Barrett's Esophagus:
Controversy and Management

History
- Norman Barrett (1950)
  “Chronic Peptic Ulcer of the Oesophagus and Oesophagitis”
- Allison and Johnstone (1953)
  “The Oesophagus Lined with Gastric Mucous Membrane”

Barrett's Esophagus
Columnar-lined Esophagus
“An esophagus in which any portion of the normal squamous lining has been replaced by a metaplastic columnar epithelium which is visible macroscopically and confirmed histologically to have intestinal metaplasia”

American College of Gastroenterology

Prevalence at Endoscopy

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naef et al (1975)</td>
<td>140</td>
<td>2.2%</td>
</tr>
<tr>
<td>Burbige and Radigan (1979)</td>
<td>8/203</td>
<td>3.9%</td>
</tr>
<tr>
<td>Rothery et al (1986)</td>
<td>58/5534</td>
<td>1.0%</td>
</tr>
<tr>
<td>Cooper and Barbezat (1986)</td>
<td>52/4448</td>
<td>1.2%</td>
</tr>
<tr>
<td>Ovaska et al (1989)</td>
<td>32/12499</td>
<td>0.25%</td>
</tr>
<tr>
<td>Herlithy et al (1984)</td>
<td>18/906</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Prevalence and Reflux Sx
Heartburn, regurgitation, dysphagia at least once per week

- Winters et al (1987) 6%
- Mann et al (1989) 6.7%
- Cameron et al (1997) 3.5%
**Prevalence and Duration of Sx**

Odds Ratio = 6.4 when symptoms > 10y

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**Population Prevalence**

- 20% of adult population have weekly reflux
- 5% of reflux patients have Barrett’s
- 1/100 General Population will be expected to have Barrett’s

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**Barrett’s and Cancer Risk**

- Van der Burgh et al (Gut 1996) 1/180 pt-y*

* 2/79 at 9.3 years follow-up died of esophageal cancer

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**Barrett’s and Cancer**

- Barrett’s patients develop adenocarcinoma at a rate of ~ 0.4% per year or 1/175 person yrs

40 X increased incidence of cancer as compared to the general population

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**Age Adjusted Incidence of Esophagogastric Adenocarcinoma In White Males in USA 1974-1994**

Devesa S: Cancer 1998;83:2049-53

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**Barrett’s Esophagus**

1. Risk factors to develop cancer
2. Natural history of Barrett’s
3. Screening for cancer
4. Management of metaplasia
5. Management of dyplasia
6. Treatment Options
Reflex and the Risk of Cancer

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>Esophageal adenocarcinoma</th>
<th>Cardia adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly GERD</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Nocturnal GERD</td>
<td>20</td>
<td>2.8</td>
</tr>
<tr>
<td>Any GERD &gt; 20yrs</td>
<td>16.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Severe GERD &gt; 20 yrs</td>
<td>43.5</td>
<td>4.4</td>
</tr>
</tbody>
</table>


Associated Risk factors

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Obesity</th>
<th>Top BMI quartile</th>
<th>&gt; 30 kg/m²</th>
<th>Asthma drugs &gt; 5 yrs</th>
<th>Tobacco</th>
<th>Dietary fat &amp; calories</th>
<th>Well done red meat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.6</td>
<td>16.2</td>
<td></td>
<td>3.1</td>
<td>2.4</td>
<td>4.1</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Reflux and the Risk of Cancer

Adenocarcinoma in Barrett’s Esophagus

<table>
<thead>
<tr>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>H pylori infection</td>
</tr>
<tr>
<td>Beer</td>
</tr>
<tr>
<td>Wine</td>
</tr>
<tr>
<td>Dietary fibre</td>
</tr>
<tr>
<td>Vit A,C,B6, E</td>
</tr>
</tbody>
</table>

Age Adjusted Rates of Esophageal and Gastric Cardia Adenocarcinoma Among White Males (1988-1994)

Barrett’s Esophagus: Genetic Factors?

NCI SEER Database 1988-1990
Annual Incidence/100,000

<table>
<thead>
<tr>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 M</td>
<td>0.6 M</td>
</tr>
<tr>
<td>0.3 F</td>
<td>0.2 F</td>
</tr>
</tbody>
</table>

P53 mutation and Barrett’s in twins
Metaplasia-Dysplasia Progression to Cancer

Clinical

Histologic

Intestinal metaplasia

Low-grade dysplasia

High-grade dysplasia

Intra-mucosal carcinoma

Invasive adenocarcinoma

Molecular markers

Ploidy

Oncogenes (cyclin D1)

Tumor suppressors (p53, p16)

DNA repair genes

Grading Dysplasia in Barrett’s Esophagus

- 250 Barrett’s esophagus cases with varying degrees of dysplasia
- Follow-up information on 138 patients.

To evaluate both inter and intra-observer variability in diagnoses, the 250 slides were each circulated twice to each of the 12 pathologists, so 24 diagnoses were rendered on each case.

Human Pathology 2001; 32:368-78

Human Pathology 2001; 32:379-88

Barrett’s Esophagus: Histology

Columnar-lined Esophagus

Metaplasia

- In 44 cases during 78 months
- 3 LGD
- 1 HG
- 0 Ca
- Endoscopic biopsy every two years

Human Pathology 2001; 32:379-88

Columnar-lined Esophagus

Low Grade Dysplasia

- In 26 patients
- 4 HGD (2-7 mo)
- 4 cancer (26 mo)
- Treat reflux
- Endoscopic biopsy in 1-3 mo.

Human Pathology 2001; 32:379-88

Columnar-lined Esophagus

High Grade Dysplasia

- In 33 patients
- 20 cancers in 10 mos

Management

Endoscopic biopsy in 1 month

Mucosectomy

Ablation

Esophagectomy

Human Pathology 2001; 32:379-88
Columnar-lined Esophagus
Intramucosal Cancer

- In 13 patients
- 13 cancers in 4 mos
- Treatment
  - Mucosectomy
  - Ablation
  - Esophagectomy

Human Pathology 2001; 32:379-88

Barrett's Esophagus: Screening Strategy

Variable Progression to Adenocarcinoma

Surveillance and Incremental Cost

Comparison of Screening Costs

- Colon Cancer $20,000 LY
- Breast Cancer $22,000 LY
- Heart Transplant $160,000 LY
- Cervical Ca Screening $250,000 LY
- Barrett's q5y at 0.4% $98,000 QALY
- Barrett's q2y at 1% $590,700 QALY

Columnar Lined Esophagus Screening

- 4 quadrant bx every 1 cm. and atypical areas
- Reviewed by two pathologists
- Metaplasia - every two years
- Low grade dysplasia - treat reflux - re-biopsy in 1 mo.
- High Grade dysplasia - re-biopsy - endoscopic U/S


Provenzale et al. Am J Gastroenterol 1999 94:2043
High Grade Dysplasia
Early Adenocarcinoma

- 43% had an adenocarcinoma
- Lesion not visible on endoscopy
  - Intramucosal (88%), Submucosal (12%)
  - Lymph node involvement (10%)
  - 90% 5 yr survival
- Lesion visible on endoscopy
  - T1 (25%)
  - Lymph node involvement (56%)
  - 5 yr survival (82%)


Location of Adenocarcinoma


Management of metaplasia

- Omeprazole 20 mg po bid or equivalent
- Prokinetics are not effective due to defective contractility of the lower esophagus or LES
- Ablation not proven to decrease the risk of cancer
- Anti-reflux surgery for ulceration, strictures and breakthrough symptoms

Endoscopic Ablation of Barrett’s

- Thirty-five patients with ablation plus:
  - Nissen (n=5)
  - PPI (n=30)
- Biopsy shows neosquamous epithelium:
  - Normal Stroma (n=15)
  - Submucosal glands without metaplasia (n=9)
  - Submucosal glands with metaplasia (n=11)

Attwood, S. Can J Gast 12:45, 1998

VA Gerd Study: AdenoCa in Barrett’s with Medicine vs. Surgery

- Patients with Barrett’s develop Ca at 0.4%/y
- Patients without Barrett’s developed Ca at 0.07%/y
- No significant difference in incidence of adenocarcinoma between medical and Nissen groups after 10 yrs followup
Medical and Surgical treatment of Barrett's esophagus (RCT)

<table>
<thead>
<tr>
<th>5 yr followup</th>
<th>PPI</th>
<th>Fundoplication</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 43</td>
<td></td>
<td>N = 58</td>
</tr>
<tr>
<td>Good clinical results</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td>+ 24 hr ph</td>
<td>43/43</td>
<td>9/58</td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>2/43</td>
<td>2/58</td>
</tr>
<tr>
<td>Cancers/yr</td>
<td>1/111</td>
<td>1/319</td>
</tr>
</tbody>
</table>


Does antireflux surgery potentially reduce the risk of malignancy?

No since 10% continue to reflux after surgery which increases over time.

Probably if there is lifelong elimination of reflux.

What is the best treatment for High Grade dysplasia?

1. Esophagectomy
2. Mucosectomy + PPI
3. Ablation + PPI

Endoscopic Mucosectomy for High Grade Dysplasia

- 95% 5 year survival rate
- 7% local recurrence rate
- 3% perforation rate

Superficial Esophageal Cancer

- Endoscopic mucosectomy
- 95% 5 year survival rate
- 7% local recurrence rate
- 3% perforation rate

Photos Courtesy: Prof. Horst Neuhaus, M.D.
Photodynamic therapy for ablation of high-grade dysplasia in Barrett's esophagus: RCT 30 centers, 485 pts

- RCT comparing PDT plus omeprazole with omeprazole only.
- Complete ablation of HGD in PDT 106/138 [77%]


<table>
<thead>
<tr>
<th>PDT/POR plus omeprazole</th>
<th>Omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGD ablated</td>
<td>106/138 [77%]</td>
</tr>
<tr>
<td>Incidence of adenocarcinoma</td>
<td>13% (n=18)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>94%</td>
</tr>
</tbody>
</table>


Why is esophagectomy better than ablation or mucosal resection for high grade dysplasia?

- Non-invasive staging with U/S or CAT scan is inadequate
- 25% of patients have greater than T1 lesions so esophagectomy is the only curative Rx
- 10% of patients with cancer have lymph node involvement

Endoscopic Ultrasound: Tumor Stage

T4Nx
T1N0

T staging = 89% accuracy

Endoscopic Ultrasound: Early Tumor Staging

Intramucosal 6/9
Submucosal 15/19

Tom Rice
Endoscopy. 2003; 35(11): 962-6

Tom Rice
Endoscopy. 2005 35(11): 962-6

Am J Gastroenterol 2004 89: 702
Endoscopic Ultrasound: Nodal Staging

N staging 86% accuracy

Recommendations for Esophageal Cancer arising in Barrett’s Mucosa

- Mucosal resection for superficial lesions in poor operative candidate
- Transhiatal esophagectomy (THE) for high grade dysplasia or early stage cancer
- Neoadjuvant chemoradiation and THE for Stage 3 cancer
- Palliative radiation
- Stent