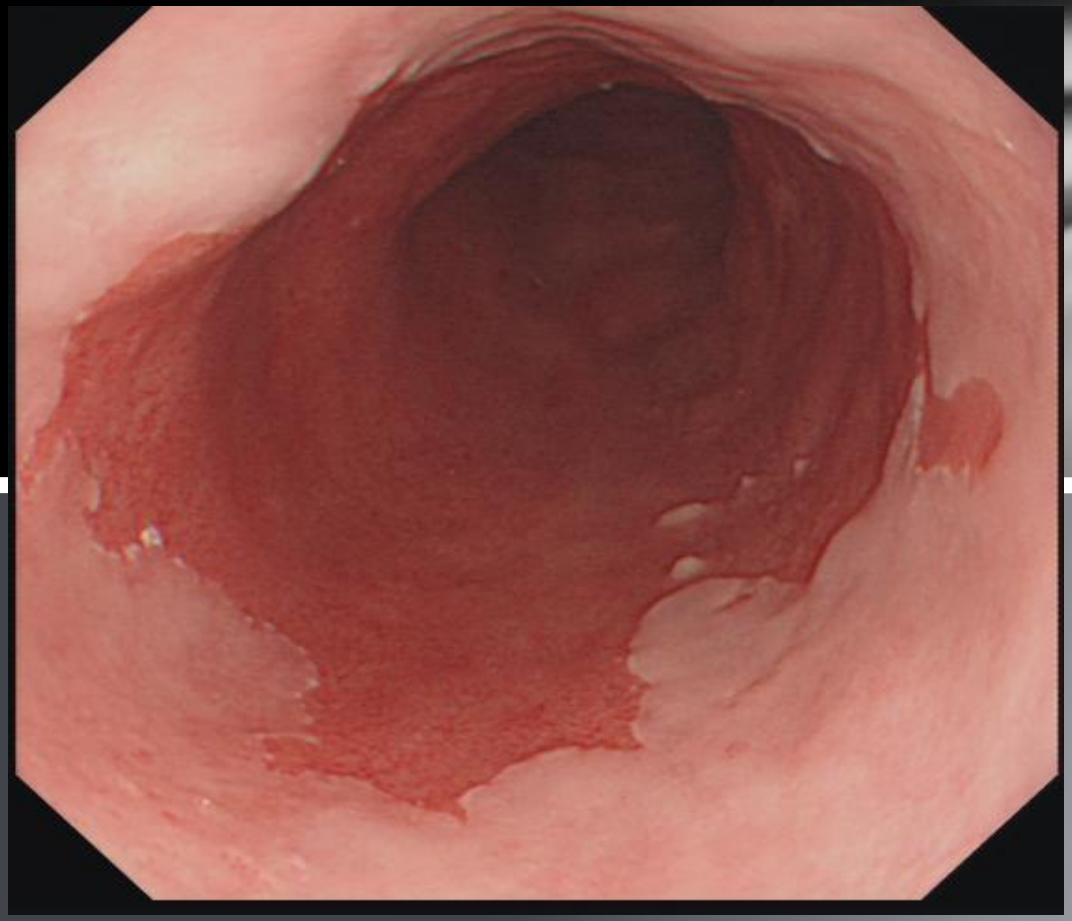
Barrett's Esophagus



Definition of GERD – American College of Gastroenterology

"GERD is defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus"

DeVault et al. Am J Gastroenterol 1999

Definition of GERD – Genval Workshop

"The term GERD should be used to include all individuals who are exposed to the risk of physical complications from gastro-esophageal reflux, or who experience clinically significant impairment of health-related well-being (quality of life) due to reflux-related symptoms, after adequate reassurance of the benign nature of their symptoms"

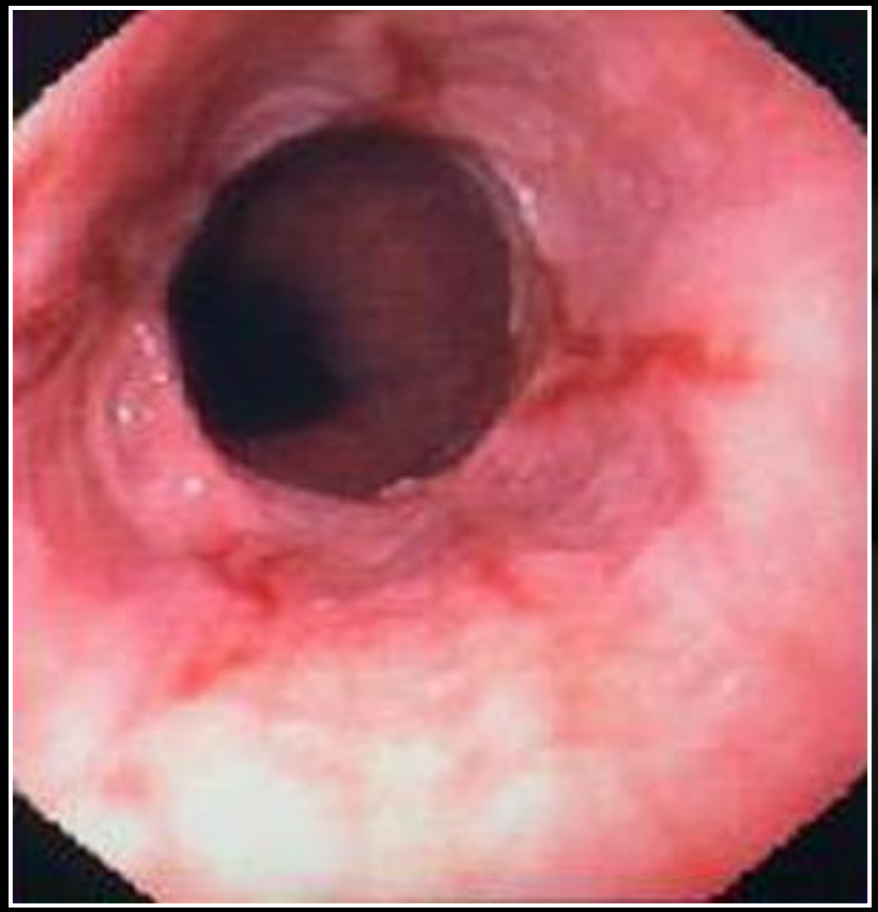
Dent et al. Gut 1999

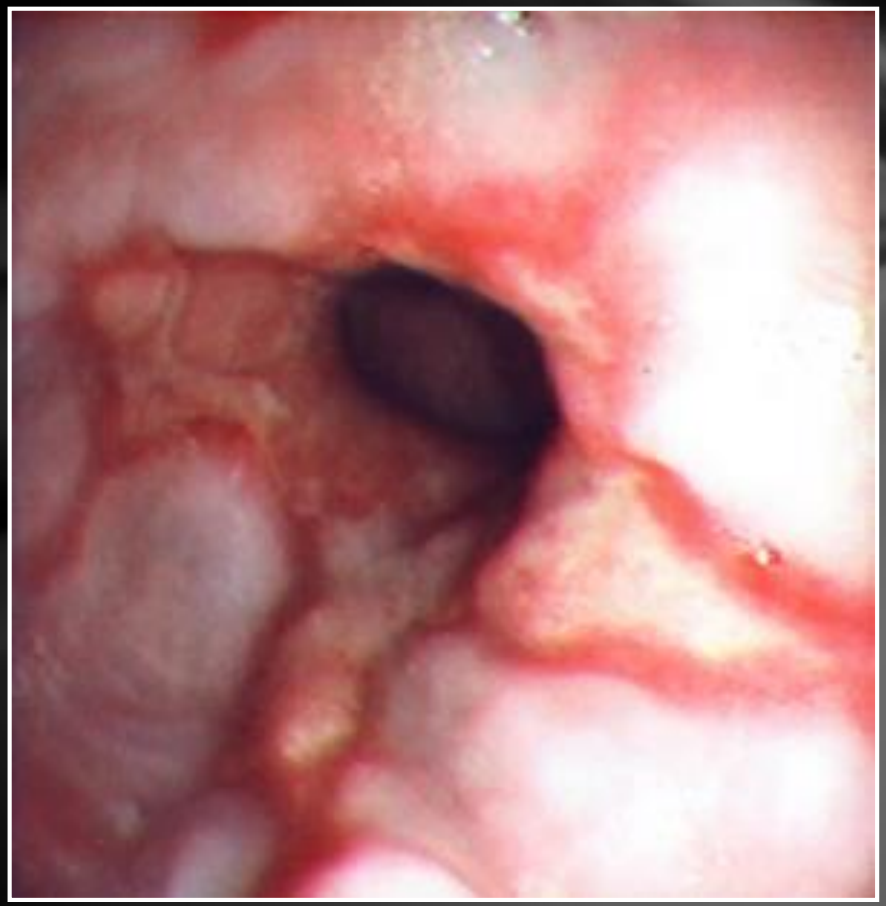
GERD – two main categories

GERD with erosive esophagitis

GERD without erosive esophagitis

Erosive Esophagitis





Symptoms are not reliably predictive of mucosal damage

Patients with and without erosive esophagitis are similar with respect to symptom severity[1]

Patients with and without erosive esophagitis are similar with respect to symptom frequency[1]

Patients with different grades of erosive esophagitis are similar with respect to symptom severity[2]

[1]Smout. Aliment Pharmacol Ther 1997
[2]Lundell et al. Gut 1999

Symptoms associated with GERD

Heartburn

Typical symptoms other than heartburn

Atypical symptoms

Other typical symptoms of GERD

Regurgitation

Dysphagia

Atypical symptoms of GERD

Throat clearing

Globus

Laryngospasm

Dental erosion

Chest pain

Hoarseness

Chronic cough

Sore throat

Wheezing

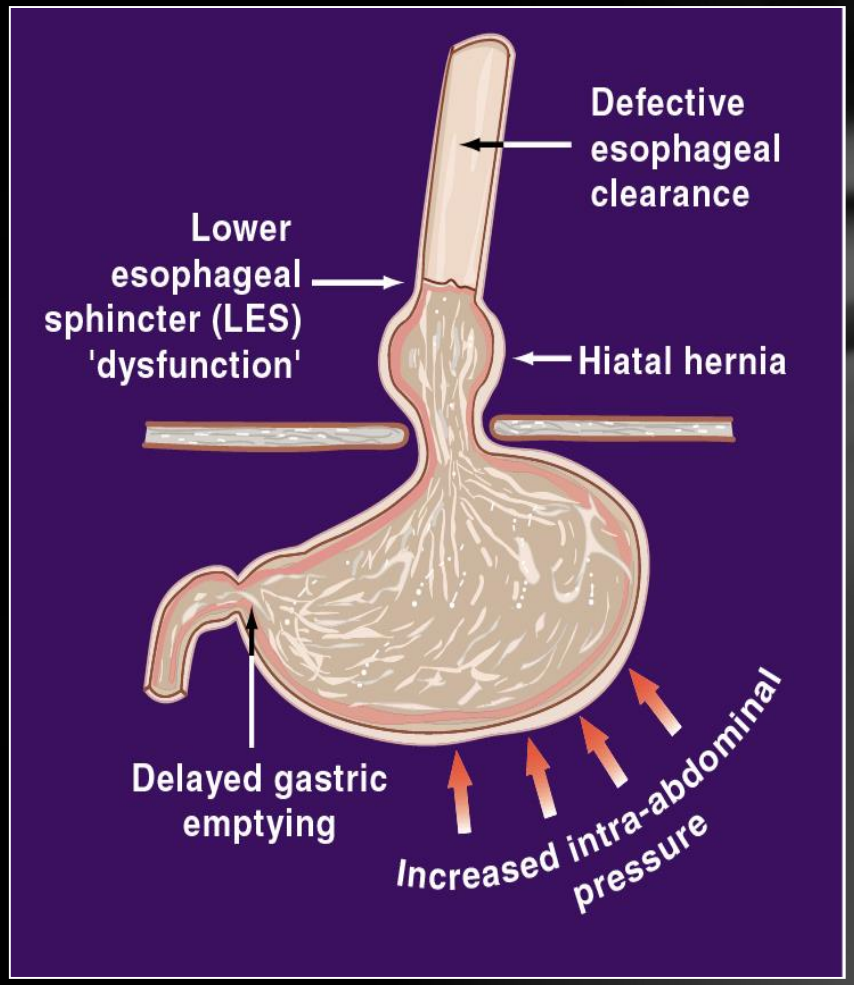
Pathogenesis of GERD – overview

GERD results from exposure of the esophageal mucosa to refluxed gastric contents

In most patients with GERD, exposure of the esophagus to refluxate is greater than normal

In a minority of patients, exposure is within normal limits; in these patients, GERD may be due to decreased mucosal resistance to refluxate

Causes of increased exposure of the esophagus to gastric refluxate



Complications of GERD

Esophageal

- Barrett's esophagus
- adenocarcinoma
- stricture
- ulceration
- bleeding

Extra-esophageal

- asthma
- reflux laryngitis
- vocal cord ulcers
- subglottic stenosis
- tracheal stenosis

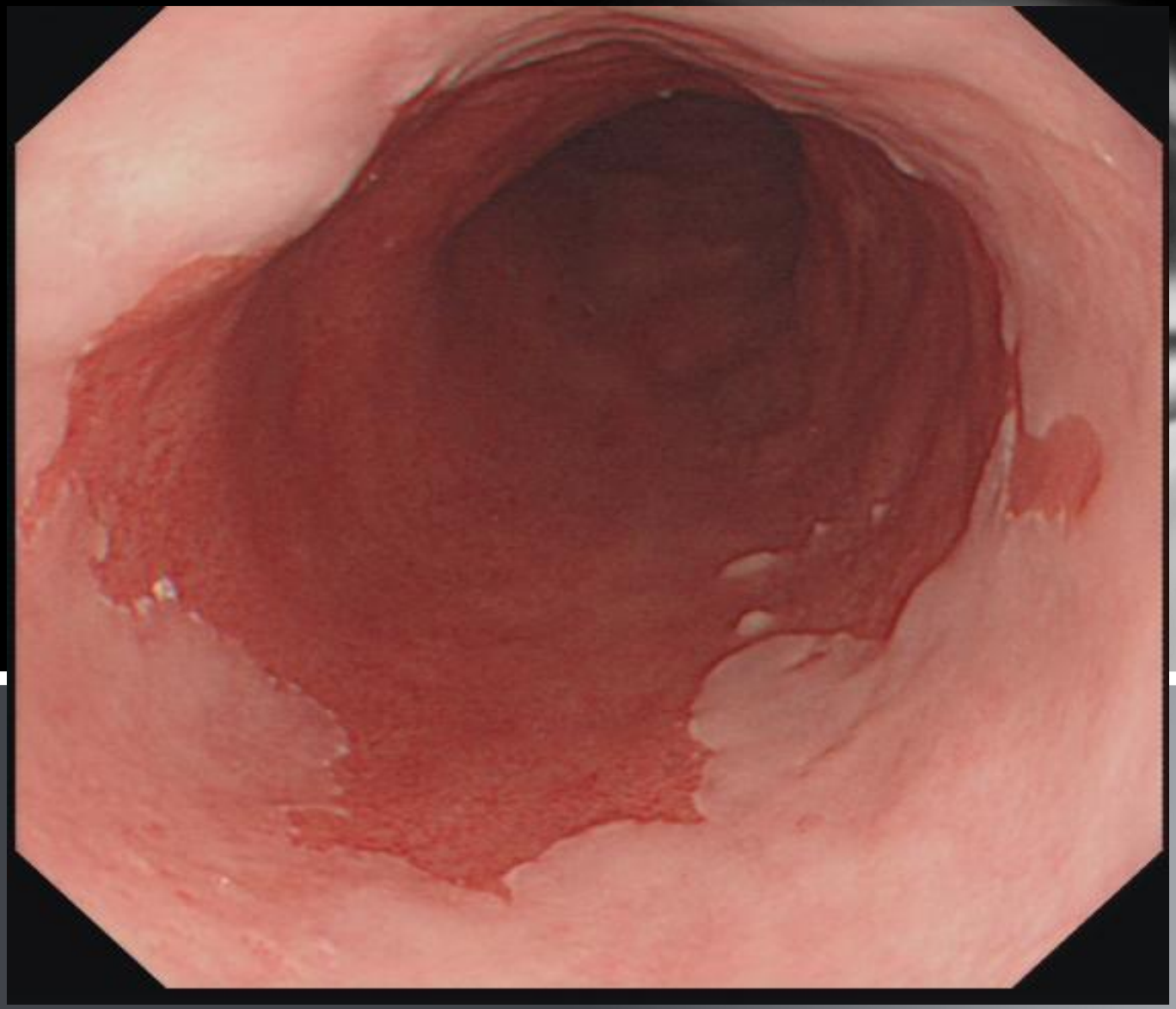
Barrett's definition

Any presence of metaplastic columnar epithelium that replaces the normal stratified squamous epithelium in the esophagus

Biopsy has to show intestinal metaplasia

Develops as a consequence of GERD

Predisposition to development of Adenocarcinoma of the esophagus



Barrett's Esophagus clinical significance

Premalignant lesion for esophageal adenocarcinoma

Patients with Barrett's esophagus may be 30–60 times more likely to develop this cancer than the general population

The reported incidence of Barrett's esophagus is rising

Barrett's Esophagus: premalignant lesion

Normal

⇌

Endoscopy-negative reflux disease

⇌

Erosive esophagitis

⇌ ?

Barrett's esophagus (5-20%)

⇌ ?

Dysplasia

↘

Esophageal adenocarcinoma

Epidemiology

Occurs in 0.9-20% population

- Long segment (> 3 cm) 3-5%
- Short segment (< 3 cm) 10-15%

Male: Female ratio 2:1

- Progression to HGD/Carcinoma (2x)

Uncommon in African Americans and Asians

Average age of diagnosis is 55 y/o

Yousef, et al, Am J Epidem 2008; 168:237

Prevalence of Barrett's Esophagus in General Population of Sweden

	BE	LSBE (≥ 2cm)	SSBE (< 2cm)	No BE
Cases (%)	16 (1.6%)	5 (0.5%)	11 (1.1%)	984 (98.4%)
% with GERD symptoms	56.3%	80.0%	45.5%	39.7%
% with esophagitis	25.0%	60.0%	9.1%	15.4%

From Ronikainen J et al. Gastroenterology 2005;129:1825-31.

Extent of Barrett's

(889 patients underwent EGD)

Long Segment (> 3 cm):	1.6%
Short Segment (< 3 cm):	6.4%
GEJ Barrett's (at Z- line):	5.6%

- Hirota, et al, Gastro 1999:116:277

Long Segment Barrett's vs Short

Longer history GERD

Worse 24 hour pH studies

- Increased proximal esophageal acid exposure

More upright and supine GERD

Lower LES pressure measurements

Decreased esophageal peristalsis amplitude

Higher prevalence of Dysplasia (24% vs. 8%)

Higher likelihood to have carcinoma

Westin et al, Am J Gastroenterol 1997; 92:407

Risk of cancer in Barrett's

Variable incidence rates in various studies

0.5% /year accepted with no dysplasia precursor

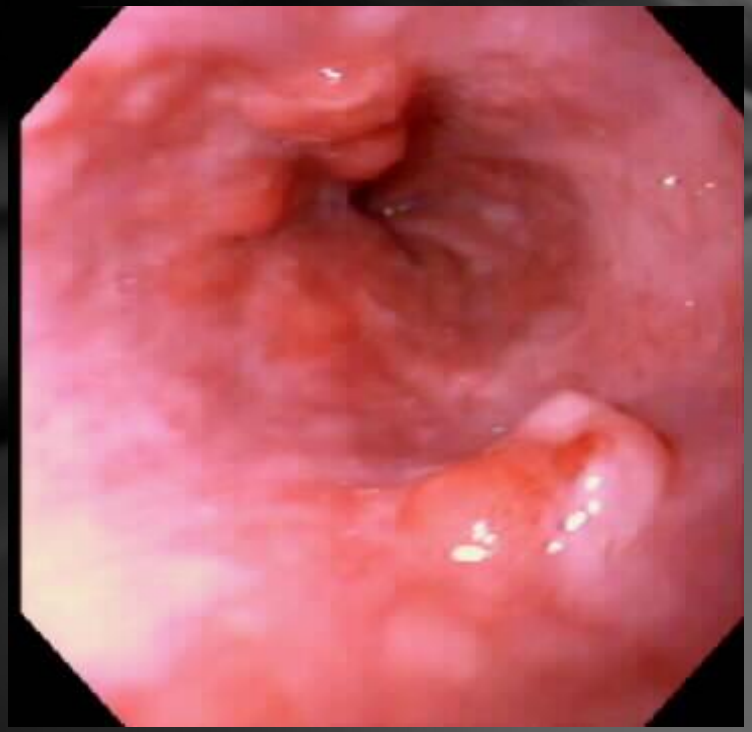
HGD → Cancer (5-8%/yr)

LGD → Cancer (??)

Increases with age

Increased with weekly GERD

Increased in males



Meta analysis: Rubenstein, et al, Alim Pharm Ther, 2010;32:1222

Screening for Barrett's Esophagus

Meta analysis:

- 1189 patients with cancer & 4666 controls

- Patients with weekly GERD symptoms were more likely to have cancer (odds ratio 4.9)
- Patients with daily GERD symptoms were more likely to have cancer (odds ratio 7.4)
- Patients with no symptoms or less than weekly GERD were not as likely
- > 40% patients had no GERD symptoms

Rubenstein, et al, Alim Pharm Ther; 2010;32:1222

Screening for Barrett's Esophagus: Problems

Relatively few cases of esophageal adenocarcinoma

- 5% esophageal cancers occur in know Barrett's

High prevalence of GERD

No prior GERD symptoms in 40% of adenocarcinoma patients

EGD & pathology diagnostic inconsistencies

No clear evidence that has impact on mortality

AGA Recommendation for Screening

>50 y/o

Males

White

Chronic GERD at lest weekly

Hiatal hernia

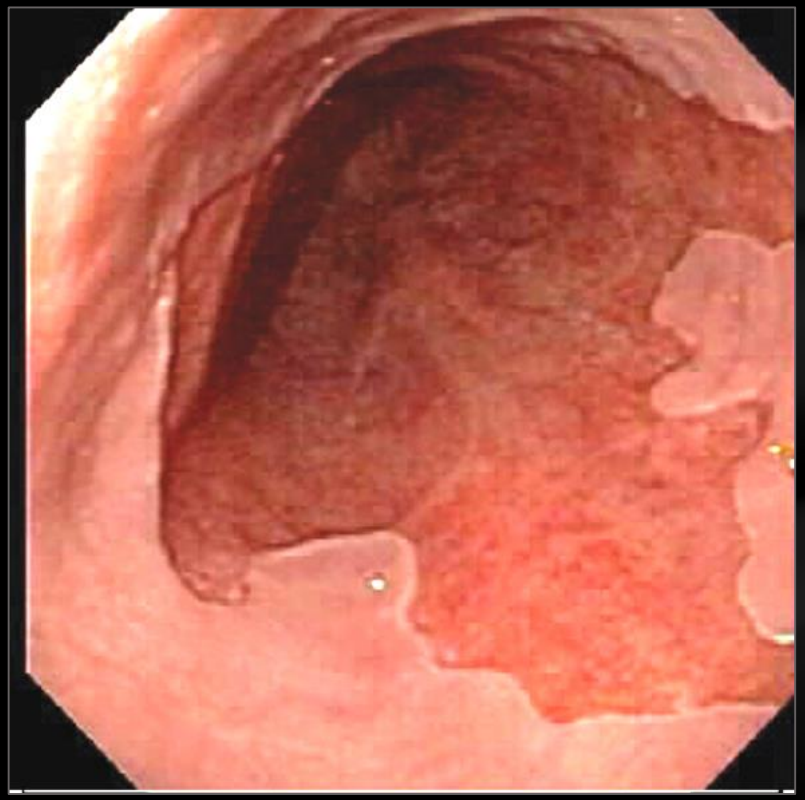
Increased BMI

Intra-abdominal body fat distribution

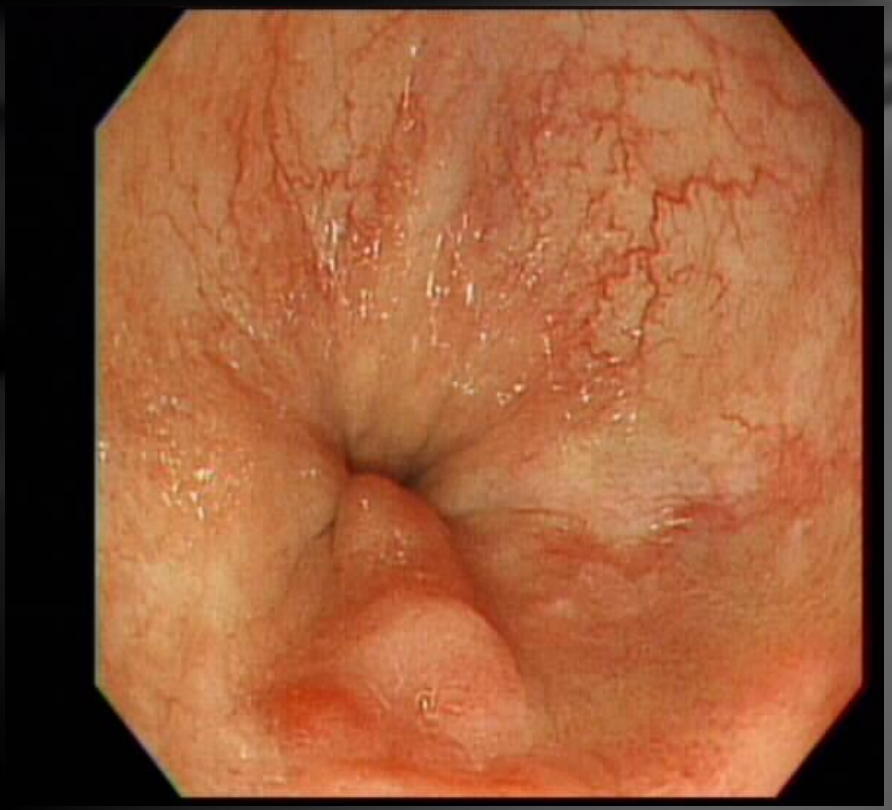
Gastroenterology 2011; 140: 1084

Surveillance of Barrett's

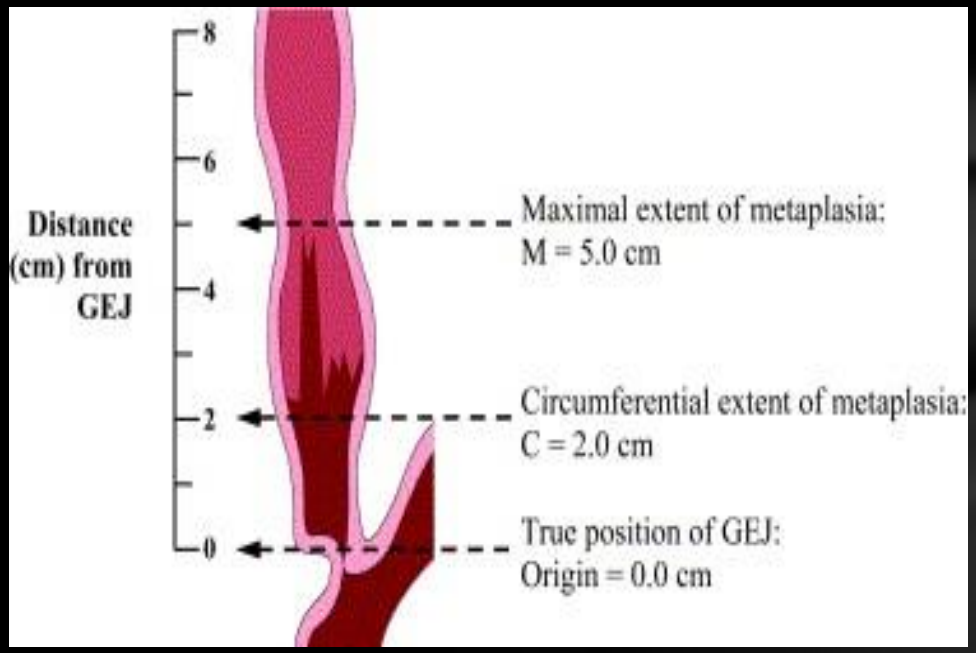
Endoscopy

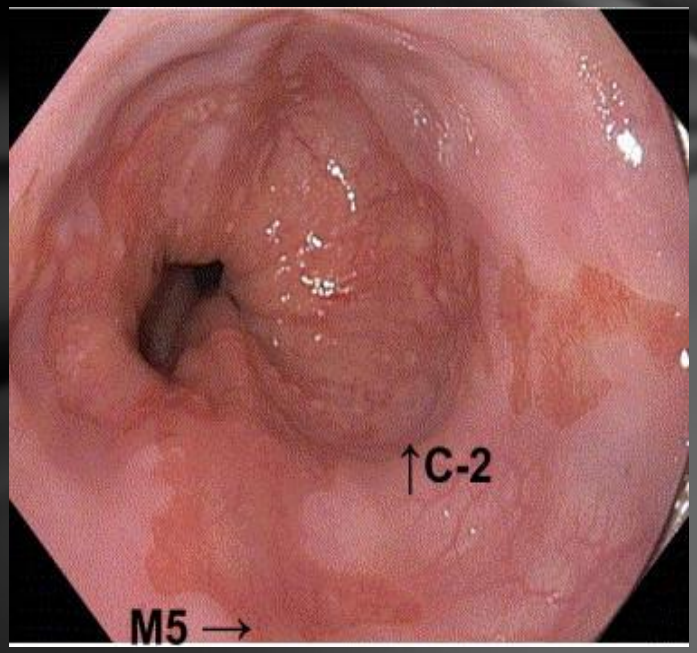


Endoscopy



Barrett's Esophagus: The Prague Classification





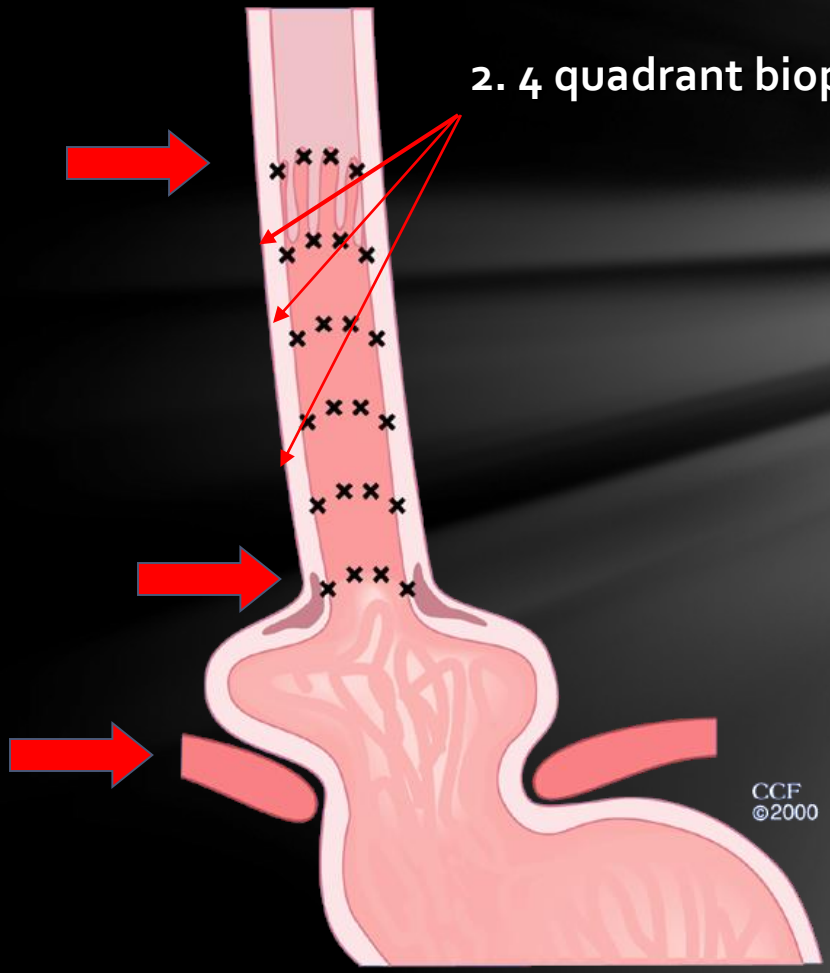
Good interobserver reliability

From Sharma P et al. Gastroenterology 2006;131:1392-9.

Barrett's Esophagus: Technique of Endoscopic Surveillance

1. Define Landmarks

2. 4 quadrant biopsies q 2 cm



From Falk GW. Techniques in GI Endoscopy 2000;2:186-93.

Endoscopic Surveillance (limitations?)

Observational studies

- Detect curable dysplasia and cancer at earlier stage

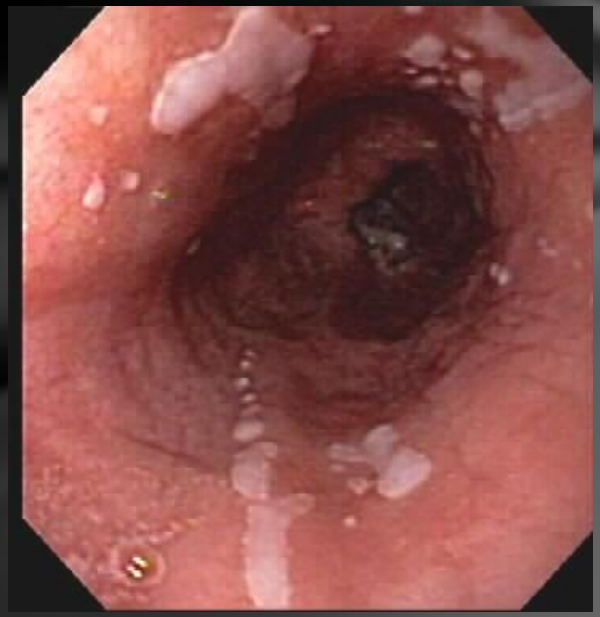
Dysplasia/early cancer

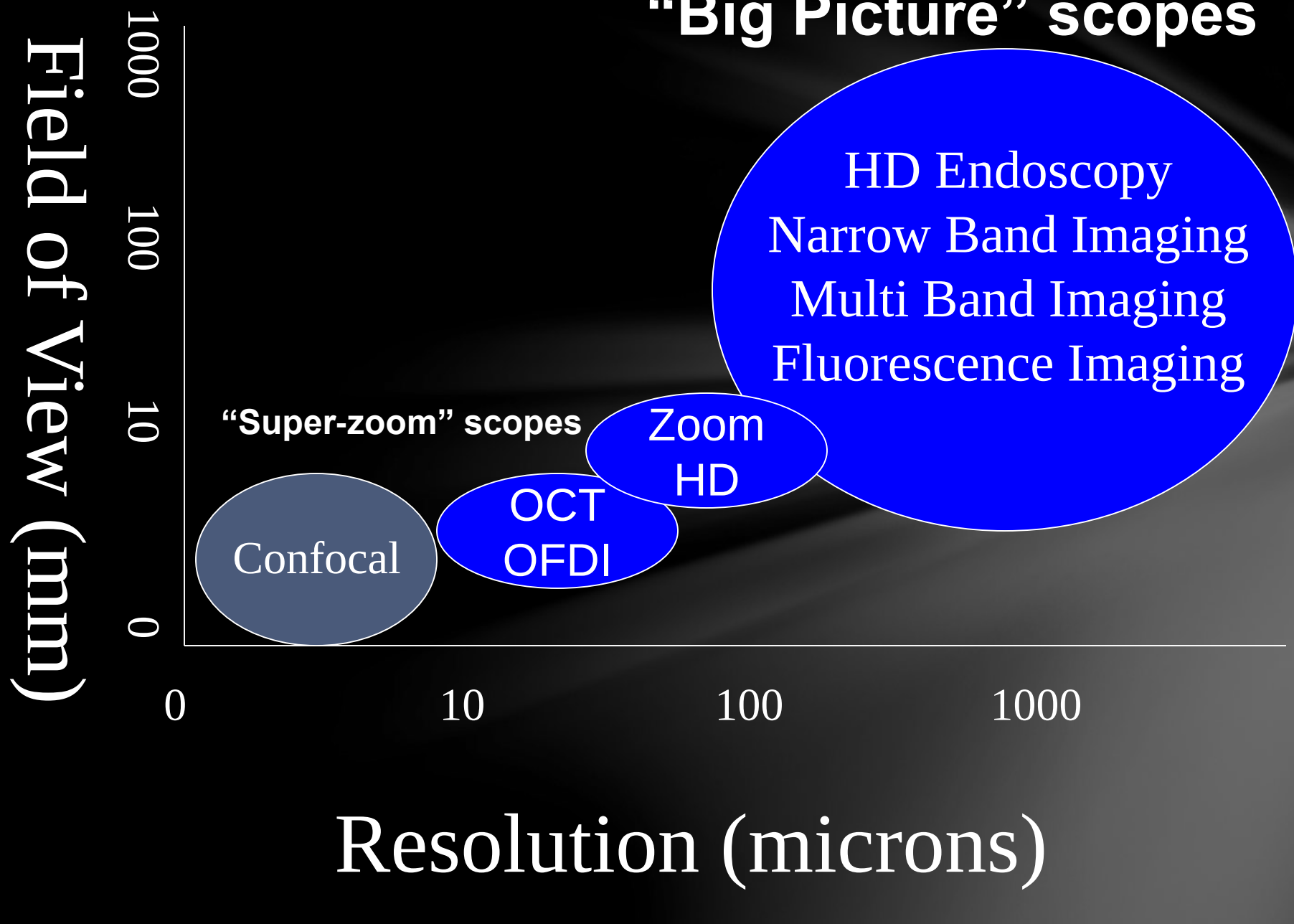
- Indistinguishable
- Patchy distribution

Interobserver variability in dysplasia interpretation

Most patients never develop cancer

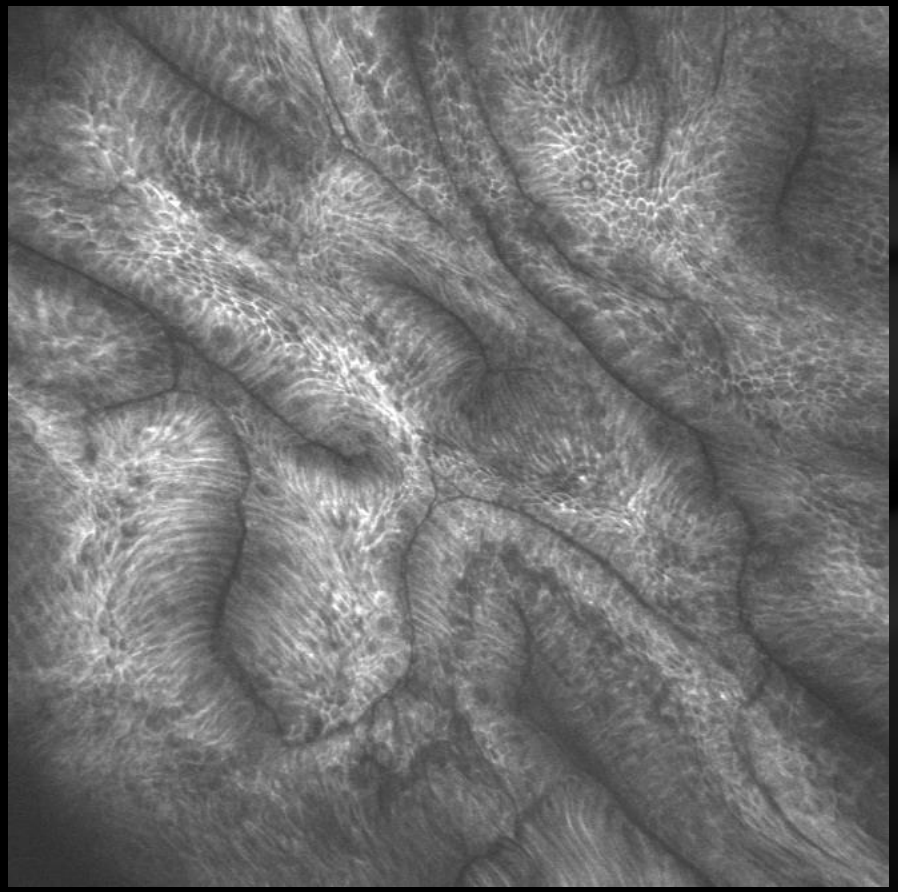
- Incidence 0.5%/year

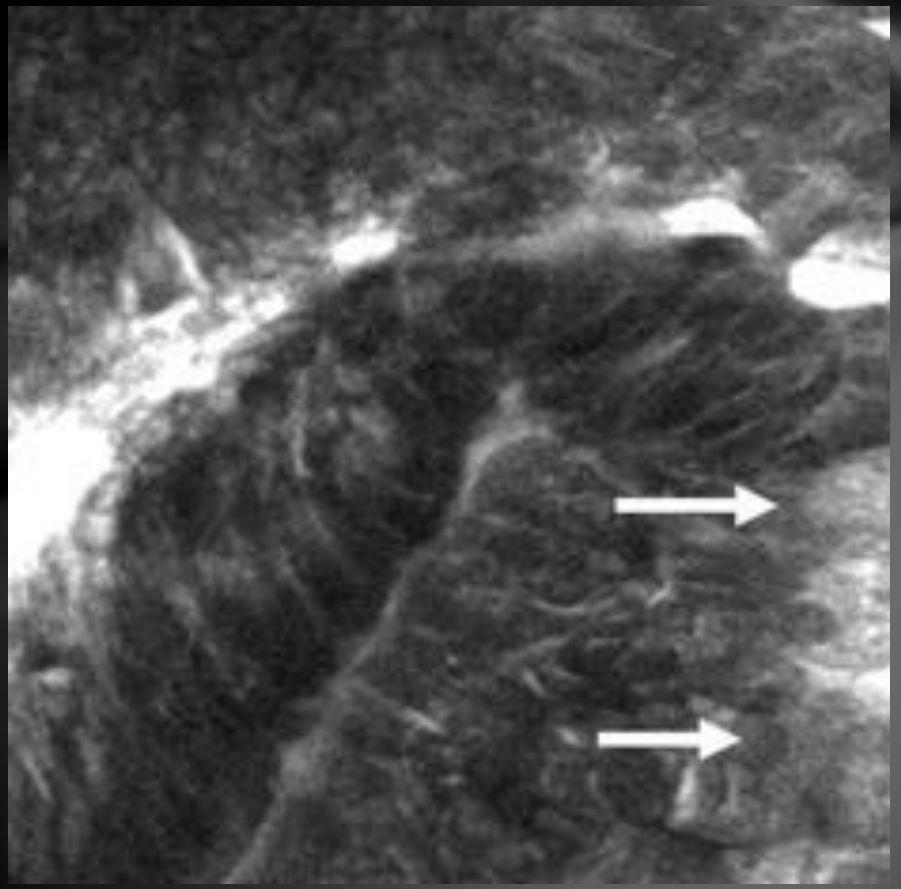



“Big Picture” scopes
HD Endoscopy
Narrow Band Imaging
Multi Band Imaging
Fluorescence Imaging
“Super-zoom” scopes
Zoom
HD
OCT
OFDI
Confocal
Field of View (mm)
1000
100
10
0
0
10
100
1000
Resolution (microns)

Confocal Images

(Esophagus)





Barrett's Treatment Modalities

PPI acid suppression

- Symptoms of acid reflux or esophagitis on endoscopy
- Reduction of HGD dysplasia or cancer progression (indirect evidence)
- pH studies show pathological acid reflux in patients with Barrett's on PPI therapy

Aspirin/NSAIDs/Statins

- 2009 meta-analysis suggest **ASA**/NSAID associated with less cancer
- Celecoxib not shown to reduce progression to dysplasia/cancer
- COX-2 inhibitors may carry high cardiac risk
- Meta-analysis with **statin** showed 28% reduction in cancer risk/Barrett's

Surgical Fundoplication

- Not more effective than medical therapy to prevent cancer
- Show similar partial regression of Barrett's as in PPI
- Decrease rate of cancer (uncontrolled studies)

Barrett's Treatment Modalities

Ablation Options:

- Endoscopic Mucosal Resection (EMR)
- Argon Plasma Coagulation (APC)
- Bipolar Coagulation
- Laser Coagulation
- Radiofrequency Ablation (RFA)
- Cryo-ablation
- Photodynamic therapy (PDT)

Treatment for Barrett's (HGD)

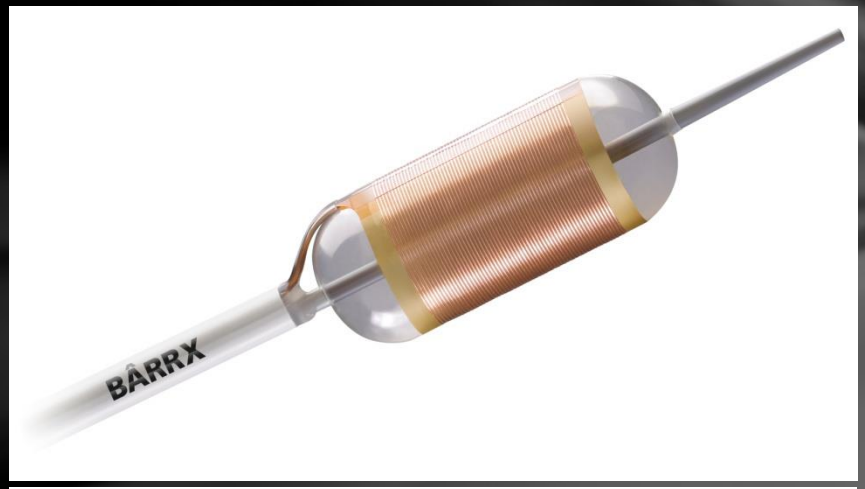
Radiofrequency Ablation

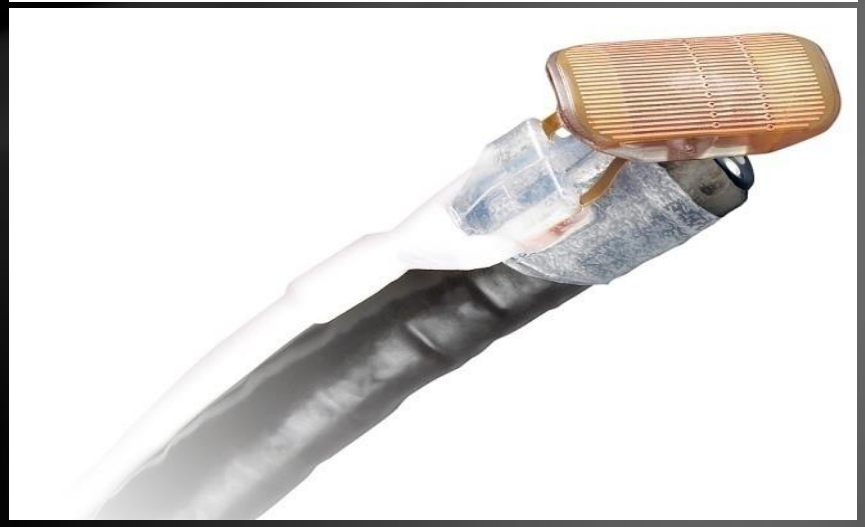
Bipolar array

Electrical field

Frictional heating of water

Ablation of the mucosa

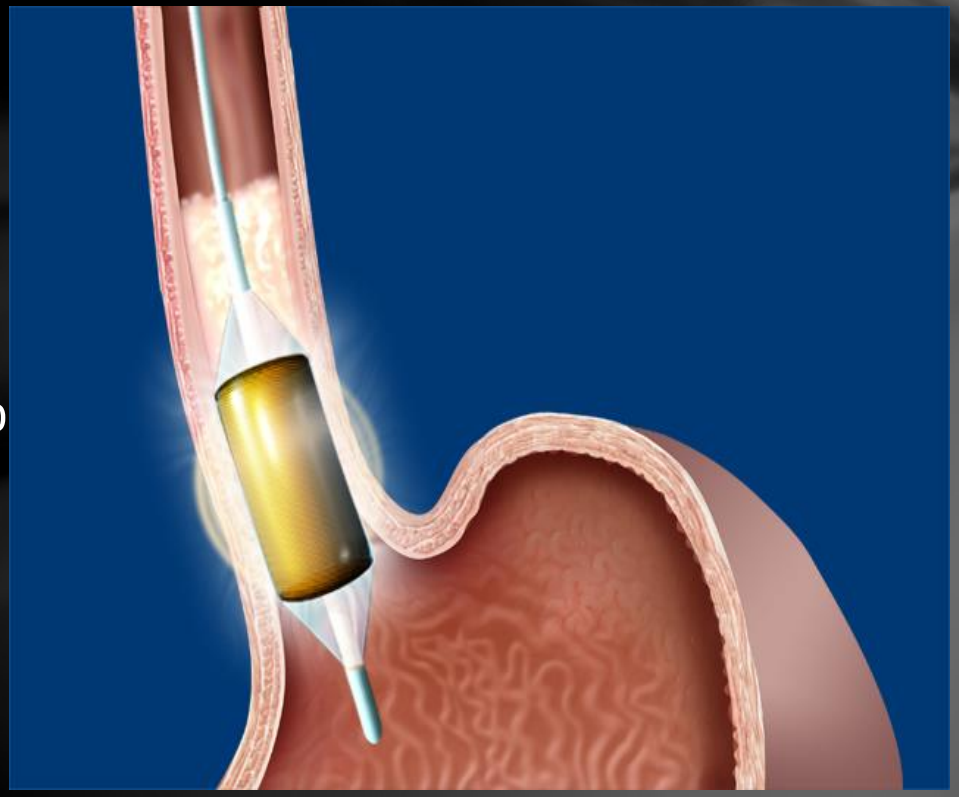




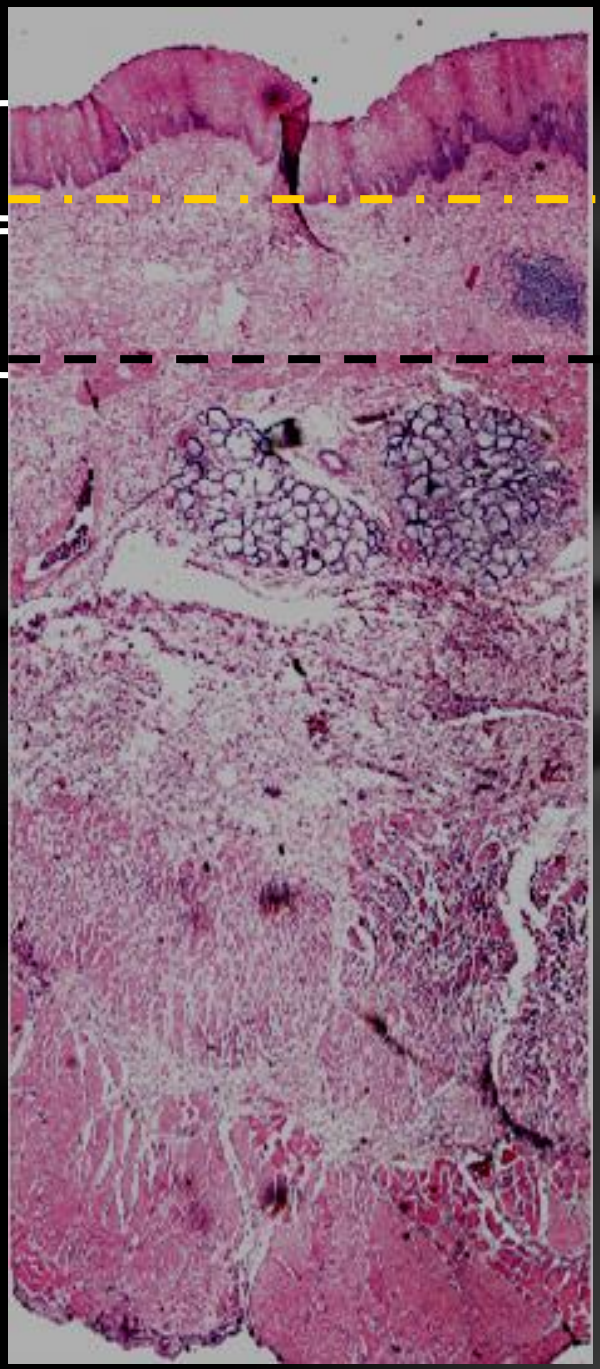
RFA Ablation HGD

Randomized sham trial

- 127 patients
- At 1 year follow up
  - LGD 91% eradicated vs. 3%
  - HGD 81% eradicated vs. 19%
  - Fewer cancers 1% vs. 9%



Anatomy and RFA



Targeted Epithelium
Thickness ~500µm

RFA
Ablation depth 500-1,000µm

Approximate EMR Depth

Esophageal epithelium ~500µm

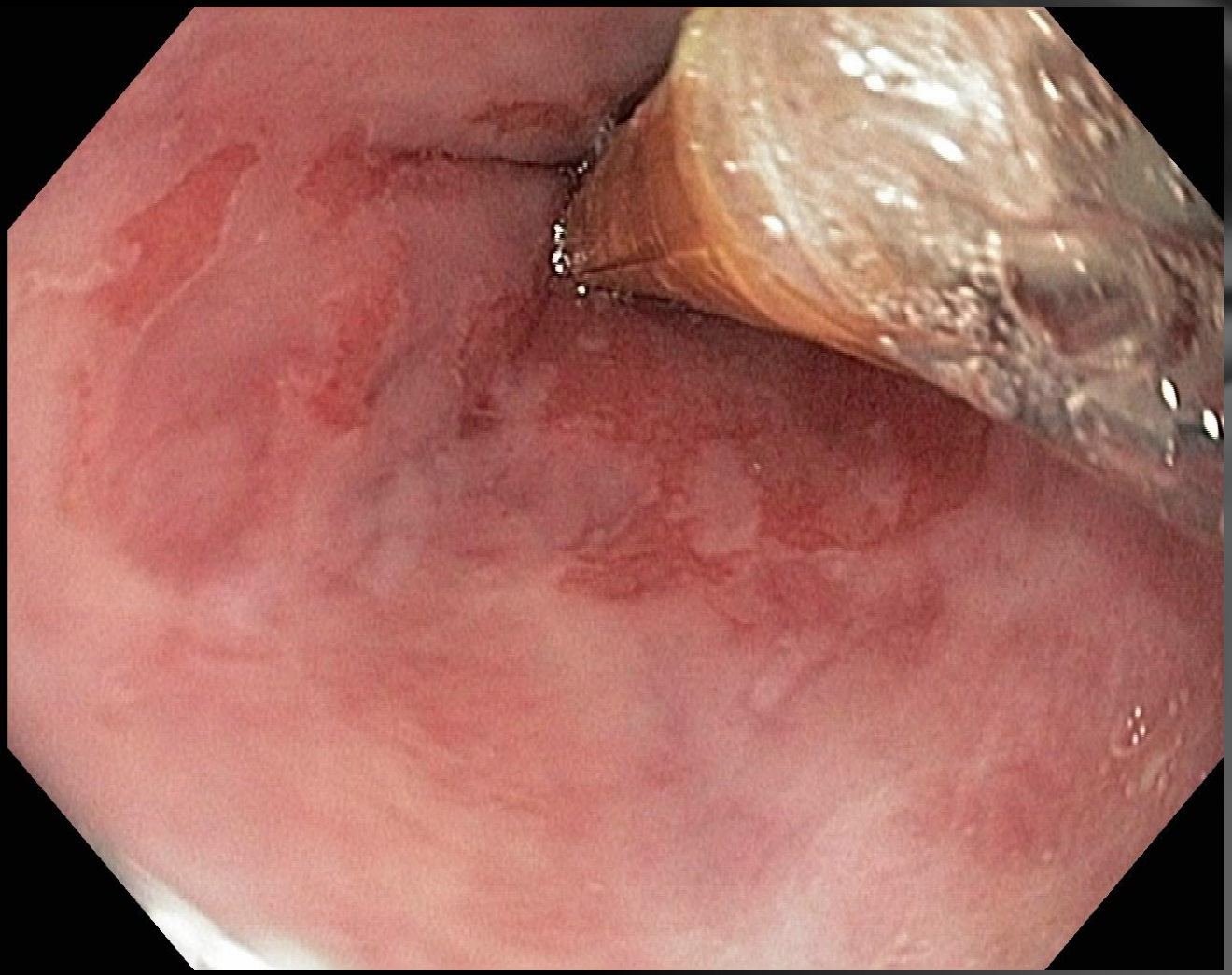
Lamina Propria

Muscularis Mucosae

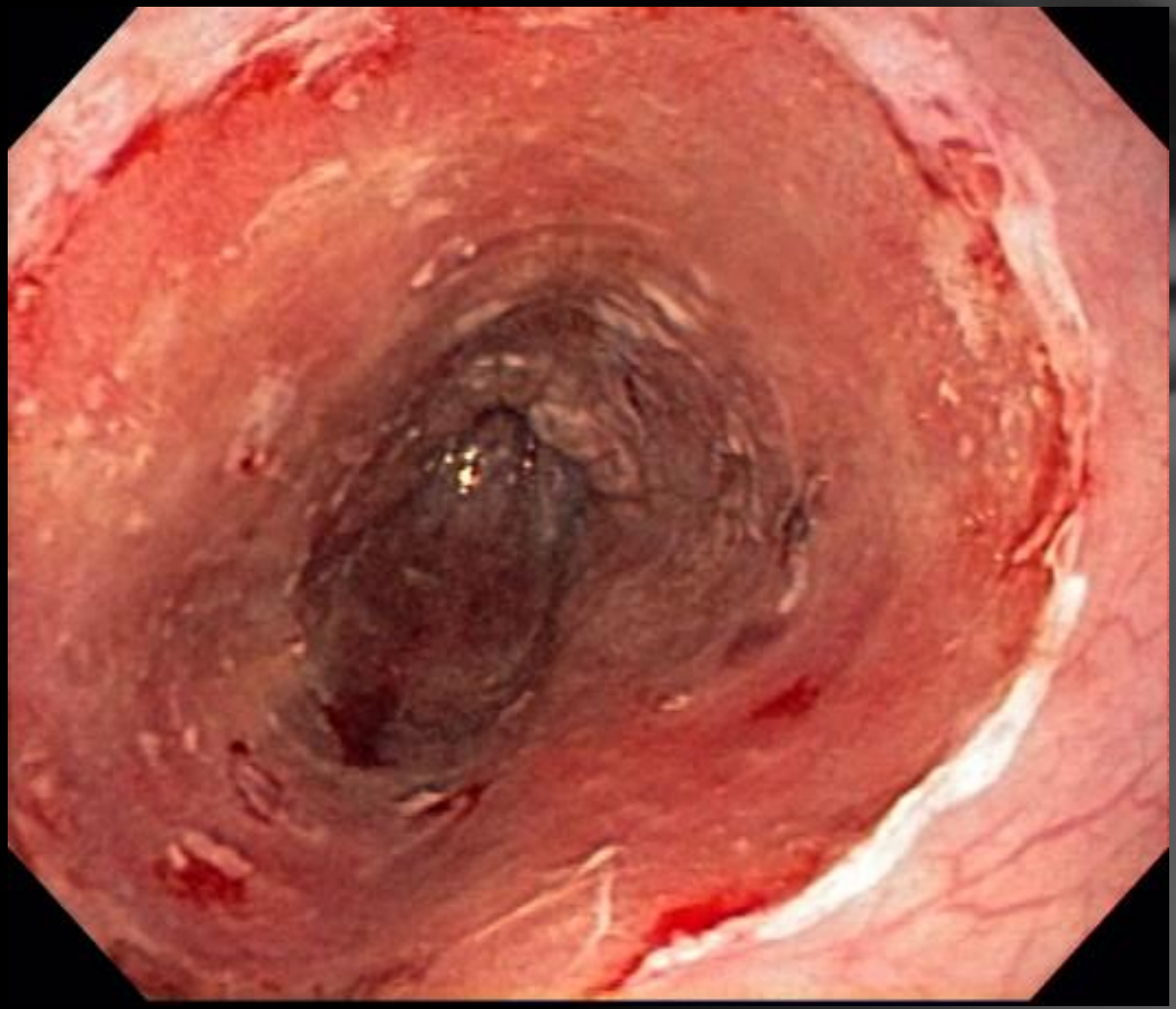
Submucosa

Muscularis Propria

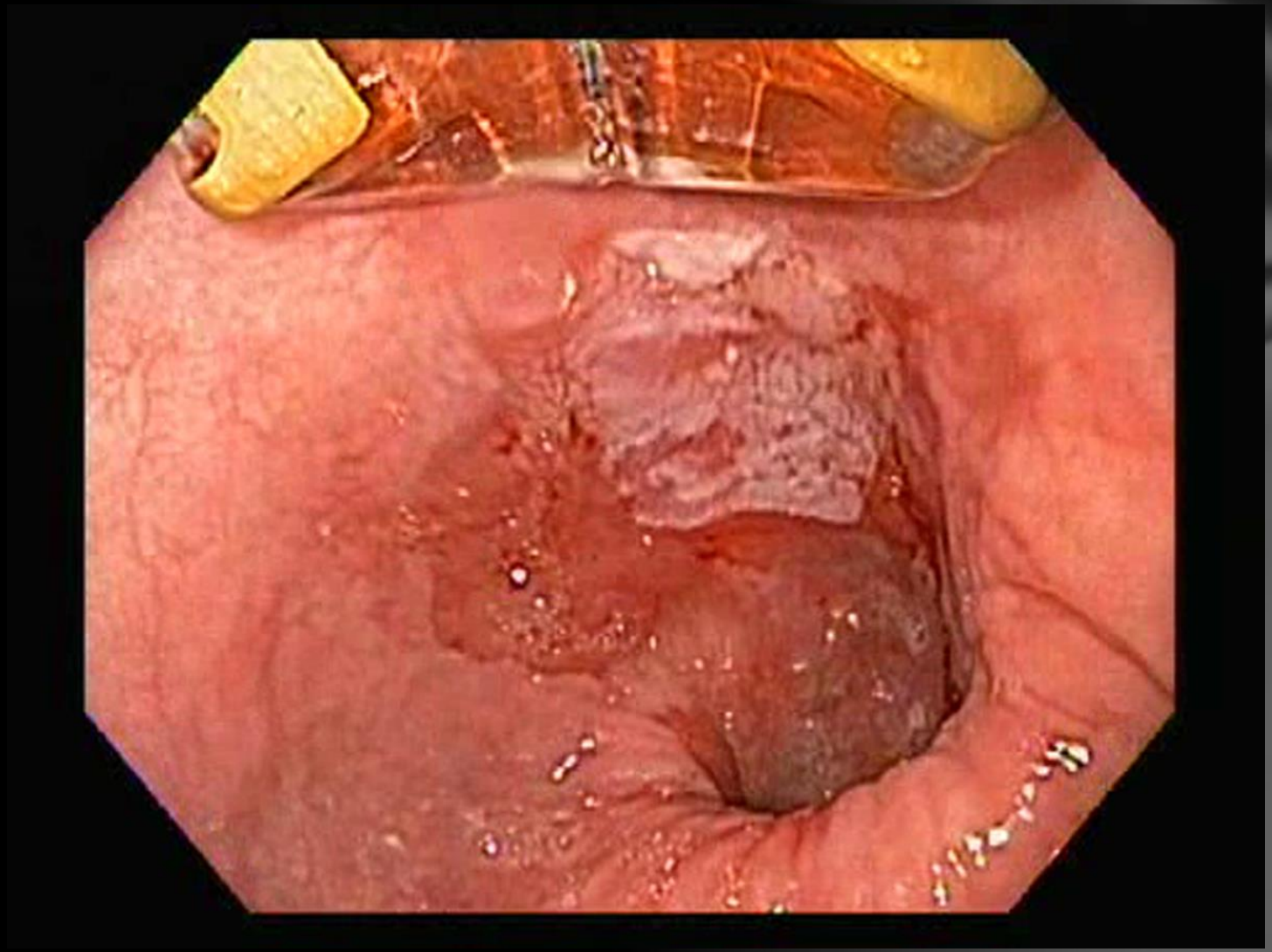
Circumferential Ablation (Radiofrequency ablation)



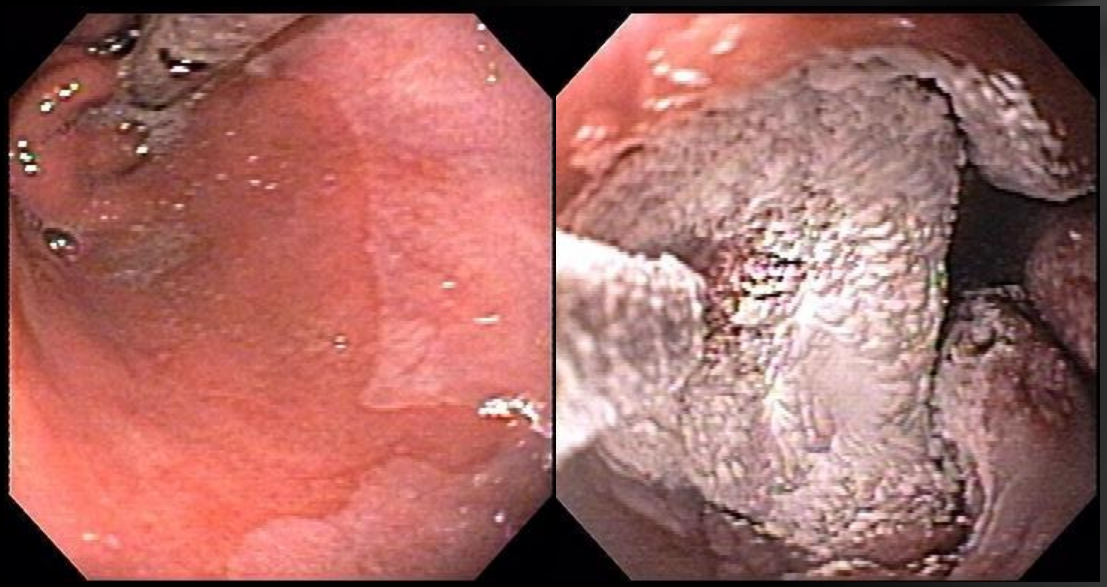
Immediate Ablation Effect (Radiofrequency ablation)



Ablation with HALO90



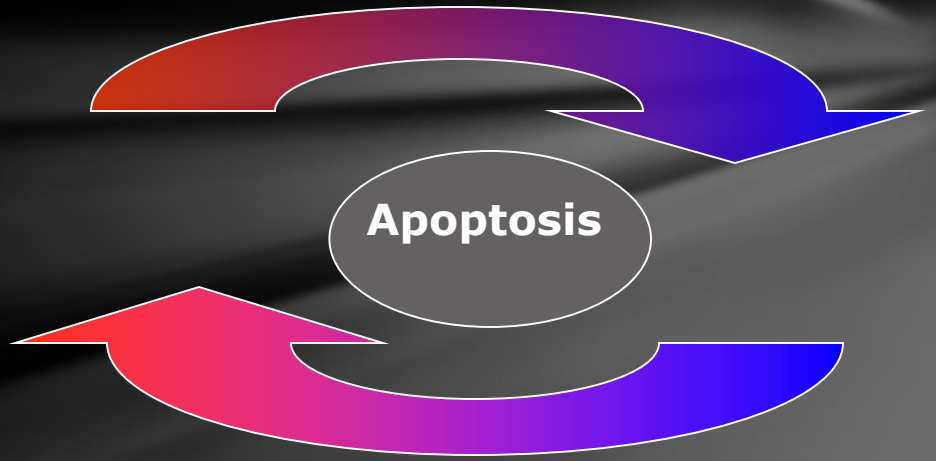
LN CryoSpray Ablation (CSA)



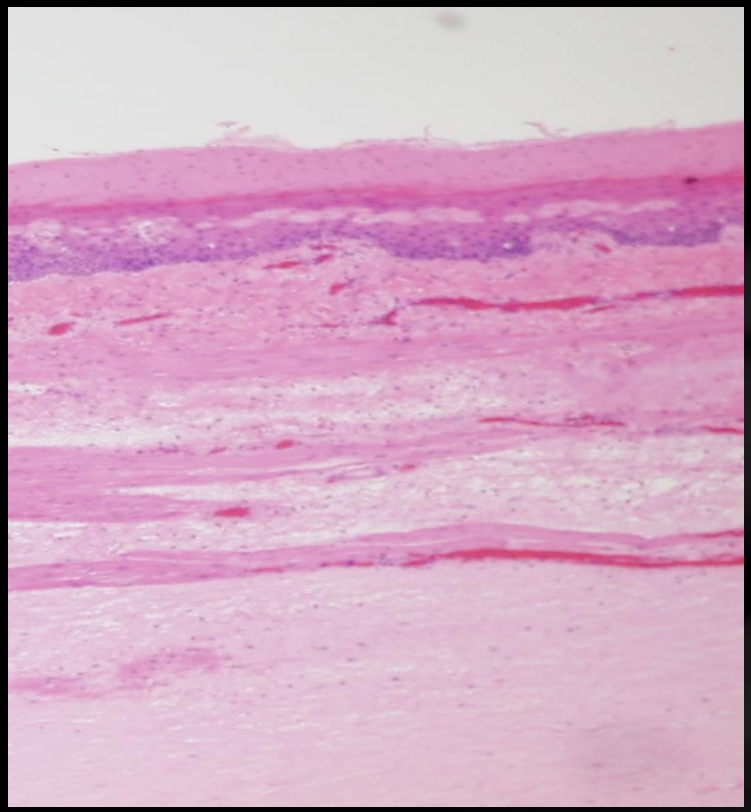
LN Cryotherapy Mechanism of Injury

The freeze-thaw cycle

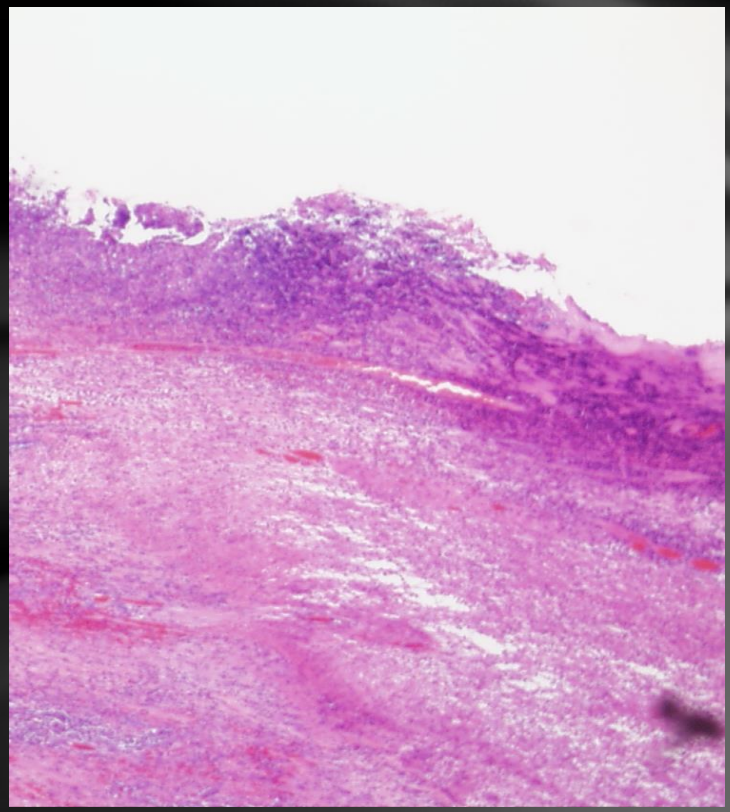
- Ice crystals disrupt lipids and cytoskeleton
- Ischemia and vascular stasis
- Reperfusion injury with cellular leakage and submucosal hemorrhage
- Inflammatory response
- Immune stimulation



LN Cryotherapy Depth of Injury



1 hour: minimal inflammation



48 hours: marked inflammation

Johnston Gastrointest Endosc 2001 A3448

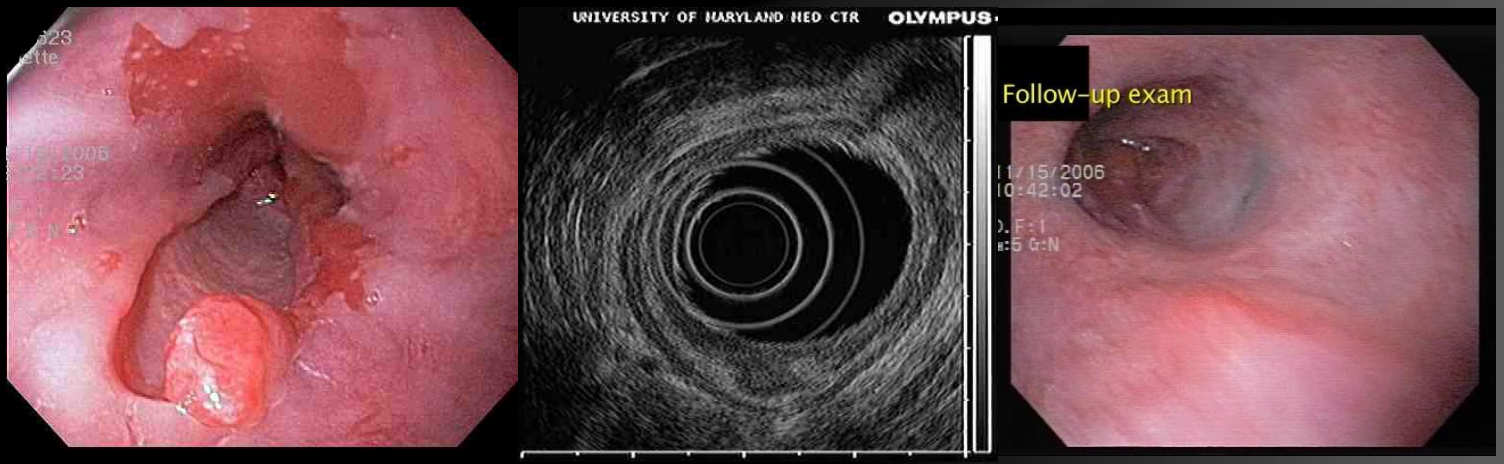
LN Cryotherapy Advantages

High patient tolerance

- Minimal chest pain
- Familiarity with concept

Able to treat uneven surfaces

Possible to treat submucosal lesions



Greenwald DDW 2007

LN Cryotherapy Risks

Strictures 4%

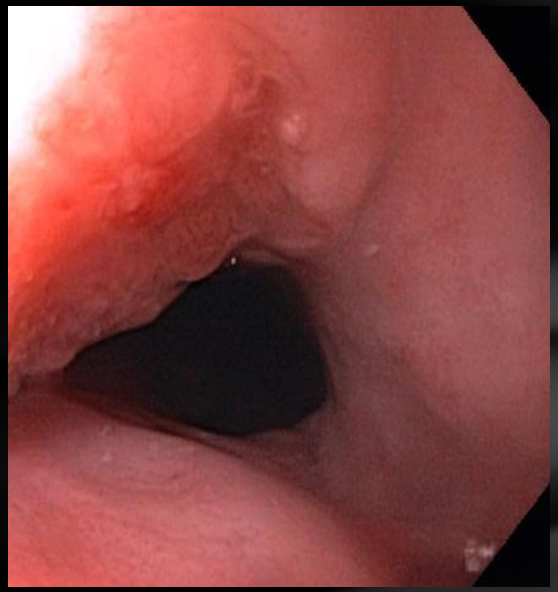
- Appears limited to those with prior narrowing or therapy

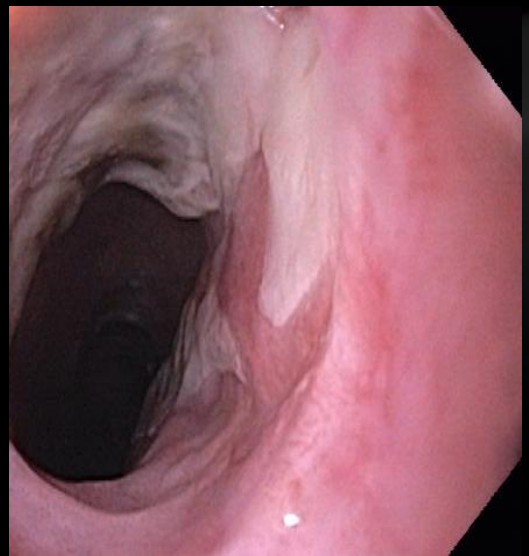
Lip ulcer

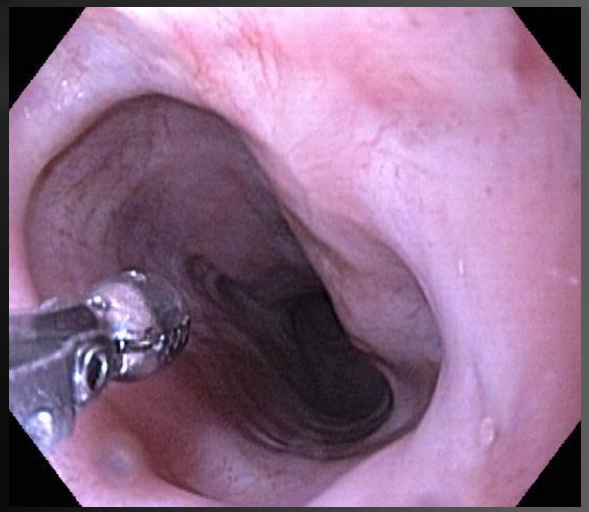
Pain usually mild – 0 to 5 days

LN Cryotherapy and Squamous Cell Cancer

Invasive SCC







Treatment for HGD

Endoscopic

- EMR
  - Can remove early cancers and give staging information
  - Best results when used with ablative therapy
- PDT
  - Increased complications, buried glands
  - 15% eventually developed cancer
- APC
  - Buried glands, incomplete destruction

Surgical

- Esophagectomy
  - Removes all tissue absolutely
  - Mortality 3-12%, morbidity

Surveillance

- Biopsy every 3 months
- Increased cancer risk compared to ablative therapy

Treatment for LGD

Efficacy for cancer prevention not established

? How long ablation will last

Still need to perform EGD for surveillance

Too many unanswered questions

AGA Recommendations

Screen

- >50 y/o, male, white
- Chronic GERD, hiatal hernia
- Increased BMI, intra-abdominal fat distribution

Treat

- PPI if drug risk is low
- ASA?? (only if cardioprotective)

Surveillance

- No dysplasia: 3-5 years
- LGD : 6-12 months
- HGD : 3 months

Therapy

- HGD : eradication with RFA, PDT, EMR, Cryo
- HGD : young pts, long segment Barrett's, multifocal