Evaluation and Treatment of Barrett’s Esophagus

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Goals

• Define patients at risk of Barrett’s esophagus
• Understand the role of chemoprevention
• Select the appropriate therapy for Barrett’s esophagus with dysplasia
• Determine which early staged cancers can be endoscopically managed
Incidence of Esophageal Adenocarcinoma (SEER)

<table>
<thead>
<tr>
<th>Sex</th>
<th>1975-1979</th>
<th>2000-2004</th>
<th>Increase %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.01 (CI = 0.90 to 1.13)</td>
<td>5.69 (CI = 5.47 to 5.91)</td>
<td>463</td>
</tr>
<tr>
<td>Female</td>
<td>0.17 (CI = 0.13 to 0.21)</td>
<td>0.74 (CI = 0.67 to 0.81)</td>
<td>335</td>
</tr>
</tbody>
</table>

Population Attributable Risk for Esophageal Adenocarcinoma

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>Pop. Attributable Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>2</td>
<td>39.7</td>
</tr>
<tr>
<td>BMI (4th quartile)</td>
<td>2.7</td>
<td>21.3</td>
</tr>
<tr>
<td>GERD Frequency</td>
<td>4.9</td>
<td>13.9</td>
</tr>
<tr>
<td>(1/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits and Vegetables</td>
<td>1.4</td>
<td>15.3</td>
</tr>
</tbody>
</table>

Engel et al. (2003) JNCI 95:1404-13
Case

- 49 yo WM, smoke 1 ppd
- Endoscopy two years ago showed erosive esophagitis, no BE found
- Reflux, 2/week
- BMI 40, increased waist hip ratio
- Is a meat eater, doesn’t eat fresh fruits or vegetables
- PMH of lung cancer resected at T1 stage
- Father passed away from esophageal cancer

Endoscopy

Biopsy demonstrated columnar metaplasia with without dysplasia. No goblet cells
Is This Barrett’s Esophagus?

- Yes
- No

Goblet Cells and Barrett’s Length

- Increased length, increased number of endoscopies, increased likelihood of IM (Ann Surg 2001;234:619-26)
  - 1-2 cm segment: 30.5% to 63.6% after 6 endoscopies
  - 2-4 cm segment: 44.8% to 88.9%
- Need 8 biopsies to diagnose IM (Am J Gastroenterol 2007;102:1154-61)
  - 1-4 biopsies: 35%
  - 4-8 biopsies: 68%
Diagnosis of Metaplasia

- **BUT** columnar epithelium can be intestinalized without goblet cells
  - CDX2 (Caudal homeobox)
  - Lgr5 (leucine-rich repeat-containing G protein-coupled receptor 5)
  - Muc2

- Patients without goblet cells can develop dysplasia and esophageal adenocarcinoma

- Do we need to have goblet cells in order to have Barrett’s esophagus?

Non-Goblet Cells Metaplasia

- Non-goblet cell metaplasia with CDX2 develops into IM (Aliment Pharmacol Ther. 2006 Dec;24(11-12):1613-21)

- Non-goblet cell metaplasia has clonal genetic abnormalities (predominantly gains FISH) (Mod Pathol. 2007 Jul;20(7):788-96)

- Cancer risk exists for non-goblet cell metaplasia (Scand J Gastroenterol. 2007 Nov;42(11):1271-4)
Non-Goblet Cell Cancer Risk

What Would You Recommend to the Patient to Decrease his Cancer Risk

• Ablation therapy: RFA
• NSAID: ASA treatment
• PPI therapy
Protective Association of ASA & NSAIDS With Esophageal Cancer: A Systemic Review

Thun
Funkhouser
Farrow
Farrow
Farrow
Coogan
Langman
Combined

Corley DA, et al., Gastroenterology 2003; 124:47

COXIB Barrett’s Trial

• 100 pts
  – LGD and HGD
  – 51 control, 49 celecoxib
  – 200 mg BID

• No difference
  – Number of biopsies with dysplasia
  – Highest degree of dysplasia

Heath, 2007 JNCI 99: 545-547
Neoplastic Progression in Barrett’s Metaplasia

Hillman, MJA 2004; 180: 387–391

El-Serag, AJG 2004, 99 (10), 1877-83
Case

- 51 yo WM with Barrett’s esophagus diagnosed 3 years ago
- PMH significant HTN, DM
  - BMI 34
- Segment is C2M4 without any bumps
- Surveillance biopsies show low grade dysplasia

What Would You Do Next?

- Endoscopy and re-biopsy in 4 quadrants every 2 centimeters throughout the columnar mucosa
- Send to another expert pathologist for interpretation
Review the Pathology

- Elizabeth Montgomery, MD: Johns Hopkins University
- Mary P. Bronner, MD: University of Washington
- John R. Goldblum, MD: Cleveland Clinic
- Joel K. Greenson, MD: University of Michigan
- Marian M. Haber, MD: Hahnemann University
- Laura W. Lamps, MD: University of Arkansas
- Gregory Y. Lauwers, MD: University of Florida
- Audrey J. Lazenby, MD: University of Alabama
- David N. Lewin, MD: Medical University of South Carolina
- Marie E. Robert, MD: Yale University
- Alicia Y. Toledano, ScD: University of Chicago
- Kay Washington, MD, PhD: Vanderbilt University
- John Hart, MD: University of Chicago

- Kappa scores on 250 slides
  - HGD/carcinoma: 0.65
  - LGD: 0.32
  - Indefinite: 0.15
  - Barretts: 0.58

Human Pathology 2001; 32:379-8

Review the Pathology

- Group Diagnosis
  - Low-grade – 4
  - High-grade – 18
  - Intramucosal carcinoma - 2
How Would You Treat the Patient?

- Surveillance every year
- Ablation

Ablation: It Works!
Probability of Being Cost Effective

Hur et al, Gastroenterology 2012;143:567–575
Probability of Being Cost Effective

CRIM is Reached

• What would you do now?
  – Surveillance of neo-junction and visible lesions in esophagus
  – No further surveillance needed
Recurrence Rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Number</th>
<th>Recurrence %</th>
</tr>
</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 2012 (Abstract)</td>
<td>592</td>
<td>16%</td>
</tr>
</tbody>
</table>

Case

- 56 yo WM with iron deficiency anemia
- Colonoscopy negative
- EGD shows
  - C6M8 Barrett’s segment
  - Lesion as shown
What Would You Do?

- Surveillance biopsy with particular attention to the lesion
- Surveillance biopsy and mucosal resection
Diagnosis

- Early adenocarcinoma
  - Margins negative
  - No lymphovascular invasion
  - Moderately differentiated

Endoscopic Techniques
## Endoscopic Techniques

### Risk Modifiers for Potential Metastasis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Increases Metastatic Potential</th>
<th>Decreases Metastatic Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor appearance</td>
<td>Ulcerated</td>
<td>Flat or polypoid</td>
</tr>
<tr>
<td>Tumor size</td>
<td>&gt; 2 cm</td>
<td>&lt; 2 cm</td>
</tr>
<tr>
<td>Depth of invasion</td>
<td>Into submucosal, &gt; 500 um</td>
<td>Intramucosal, &lt; 500 um</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Poorly differentiated</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>Angiolympathic invasion</td>
<td>Presence increases</td>
<td>Absence decreases</td>
</tr>
</tbody>
</table>
Efficacy of EMR and Ablation for T1a Adenocarcinoma

- EMR + Ablation: 42 +2.5 mths
- Follow-up
  - Endoscopic 43 mths
  - Surgery: 64 mths
- N=178
  - Surgery 46
  - Endoscopic 132


Do Early Cancers Possess Metastatic Potential?

- 10 surgically resected early cancers T1a without metastatic spread
- All 10 expressed markers of epithelial mesenchymal transition (Slug, Snail, Twist) as well as CD133 marker of cancer stem cells
- These markers were uniform across the tumor

Meta-Analysis of T1b Cancers

• 7645 patients in 105 articles
• Squamous cell cancers more likely to have metastasis node positive in 45% versus 26%
• SM1 tumors
  – Lymph nodes in 27%
  – Vascular invasion in 46%
  – Lymphatic invasion in 22%


ESD and RFA

• 30 pts with IMC treated with ESD
• Submucosal cancer found in 3
• Histological remission only found in 39%
• Follow-up endoscopy found no evidence of disease in 96% (f/U 17 mths)
• ESD not advantageous over piecemeal EMR
• Wide discrepancy between histology and clinical results

Neuhaus, Endoscopy, 2012
Summary

- Evaluation of Barrett’s esophagus requires a very careful examination for any abnormalities
- Systematic biopsies
- Dysplasia needs review
- Ablation to be considered with the finding of HGD, LGD
- All mucosal lesions should be resected