Barrett’s Ablation and Management of Dysplasia

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American College of Gastroenterology
2014 Regional Postgraduate Course
Louisiana Gastroenterology Society

Disclosures

- I have no disclosures
Objectives

- Review the epidemiology of Barrett’s Esophagus and current guidelines for its management in the U.S.
- Review the clinically available Advance Imaging technologies targeted for early detection of BE and BE associated neoplasia
- Introduce the background data related to the grades of dysplasia and associated risks of progression
- Briefly introduce the benefits and challenges to treatment options for BE
- Review the role, options and outcomes for radiofrequency ablation (RFA)

Background – Barrett’s Esophagus
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Epidemiology of BE

- Barrett’s esophagus a well recognized risk factor for esophageal adenocarcinoma (EAC)
- Incidence of EAC has been rapidly increasing in the United States
- Incidence of EAC estimated 5.31 / 100,000
- Prevalence of BE in the adult population estimated between 0.4 – 2%
- Patients with HGD or IMC, the optimal management remains controversial
- Late stage EAC remains highly lethal with a 5-year survival rate of 13 - 15%

2 Ronkainen et al. Gastroenterology 2005;129:1825-31
3 Lyday et al. Endoscopy 2010;42:272-8
5 Year Survival of Esophageal Adenocarcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>90%</td>
</tr>
<tr>
<td>T2</td>
<td>70 – 50%</td>
</tr>
<tr>
<td>T3</td>
<td>33 – 10%</td>
</tr>
<tr>
<td>T4</td>
<td>&lt;5%</td>
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</tbody>
</table>

ACG/LGS Regional Postgraduate Course - New Orleans, LA
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**Guidelines for BE Management**

2012

2011

**Selection Criteria for Screening**

- Population screening should not be offered

- Screening offered to patients with “multiple risk factors”
  - weak recommendation, moderate-quality evidence
  - many patients have BE without symptoms – unclear etiology of pathogenesis

Spechler S et al., Gastroenterology 2011; 140:1084-91
Clinical Predictors of BE/Progression

- Longstanding GERD (>8 Years)
- Age >50
- Race (Caucasian)
- Gender – Male gender
- BMI >25 at age 20 (central – obesity)
- Smoking
- Diet

Remember: approximately half of patients with BE do not have GERD

Predictors of Progression to EAC

Clinical Predictors
- Age
- Race
- Gender – Male gender
- BMI
- Smoking
- Diet
- NSAIDs, ASA, PPI

Genetic Predictors
- p53 positive; loss of heterozygosity
- DNA content abnormalities: aneuploidy/tetraploidy

Endoscopic Predictors
- Length of BE
- Hiatal hernia length
- Nodularity and visible lesions

Histopathology Predictors
- Grade of Dysplasia
- HGD >5 crypts or multifocal

1 Prasad et al, Am J Gastroenterol; 105: 1490-1502
2 Prasad et al, Am J Gastroenterol; 105: 1490-1502
Predictors of Progression to EAC

**Clinical Predictors**
- Age
- Race (Caucasian)
- Gender – Male gender (2x)
- BMI
- Smoking
- Diet
- NSAIDs, ASA, PPI

**Endoscopic Predictors**
- Length of BE
- Hiatal hernia length
- Nodularity and visible lesions

**Histopathology Predictors**
- Grade of Dysplasia*
- Extent of dysplasia: HGD

Genetic Predictors
- p53 positive; loss of heterozygosity
- DNA content abnormalities: aneuploidy/tetraploidy

**Diagnosis of BE - Standard of Care**
- Identify landmarks, map lesions etc., (TGF, SCJ, Mucosal defects – Prague Criteria)
- Take Your Time
- Distal Imaging Cap Attachment - Helpful

*Prasad et al, Am J Gastroenterol; 105: 1490-1502
**Surveillance Intervals**

**AGA 2011**
- No dysplasia: 3-5 years
- Low-grade dysplasia: 6-12 months
- High-grade dysplasia in the absence of eradication therapy: 3 months.

**ASGE 2012**

**ACG 2008**

<table>
<thead>
<tr>
<th>Dysplasia Grade and Surveillance Interval</th>
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<tbody>
<tr>
<td>Grade</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>High</td>
</tr>
</tbody>
</table>
**Surveillance Intervals**

- No dysplasia: 3–5 years
  - (consider no surveillance - ASGE guideline)

- Low-grade dysplasia: 6–12 months
  - Confirm with Expert GI Pathologist

- High-grade dysplasia in the absence of eradication therapy: 3 months
  - Resection / Ablation / Surgery recommended

**Summary: Diagnosis and Management Strategy**

- Careful White Light Endoscopy Examination
  - Longer inspection increases yield of BE associated neoplasia

- 4 quadrant mucosal biopsies (large capacity forces)
  - Every 2 cm – Non dysplastic BE
  - Every 1cm – BE associated dysplasia

- Biopsies should be evaluated by at least 2 pathologist, one of which should be an expert GI pathologist to “confirm” grades of dysplasia, if present

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1 Spechler S et al., Gastroenterology 2011; 140:1084-91
2 Gupta N, et al, Gastrointest Endosc 2012; 76:531-8
Adherence to Seattle Protocol in a U.S. Community Practice

Objectives

- Review the epidemiology of Barrett’s Esophagus and current guidelines for its management in the U.S.

- Review the clinically available Advance Imaging technologies targeted for early detection of BE and BE associated neoplasia

- Introduce the background data related to the grades of dysplasia and associated risks of each

- Briefly introduce the benefits and challenges to treatment options for BE

- Review the role, options and outcomes for radiofrequency ablation (RFA)

*Abrams et al., Clin Gastroenterol Hepatol, 2009 (7) 736-42*
Proposed Management Algorithm

2010

Overview of Virtual Chromoendoscopy (VC) Platforms

- VC is currently available across three endoscopic platforms coupled with high resolution WLE (HR-WLE)
  - Narrow band imaging (NBI) (Olympus, Tokyo, Japan)
  - i-Scan (Pentax Medical, Japan)
  - Fuji Intelligent Color Enhancement (FICE, Fujinon Corporation, Saitama, Japan)
- Real time access via a press of a button on the endoscope
- Rapid switching between the conventional HR WLE and chromoscopic images.
- Each endoscopic platform accomplishes VC with different technologies and algorithms.
Narrow Band Imaging

- Uses optical filters set at 415±30 nm; 445±30 nm; 500±30 nm to achieve the preferred appearance of vascular patterns.
i - Scan

Three software imaging algorithms for mucosal:

- Surface enhancement
- Contrast enhancement
- Tone enhancement

Fuji Intelligent Color Enhancement

- Deconstructs the real-time endoscopic WLE image into a spectral image
- Virtual electronic filters the image is reconstructed with selected wavelengths
Does Detection of IM/Dysplasia Improve with Virtual Chromoendoscopy?

High Resolution

Virtual Chromoendoscopy

Not formally recommended in the guidelines – but use virtual chromoendoscopy if you have it – no down side – push the button

Design: Prospective, controlled tandem endoscopy study

Methods: Standard resolution (SR) -> High resolution + NBI

65 patients - All with previously diagnosed dysplasia undergoing surveillance

Primary Endpoint: Whether NBI targeted biopsies could detect advanced dysplasia using fewer biopsy samples compared with SR endoscopy.

Results: Higher grades of dysplasia were found by NBI in 12 patients (18%), compared with no cases (0%) in whom standard resolution white light endoscopy with random biopsy detected a higher grade of histology (P < .001).

Conclusion: NBI detected significantly more patients with dysplasia and higher grades of dysplasia with fewer biopsy samples compared with standard resolution endoscopy.

Wolfsen et al. Gasteroenterology 2008
Advanced Mucosal Imaging of the Esophagus

- Optical Endomicroscopy
  - Confocal Laser Endomicroscopy (CLE)
    - Endoscope – Based
    - Probe – Based
  - Volumetric Laser Endomicroscopy (VLE)
    - Optical Coherence Tomography
    - Optical Frequency Domain Imaging

Optical Endomicroscopy

Endoscopic (eCLE) 2004

Probe (pCLE) 2006 and Needle (nCLE) 2013

OCT (VLE) 2013
**Representative Images of eCLE & Mainz Confocal Barrett Classification**

**Figure A.**
BE: Intestinal Metaplasia with subepithelial capillaries of regular shape beneath columnar lined epithelium visible in upper part of the mucosal layer.

**Figure B.**
BE: Columnar lined epithelium with in between dark mucin in goblet cells in upper part of the mucosal layer.

**Figure C.**
BE – Neoplasia: Black cells with irregular apical and distal borders and shapes with high dark contrast to surrounding tissue.

**Figure D.**
BE – Neoplasia: Leakage of vessels leads to a heterogenous and brighter signal intensity within the lamina propria.

**eCLE Images - BE**
**eCLE - IMC**

**In vivo endoscopy improves detection of Barrett's esophagus–related neoplasia: a multicenter international randomized controlled trial (with video)**

Marcia Irene Canto, MD, MPH, MD; Sharmila Amadasun-Ashley, MD; William Brugge, MD; Gary W. Falk, MD; Kerry B. Dunbar, MD, PhD; Zhe Zhang, PhD; Kevin Woods, MD, MPH; Jose Antonio Almario, BS, MPH; Ursula Scheib, RN; John Goldblum, MD; Arifb Varma, MD; Elizabeth Montgomery, MD; Ralf Keeslack, MD, PhD; for the Confocal Endoscopy for Barrett’s Esophagus or Confocal Endomicroscopy for Barrett’s Esophagus (CEBE) Trial Group

Baltimore, Maryland, USA

- **Design:** International, Prospective, Multicenter, Randomized, Single blinded, Controlled Trial
- **Setting:** Academic Medical Centers
- **Patients:** 192 BE patients undergoing surveillance or referred for early neoplasia
- **Primary Endpoint:** Diagnostic Yield For Neoplasia
- **Secondary Endpoints:**
  - Performance characteristics of endoscope–based CLE
  - Clinical Impact

Comparison of Diagnostic Yield For Neoplasia

Per-Biopsy Analysis

Per-Patient Analysis

eCLE Performance

**Table 2.** Performance characteristics for diagnosis of Barrett’s esophagus-related neoplasia HDWLE versus HDWLE + CLE, by group.

<table>
<thead>
<tr>
<th>Variable, %</th>
<th>Per biopsy analysis n = 978 biopsy specimens</th>
<th>Per patient analysis n = 192 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDWLE, n = 589</td>
<td>HDWLE + CLE, n = 388</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>Specificity</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td>Accuracy</td>
<td>93</td>
<td>93</td>
</tr>
</tbody>
</table>

*HDWLE, high-definition white-light endoscopy; CLE, confocal laser endomicroscopy.*

Sensitivity 95%; Specificity 92%; Positive Predictive Value 77%; Negative Predictive Value 98%; Accuracy 93%


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**Probe-based CLE (pCLE)**

A

B
**Representative Images of pCLE & Miami Classification**

- Normal squamous epithelium
  - Flat cells without crypts or cells
  - Deep vessels within papillary Mullerian loops

- Non-dysplastic Barrett's esophagus
  - Villous architecture
  - Columnar cells (black arrow)
  - Dark green cells (line arrow)

- High grade dysplasia
  - Villous structures
  - Focal crypts
  - Lymphocytes (arrow)
  - Capitalization of nuclei

- Adenocarcinoma
  - Edematous mucosa with villous architecture
  - Dark columnar cells (line arrow)
  - Infiltrated irregular vessels (black arrow)

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**ORIGINAL ARTICLE: Clinical Endoscopy**

Real-time increased detection of neoplastic tissue in Barrett’s esophagus with probe-based confocal laser endomicroscopy: final results of an international multicenter, prospective, randomized, controlled trial

Pratik Sharma, MD, Alexander E. Meining, MD, PhD, Emmanuel Corson, MD, Charles J. Lighthall, MD, Herbert C. Wolfson, MD, Aly R. Banaji, MD, Mouhier Bakour, MD, Jean-Paul Galinich, MD, Julian A. Abrams, MD, Amir Bassaghi, MD, Neil Gupta, MD, MPH, Joel E. Michalik, PhD, Gregory Y. Lowery, MD, Michael B. Wallace, MD, MPH

Kansas City, Missouri, USA; Munich, Germany; Jacksonville, Florida, USA; Nantes, France; New York, New York; Boston, Massachusetts; San Antonio, Texas, USA

- **Design:** International, Prospective, Multicenter, Randomized, Controlled Trial - 11 Endomicroscopist (7 without previous experience)

- **Setting:** Five Tertiary referral centers

- **Patients:** 101 consecutive BE patients (Surveillance or Endoscopic Treatment of HGD/IMC)

- **Primary Endpoint:** Diagnostic characteristics of pCLE
**Original Article: Clinical Endoscopy**

Real-time increased detection of neoplastic tissue in Barrett's esophagus with probe-based confocal laser endomicroscopy: final results of an international multicenter, prospective, randomized, controlled trial

Prateek Sharma, MD, Alexander R. Meining, MD, PhD, Emanuel Cerovic, MD, Charles J. Lijinsky, MD, Herbert C. Wellbery, MD, Ajay Bansal, MD, Monther Balouin, MD, Jean-Paul Goldanica, MD, Julian A. Abrams, MD, Amit Rastogi, MD, Neil Gupta, MD, MPH, Joel E. Michalik, PhD, Gregory Y. Louwars, MD, Michael B. Wallace, MD, MPH

Kansas City, Missouri, USA; Munich, Germany; Jacksonville, Florida, USA; Nantes, France; New York, New York; Boston, Massachusetts; San Antonio, Texas, USA

**Table 4.** Results: per patient analysis on sensitivity and specificity of HD-WLE, NBC, pCLE, and their combinations

<table>
<thead>
<tr>
<th>Detection of HGD/EAC</th>
<th>Sensitivity* (95% CI)</th>
<th>Specificity* (95% CI)</th>
<th>PPV* (95% CI)</th>
<th>NPV* (95% CI)</th>
<th>Patients with HGD/EAC missed (total HGD/EAC = 31, no. (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD-WLE alone</td>
<td>87.50 (76.4-94.1)</td>
<td>91.46 (86.5-92.5)</td>
<td>57.40 (43.2-71.6)</td>
<td>93.60 (85.5-99.4)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>HD-WLE or pCLE</td>
<td>91.50 (84.9-96.0)</td>
<td>91.50 (84.9-96.0)</td>
<td>55.80 (42.3-69.3)</td>
<td>95.30 (96.4-100)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>HD-WLE or NBC</td>
<td>91.50 (84.9-96.0)</td>
<td>91.50 (84.9-96.0)</td>
<td>55.80 (42.3-69.3)</td>
<td>95.30 (96.4-100)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>HD-WLE or NBC or pCLE</td>
<td>100 (100-100)</td>
<td>55.70 (44.1-67.4)</td>
<td>50 (37.6-62.4)</td>
<td>100 (100-100)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

HD-WLE, High-definition white light endoscopy; NBC, narrow-band imaging; pCLE, probe-based confocal laser endomicroscopy; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; HGD/EAC, high-grade dysplasia/early adenocarcinoma.

* Sensitivity, specificity, PPV, and NPV calculated for the detection of lesions with HGD/EAC.

**SENS 100%; SPEC 55.7%; PPV 50%; NPV 100%**

No patient’s missed with HGD/EAC
OCT – Volumetric Laser Endomicroscopy (VLE)

IMAGING EQUIPMENT

SINGLE-USE OPTICAL PROBE

OCT Volumetric Endomicroscopy

SQUAMOUS EPITHELIAL

LAMINA PROPRIA

MUSCULARIS MUCOSA

SUBMUCOSA

MUSCULARIS PROPRIA
Volumetric Laser Endomicroscopy

Squamous Epithelium
Suspicious for HGD

Criteria

NORMAL CARDIA
- Pit and Crypt Architecture
- Highly Reflective Surface
- Reduced Image Penetration

BARRETT'S
- Loss of layered architecture
- Irregular "cribriform" glands
- Glands or ducts in mucosa

HIGH GRADE DYSPLASIA
- Increased surface reflectivity
- Poor surface maturation
- High backscattering
- High nuclear to cytoplasmic ratio

ADENOCARCINOMA
- Reduced image penetration
- Loss of layered architecture

SCALE BAR = 2MM

* Image Review and Assessment performed by Dr. Gary Teamey, MGH Boston
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Changes in Clinical Practice in the Management of BE

2010

High Resolution Endoscopy
Narrow Band Imaging
Radio Frequency Ablation (RFA)
Endoscopic Mucosal Resection (EMR)

Spechler et al., Gastroenterology 2010; 138:854-869
What is the Significance of Dysplasia

- Presence of dysplasia
  - strongest single factor that predicts progression to cancer
  - impacts clinical decision making

- Estimates of annual cancer incidence
  - BE without dysplasia = 0.2-0.5%
  - BE with LGD = 0.4 to 13.4%
  - BE with HGD = 5-20%

Grade of Dysplasia and Risk

- BE without dysplasia
- LGD
- Indeterminate
- HGD
- IMC
- SMC

Risk Groups
- Extremely low-risk (NDBE)
- Intermediate risk (LGD)
- High-risk (All Others)
Low Grade Dysplasia

- Significant interobserver variability among expert GI pathologist

- Highly variable data regarding rates of progression to HGD/EAC
  - 0.4 to 13.4% year
    - Related to low no. of pts in studies/ poor study design/ no centralized pathology review

- Concept of regression

2. Hu et al., Gastroenterology 2012;143:567-78

High Grade Dysplasia

- Cancer Incidence 5 – 20% year

- Adenocarcinoma detected in 30-40% of patients with HGD s/p esophagectomy

- Multifocal HGD

- Recommend EUS to evaluate for paraesophageal lymphadenopathy

- Recommend Mucosal Ablation Therapy

2. Hu et al., Gastroenterology 2012;143:567-78
Who Should I Treat? What is the Best Method?

- Intensive surveillance
- Mucosal Resection
- Ablative therapies
  - Radiofrequency Ablation
  - Spray Cryoablation
  - Photodynamic Therapy
  - Argon Plasma Coagulation
- Surgical Resection
Suggested Benefits of EMR

- Therapeutic
- Improves diagnostic consistency
- Staging Modality
- Assessing the risk of lymph node metastasis


Radiofrequency Ablation
**AIM Dysplasia Trial**

- Multicenter, Randomized, SHAM-controlled trial comparing RFA + endoscopic surveillance versus endoscopic surveillance alone in 127 pts.
  - Randomized 2:1 / RFA:SHAM respectively
    - Grade of dysplasia (LGD vs HGD)
    - Length of BE (<4cm vs 4 – 8cm)

- 1 year outcome
  - CE-D 85.7% by ITT analysis
  - CE-D 92.3% per protocol analysis

- SHAM group offered cross over at 13 months
- All patients maintained on 40mg esomeprozole PO BID


**Durability of RFA in Patients with Dysplasia**

- Pts. Enrolled in the initial AIM Dysplasia Trial with CE-IM at 2 years - eligible for 3 year study extension
- 56 patients w/ CE-IM completed 5 year follow up
  - 32 Pts./LGD
  - 24 Pts./HGD

LGD: CE-D = 100%
HGD: CE-D = 96%
All: CE-IM = 91%

Predictors of response were NS (univariable / multivariable analysis)

Shaheen NJ et al., Gastroenterology 2011;141:460-8
What are the Published Outcomes after RFA in Other Studies of Patients with Dysplasia

Outcomes After RFA

Systematic Review by Semlitsch et al.  
(Surgical Endoscopy 2010:1-9)
- 9 Observational Studies
- At least 12 months follow up

- Complete Eradication of BE = 46-100%
- Complete Eradication of BE associated neoplasia = 71-100%
- Low complication rate
- Only mild adverse events reported
Outcomes after RFA in Barretts Associated Neoplasia

- (2013) Single Center Retrospective Cohort Study
- 262 pts – all completed RFA for HGD and IMC
- During 155 patient years of observation,
  - Recurrence occurred in 5.2%/year
  - Progression occurred in 1.9%/year
- Conclusion: Dysplastic patients should be followed post RFA

Areas of Controversy

- Sampling error of surveillance protocol utilizing HD –WLE
- Frequency and length of follow up post RFA
  - Buried Barrett’s
- Should we use other imaging modalities to help identify dysplastic areas before/ during / after treatment?
**Brief Summary of Guidelines**

- Suggest **against requiring** chromoendoscopy or optical endomicroscopy
- **Suggest against** prescribing more than once daily PPI use for acid suppression*
- Encourages shared decision making with the patient regarding surveillance/treatment should be done after confirmation of the presence or absence of dysplasia / neoplasia
- **Currently inadequate** data to support spray cryotherapy as an endoscopic eradication therapy

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**Take Home Messages**

- During Endoscopy Take Your Time
- Document Landmarks / Look for mucosal abnormalities
- **Confirm Grade of Dysplasia with Expert GI Pathologist** Prior to committing to treatment
- Many options for Treatment When Found Early
  - EMR, RFA, Spray Cryo
- **After Initial Therapy – Don’t stop Surveillance**

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1. Spechler S et al., Gastroenterology 2011; 140:1084-91
3. GERD patients should be treated at the minimal dose required to control symptoms.
**Conclusion**

- True risk of progression of LGD unclear
- RFA in patients with dysplasia is safe and well tolerated
- Controversy surrounding treatment of NDBE and LGD
- Patients status post RFA should continued to be followed due to risk of recurrence
- Surveillance strategies are unclear
- New imaging technologies may help clarify at risk individuals early for rescue therapies

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**Thank you for your Attention**

Questions?

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