Barrett’s Esophagus – Who to Treat and How?

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Conflicts of Interest

• Research Funding: Covidien, Olympus America, CSA
• Patent: Abbott Molecular Diagnostics
Questions

• Who should be treated for Barrett’s esophagus?
• What are the available therapeutic tools?
• What are the goals of therapy?
• Should patients be followed post-ablation?

Case 1: Worried mother of 2

• 39 yo WF, presents with concerns of esophageal cancer
• Husband passed away 2 years ago from esophageal adenocarcinoma
• Occasional reflux 1/month
• No risk factors
Case 1: Endoscopy

- Z line as seen at right
- No evidence of esophagitis

Would you biopsy this Z-line for BE?

Barrett’s Esophagus

- Barrett’s esophagus does not impact overall patient survival (Gut 48(3): 304-309, 2001)
- Very few patients are found to actually develop cancer (Gastroenterology 120(7): 1607-1619, 2001)
- Most people who develop Barrett’s esophagus related cancers do not know they have it (New England Journal of Medicine 365(15): 1375-1383)
**BE and Overall Survival: Olmsted County, MN**

- Overall survival at 5 years 82.5% (95% CI: 79,89)
- Median follow up 7.1 years (SD 4.8 years)

Prasad, Wang, Am J Gastroenterol 2009

**Cancer Risk in BE**

- Overall risk of progression without dysplasia:
  - Publication bias: 27 studies
  - 0.5% per year
  - Risk is 1:200 patients
- LOW RISK OF CANCER

Gastroenterology 2000;119:333-8
Largest Population Based Study

- 11,028 pts with BE in Denmark, follow up 5 yrs
  - Year 1: 131 cases of cancer
  - Subsequent yrs: 66 cases
- Incidence 1.2 cases per 1000 person-years (95% CI, 0.9 to 1.5)
- Relative risk was 11.3 (8.8 to 14.4)


Low Grade Dysplasia

- Progression rate in a meta-analysis of 24 studies
- Trend of decreasing cancer in past decade
- Evidence of publication bias (p<0.01) and study heterogeneity

Singh, Gastrointest Endosc 2014;79:897-909
RCT of LGD treatment with RFA

* Very high rate of progression in control group
* All progressors (except 1) could be treated endoscopically

JAMA. 2014;311(12):1209-1217.

LGD: 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
Current Recommendations

• Early Cancer: Intramucosal, T1a
  • No lymphovascular invasion
  • Undifferentiated cancers can be treated (Am J Gastroenterol 2012; 107:850–862)

• High grade dysplasia
• Low grade dysplasia
  • Higher risk: Agreement of multiple pathologists
  • Immunohistochemistry: p53 positive
  • Present on multiple surveillance biopsies

Case 2

• 55 yo WM presents with long history of refractory GERD, endoscopy shows Barrett’s esophagus
• Biopsies obtained from the esophagus demonstrate high grade dysplasia with possible intramucosal cancer
Would you ablate this patient?

Removing the Mucosa

- Endoscopic Mucosal Resection: Snare
- Endoscopic Submucosal Dissection: Knife
Mucosal Resection: EMR-C

Crescent Snare
25 mm Loop
2 mm diameter
165 cm length

<table>
<thead>
<tr>
<th>Length (mm)</th>
<th>Diameter (mm)</th>
<th>Scope Types</th>
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</thead>
<tbody>
<tr>
<td>12</td>
<td>12.9</td>
<td>PQ-140, 160, XQ180, 190</td>
</tr>
<tr>
<td>12</td>
<td>13.9</td>
<td>XQ140, 160</td>
</tr>
<tr>
<td>12</td>
<td>14.9</td>
<td>1T140, 1T160, 1T180</td>
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<tr>
<td>12</td>
<td>19.2</td>
<td>2T160</td>
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</table>

Single Cap and Band EMR
Multi-Band EMR

Endoscopic Submucosal Dissection

- Submucosal injection
- Involves a cutting device
- No suction used
ESD literature on esophageal cancers

- 4 compared (retrospectively) ESD and EMR

<table>
<thead>
<tr>
<th></th>
<th>En bloc resection</th>
<th>Major bleeding</th>
<th>Stricture</th>
<th>Perforation</th>
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</thead>
<tbody>
<tr>
<td>EMR</td>
<td>45% to 83%</td>
<td>1%</td>
<td>up to 9.2%</td>
<td>0 to 7%</td>
</tr>
<tr>
<td>ESD</td>
<td>95% to 100%</td>
<td>0%</td>
<td>up to 17.2%</td>
<td>1.4 to 5.6%</td>
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</tbody>
</table>

Endoscopic Submucosal Dissection vs EMR

- ESD: Removes larger sized specimens than EMR (Gastrointestinal Endoscopy 2009;70:112-20)
- Greater likelihood of en bloc resection for lesions > 1.5 cm (Gastrointestinal Endoscopy 2008;68:1066-72)
- ESD less likely recurrence and higher likelihood of en bloc resection in early gastric cancer meta-analysis (Surgical Endoscopy 2011 25(8): 2666-2677)
  - En bloc resection (OR 8.43; 95% CI 5.20-13.67)
  - Local recurrence (RR 0.13; 95% CI 0.04-0.41)
Thermal Ablation

• Thermal destruction of columnar tissue
• Acid inhibition
• Restored squamous epithelium
Radiofrequency Ablation: Halo360

Complete Response Dysplasia (CR-D) HGD Cohort (n=43)

<table>
<thead>
<tr>
<th></th>
<th>Intention to Treat</th>
<th>Per Protocol</th>
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</thead>
<tbody>
<tr>
<td>RFA</td>
<td>80%</td>
<td>91%</td>
</tr>
<tr>
<td>Sham</td>
<td>11%</td>
<td>12%</td>
</tr>
</tbody>
</table>
Complete Response Intestinal Metaplasia (CR-IM)  
All Patients (n=101)

![Bar chart showing Complete Response Intestinal Metaplasia (CR-IM) for All Patients (n=101). The chart compares Intention to Treat and Per Protocol with RFA and Sham treatments.]

**Intention to Treat**
- 77% for RFA
- 0% for Sham

**Per Protocol**
- 83% for RFA
- 0% for Sham

Stricture Occurrence

- 5 Strictures in 84 patients
  - 5 of 84 patients (6.0%)
  - 5 of 297 cases (1.7%)
- All strictures resolved with mean of 2 dilations
- All patients now complete response for IM (CR-IM)
Histological Progression

- Sham: 7/37 (18.9%)*
- RFA: 3/64 (4.7%)

Cancers
- HGD to CA, Sham: 4/18
  - 2 IMC (EMR+RFA)
  - 2 T1sm (surgery)
- HGD to CA, RFA: 1/25
  - 1 IMC (EMR+RFA)

Kaplan-Meier Ablation Durability Analysis

Duration of Complete Response-Intestinal Metaplasia (CR-IM)

Endoscopy 42(10): 781-789., 2010

ACG Regional Postgraduate Course - Williamsburg, VA
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**Goals of Therapy: Tailor to Patient**

- Complete elimination of intestinal metaplasia
  - Healthy patients who have long life expectancies
- Complete elimination of dysplasia
  - Older patients with co-morbidities
- Control of cancer (elimination of nodules)
  - Older patients with serious co-morbidities but anticipated prolonged survival

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**Cryotherapy HGD**

N=98 with HGD
- 333 treatments
- Complications
  - Strictures 3%
  - Pain 2%
  - No perforations

Intervention: cryotherapy

N=60, completed Rx  
*Gastrointest Endosc* 2010;71:680-5
Cryotherapy Focal Device

Recurrence Rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Number</th>
<th>Recurrence %</th>
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</thead>
<tbody>
<tr>
<td>Pech 2008</td>
<td>337</td>
<td>21.5%</td>
</tr>
<tr>
<td>Baddredine 2010</td>
<td>172</td>
<td>17%</td>
</tr>
<tr>
<td>Shaheen 2010</td>
<td>99</td>
<td>25%</td>
</tr>
<tr>
<td>Gupta 2013</td>
<td>592</td>
<td>16%</td>
</tr>
<tr>
<td>Ginsberg 2013</td>
<td>156</td>
<td>42%</td>
</tr>
</tbody>
</table>
Survival Free of Recurrence of CRIM Patients

Post-Therapy Surveillance

Questions

• Who should be treated for Barrett’s esophagus?
• What are the available therapeutic tools?
• What are the goals of therapy?
• Should patients be followed post-ablation?

• IMC, HGD, LGD selected
• Flat Mucosa: RFA, Cryotherapy, PDT
• Nodules: EMR, ESD
• Depending on patient, CRIM
• Follow-up should be done currently