Barrett’s Esophagus: A New Perspective

Robert Shultz, D.O.
Topics

• What is Barrett’s Esophagus?
• How is Barrett’s Esophagus developed?
  – Caused by chronic heartburn (Gastroesophageal Reflux Disease or “GERD”)
• Esophageal Adenocarcinoma
• Treatment options available
• Questions and Answers
Barrett’s Esophagus

What is Barrett’s esophagus?

- Barrett’s esophagus is a change that occurs within the cellular lining of the esophagus associated with an increased risk for developing esophageal cancer.

Approximately 3.3 million adults in the United States have Barrett’s esophagus. ¹ ²

How does Barrett’s esophagus develop? ³

- Gastroesophageal Reflux Disease (GERD) is a disorder in which stomach acid and enzymes cause injury to the esophageal lining; producing symptoms such as heartburn, regurgitation, and chest pain.

- In some patients, the damage and inflammation associated with GERD can result in genetic changes which cause the cells to change from esophageal cells to intestinal cells. This change can be seen during an endoscopy procedure and is deemed Barrett’s esophagus.

It is estimated that 13% of the people who have chronic acid reflux also have Barrett’s Esophagus. ⁴
Barrett’s Risk Factors

- Increasing age
- Men
- Caucasians
- Long-standing GERD symptoms

Progression of GERD, Barrett’s, Adenocarcinoma due to chronic GERD

Normal → Complications due to GERD → Barrett’s Esophagus

Esophageal Adenocarcinoma
Grading of Barrett's Esophagus

Biopsy from Barrett's esophagus tissue are examined by a pathologist to confirm the diagnosis and grade the severity of cellular changes (dysplasia).

Intestinal Metaplasia (IM) or Non-dysplastic Barrett’s Esophagus (NDBE)
• The earliest stage of Barrett's esophagus. Normal flat (squamous) cells are replaced with glandular intestinal cells.

Low-grade Dysplasia (LGD)
• The abnormal cells have begun to change in size, shape, or organization and may show an increase in their growth rate.

High-grade Dysplasia (HGD)
• The abnormal cells reside within the lining of the esophagus, but demonstrate an increase in abnormal growth rate and pattern.

Adenocarcinoma (Esophageal Cancer)
• The abnormal cells have a rapid and uncontrolled growth rate. The cells may also invade the deeper layers of the esophagus and spread beyond that.
Treatment Options
Fortunately, there are several
Most Common Treatment Options

- **Surveillance** – Watch and wait, Acid suppression
- **Photodynamic Therapy (PDT)** - Drug injected intravenously 48 hours prior to endoscopy, laser light treatment activates the drug which causes the Barrett's tissue to be destroyed
- **Endoscopic Mucosal Resection (EMR)** - Removal of identified areas of Barrett’s by cutting (resecting) them out using snares during an endoscopy
- **Ablation** – The use of energy to remove the Barrett’s cells in the esophagus

## Surveillance

### Pros

- Easily accessible: today’s “standard of care” for treating Barrett’s esophagus
- Most insurance companies reimburse for regular endoscopic procedures

### Cons

- Does not remove Barrett’s esophagus
- Regular endoscopy, Bx
- Anxiety and stress for some patients associated with “watching and waiting” for cellular changes

"Endoscopic Surveillance," 2005 ClevelandClinic.org, The Cleveland Clinic, 9 August 2005

<http://cms.clevelandclinic.org/digestivedisease/body.cfm?id=240>.
## PDT

<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
</table>
| • Treatment removes dysplasia in high percentage of patients  
• Allows for treatment of very early cancers  
• Non-surgical  
• Most commonly used for high-grade dysplasia (2002) | • Causes extreme sensitivity to light for 4-6 weeks following treatment  
• Patient must cover skin entirely, which includes wearing a ski mask and gloves  
• Strictures  
• Complete disappearance of Barrett’s lining occurs in only 1/3 of patients |


EMR

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Enables evaluation of changes in diseased tissue</td>
<td>• Malignant lesions or high-grade dysplasia cannot be endoscopically identified</td>
</tr>
<tr>
<td>• Frequently reveals more advanced tumor stages</td>
<td>• To avoid recurrences, large Barrett’s areas are done in piecemeal fashion</td>
</tr>
<tr>
<td>• Can be used to obtain large biopsies for diagnosis and local tumor staging</td>
<td>• Often recommended in combination with additional ablation techniques</td>
</tr>
</tbody>
</table>

## Ablation

<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
</table>
| • Fast: median time of procedure – 24 minutes  
• Non-surgical outpatient setting  
• Removes the thin layer of diseased tissue without harming the underlying tissue.  
• Allows the regrowth of normal cells  
• “Soft” strictures in up to 10% | • Mild soreness and discomfort one to three days after the procedure, typically controlled with standard pain medication  
• A liquid diet is recommended for two to seven days post procedure, based on patient’s level of comfort  
• May need more than one treatment |

Radiofrequency Ablation for Barrett’s Esophagus
Barrett’s Esophagus
Barrett’s Prevalence Estimates

• 1.6% of general adult population (3.3 M)

• 3.9% – 6.2% of general adult population (7.8-12.4 M)

• 6.8% of persons over age 40 (8.7 M)

• 25% of persons without GERD > age 50 (20 M)
Evolution of Barrett’s and Cancer

- Squamous esophagus
- Chronic inflammation
- Barrett's metaplasia
- Low-grade dysplasia
- High-grade dysplasia
- Invasive Adenocarcinoma

Injury
Acid & bile reflux

Genetics
Gender, race, ? other factors

Accumulate Genetic Changes
Relative Change in EAC Incidence

- Esophagus
- Melanoma
- Prostate
- Lung/Breast
- Colorectal

Pohl H, Welch HG. Natl Cancer Inst 2005
# Age-adjusted 5-year survival

**TABLE 2** Estimated Age-adjusted Survival (%) from 11 Cancer Types, by Country/Area

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Developed Areas</th>
<th></th>
<th></th>
<th></th>
<th>Developing Areas</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>All developing areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>United States</td>
<td>Eastern Europe</td>
<td>Western Europe</td>
<td>Japan</td>
<td>All developed areas</td>
<td>South America</td>
<td>India</td>
<td>Thailand</td>
<td>Sub-Saharan Africa</td>
<td>All developing areas</td>
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<tr>
<td>Esophagus (male)</td>
<td>14</td>
<td>6</td>
<td>18</td>
<td>25</td>
<td>15</td>
<td>7</td>
<td>13</td>
<td>13</td>
<td>4</td>
<td>17</td>
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<tr>
<td>Esophagus (female)</td>
<td>8</td>
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<tr>
<td>Stomach (male)</td>
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<tr>
<td>Colon/rectum (male)</td>
<td>66</td>
<td>35</td>
<td>56</td>
<td>65</td>
<td>56</td>
<td>50</td>
<td>28</td>
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<tr>
<td>Colon/rectum (female)</td>
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<tr>
<td>Kaposi sarcoma (male)</td>
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<td>Prostate</td>
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Esophageal Cancer: U.S. 5-Year Relative Survival Rates

### LEADING CAUSES OF DEATH, 2004 AND 2030 COMPARED

<table>
<thead>
<tr>
<th>2004</th>
<th>Deaths (%)</th>
<th>Rank</th>
<th>2030</th>
<th>Rank</th>
<th>Deaths (%)</th>
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<td>Disease or injury</td>
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<td>Disease or injury</td>
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<td>1</td>
<td>Ischaemic heart disease</td>
<td>1</td>
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<tr>
<td>Cerebrovascular disease</td>
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<td>Cerebrovascular disease</td>
<td>2</td>
<td>12.1</td>
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<tr>
<td>Lower respiratory infections</td>
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<td>Chronic obstructive pulmonary disease</td>
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<td>8.6</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5.1</td>
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<td>Lower respiratory infections</td>
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<td>3.8</td>
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<tr>
<td>Diarrhoeal diseases</td>
<td>3.6</td>
<td>5</td>
<td>Road traffic accidents</td>
<td>5</td>
<td>3.6</td>
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<tr>
<td>HIV/AIDS</td>
<td>3.5</td>
<td>6</td>
<td>Trachea, bronchus, lung cancers</td>
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<td>3.4</td>
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<tr>
<td>Tuberculosis</td>
<td>2.5</td>
<td>7</td>
<td>Diabetes mellitus</td>
<td>7</td>
<td>3.3</td>
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<td>Trachea, bronchus, lung cancers</td>
<td>2.3</td>
<td>8</td>
<td>Hypertensive heart disease</td>
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<td>2.1</td>
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<td>Road traffic accidents</td>
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<td>Stomach cancer</td>
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<td>1.9</td>
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<tr>
<td>Prematurity and low birth weight</td>
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<td>HIV/AIDS</td>
<td>10</td>
<td>1.8</td>
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<tr>
<td>Neonatal infections and other*</td>
<td>1.9</td>
<td>11</td>
<td>Nephritis and nephrosis</td>
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<td>1.6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.9</td>
<td>12</td>
<td>Self-inflicted injuries</td>
<td>12</td>
<td>1.5</td>
</tr>
<tr>
<td>Malaria</td>
<td>1.7</td>
<td>13</td>
<td>Liver cancer</td>
<td>13</td>
<td>1.4</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>1.7</td>
<td>14</td>
<td>Colon and rectum cancers</td>
<td>14</td>
<td>1.4</td>
</tr>
<tr>
<td>Birth asphyxia and birth trauma</td>
<td>1.5</td>
<td>15</td>
<td>Oesophagus cancer</td>
<td>15</td>
<td>1.3</td>
</tr>
<tr>
<td>Self-Inflicted injuries</td>
<td>1.4</td>
<td>16</td>
<td>Violence</td>
<td>16</td>
<td>1.2</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>1.4</td>
<td>17</td>
<td>Alzheimer and other dementias</td>
<td>17</td>
<td>1.2</td>
</tr>
<tr>
<td>Cirrhosis of the liver</td>
<td>1.3</td>
<td>18</td>
<td>Cirrhosis of the liver</td>
<td>18</td>
<td>1.2</td>
</tr>
<tr>
<td>Nephritis and nephrosis</td>
<td>1.3</td>
<td>19</td>
<td>Breast cancer</td>
<td>19</td>
<td>1.1</td>
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<tr>
<td>Colon and rectum cancers</td>
<td>1.1</td>
<td>20</td>
<td>Tuberculosis</td>
<td>20</td>
<td>1.0</td>
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<tr>
<td>Violence</td>
<td>1.0</td>
<td>21</td>
<td>Neonatal infections and other*</td>
<td>21</td>
<td>1.0</td>
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<tr>
<td>Breast cancer</td>
<td>0.9</td>
<td>22</td>
<td>Prematurity and low birth weight</td>
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<td>Oesophagus cancer</td>
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<td>Diarrhoeal diseases</td>
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</tr>
<tr>
<td></td>
<td>0.8</td>
<td>25</td>
<td>Malaria</td>
<td>25</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Comprises severe neonatal infections and other, noninfectious causes arising in the perinatal period.

Accessed Dec. 10, 2011
# U.S. Cancer Incidence

<table>
<thead>
<tr>
<th>General Population Cancer Incidence</th>
<th>ND-BE Cohort Cancer Incidence</th>
<th>Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esophageal cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0 per 100,000 (0.003%)</td>
<td>600 per 100,000 (0.6%)</td>
<td>200X</td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47 per 100,000 (0.047%)</td>
<td>580 per 100,000 (0.58%)</td>
<td>12X</td>
</tr>
</tbody>
</table>

Risk multiple for developing cancer conferred by NDBE or polyp versus risk of that cancer in the general U.S. population.
Natural History of BE: Long-term Risk

- **NDBE**: Lifetime risk of developing EAC: 5-8%

- In a large cohort (n=346; 85% NDBE, 15% LGD), the cumulative rate of progression to HGD/EAC was 7.4% at 5 yrs
Barrett’s Esophagus
0.5%/patient/year cancer
0.9%/patient/year HGD

Colon Polyp
0.5%/patient/year cancer
14.2M colonoscopies/year

Seef LC, et al. Gastroenterology 2004
### U.S. Cancer Incidence

<table>
<thead>
<tr>
<th></th>
<th>General Population Cancer Incidence</th>
<th>LGD Cohort Cancer Incidence</th>
<th>Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esophageal cancer</strong></td>
<td>3.0 per 100,000 (0.003%)</td>
<td>1,700 per 100,000 (1.7%)</td>
<td>560x</td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
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Risk multiple for developing cancer conferred by LGD or polyp versus risk of that cancer in the general U.S. population

Surveillance, Epidemiology and End Results (SEER)
Does ablation reduce the incidence of cancer?
Ablation Effect on Natural History

<table>
<thead>
<tr>
<th></th>
<th>NDBE</th>
<th>LGD</th>
<th>HGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural History</td>
<td>0.6%</td>
<td>1.7%</td>
<td>6.6%</td>
</tr>
<tr>
<td>(53 studies)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>After Ablation</td>
<td>0.16%</td>
<td>0.16%</td>
<td>1.7%</td>
</tr>
<tr>
<td>(65 studies)</td>
<td></td>
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<tr>
<td>NNT=45</td>
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<td>NNT=13</td>
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<td>NNT= 4</td>
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Progression risk expressed as “Per-patient-per-year” (%) risk of developing EAC
NNT calculated on 5-year basis (number needed to treat to avoid one cancer over 5 years)
### Ablation Effect on Natural History

<table>
<thead>
<tr>
<th></th>
<th>NDBE</th>
<th>LGD</th>
<th>HGD</th>
<th>Polyp</th>
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<tr>
<td><strong>Natural History</strong> (53 studies)</td>
<td>0.6%</td>
<td>1.7%</td>
<td>6.6%</td>
<td>0.58%</td>
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<td></td>
<td>NNT=45</td>
<td>NNT=13</td>
<td>NNT=4</td>
<td>NNT=38</td>
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<tr>
<td><strong>After Ablation</strong> (65 studies)</td>
<td>0.16%</td>
<td>0.16%</td>
<td>1.7%</td>
<td>0.06%</td>
</tr>
</tbody>
</table>

Progression risk expressed as “Per-patient-per-year” (%) risk of developing EAC

NNT calculated on 5-year basis (number needed to treat to avoid one cancer over 5 years)

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**Prevention of colorectal cancer by colonoscopic polypectomy.** Winawer SJ, et al. NEJM 1993
Radiofrequency Ablation

HALO RFA Device Technology
HALO<sup>FLEX</sup> Energy Generator
HALO Ablation Catheters

HALO\textsuperscript{360+}

HALO\textsuperscript{90}
Baseline, Barrett’s esophagus

Courtesy of Charlie Lightdale, M.D., Columbia Presbyterian, New York
Automated sizing to determine diameter of esophagus
Focal RFA “Touch-up”

Long-term Outcomes

Baseline

Post-RFA: 2 years
Long-term Outcomes

Baseline

Post-RFA: 2 years
Ablation Depth Control

Tightly Spaced RFA Micro-array

HALO$^{360+}$ Ablation Catheter
Adverse Events
Jan. 2005 to Nov. 2011

• Total procedures: 98,064
  – Cumulative Event Rate (by procedure) : 0.23%
    • Death procedure related: 0.00%
    • Perforation: 0.01%
    • Stricture: 0.18%
    • Mucosal injury +/- intervention: 0.01%
    • Bleeding +/- intervention 0.02%
  – Incidence rate is 1 MDR in 440 procedures
    • 1 stricture in 563 procedures
    • 1 perforation in 8,914 procedures
  – Colonoscopy perforation rates:
    • Overall – 1 perforation in 1,400 procedures
    • Therapeutic – 1 perforation in 1,000 procedures

Data provided by the manufacturer, BÂRRX Medical, Inc., and based on calculations using the FDA MAUDE database
Clinical Data

HALO Radiofrequency Ablation
Clinical evaluations have been completed in the United States and Europe demonstrating the safety and efficacy of the HALO Technology for treating all types of Barrett’s tissue.

- The “Ablation of Intestinal Metaplasia” (AIM) trial showed that 98.4% of patients with baseline non-dysplastic IM were completely free of all Barrett’s tissue at 2.5 years of follow-up.\(^8\)

- The AIM-LGD & AIM Dysplasia trials have shown that Low-grade Dysplasia can be removed in over 90% of patients treated.\(^9,11\)

- The results from the United States HGD Registry, AIM-Dysplasia trial, and AMC European studies, demonstrated that over 90% of patients can have their High-grade dysplastic Barrett’s tissue eliminated.\(^9,12,13,14\)

\(^*\) Cure rates based on initial diagnosis and one or more clinical trials.  
\(^\dagger\) In clinical studies, most patients required one circumferential ablation procedure and one or two focal ablation procedures.

LGD = Low-grade Dysplasia  
HGD = High-grade Dysplasia  
AMC = Amsterdam Medical Center
Summary

• Barrett’s esophagus and esophageal cancer is a significant and growing problem

• Barrett’s is caused by GERD.

• You don’t always have to have GERD symptoms to have Barrett’s

• Several treatment options are available
GERD: More than just heartburn?

- GERD is the third most prevalent disease in the United States\(^1\)
- Half of U.S. adults experience symptoms of GERD almost monthly while 20 percent experience symptoms weekly\(^2\)
- Epidemic of GERD is due to our “super size” culture and unhealthy eating habits
  - According to the CDC more than half of the U.S. population is overweight or obese

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