Management of Barrett’s Esophagus and Early Esophageal Cancer

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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?
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
Esophageal Adenocarcinoma is the Fastest Growing Cancer in the US

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

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

Maximal extent of metaplasia: 
M = 5.0 cm

Circumferential extent of metaplasia: 
C = 2.0 cm

True position of GEJ: 
Origin = 0.0 cm

Distance (cm) from GEJ

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/Eosoph 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/Eosoph 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
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
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).
• Upper Endoscopy may 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 y/o 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
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.”

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 yrs (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 adenocarcinomas 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 unslected BE patients. The risk of cancer or high-grade dysplasia was examined both using the British definition of BE, that is, columnar lined epithelium of the esophagus (CLE) and the American definition of
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
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
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.”
## Cancer Risk Summary

<table>
<thead>
<tr>
<th>Condition</th>
<th>1 Year</th>
<th>5 Year</th>
<th>10 Year</th>
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<tbody>
<tr>
<td>Non-dysplastic Barrett’s</td>
<td>0.3%</td>
<td>1.5%</td>
<td>3%</td>
</tr>
<tr>
<td>Low Grade Dysplasia (confirmed)</td>
<td>3%</td>
<td>15%</td>
<td>30%</td>
</tr>
<tr>
<td>High Grade Dysplasia</td>
<td>10%</td>
<td>50%</td>
<td>100%</td>
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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
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
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Endoscopic Surveillance

Seattle Protocol
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

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.
Sampling Error

- Intromucosal cancer
- Invasive cancer
- Dysplasia

Diagram:
- Squamous
- Gastric mucosa
- Metaplasia ("specialized")
- Indefinite for Dysplasia/Low Grade Dysplasia
- High Grade Dysplasia
- Cancer
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 ranked 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
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.
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
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


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


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

- **EUS Endoscopic Ultrasound**
- **Advanced OCT NvisionVLE**
- **CLE**

Graph showing resolution and image depth:
- Resolution: 1mm, 100μm, 10μm, 1μm
- Image Depth: 1mm, 10mm
Volumetric Laser Endomicroscopy
Normal *Esophageal Mucosa*
Abnormal
Loss of Layered Architecture

Normal
Esophageal Mucosa

Normal
Gastric Cardia
Buried BE
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

- APC
- Cryo
- PDT
- EMR
- RFA

Red light → Activated Photosensitizer → Photosensitized Neoplastic cells
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)
Human Esophagus

- Epithelium
- Lamina Propria
- Muscularis Mucosae
- Submucosa
- Muscularis Propria

Surgical Depth

- RFA Depth
- PDT, APC & Cryo Depth
- EMR Depth
- Surgical Depth
Histological Representation

Normal

Post RF Ablation
Circumferential Ablation

Focal Ablation
Ablation Device Family

Barrx 360  Barrx 90 Ultra  Barrx 90 “Chang Cap”  Barrx 60  NEW Barrx Channel
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 ($P<0.05$)
Disease Eradication

- **Complete Eradication of IM (All patients, n=127):**
  - Control: 2.3%
  - RFA: 77.4%
  - P < 0.001

- **Complete Eradication of Dysplasia (LGD patients, n=64):**
  - Control: 22.7%
  - RFA: 90.5%
  - P < 0.001

- **Complete Eradication of Dysplasia (HGD patients, n=63):**
  - Control: 19.0%
  - RFA: 81.0%
  - P < 0.001

**Intention-to-Treat Comparison Groups**
Disease Progression

![Bar chart showing the proportion of patients with progression of disease and progression to cancer between control and RFA groups.](chart.png)

- **Any Progression of Disease**
  - Control: 16.3%
  - RFA: 3.6%
  - Statistical significance: P<0.05

- **Any Progression to Cancer**
  - Control: 9.3%
  - RFA: 1.2%
  - Statistical significance: P<0.05
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


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.

• **Endoscopic Mucosal Resection** = 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

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<th>1 Year CA Progression Rate</th>
<th>AGA Guidelines Recommendations</th>
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<td>Non-dysplastic Barrett’s</td>
<td>0.3%</td>
<td>Surveillance (or Ablation in select individuals)</td>
</tr>
<tr>
<td>Low Grade Dysplasia (confirmed)</td>
<td>3%</td>
<td>Endoscopic Ablation</td>
</tr>
<tr>
<td>High Grade Dysplasia</td>
<td>10%</td>
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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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