

# Management of Barrett's esophagus

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**GERD**

# GERD

- >60 million adult Americans suffer from heartburn at least once a month
- >25 million experience heartburn daily
- The National Ambulatory Medical Care Survey (NAMCS) found that 38.53 million annual adult outpatient visits were related to GERD.
- For patients presenting with GERD symptoms, 40-60% or more have reflux esophagitis.
- Up to 10% of these patients will have erosive esophagitis on upper endoscopy.
- Patients with GERD generally report decreases in productivity, quality of life and overall well-being.
- GERD is a risk factor for the development of esophageal adenocarcinoma, further increasing the importance of its diagnosis and treatment.

# GERD

- US GERD Prevalence:  
estimated 18.1% to 27.8%
- Large population at risk of Barrett esophagus
- Rates of EAC are rising worldwide
- Barrett's Esophagus Prevalence:
  - U.S., general population, 5.6%

# Testing

## History

symptoms of heartburn and acid regurgitation atypical symptoms

## Testing

pH probe is accepted as the standard with a sensitivity of 85% and specificity of 95%

Endoscopy lacks sensitivity in determining pathologic reflux but can identify complications (e.g. strictures, erosive esophagitis, **Barrett's esophagus**)

Barium radiography has limited usefulness in the diagnosis of GERD and is not recommended

## Therapeutic trial.

An empiric trial of anti-secretory therapy

# Treatment

## Lifestyle modifications.

Lifestyle modifications

weight loss

avoiding recumbency several hours after meals

## Pharmacologic treatment.

H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs)

proton pump inhibitors (PPIs)

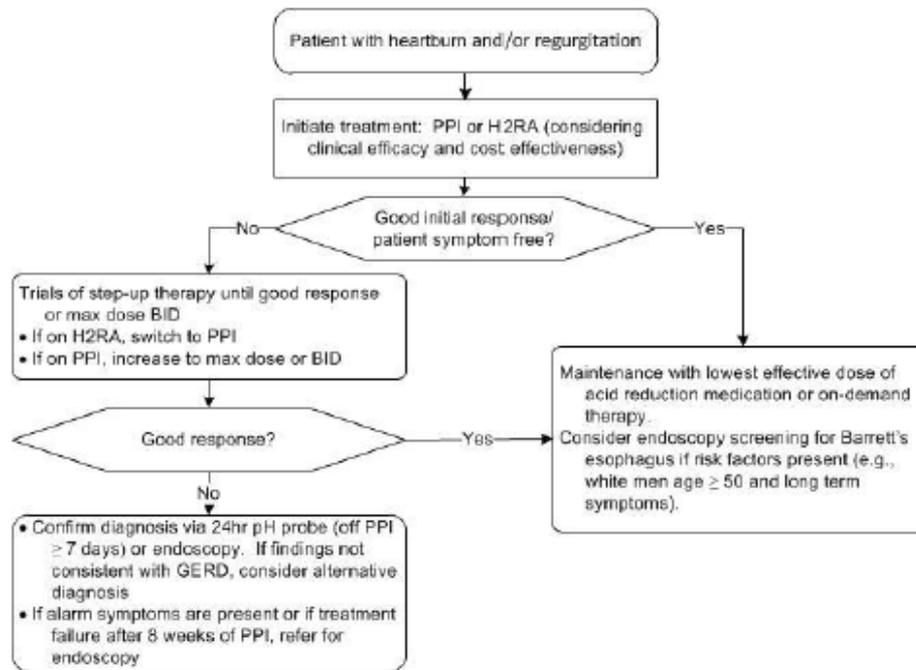
Carafate and antacids are ineffective [III A\*], but may be used as supplemental acid-neutralizing agents for certain patients with GERD [II D\*].

☐ Take PPI's 30-60 minutes prior to breakfast (and dinner if BID) to optimize effectiveness

Use generic and OTC formulations exclusively, eliminating need for prior authorizations.

☐ Patients should not be left on AST without re-evaluation of symptoms

**Figure 1. Diagnosis and Treatment of GERD**



**Table 1. Atypical Signs of GERD**

|                               |
|-------------------------------|
| Chronic cough                 |
| Asthma                        |
| Recurrent sore throat         |
| Recurrent laryngitis          |
| Dental enamel loss            |
| Subglottic stenosis           |
| Globus sensation              |
| Chest pain                    |
| Onset of symptoms at age > 50 |

**Table 2. Alarm/Warning Signs Suggesting Complicated GERD**

|                        |
|------------------------|
| Dysphagia              |
| Odynophagia            |
| GI Bleeding            |
| Iron Deficiency Anemia |
| Weight Loss            |
| Early satiety          |
| Vomiting               |

**Table 3. Lifestyle Modifications**

|   |
|---|
| Elevate head of bed 6-8 inches  |
| Decrease fatty meals  |
| Stop smoking  |
| Avoid recumbency/sleeping for 3-4 hours postprandially  |
| Avoid certain foods: chocolate, alcohol, peppermint, caffeinated coffee and other beverages, onions, garlic, fatty foods, citrus, tomato  |
| Avoid large meals   |
| Weight loss   |
| Avoid medications that can potentiate symptoms: calcium channel blockers, $\beta$ -agonists, $\alpha$ -adrenergic agonists, theophylline, nitrates, and some sedatives (benzodiazepines). |

**Table 4. Medications for Acute Treatment and Maintenance Regimens**

| Drug                    | Dose<br>Equivalents <sup>a</sup> | Dosage <sup>b</sup>             | OTC     | Generic <sup>c</sup> | Brand <sup>c</sup> |
|-------------------------|----------------------------------|---------------------------------|---------|----------------------|--------------------|
| <b>H2 antagonists</b>   |                                  |                                 |         |                      |                    |
| cimetidine (Tagamet HB) | 200 mg BID                       | 200 mg BID                      | \$15    | NA                   | \$18               |
| cimetidine (Tagamet)    | 400 mg BID                       | 400 mg BID                      | \$30    | \$11                 | \$36               |
| famotidine (Pepcid)     | 20 mg BID                        | 20 mg BID                       | \$34    | \$8                  | \$130              |
| ranitidine (Zantac)     | 150 mg BID                       | 150 mg BID                      | \$20    | \$29                 | \$220              |
| ranitidine (Zantac)     | 300 mg nightly                   | 300 mg nightly                  | \$40    | \$48                 | \$187              |
| <b>PPIs</b>             |                                  |                                 |         |                      |                    |
| lansoprazole (Prevacid) | 30 mg daily                      | 15/30 mg daily before breakfast | \$24-47 | \$32-63              | NA                 |
| omeprazole (Prilosec)   | 20 mg daily                      | 20/40 mg daily before breakfast | \$16    | \$18                 | \$180              |
| pantoprazole (Protonix) | 40 mg daily                      | 40 mg daily before breakfast    | NA      | \$17                 | \$172              |
| rabeprazole (Aciphex)   | 20 mg daily                      | 20 mg daily before breakfast    | NA      | NA                   | \$240              |

<sup>a</sup> For each drug the dose listed in this column has an effect equivalent to the doses listed in this column for other drugs.

<sup>b</sup> Maximum dose for PPIs is the highest listed dose amount, but given daily BID before breakfast and before dinner.

<sup>c</sup> For brand drugs, Average Wholesale Price minus 10%. AWP from Amerisource Bergen Wholesale Catalog 11/11. For generic drugs, Maximum Allowable Cost plus \$3 from BCBS of Michigan MAC List, 11/16/11.

# Complications from GERD

- 10-15% with GERD will develop BE
- 1-10% of those with Barrett's will develop EAC over 10-20 years
- Chronic reflux has been suspected to play a major role in the development of Barrett's esophagus (specialized columnar epithelium/intestinal metaplasia)
- Unknown if outcomes can be improved through surveillance and medical treatment.

# PREVALENCE OF BARRETT'S ESOPHAGUS

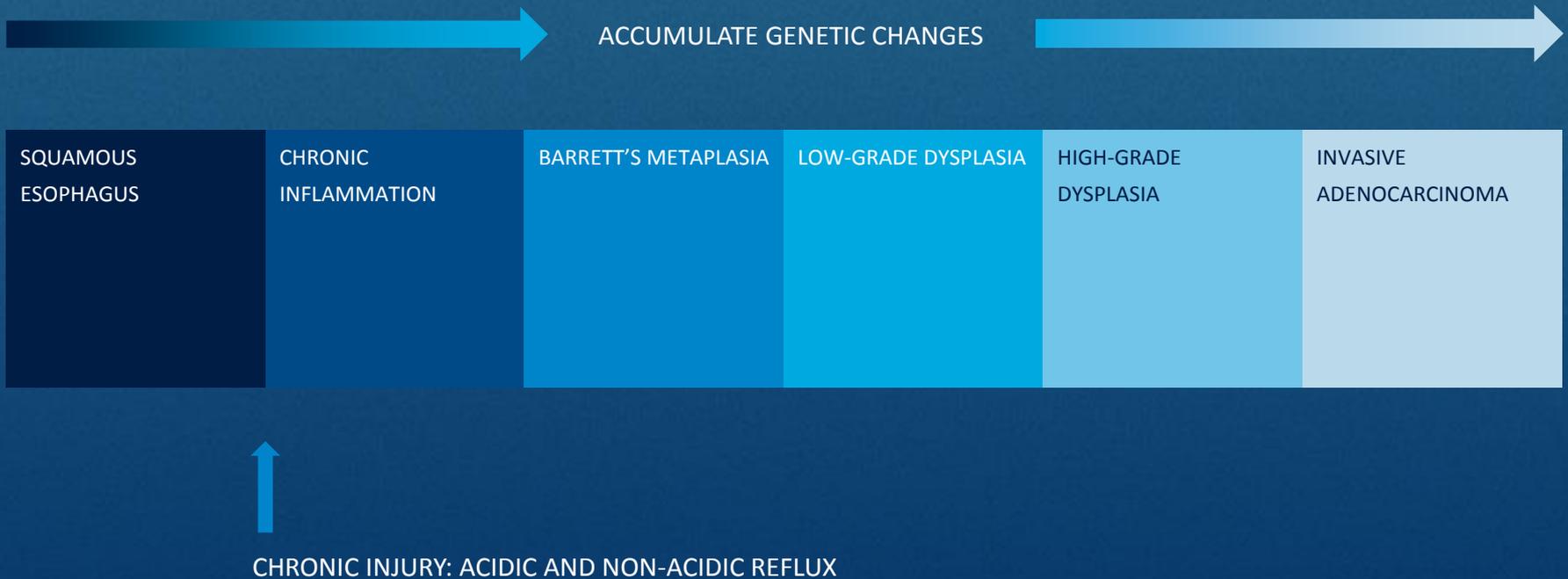
# Risk of Barrett's esophagus

- Risk BE
  - 1.2% in asymptomatic individuals
  - 2.3% in those with reflux symptoms
- Caucasians with reflux symptoms
  - 3.3% at age 30 to 40 years
  - 6.3% at age 40 to 50 years
  - 9.3% at age 50 to 60 years

# Incidence

- White, males, > 50 years of age, chronic GERD: 13.2% BE prevalence<sup>4</sup>
  - GERD and BE are risk factors for esophageal adenocarcinoma (EAC)
  - Chronic injury to normal esophageal squamous epithelium (ESE)
  - ESE is replaced by mucus-secreting columnar cells (intestinal metaplasia)
  - Diagnosis requires endoscopic and pathologic evidence of intestinal metaplasia
  - Intestinal metaplasia with goblet cells (specialized intestinal metaplasia) in U.S.
  - Intestinal metaplasia = primary risk factor for EAC

# Evolution of Barrett's and Esophageal Cancer



# Difficulty w Standard of practice

- The Problem
  - Sampling error
  - Pathologic discordance
  - Poor compliance rate with recommended protocols (51% in U.S.)<sup>1</sup>
  - Mucosal changes associated with early dysplasia/neoplasia not easily detected by standard WLE (S-WLE)<sup>2,4</sup>
  - Recurrent intestinal metaplasia (IM) is most common near GEJ, not easily detected by S-WLE<sup>3</sup>
  - BE can be misdiagnosed in biopsies from the proximal stomach (cardia)<sup>2</sup>
  - Seattle protocol is time consuming and can be costly (multiple biopsies)<sup>2</sup>
  - Subsquamous intestinal metaplasia not easily detected<sup>2</sup>

1. Sharma P, Hawes R, Bansal A, et al. Standard endoscopy with random biopsies versus narrow band imaging targeted biopsies in Barrett's esophagus: a prospective international, randomized controlled trial. *Gut* 2013;62:15-21.

2. Sharma P, Brill J, Canto M, et al. Advanced imaging in Barrett's esophagus. *Clin Gastroenterol Hepatol* 2015;13(13):2209-18.

3. Cotton C, Wolf W, Pasricha S, et al. Recurrent intestinal metaplasia after RFA for BE: endoscopic findings and anatomic location. *Gastrointest Endosc* 2015;81(6):1362-9.

4. Wolfsen H, Crook J, Krishna M, et al. Prospective, controlled tandem endoscopy study of NBI for dysplasia detection in BE. *Gastroenterology* 2008;135(1):24-31.

# Surveillance is Flawed

- Accumulation of multiple molecular abnormalities as epithelium becomes increasingly dysplastic
- BE non-dysplastic mucosa demonstrates genetic changes (molecular aberrations, loss of cell cycle control) PRIOR to morphological manifestation of neoplasia (dysplasia)
- Barrett's esophagus is polyclonal and highly mutated even in the absence of dysplasia
- Significant proportion of BE remains undiagnosed
- Surveillance unproven to reduce population mortality

Ong CJ, et al. Biomarkers in BE and EAC: predictors of progression and prognosis. World J Gastroenterol 2010;16(45):5669-5681

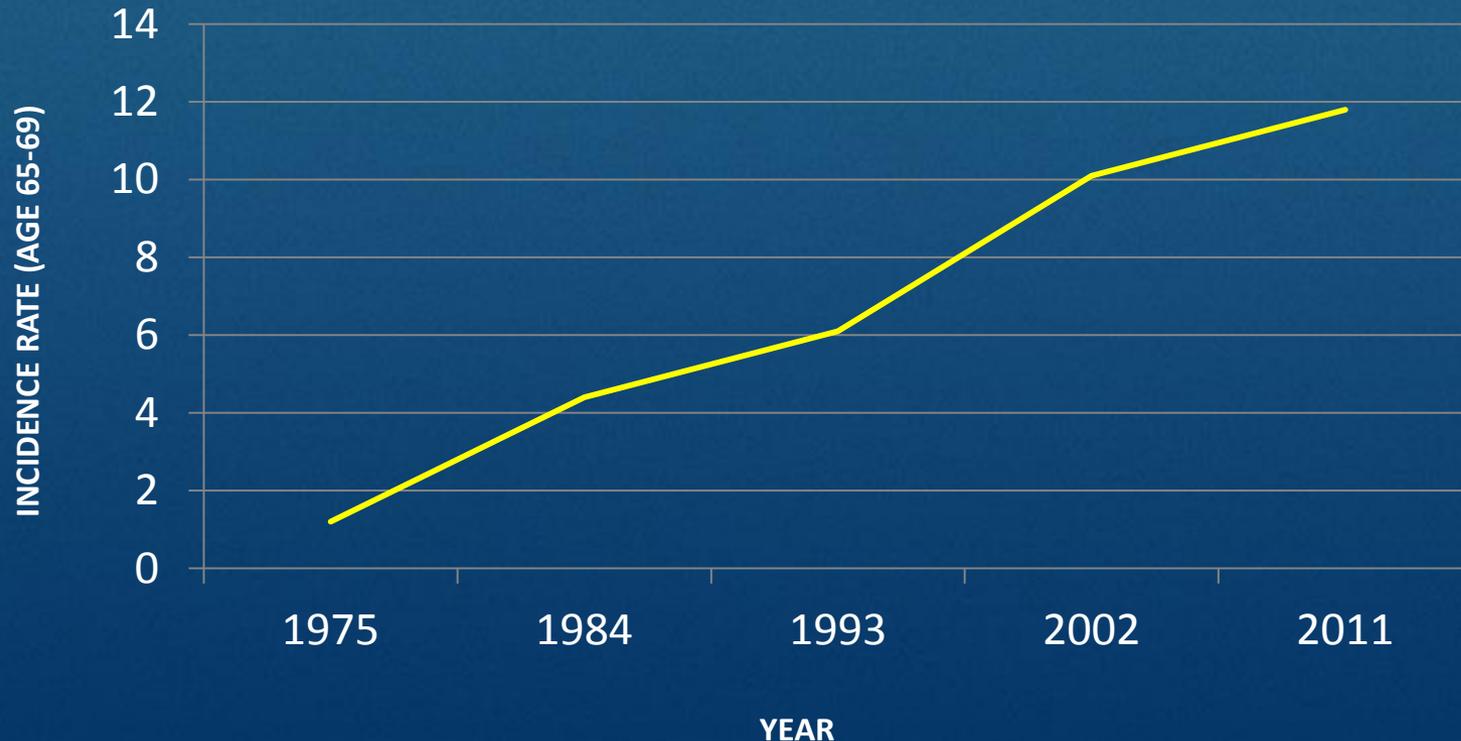
Fleischer DE, et al. The case for endoscopic treatment of ND and LGD BE. Dig Dis Sci. 2010;55(7):1918-31

Ross-Innes CS, et al. Whole genome sequencing provides new insights into the clonal architecture of BE and EAC. Nat Genet 2015;47(9):1038-46

# Esophageal Adenocarcinoma

- Esophageal cancer is 8<sup>th</sup> most common cancer
  - 6th most common cause of cancer death worldwide.
  - Rate of increase in incidence of EAC remained dramatically greater than that for other major epithelial malignancies
    - EAC incidence rates increased by 1.7% between 1997 and 2011
  - Prognosis is better in earlier stage disease.
    - Between 2004 and 2011, 16% of EAC cases were in an early stage (T1a or T1bN0M0)
  - The overall survival rate of patients with EAC remains low
    - Kaplan-Meier 5-year cause-specific survival for all cases of EAC was 22.7% and 57% in early EAC (T1N0M0)

# Increasing incidence of Esophageal Adenocarcinoma on the Rise

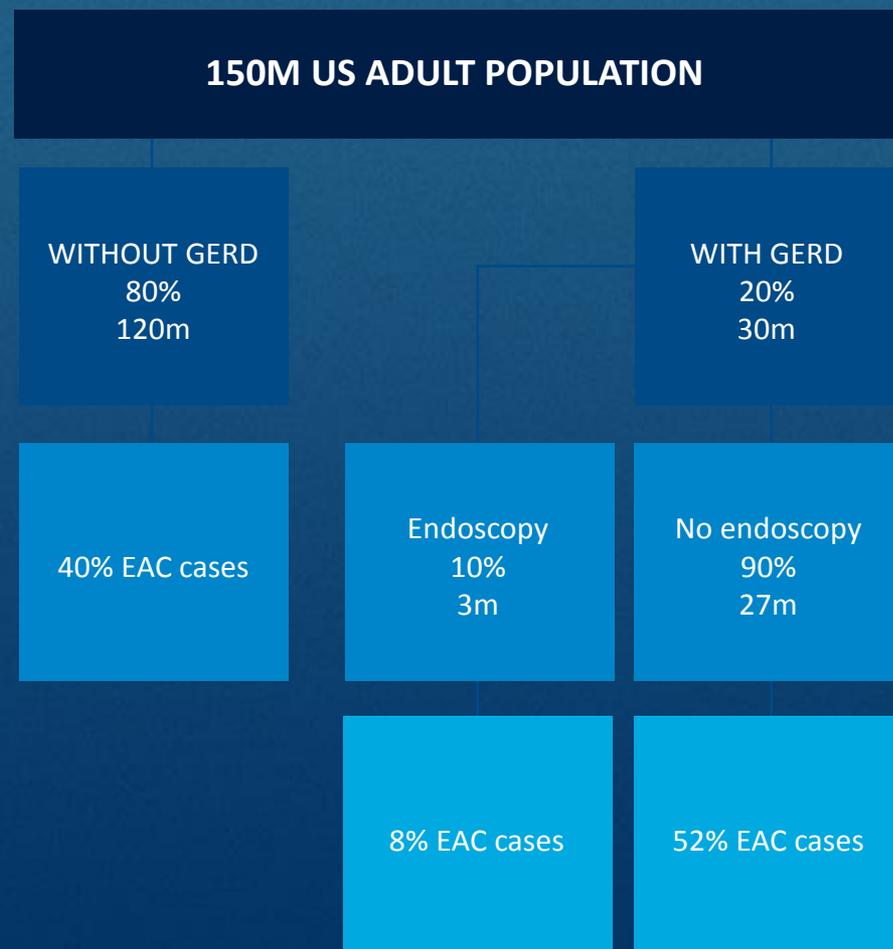


\* Incidence rates per 100,000 and age-adjusted, 1975-2012 (SEER9), both sexes, all races, esophageal adenocarcinoma only, limited to ages 65 - 69

1. SEER Cancer Statistics Animator, 1975-2012. National Cancer Institute. Bethesda, MD  
<http://seer.cancer.gov/canstat/text-version.php?dType=INCD&site=Esophagus+%28Adenocarcinoma+only%29&race=All+Races&sex=Both+Sexes>

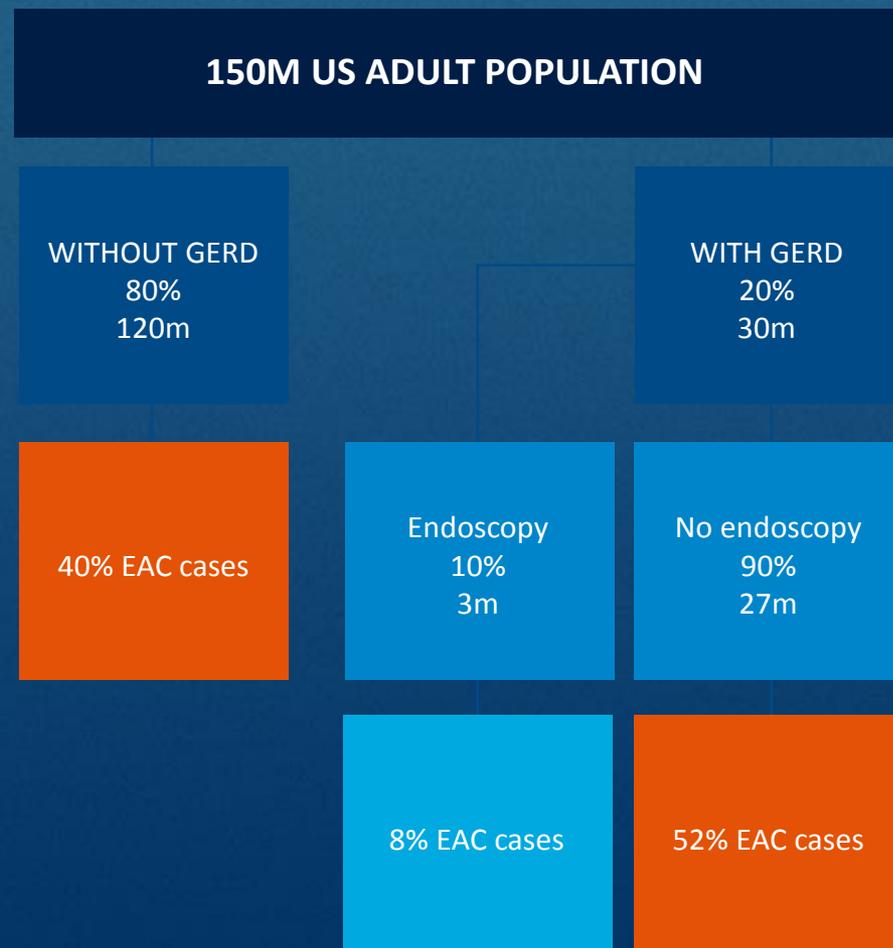
# At Risk Subgroups Missed<sup>1</sup>

- H2RAs, PPIs, fundoplication = no reduction in EAC incidence
- Current screening based on GERD symptoms will miss at least 40% of EAC cases
- Population without GERD symptoms: 80%. This group accounts for 40% of all EAC cases
- Population with GERD symptoms: 20%. This group accounts for 60% of all EAC cases
  - Few receive endoscopy (10%)
    - Account for only 8% of EAC cases



# At Risk Subgroups Missed<sup>1</sup>

- Goal: identify at-risk subgroups not currently in diagnostic algorithm:
  - Risk stratification tool to include risk factors for EAC, other than GERD symptoms
  - Obesity, smoking, diet, age, sex, race, family history, potential biomarkers, etc.
- Cytosponge
  - Diagnostic assay for Barrett's esophagus
  - Detects trefoil factor 3 (TFF3)
  - Sensitivity 80 – 90% (depending on segment length)
  - Specificity ~ 92%



# RISK FACTORS

# Risk factors for progression of BE

- Barrett esophagus is also associated with
  - Caucasian
  - Male
  - Tobacco use
  - Obesity
  - older age
  - presence of LGD
  - disease duration of more than 10 years
  - length of Barrett mucosa
  - persistent esophagitis
  - Family history
  - <30 yo at onset of GERD
  - frequent GERD symptoms ( $\geq$  weekly)
  - Hiatal hernia

# PATHOLOGY

# Barrett esophagus

- Metaplasia of squamous-lined esophagus to a columnar lined esophagus
- Begins at the gastroesophageal junction (GEJ)
- 
- GEJ is proximal ends of the gastric rugae
- Metaplasia of the esophagus with a gastric type lining

# Non-dysplasia

- Progression of NDBE to EAC 0.12% - 0.5% per year
- Absence of any risk factor in NDBE <1% risk of progression
- 6% progression to HGD or EAC without baseline dysplasia 10-year follow-up

# NDBE risk to HGD in 10 years

- Annual progression rate to HGD was 0.48% per patient per year
- Using a Kaplan-Meier Survival graph:
  - 7.3% of IM pts. developed HGD or cancer in 10 yrs.

# Indefinite for dysplasia (IND)

- 12.9% of IND developed LGD, HGD or EAC within 12 months
- 4.7% of IND developed HGD or EAC within 12 months
- Detection rates of neoplasia (LGD, HGD or EAC)
  - 25% (1 year)
  - 37% ( 2 years)
  - 47% (3 years)
- 20% of IND cases had detection of HGD or EAC within 3 years
- Recommendations:
  - Repeat biopsy within months
  - Length of BE and multi-focal IND = subset of patients at higher risk
    - Consider treating similar to LGD

# Surveillance vs RFA RCT for LGD

- RFA vs control
- Complete eradication (CR) - dysplasia (D)
- CR - intestinal metaplasia (IM)
- 3 year outcomes
- RFA patients generated mean costs of \$13,523 versus \$4,930 for controls

|       | RFA | Control | P value |
|-------|-----|---------|---------|
| CE-D  | 93% | 28%     | <0.001  |
| CE-IM | 88% | 0%      | <0.001  |

|                        | RFA  | Control | P value |
|------------------------|------|---------|---------|
| Progression to HGD/EAC | 1.5% | 26.5%   | <0.001  |
| Progression to EAC     | 1.5% | 8.8%    | =0.03   |

# Low grade dysplasia

- The incidence of EAC in patients with LGD was 0.51% for LGD (relative risk 4.8 for LGD)
- LGD progression rate to (HGD)/EAC of 2.3-9.1%/year over a median follow-up of 39 months.
- 13% progression with baseline dysplasia at the 10-year follow-up
- Confirmed LGD: incidence rate of progression to HGD/EAC was 13.4% per patient-year,
- 11% (2/19) alone progressed to EAC during follow-up
- LGD risk of progression to HGD or EAC was 85% after a duration of 109 months
- LGD and one other risk factor had a risk of progression of 18% to 40%
- Cumulative risk of progression to HGD or EAC within 3 years: estimated at 33%

Curvers WL et al. Low-grade dysplasia in Barrett's esophagus: over diagnosed and underestimated. Am J Gastroenterol 2010;105(7):1523-30

Small AJ, et al. RFA is associated with decreased neoplastic progression in patients with BE and confirmed LGD. Gastroenterology. 2015;149(3):567-570

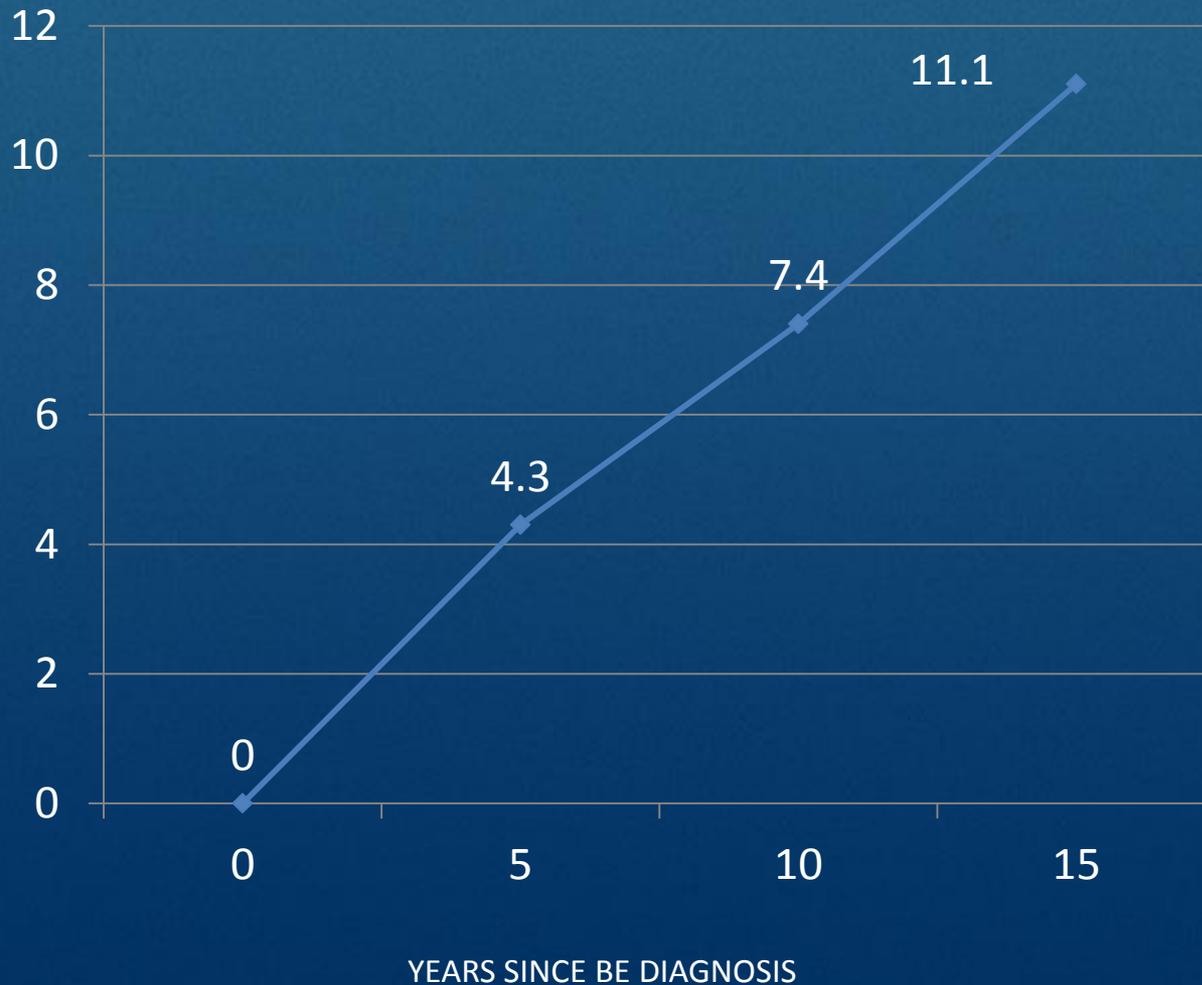
Shaheen NJ, Sharma P, et al. Radiofrequency Ablation in Barrett's Esophagus with Dysplasia. New England Journal of Medicine 2009 May;360(22):2277-85

2288.

# Risk of progression of LGD

| N   | STUDY TYPE    | PROGRESSION TO HGD/EAC <sup>1</sup>   | STUDY               |
|-----|---------------|---|---------------------|
| 127 | RCT           | 13.6% (annual rate of progression)  | Shaheen et al. 2009 |
| 147 | Prospective   | 13.4% (per patient-year)  | Curvers et al. 2010 |
| 293 | Retrospective | 9.1% (per-patient year)   | Duits et al. 2014   |
| 85  | Prospective   | 9% (annual rate of progression)   | Clark et al. 2014   |
| 136 | RCT           | 11.8% (per patient-year)  | Phoa et al. 2014    |
| 125 | Retrospective | 6.6% (annual rate of progression per Kaplan-Meier method), 14.8% first year | Small et al. 2015   |

# Cumulative Rate of Progression NDBE/LGD to HGD/EAC



# High grade

- the risk of progression was 6.58% per year

# PROGRESSION

# Pathologist Disagreement

- High variability in consensus among expert GI pathologist
- Interobserver agreement between 2 expert pathologists was only 55.6%
- Studies report up to 85% of LGD were downstaged to NDBE by expert pathologists
  - 3% of LGD was upgraded to cancer
- Pathologists continue to disagree on many aspects of dysplasia pathology

# Multifocal segments

- 1.89% Multifocal LGD increased incidence of EAC
- 0.27% Unifocal LGD increased incidence of EAC
- 0.19% short segment NDBE progresses to EAC per year

# Length of segment of NDBE

- Annual progression rate to HGD/EAC
  - 0.31%/year for length  $\leq 3$  cm
  - 0.97 %/year for length 4-6 cm
  - 1.26%/year for length 7-9 cm
  - 1.64%/year for length 10-12 cm
  - 2.41%/year for length  $\geq 13$  cm

# SCREENING

# Cancer screening

- Precancerous stage is detectable with a clinically significant risk of cancer.
- Able to significantly alter the course of the disease
- Cost-effective to the community

# Cost effectiveness of endoscopy

- Screening for BE in a population with 8% to 10%:
- The costs of screening to save 1 year of life may be closer to \$22,200 than \$10,440.42,55
- Focused on patients with GERD, symptom duration and frequency
- Majority of patients with EAC do not report symptoms of GERD
- For asymptomatic patients, the decision of when to perform an endoscopy is currently less clear.

# RFA and Cost Effectiveness<sup>1</sup>

- Decision model compared BE (IM, LGD, HGD)
  - Similar to 2009 methodology
  - Revised assumptions
- Results:
  - HGD: RFA dominant strategy
  - LGD: RFA can be cost effective if biopsy if confirmed and stable LGD
  - IM: initial RFA is cost-effective if:
    - CR-IM >85%
    - IM recurrence rates <20% over 2.5 years

GASTROENTEROLOGY 2012;143:567-575

## CLINICAL—ALIMENTARY TRACT

### The Cost Effectiveness of Radiofrequency Ablation for Barrett's Esophagus

CHIN HUR,<sup>\*,†,§</sup> SUNG EUN CHOI,<sup>‡</sup> JOEL H. RUBENSTEIN,<sup>||</sup> CHUNG YIN KONG,<sup>‡,§</sup> NORMAN S. NISHIOKA,<sup>\*,§</sup> DAWN T. PROVENZALE,<sup>¶</sup> and JOHN M. INADOMI<sup>\*\*</sup>

\*Gastrointestinal Unit and †Institute for Technology Assessment, Massachusetts General Hospital; ‡Harvard Medical School, Boston, Massachusetts; ††Division of Gastroenterology, University of Michigan Medical School, Ann Arbor, Michigan; †††Durham VA Medical Center, Duke University Medical Center, Durham, North Carolina; ††††Division of Gastroenterology, University of Washington School of Medicine, Seattle, Washington

This article has an accompanying continuing medical education activity on page e20. Learning Objective: Upon completion of this educational exercise, successful learners will be able to demonstrate have an enhanced comprehension of cost-effectiveness analysis as applied to radiofrequency ablation for different grades of Barrett's esophagus.

CLINICAL AT

1. Hur C, Choi SE, Rubenstein JH, et al. The cost effectiveness of radiofrequency ablation for Barrett's esophagus. *Gastroenterology*. 2012;143:567-575

# Indications for endoscopy

**Table 1.** Indications for Upper Endoscopy (Best Practice Advice from the Clinical Guidelines Committee of the American College of Physicians<sup>63</sup>)

- 1 Heartburn and alarm symptoms (dysphagia, bleeding, anemia, weight loss, and recurrent vomiting).
- 2 Heartburn and/or acid regurgitation that persists despite a therapeutic trial of 4-8 weeks of twice daily proton pump inhibitor therapy.
- 3 Severe erosive esophagitis after a 2-month course of proton pump inhibitor therapy to assess healing and rule out Barrett esophagus.
- 4 In men older than 50 years with chronic reflux symptoms (symptoms for more than 5 years) and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated body mass index, tobacco use, and intra-abdominal distribution of fat) to detect esophageal adenocarcinoma and Barrett esophagus.
- 5 For surveillance evaluation in men and women with a history of Barrett esophagus. In men and women with Barrett esophagus and no dysplasia, surveillance examinations should occur at intervals no more frequently than 3-5 years. More frequent intervals are indicated in patients with Barrett esophagus and dysplasia.

**Table 2.** American Society of Gastrointestinal Endoscopy Guidelines on the Role of Endoscopy in Barrett Esophagus<sup>64</sup>

- 1 Consider endoscopic screening in select patients with multiple risk factors for Barrett esophagus and esophageal adenocarcinoma, but patients should be informed that there is insufficient evidence to affirm that this practice prevents cancer or prolongs life.
- 2 If there is no dysplasia on biopsy, surveillance endoscopy should be performed no more frequently than every 3-5 years, with targeted plus 4-quadrant biopsies at every 2 cm of suspected Barrett esophagus.

# Seattle Protocol

- A small percentage of the BE mucosa is sampled
- Sampling error may occur
- 50% of patients who developed HGD or EAC while undergoing surveillance had at least 2 consecutive endoscopies documenting NDBE
- Up to 90% cases of EAC are diagnosed in patients without known history of BE

# NMI classification system

- Visualization of mucosal and vascular patterns
- Patterns can predict histology:
  - Mucosal: regular, round, oval, villous, irregular, abnormal
  - Vascular: normal, regular, irregular, abnormal
- Identify HGD and EAC in BE
- Validate a NBI classification system to predict the presence and absence of dysplasia in BE

| Mucosal Pattern (Regular) | Mucosal Pattern (Irregular) | Vascular Pattern (Regular)                         | Vascular Pattern (Irregular)             |
|---------------------------|-----------------------------|--|--|
| Circular                  | Absent                      | Situated regularly along or between mucosal ridges | Focally or diffusely distributed vessels |
| Ridged / Villous          | Irregular pattern           | Normal long branching patterns                     | Not following normal mucosa architecture |
| Tubular                   |                             |  |  |

# Limitations of Enhanced Imaging techniques

- NBI is relatively insensitive at detecting abnormal lesions near the SCJ after RFA<sup>7,8</sup>
- Inter-observer variability for abnormal pattern recognition with NBI and lack of consensus on the interpretation of these patterns<sup>1</sup>
- Currently, the accuracy of NBI for detecting lower grade disease is limited<sup>1</sup>
- Efficient use of EIT requires significant expertise and appropriate training<sup>1,3,4</sup>
- Not all societies support the use of EIT
- Some studies have shown no difference in HGD detection rates between HD-WLE and HD-NBI<sup>5</sup>
- Some studies show that a magnification scope is needed to optimize the sensitivity of NBI<sup>6</sup>
- FICE and I-Scan have been studied less than NBI and data is lacking for these modalities

1. Sharma P, Hawes R, Bansal A, et al. Standard endoscopy with random biopsies versus narrow band imaging targeted biopsies in Barrett's esophagus: a prospective international, randomized controlled trial. *Gut* 2013;62:15-21.

2. Sharma P, Brill J, Canto M, et al. Advanced imaging in Barrett's esophagus. *Clin Gastroenterol Hepatol* 2015;13(13):2209-18.

3. Mannath J, Subramanian V, Hawkey C, et al. NBI for characterization of high grade dysplasia and specialized IM in BE: a meta-analysis. *Endoscopy* 2010;42:351-359.

4. Bennett C, Moayyedi P, Corley D, et al. BOB CAT: a large scale review and Delphi consensus for management of BE with no dysplasia, IND or LGD. *Am J Gastroenterol* 2015;5:662-82.

5. Manfredi M, Dayeh B, Bhat Y, et al. Electronic chromoendoscopy. *Gastrointest Endosc* 2015;81(2):249-61.

6. Morita Y, Tanaka S, Toyonaga T, et al. Barrett's adenocarcinoma in long-segment BE successfully detected by NBI with magnifying endoscopy. *Digest Endosc* 2013;25:201-205.

7. Cotton C, Wolf W, Pasricha S, et al. Recurrent intestinal metaplasia after RFA for BE: endoscopic findings and anatomic location. *Gastrointest Endosc* 2015;81(6):1362-9.

8. Herrero L, Curvers W, Bisschops R, et al. NBI does not reliably predict residual IM after RFA in the neosquamous columnar junction. *Endoscopy* 2014;46:98-104.

# NBI detected significantly more dysplasia compared to SD-WLE

- A prospective, blinded tandem endoscopy study conducted on 65 patients with Barrett's esophagus indicated that HD-NBI without magnification was superior to SD-WLE in detecting dysplasia.
- Higher grades of dysplasia were found in 12 patients by using NBI compared with no patients by using standard-resolution WLE (18% vs 0%,  $P < .001$ ).
- In addition, more biopsy specimens were taken by using SD endoscopy with random biopsy strategies compared with NBI targeted biopsies (mean, 8.5 vs 4.7 biopsy specimen,  $P < .001$ ).
- With the use of NBI resulted in:
  - More patients with dysplasia
  - Higher grades of dysplasia
  - Fewer biopsies

## Prospective, Controlled Tandem Endoscopy Study of Narrow Band Imaging for Dysplasia Detection in Barrett's Esophagus

[Herbert C. Wolfsen](#), [Julia E. Crook](#), [Muri Krishna](#), [Sami R. Achem](#), [Kenneth R. Devault](#), [Ernest P. Bouras](#), [David S. Loeb](#), [Mark E. Stark](#), [Timothy A. Woodward](#), [Lois L. Hemminger](#), [Frances K. Cayer](#), [Michael B. Wallace](#)

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Michael B. Wallace, Section Editor

# The Data

- Abnormal mucosal/vascular patterns identified by NBI are a reliable marker for advanced dysplasia and early EAC<sup>1,2</sup>
- Regular appearing NBI surface patterns tend not to harbor HGD or EAC<sup>1</sup>
- There is a high sensitivity and specificity of irregular micro-vascular and pit patterns for prediction of HGD<sup>3</sup>
- Magnification may optimize the sensitivity of NBI<sup>4</sup>
- NBI with magnification and dual focus magnification endoscopy may be particularly useful at identifying early EAC<sup>4,5,6</sup>
- Fewer biopsies per patient and higher proportion of dysplasia identified with NBI compared to standard endoscopy<sup>1,2,7</sup>
- Compared to WLE with random biopsies, diagnostic yield of finding dysplasia or cancer increased by 34% with the addition of NBI<sup>8</sup>

1. Sharma P, Hawes R, Bansal A, et al. Standard endoscopy with random biopsies versus narrow band imaging targeted biopsies in Barrett's esophagus: a prospective international, randomized controlled trial. *Gut* 2013;62:15-21.

2. Wolfsen H, Crook J, Krishna M, et al. Prospective, controlled tandem endoscopy study of NBI for dysplasia detection in BE. *Gastroenterol* 2008;135(1):24-31.

3. Mannath J, Subramanian V, Ragunath H, et al. NBI for characterization of high grade dysplasia and specialized IM in BE: a meta-analysis. *Endoscopy* 2010;42:351-359.

4. Morita Y, Tanaka S, Toyonaga T, et al. Barrett's adenocarcinoma in long-segment BE successfully detected by NBI with magnifying endoscopy. *Digest Endosc* 2013;25:201-205.

5. Singh R, Shahzad M, Tam W, et al. Preliminary feasibility study using novel NBI system with dual focus magnification capability in BE. *Dig Endo* 2013;25:151-156.

6. Takahashi A, Oyama T. Barrett's adenocarcinoma diagnosed by NBI magnifying endoscopy. *Digest Endosc* 2013; 25:184-189.

7. Manfredi M, Dayyeh B, Bhat Y, et al. Electronic chromoendoscopy. *Gastrointest Endosc* 2015;81(2):249-61.

8. Qumseya B, Wang H, Badie N, et al. Dysplasia and neoplasia in patients with BE: meta-analysis and systematic review. *Clin Gastroenterol Hepatol* 2013;12:1562-1701.

# NBI detected significantly more dysplasia compared to SD-WLE

- Meta-analysis and systematic review
- Aim: can advanced imaging detect dysplasia and cancer compared to detection of BE neoplasia (dysplasia and cancer) with random biopsies
- 14 studies, 843 patients
- Overall, advanced imaging had a significantly higher diagnostic yield
- Subgroup analysis of virtual chromoendoscopy (VCE) and FICE):
  - Significantly increased diagnostic yield of finding dysplasia or cancer by 34% compared to WLE with random biopsies (P<0.001)

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## Dysplasia and Neoplasia in Patients with Barrett's Esophagus: Meta-Analysis and Systematic Review

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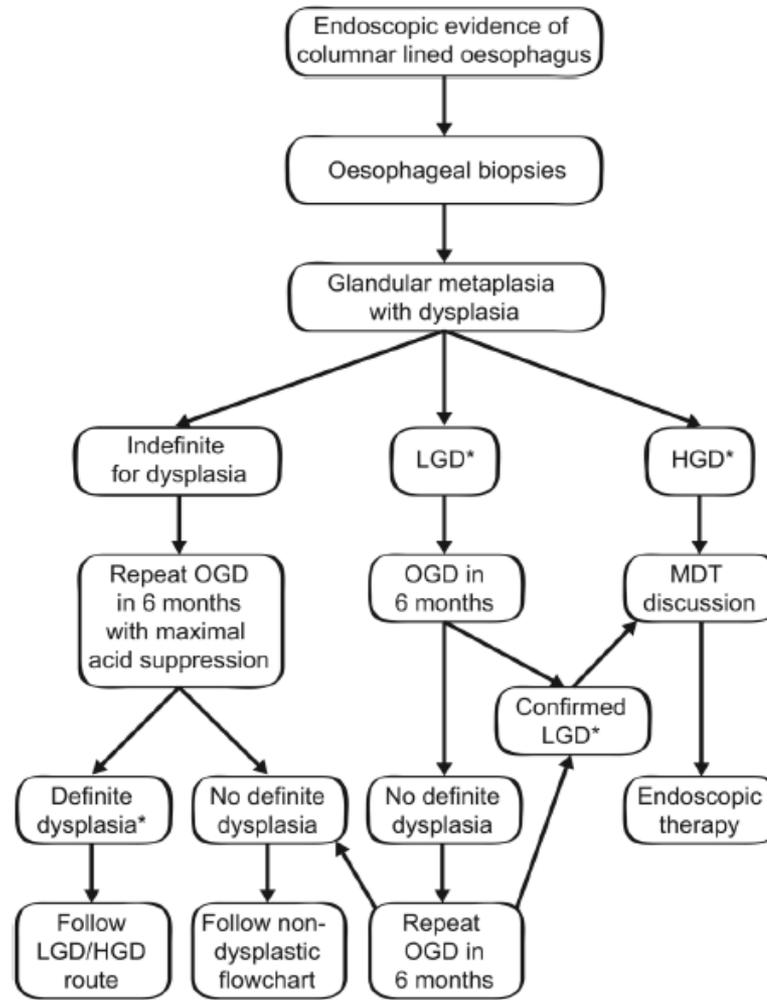
<sup>6</sup>Sections of Health Services Research & Gastroenterology and Hepatology, Baylor College of Medicine and Michael E. DeBakey VA, 2002 Holcombe Blvd (MS 152), Houston, Texas 77030

# SURVEILLANCE

# Surveillance Following CEIM

- ACG (2015)
  - NDBE
    - Every 3 to 5 years (surveillance only)
  - LGD
    - Every 6 months first year
    - Annually thereafter
  - HGD
    - Every 3 months first year
    - Every 6 months second year
    - Annually thereafter
  - Surveillance is cost effective only if:
    - Surveillance intervals can be prolonged to every 5 years (>2cm NDBE) or 3 years (LGD)

# Algorithm for BE



\* dysplasia needs to be confirmed by 2 independent GI pathologists

# Role of RFA in management of Barrett's Esophagus

- High-Grade Dysplasia Management:
  - RFA, PDT, or EMR rather than surveillance
- Low-Grade Dysplasia Management:
  - RFA should also be a therapeutic option
  - RFA is alternative to surveillance
- Nondysplastic BE Management:
  - RFA may be a preferred management option in select patients
  - Risk factors for BE and EAC include male sex, white race, age older than 50 years, family history of BE, increased duration of reflux symptoms, smoking, and obesity.
  - [RFA] may be performed in eligible patients before, during or after anti-reflux surgery

# Guidelines for RFA in NDBE

| ACG 2008 <sup>1</sup>  | ACG 2015 <sup>2</sup>  |
|--|--|
| <ul style="list-style-type: none"> <li>Two EGDs with biopsy within 1 year</li> <li>Follow-up: Endoscopy every 3 years</li> </ul> | <ul style="list-style-type: none"> <li>RFA should not be routinely applied to patients with NDBE</li> <li>Unclear about RFA in patients with risk factors for progression</li> </ul> |

| AGA 2011 <sup>3</sup>   | ASGE 2012 <sup>4</sup>                                     | SAGES 2010 <sup>5</sup>      |
|---|--|------------------------------|
| RFA, with or without EMR, for select individuals with NDBE and increased risk for progression | RFA for select patients with NDBE and risk for progression | RFA may be effectively treat |

1. Wang et al., Updated guidelines 2008 for the diagnosis and surveillance and therapy of BE. Am J Gastro 2008;3:788-97

2. Shaheen et al., ACG Clinical Guideline: Diagnosis and management of BE. Am J Gastroenterol. 2015

3. Spechler SJ, Sharma P, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011 Mar;140(3):1084-91.

4. Evans JA, Early DS, et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest Endosc. 2012 Dec;76(6):1087-94.

5. Stefanidis D, Hope WW, Kohn GP, et al. Guidelines for surgical treatment of gastroesophageal reflux disease. Surg Endosc. 2010 Nov;24(11):2647-69

**TREATMENT**

# RFA for LGD

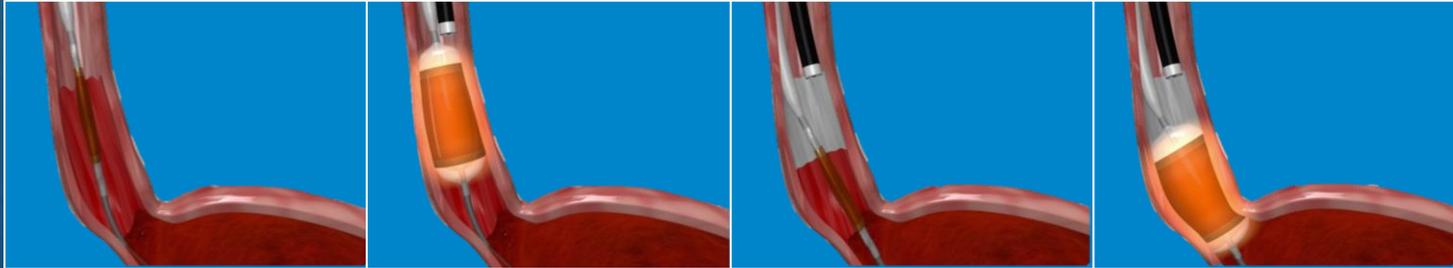
- Over a 3-year follow-up period
  - 1% of patients in RFA progressed to HGD/EAC
  - 26.5% in the not treated with RFA
  - Complete eradication of dysplasia(98%) and intestinal metaplasia (90%) by RFA was achieved in and 90%
  - Most common complication was stricture (12%)
  - Successfully managed with endoscopic dilatation

# Contraindications for RFA

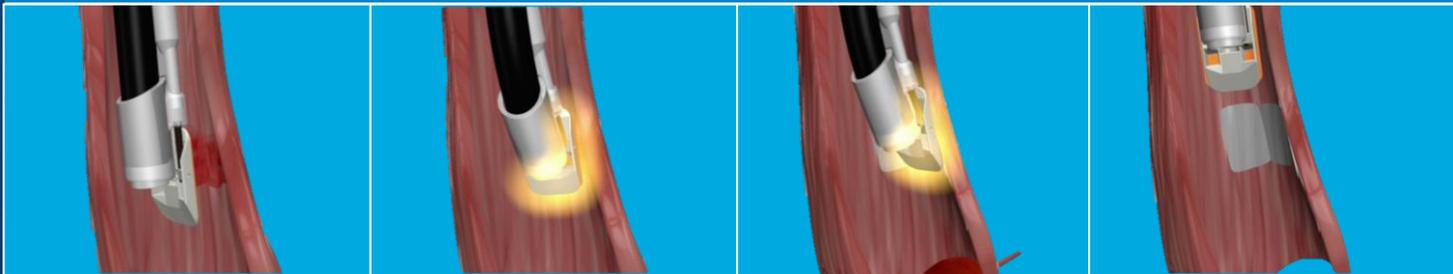
|   |   |
|---|---|
| <p>SUB-INDICATION:</p> <p>Barrett's Esophagus</p>   | <p>SUB-INDICATION:</p> <p>Bleeding and non-bleeding sites in the GI tract</p>   |
| <p>Pregnancy</p> <p>Prior radiation therapy to the esophagus</p> <p>Esophageal varices at risk for bleeding</p> <p>Prior Heller myotomy</p> <p>Eosinophilic esophagitis</p> | <p>Pregnancy</p> <p>Presence of gastric or colorectal ulcers</p> <p>History of anal incontinence</p> <p>Presence of anorectal fistulae</p> <p>Pelvic irradiation within the last six months</p> |

# Circumferential & Focal Ablation

## CIRCUMFERENTIAL ABLATION



## FOCAL ABLATION



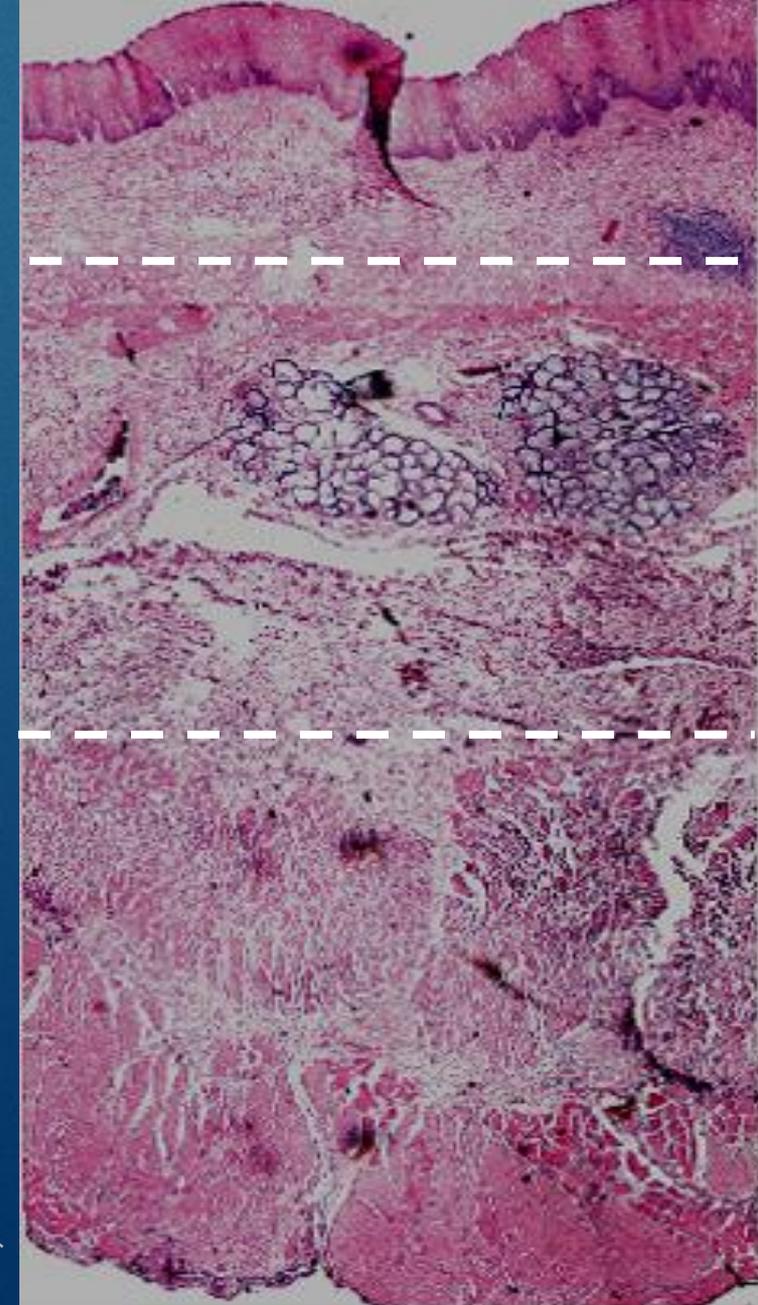
# RFA Depth



- Mechanism:
  - Electrodes spaced 250  $\mu\text{m}$  apart
  - Pre-set energy & power densities
  - Generator turns off when a pre-determined resistance level in the ablated tissues is reached (< 300 milliseconds)

# Layer of treatment of the Esophagus

- Radiofrequency Ablation Depth
- Photodynamic therapy/Multipolar electrocoagulation/Argon Plasma Coagulation
- Endoscopic Mucosal Resection
- Surgical Depth



# Complications from RFA

- Overall complication rate: 1.3% following 15,569 RFA sessions
- Stricture: 2.8% of patients
- Bleeding: 0.51% of patients
- Hospitalization: 0.85% of patients
- Perforation: 0.04% of patients
  
- Higher grade of disease  $\Rightarrow$  higher rate of complications

# RFA Adverse Events

| NOTES  | OVERALL            | STRICTURE *                          | BLEEDING   | HOSPITALIZATION              | PERFORATION               | DEATH | REFERENCE               |
|--|--------------------|--------------------------------------|--|------------------------------|---------------------------|-------|-------------------------|
| Per Patient (PPT)  | 3.8%<br>(209/5519) | 2.8%<br>(157/5519)                   | 0.51%<br>(28/5519)                               | 0.85% (47/5519)              | 0.04% (2/5519)            | 0     | Hathorn et al.          |
| Per Patient<br>Meta-analysis<br>(4342 patients)                            |                    | 5%<br>95% CI, 3%-<br>7%              | 1%<br>95% CI, 1%-<br>2%                          |                              |                           |       | Orman et al.            |
| Per Patient  | 9.8%<br>(24/244)   | 8.2%<br>(20/244)                     | 1.6% (4/244);<br>2/4 had EMR                     | 1.6% (4/244); 2/4<br>had EMR | 0                         | 0     | Bulsiewicz et<br>al.    |
| Per Patient<br>55% EMR prior to<br>RFA                                     | 6.5%<br>(39/592)   | 4.6%<br>(27/592)                     | 1.4% (8/592)                                     | 0.3% (2/592)                 | 0                         | 0     | Gupta et al.            |
| Per Patient  |                    | 4% (16/403);<br>5/16 had<br>prior ER | 1.5% (6/404);<br>4/6 after ER                    |                              | 0.2% (1/404);<br>after ER | 0     | Chadwick et<br>al.      |
| Per Patient  |                    | 2.1% (9/429)                         | 0.9% (4/429)                                     | 0                            | 0                         | 0     | Lyday et al.            |
| Per Patient  | 3.2%<br>(170/5236) | 2.4%<br>(128/5236)                   | 0.4%<br>(23/5236)                                | 0.7% (37/5236)               | 0.04% (2/5236)            | 0     | Shaheen et al.<br>(‘13) |
| Per Patient  | 3.4%<br>(4/119)    | 7.6% (9/119)<br>PPT<br>1.8% PP       | 0.8% (1/119)                                     | 2.5% (3/119)                 | 0                         | 0     | Shaheen et al.<br>(‘11) |
| Per Patient<br>7.4 % (5/68)<br>escape EMR;<br>17.6% (12/68) RFA<br>and APC | 19.1%<br>(13/68)   | 11.8% (8/68)                         | 1.5% (1/68);<br>after EMR<br>and prior to<br>RFA | 3% (2/68)                    | 0                         | 0     | Phoa et al.             |

\*Predictors of stricture: Age, female, long segment

**ERADICATION**

# RFA for high risk NDBE

- CE-IM in 78% of pts; CE-D in 91%
- Durability:
  - 93% Complete eradication-IM (year 1)
  - 90% CE-IM (year 2)
  - 89% CE-IM (year 3)

Progression occurred in 1.9%/year

- Progression to cancer:
  - 0.2% of pts during treatment
  - 0.7% of pts following CE-IM
- Recurrence occurred in 5.2%/year
- Recurrences clear after single focal RFA treatment
- **No** strictures or other serious adverse events, no buried glands

Fleischer DE et al. Endoscopy 2010 Oct

Bidari K, et al. Gastroenterology 2014

Orman ES, et al. Am J Gastroenterol 2013

Orman Es et al. Clin Gastroenterol Hepatol 2013

# Progression after RFA

|                              | NDBE         | LGD          | HGD         |
|------------------------------|--------------|--------------|-------------|
| Natural History (53 studies) | 0.6%         | 1.7%         | 6.6%        |
|                              | ↓            | ↓            | ↓           |
| After Ablation (65 studies)  | <b>0.16%</b> | <b>0.16%</b> | <b>1.7%</b> |
| NNT                          | <b>45</b>    | <b>13</b>    | <b>4</b>    |

- Progression risk expressed as “% per patient-year” risk of developing EAC
- NNT calculated on a 5-year basis (number needed to treat per year for five years to avoid one cancer) – source (<http://araw.mede.uic.edu/cgi-bin/nntcalc.pl>)

# RFA Reduces Progression in Patients with Dysplasia

| SURVEILLANCE GROUP   | RFA GROUP   |
|--|---|
| <ul style="list-style-type: none"><li>▪ <b>28.8%</b> (36 patients) in this group progressed over the follow-up period (29 patients HGD; 5 IMC; 2 submucosal EAC).</li><li>▪ 2 patients developed submucosal EAC (at 22.8 and 38.8 months after initial endoscopy) neither of whom had detection of intervening HGD</li><li>▪ <b>Annual rate of progression to HGD or EAC 6.6% (averaged)</b></li><li>▪ First year progression rate 14.8%</li><li>▪ <b>Cumulative risk of progression to HGD or EAC within 3 years was estimated at 33.0% in surveillance group</b></li></ul> | <ul style="list-style-type: none"><li>▪ RFA: CE-D 95.6%; CE-IM: 77.8%</li><li>▪ <b>Annual progression rate to HGD or EAC 0.77%</b> (averaged); single progressor:<ul style="list-style-type: none"><li>- this patient had only 1 RFA treatment for a 6 cm multifocal LGD segment, but then did not return for surveillance endoscopy for 7.5 months, at which time IMC was detected, treated with EMR</li></ul></li><li>▪ <b>Cumulative risk of progression to HGD or EAC within 3 years was estimated at 2.9% in RFA group</b></li></ul> |

# BURIED GLANDS

# Post-RFA Neosquamous Epithelium Study

- Evaluation of Barrett's mucosa prior to RFA with LGD (n=3) & HGD (n=19)
- neo-squamous epithelium after RFA in 22 pts
  - No buried glands in NSE using standard & keyhole bx (16 patients) & EMR (14 patients)

# Biopsy Depth After RFA<sup>1-2</sup>

- Conclusions:
  - No difference in biopsy depth for controls vs. ablation groups
  - Most biopsies (≥88%) reached LP or deeper
  - SSIM when present resides in the deep portion of the epithelium or in the LP<sup>2</sup>

ORIGINAL ARTICLE

Does Ablative Therapy for Barrett Esophagus Affect the Depth of Subsequent Esophageal Biopsy as Compared With Controls?

*Bergein F. Overholt, MD,\* Patrick J. Dean, MD,†  
Joseph A. Galanko, PhD,‡ and Charles J. Lightdale, MD§*

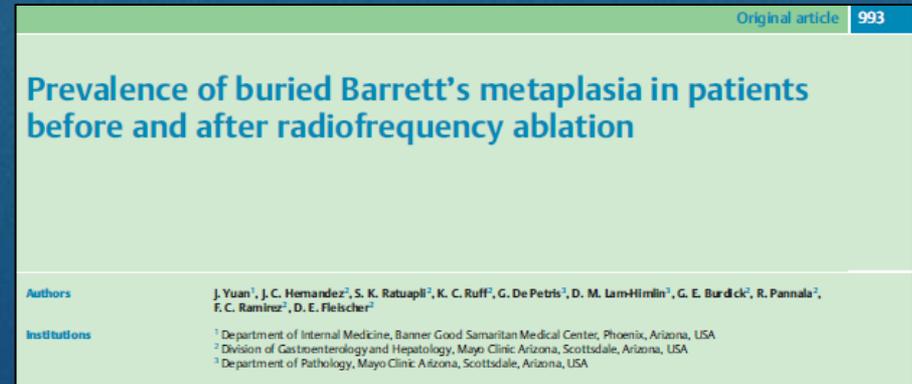
1. Overholt BF, Dean PJ, Galanko JA, Lightdale CJ. Does ablative therapy for Barrett esophagus affect the depth of subsequent esophageal biopsy as compared with controls? *J Clin Gastroenterol* 2010;44:676-681.

2. Biddestone LR, Barham CP, Wilkinson SP et al. The histopathology of treated Barrett's esophagus: squamous reepithelization after acid suppression and laser and photodynamic therapy. *Am J Surg Pathol*. 1998;22:239-245

# RFA Can Treat Buried Glands<sup>1</sup>

## MAYO CLINIC BURIED GLANDS STUDY (2012)

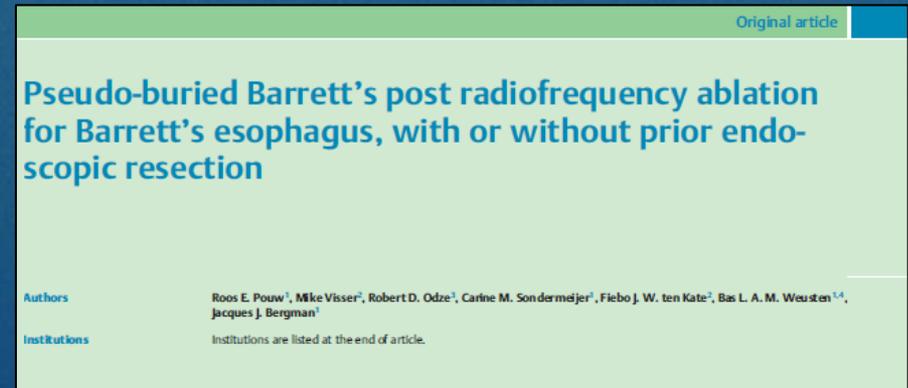
- Retrospective review of 112 BE pts. (61% with dysplasia)
- 96% dysplasia & IM eradication rate
- 15.2% had buried glands before or during treatment
- Of those who achieved endoscopic and histologic evidence of complete remission, 0% had buried glands with 30 mo. follow-up
- “...our study found that this phenomenon [buried glands] can be treated and completely eradicated with RFA.”



1. Yuan J, Hernandez JC, et al. Prevalence of buried Barrett's metaplasia in patients before and after radiofrequency ablation. *Endoscopy*. 2012 ;44(11):993-7.

# RFA Can Treat Buried Glands<sup>1</sup>

- Pseudo-Buried Barrett's Post Radiofrequency Ablation for Barrett's Esophagus, With or Without Prior Endoscopic Resection
  - Evaluation of the frequency of buried Barrett's in biopsies obtained from small residual Barrett's islands (<5mm) sampled post-RFA compared with biopsies from normal neosquamous epithelium (NSE)
  - 69 BE pts. treated with RFA received biopsies of NSE and small BE islands
  - 0.1% of biopsies from NSE contained buried glands
  - 21% of biopsies from small islands of columnar mucosa contained buried glands



1. Pouw RE, Visser M, et al. Pseudo-buried Barrett's post radiofrequency ablation for Barrett's esophagus, with or without prior endoscopic resection. *Endoscopy*. 2014 Feb;46(2):105-9.

# Subsquamous Extension of Intestinal Metaplasia<sup>1</sup>

- 110 patients with BE treated
- 138 samples were analyzed
- Maximum extent of SSIM from SCJ was measured
- 98.2% patients had SSIM
- Mean length of SSIM 3.3mm (range, 0.2 – 9.6mm)
- Conclusion:
  - Most patients with BE have subsquamous extension of intestinal metaplasia beyond the borders of visible BE
  - Biopsy and resection of neoplastic BE should extend at least 1 cm into the squamous epithelium

Original article

 ▶ Subsquamous Extension of Intestinal Metaplasia Is Detected in 98% of Cases of Neoplastic Barrett's Esophagus

Mario Anders\*, Yasmin Lucks\*, Muhammad Abbas El-Masry<sup>‡</sup>, Alexander Quaas\*, Thomas Rösch\*  , Guido Schachschal\*, Christina Bähr\*, Ulrich Gauger\*, Guido Sauter\*, Jakob R. Izbicki\*, Andreas H. Marx\*

1. Anders M, et al. Subsquamous extension of intestinal metaplasia is detected in 98 percent of cases of neoplastic BE. Clin Gastro Hepato 2014;12(3):405-10

# Subsquamous Extension of Intestinal Metaplasia<sup>1</sup>

- 47 patients with HGD or IM
- Complete BE eradication w
- Histopathological review o buried BE
- Extension of Barrett's epithelium underneath the normal squamous resection margin occurred in 28%
- Linear distance of extension ranged from 0.8 to 5.6mm
- Conclusion:
  - Biopsies and ablative therapy should extend to 1 cm beyond the margin of visible Barrett's epithelium



1. Chennat J, et al. Advanced pathology under squamous epithelium on initial EMR specimens in patients with BE and HGD...Gastro Endo 2009;70(3):417-21

# Long term Followup

- Visible lesions and nodularity removed via EMR prior to RFA
- RFA every 3 months until all visible BE ablated or cancer developed (endpoints)
- Biopsies taken at 12 months or when endpoints reached
- Periodic follow-up endoscopies performed to check for recurrence

# Poor Response to RFA

- Predictors of poor response
  - Active reflux esophagitis despite PPI
  - Endoscopic resection scar regeneration with Barrett's epithelium
  - Esophageal narrowing pre-RFA
  - Longer history of BE pre-RFA
  - Larger hiatal hernia and longer segment length<sup>2</sup>
- Circumferential RFA (balloon)
- Poor initial response: <50% regression of BE at 3 months
- 13% (36) poor initial responders
- Among poor responders:
  - Ultimate achievement of CR-D in 86% and CR-IM in 66%
  - Median 13 months treatment (v/s 7 months for good initial responders)
  - Median of 4 RFA sessions (v/s 3 sessions for good initial responders)
- poor healing

# Needed areas of further research

- The use of advanced endoscopic imaging techniques to potentially allow the extension of needed surveillance intervals in those with low risk for progression
- Validation of the consistent achievement of PIVI thresholds in the community setting
- Evidenced-based quality indicators for BE management
- Standardization of image characterization and improvement in image to pathology correlation
- Validated training tools
- Use of magnification endoscopy and NBI
  - New generation system (Olympus 190 series), dual focus mode with 70-fold magnification of mucosa
  - Met PIVI thresholds in feasibility study
- Assessment of cost effectiveness of EIT in BE

1. Sharma P, Hawes R, Bansal A, et al. Standard endoscopy with random biopsies versus narrow band imaging targeted biopsies in Barrett's esophagus: a prospective international, randomized controlled trial. *Gut* 2013;62:15-21.

2. Sharma P, Brill J, Canto M, et al. Advanced imaging in Barrett's esophagus. *Clin Gastroenterol Hepatol* 2015;13(13):2209-18.

# CONCLUSIONS

# Conclusions

- *A better understanding of the risk factors for Barrett esophagus and progression to dysplasia and a*
- *more individualized risk calculation will be useful in defining populations to consider for Barrett screening.*
- *The development of novel, nonendoscopic screening techniques and of less expensive endoscopic techniques holds promise for a cost-effective screening and surveillance method to curtail the increasing rates of EAC.*

# Conclusions

- Surveillance is hampered by sampling error and pathologic discordance
- Non-risk stratified non-dysplastic Barrett's esophagus can progress to esophageal adenocarcinoma at a rate of ~3% in 10 years
- Well-studied and commonly accepted clinical risk factors may further elevate this risk for progression
- Confirmed LGD carries a substantial annual cancer progression risk
- Most patients experience complete eradication of intestinal metaplasia
- RFA reduces the risk of neoplastic progression in all grades of Barrett's esophagus including non-dysplastic

# Conclusions

- EMR followed by RFA has been shown to be effective in treating many patients with relatively advanced disease including HGD and IMC
- Multiple Society Guidelines suggest RFA as an option in NDBE at increased risk for progression as well as for those with confirmed LGD and HGD
- The use of NBI has been shown to be effective at increasing detection rates of high-grade disease
- RFA also has hemostatic applications, such as GAVE and RP
- RFA is effective and has a favorable safety profile in academic and community settings

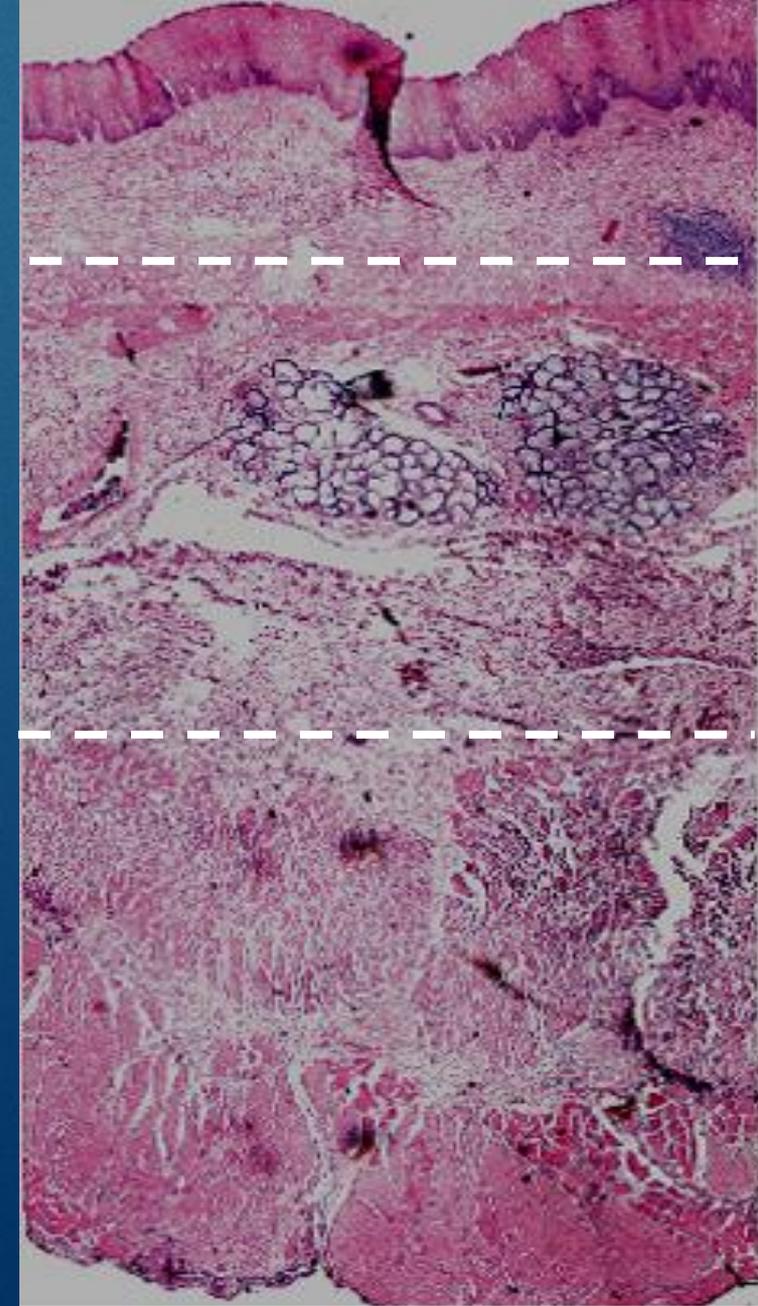
**QUESTIONS?**

# Risk calculation tool

- Michigan Barrett Esophagus prediction Tool, M-BERET
  - based on a population of men aged 50 to 79 years presenting for colorectal cancer screening who were invited to undergo upper endoscopy at the same time.
  - predominantly white (89%) and overweight.
  - Four strongest independent predictors for Barrett in the studied group: age, waist hip ratio, GERD frequency, and cigarette use.
- The receiver operator characteristic (ROC) curve for the M-BERET tool 0.72 vs. 0.6
- At a sensitivity of 80%, the tool had a specificity of 56%
- yet to be validated.

# Human Esophagus<sup>1-5</sup>

- Epithelium
- Lamina Propria
- Muscularis Mucosae
- Submucosa
- Muscularis Propria
  
- Keys to Endotherapy:
  - Uniform mucosal removal
  - Controlled depth of ablation



# ESCC

- In the East, the predominant type of esophageal cancer is ESCC
- Associated
  - alcohol consumption,
  - tobacco use including active and passive smoking,
  - high intake of pickled foods,
  - low intake of fresh fruit and vegetables,
  - low socioeconomic status,
  - poor oral hygiene,
  - frequent consumption of extremely hot drinks,
  - caustic injury,
  - radiation,
  - achalasia.

# Development and validation of a classification system to identify

## P. SHARMA ET AL., GASTROENTEROLOGY 2015 HGD and EAC in BE using NBI<sup>1</sup>

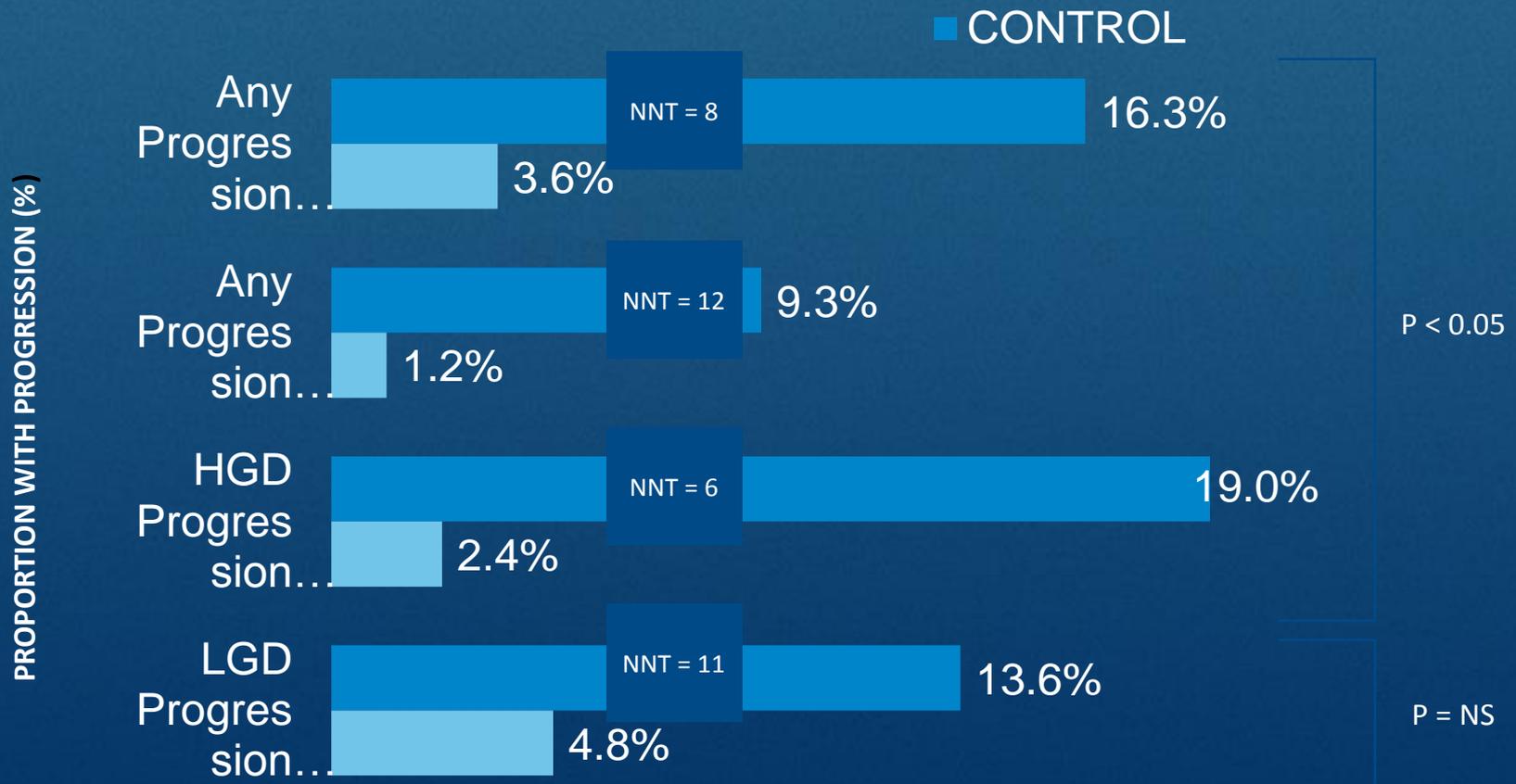
- Four phase approach including a validation step to test the BING criteria in predicting histology
- In Phase 4, experts asked to predict histopathology of 120 NBI images from Phase 2 not previously viewed, rated level of confidence of predictions as “high” or “low”

|             | Overall | High-level of confidence (62.5% of images) |
|-------------|---------|--|
| Accuracy    | 85%     | 92%  |
| Sensitivity | 80%     | 91%  |
| Specificity | 88%     | 93%  |

- Inter-observer agreement was substantial (K=0.681)
- Needs to be validated in inexperienced users and in different settings (academic versus community)

1. Sharma P, Bergman J, Goda K. Development and validation of a classification system to identify HGD and EAC in BE using NBI. Gastroenterology 2015 Nov. [Epub ahead of print]

# Disease Progression



# Risk Factors<sup>1</sup>

|   | BE  | EAC |
|---|-----|-----|
| Older age                                     | Yes | Yes |
| White race                                    | Yes | Yes |
| Male sex                                      | Yes | Yes |
| Chronic heartburn                             | Yes | Yes |
| Age < 30 at onset of GERD symptoms            | Yes | —   |
| Hiatal hernia                                 | Yes | Yes |
| Erosive esophagitis                           | Yes | Yes |
| Obesity with intra-abdominal fat distribution | Yes | Yes |
| Metabolic syndrome                            | Yes | Yes |
| Tobacco use                                   | Yes | Yes |
| Family history of GERD, BE or EAC             | Yes | Yes |
| Obstructive sleep apnea                       | Yes | —   |
| Low birth weight for gestational age          | Yes | No  |
| Preterm birth                                 | No  | Yes |
| Consumption of red meat and processed meat    | Yes | Yes |
| Human papillomavirus infection                | No  | Yes |

Spechler SJ, Souza RF. Barrett's Esophagus. N Engl J Med 2014;371:836-45

# FDA 510k Clearance for RFA<sup>1, 2</sup>:

## INDICATION FOR USE STATEMENT

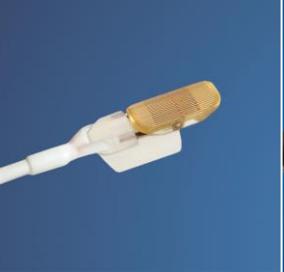
- Barrx™ 360 (formerly HALO360): “... indicated for use in the coagulation of bleeding and non-bleeding sites in the gastrointestinal tract including but not limited to the esophagus. Indications include Esophageal Ulcers, Mallory-Weiss tears, Arteriovenous Malformations, Angiomata, Barrett’s Esophagus, Dieulafoy Lesions, Angiodysplasia.”
- Indication For Use statement is inclusive of all grades of BE
- “HALO” has been replaced by “Barrx” on RFA products but remains “HALO” on FDA statement
- Barrx™ 90, Barrx™ Ultra Long, Barrx™ 60, Barrx™ Channel (formerly HALO90, HALO90 ULTRA, HALO60): identical to 360 + Gastric Antral Vascular Ectasia (GAVE) and Radiation Proctitis (RP)
  - [http://www.accessdata.fda.gov/cdrh\\_docs/pdf11/K112454.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf11/K112454.pdf)  
Accessed March 29, 2014
  - [http://www.accessdata.fda.gov/cdrh\\_docs/pdf12/K120431.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf12/K120431.pdf)  
Accessed March 29, 2014
  - <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm199999.htm>  
Accessed July 07, 2013
  - <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm199999.htm>  
Accessed July 07, 2013

1. 717-0016-01 Revision: E HALO360+ Ablation Catheter Instructions For Use

2. 717-0026-01 Revision: C/H10207: HALO90, HALO90 ULTRA, HALO60 Ablation Catheters Instructions For Use

# Barrx™ Ablation<sup>1</sup>

## FOCAL ABLATION CATHETERS

| MODEL            | BARRX™<br>ULTRA LONG   | BARRX™ 90   | BARRX™ 60  | BARRX™<br>CHANNEL  |
|------------------|--|---|--|--|
| ELECTRODE LENGTH | 40 MM  | 20 MM   | 15 MM  | 15.7 MM  |
| ELECTRODE WIDTH  | 13 MM  | 13 MM   | 10 MM  | 7.5 MM   |
|                  |  |  |  |  |

1. US130138-USA, September 2013

# Barrx™ 360 Express RFA Balloon Catheter<sup>1</sup>



1. US130138-USA, September 2013

# Barrx™ 360 Express RFA Balloon Catheter<sup>1</sup>

## KEY FEATURES

- No sizing step or sizing data to record
- Removes need to choose the correct size ablation catheter
- Capable of treating esophagi with a diameter of 18 mm to 31 mm
- Wrap/unwrap electrode design, 4cm in length

1. US130138-USA, September 2013



# Barrx™1

| ABLATION:  | CIRCUMFERENTIAL   | FOCAL   | FOCAL  | FOCAL   | FOCAL   |
|--|---|---|--|---|---|
| BARRX™<br>FLEX GENERATOR   | BARRX™ 360  | BARRX™<br>ULTRA LONG  | BARRX™ 60  | BARRX™ 90   | BARRX™<br>CHANNEL   |
|  |  |  |  |  |  |

# Progression after RFA

|                          |
|--------------------------|
| <b>Polyp<sup>2</sup></b> |
| 0.58%                    |
| 0.06%                    |
| NNT=38                   |

- Progression risk expressed as “% per patient-year” risk of developing EAC
- NNT calculated on a 5-year basis (number needed to treat per year for five years to avoid one cancer) – source (<http://araw.mede.uic.edu/cgi-bin/nntcalc.pl>)

# The Evolution of a LGD Guideline

## ACG CLINICAL GUIDELINE: DIAGNOSIS AND MANAGEMENT OF BARRETT'S ESOPHAGUS

- ACG (2008)<sup>1</sup>
  - “Low grade dysplasia requires expert pathologist confirmation and more frequent endoscopy and biopsy.”
  - “The finding of LGD warrants a follow-up endoscopy within six months to ensure that no higher grade dysplasia is present...”
  - “When two pathologists agree on the diagnosis of LGD, the patient has a greater likelihood of neoplastic progression.”
- ACG (2015)<sup>2</sup>
  - “...in patients with BE and LGD confirmed by a second pathologist, ablative therapy results in a statistically and clinically significant reduction in progression to the combined end point of HGD or EAC, or to EAC alone.”
  - “For patients with confirmed LGD...endoscopic therapy is considered as the preferred treatment modality, although endoscopic surveillance every 12 months is an acceptable alternative (strong recommendation, moderate level of evidence).”

1. Wang et al., Updated guidelines 2008 for the diagnosis and surveillance and therapy of BE. Am J Gastro 2008;3:788-97

2. Shaheen et al., ACG Clinical Guideline: Diagnosis and management of BE. Am J Gastroenterol. 2015 [Epub ahead of print]

# BE Recurrence After RFA is Rare and Less Severe Than Baseline<sup>1</sup>

- Retrospective cohort study
- 198 patients with BE
- LGD (29%), HGD (53%), IMC (14%)
- EMR for raised lesions + RFA
- Mean follow-up 3 years post CE-IM
- Rate of IM recurrence: 3.5% per person-year
- 83% histology same or less severe than baseline
- Of recurrences not associated with endoscopic findings:
  - 79% found at TGF
  - 7% found 1 cm proximal to TGF
  - 14% microscopic areas of non-dysplastic histology

Original article

 Recurrent intestinal metaplasia after radiofrequency ablation for Barrett's esophagus: endoscopic findings and anatomic location

Cary C. Cotton, BA, W. Asher Wolf, MD, MPH, Sarina Pasricha, MD, MSCR, Nan Li, MS, Ryan D. Madanick, MD, Melissa B. Spacek, ANC-BC, Kathleen Ferrell, MPAS, PA-C, Evan S. Dellon, MD, MPH, Nicholas J. Shaheen, MD, MPH 

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Received 13 October 2014, Accepted 7 December 2014, Available online 24 March 2015

1. Cotton et al. Recurrent intestinal metaplasia after RFA for BE: endoscopic findings and anatomic location. *Gastrointest Endosc* 2015;81(6):1362-9

# Rates of Recurrence and Achievement of a Second Complete Eradication of Intestinal Metaplasia in Patients Treated With RFA for BE<sup>1</sup>

WOLF WA, COTTON CC, ELURI S, ET AL. [ABSTRACT]

- 3113 patient from the US RFA Registry
- 73% male, 95% white, average age 62, average BE segment length 3.7cm
- 25% (773) had recurrence after CEIM
  - 4.8 per 100 patient-years
- Of patients with recurrence:
  - 83% recurred with NDBE
  - 52% achieved CEIM a second time

742

## Rates of Recurrence and Achievement of a Second Complete Eradication of Intestinal Metaplasia in Patients Treated With Radiofrequency Ablation for Barrett's Esophagus

W. Asher Wolf, Cary C. Cotton, Swathi Eluri, George Triadafilopoulos, Thomas Runge, Herbert C. Wolfsen, Nan Li, Srinadh Komanduri, Gary W. Chmielewski, Atilla Ertan, Evan S. Dellon, Nicholas J. Shaheen

**Background:** The majority of patients with Barrett's esophagus (BE) are successfully treated to complete eradication of intestinal metaplasia (CEIM). However, a subset of patients achieving CEIM have recurrence of BE. Limited research has assessed the fate of patients who attain CEIM then have recurrence of BE. **Aims:** We assessed the rate of patients who had recurrence of BE after CEIM, as a function of pre-treatment histology. We also assessed the pathologic grade of recurrence, and the frequency with which patients achieve a second CEIM as a function of recurrence histology. **Methods:** The U.S. RFA Registry is a study of patients undergoing RFA for BE at 35 academic and 113 community centers enrolled from 2007 to 2011. For inclusion in the current investigation, patients achieved CEIM and underwent at least one biopsy session after CEIM. We estimated rates of recurrence using the product-limit method with right censoring at the last visit. **Results:** Of 5521 patients

1. Wolf WA, et al. Rates of recurrence and achievement of a second CEIM in patients treated with RFA for BE. *Gastroenterology*, 2015;148(4):S-139

# Enhanced imaging techniques (EIT)

- Chromoendoscopy (dye based)
  - Methylene blue, acetic acid
- Chromoendoscopy (electronic or optical based)
  - Narrow Band Imaging (NBI) – Olympus America
  - Flexible Spectral Imaging Color Enhancement (FICE) – Fujinon, Inc.
  - I-Scan – Pentax, Inc.
- Confocal Laser Endomicroscopy (CLE)
  - pCLE – Cellvizio (Mauna Kea Technologies)
- Optical Coherence Tomography (OCT)
  - Volumetric Laser Endomicroscopy (VLE)
    - Nvision VLE (NinePoint Medical)

# The Evolution of a guideline

- ACG (2008)<sup>1</sup>: “Although very promising, there is not sufficient evidence at this time to recommend the use of these imaging systems on a routine basis”
- ACG (2015)<sup>2</sup>:
  - “Consideration of any endoscopic therapy in BE begins with a close inspection of the BE mucosa. The identification of mucosal irregularities including nodularity, ulceration, or flat but irregular mucosal contour is essential to detecting the areas of highest yield for neoplasia. In this role, the adjunct use of narrow light spectrum imaging technology, such as **narrow band imaging**, may **aid in detecting mucosal irregularity**.”
  - “A systematic biopsy protocol clearly detects more dysplasia and early cancer compared with ad hoc random biopsies.”
  - “Surveillance should be performed with high-definition/high-resolution white light endoscopy (strong recommendation, low level of evidence).”
  - Routine use of advanced imaging techniques **other than electronic chromoendoscopy** is not recommended for endoscopic surveillance at this time (conditional recommendation, very low level of evidence).”
  - “Several areas in particular appear poised for **paradigm-shifting advances**. These include ...the use of **advanced imaging** ... to allow recognition of areas of neoplasia within BE, ... “

1. Wang K, Sampliner R, et al. Updated guidelines 2008 for the diagnosis and surveillance and therapy of BE. Am J Gastroenterol 2008;3:788-97.

2. Shaheen N, Falk G, Iyer P, et al., ACG Clinical Guideline: Diagnosis and management of BE. Am J Gastroenterol 2015 [Epub ahead of print]Canto M, et al. Advanced imaging in Barrett's esophagus. Clin Gastroenterol Hepatol 2015;13(10):2269-18.

# Quality of Life: Results From the US

## RFA Registry<sup>1</sup>

LI N, PASRICHA S, CHMIELEWSKI J, ET AL. [ABSTRACT]

- Results

| QoL Score                                       | Baseline | Follow-up | Changes |
|---|----------|-----------|---------|
| Concern about the condition of esophagus (mean) | 6.9      | 4.1       | -2.7    |
| Negative impact on life (mean)                  | 4.8      | 2.8       | -1.9    |
| Esophageal cancer worry (mean)                  | 7.3      | 4.4       | -2.8    |

| Changes in score after RFA                      | Achieved CE-IM | No CE-IM | P-value |
|---|----------------|----------|---------|
| Concern about the condition of esophagus (mean) | -3.1           | -1.9     | <0.001  |
| Negative impact on life (mean)                  | -2.2           | -1.3     | <0.001  |
| Esophageal cancer worry (mean)                  | -3.2           | -2.0     | <0.001  |

- Conclusion:

- After RFA, significantly reduced concern about condition of esophagus, reduced negative impact on life and reduced esophageal cancer worry
- QoL measure improvement most pronounced in those who experienced CEIM.

1. Li N, et al. Impact of BE and treatment with RFA on patient QoL, results from the US RFA registry. Gastroenterology, 2015;148(4):S-216