GERD and Barrett’s Esophagus: Dysplasia and How to Treat
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Outline
- Overview of GERD
- Risk of cancer in Barrett’s esophagus
- Endoscopic surveillance
- Ablation techniques
- Endoscopic mucosal resection
- Future

GERD
- Gastroesophageal reflux disease (GERD) refers to symptoms or clinically findings caused by the reflux of gastric contents back into the esophagus.
- Occurs in about 10-20% of the US population.
Slide 4

**Risk Factors**
- Obesity
- Male gender
- Alcohol
- Tobacco
- Diet: chocolate, high fat, caffeine
- Genetics

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Slide 5

**Etiology**
- Motility disorders
  - Increased ERD
  - Weak LES
  - Weak esophageal peristalsis (i.e., Scleroderma/CREST)
  - Delayed gastric emptying
- Damage factors
  - Increased gastric acid production
  - Bile/pancreatic juice

  - Resistance factors
  - Reduced saliva/HCO3 production
  - Diminished mucosal blood flow
  - Protective mucus/Decreased epithelial GF

  - Others
  - Hiatal hernia
  - Obstructive sleep apnea

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Slide 6

[Diagram of gastroesophageal reflux disease]
Slide 7

**Lower Esophageal Sphincter (LES)**
- Forms part of a barrier to prevent reflux of gastric contents into the esophagus.
- With severe acid reflux, the resting LES pressure is usually diminished.
- Hiatal hernia changes the relationship of the diaphragm and LES and lowers threshold for relaxation of LES.

Slide 8

**Decrease LE Pressure**
- **Medications:**
  - Anticholinergics
  - B-agonists including inhalers
  - Calcium channel blockers
  - Diazepam
  - Estrogens
  - Narcotics
  - Progesterone
  - Theophylline
- **Diet:**
  - Fatty foods
  - Peppermint
  - Chocolate
  - Caffeine
  - Alcohol
  - Tobacco

Slide 9

**Clinical Presentation**
- **Classic symptoms:**
  - Substantial burning (heartburn)
  - Acid regurgitation
  - Borborygmi
- **Less common symptoms:**
  - Water brash
  - Dysphagia
  - Odynophagia
  - Chest pain
Clinical Presentation: Extraesophageal Symptoms
- Cough
- Wheeze
- Sore throat
- Repetitive throat clearing
- PND
- Throat/neck pain
- Otalgia
- Apnea
- Globus

Diagnosis
- Empiric medical therapy
- Barium studies
- Upper endoscopy
- Ambulatory pH monitoring

Empiric Trial of PPIs
- PPIs are quite effective in treating symptoms and helping to heal esophagitis.
- Expert opinion supports empiric treatment with PPI in patients with uncomplicated GERD symptoms.
- A meta-analysis of 15 studies demonstrated a 78% sensitivity and only 54% specificity for reflux using 24-hr pH as gold standard.

When Should Further Testing Be Performed?

- No response to trial of PPI
- Uncertain diagnosis
- Atypical symptoms (chest pain, ENT, pulmonary)
- Symptoms associated with complications (dysphagia, odynophagia, unexplained weight loss, GI hemorrhage, anemia)
- Recurrent symptoms
- Prior to anti-reflux surgery

Complications of GERD

- Erosive esophagitis
- Strictures
- Barrett's esophagus
- Adenocarcinoma of the esophagus

Barrett's Esophagus

- Defined as the development of a specialized columnar epithelium that replaces the normal squamous epithelium of the esophagus.
- Prevalence at endoscopy:
  - 12% in patients at routine endoscopy
  - 10% in patients with erosive esophagitis
  - 20% of patients with peptic strictures
Barrett’s Esophagus: Biopsy

- Proximal extent of the gastric folds defines the GE junction.
- Salmon color mucosa proximal to the GE junction may be Barrett’s esophagus.
- Short segment < 3cm
- Long segment > 3cm
- Prague classification:
  - C: circumferential extent
  - M: maximum extent

Evolution of Barrett’s and Cancer

- Esophageal adenocarcinoma
- Gastric cancer
- Prostate cancer
- Breast cancer
- Lung cancer
- Colorectal cancer

Change in Incidence of Cancer in U.S.

- 300-500% increase in incidence since 1970s

Pohl H, Welch HG. Journal of the National Cancer Institute, Vol. 97, No. 2, January 19, 2005


Barrett’s Esophagus: Who to Screen?

- Current recommendations for EGD*:
  - Long standing acid reflux symptoms
  - White race
  - Male sex
  - Patients over the age of 50
  - Family history of BE/esophageal cancer
- Barrett’s present in patients without symptoms of reflux but not cost-effective to screen the entire population.

*ASGE guidelines 2006/7

Controversies about Screening

- About 40-50% of patients that have esophageal CA never reported GERD.
- Large number of patients with GERD will not be affected.
- No effect on morality of esophageal CA.
- May find lesions at an earlier stage.
- Quality of life diminished.
- Life insurance premiums increased.

Advanced Imaging

- Narrow band imaging (NBI) uses an optical filter technology that improves visibility of vascular and subtle tissue structures.
- Confocal laser endomicroscopy (CLE) allows in vivo microscopic examination of tissue.
- Both modalities may improve the sensitivity of endoscopic detection of dysplasia and decrease of the number biopsies needed.
**Surveillance**

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Evaluation</th>
<th>Endoscopy</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>2 EGDs</td>
<td></td>
<td>3 to 5 years</td>
</tr>
<tr>
<td>LGD</td>
<td>Highest grade on second EGD review with expert pathologist</td>
<td>6-12 months until no dysplasia x 2</td>
<td></td>
</tr>
<tr>
<td>HGD</td>
<td>Repeat EGD with jumbo bx review with expert pathologist</td>
<td>Individualize per patient</td>
<td></td>
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**“Expert Pathologist”**

- High degree of interobserver variability with LGD, indefinite for dysplasia, and no dysplasia.
  - Expert GI pathologists: Fair for LGD (k=0.32)
  - Slight for indefinite dysplasia (k=0.15)
  - Community pathologists: Downgrading LGD to nondysplastic BE in 77% of cases
- EMR more accurate.
  
  Montgomery E Hum Path 2001  
  Curvers W GIE 2008

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**Risk of Progression**

<table>
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<tr>
<th>Risk</th>
<th>IM EAC</th>
<th>IM HGD</th>
<th>IM HGD/EAC</th>
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<tr>
<td>0.5%</td>
<td>0.5%</td>
<td>0.9%</td>
<td>0.9%</td>
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</table>


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Risk of Progression

- Multicenter cohort study of 1204 patients with a mean follow-up of 5.52 years.
- Ablation of NDBE may not be justified given the low rate of progression to cancer.
- Mean time to progression to cancer is 5 years which may justify longer intervals between surveillance EGDs.

Wani S. Clin Gastro 2011

Lifetime Risk of Developing CA

- Risk of cancer:
  - Without dysplasia: 2 to 5%
  - LGD: 8 to 10%
  - HGD: 28 to 30%
- PPI and antireflux surgery can reverse Barrett's esophagus but may not effect on the cancer risk.

Low Grade Dysplasia

- Low risk of developing malignancy
- No clear guidelines in regards to management.
- Individualize treatment:
  - Continue surveillance
  - Ablative therapy
- May not be cost effective given the need for continued surveillance.
High Grade Dysplasia

- Confirm with 4 quadrant 1cm jumbo biopsies
- Review pathology with expert pathologist
- Consider endoscopic ultrasound
- About 10-40% of surgical specimens will contain carcinoma

Esophageal Carcinoma

- One of the fastest growing cancers in the US
- Adenocarcinoma > Squamous cell carcinoma
- Barrett’s esophagus is associated with increased risk of CA of 0.5 to 1% per year.
- Patients in surveillance programs usually present in an earlier stage than those with symptomatic cancers.
- Five year survival is less than 20%

Esophageal Carcinoma

- Risk Factors:
  - Long segment Barrett’s esophagus
  - Multifocal HGD
  - Visible lesions
  - Large hiatal hernia
  - De novo Barrett’s with HGD
  - Obesity
Slide 31

Management of HGD and IMC

- Ablative therapy
- Endoscopic mucosal resection
- Esophagectomy

Slide 32

Human Esophagus

- Muscularis mucosae (Ablation Target Depth)
- Submucosa with esophageal glands
- Muscularis propria

Ablation Target

Controlling ablation depth avoids stricture

EMR Depth

Surgical Depth

Slide 33

Ablative therapy

- Laser
- Multipolar electrocoagulation (MPEC)
- Argon plasma coagulation (APC)
- Photodynamic therapy (PDT)
- Radiofrequency ablation (RFA)
- Cryoablation
Radiofrequency Ablation

- Endoscopically placed balloon-based electrode
- Uniform energy is applied for a circumferential ablation
- Depth of treatment is the muscularis mucosa.

Clinical Data Summary

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>FU</th>
<th>CR-IM</th>
<th>CR-D</th>
<th>CR-HGD</th>
<th>Buried Glands</th>
<th>Stricture Rate</th>
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<tr>
<td>AIM</td>
<td>61</td>
<td>30 mo</td>
<td>98.4%</td>
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<tr>
<td>AMC</td>
<td>12</td>
<td>14 mo</td>
<td>100%</td>
<td>100%</td>
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<td>None</td>
<td>0%</td>
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<tr>
<td>Comm Registry</td>
<td>429</td>
<td>20 mo</td>
<td>77%</td>
<td>100%</td>
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<td>None</td>
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<tr>
<td>EURO</td>
<td>24</td>
<td>15 mo</td>
<td>96%</td>
<td>100%</td>
<td>--</td>
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<td>4.0%</td>
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<tr>
<td>Emory</td>
<td>27</td>
<td>&lt;12 mo</td>
<td>93%</td>
<td>100%</td>
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<td>Henry Ford</td>
<td>66</td>
<td>Varied</td>
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<td>--</td>
<td>--</td>
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<td>Mayo</td>
<td>63</td>
<td>24 mo</td>
<td>79%</td>
<td>89%</td>
<td>--</td>
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<td>0%</td>
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<tr>
<td>LGD</td>
<td>39</td>
<td>24 mo</td>
<td>87%</td>
<td>95%</td>
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<td>0%</td>
</tr>
<tr>
<td>LND</td>
<td>42</td>
<td>12 mo</td>
<td>81%</td>
<td>91%</td>
<td>--</td>
<td>None</td>
<td>--</td>
</tr>
<tr>
<td>HGD</td>
<td>42</td>
<td>12 mo</td>
<td>74%</td>
<td>81%</td>
<td>--</td>
<td>None</td>
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Radiofrequency Ablation in Barrett’s Esophagus with Dysplasia

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Methods

Study Design

- Randomized, sham-controlled design
- 2:1 RFA vs. sham
- 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

Trial Design

- Primary endpoint: CR-IM and CR-D (12 months)
- Central expert pathology lab (Cleveland Clinic)
- Secondary endpoints:
  - Progression (advanced dysplasia and cancer)
  - Discomfort
  - Adverse events

Complete Eradication (ITT)

- Chart showing comparison of complete eradication rates between control and RFA groups.
Slide 40

Complete Eradication (PP)

Slide 41

Conclusion

- In this multi-center, randomized, sham-controlled study of RFA, there was a high rate of complete eradication of dysplasia and intestinal metaplasia and decreased disease progression in the ablation group.

Slide 42

Durability of Epithelial Reversion After RFA: Follow-up of the AIM Dysplasia Trial

[Presented at DDW 2010]

Nicholas J. Shaheen, M.D., M.P.H., David E. Fleischer, M.D., Glenn M. Eisen, M.D., M.P.H., Kenneth H. Warren, M.D., Anne F. Peery, M.D., Anthony Infantolino, M.D., Amitabh Chak, M.D., Joseph A. Galanko, Ph.D., Herbert C. Wolfsen, M.D., Gary W. Falk, M.D., V. Raman Muthusamy, M.D., and Charles J. Lightdale, M.D.

ClinicalTrials.gov number NCT00282672. Support from BARRX Medical. Study medication was provided by AstraZeneca. Statistical analysis and data management were supported by a grant (P30 DK034987) from the National Institute of Health.
Long Term Durability of Ablation

Cryotherapy
- Noncontact tissue ablation by liquid nitrogen or refrigerated gas.
- Liquid nitrogen is sprayed on the mucosa.
- Depth of penetration is 2mm.
- Two studies:
  - 30 patients with HGD underwent cryoablation
  - 98 subjects with HGD treated at 10 institutions
- 61 completed treatment
- Similar results to that of RFA.
Squamous Overgrowth

- Residual intestinal metaplasia that dwells beneath the squamous epithelium
- Reported in various treatments:
  - Laser
  - Antireflux surgery
  - PPI
  - EMR
  - PDT
- The malignant potential is undefined but reported in rates of 3.8 to 27.3% of cases.
- Usual management with endoscopic therapy.

Endoscopic Mucosal Resection

- Confined to lesions involved the superficial mucosa and not extending beyond the muscularis mucosa.
- EMR can be used for improved staging or treatment of HGD or early cancers.
- Risk of lymph node metastases in mucosal cancer is less than 5% and 14 to 45% in submucosal cancers.

EMR Techniques

- Inject and cut
- Inject, lift and cut
- Cap-assisted EMR
- EMR with ligation
EMR

- 64 patients with BE
  - 61 with early cancer and 3 with HGD
  - 97% of patients with low risk lesions had complete remission at 12 months
  - 59% of patients with high risk lesions have complete remission after multiple sessions.
  - At 10 month follow up, 2 patients had local recurrence and 1 had metachronous cancer.
  - Another study of 100 pts, recurrent or metachronous CA in 11%.

Ell, GIE, 2007

AMC Experience
(Bergman, J GI Surgery, 2008)

- 44 pts with LGD, HGD & early cancer underwent RFA
- 31 pts had prior EMR for visible abnormalities
  - 88% dysplasia & IM eradication rate
- 23 months follow up
  - 4 strictures - all responded to dilation (median of 3)
  - 3 mucosal lacerations (no tx)
- All AE pts had prior EMR
Euro I Trial
(Bergman, Clin Gastro Hep, 2009)
• First multi-center HGD/early cancer trial
• 24 pts underwent RFA with 23 receiving pre-RFA EMR for visible abnormalities.
• 2 pts had EMR after RFA
• 100% dysplasia eradication rate
• 96% IM eradication rate
• 22 months median follow up
• Adverse events: melena (n=1) & dysphagia (n=1)
Slide 55
Pathology revealed intramucosal carcinoma with clear margins.

Slide 56
Surgery vs. Endoscopic Tx
- Retrospective review of 94 patients
  - 62 Endotherapy
  - 32 Esophagectomy
  - 4 patients (6%) progressed to CA in the endotherapy group after 20 mnth follow up
  - Larger number of minor complications in the surgical group.
  - Similar findings in a 5 year follow up study.
Schembre DB, GIE, 2008
Prasad GA, Gastro, 2007

Slide 57
Combination Therapy
- A total of three studies have compared endoscopic therapy and esophagectomy.
- Endoscopic therapy includes EMR with ablative therapy.
- Five year survival for endoscopic therapy 80% compared with 95% for surgical grp.
- Surgical morbidity greater.
Prasad et al Gastro, 2009
**Role of EUS**

- EUS is more accurate than CT scan to determine the T stage and examining the celiac axis for lymphadenopathy.
- Patients with advanced staged tumors (T3) benefit from preoperative neoadjuvant chemoradiation therapy.
- Preoperative EUS is cost-effective by directing the most appropriate care.

**Esophagectomy**

- Used for the treatment of HGD and cancer.
- Transhiatal (Orringer), transabdominal transthoracic (Ivor-Lewis), Three Stage (McKeown), minimally invasive approaches
- Mortality 2-5%
- Morbidity 12-50%

**Future**

- Identify other risk factors that lead to the development of Barrett’s esophagus.
- Enhance imaging techniques to avoid biopsy.
- Investigate biomarkers to identify high risk patients.
- Long term studies of ablative therapies so that surveillance intervals may be increased or even eliminated.
Endoscopic therapy has promising results in the management of Barrett's esophagus with HGD and IMC. Combination therapy can achieve complete remission in more than 90% of patients. Patients still require intensive endoscopic surveillance.

Treatment of patients with dysplasia should be individualized based on:
- Age
- Co-Morbidities
- Extent of Barrett's metaplasia
- Patient preference