Barrett’s Esophagus & Early Esophageal Cancer

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Barrett’s Updates
- Epidemiology, cancer risk
- Detection and surveillance
- Endoscopic treatment
U.S. Esophageal Adenocarcinoma Rise

Prevalence & Incidence of Barrett’s

- 1.6% of Swedish adult population
- 3.5 million Americans (extrapolated)
- 5.6% of U.S. population (based on a SEER data simulation model)
- 13% of a VA population with GERD had Barrett’s upon screening endoscopy

Ronkainen, Gastroenterology, 2005
Sampliner, Gastroenterology, 2005
Spechler, Dis Esoph, 2010
Westhoff, GI Endoscopy, 2005
Non-Dysplastic BE Progression to Cancer in Several Large 2010/11 Studies Averaged .29% per Year

de Jonge, Gut, 2010
Desai, Gut, 2011
Wani, Clin Gastroenterol Hepatol, 2011
Bhat, J Natl Cancer Inst, 2011

IM Progression to HGD/EAC
(Falk, Sampliner, Sharma et al, CGH, 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

Patients With Nondysplastic Barrett’s Esophagi Have Low Risks for Developing Dysplasia or Esophageal Adenocarcinoma

The article has an accompanying continuing medical education activity on page 321, Learning Objective. In the end note, the author lists all figures, tables, and references of the presentation, including key points and additional information. The material addresses the progression of Barrett’s esophagus to cancer.
CLE/IM Progression to HGD/EAC
(Bhat, JNCI, 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.”

IM Progression Cancer
(Wang, Prasad et al, Am J GI, 2011)

- Population-based study (Olmsted County, MN) from 1976 to 2006
- 355 pts w/ BE of the tubular esophagus (> 1 cm) constituted a surveillance cohort
- IM cancer risk increases in a near-linear fashion indicating that per annum progression rates should be considered cumulatively
LGD Progression to EAC 
(Curvers, Am J Gastro, 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 diagnosed with BE
- 121 pts diagnosed with LGD & had f/u bxs
- 19 pts had a consensus dx of LGD
- LGD pts had a 13.4% annual progression risk for HGD or EAC
- 10.5% LGD pts developed cancer in an average f/u of just over 3 yrs

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></th>
<th>1 Year</th>
<th>5 Year</th>
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<tbody>
<tr>
<td>Non-dysplastic Barrett’s</td>
<td>0.3%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Low Grade Dysplasia (confirmed)</td>
<td>5-10%?</td>
<td>25-50%?</td>
</tr>
<tr>
<td>High Grade Dysplasia</td>
<td>10%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Barrett’s Updates

- Epidemiology, cancer risk
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Endoscopic Surveillance of Barrett’s

- Issues with surveillance
  - Sampling error
  - Pathologic discordance
  - Poor patient compliance
  - Cost-ineffective

- Surveillance does not prevent cancer
  - Over 50% of those who developed HGD or cancer while undergoing surveillance did not have findings of dysplasia (Sharma, Clin Gastro Hep, 2006)

BE Endoscopic Appearance
NBI for Barrett’s

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

Wolfsen et al 2008 Gastroenterology
Endomicroscopy

Probe Confocal Laser-induced Endomicroscopy (pCLE)
Multicenter international trial (5 centers)
Prospective, double blinded trial: WLE, NBI, pCLE
101 patients - 874 locations

Negative Predictive Value of 94% for HGD/EC
**Barrett’s Updates**

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**Endoscopic Therapies**

- APC
- Cryo
- PDT
- EMR
EUS/EMR of Early Cancer

Endoscopic Mucosal Resection
Role of EMR in Barrett’s

- EMR all raised and nodular mucosa (if possible)
  - For Diagnosis of possible early cancer
  - For Staging of submucosal invasion
  - For Therapy via resection
- EMR of flat Barrett’s (selective)
  - Focal flat abnormality (HD, NBI, Confocal)
  - Short segment with known HGD
- Caveat – once you start EMR, must finish it
  - Also may be difficult to EMR after RFA

EMR

Pros
- Obtain a tissue sample with assessment of margins for pathologic diagnosis/staging
- Can treat nodular disease
- EMR and RFA can be an effective combined modality

Cons
- Complications
  - Total Endoscopic Resection:
    - Stricture: 0-86%
    - Perforation: 1-7%
    - Minor Bleeding 9-30%
- Technical Difficulty

References:
Safety and efficacy of endoscopic spray cryotherapy for Barrett’s esophagus with high-grade dysplasia

Nicholas J. Shaheen, MD, MPH, Bruce D. Greenwald, MD, Anne F. Peery, MD, John A. Dunot, MD, Norman S. Nishioka, MD, Herbert C. Wolsen, MD, J. Steven Barsick, MD, Julian A. Abrams, MD, Kenneth K. Wang, MD, Damien Mallat, MD, Mark R. Johnston, MD, Alvin M. Zilass, MD, Jenny O. Smith, MD, James S. Barthel, MD, Charles J. Lighthale, MD

- Multi-center, retrospective review of 98 patients with HGD
- Mean BE length 5.3 cm; 3.4 Tx/pt
- Strictures in 3 pts; 2 pts with chest pain
- 60 completed all planned Cryo (included in analysis)
- 58 (97%) complete eradication of HGD
- 52 (87%) complete eradication of all dysplasia with persistent nondysplastic intestinal metaplasia
- 34 (57%) complete eradication of all intestinal metaplasia
- Subsquamous BE was found in 2 subjects (3%).

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- Multi-center, retrospective review of 79 patients with Esophageal CA
- T1-60, T2-16, and T3/4-3
- Mean tumor length = 4.0 cm (range 1-15 cm).
- 49 completed treatment.
- CR in 31 of 49 (61.2%)
- CR in 18 of 24 (75%) with T-1 cancer
- Follow-up of 10.6 months
- No SAE’s reported
- Benign stricture in 10 (13%) with esophageal narrowing from previous endoscopic resection, radiotherapy, or PDT in 9 of 10

AIM Dysplasia Trial
(Shaheen, NEJM, 2009)
• A RCT of 127 HGD & LGD pts
• 19 US medical centers
• 2:1 randomization of treatment (RFA) v. sham (surveillance)
• All pts received high dose PPIs
• EMR for visible abnormalities
• Identical biopsy protocols
• Central expert path review
• Sham pts crossover after 1 yr
<table>
<thead>
<tr>
<th>Disease Eradication</th>
<th>RFA</th>
<th>Sham</th>
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<tbody>
<tr>
<td>CR-D (HGD)*</td>
<td>81.0%</td>
<td>19.0%</td>
</tr>
<tr>
<td>CR-D (LGD)*</td>
<td>90.5%</td>
<td>22.7%</td>
</tr>
<tr>
<td>CR-IM (HGD/LGD)*</td>
<td>77.4%</td>
<td>2.3%</td>
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*P < 0.001

<table>
<thead>
<tr>
<th>Disease Progression</th>
<th>RFA</th>
<th>Sham</th>
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</thead>
<tbody>
<tr>
<td>All Progression**</td>
<td>3.6%</td>
<td>16.3%</td>
</tr>
<tr>
<td>Cancer Progression**</td>
<td>1.2%</td>
<td>9.3%</td>
</tr>
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</table>

**P < 0.05

Note: These results are drawn from an intention to treat analysis.

Shaheen, NEJM, 2009

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Issues with Surveillance:
“Endoscopic surveillance has become the standard of practice based on the unproven assumption that the practice will reduce deaths from esophageal adenocarcinoma…”

LGD is Difficult to Differentiate 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.”

Value of RFA: “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.”

NDBE Management: “… 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.”

2011 AGA Guidelines
LGD Management: “Endoscopic eradication therapy with RFA should also be a *therapeutic option* for treatment of patients with confirmed LGD in BE.”

HGD Management: “We recommend *endoscopic eradication therapy* with RFA, PDT, or EMR rather than surveillance for treatment of patients with confirmed HGD within BE.”