Barrett Esophagus Associated Dysplasia and Carcinoma

Pathology at therapeutic decision points

Marie Robert, M.D.
Yale University School of Medicine

Clinical Overview: Who is at Risk?

- Barrett found in 0.2-2% of adult population
- Risk of cancer (incidence) 0.5%/year in patients with Barrett Esophagus
- Gastro-duodenal reflux (bile, not just acid)
  - Acid suppression does not eliminate cancer risk
  - Some data suggests PPI's lead to regression of IM
  - Obesity, cigarette smoking, nutrition
- Helicobacter pylori eradication?
  - H. pylori decreases acid secretion

Decision Points in Barrett Esophagus

- First diagnosis of Barrett esophagus
  - Places patient in surveillance category
- First diagnosis of dysplasia in Barrett
  - Impacts interval of surveillance
- Diagnosis of significant neoplasia
  - High grade dysplasia, intramucosal or invasive carcinoma
  - Triggers therapeutic intervention

Case

- A 45 year old male with symptoms suggestive of gastroesophageal reflux disease for several years undergoes upper endoscopy
- The endoscopic examination is normal
- Biopsies are taken from a normal appearing gastroesophageal junction
Diagnosis: Intestinal Metaplasia at the Gastroesophageal Junction

Endoscopically normal GEJ

Diagnosis of Barrett Esophagus: Minimal Criteria

- Endoscopically visible extension of columnar mucosa upwards from the GE junction that on biopsy reveals goblet cells

- No length restrictions
  - Short and ultrashort segment Barrett

- No requirement of specific number of goblet cells
  - Each center has own bias
  - Sampling issues too large
Short segment Barrett’s

Barrett, Minimal Criteria

- Remember, cancer risk while in surveillance low
  - Neg for dysplasia = 2%
  - Low grade dysplasia = 7%
  - High grade dysplasia = 22%

- Majority of patients with Barrett related cancer present with malignancy

- Don’t increase the surveillance pool unnecessarily!

Connor, MJ, Sharma P. Tech Gastrointest Endosc. 2003;5:89-93

Methylene Blue Chromoendoscopy

Patient with suspected short-segment Barrett’s Esophagus
Special Issues in GEJ Biopsies

- Carditis
  - Chronic inflammation gives rise to expected reactive changes in gastric surface epithelial cells
- Tall Blue cells
- Multilayered epithelium
Cardia intestinal metaplasia

- Is it really cardia?
  - Identifying the LES
  - Hiatal hernia
- If not sure…repeat EGD in 1 year and be clear where the bxes are from (distal esophagus or cardia)
- Bx the rest of stomach; is there diffuse IM?

Goblet cells in the Endoscopically Normal GEJ

- Meaning of intestinal metaplasia in the GEJ or cardia controversial
  - Clinical significance given to difference in location of a few millimeters
  - Balance with fact that incidence of GEJ carcinoma has risen 5-6 fold in Western Countries
  - Barrett and GEJ cancer have more similarities than differences
- CK7 and CK20 stains, not reliable to distinguish cardia IM from esophageal IM

How to Write Report

- Squamocolumnar junctional mucosa (or squamous and columnar or gastric cardia/fundic type mucosa) with intestinal metaplasia (see note)
- Must comment on dysplasia!
- Don’t call it Barrett, but in absence of H. pylori, may have same significance
- Worth a conversation with clinicians to understand their take on issue
Decision Points in Barrett Esophagus

• First diagnosis of Barrett esophagus
  – Places patient in surveillance category
• First diagnosis of dysplasia in Barrett
  – Impacts interval of surveillance
• Diagnosis of significant neoplasia
  – High grade dysplasia, intramucosal or invasive carcinoma
  – Triggers therapeutic intervention

Case

• A 55 year old man carries a diagnosis of short segment Barrett esophagus
• Within the area of endoscopically visible Barrett epithelium, an area of nodularity is noted.
• Biopsies are taken from the nodule and the surrounding flat mucosa
Diagnosis: Intramucosal Carcinoma Arising in the Setting of Barrett Esophagus

Surveillance Guidelines in Barrett
Practice Parameters Committee, ACG, 2002

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Documentation</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Two EGD’s with biopsy</td>
<td>3 years (?5 years)</td>
</tr>
<tr>
<td>Indefinite or Low Grade</td>
<td>Highest grade on repeat</td>
<td>1 year until no dysplasia</td>
</tr>
<tr>
<td>High Grade</td>
<td>Repeat EGD to rule out cancer, expert pathologist confirmation</td>
<td>One focus- every 3 months</td>
</tr>
<tr>
<td>High Grade</td>
<td>Multifocal intervention</td>
<td></td>
</tr>
<tr>
<td>High Grade</td>
<td>Mucosal irregularity- EMR</td>
<td></td>
</tr>
</tbody>
</table>
Grading Criteria
Reid et al, Human Pathology, 19:166-178, 1988
Montgomery et al, Human Pathology, 32:368-378, 2001

- Dysplasia is graded on degree of cytologic and architectural atypia
  - Cytology = nucleus/cytoplasm (high mag)
  - Architecture = relation between glands and lamina propria (low mag)
- Surface changes vs deep gland changes
  - Presence or absence of "maturation"
- Background inflammation or ulceration
High Grade Dysplasia

- Architecture - mildly to markedly distorted
  - Crowding, loss of lamina propria, focal cribriform change
- Surface maturation - absent
- Cytology
  - Markedly enlarged nuclei at surface with frequent bizarre nuclear forms, atypical mitotic figures, loss of nuclear polarity, irregular nucleoli
- Inflammation minimal

High Grade Dysplasia: Special Concerns

- Carcinoma in situ = high end of high grade
  - Not useful term in Barrett’s esophagus
- Better to:
  - Quantify amount of high grade dysplasia present in biopsy material
  - State degree of concern for coexisting invasive carcinoma
- Be aware - distinguishing high grade from intramucosal impossible in some cases
High Grade Dysplasia

Diagnosis must be confirmed by a second experienced pathologist prior to definitive therapy.

Beyond High Grade

- Interobserver studies show excellent agreement for high grade dysplasia
  - Reid et al; Montgomery et al.
- Until recently, no need to distinguish intramucosal carcinoma (IMCA)
- Recent interobserver studies show fair to poor agreement on HG vs IMCA vs CA

Intramucosal Carcinoma

- Distinction from HG difficult
  - Architecture is most important feature
- Defined as invasion into lamina propria not beyond the muscularis mucosa; desmoplasia minimal
- Syncytial growth, back to back microglands, small clusters or single cells, dilated glands with necrosis
- Impossible to distinguish IMCA from more deeply invasive carcinoma on biopsy
- Correlation with endoscopic findings and EUS crucial
How to Write Report

Report dysplasia **intelligently**
- Important to say whether focal or diffuse
- Especially high grade dysplasia
  - One cytologic focus not same as diffuse HG!

- Have to know if random biopsy or biopsy of nodule, plaque or irregular area (likely intramucosal carcinoma)
  - Most endoscopists know & report appearance
- Compare to prior biopsies

**Intramucosal carcinoma in a background of intestinal metaplasia (Barrett Esophagus), see note**

*Note: A more deeply invasive lesion cannot be excluded. Recommend endoscopic ultrasound and additional biopsies to further characterize the lesion.*

**Question: Can p53 stains help grade dysplasia**

**Answer:**
- Not reliably
  - Ramel, 1992 5% in non-dysplastic Barrett’s; 15% in indef/LG; 45% HG; 53% CA
- If negative, does not exclude dysplasia
- Institutional preferences
Endoscopic Diagnosis?

- Chromoendoscopy
- Confocal endoscopy
- Optical Coherence Tomography
- Two photon endoscopy - non-linear infrared optics
- Still in testing stages
  - Subject to same operator dependent skills and interobserver variability
  - Needs to be validated by pathology correlation

Esophagus

Barrett’s with NBI

Barrett’s with white light

Duodenum

A

B

E

F