Endoscopic Management of Barrett’s Esophagus

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Adenocarcinoma – A Disease with a Rapidly Increasing Incidence

Not Much Progress Being Made…


Outline

• How good are we at diagnosing BE endoscopically?
• What are the risks of progression in BE?
• What are the management options for ND, LGD & HGD?
  – What data support efficacy of ablative therapy in non-dysplastic & dysplastic BE?
• What is an appropriate algorithm to follow for endoscopic intervention in BE?
Is this Barrett’s?

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Barrett’s Classification and Management

- Non-dysplastic IM
  - Surveillance every 3 years
  - Detect progression to dysplasia or cancer
- LGD (low-grade dysplasia)
  - Surveillance every 6-12 months
  - Detect progression to HGD or cancer
- HGD (high-grade dysplasia)
  - Surveillance every 3 months
  - Esophagectomy
  - EMR and ablation: options at select institutions

Progression to Cancer in HGD

<table>
<thead>
<tr>
<th>Study</th>
<th>Surveillance Period</th>
<th>Percentage</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buttar et al</td>
<td>8 Years</td>
<td>32%</td>
<td>100</td>
</tr>
<tr>
<td>Schnell et al</td>
<td>7.3 Years</td>
<td>16%</td>
<td>77</td>
</tr>
<tr>
<td>Reid et al</td>
<td>5 Years</td>
<td>59%</td>
<td>76</td>
</tr>
</tbody>
</table>

How Benign is Low-Grade Dysplasia?

- 147 subjects with a diagnosis of LGD made in a community practice in the Netherlands
- Path reviewed by 2 expert pathologists
  - Disagreements resolved by consensus
- 85% of cases were down-graded
- In the 15% who were not, the incidence rate of HGD or EAC was 13.4%/pt-yr (mean f/u: 51 months)


Is It Really Dysplastic?

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>LGD (n=83)</th>
<th>HGD (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>24.1%</td>
<td>3.9%</td>
</tr>
<tr>
<td>HGD</td>
<td>72.3%</td>
<td>23.3%</td>
</tr>
<tr>
<td>LGD</td>
<td>1.2%</td>
<td>3.9%</td>
</tr>
<tr>
<td>IND/ND-IM</td>
<td>2.4%</td>
<td>69.0%</td>
</tr>
</tbody>
</table>

Home Institution Diagnosis
Rate of Progression of Non-Dysplastic BE may be Lower than Appreciated!

- Meta-analyses suggest rate of progression to cancer of app 0.5% per pt-yr\(^1\)

![Graph showing rate of progression of BE](image)


What is ablation?

- Destruction and, ultimately, removal of a cell, epithelium, tissue
- Seminal observation: BE, when ablated in an anacidic milieu, regenerates squamous epithelium
- Mechanism: heating of tissue to the point of vaporization and/or coagulation of proteins
- Endpoint is irreversible cell injury and, ultimately, cell death
The Case for Ablation in HGD

- The risk of progression of the lesion is high
- The risk of a metachronous cancer is substantial
- The competing strategy (surgery) is morbid
- Patients are often more comfortable with a proactive strategy
- Some data to suggest a decreased cancer risk
What is the Risk of Death with Esophagectomy?

30 Day Mortality

What about lesser forms of dysplasia and metaplasia (LGD, Indefinite, ND-BE)?

- Given lower rates of progression here, side effects and costs of therapy become important
- No data showing diminished cancer risk in these patient populations

so ablation seems reasonable for HGD…
Circumferential RFA Catheter

Focal RFA Device
AIM Dysplasia Trial

U.S. multi-center, randomized, single-blind, sham-controlled clinical trial

Methods

• Randomized, sham-controlled design
  – 2:1 RFA vs sham
  – length stratified (1-4 cm vs 4-8 cm)
  – four maximum RFA sessions
  – identical biopsy protocols, equal sampling
  – 12 mo cross-over assures treatment for all
• 127 patients enrolled @ 19 centers
• Centralized pathology at Cleveland Clinic


Endpoints

• Primary
  – Complete Eradication of Dysplasia
    • RFA vs. sham
    • Analyzed by baseline grade of dysplasia
  – Complete Eradication of Intestinal Metaplasia
    • RFA vs. sham, all patients
• Secondary
  – Histological progression (HGD to CA, LGD to HGD, LGD to CA)
  – Adverse event incidence


3 year Durability

Durability of Eradication of IM Without Intervention

- IM-Free Proportion
- Days Since Eradication of IM
- Group: HGD, LGD

Shaheen NJ et al, Gastroenterology, 2011.

U.S. RFA Registry

<table>
<thead>
<tr>
<th></th>
<th>Any complication (n=159)</th>
<th>Perforation (n=2)</th>
<th>Stricture formation (n=117)</th>
<th>Bleeding (n=20)</th>
<th>Hospitalization (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient treated</td>
<td>2.9%</td>
<td>0.04%</td>
<td>2.1%</td>
<td>0.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>(n=5539)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Per procedure</td>
<td>1.1%</td>
<td>0.01%</td>
<td>0.8%</td>
<td>0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>performed (n=13829)</td>
<td></td>
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Bulsiewicz et al, DDW 2012
U.S. RFA Registry, cont.

Predicted Values and 95% CI for Total RFA sessions (360 + 90)

Total length BE

Predicted Value 95% CI

Bulsiewicz et al. DDW 2012

Evolving Technology in BE
Cryotherapy in HGD: An Initial Report

- 98 subjects w/ HGD treated at 10 institutions
  - 61 completed Rx, 27 ongoing
- 281 total procedures
  - 4.0/pt
- No perfs, no buried glands, no bleeds or chest pain requiring hospitalization
- One progression to CA

An Algorithm for Endoscopic Management of Barrett’s Neoplasia

Nodular Disease Should Be EMR’ed!

Ell C et al. GIE, 2007
What is the Likelihood of LN Involvement with IMC?

<table>
<thead>
<tr>
<th>Author, Yr</th>
<th>Intramucosal Cancers Surgically Resected</th>
<th>% Lymph Node Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pech, 2011</td>
<td>38</td>
<td>0 (0/38)</td>
</tr>
<tr>
<td>Sepesi, 2010</td>
<td>25</td>
<td>0 (0/25)</td>
</tr>
<tr>
<td>Bollschweiler, 2006</td>
<td>16</td>
<td>0 (0/16)</td>
</tr>
<tr>
<td>Stein, 2005</td>
<td>70</td>
<td>0 (0/70)</td>
</tr>
<tr>
<td>Buskens, 2004</td>
<td>35</td>
<td>0 (0/35)</td>
</tr>
</tbody>
</table>

Prevalence of Metastatic LN’s in T1 Esophageal Adenocarcinoma

Sepesi et al, JACS, 2010
Algorithm, cont.

- For subjects with nodular disease, EMR histology decides further management
  - No cancer, mucosal cancer, or maybe sm1 cancer -> ablative therapy
  - Worse than sm1 -> consideration of multimodality Rx and esophagectomy
- Flat HGD -> ablation
  - Given current data, RFA seems most appropriate

Algorithm, cont.

- LGD
  - Unifocal, elderly, and/or wishing conservative Rx -> surveillance endo’s
  - Multifocal, previously nodular, young, family hx of cancer, pathologically worried -> consider ablation
    - Caveats about lack of data on decreasing cancer
- Non-dysplastic
  - Ablation is an option, but role in average risk patients not clear
What are the Conceptual Challenges in Ablation?

- Are we defining “durability” appropriately?
  - Is ablation to be conceptualized as a one-time intervention, or as chronic recurrent suppressive therapy?
  - If we cause a procrastination of cancer for 10 yrs, that may be as good as a cure for many pts
  - WHAT IS THE NATURAL HISTORY OF RECURRENT BE POST-ABLATION?
- Are we using adequate metrics to measure changes in QoL and psychological impact?
- All of our efficacy outcomes are surrogates for cancer death
  - Are they adequate?

Conclusions

- Our current approach to BE is illogical and has not improved outcomes
- There is a compelling rationale for ablative therapy in dysplastic BE
  - But what about lesser disease?
- There are multiple strategies for ablation
- Best done by physicians committed to ablation
- RFA more effective & better tolerated than previous modalities
  - Is the neosquamous tissue really “normal?”
“The Best Day in the Life of any Barrett’s Patient is the Day their Endoscopist Dies.”

-Steve Sontag, MD