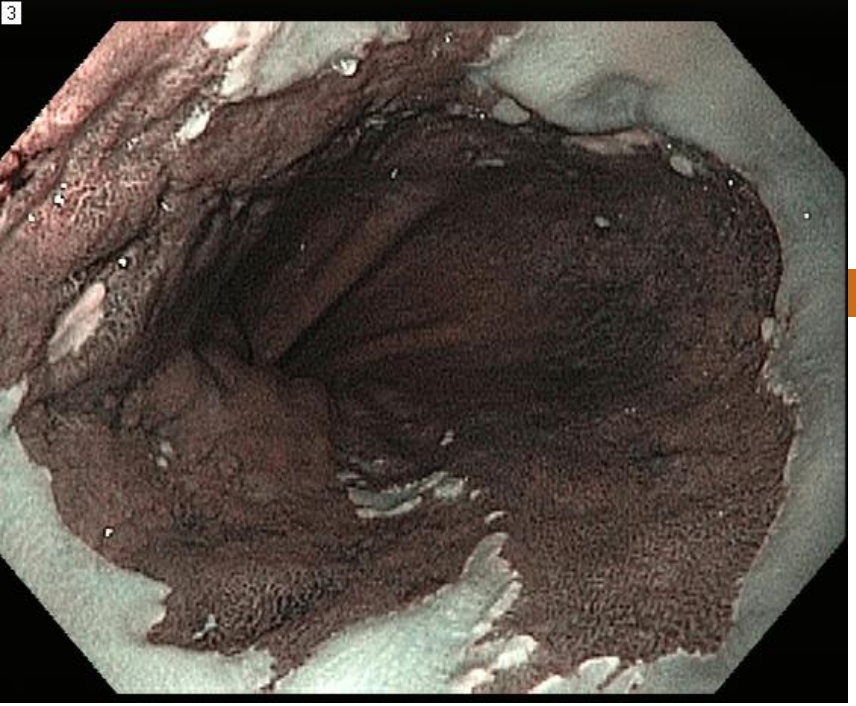
Targeted RFA





	10 x 15 mm	13 x 20 mm

APC	10x15mm	13x20mm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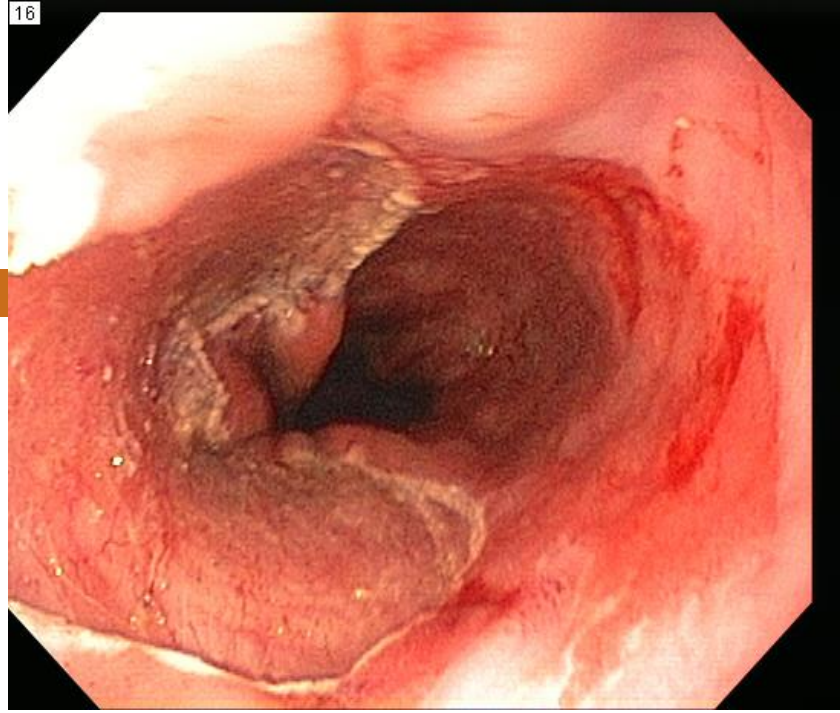
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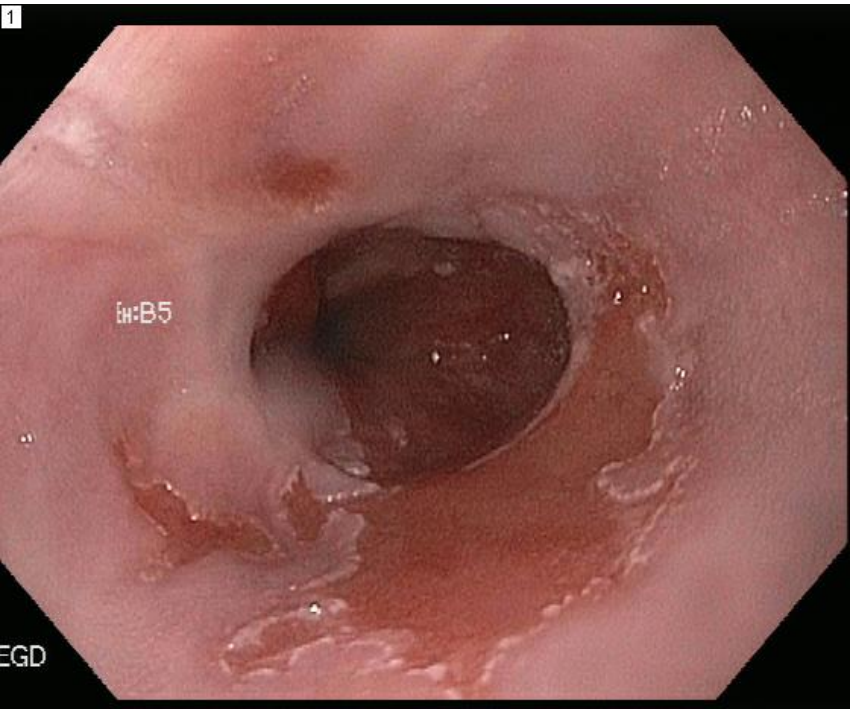
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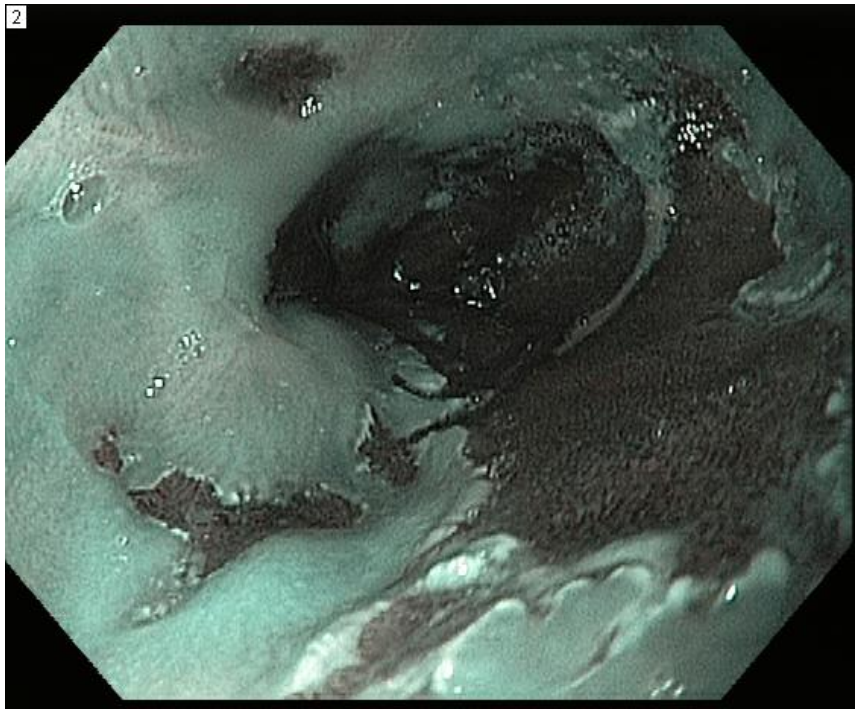
W:B5
EGD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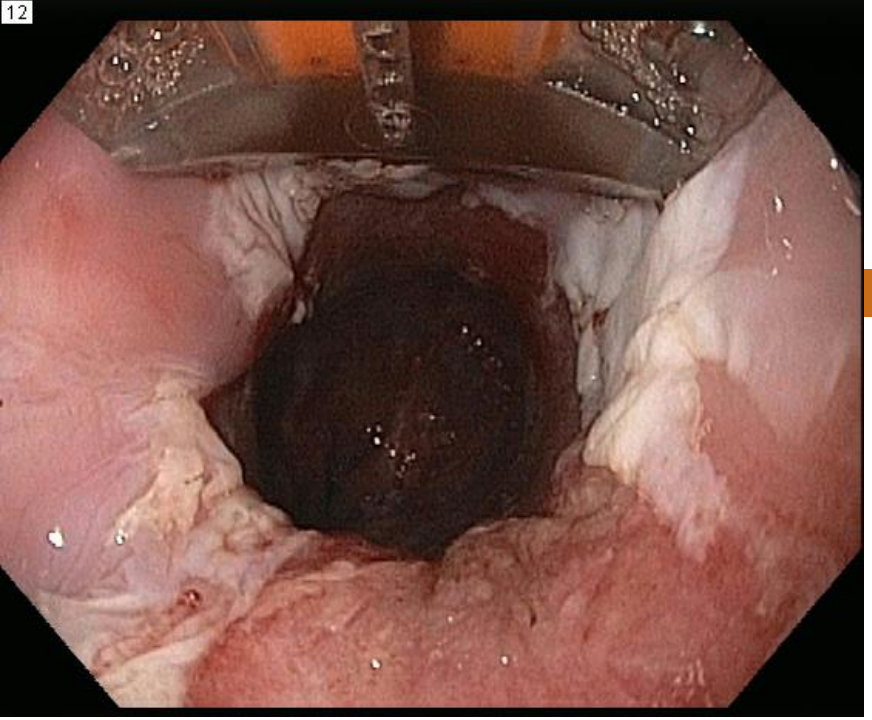
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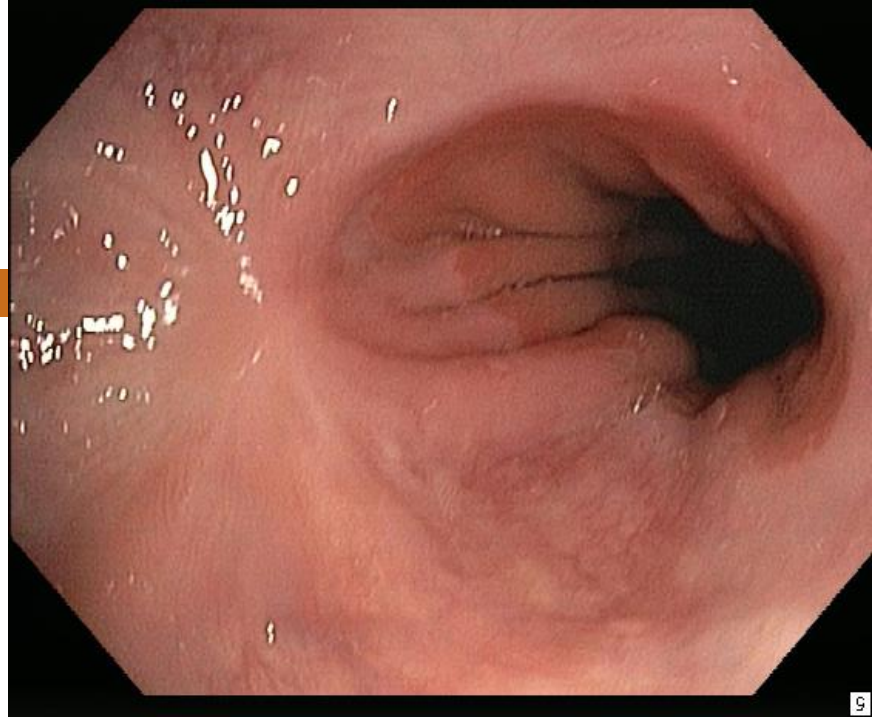
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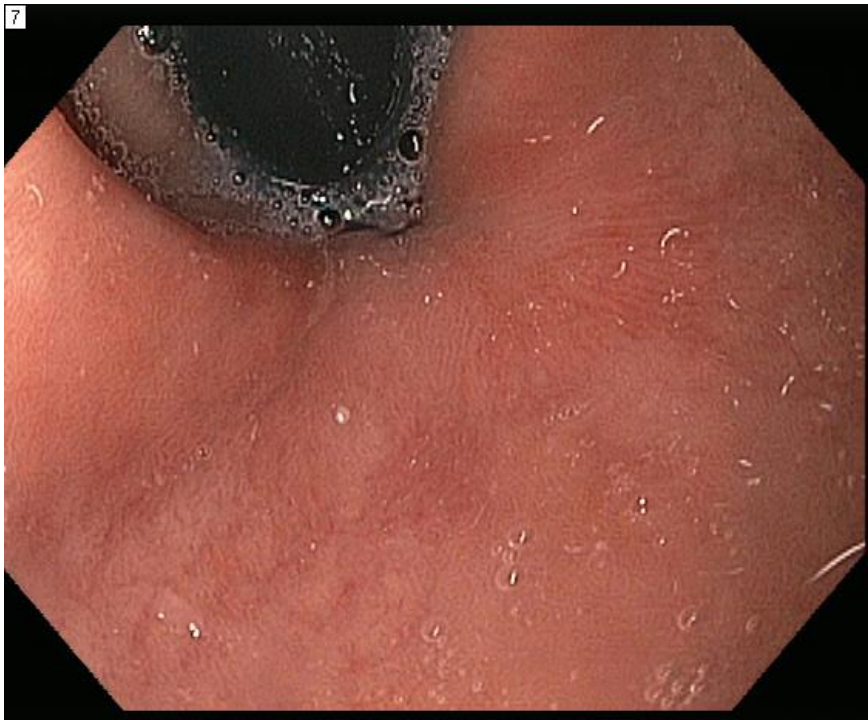
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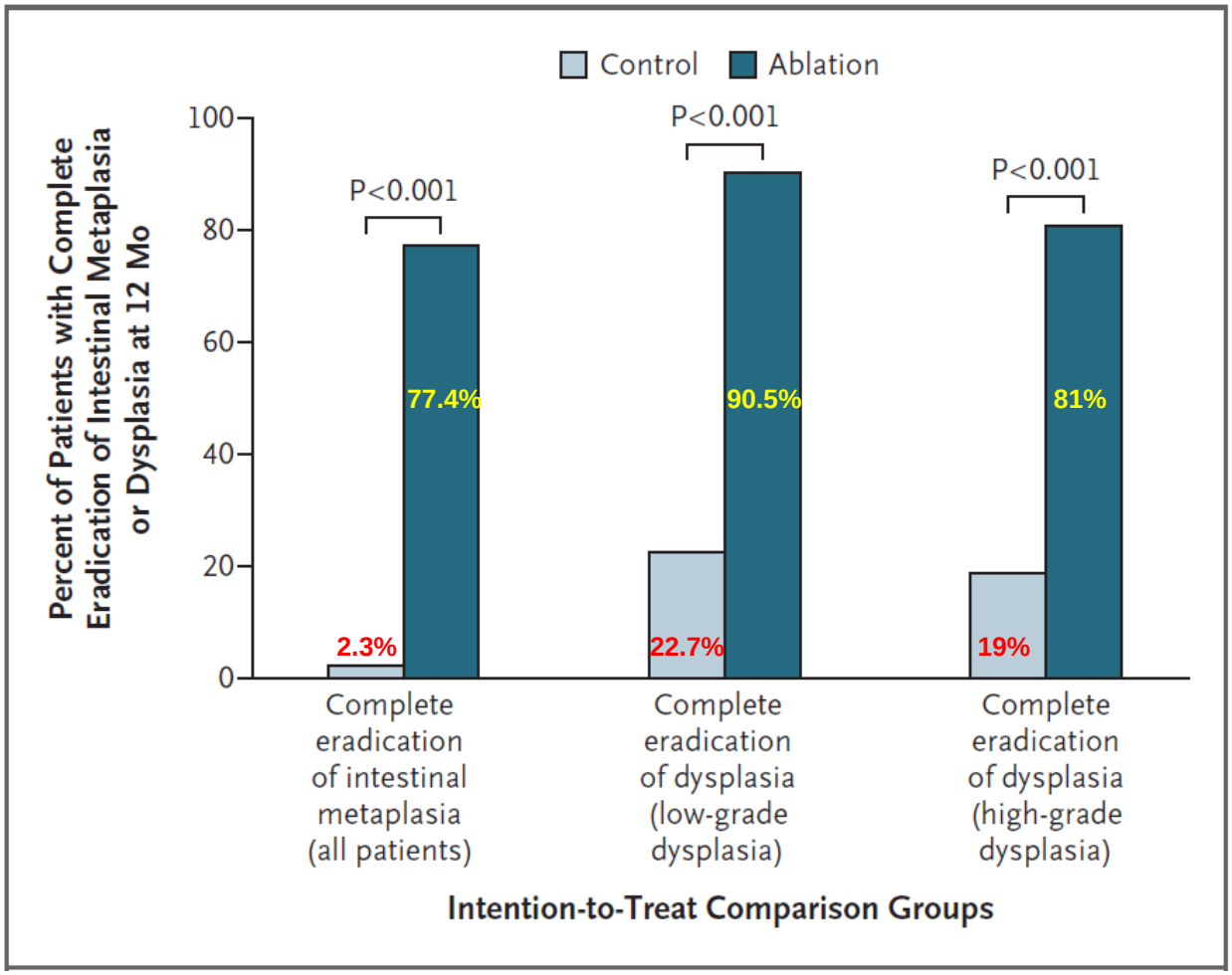
RFA: Eradication



Multicenter, sham controlled trial

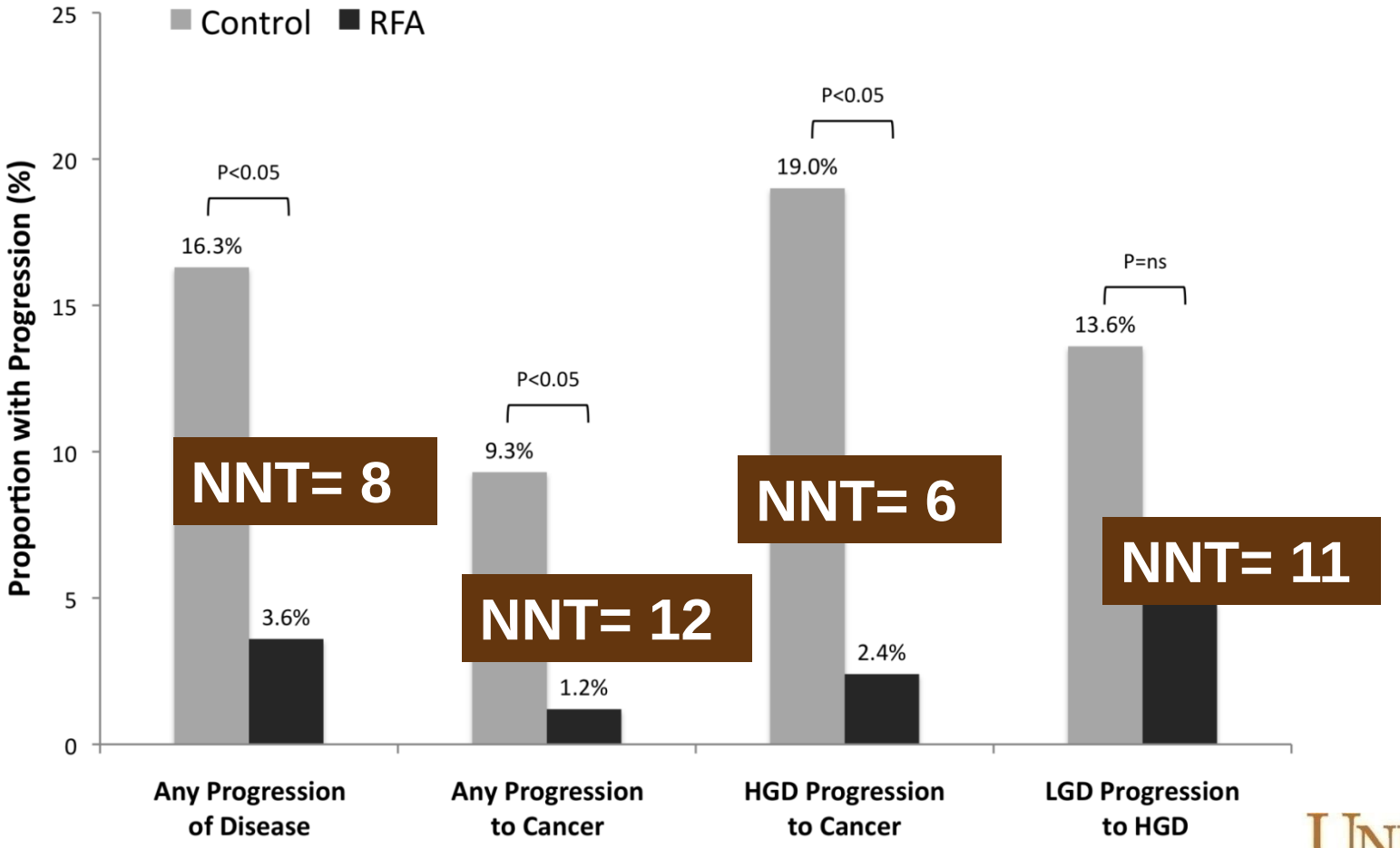
127 patients, ablation vs. sham, 12 months

Complications of ablation:

- Chest pain, UGIB (1 pt), stricture (5 pts, 6%)

Shaheen et al N Engl J Med 2009; 360:2277-2288

RFA: Disease Progression



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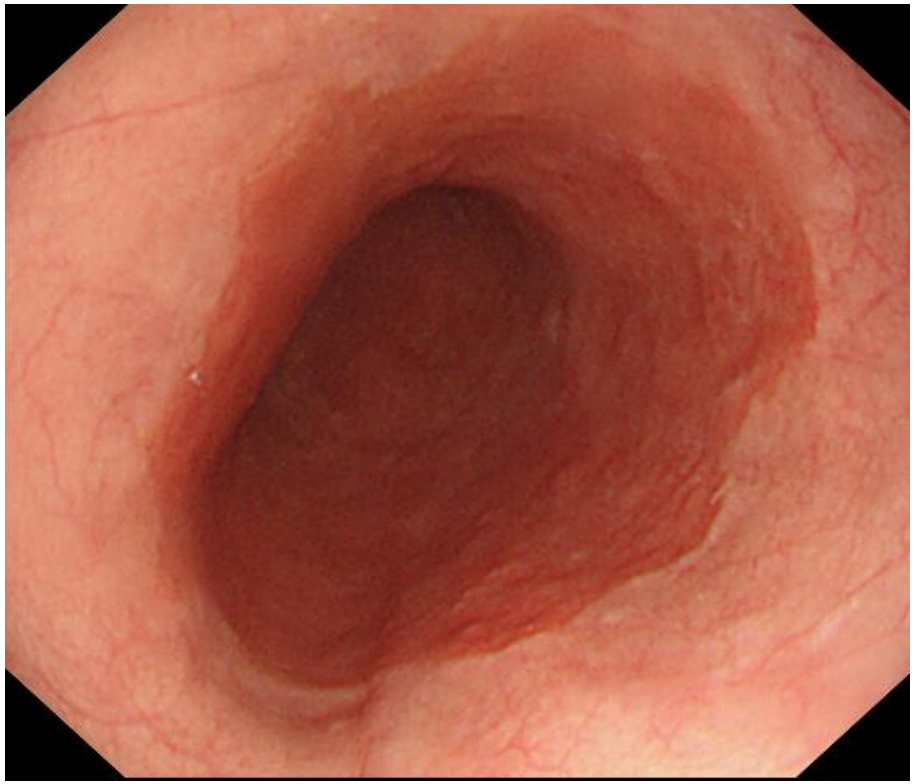
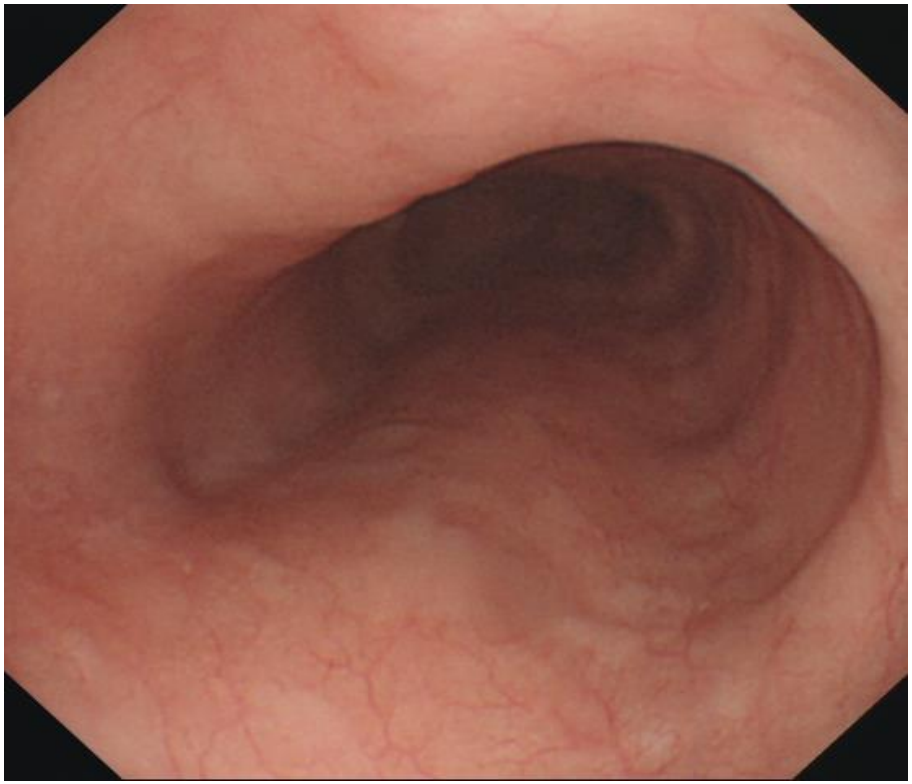
Long-term Outcomes???



Baseline



Post-RFA: 2 years

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AIM Dysplasia Trial L/T F/U

(Shaheen, Gastro, 2011)

- **Extension of the AIM Dysplasia Trial for pts with complete BE eradication after 1 yr of treatment (n=106)**
- **Dysplasia (91%) & IM (98%) eradication rate at 2 & 3 yrs**
- **0.55% per yr cancer progression rate (v. 9.3% annual cancer progression in the sham group)**
- **"In subjects with dysplastic BE, RFA therapy has an acceptable safety profile, is durable, and is associated with a low rate of disease progression for up to 3 years."**

GASTROENTEROLOGY 2011;141:460–468

CLINICAL—ALIMENTARY TRACT

Durability of Radiofrequency Ablation in Barrett's Esophagus With Dysplasia

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This article has an accompanying continuing education activity on page e13. Learning Objective: Upon completion of this activity, the successful learner will be able to describe the durability, safety and efficacy of radiofrequency ablation for dysplastic Barrett's esophagus.

Podcast interview: www.gastro.org/gastropodcast; see editorial on page 417; see Covering the Cover synopsis on page 408.

BACKGROUND & AIMS: Radiofrequency ablation (RFA) can eradicate dysplasia and intestinal metaplasia in patients with dysplastic Barrett's esophagus (BE), and reduce rates of esophageal adenocarcinoma. We assessed long-term rates of eradication, durability of neosquamous epithelium, disease progression, and safety of RFA in patients with dysplastic BE. **METHODS:** We performed a randomized trial of 127 subjects with dysplastic BE; after crossover subjects were included, 119 received RFA. Subjects were followed for a mean time of 3.05 years; the study was extended to 5 years for patients with eradication of intestinal metaplasia at 2 years. Outcomes included eradication of dysplasia or intestinal metaplasia after 2 and 3 years, durability of response, disease progression, and adverse events. **RESULTS:** After 2 years, 101 of 106 patients had complete eradication of all dysplasia (95%) and 99 of 106 had eradication of intestinal metaplasia (93%). After 2 years, among subjects with initial low-grade dysplasia, all dysplasia was eradicated in 51 of 52 (98%) and intestinal metaplasia was eradicated in 51 of 52 (98%); among subjects with initial high-grade dysplasia, all dysplasia was eradicated in 50 of 54 (93%) and intestinal metaplasia was eradicated in 48 of 54 (89%). After 3 years, dysplasia was eradicated in 55 of 56 of subjects (98%) and intestinal metaplasia was eradicated in 51 of 56 (91%). Kaplan–Meier analysis showed that dysplasia remained eradicated in >85% of patients and intestinal metaplasia in >75%, without maintenance RFA. Serious adverse events occurred in 4 of 119 subjects (3.4%); the rate of stricture was 7.6%. The rate of esophageal adenocarcinoma was 1 per 181 patient-years (0.55%/patient-years); there was no cancer-related morbidity or mortality. The annual rate of any neoplastic progression was 1 per 73 patient-years (1.37%/patient-years). **CONCLUSIONS:** In subjects with dysplastic BE, RFA therapy has an acceptable safety profile, is durable, and is associated with a low rate of disease progression, for up to 3 years.

Keywords: Esophagus; Cancer; Prevention; Endoscopic Therapy.

Several treatment options are available for the care of patients with dysplastic Barrett's esophagus (BE), including intensive endoscopic surveillance, esophagectomy, endoscopic mucosal resection (EMR), and endoscopic ablative therapy.[1] The choice between these modalities is made with consideration of the severity of dysplasia (low-grade dysplasia [LGD] vs high-grade dysplasia [HGD]), patient comorbidities, available physician expertise in providing

Abbreviations used in this paper: BE, Barrett's esophagus; CE-D, complete eradication of dysplasia; CE-M, complete eradication of intestinal metaplasia; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; LGD, low-grade dysplasia; RFA, radiofrequency ablation; SSIM, subsquamous intestinal metaplasia.

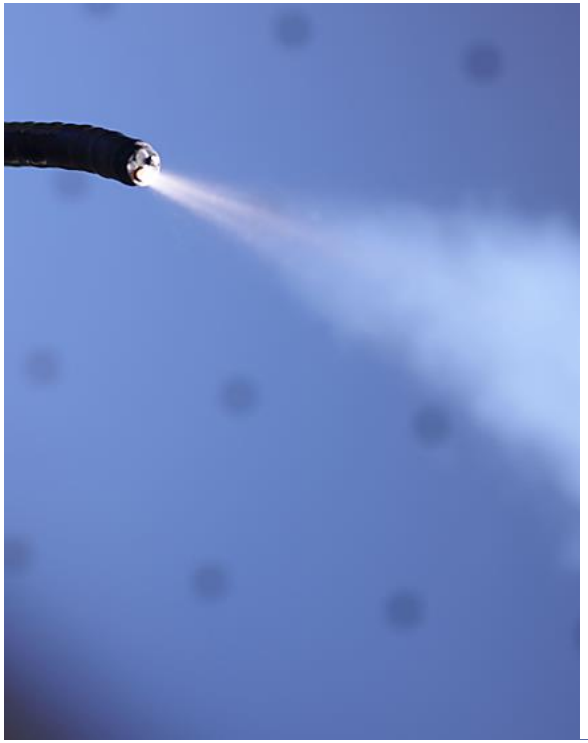
0016-5085/$36.00
doi:10.1053/j.gastro.2011.04.061

RFA in Low Grade Dysplasia

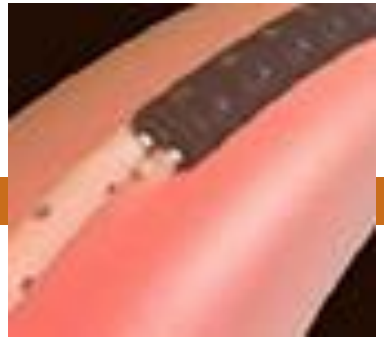
- Retrospective trial
- RFA (n=45)
- Surveillance (n=125)
- Annual rates of progression to HGD or EC
  - 0.77% RFA
  - 6.6% surveillance group

- *PPI nonuse was significantly higher in the surveillance group (26.7%) vs ablation group (2.5%)*

Cryoablation



Cryoablation



- Cryogen delivered at low pressure
  - Liquid nitrogen (-196 °C)
- 7 French catheter inserted through a diagnostic endoscope
- Placement of the Cryo-Decompression Tube (CDT)
- Physician has direct visualization
- Physician controlled treatment area
  - *Focal and broad lesions*
- Patient tolerance – minimal pain and quick return to normal routines

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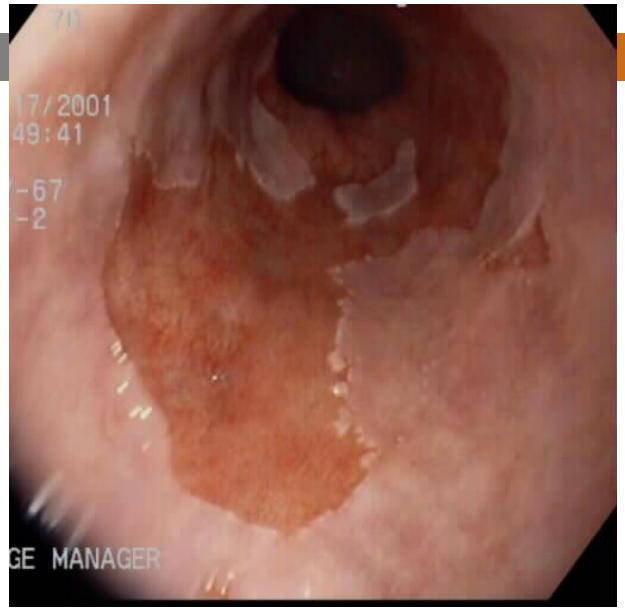
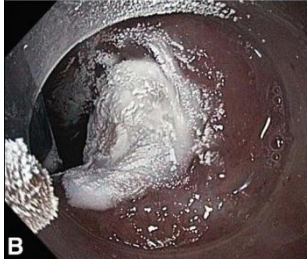
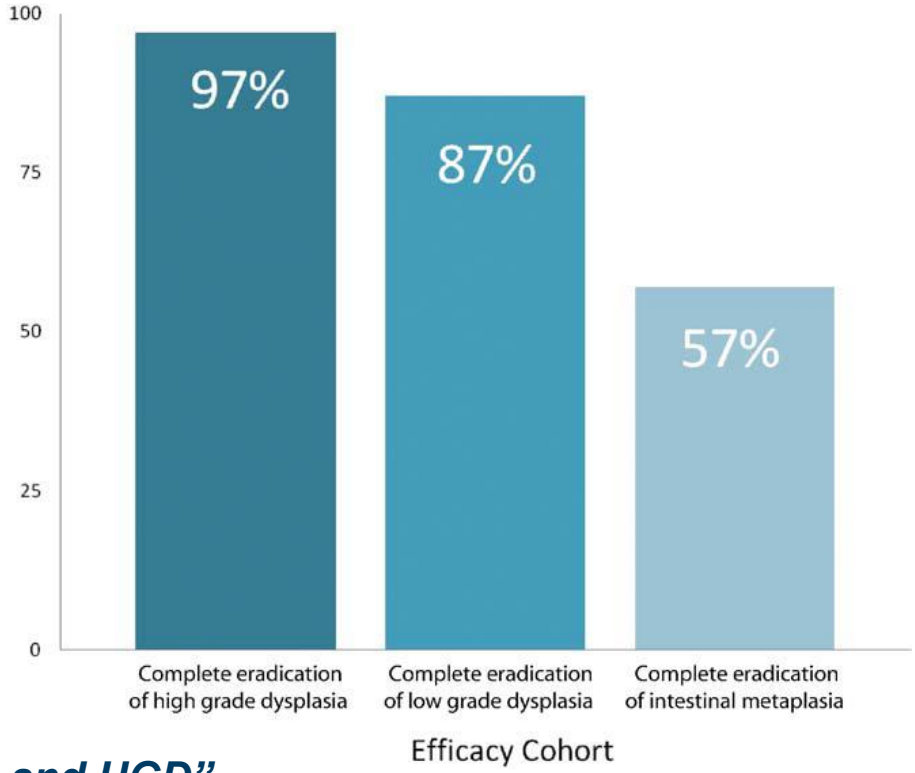
Cryoablation



Endoscopic cryotherapy



- Multicenter, retrospective study of cryotherapy for HGD
- 60 individuals
- Complications:
  - Perforation: 0
  - Stricture: 3
  - Severe pain: 2
  - Admission: 1



"Cryotherapy is well-tolerated therapy for BE and HGD"

Shaheen et al. GIE 2010

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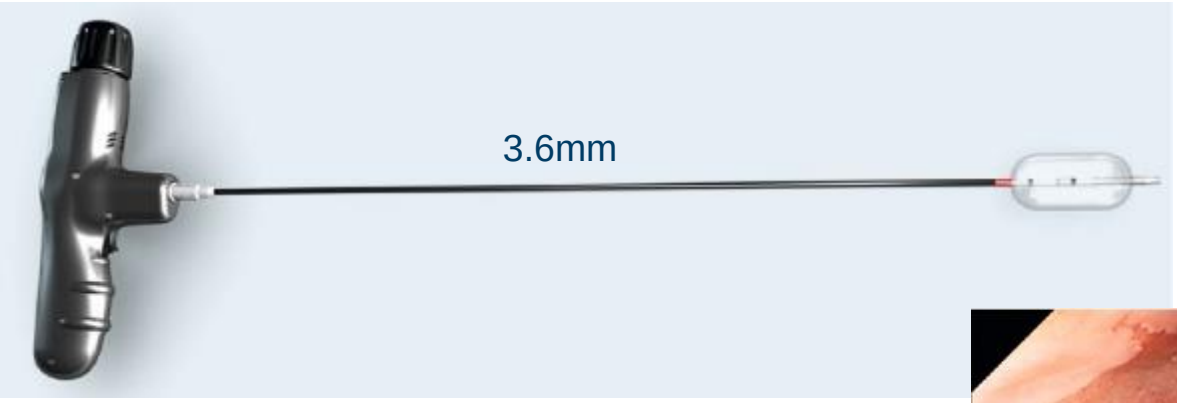
Endoscopic cryotherapy

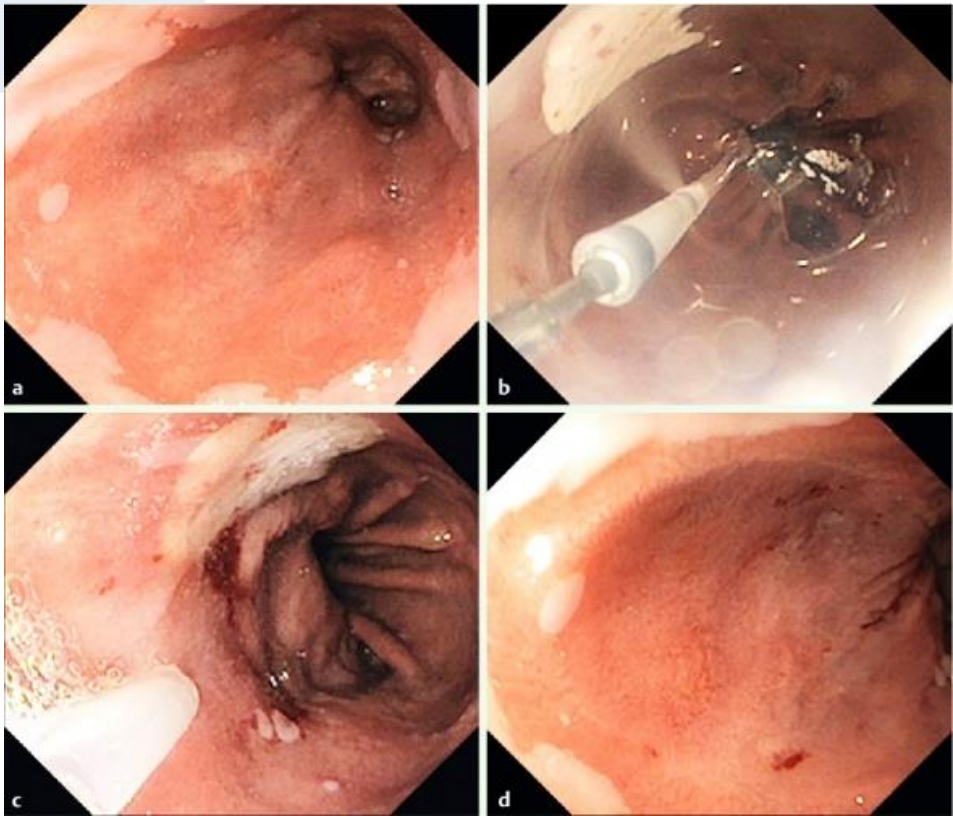
- 32 patients with BE and HGD
- Single-center, retrospective study
- Treated every 8 weeks until BE eradicated

- Results
  - CE-HGD achieved 97%
  - CE-IM achieved 81%

Gosain et al. GIE 2013

Cryoballoon Focal Ablation System





- Scholvinck et al. Endoscopy 2015

Scholvinck et al. Endoscopy 2015

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Novel Focal Cryotherapy Device: Safety and Feasibility Study

- Multicenter, prospective non-randomized trial
- 39 pts treated
  - 62 ablations, 6 failed
- Full squamous regeneration in 47
  - 6 (60%) 6 sec
  - 23 (82%) 8 sec
  - 18 (100%) 10 sec

Reepithelialization was significantly higher with increasing durations of ablation

- Scholvinck et al. Endoscopy 2015

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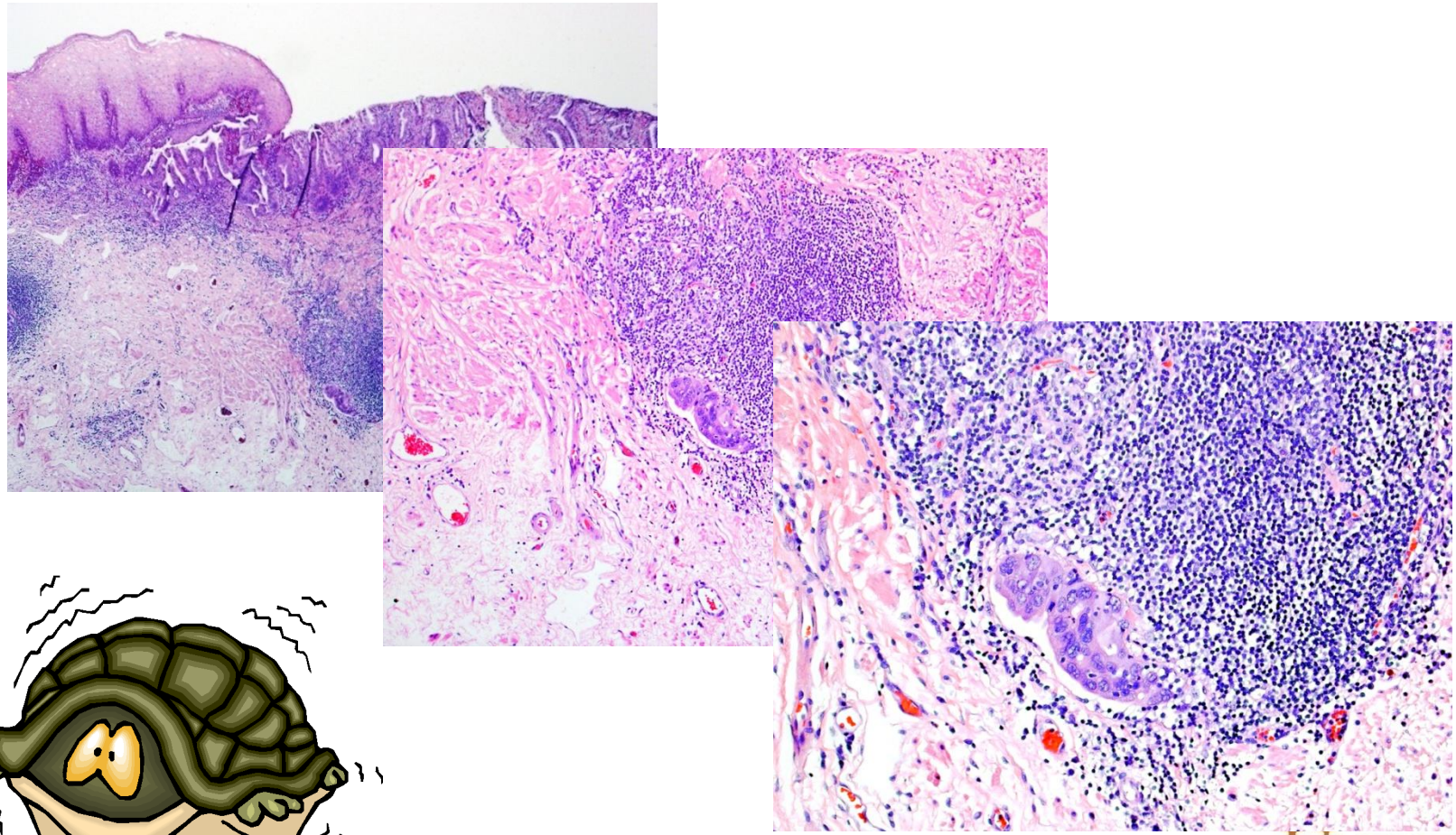
What we need….

- Long term follow up of cryotherapy
- Head to head trials comparing RFA to cryotherapy

The nemesis of ablative therapy…



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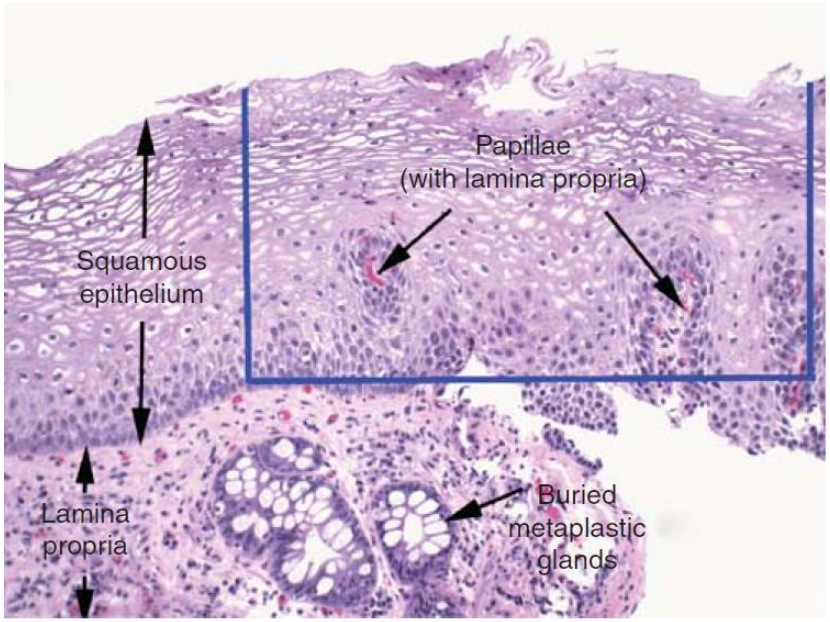
“Buried” subsquamous glands

- Estimate: 0-30%
- Development of adenoCA in subsquamous glands has been reported
- NEED SURVEILLANCE after endoscopic therapy



Wani et al. GIE. 2010, Gray et al. Am J Gastro 2011

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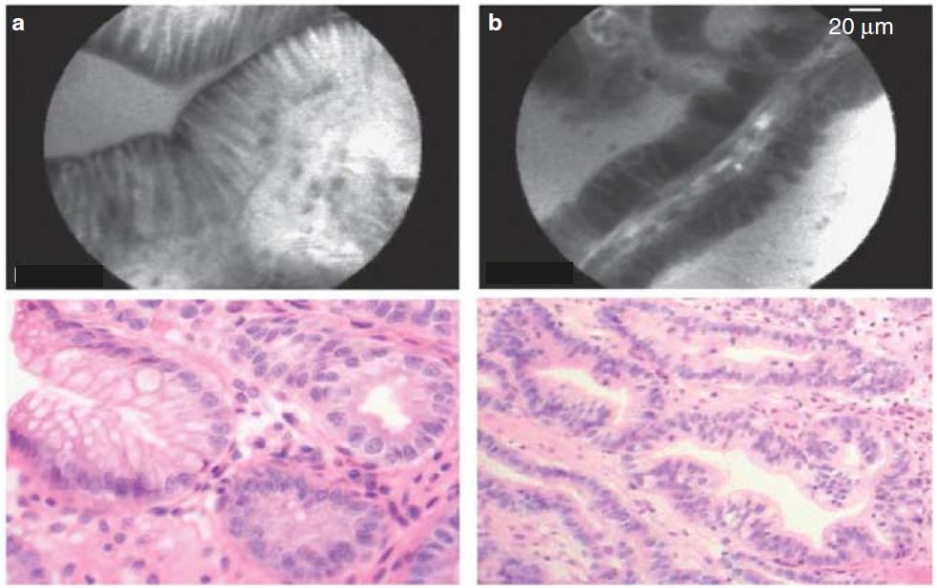
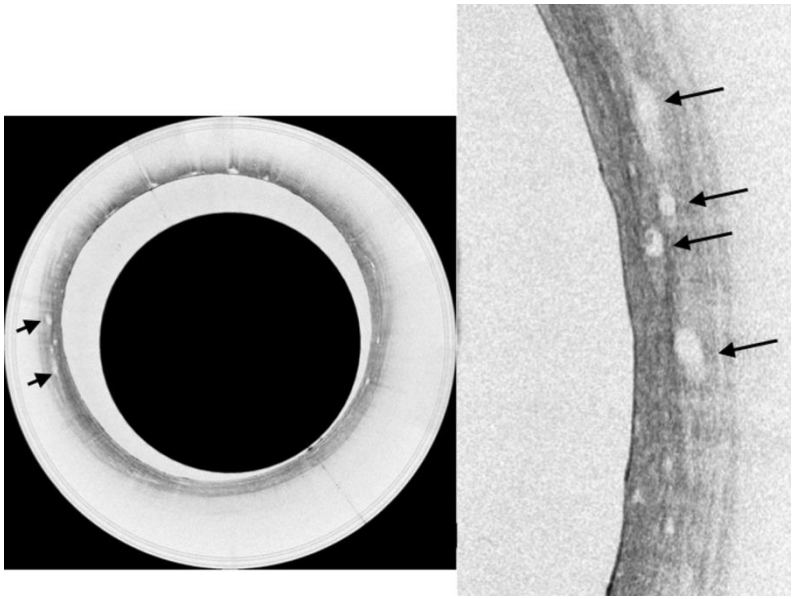
Emerging Technologies

Confocal Endomicroscopy (CLE)



Optical coherence tomography (OCT)



Gaddam et al. Am J Gastro 2011; Robles LY et al. J Surg Res 2015

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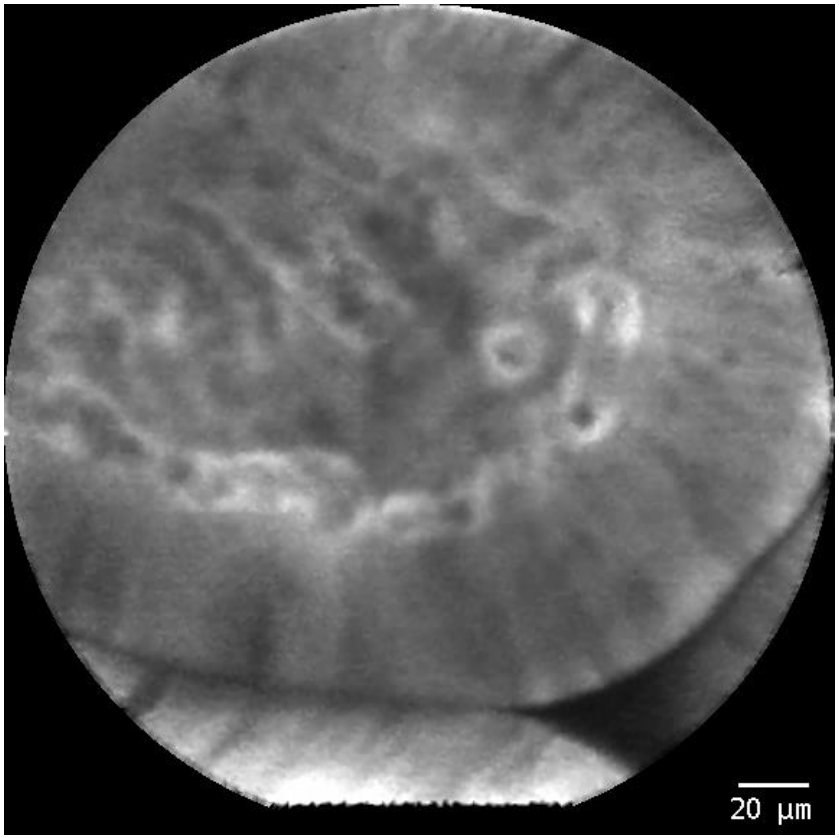
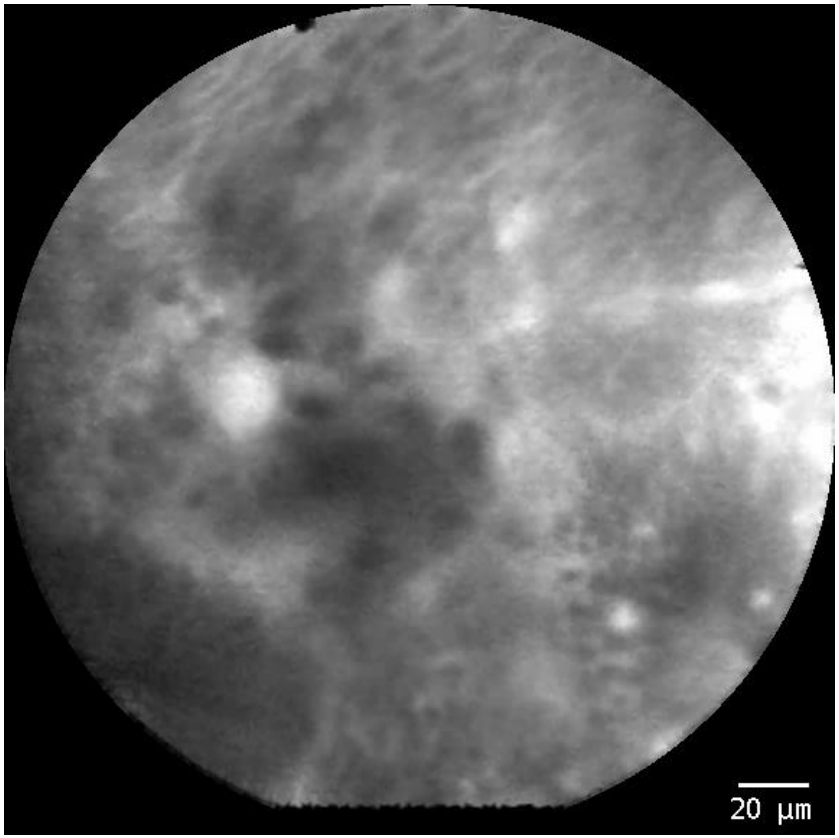
Confocal Endomicroscopy

No Dysplasia



Dysplasia



Take Home Points: ASGE Guideline

Histology	Intervention options
Non-dysplastic BE	Consider no surveillance EGD q 3-5 years with 4-quad bx every 2 cm
Low-grade dysplasia	Confirm with expert GI pathologist Repeat EGD in 6 months to confirm LGD Surveillance EGD yearly, 4-quad bx every 1-2cm Consider endoscopic resection or ablation
High-grade dysplasia	Confirm with expert GI pathologist Consider surveillance EGD every 3 months Consider endoscopic resection or ablation Consider surgical consultation

ASGE guideline: The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus

Take Home Points

- Who should receive endoscopic treatment for BE?
  - Intramucosal carcinoma, HGD and select pts with LGD
- What endoscopic treatment options should be employed?
  - Nodules: EMR, ESD followed by ablation
  - Flat BE: Ablation
    - RFA – Longer term data vs. cryotherapy