Barrett’s Esophagus 2015

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Definition of Barrett’s Esophagus:

American GI societies:
Barrett's esophagus is a change in the esophageal epithelium of any length, due to reflux of gastric contents [GERD], that can be

- Recognized at endoscopy*
- Confirmed to have intestinal metaplasia of the tubular esophagus by biopsy

In response to abnormal stimulus,
Replacement by more robust cell type (potential for dysplasia)
BARRETT’S LANDMARKS and DEFINITIONS

TERMINOLOGY

Proximal margin of any
Barrett’s
Squamocolumnar
Junction Proximal margin
of circumferential Barrett’s
Gastroesophageal
junction= End of
tubular esophagus;
Top of gastric folds
Diaphragmatic
pinch 43 cm

PRAGUE CLASSIFICATION
C4 M6
4 cm hiatal hernia
C=circumferential length- 35-39
M= total maximal length- 33-39

Understanding Barrett’s

- Barrett’s is acquired
  - Length is fixed

- Risk factors
  - Chronic GERD
  - First degree relatives with Barrett’s
  - Male
  - Caucasian
  - Hiatal hernia
  - Obesity*

- Pathogenesis unclear, but...
Pathogenesis

Normal

Barrett's Esophagus

Dysplasia

Cancer

Squamous epithelium

Columnar epithelium

With dysplasia

Adenocarcinoma

Injury & Healing - Metaplasia
Dysplasia in Barrett’s esophagus

Low-grade

High-grade

Barrett’s Surveillance

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Documentation</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Two EGDs with biopsy (4 quadrant x 2 cm) within 1 year</td>
<td>EGD/biopsy 3-5 years</td>
</tr>
<tr>
<td>Low-grade</td>
<td>Expert pathologist confirmation Repeat EGD/biopsy (4 quadrant x 1 cm) within 6 months</td>
<td>EGD/biopsy every year until no dysplasia x 2</td>
</tr>
<tr>
<td>High-grade</td>
<td>Mucosal irregularity Repeat EGD/biopsy (4 quadrant x 1 cm) within 3 months Expert pathologist confirmation</td>
<td>EMR EGD/biopsy every 3 months or Intervention based on results and patient</td>
</tr>
</tbody>
</table>
Barrett’s Dysplasia

• Substantiated Dysplasia?
  • 2nd opinion GI pathologist
  • Reflux well-controlled (BID PPI taken before meals)
    • Acute AE: headaches, diarrhea
    • Chronic AE: pneumonia, colitis, Mg, hip fracture

• Advanced Imaging endoscopy
  • HD white light exam
  • Excisional biopsy of any Mucosal Abnormalities
  • Random biopsy protocol

When is BE Dysplasia really Dysplasia?

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Home Institution Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>LGD (n= 83)</td>
</tr>
<tr>
<td></td>
<td>HGD (n= 129)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.2% 2.4%</td>
</tr>
<tr>
<td></td>
<td>72.3%</td>
</tr>
<tr>
<td>HGD</td>
<td>24.1%</td>
</tr>
<tr>
<td>LGD</td>
<td>3.9% 3.9%</td>
</tr>
<tr>
<td>IND/ND-IM</td>
<td>69.0%</td>
</tr>
<tr>
<td>LGD (n= 83)</td>
<td>23.3%</td>
</tr>
<tr>
<td>HGD (n= 129)</td>
<td>69.0%</td>
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</tbody>
</table>
BE Low Grade Dysplasia: risk stratification

Increased risk of progression
- Extent of dysplasia (focal versus diffuse)
- Agreement between pathologists
  - 0% versus 41% versus 80%
- Biomarkers
  - p53 overexpression (40% versus 10%)
  - Aneusomy, tetraploidy (29% versus 0%)
- Factors may be additive (p53 + agreement between pathologists)

Srivastava Am J Gastroenterol 2007
Skacel Am J Gastroenterol 2000
Reid Am J Gastroenterol 2000
Weston Am J Gastroenterol 2001

AIM-Dysplasia Trial

U.S. multi-center, randomized, single-blind, sham-controlled clinical trial

2:1 RFA vs sham
- Esomeprazole 40mg BID in all patients
- Prior EMR any mucosal abnormalities
- Centralized expert histology analysis
- Stratified by:
  - degree of dysplasia (LGD vs. HGD)
  - length of segment (1-4 cm vs 4-8 cm)
- Maximum of 4 RFA sessions
- Identical biopsy protocols, equal sampling
- 12 month cross-over

AIM-Dysplasia Trial

RCT of 127 Subjects with LGD & HGD

1° Outcomes:
- Ablation of all dysplasia (CR-D):
  - 81% of HGD
  - 91% of LGD
  - approx 20% of controls
- Complete eradication of IM (CRIM, CEIM):
  - 77% of RFA Rx patients
  - 2% Sham patients

AE’s: Strictures in 6% of subjects


LGD group -- No difference in progression to HGD or ACA:
Study not adequately powered, sample size too small

ACG/FGS Spring Symposium - Naples, FL
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**SURF: European multi-center RCT in 136 pts**

1° **Outcome:** Progression to HGD or ACA over 3 years

2° **Outcomes:** CR-Dysplasia, CR-IM, Adverse events

511 pts screened, LGD confirmed 247 pts, 140 pts enrolled

1:1 RFA vs Surveillance for LGD diagnosed within 18 months

- 68 patients each group, C2M4 average segment
- Esomeprazole 40mg BID in all patients
- Centralized expert histology analysis
- Maximum of 5 RFA sessions (2 circumferential, 3 focal)
- Biopsy protocol: 4Q biopsy every 2cm
  - RFA q3mos then Bx 3 months later & annually
  - Control 6, 12 months & annually

Phoa KN, JAMA 2014;311(12):1209-1217

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**RFA vs Endoscopic Surveillance for BE LGD**


- **Progression HGD or ACA:**
  - 1.5% RFA vs. 26.5% Controls

- **Progression to ACA:** 1.5% vs. 8.8%

- **Complete eradication Dysplasia (CR-D):**
  - 98.4% of RFA Rx patients
  - 27.9% Control patients

- **Complete eradication of IM (CR-IM):**
  - 90% of RFA Rx patients
  - 0% Control patients
Ablation in LGD: Could/Should it be considered?

• If risk of progression to HGD/Ca is higher? YES
• If technique is safe, effective & durable? YES
• If ablation is cost effective compared to surveillance: MAYBE

  ○ Risks of procedure should be considered:
    ○ Bleeding, Perforation, Strictures
    ○ Incomplete ablation
    ○ Sub-squamous IM

Summary of Endoscopic Management of Barrett’s Dysplasia and Neoplasia
• **Non-dysplastic**
  - Ablation is an option, but role in average risk patients not clear

• **BE & Low Grade Dysplasia:**
  - Uni-focal disease, elderly patient, and/or election for conservative Rx -> surveillance endoscopy
  - Multifocal, previously nodular, young, family hx of cancer, pathologically worried -> consider ablation
    - Caveats about lack of data on decreasing cancer

• For subjects with nodular disease, EMR histology determines further management
  - No cancer, mucosal cancer, or maybe sm1 cancer -> ablative therapy
  - Deeper than sm1 -> consideration of multimodality Rx and esophagectomy

• **Flat HGD -> endoscopic ablation**
  - RFA vs Ps-PDT
Esophageal Cancer: The 95% Problem

- Fecal DNA Analysis
- Cytology sponge
- Spectroscopy field
carcinogenesis
- VLE tethered capsule

Schlansky B et al. Aliment Pharmacol Ther, 2006
Dulai GS, Gastroenterology 2002 Corley DA, Gastroenterology 2002
Compliance and Adherence

- Only 55% GERD patients took their PPI QD x 4 weeks as prescribed
- 37% took no more than 12 days in 4 weeks
- Compliance further declines with increase in dosing
- Of 100 patients with persistent GERD symptoms on PPI: 54% were dosing suboptimally
  - 39%: PPI > 60 min AC
  - 30%: after a meal
  - 28%: at bedtime
- 52% of GERD patients reported taking their PPI at bedtime

The Gallup Organization 2000

Lifestyle Modifications

- Weight loss
- Avoiding late meals (3 hours before bedtime)
- Avoiding overfilling stomach with liquids before bedtime
- Elevation of the head of the bed
- Avoidance specific lifestyle activities (heavy meals, exercise, alcohol, chocolate, caffeine consumption) identified by patient or physician
Scope of the Problem

- GI disorders such as IBS, GERD, dyspepsia, PUD, hepatitis, CRC and others: 50 million visits to MD/DO
- Cost of caring for above: US$ 90 Billion/year
- Complementary and Alternative Medicine (CAM):
  - Those who do not get complete relief
  - Those who have side effects from traditional medicines
  - Those seeking a more natural approach
  - Tens of billions of dollars/year
  - In contrast to drugs, is believed to be harmless
  - Often used on-demand
- Cost of CAM therapies: tens of billions/year

GERD: How often is supplemental alternative medicine used?

- Survey (1999-2000) to consecutive patients in AZ and WI
- 185 surveyed (82 men; mean age 55.8 y)
  - 61.6% used alternative medicine for any reason
  - Only 3.8% used supplemental alternative medicine for GERD
    - Females 2X as likely
    - Daily acid regurgitation 5.75X
- Only a small % GERD patients seen in community-based practice use supplemental alternative medicine for GERD (despite a higher use for non-GERD related illness)
CAM and GERD

Acupuncture
- In animal models
  - Modulate gastric motility
  - Decrease gastric acid output
  - Increase VIP, Somatostatin and beta-endorphin
  - Decrease gastrin
  - Decrease in gastric acid output: blocked by naloxone when injected prior to acupuncture

Acupuncture & Acupressure
- Needles at PC-6 point on the inside of the wrist and ST-36 point on the anterior shin just below the knees
- Normal volunteers:
  - Reduces frequency of dominant contractions to 78% of baseline
  - Increases slow wave gastric contractions
  - Decreases tachygastria from 26.9% to 10.8%
Acupuncture & Acupressure

• Normal volunteers:
  • Decreased rate of TLESRs by 40% without significant
effect on LES basal pressure, residual pressure or
duration of TLESRs
  • In patients failing PPI once a day, adding acupuncture:
significantly better at controlling regurgitation, daytime and
nighttime heartburn

Zou D et al Am J Physiol Gastrointest Liver Physiol 2005;289:: G197-2-1
Dickman R et al APT 2007;26:1333-44

Acupuncture & Acupressure

• Acupuncture significantly inhibited intraesophageal acid and
bile reflux; improved GERD-related symptoms and it was safe
and well tolerated
• Electroacupuncture in 480 GERD patients (once a day x 6
weeks):
  • 24-hour intraesophageal pH, bile reflux
  • Endoscopic grading
  • Symptom scores
  • SF-36: all 8 domains increased compared to prior
treatment

Zhang CX Chin J Integr Med 2010;16:298-303
**Acupuncture**

- Patients with esophageal dysmotility (Scleroderma): prolonged transcutaneous nerve electrical stimulation (TENS) at GI acupuncture sites:
  - Normalization of sympathovagal balance
  - Increased physical functional scores
  - Decreased GI symptom scores


**Psychological Therapy**

- Anxiety and depression: increase reporting of GERD-related symptoms (particularly in NERD)
- Response to PPI may be dependent on level of psychological distress
- Psychosocial comorbidity may play a role in those failing to PPI therapy → psychological treatment may improve patient’s response

Nojkov B et al APT 2008;27: 473-82
Mizyed I APT 2009;29:351-8
Rubenstein JH et al. APT 2007;26:43-52
Kamolz T et al. Scan J Gastroenterol 2001;36:800-809
Osteopathic Manipulative Therapy in GERD: Hiatal hernia reduction technique.

[Sphincter normalization by recoil technique](Diniz L R et al. J Am Osteopath Assoc 2014;114:180-188)
Pillars of the diaphragm normalization technique