Barrett’s Esophagus: State of the Art

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University of North Carolina SOM

“Food Getting Stuck”

- 73-year-old retired Wilmington police officer who spends his time on his boat
- Food sticking in mid-chest with most meals
- Symptoms progressive, now associated with 23 lb weight loss
- GERD symptoms for <20 yrs, meditated daily with PPI x 15 yrs
- Overweight, o/w in good health
Case, Cont

- Diagnosed with stage IV esophageal adenocarcinoma
- Received chemo/RT
- Poor response with ongoing weight loss
- Wants to make it to his granddaughter’s wedding

Upper Endoscopy/Stent Palliation
The Problem

Adenocarcinoma – A Disease with a Rapidly Increasing Incidence

![Graph showing the increasing incidence of Adenocarcinoma compared to other cancers](Pohl_H_et_al._J_Natl_Cancer_Inst_2005;97:142-6)

Nicholas J. Shaheen, MD, MPH, FACG
Not Much Progress Being Made...


It Is Not Going To Change Soon...

Unfortunately, Most Presentation is Late-Stage

What About the Epidemiology of BE?


Why is all this happening?

No one knows for sure.

Some Postulate that the Increasing Cancer Incidence Could Be Secondary to the Epidemic of Obesity in the U.S.
Obesity is Strongly Associated with the Risk of AdenoCa of the Esophagus

189 Cases, 820 Controls
Adjusted for age, sex, tobacco smoking, alcohol use, socioeconomic status, reflux symptoms, intake of fruit and vegetables, energy intake, and physical activity.


Obesity Trends* Among U.S. Adults
BRFSS, 1985
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1990
(BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

Obesity Trends* Among U.S. Adults
BRFSS, 1995
(BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2000
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data          <10%           10%–14% 15%–19%           20%–24%          25%–29%          ≥30%

Obesity Trends* Among U.S. Adults
BRFSS, 2005
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data          <10%           10%–14% 15%–19%           20%–24%          25%–29%          ≥30%
Obesity Trends* Among U.S. Adults
BRFSS, 2010
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

Association Does Not Imply Causality!

The Gastroenterologists’ Perspective

I know we are helping. I see it with my eyes. And we have never been able to do more!
Endoscopists try to lower the risk of cancer death in those with chronic reflux by performing screening and surveillance endoscopy.

We scope those with chronic heartburn (screening), then periodically re-scope those with Barrett’s (surveillance).
**RFA**

**The AIM-D Trial**

RCT of 127 Subjects with LGD & HGD

- **Intervention**: RFA+PPI or Sham+PPI (2:1)
- **Follow-up**: 12 mos
- **Assessment**: Bx’s q3 mos (HGD)/ 6 mos (LGD)

**1° Outcomes:**
- Ablation of all dysplasia:
  - 81% of HGD
  - 91% of LGD
  - app 20% of controls
- Complete eradication of IM (77% of Rx, 2% Sham)

**SE’s**: Strictures in 6% of subjects


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**3 year Durability**

**Durability of Eradication of IM Without Intervention**

*Shaheen NJ et al., Gastroenterology 2011.*
Safety and Efficacy of Endoscopic Mucosal Therapy With Radiofrequency Ablation for Patients With Neoplastic Barrett’s Esophagus

WILLIAM J. BULSIEWICZ, HANNAH P. KIM, EVAN S. DELLOM, CARY C. COTTON, SARINA PASRICH, RYAN D. MADANICK, MELISSA B. SPACEK, SUSAN E. BREAM, XIAOXIN CHEN, ROY C. ORLANDO, and NICHOLAS J. SHAHEEN

Center for Esophageal Diseases and Swallowing, Department of Medicine, Division of Gastroenterology, University of North Carolina School of Medicine, Chapel Hill, North Carolina

| Table 2. Eradication Rates Based on Pretreatment Histologic Stage of Disease |
|-----------------------------|-----------------|-----------------|
|                            | PP, n (%)       | ITT, n (%)      |
| Any histology              | 188             | 210             |
| N                           | 182 (97)        | 182 (87)        |
| CED                         | 168 (89)        | 168 (80)        |
| Total treatment sessions, mean (SD)| 3.2 (1.7)    | 3.3 (1.8)      |
| RFA treatment sessions, mean (SD)| 2.7 (1.5)    | 2.8 (1.7)      |
| LGD                         | 41              | 44              |
| N                           | 41 (100)        | 41 (93)         |
| CED                         | 38 (93)         | 38 (86)         |
| Total treatment sessions, mean (SD)| 3.0 (1.6)    | 3.2 (1.9)      |
| RFA treatment sessions, mean (SD)| 2.8 (1.7)    | 3.0 (2.0)      |
| HGD                         | 158             | 135             |
| N                           | 144 (97)        | 144 (84)        |
| CED                         | 106 (90)        | 106 (76)        |
| Total treatment sessions, mean (SD)| 3.1 (1.5)    | 3.1 (1.6)      |
| RFA treatment sessions, mean (SD)| 2.7 (1.3)    | 2.7 (1.5)      |
| IMC                         | 39              | 39              |
| N                           | 27 (93)         | 27 (87)         |
| CED                         | 24 (83)         | 24 (77)         |
| Total treatment sessions, mean (SD)| 4.0 (2.4)    | 4.1 (2.4)      |
| RFA treatment sessions, mean (SD)| 2.9 (1.9)    | 2.9 (2.0)      |
The data supporting endoscopic screening and surveillance are weak and subject to bias. There is no strong evidence that what is done now makes a difference.
Is Surveillance for BE Effective?

- Some retrospective data suggest that surveillance for BE may be effective
  - Subjects developing cancer under surveillance have earlier stage disease than those presenting symptomatically
  - Subjects developing cancer under surveillance have longer survival than those presenting symptomatically

Peters JH, J Thor CV Surg 1994
van Sandick JW, Gut 1998
Corley DA, Gastroenterology 2002

Surveillance Cancers are Less Advanced

Lead Time Bias

Subject A Diagnosed

Subject B Screened and Diagnosed


Surveillance Cancers are Less Advanced?

Effect of a prior endoscopy on outcomes of esophageal adenocarcinoma among United States veterans

Joel H. Rubenstein, MD, MSc, Amnon Sonnenberg, MD, MSc, Jennifer Davis, MHSA, Laurence McMahon, MD, MPH, John M. Inadomi, MD
Ann Arbor, Michigan, Portland, Oregon, San Francisco, California, USA

155 Subjects in the US VA System, EGD from 1-5 yrs prior to diagnosis
Rubenstein JR et al, GIE 2008

GERD symptom presence and frequency are poor predictors of the presence of BE.
Many of those developing cancer have no or trivial reflux symptoms.

- Series of esophageal carcinoma demonstrate 20-51% of subjects have no or infrequent reflux symptoms
- Removal of those subjects from our endoscopy pool cuts the number of “findable” cancer by 40%.

Cheung WY et al, Carcinogenesis, 2009.  
**We are not getting to the people we need**

**Proportion of EAC Patients with Known BE**

<table>
<thead>
<tr>
<th>Proportion of EAC Patients with Known BE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No BE</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Dulai GS, Gastroenterology 2002.
Cooper GS, GIE, 2009.

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**Impact of Endoscopic Surveillance on Mortality From Barrett's Esophagus-Associated Esophageal Adenocarcinomas**

**Table 4. Associations Between Surveillance Endoscopy and Fatal Adenocarcinomas**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Case (%)</th>
<th>Control (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance examination within 3 years</td>
<td>21 (55.3)</td>
<td>61 (60.4)</td>
<td>0.82 (0.56-1.20)</td>
</tr>
<tr>
<td>Dysplasia status (main model)</td>
<td>21 (55.3)</td>
<td>61 (60.4)</td>
<td>0.99 (0.30-2.75)</td>
</tr>
<tr>
<td>Barrett's esophagus length</td>
<td>21 (55.3)</td>
<td>61 (60.4)</td>
<td>0.97 (0.38-2.50)</td>
</tr>
<tr>
<td>Dysplasia status and Barrett's esophagus length</td>
<td>21 (55.3)</td>
<td>61 (60.4)</td>
<td>1.14 (0.59-2.22)</td>
</tr>
<tr>
<td>Excluding cases with 7-12 months between Barrett's esophagus and cancer diagnoses, adjusted for dysplasia status</td>
<td>19 (52.8)</td>
<td>57 (60.0)</td>
<td>0.95 (0.32-2.70)</td>
</tr>
<tr>
<td>Excluding cases with high-grade dysplasia before 3-year surveillance interval, adjusted for other dysplasia status</td>
<td>16 (55.2)</td>
<td>36 (52.8)</td>
<td>1.00 (0.34-2.94)</td>
</tr>
<tr>
<td>Excluding cases with gastroesophageal junction adenocarcinomas, adjusted for dysplasia status</td>
<td>19 (61.3)</td>
<td>57 (67.1)</td>
<td>0.88 (0.29-2.67)</td>
</tr>
<tr>
<td>Excluding cases unable to be treated, adjusted for dysplasia status</td>
<td>18 (56.3)</td>
<td>54 (64.3)</td>
<td>0.80 (0.27-2.54)</td>
</tr>
<tr>
<td>Excluding cases with treatment-related mortality or unable to be treated, adjusted for dysplasia status</td>
<td>14 (45.9)</td>
<td>47 (69.3)</td>
<td>0.46 (0.13-1.64)</td>
</tr>
</tbody>
</table>

Total: 38 (100) 101 (100)
It is not for lack of trying...

Why the discrepancy between the Gastroenterologist and the Epidemiologist?

1) We are underestimating the cumulative effect of the individual mistakes we make!
2) We are not recognizing the impact of limiting our screenable population.

Imagine a (not so) hypothetical situation where...

- 80% of appropriate surveillance candidates actually return for their exams, AND,
- In those patients, 80% have appropriate biopsy protocols followed, AND,
- In those patients, 80% have the correct histological diagnosis made, AND,
- In those patients, 80% have the correct intervention based on that histology...
- THE OVERALL LIKELIHOOD OF SUCCESSFUL ADMINISTRATION OF SURVEILLANCE UPPER ENDOSCOPY IS 41%

So Can We Prevent Cancer in Barrett’s Esophagus?

YES!!!
But probably not by doing what we have been doing...
The Way Forward...

When You Are Looking for a Needle in a Haystack, Make the Needle Bigger, the Haystack Smaller, or Get a Stronger Pitchfork.
Making the Needle Bigger...

Making the Needle Bigger...

Nicholas J. Shaheen, MD, MPH, FACG
Making the Needle Bigger...

Making the Haystack Smaller

The Pitchforks of the Future?

How Good is the Sponge?

• 501 subjects screened in a general medicine population, EGD used as gold standard

• For BE of ≥ 1 cm:
  – Sensitivity – 73.3% (44.9-92.2%)
  – Specificity – 93.8% (91.3-95.8%)

• For BE of ≥ 2 cm:
  – Sensitivity – 90.0% (55.5-99.7%)
  – Specificity – 93.5% (90.9-95.5%)

### What is the Yield of TNE in a Primary Care Population?

<table>
<thead>
<tr>
<th>Characteristics (n = 426)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis</td>
<td>143 (34)</td>
</tr>
<tr>
<td>LA Grade A</td>
<td>73 (51)</td>
</tr>
<tr>
<td>LA Grade B</td>
<td>46 (32)</td>
</tr>
<tr>
<td>LA Grade C</td>
<td>18 (13)</td>
</tr>
<tr>
<td>LA Grade D</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Hiatal Hernia</td>
<td>180 (43)</td>
</tr>
<tr>
<td>Barrett's Esophagus</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Esophageal Mass/Nodularity</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>15 (4)</td>
</tr>
</tbody>
</table>

*Peery AF, Shaheen NJ. Jobe B. Gastrointest Endosc 2012*
Conclusions

• The epidemiology of both BE and EAC is unfavorable and worrisome
• Current screening and surveillance practices in BE are limited by poor risk stratification
• Doing what we have been doing, but harder, is not a good option
• Relatively small changes in our current paradigm would result in incremental improvements
• A “disruptive technology” is needed to improve our approach to preventing esophageal adenocarcinoma

How Might This Impact My Practice?

• For Now...
  – Obey Sutton’s Law
    • If you are going to do screening, pay attention to GERD complaints in old white males with truncal obesity
• In the Future...
  – Stay tuned for a “risk stratification panel,” which may include anthropometric measurements, demographics, genetic markers, and genotyping of important determinants of phenotypic expression
    • The biggest benefit of such a panel might be telling us who we don’t need to worry about
  – Look for a low-cost, widely available (?non-endoscopic?) screening test to open the top of the funnel
  – Surveillance will be supplanted by more active intervention
“The Best Day in the Life of any Barrett’s Patient is the Day their Endoscopist Dies.”

-Steve Sontag, MD