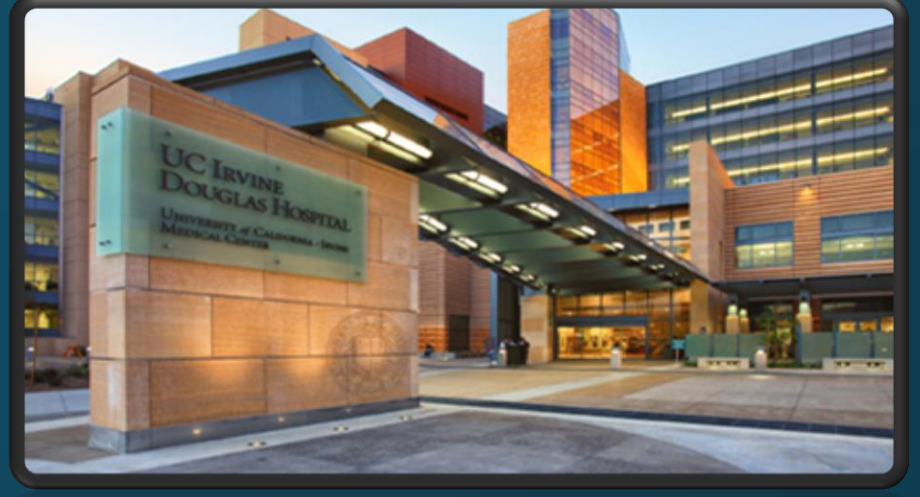
UC Irvine Health



Management of Barrett's Esophagus and Early Esophageal Cancer

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University of California, Irvine

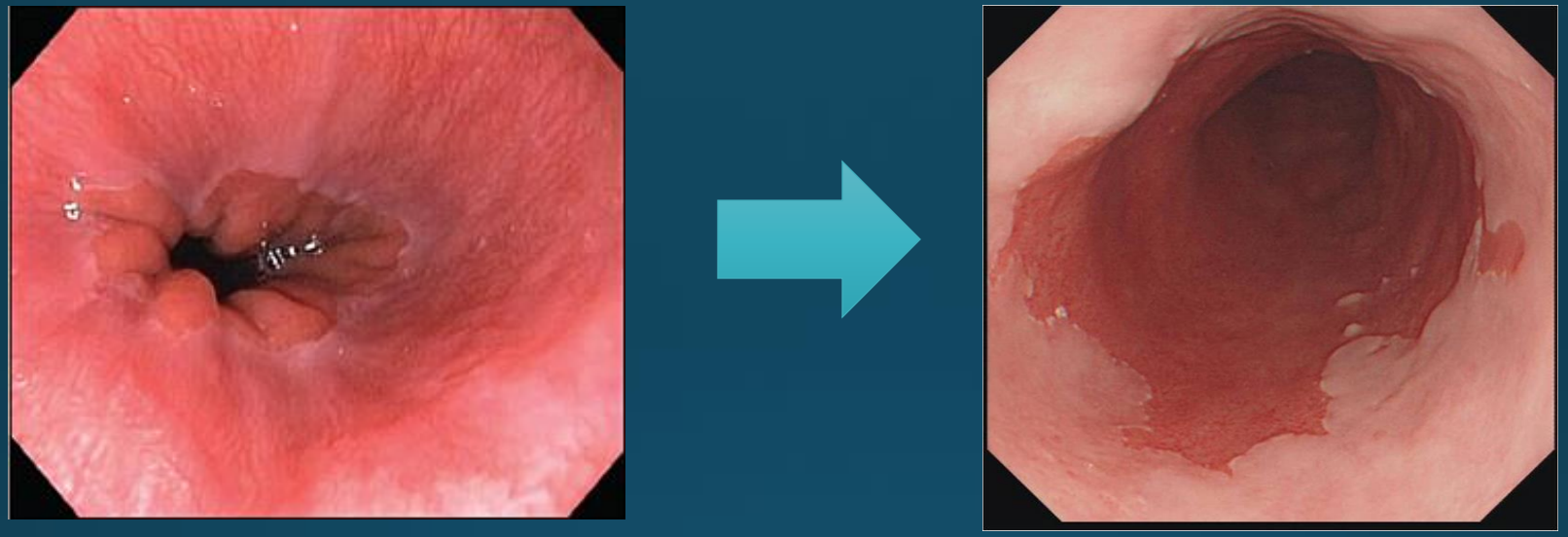
Case 1 – Tom

"My best friend just got diagnosed with Esophagus cancer. Do I need one of those scope things done?"

- 62 yo caucasian male who complains of 3x / week classic heartburn symptoms
- Has been having symptoms for > 5 years, takes OTC antacids with complete relief
- No other symptoms
- 42 pack year smoking history
- No family hx of Esophageal cancer

Would you refer him for an EGD?

Definition of Barrett's Esophagus

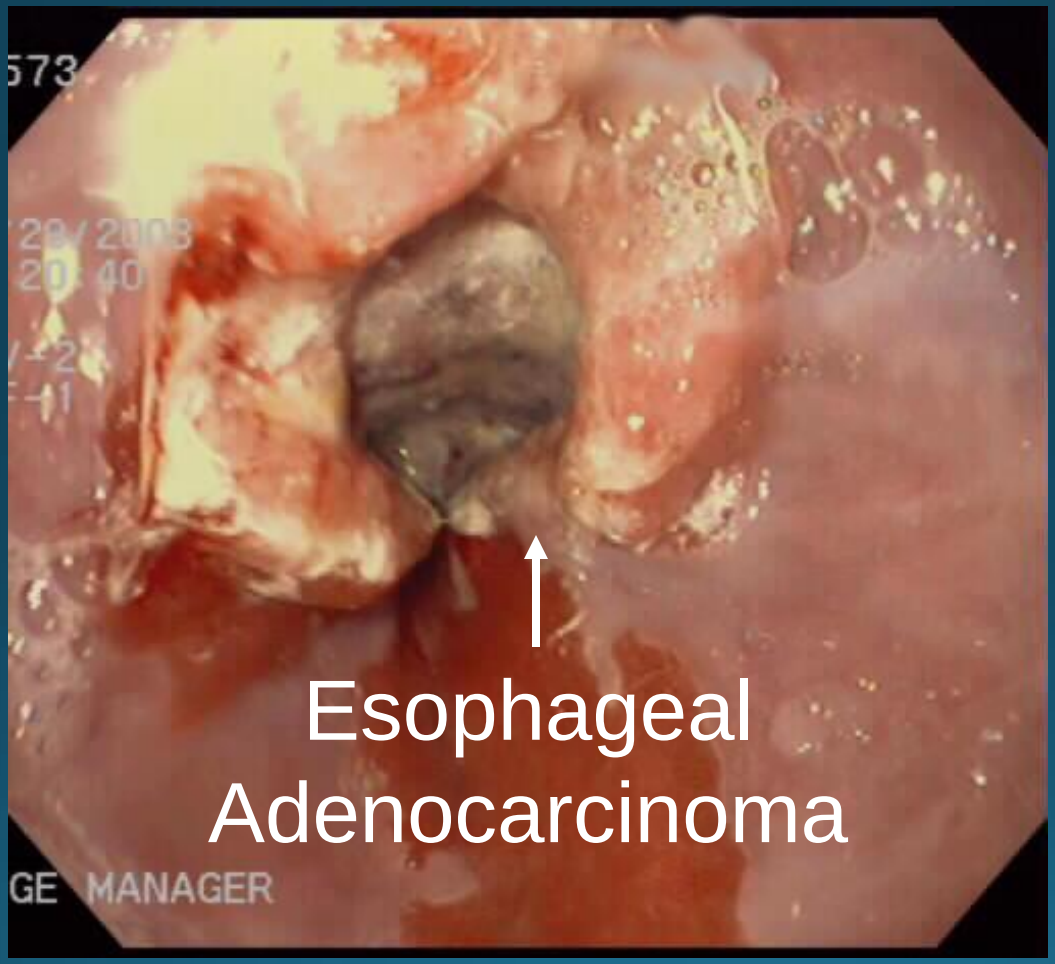


The condition in which any extent of metaplastic columnar epithelium (that predisposes to cancer development) replaces the stratified squamous epithelium that normally lines the distal esophagus

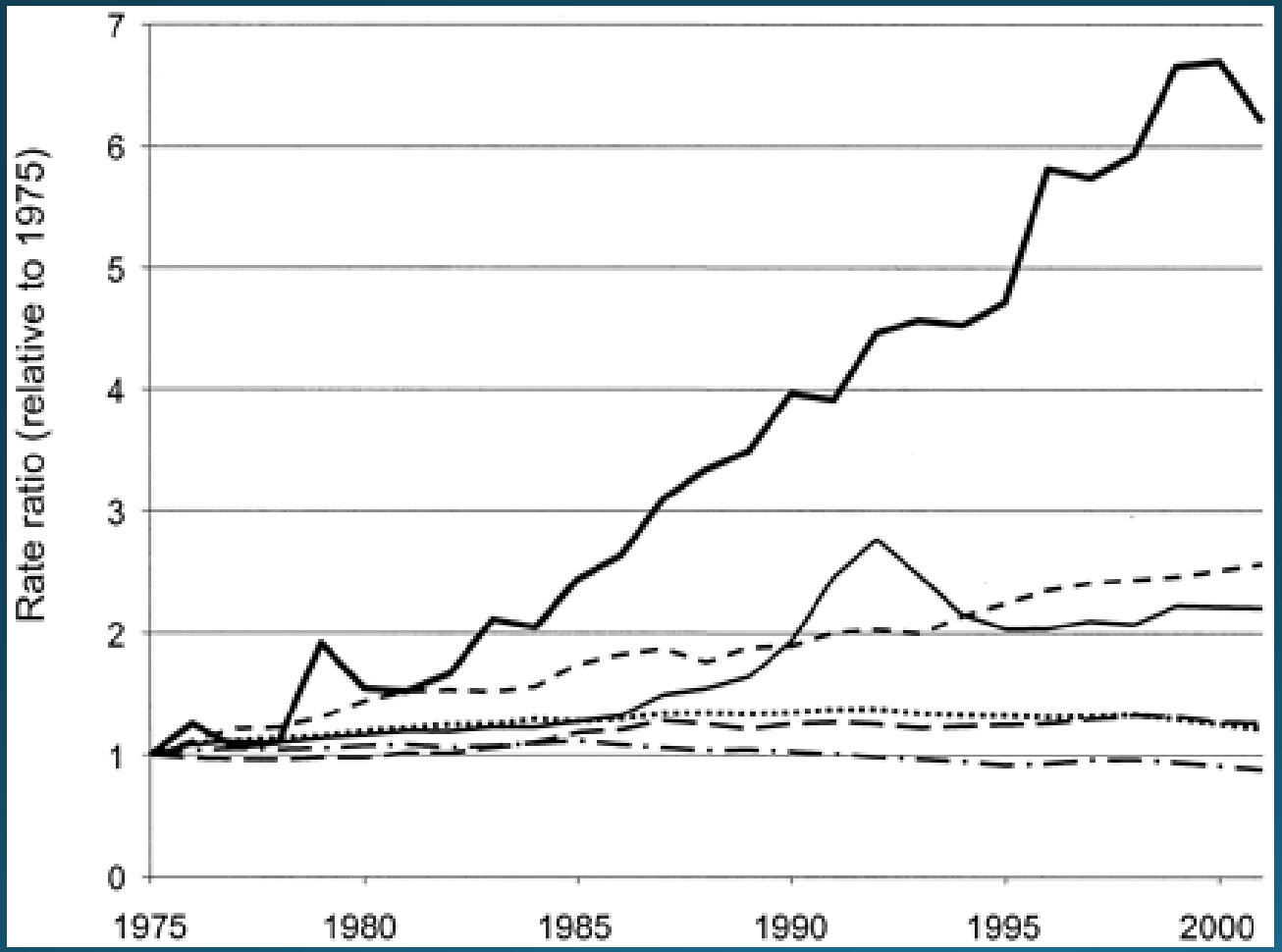
Risk of Progression

Barrett’s Esophagus

Risk of Progression



Esophageal Adenocarcinoma is the Fastest Growing Cancer in the US



Esophagus

Melanoma

Prostate

Lung/Breast

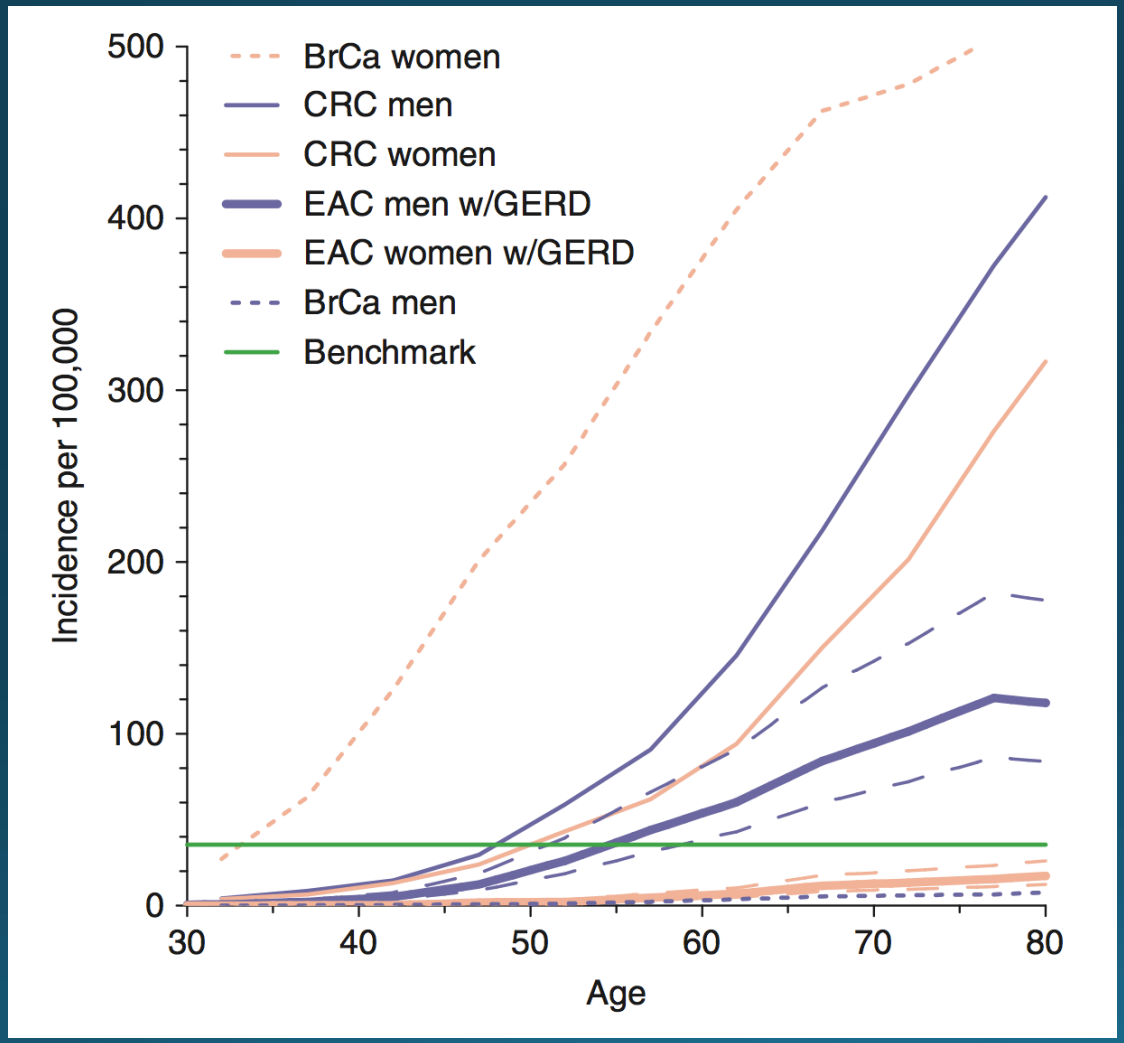
Colorectal

Pohl, J Natl Cancer Inst, 2005

Epidemiology: Barrett's Esophagus

- Mean age is 55
- Caucasian
- Uncommon in Blacks and Asians
- Male: Female 2:1 Barrett's
- Male: Female 8:1 Esoph AdenoCA

Relative Incidence of Colon, Breast, Esoph CA



BrCa women

CRC men

CRC women

EAC men w/GERD

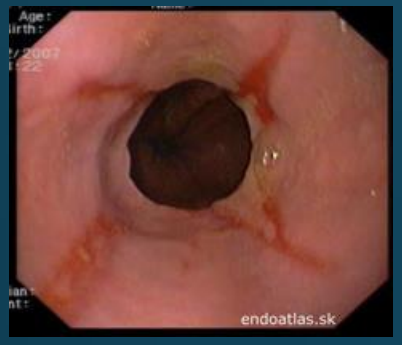
EAC women w/GERD

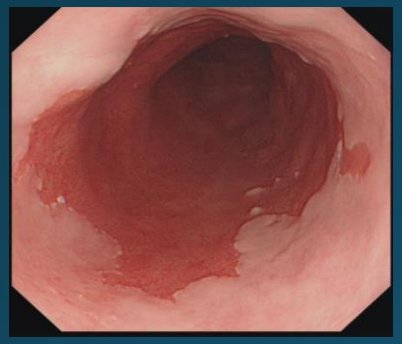
BrCa men

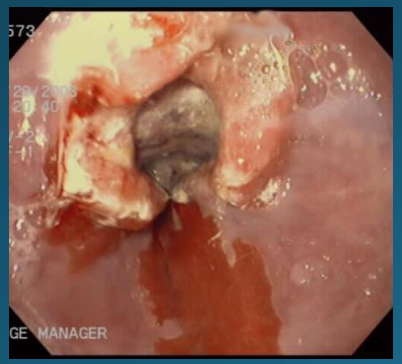
Am J Gastroenterol 2011; 106:254–260

Pathophysiology

Disease Progression







Squamous esophagus

Chronic inflammation

Barrett's metaplasia

Low-grade dysplasia

High-grade dysplasia

Adenocarcinoma

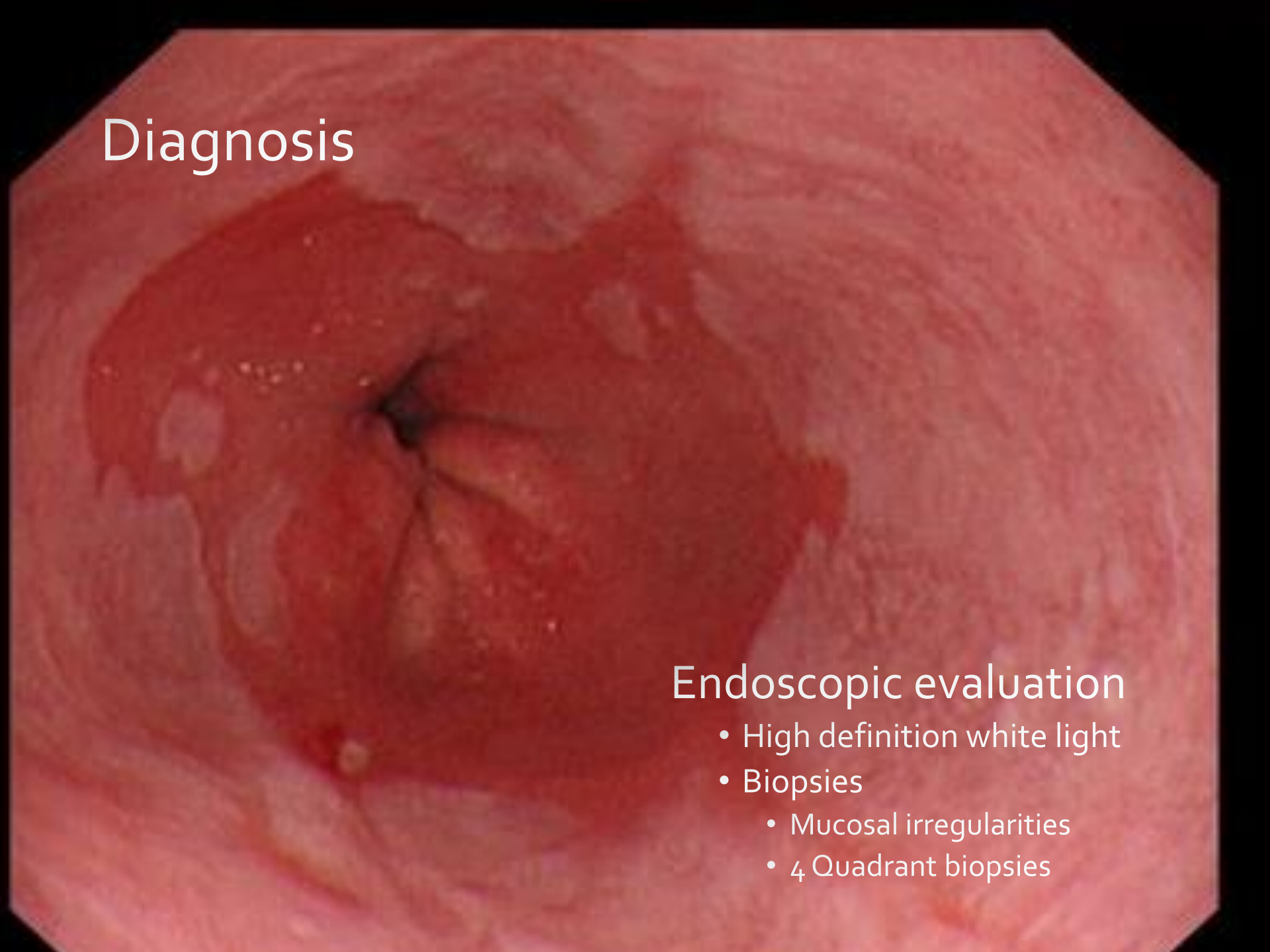
Injury: Acid and others

Genetics: Gender, race, ?other factors

Accumulate Genetic Changes

Diagnosis and Detection

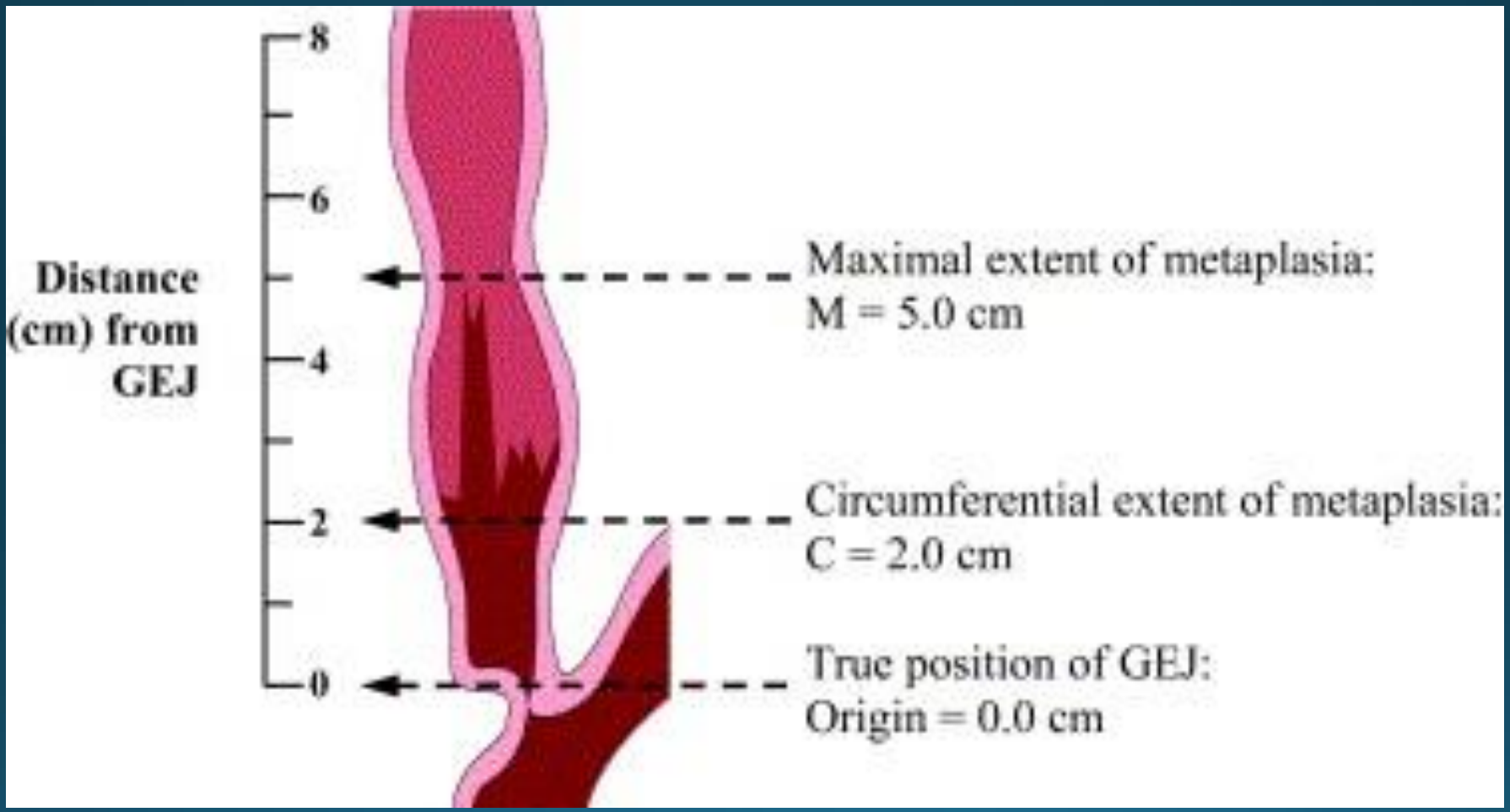
Diagnosis



Endoscopic evaluation

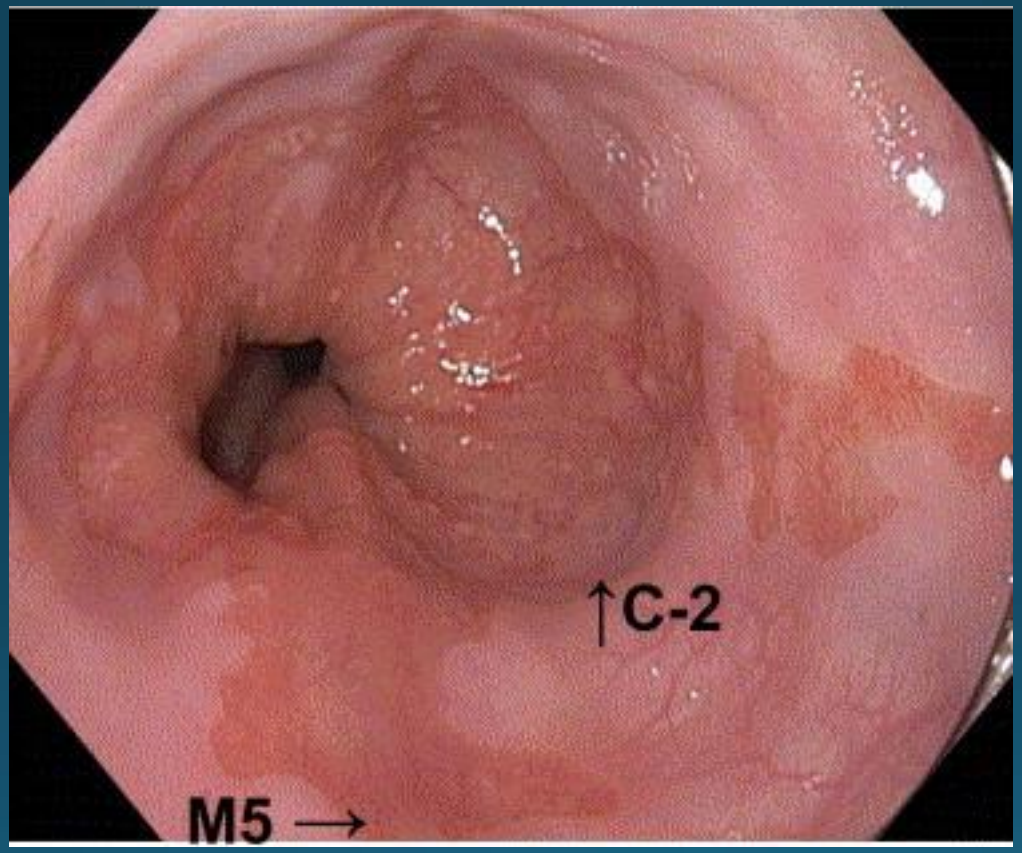
- High definition white light
- Biopsies
  - Mucosal irregularities
  - 4 Quadrant biopsies

Prague C and M Criteria

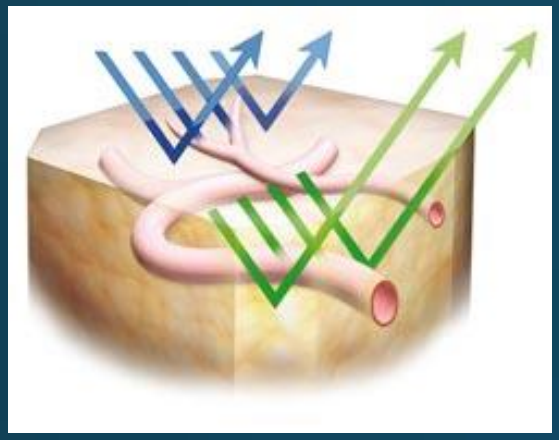


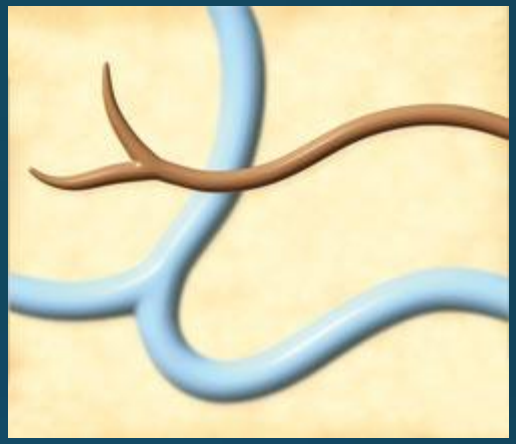
Sharma. Gastroenterology 2006

Prague C and M Criteria



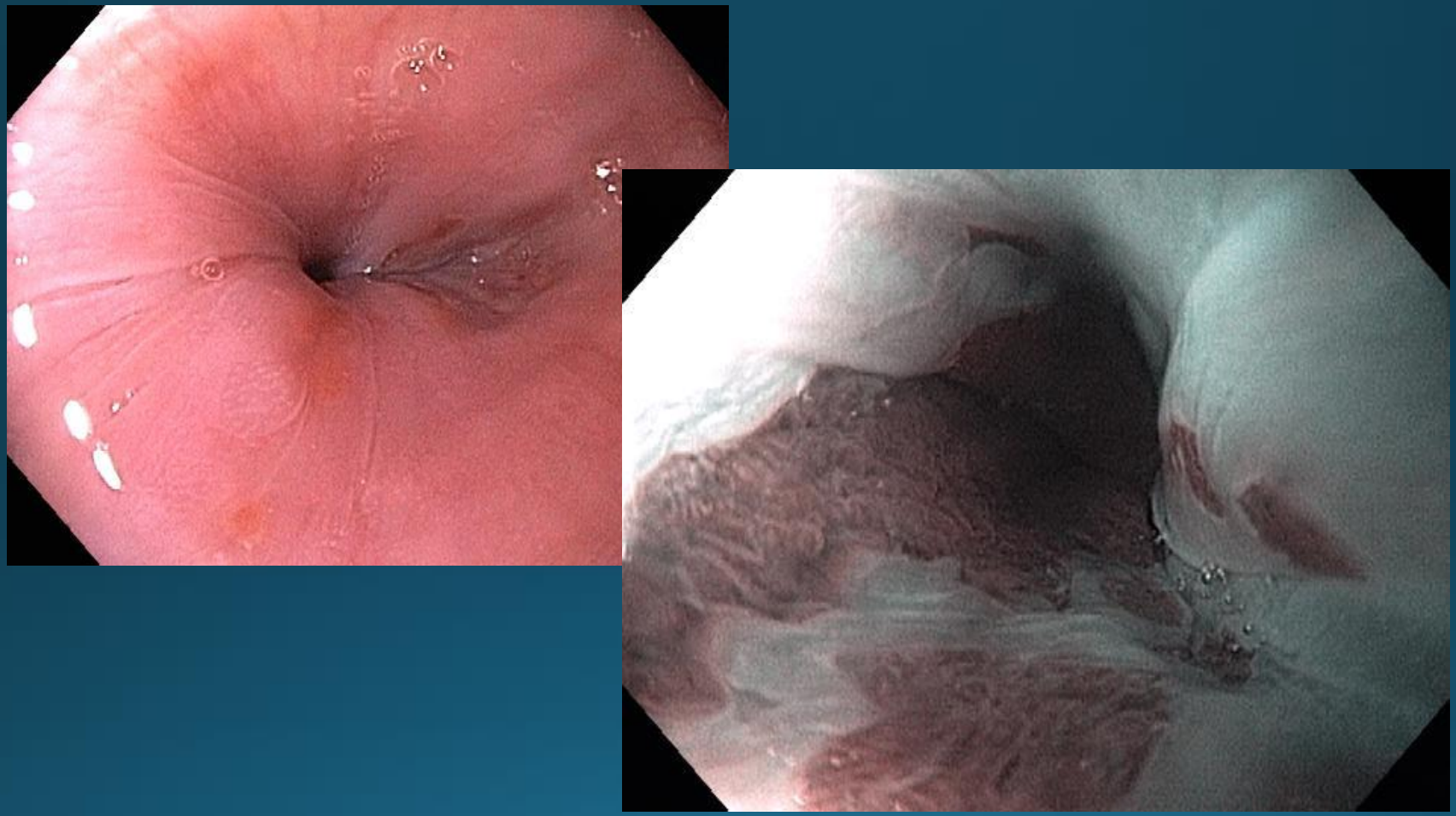
Narrow Band Imaging





- A form of virtual Chromoendoscopy
- NBI uses light of specific blue (440nm) and green (540nm) wavelengths
- Obtains an extremely high contrast image of the tissue surface
- Improves the visibility of capillaries, veins and other subtle tissue structures

NBI for Barrett's Esophagus



Screening for Barrett's Esophagus

Risk factors for Barrett's/Esoph CA

- Male
- White race
- Advanced age (> 50)
- GERD symptoms
  - Odds Ratio 6
  - Frequency of symptoms more important than severity of symptoms
- Increased BMI
- Intra-abdominal fat distribution
- Hiatal Hernia
- Smoking
- Family History of Barrett's/Esoph CA

Chak, Gut, 2002
Gopal, Dig Dis Sci, 2003
Weston, Am J Gastroenterol, 2004
Hage, Scand J Gastroenterol, 2004
Iftikhar, Gut, 1992

Bani-Hani, World J Gastroenterol, 2005
Ramus, Eur J Cancer Prev, 2012
de Jonge, Gut, 2010
Prasad, Am J Gastroenterol, 2010
Dig Dis Sci 2002

Who should be screened?

- Despite well defined risk factors, screening remains a subject of debate
  - Not clear if screening patients with heartburn identifies individuals at high risk for Esoph CA
  - >40% of pts with Esoph CA have no history of heartburn
  - Lack of data to support screening has affected Esoph CA incidence
  - Endoscopy is an expensive, invasive screening test

AGA Guidelines

Barrett's Esophagus Risk and Screening

In patients with multiple risk factors associated with esophageal adenocarcinoma (age 50 years or older, male sex, white race, chronic GERD, hiatal hernia, elevated body mass index, and intra-abdominal distribution of body fat), we suggest screening for Barrett's esophagus (weak recommendation, moderate-quality evidence).

We recommend against screening the general population with GERD for Barrett's esophagus (strong recommendation, low-quality evidence).

GASTROENTEROLOGY 2011;140:1084 –1091

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Upper Endoscopy for Gastroesophageal Reflux Disease: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians

Ann Intern Med. 2012;157(11):808-816

- Upper Endoscopy <u>may</u> be indicated:
  - *men older than 50 y with chronic GERD symptoms (symptoms for more than 5 y) and additional risk factors:*
  - *nocturnal reflux symptoms*
  - *hiatal hernia*
  - *elevated BMI*
  - *intra-abdominal distribution of fat*
  - *tobacco use*

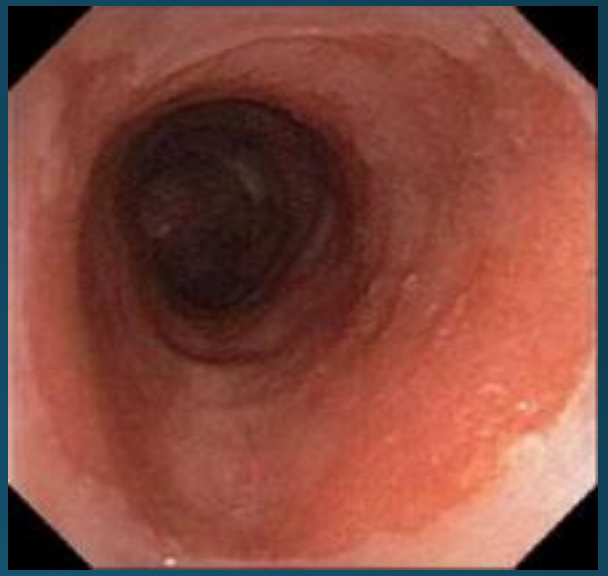
Case – Tom

- 62 yo caucasian male who complains of 3x / week classic heartburn symptoms
- Has been having symptoms for > 5 years, takes OTC antacids with complete relief
- No other symptoms
- 42 pack year smoking history
- No family hx of Esophageal cancer

Would you refer him for an EGD?

Case - Tom

- EGD is performed:
  - Long Segment Barrett's Esophagus
  - C5M5
  - Biopsies performed in 4 quadrant fashion at 5 levels of esophagus
  - Pathology report:
    - Specialized intestinal metaplasia consistent with Barrett's Esophagus with no evidence of dysplasia



"Doc, does that mean I am going to get cancer?"

Cancer risk in Barrett's Esophagus

Non-Dysplastic BE Progression to Cancer in Several Large 2010-2011 Studies Was .10% to .39% per Year

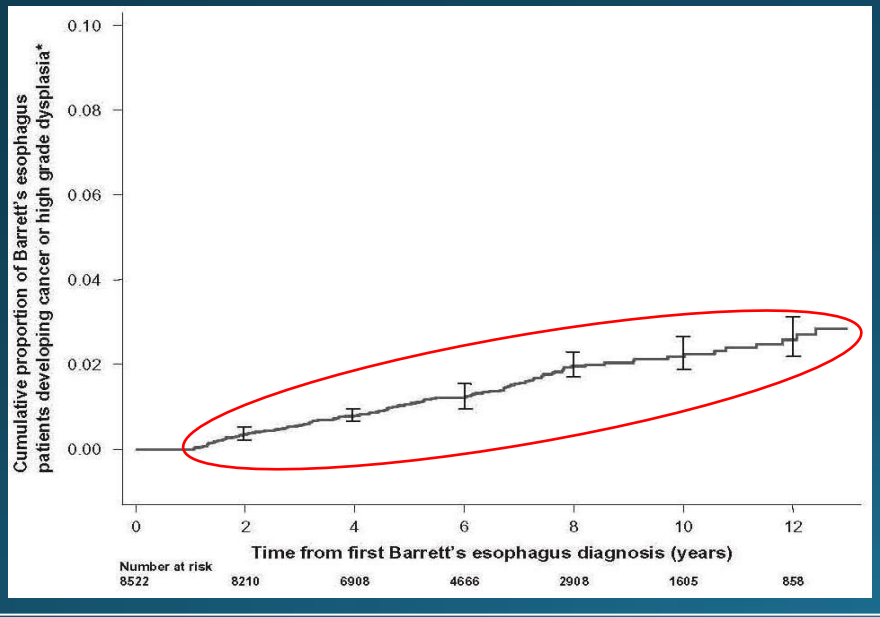
de Jonge, Gut, 2010
Desai, Gut, 2011
Hvid-Jensen, N Engl J Med, 2011
Wani, Clin Gastroenterol Hepatol, 2011
Bhat, J Natl Cancer Inst, 2011

Progression Risk Increases in a Linear Fashion

CLE/IM Progression to HGD/EAC

(Bhat, J Natl Cancer Inst, 2011)

- Population-based study (Northern Ireland Barrett's Register or NIBR) from 1993 to 2005
- 8522 IM pts were followed for a mean of 7 yrs
- "Results from the NIBR demonstrate a **constant risk** of progression to cancer over time."



ARTICLE

Risk of Malignant Progression in Barrett's Esophagus Patients: Results from a Large Population-Based Study

Shivaram Bhat, Helen G. Coleman, Fouad Yousef, Brian T. Johnston, Damian T. McManus, Anna T. Gavin, Liam J. Murray

Manuscript received October 7, 2010; revised May 9, 2011; accepted May 9, 2011.

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Background Barrett's esophagus (BE) is a premalignant lesion that predisposes to esophageal adenocarcinoma. However, the reported incidence of esophageal adenocarcinoma in patients with BE varies widely. We examined the risk of malignant progression in patients with BE using data from the Northern Ireland Barrett's esophagus Register (NIBR), one of the largest population-based registries of BE worldwide, which includes every adult diagnosed with BE in Northern Ireland between 1993 and 2005.

Subjects and Methods We followed 8522 patients with BE, defined as columnar lined epithelium of the esophagus with or without specialized intestinal metaplasia (SIM), until the end of 2008. Patients with incident adenocarcinomas of the esophagus or gastric cardia or with high-grade dysplasia of the esophagus were identified by matching the NIBR with the Northern Ireland Cancer Registry, and deaths were identified by matching with records from the Registrar General's Office. Incidence of cancer outcomes or high-grade dysplasia was calculated as events per 100 person-years (% per year) of follow-up, and Cox proportional hazard models were used to determine incidence by age, sex, length of BE segment, presence of SIM, macroscopic BE, or low-grade dysplasia. All *P* values were from two-sided tests.

Results After a mean of 7.0 years of follow-up, 79 patients were diagnosed with esophageal cancer, 16 with cancer of the gastric cardia, and 36 with high-grade dysplasia. In the entire cohort, incidence of esophageal or gastric cardia cancer or high-grade dysplasia combined was 0.22% per year (95% confidence interval [CI] = 0.19% to 0.26%). SIM was found in 46.0% of patients. In patients with SIM, the combined incidence was 0.38% per year (95% CI = 0.31 to 0.46%). The risk of cancer was statistically significantly elevated in patients with vs without SIM at index biopsy (0.38% per year vs 0.07% per year; hazard ratio [HR] = 3.54, 95% CI = 2.09 to 6.00, $P < .001$), in men compared with women (0.28% per year vs 0.13% per year; HR = 2.11, 95% CI = 1.41 to 3.16, $P < .001$), and in patients with low-grade dysplasia compared with no dysplasia (1.40% per year vs 0.17% per year; HR = 5.67, 95% CI = 3.77 to 8.53, $P < .001$).

Conclusion We found the risk of malignant progression among patients with BE to be lower than previously reported, suggesting that currently recommended surveillance strategies may not be cost-effective.

J Natl Cancer Inst 2011;103:1–9

The incidence of esophageal adenocarcinoma is rising in the United States and Europe (1,2). Despite general improvements in cancer survival in most countries, patients with esophageal adenocarcinoma have a poor prognosis, with fewer than 20% surviving for 5 years (3,4). Barrett's esophagus (BE) is the metaplastic transformation of the native esophageal squamous epithelium into columnar epithelium in response to gastroesophageal reflux. Patients with BE, a known precursor to esophageal adenocarcinoma, are estimated to carry a 30- to 60-fold increased risk of developing esophageal adenocarcinoma (5).

Endoscopic surveillance of BE is the currently accepted standard of care and aims to reduce morbidity and mortality through early detection of dysplasia or cancer (6,7). The cost-effectiveness of surveillance is dependent on the risk of progression of BE to cancer (8–10). However, a wide variation in the incidence of esophageal adenocarcinoma in BE has been observed, ranging from 0% to 3.5% per annum (11,12). Also, it is not currently known whether the rate of progression of BE to esophageal adenocarcinoma varies with time from diagnosis of BE. Change in risk over time has implications regarding both the need for, and the frequency of, endoscopic surveillance.

The aim of this study was to examine the risk of adenocarcinoma or high-grade dysplasia in a large cohort of unselected BE patients. The risk of cancer or high-grade dysplasia was examined using both the British definition of BE, that is, columnar lined epithelium of the esophagus (CLE) and the American definition of

IM Progression to Cancer

IM Progression to HGD/EAC

(Wani, Clin Gastroenterol Hepatol, 2011)

- Multi-center outcomes project
- 1204 pts were followed for a mean of 5.5 yrs
- **2.9%** of IM pts developed cancer in 10 yrs
- **7.3%** of IM pts developed HGD or cancer in 10 yrs

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2011;9:220–227

Patients With Nondysplastic Barrett's Esophagus Have Low Risks for Developing Dysplasia or Esophageal Adenocarcinoma

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This article has an accompanying continuing medical education activity on page e26. Learning Objectives—At the end of this activity, the learner will appreciate that the rate of progression to low-grade dysplasia is much higher than the incident rate per year for esophageal cancer for Barrett's esophagus; appreciate the risk factors for progression to esophageal cancer in patients with Barrett's esophagus; and recognize the wide variability in the previous reporting of progression of Barrett's esophagus to cancer.

See editorial on page 194.

BACKGROUND & AIMS: The risks of dysplasia and esophageal adenocarcinoma (EAC) are not clear for patients with nondysplastic Barrett's esophagus (NDBE); the rate of progression has been overestimated in previous studies. We studied the incidences of dysplasia and EAC and investigated factors associated with progression of BE. **METHODS:** The BE study is a multicenter outcomes project of a large cohort of patients with BE. Neoplasia was graded as low-grade dysplasia, high-grade dysplasia (HGD), or EAC. Patients followed up for at least 1 year after the index endoscopy examination were included, whereas those diagnosed with dysplasia and EAC within 1 year of diagnosis with BE (prevalent cases) were excluded. Of 3334 patients with BE, 1204 met the inclusion criteria (93.7% Caucasian; 88% male; mean age, 59.3 y) and were followed up for a mean of 5.52 years (6644.5 patient-years). **RESULTS:** Eighteen patients developed EAC (incidence, 0.27%/y; 95% confidence interval [CI], 0.17–0.43) and 32 developed HGD (incidence, 0.48%/y; 95% CI, 0.34–0.68). The incidence of HGD and EAC was 0.63%/y (95% CI, 0.47–0.86). There were 217 cases of low-grade dysplasia (incidence, 3.6%/y; 95% CI, 3.2–4.1). Five and 10 years after diagnosis, 98.6% (n = 540) and 97.1% (n = 155) of patients with NDBE were cancer free, respectively. The length of the BE was associated significantly with progression (EAC <6 cm, 0.09%/y vs EAC ≥6 cm, 0.65%/y; $P = 0.001$). **CONCLUSIONS: There is a lower incidence of dysplasia and EAC among patients with NDBE than previously reported. Because most patients are cancer free after a long-term follow-up period, surveillance intervals might be lengthened, especially for patients with shorter segments of BE.**

Keywords: Barrett's Esophagus; Dysplasia; Esophageal Adenocarcinoma; Esophageal Cancer; Screening; Surveillance; Prevention.

Barrett's esophagus (BE), a known complication of chronic gastroesophageal reflux disease, is a well established premalignant lesion for esophageal and gastroesophageal adenocarcinoma.[1,2] Approximately 10% to 15% of patients with chronic gastroesophageal reflux disease are diagnosed with BE. In addition, BE has been reported in patients with no reflux symptoms.[3] The risk of esophageal adenocarcinoma (EAC) is increased 30 to 40 times among patients with BE compared with those without this condition. EAC continues to increase at a rate greater than any other cancer in the Western world (>500% since the 1970s), exceeding that of other more common cancers such as breast, colon, lung, and prostate cancer.[4] In 2009, it is estimated that 16,470 new cases of esophageal cancer will be diagnosed in the United States, of which close to 60% will be adenocarcinomas.[5] Despite all the recent advances in the diagnosis and management of this lethal cancer, the overall 5-year survival rate remains dismal (15%–20%).[6]

Although not evaluated in randomized controlled trials, surveillance of patients with BE is recommended by all major gastroenterology societies and published guidelines.[1,7] Multiple observational studies suggest that endoscopic surveillance is associated with detection of EAC at an earlier stage along with improved survival.[8,9] However, the burden of endoscopic surveillance of BE patients is significant and continues to generate a great deal of controversy.[10,11] In addition, there has been a lot of interest in the endoscopic ablation of nondysplastic BE (NDBE). The true incidence of EAC in patients with BE is central to determining the effectiveness of surveillance endoscopy or any intervention strategy. The exact incidence of EAC

Abbreviations used in this paper: BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SD, standard deviation.

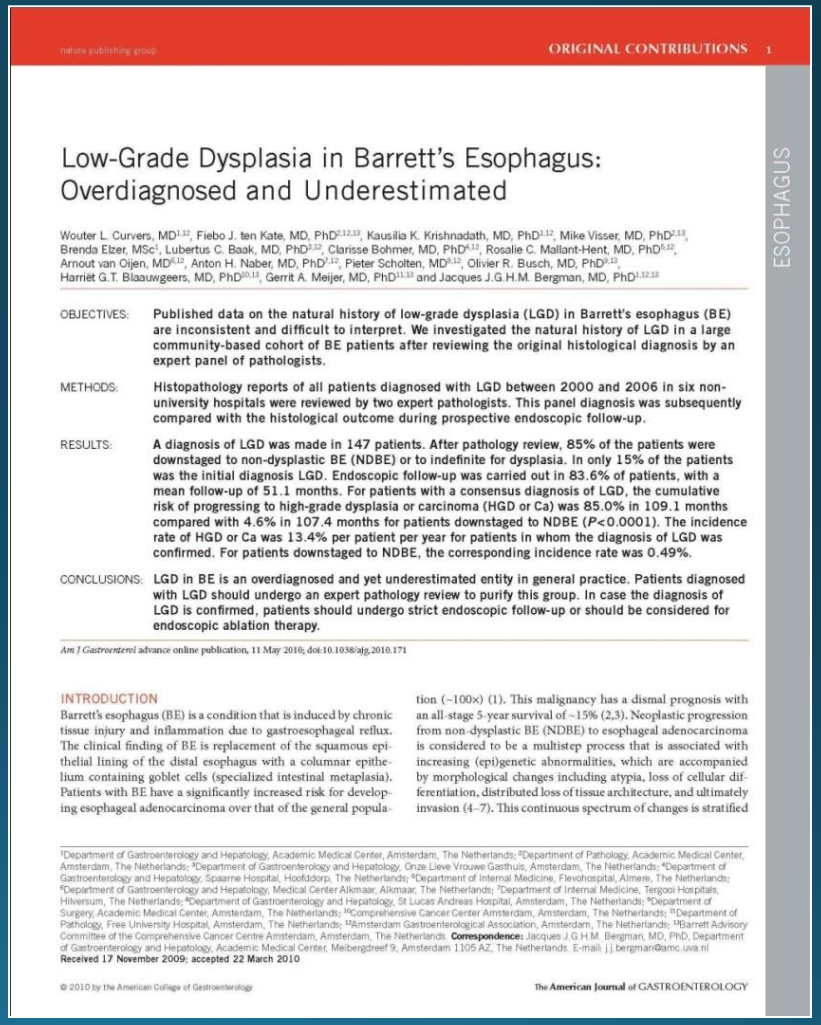
1542-3565/$36.00
doi:10.1016/j.cgh.2010.11.008

Confirmed LGD Carries a Substantial Annual Cancer Progression Risk

LGD Progression to EAC

(Curvers, Am J Gastroenterol, 2010)

- Population-based study (Amsterdam Gastroenterological Association Barrett's Registry) from 2000 to 2006
- Histology reports from six community hospitals were reviewed by two expert GI pathologists
- 1,198 pts were diagnosed with BE
- 121 pts were diagnosed with LGD & had follow up biopsies
- 19 pts had a consensus dx of LGD
- **LGD pts had a 3.4% annual cancer progression risk**



ESOPHAGUS

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

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]

OBJECTIVES: **Published data on the natural history of low-grade dysplasia (LGD) in Barrett's esophagus (BE) are inconsistent and difficult to interpret. We investigated the natural history of LGD in a large community-based cohort of BE patients after reviewing the original histological diagnosis by an expert panel of pathologists.**

METHODS: **Histopathology reports of all patients diagnosed with LGD between 2000 and 2006 in six non-university hospitals were reviewed by two expert pathologists. This panel diagnosis was subsequently compared with the histological outcome during prospective endoscopic follow-up.**

RESULTS: **A diagnosis of LGD was made in 147 patients. After pathology review, 85% of the patients were downstaged to non-dysplastic BE (NDBE) or to indefinite for dysplasia. In only 15% of the patients was the initial diagnosis LGD. Endoscopic follow-up was carried out in 83.6% of patients, with a mean follow-up of 51.1 months. For patients with a consensus diagnosis of LGD, the cumulative risk of progressing to high-grade dysplasia or carcinoma (HGD or Ca) was 85.0% in 109.1 months compared with 4.6% in 107.4 months for patients downstaged to NDBE ($P<0.0001$). The incidence rate of HGD or Ca was 13.4% per patient per year for patients in whom the diagnosis of LGD was confirmed. For patients downstaged to NDBE, the corresponding incidence rate was 0.49%.**

CONCLUSIONS: **LGD in BE is an overdiagnosed and yet underestimated entity in general practice. Patients diagnosed with LGD should undergo an expert pathology review to purify this group. In case the diagnosis of LGD is confirmed, patients should undergo strict endoscopic follow-up or should be considered for endoscopic ablation therapy.**

Am J Gastroenterol advance online publication, 11 May 2010; doi:10.1038/ajg.2010.171

INTRODUCTION

Barrett's esophagus (BE) is a condition that is induced by chronic tissue injury and inflammation due to gastroesophageal reflux. The clinical finding of BE is replacement of the squamous epithelial lining of the distal esophagus with a columnar epithelium containing goblet cells (specialized intestinal metaplasia). Patients with BE have a significantly increased risk for developing esophageal adenocarcinoma over that of the general population (~100×) (1). This malignancy has a dismal prognosis with an all-stage 5-year survival of ~15% (2,3). Neoplastic progression from non-dysplastic BE (NDBE) to esophageal adenocarcinoma is considered to be a multistep process that is associated with increasing (epi)genetic abnormalities, which are accompanied by morphological changes including atypia, loss of cellular differentiation, distributed loss of tissue architecture, and ultimately invasion (4–7). This continuous spectrum of changes is stratified

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Received 17 November 2009; accepted 22 March 2010

Progression Risk for HGD Patients

BADCAT Consensus Statement

(Bennett, Gastroenterology, 2012)

- An int'l, multidisciplinary, evidence-based review of BE management strategies using 80% agreement as a threshold for all consensus statements
- "Risk of progression from HGD to cancer is approximately **10%** per year."

Consensus Statements for Management of Barrett's Dysplasia and Early-Stage Esophageal Adenocarcinoma, Based on a Delphi Process

Podcast interview: www.gastro.org/gastropodcast. Also available on iTunes. See Covering the Cover synopsis on page 273; see editorial on page 282.

BACKGROUND & AIMS: Esophageal adenocarcinoma (EA) is increasingly common among patients with Barrett's esophagus (BE). We aimed to provide consensus recommendations based on the medical literature that clinicians could use to manage patients with BE and low-grade dysplasia, high-grade dysplasia (HGD), or early-stage EA. METHODS: We performed an international, multidisciplinary, systematic, evidence-based review of different management strategies for patients with BE and dysplasia or early-stage EA. We used a Delphi process to develop consensus statements. The results of literature searches were screened using a unique, interactive, Web-based data-editing platform; we used 11,904 papers to inform the choice of statements selected. An a priori threshold of 80% agreement was used to establish consensus for each statement. RESULTS: Eighty-one of the 91 statements achieved consensus despite generally low quality of evidence, including 8 clinical statements: (1) specimens from endoscopic resection are better than biopsies for staging lesions, (2) it is important to carefully map the size of the dysplastic areas, (3) patients that receive ablative or surgical therapy require endoscopic follow-up, (4) high-resolution endoscopy is necessary for accurate diagnosis, (5) endoscopic therapy for HGD is preferred to surveillance, (6) endoscopic therapy for HGD is preferred

Abbreviations used in this paper: BAD CAT, Barrett's dysplasia and cancer task force; BE, Barrett's esophagus; EA, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; LGD, low-grade dysplasia; RFA, radiofrequency ablation.

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http://dx.doi.org/10.1053/j.gastro.2012.04.032

Cancer Risk Summary

	1 Year	5 Year	10 Year
Non-dysplastic Barrett's	0.3%	1.5%	3%
Low Grade Dysplasia (confirmed)	3%	15%	30%
High Grade Dysplasia	10%	50%	100%

What options can we offer our patient with long segment non-dysplastic BE?

- A) Endoscopic surveillance
- B) Referral for mucosal ablation of Barrett's tissue
- C) High dose PPI to reverse Barrett's Metaplasia
- D) Anti-reflux surgery to reverse Barrett's and prevent progression to cancer

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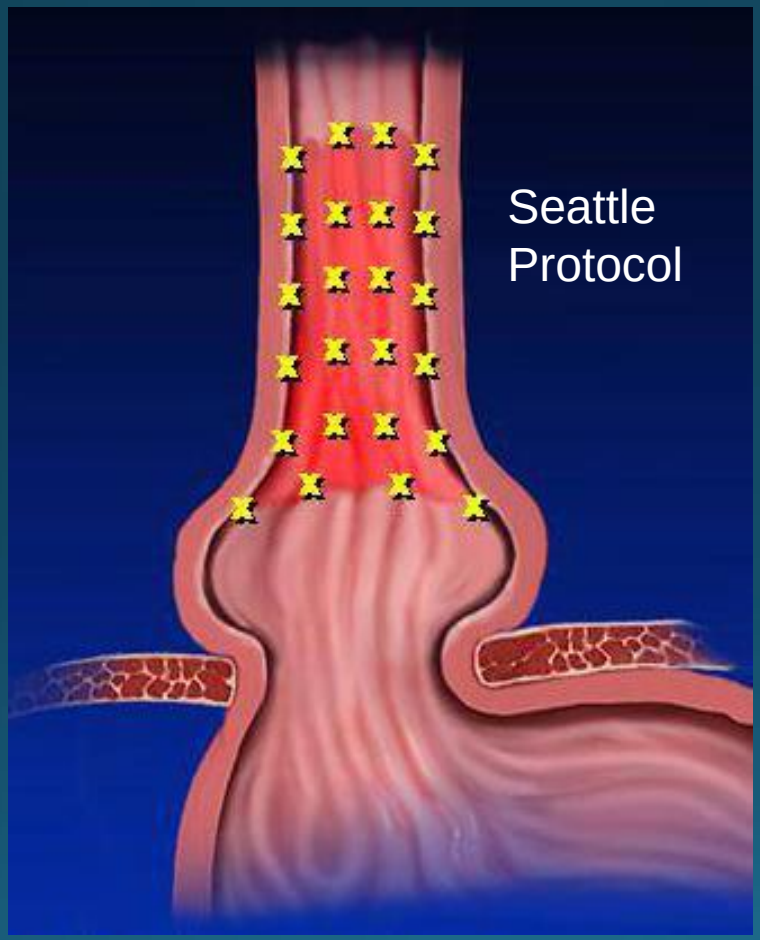
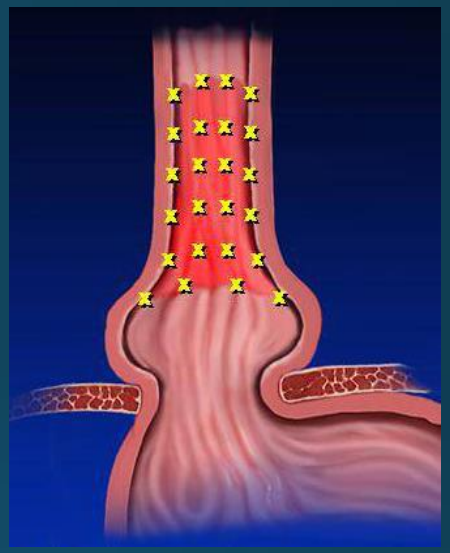
Endoscopic Surveillance



Issues with Surveillance

- Sampling error
  - Poor GI adherence to Seattle Protocol
- Pathologic discordance
- Poor patient compliance
- Cost-ineffective



- Surveillance may not prevent cancer
  - Large multicenter cohort study
  - 618 patients followed for 2546 patient-years
  - 53% of those who developed HGD or cancer while undergoing surveillance did not have findings of dysplasia on two initial prior endoscopies

Sharma. Clin Gastroenterol Hepatol. 2006 May;4(5):566-72

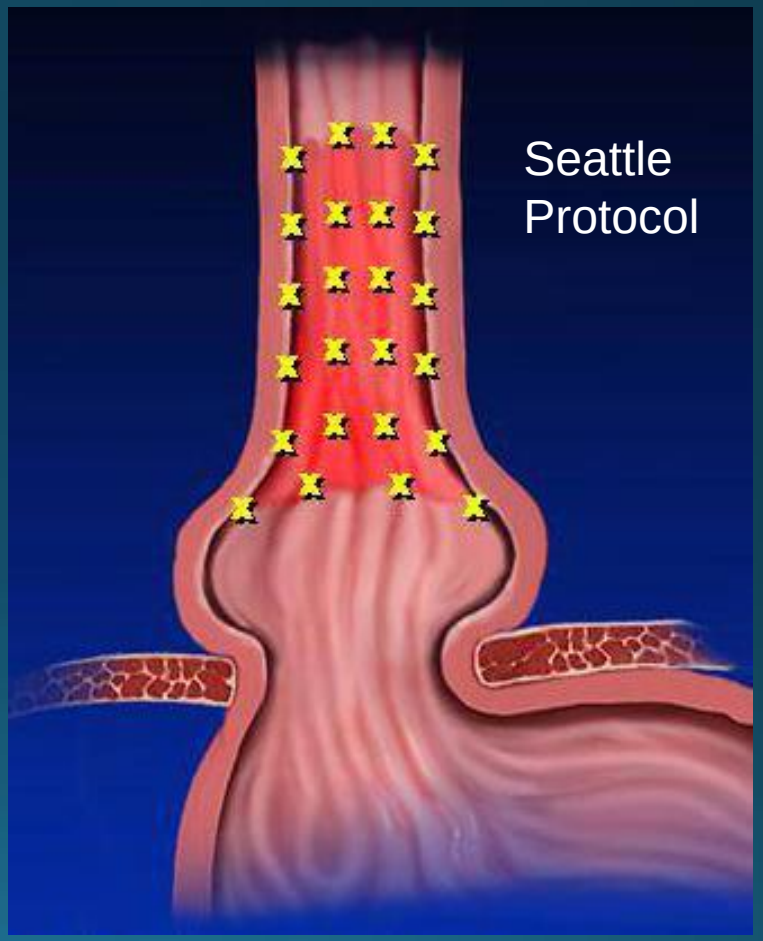
Endoscopic Surveillance

Endoscopic Surveillance in Patients With Barrett's Esophagus

We suggest that endoscopic surveillance be performed in patients with Barrett's esophagus (weak recommendation, moderate-quality evidence).

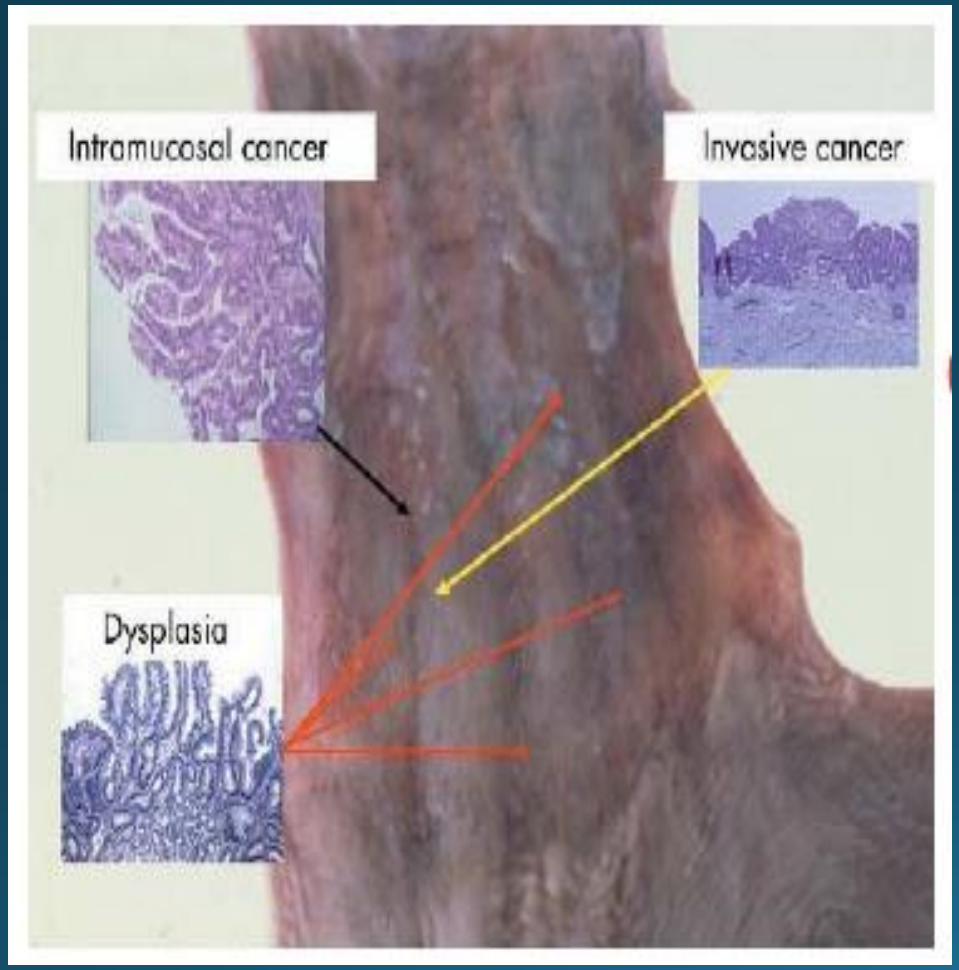
We suggest the following surveillance intervals (weak recommendation, low-quality evidence):

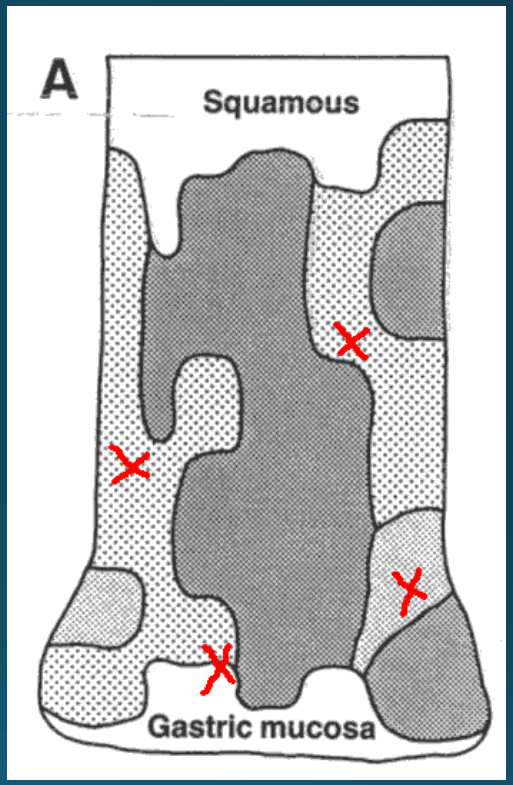
- No dysplasia: 3–5 years
- Low-grade dysplasia: 6–12 months
- High-grade dysplasia in the absence of eradication therapy: 3 months.

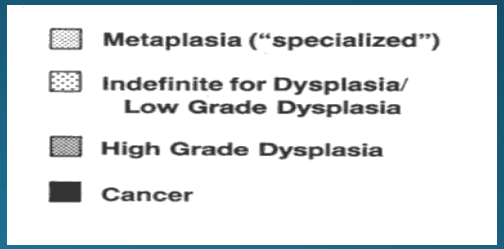


GASTROENTEROLOGY 2011;140:1084 –1091

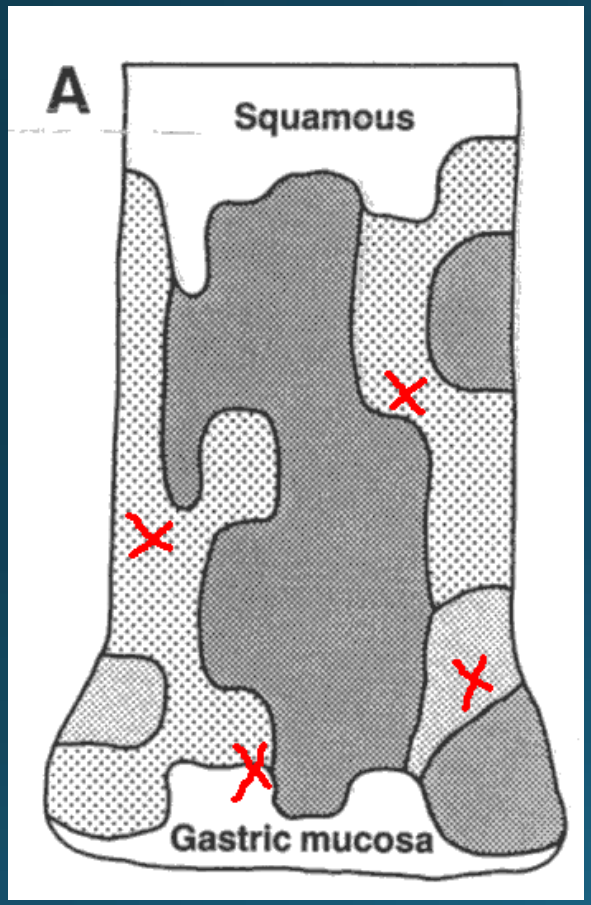
Sampling Error





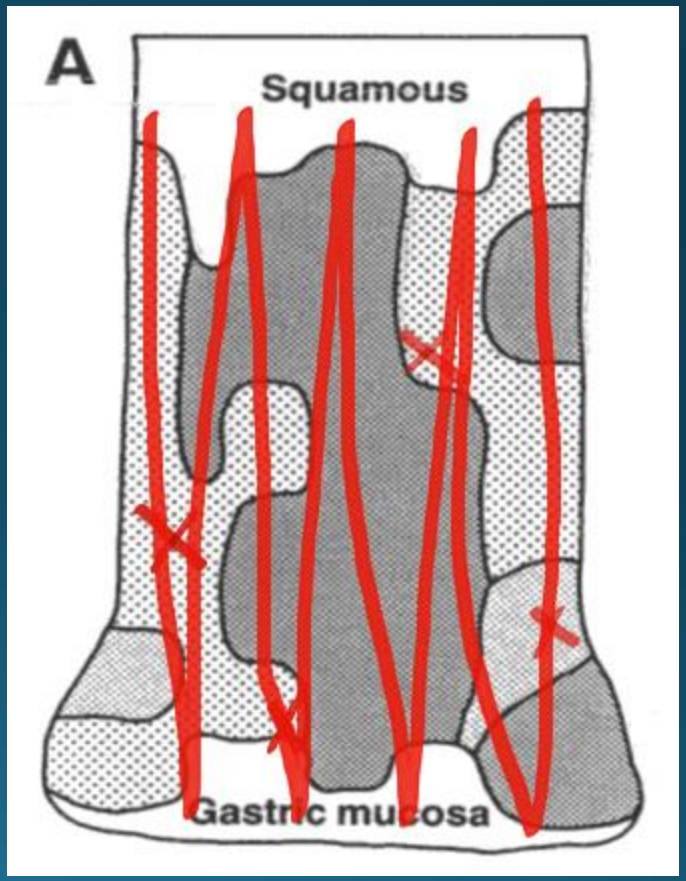


Theoretical advantage to brush sampling

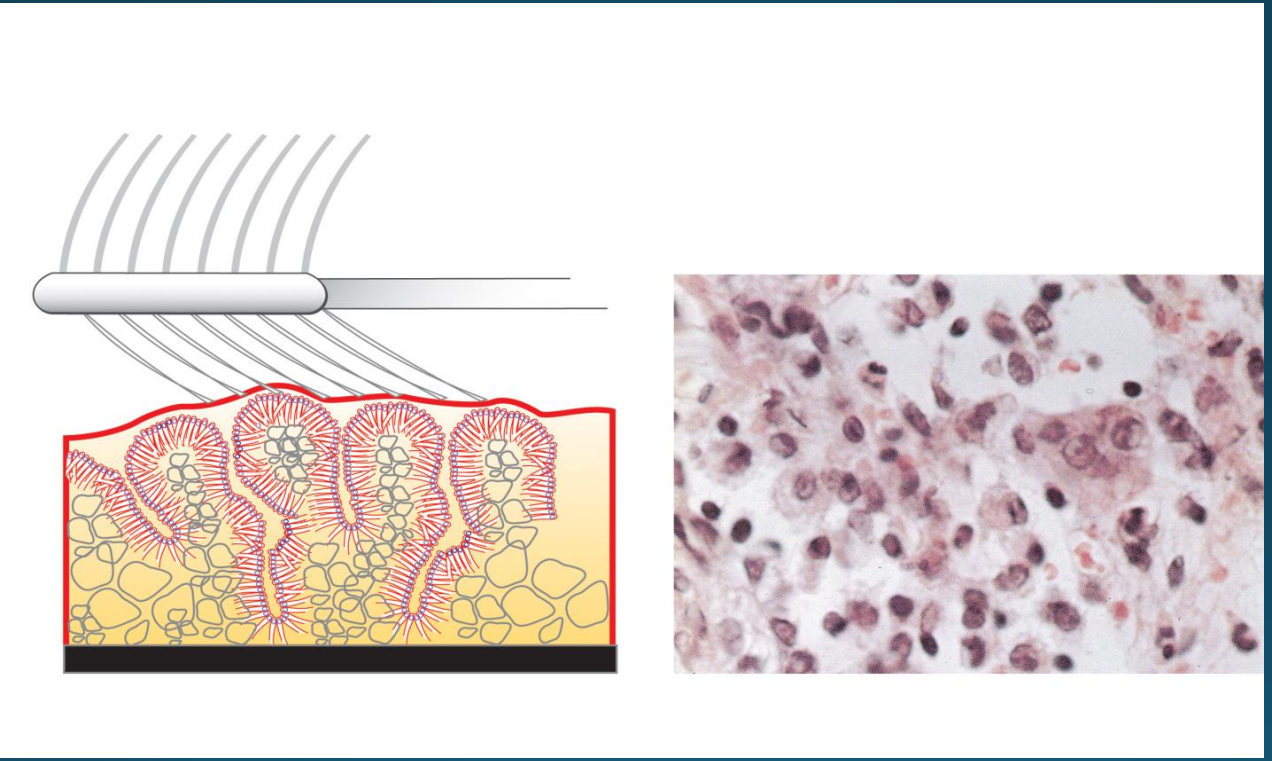


Forceps biopsy has significant potential for sampling error

The brush biopsy samples a much larger area



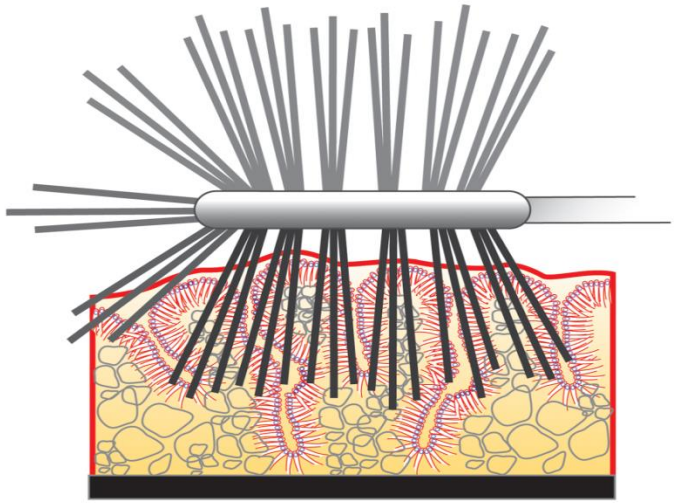
Standard Brush Cytology has limitations

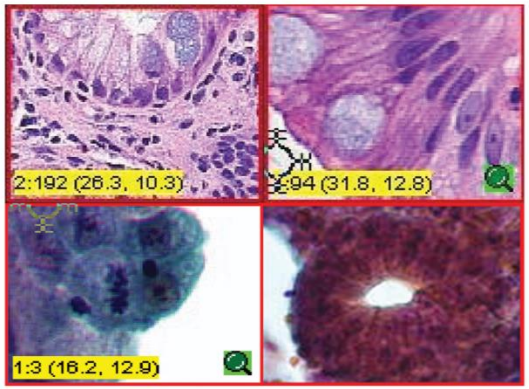


Exfoliative cytology is not designed to effectively sample glandular tissue

New Biopsy Brush

- EndoCDx WATS^{3D} Brush
  - More abrasive
  - Obtains transepithelial biopsy



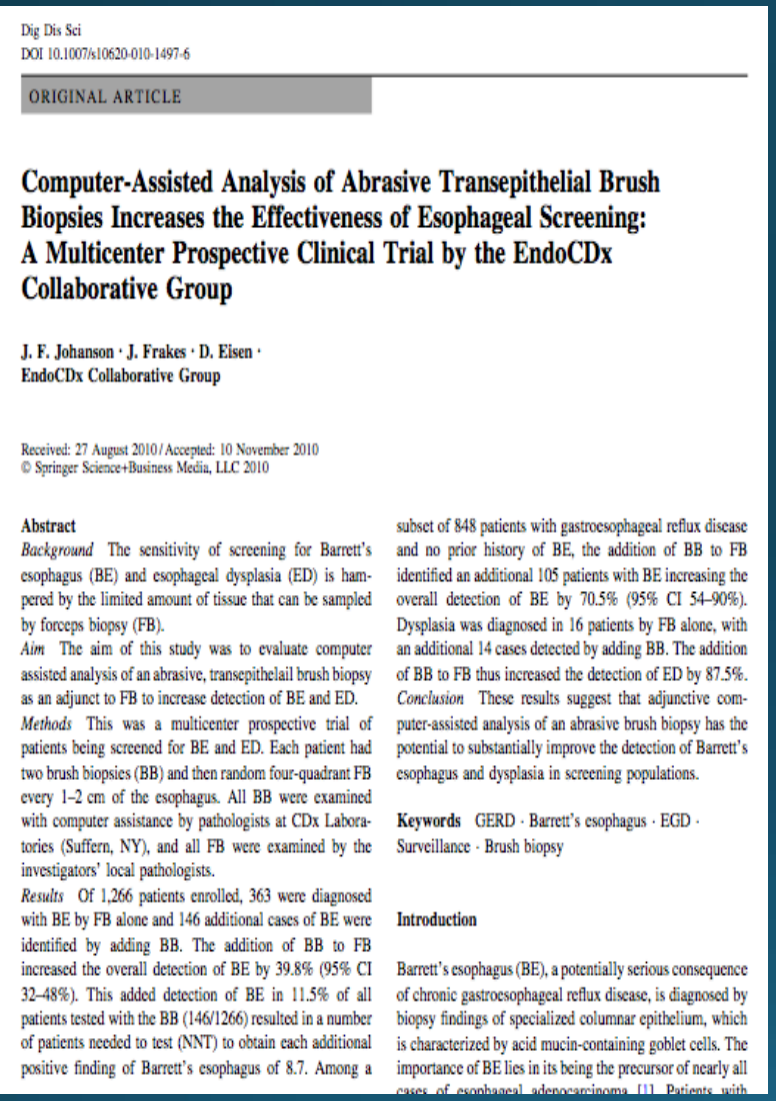


CDx Computer Assisted Analysis

Each cell on the specimen is rank ordered for:

- abnormal cellular morphology
- signature spectral abnormality of molecular diagnostics
- cytometric evaluation of nuclear DNA content

- The Computer brings the highest risk cells to the attention of the pathologist



Dig Dis Sci
DOI 10.1007/s10620-010-1497-6

ORIGINAL ARTICLE

Computer-Assisted Analysis of Abrasive Transepithelial Brush Biopsies Increases the Effectiveness of Esophageal Screening: A Multicenter Prospective Clinical Trial by the EndoCDx Collaborative Group

J. F. Johanson · J. Frakes · D. Eisen · EndoCDx Collaborative Group

Received: 27 August 2010 / Accepted: 10 November 2010

Abstract

Background The sensitivity of screening for Barrett's esophagus (BE) and esophageal dysplasia (ED) is hampered by the limited amount of tissue that can be sampled by forceps biopsy (FB).

Aim The aim of this study was to evaluate computer assisted analysis of an abrasive, transepithelail brush biopsy as an adjunct to FB to increase detection of BE and ED.

Methods This was a multicenter prospective trial of patients being screened for BE and ED. Each patient had two brush biopsies (BB) and then random four-quadrant FB every 1–2 cm of the esophagus. All BB were examined with computer assistance by pathologists at CDx Laboratories (Suffern, NY), and all FB were examined by the investigators' local pathologists.

Results Of 1,266 patients enrolled, 363 were diagnosed with BE by FB alone and 146 additional cases of BE were identified by adding BB. The addition of BB to FB increased the overall detection of BE by 39.8% (95% CI 32–48%). This added detection of BE in 11.5% of all patients tested with the BB (146/1266) resulted in a number of patients needed to test (NNT) to obtain each additional positive finding of Barrett's esophagus of 8.7. Among a subset of 848 patients with gastroesophageal reflux disease and no prior history of BE, the addition of BB to FB identified an additional 105 patients with BE increasing the overall detection of BE by 70.5% (95% CI 54–90%). Dysplasia was diagnosed in 16 patients by FB alone, with an additional 14 cases detected by adding BB. The addition of BB to FB thus increased the detection of ED by 87.5%.

Conclusion These results suggest that adjunctive computer-assisted analysis of an abrasive brush biopsy has the potential to substantially improve the detection of Barrett's esophagus and dysplasia in screening populations.

Keywords GERD · Barrett's esophagus · EGD · Surveillance · Brush biopsy

Introduction

Barrett's esophagus (BE), a potentially serious consequence of chronic gastroesophageal reflux disease, is diagnosed by biopsy findings of specialized columnar epithelium, which is characterized by acid mucin-containing goblet cells. The importance of BE lies in its being the precursor of nearly all cases of esophageal adenocarcinoma [1]. Patients with

Multicenter Barrett's screening program

1266 patients underwent FB q1-2cm + BB

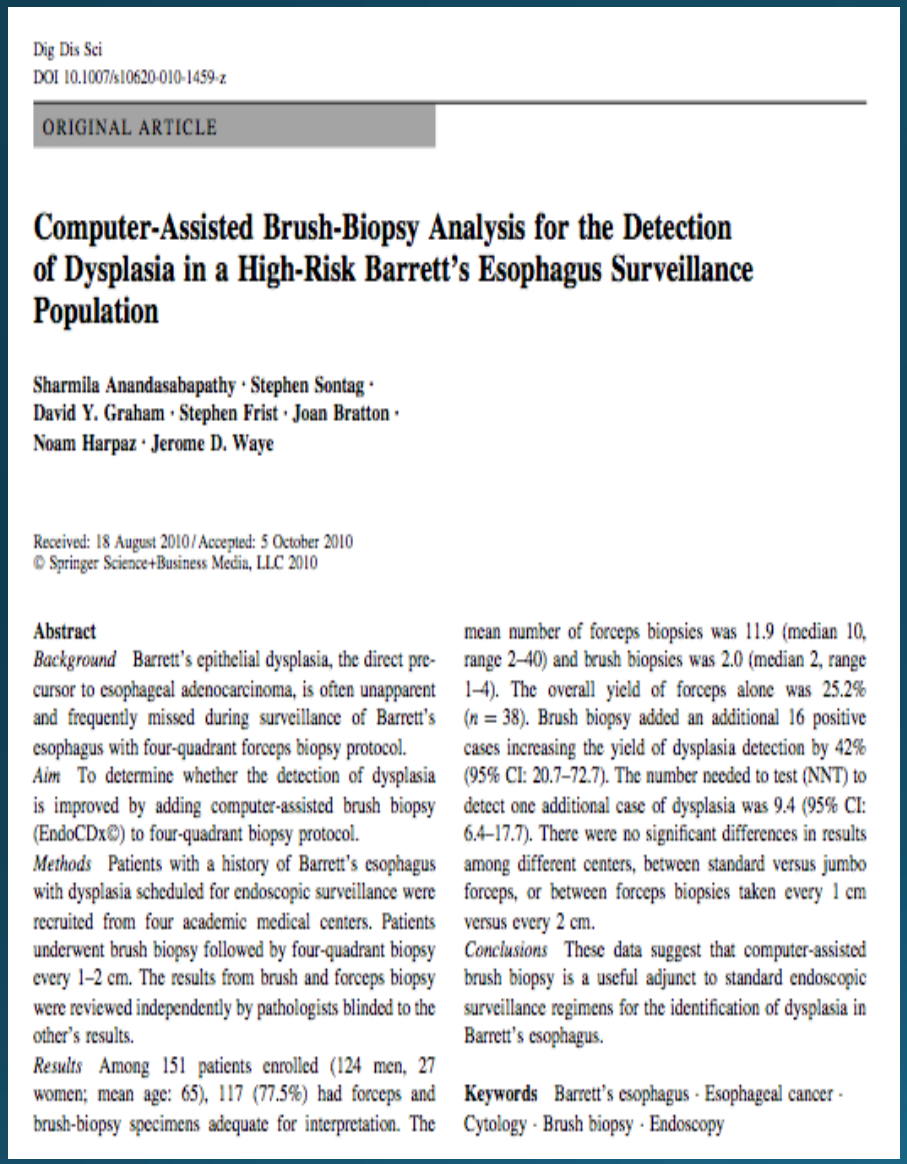
***Results*:**

- Brush biopsy increased the detection of BE by 39.8%
- NNT to obtain each additional positive finding of BE: 8.7

Conclusions

"*Adjunctive computer-assisted analysis of an abrasive brush biopsy has the potential to substantially improve the detection of Barrett's esophagus and dysplasia in screening populations.*"

Johanson, J.F. et al.
Dig Dis Sci. 2011 Mar;56(3):767-72.



Dig Dis Sci
DOI 10.1007/s10620-010-1459-z

ORIGINAL ARTICLE

Computer-Assisted Brush-Biopsy Analysis for the Detection of Dysplasia in a High-Risk Barrett's Esophagus Surveillance Population

Sharmila Anandasabapathy · Stephen Sontag · David Y. Graham · Stephen Frist · Joan Bratton · Noam Harpaz · Jerome D. Waye

Received: 18 August 2010 / Accepted: 5 October 2010

Abstract

Background Barrett's epithelial dysplasia, the direct precursor to esophageal adenocarcinoma, is often unapparent and frequently missed during surveillance of Barrett's esophagus with four-quadrant forceps biopsy protocol.

Aim To determine whether the detection of dysplasia is improved by adding computer-assisted brush biopsy (EndoCDx©) to four-quadrant biopsy protocol.

Methods Patients with a history of Barrett's esophagus with dysplasia scheduled for endoscopic surveillance were recruited from four academic medical centers. Patients underwent brush biopsy followed by four-quadrant biopsy every 1–2 cm. The results from brush and forceps biopsy were reviewed independently by pathologists blinded to the other's results.

Results Among 151 patients enrolled (124 men, 27 women; mean age: 65), 117 (77.5%) had forceps and brush-biopsy specimens adequate for interpretation. The mean number of forceps biopsies was 11.9 (median 10, range 2–40) and brush biopsies was 2.0 (median 2, range 1–4). The overall yield of forceps alone was 25.2% ($n = 38$). Brush biopsy added an additional 16 positive cases increasing the yield of dysplasia detection by 42% (95% CI: 20.7–72.7). The number needed to test (NNT) to detect one additional case of dysplasia was 9.4 (95% CI: 6.4–17.7). There were no significant differences in results among different centers, between standard versus jumbo forceps, or between forceps biopsies taken every 1 cm versus every 2 cm.

Conclusions These data suggest that computer-assisted brush biopsy is a useful adjunct to standard endoscopic surveillance regimens for the identification of dysplasia in Barrett's esophagus.

Keywords Barrett's esophagus · Esophageal cancer · Cytology · Brush biopsy · Endoscopy

Multicenter Surveillance Program

117 patients underwent FB + BB

Results

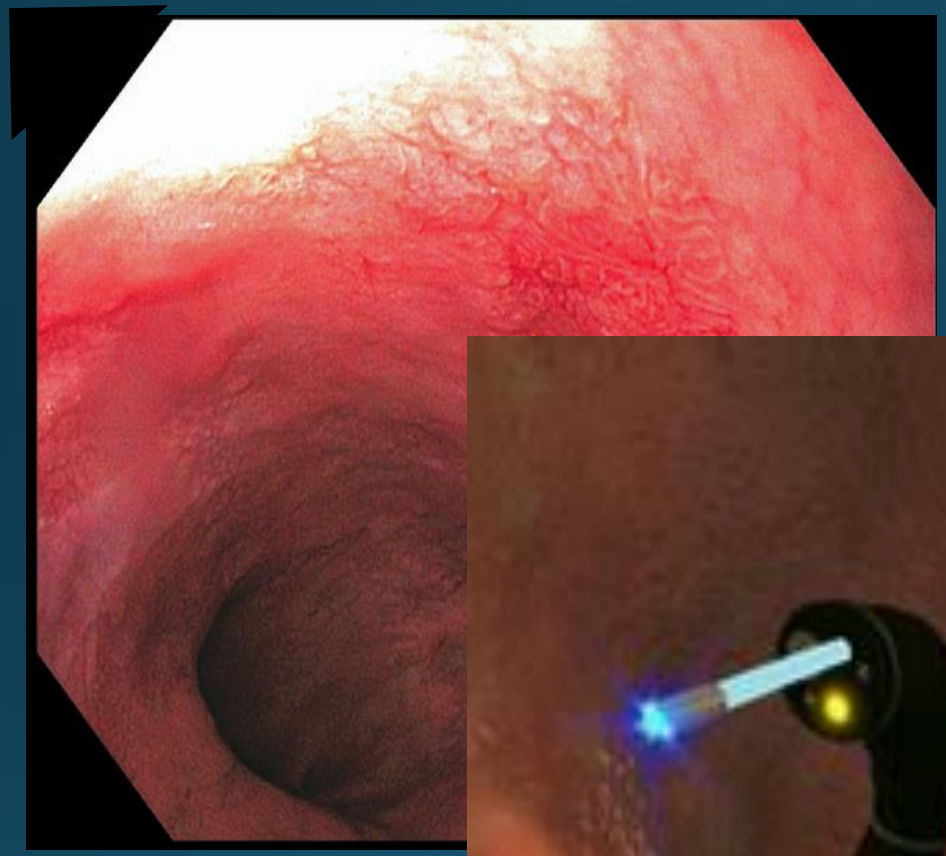
- Brush biopsy increased the detection of dysplasia by 42% (38 → 56)
- NNT to detect one additional case of dysplasia: 9.4

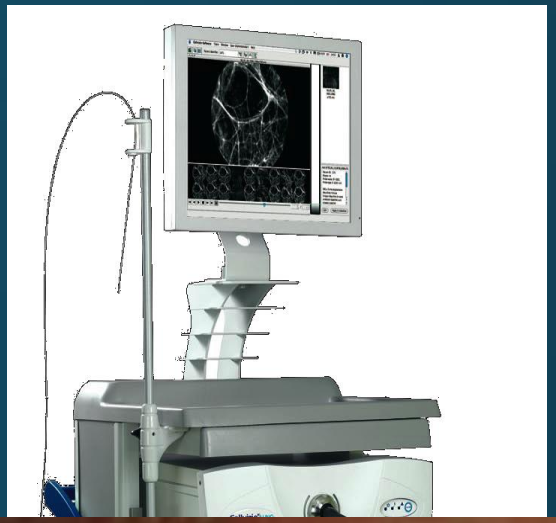
Conclusions

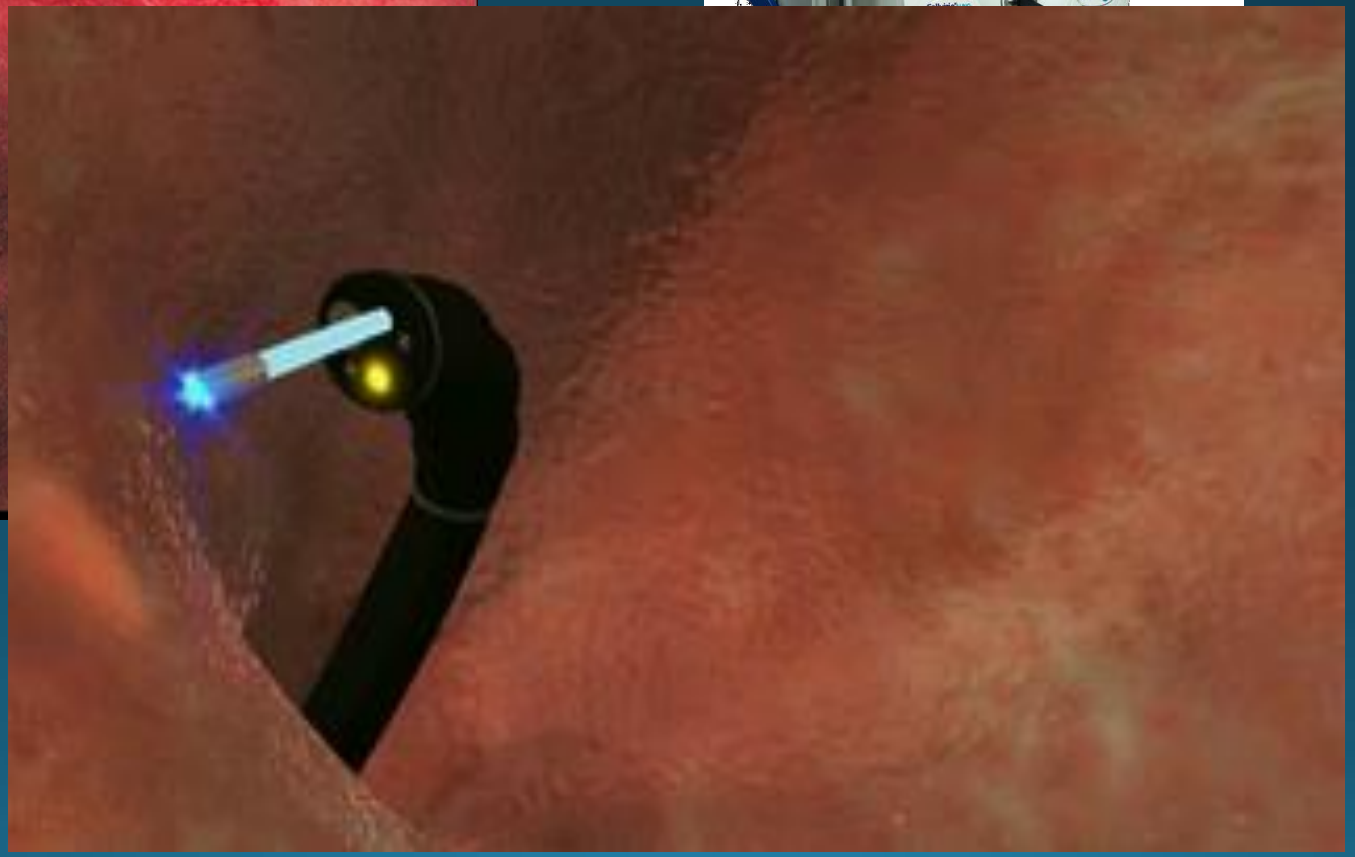
"Computer-assisted brush biopsy is a useful adjunct to standard endoscopic surveillance regimens for the identification of dysplasia in Barrett's esophagus."

Anandasabapathy, S. et al
Dig Dis Sci. *2011 Mar;56(3):761-6.*

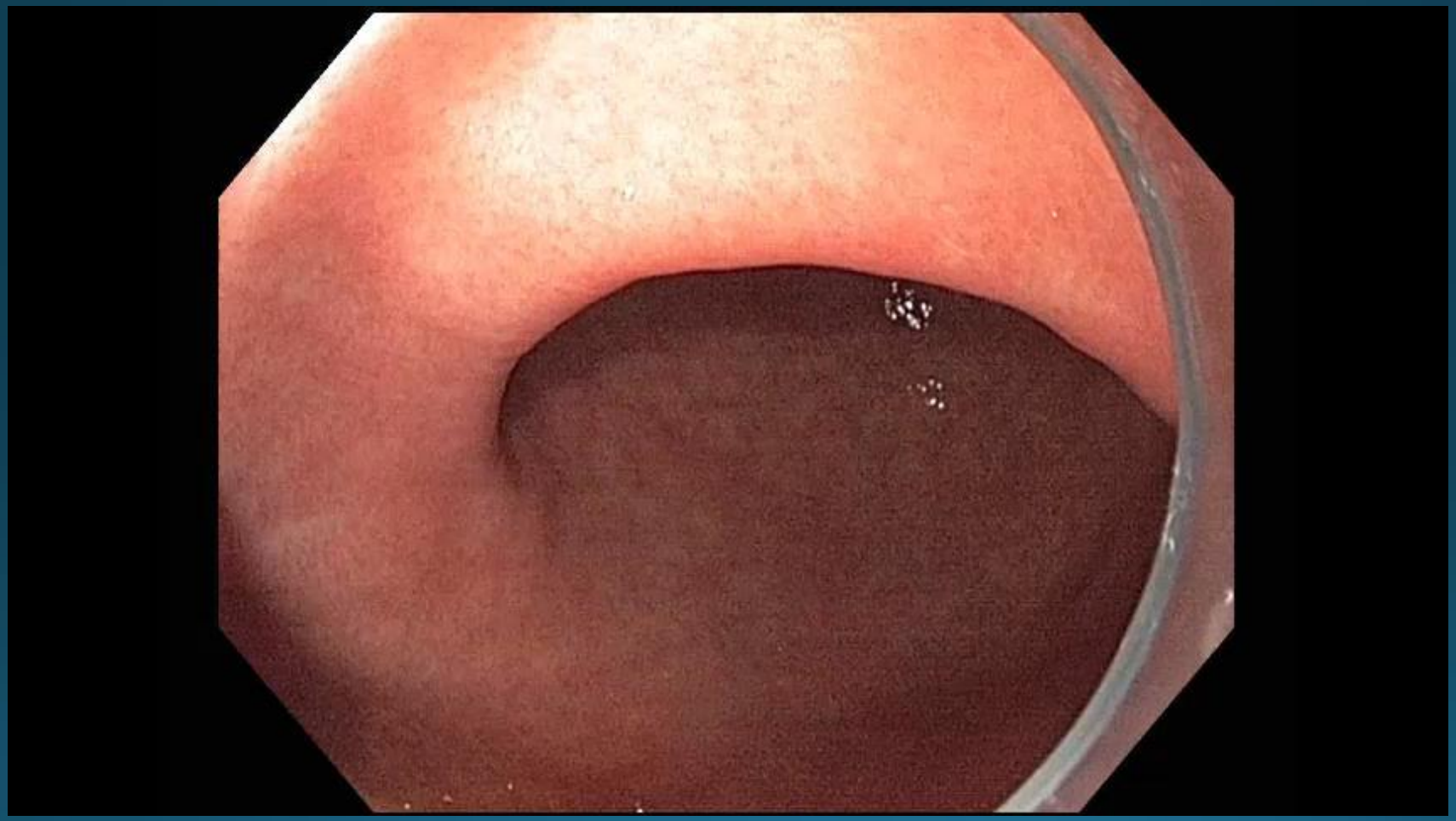
Endomicroscopy







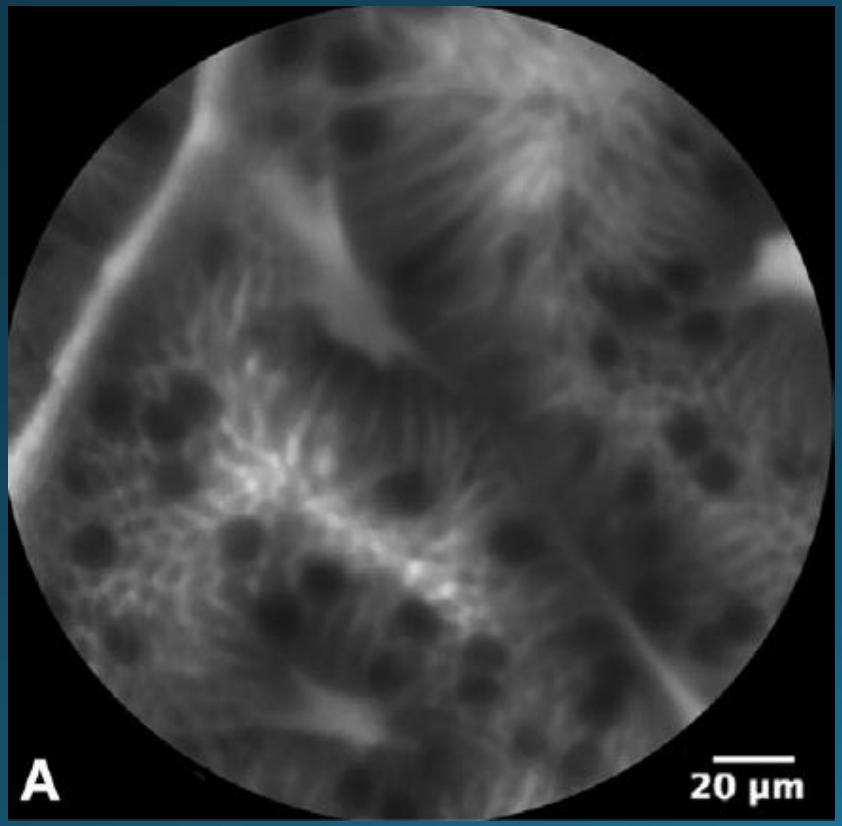
Probe Based Confocal Laser-induced Endomicroscopy (pCLE)

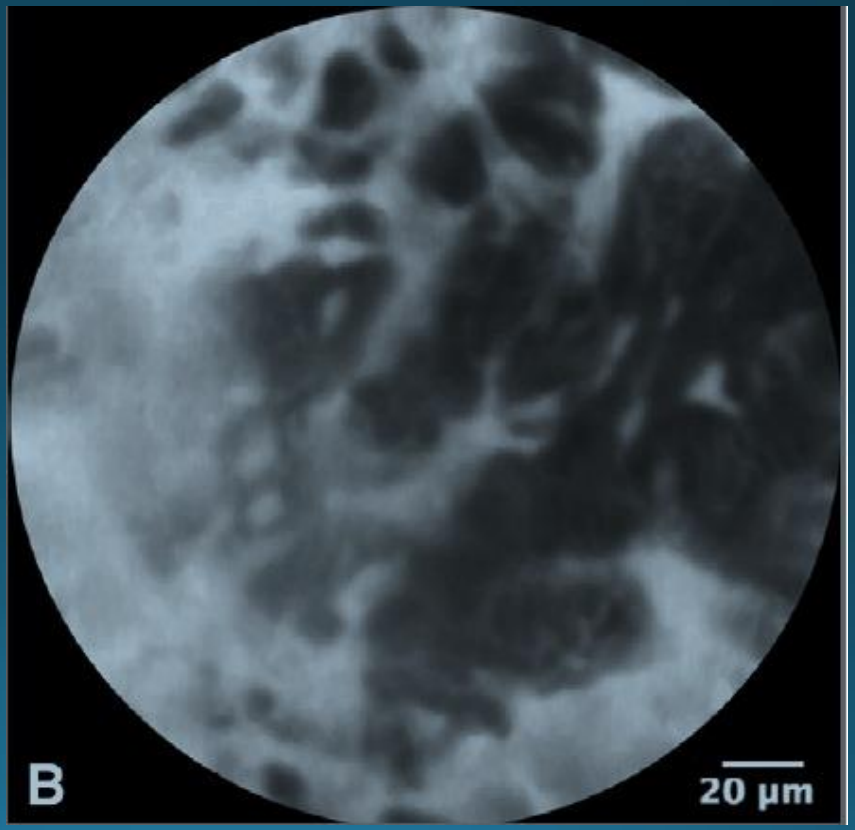


Real-time increased detection of neoplastic tissue in Barrett's esophagus with pCLE: final results of an international multicenter, prospective, randomized, controlled trial

P. Sharma, A. Meining, E. Coron, C. Lightdale, H. Wolfsen, A. Bansal, M. Bajbouj, J.-P. Galmiche, J. Abrams, A. Rastogi, N. Gupta, J. Michalek, G. Lauwers, M. Wallace

GASTROINTESTINAL ENDOSCOPY Vol. 74, Issue 3, Sep 2011, Pages 465-472





DONT BIOPCE TRIAL

Real-time increased detection of neoplastic tissue in Barrett's esophagus with pCLE: final results of an international multicenter, prospective, randomized, controlled trial

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GASTROINTESTINAL ENDOSCOPY Vol. 74, Issue 3, Sep 2011, Pages 465-472

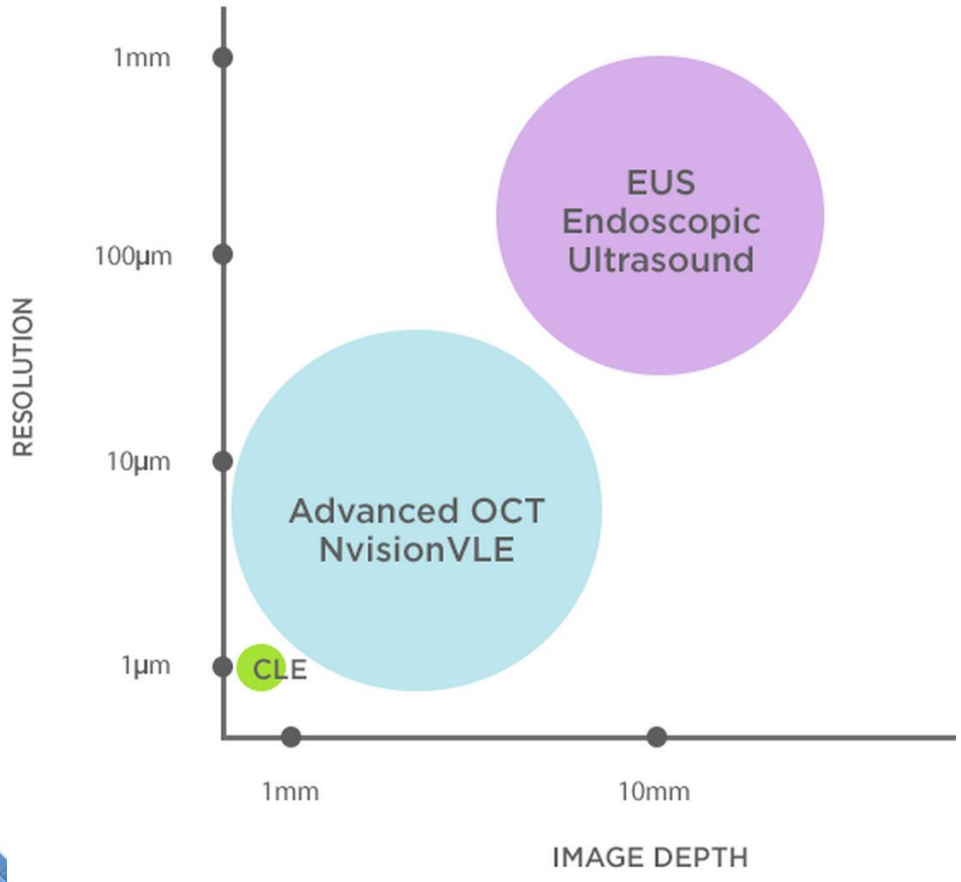
- Multicenter International trial (5 centers)
- Prospective, double blinded trial: WLE, NBI +/- pCLE
- 101 patients - 874 esophageal locations

RESULTS:

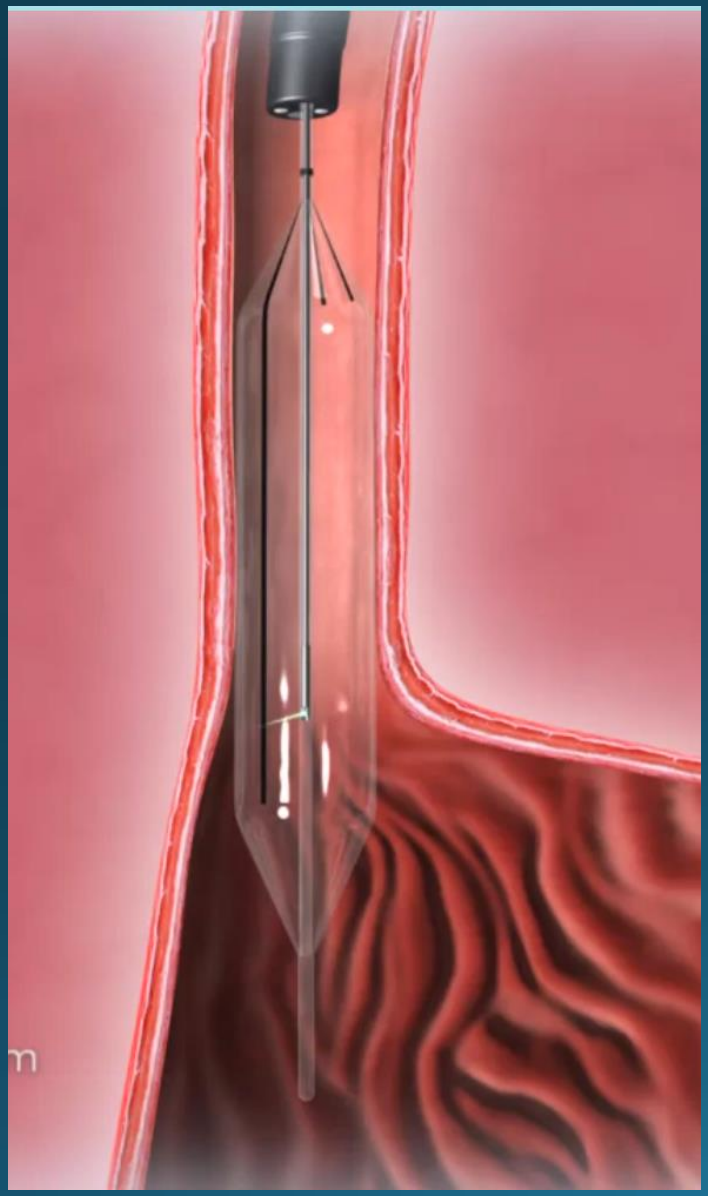
More patients with HGD were found when pCLE was added

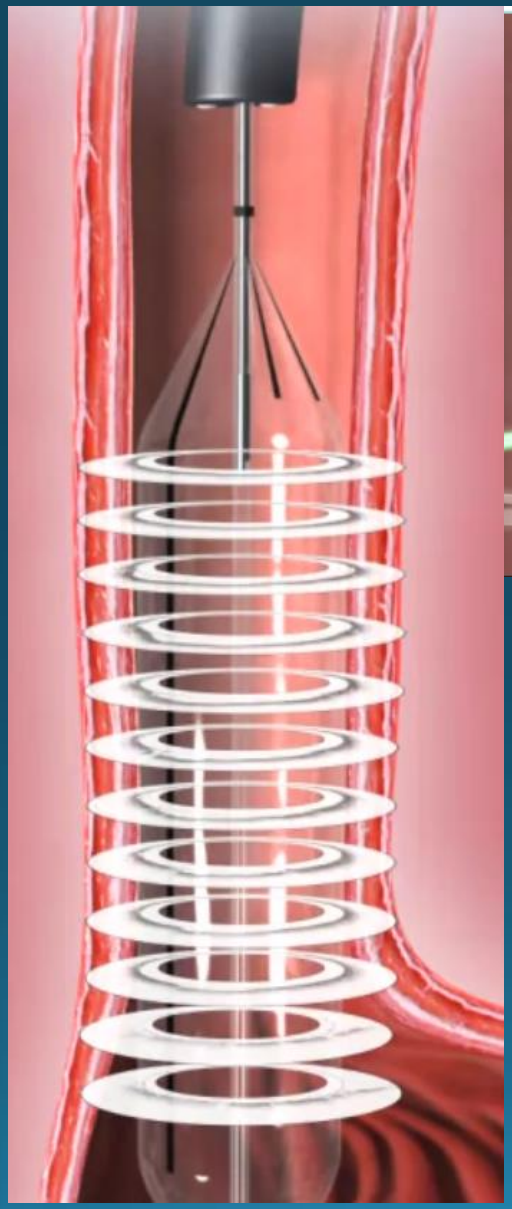
With pCLE, Negative Predictive Value for HGD/EC was 94%

Volumetric Laser Endomicroscopy

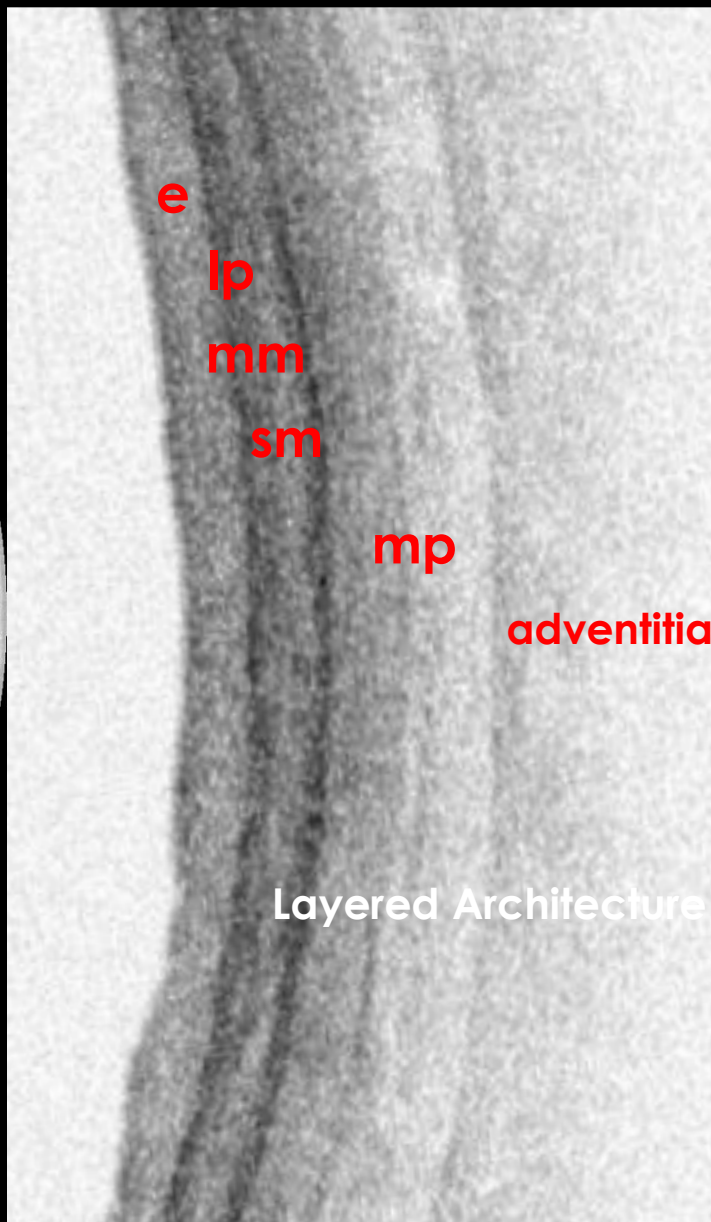


Volumetric Laser Endomicroscopy





Normal ***Esophageal Mucosa***



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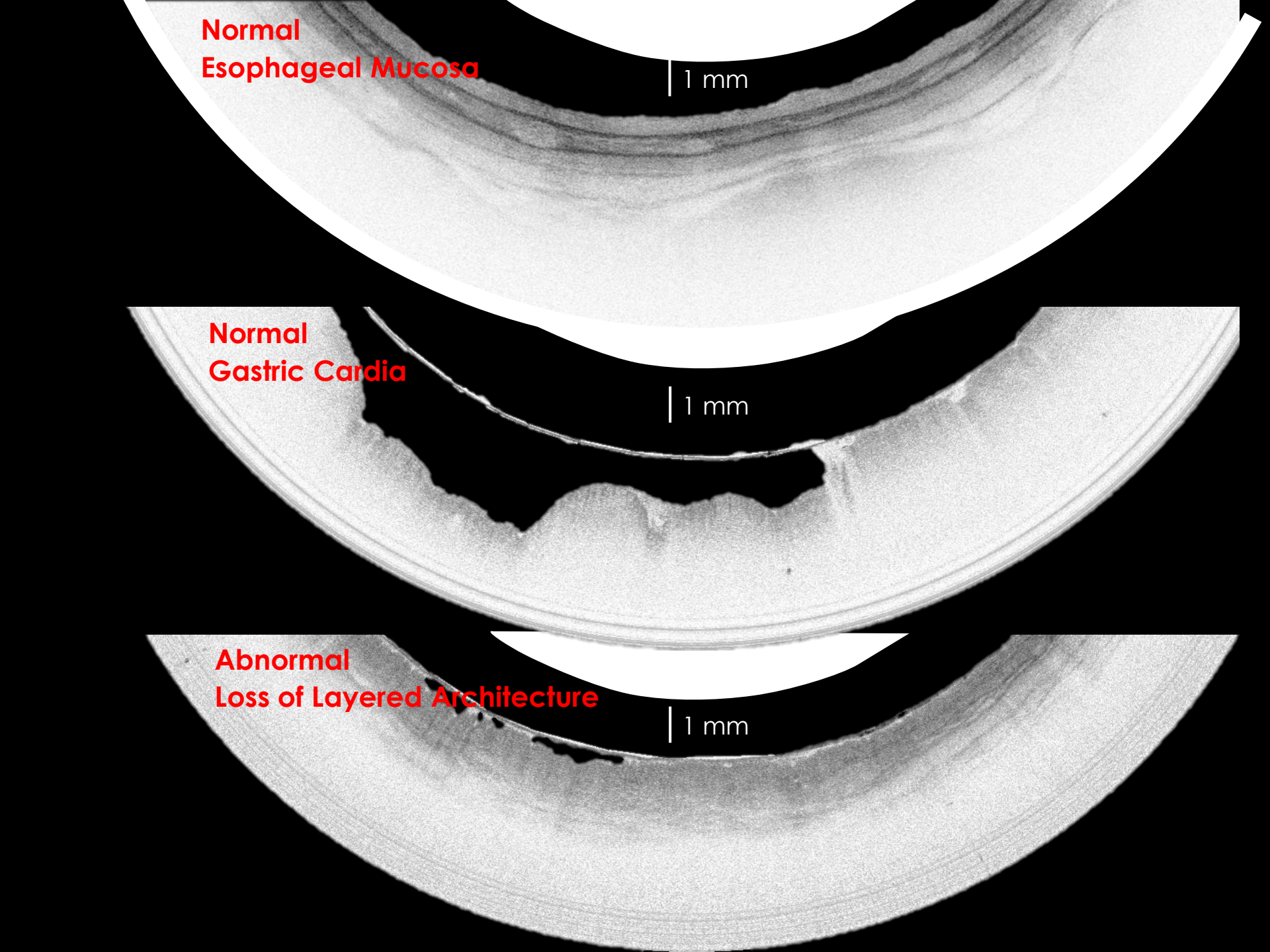
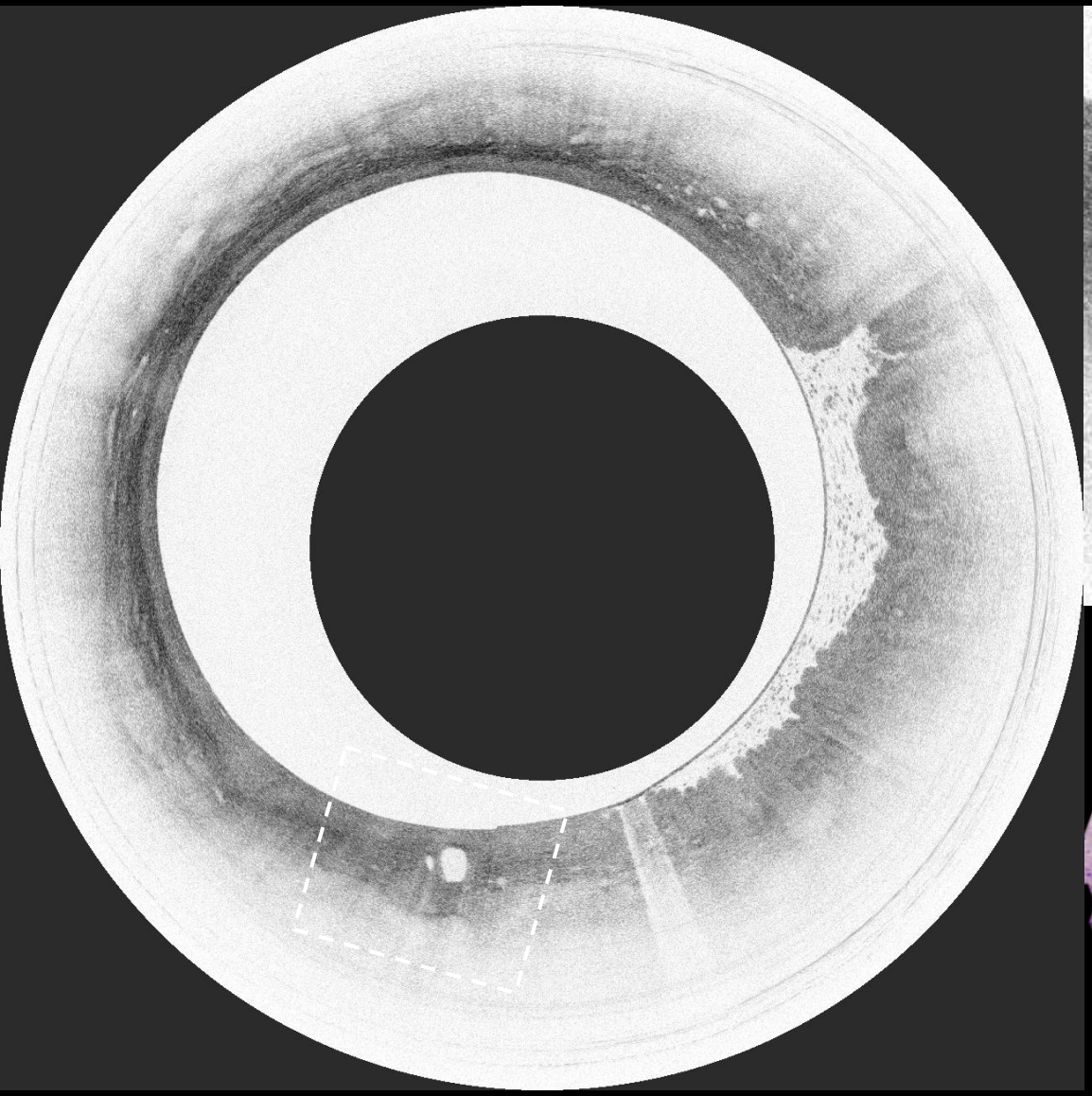
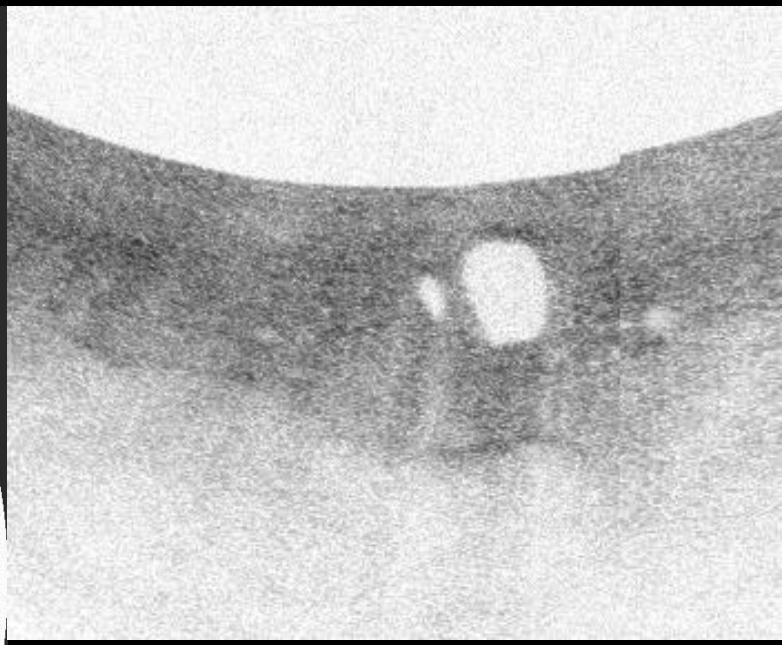
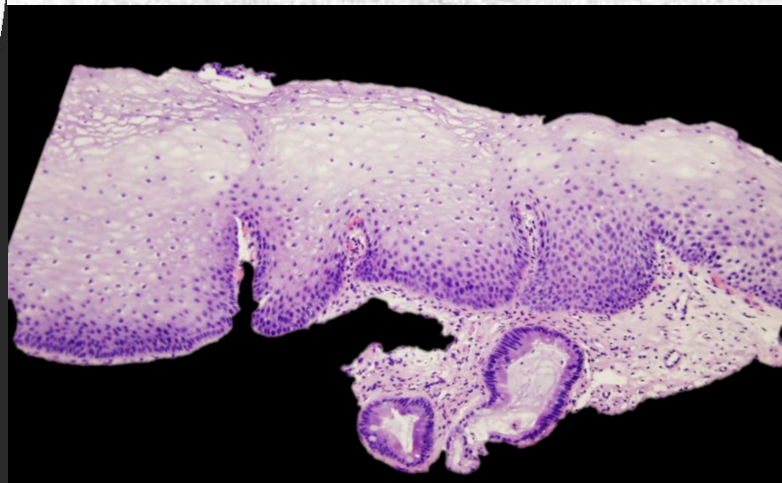

Normal
Esophageal Mucosa
1 mm
Normal
Gastric Cardia
1 mm
Abnormal
Loss of Layered Architecture
1 mm

Buried BE







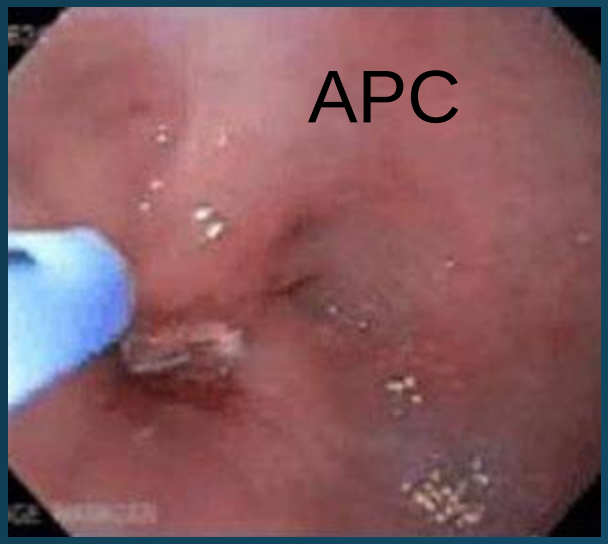
K. Chang, MD. UC Irvine Medical Center

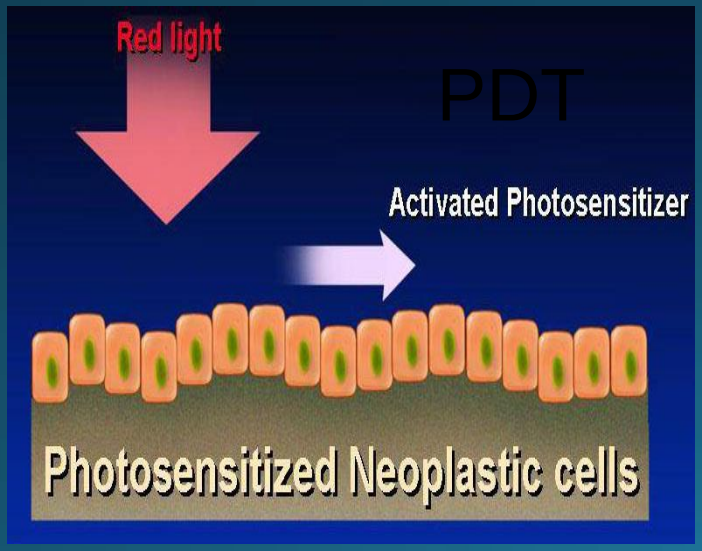
Therapy:
Endoscopic Mucosal Ablation

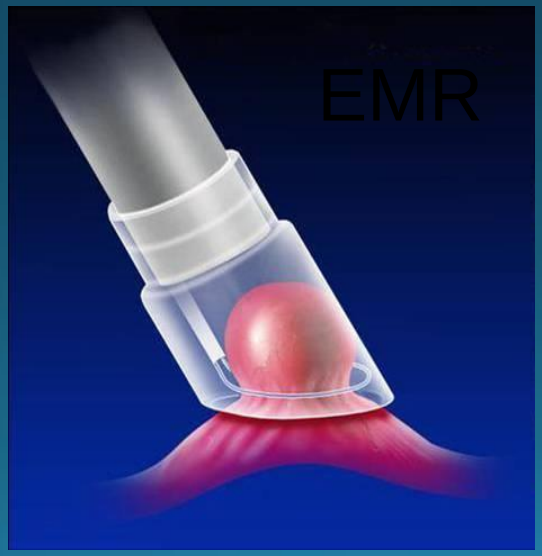
An ideal therapy would ...

- Completely eradicate the lesion
- Be safe & well-tolerated
- Prevent neoplastic progression
- Alter life-long surveillance

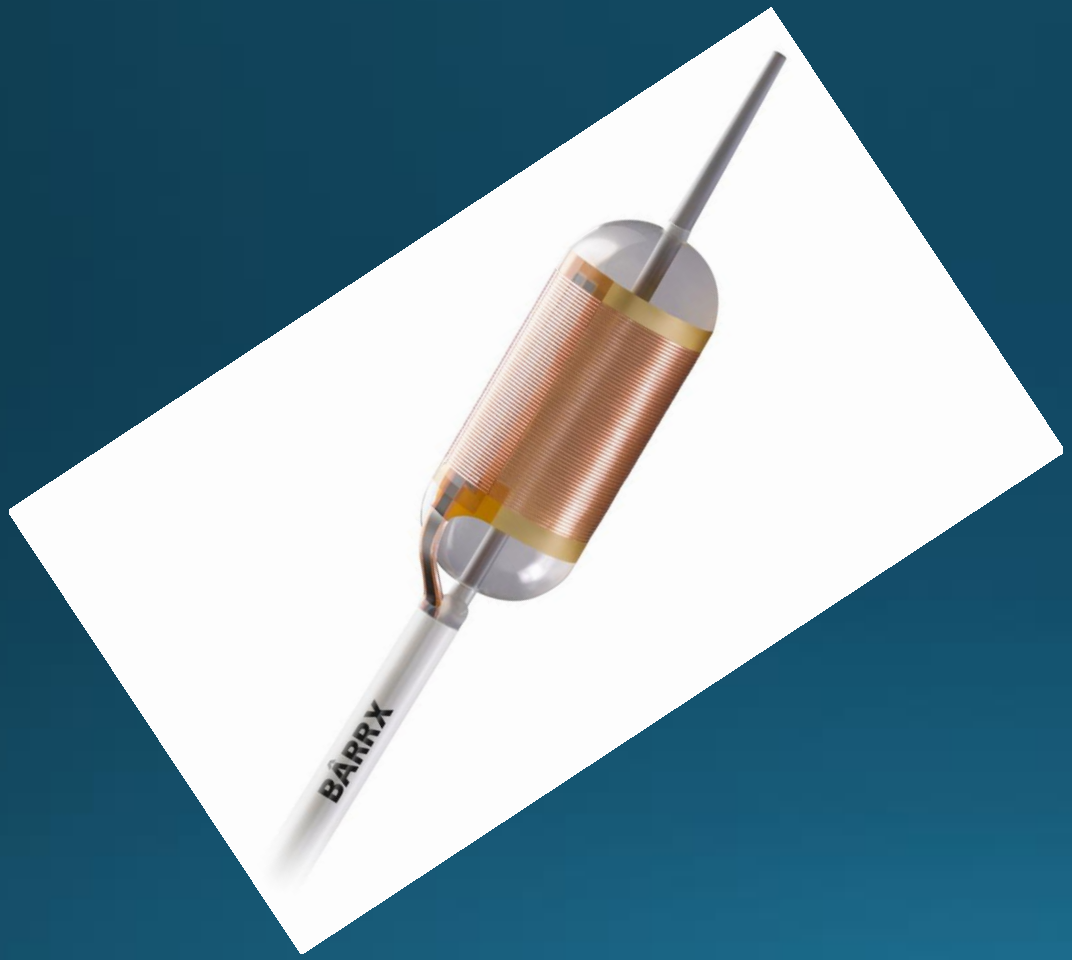
Mucosal Ablation



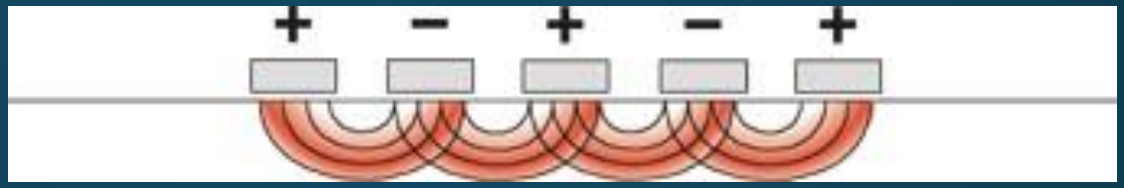




Radiofrequency Ablation



Proprietary Properties of RFA Lead to a Precise Ablation Depth (Mucosa-Submucosa Border)

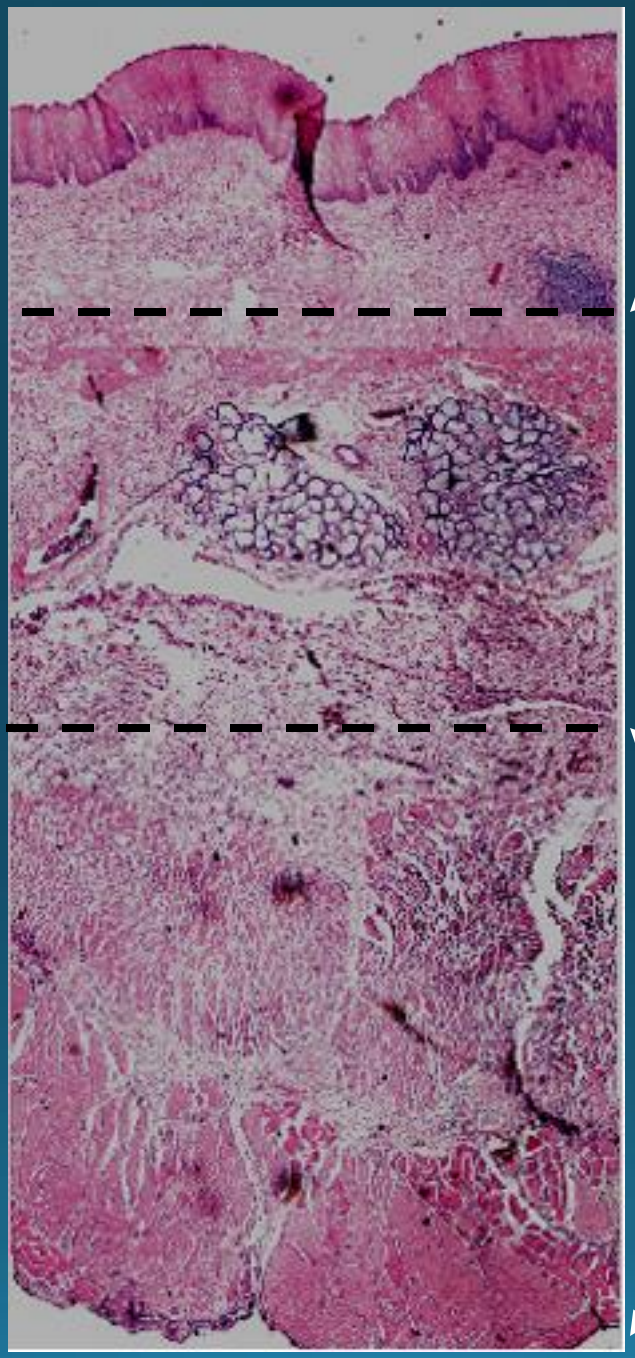


Mechanisms

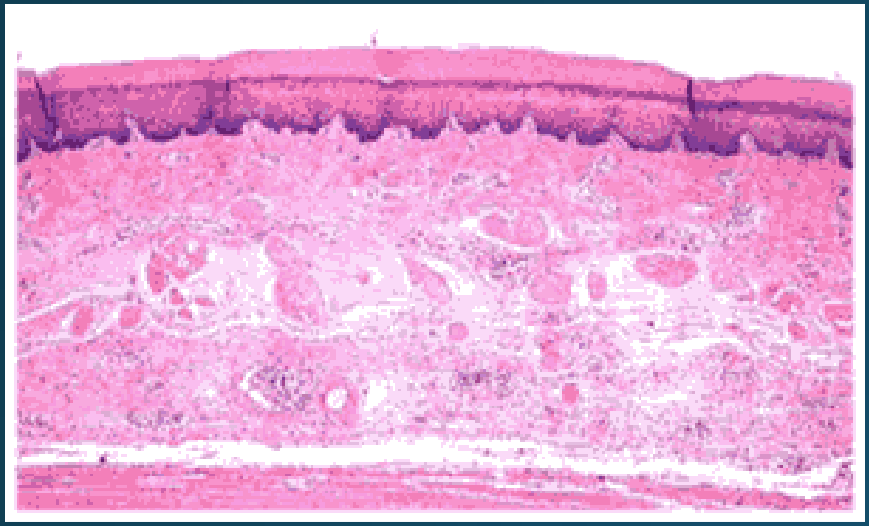
1. Tightly spaced electrodes (250 µm apart)
2. Proven pre-set energy & power densities
3. Generator turns off when a pre-determined resistance level in the ablated tissues is reached (mean of 0.3s)

Ganz, Gastrointest Endosc, 2004

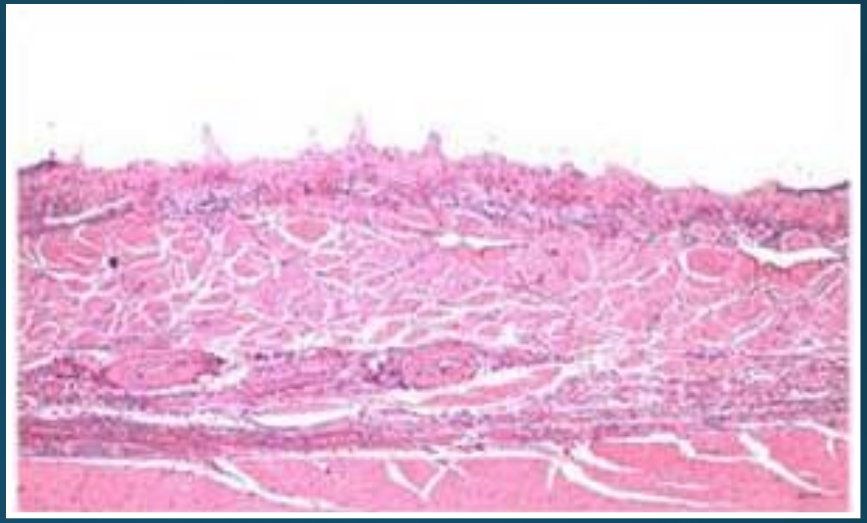
Human Esophagus



Histological Representation

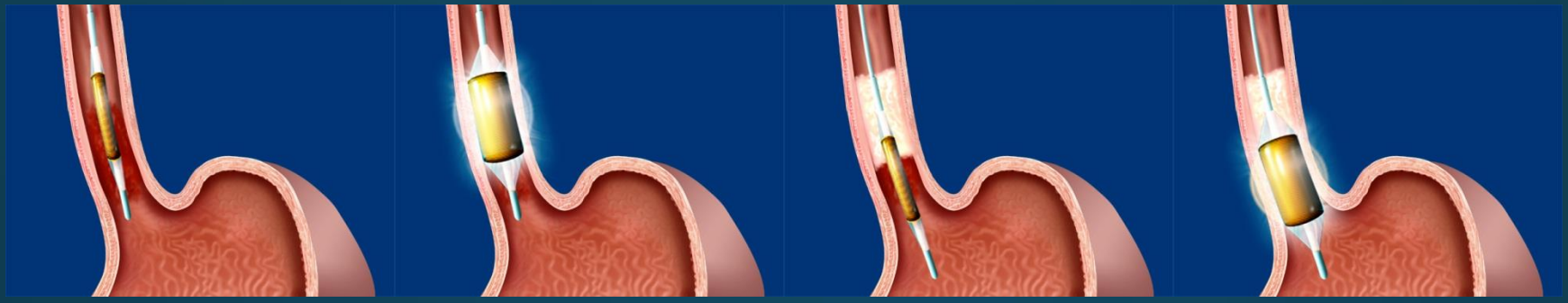


Normal

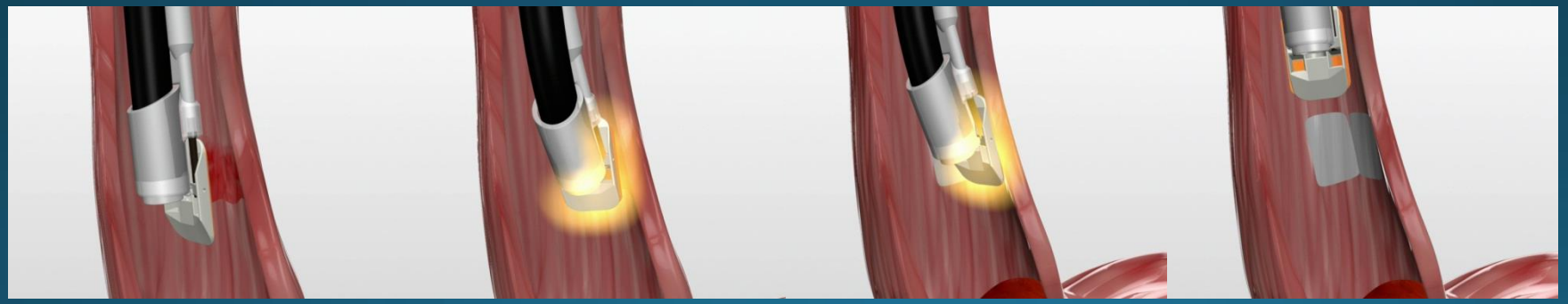


Post RF Ablation

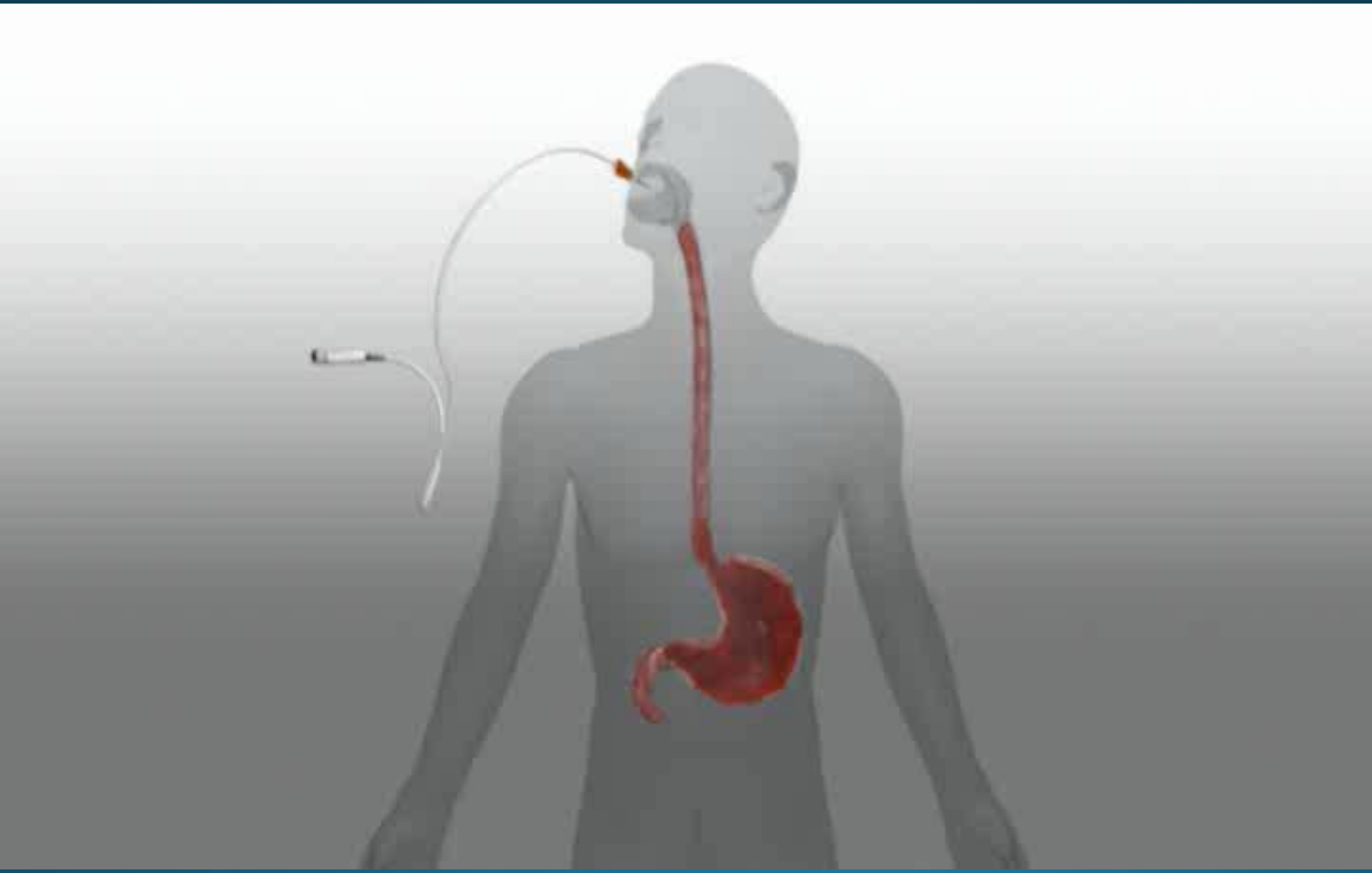
Circumferential Ablation

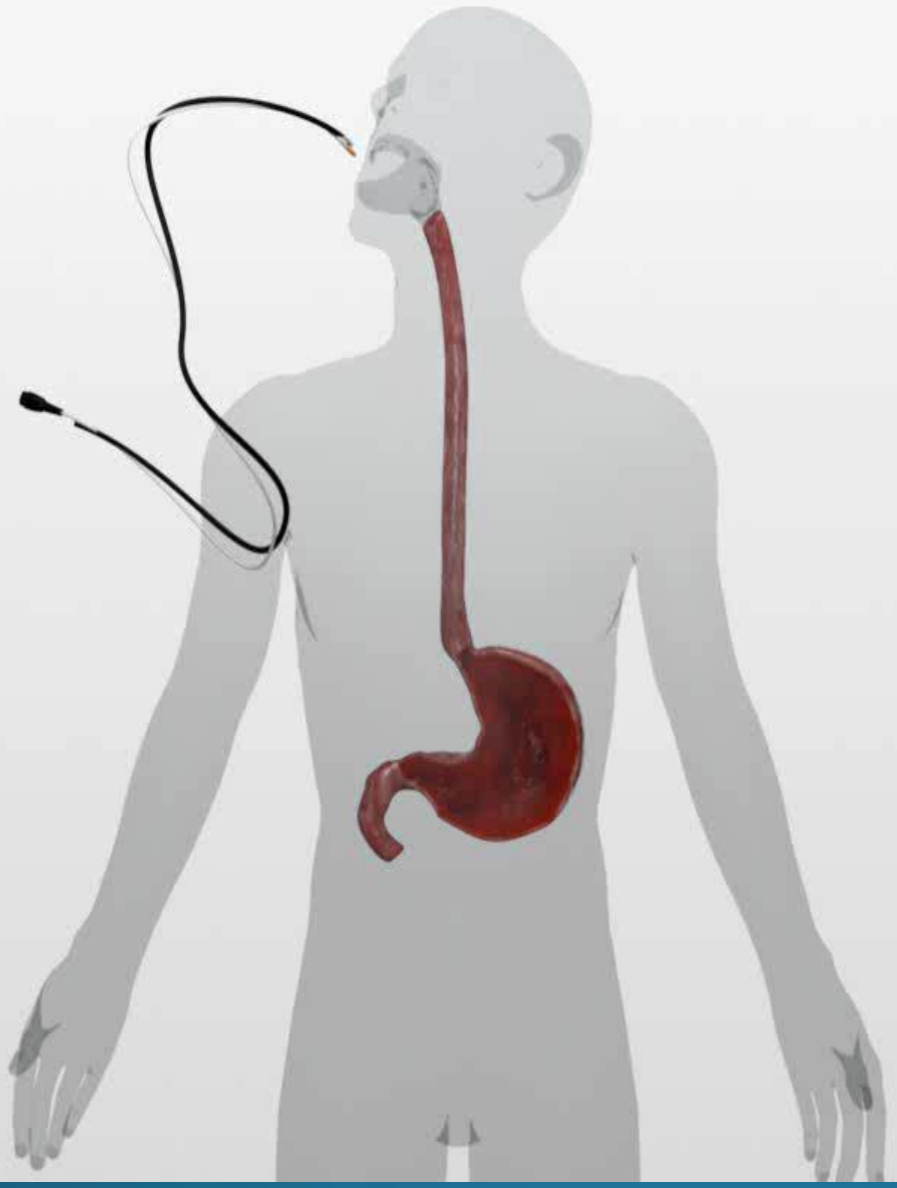


Focal Ablation

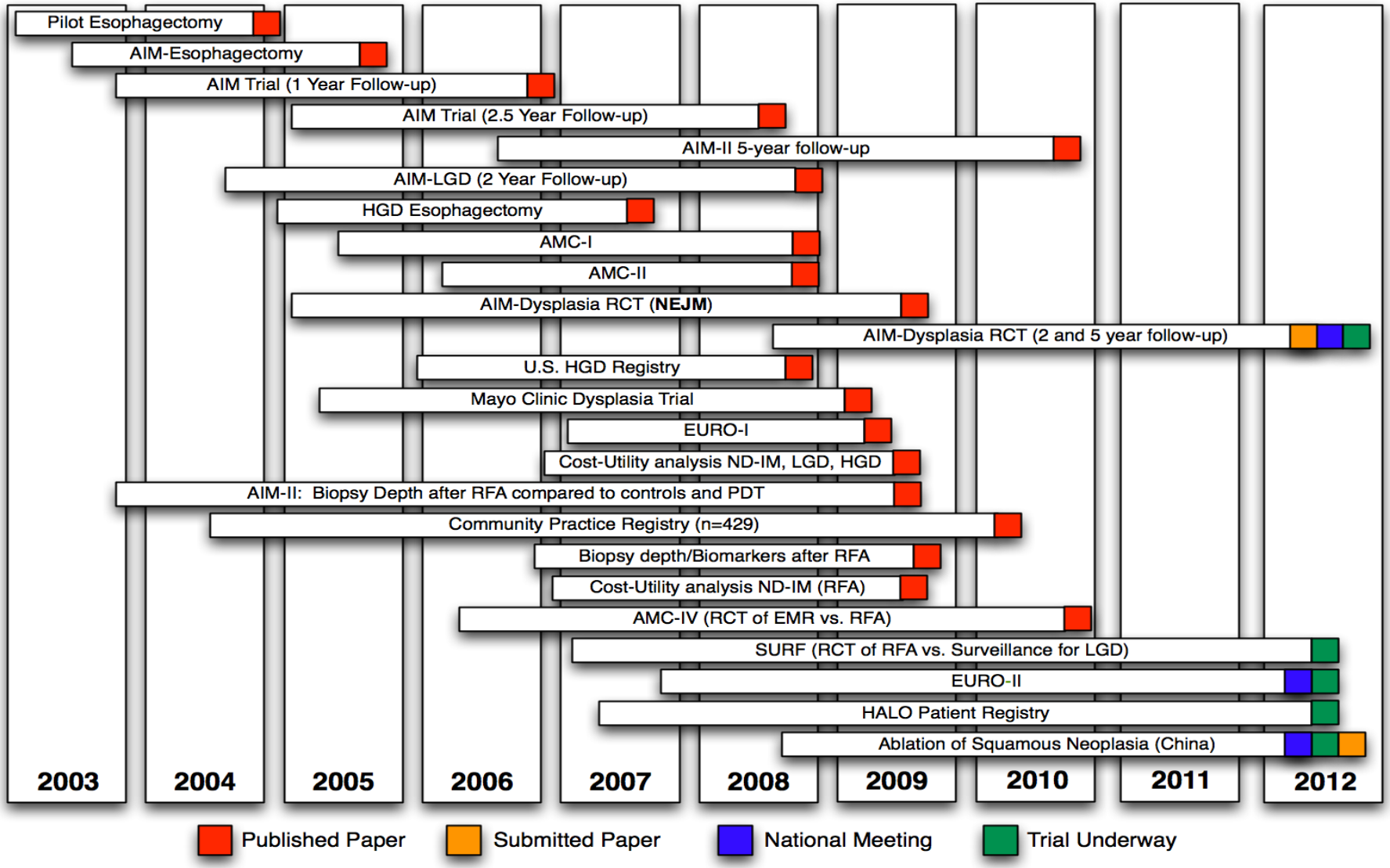


Ablation Device Family





Clinical Trial Timeline
Studies Assessing the HALO^{90} and HALO^{360} Ablation Systems

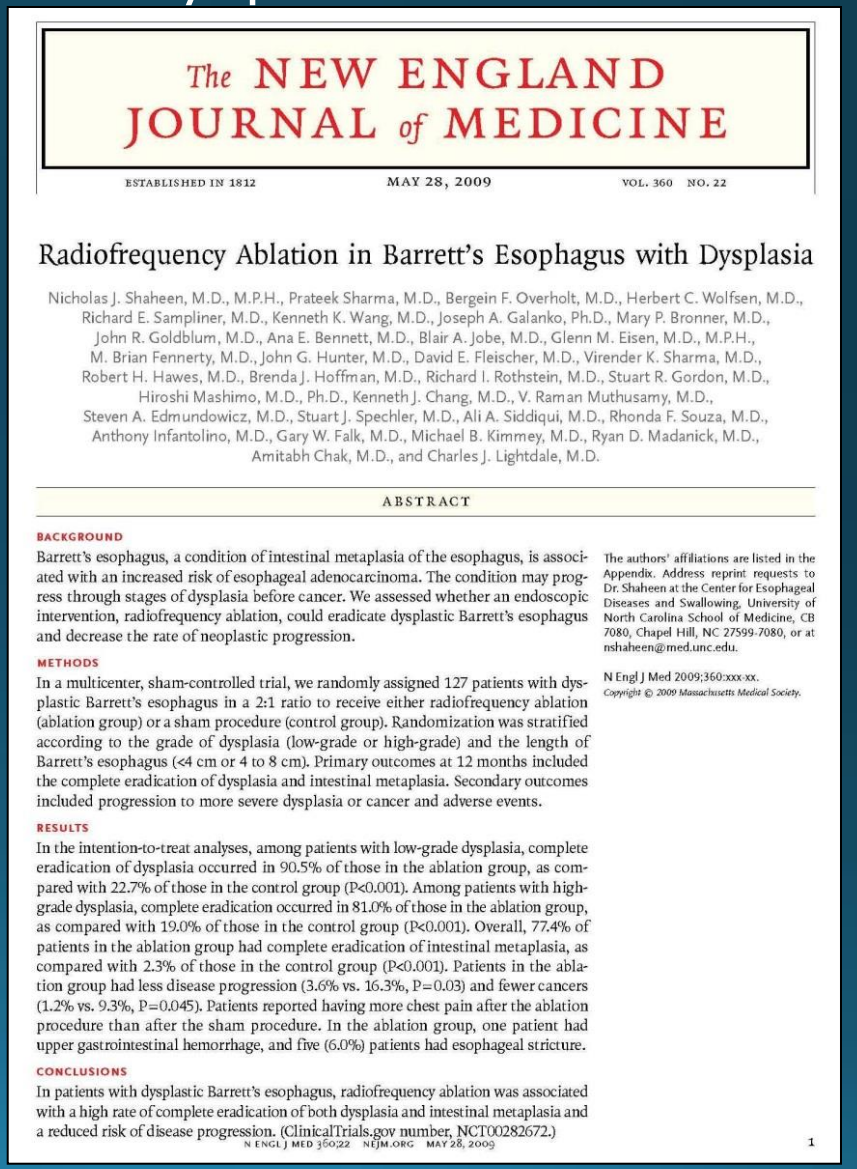


RFA for Barrett's Esophagus with Dysplasia

AIM Dysplasia Trial

(Shaheen, N Engl J Med, 2009)

- A RCT of 127 HGD & LGD pts
- 19 US medical centers
- Pts were randomized to treatment (RFA) & sham (surveillance) arms
- A statistically significant difference was demonstrated at 1 yr for both
  - Disease eradication (**P<0.001**)
  - Disease progression (**P<0.05**)



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Radiofrequency Ablation in Barrett's Esophagus with Dysplasia

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ABSTRACT

BACKGROUND

Barrett's esophagus, a condition of intestinal metaplasia of the esophagus, is associated with an increased risk of esophageal adenocarcinoma. The condition may progress through stages of dysplasia before cancer. We assessed whether an endoscopic intervention, radiofrequency ablation, could eradicate dysplastic Barrett's esophagus and decrease the rate of neoplastic progression.

METHODS

In a multicenter, sham-controlled trial, we randomly assigned 127 patients with dysplastic Barrett's esophagus in a 2:1 ratio to receive either radiofrequency ablation (ablation group) or a sham procedure (control group). Randomization was stratified according to the grade of dysplasia (low-grade or high-grade) and the length of Barrett's esophagus (<4 cm or 4 to 8 cm). Primary outcomes at 12 months included the complete eradication of dysplasia and intestinal metaplasia. Secondary outcomes included progression to more severe dysplasia or cancer and adverse events.

RESULTS

In the intention-to-treat analyses, among patients with low-grade dysplasia, complete eradication of dysplasia occurred in 90.5% of those in the ablation group, as compared with 22.7% of those in the control group (P<0.001). Among patients with high-grade dysplasia, complete eradication occurred in 81.0% of those in the ablation group, as compared with 19.0% of those in the control group (P<0.001). Overall, 77.4% of patients in the ablation group had complete eradication of intestinal metaplasia, as compared with 2.3% of those in the control group (P<0.001). Patients in the ablation group had less disease progression (3.6% vs. 16.3%, P=0.03) and fewer cancers (1.2% vs. 9.3%, P=0.045). Patients reported having more chest pain after the ablation procedure than after the sham procedure. In the ablation group, one patient had upper gastrointestinal hemorrhage, and five (6.0%) patients had esophageal stricture.

CONCLUSIONS

In patients with dysplastic Barrett's esophagus, radiofrequency ablation was associated with a high rate of complete eradication of both dysplasia and intestinal metaplasia and a reduced risk of disease progression. (ClinicalTrials.gov number, NCT00282672.)

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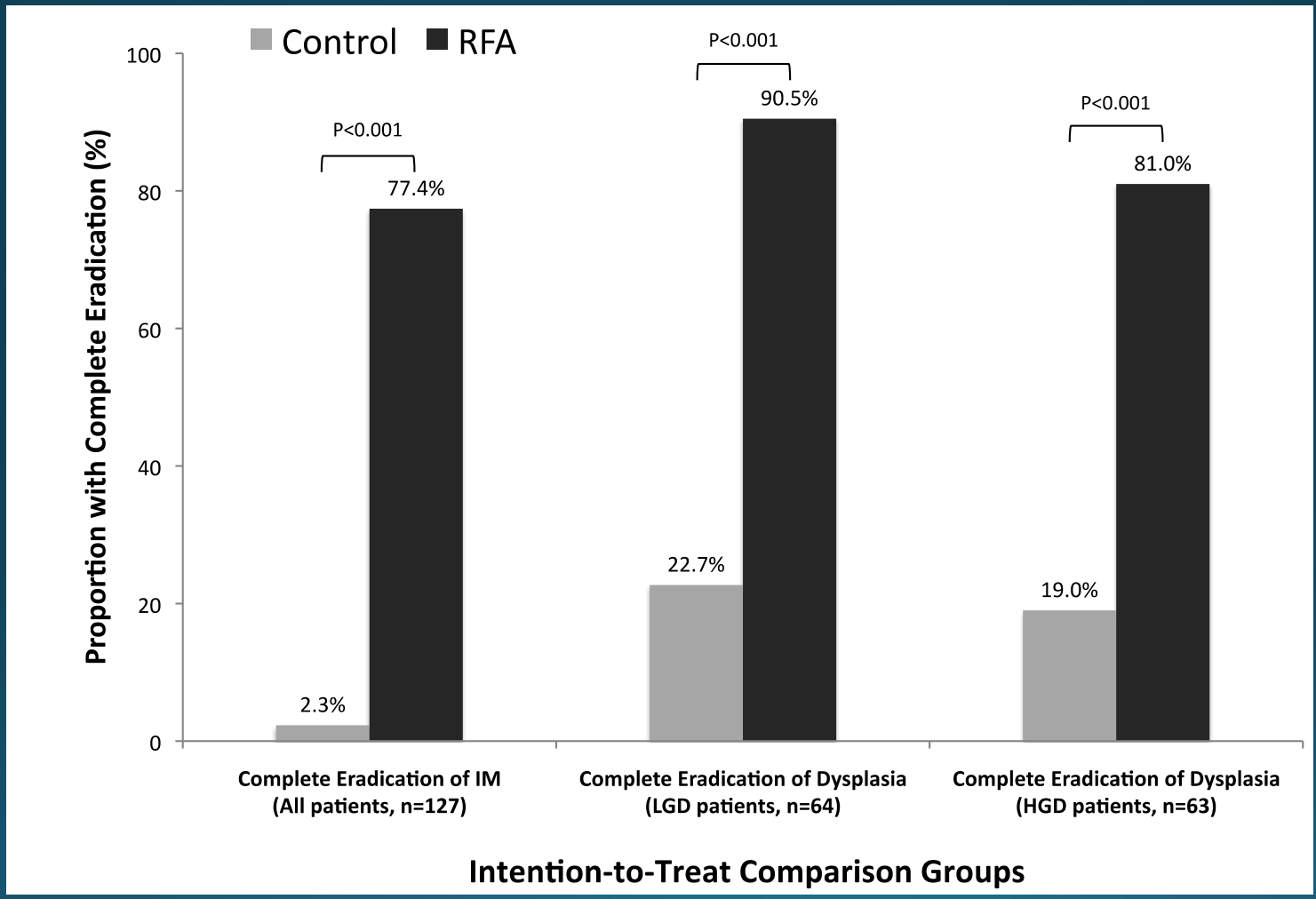
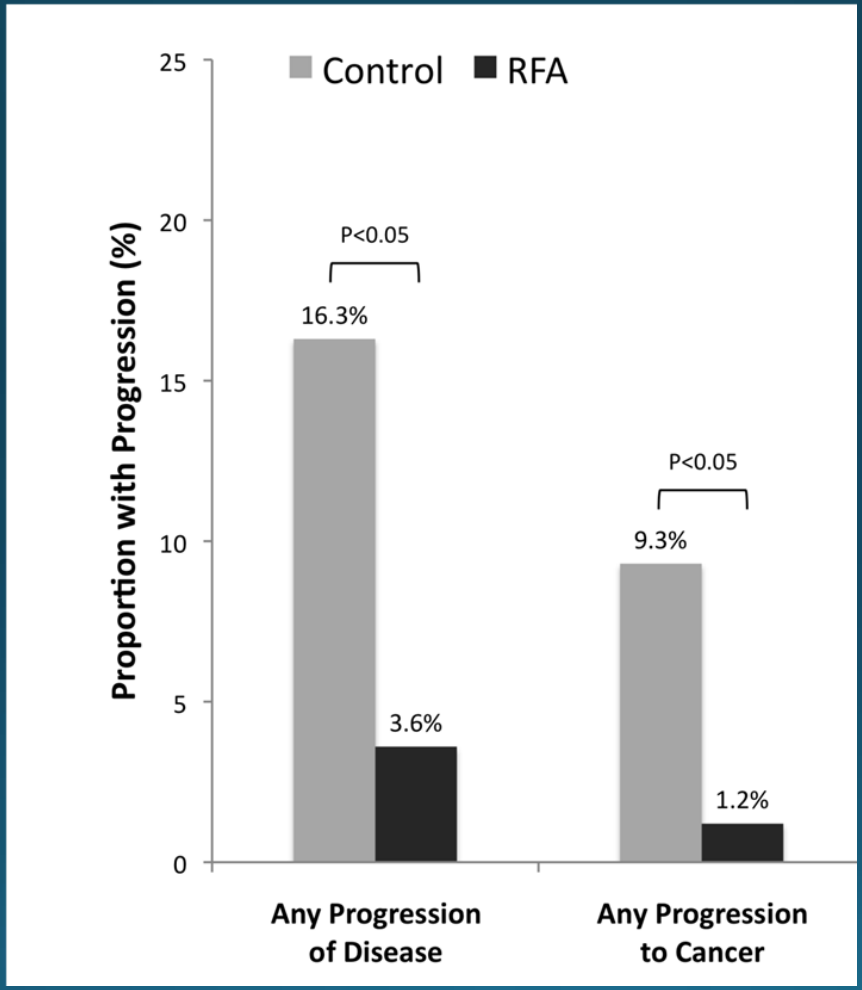
N Engl J Med 2009;360:xxx-xx.

Disease Eradication



Disease Progression



RFA Reduces Progression in Confirmed Low-Grade Dysplasia

SURF Trial, Phoa, JAMA, 2014

- European multicenter RCT of 136 confirmed LGD pts
- Pts randomized 1:1 to treatment (RFA) and control (surveillance) arms
- Complete eradication (CE) at 1 year:
  RFA: 88% CEIM, 93% CED
  Control: 0% CEIM, 28% CED (p<0.001)
- After median **36 mos** follow-up: **26.5%** of controls progressed to HGD/EAC vs. **1.5%** after RFA (p<0.001

  8.8% of controls progressed to EAC vs. **1.5%** after RFA (p<0.03
- Study terminated secondary to superiority of RFA and patient safety concerns should the trial continue

Research

Original Investigation

Radiofrequency Ablation vs Endoscopic Surveillance for Patients With Barrett Esophagus and Low-Grade Dysplasia
A Randomized Clinical Trial

K. Nadine Phoa, MD; Frederike G. I. van Vilsteren, MD; Bas L. A. M. Weusten, MD; Raf Bisschops, MD; Erik J. Schoon, MD; Krish Ragunath, MD; Grant Fullarton, MD; Massimiliano Di Pietro, MD; Narayanasamy Ravi, MD; Mike Visser, MD; G. Johan Offerhaus, MD; Cees A. Seldenrijk, MD; Sybren L. Meijer, MD; Flebo J. W. ten Kate, MD; Jan G. P. Tijssen, PhD; Jacques J. G. H. M. Bergman, MD, PhD

IMPORTANCE Barrett esophagus containing low-grade dysplasia is associated with an increased risk of developing esophageal adenocarcinoma, a cancer with a rapidly increasing incidence in the western world.

OBJECTIVE To investigate whether endoscopic radiofrequency ablation could decrease the rate of neoplastic progression.

DESIGN, SETTING, AND PARTICIPANTS Multicenter randomized clinical trial that enrolled 136 patients with a confirmed diagnosis of Barrett esophagus containing low-grade dysplasia at 9 European sites between June 2007 and June 2011. Patient follow-up ended May 2013.

INTERVENTIONS Eligible patients were randomly assigned in a 1:1 ratio to either endoscopic treatment with radiofrequency ablation (ablation) or endoscopic surveillance (control). Ablation was performed with the balloon device for circumferential ablation of the esophagus or the focal device for targeted ablation, with a maximum of 5 sessions allowed.

MAIN OUTCOMES AND MEASURES The primary outcome was neoplastic progression to high-grade dysplasia or adenocarcinoma during a 3-year follow-up since randomization. Secondary outcomes were complete eradication of dysplasia and intestinal metaplasia and adverse events.

RESULTS Sixty-eight patients were randomized to receive ablation and 68 to receive control. Ablation reduced the risk of progression to high-grade dysplasia or adenocarcinoma by 25.0% (1.5% for ablation vs 26.5% for control; 95% CI, 14.1%-35.9%; $P < .001$) and the risk of progression to adenocarcinoma by 7.4% (1.5% for ablation vs 8.8% for control; 95% CI, 0%-14.7%; $P = .03$). Among patients in the ablation group, complete eradication occurred in 92.6% for dysplasia and 88.2% for intestinal metaplasia compared with 27.9% for dysplasia and 0.0% for intestinal metaplasia among patients in the control group ($P < .001$). Treatment-related adverse events occurred in 19.1% of patients receiving ablation ($P < .001$). The most common adverse event was stricture, occurring in 8 patients receiving ablation (11.8%), all resolved by endoscopic dilation (median, 1 session). The data and safety monitoring board recommended early termination of the trial due to superiority of ablation for the primary outcome and the potential for patient safety issues if the trial continued.

CONCLUSIONS AND RELEVANCE In this randomized trial of patients with Barrett esophagus and a confirmed diagnosis of low-grade dysplasia, radiofrequency ablation resulted in a reduced risk of neoplastic progression over 3 years of follow-up.

TRIAL REGISTRATION trialregister.nl Identifier: NTR1198

Editorial page 1205

CME Quiz at jamanetworkcme.com and CME Questions page 1247

Author Affiliations: Author affiliations are listed at the end of this article.

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JAMA. 2014;311(12):1209-1217. doi:10.1001/jama.2014.2511

Phoa K, van Vilsteren FI, Weusten BM, et al. Radiofrequency Ablation vs Endoscopic Surveillance for Patients With Barrett Esophagus and Low-Grade Dysplasia: A Randomized Clinical Trial. JAMA 2014;311:1209-1217.
Trial funded by Covidien, GI Solutions

RFA Safety Profile

MDRs April 2005 to March 2012

- Total cases: 104,268
- Total MDRs: 242
  - Cumulative rate: 0.23%
    - death: 0.00%
    - stricture: 0.18%
    - perforation: 0.01%
    - mucosal injury: 0.01%
    - transient bleeding: 0.02%
  - Incidence rate is 1 MDR in 430 cases
    - 1 stricture in 557 cases
    - 1 perforation in 9479 cases
      - Screening colonoscopy, no polypectomy, 1 in 6,000
      - Colonoscopy with simple polypectomy, 1 in 1,500

RFA Patient Tolerance

- Generally well tolerated
- Most common symptoms are pain and dysphagia
- Pain generally greater after circumferential ablation and after the treatment of longer segment disease

- From the AIM Trial:
  - Median scores for chest pain and dysphagia were < 25/100 on day 1 and generally decreased to 0/100 by day 4
  - The "worst" 10% of patients had scores of 70/100 for chest pain and dysphagia on day 1 with a decrease to 0/100 by day 10

Fleischer et al. Endoscopy 2010

Barrett's Management Guidelines

Endoscopic Therapy
For High-Grade Dysplasia

- **Value of Radiofrequency Ablation:** "RFA can lead to reversion of the metaplastic mucosa to normal appearing squamous epithelium in a high proportion of subjects at *any stage* of BE."

- **High Grade Dysplasia Management:** "We recommend *endoscopic eradication therapy* with RFA, PDT, or EMR rather than surveillance for treatment of patients with *confirmed* HGD within BE."

AGA Medical Position Statement GASTROENTEROLOGY 2011;140:1084 –1091

Endoscopic Therapy
For Low-Grade Dysplasia

- **LGD is Difficult to Differ from HGD:** "Because dysplasia progresses to cancer in a manner that lacks definitive markers of progression, there are *no well-defined cutoff points* that separate LGD from HGD at this time."

- **Low Grade Dysplasia Management:** "Endoscopic eradication therapy with RFA *should* also be a *therapeutic option* for treatment of patients with *confirmed* LGD in BE."

AGA Medical Position Statement GASTROENTEROLOGY 2011;140:1084 –1091

Endoscopic Therapy
For Non-Dysplastic BE

- "… we suggest that RFA, with or without EMR, *should* be a *therapeutic option for select individuals* with NDBE who are judged to be at increased risk for progression to HGD or cancer."

- "Specific criteria that identify this population have not been fully defined at this time."

AGA Medical Position Statement GASTROENTEROLOGY 2011;140:1084 –1091

What does the Future have in store for Barrett's Esophagus?

Biomarkers are on the way

Population-Based Study Reveals New Risk-Stratification Biomarker Panel for Barrett's Esophagus

- Nested case-control study
- Population based Northern Ireland BE Registry
- Cases who progressed to HGD/EAC (n=89) matched to controls (non-progressors n=291)
- Biomarkers evaluated:
  - Abnormal DNA Content, p53, Cyclin A expression
  - Sialyl Lewis, Lewis X, Aspergillus oryzae lectin, Binding of wheat germ agglutinin
  - Presence of LGD by expert pathologists

Bird-Lieberman et al. GASTROENTEROLOGY 2012;143:927–935

Biomarkers are on the way

Population-Based Study Reveals New Risk-Stratification Biomarker Panel for Barrett's Esophagus

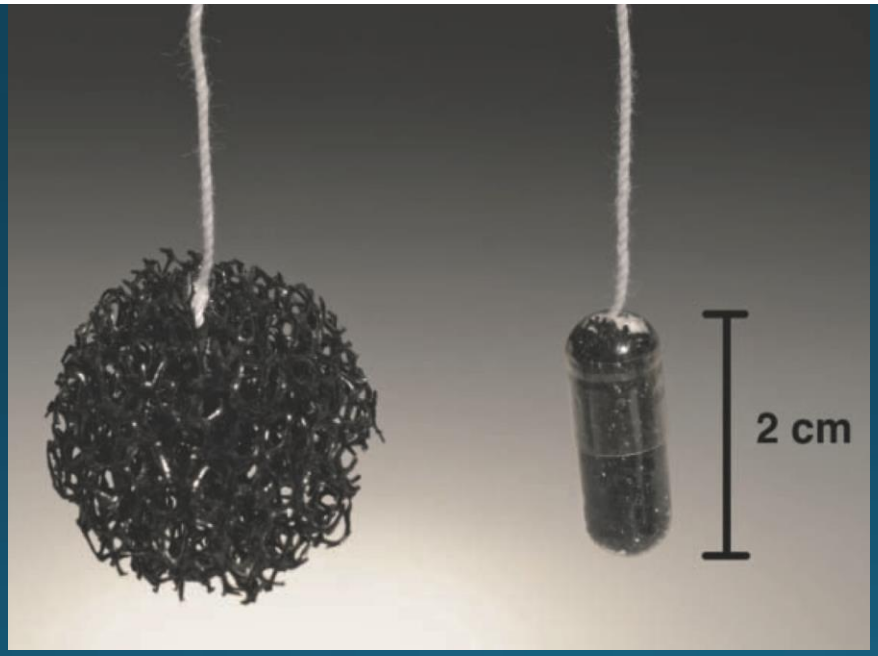
- Results:
  - All biomarkers tested other than Lewis X were associated with progression to HGD/EAC
  - A simplified 3-biomarker panel model showed significant stepwise progression:
    - Aspergillus oryzae lectin
    - DNA content abnormalities
    - Presence of LGD

Each marker independantly increased odds of progression to EAC four-fold

Bird-Lieberman et al. GASTROENTEROLOGY 2012;143:927–935

Non-invasive screening

Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study

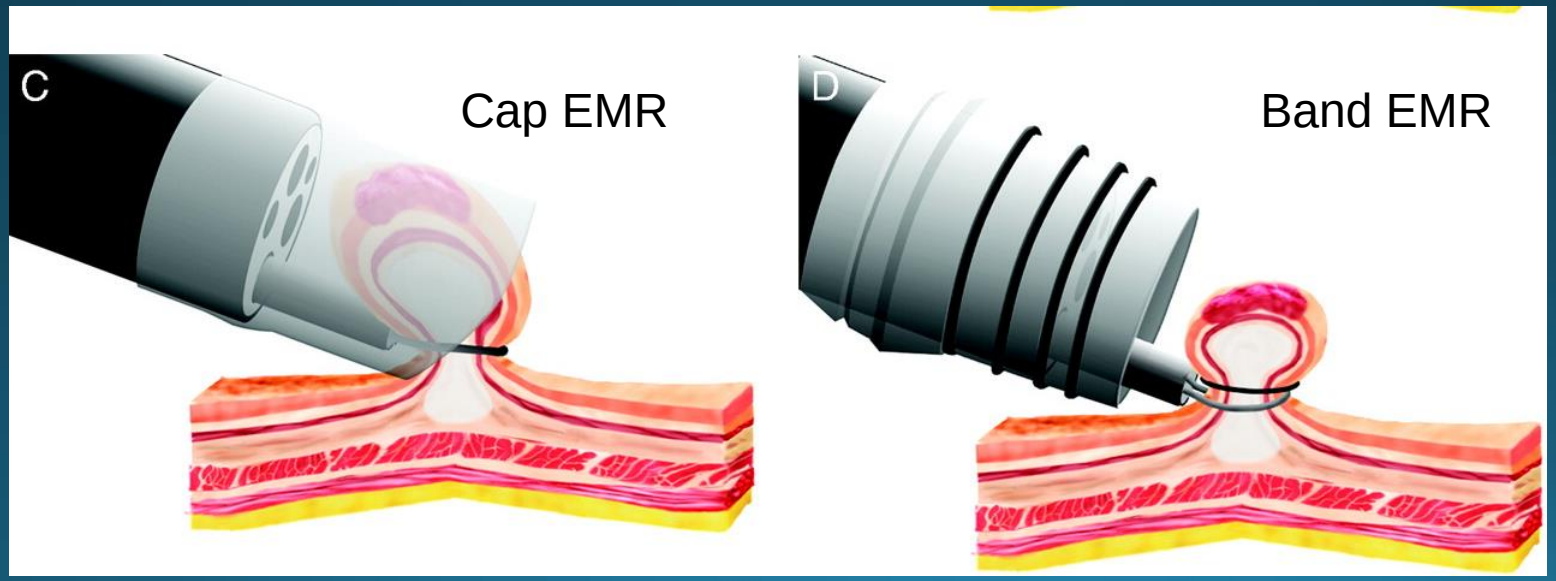


Cytosponge

BMJ. 2010 Sep 10;341:c4372

Early Esophageal Cancer (T1a)

- Generally found on Barrett's surveillance.
- **E**ndoscopic **M**ucosal **R**esection = Esophagectomy for outcomes in low risk T1aN0MO grade I (stage IA) EAC at high risk centers.
- Overall excellent long term outcomes in stage IA EAC.



Summary

- Barrett's Esophagus:
  - Metaplastic columnar epithelium replaces the stratified squamous epithelium
- Due to reflux of gastric acid + other gastric contents

- Risk Factors:
  - Male, Age > 50, Caucasian, Smoker
  - Obese, Intra-abdominal fat distribution, Family Hx

Summary

- Screening:
  - Weak Recommendation for Endoscopic screening in patients with multiple risk factors
- Surveillance:
  - Weak Recommendation for Endoscopic Surveillance of patients with Barrett's using Seattle Protocol
  - New Technology to improve this issue is here:
    - Confocal Laser endomicroscopy
    - EndoCDx WATS 3D biopsy brush
    - Volumetric Laser Endomicroscopy

Summary

	1 Year CA Progression Rate	AGA Guidelines Recommendations
Non-dysplastic Barrett's	0.3%	Surveillance (or Ablation in select individuals)
Low Grade Dysplasia (confirmed)	3%	Endoscopic Ablation
High Grade Dysplasia	10%	Endoscopic Ablation

Radiofrequency Ablation appears to be a highly effective and durable ablation modality, long term data indicates recurrence may occur but at a low rate

Thank you for your attention

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