MANAGEMENT OF BARRETT’S RELATED NEOPLASIA IN 2018

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Division of Gastroenterology and Hepatology
University of Colorado Anschutz Medical Campus
DISCLOSURES

• Supported by the U of Colorado DOM Outstanding Early Scholars Program
• Paul R O’Hara II Endowed Chair in Esophageal Cancer – Madeleine Kane
• NIH-NIDDK U01DK104833 (SVI)
• Supported by the ASGE Endoscopy Research Award (2015, 2017), ACG Clinical Research Award
• Educational Grants – Cook, Medtronic, Boston Scientific
• Consultant – Medtronic, Boston Scientific
ESOPHAGEAL ADENOCARCINOMA
RISING INCIDENCE OF ESOPHAGEAL ADENOCARCINOMA

Rate per 1,000,000


Adenocarcinoma
Squamous Cell Carcinoma
Not otherwise specified

OBJECTIVES

- Role of confirmation of diagnosis by expert GI pathologists
- Review the goals of advanced imaging techniques?
- Role of EMR in BE patients
- What is the optimal management strategy for BE with dysplasia (LGD and HGD) and mucosal cancer
- Candidates for endoscopic eradication therapy
- Management of the post-ablation patient
- Quality indicators and updated guidelines
GUIDELINE

Endoscopic eradication therapy for patients with Barrett’s esophagus–associated dysplasia and intramucosal cancer

Prepared by: STANDARDS OF PRACTICE COMMITTEE
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Development of Quality Indicators for Endoscopic Eradication Therapies in Barrett’s Esophagus: The TREAT-BE (Treatment With Resection and Endoscopic Ablation Techniques for Barrett’s Esophagus) Consortium

Sachin Wani, MD,1,2, V. Raman Muthusamy, MD,2, Nicholas J. Shaheen, MD, MPH,3, Rena Yadlapati, MD,4, Robert Wilson, BA,1, Julian A. Abrams, MD, Jacques Bergman, MD, PhD,5, Amitabh Chak, MD,6, Kenneth Chang, MD,7, Ananya Das, MD,8, John Dumot, MD,9, Steven A. Edmundowicz, MD,10, Glenn Eisen, MD,11, Gary W. Falk, MD,12, M. Brian Fennerty, MD,13, Lauren Gerson, MD, MPH,14, Gregory G. Ginsberg, MD,15, David Grande, BA,16, Matt Hall, PhD,17, Ben Harrel, MLIS,18, John Inadomi, MD,19, Janusz Jankowski, MD,15, Charles J. Lightdale, MD,20, Jitin Makker, MD,21, Robert D. Odze, MD,22, Oliver Triadalopoulos, MD,23, Michael B. Wallace, MD,24, Kenneth Wang, MD,25, John Cheng, MD,26, Michael J. Lipton, MD,27, and the TREAT-BE Investigators

Am J Gastroenterol advance online publication, 1 June 2017. doi:10.1038/ajg.2017.166

Development of quality indicators for endoscopic eradication therapies in Barrett’s esophagus: the TREAT-BE (Treatment with Resection and Endoscopic Ablation Techniques for Barrett’s Esophagus) Consortium

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This document was reviewed and approved by the governing boards of the American Society for Gastrointestinal Endoscopy and the American College of Gastroenterology. It appears simultaneously in Gastrointestinal Endoscopy and the American Journal of Gastroenterology.
In Barrett’s esophagus patients with LGD AND HGD being considered for EET, we suggest confirmation of diagnosis by at least one expert GI pathologist or panel of pathologists compared to review by a single pathologist.

Strength of recommendation: Conditional

Quality of evidence: Low

Wani S et al. Gastrointest Endosc 2018 (in press)
# INTEROBSERVER VARIABILITY AMONG PATHOLOGISTS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Biopsy Kappa (95% CI)</th>
<th>EMR Kappa (95% CI)</th>
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<tbody>
<tr>
<td>NDBE</td>
<td>0.57 (0.52-0.62)</td>
<td>0.51 (0.46-0.56)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>LGD/IND</td>
<td>0.22 (0.17-0.27)</td>
<td>0.33 (0.28-0.39)</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
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<tr>
<td>HGD</td>
<td>0.35 (0.3-0.4)</td>
<td>0.43 (0.38-0.48)</td>
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<tr>
<td></td>
<td>Fair</td>
<td>Moderate</td>
</tr>
<tr>
<td>EAC</td>
<td>0.71 (0.66-0.76)</td>
<td>0.68 (0.63-0.73)</td>
</tr>
<tr>
<td></td>
<td>Substantial</td>
<td>Substantial</td>
</tr>
</tbody>
</table>

Wani S et al, CGH 2010
## INTEROBSERVER VARIABILITY AMONG PATHOLOGISTS

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Wani S et al, CGH 2010
Expert pathology review results in a change in diagnosis (upstaging or downstaging) in 55% of patients. Majority of patients are downgraded to lower pathologic diagnosis.
IMPACT OF EXPERT PATHOLOGY REVIEW ON RISK OF PROGRESSION

• Duits et al
  - 255 patients with LGD
  - Number of pathologists associated with risk of progression to neoplasia (dose-response effect)
  - 3 pathologists agreed (OR 47.14)

• Qumseya et al
  - Increased cumulative risk and incidence of progression based on expert pathology review
  - Confirmed LGD based on expert pathology review associated with a higher rate of disease progression

Duits et al. Gastroenterology 2017; Qumseya B et al. Am J Gastroenterol 2017
For patients in whom a diagnosis of dysplasia has been made, the rate at which the reading is made by a GI pathologist or confirmed by a 2nd pathologist prior to EET.

Type of measure: **Process**
Performance target: **90%**
HIGH RESOLUTION ENDOSCOPY

STANDARD OF CARE
NARROW BAND IMAGING
STANDARDIZED CONSENSUS DRIVEN CLASSIFICATION SYSTEM
ADVANCED IMAGING TO GUIDE EET

- Highest interest level
- Least amount of data
- NBI most widely used technique
- VLE based laser marking
The rate at which landmarks and length of BE is documented using the Prague criteria and presence or absence of visible lesions is documented.

Type of measure: **Process**

Performance target: **90%**
The rate at which the BE segment is inspected using HD-WLE

Type of measure: Process
Performance target: 95%
BASIS OF ENDOSCOPIC THERAPY

HGD
Risk of LN metastasis: 0%
Candidates for EET: yes

Intramucosal cancer
Risk of LN metastasis: 0%–2%
Candidates for EET: yes

Submucosal cancer
Risk of LN metastasis: 0%–54%
Candidates for EET: no

Komanduri S, Muthusamy V, Wani S, Gastroenterology (in press)
In Barrett’s esophagus patients with confirmed HGD/IMC, we recommend against surgery compared with EET.

Strength of recommendation: Strong
Quality of evidence: Very low
# ESOPHAGECTOMY vs. EET

- No difference in 5-yr survival (RR 0.88, 95% CI 0.74-1.04)
- EET group had significantly lower adverse events (RR 0.38, 95% CI 0.2-0.73)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>Pech 2011</td>
<td>0.97</td>
<td>0.86</td>
<td>1.10</td>
<td>0.64</td>
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<td>Prasad 2007</td>
<td>1.00</td>
<td>0.92</td>
<td>1.09</td>
<td>0.99</td>
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<td>Prasad 2009</td>
<td>1.03</td>
<td>0.87</td>
<td>1.21</td>
<td>0.75</td>
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<td>Wani 2014</td>
<td>0.31</td>
<td>0.19</td>
<td>0.51</td>
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<tr>
<td>Schmidt 2014</td>
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<td>0.69</td>
<td>1.07</td>
<td>0.17</td>
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<td></td>
<td>0.88</td>
<td>0.74</td>
<td>1.04</td>
<td>0.14</td>
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</table>

Meta Analysis

Wani S et al. Gastrointest Endosc (in press)
In Barrett’s esophagus patients referred for EET, we recommend endoscopic resection of all visible lesions compared to no endoscopic resection of visible lesions

Strength of recommendation: Strong
Quality of evidence: Moderate

Wani S et al. Gastrointest Endosc (in press)
STAGING EMR
EMR resulted in change in pathologic diagnosis in 39% (95% CI 34-45) of all patients. Majority of patients were upgraded to a higher pathologic diagnosis.

<table>
<thead>
<tr>
<th>Event rate and 95% CI</th>
<th>Event Lower Limit</th>
<th>Event Upper Limit</th>
<th>Event p-Value</th>
<th>Meta Analysis 95% CI</th>
<th>Event Lower Limit</th>
<th>Event Upper Limit</th>
<th>Event p-Value</th>
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<td>Koutsampas</td>
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<tr>
<td>Telakis</td>
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<td>0.32</td>
<td>0.57</td>
<td>0.36</td>
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<td>Wani</td>
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<td>Westra</td>
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<td>0.23</td>
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<td>Thota</td>
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<td>0.01</td>
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<td>Elsadek</td>
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<td>0.00</td>
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<td>-1.00</td>
<td>-0.50</td>
<td>0.00</td>
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<tr>
<td>Nijhawan</td>
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<td>0.63</td>
<td>0.55</td>
<td>-1.00</td>
<td>-0.50</td>
<td>0.00</td>
</tr>
<tr>
<td>Chennat</td>
<td>0.45</td>
<td>0.32</td>
<td>0.59</td>
<td>0.48</td>
<td>-1.00</td>
<td>-0.50</td>
<td>0.00</td>
</tr>
<tr>
<td>Moss</td>
<td>0.48</td>
<td>0.37</td>
<td>0.59</td>
<td>0.73</td>
<td>-1.00</td>
<td>-0.50</td>
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<tr>
<td>Konda</td>
<td>0.50</td>
<td>0.40</td>
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<td>-0.50</td>
<td>0.00</td>
</tr>
</tbody>
</table>
# Grade of dysplasia & Cancer Risk

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cancer Incidence</th>
<th>(95% CI)</th>
<th>Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>0.598%/yr</td>
<td>0.516-0.7</td>
<td>Low</td>
</tr>
<tr>
<td>LGD</td>
<td>1.70%/yr</td>
<td>1.31-2.09</td>
<td>Intermediate</td>
</tr>
<tr>
<td>HGD</td>
<td>6.58%/yr</td>
<td>4.97-8.18</td>
<td>High</td>
</tr>
</tbody>
</table>

Rastogi et al. Gastrointest Endosc 2008  
Wani S et al. Am J Gastroenterol 2009
PRINCIPLES OF ENDOSCOPIC ERADICATION THERAPIES

- Resection of neoplastic lesion – lesion with highest dysplasia grade
- Eradication of remaining Barrett’s esophagus (reduce the risk of metachronous neoplasia)
- Management of complications
- Enrollment in surveillance programs and address recurrences
Endoscopic Eradication Therapies: The Options

• Thermal techniques:
  - APC
  - MPEC
  - Lasers (Nd:YAG, KTP:YAG)
  - RFA

• Photochemical:
  - PDT

• Mechanical:
  - EMR

• Others:
  - Cryoablation
  - Ultrasonic ablation

• Multimodality therapies

Wani S et al. Gastrointest Endosc 2010
AIM – DYSPLASIA TRIAL

- 128 patients with BE and dysplasia (LGD/HGD)
- Mean BE length 5 cm; 12 month follow up

- LGD Eradication (n=64)
  - 23%

- HGD Eradication (n=63)
  - 19%

- IM Eradication (n=127)
  - 2%

*Shaheen N et al. NEJM 2009
ASGE GUIDELINES FOR ENDOSCOPIC ERADICATION THERAPY

In Barrett’s esophagus patients with confirmed HGD, we recommend EET compared to surveillance

Strength of recommendation: Strong
Quality of evidence: Moderate

Wani S et al. Gastrointest Endosc (in press)
### Natural History of LGD

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Incident cases</th>
<th>Incidence rate %/year (95% CI)</th>
<th>Mean time to development (years, SD range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGD</td>
<td>21</td>
<td>1.6 (1.05-2.46)</td>
<td>2.86 (4.22)</td>
</tr>
<tr>
<td>EAC</td>
<td>6</td>
<td>0.44 (0.2-0.98)</td>
<td>4.41 (1.49)</td>
</tr>
<tr>
<td>HGD/EAC</td>
<td>24</td>
<td>1.83 (1.23-2.74)</td>
<td>3.08 (2.57)</td>
</tr>
</tbody>
</table>

Wani S et al, Gastroenterology 2011
AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW

Diagnosis and Management of Low-Grade Dysplasia in Barrett’s Esophagus: Expert Review From the Clinical Practice Updates Committee of the American Gastroenterological Association

Sachin Wani, Joel H. Rubenstein, Michael Vieth, and Jacques Bergman

1University of Colorado, Anschutz Medical Campus, Aurora, Colorado; 2Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan; 3University of Michigan Medical School, Ann Arbor, Michigan; 4Klinikum Bayreuth, Bayreuth, Germany; and 5Academic Medical Center, Amsterdam, The Netherlands
SURVEILLANCE vs. ABLATION IN LGD

- Ablation reduced risk of progression to HGD/EAC by 25%
  - 1.5% ablation vs. 26.5% controls (95% CI 14.1-35.9%, \( p<0.001 \))

- Ablation reduced risk of progression to EAC by 7.4%
  - 1.5% ablation vs. 8.8% controls (95% CI 0.0-14.7%, \( p=0.03 \))
In Barrett’s esophagus patients with LGD, we suggest EET compared to surveillance; however, patients who place a high value on avoiding adverse events related to EET may choose surveillance as the preferred option.

Strength of recommendation: Conditional
Quality of evidence: Moderate

Wani S et al. Gastrointest Endosc (in press)
EFFECTIVENESS DATA

- Orman 2013
- Gupta M. 2013
- Phoa et al 2013
- Haidry 2013
- Guanet Argente 2013
- Pandita (US RFA) 2014
- Haidry 2015
- Phoa 2016
- Wani 2016

Legend:
- CE-IM
- CE-D
- Recurrence

(%)
The rate at which complete eradication of neoplasia is achieved by 18 months in patients with BE-related dysplasia or intramucosal cancer referred for EET

Type of measure: Outcome
Performance target: 80%

Wani S et al. Am J Gastroenterol and Gastrointest Endosc 2017
The rate at which complete eradication of intestinal metaplasia is achieved by 18 months in patients with BE-related dysplasia or intramucosal cancer referred for EET

Type of measure: Outcome
Performance target: 70%
Adverse Events

- Meta-analysis – 37 studies
- Pooled rate (RFA +/- EMR): 8.8% (95% CI 6.5-11.9)
- Strictures: 5.6% (95% CI 4.2-7.4)
- Bleeding: 1% (95% CI 0.8-1.3%)
- Perforation: 0.6% (95% CI 0.4-0.9)
- Adverse events higher with EMR (RR 4.4)
- BE length and baseline histology predictors of adverse events

Qumseya B, Wani S CGH 2016
The rate at which adverse events are being tracked and documented in individuals post EET

Type of measure: Process
Performance target: 95%
RECURRENCE OF INTESTINAL METAPLASIA AND NEOPLASIA

• Meta analysis – 33 studies
• Pooled incidence any recurrence: 6.5 (95% CI 4.8-8.1)/100 patient-years
• Incidence of IM: 4.2 (95% CI 2.9-5.4)/100 patient-years
• Incidence of early neoplasia: 1.4 (95% CI 0.9-1.8)/100 patient-years

Fuji et al, Endosc Int Open 2017
During endoscopic surveillance after EET, the rate at which biopsies of any visible mucosal abnormalities are performed

Type of measure: Process
Performance target: 95%
Approach to BE related neoplasia

Patient with Barrett’s esophagus related neoplasia

Consider referral to tertiary care center

Confirm diagnosis by expert GI pathologist
Evaluation and discussion in clinic

Accurate diagnosis and staging
• Repeat EGD using HD-WLE, advanced imaging and EUS
• Define extent by Prague C&M criteria and visible lesions by Paris classification

Endoscopic resection of all visible lesions

Highest histologic grade based on above evaluation

Submucosal Cancer

High grade dysplasia or intramuscosal cancer

Low grade dysplasia

Surgical referral for esophagectomy (EET only in T1b cancer with favorable features and poor-surgical candidate)

EET (resection or ablation)

Enroll in surveillance program post complete eradication of intestinal metaplasia and neoplasia

EET in confirmed LGD (expert GI pathologist, at least 2 EGDs with LGD) OR surveillance q6-12 months

Wani et al, Gastro Clinics N Am 2015
Esophageal & Gastric Multidisciplinary Clinic
Established August 2013
THANK YOU