Barrett’s Esophagus: Old Dog, New Tricks

Stuart Jon Spechler, M.D.
Chief, Division of Gastroenterology,
VA North Texas Healthcare System;
Co-Director, Esophageal Diseases Center,
Professor of Medicine,
Berta M. and Cecil O. Patterson Chair in Gastroenterology,
UT Southwestern Medical Center

Barrett’s Esophagus
The condition in which a metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus

Affects 5.6% of adult Americans

Metaplasia
One type of adult tissue replaces another
Response to chronic tissue injury

Stratified Squamous Epithelium
(Normal Esophagus)

Intestinal Metaplasia
(Barrett's Esophagus)

GERD
Reflux Esophagitis

Esophageal mucosal damage can heal through:
Regeneration of squamous epithelium
Columnar metaplasia

Pathogenesis of Barrett's Metaplasia

Potential Progenitor Cells for Columnar Metaplasia

- **Mature squamous cells** change into columnar cells
  - Transdifferentiation – involves individual differentiated cells

- **Immature progenitor cells**
  - Can produce and maintain multiple different cell types

  - **Progenitor cells native to esophagus**
    - Basal cells of squamous epithelium
    - Cells in submucosal gland ducts

  - **Progenitor cells in proximal stomach**
    - Gastric cardia
    - Embryonic-type cells at GEJ

  - **Progenitor cells from bone marrow**

  Must involve reflux-related reprogramming of the expression of developmental transcription factors

Goblet Cells

Squamous Epithelium

Intestinal Metaplasia
**British Society of Gastroenterology**
**Definition of Barrett’s Esophagus 2014**

“An esophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1 cm) above the GOJ and confirmed histopathologically from oesophageal biopsies.”


**Includes cardiac mucosa**

- Can be metaplastic, acquired as a result of reflux
- Expresses molecular markers of intestinal differentiation (e.g. villin, CDX2)
- Exhibits DNA content abnormalities similar to intestinal metaplasia
- One study suggests cancer risk is similar to that for intestinal metaplasia

Intestinal Metaplasia (with goblet cells)

• Estimates of cancer risk in Barrett's based on studies that included patients with intestinal metaplasia either primarily or exclusively

• Goblet cell unlikely to be cell of origin for adenocarcinoma, but goblet cell a good marker for malignant predisposition

• Most studies suggest cancer risk for cardiac mucosa alone is minimal


Disagreement on Histological Criteria for Barrett's Esophagus

• Should Barrett's esophagus be defined as...

  a histological curiosity?
  (a mucosal metaplasia irrespective of its clinical importance)

  a medical condition?
  (a mucosal metaplasia that predisposes to cancer)

Barrett’s Esophagus

**Conceptual Definition**

The condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus

**Diagnostic Criterion**

Intestinal metaplasia (with goblet cells) in the esophagus


Risk Factors for Barrett's Esophagus and Esophageal Adenocarcinoma

• **Chronic GERD**
  Heartburn, hiatal hernia

• **Age >50 years**
  Uncommon in children

• **Male sex**

• **White race**
  Less common in African-Americans, Uncommon in Asians

• **Obesity**
  Intra-abdominal fat distribution
AGA Medical Position Statement on Endoscopic Screening for Barrett’s Esophagus

- We recommend against screening the general population with GERD for Barrett’s esophagus.
- In patients with multiple risk factors associated with esophageal adenocarcinoma, we suggest screening for Barrett’s esophagus.

Chronic GERD, hiatal hernia, age ≥50, male gender, white race, elevated BMI, intra-abdominal body fat distribution


U.S. Incidence of Esophageal Adenocarcinoma Has Been Rising

- 1990s Estimate: 1% per year
  1 in 100 patients per year

- 2000s Estimate: 0.5% per year
  1 in 200 patients per year

- 2015 Estimate: 0.25% per year
  1 in 400 patients per year

Endoscopic Surveillance Might Not Decrease Mortality from Esophageal Adenocarcinoma

- 8,272 pts. with Barrett’s esophagus (BE)
- Surveillance endoscopy within 3 years was NOT associated with decreased risk of death from esophageal cancer (adjusted odds ratio 0.99; 95% CI 0.36-2.75)

Do Proton Pump Inhibitors (PPIs) Prevent Cancer in Barrett’s Esophagus?

- PPIs are the most effective medical treatment for reflux esophagitis
  - Decrease gastric acid production
  - Decrease acid reflux
  - Heal reflux esophagitis

- Evidence that PPIs prevent carcinogenesis in Barrett’s esophagus is indirect and not proven in controlled trials.

PPIs Reduce the Risk of Neoplastic Progression in Barrett’s Esophagus

540 Barrett’s patients, median follow-up 5.2 years

PPI use associated with 75% reduction in risk of neoplastic progression


AGA Medical Position Statement on the Treatment of GERD in Barrett’s Esophagus

- GERD therapy with medication effective to treat GERD symptoms and to heal reflux esophagitis is clearly indicated.

- Antireflux surgery is not more effective than medical therapy for prevention of cancer in Barrett's esophagus.

- We recommend against attempts to eliminate esophageal acid exposure (PPIs in doses >once daily or antireflux surgery) for cancer prevention.


AGA Medical Position Statement on Endoscopic Surveillance for Barrett’s Esophagus

- We suggest that endoscopic surveillance [with biopsy] be performed in patients with Barrett’s esophagus.

- We suggest the following surveillance intervals:
  - No dysplasia: 3-5 years
  - Low-grade dysplasia: 6-12 months
  - High-grade dysplasia in the absence of eradication therapy: 3 months

The Cancer Risk for High-Grade Dysplasia in Barrett’s is Sufficient to Warrant Intervention

~6% per year


AGA Medical Position Statement on the Management of Barrett’s Esophagus

• We recommend endoscopic eradication therapy rather than surveillance for treatment of patients with confirmed high-grade dysplasia in Barrett’s esophagus.

Accurate T Staging **Crucial** to Determine if Curative Endoscopic Therapy Feasible

- High Grade Dysplasia, Intramucosal Carcinoma
  
  *Lymph node metastases in 1%-2%*
  
  *Curative endoscopic therapy feasible*

- Submucosal invasion
  
  *Lymph node metastases in >10%*
  
  *Failure rate for endoscopic therapy unacceptable*

- Endoscopic mucosal resection (EMR) the best procedure for T staging

---

**Systematic Review**: Risk of Lymph Node Metastases for High Grade Dysplasia (HGD) or Intramucosal Carcinoma (IMC) in Barrett’s Esophagus

- Reviewed studies that included:
  - Patients who had esophagectomy for HGD or IMC and
  - Final surgical pathology results (lymph node status)
- **Identified 70 relevant articles**
  - 1,874 patients who had esophagectomy for HGD (524 patients) or IMC (1,350 patients)
  - **Lymph node metastases in 26 of 1,874 patients** *(1.39%, 95% CI 0.86% - 1.92%)*

**Excerpts from Dunbar K, Spechler S. Am J Gastroenterol 2012;107:850.**

---

**EMR is as much a staging procedure as it is a therapeutic procedure.**

If EMR shows submucosal invasion, then endoscopic therapy is not advised.
Radiofrequency Ablation (RFA)

Closely spaced electrodes

Radiofrequency Ablation of Barrett’s Esophagus

Randomized, Sham-Controlled Trial of Radiofrequency Ablation for Dysplasia in Barrett’s


Radiofrequency Ablation of Dysplasia Prevents Neoplastic Progression at One Year

Complications of Radiofrequency Ablation in 84 Patients

5 esophageal strictures (6%)
1 UGI Bleed (1%)
2 hospitalizations for chest pain (2%)


Randomized Trial of RFA vs. Surveillance for Low-Grade Dysplasia (LGD) in Barrett's Esophagus

- 136 patients with LGD confirmed by expert pathologist
  - Randomized to RFA (68 pts.) or surveillance (68 pts.)
- Progression to high-grade dysplasia or cancer at 3 years
  - 1.5% RFA group
  - 26.5% surveillance group
  - 7.4% ↓ risk of cancer (95% CI 0-14.7%, P=.03)

Phoa KN. JAMA 2014;311:1209.

Data & Safety Monitoring Board early termination:
RFA superior to surveillance for preventing neoplastic progression
Potential for patient safety issues if trial continued

Issues
- 28% of patients in surveillance group had no dysplasia detectable on follow-up
- No patient in surveillance group developed an unresectable tumor
- No patient in surveillance died of cancer

Phoa KN. JAMA 2014;311:1209.

Endoscopic Eradication Therapy for Mucosal Neoplasia in Barrett's Esophagus 2015

- EMR of mucosal irregularities for staging and therapy
- Radiofrequency ablation of remaining Barrett's metaplasia to minimize metachronous neoplasia
Recurrence of Neoplasia and Metaplasia after Endoscopic Eradication of Mucosal Neoplasia

- 246 patients with HGD or IMC in Barrett’s esophagus
  - Completely eradicated intestinal metaplasia (IM) in 80%


RFA for Non-Dysplastic Barrett’s Esophagus?

- Generally requires several endoscopies for complete eradication
- Complication rate low, but not trivial
- Substantial rate of recurrence of metaplasia
- Efficacy in preventing cancer not established
- Does not eliminate need for surveillance

AGA Medical Position Statement on the Management of Barrett’s Esophagus

- Endoscopic eradication therapy is not suggested for the general population of patients with Barrett’s esophagus in the absence of dysplasia.

- RFA should be a therapeutic option for select individuals with non-dysplastic Barrett’s esophagus who are judged to be at increased risk for progression to HGD or cancer.

Specific criteria that identify this population have not been fully defined.

• **Knowledge** is knowing a tomato is a fruit.

• **Wisdom** is knowing not to put it in a fruit salad.