Barrett’s with Low-Grade or No Dysplasia: Ablate or Survey

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Barrett esophagus (BE)

- BE affects 2% of the adult population, particularly those with heartburn and those undergoing endoscopy.

- Conversion rate from BE to EAC is at least 0.5% per year (0.2-0.6%).

- Effective intervention at early stage would reduce the risk of malignant progression.

Incidence of Esophageal Adenocarcinoma (EAC)

Relative Change in the Incidence of Esophageal Adenocarcinoma and Other Cancers (1975-2001)

- Esophageal adenocarcinoma
- Lung cancer
- Melanoma
- Breast cancer
- Prostate cancer
- Colorectal cancer

Rate ratio (relative to 1975)

Pohl H, Welch HG JNCI J Natl Cancer Institute 2005;97:142-146
Screening of BE

Screening the entire population?

• All models evaluating ENDOSCOPY for screening BE in the entire population concluded that this is not cost effective.
Screening of BE

- The AGA recommends screening for BE in:
  1. Individuals older than 50 years
  2. with symptomatic GERD
  3. and at least 1 additional risk factor for EAC


- A proportion of patients with EAC report no GERD symptoms

Screening of BE

- Aggravating factors for progression to EAC
  - Male sex
  - Age over 50 years
  - White race
  - Obesity
  - Chronic symptomatic GERD
  - Alcohol and tobacco use

*Ernst J. Kuipers et al. Natural History of Barrett’s Esophagus* Digestive Diseases and Sciences (2018)
Definition of BE

• Differences on BE definitions between Britain, USA and ESGE persist

• BSG: non-IM allowed, Length ≥1 cm
• ACG, AGA: IM only allowed
• ESGE: IM and a length ≥1

(Unless there is a visible abnormality)

Endoscopic management of Barrett’s esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement 2017
Definition of BE

**STATEMENT 1**
The diagnosis of BE is made if the distal esophagus is lined with columnar epithelium with a minimum length of 1 cm (tongues or circular) containing specialized intestinal metaplasia at histopathological examination.
**Definition of BE**

**STATEMENT 5**
Endoscopy reports of patients with BE should include:

i. the extent of BE using the Prague criteria (circumferential extent [C], maximum extent [M]), and any separate islands proximal to the maximal extent;

ii. A description of location (in cm from the incisors and clockwise orientation) of any visible abnormality within the Barrett’s epithelium, in addition to lesion size (mm) and macroscopic appearance using the Paris classification;

iii. The presence or absence of erosive esophagitis using the Los Angeles classification;

iv. The location of biopsies taken from the Barrett’s segment (number of biopsies and location in cm from the incisors);

v. Appropriate photo documentation of the landmarks and of all visible Barrett’s epithelium, as well as any visible lesions.

**STATEMENT 6**
Biopsy samples should be taken from all visible mucosal abnormalities. In addition, random 4-quadrant biopsies should be collected every 2 cm within the Barrett’s segment, starting from the upper end of the gastric folds. Biopsies from each level should be collected in and presented to the pathologist in a separate container.
Modified Vienna Criteria

- No dysplasia
- Indefinite for dysplasia
- LGIN (low-grade adenoma / dysplasia)
- HGIN (HG adenoma / dysplasia, non-invasive carcinoma, or suspicion of invasive carcinoma)
- Invasive epithelial neoplasia (intramucosal carcinoma, submucosal carcinoma, or beyond)
No-Dysplasia BE

- Provided that the initial (diagnostic) endoscopy is performed according to the standards:
  - High definition endoscopy
  - Adequate setting
  - Sufficient number of random biopsies

**STATEMENT 7**

Surveillance intervals for nondysplastic BE should be stratified according to the length of the Barrett's segment.

i. Irregular Z-line/columnar-lined esophagus < 1 cm: no endoscopic surveillance

ii. Maximum extent of BE ≥ 1 cm, **and** < 3 cm: 5 years

iii. Maximum extent of BE ≥ 3 cm **and** < 10 cm: 3 years

Patients with BE with a maximum extent ≥ 10 cm should be referred for surveillance endoscopies to a BE expert center.

If a patient has reached 75 years of age at the time of his/her last surveillance endoscopy and has no previous evidence of dysplasia, no subsequent surveillance endoscopies should be performed.
Adherence to the Seattle Biopsy Protocol

Adherence to Biopsy Guidelines for Barrett's Esophagus Surveillance in the Community Setting in the United States

Endoscopic treatment

- Endoscopic therapy using RFA for all patients with non-dysplastic Barrett’s esophagus is not cost-effective
  

- Management strategy of biomarker-based RFA-ablation of high-risk patients with non-dysplastic Barrett’s esophagus
  
  *Das A, et al. Endoscopic ablation is a cost-effective cancer preventative therapy in patients with Barrett’s esophagus who have elevated genomic instability. Endosc Int Open. 2016*
Chemoprevention

Esomeprazole and aspirin in Barrett’s oesophagus (AspECT): a randomised factorial trial

Indefinite for Dysplasia

It is an interim diagnosis

**STATEMENT 10**

Patients with a diagnosis of “indefinite for dysplasia” confirmed by a second expert GI pathologist should be managed with optimization of antireflux medication and repeat endoscopy at 6 months.

If no definite dysplasia is found in subsequent biopsy samples (including if the biopsies are again classified as “indefinite for dysplasia”), then the surveillance strategy should follow the recommendation for nondysplastic BE.
Low-Grade Dysplasia

• 60-year-old man
• Endoscopy for BE surveillance: C3M4
• On Biopsy: LGD

What is more appropriate?
A- Repeat endoscopy after 6 m
B- RFA
C- Revision of biopsies
Low-Grade Dysplasia

- 60-year-old man
- Endoscopy for BE surveillance: C3M4
- On Biopsy: LGD

What is more appropriate?

A- Repeat endoscopy after 6 m
B- RFA
C- Revision of biopsies

**STATEMENT 12**

Patients with LGD on random biopsies confirmed by a second expert GI pathologist should be referred to a BE expert center. A surveillance interval of 6 months after confirmed LGD diagnosis is recommended.

**i.** If no dysplasia is found at the 6-month endoscopy, the interval can be broadened to 1 year. After two subsequent endoscopies negative for dysplasia, standard surveillance for patients with nondysplastic BE can be initiated.

**ii.** If a confirmed diagnosis of LGD is found in the subsequent endoscopies, endoscopic ablation should be offered.
Low Grade Dysplasia

• If ablation is not undertaken: 6 to 12 monthly surveillance is recommended

_dietro M, Fitzgerald RC; BSG Barrett’s guidelines working group. Revised British Society of Gastroenterology recommendation on the diagnosis and management of Barrett’s oesophagus with low-grade dysplasia. Gut 2018_
Radiofrequency Ablation vs Endoscopic Surveillance for Patients With Barrett Esophagus and Low-Grade Dysplasia
A Randomized Clinical trial

Primary and Secondary Efficacy Outcomes

Occurrence of Progression to HGD or Adenocarcinoma
Low-Grade Dysplasia

• Dysplasia Detection Rate?
• Expert Pathologist ??
• Downgrading reported in academic settings. Real World???
Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate

<table>
<thead>
<tr>
<th></th>
<th>Group A Dedicated list (n=142)</th>
<th>Group B Nondedicated list (n=587)</th>
<th>P value (Group A vs. Group B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (SEM), years</td>
<td>62 (1.03)</td>
<td>62 (0.59)</td>
<td>0.62</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>87 (61)</td>
<td>392 (67)</td>
<td>0.24</td>
</tr>
<tr>
<td>Length – maximal extent, mean (SEM), cm</td>
<td>3.7 (0.25)</td>
<td>4.1 (0.14)</td>
<td>0.25</td>
</tr>
<tr>
<td>Prague documentation, n (%)</td>
<td>132 (93)</td>
<td>96 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of biopsies per 2 cm, mean (SEM)</td>
<td>4.0 (0.16)</td>
<td>2.0 (0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with ≥4 biopsies per 2 cm, n (%)</td>
<td>110 (78)</td>
<td>109 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seattle protocol technique, n (%)</td>
<td>109 (77)</td>
<td>56 (10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Benchmark Quality Criteria

1. Percentage of IND diagnoses
2. Intraobserver Agreement
3. Percentage agreement compared with a consensus gold standard diagnosis
4. Percentage of cases of HGD misdiagnosed as NDBE.
Published in final edited form as:

**BOB CAT: A Large-Scale Review and Delphi Consensus for Management of Barrett’s Esophagus With No Dysplasia, Indefinite for, or Low-Grade Dysplasia**
Risk factors for escalation and de-escalation

**General population**
- Males at higher risk aged > 60 year-old with uncontrolled GERD symptoms for > 10 years

**Barrett’s esophagus**
- Higher risk groups (including age 50 years or older, white race, male sex, central obesity and symptoms)

**Indefinite for diagnosis**
- IND is an interim diagnosis only

**Lower risk LGD**
- Present on only one occasion, or LGD absent after 2 consecutive follow up endoscopies

**Higher risk LGD**
- Long segment, multifocal, persistent visible lesion
**General population**

Endoscopic screening only in higher risk groups

- Endoscopic surveillance in higher risk groups, unless life expectancy < 5 years
- If visible lesion, ER for diagnosis then appropriate ablative therapy

**Barrett’s esophagus**

Endoscopic screening in higher risk groups, unless life expectancy < 5 years

- If visible lesion, ER for diagnosis then appropriate ablative therapy

**Indefinite for Dysplasia**

Close follow up of IND, with short intervals between surveillance (in year), and careful biopsy sampling, to detect prevalent neoplasia.

- Increase acid suppressive therapy

**Lower risk LGD De-Escalate**

LGD on a single occasion ➔ continued (intensive 6-12 month) surveillance.

- Confirmed absence of LGD after 2 consecutive endoscopies ➔ revert to routine surveillance.

**High Risk LGD Escalate**

Ablative therapy with follow up

- If visible lesion ER (+ablative therapy) + follow up
Future Strategies

Development and Validation of a Model to Determine Risk of Progression of Barrett’s Esophagus to Neoplasia

Progression of BE score (PIB)

PIB Risk Score:
- Male Sex: 9 points
- Cigarette Smoking: 5 points
- BE length: 1 point/cm length
- Confirmed Low Grade Dysplasia: 11 points

Risk Pyramid for Progression in Barrett's:
- High (>20 points): Annual Risk progression 2.1%
- Intermediate (11-20 points): Annual Risk progression 0.73%
- Low (0-10 points): Annual Risk progression 0.13%
Cumulative Incidence Probabilities

Risk of Progression

A

Cumulative Risk Probability

B

Points 0-10 (n = 214) Points 11-20 (n = 439) Points 21+ (n = 155)

Progression to HGD/CA

0 2 4 6 8 10 12 14

0.70 0.75 0.80 0.85 0.90 0.95 1.00

Years

Progression free

C statistic = 0.7

REF

HR = 5.6

HR = 18.4

Points 0-10

Points 11-20

Points 21+
Biomarkers

- Biomarkers may provide a diagnostic or predictive yield over traditional histology, such as p53, an adjunct to routine histological assessment of dysplasia.
Biomarkers

Somatic sequencing of Barrett's tissue (i.e. mutations, whole genomic doubling)

Germline Susceptibility (i.e. SNPs)

Family history

Environmental Risk factors: GERD, Cigarette Smoking, Body-mass Index

Patient with Barrett's esophagus

Neoplasia Risk Prediction Model
Sources of Biomarkers

- **Electronic nose:** Detection of VOCs
- **Tethered capsule:** Collection of cells and images
- **Endoscopic biopsy:** Samples esophageal tissue
- **Endoscopic imaging:** Visualizes markers in real time
- **Blood sample:** DNA encoded markers

VOCs

- Nose
- Mouth
- Artery
- Esophagus
- Lungs
- Stomach
Key Messages

• The most cost-effective management of individuals with BE and no dysplasia is surveillance
Key Messages

• BE with LGD: Strategies in which an endoscopy is repeated to confirm the accuracy of the diagnosis yield greater cost-effectiveness compared with strategies in which there is immediate treatment of all new diagnoses of low-grade dysplasia
Key Messages

• Recommendations will likely change with advances in risk stratification, advances in endoscopic treatment, and reductions in procedure costs.