1. Review pathology and pathophysiology of eosinophilic esophagitis
2. Review pathology of reflux esophagitis
3. Compare and contrast pathology of eosinophilic esophagitis and reflux
4. Review pathology of infectious and pill induced esophagitis
Eosinophilic Esophagitis from A to Z-Line
Jed K. Greenem, M.D.
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University of Michigan Medical School
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The objectives of this presentation are:
- Review the endoscopic and histologic features of reflux esophagitis and compare and contrast them to other forms of eosinophilic esophagitis, primary eosinophilic esophagitis, CMV esophagitis, herpes esophagitis, and pill-induced esophagitis.
- In the past, the differential diagnosis of eosinophilic esophagitis has been challenging, but recent advances in molecular techniques have made it easier to identify the causative agents of eosinophilic esophagitis.
- The diagnostic challenge of eosinophilic esophagitis is to determine whether the eosinophils are secondary to a primary condition or if they are the result of a primary eosinophilic esophagitis.

Histopathology:
- The histologic diagnosis of HSV esophagitis depends upon the identification of viral inclusions within the squamous epithelium. HSV inclusions are typically large, oval, and have a dense nuclear core with a clear halo.
- The histologic diagnosis of CMV esophagitis is based on the identification of intranuclear and/or intracytoplasmic inclusions in infected cells. CMV inclusions are typically large, round, and have a dense nuclear core with a clear halo.

Parasites:
- The most common parasite infection of the esophagus is Chagas' disease. The infecting organisms are Trypanosoma cruzi, which is transmitted to humans through the bite of triatomid bugs.
- Other infectious agents:
  - Absidia
  - Cryptosporidium
  - Pneumocystis carinii
  - MAI

Bacteria:
- While bacteria may be seen in eosinophilic esophagitis for a number of reasons, primary bacterial esophagitis is uncommon. Bacteria may be secondary to CMV or HSV infection, or they may be due to obstruction from Candida or other fungi.

Cytomegalovirus (CMV):
- CMV infection can be diagnosed via identification of viral inclusions in infected cells. The inclusions are typically large, oval, and have a dense nuclear core with a clear halo.
- The histologic diagnosis of CMV esophagitis is based on the identification of intranuclear and/or intracytoplasmic inclusions in infected cells. CMV inclusions are typically large, round, and have a dense nuclear core with a clear halo.

Eosinophilic Esophagitis:
- Eosinophilic esophagitis (EE) is an increasingly recognized disease entity typified by dysphagia in patients who often have atopy. EE has been described clinically as "sabras of the esophagus." EE is a condition characterized by the presence of eosinophils in the esophageal tissue, often in large numbers, leading to inflammation and obstruction.

Candidal Esophagitis:
- Several species of Candida are part of the normal flora of the esophagus, including Candida albicans, C. dubliniensis, and C. glabrata. These species are often seen in patients with Candida esophagitis.
- Histologically, Candida esophagitis is characterized by the presence of pseudohyphae, which are often found in patients with Candida esophagitis. Pseudohyphae are often seen in patients with Candida esophagitis, and may be seen in patients with other forms of esophagitis.

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The Red Goose Blues

I went to see the doctor cause I had some heartburn.
He said I was suffering from a bad case of GERD.
I’m hungry and I’m sober and I’m climbing the wall
He said the squamous mucosa that lines my goose
Its all inflamed from too much gastric juice.
My esophageal sphincter doesn't seem to function,
I've got erythema above my GE junction.

No more chocolate and no more alcohol.
I'm hungry and I'm sober and I'm climbing the wall.

I've had enough of this pain in my neck.
I can't stand the taste of this antacid deck.
Reflux esophagitis running around my brain.
This stuff's enough to make you go insane.

The pain in my throat makes me crazy as a loon.
If I don't get relief I won't finish this tune.
Payin all this money to a bunch of rich quacks.
If they don't get me better I'll have em all whacked.

My goose is red so now I have the blues.
Better figure out what's wrong with me before I sue.

References:
**Esophagitis from A to Z-Line**

Joel K. Greenson, M.D.
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**Esophagitis**

- Reflux
  - Acid or Alkaline
- Eosinophilic
- Iatrogenic
  - Pill induced or NG tube
- Infectious

**Reflux Disease**

Clinical: Heartburn
Endoscopic: Erythema, red streaks, ulcers
Histologic: Squamous hyperplasia, inflammation (eos, pmns)
Physiologic: 24-hour pH monitor

**Reflux Esophagitis**

- Basal Cell Hyperplasia
- Elongation of the vascular papillae
- Intraepithelial eos/polys
- Balloon cells
- Vascular lakes
Is it important to DX Reflux?

- Pediatric cases
  - A positive biopsy could lead to a fundoplication
- Differentiate from eosinophilic esophagitis
- Differentiate from infection (location is key)
- Rule out Barretts

Causes of Intra-epithelial Eosinophils

- Reflux (either acid or alkaline)
- Eosinophilic Gastroenteritis (EG)
- Eosinophilic Esophagitis (EoE)
- Drug/pill induced esophagitis
- Infections
**Eosinophilic Esophagitis**

- Male patients with history of allergy/atopy (M:F = 2-4:1)
- Chronic dysphagia, often since childhood
  - Food impaction common
- Endoscopy shows multiple rings (felinization) furrows and or strictures. May also have pinpoint white exudates
- May have elevated eos in peripheral blood

**Similar to reflux but with large numbers of eos**

- Typically >20 or 25 eos/HPF
  - Often between 50-100, but we don't really know the lower threshold for diagnosis
- Superficial aggregates or microabscesses of eos
- Eos may be patchy, both proximal and distal
>20 Eosinophils/HPF

<table>
<thead>
<tr>
<th>Proportion (Eo&gt; 20hpf)</th>
<th>EoE</th>
<th>EG</th>
<th>GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>58/63</td>
<td>5/7</td>
<td>5/116</td>
</tr>
<tr>
<td>Pediatric patients</td>
<td>18/20</td>
<td>4/6</td>
<td>1/32</td>
</tr>
<tr>
<td>Adult patients</td>
<td>40/43</td>
<td>1/1</td>
<td>4/84</td>
</tr>
</tbody>
</table>

**Basal Cell Hyperplasia**

- <20%
- 20-33%
- 33-40%
- 40-50%
- >50%

- **EE**
- **GERD**

**20-33%**

**>50%**
Pill-induced Esophageal Injury

- Doxycycline
- Emepromium Bromide
- KCL
- Quinidine - forms mass-like lesion
- Fe++ Sulphate
- NSAIDs
- Alendronate

Infectious Esophagitis

- Immunocompromised Host
  - Steroids, Chemo/Rad therapy, AIDS, Transplant patients
- Endoscopic Appearance
- Location
  - Often more proximal than reflux

Candidal Esophagitis

- Normal Flora, ubiquitous agent
- May gain selective advantage after antibiotics or in immunocompromised
- Acute presentation of odynophagia/dysphagia
- Endoscopic appearance of white - yellow plaques - “cottage cheese”
**Candidal Esophagitis**

**Histopathology**
- Clumps of necrotic squamous debris
- Neutrophils in surface epithelium
  - Sometimes large aggregates of lymphocytes
- Pseudohyphae grow perpendicular to axis of superficial squamous cells
- PAS or GMS stains help identify organism

**Herpes Esophagitis**

Acute presentation of odynophagia/dysphagia, may have GI bleeding
- Endoscopic appearance of grouped vesicles, erosions, or ulcers - depending on stage
- Located in mid to lower 1/3 of esophagus

**Herpes Esophagitis**

**Histopathology**
- Viral inclusions in squamous epithelium
  - Cowdry A and B inclusions
- Multinucleated cells with smudgy nuclear inclusions
- Aggregates of macrophages in exudate
CMV Esophagitis

- Reactivation in immunocompromised hosts
  - AIDS and Transplant patients at high risk
- Accompanied by systemic infection
  - unlike HSV
- Clinical presentation identical to HSV
- Single distal ulcer most common endoscopic appearance
CMV Esophagitis Histopathology

- Nuclear and cytoplasmic inclusions present in endothelial cells, macrophages, smooth muscle / stromal cells - not present in squamous cells
- Nuclear inclusion is classically Cowdry type A
- Cytoplasm of cell may show granular inclusions, but these form after nuclear inclusions and may not be present in small biopsy specimens
**HIV Associated Esophagitis**

- Giant esophageal ulcers for which no pathogen can be found
  - Deep ulcers in mid or distal esophagus, often greater than 1 cm in diameter
  - HIV RNA present by in-situ studies
  - Treatment with steroids is helpful, but patients often relapse after steroids are withdrawn

**Immunocompromised Pt**
Gastroesophageal Junction Pathology:
Diagnostic and Controversial Issues
Robert D. Odze, MD, FRCPC

BULLET POINTS

• The gastric cardia is the area of mucosa located distal to the GEJ (proximal aspect of gastric folds), and proximal to the portion of stomach composed entirely of oxyntic mucosa. It varies in length between individuals, and is most often composed of either pure mucous glands or a mixture of mucous glands and oxyntic glands.

• Most studies suggest that the cardia is congenital in origin, but that columnar metaplasia of squamous mucosa results in an apparent extension of the “cardia” into the distal esophagus.

• Etiology of inflammation and metaplasia in the GEJ region is most often due to GERD or H. Pylori infection. However, the pathogenesis and risk of neoplasia in these two conditions are different. Pathologists should try to separate these disorders using all available clinical, radiologic and pathologic information, whenever possible.

• Multilayered epithelium is a precursor to Barrett’s esophagus and represents a histologic marker of GERD and columnar metaplasia of the distal esophagus.
The gastroesophageal junction (GEJ) is a poorly defined anatomic area that represents the junction between the distal esophagus and the proximal stomach (cardia). This is an area that is commonly exposed to the injurious effects of gastroesophageal reflux disease (GERD) and *H. pylori* infection. There are two major pathologic disorders affecting the GEJ: Barrett’s esophagus and gastric carditis. Both of these diseases may result in chronic inflammation and the subsequent development of intestinal metaplasia (IM), which increases the risk of developing esophageal adenocarcinoma. Over several decades, there has been a dramatic rise in the incidence of adenocarcinoma of the GEJ region, which is presumed to be related to GERD. This is, in fact, related to problems in evaluating anatomic parameters in the GEJ, undiagnosed manifestations of endoscopic and pathologic methods, and inconsistent use of definitions and terminology used to define and diagnose the anatomic and pathologic anatomy of this region. For instance, many studies have failed to standardize endoscopic evaluation, or image ranges of biopsies, or use different definitions of IM. This may explain the wide ranges of reported incidence of IM, the types of biopsies used, the use of different endoscopic and pathologic methods of evaluation, and the use of different axes in determination of IM. In addition, the use of endoscopic biopsy in the evaluation of IM has been shown to provide a high yield of IM, and a low degree of diagnostic uncertainty, as compared to other diagnostic methods for IM.

**Inflammatory Changes in the GEJ Region**

Inflammatory changes in the GEJ region may be caused by GERD, *H. pylori* infection, or other, as yet unidentified, etiologic factors. IM in the GEJ may be caused by GERD, *H. pylori* infection, or other, as yet unidentified, etiologic factors. The type and pattern of IM at the GEJ may explain the association between the finding of IM in biopsies of the GEJ region and male gender, white race, and higher patient age, features representative of a GERD clinical profile. There is also evidence to suggest that the length of mucosa composed of either pure mucous glands, or mixed mucous/oxyntic glands, increases with age, and is presumed to be related to ongoing "physiologic" GERD. In fact, the increase in length of mucosa composed of either pure mucous glands, or mixed mucous/oxyntic glands, may be caused by GERD, and is presumed to be related to ongoing "physiologic" GERD.

**Gastroesophageal Reflux Disease and *H. pylori* Infection**

Gastroesophageal reflux disease and *H. pylori* infection are the major etiologic factors in the development of IM in the GEJ region. In adult individuals, both these etiologic agents may, in fact, act synergistically to cause inflammation 

**Pathologic Features**

Pathologic features of inflammation in the GEJ region are similar to those observed in the esophagus. A dense infiltrate of inflammatory cells is a common feature of inflammation in the GEJ region. Inflammation in the GEJ region may be caused by GERD, *H. pylori* infection, or other, as yet unidentified, etiologic factors. The type and pattern of IM at the GEJ may explain the association between the finding of IM in biopsies of the GEJ region and male gender, white race, and higher patient age, features representative of a GERD clinical profile.

**Intestinal Metaplasia of the GEJ**

**Prevalence**

Intestinal metaplasia of the GEJ is a common finding in the GEJ region. In fact, the prevalence of intestinal metaplasia in the GEJ region is higher than in the esophagus. However, the clinical significance of intestinal metaplasia in the GEJ region is not well understood. Some studies have shown a higher prevalence of intestinal metaplasia in the GEJ region than in the esophagus. However, the clinical significance of intestinal metaplasia in the GEJ region is not well understood. Some studies have shown a higher prevalence of intestinal metaplasia in the GEJ region than in the esophagus. However, the clinical significance of intestinal metaplasia in the GEJ region is not well understood.

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epithelium in the esophagus and/or the subepithelium mesenchyme of the esophagus. Interestingly, recent studies suggest that metaplastic and dysplastic epithelium in the stomach may derive from bone marrow cells, but this theory has never been investigated in the esophagus. Nevertheless, based on a series of experiments by Yilmaz et al and Li et al, it is now firmly believed that metaplastic epithelium in the esophagus is derived from cells that are, in fact, intrinsic to the esophagus rather than the stomach. There is also some evidence to suggest that esophageal muscular ducts harbor stem cells that can differentiate into columnar epithelium.

Some authors suggest that the squamous to columnar cell transition in the distal esophagus occurs via an intermittent, or transitional phase prior to metaplasia. In 1995, Shields et al proposed the presence of a distinctive type of multilayered epithelium (IME) that shows morphologic and cytogenetic characteristics of both squamous and columnar epithelium. These investigators hypothesized that acid-induced alteration of squamous epithelium exposes an as yet unidentified stem cell, which upon receiving an adequate stimulus, is destined to differentiate toward a columnar phenotype after passing through an immature IMF phase. Multilayered epithelium is a biologically active epithelium that is phenotypically similar to fully developed BE. This epithelium has been shown by Glickman et al to contain a high capacity for cell proliferation and differentiation. It has also been shown to be highly associated with BE in a prospective biopsy study by Shields et al. Multilayered epithelium was also recently identified by Dicks et al in a tissue study of IM with Barrett's metaplasia and ulcers where IME was 5% (3 of 60) of the total epithelial thickness of the Barrett's esophagus. These patients also had a hiatal hernia. Therefore, regardless of the presence of IM in the distal esophagus, changes in the IME region in a biopsy study by Wachowicz et al. In their study, 50% of patients with GERD with IM had IME which was 4.2% of the total epithelial thickness. Conversely, the presence of IME in the distal esophagus may derive from bone marrow cells, but this theory has never been investigated in the esophagus.

In the stomach, the factors responsible for the conversion of metaplastic columnar epithelium to normal squamous epithelium remain unknown. In one study by Sharma et al, the dysplasia risk was shown to be greater in patients with short-segment BE versus those with IM of the gastric cardia only. In that study, the prevalence of dysplasia in patients with short-segment BE versus those with BE was 11.5% versus 1.3%, with an incidence of 4.5% and 1.3%, respectively. In another study by the same lead author, incidence of dysplasia in patients with short-segment BE was 5.7% per year. However, in both these studies, the risk of neoplasia was not defined specifically for patients with either shorter BE or for those columnar epithelium cells in the distal esophagus. The presence of Barrett's metaplasia in the distal esophagus (i.e. short-segment BE) probably has a higher likelihood of progression to neoplasia compared to patients with IM of the more proximal esophagus related to reflux infection. Clearly, this issue requires further investigation.

### Differential Diagnosis of H. pylori in BE/GIS

As noted above, it is important to distinguish between metaplastic columnar epithelium from columnar metaplasia of the distal esophagus, gastric fundus, and duodenal papilla. The presence of an active esophagitis in the squamous epithelium of the esophagus, combined with the finding of a normal antrum or corpus is strong evidence in favor of GERD as the cause of “GEJitis”. Conversely, the presence of active reflux in the esophagus and/or the subepithelium mesenchyme of the esophagus may be derived from bone marrow cells, but this theory has never been investigated in the esophagus. Nevertheless, based on a series of experiments by Yilmaz et al and Li et al, it is now firmly believed that metaplastic epithelium in the esophagus is derived from cells that are, in fact, intrinsic to the esophagus rather than the stomach. There is also some evidence to suggest that esophageal muscular ducts harbor stem cells that can differentiate into columnar epithelium. In contrast, IM that develops in the true gastric cardiac region is a distinct entity from columnar epithelium related to GERD, or BE. Unfortunately, the low sensitivity of these stains regardless of the site of origin. Some have advocated the use of Alcian blue to distinguish distended nongoblet columnar cells in the distal esophagus or from the proximal cardia from metaplastic columnar epithelium in the distal esophagus (i.e. ultrashort or short-segment BE).

H. pylori infection is usually composed of a mixture of incomplete and complete-type IM. This epithelium has been shown by Glickman et al to contain a high capacity for cell proliferation and differentiation. It has also been shown to be highly associated with BE in a prospective biopsy study by Shields et al. Multilayered epithelium was also recently identified by Dicks et al in a tissue study of IM with Barrett's metaplasia and ulcers where IME was 5% (3 of 60) of the total epithelial thickness of the Barrett's esophagus. These patients also had a hiatal hernia. Therefore, regardless of the presence of IM in the distal esophagus, changes in the IME region in a biopsy study by Wachowicz et al. In their study, 50% of patients with GERD with IM had IME which was 4.2% of the total epithelial thickness. Conversely, the presence of IME in the distal esophagus may derive from bone marrow cells, but this theory has never been investigated in the esophagus.

### References


### Summary of Studies Designed to Evaluate Cardia Mucosa

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Specimen (N)</th>
<th>Relation Gastric Fields</th>
<th>Population</th>
<th>Mucous Glands</th>
<th>Mixed Glands</th>
<th>Oxyntic Glands</th>
<th>Mean Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glickman Biopsies</td>
<td>Below GEJ (N=74)</td>
<td>Below GEJ</td>
<td>0.1 – 18 yr (median:13 yr)</td>
<td>81%</td>
<td>19%</td>
<td>0%</td>
<td>&lt;1.0 mm</td>
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<tr>
<td>Kilgore</td>
<td>Autopsy Below GEJ</td>
<td>16 days-18 yr (mean: 6.3 yr)</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>1.0 mm</td>
<td></td>
</tr>
<tr>
<td>Deslaur</td>
<td>Autopsy Below SCJ</td>
<td>Below SCJ</td>
<td>1day-18 yr (mean:2.2 yr)</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Park</td>
<td>Autopsy (N=30)</td>
<td>Below SCJ</td>
<td>Postnatal, 10 days-15 yr</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>&lt;1.0 mm</td>
</tr>
<tr>
<td>Meranese Biopsies</td>
<td>Below SCJ (N=100)</td>
<td>Below SCJ</td>
<td>21-87 yr (mean:50 yrs)</td>
<td>62%</td>
<td>38%</td>
<td>0%</td>
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<tr>
<td>Sarbia Resection</td>
<td>Below SCJ (N=36)</td>
<td>Below SCJ</td>
<td>Adults (56%) Entire</td>
<td>61%</td>
<td>0%</td>
<td>39%</td>
<td>Mucous glands (1-15 mm) Mixed mucous/glands (1-24 mm)</td>
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<tr>
<td>Chandrasoma</td>
<td>Autopsy (N=9)</td>
<td>Below SCJ</td>
<td>Retrospective; mainly adults</td>
<td>26%</td>
<td>44%</td>
<td>30%</td>
<td>-</td>
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<tr>
<td>Zhou</td>
<td>Autopsy (N=77)</td>
<td>Below SCJ</td>
<td>Postnatal (15-39 wk)</td>
<td>5%</td>
<td>55%</td>
<td>35%</td>
<td>-</td>
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<tr>
<td>Liu</td>
<td>Autopsy (N=198)</td>
<td>Below SCJ</td>
<td>Postnatal (14 wk – 17 yr)</td>
<td>48%</td>
<td>40%</td>
<td>6%</td>
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</tbody>
</table>

### Barrett’s versus Carditis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Ultrashort BE</th>
<th>Gastric Carditis</th>
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<tbody>
<tr>
<td>Clinical:</td>
<td>M&gt;F, older</td>
<td>M=F, younger</td>
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<tr>
<td>Etiology:</td>
<td>GERD</td>
<td>H. Pylori, other</td>
</tr>
<tr>
<td>Pathogenesis:</td>
<td>Squamous→columnar</td>
<td>Columnar→columnar</td>
</tr>
<tr>
<td>Cancer risk:</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Treatment:</td>
<td>Acid suppression, Surgery</td>
<td>Antibiotics, Surveillance</td>
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</table>

### Prevalence of SSBE and IM at the Cardia in Endoscopic Series

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>SSBE</th>
<th>IM-Cardia</th>
<th>IM-GEJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specchler</td>
<td>142</td>
<td>12%</td>
<td>6%</td>
<td>-</td>
</tr>
<tr>
<td>Cameron</td>
<td>80</td>
<td>13%</td>
<td>8%</td>
<td>-</td>
</tr>
<tr>
<td>Johnston</td>
<td>172</td>
<td>9%</td>
<td>7%</td>
<td>-</td>
</tr>
<tr>
<td>Cameron</td>
<td>200</td>
<td>9%</td>
<td>14%</td>
<td>-</td>
</tr>
<tr>
<td>Chalasani</td>
<td>87</td>
<td>8%</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td>Hirota</td>
<td>104</td>
<td>8%</td>
<td>23%</td>
<td>-</td>
</tr>
<tr>
<td>Morales</td>
<td>833</td>
<td>6%</td>
<td>6%</td>
<td>-</td>
</tr>
<tr>
<td>Nandurkar</td>
<td>158</td>
<td>-</td>
<td>30%</td>
<td>-</td>
</tr>
<tr>
<td>Trudgill</td>
<td>120</td>
<td>-</td>
<td>18%</td>
<td>-</td>
</tr>
</tbody>
</table>

### Dysplasia and/or Cancer in BE or Carditis with IM

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>LSBE</th>
<th>SSBE</th>
<th>GEJ (cardia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirota1 (1999) (Prevalence)</td>
<td>110</td>
<td>31%</td>
<td>10%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Sharma2 (2000) (Prevalence) (Incidence)</td>
<td>253</td>
<td>-</td>
<td>11.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Sharma2 (1997) (Incidence)</td>
<td>59</td>
<td>-</td>
<td>5.7%</td>
<td>-</td>
</tr>
<tr>
<td>Morales2 (2000) (Incidence)</td>
<td>28</td>
<td>-</td>
<td>-</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

1Dysplasia or cancer
2Dysplasia only

### Pathogenesis of Intestinal Metaplasia

**Esophagus (squamous → columnar transition):**
GERD → esophagitis → ulceration → columnar metaplasia → chronic inflammation → Int. metaplasia → dysplasia → carcinoma

**Stomach (columnar → columnar transition):**
H. Pylori → gastritis → Int. metaplasia → dysplasia → carcinoma
**BE Definition Unclear**
Non-Goblet Cells are “Intestinalized”

<table>
<thead>
<tr>
<th>Type of Cell</th>
<th>Colonic-type Mucin</th>
<th>CDX2</th>
<th>HepPar</th>
<th>Villin</th>
<th>DAS-1</th>
<th>LOH</th>
<th>P16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goblet cells</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>80%</td>
</tr>
<tr>
<td>Non-Goblet cells</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>20%</td>
</tr>
<tr>
<td>Multilayered Epithelium</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

**Pathogenesis of Barrett’s Esophagus**

**Esophageal Metaplasia vs. Gastric Carditis**

**Clinical Features**

<table>
<thead>
<tr>
<th>Clinical Profile</th>
<th>Metaplasia</th>
<th>Carditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiatus hernia</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>GERD clinical profile</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Heartburn</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>White/males</td>
<td>+ +</td>
<td>+/-</td>
</tr>
<tr>
<td>Young age</td>
<td>+ +</td>
<td>+ +/-</td>
</tr>
<tr>
<td>Alcohol</td>
<td>+ +</td>
<td>+ +/-</td>
</tr>
<tr>
<td>Tobacco</td>
<td>+ +</td>
<td>+ +/-</td>
</tr>
<tr>
<td>Irregular Z line or tongues</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

**Pathologic Features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Metaplasia</th>
<th>Carditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous re-epithelialization</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hybrid glands</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Esophageal glands/ducts</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Multilayered epithelium</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Marked atrophy/disarray</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Diffuse incomplete IM</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Distal Gastritis</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Neutrophils/lymphocytes/plasma</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>H. Pylori</td>
<td>+/-</td>
<td>+/-</td>
</tr>
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</table>

**Barrett’s CK 7/20 Staining**

<table>
<thead>
<tr>
<th>Author</th>
<th>LSBE</th>
<th>SSBE</th>
<th>USBE</th>
<th>Cardia</th>
<th>Fundus</th>
<th>Antrum</th>
<th>Location of Intestinal Metaplasia</th>
<th>% Barrett’s Pattern</th>
<th>Prospective</th>
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</thead>
<tbody>
<tr>
<td>Schilling (2005)*</td>
<td>17%</td>
<td>30%</td>
<td>-</td>
<td>0%</td>
<td>-</td>
<td>5%</td>
<td>LSBE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glickman (2001)*</td>
<td>91%</td>
<td>98%</td>
<td>-</td>
<td>90%</td>
<td>-</td>
<td>14%</td>
<td>SSBE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>El-Zimany (2001)</td>
<td>39%</td>
<td>-</td>
<td>-</td>
<td>35%</td>
<td>4%</td>
<td>24%</td>
<td>USBE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waller (2001)</td>
<td>88-100%</td>
<td>75%</td>
<td>21%</td>
<td>16.7%</td>
<td>-</td>
<td>-</td>
<td>Cardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ornato (1999)</td>
<td>94-100%</td>
<td>75%</td>
<td>21%</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
<td>% Barrett’s Pattern</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CK 7/20 Immunostaining Limitations**

1. Results depend on site of biopsy (not etiology)
2. Interobserver variability in interpretation
3. Needs standardized technical/diagnostic criteria
4. Requires sufficient amount of IM and proper orientation (40-60% exclusion rate)
GEJ Pathology: Sign-Out Strategy

1. Type of Epithelium: Columnar or Squamocolumnar Mucosa (mucous, mixed, oxyntic)

2. Intestinal Metaplasia: No Yes

3. Pathologic Features of Columnar Metaplasia:

4. Diagnosis:
   - "Columnar metaplasia of Distal Esophagus" Needs Endoscopic correlation
   - "Barrett’s Esophagus" Needs Endoscopic correlation
Bullet Points:
- A huge number of studies have examined potential markers of neoplastic risk in Barrett’s esophagus patients, but only a few markers appear to have potential utility in this regard.
- The utility of DNA ploidy studies, proliferation markers, p53 abnormalities and p16 abnormalities in the neoplastic risk assessment of Barrett’s esophagus will be discussed.
Barrett's esophagus is an acquired metabolic change that occurs in the distal esophagus secondary to chronic gerd. When the normal squamous epithelium is replaced by a columnar epithelium containing a mixture of cell types and architectural patterns resembling both gastric and intestinal mucosa. The three major types of epithelium include (a) a fundic type containing parietal cells and chief cells, (b) a gastric type containing mucus-secreting columnar cells of the cardiac type, and (c) a distinctive specialized intestinal type as indicated by the presence of goblet cells. It is this latter type of specialized columnar epithelium that defines Barrett's esophagus.

Estimates of the prevalence of Barrett's esophagus suggest that this disorder may occur in as many as 1% of the population. In the general population, the prevalence increases with age, and increases in frequency among older individuals so that by the age of 60 it may occur in up to 10% of people. The exact incidence is unknown as the condition affects the lining of major motor plexus, and it remains unclear as to why some patients with reflux do not develop Barrett's esophagus. For example, in Japan where reflux commonly occurs, Barrett's esophagus is relatively rare.

The significance of identifying Barrett's esophagus is that this condition carries with it a risk for the development of esophageal adenocarcinoma. Carcinogenesis that arise in columnar-lined segments of the esophagus are part of a dysplasia-adenocarcinoma sequence similar to that seen in the patients with inflammatory bowel disease. Dysplasia and associated metaplasia within the Barrett's esophagus is the result of development of invasive carcinomas in patients with Barrett's esophagus.

Many chronic inflammatory conditions are associated with increased risk of neoplastic transformation. In the gastrointestinal tract, cancer risk is increased in patients with chronic inflammatory bowel disease. In the stomach, the inflammation associated with Helicobacter pylori infection predisposes to the development of carcinomas and lymphomas. In Barrett's esophagus, the inflammation is often widespread and multifocal, suggesting that neoplastic progression may result from abnormalities occurring over large regions of the affected mucosa. Recent studies suggest that these mechanisms may be at work in Barrett's esophagus as well, and that a field effect occurs over the entire Barrett's mucosa (3). These changes are likely attributable to an increased rate of genetic modification facilitated by increased cell proliferation, inflammation, and infection. Concurrent increased of effective proliferation resulting from the repair of the damaged mucosa also contribute to genetic damage. Rapidly dividing cells are known to be at increased risk for underlying mutation when compared to quiescent cells. Furthermore, cell proliferation is required to fix genetic damage within the cell population.

Cancer risk in patients with Barrett's esophagus progressively increases as the epithelial changes undergoes changes from Barrett's metaplasia to low grade dysplasia, high-grade dysplasia and ultimately invasive carcinoma. Therefore, patients diagnosed with Barrett's esophagus undergo routine endoscopic surveillance so that precancerous dysplasia might be detected prior to the development of cancer. There are several difficulties, however, in determining which patients will ultimately progress to cancer. First, diagnostic difficulties may exist in establishing the diagnosis of dysplasia in the first place. Problems a pathologist may face in establishing a diagnosis of dysplasia include difficulties relating to sampling error, the distinction of reactive changes from dysplastic changes. Thomas argues that computerized morphometric analyses may additionally aid in distinguishing differing grades of dysplasia (4).

DNA Ploidy Studies

Generally, the abnormalities in DNA ploidy poorly correlate with conventional histologic diagnoses of dysplasia in Barrett's esophagus. Several studies have reported that hyperdiploid DNA ploidy patterns have an adverse impact on survival in patients with esophageal cancer (5,6). However, neither is it easy to determine the significance of changes in DNA content when compared to the normal tissue of Barrett's esophagus.

DNA ploidy studies, expression of proliferation markers, and expression of the tumor suppressor proteins p53 and p16.

p53 Polypeptide

The p53 gene is the most frequently mutated gene identified to date in human cancers, and is widely recognized as a tumor suppressor gene whose deletions and/or inactivation predisposes to the development of cancer in a small biopsy because high levels of aneuploidy generally occur only in patients with high degrees of dysplasia or adenocarcinoma. A normal DNA ploidy pattern in a biopsy indefinite for dysplasia is typically observed. However, in the setting of chronic inflammatory conditions, it is often widespread and multifocal, suggesting that neoplastic progression may result from abnormalities occurring over large regions of the affected mucosa. Such comparative histology and ploidy analyses, however, must generally be carried out using Feulgen staining and image analysis since flow cytometric DNA ploidy analysis and histologic analysis cannot be performed on the same tissue specimen. Flow cytometry and electron microscopy are required to determine a histologically characterized focus of dysplasia. As a result, the tissue submitted for flow cytometry may not be representative of the tissue used for histologic examination. In addition, most techniques employed in ploidy analysis are expensive and cumbersome, and are therefore difficult to implement as a part of routine practice.

Proliferation Markers

Carcinogenesis and chromosomal staining for MB-1, the Ki-67 proliferation antigen, shows gradually increasing expression in the Barrett's esophagus to esophageal adenocarcinoma sequence (6-14). MB-1 expression has been reported in approximately 25% of cells in non-dysplastic Barrett's esophagus, and up to 87% of cells in adenocarcinoma. In addition, the pattern of MB-1 expression is abnormal in dysplasia versus non-dysplastic mucosa. In Barrett's esophagus without dysplasia the cells expressing Ki-67 are limited to the bases of the crypts, whereas in dysplasia, the proliferating cells extend upward into the upper portion of the crypt and onto the mucosal surface. A recent study suggests that the combined use of MB-1 and p53 staining may be of value in decreasing interobserver variation in the diagnosis of Barrett's associated dysplasia (15).

p53 Alterations

p53 may be found in approximately 1% of people (2). Barrett's esophagus preferentially affects white males and it remains unclear whether the gender and race differences observed are due to environmental or genetic factors. Furthermore, while it is possible to develop Barrett's esophagus. For example, in Japan where reflux commonly occurs, Barrett's esophagus is relatively rare. p53 altertions may occur as a result of infection predisposes to the development of adenocarcinoma.

p53 Inactivation

INK4a lesions are common, early changes that may occur as a result of associated dysplasia is unclear (27).

From all of these studies we conclude that there is no single molecular marker that will suffice to allow us to predict who will or will not develop cancer in the setting of Barrett's esophagus. Carcinogenesis in Barrett's esophagus is the result of an accumulation of alterations in many different genes. Therefore, it is likely that we will be required to develop panels of markers, and there may be, in differing combinations, clues to predict neoplastic risk in individual patients. We have clearly not yet achieved this level of sophistication in our understanding of Barrett's- associated neoplasia. With additional large, long-term follow-up studies, however, we may someday reach this goal.

References:

11. Keswani RN, Noffsinger A, Waxman I, Bissonette M. Clinical use of p53 in Barrett's esophagus. Carcinogenesis is a multi-step process that occurs as a result of alterations in many different genes. Therefore, it is likely that we will be required to develop panels of markers, and there may be, in differing combinations, clues to predict neoplastic risk in individual patients. We have clearly not yet achieved this level of sophistication in our understanding of Barrett's- associated neoplasia. With additional large, long-term follow-up studies, however, we may someday reach this goal.
NEOPLASTIC RISK ASSESSMENT IN BARRETT’S ESOPHAGUS

Amy Noffsinger, MD
The University of Chicago

Barrett's Esophagus
- Acquired metaplastic change in the esophagus
- Secondary to chronic gastroesophageal reflux
- Three major types of epithelium
  - Fundic type
  - Junctional or cardiac type
  - Specialized intestinal epithelium
    + defines Barrett's esophagus.

Barrett's-Associated Carcinoma
- Develops through a dysplasia-adenocarcinoma sequence similar to that in IBD
- Cancer risk is likely due to chronic inflammation and resultant increased proliferation and DNA damage
- Dysplasia is often widespread and multifocal
- As a result, Barrett's patients undergo routine endoscopic surveillance

Difficulties in Determining Cancer Risk
- Diagnostic difficulties exist in establishing the diagnosis of dysplasia
  - Sampling error
  - Distinction of reactive changes from low grade dysplasia
  - Difficulties in differentiating high-grade dysplasia from invasive carcinoma
  - Diagnostic confirmation may help
- Even dysplasia is present, it is not certain that the patient will continue to progress to cancer

Ancillary Studies in Barrett’s Neoplasia
- Huge number of studies have examined potential markers
- Only a few markers appear to have potential in this regard
  - DNA ploidy studies
  - Proliferation markers
  - p53 abnormalities
  - p16 abnormalities
**DNA Ploidy Studies**
- Abnormalities in DNA ploidy correlate well with conventional histologic diagnoses.
- DNA aneuploidy increases as the histologic grade of dysplasia increases.
- Even specimens histologically negative or indefinite for dysplasia may contain aneuploid cells.

**DNA Ploidy Analysis in Biopsies**
- May help differentiate reactive from dysplasia.
- High levels of aneuploidy correlate with high grade dysplasia or carcinoma.
- Normal ploidy in a biopsy indefinite for dysplasia might provide reassurance that the lesion may not progress.
- Abnormal ploidy might prompt rebiopsy or more frequent surveillance.

**Feulgen Staining or Image Analysis**
- Expensive and cumbersome to perform routinely.

**Proliferation Markers**
- Ki-67 expression increases with increasing dysplasia.
- Ki-67 pattern of expression is also altered.
- A recent study suggests the combined use of MIB-1 and p53 staining may be of value in decreasing interobserver variation in the diagnosis of Barrett’s associated dysplasia.

**p53 Alterations**
- p53 gene is the most frequently mutated gene in human cancers.
- Widely recognized as a tumor suppressor gene.
- Implicated in control of cell proliferation, differentiation, DNA repair and synthesis, and apoptosis.
- Causes cell cycle arrest in response to DNA damage.

**p53 Alterations in Barrett’s Esophagus**
- Common in esophageal adenocarcinomas and Barrett’s associated high-grade dysplasia.
- Also occur with lower frequency in low grade dysplasia.
- Rare in metaplastic Barrett’s epithelium without dysplasia.
- p53 alterations reportedly occur with greater frequency in patients who will ultimately progress to high-grade dysplasia or carcinoma.
p53 and Barrett’s Esophagus
- Can p53 IHC be used as a complementary test with histologic evaluation in the diagnosis of dysplasia in patients with Barrett’s esophagus?
- High rates of both false positive and negative results
- Staining characteristics of different p53 antibody clones vary
- There remain patients without evidence of p53 abnormalities who progress to develop cancer
- There are also some with p53 mutations who do not

p16 Inactivation
- Inactivation p16 is common in human tumors
- Gene is located on chromosome 9
- Encodes a cell cycle regulatory protein that inhibits cyclin dependent kinases 4 and 6
- Prevents phosphorylation of the retinoblastoma gene product
- Blocks cell cycle progression in the G1-S phase
- Inactivation occurs as a result of mutation, deletion or methylation

p16 Alterations in Barrett’s Esophagus
- Allelic loss of p16 is common in esophageal adenocarcinomas
- Early event in the Barrett’s esophagus-dysplasia-adenocarcinoma sequence
- Provides affected cells with a survival advantage
- p16 LOH has been reported in 35% of biopsies from Barrett’s patients without dysplasia
- p16 loss may be a marker for patients at risk for later development of dysplasia or carcinoma
- p16 loss may be identified by IHC, but the practical utility of this stain is still unclear.

Take Home Message
- Carcinogenesis is a multi-step process that occurs as a result of alterations in many different genes
- There is no single molecular marker that will allow us to predict who will or will not develop cancer in the setting of Barrett’s esophagus
- It is likely that we will be required to develop panels of markers, which may, in differing combinations, allow us to predict neoplastic risk in individual patients
Modern endoluminal therapeutic modalities: the pathologist’s perspective

Gregory Y. Lauwers, M.D.

Bullet points:

• In response to the increasing incidence of Barrett’s oesophagus-related neoplasms and of the risks associated with surgery, novel endoscopic therapies have been developed by gastroenterologists.

• Whether it is endoscopic mucosal resection (EMR) or ablative therapies such as photodynamic therapy (PDT) or laser ablation, they offer new challenges and opportunities for pathologists to assert themselves in the multidisciplinary team treating these patients.

• The current experiences related to EMR and PDT will be reviewed and a focus will be placed on the histopathologic features important in the evaluation of tissues gathered during treatment and follow up of patients.
The current guidelines for EMR are evolving, and no standard has been specifically set for EMR in large lesions, usually yields several mucosal fragments and essentially prevents the pathologists from accurately interpreting the biopsy specimens. Accurate staging to differentiate dysplasia and intramucosal carcinoma from invasive adenocarcinoma with submucosal invasion is critical in determining individual patient management. Despite significant advances, endoscopic ultrasonography (EUS) has only a 72% to 95% accuracy rate in differentiating between mucosal (T1m) and submucosal (T1sm) disease.

In our experience, 44% of EMRs with positive lateral circumferential margin(s) and negative deep margin (including all redefined with PDT) had local recurrence and/or regional lymph node metastases following up for 23 months. However, 36% of EMRs with positive deep margin showed residual tumors despite the use of photodynamic therapy in some cases.

EMR is more accurate in staging early neoplastic lesions

Accurate staging to differentiate dysplasia and intramucosal carcinoma from adenocarcinoma with submucosal invasion is critical in determining individual patient management. Despite significant advances, endoscopic ultrasonography (EUS) has only a 72% to 95% accuracy rate in differentiating between mucosal (T1m) and submucosal (T1sm) disease. Overstaging by EUS occurs in 0% to 12.5% of cases and understaging in 16% to 20% of cases.

In one series, EMR was absent in 17% of patients with evidence of submucosal invasion on EUS. However, EMRs allowed more precise identification of the level of invasion, with pathologic analysis showing submucosal invasion in 40% of patients staged as intramucosal adenocarcinoma by EUS. All the submucosal cancers were associated with nodular lesions except in one case, while submucosal invasion in flat, non-ulcerated BE with HGD in biopsy specimens seems to be uncommon. In our experience, EMR correctly staged 75% of the lesions as intramucosal (T1m) or invasive (T1sm) tumor(s). A reported case of EUS understaging 78% of lesions was 0.03.

EMR improves diagnostic accuracy

Interobserver variation is a vexing problem for surgical pathologists. Reid et al. achieved only a 61% interobserver agreement when evaluating thre categories (negative for dysplasia; indefinite for dysplasia and low-grade dysplasia; high-grade dysplasia and carcinoma). More recently, a group of 12 observers reviewing 125 biopsies could reach only an interobserver kappa value of 0.50 (representing about 70% of interobserver concordance) when distinguishing the three 5 categories. The reasons for diagnostic differences may be multiple, including the experience of the observers (not the case in the publications cited above) and quality of material, systems (including features ranging from quality of the slides, staining, sections) to size of the specimen sampled. Another cause is likely to be the very nature of dysplasia, a biological process encompassing a continuum of changes for which defining a fixed point, i.e., a specific grade, is sometimes difficult.

In our experience, a change in diagnosis from the original biopsy is noted in 37% of the cases, with the biopsy underreporting the neoplastic grade in 21% of the cases and overreporting in 16% of the cases. Others have reported similar results. Coia et al reported a change in diagnosis in 26% of cases based on examination of the same EMR specimen. In their series of 23 patients undergoing segmental EMR, Leaf et al reported that of 52 patients with an initial diagnosis of IMC were upstaged to invasive carcinoma. Obviously, these changes in grade and stage may have a significant impact on patient outcome, as lymph node metastases can be observed in up to 8% of IMC and up to 21% of submucosal tumors.

In our experience, G. Y. Lauwers et al. observed the use of EMR as a staging tool and diagnostic test for biopsy specimens. The results may relate to the larger tissue sampling compared to biopsies and the ability to evaluate mucosal landmarks such as double mucosal invaginations. In our series, none of the 25 biopsies had 100% interobserver agreement among all reviewers, although 13 cases (52%) were given diagnosis that differed by only one grade (from low to moderate), 14 cases (56%) differed by 2 grades, and there was disagreement in 4 different grades were recorded in 12% of the biopsies. Of the 25 corresponding EMRs, all reviewers gave the same diagnosis in 16% of the EMRs, including three intramucosal adenoma and one invasive adenocarcinoma. Another 13 cases were given diagnosis that differed by one grade, 10% were diagnosed as dysplasia or intramucosal adenoma, and 5 cases were diagnosed as either slightly or significantly over- or understaging. On EMRs, all the adenomas and some of the submucosal cancers were associated with nodular lesions except in one case, while submucosal invasion in flat, non-ulcerated BE with HGD in biopsy specimens seems to be uncommon. In our experience, EMR correctly staged 75% of the lesions as intramucosal (T1m) or invasive (T1sm) tumor(s). A reported case of EUS understaging 78% of lesions was 0.03.

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likely to persist after PDT (4% of proximal lesions versus 15.3%). The reason is unclear.

1. Ackroyd R, Brown NJ, Davis MF, et al.: The rate. Thus, mucosal/submucosal invasive adenocarcinomas (pT1) are less likely to be treated with PDT. Since long segment BE frequently carries multiple neoplastic clones, it is likely that post-PDT persistence is a reflection of neoplastic clones excised after PDT. Further evidence that mutations of the TP53 gene are not an early event is provided by analysis of the diastase-resistant protein.

PDT/PDT buried Barrett epithelium and carcinoma

After PDT, Barrett's mucosa concealed by restored squamous epithelium (buried BE) is reported in 0% to 40%2,8,19,46,47,69,72,73 of patients (n=1) before treatment, rose to 35.1% (n=13) of those after PDT. Although the patients with buried neoplasms responded to further treatment similarly to those with only surface neoplasms, the detection of buried neoplasms is difficult without reliable clinicopathological characteristics. Therefore, endoscopic surveillance with extensive biopsies and thorough pathological evaluation is critical.

In conclusion, whether evaluating endoscopic mucosal reactions or diagnosing post-PDT follow-up biopsies or other ablative therapies, the histopathological interpretation, and thus the path of the histopathologist, is crucial in the validation of these new therapeutic methods.

REFERENCES


Modern Endoluminal Therapeutic Modalities: The Pathologist's Perspective

Gregory Y. Lauwers, M.D
Massachusetts General Hospital
Harvard Medical School
Boston, USA

Old Paradigm

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Staging</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Biopsies</td>
<td>EUS</td>
<td>Esophagectomy</td>
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</table>

(Interobserver variation)

New Paradigm

| Bx+EMR | EUS+EMR | PDT; RFA; Argon; EMR |

Management Options for BE w/HGD and IMC

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical Resection</td>
<td>Resects HGD &amp; any occult malignancies</td>
</tr>
<tr>
<td>Observation</td>
<td>Risk of developing CA may be fairly low</td>
</tr>
<tr>
<td>Endoscopic Therapy</td>
<td>Low morbidity/mortality Outpatient procedure</td>
</tr>
</tbody>
</table>

Therapeutic efficacy of EMR

• Prospective series of 100 pts w/ “low risk” CAs (well- mod. diff., < 20mm, confined to the mucosa without angiolymphatic inv. or ulcer on endoscopy)
  - no death and overall recurrence rate of 11% during a mean F-U of 36.7 months (range, 2-83 mo.)

• Other reports:
  - Positive margins: 62.5-83% of the cases.
  - 44% of cases w/ positive lateral/circumferential margin(s) and negative deep margin had no residual tumor and/or recurrence (median F-U of 23 months).
  - 86% of EMRs w/ positive deep margin showed residual tumors despite the use of PDT in some cases.

EMR: more accurate than EUS in staging early neoplasms

• EUS: 72-95% accuracy in distinguishing T1m / T1sm disease.
  - Overstaging: 0% - 12.5% of cases
  - Understaging: 16-20% of cases

• EMRs can detect submucosal invasion in 40% of cases staged as intramucosal CA by EUS.

• MGH experience: EUS correctly staged 70% of intramucosal (n=10) or invasive (submucosal) tumor (n=2).
  - overstaged 3 lesions (pT1sm for actual mucosal lesions) and understaged two (pT1A for actual intramucosal neoplasms).

Diagnostic Advantage of EMR

• EMR is superior to biopsy for diagnosing superficial gastroesophageal tumors, particularly for large (>10 mm) lesions.

• Change in diagnosis (compared to bx) noted in 37% of the cases:
  - Biopsies underreporting the neoplastic grade in 21% of the cases
  - Biopsies over-reporting grade in 16% of the cases.
**EMR improves diagnostic consistency**

- 9 pathologists / 3 academic centers
- 25 pairs of esophageal EMR specimens and peri-operative bx of the same lesions

<table>
<thead>
<tr>
<th></th>
<th>ICC*</th>
<th>KC**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsies</td>
<td>0.938</td>
<td>0.677</td>
</tr>
<tr>
<td>EMRs</td>
<td>0.997</td>
<td>0.831</td>
</tr>
</tbody>
</table>

*Intraclass correlation; **Kendall's coefficient of concordance

Proportion of agreement for EMRs better than for bx (p=0.015)

**Photodynamic Therapy**

1. Inactive photosensitive drug accumulates within the epithelium.
2. Activation by laser light of an appropriate wavelength.
3. Generation of high energy cytotoxic singlet oxygen molecules that damage the tissue.

**Good clinical response to PDT**

- 67-100% of dysplasia and/or superficial CAs disappear, using either 5-ALA or sodium porfimer.
  - PDT is usually combined with other ablative methods.
  - Decrease the risk of metachronous adenocarcinomas.
- Mucosal/submucosal invasive adenocarcinomas are less likely to be successfully treated than HGD.
  - no evidence of recurrence in only 25% of pT1b/limited pT2 tumors (limited follow-up) (AJSP 2006;30:114-8) (MGH data)
  - Higher success rate for HGD (90%) and IMC (82%).
  - Progression of HGD or IMC to invasive cancer is low, varying from 4 to 13% (GIE 2005;62;:488-98) (MGH data)

**Resistance to photodynamic therapy**

- Higher neoplastic grade
- Histologic grade of resistant neoplasia is unchanged after PDT (62.5%).
- Distally located lesions are more likely to persist (4% of proximal lesions vs 15.3%) after PDT
- Diffuse and multifocal neoplastic disease prone to persist
  - all patients responding to a single PDT course (+/- fulguration) had a short span of neoplasia (<4 cm) while 2/3 of patients with neoplasia spanning > 4 cm needed more than one.
- Most re-emergence of neoplasia after initial eradication (92% of the cases) arose at the original site.

**Post PDT buried BE and neoplasia**

- BE concealed by restored squamous epith.:0-40%
- Buried neoplasms in 0-3.7%, of the patients.
  - risk of unnoticed malignant transformation.
- MGH experience:
  - Completely buried BE (none before PDT): 17.3% of pts
  - Completely buried neoplasms:1.9% pre-up to 35% post.
  - 7.4% of the residual neoplasms were completely concealed and 57.9% of these represented the highest grade and usually sole residual neoplastic focus.
New Developments in the Endoscopic Diagnosis and Management of Barrett's Esophagus

Prateek Sharma, MD

Key Clinical Management Points:

- Endoscopic recognition of a columnar lined distal esophagus is crucial to ensure an accurate diagnosis of Barrett’s esophagus.
- Treatment is currently aimed at controlling symptoms of GERD and does not appear to have a major impact on dysplasia or cancer risk.
- Chemoprevention trials have been initiated in patients with Barrett’s esophagus.
- Endoscopic therapies benefit a sub group of patients with high grade dysplasia and early adenocarcinoma.
New Developments in the Endoscopic Diagnosis and Management of Barrett's Esophagus

Praveen Sharma, MD
Associate Professor of Medicine
University of Kansas School of Medicine
VA Medical Center
Kansas City, USA

Introduction

Barrett's Esophagus (BE) is a metaplastic change in the esophagus that results in replacement of the normal squamous lined epithelium with intestinal metaplasia. The incidence of esophageal adenocarcinoma has rapidly increased in recent years and BE has been found to be present as a precursor lesion in many of these cases. Patients with BE are thought to have an annual risk of developing esophageal cancer of 0.5% per year, substantially higher than the general population, but the absolute risk of developing cancer in BE patients is low.

Diagnosis of BE

The definition of BE has evolved over time. BE was recently defined during a workshop sponsored by the American Gastroenterological Association in February 2003 (BE Chicago Workshop) as, “a displacement of the squamocolumnar junction proximal to the gastroesophageal junction with the presence of intestinal metaplasia.” Endoscopic assessment of the extent of Barrett’s esophagus (endoscopically visible esophageal columnar mucosa) is dependent on correctly locating esophageal landmarks such as the gastroesophageal junction (GEJ). Lack of simple, standardized criteria for identifying these landmarks and reliably measuring the extent of Barrett’s esophagus has hindered consistency in research and clinical practice.

remission rates (86%) were observed over a follow-up time period of 5 years. The 5 year survival rate was 89% with an overall complication rate of 15%. Recurrences as well as metachronous lesions were observed in 20% of the patients indicating that close follow up after endoscopic treatment is still required in these patients. Similarly, results from a large multicenter randomized trial showed a significant decrease in cancer progression in HGD patients treated with photodynamic therapy (PDT). Such patients should probably be referred to high volume and expert endoscopy centers to minimize the mortality associated with endoscopic resection and ablation.

Key Clinical Management Points:

- Endoscopic recognition of a columnar lined distal esophagus is crucial to ensure an accurate diagnosis of Barrett’s esophagus
- Treatment is currently aimed at controlling symptoms of GERD and does not appear to have a major impact on dysplasia or cancer risk
- Chemoprevention trials have been initiated in patients with Barrett’s esophagus
- Endoscopic therapies benefit a sub-group of patients with high grade dysplasia and early adenocarcinoma

Recommended Reading:


The Prague C and M criteria

In BE patients, the proximal level of the squamocolumnar junction (SCJ) or Z-line is such that it no longer coincides with the gastroesophageal junction (GEJ). The resulting columnar-lined mucosa of the distal esophagus appears salmon-pink in color, and is readily visible by endoscopic examination. Biopsies can then be obtained from this area of suspected BE (endoscopic BE) to further characterize the tissue and to specifically document intestinal metaplasia. Thus, reliable diagnosis of BE, with its associated risk for esophageal adenocarcinoma, depends firstly on the effective recognition of endoscopic features of the suspected BE segment, followed by technically adequate histological sampling of the metaplastic esophageal mucosa to screen for intestinal-type metaplasia. Apart from biopsy sampling, measurement of the extent of BE is also clinically relevant, since this influences the risk of developing adenocarcinoma. For instance, the Rotterdam Esophageal Tumour Study Group found that a doubling of the length of BE increased the risk of adenocarcinoma by 1.7 times.

Despite the importance of accurate endoscopic recognition and grading of BE, there is no consensus-based, authoritative guidance on how this should be done. Accordingly, a variety of ad hoc and frequently inadequately specified and validated approaches have been used. For instance, grading of patients into those with variably defined ‘short’ and ‘long’ segments of BE is an unsatisfactory crude approach. An international Barrett’s esophagus working group was convened to standardize to endoscopic measurement of Barrett’s esophagus. The working group developed criteria to assess the circumferential and the maximal extent of esophageal columnar tissue, the Prague C and M criteria. Using these criteria, circumferential Barrett’s esophagus extending to 3 cm above the GEJ with a tongue extending 5 cm above the GEJ would be described as C3M5, while a tongue extending 3 cm above the GEJ with no circumferential extent of Barrett’s esophagus would be designated C0M0.

For the detection of dysplasia in patients with BE, four quadrant biopsies every 1-2 cm of the endoscopically recognized area of BE should be obtained. Given that these biopsies are random in nature and sample only a small surface area of the BE segment, a number of new techniques (i.e. magnification endoscopy, spectroscopy, optical coherence tomography, etc.) are being evaluated to increase the yield of detecting dysplastic and neoplastic tissue. Although these technologies are not yet readily available for routine clinical use, they will dramatically change surveillance practices in BE patients in the future.

Treatment

A reasonable initial step in treatment of BE is eliminating symptoms of reflux, and healing esophagitis. The importance of reflux control has been proposed by studies that demonstrate that acid reflux predisposes to proliferation, and some studies have even cited gastroesophageal reflux in the activation of protein kinase regulated pathways resulting in decreased apoptosis in cell lines exposed to acid. Although proton pump inhibitors can heal and treat GERD in patients with BE, acid suppression therapy has not yet clearly demonstrated a reduction in cancer risk. The option of surgery can be considered in some individuals with BE for the treatment of their underlying gastroesophageal reflux disease. Although studies in the surgical literature argue for histological regression in individuals after antireflux surgery, cases of high grade dysplasia and cancer have been reported even after these procedures. Most recently, a meta-analysis concluded that the risk of adenocarcinoma in individuals with BE was not significantly decreased by anti-reflux surgical procedures.

Endoscopic therapies for the treatment of BE are a more recent mode of therapy. Although the majority of the area of BE can be replaced by neo-squamous mucosa, persistent metaplastic tissue is often detected underlying the squamous tissue. Given the low risk of cancer in patients with non dysplastic BE or even with low grade dysplasia, endoscopic ablation treatments cannot be recommended outside of protocols in these patients. In patients with high grade dysplasia, however, the risk of progression to cancer can be as high as 25-37%. In these patients, aggressive surveillance, early surgical resection, or endoscopic ablation may be considered. Endoscopic therapies including mucosal resection and photodynamic ablation hold promise given the alternative - esophagectomy. However, long term data are lacking in this field and the number of patients treated with endoscopic therapies have also been small. The group of investigators from Germany are to be commended for reporting 5 year follow up data on Barrett’s esophagus with high grade dysplasia and early carcinoma. Excellent complete
New Developments in the Endoscopic Diagnosis and Treatment of Barrett's Esophagus
Prateek Sharma, MD
Kansas City

**Rising Incidence of Esophageal Adenocarcinoma**

<table>
<thead>
<tr>
<th>Year</th>
<th>Adenocarcinoma</th>
<th>Squamous Cell Carcinoma</th>
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<tbody>
<tr>
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<td>5</td>
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</tr>
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<td>10</td>
<td>15</td>
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</tr>
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<td>1985</td>
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<td>20</td>
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<td>1990</td>
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<td>1995</td>
<td>25</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>2000</td>
<td>30</td>
<td>35</td>
<td>50</td>
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</table>

Pohl H et al, J Natl Cancer Inst 2005

**Why have an Endoscopic classification system for Barrett's Esophagus?**

- BE is common
- BE is associated with dysplasia and esophageal adenocarcinoma
- Terminology issues
- Recognition of endoscopic landmarks

**Esophagectomy: High-Volume Hospitals Have Lower Mortality Rates**

<table>
<thead>
<tr>
<th>Number of esophagectomies</th>
<th>Adjusted Mortality Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>20.3</td>
</tr>
<tr>
<td>20</td>
<td>17.8</td>
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<tr>
<td>30</td>
<td>16.2</td>
</tr>
<tr>
<td>40</td>
<td>11.4</td>
</tr>
<tr>
<td>50</td>
<td>8.4</td>
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</tbody>
</table>

Birkmeyer et al, NEJM 2002

**Circumferential EMR for BE**

- Length: 2-9 cm
- Bands: 3-18
- Length: 3-10 cm
- Bands: 5-42

Overall success: 10 patients (8 cancer, 2 HGD)
Median age: 62 years

<table>
<thead>
<tr>
<th>Overall success</th>
<th>9</th>
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<tbody>
<tr>
<td>1 session</td>
<td>5</td>
</tr>
<tr>
<td>2-5 session</td>
<td>4</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
</tr>
<tr>
<td>Stricture</td>
<td>7</td>
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</tbody>
</table>

Soehendra N et al, Gastrointest Endosc 2006

**PDT: 5 Year Follow Up**

- 228 HGD patients
- PDT (138), observation (70)

<table>
<thead>
<tr>
<th>Progression to cancer</th>
<th>Observation</th>
<th>PDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>28%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>13%*</td>
<td>19%*</td>
</tr>
</tbody>
</table>

Overholt B et al, DDW 2006
Endoscopic Therapy: Limitations

- Strictures: EMR >75% circumference
- \textit{En bloc} resection difficult: Margins +
- Non uniform light exposure
- Persistence of genetic abnormalities

Conclusions: Endoscopic Diagnosis

- Clear identification of endoscopic landmarks is the basis for an endoscopic diagnosis
- The reliability of using the Prague C&M criteria for the endoscopy grading of BE is excellent
- Endoscopic recognition of lengths of BE < 1cm have very low reliability
- The reliability for the endoscopic recognition of landmarks (eg. GEJ, hiatus) are excellent

Summary Endoscopic Treatment

- Endoscopic therapies appear very promising in the treatment of dysplasia and cancer of the esophagus
- The goal should be complete eradication of at risk mucosa
- Patient factors (age, extent of disease, comorbidities, multiple procedures) and endoscopist factors (expertise) should be taken into consideration